The Chemistry of Dienes and Polyenes. Volume 2
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CHAPTER **9**

Synthetic applications of dienes and polyenes, excluding cycloadditions

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I. INTRODUCTION

The reactivity of polyenes is influenced by their substituents, and whether or not the multiple double bonds of the unsaturated hydrocarbon are conjugated or isolated from

one another. The π-system of a polyene may be fully conjugated, or there may be one or more pairs of conjugated double bonds isolated from the other π-bonds in the molecule, or, alternatively, each of the carbon–carbon double bonds in the polyene may be isolated from one another. Conjugated π-systems react differently with electrophiles than isolated double bonds. Addition of hydrogen to isolated double bonds has been previously discussed in this series and will not be addressed here[1]. Allenes and cumulenes constitute an important class of polyenes which will not be considered here as they have already appeared in this series[2] and in other more comprehensive reviews[3,4].

The reactions of dienes and other polyenes can be broadly classified as either addition reactions, coupling (or substitution reactions) or rearrangements (including metathesis reactions). This chapter will present recent examples from the literature of synthetic transformations involving polyenes. Cycloaddition and ring closing metathesis reactions appeared in volume one of this series and therefore will not be covered in this chapter. Citations for more detailed descriptions of the individual reactions discussed in this chapter and for more comprehensive reviews appear in the text.

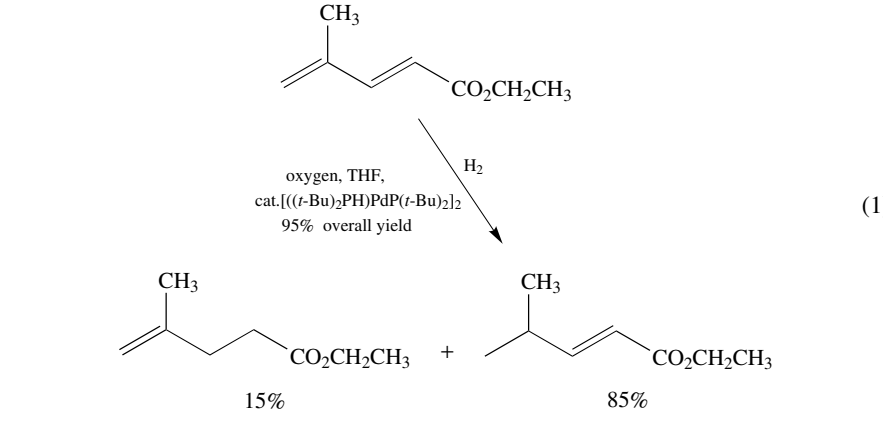
II. ADDITION REACTIONS

If the double bonds of a polyene are not conjugated with other π-systems in the molecule, addition to one of the π-bonds will proceed in a similar fashion to addition to a simple alkene. Usually addition to one of the bonds is preferred, because it is either more highly substituted and, as a result, has enhanced electron density, or because it has fewer substituents and is less hindered and more accessible to the electrophile. Alternatively, one of the double bonds of a polyene may be activated by the presence of a heteroatom at the allylic position.

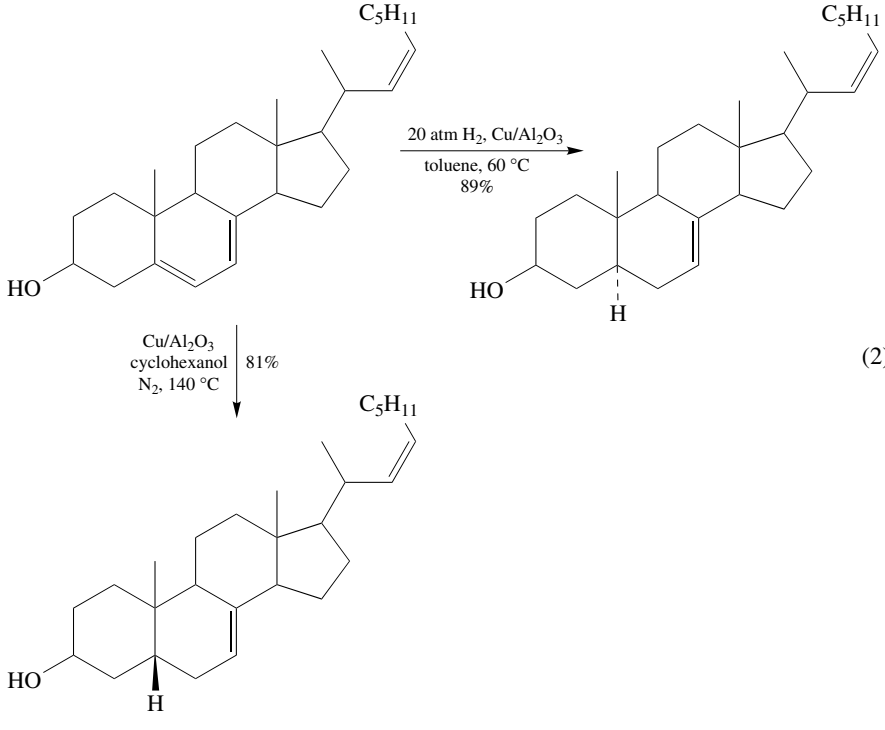
1,3-Dienes undergo both 1,2- and 1,4-addition to the carbons of the conjugated system to give the corresponding 1,2- and 1,4-substituted alkenes, respectively. The regioselectivity of the addition depends on the nature of the electrophile as well as on the reaction conditions. Deuteriation of conjugated dienes on cadmium monoxide, cobalt oxide (Co_3O_4) and chromium(III) oxide shows selectivity for 1,2-hydrogenation in the presence of the cadmium and cobalt oxides, and for 1,4-addition on chromium(III) oxide[5]. Selective 1,2-hydrogenation of simple and functionalized conjugated dienes using metal complexes as catalysts has been investigated[6]. The binuclear palladium complex, $[((t\text{-}Bu)_2PH)PdP(Bu\text{-}t)_2]_2$, has been used to catalyze the selective hydrogenation of conjugated diene esters, ketones and nitro compounds to the corresponding functionalized monoenes[7]. 1,2-Addition of hydrogen is selective for the double bond further from the electron-withdrawing group; thus, the major alkene formed on selective reduction of ethyl 4-methyl-2,4-pentadienoate is the α,β-unsaturated ester (equation 1). The reaction proceeds under mild conditions and in the presence of oxygen.

1,2-Hydrogenation of the conjucated cyclohexadienyl ring B of 3β-sterols has been accomplished using catalytic amounts of Cu/Al_2O_3[8]. Addition is selective for the double bond nearer the hydroxy group. In addition to regioselectivity, the stereochemistry of the epimer formed can be reversed by changing the hydrogenation conditions (equation 2).

Halogenation of conjugated dienes proceeds chiefly by 1,4-addition with molecular halogens (equation 3). 1,2-Addition is favored in the presence of pyridine–halogen complexes and amine tribromide salts (equation 4)[9]. The stereochemistry of 1,4-bromine addition with 2,4-hexadienes and cyclopentadiene is primarily *anti* in the presence of amine, but *syn* with molecular halogen in the absence of amine.



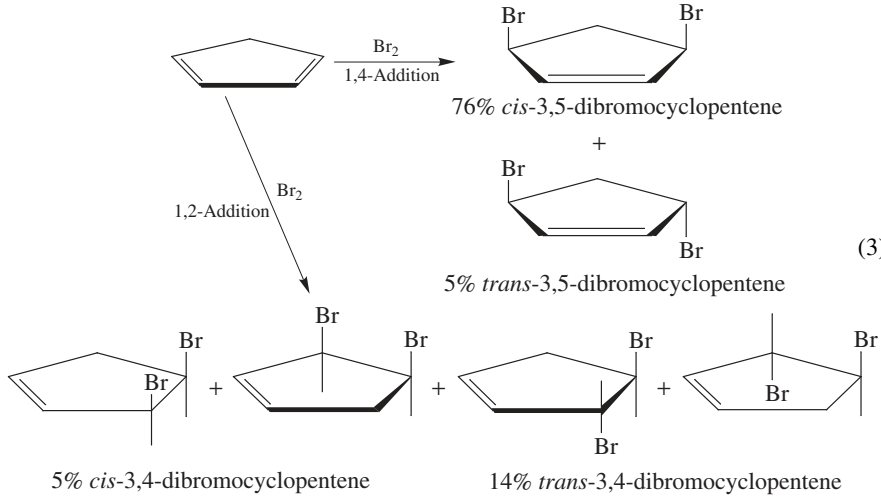
(1)

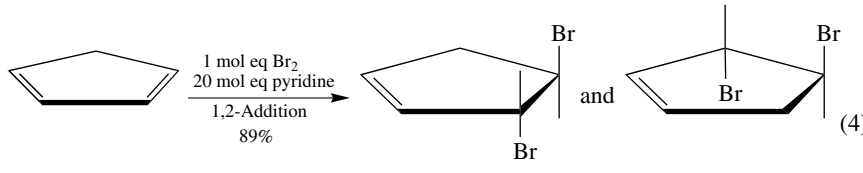


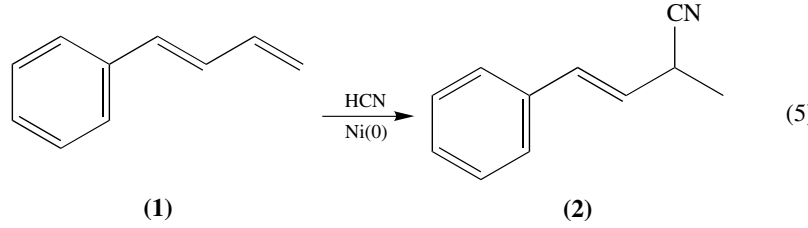
(2)

Hydrocyanation of aliphatic conjugated dienes in the presence of Ni(0) complexes gives diene rearrangement products and β,γ-unsaturated nitriles in 10–90% yields[10]. Dienes other than 1,3-butadiene do not produce terminal nitriles, implying that the more highly substituted π-allyl nickel complex is favored. Thus, reaction of 1-phenylbuta-1,3-diene **(1)** affords (*E*)-2-methyl-4-phenylbut-3-enenitrile **(2)** as the sole product (equation 5). The

use of chiral Ni complexes, however, displays only low levels of asymmetric induction.



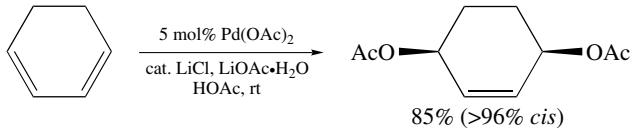


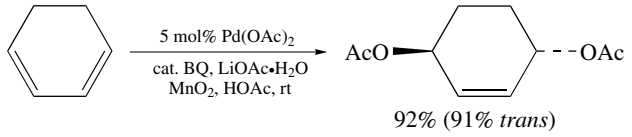


Stereo- and regioselective palladium-catalyzed oxidation of 1,3-dienes in acetic acid to give 1,4-diacetoxy-2-alkenes has been accomplished using MnO_2 and catalytic amounts of *p*-benzoquinone (BQ)[11]. The reaction can be made to take place with *cis*- or *trans*-1,4-diacetoxylation across the diene in cyclic systems as shown in equation 6.

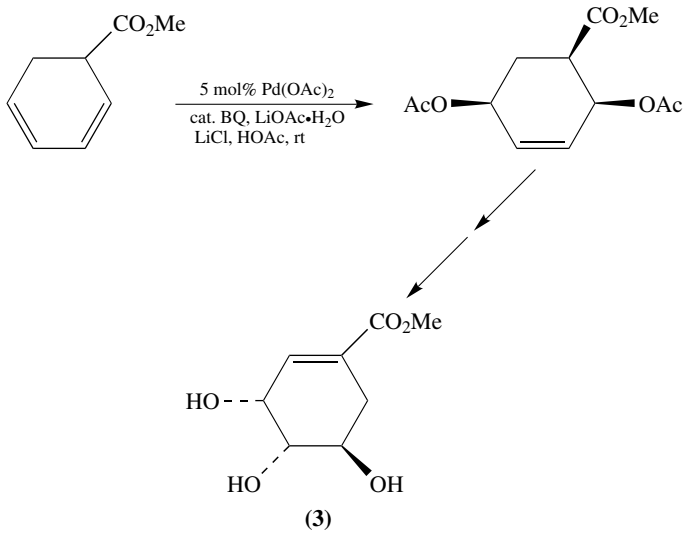
In acyclic systems the 1,4-relative stereoselectivity was controlled by the stereochemistry of the diene. Thus, oxidation of (*E*,*E*)- and (*E*,*Z*)-2,4-hexadienes to their corresponding diacetates affords *dl* (>88% *dl*) and *meso* (>95% *meso*) 2,5-diacetoxy-3-hexene, respectively. A mechanism involving a *trans*-acetoxypalladation of the conjugated diene to give an intermediate (π-allyl)palladium complex, followed by either a *cis* or *trans* attack by acetate on the allyl group, has been suggested. The *cis* attack is explained by a *cis* migration from a (σ-allyl)palladium intermediate. The diacetoxylation reaction was applied to the preparation of a key intermediate for the synthesis of *dl*-shikimic acid, **3**,

as shown in equation 7.





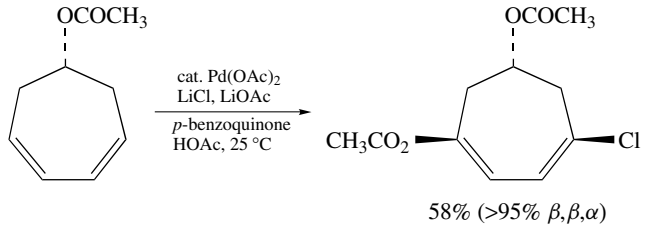
(6)



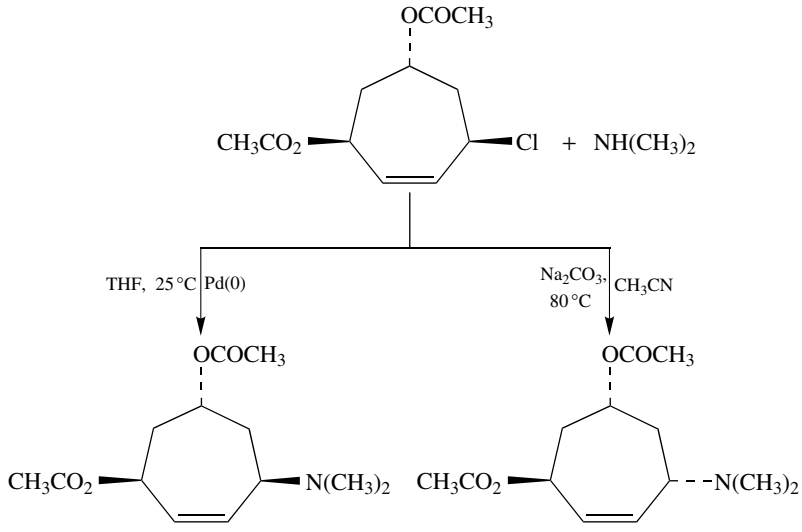
(7)

(3)

Amino alkenols have been prepared by palladium-catalyzed chloroacetoxylation and allylic amination of 1,3-dienes. 1,4-Acetoxychlorination is stereospecific and cyclic dienes give an overall *cis*-1,4-addition[12]. Acetoxychlorination of 6-acetoxy-1,3-cycloheptadiene afforded only one isomer as shown in equation 8. Sequential substitution of the allylic chloro group can occur with either retention or inversion, thereby allowing complete control of the 1,4-relative stereochemistry (equation 9).



(8)



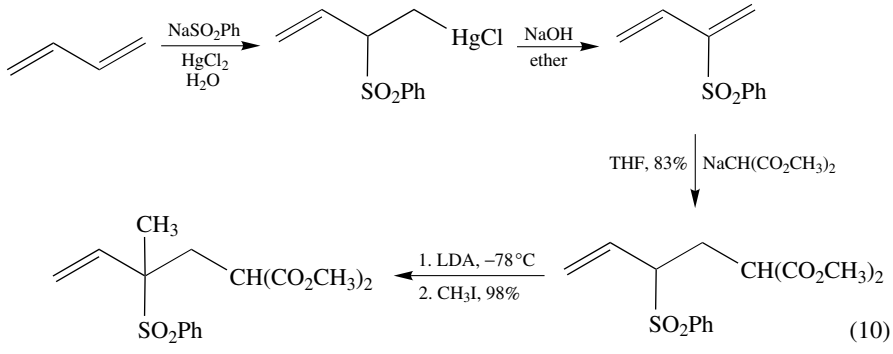
(9)

Using a similar approach, 1-acetoxy-4-diethylamino-2-butene and 1-acetoxy-4-benzylamino-2-butene were prepared. Treatment of 1,3-butadiene with LiCl–LiOAc in the presence of $Pd(OAc)_2$ and *p*-benzoquinone in acetic acid gave 91% 1-acetoxy-4-chloro-2-butene ($E/Z = 90/10$). Subsequent allylic amination with diethylamine, catalyzed by $Pd(PPh_3)_4$ in THF, produced mainly (*E*)-1-acetoxy-4-diethylamino-2-butene[13].

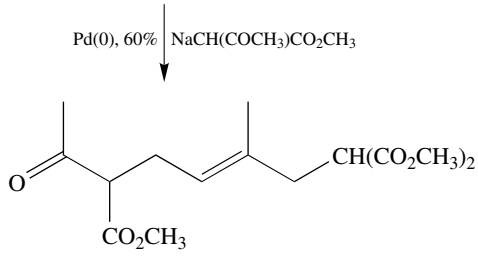
Allylic and dienyl sulfones have been prepared by conjugate addition to 1,3-dienes[14]. Phenylsulfonylmercuration of conjugated dienes gives mercury adducts which can be treated with base to afford phenylsulfonyldienes[15]. 2-(Phenylsulfonyl)-1,3-dienes can be stereo- and regioselectively functionalized via Michael addition of nucleophiles to give allylic sulfones. A key intermediate in the synthesis of a Monarch butterfly pheromone **4** was prepared by Bäckvall and Juntunen[16] by alkylation and subsequent palladium-catalyzed substitution of the allylic sulfone formed by Michael addition of dimethyl malonate to 2-(phenylsulfonyl)-1,3-butadiene (equation 10).

1- and 2-Nitro-1,3-dienes have been obtained from conjugated dienes by various methods[17–20]. Nitrodienes have proven to be useful synthetic intermediates and react with electron-rich alkenes to give nitronates[21–25]. Bäckvall has demonstrated that 2-nitro-1,3-dienes, prepared by a nitroselenation-elimination sequence, are useful intermediates in the preparation of unsaturated 1,4-dicarbonyl compounds (equation 11)[26].

Ceric ammonium nitrate promoted oxidative addition of silyl enol ethers to 1,3-butadiene affords 1 : 1 mixtures of 4-(β-oxoalkyl)-substituted 3-nitroxy-1-butene and 1-nitroxy-2-butene[27]. Palladium(0)-catalyzed alkylation of the nitroxy isomeric mixture takes place through a common η^3 palladium complex which undergoes nucleophilic attack almost exclusively at the less substituted allylic carbon. Thus, oxidative addition of the silyl enol ether of 1-indanone to 1,3-butadiene followed by palladium-catalyzed substitution with sodium dimethyl malonate afforded 42% of a 19 : 1 mixture of methyl (*E*)-2-(methoxycarbonyl)-6-(1-oxo-2-indanyl)-4-hexenoate **(5)** and methyl 2-(methoxycarbonyl)-4-(1-oxo-2-indanyl)-3-vinylbutanoate **(6)**, respectively (equation 12).



(10)



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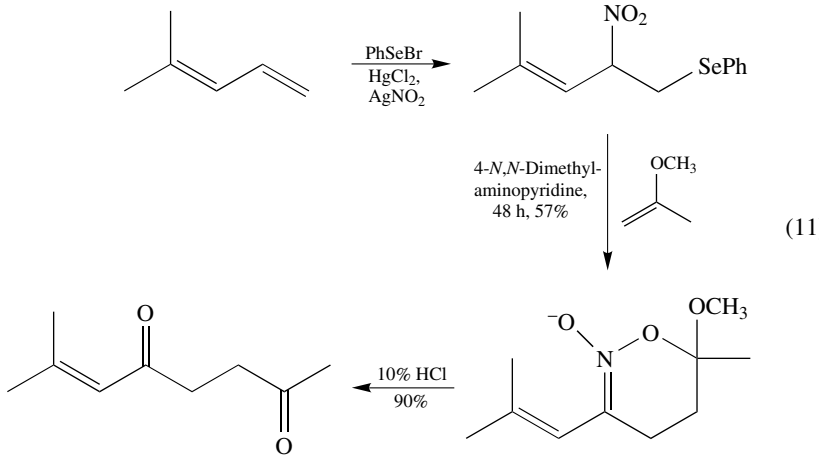
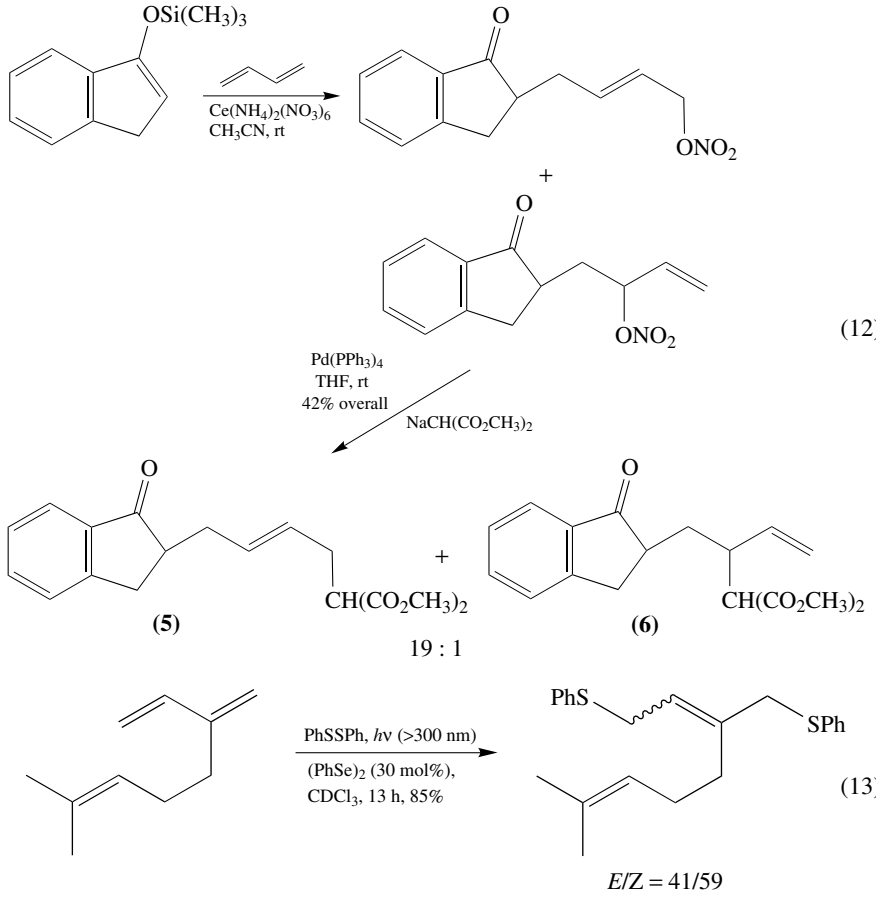


(11)

1,4-Dithiolation of conjugated dienes occurs on photolysis of disulfides in the presence of 1,3-dienes. However, the reaction is not clean and generally affords a polymeric mixture. Irradiation of diphenyl disulfides and 1,3-dienes in the presence of diphenyl diselenide was recently reported to provide the corresponding 1,4-dithiolation products selectively in good yields (equation 13)[28].



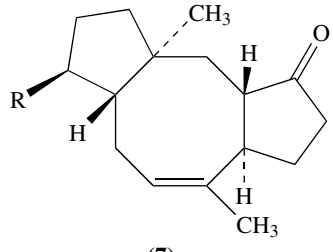
(12)

(13)

III. OXIDATION REACTIONS

Polyenes containing isolated double bonds undergo oxidation reactions similar to their alkene analogs. Thus, in the enantioselective synthesis of the tricyclic nucleus of ceroplastol I **(7a)**, Snider and Yang[29] prepared diene **8** which they transformed in four steps to diene **9** (equation 14). Osmylation of the diene with OsO_4 and 4-methylmorpholine N-oxide (NMO) generated the corresponding tetrol. Further oxidation of the tetrol with $NaIO_4$ gave keto aldehyde **10**. McMurry coupling of **10** afforded the tricyclic system **11** which, on deprotection of the silyl ether, was oxidized to the ketone to complete the synthesis of **7b**.

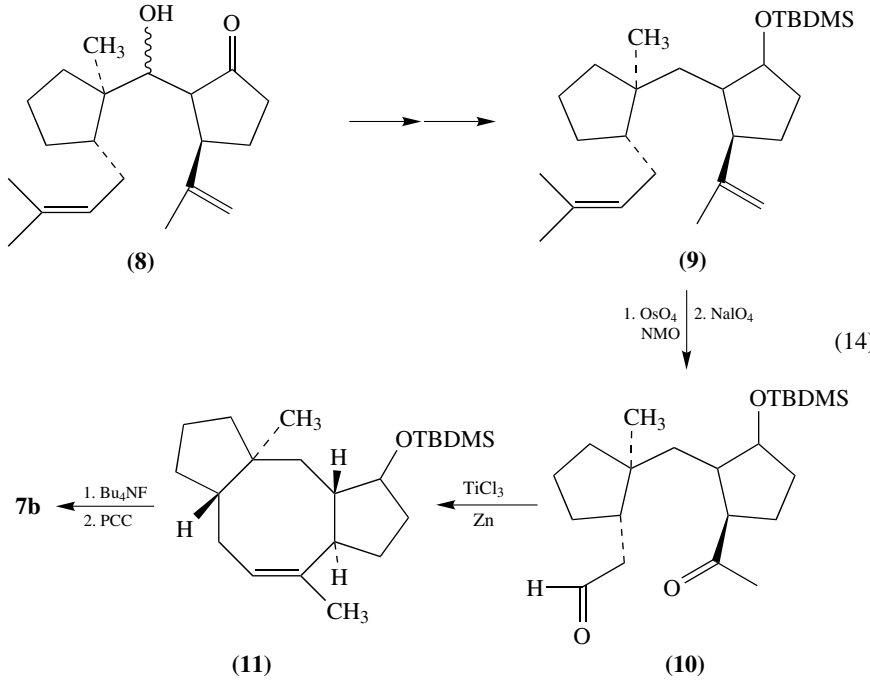
The regioselectivity of oxidation in nonconjugated polyenic systems is generally influenced by steric and electronic factors, or anchimeric effects. A comprehensive review of asymmetric epoxidation of allylic alcohols, including dienols and trienols, has recently been published[30]. The procedure first described by Katsuki and Sharpless[31] has proven to be one of the most effective methods for selectively epoxidating double bonds in polyfunctional systems with high stereo- and regioselectivities. Thus, epoxidation of pyrandienol **12** with titanium(IV) isopropoxide and (*R*,*R*)-(+)-diethyl tartrate (DET) selectively occurs at



(7)

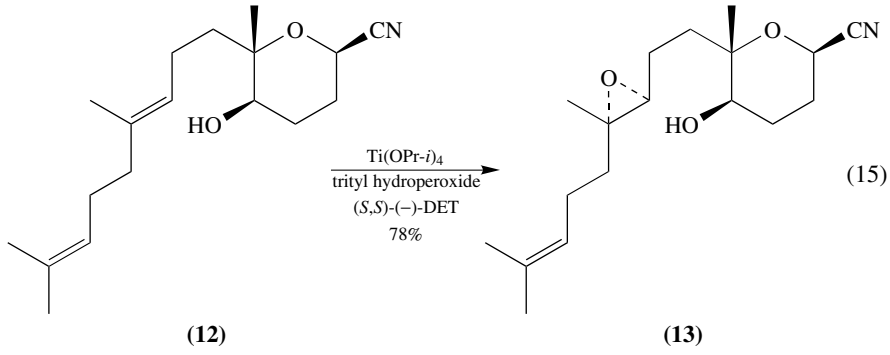
(7a) R = (*E*)-1,5-dimethyl-4-hexen-6-ol
(7b) R = H

the double bond nearest the pyran ring furnishing epoxide **13** exclusively (equation 15)[32]. The observed regio- and steroselectivity for this reaction is presumably due to anchimeric assistance by the hydroxy substituent on the pyran ring.



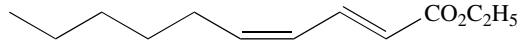
(14)

Asymmetric monoepoxidation of conjugated dienes has been accomplished via (salen)Mn(III)-catalyzed [salen = *N*,*N*′-bis(salicylidene)ethylenediamine] oxidation. The reaction exhibits regioselectivity for attack at *cis* double bonds of *cis,trans*-conjugated dienes, and affords *trans* epoxides as the major products from *cis* olefins[33]. Thus, diene **14** gave optically active *trans*-vinylepoxide **15** as the major product with 87% ee as shown in equation 16.

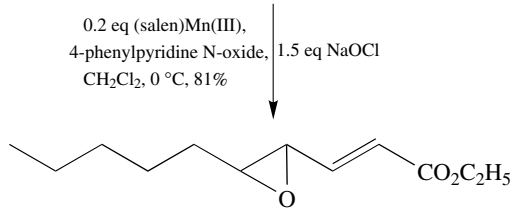


(15)

(12) **(13)**



(14)



(16)

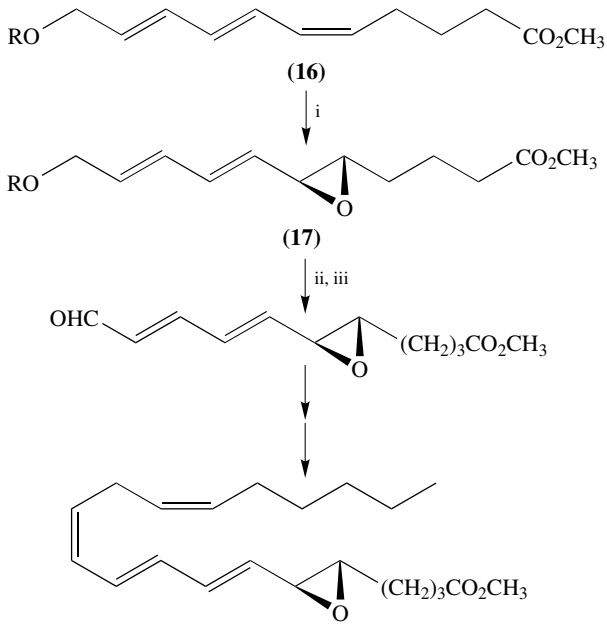
(15)

The successful application of this method was illustrated with a series of model dienes, and with the formal synthesis of leukotriene A_4 methyl ester, a complex polyene monoepoxide, from the intermediate epoxyundecadienoate **17** prepared by selective epoxidation of trienyl ester **16** (equation 17).

Asymmetric monoepoxidation of conjugated dienes has also been accomplished using a fructose-derived chiral ketone catalyst and oxone as the oxidant (equation 18)[34]. High regioselectivities and enantioselectivities are realized under these conditions. The regioselectivity of monoepoxidation of unsymmetric dienes can be regulated by using steric and electronic control. The reaction has been found to tolerate a variety of functional groups including hydroxyl groups, silyl ethers and esters.

A more unusual monoepoxidation was observed when 1-halo-1,3-cyclohexadienes were treated with aqueous solutions of potassium permangnate[35]. Oxidation of **18** resulted in formation of the unusual halo-epoxydiol **19** as the major oxidation product (equation 19). Hydrolysis of **19** with water in the presence of Al_2O_3 afforded the rare inosose **20** in high yield.

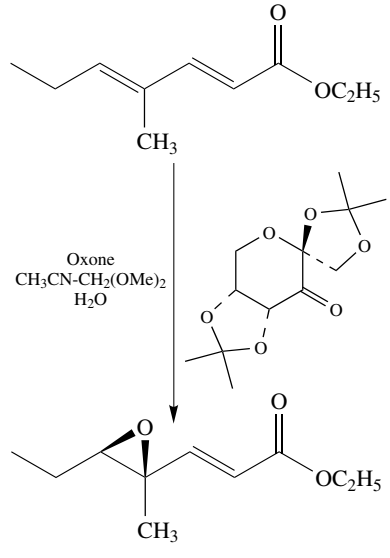
In an elegant synthesis of structurally simplified analogs of daphnane diterpene resiniferatoxin **(21)**, which possess the unusual 2,9,10-trioxatricyclo[4.3.1.0]decane system, cyclohexadiene was transformed into an endoperoxide[36]. Reaction of 1,3-cyclohexadiene with singlet oxygen generated *in situ* from oxygen and 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine stereoselectively transformed the cyclic diene into *cis*-cyclohex-2-ene-1,4-diol (equation 20). Reduction of the reactive endoperoxide intermediate was accomplished with thiourea. Silylation of the diol followed by epoxidation with *m*-chloroperbenzoic acid (mCPBA) afforded mainly the *anti*-epoxide. Ring opening of the epoxide with an



(17)

Leukotriene A_4 methyl ester

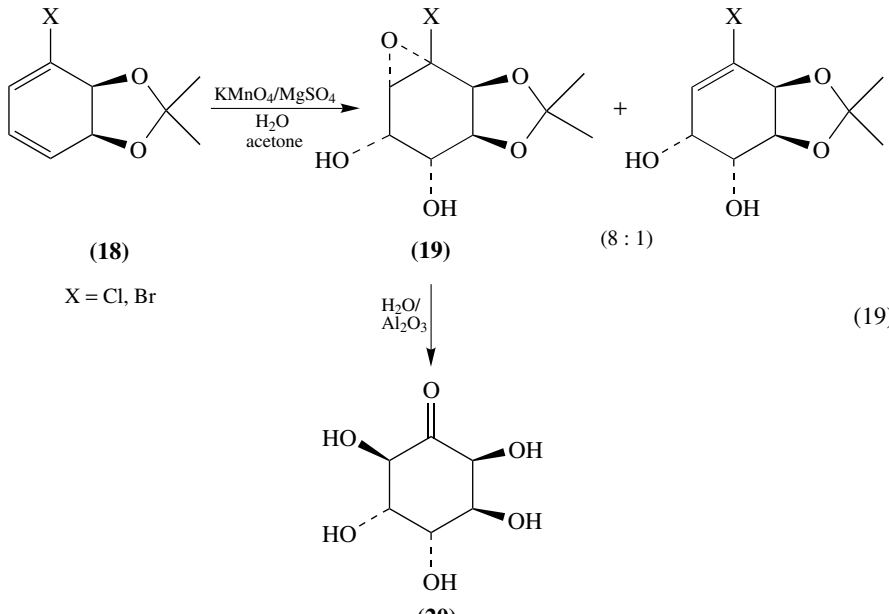
(i) 1.2 eq NaOCl, pH 11.3, 20 mol% 4-phenylpyridine-*N*-oxide, 4 mol% (salen)Mn(III); (ii) NH_3, CH_3OH; (iii) activated MnO_2



(18)

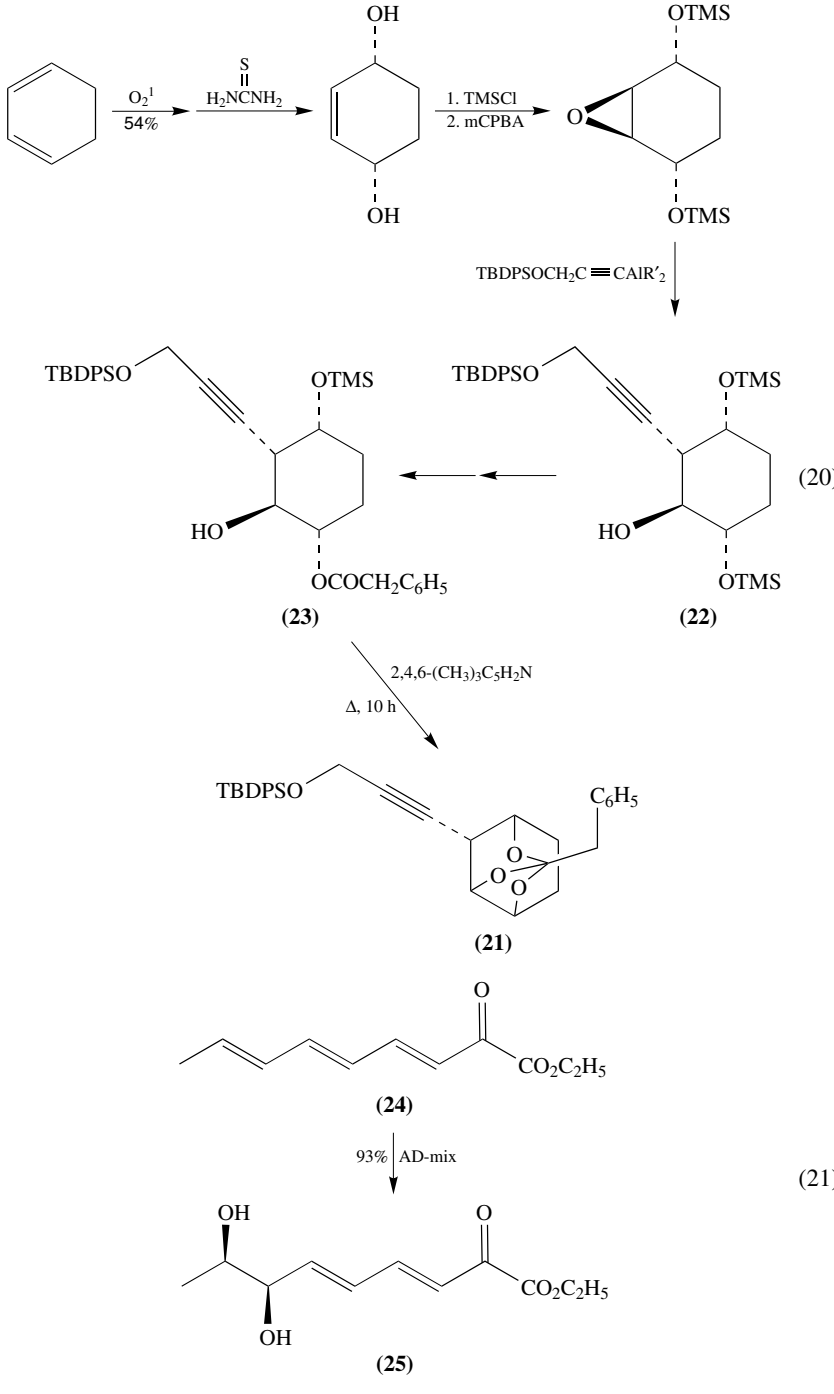
82% (95% ee)

alkynylalane produced intermediate **22** that was transformed in four steps to compound **23**. The desired trioxatricyclo[4.3.1.0]decane system, **21**, was acquired in 73% yield on refluxing **23** for 10 h in 2,4,6-trimethylpyridine.

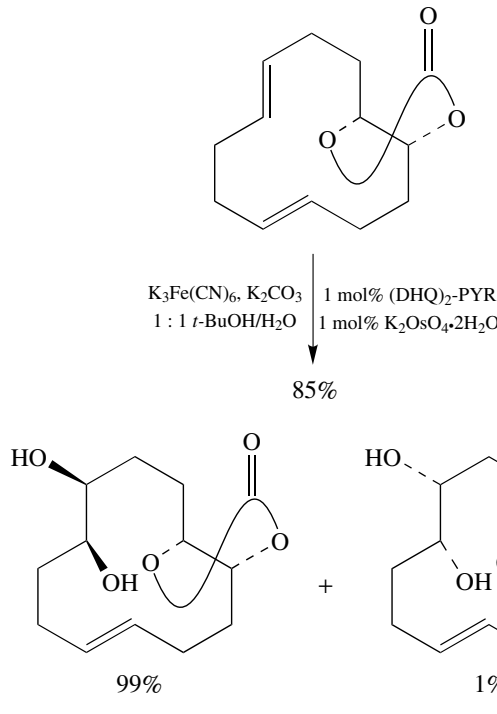


(19)

Conjugated dienes can be hydroxylated to the corresponding tetrols with catalytic amounts of osmium tetroxide in the presence of water, acetone and equimolar amounts of *N*-methylmorpholine[37]. High stereoselectivities were achieved for 1,4-disubstituted *trans*-1,3-butadienes. Less substituted 1,3-dienes or those with *cis* double bonds showed lower stereoselectivities for hydroxylation. Thus, while (*E*,*E*)-1,4-diphenyl-1,3-butadiene afforded 1,4-diphenyl-1,2,3,4-tetrahydroxybutane in 87% yield with a 16 : 1 preference for the 2,3-*anti* over the 2,3-*syn* isomer, hydroxylation of 1,3-butadiene resulted in an 80% yield of the corresponding tetrol with lowered selectivity (5 : 1 2,3-*anti* to 2,3-*syn* addition). Hydroxylation of (*E*,*Z*)-2,4-hexadiene resulted in only a 2 : 1 preference for *anti* versus *syn* addition. The reaction was also much less successful when applied to polyenes. However, catalytic osmylation of dienes and triene esters was found to proceed with high regio- and stereoselectivity when chiral esters of dihydroquinidines, such as 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine, are employed as ligands[38]. A typical asymmetric dihydroxylation procedure employs one mole percent ligand and one mole percent of $K_2OsO_4 \cdot 2H_2O$, generally referred to as an AD-mix[39]. Selective asymmetric dihydroxylation of polyenes has subsequently been realized using the Sharpless asymmetric dihydroxylation procedure[39]. In many cases excellent regioselectivities of stereoregular polyhydroxylated carbon chains were obtained. The observed selectivities were explained in terms of electronic and/or steric effects inherent to the substrate, superimposed on the substrate's favorable or unfavorable interactions with the binding pocket of the AD ligand. Thus, (*E*, *E*, *E*) ethyl 2-oxo-3,5,7-nonatrienoate **(24)** was selectively mono-dihydroxylated at the distal double bond to afford **25** in excellent yield with 95% ee (equation 21).


OH
OTMS
S
O_2[1]
54%
H_2NCNH_2
1. TMSCl
2. mCPBA
O
OH
OTMS
$TBDPSOCH_2C{\equiv}CAlR'_2$
TBDPSO
OTMS
HO
$OCOCH_2C_6H_5$
(23)
(22)
(20)
$2,4,6\text{-}(CH_3)_3C_5H_2N$
Δ, 10 h
C_6H_5
(21)
$CO_2C_2H_5$
(24)
93% AD-mix
(21)
(25)

Unexpectedly high enantioselectivities were also realized for medium and large ring dienes with *trans* double bonds using the pyrimidine (PYR) ligands (equation 22).



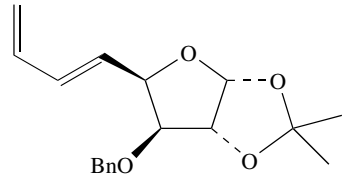
(22)

$(DHQ)_2$-PYR = Hydroquinone 2,5-diphenyl-4,6-pyrimidinediyl diethene

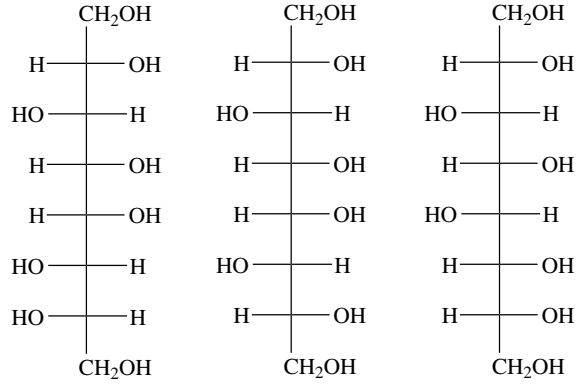
The diastereoselective synthesis of higher sugars was accomplished by *bis*-osmylation of sugar derived dienes using OsO_4-NMO[40]. As shown in equation 23, osmylation of diene **26** afforded diastereomeric sugars **27**, **28**, and **29** in 90% overall yield in a 6.6 : 1.2 : 1.0 ratio, respectively.

A stereoselective osmylation approach was applied to the synthesis of C(1)−C(7) and C(7)−C(13) subunits of erythronolide A[41]. A key synthon of the erythronolide A seco acid, **30**, was prepared in an enantiomerically pure form by utilizing a stereoselective osmylation of the chiral hydroxy (*Z*,*E*)-diene ester **31** and subsequent hydrogenation of the resulting butenolide **32** (equation 24).

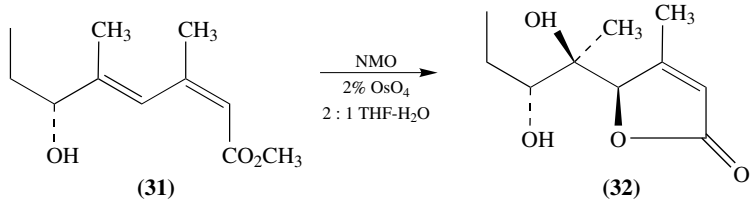
Regio- and stereoselective dihydroxylation of dienes functionalized at the allylic position with a benzene sulfone group has been reported[42]. Osmylation of dienic sulfones **33**, a potential key synthon for forskolin, occurred exclusively on the Δ^{6-7} double bound and preferentially from the α-face of the *trans*-fused bicyclic molecule, presumably due to a combination of steric and electronic factors (equation 25). While the reaction of diene sulfones proceeded sluggishly under catalytic conditions, treatment of **33a** with a stoichiometric amount of OsO_4 resulted in quantitative yield of diastereomeric diols **34a** and **35** in a 9 : 1 ratio, respectively. Protecting the hydroxy group of the dienol as its *t*-butyldimethylsilyl ether **(33b)** affords diol **34b** exclusively.



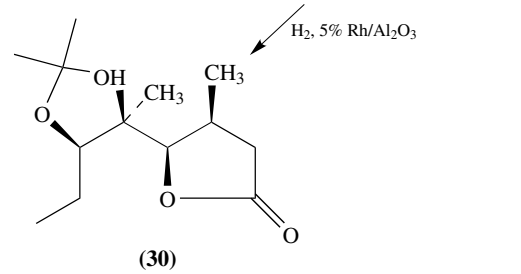
(26)



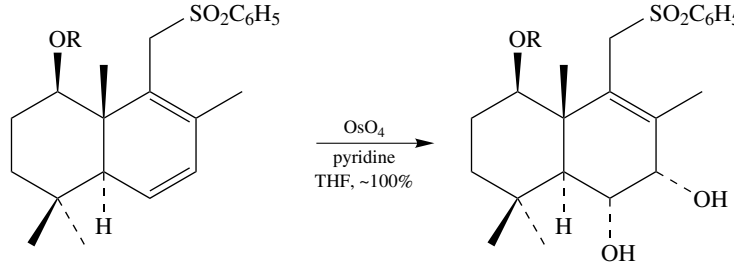
(27) **(28)** **(29)** (23)



(31) **(32)**



(30) (24)

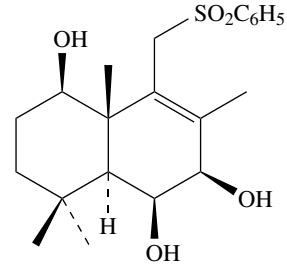


(33a) R = H
(33b) R = TBDMS

(34a) R = H
(34b) R = TBDMS

(25)

+

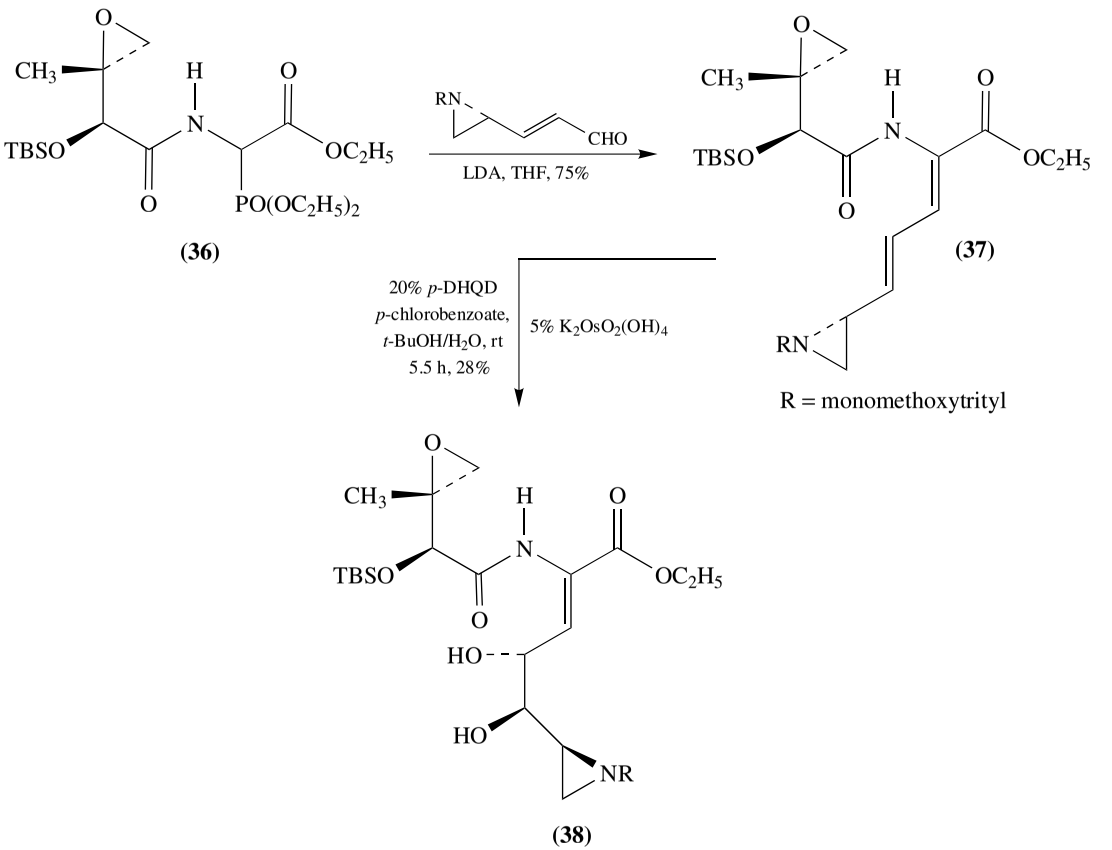


(35)

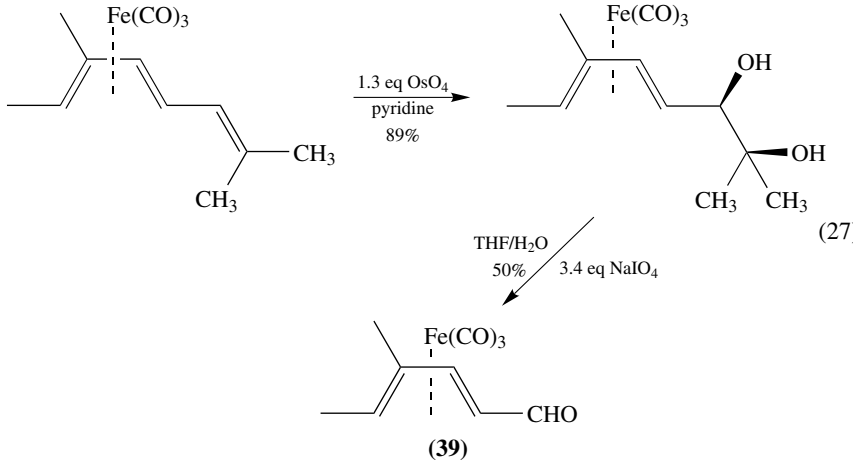
Sharpless' asymmetric dihydroxylation procedure was applied to the synthesis of the side chain of azinomycin A (equation 26)[43]. Horner–Emmons condensation of phosphonate **36** with a β-aziridine substituted acrolein afforded dehydroamino acid diene **37**. Treatment of the diene with catalytic amounts of an osmium reagent and dihydroquinidine (DHQD) *p*-chlorobenzoate resulted in asymmetric dihydroxylation, producing diol **38**. Diol **38** was further converted to the naphthyl ester.

Isolated double bonds can be oxidatively cleaved in systems containing a conjugated diene moiety if it is protected as a tricarbonyl(diene)iron complex[44]. Dienal **39** was acquired in 49% yield by a two-step osmylation–periodate cleavage sequence (equation 27). In contrast, ozonolysis of the polyene complexes is reported to lead to destruction of the complex.

Substituted 4,5-dihydro-5-vinylisoxazoles **(40)**, obtained by regio- and stereospecific cycloaddition of nitrile oxides to dienes, undergo smooth osmium-catalyzed *cis*-hydroxylation to give amino-polyol precursors (equation 28)[45]. The reaction is *anti* selective, the diastereomeric ratios ranging from 73 : 27 up to $\geqslant$99 : 1. Highest stereoselectivities were observed when R^3 was methyl. Thus, whereas osmylation of **40a** afforded a 78 : 22 mixture of **41a** and **42a**, respectively, in 80% overall yield, similar treatment of **40b** resulted in a 92 : 8 mixture of **41b** and **42b**, respectively, in 70% overall yield. The cycloaddition-osmylation sequence allows control of the relative configuration of up to 4 contiguous asymmetric centers.

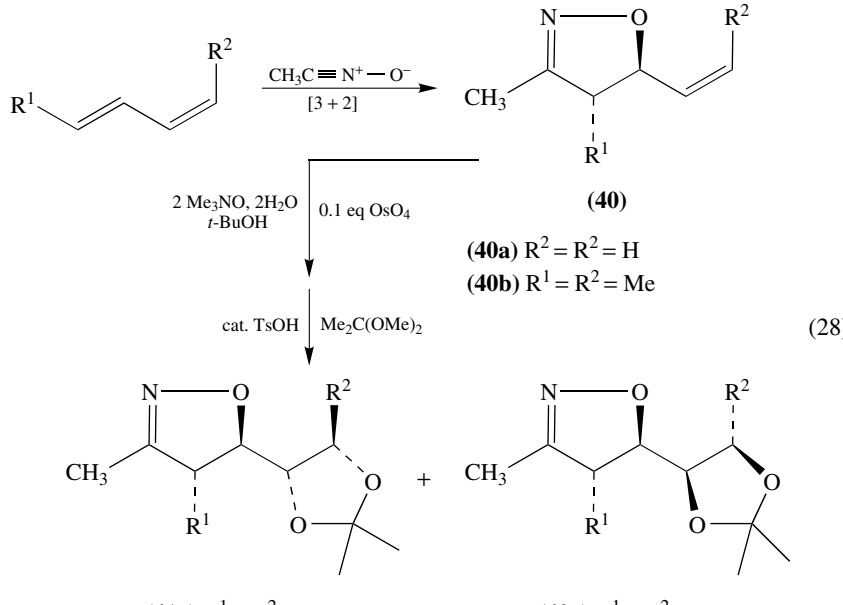

CH3
H
O
TBSO
N
OC2H5
O
PO(OC2H5)2
(36)
RN
CHO
LDA, THF, 75%
(37)
R = monomethoxytrityl
20% p-DHQD
p-chlorobenzoate,
t-BuOH/H2O, rt
5.5 h, 28%
5% K2OsO2(OH)4
HO
NR
(38)

(26)



(27)

(39)



(40)

(40a) $R^2 = R^2 = H$
(40b) $R^1 = R^2 = Me$

(28)

(41a) $R^1 = R^2 = H$
(41b) $R^1 = R^2 = Me$

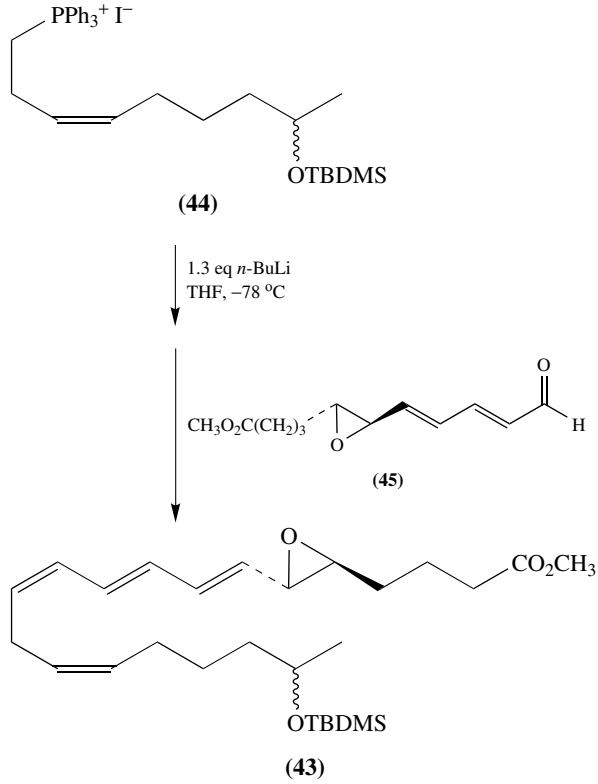
(42a) $R^1 = R^2 = H$
(42b) $R^1 = R^2 = Me$

IV. COUPLING REACTIONS

Polyenes are most often synthesized by cross-coupling reactions between unsaturated systems. Typically these reactions require an activated carbon, often in the form of an organometallic reagent. Enolates and phosphonium ylides, Wittig-type reagents, are also commonly employed in carbon–carbon bond formation. Pericyclic rearrangements also result in the generation of new carbon–carbon bonds and will be treated separately.

A. Wittig Reactions of Dienes and Polyenes

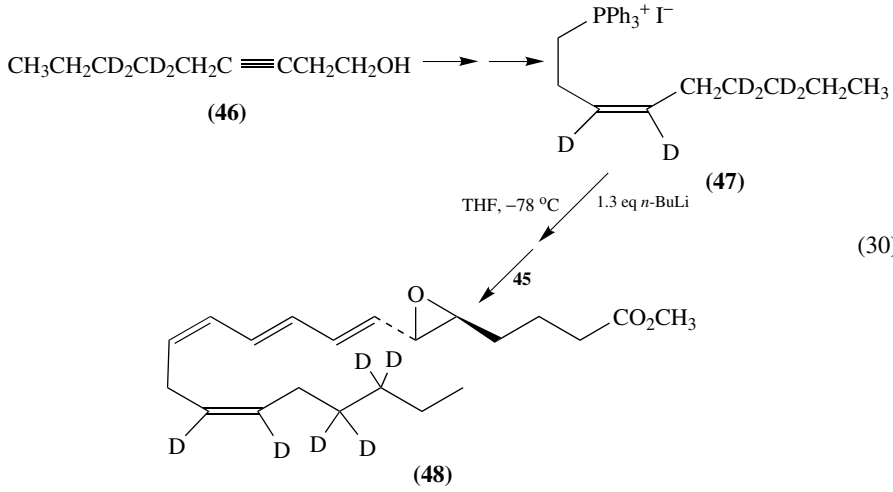
The Wittig reaction and its numerous derivations have undoubtedly proven to be one of the most useful and efficient methods for forming carbon–carbon double bonds[46]. The reaction of an organophosphorus reagent with an aldehyde or ketone has also been frequently employed to extend simple dienals and dienones into more elaborate polyene systems. A key step in the convergent synthesis of the TBDMS-protected leukotriene A_4 methyl ester, 19*R*,*S*-*t*-butyldimethylsiloxy-5*S*,6*S*-epoxyeicosa-7*E*,9*E*,11*Z*,14*Z*-tetraenoate **(43)**, was accomplished using a Wittig reaction between homoallylic phosphorus ylide **44** and C1–C11 chiral epoxy dienal **45**, derived from (−)-2-deoxy-D-ribose, shown in equation 29[47].



(29)

A similar approach had been reported earlier by Bestmann and coworkers[48] in their synthesis of hexadeuteriated leukotriene A_4 methyl ester. C-alkylation of the tetrahydropyranyl ether of 3-butyn-1-ol with 2,2,3,3-tetradeuterio-1-iodopentane, prepared in 4 steps from propargyl alcohol, and subsequent protective group removal afforded the tetradeuteriated acetylenic alcohol **46** (equation 30). Semideuteriation of the alkynol and further transformation by known methods produced the labeled key reagent 3,4,6,6,7,7-hexadeuterio-(*Z*)-(3-nonen-1-yl)triphenylphosphonium iodide **(47)**. Wittig olefination of epoxy dienal **45** with the labeled ylide generated from **47** completed the synthesis of

hexadeuteriated leukotriene A_4 methyl ester in 78% yield from **48**.



(30)

The Wittig reaction was employed to fuse diene **49** and aldehyde **50**, in the final stages of the stereoselective synthesis of epothilone B, a macrocyclic compound with potential antifungal properties (equation 31)[49].

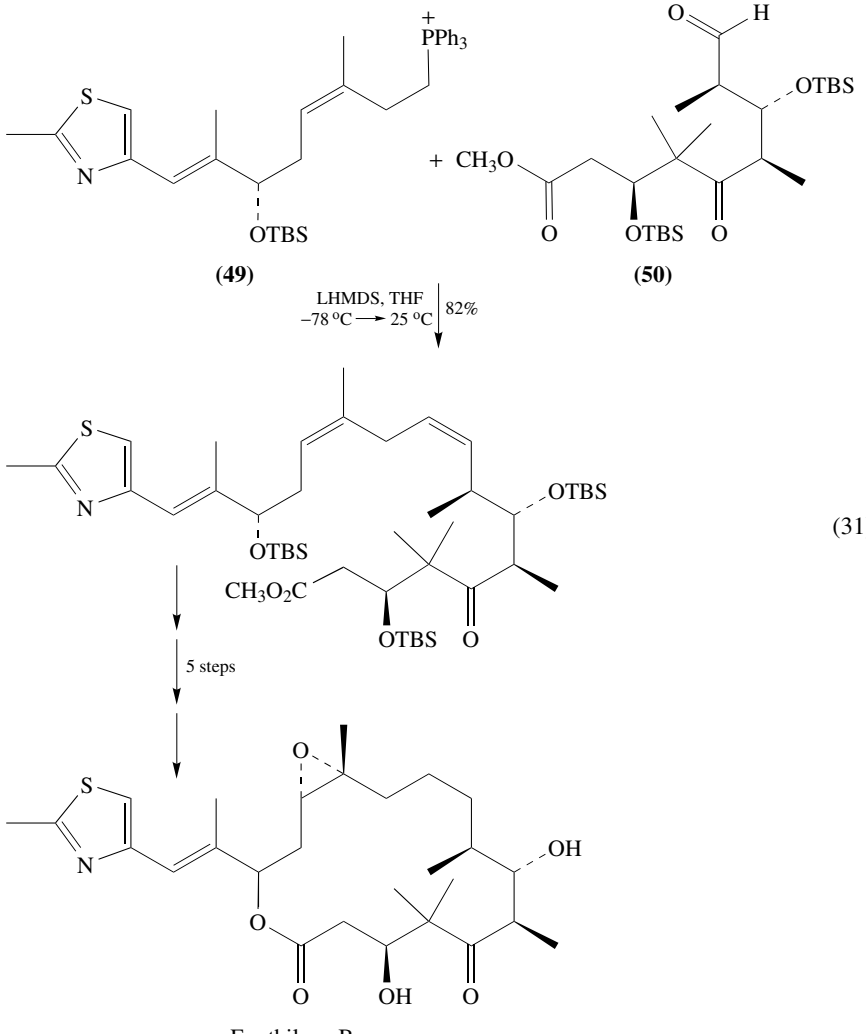
A series of conjugated polyenes capped with chromophores and containing an androstane spacer were synthesized by Wittig or Wittig-type olefinations from epi-androsterone **51**[50]. For example, vinyl carboxaldehyde **52**, prepared from **51** in 60% yield as shown in equation 32, was treated with 9-anthrylmethylphosphonium bromide and *n*-butyllithium to give diene **53**. Exocyclic diene **53** was subsequently oxidized to vinyl carboxaldehyde **54**. The androsterone vinyl aldehyde intermediate could either be treated with a tetraphenylporphyrinpolyenyl phosphonium ylide, or, as shown below, the phosphonium salt of the androsterone **(55)** could be reacted with TPP polyeneal **56**. The desired all-(*E*) isomer, **57**, was obtained from the (*E*)/(*Z*)-isomeric mixture by chromatographic purification.

B. Coupling Promoted by Organometallic Reagents

Main group and transition metals have been employed to couple unsaturated carbon chains, either by way of a σ-carbon–metal complex, in which the carbon can be either sp-, sp^2- or sp^3-hybridized, or via π-complexes of carbon–carbon bonds with the metal. While the Grignard reaction is perhaps still one of the most widely employed methods, requiring relatively mild reaction conditions and inexpensive reagents, many other organometallic reagents have been developed which are less sensitive to moisture or require only catalytic amounts of the metal. The Stille reaction is a highly acclaimed versatile synthetic technique which has been extensively reviewed[51]. In this reaction, allyl and vinyl stannanes react with organohalides or sulfonates in the presence of palladium catalysts to afford a cross-coupled unsaturated product. Intramolecular palladium-catalyzed additions of esters containing vinyl triflate and vinylstannane groups afford macrocyclic lactones[52,53].

The 20-membered all-*E* tetraene macrolide system **58** was prepared by intramolecular cyclization of vinyl stannane **59** in the presence of tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3) and triphenylarsine, as shown in equation 33[54]. *E*,*E*-Dienamines have been

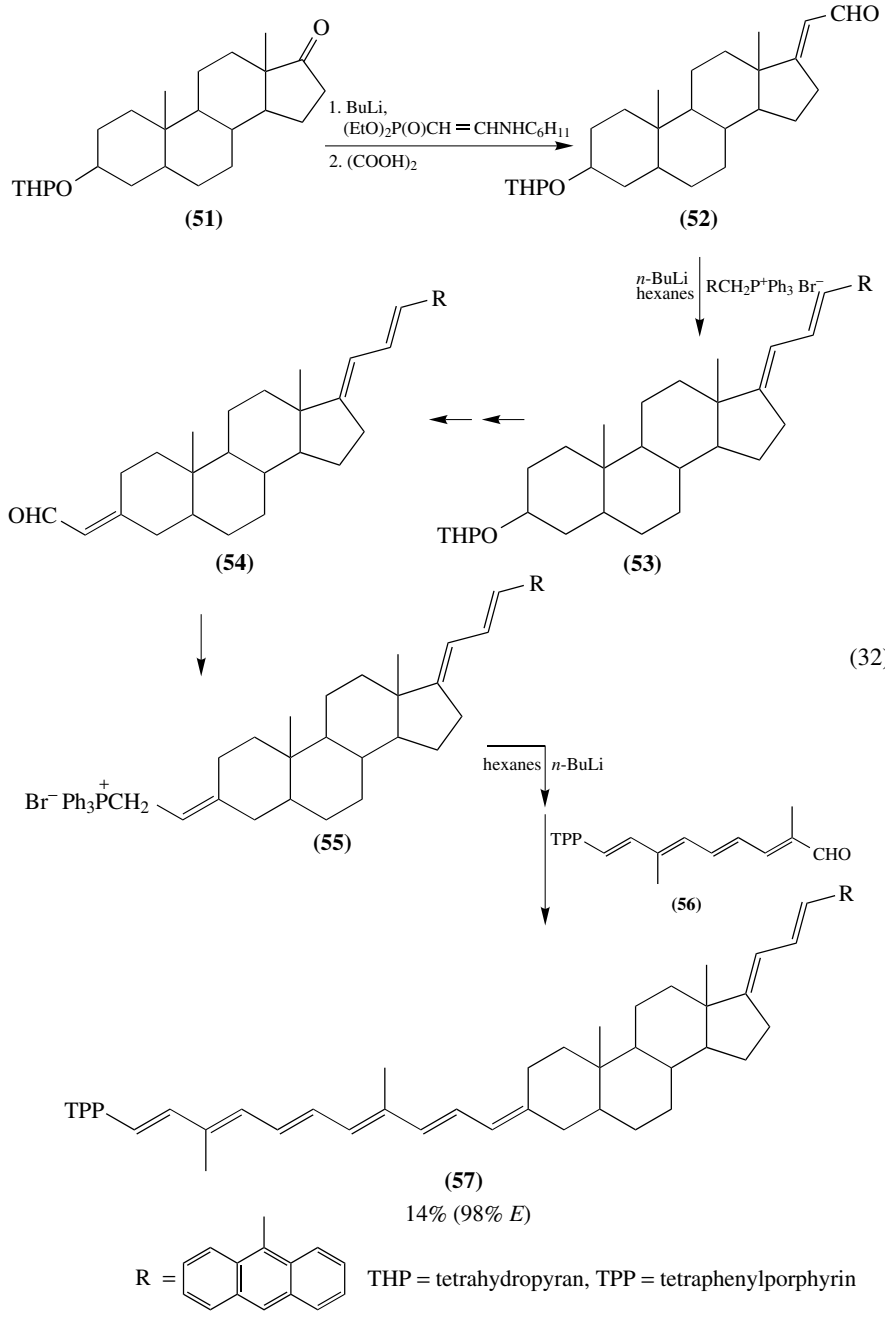
prepared by the palladium-catalyzed coupling of vinyl iodides with hydrostannylated FMOC-propargylamines, as shown in equation 34[55].



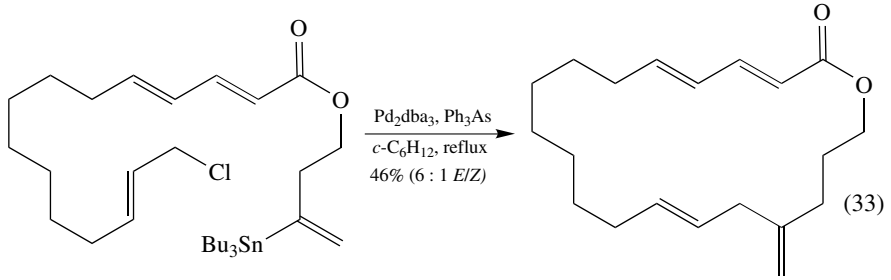
(31)

Epothilone B

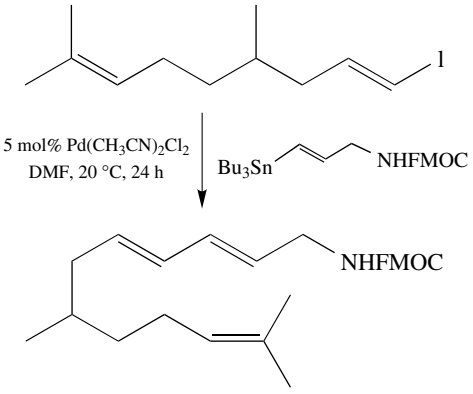
Stannylated dienyne **60** serves as an all-*E* 1,6-dimetallohexatriene equivalent[56]. Vinyl stannane **60** was prepared from stannyl enal **61** by Wittig coupling with the ylide derived from the known salt of **62**, affording **60** in high yields and usually with better than 90 : 10 *E*/*Z* selectivity (equation 35). Tin–lithium exchange followed by conversion to the organozinc derivative provides a reactive intermediate **63** which, in the presence of catalytic $Pd(PPh_3)_4$, was coupled with vinyl iodide **64** in THF. Removal of the acetylenic silyl moiety was accomplished with K_2CO_3 in EtOH at room temperature resulting in tetraenyne **65** in good overall isolated yield.


