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Theoretical and Experimental Insights Into Cycloaddition Reactions

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Introduction

Cycloadditions continue to fascinate chemists of synthetic, mechanistic, and theoretical persuasions alike. Reactions such as the Diels-Alder reaction, 1,3-dipolar cycloadditions, and carbene cycloadditions continue to be proven worthy in elegant natural product syntheses, the quantification of reactivity, selectivity and stereochemical relationships and the elucidation of mechanisms of various cycloadditions are seemingly never-ending challenges, and the controversy about the timing of bond formation in cycloadditions has been taken up by theoretical chemists. In this article, I will touch on all of these areas of interest, relying most heavily on recent investigations carried out by my enthusiastic colleagues at Louisiana State University. Since much of the work described in this article is reported here for the first time, I am pleased to acknowledge the contributions of my recent co-workers in this area of chemistry: Pierluigi Caramella, Linda N. Domelsmith, Debabrata Mukherjee, Cielo Santiago, Inga-Mai Tegmo-Larsson, Arturo Battaglia, Stephen E. Reiter, Lee C. Dunn, Robert Strozier, Robert Patterson, Alexander Bimanand, Hambersoom Gosti-Babaians, and Ruth Wells Gandour.

Mechanisms of Cycloadditions

The controversy about the timing of bond formation in cycloadditions continues. Although stepwise reactions involving zwitterionic intermediates can be detected more or less reliably by solvent polarity effects on rates, the distinction between mechanisms involving diradical intermediates or no intermediates at all (concerted pathways) is a more subtle one. Whereas the articles of debate were formerly experimental data, the discussion has now expanded into the theoretical realm.

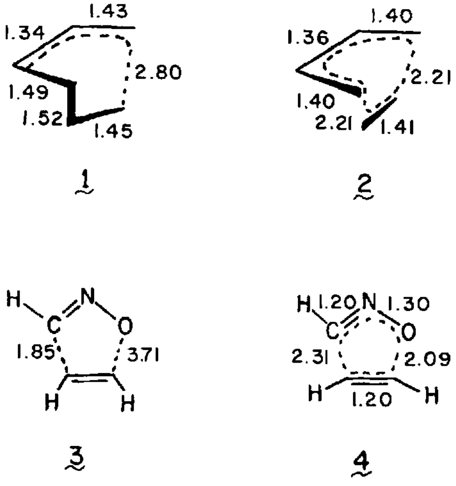


Fig. 1. Calculated cycloaddition transition state geometries[1–4]

MINDO/3 calculations with 2 x 2 Cl by Dewar, Kirschner, and Griffin implicated the biradicaloid transition state, *1*, for the cycloaddition of butadiene to ethylene[1], while *ab initio* calculations using the STO-3G basis set and 3 x 3 CI indicated that the symmetrical transition state, *2*, was involved in the lowest energy pathway for the reaction[2]. Similarly, for the cycloaddition of fulminic acid to acetylene, Dewar found a very asynchronous, or biradicaloid geometry, *3*, by MNDO calculations[3], whereas Poppinger found a nearly synchronous one, *4*[4]. These results suggested to us that there was some systematic difference in the handling of allowed cycloadditions by semi-empirical (MINDO, MNDO, etc.) and *ab initio* techniques.

In order to test this hypothesis, calculations were carried out by various techniques for various models of asynchronous (biradicaloid) and synchronous transition states. The results of these calculations are shown in Figs. 2 and 3[5]. For the Diels-Alder reaction, the procedure consisted of optimizing the butadiene-ethylene coordinates by MINDO/3 for certain fixed values of r'_{11} and r'_{22} (Fig. 2). The resulting geometries were than used as input for calculations by the other techniques. For fulminic acid-ethylene, the Poppinger transition state was chosen as the mid-point, and r_{CC} and r_{CO} were varied, while the fulminic acid and acetylene fragments were held fixed. Operationally, this variation was carried out by a variation in α (Fig. 3).

In both cases, asynchronous, or biradicaloid, geometries are favored by methods which neglect differential overlap (MINDO/2, MINDO/3, and CNDO/2), while syn-

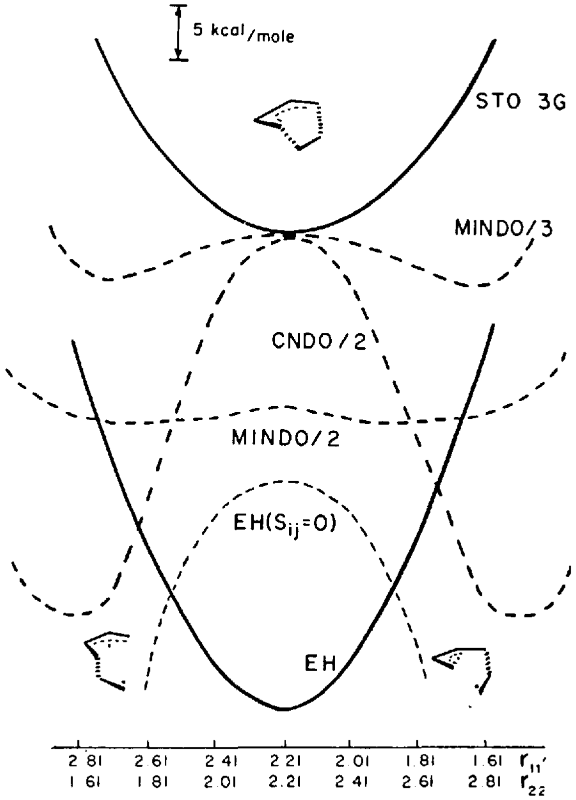


Fig. 2. Energies of unsymmetrical "one-bond" and symmetrical "two-bond" Diels-Alder "transition-state" geometries by various calculational techniques[5]. (Reprinted with permission from the *Journal of the American Chemical Society*. Copyright by the American Chemical Society.)

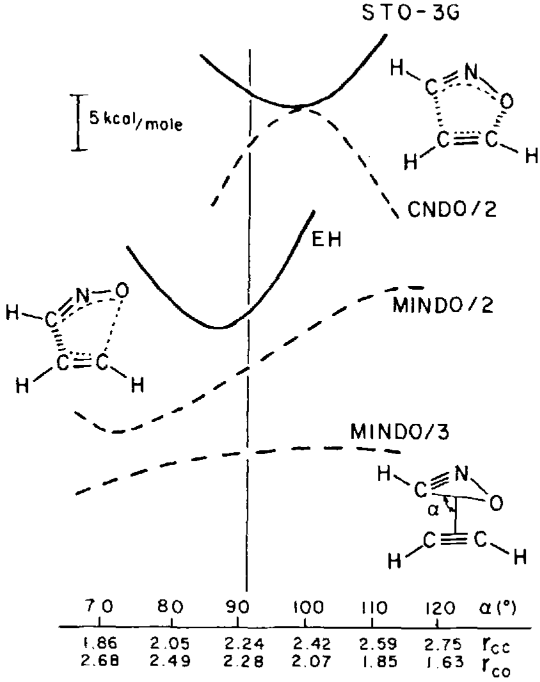


Fig. 3. Energies of unsymmetrical "one-bond" and symmetrical "two-bond" "transition-state" geometries for fulminic acid-acetylene by various calculational techniques[5]. (Reprinted with permission from the the *Journal of the American Chemical Society*. Copyright by the American Chemical Society.)

chronous geometries are favored by methods including overlap (*ab initio* STO-3G and EHT). While various criticisms can be (and have been)[1a] leveled at such comparisons, it seems clear that there is a fundamental difference in the two general types of calculations. We proposed that the neglect of overlap in semi-empirical techniques causes this dichotomy[5], while others have pointed out various idiosyncrasies in parameterizations of semi-empirical calculations which might cause these discrepancies[6].

When two molecules approach each other, the filled orbitals of these molecules begin to overlap, leading to a destabilization referred to as exchange, or closed-shell, repulsion. For the interaction of filled orbital ϕ_i with filled orbital ϕ_j, the destabilization, ΔE, is given by the expression below[7]:

$$\Delta E = \frac{4}{1 - S_{ij}^2} (\epsilon_{av} S_{ij}^2 - H_{ij} S_{ij}) \qquad (1)$$

In this equation, ϵ_{av} is the average energy of ϕ_i and ϕ_j, or $(\epsilon_i + \epsilon_j)/2$, S_{ij} is the overlap of ϕ_i with ϕ_j, and H_{ij} is the resonance integral for the interaction of ϕ_i with ϕ_j. This equation is the exact expression arising from the solution of a 2 x 2 determinant. In order to understand qualitatively how this expression varies as a function of ϵ_{av}, Epiotis has used the Mulliken approximation, $H_{ij} \cong kS_{ij}$[8]. Further assuming that $S_{ij}^2 \ll 1$, Eq. (1) simplifies to Eq. (2):

$$\Delta E = 4S_{ij}^2 (\epsilon_{av} - k) \qquad (2)$$

Since k is a large negative number, ΔE is always a destabilizing quantity, which decreases as ϵ_{av} becomes more negative. Therefore, high-lying orbitals repel each other, or cause more closed-shell repulsion, than low-lying ones. However, one might instead use the Wolfsberg-Helmholtz approximation: $H_{ij} = \frac{k'}{2} (\epsilon_i + \epsilon_j) S_{ij}^2 = k'\epsilon_{av}S_{ij}$, whereupon, Eq. (1) simplifies to:

$$\Delta E = 4S_{ij}^2\epsilon_{av}(1-k) \qquad (3)$$

The constant k used by Hoffmann in EHT calculations is 1.75, which leads to a very simple expression:

$$\Delta E = -3S_{ij}^2\epsilon_{av} \qquad (4)$$

By contrast to Eq. (2), Eq. (4) predicts that the closed-shell repulsion will increase as the ϵ_{av} decreases (become more negative). In spite of this apparent conflict between the two approximations, it is likely that the higher-lying the interacting filled orbitals, the more repulsion will occur, because of the dominance of the overlap term. That is, the higher-lying the molecular orbital, the more nodes will be present — and, therefore, the larger the coefficients on the average. Furthermore, as the principal quantum number of an atomic orbital increases, the orbital extends more in space and overlaps better with orbitals on adjacent atoms. However, in contrast to the change in energy of an individual orbital, there is no dependence upon the difference in energy between the interacting orbitals.

Returning to the Diels-Alder reaction, the symmetrical transition state will have no closed-shell repulsion between the HOMO's, due to the opposite symmetries, and resulting zero overlap, of these orbitals (Fig. 4)[5]. In an asynchronous transition state, the overlap of all π orbitals occurs, and closed-shell repulsion will increase. As Epiotis has pointed out for aromatic molecules[8], it is possible to gener-

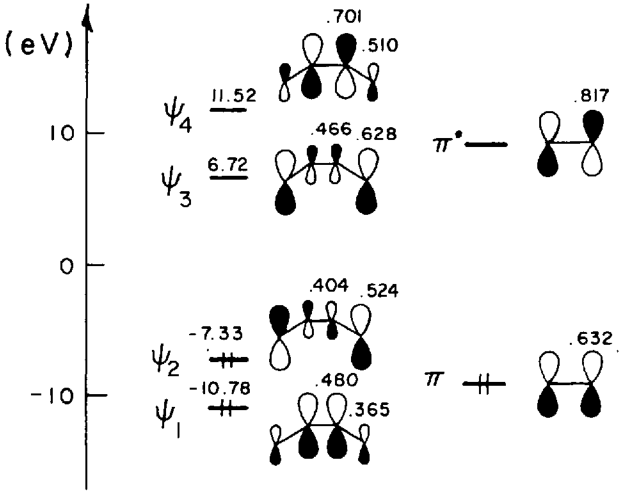


Fig. 4. STO-3G MO's of butadiene and ethylene[5]. (Reprinted with permission from the *Journal of the American Chemical Society.* Copyright by the American Chemical Society.)

alize this situation: in thermally-allowed cycloadditions, there will be no overlap between the HOMO's of the two addends in a symmetrical transition state, and less closed-shell repulsion between π orbitals than in an asynchronous transition state.

Since semi-empirical computational methods neglecting overlap do not include the symmetry-dependent repulsive effect, such methods are likely to underestimate the stability of a symmetrical transition state relative to an unsymmetrical one. Two factors prevent us from making the apparently inescapable conclusion that Diels-Alder transition states are symmetrical. First, neither the *ab initio* nor semi-empirical techniques used are particularly accurate, if for different reasons. It is conceivable that extensive CI would improve the energy of the biradicaloid transition state which is calculated to be a few kcal/mol higher in energy than the synchronous one by STO-3G with 3 x 3 CI. Second, McIver has shown that cycloadditions should never have high symmetry, although his theorem would not rule out a slightly asynchronous transition state[9)].

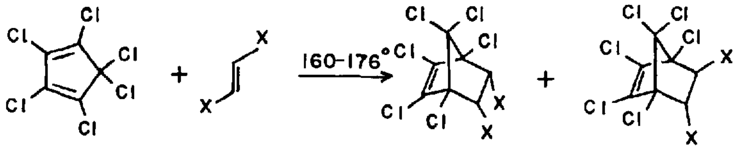
In fact, the cycloaddition of butadiene to ethylene, as well as cycloadditions of similar non-polar dienes to non-polar alkenes seem experimentally to be cases where concerted and stepwise (biradical or biradicaloid) mechanisms compete. We have recently discussed a number of cases, such as the dimerization of butadiene, piperylene, and chloroprene, the cycloadditions of butadiene or methylated dienes to halogenated alkenes, and others, where non-stereospecificity and competitive formation of [2 + 2] adducts indicate that mechanisms involving diradical intermediates compete with concerted mechanisms[10)]. Alternatively, one could claim, with Firestone, that these reactions, both [4 + 2] and [2 + 2], involve diradical intermediates[11)]. In our opinion, it is possible to believe that a "concerted component can coexist with the diradical one", and that both mechanisms can occur "in the very same vessel"[11)]. Bartlett's experiments on diene-haloalkene cycloadditions have also been interpreted in this way[12)].

However, as the diene is made a better donor, and the dienophile a better acceptor, or *vice versa,* the energetic advantage of the concerted path over the stepwise seems to increase[10)]. That is, the amount of [2 + 2] adduct formed diminishes, and the reactions become more highly stereospecific. It is cycloadditions of electron-rich dienes to electron-deficient alkenes which constitute the classic Diels-Alder reactions – stereospecific [4 + 2] cycloadditions.

An excellent example of this was interpreted, however, by Mark, to be the result of incursion of a diradical mechanism with steric hindrance causing rotation[13)]. As shown in Fig. 5, the cycloadditions of the relatively electron-rich *trans*-2-butene to the electron-deficient hexachlorocyclopentadiene gives the Diels-Alder adduct stereospecifically, but when the alkene is made more electron-deficient, the stereospecificity disappears[13)]. We interpret this as the result of a change in mechanism from concerted in the first case, to an increasing contribution of a stepwise mechanism, with diradical intermediates, as one proceeds down the series.

In order to understand how the degree of concert can be influenced by the relative polarity of the reactants, it is necessary to look more closely at energetic changes occurring in the Diels-Alder reaction.

Figure 6 is a sketch of the change in butadiene and ethylene π orbitals along the Salem-Hehre *ab initio* Diels-Alder pathway[2)]. As noted by these authors, and earlier



X	%	%
Cl	95	5
CN	43	57
Ph	29	71
CO_2Me	27	73
COCl	16	84
Me	~0	~100

Fig. 5. Stereoselectivities of some hexachlorocyclopentadiene cycloadditions[13)]

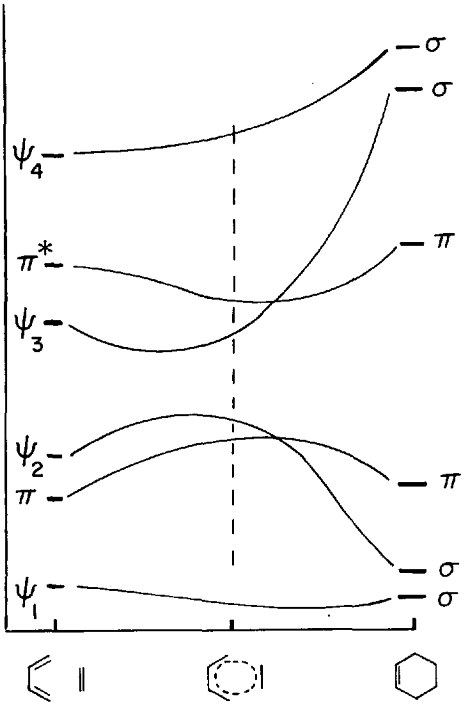


Fig. 6. Schematic representation of π MO energy changes along the Salem-Hehre concerted Diels-Alder surface[2)]

by Jorgensen[14)], the frontier orbital concept does not seem to hold here, for, rather than having stabilization of the diene and alkene HOMO's, and simultaneous destabilization of the LUMO's, early along the reaction pathway, these orbitals rise and fall, respectively, until the transition state (T.S.) is reached. As will be discussed in more detail later in this article, this behavior of the frontier MO's is compatible with the idea that the initial energy change along a cycloaddition reaction coordinate are caused by repulsive interactions between the molecules and molecular distortions[10)].

These interactions and distortions cause the HOMO's to increase in energy and the LUMO's to decrease in energy. Fukui has called this behavior the principle of "frontier orbital narrowing"$^{15)}$. It occurs because closed-shell repulsions between filled orbitals raise the occupied MO energies, and mutual overlap of vacant orbitals lowers these. Secondly, as the double bonds of reactants are stretched towards product geometries, the HOMO's rise in energy, while the LUMO's fall. As this happens, stabilizing HOMO-LUMO interactions begin to increase, and eventually, at the transition state, these stabilizing interactions overcome the distabilizing ones. In Evans-Polanyi language$^{16)}$, at the transition state the molecules switch over from distorted, or vibrationally excited, reactants, to distorted products.

Another computationally fruitful way to think about these reactions is to first distort the addends to their transition state geometries, and to compare the energies of these isolated species with that of the transition state. Using the Salem-Hehre transition state, 64 kcal/mol is required to distort the isolated molecules to their transition state geometries, and uniting these distorted moieties causes a stabilization of 25 kcal/mol. Past the transition state, the stabilization energy increases faster than the destabilization.

The transition state leading to the extended diradical intermediate$^{2)}$, *5*, has less distorted fragments, but also less stabilization from interaction, that for the synchronous transition state. According to STO-3G calculations, distorting butadiene and ethylene to the diradical transition state geometries requires a total of only 37 kcal/mol, but uniting these causes a further destabilization of 15 kcal/mol. Clearly, the lesser distortion of the addends in the biradicaloid transition state is important in making this species nearly as stable as the concerted transition state. Even though these calculations are very crude, an important and non-obvious conclusion can be drawn: for non-polar addends, the concerted and biradicaloid transition states are nearly the same in energy because of near-cancellation of several factors:

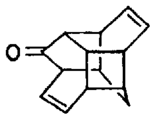
(1) the biradicaloid transition state has much less destabilization energy than the concerted transition state, primarily because of the much greater distortion of the butadiene moiety in the latter (towards a 2-butene-1,4-diyl diradical) as compared to the former (towards an allylmethylene diradical);

(2) the concerted transition state experiences much larger stabilizing interactions (more HOMO-LUMO overlap and less closed-shell repulsion) than the biradicaloid transition state.

In an earlier discussion$^{10)}$, we have shown how the greater stabilization of the 4-center, or concerted, transition state over the 2-center, or biradicaloid, is magnified as the complementary polarity of the addends increases. That is, a weakly stabilizing frontier orbital interaction may favor the 4-center over the 2-center by a small amount, but as the magnitudes of these interactions are increased, the difference between them increases also.

An additional feature revealed by the considerations about molecular distortions is that as the complementary polarities of the addends increases, less distortion of addends will be required to reach the transition state. For example, for a high-lying diene HOMO and low-lying dienophile LUMO, the stabilizing HOMO-LUMO interaction will surpass the destabilizing molecular distortion energy quite early along the reaction coordinate. This will clearly favor the concerted mechanism over the stepwise, since the primary factor favoring the biradicaloid transition state for non-polar addends will be reduced to a large extent. These considerations lead to the conclusion that concerted cycloaddition transition states will be favored over biradicaloid ones to a large extent only for good donor-acceptor pairs.

This will apply not only to Diels-Alder reactions, but to other Woodward-Hoffmann symmetry-allowed reactions, as well. For example, the good donor-acceptor pair, cycloheptatriene and tropone, react to give only the allowed ([6 + 4], then [4 + 2]) adduct *6*[17], while cycloheptatriene dimerizes to give not only the analogous adduct, *7*, but the forbidden, [6 + 2] adduct, *8*, as well as several other unidentified dimers[18].



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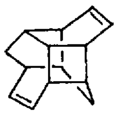

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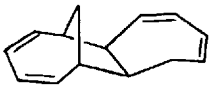

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Presumably, the latter is a case where biradical mechanisms occur due to the lack of strong donor-acceptor stabilization.

Nitrone Regioselectivity

Prior to 1973, nitrones were believed to add to monosubstituted dipolarophiles in a unidirectional fashion, giving 5-substituted adducts exclusively (Fig. 7). An exception to this behavior was reported by Huisgen: a mixture of 4- and 5-substituted isoxazolines form in the reaction of methyl propiolate with C-phenyl-N-methylnitrone[19], as shown in Fig. 7.

In the course of a general investigation of the electronic structures of 1,3-dipoles[20], we rationalized this behavior according to the reasoning shown schemati-

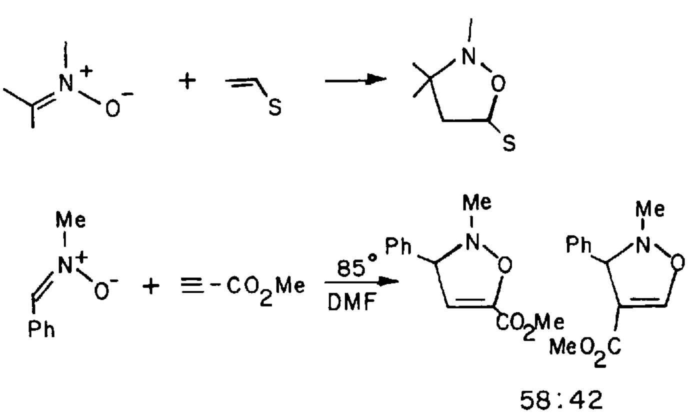


Fig. 7. Regioselectivities of two nitrone cycloadditions

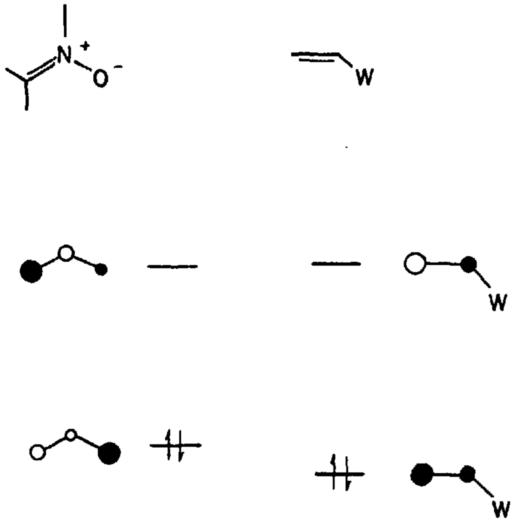


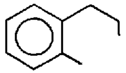
Fig. 8. HOMO's and LUMO's of a nitrone and an electron-deficient dipolarophile. (The diameters of the circles represent coefficient magnitudes.)

cally in Fig. 8. Nitrones are Sustmann "Type II" dipoles$^{21)}$, and can behave as either nucleophilic or electrophilic reagents. With dipolarophiles such as styrene, enol ethers, and similarly electron-rich species, the interaction of the nitrone LUMO with the dipolarophile HOMO is the dominant frontier orbital interaction. Since all of these alkenes have the largest HOMO coefficient at the unsubstituted terminus, while the nitrone has the largest LUMO coefficient at the carbon terminus, these two positions become united in the more stabilized transition state, and the 5-substituted isomer is formed preferentially.

Weakly electron-deficient molecules such as methyl acrylate and acrylonitrile have similar interactions between both pair of frontier orbitals. Electron-deficient alkenes have the largest terminal coefficient at the unsubstituted carbon in both the HOMO and LUMO, although the LUMO polarization is greater than that of the HOMO (see later section on "Amphoteric Substituents"). Since the largest HOMO coefficient is on oxygen in the nitrone, the two pairs of frontier orbital interactions preferentially stabilize different transition states. For weakly electron-deficient alkenes, the dipole LUMO-dipolarophile HOMO interaction still dominates, favoring 5-substituted adducts, but for more highly electron-deficient alkenes, such as methyl propiolate, the dipole HOMO-dipolarophile LUMO interaction begins to dominate, and 4-substituted adducts are also formed. Such an explanation led to the prediction that further lowering of the dipolarophile LUMO energy – that is, increasing the dipolarophile electron affinity (EA) – or raising of the nitrone HOMO energy – that is, decreasing the nitrone IP – would lead to more of the 4-substituted adduct. This prediction was experimentally verified$^{22)}$, as shown in Table 1.

There is not a quantitative relationship between the nitrone IP's and the amount of 4-substituted isomer formed, but there is a general trend of increasing percentage of 4-substituted adduct as the IP of the nitrone decreases$^{23)}$, or the electron affinity (EA) of the dipolarophile increases. In Table 1, the first two π IP's of the nitrone

Table 1. Percentage of 4-substituted adduct (±5%) obtained in cycloadditions of nitrones to electron-deficient dipolarophiles

Nitrone substituents		(π IP's, eV)	"IP_{av}"	Dipolarophile					
C	*N*			Methyl acrylate	Acrylonitrile	Phenyl vinyl sulfone	Nitroethylene	Methyl propiolate	Cyanoacetylene
H	*t*-Bu	8.64	8.64	0	0	30	≈0	30	50
Ph	Me	8.01, 9.91	8.64	0[a]	0	68	100	58[a]	100
		7.81, 9.99	8.54	0[b]	80		100[c]		100
Mesityl	Me	8.08, 9.1	8.42	50	85	100	100	100	100
Cyclopropyl	Me	8.30	8.30	≈30		≈50			
Hexatrien-1,6-diyl	Me	7.28, 9.65	8.07			100			

[a] Huisgen, R., Seidl, H., Brüning, I.: Chem. Ber. *102*, 1102 (1969).
[b] Huisgen, R., Hauck, H., Grashey, R., Seidl, H.: Chem. Ber. *101*, 2568 (1968).
[c] Seidl, H., Huisgen, R., Knorr, R.: Chem. Ber. *102*, 904 (1969).

have been listed[24)], since, in cases of conjugated systems, the HOMO may have a low IP, but be delocalized away from the CNO moiety. In such cases, a weighted average of the first two IP's (2/3 IP_1 + 1/3 IP_2), "IP_{av}", is used to show that the net electron-donor abilities of the nitrones increase going from top to the bottom of the column in Table 1.

Although the arguments given above are based only on orbital energies, donor substituents on the nitrone carbon have an additional influence on the nitrone HOMO, causing the oxygen coefficient to increase at the expense of the carbon[23)]. This also reinforces the preference for 4-substituted adduct as the nitrone IP decreases.

The Influence of Molecular Distortions Upon Reactivity

The discussion up to now has dealt primarily with the interactions between the orbitals of the isolated molecules in ground-state geometries. In the case of the Diels-Alder mechanism, the influence of geometrical distortions was discussed briefly, and here this subject will be taken up in more detail.

The Trimerization of Acetylene

An example which we have studied only cursorily, but which nevertheless reveals much about the importance of molecular distortions in chemical reactions, is the trimerization of acetylene to form benzene (Fig. 9). This reaction was brought to our attention by the work of Vollhardt, who found that a cyclic triacetylene, 1,5,9-cyclo-dodecatriyne, undergoes reaction only at elevated temperature to give products suggestive of the intermediacy of tris-cyclobutenanenzene[25)].

Because the trimerization of acetylene is so enormously exothermic (−143.6 kcal/mol) and is allowed by the Woodward-Hoffmann rules, one might expect a very low activation energy for this transformation. The decrease in entropy might be costly, but should not be prohibitive in intramolecular cases. Experimentally, acetylene undergoes reaction at 400 °C in the gas phase to give a wide variety of products, of which benzene constitutes only a small fraction[26)].

Our computations indicate that there is a large activation barrier for this reaction[27)]. Both MINDO/3 and *ab initio* STO-3G calculations were used in preliminary investigations, and the results of a "surface scan" by the former in which D_{3h} sym-

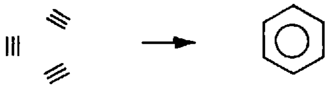


Fig. 9. Trimerization of acetylene

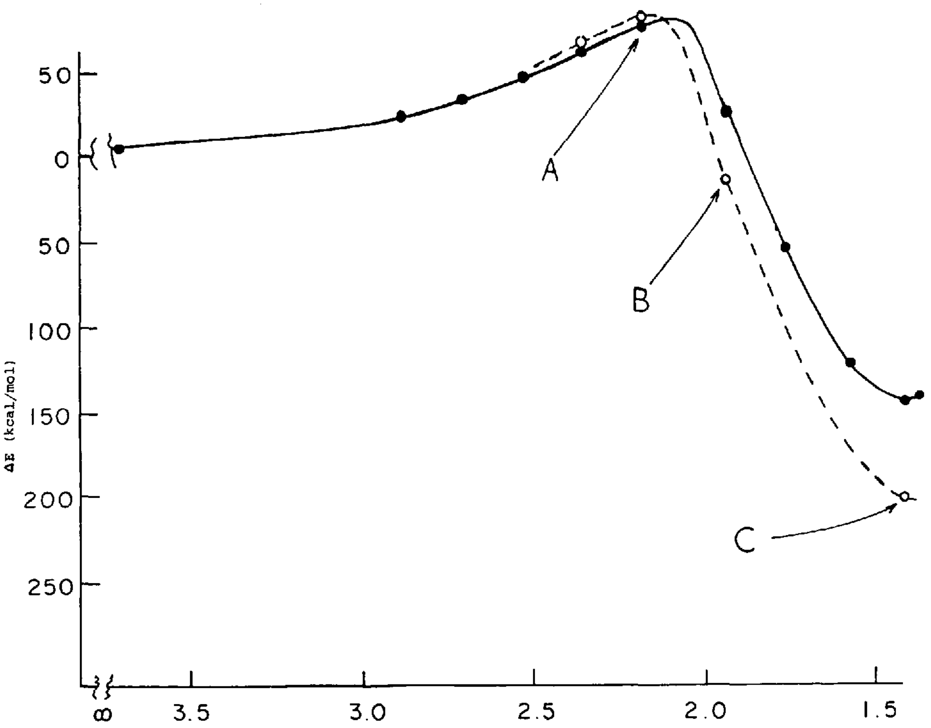


Fig. 10. MINDO/3 D_{3h} surface for acetylene trimerization (•). The open circles are obtained by STO-3G calculations

metry was maintained but all other variables were optimized along the reaction coordinate, are shown in Fig. 10. The heat of reaction calculated by MINDO/3 (−145 kcal/mol) is in excellent accord with the experimental value (−144 kcal/mol), and an activation enthalpy (actually an upper limit because of the geometrical constraints imposed in this surface scan) of about 80 kcal/mol is predicted by these calculations. Although *ab initio* STO-3G calculations predict the energy of reaction (−288 kcal/mol) much less accurately, the predicted energy of the transition state of about 80 kcal/mol above three acetylene molecules agrees with the MINDO/3 calculations. Because of an even less thorough geometry search in the STO-3G calculations, and because CI was not used, 80 kcal/mol should be considered to be an upper limit for the activation energy of this reaction.

Although these surface scans are approximate, and probably suffer somewhat from the requirement of D_{3h} symmetry, they do reveal that this remarkably exothermic, and thermally allowed, reaction has an unusually high activation barrier. Acetylene is neither a good donor nor a good acceptor, and the approach of three acetylenes, even in a geometry which produces both in-plane and out-of-plane aromatic sextets, results in no strong HOMO-LUMO interactions. Repulsive interactions due to the overlap of filled orbitals of the three molecules occur, but the filled and vacant orbitals of the acetylenes are too far apart in energy for any appreciable stabilization to occur. Only when substantial distortions of the acetylenes away from linearity occur are the HOMO's raised and the LUMO's lowered sufficiently for appreciable interaction to take place, and then the reaction occurs rather precipitously. When the non-bonded carbons of two acetylenes are 4.6 Å from each other, only miniscule energy changes have occurred. When r is between 3.7 and 2.2 Å, the energy rises dramatically and the molecules distort appreciably. Both MINDO/3 and *ab initio* STO-3G calculations indicate that most of this distortion is HCC bending, so that the pseudo-transition states resemble highly *cis*-bent acetylenes retaining the triple bond lengths, as shown in Fig. 11. The sudden drop in energy results from an abrupt switch-over from a distorted acetylene trimer surface to a distorted benzene surface. As shown in the figure, at r = 1.92 Å, the molecule has become a distorted benzene, the former triple bond having stretch to essentially a double bond length, and the HCC angle closing to a value, 130° or 126° in the two calculations, near that (120°) of benzene.

The molecular reorganization is sudden because of the near-crossing of MOs which occurs at the transition state in the enforced reaction path. While the acetylene trimerization is thermally allowed in the sense that all occupied orbitals of the reactant correlate with occupied orbitals of the product, extensive mixing of occupied and vacent orbitals in required to convert reactant orbitals into product orbitals. The crucial correlation involves the three in-plane π orbitals of three acetylene molecules, and three σ orbitals of benzene, shown in Fig. 12. The representation in Fig. 12 is oversimplified in that the benzene orbitals are much more extensively delocalized than is suggested by this picture, due to mixing of these orbitals with three other σ orbitals, as well as with the hydrogen orbitals. A simpler analogy, the bond-switch for three hydrogen molecules, can be analyzed more exactly without the complications arising from mixing of other orbitals. Extensive calculations have been carried out for the 3 H_2 surface by Wright[28] and by Dixon, Stevens, and Herschbach[29]. The best calculations indicate an activation energy of 66 kcal/mol for this degenerate reaction, considerably below the bond dissociation energy of 109.5 kcal/mol for dissociation of a hydrogen molecule, but remarkably high for an "allowed" reaction. Figure 13 shows a correlation diagram for the degenerate hexagonal 3 H_2 bond-switch. On the left and right are shown the MO's of three weekly-interacting hydrogen molecules. An orbital symmetry correlation diagram would show a correlation of bonding orbitals on the left with those on the right. However, following the progress of the reaction in a stepwise fashion clearly reveals the origin of the large

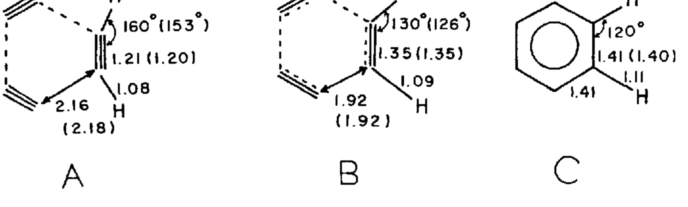


Fig. 11. Optimized geometries of points A, B, and C in Fig. 10. Bond lengths and angles are for MINDO/3 calculations, as are scale drawings, while values in parentheses are from the STO-3G calculations

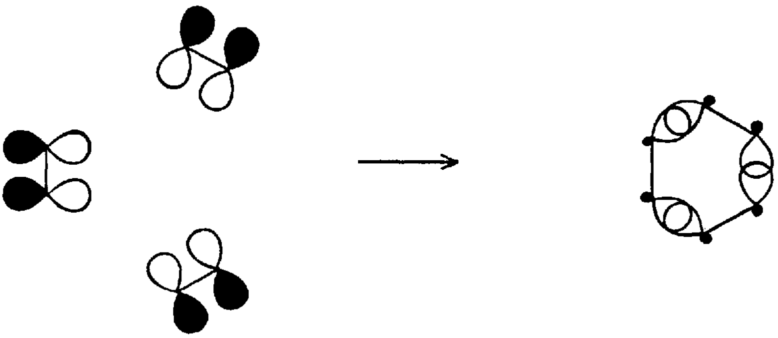


Fig. 12. Qualitative correlation between three in-plane π MO's of acetylenes and σ orbitals of benzene

barrier to reaction. If the original orbital shapes were retained, but nuclear motions occurred, such a hypothetical occurrence would lead to a crossing of the filled and vacant orbital energies, since the degenerate HOMO's of the starting 3 H_2 become predominantly antibonding in the product, while the degenerate LUMO's of the starting 3 H_2 will become mostly bonding. In the real situation, this will not occur,

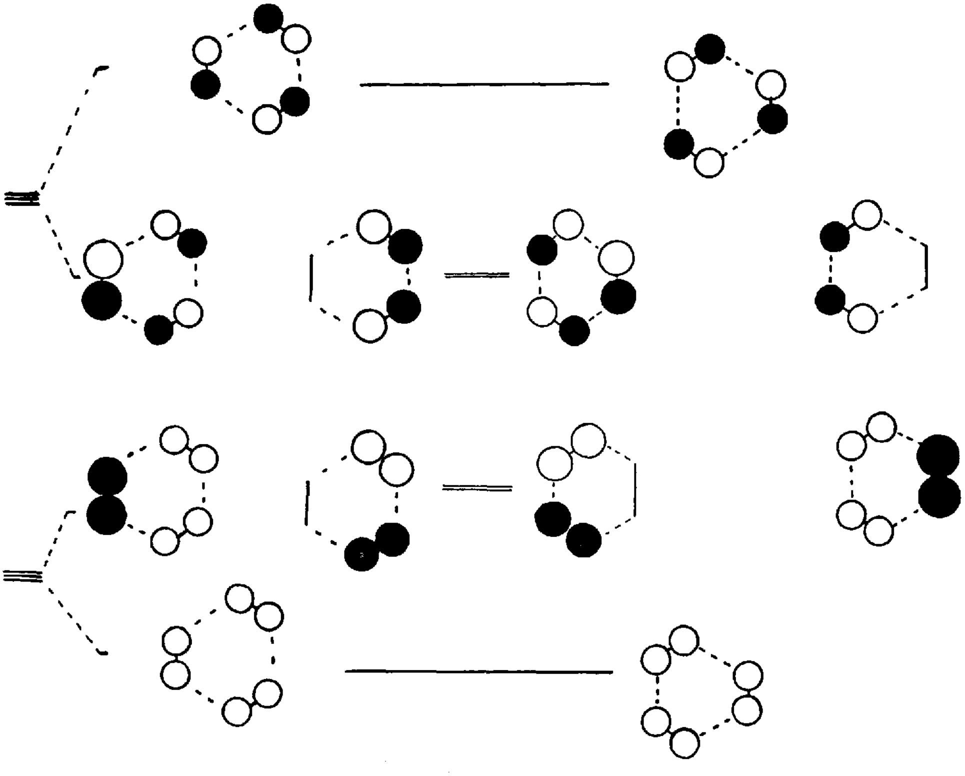


Fig. 13. Correlation diagram for degenerate bond-switch in three hydrogen molecules

since the HOMO's and LUMO's have the same symmetry, and mix as the bond-breaking and bond-making processes begin to occur. However, since the extent of this mixing depends upon the difference between the energies of the interacting orbitals, no substantial mixing can occur until appreciable stretching of the H—H bonds take place. For this, and any other, symmetry-allowed reaction there is an intended crossing of bonding and antibonding orbitals. For allowed reactions, the crossing never occurs, but much distortion of the close-shell reactants must occur in order for the electron density in bonding regions of the reactants to be transferred to bonding regions in the product. There is a difference between allowed and forbidden reactions: allowed reactions have avoided crossings at the one-electron (orbital interaction) level, while forbidden reactions avoid crossings only at the two electron (configuration interaction) level.

This example clearly shows the importance of the energy of geometrical distortions upon activation energies, and makes the origin of the high reactivities of strained molecules somewhat more obvious. In two other studies of the influence of geometrical distortions upon reaction rates, we have found that the electronic characteristics of molecules can be profoundly altered by relatively minor geometrical alterations:

(1) in the nitrilium betaine series of 1,3-dipoles, the geometry of the molecule determines which terminus is more nucleophilic;

(2) alkynes are made unusually electrophilic, but not particularly electrophilic, by geometrical distortions.

Geometries of Nitrile Ylides

Our initial interest in this area arose from the observation that the orbitals of the commonly accepted planar geometry of the parent nitrile ylide do not correctly account for the cycloaddition regioselectivities observed for these species. Thus, as shown by the examples in Fig. 14, the digonal carbon is the nucleophilic center of the molecules, whereas the HOMO of the planar species has the largest coefficient at the trigonal carbon, which should, therefore, be the more nucleophilic center of the molecule. However, full optimization of the geometry of nitrile ylide using the

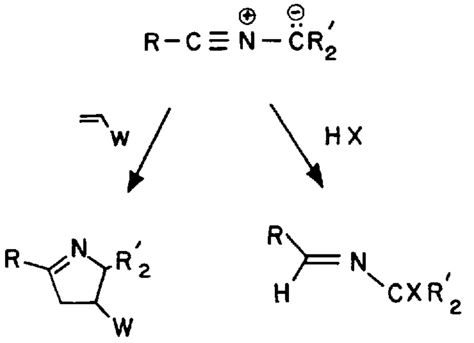


Fig. 14. Regiochemistry of nitrile ylide additions and cycloadditions. (W = electron-withdrawing group)

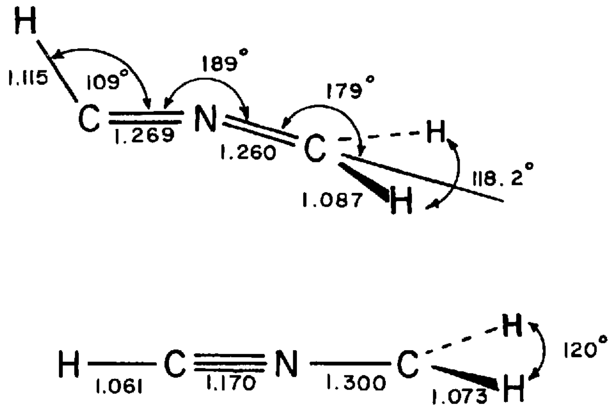


Fig. 15. Fully optimized and planar geometries of nitrile ylide

STO-3G basis set gave the results shown in Fig. 15[30], and MINDO/3 calculations gave similar results[31]. In the non-planar species, the digonal carbon is clearly more nucleophilic than the trigonal. In classical terms, the digonal center becomes more electronegative than the trigonal by bending, which causes the formal lone-pair orbital to mix in s character, and become stabilized.

There is a delicate balance between the relative energies of the planar and non-planar species as the component atoms of, or substituents on, various nitrilium betaines are varied. Table 2 summarizes the calculations for substituted derivatives of the parent nitrile ylide[32].

Acceptors at C_3 stabilize the planar species relative to the bent. This is reflected both in the differences in energy between planar and bent species, and in the optimized geometries, where the XC_1N angle has increased, r_{C_1N} has shortened, and r_{NC_3} has lengthened. By STO-3G, the opposite trend is found for substitution of a

Table 2. Geometries and energies of substituted nitrile ylides

Nitrile ylide	E(planar) − E(bent) STO-3G[a] (kcal/mol)	MINDO/3[b]	Optimized geometries STO-3G[c] (MINDO/3)[b] $< XC_1N$(°)	r_{C_1N}(Å)	r_{NC_3}(Å)
$HCNCH_2$	22.4	16.4	109 (116)	1.27 (1.22)	1.26 (1.26)
HCNCHCHO	14.6	6.1	(124)	(1.20)	(1.29)
HCNCHCN	11.7	11.9	112 (118)	1.26 (1.22)	1.27 (1.27)
$HCNCHCH_3$	25.6	14.9	108 (116)	1.27 (1.22)	1.26 (1.27)
$NCCNCH_2$	9.4	8.1	120 (127)	1.26 (1.22)	1.26 (1.26)
$(CHO)CNCH_2$	7.1	3.4	(135)	(1.21)	(1.26)
CH_3CNCH_2	9.4	8.1	118 (133)	1.26 (1.21)	1.26 (1.27)

[a] Geometries are those optimized by STO-3G for the parent molecules.
[b] Geometries are fully optimized for the substituted compounds by MINDO/3.
[c] Only the geometrical parameters listed are optimized by STO-3G.

donor, methyl, at C_3. As expected on the basis of simple resonance arguments, the propargyl type planar structure is favored by acceptors at C_3, while the allenyl is preferred for donors at C_3.

However, the simple resonance argument would not have predicted the trends for substitution at C_1. All substituents, whether donor or acceptor, reduce the energy difference between planar and bent species, and flatten the molecule considerably. The effect here cannot be a simple electronegativity effect, since both donors and acceptors have a similar effect. Instead, flattening seems to be the result of increased conjugation between the allenyl lone-pair orbital and the carbonyl or cyano group. In MO terms, flattening of the nitrile ylide raises the HOMO, and increases the p character of the HOMO at C_1, allowing better interaction with the LUMO of the acceptor. This was verified by a study of the barrier to rotation about the formyl-C_1 bond in 1-formylnitrile ylide. Conformation A, shown in Fig. 16, was found to be 3.5 kcal/mol less stable than conformation B according to STO-3G. Conformation B allows stabilizing "conjugation", or interaction between the HOMO of the ylide and LUMO of the aldehyde. This conjugation will be further increased by flattening. In fact, the planar structure has an 8 kcal/mol barrier to rotation, since the conjugation is maximized in B and minimized in A.

Finally, the influence of two conjugating substituents, phenyl and vinyl, at C_1 was studied, since most of the nitrile ylides studied chemically have an aryl substituent at C_1. For each molecule, four geometries were computed, corresponding to the planar or bent species with the groups in conformations similar to either A or B shown for formyl in Fig. 16. Although STO-3G and MINDO/3 disagree substantially on the relative energies of these species, all calculations are in accord that the nitrile ylide will be substantially flattened, with the difference in energy between bent and planar nitrile ylides only 7–11 kcal/mol. For both 1-phenyl and 1-vinyl substituted molecules, MINDO/3 predicts $< XC_1N = 132°$, $r_{C_1N} = 1.21$ Å and $r_{NC_3} = 1.27$ Å.

A calculation on a more highly substituted ylide has been carried out by Dewar and Turchi[33]. This species, 3-carbomethoxy-3-carboxamido-nitrile ylide has an HC_1N angle of 132°.

How do these results correspond to the chemistry of nitrile ylides, and the variations observed upon substitution? Because of preparative limitations, most nitrile ylides which have been studied have a l-aryl substituent and frequently a 3-alkyl

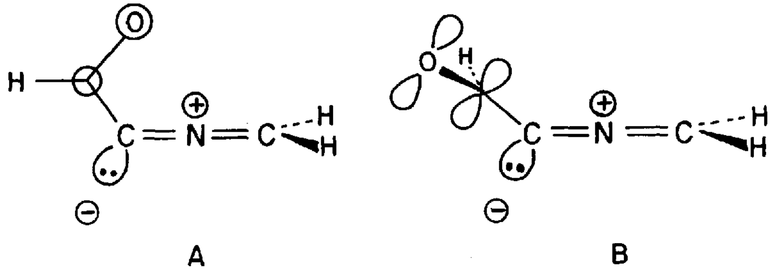


Fig. 16. Conformations of 1-formynitrile ylide

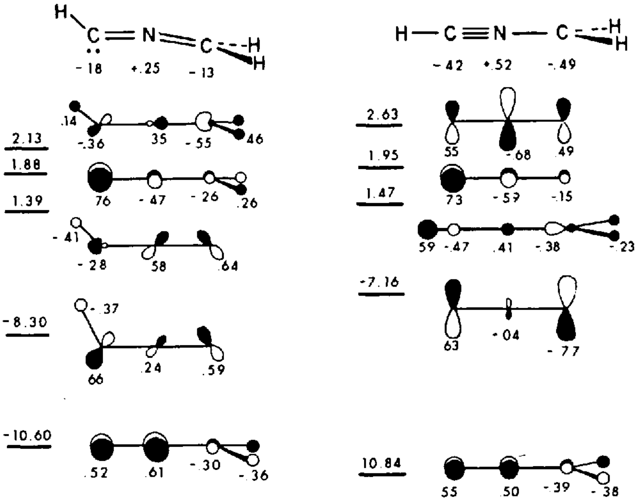


Fig. 17. Frontier molecular orbitals of bent and linear nitrile ylides. (Reprinted with permission from the *Journal of the American Chemical Society*. Copyright by the American Chemical Society.)

or 3-aryl substituent[34]. Our calculations suggest that these species will be bent, and have the frontier molecular orbitals shown schematically in Fig. 17. For such species, C_1 is more nucleophilic, and chemical behavior as summarized in Fig. 15 is observed. Exceptions are found for nitrile ylides containing two trifluoromethyl groups at C_3[35]. According to our calculations, two strongly electron-withdrawing groups would be expected to give a planar or nearly planar species, with C_3 the most nucleophilic site, due to the HOMO shape shown in Fig. 17. Burger and co-workers find in fact that the regioselectivity of cycloaddition of such species is opposite to that of arylalkyl nitrile ylides[35]. Padwa and co-workers have discovered a number of interesting intramolecular nitrile ylide and other nitrilium betaine cycloadditions, in which still different behavior is found[34, 36]. Figure 18

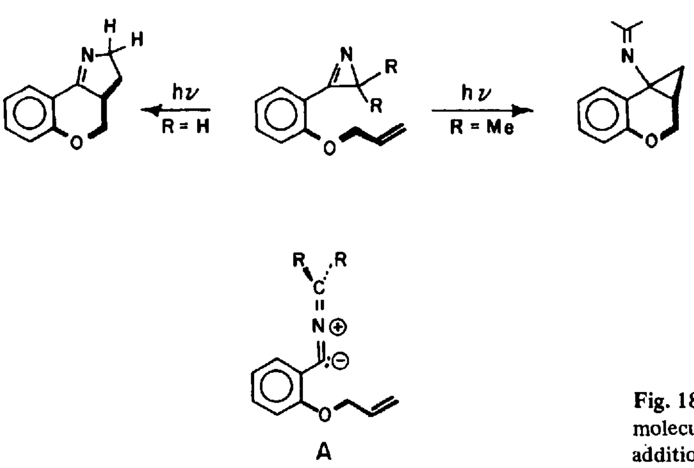


Fig. 18. Examples of intramolecular 1,3- and 1,1-cycloadditions of nitrile ylides

shows a normal 1,3-dipolar cycloaddition of a photochemically generated nitrile ylide to a double bond. A variety of controls have shown that these cycloadditions involve the ground state of the nitrile ylide[34)], and such reactions are believed to involve the "parallel planes" approach of dipole to alkene. However, the analogous dimethyl species undergoes a 1,1-cycloaddition, as shown on the right of Fig. 18. Our calculations indicate that C_3 dimethylation should enforce the bending of a nitrile ylide, so that a species such as A will be formed. Bending also makes C_1 of the nitrile ylide more carbene-like, in that essentially an in-plane lone pair (the HOMO – see Fig. 17) and an out-of-plane vacant orbital (the SLUMO in Fig. 17) are present. Bending of the nitrile ylide decreases the probability of 1,3-dipolar cycloadditions; since the parallel planes geometry is unattainable, and increases the electrophilicity of C_1. Both of these effects cause the 1,1-cycloaddition to occur for the dimethylated ylide. The monomethyl compound gives both 1,1- and 1,3-adducts while the compound with both R = CF_3 gives only 1,3-adduct[38)]. Thus, when the nitrile ylide is flattened, 1,3-dipolar cycloaddition is favored, but upon bending, 1,1-cycloaddition becomes of increasing importance. More recently, Padwa has shown that nitrile imines, which our calculations show are "flatter" than nitrile ylides, undergo only 1,3-dipolar cycloadditions in similar cases[36)].

