The Chemistry of Dienes and Polyenes. Volume 1
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CHAPTER **10**

Analysis of dienes and polyenes and their structure determination

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I. INTRODUCTION

In the last fifteen years most efforts aimed at identification and structure determination of dienes and of polyenes were related to studies of bio-originated compounds. The analysis of dienes and polyenes has not been reviewed, so far. The analysis of double bonds containing molecules utilizes the chemical reactivity of the bonds, and hence conjugated double bonds require different approaches than methods used for non-conjugated double bonds. One example is the use of the Diels-Alder reaction which yields derivatives of conjugated dienes whereas isolated double bonds are not affected. Some of the methods

reviewed are very basic and have been in use for many years; others are very specific for the family of compounds studied, as exemplified for carotenoids.

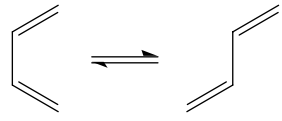
The determination of the structure of synthetic dienes and polyenes is somewhat easier than the identification and structure determination of natural products. Obviously, this stems from the need to separate the latter compounds from very complex mixtures.

The theoretical analysis of the spectra (mostly IR and UV-VIS) of polyenes has been reviewed twice in the last 20 years[1,2]. These reviews concentrate on understanding their biological role and the extension of polyene application. However, both reviews do not cover the structure determination of dienes and polyenes.

One important reason why biologists and biochemists are interested in polyenes is related to the fact that they are light-harvesting antennas and are responsible for triggering the vision signal[1,2]. Moreover, long-chain polyenes appear in vitamins and carotenoids as well as in many antibiotics. Another reason is that the polymeric form, such as polyacetylene, is a natural photo-conductive matter that upon doping becomes conductive, comparable with copper! These properties have ignited the interest of chemists in the synthesis of polyene polymers for 'molecular electronics'. These conjugated functional polymers may be designed to serve as tunable electro-light emitting diodes (LED).

II. SPECTROSCOPIC METHODS

The use of UV-VIS spectra to analyse dienes and polyenes was historically the first method of choice. The spectra of isolated non-conjugated polyenes is actually the superposition of the spectrum of each one of the double bonds. For each double bond the spectrum depends on the various substituents and also on its location in the molecule. It also depends on the stereochemistry, since conjugated double bonds have either *E* or *Z* configuration around each π-bond but also a *cisoid* and *transoid* conformer[3] around the single bond marked as s-*cis* and s-*trans*[4].



s-*cis* s-*trans*

Polyenes can undergo rotation easily about the 'single' bond at room temperature. The s-*trans* conformers are generally more stable because steric interactions in them are minimized.

The s-*cis* conformers tend to be distorted from planarity, and this may influence the UV spectra, as shown by the comparison of butadiene **(1)** and cyclopentadiene **(2)**.

(1) **(2)**

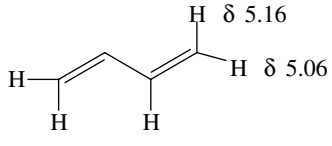
λ 220 nm (ε 20900) λ 238.5 nm (ε 3400)

It is evident that the s-*cis* frozen conformation in the ring of **2** shows a batochromic shift, but a much lower absorption (ε) in comparison with butadiene **(1)**. Woodward and

Fieser and Fieser[5] used an empirical correlation, based on a wide range of compounds, between the diene structure and λ_{max}. This empirical correlation of structure and ultraviolet absorption followed a regular pattern, allowing the calculation of λ_{max} with reasonable accuracy. The early rules were: parent diene 214 nm; for cisoid add 39 nm, extended conjugated diene 30 nm. In the studies of steroids and other cyclic terpenoids these rules were employed to differentiate between homoannular dienes and exocyclic enes (see also Section VII.A)[5]. A more theoretical approach is presented for longer conjugated polyenes, i.e. hexatriene, octatetraene, etc., that have geometrical isomers, i.e. *cis*-polyenes and *trans*-polyenes. For butadiene, all vibrational frequencies have been observed in the IR or Raman spectra[2]. The theoretical analysis of the vibrational properties and the frequencies were reviewed in 1991 by Orlandi and coworkers; their review contains 251 references[2]. However, this review does not offer the analytical tools needed for structural determination. Furthermore, all polyenes examined are conjugated with no branching or ring effects.

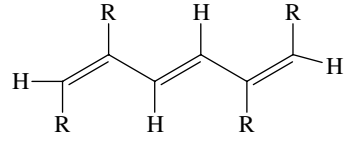
In general, it is noteworthy that one can use the lowering of the energies required to either excite (UV-VIS) or stretch (IR, Raman) the C=C bond with the extension of the polyene system. We have mentioned the batochromic effect (Woodward rule)[5] and will discuss the C=C stretch frequency which correlates with the length of the polyene (e.g. 1640 cm^{-1} for butadiene and 1490 cm^{-1} for the β-carotene homologs, respectively). These correlations can supplement other spectroscopic data to assess the length of the polyene conjugated systems. Of course, the extreme case is cyclic conjugated aromatic systems which are beyond the scope of the present review.

Very powerful tools for the study of dienes and, to some extent, polyenes (in particular annular polyenes) are both ^1H and ^{13}C NMR spectroscopies, which will be discussed in a separate section. As previously mentioned 1,3-butadiene is more stable in the s-*trans* conformation and in the ^1H NMR spectrum both butadiene **(1)** and 2,3,6,7-tetramethyl-2,4,6-octatriene **(3)** display the vinyl proton at a low chemical shift value. In these simple examples the δ value can be predicted theoretically. The ^1H NMR spectrum of a C_{25}-branched isoprenoid was examined as part of the structural determination for biomarkers and is shown in Figure 1[6]. The other spectral and structure assignments are described later in this review.



δ 6.27

(1)



δ 6.62

(3)

R = CH_3

Figure 1 shows a partial ^1H NMR spectrum for H-23, H-5 and H-24 a,b (see the formula of the C_{25} polyene, **4**). These are the hydrogens on the alkenic position and the multiplet between 4.89–5.76 δ (ppm) integrates to four hydrogens, i.e. to a vinyl functionality. Since this is an isoprenoid skeleton it is clear that the position of the double bond must be at C-24. Proton H-23 appears at a lowest field as a heptet due to *cis* coupling with H-24a, *trans* coupling with H-24b and an additional coupling with the vicinal H-22. This indicates the presence of a single H-22 allylic proton, thus supporting the assignment. The double bond between C-5 and C-6 shows the influence of the H-4 allylic hydrogens. These assignments and further discussion on decoupling and ^{13}C NMR spectrum appear in Belt and coworkers[6].

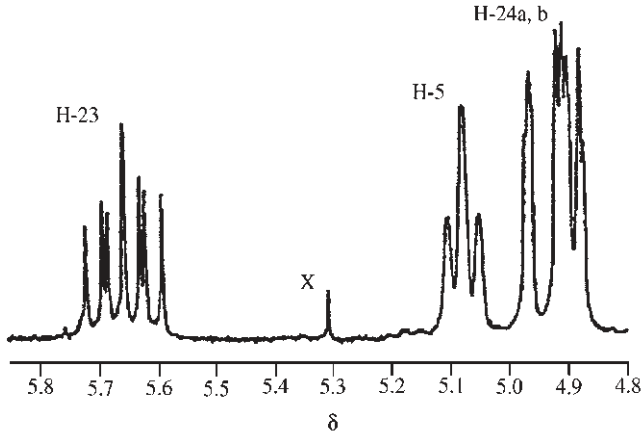
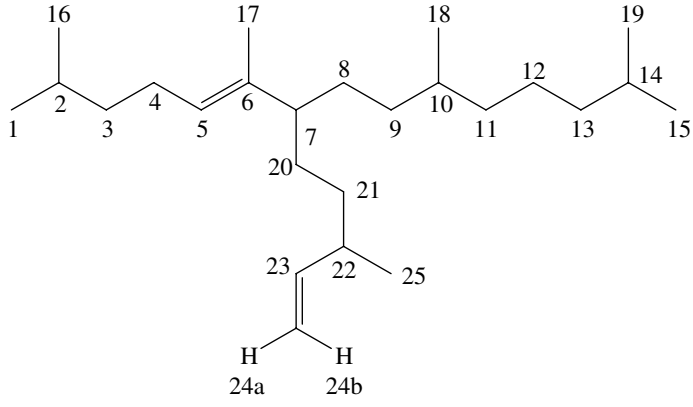


FIGURE 1. The ^{1}H NMR spectrum of the double bonds region (δ 4.8–5.8 ppm) of the high branched C_{25}, compound **4**. The signal X is due to an impurity (see Belt and coworkers[6])

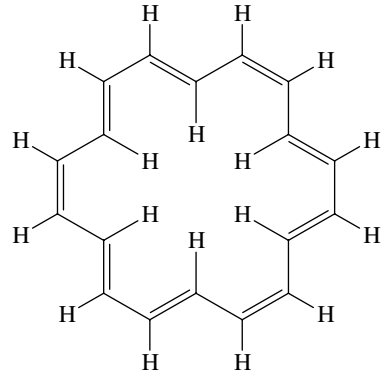


(4)

Although we have stated that we will not include aromatic structures, large π systems of polyenes give rise to long conjugated systems, with very strong shielding and deshielding effects. The annulene family contains systems having the $(4n + 2)$ π-electrons which, according to Hückel, should have a cyclic delocalization but are diatropic. An example is [18] annulene (**5**), where the 12 outer hydrogens absorb at δ 9.28 ppm and the 6 inner hydrogens absorb at δ 2.99 ppm.

In contrast, if the same polyene were to be 'open', no ring current would exist and the NMR spectrum would be very different (see discussion on carotenoids).

Dienes and polyenes show a pronounced molecular ion in the mass spectra and hence the molecular weight of polyenes can be determined by positive ion mass spectra. The easy removal of a π-electron from a diene is usually the reason for the distinct $M^{\bullet+}$. The mass spectral investigation of conjugated polyenes is somewhat similar to that of aromatic structures, due to the high stability of the rearranged ions formed after the



(5)

first electron removal. This phenomenon will be discussed in more detail in the section devoted to carotenoids. For a general discussion on the mass spectrum (MS) of dienes, see Budzikiewicz and coworkers[7]. Since dienes and polyenes are highly sensitive to photodissociation this method was also employed in conjunction with MS[8] for the study of branched dienes.

III. SEPARATION AND CHROMATOGRAPHY OF DIENES AND POLYENES

Chemical separation of conjugated dienes and other polyunsaturated hydrocarbons is based on the availability of π delocalized electrons. The use of a strong dienophile (e.g. tetracyanoethylene, TCNE) will derivatize only conjugated dienes, thus separating the polyunsaturated compounds into two groups. However, such derivatization is not always reversible since a retro-Diels–Alder reaction may require a high temperature. Hence, the retrieved compounds may be the thermostable ones and not those present in the initially analysed mixture.

Even simple dienes and polyenes are difficult to classify in comparison with alkenes. Whereas bromination, oxidation and reaction with tetranitromethane (TNM) can identify the number of double bonds and their location in the molecular structure, conjugated double bonds produce very complex mixtures. Furthermore, many of the tests based on π-complexation can also apply for aromatic moieties. An example is the TNM π-complex which is yellow with benzene and orange with naphthalene and the tests are therefore non-specific.

Basically, the chromatographic separation of dienes and polyenes is similar to that of alkenes. Both gas chromatography (GC) and liquid chromatography (LC or HPLC) can be employed. For low molecular weight, more volatile diene/GC is usually good enough. If a better separation is needed, this can be enhanced by Ag^{+}-π-complexation. HPLC is employed either for more polar derivatives of polyenes or for non-volatile high molecular weight compounds (see special discussion on carotenoids). The use of small particle size silver-nitrate-impregnated silica as stationary phase was adapted for HPLC separation of unsaturated hydrocarbons from petroleums and bitumens[9,10]. The same approach can be used in thin layer chromatography (TLC) to separate the unsaturated components (10% $AgNO_3$/silica gel w/w)[10].

We will discuss in some detail examples where various methods of separation, including chemical derivatization, were complemented by spectroscopic identification. However, even the use of the most advanced analytical methods frequently yields only partial

structure determination, and for more complex compounds comparison with a model compound is the only solution to *total* structure determination.

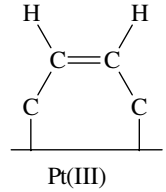
Higher molecular weight dienes and polyenes which are solid and can be crystallized make it possible to study their structure by X-ray diffraction. This, of course, will give information only about the crystalline form (see discussion on steroids and antifungal molecules, Section VII).

IV. THERMAL DESORPTION AND ELECTRON ENERGY LOSS SPECTROSCOPY

Structure determination of unsaturated compounds can be supplemented by thermal desorption (TD) and electron energy loss (EEL) spectroscopies. The two methods use the chemisorption of *cis* and *trans* enes or dienes to the Pt(111) surface over a range of temperatures[11]. The experimental equipment and procedures described[12] show these methods to be employed for dienes such as 1,3-butadiene. At very low temperature the diene is adsorbed on Pt(111) and the thermal desorption is followed by increasing the temperature.

Figure 2 shows a comparison of C_4 hydrocarbon desorption spectra of Pt(111) monitoring temperature and *m*/*z* of 2, 54, 56, 58 using a mass spectrometer. The TD spectrum for a monolayer of 1,3-butadiene is compared with 1-butene, *cis*-2-butene and *trans*-2-butene. Monitoring of the hydrogen thermal desorption shows that for the 1,3-diene no hydrocarbon desorption is recorded, but rather a destructive dehydrogenation of the diene. In the monoenes, up to 300 K one can see the release of *m*/*z* 56 ($C_4H_8^+$) followed at higher temperature by the release of hydrogen, whereas in the diene (Figure 2c) only H_2^+ (*m*/*z* 2) is monitored.

The electron energy loss spectra (EEL) in Figure 3 shows the IR vibrational difference of *cis* and *trans* alkenes up to 170 K, arising from different geometry of the two σ bonds between the metal and the double bond. At 300 K this difference is erased and both form C_4H_6, by loss of hydrogen[11]. The bond formed by the diene (1,3-butadiene) is shown to have the same vibrational properties. Hence, the authors conclude that the end product adsorbed is:



Pt(III)

V. MASS SPECTROMETRY

Simple dialkenes of general formula C_nH_{2n-2} produce a fragmentation pattern which depends upon the relative location of the two double bonds (Scheme 1). The nonconjugated dienes fragment corresponding to the respective allylic fission[13]. The nonconjugated dienes fragmentation pattern is dominated by β-cleavage and the formation of a $C_3H_6^+$ ion if rearrangement is possible (Scheme 1)[6]. The allylic fission[13] is not preferred in conjugated systems, hence the formation of the diene-ion which can be stabilized by cyclization. However, if one examines conjugated dienes and polyenes such as terpenes, the most abundant ion is the $[M - 1]^+$ base peak formed by loss of a single hydrogen atom. Apart from this ion the other abundant ions are the *m*/*z* 53 and *m*/*z* 39, formed by

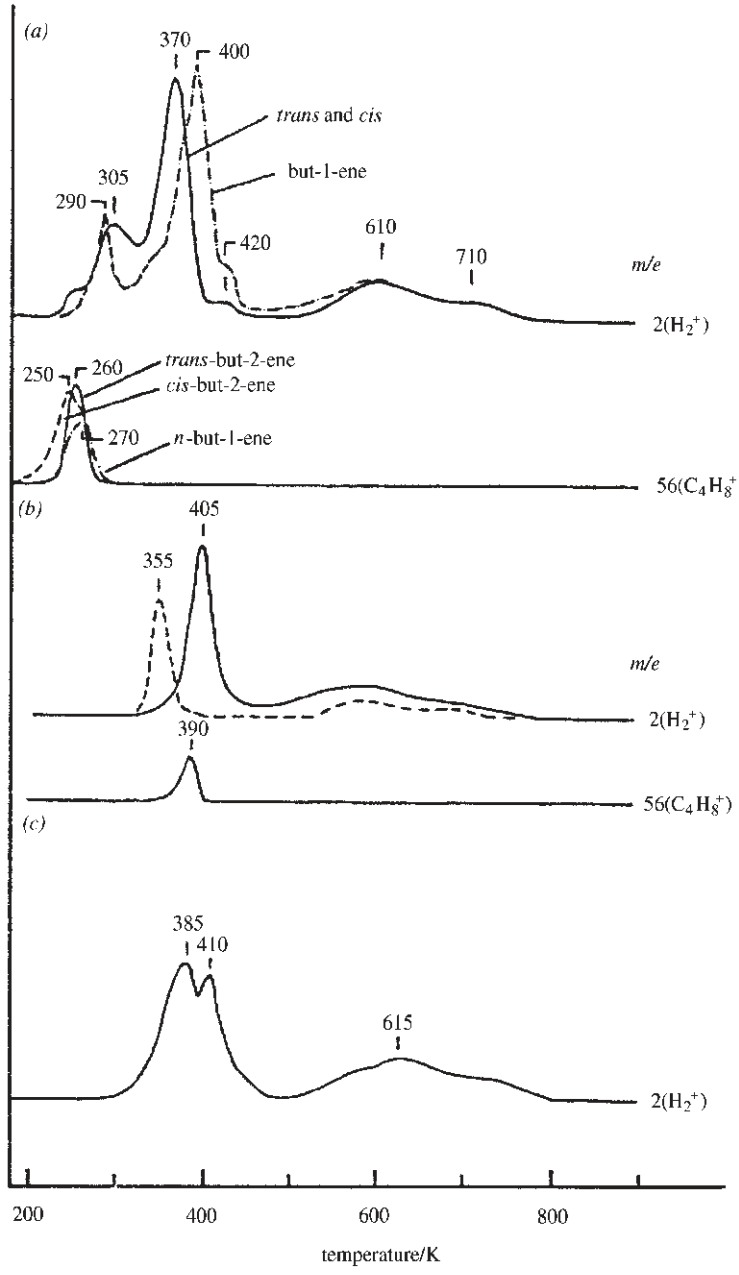


FIGURE 2. Thermal desorption spectra for monoenes and a diene C_4 hydrocarbon, chemisorbed on Pt(III). (a) *cis*-but-2-ene and *trans*-but-2-ene, (b) but-2-yne and (c) 1,3-butadiene. $\theta = 1$ (full line) $\beta = 3\text{KS}^{-1}$ for all. The monitoring of m/z 2, 54, 56, 58 was done by MS (see Avery and Sheppard[11] and references cited therein)

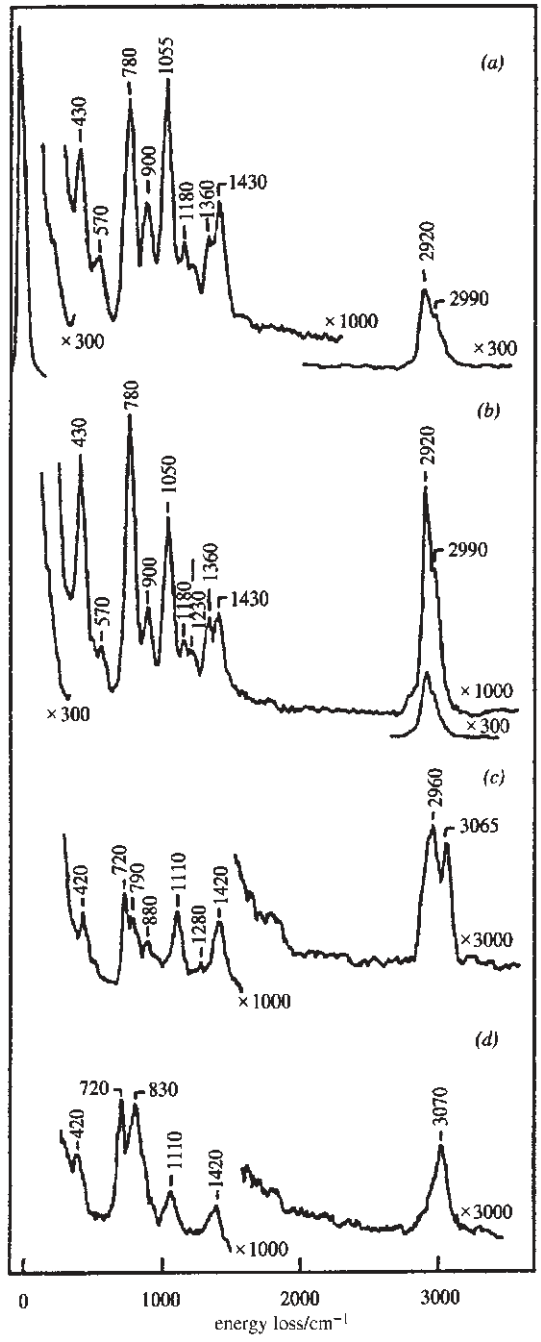
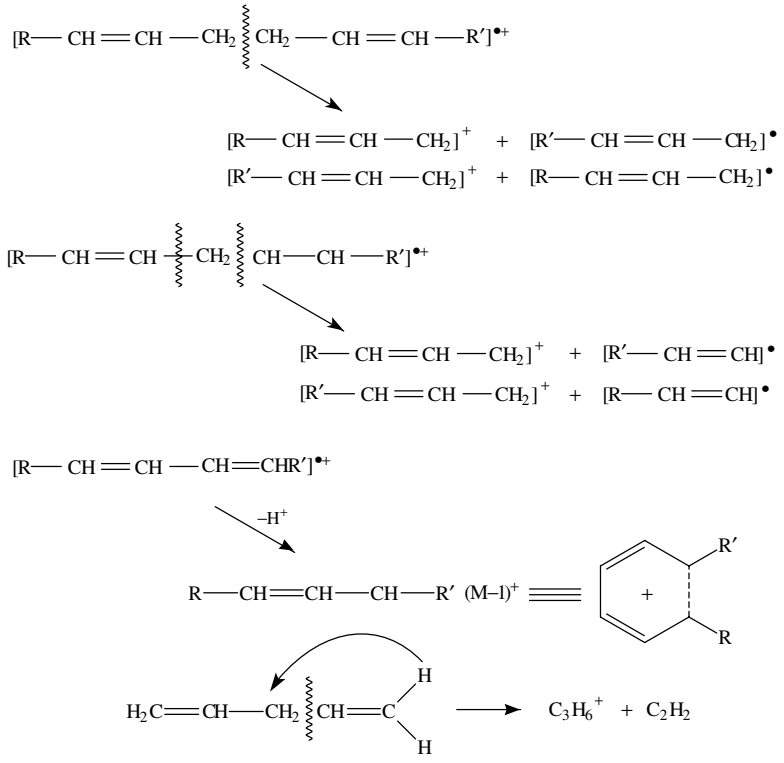
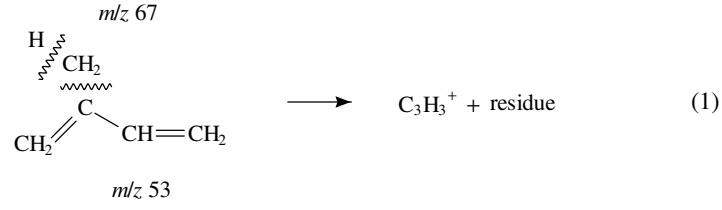


FIGURE 3. Electron energy loss spectra from 1,3-butadiene, chemisorbed on Pt(III) at (a) 170 K, (b) 300 K, (c) 385 K and (d) 450 K[11]



SCHEME 1

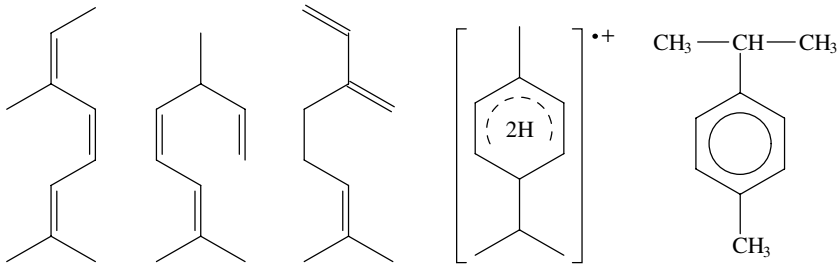
the cleavage shown in equation 1.



(1)

The next conjugated triene of the isoprenoid structure is the *allo*-ocimene **(6)**. *β*-Ocimene **(7)** and myrcene **(8)** also have a triene moiety but only two of their double bonds are conjugated. Comparison of these three isomeric trienes gives insight into the manner in which the relative positions of the double bonds control the fragmentation (Figure 4). The obvious mass spectral differences show that conjugation yields a higher abundance of the M^+ (136) and the base peak of compound **6** is derived by the loss of a methyl group (*m*/*z* 121). These two ions are much less abundant for **7** and **8**, both showing *m*/*z* 93 as the most abundent signal whilst **8** shows also *m*/*z* 69[7].

Cyclic dienes of the terpene family are also very interesting. The MS of the $C_{10}H_{16}$ compounds are discussed extensively in Budzikiewicz and coworkers.[7]. All of them transform



(6) **(7)** **(8)** **(9)** *m/z* 136 **(10)** *m/z* 134

into the ion **9**, having a structure which is very similar to the ion formed from the aromatic cumene **(10)** but differing by 2 hydrogens (*m/z* 136 vs 134), see also compounds **11–14**.

The similarity of the MS spectra of isoterpinolene **(11)**, terpinolene **(12)**, α-terpinene **(13)** and the *allo*-ocimene **(7)** is striking. Whereas the hydrogen rearrangements suggested to explain this similarity might be speculative, they offer a reasonable explanation for the almost identical MS of the open and closed diene structures with that of the triene **(7)** spectrum.

The rupture of an allylic bond, followed by an energetically favoured hydrogen migration, leads to the linear, ionized conjugated triene **(14)**. The molecular ion of triene **14** is comparable to the compound **7** molecular ion[7].

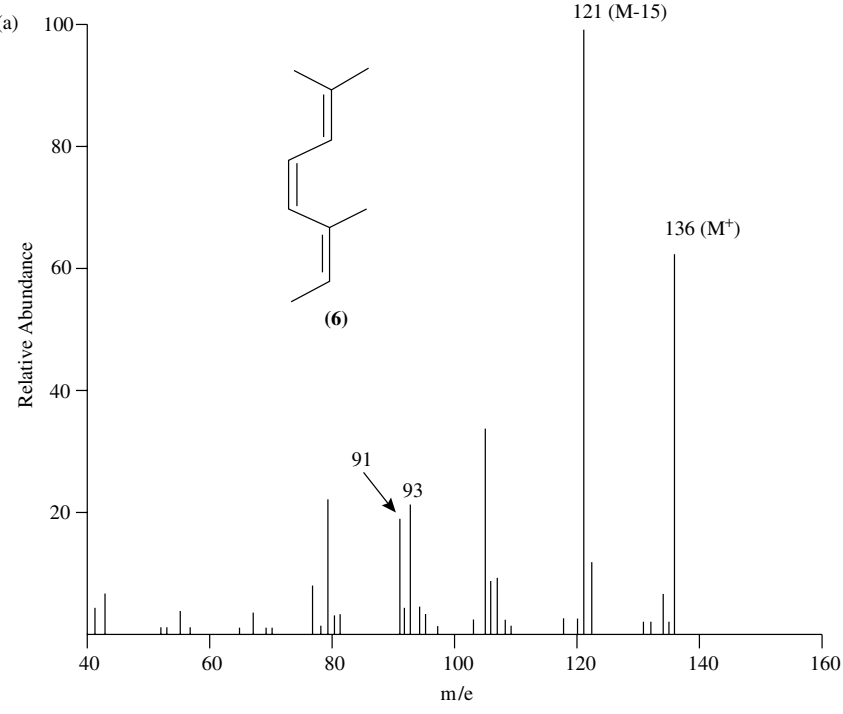


FIGURE 4. Mass spectra of (a) *allo*-ocimene **(6)**, (b) β-ocimene **(7)** and (c) myrcene **(8)**[7]

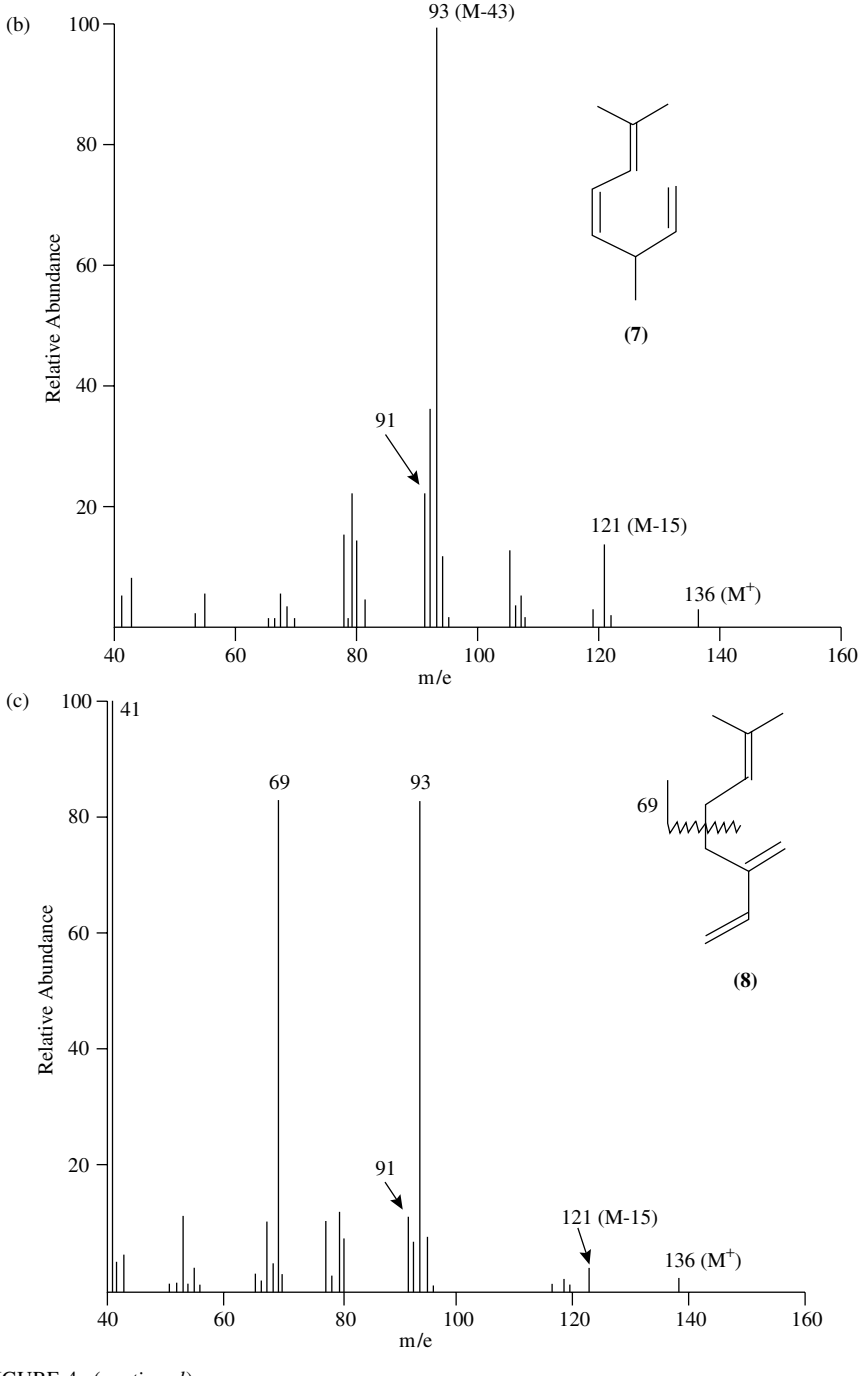
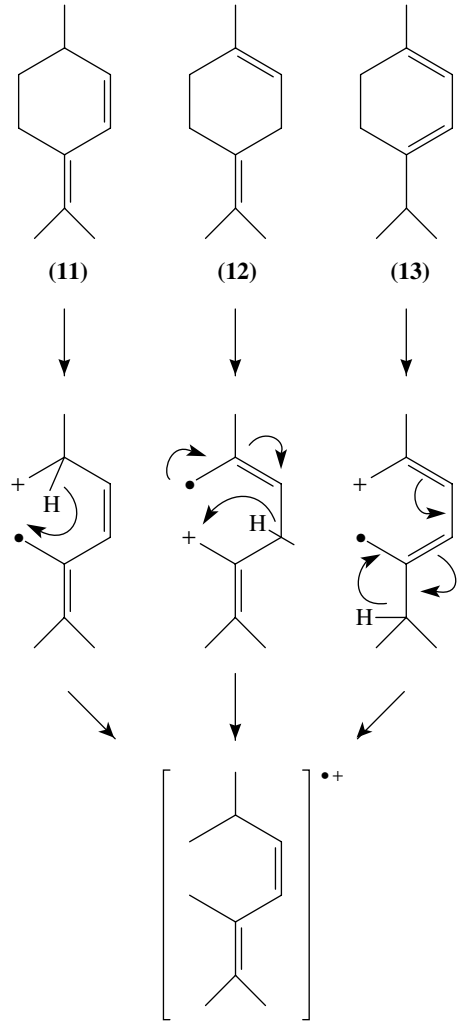


FIGURE 4. (*continued*)



(11) **(12)** **(13)**

(14)

Higher terpenes with diene and polyene moieties have also been investigated by mass spectrometry. However, we should be aware of the possibility that the molecular ion, such as that for $C_{30}H_{50}$ (C_nH_{2n-10}) at *m/z* 410, may indicate, e.g., 6 unsaturated bonds or 5 rings and only one ene unit. A comparison of the MS of squalene and an unknown compound 'X' with an *m/z* 410 molecular ion is shown in Figure 5. The large ionized fragments down to *m/z* 299 may indicate similarity of the spectra, but the base peak for compound 'X' at *m/z* 191 indicates a hopene structure[14]. The use of this *m/z* 191 fragment for the identification of the hopanes and hopenes was reviewed extensively by Aizenshtat[15].

Squalene is a unique natural product of a $C_{30}H_{50}$ structure with 6 non-conjugated double bonds. Hence, its MS shows a fragmentation pattern typical of non-conjugated

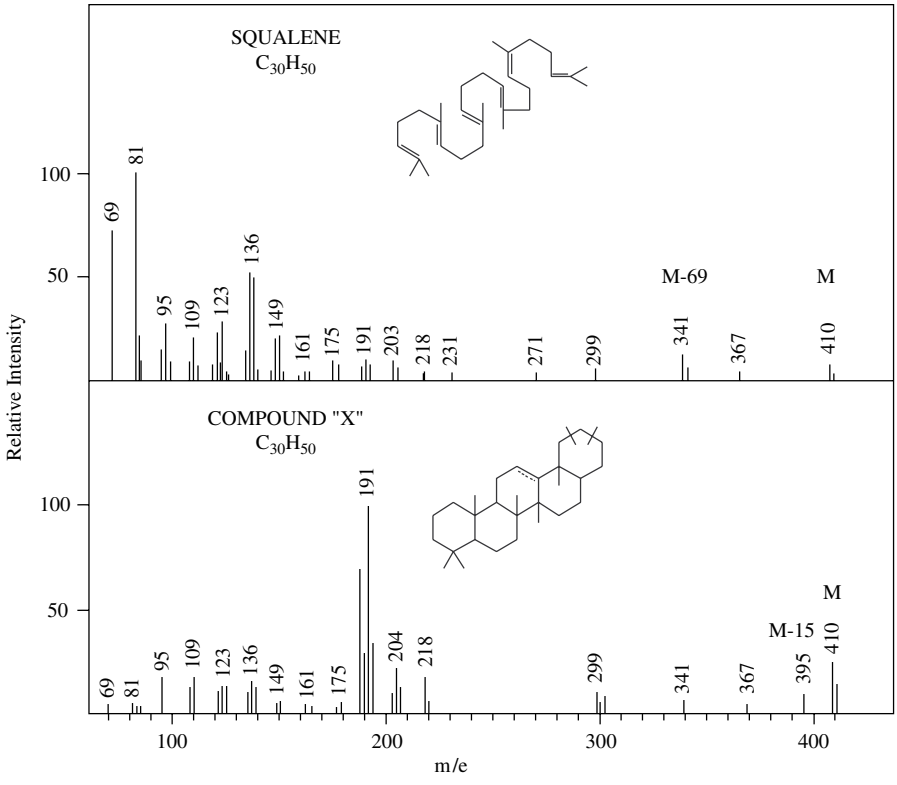


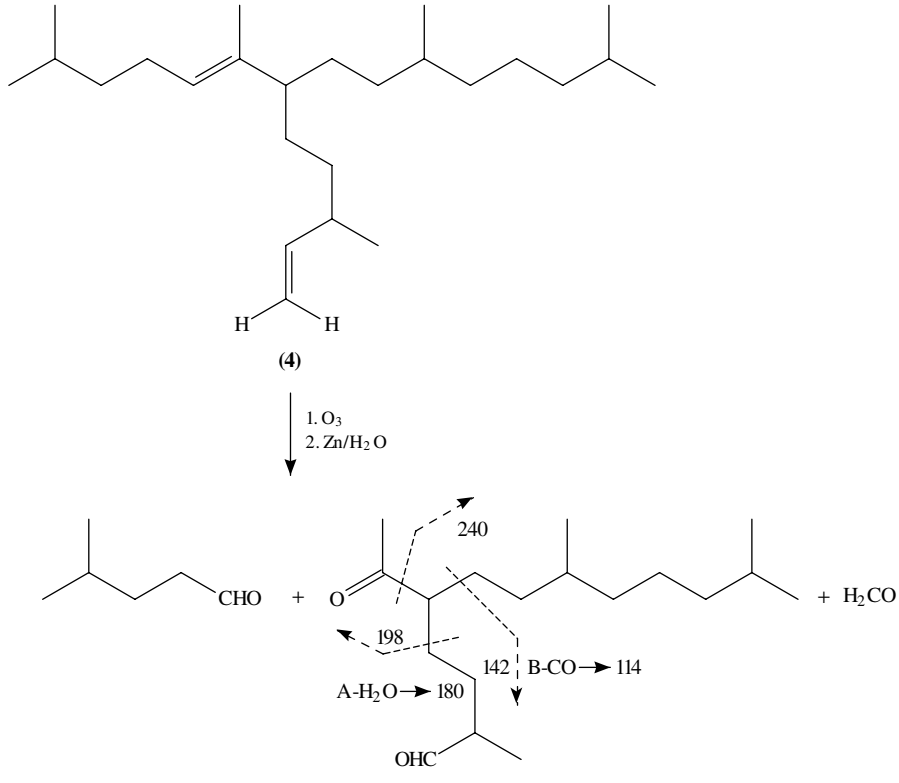
FIGURE 5. Mass spectra of two $C_{30}H_{50}$ isomers. Squalene and hopene (compound X) are isolated from a sedimentary organic matter[14,15]

various polyenes and the base peak at *m/z* 81 and the abundant next peak at *m/z* 136 resemble the spectra of the terpenes discussed previously.

Polyunsaturated (dienes and trienes) lipids found in sediments have been proven to be valuable tools in the determination of palaeo-water temperatures[6,16–18]. These C_{20}, C_{25} and C_{30} highly branched isoprenoids were investigated analytically by all the tools suggested in this review. We will select one diene to demonstrate the use of the MS, oxidation (bis-epoxidation) MS and ^{1}H NMR techniques previously discussed. This diene, 2,6,10,14-tetramethyl-7-(3-methylpent-4-enyl)pentadec-5-ene **(4)**, shows the fragmentation pattern given in Scheme 2.

Compound **4** was epoxidized to give **15** (Scheme 3) and the MS fragmentation of **15** is given by the broken-line *m/z* (relative abundance). To ensure the location of the double bonds, the epoxidation and the MS of **15** was compared with the products of the ozonolysis identified by GC and MS (as marked by the broken lines)[6]. The use of the various derivatization products via oxidation, combined with other spectroscopic methods, is discussed in Section III.

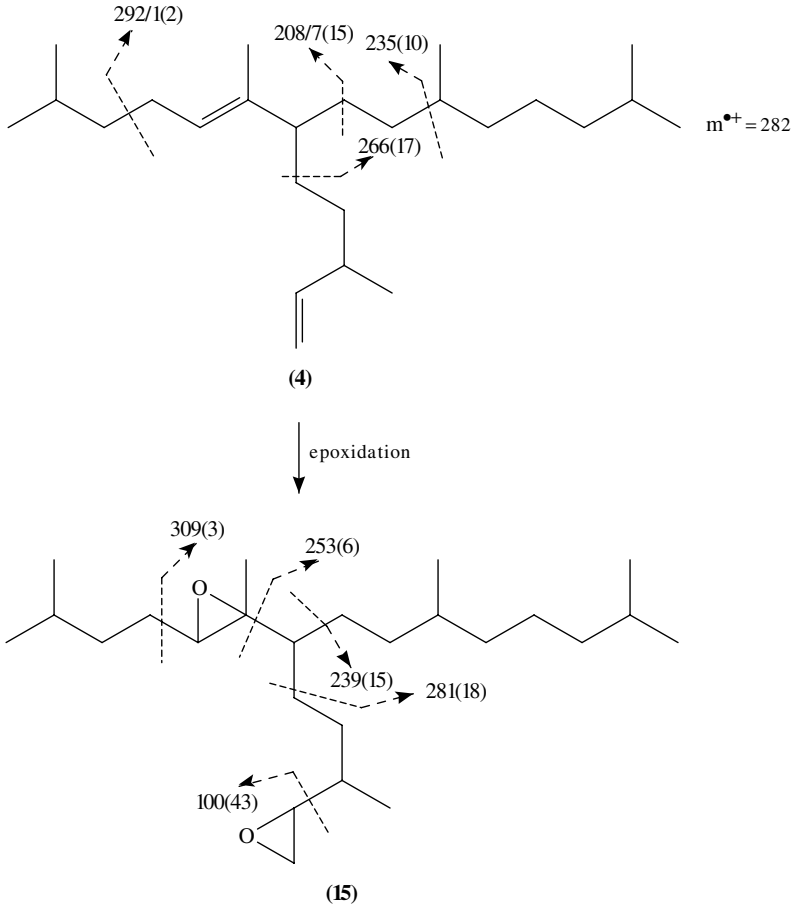
The MS studies of carotenoids have been reviewed previously[19–21]. Most carotenes show a molecular ion. Some carotenes with cyclic end moieties fragment to yield the tropylium ion (*m/z* 91) and some yield the *m/z* 105 xylene fragment. Specific deuteriation



SCHEME 2

of the carotenoid structure helps in the MS assignments and facilities the structure determination. We should bear in mind that some of the carotenoids, e.g. *Xanthomonas*, have oxygen functional groups such as ketones, ethers and phenols and hence they show a different MS fragmentation patterns[22]. The halogenated substituent of *Xanthomonas* polyenes was identified first by MS and the bromine isotopic pattern was characterized[23]. Many ionization methods have been attempted for the studies of carotenoids. Among these, electron impact (EI) was the simplest and only the field desorption technique yielded useful results up to 1990[24].

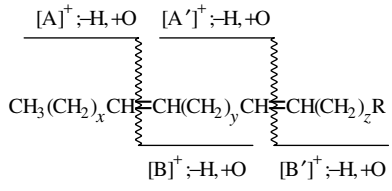
Chemical and other physical methods of ionization were also employed for the structural determination of dienes and polyenes. Such is the case for the recent investigation of aliphatic dienes and trienes by chemical ionization with nitric oxide (NO^+)[25]. It has been known since 1975 that olefins can be chemically ionized by NO^+ [CI(NO)][26]. Two distinct processes may apparently occur: (i) electrophilic addition of NO^+ to the ene leading to $[M + NO]^+$ ion and (ii) an oxidative cleavage (possibly catalysed by the surface) $R{-}CH{=}CH{-}R' \longrightarrow [RCO]^+$ and/or $[R'CO]^+$. Budzikiewicz and coworkers[25] do not have the answer as to which of the two processes dominate, but they have shown experimentally with a series of acetoxyalkadiene that both pathways (i) and (ii) depend on the reaction conditions. For alkadienes and a C_{10}-triene carboxylic acid the position of the double bond can be easily determined if it is in a terminal position C_1. However, if the double bonds are located somewhere in the middle of the carbon chain the ionization



SCHEME 3

by NO^+ yields an abundance of ions which make the determination of the location of the position quite difficult. Measurement of the chemical ionization (NO^+) spectra of the corresponding epoxides or collision activation studies can yield helpful data[25].

Scheme 4, which is discussed in detail elsewhere[25], is an example. If $y = 0$ we have a conjugated system; however, for $y = 1$ the β-cleavage leads to a m/z 83 for $x = 1$ $[CH_3CH_2CH{=}CH{-}C{\equiv}O]^+$. This fragment is not always detectable.



SCHEME 4

TABLE 1. Relative abundances[a] for PDPI/MS of hexadienes

Photoionization energy (eV)	Compound	Fragment (*m/z*)								
		CH_3 (15)	C_2H_3 (27)	C_2H_5 (29)	C_3H_3 (39)	C_3H_5 (41)	C_4H_7 (55)	C_5H_5 (65)	C_5H_6 (66)	C_5H_7 (67)
10.49	Hexa-1,3-diene	27	6	1	30	19	—[b]	12	100	12[c]
	Hexa-1,4-diene	24	48	24	100	41	20	11	89	—[d]
	Hexa-1,5-diene	—[b]	—[b]	—[b]	100	77	—[b]	—[b]	—[b]	—[b]
	Hexa-2,4-diene	18	6	2	24	23	1	12	100	8[c]
9.68	Hexa-1,3-diene	2	2	1	9	14	1	10	100	12
	Hexa-1,4-diene	2	3	11	38	55	28	16	100	4c
	Hexa-1,5-diene	—[b]	—[b]	—[b]	32	100	—[b]	—[b]	—[b]	—[b]
	Hexa-2,4-diene	4	3	1	12	22	2	14	100	19

[a]Relative to the most intense photo-dissociation peak; ionic fragmentation of the parent molecule is not included.
[b]No peak observed; species is typically in less than 1–5% abundance.
[c]Corrected for photo-ionization background.
[d]All signals observed are from photo-ionization background.

In Section I the sensitivity of conjugated systems to possible photo-dissociation (PD) was mentioned. If this PD is conducted in the ionization chamber of a mass spectrometer, a PDPI/MS (photo-dissociation, photo-ionization/mass spectrometry) can be measured[7]. The examination of the PDPI/MS spectra of hexa-1,3-, 1,4-, 1,5- and 2,4-dienes using 9.68 and 10.49 eV photo-ionization (PI) is summarized in Table 1.

The fragments formed CH_3 (*m/z* 15) up to C_5H_7 (*m/z* 67), are recorded by the MS and are semi-quantified. Since the photo-ionization leads first to β-cleavage, the 1,3-diene leads to $CH_3^{\bullet}$ and $C_5H_7^{\bullet}$; however, the ionization of the methyl radical is recorded only at 10.49 eV. Table 1 does not record the ionic parent molecule and fragmentation. It is seen that the data can be used to locate the double bonds of the diene. Whereas the β-cleavage is the dominant PDPI/MS, rearrangement of fragments may also occur[27].

VI. CHEMICAL DERIVATIZATIONS

To support the various spectroscopic methods for structure determination of dienes and polyenes we will mention some typical chemical reactions yielding derivatives that aid in the location of the double bonds, assign the *cis* or *trans* geometry and indicate whether these double bonds are conjugated. It is not our intention to review the chemical versatility of dienes and polyenes but rather to show some cases where the variation helps in the analysis.

Most methods used for analysis of alkenes, such as bromination and hydrogenation, can be employed to determine the number of double bonds in polyenes. These methods were also employed to classify various petroleums ('bromine number'). However, these classical methods are employed less in analysis of conjugated dienes and polyenes mostly because the products produce a less informative mixture than in the alkene case.

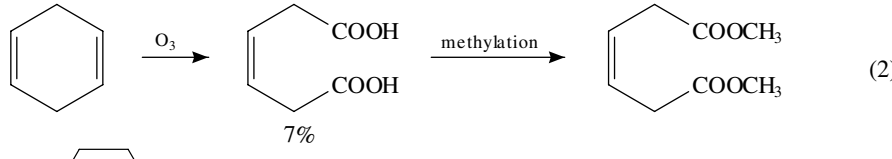
Neumann and Khenkin[28] review most of the various oxidation methods of dienes and polyenes and their mechanisms. They obviously emphasize the difference between non-conjugated and conjugated dienes and polyenes in selected oxidation reactions.

Conjugated dienes and polyenes lead to unique cases of conjugated oxidations, such as the formation of endoperoxide by singlet oxygen attack on the *endo*-diene, e.g. α-terpinene[29].

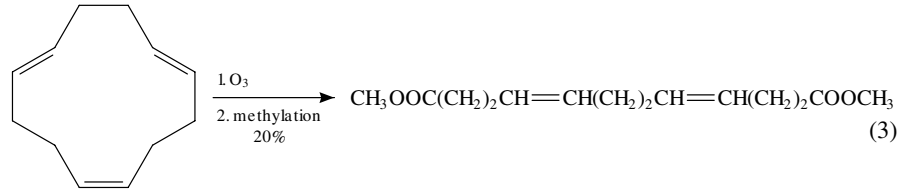
For analysis of dienes and polyenes via oxidations one has to distinguish between the formation of an oxidized product of the target molecule (epoxide, peroxide, ozonide etc.) and the oxidative fragmentation of the molecule as in the case of ozonolysis[30]. Both

approaches have been extensively reviewed, but mostly for mono-enes or for cases of independent/non-conjugated dienes and polyenes. Examination of the use of oxidative ozonolysis of natural rubber (polyene) and synthetic polyene polymers shows possible structure determination by GC analysis of the methyl esters of the acids formed (FAME method)[30,31].

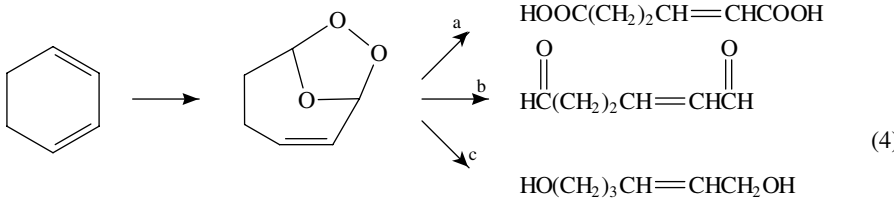
The use of both 'ozonation' and 'ozonolysis' is reviewed[32]. 'Ozonation' leads to ozonide and 'ozonolysis' leads to oxidized fragments, showing the use of both oxidative ($AgNO_3$) or reductive [$(CH_3)_2S$ or Ph_3P] methods to produce the FAME (fatty acids methyl esters) that by subsequent GC analysis enabled determination of the position of the double bonds in the original molecule (equations 2–4).



(2)



(3)



(4)

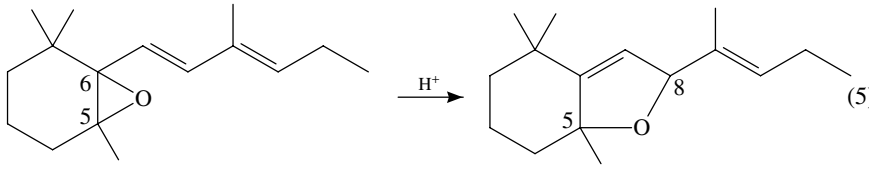
a = Ag_2O
b = $Ba(OH)_2$/Acetone
c = $NaBH_4$

The selectivity of the ozone reaction facilitates differentiation between conjugated bonds and isolated double bonds. Conjugated dienes form mono ozonide, which was claimed to inhibit reaction at the second double bond[33]. Hence, the yield of ozonolysis of one bond is much higher in 1,3-cyclohexadiene than in 1,4-cyclohexadiene and the same was found for other conjugated dienes[33]. Since the end products of the ozonolysis depend on the secondary treatment by the oxidation agents (Ag_2O, H_2O_2, SeO_2 etc.) or reducing agents [$(CH_3)_2S$, $NaBH_4$, H_2/Pd-$CaCO_3$-PbO etc.], the chromatographic or spectroscopic identification must take into consideration the type of product.

A very important point to remember when using ozonolysis for structural investigation of polyenes is that the transoid bond is attacked preferentially[34]. Hence, the advantage of the ozonolysis in polymeric matter is obvious: the fragments formed are easier to analyse and they are also indicative of the double-bond positions (see Schemes 1 and 2).

In principle, all of the methods for selective oxidations of di- and polyenes[28] can be employed for analytical derivatization. However, the complexity of products obtained rules out some of these. Despite this, epoxidation of selected double bonds is used for comparison of spectra (see previous discussion on MS). Epoxidation of isolated non-conjugated

double bonds is carried out mostly by peracids[32]. In recent works it is reported that metal oxides can catalyze hydrogen peroxide oxidation to form epoxides[35]. The bulk of the available information relates to epoxidation of non-conjugated double bonds. Some examples of the use of *tert*-butylhydroperoxide (TBHP) show that epoxidation increases with the increased nucleophilicity of the double bond and some spatial consideration must also control the regioselectivity. Conjugated dienes react slower and stepwise[36]. In carotenoids an 'epoxide' test was developed. The naturally occurring 5,6-epoxide **(16)** isomerizes under acidic catalysis to the 5,8-ether **(17)** leading to hypsochromic shift in the visible spectrum of the carotenoid[50] (equation 5). This is a very interesting rearrangement that may indicate why epoxidation of conjugated polyenes yields a complex mixture. Therefore, it is recommended to use the epoxidation mostly in cases of non-conjugated dienes and polyenes.

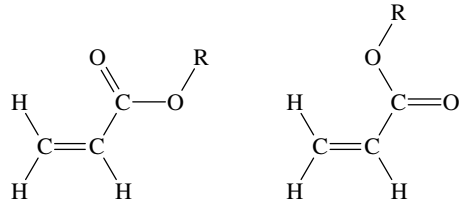


(5)

(16) **(17)**

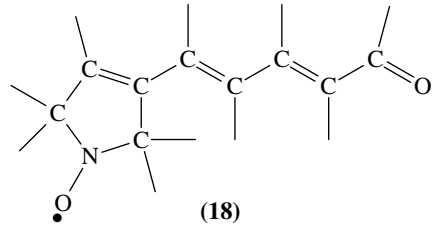
In general, one can use a variety of oxidation techniques to form derivatives of dienes and higher polyenes for their analysis; however, the information obtained with conjugated systems is muddled by the complexity of products. Also, it is obvious that since the oxidized derivatives contain different functionalities, e.g. epoxides, alcohols, acids etc., the analytical techniques employed should also be variable (see also Scheme 2).

