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I am submitting herewith a dissertation written by Julian Everette Parker III, entitled "An Investigation of Possible Anionic [1,4] Sigmatropic Shifts in Bicyclo[3.1.0]hex-2-enes." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

Ronald M. Magid, Major Professor

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Donald C. Kleinfelter

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Hilton A. Smith
Vice Chancellor
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AN INVESTIGATION OF POSSIBLE ANIONIC [1,4] SIGMATROPIC SHIFTS IN BICYCLO[3.1.0]HEX-2-ENES

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Julian Everette Parker, III

December 1976

1303772

DEDICATION

The author dedicates this dissertation to his wife, Brenda, for her encouragement, financial support, understanding, and assistance during the course of this investigation and to Dr. Ronald M. Magid, Dr. Richard M. Pagni and Dr. J. M. Riemann whose doors were always open.

ACKNOWLEDGMENT

The author wishes to express his sincere gratitude and deepest appreciation to Dr. Ronald M. Magid for his advice and encouragement during the course of this work, his patience and assistance during the writing of this dissertation, and his unyielding dedication to teaching and to chemistry.

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Appreciation is also extended to the Petroleum Research Fund for financial assistance for the summers 1973 and 1974, to E. I. duPont de Nemours and Company for their financial support of the seminar program and assistance in the purchase of many of the instruments used in this work, and to the University of Tennessee for a teaching assistantship for years 1971—1976, and to the Chemistry Department for a summer scholarship for 1975.

ABSTRACT

The reaction of ethylidene iodide with indene in the presence of either a zinc-copper couple or diethylzinc was examined. The reaction involving the zinc-copper couple produced only intractable tars. The use of diethylzinc produced a 3:1 mixture of endo- and exo-6-methyl-2,3-benzobicyclo[3.1.0] hex-2-ene, in contrast to the claim by Furukawa, et al., that only the endo isomer is formed.

The catalyzed reaction of ethyl diazoacetate and indene was examined and a method of separating the epimeric cyclopropanes by a stereoselective saponification was developed. The synthesis of exo-6-methyl-2,3-benzobicyclo[3.1.0]hex-2-ene by the preparation of the exo cyclopropylcarbinyl mesylate and reduction with $LiAlH_4$ was investigated.

The syntheses of 2,5,5-trimethylcyclohexa-1,3-diene, 2-phenyl-5,5-dimethylcyclohexa-1,3-diene, and 3-phenyl-1,5,5-trimethylcyclohexa-1,3-diene are reported and the attempted generation of an anion that would undergo an anionic [1,4] sigmatropic shift of an alkyl group is discussed.

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CHAPTER I

INTRODUCTION

A. General Introduction

The concept of the conservation of orbital symmetry is a familiar principle used by quantum mechanicians and spectroscopists. The application of this concept to organic reactions remained obscure[1-4] until the preliminary communication in 1965 by R. B. Woodward and Roald Hoffmann.[5] Their paper was concerned with the role of orbital symmetry in electrocyclic transformations.

The application of orbital correlation diagrams to electrocyclic reactions[6] and cycloadditions[7] as well as the selection rules for sigmatropic reactions[8] appeared shortly after the initial publication. Two final communications dealt with the application of this concept to the role played by orbital symmetry in determining the endo-exo relationships in concerted cycloadditions[9] and orientation effects in sigmatropic reactions.[10]

These papers served as the basis for: (a) the reexamination of what had been poorly understood reactions; (b) verification of the principle of orbital symmetry; (c) observations of apparent exceptions; and (d) new derivations or descriptions of the concept. More importantly, the principle of the conservation of orbital symmetry allowed for postulation of new reactions. The principle also allowed "risky" predictions (the expectation of an event which is in direct opposition to and would refute accepted theory) to

be made concerning energy sources, concertedness, and the stereochemical results of these new reactions. The success of this theory in explaining "no-mechanism" reactions,[11] coupled with the verification of many of the "risky" predictions, served to insure its rapid acceptance.

The amount of understanding and research generated by this theory has been equaled only by the development of conformational analysis or by the appreciation of the phenomenon of resonance in organic chemistry. When the definitive review in this area appeared in 1969 only four years after the initial communication, it contained over 400 references.[12] Since the first publications in 1965, there have been more than 250 books and review articles published concerning the theory and related developments. Very few concepts in organic chemistry have provided scientists with such a fertile area of research.

Although a considerable amount of effort has been directed in this area in the last ten years, only a few reactions can be considered to be completely characterized in terms of the generality of the mechanistic conclusions, scope, and synthetic potential. Many reactions have been only partially characterized or have not been investigated in terms of source of energy, concertedness, and stereochemical results.

Even those reactions that have been examined may, in some instances, be explained by less esoteric theories such as the principle of least motion[13-19] which states that the most favored pathway

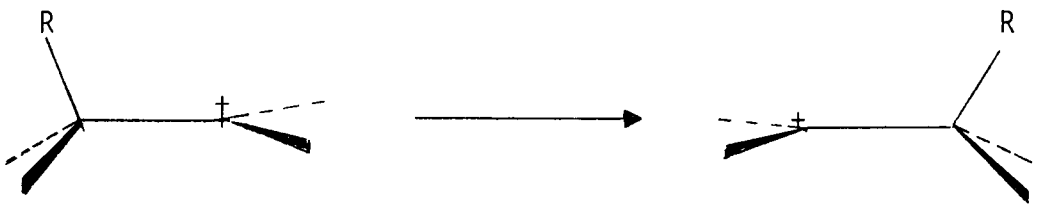
is the one which involves the least change in atomic position and electronic configuration. Perturbation theory[2, 24-26] and configuration interaction[20-23] have also found applications in understanding pericyclic reactions, as well as organic reactions in general. Recently the use of connectivity cycles has been invoked in an attempt to generalize the Woodward-Hoffmann Rules[27] for pericyclic reactions.[28] In general, all of these other theories lead to the same conclusions as is found from the application of the conservation of orbital symmetry.

Berson has argued that a real test of orbital symmetry only occurs when the predictions of these rules are in direct opposition to the predictions derived from one of the alternative explanations.[29] Sigmatropic reactions, a class of pericyclic reactions, offer a good arena for such duels to be constructed. Berson and Nelson[30] have provided one such contest. They examined the [1,3] suprafacial migration of an alkyl group in which the conservation of orbital symmetry was pitted against the principle of least motion. In this particular case, the former was victorious, but further investigations of related systems were not as clear in this distinction.[31,32] This reaction is typical of the numerous neutral systems which have been investigated.[33-36] A similarly large effort has gone into the study of sigmatropic reactions in ionic systems.

B. Ionic [1,2] Sigmatropic Shifts

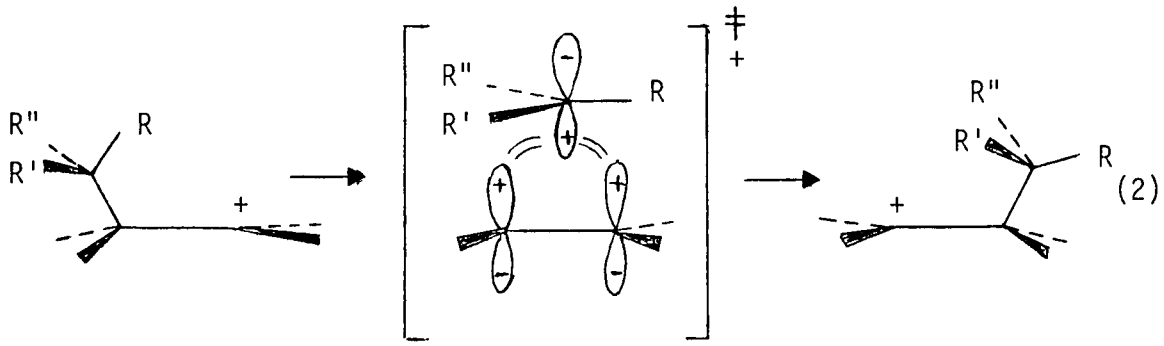
1. Cationic [1,2] Sigmatropic Shifts

One of the most familiar carbonium ion reactions is the Wagner-Meerwein rearrangement, a cationic [1,2] sigmatropic shift.



(1)

When this reaction is evaluated in terms of orbital symmetry conservation, the predicted result is that the reaction, if concerted and suprafacial, will proceed with retention of configuration of the migrating group.

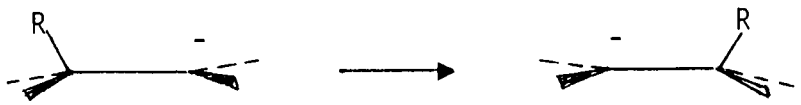


(2)

In those cases in which the stereochemistry has been examined, the migrating group always retains its configuration.[37-39] Although the prediction of orbital symmetry conservation appears to have been verified experimentally, it must also be noted that consideration of the principle of least motion results in the same prediction.[15-19] Thus cationic [1,2] sigmatropic shifts can not be considered as an adequate test of the conservation of orbital symmetry.

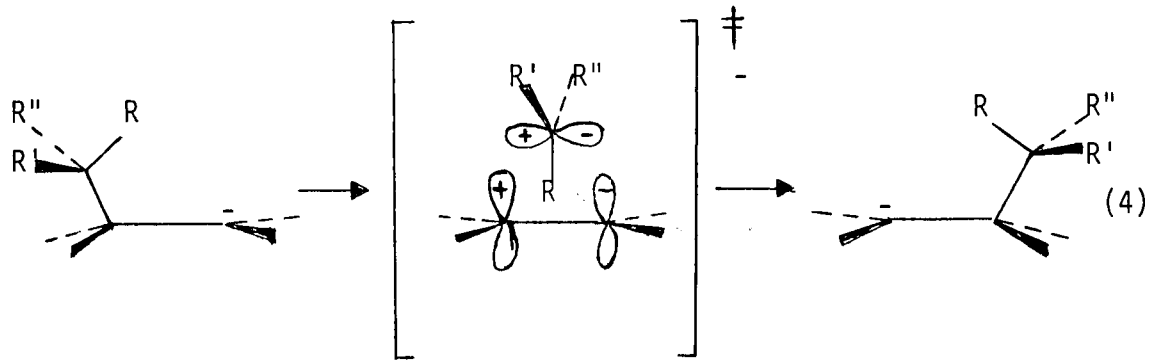
2. Anionic [1,2] Sigmatropic Shifts

Two of the more familiar anionic organic rearrangements are the Stevens and Wittig reactions[40,41] which are heteroatomic examples of the anionic [1,2] sigmatropic shift.



(3)

Examination of this process in terms of orbital symmetry conservation results in the prediction that the reaction, if concerted and suprafacial, will proceed with inversion of configuration of the migrating group.

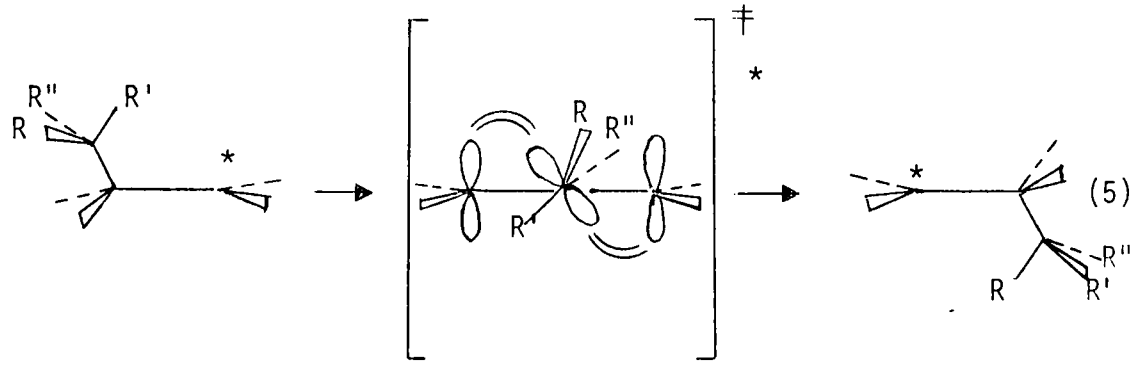


(4)

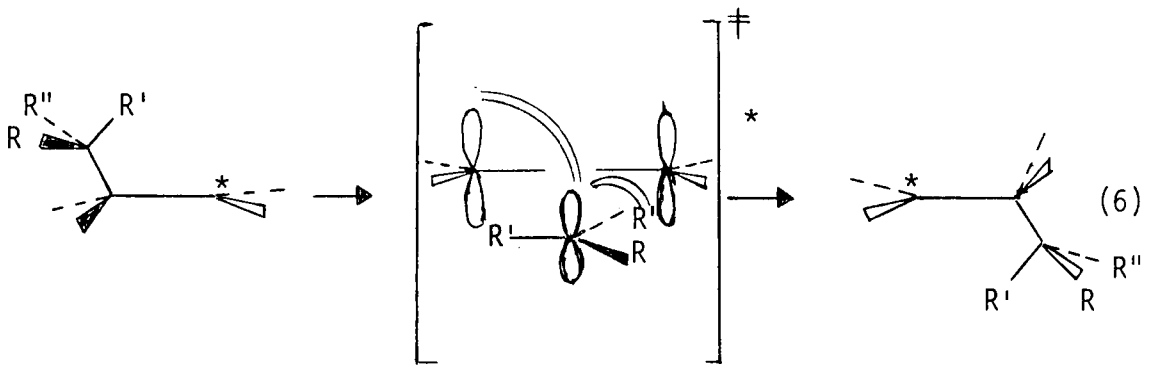
The likelihood of such an inversion of configuration of the migrating moiety is low on the basis of poor orbital overlap during the rearrangement and steric interaction of the migrating group with the substrate in the transition state.