O
THPO
1. BuLi,
(EtO)2P(O)CH=CHNHC6H11
2. (COOH)2
CHO
THPO
(51)
(52)
n-BuLi
hexanes
RCH2P+Ph3 Br–
R
R
OHC
THPO
(54)
(53)
R
Br– Ph3P+CH2
(55)
hexanes
n-BuLi
TPP
CHO
(56)
R
TPP
(57)
14% (98% E)
R =
THP = tetrahydropyran, TPP = tetraphenylporphyrin

(32)

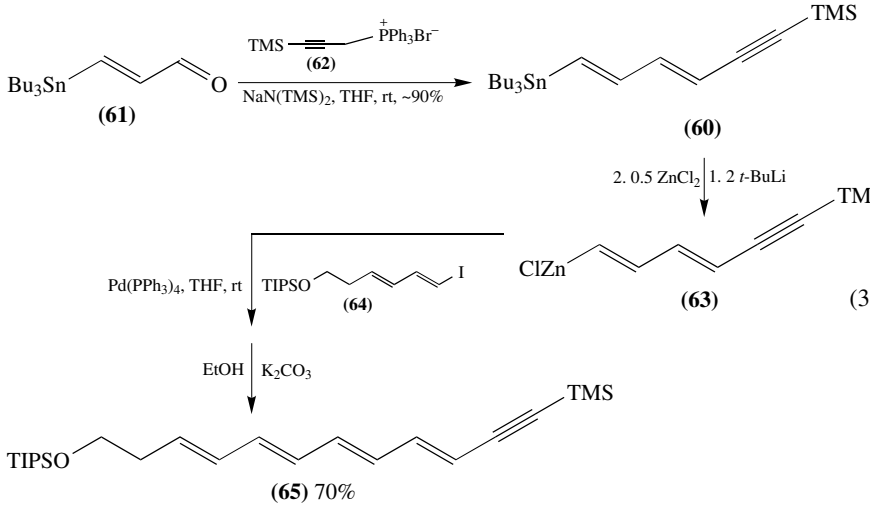


(59) (58) (33)



(34)

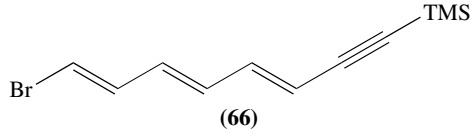
65% ($E : Z = 85 : 15$)
FMOC = 9-Fluorenylmethoxycarbonyl



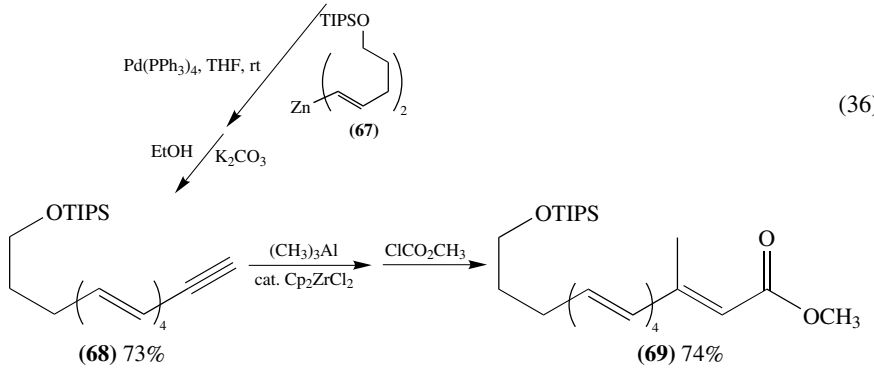
(35)

(65) 70%

Alternatively, bromo trienyne **66**, prepared by the Wittig reaction of TMS-capped propargyl ylide with *E*,*E*-5-bromo-2,4-pentadienal, could be coupled with dienyl zinc reagent **67**, as illustrated in equation 36[57]. Subsequent desilylation followed by treatment with trimethyl aluminum in the presence of catalytic Cp_2ZrCl_2 afforded the alane of tetraenyne **68** which, on exposure to chloroformate, gave essentially all-*E* polyene ester **69**.



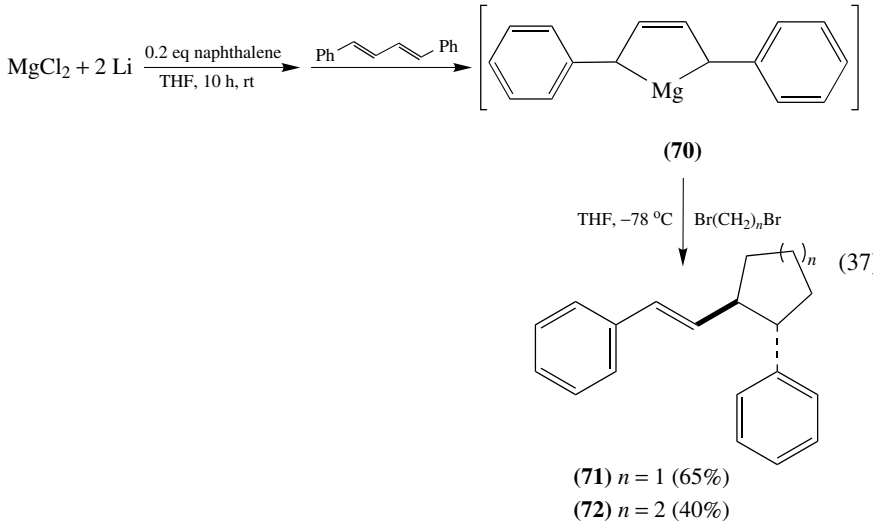
(66)



(36)

(68) 73% **(69)** 74%

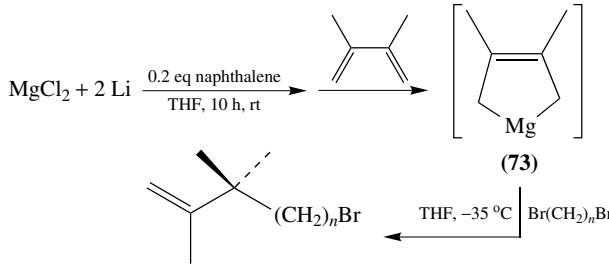
Magnesium complexes of 1,3-dienes have been used to form carbocycles and ω-bromoalkenes[58]. 1,4-Diphenyl-2-butene-1,4-diylmagnesium **(70)** was prepared by reacting (*E*,*E*)-1,4-diphenyl-1,3-butadiene with magnesium freshly generated by reducing anhydrous magnesium chloride with lithium in THF (equation 37). While **70** reacted with



(37)

(71) $n = 1$ (65%)
(72) $n = 2$ (40%)

1,3-dibromopropane and 1,4-dibromobutane to give carbocycles **71** and **72**, respectively, the magnesium complex of 2,3-dimethyl-1,3-butadiene, **73**, gave good yields of the corresponding brominated acyclic products **74** and **75** at low temperatures (equation 38). Cyclization was accomplished after refluxing the reaction mixture in THF for several hours.

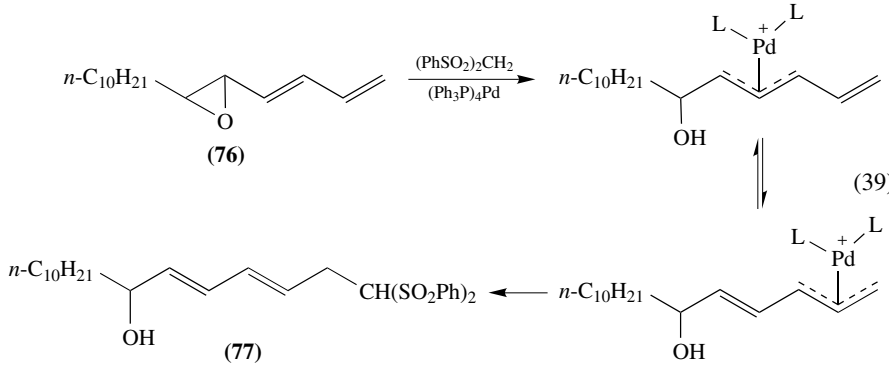


(38)

(74) $n = 1$ (72%)
(75) $n = 2$ (79%)

Manganese(III) has also proven to be effective in promoting carbon–carbon bond formation between alkenes or dienes with carbonyl compounds[59].

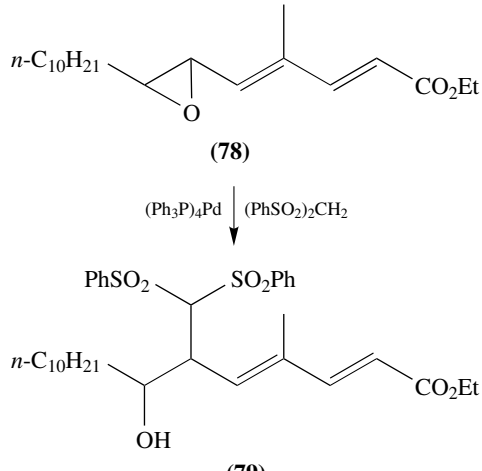
The regioselectivity in palladium-catalyzed alkylations has been attributed to the dynamic behavior of trihapto pentadienyl metal complexes[60]. For example, competing electronic and steric effects influence product formation in dienyl epoxides, but in palladium-catalyzed reactions steric factors were often found to be more important. Thus, alkylation of dienyl epoxide **76** with bulky nucleophiles such as bis(benzenesulfonyl)methane in the presence of $(Ph_3P)_4Pd$ occurred exclusively at the terminal carbon of the dienyl system producing allyl alcohol **77** (equation 39). However, the steric factors could be overcome by electronic effects when one of the terminal vinylic protons was replaced with an electron-withdrawing group. Thus, alkylation of dienyl epoxide **78** affords homoallylic alcohol **79** as the major product (equation 40).



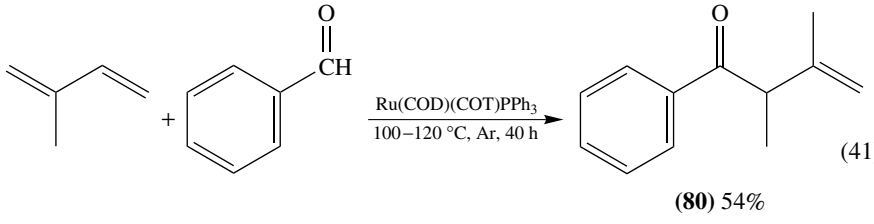
(39)

Ruthenium-catalyzed hydroacylation of 1,3-dienes with aromatic and heteroaromatic aldehydes occurs in relatively good yields to afford the corresponding β,γ-unsaturated ketones[61]. Isoprene and benzaldehyde were treated with 4 mol% Ru(COD)(COT) (COD = 1,5-cyclooctadiene, COT = 1,3,5-cyclooctatriene) and 4 mol% PPh_3 under argon for 40 hours to give 54% **80** (equation 41). The key intermediate is an acyl-η^3-(allyl)ruthenium complex which undergoes reductive elimination to give the corresponding

ketones. Aliphatic aldehydes, on the other hand, were not effective substrates in this reaction. Interestingly, carbon monoxide is not needed to suppress decarbonylation of aldehydes.



(40)



(41)

(80) 54%

V. DIMERIZATION REACTIONS

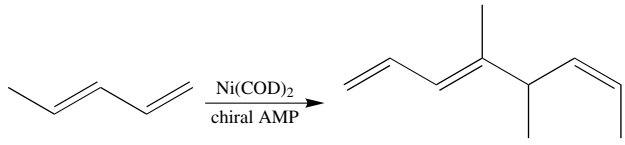
Dimerization of conjugated dienes and trienes is generally accomplished at elevated temperatures or in the presence of metal catalysts. Linear dimerization of butadiene occurs readily at room temperature on nickel catalysts bearing aminophosphinite (AMP) ligands, and the reaction rate is reportedly twice that observed in other nickel systems employing either morpholine, ethanol or P-methyloxaphospholidines as modifiers[62]. 1,3-Pentadiene dimerizes in the presence of 1 mol% nickel catalyst to give a diastereomeric mixture of 4,5-dimethyl-1,3,6-octatriene as shown in equation 42.

While linear dimerization of dienoic esters can also be accomplished with nickel-AMP systems, other functionalized dienes undergo little or no conversion. The reaction of methyl hexa-2,4-dienoate, **81**, furnishes diastereomeric trienoic diesters **(82)** in high yields (equation 43).

3-Methylene-1,4-pentadiene **(83)**, prepared by flash vacuum pyrolysis of 1,5-diacetoxy-3-(acetoxymethyl)pentane, dimerizes at 95 °C in benzene to give predominantly one isomer of 1,4,4-trivinylcyclohexene **(84)** as the major product (equation 44)[63].

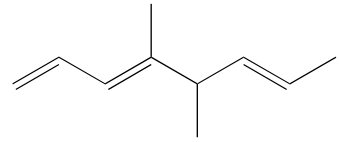
Similar investigations with the conformationally restricted triene **85** led the authors to conclude that dimerization proceeds by a two-step mechanism involving initial

formation of a diradical species, followed by rapid ring-closure to yield [4 + 2] dimer **86** (equation 45).



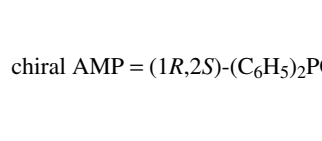
E,*Z*; ee = 90%

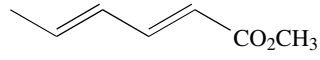
+



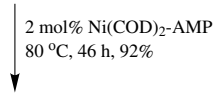
E,*E*; ee = 35%

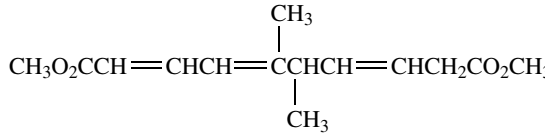
(42)





(81)

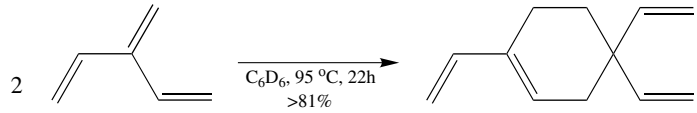




(43)

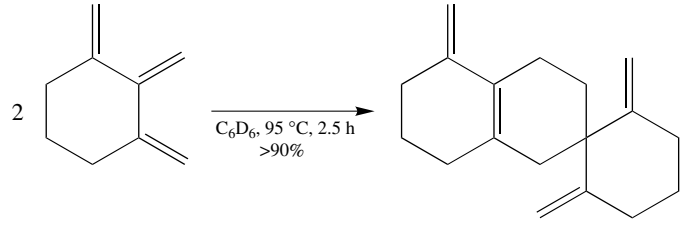
(82) 85% *E,E,E*; 13% *E,E,Z*

AMP = $(C_6H_5)_2POCH(C_6H_5)CH(CH_3)NHCH_3$



(44)

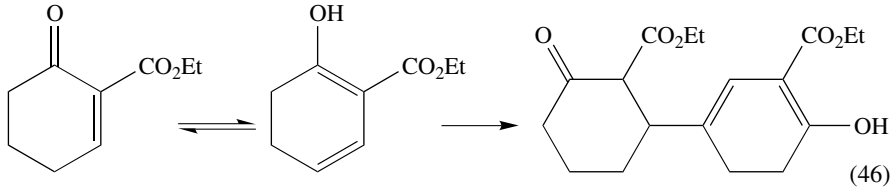
(83) **(84)**



(45)

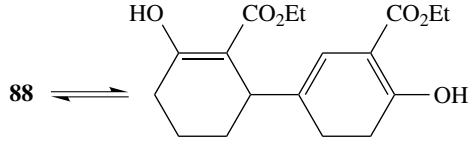
(85) **(86)**

Cycloalkenone-2-carboxylates tautomerize to conjugated dienols in the presence of either acids or bases. Iron(III) catalysts have also been found to promote enone–dienol equilibration, and, at room temperature, dimerization[64]. Thus, treating **87** with 1 mol% iron(III) chloride hexahydrate in methylene chloride at room temperature affords **88** in 81% yield (equation 46). The cyclohexadiene–cyclohexanone is in a rapid equilibrium with its triendiol tautomer, **89** (equation 47).



(46)

(87) **(88)**



(47)

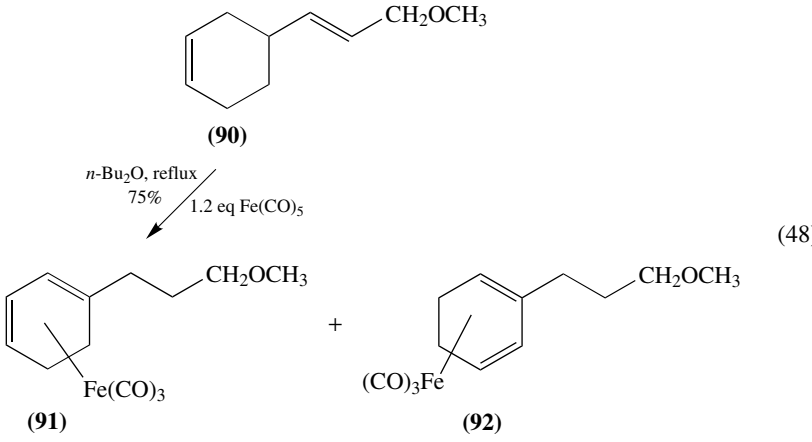
(89)

VI. PREPARATION OF METAL–POLYENE COMPLEXES

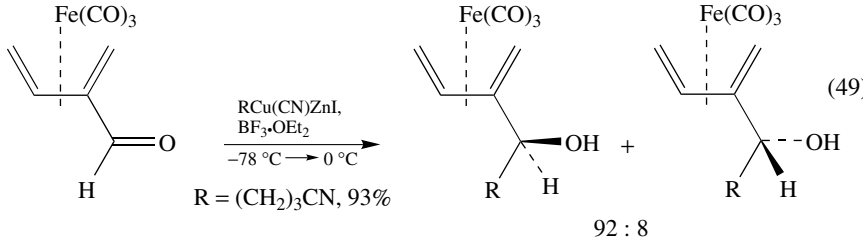
(η^4-Diene)tricarbonyliron complexes have found use as synthons for the preparation of functionalized dienes. Substituted 4-vinylcyclohexene derivatives are isomerized by pentacarbonyliron into a mixture of conjugated cyclohexadiene tricarbonyl iron complexes[65]. When the 4-vinyl cyclohexene **90** was refluxed with 1.2 equivalents of $Fe(CO)_5$ in di-*n*-butyl ether, a 3 : 1 mixture of cyclohexadiene isomers **91** and **92** was acquired in 75% overall yield (equation 48).

The diastereoselective formation of dienol tricarbonyliron complexes on treating (η^4-2,4-pentadienal)$Fe(CO)_3$ with functionalized zinc–copper reagents has been investigated (equation 49)[66]. Cyano-substituted complexes undergo intramolecular nucleophilic additions when treated with lithium diisopropylamide (LDA) as shown in equation 50.

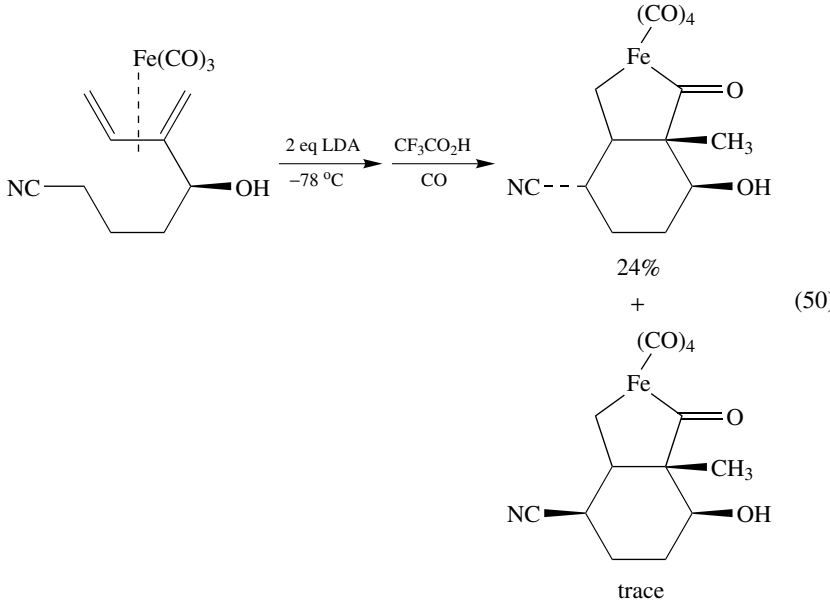
Acylation of terminal alkenes by (η^4-2,4-pentadienoyl chloride)$Fe(CO)_3$ proceeds in high yield in the presence of Lewis acid catalysts[67]. As shown in equation 51, the reaction generally produces a mixture of (η^4-diene)tricarbonyliron complexes of the β-chloroketone and β,γ-unsaturated ketone.


CH2OCH3
(90)
n-Bu2O, reflux
75%
1.2 eq Fe(CO)5
CH2OCH3
Fe(CO)3
(91)
+
CH2OCH3
(CO)3Fe
(92)
3 : 1

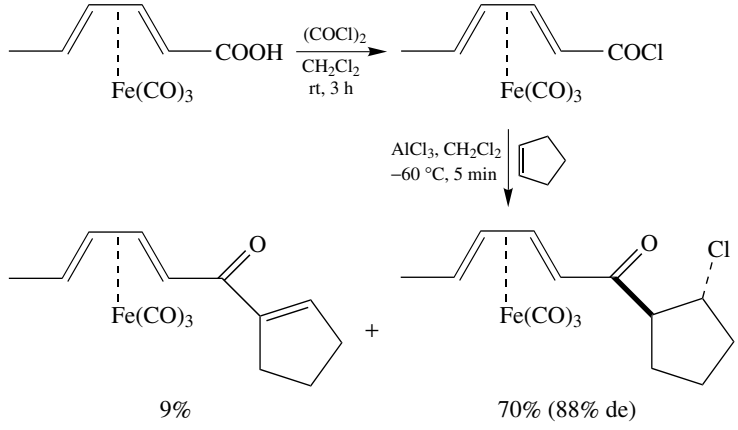
(48)


Fe(CO)3
O
H
RCu(CN)ZnI,
BF3•OEt2
−78 °C → 0 °C
R = (CH2)3CN, 93%
Fe(CO)3
OH
R
H
+
Fe(CO)3
OH
R
H
92 : 8

(49)


Fe(CO)3
NC
OH
2 eq LDA
−78 °C
CF3CO2H
CO
(CO)4
Fe
O
CH3
NC
OH
24%
+
(CO)4
Fe
O
CH3
NC
OH
trace

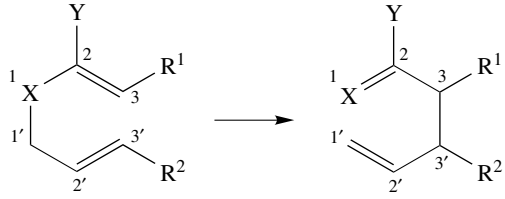
(50)



(51)

VII. REARRANGEMENTS

The popularity of [3,3]-sigmatropic rearrangements in organic synthesis derives from the ability of such reactions to generate stereogenic centers from the sp^2-hybridized carbons. The formation of these chiral centers can take place at a distance from other functional groups and chiral auxiliaries in the molecule[68]. The general equation for [3,3]-sigmatropic rearrangements and their asymmetric counterparts is depicted in equation 52.



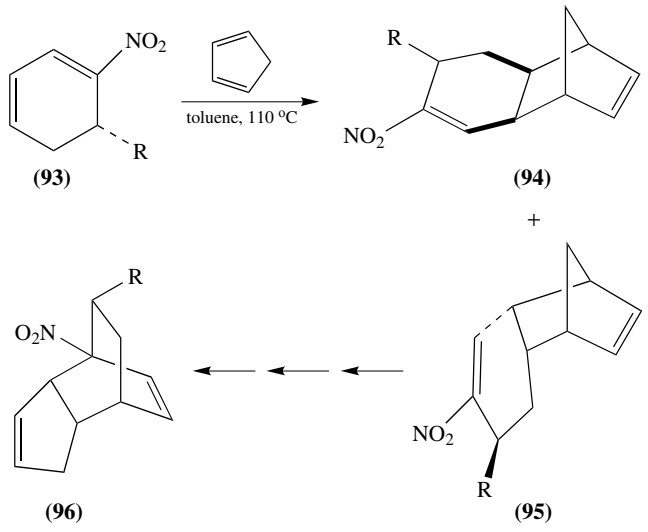
(52)

This section will focus on recent examples of asymmetric [3,3]-sigmatropic rearrangements involving dienes and polyenes. Attention will be given to Cope and Claisen rearrangements, as well as to several of their variants. For more exhaustive reviews of the subject, the reader is referred elsewhere[69,70].

A. Cope Rearrangement

Discovered in 1940, the Cope rearrangement is an all-carbon version of the [3,3]-sigmatropic rearrangement depicted in equation 52 (i.e. X and Y are carbon). Reactions in which X is a heteroatom (i.e. oxygen, nitrogen, sulfur) and Y is carbon are hetero variants, the most widely used being the Claisen rearrangement where X is oxygen[69]. Cope rearrangements can be performed thermally[68,69,71] or photochemically[72]. The Cope rearrangement of dienes has found utility in a number of regio- and stereoselective syntheses of ring systems[71,73,74]. Román and coworkers[71] have recently reported an enantioselective synthesis of 1-nitrotricyclo[5.2.2.$0^{2,6}$]undeca-3,8-dienes which involves an asymmetric

Diels–Alder reaction, followed in tandem by a Cope rearrangement (equation 53).



(53)

(a) R = *D*-manno-$(CHOAc)_4$-CH_2OAc
(b) R = *D*-manno-$(CHOH)_4$-CH_2OH
(c) R = CHO
(d) R = CH_2OH

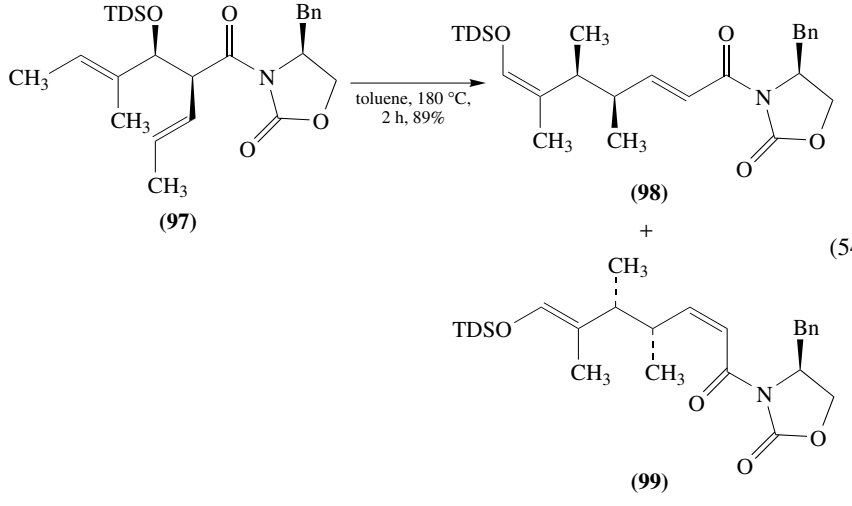
Nitrocyclohexadiene **93a** reacted with 4.0 equivalents of cyclopentadiene in toluene at 110 °C for 96 h, producing the 10-glyco-1-nitrotricyclo[5.2.2.$0^{2,6}$]undeca-3,8-diene **96a** in 70% yield. Subsequent treatment with potassium carbonate in a methanol–water (9 : 1) solution followed by oxidative cleavage of the sugar side chain with sodium metaperiodate afforded aldehyde **96c**. Reduction of the aldehyde with sodium borohydride produced alcohol **96d**.

Schneider and Rehfeuter[68] have reported that enantiomerically pure 1,6-disubstituted-1,5-dienes with an aldol substitution pattern can undergo stereoselective Cope rearrangements in good yield. For example, 1,5-diene **97** underwent Cope rearrangements in toluene in sealed flasks at 180 °C for 2 h to afford, after chromatography, an 89% yield of a 97 : 3 diastereomeric mixture of **98** and **99**, respectively (equation 54).

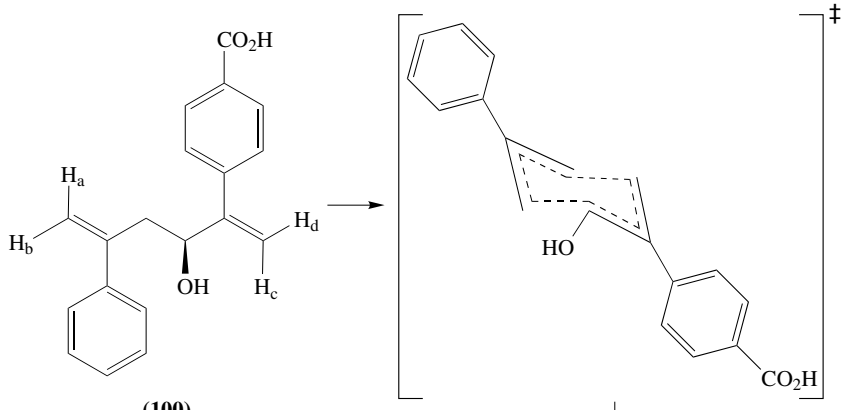
The oxy-Cope and anionic oxy-Cope rearrangements have found more widespread use in stereoselective synthesis than the Cope rearrangement[70,75–79]. Anionic oxy-Cope rearrangements can often be performed at or near room temperature. The rearrangement is compatible with many functional groups, and stereogenic centers are often introduced with a high degree of predictability[70].

An antibody, originally generated against a diaryl substituted cyclohexanol derivative, has been employed to catalyze the oxy-Cope rearrangement of hexadiene **100** to aldehyde **101** (equation 55)[80,81]. A rate enhancement of 5300-fold over the uncatalyzed reaction was achieved.

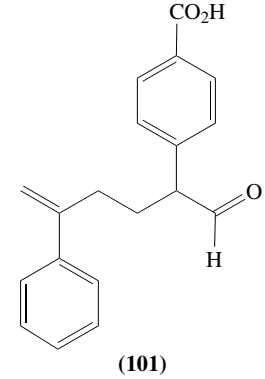
In the total synthesis of cerorubenic acid-III methyl ester **(105)**, diene **102** was converted to enantiopure tricyclic ketone **103** through an anionic oxy-Cope rearrangement (equation 56)[82]. Conversion of **102** to **103** afforded the entire ABC substructure of **104** and **105**, most notably the double bond occupying a bridgehead site.



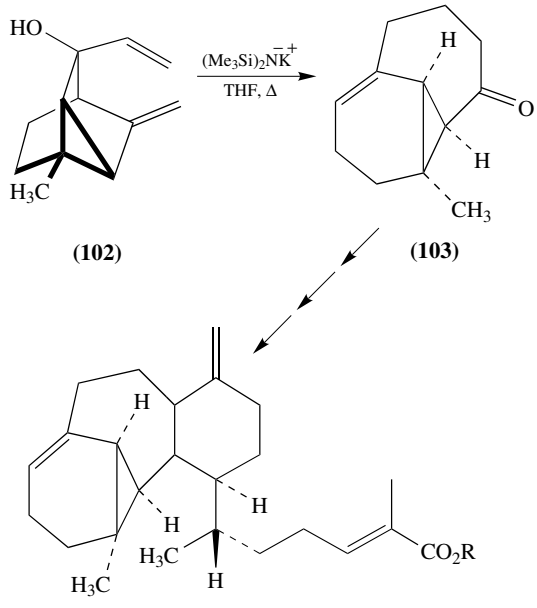
(97) **(98)** **(99)** (54)



(100) (55)



(101)

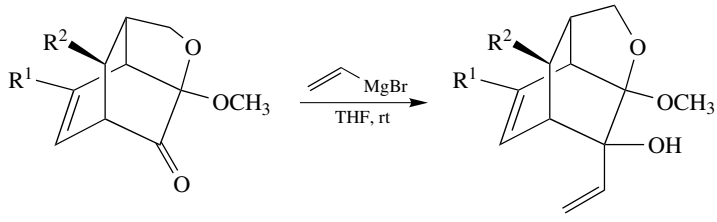


(102) **(103)**

(56)

(104) R = H
(105) R = Me

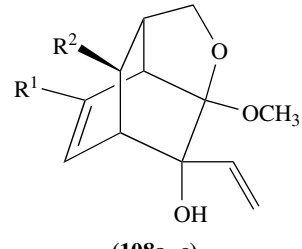
2-Vinylbicyclo[2.2.2]oct-5-en-2-ols **107a–c** and **108a–c**, bearing dialkoxy substituents at the C-3 position, underwent base catalyzed [3,3]- and [1,3]-sigmatropic rearrangements to yield a stereocontrolled route to *cis*-decalins and bicyclo[4.2.2]dec-7-en-4-ones (equation 57)[83]. Compounds **106a–c** were converted to diastereomeric alcohols **107a–c**



(106) **(107a–c)**

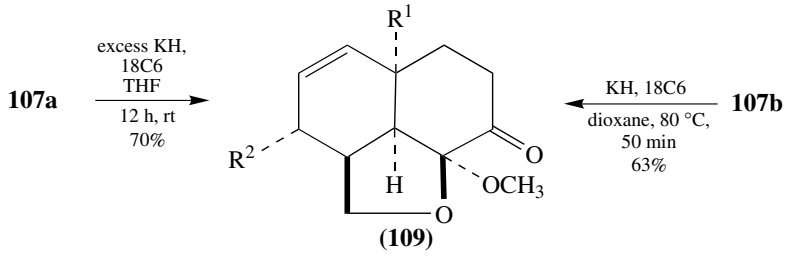
(a) R^1 = H, R^2 = Ph
(b) R^1 = CH_3, R^2 = Ph
(c) R^1 = CO_2CH_3, R^2 = CH_3

\+



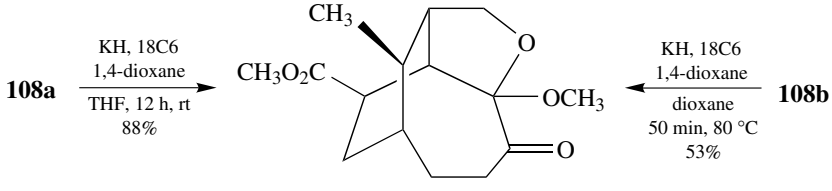
(108a–c)

(57)



(109)

(**a**) $R^1 = H$, $R^2 = Ph$
(**b**) $R^1 = CH_3$, $R^2 = Ph$



(110)

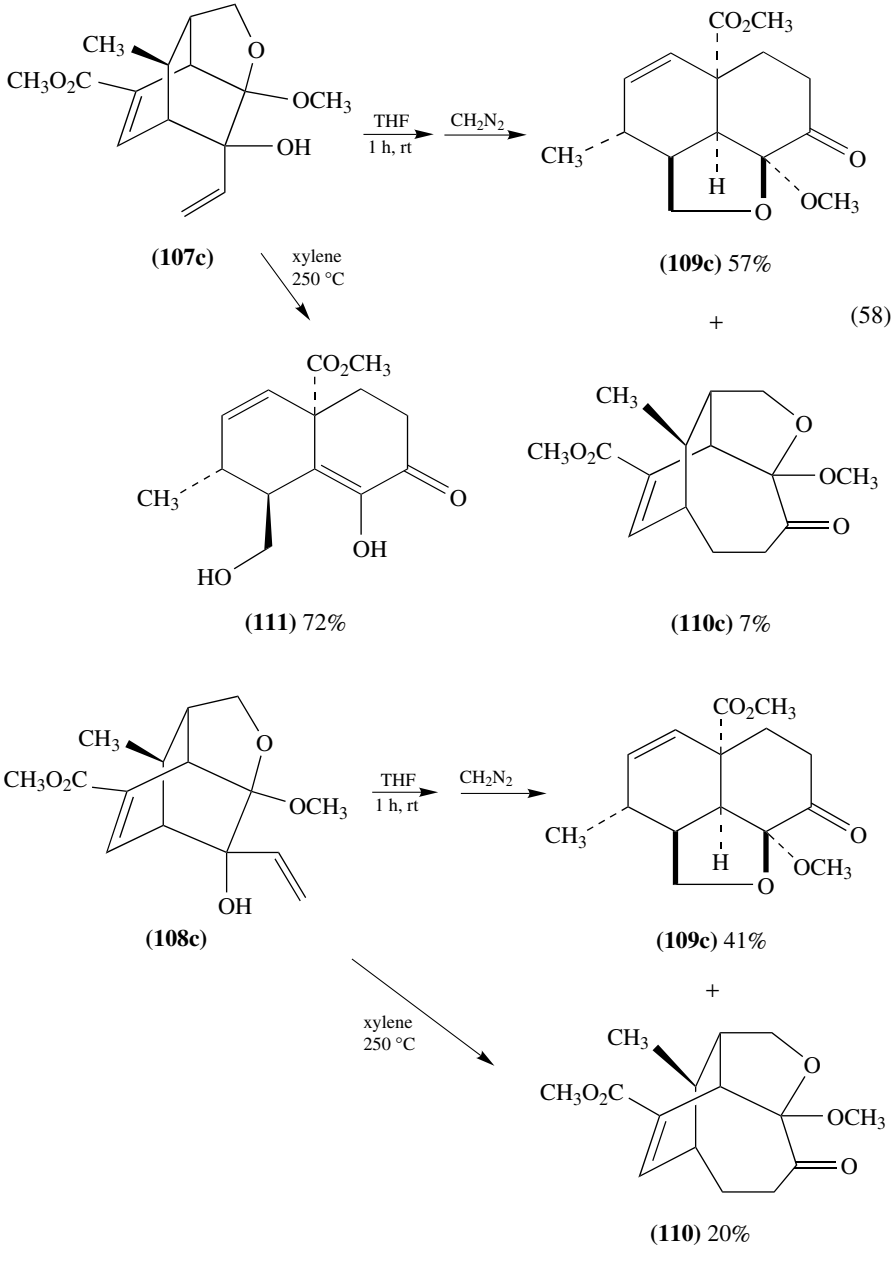
(a) $R^1 = H$, $R^2 = Ph$
(b) $R^1 = CH_3$, $R^2 = Ph$

and **108a–c** by treatment with vinylmagnesium bromide. Alcohols **107a** and **107b** underwent anionic oxy-Cope rearrangements on exposure to excess KH (5 equiv.) and in the presence of 18-crown-6 ether (3 equiv.) to produce compounds **109a** and **109b**, respectively. When subjected to similar conditions, however, alcohol **108a** and **108b** underwent [1,3]-rearrangement to yield the ring enlargement products **110a** and **110b**, respectively.

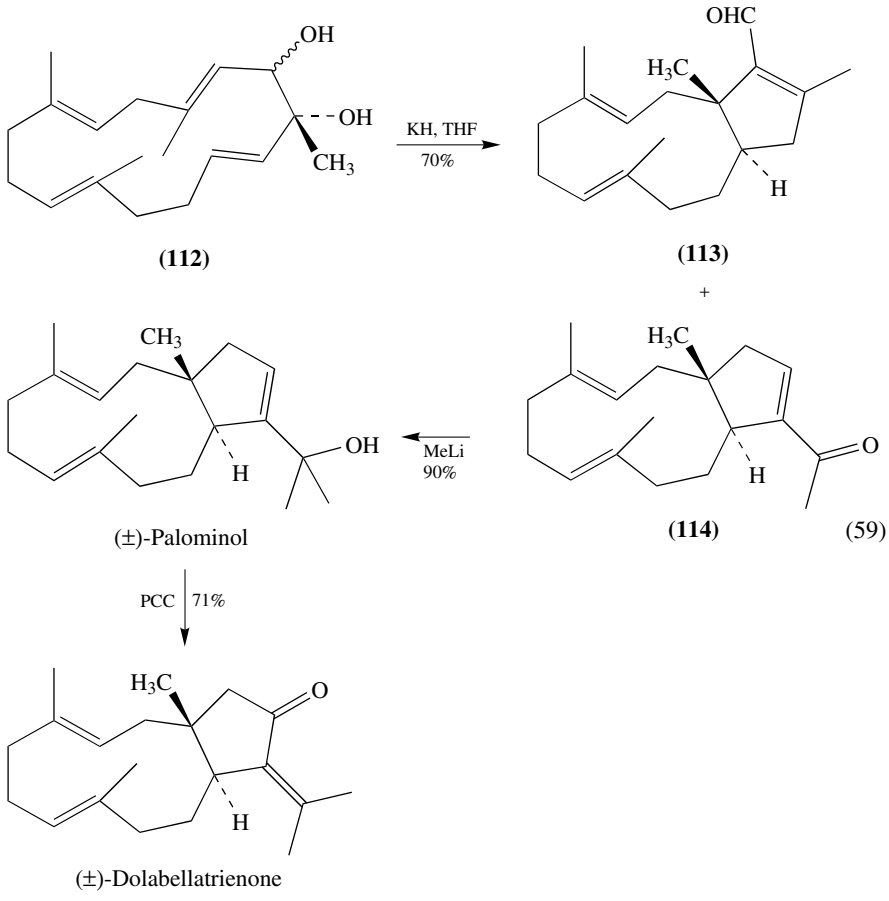
When R^1 was methoxycarbonyl **(106c)**, however, the reaction of each of the resulting diastereomeric bicyclic dienes, **107c** and **108c**, afforded products **109c** and **110c**. Interestingly, heating **107c** in a sealed tube resulted in a 72% yield of the fused-bicyclic enol **(111)**, presumably from hydrolysis of **109c**. On the other hand, heating **108c** produced only the ring enlarged product **110c** in 61% yield (equation 58).

In the synthesis of (±)-palominol and (±)-dolabellatrienone from farnesol, Corey and Kania[84] employed a dianion accelerated oxy-Cope rearrangement to form the 11,5-*trans*-fused ring system of the dolabellanes. Diol **112** was treated with potassium hydride in THF to afford a 1 : 1 mixture of products with *trans*-11,5-fused ring systems, **113** and **114** (equation 59). Bicyclic α,β-unsaturated methyl ketone **114** was then converted to (±)-palominol in 90% yield with methyllithium. Subsequent oxidation of (±)-palominol with PCC gave (±)-dolabellatrienone in 71% yield.

N-Glycosyl homoallylamines have been shown to undergo a stereocontrolled Lewis acid-catalyzed aza-Cope rearrangement to produce chain-extended amino sugars[85]. The reactions proceed in good to excellent yields with high stereoselectivity. Schiff base **115** was converted to *N*-galactosyl-*N*-homoallylamine **116** by $SnCl_4$-induced addition of allyltrimethylsilane or allyltributylstannane (equation 60).



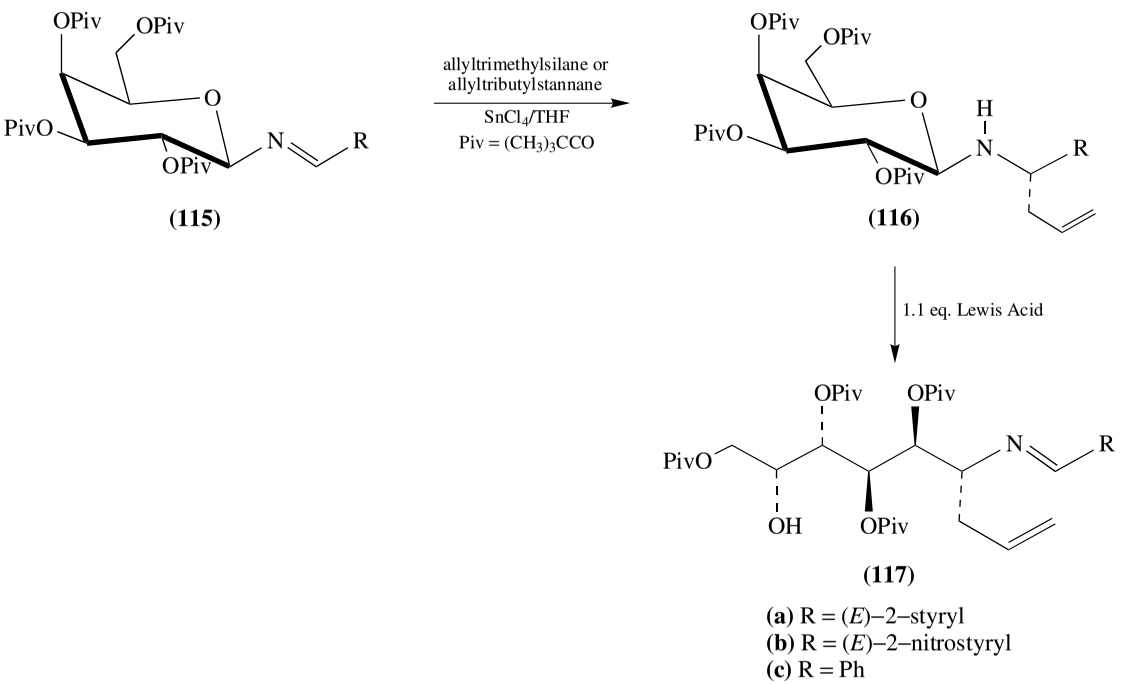
The mechanism involves conversion of *N*-homoallylamine **116a** to imine **117a** via a Lewis acid-catalyzed cationic aza-Cope rearrangement (equation 61). Various Lewis acids were tested with yields ranging from 40–99% with high diastereoselectivities.



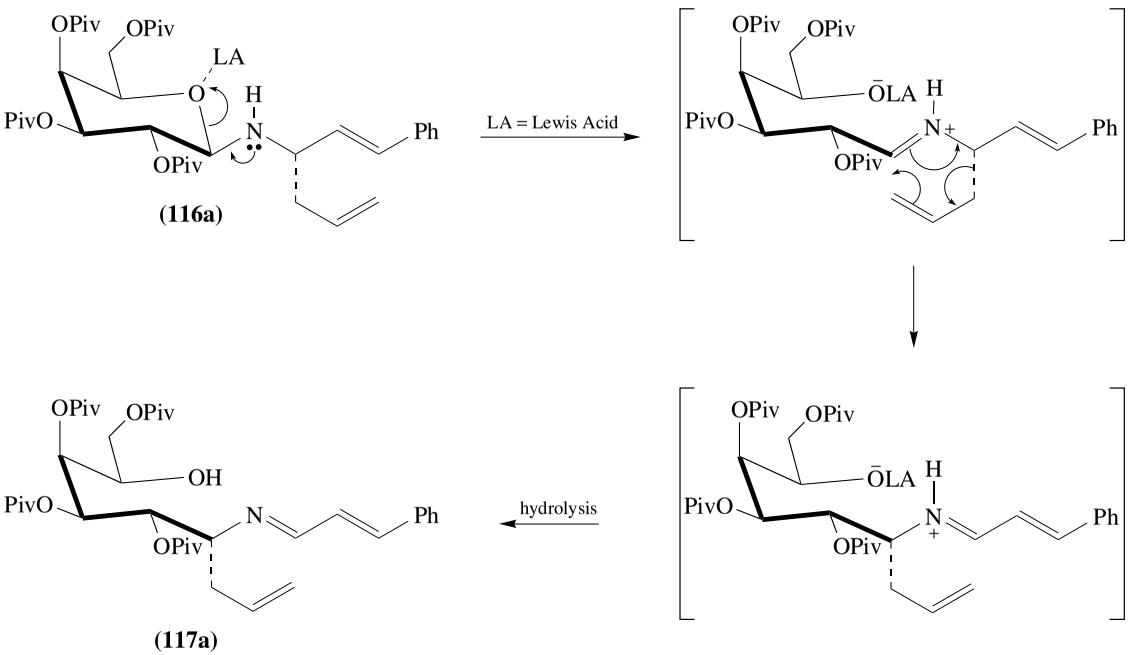
B. Claisen Rearrangement

The Claisen rearrangement, discovered in 1912, has proven to be a powerful tool for the stereoselective generation of C−C bonds[69]. It is widely employed in complex multistep syntheses (see, for example, References 86–89) and has inspired many variations, including the Carroll (1940), Eschenmoser (1964), Johnson (1970), Ireland (1972) and Reformatsky-Claisen (1973) reactions[69].

Sattelkau and Eilbracht[90] have exploited the Claisen rearrangement of allyl vinyl ethers in their synthesis of several spiro compounds. As shown below in equation 62, 7,9-dimethyl-1,4-dioxa-spiro[4,5]decan-8-one, **118**, was converted to α,β-unsaturated ester **119** which was reduced to allyl alcohol **120**[90b]. Allyl vinyl ether **121** underwent a rhodium-catalyzed Claisen rearrangement to afford 7*t*,13*t*-dimethyl-1,4-dioxa-(8rC^9)-dispiro[4.2.4.2]tetradecan-10-one **(122)** in 36% yield.

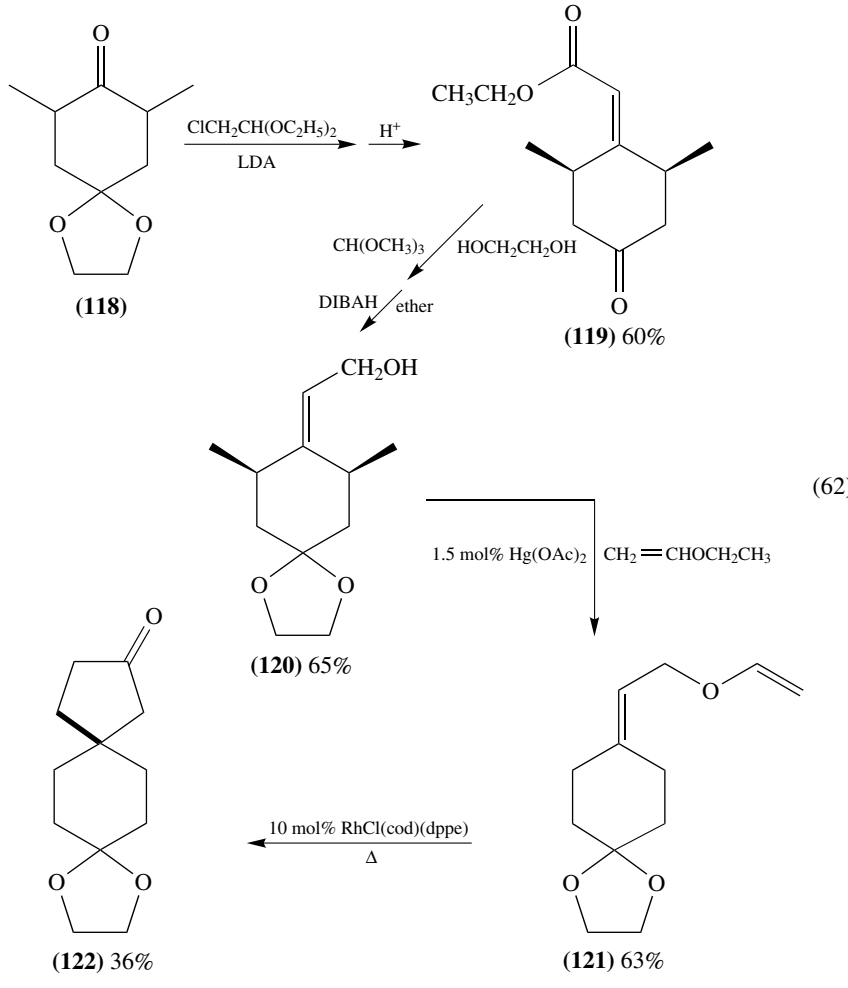

OPiv
OPiv
O
PivO
N
R
OPiv
(115)
allyltrimethylsilane or
allyltributylstannane
SnCl4/THF
Piv = (CH3)3CCO
OPiv
OPiv
O
H
PivO
N
R
OPiv
(116)
1.1 eq. Lewis Acid
OPiv
OPiv
PivO
N
R
OH
OPiv
(117)
(a) R = (E)–2–styryl
(b) R = (E)–2–nitrostyryl
(c) R = Ph

(60)


OPiv
OPiv
LA
O
H
N
PivO
OPiv
Ph
(116a)
LA = Lewis Acid
ŌLA
N+
hydrolysis
OH
(117a)

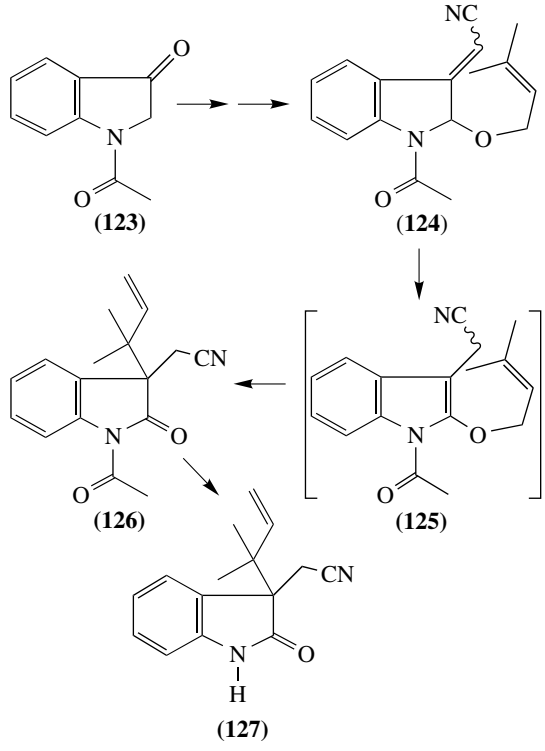
(61)

N-Acetyl indolin-3-one **123** was converted to 3-cyanomethyl-3-(1,1-dimethylallyl) indol-2-one, **127**, by a successive isomerization–Claisen rearrangement sequence (equation 63)[91]. *N*-Acetylindolin-3-one **123** was converted in two steps to a mixture of *E*- and *Z*-isomers of **124**. Isomerization of both isomers of **124** to **125** was accomplished with DBU. Claisen rearrangement of **125** afforded a 13% yield of **126**, which was subsequently deprotected to give 3-cyanomethyl-3-(1,1-dimethylallyl)indol-2-one, **127**, in 47% yield.

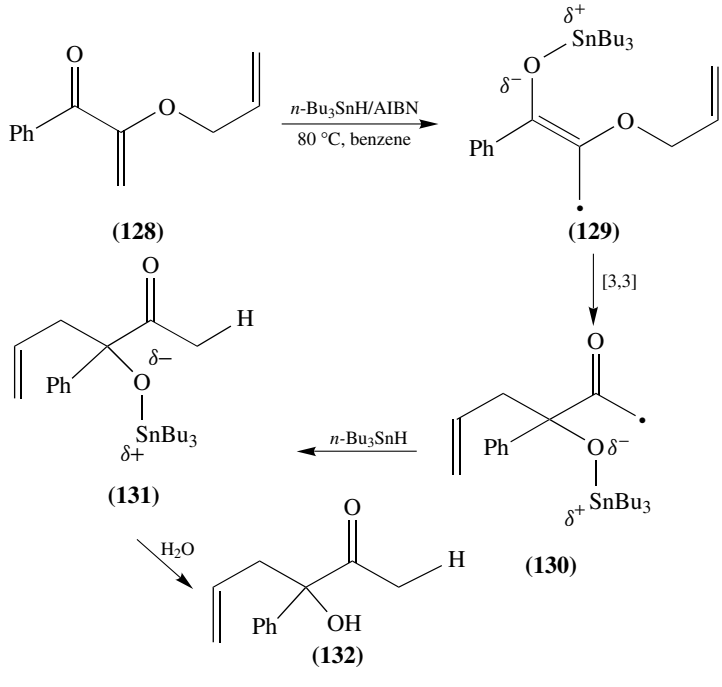


(62)

Ketyl radical anions generated from α-allyloxy-α,β-unsaturated ketones have been used to trigger [3,3]-sigmatropic rearrangements resulting in the formation of α-hydroxy-γ,δ-unsaturated methyl ketones (equation 64)[92]. It was postulated that formation of the tin(IV) enolate and allylic radical species **129** should induce a [3,3]-Claisen rearrangement to form the tin(IV) alkoxide radical **130**. This radical anion can undergo hydrogen atom abstraction to yield tin alkoxide **131** which, on quenching with water, affords alcohol **132**. To test this hypothesis, a series of six dienones were treated with tin hydride and AIBN. Refluxing

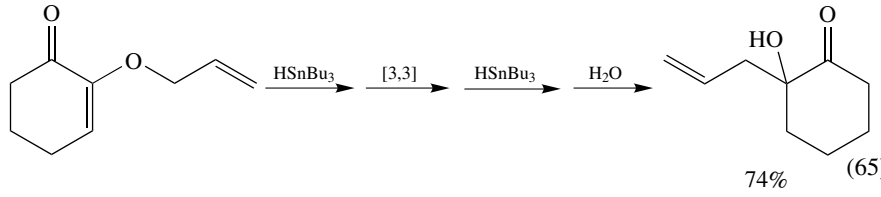

NC
O
N
O
O
(123)
(124)
CN
(126)
(125)
CN
(127)

(63)


Ph
O
O
n-Bu3SnH/AIBN
80 °C, benzene
δ+
SnBu3
δ−
(128)
(129)
[3,3]
H
δ−
Ph
SnBu3
δ+
n-Bu3SnH
(131)
(130)
H2O
OH
(132)

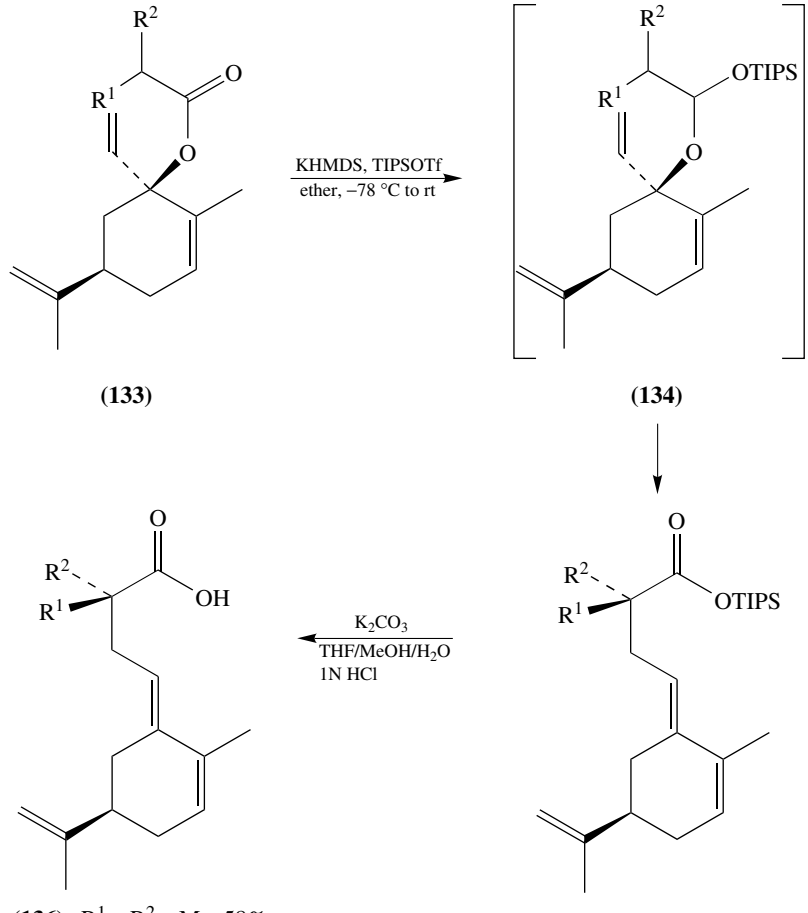
(64)

resulted in the corresponding α-hydroxy ketones in yields ranging from 51% to 74%. A typical example is shown in equation 65.



(65)

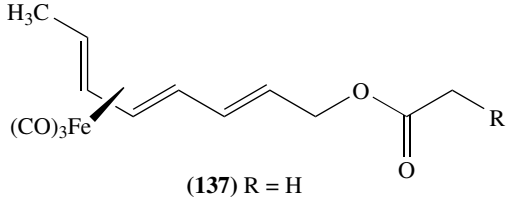
Alkylidene cyclohexenes were synthesized stereoselectively from bis-allyl silylketene acetals derived from cyclohexenones[93]. As shown in equation 66, Ireland Claisen rearrangement of ester **133** gave only *E*-diene **136**. Reaction of **133** with potassium



(66)

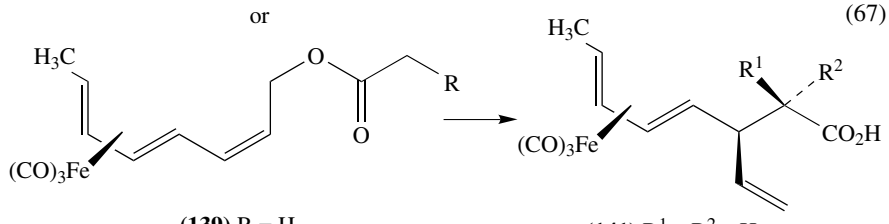
bis(trimethylsilyl)amide (KHMDS) and tris(isopropylsilyl)trifluoromethane sulfonate (TIPSOTF) in ether at −78 °C, followed by warming the reaction mixture to room temperature, afforded **135**, produced from the rearrangement of **134**. Hydrolysis of **135** yielded acid **136**.

Iron(tricarbonyl) was employed to control the diastereofacial selectivity in the enolate Claisen rearrangement of some trienylic esters[94]. Trienylic esters **137** and **139** underwent successful enolate Claisen rearrangements to afford **141** when treated with 1.05–1.15 equiv. of KHMDS in THF with 23% HMPA as cosolvent and 1.2 equiv. of TBDMSCl as an internal silylating agent (equation 67). Compound **137** yielded carboxylic acid **141** in 70–80% as a single diastereomer, while the yield from compound **139** was 45–50%. TBDMSOTf was used as an internal silylating agent for esters **138** and **140**. In contrast to the results obtained with **137** and **139**, inseparable mixtures of diastereomers **142** and **143** were obtained in 85–95% yield.



(137) R = H
(138) R = CH_3

or

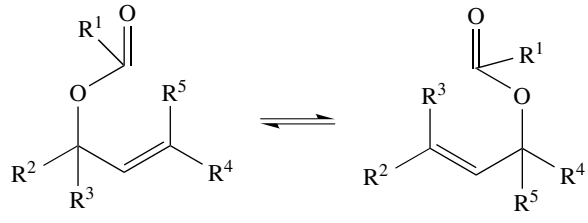


(67)

(139) R = H
(140) R = CH_3

(141) $R^1 = R^2 = H$
(142) $R^1 = H$, $R^2 = CH_3$
(143) $R^1 = CH_3$, $R^2 = H$

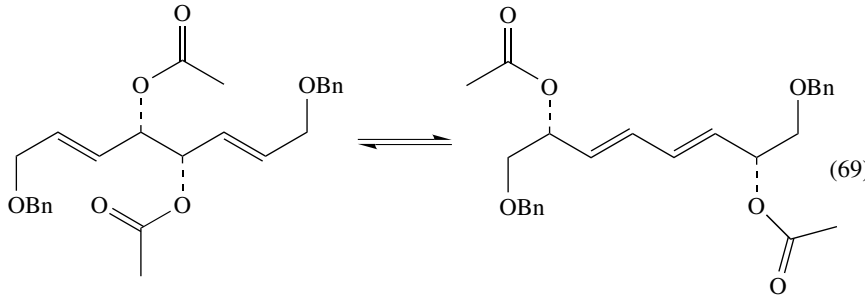
An interesting variation of the Claisen rearrangement is the hetero-Claisen rearrangement in which an allylic functionality containing a secondary hydroxyl group can be formed with controlled configuration of the allylic stereogenic center[95]. As depicted in equation 68, the rearrangement is a thermodynamically controlled equilibrium process.



(68)

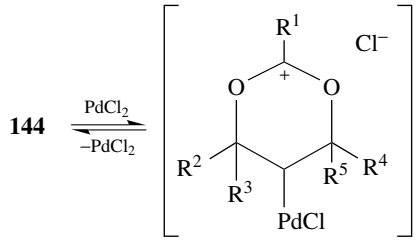
Using this hetero-Claisen rearrangement, Saito and coworkers[95] have recently shown that octadiene **144** can be converted to the rearranged product **145** with total retention of

stereochemistry of the chiral centers in **144** (equation 69). The reaction was performed at room temperature in methylene chloride with 20 mol% $PdCl_2(CH_3CN)_2$ as catalyst. Furthermore, other possible isomers, such as **146** and **147**, were not detected, even when the reaction was discontinued at an early stage. The reaction was postulated to proceed through a 1,3-dioxanium ion as shown in equation 70. This mechanism is commonly referred to as 'cyclization-induced rearrangement catalysis'.



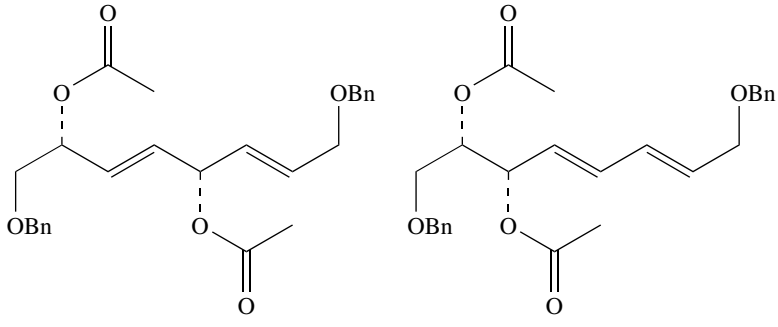
(69)

(144) **(145)**



(70)

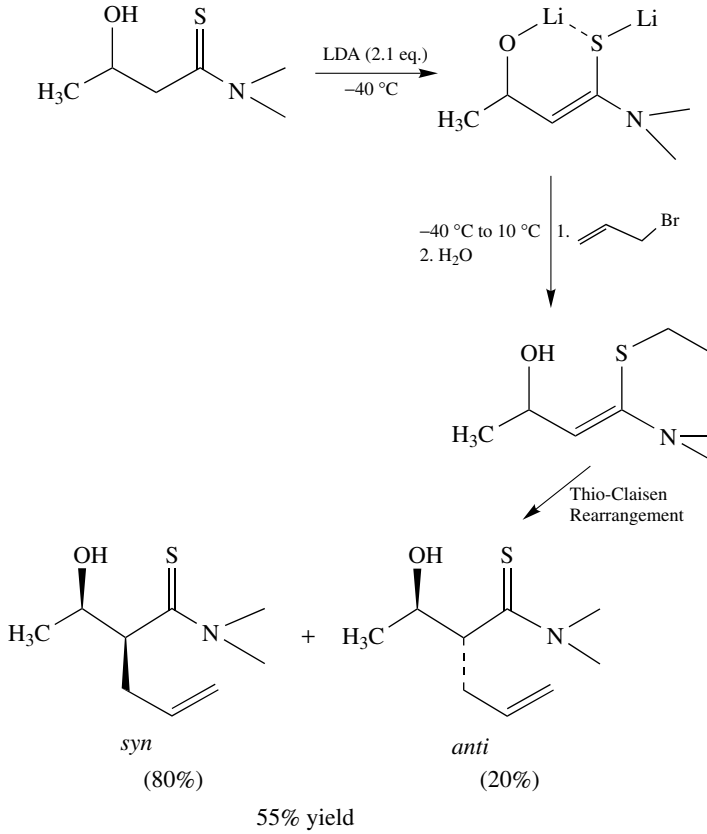
1,3-dioxanium ion



(146) **(147)**

(*Z*)-*S*-Allylic ketene aminothioacetals underwent thio-Claisen rearrangement at room temperature to give *N*,*N*-dimethyl *β*-hydroxy *α*-allylic thioamides[96]. *β*-Hydroxy-*N*,*N*,-dimethylthioamides were deprotonated with LDA to afford a chelated dianion with *Z*-configuration. Alkylation of this dianion gave the corresponding *Z* *α*-hydroxy *S*-allylic

ketene dimethylamino thioacetals. These compounds underwent [3,3]-sigmatropic rearrangement at room temperature to afford *syn N*,*N*-dimethyl β-hydroxy α-allylic thioamides in yields ranging from 30% to 70%. The preference for the *syn* over the *anti* diastereomer was generally found to be in excess of 4 : 1. An example is given in equation 71.



(71)

55% yield

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CHAPTER **10**

Rearrangements of dienes and polyenes

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I. INTRODUCTION

The rearrangements of dienes and polyenes are numerous and of different types. Many of these reactions have been known for a long time (see, e.g., the books in References[1–7] and reviews[8–11]), and they have not only been widely adopted for organic synthesis but also used as a basis for important theoretical generalizations and concepts. New synthetic methods were developed and our knowledge of organic reactions mechanisms was extended during the investigation of these rearrangements. It is sufficient to note that one of the outstanding achievements of theoretical organic chemistry in the last thirty years resulted from an analysis of cyclizations and rearrangements of diene systems, namely, the principle of conservation of orbital symmetry.

In general, the rearrangements of dienes and polyenes can be both thermal and photochemical reactions (the latters are not included in this chapter), and can be catalyzed by acids, bases, metal complexes and enzymes. They can be degenerate processes or occur with the introduction or elimination of functional groups, be accompanied by shifts of multiple bonds or by migrations of atoms or groups and they may lead to cyclizations.

Such a variety of transformations complicates attempts at a general classification of the field. Moreover, it is difficult even to specify the term 'rearrangement'. In this respect the interesting suggestion of Balaban and Fârcasiu is noteworthy[12]. According to them, 'rearrangements' are only the transformations which conserve neither the molecular nor the structural formula of the starting material (e.g. the pinacol rearrangement), while reactions which conserve the molecular but not the structural formula are named 'isomerizations' (e.g. dienone–phenol and Claisen rearrangements). The process which conserves both features is called 'automerization' (and a more common term now is 'degenerate rearrangements').

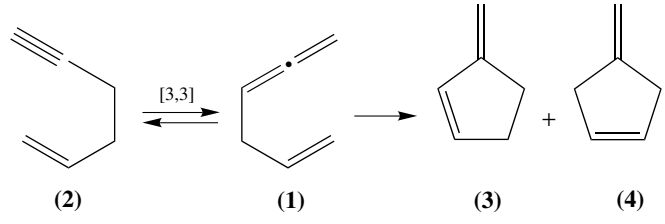
In view of the above we have arranged the material according to the structural features by using a subdivision into cumulated, conjugated and non-conjugated dienes and polyenes.

II. REARRANGEMENTS OF ALLENES AND CUMULENES

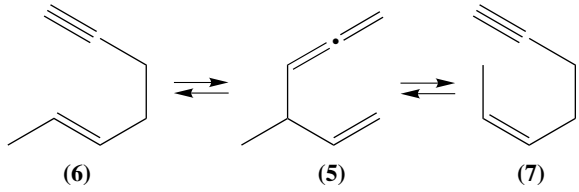
The title reactions are discussed in a series of reviews[13–15]. However, the most complete and detailed description of rearrangements involving allenes was presented in Huntsman's comprehensive survey[16], wherein the cumulated systems were considered as either the starting materials, the intermediates or the reaction products. More recently, very detailed reviews devoted to vinyl cations and containing numerous examples of rearrangements of cumulenes and other polyenes were published[17,18]. Therefore, this section will cover only relatively recent publications.