Whereas the classical reactions of dienes and polyenes are described in textbooks and in the present volume, some unique derivatives were suggested for structure elucidation. Such is the case with the synthesis of conjugated polyene carbonyl derivatives of the nitroxide spin-label 2,2,5,5-tetramethyl-1-oxypyrroline[37]. In particular, the exact conformation of an oxygen-containing functional group, such as that shown below, cannot be assigned by NMR. Conformational analyses have been carried out with the aim of understanding *cis–trans* isomerization of the retinal[38] and other biochemically interesting aldehydes, acids and esters with long conjugated unsaturated systems. These analyses included dipole moment measurements[39], IR and microwave spectroscopy[40], NMR[41] and theoretical calculations. These techniques were found to possess insufficient sensitivity to assign precise molecular structures, in solution. In particular, even advanced ^{1}H and ^{13}C NMR methods cannot assign the protons of the s-*cis* and s-*trans*, and hence the exact conformation of the oxygen-containing functional group forms below.



s-*cis* s-*trans*

An example is the structure of the derivative **18** formed by reacting the labelled oxypyrrolinyl with 2,4-pentadienal.



(18)

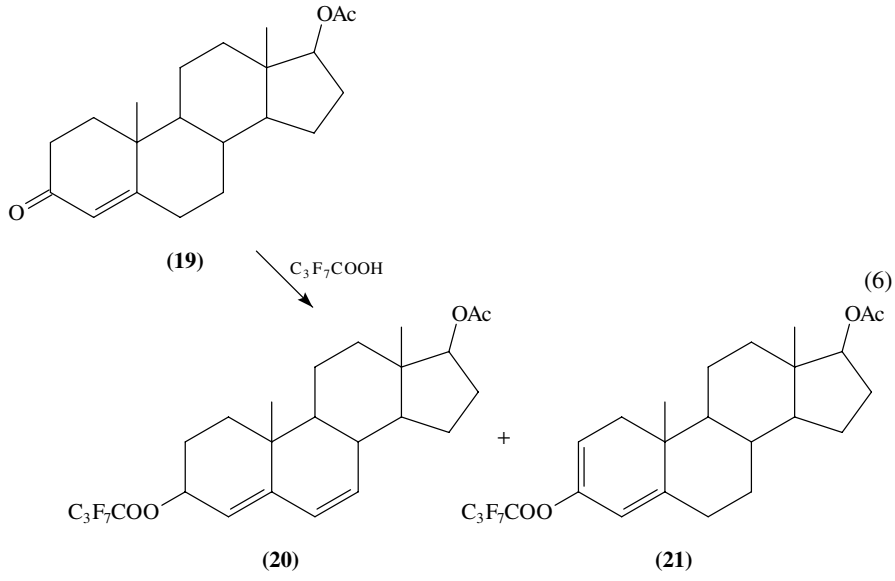
As most of the nitroxyl spin-labelled synthetic derivatives of conjugated polyenes are light yellow crystals, the bond lengths were determined by X-ray crystallography[38]. The spectroscopic method used to measure the conformation is electron nuclear double resonance (ENDOR). It is beyond the scope of the present review to explain the method[38] but the authors of the pertinent paper conclude that ENDOR is an accurate non-crystallographic method to determine polyene structures in solution.

Some derivatization methods mentioned in other sections of this review include chemical ionization by nitric oxide (MS) or epoxidation (MS), formation of π-complexes for NMR (shift agents) etc. Also, the Diels–Alder reaction, which was mentioned several times as a tool for derivatization of conjugated dienes and polyenes, was extensively described and reviewed in the literature.

VII. SELECTED EXAMPLES OF MULTI-PARAMETER ANALYSIS FOR DIENES AND POLYENES: STRUCTURE DETERMINATION

A. Enolic Dienes Derived from Testosterone-17β-acetate

Enolization of α,β-unsaturated ketones, e.g. **19**, under strong acid conditions leads to a mixture of homoannular and heteroannular $\Delta^{2,4}$- and $\Delta^{4,6}$-dienes (e.g. **20** and **21**; see equation 6)[42].



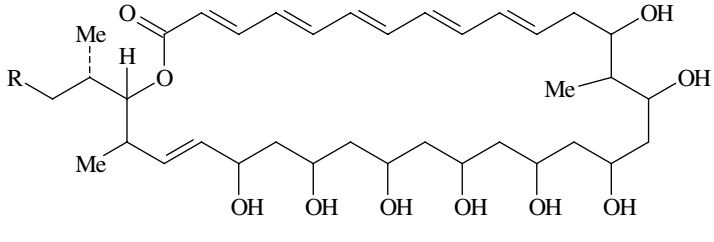
(19) **(20)** **(21)** (6)

The heteroannular diene is thermodynamically more stable and the UV spectra of the two dienes differ, as suggested by Woodward and Fieser's rules[5].

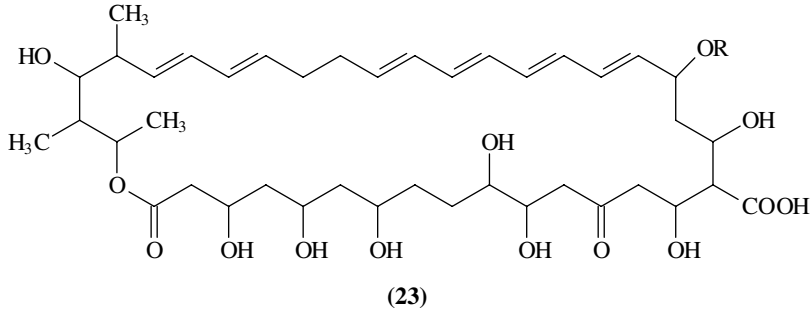
The heptafluorobutyrate derivative was selected for gas chromatographic separation, using electron capture detector (ECD), in order to enable the detection of ultramicro quantities[43]. The interest in the analysis of natural and synthetic hormones in very small concentrations enhanced the development of the GC method, in comparison with the UV study.[44]

B. Antiviral and Antifungal Mycoticin (A and B) Partial Structure Determination

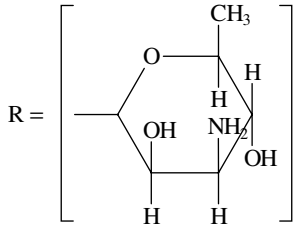
The natural products Mycoticin A (**22**, R = H) and B (**22**, R = Me) belong to the skipped-polyol-polyene class of antibiotics. Our analytical interest here is to use this very complex molecular structure to demonstrate some of the tools employed, mainly for the elucidation of the polyene part of the molecule. This family of 'polyene macrolide class' was discovered in 1950[45] with the finding of Nystatin **(23)**, which is produced by the *Streptomyces* bacteria. The exact structure was elucidated only in 1970 by Chong and Rickards[46] and, in 1971, Nystatin A_1 **(23)** and A_2 (not shown in this review) were separated.



(22)



(23)



Mystatin is a light-yellow optically active solid (d.p. > 160 °C) with UV λ_{max} 290, 307, 322 nm. Many of the polyene mycolides (e.g. Amphotericin B) are yellow solids with a similar conjugated transoid (5 to 7 double bonds) system, claimed to be derived, by structure similarity, from α-prinarate $CH_3CH_2(CH{=}CH)_4(CH_2)_7COOCH_3$. Some 200 members of this family were isolated and the structures of 40 of them were elucidated. Up to 1987 the only claim for full stereochemical elucidation by various techniques was for Amphotericin B[47]. Despite the fact that most of these compounds are solids, not all of them could be determined structurally by X-ray crystallographic methods and this includes the structures of Mycoticin A, B and derivatives[47]. Hence, other chemical and spectrocopical methods had to be employed. For spectroscopic measurements the free OH-groups were formylated, and the tetraformyl derivative exhibited well-resolved signals in the ^{1}H NMR and ^{13}C NMR spectra[48]. For this derivative use of the 2D COSY NMR and NOE techniques enabled a better assignment of non-equivalent hydrogens. The polyene part showed the all-*trans* stereochemistry. Ozonolysis of the tetraacetonide derivative **(24)** followed by $NaBH_4$ reduction provided three, readily separable products **25–27** (see Scheme 5)[48] whereas the polyene conjugated system is totally oxidized to small water-soluble acids.

VIII. ANALYSIS OF CAROTENOIDS AS AN EXAMPLE OF POLYENE STUDIES

This section is based on a review written in 1985 by Liaaen-Jensen and Andrewes[49] and a book on Natural Products by Ikan[50]. Both reviews cover some 200 references and discuss the various isolation and identification methods at length. It is therefore redundant to repeat the information presented in them.

Nevertheless, during inspection of the above-mentioned reviews and many of the works cited therein, many excellent analytical methods which can be applied to other polyene molecules were found.

Since the recognition of the carotenoid family of pigments, approximately 500–600 naturally occurring members of the various families were recognized. The C_{40} skeleton of 8 isoprenoid units (tetraterpenoid) allows endless combinations with various positions carrying substituted groups such as alcohols, ketones, acids and others. The characteristic property which makes the carotenoids natural pigments is the long polyene conjugated systems. Carotenoids are found in almost all photosynthesizing biota from quite primitive bacteria to fruits and high plants. Because of their natural source many food manufacturers use carotenoids as food colors, hence the commercial interest.

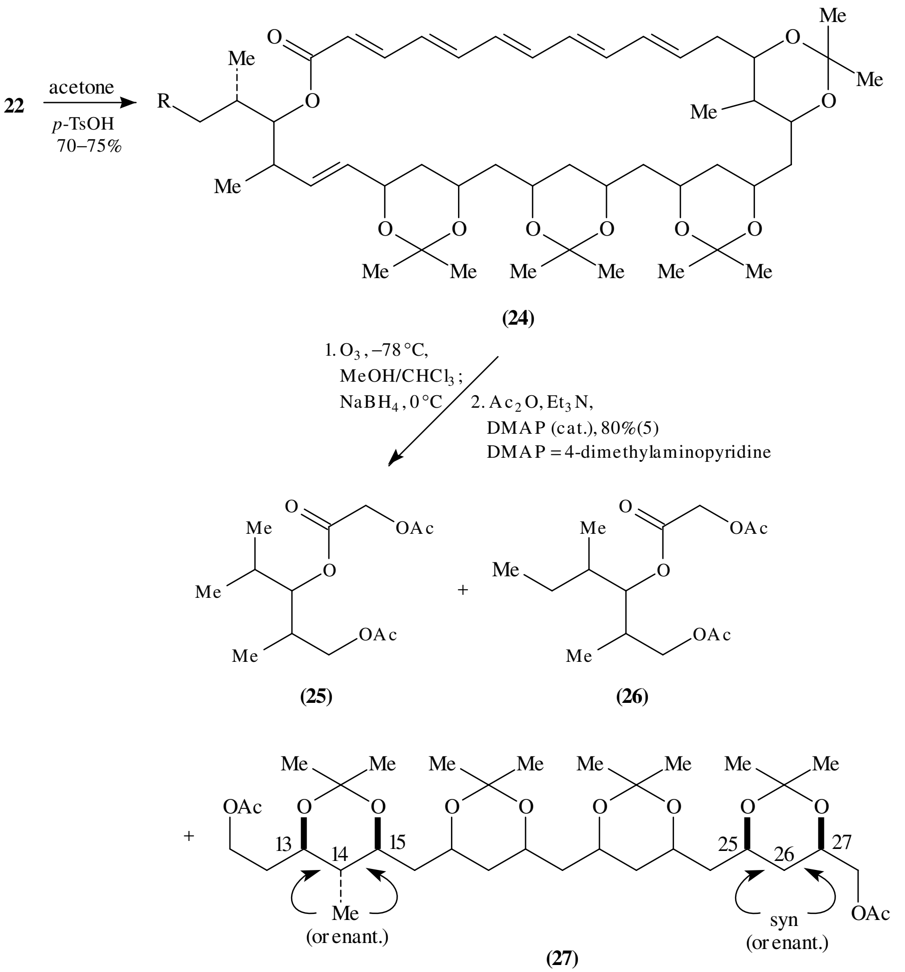
Ikan's book on laboratory techniques[50] concentrates on the origin and isolation procedures of carotenoids. The spectra given (IR, UV-VIS and NMR, MS) help also to classify the various carotenoids. The longest open conjugated system (no rings) is found in lycopene, **28**, which contains 11 conjugated and 2 non-conjugated double bonds, has an all-*trans* geometry and possesses a very intensive red colour (λ_{max}^{EtOH} 443, 472, 504 nm). This 536-dalton molecular weight ($C_{40}H_{56}$) polyene is analysed well by MS with most abundant fragments appearing at *m/z* 145, 119, 105, 93, 91, 86, 69 (base peak), 41 as shown below. The ^{1}H NMR and ^{13}C NMR assignments for the hydrogens and carbons double bond are as follows:

^{13}C NMR (in $CDCl_3$) in ppm

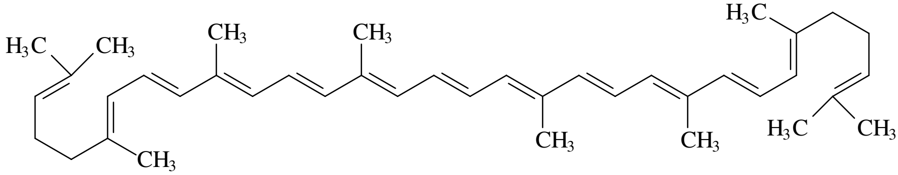
C-1 131.64; C-2 124.12; C-3 26.83; C-4 40.30; C-5 139.30; C-6 125.94; C-7 124.87; C-8 135.54; C-9 136.15; C-10 131.64; C-11 125.21; C-12 137.46; C-13 136.54; C-14 132.71; C-15 130.17; C-16 25.66; C-17 17.70; C-18 16.97; C-19 12.90; C-20 12.81.

^{1}H NMR (in $CDCl_3$) in ppm

H-2 δ5.11; H-3/H-4 2.11; H-6 5.95; H-7 6.49; H-8 6.25; H-10 6.19; H-11 6.64; H-12 6.35; H-14 6.23; H-15 6.63.



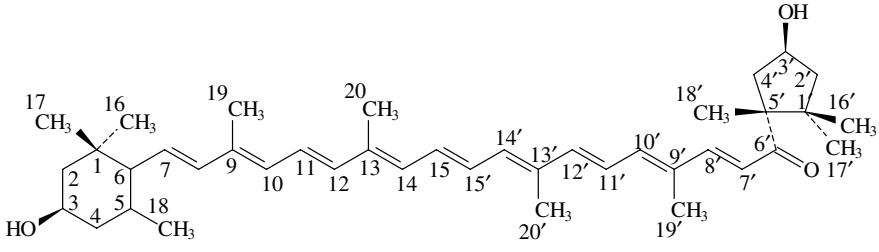
SCHEME 5



(28)

Mass spectrum
m/z 536 (21.7%, M), 145 (38%), 119 (34%), 105 (47%), 93 (36%), 91 (47%), 81 (36%), 69 (100%), 41 (57%).
λ_{max}^{EtOH} 443, 472, ($\varepsilon = 3.10^5$) 504 nm.

For comparison the ^{1}H and ^{13}C NMR spectra, the mass spectral fragments and the UV-VIS spectrum of Capsantin, **29** (the red colour of paprika), are as follows:



(29)

^{1}H NMR (in $CDCl_3$) in ppm

0.840[s,3H, Me (16′)], 1.075[s, 6H, Me(16), Me(17)], 1.207[s, 3H, Me(17′)], 1.367[s, 3H, Me(18′)], 1.736[s, 3H, Me(18)], 1.957[s, 3H, Me(19′)], 1.974[s, 6H, Me(19), Me(20)], 1.989[s, 3H, Me(20′)], 2.39[ddd, J = 17.6, *ca* 1.5, 1H, Hα–C(4)], 2.96[dd, J = 15.5, 9, 1H, Hα–C(4′)], *ca* 4.00[br, m, 1H, Hα–C (3)], 4.52[m, 1H, Hα–C(3′)], 6.13[s, 2H, H-C(7), H-C(8)], 6.16[d, J = 11.6, 1H, H-C(10)], 6.26[d, J = 11; 1H, H-C(14)], 6.35[d, J = 11, *ca* 1H, H-C(14′)], 6.36[d, J = 15, 1H, H-C(12)], 6.45[d, J = 15, 1H, H-C(7′)], 6.52[d, J = 15, 1H, H-C(12′)], 6.55[d, J = 11, 1H, H-C(10′)], *ca* 6.6–6.8[m, 4H, H-C(11), H-C(11′), H-C(15); H-C(15′)], 7.33[d, J = 15, 1H, H-C(8′)].

^{13}C NMR (in $CDCl_3$) in ppm

12.75[C(19)], 12.79[C(20)], 12.84[C(19′)], 12.90[C(20′)], 21.39[C(18′)], 21.63[C(18)], 25.16[C(17′)], 25.95[C(16′)], 28.80[C(16)], 30.32[C(17)], 42.69[C(4)], 44.01[C(1′)], 45.49[C(4′)], 48.61[C(2)], 51.06[C(2′)], 59.01[C(5′)], 65.41[C(3)], 70.44[C(3′)], 121.04[C (7′)], 124.13[C(11′)], 125.58[C(11)], 125.93[C(7)], 126.30[C(5)], 129.74[C(15′)]; 131.27[C(10)], 131.68[C(15′)], 132.39[C(14)], 133.69[C(9′)]; 135.24[C(14′)]; 135.93[C (13′)], 137.46[C(12)], 137.60[C(13)], 137.85[C(6)], 138.51[C(8)], 140.63[C(10′)], 141.97[C(12′)], 146.86[C(8′)], 202.82[C(6′)].

Mass spectrum

m/z 584 (75%, M), 478 (62%), 429 (6%), 145 (51%), 127 (36%), 109 (100%), 106 (31%), 105 (44%), 91 (65%), 83 (56%).

$\lambda_{max}^{benzene}$ 486 ($\varepsilon = 1.2 \times 10^5$), 520 nm.

All polyenes are susceptible to changes under various chemical conditions: oxygen, peroxides, light, acids and elevated temperature, etc. Therefore, one should bear in mind that carotenoid separation must be very carefully planned. Various extractions and liquid chromatographies are offered[51] with special separation by partition between immiscible solvent systems. Another problem caused during separation is a geometrical isomerization usually in the *cis* ⟶ *trans* direction. During the 1950s column chromatography was exclusively used, whereas since then TLC and PTLC (Preparative Thin Layer Chromatography) are employed[51]. HPLC (High Performance LC), both reversed phase and on regular silica (>5 μ), are used with various UV-VIS detectors (see Section III).

The carotenoids exhibit very high ε values of 10^5–3×10^5 and hence very small quantities can be detected. Due to the high molecular weights of carotenoids and other polyenes GC can be employed only with the perhydrogenated compounds[15] due to the high temperatures needed[52].

Although ^{1}H NMR and ^{13}C NMR spectroscopy of dienes and polyenes is discussed elsewhere, these tools of analysis are very nicely demonstrated in the studies of carotenoids.

The advancement of >400 MHz NMR instruments with spin decoupling and Fourier transform software now allows identification of individual olefinic protons of nanogram carotenoids[53]. We have shown two examples (lycopene and capsantin) for which the chemical shifts have been employed in the assignment of relative configuration[49]. As for review of the ^{13}C NMR of carotenoids, Englert in 1981[54] gave information especially on the position of the *cis* double bonds in a polyene chain.

The fragmented ions are stabilized in aromatic structures and therefore their formation may be misleading. However, some carotenoids do have aromatic moieties (e.g. flexirulein and some of the xanthomonadins). Therefore, if we examine the MS of capsanthin (see above) we see the base peak at *m/z* 109 (C_7H_9O or C_8H_{13}) next in abundance to the molecular peak (75%) at *m/z* 584 and the tropylium ion $C_7H_7^+$ (65%) at *m/z* 91. It is interesting that although lycopene has no ring structures it exhibits an *m/z* 91 fragment as a very strong peak. It is therefore very helpful to check for the presence of other functional groups such as OH, CO, etc. by IR spectroscopy.

The carotenoid family have chiral centres which enable the use of circular dichroism. However, the chirality of carotenoids is not sufficiently characteristic so that the chiroptical properties do not serve as a good analytical tool.

Various chemical derivatizations of natural carotenoids may serve to improve separation and lead to better characterization of structure. These methods are discussed in Section VI.

IX. ACKNOWLEDGEMENTS

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X. REFERENCES

1. B. S. Hudson, B. E. Kohler and K. Schulten, *Excited States*, **6**, 1 (1982); B. S. Hudson and B. E. Kohler, *Annu. Rev. Phys. Chem.*, **24**, 437 (1974).
2. G. Orlandi, F. Zebetto and M. Z. Zgierski, *Chem. Rev.*, **91**, 867 (1991).
3. J. G. Aston, Ph.D. Thesis, Univ. of California, Berkeley (1946).
4. L. H. Carreia, *J. Chem. Phys.*, **62**, 3851 (1975).
5. (a) R. B. Woodward, *J. Am. Chem. Soc.*, **64**, 72 (1942).
   (b) L. F. Fieser and M. Fieser, *Steroids*, Reinhold, New York, 1959, pp. 15–21.
6. S. T. Belt, D. A. Cooke, S. J. Hird and S. Rowland, *J. Chem. Soc., Chem. Commun.*, 2077 (1994).
7. H. Budzikiewicz, C. Djerassi and D. H. Williams, *Interpretation of Mass Spectra of Organic Compounds*, Holden-Day, San Francisco, 1964.
8. S. E. Van Bramer and M. V. Johnson, *Org. Mass Spectom.*, **27**, 949 (1992).
9. B. A. Dimitrova, *C.R. Acad. Bulg. Sci.*, **32**, 1381 (1979).
10. S. J. Hird, R. Evens and S. J. Rowland, *Marine Chemistry*, **37**, 117 (1992).
11. N. R. Avery and N. Sheppard, *Proc. R. Soc. London. Ser. A*, **405**, 27 (1986).
12. N. R. Avery and N. Sheppard, *Proc. R. Soc. London. Ser. A*, **405**, 1 (1986).
13. R. I. Reed, *Application of Mass Spectrometry to Organic Chemistry*, Academic Press, New York, 1966.
14. J. Oró and D. Nooner, 'Cosmochemical and Geochemical Application of Mass Spectrometry', in *Practical Mass Spectrometry* (Ed. B. S. Middleditch), 2nd edn., Plenum Press, New York and London, 1981, pp. 327–359.
15. Z. Aizenshtat, in *The Chemistry of Alkanes and Cycloalkanes* (Eds. S. Patai and Z. Rappoport), Chap. 7, Wiley, Chichester, 1992, pp. 289–349.
16. J. P. Jasper and J. M. Hayes, *Nature*, **347**, 462 (1990).
17. M. Lyle, *Nature*, **356**, 385 (1992).
18. G. Eglinton, S. A. Bradshaw, A. Rosell, M. Sarnthein, U. Pflaumann and R. Tiedemann, *Nature*, **356**, 423 (1992).

19. W. Vetter, G. Englert, N. Rigassi and U. Schwieter, in *Carotenoids* (Ed. O. Isler), Birkhäuser, Basel, 1971, pp. 189–266.
20. C. R. Enzell and I. Wahlberg, in *Biochemical Application of Mass Spectrometry* (Eds. G. R. Waller and O. C. Dermer), Wiley, New York, 1980, pp. 407–436.
21. H. Budzikiewicz, in *Carotenoid Chemistry and Biochemistry* (Eds. G. Britton and T. W. Goodwin), Pergamon, Oxford, 1982, pp. 155–166.
22. H. Achenbach, W. Kohl, A. Böttger-Vetter and H. Reichenbach, *Tetrahedron*, **37**, 559 (1981).
23. A. G. Andrews, S. Hertzberg, S. Liaaen-Jensen and M. P. Starr, *Acta Chem. Scand.*, **27**, 2383 (1973).
24. C. D. Watts, J. R. Maxwell, D. E. Games and M. Rossiter, *Org. Mass Spectrom.*, **10**, 1102 (1975).
25. H. Budzikiewicz, S. Blech and B. Schneider, *Org. Mass Spectrom.*, **26**, 1057 (1991).
26. D. F. Hunt and T. M. Harvey, *Anal. Chem.*, **47**, 2136 (1975).
27. J. Adams, *Mass Spectrom. Rev.*, **9**, 141 (1990).
28. R. Neumann and A. M. Khenkin, Chapter 20 in this volume.
29. K. A. Jorgensen and B. Schiott, *Chem. Rev.*, **90**, 1483 (1990).
30. V. N. Odinokov and G. A. Tolstikov, *Russ. Chem. Rev.*, **50**, 1207 (1981).
31. G. P. McSweeny, *J. Polym. Sci., A-1*, **6**, 2 (1968).
32. D. Swern, *Organic Peroxides*, Vol 2, Wiley Interscience, New York, 1971.
33. I. E. Pokrovskaya, A. T. Menyailo and A. K. Yakovleva, in *Progress in the Chemistry of Organic Peroxy Compounds and Autooxidation* (Ed. N. M. Emanuel), Khimia, Moscow, 1969, p. 124.
34. V. N. Odinokov, R. S. Bakeeva and G. A. Tolstikov, *Izv. Akad. Nauk SSSR., Ser. Khim.*, 2836 (1978).
35. J. Itakura, H. Tanaka and H. Ito, *Bull. Chem. Soc. Jpn.*, **42**, 1604 (1969).
36. R. Clarke, M. Gahagan, R. K. Mackie, D. F. Foster, D. J. Cole-Hamilton, M. Nicol and A. W. Montford, *J. Chem. Soc., Dalton Trans.*, 1221 (1995).
37. D. Mustafi, W. E. Boisvert and M. W. Makimen, *J. Am. Chem. Soc.*, **115**, 3674 (1993).
38. G. Wald, *Science*, **162**, 230 (1968).
39. G. K. Estok and J. S. Dehn, *J. Am. Chem. Soc.*, **77**, 4769 (1955) and references cited therein.
40. E. A. Cherniak and C. C. Costain, *J. Chem. Phys.*, **45**, 104 (1966).
41. R. Rowan III, J. A. McCammon and B. D. Sykes, *J. Am. Chem. Soc.*, **96**, 4773 (1974) and references cited therein.
42. S. K. Malhorta and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 1997 (1964).
43. P. Devaux and E. C. Horning, *Anal. Lett.*, **2**, 637 (1969).
44. L. Dehennin and R. Scholler, *Tetrahedron*, **29**, 1591 (1973).
45. E. L. Hazen and R. Brown, *Science*, **112**, 423 (1950).
46. C. N. Chong and R. W. Rickards, *Tetrahedron Lett.*, 5145 (1970); E. Borowski, *Tetrahedron Lett.*, 685 (1971).
47. S. L. Schreiber and M. T. Goulet, *Tetrahedron Lett.*, **28**, 6001 (1987) and references cited therein.
48. S. L. Schreiber and M. T. Goulet, *Tetrahedron Lett.*, **28**, 6005 (1987) and references cited therein.
49. S. Liaaen-Jensen and A. G. Andrewes, in *Methods in Microbiology*, Vol. 18, Chap. 8, Academic Press, New York, 1985, pp. 235–255.
50. R. Ikan, *Natural Products, a Laboratory Guide*, 2nd edn., Academic Press, New York, 1991.
51. B. H. Davis, in *Chemistry and Biochemistry of Plant Pigment* (Ed. T. W. Goodwin), Vol 2, Academic Press, New York, 1976, pp. 38–155.
52. R. F. Taylor and M. Ikawa, in *Methods in Enzymology* (Eds D. B. McCormick and L. M. Wright), Vol. 67, Academic Press, New York, 1980, pp. 233–261.
53. A. Fiksdahl, T. Bjørnland and S. Liaaen-Jensen, *Phytochemistry*, **23**, 649 (1984).
54. G. Englert, in *Carotenoid Chemistry and Biochemistry* (Eds. G. Britton and T. W. Goodwin), Pergamon Press, Oxford, 1981, pp. 107–134.

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CHAPTER **11**

Intramolecular cyclization of dienes and polyenes

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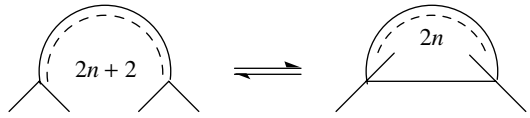
I. INTRODUCTION

This chapter deals with thermal ring-closure reactions of dienes and polyenes resulting in carbocyclic compounds; the formation of heterocycles is mentioned only occasionally. The account is highly selective, concentrating on recent work, since two comprehensive general reviews have appeared[1,2]. Other pertinent reviews are cited at appropriate places in the text.

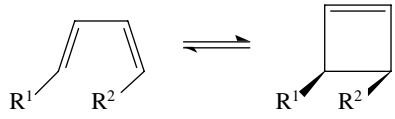
II. ELECTROCYCLIC REACTIONS

The cyclization of fully conjugated polyenes containing $2n + 2$ π-electrons (equation 1) was termed 'electrocyclic' by Woodward and Hoffmann, who showed that the steric course of such reactions was governed by the rules of orbital symmetry[3].



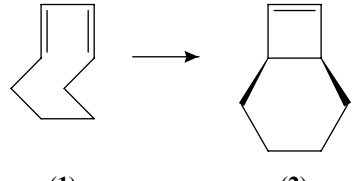
(1)

The thermal ring-closure of butadienes to cyclobutenes proceeds in a conrotatory fashion (equation 2) but this reaction is only observed in special cases because, in general, the equilibrium lies on the side of the open-chain isomer.



(2)

The strained *cis,trans*-1,3-cyclooctadiene **1** cyclizes quantitatively at 80 °C to the bicyclo[4.2.0]octene **2** (equation 3). The higher homologue **3** exists in equilibrium with the bicyclic isomer **4** above 175 °C (equation 4)[4].



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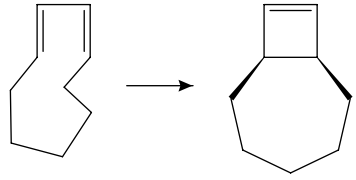
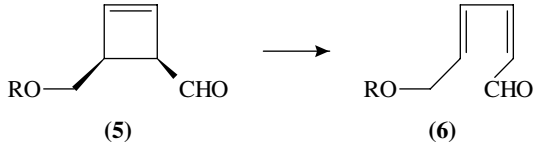


(4)

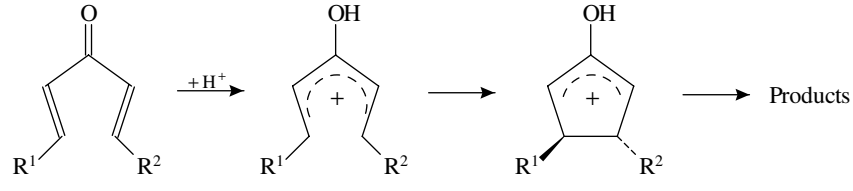
Ring-opening of cyclobutenes to butadienes is very common; a recent example is the formation of the aldehyde **6** in greater than 97% diastereomeric purity from the cyclobutene **5** (R = 4-methoxybenzyl) above −78 °C (equation 5)[5].



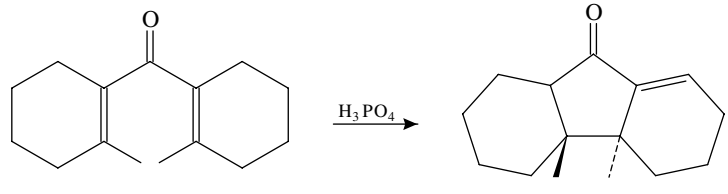
(5)

The acid-catalysed ring-closure of divinyl ketones to cyclopentenones (equation 6), the Nazarov reaction[6–8], represents a conrotatory electrocyclization of 4π-cyclopentadienyl cations. The conrotatory course of the reaction was confirmed for the case of the dicyclohexenyl ketone **7**, which yielded solely the tricyclic ketone **8** on treatment with phosphoric acid (equation 7)[3b]. Cycloalkanocyclopentenones **10** with *cis*-fused rings are obtained from the trimethylsilyl-substituted ketones **9** (n = 1, 2 or 3) and iron(III) chloride and

subsequent aqueous work-up (equation 8). In the cyclization of the cyclopentene derivatives **11**, the silyl moiety exerts a remote stereocontrol: the isomers **12** and **13** are formed in the ratios 54:46, 62:38, 76:24 and 79:21 as the silyl group varies from $SiMe_3$ to $SiMePh_2$, $SiPh_3$ and $Si(Pr\text{-}i)_3$ (equation 9)[9].



(6)



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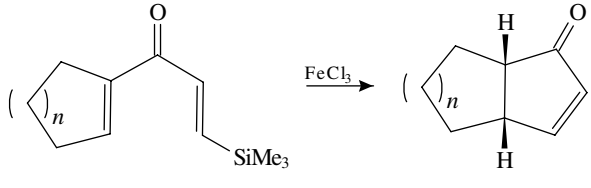
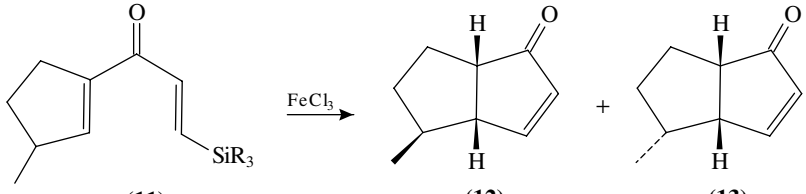


(8)

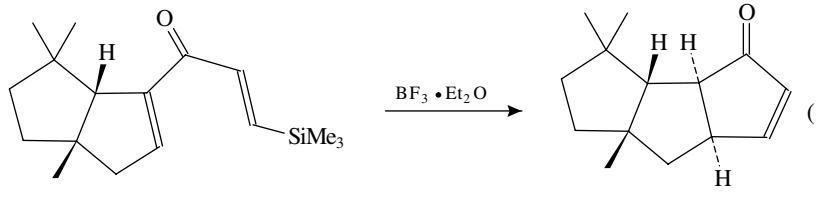
(9) (10)



(9)

(11) (12) (13)

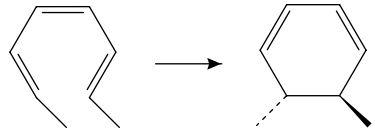
The action of boron trifluoride etherate on the ketone **14** results in the tricyclic ketone **15** in 80% yield (equation 10)[10].



(10)

(14) (15)

The thermal disrotatory cyclization of hexatrienes leads to cyclohexadienes (equations 11 and 12)[11–13].



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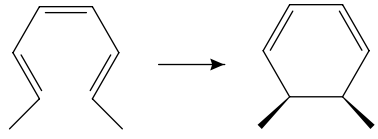
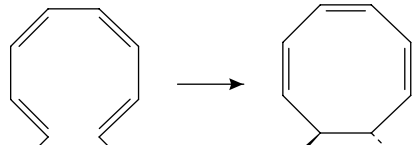


(12)

The predicted conrotatory cyclization of octatetraenes was confirmed for the case of the methyl-substituted compounds, which above 16 °C readily formed the cyclooctatrienes shown in equations 13 and 14)[14]. We conclude this section with an electrocyclic reaction involving ten π-electrons, that is, the formation of azulene **(17)** when the fulvene **16** is heated (equation 15)[15,16].



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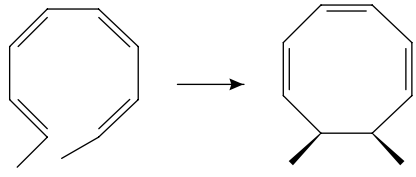

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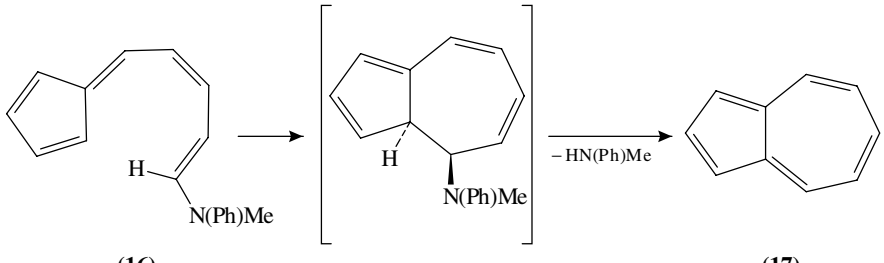
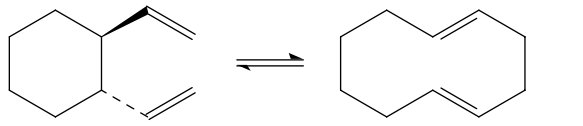


(16) **(17)** (15)

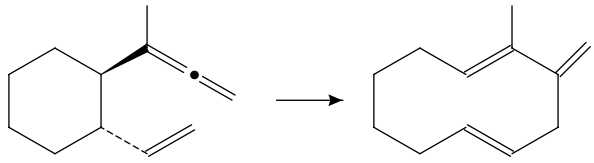
III. A COPE REARRANGEMENT

The 'Cope ring-expansion' of *trans*-1,2-divinylcyclohexane results in 1,5-cyclodecadiene (equation 16); however, the equilibrium favours the monocyclic compound[17]. In the case of the allene **18**, ring-expansion occurs: at 90 °C the methylenecyclodecadiene **19** is formed

in greater than 99% yield (equation 17)[18].



(16)

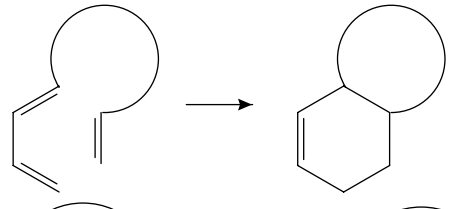


(17)

(18) **(19)**

IV. INTRAMOLECULAR DIELS–ALDER REACTIONS

Several reviews on intramolecular Diels–Alder reactions have appeared[19–23]. The products may be either fused (equation 18) or bridged (equation 19). The vast majority of reported examples of the reaction result in fused products; bridged compounds are rarely observed and only in cases where the diene and dienophile are separated by ten or more carbon atoms, e.g. **20** ⟶ **21** (equation 20)[24]. The decatriene **22** cyclizes at 200 °C to the *trans*-fused octalins **23** and **24** (equation 21)[25,26]. Heating the ester **25** yields a 1:1 mixture of the *cis*- and *trans*-octalins **26** and **27** (equation 22)[27]. The palladacycle



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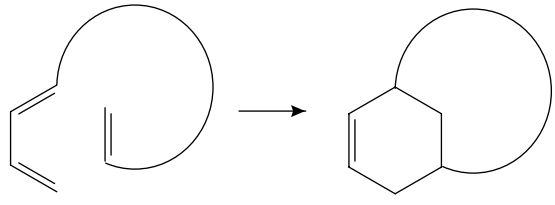

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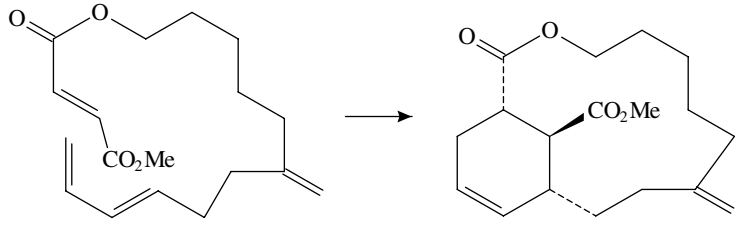
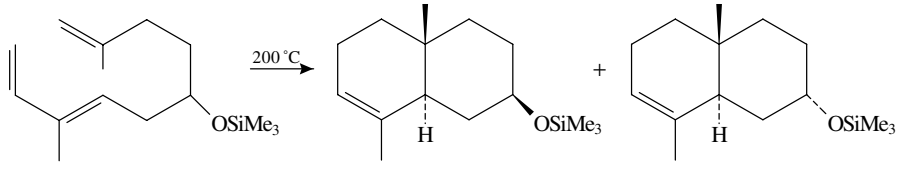


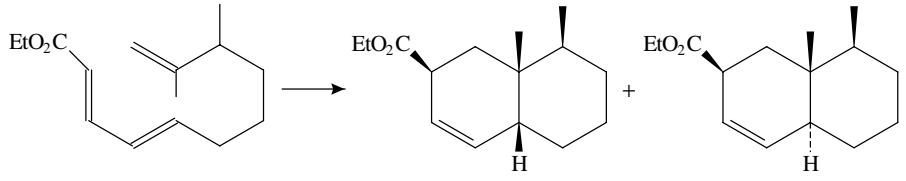
(20)

(20) **(21)**

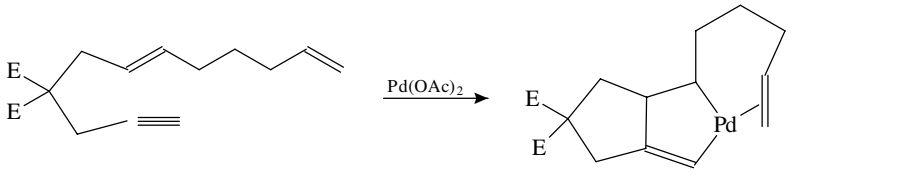
29, produced from the dienyne **28** (E = CO_2Me) and palladium(II) acetate in boiling toluene, decomposes to the triene **30**, which forms the cyclization product **31** in 72% overall yield (equation 23)[28]. Thermal ring-closure of **32** gives the *trans*-fused tricyclic alcohol **33** (equation 24)[29].



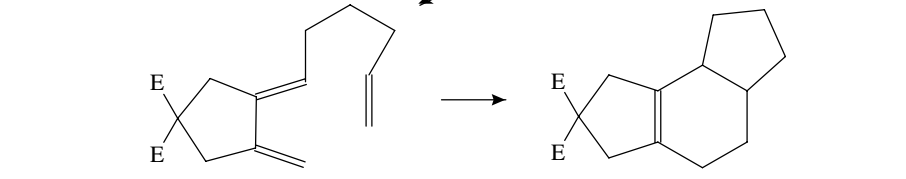
(22) **(23)** **(24)** (21)



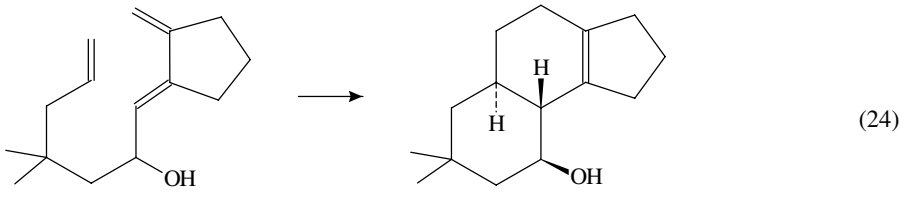
(25) **(26)** **(27)** (22)



(28) **(29)** (23)

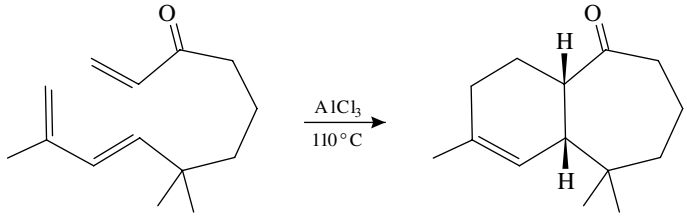


(30) **(31)**



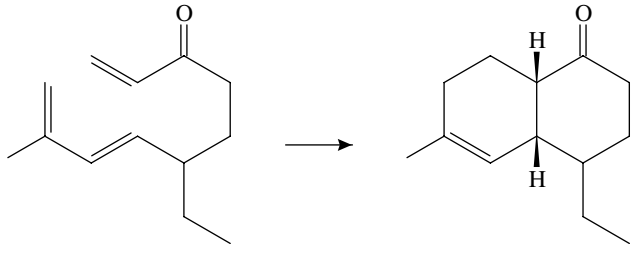
(32) **(33)** (24)

A number of stereospecific intramolecular Diels–Alder reactions of trienones leading to *cis*-fused products have been described. The ketone **34** forms solely compound **35** on treatment with aluminium trichloride at 110 °C (equation 25)[30]. The lower homologue **36** undergoes a spontaneous cyclization to **37** below 20 °C (equation 26)[31] and the isomeric ketones **38** and **40** similarly give **39**[32] and **41**[33], respectively (equations 27 and 28).



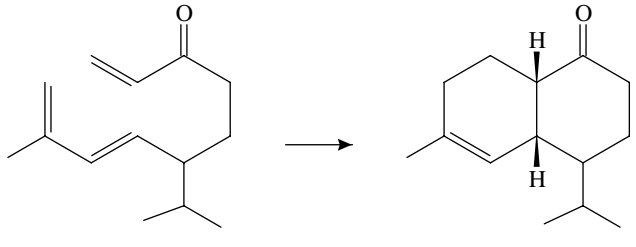
(25)

(34) **(35)**



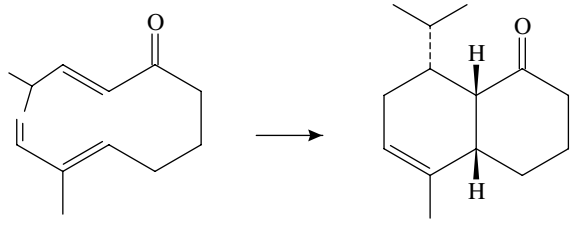
(26)

(36) **(37)**



(27)

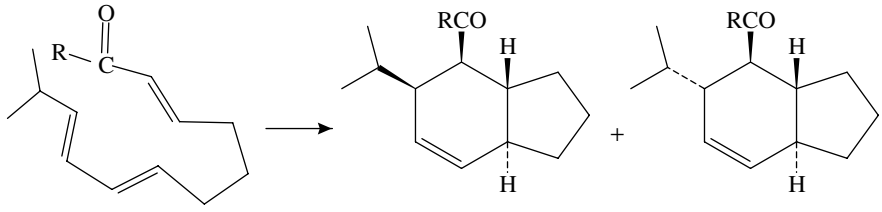
(38) **(39)**



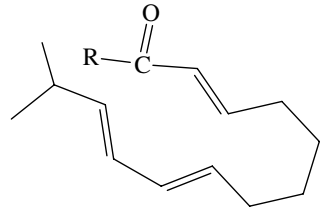
(28)

(40) **(41)**

The stereoselectivity of the thermal ring-closure of the dodecatrieneones **42** is determined by the nature of the remote group R. *trans*-Fused products **43** predominate over *cis*-products **44** and their ratio increases as R varies from MeO through Me to H (equation 29). If the reactions are catalysed by diethylaluminium chloride only *trans*-compounds are formed. The homologues **45** behave similarly[34]. In contrast, the 7-azadeca-1,3,9-trienes **46** (X, Y = H_2 or O) yield more of the *cis*- than the *trans*-fused compounds, regardless of the nature of X and Y (equation 30)[35].



(42) **(43)** **(44)** (29)



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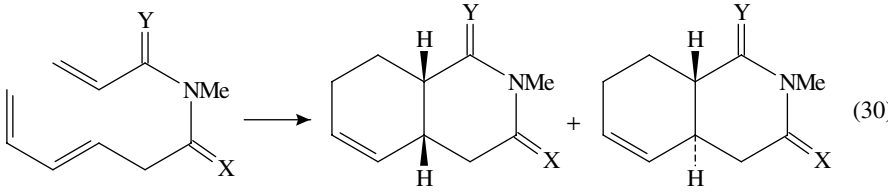
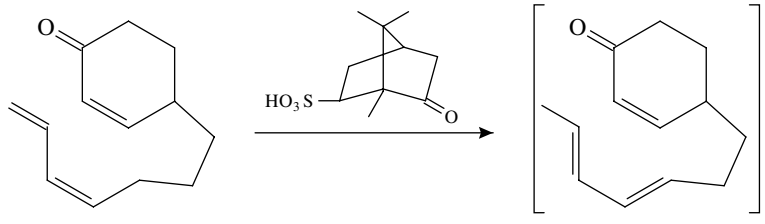


(46) major minor (30)

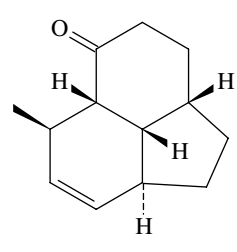
The acid-catalysed intramolecular ring-closure of the heptadienylcyclohexenone **47** yields the tricyclic compound **49** via the rearranged intermediate **48**, the product of a proton shift (equation 31)[36]. Similarly, 1,9,11-dodecatrien-3-one **(50)** gives a mixture containing 94% of **51** and only 6% of the unrearranged product **52** (equation 32)[36]

ortho-Quinodimethanes possessing a suitably positioned double bond undergo intramolecular Diels–Alder reactions spontaneously (equation 33)[37]. The quinodimethanes have been generated by thermolysis of 3-isochromanones (equation 34)[38] by the action of tetrabutylammonium fluoride on *o*-(1-trimethylsilylhept-6-enyl)benzyltrimethylammonium iodide (equation 35)[39] and by heating alkenyl-dihydrobenzo[*c*]thiophen 2,2-dioxides at 240 °C in diethyl phthalate (equation 36)[40]. The tricyclic hydrocarbons **53**



(47) **(48)**

(31)



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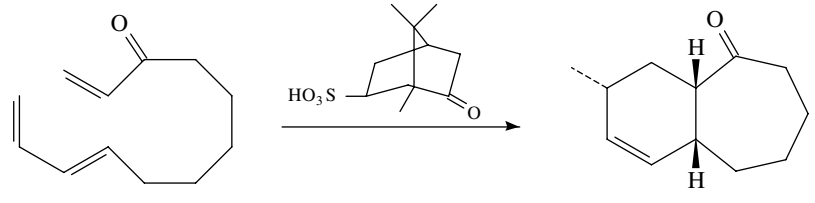
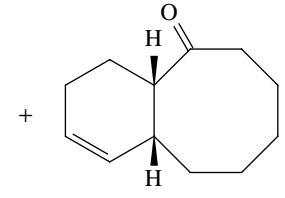


(50) **(51)**

(32)



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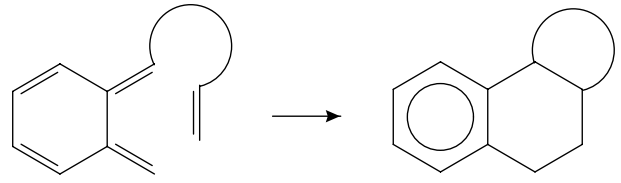
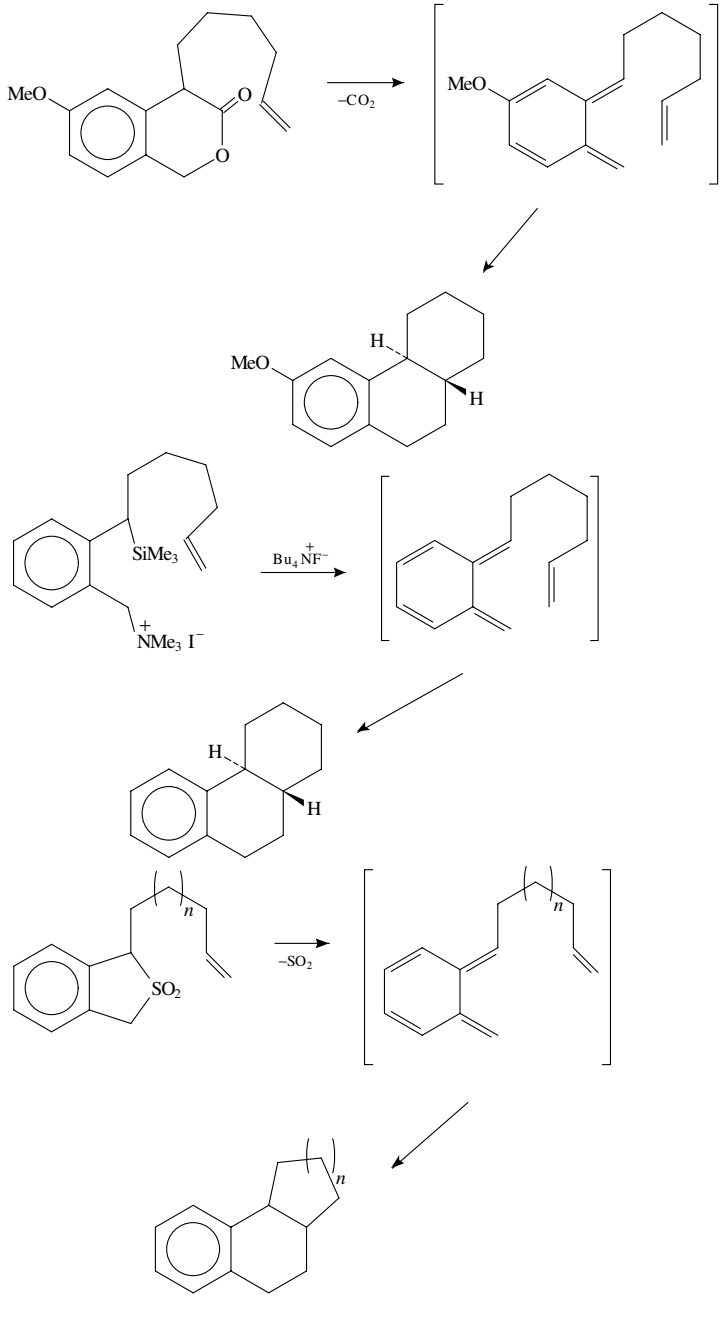


(33)



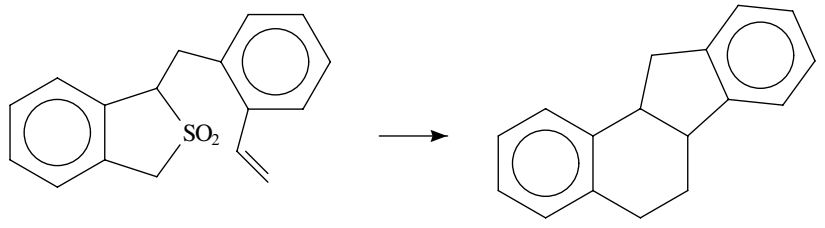
(34)

(35)

(36)

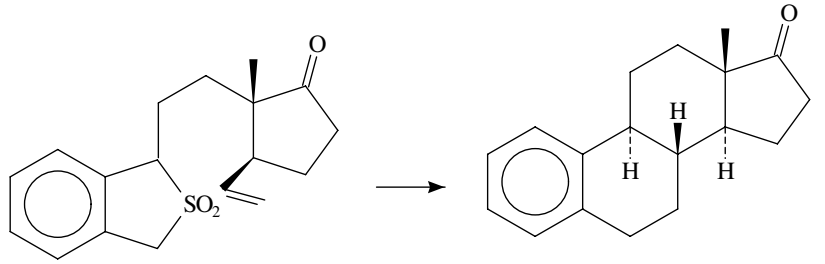
(53)

($n = 1$ or 2) were obtained in 85–89% yields in this way and **54** gave the tetracycle **55** (equation 37)[40]. The products are obtained as mixtures of *cis*- and *trans*-isomers with the latter predominating. The reaction was applied to the total synthesis of estra-1,3,5-(10)-trien-17-one **(56)** (equation 38)[41]. The thermal ring-opening of benzocyclobutenes results in *ortho*-quinodimethanes (equation 39). Thus the dextrorotatory estradiol derivative **58** was prepared in 77% yield by heating **57** (equation 40)[42]. The cyclopentadienylcobaltdicarbonyl-catalysed addition of bis(trimethylsilyl)acetylene to the enediyne **59** generates the benzocyclobutene **60**, which forms the octahydrophenanthrene **61** containing less than 5% of the *cis*-isomer (equation 41)[43].