The suprafacial path is the only process usually considered in most [1,2] and [1,3] sigmatropic reactions whether they involve

neutral, cationic or anionic systems. The other topological process, the antarafacial migration, is generally considered geometrically improbable,[42] although it has been postulated in some cases.[32]



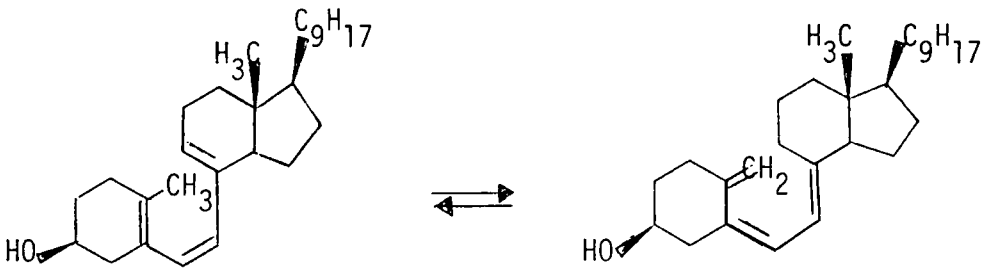
(5)



(6)

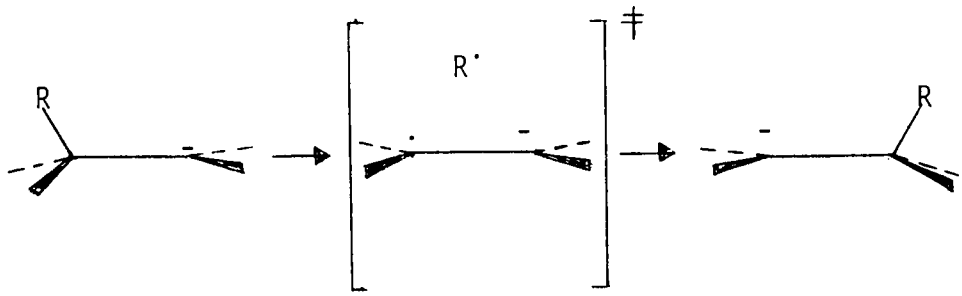
* -Cation or Anion

Antarafacial migrations, however, are geometrically attainable in higher order [1,j] sigmatropic reactions.[34] One of the earliest examples of an antarafacial [1,7] sigmatropic shift is the thermal equilibration of precalciferol 1 and calciferol 2.[43]



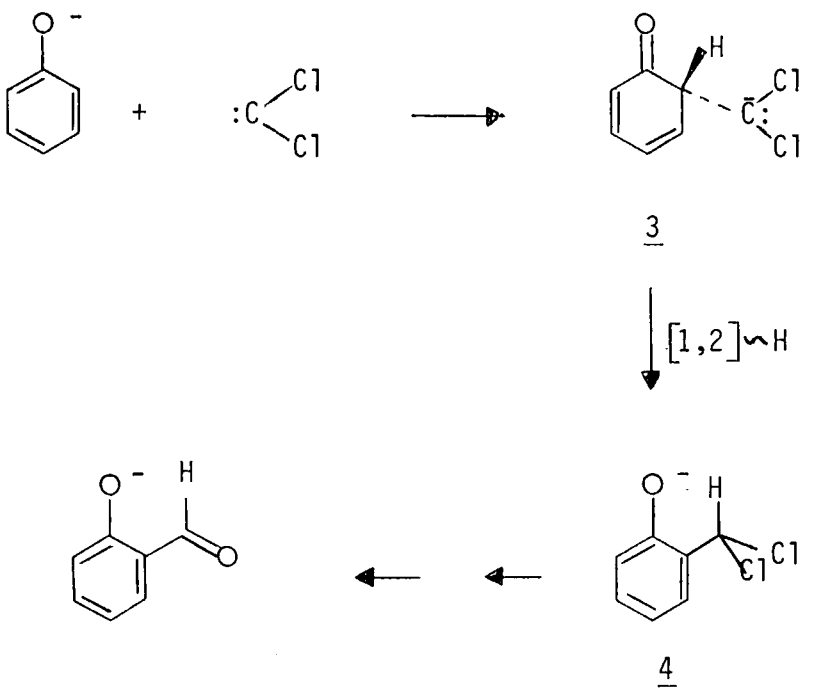
1 2 (7)

The anticipated low incidence of the concerted anionic [1,2] sigmatropic migration with inversion has been verified experimentally.[40,41] The reaction apparently proceeds by a step-wise homolytic cleavage-recombination, radical/anion—radical pair pathway.



(8)

Kemp[44] in investigating the proposed [1,2] sigmatropic shift of hydrogen in the Reimer-Tiemann reaction has provided one of the most elegant demonstrations of the power of orbital symmetry. The generally accepted mechanism for the Reimer-Tiemann reaction involves the conversion of intermediate 3 into 4 by a 1,2 shift of hydrogen.

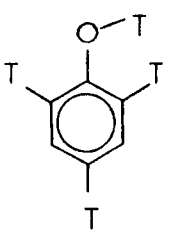


3

4

(9)

Such a [1,2] sigmatropic shift is a forbidden process, suprafacially. If this reaction does involve a [1,2] shift, the formyl proton of the product would originate from either the 2 or 6 position of the starting phenol. Tritiated phenol 5 was synthesized in order to investigate this mechanism.



(10)

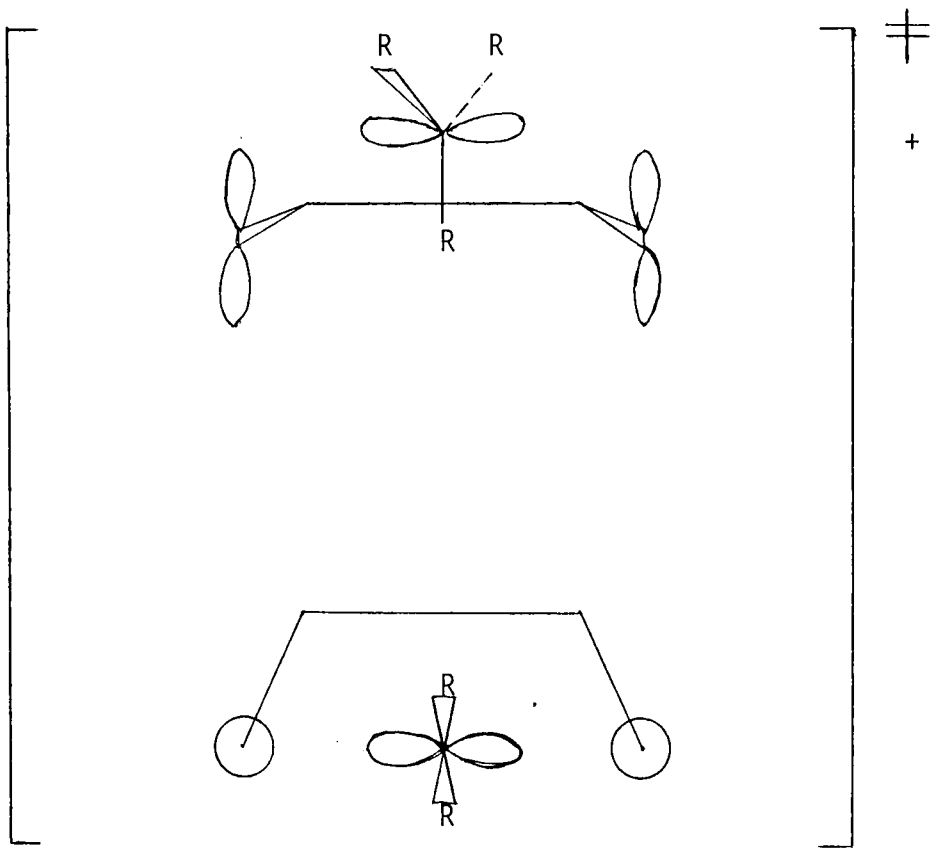
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When phenol 5 was allowed to react under typical Reimer-Tiemann conditions and the salicyaldehyde produced was analyzed, it was found that no tritium had been incorporated into the formyl group. However, when unlabeled phenol was allowed to react under Reimer-Tiemann conditions with HTO as the solvent, analysis showed almost exclusive incorporation of tritium into the formyl position; a similar incorporation of deuterium occurred when the reaction was carried out in D_2O. These results rule out the direct conversion of 3 into 4 by a [1,2] sigmatropic shift. Thus, in a system in which there exists a very large thermodynamic driving force to form product, the most direct route to product, an orbital symmetry forbidden process, is bypassed apparently in favor of the circuitous route involving proton transfers to and from solvent. Whether orbital symmetry is really controlling this reaction is debatable, but the results are quite consistent with the predictions concerning [1,2] sigmatropic migrations of hydrogen.

C. General Consideration of Ionic [1,4] Sigmatropic Shifts

Orbital symmetry analysis of the ionic [1,4] sigmatropic shifts yields the following conclusions: (a) the cationic [1,4] sigmatropic migration of an alkyl group, if concerted and suprafacial, will occur with inversion of configuration of the migrating center; (b) the anionic [1,4] sigmatropic migration of an alkyl group, if concerted and suprafacial, will occur with retention of configuration

of the migrating center; and (c) neither the cationic nor the anionic [1,4] sigmatropic shift should involve any severe interaction between the migrating moiety and the substrate, as illustrated for the cationic transition state 6.



(11)

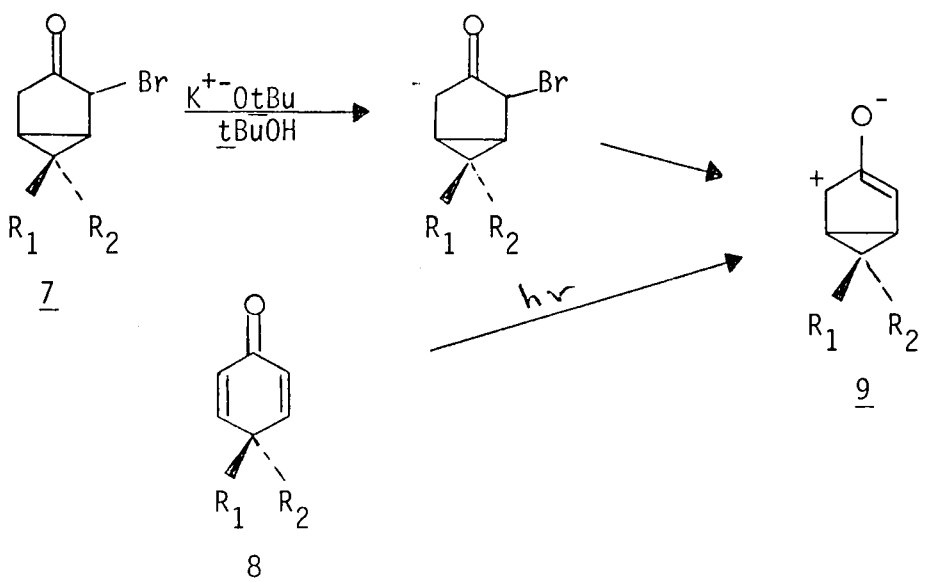
6

D. Cationic [1,4] Sigmatropic Shifts, the Ring-Walk Phenomenon

A number of cationic [1,4] sigmatropic shifts of an alkyl group have been reported. Swatton and Hart[45] have observed the migration of a cyclopropyl ring about four of the five sides of

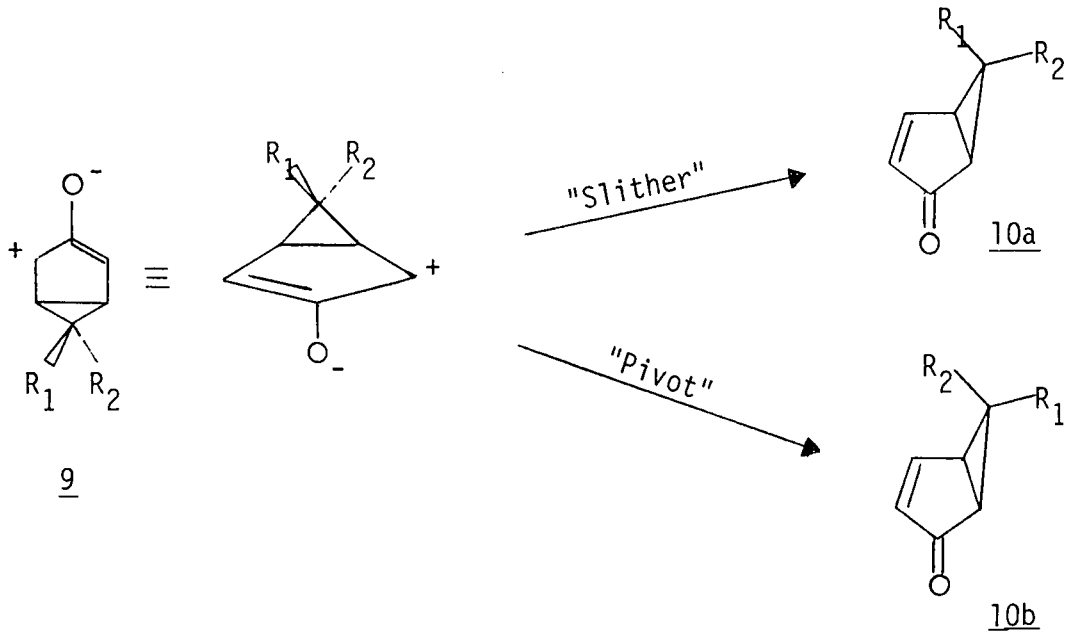
a five-membered ring. This experiment did not provide any information concerning the stereochemistry of the migrating carbon atom in this [1,4] sigmatropic shift. Circumambulation or ring-walk of the cyclopropyl ring in neutral systems has also been reported[36, 46-50]

There have been a number of studies carried out in which the stereochemistry of the migrating cyclopropyl carbon has been determined. Two of these investigations appeared in back-to-back communications in 1968. Zimmerman and Crumrine[51] investigated the rearrangement of the postulated zwitterion 9 obtained either by photolysis of dienone 8 or by treatment of bromobicyclic ketone 7 with potassium t-butoxide in t-butyl alcohol.