Alkyne and Alkene Reactivities

Our studies of the distortions of alkynes and alkenes are of even more general significance[41)]. Once again, we were drawn to this area of chemistry by a number of puzzling observations in the area of cycloaddition reactions, but it soon became apparent that the unusual behavior of alkynes as compared to alkenes was by no means confined to cycloaddition chemistry: alkynes are usually less reactive than alkenes toward electrophiles, but alkynes greatly surpass alkenes in reactivities toward nucleophiles. In cycloaddition chemistry, striking differences in regioselectivity (Fig. 7) are also observed. As described previously, electron-deficient acetylenes generally behave as if they were considerably more electron-deficient than the corresponding alkenes. However, this behavior is not explicable in terms of simple frontier molecular orbital theory.

The relative ionization potentials of ethylene (10.5 eV)[39)] and acetylene (11.4 eV)[39)] are in the order expected for the greater rate of reaction of the former with electrophiles. From the viewpoint of frontier molecular orbital theory, the HOMO of an alkene is higher in energy, and interacts more strongly with an electrophile LUMO, than that of the corresponding alkyne. The LUMO of an alkyne is more antibonding, and higher in energy, than that of the corresponding alkene. The measured vertical electron affinities of acetylene and ethylene are –2.6 eV[40)] and –1.8 eV[40)], respectively. This suggests that the alkyne LUMO should interact less strongly than an alkene LUMO with the HOMO of a given nucleophile. This leads to the frontier molecular orbital prediction that alkenes should be more reactive than alkynes toward nucleophiles, in disagreement with experiment. However, computations show that the solution of this dilemma lies in the molecular distortions which occur in the transition states of nucleophilic additions, and the orbital energy changes which accompany these distortions.

Stretching the CC bonds of ethylene or acetylene causes the CC bonding orbitals to be destabilized and the CC antibonding orbitals to be stabilized, as expected, since both bonding and antibonding interactions are decreased as bond length is increased from the equilibrium distance. Although this distortion should accompany attack by either electrophiles or nucleophiles on the alkenes or alkynes, this distortion does not alter the expectation that ethylene will be more reactive than acetylene towards both electrophiles and nucleophiles, since the changes in frontier orbital energies are comparable in both alkenes and acetylenes.

However, bending of acetylene and ethylene causes the differential stabilization of the alkyne LUMO required to explain the greater reactivities of such species toward nucleophiles as shown in Fig. 19. The same trends are observed for "*trans*" bending or "one-end" bending. Even for relatively modest bending of these molecules, the LUMO of acetylene drops below that of ethylene. Thus, in the transition states for attack of nucleophiles, where the molecules will be somewhat distorted (*vida infra*), the LUMO of acetylene has greater stabilizing interaction with the nucleophile HOMO than is the case for ethylene. By contrast, the HOMO energies of acetylene and ethylene change very little upon bending, so that such distortions will not facilitate attack of electrophiles on these species, as is confirmed by the computed geometries for the symmetrical attack of a proton on acetylene[42] or ethylene[43].

What is the origin of the drastic acetylene LUMO lowering upon bending as compared to the much smaller lowering of the ethylene LUMO? In acetylene, several σ^* orbitals (σ_u^* and σ_g^*) are only slightly higher in energy than the π^* orbital, and upon reduction of symmetry below $D_{\infty h}$, one or the other of these orbitals can mix substantially with, and greatly lower the energy of, the π^* LUMO, as shown in Fig. 19.

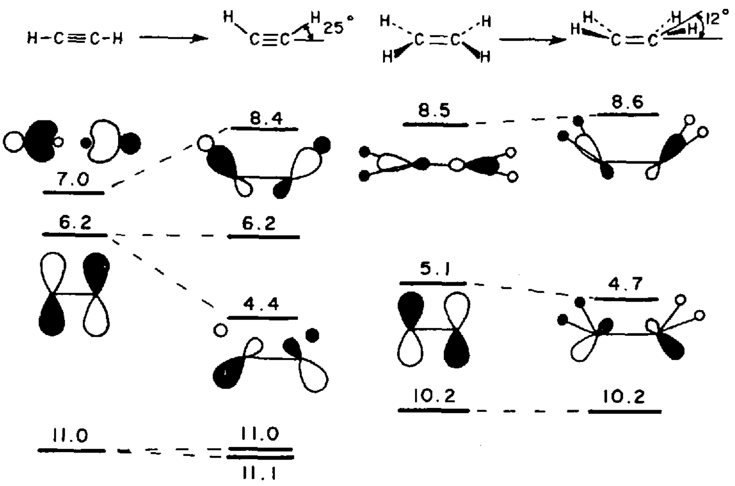


Fig. 19. Changes in frontier orbital energies upon bending distortions of acetylene and ethylene (4-31G)

Although ethylene has similar σ^* orbitals, these are not only appreciably different in energy from the π^* orbital of ethylene, but the overlap between the hydrogen orbitals and the ethylene π^* orbitals is smaller upon bending; both effects cause much less mixing of these orbitals upon deplanarization of ethylene.

The decrease in the acetylene π^* energy upon bending has been noted earlier by others. In the classic 1953 papers, Walsh showed that the π^* orbital energies for linear HAAH drop in energy and become CH bonding orbitals for "rectangular acetylene"[44]. Other calculations have also shown the LUMO drop upon bending[44, 45], but for the most part these calculations have been concerned with the change in geometry of acetylene from linear to *trans*-bent upon electronic excitation[46], or with the influence of bending on reactions with electrophiles[47].

The fact that the π^* orbital drops drastically on bending is, of course, related to the fact that the vinyl anion (sp^2 lone pair) is more stable than the ethyl anion (higher energy sp^3 lone pair). That is, upon bending, more s character is mixed into the LUMO of the alkyne, which ultimately becomes the sp^2 anion lone pair upon addition of a nucleophile. However, our treatment also explains why nucleophilic attack on alkynes is preferred even for early transition states or for those reactions, such as cycloadditions and thermal rearrangements, in which anions are not formed.

The calculations also suggest why *trans* addition of nucleophiles to alkynes is invariably observed, and why the apparently unusual trajectories proposed by Baldwin[48] for such attacks occur. Table 3 shows the energy changes which occur upon various distortions of acetylene and ethylene, as well as energies of interaction of the various geometries of these species with hydride ion, a model nucleophile.

Trans-bending of acetylene requires little more energy than one-end bending, while *cis*-bending requires significantly more energy. Out-of-plane bending of the hydrogens in ethylene requires more energy than for the same bending of acetylene. Our calculations involved a smaller angular distortion of ethylene, so that the energies are similar in the acetylene and ethylene cases.

The origin of the easier *trans*-bending of acetylene is revealed by the orbital energy changes which occur upon various types of bending, using the concept that that distortion is favored which maximizes $\pi^* - \sigma$ and $\sigma - \pi^*$ interactions, both of which are two-electron stabilizing interactions. The lowest-lying σ^* orbital, shown in Fig. 19, is of the correct symmetry (σ_u^*) to mix with the π HOMO of acetylene upon *trans*-bending, while *cis*-bending can be accompanied by similar mixing only with a higher energy σ_g^* orbital. Similarly, the highest σ orbital is σ_g and can mix with the π^* LUMO upon *trans*-bending, while only a lower-lying σ_u orbital can mix with the LUMO upon *cis*-bending. Such mixing, although small, can account for the greater ease of *trans*-bending.

This preference for *trans*-bending is magnified upon interaction with a hydride (Table 3). Thus, even for a very early transition state, a strong preference for *trans*-bending will occur. Experimentally, this is magnifested in the strong preference for *anti* addition stereochemistry in nucleophilic additions[49, 50]. For ethylene, there is a much smaller preference for *trans*-bending, and, more significantly, whereas the interaction of hydride with undistorted ethylene is much less unfavorable than the interaction with acetylene – due to lower energy LUMO of the former in the undistorted geometry – the interaction of hydride with *trans*-bent acetylene or

Table 3. 4-31G energy changes (kcal/mol) for distortions of acetylene and ethylene and interactions with hydride

Molecule	Molecular Distortions[a]			
	Undistorted	One-center bend	*trans* two-center bend	*cis* two-center bend
Acetylene	0	5.3	8.4	13.1
Acetylene + Hydride at 2 Å	30.0 (90°)	8.4 (120°)	5.5 (119°)	12.0 (121°)
Acetylene + Hydride at 1.5 Å	60.6 (90°)	12.9 (118°)	7.6 (119°)	9.8 (117°)
Ethylene	0	3.5	6.2	7.8
Ethylene + Hydride at 2 Å	24.7 (90°)	4.1 (118°)	4.0 (119°)	8.0 (118°)
Ethylene + Hydride at 1.5 Å	43.7 (90°)	10.5 (116°)	7.3 (116°)	8.3 (115°)

[a] Each bend was 25° for acetylene, or 11.9° for the HCH bisector of ethylene, each corresponding to a 42% geometry change from acetylene to ethylene, or ethylene to ethane. The H ⊖ CC angles were optimized and are shown in parentheses.

ethylene is equally-favorable – a result we attribute directly to the lower energy, and more directed character of the LUMOs of bent alkynes.

Potential energy scans of the hydride addition surface using 4-31G calculations led to the transition states for reaction of hydride with acetylene and ethylene shown in Fig. 20. Although these transition states are both about 2 kcal/mol above the isolated reactants in energy, the qualitative picture described above is confirmed: bending of acetylene is far more significant than stretching. In fact, the CCH bond angles in the transition states for attack on acetylene are appreciably distorted toward those of the product, in spite of the very similar energies of reactants and transition states.

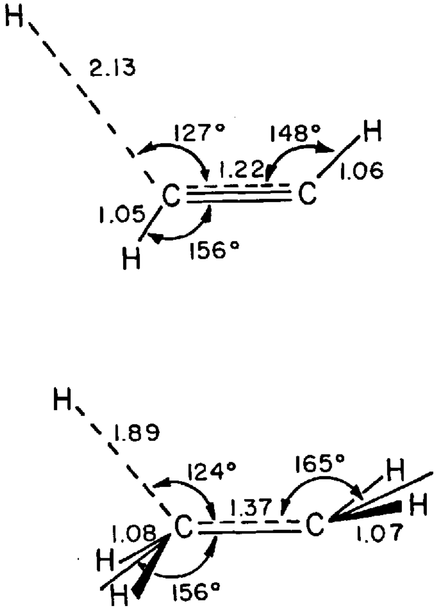


Fig. 20. 4-31G transition states for hydride addition to acetylene and ethylene[41)]

The greater bending of acetylene is more than compensated for by the increased stabilization upon interaction, a result which we attribute to increased hydride HOMO-acetylene LUMO interactions. *Trans*-bending is strongly favored over one-end or *cis*-bending, even for this very "early" transition state, since a constrained *cis*-bent transition state collapses to the *trans*-bent without activation upon attempted optimization.

Independent of our work, Dykstra, Arduengo, and Fukunaga have studied the addition of hydride to acetylene using a more extensive basis set and correlation energy corrections[51]. Although their calculations give a more realistic activation energy (16 kcal/mol), the transition state geometry is very similar to that shown in Fig. 20.

These results rationalize, in MO terms, the greater reactivity of alkynes than alkenes toward nucleophiles, and the *trans*-stereoselectivity of nucleophilic additions to alkynes. It is now clear why alkynes behave as if the LUMO energies of these molecules were lower than those of the corresponding alkenes: the effective EAs of alkynes are higher than those of alkenes. There are further consequences.

(1) The stereoselective *trans*-reduction of alkynes by dissolving metals[52] is a consequence of the drastic LUMO stabilization upon bending, and of the easier *trans*-bending of the alkyne molecule.

(2) Based on empirical evidence, Baldwin recently suggested that electrophiles and nucleophiles attack alkynes, $RC \equiv CR$ with the reagent, X, approaching such that the angle RCX = 120°[48]. At first site, the proposed trajectory seems theoretically untenable, since it seems to require attack of the nucleophile in a sense which would lead to little interaction with the LUMO, and would require the angle XCC = 60°. However, theory now predicts that the RCX angle will also be near 120°!

(3) The fact that Cope rearrangements of alkynes proceed as readily as those of alkenes[53] has been puzzling, since it would appear that the transition state would be more easily attained in the case of alkenes. However, our results indicate that considerable bending of the acetylenic units occurs easily in the transition state, since the energy required is counteracted by increased HOMO-LUMO interaction. Thus, in spite of appearances, acetylenes can enter into sigmatropic shifts without significant strain.

Orbital Polarization – Substituent Amphoterism

Charge-transfer interactions between frontier molecular orbitals are clearly not the only factors which determine the relative stabilities of various transition states, in spite of the fact that frontier orbital theory has been remarkably successful in accounting for relative reactivities and regioselectivities in various reactions. For example, frontier molecular orbital theory is based on orbital shapes and energies present in the isolated molecules, and these are expected to change upon the approach of one molecule to another.

We have carried out model calculations to determine how the approach of one reagent to another will influence polarization of frontier molecular orbitals[57]. As will

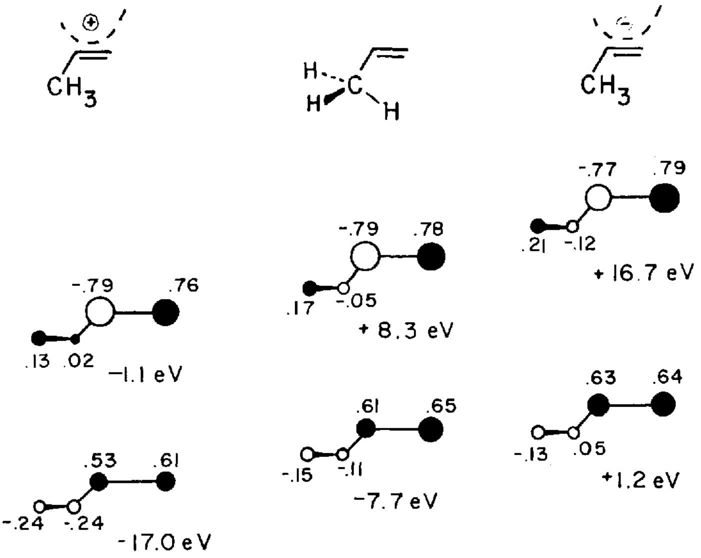


Fig. 21. Frontier orbitals of (center) propene, and propene polarized by (left) a positive charge and (right) a negative charge[57]

be shown later, the resulting polarization is of significance in accounting for some anomalies observed in cycloaddition regioselectivity.

In the center of Fig. 21, the HOMO and LUMO of propene are shown. The polarization of the HOMO is relatively large, and that of the LUMO is smaller and in the opposite direction. These polarization are examples of generalizations we have made earlier[10, 22, 54]. In order to determine how the approach of a nucleophilic or electrophilic reagent will influence the polarization, calculations were carried out on propene in the presence of a negative or positive charge, respectively, placed in an H 1s orbital at 1.5 Å above the center of the double bond. The effect of a positive charge is to decrease the orbital energies, a result of Coulombic attraction between the positive charge and the electrons in each orbital. In terms of physical measurables, the ionization potential and electron affinity of propene would both be increased in the presence of a positive charge. The influence of a negative charge, shown at the right of Fig. 21, is just the opposite.

The positive charge increases the polarization of both the HOMO and LUMO, so that the coefficient at the unsubstituted carbon is much larger than that at the methylated carbon, while the LUMO polarization is increased in the opposite direction. However, the effect of the negative charge is to reverse the polarization to some extent. The HOMO remains polarized in the same direction, but the LUMO polarization is reversed.

The reason for this is outlined in Fig. 22, which shows in the center of the diagram, the π orbitals of ethylene, and the π donor and acceptor orbitals of a generalized substituent. As shown at the left of the diagram, donor substituents cause polarization like that of propene, since the low-lying orbital causes the π to mix in

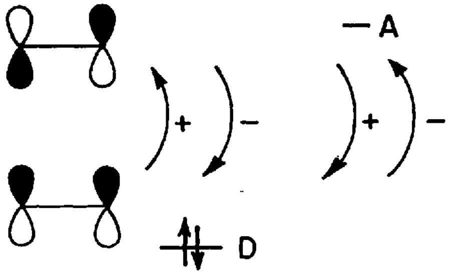


Fig. 22. Schematic representation of polarization caused by substituent having both donor and acceptor orbitals

some of the π^* in a negative fashion at the site of substitution, and, to a smaller extent, the π to mix into the π^* in a positive fashion[55]. The methyl group acts as a hyperconjugative donor through the influence of the filled "π_{CH_3}" orbital, while, in principle, the methyl group, and other donor orbitals also have vacant orbitals of π symmetry, can also be a hyperconjugative acceptor by the influence of the vacant "$\pi^*_{CH_3}$" orbital. The donor effect of the methyl and other donors generally dominates.

However, when an electron-rich reagent, modelled here by a negative charge, approaches the double bond, both electrostatic interactions and charge-transfer will raise the π and π^* energies, so that the π^* orbital will drift up in energy, where it will be influenced more by the A (e.g. $\pi^*_{CH_3}$) acceptor orbital than by the D(e.g. π_{CH_3}) donor orbital. The acceptor orbital, A, causes some of the π orbital to be mixed into the π^* in an antibonding fashion, thus diminishing the LUMO coefficient at the site of substitution and increasing the remote LUMO coefficient. The HOMO polarization is decreased because A causes the π^* LUMO to be mixed in a positive fashion at the site of substitution into the π HOMO, partially counteracting the polarizing influence of the D orbital[54, 55]. A positive charge simply magnifies the dominance of the D over the A orbital so than polarization increases.

Similar calculations were also carried out for acrylonitrile, shown in Fig. 23. Upon approach of a nucleophile, modeled by a hydride, the polarization of the LUMO is accentuated, while that of the HOMO is reversed as compared to the direction of polarization in the isolated molecule. This clearly results from a greater influence of the π^*_{CN} than the π_{CN} upon both the π LUMO and HOMO of the alkene. In the isolated molecule, the π^*_{CN} orbital dominates the LUMO polarization, but the π_{CN} influence on the HOMO slightly surpasses that of the π^*_{CN}, leading to the polarization shown. Upon approach of an electrophile, modeled here by a proton, the HOMO polarization is accentuated, while that of the LUMO is decreased. Here the π_{CN} influence on both orbitals increases. Once again, the contributions of the cyano group to the HOMO and LUMO in various models proves the validity of this explanation.

The results not only indicate that the cyano group can act as a donor in cases of extreme electron-demand (at least where HOMO polarization is concerned), but removes some uncertainty as to the "true" HOMO polarization in unsymmetrical electron-deficient alkenes[56]. In fact, as an electrophile approaches such a species, the less substituted terminus gains electron density, and is, therefore, the predicted site of attack by electrophiles.

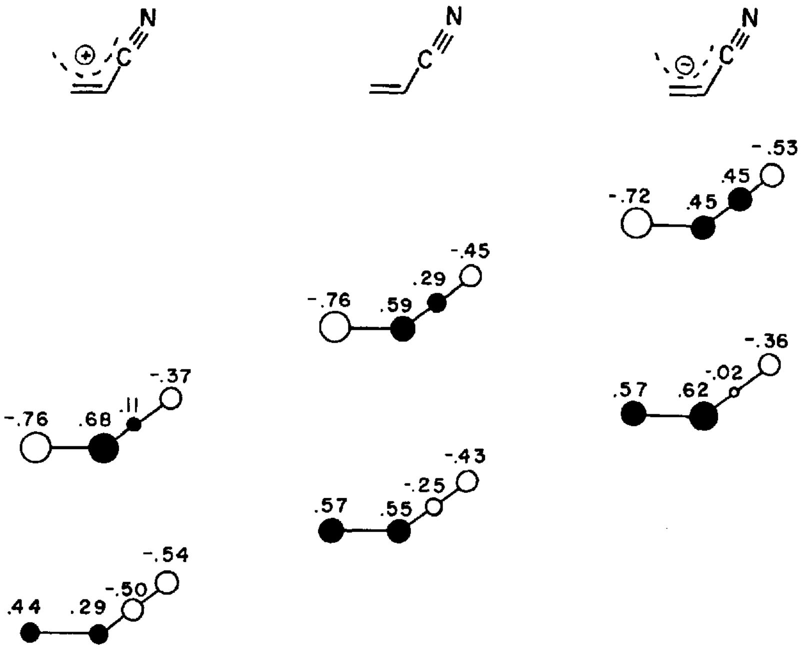


Fig. 23. Frontier orbitals of (center) acrylonitrile, and acrylonitrile polarized by (left) a positive charge and (right) a negative charge[57)]

These results have important bearing on the regioselectivity of attack of nucleophilic and electrophilic species on substituted alkenes. They help us understand why donor-substituted ethylenes are attacked exclusively at the unsubstituted terminus by electrophiles. Not only is the HOMO polarized in such a fashion that the largest terminal coefficient is on the unsubstituted carbon, but this polarization is increased as the electron-deficient reagent approaches the double bond. Thus, the small polarization of the HOMO in the ground state can lead to large, chemically-significant, polarization in the transition state. Similarly, the polarization of the LUMO of an electron-deficient alkene is magnified upon approach of a nucleophile, or electron-rich reagent. However, the most novel, and counter-intuitive, results occur when a nucleophilic reagent approaches an electron-rich alkene with a substituent which also has acceptor orbitals, or an electrophilic reagent approaches an electron-deficient alkene with a substituent also having donor orbitals available. In such cases, the LUMO or HOMO polarizations, respectively, can be reversed by the approaching reagents. The chemical significance of such effects will occur when a donor substituent makes a relatively electrophilic alkene unsymmetrical, or an acceptor substituent makes a relatively nucleophilic alkene unsymmetrical. We have pointed out numerous examples of the latter type[20, 22)], and the current polarization arguments reinforce our earlier deductions. That is, as described earlier, the cycloaddition of relatively electron-deficient 1,3-dipoles to moderately electron-deficient alkenes proceeds in a direction such that the most electrophilic centers of both species become united in the transition state. However, if the 1,3-dipole is the more electrophilic species, then it induces polarization of the electron-deficient alkenes such that the more electrophilic terminus also becomes the more nucleophilic terminus.

An example of the opposite type can be found in the cycloadditions of electron-rich species to electron-deficient compounds made unsymmetrical by an electron donor. Bohlmann and co-workers recently reported several Diels-Alder reactions of substituted benzoquinones [Fig. 24, Eq. (1)], and pointed out that the regioselectivities of these Diels-Alder reactions could not be understood on the basis of frontier molecular orbital (FMO) theory[58].

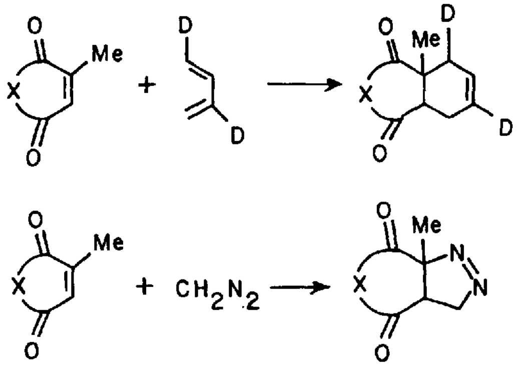


Fig. 24. Examples of cycloadditions of unsymmetrical electron-rich dienes and 1,3-dipoles to electron-deficient alkenes made unsymmetrical by a methyl substituent

There are numerous other reactions of this type in the literature, as summarized in Fig. 24[59, 60]. All of these reactions are of a special kind which previously has not been treated explicitly by frontier MO theory: namely, the electron-deficient partner in the cycloaddition is made unsymmetrical by substitution of a methyl group, which, until recently, has been thought of as a monolithic donor group. Our previous generalizations about the shapes of frontier MO's suggest that a donor substituent, including a methyl group, should cause the π^* LUMO of an otherwise symmetrical alkene to be polarized in such a fashion that the larger LUMO coefficient will be possessed by the donor-substituted carbon. Bohlmann's HMO calculations on the quinones used in his studies[58], as well as numerous calculations on donor-substituted alkenes[10, 54] of various types verify this generalization. Thus, in all of the cases summarized in Fig. 24, frontier MO theory, based on MO's of isolated reactants, would predict formation of the wrong product.

However, the previous discussion suggests that the polarization of the LUMO is reversed upon approach of a nucleophilic reagent to a methyl-substituted double bond; that is, the LUMO polarization is dominated by the acceptor nature of the methyl group (via the $\pi^*_{CH_3}$ orbital) upon approach of an electron-rich reagent. In such a case, the more nucleophilic terminus of the diene or dienophile will attack the less substituted alkene terminus, which becomes the site of higher LUMO coefficient upon approach of the nucleophilic molecule. The effect is a transition state analog of the recent gas phase equilibrium and isotope effects found for methyl substituted anions. Thus, anions are stabilized by alkyl groups in the gas phase as a result of the admixture of the high-lying anion lone-pair orbital with the relatively low-lying $\pi^*_{CH_3}$ of the methyl group, or the analogous acceptor orbitals of larger alkyls[61]. In such cases, these two-electron stabilizing interactions surpass the four-electron destabilizing interactions between the anion lone-pair and the alkyl π_{CH_3} orbitals[61b, 62].

Secondary Orbital Interactions or Orbital Polarization?

The effect described here seems fully capable of rationalizing the phenomena discussed. However, at least one other effect parallels the changes in polarization described in the last section. Like any qualitative quantum mechanical effect, generalizations and predictions are easily made, but experiments must be devised, or quantitative computations attempted, in order to determine whether the effect is of chemical significance. For example, the basis of the Woodward-Hoffmann rules is certainly correct, and "allowed" reactions appear to be 10–15 kcal/mol more favored than similar "forbidden" reactions in many cases. It would have been possible, in principle, that allowed reactions would have been 0.1 kcal/mol more favorable than forbidden. If such had been the case, then the Woodward-Hoffmann Rules would have been of no chemical significance! The magnitude of the effects, not the correctness of the arguments, is what is in question for the phenomena discussed here.

Returning to the question of the influence of donor substituents on reactions of alkenes with nucleophiles, or of acceptor substituents on reactions of alkenes with electrophiles, it has been proposed in the previous section that because of changes in orbital energies upon approach of a reagent to an alkene, the polarization of frontier molecular orbitals can change, with donors acting as acceptors, or *vice versa.* Secondary orbital interactions provide an alternative explanation. Figure 25 shows the LUMO of a donor-substituted alkene and the HOMO of an acceptor-substituted alkene. In both cases, the substituent orbital is mixed with the alkene in an antibonding fashion. When a reagent approaches the substituted carbon, secondary orbital interactions with the substituent orbital will partially nullify the primary interaction. This repulsive secondary orbital interaction will favor attack at the more remote terminus, where such secondary orbital interactions will be absent. This effect gives exactly the same predictions as the polarization effects discussed in the last section.

Fortunately, the correct explanation of which of these effects is dominant is subject to experimental test. If a donor substituent possessing no low-lying vacant orbital of π symmetry, such as R_2N or RO is placed on an electron-deficient alkene, then the reversal of polarization cited in the last section cannot occur. However, the secondary orbital interactions described here will still be present. Thus, cycloadditions

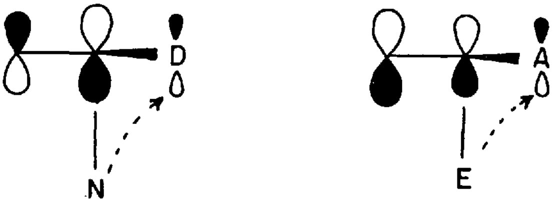


Fig. 25. The LUMO of a donor-substituted alkene and HOMO of an acceptor substituted alkene. Approach of a nucleophilic (N) to the former, or electrophile (E) to the latter at the substituted carbon will result in repulsive secondary orbital interactions (– – –) with the substituent

of unsymmetrical electron-rich dienes or 1,3-dipoles to electron-deficient alkenes made unsymmetrical by R_2N or RO will give the same orientation as when Me is present if secondary orbital interactions dominate, but opposite orientation if frontier orbital polarization is present. Such experimental tests are underway$^{63)}$.

Although it is impossible to design an acceptor lacking a filled orbital of π symmetry, there may be substituents (e.g. CF_3), in which the appropriate orbital is too low in energy ever to reverse the HOMO polarization significantly (to give the larger coefficient at the unsubstituted terminus). In such a case, it might be possible to test the influence of polarization versus secondary orbital interactions on regioselectivity of attack by electrophiles on electron-deficient systems.

In fact, this ambiguity between polarization and secondary orbital interactions is akin to a similar ambiguity in "orbital distortion" explanations of stereoselectivity. Liotta suggested that the direction of attack on alkenes lacking a plane of symmetry was determined by "orbital distortion" due to $\sigma - \pi$ mixing$^{64)}$. Fukui has proposed a similar explantion for the direction of attack of electrophiles on norbornene and related bicyclic systems$^{65)}$. It is believed that most stereoselectivity phenomena have been explained in this way by Liotta and Burgess$^{66)}$.

It has been shown in work by Caramella that these effects could be due to secondary orbital interactions$^{67, 68)}$ but in this case the difference is more a matter of semantics than quantum mechanics. That is, both approaches suggest that unequal electron density on one side of a double bond in the HOMO or LUMO causes preferred attack on one side of the bond.

Rates of Cycloadditions to Electron-Rich Alkenes

The secondary orbital interactions described in the previous section seem to be manifested in the rates of cycloadditions of electron-rich alkenes to electron-deficient dienes and 1,3-dipoles. We have undertaken systematic kinetic and theoretical studies designed to unravel the origin of electron donor substituent effects. Such substituents provide special problems. For example, although the rates of reactions of electrophilic reagents with alkenes should be increased by electron-donor substitution on the alkene, alkyl substituents frequently diminish reaction rates. That is, increasing the number of alkyl groups on an alkene, or increasing the size of the alkyl group on an alkene, often diminishes the rate of electrophilic addition$^{69)}$.

In order to probe this phenomenon quantitatively in an uncharged system where solvation effects are known to be relatively unimportant, the rates of cycloadditions of two relatively electron-deficient 1,3-dipoles, *p*-methoxy and *p*-nitro benzonitrile oxides (MBNO and NMBO, respectively) to a series of simple alkenes – propene, 1-butene, 1-pentene, 1-hexene, 3-methyl-1-butene, 3,3-dimethyl-1-butene and isobutene – were measured$^{70)}$. In each of these reactions, only the 5-alkyl-3-arylisoxazolines were formed.

The rates of these reactions were determined by following the disappearance of the nitrile oxide band at 2290 cm^{-1} in the infrared spectrum, under conditions where the rates of dimerization of the nitrile oxides are negligible compared to the rates of

Table 4. Rates of cycloadditions to benzonitrile oxides to alkylethylenes in CCl_4 (l/mol-sec x 10^3)[70]

Alkene, $CH_2 = C(R)(R^1)$			Substituted benzonitrile oxide	
R	R'	IP[71]	p-NO_2 (25 °C)	p-MeO (20 °C)
H	H	10.52		
Me	H	9.90	13.4	2.41[a]
Et	H	9.79	12.9	2.41
Pr	H	9.68	12.6	2.38
Bu	H	9.64	12.9	2.39
i-Pr	H	9.69	11.3	2.08
t-Bu	H	9.61	7.26	1.44
Me	Me	9.40	4.79	0.691

[a] The propene rate was measured at −12.5 °C and was found to be identical (0.090 x 10^{-3}) to that of 1-butene at the same temperature.

cycloadditions to alkenes. The results are given in Table 4, which also lists ionization potentials of the various alkenes studied here[71]. Huisgen et al. have measured the relative rates of cycloadditions of benzonitrile oxide to an extensive series of alkenes[72]. These authors found that in ether at 25 °C, the relative rates of cycloadditions to ethylene, propene, and 1-hexene are 1:0.32:0.31[72].

In accord with the electrophilic nature of the nitrile oxides, NBNO reacts about ten times faster than MBNO with all of the alkenes studies here[73]. This is compatible with the dominant interaction of the 1,3-dipole LUMO with the alkene HOMO: the nitro group should lower the LUMO energy of the nitrile oxide and increase the interaction of this orbital with the alkene HOMO, accelerating the reaction. This nitrile oxide LUMO-alkene HOMO interaction also governs the regioselectivity of the cycloaddition, since the unsubstituted terminus of the alkene (larger HOMO coefficient) prefers to become bonded to the carbon terminus of the nitrile oxide (larger LUMO coefficient) in the transition state.

However, this interaction should also be increased by alkyl substituents, which lower the alkene IP, or, equivalently, raise the alkene HOMO energy. Experimentally, there is either no change in rate, or a small decrease, as the IP of the alkene decreases. Thus, an apparent contradiction is revealed in these examples: dipole LUMO-alkene HOMO control nicely accounts for regioselectivity and the nitrile oxide substituent effect, but does not explain the decrease in rate for increasing alkyl substitution. More potent electron-donors do, indeed, accelerate the reaction, but only feebly. For example, butyl vinyl ether reacts 2.1 times faster than ethylene with BNO at 0 °C, while styrene reacts only 1.2 times faster than ethylene with BNO, in spite of the low IP of styrene (8.48 eV)[72].

The decrease in rate of reaction upon alkylation of alkenes, like that observed for other electrophilic additions, is a steric effect. However, calculations which we have performed on these systems[74] indicate that alkyl groups decrease the rate of reaction not only by increasing exchange, or closed-shell, repulsion between the nitrile oxide and the alkyl substituents, but by slightly decreasing charge-transfer interactions. This appears to be a general feature for electrophilic attack on electron-rich alkenes: since the HOMO of donor-substituted alkenes invariably has a substituent orbital mixed in an antibonding fashion with the vinyl π orbital, an incoming electrophile which interacts with both vinyl carbons (a "two-bond" electrophile)[4] will also experience an antibonding interaction with the substituent orbital, as shown earlier in Fig. 25.

Much larger effects of this type are observed in cycloadditions of enol ethers to tetrazines (Fig. 26), a reaction shown by Sauer and co-workers to be an example of a Diels-Alder reaction "with inverse electron demand"[75]. The rates of 3,6-di-(2′-pyridyl)-s-tetrazine to various enol ethers and styrenes are summarized in Fig. 27. These were obtained by measuring the disappearance of the 540 nm band in the absorption spectra of the tetrazine[76]. These results are of particular interest, since there is little or no correspondence between the electron-donor ability of the enol ether, as measured by the π ionization potentials (Table 5), and the rate of reaction of the enol ether. For example, although the conversion of methyl vinyl ether to 1,1-dimethoxyethylene results in a 4.3 times increase in rate, in line with the 0.2 – 0.3 eV decrease in IP, the 1,2-dimethoxyethylenes are 13 to 25 times less reactive than methyl vinyl ether, even though the IPs of these molecules are much lower

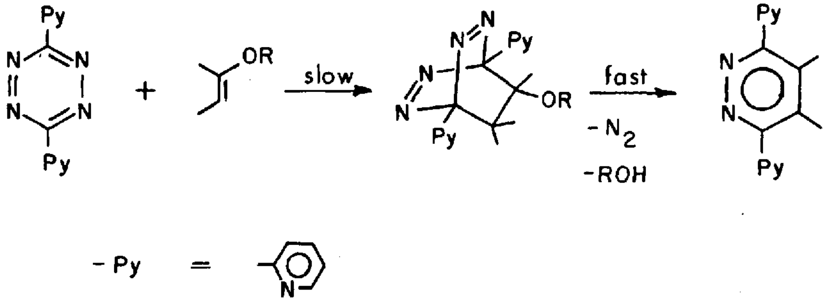


Fig. 26. Cycloadditions of dipyridyl-s-tetrazine to enol ethers

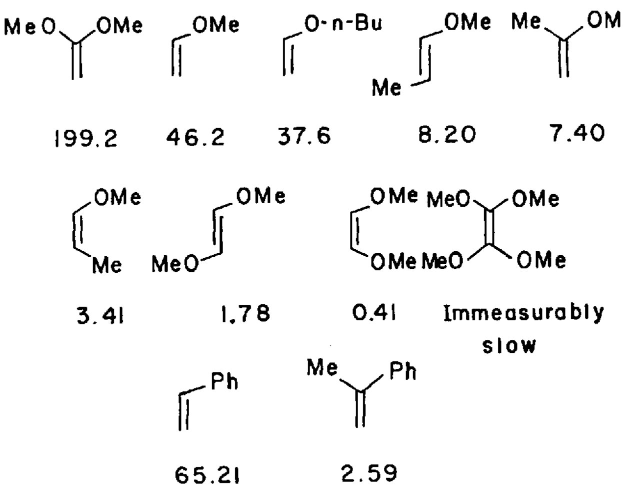


Fig. 27. Rate constants of 3,6-di(2′-pyridyl)-s-tetrazeine addition to enol ethers and styrenes: $10^5 k_2$ (l · mole^{-1} sec.$^{-1}$) in dioxane, 25 °C[76]

Table 5. Ionization potentials of enol ethers

Enol ether	IP (pes)^{a}	IP (from CT)^{d}	IP (STO-3G)^{f}
CH_2=CHOMe	9.05^{g} (9.14)^{h}	9.19 (9.20)^{e}	9.04
CH_2=CHOEt	9.07 (8.95)^{h}	9.07 (9.07)^{e}	–
CH_2=CHO-n-Bu	9.10^{h} (9.15)^{h}	9.04	–
CH_2=CHO–i–Pr	8.89 (8.84)^{h}	– (8.99)^{e}	8.78
CH_2=CHO-t-Bu	8.75 (8.77)^{h}	– (8.95)^{e}	–
E-MeCH=CHOMe	–	–	8.80
Z-MeCH=CHOMe	–	–	8.64
E-MeCH=CHOEt	8.47^{b}	8.75	–
Z-MeCH=CHOEt	8.53 (8.48)^{b}	8.75	–
$(Me)_2C$=CHOMe	8.20	–	–
$(Me)_2C$=CHOEt	8.20 (8.04)^{b}	8.56	–
Z-MeOCH=CHOMe	8.39	–	8.05
E-EtOCH=CHOEt	8.23	8.30	–
Z-EtOCH=CHOEt	8.15	–	–
CH_2=C(Me)OMe	8.88^{c}	– (8.85)^{e}	8.83
$CH_2=C(OMe)_2$	8.81^{c}	–	8.70
$H_2C=C(OEt)_2$	8.30^{g}	–	–

[a] Unless indicated otherwise, these values were measured by Taylor, G., unpublished results reported in: Shore, N. E., Turro, N. J.: J. Am. Chem. Soc. *97*, 2482 (1975).

[b] Schmidt, W.: unpublished results referred to in: Huisgen, R., Meyr, H., Tetrahedron Lett. *1975*, 2965.

[c] Santiago, C., Houk, K. N., unpublished results.

[d] Calculated assuming ethyl vinyl ether (IP = 9.07), and the TCNE charge transfer maximum reported in Arimats, T., Osngi, J.: Rev. Phys. Chem. Japan *44*, 25 (1974).

[e] Calculated in footnote b using TCNE CT maxima from Ledwith, A., Woods, H. J.: J. Chem. Soc. (*B*), 310 (1970).

[f] Calculated from STO-3G orbital energies using equation $IP = 0.662\ (\epsilon)+4.193$ which is a least-squares treatment of IP's in footnote a.

[g] Wittel, K.: Dissertation, Frankfurt, West Germany, 1973.

[h] Friege, H., Klessinger, M.: J. Chem. Research (*S*), 208 (1977).

than those of methyl vinyl ether or 1,1-dimethoxyethylene. Similarly, methylation lowers the IPs of the alkenes, but decreases the rate of reaction when attached at either the α- or β-carbon. Tetramethoxyethylene, which should have a very low IP, does not react at a measurable rate under our conditions! The effects here are undoubtedly a rather complex combination of conformational changes in the methoxy groups, electronic, and steric effects. That is, methyl vinyl ether prefers the so-called "planar" conformation of the methoxy group, but multi-methoxy alkenes probably have one or more non-planar methoxy groups, and greater steric repulsion for an approaching reagent than would be expected for the methoxy group in methyl vinyl ether. In addition, a more specific steric effect involving the "business' frontier orbital is possible in electron-rich alkenes which is not present in electron-deficient alkenes. That is, as shown in Fig. 28, the HOMO of an electron-donor always has the donor orbital mixed in an antibonding fashion, and approach of a diene will result in a destabilizing secondary orbital interaction which will partially cancel out

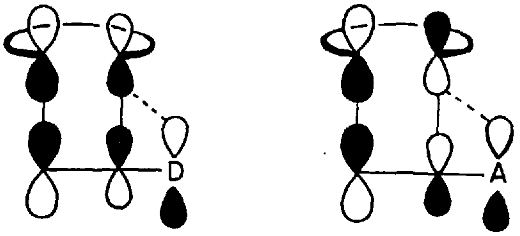


Fig. 28. (Left) the HOMO of an electron-rich alkene mixing with the LUMO of a 4n π reagent; (right) the LUMO of an electron-deficient alkene mixing with the HOMO of a 4n + 2 π reagent. (Dotted lines indicate secondary orbital interactions with the substituent.)

the stabilizing primary orbital interactions. On the other hand, an electron-deficient alkene has a relatively low-energy LUMO because of the bonding admixture of an acceptor orbital. Thus, the interaction with the HOMO of an electron-rich reagent will result in a secondary orbital interaction which reinforces the primary stabilization. Thus, whereas sequential addition of electron acceptors lowers alkene LUMO energies and causes a regular increase in reaction rate[77], addition of electron-donors may cause only a small increase in rate or even a decrease in reactions of alkenes with electrophilic reagents. We are probing this effect in more detail.

Periselectivity in Fulvene Cycloadditions

We conclude this article with a brief summary of our recent work on fulvene cycloadditions, an area in which a theoretical prediction led to the discovery of a new type of cycloaddition, and eventually to a viable method for the synthesis of the azulene ring skeleton.

Figure 29 shows the frontier molecular orbitals of fulvene, a molecule which can react as a 2 π, 4 π, or 6 π addend. As we and others have discussed[78, 79] the very different localization of the HOMO and LUMO suggest different sites of attack by electrophilic and electrophilic reagents. This feature is common in non-alternant

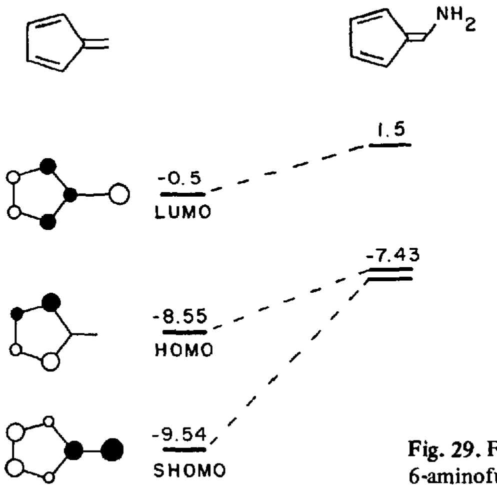


Fig. 29. Frontier molecular orbitals of fulvene and 6-aminofulvene

hydrocarbons, but not in alternant hydrocarbons, where the HOMO and LUMO are localized in the same regions of space.

Nucleophiles attack C-6, since this is the site of highest LUMO coefficient. Similarly, nucleophilic 4 π addends should cycloadd across the 2 and 6 positions, with the more nucleophilic end of the 4 π addend attacking C-6. By contrast, electrophiles attack C-2, the site of highest HOMO coefficient, and electrophilic 4 π addends can only add across C-2 and C-3, due to the node at C-6. The presence of the second highest occupied MO (SHOMO) of the fulvene complicates this simple picture, and substituents may drastically change the HOMO shape, as described below. Nevertheless, this picture does help explain, at least qualitatively, the varying periselectivity of diene and 1,3-dipole cycloadditions to fulvenes.

We have described the cycloadditions of a variety of dienes, ranging from cyclopentadiene to cyclopentadienones with alkyl and aryl fulvenes[80–82]. In these cases, only the [4 + 2] cycloadducts across the 2 and 3 positions are observed. Similarly, 1,3-dipoles such as nitrones and nitrile oxides add in this fashion, as well. We discovered the first authentic [6 + 4] cycloaddition of a fulvene in 1970[83]. The cycloadditions of tropone to fulvenes, which we originally suggested involved [6-fulvene + 4-tropone] cycloadditions, now appear to be [6-tropone + 4-fulvene] cycloadditions[81].

We predicted that electron-rich 1,3-dipoles in addition to diazomethane, such as nitrile ylides, would react in this fashion as well, and in 1978, Padwa and Nobs reported just such a reaction, shown in the second equation in Fig. 30. This reaction also gives some [4 + 2] adduct, in which the most nucleophilic terminus of the dipole has added to the 6-position of the fulvene. We have also found that electron-rich dienamines add to fulvenes in high yield (third equation of Fig. 30)[85]. These results

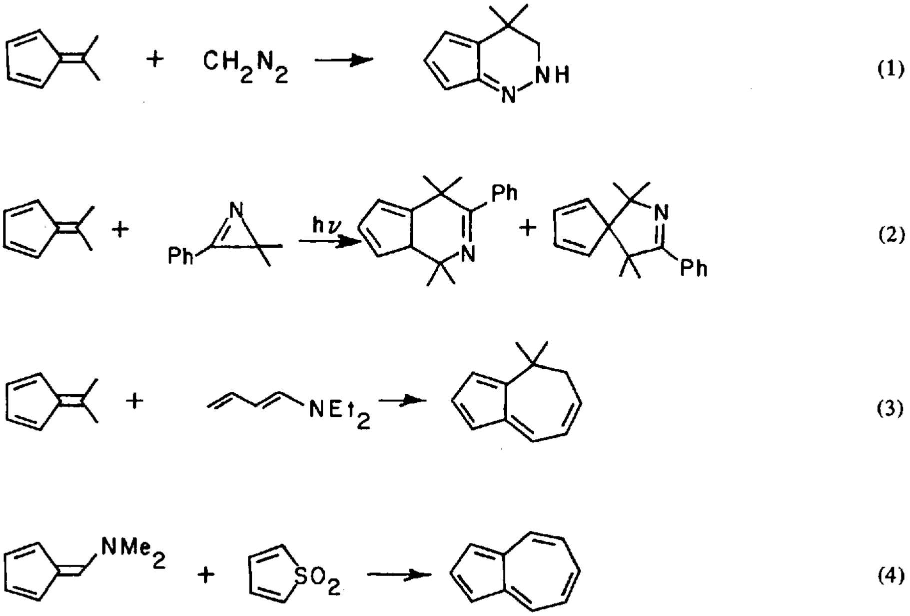


Fig. 30. [6 + 4] Cycloadditions of fulvenes to electron-rich species, and of aminofulvenes to electron-deficient thiophene dioxides

are clearly related to the high electrophilicity of C-6 of fulvenes dictated by the LUMO, and the allowed nature of the [6 + 4] cycloadditions.

It is also possible to observe [6 + 4] cycloadditions when the very electron-rich 6-dimethylaminofulvenes undergo reaction with electron-deficient dienes, thiophene dioxides[86] and coumalic esters[87], as well as the relatively electrophilic 1,3-dipole, benzonitrile oxide[88]. The frontier orbital picture here is somewhat more complex, in that the dimethylamino substituent causes the HOMO and SHOMO to be nearly degenerate[78] (Fig. 29). In such a case, [6 + 4] cycloaddition again occurs, since now

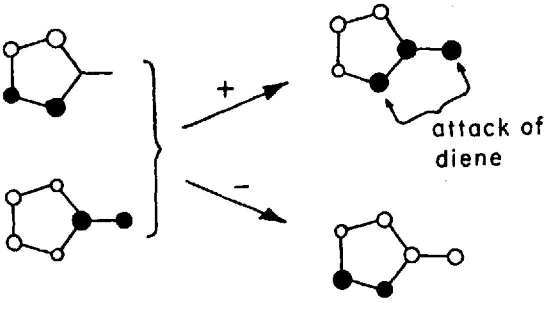


Fig. 31. HOMO of SHOMO of 6-dimethylaminofulvene (CNDO/2) and linear combinations

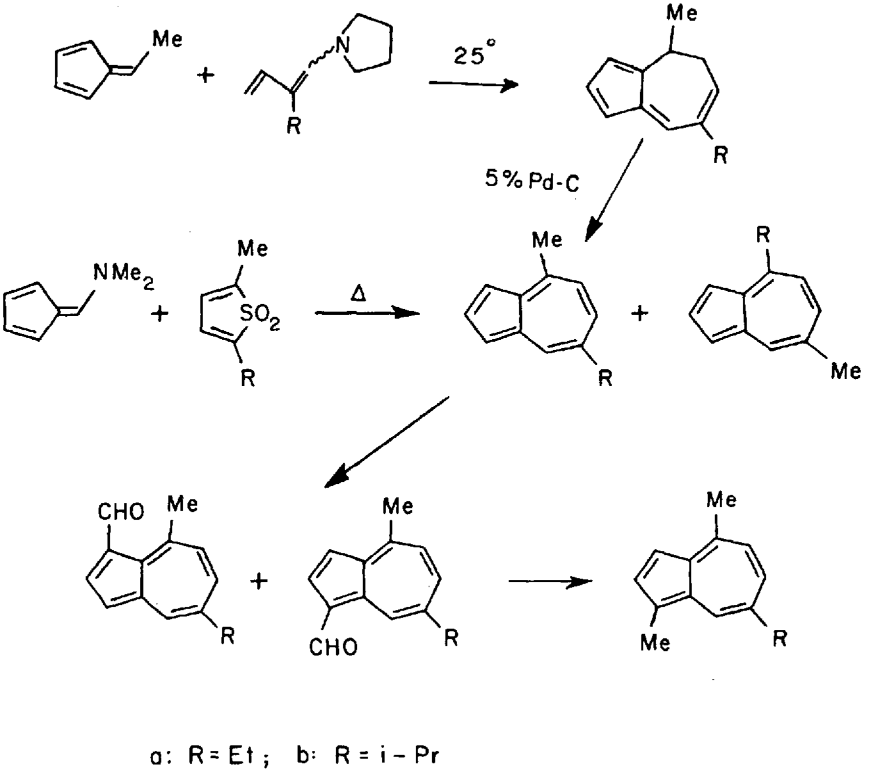


Fig. 32. Applications of [6 + 4] cycloadditions to the synthesis of chamazulene and guaiazulene

interaction of the diene LUMO across the 2 and 6 positions is again favorable. Since the two highest occupied orbitals are nearly degenerate, we can legitimately take linear combinations of these. As shown in Fig. 31, one of these orbitals is like that of a triene, with large coefficients of the same sign at C-2 and C-6.