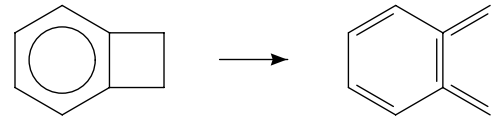
(37)

(54) **(55)**

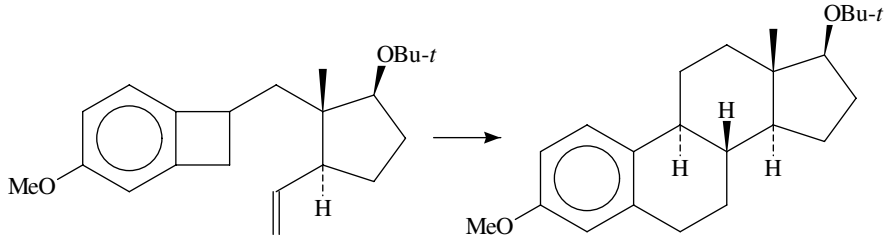


(38)

(56)

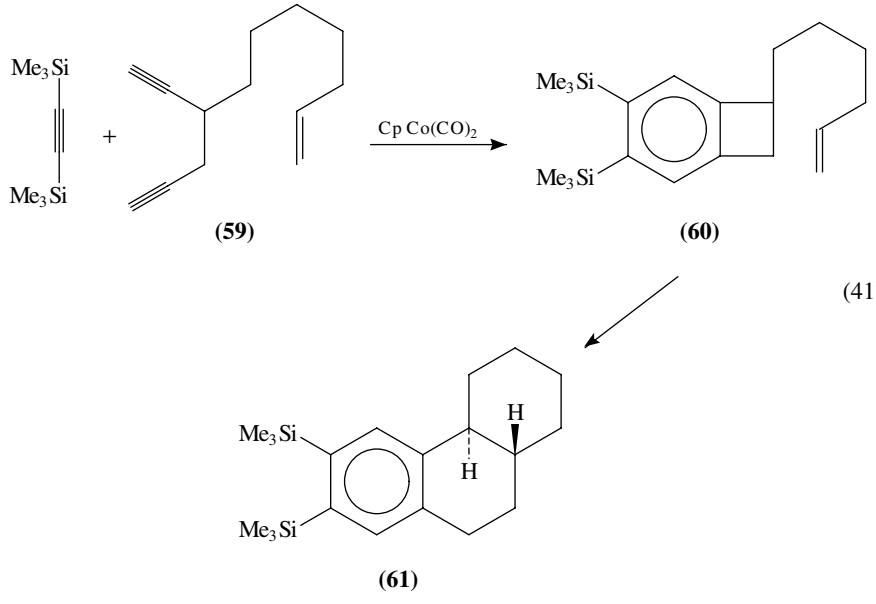


(39)



(57) **(58)**

(40)

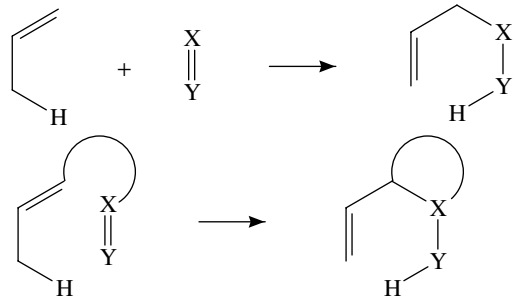


(59) **(60)** (41)

(61)

V. INTRAMOLECULAR ENE REACTIONS

The ene reaction (equation 42) is the 'indirect substituting addition' of an unsaturated compound X = Y to an olefin possessing an allylic hydrogen atom, which is transferred in the process[44,45]. The intramolecular version of the reaction (equation 43) has been applied to the formation of five-, six- and seven-membered rings[46].

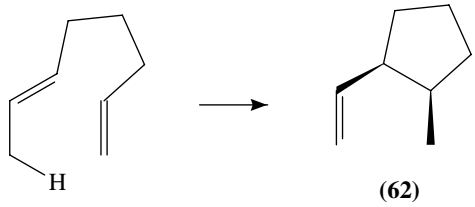


(42)

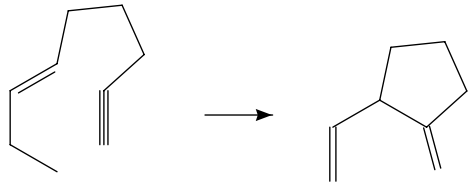
(43)

1,6-Octadiene cyclizes to *cis*-1-methyl-5-vinylcyclopentane **(62)** at 450 °C (equation 44a)[47]. An analogous reaction of the enyne **63** gives 1-methylene-2-vinylcyclopentane (equation 44b)[48]. Heating the 1,7-diene **64** at 490 °C results in a mixture of *cis*- and *trans*-1-isopropenyl-2-methylcyclohexane, **65** and **66**, respectively (equation 45)[49]. The presence of the ester group in **67** facilitates its cyclization: it undergoes ring-closure at 400 °C to give **68** as a mixture of three diastereomers (equation 46)[49]. The [3.3.3]propellane **70** is formed in 76% yield when compound **69** is heated to 250 °C (equation 47)[50]. Thermolysis of the cyclohexene derivative **71** yields a mixture of the spiro-compounds **72** and **73** (equation 48)[51]. Lewis-acid catalysis of intramolecular ene

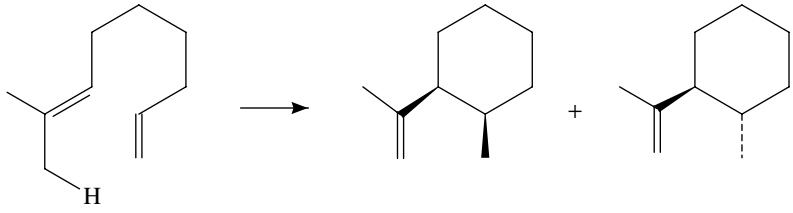
reactions has been observed. The diene **74** undergoes ring-closure to the *trans*-cyclohexane derivative **75** in boiling *o*-dichlorobenzene (equation 49). In the presence of zinc bromide the reaction takes place at room temperature[52]. The chiral analogue **76** cyclizes in the presence of zinc bromide at 25 °C to afford a 96:4 mixture of the ene-products **77** and **78** diastereo- and enantioselectively (equation 50)[53].



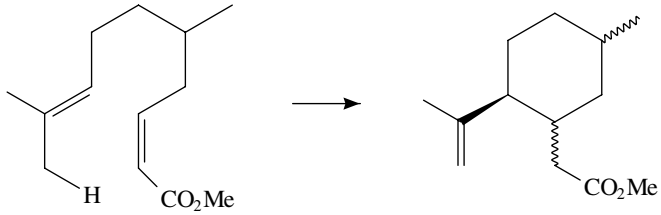
(62) (44a)



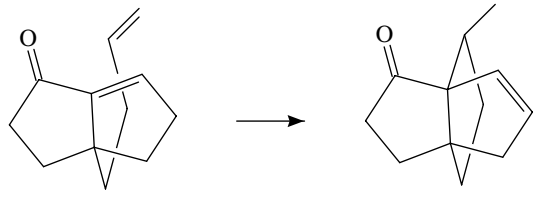
(63) (44b)



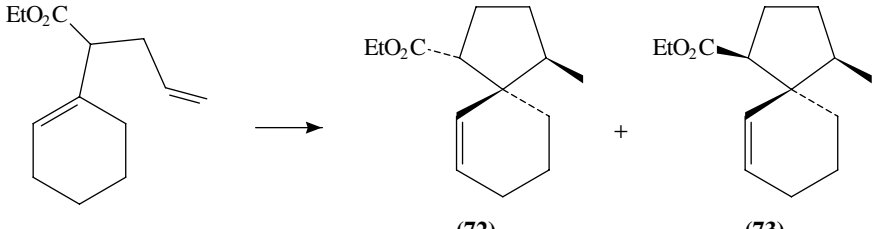
(64) **(65)** **(66)** (45)



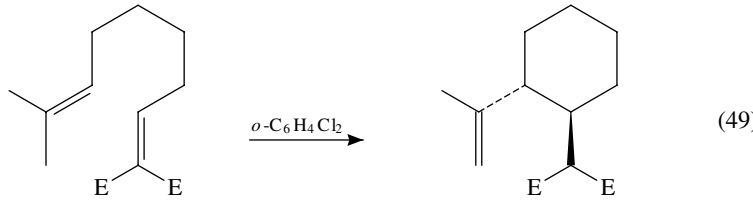
(67) **(68)** (46)



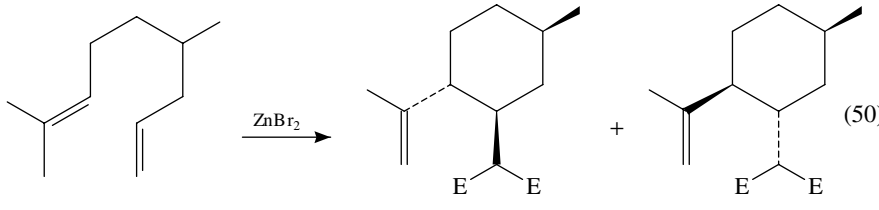
(69) **(70)** (47)



(71) **(72)** **(73)** (48)

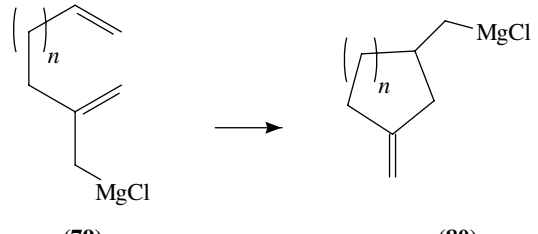


(74) E = CO_2Me **(75)** (49)

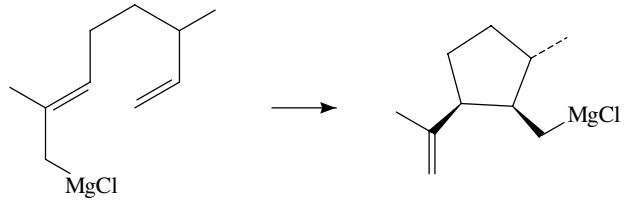


(76) E = CO_2Me **(77)** **(78)** (50)

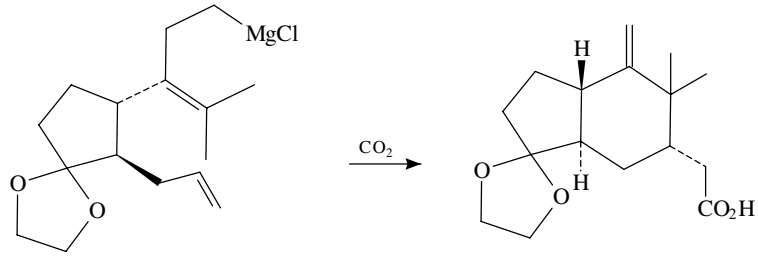
Ene reactions involving transfer of a metal rather than hydrogen are known as 'metallo ene reactions'[54]. In an intramolecular version of the reaction, the Grignard reagents **79** (n = 1, 2 or 3) undergo ring-closure to **80** on heating (equation 51)[55] and 2,6-dimethyl-2,7-octadienylmagnesium chloride **(81)** forms the cyclopentane derivative **82** (equation 52)[56]. The rearranged carboxylic acid **84** is obtained from **83** and carbon dioxide (equation 53)[57]. Similarly, successive treatment of the norbornene derivative **85** with magnesium and carbon dioxide affords the tricyclic acid **86** (equation 54)[58]. The disulphones **87** (R = H or Me) form palladium complexes **88** (L = ligand) by the combined action of bis(dibenzylideneacetone)palladium and triphenylphosphine; the complexes cyclize in acetic acid in a 'palladium ene reaction' to yield derivatives **89** of cyclopentane (equation 55)[59].



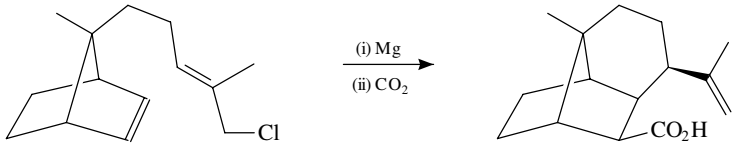
(79) **(80)** (51)



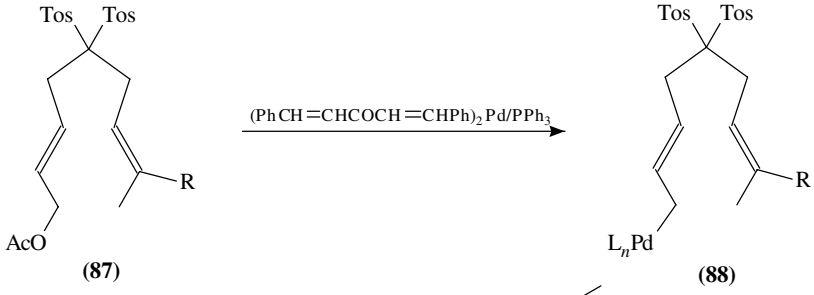
(81) (82) (52)



(83) (84) (53)



(85) (86) (54)

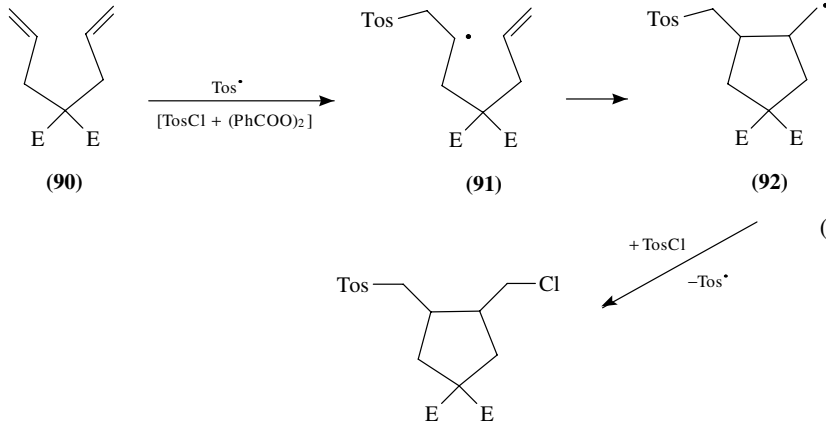


(87) (88) (55)

(89)

VI. FREE-RADICAL CYCLIZATIONS

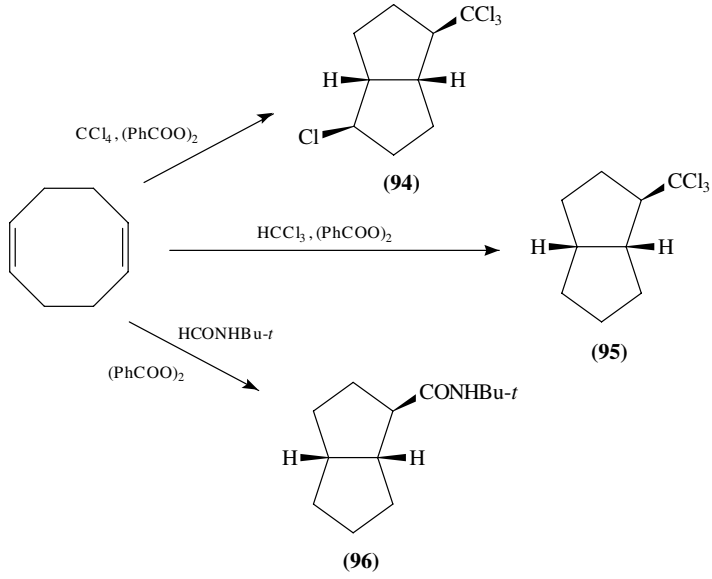
Free-radical chain reactions have been reviewed[60]. The cyclization of dienes by the action of free radicals is illustrated for the case of the 1,6-heptadiene derivative **90** (E = CO_2Me) in equation 56. Treatment with tosyl radicals, produced from tosyl chloride and a catalytic amount of dibenzoyl peroxide, generates the radicals **91**, which cyclize to **92**. The latter reacts with tosyl chloride to form **93** and tosyl radicals are regenerated. The product is obtained in 85% yield as a 6:1 mixture of *cis*- and *trans*-isomers[61].



(56)

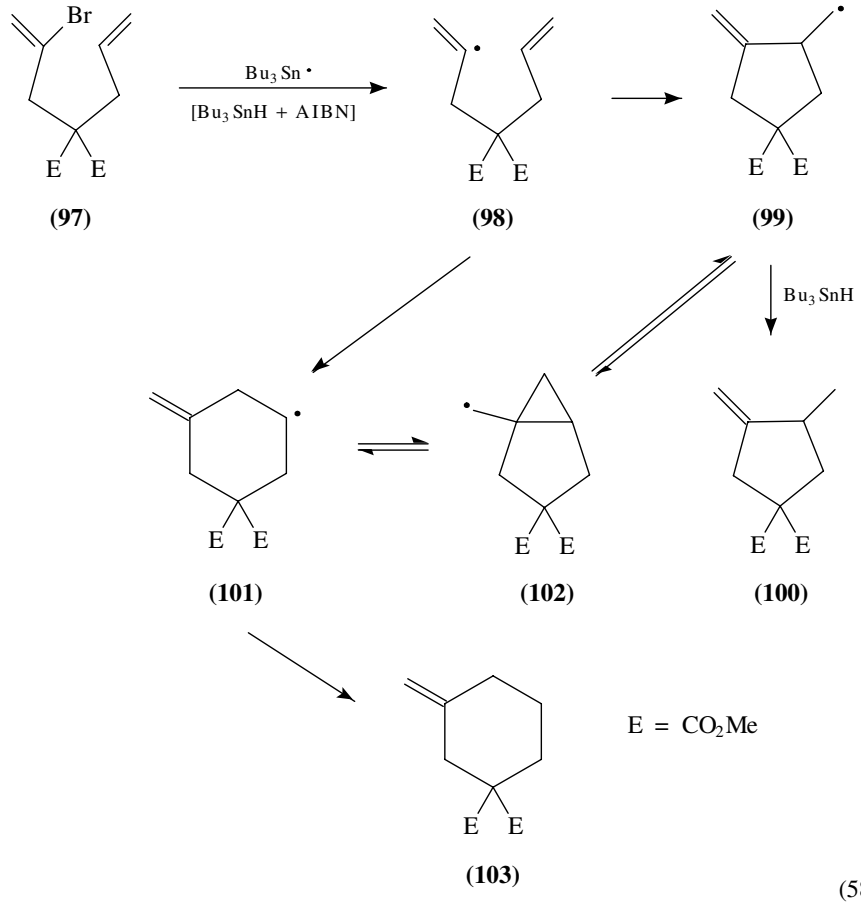
E = CO_2Me

A similar reaction of 1,5-cyclooctadiene with trichloromethyl radicals, produced from carbon tetrachloride and dibenzoyl peroxide, leads to 2-chloro-6-trichloromethylbicyclo-[3.3.0]octane **(94)**, with chloroform and dibenzoyl peroxide the analogue **95** is obtained and *N*-*t*-butylformamide affords compound **96** (equation 57)[62,63].



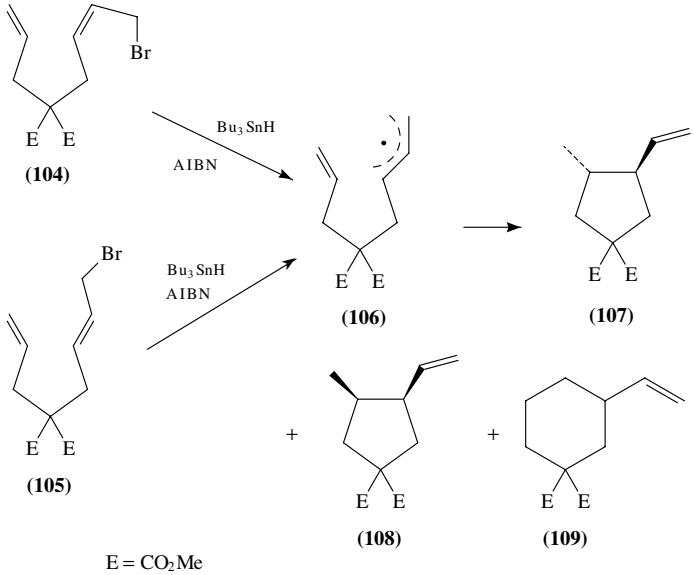
(57)

The diester **97** reacts with tributyltin radicals, produced from tributyltin hydride and AIBN (2,2′-bisazoisobutyronitrile), to form the vinyl radical **98**, which cyclizes to the methylenecyclopentylmethyl radical **99**. Abstraction of hydrogen from tributyltin hydride yields the product **100**. An alternative cyclization of **98** gives the methylenecyclohexyl radical **101** and thence dimethyl 3-methylenecyclohexanedicarboxylate **(103)**. The proportion of the products **100** and **103** depends on the concentration of the reactant **97**: at 0.02 molar concentration the products are formed in the ratio 3:1; at 1.7 molar concentration only **100** is observed. It is suggested that the cyclohexyl radical **101** might also arise from the cyclopentylmethyl radical **99** via the bicyclic radical **102** (equation 58)[64,65]. An analogous cyclization of the allyl radical **106**, generated from the bromides **104** or **105**, affords a 6:3:1 mixture of compounds **107**, **108** and **109** (equation 59)[66].

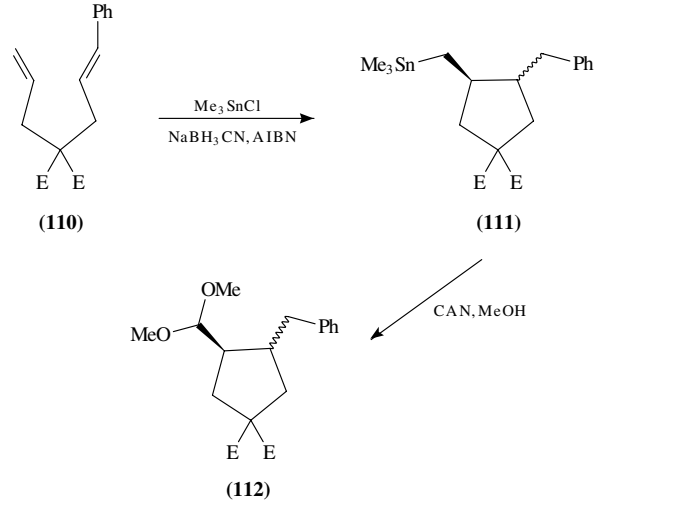


(58)

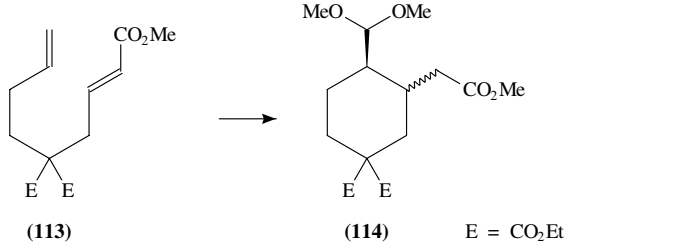
The diester **110** (E = CO_2Et) reacts with a mixture of trimethyltin chloride and sodium cyanoborohydride under AIBN catalysis to give the cyclopentane **111** as a 4:1 mixture of *cis*- and *trans*-isomers. The products are destannylated to the acetals **112** by treatment with methanolic ceric ammonium nitrate (CAN). The 1,7-octadienyl derivative **113** was similarly converted into the cyclohexanes **114** (*cis/trans* = 1:1) (equation 60)[67].


Br
E E
(104)
Bu3SnH
AIBN
(106)
(107)
Br
Bu3SnH
AIBN
(105)
+
+
(108)
(109)
E = CO2Me

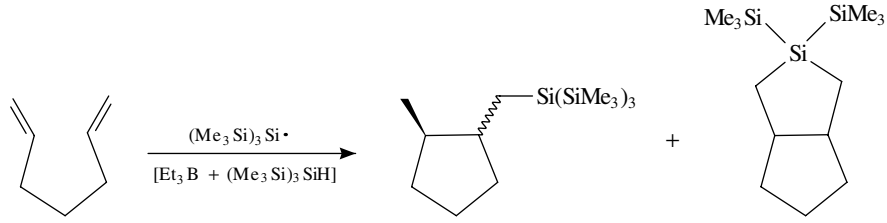
(59)


Ph
E E
(110)
Me3SnCl
NaBH3CN, AIBN
Me3Sn
Ph
(111)
CAN, MeOH
OMe
MeO
Ph
(112)

(60)


CO2Me
E E
(113)
MeO
OMe
CO2Me
(114)
E = CO2Et

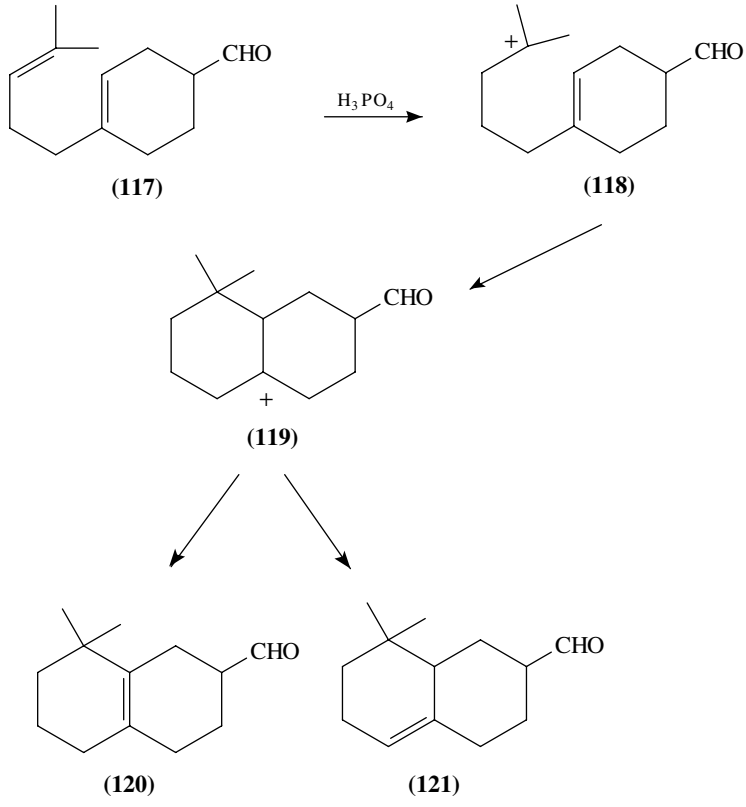
The action of a catalytic amount of triethylborane on tris(trimethylsilyl)silane induces the formation of tris(trimethylsilyl)silyl radicals, which promote the ring-closure of 1,6-heptadiene to a mixture of the *cis*- and *trans*-cyclopentane derivatives **115**, together with a small amount of the silicon heterocycle **116** (equation 61)[68].



(115) **(116)** (61)

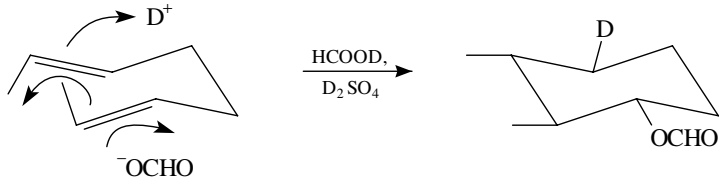
VII. CATIONIC CYCLIZATIONS[69–71]

The dienaldehyde **117** cyclizes to a mixture of the octalins **120** and **121** on treatment with concentrated orthophosphoric acid. It was suggested that the reaction is initiated by formation of the cation **118**, which undergoes ring-closure to the bicyclic cation **119**. Proton loss in two alternative ways leads to the products (equation 62)[72].



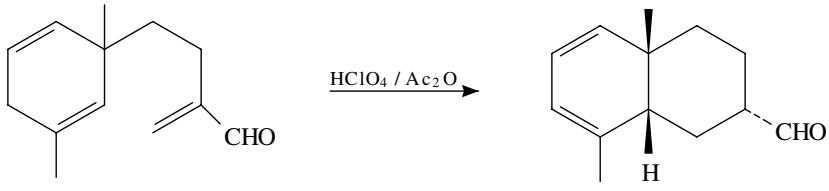
(117) **(118)** **(119)** **(120)** **(121)** (62)

Treatment of *trans,trans*-2,6-octadiene (**122**) with deuteriated formic acid HCO_2D in the presence of deuteriosulphuric acid gave the cyclized formate ester **123**. A concerted mechanism (equation 63) was proposed for this reaction[73]. The stereospecific ring-closure of the 1,4-cyclohexadiene derivative **124** in acetic anhydride/perchloric acid affords the octalin **125**, which was isolated as the diacetate **126** (equation 64)[74].



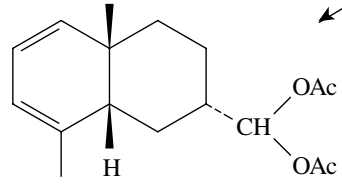
(63)

(122) **(123)**



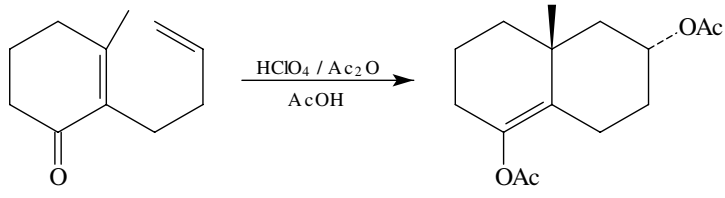
(124) **(125)**

(64)



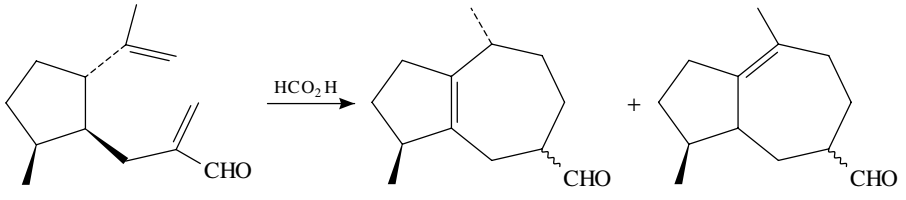
(126)

Another example of the formation of an octalin is the conversion of the cyclohexenone **127** into the enol acetate **128** by the action of acetic anhydride and perchloric acid in the presence of acetic acid (equation 65)[75]. The acid-induced ring-closure of the cyclopentane derivative **129** gives a 85% yield of a mixture of the octahydroazulenes **130** and **131** (equation 66)[76].



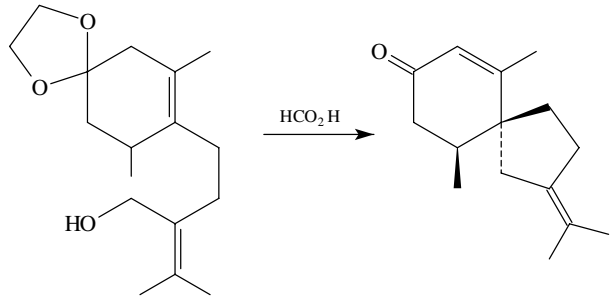
(65)

(127) **(128)**



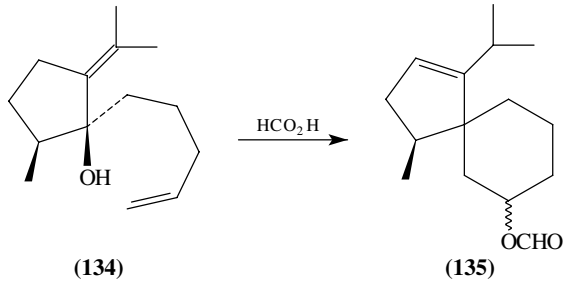
(129) **(130)** **(131)** (66)

The formation of a number of spiro compounds by cationic cyclization has been reported. Formic acid transforms the ketal **132** into **133** in 40% yield (equation 67)[77] and the alcohol **134** into the formate **135** (35%) (equation 68)[78]. The alcohols **136** and **138** yield the spiro compounds **137** (45–50%) (equation 69)[79] and **139** (25%) (equation 70)[80], respectively. Pallescensin A **(141)** is produced in 84% yield by the twofold cyclization of the furan derivative **140**, induced by boron trifluoride (equation 71)[81].



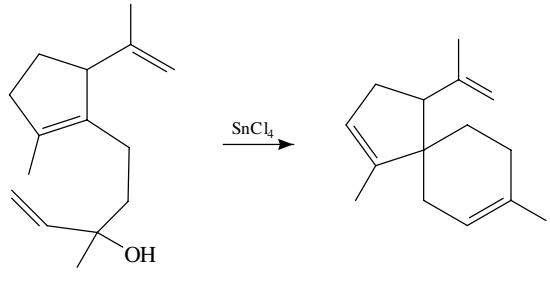
(67)

(132) **(133)**



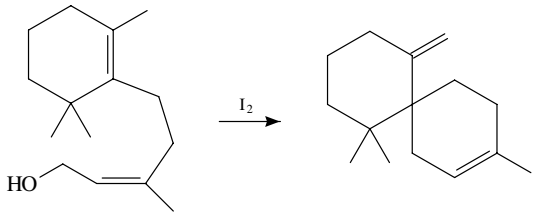
(68)

(134) **(135)**



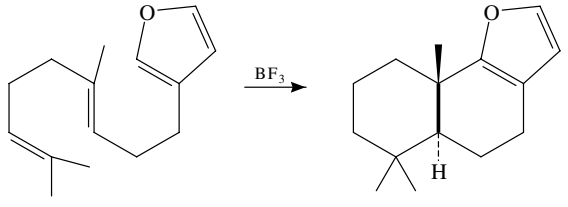
(69)

(136) **(137)**



(70)

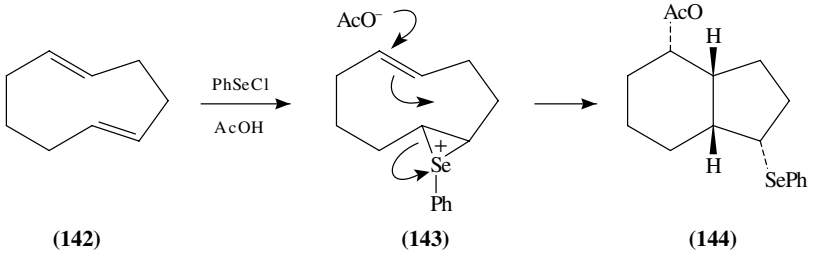
(138) **(139)**



(71)

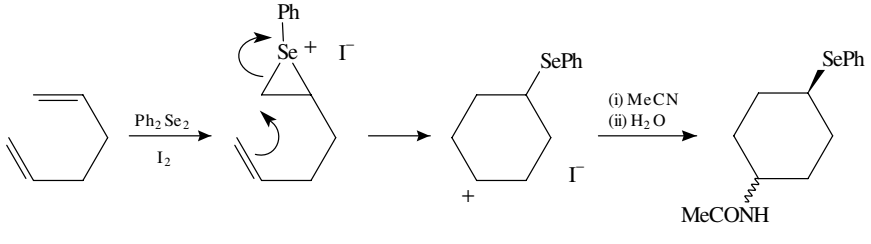
(140) **(141)**

Treatment of cyclonona-1,5-diene **(142)** with benzeneselenyl chloride in acetic acid yields solely the bicyclic product **144** via the episelenonium ion **143** (equation 72)[82]. The reaction of 1,5-hexadiene with benzeneselenyl iodide, generated from diphenyl diselenide and iodine in acetonitrile, likewise results in addition-cyclization. The substituted cyclohexane **145** is obtained as a mixture of *cis*- and *trans*-isomers (equation 73)[83]. Thallium(III) compounds effect the ring-closure of dienols. Thus geraniol **(146)** yields a mixture of the cyclic ethers **147–149** (equation 74)[84] and nerol **(150)** gives **151**, **152** and a mixture of four diastereomers having the gross structure **153** (equation 75)[85]. Treatment of *o*-geranylphenol **(154)** with thallium trifluoroacetate, followed by hydrolysis, affords the tricyclic benzopyrans **155** and **156** (equation 76)[86].



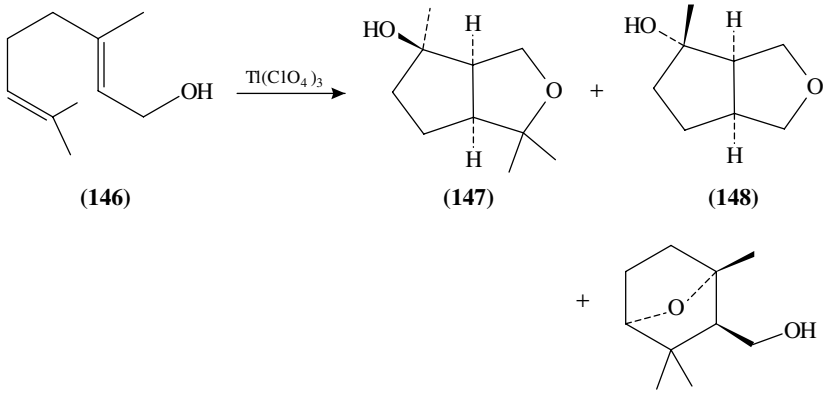
(72)

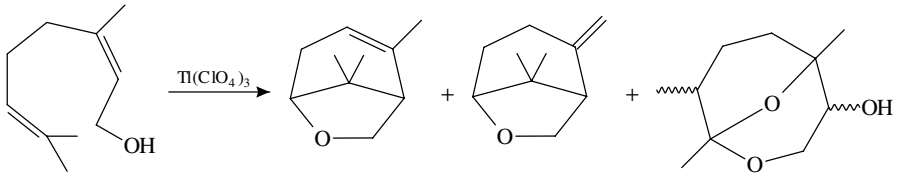
(142) **(143)** **(144)**

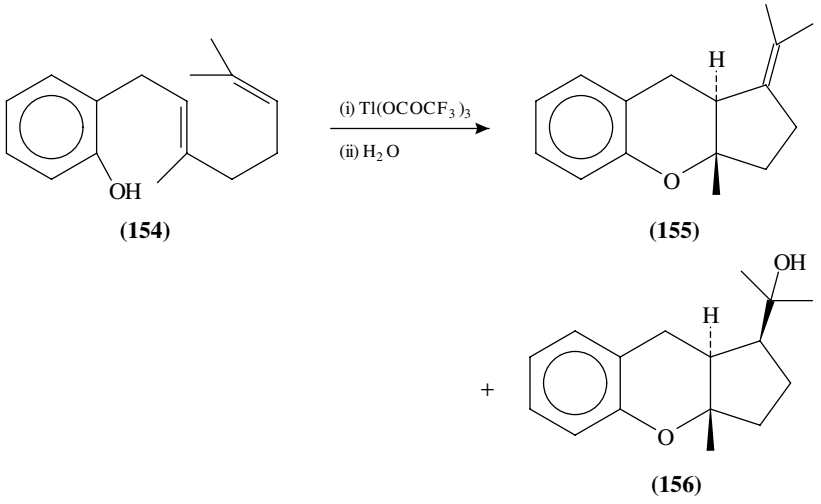


(145)

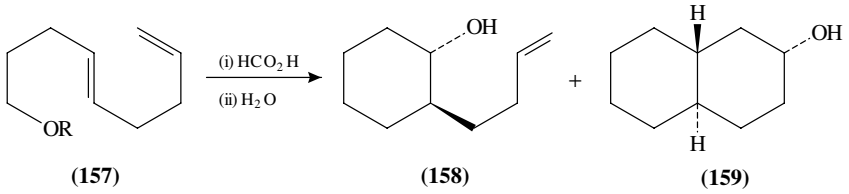
(73)



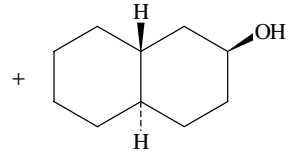




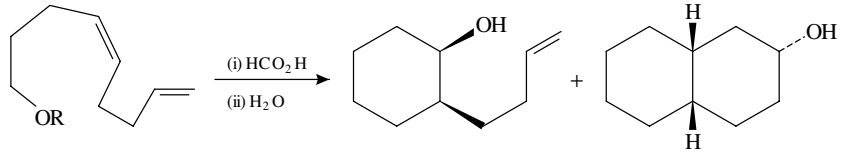
Ionization of *p*-nitrobenzenesulphonate esters of dienols generates carbocations which undergo cyclization. Thus *trans*-5,9-decadienyl *p*-nitrobenzenesulphonate **(157)** (R = $O_2SC_6H_4NO_2$-*p*) reacts with formic acid, followed by hydrolysis, to yield the butenylcyclohexanol **158**, together with the decalinols **159** and **160** (equation 77)[87]. The *cis*-ester **161** affords the *cis*-products **162–164** (equation 78)[88]. The steric course of these reactions is consistent with a concerted mechanism (equation 79).



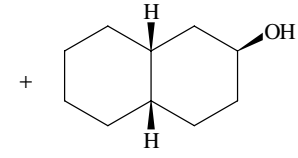
(157) **(158)** **(159)**



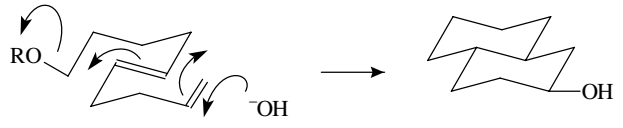
(160) (77)



(161) **(162)** **(163)**

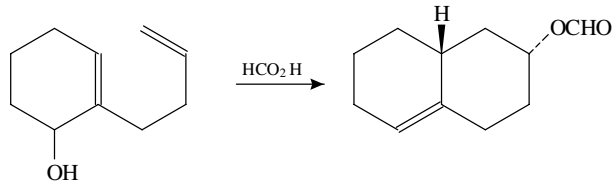


R = $O_2SC_6H_4NO_2$-*p* **(164)** (78)

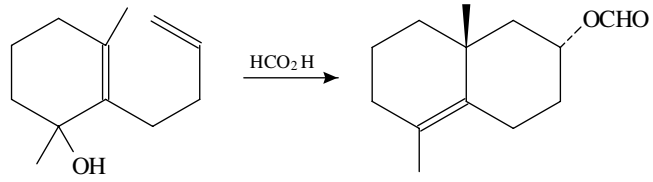


(79)

The octalinyl ester **166** is produced in excellent yield when the butenylcyclohexenol **165** is treated with formic acid at room temperature (equation 80)[89]. The dimethyl analogue **167** reacts similarly to give **168** (equation 81)[90]. The trifluoroacetic acid-catalysed ring-closure of the ketene thioacetal **169** to give a 1:2 mixture of the *cis*- and *trans*-ketones **170** and **171** (equation 82) has been reported[91].

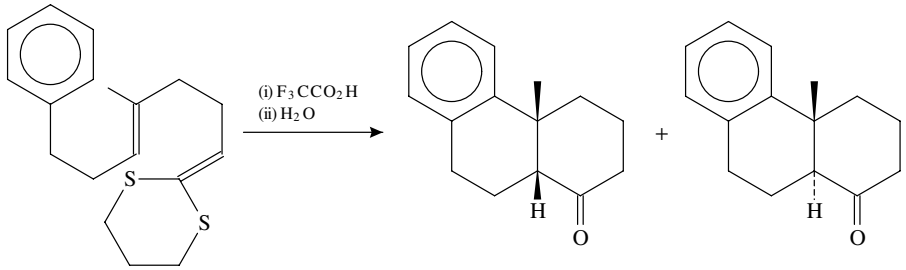


(165) **(166)** (80)



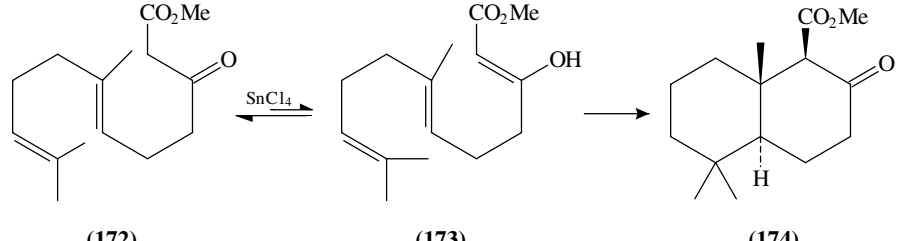
(81)

(167) **(168)**

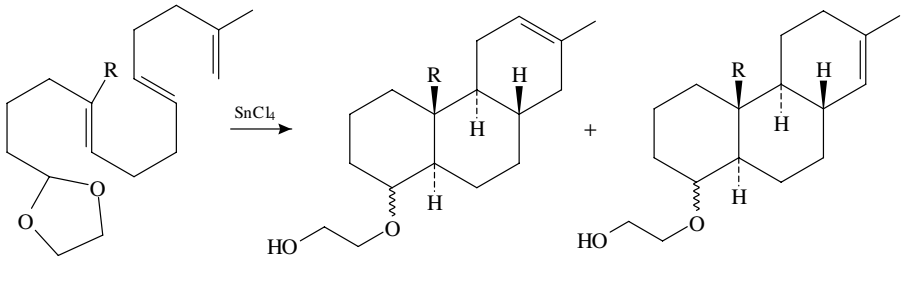


(169) **(170)** **(171)** (82)

The formation of the decalinone **174** in 68% yield in the reaction of the dienone **172** with tin(IV) chloride (equation 83) is thought to proceed by way of the enol **173**[92]. The triene **175** (R = H) cyclizes quantitatively to a mixture of the isomeric dodecahydrophenanthrenes **176** and **177** when treated with tin(IV) chloride at 0 °C (equation 84)[93]; the homologue **175** (R = Me) reacts analogously[94].

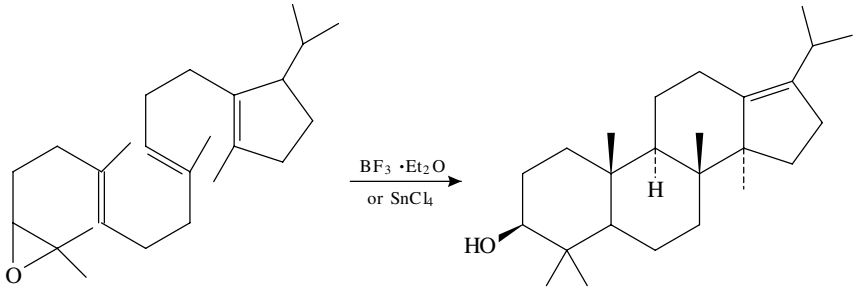


(172) **(173)** **(174)** (83)

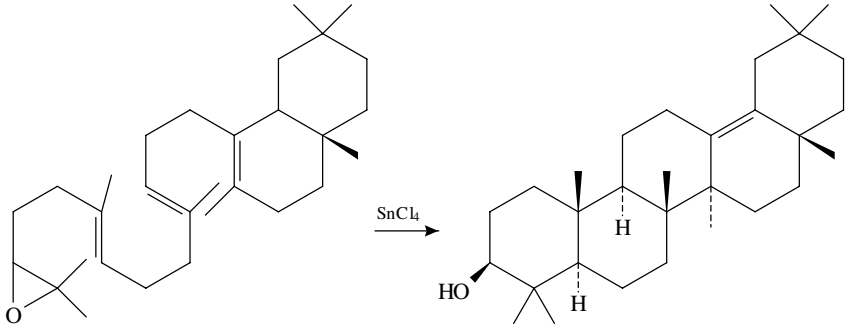


(175) **(176)** **(177)** (84)

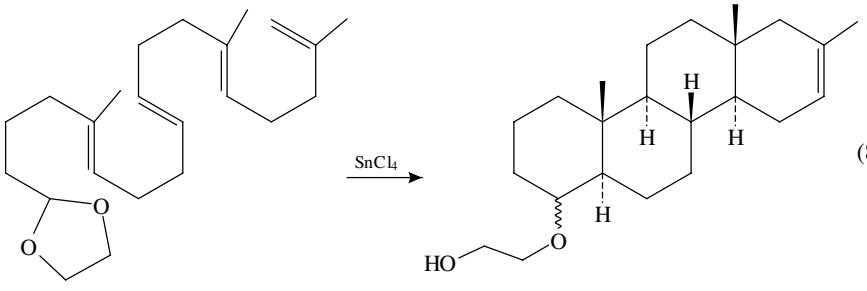
The tetracyclic alcohol **179** is produced by the action of boron trifluoride etherate or tin(IV) chloride on the oxirane **178** (equation 85)[95]. A similar cyclization of the oxirane **180** yields DL-δ-amyrin **(181)** (equation 86)[96]. In the $SnCl_4$-catalysed ring-closure of the tetraene **182** to the all-*trans*-tetracycle **183** (equation 87) seven asymmetric centres are created, yet only two of sixty-four possible racemates are formed[97]. It has been proposed that multiple ring-closures of this kind form the basis of the biosynthesis of steroids and tetra- and pentacyclic triterpenoids, the 'Stork–Eschenmoser hypothesis'[98,99]. Such biomimetic polyene cyclizations, e.g. the formation of lanosterol from squalene (equation 88), have been reviewed[69,70].



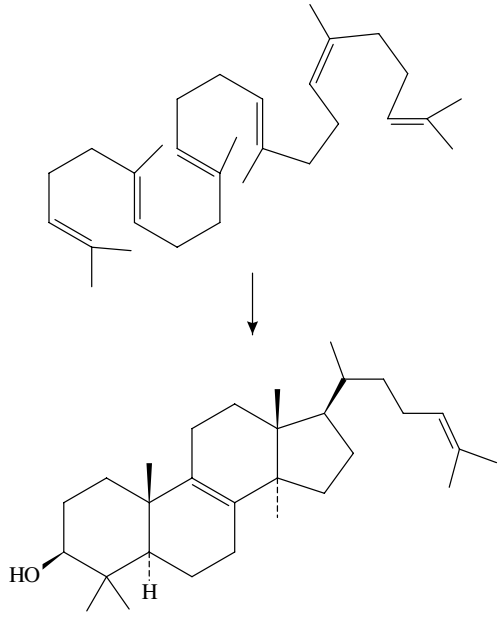
(178) **(179)** (85)



(180) **(181)** (86)

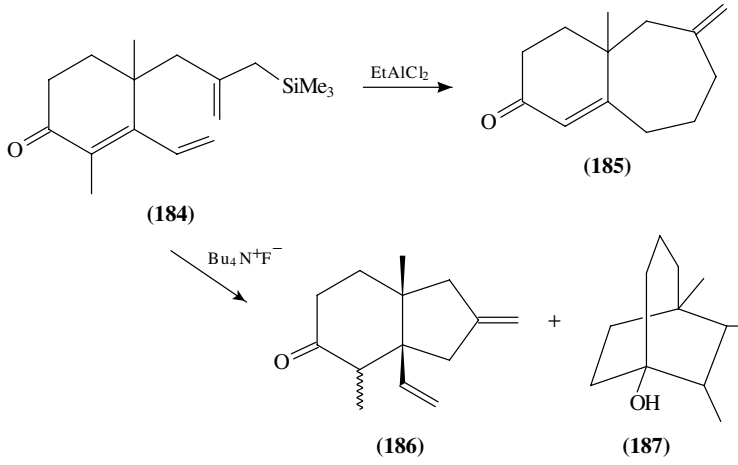


(182) **(183)** (87)

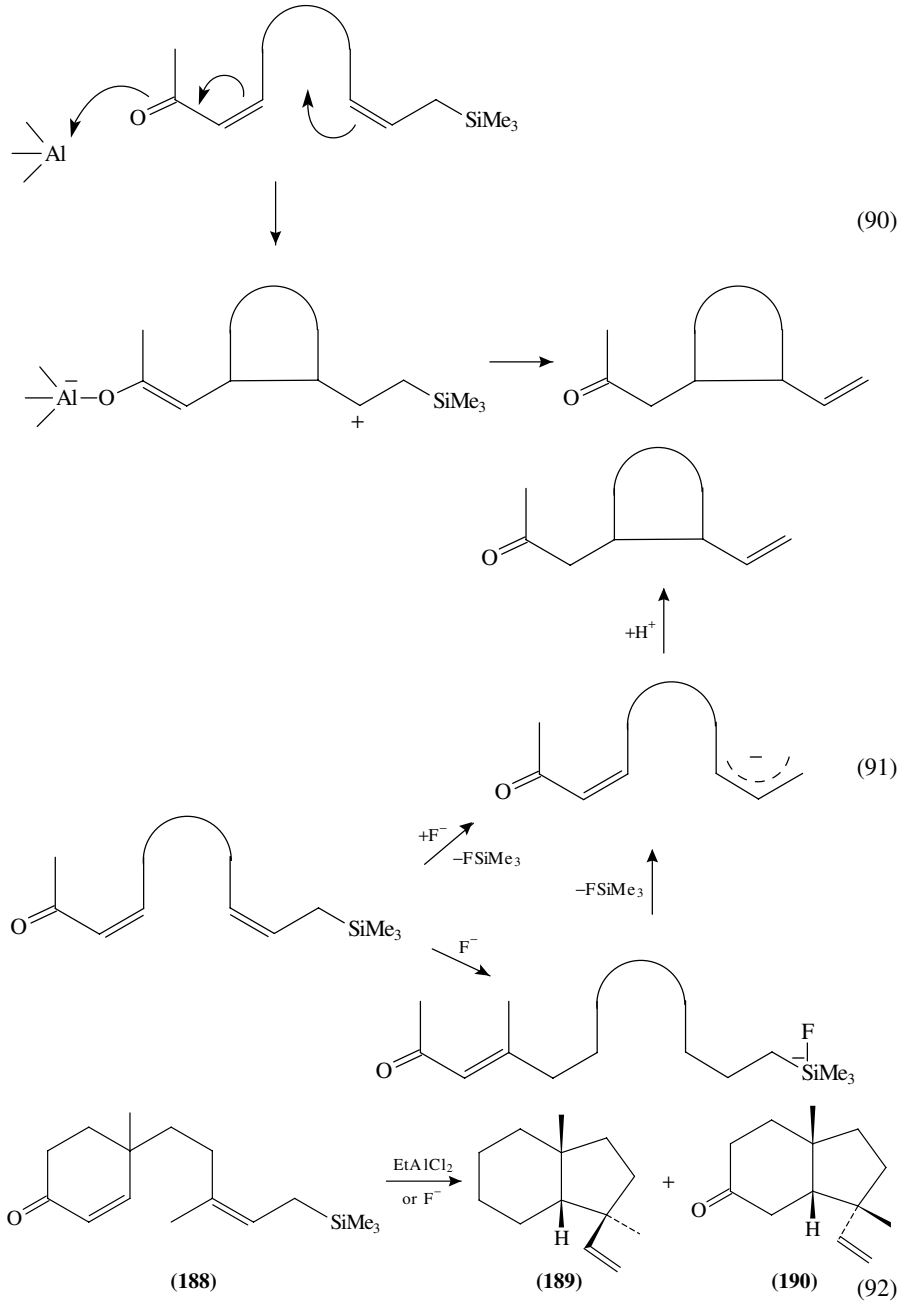


(88)

Cyclization reactions of vinyl- and alkynylsilanes have been reviewed[100]. The course of the reaction of the cyclohexenone derivative **184** depends on the catalyst employed: ethylaluminium dichloride gives solely the product **185** of 1,6-addition, whereas tetrabutylammonium fluoride yields a mixture containing 69% of the '1,4-adduct' **186** and 31% of the bridged compound **187** (equation 89)[101]. Intramolecular addition reactions of allylic silanes[102] may also be catalysed by Lewis acids (equation 90) or fluoride ions, and in this case an allyl anion or a pentavalent silicon intermediate may be involved (equation 91). Such reactions are exemplified by the formation of a 1:5 mixture of the diastereomers **189** and **190** when the cyclohexenone derivative **188** is treated with ethylaluminium dichloride (equation 92). In the presence of fluoride anion the ratio of the isomers is reversed[103].