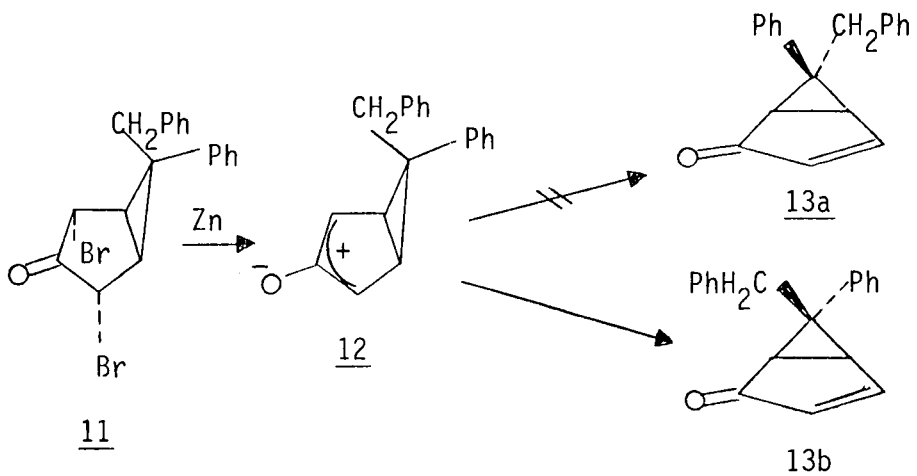
(12)

Zwitterion 9 may proceed to product 10a or 10b by either the "slither" mechanism (inversion of configuration), or the "pivot" mechanism (retention of configuration), respectively.



9 10a 10b (13)

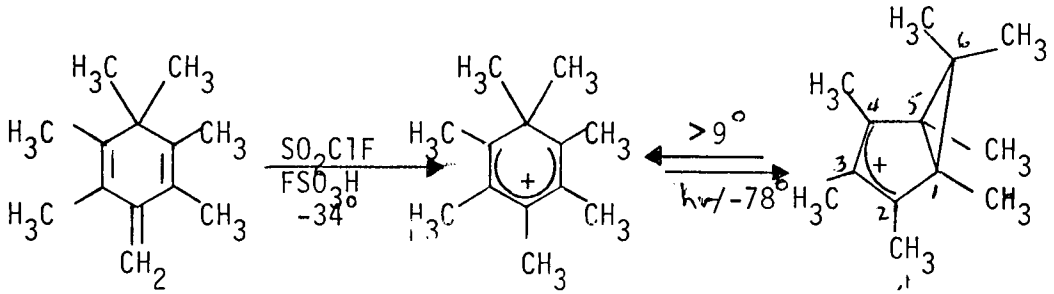
The results obtained by these workers were consistent with 99.5% of the reaction's proceeding by the "slither" mechanism, as expected for a cationic [1,4] sigmatropic shift of an alkyl group. Brennan and Hill[52] examined the stereochemistry of the rearrangement of dibromobicyclic ketone 11 with zinc,



11 12 13a 13b (14)

and obtained the unsaturated bicyclic ketone 13b. This reaction also proceeds with inversion of configuration of the migrating carbon, as expected for the cationic [1,4] sigmatropic migration of an alkyl group.

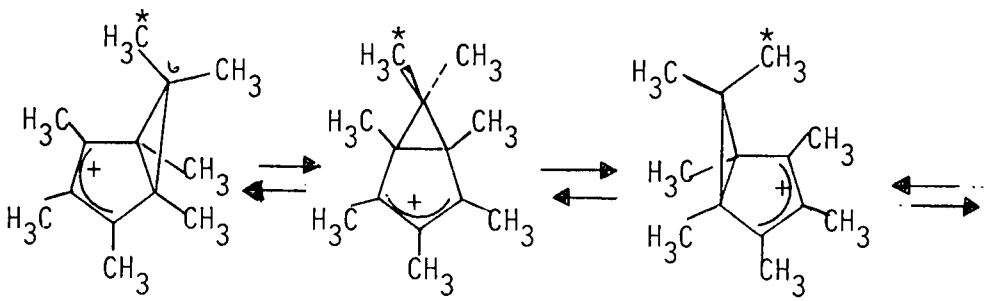
One of the most elegant examples of this inversion of configuration of the migrating center in a cationic [1,4] sigmatropic shift has been provided by Childs and Winstein.[53-55] These workers examined the temperature-dependent NMR spectrum of heptamethylbicyclo[3.1.0]hexenyl cation (16) obtained by photolysis at -78° C of heptamethylbenzenonium ion (15) which was, in turn, obtained by treating hydrocarbon 14 at -34° C with a 2:1 SO_2ClF—FSO_3H solution.



14 15 16 (15)

The photochemical conversion of carbocation 15 into 16 occurs by an allowed disrotatory ring-closure. Because the thermally allowed concerted reversion of 16 to 15 would have to proceed with conrotation, a geometrically unreasonable process, 16 is a relatively stable long-lived species. The NMR spectrum of 16 was examined in the temperature range of -110° to -9°. As the temperature was raised

from -110° to ca. -87°, the signals of the five methyl groups on the five-membered ring broadened and coalesced. Higher temperatures resulted in this signal's becoming a sharp singlet, while the two signals for the methyl groups on C_6 remained distinct and showed no sign of averaging even up to a temperature of -9°. At -9° carbocation 16 was converted into 15, presumably by the orbital symmetry forbidden disrotatory process. These workers concluded that this five-fold degenerate scrambling in carbocation 16 involved the circumambulation of the cyclopropyl atom C_6 around the five-membered ring, equilibrating structures 16, 16a, 16b, etc. In Equation 16, the starred CH_3 remains over the ring indicating inversion at C_6 as expected for an allowed [1,4] process.



(16)

16 16a 16b

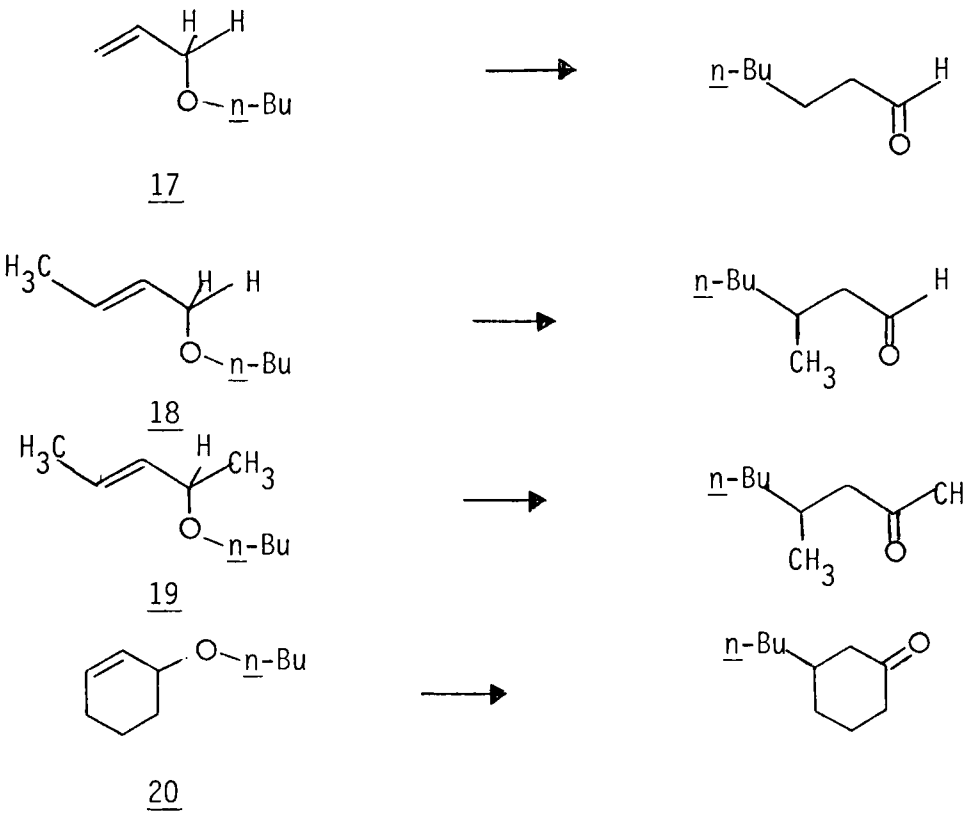
It was also shown that the allowed process (circumambulation) is more than 50,000 times faster than the forbidden process (ring-opening). Similar studies have been conducted by the research groups of Berson,[56,57] Schuster,[58,59] and Hart.[60]

It should be recognized that in every cationic [1,4] sigmatropic migration of an alkyl group, inversion of configuration of the migrating center has been observed. Although it would appear that the Rules have been verified, it should be noted that this inversion of configuration of the migrating group is also the expected result of the application of the principle of least motion[57] to these reactions. Thus, cationic [1,4] sigmatropic shifts of an alkyl group do not provide a good test of the principle of the conservation of orbital symmetry.

E. Anionic [1,4] Sigmatropic Shifts

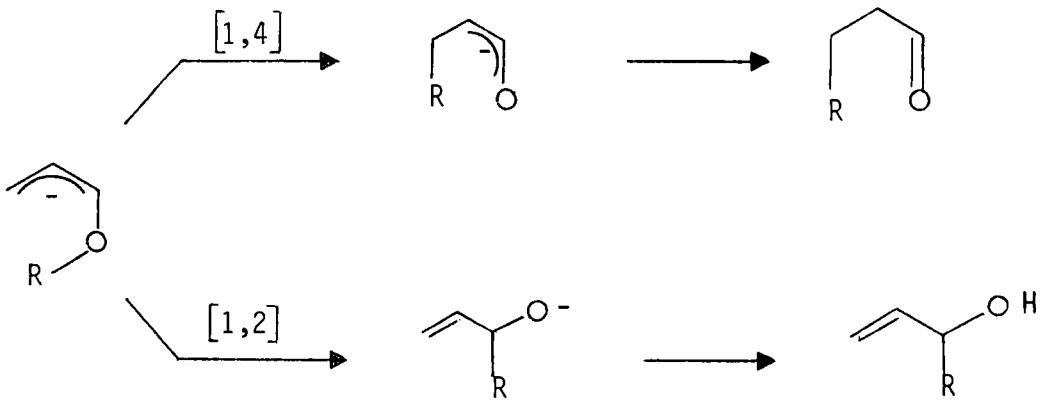
Anionic [1,4] sigmatropic shifts involving either a hydrogen or an alkyl group as the migrating moiety have been observed. Orbital symmetry conservation consideration of these reactions predicts: (a) the anionic [1,4] sigmatropic shift of a hydrogen will proceed suprafacially; and (b) the anionic [1,4] shift of an alkyl group will proceed suprafacially with retention of configuration or, with great difficulty, antarafacially with inversion of the migrating group.

Felkin and Tambuté observed an anionic [1,4] shift of an alkyl group in their investigation of the Wittig rearrangement of alkyl allyl ethers.[61] The ethers 17-20, when treated with a 30% excess of an equimolar mixture of propyllithium and TMEDA (N,N,N',N'-tetramethylethylenediamine), all afforded the corresponding aldehyde or ketone in yields of about 30%. The same result was obtained when THF (tetrahydrofuran) was substituted for TMEDA.



(17)

Products resulting from anionic [1,2] sigmatropic shifts were also formed under these conditions.

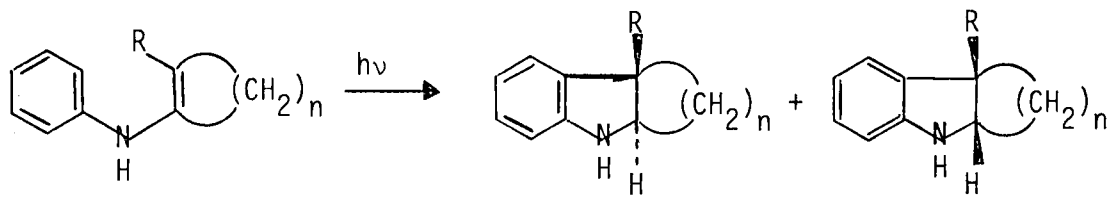


(18)

No stereochemical information concerning the migrating center was available from this study. When the ethers were treated with propyllithium in pentane without TMEDA or THF being present, the reaction led only to S_N2' products. Thus, when ether 17, in Equation 17, was treated with propyllithium in pentane, the product of the reaction was 1-hexene in 73% yield.

Only trace amounts of the Wittig rearrangement products were obtained under these conditions. It appears that a complexing agent like TMEDA or THF is necessary for proton abstraction to occur when using organolithiums.[62]

Chapman,et al.,[63,64] proposed a thermal anionic [1,4] sigmatropic shift of a hydrogen to explain the stereochemistry of the product produced from the photolysis of N-arylenamines.