These [6 + 4] cycloadditions are of more than theoretical interest. Figure 32 shows how these reactions have recently been applied in our laboratories to the synthesis of chamazulene and guaiazulene[89], two molecules isolated from natural sources. In both cases, some "classical" chemistry had to be carried out, in order to regioselectively incorporate the C-1 methyl substituent, since cycloadditions of ring substituted azulenes gave the wrong regioisomeric products[90]. Several points are of note: the cycloaddition of the unsymmetrical thiophene dioxides proved a pleasant surprise in the relatively high regioselectivity (4:1), favoring the needed regioisomers in both cases. The cycloadditions of dienamines are regiospecific, attesting to the strong polarization of the dienamine HOMO and the fulvene LUMO. The Vilsmeier reactions proceed with high regioselectivity, due to both the steric and electronic influence of the methyl group at C-4. Although the yields of the thiophene dioxide cycloadditions are low, the ease of separation of the azulenes from polar byproducts make these reactions convenient ones.

Conclusion

In this article, a description has been given of theoretical and experimental investigations of the factors beyond frontier molecular orbital interactions which are important in influencing mechanisms, rates, and regioselectivities of cycloadditions and related reactions of unsaturated systems. Closed-shell repulsion, geometrical distortions, polarization, and secondary orbital interactions have all been shown to be influential. Electrostatic interactions and correlation effects have not been discussed, but will provide further refinements – or confusion, depending upon the reader's point of view! As Professor Huisgen recently commented, there are now a distressingly large number of "buttons to push", to explain various phenomena[91]. This is, indeed, the case at the present time, primarily due to our limited knowledge about the magnitudes of these many effects. The cases discussed here constitute examples where the cited effects seem to prevail over others, but similar effects will be present to some extent in all reactions. Our current research efforts constitute attempts to understand more generally when these effects are significant, and to be able to understand and predict rates and products of organic reactions.

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The Development of Polyquinane Chemistry

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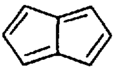
Table of Contents

I. Introduction

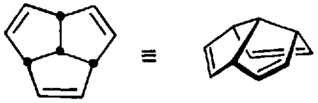
The polyquinanes comprise a class of fused ring compounds containing only cyclopentane rings. Although a large number of molecular types can be thought of as members of this series, several have been especially intriguing to organic chemists. The origins of polyquinane chemistry date back to Armit and Robinson[1) who pointed out the similarity of pentalene (*1*) to naphthalene and postulated that this



1

hydrocarbon might be aromatic. Numerous experimental investigations were spawned in an effort to gain access to derivatives of *1*. Until recently, all of these proved fruitless. The question of the nature of the bonding in *1* simultaneously motivated numerous theoretical studies,[2–7) many continuing to the present day.[8–13)

Quite understandably, the early work in this area was confined to the chemistry of the bicyclo[3.3.0]octane, or diquinane, system. Recognition in more recent times that a number of natural products possess polyquinane skeletons and that access to compounds from natural sources may be gained through polyquinane intermediates has led to a more broad-based interest in, and appreciation of, synthetic methodology in this field. With a concurrent burgeoning concern with molecules endowed with fascinating topology such as triquinacene (*2*) and the pentagonal dodecahedrane (*3*), the modern evolution of polyquinane chemistry has been both rapid and rewarding.



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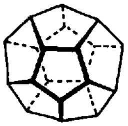


3

In this review, we propose to survey in rather broad detail the synthetic developments which have taken place to this time. The intention has been to gather together numerous facets of pertinent synthetic methodology, many of them ingenious, some of historical interest, which might serve to stimulate new ventures in polyquinane chemistry.

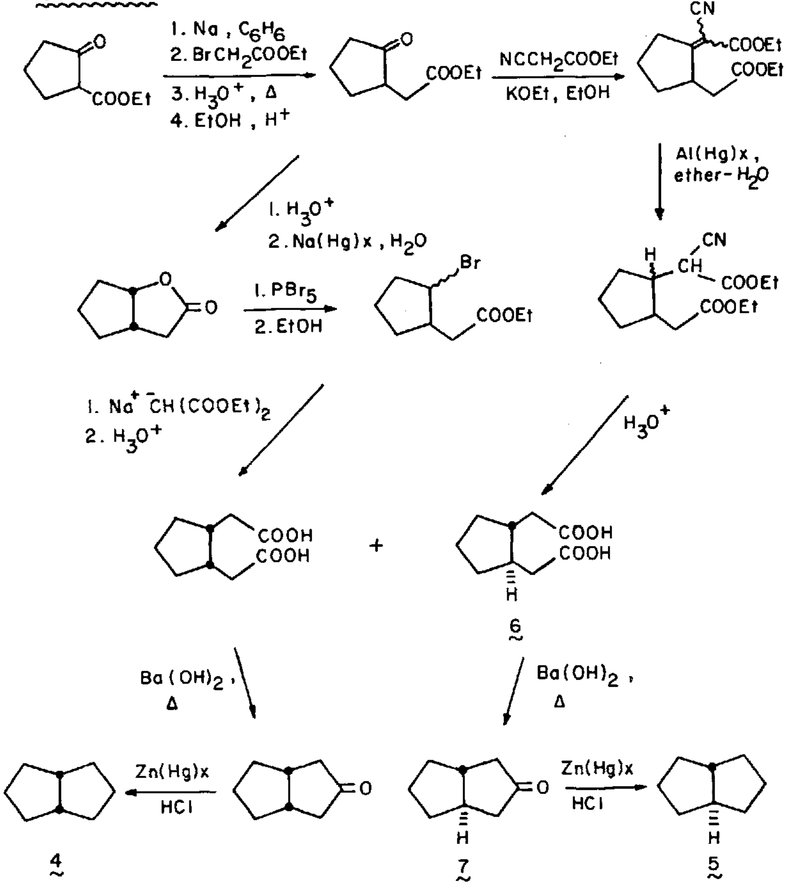
II. The Preparation of *cis*- and *trans*-Bicyclo[3.3.0]octanes

A. Classical Synthetic Approaches

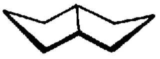
The parent hydrocarbons *4* and *5* were prepared early by Linstead and Meade as shown in Scheme 1.[14) Subsequent to the elaboration of 2-carbethoxycyclopentanone by Dieckmann cyclization of diethyl adipate, the synthetic plan relies upon the elaboration of vicinal acetic acid moieties and barium hydroxide promoted decarboxylative cyclization. Improvements in this route to the simplest of the bicyclo[3.3.0]octanes were arrived at later in Granger's laboratory.[15] The chiral nature of *trans* diacid *6* permitted its resolution by means of the brucine salt and subsequent conversion to optically active ketone *7*, $[\alpha]_D^{18}$ + 437 ° (*c* 1.058),[16] whose absolute configuration has been established.[17] Clemmensen reduction of dextrorotatory *7* expectedly gave rise to racemic *5*.

When combusted as liquids at constant volume, *5* was shown to have a heat of combustion 6.1 kcal/mole larger than that of *4*.[18] More recent thermochemical studies place this difference at 6.4 kcal/mole.[19] On this basis, all higher polyquinanes which have *cis*-locked vicinal bridgehead hydrogens are expected to partake of greater thermodynamic stability than their transoid structural isomers. In their assessment of the relative stabilities of bicyclooctane isomers, Schleyer and coworkers found *4* to have a high entropy content and attributed this property to the

SCHEME 1



structural flexibility provided by the *cis* ring juncture.[20, 21] Force field calculations by Allinger's group showed the $\underline{C}_s$ twist conformation of *4* to be of lower energy than the $\underline{C}_{2v}$ crown form by only 0.1 kcal/mole.[22] However, allowance must be made for the fact that the $\underline{C}_{2v}$ structure has a symmetry number of 2. As a result,



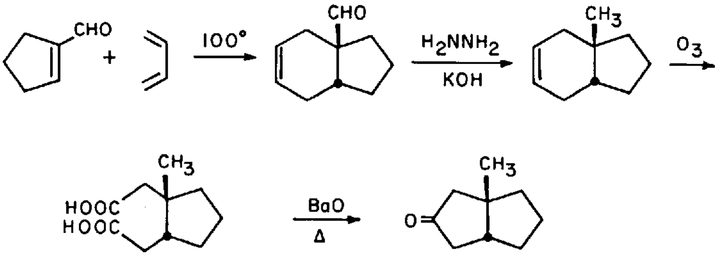
$\underline{C}_{2\underline{v}}$

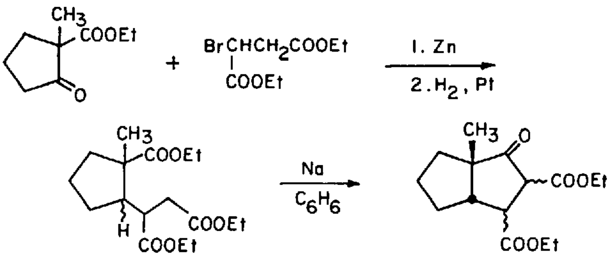
$\underline{C}_{\underline{s}}$

the $\underline{C}_s$ form can be expected to dominate by a factor of at least 2 : 1 at room temperature. This conclusion has proven to be consistent with spectroscopic results.[23, 24]

Although the pyrolysis of barium salts of dicarboxylic acids has continued to be exploited as a convenient route to 3-keto derivatives (Scheme 2),[25, 26] Dieckmann cyclization procedures have without doubt been accorded the greatest amount of attention.[27–38] Ruzicka and co-workers appear to have been the first to utilize base-catalyzed intramolecular condensations of this type.[27] The closely timed independent work of Mitter and Banerjee which resulted in a synthesis of *8* exemplifies the ready availability of starting materials and the simplicity of the method.[28] The

SCHEME 2





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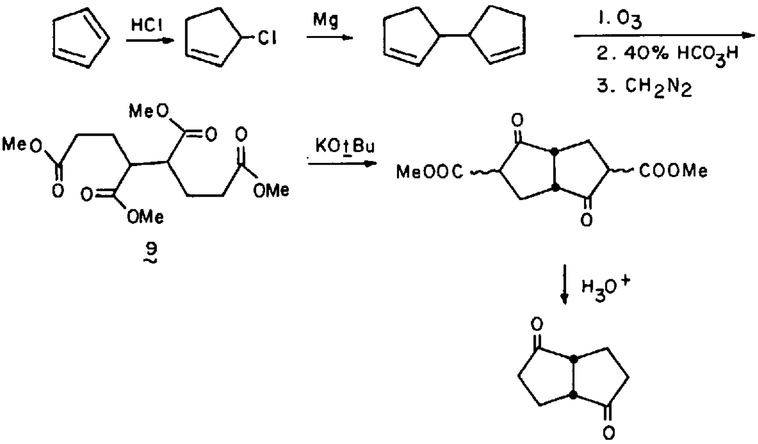
route devised by Dauben to gain access to diketone *10* carries a certain touch of elegance.[33] Tetraester *9* is also available from the free radical-induced coupling of dimethyl glutarate.[33, 38] Due to the strongly basic conditions of reaction, the



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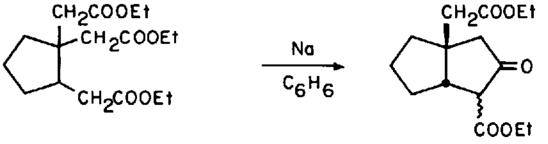
10

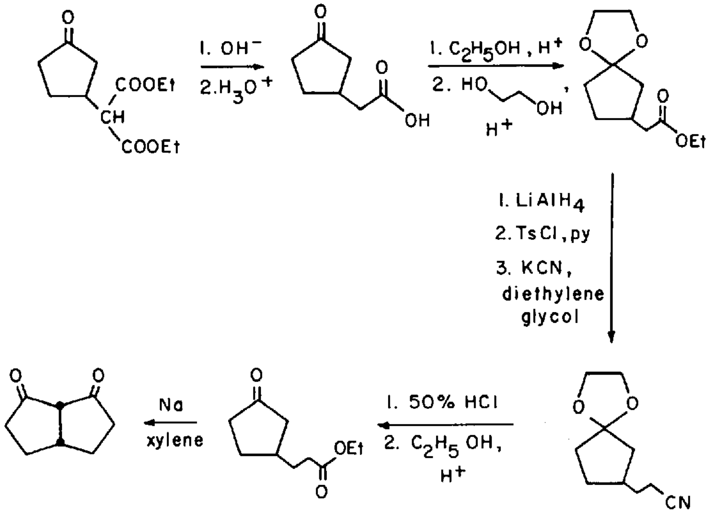
Dieckmann procedure unfortunately does not permit wide latitude in the number and nature of additional functional groups which can be tolerated. The effective synthesis of *11* denotes that an additional ester substituent may be tolerated.[37)]



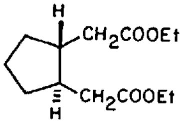
11

However, in most cases such as that shown in Scheme 3,[35)] it becomes necessary to

SCHEME 3



make use of blocking groups. Other disadvantages have also become apparent. Thus,

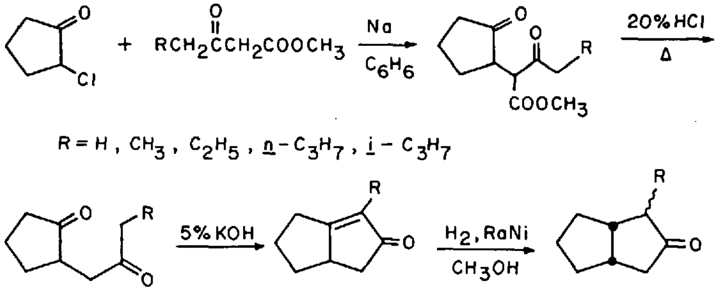


12

diester *12* has been shown to be resistant to closure when heated with sodium in benzene.[36)]

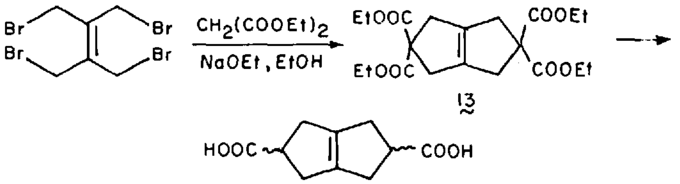
Two additional carbonyl condensation reactions which made their appearence in the 1950's provide ring closure capability of synthetic value. The first has been described by Paul and Wendel and utilizes 2-chlorocyclopentanone as starting material.[39)] Subsequent to alkylation with an acetoacetic ester and deesterification, the

SCHEME 4

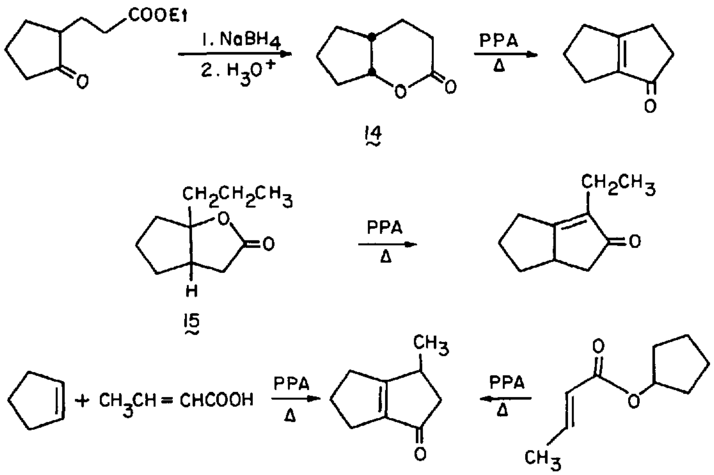


resultant 1,4-diketone is exposed to dilute base and subsequently hydrogenated to furnish 2-substituted 3-keto derivatives (Scheme 4).

Finally, Cope and his co-workers discovered that tetra(bromomethyl)ethylene can be multiply alkylated in low yield by diethyl malonate to give 3,3,7,7-tetracarbethoxybicyclo[3.3.0]oct-1(5)-ene (*13*).[40)] This substance can be decarboxylated and further modified structurally.

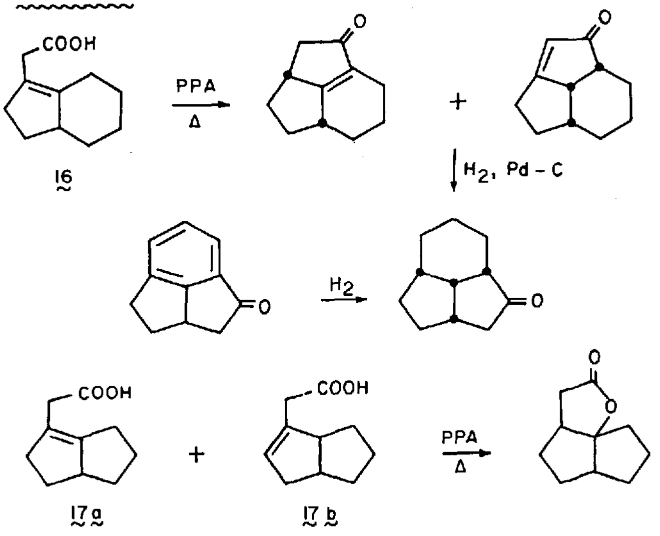


The role of acid-catalyzed reactions in bicyclo[3.3.0]octane synthesis has also been a major one. It is now well established that δ-lactones (e. g., *14*)[41)] and certain γ-lactones (*15*)[42)] undergo dehydrative cyclization when heated with polyphosphoric

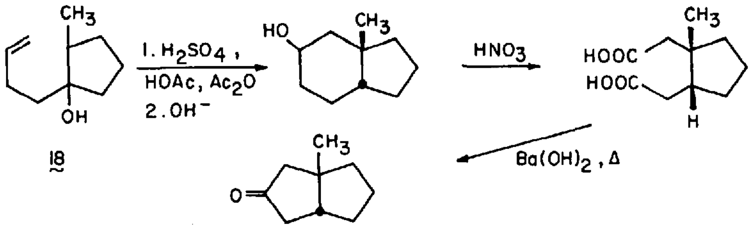


acid. These conditions allow also for the direct acylation-cyclization of cyclopentene with acrylic acids[43] as well as the closure of α,β-unsaturated esters of cyclopentanol.[44] In this connection, it is interesting to note that while Cargill and co-workers[45] found carboxylic acid *16* to be amenable to cyclization in PPA or methanesulfonic acid-phosphorus pentoxide,[46] comparable attempted dehydration of the lower homologous systems *17a* and *17b* resulted only in γ-lactone formation (Scheme 5).

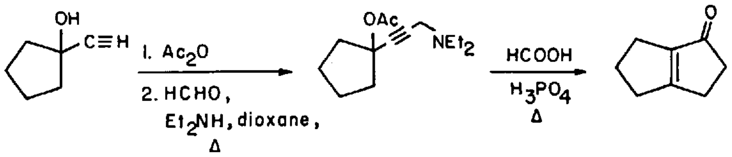
SCHEME 5



The discovery in 1938 of the ease with which alcohol *18* can be cyclized when treated with a mixture of sulfuric acid, acetic acid, and acetic anhydride[47] has served as the basis for many fruitful synthetic transformations of higher complexity.[48]

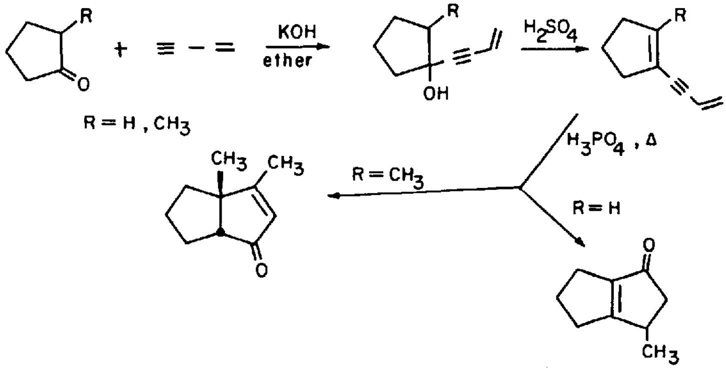


Similar applications of acetylene chemistry appear equally promising, but have been less intensively studied. In an early contribution to this subject, Islam and Raphael observed that the product of sequential acetylation and Mannich chain extension of cyclopentylethynyl alcohol did undergo cyclization when heated in a mixture of formic and phosphoric acids, although in low yield (7 %).[49] Greater



efficiency appears available through use of vinylacetylene as described in Scheme 6.[50, 51] This last method will, of course, inevitably position a methyl substituent β to the carbonyl group.

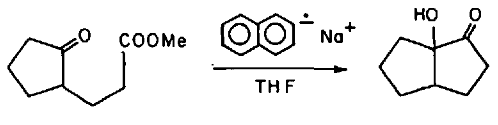
SCHEME 6



B. Modern Annulation Reactions

Due to the intense interest in steroid chemistry in the first half of the 20th century, much attention was accorded to annulation reactions involving the fusion of six-membered rings to preexisting carbocyclic frames.[52] The ability of organic chemists to effect five-ring annulation lagged far behind. In the last decade, this state of affairs has been redressed somewhat, chiefly as the result of the rapid evolution of synthetic methods chemistry during this period.

The ready availability of propionate esters such as *19* through application of enamine chemistry has caused the reductive cyclization of such molecules under



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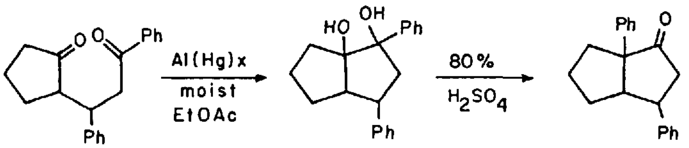
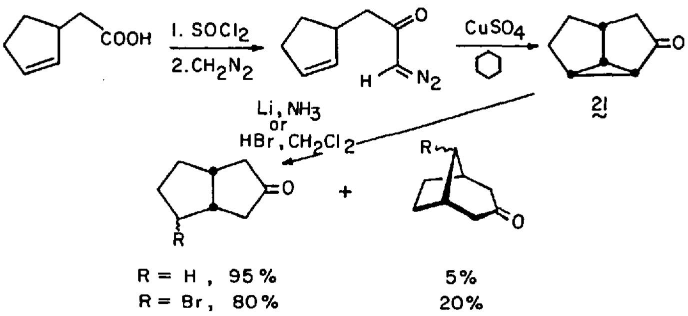


20

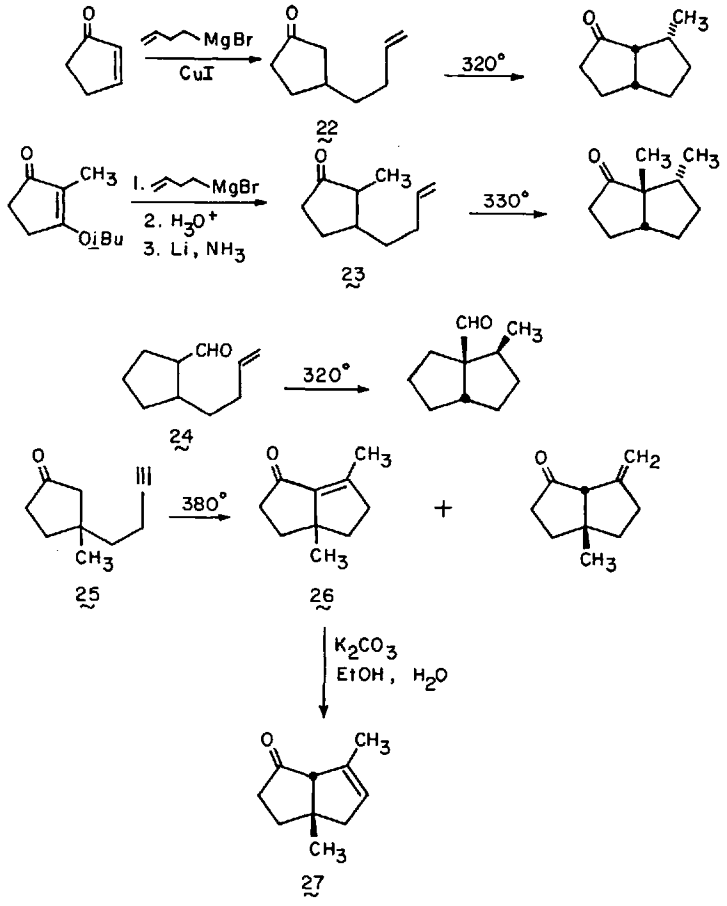
acyloin conditions to be an attractive synthetic entry to bicyclo[3.3.0]octanes.[53] The analogous closure of *20* emphasizes that the related pinacol reduction is also well suited to this purpose.[54]

Monti and his co-workers have successfully demonstrated not only the efficiency of intramolecular ketocarbene capture in the production of tricyclo[3.3.0.0^{2,8}]octan-3-one (*21*), but also the marked stereoselectivity of its dissolving metal cleavage and ring opening under acidic conditions (Scheme 7).[55] Prevailing stereoelectronic and thermodynamic factors favor predominant conversion to bicyclo[3.3.0]octyl end products.

SCHEME 7

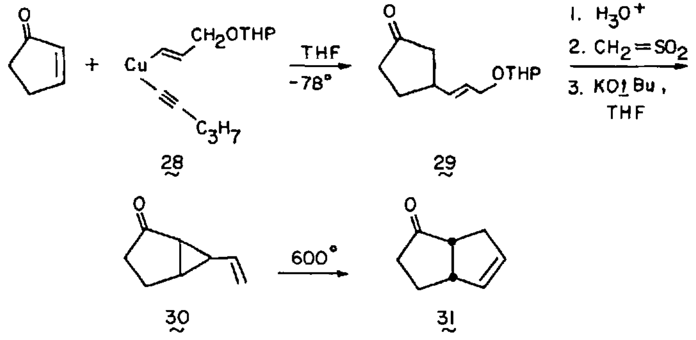


Not surprisingly, the rapid advances in organocuprate chemistry have had an impact in the polyquinane area. By means of conjugate 1,4 cuprate addition, 3-substituted cyclopentanones such as *22* now become accessible in a minimal number of steps. Detailed study of the thermal activation of *22* by Conia and co-workers has shown the ketone to be capable of efficient cyclization above 300°.[56] The comparable behavior of *23*,[56] *24*,[56] and *25*[57] illustrates the generality of the method. Interestingly, conjugated enone *26* has been found to be disfavored by approximately 2.4 kcal/mole relative to *27* because of ring strain.[57]



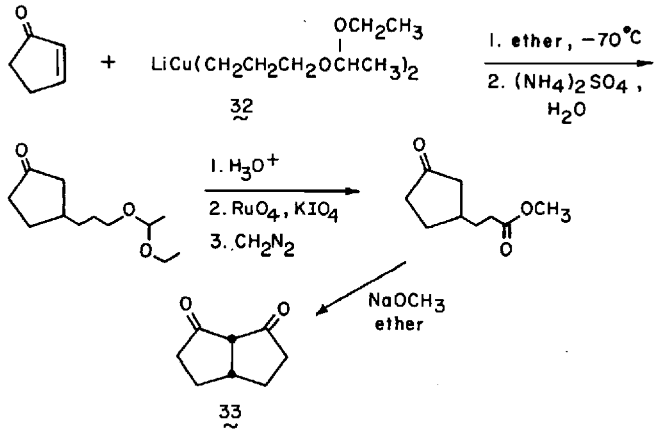
Corey and Wollenberg have found it possible to introduce a THP-blocked *trans* allylic alcohol unit *via* reaction of 2-cyclopentenone and other cyclic enones with the highly reactive mixed cuprate *28*.[58] Through hydrolysis, mesylation, and base-promoted cyclization of adduct *29*, the vinylcyclopropane *30* was obtained (Scheme 8). Thermolysis at 600 °C caused ring expansion to *31*.

SCHEME 8



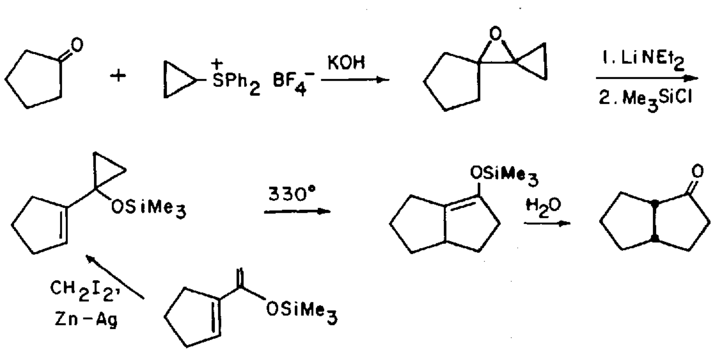
The Eaton group has developed an efficient synthesis of the 2,8-diketo derivative *33* by hydroxypropylation (Scheme 9).[59, 60] The key reagent here is the cuprate *32* which can readily be prepared in large quantities. Once the sidechain is added, the blocking group is easily removed and the primary hydroxyl function selectively oxidized in preparation for the necessary Dieckmann closure (compare Scheme 3).

SCHEME 9



The vinylcyclopropane to cyclopentene rearrangement is seemingly broadly applicable to solution of the five-ring annulation problem. Besides the example cited in Scheme 8, routes provided by Trost,[61] Miller,[62a] and Conia[62b] are conceptually attractive. Thus, we see that reaction of a cyclopentanone with the cyclopropyldiphenylsulfonium ylide provides an oxaspiropentane which can be opened efficiently with an amide base (Scheme 10). The resulting silylated cyclopropanol can be isomerized under moderate conditions and subsequently hydrolyzed to give a bicyclo[3.3.0]octan-2-one. Alternate access to the silylated cyclopropanol can be

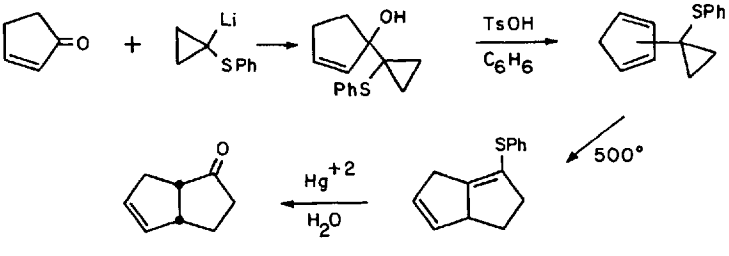
SCHEME 10



gained from l-acetylcyclopentene via the Simmons-Smith cyclopropanation of its trimethylsilyl enol ether.

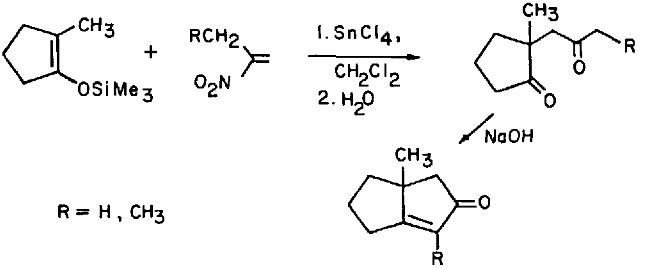
Should added unsaturation be desired, the condensation of a 2-cyclopentenone with lithio cyclopropylphenyl sulfide makes possible the formation of an allylic alcohol which can be dehydrated quantitatively (Scheme 11). Thermal rearrangement, followed by mercuric ion-promoted hydrolysis of the vinylsulfide part structure completes the synthetic transformation.

SCHEME 11



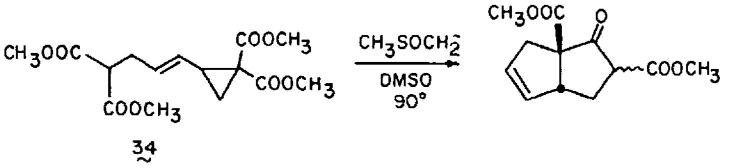
The electrophilic character of aliphatic nitroolefins and the synthetic equivalency of nitro and carbonyl groups have been exploited in a recently developed regiospecific route to bicyclo[3.3.0]octenones (Scheme 12).[63] With stannic chloride as catalyst,

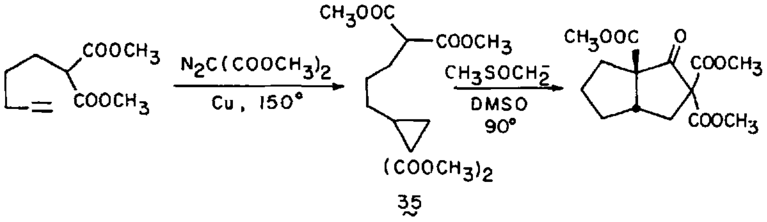
SCHEME 12



the Michael reaction of a cyclopentanone enol ether to a nitroolefin occurs under exceptionally mild conditions to produce a nitronic acid intermediate. Such compounds are very susceptible to hydrolysis and afford 1,4-diketones without the need for isolation of nitro ketones. Standard alkaline treatment of the 1,4-diketones results in elaboration of the second five-membered ring.

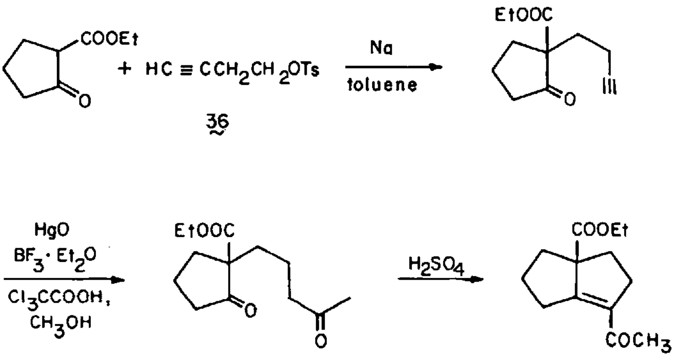
As part of a study of ring construction through transposition of activated cyclopropanes, Danishefsky's group has scrutinized the feasibility of intramolecular homoconjugate nucleophilic additon.[64] Two of the substrates examined were *34* and *35* and these were found to undergo rather efficient closure to bicyclo[3.3.0]octane derivatives when treated with strong base. The somewhat elevated temperatures allow both the cyclopropane fission and subsequent Dieckmann condensation to proceed at respectable rates.





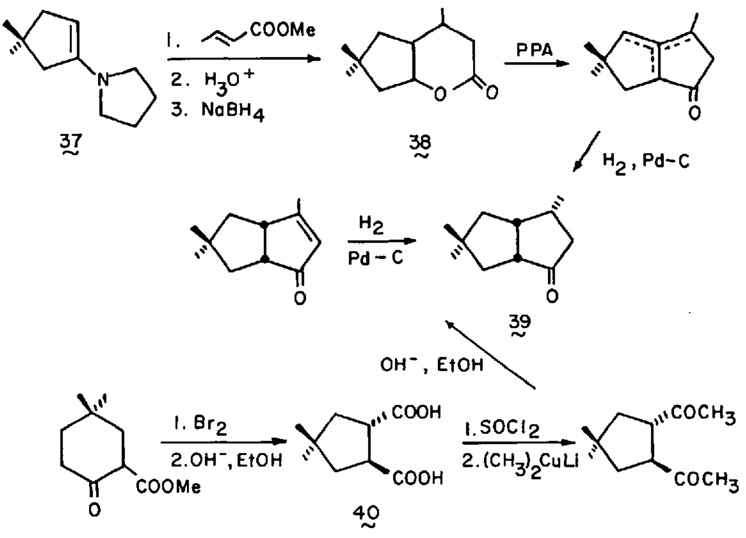
Condensation of 2-carbethoxycyclopentanone with tosylate *36* under basic conditions results in the introduction of a sidechain which can be hydrated and cyclized to give an acetylbicyclo[3.3.0]octene.[65] This procedure, although rather classical, is capable of generating a highly functionalized substrate (Scheme 13).

SCHEME 13



While the condensation of enamine *37* with methyl *trans*-2-butenoate, followed by acid hydrolysis and sodium borohydride reduction affords lactone *38* with reasonable efficiency, the cyclodehydrative ring contraction of this intermediate with PPA gives a mixture of bicyclo[3.3.0]octenones in abysmal ($< 5\ \%$) yield.[66] To circumvent this difficulty and enable the large scale production of *39*, 2-carbomethoxy-4,4-dimethylcyclohexanone was initially transformed to *trans* diacid *40* under Favorskii conditions (Scheme 14). Conversion to the diacid chloride and condensation with lithium dimethylcuprate resulted in formation of the diacetyl derivative. In basic solution, the latter is reported to experience epimerization and aldol cyclization with dehydration in 82 % yield. With hydrogen and palladium on charcoal, the essentially quantitative production of *39* was achieved.[66]

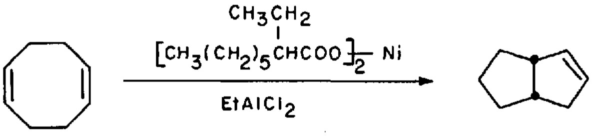
SCHEME 14



C. Transannular Medium-Ring Cyclizations

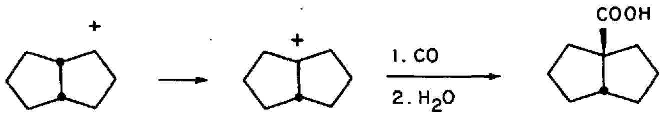
1. Polar and Free Radical Reactions Involving 1,5-Cyclooctadiene

1,5-Cyclooctadiene is a cyclic polyolefin particularly prone to transannular closure under a variety of conditions. With certain metal complexes such as that described below, isomerization to *cis*-bicyclo[3.3.0]oct-2-ene has been observed.[67] Phenyl-



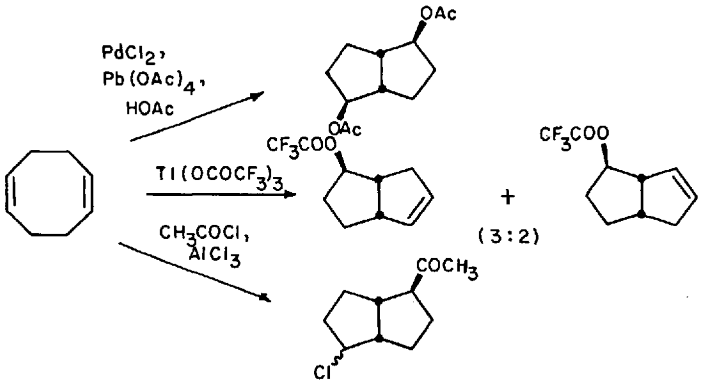
potassium in heptane at 175 °C (autoclave conditions) is known to produce the same chemical change.[68] 1,3- and 1,4-Cyclooctadiene behave comparably.[68, 69] The key intermediate here is the dianion *41* which has been shown to undergo disrotatory cyclization to *42* with a half-life of 80 minutes at 35 °. Thermodynamics clearly favor *42* to the extent of at least 1.5 kcal/mole.[69]

Under standard Koch-Haaf conditions, 1,5-cyclooctadiene is converted *via* cation *43* to the thermodynamically favored tertiary system *44* which is captured to deliver carboxylic acid *45*.[70, 71] When a hydrogen fluoride catalyst solvent system is utilized, however, the 2-carboxylic acid is formed instead.[72]



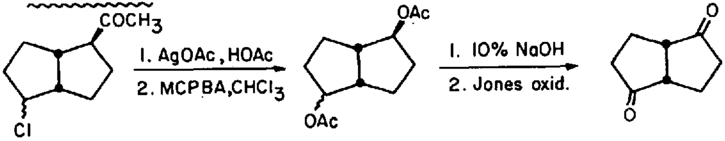
43 44 45

With other electrophilic reagents, transannular closures are inevitably encountered.[73–80] In some cases, complex mixtures result. Occasionally, these reactions afford a rather homogeneous product. Some examples follow.

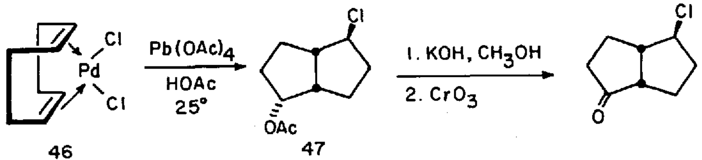


Further chemical transformations of these substances have been utilized on various occasions to gain entry to functionalized bicyclo[3.3.0]octanes (Scheme 15).

SCHEME 15

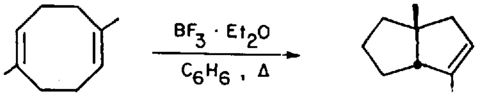


The palladium chloride complex of 1,5-cyclooctadiene is similarly prone to transannular bonding. A report by Chung and Scott described the smooth conversion of *46* to *47* at room temperature in the presence of lead tetraacetate.[81]



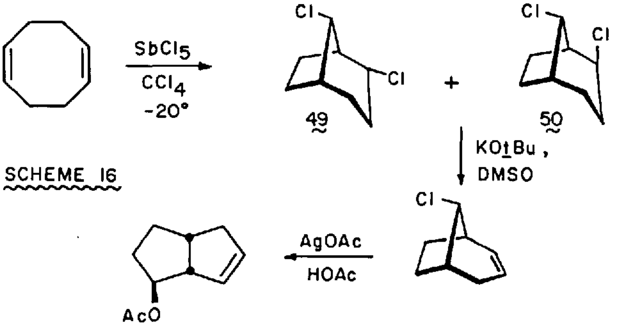
46 47

The regiospecific cyclization of the dimethyl derivative *48* in the presence of boron trifluoride etherate has been detailed.[82)]



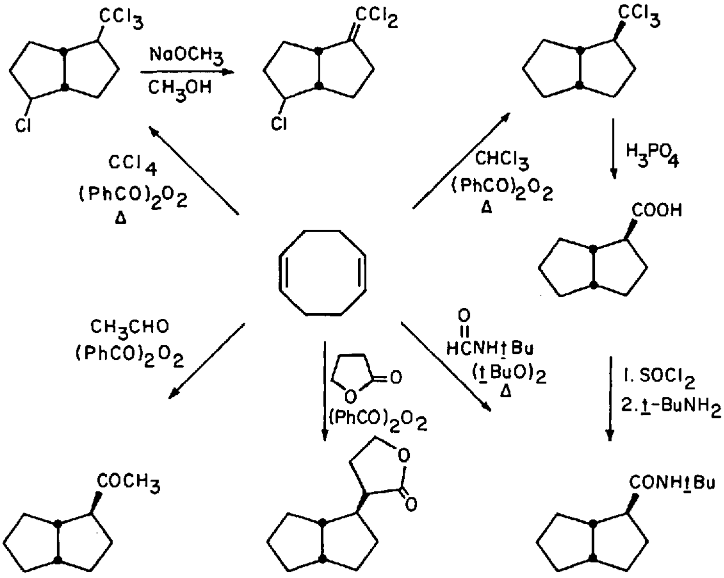
48

Uemura and co-workers have demonstrated that reaction of 1,5-cyclooctadiene with antimony pentachloride in carbon tetrachloride at –20 ° leads to a mixture of the epimeric dichloro bicyclo[3.2.1]octanes *49* and *50*.[83)] Through dehydrochlorination and Ag^+-promoted ionization, a bicyclo[3.3.0]octenyl acetate was produced (Scheme 16).



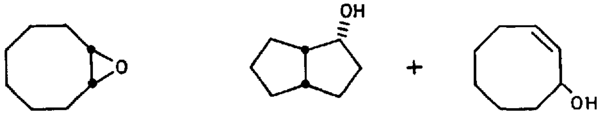
SCHEME 16

Transannular free radical 1,5-cycloadditions to 1,5-cyclooctadiene are equally prevalent, frequently cleaner, and capable of providing convenient access to bicyclo[3.3.0]octyl derivatives.[84–86)]



2. Base-Promoted Cyclizations of Cyclooctene Epoxides

The stereospecific conversion of *cis*-cyclooctene epoxide to alcohol *51*, first reported by Cope,[87] has been examined in greater detail recently.[88–90] Of importance is

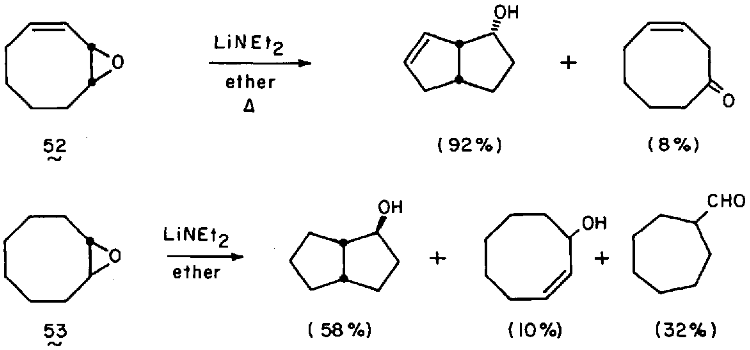


51

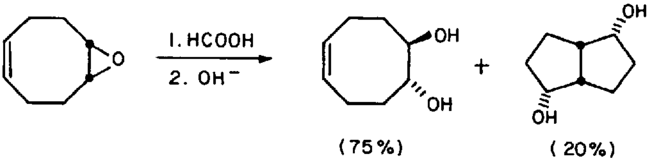
	51	
C_6H_5Li, benzene	50	27
$LiNEt_2$, ether	70	16
KO*t*Bu	100	–
Li_3PO_4	100	–
$LiN(C_3H_7\text{-}i)_2$, hexane	98	2
$LiNEt_2$, LiBr, hexane	80	20
$LiNEt_2$, hexane	20	80

recognition of the fact that the level of transannular cyclization is highly dependent upon both the nature of the base and the solvent. A base stronger than sodium ethoxide in ethanol is seemingly necessary.

In view of the analogous behavior of 1,3-cyclooctadiene monoepoxide (*52*), it appears that the double bond in this molecule has little effect on the course of the reaction.[88] When the *trans* epoxide *53* is involved, the hydroxyl group in the bicyclic alcohol is oriented *exo* and a reasonable amount of ring contracted aldehyde can be isolated.[87]



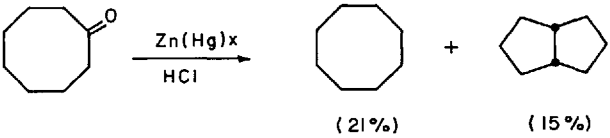
Attempts to induce transannular bonding in 1,5-cyclooctadiene monoepoxide have been moderately successful, but under acidic conditions only.[91, 92]



3. Other Transannular Rearrangements

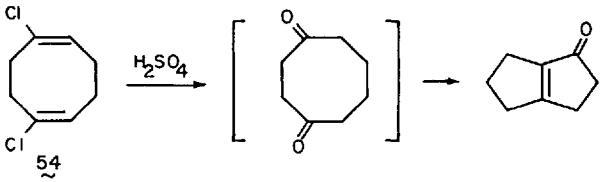
Russian workers have demonstrated that cyclooctane can be dehydrogenated to *cis*-bicyclo[3.3.0]octane when passed in the gas phase over a heated catalyst such as platinum on carbon, platinum and iron on carbon, or nickel on Kieselguhr.93–98) Unfortunately, the yields are highly variable (0.5–70 %) and details of these processes are scanty. Perhaps more promising is their discovery that *n*-octane and its cyclodehydrogenation product *n*-propylcyclopentane can be converted to the bicyclic hydrocarbon under comparable conditions.

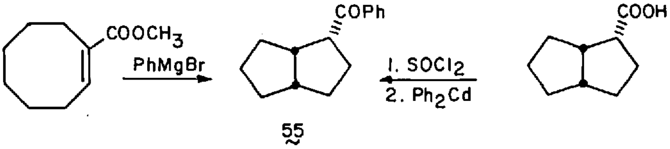
Whereas cyclooctanone undergoes Wolff-Kishner reduction to give exclusively cyclooctane, reduction under Clemmensen conditions affords bicyclo[3.3.0]octane as well.99) This finding again points up the risks which one takes in maintaining structural integrity when recourse is made to amalgamated zinc in strongly acidic solution as a reducing agent.



Chloroprene is dimerized to *54* when heated. When the dimer is treated with sulfuric acid, hydrolysis to 1,4-cyclooctanedione occurs and this diketone experiences transannular closure under the reaction conditions.100)

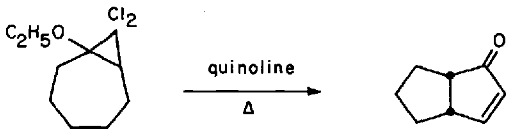
Cope and Brown have reported that treatment of 1-carbomethoxycyclooctene with phenylmagnesium bromide gives ketone *55* among other products.101) The



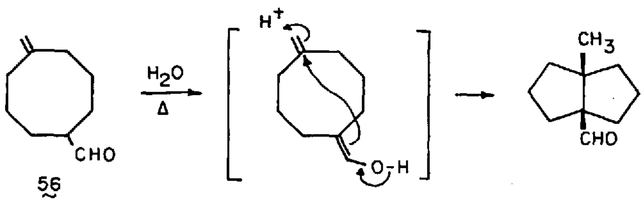


endo stereochemistry of the benzoyl group was established by chemical interconversion.

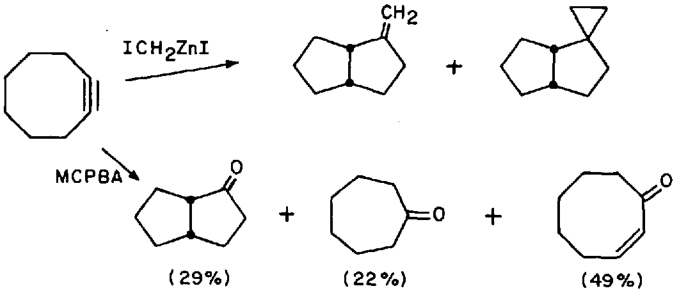
Unlike its lower homolog, the dichlorocarbene adduct of 1-ethoxycycloheptene is converted in hot quinoline not to ring expanded 1-ethoxy-1,3,5-cyclooctatriene but instead to *cis*-bicyclo[3.3.0]oct-3-en-2-one in low yield.[102)]



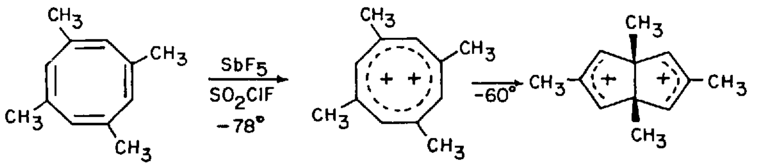
When simply heated in water, the aldehyde *56* undergoes a novel transannular reaction which presumably proceeds *via* the enol form as illustrated.[103)]



Upon reaction with the Simmons-Smith reagent[104)] or *m*-chloroperbenzoic acid,[105)] cyclooctyne is transformed at least in part to products of the bicyclo[3.3.0]octane type.