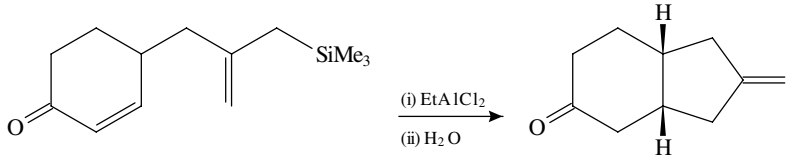


(89)



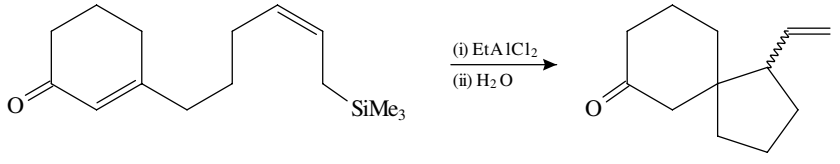
Cyclization of the allylic trimethylsilane **191** with ethylaluminium dichloride, followed by hydrolysis, gives solely the *cis*-fused product **192** (equation 93)[104]. Under similar

conditions, the cyclohexenone **193** yields the spiro compound **194** as a mixture of diastereomers (equation 94)[104].



(93)

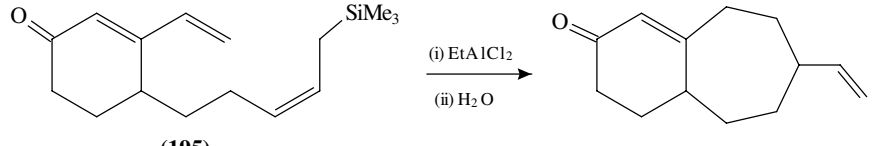
(191) **(192)**



(94)

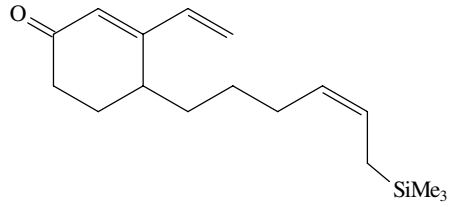
(193) **(194)**

A seven-membered ring is formed in the cyclization of **195** (equation 95)[105]. The homologue **196** affords the fused cyclooctane **197**, together with the *cis*- and *trans*-decalinones **198** (equation 96)[106]. Six-, seven- and eight-membered rings are produced in Lewis acid-catalysed reactions of various cyclohexenones with side-chains terminating in allylic trimethylsilyl groups (equations 97–99)[107].



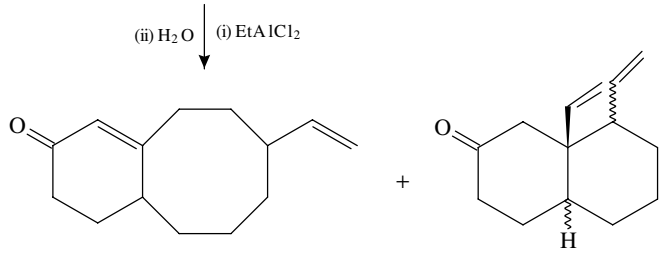
(195)

(95)

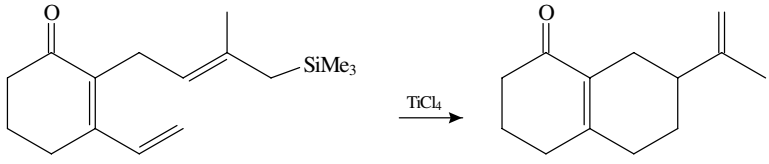


(196)

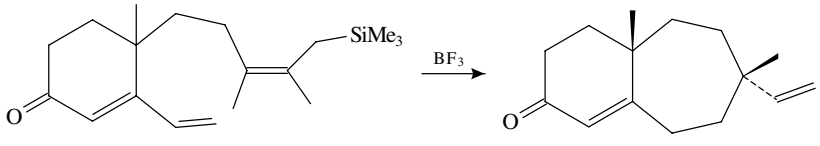
(96)



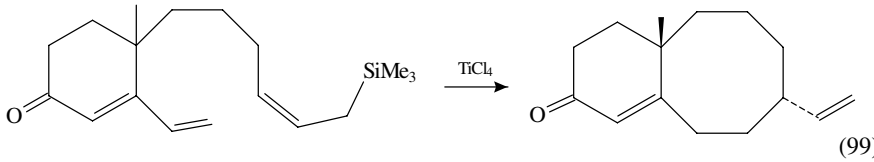
(197) **(198)**



(97)



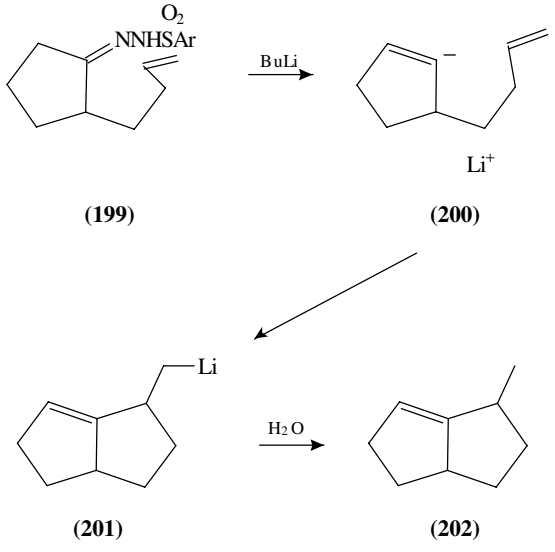
(98)



(99)

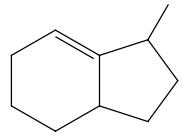
VIII. ANIONIC CYCLIZATIONS

Treatment of the 2,4,6-triisopropylbenzenesulphonylhydrazone **199** of 2-(3-butenyl)cyclopentanone with butyllithium generates the lithium compound **200**, which cyclizes spontaneously to **201**. Aqueous work-up gives the bicyclic hydrocarbon **202** in good yield (equation 100). The six-membered ring analogue **203** is formed in very poor yield by this method. Ring-closure of the acyclic lithium derivative **204** gives 65% of *cis*-2,4-dimethylmethylenecyclopentane **(205)** (equation 101)[108].

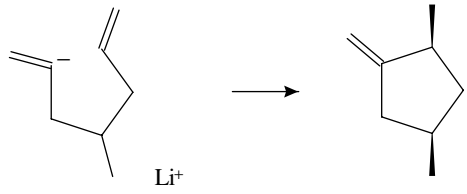


(100)

Ar = 2, 4, 6-*i*-$Pr_3C_6H_2$

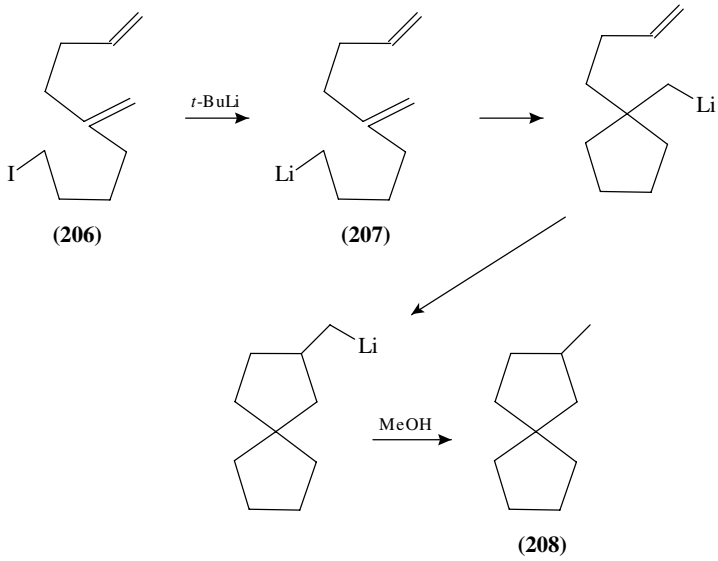


(203)

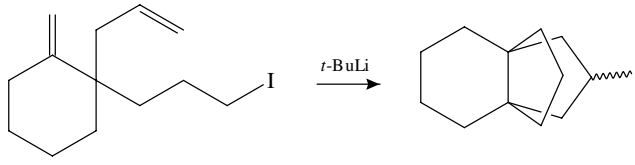


(204) **(205)** (101)

The action of *t*-butyllithium on 5-methylene-8-nonenyl iodide **(206)** leads to the lithium compound **207**, which undergoes a 'tandem cyclization' to yield eventually 84% of 2-methylspiro[4.4]nonane **(208)** (equation 102). An analogous reaction of the iodide **209** (equation 103) results in the [4.3.3]propellane **210** (81%) as a mixture of *endo*- and *exo*-isomers[109].

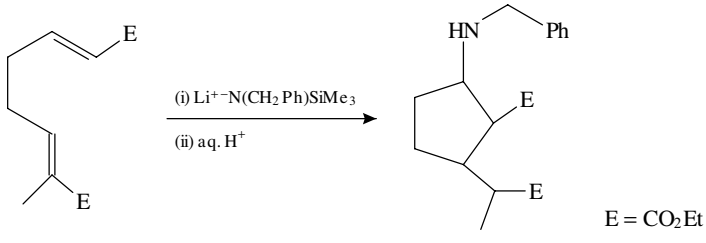


(206) **(207)** **(208)** (102)

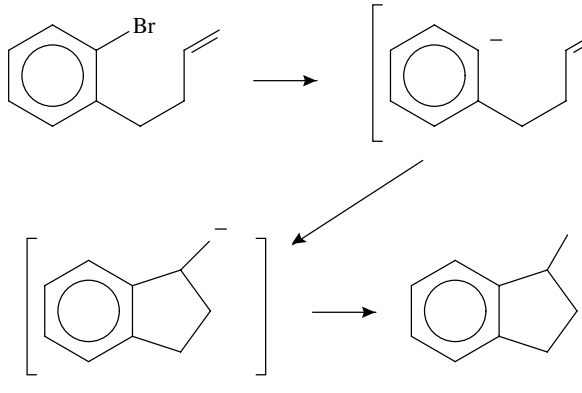


(209) **(210)** (103)

Treatment of the diester **211** (E = CO_2Et) with lithium *N*-benzyltrimethylsilylamide, followed by aqueous acid, yields the cyclopentane derivative **212**, the product of an intramolecular Michael addition (equation 104)[110]. 1-Methylindane is produced in moderate yield by the electrochemical reduction of *o*-bromo-(3-butenyl)benzene (equation 105)[111].

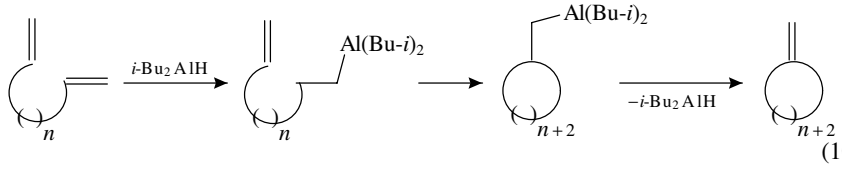


(211) **(212)** (104)

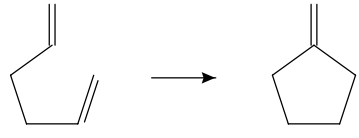


(105)

Diisobutylaluminium hydride catalyses the ring-closure of various dienes. It is proposed that the process involves addition of the aluminium hydride to a terminal double bond, followed by ring-closure and, finally, elimination of the catalyst (equation 106). Thus 1,5-hexadiene gives methylenecyclopentane **(213)** (equation 107), 1,6-heptadiene gives methylenecyclohexane **(214)** (equation 108), 4-vinylcyclohexene gives bicyclo[3.2.1]oct-2-ene **(215)** (equation 109) and the spiro compound **217** is obtained from 5-methylene-1,8-nonadiene **(216)** (equation 110)[112].

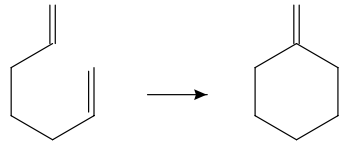


(106)



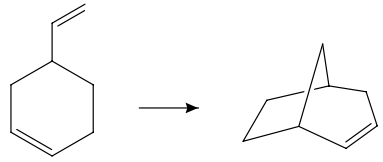
(107)

(213)



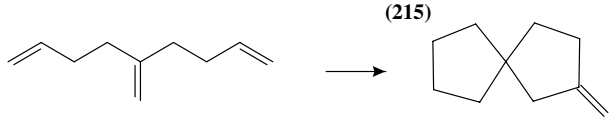
(108)

(214)



(109)

(215)

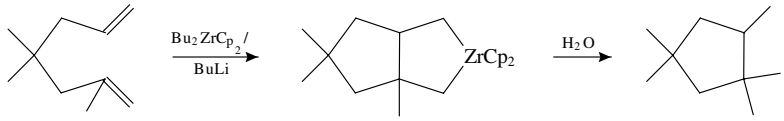


(110)

(216) **(217)**

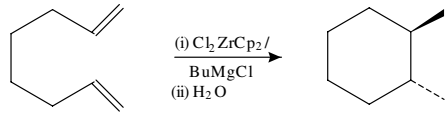
IX. METAL-CATALYSED CYCLIZATIONS

Zirconocene, $ZrCp_2$, generated in situ from zirconocene derivatives, mediates diverse ring-closures[113]. Thus treatment of 2,4,4-trimethyl-1,6-heptadiene with butyllithium and Bu_2ZrCp_2 yields the zirconium complex **218**, which gives 1,1,3,3,5-pentamethylcyclopentane on aqueous work-up (equation 111)[114]. The reaction of 1,7-octadiene with butylmagnesium chloride and a catalytic amount of zirconocene dichloride, followed by water, gives *trans*-1,2-dimethylcyclohexane **(219)** in excellent yield (equation 113)[115]; similarly, the diene ether **220** affords the cyclopentane derivative **221** (equation 113)[116].



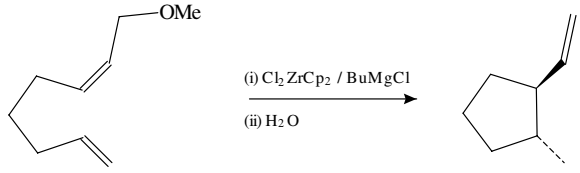
(218)

(111)



(112)

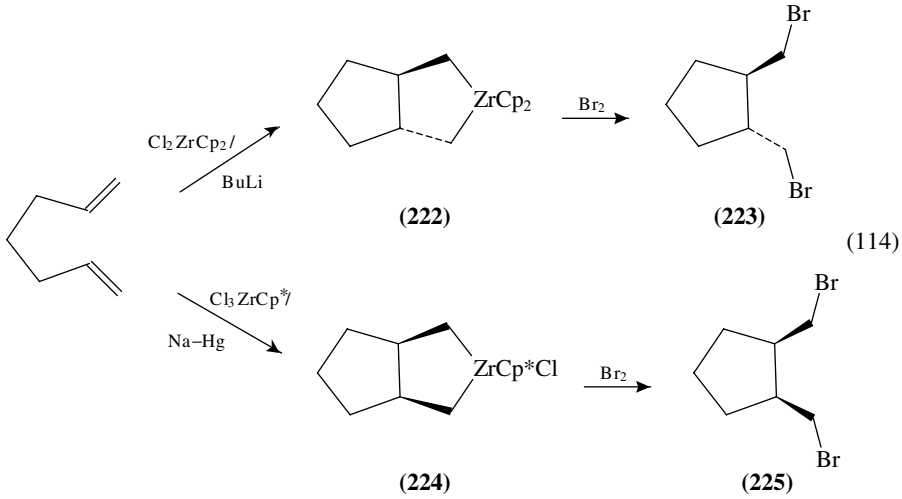
(219)



(113)

(220) **(221)**

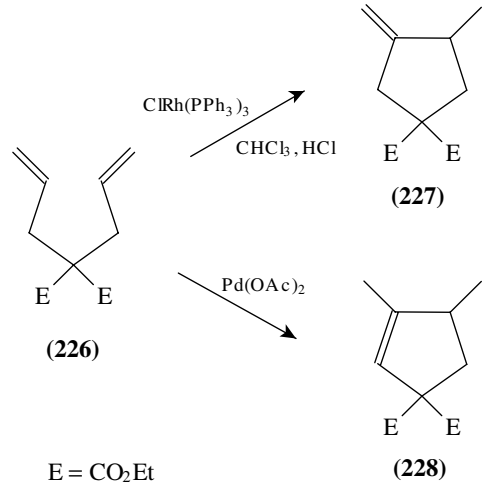
1,6-Heptadiene and zirconocene, generated from zirconocene dichloride and butyllithium, form an intermediate, presumably the metallocycle **222**, which is transformed into *trans*-1,2-di(bromomethyl)cyclopentane **(223)** by the action of bromine at −78 °C. In contrast, a similar reaction of 1,6-heptadene with Cp^*ZrCl (Cp^* = pentamethylcyclopentadienyl) (from Cp^*ZrCl_3 and sodium amalgam) gives solely the *cis*-isomer **225** via the complex **224** (equation 114)[117].



(222) **(223)** (114)

(224) **(225)**

The diester **226** undergoes ring-closure to the methylenecyclopentane derivative **227** in the presence of a catalytic amount of chlorotris(triphenylphosphine)rhodium in boiling chloroform saturated with hydrogen chloride. In contrast, if the reaction is catalysed by palladium(II) acetate, the isomeric cyclopentene **228** is produced (equation 115)[118].



(227) (115)

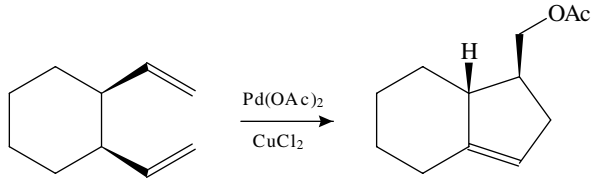
(226)

(228)

E = CO_2Et

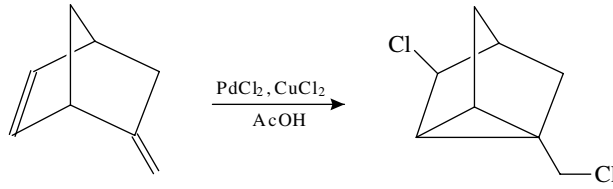
Dienes are oxidized by palladium(II) salts; if copper(II) chloride is added, the reactions become catalytic with respect to the palladium salt. Thus *cis*-divinylcyclohexane reacts

with palladium(II) acetate to give the bicyclic acetate **229** stereospecifically (equation 116), 5-methylenenorbornene and palladium(II) chloride/copper(II) chloride in acetic acid afford compound **230** (equation 117) and 5-vinylnorbornene **231** is transformed into a mixture of *endo*- and *exo*-**232** (equation 118)[119].



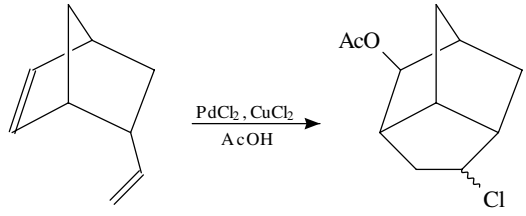
(116)

(229)



(117)

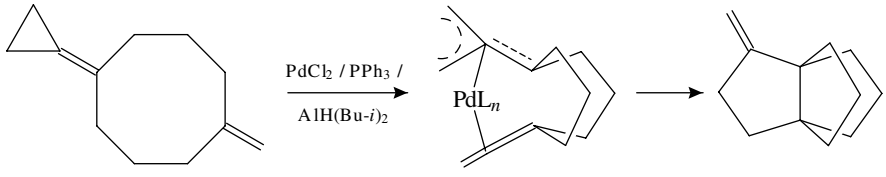
(230)



(118)

(231) **(232)**

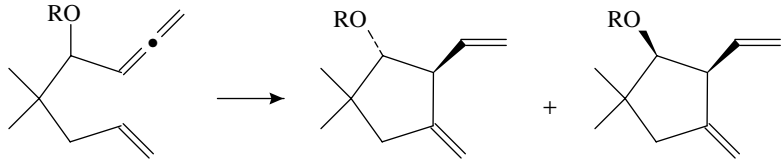
'Tandem cyclization' of 1-cyclopropylidene-5-methylenecyclooctane **(233)** with palladium(II) chloride/triphenylphosphine in the presence of diisobutylaluminium hydride leads to the [3.3.3]propellane **235** in 74% yield by way of the proposed intermediate **234** (L = ligand) (equation 119)[120].



(223) **(234)** **(235)** (119)

A nickel-chromium catalyst prepared from chromous chloride and (*p*-diphenylphosphinopolystyrene)nickel dichloride mediates the ring-closure of the ene-allene **236** (R = H) to a mixture of 3.4 parts of **237** and 1 part of **238** (equation 120)[121]. An analogous reaction of the *t*-butyldimethylsilyl ether of **236** yields solely the (*E*)-isomer **237** (R = *t*-BuMe$_2$Si). Cyclization of the ene-allene **239** affords the perhydroindane **240** in 72%

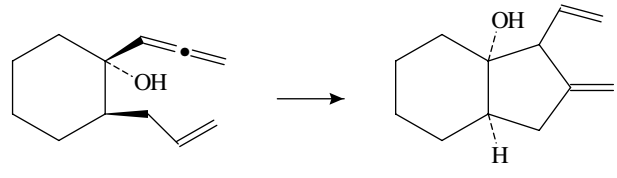
yield (equation 121)[121].



(120)

(236) **(237)** **(238)**

R = H, *t*-BuMe$_2$Si

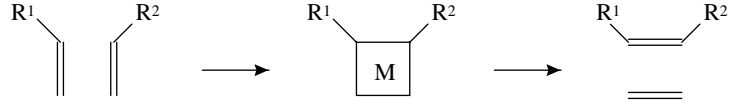


(121)

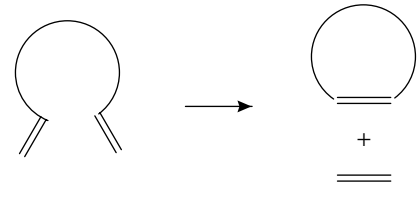
(239) **(240)**

X. RING-CLOSING METATHESES

The metal-catalysed olefin metathesis (equation 122) when applied to dienes results in ring-closure and expulsion of an olefin (equation 123). Thus the molybdenum carbene complex **241** promotes the decomposition of the 1,6-heptadiene derivative **242** to a mixture of the cyclopentene **243** and ethylene (equation 124)[122]. An analogous reaction of the alcohol **244** gives **245** (equation 125), and 4-benzyloxy-1,7-decadiene **(246)** affords the cyclohexene **247** and 1-butene (equation 126). These transformations, which occur in benzene at room temperature, proceed in excellent yields[122].

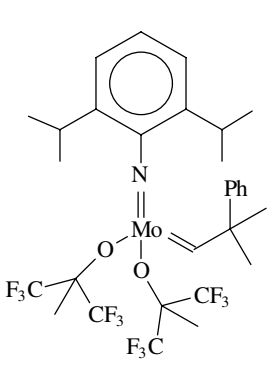


(122)

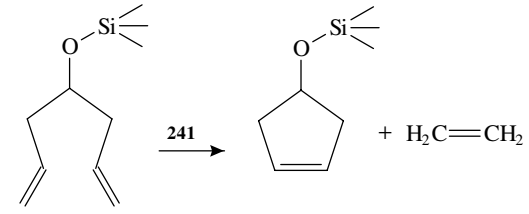


(123)

Metatheses of 1,7-octadienes containing various functional groups are catalysed by ruthenium carbene complexes of the type **248**. For instance, the alcohol **249** (R = CH_2OH), the aldehyde **249** (R = CHO) and the carboxylic acid **249** (R = CO_2H) are all converted into the corresponding cyclohexenes **250** in 82–88% yields (equation 127) and the heterocycles **252** (n = 0, 1 or 2) are efficiently produced from the amides **251** (equation 128)[123].

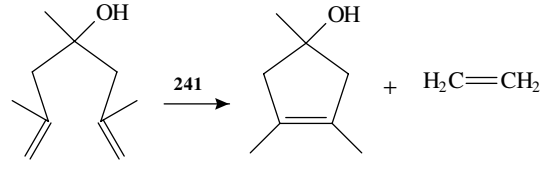


(241)



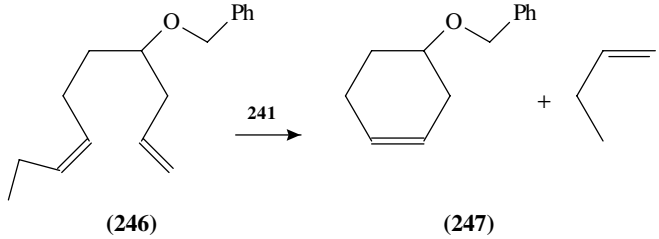
(242) **(243)**

(124)



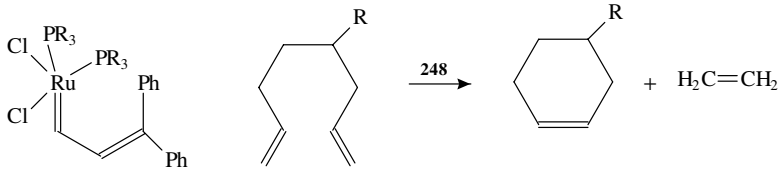
(244) **(245)**

(125)



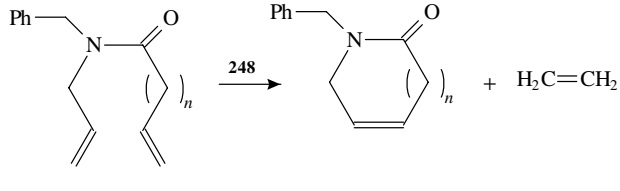
(246) **(247)**

(126)



(248) **(249)** **(250)**

(127)



(251) **(252)**

(128)

XI. REFERENCES

1. M. Vandewalle and P. De Clerq, *Tetrahedron*, **41**, 1767 (1985).
2. C. Thebtaranonth and Y. Thebtaranonth, *Tetrahedron*, **46**, 1385 (1990).
3. (a) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc*., **87**, 395 (1965).
   (b) R. B. Woodward and R. Hoffmann, *The Conservation of Orbital Symmetry*, Verlag Chemie, Weinheim, Germany, 1970.
4. K. M. Shumate, P. C. Neuman and G. J. Fonken, *J. Am. Chem. Soc*., **87**, 3996 (1965).
5. K. J. Hodgetts, S. T. Saengchantara, C. J. Wallis and T. W. Wallace, *Tetrahedron Lett*., **34**, 6321 (1993).
6. I. N. Nazarov, *Usp. Khim*., **18**, 377 (1949); *Chem. Abstr*., **45**, 6572 (1951).
7. I. N. Nazarov, *Usp. Khim*., **20**, 71 (1951); *Chem. Abstr*., **48**, 611 (1954).
8. Review: C. Santelli-Rouvier and M. Santelli, *Synthesis*, 429 (1983).
9. (a) S. E. Denmark and T. K. Jones, *J. Am. Chem. Soc*., **104**, 2642 (1982).
   (b) S. E. Denmark, K. L. Habermas, G. A. Hite and T. K. Jones, *Tetrahedron*, **42**, 2821 (1986).
10. G. T. Crisp, W. J. Scott and J. K. Stille, *J. Am. Chem. Soc*., **106**, 7500 (1984).
11. D. S. Glass, J. W. H. Watthey and S. Winstein, *Tetrahedron Lett*., 377 (1965).
12. E. N. Marvell, G. Caple and B. Schatz, *Tetrahedron Lett*., 385 (1965).
13. E. Vogel, W. Grimme and E. Dinne, *Tetrahedron Lett*., 391 (1965).
14. R. Huisgen, A. Dahmen and H. Huber, *J. Am. Chem. Soc*., **89**, 7130 (1967).
15. (a) K. Ziegler and K. Hafner, *Angew. Chem*., **67**, 301 (1955).
    (b) K. Hafner, *Justus Liebigs Ann. Chem*., **606**, 79 (1957).
16. H. Rösler and W. König, *Naturwissenschaften* **42**, 211 (1955).
17. P. S. Wharton and D. W. Johnson, *J. Org. Chem*., **38**, 4117 (1973).
18. E. Vedejs and A. Cammers-Goodwin, *J. Org. Chem*., **59**, 7541 (1994).
19. W. Oppolzer, *Angew. Chem., Int. Ed. Engl*., **16**, 10 (1977).
20. G. Brieger and J. N. Bennett, *Chem. Rev*., **80**, 63 (1980).
21. E. Ciganek, *Org. React.* (*N.Y.*), **32**, 1 (1984).
22. A. G. Fallis, *Can. J. Chem*., **62**, 183 (1984).
23. D. Craig, *Chem. Soc. Rev*., **16**, 187 (1987).
24. (a) F. Näf and G. Ohloff, *Helv. Chim. Acta*, **57**, 1868 (1974).
    (b) F. Näf, R. Decorzaht, W. Giersch and G. Ohloff, *Helv. Chim. Acta*, **64**, 1387 (1981).
25. S. R. Wilson and D. T. Mao, *J. Am. Chem. Soc*., **100**, 6289 (1978).
26. S. D. Burke, T. W. Powner and M. Kageyama, *Tetrahedron Lett*., **24**, 4532 (1983).
27. F. Näf, R. Decorzaht and W. Thommen, *Helv. Chim. Acta*, **65**, 2212 (1982).
28. B. M. Trost, *Acc. Chem. Res*., **23**, 34 (1990).
29. B. M. Trost and D. C. Lee, *J. Org. Chem*., **54**, 2271 (1989).
30. E. Wenkert and K. Naemura, *Synth. Commun*., **3**, 45 (1973).
31. O. P. Vig, I. R. Trehan and R. Kumar, *Ind. J. Chem*., **15B**, 319 (1977).
32. D. F. Taber and B. P. Gunn, *J. Am. Chem. Soc*., **101**, 3992 (1979).
33. J. L. Gras, *J. Org. Chem*., **46**, 3738 (1981).
34. W. R. Roush, A. P. Essenfeld and J. S. Warmus, *Tetrahedron Lett*., **28**, 2447 (1987).
35. S. F. Martin, S. A. Williamson, R. P. Gist and K. M. Smith, *J. Org. Chem*., **48**, 5170 (1983).
36. P. A. Grieco, J. P. Beck, S. T. Handy, N. Saito and J. F. Daeuble, *Tetrahedron Lett*., **35**, 6783 (1994).
37. Review: W. Oppolzer, *Synthesis*, 793 (1978).
38. (a) R. J. Spangler and B. G. Beckmann, *Tetrahedron Lett*., 2517 (1976).
    (b) R. J. Spangler, B. G. Beckmann and J. H. Kim, *J. Org. Chem*., **42**, 2989 (1977).
39. Y. Ito, M. Nakatsuka and T. Saegusa, *J. Am. Chem. Soc*., **102**, 863 (1980).
40. W. Oppolzer, D. A. Roberts and T. G. C. Bird, *Helv. Chim. Acta*, **62**, 2017 (1979).
41. K. C. Nicolaou, W. E. Barnette and P. Ma, *J. Org. Chem*., **45**, 1463 (1980).
42. T. Kametani, H. Matsumoto, H. Nemoto and K. Fukumoto, *Tetrahedron Lett*., 2425 (1978).
43. R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc*., **98**, 6755 (1976).
44. K. Alder, F. Pascher and A. Schmitz, *Chem. Ber*., **76**, 27 (1943).
45. For reviews sec: (a) H. M. R. Hoffmann, *Angew. Chem., Int. Ed. Engl*., **8**, 556 (1969).
    (b) G. V. Boyd, in S. Patai (Ed.), *The Chemistry of Functional Groups, Supplement A. The Chemistry of Double-bonded Functional Groups*, Vol. 2, Wiley, Chichester, 1989, p. 477.
46. Review: W. Oppolzer and V. Snieckus, *Angew. Chem., Int. Ed. Engl*., **17**, 476 (1978).
47. W. D. Huntsman, V. C. Solomon and D. Eros, *J. Am. Chem. Soc*., **80**, 5455 (1958).

48. W. D. Huntsman and R. P. Hall, *J. Org. Chem*., **27**, 1988 (1962).
49. W. D. Huntsman, P. C. Lang, N. L. Madison and D. A. Uhrick, *J. Org. Chem*., **27**, 1983 (1962).
50. (a) W. Oppolzer and F. Marazza, *Helv. Chim. Acta*, **64**, 1575 (1981).
    (b) W. Oppolzer and K. Bättig, *Helv. Chim. Acta*, **64**, 2489 (1981).
51. (a) W. Oppolzer and K. K. Mahalanabis, *Tetrahedron Lett*., 3411 (1975).
    (b) W. Oppolzer, K. K. Mahalanabis and K. Bättig, *Helv. Chim. Acta*, **60**, 2388 (1977).
52. L. F. Tietze and U. Beifuss, *Justus Liebigs Ann. Chem*., 321 (1988).
53. L. F. Tietze, U. Beifuss and M. Ruther, *J. Org. Chem*., **54**, 3120 (1989).
54. Review: H. Lehmkuhl, *Bull. Soc. Chim. Fr*., 87 (1981).
55. W. Oppolzer, R. Pitteloud and H. F. Strauss, *J. Am. Chem. Soc*., **104**, 6476 (1982).
56. W. Oppolzer and A. Nakao, *Tetrahedron Lett*., **27**, 5471 (1986).
57. W. Oppolzer and R. Pitteloud, *J. Am. Chem. Soc*., **104**, 6478 (1982).
58. W. Oppolzer, H. F. Strauss and D. P. Simmons, *Tetrahedron Lett*., **23**, 4673 (1982).
59. W. Oppolzer and J.-M. Gaudin, *Helv. Chim. Acta*, **70**, 1477 (1987).
60. D. P. Curran, *Synthesis*, 417 and 489 (1988).
61. C. -P. Chuang and T. H. J. Ngoi, *Tetrahedron Lett*., **30**, 6369 (1989).
62. R. Dowbenko, *Tetrahedron*, **20**, 1843 (1964).
63. L. Friedman, *J. Am. Chem. Soc*., **86**, 1885 (1964).
64. G. Stork and N. H. Baine, *J. Am. Chem. Soc*., **104**, 2321 (1982).
65. G. Stork and R. Mook, Jr., *Tetrahedron Lett*., **27**, 4529 (1986).
66. G. Stork and M. E. Reynolds, *J. Am. Chem. Soc*., **110**, 6911 (1988).
67. S. Hanessian and R. Léger, *J. Am. Chem. Soc*., **114**, 3115 (1992).
68. K. Miura, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn*., **66**, 2348 (1993).
69. Review: E. E. van Tamelen, *Acc. Chem. Res*., **8**, 152 (1974).
70. Review: W. S. Johnson, *Angew. Chem., Int. Ed. Engl*., **15**, 9 (1976).
71. Review: N. Gnonlonfoun, *Bull. Soc. Chim. Fr*., 862 (1988).
72. G. Ohloff, *Justus Liebigs Ann. Chem*., **606**, 100 (1957).
73. H. E. Ulery and J. H. Richards, *J. Am. Chem. Soc*., **86**, 3113 (1964).
74. J. A. Marshall and P. G. M. Wuts, *J. Org. Chem*., **42**, 1794 (1977).
75. J. L. Cooper and K. E. Harding, *Tetrahedron Lett*., 3321 (1977).
76. (a) N. H. Andersen and H. S. Uh, *Synth. Commun*., **3**, 125 (1973).
    (b) N. H. Andersen and H. S. Uh, *Tetrahedron Lett*., 207 (1973).
    (c) N. H. Andersen and F. A. Golec, Jr., *Tetrahedron Lett*., 3783 (1977).
77. P. M. McCurry, Jr., R. K. Singh and S. Link, *Tetrahedron Lett*., 1155 (1973).
78. H. Wolf and M. Kolleck, *Tetrahedron Lett*., 451 (1975).
79. P. Naegeli and R. Kaiser, *Tetrahedron Lett*., 2013 (1972).
80. S. Kanno, T. Kato and Y. Kitahara, *J. Chem. Soc., Chem. Commun*., 1257 (1967).
81. D. Nasipuzi and G. Das, *J. Chem. Soc., Perkin Trans. 1*, 2776 (1979).
82. D. L. J. Clive and G. Chittattu, *J. Chem. Soc., Chem. Commun*., 441 (1978)
83. A. Toshimitsu, S. Uemura and M. Okano, *J. Chem. Soc., Chem. Commun*., 87 (1982).
84. Y. Yamada, H. Sanjoh and K. Iguchi, *J. Chem. Soc., Chem. Commun*., 997 (1976).
85. Y. Yamada, H. Sanjoh and K. Iguchi, *Tetrahedron Lett*., 1323 (1979).
86. Y. Yamada, S. Nakamura, K. Iguchi and K. Hosaka, *Tetrahedron Lett*., **22**, 1355 (1981).
87. (a) W. S. Johnson, *Pure Appl. Chem*., **7**, 317 (1963).
    (b) W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques and J. K. Crandall, *J. Am. Chem. Soc*., **86**, 1959 (1964).
    (c) W. S. Johnson and J. K. Crandall, *J. Org. Chem*., **30**, 1785 (1965).
88. W. S. Johnson, D. M. Bailey, R. Owyang, R. A. Bell, B. Jacques and J. K. Crandall, *J. Am. Chem. Soc*., **86**, 2085 (1964).
89. W. S. Johnson, W. H. Lunn and K. Fitzi, *J. Am. Chem. Soc*., **86**, 1972 (1964).
90. J. A. Marshall, N. Cohen and A. R. Hochstettler, *J. Am. Chem. Soc*., **88**, 3408 (1966).
91. R. S. Brinkmeyer, *Tetrahedron Lett*., 207 (1979).
92. R. W. Skeean, G. L. Trammell and J. D. White, *Tetrahedron Lett*., 525 (1976).
93. W. S. Johnson and R. B. Kinnel, *J. Am. Chem. Soc*., **88**, 3861 (1966).
94. G. D. Abrams, W. R. Bartlett, V. A. Fung and W. S. Johnson, *Bioorg. Chem*., **1**, 243 (1971).
95. E. E. van Tamelen, G. M. Milne, M. I. Suffness, M. C. Rudler-Chauvin, R. J. Anderson and R. S. Achini, *J. Am. Chem. Soc*., **92**, 7202 (1970).
96. E. E. van Tamelen, M. Seiler and W. Wierenga, *J. Am. Chem. Soc*., **94**, 8229 (1972).

97. (a) W. S. Johnson, K. Wiedhaup, S. F. Brady and G. L. Olson, *J. Am. Chem. Soc*., **90**, 5277 (1968).
(b) W. S. Johnson, K. Wiedhaup, S. F. Brady and G. L. Olson, *J. Am. Chem. Soc*., **96**, 3979 (1974).
98. G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc*., **77**, 5068 (1955).
99. A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955).
100. T. A. Blumenkopf and L. E. Overman, *Chem. Rev*., **86**, 857 (1986).
101. G. Majetich, K. Hull, J. Defauw and R. Desmond, *Tetrahedron Lett*., **26**, 2747 (1985).
102. Review: D. Schinzer, *Synthesis*, 263 (1988).
103. G. Majetich, J. Defauw, K. Hull and T. Shawe, *Tetrahedron Lett*., **26**, 4711 (1985).
104. D. Schinzer, *Angew. Chem., Int. Ed. Engl*., **23**, 308 (1984).
105. D. Schinzer, J. Steffen and S. Sólyom, *J. Chem. Soc., Chem. Commun*., 829 (1986).
106. D. Schinzer, G. Dettmer, M. Ruppelt and S. Sólyom, *J. Org. Chem*., **53**, 3823 (1988).
107. G. Majetich, J. Defauw and C. Ringold, *J. Org. Chem*., **53**, 50 (1988).
108. A. R. Chamberlin, S. H. Bloom, L. A. Cervini and C. A. Fotsch, *J. Am. Chem. Soc*., **110**, 4788 (1988).
109. W. F. Bailey and K. Rossi, *J. Am. Chem. Soc*., **111**, 765 (1989).
110. T. Uyehara, N. Shida and Y. Yamamoto, *J. Chem. Soc., Chem. Commun*., 113 (1989).
111. M. D. Koppang, G. A. Ross, N. F. Woolsey and D. E. Bartak, *J. Am. Chem. Soc*., **108**, 1441 (1986).
112. P. W. Chum and S. E. Wilson, *Tetrahedron Lett*., 1257 (1976).
113. Review: E. Negishi, *Acc. Chem. Res*., **20**, 65 (1987).
114. J. P. Maye and E. Negishi, *Tetrahedron Lett*., **34**, 3359 (1993).
115. K. S. Knight, D. Wang, R. M. Waymouth and J. Ziller, *J. Am. Chem. Soc*., **116**, 1845 (1994).
116. K. S. Knight and R. M. Waymouth, *Organometallics*, **13**, 2575 (1994).
117. (a) W. A. Nugent and D. F. Taber, *J. Am. Chem. Soc*., **111**, 6435 (1989).
(b) F. E. McDonald and P. A. Wender, *Chemtracts: Org. Chem*., **3**, 42 (1990).
118. (a) R. Grigg, T. R. B. Mitchell and A. Ramasubbu, *J. Chem. Soc., Chem. Commun*., 669 (1979).
(b) R. Grigg, T. R. B. Mitchell and A. Ramasubbu, *J. Chem. Soc., Chem. Commun*., 27 (1980).
(c) R. Grigg, J. F. Malone, T. R. B. Mitchell, A. Ramasubbu and R. M. Scott, *J. Chem. Soc., Perkin Trans. 1*, 1745 (1984).
119. A. Heumann, M. Reglier and B. Waegell, *Angew. Chem., Int. Ed. Engl*., **18**, 866 (1979).
120. S. Yamago and E. Nakamura, *J. Chem. Soc., Chem. Commun*., 1112 (1988).
121. B. M. Trost and J. M. Tour, *J. Am. Chem. Soc*., **110**, 5231 (1988).
122. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc*., **115**, 3800 (1993).
123. (a) G. C. Fu, SB. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc*., **115**, 9856 (1993).
(b) J. E. Audia, *Chemtracts*: *Org. Chem*., **7**, 406 (1994).

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CHAPTER **12**

The effect of pressure on reactions of dienes and polyenes

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I. INTRODUCTION

Pressure in the range of 1–20 kbar (units of pressure: 1 kbar = 100 MPa = 0.1 GPa = 1013.25 atm) has a strong effect on rate and position of equilibrium of many chemical reactions. Processes accompanied by a decrease of volume are accelerated by pressure and the equilibria are shifted toward the side of products while those accompanied by an increase of volume are retarded and the equilibria are shifted toward the side of

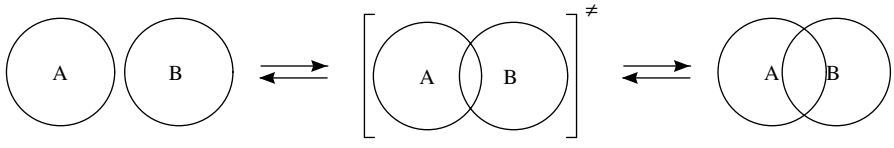
reactants. Therefore, the application of high pressure seems to be particularly useful in controlling the course of competitive and consecutive reactions and can lead to an improvement of chemo-, regio- and stereochemistry. In this chapter our major interest is focused on the effect of pressure on pericyclic reactions of dienes and polyenes in compressed liquid state or in compressed solution, including cycloadditions such as the most important Diels–Alder [4 + 2] cycloadditions of conjugated dienes, [2 + 2] cycloadditions of cumulated dienes, or higher cycloadditions involving trienes and tetraenes, as well as sigmatropic and electrocyclic rearrangements.

Processes with gaseous reactants are excluded here. Due to the large compressibility of gases an increase of pressure (up to 1 kbar) leads essentially only to an increase of gas concentration, and hence to an acceleration of bimolecular processes in which gases are involved as reactants. The effect of pressure on a chemical reaction in compressed solution is largely determined by the volume of reaction (ΔV) and the volume of activation ($\Delta V^{\neq}$). It is not the purpose of this chapter to provide a complete survey of reactions of dienes and polyenes which have been investigated at elevated pressures. There are many excellent monographs (e.g. References 1–4) and reviews (e.g. References 5–16) on this topic which cover the literature up to early 1990. After a short introduction into the basic concepts necessary to understand pressure effects on chemical processes in compressed solutions, our major objective is to review the literature of the past ten years.

II. VOLUME OF ACTIVATION AND REACTION

Static high pressure in the range of 1–20 kbar, frequently used for the investigation of organic reactions in compressed fluids or solids, can be generated with relatively simple devices[1,3]. A list of some suppliers delivering commercially available high-pressure equipment is cited[17]. Pressure influences the physical properties of matter such as boiling and melting point, density, viscosity, solubility, dielectric constant and conductivity. Before carrying out high-pressure experiments it is important to have some knowledge of these effects. The melting points of most liquids used as common solvents are raised by pressure (*ca* 15–20 °C per 1 kbar). Therefore it is necessary for a high-pressure experiment which is planned to be performed in solution, that a solvent is used which does not solidify under the chosen conditions. The solubility of gases in liquids is increased, and that of solids usually decreased, by raising the pressure. Therefore, the solid solutes of saturated solutions may precipitate during the generation of pressure and no longer be accessible for the reaction. The viscosity of liquids increases approximately twofold for each kilobar increase. Knowledge of this effect is particularly important for diffusion-controlled processes. Finally, the compressibility of liquids and solids is usually small compared to that of gases. For that reason experiments with compressed liquids and solids are far less dangerous than those with compressed gases. A detailed discussion of the pressure effect on physical properties of matter can be found in the literature[1].

The effect of pressure on chemical equilibria and rates of reactions can be described by the well-known equations resulting from the pressure dependence of the Gibbs enthalpy of reaction and activation, respectively, shown in Scheme 1. The volume of reaction (ΔV) corresponds to the difference between the partial molar volumes of reactants and products. Within the scope of transition state theory the volume of activation can be, accordingly, considered to be a measure of the partial molar volume of the transition state (TS) with respect to the partial molar volumes of the reactants. Volumes of reaction can be determined in three ways: (a) from the pressure dependence of the equilibrium constant (from the plot of $\ln K$ vs p); (b) from the measurement of partial molar volumes of all reactants and products derived from the densities, d, of the solution of each individual component measured at various concentrations, c, and extrapolation of the apparent molar volume Φ



Forward reaction: decrease of volume (ΔV, $\Delta V^{\neq} < 0$) ⇒ accelerated by pressure

Reverse reaction: increase of volume (ΔV, $\Delta V^{\neq} > 0$) ⇒ retarded by pressure

$$\Delta V = \left(\frac{\partial \Delta G}{\partial p}\right)_T = \left(\frac{-\partial \ln K_p}{\partial p}\right)_T \cdot RT \qquad \Delta V^{\neq} = \left(\frac{\partial \Delta G^{\neq}}{\partial p}\right)_T = \left(\frac{-\partial \ln k_p}{\partial p}\right)_T \cdot RT$$

ΔV, $\Delta V^{\neq}$: volumes of reactions and activation;
K_p: equilibrium constant at pressure p;
k_p: rate constant at pressure p;
ΔG, $\Delta G^{\neq}$: Gibbs enthalpy and Gibbs enthalpy of activation.

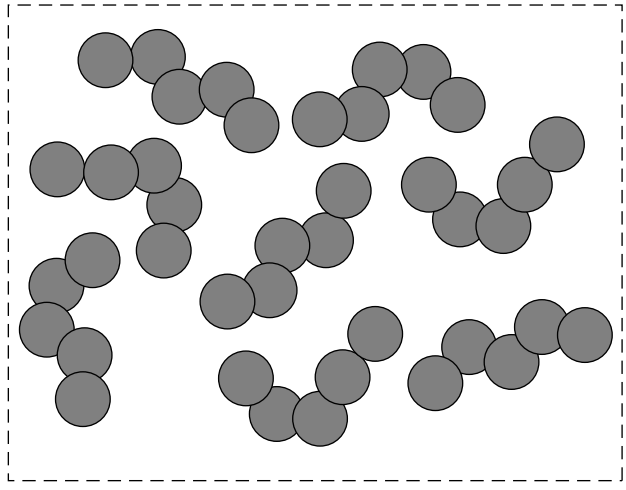
$$\Delta V = V(\mathrm{A-B}) - [V(\mathrm{A}) + V(\mathrm{B})]$$
$$\Delta V^{\neq} = V([\mathrm{A\text{-}\,-\,-\,-\,-\,B}]^{\neq}) - [V(\mathrm{A}) + V(\mathrm{B})]$$

SCHEME 1. Volumes of activation and reaction

vs c to $c = 0$. (Scheme 2); (c) from the direct measurement of the difference between the volumes of reactants and products employing dilatometry. To a first approximation the molar volume of neat liquid compounds ($V_M = M/d$) and, hence, the reaction volumes can be calculated with additive group increments which were derived empirically by Exner[18] for many groups such as CH_3, CH_2, or CH from the molar volumes, V_M, easily determined from the known densities for many different types of compounds. This method is comparable to that of the calculation of enthalpies of formation by the use of Franklin[19] or Benson[20] group increments. In all cases where the volume of reaction could be determined by at least two independent methods, the data were in good agreement[21].

Volumes of activation can be unambiguously determined only from the pressure dependence of the rate constants. Attempts to obtain volumes of activation from the correlation of rate constants with the solubility parameter δ[22] or the cohesive energy density parameter (ced)[23], which are related to the internal pressure of solvents, have not led to clear-cut results.

Volumes of activation and reaction are themselves also pressure-dependent as shown for the volume of activation in Figure 1. There is no theory explaining this pressure dependence which would allow the volume of activation or reaction to be determined over a larger range of pressure. Therefore, several empirical relations are employed to fit the pressure dependencies of rate and equilibrium constants[24] from which the least-squares fit [$\ln k(p) = a + b \cdot p$, $\ln k(p = 0) = a$, $\Delta V^{\neq} = -b \cdot R \cdot T$ or $\ln K(p) = a' + b' \cdot p$, $\ln K(p = 0) = a'$, $\Delta V = -b' \cdot RT$] is the simplest and in many cases also the most reliable method of computing $\Delta V^{\neq}$ and ΔV. It is only applicable in the low-pressure range (<2000 bar) where the dependencies of $\ln k(p)$ or $\ln K(p)$ on pressure p are usually linear. Thus, this method requires a very precise measurement of the rate constants at relatively low-pressures (1–2000 bar) where the pressure effect on the rate constants is relatively



V_W: van der Waals volume ($cm^3\,mol^{-1}$)
(intrinsic molar volume of ground and transition structures)

V_M: molar volume ($cm^3\,mol^{-1}$)
(empty space included) $V_M = \dfrac{M}{d}$

V: partial molar volume ($cm^3\,mol^{-1}$) $V = \lim\limits_{c \to 0} \Phi$ $\Phi = \dfrac{M}{d_0} - \dfrac{1}{c} \cdot \dfrac{d - d_0}{d_0}$

η: packing *coefficient* $\eta = \dfrac{V_W}{V_M}$

M ($g\,mol^{-1}$): molar mass of the solute
d ($g\,cm^{-3}$): density of the solution
d_0 ($g\,cm^{-3}$): density of the pure solvent
c (mol^{-1}): concentration of the solute

SCHEME 2. Van der Waals volumes, partial molar volumes and packing coefficients

small. If data over a larger pressure range are to be used, nonlinear least-squares fits have to be applied[24]. Due to the pressure dependence of $\Delta V^{\neq}$ and ΔV we need to select a pressure to which volumes of activation and reaction refer, so that the values can be compared with one another. The choice has universally been that of zero pressure ($p = 0$). The values of activation volumes calculated at $p = 0$ differ only by immeasurably small amounts from those at atmospheric pressure ($p \approx 1$ bar), so that comparison with the reaction volumes, calculated from the partial molar volumes of the reactants and products determined at atmospheric pressure, is feasible.