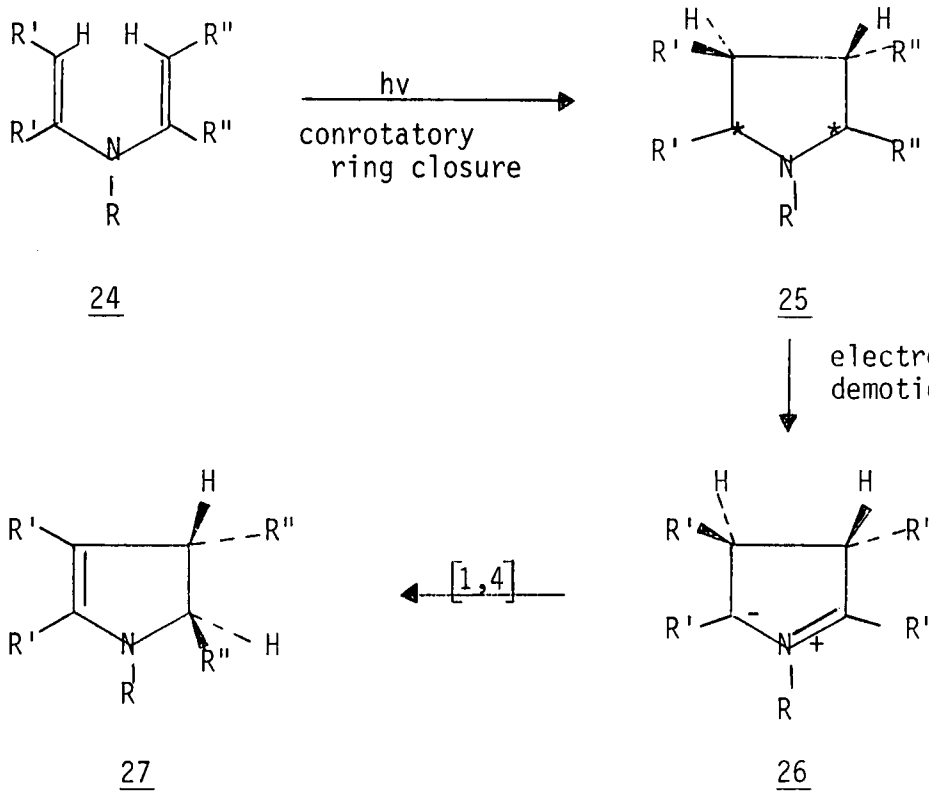
21 22 23

(19)

a	R=H,n=4	71%	3%
b	R=H,n=5	68%	5%
c	R=CH_3,n=4	77%	0%

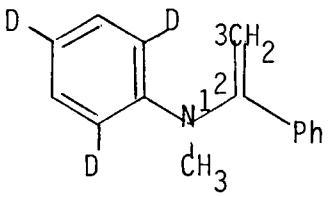
Irradiation of compounds 21a—21c led to the predominant formation of trans product 22a—22c (Equation 19). These workers viewed

the formation of the trans-fused products as occurring by the photochemically allowed conrotatory ring-closure of 24 to 25 (Equation 20). This ring-closure is followed by electron demotion to produce dipolar species 26, which then undergoes a suprafacial [1,4] sigmatropic shift of hydrogen to form the trans-2,3-disubstituted product 27 (Equation 20).



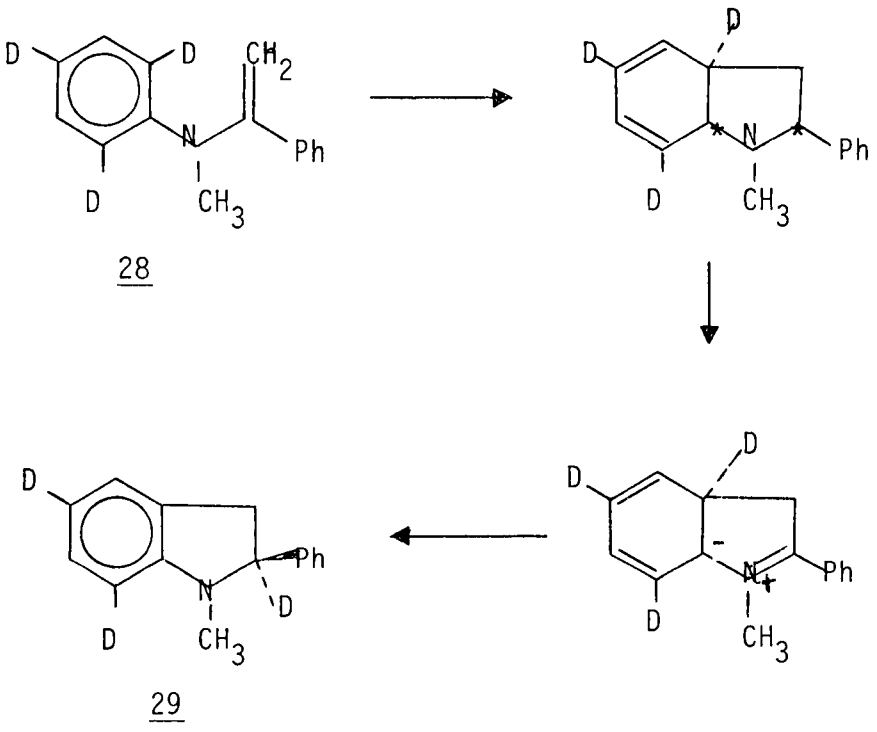
24 25 26 27 (20)

This mechanism explains the formation of the trans compounds, but it is not clear how the cis products 23a-c are formed. To investigate this question, these workers synthesized and studied the photolysis of the deuterium labeled compound 28.[64]



28

If the reaction proceeds by the mechanism involving the [1,4] shift, the deuterium label should be found on C_2 of 29 (Equation 21).

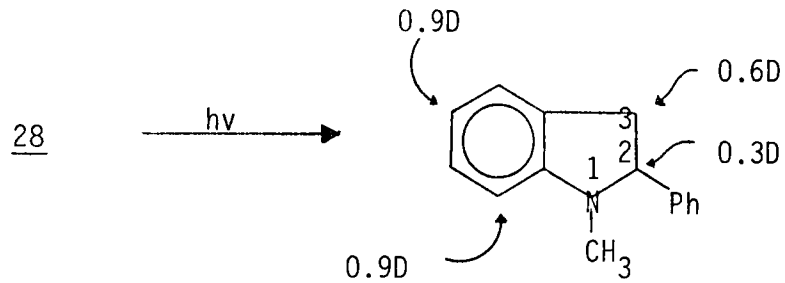


28

(21)

29

When the product from irradiation of 28 was analyzed for deuterium it was found that the label was distributed not only at C_2, but also at C_3 in 29 (Equation 22).

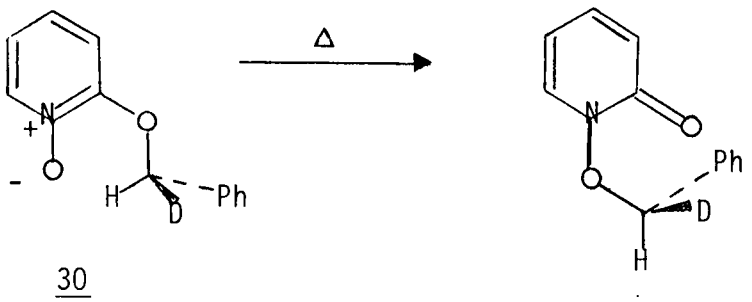


(22)

29

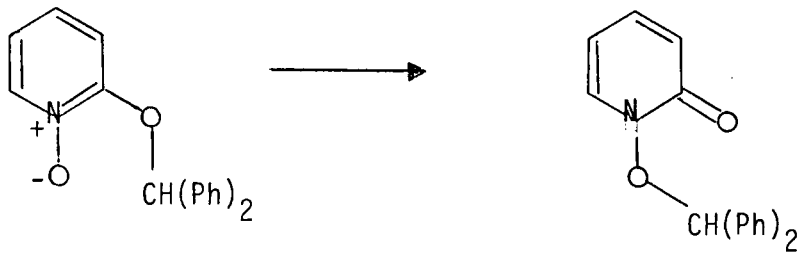
Chapman, et al., interpreted this as resulting from competition between the [1,4] shift and two [1,2] shifts. Although anionic [1,2] shifts are forbidden, it was pointed out that a concerted process in which two [1,2] shifts occur simultaneously in the excited state is an allowed reaction in terms of orbital symmetry conservation. Whether the shift occurs in the ground state or in the excited state could not be determined. Attempts to trap the postulated dipolar species 26 (Equation 20) with maleic anhydride were unsuccessful. Although the stereochemistry of the photolysis of 21 (Equation 19) is readily explained by a [1,4] shift, the deuterium labeling experiment casts considerable doubt upon such a mechanism's being the major pathway in the formation of the tricyclic products.

An anionic [1,4] suprafacial shift with retention of configuration of the migrating group has been observed by Schöllkopf and Hoppe.[65] These workers examined the rearrangement of α-alkoxypyridine-N-oxide 30 to N-alkoxy-α-pyridone 31 (Equation 23).



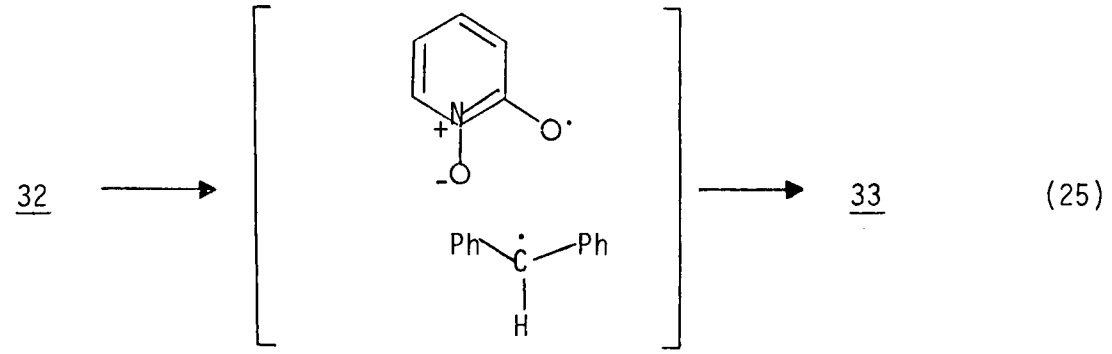
30 31 (23)

The reaction was found to proceed with 80% retention of configuration in the migrating group and without observation of CIDNP (Chemically Induced Dynamic Nuclear Polarization) signals. In contrast, when alkoxypyridine-N-oxide 32 rearranged to N-alkoxy-α-pyridone 33 (Equation 24), CIDNP signals were observed.



32 33 (24)

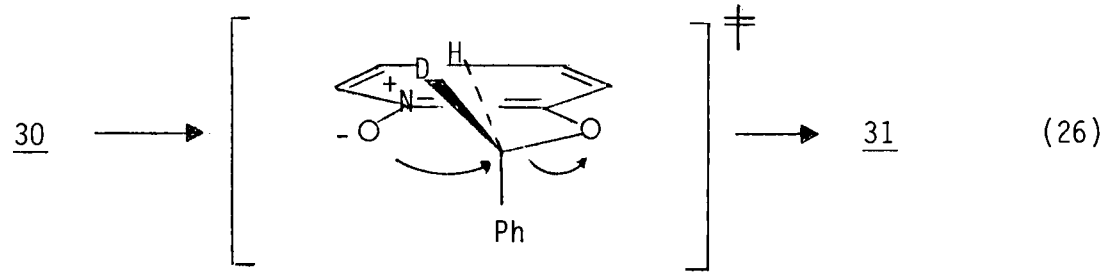
Because of the absence of CIDNP signals in the rearrangement of 30 to 31 (Equation 23), these workers concluded that this reaction proceeded by a concerted rather than a radical pathway. However, the conversion of 32 into 33 (Equation 24) was considered to proceed, to a large extent, by the step-wise radical/radical-anion cleavage recombination pathway forming 34 as the intermediate (Equation 25).



(25)

34

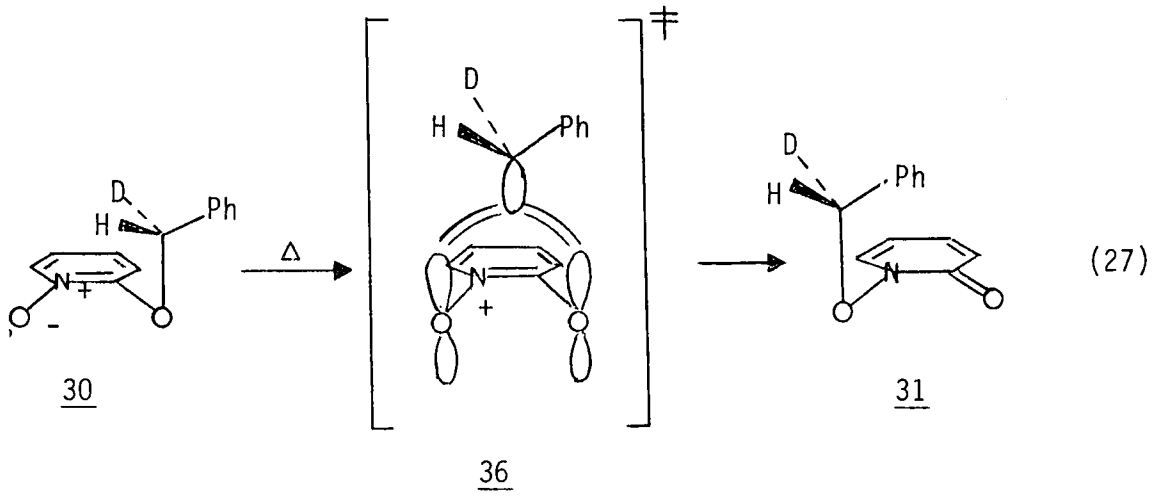
This change in mechanism is probably due to the inherent stability of radical 34. Although the result of the rearrangement of 30 into 31 (Equation 23) is quite consistent with the concepts of orbital symmetry, is this reaction a true test of the power of the conservation of orbital symmetry? What is the prediction of least motion for this reaction? What other mechanism can be envisioned for the rearrangement? Schöllkopf and Hoppe believe that the most likely mechanism for this rearrangement, other than either the sigmatropic shift or the radical cleavage-recombination pathway, is the intramolecular S_N2 mechanism proceeding through transition state 35 (Equation 26).