Electrolytic reduction of 4-cyclooctenone leads smoothly in 64 % yield to *cis*-bicyclo[3.3.0]octan-1-ol.[106)] The thermolysis of octachlorocyclooctatetraene produces perchlorinated bicyclo[3.3.0]octatrienes,[107, 108)] several of which have been examined in detail by X-ray structural methods.[109)] The 1,3,5,7-tetramethylcyclooctatetraene dication (*57*), generated by oxidation of the neutral hydrocarbon with antimony pentafluoride in SO_2ClF at −78 °C and below, is subject to disrotatory cyclization above −60°.[110)] The latter step does not follow orbital sym-



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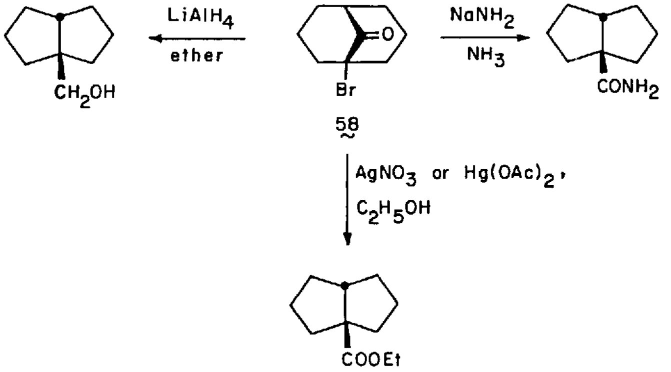
metry guidelines, but probably reflects instead the greater thermodynamic stability of *cis*-3a,6a-dihydropentalene derivatives (some charge separation develops) and the greater π-π overlap in the allylic segments of the bicyclic dication.



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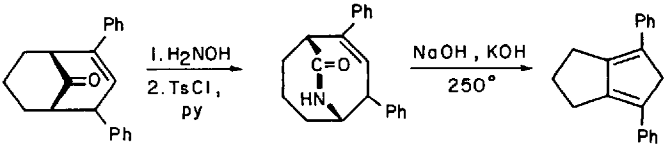
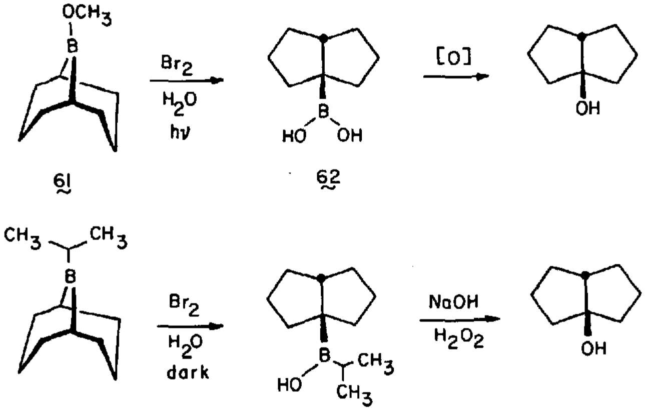


59 60

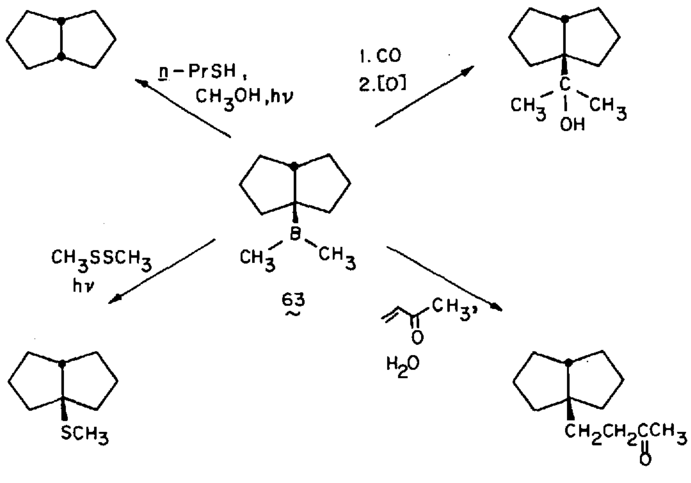
The ring contraction of bridged α-bromo ketone *58*[111] has been the subject of considerable synthetic application.[112] The somewhat related behavior of lactam *59*[113] under conditions of alkaline fusion is also interesting.[114] Diene *60* forms a crystalline maleic anhydride adduct, a dark purple picrate, and a brick red adduct with 1,3,5-trinitrobenzene.

More recently, Brown and co-workers have demonstrated that six-membered boracyclanes are likewise capable of ring contraction. As an example, the light-induced reaction of bromine with 9-methoxy-9-borabicyclo[3.3.1]nonane (*61*) in the presence of water affords the boronic acid *62* which is in turn readily oxidized to the alcohol in 65 % overall yield.[115] The structurally related B-alkyl-9-BBN derivatives react under comparable conditions but in the dark to deliver analogous products.[116]



Lithium dialkyl-9-borabicyclo[3.3.1]nonane “ate“ complexes react with acetyl chloride *via* hydride transfer to form *cis*-bicyclo[3.3.0]oct-1-yldialkylboranes.[117] The conversion of B-methyl-9-BBN to *63* upon sequential treatment with methyllithium and acetyl chloride (93 % yield) illustrates the procedure. As shown in Scheme 17, these organoboranes can serve as valuable intermediates for the preparation of a variety of 1-substituted *cis*-bicyclo[3.3.0]octanes in high yield.

SCHEME 17

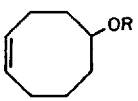


Finally, the Ag$^+$ induced intramolecular alkyl coupling reaction of 9-BBN with alkaline silver nitrate in aqueous methanol as a route to *cis*-bicyclo[3.3.0]octane is to be noted.[118]

D. Carbonium Ion Chemistry

1. Solvolytic Processes

The acetolysis and trifluoroacetolysis of sulfonate esters corresponding to *64–69* have been examined in various laboratories and shown to produce several bicyclo-



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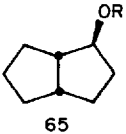

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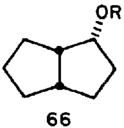

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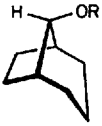

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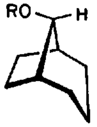

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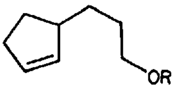
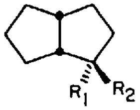


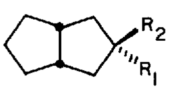
69

[3.3.0]octane derivatives as products.[119–123] Given the *exo/endo* rate ratio of *65*-Ts and *66*-Ts in acetic acid (1.3) and ethanol (0.8), little or no anchimeric assistance is apparent. While *66*-Ts solvolyzes with good first-order kinetics, the acetolysis of *65*-Ts is accompanied by internal return to *68*-Ts, a phenomenon which is similarly encountered with *64*-Ts which gives *65*-Ts.[123] In each case, the proportions of products differ and it therefore seems likely that product formation is controlled to some degree by the stereochemistry of the ion-pair intermediates.

The U-shape of the bicyclo[3.3.0]octane frame prompted Brown and his coworkers to examine the solvolytic behavior of the tertiary *exo/endo* pairs *70* and *71*



70 a, $R_1 = CH_3$, $R_2 = OPNB$
b, $R_1 = OPNB$, $R_2 = CH_3$

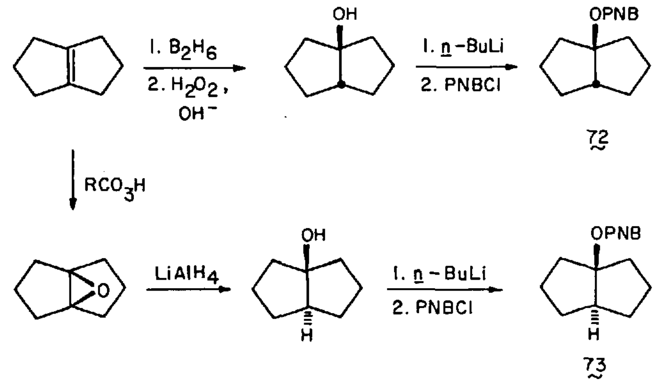


71 a, $R_1 = CH_3$, $R_2 = OPNB$
b, $R_1 = OPNB$, $R_2 = CH_3$

for evidence of steric hindrance to ionization.[124] At the 2 position (*70*), the *exo/endo* rate ratio is 17 and this value decreases to 1.7 in the 3-substituted derivatives (*71*). The conclusion arrived at is that the rates of ionization of the *endo* isomers are not facilitated by relief of steric strain in these molecules.

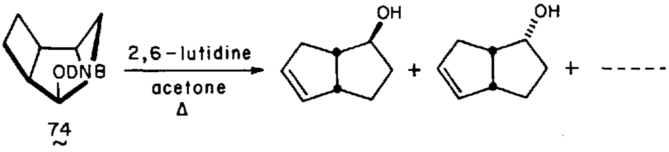
The *cis* and *trans* bridgehead *p*-nitrobenzoates *72* and *73* have also been synthesized stereospecifically (Scheme 18) and solvolyzed in 60 % acetone.[125] The rates

SCHEME 18

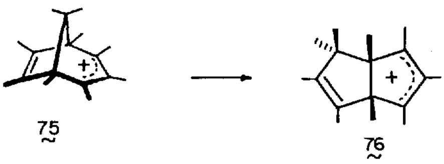


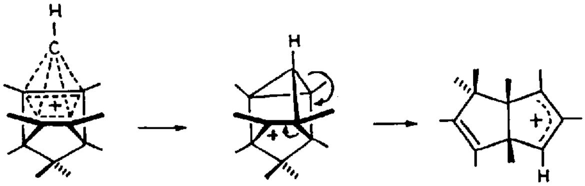
which were observed did not correspond to those anticipated for conversion of both stereoisomers to the same cation intermediate. Rather, the product composition proved to be a function of the stereochemistry of the starting material.

The ionization of *74* in acetone buffered with 2,6-lutidine has been shown to proceed with rupture of both of its micro rings to give chiefly the *exo*- (23 %) and *endo-cis*-bicyclo[3.3.0]oct-2-en-6-ols (29 %), in addition to other products.[126)]



Hart and Kusuya have documented the remarkable properties of the nonamethylbicyclo[3.2.1]octa-3,6-dien-2-yl cation (*75*) as generated by ionization of the alcohol in magic acid.[127)] Below −60 °C in this solvent system, *75* undergoes both a rapid circumambulatory process (NMR observable) and a slower bridge shift (deuterium labelling necessary for observation). At or above −60 °C, *75* rearranges irreversibly to the [3.3.0] ion *76*, the preferred pathway involving cyclopropylcarbinyl-cyclopropylcarbinyl rearrangement. This mechanism differs from that followed by cation *77* which has been shown to give *78* by collapse of the classical species readily





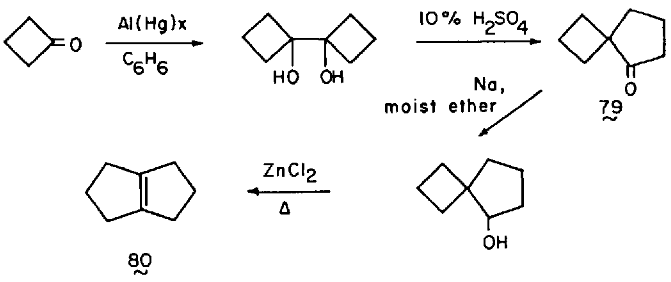
77 78

derived from *77*.[128] Interestingly, on standing in CF_3COOD all nine methyl groups of cation *76* become labeled, but at different rates.

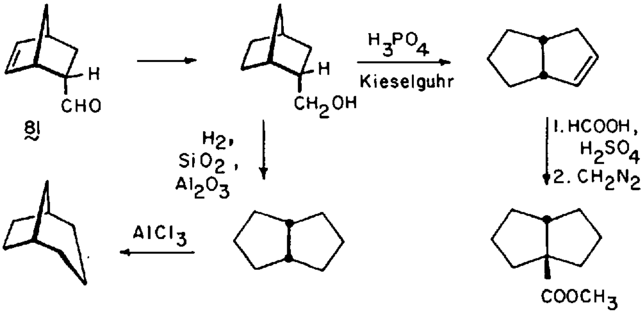
2. Acid-Catalyzed Transformations

An interesting double ring expansion sequence developed by Vogel involves the initial pinacol coupling of cyclobutanone, isomerization to ketone *79* in acid, followed by reduction and Lewis acid-promoted Wagner-Meerwein rearrangement with dehydration (Scheme 19).[129] For preparative purposes, *80* can be more readily prepared by Ramberg-Bäcklund rearrangement[130] of 1-bromo- or 1-chloro-9-thiabicyclo[3.3.1]nonane 9,9-dioxide.[131, 132]

SCHEME 19

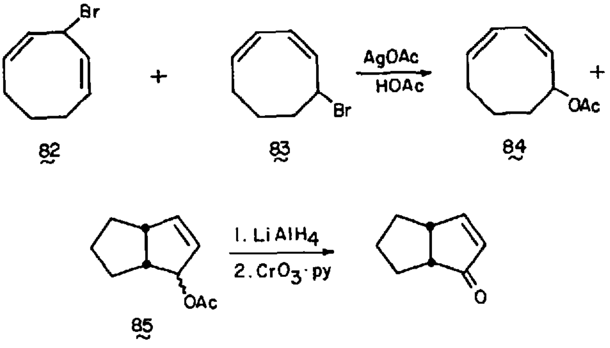


Work has been reported on the conversion of aldehyde *81*, the Diels-Alder cycloadduct of acrolein and cyclopentadiene, to its fully saturated primary alcohol and thereafter to bicyclo[3.3.0]octyl hydrocarbons.[133] A silica/alumina catalyst system provides *cis*-bicyclo[3.3.0]octane, while phosphoric acid and Kieselguhr gives the Δ^2-olefin. Since this cyclic alkene reacts under Koch-Haaf conditions to produce the

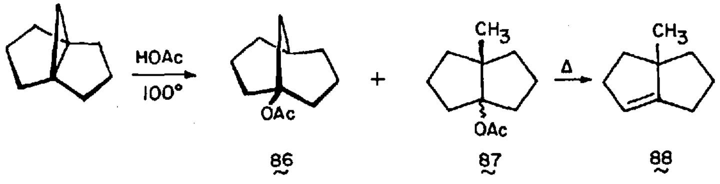


1-carboxylic acid,[134] this pathway represents a potentially useful route to 1-substituted derivatives. Since bicyclo[3.2.1]octane is more stable than its [3.3.0] counterpart,[20] and can be obtained upon exposure of the latter to aluminum chloride,[18] some precautions must be taken during isomerizations of this type not to attain conditions which are too forcing.

Reaction of 1,3-cyclooctadiene with N-bromosuccinimide results in the formation of dibromides *82* and *83*, treatment of which with silver acetate in acetic acid provides the acetates *84* (80 %) and *85* (20 %).[135] The bicyclic acetate can readily be separated and transformed to the corresponding enone.



The addition of acetic acid to [3.3.1]propellane at somewhat elevated temperatures results in approximately equal levels of central and edge bond cleavage to give

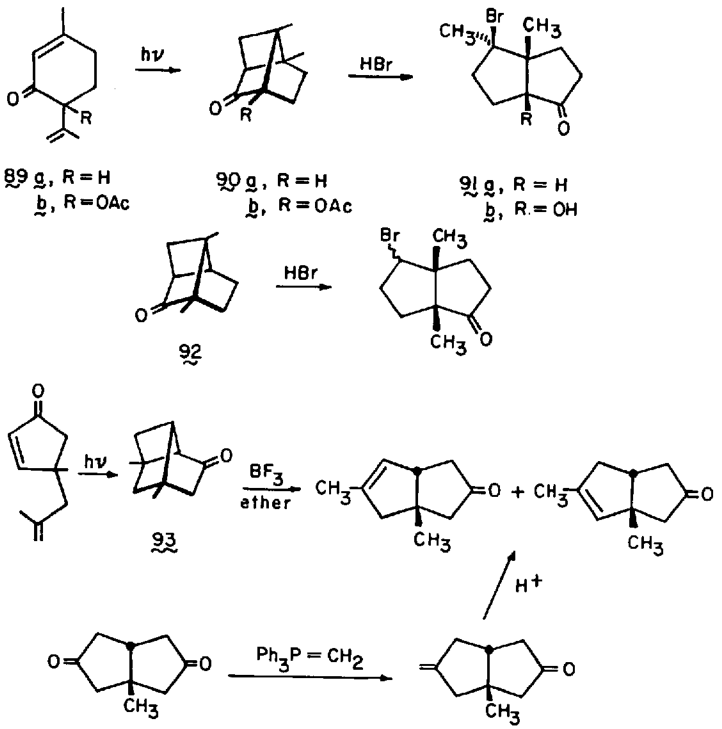


86 and *87*.[136] Through pyrolysis, *87* may be transformed to the trisubstituted olefin *88*.

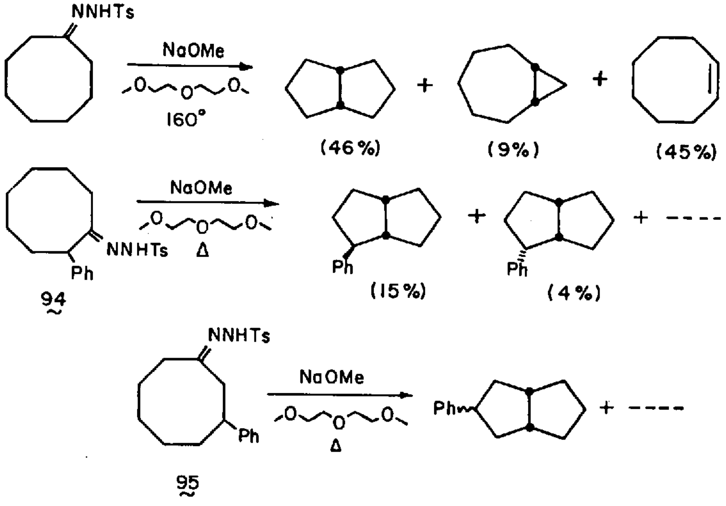
A group of interesting cyclobutane cleavage reactions have been described which provide an attraction pathway to substituted bicyclo[3.3.0]octanones.[137, 138] For example, photocyclization of (+)-isopiperitone (*89a*) leads to *90a* which gives *91a* in the presence of hydrogen bromide. 3,8-Cyclocamphor (*92*) behaves analogously. When boron trifluoride is employed, a double bond results in the ring opened products.

E. Carbenic Rearrangements

In pioneering work, Friedman and Shechter demonstrated that the thermolysis of diazocyclooctane affords *cis*-bicyclo[3.3.0]octane as the major product.[139] The

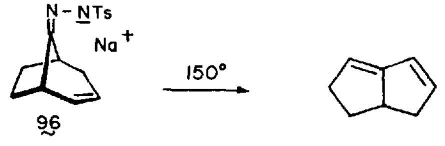


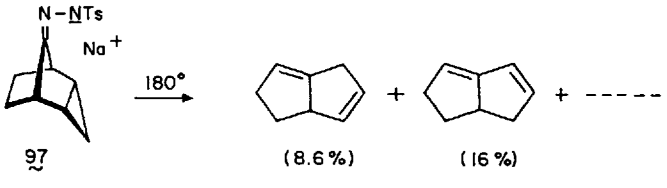
high level of transannular carbenic insertion and the stereoselectivity of this process is believed to be due to proximity factors, axial hydrogen transfer, and retention of configuration which operates during carbene attack. Through examination of the aprotic decompositions of tosylhydrazones *94* and *95*, Cope and Hecht showed that the presence of a phenyl group did not appear to increase the lability of benzylic



hydrogen toward the insertion reaction.[140)] In this sense, therefore, the intermediate carbenes lack selectivity.

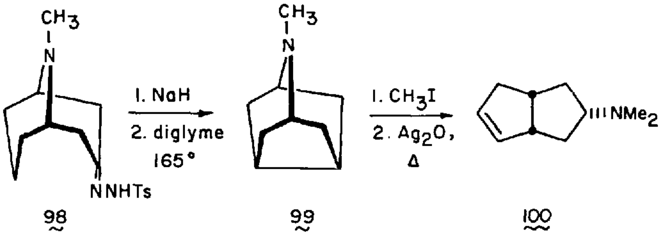
Suitably constructed bridged carbenes exhibit a tendency for structural rearrangement and undergo the so-called "foiled methylene reaction"[141, 142)] with formation of bicyclo[3.3.0]octane derivatives. The behavior of *96*[143)] and *97*[144)] exemplifies such conversions. Carbonium ion analogies to such reactions are known.[145)]





In contrast, carbenes in the bicyclo[3.3.0]octane series appear to be normal in their reactivity.[146)]

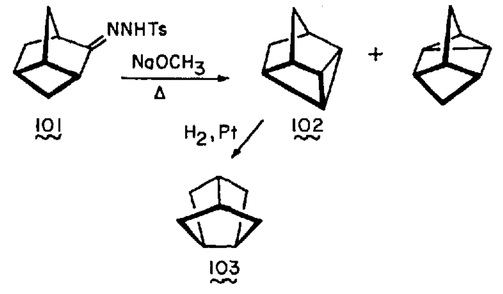
Two interesting synthetic applications of carbene chemistry should be cited here. The first, due to Sasaki and his co-workers, takes advantage of the steric situation present in pseudopelletierine tosylhydrazone (*98*).[147)] Pyrolytic decomposition of the sodium salt of *98* in diglyme gave *99* in 80 % yield.



The Hofmann degradation of the methiodide of this amine afforded stereochemically homogeneous *100*.

In the second, aprotic decomposition of tosylhydrazone *101* was shown to proceed with conventional cyclopropane ring formation.[148)] On catalytic hydrogenation, one of the two products (*102*) was converted to tricyclo[$3.3.0.0^{3,7}$]-octane (*103*) (Scheme 20). This hydrocarbon is not only a dehydrobicyclo[3.3.0]-octane but is also of interest because of its bisnor relationship to adamantane.

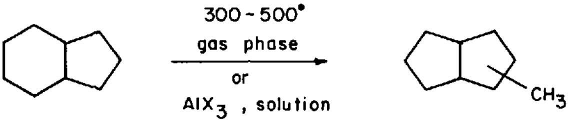
SCHEME 20



Furthermore, the structure has D_{2d} symmetry and contains the most twisted norbornane skeleton on record. The solvolytic behavior of certain of its derivatives has been studied.[148]

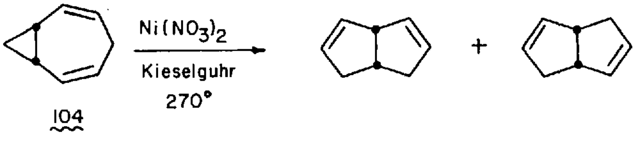
F. Thermally Induced Isomerizations

A number of papers have been published describing the thermal isomerization reactions of bicyclo[2.2.2]oct-2-ene, bicyclo[3.2.1]oct-2-ene, and norcamphene to bicyclo[3.3.0]octenes.[149–152] The gas phase and solution phase isomerization of perhydroindane to a mixture of methyl substituted bicyclo[3.3.0]octanes has also



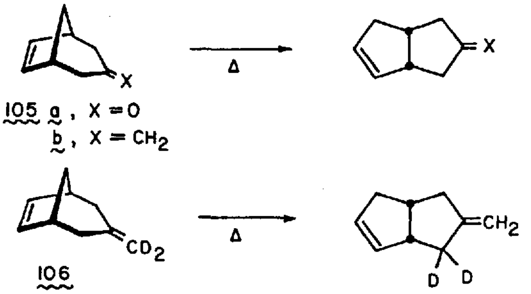
been observed.[153] When heated to 320 ° in the presence of cobaltic fluoride, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, and bicyclo[3.3.0]octane are converted to perfluorobicyclo[3.3.0]octane.[154] These results have been rationalized in terms of cobaltic fluoride acting either as a strong Lewis acid or as an oxidizing species.

When 3,4-homotropilidene (*104*) is heated to approximately 300 °C, isomerization to *cis*-bicyclo[3.3.0]octa-2,6-diene is encountered.[155] A diradical intermediate is presumably involved. Passage of *104* over a supported nickel catalyst at 270 °C diverts the rearrangement chiefly to the 2,7-diene.



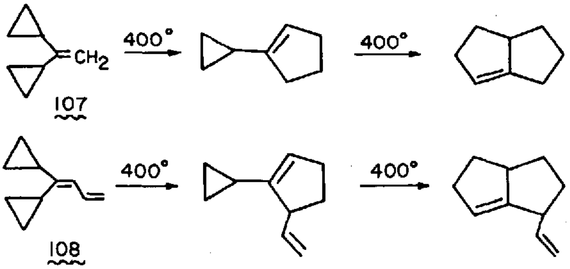
Grimme has reported the smooth conversion of 1,4-cyclooctadiene to *cis*-bicyclo[3.3.0]oct-2-ene in the gas phase at 325 °C.[156] Thermolysis of bicyclo[3.2.1]octa-

2,6-diene in a flow system at 550–600 ° and 2 torr (contact time *ca* 1 sec) yields *cis*-bicyclo[3.3.0]octa-2,6-diene in 45 % yield together with 1-vinyl-1,3-cyclohexadiene and several minor products.[157)] The ketone *105a* and diene *105b* undergo similar reactions.[158)] On the basis of the result obtained with the deuterium labeled substrate *106*, a Cope rearrangement, 1,3-sigmatropic shift of C_2, formation and reclosure of a bisallylic diradical, or a mixture of these mechanism is at work.



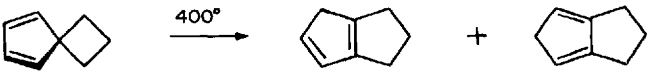
105 a, X = O
b, X = CH2
106

The dicyclopropyl systems *107* and *108* undergo sequential vinylcyclopropane to cyclopentene rearrangements at 400 °C.[159, 160)]



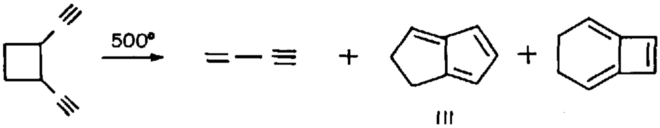
107
108

A convenient route to the tetrahydropentalenes *109* and *110* has been discovered through pyrolysis of spiro [3.4]octa-5,7-diene.[161)]



109 110

In their study of the thermolysis of *cis*- and *trans*-1,2-diethynylcyclobutane, Eisenhuth and Hopf have observed that substantial levels of dihydropentalene *111*

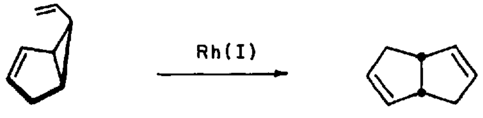


111

		111	
trans	52 %	43 %	4.5 %
cis	---	95 %	2.5 %

are produced.[162)] The response of *trans*-1-ethynyl-2-vinylcyclobutane to thermal activation has also been examined.[163)]

A search for possible degenerate behavior in bicyclo[3.3.0]octa-2,6-dienes[164)] has not produced clear results due to structural misassignments.[126)] The normal Cope rearrangement of *112* can be redirected through coordination to rhodium (I) to

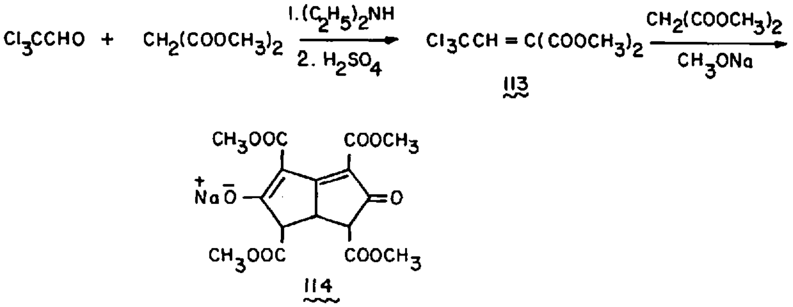


112

give *cis*-bicyclo[3.3.0]octa-2,6-diene.[165)] The *trans* isomer of *112* shows similar reactivity differences.[166)]

G. Polycondensation Reactions

The earliest description of a bicyclo[3.3.0]octane synthesis is due to Vossen[167)] who, while working in Schroeter's laboratory,[168)] discovered that *113* condenses with dimethyl malonate in the presence of sodium methoxide to give a red crystalline salt assigned structure *114*. Unequivocal confirmation of this structural assignment was obtained several decades later,[169–171)] particularly at the hands of



$$Cl_3CCHO + CH_2(COOCH_3)_2 \xrightarrow[2.\ H_2SO_4]{1.\ (C_2H_5)_2NH} Cl_3CCH=C(COOCH_3)_2 \xrightarrow[CH_3ONa]{CH_2(COOCH_3)_2}$$

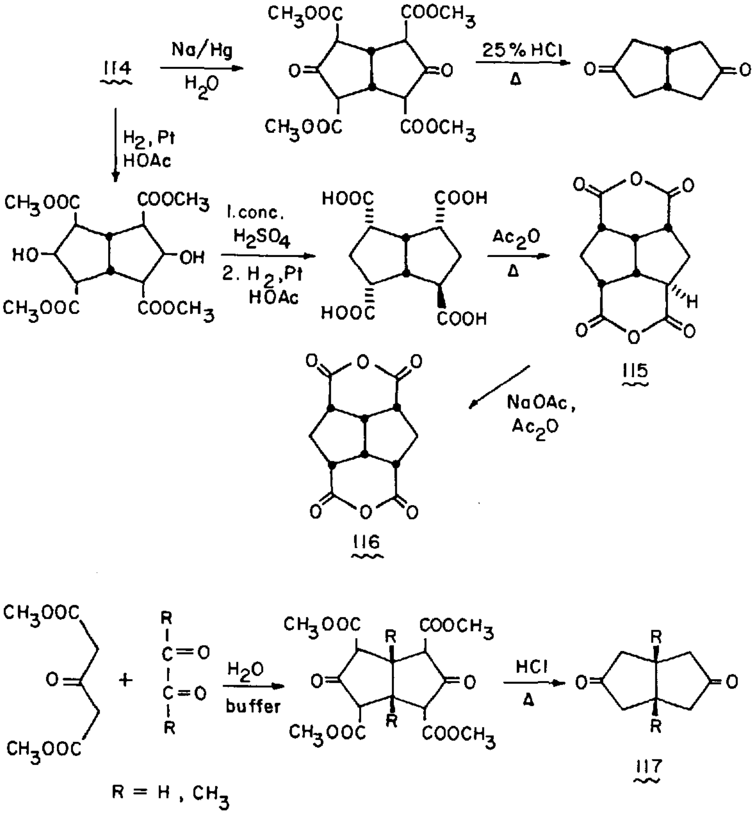
113

114

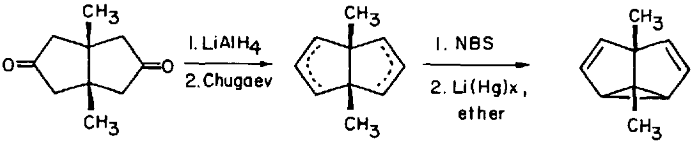
Yates[172)] and Boekelheide.[173)] As outlined in Scheme 21, Schroeter and Vossen's red salt is a particularly attractive precursor to the 3,7-dione[164, 172)] and the epimeric dianhydrides *115* and *116*.[172)]

A simpler and more versatile route to comparably functionalized bicyclooctanes has been developed more recently by Weiss and his co-workers.[174–176)] Specifically, the reaction of 1,2-dicarbonyl compounds with dimethyl 3-ketoglutarate (dimethyl acetonedicarboxylate) in aqueous solution at pH 5, or preferably in a citrate-phosphate buffer, followed by hydrolytic decarboxylation, affords *117* in good

SCHEME 21



yield. The utilization of such diketones for the synthesis of methyl substituted semibullvalenes, e. g., *118*, is particularly noteworthy.[177, 178]

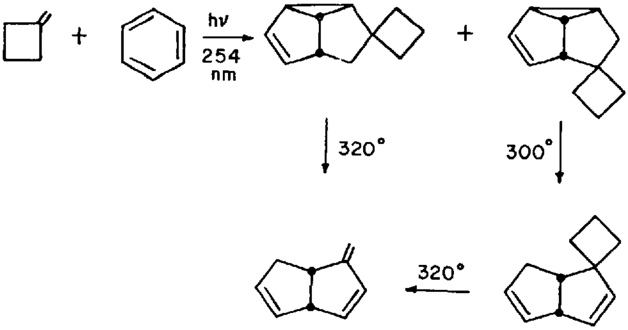


118

Polycondensation reactions of the type described in this section are well suited to the preparation of higher quinane systems. Such processes will be exemplified at appropriate locations later in this review.

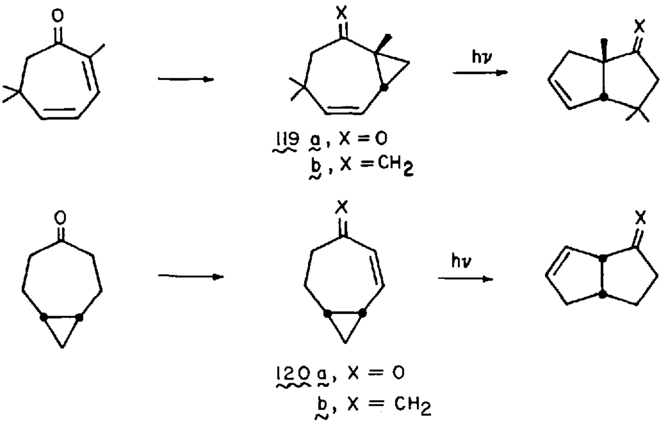
H. Photochemical Syntheses

Under suitable photochemical conditions, benzene will undergo 1,3-cycloaddition to select olefins with formation of adducts containing the semibullvalene nucleus. 1,2-Dichloroethylene,[179] methylenecyclobutane,[180] and vinylene carbonate[181] are



exemplary.[182, 183] In certain cases, thermolysis of the adducts results in operation of a homo[1,5]sigmatropic shift and delivery of unsaturated bicyclo[3.3.0]octanes.

The ability of conjugated *cis*-bicyclo[5.1.0]octenones and their methylene analogs, e. g., *119* and *120*, to undergo bond switching reactions from their excited states has been examined by Paquette.[184] The photoisomerizations of both *119a* and *119b* proceed efficiently from their singlet states. Enone *120a* behaves com-

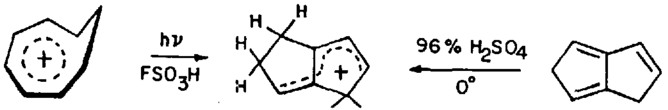


119 a, X = O
b, X = CH_2

120 a, X = O
b, X = CH_2

parably, but diene *120b* undergoes photoinduced vinylcyclopropane-cyclopentene rearrangement exclusively from its triplet state. These differences have been rationalized in terms of conformational factors, particularly as they relate to bond overlap in the S_1 and transoid T_1 states.

The feasibility of light-promoted valence isomerization as a route to bicyclooctanes has been demonstrated as illustrated for *121*[185] and *122*,[186] but the possible synthetic utility of such chemical changes have not been exploited. Photoisomerization studies of the four geometrical isomers of 1,5,9-cyclononatriene have been reported.[187] The predominant process is *cis-trans* isomerization of the olefinic bonds which transforms each of the isomers into the same photostationary mixture of all four trienes. In addition, however, there occurs an irreversible isomerization to *123*.



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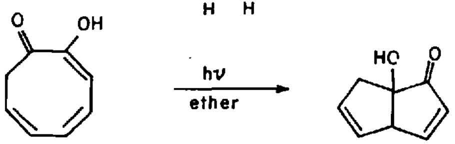

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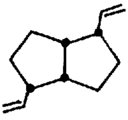

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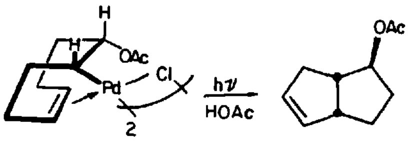
The irradiation of palladium complex *124* in acetic acid has been found to promote depalladation and transannular carbon-carbon bond formation.[188)]



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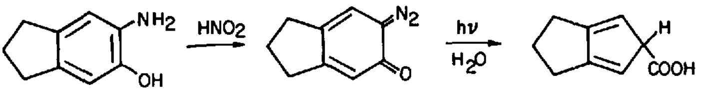
Examples are known of photoextrusion reactions which occur with ring contraction and provide bicyclo[3.3.0]octane derivatives. 1,2-Quinone diazides (e. g., *125*)[189, 190)] and bicyclo[3.3.1]nonan-9-ones (e. g., *126*)[191, 192)] are particularly



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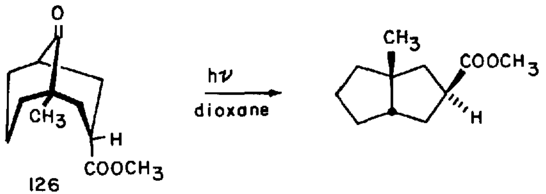
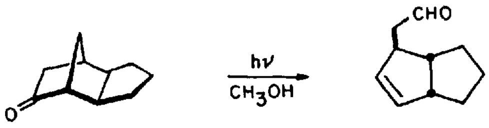
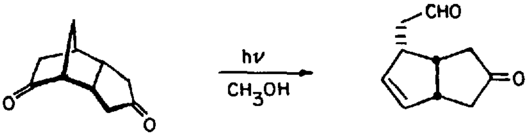


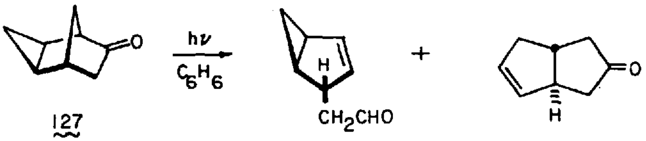
126

responsive to treatment with light. The photodecarbonylations experienced by *126* and its C_3 epimer are completely stereospecific (inversion of configuration). Although this phenomenon has been explained in terms of alkyl radical assisted loss of carbon monoxide, a simpler mechanism involving closure of carbenacyclooctanes cannot be ruled out.

2-Norbornanones experience α-cleavage on the side of the more highly substituted carbon when irradiated, the intermediate acyl radicals ultimately undergoing intramolecular C-H abstraction to generate unsaturated aldehydes.[193, 194] The behavior of the two rigid β,γ-cyclopropyl ketones *127* and *128* is interesting in view of the fact that the stereochemistry of the starting materials carries over into the bicyclooctenone product.[195]







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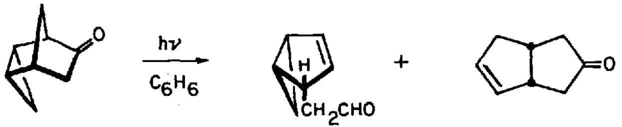


128

Bicyclo[3.3.0]octanones are photolabile in their own right and experience ring opening when irradiated. Coyle has demonstrated that the overriding factor in product formation from the diradical intermediates is the distance between the hydrogen atom which is transferred and the radical center to which it migrates.[196]

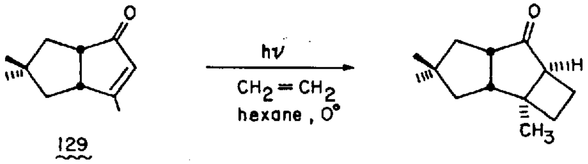
The intramolecular photochemical [2+2] cycloaddition of bicyclo[3.3.0]octadienes has been examined by several groups.[128, 197–199] A striking example of a synthetic application of this chemistry is given in Scheme 22.

SCHEME 22

102

103

Finally, bicyclo[3.3.0]octenones such as *129* have been found capable of [2+2] photocycloaddition to simple alkenes, the ring forming process occurring with high stereoselectivity from the less hindered surface.[200)]



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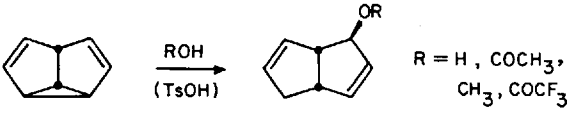
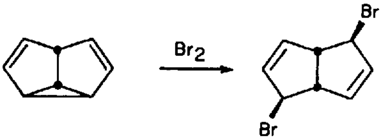
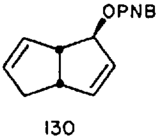
I. Ring Opening Reactions of Semibullvalenes

The highly reactive semibullvalene structure undergoes facile acid-catalyzed 1,4-addition of protic solvents to one of the vinylcyclopropane units.[201)] The reaction





places the -OR group *exo* on the bicyclo[3.3.0]octyl frame and leads only to 3,7-diene derivatives. Through a study of bromine addition to the fluxional hydrocarbon, it was possible to determine with the aid of X-ray analysis that such biparticulate electrophilic additions occur stereospecifically *exo, exo*.[202)] To gain added information on the product-forming cation, Moriarty and Yeh studied the acetolysis of *130* and *131*. The relative reactivity order was shown to be 1 : 10.[201)] Consequently, the homoallylic double bond in *130* is rate retarding by a factor of about ten. This corresponds to a negative inductive effect with no compensatory delocalization. This is as expected since *132* would be antiaromatic or antibicycloaromatic.



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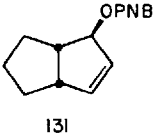

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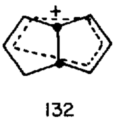

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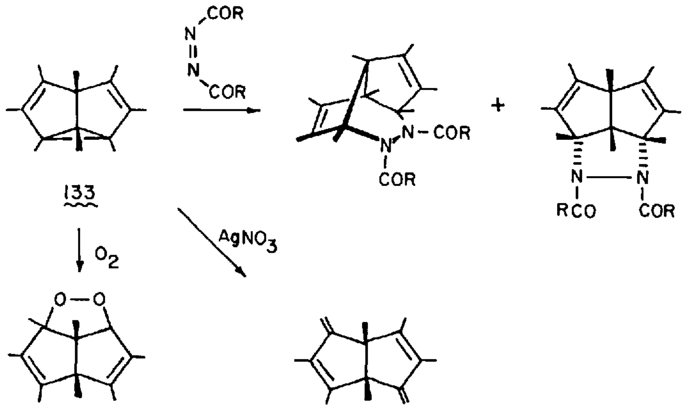
With octamethylsemibullvalene (*133*), 1,6-addition can compete with the 1,4 process under certain circumstances.[203–205)] The response of *133* to the action of silver nitrate is also notable.[203)]



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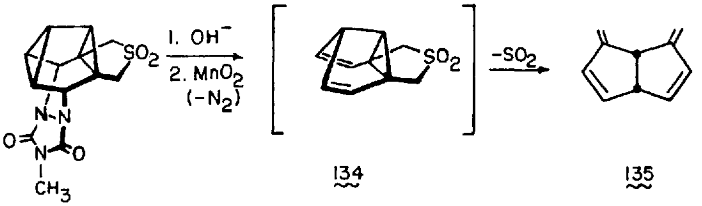
Paquette and co-workers have reported on the facile cheletropic extrusion of sulfur dioxide from the heterocyclic annulated semibullvalene *134* which furnishes *135*.[206] This tetraene is seen to be a double-bond isomer of 1,6-dimethylpentalene.



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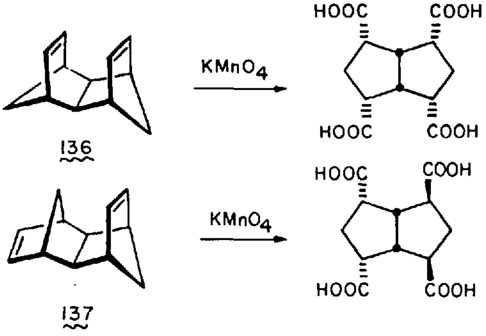
J. Oxidative Ring Cleavages

Oxidative fission of carbon-carbon bonds has played a pivotal role in the preparation of functionalized bicyclo[3.3.0]octane derivatives. More specifically, aqueous permanganate has been used extensively to prepare both di-[207–209] and tetracarboxylic acids.[173, 210] As shown in the case of *136* and *137*, the advantage of the method resides in the ability to build stereochemistry into the precursor molecule.



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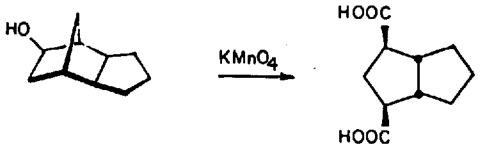
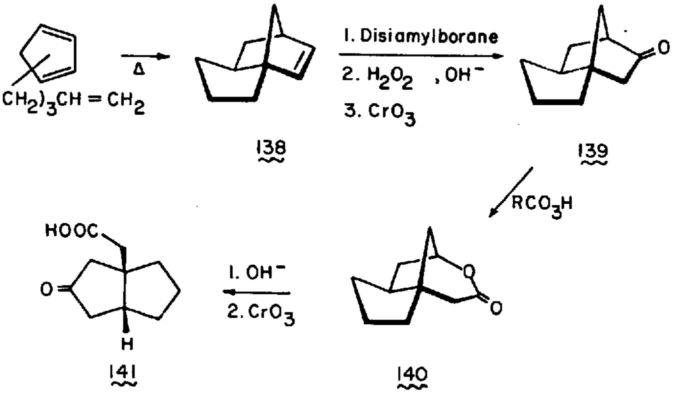
The permanganate or nitric acid oxidation of alcohols and ketones has proved to be equally popular.211–215)



Somewhat less direct procedures have also been recognized. In 1967, Corey and Glass described the preparation of hydrocarbon *138* and its conversion through hydroboration and oxidation to ketone *139* (Scheme 23).216) Subsequent Baeyer-Villiger oxidation proceeded with migration of the more highly substituted bridgehead carbon atom to give *140* whose saponification and oxidation led to the angularly substituted bicyclooctanone *141*.

SCHEME 23



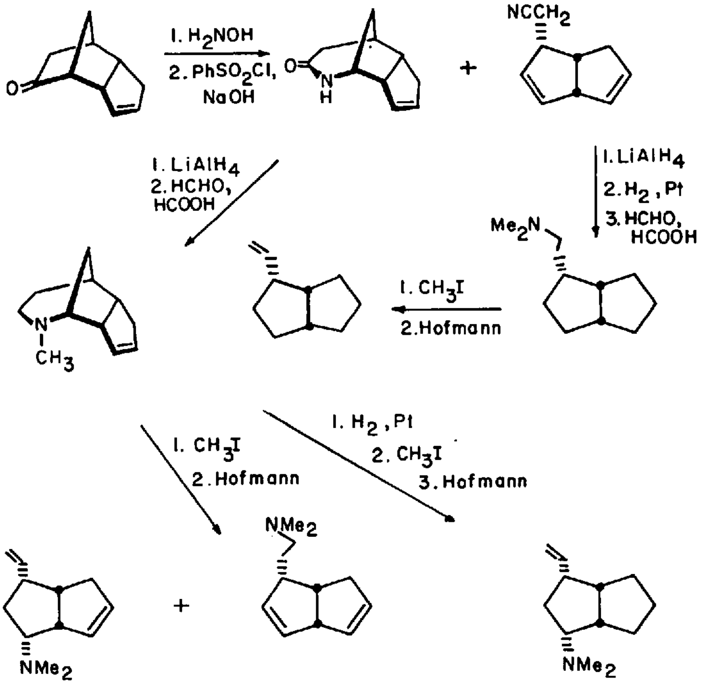
Gates and Malchick utilized the Beckmann rearrangement for their purposes (Scheme 24).217) When the Hofmann degradation of *142* and *143*, followed by catalytic dehydrogenation over 5 % palladium on asbestos at 300–310 °C, afforded not 1-vinylpentalene but azulene, the workers concluded that the former was thermodynamically unstable relative to the latter.

K. Cycloaddition Chemistry

The elaboration of ketone *144* by cycloaddition of ketene to cyclopentadiene has been known for some time.218) The Tiffeneau-Demjanov ring expansion of *144* was first described by Roberts and Gorham in 1952219) and the use of diazomethane to achieve the same objective clarified by Paquette in 1974.126) Under both sets of conditions the 1-keto derivative predominates, the more so in the first instance.

1-Morpholinocyclopentene has been used to elaborate bicyclo[3.3.0]octane derivatives through cycloaddition to cyanoallene220) and the reagent produced from 2,4-dibromo-3-pentanone and diiron ennacarbonyl.221)

SCHEME 24



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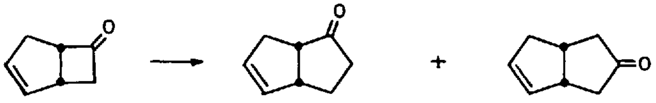
143



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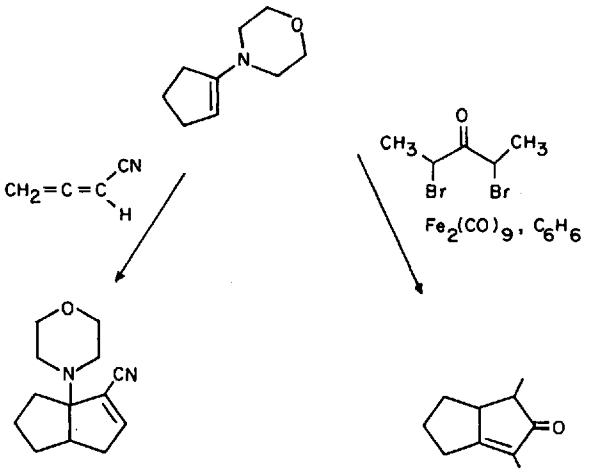
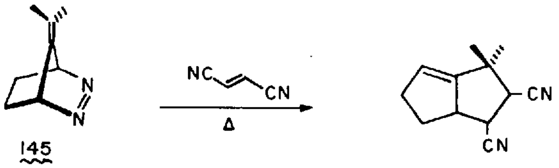
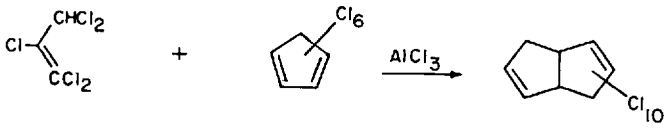


2-Isopropylidenecyclopentane-1,3-diyl, as generated by the thermolysis of azo compound *145* can be trapped efficiently with such acceptors as fumaronitrile, *cis*- and *trans*-1,2-dichloroethylene, dimethyl maleate, and dimethyl fumarate.[222]



West and co-workers have demonstrated the feasibility of promoting cycloaddition between hexachlorocyclopentadiene and 1,1,2,3,3-pentachloropropene in the presence of anhydrous aluminum chloride.[223]



III. Pentalene Chemistry

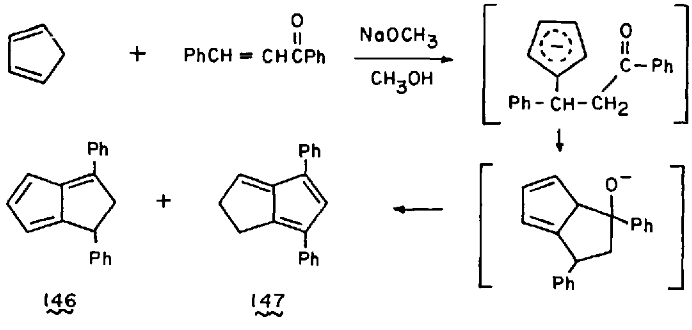
The peculiarity of the pentalene molecule resides in its central bond which connects nonalternant atoms (a perturbed [8]annulene), its completely conjugated and alternating π bond periphery, and its apparent antiaromatic nature. The transannular bond conveys planarity to the structure without contributing to its stabilization. Consequently, pentalene is expected to be highly reactive since, in a sense, it has ground state properties customarily found in excited states. The many early attempts to synthesize pentalene have been reviewed[224–226] and will not be considered *per se* here. Suffice it to say that the lability of minimally substituted pentalenes ultimately required the implementation of rather specific reaction conditions for their successful synthesis (*vide infra*).