Processes accompanied by a decrease in volume, such as C−C bond formation, in which the distance between two carbon atoms decreases from the van der Waals distance of *ca* 3.6 Å to the bonding distance of *ca* 1.5 Å, are accelerated by raising the pressure and equilibria are shifted toward the side of products ($\Delta V^{\neq} < 0$, $\Delta V < 0$). The reverse reaction, a homolytic bond cleavage, leads to an increase in volume ($\Delta V^{\neq} > 0$, $\Delta V > 0$). Pressure induces a deceleration of such a process and a shift in equilibrium toward the side of reactants. However, in an ionization, such as an ionic dissociation, the attractive interaction between the ions generated and the solvent molecules leads to a contraction

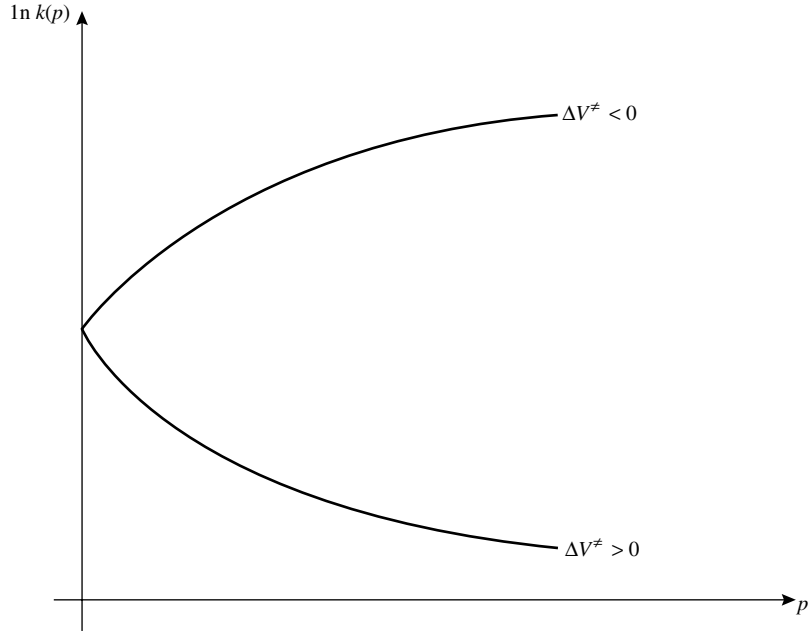


FIGURE 1. Nonlinear slope of the dependence between rate of reaction $\ln k(p)$ and pressure p

of the solvent cage, and hence of the volume, that is generally much stronger than the expansion of volume resulting from the bond dissociation. Thus, the overall dominant effect, called *electrostriction*, leads to negative volumes of activation and reaction ($\Delta V^{\neq} < 0$, $\Delta V < 0$). Neutralization of charges releases the molecules of the solvent cage, leading to positive volumes of activation and reaction ($\Delta V^{\neq} > 0$, $\Delta V > 0$). A similar but less pronounced trend due to the effect of *electrostriction* is observed for charge concentration and charge dispersal, respectively. An increase in steric crowding in the transition or product states results in a volume contraction ($\Delta V^{\neq} < 0$, $\Delta V < 0$). Finally, in the case of diffusion control the rate of reaction depends on the viscosity of the medium. As already pointed out, pressure induces an increase in the dynamic viscosity and, hence, a deceleration of diffusion-controlled processes ($\Delta V^{\neq} > 0$).

As noted earlier for the generation and neutralization of charges, the change in the intrinsic volumes of the reacting molecules is responsible for the overall change in molar volumes observed experimentally only to a minor extent. Similar conclusions can be drawn, e.g., for neutral pericyclic rearrangements, from the comparison of the volumes of activation and reaction determined experimentally with the change in the intrinsic volumes of the reacting molecules discussed in Section IV. The intrinsic volume of a ground or transition structure is defined by the space occupied by the atomic *van der Waals* spheres and can be obtained by numerical integration employing the atomic cartesian coordinates resulting from experimental data, molecular mechanics or quantum mechanical calculations and the *van der Waals* radii [e.g. $R_W(C) = 1.80$ Å, $R_W(H) = 1.17$ Å] derived from crystallographic data[25]. The intrinsic volumes of ground structures can also be calculated from tables of group contributions published by Bondi[26]. The *van der Waals* volume V_W is the intrinsic volume of a ground or transition structure multiplied by

Avogadro's number. The ratio V_W/V_M is defined as the packing coefficient η. The packing coefficients calculated from the V_W and V_M values of simple hydrocarbons[25a] are in the range $\eta = 0.5$ to 0.6. The empty space between the single molecules can be attributed to the so-called void volume and expansion volume required for the thermally induced motions and collisions of the molecules in the liquid state[27]. The importance of change in the packing coefficient and, hence, in the void and expansion volume for the effect of pressure on a reaction will be discussed in the following sections.

III. CYCLOADDITIONS

A. Intermolecular Diels–Alder Reactions

1. Mechanistic aspects

Many Diels–Alder [4 + 2] cycloadditions show a powerful pressure-induced acceleration, which is often turned to good synthetic purpose as discussed in Section III.A.2. Table 1 illustrates the effect of pressure on the Diels–Alder reaction of isoprene with acrylonitrile as a representative example. This reaction is accelerated by a factor of 1650 by raising the pressure from 1 bar to 10 kbar[28].

The activation volumes of many Diels–Alder reactions obtained from the pressure dependence of the rate constants are usually highly negative, $\Delta V^{\neq} \approx -25$ to -50 cm^3 mol^{-1} (Tables 2 and 3); sometimes they are even more negative than the corresponding reaction volumes. For a comparison between volumes of activation and reaction it is necessary to determine both data at the same temperature which is, however, not feasible in most cases. The measurement of pressure dependence of rate constants frequently requires a temperature different from that used for the determination of partial molar volumes of reactants and products (in general, room temperature). Therefore, activation volumes have to be extrapolated to room temperature or the reaction volumes, correspondingly, to the temperature of reaction. The measurement of the temperature dependence of activation volumes requires a large collection of experimental data. To the best of our knowledge only one case, the Diels–Alder dimerization of isoprene, has been reported in the literature[29]. With modern thermostated densimeters it is much easier to determine the temperature dependence of partial molar volumes, and hence of reaction volumes. From these data El'yanov and coworkers[30] extrapolated a generally applicable equation (equation 1) to describe the temperature dependence of activation and reaction volumes. The dependence determined for the isoprene dimerization[29] is in accord with the El'yanov equation.

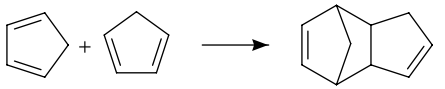
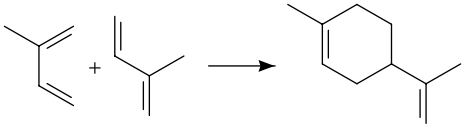
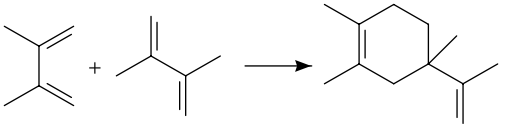
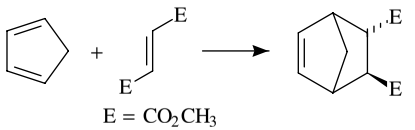
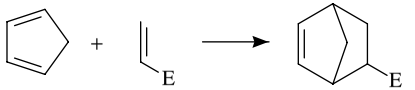
$$\Delta V^{\neq}_{25} = \Delta V^{\neq}_{T}/[1 + 4.43 \times 10^{-3}\ \mathrm{K}^{-1}(T - 25\,^{\circ}\mathrm{C})] \quad (1)$$

In Table 2 Diels–Alder reactions are complied showing ratios of activation volume to reaction volume that are smaller than or close to unity ($\Theta = \Delta V^{\neq}/\Delta V \leqslant 1$) and in Table 3 those that are close to or even larger than unity ($\Theta \geqslant 1$). Within the scope of transition state theory, the activation volume can be considered to be a measure of the partial molar volume of the transition state [$\Delta V^{\neq} = V^{\neq} - \Sigma V$ (reactants)]. Accordingly, the transition state volumes of these reactions are close to or even smaller than the

TABLE 1. Pressure-induced rate acceleration of the Diels–Alder reaction of isoprene with acrylonitrile at 21 °C ($\Delta V^{\neq} = -35.4$ cm^3 mol^{-1}, $\Delta V = -37.0$ cm^3 mol^{-1})[28]

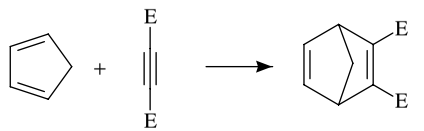
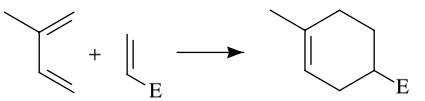
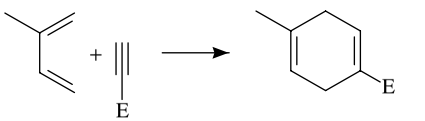
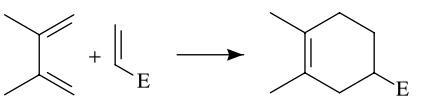
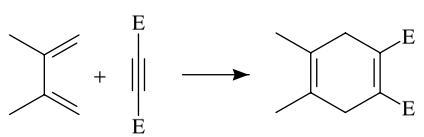
p (bar)	1000	1500	2000	3000	5000	8000	10 000
$k(p)/k$ (1 bar)	3.4	7.0	10.5	24.4	74.4	561	1650

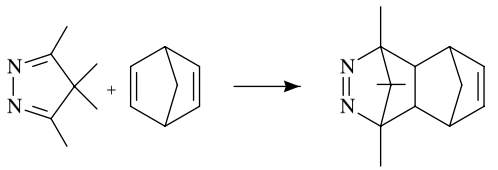
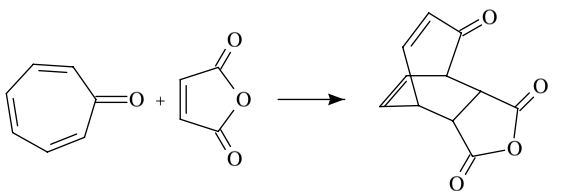
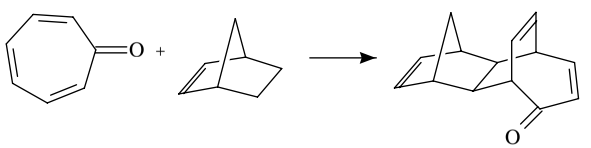
TABLE 2. Volume data of selected Diels–Alder reactions showing ($\Delta V^{\neq}$: ΔV) ratios smaller than unity ($\Theta < 1$)

	Reaction	Solvent	T(°C)	$\Delta V_T^{\neq a}$	$\Delta V_{25}^{\neq a}$	$\Delta V_{25}{}^{a}$	Θ^{b}	Reference
(1)		*n*-BuCl	40	−23.7	−22.2	−33.0	0.67	31
(2)			70	−42.0	−35.0	−47.8	0.73	32
(3)		*n*-BuBr	70	−33.0	−27.5	−44.9	0.61	33
(4)	 E = CO_2CH_3		30	−32.7	−32	−36.7	0.87	31
(5)		*n*-BuCl	40	−30.1	−28.3	−33.5	0.84	31

(*continued overleaf*)

TABLE 2. (*continued*)

	Reaction	Solvent	T(°C)	$\Delta V_T^{\neq a}$	$\Delta V_{25}^{\neq a}$	$\Delta V_{25}{}^a$	Θ^b	Reference
(6)		$MeCO_2Et$	10	−30.2	−32.2	−36.1	0.89	34
(7)		*n*-BuBr	25	−31.5	−31.5	−37	0.85	35
(8)		CH_2Cl_2	82	−43	−34.6	−39.5	0.88	36
(9)		*n*-BuCl	40	−30.2	−28.3	−34.7	0.82	31
(10)		*n*-BuCl	58	−39.1	−34.1	−38.8	0.88	36

(11)		MePh	130	−41.0	−28.0[c]	−28.8[c]	0.97	37
(12)		DMF	105	−16.8	−14.0[d]	−25.5[d]	0.55	38
(13)		*i*-PrPh	135	−30.0	−22.5[d]	−33.5[d]	0.67	38
		DMF	135	−27.8	−20.9[d]	−32.1[d]	0.65	

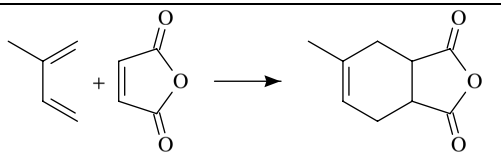
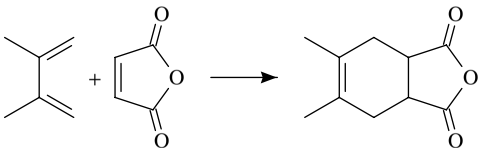
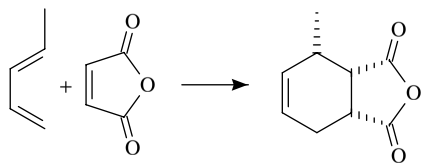
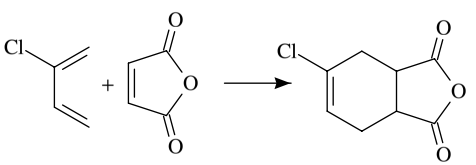
[a] In $cm^3\ mol^{-1}$; $\Delta V_T^{\neq}$ determined from the pressure dependence of the rate constant at temperature T; $\Delta V_{25}^{\neq}$ determined from the temperature dependence of the activation volumes (entry 2) or generally extrapolated by using equation 1.

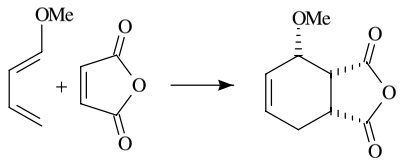
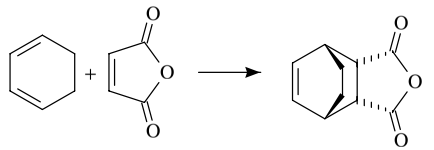
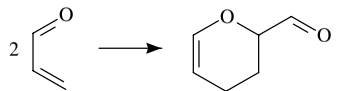
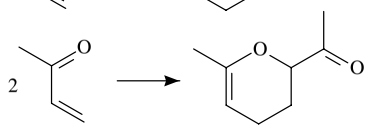
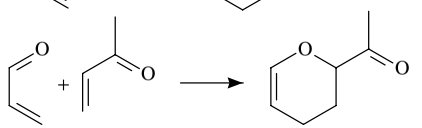
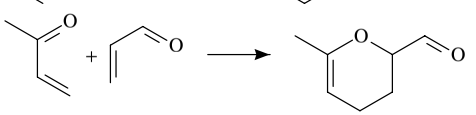
[b] $\Theta = \Delta V_{25}^{\neq} : \Delta V_{25}$.

[c] At 20 °C.

[d] At 60 °C.

TABLE 3. Volume data of selected Diels–Alder reactions showing ($\Delta V^{\neq}$: ΔV) ratios equal to or larger than unity ($\Theta > 1$)

	Reaction	Solvent	T(°C)	$\Delta V_T^{\neq a}$	$\Delta V_{25}^{\neq a}$	$\Delta V_{25}{}^a$	Θ^b	Reference
(1)		$(i\text{-Pr})_2O$		−38.5	−36.9	−38.3	0.96	
		Me_2CO		−39.0	−37.3	−35.9	1.04	
		MeCN		−37.5	−35.9	−34.5	1.04	
		n-BuCl	35	−38.0	−36.4			39
		AcOEt		−37.4	−35.8	−36.8	0.97	
		$ClCH_2CH_2Cl$		−37.0	−35.4	−35.5	0.99	
		CH_2Cl_2		−39.8	−38.1	−33.4	1.14	
(2)		*n*-BuCl	30	−41.3	−40.4	−35.5	1.14	31
(3)		*n*-BuCl	35	−44.7	−42.8	−31.9	1.22	31
(4)		MeCN	65	−41.6	−35.3	−36.9	0.96	31

(5)		MeCN		−32.0	−30.6	−32.4	0.94	
		$(MeO)_2CH_2$		−53.6	−51.3	−32.2	1.6	
		n-BuCl	35	−45.4	−43.5	−35.5	1.23	40
		$MeNO_2$		−43.7	−41.2	−28.2	1.46	
		$ClCH_2CH_2Cl$		−43.7	−41.8	−30.4	1.37	
(6)		CH_2Cl_2	35	−37.2	−35.6			41
(7)		*n*-C_7H_{16}	70	−37.0	−30.8	−28.6	1.08	42
(8)		*n*-C_7H_{16}	70	−41.0	−34.2	−32.3	1.06	42
(9)		*n*-C_7H_{16}	70	−36.5	−30.4			42
(10)		*n*-C_7H_{16}	70	−35.0	−29.2	−29.7	0.98	42

[a] In $cm^3\ mol^{-1}$; $\Delta V_T^{\neq}$ determined from the pressure dependence of the rate constant at temperature T; $\Delta V_{25}^{\neq}$ extrapolated by using equation 1.

[b] $\Theta = \Delta V_{25}^{\neq} : \Delta V_{25}$.

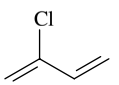
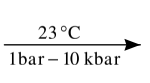
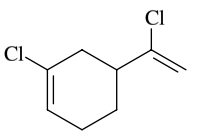
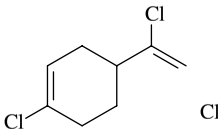
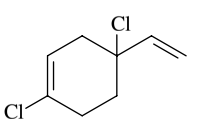
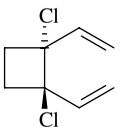
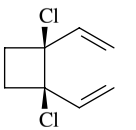
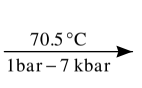
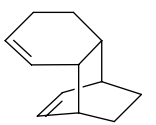
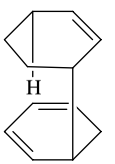
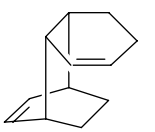
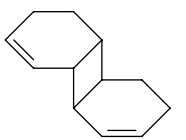
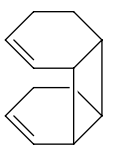
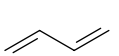
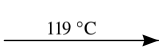
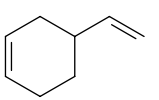
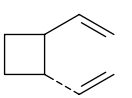
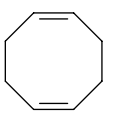
corresponding product volumes. The surprising result, that in some Diels–Alder reactions the transition state is smaller in volume than the product, could be confirmed by the *retro*-Diels–Alder reactions of the furan-acrylonitrile[43] and *N*-benzoylpyrrole-*N*-phenylmaleic imide[44] [4 + 2] cycloadducts which are both accelerated by pressure, having therefore negative volumes of activation ($\Delta V^{\neq} = -2.0$ and -8.3 cm^3 mol^{-1}, respectively). The *retro*-Diels–Alder reaction of dihydrobarrelene (bicyclo[2.2.0]octa-2,5-diene) leading to benzene and ethene is, however, retarded by pressure ($\Delta V^{\neq} = +3.1$ cm^3 mol^{-1})[45].

The finding that in several Diels–Alder reactions the transition state volume is smaller than the product volume is not well understood, and seems to contradict the generally accepted relation between molecular structure and its volume. In the transition state the new bonds between diene and dienophile are only partially formed (according to quantum mechanical calculations, the distance of the newly forming σ bonds in the transition state is in the range between 2.1 and 2.3 Å[46]). Therefore, the van der Waals volumes of the transition states are calculated to be generally larger than those of the products (*vide infra*). Eckert and coworkers[47] gave two explanations for the ratio $\Theta = \Delta V^{\neq}/\Delta V > 1$ in the Diels–Alder reactions with maleic anhydride as dienophile: viz. a larger dipole moment and secondary orbital interactions[48] in the transition state which can only occur in the transition states of *endo*-Diels–Alder reactions. The dipole moment of the transition state in the reaction of isoprene with maleic anhydride (entry 1 in Table 3) was estimated to be 1.6 Debye larger than that of maleic anhydride, but almost equal to that of the product. Thus, the effect of *electrostriction* should be operative to a similar extent in the transition state and product and may not explain the observed difference between $\Delta V^{\neq}$ and ΔV. Therefore, the authors concluded that secondary orbital interactions must be the primary reason for the more negative activation volume. But Seguchi, Sera and Maruyama[49] observed a very small difference between the activation volumes of *endo*- and *exo*-Diels–Alder reactions (e.g. reaction of 1,3-cyclopentadiene with dimethyl maleate: $\delta\Delta V^{\neq} = \Delta V^{\neq}(endo) - \Delta V^{\neq}(exo) = 0.8$ cm^3 mol^{-1}). This finding seems to rule out that secondary orbital interactions are important and induce a large contraction of the transition state volume in the *endo* reaction. Therefore, this issue remains unresolved. As we shall discuss later, the molecular packing of the entire ensemble consisting of solute and solvent molecules and its reorganization during the course of reaction are most important for the magnitude of activation and reaction volume. An effective packing of molecules around the globular transition state (which may also be due to restricted vibrations and rotations) may contribute to the observed differences between $\Delta V^{\neq}$ and ΔV of the Diels–Alder reactions listed in Table 3.

The observation that the transition state volumes in many Diels–Alder reactions are product-like, has been regarded as an indication of a concerted mechanism. In order to test this hypothesis and to gain further insight into the often more complex mechanism of Diels–Alder reactions, the effect of pressure on competing [4 + 2] and [2 + 2] or [4 + 4] cycloadditions has been investigated. In competitive reactions the difference between the activation volumes, and hence the transition state volumes, is derived directly from the pressure dependence of the product ratio, $[4 + 2]/[2 + 2]_p = [4 + 2]/[2 + 2]_{p=1} \cdot \exp\{-\delta\Delta V^{\neq} \cdot (p - 1)/\mathrm{RT}\}$. All [2 + 2] or [4 + 4] cycloadditions listed in Tables 3 and 4 doubtlessly occur in two steps via diradical intermediates and can therefore be used as internal standards of activation volumes expected for stepwise processes. Thus, a relatively simple measurement of the pressure dependence of the product ratio can give important information about the mechanism of Diels–Alder reactions.

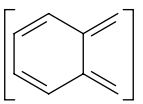
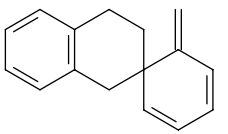
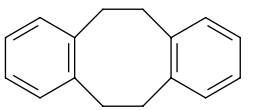
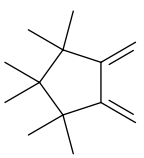
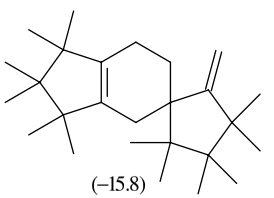
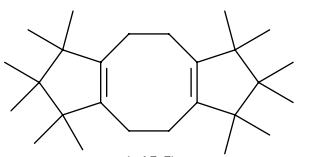
In the thermal dimerization of chloroprene **1** (Table 4, entry 1) the activation volumes for two [4 + 2] cycloadditions leading to **2** and **3** were found to be smaller (more negative) than those of the third [4 + 2] and the [2 + 2] cycloadditions leading to **4**, **5** and **6**, respectively. Stewart[50] explained these results in terms of concerted Diels–Alder

TABLE 4. Activation volumes $\Delta V^{\neq}$ ($cm^3\ mol^{-1}$), given in parentheses, and differences in activation volumes $\delta\Delta V^{\neq}[= \Delta V^{\neq}(4+2) - \Delta V^{\neq}(2+2)]$ ($cm^3\ mol^{-1}$) of competing [4 + 2] and [2 + 2] or [4 + 4] cyclodimerizations

Reaction	[4+2] Cycloadducts ($\Delta V^{\neq}$)	[2+2] or [4+4] Cycloadducts ($\Delta V^{\neq}$)	$\delta\Delta V^{\neq}$	Reference
(1) 2  **(1)**  23 °C, 1 bar – 10 kbar	 **(2)** (–31);  **(3)** (–29);  **(4)** (–22)	 **(5)** (–22);  **(6)** (–22)	–9 –7 0	50
(2) 2  **(7)**  70.5 °C, 1 bar – 7 kbar	 **(8)** (–28);  **(9)**[a] (–32);  **(10)** (–22)	 **(11)** (–18);  **(12)** (–22)	–10[b] –14[c] 0[d]	51
(3) 2  **(13)**  119 °C, 600 – 5300 bar	 **(14)** (–38.4)	 **(15)** (–20.9);  **(16)** (–34.0)	–17.5[e] –4.4[f]	52

(*continued overleaf*)

TABLE 4. (*continued*)

Reaction	[4+2] Cycloadducts ($\Delta V^{\neq}$)	[2+2] or [4+4] Cycloadducts ($\Delta V^{\neq}$)	$\delta\Delta V^{\neq}$	Reference
(4) 2  80 °C, 1–6800 bar			–5	53
(5) 2  79.1°C, 550–9300 bar	 (–15.8)	 (–15.5)	–0.3	54

[a] [6 + 4]-Ene reaction.
[b] $\Delta V^{\neq}$(**8**) − $\Delta V^{\neq}$(**11**).
[c] $\Delta V^{\neq}$(**9**) − $\Delta V^{\neq}$(**11**).
[d] $\Delta V^{\neq}$(**10**) − $\Delta V^{\neq}$(**12**).
[e] $\Delta V^{\neq}$(**14**) − $\Delta V^{\neq}$(**15**).
[f] $\Delta V^{\neq}$(**14**) − $\Delta V^{\neq}$(**16**).

reactions competing with stepwise [2 + 2] cycloadditions. According to its larger (less negative) activation volume, the third Diels–Alder dimer **4** should be also formed in nonconcerted fashion. Similarly, it can be concluded from the pressure dependence of the 1,3-cyclohexadiene dimerization (Table 4, entry 2) that the *endo*-Diels–Alder dimer **8** and the [6+4]ene product **9** are formed concertedly while the *exo*-Diels–Alder adduct **10** and [2+2] cyclodimers **11** and **12** arise via diradical intermediates. According to the activation volume data, the Diels–Alder dimerization of 1,3-butadiene and *o*-quinodimethane (Table 4, entries 3 and 4, respectively) also fall into the class of concerted processes while the [4 + 2] cyclodimerization of hexamethyl bis(methylene)cyclopentane (entry 5) seems to occur in a stepwise fashion. In Table 5 only the Diels–Alder reaction of 1,3-butadiene with α-acetoxyacrylonitrile (entry 1) seems to proceed concertedly while all other Diels–Alder adducts and *homo*-Diels–Alder adducts are probably formed in stepwise processes comparable to the corresponding competitive [2 + 2] cycloadditions. Stereochemical investigations of the chloroprene and 1,3-butadiene dimerization[52] with specifically deuteriated derivatives [(*E*)-1-deuteriochloroprene and (*Z*, *Z*)-1,4-dideuterio-1,3-butadiene] confirm the conclusions drawn from the activation volumes. As suggested by the activation volumes, the nonstereospecific course of the [4 + 2] dimerization of (*E*)-1-deuteriochloroprene leading to deuteriated **4** provides clear-cut evidence that this reaction proceeds in a stepwise fashion, while the almost stereospecific course of the [4 + 2] dimerization of (*Z*, *Z*)-1,4-dideuterio-1,3-butadiene provides good evidence for a predominant concerted mechanism in competition with a small amount of stepwise reaction, which can be almost completely suppressed by high pressure.

One question that needs to be addressed is: why are the activation volumes of pericyclic reactions smaller (more negative) than those of the corresponding stepwise reactions? In the past it was assumed that the simultaneous formation of two new σ bonds in a pericyclic [4 + 2] cycloaddition leads to a larger contraction of volume than the formation of one bond in the rate-determining transition state of a stepwise process. The interpretation presented[52] is limited by the scope of the Eyring transition state theory where the activation volume is related to the transition state volume, as mentioned above, and does not incorporate dynamic effects related to pressure-induced changes in viscosity[63a,b]. In a very recent study of the pressure effects on the thermal *Z*/*E* isomerization of substituted azobenzenes and *N*-benzylideneanilines in a viscous solvent, T. Asano and coworkers[63c] found that the pressure effects observed in the lower pressure region ($p \leqslant 2$ kbar) were in accordance with transition state theory. At higher pressure, however, the effects of the further increasing viscosity become predominant and all reactions (also those which were first accelerated by an increase of pressure) were retarded.

For the pericyclic and stepwise cycloadditions of ethene to 1,3-butadiene (the prototype of Diels–Alder reactions) the van der Waals volumes V_W of ground and transition structures shown in Table 6 were calculated following the method of Nakahara and coworkers[25a] and compared with the corresponding molar volumes *V* in order to uncover the effect of the different bonding on the volumes of transition states. The packing coefficient η, defined as the ratio V_W/V of cyclohexene, is significantly larger than those of the three isomeric hexadienes. Generally, η is found to be larger for cyclic compounds than for the corresponding acyclic ones.

From the data listed in Table 6 the *van der Waals* volume of the Diels–Alder reaction[13,25,52,65] can be calculated to be with $\Delta V_W = -11.2$ cm^3 mol^{-1} only roughly one-quarter of the experimentally accessible volume of reaction ($\Delta V = -41.7$ cm^3 mol^{-1}) (Scheme 3). Consequently, a significant part of the observed ΔV results from the higher packing of the cyclic product (compared to the acyclic reactants) rather than from the changes in bonding. The difference between the *van der Waals* volume of activation calculated for the pericyclic and stepwise reaction is small ($\delta\Delta V_W^{\neq} = -1.7$ cm^3 mol^{-1}) and is inconsistent with the experimental data listed in Tables 4 and 5. In order to explain

TABLE 5. Activation volumes $\Delta V^{\neq}$ ($cm^3\,mol^{-1}$), given in parentheses, and differences in activation volumes $\delta\Delta V^{\neq}$ ($cm^3\,mol^{-1}$) of competing [4 + 2] and [2 + 2] cycloadditions

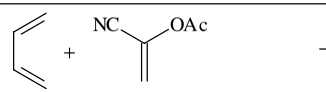
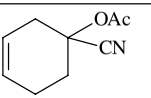
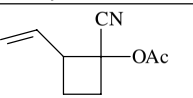
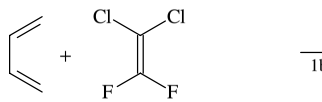
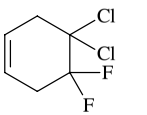
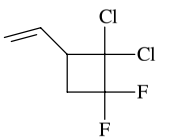
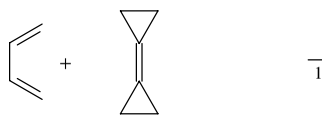
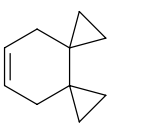
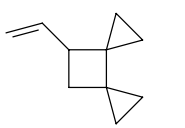
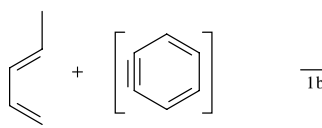
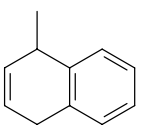
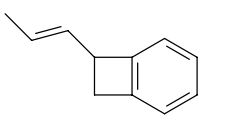
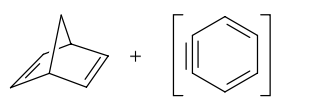
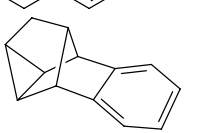
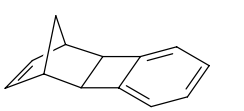
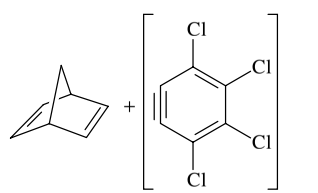
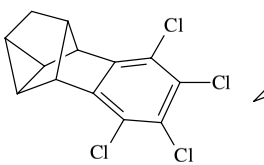
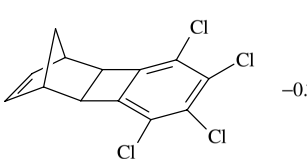
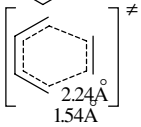
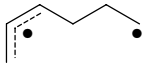
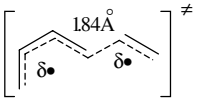
Reaction	[4+2] Cycloadducts	[2+2] or [4+4] Cycloadducts	$\delta\Delta V^{\neq}$	Reference
(1) 			–11.5	55,56
(2) 			0	56,57
(3) 			–2	58,59
(4) 			0	59,60
(5) 			0	59,61
(6) 			–0.7	62

TABLE 6. Comparison between molar volumes V, van der Waals volumes V_w ($cm^3\,mol^{-1}$) and packing coefficients η for selected examples of acyclic and cyclic ground and transition states

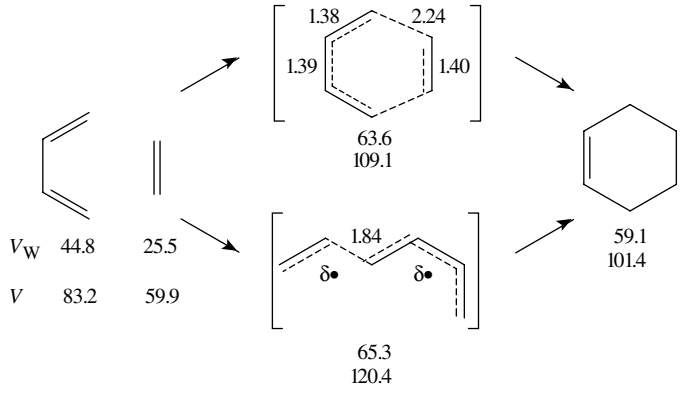
Compound	d	$V = M/d^a$	$V_w^{a,b}$	$\eta = V_w/V$
$CH_2{=}CH_2$		59.9[c]	25.5	0.4257
$CH_2{=}CH{-}CH{=}CH_2$		83.2[c]	44.8	0.5385
$CH_2{=}CH{-}CH_2{-}CH_2{-}CH{=}CH_2$	0.6880	119.4	63.9	0.5354
$CH_2{=}CH{-}CH_2{-}CH{=}CH{-}CH_3$	0.7000	117.7	63.9	0.5443
$CH_2{=}CH{-}CH{=}CH{-}CH_2{-}CH_3$	0.7050	116.5	63.8	0.5475
	0.8102	101.4	59.1	0.5829
		109.1[d]	63.8	0.5829
		118.7[e]	64.4	
		120.4[e]	65.3	0.5424

[a] In $cm^3\,mol^{-1}$.
[b] For the calculation of van der Waals volumes, cartesian coordinates resulting for ground structures from molecular mechanics calculations[64a] and for transition structures from *ab initio* calculations[64b] and the following van der Waals radii were used: $R_w(H) = 1.17$ Å; $R_w(C) = 1.80$ Å.
[c] Calculated with volume increments[18].
[d] With the packing coefficient of cyclohexene ($\eta = 0.5829$).
[e] Calculated with the average of the packing coefficients determined for the three isomeric hexadienes ($\eta = 0.5424$).

the finding that the activation volume of a pericyclic reaction is significantly more negative than that of the corresponding stepwise process, it has been assumed[13,52] that the packing coefficient of the pericyclic transition state is similar to that of the cyclic product, and therefore larger than the packing coefficient of the acyclic transition state of the stepwise process. The difference between the activation volumes calculated by using the packing coefficients of cyclohexene and the average of the three hexadienes (Table 6) for the transition states of the pericyclic and stepwise Diels–Alder reactions, respectively, is with $\delta\Delta V^{\neq} = -11$ $cm^3\,mol^{-1}$ (Scheme 3) well in accord with the experimental findings (Tables 4 and 5). Therefore, the analysis of activation volumes seems to provide important information regarding whether the geometry of a transition state is cyclic or acyclic. The conclusions drawn from this simple analysis are strongly supported by Monte Carlo simulations resulting in activation and reaction volumes for the Diels–Alder reaction of ethene with 1,3-butadiene and the dimerization of 1,3-butadiene[52]. The analysis of packing coefficients also explains why pericyclic rearrangements are accelerated by pressure showing negative volumes of activation (see below).

2. Synthetic application

The powerful pressure-induced acceleration of most Diels–Alder reactions due to their highly negative volumes of activation has been exploited for synthetic purposes. Reviews



$$\Delta V_W = 59.1 - (44.8 + 25.5) = -11.2 \text{ cm}^3 \text{ mol}^{-1}$$
$$\Delta V_W^{\neq} = 63.6 - (44.8 + 25.5) = -6.7 \text{ cm}^3 \text{ mol}^{-1} \text{ (pericyclic process)}$$
$$\Delta V_W^{\neq} = 65.3 - (44.8 + 25.5) = -5.0 \text{ cm}^3 \text{ mol}^{-1} \text{ (diradical process)}$$
$$\delta\Delta V_W^{\neq} = -1.7 \text{ cm}^3 \text{ mol}^{-1}$$

$$\Delta V = 101.4 - (83.2 + 59.9) = -41.7 \text{ cm}^3 \text{ mol}^{-1}$$
$$\Delta V^{\neq} = 109.1 - (83.2 + 59.9) = -34.0 \text{ cm}^3 \text{ mol}^{-1} \text{ (pericyclic process)}$$
$$\Delta V^{\neq} = 120.4 - (83.2 + 59.9) = -22.7 \text{ cm}^3 \text{ mol}^{-1} \text{ (diradical process)}$$
$$\delta\Delta V_W^{\neq} = -11.3 \text{ cm}^3 \text{ mol}^{-1}$$

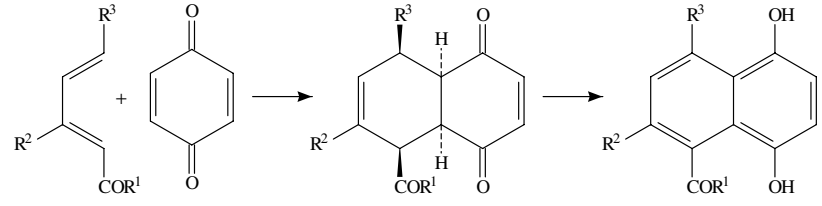
SCHEME 3. Comparison of van der Waals volumes of reaction and activation with the volumes of reaction and activation calculated for a pericyclic and stepwise Diels–Alder reaction of 1,3-butadiene with ethene

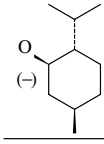
on the synthetic application of pressure-induced Diels–Alder reactions can be found in Chapter 11 on Synthesis by J. Jurczak in Reference 2, in Chapters 9 and 10 by T. Ibata on Diels–Alder reactions of alicyclic and acyclic dienes and of heterocyclic dienes, respectively, in Reference 3 and in References 9 and 11. In this chapter we only survey the more recent literature.

At atmospheric pressure the Diels–Alder adducts of 1,4-benzoquinones are often not stable under the conditions of reaction and undergo an isomerization leading to the corresponding hydroquinones (Scheme 4). Due to the acceleration at high pressure the temperature of reaction can be lowered so that the secondary isomerization does not proceed and the primary Diels–Alder adduct can be isolated in good yields. The diastereoselectivity at high pressure induced by a chiral auxiliary, however, is with a diastereomeric excess of d.e. = 36%, only moderate.

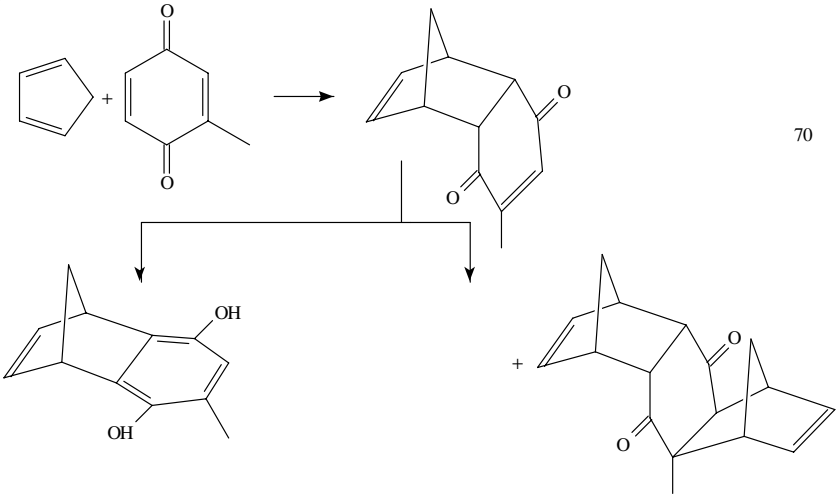
Diels–Alder reactions with acyclic and carbocyclic dienes are compiled in Scheme 5. The comparison between the Lewis-acid catalyzed and pressure-induced reaction (entry 1) shows that the application of high pressure, particularly in acid-sensitive systems, can sometimes lead to a better yield. Furthermore, pressure may shift the product ratio, if the activation volumes of the competing reactions are different, so that the application of pressure may also be useful in highly reactive systems, e.g. the reactive indenone **17** as dienophile, provided that a shift in the product ratio is desired. At atmospheric

(1)



R^1	R^2	R^3		Yield		Reference
OMe	Et	H	1 bar, 80 °C, 65 h	–	only product to be isolated	66
			15 kbar, 20 °C, 3 h	60%		67, 68
OEt	H	CH_2OSiMe_3	15 kbar, 20 °C, 65 h	84%		
OEt	H	Me	1 bar, 80 °C, 24 h	no reaction		67, 68
			15 kbar, 20 °C, 18 h	92%		
 (–)	H	H	15 kbar, 20 °C, 22 h	58%; d.e. 36%		69

(2)



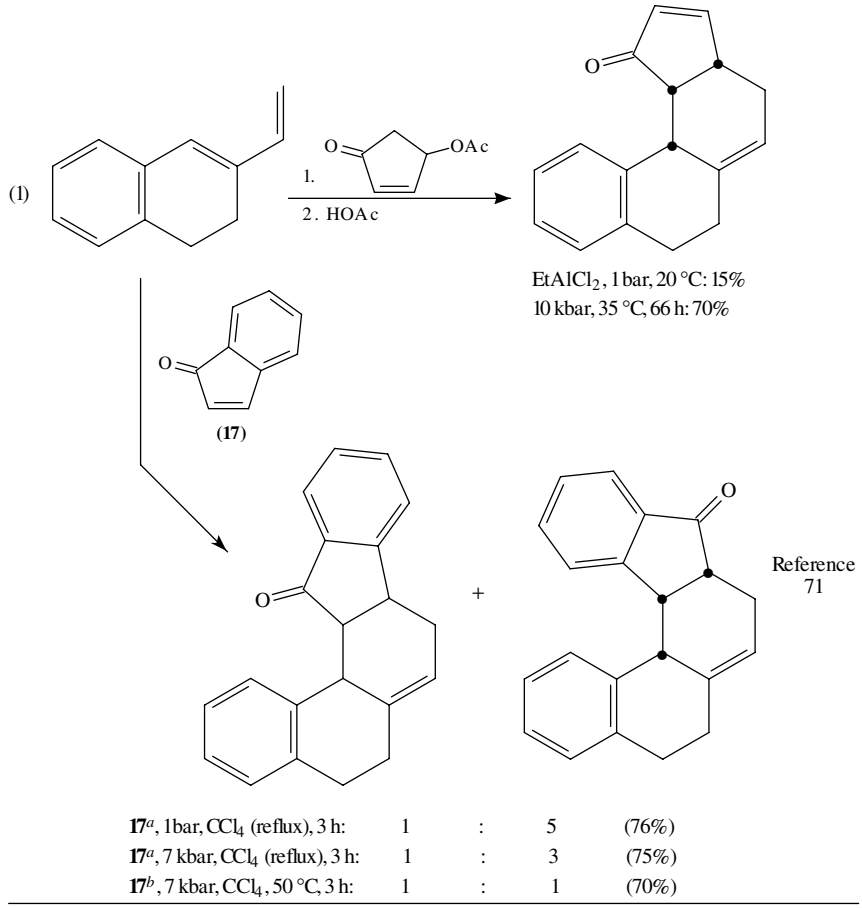
70

7-8 kbar, 75-80 °C;	4	:	1
1bar, 75-80 °C;	no bisadducts		

SCHEME 4. Diels–Alder reactions with 1,4-benzoquinones as dienophiles

pressure and 130 °C the Danishefsky diene[79] reacts with the polyfunctional dienophile (entry 2) in the fashion of a *hetero*-Diels–Alder reaction leading, after elimination of methanol during the work-up, to dihydropyrones as major products. At 10 kbar a reaction, leading, however, to a carbocyclic adduct, proceeds readily at room temperature. The example in entry 2 illustrates that pressure can be an important tool to control selectivity

in competitive processes. The next example in entry 3 shows that this can also be the case for consecutive reactions. Cyanoacetylene is only a moderate dienophile reacting, for example, with 1,3-cyclohexadiene only at a temperature of *ca* 100 °C at which the primary Diels–Alder adduct is thermally not stable and undergoes a *retro*-Diels–Alder reaction, producing benzonitrile and ethene. At high pressure the reaction occurs already at lower temperatures. Under these conditions the primary adduct is stable and can be isolated in good yields. A similar effect of pressure was observed in the thermal trimerization of cyanoacetylene producing 1,2,4- and 1,2,3-tricyanobenzene as major products at 160 °C and atmospheric pressure[80]. At 12 kbar the trimerization occurs already at 40 °C, leading to the thermally labile 2,3,5-tricyano-Dewar benzene as major product which isomerizes to 1,2,4-tricyanobenzene upon heating to a temperature ⩾50 °C. The high-pressure results are good evidence that the thermal trimerization of cyanoacetylene occurs by a sequence of reactions consisting of a [2 + 2] cycloaddition (producing the

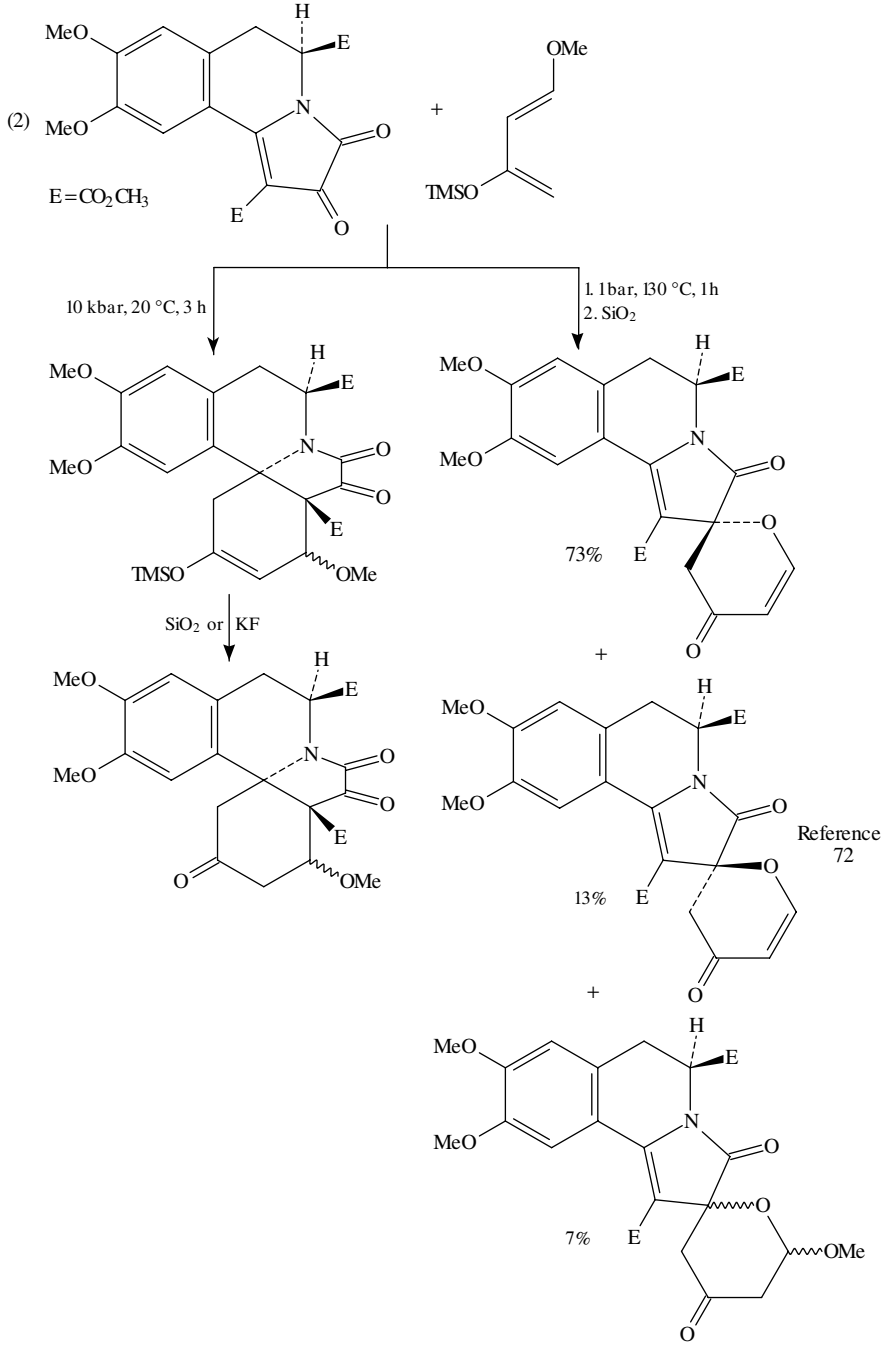


17[a], 1 bar, CCl_4 (reflux), 3 h:	1	:	5	(76%)
17[a], 7 kbar, CCl_4 (reflux), 3 h:	1	:	3	(75%)
17[b], 7 kbar, CCl_4, 50 °C, 3 h:	1	:	1	(70%)

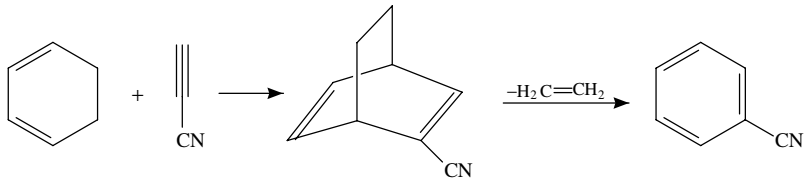
[a] Generated in situ from 2-bromindanone and Et_3N.

[b] Isolated **17** as starting material.

SCHEME 5. Diels–Alder reactions with acyclic and carboxyclic dienes

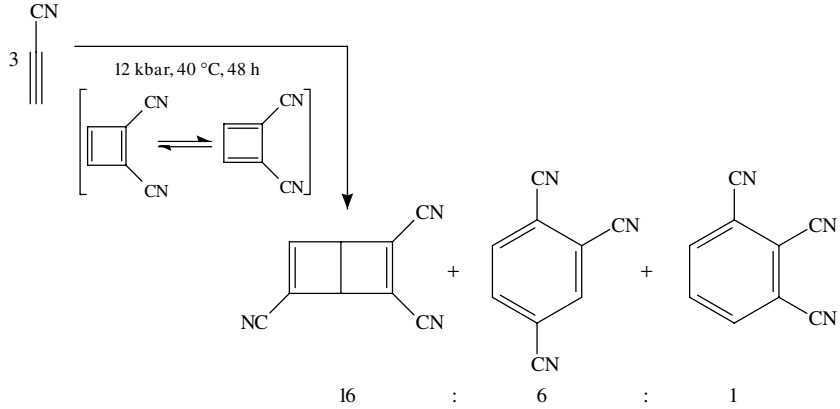


SCHEME 5. (*continued*)



1 bar, 100 °C, 24 h: 6% 68%
9.4 kbar, 50 °C, 24 h: 87% 0%

(3) Reference 73



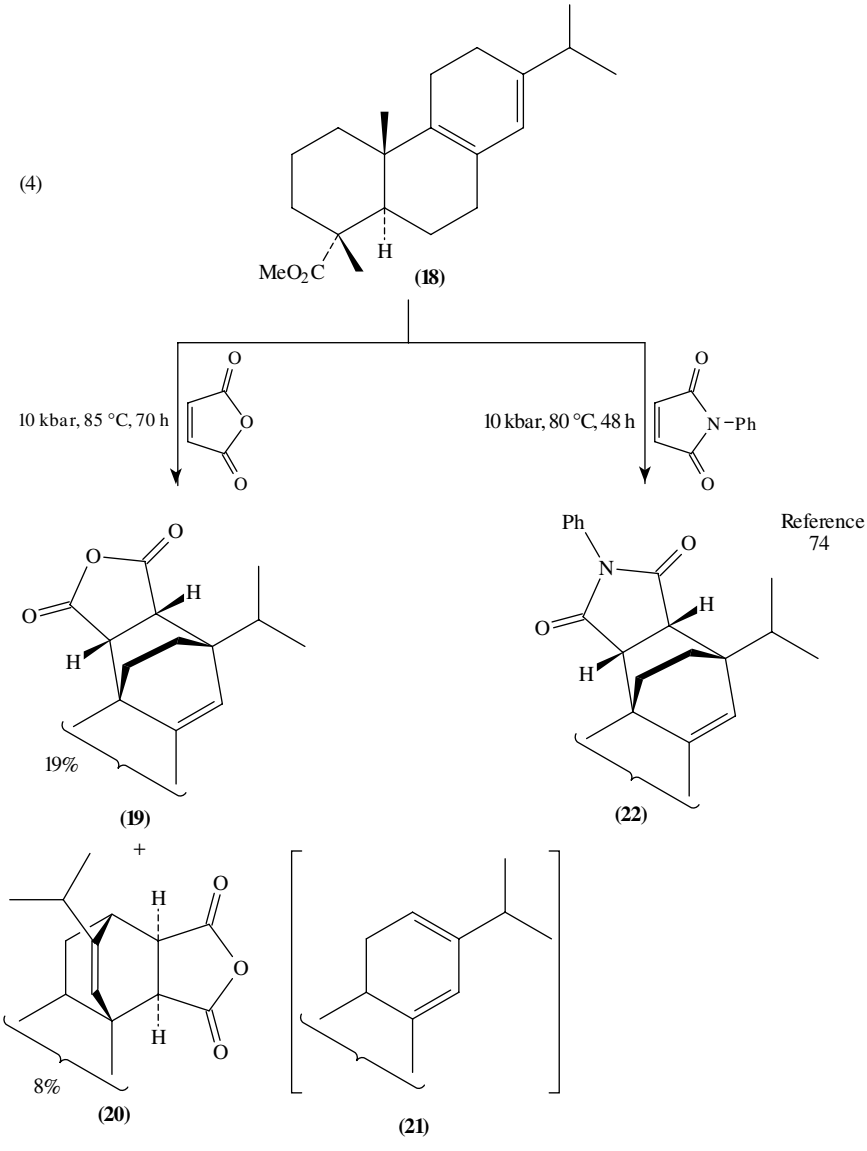
16 : 6 : 1

SCHEME 5. (*continued*)

highly reactive 1,2-dicyanocyclobutadiene), a Diels–Alder reaction of the cyclobutadiene intermediate with an excess of cyanoacetylene (leading to Dewar benzenes like the isolated 2,3,5-tricyano derivative) and an aromatization of Dewar benzenes yvia orbital symmetry-forbidden electrocyclic ring-opening.