(26)

35

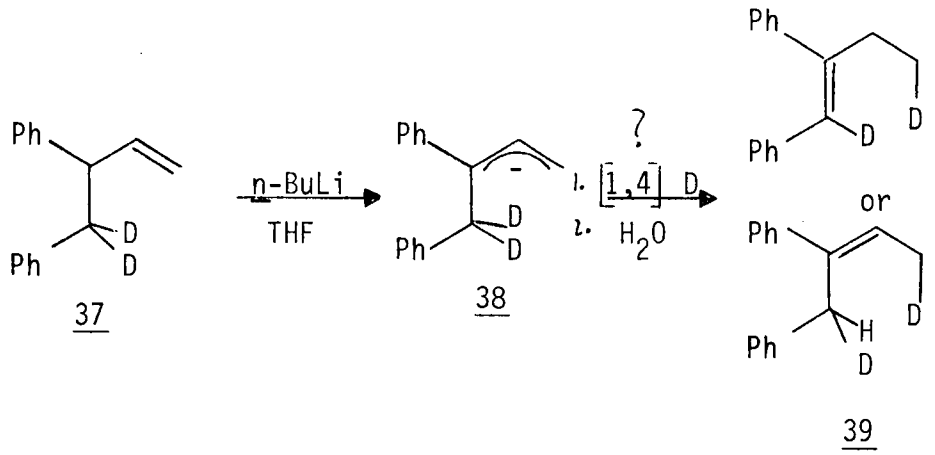
If this is the operative mechanism for this rearrangement, inversion of configuration of the migrating center should result. Clearly, then, such a mechanism is not responsible for the conversion of 30 into 31 (Equation 23). One could conclude that here is a true test of orbital symmetry, but one should first answer the question: what does the principle of least motion predict? The pathway in which transition state 36 is formed appears to be a more likely candidate than 35 for the least motion process.



30 36 31 (27)

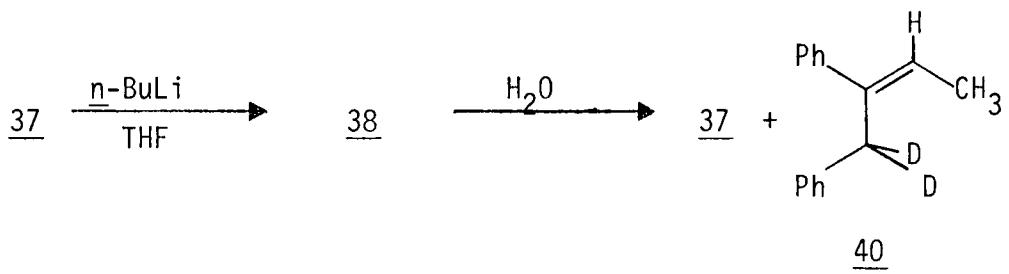
Such a mechanism predicts retention of configuration of the migrating center as was also predicted by orbital symmetry, and as is, in fact observed. Thus a true test of orbital symmetry remains to be designed.

Magid and Wilson,[66] searching for [1,4] shifts in an all carbon framework, examined the reaction of 37 with n-butyllithium (Equation 28).



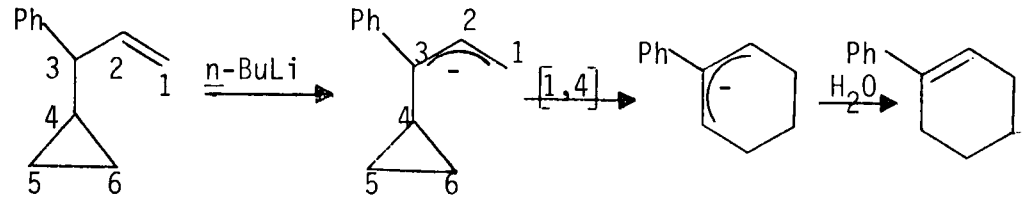
(28)

Treatment of 37 with n-butyllithium in hexane/THF yielded a deep-red solution which was refluxed overnight. Quenching of this still deep-red solution gave a mixture of 37 and 40 (Equation 29).



(29)

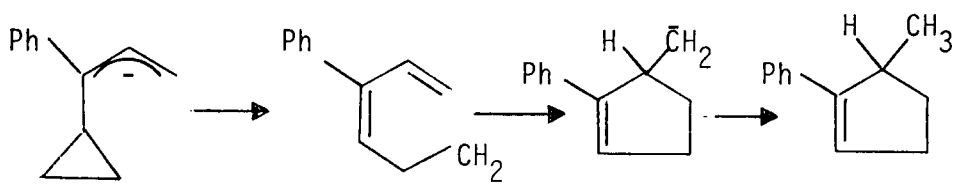
No evidence of deuterium scrambling could be obtained, thus ruling out any sigmatropic reaction of the type 37⟶39 (Equation 28). These workers also examined the reaction of 41 with n-butyllithium. This reaction should provide anion 42 which would generate, after quenching, 44 if a [1,4] shift of C_6 occurs (Equation 30).



(30)

41 42 43 44

Treatment of 41 with one equivalent of n-butyllithium in hexane/TMEDA followed by heating at 60° for 1 hr and then quenching with H_2O. yielded 46 as the only characterizable product. The authors suggested that formation of 46 resulted from initial ring-opening of anion 42 to 45, followed by cyclization to the five-membered ring (Equation 31).



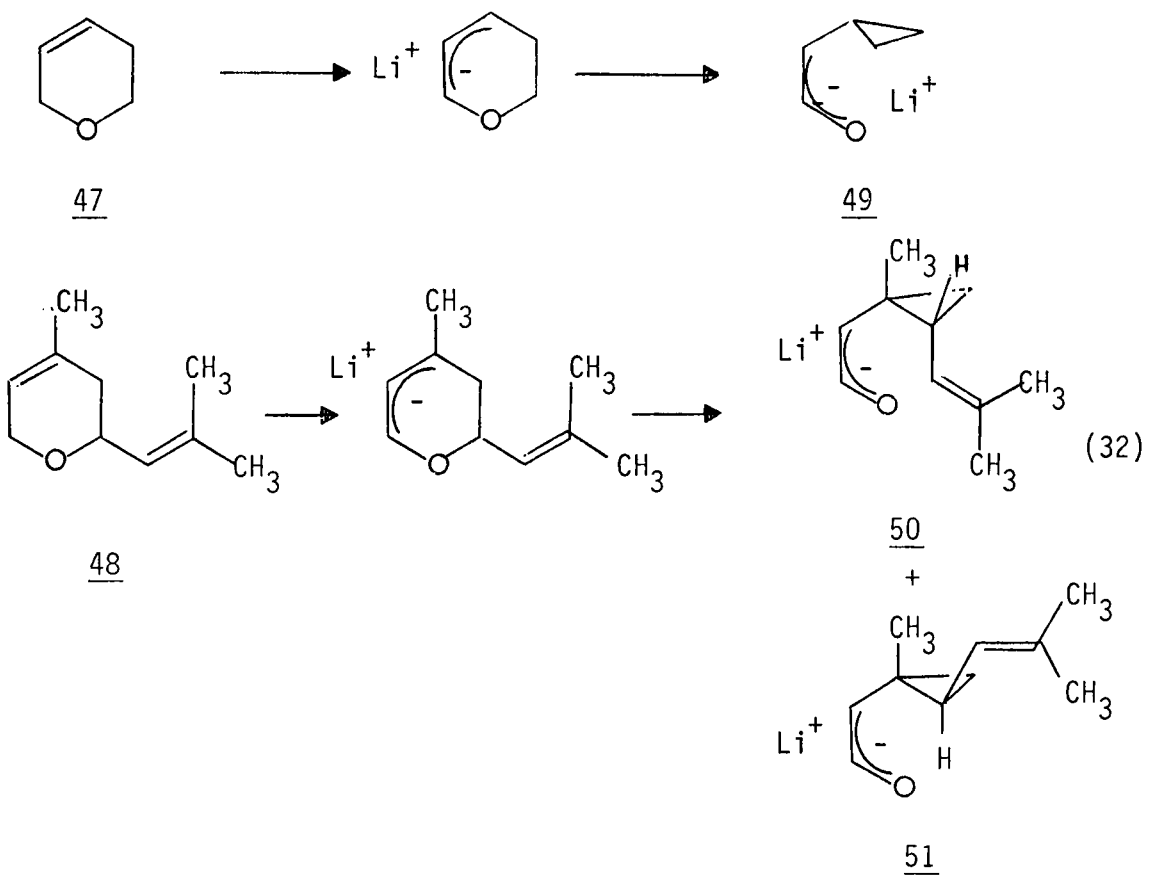
(31)

42 45 46

Kinetic and/or thermodynamic reasons were cited by the authors for the failure to observe the [1,4] shift of hydrogen in the anion 38 (Equation 29). No explanation was offered for the failure to observe the [1,4] shift of a carbon atom in Equation 31.

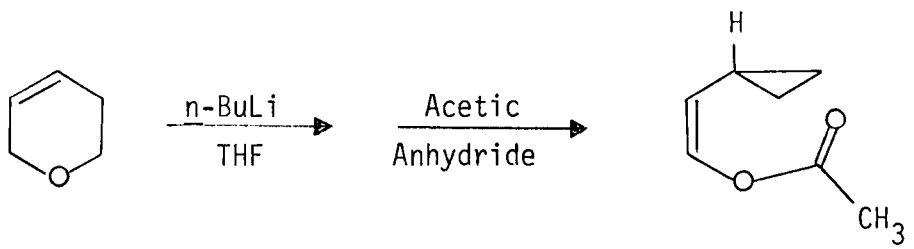
Rautenstrauch[67] has studied the lithiation of 5,6-dihydro-2H-pyran 47 and nerol oxide 48, and subsequent rearrangement to

form the respective lithium cyclopropyl enolates 49 and 50 and 51 (Equation 32).



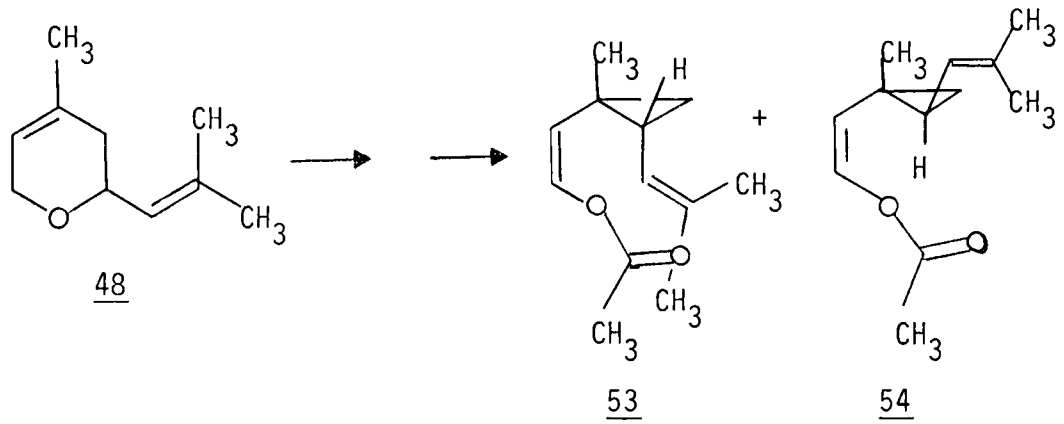
47 49 48 50 + 51 (32)

When 47 was treated with n-butyllithium in THF at -27°, and the product then quenched with acetic anhydride, cis-acetoxyvinylcyclopropane 52 was found as the only detectable product (Equation 33).



47 52 (33)

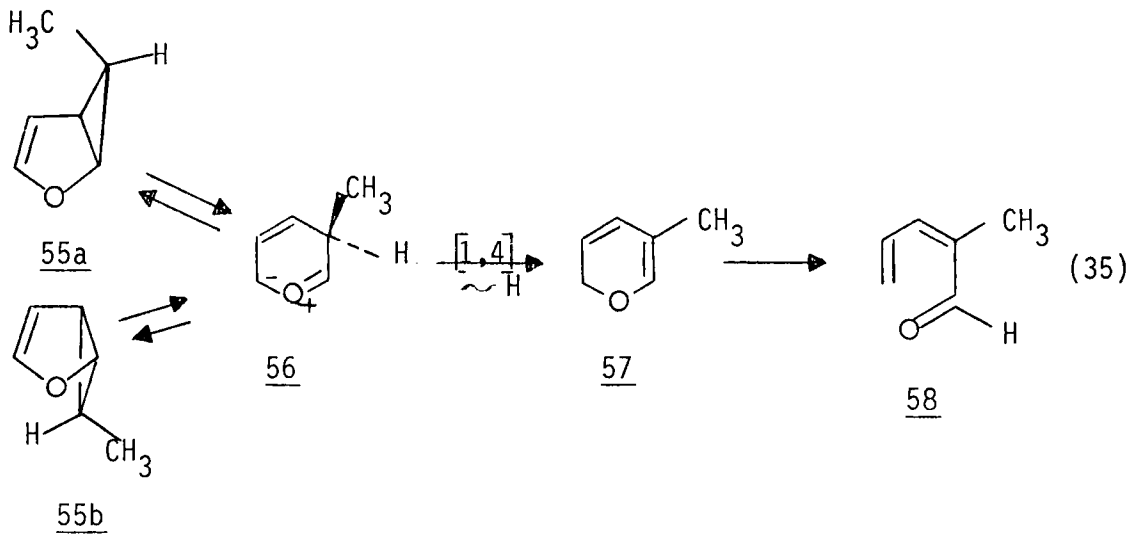
Treatment of nerol oxide 48 with n-butyllithium in THF at -27°, and quenching with acetic anhydride produced 53 and 54 as the only detectable products (Equation 34).