A. Preparation of Dihydropentalenes

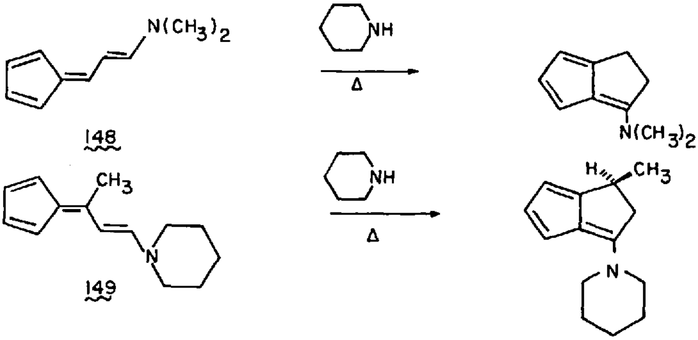
With sodium methoxide as base, cyclopentadiene reacts with benzalacetophenone to give a mixture of the diphenyl dihydropentalenes *146* and *147* (Scheme 25).[227] Once Michael addition occurs, a second deprotonation generates a new cyclopentadienide anion which is ideally constructed for intramolecular cyclization and dehydration.

In a radically different approach to this problem, Kaiser and Hafner demonstrated that structures of the type *148* and *149* are capable of cyclization when heated to reflux in piperidine (106 °C).[228] Simply by modifying the position and

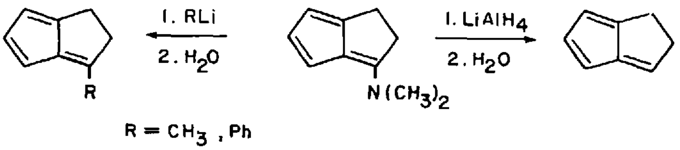
SCHEME 25



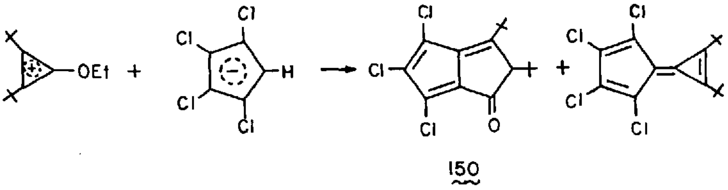
extent of methyl substitution on the sidechain, comparable closure could be made to occur even at temperatures below 20 °C.[229)] A particularly useful facet of this



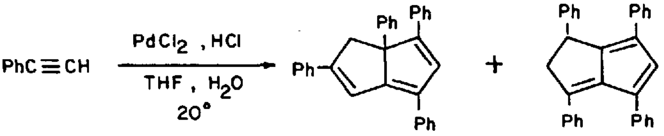
chemistry is the ease with which the dialkylamino group of these dihydropentalenes can be displaced with lithium reagents or removed by hydride reduction.[228)]



By reaction of di-*tert*-butylethoxycyclopropenium fluoroborate with the tetrachlorocyclopentadienide anion, it is possible to gain access to ketone *150*, the *β*-chlorine in which is subject to replacement with nucleophiles.[230)]



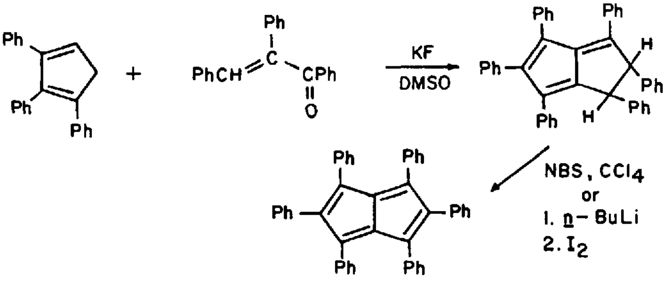
The remarkable cyclotetramerization of phenylacetylene under conditions of palladium (II) catalysis has been reported.[231] An X-ray crystal structure analysis has been performed on *151*.



151

B. Synthesis and Reactions of Pentalenes

The first pentalene to be synthesized free of fused rings was the hexaphenyl derivative (*152*).[232] The approach involved fluoride ion-catalyzed Michael addition-Knoevenagel dehydration of 1,2,3-triphenylcyclopentadiene with 1,2,3-triphenylpropenone and subsequent oxidation with N-bromosuccinimide in CCl_4.



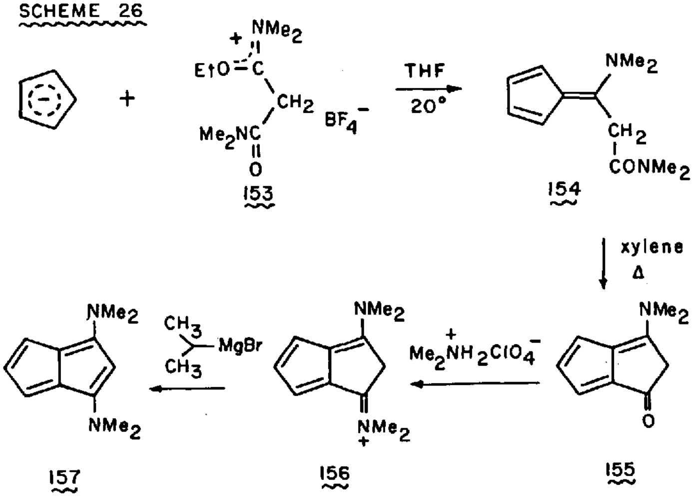
152

Alternatively, sequential treatment with *n*-butyllithium and iodine introduced the fourth double bond. Although solutions of *152* are air sensitive, the green-brown crystalline solid appears to be entirely stable. Heating of *152* with excess dimethyl acetylenedicarboxylate gives dicarbomethoxyhexaphenylazulene.

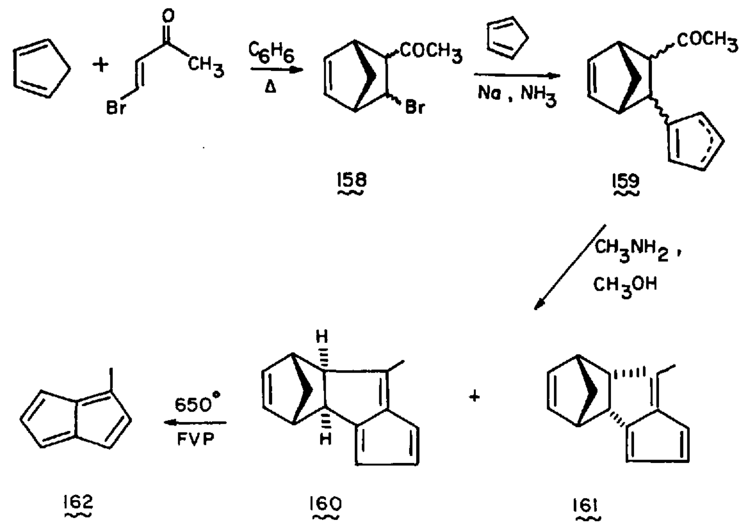
The dark blue crystalline 1,3-bis(dimethylamino)pentalene (*157*) was the second derivative to yield to synthesis (Scheme 26).[233] Upon condensation of sodium cyclopentadienide with the salt *153*, there is obtained the fulvene *154* which can be cyclized with loss of dimethylamine when heated in xylene. Treatment of the resulting ketone (*155*) with dimethylammonium perchlorate afforded the salt *156* which was successfully deprotonated with isopropylmagnesium bromide. Interestingly, *155* could be reversibly converted to its blue-colored enolate without polymerization or decomposition.

The simplest pentalene yet known, the 1-methyl derivative, has been prepared by making recourse to a retro-Diels-Alder degradation as the generative step under flash vacuum pyrolysis conditions (Scheme 27).[234] Addition of 4-bromo-3-buten-2-

SCHEME 26

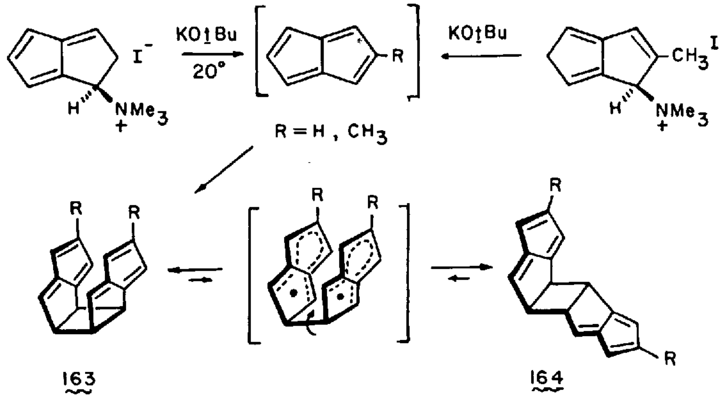


SCHEME 27



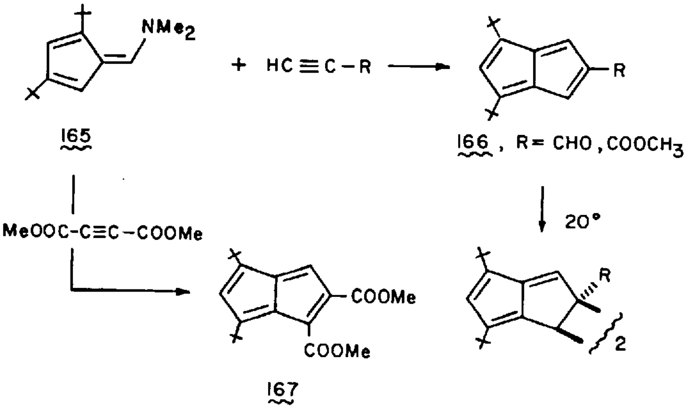
one to cyclopentadiene gave the adduct *158* which when treated with sodium cyclopentadienide was transformed into *159*. Cyclization of *159* to a mixture of *160* and *161* was achieved with methylamine in methanol. Thermolysis of these hydrocarbons at 650 °C in the gas phase and condensation in a cryostat at –196 °C gave the desired *162* which was found to dimerize rapidly at –150 °C and above. Spectral measurements (UV, IR) taken on *162* at –196 °C indicate polyolefinic character.

The complication caused by dimerization persists during attempts to prepare pentalene itself, the 2-methyl derivative, and the 1,3-dimethyl substituted ring system.[235] Careful work by Hafner's group has demonstrated that formation of *syn-cis* dimers of the type *163* is kinetically preferred, but that isomerization to the thermodynamically favored *anti-cis* form (*164*) can be realized thermally.[236] The

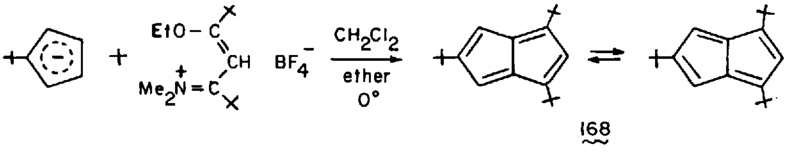


structural assignments to *163* and *164* have been confirmed through X-ray studies.[237] On photolysis at −196 °C, some of these dimers revert to the highly thermolabile monomers.[238]

As the steric bulk of the ring substituents is increased and their number reaches a critical level, dimerization is retarded. For example, the cycloadducts (*166*) of fulvene *165* with propargylic aldehyde or methyl propiolate are reported to undergo dimerization at 20 °C, while the dimethyl acetylenedicarboxylate adduct *167* is stable under these conditions.[239]

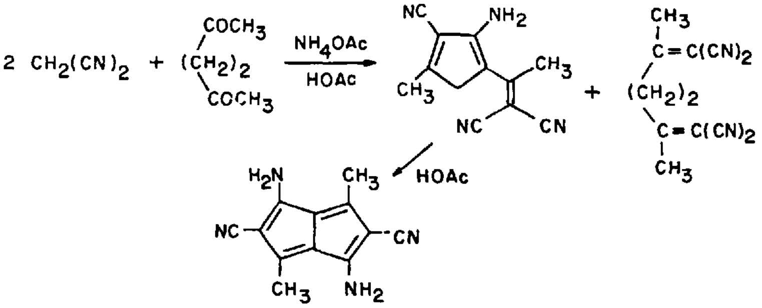


In this connection, 1,3,5-tri-*tert*-butylpentalene (*168*) is a particularly interesting molecule. Synthesized in a strikingly simple and elegant manner,[240] this deep blue

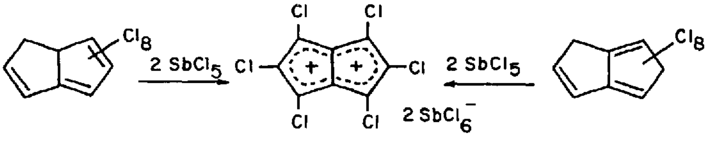


crystalline solid is stable for several hours at room temperature in the absence of air, while a dilute hexane solution is stable for several days under nitrogen. Dimer formation has not yet been observed. The ring proton signals of *168* are shifted upfield relative to those of heptalene, cyclooctatetraene, fulvene, and 1,2-dihydropentalene, and compare closely with the outer protons of [16]annulene and 1,7-methanol[12]-annulene, both of which exhibit a paramagnetic ring current. Accordingly, a paramagnetic ring current is probably operative within *168*, possibly because of its antiaromatic character. Since its ^{13}C NMR spectrum is characterized by only five ring carbon signals, this pentalene is probably experiencing rapid oscillation as shown, although a delocalized structure cannot be ruled out on this basis. The cycloaddition of *168* to cyclooctyne is recognized to give a fused azulene system.[241)]

More highly functionalized nonannulated pentalenes are also available by the procedure of Hartke and Matusch.[242)]



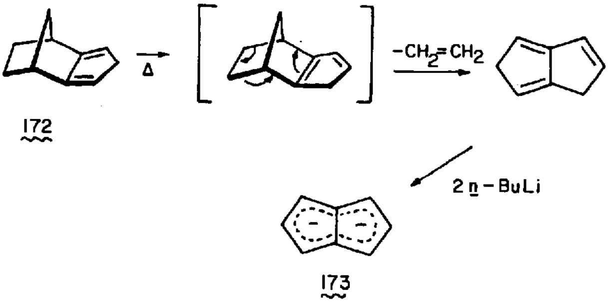
The chlorocarbons *169* and *170* are claimed to undergo reaction with antimony pentachloride with formation of the hexachloropentalenyl dication (*171*).[243)] When exposed to HCl, *171* reverts to *170*. Unfortunately, definitive spectral evidence for *171* is lacking.



169 171 170

C. The Pentalenyl Dianion

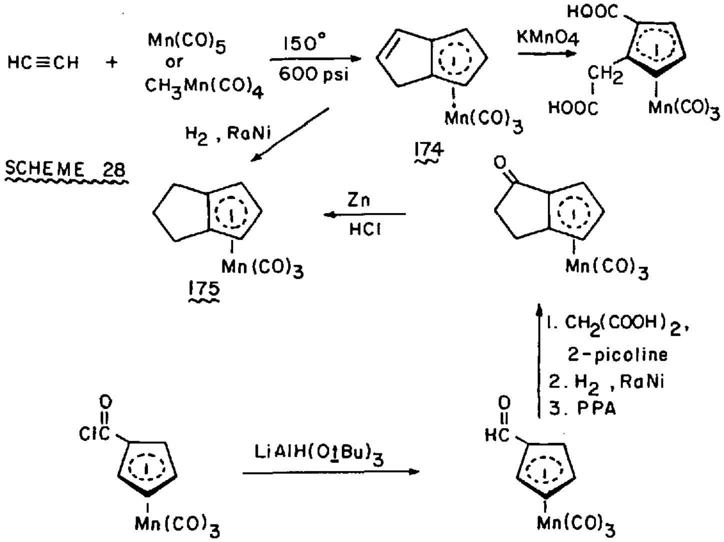
Although Hückel molecular orbital theory is not completely consistent in its application to nonalternant systems such as the pentalenyl dianion, it does implicate a certain degree of stabilization for this species. If the transannular bond introduces little or no perturbation, then the pentalenyl dianion is seen to be closely related to the cyclooctatetraene dianion. Katz and his co-workers successfully developed a convenient synthesis of *173* and determined its spectral properties.[244] Through pyrolysis of isodicyclopentadiene (*172*) in a nitrogen stream at 575 °C, ethylene is liberated in a retro-Diels-Alder cleavage and dihydropentalene is produced. The



addition of two equivalents of n-butyllithium results in twofold deprotonation of the latter hydrocarbon and generation of the dianion. The proton chemical shifts of *173* are in agreement with expectations based upon ring-current deshielding acting in opposition to the shielding effect associated with the doubly negative charge. The negative charge does, however, appear to be somewhat more concentrated at the α- than the β-positions. The longest wavelength maximum in the UV spectrum of dilithium pentalenide appears at 295 nm, in striking contrast to the behavior of lithium cyclopentadienide which has no high intensity maximum above 205 nm.

D. Metal Complexes of Pentalene

Like cyclobutadiene,[245] trimethylenemethane,[246] heptafulvene,[247] and other labile molecules, pentalene can be expected to be greatly stabilized as the result of

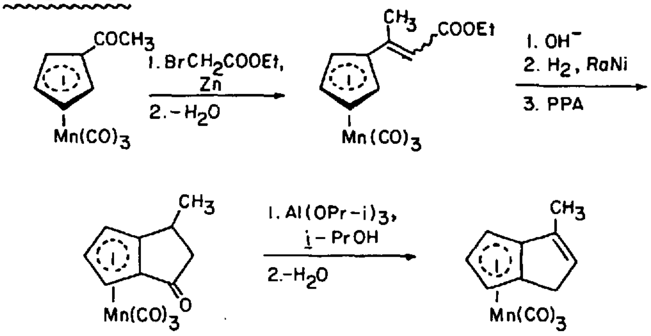


SCHEME 28

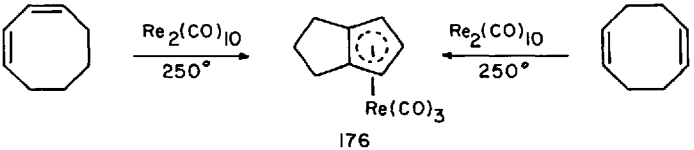
coordination to a transition metal. This thesis has received considerable support; there now exist a number of synthetic entries to pentalene complexes.

It is perhaps first appropriate to consider how the coordination chemistry of lesser unsaturated derivatives evolved. In pioneering work by Coffield and his coworkers, it was demonstrated that reaction of acetylene with manganese pentacarbonyl or methylmanganese tetracarbonyl under autoclave conditions led to production of the complex *174* (Scheme 28).[248] The cyclopentadienyl unit in *174* is of course stable to permanganate oxidation and catalytic reduction. The structure proof of *174* relied upon *175* as the relay, as well as an independent synthesis from dihydropentalene.[249] The chemistry of substituted cyclopentadienylmanganese tricarbonyl complexes is rather extensive,[250–252] the reactions shown in Scheme 29 serving as further illustration of the synthetic utility of these compounds.

SCHEME 29



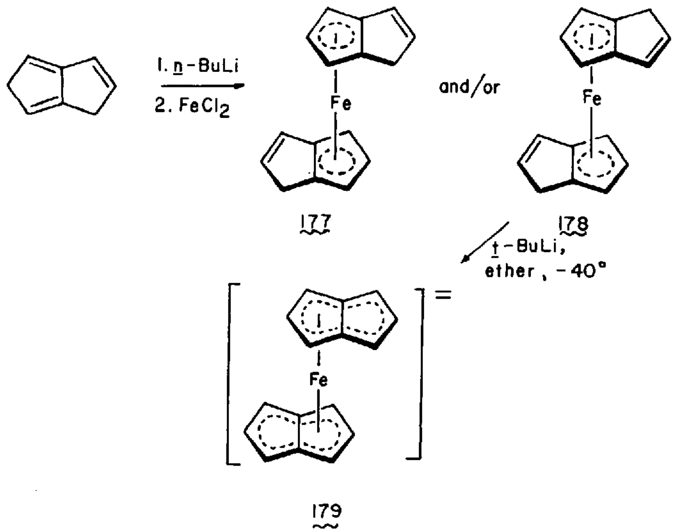
When heated with dirhenium dodecacarbonyl, both 1,3- and 1,5-cyclooctadiene experience transannular cyclization with formation of the complex *176*.[253] An X-ray crystal structure analysis of *176* is available.

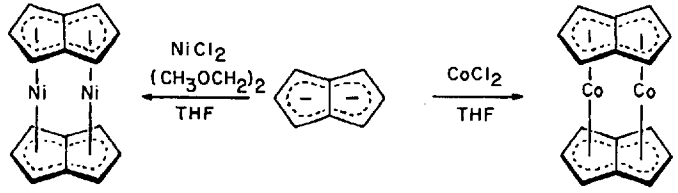


176

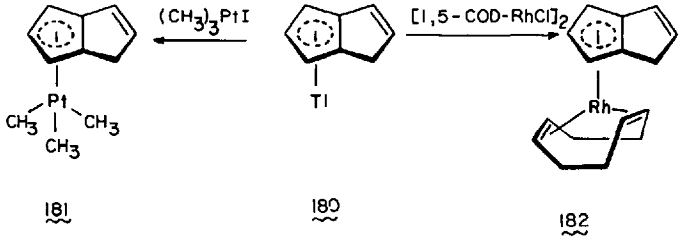
Katz and Rosenberger have observed that the anion of dihydropentalene undergoes conventional reaction with ferrous chloride to give the substituted ferrocene *177* and/or *178*.[254] This product is capable of further deprotonation in the presence of *tert*-butyllithium, affording the dipentalenediyliron dianion (*179*).

A significant number of sandwich compounds of this general type are now known, although the subject will not be expounded upon here. In particular, it has proven feasible to construct such molecules from preexisting ferrocene derivatives. Alternatively, the pentalenyl dianion has been reported to react with $FeCl_2$, $CoCl_2$, and $NiCl_2$ with direct formation of pentalene complexes.[255, 256]

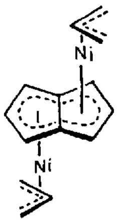




The thallium salt *180* which can be prepared in nearly quantitative yield by treatment of dihydropentalene with thallium sulfate in aqueous sodium hydroxide solution, can be directly transformed into dianion *179* as well as the complexes *181* and *182*.257)



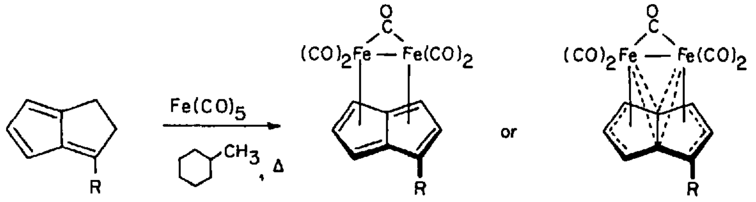
Reaction of allylnickel chloride with dilithium pentalenide in tetrahydrofuran solution at −20 °C and below yields a stable, deep green, monomeric complex, 258) X-ray crystal structure analysis of which shows the molecule to possess a center of symmetry and to have the nickel atoms *trans* to each other as in *183*.259)



183

Similar reactions have led to the preparation of tetraallyldihydropentalenylenedichromium and hexaallyldihydropentalenylenedizirconium.$^{258)}$

A further notable development is the finding that 3-phenyl- and 3-dimethylamino-1,2,-dihydropentalene enter into reaction with iron pentacarbonyl in refluxing deoxygenated methylcyclohexane to give (octahapto-1-R-pentalene-μ-carbonyl)-tetracarbonyldiiron complexes.$^{260)}$ The spectral data for these substances are consistent with either formulation *184* or *185*. Under these conditions, dihydropentalene affords no comparable complex. However, through use of $Fe_2(CO)_9$ in refluxing ether, it has proven possible to prepare the parent diiron complex.$^{261)}$ As before, it is not yet possible to distinguish between a rapidly equilibrating mixture of the bond shift isomers of *184* (R=H) or the delocalized bis-π-allyl structure *185* (R=H).

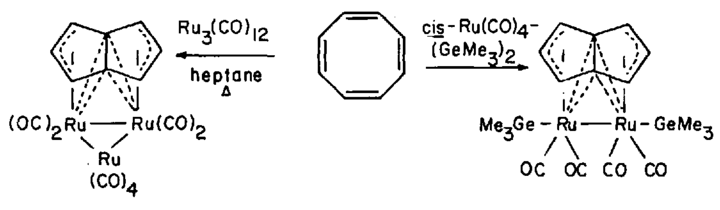


184

185

Weidmuller and Hafner have observed that fission of pentalene dimers can be achieved by transition metals and, in particular, to yield complexes of the type *184* or *185* when treated with $Fe_2(CO)_9$ at 50 °C in methylcyclohexane under a carbon monoxide atmosphere.$^{262)}$ The complexes of pentalene and 1,3-dimethyl-pentalene were given particularly close scrutiny.

Experiments with cyclooctatetraene and its methyl and phenyl derivatives have demonstrated that reaction with certain ruthenium carbonyl complexes can occur with transannular bonding to give pentalene complexes directly.$^{263, 264)}$ The structures of these unique molecules have been confirmed by X-ray crystallography.

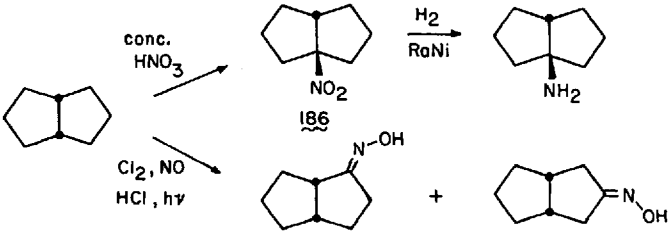


The thermal conversion of *cis*-bicyclo[6.1.0]nona-2,4,6-trienediiron hexacarbonyl to *184* or *185* (R=CH_3) and other complexes has been reported.[265, 266]

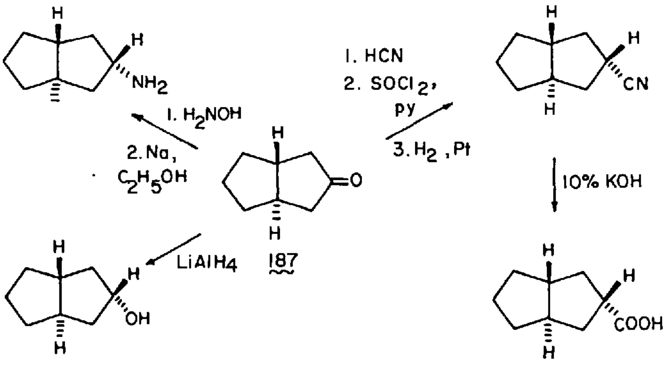
IV. Functional Group Manipulation Within Bicyclo[3.3.0]octanes

In this chapter, we document the many transformations to which compounds having the bicyclo[3.3.0]octane framework have been subjected. Since many of these reactions can now be regarded as "classical", we have not attempted to be completely exhaustive in our coverage. Rather, the interconversions discussed have been selected because they are exemplary. To our knowledge, however, the reference citations made in this and earlier sections constitute a complete listing. Any search for information on these compounds in thereby simplified to this extent.

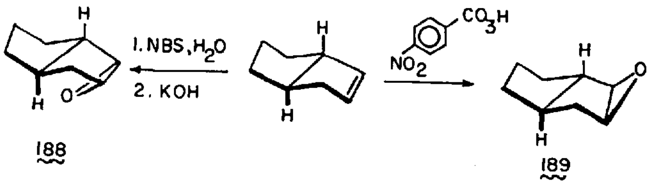
Reports of the direct functionalization of *cis*-bicyclo[3.3.0]octane are few. In concentrated nitric acid, this parent hydrocarbon is converted in modest yield to the angular nitro compound *186*.[112] In tandem with a catalytic hydrogenation step, this route constitutes a reasonable procedure for the preparation of the tertiary amino derivative. Suitable degradation of the 1-carboxylic acid is to be preferred however. Photooximation, on the other hand, occurs at methylene sites and affords the 2- and 3-oximes in a 2 : 1 ratio.[267]



As a consequence of the axial symmetry of *trans*-bicyclo[3.3.0]octane, the question of *exo* or *endo* stereochemistry in its 3-substituted derivatives is nonexistent.[268, 269] Accordingly, the various reactions illustrated for ketone *187* lead to a single homogeneous product.

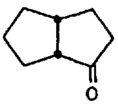


The pair of electrophilic additions to *trans*-bicyclo[3.3.0]oct-2-ene which have been studied are characterized by total stereoselectivity, the preferred direction of



attack being *cis* to the proximal angular hydrogen.[270] Whereas lithium aluminum hydride reductive ring opening of *188* proceeds to the extent of 95 % cleavage of C_3-O bond, *189* reacts predominantly (92 %) by fission of the C_2-O bond.

When the five-membered rings are *cis* fused, attack of reagents from the *exo* surface is generally highly favored. When the functional group undergoing chemical change is more centrally located on the U-shaped structure as it is with *190* and *191*, the stereoselectivity is greatest.[271–275] This trend is continued in the $\Delta^{2,3}$ unsaturated derivatives *192–194*,[273, 274] but appears to taper off somewhat when the carbonyl group is at C_3.[15, 276] Unfortunately, the latter studies are somewhat dated and therefore lacking in analytical refinement. As usual, the steric bulk of the attacking reagent is also critical to the product distribution.



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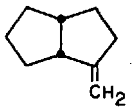
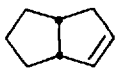


191

	% exo	*% endo*		*% exo*	*% endo*
$LiAlH_4$	75	25	1. $Hg(OAc)_2$	89	11
CH_3MgX	98	2	2. $NaBH_4$		
Disiamylborane	98	2			
H_2, RaNi	> 95				



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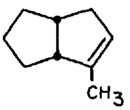

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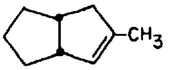
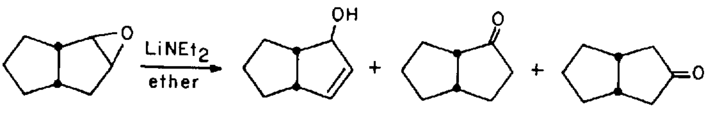


194

	192	193	194
1. $Hg(OAc)_2$	89% *exo*	84% *exo*	89% *exo*
2. $NaBH_4$	11% *endo*	16% *endo*	11% *endo*

The stereospecific syntheses of the 2α- and 2β-*cis*-bicyclo[3.3.0]octanols have been described,[277] as have stereospecific approaches to 3,7-disubstituted derivatives.[278]

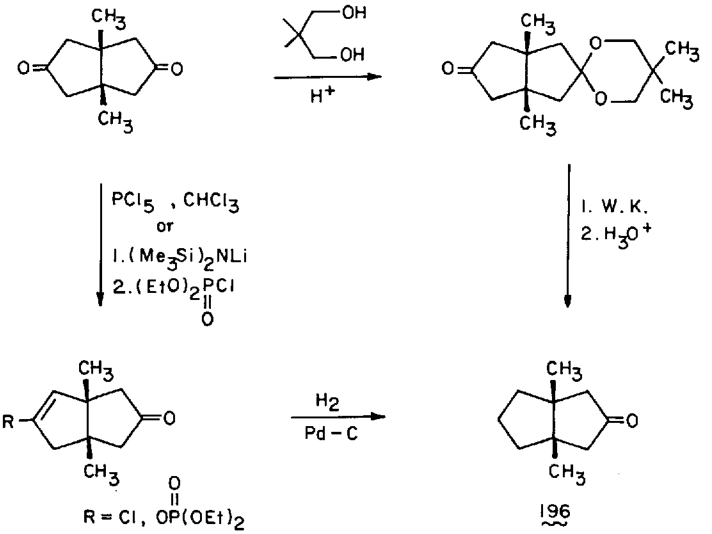
Crandall has shown that epoxide *195* is isomerized with ethereal lithium diethylamide chiefly to the allylic alcohol (76 %) and claimed that carbenic insertion products are absent.[279]

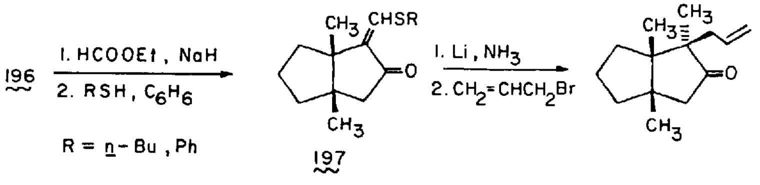


195

Coates, Mason and Shah have examined the effect of angular methyl groups on the stereochemical course of the alkylation of ketone *196* which they prepared according to Scheme 30.[280] In this molecule, the top face (as drawn) differs from the bottom face in having one less carbon but an additional hydrogen on each of the α carbons and no ring. The results indicate that the surface of the molecule occupied by the methyl groups is less sterically demanding. Thus, reduction-allylation of *197* leads only to the stereoisomer having the *exo* allyl group.

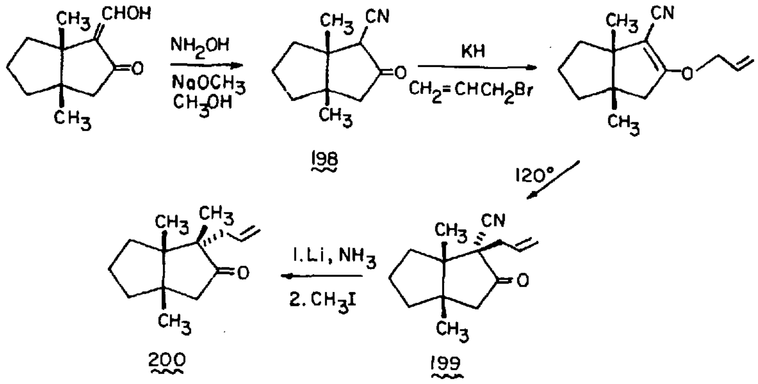
SCHEME 30





In a related study, the enolate of cyano ketone *198* was O-allylated and subjected to Claisen rearrangement (Scheme 31). The allyl group migrated only to the *exo* face

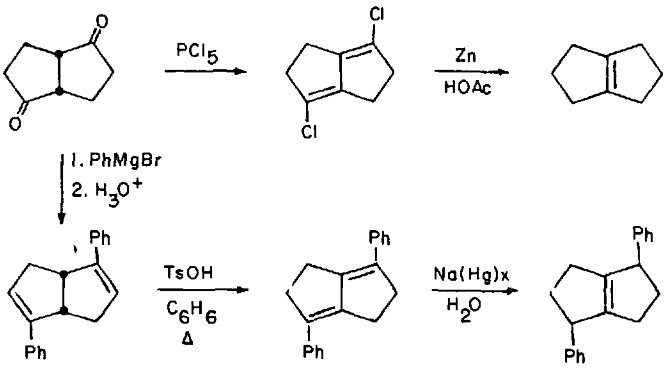
SCHEME 31



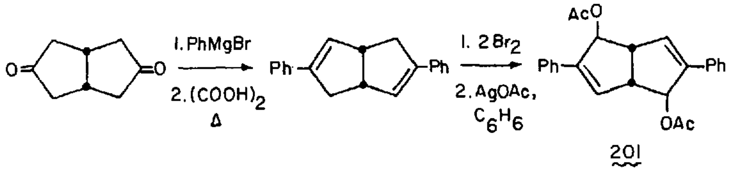
of C_2. Reductive methylation[281] of *199* gave *200* with excellent stereochemical purity. This last reaction has given evidence of being broad in scope.[280]

Several methods have been employed to introduce unsaturation into the bicyclo[3.3.0]octane framework. In one of the earliest studies, Wawzonek developed a two-step conversion of the 2,6-dione to the $\Delta^{1,5}$-olefin (Scheme 32).[282] This chemistry also found application in the preparation of 2,6-derivatives of this ring system.

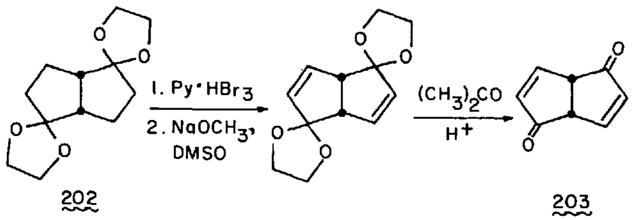
SCHEME 32



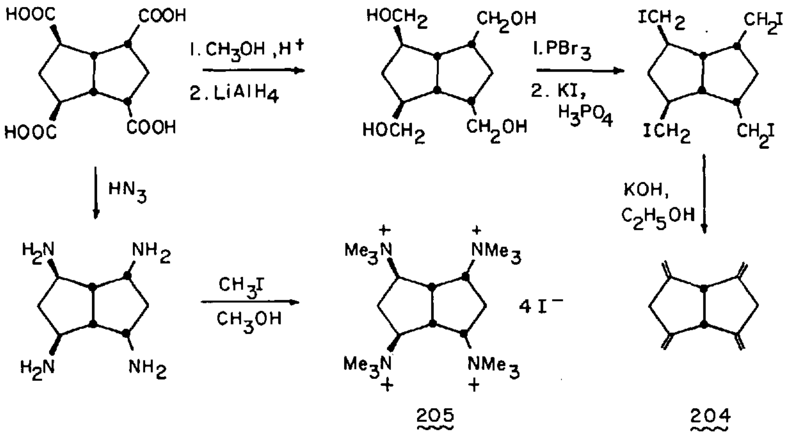
A comparable scheme was applied by Treibs and Hauptmann to their synthesis of *201* which they hoped (in vain) would be a suitable precursor to 2,5-diphenylpentalene.[283]



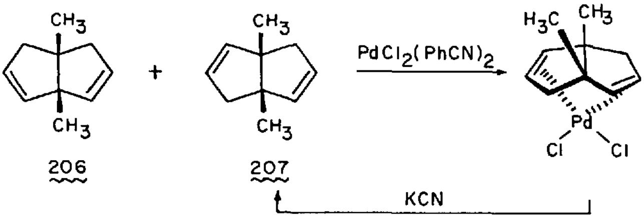
The novel and synthetically useful[284)] dienedione *203* has been obtained by bromination-dehydrobromination of diketal *202*, followed by ketal exchange.[33, 38)]



While the classical route to tetraene *204* was reduced to practice with little difficulty, attempts to convert *205* to pentalene failed for reasons discussed earlier.[285)]



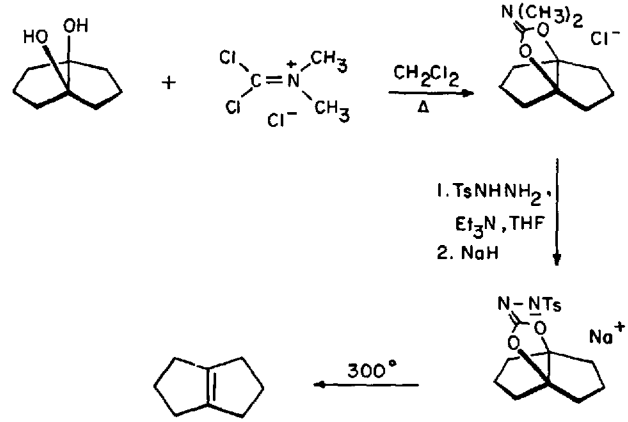
Askani and Sonmez have shown that separation of dienes *206* and *207* may be



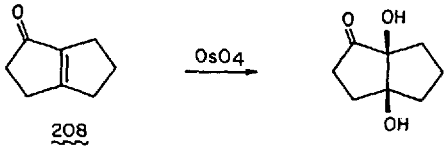
achieved efficiently through selective complexation of the latter to palladium chloride.[286)] Liberation of *207* from its complex simply requires skaking with potassium cyanide.

Borden and his co-workers have applied their vic-dehydroxylation procedure to *cis*-1,5-bicyclo[3.3.0]octanediol with success (Scheme 33).[287)]

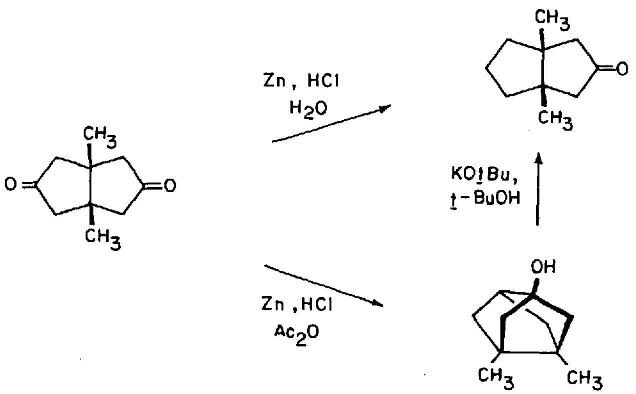
SCHEME 33



While ketone *208* is seemingly incapable of allylic oxidation, it does react with osmium tetroxide to provide the *cis* diol.[288)]

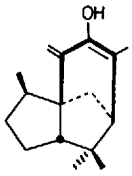


The Clemmensen reduction of the 1,5-dimethyl-3,7-dione is sensitive to conditions.[289)] When the reaction was carried out in aqueous hydrochloric acid, the monoketone was formed as the major product. In contrast, the use of acetic anhydride as solvent resulted in 1,5-transannular closure to a bridgehead bisnoradamantanol. This alcohol is subject to base promoted cleavage in an apparent S_E1 reaction leading to *cis*-1,5-dimethylbicyclo[3.3.0]octan-3-one. The stereochemistry of electrophilic attack in this cleavage has been examined and found to occur with retention of configuration at the carbon leaving group.[290)]



V. Natural Products Synthesis

The higher complexity of many natural products frequently challenges organic chemists to utilize all established stereochemical information while developing their synthetic schemes. Recent years have witnessed an increase in the number of natural products which have bicyclo[3.3.0]octane part structures. In addition to those whose syntheses follow, one can cite further examples such as α-pipitzol (*209*),[291] β-pipitzol (*210*),[291] shellolic acid (*211*),[292, 293] and pentalenolactone (*212*).[294] Although α-pompene was originally formulated as a close structural relative of these molecules,[295] the assignment was later revised to *213* and the hydrocarbon is now recognized to posses a diquinane moiety bridged in a different fashion.[296] β-Pompene is the internal double bond isomer of *213*.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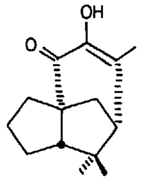
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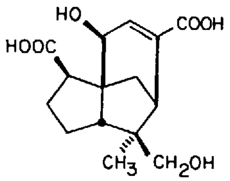

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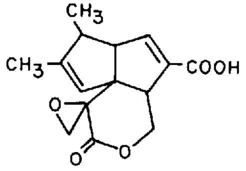

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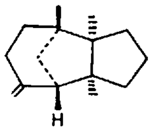
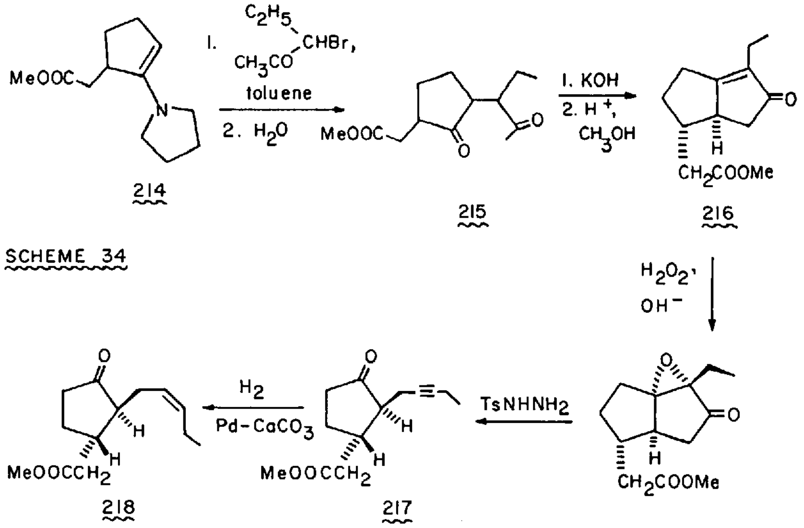


213

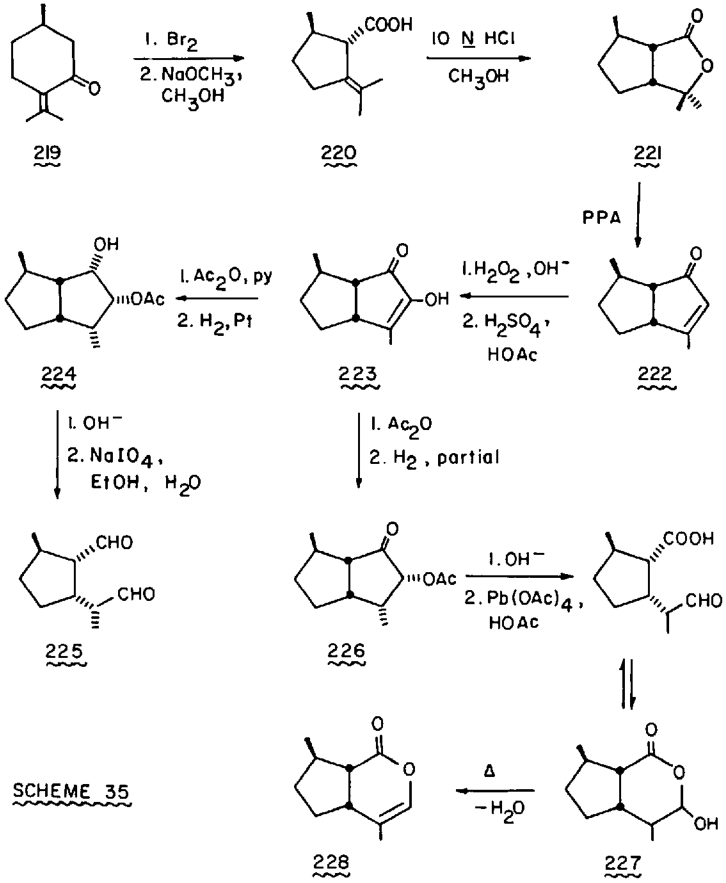
Alongside these developments has arisen an increased awareness that the bicyclo[3.3.0]octane ring system can serve as a versatile template in the synthetic elaboration of nonquinane compounds of nature. Although this work necessarily builds on many of the phenomena described earlier, it is generally exciting for its conceptual originality.

A. Syntheses of Nonquinane Compounds Proceeding Through Bicyclo[3.3.0]octane Intermediates

Methyl jasmonate (*218*) has a *trans*-locked, 2,3-disubstituted cyclopentanone structure.[297] The synthetic route devised by Sisido and co-workers, outlined in Scheme 34, is direct and requires no isomer separation.[298] Reaction of the pyrrolidine enamine of methyl 2-oxycyclopent-1-yl acetate (*214*) with 3-bromo-2-pentanone in toluene gave *215* after hydrolysis. An intramolecular aldol condensation afforded *216* (note double bond migration) whose epoxidation followed by treat-



SCHEME 34



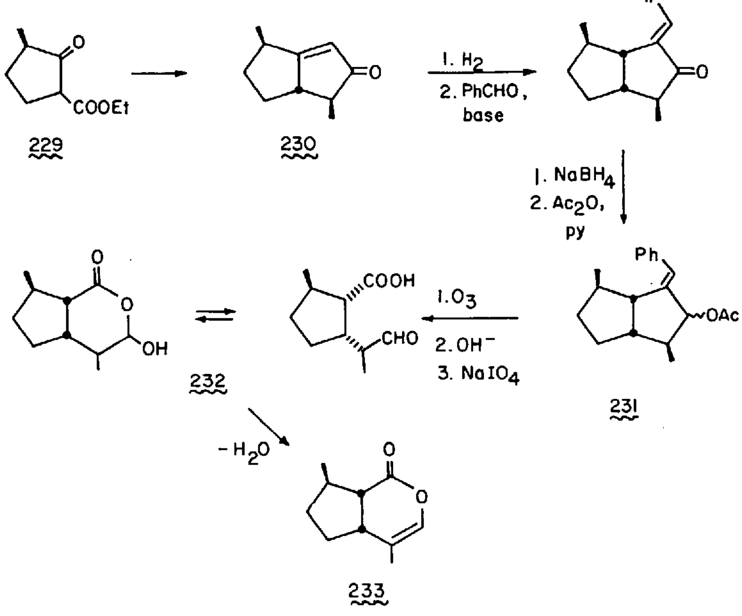
SCHEME 35

ment with tosylhydrazine gave *217*. Controlled catalytic hydrogenation of *217* provided methyl jasmonate.

Cavill and his co-workers have reported stereospecific syntheses of the enantiomers of two naturally occurring cyclopentanoid monoterpenes, iridodial and nepetalactone, from the common precursor D-(+)-pulegone (*219*, Scheme 35).[299] Favorskii ring contraction of *219* afforded *trans*-puleginic acid (*220*) which undergoes facile acid-promoted cyclization in acidic solution. In the presence of polyphosphoric acid, lactone *221* was converted to bicyclooctenone *222* *via* a ring opening and dehydrative cyclization pathway. Epoxidation and acid-catalyzed rearrangement yielded α-hydroxy enone *223* whose acetylation and exhaustive catalytic hydrogenation led to *224*, a bicyclo[3.3.0]octane having well defined stereochemistry at six of its eight constituent ring carbon atoms. Upon saponification and periodate cleavage, *224* was transformed to dialdehyde *225*, the enantiomer of natural iridodial. Alternatively, acetylation and partial hydrogenation of *223* gave *226* which, upon sequential treatment with base and lead tetraacetate, was converted to *227*. When heated, this last intermediate underwent dehydration to furnish *228*, the enantiomer of natural nepetalactone.