The partially hydrogenated phenanthrene derivative **18** (entry 4) is a very moderate diene due to the steric crowding caused by the substituents and the anulated rings, and it reacts even with highly reactive dienophiles such as maleic anhydride (MA) or N-phenylmaleic imide only at high pressure. The minor product **20** in the reaction with MA obviously stems from diene **21**. This can be explained by a double-bond isomerization **18** → **21** prior to the cycloaddition, certainly catalyzed by traces of acid present in the MA. In the absence of acid only the Diels–Alder adduct **22** derived from diene **18** was observed. In the reaction of diene **23** with MA (entry 5) a similar sequence of steps was observed. A [1,5] shift of the C−O bond in **23**, again certainly acid-catalyzed, produces the diene **26** followed by the Diels–Alder reaction with MA to give **24** and **25**.

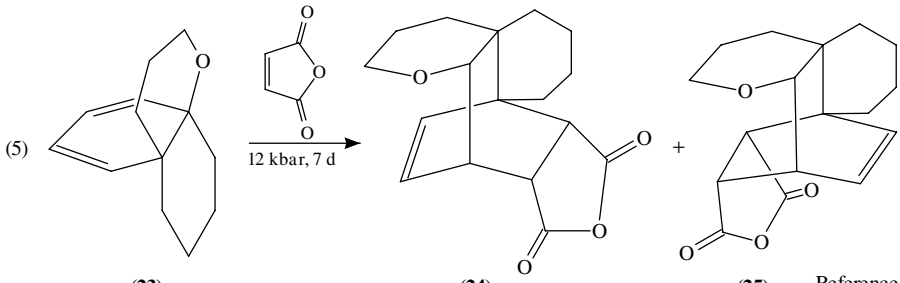
The effect of pressure on pericyclic additions of cycloheptatriene (entry 6) to various olefins [such as tetracyanoethene (TCNE), acrylonitrile, dimethyl acetylenedicarboxylate (DMAD), methyl propiolate and diethyl azocarboxylate] reacting as dienophiles or enophiles was studied by Jenner and Papadopoulos.[76,77] All reactions are strongly accelerated by pressure and show a larger selectivity at high pressure than at atmospheric pressure. At high pressure generally the Diels–Alder adducts derived from the valence tautomeric norcaradiene form are favored over the adducts resulting from an initial ene reaction to the cycloheptatriene followed by a valence bond isomerization and a subsequent Cope rearrangement, as shown for the reaction of cycloheptatriene with DMAD. In this case the preference of the Diels–Alder reaction at high pressure can be



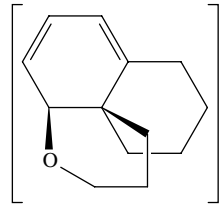
SCHEME 5. (*continued*)

rationalized by the observation that in the Diels–Alder reaction the volume of activation is more negative because the number of cyclic interactions is larger in the transition state of the Diels–Alder reaction than in that of the ene reaction (*vide infra*).

Generally, benzene and naphthalene derivatives show only little reactivity as dienes in Diels–Alder synthesis, contrary to anthracene and the higher acene derivatives which are frequently used as dienes. Exceptions are the reactions of benzene and naphthalene derivatives with highly reactive dienophiles such as dicyanoacetylene (DCA), which



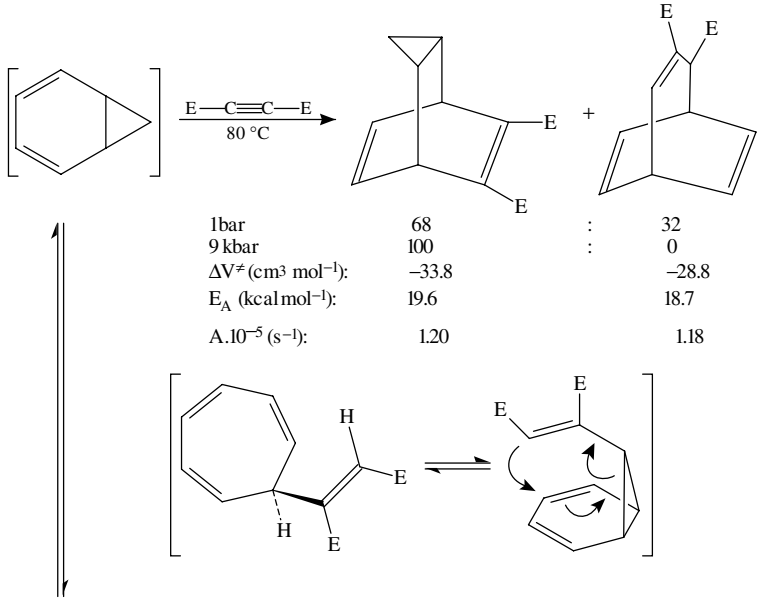
(23) **(24)** 19% **(25)** 34% Reference 75



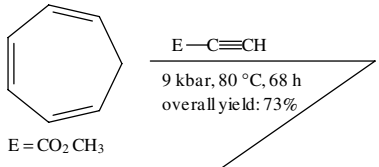
(26)

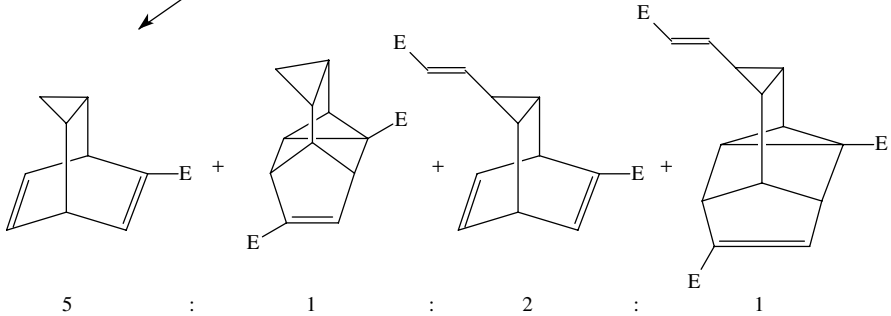
SCHEME 5. (*continued*)

require either high temperatures (180 °C) or a Lewis-acid catalyst ($AlCl_3$) at 25 °C[80,81]. Strained benzene derivatives like [2.2]paracyclophane react with DCA thermally at lower temperatures (120 °C)[81,82]. One reason why Diels–Alder reactions with benzenoid aromatics are rare is probably the unfavorable $T\Delta S$ term which causes the equilibrium to be shifted toward the reactants at the high temperatures which are necessary in these cases for the progress of the reaction. High pressure has two favorable effects on these reactions: the equilibrium is shifted by pressure toward the products due to the highly negative volumes of reaction, and the rate of reaction is enhanced due to the highly negative volumes of activation so that the temperature of the reaction can be lowered and the unfavorable $T\Delta S$ term becomes less important. An early example is the Diels–Alder cycloaddition of naphthalene to maleic anhydride (MA) leading to a mixture of *endo*- and *exo*-adduct which proceeds only at high pressure[83]. According to a more recent investigation, the precipitation of the adducts under the high-pressure conditions seems to be the main reason why this reaction is shifted toward the adducts which can be isolated in high yields[84]; [2.2]paracyclophane (Scheme 6: entry 1) reacts with MA and various maleic imide derivatives to give the *endo*- and *exo*-(1:2)-Diels–Alder adducts only at high pressure. At atmospheric pressure no reaction was observed up to 180 °C. An interesting case is the reaction of azulene and its derivatives **27** with DMAD (entry 2) which occurs at atmospheric pressure only at temperatures of about 200 °C to produce the diester-substituted heptalenes of type **29** in some reactions. At high pressure azulenes **27** already react with DMAD between 30 and 50 °C to give Diels–Alder adducts of type **28** which undergo rearrangement to the heptalenes **29** and cycloreversion to **27** as well. According to a recent investigation by Hansen and coworkers[88], the rearrangement **28** → **29** proceeds through the zwitterionic and tricyclic intermediates **30** and **31** and not through a diradical intermediate as proposed in the original publications[86,87]. Azulenes **32** and **33** were formed in few cases. The highly reactive benzyne adds to azulene in a Diels–Alder



(6) Reference 76–78

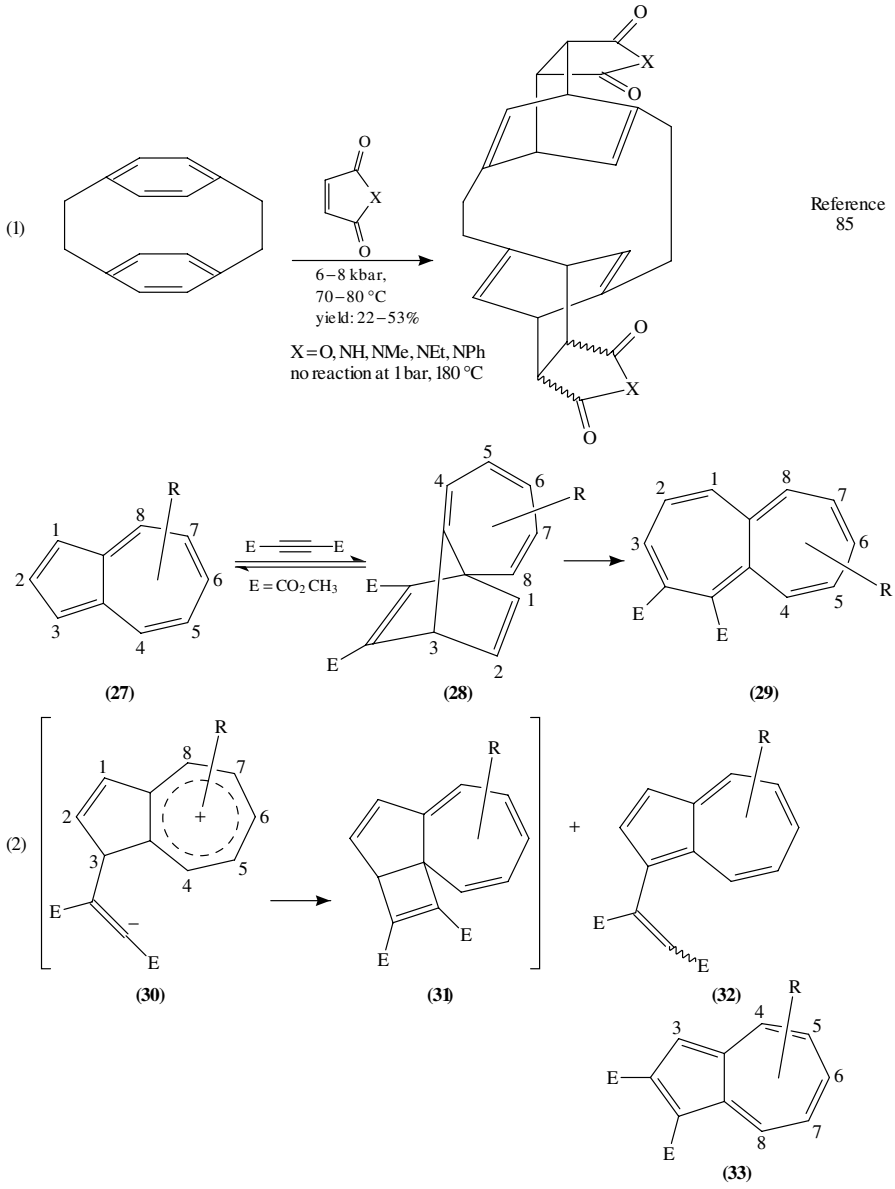




SCHEME 5. (*continued*)

fashion already at atmospheric pressure[89]. The Diels–Alder adducts of type **28** contain an almost planar cycloheptatriene ring. Therefore, they are also interesting for structural purposes concerning, for example, the question of homoaromaticity[90].

11-Methylene-1,6-methano[10]annulene **34** reacts with dicyanoacetylene (DCA) at 60 °C and atmospheric pressure producing the (1:1) Diels–Alder adduct at low conversion (<10%). The latter is not stable under the conditions of the reaction and undergoes a



SCHEME 6. Diels–Alder reactions with benzoid and nonbenzoid aromatic carbocycles as diene

cycloreversion leading to phthalonitrile and phenylacetylene as final products (Scheme 7). The strained methylenecyclopropabenzene **35** suggested as one primary product of the cycloreversion could not be detected. At 7 kbar the (1:1) adduct shows entirely different reactions leading to the formation of two (2:1) adducts **36** and **37** and no cycloreversion. The pressure-induced addition of DCA to the (1:1) adduct is obviously controlled by the

Compound	R	Conditions of reaction	Yields (%) (related to the turnover of the azulene)		Reference
			28	**29**	
27a	H	7 kbar, 50 °C, 67 h	39	11	86, 87
27b	1-Me	6.9 kbar, 50 °C, 67 h	50	13	86, 87
		7 kbar, 30 °C, 68 h	24	—	88
27c	4,6,8-Me_3	6.5 kbar, 50 °C, 68 h	—	30[a]	86, 87
27d	3,6-Me_2	7 kbar, 30 °C, 48 h	25		88
27e	1,4,6-Me_3	7 kbar, 30 °C, 48 h	7		88
27f	1,5,7-Me_3	7 kbar, 30 °C, 61 h	22		88
27g	1,4,6,8-Me_4	7 kbar, 30 °C, 69 h	41[b]		88
27h	1,4-Me_2, 7-*i*-Pr	5.5 kbar, 30 °C, 95 h	62[c]	8	88
27i	1,2,4,6,8-Me_5	7 kbar 30 °C 42 h	38		88
27k	1,2,4,8-Me_4, 6-*t*-Bu	7 kbar, 30 °C, 66 h	40		88

[a] 40% of **32c** and 4% of **33c**
[b] 8% of **32g**
[c] 15% of **32h**.

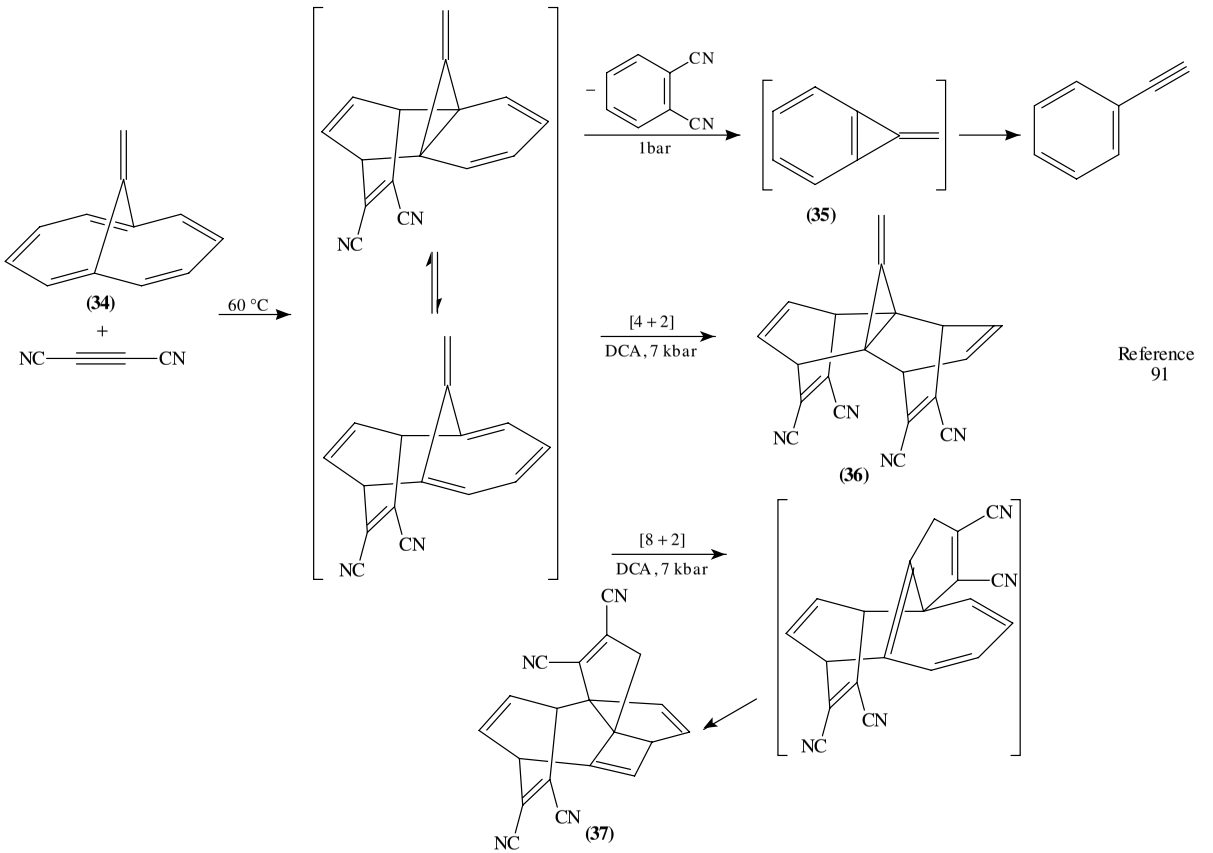
SCHEME 6. (*continued*)

(with respect to the NMR time scale) rapid equilibrium between the valence tautomeric bridged norcaradiene and the heptafulvene structure. [4 + 2] cycloaddition of DCA to the norcaradiene moiety leads to the symmetrical (2:1) adduct **36**, while [8 + 2] cycloaddition of DCA to the heptafulvene moiety followed by an electrocyclization leads to the unsymmetrical adduct **37**.

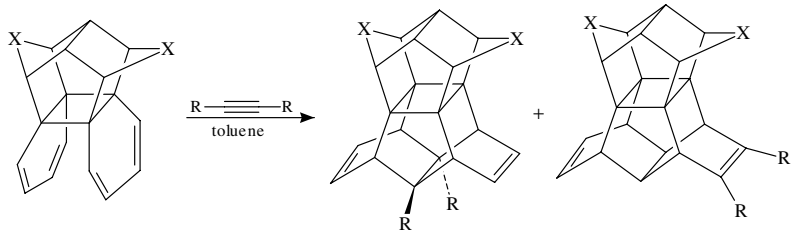
Scheme 8 shows examples of competitive 'pincer' and 'domino' cycloadditions with *syn-o,o′*-dibenzene derivatives **38**. The selectivity depends strongly on the nature of the acetylenic dienophile as well as of the *syn-o,o′*-dibenzene derivative. Preferential formation of the 'pincer' **39** adduct and of the 'domino' adduct **40** occurs, respectively, with DCA (entry 1) or DMAD (entry 2). The approach of the linear DCA to the center of the two cyclohexadiene rings may be supported by noncovalent interaction between the orthogonal π-bonds of DCA and the inner faces of the electron-rich cyclohexadiene units while the sterically larger ester groups may prevent this orientation. Thus, DMAD approaches preferentially from the outer face of one cyclohexadiene unit. In the reaction of DCA with the dibenzo-substituted bis-diene (entry 3), one of the benzene rings can successfully compete with one cyclohexadiene ring to complex DCA, so that the formation of the 'domino' adduct **40** is favored. High pressure induces a large rate enhancement but no significant change in selectivity. This finding supports the conclusion that either the 'pincer' or the 'domino' cycloaddition consists of two consecutive Diels–Alder reactions.

The synthesis of the macrocycles **43** (Scheme 9) is an example of repetitive, highly stereoselective Diels–Alder reaction between bis-dienes **41** and bis-dienophiles **42**, containing all oxo or methano bridges *syn* to one another. The consecutive inter- and intramolecular Diels–Alder reactions only succeed at high pressure. Obviously, both reactions are accelerated by pressure. The macrocycles are of interest in supramolecular chemistry (host–guest chemistry) because of their well-defined cavities with different sizes depending on the arene spacer-units.

If the oxo (or methano) bridges are not exclusively *syn* to one another in either the bis-dienophiles or bis-dienes, then the pressure-induced repetitive Diels–Alder reactions (proceeding again highly stereoselectively) produce rigid ribbon-type oligomers on a nanometer scale (Scheme 10: entry 1). Bis-diene **45** reacts less stereoselectively than bis-diene **44** and forms with bis-dienophiles such as **46** the ribbon-type oligomers **47**



SCHEME 7. Competition between cycloadditions and *retro*-Diels–Alder reactions in the reaction of dicyanoacetylene and 11-methylene-1,6-methano[10]annulene



(38) 'pincer' **(39)** 'domino' **(40)**

		T(°C)	time (h)	**39**	:	**40**
(1)	X = CH_2, R = CN					
	1 bar	100	4	74	:	26
	12 kbar	25		85	:	15
(2)	X = CH_2, R = CO_2CH_3					
	1 bar	100	80	3	:	97
	14 kbar	25		3	:	97
(3)	X = *o*-C_6H_4, R = CN					
	1 bar	25		0	:	100
	1 bar	80		4	:	96
	1 bar	100		12	:	88
	14 kbar	25		0	:	100

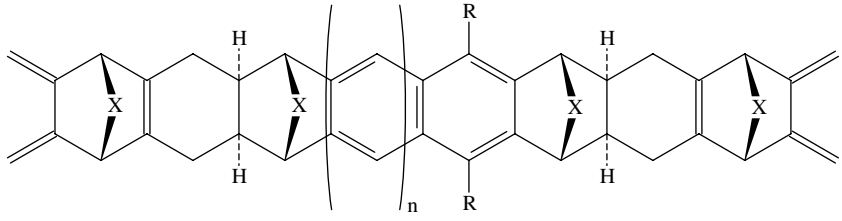
SCHEME 8. Competition between 'pincer' and 'domino' Diels–Alder reactions in the synthesis of pagodane precursurs[92]

with long chain-lengths (Scheme 10: entry 2). The more flexible ribbon-type structures **50** can be obtained by repetitive Diels–Alder reactions of bis-diene **48** with DMAD as bis-dienophile (Scheme 10: entry 3). The cage compound **49** is formed in an undesired side-reaction. The application of high pressure leads here to a larger conversion of starting materials and to a higher degree of polymerization.

All Diels–Alder reactions of tropones **51** as dienes with different types of dienophiles shown in Scheme 11 are accelerated by pressure, so that in some cases the desired cycloadducts are only formed at high pressure. An interesting synthetic equivalent of the unreactive acetylene in Diels–Alder syntheses is the oxanorbornadiene derivative **52** (Scheme 11: entry 2). **52** reacts with tropones forming the adducts **53, 54** and **55**, which undergo a *retro*-Diels–Alder reaction leading to **56** and **57**, the formal [4+2] cycloadducts of tropones to acetylene.

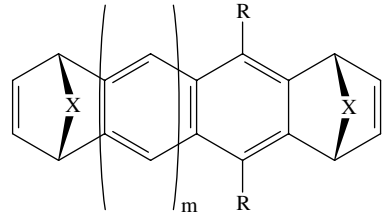
Buckminsterfullerene C_{60} generally reacts as electron-deficient dienophile or dipolarophile in numerous Diels–Alder or 1,3-dipolar cycloadditions[103]. The rates of reaction are again enhanced by an increase of pressure so that the yields are usually better at high pressure than at atmospheric pressure (Scheme 12).

The heteroaromatic compounds like furans, pyrroles or thiophenes cannot be generally used as dienes in Diels–Alder syntheses, because at the higher temperature required for the addition of less reactive dienophiles, the equilibrium is on the side of the starting materials due to the unfavorable $T\Delta S$ term comparable to the benzenoid aromatic compounds as mentioned. High pressure again shows the two effects already discussed: the shift of the equilibrium toward the products and the enhancement of the rate of reaction which allows the temperature of reaction to be lowered. One



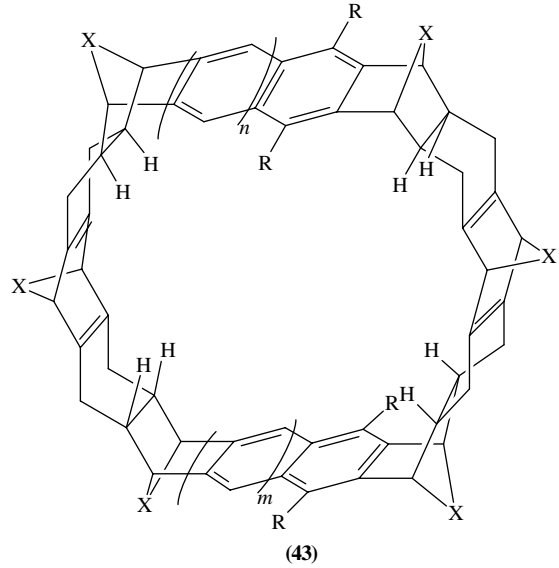
(41)

X = O, CH_2
R = H, OCH_3
n = m = 0, 1
n = 1, m = 0



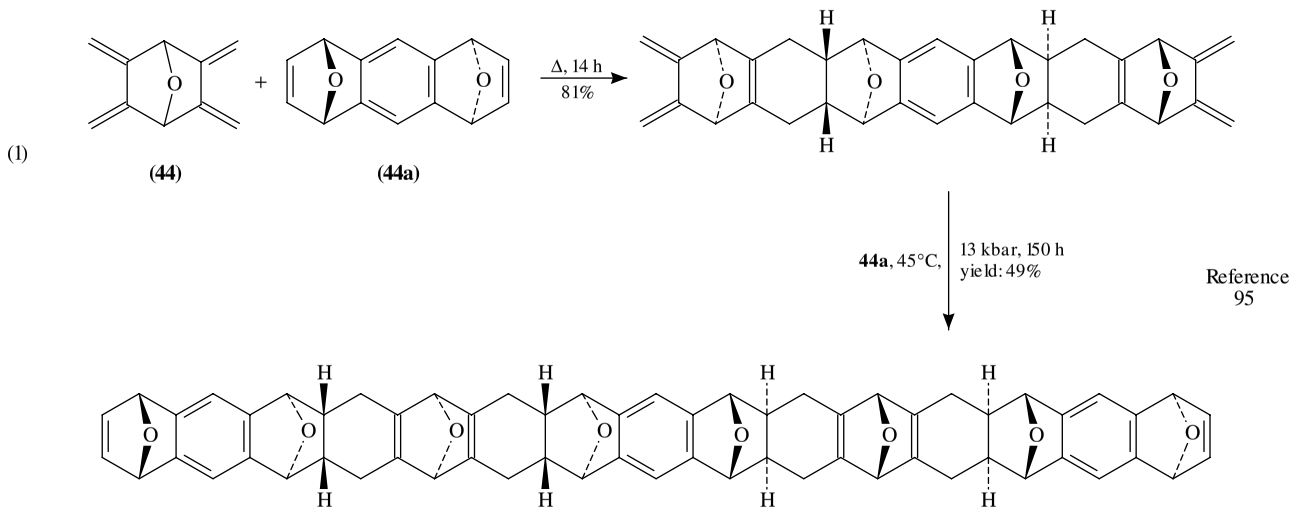
(42)

8 – 12 kbar

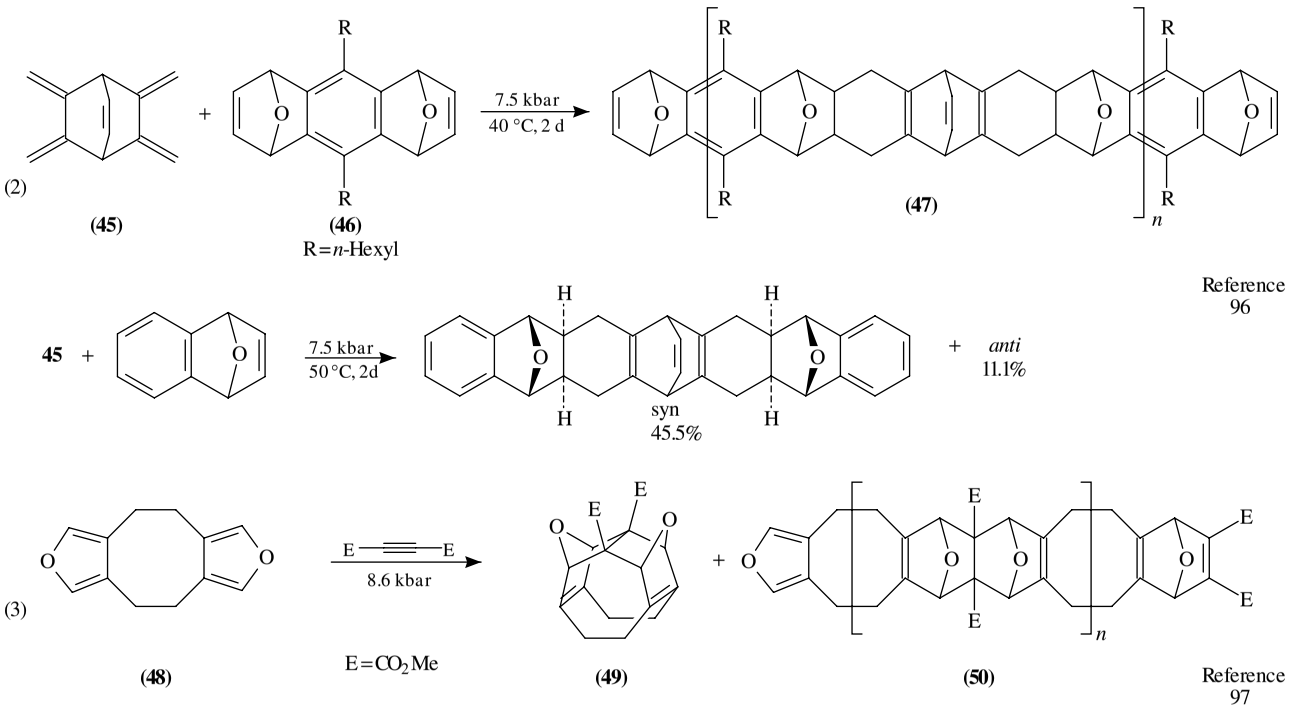


(43)

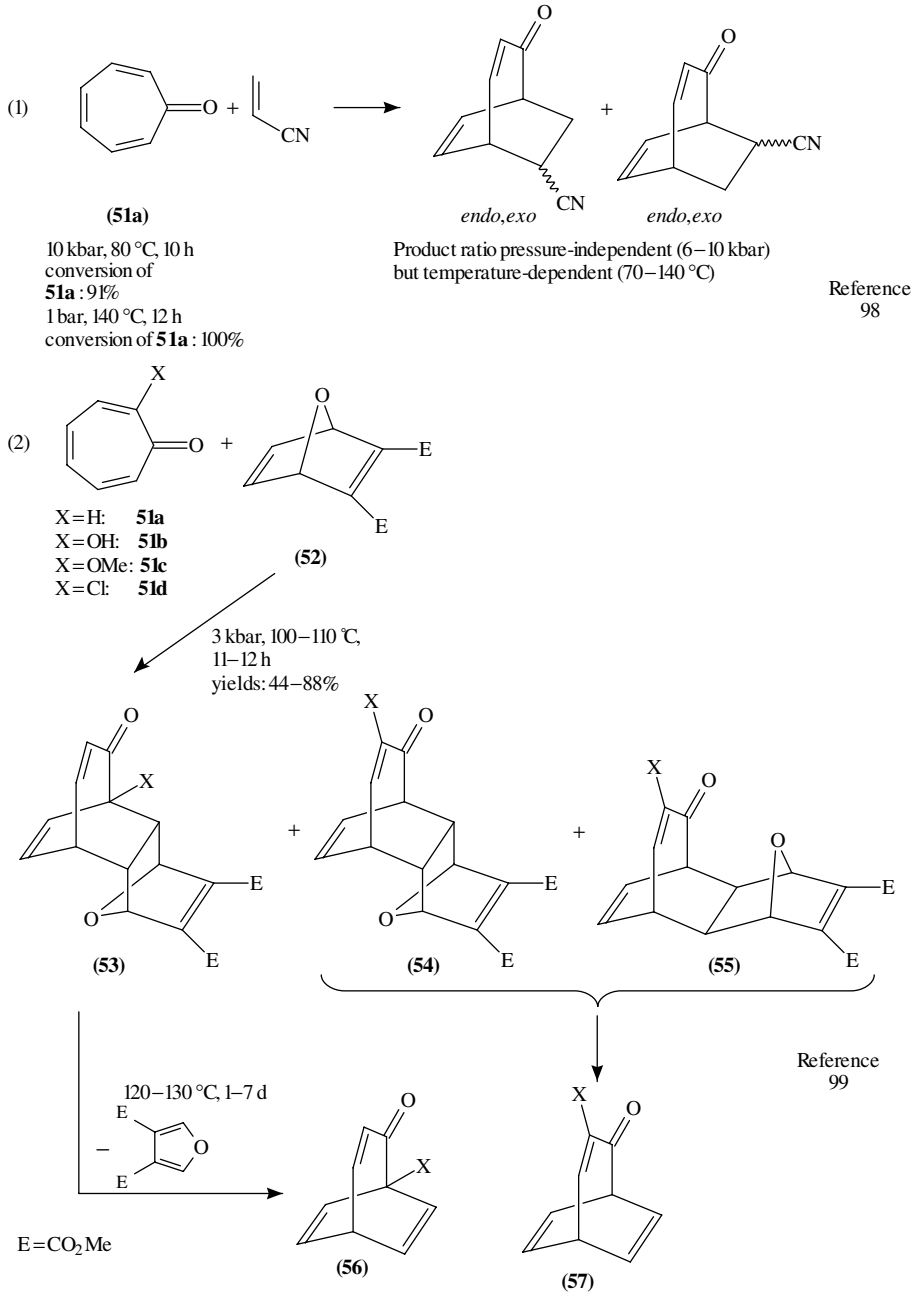
SCHEME 9. Repetitive Diels–Alder reactions in the synthesis of macrocycles having cavities of different size[93,94]



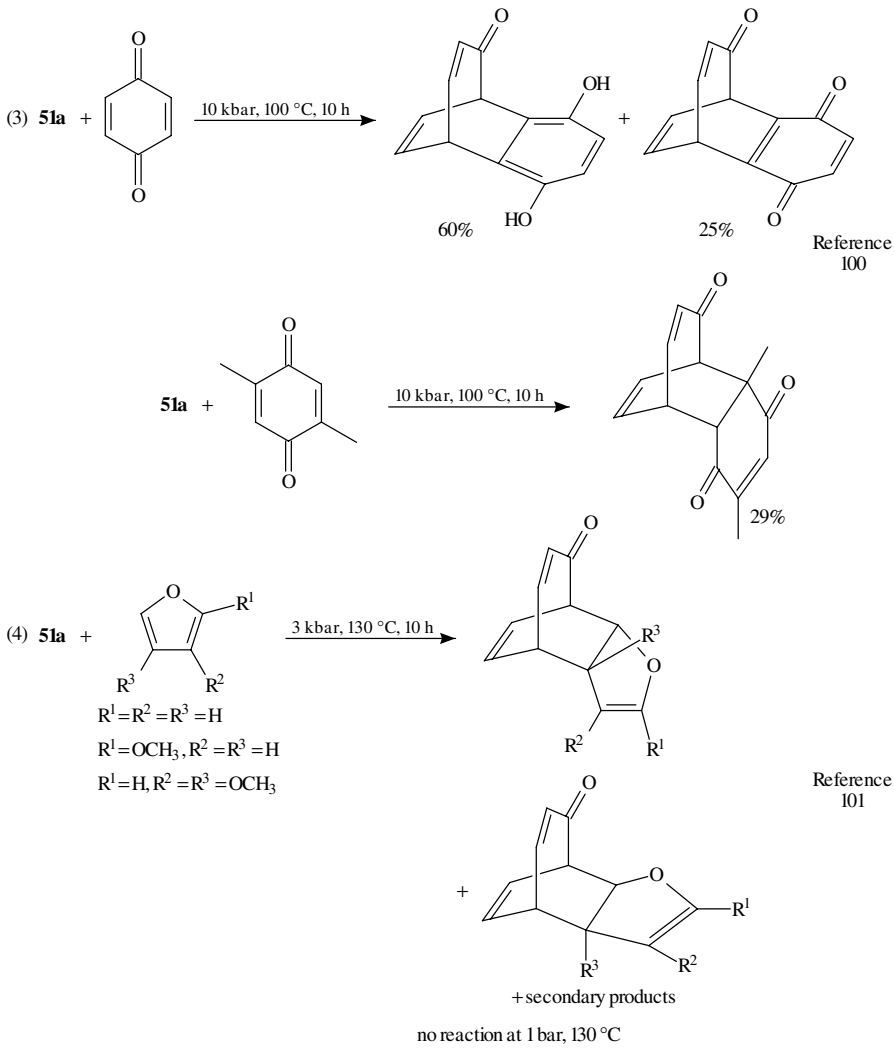
SCHEME 10. Ribbon-type oligomers and polymers via repetitive Diels–Alder reactions



SCHEME 10. (*continued*)

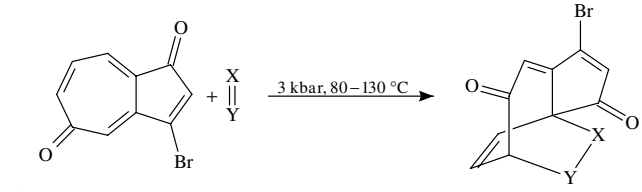


SCHEME 11. Diels–Alder reactions of tropones as dienes

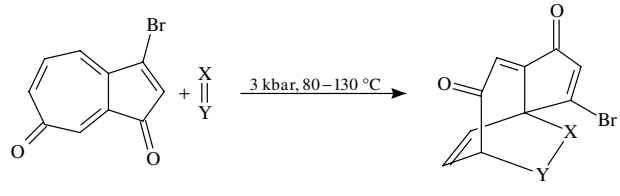


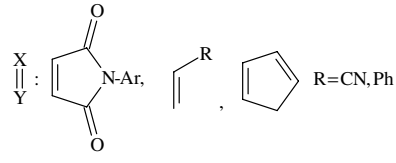
SCHEME 11. (*continued*)

of the most prominent examples is the synthesis of a cantharadine precursor by the cycloaddition of furan to the substituted maleic anhydride shown in Scheme 13, entry 1, which occurs only at high pressure or when catalyzed by $LiClO_4$. Other examples of pressure-induced Diels–Alder reactions with five- and six-membered heterocyclic dienes such as furans, pyrroles, oxazoles, isopyrazoles, phospholes, α-pyrones and pyridones are depicted in Scheme 13. High pressure is here not only useful for synthetic purposes, but also provides important information concerning the course of reaction. One example is the addition of cyanoacetylene to furan and furanobenzocyclophane **63** (Scheme 13: entries 4 and 5) leading to the (2:1) adducts **61** and **66**, respectively, as the major products at 160 °C and atmospheric pressure. In analogy to the trimerization of cyanoacetylene (Scheme 5: entry 3) and the addition of

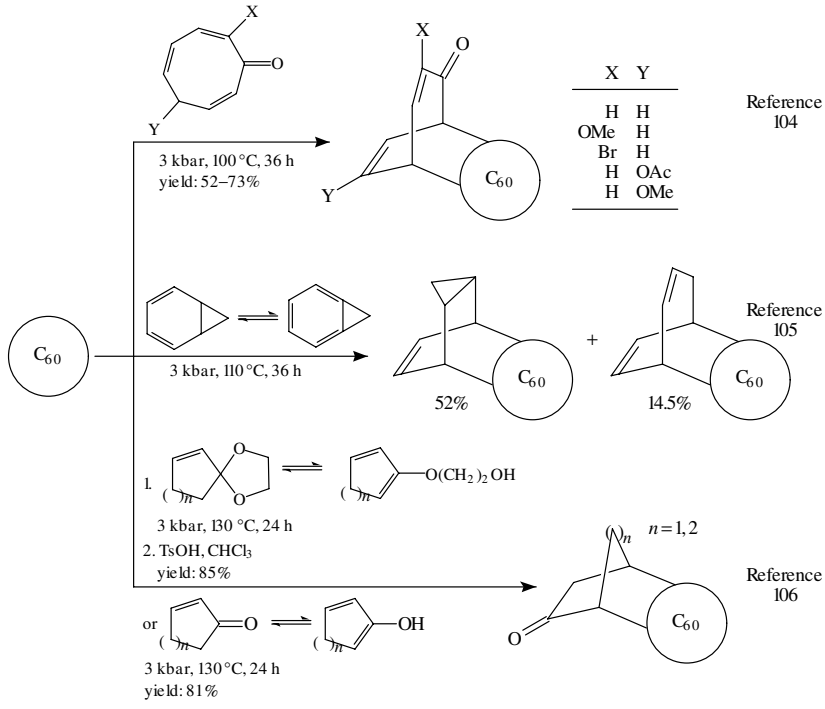


(5)





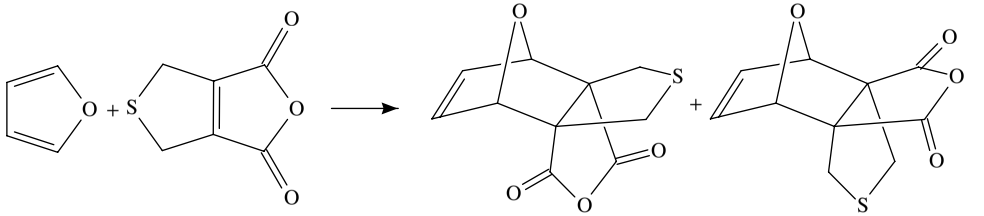
SCHEME 11. (*continued*)



SCHEME 12. Diels–Alder reactions with fullerenes as dienophiles

(a) Furans

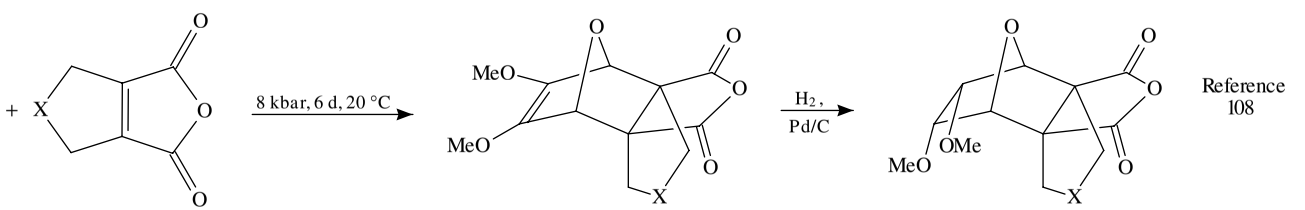
(1)



4–15 kbar, 20 °C, 40–100% conversion — 1 : 4 (pressure independent)

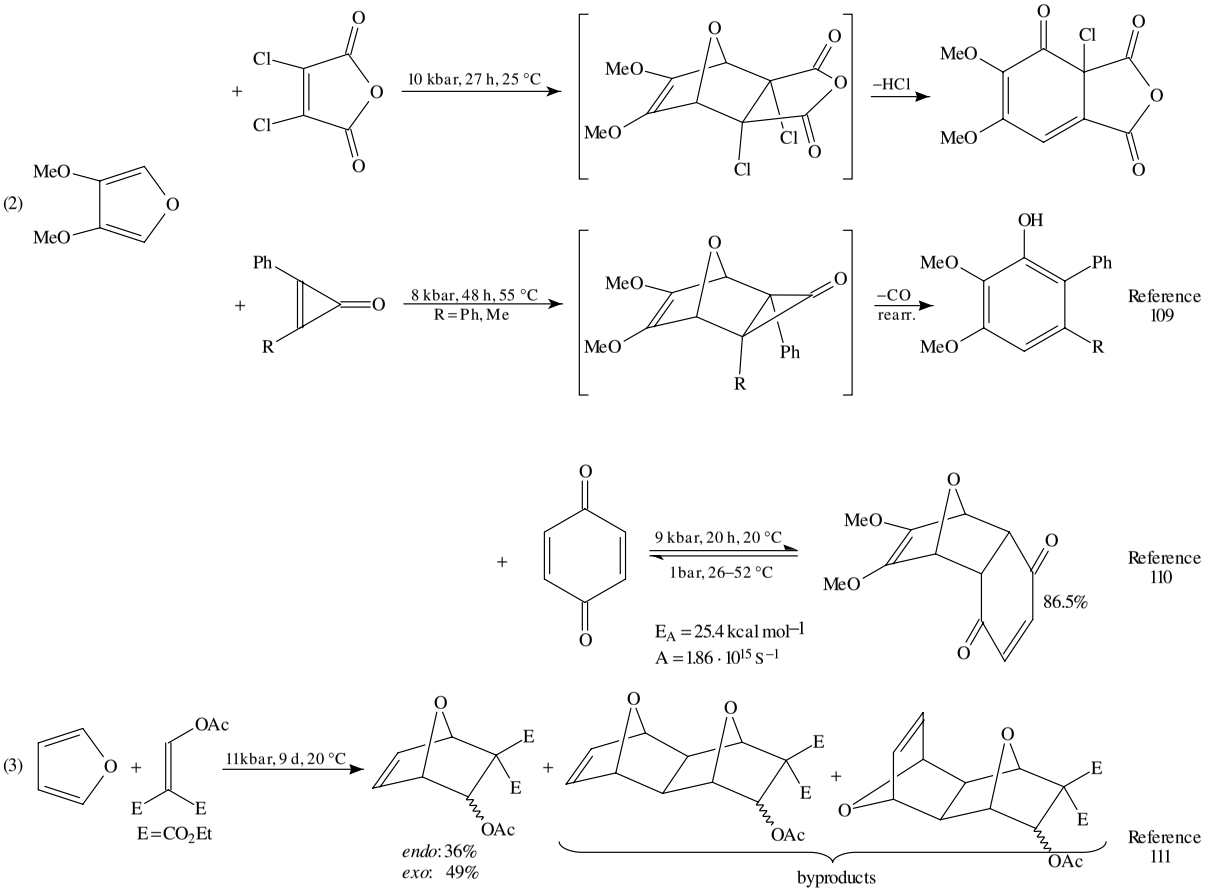
5 M $LiClO_4$, Et_2O, 20 °C, 10 h, yield: 70% — 1 : 5.7

Reference 107



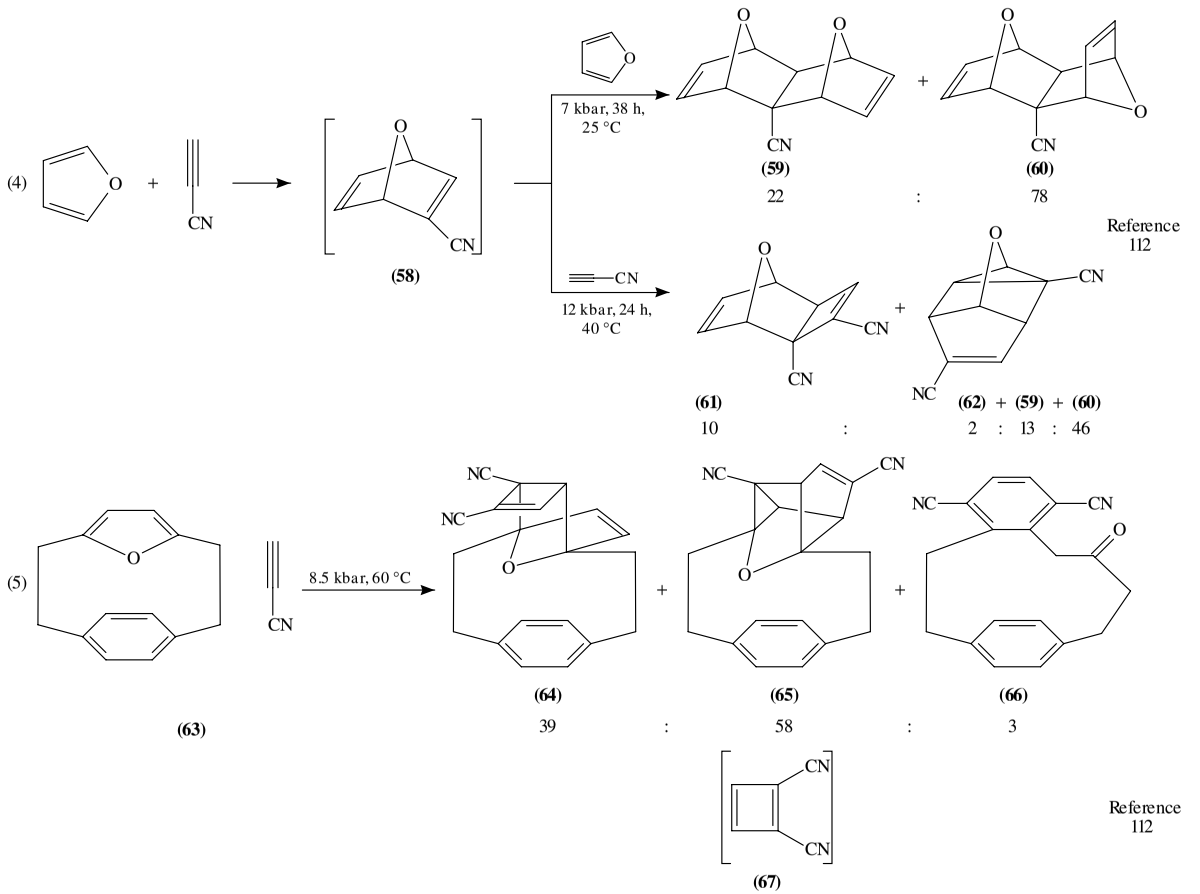
X: CH_2CH_2, $CHMeCH_2$, $CHMeCHMe$, CH_2
yields: 18–28%

Reference 108

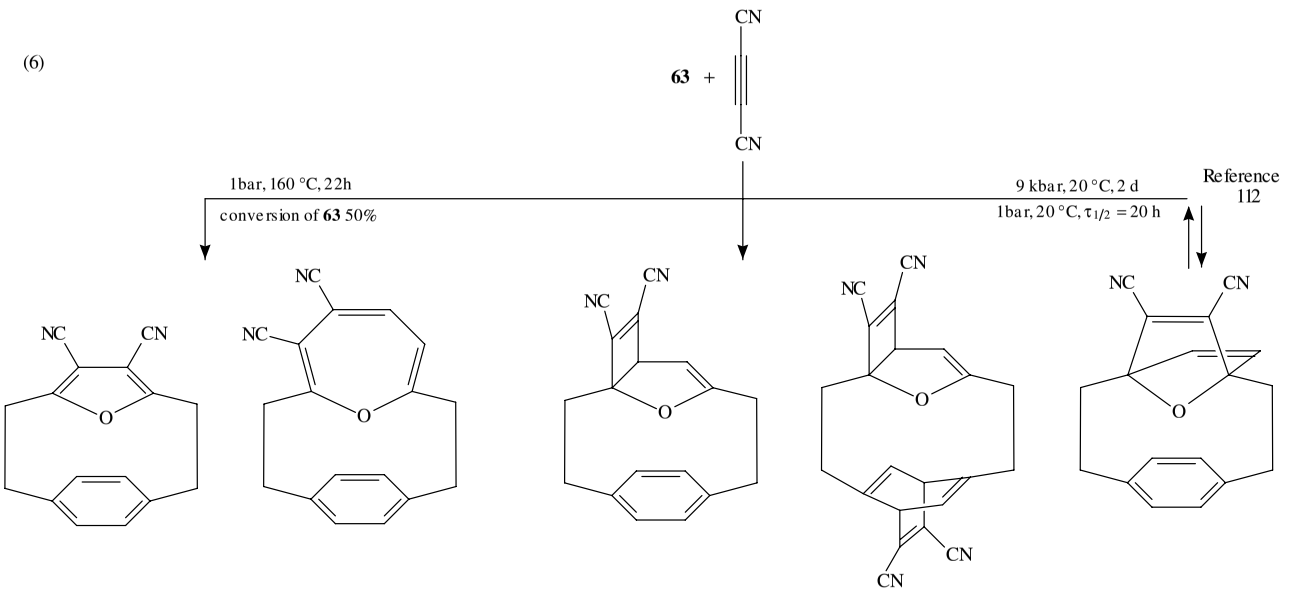


SCHEME 13. Diels–Alder reactions with heterocyclic dienes

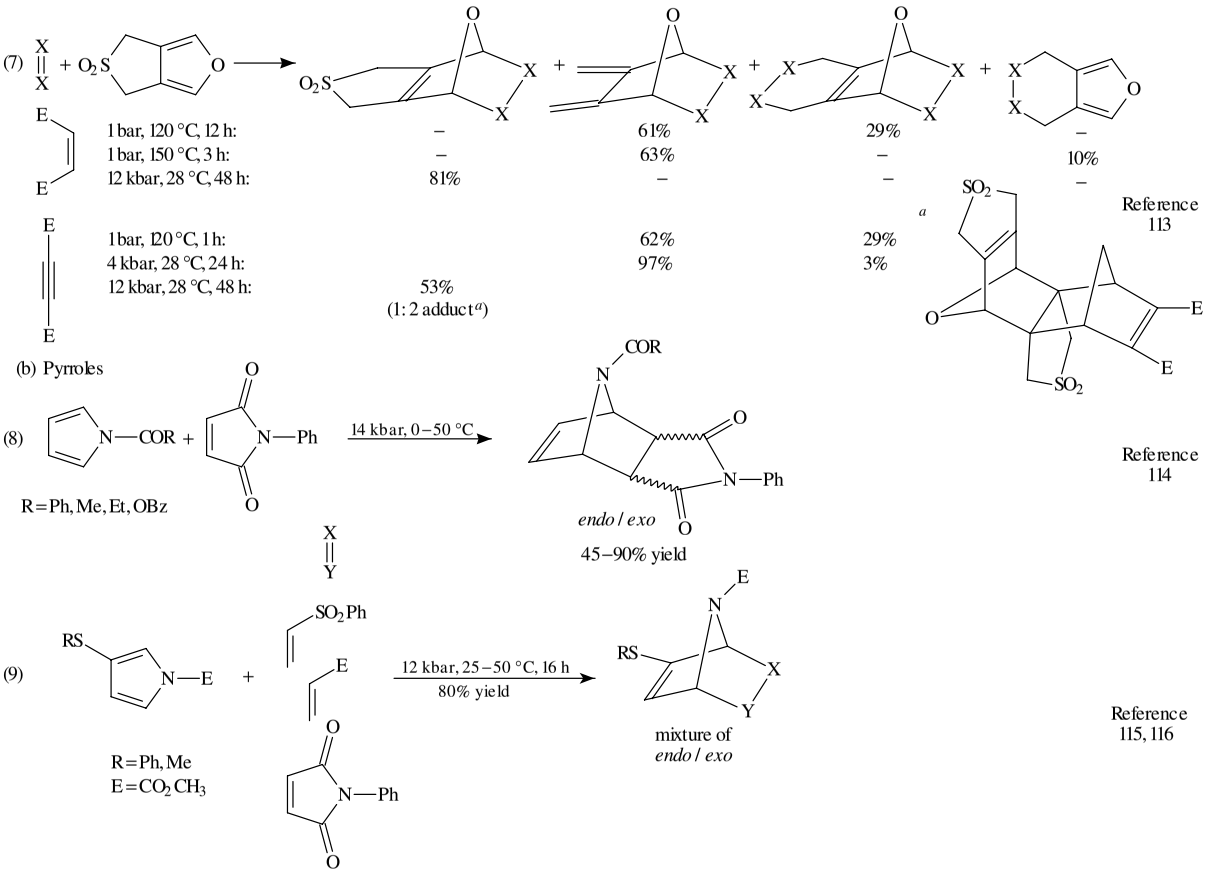
(*continued*)