Generally, the rearrangements of allenes and cumulenes can lead to acetylene derivatives, to conjugated dienes and, in certain cases, to non-conjugated dienes[16]. A unique combination of all these transformations is presented by the rearrangements of 1,2,5-trienes **(1)** where a reversible [3,3]-sigmatropic rearrangement is accompanied by a slower cyclization to the methylenecyclopentene derivatives **3** and **4** (equation 1). The kinetics of various interconversions of methyl substituted 1,2,5-alkatriene homologues of **1** and 1-alken-5-ynes **(2)** are described in detail in a review[16]. In another example, the gas-phase pyrolysis of 4-methyl-1,2,5-hexatriene **5** at 310–320 °C for 20–90 min was recently reported[19]. Rate constants and Arrhenius parameters show that the reactions **5** → **6** and

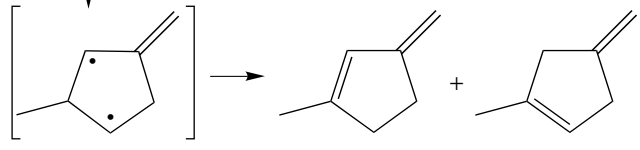
5 → **7** correspond to [3,3]-sigmatropic Cope-type rearrangements, whereas the cyclization of triene **5** to dienes **9** and **10** proceed via the diradical **8** (equation 2). The kinetic data are consistent with a concerted rearrangement of the 1,2,5-triene into its isomeric enynes but the authors do not exclude the possibility that for certain substituents the non-concerted process could become competitive. It should be noted that results were reported which exclude a cyclohexene-1,4-diyl diradical as an intermediate in the thermal acetylenic Cope rearrangement (i.e. the 'cyclization–cleavage' mechanism)[20] (see also Section IV.C.1).



(2) (1) (3) (4) (1)



(6) (5) (7) (2)



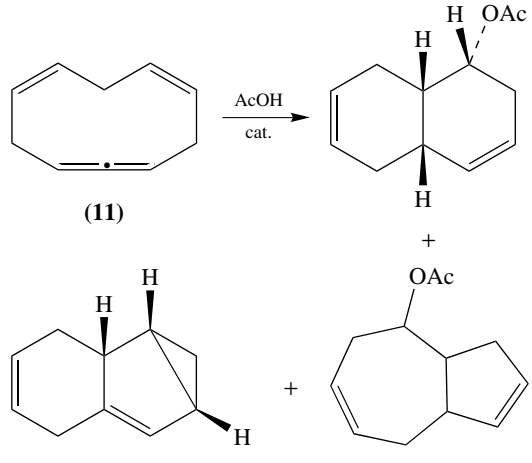
(8) (9) (10)

The cyclic 1,2,5-trienes **11** and **12** rearrange in the presence of ten different catalysts [e.g. $HgSO_4$, $Hg(OAc)_2$, AgOAc, CuOAc] in acetic acid to various unsaturated bicyclic derivatives[21] (equations 3 and 4). It is interesting that **13**, the cyclic allene isomer of **12**, forms with mercuric acetate in AcOH followed by reduction with $LiAlH_4$ only the alcohols **14** and **15** (in a ratio 92 : 8) rather than the rearranged product **16**. The authors suggest that the cyclopropyl ring stabilizes the cationoid intermediate and thus prevents it from rearrangement[21] (equation 5).

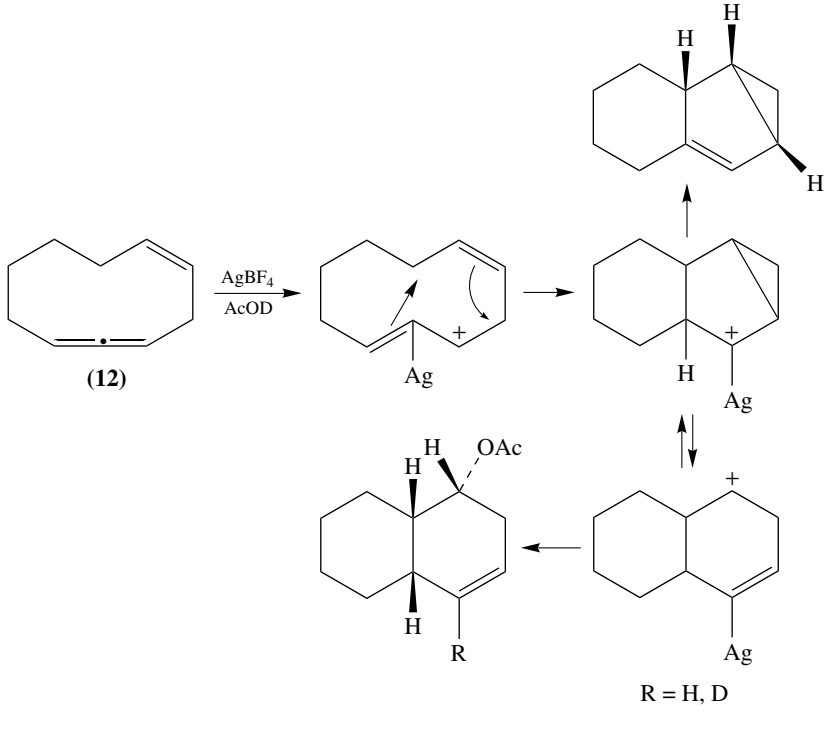
The cyclic diradical, 2-methylene-1,4-cyclohexadiyl (**18**), can be formed from the hepta-1,2,6-triene **17**[22,23]. Thermolysis of **17** gives 3-methylene-1,5-hexadiene **19** as a Cope rearrangement product, while the same treatment (155 °C, benzene) in the presence of SO_2 leads to sulfones **20** and **21** instead of **19** (equation 6). It was shown that sulfone **20** is obtained by reaction of SO_2 with the rearrangement product **19**, while sulfone **21** originates directly from the diradical **18**.

This finding confirms an opinion that, at least in some cases, diradicals such as **18** can be the actual intermediates in the non-concerted Cope rearrangement, so-called 'stepwise cyclization-then-cleavage' mechanism. Berson and coworkers who previously excluded diyl intermediate in the acetylenic Cope rearrangement[20] designed in their next work[24]

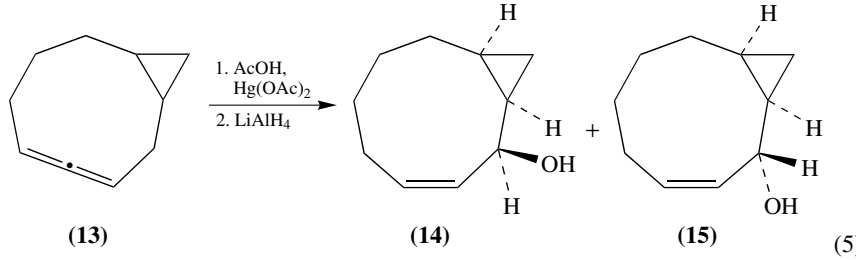
a new test structure to stabilize the possible diradical through conjugation and thereby encourage the stepwise path. Gas-phase pyrolysis of the enantiomerically pure test compound (*R*,*E*)-**22** (214–255 °C, 32–260 min) has resulted in the triene **23** (equation 7). Its stereochemical analysis had confirmed the possibility to divert the Cope rearrangement from its normally concerted mechanism into a stepwise one, proceeding via a conformationally mobile diradical intermediate[24].



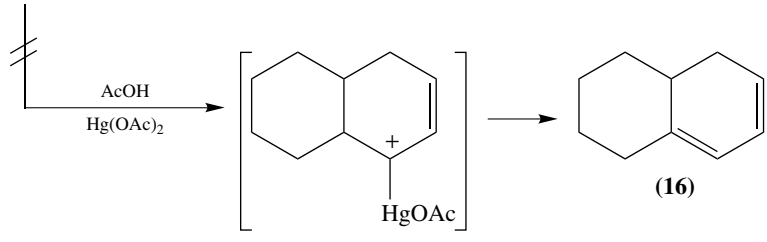
(3)



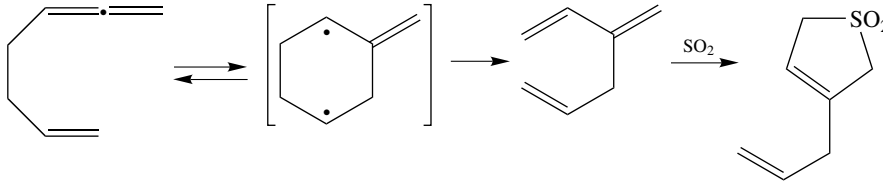
(4)



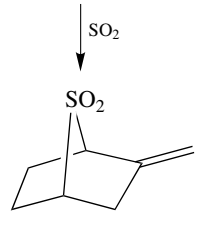
(13) **(14)** **(15)** (5)



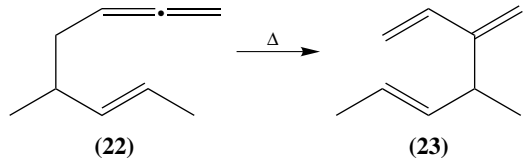
(16)



(17) **(18)** **(19)** **(20)** (6)



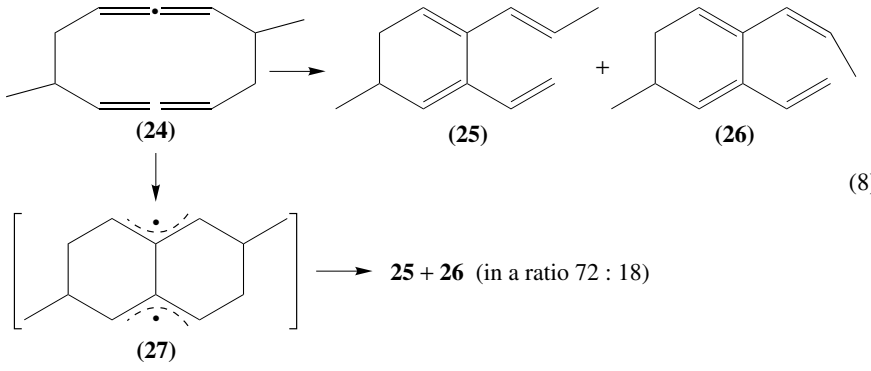
(21)



(22) **(23)** (7)

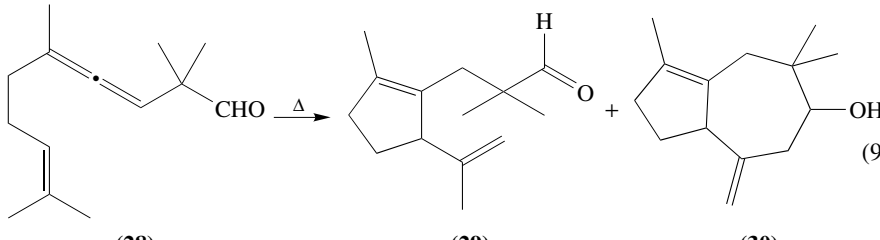
Another type of diradical intermediate species **(27)** in Cope rearrangement is formed during thermolysis of optically active *trans*-4,9-dimethyl-1,2,6,7-cyclodecatetraene **24**[25] which was studied in order to distinguish between concerted and stepwise mechanisms of Cope rearrangement. The transformation of optically active *trans*-**24** via a concerted mechanism would lead to optically active tetraenes **25** and **26**, while the participation

of diradical **27** will result in the loss of optical activity (equation 8). It was found that bis-allene *meso*-**24** undergoes thermolysis at 200 °C to form optically active products **25** and **26**. In contrast, the transformation of *rac*-**24** involves a competition between concerted and nonconcerted pathways. The different behavior of the two isomers can be explained by the boat and chair geometries, respectively, of the two transition states.

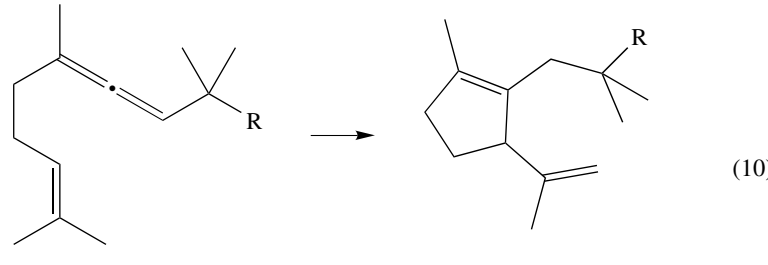


(8)

Thermolysis of the functionally substituted 1,2,6-trienes **28** and **31a–d** leads by Cope rearrangements to dienes **29, 30** and **32a–d** (equations 9 and 10), respectively[26]. The reactions of aldehyde **28** occur at a relatively high temperature (>170 °C) to furnish both **29** and **30**. Product **29** can be cyclized to **30** by heating. The similar thermolysis of the Shiff base **33** obtained from aldehyde **28** proceeds via two steps to afford the separable analogous products **34** and **35** (equation 11)[27].

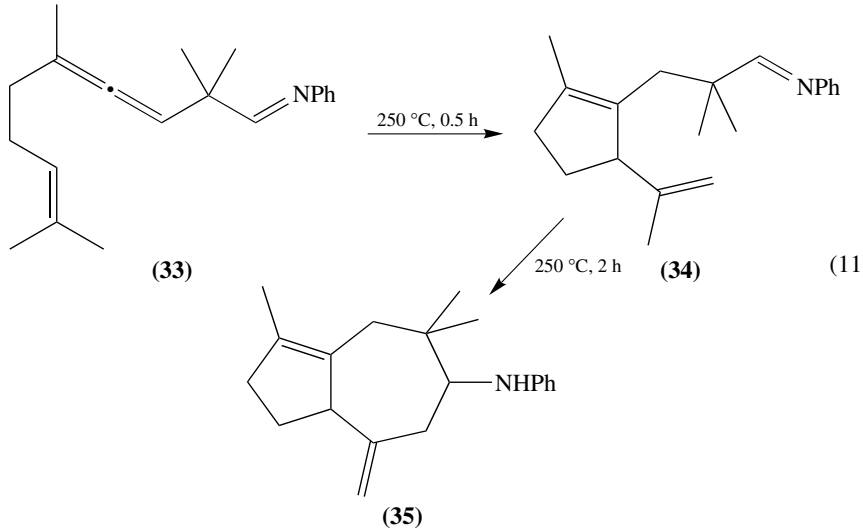


(9)



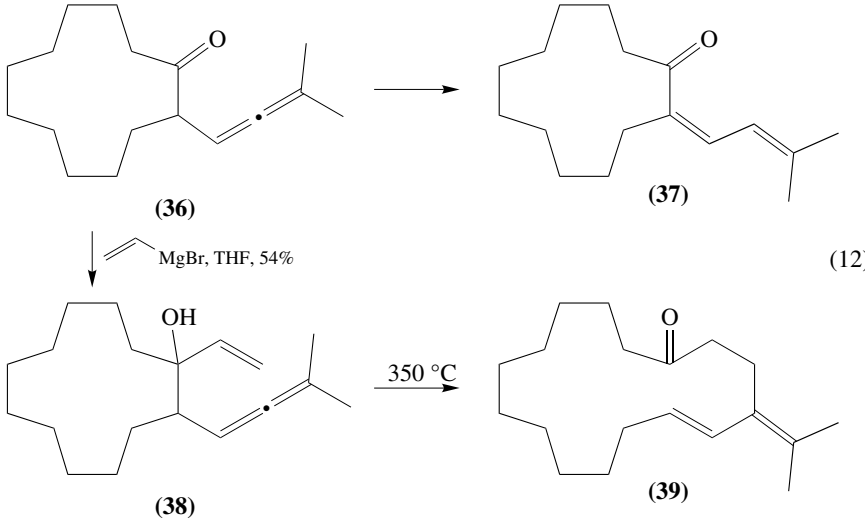
(10)

(a) R = CH_2OH, (b) R = CH_2OAc, (c) R = COOMe, (d) R = $CH(OMe)_2$



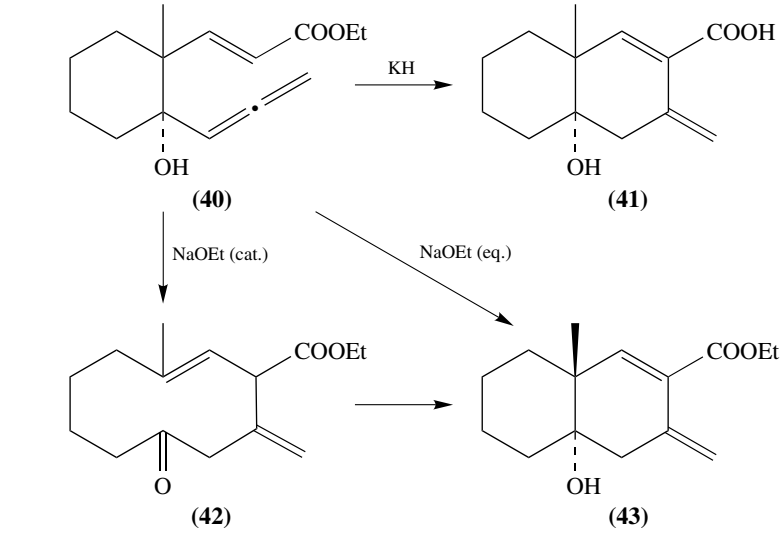
(11)

Similar to the typical Cope rearrangement for dienes (Section IV.C), the allene systems can also participate in oxy-Cope rearrangements (Section IV.D). Generally, it should be noted that only a few examples of both thermal and base-catalyzed oxy-Cope rearrangements are known in which one of the π-systems is replaced by an allenic fragment. Thus, alcohol **38** rearranges at 350 °C to ketone **39** in 80% yield (equation 12)[28]. It is interesting that triene **38** does not undergo a photochemical isomerizations, even during prolonged UV irradiation in ether in the presence of acetone as a photosensitizer. The starting allenic ketone **36** has been converted into conjugated dienone **37** by both acid and base catalysis[28].

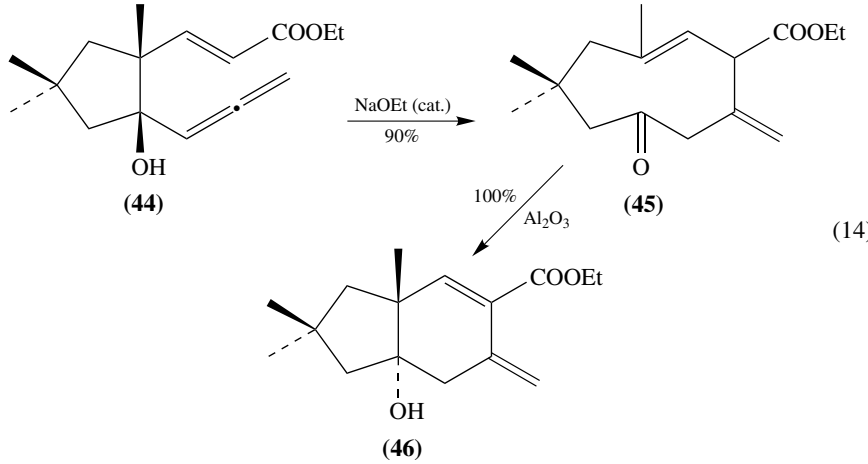


(12)

Anionic oxy-Cope rearrangement of allene alcohol **40** under standard conditions (KH, 18-crown-6, I_2, THF, 2 h at 20 °C, in 40% yield) gave rise to the carboxylic acid **41** (equation 13)[29]. Treatment of **40** with a catalytic amount of NaOEt (THF, 20 °C, 12 h) forms the cyclodecenone **42** in 80% yield while the bicyclic product **43** is formed in the presence of a stoichiometric amount of sodium ethoxide (THF, 20 °C, 12 h, 85%). Formation of **43** apparently proceeds via the initial oxy-Cope rearrangement of **40** to the ring enlargement product **42**, followed by a transannular reaction. A similar result was obtained when the oxy-Cope rearrangement of the cyclopentane derivative **44** gave the hydrindane **46** (equation 14)[29]. The isolated dienone **45** cyclizes to form the dienol **46** during purification with Al_2O_3. Compound **46** can serve as a potential synthon for the sesquiterpenoid candicansol[29].

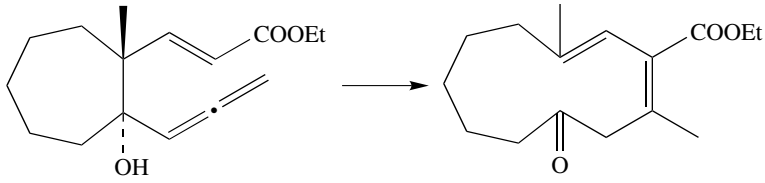


(13)



(14)

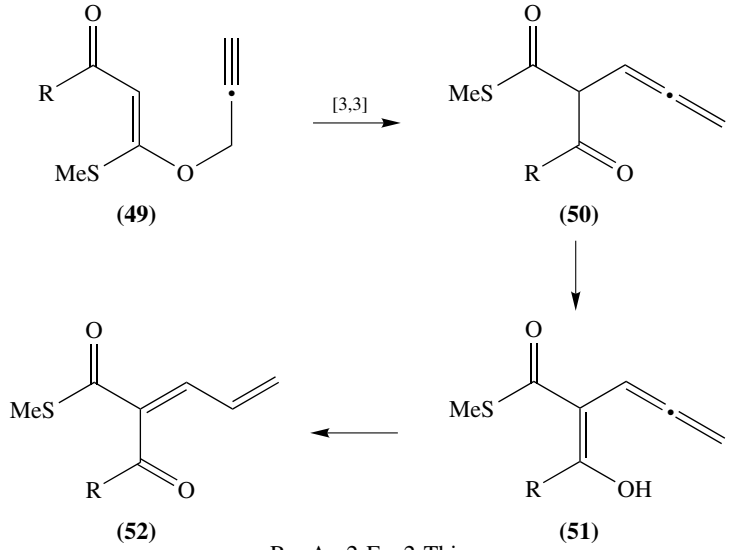
Furthermore, the oxy-Cope rearrangement of allenic cycloheptane alcohol **47** (NaOEt, THF, 20 °C, 12 h, 80%) gave rise only to ring-enlarged product **48** without transannular cyclization (equation 15)[29]. The above transformations can be rationalized either by the fragmentation–recombination mechanism or by a concerted oxy-Cope mechanism[29].



(15)

(47) **(48)**

The Claisen rearrangement of *O*,*S*-ketal **49** under neutral conditions (refluxing toluene or xylene) leads to the intermediate **50** which undergoes a rearrangement to the diene ester **52** through enolization and a subsequent 1,5-hydrogen shift within intermediate **51** that carries the hydroxy group at the double bond end (equation 16)[30].



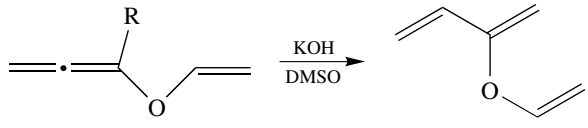
(16)

(49) **(50)** **(51)** **(52)**

R = Ar, 2-Fu, 2-Thi

Investigations of base-catalyzed isomerizations of allene derivatives have been recently continued. For instance, the rearrangement of allene ethers **53** under superbasic conditions (KOH-DMSO) is considered as one of the steps in hydration of acetylene derivatives (equation 17)[31,32].

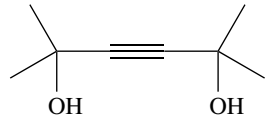
However, acid-catalyzed isomerization attracts more attention, probably due to its connection with the recent intensive development of carbenium ion chemistry. It is common knowledge that effective methods for stabilization of reactive carbocations have been known since 1962 while base-catalyzed processes with the participation of carbanions were developed more than 100 years ago.



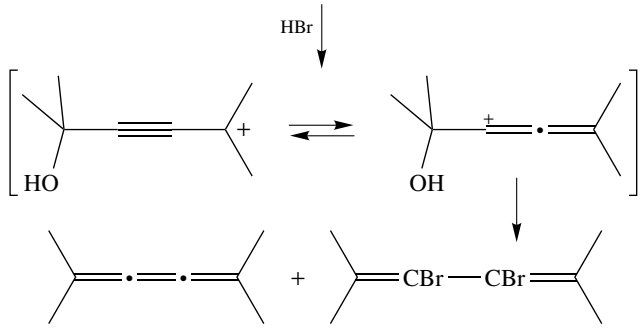
(53) (for R = Me) (17)

R = Me, Et, Pr, *i*-Pr, *n*-Bu, *t*-Bu

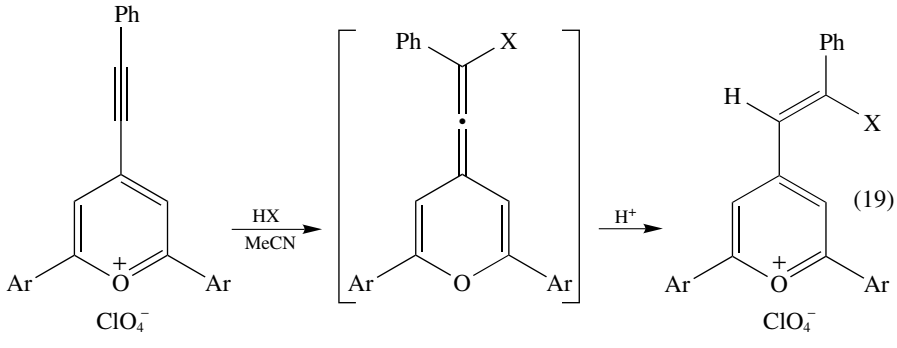
The various products obtained from acetylenic diols **54** in the presence of acids suggest the formation and interconversion of acetylene–allene–diene cationoid intermediates (equation 18)[33]. The allene intermediates can be sometimes isolated and they were reported as participants in the acid-catalyzed reactions of alkynylpyrylium salts **55**, a driving force of which is an aromatization of the pyrane ring (equations 19–21)[34,35].



(54)

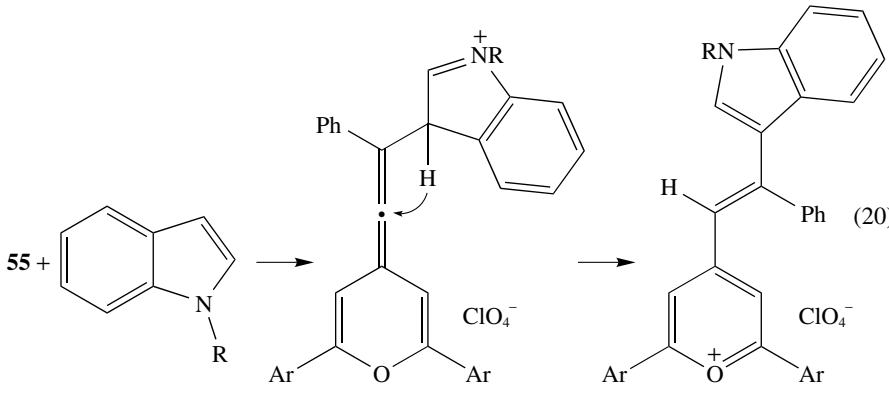


(18)



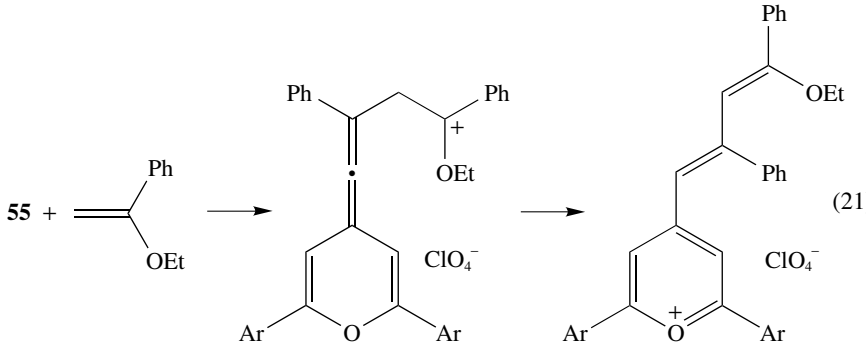
(55) (19)

X = Cl, Br; Ar = Ph , 4-$MeOC_6H_4$



(20)

Ar = Ph, *p*-$MeOC_6H_4$



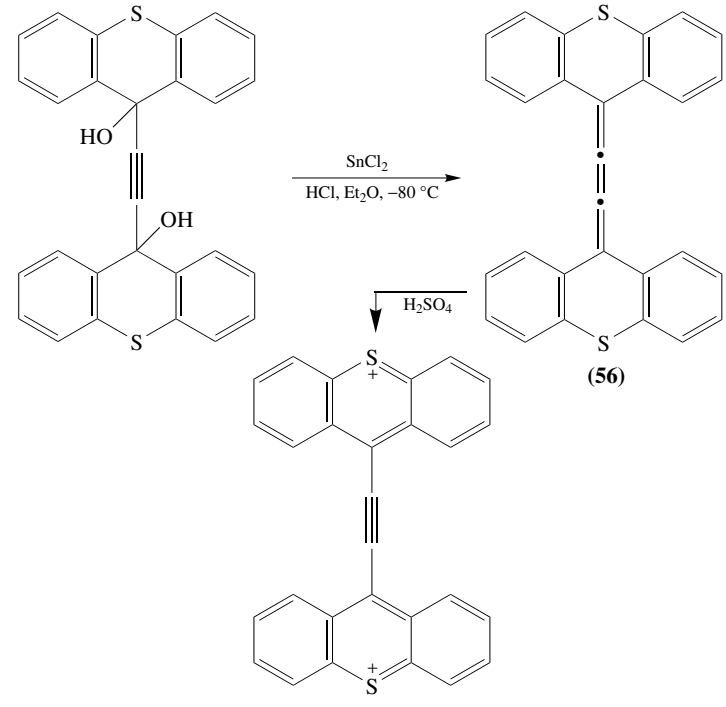
(21)

Ar = Ph, *p*-$MeOC_6H_4$

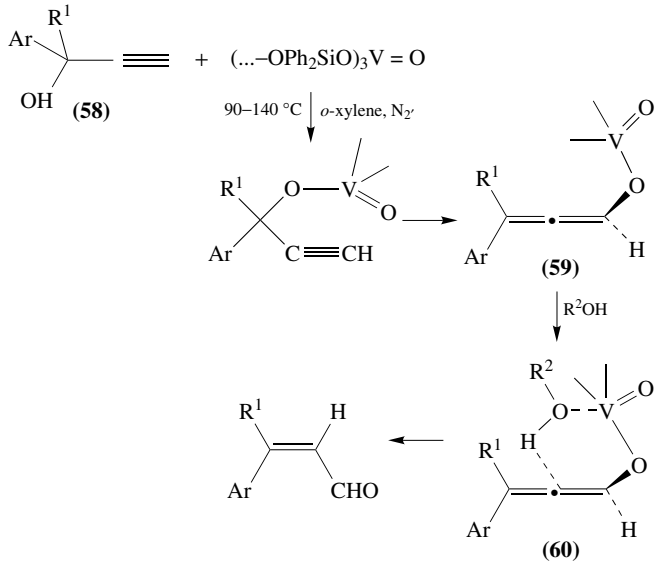
In a search of π-donor systems for the preparation of compounds having a metallic conductivity, the bis-thioxanthene cumulene **56** was obtained. It was oxidized by conc. H_2SO_4 to the acetylenic dication **57** rather than undergoing the expected protonation of the multiple bonds (equation 22)[36].

The rearrangement of arylethynyl carbinols **58** that occurs via allene intermediates **59** and **60** in the presence of a polymeric silylvanadate catalyst[37] (equation 23) is noteworthy.

In the 1980s an extensive investigation of allenyl cations **62**, which were generated from haloallenes **61** and reacted with various nucleophilic reagents, was carried out (for reviews of previous work, see References 16, 18, 38 and 39). The conditions under which stepwise and concerted cycloaddition reactions take place were studied. For example, a treatment of chlorotriphenylallene **61** with silver trifluoroacetate in the presence of cyclopentadiene in pentane and subsequent work up with KOH/EtOH gave a mixture of products **63–66**, **68–70** in 95% total yield (equations 24 and 25)[40]. An analysis of the reaction products has shown that the dienes **65** and **66** can be formed via a stepwise [2 + 2]-cycloaddition while compounds **68** and **69** were produced by a concerted [4 + 2]-cycloaddition through the intermediate allyl cation **67**[40,41]. A change of the reaction conditions resulted in the isolation of triphenylallenium hexachloroantimonate **71** which can be easily hydrated to the ethynyl carbinol **72** and the unsaturated ketone **70** in a ratio of



(22)

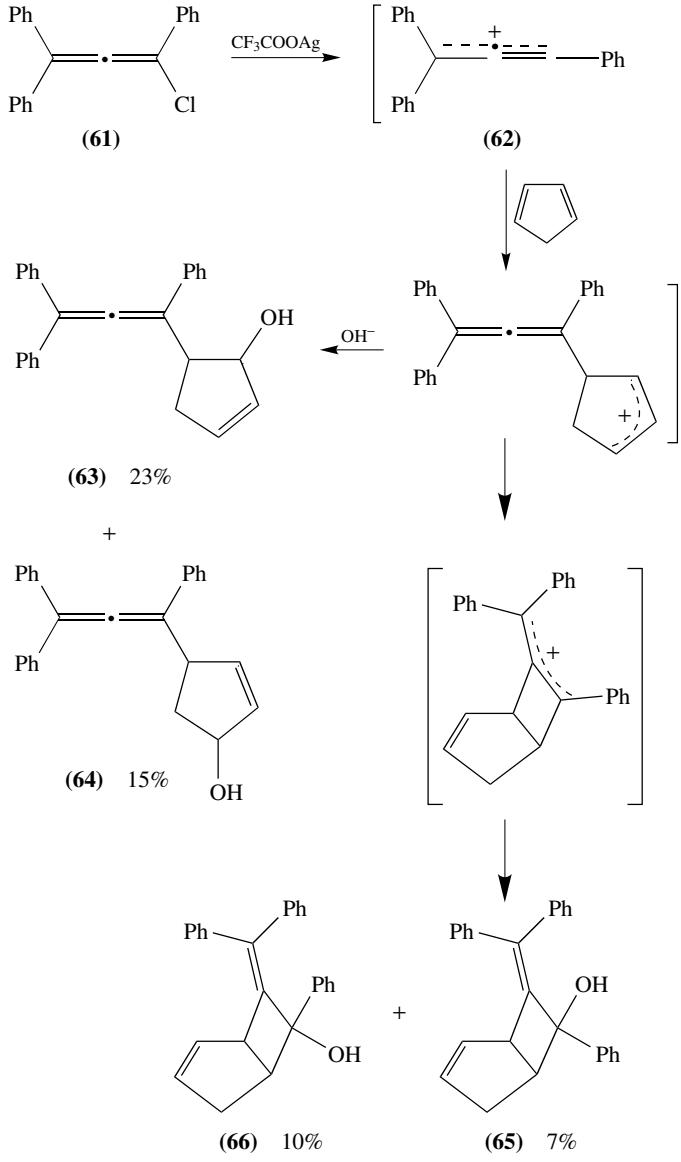


(23)

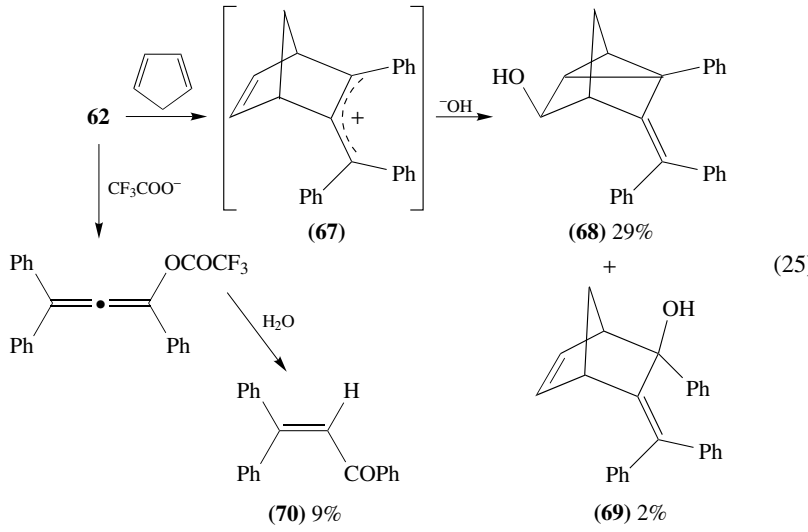
R = H, Me; Ar = Ph, 4-*i*-PrC_6H_4, 4-*t*-BuC_6H_4, 4-MeOC_6H_4, 4-MeC_6H_4, 2,4-$Me_2C_6H_3$

44 : 56 (equation 26)[42]. The reaction of the solution of the salt **71** in liquid SO_2 at $-30\,^{\circ}C$ with a solution of cyclopentadiene in dichloromethane, followed by an alkali hydrolysis of the reaction mixture obtained, gave rise to a mixture of the aforementioned bicyclic products **65** and **66** and the secondary alcohol **73** in a 39 : 50 : 11 ratio (equation 27)[42].

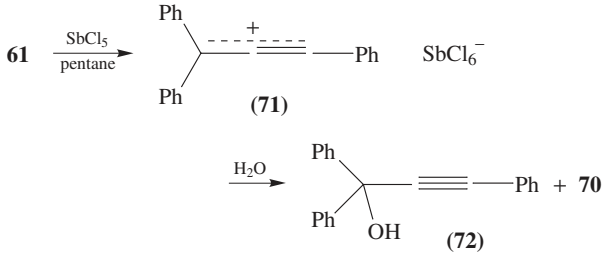
It is interesting to mention the cyclizations of allene systems which are accompanied by rearrangements. Protonation of the bis-cumulene **74** by 5% H_2SO_4 in aqueous acetone produces the adamantane derivative **75** in 95% yield (equation 28)[43].



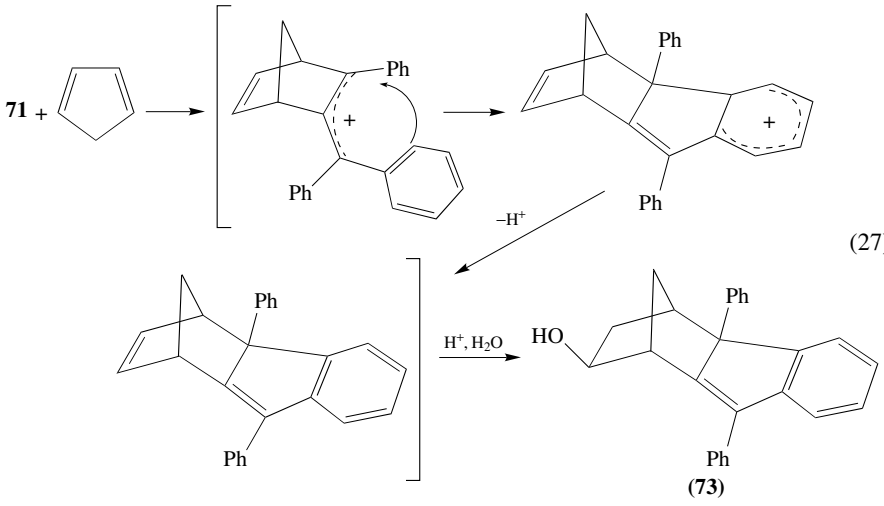
(24)


62
Ph
Ph
+
Ph
Ph
(67)
$^{-}$OH
HO
Ph
Ph
Ph
(68) 29%
+
CF3COO−
Ph
Ph
OCOCF3
Ph
H
Ph
COPh
(70) 9%
H2O
OH
Ph
Ph
Ph
(69) 2%

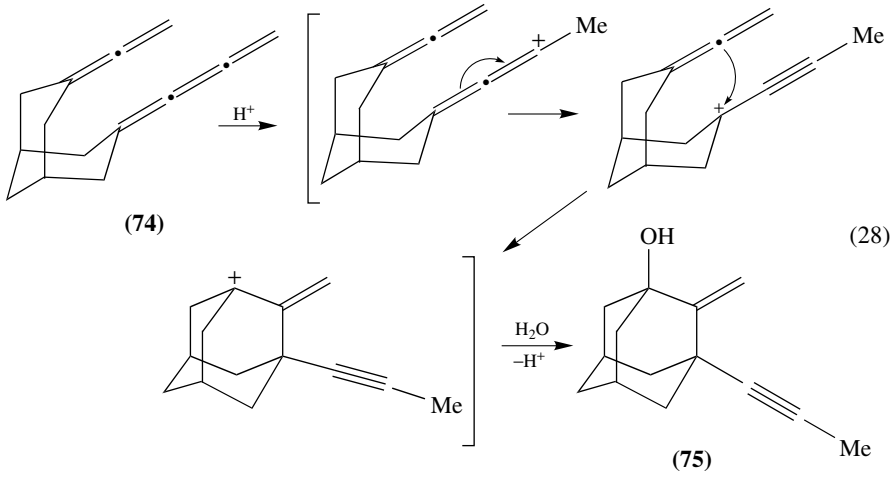
(25)


61
SbCl5
pentane
Ph
+
Ph
Ph
SbCl6−
(71)
H2O
Ph
Ph
Ph
OH
(72)
+ 70

(26)


71 +
Ph
+
Ph
Ph
+
Ph
Ph
–H+
Ph
Ph
H+, H2O
HO
Ph
Ph
(73)

(27)



(28)

III. REARRANGEMENTS OF CONJUGATED DIENES AND POLYENES

A. Vinylcyclopropanes and Related Systems

This wide range of transformations includes many reactions which are one way or another connected with cyclopropane derivatives. The cyclopropane moieties can be part of the structure of both the linear dienes or of annulated polycyclic unsaturated systems as well as being part of a spiro compound.

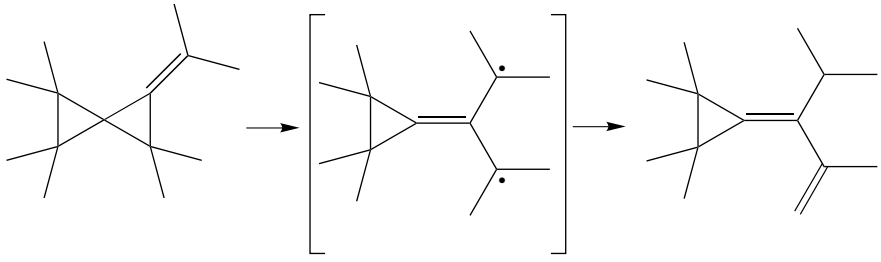
One such typical transformation is the thermal isomerization of the spiropentane derivative **76** into triene **80** which is assumed to occur via the diene intermediate **78** with the intermediate participation of the cyclopropyl–trimethylenemethane (TMM) **77** and the vinyl–TMM **79** diradicals (equation 29)[44]. It was shown by using deuterium labels that the diradical **79** forms the triene **80** by 1,6-hydrogen shift. The pathway **76** → **80** which occurs via tetramethylene–ethane diradical was recognized as a less probable route.

Tetramethylene–ethane (TME), or 2,2′-bis-allyl diradical **81**, was suggested as an intermediate in the thermal dimerization of allene, as well as in the interconversions of 1,2-dimethylenecyclobutane **82**, methylenespiropentane **83**, bis-cyclopropylidene **84** and other bicyclic systems (equation 30)[45]. The isolation of two different isomeric dimethylene cyclobutanes **87** and **88** (in a *ca* 2 : 1 ratio) after the thermal rearrangement of the deuteriated 1,2-dimethylene cyclobutane **85** suggests that the rearrangement proceeds via a 'perpendicular' tetramethyleneethane diradical (2,2′-bisallyl) **86** (equation 31)[45].

The participation of the above mentioned trimethylenemethane (TMM) diradicals in the thermal rearrangements of methylenecyclopropanes was also investigated by using systems containing an additional vinyl group which was part of rings fused with the cyclopropane (equations 32 and 33)[46,47]. The diene **91** was obtained from dichloride **89** (in 50% yield) via the diene intermediate **90** which undergoes the so-called methylenecyclopropane rearrangement to diene **91**.

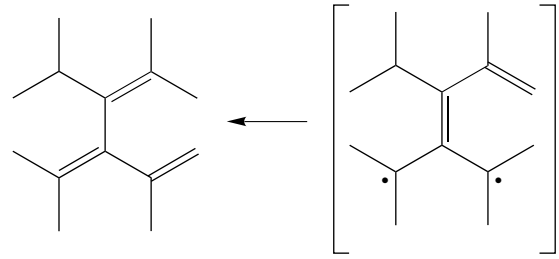
However, bicyclic dichloride **95** under the same conditions was converted into diene **96** and not to the rearrangement product **94** (equation 33). This result is explained by the larger size of the ring, which is far less strained than that in diene **90**[46]. The gas-phase thermolysis of diene **91** at 126–186 °C afforded an almost equimolar mixture of bicyclic diene **92** and triene **93** which are formed, presumably, via the TMM-diradicals

98a and **98b** (equation 34). Heating of diene **96** in DMF gave the triene **97** as a result of hydrogen shift (equation 33)[46]. The intermediate **99** was isolated by using flash pyrolysis of compound **91** at a temperature of 200 (±5) °C and a pressure of 10^{-3} Torr. As expected, this *cis*-2-vinyl-1,3,5-hexatriene **99** rearranges smoothly at 220 °C to yield only the triene **93**[48].

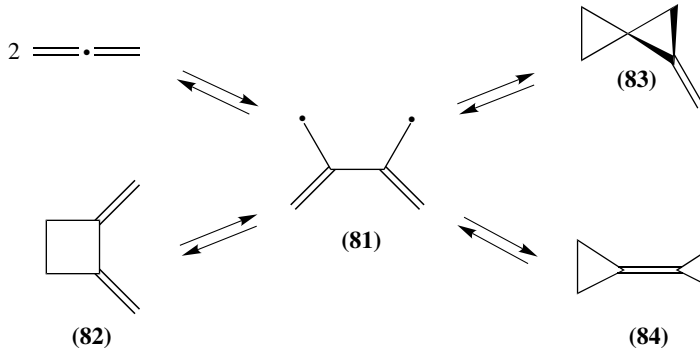


(76) **(77)** **(78)**

(29)

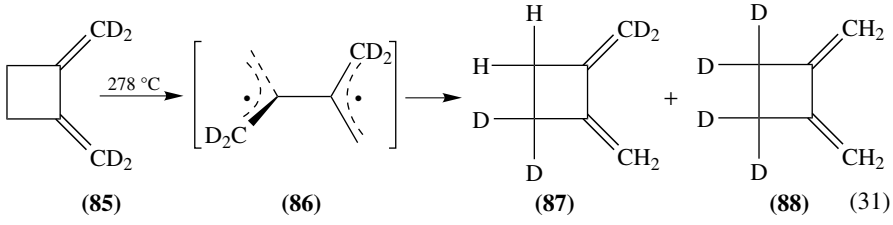


(80) **(79)**

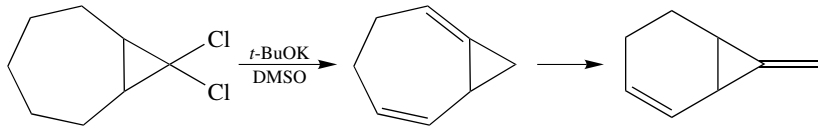


(83) **(81)** **(82)** **(84)**

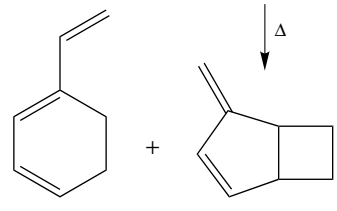
(30)



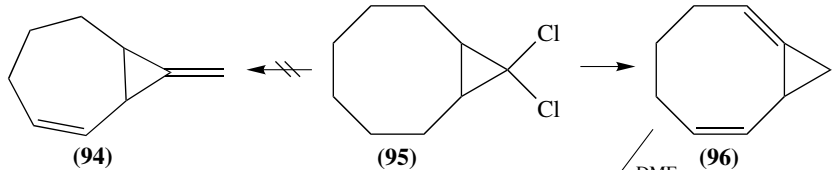
(85) **(86)** **(87)** **(88)** (31)



(89) **(90)** **(91)**

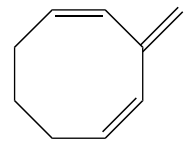


(93) **(92)** (32)

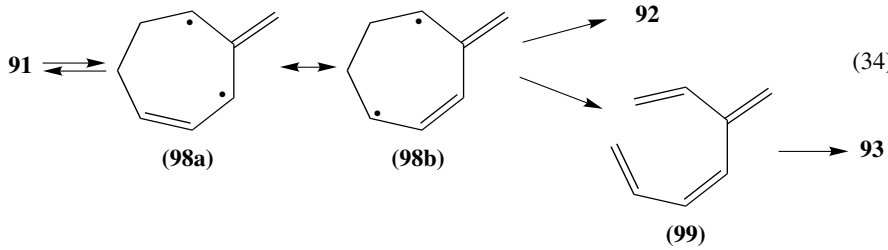


(94) **(95)** **(96)**

(33)



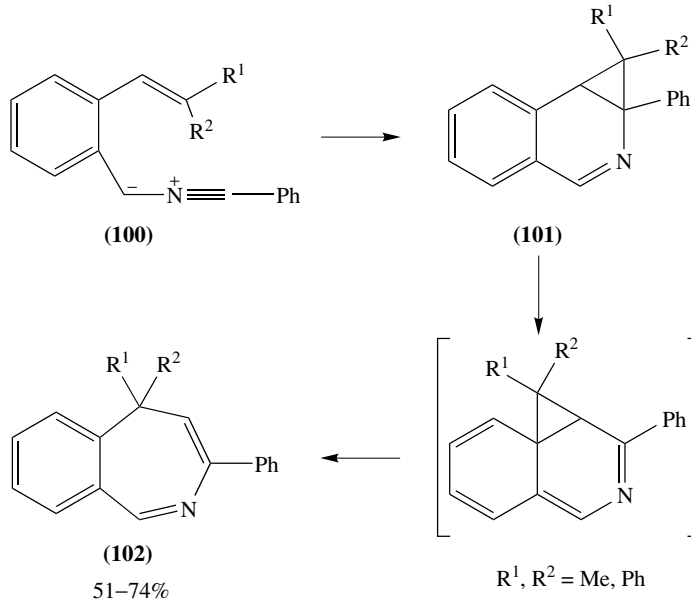
(97)



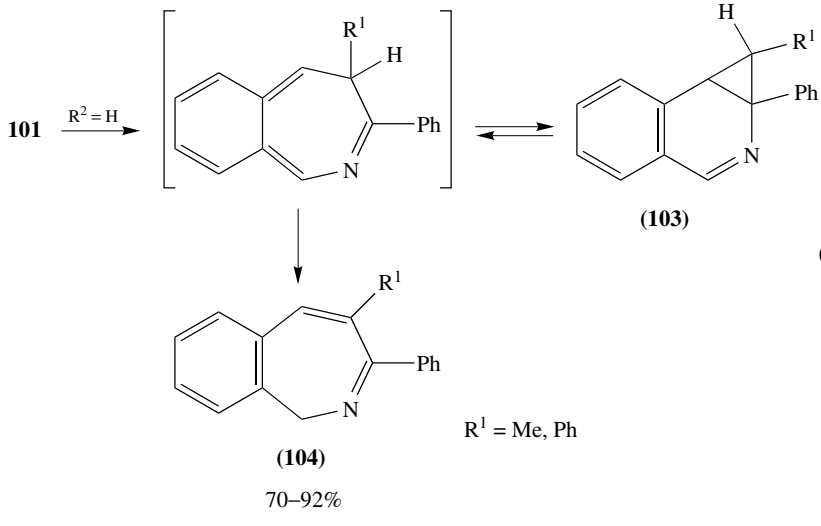
(98a) **(98b)** **(99)** (34)

The thermal rearrangements of vinylcyclopropanes to form cyclopentenes as well as 1,4-hexadienes by homodienyl [1,5]-shift are well-known[16,49–51] and even described in textbooks (see, e.g., Chapter 18 in Reference 4). However, the heteroanalogous transformations are less known.

Thus, cycloprop[*c*]isoquinolines **101** obtained by a stereospecific 1,1-cycloaddition of nitrile ylides **100** undergo two distinct thermal (80 °C) rearrangements depending on the substituents in the cyclopropane ring (equations 35 and 36)[52].



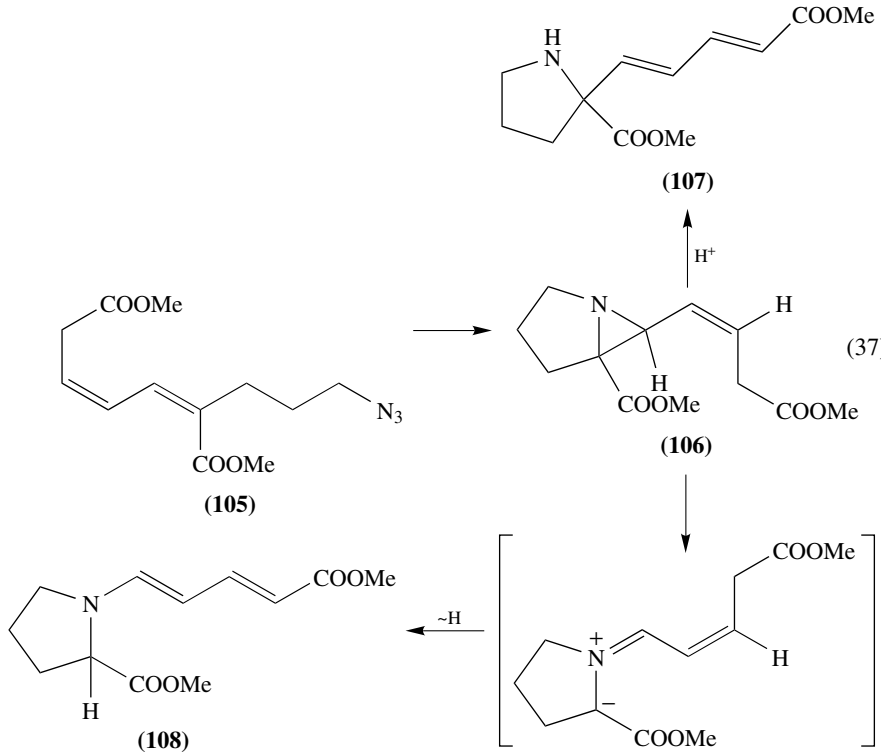
(35)



(36)

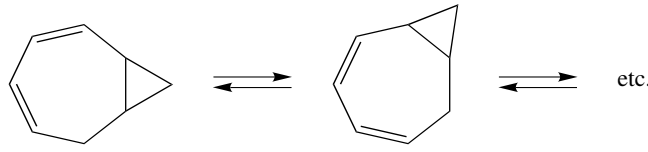
If one of the substituents R^1 or R^2 is hydrogen, then the interconversion of the *endo*- and *exo*-isomers (**101** and **103**) is accompanied by an irreversible transformation into 1*H*-2-benzazepines **104** (equation 36). Otherwise (i.e. when R^1, $R^2 \neq H$) the rearrangement of compounds **101** is slower and leads to formation of 5*H*-2-benzazepine system **102** (equation 35)[52].

Interesting rearrangements proceed upon refluxing the azido diene **105** in benzene solution and form 61% of the vinylaziridine **106** as a mixture of diastereoisomers and the vinylogous urethane **108** (28%) (equation 37)[53]. It was shown that the process **106** → **108** occurs entirely at elevated temperature (refluxing xylene, *ca* 140 °C). However, treatment of the aziridine **106** with *p*-toluenesulfonic acid in THF at room temperature gives rise to *trans,trans*-1,3-butadiene carboxylic ester **107** in 98%[53].

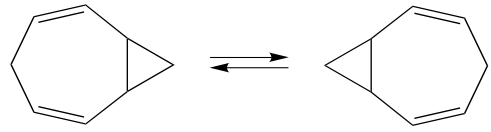


(37)

In bicyclo[5.1.0]octa-2,4-diene **109** which is quite stable at room temperature the so-called degenerate *butadienylcyclopropane rearrangement* takes place at elevated temperatures (above 110 °C), and it can be revealed by using the deuterium labels (equation 38)[54]. This transformation is interesting because the bicyclic diene **109** shows the invariable NMR spectra within the temperature range between −80 °C and +180 °C. Such unusual behavior differs from the rapid reversible Cope rearrangement of isomeric diene **110** which already proceeds at room temperature (so-called 'fluxional structure') (equation 39)[1,55]. The rearrangements of related divinylcyclopropanes as non-conjugated dienes will be considered in Section IV.C.2.d).

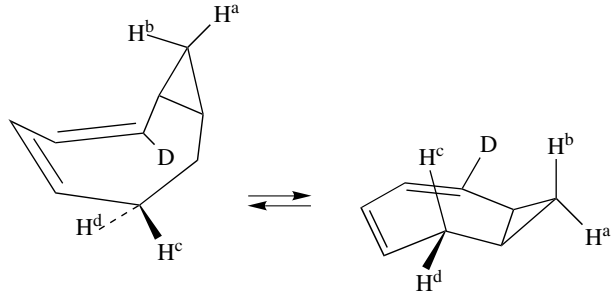


(109) (38)

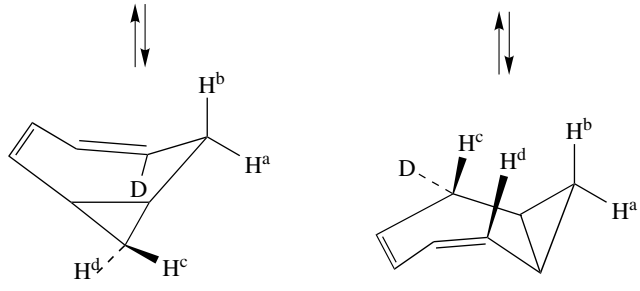


(110) (39)

It was found that heating of the deuteriated bicyclodiene **111** at 110 °C was accompanied by two competitive processes having comparable rates: (a) butadienylcyclopropane rearrangement via a transoid transition state (**111** ⇌ **113**) and (b) *endo,endo*-1,5-hydrogen shift (**112** ⇌ **114**) (equation 40)[54,56].



transoid **(111)** cisoid **(112)**

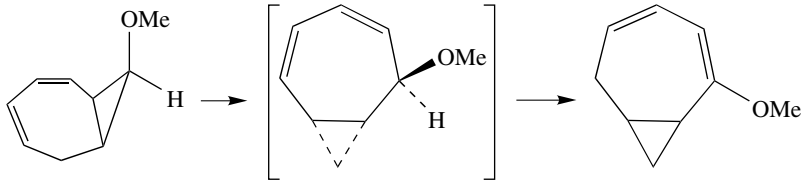


(113) **(114)** (40)

It was shown that [1,5]-hydrogen shift occurs in this case about 30 times more quickly than that in the cycloheptatriene, while the butadienylcyclopropane rearrangement proceeds 3×10^{-9} slower than the Cope rearrangement of the isomeric 2,5-diene **110**[54].

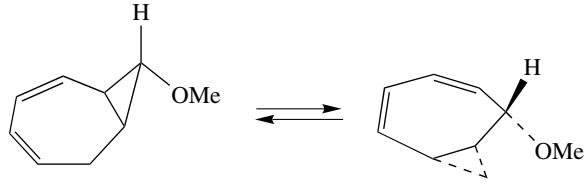
This difference in reaction rates can be attributed to different energies of corresponding transition states. According to the Woodward–Hoffmann rules[57], the Cope rearrangement is a sigmatropic [3,3]-shift (see Section IV.C.1) while the butadienylcyclopropane rearrangement can be considered as an sigmatropic antarafacial [1,5]-shift with inversion at the migrating carbon atom.

The thermolysis of the bicyclodiene **109** at 225 °C gives rise to equilibrium mixture of cyclooctatriene and its transformation products (see below)[54]. More recently the influence of a methoxy group on the thermal behavior of the bicyclo[5.1.0]octa-2,4-diene system was studied[56]. Heating of 8-*endo*-methoxydiene **115** in cyclooctane at 95 °C gaves rise to methoxy substituted diene **117** and not to the product **116** of butadienylcyclopropane rearrangement (equation 41). The thermolysis of the 8-*exo*-isomer **118** has taken place as an equilibrium reaction to give 6-*endo*-methoxy diene **119** (equation 42)[56]. These two reaction partners were separated by TLC.



(41)

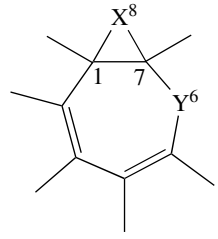
(115) **(116)** **(117)**



(42)

(118) **(119)**

Recently, molecular orbital calculations (MP2/6-31G*//RHF/6-31G* level) which cover a series of bicyclic systems from the stable bicyclic compound **109** to the unknown 6,8-dioxabicyclo[5.1.0]octa-2,4-diene (2,3-epoxyoxepin, **120**), as well as the two intermediate 8-oxa- **(121)** and 6-oxa- derivatives **(122)**, were carried out[58]. These structures are interesting because the bicycle **120** is suggested as a transient intermediate in the metabolic oxidation of benzene leading to the muconaldehyde, which is responsible for the hematotoxicity of benzene.

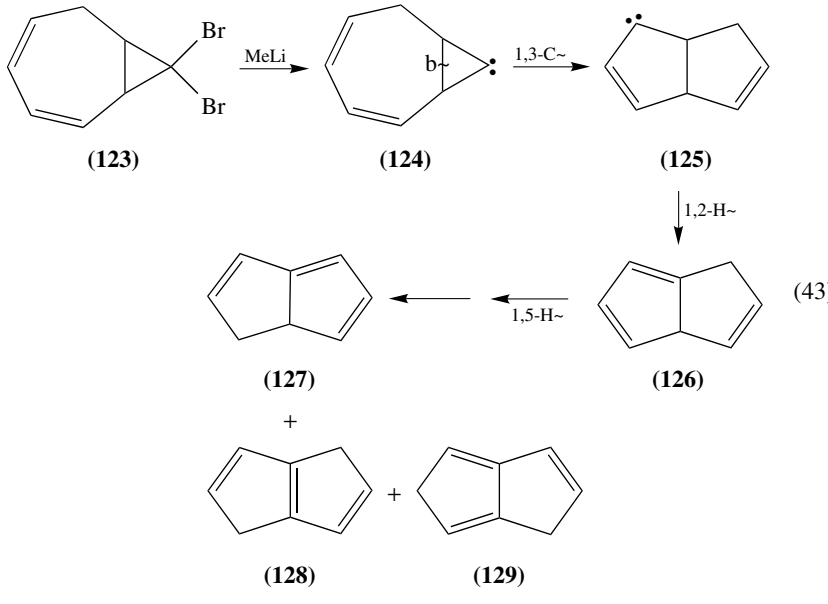


(109) $X^8 = Y^6 = CH_2$
(120) $X^8 = Y^6 = O$
(121) $X^8 = O$; $Y^6 = CH_2$
(122) $X^8 = CH_2$; $Y^6 = O$

From the calculations on **109**, **120**–**122**, as well as that of the corresponding ring fission products, the influence of oxygen substitution on some reactions such as the interconversion between cisoid and transoid bicyclic conformers, the degenerate Cope rearrangement and the 1,5-hydrogen shift, in which the overall structure is conserved, as well as the ring fission reactions in which both three-membered and the seven-membered rings are broken, was traced. It was shown that the oxygen substitution has little effect on the interconversion and the 1,5-hydrogen shift. However, the Cope rearrangement of structure **120** is much slower than that of compound **109**[58].

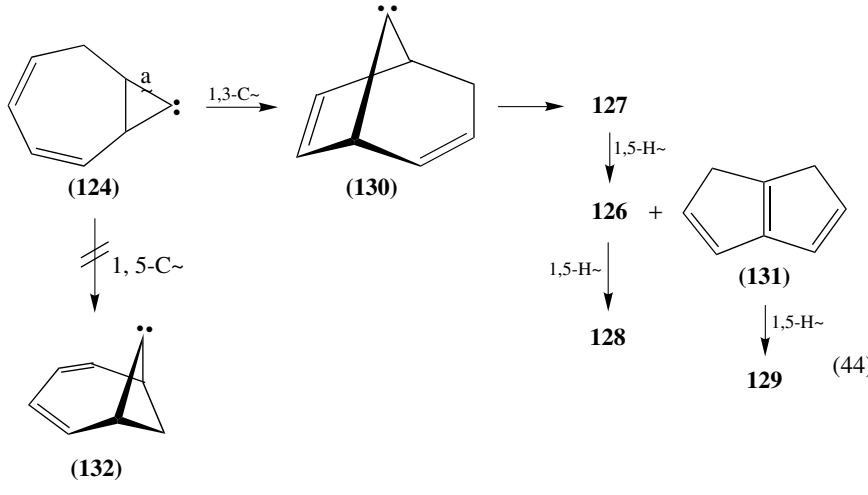
A cascade of rearrangements occurs upon interaction of methyllithium with 8,8-dibromodiene **123**. The carbenes **124** and **125** are intermediates of these reactions (so-called 'carbene–carbene rearrangements') which proceed via 1,3-C-migrations (Skattebøl rearrangement) followed by successive 1,2-H- and 1,5-H-shifts to yield dihydropentalenes **126**–**129** by cleavage of distal bond 'b' (equation 43)[59]. Another scheme suggests a different pathway for the transformation of carbene **124**, namely through a cleavage of the lateral bond 'a' and 1,3-carbon migration to furnish the 7-homonorbornadienylidene **130**. The subsequent 1,2-vinyl shift leads to the dihydropentalenes **127** which rearrange to compounds **128** and **129** via intermediates **126** and **131**, respectively (equation 44)[59]. Pathway **124** → **130** was supported by C-labelling of the starting material **123** as well as by the known reactivity of carbene **130**[59].

Since the reactive substructure of *cis*-2-(1,3-butadienyl)cyclopropylidene is contained in the bicyclic carbene **124**, there is a possibility that a carbene–carbene rearrangement occurs together with 1,5-carbon migration. Analysis of the probable reaction pathways allows one to conclude that 1,5-C-migration (**124** → **132**) in the fixed *cis*-1,3-butadienyl fragment of structure **124** is impossible. The 1,3-carbon migration (**124** → **130**) which takes place instead is mechanistically analogous to the vihylcyclopropylidene–cyclopentylidene



(123) **(124)** **(125)** **(126)** **(127)** **(128)** **(129)** (43)

rearrangement (Skattebøl reaction). Other carbene–carbene rearrangements including a participation of 'foiled methylenes'[60] are discussed elsewhere[48].



(44)

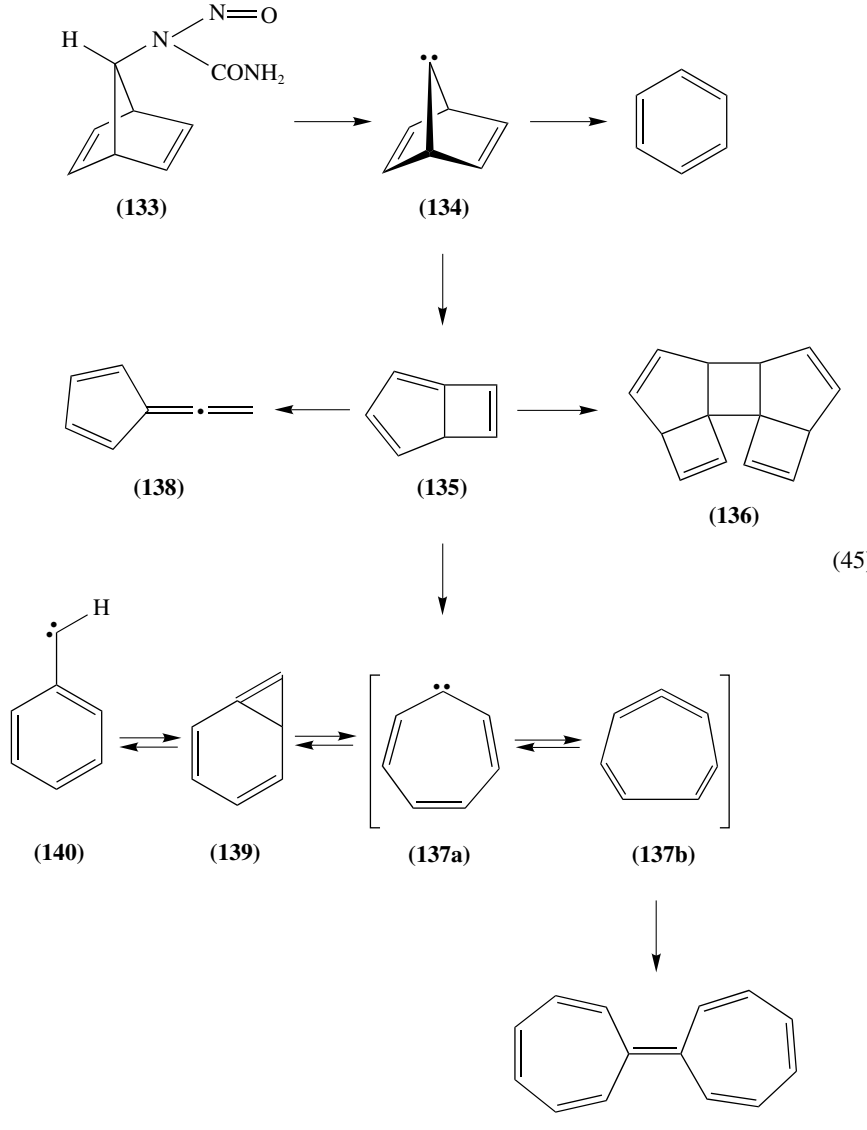
One of the principal 'foiled carbenes', i.e. 7-norbornadienylidene **134**, is described in the literature[61]. This dienyl carbene can be generated by pyrolysis (200–400 °C) of the corresponding N-nitrosourea **133** and it undergoes a series of transformations including a loss of carbon to produce benzene as well as rearrangements to bicyclo[3.2.0]heptatriene **135**. The latter either dimerizes to give the tetraene **136** or undergoes a ring opening to form cycloheptatrienylidene **(137a)** ⇌ cycloheptatetraene **137b**, or rearranges to fulvene-allene **138** (equation 45)[61].

The seven-membered ring system **137** can rearrange to bicyclo[4.1.0]heptatriene ('fused cyclopropene') **139** and benzylidene **(140)**. This rearrangement underlies the arylcarbene ring-expansion mechanism which was first proposed by Vander Stouw and colleagues in 1972 to explain the formation of styrene during thermolysis (150–350 °C) of various (2-methylphenyl)diazomethanes **141**[62]. According to this mechanism, the intermediate 2-methylbenzylidenes **142** can isomerize to give the fused cyclopropenes **143** and the corresponding 2-methylcycloheptatrienylidenes **144** which are capable of (1) undergoing a carbon–hydrogen insertion to provide fused alkylidenecyclopropanes **145** and then styrenes, and/or (2) rearranging to fused cyclopropenes **146** with subsequent isomerization into 1-phenyl-1-ethylidenes **147** and then to styrenes (equation 46). A possible alternative is a direct conversion of the cyclopropenes **143** to **146**, followed by styrene formation.