The total synthesis of *dl*-nepetalactone itself was achieved a short time earlier by Sakan's group (Scheme 36).[300] In their approach, the first bicyclooctenone inter-

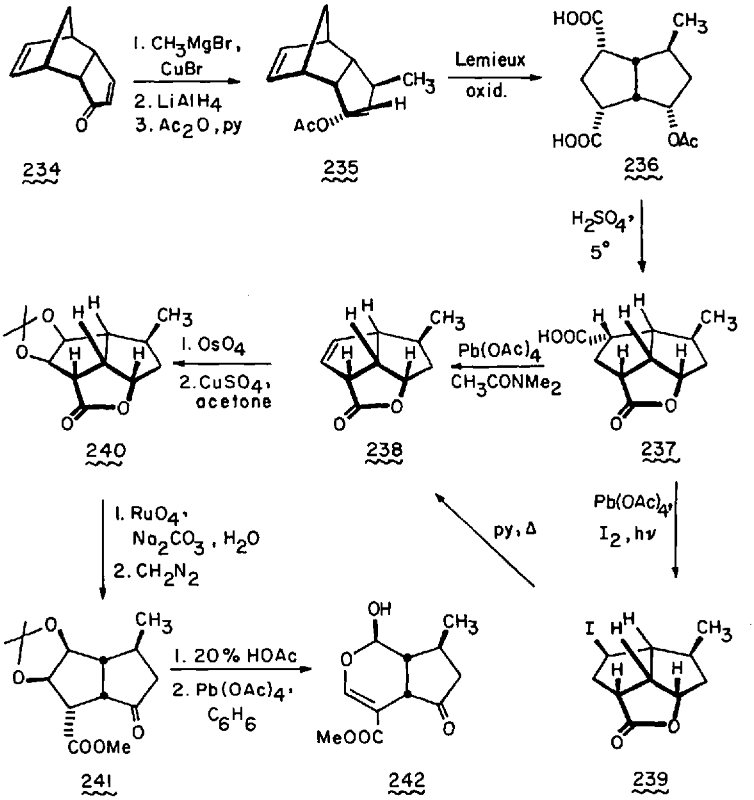
SCHEME 36



mediate (*230*) was arrived at by condensation of the enolate of *229* with 3-bromo-1-butyne, hydration of the triple bond, and aldol condensation. Standard chemical transformations provided the acetate *231* whose sequential ozonolysis, saponification, and periodate cleavage yielded *232*. Upon dehydration of this last intermediate, *dl*-nepetalactone (*233*) was obtained.

Three other structurally related oxygenated bicyclic molecules are verbenalol (*242*), iridomyrmecin (*247*), and forsythide aglycone dimethyl ester (*256*). All have been synthesized in racemic form. Sakan and Abe's preparative route to *242* is elegantly designed (Scheme 37).$^{301)}$ Readily available ketone *234* was treated in turn

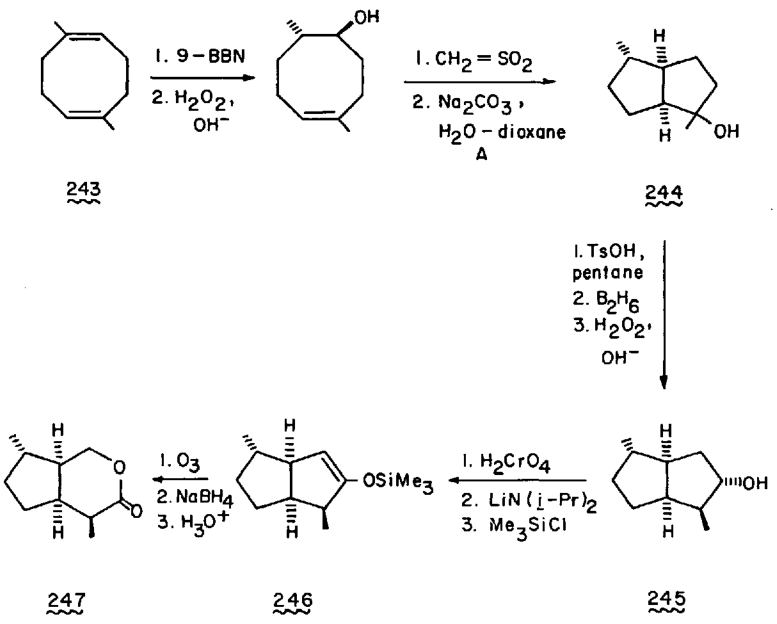
SCHEME 37



with the methylmagnesium bromide-cuprous bromide reagent, lithium aluminum hydride, and acetic anhydride in pyridine. This sequence unequivocally defined the third and fourth asymmetric centers in the bicyclooctane *236*. The first two chiral sites were predetermined by the *endo* stereochemistry of *234* and the fifth and sixth by Lemieux oxidation of *235*. The U-shaped geometry of *236* allowed for ready lactonization in sulfuric acid to give *237*. Oxidative decarboxylation of the carboxyl group may be achieved in one step by direct treatment with lead tetraacetate in pyridine or in a two-step procedure involving iodolactone *239*. Osmylation of the double bond in *238* resulted in *exo* placement of the two hydroxyl groups. This intermediate was converted to its acetonide and the lactone ring was hydrolyzed, oxidized, and esterified to yield *241*. Removal of the acetonide blocking group and oxidative cleavage with lead tetraacetate afforded the desired *242*.

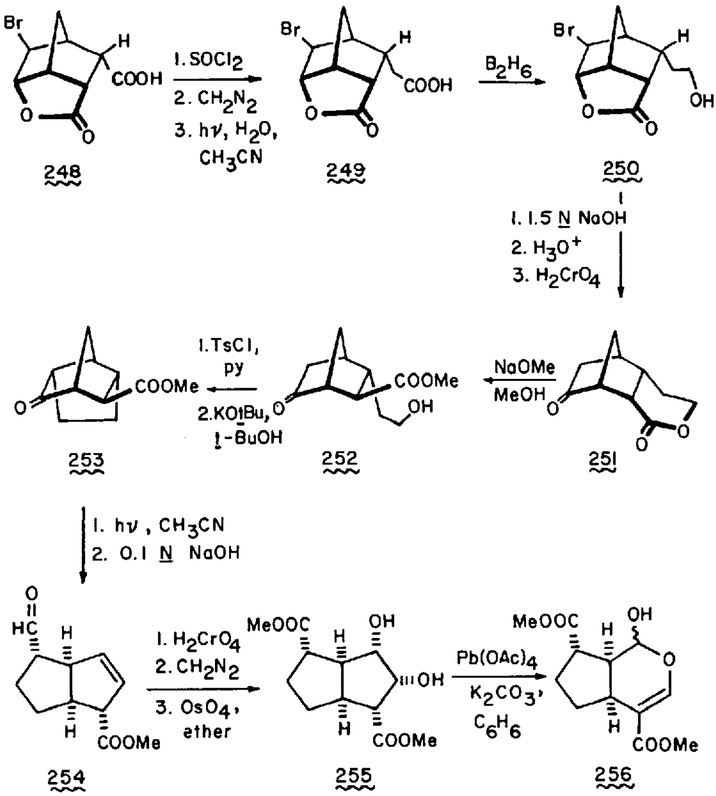
The synthesis of iridomyrmecin (*247*) took advantage of the high transannular reactivity which frequently operates in eight-membered rings (*vide supra*). To this end, 1,5-dimethyl-1,5-cyclooctadiene (*243*) was monohydroborated, treated with sulfene, and solvolyzed in buffered aqueous dioxane to give the bicyclic alcohol *244* (Scheme 38).[302] Dehydration of *244* led to the $\Delta^{2,3}$-olefin, hydroboration-oxidation of which proceeded with good stereochemical control to give *245*. This compound was oxidized by Jones' reagent to the ketone whose kinetic enolate was trapped with trimethylsilyl chloride. The resulting *246* was ozonized and the aldehyde acid so produced was reduced with sodium borohydride and cyclized in acid to afford *247*.

SCHEME 38

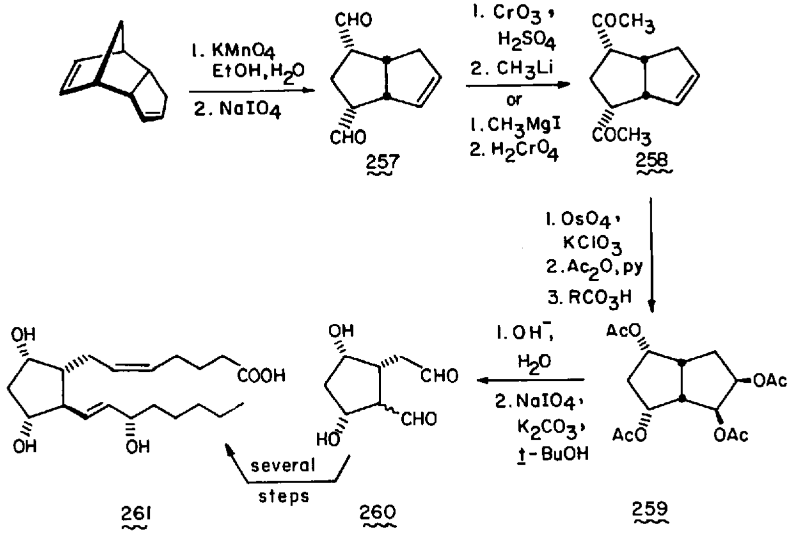


The route to forsythide aglycone dimethyl ester (*256*) required *248*, readily obtainable from the Diels-Alder adduct of cyclopentadiene and maleic anhydride (Scheme 39).[303] Chain extension by means of a modified Arndt-Eistert sequence and selective reduction of the carboxyl group gave *250* which was then subjected to an imaginative lactone interchange, ultimately affording *251*. Methoxide-promoted lactone ring opening, followed by tosylation of the alcohol and intramolecular cyclization with *t*-butoxide produced keto ester *253*. When irradiated, the ketone carbonyl of *253* experienced α fission and intramolecular hydrogen transfer to generate an aldehyde group and a double bond. Exposure of this product to dilute base caused epimerization to the thermodynamically more stable *254* as expected. Rather standard chemical transformations produced *255* which was converted to *256* upon oxidative cleavage of the diol with lead tetraacetate.

SCHEME 39



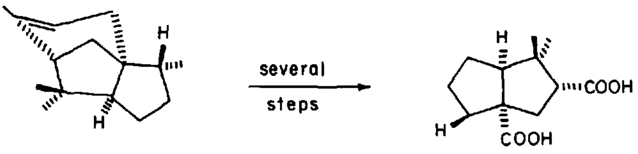
SCHEME 40



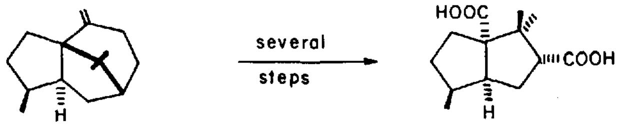
Brewster and his co-workers have reported a synthesis of prostaglandin $PGF_{2\alpha}$ (*261*) designed with a heavy dependence on bicyclo[3.3.0]octane intermediates (Scheme 40).[304] *endo*-Dicyclopentadiene was converted by hydroxylation and periodate cleavage to *endo, endo* dialdehyde *257*. Homologation to the diacetyl compound *258* was carried out by two different procedures as illustrated. Hydroxylation and acetylation of the double bond followed by twofold Baeyer-Villiger rearrangement afforded tetraacetate *259*. The corresponding tetraol was cleaved with periodate to give *260*, the pivotal intermediate for the construction of *261*.

B. Syntheses of Compounds Having a Diquinane Part Structure

Before entering into a discussion of synthesis, it should be pointed out that the sesquiterpene class is particularly rich in molecules that have bicyclo[3.3.0]octane subunits. Cedrene (*262*) and γ-patchoullene (*264*) are representative examples as



262 263

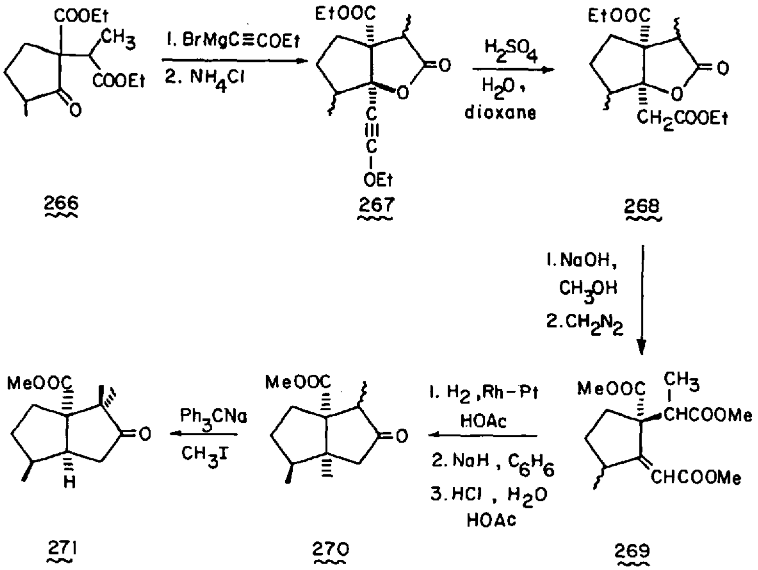


264 265

made clear by the degradative work on these molecules which has produced dicarboxylic acids *263* and *265*, respectively, together with additional related structures.[305] Due to the complexity of such molecules, their total synthesis from bicyclooctane intermediates may not always be feasible and frequently is not. To keep within the theme of this review, attention is given herein only to syntheses which do utilize diquinanes as building blocks.

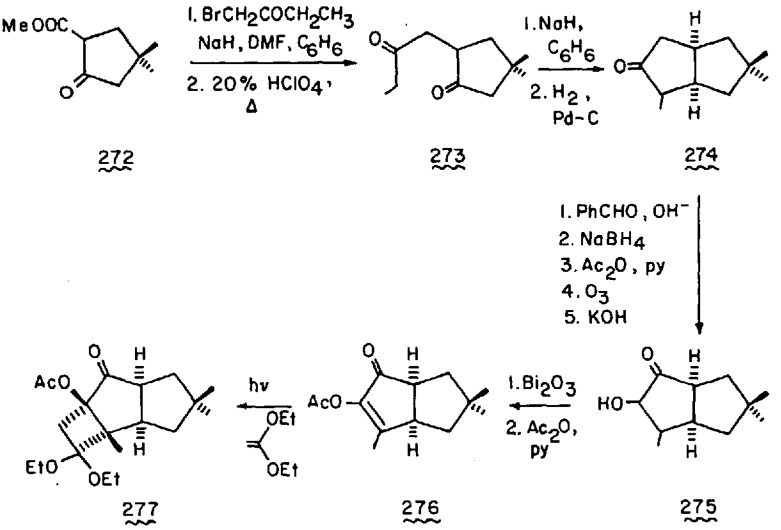
Keto ester *271* is a degradation product of patchouli alcohol; its synthesis was reported by Dev and co-workers in 1966 (Scheme 41).[306] The key step in their approach was the 1,2-addition of ethoxyacetylenemagnesium bromide to keto ester *266*. After hydration of the triple bond in *267*, the lactone ring was opened under mildly alkaline conditions to give, after treatment with diazomethane, the seco diester *269*. After catalytic hydrogenation and Dieckmann cyclization, the third methyl group was introduced by standard alkylation methodology. Since *trans* locked diesters do not undergo closure under Dieckmann conditions (*vide infra*), any quantity of that isomer which may have formed at the hydrogenation stage would not be carried further.

SCHEME 41



An expeditious stereospecific synthesis of the protoilludane skeleton has been actively pursued by Matsumoto's group. In his first approach (Scheme 42),[307)] bicyclooctanone *274* was smoothly elaborated in classical fashion. Using a five-step sequence to effect a 1,2-carbonyl transposition with retention of a hydroxyl group at the original carbonyl site, these workers then prepared *275*. Oxidation of this intermediate followed by enol acetylation afforded *276*. When this enone was irradiated

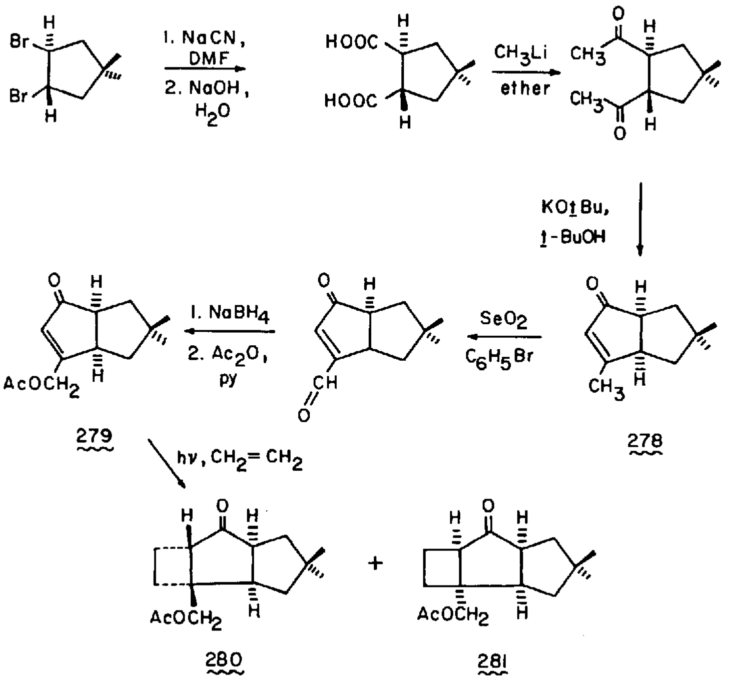
SCHEME 42



in the presence of 1,1-diethoxyethylene, regio- and stereospecific [2+2] cycloaddition occurred and the desired adduct *277* was obtained.

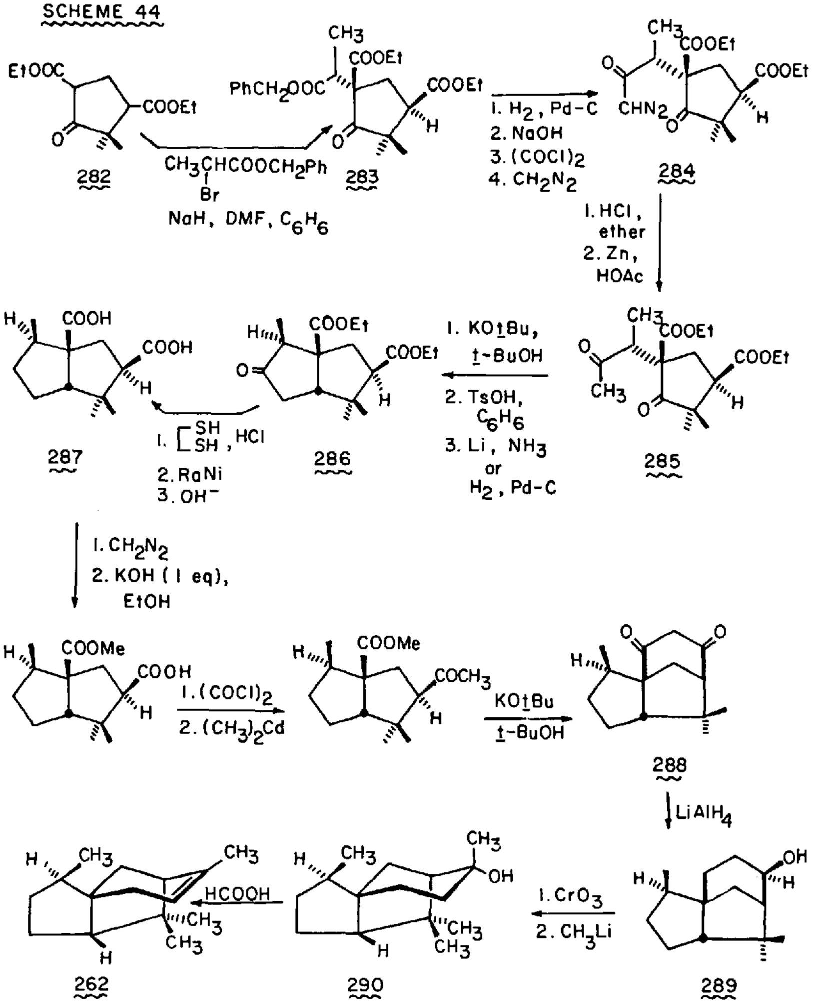
In a second series of experiments,[308)] the enone *278* was first elaborated as shown in Scheme 43 (note equilibration prior to cyclization). On exposure to selenium dioxide in bromobenzene solution, the allylic methyl group in *278* underwent oxidation to the aldehyde level. Subsequent controlled reduction and acetylation gave acetoxy ketone *279*. The subsequent [2+2] photochemical cycloaddition of this intermediate to ethylene was not stereospecific, both *280* and *281* being obtained.

SCHEME 43



The classic work in this area is due to Stork and Clarke whose total syntheses of cedrene (*262*) and cedrol (*290*) were reported as early as 1955 (Scheme 44).[309)] Diethyl 4,4-dimethyl-5-keto-1,3-cyclopentane dicarboxylate (*282*) was alkylated with benzyl α-bromopropionate and the resulting triester (*283*) was hydrogenolyzed over palladium on charcoal and converted *via* the acid chloride to diazoketone *284*. This intermediate was converted in two steps to methyl ketone *285* which gave a bicyclic aldol on treatment with potassium *tert*-butoxide (note equilibration of methyl group). Dehydration was easily effected and reduction of the enone so formed to *cis* fused keto diester *286* was accomplished through catalytic or dissolving metal reduction. Removal of the ketone carbonyl was achieved by desulfurization of the dithioketal. Resolution of diacid *287* was successfully realized by way of its quinine salt, conversion of the 1-isomer to *288* following established procedures which take advantage

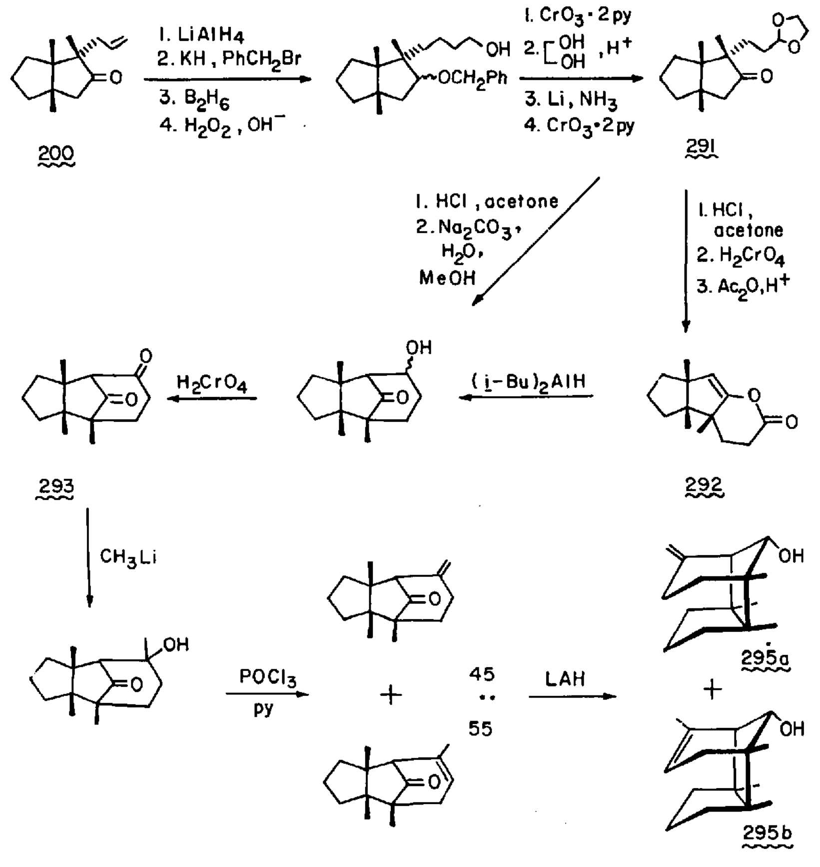
SCHEME 44



of the differing steric environment of the ester groups. In an unprecedented reaction, the direct lithium aluminum hydride reduction of *288* gave the saturated alcohol *289*, whose oxidation and condensation with methyllithium furnished *l*-cedrol (290). Dehydration of *290* with formic acid comprised the method for conversion to cedrene (*262*).

In recent work Coates, Mason and Shah have successfully achieved the synthesis of gymnomitrol (*295a*).[280] Since intramolecular aldol condensation of the aldehyde obtained by hydrolysis of *291* (Scheme 45) was unfavorable, conversion to enol lactone *292* was effected. Dibal-H reduction of *292* resulted directly in aldolization of the intermediate lactol, oxidation of which afforded *293*. The latter was converted successfully to keto alcohol *294* by capitalizing on the different steric environments about the carbonyl groups. Sequential dehydration and hydride reduction of *294* gave a 45:55 mixture of exo and endocyclic isomers *295a* and *295b* which were separated by TLC.

SCHEME 45



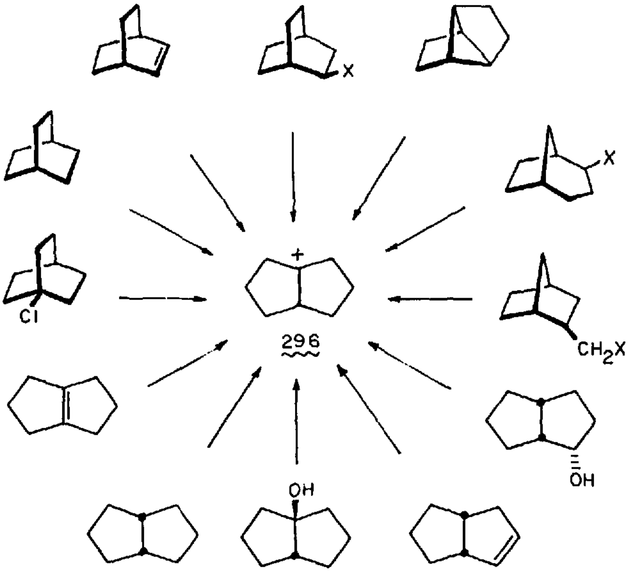
VI. NMR Data on Bicyclo[3.3.0]octanes

Olah and Liang were able to establish by means of ^{1}H NMR studies in superacidic solutions at −78 °C that all bicyclooctyl systems rearrange to the [3.3.0] cation *296* (Scheme 46).$^{311)}$ When *296* was allowed to warm to 0 °C, it rearranged irreversibly to the 2-methylnorbornyl cation.

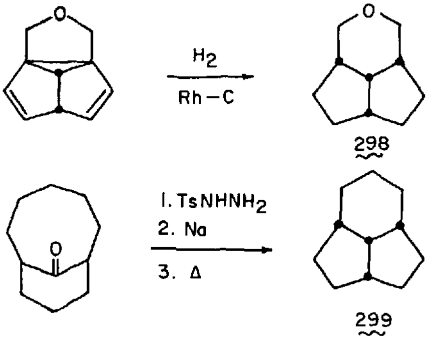
Using comparable experimental conditions, Bollinger and Olah examined the protonation of *syn*- and *anti*-octamethyltricyclo[4.2.0.0^{2,5}]octa-3,7-diene, octamethylsemibullvalene, and octamethylcyclooctatetraene and found in every case that the major species produced was the octamethylbicyclo[3.3.0]octadienediyl dication (*297*).$^{312)}$

^{1}H NMR spectroscopy has also been used to advantage in establishing the *endo* stereochemistry of 2,8-bridged bicyclo[3.3.0]octanes such as *298* and *299*.$^{313, 314)}$

SCHEME 46



297

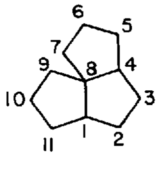


^{13}C NMR studies of bicyclo[3.3.0]octyl cations[315] and neutral molecules have recently made their appearance.[316–318] In particular, Whitesell and Matthews' detailed analysis of the spectra of 52 mono- and polyfunctionalized bicyclo[3.3.0]-octanes is singled out as a particularly useful source reference.[318]

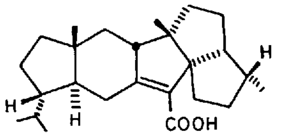
VII. Synthesis and Chemistry of Triquinanes

A. Derivatives of Tricyclo[6.3.0.0^{4,8}]undecanes

The tricyclo[6.3.0.0^{4,8}]undecane ring system (*300*), which contains a bridged spirane arrangement of three cyclopentane rings, has been shown to be a segment of



300

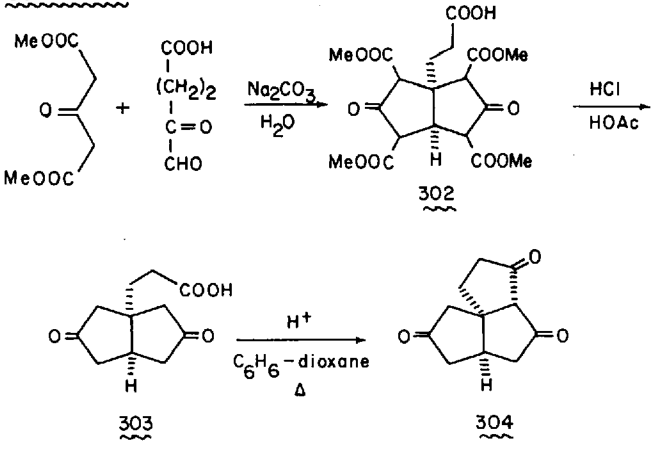


301

the carbon skeleton of retigeranic acid (*301*), a pentacyclic sesterterpene produced by *L. retigers.*[319)]

The simplest derivative of this ring system known at present is the triketone *304* (Scheme 47).[320)] Condensation of 4,5-dioxopentanoic acid with dimethyl β-ketoglutarate in aqueous sodium carbonate solution was shown to give *302* in 80 % yield.

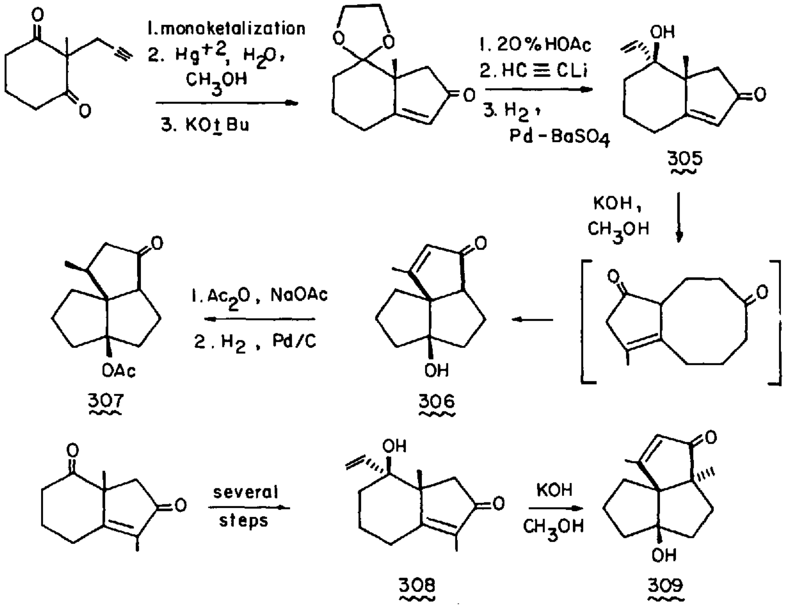
SCHEME 47



Heating of the derived diketo acid (*303*) with naphthalene-l-sulfonic acid in benzene-dioxane solution promoted cyclization and formation of *304* (60 %).

In an alternative approach to molecules of this type, Dauben and Hart examined the base-catalyzed rearrangement of vinylogous β-hydroxy ketones such as *305* and *308* (Scheme 48).[321)] Their conversion to *306* and *309* can be accounted for in terms of a vinylogous retro-aldol condensation followed by intramolecular 1,4 addition of an intermediate dienolate to the resulting enone moiety. Subsequent to this reaction, conjugation of the double bond away from the ring juncture followed by a transannular vinylogous aldol condensation produces the observed products.

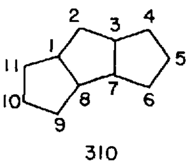
SCHEME 48



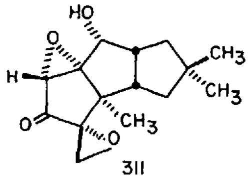
The *cis-cis* stereochemistry is based upon thermodynamic considerations and ultraviolet data.

B. The Tricyclo[6.3.0.0^{3,7}]undecane Ring System

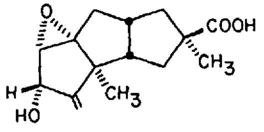
Serial fusion of three five-membered rings generates the tricyclo[6.3.0.0^{3,7}]undecane



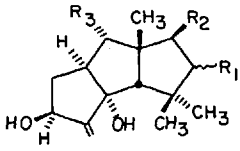
310



311



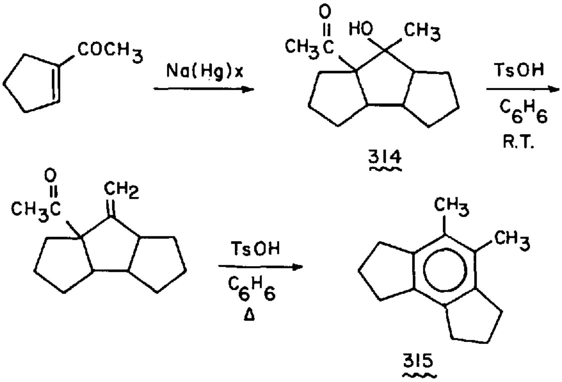
312



313 a, $R_1 = R_2 = R_3 = H$
b, $R_1 = R_3 = H, R_2 = OH$
c, $R_1 = R_2 = H, R_3 = OH$
d, $R_1 = OH, R_2 = R_3 = H$

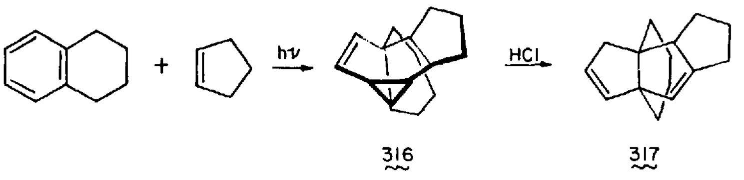
carbon framework (*310*). Interestingly, three types of naturally occurring sesquiterpenoids possess this basic structure. They are coriolin (*311*), isolated from the culture broth of *Coriolis consors*,[322)] hirsutic acid C (*312*) and complicatic acid (the keto form), isolated from stirred fermentations of *Stereum hirsutum* and *Stereum complicatum*[323)] and four capnellane derivatives (*313*), isolated from the soft coral *Capnella imbricata.*[324)] Several of these compounds display significant levels of biological activity and consequently have attracted considerable interest recently.

The earliest work in this area is due to Casals who observed that reduction of 1-acetylcyclopentenes with sodium amalgam gave products such as *314*.[325)] With



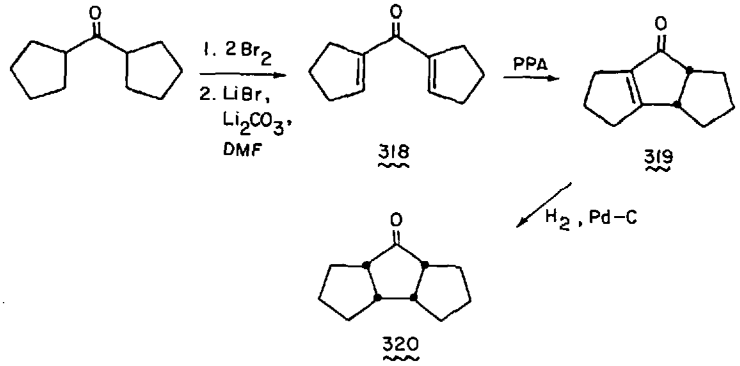
p-toluenesulfonic acid in benzene at room temperature, these ketols could be dehydrated effectively, although more elevated temperatures resulted in their transformation to *as*-indacenes (*315*).[326)]

In the course of a study of the scope of photo-1,3-additions of aromatics to olefins, Srinivasan and co-workers examined the reaction of tetralin with cyclopentene and observed the formation of adduct *316*.[327)] When treated with a catalytic quantity of hydrogen chloride, *316* was rapidly isomerized to *317*, an annulated tricyclo[6.3.0.0^{3,7}]undecadiene structure.



The first systematic approaches to *cis,syn,cis* stereoisomers of this ring system were recently described by Eaton and co-workers.[328)] To gain access to monoketone *320* (Scheme 49), dicyclopentyl ketone was directly brominated and dehydrobrominated. The resulting cross-conjugated ketone *318* underwent acid catalyzed cyclization to provide the first tricyclic intermediate (*319*). Catalytic hydrogenation of *319* led stereospecifically to *320*. Its six ^{13}C resonance lines require that the molecule have C_2 or C_s symmetry. The stereochemistry of this product was ulti-

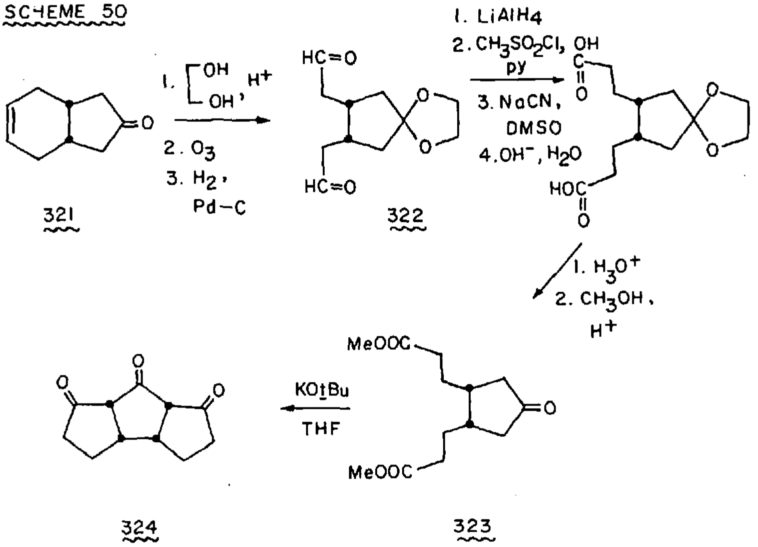
SCHEME 49



mately confirmed by conversion to the ethylene ketal and ^{13}C NMR analysis of this substance. Since the two ketal carbons show nonequivalent chemical environments, only C_s forms are allowed; the *trans,trans* ring fused possibility was logically dismissed.

The synthesis of triketone *324*, functionalized in all three rings, began by ketalization and ozonolysis of *321* (Scheme 50). Chain extension of dialdehyde *322* to

SCHEME 50

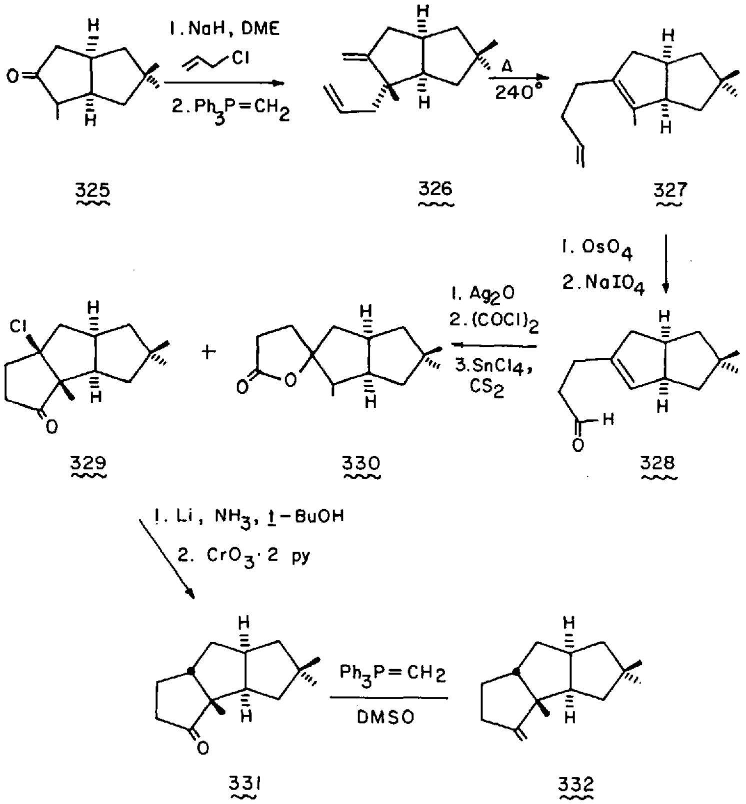


keto diester *323* was achieved by classical methods. When exposed to potassium *t*-butoxide in tetrahydrofuran, cyclization occurred as expected to give *324*. The spectral properties of this β-triketone reveal that it exists predominantly in the unenolized form. *cis*-Bicyclo[3.3.0]octane-2,8-dione behaves comparably,[35] presumably because of the difficulty experienced by a three carbon chain in bridging while still being held in an adjacent fused cyclopentane ring.

Whereas the stereochemistry associated with *320* and *324* is necessarily that which must be developed for the elaboration of peristylane and the pentagonal dodecahedrane (*vide infra*), the sesquiterpenoids *311–313* have *cis,anti,cis* ring fusions. This arrangement is clearly less strained and a much broader range of reactions can be utilized to develop such three-dimensional features as will now be illustrated.

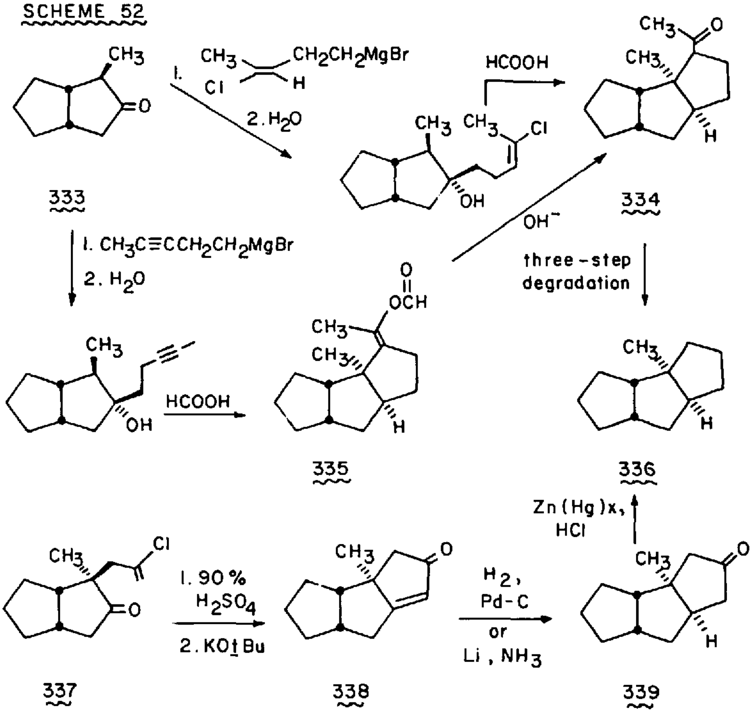
Both hirsutic acid and complicatic acid have been assumed to be derived biogenetically from a parent hydrocarbon having the structure *332*. Its biogenesis from a farnesyl precursor *via* a complex rearrangement was independently demonstrated using ^{13}C NMR spectroscopy.[329, 330] Furthermore, its presence in the hydrocarbon fraction from extracts of *Coriolis consors* has now been recognized and its role as a precursor in coriolin biosynthesis[331] claimed.[332] This sesquiterpene (*332*) has been given the name hirsutine and its synthesis has now been reported (Scheme 51).[332] Treatment of the enolate of *325* with allyl chloride proceeded stereoselectively from the less hindered side; subsequent methylenation by the Witting procedure gave *326*. Upon heating to 240 °C, this dienic hydrocarbon underwent Cope rearrangement and the isomeric diene (*327*) was transformed into aldehyde *328* by selective osmylation and periodate cleavage. The derived carboxylic acid was converted to the acid chloride and treated with stannic chloride in carbon disulfide to achieve intramolecular acylation. A 1 : 1 mixture of *329* and *330* was

SCHEME 51



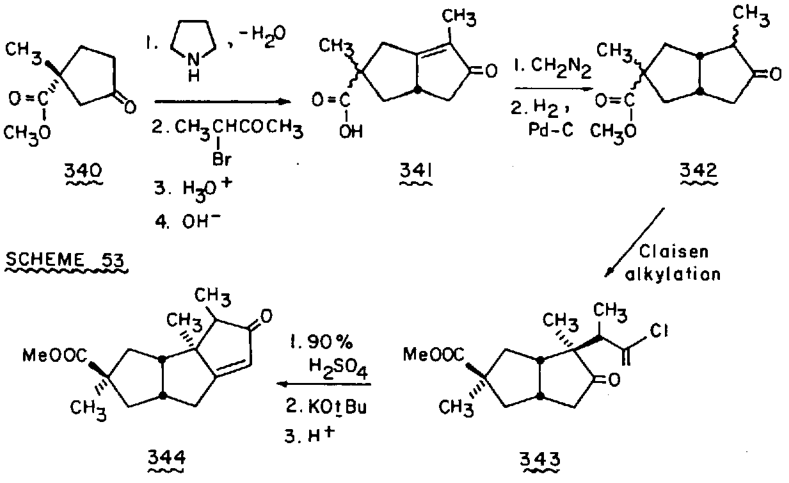
obtained. Dissolving metal reduction of the chloro ketone, followed by oxidation, yielded the norketone *331* which was converted to hirsutine with methylenetriphenylphosphorane.

As part of their studies of the synthesis of hirsutic acid C, Lansbury and coworkers developed a stereoselective synthesis of norhirsutanes (Scheme 52).[333] Model experiments involved the addition to ketone *333* of Grignard reagents derived



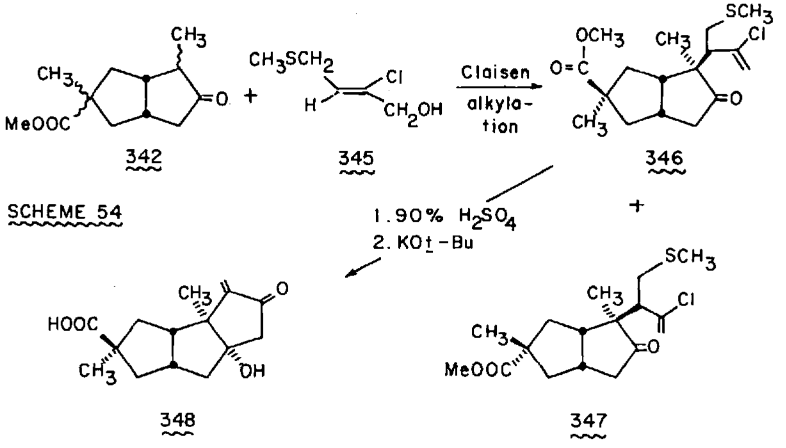
from 2-chloro-5-bromo-2-pentene and 1-bromo-3-pentyne. The resulting alcohols were subjected to formolytic cyclization and the tricyclic products so formed (*334* and *335*, respectively) were degraded to *336*. Ketone *333* was also subjected to Claisen alkylation[334] with β-chloroallyl alcohol, leading to *337*. When *337* was hydrolyzed and the resulting dione aldolized, tricyclic ketone *338* resulted. Catalytic hydrogenation or lithium in ammonia reduction afforded *339* whose Clemmensen reduction also gave *336*. This sequence identified both the steric course and regioselectivity of the Claisen alkylation procedure.

Their more directed approach to hirsutic acid utilized *341* as starting material (Scheme 53).[335] This diketo ester was the major product obtained from alkylation of the pyrrolidine enamine of *340* with 3-bromo-2-butanone and aldolization in aqueous base. Reesterification with diazomethane and catalytic hydrogenation generated the *cis*-fused bicyclooctane nucleus. The subsequent Claisen alkylation of *342* proved to be stereoselective, affording *343* as the major product. Cyclization as before furnished *344* whose further transformations are currently being examined.



SCHEME 53

Hirsutic acid C has been observed to rearrange to a biologically active isomer called hirsutic acid N or isohirsutic acid which has been formulated as *348*. A convergent, stereocontrolled sythesis of this molecule has also been described by Lansbury (Scheme 54).[336] Claisen alkylation of *342* with *345* again proved to be site-



SCHEME 54

and stereoselective, leading to *346* and *347* in a 3 : 2 ratio. Pure *346* was then hydrolyzed and cyclized in the now established fashion to deliver *348*.

