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Title: Exploratory Studies of the Mechanism of 1,3 Sigmatropic Ring Expansion Reactions

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The potassium salts of certain 1-vinylcycloalk-3-en-1-ols have been found to undergo sigmatropic ring expansion rearrangements in HMPA. Preliminary investigations of several benzo-substituted medium ring systems were undertaken in order to determine which of these was best suited for further study. A synthetic sequence leading to the formation of 5-methyl-6-vinyl-7,8,9,10-tetrahydro-6-benzocyclo-octenol, which will be used in a study of the stereochemistry of the 1,3 sigmatropic ring expansion reaction, was carried out.

Exploratory Studies of the Mechanism of 1,3 Sigmatropic Ring Expansion Reactions

by

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Typed by Shanda L. Smith for Corinne James

TO

Zink, Pat and Jim

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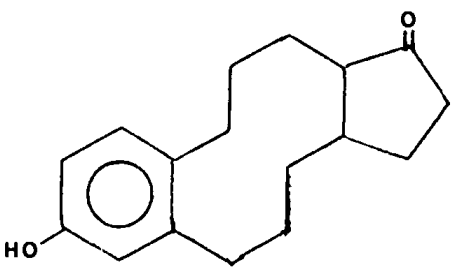
Exploratory Studies of the Mechanism of 1,3 Sigmatropic Ring Expansion Reactions

I. INTRODUCTION

The 1,3 sigmatropic ring expansion reaction discussed herein is of interest as a synthetic procedure which could be used in the synthesis of 8:9, 13:14-disecosteroids such as 1. It is hoped that such disecosteroids would show some anti-fertility activity.



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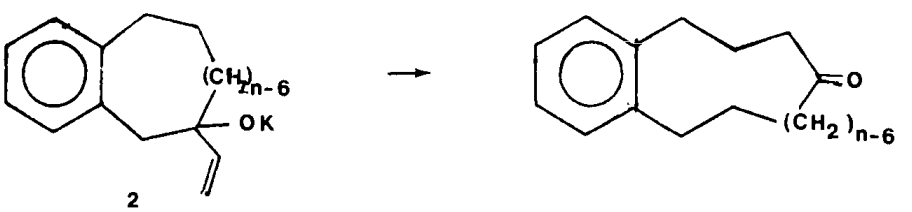
The mechanism of anionic sigmatropic rearrangements (Scheme 1) has not been established and efforts were directed towards a study of the stereochemistry of the migrating carbon. The synthesis of 5-methyl-6-vinyl-7,8,9,10-tetrahydro-6-benzocyclooctenol is reported, along with the results of preliminary studies of several medium ring systems.



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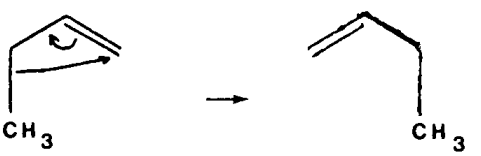
Scheme 1 n=7,8,9

II. HISTORICAL

A. Part I: Introduction

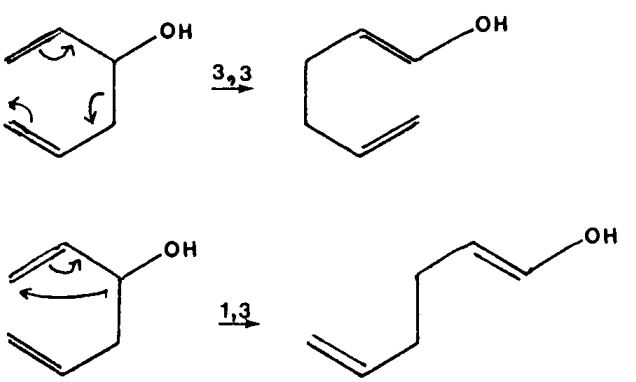
Woodward and Hoffmann have defined an i,j sigmatropic shift as the intramolecular migration of a sigma bond across a pi electron framework to a new location between atoms which are (i-1) and (j-1) atoms removed from the original location of the bond (1). An example of a 1,3 sigmatropic shift is given below (Scheme 2).

Scheme 2



One class of sigmatropic rearrangements includes the oxy-Cope rearrangements (2). These rearrangements take place in a 3-hydroxy-1,5-diene system; 3,3 and 1,3 rearrangements leading to the formation of an enol (Scheme 3) are referred to as oxy-Cope rearrangements (2).

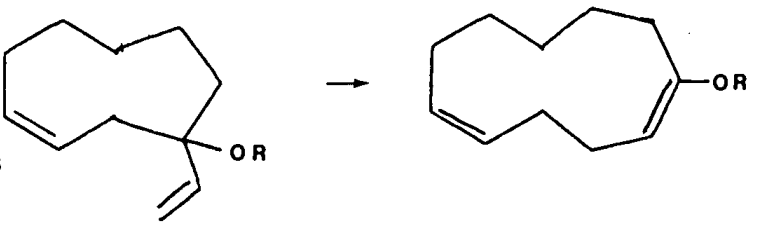
Scheme 3



In 1970 R.W. Thies developed a two carbon ring expansion reaction utilizing the oxy-Cope rearrangement (Scheme 4) (3). This reaction has been extended by Thies and his coworkers to include reactants

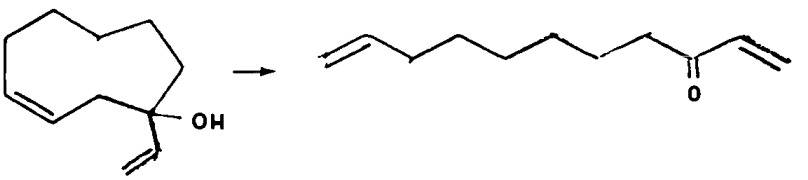
Scheme 4

R= H, CH_3, $Si(CH_3)_3$

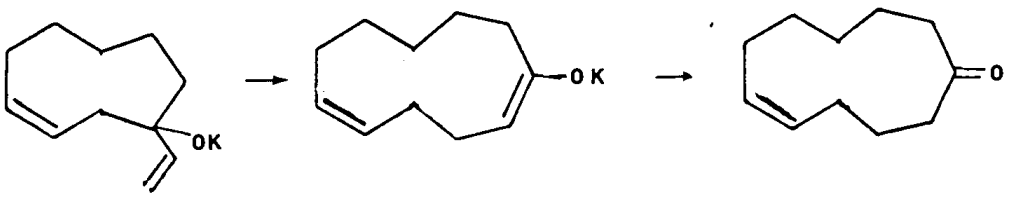


in which the hydroxy group is replaced by a methoxy or siloxy group (R = $Si(CH_3)_3$) (4). α-Hydroxy olefin cleavage (Scheme 5) is a major side reaction in the oxy-Cope rearrangement and the use of the siloxy-Cope modification eliminated such cleavage resulting in dramatically improved yields of rearranged products (4).

Scheme 5



A further modification of the oxy-Cope ring expansion of Thies and Seitz involved the rearrangement of the potassium alkoxide 3 (5). The best yields of rearranged products were obtained when the potassium



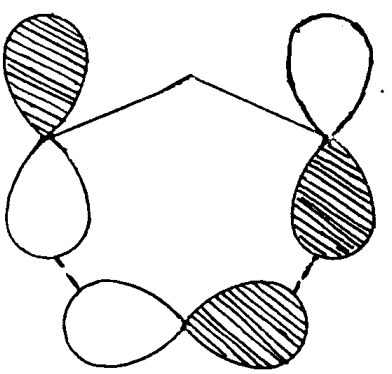
3

alkoxide was rearranged in hexamethyl phosphoric triamide (HMPA) (5). The use of potassium alkoxides in highly dissociating solvents was first reported by Evans and Golob for a 3,3 oxy-Cope rearrangement (6).

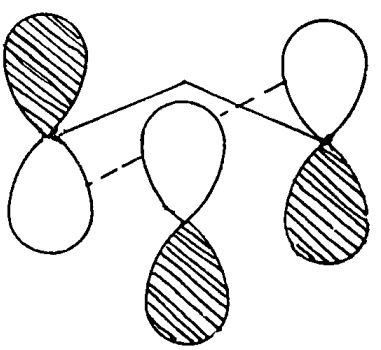
The mechanism of the potassium alkoxide rearrangements has not yet been determined.

Woodward and Hoffman, in their treatise on pericyclic reactions, introduced the terms 'allowed' and 'forbidden' (1). These terms were used in a literal sense; a forbidden reaction could not occur by way of a concerted mechanism. A reaction whose outcome was not correctly predicted by the use of orbital symmetry rules had to occur by a non-concerted mechanism.

The Woodward-Hoffman rules predict that a 1,3 sigmatopic shift should occur suprafacially on the allylic framework with inversion of stereochemistry at the migrating group (si) or antarafacially on the allylic framework with retention at the migrating group (ar) if the rearrangement takes place under orbital symmetry control (1). These alternatives are illustrated below.



si



ar

Several researchers (7,8,9,10,11) have found fault with the strict use of allowed and forbidden and have postulated alternative theories to account for observed behavior of systems which do not fit well into the concerted or diradical categories.

Dewar (7) has postulated a theory of pericyclic reactions based on the concept of aromaticity. The selection rules derived from this theory are the same as the Woodward-Hoffmann rules; however, the term allowed is replaced by the term favored. A pericyclic reaction involving the cyclic permutation of bonds is considered in the same way as the transformation from one Kekulé structure to another. The transition states in reactions which occur thermally are thus made lower in energy in an analogous fashion to the resonance stabilization of aromatic compounds. The gain in energy due to such stabilization may or may not be large enough to prevail when such factors as steric hindrance and ring strain are also present in the transition state. This treatment allows for the occurrence of concerted reactions which result in formal violations of the selection rules.

The stabilization of symmetry forbidden transition states has been approached by Schmidt from a dynamical viewpoint (8). An overestimation of the force constants of chemical bonds has led, Schmidt believes, to the opinion that symmetry forbidden reactions occur by non-least motion pathways. The stabilization of the product at the expense of the reactant, as in cases where there is geometric or steric strain in the reactant, but not in the product, would lower the activation energy for symmetry forbidden pathways. The destabilization

of an open-shell (triplet diradical) intermediate would also stablize a concerted pathway relative to a non-concerted pathway.

Baldwin has suggested that the inclusion of configuration interaction in theoretical treatments will result, in some cases, in a symmetry forbidden pathway with a very low activation energy (9). Such a forbidden pathway could compete effectively with possible orbital symmetry allowed pathways (9).

Berson believes that the order of preference of transition states should be allowed forbidden diradical and that the energy differences between transition states are small enough that steric and other considerations could upset the order (10). Subjacent orbital effects (configuration interaction) are invoked to justify this conclusion (10).