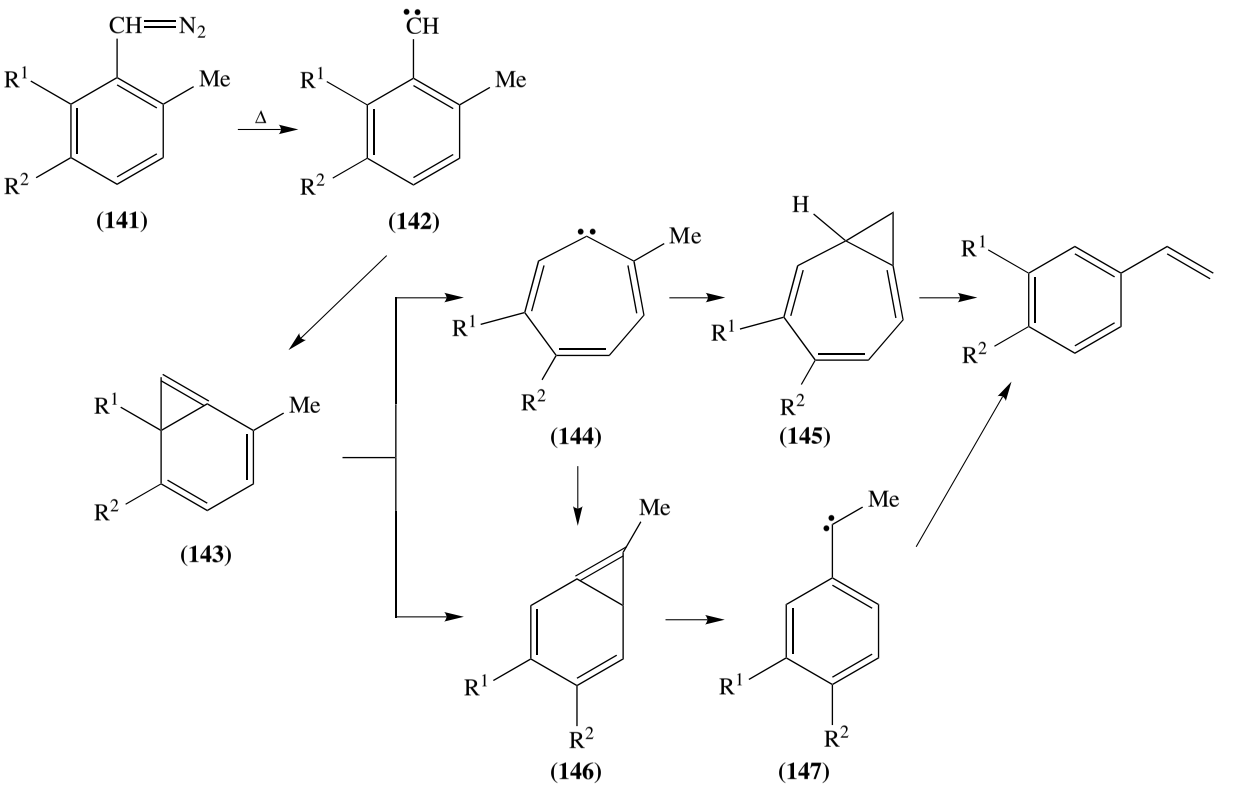
The above transformations are very important from the point of view of industrial technology for high temperature cracking of alkylaromatics and therefore are of great interest for basic science. Thus, the reported interconversion between benzylcarbenes (e.g. **142** and **147**) and cycloheptatrienylidenes (e.g. **144**)[63] can occur via the intermediate bicyclo[4.1.0]heptatrienes (**143** and **146**). This work[63] contains also a brief survey of related publications. It should be noted that its authors utilize a dehydrogenation method rather than thermolysis because the former is an attractive route due to the possibility of preparing the target bicycloheptatrienes as their ground states at or below room temperature in solution and without any excited states.

It was found that the treatment of compound **148** with *t*-BuOK in THF gave the starting material (39%) and *tert*-butyl ethers **149** and **150** (in 43% combined yield) in a ratio 3 : 2 (equation 47)[63].

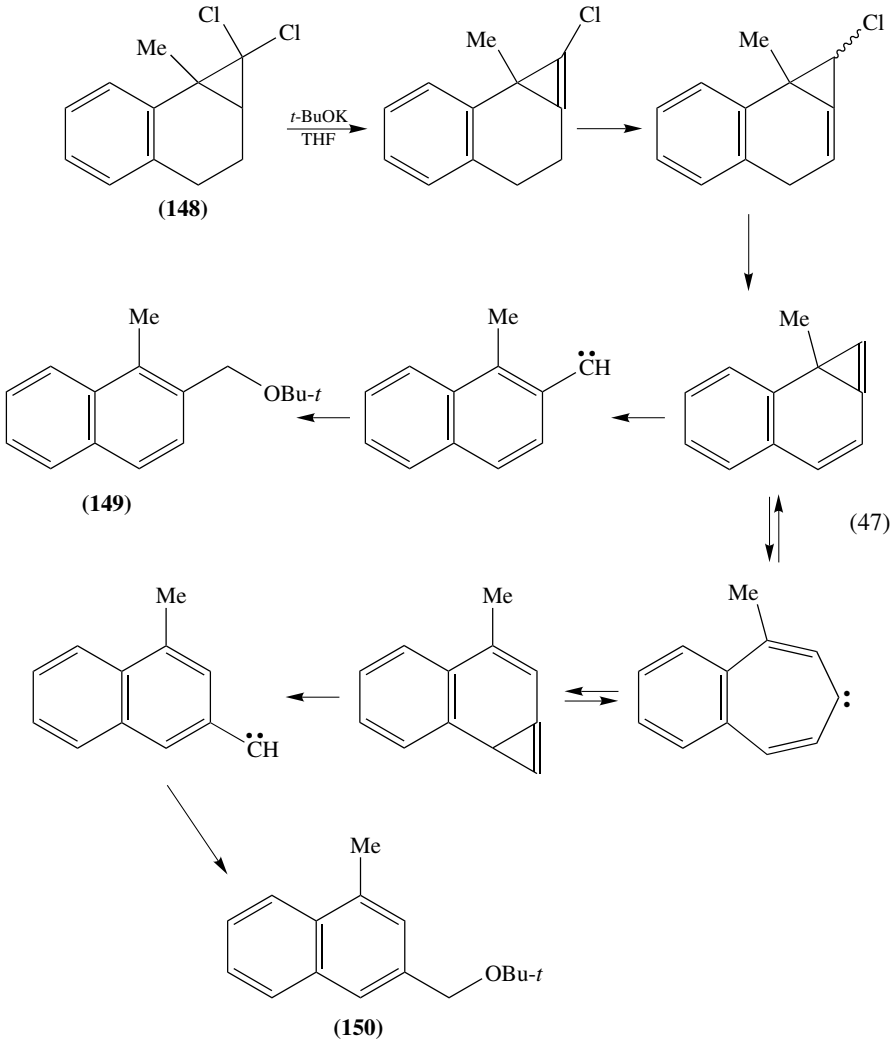
Another paper[64], which also contains a literature survey about the problem discussed, describes the rearrangements of C_7H_6 systems which can be generated by thermolysis of phenyldiazomethane. By using spectral methods and chemical reactions, the formation of bicyclo[4.1.0]hepta-2,4,6-triene **(139)**, cycloheptatrienylidene **(137a)** and bicyclo[3.2.0] hepta-1,3,6-triene **(135)** was excluded, and evidence for the formation of intermediate cycloheptatetraene **(137b)** (see equation 45) was furnished.



(45)



(46)



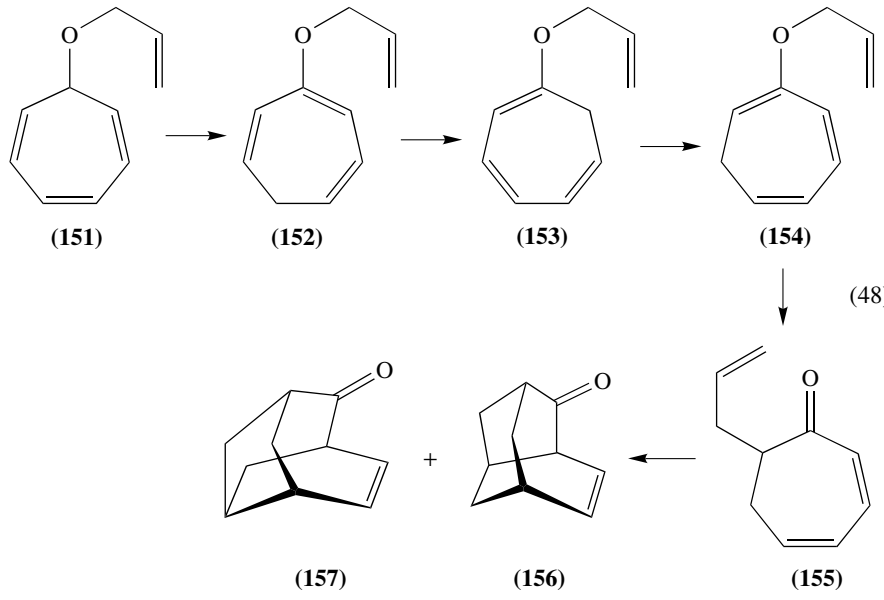
(47)

B. Cyclic Polyenes

1. Cycloheptatrienes

For cycloheptatriene and a series of its derivatives various thermal unimolecular processes, namely conformational ring inversions, valence tautomerism, [1,5]-hydrogen and [1,5]-carbon shifts, are known. An example of such multiple transformations was described[65] which can provide a facile approach to new polycyclic structures by a one-step effective synthesis (yields up to 83%) of the two unique ketones **156** and **157**. The thermolysis of the neat ether **151** at 200 °C for 24 h gives initially the isomeric allyl vinyl

ethers **152–154** by successive [1,5]-hydride shifts, and subsequent Claisen rearrangement (see Section IV.E.1) provides the allyl cycloheptadienone **155** which easily undergoes an intramolecular Diels–Alder reaction to afford a 50 : 50 mixture of the two isomeric ketones **156** and **157** (equation 48)[65].

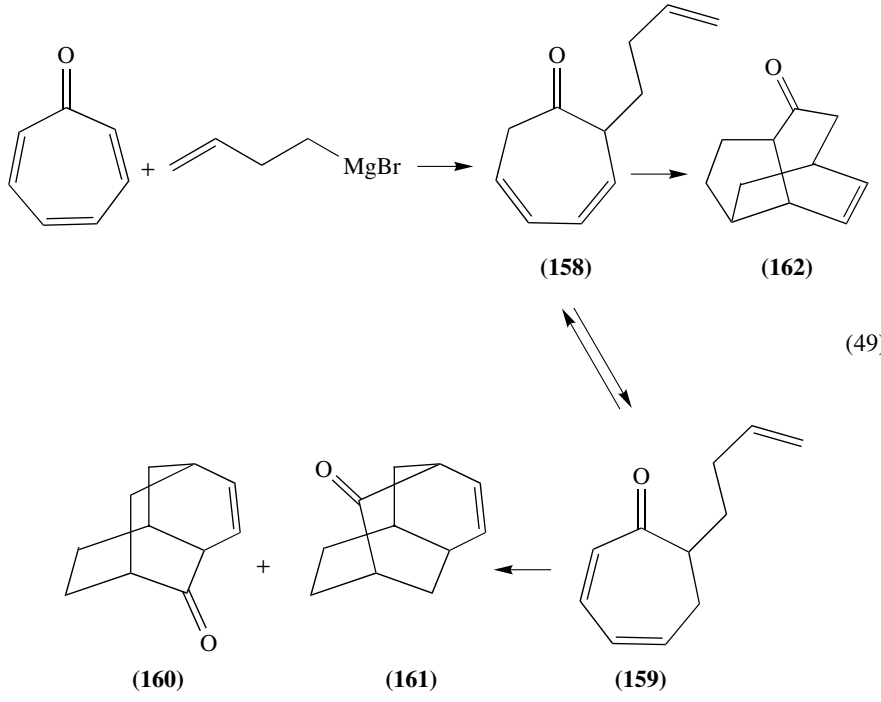


These transformations were applied to develop a new promising method for synthesis of various bridged polycyclic systems[66], viz. ketones **160** and **161.** Tropone reacts with butenyl magnesium bromide (−78 °C, 75%) to form a mixture of 2-(3-butenyl)dihydrotropones **158** and **159**, the pyrolysis of which (200–210 °C, neat or in heptane solution) leads to 60% total yield of the isomeric homoprotoadamantenones **160** and **161** and the tricyclic ketone **162** in a ratio of 58 : 18 : 24, respectively (equation 49)[66].

Similar results were obtained for the synthesis of azapolycycles having relatively rigid skeletal frameworks. Thus, refluxing of *N*-substituted *N*-allylamines **163** under conditions of high dilution in xylene gave the cycloadducts **164** in 67% yield along with the products of hydrogen shift **165** and **166** (equation 50)[67].

A novel thermal rearrangement with loss of sulfur dioxide leading to the stilbene or styrene derivatives **169** and **170** in highly stereospecific manner was carried out by heating (in dioxane, DMSO, dioxane–water or THF) the sulfene-tropone adducts (γ-sultones) **167** or **168** (equations 51 and 52)[68].

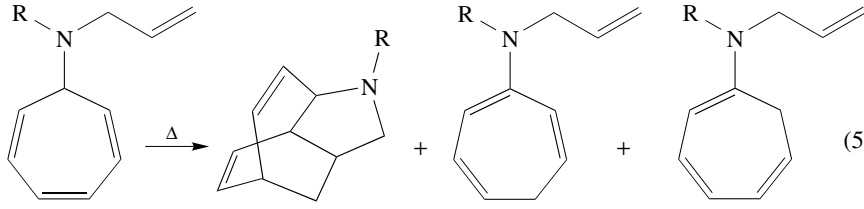
It is worthwhile mentioning here that the thermal hydrogen shifts can occur not only in the cyclic seven-membered substrates but also in open-chain systems. For example, the antarafacial thermal [1,7]-sigmatropic hydrogen shift in epimeric *cis*-isotachysterol analogues **171** and **172** which give **173** and **174** was reported (equations 53 and 54)[69]. This work was carried out in order to investigate the reactions of parent previtamin D_3 to afford vitamin D_3. However, it should be noted that an analogous example was already known for a long time (see e.g. Chapter 7 in Reference 5).



(49)

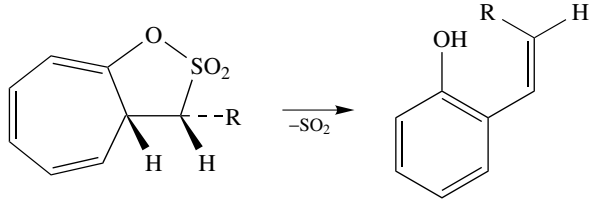
2. Cyclooctatrienes

The reversible rearrangement of 1,3,5-cyclooctatriene **175** into bicyclo[4.2.0]octa-2,4-diene **176** was first postulated[70] and then corroborated[71] by Cope and coworkers almost 50 years ago. These authors[71] and their followers[72] have shown that isomers **175** and **176** can be separated and both undergo interconversion to the same equilibrium mixture of 85% **175** and 15% **176** by a short-term heating at 80–100 °C (equation 55). This equilibrium system was later investigated intensively, including the finding of the conditions of the photochemical transformations[72]. However, from the synthetic standpoint the system consisting of the fused cyclooctatriene and cyclopropane rings is apparently the most interesting. An initial short communication about the behavior of such systems was published in 1961[73]. The norcaradiene vinylogue, *cis*-bicyclo[6.1.0]nona-2,4,6-triene **177**, as well as some of its derivatives were obtained by addition of carbenes to the cyclooctatetraene. It was shown that the bicyclic triene **177** is thermally labile and rearranges easily already at 90 °C without any catalyst to the indene derivative **178** (equation 56)[73]. The dihalocarbene adducts **179** in which the halogen atoms show no solvolytic activity rearrange almost quantitatively at 80–90 °C to afford the indene derivatives **181**. The location of the halogen atoms in the products **181** allows one to exclude the possibility that the bicyclic compounds **179** rearrange via the cyclononatetraene intermediate **182**. Instead, the tricyclic structures **180** are assumed to be the most probable intermediates in this process (equation 56)[73].

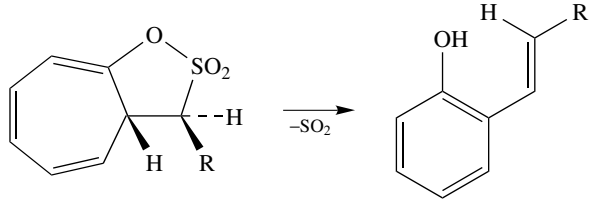


(163) (164) (165) (166) (50)

R = COOEt, COOBu, COMe, COPh

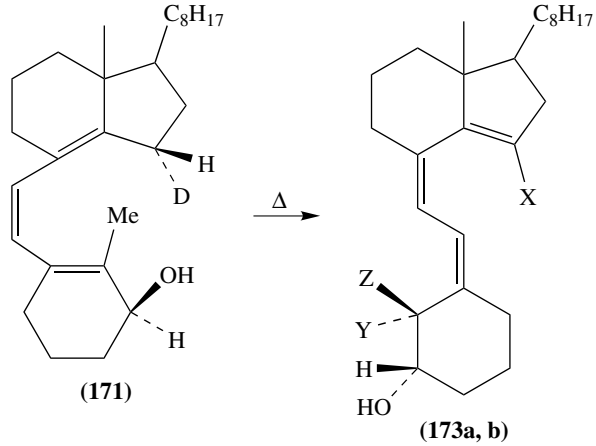


(167) (169) (51)

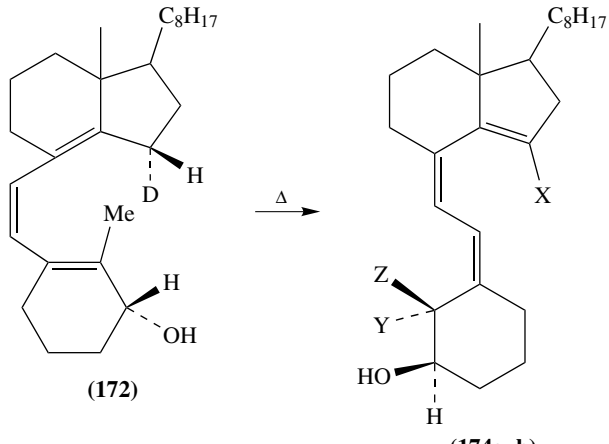


(168) (170) (52)

R = Ph, Ar, PhCO, CN, SO_2Me, $CH{=}CH_2$ (90 °C, 6–10 h, 40–95%)



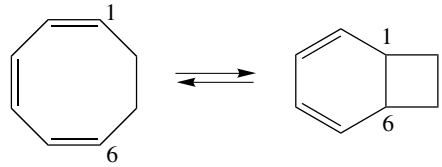
(171) (173a, b) (53)



(54)

(172) **(174a, b)**

(173a, 174a) X = D, Y = Me, Z = H
(173b, 174b) X = H, Y = D, Z = Me



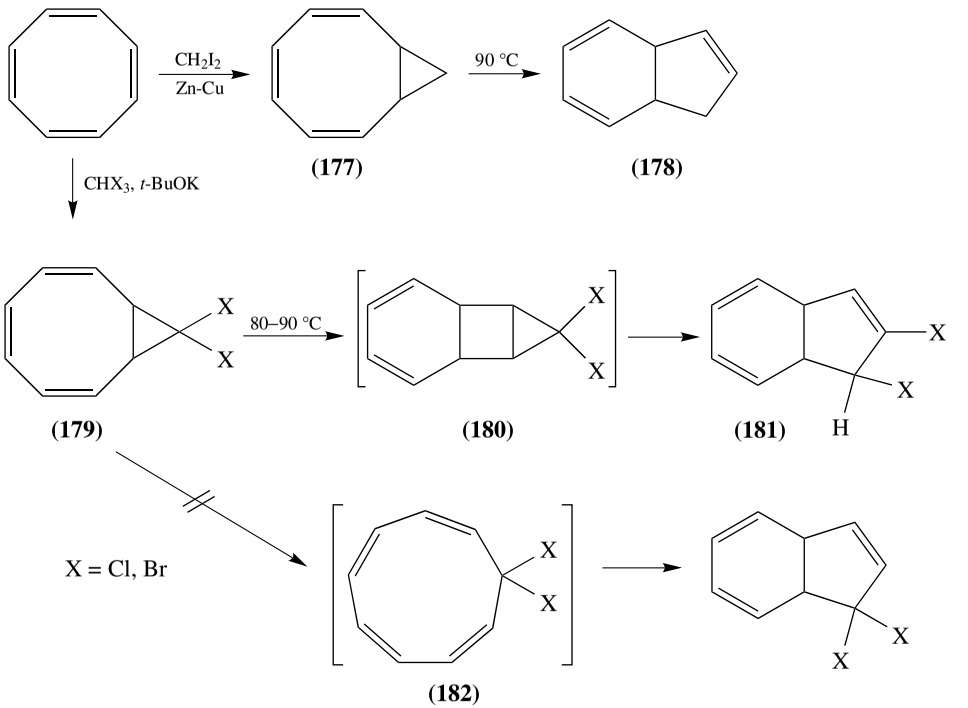
(55)

(175) **(176)**

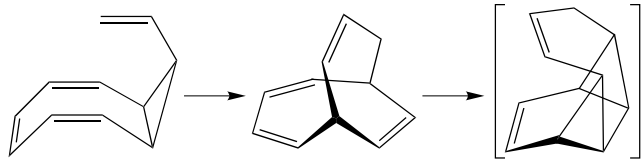
It was shown[74] that the folded conformation of bicyclic substrates is a prerequisite for isomerizations such as **177** → **178**. Thus, *syn*-9-vinyl triene **183**, being in the open conformation, undergoes an unusual Cope rearrangement to give the intermediate **184** which starts a cascade of thermal isomerizations at 60–65 °C (equation 57) whereas the *anti*-9-vinyl epimer **185** rearranges into the indene derivative **186** at 110 °C in benzene solution (equation 58)[74].

Further, the thermal decomposition of the dry sodium or lithium salt of the tosylhydrazone **187** gives a complex mixture of products **189**–**195**[75] (equation 59). The authors suggest that the cyclooctatetraene **189** can be formed via two-bond cleavage reaction of **188** typical for cyclopropylcarbenes. The *trans*-9,10-dihydronaphthalene **192** is most likely the rearrangement product of the intermediate **196** which occurs via cyclodecapentaene **197** (equation 60). The formation of *cis*-9,10-dihydronaphthalene **194** and *cis*-1-phenylbutadiene **190** provides mechanistic mysteries, although two-step reactions leading to them can be imagined (equation 61).

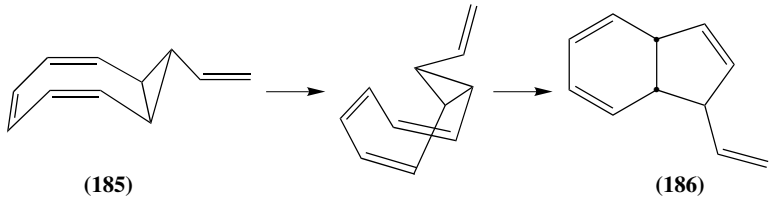
The formation of the bridged product **191** was investigated using the cyclopentadiene system as a model. Thus, the salt of the tosylhydrazone **198** was prepared and thermolyzed in order to examine three possible variants of rearrangements (equation 62)[75]. Analysis of the reaction products **200**–**202** and their transformations [e.g. the pyrolysis of bicyclic triene **202** to *cis*-8,9-dihydroindene **203** (equation 63) rather than to product **200** or **201**] allows one to conclude that the mechanism involves a transformation of carbene **188** into diradical **204** which can be the precursor of all the products observed (equation 64)[75]. An analogous conversion takes place via radical **205** in the case of carbene **199** (equation 65).


CH2I2
Zn-Cu
90 °C
CHX3, t-BuOK
(177)
(178)
X
X
80–90 °C
X
X
X
X
H
(179)
(180)
(181)
X = Cl, Br
X
X
X
X
(182)

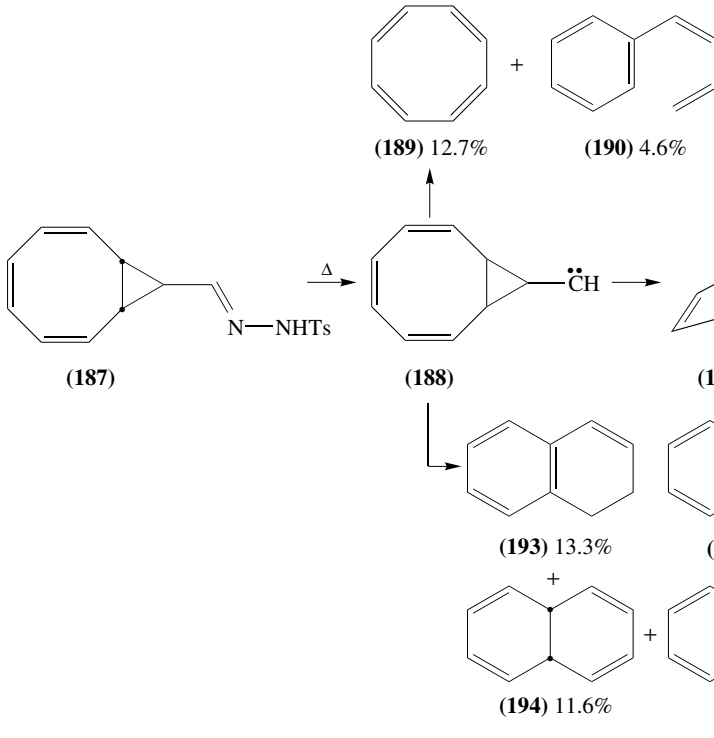
(56)



(183) **(184)** (57)



(185) **(186)** (58)

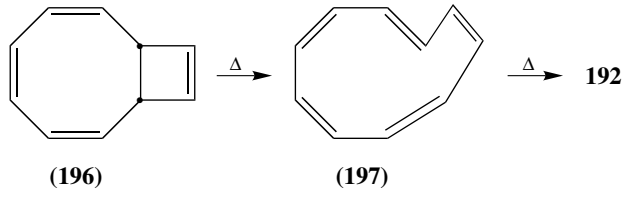


(189) 12.7% **(190)** 4.6%

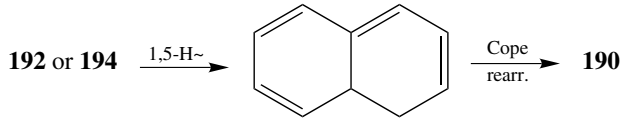
(187) **(188)** **(191)** 37.8% (59)

(193) 13.3% **(192)** 20%

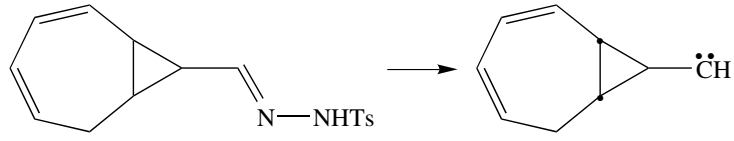
(194) 11.6% **(195)**



(196) (197) (60)

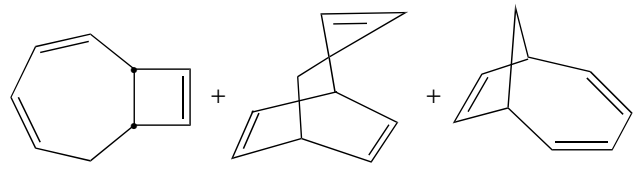


(61)

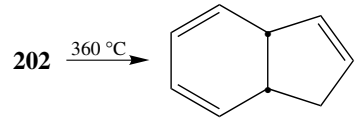


(198) (199)

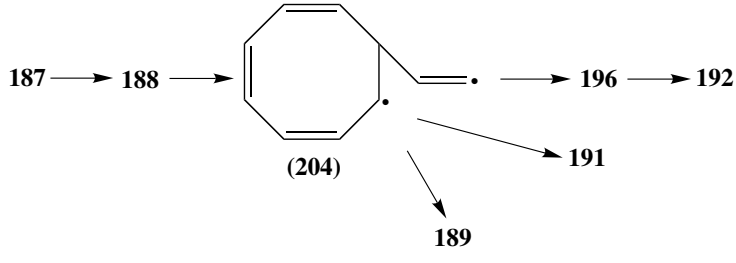
(62)



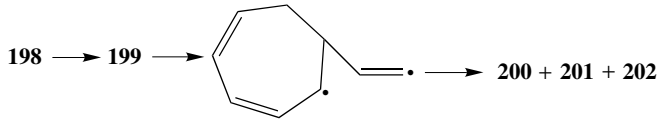
(202) 27% (201) 12% (200) 37%



(203) (63)

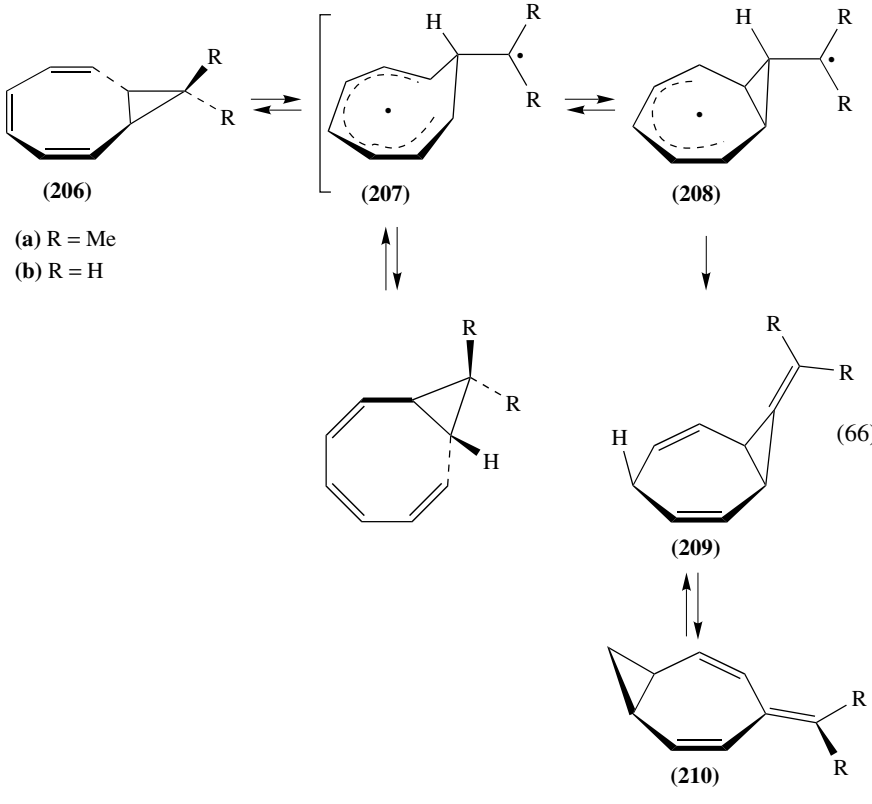


(204) (64)



(205) (65)

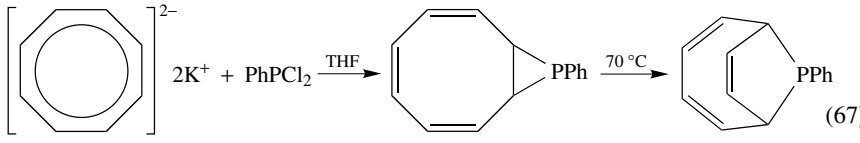
It should be noted that, in contrast to well-known *cis*-bicyclo[6.1.0]nonatrienes, the thermal behavior of *trans*-bicyclo[6.1.0]nonatrienes has been insufficiently explored[76–78]. It was found that the thermolysis of *trans*-nonatriene **206a** and the parent compound **206b** occurs surprisingly easily to form the previously unknown 3,4-homoheptafulvene system **210**. Using an optically active compound **206a**, a degenerate cyclopropane-walk-rearrangement which precedes the structural isomerization was detected. In both processess the diradical *exo*-**207** was considered to be a possible intermediate (equation 66)[77]. The thermolysis of triene **206a** (180 °C, degassed benzene, 3 h, conversion 100%) and **206b** (200 °C, degassed toluene, 10 min, 90% conversion) gives in every case only the sole product **210a** or **210b**. Compounds **210a** and **210b** are very sensitive to air and prone to undergo polymerization. The probable mechanism for process **206** → **210**



(66)

includes a cleavage of distal bond in cyclopropane ring of **206** to give the diradical intermediate **207**, which undergoes an electrocyclic ring closure to form the diradical **208**. A subsequent hydrogen shift leads to the homotropylidene **209** which relieves the excessive internal strain by a rapid Cope rearrangement into the homoheptafulvene **210**.

Interesting transformations in which the phosphorus analogues of bicyclo[6.1.0]nona-2,4,6-triene undergo various rearrangements were reported. Thus, dipotassium cyclooctatetraenide reacts with dichlorophenylphosphine in THF to give an adduct **211** which isomerizes upon heating to bicyclic triene **212** (equation 67)[79]. The same approach was utilized to prepare the bridged phosphonium barbaralanes **215a** ⇌ **215b** which are degenerate Cope systems (equation 68)[80] (see also Section IV.C.2.d). The alkylation of the 9-phospha derivatives **213** with trialkyloxonium salts leads to products **215**, presumably via the intermediate phosphonium salts **214** which undergo a disrotatory ring opening, followed by successive conversions of cationic bicyclic ylides. The P-barbaralane **215** demonstrates the rapid degenerate Cope rearrangement above 25 °C which can be frozen below −72 °C[80].



(67)

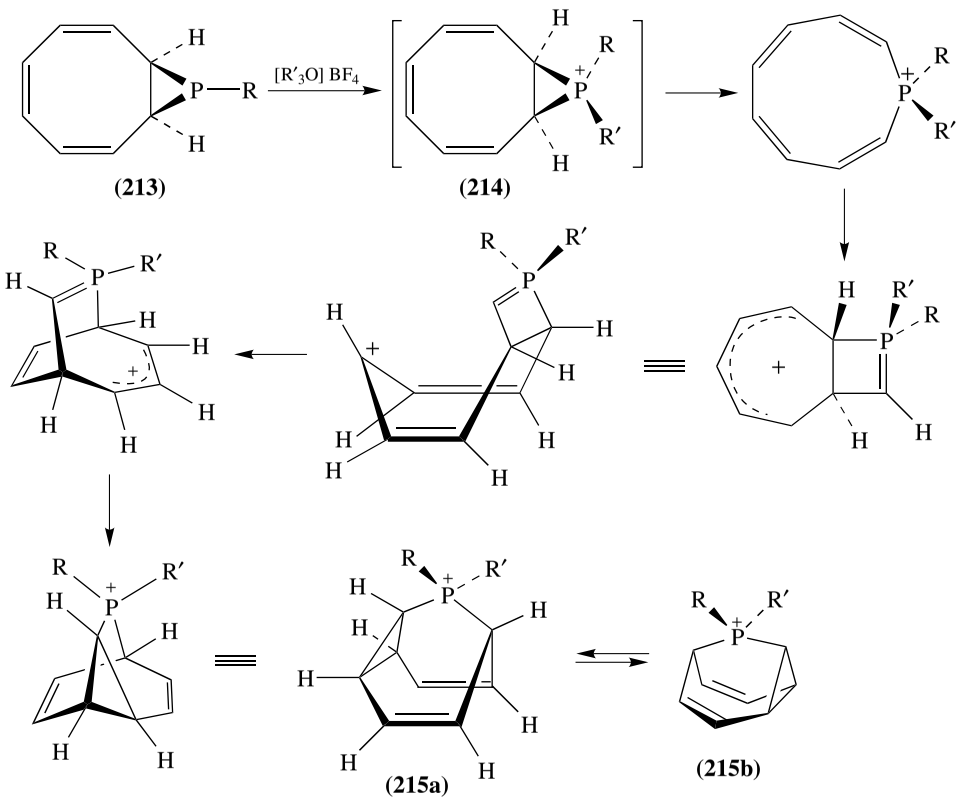
(211) **(212)**

The reaction of phenyllithium with the bridged phosphine oxide **216** gives the rearrangement product **217** in 60% yield (equation 69)[81]. The behavior of the heterocyclic system **218** toward oxidizing reagents and a new pathway for its skeletal rearrangement were described[82]. Treatment of compounds **218** with hydrogen peroxide or *tert*-butyl hydroperoxide at −15 °C leads to a cleavage of the C−C bond of the three-membered ring to form the relatively instable phosphonin ring system **219**. When the latter was warmed to 25 °C it was completely rearranged to dihydrophosphindole **220** (equation 70)[82].

3. Cyclooctatetraenes

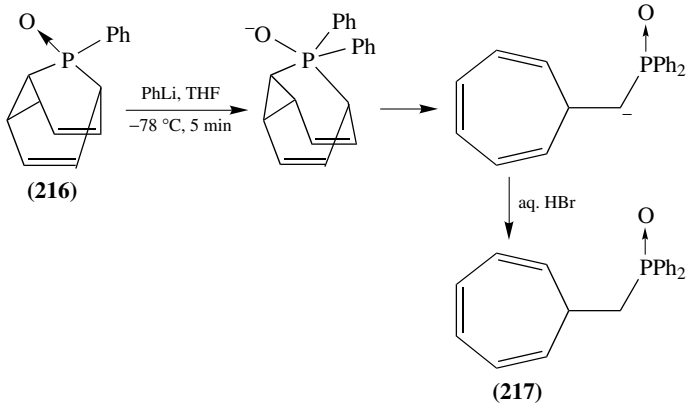
The numerous transformations of cyclooctatetraene **189** and its derivatives include three types of structural changes, viz. ring inversion, bond shift and valence isomerizations (for reviews, see References 83–85). One of the major transformations is the interconversion of the cyclooctatetraene and bicyclo[4.2.0]octa-2,4,7-triene. However, the rearrangement of cyclooctatetraene into the semibullvalene system is little known. For example, the thermolysis of 1,2,3,4-tetra(trifluoromethyl)cyclooctatetraene **221** in pentane solution at 170–180 °C for 6 days gave three isomers which were separated by preparative GLC. They were identified as 1,2,7,8-tetrakis(trifluoromethyl)bicyclo[4.2.0]octa-2,4,7-triene **222** and tetrakis(trifluoromethyl)semibullvalenes **223** and **224** (equation 71)[86]. It was shown that a thermal equilibrium exists between the precursor **221** and its bond-shift isomer **225** which undergoes a rapid cyclization to form the triene **222**. The cyclooctatetraenes **221** and **225** are in equilibrium with diene **223**, followed by irreversible rearrangement to the most stable isomer **224** (equation 72)[86].

The interaction of cyclooctatetraene as a dienophile with the diazadiene, 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine **226**, is accompanied by nitrogen elimination and gives rise to the 1,1-adduct **227**. The latter displays interesting thermal rearrangements depending on the solvent polarity and temperature (equation 73)[87]. In toluene solution a [1,3]-carbon

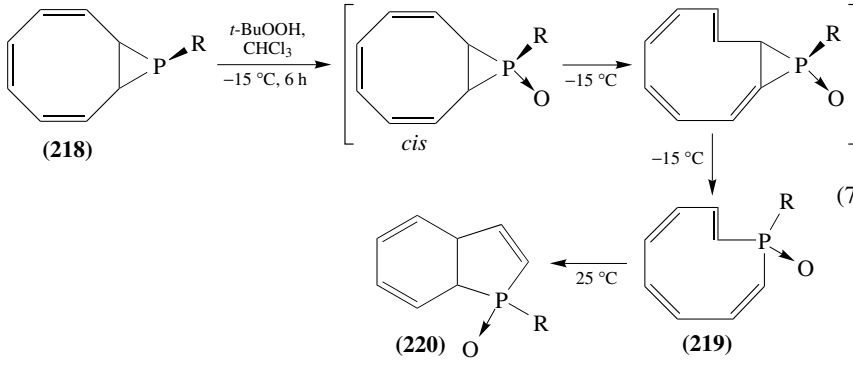


R = Me, *t*-Bu, CH_2Ph, Ph; R′ = Me, Et

(68)

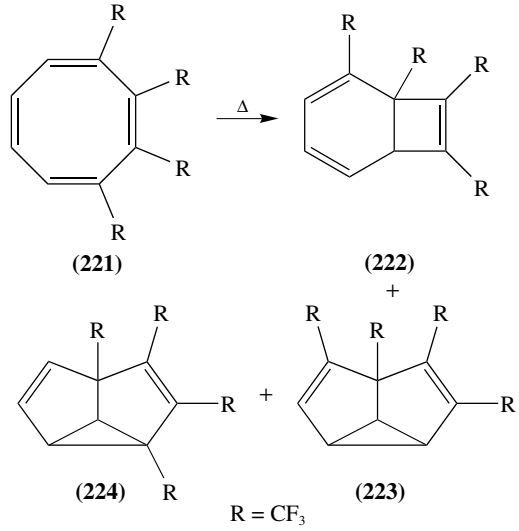


(216) **(217)** (69)



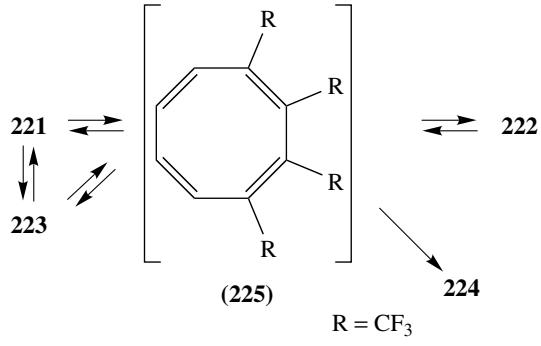
(218) **(220)** **(219)** (70)

R = *t*-Bu, Ph

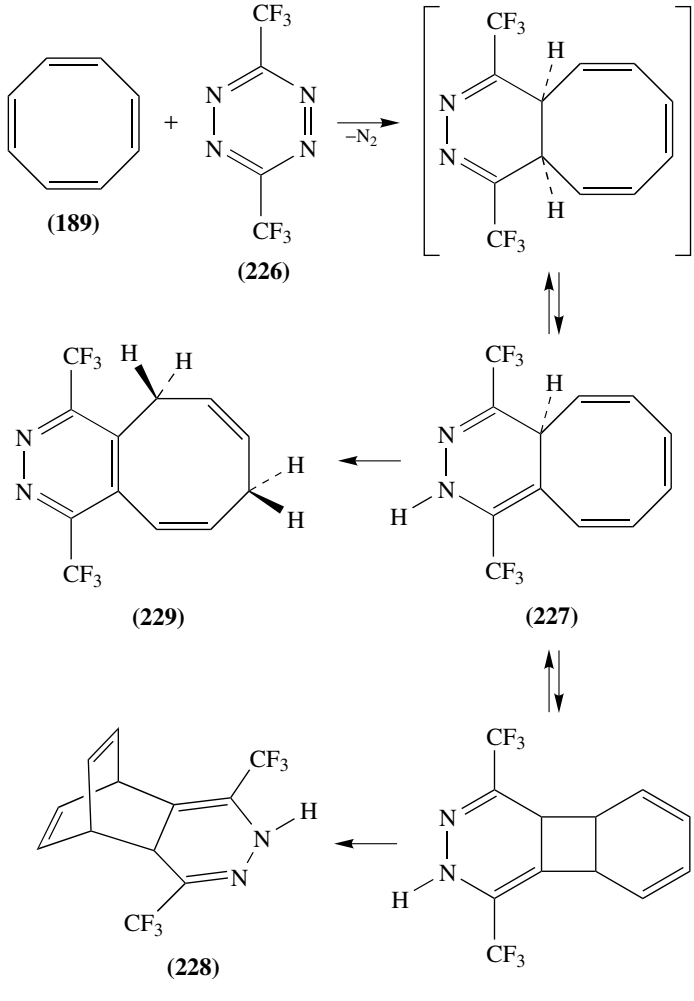


(221) **(222)** **(224)** **(223)** (71)

$R = CF_3$


R
R
R
R
221
222
223
(225)
224
R = CF3

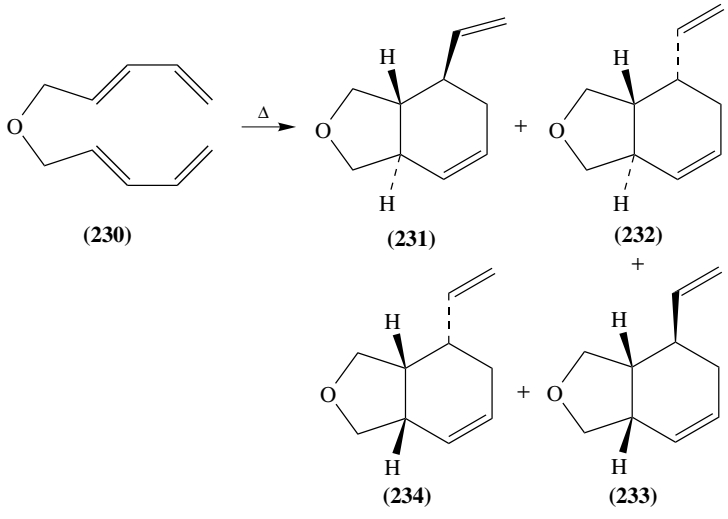
(72)


CF3
N
N
N
N
CF3
(189)
(226)
–N2
H
H
(227)
(229)
(228)

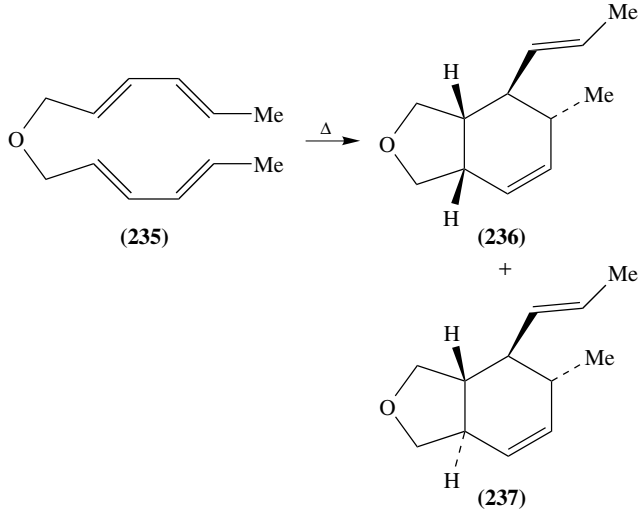
(73)

migration occurs at 111 °C (10 h) to afford the barreleno[*d*]pyridazine **228** while the isomer of **228**, i.e. the dihydrocyclooctapyridazine **229**, is formed in the more polar nitromethane (2 days at 90 ± 2 °C). Presumably, **229** is more stable than **228** and it originates from the adduct **227** via proton-shift tautomerism and [1,5]-sigmatropic hydrogen shift. No equilibrium between compounds **228** and **229** via intermediate **227** was observed[87].

In connection with the behavior of the eight-membered ring system, it is interesting to mention that the uncatalyzed thermolysis of the open-chain tetraene ether **230** in toluene at 150 °C (11 h) gives rise to a mixture of four intramolecular Diels–Alder products **231–234** in 80% total yield (equation 74)[88]. The thermolysis of dimethyl homologue **235** (toluene, 150 °C, 11 h, 81%) affords the *cis*-fused cyclohexene derivative **236** and

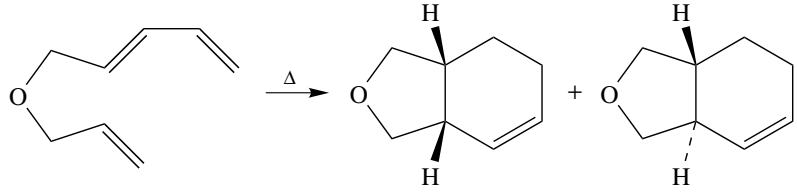


(74)



(75)

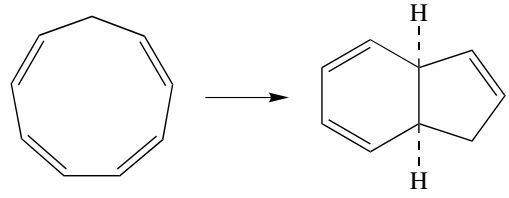
the *trans*-fused isomer **237** in a 1 : 4 ratio (equation 75)[88]. The thermolysis of the triene ether **238** (150 °C, 5 h, 45%) results in a mixture of *cis*- and *trans*-fused isomers **239** and **240** in a 3 : 1 ratio (equation 76)[88]. It should be noted that these cyclizations rank with the Cope rearrangements of divinylcyclobutanes (see Section IV.C.2.c).



(76)

(238) **(239)** **(240)**

The tetra-*cis*-cyclononatetraene **241** is unstable and easily rearranges at 23 °C ($t_{1/2}$ ~ 50 min) to the isomeric *cis*-8,9-dihydroindene **242** (equation 77)[89]. It is interesting, however, that the iron(III) tricarbonyl complex of tetraene **241** is stable for many days at room temperature and isomerizes to the Fe-complex of **242** only upon heating in octane at 101 °C[89]. The principle of stabilization of the reactive multiple bonds with metal carbonyl complexes is well-known in modern organic synthesis (e.g. see the acylation of enynes[90]).

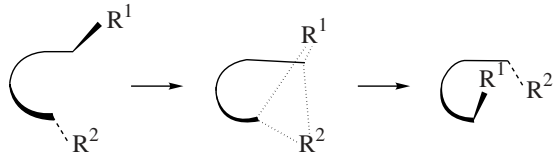


(77)

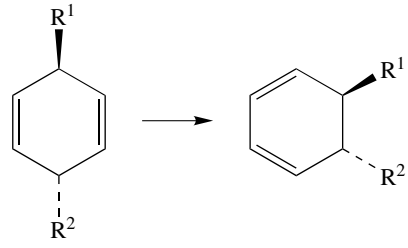
(241) **(242)**

4. Dyotropic rearrangements

Dyotropic rearrangements are uncatalyzed concerted dihydrogen exchange reactions, another class of orbital symmetry controlled processes, which involve the simultaneous migration of two σ-bonds. These conversions can be both thermal and photochemical. They can be subdivided into two types: (1) reactions in which two migrating σ-bonds interchange their positions (equation 78), and (2) reactions without such positional interchange (equation 79)[91,92].

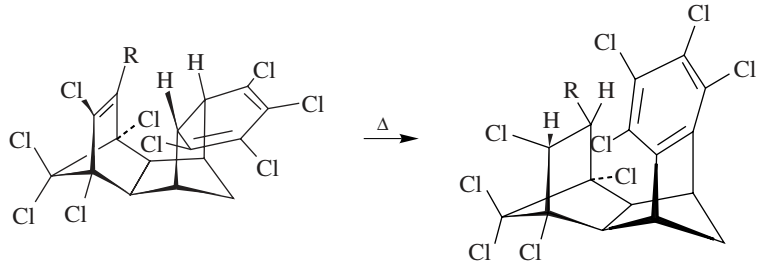


(78)



(79)

The discovery of a new reaction, the transannular dihydrogen transfer, was reported in 1965[93]. Mackenzie found that the polychloro-*endo,endo,exo*-1,4 : 5,8-dimethanooctahydroanthracenes **243**, having an isodrine carbon framework (isodrine is the *endo,endo*-isomer of aldrin, the known insecticide HHND), rearrange smoothly to form the isomers **244** (equation 80). This exothermic reaction proceeds when pure crystalline compounds **243** undergo heating and melting near 180 °C. The isomerization of **243** also occurs at much lower temperature (110 °C) in solution. No effect of catalysts such as boron trifluoride, palladium on carbon or chloranil was observed, i.e. this reaction is purely intramolecular. The author has already noted in this paper[93] that the reaction is probably assisted by the energy released on aromatization of the dienes-containing ring, together with some reduction in the overall steric strain in the system due to aromatization of the six-membered ring and saturation of the C1C=CR bridge.



(80)

(243) **(244)**

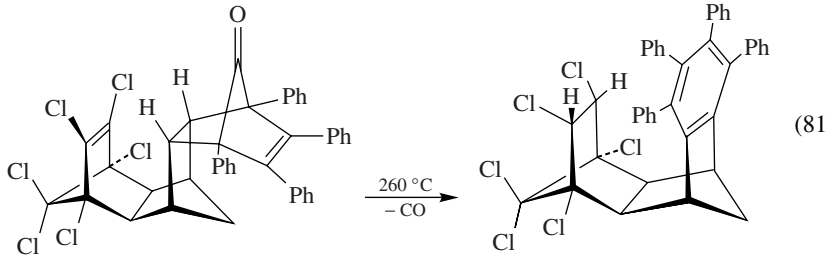
R = Cl, OEt, OMe

The reaction was investigated later in more detail[94–97]. It was suggested that these isomerizations are almost certainly concerted sigmatropic rearrangements. However, independent of their mechanism these reactions can be considered as disproportionations in which at least one fragment achieves a high degree of stabilization. Further examples of this rearrangement include polycarbocyclic as well as heterocyclic derivatives (equations 81–83)[95,96].

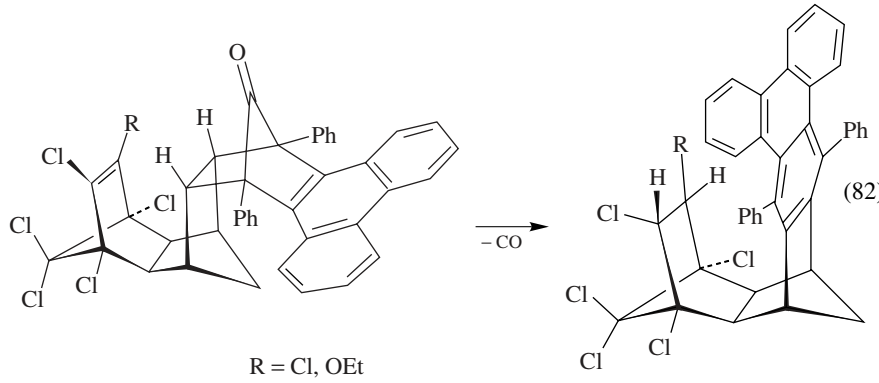
The methods for synthesis of starting cyclic dienes, the rearrangement conditions and kinetic characteristics of basic substrate reactions over a wide range of substitution variations were generalized in work[97] which included a quite detailed survey of related publications.

Furthermore, a brief review of dyotropic rearrangements starting with the hypothetical transformations of 1,2-disubstituted cyclobutenes was published[98] in which two types of these processes were described and a general theory covering such rearrangements was outlined. Quantum chemical calculations of the reaction barrier for the dihydrogen

exchange reaction between ethane and ethylene were discussed[99] (see also the diimide reduction of olefins[100]).

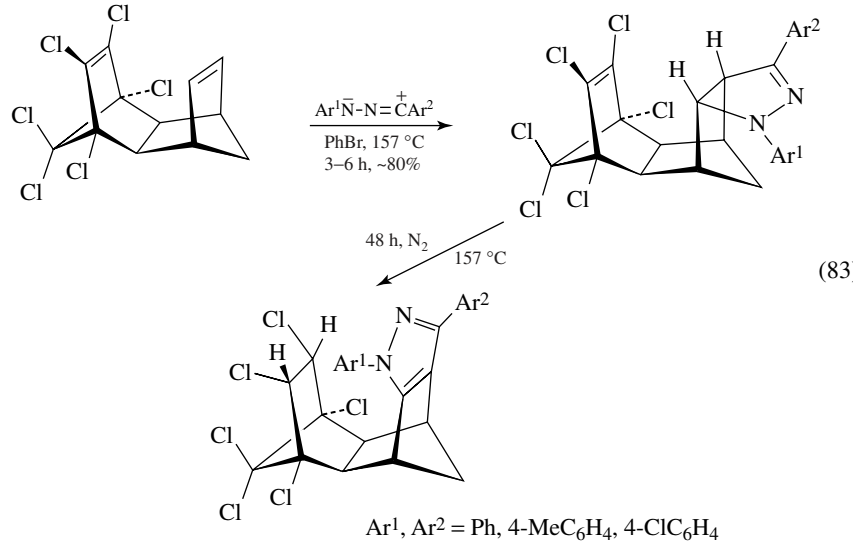


(81)



(82)

R = Cl, OEt

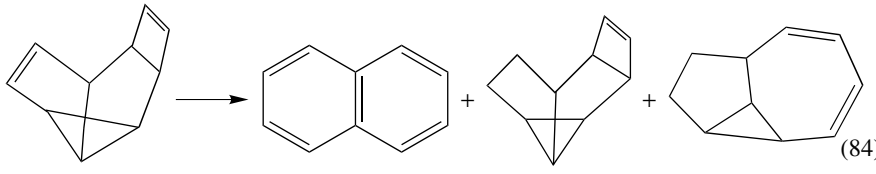


(83)

Ar^1, Ar^2 = Ph, 4-MeC_6H_4, 4-ClC_6H_4

The isodrine framework was used for synthesis of 'pagodane' in which one of the key steps is Mackenzie's transannular dyotropic hydrogen transfer[101]. Also, a 'very intriguing'

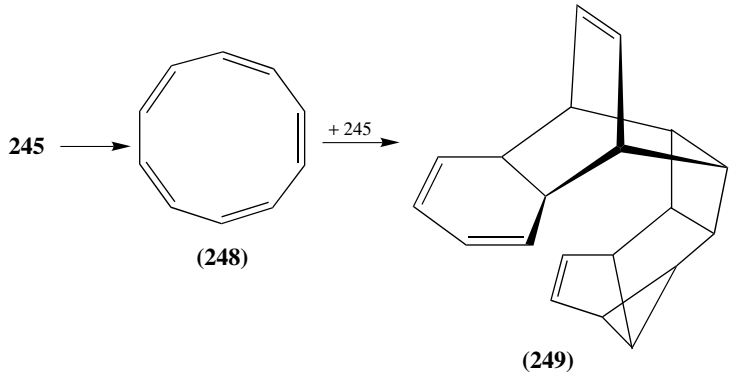
process was found upon thermal decomposition of the tetracyclic diene **245**[102]. When **245** is heated at 200 °C in cyclohexane solution, it undergoes a rapid ($t_{1/2} \sim 1$ h) thermal disproportionation to afford naphthalene (43%) and the two new hydrocarbons **246** and **247** whose ratio depends upon the extent of decomposition (equation 84). Rate studies indicated that compound **246** can be thermally rearranged into **247**. At 230 °C only the latter could be isolated.



(84)

(245) **(246)** **(247)**

Using deuterium labelling it was shown that the isotope atoms lost from precursor **245** in the formation of naphthalene are almost exactly those picked up by a second molecule **245** which gives the olefin **246**. No reorganization of the carbon framework takes place. The transfer of two hydrogen or deuterium atoms with high degree of specificity can include an initial addition of the presumable intermediate **248** to diene **245** to form a transient cage species such as **249**, which can subsequently split into $C_{10}H_8$ and $C_{10}H_{12}$ moieties (equation 85). This scheme can account for the preferential hydrogenation of the double bond in the cyclopentene ring rather than of the cyclobutene ring within structure **245**[102].



(85)

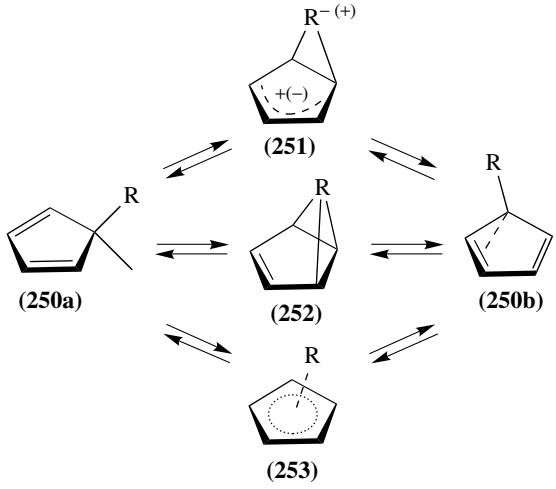
(248) **(249)**

C. Circumambulatory Rearrangements

The discovery in 1956 of the ability of certain organometallic groups to migrate along the cyclopentadiene ring perimeter[103] stimulated the development of the fundamental concept of fluctuating molecular systems (called also 'structurally non-rigid system')[3]. More recently it was shown that migrating moieties having a Main Group (III–VI) central atom are also capable of a fast, intramolecular sigmatropic shift around a cyclopentadiene ring which can be detected by using NMR spectroscopy[9,104,105]. At present the processes of dynamic sigmatropic rearrangements (named also 'circumambulatory' as well as 'merry-go-round', 'ring walk', 'ring runner' and 'ring whizzer', but more generally 'fluxional'

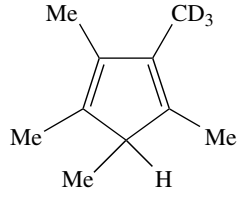
or 'degenerate' rearrangements) involve already the elements of all the groups (except Group VIII) of the periodic system.

The general picture of intramolecular migrations of substituents R in the cyclopentadiene ring (equation 86) covers the intermediates or transition states of η^2-type (1,2- or 1,5-shift) **(251)**, η^3-type (1,3-shift) **(252)** and η^5-type (randomization because of the formation of a π-complex or ion-pair structure) **(253)**. Furthermore, other possible routes are a randomization with formation of tight or solvent-separated ion pairs (e.g. in the case of arylazo groups) and radical pairs as well as intermolecular mechanisms. The experimental determination of the specific rearrangement mechanism is usually based on line-shape analysis of the temperature-dependent NMR spectra of the rearranging compound. Since a number of extensive reviews[106–109] about walk rearrangements are available, we will consider only briefly the information concerning walk rearrangements recently obtained.

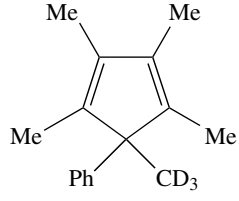


(86)

Degenerate sigmatropic rearrangement of 1,2,3,4,5-pentamethylcyclopentadiene (here and below designated as PMCPD) involving a migration of hydrogen was investigated using the dynamic NMR (DNMR) technique on system **254**[110]. The activation energy was estimated to be 106.8 ± 1.25 kJ mol^{-1} (for comparison, the activation energy for Si-migrants is 54.9 to 64 kJ mol^{-1}) (for reviews, see Reference 108).



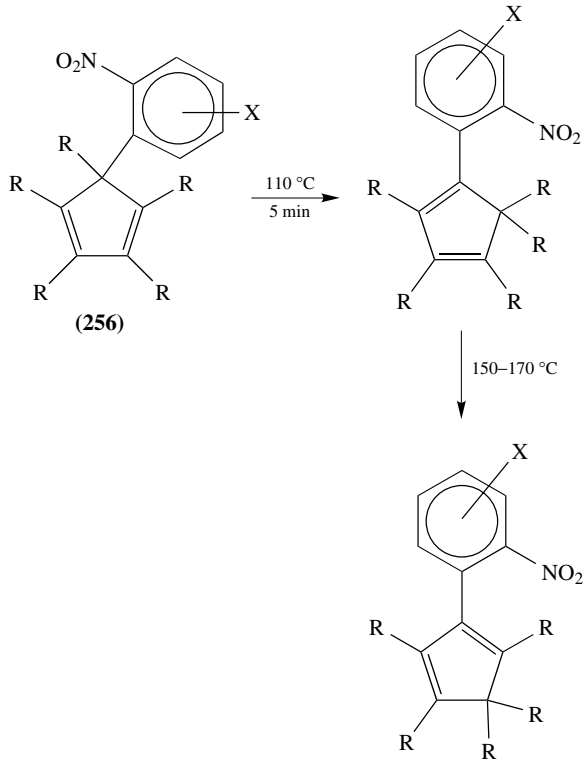
(254)



(255)

The carbonotropic migrations include a number of various migrants. A migration of phenyl group in system **255** was shown[111] to involve a [1,5] migration mechanism with an activation energy of 154.9 ± 1.25 kJ mol^{-1}. However, a migration of the

methoxycarbonyl group with $\Delta G^{\neq}_{298} \sim 109-126$ kJ mol^{-1} was observed in the system **256** (equation 87)[112,113]. The [1,5]-sigmatropic formyl migration in the 5-formyl-PMCPD system occurs rapidly at 25 °C with $\Delta G^{\neq}_{298} = 61.9$ kJ mol^{-1} [114].



(87)

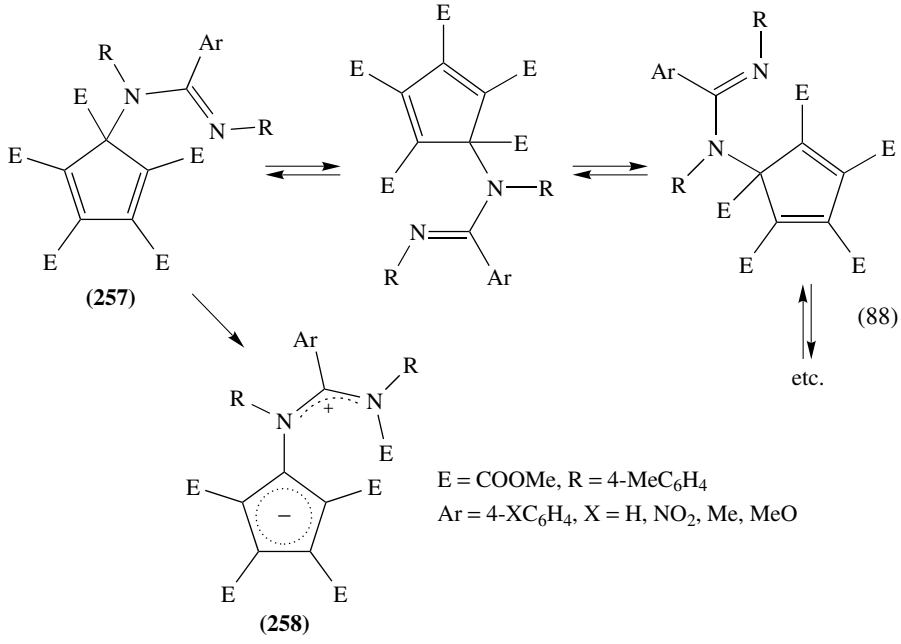
R = COOMe X = H, 4-NO_2, 6-NO_2

It is considered that [1,5] alkyl shifts usually require temperatures above 330 °C and proceed with free energies of activation greater than 180 kJ mol^{-1}. The 1,5-migratory aptitude of the formyl group is comparable with that of a trimethylsilyl group. However, 5-acetyl- and 5-ethoxycarbonyl-PMCPDs under the same conditions show a temperature-invariant ^{1}H NMR spectra, i.e. the migratory aptitude decreases in order CHO $\gg$ COMe $\sim$ COOMe[114].

It was found that the migratory aptitude of an acyl group can be increased by the introduction of strong σ-acceptor substituents. Fairly rapid [1,5]-sigmatropic migrations of trihaloacetyl groups (CF_3CO, $\Delta G^{\neq}_{298} = 86.1$ kJ mol^{-1}; CCl_3CO, $\Delta G^{\neq}_{298} = 103.3$ kJ mol^{-1}) were observed in systems 5-CX_3CO-PMCPD (X = F, Cl) using DNMR[115].

Fivefold degenerate reversible [3,3]-sigmatropic shifts were first reported in 1988[116,117] in the CPD-amidine system **257**, where $\Delta G^{\neq}_{298} = 117$ to 120 kJ mol^{-1} (equation 88) (for aza-Cope rearrangements see Section IV.E.2). In addition, a slow accumulation of a colored by-product was observed at elevated temperatures. This was identified as a product of a novel intramolecular carbon to nitrogen 1,4-shift of the methoxycarbonyl

group to give the N-ylides **258** (equation 88)[118]. The reaction proceeds upon heating *o*-dichlorobenzene solutions of benzamidines **257** at 120–140 °C for 0.5–1 h.

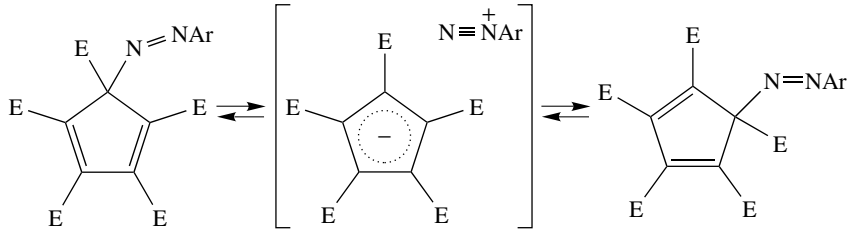


Migrations of arylazo groups were first detected in the 1,2,3,4,5-penta(methoxycarbonyl) cyclopentadiene **259** (equation 89)[119–122]. The randomization mechanism was considered as most probable because the reaction rate increases with increase in the solvent polarity ($\Delta G^{\neq}_{298} = 56.9$ to 69.1 kJ mol^{-1}).

The migrations of nitro group were ascribed to [1,5]-sigmatropic shifts [in Ph_2O or $(CD_3)_2SO$ solutions at 172 °C, $\Delta G^{\neq} = 105.6 \pm 0.4$ kJ mol^{-1}] in 5-nitro-PMCPD system **260** (degenerate rearrangement)[123] as well as in 5-nitro-5-methyl-1,2,3,4-tetra(methoxycarbonyl) CPD **261** (**261a** + **261b**)[124] and 5-nitro-5-alkyl-1,2,3,4-tetra(methoxycarbonyl) CPD **262** (**262a** + **262b**)[125]. A **261a** ⇌ **261b** equilibrium (in a ratio 0.85 : 0.15) is established within 20 min at 80 °C in chlorobenzene solution ($\Delta G^{\neq}_{298} \sim 109$ kJ mol^{-1}).

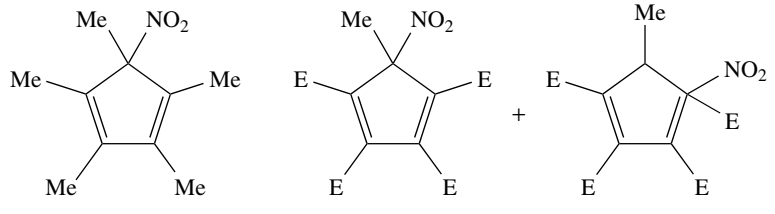
The reversible non-degenerate migrations of aryloxy and aroyloxy groups were studied by using pentaphenyl-substituted cyclopentadiene systems **263** and **265** (equations 90 and 91)[126,127]. The transition states **(264)** are assumed to be η^2-dipolar structures according to MINDO/3 calculations[126]. The conversion **265** ⇌ **266** most probably proceeds via a [3,3]-sigmatropic shift, i.e. via Cope rearrangement. Analogous [3,3]-sigmatropic shifts were found in the 5-(4-methylphenyl)-5-acyloxy-1,2,3,4-tetraphenyl CPD ($\Delta G^{\neq}_{298} = 109–146$ kJ mol^{-1}) (**265**, $R^2 = CF_3$, CCl_3, $CHCl_2$, CH_2Cl, CH_3)[128]. The above-mentioned migrations of amidinyl and acyloxy groups were generalized[129].