48 53 54 (34)

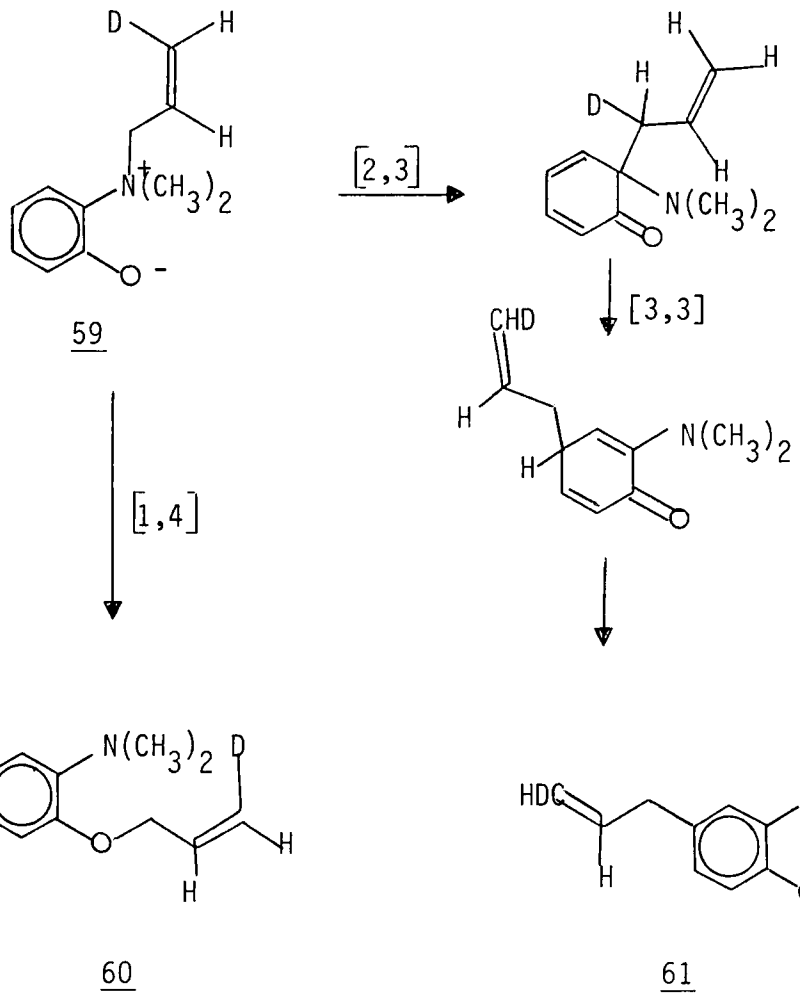
Rautenstrauch concludes that these transformations are the result of a concerted [1,4] sigmatropic shift forming the cyclopropyl lithium enolate. The formation of the cyclopropyl ring and its incipient ring strain is apparently compensated for by generation of the lithium enolate.

Chuche and coworkers[68] postulated the occurrence of a [1,4] sigmatropic shift of hydrogen to explain the appearance of the dienal 58, in Equation 35, in their study of the pyrolysis of endo- and exo-6-methyl-2-oxabicyclo[3.1.0]hex-3-ene, (55a) and (55b), respectively.



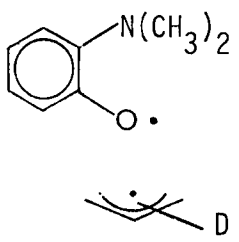
Pyrolysis of a 60/40 mixture of 55a and 55b at 380° resulted in formation of dienal 58 and a 33/67 mixture of recovered 55a and 55b. These results were explained as arising from an equilibrium between 55a and 55b via dipolar species 56. Symmetry-allowed disrotatory ring closure of 56 can produce either 55a or 55b. Dienal 58 is produced by the [1,4] sigmatropic shift of hydrogen to form 57, which then undergoes an electrocyclic ring-opening to form 58. It appears that [1,4] shifts of hydrogen occur quite readily in systems that contain a dipolar species.[63,64]

Ollis and coworkers[69,70] have provided evidence for a [1,4] sigmatropic shift. The rearrangement of the deuterium labeled 2-oxyanilinium ylide 59 at 60° yielded ether 60 and phenol 61, Equation 36.



59 60 61 (36)

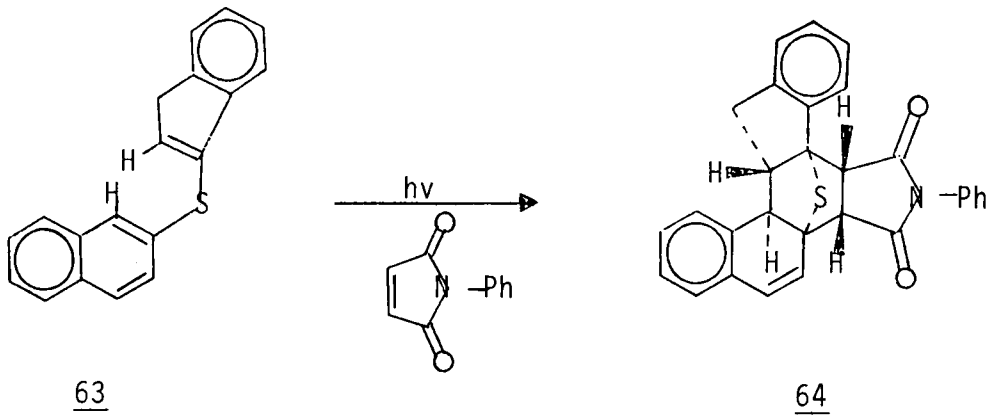
The formation of the allylphenol was found to be accompanied by a CIDNP signal. This labeling study and the investigation of the observed CIDNP signals led these workers to conclude that the major processes in this reaction are the concerted [1,4] shift forming ether 60 and the consecutive [2,3] and [3,3] shifts forming phenol 61, Equation 36. The minor pathway for formation of 60 and 61 is believed to involve the formation and recombination of the radical pair 62.



62

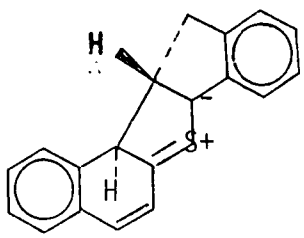
The ether 60 is formed in 25% yield, while the phenol 61 is found in 50% yield in Equation 36. It is interesting that the process which involves loss of aromatic character (consecutive [2,3] and [3,3] shifts) is the major pathway for this reaction. This result, as well as the rarity of anionic [1,4] shifts in other systems, suggests that the [1,4] sigmatropic shift possesses a relatively high energy of activation. No information concerning the stereochemistry of the migrating center was available in this study.

Schultz and DeTar[71,72] have postulated an anionic [1,4] sigmatropic shift of hydrogen in their study of naphthyl vinyl sulfides. They have also been able to trap an analog of the dipolar species suggested by Chapman[63,64] and were able to distinguish between two consecutive [1,2] shifts and a [1,4] shift. When 63 was photolyzed in the presence of excess N-phenylmaleimide, a single cycloadduct 64 was obtained, Equation 37.



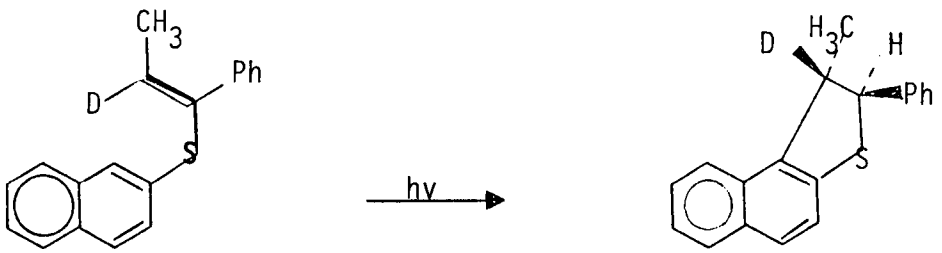
63 64 (37)

Clearly the cycloadduct comes from trapping of thiocarbonyl ylide 65



65

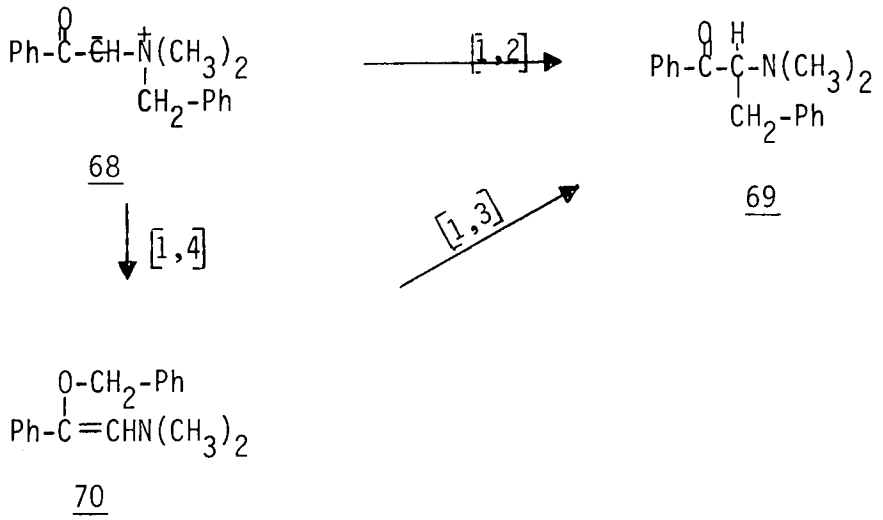
produced by the conrotatory ring closure of 63, by N-phenylmaleimide. The question of whether the conversion of thiocarbonyl ylides into dihydrothiophenes by either two [1,2] shifts or a [1,4] shift has been elucidated by the irradiation of naphthyl vinyl sulfide 66 which produces only the dihydrothiophene 67, Equation 38.



66 67 (38)

Thus, in the case of naphthyl vinyl sulfides, only [1,4] sigmatropic shifts are important in the conversion of thiocarbonyl ylides into dihydrothiophenes. Schultz and DeTar conclude that the conversion of naphthyl vinyl sulfides into dihydrothiophenes proceeds by photochemically allowed, conrotatory ring closure to a thiocarbonyl ylide. This ylide is then transformed into product by a suprafacial [1,4] sigmatropic shift of hydrogen. Again [1,4] sigmatropic shifts appear to be facilitated by dipolar intermediates.[63-65, 68-70]

Pine and Cheney[73] have investigated the possibility that the Stevens rearrangement could proceed by a two-step sequence of an allowed [1,4] shift and a forbidden [1,3] sigmatropic shift. Ylide 68 is converted into 69 in 1—2 minutes at 70° C. Compound 69 may be produced directly by a forbidden [1,2] shift[40,41,44] or by the two-step sequence in Equation 39.



(39)

In order to investigate this latter possibility, these workers synthesized the enamine enol ether 70, in Equation 39. Attempted conversion of 70 into 69 was unsuccessful under normal rearrangement conditions. Only under "forcing" conditions could 70 be converted into 69, and then only in low yields. Pine and Cheney conclude that a rapid reversible [1,4] sigmatropic conversion between ylide 68 and enamine enol ether 70 does not take place under the conditions of the Stevens rearrangement.

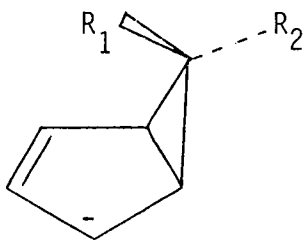
Mislow and coworkers have investigated a system in which a [1,4] shift is the only reasonable mechanistic pathway for the rearrangement of 10-aryl-10-thioanthracenes.[74,75] But, again, although the result is consistent with orbital symmetry conservation, the reaction involves a [1,4] shift from a dipolar intermediate

and does not permit determination of the stereochemistry of the migrating moiety.

F. Statement of the Problem

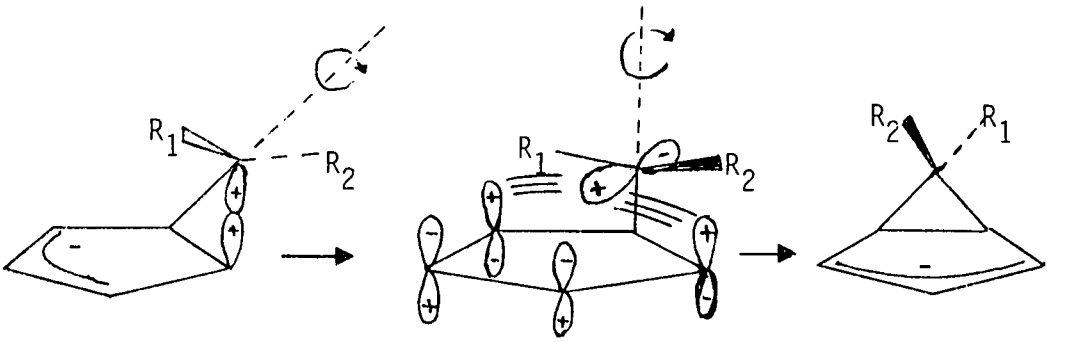
A considerable amount of effort has been expended in the investigation of sigmatropic shifts in ylides and in dipolar intermediates.[63-65, 68-75] Anionic [1,4] shifts of hydrogen and alkyl groups have been observed in these systems, but little work has been reported concerning such shifts in hydrocarbon substrates. Those cases in which anionic [1,4] shifts have been observed do not provide an adequate test of orbital symmetry.

A hydrocarbon system can be designed in which anionic [1,4] shifts can be investigated and which will provide an arena for the duel between orbital symmetry and least motion. This involves the study of the appropriately substituted bicyclo[3.1.0]hexenyl anion 71.