Epiotis has gone so far as to refer to the extensive use of the Woodward-Hoffmann rules as "an unfortunate brainwashing" (11). Epiotis' approach involves the consideration of the polarity of the reactants to arrive at the dominant MO interaction which controls the course of the reaction. For sigmatropic shifts, the ionization potential and the electron affinity of the migrating framework and migrating group are calculated. The quantity I-A is calculated for each possible reaction pathway. Potential energy surfaces are then constructed and the lowest energy reaction pathway determined. This pathway may or may not coincide with the Woodward-Hoffmann allowed process. Epiotis' theory is extremely sensitive to substituent and solvent effects and predicts the large rate enhancement observed in the rearrangement of potassium alkoxides in highly dissociating solvents.

Carpenter has developed a simple model for predicting the effect of substituents on the rates of thermal pericyclic reactions (12). The transition state of a rearrangement is treated as a cyclic array of orbitals. The energy levels of this cycle are calculated as they would be for the analogous completely conjugated hydrocarbon. Substituents are classified as pi electron donors or acceptors. Donors are represented by a carbon with a fully occupied 2p orbital and acceptors by an empty carbon 2p orbital. Total pi electron energies for reactants and transition states are then determined using simple Hückel MO theory. The difference in reactant and transition state energies leads to a prediction of the effect of the substituent on the rate of the rearrangement relative to the rate of rearrangement of the unsubstituted case. This model predicts the changes in rates for rearrangements which occur via either Woodward-Hoffmann allowed or forbidden pathways.

B. Part II: 1,3 Sigmatropic Shifts of Neutral Hydrocarbons

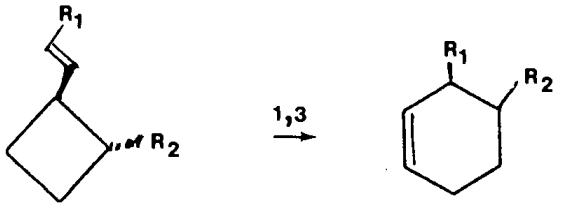
Much effort has been devoted to the investigation of the mechanisms of 1,3 sigmatropic shifts of neutral molecules. Although many molecules will undergo 1,3 rearrangement to give nearly exclusively the products predicted by orbital symmetry rules, the mechanisms of some well-studied rearrangements are undetermined.

One of the most extensive studies of 1,3 sigmatropic shifts involves the rearrangement of vinylcyclobutanes (Scheme 6). Thermochemical-kinetic and elaborate stereochemical investigations of this

group of rearrangements have been carried out by Berson and his co-workers (10,13,14,15).

Activation parameters for this series of rearrangements appear to be consistent with those predicted by bond dissociation energies

Scheme 6



4a R_1=H, R_2= 

4b R_1=H, R_2= C_2H_5

4c R_1=CH_3, R_2= 

4d R_1=CH_3, R_2= 

5a R_1=H, R_2=  trans-

5b R_1=H, R_2=C_2H_5

5c R_1=CH_3, R_2=  trans-

5d R_1=CH_3, R_2=  cis-

for a diradical mechanism (10). The stereochemical data appear to be at odds with such a mechanism (10). The rearrangements of 4a, 4b, 4c and 4d give inversion:retention ratios of 54:46, 59:41, 53:47, and 50:50 respectively (10,14). The presence of a diradical intermediate could be responsible for this almost complete stereorandomization (10). The small excess of inversion could indicate that a small protion of the reaction mixture is under orbital symmetry control (10).

The divinyl and dipropenyl compounds 4a, 4c, and 4d would provide a degree of stability to a diradical intermediate because of possible allylic stabilization. Such stabilization would not be available in 4b where an ethyl group replaces one of the vinyl groups. The stereochemical outcome of the rearrangement of 4b is nearly the same

as that of 4a, the divinyl analog; Berson feels that this result does not support a diradical mechanism for this reaction (10).

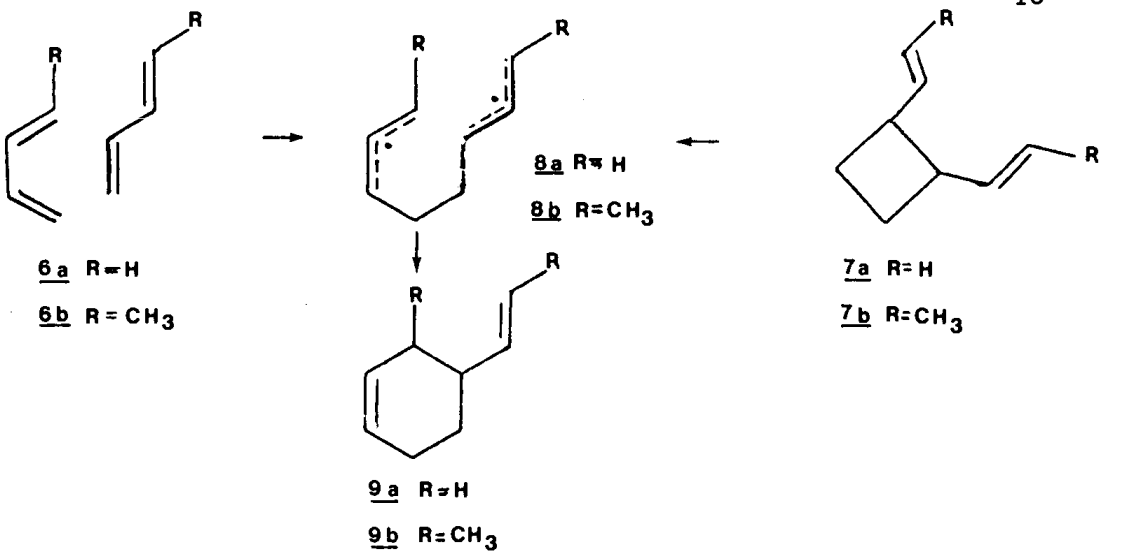
For the trans-dipropenyl compounds 4c and 4d, the stereochemistry at both the migrating group and the migrating framework may be determined from the product mixtures (13). The results of the rearrangements of 4c and 4d are given in Table 1. These results do not support formation of a planar intermediate because in such an intermediate, there would be no factor limiting antarafacial participation of the allylic framework to the samll proportion observed experimentally (10).

Table 1 (16)

Reactant	Products			
	allowed		forbidden	
	si	ar	sr	ai
4c	50.2	6.0	41.1	2.7
4d	49.5	2.8	46.8	0.9

A diradical intermediate would not be consistent with the observed results unless special stereochemical properties were attributed to it (10).

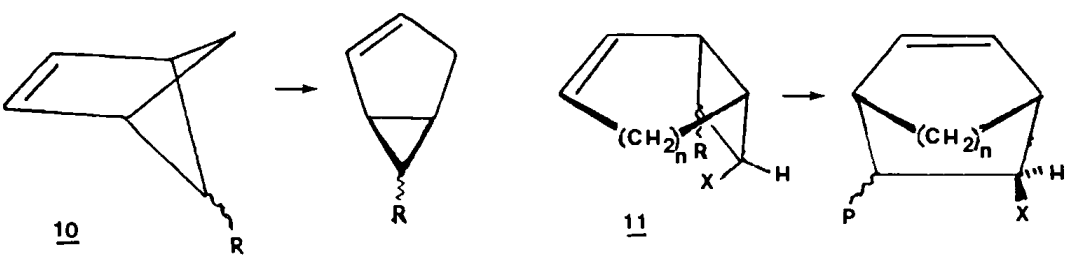
The Diels-Alder dimerization of 6a to 9a and the 1,3 sigmatropic rearrangement of 7a are predicted by thermochemical-kinetic methods to take place by way of a common biradical intermediate 8a (15). Berson extends this prediction to include the rearrangement of 7b and the dimerization of 6b (15). The sigmatropic rearrangements of 7a and 7b exhibit a slight preference for inversion at the migrating group; however, retention at what would be the same site in a common



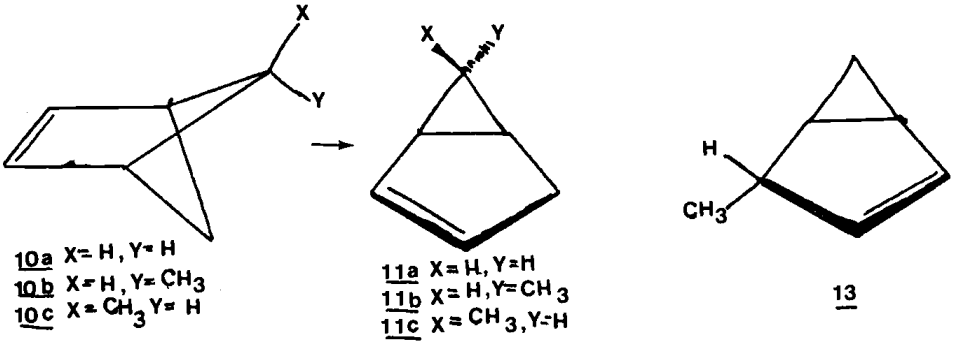
diradical intermediate is observed in more than 90 percent of the product of the Diels-Alder reactions of 6a and 6b (15).

Thermochemical-kinetic predictions are clearly not in agreement with stereochemical evidence. Berson believes that there is an element of orbital symmetry control in the sigmatropic shifts of 7a and 7b that affects the stereochemical outcome of both Woodward-Hoffman allowed and forbidden pathways (15).

Bicyclic systems such as 10 and 11 are geometrically constrained such that 1,3 sigmatropic rearrangements may only take place suprafacially on the allylic framework.



A kinetic analysis of the rearrangement of 10a to 12a by Frey and his coworkers gave activation parameters in agreement with those



10a X=H, Y=H
10b X=H, Y=CH3
10c X=CH3 Y=H

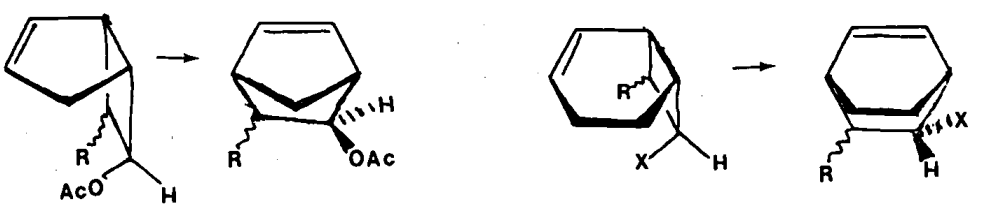
11a X=H, Y=H
11b X=H, Y=CH3
11c X=CH3, Y=H

13

predicted by thermochemical-kinetic theory for a concerted reaction (16). Thermochemical-kinetic predictions for activation energies for a stepwise biradical mechanism are also close to experimental values, but the authors felt that the difference between experimental and predicted values for the diradical was greater than the combined probable errors (16).