Degenerate migrations of PhSe and PhS groups ($\Delta G^{\neq} = 84.6 \pm 0.4$ and 102 ± 0.4 kJ mol^{-1}, respectively) were observed in PMCPD systems[130–135]. The authors suggest a mechanism of PhSe and PhS migrations similar to that for ArO migrations, i.e. via dipolar η^2-states, while the dithioacyloxy groups [−SC(S)R] are assumed to migrate analogously



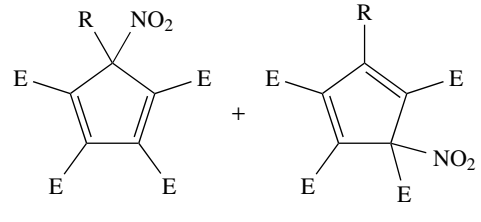
(259)

E = COOMe, Ar = 2-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 2,4-$(NO_2)_2C_6H_3$, 2,6-$(NO_2)_2C_6H_3$, 2,4,6-$(NO_2)_3C_6H_2$



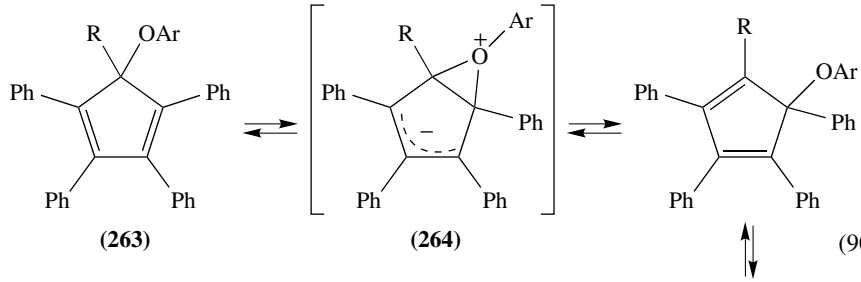
(89)

(260) **(261a)** **(261b)**



(262a) **(262b)**

E = COOMe; R = Me, *i*-Pr, CH_2COOMe, CH_2COMe



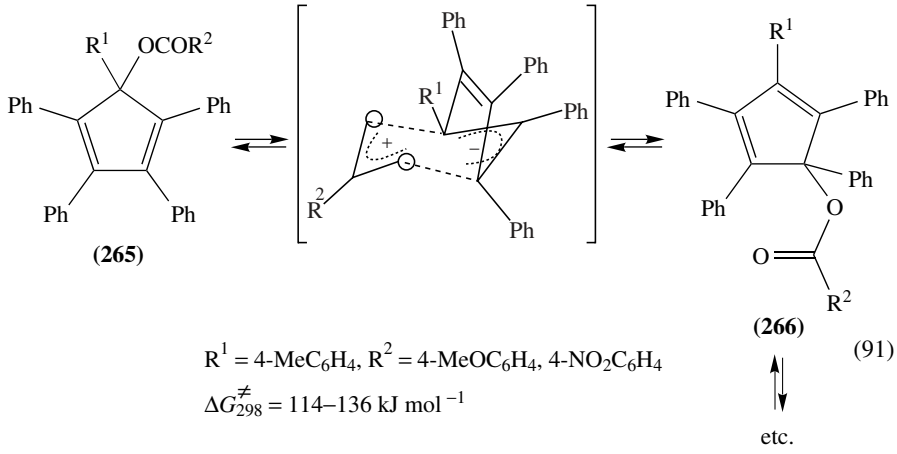
(263) **(264)**

(90)

R = XC_6H_4, X = H, Me, NH_2, MeO, Cl, NO_2

$\Delta G^{\neq}_{453}$ = 99–110 kJ mol^{-1}

to acyloxy groups (with an energy barrier of 100–125 kJ mol^{-1})[136]. The synthesis and rearrangements of 5-(1,2,3,4,5-pentaphenylcyclopentadienyl)isoselenocyanate were recently reported[137].



(91)

Using quantum-chemical calculations (MINDO/3, MNDO) the migrations of SH and OH groups in the cyclopentadiene system were discussed[138]. The calculations have confirmed a preference for 1,2-shift with η^2-structure of the transition state.

The [1,5]-sigmatropic shifts of chlorine and bromine atoms were investigated in the CPD system[109,139]. The comparison of migrations of N-centered (NCS) and S-centered [SPh, SC(OEt)=S] groups in the corresponding derivatives of cyclopentadiene, 1,2,3-triphenylcyclopropene and cycloheptatriene was carried out by using the dynamic ^{1}H and ^{13}C NMR spectroscopy[140]. The migrations of the phenylthio group around a perimeter of the cycloheptatriene ring proceed by a 1,2-shift mechanism (see also References 141 and 142). The 1,3-shift ([3,3]-sigmatropic migration) of azide group in the cycloheptatriene system was observed in liquid SO_2 solutions by using DNMR and is dependent on the solvent polarity[143].

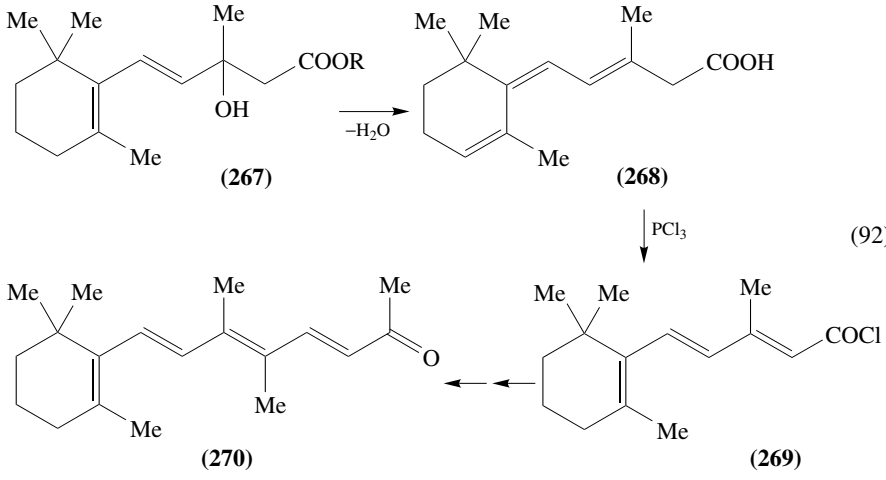
Finally, theoretical studies of haptotropic rearrangements of polyene-ML_n complexes were reported together with detailed literature surveys[144,145].

D. Retroionylidene Rearrangement

The transformations of compounds which are precursors for vitamin A and carotenoids have a special position among the rearrangements of the conjugated polyenes. Numerous isomerizations such as *cis–trans*-isomerization, the dehydration of polyunsaturated acetylenic carbinols etc. were utilized to prepare the various carotenoides (e.g. β-carotene, lycopene, cryptoxanthin, zeaxanthin) (for reviews, see References 146 and 147). However, one of these rearrangements turned out to be a considerable hindrance for the synthesis of target products.

It was found that the simultaneous dehydration and saponification of the hydroxy ester **267** used for synthesis of the β-carotene precursor, ketone C_{18} **(270)**, was accompanied by a very facile allylic rearrangement which gave rise to the C_{15} acid **(268)** having, however, a different arrangement of double bonds than that in β-ionone[146,148]. It was shown that treatment of acid **268** with the specially purified phosphorus trichloride results

in another isomerization (in 99% yield) which affords acid chloride **269** having a 'normal' arrangement of double bonds[148] (equation 92).



Oroshnik and coworkers have described the dehydration of the substituted β-ionol **271** which gave the retrovitamin A methyl ether **272** as a major product together with a very small amount of the target vitamin A methyl ether **273** (equation 93)[149,150]. They have discussed the possible mechanism of this reaction which was called the 'retroionylidene rearrangement'. It was proposed to call the products of this rearrangement 'retroionylidene compounds'.

It was shown by many examples[146] that the majority of methods used for synthesis of vitamin A gave rise to biologically inactive or little active products owing to this retroionylidene rearrangement. This reaction proceeds when the starting compound contains a side chain which is fully conjugated with a double bond in a six-membered ring (e.g. equations 92 and 93). Such reactions are usually the dehydrations of carbinols by using acids, iodine, phenyl isocyanate etc. Therefore, the first really successful industrial synthesis of vitamin A which was developed includes the intermediate **274** incapable of undergoing the retroionylidene rearrangement[146].

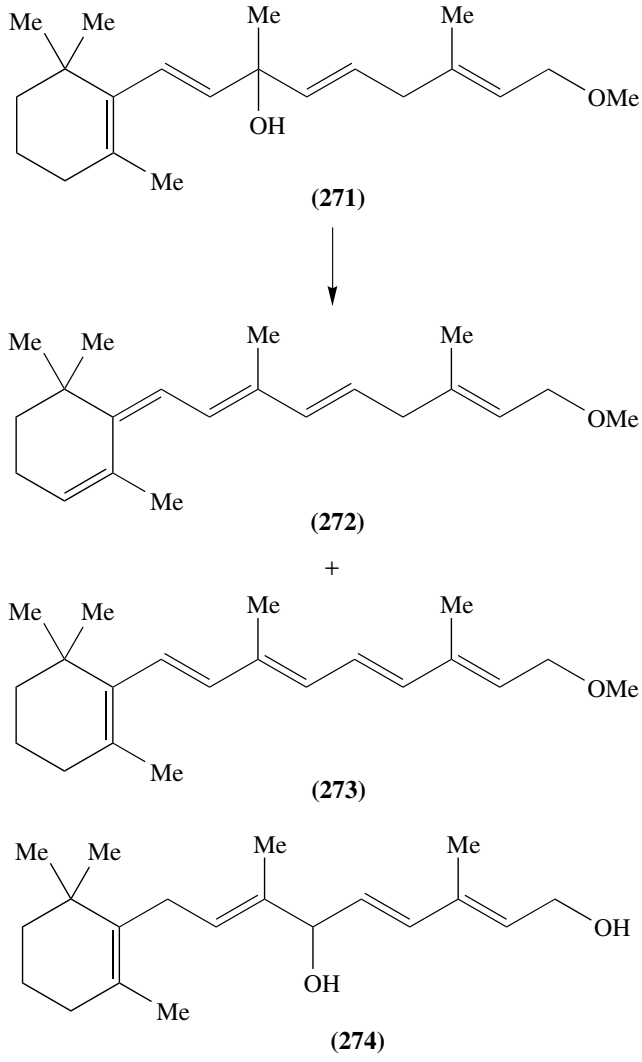
In that way, one of the principal approaches to the preparation of vitamin A derivatives consists of a selection of starting and/or intermediate structures which cannot be rearranged. In contrast, the object of another approach is to search the conditions of the reverse transformation, i.e. a rearrangement of retro-structures to the desirable ionylidene systems. Most frequently, basic reagents (e.g. NaOH, KOH, AcOK, pyridine, AlkONa etc.) are used for this purpose but an application of acid reagents is also known[146].

It is interesting that the retroionylidene rearrangement is suppressed when the compound to be dehydrated contains strong electron-withdrawing substituents (equations 94–96). Another method to prevent the retroionylidene rearrangement consists in the introduction of a carbon–carbon triple bond conjugated with the ring and retention of this bond up to the end step of synthesis[146] (e.g. equation 97).

E. Carbocation Rearrangements of Cyclodienes and Polyenes

Shubin and colleagues have described a series of rearrangements of unsaturated cyclic systems which occur via cationoid intermediates. Protonation of the triene **275** with

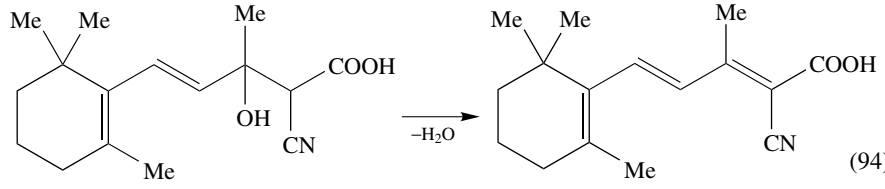
$HSO_3F–SO_2FCl$ at −120 °C proceeds to form the cycloheptatrienes **276** and **277** (equation 98)[151]. However, under the same conditions, as well as in the presence of H_3PO_4, the analogous propargyl substituted diene **278** affords the much more active vinyl cation **279**, thus changing the reaction pathway[152] (equation 99). The cyclic ketone **280** obtained was also obtained upon treatment of the tetraene **281** with H_3PO_4[152].



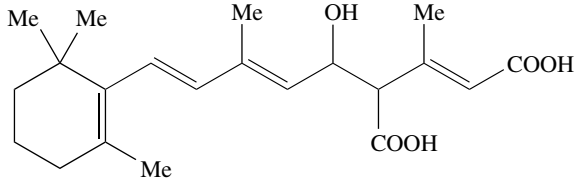
(93)

Introduction of methyl substituents into the propargyl fragment changes again the situation. The penta- and hexamethylated homologues **(282)** react with $FSO_3H–SO_2ClF–CD_2Cl_2$ (1 : 9 : 2, v/v) at −120 °C to form the vinyl cations **283** and then the allyl cations

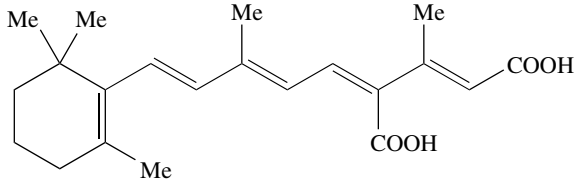
284 which transform to the cyclic cations **285** capable of a walk rearrangement. These cations, which can be produced also by action of H_3PO_4, undergo an electrocyclic ring opening to furnish the styrene derivatives **286** (equation 100)[153,154].

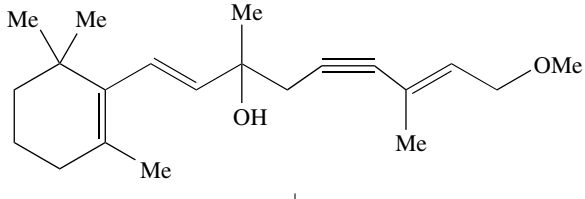


(94)

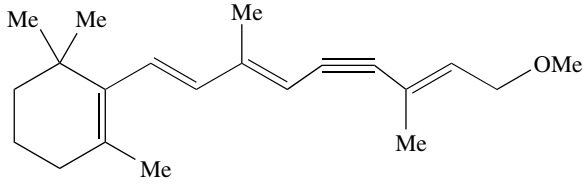


(95)



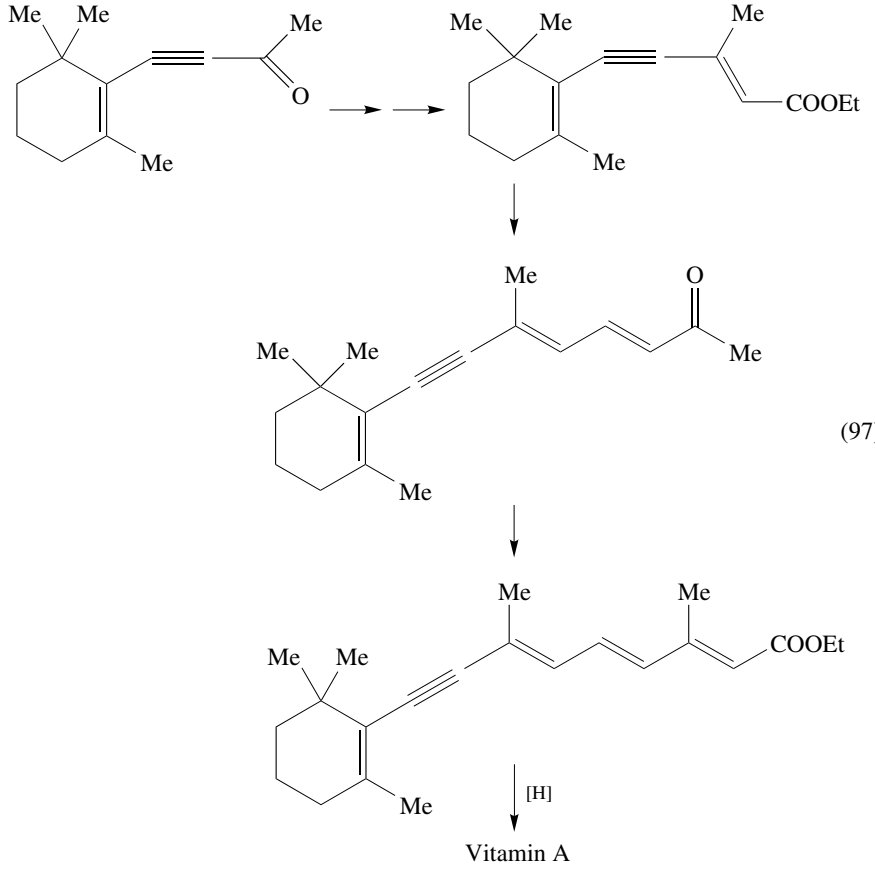


(96)



The polysubstituted benzenes **291** and **292** were also obtained by protonation of the cyclohexadiene derivatives **287**–**289** (equation 101)[155]. The migration of the propynyl

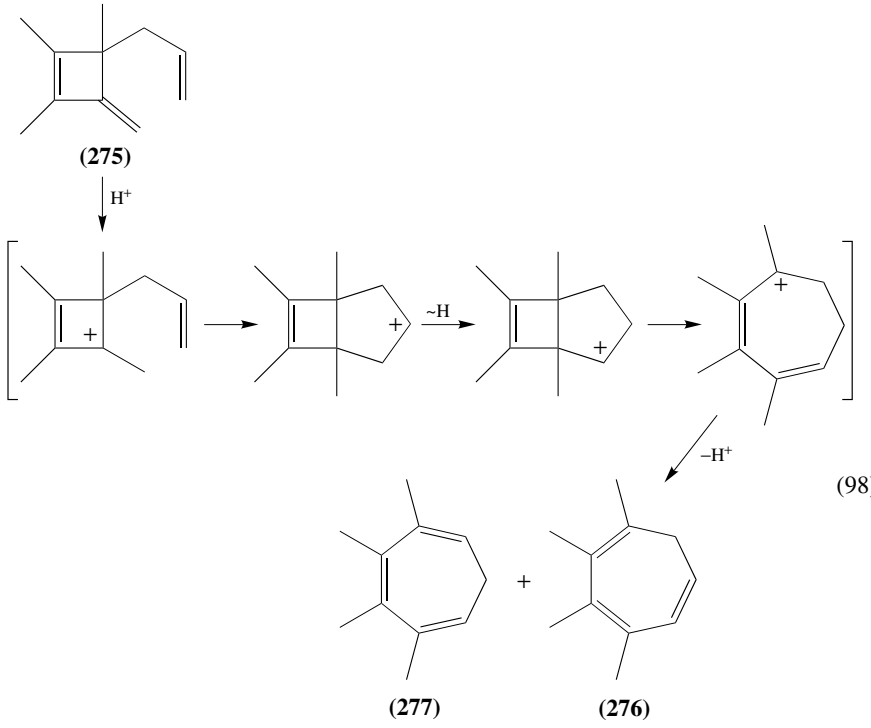
fragment in the cationoid intermediate **290** is assisted by subsequent aromatization. Analogous transformations take place during a dienone–phenol rearrangement including conjugated systems (see Section IV.A).



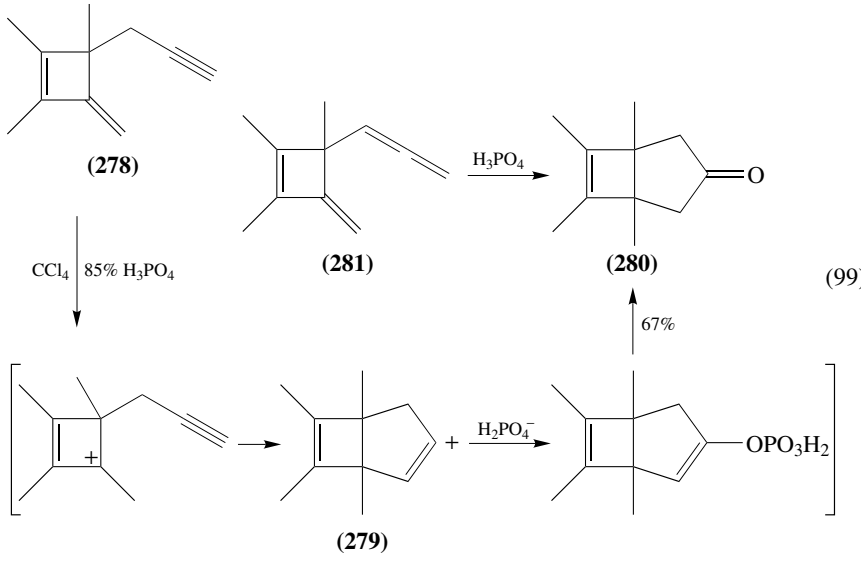
(97)

In the course of dolastane synthesis (the dolastanes are a group of marine diterpenes) interesting rearrangements catalyzed by Lewis acids were found. Treatment of the trienone **293** with excess (1.5 eq) ethylaluminum dichloride at low temperatures (−5 °C, 48 h) gave the tetracyclic enone **295** in 53% yield while the tricyclic dienone **296** (50%) was formed at room temperature (equation 102)[156]. It was assumed that both products can be derived from the common zwitterion **294** which undergoes intramolecular alkylation at low temperatures (path a) whereas an alkyl shift takes place at elevated temperatures (path b), followed by a 1,2-hydride shift (equation 102).

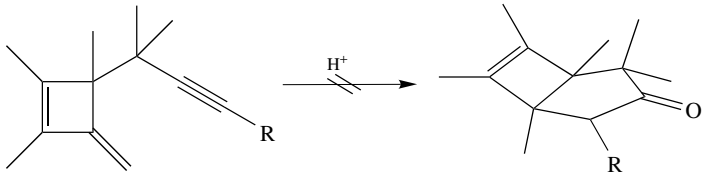
The rearrangement of the conjugated diene **298** to the non-conjugated one **299** was found in the course of the investigation of lauren-1-ene conversions in the presence of *p*-toluenesulfonic acid (equation 103)[157]. Tricyclic ketone **297** in cold benzene transforms slowly into diene **298**, but a further conversion to diene **299** occurs in refluxing benzene.


(275)
H+
~H
–H+
(277)
(276)

(98)

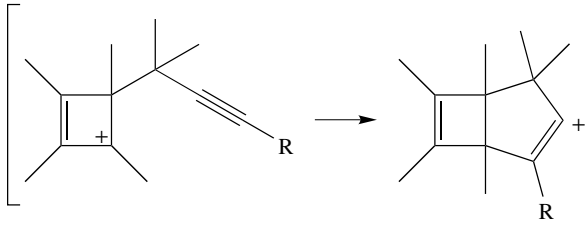

(278)
H3PO4
O
(281)
(280)
CCl4
85% H3PO4
67%
H2PO4–
OPO3H2
(279)

(99)



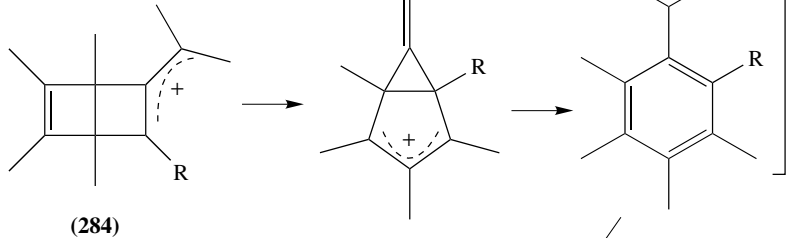
(282)

R = H, Me

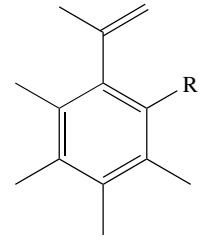


(283)

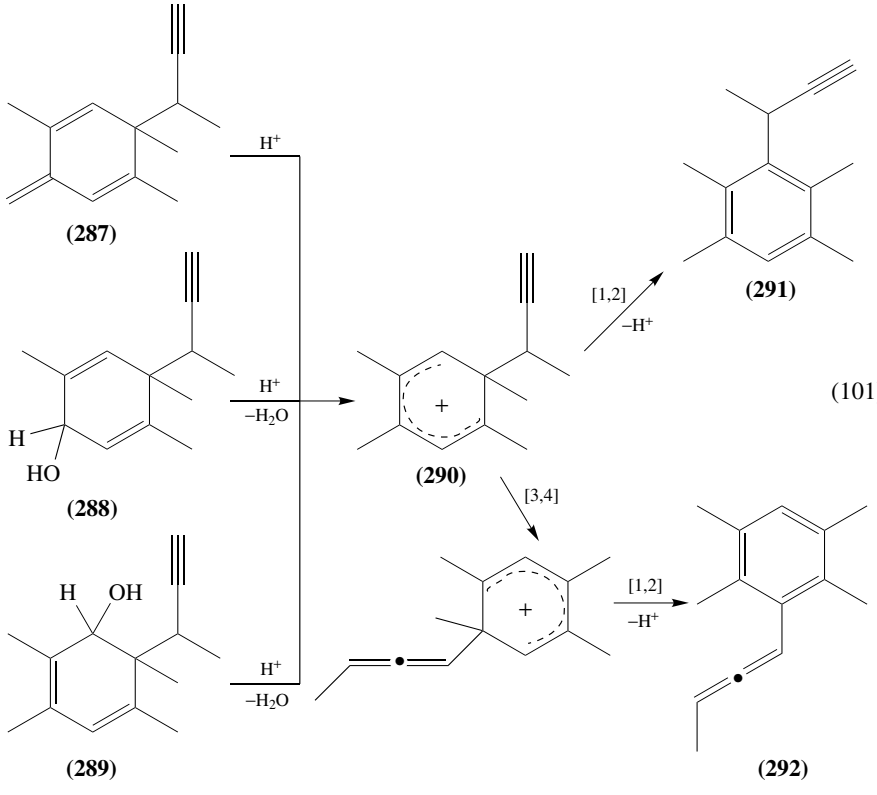
(100)



(284) **(285)**



(286)

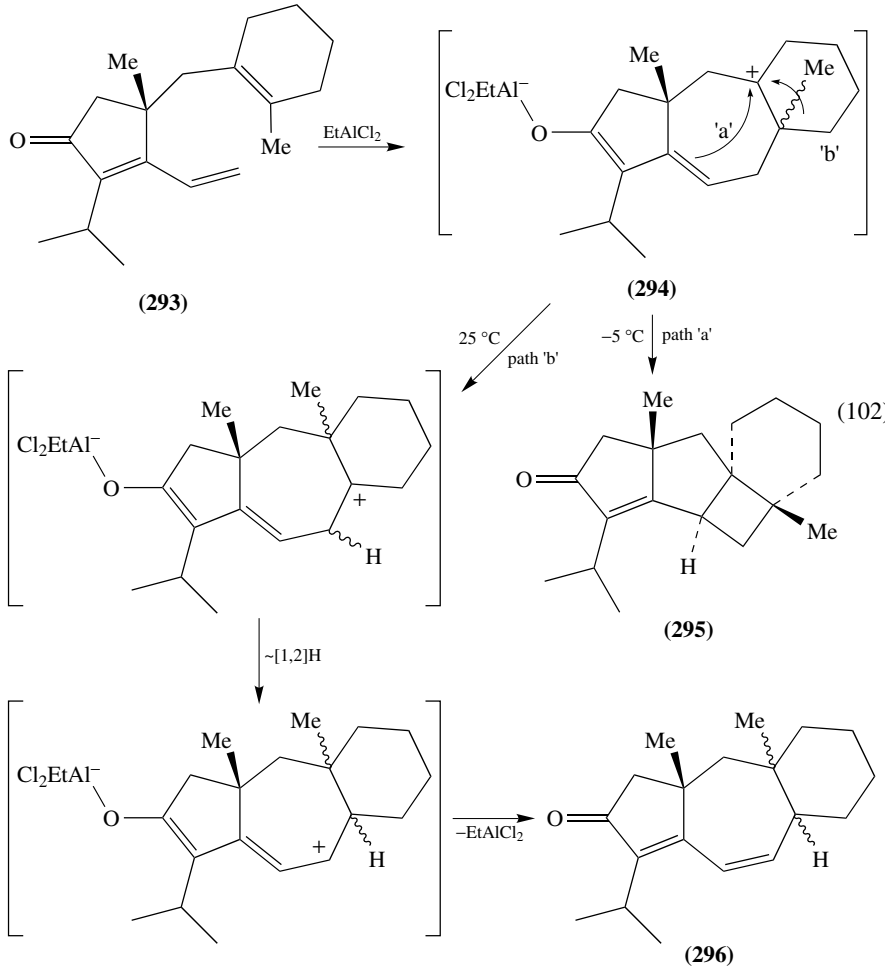


(101)

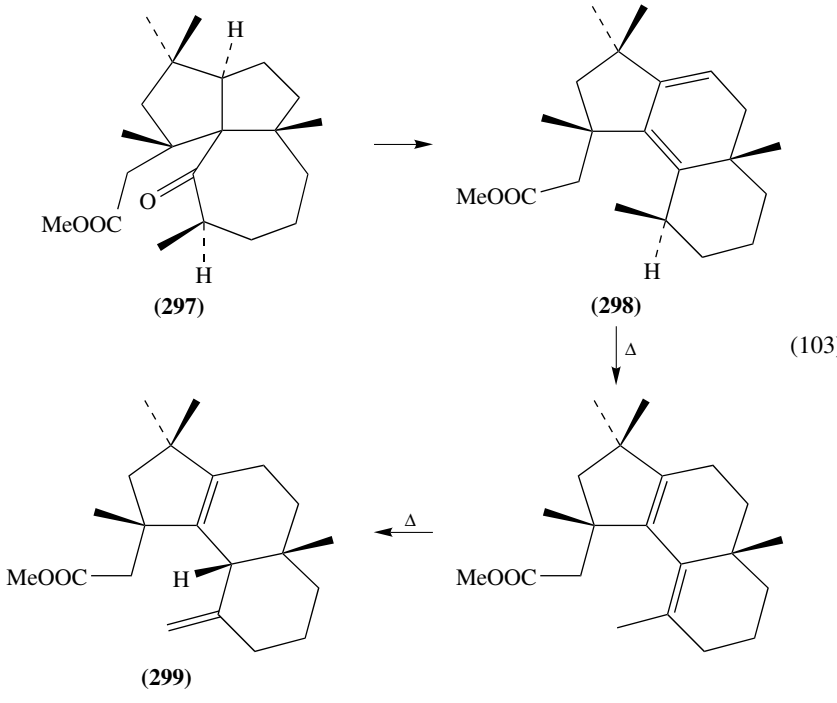
IV. REARRANGEMENTS OF NON-CONJUGATED DIENES AND POLYENES

A. Dienone–Phenol Rearrangements

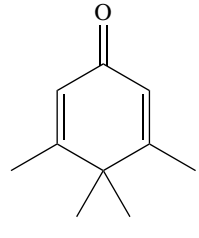
In general, the dienone–phenol rearrangements can be represented by acid-catalyzed transformation of the dienones **300** to phenols **301** which proceed with migration of group R and aromatization of the ring (equation 104). However, there are numerous variants of this reaction depending upon the structure of starting cyclic dienes and the nature of substituents as well as on the reaction conditions. These various pathways of the dienone–phenol rearrangement were already shown in one of the first reviews[158]. It is emphasized in Miller's very detailed survey[159] that both linearly-conjugated (*'ortho'*) 2,4-cyclohexadienones and cross-conjugated (*'para'*) 2,5-cyclohexadienones are incapable of undergoing the thermal rearrangements. In contrast, cyclohexadienones containing allyl substituents rearrange easily at relatively low temperatures (20–80 °C)[159]. It was shown that acid-catalyzed rearrangements of cyclohexadienones can occur, including [1,2]-, [1,3]-, [1,4]-, [1,5]-, [3,3]-, [3,4]- and [3,5]-migrations of carbon–carbon bonds[159].



The mechanism of dienone–phenol rearrangement was investigated very thoroughly in work of Vitullo and colleagues[160–164]. It was established that the first step is a protonation (or coordination with Lewis acid) of the carbonyl oxygen to form a cyclohexadienyl cation. The second step includes a migration of a group (aryl or alkyl) to the adjacent electron-deficient carbon atom. The subsequent elimination of proton leads to the stable phenol (equation 104). By using deuterium isotope effects it was shown[161,164] that the rate-determining step is unequivocally the migration, which occurs even in the presence of very high acid concentrations. The competitive migratory aptitudes established for various groups (e.g. Me, MeO) as well as the kinetic parameters of the dienone–phenol rearrangement depending on the acid concentration[162,163] confirm the reaction mechanism assumed.

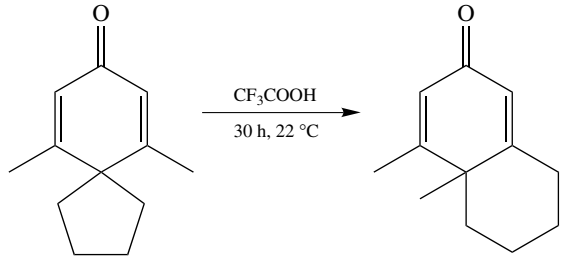


Besides aromatization, the energy resulting from relief of cyclic strain can be a driving force of the dienone–phenol rearrangement. Thus, it was reported that dienone **302** is



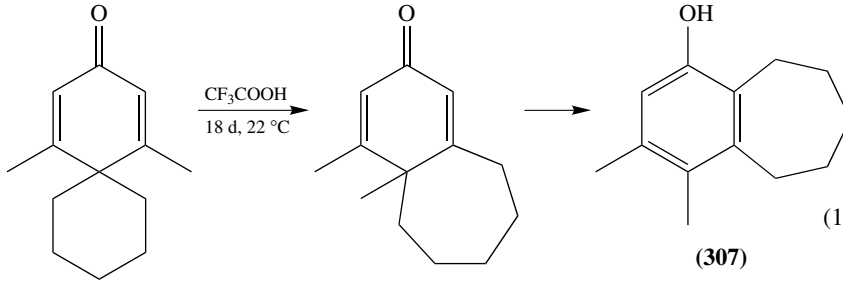
(302)

quite stable in trifluoroacetic acid, whereas the dienones **303** and **305** rearrange to give the ring-enlargened dienones **304** and **306** (equations 105 and 106). However, only product **306** is capable of undergoing a further transformation into the stable final phenol **307**[165].



(105)

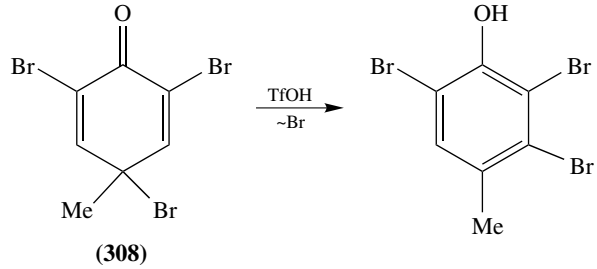
(303) **(304)**



(106)

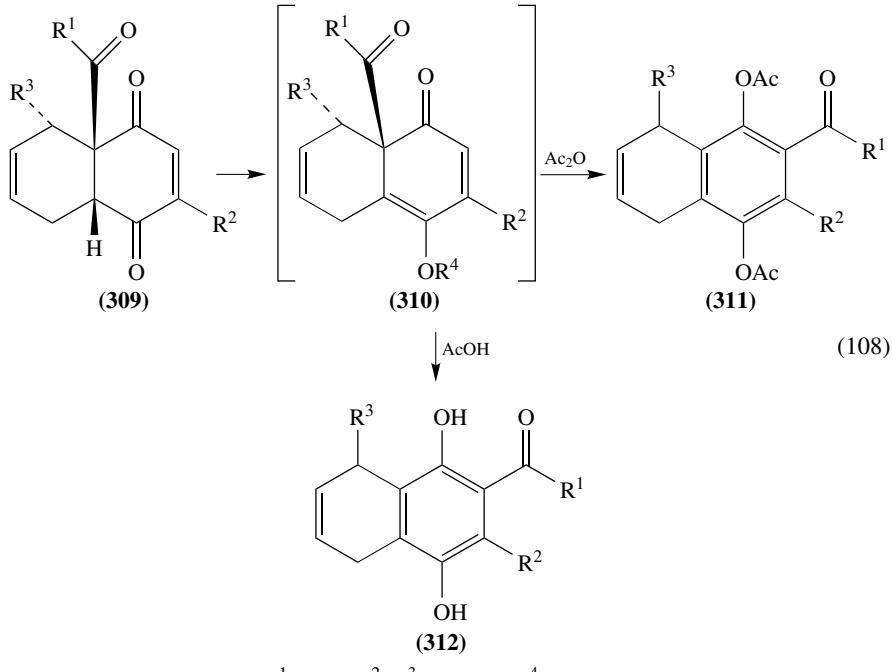
(305) **(306)** **(307)**

The dienone–phenol rearrangements can occur with transposition of other migrants. For example, the migration of a bromine atom rather than of a methyl group was observed upon treatment of the tribromodienone **308** with trifluoromethanesulfonic acid (equation 107)[166]. The migrations of angular acyl substituents were investigated by using the bicyclic Diels–Alder products **309** obtained from buta-1,3-diene and acetyl-1,4-benzoquinone[167–169]. In refluxing acetic anhydride adducts **309** gave 2-acetyl-5,8-dihydronaphthalenes **311**, whereas the corresponding 5,8-dihydro-1,4-dihydroxynaphthalenes **312** were formed upon refluxing in acetic acid (equation 108)[167]. It was shown that no 'retrodiene-recombination' pathway takes place during the isomerization, which is an intramolecular process with more than 90% regioselectivity. It corresponds to a [1,5]-acetyl shift in the enol **310** (R^4 = H) or in its acetate (**310**, R^4 = Ac).



(107)

(308)

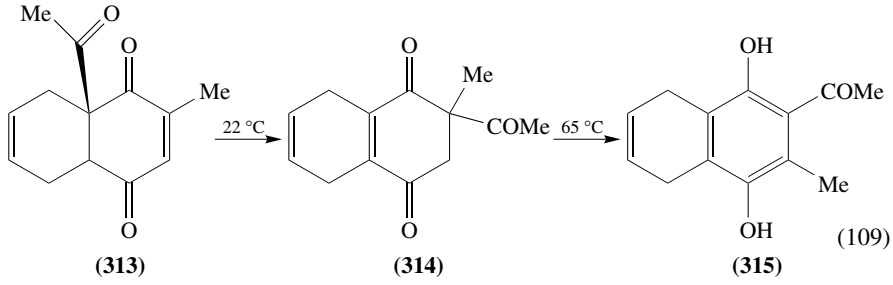


(108)

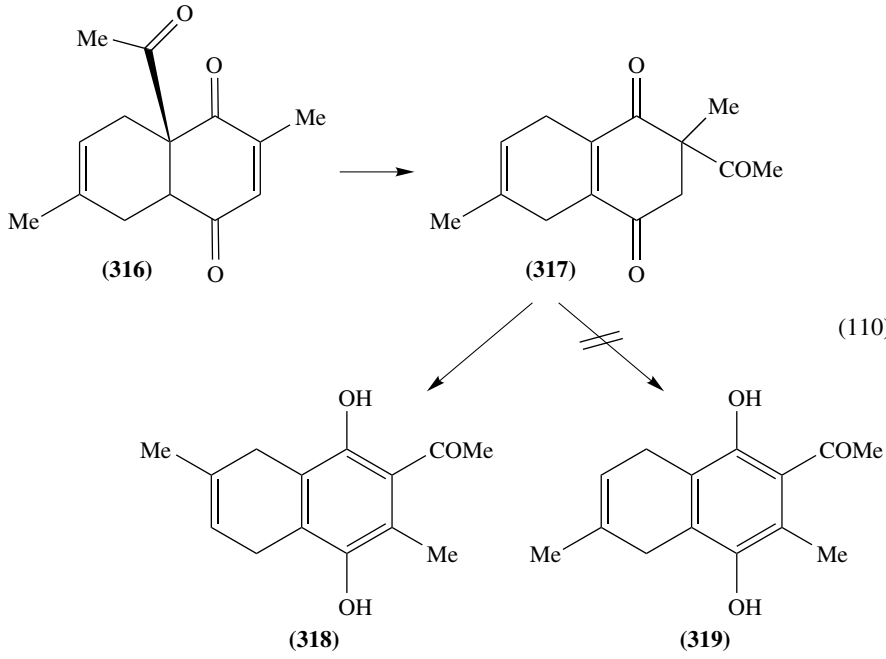
R^1 = Me; R^2, R^3 = H, Me; R^4 = H, Ac

The behavior of Diels–Alder adducts substituted at the C(3) position **(313)** is different because the substituent has to prevent an aromatization. Treatment of triketone **313** with pyridine–methanol (1 : 1, v/v) at 22 °C results in the expected [1,5]-acetyl shift and gives a good yield of the triketone **314**, which isomerizes smoothly when heated in the same medium at 65 °C to furnish dihydronaphthalene **315** (equation 109)[168]. Similar treatment of the triketone **316** affords the bicyclic product **318** rather than **319**, presumably via the intermediate **317** (equation 110)[168].

Acyl migrations in the acylbenzoquinone cycloadducts were also described elsewhere[170]. It was shown that the direction of acyl migrations in the cycloadducts obtained from dienes and 2-acetyl- as well as 2-benzoyl-1,4-benzoquinones depends on the substituents in diene fragment.

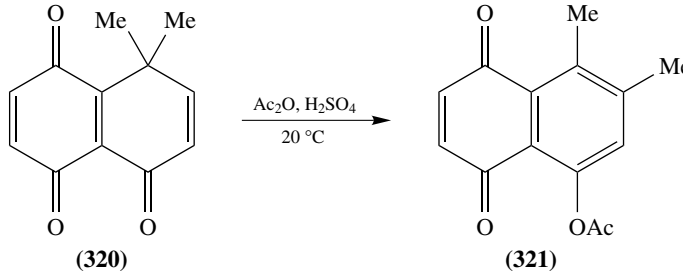


(109)



(110)

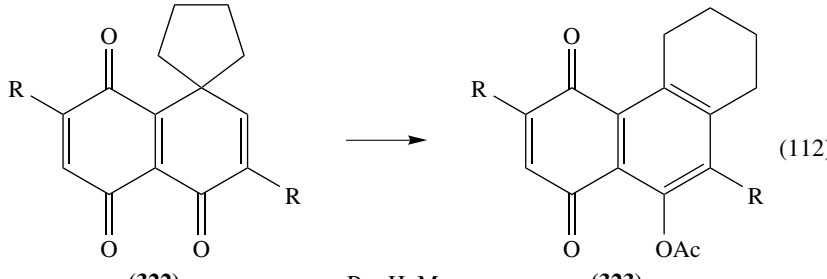
An attempt to carry out the Thiele–Winter acetoxylation of triketone **320** (Ac_2O, H_2SO_4, 20 °C) gave rise to the product of dienone–phenol rearrangement **321** in 83% yield (equation 111)[171]. This reaction was claimed to be a convenient entry into the tetrahydrophenanthrene-1,4-quinone **323**, starting from the spiro(cyclopentanonaphthalene) triones **322** (equation 112). The rearrangements of cyclohexadiene systems can also be catalyzed by Lewis acids; for example, under metalation conditions with $HgCl_2$ (HgO, $NaHCO_3$, THF, 20–45 °C) products **324** and **325** are formed in a 5 : 1 ratio (equation 113)[172].



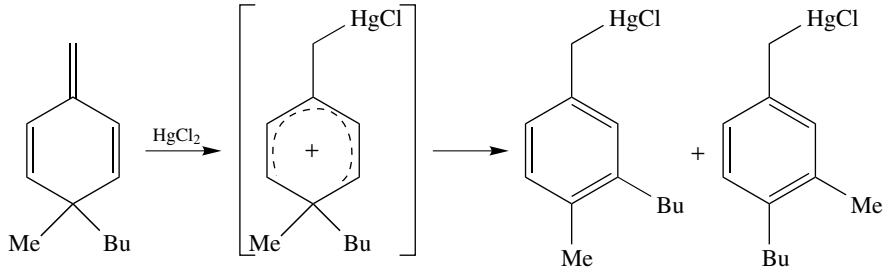
(111)

In contrast to well investigated acid-catalyzed rearrangements of the cross-conjugated cyclohexadienones mentioned above, the isomerizations of linearly-conjugated cyclohexadienones have not received much attention, except for special cases in which allyl groups migrate. Acid-catalyzed rearrangements of conjugated 2,4-cyclohexadienones can occur via [1,2]- and [1,5]-shifts depending on the nature of the migrant. Thus, dienone **326** isomerizes by a [1,2]-shift of a methyl group (equation 114) whereas the dienone **327**

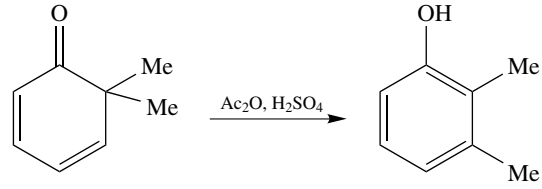
transforms into 2-benzyl-6-methylphenol **328** (AcOH + 1% H_2SO_4, or aqueous dioxane + HCl, 25 °C, 20 min) (equation 115)[173]. The migration of a benzyl group to the C(2) position can proceed even if the latter is occupied by a *tert*-butyl group. The rearrangement of the dienone **329** (in 2N HCl in 80% aqueous methanol) results in partial elimination of the *tert*-butyl group to provide 2-benzyl-6-methylphenol **328** and 5-benzyl-2-*tert*-butyl-6-methylphenol **330** in a 5 : 7 ratio (equation 116)[173].



(322) **(323)** (112)



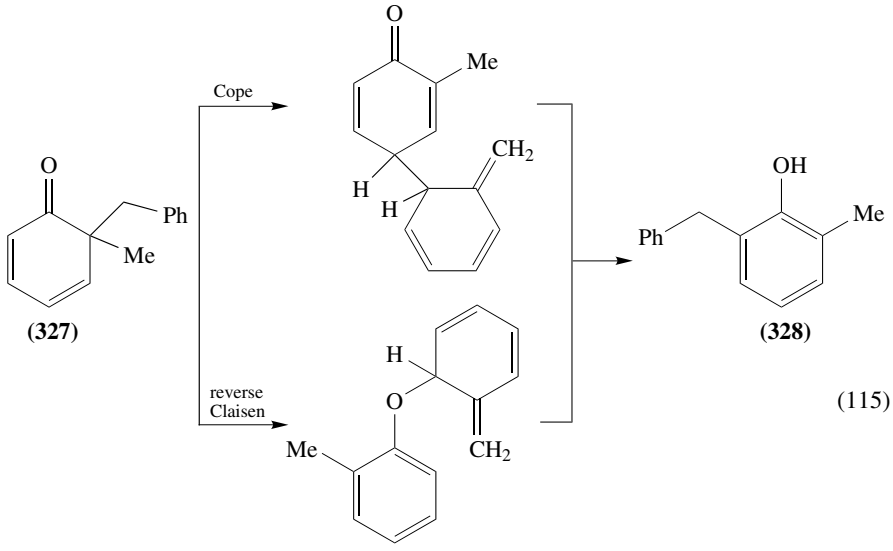
(324) **(325)** (113)



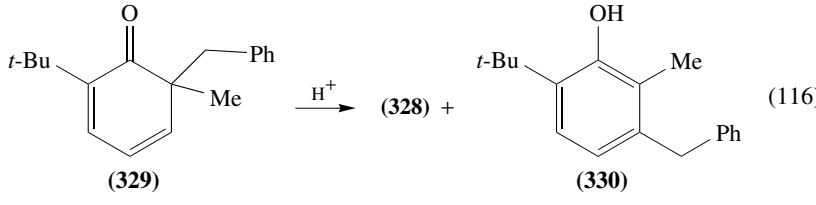
(326) (114)

Various mechanisms are discussed for the migration of a benzyl group including, e.g., a two-stage Cope or reverse Claisen rearrangement as well as a preference of direct [1,5]-shift over successive Wagner–Meerwein migrations (equation 115)[173].

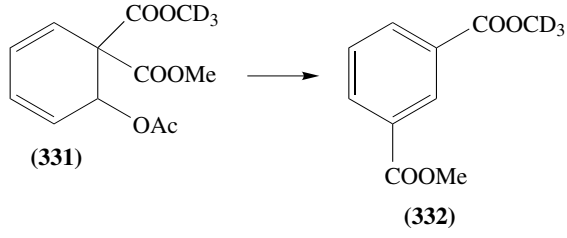
Besides catalyzed rearrangements, thermal isomerizations in a series of linearly-conjugated cyclohexadiene systems, which are accompanied by migrations of various groups having a complex structure, are also known. The thermal sigmatropic migrations of methoxycarbonyl groups proceed upon pyrolysis of the acetoxydiene **331** to give dimethyl isophthalate **332** without a change in the isotope distribution (equation 117)[174]. This excluded a radical-chain mechanism and confirms the complete intramolecularity of the rearrangement. By using NMR spectral analysis the behavior of the deuterium labeled



(115)



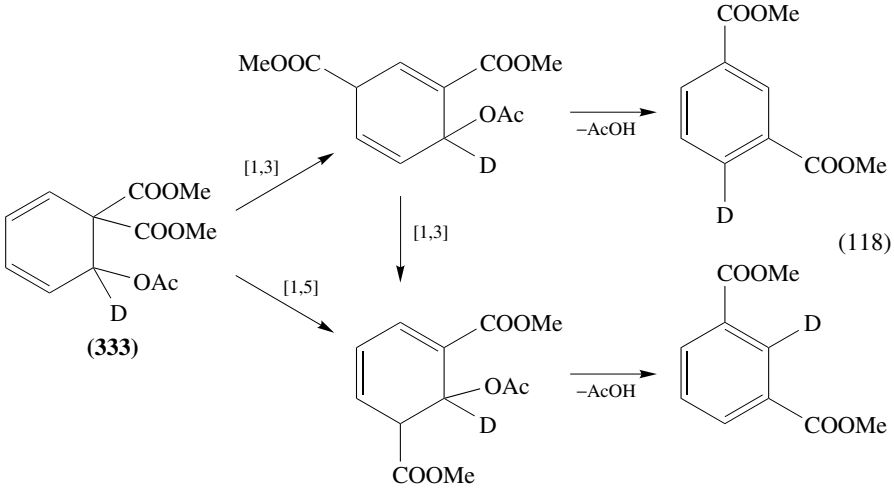
(116)

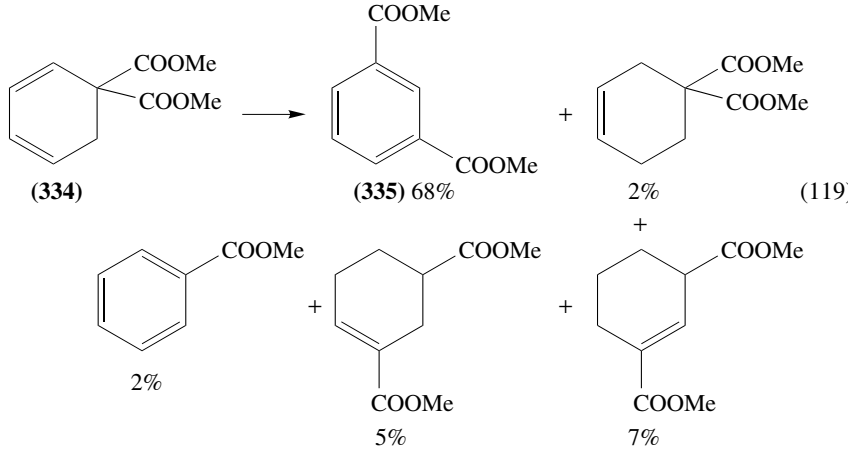


(117)

triester **333** was investigated in order to distinguish two possible pathways: (1) direct [1,3]-methoxycarbonyl migration, and (2) direct [1,5]- or two successive [1,3]-shifts. Path (1), which involves a single [1,3]-shift, was excluded in this way, whereas the [1,5]-shift mechanism was found to fit the observations without special assumptions (equation 118).

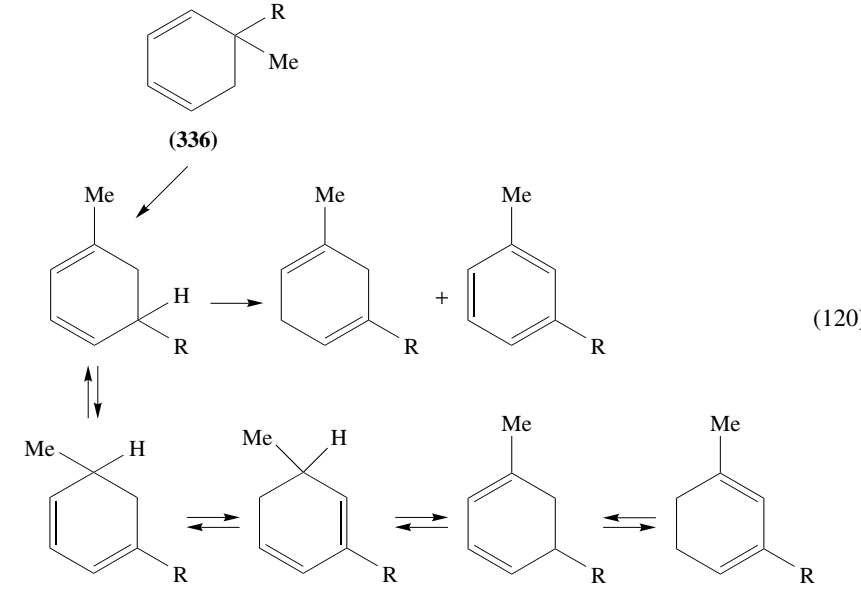
The presence of an acetoxy group is not a necessary condition for the methoxycarbonyl rearrangement. Thus, the pyrolysis of diene **334** (300–320 °C, 1 h, 97% conversion) gave the diester **335** as the major product (equation 119)[174]. Dicarboxylates like **334** were suggested to be the intermediates in pyrolysis (420 °C, flow system) of dimethyl and diethyl 2-acetoxycyclohex-3-ene 1,1-dicarboxylates[175].



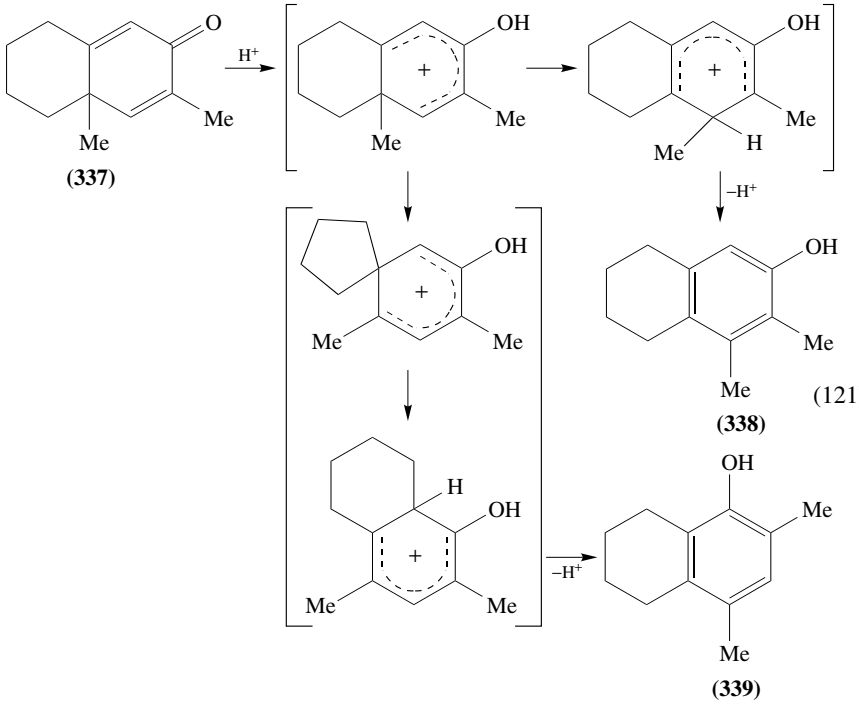


The comparative migratory aptitudes of formyl, acetyl and methoxycarbonyl groups relative to hydrogen atom in thermal [1,5]-sigmatropic shifts were studied by measuring the rearrangement rates of 1-R-1-methylcyclohexa-2,4-dienes **336**[176]. In comparison with 1-methylcyclohexa-2,4-diene (**336**, R = H) it was found that a formyl group migrates faster than hydrogen by more than two orders of magnitude, a methoxycarbonyl group is slower by a factor of about 70 and an acetyl group has a comparable migration aptitude to hydrogen (equation 120)[176].

Different directions in rearrangement of the same precursor were shown by using the bicyclic dienones **337** (equation 121)[177]. The formation of two different products, **338** by methyl migration and **339** by a stepwise cyclohexane ring migration, is considered confirmation of a multistage mechanism.

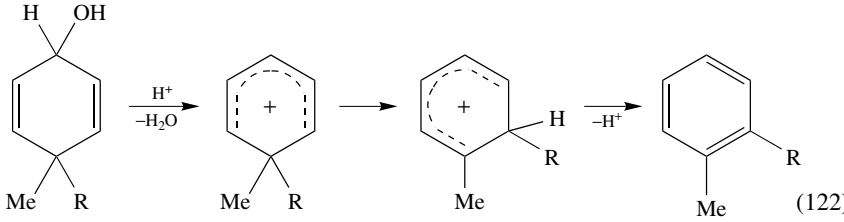


(120)



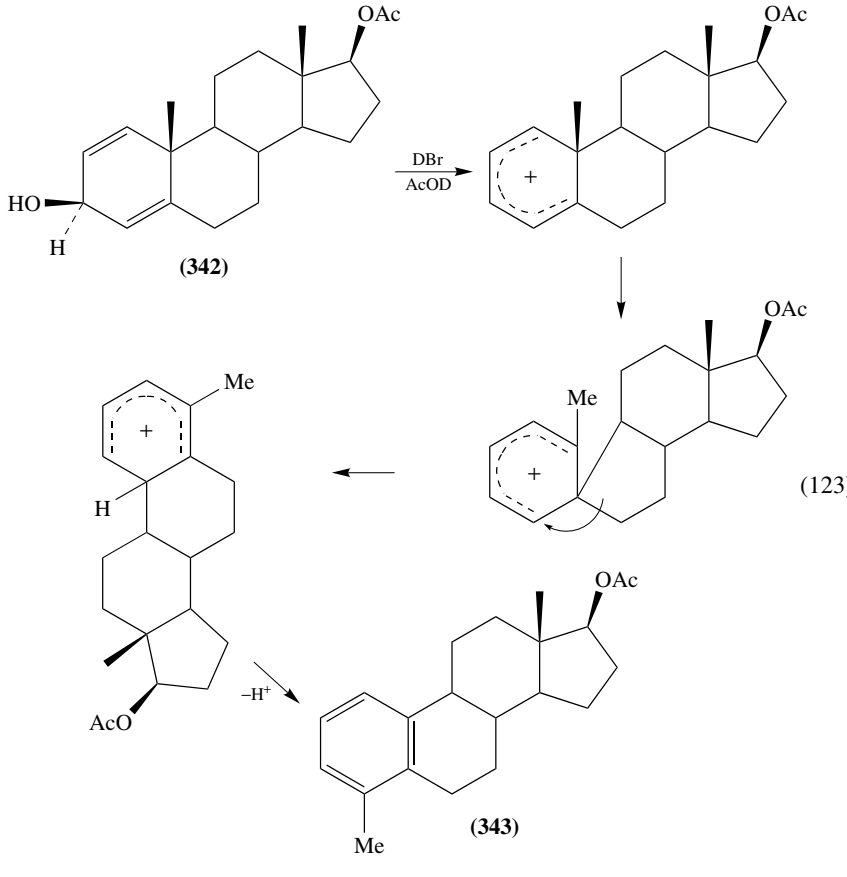
(121)

Besides the dienone–phenol rearrangement there are also several types of a related dienol–benzene rearrangement in which the intermediate cyclohexenyl cation **341** is generated from cyclohexadienols **340** by elimination of the appropriate nucleofuge, e.g. hydroxy group, rather than by addition of an electrophile as above (equation 122)[178]. Such nucleofuge can also be a chlorine atom (see also equation 101). The mechanism of the dienol–benzene rearrangement in a series of steroides was studied by using ^{2}H NMR spectroscopy during the transformations of the steroid alcohol **342** (equation 123)[179]. The



(340) **(341)** (122)

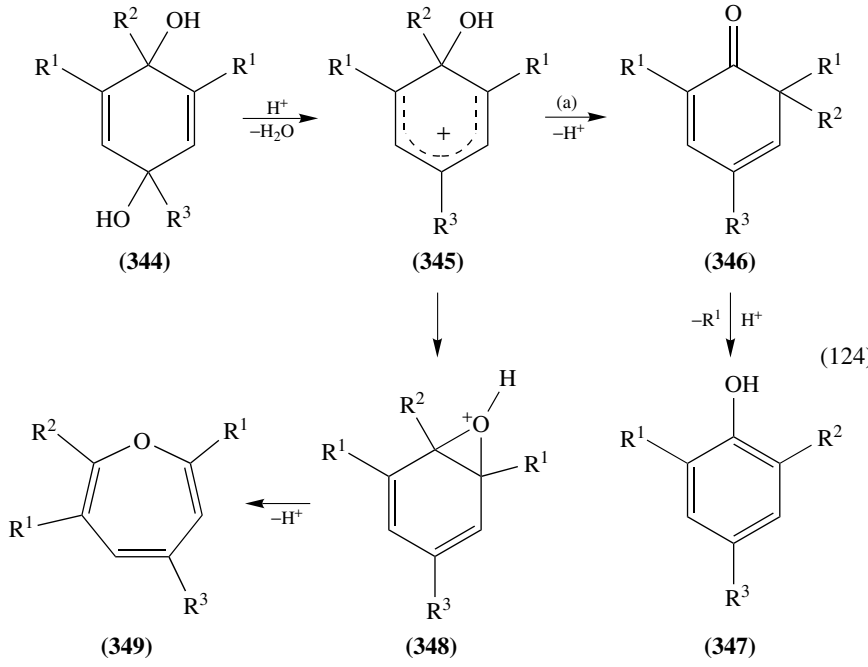
R = Me, CCl_3



(342) (123) **(343)**

absence of a deuterium label in the aliphatic fragment of the final structure **343** suggests that the rearrangement proceeds by a cleavage of the C(3)−O bond rather than through a prior dehydration to 1,3,5(6)-triene and subsequent reprotonation[179].

A related dienediol–phenol rearrangement which can occur by different pathways was reported as a new method for synthesis of the oxepine system[180]. Protonation of the starting diol **344** produces a cation **345** which can follow 'normal' dienone–phenol rearrangement (path a) when the substituents R^2 = Me, Ph and R^1 = *t*-Bu are eliminated in the step **346** → **347**. However, when R^1 = *t*-Bu and R^2 is a substituted phenyl which decreases the nucleophility, the cationoid intermediate **345** cyclizes to the oxonium ion **348** (path b) which then undergoes deprotonation to give the oxepine **349** (equation 124)[180].

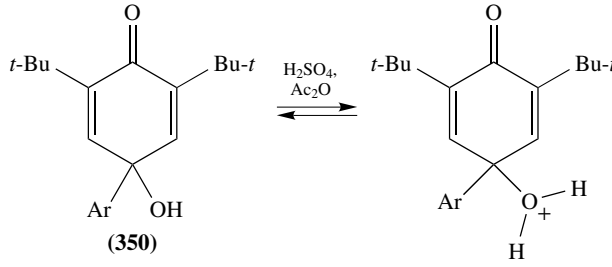


(124)

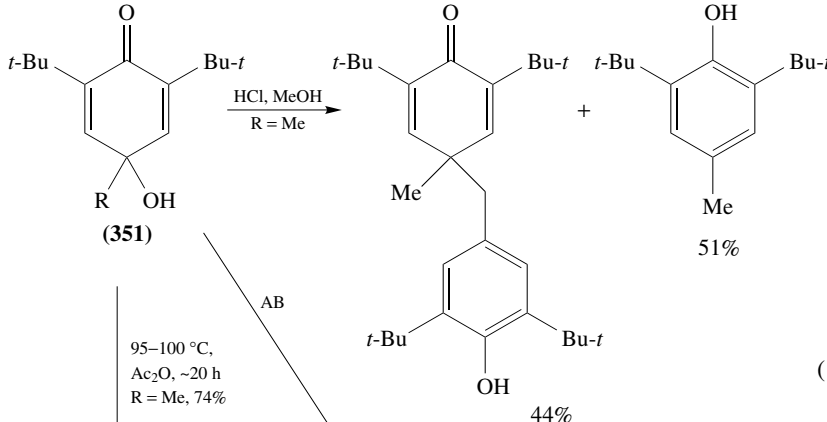
R^1 = Me, Ph, *t*-Bu; R^2 = Me, Ph, Ar; R^3 = *t*-Bu, Ph, Ar

Various transformations take place upon interaction of acid reagents with hydroxycyclohexadienones containing both hydroxy and carbonyl groups. Thus, treatment of compound **350** with an $Ac_2O + H_2SO_4$ mixture leads to elimination of the OH group and substitution of a *tert*-butyl moiety (equation 125)[181]. An analogous behavior of 4-alkyl-substituted dienones **351** in the presence of Ac_2O or other acidic reagents was described a few year later (equation 126)[182].

A two-step transformation of conjugated dienes into non-conjugated ones was proposed for the synthesis of the difficult to-obtain lapachol **(355)** (a member of a class of antimalarial agents having an activity against the Walker carcinosarcoma 256) from the more available isolapachol **352**[183]. This method consists in an oxidative cyclization of isolapachol **352** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to form a mixture of the products **353** and **354** (equation 127). Treatment of this mixture with dilute acid in

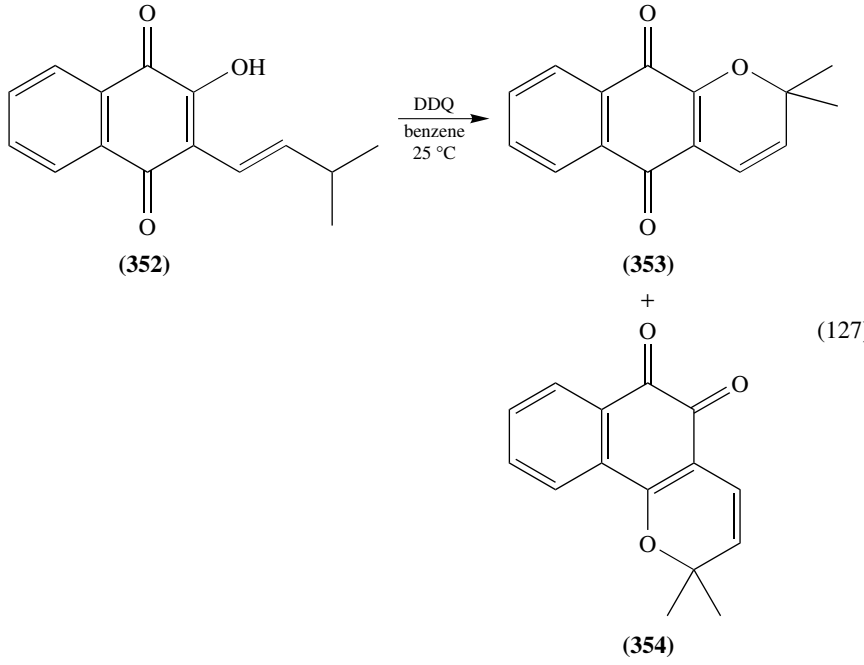


(125)



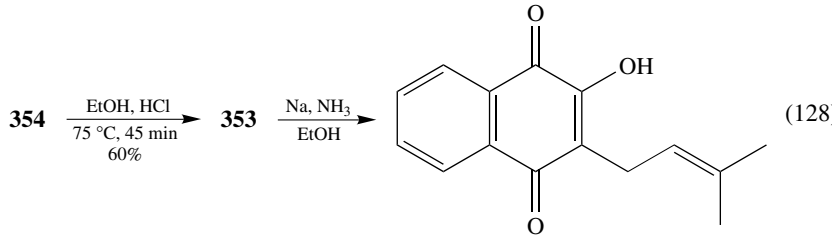
(126)

R = Me, Et, *i*-Pr, *t*-Bu, $(CH_2)_2CH_2OH$



(352) **(353)** **(354)** (127)

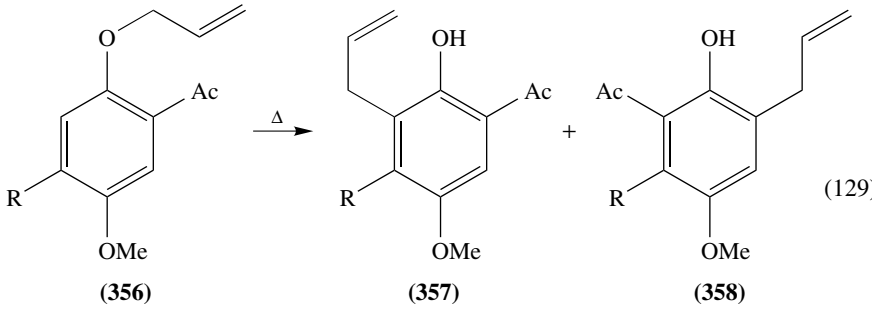
ethanol leads to '*ortho–para*'-rearrangement to afford 60% yield of the single product **353**. The ring opening of the α-pyrane fragment by Na in NH_3 gives the target lapachol in *ca* 20% yield (equation 128)[183].



(355) (128)

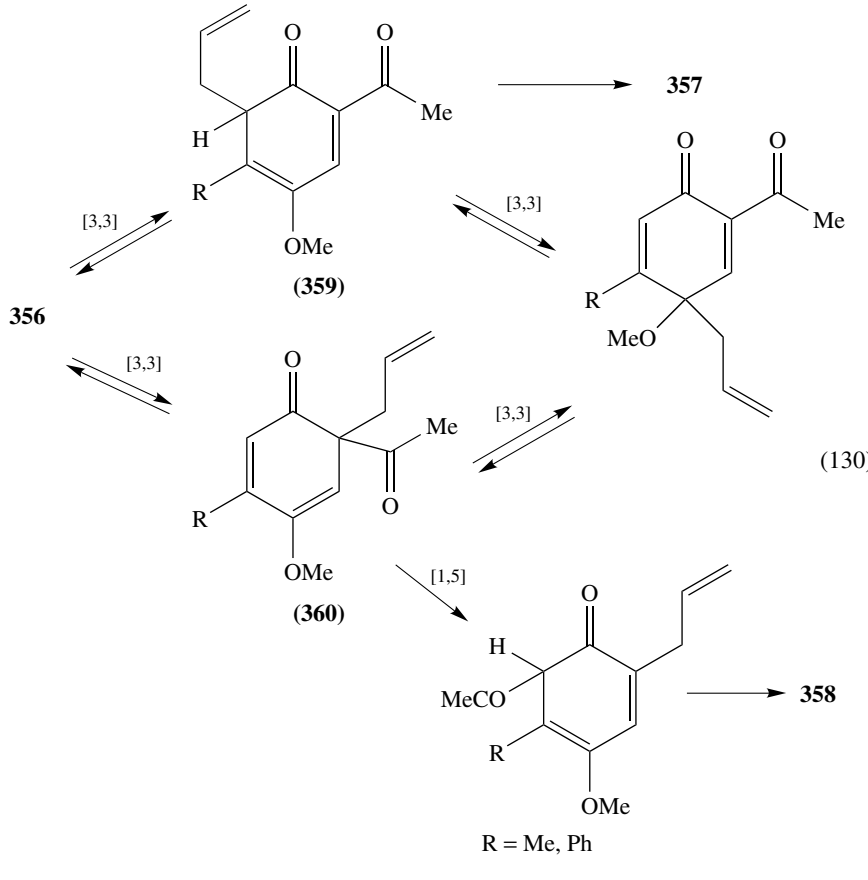
The competition of Claisen rearrangement and [1,5]-acetyl shift upon thermal treatment of allyl aryl ether **356** resulted in a mixture of the expected Claisen product **357** and its isomer **358** (equation 129)[184]. It was assumed that the usual Claisen rearrangement (Section IV.E.1) resulted in an equilibrium with the intermediates of successive [3,3]-sigmatropic shifts. The cyclohexa-2,4-dienones **359** and **360** formed leave this equilibrium cycle due to enolization to form the Claisen product **357** or because of [1,5]-shift followed by enolization give the unexpected product **358** (equation 130).