71

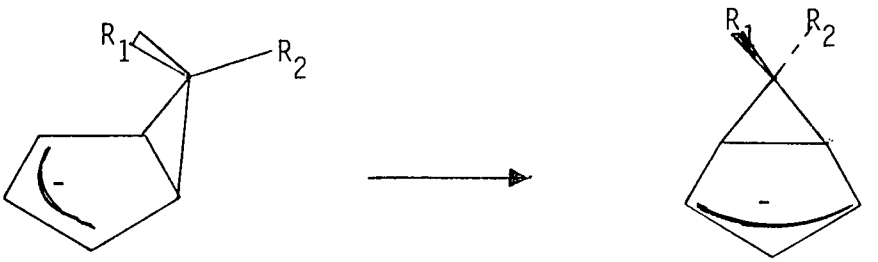
Outlined in Equation 40 is the expected orbital symmetry controlled pathway for the anionic [1,4] shift of C_6.



(40)

71 72

The least motion pathway is depicted in Equation 41.

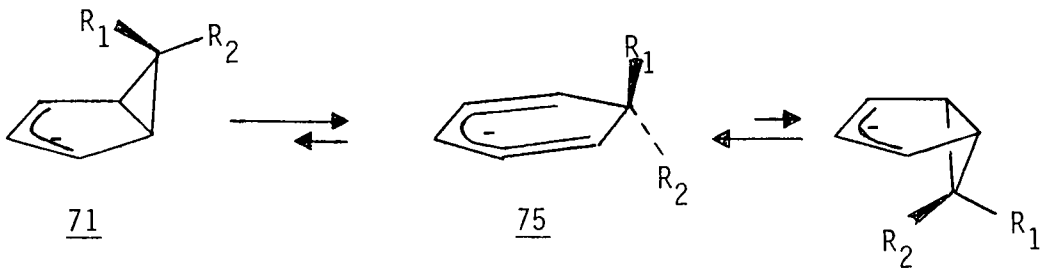


(41)

71 73

This system is quite similar to cationic [1,4] sigmatropic shifts (ring-walk cases) in that least motion migration of C_6 should occur with inversion of configuration (Equation 41). In contrast, the principle of conservation of orbital symmetry now predicts that migration of C_6 will proceed with retention of configuration (Equation 40). It would appear that epimerization of 71 would provide the necessary evidence for the orbital symmetry controlled [1,4] shift. However

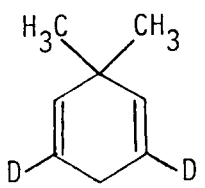
a second mechanism for epimerization is likely to occur simultaneously in this system. This pathway involves the allowed electrocyclic disrotatory processes in which 71 is equilibrated with 74 via 75 in Equation 42.[68]



71 75 74 (42)

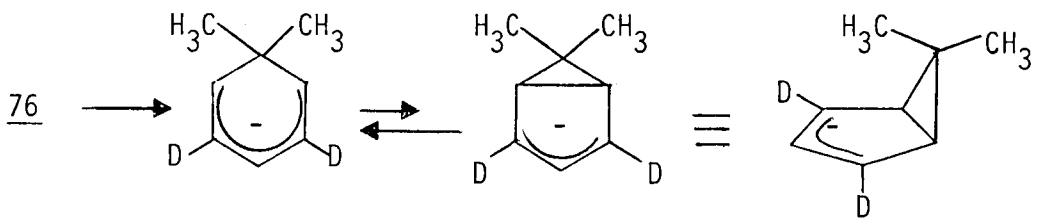
The symmetry-allowed ring-opening of 71 to 75, unlike the forbidden process in the cationic case,[51-60] should be very facile. In order to distinguish between the sigmatropic and electrocyclic processes, a label must be placed on the five-membered ring of 71.

Magid and Wilson, in an attempt to demonstrate the occurrence of an anionic [1,4] shift, synthesized 76.[76]



76

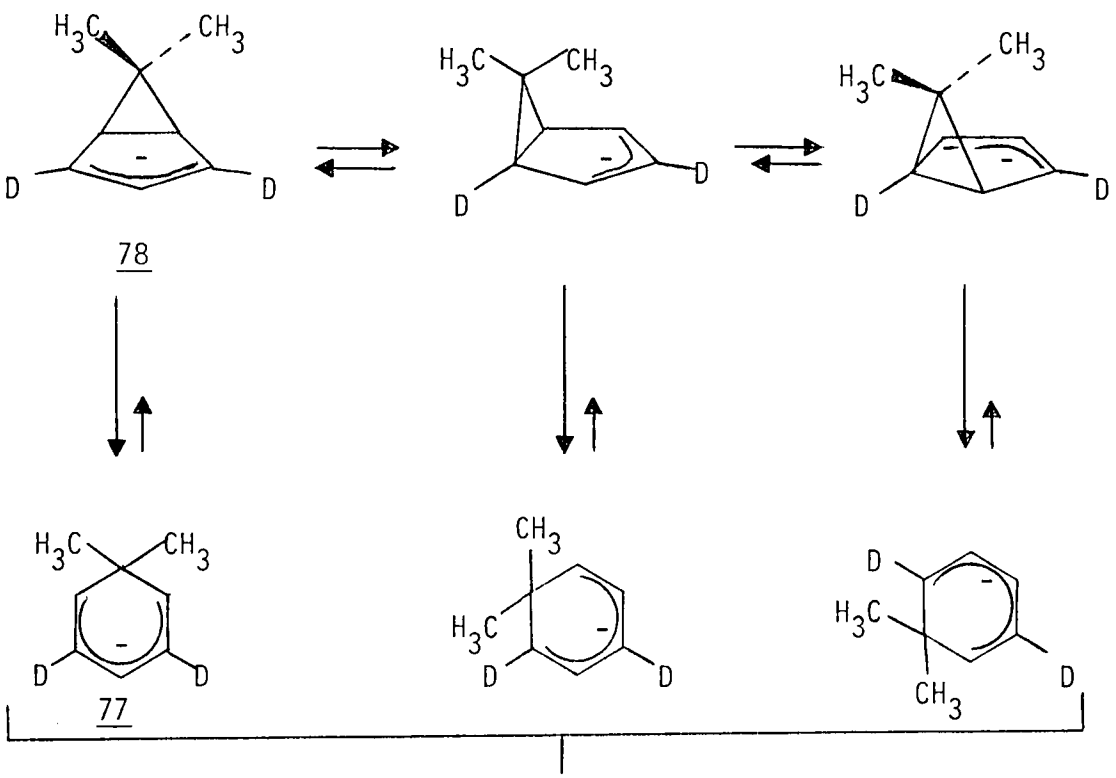
Treatment of 76 with n-butyllithium was expected to form anion 77.

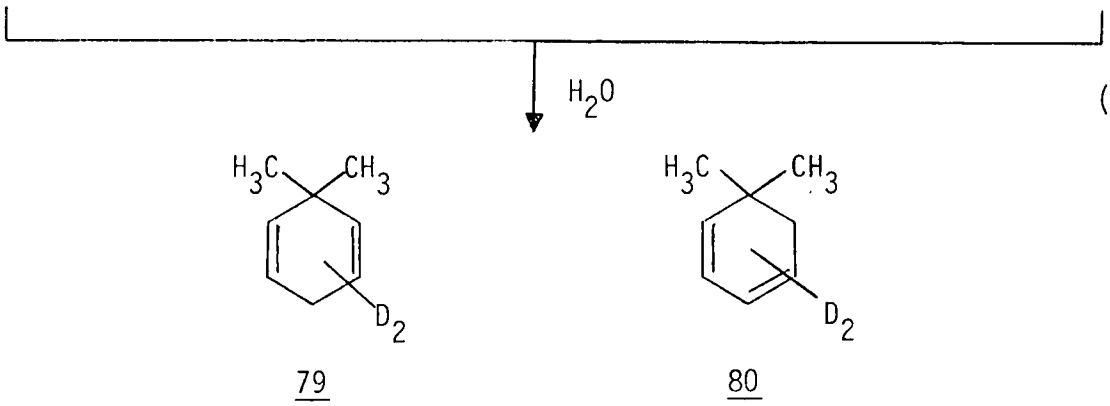


(43)

77 78

It was anticipated that an equilibrium would be established between 77 and 78.[77,78] This equilibrium will not affect the labeling pattern of the products formed on quenching unless a series of [1,4] shifts ensues (Equation 44).



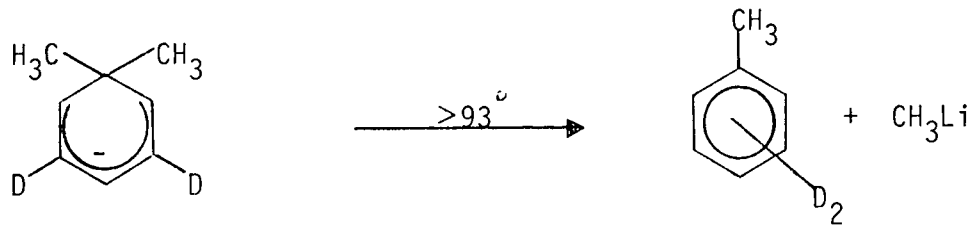


(44)

79 80

Assuming complete equilibration by a series of [1,4] shifts, the expected NMR integrated ratio of methyl:allyl:vinyl = 6.0:1.6:2.4. If the [1,4] shift does not occur, the integrated ratio of methyl: allyl:vinyl = 6:2:2.

When 76 was treated with n-butyllithium in hexane/TMEDA at 0° and quenched, a mixture of 79 and 80 was formed in the ratio of 69:31. The integrated ratio of methyl:allyl:vinyl for this mixture was 6:2:2. No deuterium label scrambling was detected. The same results were obtained when the reaction was carried out at 93°. Attempts to study the reaction at temperatures above 93° were not successful because of the conversion of 76 into toluene-d_2, presumably by expulsion of methyllithium from 77 (Equation 45).

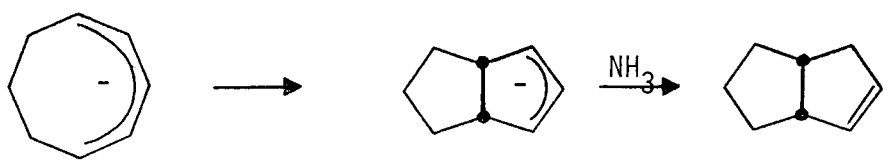


(45)

77

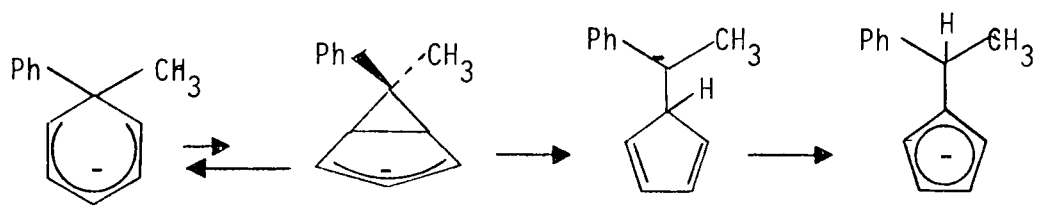
No attempt was made to examine the position of the deuterium label in the toluene-$\underline{d}_2$ generated.

The failure to observe deuterium label scrambling may well be either the result of the inability of this system to achieve the equilibrium in Equation 43 or the failure of the [1,4] shift to occur under the reaction conditions. A similar type of equilibrium (Equation 46) has been observed in a system in which a five-membered ring was formed.[78,79]



(46)

Only one case has been reported in which a three-membered ring was formed (Equation 47).[77]



(47)

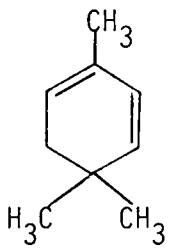
The possible inability of the equilibrium between 77 and 78 (Equation 43) to be attained may be due to 77's homoaromatic character. However, Kloosterziel and Van Drunen[79] could find no evidence for any homoaromatic character in the parent cyclohexadienyl anion (81).



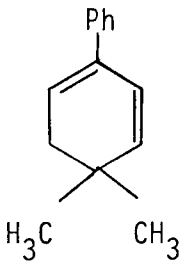
81

Bates and coworkers[80,81] have examined the NMR spectrum of unlabeled 77 and could not find any evidence for either homoaromaticity or for the equilibrium in Equation 43.

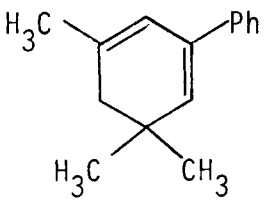
Compounds 82, 83, and 84 were chosen as possible candidates for the observation of an anionic [1,4] sigmatropic shift of an alkyl group.