The rearrangement of 10b gives nearly exclusively 12b as the product; the reaction mechanism is probably a concerted one (17). In contrast, the rearrangement of 10c results in the production of 56.5 percent 12c, 25.2 percent 12b and 18.3 percent of a third product 13 (17). The authors, Roth and Friedrich, believe that a biradical mechanism is indicated for the rearrangement of 10c.

When an exo-substitutent is present in a structure such as 14, Berson and his coworkers observe at least a ten-fold preference for



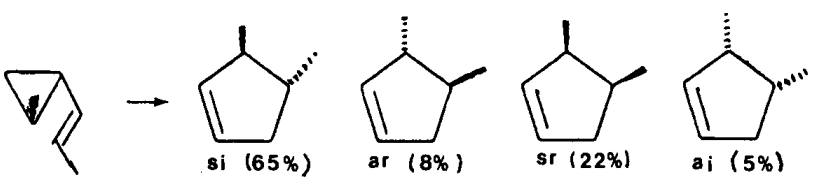
14 16 15

inversion over retention in the 1,3 sigmatropic rearrangement to 16 (18). When R is endo, there is a seven-fold preference for retention (18). The rearrangement of exo-substituted 15 gives only a slight excess of inversion product, whereas a 12- to 15-fold excess of retention product is observed in the rearrangement of endo-substituted 15 (18). Berson suggests that there is orbital overlap in all of the rearrangements of 14 and 15 and that the greater flexibility of 15 makes the transition state leading to retention in the product more favorable than it is in the rearrangement of 14 (18).

In the bicyclic systems 10, 14 and 15, steric factors are very important in determining the outcome of the rearrangements. The energy difference between the orbital symmetry-controlled allowed process and the forbidden process cannot be very large if the presence of an endo methyl group is enough to cause an apparent change in mechanism.

Experimental and theoretical studies have been done on the vinylcyclopropane rearrangement (19). Calculations predict that the vinylcyclopropane rearrangement should proceed through a diradical intermediate and that almost complete stereorandomization should be observed in the product (19). Simpson and Richey concluded from studies involving methoxy and phenyl substituents that a planar biradical

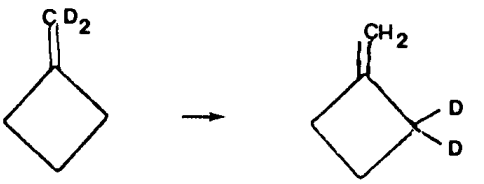
Scheme 7



intermediate was probably involved in the reaction (20). A complete analysis of the stereochemistry of the product cyclopentenes by Andrews and Baldwin indicates that such an intermediate is unlikely (Scheme 7) (19).

The thermal rearrangement of methylene cyclobutanes has been investigated by Baldwin and Fleming (Scheme 8) (21,22). The kinetics of the rearrangement of several substituted methylenecyclobutanes were studied in an attempt to demonstrate that a large proportion of the rearrangement was taking place antarafacially on the allylic framework (22). Baldwin and Fleming were, however, unable to unravel all of the kinetics and were only able to conclude that at least 17 percent and possibly more than 65 percent of the reaction occurred antarafacially (22).

Scheme 8

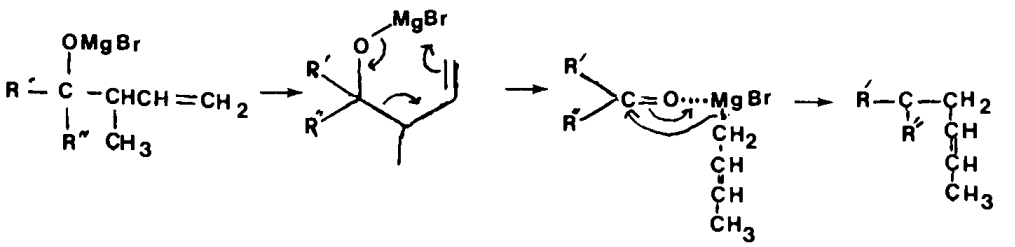


C. Part III: Anionic Rearrangements

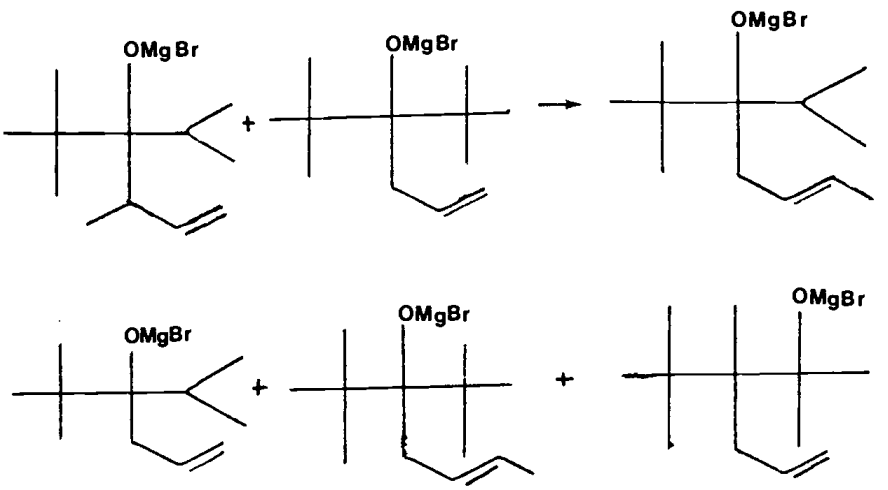
The first example of the presence of a metal-oxygen bond initating carbon skeleton rearrangement was observed by Benkeser and Broxterman in 1969 in the reaction of crotylmagnesium bromide with hindered ketones (23). An initial high yield of α-methyl allyl products decreases in time accompanied by an increase in crotyl products and

recovered starting ketone (23). Two mechanisms have been proposed to account for the change in products; the first involves the reversible

Scheme 9



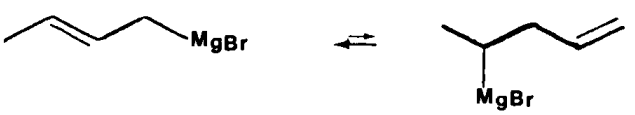
addition of the Grignard reagent to the ketone (Scheme 9) (23). The reversible Grignard mechanism is supported by the results of the following crossover experiment (24):



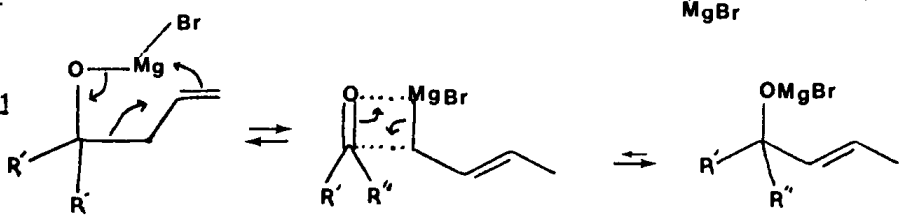
The other proposed mechanism hinges on the equilibrium existing between the two forms of the crotyl Grignard (Scheme 10) (25). The mechanism for the equilibrium is shown in Scheme 11 (25).

The authors were able to suppress formation of the crotyl adduct in nearly all cases by using very mild reaction conditions, e.g., -78°

Scheme 10



Scheme 11

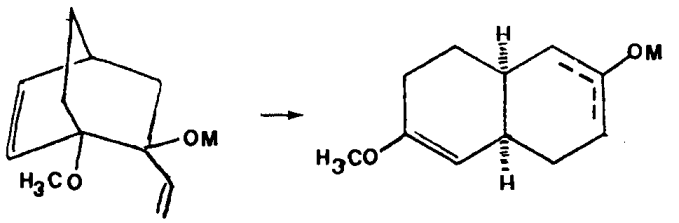


and a reaction time of 30 minutes (25). An exception was di-t-butyl ketone which gave exclusively the crotyl product under the above conditions, however, when the magnesium bromalkoxide salt of di-t-butyl- -methylcarbinol was prepared at -78° and allowed to stand for two hours, no crotyl adduct was observed (25). In another experiment the authors were able to trap the enol form of the alkoxide; hence the apperance of starting ketones in alkoxide reversal reactions was shown to be the result of enolization of the ketone by the alkoxide (25). The authors concluded that the formation of crotyl products can result either from an alkoxide reversal process (Scheme 9) or from the crotyl form of the Grignard and the ketone in a four center transition state (25).

The most versatile of the modifications of the thermal 1,3 shift is the rearrangement of potassium alkoxides in highly dissociating solvents. Evans and Golob, in 1975, first investigated this powerful substituent effect (6). They studied the oxy-Cope reactions of several alkoxides (Scheme 12) (6). When the metal was lithium or magnesium bromide, the system exhibited no rearrangement after 24 hours in refluxing THF; when sodium was the metal, the system rearranged to the enolate in a reaction with a half life of 1.2 hours (6). The most

Scheme 12

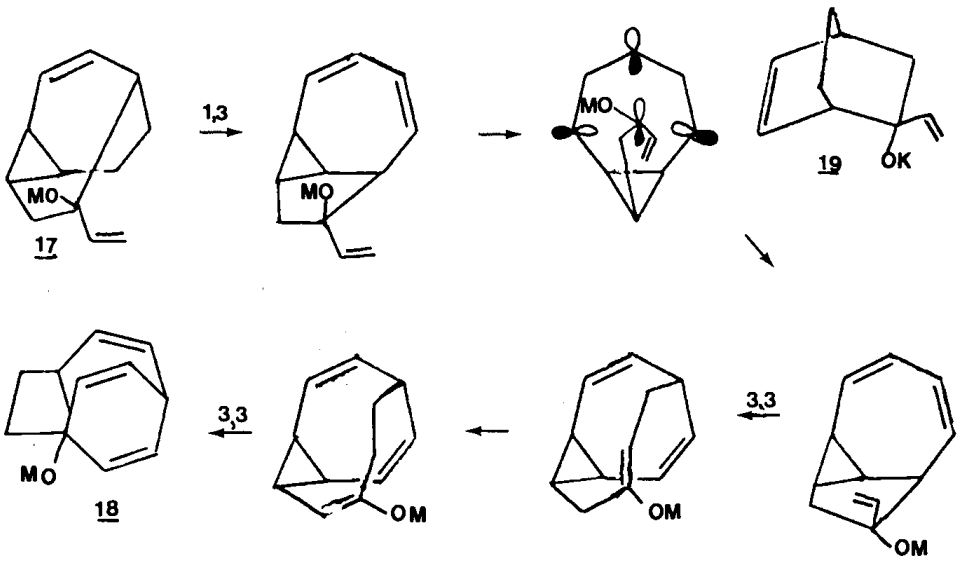
M = Li , MgBr, Na, K



dramatic results were obtained when potassium was used as the metal (rearrangement in THF occurred within several minutes); the use of four equivalents of 18-crown-6 in THF or of HMPA as the solvent gave rise to an additional 180-fold increase in the rate (6). The rate was increased 10^{10} to 10^{17} times for alkoxide in 18-crown-6 over the corresponding alcohol (6). Wilson and coworkers, in 1977, in a study of 1,3 sigmatropic shifts in acyclic systems found cation and solvent dependence similar to those observed by Evans for 3,3 sigmatropic shifts (26).