Unusual examples of the dienone–phenol rearrangement include the reactions of 1,4-dihydrosilabenzene **361** which rearranges in two directions upon treatment with BCl_3 or during purification on silica gel (equation 131)[185].



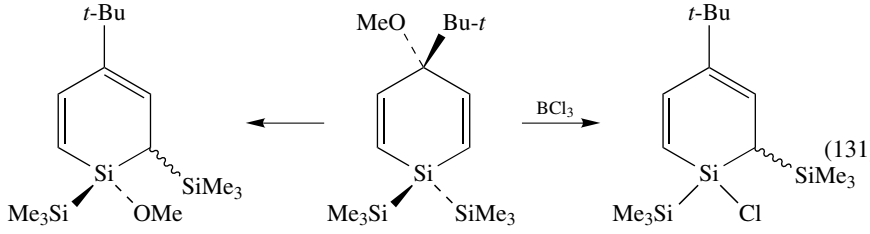
(356) (357) (358) (129)

(a) R = Ph
(b) R = Me



(130)

Finally, it should be noted that there are various reactions which can be called 'phenol–dienone' rearrangements. They proceed upon halogenation, nitration and alkylation of phenols as well as in the course of radical reactions of phenols[186].

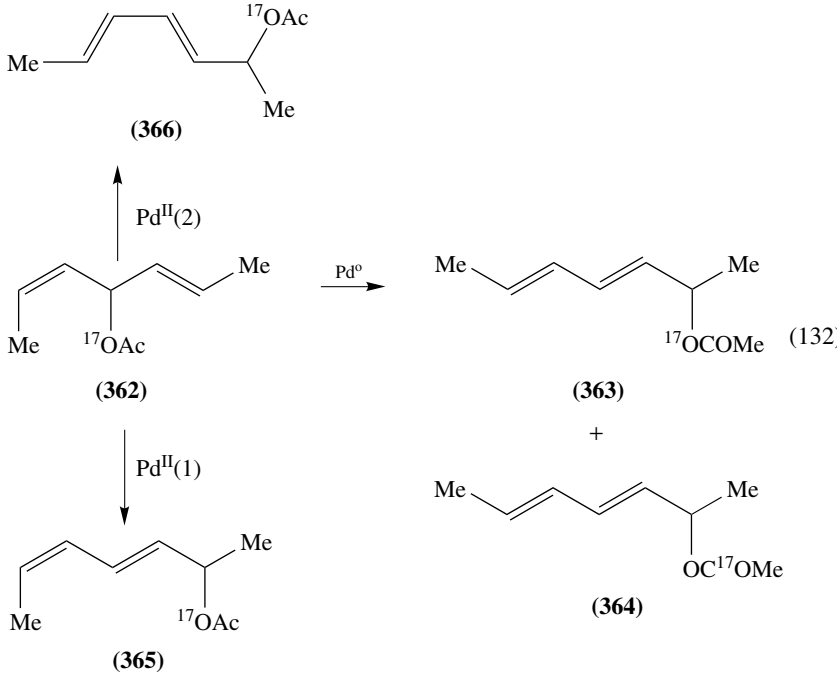


(131)

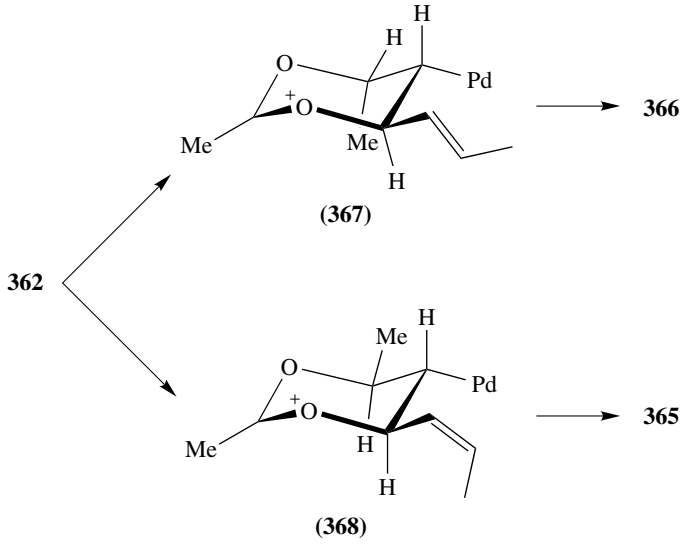
(361)

B. Carbocation Reactions of Non-conjugated Dienes

The mechanism of the catalysis in the rearrangements of 4-acetoxyhepta-2,5-dienes was investigated by using the ^{17}O-labeled acetate **362** in the presence of Pd^0 and Pd^{II} catalysts[187]. It was shown by ^{17}O NMR spectroscopy that the reaction catalyzed by Pd^0 affords a 1 : 1 mixture of the dienes **363** and **364** which results from the Pd-coordinated pentadienyl species intermediate and ^{17}O-acetate (equation 132). By using two Pd^{II}-catalysts, viz. $(RCN)_2PdCl_2$ (R = Me, Ph) [Pd^{II}(1)] and $(Ph_3P)_4Pd$ [i.e. Pd^{II}(2)], two rearrangement products **365** and **366**, respectively, were obtained. The heterocyclic 1,3-dioxanium cations **367** and **368** were assumed to be intermediates of these isomerizations (equation 133).



(132)



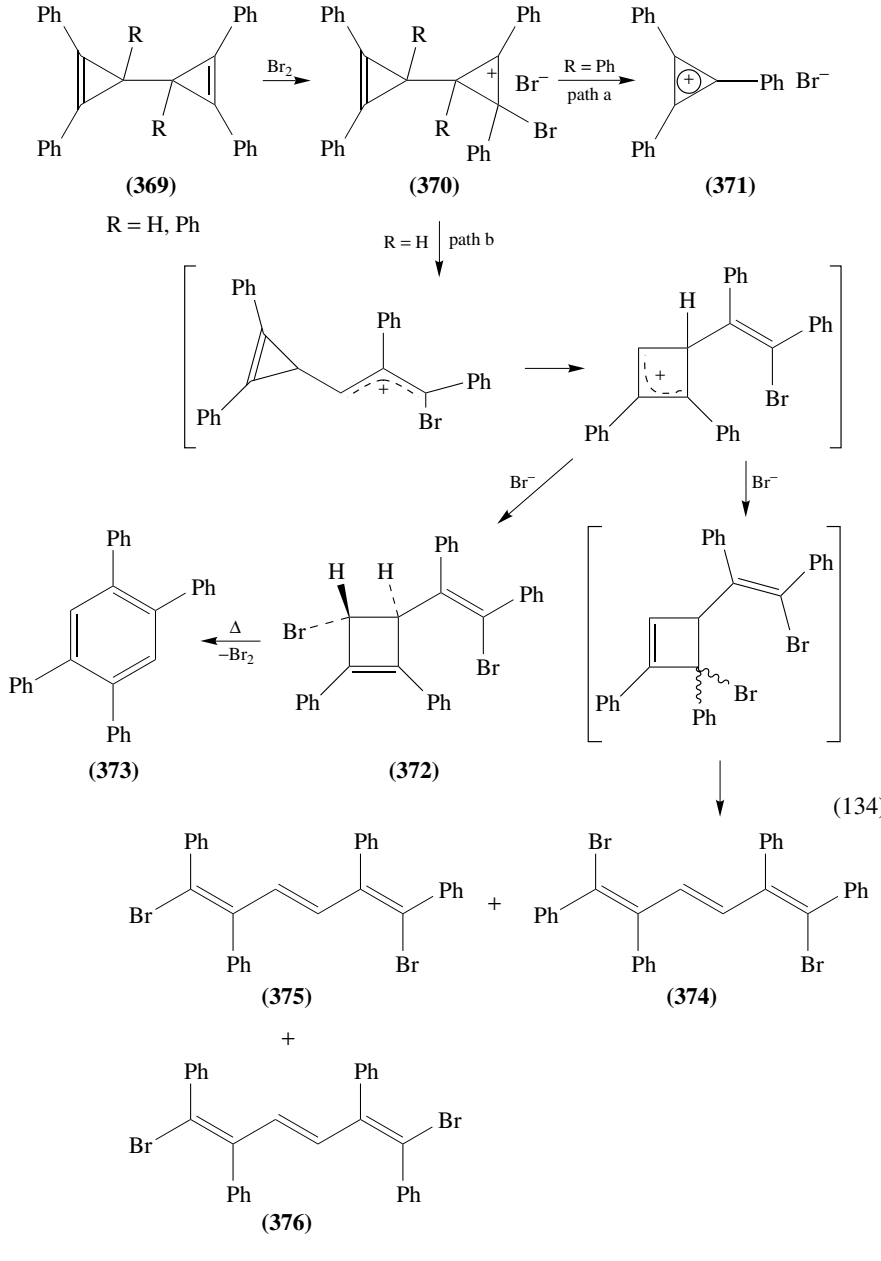
(133)

Bromination of bicyclopropenyl system **369** at ambient temperature in absolute $CHCl_3$ leads either to diene **372** (15%) and trienes **374–376** (15%, 35% and 10%, respectively) when R = H, or to the stable cyclopropenium salt **371** (95%) when R = Ph (equation 134)[188]. The electrophilic attack of bromine on compounds **369** creates the cationoid intermediates **370** which undergo either fragmentation to salt **371** (path a) or an electrocyclic ring opening (path b). When diene **372** is heated at about 150 °C in the solid state it rearranges to 1,2,3,5-tetraphenylbenzene **373** with concomitant loss of bromine.

Similarly, the bromination of 2-bromobenzobarrelene **377** gives a mixture of tribromo products which were separated by column chromatography (equation 135)[189]. The major product **378** was isolated in 58% yield (whereas the combined yield of the rest of products was 37%). By using ^1H and ^{13}C NMR it was shown that bromine was added to the unsubstituted double bond only.

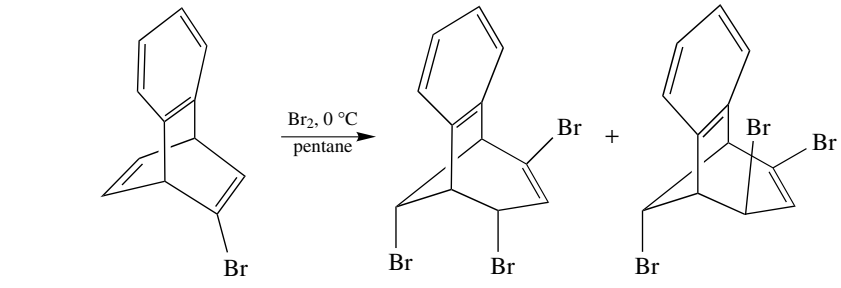
The iodination of *cis*-bicyclo[4.3.0]nona-3,7-diene **379** in CCl_4 is accompanied by a regio- and stereospecific transannular cyclization (see below) to form 40% of the diiodobrexane **380** which can be transformed into brexa-4,8-diene **381** (*t*-BuOK, DMSO, 120 °C, 12 h, 70%) (equation 136)[190]. The mechanism of this rearrangement was studied by reacting diene **382** with the deuteriated superacid $DSO_3F–SO_2FCl$ (−115 °C) to afford the brendane derivatives[191]. According to the ^1H NMR data the protonation of **382** gives a mixture of ions **383** and **384** (equation 137). The quenching of the acidic mixture with a $MeOH–Et_2O$ (2.5 : 1, v/v) mixture affords a mixture of diene **385** and methyl ether **386** in a 1 : 10 ratio (equation 138)[191].

Ionic hydrogenation of the same bicyclic diene **382** by Et_3SiH in the presence of CF_3COOH at room temperature or at 80 °C via ions **387** and **388** is accompanied by transannular cyclizations (equation 139)[192]. The behavior of diene **382** under Ritter reaction conditions (MeCN, H_2SO_4) reveals new possibilities to control the transannular cyclizations (equation 140)[193]. Depending on the sulfuric acid concentration, the reaction temperature and the presence of a nucleophilic solvent, these transformations can be directed to the formation of either the bicyclic amides **389** and **390** having the precursor structure or the tricyclic products **391**[193].

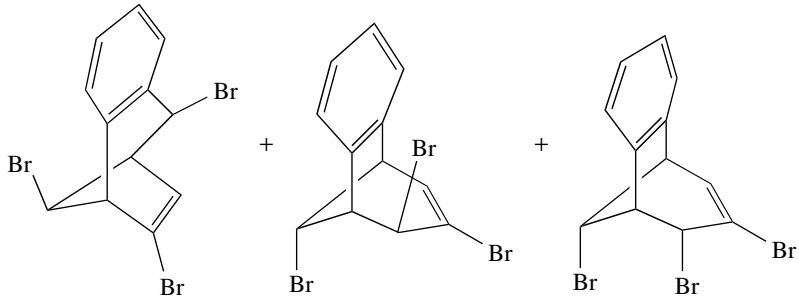


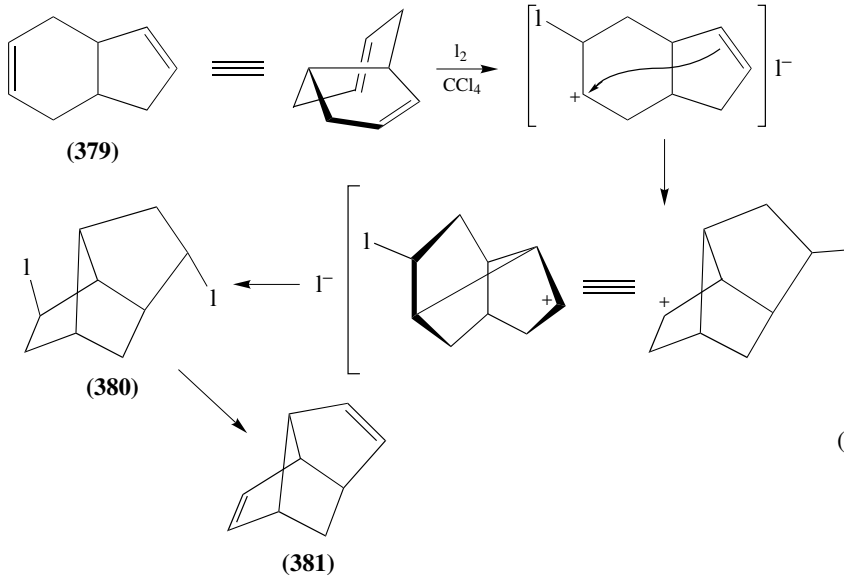
Under Ritter reaction conditions the cycloocta-1,5-diene **392** is prone to undergo transannular cyclization into *cis*-bicyclo[3.3.0]octane derivatives (equation 141)[194]. Norbornadiene **393** and 5-ethylidenenorbornene **394** rearrange under the same conditions to

afford the polycyclic amides (equations 142 and 143)[194]. Brexadiene **381** undergoes Wagner–Meerwein rearrangement under Ritter reaction conditions (MeCN, 20 °C, 1.5 h, 50–60%) (equation 144)[195].

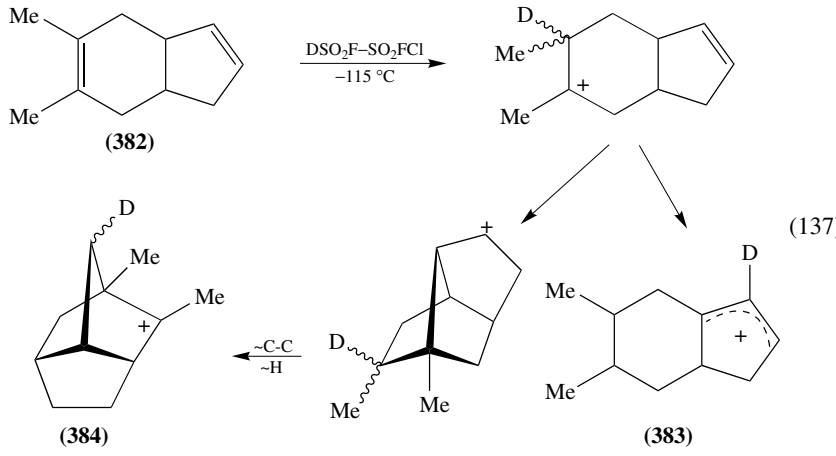


(377) **(378)** (135)

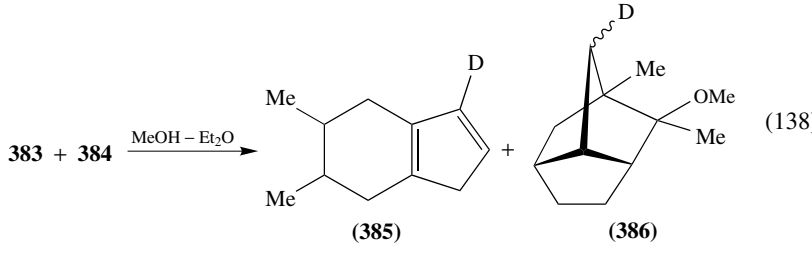




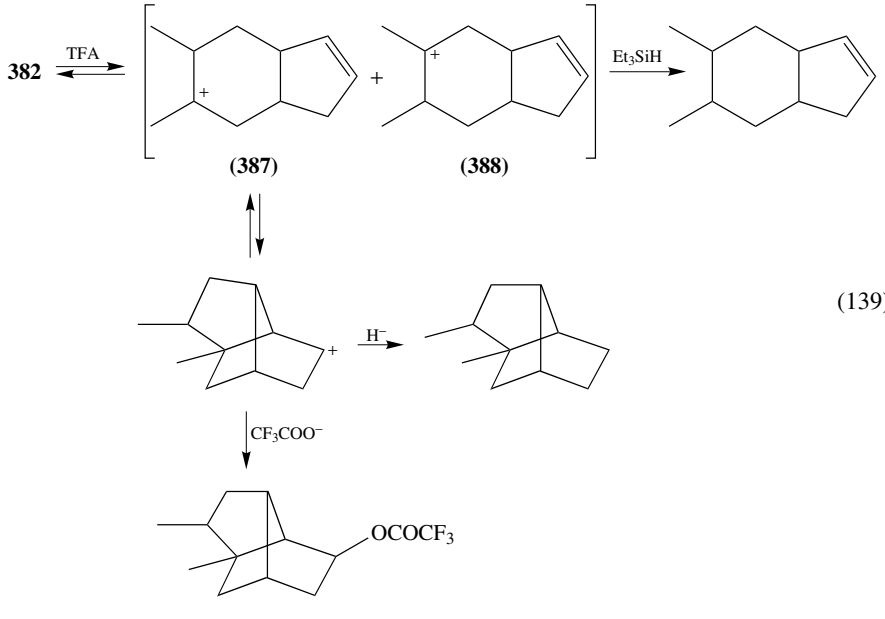
(379) **(380)** **(381)** (136)


Me
Me
(382)
DSO2F–SO2FCl
–115 °C
D
Me
Me
~C-C
~H
(384)
(383)

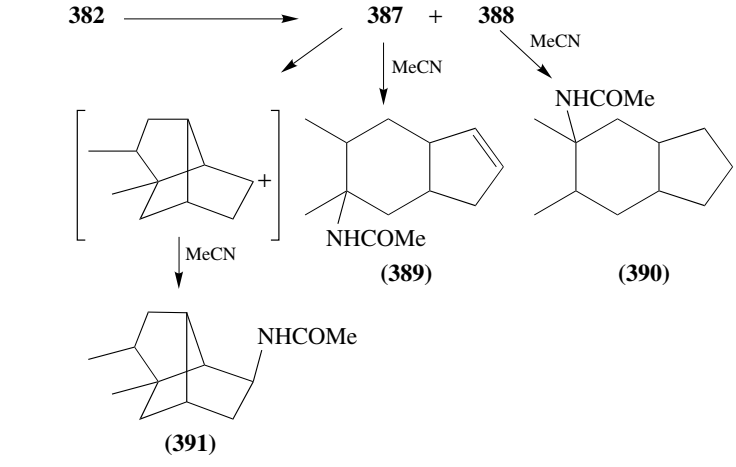
(137)


383 + 384
MeOH – Et2O
(385)
(386)

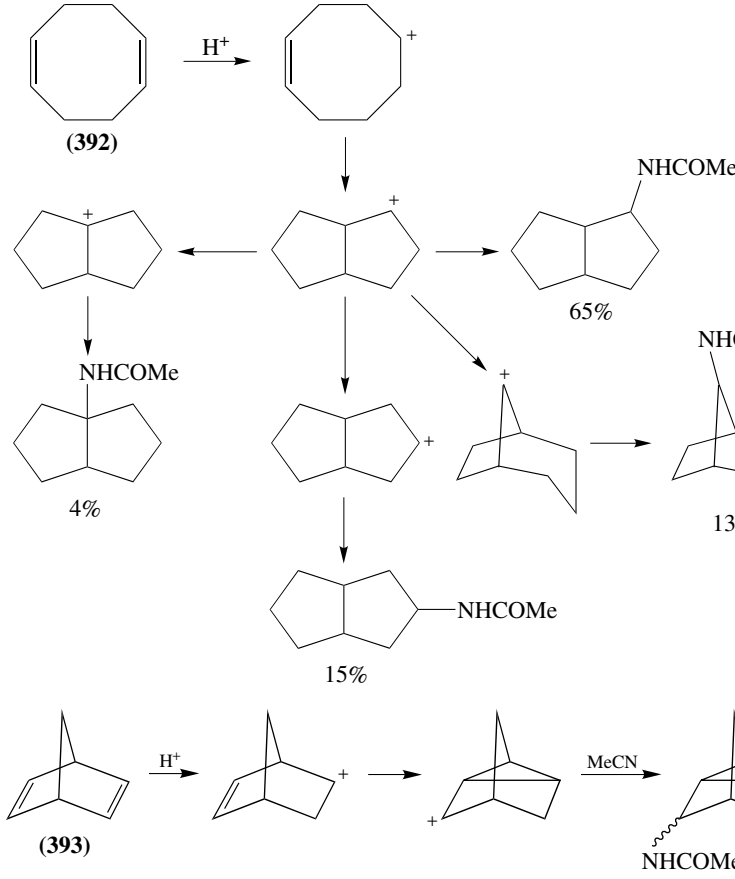
(138)


382
TFA
(387)
(388)
Et3SiH
H–
CF3COO–
OCOCF3

(139)


382
387
+
388
MeCN
MeCN
NHCOMe
NHCOMe
(389)
(390)
MeCN
NHCOMe
(391)

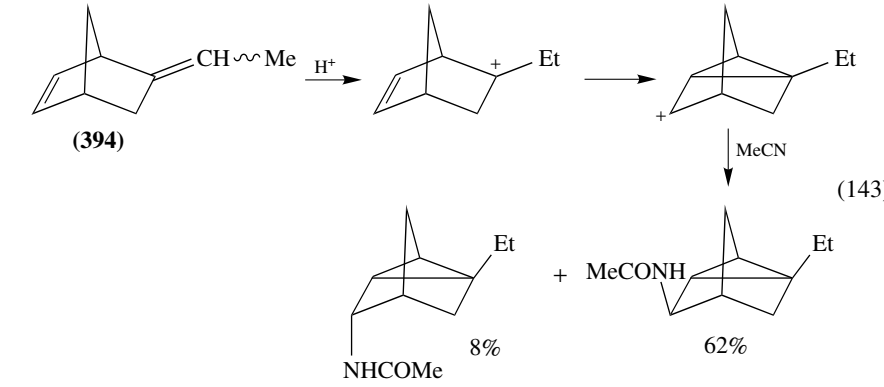
(140)


H+
(392)
NHCOMe
65%
NHCOMe
4%
NHCOMe
13%
NHCOMe
15%

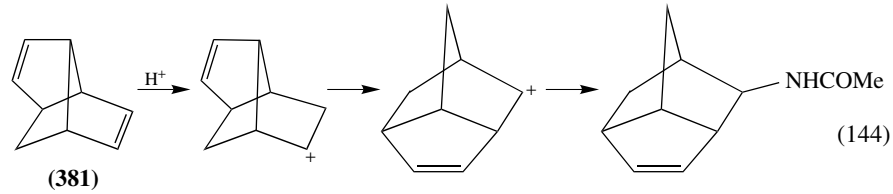
(141)

H+
MeCN
(393)
NHCOMe

(142)

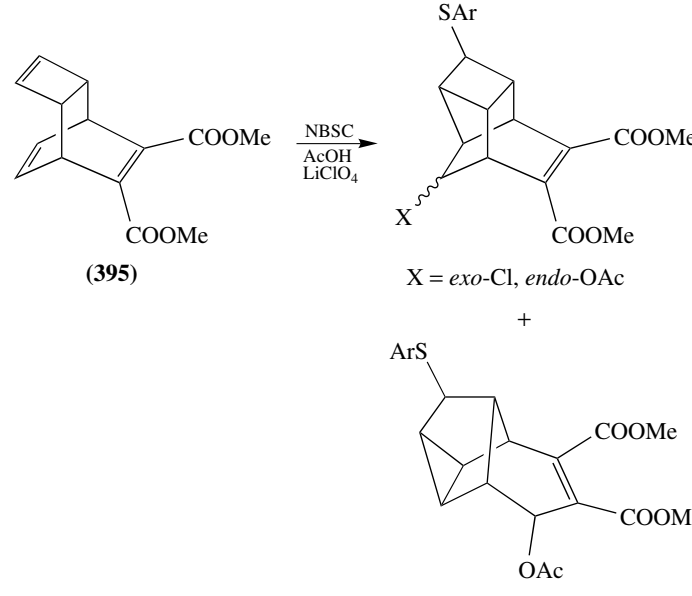


(394) (143)



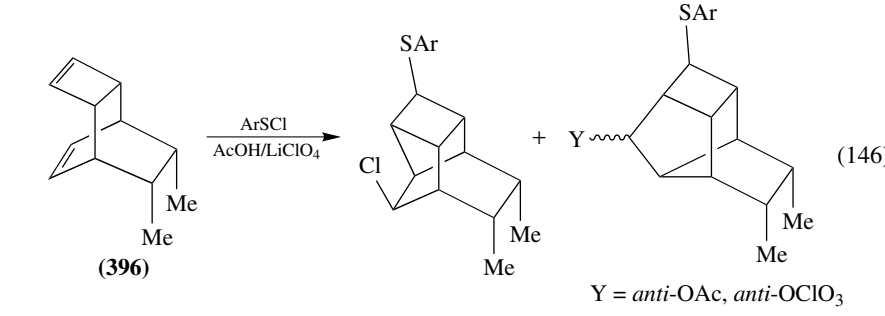
(381) (144)

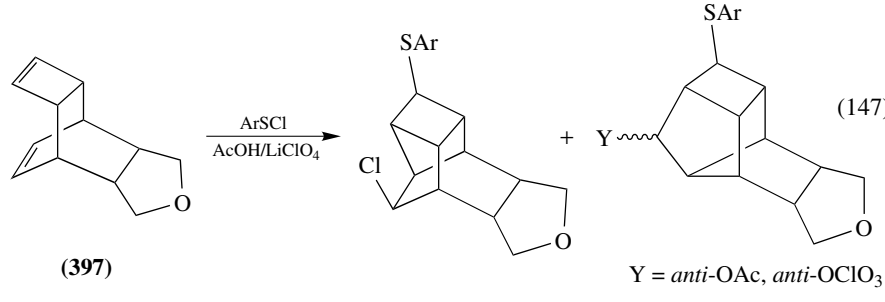
Wagner–Meerwein rearrangements occur also when arylsulfenyl chlorides or the mixtures $R_2NCl + SO_3$ (R = piperidino, morpholino) add to norbornadiene **393**[196,197]. An addition of 2-nitro- (NBSC) or 2,4-dinitrobenzenesulfenyl chloride to the polyenes **395**–**397** in AcOH and under 'doping conditions' (AcOH, with $LiClO_4$) is accompanied by Wagner–Meerwein rearrangements (equations 145–147)[198]. Thus, new types of struc-

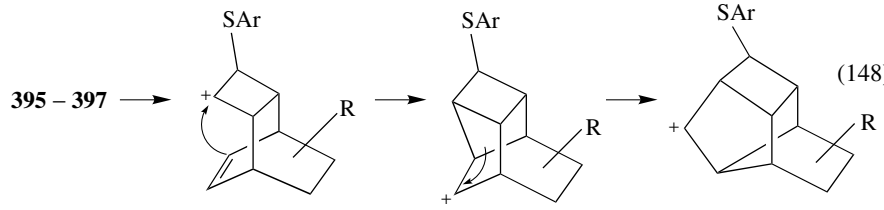


(395) (145)

tural Wagner–Meerwein rearrangements leading to the unusual cage structures, following the general mechanism, were discovered (equation 148).

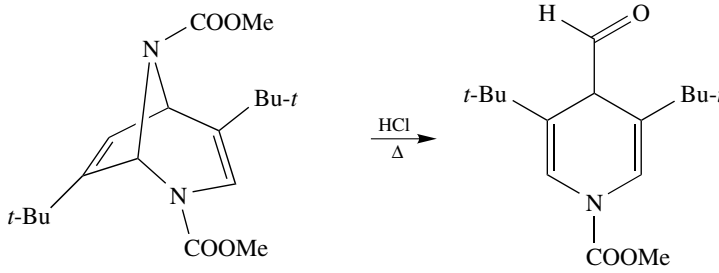






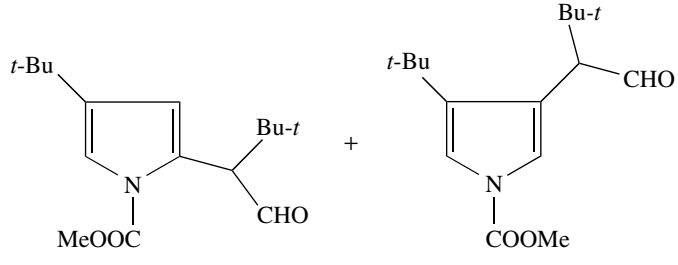
An interesting rearrangement of a bridged heterocyclic system proceeds under conditions of acid catalysis. The pyridine and pyrrole derivatives **(399–401)** were obtained in 31%, 14% and 10% yields, respectively, upon heating the diazabicyclic diene **398** in refluxing methanol for 12 h in the presence of 2M HCl (equation 149)[199]. The transannular cyclizations which were repeatedly mentioned above are typical transformations also for dimethylcyclooctadiene **402**[200,201]. It was shown that diene **402** in the presence of *p*-toluenesulfonic acid or $BF_3 \cdot Et_2O$ forms the bicyclic olefin **403** rather than its bicyclic isomer **404**[200]. When this reaction was carried out in aqueous medium containing an equivalent amount of *p*-TsOH, the isomeric bicyclooctane system **405** was obtained (equations 150 and 151).

A quite detailed review of transannular cyclizations was published[201] wherein their important role in biomimetic syntheses of sesquiterpenes as well as explanation of the biogenetic formation of the polycyclic natural compounds from their monocyclic precursors is discussed. The great significance of these transformations for the synthesis of natural products is also emphasized in a series of reviews which describe the cyclizations to form terpene derivatives, e.g., of the germacrane and humulene systems[202–206].

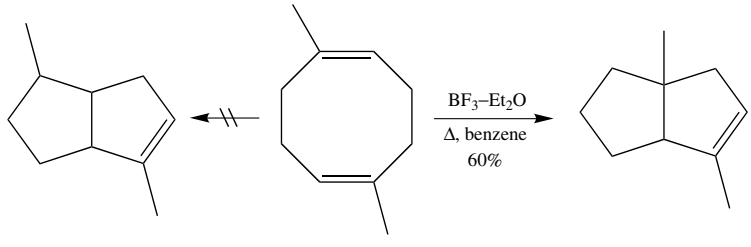


(398) **(399)**

(149)

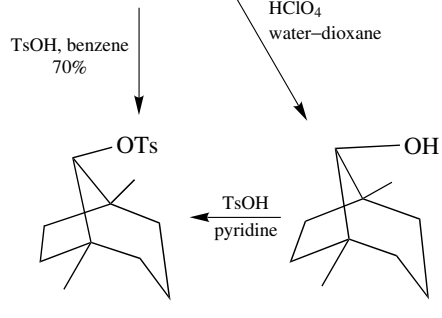


(401) **(400)**



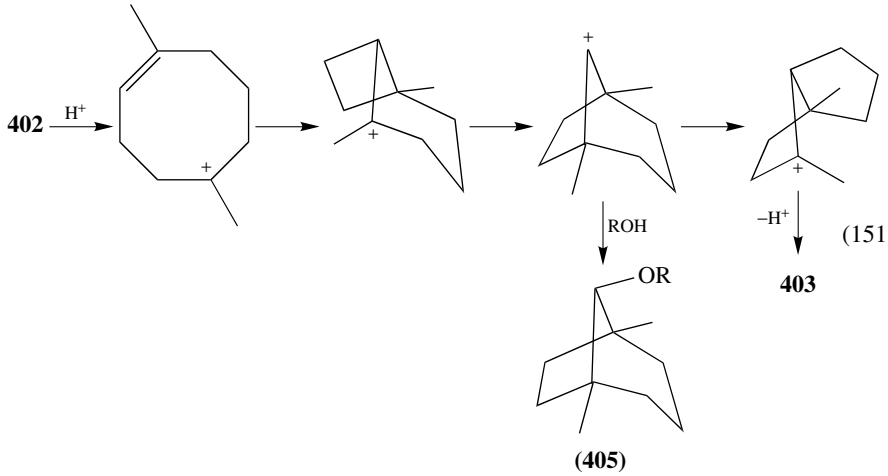
(404) **(402)** **(403)**

(150)



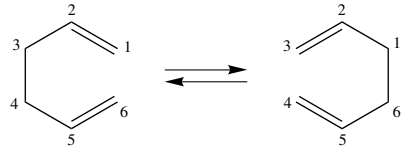
C. Cope Rearrangement

The main information available on the rearrangement of dienes and polyenes probably relates to the Cope rearrangement and its modifications. To our knowledge, more than 550 papers published since 1980 are devoted to this field, not counting the numerous descriptions in textbooks, monographs and the patent literature. Since there is no possibility to cover here all the voluminous information, we will consider, therefore, only the principal recent trends.



(151)

The Cope rearrangement and its variants are described very thoroughly in numerous reviews (see, e.g., References 11, 207 and 208). In general, these reactions can be represented by an extremely laconic scheme (equation 152). This system can also include cumulenes[24,25] and acetylene fragments[209] as well as various substituents and heteroatoms (see Sections IV.D and E).



(152)

1. Mechanistic considerations

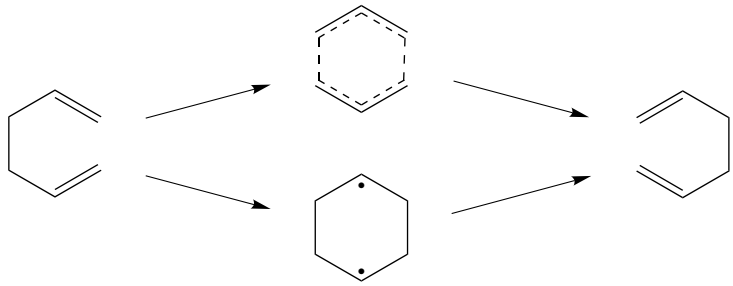
Along with a very wide synthetic application the Cope rearrangement continues to be a subject of intense debates. The key mechanistic question is whether the rearrangement of 1,5-hexadiene derivatives is concerted and passes via a six-electron 'aromatic' transition state, or whether it involves the formation of a diradical intermediate, i.e. a 'cyclization-cleavage' mechanism. In the former case, bond making and bond breaking occur synchronously (a survey of this question has been published[210]).

Cope himself formulated this transformation as what would now be called 'a synchronous pericyclic reaction'. This interpretation was supported by Woodward–Hoffmann's analysis of pericyclic processes. The Cope rearrangement of 1,5-hexadiene derivatives was regarded therefore for a long time as a classical example of an 'allowed' pericyclic reaction

which takes place via an aromatic transition state having a chair geometry. However, in 1971 Doering and coworkers[211] suggested an alternative non-synchronous mechanism in which formation of the new [C(1)−C(6)] bond precedes the rupture of the old [C(3)−C(4)] bond, and where the transition state can be formally represented as a diradical-like species derived from the 1,4-cyclohexylene diradical (so-called 'biradicaloid') (see Section II).

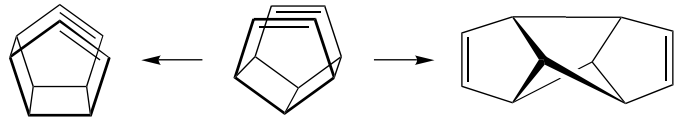
This problem was intensively studied both experimentally and theoretically. The quantum chemical calculations were carried out using various methods at different levels. The earlier calculations for the Cope rearrangement based on a CASSCF wave function for six electrons in the bonds rearranged were found to overestimate the diradical character of the wave function[212,213]. More recently, MP2 methods for the multireference wave function have been developed whose application to an estimate of the energy of the chair transition state has been described[214]. AM1 calculations of alternative transition states for the Cope rearrangement of 1,5-hexadiene derivatives have been discussed by Dewar and colleagues[215−217].

Using a valence bond scheme parametrized with an effective Hamiltonian technique, it was shown that the mechanistic preference for a synchronous pathway with an aromatic transition state versus a non-synchronous mechanism via biradicaloid intermediate can be controlled by two factors: (1) the stability of the long bond in the Dewar valence bond structure, and (2) the softness of the Coulomb interaction between the end methylene groups in the 1,5-diene chain. This means that the mechanism of rearrangement (equation 153) can strongly depend on substituents[218].



(153)

An AM1 study of the structure and mechanism of a degenerate Cope rearrangement, as well as a comparison with bullvalene and other $C_{10}H_{10}$ isomers, have been described[219] for hypostrophene **406** which was first obtained in 1971 by Pettit and coworkers[220]. Hydrocarbon **406** is capable of undergoing a degenerate isomerization and, at 80 °C, it can rearrange into another $(CH)_{10}$ isomer **407** (equation 154)[219]. The semiempirical AM1 SCF (self-consistent field) MO calculations for the degenerate Cope rearrangement of **406** show that the activation energy is greater than that for the comparable rearrangement of bullvalene, barbaralane and semibullvalene (see also Section IV.C.2.d).

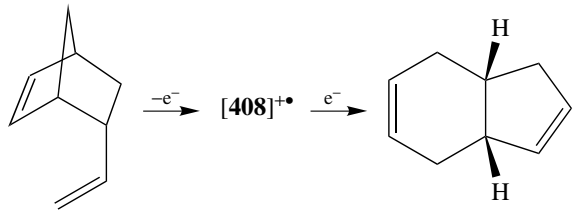


(154)

(406) **(407)**

The first evidence that the radical cation generated by a single-electron transfer (SET) of an unsymmetrical 1,5-diene **408** can undergo a [3,3]-sigmatropic shift (Cope reaction)

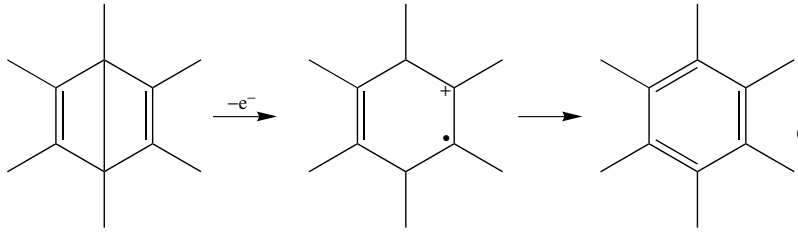
at 100–150 K to form diene **409** whereas the neutral Cope rearrangement **408** → **409** occurs at 400–440 K only (equation 155) (see also Section IV.C.1.b) was reported in 1992[221]. This demonstration of a normal Cope rearrangement at the radical cation stage involved ESR measurements. The very detailed magnetic resonance studies (CIDNP and ESR) as well as *ab initio* calculations of the radical derived from various hexadiene systems (dicyclopentadiene, semibullvalene, barbaralane) have established three distinct structural types for such radical cations, namely a 'dissociative' species containing two separate allylic fragments, cyclohexane-1,4-diyl radical cations in a chair conformation and bridged cyclooctadiene-diyl structures (boat conformers)[222]. This work states that the radical cations derived from 1,5-hexadiene systems are related to the putative mechanistic extremes of the Cope rearrangement. However, most generally this reaction can be formulated via three mechanistic extremes: (1) an associative mechanism when addition precedes cleavage, (2) a dissociative mechanism when cleavage precedes addition (*vide infra*) and (3) a concerted mechanism via synchronous addition and cleavage. The extensive experimental and theoretical investigations have established that the thermal Cope rearrangements proceed via the concerted mechanism[222]. The chair-like and boat-like conformations of the transition state in Cope rearrangement involving diradical intermediates were discussed in the publications mentioned above[24,25].



(155)

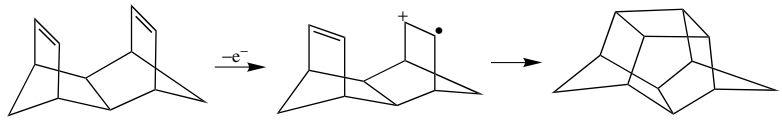
(408) **(409)**

A radical-cation Cope rearrangement of 2,5-diphenylhexa-1,5-dienes under electron ionization conditions (by mass spectrometry at 70 eV) has been described to occur in the gas phase. The reaction directionality differs from that in a thermal transformation[223]. The rearrangement of hexamethyl-Dewar-benzene **410** into hexamethylbenzene (equation 156) as well as the closure of the bridged hexahydrodiene **411** into the so-called 'birdcage hydrocarbon' **412** proceed during hemin-catalyzed epoxidation via a radical cation intermediate (equation 157)[224]. These processes are Cope-like rearrangement because two double bonds are separated by one CH_2 group in **410** and by three sp^3-hybridized C-atoms in **411**.



(156)

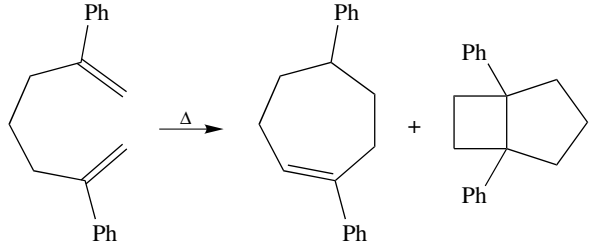
(410)



(157)

(411) **(412)**

Numerous attempts to experimentally confirm the possibility of the diradical mechanism of the Cope rearrangement were conducted for example, by the introduction of substituents which are capable of stabilizing the radicals (e.g., the cyano or phenyl group) (for a review, see Reference 225). A peculiar approach to develop a reliable model of a non-concerted, diradical mechanism closely related to the Cope rearrangement was described[225]. It involves the insertion of a seventh carbon atom between positions C(3) and C(4) in 1,5-hexadiene, and was called a 'frustrated' Cope rearrangement. The authors believe[225] that the resulting system would still be able to undergo the first step of the rearrangement, i.e. the formation of a single C−C bond between the terminal atoms of the 1,5-diene, but it would be unable to complete the second step, i.e. the cleavage of the C(3)−C(4) bond (equation 158). Heating of 1,6-heptadiene **413** in *o*-dichlorobenzene at 220 °C for 401 h gave the cyclic olefin **414** (49%) along with the saturated bicycle **415** (19%) and the unconverted precursor **413** (32%). It was concluded that when the lifetimes of the conjectured diradicals become longer due to unavoidable conformational barriers which protect them from instantaneous collapse, the diradicals become the intermediates and can be more or less easily detectable[225].

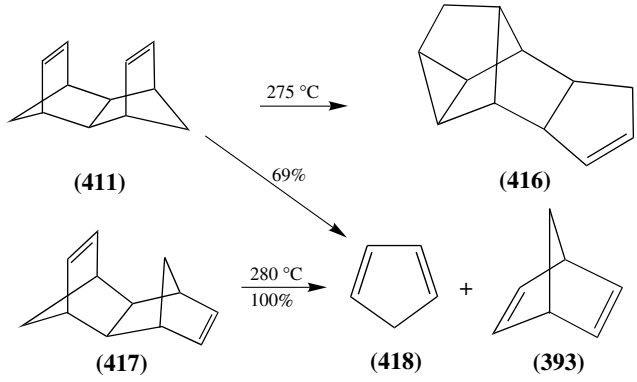


(158)

(413) **(414)** **(415)**

Another example of a similar approach for a novel type of homo-Cope rearrangement by thermolysis of the sterically rigid 1,5-heptadiene derivative *endo,endo*-dimethanenaphthalene **411** was described[226]. Relatively small structural variations in this system seem to bring about a change from a pericyclic to a stepwise mechanism. Gas-phase thermolysis of **411** at 275 °C under carefully controlled conditions (primarily in order to exclude an acid catalysis) leads to isomerization to the polycyclic olefin **416** (31%) besides the expected retro-Diels–Alder products, cyclopentadiene **418** and norbornadiene **393** (formed in 69% combined yield) (equation 159)[226]. The *endo,exo*-isomer **417** forms under the same conditions only the latter two products (**418**, **393**) without rearrangement. Thus, one of the possible mechanisms, i.e., via a retro-Diels–Alder step, can be excluded. These results confirm a pericyclic *homo*-Cope rearrangement of *endo,endo*-**411** to **416**. This novel rearrangement was further studied by using structurally related *exo*-isopropylidene-substituted systems (**419**, *endo,endo*-; **423**, *exo,endo*-; and **424**, *endo,exo*-) (equations 160–162)[226]. Similarly to compound **411** the asymmetrical isomer **419** having face-to-face arrangement of the two *endo*-cyclic π-bonds was transformed on thermolysis at 220 °C to the rearrangement product **420** and the retro-Diels–Alder products **393**, **418**, **421** and **422**

(equation 160), whereas only dimethylfulvene **421** and norbornadiene **393** resulted from thermolysis of the *exo,endo*-triene **423** (equation 161). However, the *endo,exo*-isomer **424** undergoes predominant rearrangement to form the polycyclic diene **425** (equation 162). It was concluded from these findings, as well as from the activation entropy values, that the rearrangements of compounds **419** and **424** are stepwise processes, in contrast to the pericyclic *homo*-Cope mechanism of the parent system **411**. The change in the mechanism may be explained by a different stabilization of the potential diradical intermediates.



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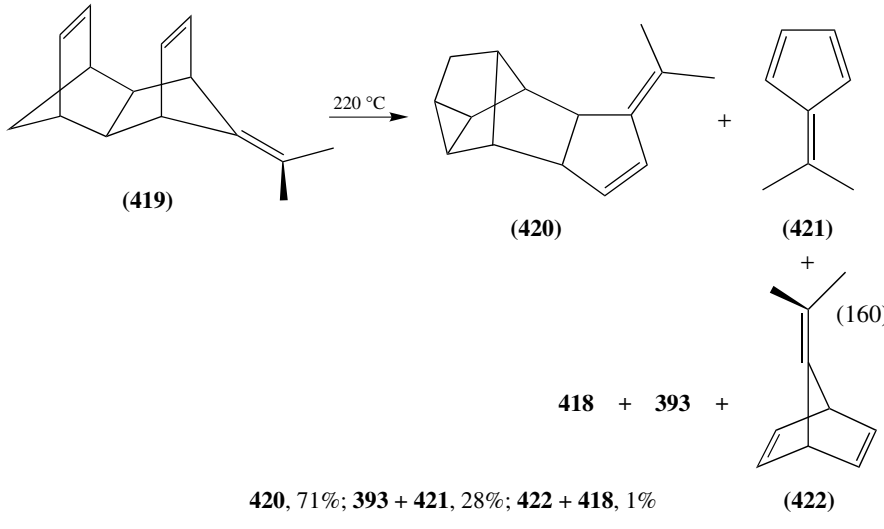
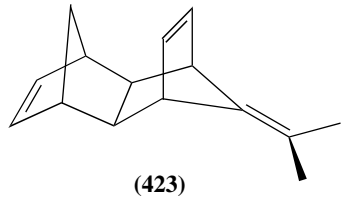


(160)

420, 71%; **393** + **421**, 28%; **422** + **418**, 1%



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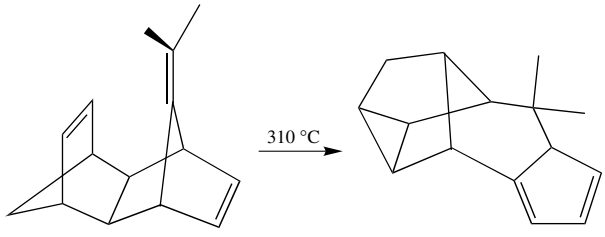
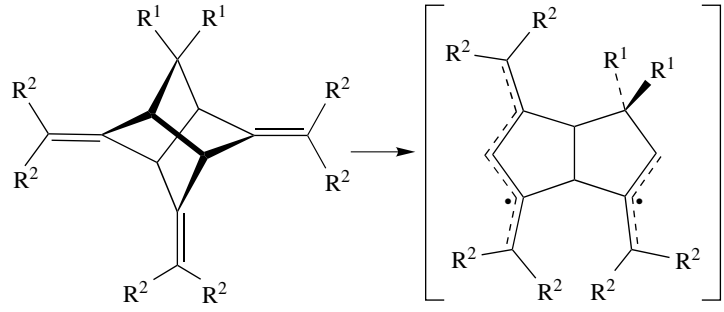


(424) **(425)** 63%

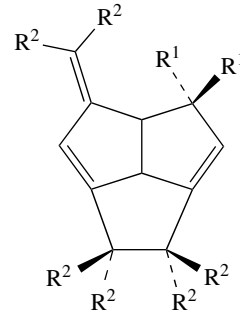
(162)

Gleiter and colleagues have described very interesting candidates for a two-step Cope rearrangement, namely the stellatriene **426a**, its hexamethyl derivative **426b** and the spirocyclic derivatives **426c** and **426d**[227,228]. These trienes and the corresponding dienones rearrange to form triquinane derivatives **427** at temperatures between 25 °C and 50 °C (equation 163). These reactions can be formulated as a stepwise Cope rearrangement involving a diradical mechanism. The thermal lability of the stellatriene derivatives [$t_{1/2}$ (30 °C) for **426a**, **426b** and **426d** equals 30, 75 and 300 min, respectively] can be attributed to the very easy cleavage of one of the long central bonds. The introduction of an alkyl group is one of the two general approaches to increase the stability of this strained structure.



(426a–d)

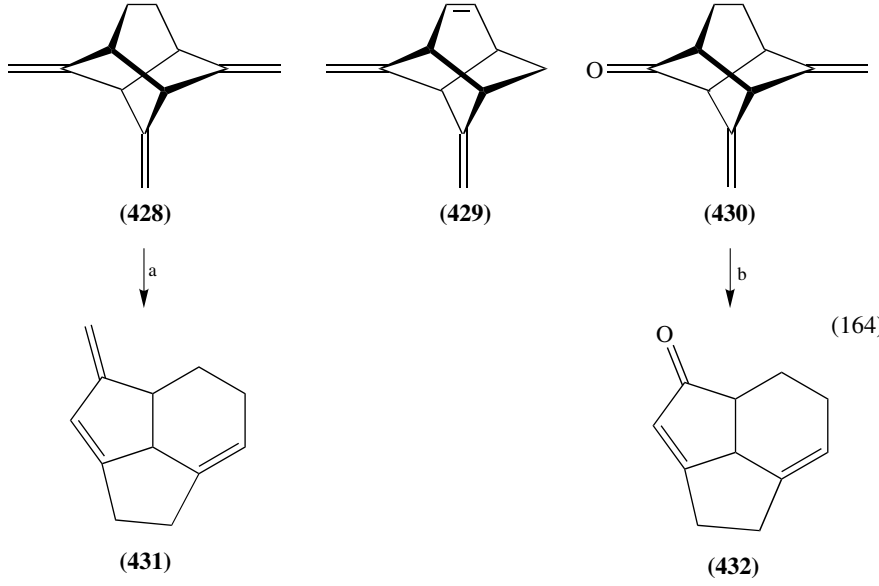
(163)



(427a–d)

(**a**) $R^1 = R^2 = H$
(**b**) $R^1 = H$; $R^2 = Me$
(**c**) $R^1R^1 = (CH_2)_4$; $R^2 = H$
(**d**) $R^1R^1 = (CH_2)_4$; $R^2 = Me$

Another possibility to overcome this lability consists in a release of strain by elongation of the 2,7-bridge, for example, by using compounds **428** and **429** and also dienone **430** (equation 164)[228]. Triene **429** is almost as labile as compound **426b** whereas the halflives of the stellatriene **428** and the dienone **430**, both having the two-carbon bridges and forming the polycycles **431** and **432**, are 560 h and 102 h at 80 °C, respectively.



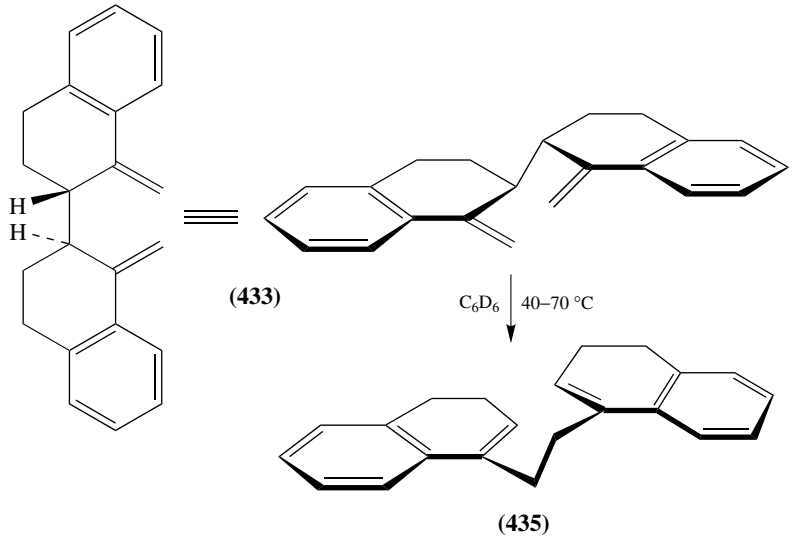
(428) **(429)** **(430)** (164)

(431) **(432)**

(**a**) 100 °C, toluene, 7 days
(**b**) 80 °C, benzene, 15 days

An influence of phenyl substituents on the geometry of the transition state was studied by using the *d*,*l*- and *meso*-isomers **433** and **434** of a polycyclic diene[229]. The *d*,*l*-diastereoisomer **433** is constrained to undergo Cope rearrangement in the chair conformation whereas the *meso*-diastereoisomer **434** is constrained to have a boat transition state: The activation free energies for their unimolecular [3,3]-sigmatropic rearrangement to give products **435** and **436** are 25.2 ± 2.9 (for **433**) and 38.1 ± 3.7 (for **434**) kcal mol^{-1} and from them a $k_{d,l}/k_{meso}$ ratio of 7×10^6 at 150 °C was determined (equations 165 and 166)[229].

Doering and coworkers[230] have suggested distinguishing two types of positions in the hypothetical 'aromatic' transition state of the thermal Cope rearrangement, designated as 'a' ('active') and 'n' ("nodal") (equation 167). Previous examinations of radical-stabilizing substituents have concentrated on their influence in the 'n' positions. In order to obtain a quantitatively reliable estimate for the effect on the 'a' positions, the activation parameters of the degenerate rearrangement of 1,4-diphenyl-1,5-diene **(437)** ^{13}C-labeled in the C(6) position were evaluated. It was concluded that two phenyl groups in the 'a' positions have lowered the activation enthalpy by 32.2 kJ mol^{-1} relative to the parent 1,5-hexadiene while two phenyl groups in the 'n' positions of 3,5-diphenyl-1,5-hexadiene have lowered the activation enthalpy by 71.2 kJ mol^{-1}. These results explain an advantage of using phenyl substituents in order to construct systems which enable one to change the concerted mechanism of the Cope rearrangement toward the two-step, so-called 'diyl' mechanism[230].



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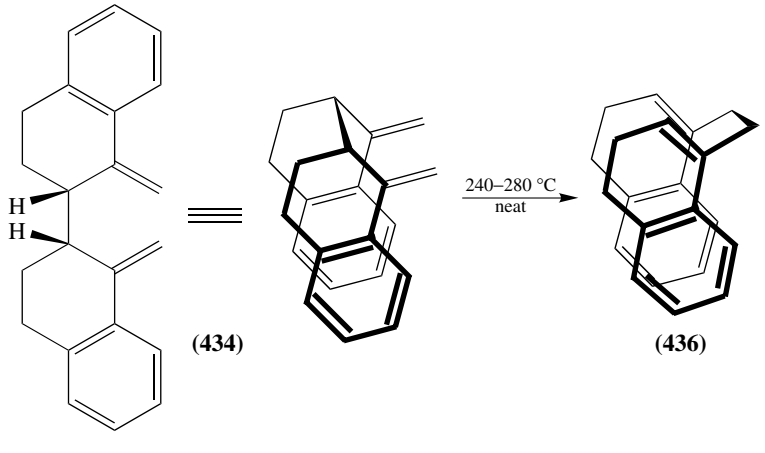

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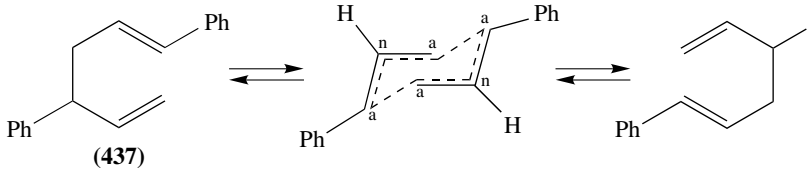
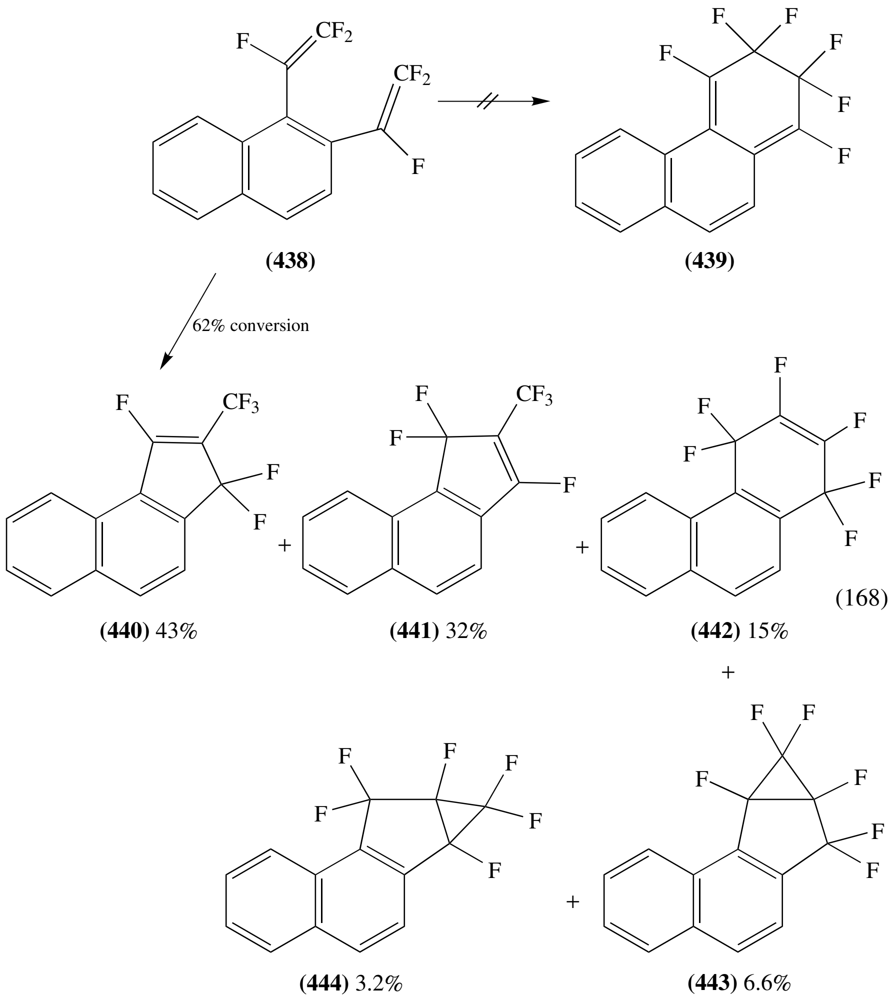


(167)

The Cope rearrangement mechanism can be also strongly affected by other substituents. Thus, the 'normal' electrocyclic process in the thermal isomerization of divinyl aromatics has been suppressed relative to the thermolysis of 1,2-bis(trifluorovinyl)naphthalene **438** (in benzene, at 193 °C, 24 h)[231]. Three major products **440**–**442** were isolated from the reaction mixture, but none of them was the expected product **439**. Also formed in low

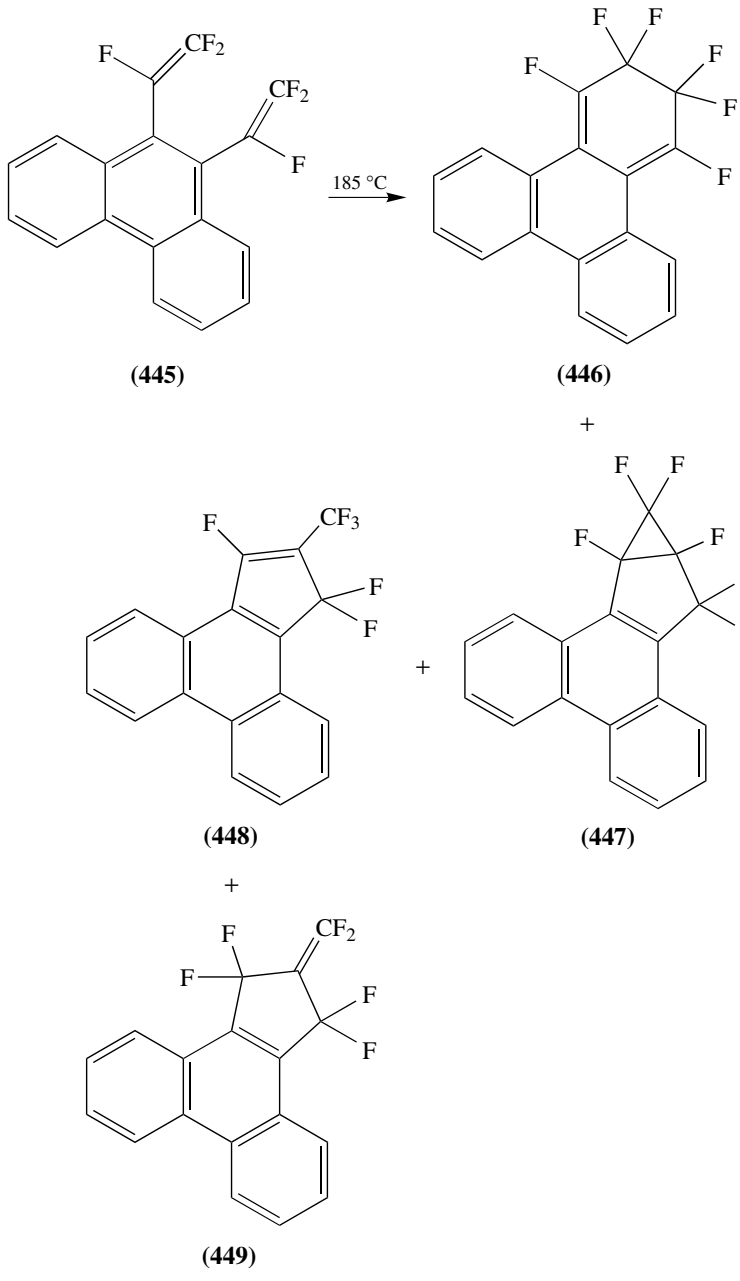
yields were **443** and **444** (equation 168). The thermolysis of the more thermodynamically favorable phenanthrene derivative **445** has provided a greater insight into the chemistry of this process[231]. A small amount of the electrocyclic product **446** was obtained, but again the main products were **447**–**449**, i.e, the major reaction observed was similar to that for compound **438** (equation 169).



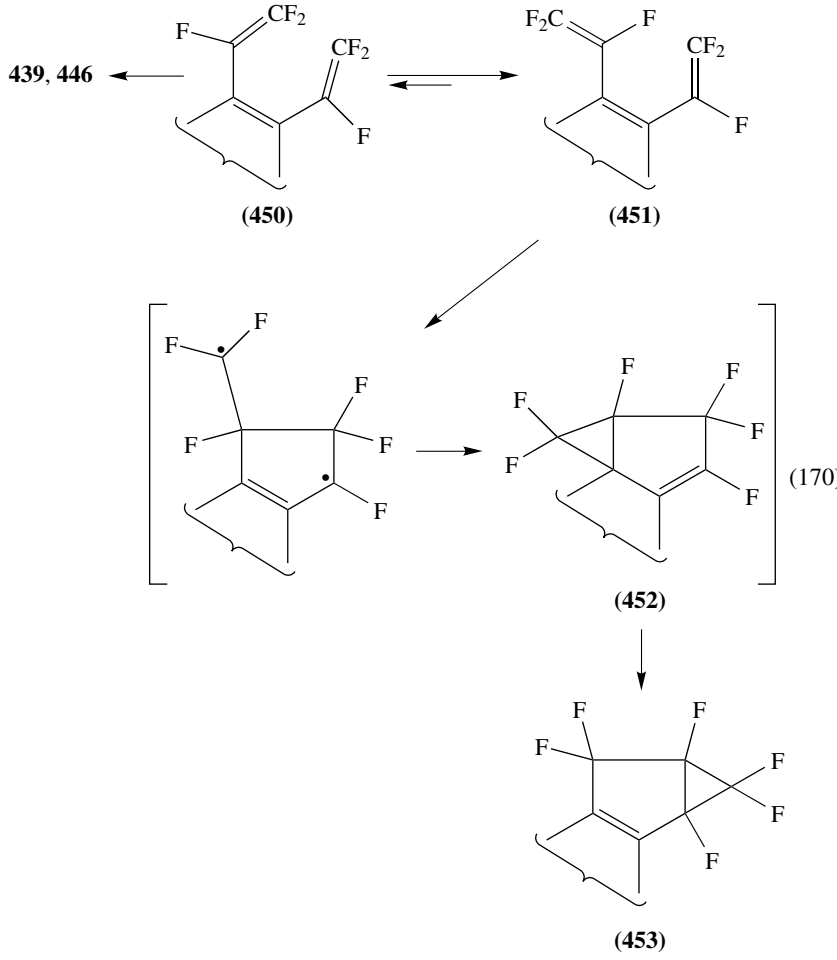
(168)

It should be noted that products like **443** and **447** are the normal products of photochemical reactions of acyclic 1,3,5-hexatrienes, as well as of divinyl aromatics, but are quite unusual for thermal transformations of such substrates. Presumably, the electrostatic repulsion between CF_2 groups prevents the formation of conformation **450** which is necessary for the electrocyclic ring closure (i.e. **438** → **439** and **445** → **446**). Instead, it leads to conformation **451** which is favorable to generate the diradical and then the fused vinylcyclopropane intermediates **452** (equation 170). Note that the rearrangement **452** → **453**

(corresponding to formation of products **443**, **444** and **447**) is essentially a 'vinylcyclopropane rearrangement' (Section III.A), whose driving force is an aromatization of an annulated system.



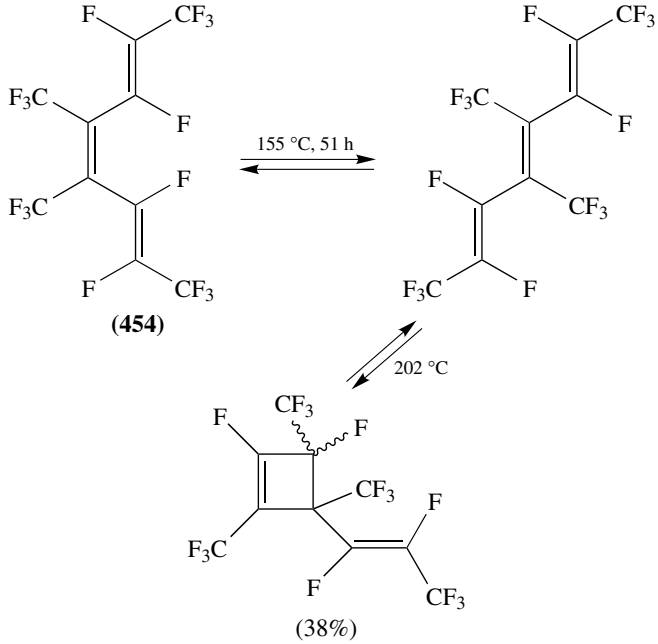
(169)



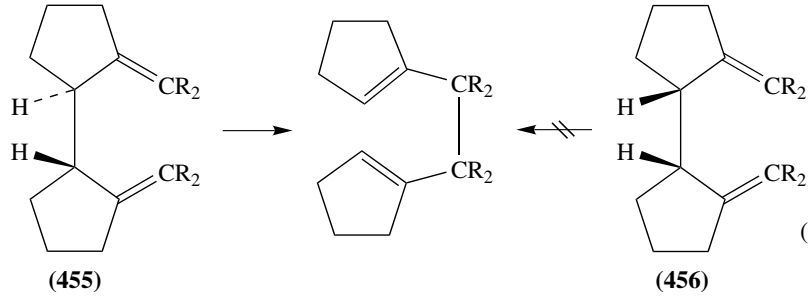
The acyclic fluorinated 1,3,5-hexatriene system **454** is also resistant to 6π-electron electrocyclic ring closure at temperatures up to 200 °C while the analogous hydrocarbons cyclize easily at 160 °C (equation 171)[232].

The rearrangements of the diastereoisomeric dienes **455** and **456** are compared in the same work[232]. In accordance with the results of a similar investigation[229] (equations 165 and 166) the isomer **455** (R = F) undergoes a Cope rearrangement more easily than its hydrocarbon counterpart (**455**, R = H) while the Cope rearrangement of isomers **456** (R = H, F) is strongly inhibited (equation 172). The contrasting behavior of compounds **455** and **456**, as well as of **433** and **434**, is ascribed to steric repulsions of the *cis*-fluorine C(1) and C(6) substituents in the former pair as well as to the presence of bulky phenyl groups in the latter pair of compounds.