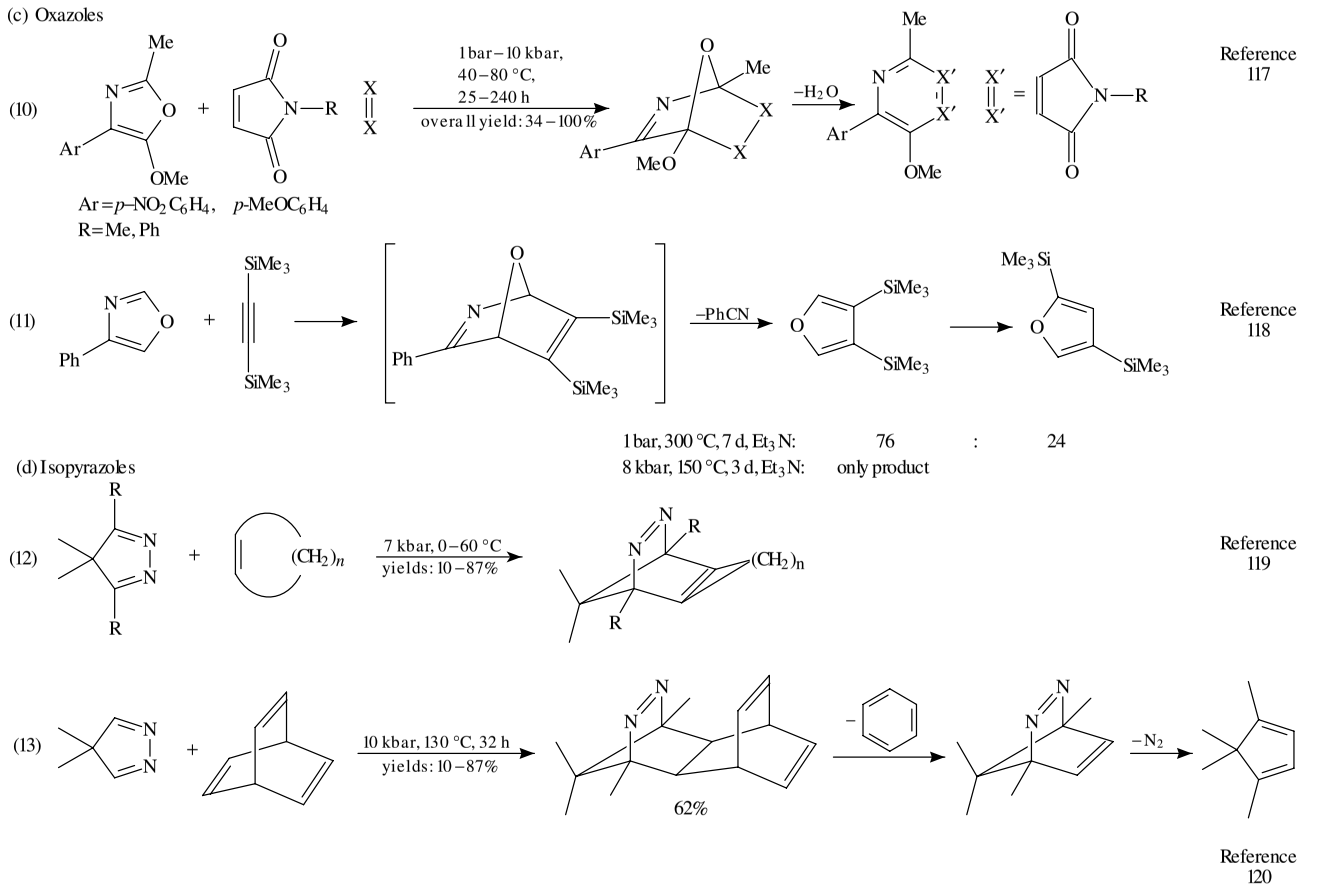
SCHEME 13. (*continued*)



SCHEME 13. (*continued*)

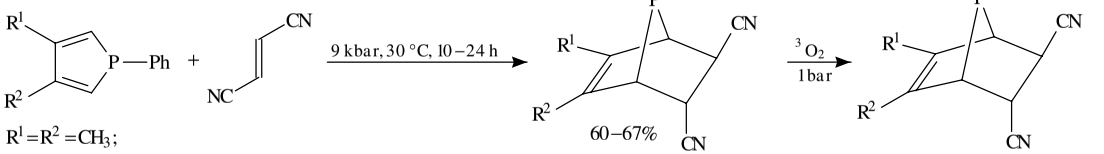


SCHEME 13. (*continued*)



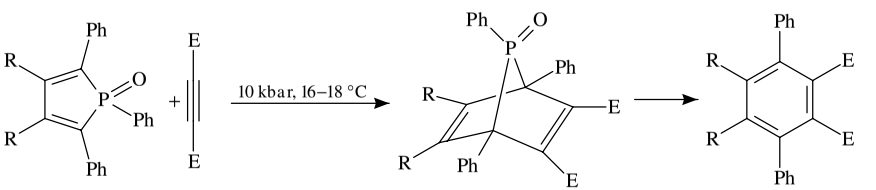
SCHEME 13. (*continued*)

(e) Phospholes

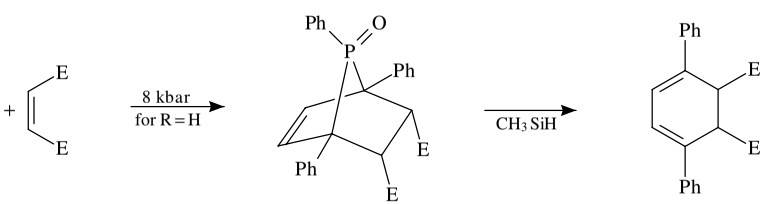
(14) 

$R^1 = R^2 = CH_3$;
$R^1 = H, R^2 = CH_3$;
$R^1 = R^2 = H$

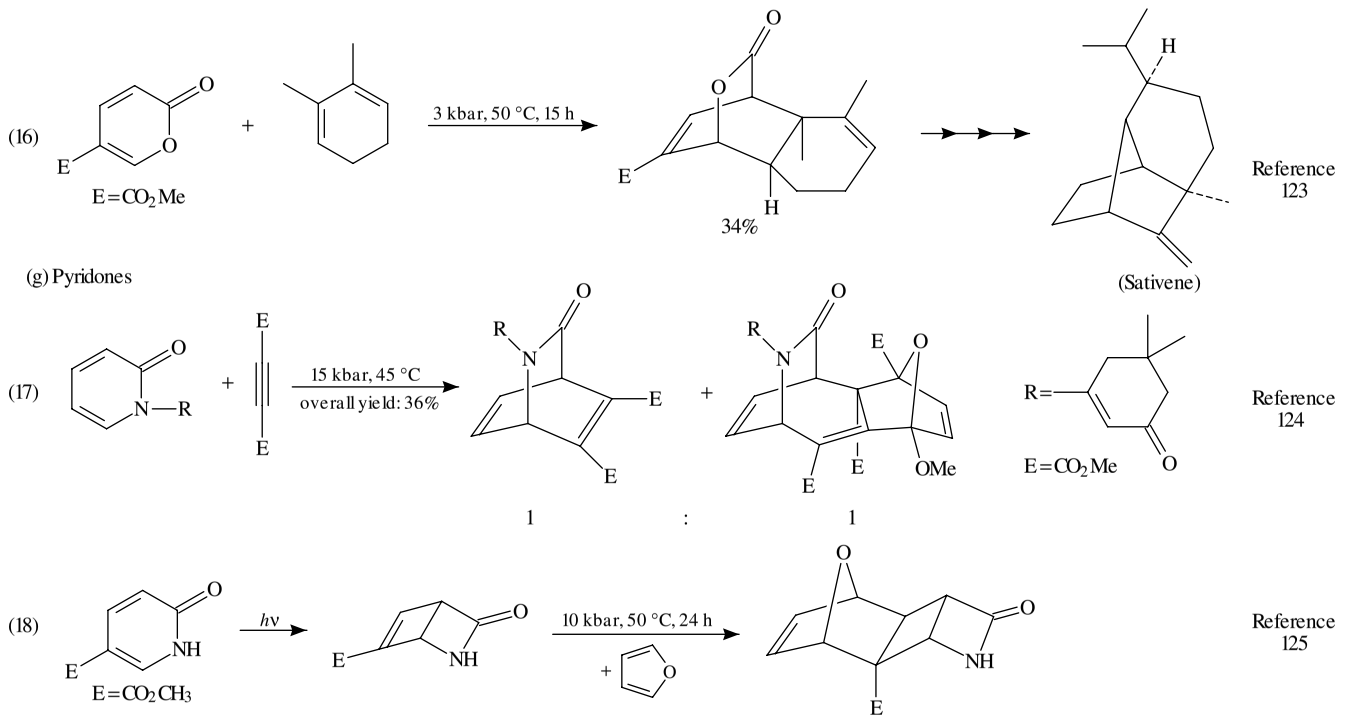
Reference 121



(15) R = Ph, H E = CO_2Me, COBu-t, COAr

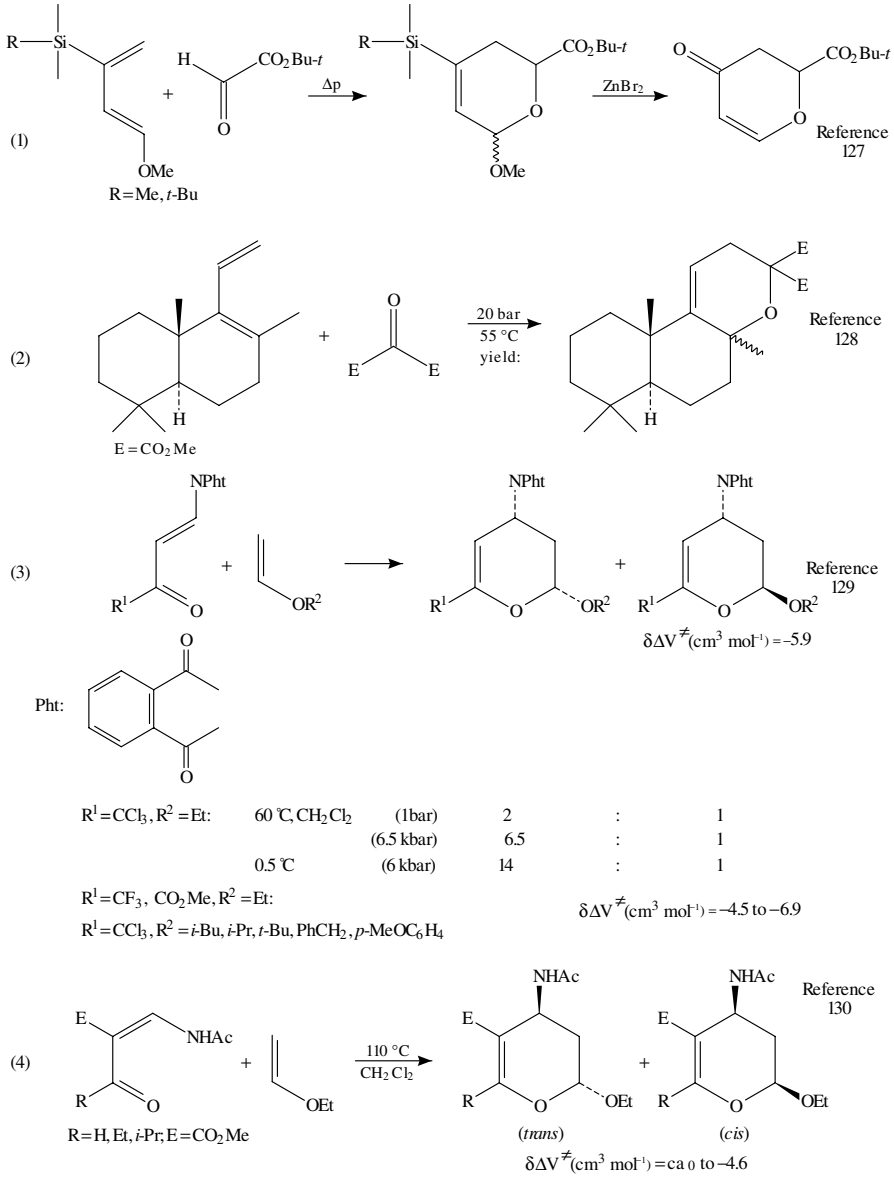


SCHEME 13. (*continued*)



SCHEME 13. (*continued*)

cyano acetylene to [2.2]paracyclophane[126] the cyclobutadiene **67**, the [2 + 2] cyclodimer of cyanoacetylene, was assumed to be the intermediate in these reactions. From the investigation of the pressure effect it could be concluded that oxanorbornadienes such as **58** and not cyclobutadiene **67** are intermediates in the formation of **61** and **62** or **64** and **65** whereas **67** is indeed an intermediate on the reaction path from **63** to **66**. In the



SCHEME 14. Diels–Alder reaction with acyclic heterodienophiles and heterodienes

reaction of **63** with dicyanoacetylene (DCA) (Scheme 13: entry 6) which gives **68** and **69** at 1 bar, the effect of pressure reveals that the [4+2] cycloadduct **72** formed in a kinetically controlled reaction is less stable than the [2+2] cycloadduct **70**, the precursor of the oxepin **69**. In reaction of **63** with DCA catalyzed by $LiClO_4$, only the thermodynamically more stable [2+2] cycloadduct **70** is obtained at 8.5 kbar and 60 °C both **69** and **70** are formed, whereas at 9 kbar and 20 °C the [4 + 2] adduct **72** can be observed.

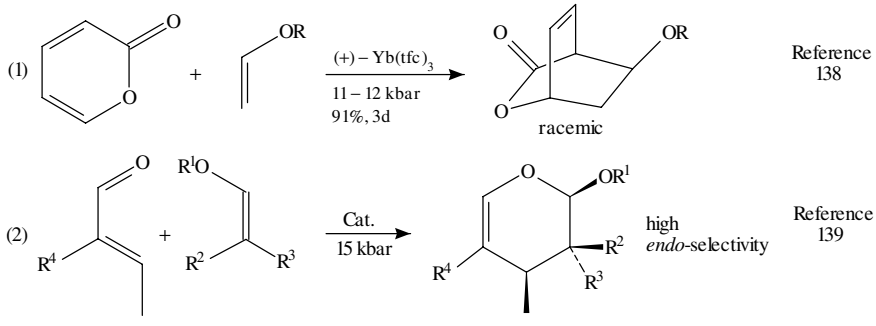
In Scheme 14 the effect of pressure on Diels–Alder reactions with acyclic heterodienophiles or heterodienes is presented. The application of high pressure leads also in these reactions to an enhancement of rates and improvement of yields. The hetero-Diels–Alder reaction (entry 3) is a good example of the interplay between pressure and temperature. At high pressure the rate of reaction as well as the diastereoselectivity are increased. The pressure-induced acceleration allows the temperature of reaction to be lowered, which leads to a further increase of diastereoselectivity.

Breslow[131], Grieco and coworkers[132] and Engberts and coworkers[133] have found that the rates of cycloadditions can be strongly enhanced by conducting them in water or in saturated $LiClO_4$–diethyl ether solution. These enhancements are comparable to the enhancement of rates of reaction by high pressure in conventional organic solvents. Suggested origins of these effects are high internal solvent pressure, hydrophobic association, micellar catalysis, solvent polarity and hydrogen bonding. Blake and Jorgensen[134] found in a Monte Carlo simulation of the solvent effect on the Diels–Alder reaction between 1,3-cyclopentadiene (CP) and methyl vinyl ketone (MVK) that the interaction between water and the transition state leads to a substantial stabilization whereas the interaction between water and the reactants or adduct is small. Propane as solvent has accordingly no significant influence on the stability of the transition state, the reactants or the adduct. The authors concluded that the aqueous acceleration of the reaction between CP and MVK is due to the hydrophobic association, as well as to a nonhydrophobic component stemming from enhanced polarization of the transition state that lead *inter alia* to stronger hydrogen bonds at the carbonyl oxygen. The various methods for acceleration and selectivity enhancement of Diels–Alder reactions were recently reviewed by Pindur and coworkers[135].

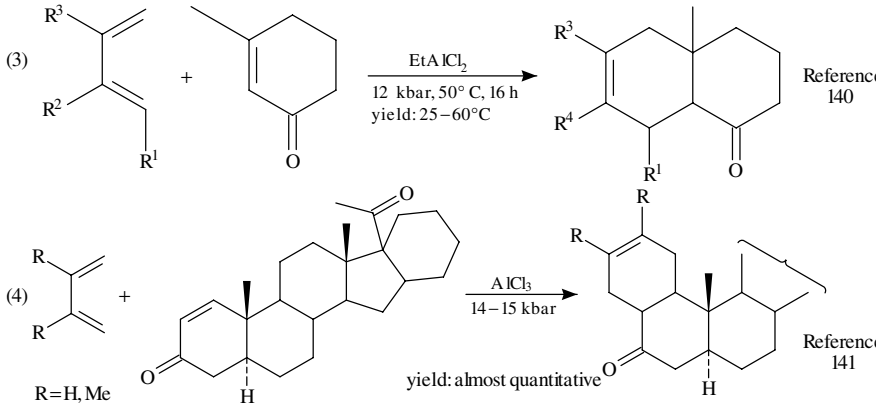
A study of the pressure effect on reactions in H_2O by Jenner[136] showed that the Diels–Alder cycloaddition of furan or 1-methylfuran to acrylic acid derivatives is less sensitive to pressure in aqueous solution than in an organic solvent such as CH_2Cl_2. Isaacs and coworkers[137] found, however, that the pressure effect on the Lewis-acid or $LiClO_4$ catalyzed Diels–Alder reaction of isoprene with N-phenylmaleic imide is larger (more negative activation volume) than that on the corresponding uncatalyzed reaction. Similar results were also obtained for the Diels–Alder reaction between 9-anthranceneethanol and N-ethylmaleic imide. The Diels–Alder reactions shown in Scheme 15, entries 1–4, illustrate that the combination of high pressure and Lewis-acid catalyst can have a synergetic effect. The reactions are observed only at high pressure in the presence of the catalysts. The examples shown in Scheme 15, entries 5 and 6, demonstrate that pressure can have a strong effect on the diastereoselectivity of catalyzed reactions. In one case (entry 6) the selectivity is reversed by pressure. In another case, the intramolecular Diels–Alder reaction catalyzed by a chiral titanium complex (entry 8), the enantioselectivity is increased by pressure from 4.5%ee at 1 bar to 20.4%ee at 5 kbar.

B. [2 + 2] Cycloadditions of Cumulated Dienes

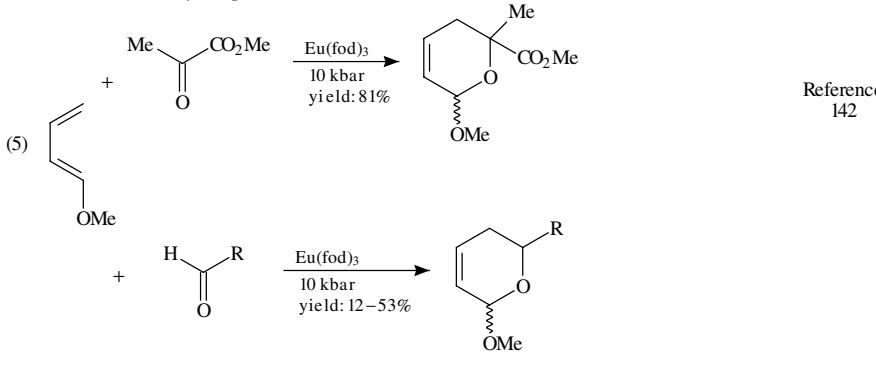
[2 + 2] Cycloadditions involving ketene derivatives as one or both reaction partners are assumed to be rare examples of concerted $[\pi_s^2 + \pi_a^2]$ cycloadditions[146]. The activation volumes determined for the [2 + 2] cyclodimerization and the [2 + 2] cycloadditions



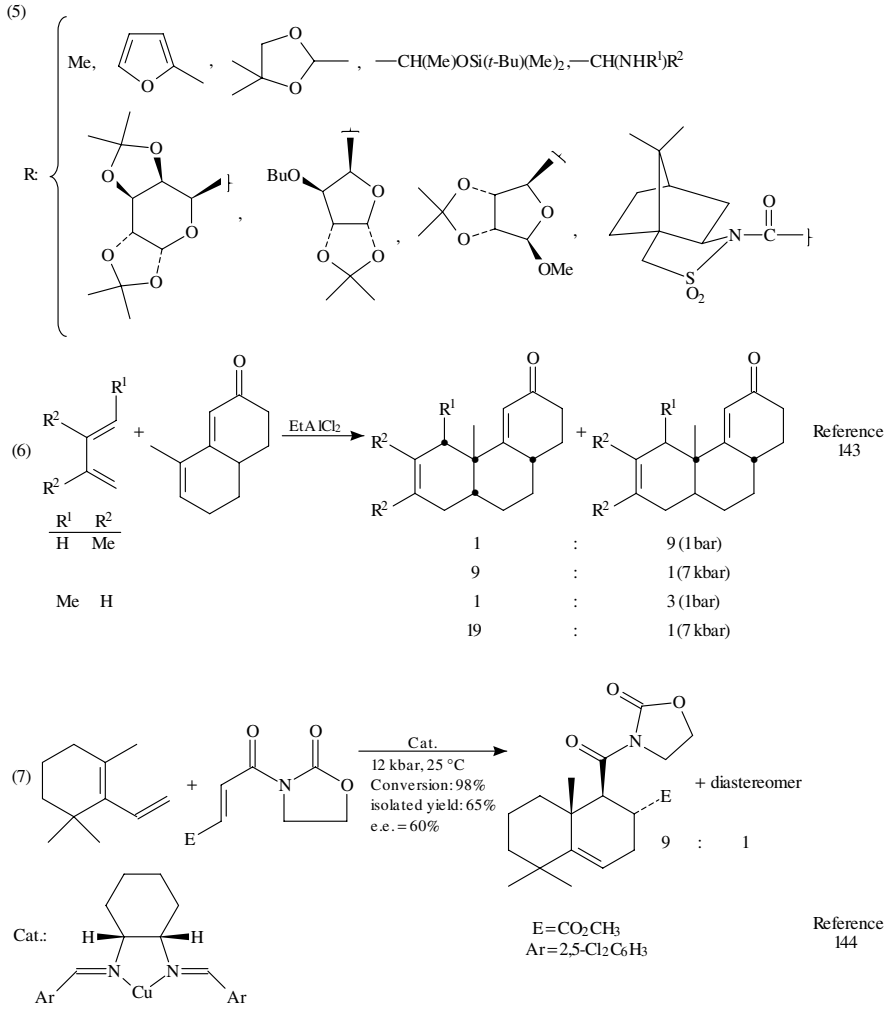
Cat.: $Eu(fod)_3$, $Eu(tfc)_3$, $Eu(hfc)_3$, $Pr(tfc)_3$, $Yb(tfc)_3$
In the absence of catalyst no reaction up to 50 °C
asymmetric induction: R^1 = CH((Me)(Ph)), R^2 = Me, R^3 = R^4 H: d.e. = 19 to 45%



In the absence of catalyst or pressure no reaction occurs.

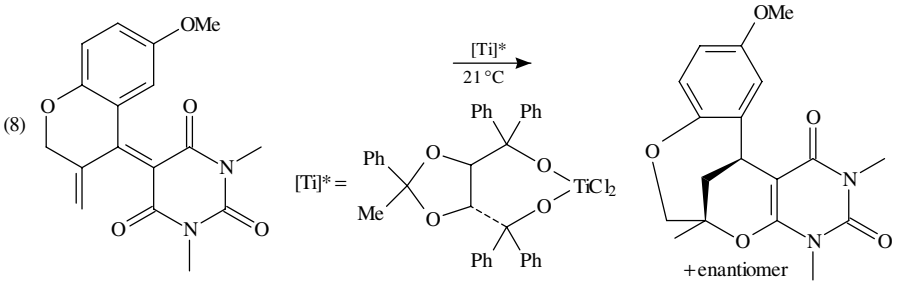


SCHEME 15. Catalyzed Diels–Alder reactions

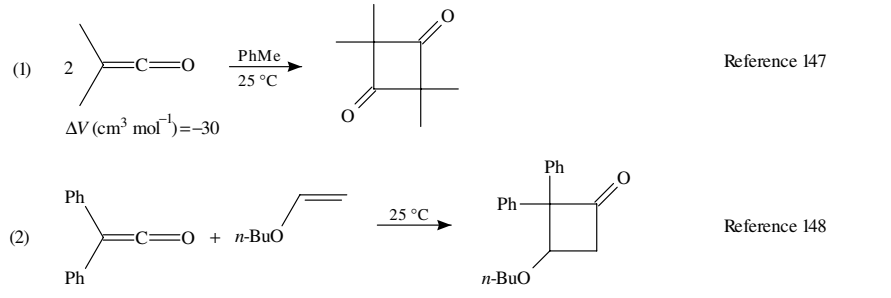


SCHEME 15. (*continued*)

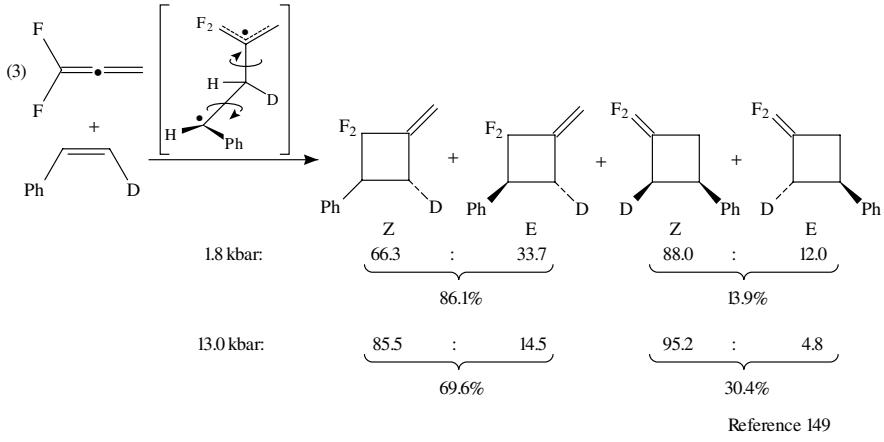
of diphenylketene to various enol ethers turned out to be highly negative (Scheme 16: entries 1 and 2). Kelm, Huisgen and coworkers studied the mechanism of the reaction of diphenylketene with *n*-butyl vinyl ether in great detail. Although the rate constants at atmospheric pressure could be successfully correlated with the term $[(\varepsilon - 1)/(2\varepsilon + 1]$ containing the dielectric constants (ε) of the solvents used, indicating an increase of polarity during the reaction, the very large solvent dependencies of $\Delta V^{\neq}$ and ΔV were erratic and not understandable. The authors found a fairly good correlation between the partial molar volumes of the reactants and the solvent cohesion energy density (ced), but the correlation failed for those of the transition state and the product. Thus, the effect of pressure leads to a powerful acceleration of these [2 + 2] cycloadditions comparable to that of Diels–Alder reactions, which may be useful for synthetic purposes but does not provide further insight into the mechanism of this reaction.



SCHEME 15. (*continued*)

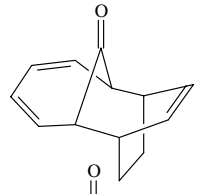
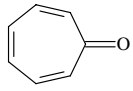
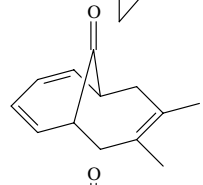
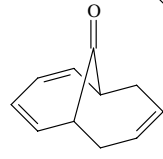
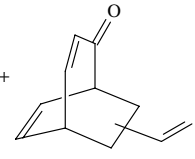


Solvent	$\Delta V^{\neq}$ (cm^3 mol^{-1})	ΔV (cm^3 mol^{-1})
PhCN	–22	–10.4
c-C_6H_{12}	–26	–31.3
CH_2Cl_2	–29	–26.2
PhCl	–30	–26.4
PhH	–44	–23.0
PhMe	–52	–29.0

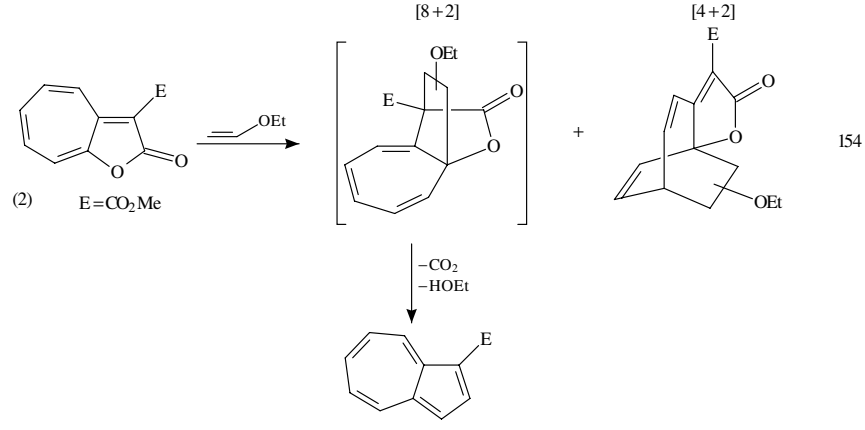


SCHEME 16. [2 + 2] Cycloadditions of cumulated dienes

Dolbier and Weaver[149] investigated the effect of pressure on the stereo- and regioselectivity in a certainly stepwise [2 + 2] cycloaddition of 1,1-difluoroallene to (*Z*)-*β*-deuteriostyrene (Scheme 16: entry 3). In order to explain the pressure-induced increase in stereoselectivity the authors concluded that, in the diradical intermediate at high pressure, the ring-closure reactions leading to the (*Z*)-configured methylenecyclobutane derivatives are favored over bond rotation, which is a prerequisite for the formation of (*E*)-configurated methylenecyclobutanes.

Reaction					$\Delta V^{\neq a}$	ΔV^{a}	Reference
	i-PrPh, 80 °C				–37.6[b]	–36.1[c]	151
(1) 	*i*-PrPh, 80 °C				–33.1[b]	–34.9[c]	151
	MePh, 50 °C		+		–31.0[d]	–33.6[c]	152
		[6+4]		[4+2]			
product ratio	(p = 0.9 kbar)	10.0	:	1			
	(p = 6.9 kbar)	10.8	:	1			
	$\delta\Delta V^{\neq a)} = \Delta V^{\neq}$ [6+4] $- \Delta V^{\neq}$ [4+2] = –0.3						

[a] In cm^3 mol^{-1}. [b] At 80 °C. [c] At 60 °C[153]. [d] At 50 °C.



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SCHEME 17. [6 + 4] and [8 + 2] Cycloadditions of tropone and a heptafulvene derivative

C. Higher Cycloadditions Involving Trienes and Tetraenes

The pressure dependence of the orbital symmetry-allowed [6 + 4] cycloaddition of tropone with 1,3-dienes was first studied by le Noble and Ojosipe[150], who reported extremely small absolute values of $\Delta V^{\neq}$ and ΔV. A reinvestigation by Takeshita and his coworkers[151] showed, however, that the activation and reaction volumes of these cycloadditions are of the same order of magnitude as those of Diels–Alder reactions (Scheme 17: entry 1). Dogan[152] confirmed this finding with a study of the reaction between 1,3-butadiene and tropone in which a [6 + 4] cycloaddition competes with a [4 + 2] Diels–Alder reaction. The activation volume of the overall reaction was again found to be highly negative. However, the ratio between the [6+4] and [4+2] cycloadduct turned out to be almost pressure-independent, which means that the difference between the activation volumes ($\delta\Delta V^{\neq}$) is almost zero and hence the activation volumes of both reactions are of the same value.

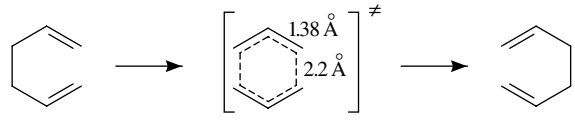
Tropone can also react as a tetraene component in [8 + 2] cycloadditions including the C=O double bond. Tropone reacts, e.g., with 1,1-diethoxyethene (at 120 °C, 10 h, 1 bar) to give the corresponding [4 + 2], [8 + 2] and [6 + 4] cycloadduct in yields of 1.1, 9.1 and 3.1%, respectively (conversion of tropone: 16%). At 3 kbar, 120 °C, only the [4 + 2] and [8 + 2] cycloadducts were formed in yields of 13 and 17%, respectively (conversion of tropone: 30%)[155]. Tropone reacts with 2,3-dihydrofuran in a similar fashion leading to the corresponding [8 + 2] and [4 + 2] cycloadducts. The product ratio is again pressure-dependent[156]. The heptafulvene derivative shown in Scheme 17 can undergo a [8 + 2] cycloaddition leading to methyl azulene-1-carboxylate, obviously after elimination of CO_2 and ethanol from the undetected primary cycloadduct. The [8+2] cycloaddition competes with [4 + 2] cycloadditions. Study of the pressure effect on the competitive reactions showed that the formation of the [4 + 2] cycloadduct is reversible even at 10 kbar, and that the [4 + 2] cycloadduct is not directly converted to methyl azulene-1-carboxylate. Thus, the azulene formation can only occur via the intermediate [8 + 2] cycloadduct.

IV. PERICYCLIC REARRANGEMENTS

Many pericyclic rearrangements show a pressure-induced acceleration which is characterized by a negative volume of activation[157]. The effect, which is usually smaller than that of intermolecular cycloadditions, may be explained with different packing coefficients of cyclic and acyclic states as already discussed for the pericyclic and stepwise cycloadditions.

A. Sigmatropic [3.3] Shifts: Cope and Claisen Rearrangements

On the basis of stereochemical and kinetic investigations, most Cope rearrangements are regarded as being pericyclic processes[158]. The van der Waals volumes calculated for the parent 1,5-hexadiene and the pericyclic transition state are approximately the same (Scheme 18). This is understandable since in the symmetrical transition state the bond breaking and making have proceeded to the same extent so that the effects of the two processes on the van der Waals volume compensate each other and no great overall effect of pressure on the Cope rearrangement is to be expected. If it is assumed that, by analogy with the pericyclic and stepwise cycloadditions already discussed, the transition state here also exhibits a larger packing coefficient because of its cyclic geometry, the activation volume ought to be negative. The activation volume can be estimated at approximately $-10\ \mathrm{cm^3\,mol^{-1}}$ if the packing coefficient determined for cyclohexene is used for the unknown packing coefficient of the transition state. In fact, negative activation volumes of the expected size were found for the Cope rearrangements and related Claisen



V_W	63.9	63.6	$\Delta V_W^{\neq} = -0.3$
V	119.4	109.1	$\Delta V^{\neq} = -10.3$

All volumes are given in $cm^3\ mol^{-1}$. The structural parameters necessary for the calculation of the van der Waals volume for the transition state (TS) were taken from *ab initio* calculations[159,160]. The partial molar volume for the TS was calculated from the equation:

$$V(\mathrm{TS}) = V_W(\mathrm{TS})/\eta(\text{cyclohexene});\ \eta V_W/V = 0.5829(\text{cyclohexene})$$

SCHEME 18. van der Waals volume of activation $\Delta V_W^{\neq}$ and volume of activation $\Delta V^{\neq}$ calculated for degenerate Cope rearrangement of 1,5-hexadiene

rearrangements shown in Scheme 19. However, the reacting compounds are highly polar, so the negative activation volumes could also be due to electrostriction effects rather than as a consequence of the cyclic transition states.

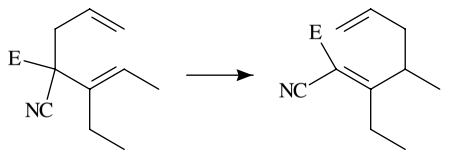
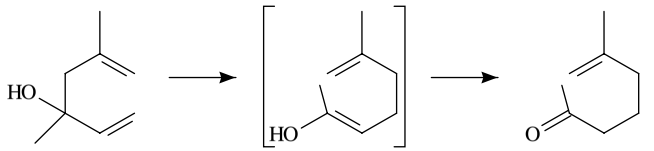
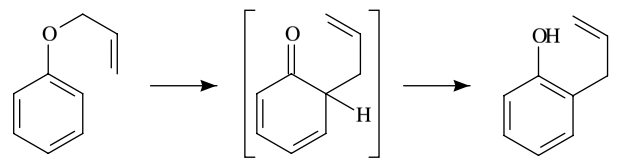
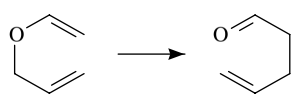
The activation volumes obtained from the pressure dependence of the Cope rearrangements in pure hydrocarbons, in which electrostriction effects caused by polar substituents should be negligible, were in good agreement with that predicted for the parent system (Scheme 20: entries 1–4). This concept elucidates why the degenerate Cope rearrangement in bullvalene, investigated by Merbach, le Noble and coworkers[166] with pressure- and temperature-dependent NMR spectroscopy, shows no significant pressure effect ($\Delta V^{\neq} = -0.5\ cm^3\ mol^{-1}$) (Scheme 20: entry 5). As a result of the fixed stereochemistry due to the rigid bullvalene skeleton no new cyclic interaction, in the sense discussed here, appears in the transition state.

B. Potential Sigmatropic [1.*n*] Shifts (Hydrogen, Carbon, Silicon)

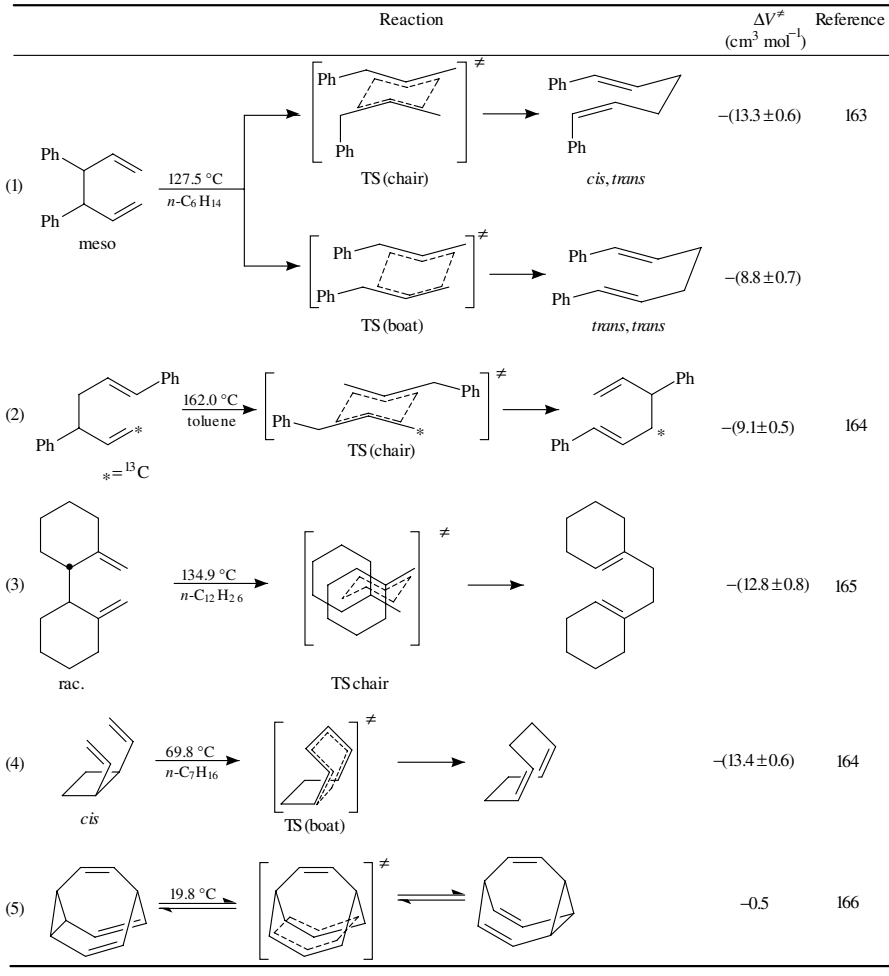
In Scheme 21 the activation volume data for some potential sigmatropic [1,*n*] carbon, silicon or hydrogen shifts ($n = 3$–9) are summarized. Analogously to the Cope rearrangement (sigmatropic [3,3] carbon shift) the activation volumes turned out to be negative in cases of pericyclic mechanism while the activation volumes are positive in cases of dissociative mechanism. The [1,4] shift of a benzyl or benzhydryl group in 1-alkoxypyridine-N-oxides (Scheme 21: entry 3), is particularly instructive. From the completely different pressure response of the two reactions, le Noble and Daka[169] concluded that the shift of the benzyl group occurs via a pericyclic mechanism while that of the benzhydryl group proceeds via a dissociative radical-pair mechanism. The conclusion drawn from the different activation volumes is in full accord with the stereochemical finding of retention of configuration in the PhCHD migration and the observation of a CIDNP (Chemically Induced Dynamic Nuclear Polarization) effect in the Ph_2CH migration[173].

C. Electrocyclic Rearrangements

In the transition state of the electrocyclization of (*Z*)-1,3,5-hexatriene to 1,3-cyclohexadiene (Scheme 22: entry 1) a new six-membered ring develops analogously

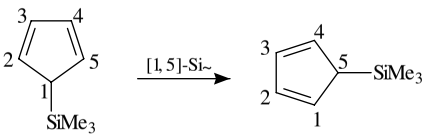
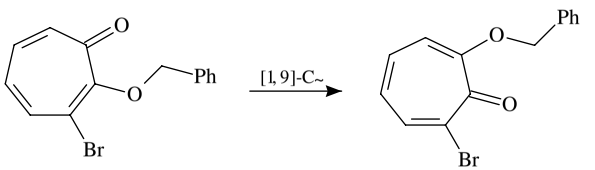
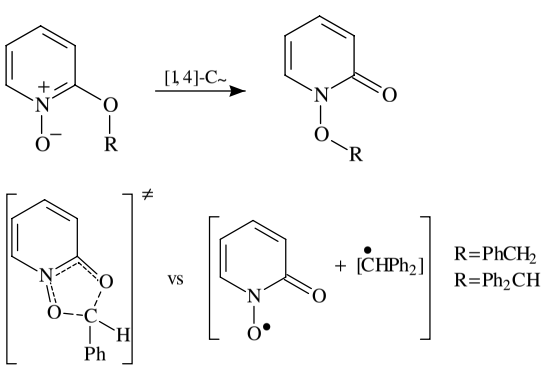
	Reaction	T(°C)	Solvent ($cm^3\ mol^{-1}$)	$\Delta V_T^{\neq}$	Reference
(1)		119	decalin	−6.7	161
(2)		180	*N*-methyl-pyrrolidone	−9.7	162
(3)		160	decalin	−7.7	161
(4)		130.4	neat	−18	161

SCHEME 19. Activation volumes of Cope and Claisen rearrangements in polar 1,5-hexadiene systems

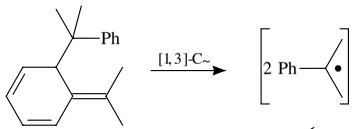
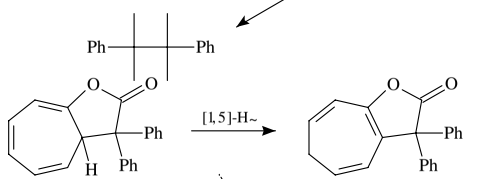
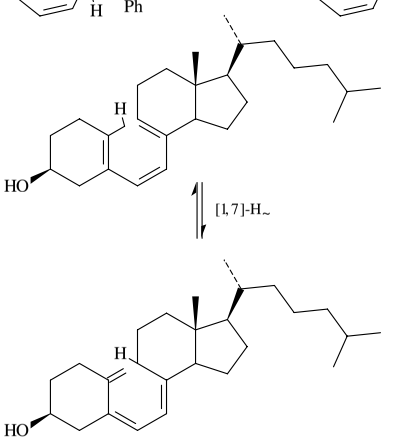


SCHEME 20. Activation volumes of Cope rearrangements in unpolar 1,5-hexadiene systems

to that of the Cope rearrangement. The electrocyclization is accelerated by an increase in pressure. The activation volume determined at different temperatures listed in Scheme 22 is about $-10\ cm^3\ mol^{-1}$ and corresponds to those of the Cope rearrangements (Scheme 20). Over the temperature range of about 20 °C investigated the activation volume does not show any significant temperature dependence within the experimental limits of error $\pm 1\ cm^3\ mol^{-1}$. From the volume data shown in Scheme 22, the packing coefficient of the transition state is calculated to equal approximately that of the cyclic product and differs substantially from that of the acyclic reactant. This result provides good evidence for the assumption used in the explanation of the pressure effect on pericyclic reactions. From the complete volume data set of the (*Z*)-1,3,5-hexatriene $\rightarrow$ 1, 3-cyclohexadiene isomerization, the activation volume of the reverse reaction, the electrocyclic ring-opening 1,3-cyclohexadiene $\rightarrow$ (*Z*)-1,3,5-hexatriene can be extrapolated to be slightly positive ($\Delta V^{\neq} = +4\ cm^3\ mol^{-1}$). The electrocyclic

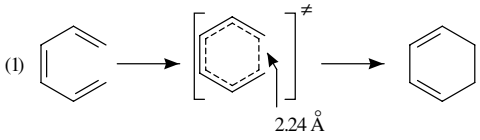
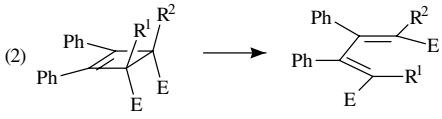
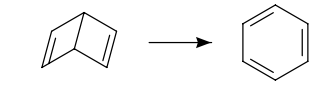
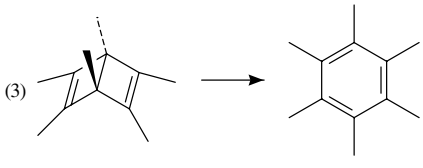
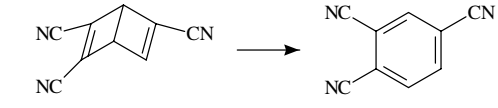
	Reaction	T(°C)	Solvent	$\Delta V_T^{\neq}$ ($cm^3\ mol^{-1}$)	Reference
(1)		68	Benzene-freon	−12.5	167
(2)		130	*i*-Pr-Ph	−11.1	168
(3)		100	diglyme	−30 +10	169

SCHEME 21. Activation volumes of potential sigmatropic [1,*n*] shifts ($n = 3,4,5,7,9$)

	Reaction	T(°C)	Solvent	$\Delta V_T^{\neq}$ ($cm^3\ mol^{-1}$)	Reference
(4)		20	cyclohexane	+6	170
(5)		130	n-Bu_2O	−2.2	171
(6)		20	benzene/ toluene	$< -5^a$	172

[a] Estimated from two experiments at 1 bar and 15 kbar.

SCHEME 21. (*continued*)

Reaction	T(°C)	$\Delta V_T^{\neq a}$	ΔV_T^{a}	θ	Reference
(1) 	101.2	–9.8	–14.4	0.68	
	108.1	–10.8	–14.8	0.73	
	117.5	–10.9	–15.2	0.72	174
	122.4	–10.3	–15.4	0.67	
V_W^a 61.2 58.6 57.0					
V^b 118.7 107.9 103.9					175
η 0.5156 0.5431 0.5486					
(2) 					176, 177
R^1=H, R^2=H		–1 to –2			
R^1=R^2=Me		–7			
R^1=H, R^2=Me	70	–12.7	–23[c]		
	20	+5			178
(3) 	140	–12	–22		178, 179
	51.3	≈0			180

[a] In $cm^3\,mol^{-1}$; the reaction volume ΔV_T was calculated from the partial molar volumes V_T determined by the temperature dependence of the densitites of reactant or product according to Scheme 2.

[b] 108.1 °C in toluene.

[c] In toluene.

SCHEME 22 Activation and reaction volumes of electrocyclic rearrangements

ring-opening of heavily substituted cyclobutene derivatives, however, shows negative activation volumes of different size depending on the substitution pattern (Scheme 22: entry 2). This result indicates that other effects, such as an increase of steric crowding, contribute to the activation volume, overcompensating the effect of ring-opening. A clear-cut example is the ring-opening of Dewar benzene to benzene. The isomerization of the parent Dewar benzene is retarded by pressure ($\Delta V^{\neq} = +5\ cm^3\,mol^{-1}$) (Scheme 22: entry 3) whereas the isomerization of the hexamethyl derivative is accelerated by pressure ($\Delta V^{\neq} = -12\ cm^3\,mol^{-1}$). The negative volume of activation of the latter isomerization can be again explained by steric crowding of the six methyl groups which is larger in the planar hexamethylbenzene than in the nonplanar precursor, overcompensating the volume-increasing effect of ring-opening.

D. Intramolecular Diels–Alder Reactions

In intramolecular Diels–Alder reactions, two new rings are formed. There are examples of relatively large pressure-induced accelerations which can be exploited for preparative purposes (Scheme 22: entries 1–5). These compounds, without exception, contain polar groups and are therefore not very suitable for the analysis of the relation between pressure effect and ring formation. The strong solvent dependence of the activation volume of the intramolecular Diels–Alder reaction shown in Scheme 23, entry 2, turned out to be largely the result of the strongly solvent-dependent partial molar volume of the reactant — V(reactant) — whereas the partial molar volume of the transition state [$V^{\neq} = \Delta V^{\neq} + V$(reactant)] appears to be almost unaffected by the nature of the solvents. The activation volumes of the intramolecular Diels–Alder reactions in the pure hydrocarbon systems (Scheme 23: entries 6 and 7) were found to be $\Delta V^{\neq} = -24.8\ \mathrm{cm^3\,mol^{-1}}$ or $\Delta V^{\neq} = -37.6$ and $-35.0\ \mathrm{cm^3\,mol^{-1}}$, respectively. The absolute values here are approximately twice as large as, or even larger than, those observed for the Cope rearrangements or the electrocyclization of 1,3,5-hexatriene to 1,3-cyclohexadiene. From this it was extrapolated that each additional five- or six-membered ring formed in the rate-determining step of reactions contributes about -10 to $-15\ \mathrm{cm^3\,mol^{-1}}$ to the activation volume.

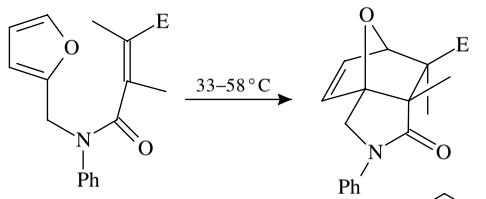
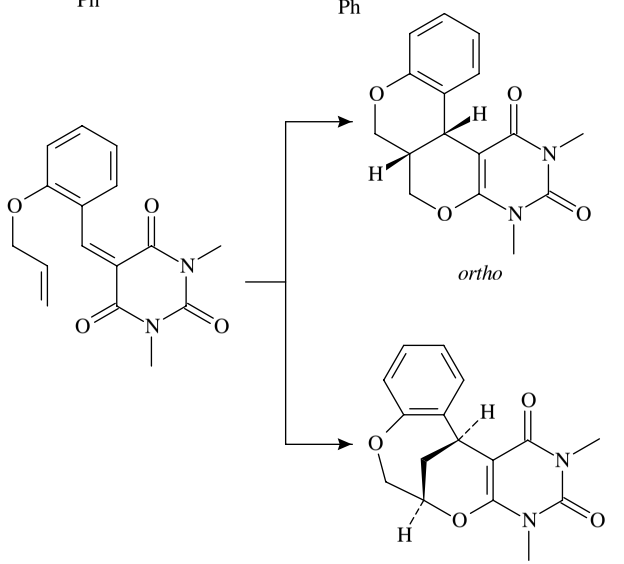
A particularly instructive example is the thermolysis of (*Z*)-1,3,8-nonatriene in which an intramolecular Diels–Alder reaction competes with a sigmatropic [1,5] hydrogen shift (Scheme 24). The use of high pressure here enables a reversal of the selectivity. At 150 °C and 1 bar the [1,5] hydrogen shift passing through a monocyclic transition state is preferred. At 7.7 kbar the intramolecular Diels–Alder reaction is preferred due to its bicyclic transition state.

E. The Relationship between Activation or Reaction Volume and Ring Size

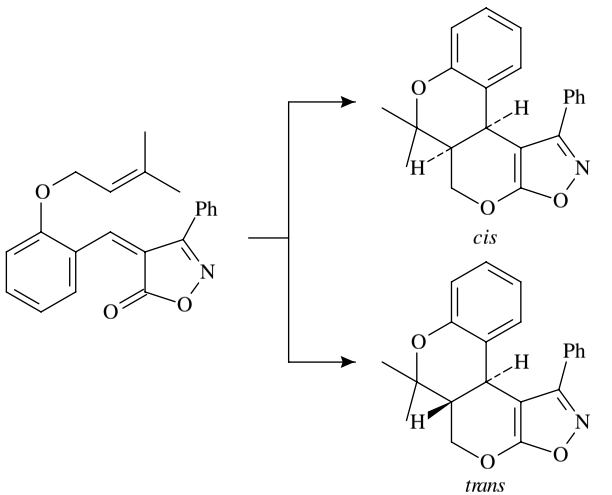
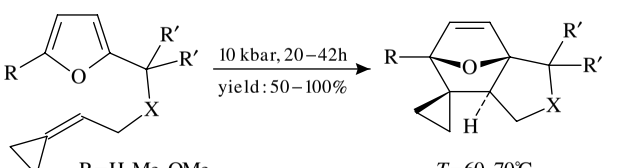
The investigation of the pressure effect on the rearrangement and cleavage of *trans*-1,2-divinylcyclobutane showed that the volume of reaction depends not only on the number but also on the size of the newly forming ring. In contrast to the Cope rearrangement of *cis*-1,2-divinylcyclobutane (Scheme 20: entry 4) the competitive reactions of *trans*-1,2-divinylcyclobutane leading to 4-vinylcyclohexene, 1,5-cyclooctadiene and 1,3-butadiene are slowed by pressure and the volumes of activation become positive, consistent with the hypothesis of the opening of the cyclobutane ring leading to an acyclic diradical intermediate (Scheme 25). Because the product ratio shows no significant pressure dependence, the activation volumes of the individual reactions are essentially equal. It was concluded here that in the diradical intermediate neither ring closure reactions nor cleavage are product-determining, contrary to the [2 + 2] cycloaddition shown in Scheme 16, entry 3. Probably pressure-independent rotations about C−C bonds in the diradical determine the distributions among the three products.