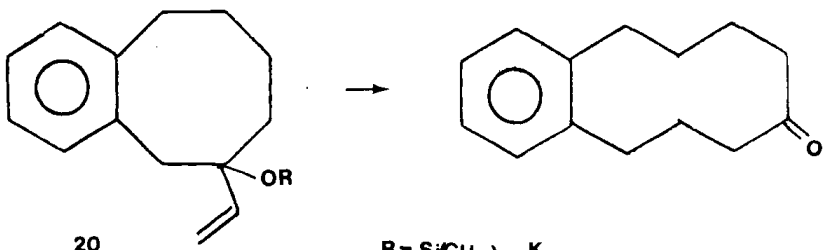
The rearrangement of 17 to 18 would be expected to be unfavorable due to geometric conditions similar to those which exist in 19, however, Miyashi and coworkers found that this rearrangement occurred at 66°

Scheme 13



in the presence of six equivalents of 18-crown-6 ether with a half life of 0.06 seconds (28). An investigation of the fate of several proposed intermediates when subjected to the reaction conditions, coupled with deuterium labeling studies, led to the conclusion that the reaction probably involved a series of sigmatropic shifts (Scheme 13) (28).

Thies and Seitz compared the rearrangements of the siloxy and potassium alkoxide derivatives of 1-vinylcyclononenols and 1-vinylcyclodecenols to cycloundecenones and cyclododecenones, respectively (5). The predominant products arose from 1,3 sigmatropic shifts and retained the original stereochemistry at the double bond (5). The siloxy rearrangements for these systems were found to give better yields than the corresponding potassium alkoxide rearrangements; however, for the benzocyclooctol system 20, the yield for the rearrangement of the potassium salt in HMPA was higher (5).

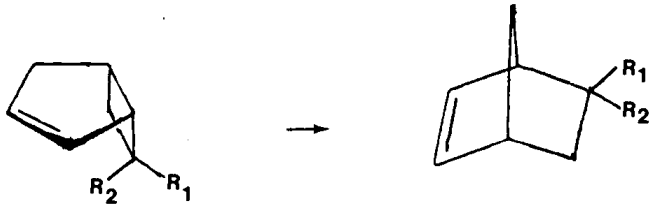


20 R = $Si(CH_3)_3$, K

The mechanism of the anionic oxy-Cope rearrangements is unclear. Experimental studies using stereochemical probes and theoretical studies of the nature of the bond cleavage have been conducted in an effort to determine the mechanism (6,27,28,29).

In the initial investigation of alkoxide rearrangements, Evans found that while the potassium salt of 2-endo-vinyl-2-exo-hydroxybicyclo[2.2.2]oct-5-ene rearranged in HMPA or 18-crown-6 at room temperature in several minutes, the 2-exo-vinyl-2-endo-hydroxy isomer failed to rearrange after 24 hours at 66° (6).

Wilson and Mao determined that the transformation of anionic bicyclo[3.2.0]heptenols 21 and 22 to norbornenols 23 and 24 was consistent with Berson's study of the 1,3 shift in bicyclo[3.2.0]-heptanes (10,27). The exo-substituted isomer 21 rearranged to 23 and 24 in an 8:1 ratio (27). The preference for inversion over retention



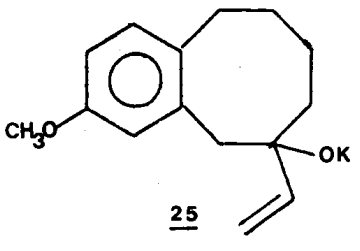
21 R_1=OH, R_2= H
22 R_1=H, R_2= OH

23 R_1= OH, R_2=H
24 R_1=H, R_2=OH

in the neutral compound was 19:1 (10). The endo substituted bicyclo [3.2.0.] heptenol 22 rearranged with predominant retention (27). A ratio of 23 to 24 of 6 to 1 was consistent with Berson's result of a 7 to 1 ratio of retention to inversion (10,27). Berson used his study of the neutral compounds to justify the existence of a forbidden concerted mechanism over a diradical mechanism (10). Wilson and Mao concluded that while their findings, particularly the results of the rearrangement of the endo-substituted compound, resembled Berson's findings for the corresponding neutral compound, the possibility of a non-concerted mechanism cannot be ruled out since the thermodynamic ratio of 23 to 24 is 6 to 1 (27).

In all of the aforementioned stereochemical investigations, a diradical intermediate was considered unlikely when one stereoisomeric product predominated over another (6,27,28). If such a diradical did exist, it would have to have a barrier to epimerization greater than the barrier to ring closure.

The rearrangements of 20 and 25 were subjected to kinetic analysis (32). The rearrangement of 25 was found to be three times faster than the rearrangement of the non-methoxy analog 20. This finding indicates that the benzylic position experiences a considerable negative charge during the reaction (32). The formation of a fully ionic intermediate or a similar highly polarized species is likely (32). If an intermediate such as 26 were formed, fragmentation products would be expected. No fragmentation is observed for the rearrangements of 20 and 25, but the fragmentation product toluene is observed in the rearrangement of 27 (32).



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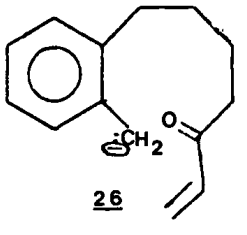

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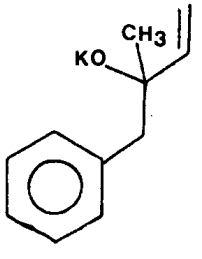
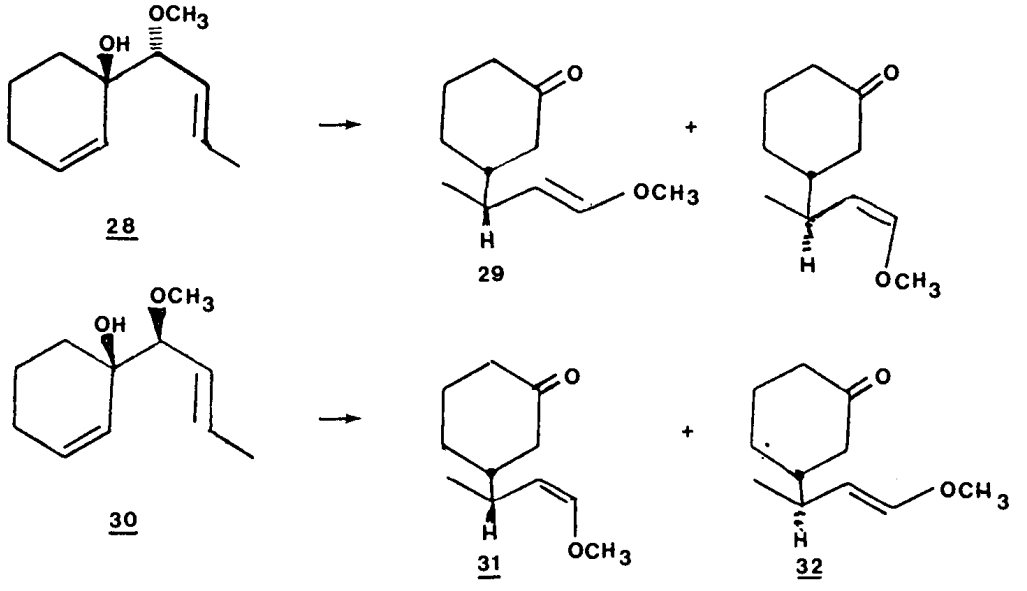


27

Evans and Baillargeon, in another approach to the problem, have undertaken theoretical studies of substituent effects on carbon-carbon bond dissociation energies (29,30). They have found that the presence of negatively charged oxygen instead of an alcohol favors carbon-carbon bond homolysis over heterolysis by 13-17 kcal per mole in the gas phase (30). This evidence indicates that a radical-radical

anion is a possible intermediate; the negative charge would be localized on the oxygen (30). In contrast, Evans also found that the 3,3 rearrangement of 28 was highly stereospecific and that a chair transition state led to 29 (31). The rearrangement of 30 is less stereospecific because of the presence of what would be an axial substituent



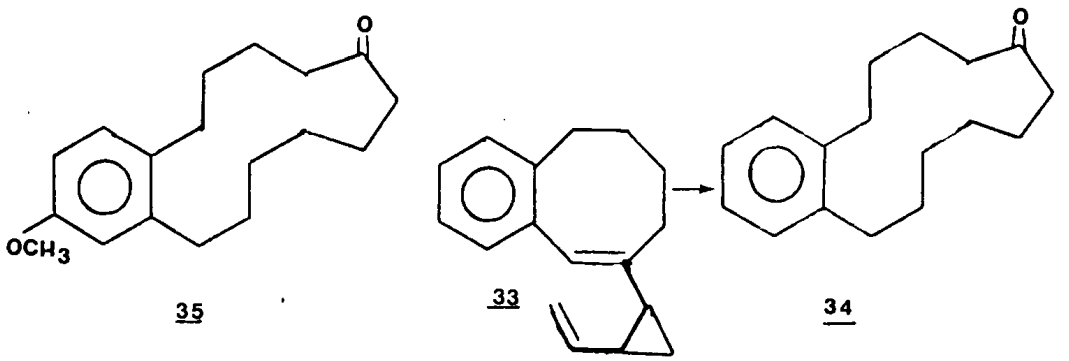
in the chair transition state (31). A chair transition state and a high degree of stereospecificity would be expected if the reaction were taking place via a concerted pathway.

III. RESULTS AND DISCUSSION

A. Part I: Preliminary Studies

Preliminary investigations were carried out on several medium ring systems in order to determine which of these was best suited for further study.