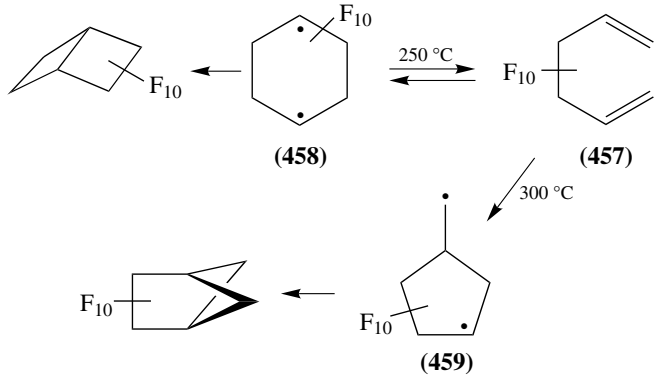
The competition of the Cope rearrangement with cyclization processes was reported for perfluoro-1,5-hexadiene **457**[233]. The cyclizations proceed undoubtedly via the corresponding diradicals **458** and **459** (equation 173). This course of events was revealed by using a


F
CF3
F3C
F
F3C
F
F
CF3
155 °C, 51 h
202 °C
(454)
(38%)

(171)

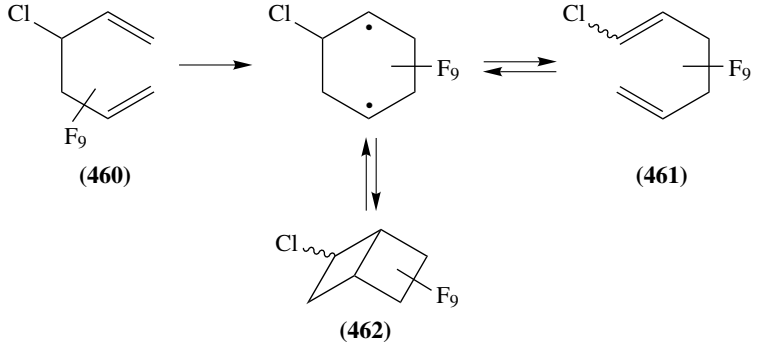

H
H
CR2
CR2
CR2
CR2
CR2
CR2
(455)
(456)

(172)


F10
F10
F10
250 °C
300 °C
(458)
(457)
(459)

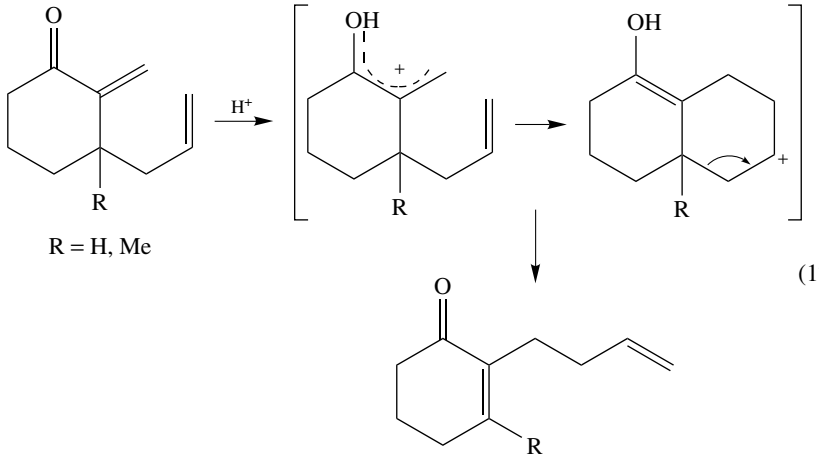
(173)

Cl-labeled fluorinated 1,5-hexadiene **460** (equation 174). The rearrangement occurs slowly above 210 °C to furnish compound **462** but without formation of Cope product **461**. The latter was detected only when the reaction was conducted for 2.5 days at 210 °C, when the **461** : **462** ratio was still only 1 : 10.



(174)

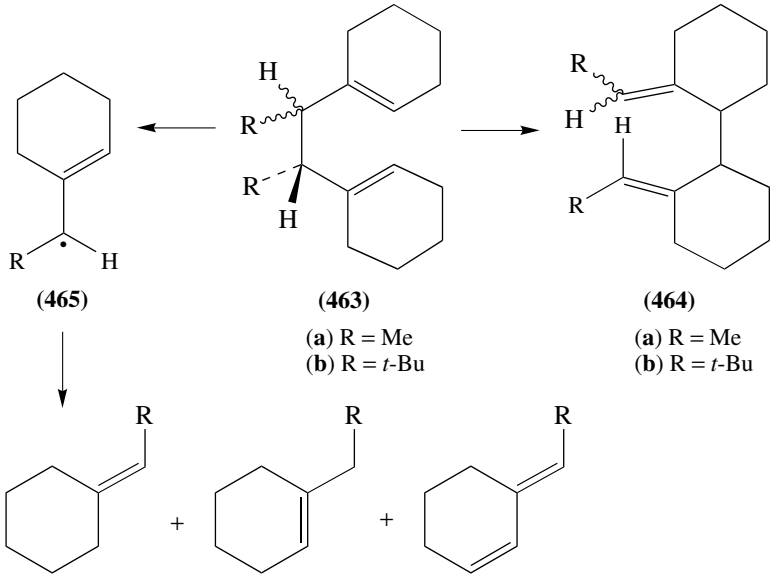
The influence of substituents on the Cope rearrangement can also originate from acid catalysis conditions. For instance, the rearrangement of 1,5-dienes having an acyl substituent at the C(2) position is strongly accelerated by both protic and Lewis acids (equation 175)[234]. The bulky substituents can also lead to a competition with the Cope rearrangement, with homolytic bond cleavage. For example, diene **463a**, which is less sterically hindered than diene **463b**, undergoes preferably a thermal Cope rearrangement to give diene **464a**. However, the thermolysis of the more strained **463b** affords the products of both Cope rearrangement **464b** and homolysis via radical **465** (equation 176)[235].



(175)

The dissociative mechanism of the Cope rearrangement casually mentioned above[222] can be illustrated by two examples of Pd-catalyzed reactions. The migration of an allyl group from carbon to carbon in the pyridine system **466** occurs in the presence of a Pd^0 catalyst[236]. Refluxing dilute solutions of precursors **466** (R^1, R^2 = H, Me) in toluene for 7 h or in *n*-heptane for 24 h gave derivatives **468**. The pyridine allyl ether **469** was also

converted to **468** by reflux for 24 h in dibutyl ether. However, all attempts to effect the thermal rearrangement of **466** ($R^1 = R^2 = Me$) failed. It was found that addition of a catalytic amount (4 mol%) of $(Ph_3P)Pd$ to solutions of various compounds **466** at room temperature catalyzed the allyl migration in both ether **469** (from O to C) and **466** (from C to C) in nearly 100% yields (equation 177). The authors[236] believe that this rearrangement of compounds **466** does not proceed via a 'cyclization-induced rearrangement'[237]. It seems more likely that ion pairs such as **467** having an extensively delocalized negative charge, can be formed. A similar explanation for the Pd^{II} catalyzed Cope rearrangement of 1,5-dienes was reported because the 1,5-dienes could generate acetone in the presence of oxygen and $(PhCN)_2PdCl_2$[238]. The general problems of catalysis in Cope and Claisen rearrangements were summarized in a survey[11].

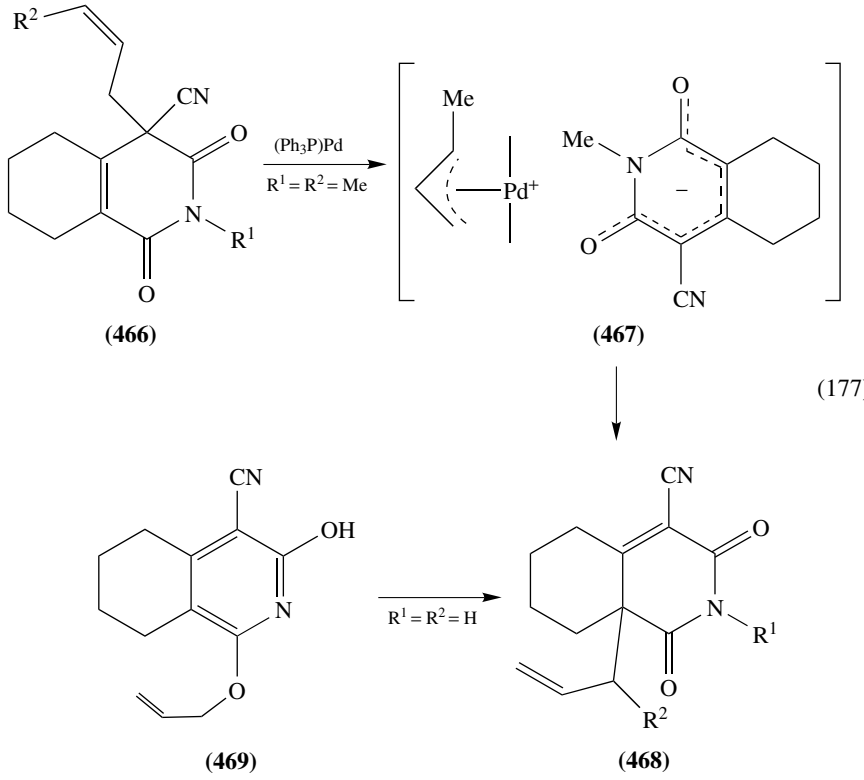


(176)

To shift an equilibrium Cope rearrangement in the desired direction, different driving forces such as aromatization, conjugation, strain or irreversible consecutive reaction of one of the dienes can be exploited. For example, the method for synthesis of the biologically active 3-indoleacetic acid derivatives is based on tandem Wittig olefination and Cope rearrangement induced by aromatization[239]. Treatment of indolin-3-ones **470** with phosphonium ylides **471** (R^3 = COOMe, COOBu-*t*, CN, COMe, COPh; R^4 = H, Me) affords dienes **472** which undergo the Cope rearrangement (refluxing toluene, 5–72 h, 32–87%) to give the indole derivatives **473** (equation 178)[239]. The first example of the transformation of polyolefinic hydrocarbons to their aromatic isomers as a result of Cope rearrangement was reported recently[240].

As appropriate model compounds for these reactions[240] the bridgehead substituted dihydro-4-methyleneazulenes **474** were employed. Allyl-, crotyl- and propargyl-substituted dihydroazulenes **474** and **476** can be easily rearranged to the 4-substituted azulenes **475** and **477** (equations 179 and 180) whereas all attempts to obtain 4-benzylazulene **479** by rearrangement of precursor **478** gave only polymeric products (equation 181). Undoubtedly, this failure can be explained by the fact that the Cope rearrangement becomes very

difficult or even impossible if one of the unsaturated fragments in the diene is part of an aromatic structure. However, it was shown that systems **480** derived from 2- or 3-benzo[*b*]thiophene are capable of undergoing the Cope rearrangement (equation 182)[241].

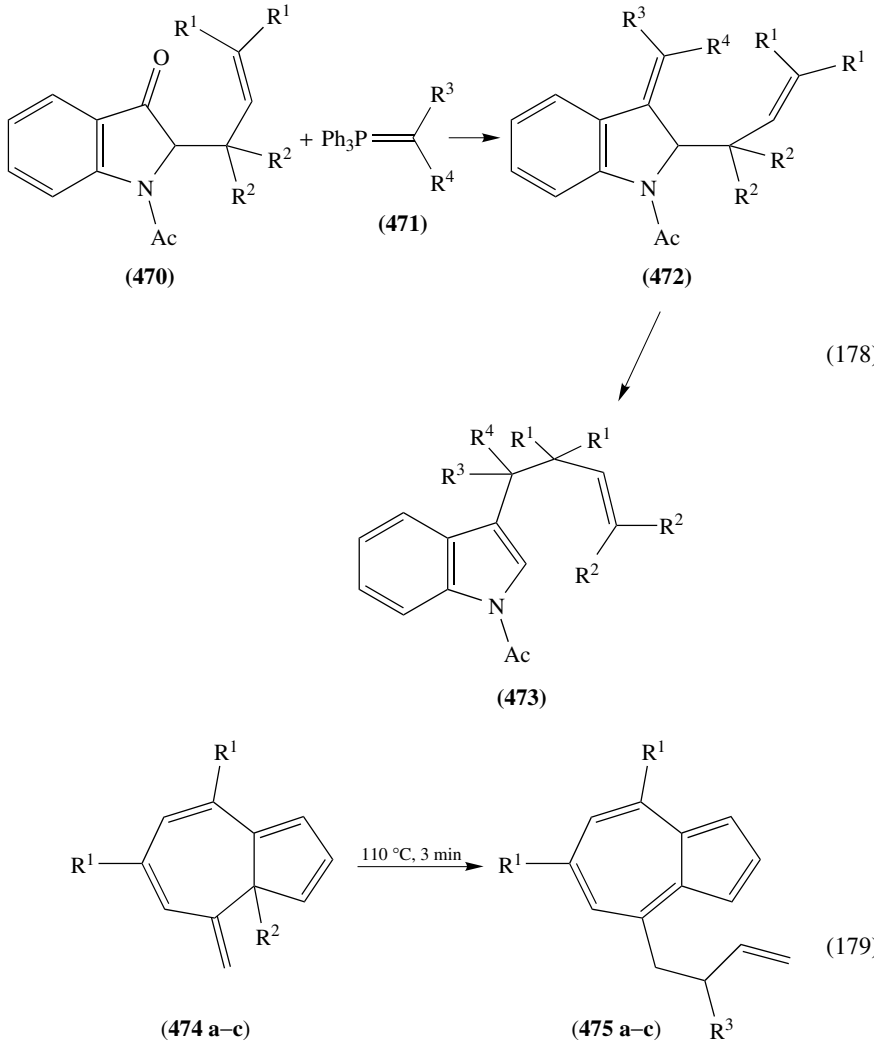


(177)

Apparently, the aromatization of the heterocyclic cation serves as a driving force of the Cope rearrangement in the transformation of the 3-formyl-4-allyl-4*H*-pyrane **(481)** into poly-substituted pyrylium salt **483** which presumably proceeds via **482** (equation 183)[242].

An irreversible consecutive reaction as a driving force to shift an unfavorable Cope rearrangement equilibria in the needed direction can be illustrated by the Cope–Claisen tandem process used for the synthesis of chiral natural compounds[243]. It was found that thermolysis of *trans*-isomeric allyl ethers **484** or **485** at 255 °C leads to an equilibrium mixture of the two isomers in a 55 : 45 ratio without conversion into any other products (equation 184). Under the same conditions the isomer **487** rearranges to give the Cope–Claisen aldehyde **491** (equation 185). Presumably, the interconversion **484** ⇌ **485** proceeds via intermediate **486** whose structure is not favorable for Claisen rearrangement. In contrast, one of the two cyclodiene intermediates of process **487** ⇌ **488** (viz. **490** rather than **489**) has a conformation appropriate for irreversible Claisen rearrangement[243].

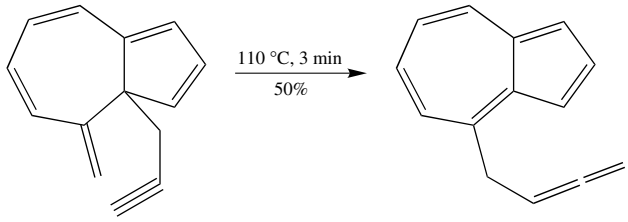
It should be noted that the stereochemical aspects of the Cope rearrangement are widely used for synthesis of various natural products, e.g. of the elemene-type derivatives **493**–**496** starting from germacrene-type sesquiterpenes **492** having cyclodeca-1,5-diene structure with stable conformations (equation 186)[244].



2. Reactions of divinylcycloalkanes

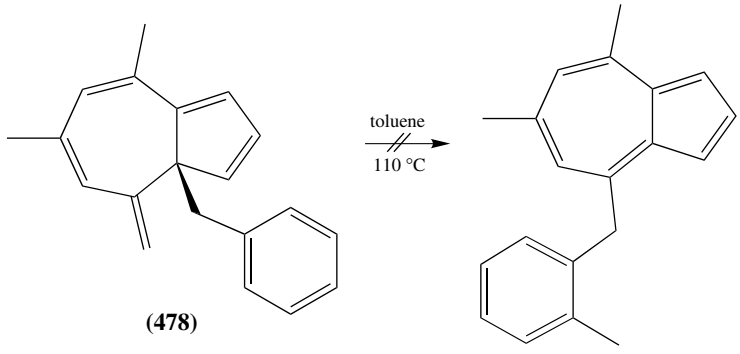
A large group of the peculiar 1,5-diene derivatives includes 1,2-divinylcycloalkanes in which one of the vinyl groups or even both can be part(s) of a carbo- or a heterocycle. Such structures were already mentioned above (e.g. **110**, **381**, **406**, **408**, **420**, **484**), and we will consider here their synthetic utility.

a. Divinylcyclohexanes. A key step in the synthesis of tricyclic ring systems containing the stereogenic centers of the morphine structure is a Cope rearrangement of ketone **497** to dienone **498** (xylenes, 250 °C, 22 h, 88%) (equation 187)[245].



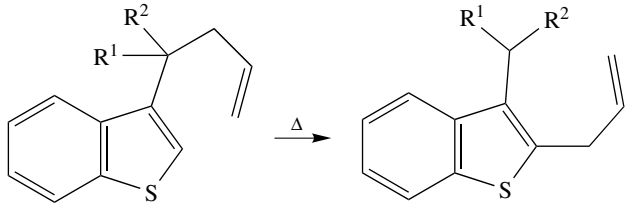
(180)

(476) **(477)**



(181)

(478) **(479)**

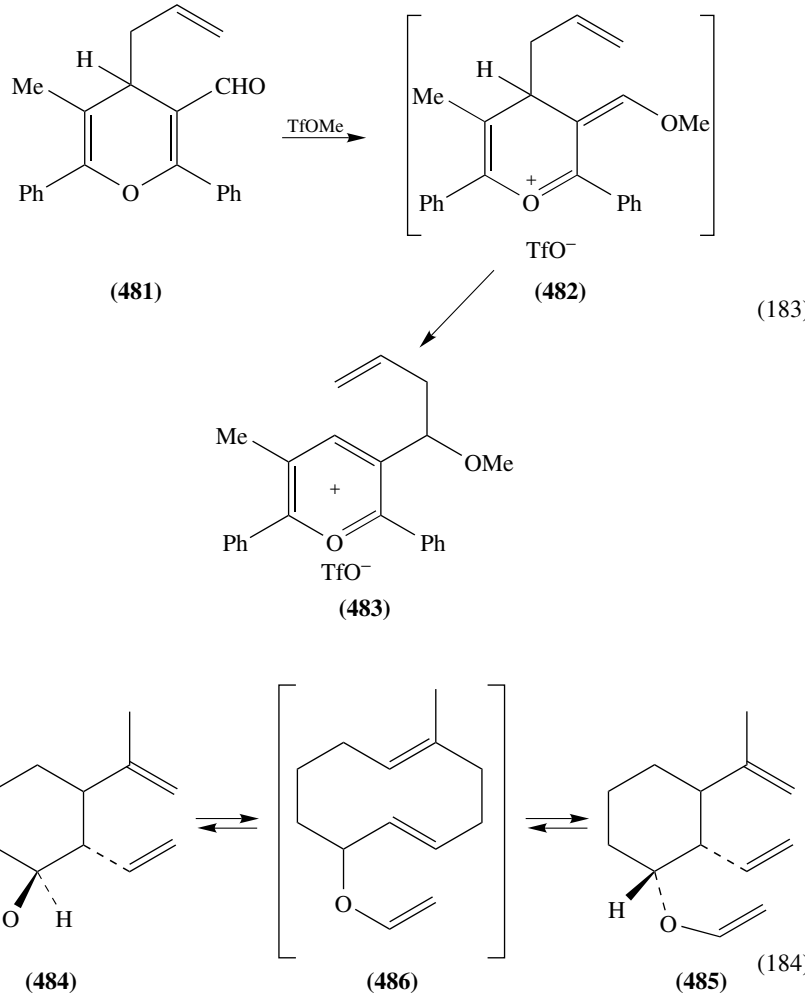


(182)

(480)

(**a**) $R^1 = R^2 = COOEt$ (215–225 °C, 11 h, 8%)
(**b**) $R^1 = CN$, $R^2 = COOEt$ (205–215 °C, 7 h, 6%)

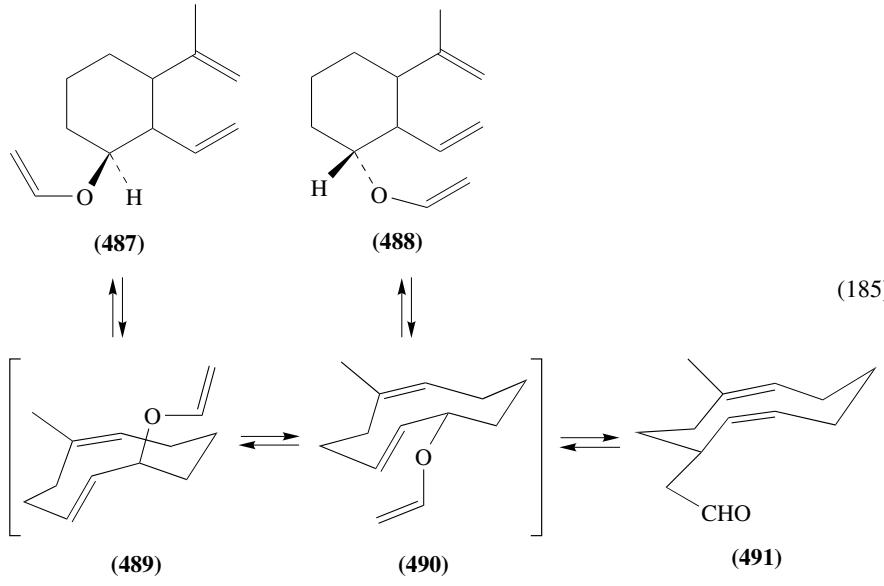
Interesting examples of a tandem Cope–Cope rearrangement are represented by the transformation of Cookson's diester **499**, which proceeds thermally to afford its ring-degenerate isomer **500** (330–350 °C, as a melt) (equation 188)[246], and by thermal isomerization of bicyclic triene **501** into hexahydro-1-vinylnaphthalene **502** upon heating in chlorobenzene at 220 °C for 20 h (equation 189)[247].



b. Divinylcyclopentanes. A peculiar cycle of two photochemical and one thermal isomerization was reported for 1,3-bis(α-naphthyl)propane **503**. The thermal rearrangement of the divinylcyclopentane **504** is presumably assisted by the conjugation created in the dihydronaphthalene fragments of product **505** (equation 190)[248].

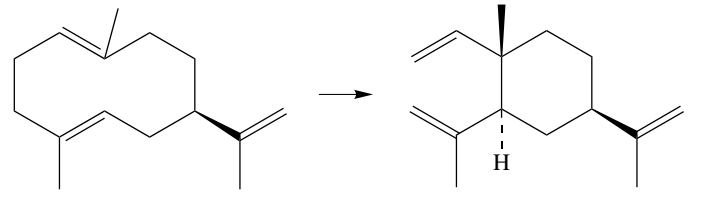
It was found that Cope rearrangement of the structurally rigid tetracyclic molecule **506** is remarkably accelerated by creating a remote (i.e. non-conjugated) carbenium ion center by an ionization of a ketal group (equation 191)[249]. The possibility of both classical and non-classical ion participation in this Cope rearrangement was revealed by using MNDO calculations.

The brief survey of various catalysts for the isomerization of vinylnorbornene **408** into ethylidenenorbornene **394** as well as the effectiveness of potassium amide in liquid ammonia for this purpose were described (equation 192)[250]. One step in the synthesis

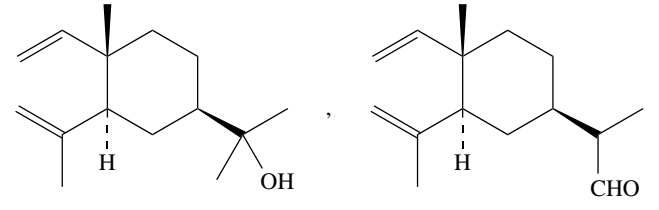


(487) **(488)** (185)

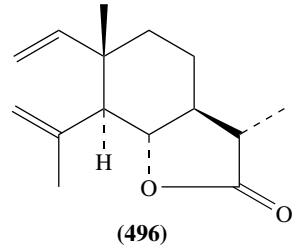
(489) **(490)** **(491)**



(492) **(493)** ;

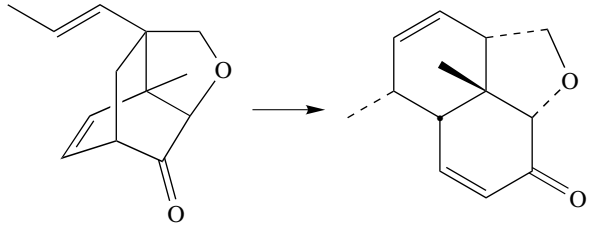


(494) , **(495)** , (186)

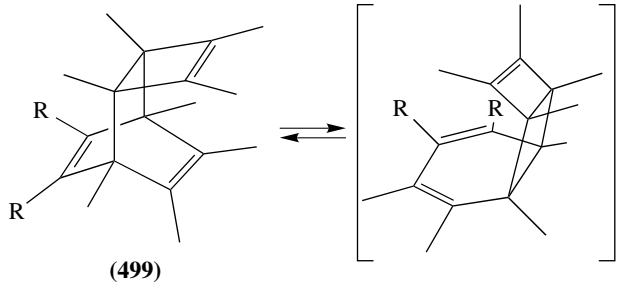


(496)

of 12-oxophytodienoic acid related to prostaglandines includes a Cope rearrangement of 5-vinylnorborn-2-ene **507** into the bicyclic diene **508** (equation 193)[251]. Similar rearrangements were also used for the preparation of prostaglandines (equations 194 and 195)[252,253]. The rearrangements of the tetracyclic systems **509** and **510** containing the vinylnorbornene fragment were employed to obtain the spiroepoxy cyclohexadienones **511** and **512** (equations 196 and 197)[254]. The angularly alkylated tricyclic esters **513** are very unstable and rapidly undergo an unusual Cope rearrangement to form the bridged ketones **514** even at an ambient temperature (equation 198)[255].



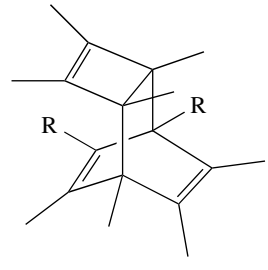
(497) **(498)** (187)



(499)

R = COOMe

(188)

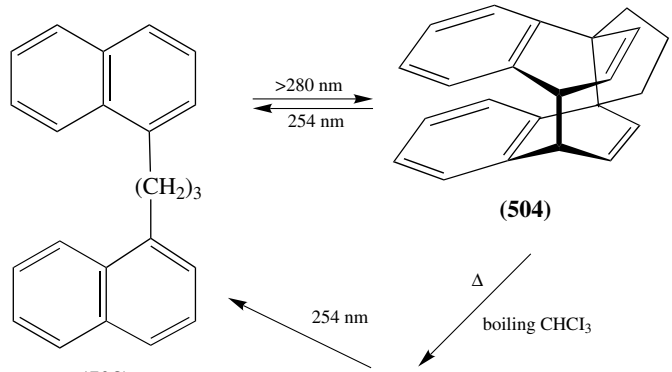


(500)

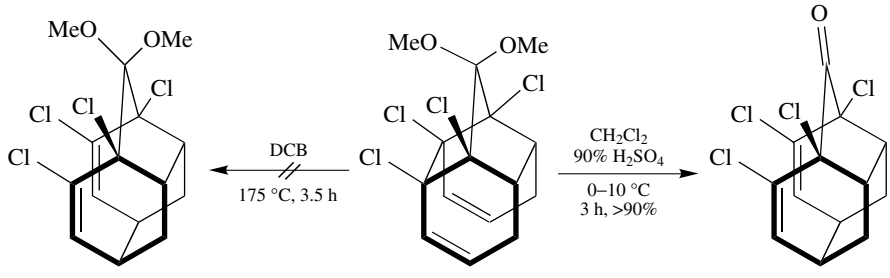
Rigid polycarbocyclic isomeric ketals **515** and **516** undergo a Cope rearrangement to afford the diketones **517** and **518** on heating in a H_2O–THF mixture at 55 °C in the presence of *p*-TsOH (equations 199 and 200)[256]. The rearrangements of bridged ketones

519 to α,β-unsaturated ketones **520** were reported to be greatly accelerated by both sulfuric acid and Lewis acids (equation 201)[234]. A very similar rapid Cope rearrangement was described for the SO_2-bridged polycyclic triene **521** (equation 202)[257].

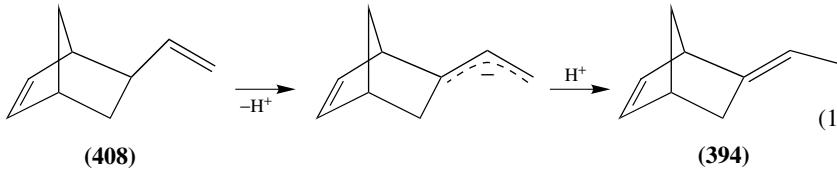
(501) **(502)** (189)



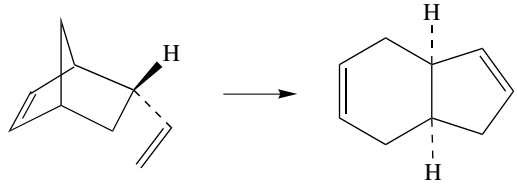
(503) **(504)** **(505)** (190)



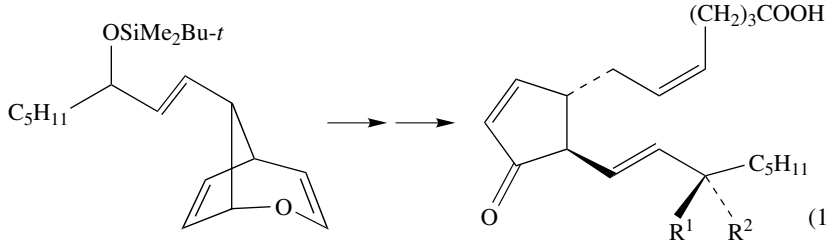
DCB = *o*-dichlorobenzene **(506)** (191)



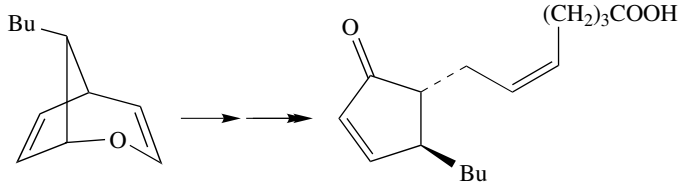
(408) (394) (192)



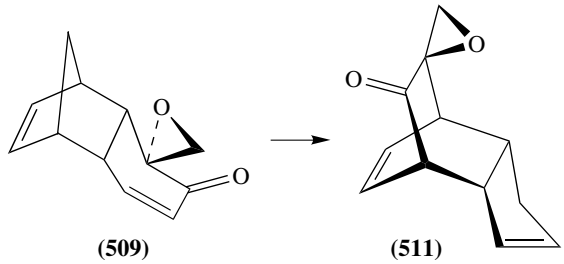
(507) (508) (193)



R^1, R^2 = H, OH (194)

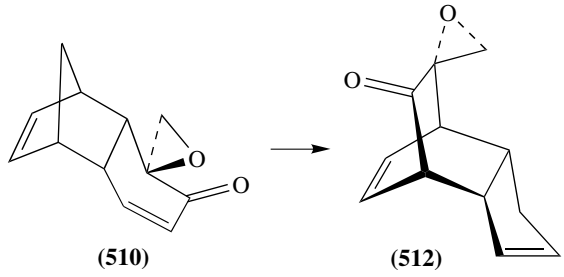


(195)

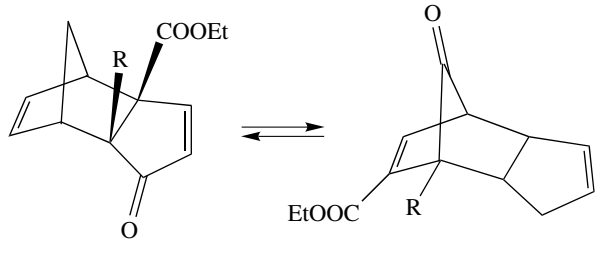


(509) (511) (196)

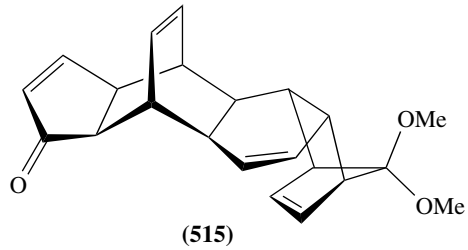
c. Divinylcyclobutanes. Thermal rearrangements of divinylcyclobutanes to form *cis*,*cis*-1,5-cyclooctadienes and 4-vinylcyclohexenes are well-known[88,230] and were already mentioned (see Section III.B.2, References 71 and 72). For example, thermolysis of the



(510) (512) (197)

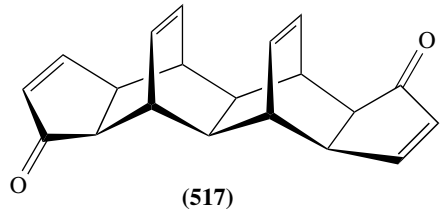


(513) (514) (198)



(515)

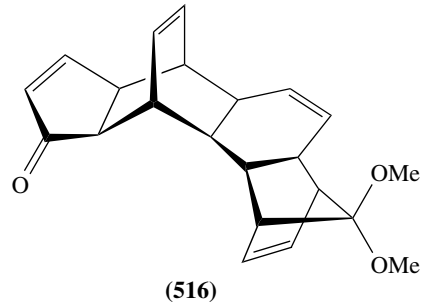
70% H^+ (199)



(517)

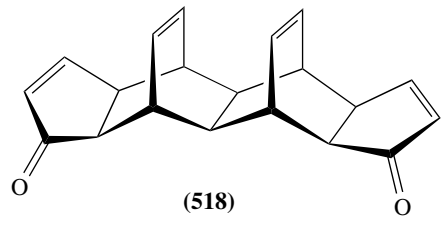
cycloadduct **522** obtained by photocyclization of the corresponding open-chain diethoxycarbonyl-substituted tetraene gives only *cis*-fused cyclooctadiene **523** (benzene, 130 °C, 4 h, *ca* 100%) (equation 203)[258]. However, more vigorous conditions (200 °C, 24 h) are required for the rearrangement of the isomeric cycloadduct **524** in which the cyclooctadiene **523** is again the major product (50%) together with the bicyclic diene **525**. Similarly, the heteroanalogues **526** and **527** undergo thermolysis at 200 °C for 22 h to yield *cis*-fused heterobicyclic product **528** (75%) (equation 204)[258]. Substrates **529** containing a

four-carbon chain between diene fragments are capable of cyclizing photochemically to afford the cycloadducts which undergo thermolysis to the cyclooctadienes **530**–**532** (in a ratio 5 : 1 : 2) in 42% total yield (equation 205)[258].

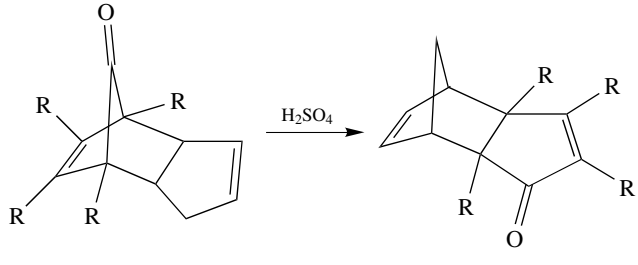


(516)

(200)

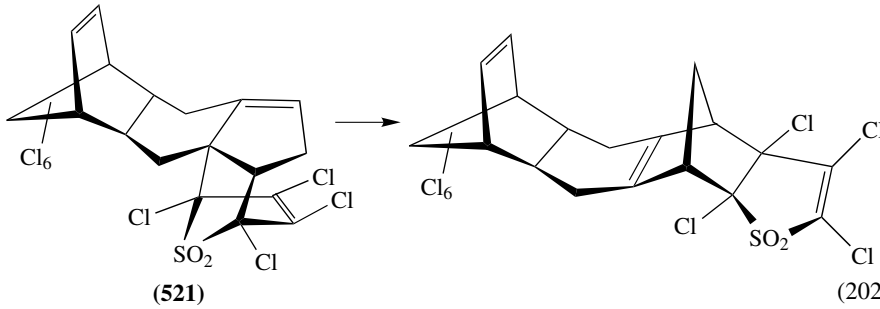


(518)



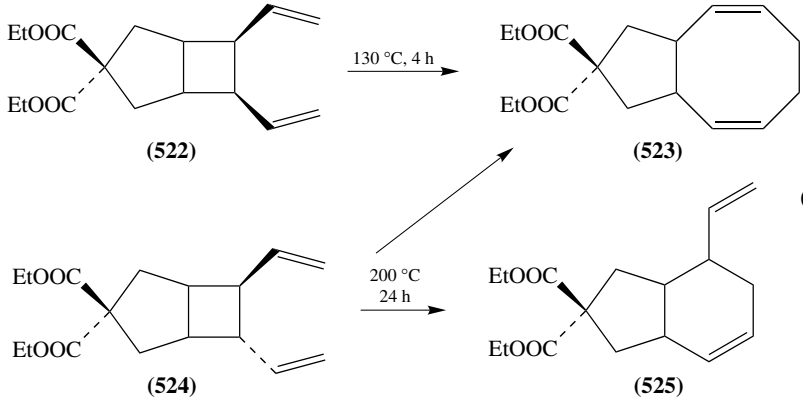
(519) R = H, Cl **(520)**

(201)

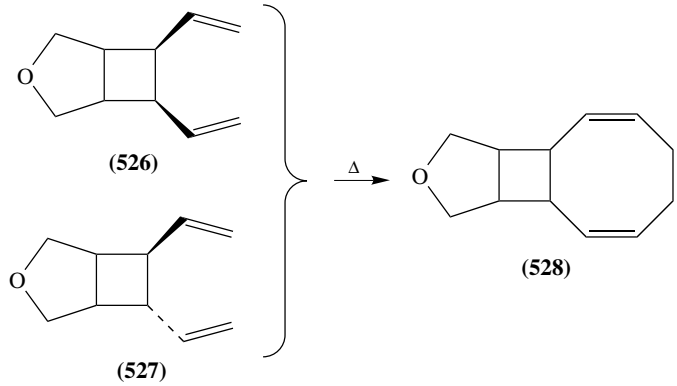


(521)

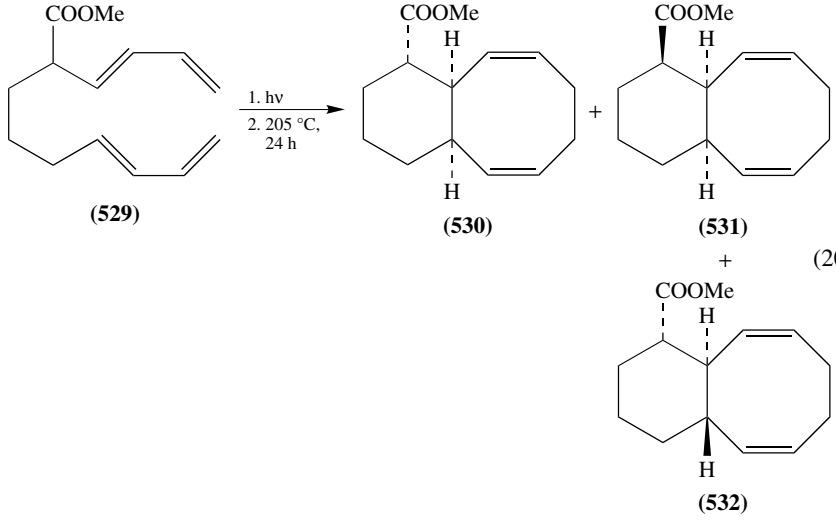
(202)



(522) **(523)** **(524)** **(525)** (203)

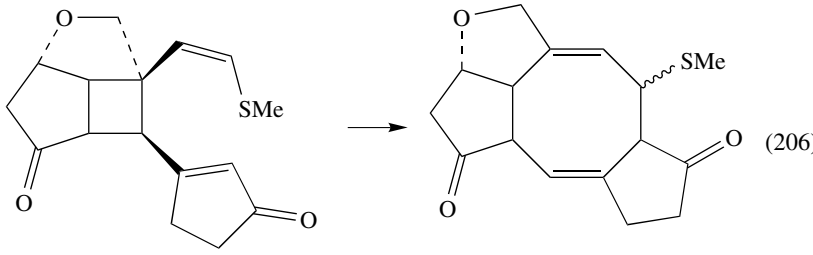


(526) **(527)** **(528)** (204)



(529) **(530)** **(531)** **(532)** (205)

The dicyclopenta[*a*,*d*]cyclooctane structure **534** which constitutes a characteristic element of some terpenoids was obtained in 100% yield by a very facile Cope rearrangement of the highly functionalized divinylcyclobutane derivative **533** on heating in benzene at 55 °C for 4 h. The mild conditions can be due to participation of the lone pair of the sulfur atom or to the strain energy of the divinylcyclobutane fragment (equation 206)[259].

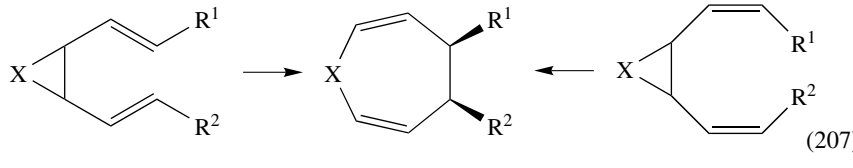


(206)

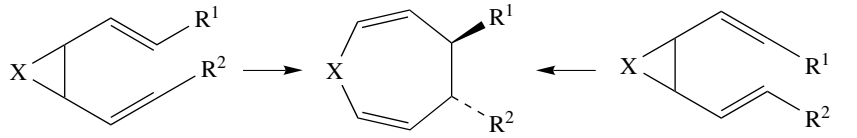
(533) **(534)**

d. Divinylcyclopropanes. Among the reactions discussed, the rearrangements of divinylcyclopropanes are of most importance. For instance, in the synthesis of various natural products containing densely functionalized seven-membered rings, the Cope rearrangement of *cis*-divinylcyclopropanes turned out as a most effective method with respect to stereocontrol, as it proceeds under mild conditions with very predictable stereochemistry. Therefore, a general approach which is based on a tandem 'cyclopropanation–Cope rearrangement' reaction is widely practiced. It is summarized in a recent survey[260].

In general, this approach can be represented by equations 207 and 208 wherein the formation of *cis*- and *trans*-substituted seven-membered rings (e.g. tropones or oxepines) is controlled by selection of appropriate isomeric divinylcyclopropanes or divinylepoxides as precursors. We will discuss here a series of examples which are not covered by a recent review[260].

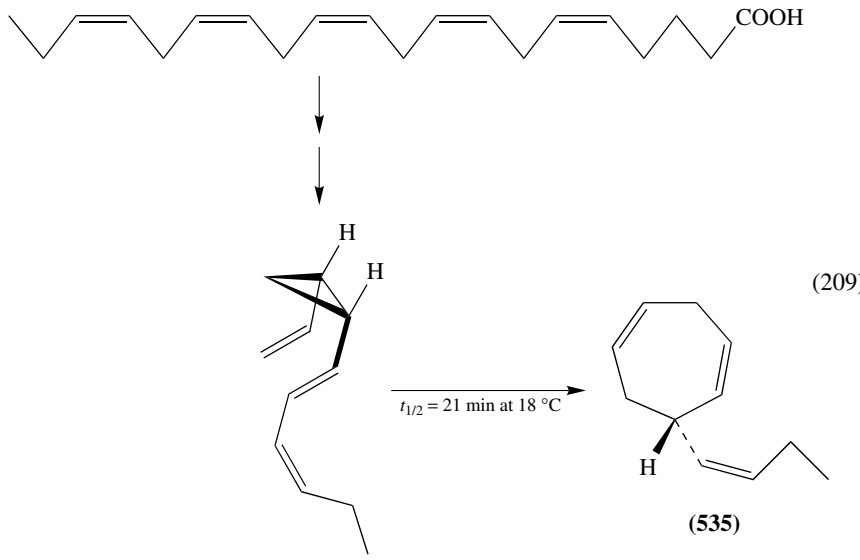


(207)



$X = CH_2, O$ (208)

To prepare ectocarpene **535** and desmarestene **536** which are examples of plant chemoattractants, synthetic approaches which can be named 'cyclopropanation–Cope rearrangement' (equation 209) and 'Wittig reaction–Cope rearrangement' (equation 210), respectively, were employed[261]. It suffices to say that the end products **536** and **537** were isolated in high enantiomeric purity (⩾94% ee).



(209)

(535)

A stereoselective convergent synthesis of hydroazulenes **538** was also based on a tandem intermolecular cyclopropanation–Cope rearrangement sequence with predictable stereocontrol (equation 211)[262].

It was emphasized that a particular advantage of this approach over other synthetic strategies based on Cope rearrangement consists in the facile way of selectively preparing *cis*-divinylcyclopropane intermediates[262].

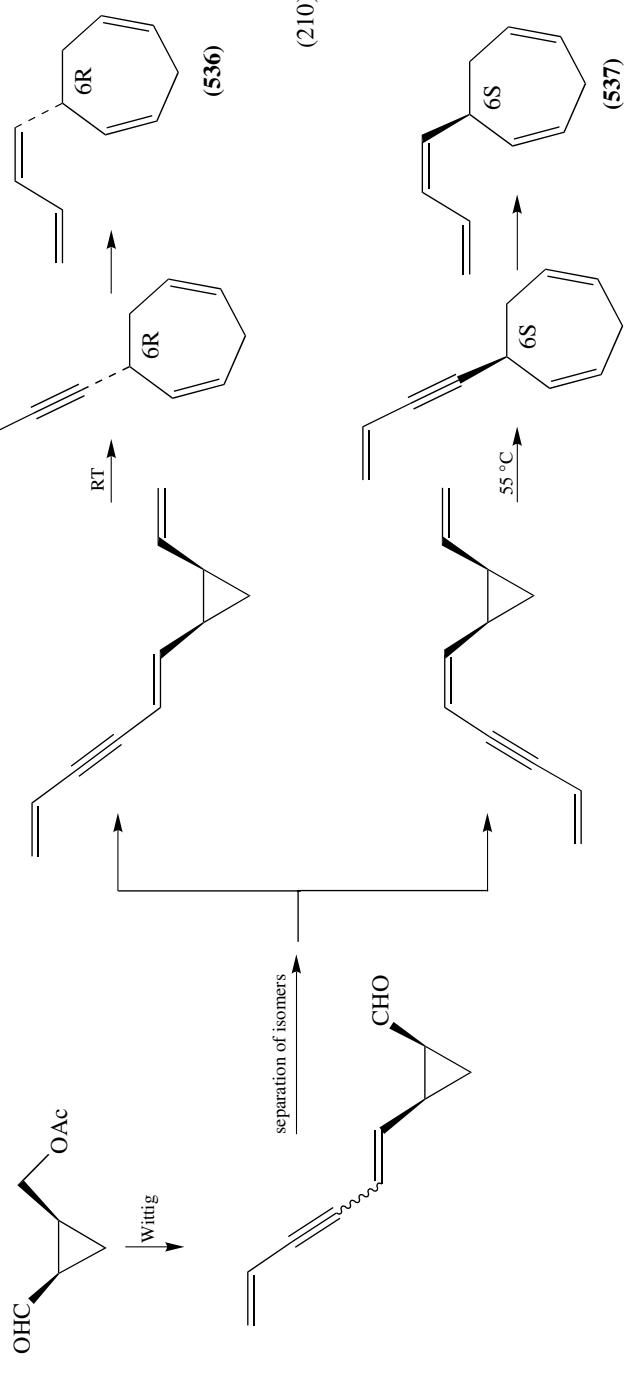
A method for highly efficient asymmetric cyclopropanation with control of both relative and absolute stereochemistry uses vinyldiazomethanes and inexpensive α-hydroxy esters as chiral auxiliaries[263]. This method was also applied for stereoselective preparation of dihydroazulenes. A further improvement of this approach involves an enantioselective construction of seven-membered carbocycles **(540)** by incorporating an initial asymmetric cyclopropanation step into the tandem cyclopropanation–Cope rearrangement process using rhodium(II)-(*S*)-N-[*p*-(*tert*-butyl)phenylsulfonyl]prolinate [$Rh_2(S-TBSP)_4$] **539** as a chiral catalyst (equation 212)[264].

An interesting approach to form a divinylcyclopropane structure capable of rearranging into seven-membered functionalized derivatives consists of the silyloxylation of cyclic ketones **541** followed by a spontaneous Cope rearrangement to produce the cyclic enol esters **542** which then hydrolyzed to ketones **543** (equation 213)[265].

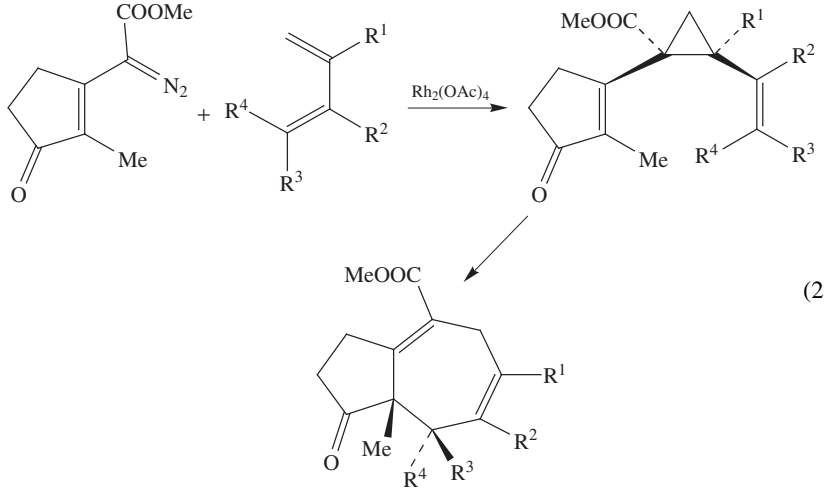
Flash vacuum pyrolysis of tricyclo[7.1.0.$0^{4,6}$]deca-2,7-diene **544** is accompanied by a long cascade of rearrangements leading to various azulenes (equation 214)[266]. The structures of these products were determined by using the chlorine atoms as labels for the ^{13}C NMR measurements.

The dihydroxyoxepine moiety is a part of a fungal metabolite such as aranotin acetate exhibiting an antiviral activity. To prepare the 4,5-dihydroxyoxepines **546**, the Cope rearrangement of the corresponding divinylepoxides **545** was used (equation 215)[267–269].

In principle, the divinylcyclopropane structure discussed here is incorporated into very well known systems such as bullvalene **547**, barbaralane **548** and semibullvalene **549**, which very easily undergo a Cope rearrangement.


OHC
OAc
Wittig
separation of isomers
CHO
RT
55 °C
6R
6R
6S
6S
(536)
(537)

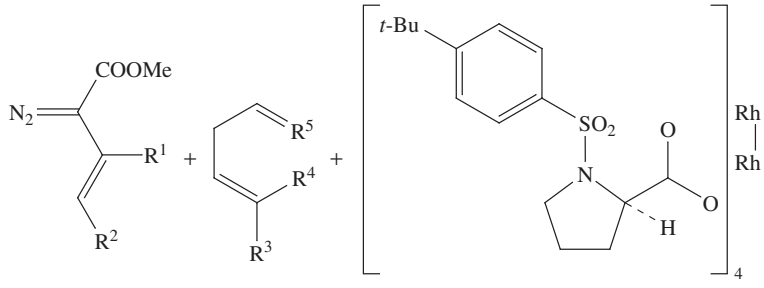
(210)



(211)

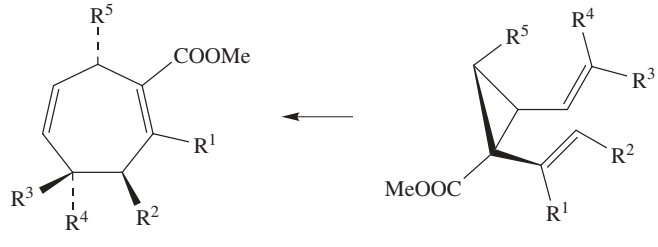
(538)

R^1, R^2 = H, Me; R^3, R^4 = H, OAc



(539)

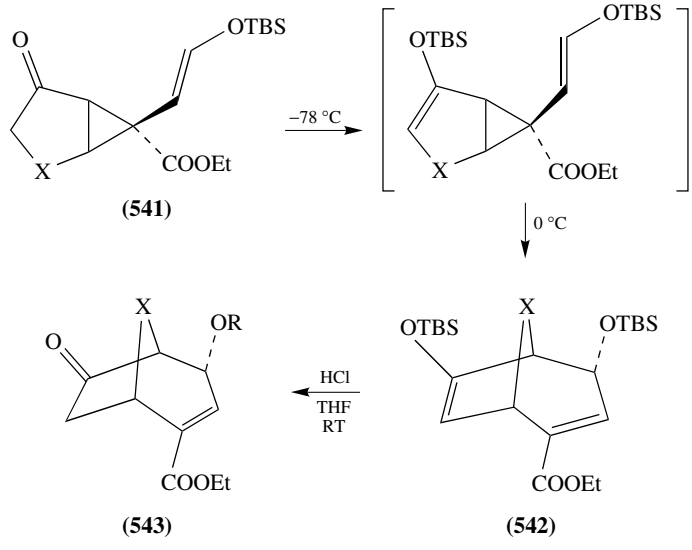
(212)



(540)

R^1 = H, Me; R^2 = H, Me, Ph, $CH=CH_2$, COOEt

R^1–R^2 = cyclo$(CH_2)_3$, cyclo$(CH_2)_4$

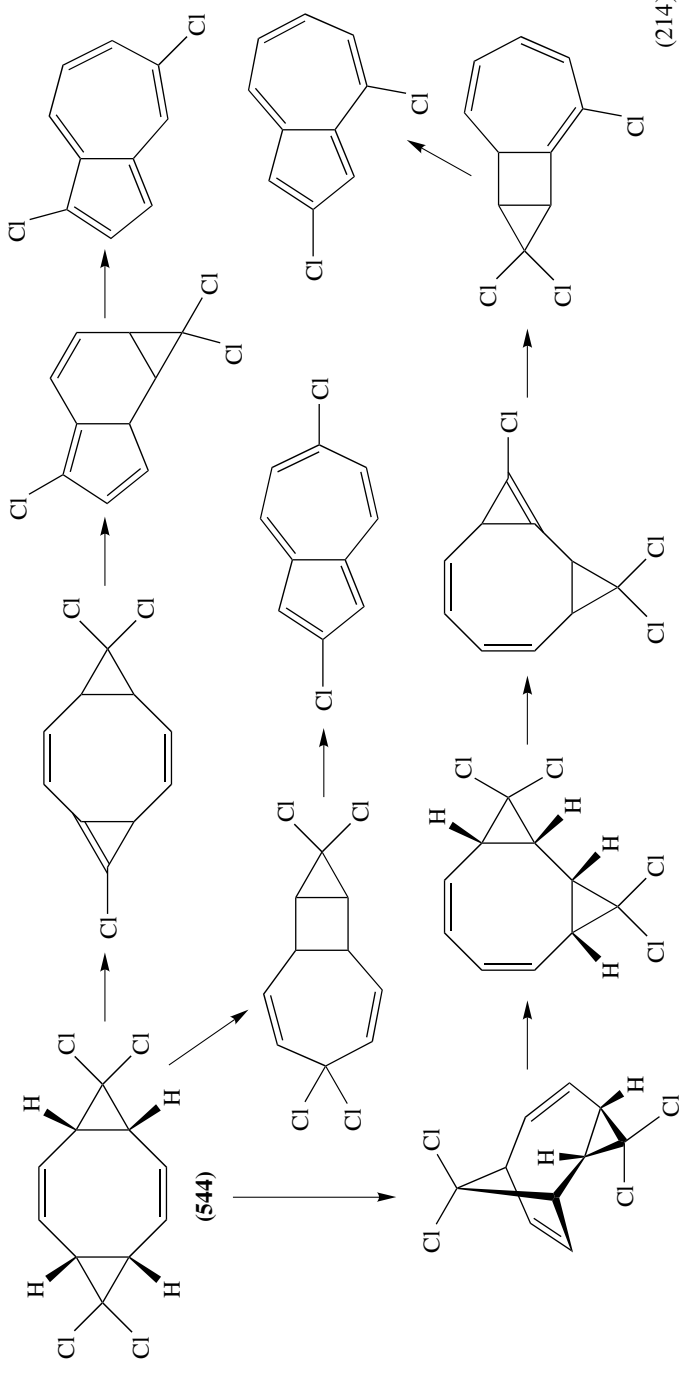


(213)

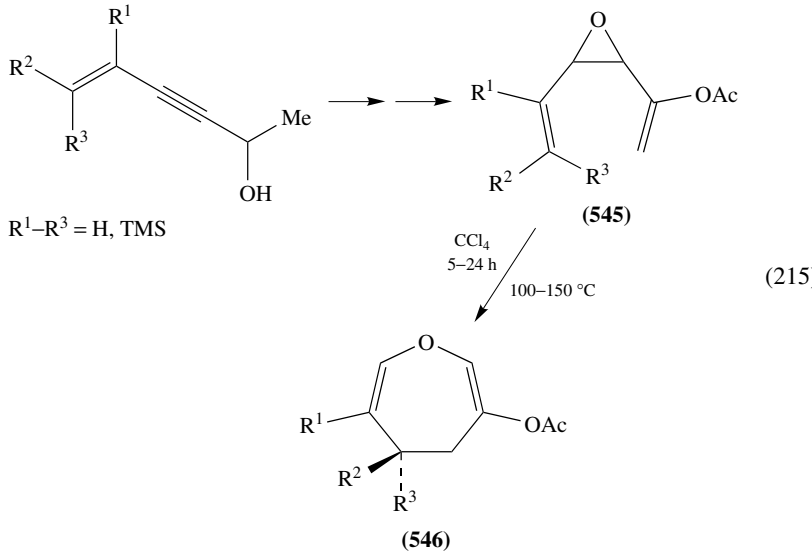
In spite of a very voluminous literature about bullvalene **547**, investigations in this field are still in progress. The solid state isomerizations of bullvalene in the temperature range between $-40\,^{\circ}C$ and $+85\,^{\circ}C$ were studied by using the carbon-13 magic angle spinning method (MAS NMR)[270]. These measurements have allowed to trace the separate steps of multiple Cope rearrangements as well as to estimate the activation energies of approximately 62.8 kJ mol^{-1} for the concerted Cope rearrangement/reorientation. The Cope rearrangement and the molecular reorientation in solid bullvalene have also been investigated by deuterium NMR spectroscopy in the temperature range $-13\,^{\circ}C$ to $+80\,^{\circ}C$[271].

Substituted bullvalenes no longer have the freely fluctuating structure. The preferable isomers are accompanied by others and equilibrium can be studied by means of low-temperature NMR spectroscopy. Since the bullvalene itself has four different positions in a rapid and reversible interconversion, some isomers of the substituted bullvalenes can possess a higher stability depending on the nature of substituents. Schröder and coworkers have investigated trimethyl- and tetramethylbullvalenes, hexamethylbibullvalenyl, penta- and hexabromobullvalenes as well as bullvalenes having one to six phenyl substituents[272−274]. The 4-, 6- and 10-positions in methyl-substituted bullvalenes are slightly preferable in respect to the 3-, 7- and 9-positions. No structure with a vicinal arrangement of two methyl groups was observed[272]. In contrast, pentabromobullvalenes constitute an equilibrium mixture of four isomers which can be separated by column chromatography. Two isomeric hexabromobullvalenes have virtually lost the ability for interconversion and they can be isolated as stable compounds[273]. Concerning the phenyl-substituted derivatives, some isomers starting with triphenylbullvalenes have exhibited a relatively high kinetic stability. This stability culminates for two isomers of hexaphenylbullvalenes which behave similarly to the hexabromo derivatives[274].

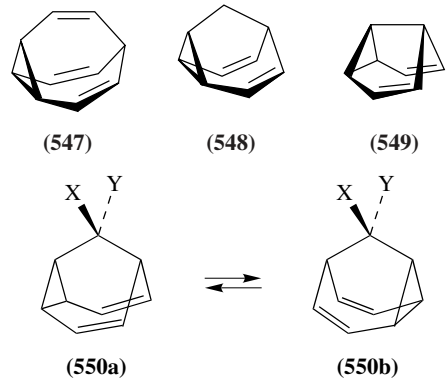
Barbaralane **548** (tricyclo[3.3.1.0^{4,6}]nona-2,7-diene) was first described in 1967 (see Reference 80 and literature cited therein). Barbaralane and its derivatives functionalized in the C(9) position **(550a,b)** are degenerate Cope systems whose equilibrium can be frozen


(544)
(214)

only at about −100 °C (equation 216). The activation energy for the interconversion of barbaralanes is about 36 kJ mol^{-1} and that for barbaralone is 49.4 kJ mol^{-1} [80].



(215)

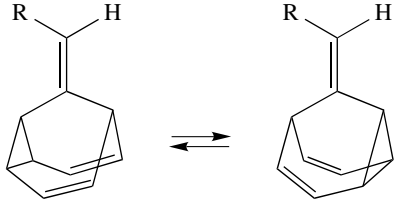


(216)

X = Y = H; X, Y = O (barbaralone); X = H, Y = OH; X = H, Y = Cl

The behavior of methylenebarbaralanes **551** monosubstituted in the methylene group is of great interest in respect to two problems: (1) the preference of either the *cis*-**(551a)** or *trans*-configuration **(551b)**, and (2) the possibility to determine the dependence of Cope rearrangement rate on the substituents (equation 217). According to ^{1}H NMR data obtained for these molecules having the fluctuating bonds and to temperature-dependent NMR spectra, structure **551a** is the more stable one[275]. It was found that 2,4,6,8-tetraphenyl- **(552)** and 2,6-dicyano-4,8-diphenylbarbaralane **(553)** in solution are capable of extremely rapid Cope rearrangement[276]. Compound **553** exists in solution as

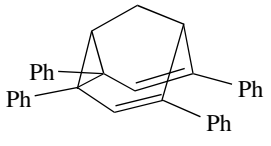
a pair of very quickly rearranging degenerate valence tautomers while the degeneracy is lifted in the solid state. As a result, the crystal consists of two rapidly rearranging but non-equivalent valence tautomers[276].



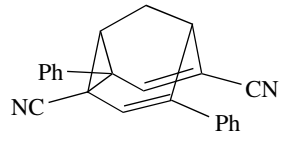
(217)

(551a) **(551b)**

R = H, F, Me, Ph, COOEt

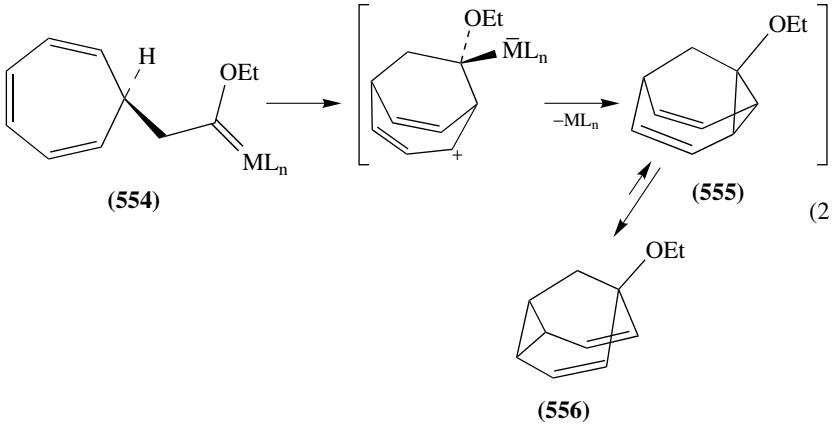


(552)



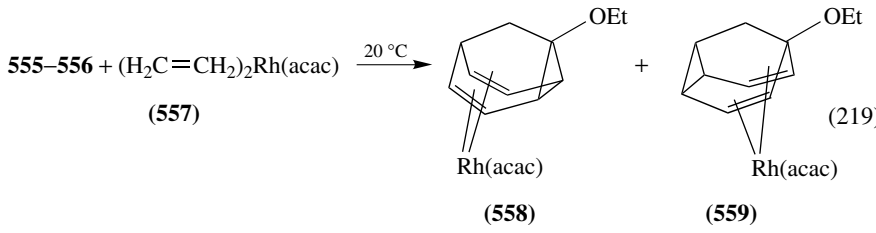
(553)

Thermolysis of (cycloheptatrienylmethyl)carbene complexes **554** [toluene, 1–2 h, 80–100 °C; $ML_n = Cr(CO)_5, W(CO)_5$] affords an equilibrium mixture of 4,5-homotropilidenes **555** and **556**. According to the NMR data and the results of AM1 calculations, the formation of isomer **556** (equation 218) is strongly favored[277]. This course of events was called 'intramolecular cyclopropanation', and it was shown that the equilibrium between the 4,5-homotropilidene complexes is significantly different from that of the metal-free ligands. By reaction of the latter (**555** and **556**) with bis(ethylene)rhodium 1,3-pentanedionate **557**, the complexes **558** and **559** of both 4,5-homotropilidenes were obtained in a 1 : 3 ratio. These complexes are non-fluxional and are configurationally stable at room temperature (equation 219)[277].



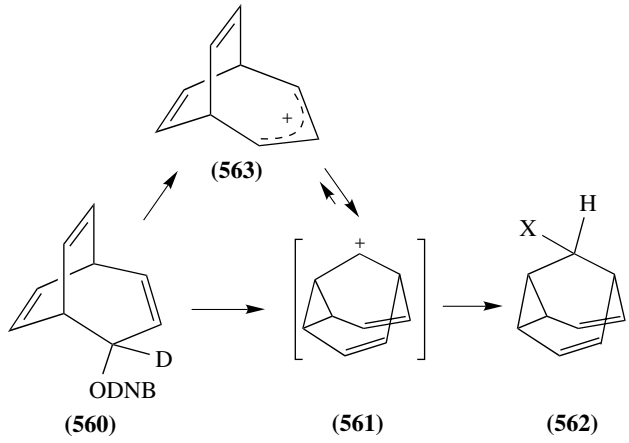
(554) **(555)** **(556)**

(218)

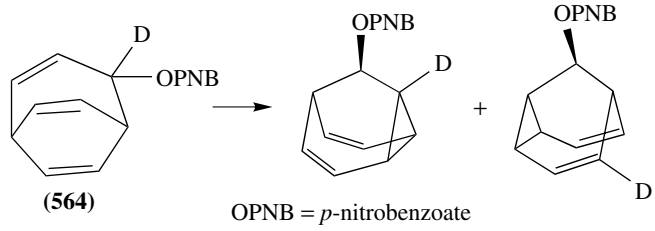


(219)

By means of deuterium labeling, the degree of degeneracy achieved during interconversions of bicyclic triene **560** and barbaralol **562** was studied[278]. Solvolysis of triene **560** (75 °C, 60% aqueous acetone with 10% excess lutidine) gave two products in a 1 : 1 ratio, namely 9-barbaralyl dinitrobenzoate **(562a)** and 9-barbaralol **(562b)**. The deuterium distribution in these products was determined by NMR. It was suggested that the 9-barbaralyl cation **561** is more stable than the bicyclononatrienyl cation **563** (equation 220)[278]. An analogous independent comparison of cations **561** and **563** was made at the same time by using the solvolysis (80% aqueous acetone, 100–125 °C) of bicyclotriene *p*-nitrobenzoate **(564)** (equation 221)[279].



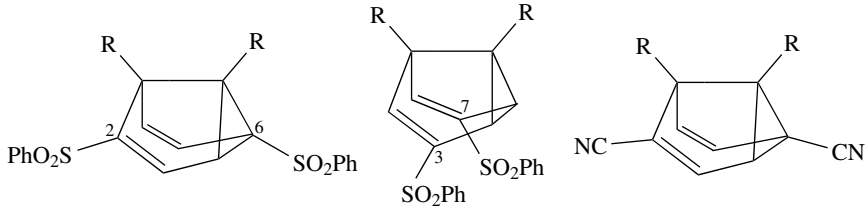
(220)



(221)

The various derivatives of another fluxional system, i.e. semibullvalene **549**, have been described in a series of publications[280–283]. To estimate the influence of substituents at

the bridgehead position as well as the effect of the size of 1,5-fused rings, the functionalized semibullvalenes **565** and **566** were studied by using X-ray diffraction analysis and ^{13}C NMR spectroscopy[280]. It is interesting that cyano groups in the 2,6-positions **(567)** impart unusual properties to semibullvalenes, for instance a color in the absence of any chromophor and a reversible thermochromism, while no such influence is observed in the case of the 3,7-dicyano derivatives.

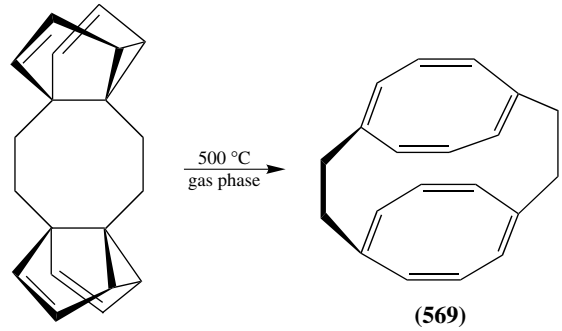


(565) **(566)** **(567)**

R = H, Me

(a) R = H, **(b)** R = Me,
(c) RR = $(CH_2)_3$, **(d)** RR = $(CH_2)_4$,
(e) RR = $(CH_2)_6$, **(f)** RR = $(CH_2)_{10}$

The synthetic application of semibullvalenes can be illustrated by the preparation of the double-decked [8]-annulene **569** from the thermal rearrangement of bis(semibullvalene) **568** (equation 222)[284].