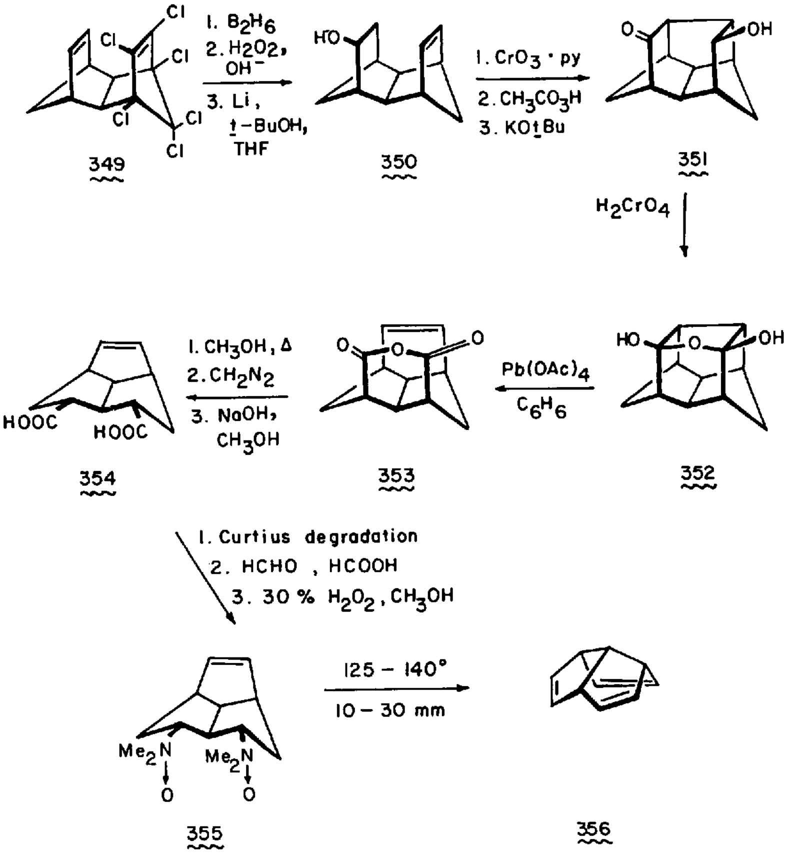
C. The Chemistry of Triquinacene

1. Synthetic Entries to the Parent Hydrocarbon

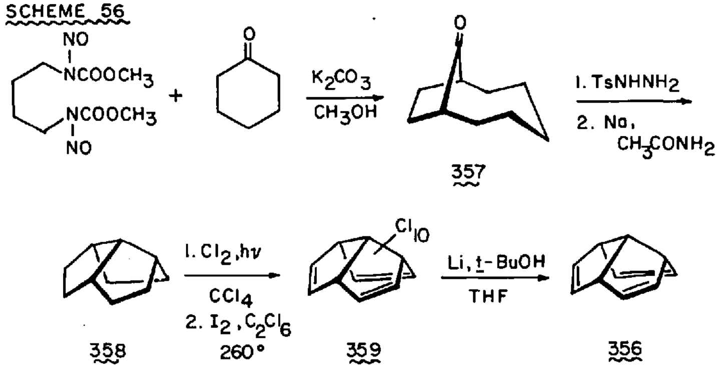
The initial synthesis of triquinacene (*356*) and, in fact, the coinage of its trivial name are due to Woodward and co-workers (Scheme 55).[337] The lengthy route began with isodrin (*349*) which was converted to alcohol *350* by a procedure devised by

Winstein.[338] Sequential oxidation, epoxidation, and base-promoted transannular cyclization gave *351*, oxidation of which provided the interesting stable diketone hydrate *352*. Through use of lead tetraacetate, the cage structure of *352* was cleaved and anhydride *353* obtained. After diesterification, the functional groups were equi-

SCHEME 55



SCHEME 56

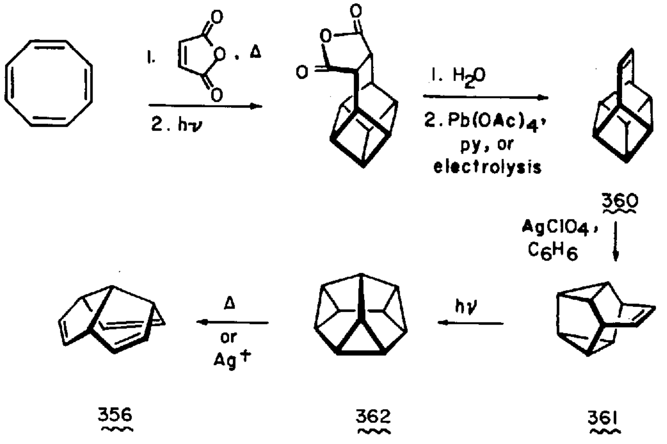


librated to the *exo,exo* positions. Diacid *354* so obtained was subjected to Curtius degradation, N,N-dimethylation and N-oxide pyrolysis to give the desired triene.

The next synthesis of *356* to be described was reported by Jacobson (Scheme 56).[339] In this sequence, 1,4-bis(diazo)butane was generated in the presence of cyclohexanone to give the double ring expanded bridged ketone *357*. Carbenic decomposition of the tosylhydrazone sodium salt of *357* under thermal conditions afforded tricyclo$[5.2.1.0^{4,10}]$decane (*358*). Forcing chlorination of *358* was reported to provide a mixture of extensively halogenated products which could be converted to *359* in a thermal chlorination-dehydrochlorination process by heating with iodine in hexachloroethane. Reductive dechlorination of *359* completed the synthesis which has witnessed several improvements over the years.[340–342]

Interest in the valence bond isomers of $(CH)_{10}$ spawned the third triquinacene synthesis. Basketene (*360*) which is obtainable from cyclooctatetraene as illustrated in Scheme 57[343, 344] is subject to rearrangement to snoutene (*361*) under the catalytic influence of silver ions.[345] Although *361* is very stable to thermal ring opening,[346] it is readily converted to diademane (*362*) upon irradiation.[347] Diademane has been transformed to triquinacene by both thermal [2+2+2] cycloreversion[347, 348] and silver ion-assisted rearrangement.[349]

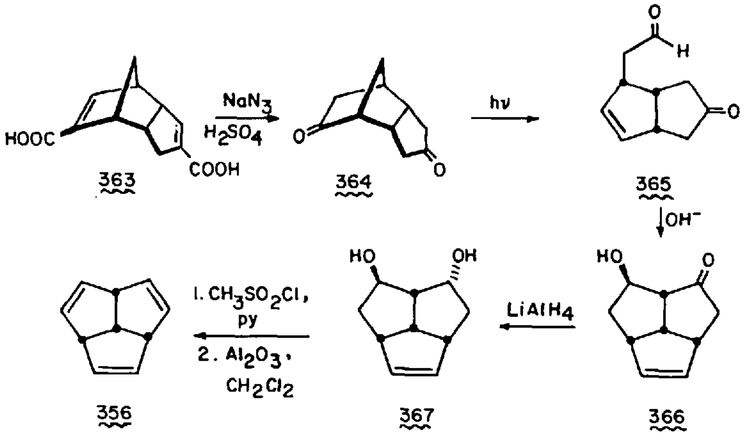
SCHEME 57



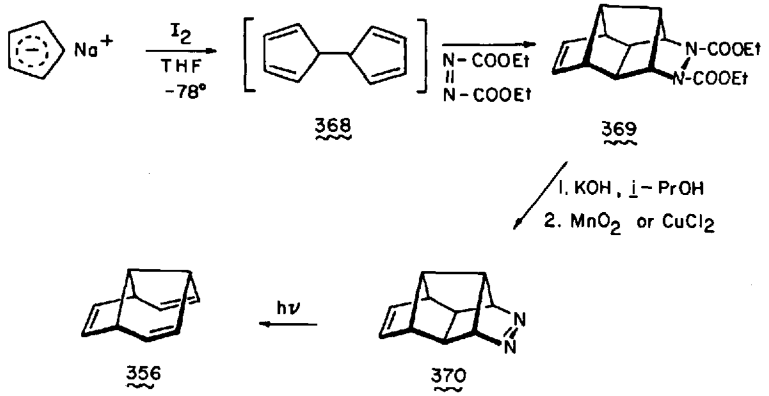
A most expeditious synthesis of triquinacene was described by Deslongchamps and his co-workers in 1973 (Scheme 58).[350] This approach comprised degradation of Thiele's acid (*363*) to diketone *364* and photolysis of this intermediate to give keto aldehyde *365*. Aldolization of *365* led to construction of the tricyclic nucleus; sequential hydride reduction, mesylation, and elimination of this intermediate over alumina efficiently provided *356*.

The shortest synthesis of triquinacene is the four-step conversion from cyclopentadiene described by Wyvratt and Paquette (Scheme 59).[351, 352] Oxidative coupling of sodium cyclopentadienide with iodine generated 9,10-dihydrofulvalene (*368*)[353, 354] which was treated *in situ* with diethyl azodicarboxylate. The resulting

SCHEME 58



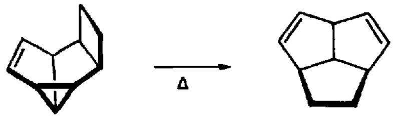
SCHEME 59



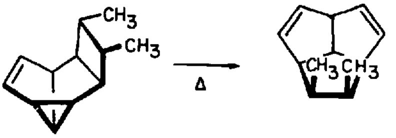
Domino Diels-Alder adduct (*369*) was hydrolyzed and oxidized to give azo compound *370* whose photolysis gave *356* in 60 % yield together with three other $C_{10}H_{10}$ isomers.

2. Preparation of Functionalized Triquinacenes

Cyclobutene has been reported to undergo 1,3 cycloaddition to benzene under photolysis conditions.$^{355)}$ Although the *endo* stereochemistry of the cyclobutane ring in this adduct is assumed (see *371*), pyrolysis of the hydrocarbon at *ca* 250 °C gave dihydrotriquinacene *372* as the major product. Using *cis*-3,4-dimethylcyclobutene, *373* was obtained and similarly transformed to *374* without loss of stereochemistry by thermolysis.$^{376)}$



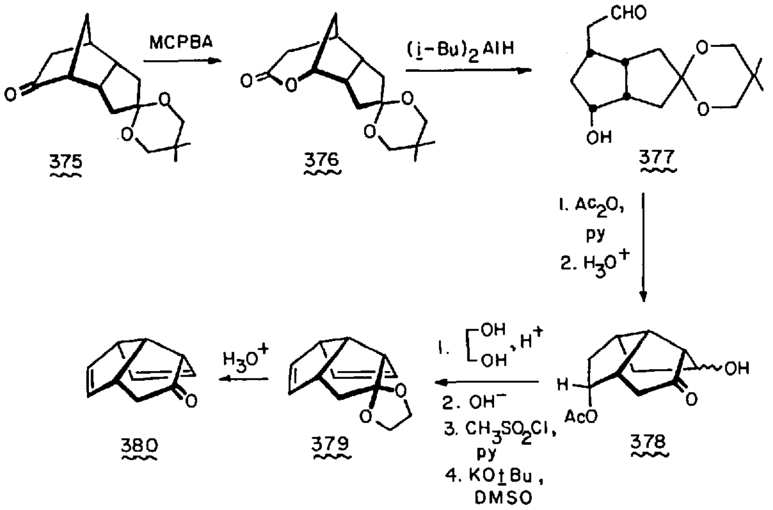
371 372



373 374

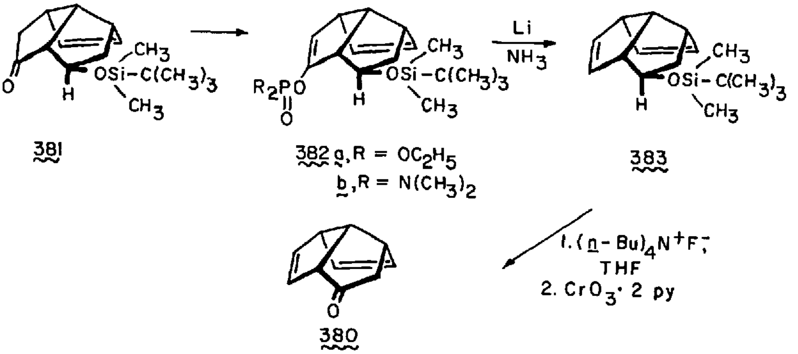
Two syntheses of racemic 2,3-dihydrotriquinacen-2-one (*380*) have been described. The first approach consisted in the selective monoketalization of diketone *364* with 2,2-dimethylpropane-1,3-diol and Baeyer-Villiger oxidation of *375* (Scheme 60).[357)] Although two lactones were produced, *376* could be freed of its isomer by selective alkaline hydrolysis. Diisobutylalumium hydride reduction of *376* afforded *377*, the acetate of which was converted by acid treatment to *378*. Ketalization of this isomeric mixture, followed by hydrolysis, mesylation, and treatment with potassium *t*-butoxide in dimethyl sulfoxide afforded diene ketal *379*. Deketalization then liberated the desired ketone.

SCHEME 60



The second approach capitalized on the availability of hydroxy ketone *366* (Scheme 61).[358)] The derived *t*-butyldimethylsilyl ether (*381*) was transformed to the enol diethyl phosphate (*382a*) or N, N, N', N'-tetramethylphosphordiamidate (*382b*) and reduced with lithium in ammonia. No overreduction was observed, *383*

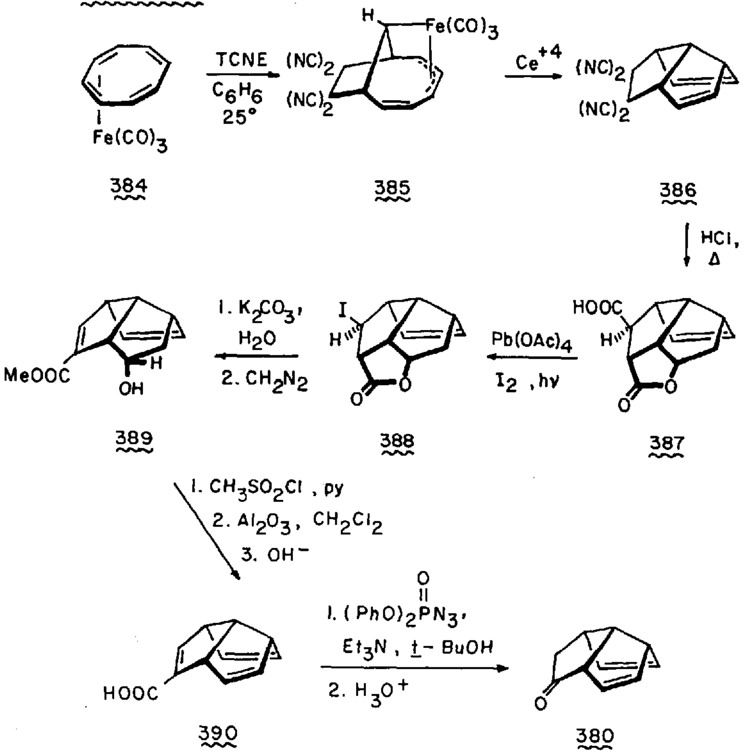
SCHEME 61



being isolated in good yields. Treatment of *383* with tetrabutylammonium fluoride in tretrahydrofuran and Collins oxidation completed the sequence. An improved version of this reaction scheme makes use of the tetrahydropyranyl blocking group.[393)]

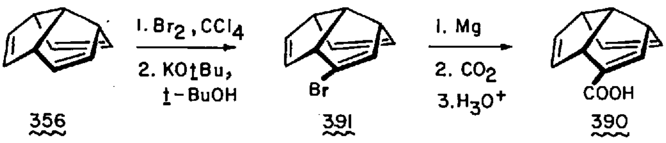
The successful elaboration of optically pure (+)-2,3-dihydrotriquinacen-2-one was accomplished by making recourse to a number of fascinating transformations (Scheme 62). There is special interest in the resolved forms of functionalized tri-

SCHEME 62



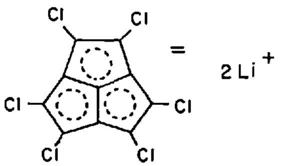
quinacenes because of the existing relationship between the dissymmetry of such molecules and the structural features of the corresponding "dimers" (*vide infra*). When treated with tetracyanoethylene, cyclooctatetraeneiron tricarbonyl (*384*) entered into efficient 1,3 cycloaddition with formation of the σ,π-iron complex *385*.[359, 360] Confirmation of this structural assignment and establishment of the indicated stereochemistry was achieved by X-ray analysis.[360] This process has been shown to be general for a wide variety of cyclooctatetraene derviatives, with interesting directive effects being observed.[361] Oxidative degradation of *385* with ceric ammonium nitrate in 95 % ethanol gave *386* which was converted to acid lactone *387* by hydrolysis with concentrated hydrochloric acid.[358, 362] Treatment of *387* with lead tetraacetate and iodine under conditions of concomitant irradiation gave iodolactone *388* whose hydrolysis with aqueous potassium carbonate solution proceeded with simultaneous dehydroiodination. Esterification of the hydroxy acid with diazomethane afforded *389*. Introduction of the third double bond was effected by direct dehydration with ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt or more conveniently by conversion to the mesylate and exposure to alumina in methylene chloride. Subsequent saponification provided triquinacene-2-carboxylic acid (*390*), the resolution of which was achieved efficiently by fractional crystallization of the (+)-(*R*)-α-phenethylamine salts. The less soluble diastereomer afforded enantiomerically homogeneous (-)-*390* upon acidification. Curtius degradation of (-)-*390* with diphenylphosphoric azide gave optically pure (+)-*380*, whose absolute configuration (as illustrated) was established by appropriate chiroptical measurements.[358]

Woodward and Repic have succeeded in preparing (+)-*390* by sequential bromination-dehydrobromination of triquinacene, formation of the Grignard reagent



from the bromide so obtained (*391*), and carboxylation with carbon dioxide.[363] (–)-Quinine was employed for the resolution.

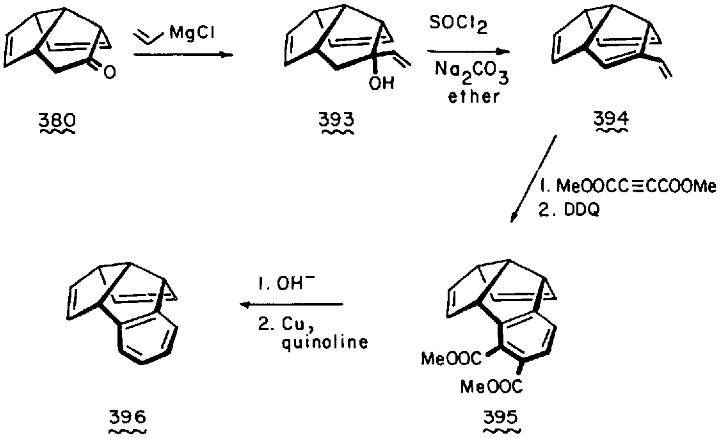
The preparation of dilithium hexachloroacepentylenediide *392* has been claimed, although convincing proof of this structure is not available. The species is stable in solution at –70 °C.[364]



392

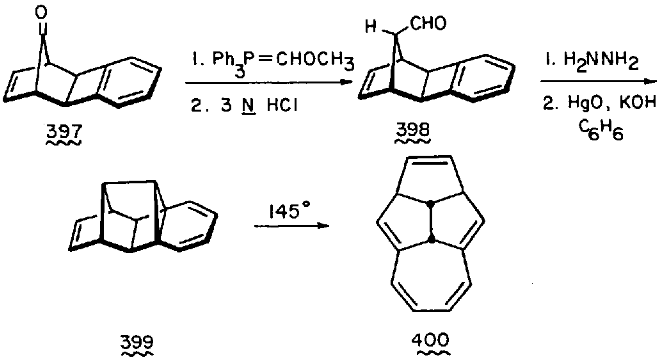
A synthesis of benzotriquinacene (*396*) has recently been described (Scheme 63).[365, 366] Vinylmagnesium chloride transformed ketone *380* into vinyl alcohol *393* whose dehydration gave 2-vinyltriquinacene (*394*). Addition of dimethyl acetylenedicarboxylate to *394* followed by dehydrogenation led to adduct *395* which underwent ready saponification and copper-catalyzed decarboxylation to give *396*.

SCHEME 63



Hydrocarbon *400*, a triquinacene derivative as well as a member of the [12]-annulene family, has also been prepared (Scheme 64).[367] Benzotricyclo-

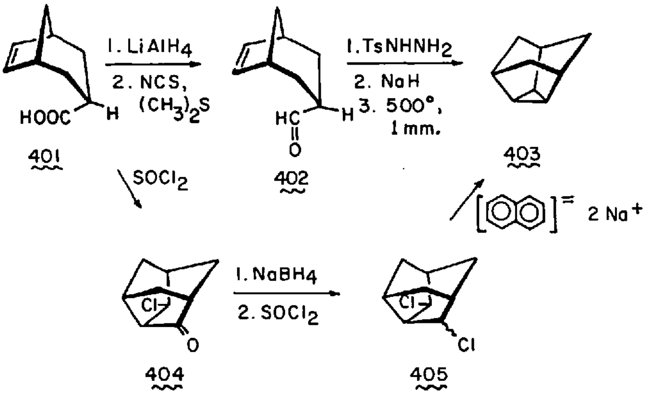
SCHEME 64



[4.2.1.0^{2,5}]nona-3,7-dien-9-one (*397*), available from cyclopentadiene and benzocyclobutadiene,[368] was converted to aldehyde *398* *via* the methoxy Wittig reaction and subsequent acid hydrolysis. Oxidation of the corresponding hydrazone with mercuric oxide led directly to the insertion product *399* which exists in the norcaradiene form. Thermolysis of *399* at 145 °C for 7 min produced *400*.

Finally, we describe the two syntheses of [3]peristylane (*403*) reported by Garratt and White.[369] This hydrocarbon is constructed of three cyclopentane rings which are mutually fused in a manner which also generates a cyclopropane ring. Subsequent to the conversion of norbornadiene to *endo*-3-carboxybicyclo[3.2.1]oct-6-ene (*401*) by an established route,[370] this acid was reduced and reoxidized to the aldehyde level (Scheme 65). Pyrolysis of the sodium salt of the corresponding tosylhydrazone led directly to *403*. Alternatively, treatment of *401* with thionyl chloride resulted in the formation of *exo*-4-chloronoradamantan-2-one (*404*) which was reduced to the corresponding alcohol. Reaction with thionyl chloride provided dichloride *405*, the reduction of which with disodium naphthalenide also gave *403*.

SCHEME 65

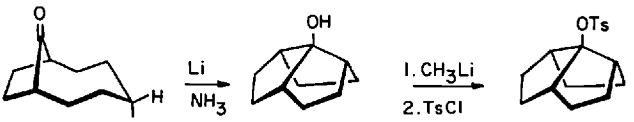


3. Physico-Chemical Studies with Triquinacene Systems

The detailed molecular geometries of triquinacene[371] and perchlorotriquinacene[372] have been revealed by X-ray analysis. Both molecules were observed to have nearly ideal C_{3v} symmetry in the crystal. The ultraviolet spectrum of triquinacene is characterized by a maximum at 187 nm (ϵ 13,000) and a long wavelength shoulder at *ca* 205 nm (ϵ 5,000).[373] Its photoelectron spectrum exhibits two bands at 9.0 and 9.5 eV assigned to ionizations from the e(π) and a_1 (π) levels respectively.[374, 375] This split is much smaller than that seen with 1,4,7-cyclononatriene[376] and C_{16}-hexaquinacene[377] and has been construed to be the result of minimal through-space interaction.[378] This conclusion is in complete agreement with its chemical properties.

Perhydrotriquinacene (*358*) has a gas-phase enthalpy of formation of -102.39 kJ mol^{-1},[379] suggesting that the latent strain in the pentagonal dodecahedrane molecule should be rather lower than that predicted by Allinger's force field calculations[380] and somewhat more comparable to the molecular mechanics prediction advanced by Schleyer.[381] The existing discrepancy arises because both molecules possess an unusually large number of nonbonded H-H interactions, the repulsive nature of which are given undue emphasis in the Allinger approximation.

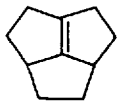
The polychlorination of *358* has already been discussed.[339] Upon reaction with carbomethoxynitrene generated by thermal decomposition of methyl azidoformate, the four possible methyl urethanes are produced. When the product distribution was evaluated on a per-hydrogen basis, a reactivity ratio of 4.0 : 3.8 : 1.0 for the tertiary apical, tertiary nonapical, and methylene positions was denoted.[382] From the behavior of this nitrene toward other systems which suggests that the carbon atom directly involved in the transition state has free radical character, the conclusion was reached that the relative free radical reactivities at the different positions in *358* are quite normal. The conclusion was reached that this hydrocarbon is relatively strain free. The same workers found that chromyl acetate oxidation of *358* resulted in preferential attack at tertiary carbons with the exception that no apical alcohol was produced.[382] This was the first indication that C_{10} is poor in supporting positive charge. Later, this phenomenon was placed on a quantitative basis by Bingham and Schleyer.[383] Available by reductive cyclization of keto tosylate *406*,[384] tertiary alcohol *407* was converted to its tosylate (*408*) by conventional methodology. This



406 407 408

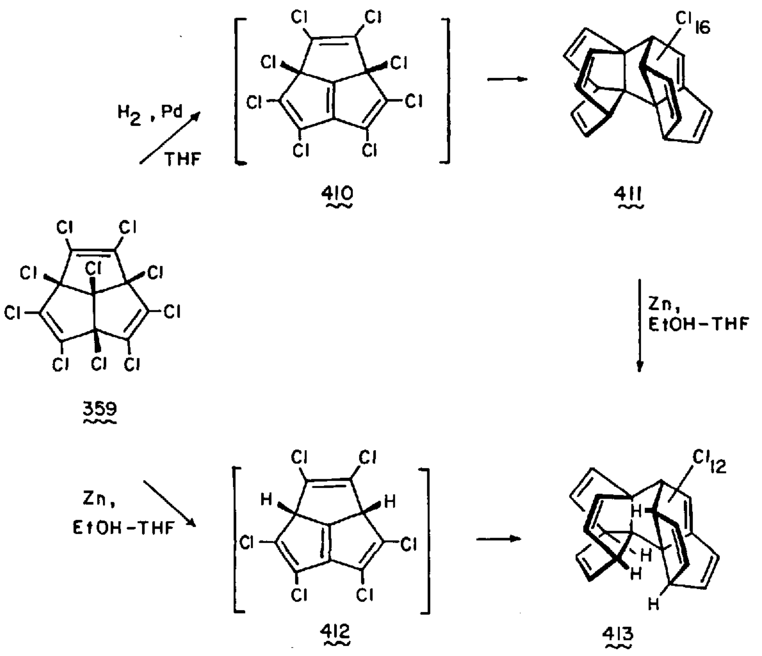
molecule was found to solvolyze at a rate 10^9 times slower than that predicted on the basis of semiempirical calculations involving total strain energies. It was suggested that an electronic effect not taken into account by such theory but accentuated by the unique geometry of *408* is the origin of this discrepancy. The hypothesis was advanced that the level of stabilization available to a nonplanar carbocation is dependent upon the dihedral angles between the substituents on the charged carbon and an adjacent atom, maximum stabilization being realized when the most stabilizing substituent is *trans-staggered* with the vacant orbital.

When treated with aluminum chloride in refluxing hexane, perhydrotriquinacene was rapidly isomerized to adamantane.[382] Exposure of 1-, *exo*-2, or *endo*-2-perhydrotriquinacenol to fluorosulfonic acid, followed by aqueous quenching, has been shown to produce 1-adamantanol. McKervey and his co-workers have found that *358* exchanges ten hydrogen atoms when subjected to exchange with deuterium and palladium.[385] On this basis, the prediction was made that olefin *409* (presently an unknown molecule) should be a compound of moderate stability.



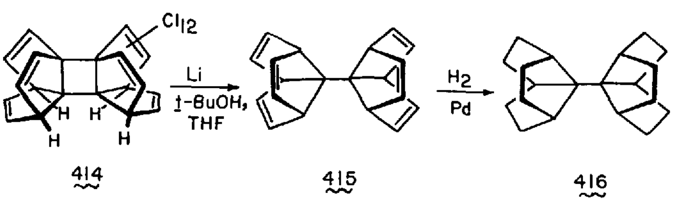
409

In this connection, Jacobson has observed that the mild catalytic hydrogenation of perchlorotriquinacene (*359*) gave dimer *411* while reduction with zinc dust in a



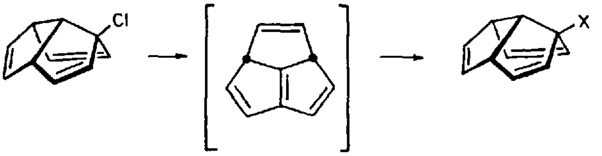
tetrahydrofuran-ethanol solvent system produced *413*.[386] The intermediates which were invoked were *410* and *412*, respectively. The dimers proved to be interconvertible chemically. Furthermore, at 200 °C they appear to exist in equilibrium with their monomers *410* and *412*. In a pivotal experiment, a solution of *411* and ethylene in carbon tetrachloride was found, after heating briefly to 210 °C, to contain the Diels-Alder adduct of *410* and ethylene.[386]

Upon heating to 280 °C for short periods of time, *413* can be rearranged to the more stable cyclobutanoid isomer *414*. Reductive dechlorination of this dimer pro-



duced the fascinating molecule *415* which could, of course, be hydrogenated to *416*.[387]

Additionally, *417*, which can be prepared admixed with 1,4-dichloro- and 1,4,7-trichlorotriquinacene upon photochlorination of *356* with *t*-butyl hypochlorite in



417 418 419 a, X = OH

b, X = OCH_3

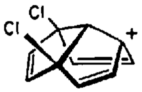
c, X = $N(CH_3)_2$

$CFCl_3$ at −50 °C, has been reported to undergo complete hydrolysis to *419a* within 30 minutes at room temperature in 80 % dioxane-water.[388] Methanolysis gave *419b* and reaction with dimethylamine *419c*. Dehydrotriquinacene (*418*) is believed to be the key intermediate in these reactions.

That this mechanistic pathway is followed is of some interest since the 1-triquinacenyl cation (*420*) has been shown on the basis of semiempirical calculations to be a twofold allyl-stabilized bridgehead ion.[389] This cation, as well as *421* and *422*, could be generated by allowing the respective chlorides to react with antimony pentafluoride in SO_2ClF at −78 °C.[388] The ^1H and ^{13}C NMR spectra have been recorded and suggest that almost planar divinyl carbonium ion units are present in

420

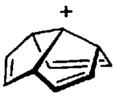
421



422

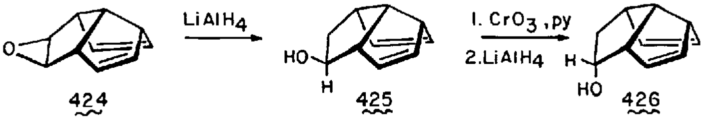
these species. Their relative kinetic stability increases with increasing chlorine substitution. Thus, *420* underwent decomposition at −40 °C whereas *422* could still be detected after 15 minutes at 25 °C. These cations were also trapped with sodium methoxide in methanol.

Interestingly, Bischof predicts that cation *423* ought to be stabilized as well, although to a lesser extent, because of σ-π interaction.[389] This point remains to be tested experimentally.

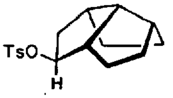


423

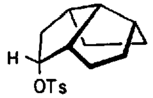
Upon peracid oxidation, triquinacene was converted to exo epoxide *424* in 75 % yield. Lithium aluminum hydride reduction of *424* in tetrahydrofuran afforded *425*; oxidation and a second reductive step gave the *endo* epimer *426*.[373] As expected, the infrared spectrum of *426* (but not that of *425*) possesses a characteristic band of intramolecularly hydrogen-bonded hydroxyl at 3548 cm^{-1}, shifted 50 cm^{-1} from the free OH band at 3598 cm^{-1}. Catalytic hydrogenation provided the saturated epimeric



424 425 426

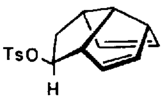


$k_{rel}^{100^\circ}$ 16.4

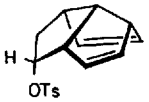


$k_{rel}^{100^\circ}$ 5.2 $k_{exo/endo} = 3.2$

alcohols. The four derived tosylates have been subjected to acetolysis in buffered acetic acid. The relative rate data are given below:



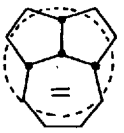
$k_{rel}^{100^\circ}$ 4.4



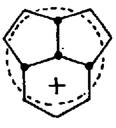
$k_{rel}^{100^\circ}$ 1 $k_{exo/endo} = 4.4$

The *exo/endo* rate ratio in the unsaturated series compares closely to that observed with the saturated tosylates; homoconjugative interaction is therefore not apparent. Also, the products were those expected for solvolysis without participation.[373)] The dihydrotriquinacenyl tosylates solvolyze more slowly due the inductive contributions of the double bonds. The geometry of the pπ orbitals in the *exo* isomer are seen to have a very poor alignment for neighboring group participation.

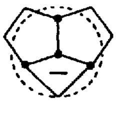
In a recent series of investigations, precursors to the "anchored" trishomoaromatic cyclooctatetraenide (*427*),[390)] tropylium (*428*),[391, 392)] and cyclopentadienide (*429*) systems[393)] were synthesized, but no evidence for extended homoaromaticity[394)] was found upon generation of these ions.



427

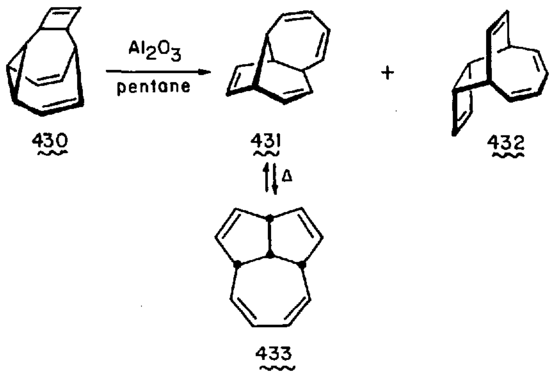


428

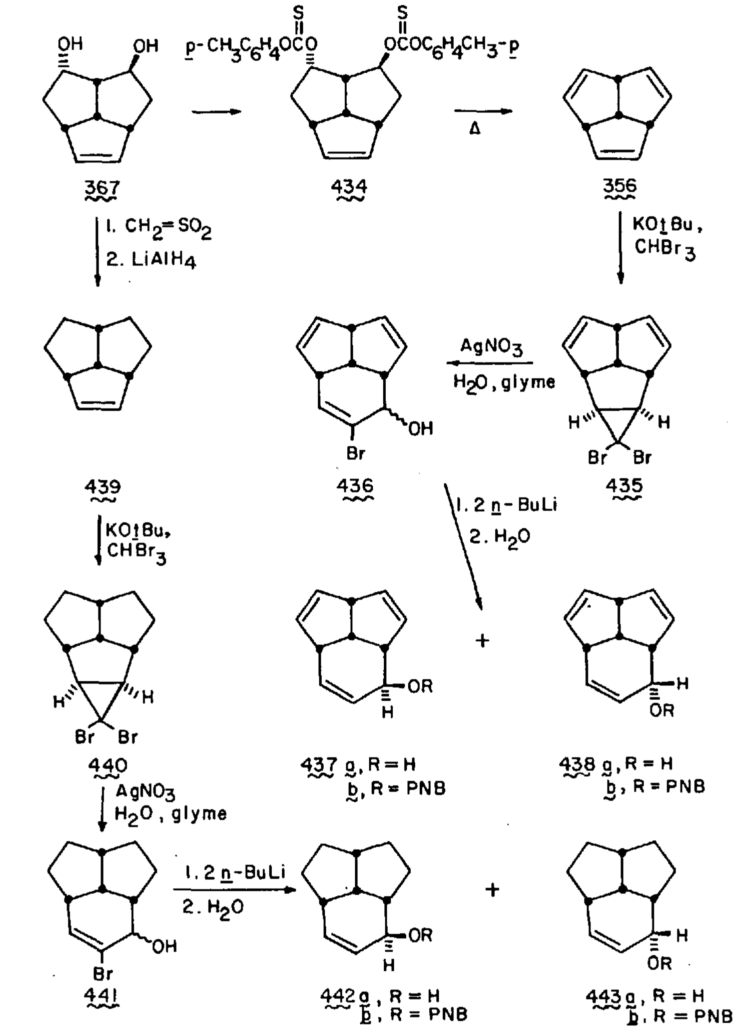


429

Tetraene *433* was prepared in two steps from the readily available Schröder hydrocarbon *430*.[395)] Woelm activity I neutral alumina caused rearrangement of *430* to a mixture of *431* and *432*. Thermolysis of *431* at 380 °C in a flow system afforded *433*.[390)] Dissolving metal reduction of *433* did not give a rise to a spectroscopically recognizable dianion species. Electrochemical measurements were equally disappointing.


Al_2O_3
pentane
430
431
+
432
Δ
433

SCHEME 66

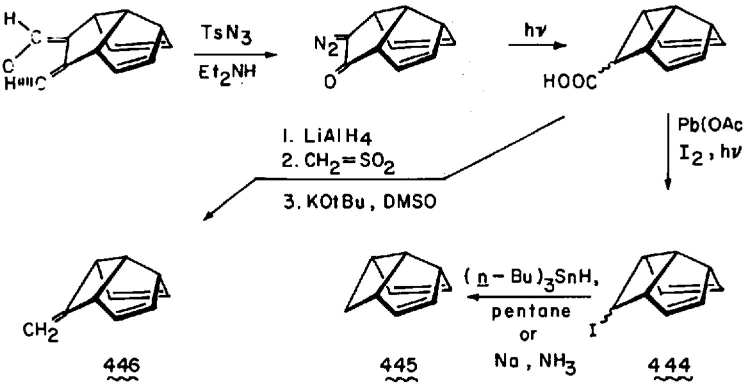

OH
OH
p-$CH_3C_6H_4OC$(=S)O
OC(=S)$OC_6H_4CH_3$-p
367
434
Δ
356
1. $CH_2=SO_2$
2. $LiAlH_4$
KOtBu, $CHBr_3$
AgNO$_3$
H_2O, glyme
OH
Br
H
H
Br
Br
439
436
435
KOtBu, $CHBr_3$
1. 2 n-BuLi
2. H_2O
+
OR
H
H
OR
H
H
Br
Br
440
437 a, R = H
b, R = PNB
438 a, R = H
b, R = PNB
$AgNO_3$
H_2O, glyme
1. 2 n-BuLi
2. H_2O
+
OH
Br
OR
H
H
OR
441
442 a, R = H
b, R = PNB
443 a, R = H
b, R = PNB

New synthetic approaches to triquinacene and its tetrahydro derivatives were developed to gain access to the four *p*-nitrobenzoates whose structures are given in Scheme 66.[392] In both instances, *exo,endo* diol *367* served as starting material. Conversion to bisthionocarbonate *434*[396] and heating to 230 °C gave triquinacene in 60–70% yield. Pyrolysis of the diacetate has proven to be equally expeditious.[397] Reaction of *356* with dibromocarbene gave predominantly *435* which could be ring expanded to *436* on exposure to silver nitrate in aqueous dimethoxyethane. The preferred debromination of *436* consisted of its its inverse addition to two equivalents of *n*-butyllithium followed by quenching with water. The stereochemical assignments to *437a* and *438a* were made on the basis of spectral data and oxidation to the related ketone whose reduction with diisobutylaluminum hydride returned *438a*. Tetrahydrotriquinacene (*439*) was readily prepared by hydride reduction of the dimesylate of *367*. Application of the same reaction sequence led to *442a* and *442b*.

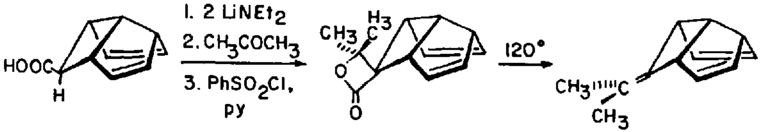
Kinetic measurements involving the four *p*-nitrobenzoates revealed their rates of ionization to differ by a factor of only 43 at 111 °C, with the more highly unsaturated molecules again proving to be the less reactive.[392] These findings were interpreted in terms of the absence of neighboring double bond participation. Neither could evidence for trishomotropylium ion character be gained from studies in superacidic media.[391, 392]

The approach employed for the preparation of nortriquinacene derivatives was based upon ring contraction of the α-diazocarbonyl derivative and subsequent degradation of the epimeric carboxyl derivatives (Scheme 67).[393] All attempts to deprotonate hydrocarbon *445* have proven unsuccessful. Metal reduction studies on *444* and the related chlorides also failed to provide evidence for formation of a stabilized carbanion. Calculations agree with the absence of significant homoconjugation in *429*. For example, this species is predicted to have a pyramidal rather than a trigonal anionic carbon.[393] In addition, *exo*-methylene derivatives of nortri-

SCHEME 67



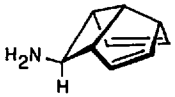
quinacene such as *446* and *447* show no chemical or ^{13}C NMR evidence for homoconjugative interaction. Photoelectron spectroscopy has also confirmed that the exocyclic double bond does not interact with the endocyclic π bonds in these systems.[398)]



447

To gain information on the thermodynamic stability of *429* relative to other $(CH)_9^-$ isomers as well as the full complement of reversible charge control criteria for the nortriquinacene ring system, Paquette and co-workers have studied the pericyclic transforms of *429* and the related cation *448*.[399)] Upon deamination of amine *449*, prepared by Curtius degradation of the exo carboxylic acid, clean conversion to alcohol *450a* was observed. Quantitatively similar results were found when *exo-444* was exposed to silver perchlorate in aqueous acetone. When *p*-nitrobenzoate *450b* was subjected to methanolysis, a 7 : 1 mixture of *450c* and the likewise unrearranged

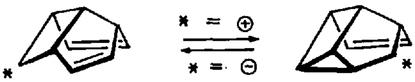
448



449

450 a, R = OH
b, R = OPNB
c, R = OCH_3
d, R = Cl

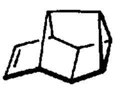
endo methyl ether was obtained. No proclivity for skeletal rearrangement to *448* was apparent. On the anionic side, dissolving metal reduction of *444* provided nortriquinacene (*445*) exclusively. When chloride *450d* was comparably reduced, *445* was produced predominantly. This evidence has established that carbon skeletons *445**



445* 450*

and *450** are interconvertible merely by controlling the formal charge (*) on the system.

When dilute solutions of triquinacene in pentane were irradiated in a quartz falling-film recycling apparatus at –40 °C, there occurred slow photoisomerization



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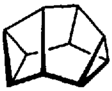
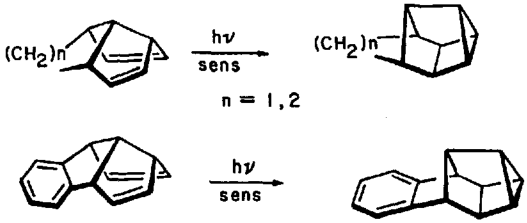
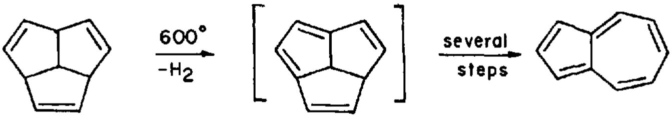


452

to eight products.[400)] Although none of these proved to be diademane (*362*), the two principal new structures were the novel pentacyclic and hexacyclic molecules *451* (26 %) and *452* (49 %). The triplet-sensitized photorearrangements of 2,3-dihydrotriquinacene, nortriquinacene, and benzotriquinacene have also been examined and found to proceed exclusively *via* intramolecular [$2\pi + 2\pi$] cycloaddition.[401)] An all-encompassing mechanistic scheme has been delineated.[401)]

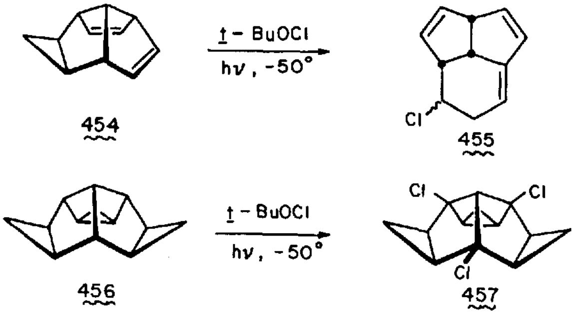


Scott and Agopian have described the thermal conversion of triquinacene to azulene at 600 °C in a quartz flow system.[402)] The process requires the loss of two hydrogen atoms, possibly as molecular hydrogen. The dehydrotriquinacene *453* could be a key reactive intermediate.



453

When subjected to the Conia modification of the Simmons-Smith reaction or cuprous chloride-catalyzed diazomethane decomposition, triquinacene was converted to two monocyclopropanated, two doubly cyclopropanated, and two triply cyclopropanated products.[403)] Subsequent photochlorination of *454* with *t*-butyl hypochlorite at −50 °C has been shown to proceed with ring expansion and formation of *455*.[404)] In contrast, *all-exo*-trishomotriquinacene (*456*) could be converted to trichloride *457* with retention of the hexacyclic carbon framework.[404)]



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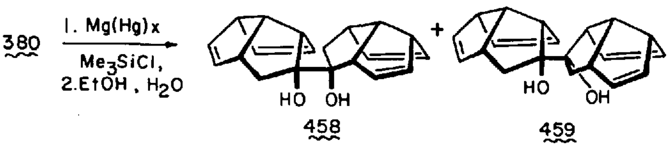
455

456

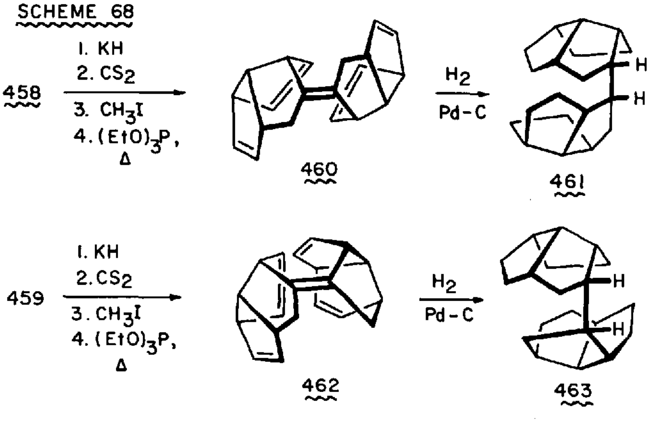
457

4. Coupling of Triquinacenes. The Bivalvanes and Related Molecules

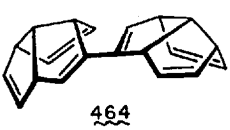
Due to the inherent dissymmetry of monosubstituted triquinacenes, dimerization of such compounds will generate a pair of coupling products (*meso* and *dl*) if the *monomer* is *racemic*. Only when bonding between optically pure triquinacenes of the same chirality results can it be guaranteed that the formation of *meso* dimer will be precluded. In their study of the pinacolic reduction of *dl*-2,3-dihydrotriquinacen-2-one, Paquette and co-workers showed that approximately equal amounts of the *dl* diol *458* and *meso* isomer *459* resulted.[405] When enantiomerically pure (+)-*380* was used, *458* was the exclusive reductive coupling product because of enforced enantiomer recognition. Strong preference for *exo,exo* carbon-carbon bond formation was evident. Analogous results were obtained with *racemic* and optically pure hexahydrotriquinacen-2-one. Conversion of these diols to their thionocarbonates and subsequent treatment with triethyl phosphite at the reflux temperature provided such olefins as *460* and *462* stereospecifically (Scheme 68). Their individual catalytic reduction provided *dl*- and *meso*-bivalvane (*461* and *463*), respectively.[405]



SCHEME 68



In the above study, diols *458* and *459* were separated by preparative high pressure chromatography. A rapid, efficient, and nondestructive separation of dimers in the *dl* series from those of the meso type which involves no chromatography has also been devised.[406] The procedure involves direct dehydration of the *458*/*459* mixture, preferably with phosphorus oxychloride in pyridine, and treatment of the unpurified hexaenes *464* and *465* with 0.5 molar equivalent of N-methyltriazolinedione at low temperature. Under such conditions, only the *meso* isomer enters into Diels-Alder reaction since only the s-*cis* conformation of its conjugated diene moiety makes possible simultaneous *exo* bonding of the dienophile to both termini. Adduct *466* was precipitated from solution leaving pure *464* in the supernatant. Submission of the adduct to hydrolysis-oxidation returned *465*. The alkali metal-ammonia reduction of *464* and *465* has been examined for its stereochemical outcome.[406)]



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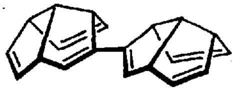

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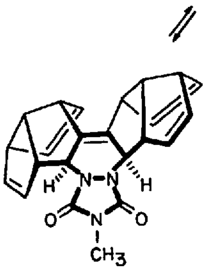
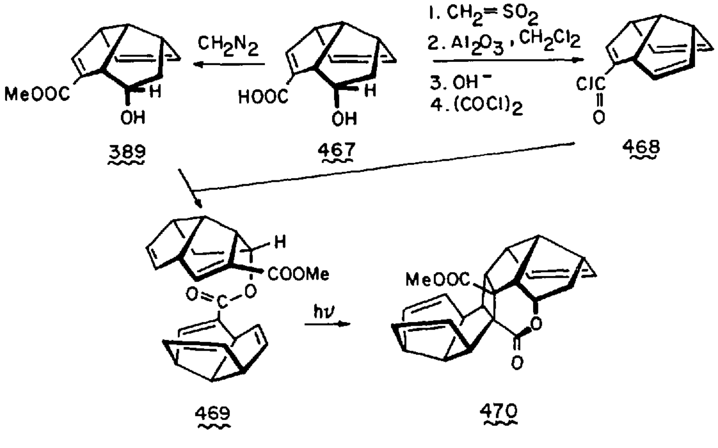


466

For purposes of stereochemical control, Woodward and Repic first resolved hydroxy acid *467* with (–)-quinine.[363)] The optically active material was then in part treated with diazomethane to give (+)-*389* and in part converted to the (+)-acid chloride *468* (Scheme 69). When the two resolved triquinacene halves (necessarily of the same chirality) were combined in the presence of lithium 2,2,6,6-tetramethylpiperidide, diester *469* was obtained. Upon irradiation in acetonitrile solution

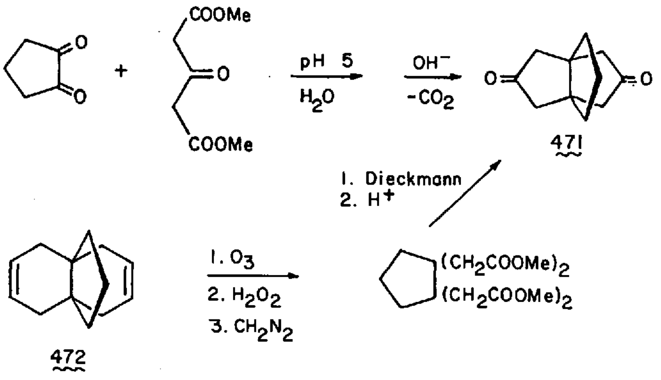
SCHEME 69



through Pyrex in the presence of *m*-methoxyacetophenone as sensitizer, *469* cleanly underwent [$2\pi + 2\pi$] closure to *470*. This ester lactone proved to be extremely resistant to hydrolysis by hydroxide ion and to ring opening with a variety of other reagents. Pyrolysis of the derived diester has yet to be examined as a possible route to dicarbomethoxydodecahedrane.