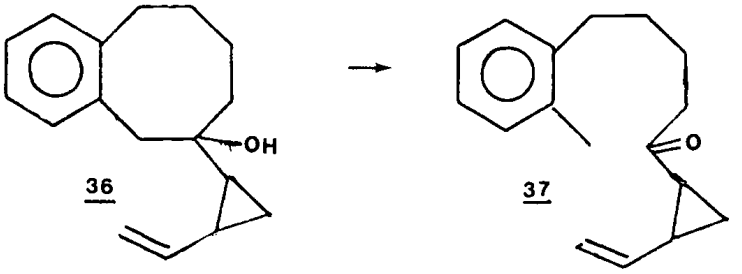
The thermal rearrangement of 33 was of interest, both from a mechanistic point of view and as an intermediate in the synthesis of 8:9,13:14-disecosteroids such as 35.



35 33 34

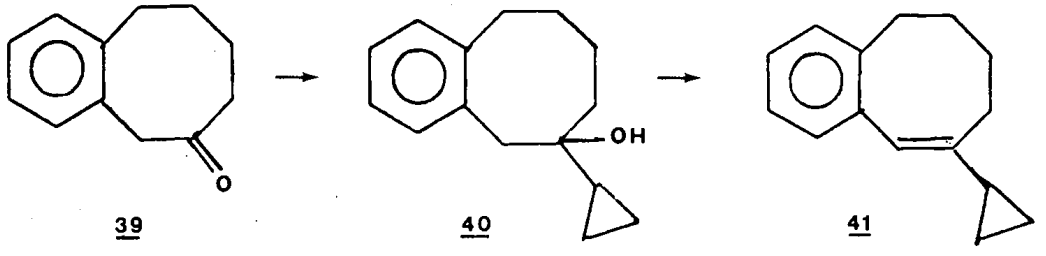
The attempted anionic rearrangement of the 2-vinyl-cyclopropyl-benzocyclooctenol 36 was known to result in fragmentation to 37 (33). Fragmentation could not occur if the 2-vinylcyclopropylbenzocyclo-octene 33 were rearranged thermally. A preliminary study was under-taken using 6-cyclopropyl-7,8,9,10-tetrahydrobenzocyclooctene as a model compound.

The method of Evans, Carooll and Truesdale (34) was used as previously reported by Thies and Seitz (5) to prepare 7,8,9,10-tetra-



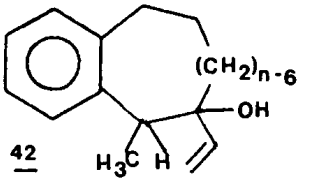
36 37

hydro-6(5H)-benzocyclooctenone 39 from commercial purchased benzo- • suberone. The cyclopropylbenzocyclooctenol derivative was prepared from 39 and the cyclopropyl Grignard reagent. Elimination was effected using glacial acetic acid in refluxing ethanol. This is not a standard procedure for the elimination of an alcohol, but the tertiary alcohol on 40 apparently is eliminated upon protonation of the alcohol by acetic acid.



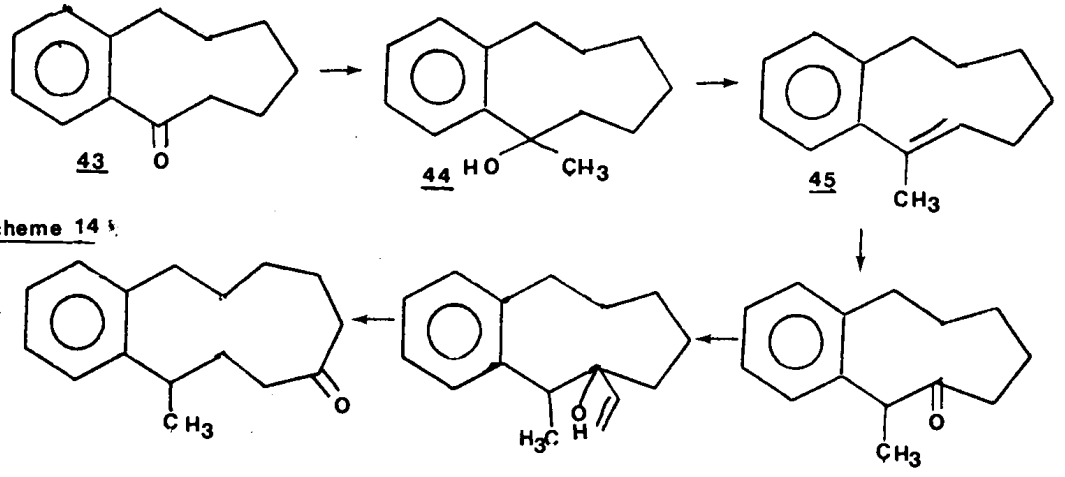
39 40 41

Although no difficulties were encountered with the project outlined above, stereochemical studies involving 1,3 sigmatropic shifts were undertaken and the vinylcyclopropyl system set aside. The stereochemical integrity of the carbon at the migrating center following anionic or thermal rearrangement was the focal point of the studies. Attempts were made to synthesize a compound such as 42.



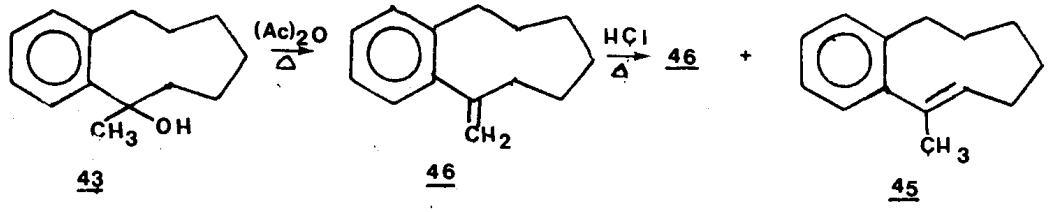
42

The synthetic pathway which was to be followed is outlined in Scheme 14. The alkylation of the ketone 43 with methyl lithium gave an 82 percent yield of 44. The elimination of the alcohol moiety with acetic anhydride did not, however, give 45. Analysis of the



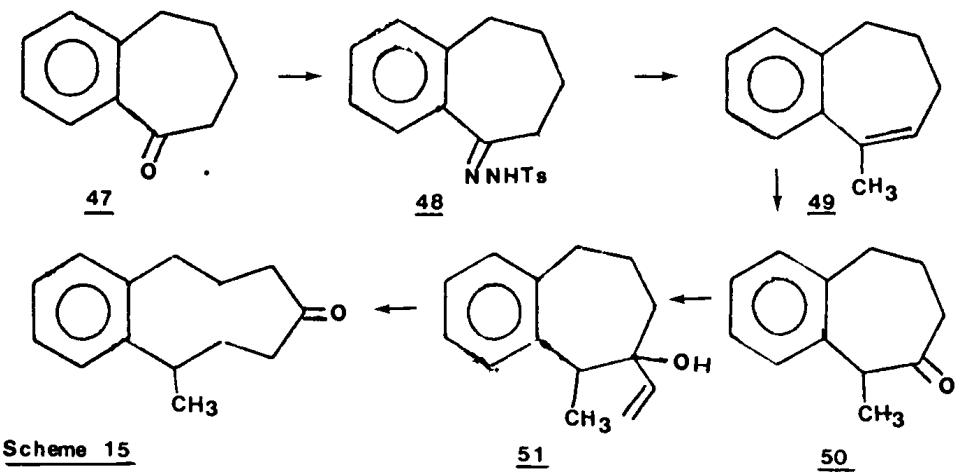
Scheme 14

NMR spectrum of the product indicated formation of the exo-methylene derivative 46. Attempts to isomerize the product in refluxing hydrochloric acid gave rise to a ca, 50:50 mixture of 45 and 46 (Scheme 14).



43 46 45

Attention was focused on the seven membered ring system. The planned synthetic sequence is outlined in Scheme 15.



47 48 49 51 50

Scheme 15

Benzosuberone was purchased and the tosylhydrazone prepared in 62 percent yield in refluxing ethanol. The methods of Shapiro, et al. (36) and of Chamberlin (37) were combined in a procedure for the synthesis of 49 using butyllithium/tetramathylethylenediamine as a base and methyl iodide as the alkylating agent.

Concurrently with the above work, the preparation and attempted rearrangement of 8,9-dihydro-6-vinyl-6(5H)-benzocycloheptanol were carried out. The conversion of α-tetralone to 8,9-dihydro-6(5,7H)-benzocycloheptenone was effected via the amino methyl alcohol using a modification of the method of Evans, Carrol and Truesdale (34). An 18-crown-6 ether complex of potassium cyanide was used as a catalyst rather than zinc iodide as was used by Evans, Carrol and Truesdale in the formation of the cyanohydrin. This modification improved yields for some medium ring systems and simplified the experimental procedure (35). The reaction sequence was repeated several times and consistently gave yields of less than 10 percent. This is in contrast

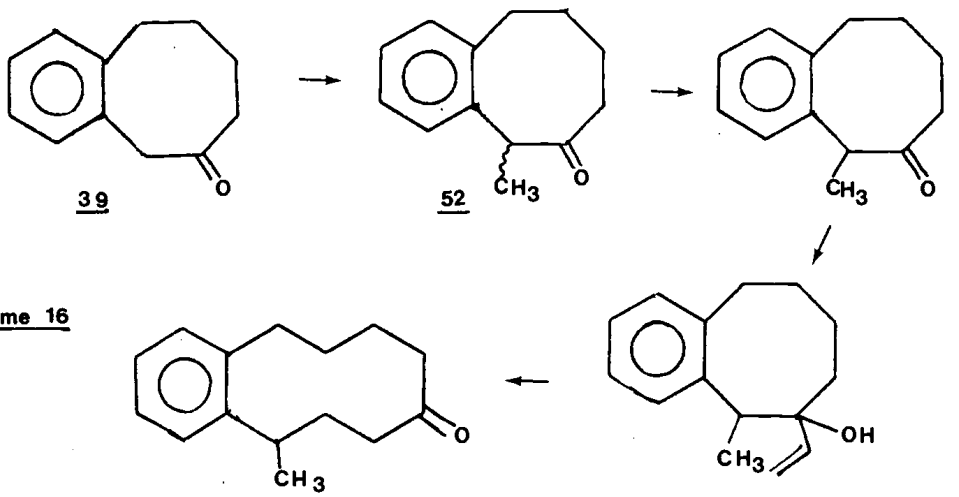
to yields of 80 percent or better when the same reaction sequence is used to generate 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone from benzosuberone and in contrast to a yield of 64 percent reported by Evans, Carrol and Truesdale (34) for the formation of 8,9-dihydro-6(5,7H)-benzocycloheptenone.