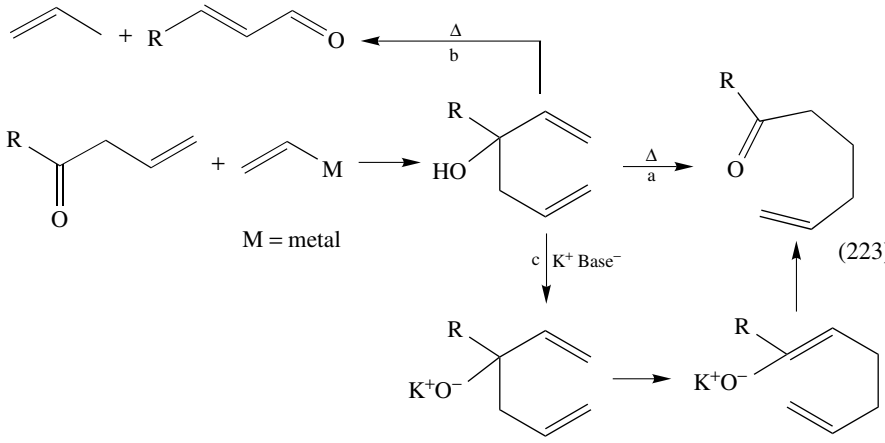
(222)

(568) **(569)**

D. Oxy-Cope Rearrangement

As mentioned above, the introduction of functional substituents into diene systems can change the conditions and sometimes even the direction of their rearrangements. In other words, the functionalization extends very considerably the synthetic potential of the rearrangement. The most obvious case is the oxy-Cope rearrangement, which is widely adopted now in organic synthesis since the preparative value of this reaction stems from the following important factors: (1) readily available starting materials; (2) high potential of efficient chirality transfer; (3) ample possibilities to control the reaction rate using, e.g., an anionic variant, and (4) the readiness of the resulting unsaturated carbonyl compounds to participate in further transformations. In addition, the oxy-Cope rearrangement can be

virtually made irreversible. Consequently, the oxy-Cope rearrangement can be represented by a general scheme (equation 223).



(223)

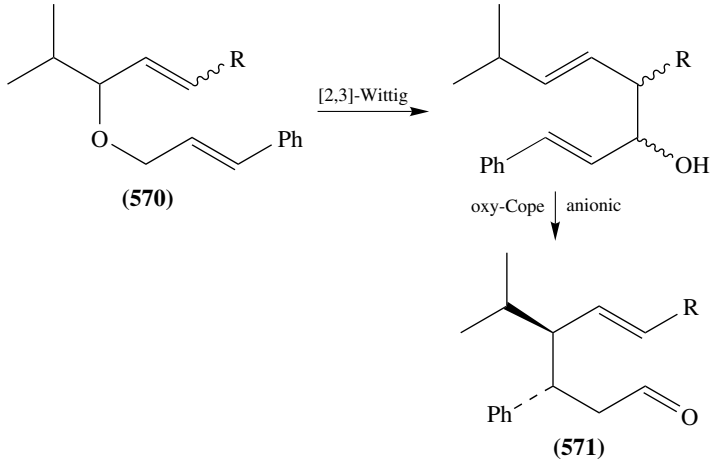
The oxy-Cope rearrangement can be thermally induced (equation 223, path a) but this process competes with an other well-established, concerted pericyclic reaction, i.e. the β-hydroxyolefin retro-ene cleavage (path b)[209]. However, it was found that the oxy-Cope rearrangement can be accelerated under base-catalysis conditions (e.g. in the presence of potassium alkoxides) by a factor of 10^{12} (the so-called 'anionic oxy-Cope rearrangement', path c)[285,286]. This base-induced acceleration is attributable to a dramatic decrease in the strength of the carbon–carbon bond adjacent to the OX-group in the sequence (OX = OH, ONa, OR, O^-) from about 384.3 ± 5 kJ mol^{-1} to 310.7 kJ mol^{-1}, according to *ab initio* calculations[287]. It is noteworthy that the rate of oxy-Cope rearrangement can be also affected by high pressure in the range 0.1–10 kbar. From experimental data for a family of [3,3]-sigmatropic rearrangements including the oxy-Cope process, an equation was derived which correlates the reaction rate and the pressure applied. The results corroborate the concerted mechanism of oxy-Cope rearrangement[288].

The synthetic aspects of the oxy-Cope rearrangement have been throughly summarized in a comprehensive review[289]. From the recent literature data, it is concluded that the anionic oxy-Cope process is most frequently used owing to a combination of low reaction temperature, a favorable thermodynamic driving force and high stereoselectivity. When the precursors are properly designated stereochemically, the oxy-Cope rearrangement provides a high level of diastereoselection and asymmetric transmission[290,291].

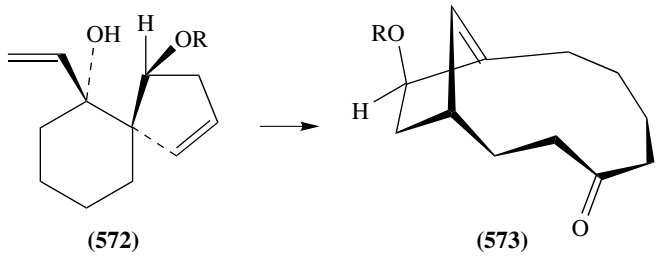
For instance, the one-pot tandem reaction '[2,3]-Wittig–anionic oxy-Cope rearrangement' affords the unsaturated aldehydes **571** starting from the bis-allylic ethers **570** at a high level of stereocontrol[291–294] (equation 224). It was shown that the efficiency of chirality transfer in anionic oxy-Cope rearrangements is determined only by the orientational preference of the oxyanionic bond in the precursors having a single carbinol carbon chiral center[295].

However, the resulting carbonyl products of the oxy-Cope rearrangement are sometimes very sensitive to strong bases. In certain cases this complication can be overcome by simply heating the starting carbinols which have a protective group at the oxygen atom. The rearrangement of spirobicycle **572** to bridged ketone **573** failed upon treatment with KH, $KN(SiMe_3)_2$ and other potassium bases, but it was carried out in 92% yield by

heating diene **572** in decalin at 190 °C for 9 h (equation 225)[296]. A similar, purely thermal oxy-Cope rearrangement was described using the siloxy-substituted polyfunctionalized 1,5-dienes **574** (equation 226)[297,298].

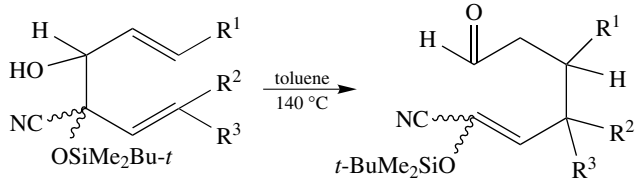


(570) **(571)** (224)



(572) **(573)** (225)

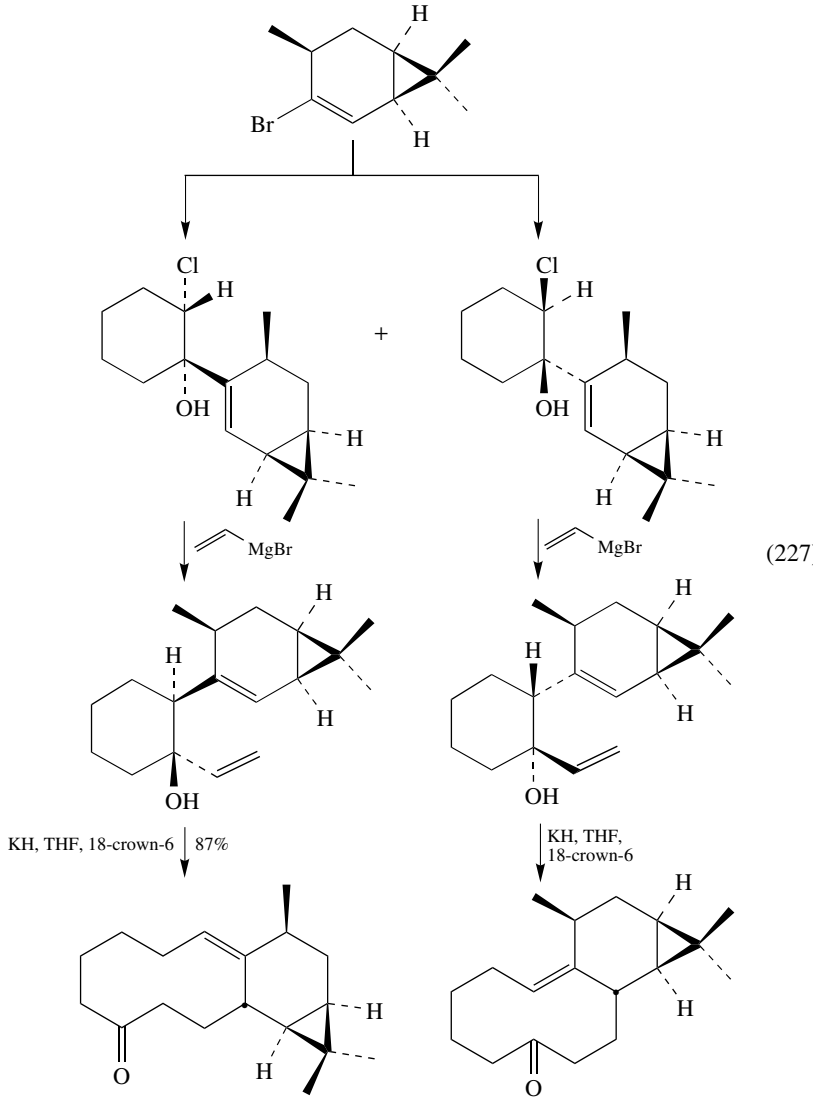
R = *t*-BuMe$_2$Si (TBDMS)



(574) (226)

An example of an intramolecularly competitive anionic oxy-Cope rearrangement was reported for synthesis of a carbon framework closely related to phorbol, a tetracyclic azulene derivative (cyclopropanebenzazulene) (equation 227)[299]. The synthetic approaches to potential precursors of taxane diterpenes and their structural analogues **577** were based on an anionic oxy-Cope rearrangement of bridged dienol **575** to form the tricyclic ketones **576** (equation 228)[300–303]. In the course of this investigation the first example of a thermally-induced retro-oxy-Cope rearrangement was found. In general, the oxy-Cope rearrangement is reputed to be an irreversible transformation (*vide supra*); however, when a solution of

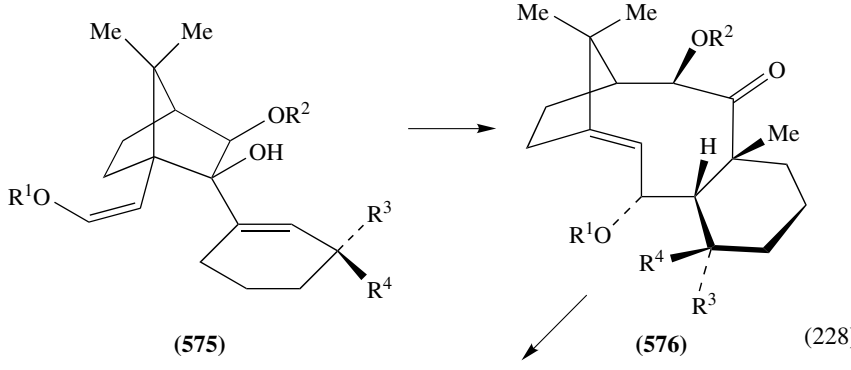
the unsaturated ketone **578** in toluene was refluxed under nitrogen for 5 days, two components of the reaction mixture were separated by chromatography (equation 229)[304]. A comparable heating of carbinol **579** for 3 days gave a mixture of 62% product **578** and 27% of the starting material **579**.



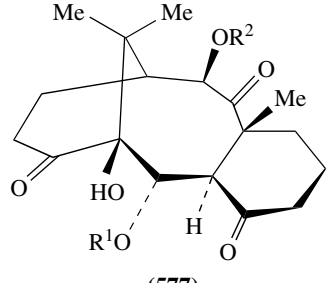
(227)

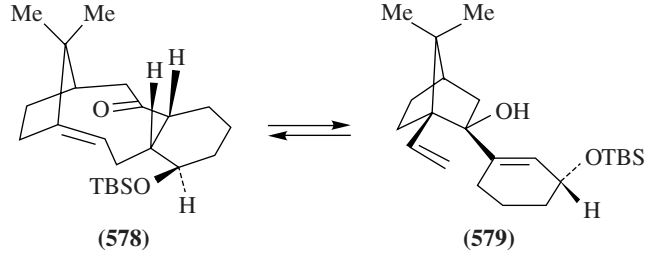
Anionic oxy-Cope rearrangement was also employed for the enantioselective total synthesis of compounds related to marine metabolites (equation 230)[305–307], as well as for the preparation of diterpenoide vinigrol (equation 231)[308] and cerorubenic acid-III

(equation 232)[309,310]. The anionic oxy-Cope rearrangement of bicyclo[2.2.2]octadienols **580** serves as a key step for the construction of substituted bicyclo[5.3.1]undecenones **581** and provides a convenient entry to the AB ring system of the taxane diterpenes (equation 233)[311]. Another approach to taxane derivatives is based on oxy-Cope rearrangement of 1,2-divinylcyclobutane alkoxides (see Section IV.C.2.c) (equation 234)[312]. Total synthesis of natural (−)-vulgarolide **584** from bicyclo[2.2.2]octadienol **583** uses also the anionic oxy-Cope rearrangement (equation 235)[313].



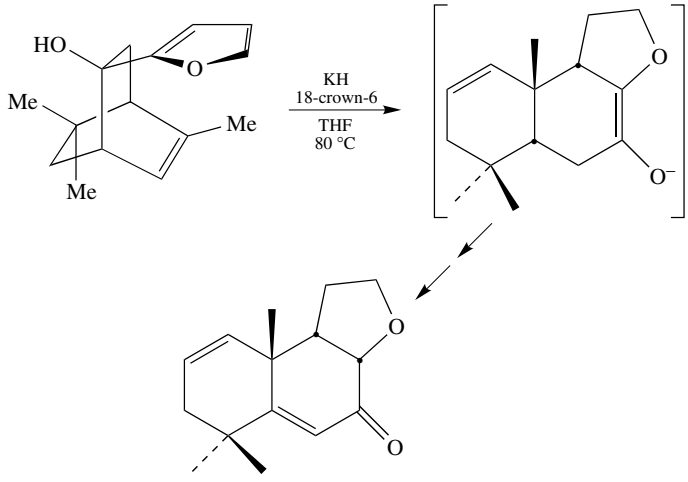
(228)



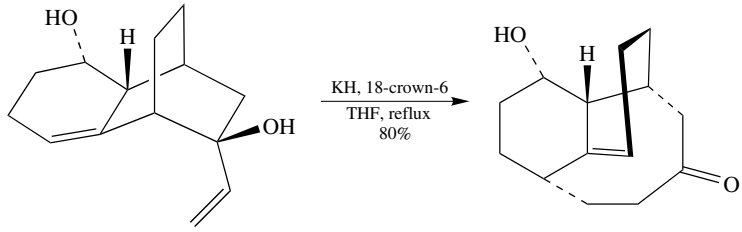


(229)

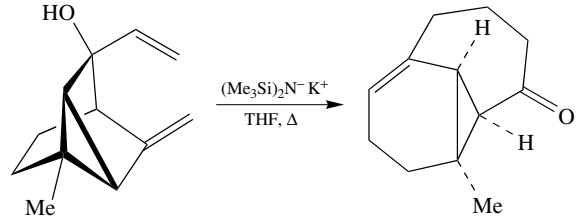
Anionic[29,314] and thermal[315] oxy-Cope rearrangements were reported as steps in the syntheses of various bicyclic systems **586** from divinylcycloalkanes **585** (see Section IV.C.2) (equation 236). The same anionic scheme was applied to prepare (±)-africanol and (±)-isoafricanol (hydroazulene systems)[316] as well as ajmaline-related alkaloids (equation 237)[317].



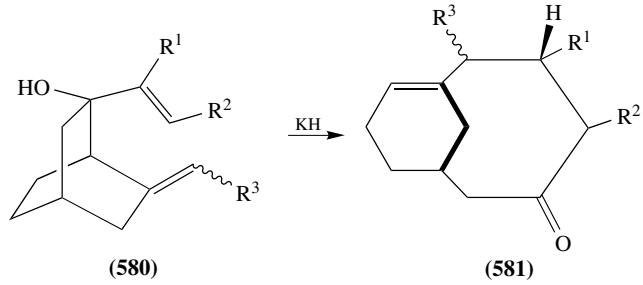
(230)



(231)



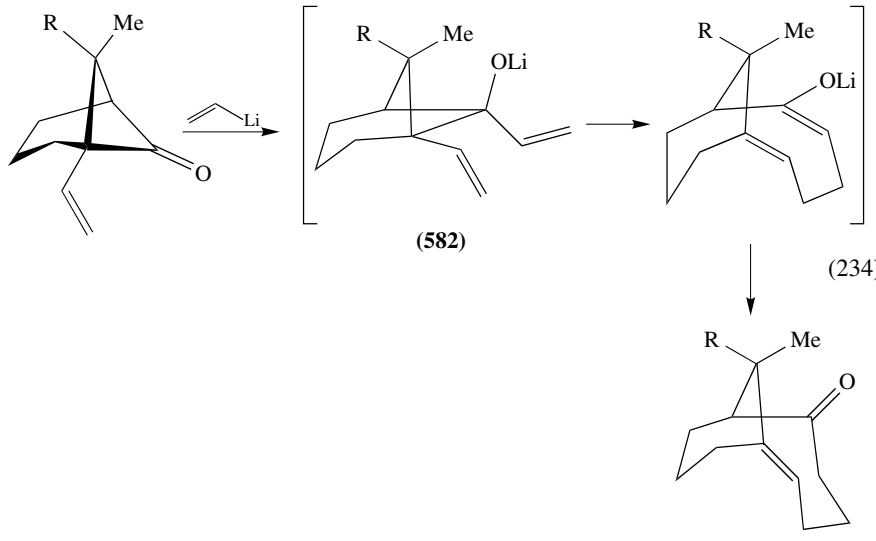
(232)



(580) **(581)**

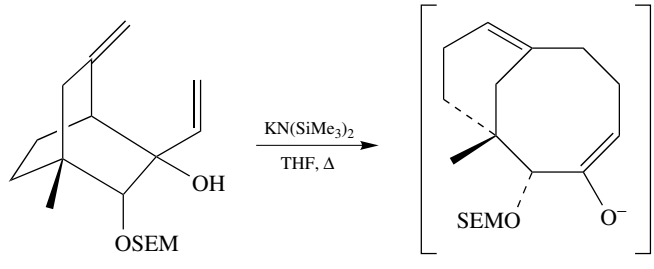
(233)

$R^1 = H$, $R^2 = H$, Me, $R^1R^2 = (CH_2)_4$; $R^3 = H$, Me, MeO



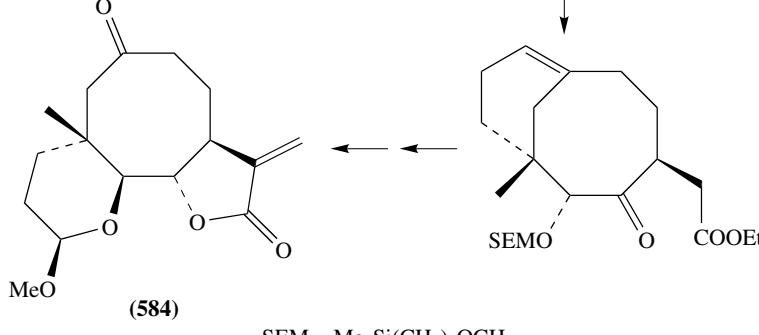
(582)

(234)



(583)

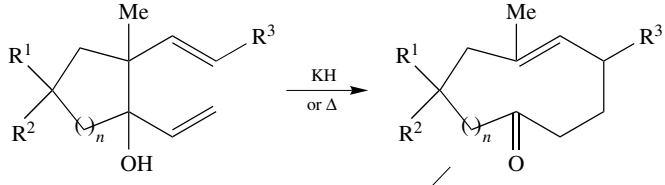
(235)



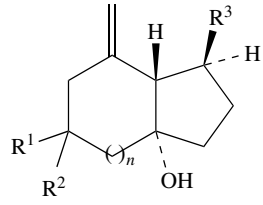
(584)

SEM = $Me_3Si(CH_2)_2OCH_2$

The estradiol derivative **588** was obtained in 91% yield via oxy-Cope rearrangement, which proceeded smoothly when the tertiary alcohol **587** was exposed to potassium hydride/18-crown-6 in THF at ambient temperature under an inert atmosphere

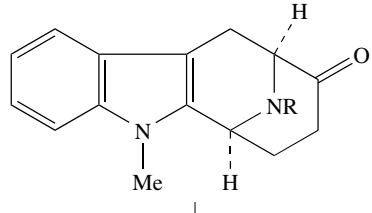


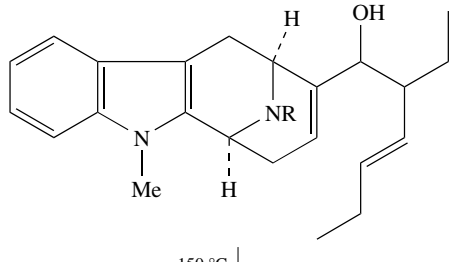
(585)



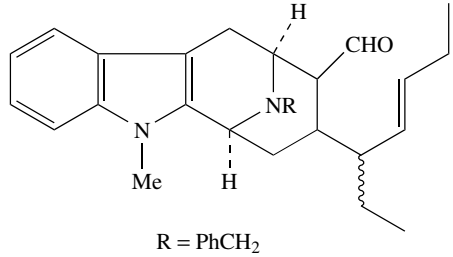
(586)

(236)



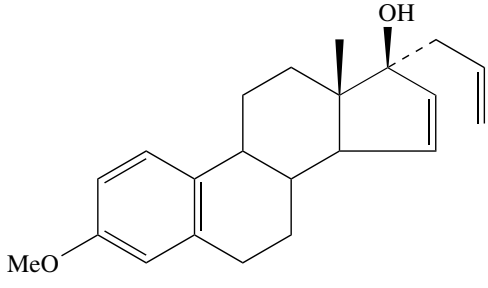


(237)



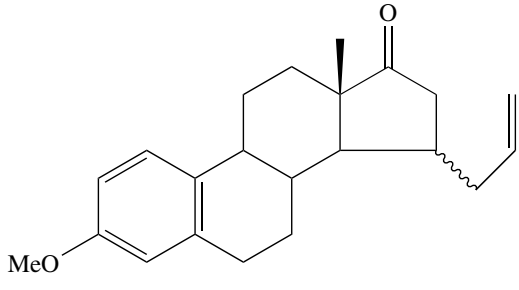
R = $PhCH_2$

(equation 238)[318]. Thermal oxy-Cope rearrangements were used to form the diterpene (equation 239)[319] and oxygen-bridged sesquiterpene (equation 240)[320] frameworks.

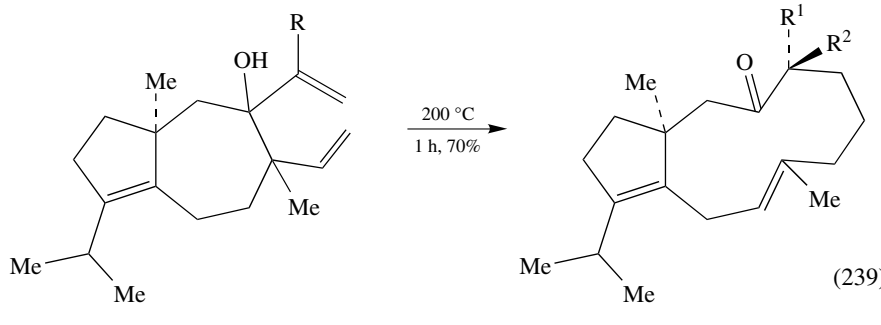


(587)

(238)



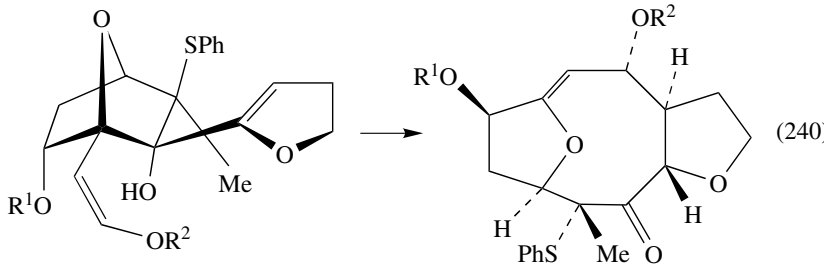
(588)



(239)

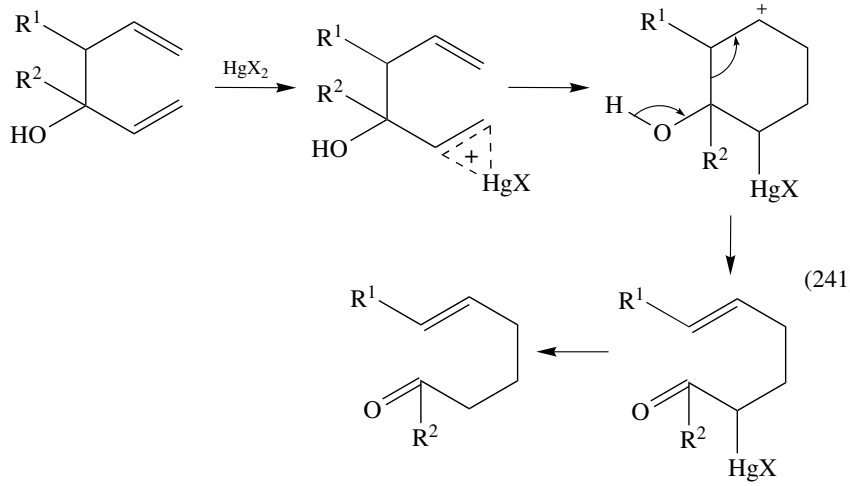
R = H, Me

$R^1 = R^2 = H$
$R^1 = H, R^2 = Me$
$R^1 = Me, R^2 = H$



(240)

The oxy-Cope rearrangement can be carried out using catalysis by mercury trifluoroacetate (equation 241)[321] as well as an antibody catalysis[322]. Reaction of two equivalents of 1-lithio-3,4-dihydronaphthalene with acenaphthenequinone at 0–20 °C affords a derivative of tricyclo[4.3.0.0^{5,9}]nonane **589** by double oxy-Cope rearrangement (equation 242)[323]. Another example of a little known double oxy-Cope rearrangement is the reaction of tricarbonyl chromium complex **590**, which undergoes a sequential transformation consisting of the double addition of vinyl lithium derivatives to the keto groups and subsequent double oxy-Cope rearrangement under very mild conditions (−78 °C) (equation 243)[324].



(241)

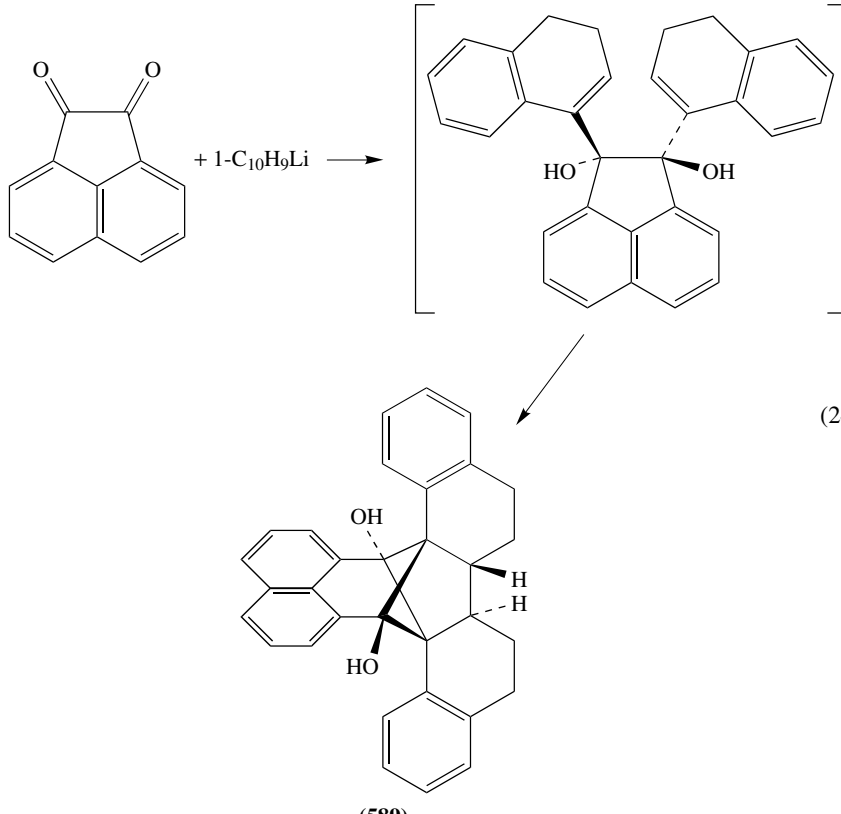
R^1, R^2 = Me, R^1R^2 = $(CH_2)_4$, $(CH_2)_{10}$ (35–75%)

X = $OCOCF_3$

E. Hetero-Cope Rearrangements

In principle, Cope-type rearrangements can occur in any 1,5-diene system consisting of six carbon and/or heteroatoms (equation 244). However, despite the apparent variety of potential possibilities, few examples of hetero-Cope rearrangements are known up to now. It should be noted that the structures depicted in equation 244 which can generally contain up to six heteroatoms are no longer real dienes. Nevertheless, we will briefly

consider the principal types of such systems as well as their transformations (for reviews, see Reference 325).

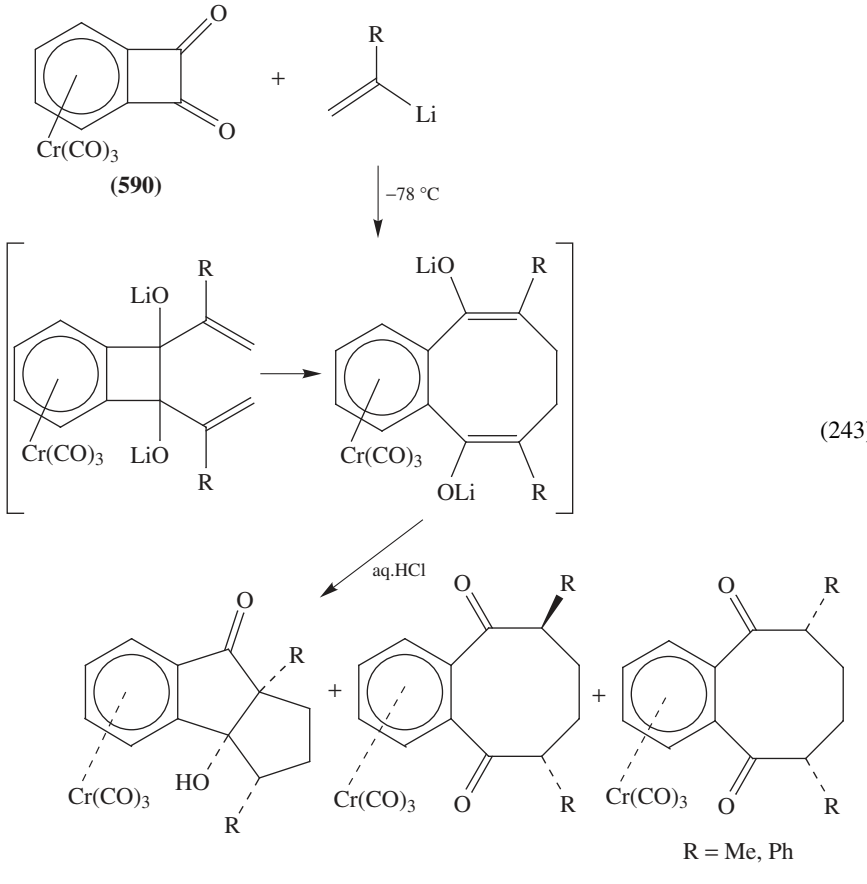


(242)

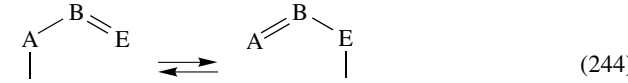
(589)

1. Claisen and related rearrangements

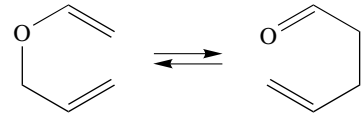
Among the hetero-Cope processes the Claisen rearrangement is the most known. It was discovered in 1912[326] as the first in a series of related [3,3]-sigmatropic isomerizations such as the Cope rearrangement. The synthetic significance of this reaction is obvious even by the numerous reviews about Claisen rearrangement (a list of 25 surveys since 1940 till 1979 is given in Reference 327; see also reviews 208 and 326). In principle, the Claisen rearrangement can be generalized by equation 245, i.e. it is a rearrangement of aliphatic allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds. It has been well established that a Claisen rearrangement proceeds through a cyclic chair transition state as an intramolecular concerted [3,3]-sigmatropic isomerization. The influence of substituents on the Claisen rearrangement[328,329] as well as some stereochemical aspects such as face selection have been studied recently[330]. Various synthetic methods such as tandem thermal Claisen–Cope rearrangements of coumarate derivatives **591** (equation 246)[331,332] were developed on the basis of Claisen rearrangement.



(243)

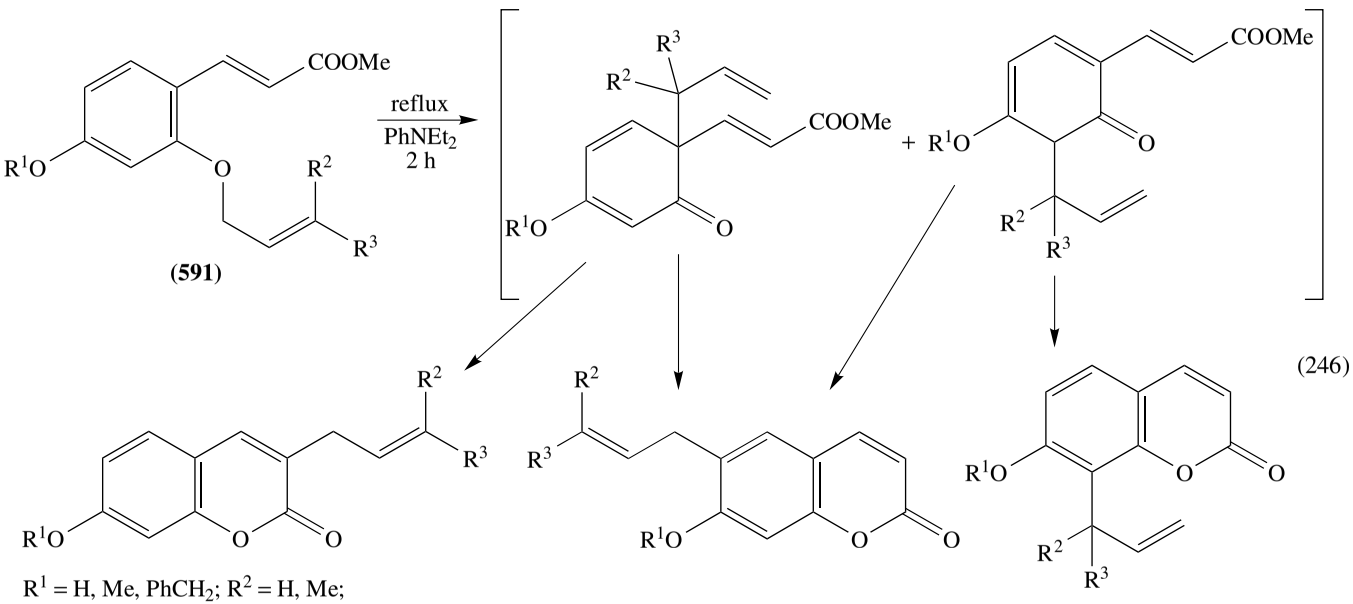


(244)



(245)

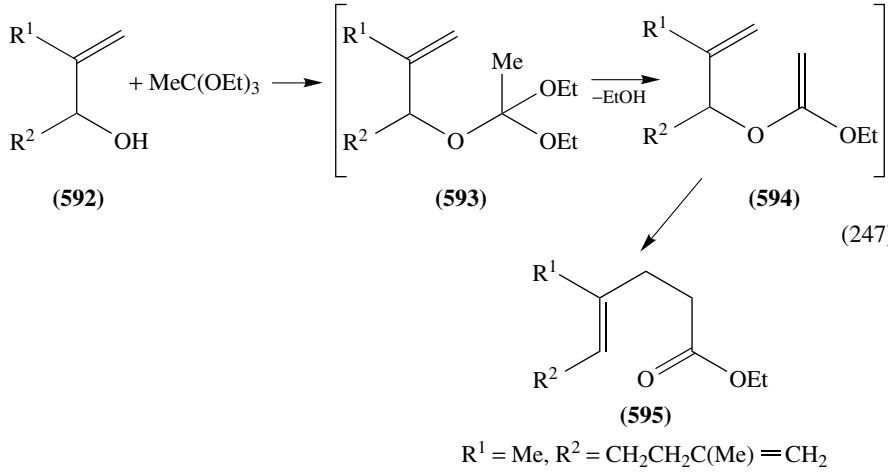
Further, the elegant biogenetic-like method for constructing steroid systems by a cascade of cyclizations deserves special attention. A simple, highly stereoselective version of the Claisen rearrangement leading to *trans*-trisubstituted olefinic bonds was discovered in 1970 by Johnson and colleagues[333]. This method is based on heating an allylic alcohol **592** with excess ethyl orthoacetate in the presence of a trace of weak acid (e.g. propionic acid). The dialkoxycarbenium cations evidently formed under such conditions react with the hydroxy group of alcohol **592** to give the mixed orthoesters **593** and then ketene



R^1 = H, Me, $PhCH_2$; R^2 = H, Me;

R^3 = H, Me, $(CH_2)_2CH{=}CMe_2$, $(CH_2)_2CH{=}C(Me)\text{-}(CH_2)_2CH{=}CMe_2$, etc.

acetals **594**, which undergo rearrangement to form the olefinic esters **595** in good yields (*ca* 90%) (equation 247). This general approach was later used for a series of biomimetic syntheses of various polycycles. For instance, the total synthesis of all-*trans*-squalene **597** from succinic dialdehyde **596**, which is about 98% stereoselective for each double bond, is exemplified by the synthetic sequence of equation 248[333]. Further examples of this fruitful approach to the synthesis of steroid systems (equations 249 and 250) were described in numerous papers[334–343] and reviews[344,345].

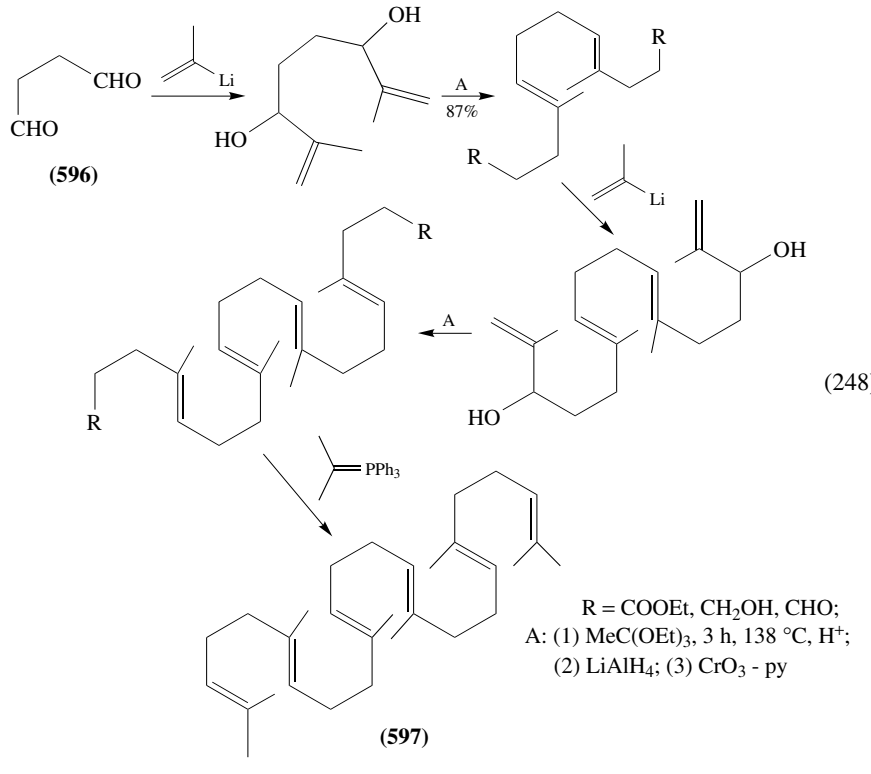


(247)

An analogous method based on treatment of the carbohydrate allyl alcohol **598** with an orthoester followed by Claisen rearrangement (called here the 'oxa-Cope rearrangement') was employed for the preparation of sphingosines (equation 251)[346]. An interesting example of a tandem reaction consisting of Claisen rearrangement and a subsequent shift of a carbon–carbon double bond was described as 'a silicon mediated homo-Claisen rearrangement' (equation 252)[326].

Along with the Claisen rearrangement, other related reactions are applicable for the preparation of natural products. For instance a [2,3]-Wittig rearrangement is one step in the stereospecific synthesis of HMG-CoA reductase inhibitor pravastatin[347] and in the total synthesis of the HMG-CoA synthase inhibitor 1233A[348] according to the general scheme (equation 253).

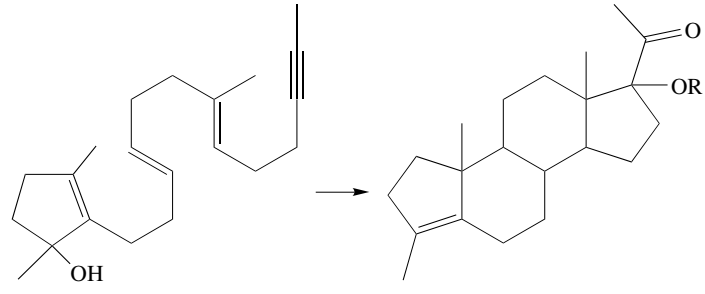
In order to prepare *cis*-jasmone, a route to γ-ketoaldehydes was developed by using a thio-Claisen rearrangement (equation 254)[349]. The same rearrangement is the basis of a methodology for the diastereoselective synthesis of some branched homoallylic amine derivatives[350]. The rearrangement occurs at room temperature (equation 255). Schroth and coworkers have investigated[351,352] the stereochemistry and reaction conditions for the chemical transformations of 3-*exo*-3′-*exo*-(1*R*, 1′*R*)-bis-thiocamphor **601** as a versatile source of functionally different 3,3′-bibornane derivatives. Compound **601** was obtained from (1*R*)-thiocamphor **599** with sodium hydride in benzene and subsequent oxidation with iodine in benzene. The intermediate disulfide **600** undergoes a spontaneous 'dithio-Cope' rearrangement to form **601** (equation 256). A similar thermal **602** → **603** rearrangement was assumed to be one step in the preparation of heterocyclic 1,2-dithiine precursors for the synthesis of 'dithioxothioindigo' (equation 257)[353].



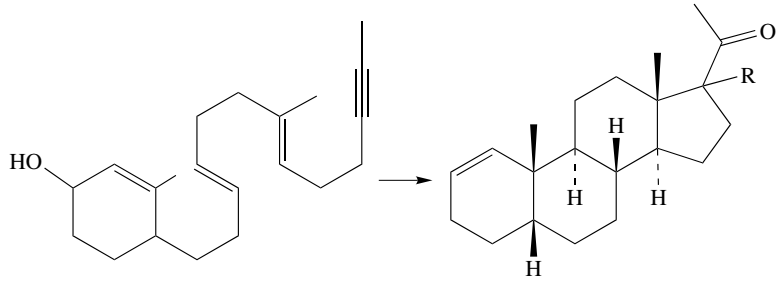
(596)

(597)

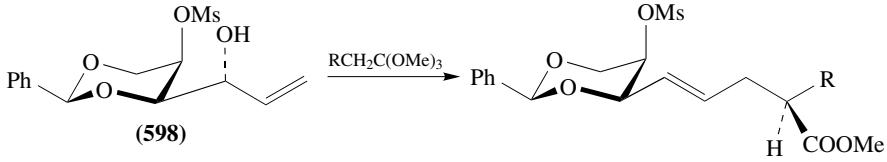
(248)



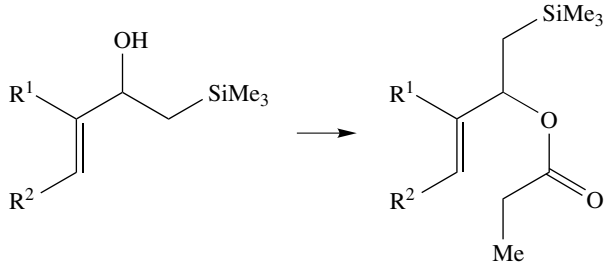
(249)



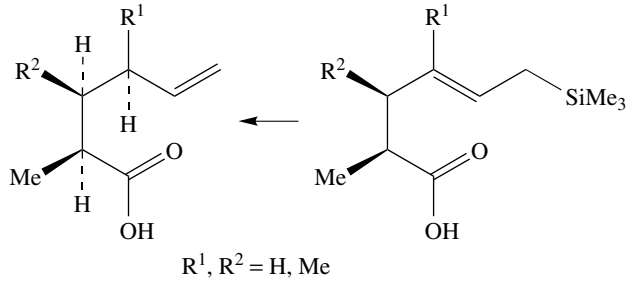
(250)



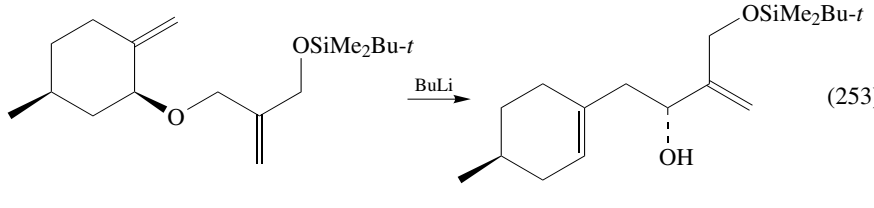
R = H, Me, Pr (251)



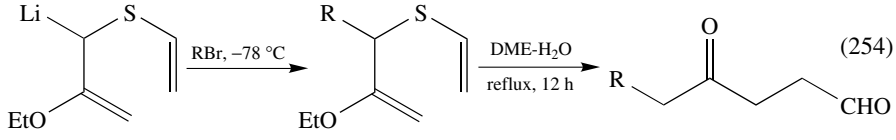
(252)



R^1, R^2 = H, Me



(253)

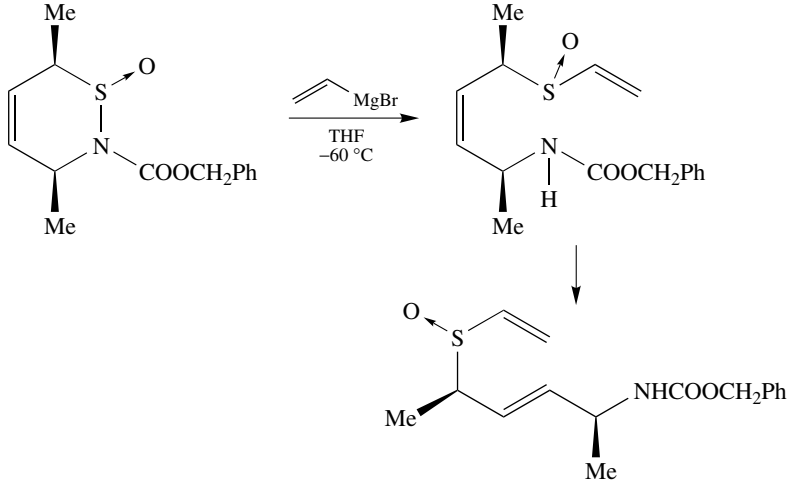


(254)

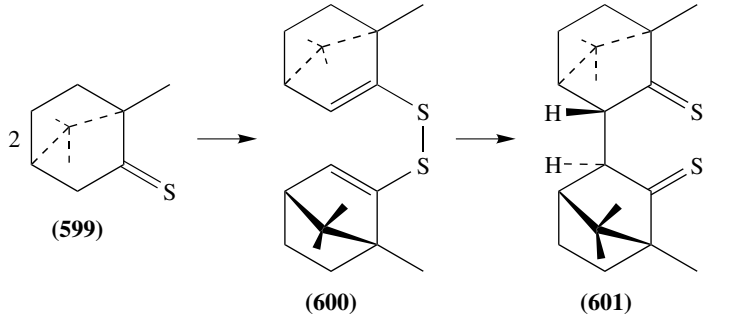
R = *n*-C_5H_{11}(66%), allyl (70%), $CH_2CH{=}CHEt$ (56%)

A disputable problem of the cationic 'oxa-Cope' rearrangement (equation 258) is whether open-chain oxonium ions are formed during transformations of 4-vinyl-1,3-dioxolanes **604** into acyltetrahydrofurans **605** (equation 259) as well as of methyl

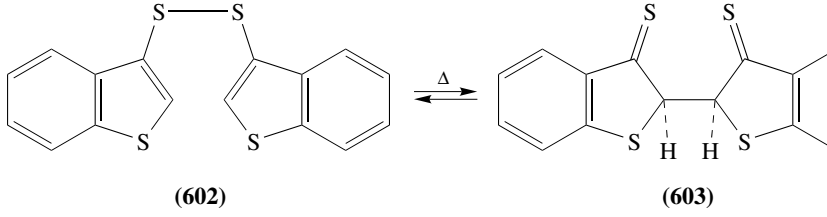
2-acetoxy-2-alkenoxyacetates **606** into tetrahydropyran derivatives **607** (equation 260)[354–356]. It is well known that the introduction of a charged atom causes a large increase in the [3,3]-sigmatropic rearrangement rate[11,325]. Typical examples are the anionic oxy-Cope rearrangement (*vide supra*) and the 2-azonia-Cope rearrangement



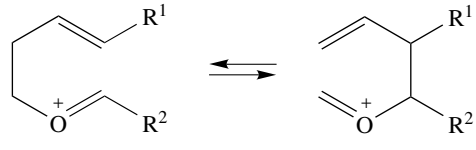
(255)



(256)

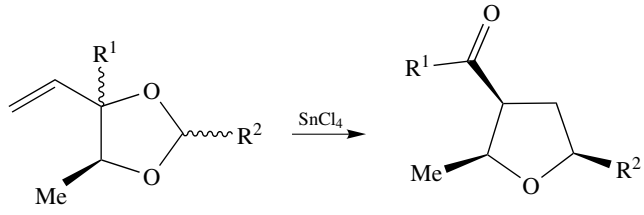


(257)



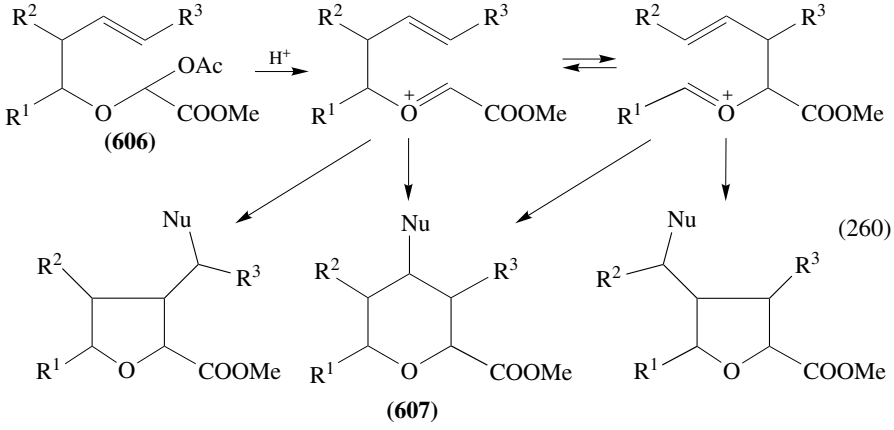
(258)

(*vide infra*). The so-called aza-Cope–Mannich reaction (**608** → **609**) constitutes an elegant entry to 3-acyl-pyrrolidines **609** which can be very useful in alkaloid total syntheses (equation 261)[356]. In a recent paper[356] clear evidence is presented that 2-oxonia-Cope rearrangement does proceed via intermediates **608** (X = O) in certain cases.



(604) **(605)** (259)

R^1 = Me, Bu; R^2 = Me, Ph, (*E*)-CH═CHMe



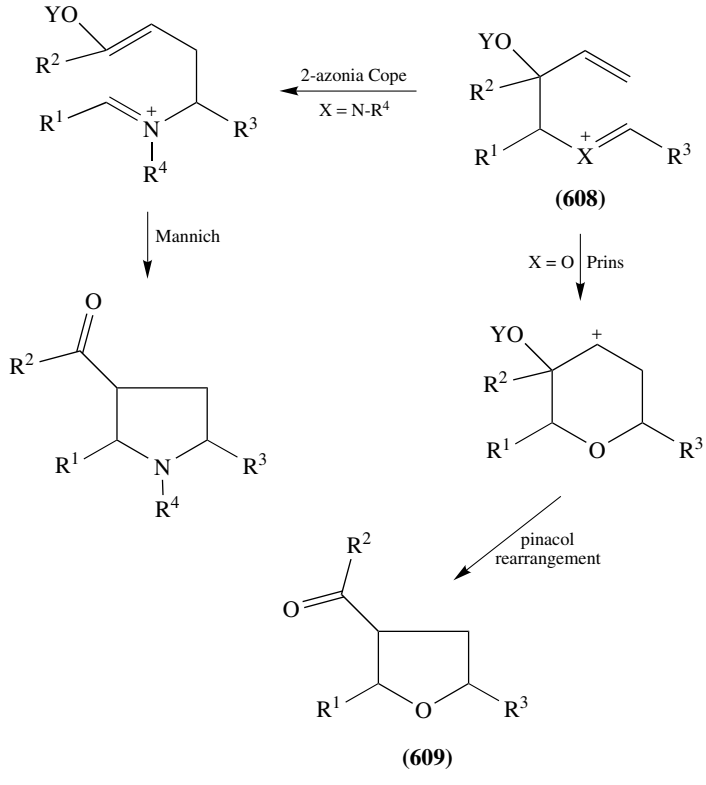
(260)

R^1 = H, Me, CO_2Me, CO_2Et, *c*-C_6H_{11}; R^2 = H, Me;
R^3 = H, Pr, $SiMe_3$; Nu = Cl (from $SnCl_4$)

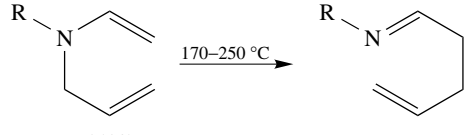
2. Aza-Cope rearrangements

There is no unity of opinion in the literature concerning a classification, i.e, whether to call these transformations aza-Claisen or aza-Cope rearrangements. It is accepted that the term 'aza-Claisen' should be reserved only for those processes in which a carbon atom in the allyl vinyl ether system has been replaced by nitrogen[357]. Three different types of aliphatic 3-aza-Cope reactions which were studied theoretically are the rearrangements of 3-aza-1,5-hexadienes (**610**, equation 262), 3-azonia-1,5-hexadienes (**611**, equation 263) and 3-aza-1,2,5-hexatrienes (**612**, equation 264) (the latter is a 'ketenimine rearrangement')[357].

Examples of synthetic applications of these three principal reaction types can be illustrated by the $TiCl_4$-catalyzed interaction of the allylamine **613** with 2-phenylpropanal **614** in refluxing toluene (equation 265)[358] as well as by the $ZnCl_2$ promoted rearrangement of N-allylated benzoyl substituted heterocyclic keteneaminals **615** (equation 266)[359].

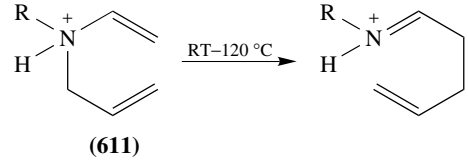


(261)



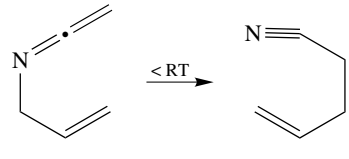
(610)

(262)



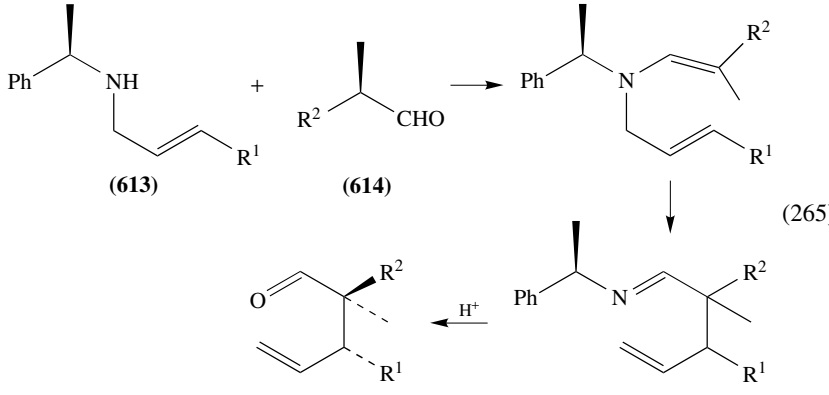
(611)

(263)



(612)

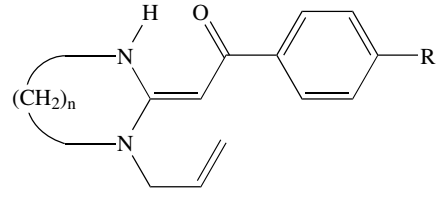
(264)



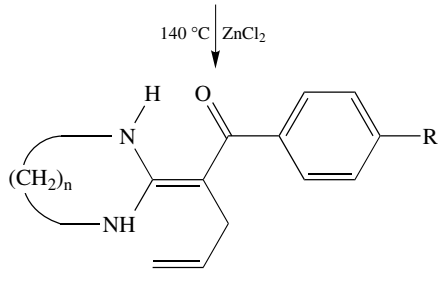
(613) (614)

(265)

R^1 = H, Me; R^2 = Me, Ph



(615)

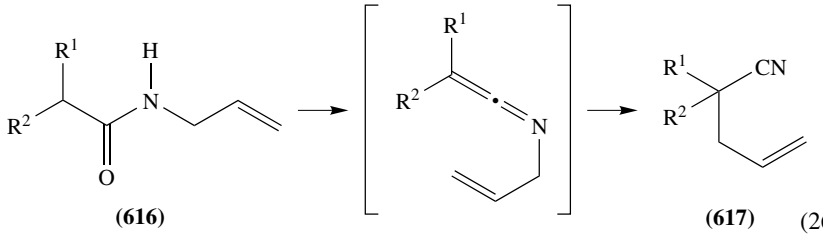


(266)

R = H, OMe

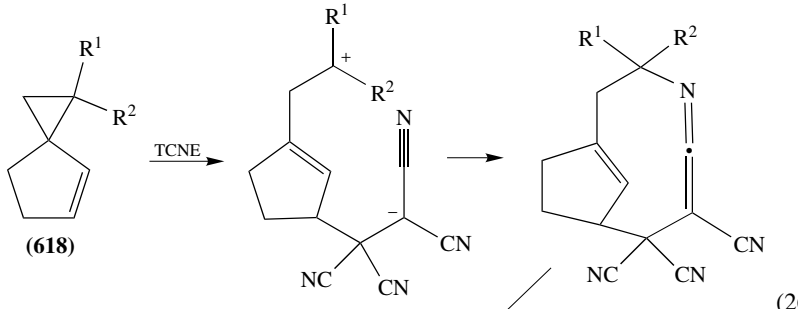
The stereochemical aspects of the 3-aza-Cope rearrangement of acyclic N-alkyl-N-allylenamines were compared with those of the O-analogues in Claisen rearrangement[360,361]. The transformation of the readily available N-allylamides **616** into nitriles **617** occurs via ketenimine rearrangement at room temperature ($Ph_3PBr_2/Et_3N/CH_2Cl_2$, 5–10 h, 30–89%) (equation 267)[362]. Ketenimine rearrangement also takes place during the interesting transformation of spiro[2,4]hept-4-ene derivatives **618** in the presence of tetracyanoethylene (TCNE) (equation 268)[363,364].

However, a better known version of the 2-aza-Cope rearrangement is that carried out by using 2-aza-1,5-hexadienes **619** (equation 269) and particularly their iminium ion counterparts, usually N-acyliminium cations **620** (equation 270)[365,366] (for reviews, see also Reference 367). Aza-Cope rearrangement of the norbornene ester **621** leads to tetrahydropyridine ester **622** when allowed to stand in solution at room temperature for

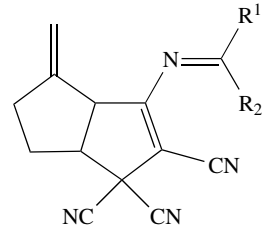


(616) **(617)** (267)

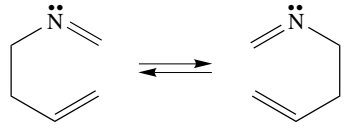
R^1 = Me, H; R^2 = Ph, CO_2Me, $(CH_2)_2CH_2Br$



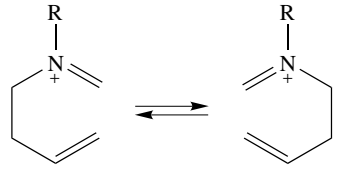
(618) (268)



R^1 = Pr, R^2 = Me; R^1 = R^2 = Pr



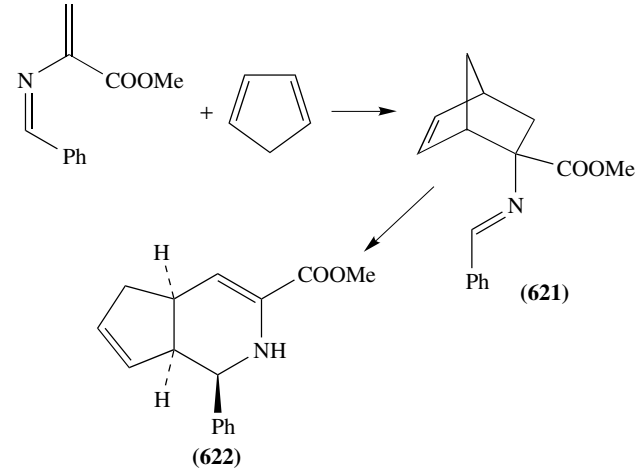
(619) (269)



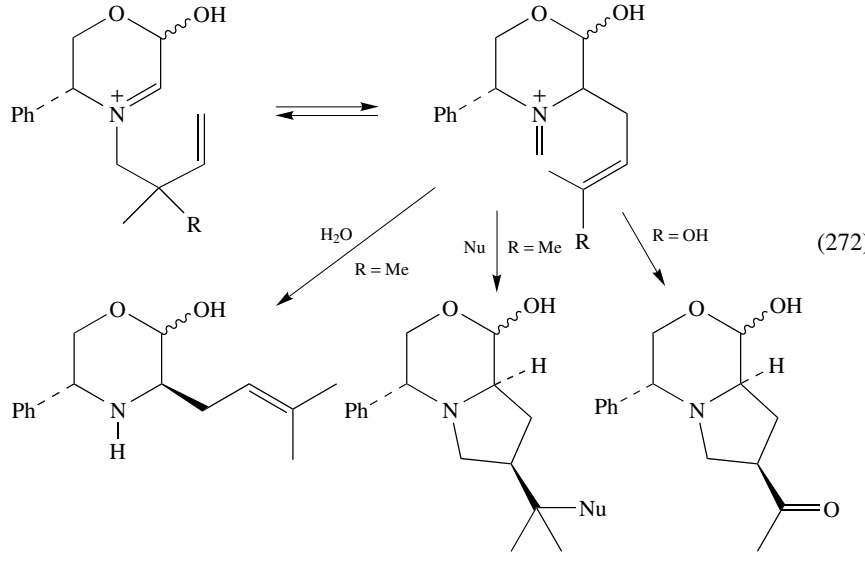
(620) (270)

R = H, Alk, Ac

10 days (equation 271)[368]. The tandem 'aza-Cope rearrangement–Mannich cyclization' (see the general scheme in equation 261) was successfully used to form the pyrrolidine ring in the course of synthesis of many natural compounds such as the antifungal antibiotic preussin[369] and strychnine[370,371]. The scope and mechanism of these useful reactions were investigated[372]. Various syntheses of natural products were carried out using tandem reactions in which the first step was a cationic aza-Cope rearrangement and the second step was either an iminium ion hydrolysis, a nucleophile-induced ene-iminium cyclization or a Mannich reaction (equation 272)[373].



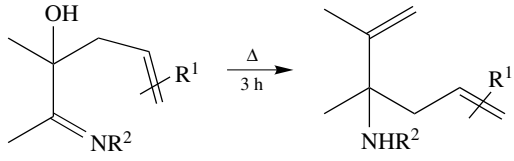
(271)



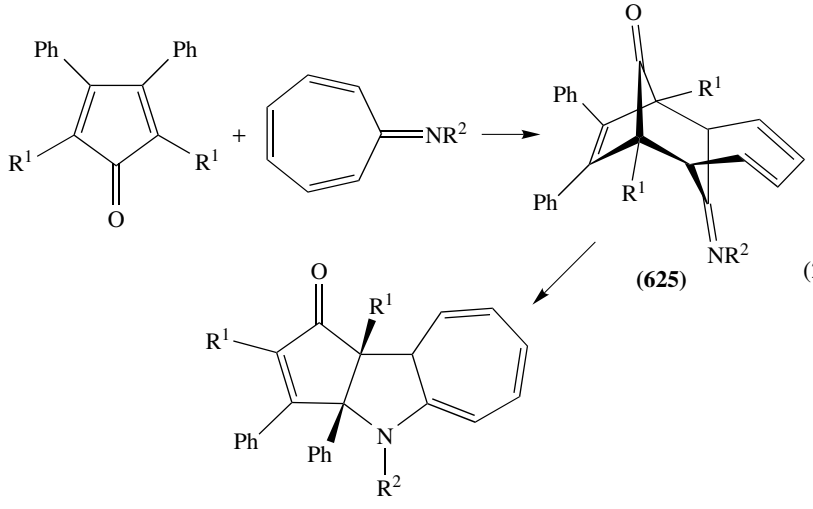
(272)

There are few examples of 1-aza-Cope rearrangements, e.g. the transformation of α-hydroxyimines **623** to aminoketones **624** in refluxing diglyme (equation 273)[374]. Diels–

Alder adducts of cyclopentadienones with azaheptafulvenes **(625)** gave the tricyclic products **626** upon heating (refluxing benzene, 96 h, argon, in the dark) (equation 274)[375].



(623) **(624)** (273)

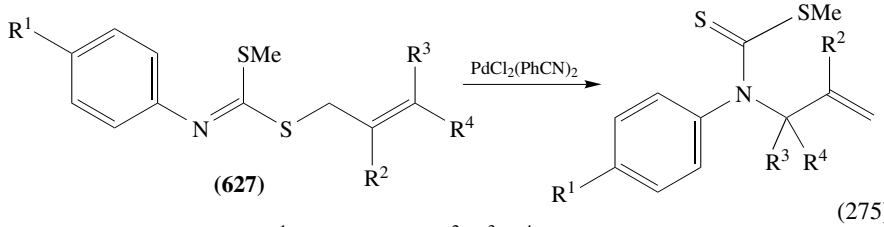


(625) (274)

(626)

3. Multihetero-Cope rearrangements

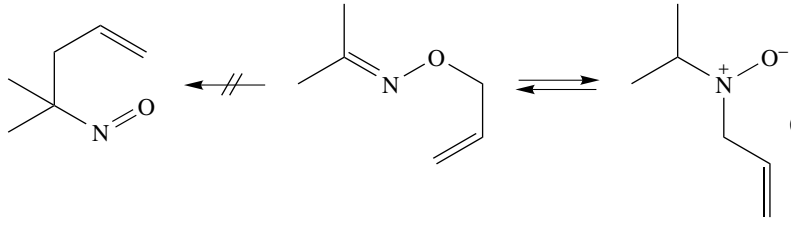
This series of rearrangements includes the dithia-Claisen rearrangement mentioned above (Section IV.E.1) as well as the palladium-catalyzed [3,3]-sigmatropic isomerizations of allyl methyl N-aryldithiocarbonimidates **627** (refluxing dioxane, 20 h, 62–90%) (equation 275)[376] and a Pd^{II}-catalyzed tandem [2,3]-sigmatropic shift, followed by 1,3-dipolar cycloaddition which takes place at equilibrium between O-allyl ethers of oximes **628** and the corresponding N-allyl nitrones **629** (equation 276)[377].



(627) (275)

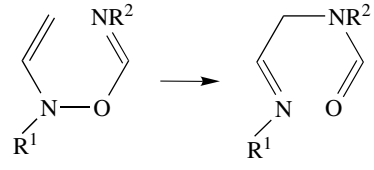
R^1 = H, Cl, OMe; R^2, R^3, R^4 = H, Me

Multihetero-Cope rearrangements were used for the preparation of heterocycles containing an imidazole ring (equations 277 and 278)[378] and α-amidoketones

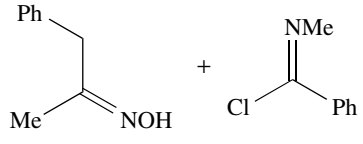


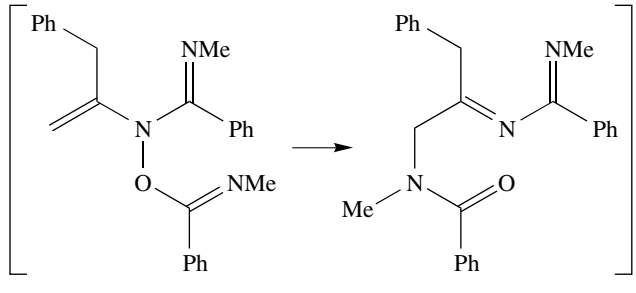
(276)

(628) **(629)**

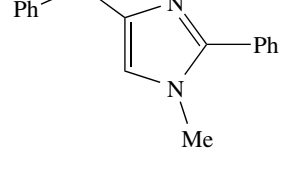


(277)

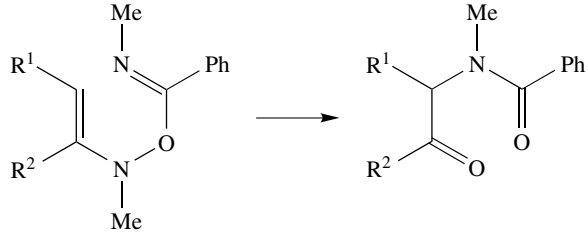




(278)

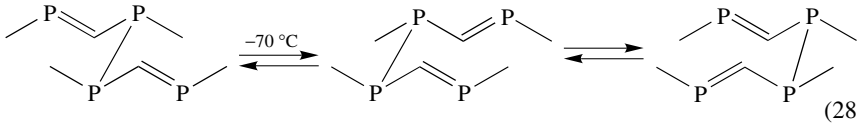


(equation 279)[379]. Finally, it should be noted that *ab initio* calculations as well as a brief literature survey were published about phospha-Cope rearrangements (equations 280 and 281)[380].

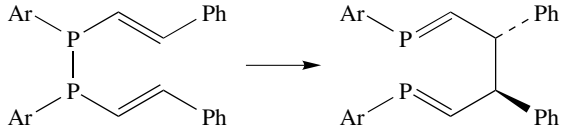


(279)

$R^1 = H, R^2 = Me; R^1 = Me, R^2 = Ph; R^1R^2 = (CH_2)_4$



(280)



(281)

Ar = 2,4,6-(*t*-Bu)$_3$C$_6$H$_2$

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