The volumes of reaction determined for the isomerization of *trans*-1,2-divinylcyclobutane to 4-vinylcyclohexene or 1,5-cyclooctadiene, in which a six- or eight-membered ring is formed, respectively, at the expense of a four-membered ring, were found to be highly negative. This observation of the decrease in volume from the four- to the six- or eight-membered ring indicates that the activation volumes of cyclizations also depend on the size of the newly forming ring. The van der Waals volumes of the cyclic structures do not differ from each other appreciably and cannot explain the observed differences between the reaction volumes.

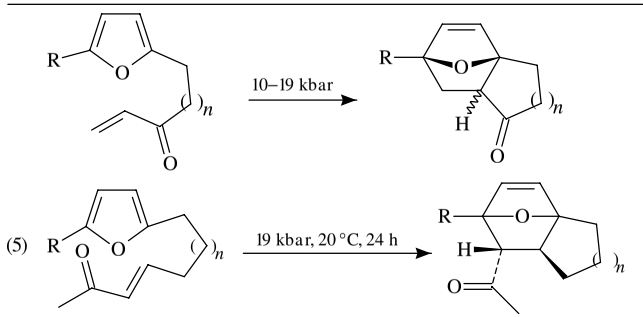
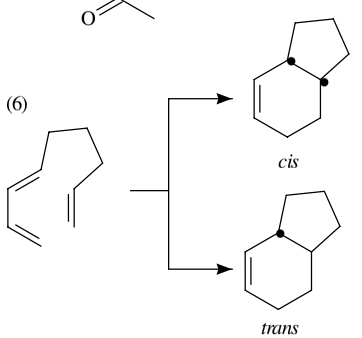
The volumes of reaction calculated for the hypothetical cyclizations of *n*-alkenes to the corresponding cycloalkanes by the use of experimentally observed partial molar volumes[190] confirm the trend derived from the ring enlargements shown in Scheme 25.

		Solvent	$\Delta V_T^{\neq a}$	$\Delta V_{20}^{\neq a}$	$\Delta V_{20}{}^a$	Reference
(1)			–25		–23	181
(2)	 *ortho*	CH_2Cl_2 THF PhMe MeCN	–33.1 –34.2 –17.0 –13.4	–23.6 –24.4 –9.5 –12.5	–30 –35 –18 –15	182
	meta	CH_2Cl_2 THF PhMe MeCN	–32.1 –32.7 –15.2 –12.1			
	$T = 110\,^{\circ}C$; *ortho* : *meta* = (3.8 – 6.8) : 1					

SCHEME 23. Intramolecular Diels–Alder reactions

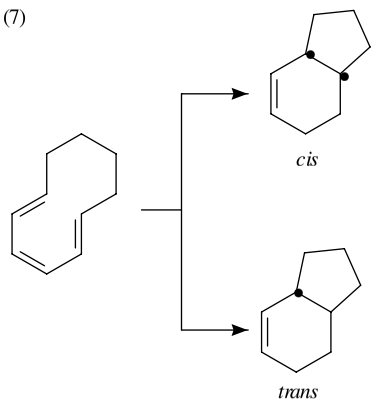
		Solvent	$\Delta V_T^{\neq a}$	$\Delta V_{20}^{\neq a}$	$\Delta V_{20}{}^a$	Reference
(3)	 *cis*	CH_2Cl_2	−19.4			183
	trans	CH_2Cl_2	−17.9			
	T=70°C; *cis* : *trans* = (5.5 − 6.8) : 1					
(4)	 R = H, Me, OMe; R′ = H, Me, =O; X = O, NMe	MeCN/ THF	−15.9			184
	T = 60–70°C for R = R′ = H, X = O:					

SCHEME 23. (*continued*)

		Solvent	$\Delta V_T^{\neq a}$	$\Delta V_{20}^{\neq a}$	$\Delta V_{20}{}^a$	Reference
(5)						185
(6)		n–C_6H_{14}	−24.8			186
		n–C_6H_{14}	−24.8			

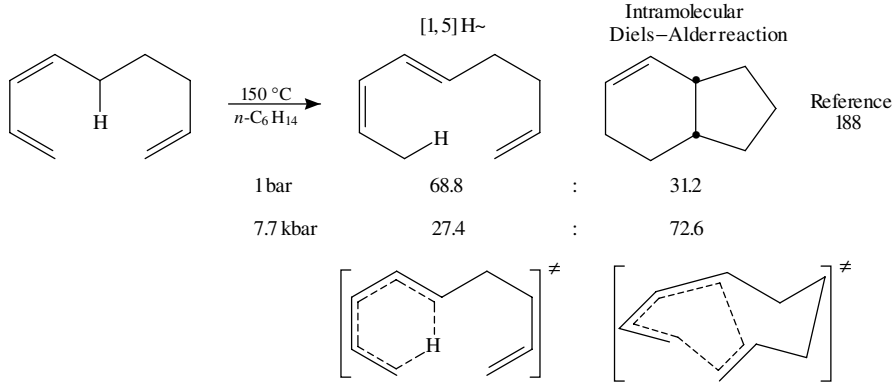
T = 153.2 °C; *cis* : *trans* = 3.0 : 1

SCHEME 23. (*continued*)

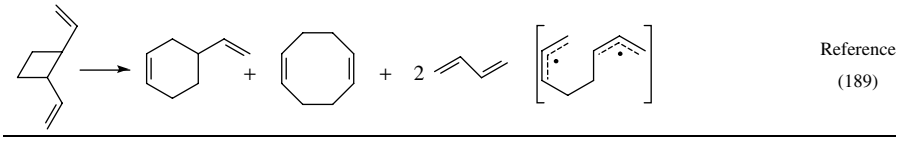
	Solvent	$\Delta V_T^{\neq a}$	$\Delta V_{20}^{\neq\ a}$	$\Delta V_{20}{}^a$	Reference
(7)  *cis* *trans* $T = 172.5\,^{\circ}C$; *cis* : *trans* = 1.2 : 1	n–C_7H_{16}	−37.6			187
	n–C_7H_{16}	−35.0			

[a] In $cm^3\,mol^{-1}$; the $\Delta V_{20}^{\neq}$ values were extrapolated from the $\Delta V_T^{\neq}$ values by using the El'yanov equation(equation I).

SCHEME 23. (*continued*)



SCHEME 24. The effect of pressure on the competitive rearrangements of *cis*-1,3,8-nonatriene



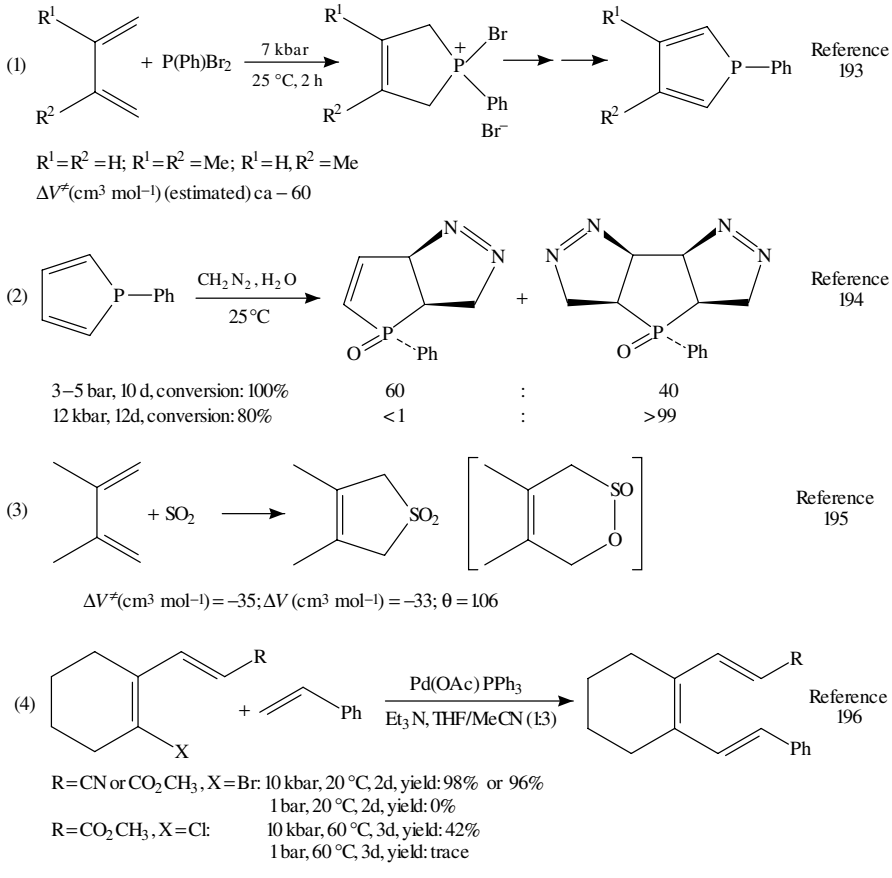
V_W ($cm^3\ mol^{-1}$):	79.3	77.5	76.6	$2 \times 44.8 = 89.6$	82.4
$\Delta V^{\neq}$ ($cm^3\ mol^{-1}$) (159.6 °C):		$+(4.2 \pm 0.7)$	$+(4.1 \pm 0.4)$	$+(5.0 \pm 9.5)$	
V ($cm^3\ mol^{-1}$) (159.6 °C):	162.0	149.0	135.2		
$\eta = V_W/V$	0.4895	0.5201	0.5666	0.4958	
V ($cm^3\ mol^{-1}$) (20.0 °C):	140.0	130.4	122.6	$2.83.2 = 166.4$	
ΔV ($cm^3\ mol^{-1}$):		$130.4 - 140.0 = -9.6$	$122.6 - 140.0 = -17.4$	$166.4 - 140.0 = +26.4$	

SCHEME 25. Activation and reaction volumes of the ring enlargment of *trans*-1,2-divinylcyclobutane

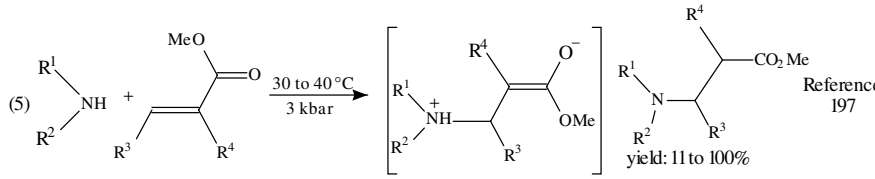
The volumes of reaction decrease continuously from formation of cyclopropane (from 1-propene: $\Delta V = -5.5\ cm^3\ mol^{-1}$) up to the formation of cyclodecane (from 1-decene: $\Delta V = -32.3\ cm^3\ mol^{-1}$) and then seem to be constant for the larger rings, whereas the van der Waals volumes of reaction are approximately equal ($\Delta V_W = -4.4$ to $-4.9\ cm^3\ mol^{-1}$) with the exception of the cyclopropane, cyclobutane and cyclopentane formation, and therefore independent of the ring size. Provided that the activation volumes depend similarly on the ring size, the formation of larger rings should be dramatically accelerated by pressure. The intramolecular Diels–Alder reactions of (*E*)-1,3,8-nonatriene and (*E*)-1,3,9-decatriene, in which either a new five- and six-membered ring or two new six-membered rings are formed, seems to be the first example for the validity of this assumption (Scheme 23: entries 6 and 7). Furthermore, this ring-size effect explains why the activation volume of the formation of three-membered rings in cheleotropic reactions of carbenes with alkenes[191] and of the five-membered rings in 1,3-dipolar cycloadditions[23,25,192] are substantially less negative than those of the formation of six-membered rings in the Diels–Alder reactions.

V. MISCELLANEOUS REACTIONS OF DIENES AND POLYENES

Other reactions than the pericyclic processes discussed in the previous sections can profit from high pressure. Scheme 26 shows a few recent examples which are related to the topic of this chapter. In the addition of dibromophenylphosphane to 1,3-dienes (Scheme 26: entry 1) charge separation and ring formation lead to a dramatic decrease in volume [$\Delta V^{\neq}$ (estimated) ≈ -60 cm^3 mol^{-1}] so that this reaction is strongly accelerated by pressure. The first step in the reaction of diazomethane with 1-phenylphosphole (Scheme 26: entry 2) is certainly the addition of diazomethane to the phosphorus ($R_3P + CH_2N_2 \rightarrow R_3P{=}N{-}N{=}CH_2$)[199] followed by hydrolysis leading to the highly reactive 1-phenylphosphole-1-oxide which reacts with diazomethane in the fashion of a 1,3-dipolar cycloaddition to form the monoadduct and subsequently the bisadduct. (In the absence of water none of the cycloadducts is formed[200].) Apparently, high pressure has a strongly rate-enhancing effect on the first addition of diazomethane and the 1,3-dipolar cycloaddition as well, so that the reaction is almost completed at 12 kbar within 12 hours compared to 10 days at 3–5 bars where the monoadduct is formed preferentially.



SCHEME 26. Miscellaneous reaction of dienes and polyenes



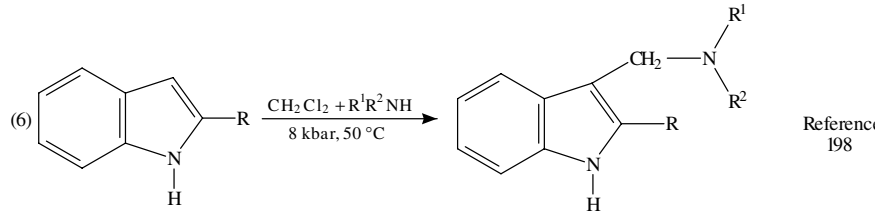
R^1 = *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, R^2 = H, $R^3 = R^4 = H$

$R^1 = R^2$ = *n*-Pr R^3 = Me, R^4 = H

R^3 = H, R^4 = Me

$\Delta V^{\neq}$ ($cm^3\ mol^{-1}$) = − (42 to 53)

ΔV ($cm^3\ mol^{-1}$) = − (25 to 26)



SCHEME 26. (*continued*)

The addition of SO_2 to 1,3-dienes is considered to be an example of a linear cheleotropic reaction. The activation volume of the reaction between SO_2 and 2,3-dimethyl-1,3-butadiene was found by Isaacs and Laila to be more negative than the reaction volume ($\theta = \Delta V^{\neq}/\Delta V = 1.06$) (Scheme 26: entry 3). Comparable to several Diels–Alder reactions, the transition state volume is smaller than that of the product. Due to the large θ value one might speculate that in the rate-determining step the Diels–Alder adduct (the six-membered ring sulfinic ester)[201] is formed followed by a rearrangement to the observed five-membered ring sulfone.

The palladium-catalyzed Heck reaction of styrene with bromo- or chlorodienes leading to conjugated trienes (Scheme 26: entry 4) is also accelerated by pressure and the yields can be improved from 0% at 1 bar to 42–98% at 10 kbar. These findings indicate that the rate-determing steps of the Heck reaction are associative. The Heck coupling between aryl nonaflates (nonafluorobenzenesulfonate, ArONf) and 2,3-dihydrofuran in the presence of $Pd(OAc)_2$ and a chiral ligand [(R)-BINAP] shows a higher enantioselectivity at 10 kbar than at 1 bar[202]. The nucleophilic addition of primary and secondary amines to methyl acrylates (Scheme 26: entry 5) shows a powerful pressure-induced acceleration (with activation volumes smaller than the corresponding reaction volumes, $\theta = \Delta V^{\neq}/\Delta V > 1$). These findings are understandable on the assumption that in the rate-determing step a zwitterionic intermediate is formed. A pronounced effect is also observed for the Mannich reaction of indoles with dichloromethane and secondary amines (Scheme 26: entry 6) indicating that polar intermediates are involved in this reaction.

VI. CONCLUDING REMARKS

The packing coefficient, $\eta = V_W/V$, has been demonstrated to be a valuable tool with which to explain the effect of pressure on many pericyclic reactions. The finding, that η

of cyclic structures is larger than that of the corresponding acyclic structures, explains the preference of pericyclic cycloaddition over the corresponding stepwise reactions at high pressure and the negative activation volumes of many pericyclic rearrangements. The size of η depends on the number and size of the newly forming rings. This explains why, e.g., intramolecular Diels–Alder reactions involving bicyclic transition state are favored over rearrangements involving monocyclic transition states.

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VIII. REFERENCES

1. N. S. Isaacs, *Liquid Phase Pressure Chemistry*, Wiley, New York, 1981.
2. W. J. le Noble (Ed.), *Organic High Pressure Chemistry*, Elsevier, Amsterdam, 1988.
3. E. K. Matsumoto and R. M. Cheson (Eds.), *Organic Synthesis at High Pressure*, Wiley, New York, 1991.
4. R. van Eldik and C. D. Hubbard (Eds.), *Chemistry Under Extreme or Non-Classic Conditions*, Spektrum Academischer Verlag, Heidelberg; Wiley, New York, in press.
5. T. Asano and W. J. le Noble, *Chem. Rev.*, **78**, 407–489 (1978).
6. R. van Eldik, T. Asano and W. J. le Noble, *Chem. Rev.*, **89**, 549–688 (1989).
7. W. J. le Noble and H. Kelm, *Angew. Chem.*, **92**, 887–904 (1980); *Angew. Chem. Int. Ed. Engl.*, **19**, 841–856 (1980).
8. W. J. le Noble, *Chem. unserer Zeit*, **17**, 152–162 (1983).
9. G. Jenner, *J. Chem. Soc., Faraday Trans. 1*, **81**, 2437–2460 (1985).
10. K. Matsumoto, A. Sera and T. Uchida, *Synthesis*, 1–26 (1985).
11. K. Mastumoto and A. Sera, *Synthesis* 999–1027 (1985).
12. W. J. le Noble, in *High Pressure Chemistry and Biochemistry*, (Eds. R. van Eldik and J. Jonas), D. Reidel, Dordrecht, 1987, pp. 279–293 and 295–310.
13. F. -G. Klärner, *Chem. unserer Zeit*, **23**, 53–63 (1989).
14. F. -G. Klärner, V. Ruster, B. Zimny and D. Hochstrate, *High Pressure Res.*, **7**, 133–135 (1991).
15. N. S. Isaacs, *Tetrahedron*, **47**, 8463–8497 (1991).
16. M. Buback, *Angew. Chem.*, **103**, 658–670; (1991), *Angew. Chem., Int. Ed. Engl.*, **30**, 641–653 (1991).
17. (a) Nova Swiss, Nova Werke AG, Vogelsangstraße 24, CH-8307 Effretikon, Switzerland.
    (b) Bernd Dieckers GmbH, Meß- und Prüfanlagen-Technik, Hagwinkel 46, D-47877 Willich-Neersen, Germany.
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18. O. Exner, 'Empirical calculations of molar volumes', Chap. 2, p. 19 in Reference 2.
19. J. L. Franklin, *Ind. Eng. Chem.*, **41**, 1070 (1949).
20. S. W. Benson, *Thermochemical Kinetics*, 2nd ed., Wiley, New York, 1976.
21. W. J. le Noble, in *High Pressure Chemistry and Biochemistry* (Eds. R. van Eldik and J. Jonas), D. Reidel, Dordrecht, 1987, pp. 279–293.
22. (a) H. Olsen and J. P. Snyder, *J. Am. Chem. Soc.*, **100**, 285 (1978). The authors derived the volumes of activation for the N_2 elimination of various bicyclic and tricyclic azo compounds from the solvent dependence by using the solubility parameter δ. A direct comparison with activation volumes determined by the pressure dependence is here impossible, since activation volumes have been determined by the use of the latter method only for the N_2 elimination from acyclic azo compounds.

(b) R. C. Neumann, Jr., and G. Al. Binegar, *J. Am. Chem. Soc.*, **105**, 134 (1983).
(c) R. C. Neumann, Jr. and G. D. Lockyer, Jr., *J. Am. Chem. Soc.*, **105**, 3982 (1983).
(d) R. C. Neuman, Jr. and M. J. Amrich, Jr., *J. Org. Chem.*, **45**, 4629 (1980).
23. G. Swieton, J. von Jouanne, H. Kelm and R. Huisgen, *J. Org. Chem.*, **48**, 1035 (1983).
24. T. Asano and T. Okada, *J. Phys. Chem.*, **88**, 238 (1984).
25. (a) Y. Yoshimura, J. Osugi and M. Nakahara, *Bull. Chem. Soc. Jpn.*, **56**, 680 (1983); Y. Yoshimura, J. Osugi and M. Nakahara, *J. Am. Chem. Soc.*, **105**, 5414 (1983).
(b) The van der Waals volumes V_W can be calculated by the computer program MOLVOL: U. Artschwager-Perl, *Cycloadditionen unter hohem Druck*, Ph.D. Dissertation, Ruhr-Universität Bochum, 1989. This program uses the cartesian coordinates of a molecular structure resulting from a force field or quantum mechanical calculations and can be obtained on request V_W of ground states can also be calculated from tables of group contributions to the van der Waals volumes published by A. Bondi[26].
26. A. Bondi, *J. Chem. Phys.*, **68**, 441 (1964).
27. T. Asano and W. J. le Noble, *Rev. Phys. Soc. Jpn.*, **43**, 82 (1973).
28. G. Jenner, *Angew. Chem.*, **87**, 186 (1975); *Angew. Chem. Int. Ed. Engl.*, **14**, 137 (1975).
29. J. Rimmelin and G. Jenner, *Tetrahedron*, **30**, 3081 (1974). A recent measurement of the pressure and temperature dependence of the electrocyclic ring-closure of *Z*-1,3,5-hexatriene to 1,3-cyclohexadiene in the range of 200 to 2500 bar and 100 to 125 °C does not show a significant temperature dependence of the activation volume (M. K. Diedrich and F. -G. Klärner, unpublished results).
30. B. S. El'yanov and E. M. Gonikberg, *J. Chem. Soc., Faraday Trans. 1.*, **75**, 172 (1969); B. S. El'yanov and E. M. Vasylvitskaya, *Rev. Phys. Chem. Jpn.*, **50**, 169 (1980).
31. K. Seguchi, A. Sera and K. Maruyama, *Bull. Chem. Soc. Jpn.*, **47**, 2242 (1974).
32. J. Rimmelin and G. Jenner, *Tetrahedron*, **30**, 3081 (1974).
33. G. Jenner and J. Rimmelin, *Tetrahedron Lett.*, **21**, 3039 (1980).
34. J. R. Mc Cabe and C. A. Eckert, *Ind. Eng. Chem. Fundam.*, **13**, 168 (1973).
35. C. Brun and G. Jenner, *Tetrahedron*, **28**, 3113 (1972).
36. G. Jenner, *New J. Chem.*, **15**, 897 (1991).
37. K. Beck, S. Hünig, F. -G. Klärner, P. Kraft and U. Artschwager-Perl, *Chem. Ber.*, **120**, 2041 (1987).
38. H. Takeshita, S. Sugiyama and T. Hatsin, *Bull. Chem. Soc. Jpn.*, **58**, 2490 (1985).
39. R. A. Grieger and C. A. Eckert, *Trans. Faraday Soc.*, **66**, 2579 (1970).
40. R. A. Grieger and C. A. Eckert, *Ind. Eng. Chem. Fundam.*, **10**, 369 (1971).
41. J. R. McCabe and C. A. Eckert, *Ind. Eng. Chem. Fundam.*, **13**, 168 (1974).
42. J. Rimmelin, G. Jenner and H. Abdi-Oskoui, *Bull. Soc. Chim. Fr.*, 341 (1977).
43. G. Jenner, M. Papadopoulos and J. Rimmelin, *J. Org. Chem.*, **48**, 748 (1983).
44. A. V. George, and N. S. Isaacs, *J. Chem. Soc., Perkin Trans. 2.*, 1845 (1985).
45. V. Breitkopf and F. -G. Kläner, unpublished results.
46. K. N. Houk. Y. Li and J. D. Evanseck, *Angew. Chem.*, **104**, 711 (1992) *Angew. Chem., Int. Ed. Engl.*, **31**, 682 (1992) Y. Li and K. N. Houk, *J. Am. Chem. Soc.*, **115**, 5414 (1993).
47. (a) R. A. Grieger and C. A. Eckert, *J. Am. Chem. Soc.*, **92**, 2918, 7149 (1970); *Trans. Farad. Soc.* **66**, 2579 (1970).
(b) J. R. McCabe and C. A. Eckert, *Ind. Eng. Chem., Fundam.*, **13**, 168 (1973).
48. According to recent quantum mechanical calculations, the importance of secondary orbital interactions, which have also been frequently used to explain the *endo* diastereoselectivity of Diels–Alder reactions, seems to be questionable and to be reserved for special cases like the addition of cyclopropene to various dienes. T. Karcher, W. Sicking, J. Sauer and R. Sustmann, *Tetrahedron Lett.*, **33**, 8027 (1992); R. Sustmann and W. Sicking, *Tetrahedron*, **48**, 10293 (1992); Y. Apeloig and E. Matzner, *J. Am. Chem. Soc.*, **117**, 5375 (1995).
49. K. Seguchi, A. Sera and K. Maruyama, *Tetrahedron Lett.*, 1585 (1973).
50. C. A. Stewart Jr., *J. Am. Chem. Soc.*, **94**, 635 (1972).
51. F. -G. Klärner, B. M. J. Dogan, O. Ermer, W. v. E. Doering and M. P. Cohen, *Angew. Chem.*, **98**, 109 (1986) *Angew. Chem. Int. Ed. Engl.*, **25**, 110 (1986).
52. U. Deiters, F. -G. Klärner, B. Krawczyk and V. Ruster, *J. Am. Chem. Soc.*, **116**, 7646 (1994).
53. W. R. Roth and B. P. Scholz, *Chem. Ber.*, **114**, 3741 (1981); M. Bartmann *Zur Chemie des o-Chinodimethans und seiner Homologen*, Ph. D. Dissertation, Ruhr-Universität Bochum,

1980, B. M. J. Dogan *Organische Reaktionen unter hohem Druck; der Druckeffekt auf Konkur renzreaktionen*, Ph. D. Dissertation, Ruhr-Universität Bochum, 1984.
54. J. Baran, H. Mayr, V. Ruster and F. -G. Klärner, *J. Org. Chem.*, **54**, 5016 (1989).
55. J. C. Little, *J. Am. Chem. Soc.*, **87**, 4020 (1965).
56. V. Ruster, *Konkurrierende Cycloadditionen unter hohem Druck*, Ph. D. Dissertation, and *Organische Reaktionen unter hohem Druck; Konkurrenz von [2+2]- und [4+2]-Cycloadditionen*, Diplomarbeit, Ruhr-Univeristät Bochum, 1991 bzw. 1987.
57. P. D. Bartlett and K. E. Schmeller, *J. Am. Chem. Soc.*, **90**, 6077 (1968). J. S. Swenton and P. D. Bartlett, *J. Am. Chem. Soc.*, **90**, 2056 (1968).
58. D. Kaufmann and A. de Meijere, *Angew. Chem.*, **85**, 151 (1973); *Angew. Chem., Int. Ed. Engl.*, **12**, 159 (1973).
59. B. M. J. Dogan, *Organische Reaktionen unter hohem Druck; der Druckeffekt auf Konkurrenzreaktionen*, Ph. D. Dissertation, Ruhr-Universität Bochum, 1984.
60. M. R. de Camp, R. H. Levin and M. Jr. Jones, *Tetrahedron Lett.*, **15**, 3575 (1974).
61. H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961); H. D. Martin, S. Kagabu and H. J. Schiwek, *Tetrahedron Lett.*, **41**, 3311 (1975).
62. W. J. le Noble and R. Mukhtar, *J. Am. Chem. Soc.*, **96**, 6191 (1974).
63. (a) L. N. Kowa, D. Schwarzer, J. Troe and J. Schroeder, *J. Chem. Phys.*, **97**, 4827, (1992).
(b) M. A. Firestone and M. Vitale, *J. Org. Chem.*, **46**, 2160 (1981).
(c) T. Asano, H. Furika and H. Sumi, *J. Am. Chem. Soc.*, **116**, 5545 (1994); H. Sumi and T. Asano, *J. Chem. Phys.*, **102**, 9565 (1995); T. Asano, K. Cosstick, H. Furuta, K. Matsuo and H. Sumi, *Bull. Chem. Soc. Jpn.*, **69**, 551 (1996).
64. (a) PCMODEL, Serena Software, 1992, U. Burkert and N. L. Allinger, *'Molecular Mechanics'*, ACS Monograph Series, no. 175.
(b) Y. Li and N. K. Houk, *J. Am. Chem. Soc.*, **115**, 5414 (1993).
65. Similar calculations of van der Waals volumes have been carried out: R. A. Firestone and G. M. Smith, *Chem. Ber.*, **122**, 1089 (1989).
66. T. -T. Li and Y. L. Wu, *J. Am. Chem. Soc.*, **103**, 7007 (1981).
67. W. G. Dauben and W. R. Baker, *Tetrahedron Lett.*, **23**, 2611 (1982).
68. T. -T. Li and T. C. Walsgrove, *Tetrahedron Lett.*, **22**, 3741 (1981).
69. A. P. Kozikowski, T. Konoike and T. R. Nieduzak, *J. Chem. Soc., Chem. Commun.*, 1350 (1986).
70. S. Srivasta, A. P. Marchand, V. Vidyasagar, J. L. Flippen-Anderson, R. Gilardi, C. George, Z. Zachwieja, and W. J. le Noble, *J. Org. Chem.*, **54**, 247 (1989).
71. L. Minuti, A. Taticchi, E. Gacs-Baitz, and A. Marocchi, *Tetrahedron*, 1995, *51*, 8953–8958 (1995).
72. Y. Tsuda, S. Hosoi, N. Katagiri, C. Kaneko, and T. Sano, *Chem. Pharm. Bull.* 1993, *41*, 2087–2095 (1993).
73. V. Breitkopf, H. Hopf, F. -G. Klärner, B. Witulski, and B. Zimny, *Liebigs Ann.*, 1995, 613–617 (1995).
74. H. Katsuki, M. Kataoka, K. Matsuo, S. Suetomo, M. Shiro, and H. Nishizawa, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2773–2776 (1993).
75. L. A. Paquette, B. M. Brauen and R. D. Rogers, *J. Org. Chem.*, **60**, 1852 (1995).
76. G. Jenner, and M. Papadopoulos, *J. Org. Chem.*, **51**, 585 (1986).
77. G. Jenner and M. Papadopoulos, *Tetrahedron Lett.*, **26**, 3335 (1985).
78. M. J. Goldstein and A. H. Gevirtz, *Tetrahedron Lett.*, **6**, 4413 (1965).
79. S. Danishefsky and T. Kitahara, *J. Am. Chem. Soc.*, **96**, 7807 (1974).
80. Review on the synthesis and reactions of cyanoacetylene and dicyanoecetylene: E. Ciganek, W. J. Linn and O. W. Webster, in *The Chemistry of Functional Groups. The Chemistry of the Cyano Group* (Ed. Z. Rappoport), Wiley-Interscience, London, 1970, pp. 423–638.
81. E. Ciganek, *Tetrahedron Lett.*, 3321 (1967).
82. H. Hopf, B. Witulski, P. G. Jones and D. Schomburg, *Justus Liebigs Ann. Chem.*, 609 (1995).
83. W. H. Jones, D. Mangold and H. Plieninger, *Tetrahedron Lett.*, 267 (1962); H. Plieninger, D. Wild and J. Westphal, *Tetrahedron Lett.*, 5561 (1969).
84. V. Breitkopf and F. -G. Klärner, unpublished results.
85. K. Matsumoto, *Chem. Lett.*, 1681 (1985).
86. F. G. Klärner, B. Dogan, W. R. Roth and K. Hafner, *Angew. Chem.*, **94**, 721 (1982); *Angew. Chem., Int. Ed. Engl.*, **21**, 708 (1982); *Angew. Chem., Suppl.*, 1499 (1982).

87. B. M. J. Dogan, *Organische Reaktionen unter hohem Druck; der Druckeffekt auf Konkurrenzreaktionen*, Ph.D. Dissertation, Ruhr-Universität Bochum, 1984.
88. R. -A. Fallahpour and H. -J. Hansen, *Helv. Chim. Acta*, **78**, 1419, 1933 (1995) and references cited therein.
89. T. M. Cresp and D. Wege, *Tetrahedron*, **42**, 6713 (1986).
90. O. Ermer, F. -G. Klärner and M. Wette, *J. Am. Chem. Soc.*, **108**, 4908 (1986).
91. F. -G. Klärner, B. M. J. Dogan, R. Weider, D. Ginsburg and E. Vogel, *Angew. Chem.*, **98**, 344 (1986); *Angew. Chem., Int. Ed. Engl.*, **25**, 346 (1986).
92. (a) W. -D. Fessner, C. Grund and H. Prinzbach, *Tetrahedron Lett.*, **30**, 3133 (1989).
(b) F. -G. Klärner, U. Artschwager-Perl, W. -D. Fessner, C. Grund, R. Pinkos, J. P. Melder and H. Prinzbach, *Tetrahedron Lett.*, **30**, 3137 (1989).
93. J. Benkhoff, R. Boese, F. G. Klärner and A. E. Wigger, *Tetrahedron Lett.*, **35**, 73 (1994),
94. (a) F. H. Kohnke, A. M. Z. Slawin, J. F. Stoddart and D. J. Williams, *Angew. Chem.*, **99**, 941 (1987); *Angew. Chem., Int. Ed. Engl.*, **26**, 892 (1987),
(b) F. H. Kohnke and J. F. Stoddart, *Pure Appl. Chem.*, **61**, 1581 (1989).
(c) P. R. Ashton, G. R. Brown, N. S. Isaacs, D. Guiffrida, F. H. Kohnke, J. P. Mathias, A. M. Z. Slawin, D. R. Smith, J. F. Stoddart and D. J. Williams, *J. Am. Chem. Soc.*, **114**, 6330 (1992).
(d) J. P. Mathias and J. F. Stoddart, *Chem. Soc. Rev.*, **21**, 215 (1992),
(e) P. R. Ashton, U. Girreser, D. Giuffrida, F. H. Kohnke, J. P. Mathias, F. M. Raymo, A. M. Z. Slawin, J. F. Stoddart and D. J. Williams, *J. Am. Chem. Soc.*, **115**, 5422 (1993).
95. P. R. Ashton, J. P. Mathias and J. F. Stoddart, *Synthesis*, 221 (1993).
96. S. Wegener and K. Müllen, *Macromolecules*, **26**, 3037 (1993).
97. M. Pollmann and K. Müllen, *J. Am. Chem. Soc.*, **116**, 2318 (1994).
98. Z. -H. Li, A. Mori and H. Takeshita, *Bull. Chem. Soc. Jpn.*, **63**, 3713 (1990).
99. G. R. Tian, S. Sugiyama, A. Mori and H. Takeshita, *Chem. Lett.*, 1557 (1987); *Bull. Chem. Soc. Jpn.*, **61**, 2393 (1988).
100. A. Mori, Z. -H. Li, H. Nakashima and H. Takeshita, *Bull. Chem. Soc. Jpn.*, **63**, 1636 (1990).
101. (a) S. Sugiyama, T. Tsuda, A. Mori, H. Takeshita and M. Kodama, *Bull. Chem. Soc. Jpn.*, **60**, 3633 (1987).
(b) S. Sugiyama, T. Tsuda, A. Mori, H. Takeshita and M. Kodama, *Chem. Lett.*, 1315 (1986).
102. T. Nozoe, H. Takeshita, Y. Z. Yan and A. Mori, *Synlett*, **375**, 377 (1995).
103. Review: A. Hirsch, *Angew. Chem.*, **105**, 1189 (1993); *Angew. Chem., Int. Ed. Engl.*, **32**, 1138 (1993).
104. (a) H. Takeshita, J. -F. Lin, N. Keto and A. Mori, *Chem. Lett.*, 1697 (1993),
(b) H. Takeshita, J. -F. Lin, N. Kato, A. Mori and R. Isobe, *J. Chem. Soc., Perkin Trans. 1*, 1433 (1994).
105. J. -F. Lin, N. Keto, A. Mori, H. Takeshita and R. Isobe, *Bull. Chem. Soc. Jpn.*, **67**, 1507 (1994).
106. H. Takeshita, J. -F. Lin, N. Kato, A. Mori and R. Isobe, *Chem. Lett.*, 377 (1995).
107. (a) W. G. Dauben, C. R. Kessel and K. H. Takemura, *J. Am. Chem. Soc.*, **102**, 6893 (1980); W. G. Dauben, J. M. Gerdes and D. B. Smith, *J. Org. Chem.*, **50**, 2576 (1985),
(b) P. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
108. K. Matsumoto, S. Hashimoto, Y. Ikemi and S. Otawi, *Heterocycles*, **24**, 1835 (1986).
109. K. Matsumoto, Y. Ikemi, S. Hashimoto, H. S. Lee and Y. Okamoto, *J. Org. Chem.*, **51**, 3729 (1986).
110. J. Jurczak, A. L. Kawczynski and T. Kozluk, *J. Org. Chem.*, **50**, 1106 (1985).
111. A. Sera, M. Ohara, T. Kubo, K. Itoh, H. Yamada and Y. Mikata, *J. Org. Chem.*, **53**, 5460 (1988).
112. V. Breitkopf, P. Bubenitschek, H. Hopf, P. G. Jones, F. -G. Klärner, D. Schomburg, B. Witulski and B. Zimny, *Liebigs Ann.*, in press. H. Hopf, E.-G. Keärner, B. Witulski and B. Zimny, unpublished results.
113. T. Suzuki, K. Kubomura and H. Takayama, *Heterocycles*, **34**, 961 (1994).
114. M. B. G. Drew, A. V. George, N. S. Isaacs and H. S. Rzepa, *J. Chem. Soc., Perkin Trans. 1*, 1277 (1985).
115. R. W. M. Aben, J. Keijsers, B. Hams, C. G. Kruse and H. W. Scheeren, *Tetrahedron Lett.*, **35**, 1299 (1994).
116. J. Keijsers, B. Hams, C. Kruse and H. Scheeren, *Heterocycles*, **29**, 79 (1989).
117. T. Ibata, H. Nakawa, Y. Isogami and K. Matsumoto, *Bull. Chem. Soc. Jpn.*, **59**, 3197 (1986).

118. (a) Z. Z. Song, Z. Y. Zhon, T. C. W. Mak and H. N. C. Wong, *Angew. Chem.*, **105**, 406 (1993); *Angew. Chem., Int. Ed. Engl.*, **32**, 432 (1993).
(b) F. G. Klärner and C. Heinemann, unpublished results.
119. K. Beck, S. Hünig, F. -G. Klärner, P. Kraft and U. Artschwager-Perl, *Chem. Ber.*, **120**, 2041 (1987).
120. S. Hünig, P. Kraft, F. -G. Klärner, U. Artschwager-Perl, K. Oeters and H. -G. von Schnering, *Liebigs Ann.*, 351 (1995).
121. (a) K. Matsumoto, S. Hashimoto and S. Otani, *Heterocycles*, **22**, 2713 (1984),
(b) K. Matsumoto, S. Hashimoto and T. Uchida, *Heterocycles*, **30**, 201 (1990).
122. N. S. Isaacs and G. N. El-Din, *Synthesis*, 967 (1989).
123. T. Hatsui, T. Hashiguchi and H. Takeshita, *Chem. Lett.*, 1415 (1994).
124. K. Matsumoto, K. Hamada, T. Uchida and H. Yoshida, *Heterocycles*, **29**, 21 (1989).
125. H. Nakano and H. Hongo, *Chem. Pharm. Bull.*, **41**, 1885 (1993).
126. B. Witulski, L. Ernst, P. J. Jones and H. Hopf, *Angew. Chem.*, **101**, 1290 (1989); *Angew. Chem., Int. Ed. Engl.*, 28, 1279 (1989); B. Witulski, L. Ernst, H. Hopt and P. C. Jones, *Chem. Ber.*, **123**, 2015 (1990); H. Hopf and B. Witulski, *Pure Appl. Chem.*, **65**, 47 (1993).
127. J. Jurczak, A. Golebiowski and A. Rahm, *Tetrahedron. Lett.*, **27**, 853 (1986).
128. W. M. Daniewski, E. Kubek and J. Jurczak, *J. Org. Chem.*, **50**, 3963 (1985).
129. (a) L. F. Tietze, T. Hübsch, J. Oelze, C. Ott, W. Tost, G. Wörner and M. Buback, *Chem. Ber.*, **125**, 2249 (1992).
(b) L. F. Tietze, T. Hübsch, E. Voss, M. Buback and W. Tost, *J. Am. Chem. Soc.*, **110**, 4065 (1988).
(c) M. Buback, K. Gehrke, C. Ott and L. F. Tietze, *Chem. Ber.*, **127**, 2241 (1994).
(d) M. Buback, J. Abeln, T. Hübsch, C. Ott and L. F. Tietze, *Liebigs Ann.*, 9 (1995).
130. L. F. Tietze, T. Hübsch, C. Ott, G. Kuchta and M. Buback, *Liebigs Ann.*, 1 (1995); M. Buback, W. Tost, L. F. Tietze and E. Voß, *Chem. Ber.*, **121**, 781 (1988).
131. R. Breslow, *Acc. Chem. Res.*, **24**, 164 (1991), and references cited therein.
132. A. Grieco, J. J. Nunes and M. D. Gaul, *J. Am. Chem. Soc.*, **112**, 4595 (1990).
133. W. Blokzijl, M. J. Blandamer and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, **113**, 4241 (1991).
134. J. F. Blake and W. L. Jorgensen, *J. Am. Chem. Soc.*, **113**, 7430 (1991).
135. U. Pindur, G. Lutz and C. Otto, *Chem. Rev.*, **93**, 741 (1993).
136. G. Jenner, *Tetrahedron Lett.*, **35**, 1189 (1994).
137. N. S. Isaacs and L. Maksimovic, *High Pressure Res.*, **13**, 21 (1994).
138. G. H. Posner and Y. Ishihara, *Tetrahedron Lett.*, **35**, 7545 (1994).
139. D. A. L. Vandenput and H. W. Scheeren, *Tetrahedron*, **51**, 8383 (1995).
140. R. W. M. Aben, L. Minati, H. W. Scheeren and A. Taticchi, *Tetrahedron Lett.*, **32**, 6445 (1991).
141. B. S. El'yanov and E. M. Gonikberg, *Bull. Russ. Acad. Sci. Div. Chem. Sci.*, **41**, 1253 (1992).
142. J. Jurczak, A. Golebiowski and T. Bauer, *Synthesis*, 928 (1985); A. Golebiowski, J. Jacobssson and J. Jurczak, *Heterocycles*, **24**, 1205 (1986); J. Jurczak and T. Bauer, *Carbohydr. Res.*, C1 (1987); J. Jurczak, T. Bauer and S. Jarosz, *Tetrahedron*, **42**, 6477 (1986); A. Golebiowski, J. Jacobsson and J. Jurczak, *Tetrahedron*, **43**, 3063 (1987); T. Bauer, C. Chapuis and J. Jurczak, *Helv. Chim. Acta*, **72**, 482 (1989).
143. L. Minuti, A. Taticchi, E. Gaes-Beitz and E. Wenkert, *Tetrahedron*, **51**, 10033 (1995).
144. J. Knol, A. Meetsma and B. L. Feringa, *Tetrahedron Asymmetry*, **6**, 1069 (1995).
145. L. F. Tietze, C. Ott, K. Gerke and M. Buback, *Angew. Chem.*, **105**, 1536 (1993); *Angew. Chem., Int. Ed. Engl.*, **32**, 1485 (1993).
146. L. Ghosez and M. J. O'Donnell Pericyclic Reactions of Cumulenes, in *Pericyclic Reactions*, Vol. II (Ed. A. P. Marchand and R. E. Lehr), Academic Press, New York, 1977.
147. N. S. Isaacs and E. Rannela, *J. Chem. Soc., Perkin Trans. 2*, 1555 (1975).
148. G. Swieton, J. von Jouanne, H. Kelm and R. Huisgen, *J. Chem. Soc., Perkin Trans. 2*, 37 (1983).
149. W. R. Dolbier and S. L. Weaver, *J. Org. Chem.*, **55**, 711 (1990).
150. W. J. le Noble and B. A. Ojosipe, *J. Am. Chem. Soc.*, **97**, 5939 (1975).
151. H. Takeshita, S. Sugiyama and T. Hatsui, *J. Chem. Soc., Perkin Trans. 2*, 1491 (1986); S. Sugiyama and H. Takeshita, *Bull. Chem. Soc. Jpn.*, **60**, 977 (1987).
152. B. M. J. Dogan, *Organische Reaktionen unter hohem Druck; der Druckeffekt auf Konkurrenzreaktionen*, Ph. D. Dissertation, Ruhr-Universität Bochum, 1984.
153. The partial molar volumes of tropone, 1,3-butadiene and the [6 + 4] cycloadduct were measured by Dogan[152] to be $V = 88.8$, 83.1 and 153.2 $cm^3\ mol^{-1}$, respectively, at 21 °C and extrapolated

to be 99.8, 87.9 and 154.1, respectively, at 60 °C using the values measured by Takeshita and coworkers[151] for the reaction of tropone with 2,3-dimethylbutadiene.
154. A. Mori, Y. Nukii, H. Takeshita and T. Nozoe, *Heterocycles*, **35**, 863 (1993).
155. H. Takeshita, H. Nakashima, S. Sugiyama and A. Mori, *Bull. Chem. Soc. Jpn.*, **61**, 573 (1988).
156. Z. Li, A. Mori, H. Takeshita and Y. Nagano, *Chem. Express*, **7**, 213 (1992).
157. T. Asano, Chap. 2 in Reference 3; G. Jenner, Chap. 6 in Reference 2.
158. W. Roth, and W. v. E. Doering, *J. Am. Chem. Soc.*, **112**, 1722 (1990), and references cited therein.
159. K. N. Houk. Y. Li and J. D. Evanseck, *Angew. Chem.*, **104**, 711 (1992); *Angew. Chem., Int. Ed. Engl.*, **31**, 682 (1992).
160. K. Morokuma, W. T. Borden and D. A. Hrovat, *J. Am. Chem. Soc.*, **110**, 4474 (1988).
161. C. Walling and M. Naiman, *J. Am. Chem. Soc.*, **84**, 2628 (1962).
162. G. A. Stashina, E. N. Vasil'vitskaya, G. D. Gamalevich, B. S. El'yanov, E. P. Serebryakov and V. M. Zhulin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 329 (1986); *Chem. Abstr.*, **104**, 224412q (1986).
163. M. K. Diedrich, D. Hochstrate, F. -G. Klärner and B. Zimny, *Angew. Chem.*, **106**, 1135 (1994); *Angew. Chem., Int. Ed. Engl.*, **33**, 1079 (1994).
164. W. von E. Doering, L. Birladeanu, K. Sarma, J. H. Teles, F. -G. Klärner and J. S. Gehrke, *J. Am. Chem. Soc.*, **116**, 4289 (1994).
165. P. Jansen, *Der Druckeffekt auf die Cope-Umlagerung: Druckabhängigkeit der Umlagerung von dl-2,2-Bismethylencyclohexan zu 1,2-Di-(1-cyclohexenyl)-ethan*, Diploma thesis, Universität Bochum, 1994.
166. E. M. Schulman, A. E. Merbach, M. Turin, R. Wedinger and W. J. le Noble, *J. Am. Chem. Soc.*, **105**, 3988 (1983).
167. A. E. Merbach, E. M. Schulman, M. Turin, R. Wedinger and W. J. le Noble, *J. Am. Chem. Soc.*, **105**, 3988 (1983).
168. S. Sugiyama, A. Mori and H. Takeshita, *Chem. Lett.*, 1247 (1987).
169. W. J. le Noble and M. R. Daka, *J. Am. Chem. Soc.*, **100**, 5961 (1978).
170. R. C. Neuman and M. J. Amrich, *J. Org. Chem.*, **45**, 4629 (1980).
171. S. Sugiyama and H. Takeshita, *Chem. Lett.*, 1203 (1986).
172. W. G. Dauben, B. A. Kowalczyk and D. J. H. Funhoff, *Tetrahedron Lett.*, **29**, 3021 (1988).
173. U. Schöllkopf and I. Hoppe, *Justus Liebigs Ann. Chem.*, **765**, 153 (1972).
174. M. K. Diedrich and F. -G. Klärner, unpublished results.
175. The structural parameter necessary for the calculation of V_W was taken from an *ab initio* calculation. J. E. Baldwin, V. P. Reddy, L. J. Schaad and B. A. Hess, Jr., *J. Am. Chem. Soc.*, **110**, 8554 (1988).
176. R. Mündnich, H. Plieninger and H. Vogler, *Tetrahedron*, **33**, 2661 (1977).
177. R. Mündnich and H. Plieninger, *Tetrahedron*, **34**, 887 (1978).
178. (a) W. J. le Noble, K. R. Brower, C. Brower and S. Chang, *J. Am. Chem. Soc.*, **104**, 3150 (1982).
(b) W. J. le Noble, *J. Chem. Educ.*, **44**, 729 (1967).
179. R. Mündnich and H. Plieninger, *Tetrahedron*, **32**, 2335 (1976).
180. V. Breitkopf, H. Hopf, F. -G. Klärner, B. Witulski and B. Zimny, *Justus Liebigs Ann. Chem.*, 613 (1995).
181. N. S. Isaacs and P. G. van der Beeke, *J. Chem. Soc., Perkin. Trans. 2*, 1205 (1982).
182. M. Buback, K. Gerke, C. Ott and L. F. Tietze, *Chem. Ber.*, **127**, 2241 (1994).
183. M. Buback, J. Abeln, T. Hübsch, C. Ott and L. F. Tietze, *Justus Liebigs Ann. Chem.*, 9 (1995).
184. T. Heiner, S. Michalski, K. Gerke, G. Kuchta, M. Buback and A. de Meijere, *Synlett*, 355 (1995).
185. (a) L. M. Harwood, S. A. Leening, N. S. Isaacs, G. Jones, J. Pickard, R. M. Thomas and D. Wetkin, *Tetrahedron Lett.*, **29**, 5017 (1988).
(b) S. J. Burrell, A. E. Derone, M. S. Edenborough, L. M. Harwood, S. A. Leening and N. S. Isaacs, *Tetrahedron Lett.*, **26**, 2229 (1985).
186. M. K. Diedrich, D. Hochstrate, F. -G. Klärner and B. Zimny, *Angew. Chem.*, **106**, 1135 (1994); *Angew. Chem., Int. Ed. Engl.*, **33**, 1079 (1994).
187. M. K. Diedrich and F. -G. Klärner unpublished results; M. K. Diedrich, *Der Druckeffekt auf die Bildung von Cyclen in Abhängigkeit von der Ringgröße*, Ph. D. Dissertation, Universität Essen, 1995.

188. M. K. Diedrich, D. Hochstrate, F. -G. Klärner and B. Zimny, *Angew. Chem.*, **106**, 1135 (1994); *Angew. Chem., Int. Ed. Engl.*, **33**, 1079 (1994).
189. W. v. E. Doering, L. Birladeanu, K. Sarma, J. H. Teles, F. -G. Klärner and J. -S. Gehrke, *J. Am. Chem. Soc.*, **116**, 4289 (1994).
190. M. K. Diedrich and F. -G. Klärner, unpublished results.
191. N. J. Turro, M. Okamoto, I. R. Gould, R. A. Moss, W. Lawrynowicz and L. M. Hadel, *J. Am. Chem. Soc.*, **109**, 4973 (1987).
192. (a) V. M. Zhulin, Z. G. Makarov, M. M. Krayushkin, E. B. Zhuravleva and A. M. Beskopyl'nyi, *Dokl. Akad. Nauk SSSR*, 280, 917 *Chem. Abstr.*, **103**, 57502 (1985).
(b) V. M. Zhulin and E. B. Zhuravleva, *Dokl. Akad. Nauk SSSR*, **290**, 383 (1986); *Chem. Abstr.*, **106**, 175517h (1987).
193. N. S. Isaacs and G. N. El-Dim, *Synthesis*, 967 (1989) *Tetrahedron*, **45**, 7083 (1989).
194. F. -G. Klärner, D. Oebels and W. S. Sheldrick, *Chem. Ber.*, **126**, 473 (1993).
195. N. S. Isaacs and A. Laila, *J. Phys. Org. Chem.*, **7**, 178 (1994).
196. K. Voigt, U. Schick, F. G. Meyer and A. de Meijere, *Synlett.*, 189 (1994). Review: A. de Meijere and F. E. Meyer, *Angew. Chem.*, **106**, 2473 (1994), *Angew. Chem. Int. Ed. Engl.*, **33**, 2379 (1994).
197. G. Jenner, *New. J. Chem.*, **19**, 173 (1995).
198. K. Matsumoto, T. Uchida, S. Hashimoto, Y. Yonezawa, H. Iida, A. Kakehi and S. Otani, *Heterocycles*, **36**, 2215 (1993).
199. G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955).
200. The oxidized 1,3-dipolar cycloadducts are also formed in the reactions of phospholes with diazomethane in the presence of oxygen. N. S. Isaacs and G. N. El-Din, *Tetrahedron Lett.*, **28**, 7083 (1989).
201. Cyclic sulfinic esters undergo a mutual interconversion to the corresponding 1,3-dienes and SO_2: F. Jung, M. Molin, R. van den Elzen and T. Durst, *J. Am. Chem. Soc.*, **96**, 935 (1974); R. F. Heldeweg and H. Hogeveen, *J. Am. Chem. Soc.*, **98**, 2341 (1976).
202. S. Hillers and O. Reiser, *Tetrahedron Lett.*, **34**, 5265 (1993).