A vinyl Grignard reagent was used to convert 50 to 51. Rearrangement of 51 with potassium hydride in HMPA was attempted; however, an NMR analysis of the product showed only recovered starting material. The rearrangement of the eight membered ring analog of 51 takes place at room temperature in 5.5 hr (33) and similar conditions were expected to cause the rearrangement of the seven membered ring compound 51. Rearrangement of 51 did not occur, however, even after stirring for ten hours at 45°. The use of more vigorous conditions was not attempted because of the risk of decomposition of the solvent (HMPA).

The failure of 51 to rearrange was unexpected and warrants further study. The stereochemistry of the 1,3 sigmatropic shift was the focal point of our studies, so work on the synthetic pathway of Scheme 15 was not completed and studies involving the eight-membered ring analog were undertaken.

B. Part II: Preparation and rearrangement of 5-methyl-7,8,9,10-tetrahydro-6-vinyl-6-benzocyclooctenol

Efforts were directed to a study involving the rearrangement of 7,8,9,10-tetrahydro-6-vinyl-6-benzocyclooctenol. The preparation of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone 39 has been reported previously (5). It was expected that once alkylation was effected,

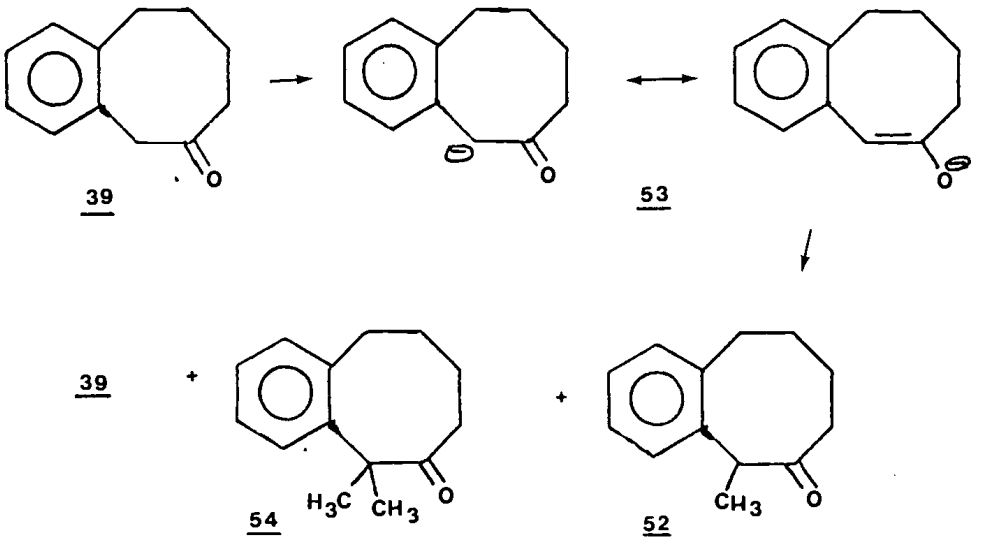


Scheme 16

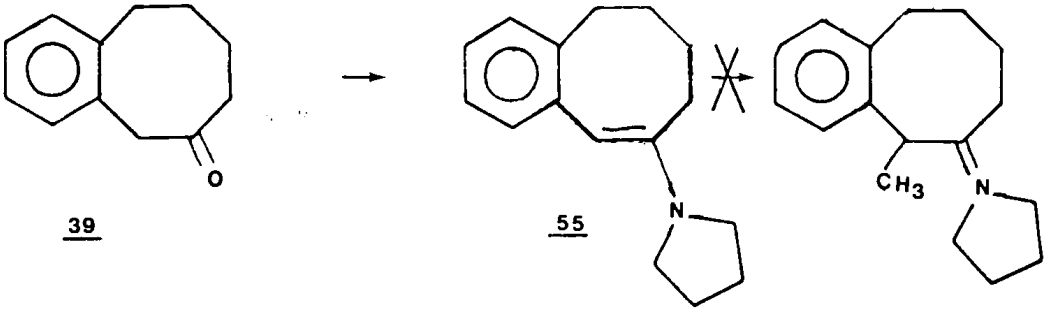
the α-methyl ketone could be resolved. Vinyl Grignard reagent could then be used and the resulting alcohol rearranged in potassium hydride and HMPA. The stereochemistry of the alcohol carbon (C-6) would be of less interest, as that carbon would not be chiral in the product. (Scheme 16)

The preparation of pure 5-methyl-7,8,9,10-tetrahydro-6-(5H)-benzocyclooctenone was much more difficult than had been originally anticipated. Several synthetic approaches were tried before one was found which gave reasonable yields of the desired compound.

The simplest approach involved the formation of the enolate anion 53 with lithium diethyl amide followed by methylation with iodomethane. The alkylation of 3-vinylcyclooctenone and 3-vinylcyclodecenone had been carried out using this procedure (35). This pathway gave relative yields (based on glc) of 10 percent, 50 percent and 38 percent of recovered starting material 39, the desired α-methyl ketone 52 and α,α-dimethyl ketone 54, respectively. The separation of a useful quantity of 52 from 39 and 54 was not considered likely because of the similarity of these three products.



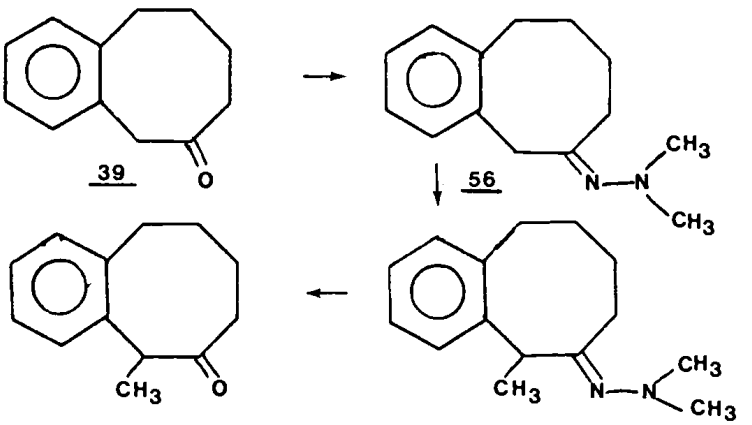
In an effort to overcome the problem of dialkylation which was encountered with the enolate, the enamine derivative of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone was prepared by the method of Stork, et al. (38). No difficulty was encountered in the preparation of the enamine, but alkylation did not occur even when the enamine was subjected to a considerable excess of alkylating agent and vigorous conditons (100°, 48 hr.). Alkylation at the nitrogen atom is known to be an undesirable side reaction in enamine alkylation reactions (38). Hydrolysis of the product of N-alkylation gives recovered starting ketone and an acid soluble alkylated pyrollidine which is washed



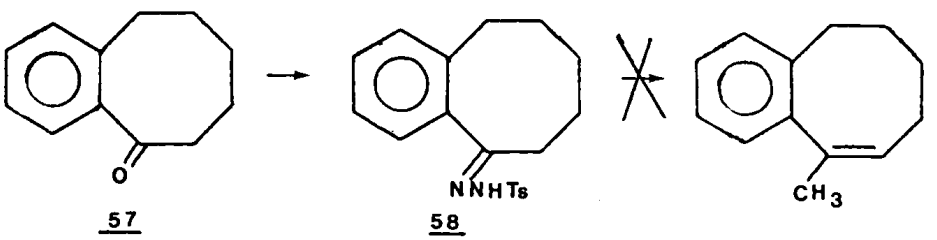
out of the organic layer (38). The failure of the enamine 55 to alkylate is probably due to such N-alkylation.

The synthetic route outlined in Scheme 17 was then attempted. The dimethyl hydrazone was prepared by the method of Newkome and Fischel (39). Attempted alkylation gave a product which was not identifiable from its NMR spectrum.

Scheme 17



The combined methods of Shapiro, et al. (36) and of Chamberlin (37) used in the preparation of 5-methyl-8,9-dihydro-(7H)-benzocycloheptane reported above were applied to the preparation of 5-methyl-7,8,9,10-tetrahydrobenzocyclooctene. The starting ketone 56 was

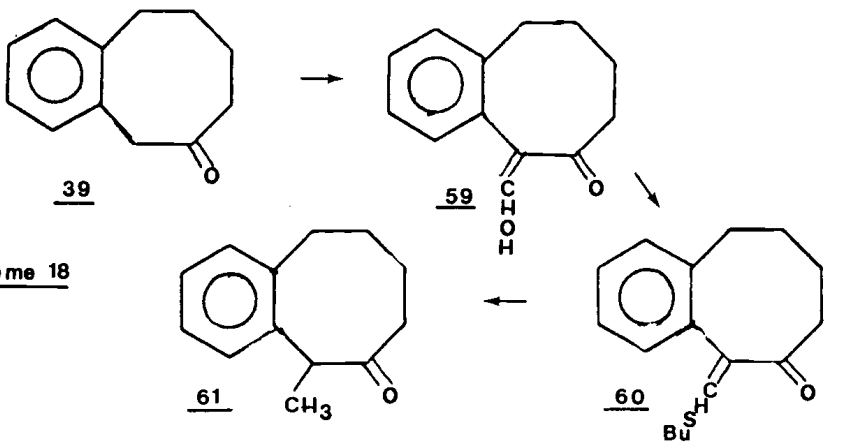


57 58

prepared by the method of Caubere (40). The tosylhydrazone 58 was prepared from 56 in room temperature methanol (46). The anion was generated with butyllithium in TMEDA/hexane. Attempted alkylation of the anion with either iodomethane or dimethyl sulfate was unsuccessful. Shapiro, et al., (36) have reported that the alkylation

of trisylhydrazones leads to higher yields of substituted product than does the alkylation of the corresponding tosylhydrazones. An attempt at preparation of the trisylhydrazone derivative of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone was unsuccessful.

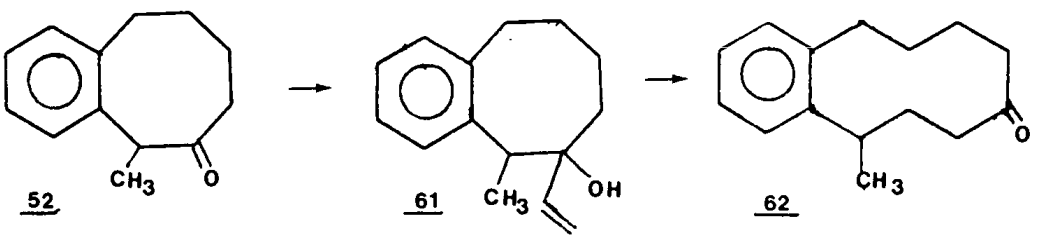
A less direct approach involving the formation of the hydroxymethylene derivative was tried (Scheme 18). The method of Johnson



Scheme 18

and Posvic (42) was used to prepare 5-hydroxymethylene-7,8,9,10-tetrahydro-6-benzocyclooctenone 59 in 69 percent yield. The thiobutyl compound 60 was prepared by the method of Ireland and Marshall (43). The thiobutyl derivative was reduced with Raney nickel to 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone 52.