D. [3.3.3]Propellanes

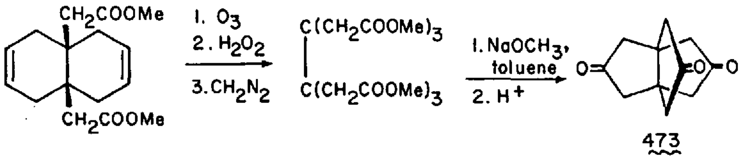
By condensation of cyclopentane-1,2-dione with dimethyl β-ketoglutarate, Weiss and Edwards were able to prepare the [3.3.3]propellanedione *471*,[174] a molecule in which three cyclopentane rings are conjoined through a common carbon-carbon



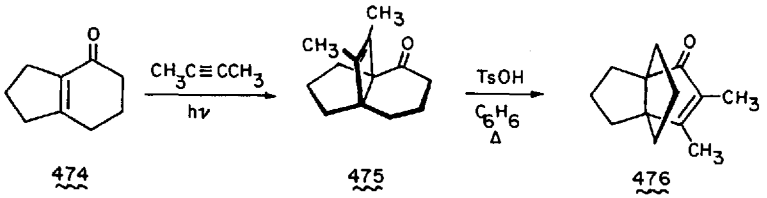
bond.[407] The structure of this diketone was later proved by an oxidation-cyclization sequence beginning with *472*.[408]

A closely comparable approach was utilized in the preparation of [3.3.3]propellane-3,7,10-trione (*473*, Scheme 70).[408]

SCHEME 70

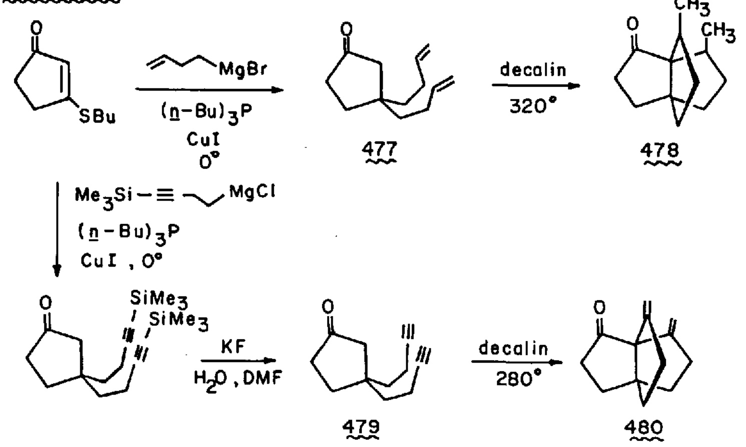


In an alternative route to such molecules, Cargill and Crawford demonstrated that the photocycloadduct of cicyclo[4.3.0]non-1(6)-en-2-one (*474*) and 2-butyne, *i.e.*, *475*, was subjected to acid-catalyzed isomerization with formation of *476*.[409]

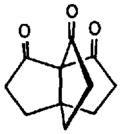


Conia has prepared the interesting [3.3.3]propellanes *478* and *480* by thermal cyclization of the appropriate β,β-disubstituted cyclopentanones *477* and *479*, respectively (Scheme 71).[410, 411]

SCHEME 71



Through careful ozonolysis of *480* in the presence of pyridine, it has proved possible to prepare triketone *481*. The X-ray crystal structure analysis of *481* clearly



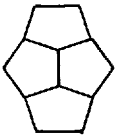
481

shows the lack of repulsive interaction between the keto groups. Instead, weak attractive interactions appear to prevail.[412)] The photoelectron spectrum shows couplings between the *n* orbitals on the oxygen atoms, the energy level separation being 0.50 eV.

A significant number of heteroatomic [3.3.3] propellanes have been described.[413)]

VIII. The Elaboration of Tetraquinane Frameworks

Of the four non-propellane members of the tetraquinane family, one is a dodecane derivative (*482*), one is composed of thirteen carbon atoms (*483*), and two are tetradecanes (*484* and *485*). Chemistry relating to these systems is just beginning to evolve and future developments in this area are awaited.



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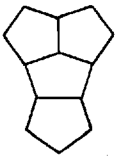

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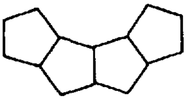

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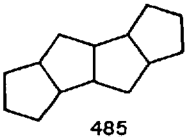
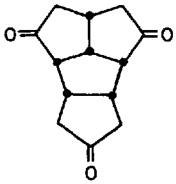


485

Three tetracyclo[5.5.1.$0^{2,6}$.$0^{10,13}$]tridecanes are known at present. The reaction of glyoxal with dimethyl 3-ketoglutarate in aqueous solution at room temperature and pH 5 to give after treatment with acid *cis*-bicyclo[3.3.0]octane-3,7-dione has been discussed previously. More careful study of this condesation has led to the discovery that the two tetracyclic triketones *486* and *487* are also formed in low



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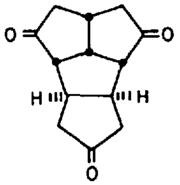
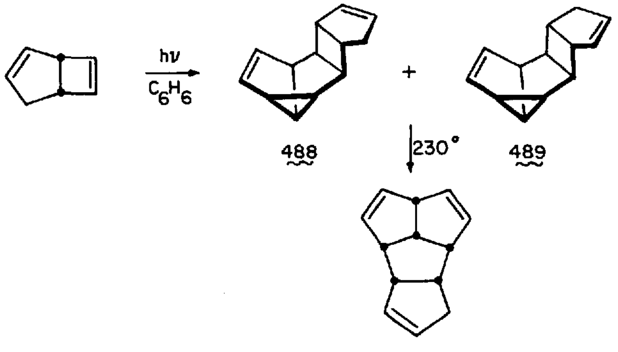


487

yield.[175] An X-ray crystal structure analysis has been performed on the *all-cis* isomer.[414]

In a most elegant manner, Srinivasan has prepared hydrocarbon *490* from benzene and cycloheptatriene in only three steps.[356] Thus, irradiation of a benzene solution of bicyclo[3.2.0]hepta-2,6-diene gave a mixture of *488* and *489* as major

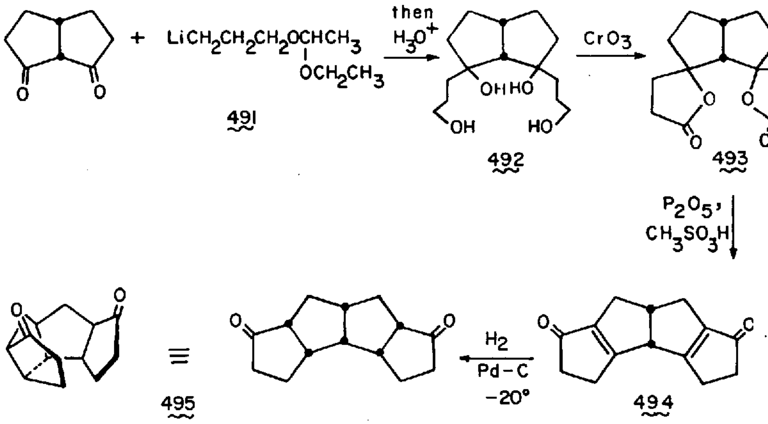


488 489 490

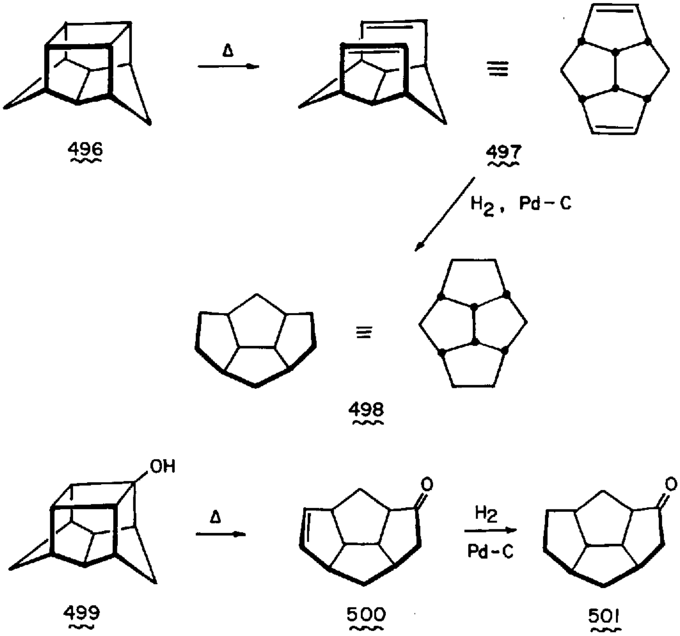
products. When heated at 230 °C for 90 minutes, these pentacyclic photoadducts were observed to rearrange smoothly to *490*.

Eaton and his co-workers found it possible to prepare the tetracyclo[6.6.0.$0^{2,6}$.$0^{10,14}$]tetradecanes *494* and *495* through implementation of the double annulation sequence illustrated in Scheme 72.[46, 60, 415] Twofold addition of the 3-lithiopropyl acetaldehyde acetal *491* to *cis*-bicyclo[3.3.0]octane-2,8-dione followed by hydrolysis afforded tetraol *492*, the oxidation of which gave dilactone *493*. Intramolecular Friedel-Crafts acylation within *493* was effected preferably with phosphorus pentoxide in methanesulfonic acid. Catalytic hydrogenation of *494* could be accomplished with good overall stereoselectivity when carried out at −20 °C in acetone over palladium-on-carbon.

SCHEME 72



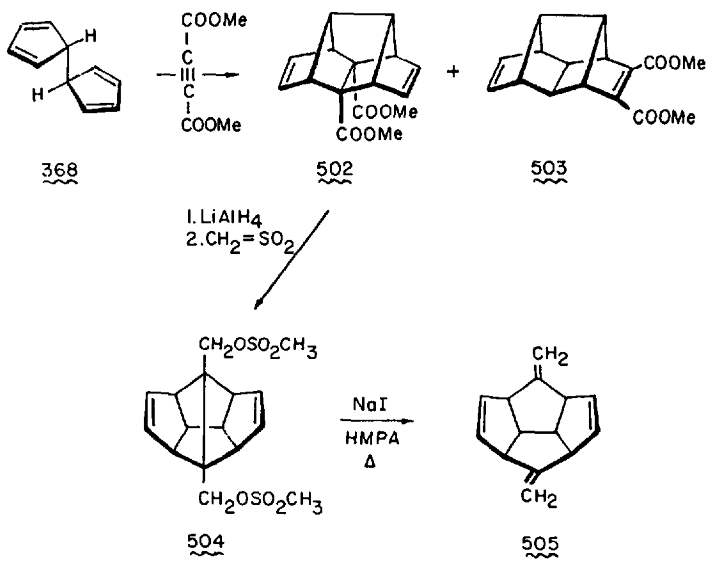
SCHEME 73



As a consequence of the fact that the *all-cis*-tetracyclo$[7.2.1.0^{4,11}.0^{6,10}]$dodecane framework can be considered a molecular cornerstone for possible elaboration of the pentagonal dodecahedrane, it is the tetraquinane framework which has attracted the greatest attention. The parent saturated hydrocarbon has been demonstrated by Fukunaga and Clement to be amenable to ready synthesis (Scheme 73).[416] Thus, pyrolysis of birdcage hydrocarbon *496* over heated quartz chips at 500–600 °C afforded *497* which proved, somewhat surprisingly, to be an air-sensitive, colorless wax. Its tetrahydro derivative *498* is an air stable but tacky substance. The birdcage alcohol *499* rearranged more reaily than *496*; the resultant cyclobutane cleavage was again decidedly regiospecific in the direction of the least strained ketone *500*. Catalytic hydrogenation of the latter compound readily gave *501*.

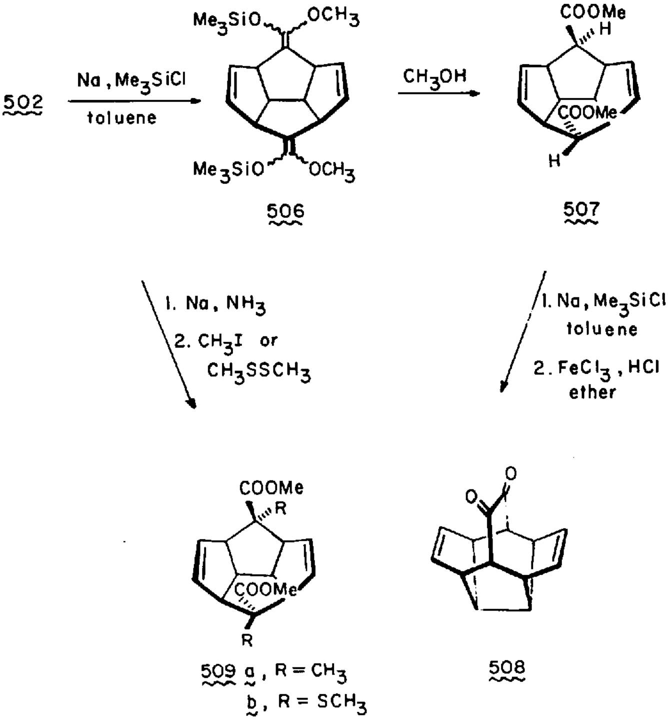
9,10-Dihydrofulvalene (*368*) has been reported to enter into Domino Diels-Alder cycloaddition with dimethyl acetylenedicarboxylate to give an *ca* 1 : 1 mixture of the polycondensed diesters *502* and *503* (Scheme 74).[352, 354, 417] These products can be most readily separated by selective saponification of the less hindered isomer. Both molecules contain the fundamental *all-cis*-tetracyclo$[7.2.1.0^{4,11}.0^{6,10}]$dodecane nucleus but with an additional bond across the central portion. In *502*, this linkage can be cleaved by a number of methods to produce appreciably more functionalized derivatives of the parent system. The first method to be applied involved its reduction with lithium aluminum hydride and conversion of the resulting diol to dimesylate *504*.[352, 417] Subsequent heating of *504* with sodium iodide in anhydrous hexamethylphosphoramide at 130 °C for 48 hr afforded the tetraene *505*. In the ^1H NMR spectrum of *505*, the eight olefinic protons appear as two four-proton singlets at δ 5.28 and 4.83, the remaining four hydrogens appearing as a rather narrow multiplet at δ 3.80–3.35. Its inherent molecular symmetry was

SCHEME 74



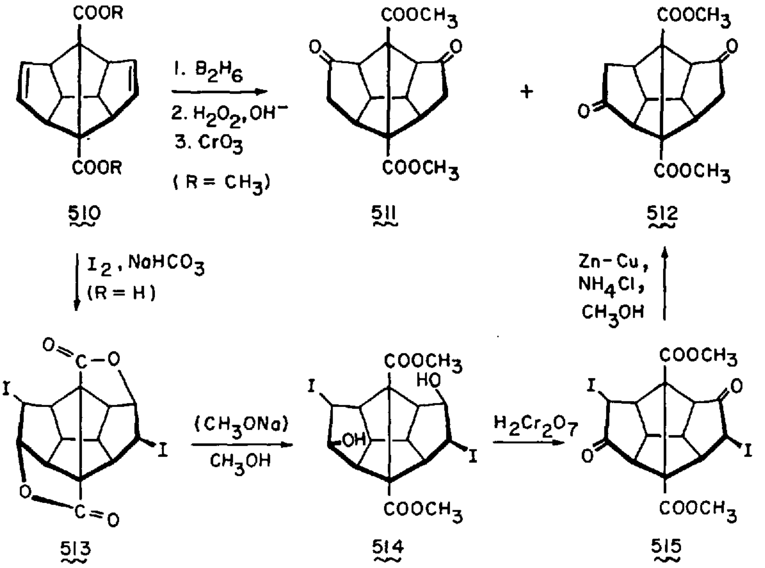
further revealed by its five-line ^{13}C NMR spectrum. Unlike *497* and *500*, *505* is stable to the atmosphere.

A more direct method of cleavage has been developed which consists of heating *502* overnight in toluene with a dispersion of sodium and chlorotrimethylsilane.[352, 418] This procedure led efficiently to *506* whose hydrolysis with dry methanol (kinetic quenching) resulted in the production of a mixture of dihydro diesters rich in *507* (77 %). The structurally rigid *508* and related α-diketones have subsequently been elaborated from this diester as starting material.[418] Related *endo,endo* diesters bearing external methyl and methylthio substituents (*509*) have also been synthesized.[419]



Diketo diester *512* has played a key role in one of Paquette's approaches to the pentagonal dodecahedrane. Direct hydroboration-oxidation of *502* provided as the principal product the unwanted isomer *511* (49 %) rather than *512* (30 %). This complication was circumvented by the improvisation of the "cross-corner" oxygenation sequence outlined in Scheme 75.[420, 421] The iodolactonization of diacid *510* proceeded with high efficiency to give *513* which underwent cleavage to *514* in the presence of methanolic sodium methoxide at room temperature. Oxidation to α-iodo ketone *515* followed by reductive deiodination with zinc-copper couple and ammonium chloride in methanol solution furnished isomerically pure *512*.

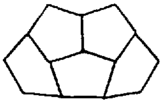
SCHEME 75



IX. The C_{14}-Pentaquinane System

Because of the cumbersome and usually exasperating nature of the von Baeyer system of formal nomenclature,[422] especially when applied to complex polycyclic systems, a colloquial nomenclature has been developed for the higher polyquinanes.[415, 423] The system applies only to polycondensed, fused, equal-size ringed molecules (no spiro fusions) and states the total number of carbon atoms, the number of basic rings, and their size. An indicator of ring juncture stereochemistry is also required; on occasion, a symmetry designation must be added. Thus, *all-cis-484* is (C_s)-C_{14}-tetraquinane and *all-cis-485* is (C_2)-C_{14}-tetraquinane.

Six fundamental pentaquinane systems are possible; of these, *516* is composed of fourteen carbon atoms, *517* of fifteen carbon atoms, *518* and *519* of sixteen carbon atoms, and *520* and *521* of seventeen carbon atoms.[423] The little that is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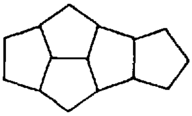
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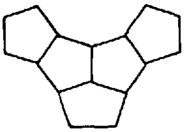
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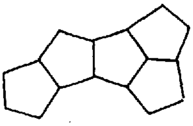
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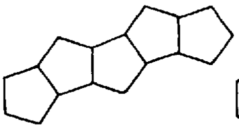
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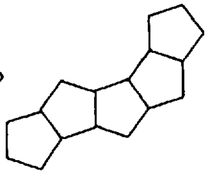
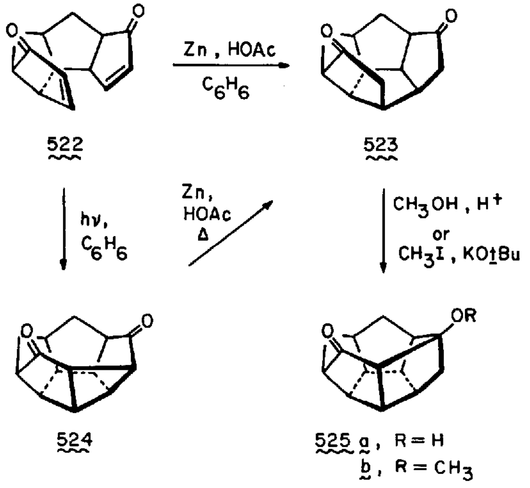

521

known about these systems is due to Eaton who found it possible to prepare the C_{14}-pentaquinane system from the (C_s)-C_{14}-tetraquinane precursor *495*.[60, 415] Double bonds were introduced into the terminal rings of *495* by bromination-dehydrobromination of intermediate ketals. When the resulting bis-enone (*522*) was treated with zinc and acetic acid, *trans*-skeletal reductive coupling occurred to produce *523* (Scheme 76). In actuality, this transformation was better carried out by a less direct procedure consisting of the photochemical closure of *522* and subsequent reductive cleavage of the 1,4-dicarbonyl system. Seemingly, *523* is prone to aldolization giving *525a*. In a related process, reaction of *523* with acidic methanol or methyl iodide and base cleanly furnished methoxy ketone *525b*. The driving force for such closures has been attributed to steric relief from crowding by the internal methylene hydrogens.

SCHEME 76

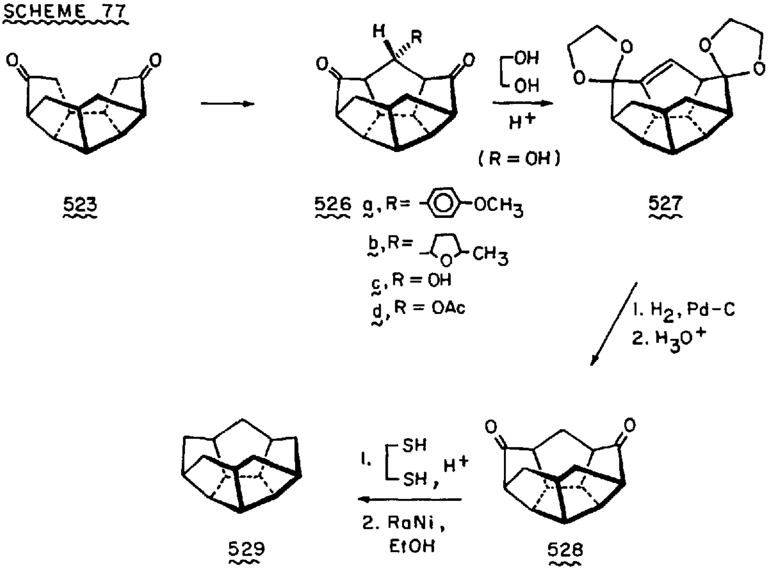


X. Synthetic Approaches to Hexaquinacenes

A. Peristylanes (C_{15}-Hexaquinanes)

Dione *523* has been shown to condense readily with aldehydes such as *p*-anisaldehyde and 5-methylfurfural in aqueous alcoholic sodium hydroxide with formation of peristylanes *526a* and *526b*.[415] A comparable reaction occurred with ethyl formate to give *526c*, although in this case the procedure is more delicate and requires closer attention. The alcohol was not isolated as such but converted directly to its acetate (*526d*). Further, treatment of *526c* with ethylene glycol and acid afforded *527* which was hydrogenated and hydrolyzed to produce *528* (Scheme 77). The peristylane hydrocarbon (*529*) was obtained by thioketalization of the 2,6-dione (*528*) with

SCHEME 77

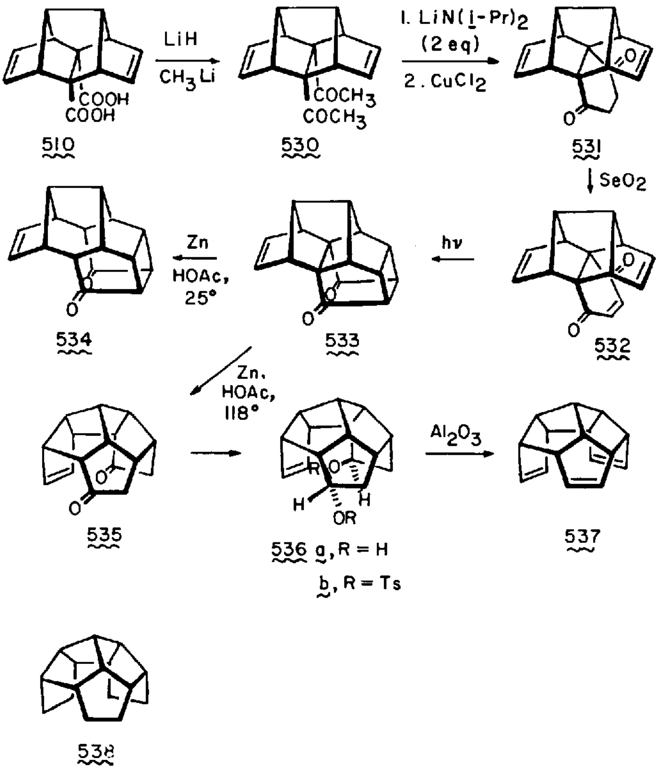


ethanedithiol and acid, followed directly by reduction with Raney nickel in refluxing ethanol. In agreement with the fivefold symmetry of this fascinating $C_{15}H_{20}$ molecule, its 270 MHz ^{1}N NMR spectrum shows only four groups of absorptions of equal intensity and its ^{13}C NMR spectrum consists of only three signals.

B. C_{16}-Hexaquinacenes

The equally aesthetically pleasing C_{16}-hexaquinacene molecule (*537*) has recently been synthesized in nine steps from sodium cyclopentadienide (Scheme 78).[424)] Dicarboxylic acid *510*, which can be obtained directly from cycloadditon of dimethyl acetylenedicarboxylate to 9,10-dihydrofulvalene followed by hydrolysis, was treated with lithium hydride and methyllithium to give diketone *530*. To generate the 1,4-cyclohexanedione part structure of *531* without the complication of aldolization, *530* was first treated with two equivalents of lithium diisopropylamide in tetrahydrofuran-hexane at −78 °C and the resulting bis-enolate anion solution was added inversely to anhydrous cupric chloride dissolved in dimethylformamide. Subsequent heating of *531* with selenium dioxide in dioxane gave *532* with retention of molecular C_{2v} symmetry. Photocyclization of *532* (benzene, 3500 Å) afforded the cage diketone *533* which underwent cleavage of its internal bond upon treatment with zinc and acetic acid at room temperature. At the reflux temperature, both 1,4-dicarbonyl systems were reduced to deliver *535*. Sequential hydride reduction, tosylation, and alumina-promoted elimination of this diketone provided C_{16}-hexaquinacene (*537*). Catalytic hydrogenation of the triene led to the parent saturated hydrocarbon *538*.[425)] The chemical and physical properties of *537* which are now under active investigation should prove of interest.

SCHEME 78

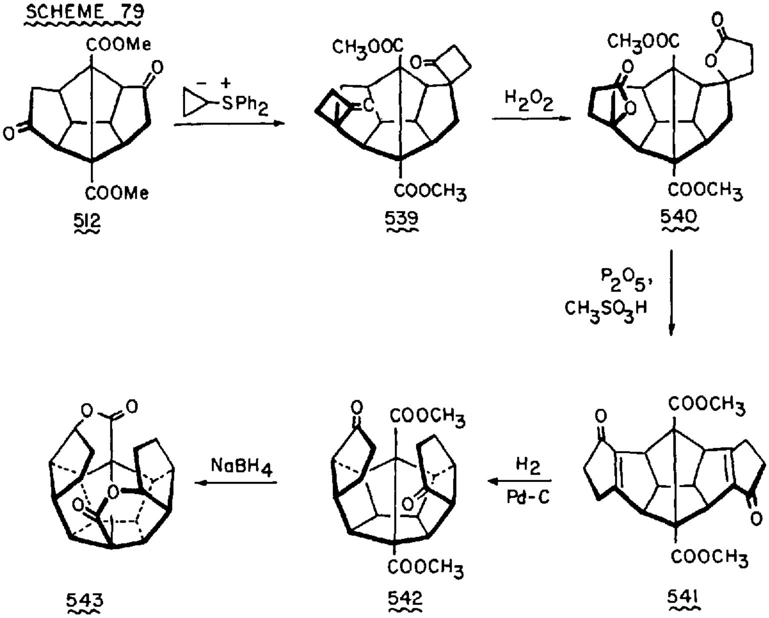


C. C_{18}-Hexaquinacenes

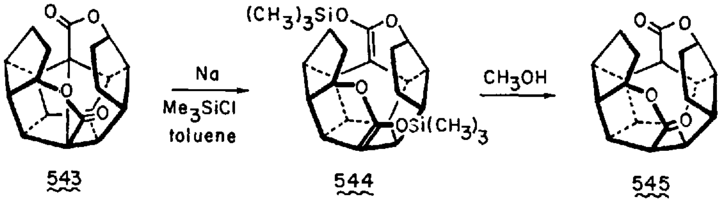
The C_2 symmetry of diketo diester *512* reduces any evaluation of its further chemical transformations to one of manupulating only two different carbonyl groups (ketone and ester). By means of a three-step sequence (Scheme 79) involving bis-spiroannulation with cyclopropyldiphenysulfonium ylide, Baeyer-Villiger oxidation, and acid-promoted rearrangement, it has proven possible to add six additional carbons symmetrically to a preexisting C_{14} frame with generation of two new fused cyclopentenone rings as in *541*.[420, 421] Catalytic hydrogenation of this hexaquinane proceeded stereospecifically with delivery of hydrogen exclusively from the sterically unencumbered convex face, necessitating that the cyclopentanone rings be projected to the inner regions of the developing sphere. The highly folded nature of *542* was revealed by sodium borohydride reduction which furnished dilactone *543* in excellent yield. The relatively simple ^{1}H and ^{13}C NMR spectra (ten lines) of *543* confirmed the maintenance of a molecular C_2 axis. The presence of this symmetry element was taken to mean that *543* can be viewed as a molecule possessing but a single functional group.

Because the sphericality of *543* should direct all reagents to convex approach for steric reasons, reductive cleavage of the internal bond was expected to result in exo

SCHEME 79

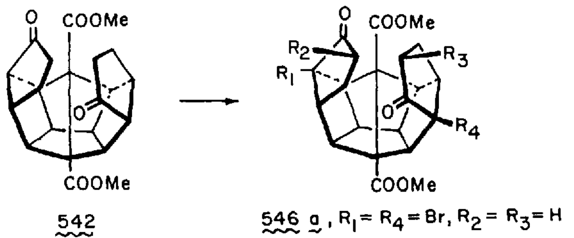


protonation and formation of *545*. This was achieved by treatment of *543* with sodium and chlorotrimethylsilane in refluxing toluene and subsequent hydrolysis of bistrimethylsilyl enol ether *544* in methanol. The exact structure of *545* has been



confirmed by an X-ray analysis.$^{426)}$ As constituted, *545* is a triseco precursor to the pentagonal dodecahedrane structure, having all necessary twenty carbon atoms predisposed in the proper fashion.

Several of the intermediates in Scheme 79 have been shown to undergo interesting reactions. For example, diketo diester *542* reacted with N-bromosuccinimide in carbon tetrachloride to give exclusively dibromide *546a*.$^{427)}$

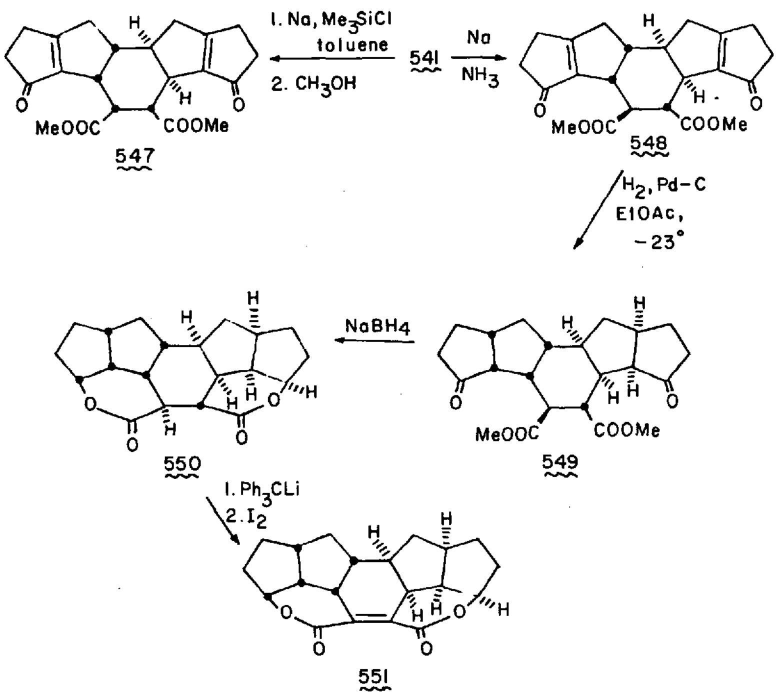


546 a, $R_1 = R_4 = Br$, $R_2 = R_3 = H$
b, $R_1 = R_4 = H$, $R_2 = R_3 = OAc$

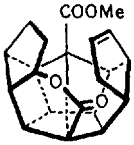
In contrast, the regiochemistry of bromine introduction with 2,4,4,6-tetrabromocyclohexa-2,5-dienone was R_2, R_2R_1, $R_2R_1R_3$, and finally $R_2R_1R_3R_4$ (see *546*).[427] Apparently, placement of the first bromine at R_2 activated R_1 to electrophilic attack by this reagent such that substitution at the proximate tertiary site was kinetically favored over that at R_3.

Bisenone *541* reacted with lead tetraacetate at the secondary α-carbons. Catalytic hydrogenation of this product gave *546b*.[428] A novel 1,6-fragmentation has been reported to occur upon sodium reduction of *541*. Through use of a sodium dispersion and chlorotrimethylsilane in toluene, followed by methanolysis, *547* was obtained. Sodium in liquid ammonia furnished the axially symmetric *548*, controlled low-temperature hydrogenation of which led with excellent stereochemical control to *549* (Scheme 80).[421] Upon sodium borohydride reduction, *549* was transformed to *550* which could be oxidized to *551* with an *in situ* iodination-dehydroiodination sequence.

SCHEME 80



With certain reagents, the closed lactone *543* has proven resistant to cleavage of both of its oxygenated rings. For example, with trimethyloxonium fluoroborate in dichloromethane or hydrogen bromide in methanol, one ring could be opened but not the other, even under forcing conditions.[429] Evidently, a conformational change accompanied conversion to *552* and *553* which led to improper stereoalignment for facile repetition of the first reaction. This drawback could be overcome with other more powerful reagents such as triphenylphosphine dibromide in acetonitrile and hydrogen chloride in methanol. Dibromo anhydride *554* also resulted



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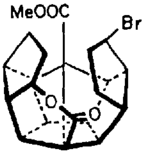

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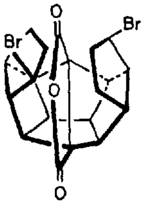

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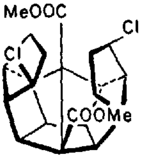

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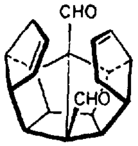
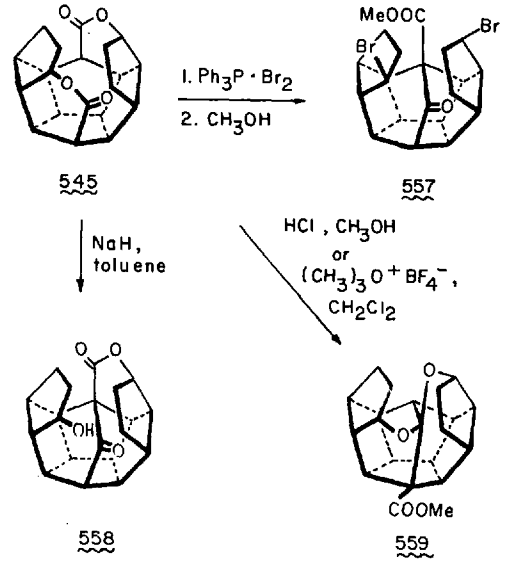


556

when *553* was treated with triphenylphosphine dibromide.[430] However, neither *554* nor *555* has proven to be a serviceable precursor to the unknown diene dialdehyde *556*.

The extreme susceptibility of open dilactone *545* to transannular cyclization under both alkaline and acidic conditions has also been established.[429, 431] Several more notable examples are illustrated in Scheme 81. Such reactivity has been attributed

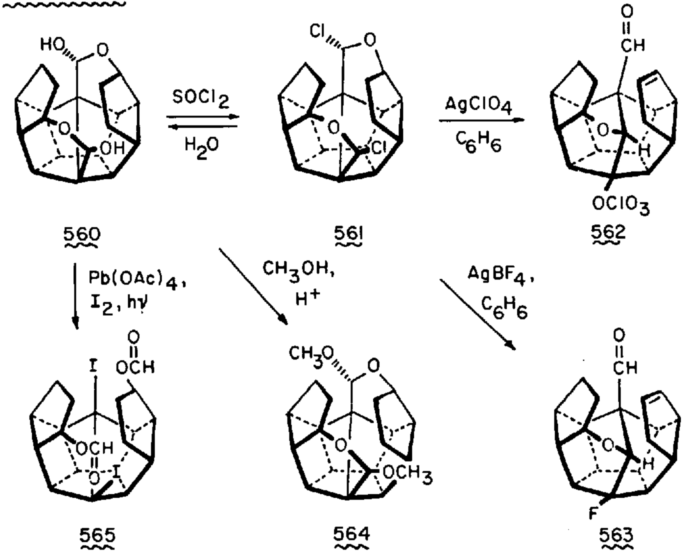
SCHEME 81



buted to proximity effects and the low degree of solvation, if any, in the interior of the molecule.

The propensity for intramolecular transannular bonding could be controlled during lithium aluminum hydride reduction, the symmetric lactol *560* being obtained from *543* in good yield.[431)] The indicated structure was not the product of kinetic control; rather, equilibration of the hydroxyl groups was noted to occur during workup and recrystallization. When dissolved in thionyl chloride, *560* was quantitatively converted to bis-chloro ether *561* (Scheme 82). On treatment with silver salts, *561* did not experience ring opening with formation of *556*. Rather, 1,2-Wagner-Meerwein shift of the central bond occurred with covalent capture of the counterion, even perchlorate (see *562* and *563*). The most unusual structural features of *562* have been confirmed by X-ray analysis.[426)] Although *564* could be obtained readily, it too proved sensitive to carbonium ion rearrangement. The conversion of lactol *560* to bis-iodoformate *565* when treated with lead tetraacetate and iodine with irradiation is also notable.[427)]

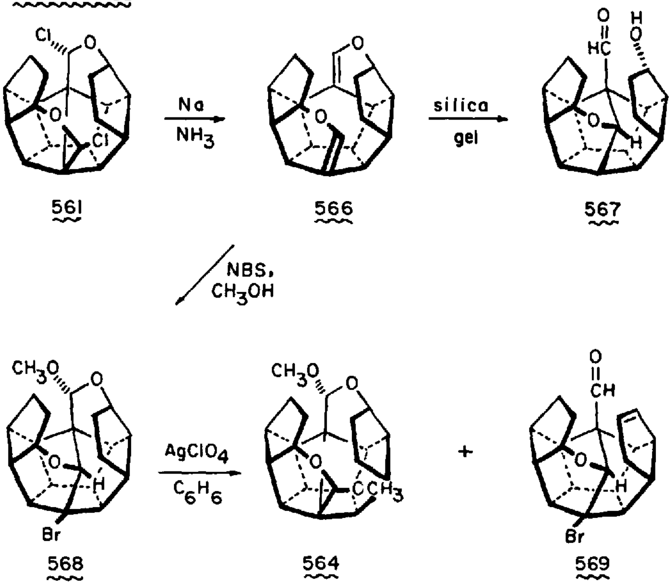
SCHEME 82



Bis-chloro ether *561* was reduced with sodium in liquid ammonia to give the bisdihydropyran *566*.[429, 431)] This versatile intermediate was shown to also be subject to transannular bonding. The conversions to *567* on silica gel chromatography[427)] and *568* with N-bromosuccinimide in methanol[428)] are exemplary. Interestingly, the reaction of *568* with silver perchlorate in benzene gave *564* and *569*, thus demonstrating the ability to reconstitute the central bond after it had been disrupted (Scheme 83).[428)]

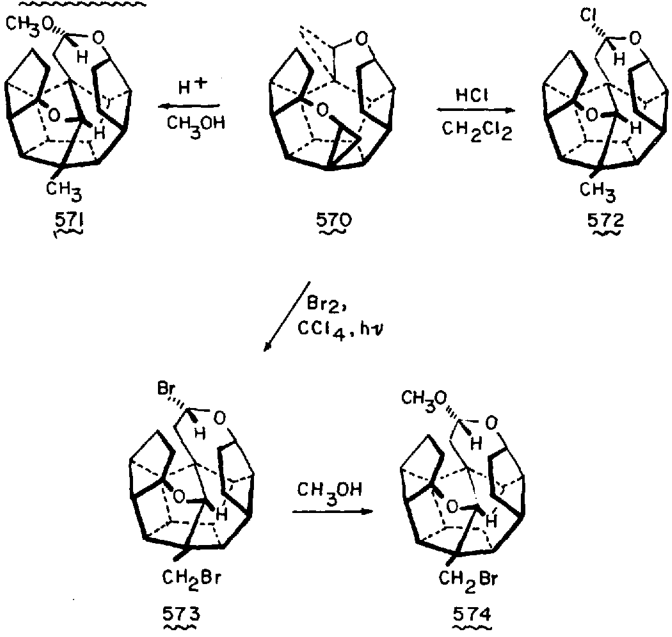
Under Simmons-Smith conditions, bis-dihydropyran *566* was smoothly cyclopropanated; but *570* was also subject to transannular reactions under certain con-

SCHEME 83



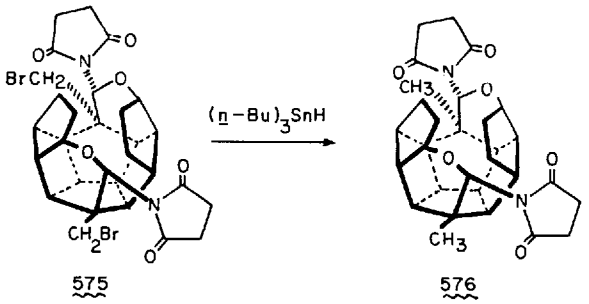
ditions as shown by its conversion to *571* in acidic methanol and to *572* with hydrogen chloride in dichloromethane (Scheme 84).[427] When treated with bromine in carbon tetrachloride solution under conditions of irradiation, analogous results were

SCHEME 84



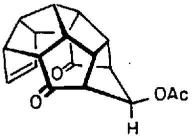
obtained. The dibromide which was isolated in good yield proved to be *573*; solvolysis of its α-halo ether functionality could be achieved with high selectivity as expected.[427]

When *570* was heated with N-bromosuccinimide, smooth ring cleavage occurred to give *575*, treatment of which with tri-*n*-butyltin hydride removed the bromine atoms in conventional fashion.[427, 429] In *576*, the aldehyde oxidation level has been retained at the pair of functionalized carbons. Further studies of this interesting intermediate are planned.



XI. Higher Polyquinanes

Base promoted condensation of diketone *535* with ethyl formate, followed by acetylation, afforded the functionalized C_{17}-heptaquinane *577*.[432]



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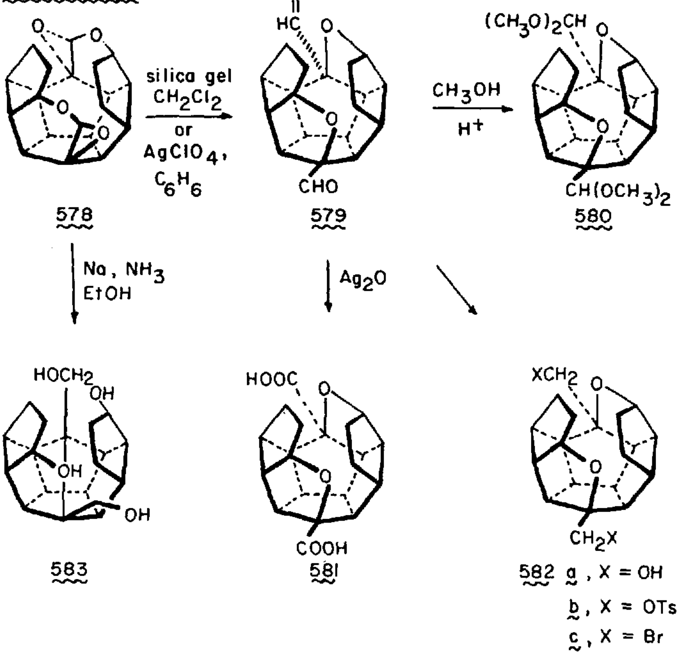
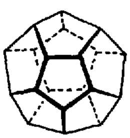
In contrast to the electrophilic chemistry of bis-cyclopropyl ether *570* where the three-membered ring was ruptured to generate a transient oxonium ion, experiments with diepoxide *578* proceeded with ring opening toward the developing tertiary cation center. When placed on silica gel or treated with anhydrous silver perchlorate in benzene, for example, *578* was transformed efficiently into dialdehyde *579* (Scheme 85).[427, 429, 433] The dioxa-C_{20}-octaquinane ring system of *579* is formally a heterocyclic trisecododecahedrane and, as such, represents the most highly condensed spherical molecule yet known. As illustrated in the scheme, this molecule has exhibited classical reactivity. The impression should not be left that *578* does not undergo transannular bonding. A most blatant example can be found in its conversion to tetraol *583* when reduced with sodium in liquid ammonia containing a proton source such as ethanol.[433]

SCHEME 85



The as yet unknown pentagonal dodecahedrane molecule (*3*) with its high I_h (icosahedral) symmetry and aesthetic allure has recently been studied from group theory, graph theory, and molecular orbital theory viewpoints.[434] Its vibrational frequencies have also been computed.[435] The spherical $(CH)_{20}$ hydrocarbon of structure *584*, to which we append the name ditrigonal dodecahedrane, has been given no attention. Although this molecule is much less symmetrical than *3*, it does possess comparable sphericality and a fascinating topology. Its three essentially planar cyclohexane rings, whose geometry is enforced by structural factors, are particularly worthy of note. Further, the presence of three cyclobutane rings causes it to be an attractive and reasonable target for organic synthesis.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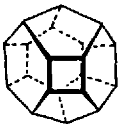

584

XII. Summary

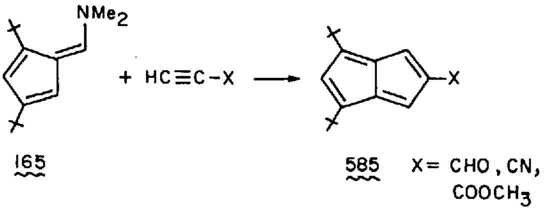
Although various bicyclo[3.3.0]octane derivatives have been known for several decades, the chemistry of this ring system and the higher polyquinanes has developed particularly rapidly in the last decade. These developments have been stimulated by a wide range of interests and have encompassed a broad spectrum of research chemists. One may now safely claim that polyquinanes are readily available molecules. The more complex members of this class, particularly those endowed with all-cis stereochemistry, take on a "sphere-like" topology and conformational rigidity. As sphericality increases, the ability of a molecule to exclude solvation from its inner core is enhanced. Can smaller molecules or atoms be occluded therein? And what about completely enclosed structures such as the pentagonal dodecahedrane? What unique properties will characterize compounds of this type? It is the quest for such information that will propel the field of polyquinane chemistry rapidly forward in the years to come. The increasing complexity of natural products having multiply fused cyclopentanoid rings will generate a comparably high level of chemical investigation in this field.

Acknowledgments. This work was supported by grants from the National Institutes of Health (AI-11490) and the National Science Foundation. The actual writing of this review was undertaken while the author was a Fellow of the John Simon Guggenheim Memorial Foundation.

XIII. Addendum

(Section IIIB)

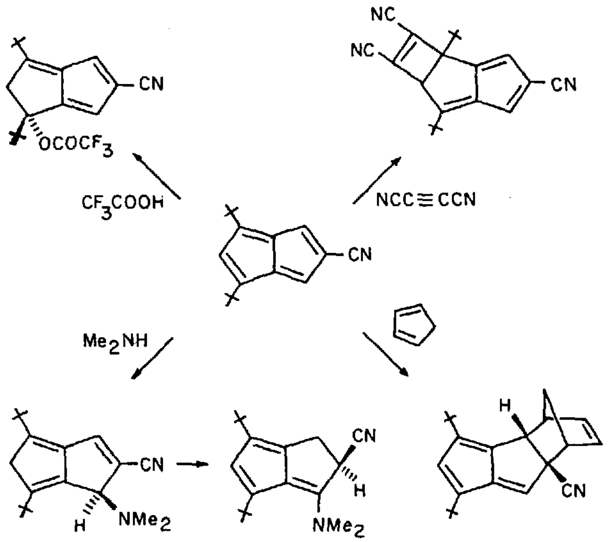
Suda and Hafner have observed that fulvene *165* also cycloadds to acetylenes possessing only one electron-withdrawing group to give *585*.[436] At room temperature, these pentalenes are in equilibrium with their dimers.



In yet another investigation, these workers determined that *585*-CN is susceptible to electrophilic attack at the 5-position, nucleophilic attack at the 1- (or 3-) position, dienophile attack at the 4,5-position, and Diels-Alder cycloaddition at its electron-deficient ring.[437] The differences in regioselectivity are impressive.

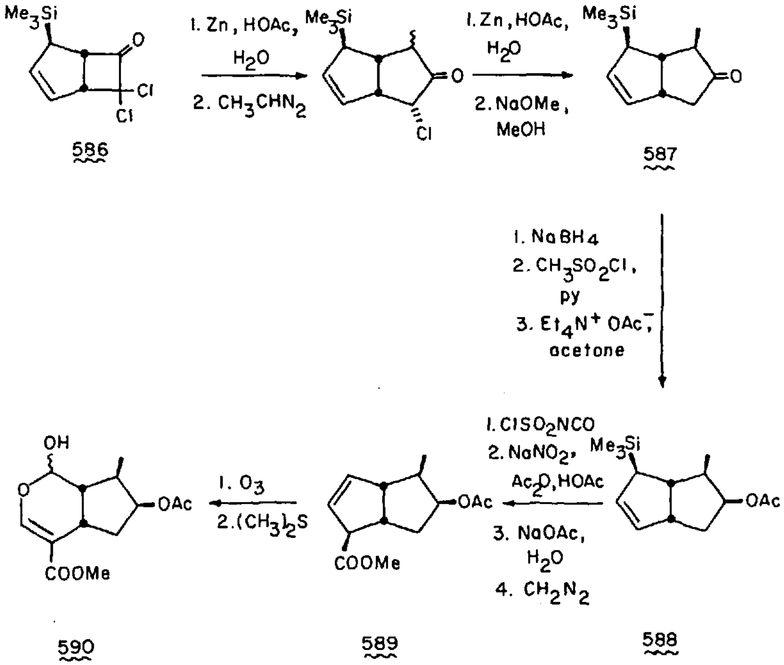
(Section VA)

Au-Yeung and Fleming have devised a new alternative synthesis of loganin (*590*) based upon allylsilane chemistry.[438] The bicyclic ketone *586*, obtained by cycloaddition of dichloroketene to trimethylsilylcyclopentadiene, was monodechlorinated, ring expanded with diazoethane, and again dehalogenated prior to equilibration



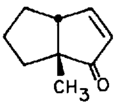
(Scheme 86). Three standard chemical operations on *587* afforded *588* which reacted with chlorosulfonyl isocyanate to provide *589* after suitable hydrolysis and esterification. Direct ozonolysis of this last intermediate gave loganin.

SCHEME 86



(Section VI)

Karpf and Dreiding have found it possible to distinguish between *591* and *592* on the basis of ^{1}H NMR.439)



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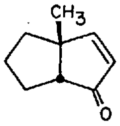
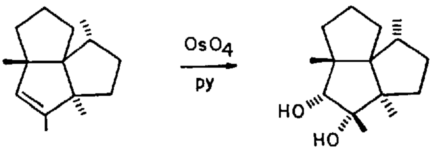


592

(Section VIIA)

A new sesquiterpene called isocomene (*593*) has been isolated from the dried stems and leaves of the goldenrod *Isocoma Wrightii*. Its structure was established by conversion to diol *594* and analysis of the latter by X-ray methods.440)



593 594

Note Added in Proof

In an attempt to maintain the subject matter as current as possible, the following recent references are listed in a format following the contents of the review:

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