Resolution of the ketone 52 was not carried out, but it was established that the presence of the methyl group did not hinder the addition of the vinyl Grignard reagent to the ketone, nor the ring expansion step leading to the benzocyclodecenone 62. (Scheme 19). The yields of reactions to the unsubstituted ketone 39 with the vinyl Grignard reagent are restricted because of enolization of the starting ketone (44). The vinyl Grignard reagent reacts readily with 5-methyl-6-benzocyclooctenone and the reaction goes nearly to completion in



52 61 62

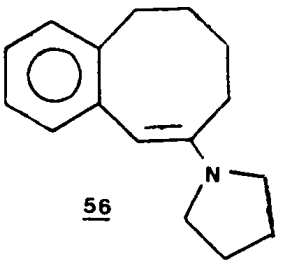
Scheme 19

contrast with the reaction of the unsubstituted ketone where the best yields obtained are 50-60 percent even when a sample of ketone is repeatedly allowed to react with an excess of vinyl Grignard (44).

The rearrangement of 61 to 62 was carried out without difficulty under the same conditions used by Seitz (33) for the rearrangement of 7,8,9,10-tetrahydro-6-vinyl-6-benzocyclooctenol.

The synthetic sequence leading to the formation of 5-methyl-6,7,8,9,10,11-hexahydro-8-benzocyclodecenone is thus complete and the ring expansion route need only be carried out using optically active 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone.

The method of Adams, Chapman, Sieja and Welstead (45) is one of several that could be used to resolve the ketone 52. This method involves the formation of the pyrrolidine enamine of the ketone. The enamine of 7,8,9,10-tetrahydro-6-benzocyclooctenone was formed without difficulty and there is no reason to assume that the presence of the 5-methyl substituent will have a substantial effect on the rate of enamine formation, although steric considerations might lead to formation of 63 rather than an analog of 56 (38). The procedure for the resolution of the ketone calls for the d-camphor-10-sulfonate salt of the enamine to be formed (13). Systematic recrystallization effects separation of the diastereomeric salts and hydrolysis of the salts



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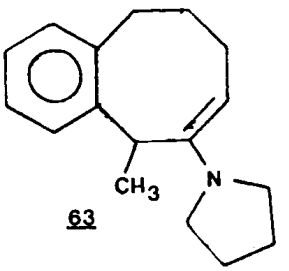

63

in dilute aqueous potassium hydroxide at room temperature for five minutes results in formation of the separated enantiomeric ketones (13).

The ring expansion of the optically active ketone should provide some insight into the mechanistic question. The production of totally racemic benzocyclodecenone could be indicative of a biradical mechanism. Inversion of stereochemistry at the methyl group (migrating center) would be evidence for orbital symmetry control of the rearrangement.

IV. EXPERIMENTAL

A. General Laboratory Procedures and Conditions

All reactions involving air or moisture sensitive materials were carried out under a nitrogen atmosphere. Solvents were purchased commercially and purified or dried using standard procedures.

Nuclear magnetic resonance spectra were recorded on Varian HA-100 (100 MHz), EM-360 (60 MHz) and FT-80 instruments. Infrared spectra were obtained on a Perkin-Elmer 727B. High resolution mass spectra were obtained from a CEC 110B instrument.

Gas-liquid chromatography (GLC) analyses were performed on a Varian 920 (0.25 in. columns) with a thermal conductivity detector and on a Varian Series 1200 (0.125 in. columns) with a flame ionization detector. The GLC columns are identified as follows:

Column A: 4' x 0.125 in. 7.4% OV101 on Chromosorb W, 80-100

Column B: 2' x 0.125 in. 5.0% OV101 on Chromosorb W, 80-100

Column C: 10' x 0.125 in 4.2% stabilized DEGS on Chromosorb G, 80-100

Column D: 4.85' x 0.250 in. 10% OV101 on Chromosorb G, 60-80

Column E: 10' x 0.250 in. 16.5% OV101 on Chromosorb G, 80-100

GLC data is reported as: column X, column temperature, flow rate.

Standard workup involves diluting the reaction mixture with diethyl ether, washing twice with distilled water, washing once with saturated sodium bicarbonate solution, and finally washing with saturated ammonium

chloride solution. Products were concentrated by removing the solvent with a rotary evaporator under reduced pressure.

B. Preparation of 6-cyclopropyl-7,8,9,10-tetrahydro-6(5H)-benzocyclooctenol (40)

A 63 percent yield was obtained in the preparation of 6-cyclopropyl-7,8,9,10-tetrahydro-6(5H)-benzocyclooctenol. The cyclopropyl Grignard reagent was prepared from 0.418 g (17 mmoles) of magnesium turnings (Baker) and 1.35 mL (17.2 mmoles) of cyclopropyl bromide (Aldrich) in 15 mL dry THF. A few crystals of iodine and a gentle heating were necessary to initiate formation of the Grignard reagent. After 30 minutes a dropping funnel charged with 1.5 g (8.6 mmoles) of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone was placed on the flask and the ketone added to the Grignard reagent over a 10 minute period. The reaction was quenched with a few mL saturated ammonium chloride solution after stirring overnight. The reaction mixture was worked up in the standard manner and gave the alcohol 40 as product: NMR ($CDCl_3$): δ 7.3-7.0 (s, 4H), 3.4 (s, 2H), 2.9-2.4 (m, 2H), 2.3-1.3 (m, 6H), 0.7-0.3 (m, 5H).

C. Preparation of 6-cyclopropyl-7,8,9,10-tetrahydrobenzocyclooctene (41)

A solution of 0.5 g (2.3 mmoles) of 6-cyclopropyl-7,8,9,10-tetrahydro-6(5H)-benzocyclooctenol and 1 mL glacial acetic acid (Dupont) in 5 mL of absolute ethanol was refluxed overnight. Elimination of the alcohol was ca. 75 percent complete: NMR ($CDCl_3$): δ 7.3-7.0 (m, 4H),

6.2 (s, 0.75H), 3.4 (s, 0.50H), 2.9-2.4 (m, 2H), 2.3-1.3 (m, 6H), 0.7-0.3 (m, 5H).

D. Preparation of 6,7,8,9,10,11-hexahydro-5-methyl-5-benzo-cyclononenol (44)

To a stirred solution of 0.10 g (0.53 mmoles) of 6,7,8,9.10,11-hexahydro-5-benzocyclononenone in 2 mL of THF at 0° was added an excess (0.5 mL, 8 mmoles) methyllithium (Ventron). The solution was allowed to stir overnight at room temperature, then quenched with a few mL of saturated ammonium chloride solution and worked up in the standard manner. The product 44 was obtained in 82 percent yield: NMR ($CDCl_3$): δ7.4-7.0 (m, 4H), 2.8-2.6 (m, 2H), 2.1-1.0 (m, 13H, contains broad singlet at δ1.2).

E. Attempted preparation of 5-methyl-8,9,10,11-tetrahydro-(6H)-benzocyclononene (45)

A solution of 0.08 g (0.4 mmoles) 6,7,8,9,10,11-hexahydro-5-methyl-5-benzocyclononenol in 2 mL acetic anhydride was allowed to reflux for 2 hr. The solution was then diluted with a few mL of ether and worked up in the standard manner. The product was 5-methylene-6,7,8,9,10,11-hexahydrobenzocyclononene: NMR (CCl_4): δ7.2-6.9 (m, 4H), 5.2 (bs, 1H), 4.8 (d, J=2 Hz, 1H) 2.9-2.6 (m, 2H), 2.5-1.5 (m, 10H).

At attempt was made to isomerize the product by allowing it to reflux in a solution of concentrated hydrochloric acid (Dupont) for 1 hr. A ca. 50:50 mixture of the 5-methyl:5-methylene compounds was

obtained: NMR (CCl_4): δ 7.2-6.9 (m), 5.5-5.4 (broad m), 5.2 (bs), 4.8 (d, J=2Hz), 2.9-2.6 (m), 2.5-1.5 (m).

F. Preparation of the tosylhydrazone of benzosuberone (48)

The tosylhydrazone of benzosuberone was prepared in 62 percent yield by refluxing for 1 hr a mixture of 3.0 g (19 mmoles) benzosuberone (Aldrich) and 3.0 g (19 mmoles) tosylhydrazine in a minimum amount of absolute ethanol and recrystalizing the product: NMR ($CDCl_3$): δ8.0-7.8 (m, 2H), 7.4-7.0 (m, 6H), 2.7-2.5 (t, J=5Hz, 2H), 2.5-2.3 (m, 5H contains singlet at δ2.5), 1.9-1.5 (m, 4H).

G. Preparation of 5-methyl-8,9,-dihydro-(7H)-benzocycloheptene (49)

5-methyl-8,9-dyhydro-(7H)-benzocycloheptene was prepared by a combination of the methods of Shapiro, et al. (47) and of Chamberlin (48) from 0.348 g (1 mmole) of the tosylhydrazone of benzosuberone and 1.4 mL (3 mmoles) butyllithium (2.2 M) in 10 mL 50 percent N,N,N'-trimethylethylenediamine (TMEDA)/ 50 percent hexane. A 1 mL (15 mmoles) portion of iodomethane (Mallinckrodt) was used to methylate the dianion. The product was purified by flash chromatography (49) using 80 percent pentane/20 percent diethyl ether and vacuum transferred at 50° and 1 mm Hg: NMR (CCl_4) δ7.2-7.0 (m, 4H), 6.0-5.8 (m, 1H), 2.6-2.4 (t, J=7Hz, 2H), 2.2-1.7 (m, 7H, contains broad singlet at δ2.1). IR (neat): 3100, 3050, 2950, 2850, 1610, 1510, 1475, 1320, 1200, 1160, 1100, 1060, 1030, 830, 800, 760 cm^{-1}.

Another preparation gave a mixture of the above product and the exo-methylene isomer.

H. Attempted methylation of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone

To a solution of 0.9 mmoles butyllithium (Aldrich) in dry THF at 0° was added 100 mL (0.9 mmoles) freshly distilled diethylamine (MCB). This mixture was stirred for 5 minutes, cooled to -78° and 0.14 g (0.8 mmoles) of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone was added. This solution was stirred 5 minutes. The mixture was taken up into a syringe and injected into a flask containing 1.6 mL dry DMSO and 0.4 mL (7 mmoles) iodomethane (Mallinckrodt) at room temperature. This solution was allowed to react for 10 minutes, then diluted with pentane and a small amount of distilled water. Standard work up procedure was used. Analysis of the product by glc revealed a mixture of unreacted starting material 39, the 5-methyl derivative 52; and the 5,5-dimethyl derivative 54 (column B, 125°, 30 ml/min; ca. 10 percent starting material 39 with shortest retention time, 50 percent 5-methyl 52 with a slightly longer retention time, and 38 percent 5,5-dimethyl 54 with the longest retention time).

I. Preparation of the enamine derivative of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone (55)

The enamine derivative was prepared by the method of Stork, et al. (503) from 0.58 g (2.9 mmoles) of the ketone and 1.0 mL (12 mmoles) pyrrolidine (Baker) in 25 mL dry toluene. The enamine was not purified, but the formation of the adduct was indicated by the crude NMR: (CCl_4): δ7.2-6.9 (m), 5.1 (bs), 3.2-3.1 (m), 2.8-2.5 (m), 2.1-1.3 (m).

J. Attempted methylation of the enamine of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone

The method of Stork, *et al.* (50) was used. A mixture of 3 mmoles of the enamine was heated to reflux with 1.2 mL (20 mmoles) iodomethane (Mallinckrodt) and 2 mL dry dioxane. After 15 hr at 43°, glc analysis (column A, 140°, 25 mL/min) indicated that less than 5 percent of the enamine had reacted. The mixture was heated to 100° and allowed to reflux for 48 hr. Glc analysis still indicated very little reaction. The iodomethane and dioxane were removed by distillation and an NMR spectrum taken of the soluble (CCl_4) products: δ7.2-7.1 (m, 4H), 3.8-3.7 (m, 2H, contains singlet at δ3.7), 2.9-2.6 (m, 2H), 2.4-1.2 (m, 9H, contains small doublet at 1.4-1.2, J=6 Hz).

K. Preparation of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone N,N-dimethyl hydrazone (56)

The N,N-dimethylhydrazone was prepared in 35 percent yield by the method of Newkome and Fischel (51) from 0.50 g (2.8 mmoles) of the ketone and 0.7 mL (8.4 mmoles) N,N-dimethyl-hydrazine (MCB) in 5 mL of absolute ethanol: NMR (CCl_4): δ7.5-7.0 (m, 4H), 4.0 (s, 1H), 3.7 (s, 1H), 3.0-2.5 (m), 2.5 (s), 2.4 (s) (δ3.0-2.4 integrates for a total of 8H), 1.9-1.5 (m, 6H). NMR integration indicates that the product is a *ca.* 50:50 mixture of the syn:anti isomers.

L. Attempted preparation of 5-methyl-7,8,9,10-tetrahydrobenzocyclooctenone N,N-dimethylhydrazone

The reaction was carried out according to the procedure of Corey and Enders (52) using 217 mg (0.9 mmoles) of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone N,N-dimethyl-hydrazone and 0.9 mmoles freshly prepared lithium diisopropylamide in 5 mL dry THF. An unidentified product was obtained: NMR (CCl_4): δ7.5-6.5 (m), 4.0-3.6 (m), 3.1-0.7 (m).

M. Preparation of 7,8,9,10-tetrahydro-5(6H)-benzocyclooctenone tosylhydrazone (58)

The tosylhydrazone derivative of 7,8,9,10-tetrahydro-5(6H)-benzocyclooctenone wa prepared in 58 percent yield by the method of Swenson and Danino (46). To a stirred solution of 400 mg (1 mmole) tosylhydrazine in a few mL of methanol was added 364 mg (1 mmole) of the ketone. This solution was allowed to stir overnight at room temperature. The methanol was then poured off and the white crystalline product washed with methanol and allowed to dry. The NMR spectrum was identical with that of an authentic sample.

N. Attempted preparation of 5-methyl-7,8,9,10-tetrahydrobenzocyclooctene

The methods of Shapiro, et al. (47) and of Chamberlin (48) were combined in a procedure similar to that used in the preparation of 5-methyl-8,9,-dihydro-(7H)-benzocycloheptene. To a solution of 200 mg (0.55 mmoles) of the tosylhydrazone of 7,8,9,10-tetrahydro-5(6H)-benzocyclooctenone in 1 mL of TMEDA was added 0.55 mL (1.65 mmoles)

2.2 M butyllithium. When iodomethane was used as the methylating agent (0.4 mL, 6.5 mmoles, Mallinckrodt), the product was 7,8,9,10-tetrahydrobenzocyclooctene: NMR (CCl_4): δ7.5-7.0 (m, 4H), 6.5-6.3 (d of t, J=2,12, 1H), 5.9-5.6 (quintet, J=4, 1H), 2.7-1.2 (m, 8H). IR (neat): 3080, 3020, 2950, 2870, 1500, 1460, 1360, 1300, 1270, 1150, 1100, 1050, 1030, 820, 76- cm^{-1}. When dimethylsulfate (1 mL, 10 mmoles, Baker) was used as the methylating agent, an unidentified product exhibiting no vinyl protons in its NMR spectrum was obtained.

O. Preparation of 5-hydroxymethylene-7,8,9,10-tetrahydro-6-benzocyclooctenone (59)

The hydroxymethylene derivative of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone was prepared in 69 percent yield by the method of Johnson and Posvic (53) from 3.2 g (18.7 mmoles) of 7,8,9,10-tetrahydro-6(5H)-benzocyclooctenone, 2.0 g (38 mmoles) sodium methoxide (Mallinckrodt), and 2.9 mL (38 mmoles) ethyl formate (Baker) in 40 mL of dry toluene: NMR (CCl_4): δ8.5 (s, 1H), 7.8-6.8 (m, 5H), 3.0-1.2 (m, 8H). IR (neat): 3300 (braod), 3100, 3050, 2950, 2900, 1650 (strong, broad), 1500, 1450, 1350, 1250, 1200, 1100, 1000, 950, 760, 750 cm^{-1}.

P. Preparation of 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone (52) from 5-hydroxymethylene-7,8,9,10-tetrahydro-6-benzocyclooctenone (59)

The method of Ireland and Marshall (54) was used to prepare 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone in 47 percent yield. A solution of 2.5 g (12.3 mmoles) 5-hydroxymethylene-7,8,9,10-tetra-

hydro-6-benzocyclooctenone, 1.5 g (16 mmoles) butanethiol (Aldrich), and a trace of paratoluenesulfonic acid (Mallinckrodt) in 50 mL benzene was refluxed with a Dean-Stark trap. The progress of the reaction was followed by thin layer chromatography (30 percent ethyl acetate-70 percent pentane). No attempt was made to isolate the thiol compound; when the reaction appeared to have gone to completion (after refluxing 5 hr), the Dean-Stark trap was removed and replaced with a short path. The benzene and remaining butanethiol were removed by distillation.

Raney nickel was freshly prepared by the method of Fieser and Fieser (55).

The short path was replaced by a reflux condensor and ca. 7 g of the freshly prepared Raney nickel in ethanol was added to the reaction vessel. The reaction was heated to reflux temperature and glc analysis was used to follow the reaction progress (Column A, 170°, 35 mL/min). The retention times of the 5-n-butylthiomethylene compound and the product 5-methyl compound were 4.7 min and 0.9 min, respectively. After 2 hr, ca. 3 g Raney nickel was added. The reaction appeared to have gone to completion after 7 hr. Diethyl ether was added to the reaction vessel and the Raney nickel removed by filtration with celite. The filtrate was subjected to standard work up. The analytical sample was obtained by preparative glc (Column C, 160°, 20 mL/min). Retention time of the 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone under these conditions was 13 min: NMR (CCl_4): δ7.1 (S, 4H), 3.7 (q, J=6, 1H), 3.0-2.3 (m, 11H, contains d at δ2.5-2.3, J=6); IR (CCL_4): 3150, 3100, 2950, 2900, 1710, 1550,

1500, 1450, 1260, 1220, 1120, 1090, 1080, 1050, 1020, 990 cm^{-1}, m/e 188.120 (calculated for $C_{13}H_{16}O$: 188.120).

Q. Preparation of 5-methyl-6-vinyl-7,8,9,10-tetrahydro-6-benzocyclooctenol (61)

A solution of 5.0 mL of vinyl Grignard reagent (56) (1.3 M) in THF was placed under vacuum (1.0 mm Hg) until all the THF was removed. The vacuum was replaced by a nitrogen atmosphere and the dry Grignard reagent dissolved in dry ether. The system was heated to reflux and a solution of 150 mg (0.8 mmoles) of 5-methyl-7,8,9,10-tetrahydro-6-benzocyclooctenone in 5 mL dry ether was added to the reaction vessel. Glc analysis (Column A, 145°, 30 mL/min) showed that the reaction had proceeded to greater than 90 percent completion after 2 hr. The reaction mixture was quenched with saturated ammonium chloride solution and worked up using the standard procedure. The analytical sample was obtained by preparative glc: (Column D, 160°, 20 mL/min, retention time: 21 min.): NMR (CCl_4): δ7.3-7.1 (m, 4H), 6.5 (d of d, J=10, 16 Hz, 1H), 5.5 (d of d, J=16, 1.5 Hz, 1H) 5.2 (d of d, J=10, 1.5 Hz, 1H), 3.7-3.2 (q, J=8, 1H), 2.8-2.6 (m, 3H), 2.2-1.3 (m, 9H, contains d at δ1.5-1.3); IR (neat): 3500 (broad), 3100, 3050, 2950, 2900, 1500, 1460, 1380, 1160, 1140, 1120, 1040, 1000, 820, 760 cm^{-1}; m/e 216.152 (calculated for $C_{15}H_{20}O$: 216.151).

R. Preparation of 5-methyl-6,7,9,10,11,12-hexahydro-8-benzocyclodecenone (62)

The 5-methyl-6-vinyl-7,8,9,10-tetrahydro-6-benzocyclooctenol (100 mg, 0.5 mmoles) was rearranged with 100 mg (0.6 mmoles) potassium hydride (Alfa, 22 percent in oil) in 2 mL dry HMPA by the method of E.P. Seitz (33). The major product (80 percent) was 5-methyl-6,7,9,10,11,12-hexahydro-8-benzocyclodecenone. The analytical sample was prepared by preparative GLC (Column E, 170°, 20 mL/min, retention time: 12.5 min.): NMR ($CDCl_3$): δ7.2-7.1 (m, 4H, contains sharp singlet at δ7.1), 3.3-2.8 (m, 1H), 2.7-1.1 (m, 15H, contains doublet at δ1.3-1.2, J=5); IR (CCl_4): 3000, 2950, 2900, 1720 (sharp), 1600, 1580, 1560, 1270, 1230, 1100, 1020, 1000 cm^{-1}; m/e 216.149 (calculated for $C_{15}H_{20}O$: 216.151).

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