82

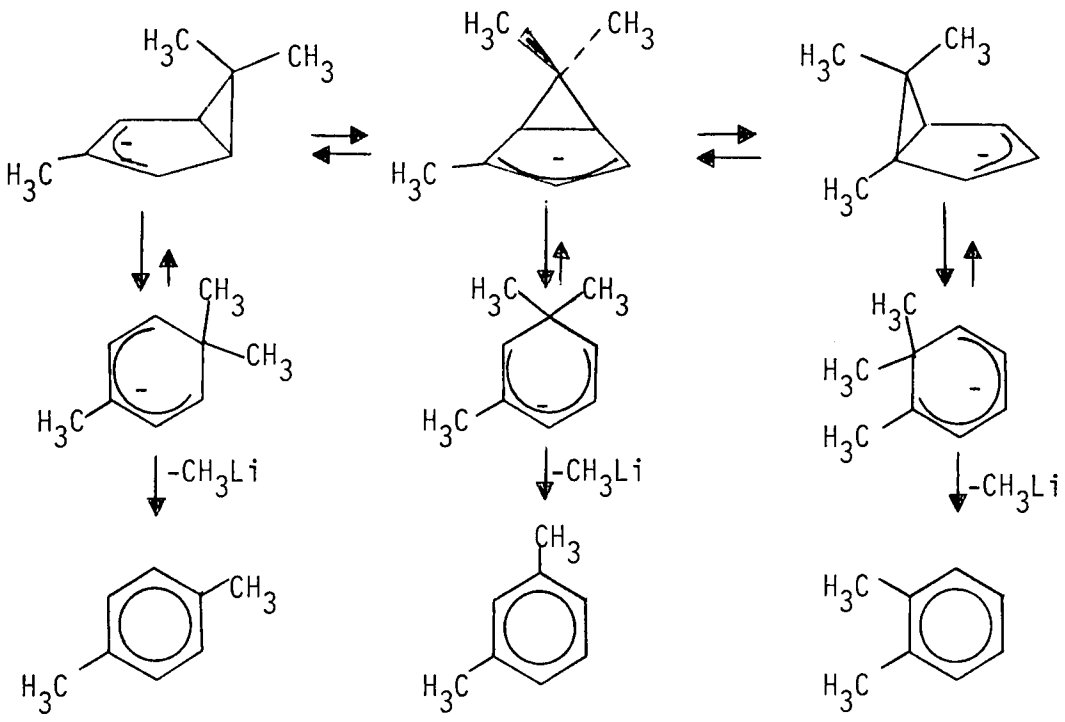


83

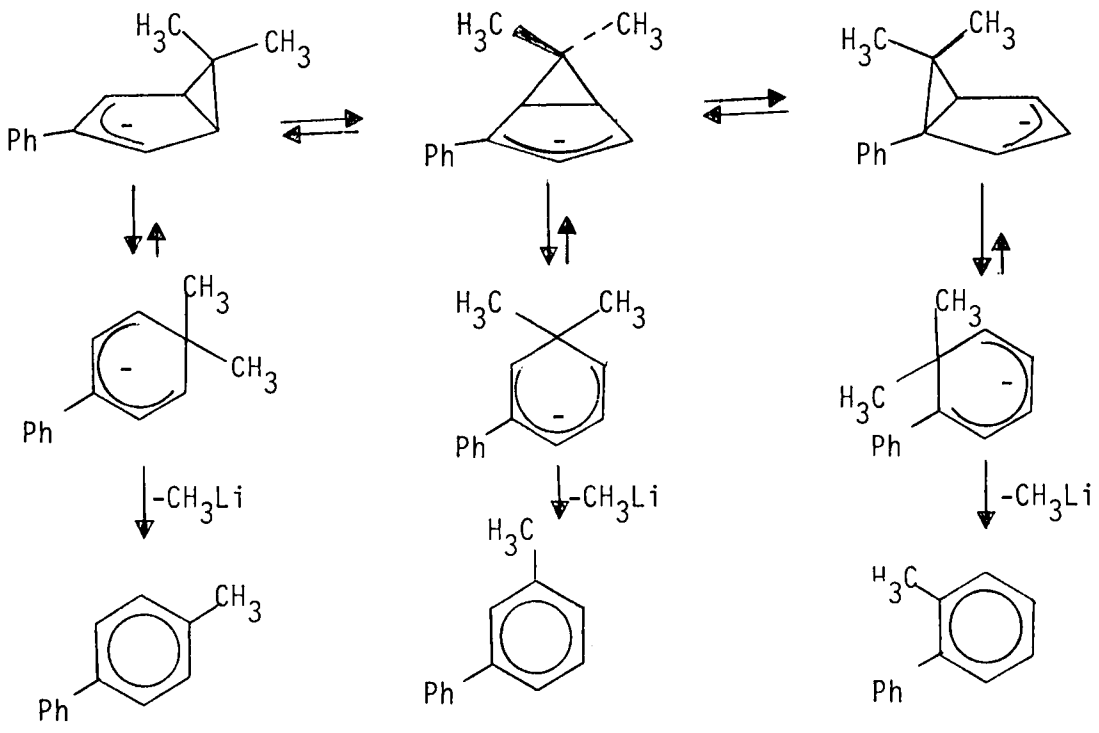


84

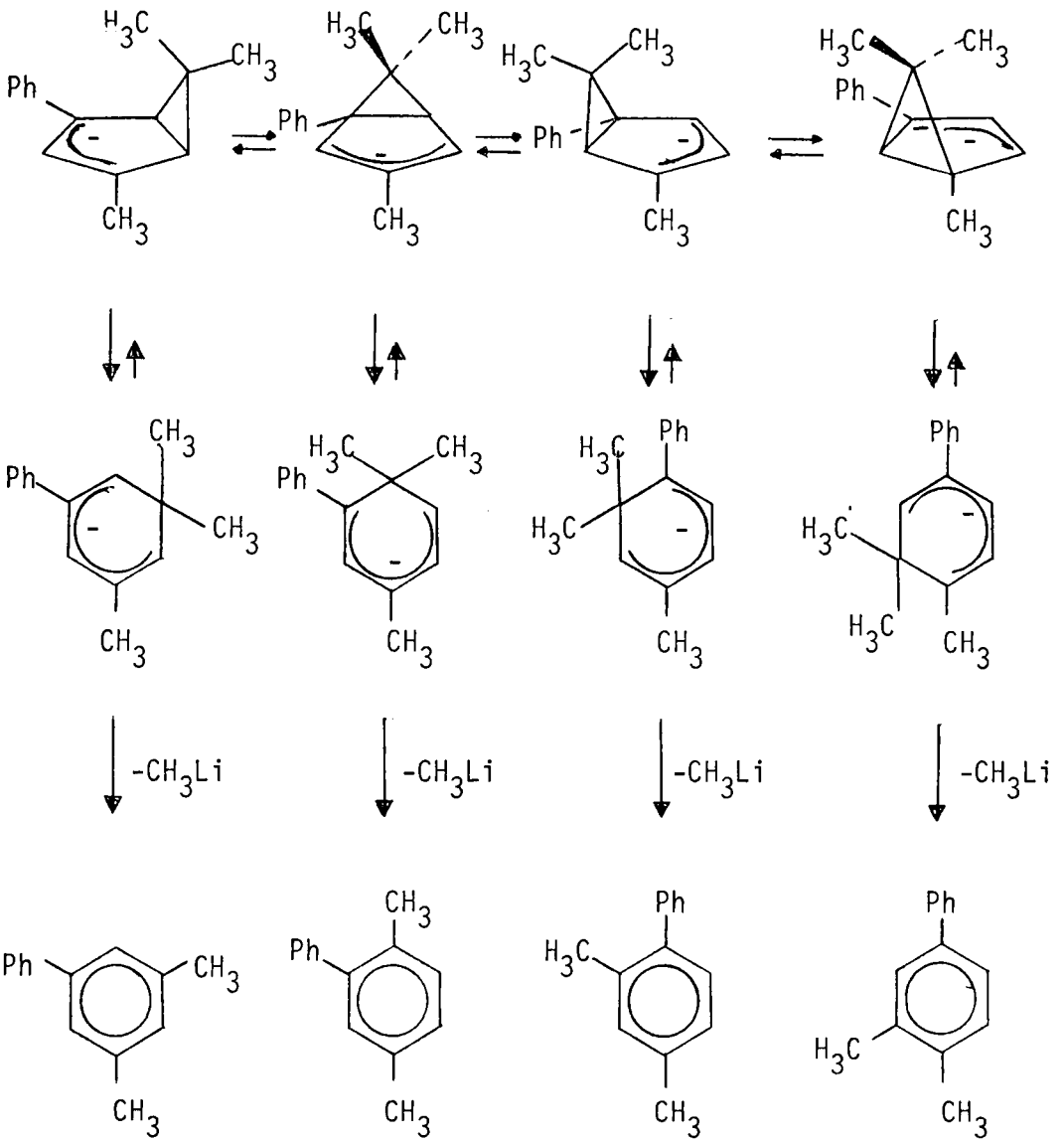
In the event that higher temperatures are needed for the rearrangement, the expulsion of methyllithium from any of these compounds would lead to readily identifiable products (Equations 48-50).



(48)



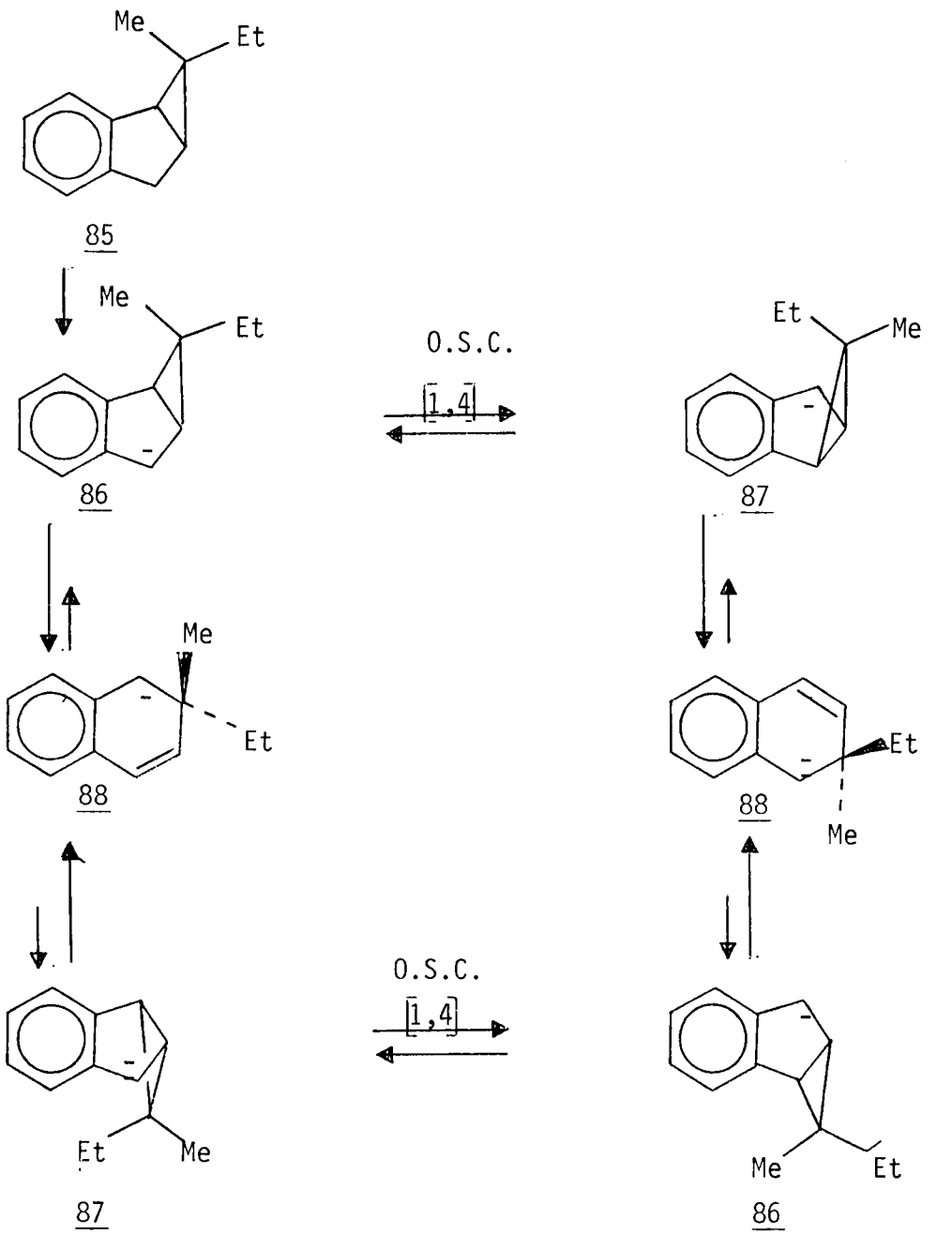
(49)



(50)

This series of compounds, however, will not provide any information concerning the stereochemistry of the anionic [1,4] shift.

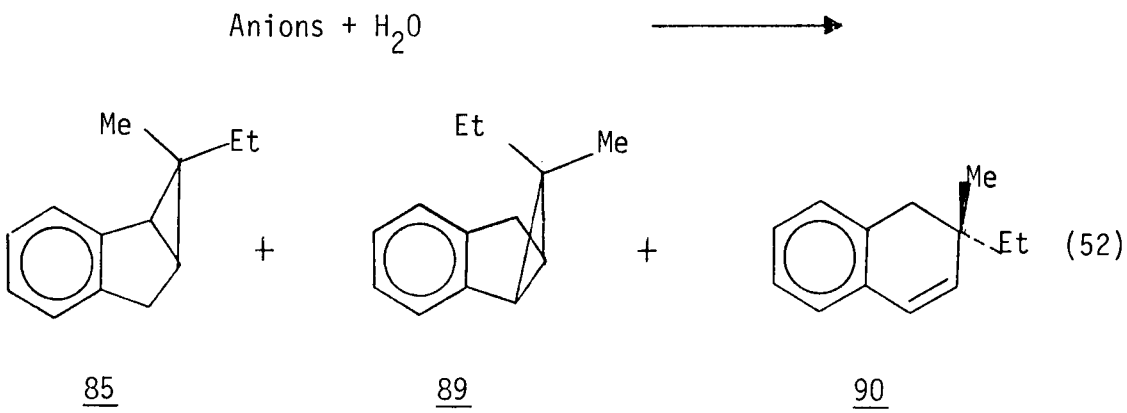
A system which will provide such information about the migrating center is outlined in Equation 51.



(51)

O.S.C.—Orbital Symmetry Control

Optically active 85 upon deprotonation should provide anion 86. Anion 86 can then undergo the symmetry-controlled [1,4] shift to 87 and/or the electrocyclic process to 88. Anion 88 may then be converted either into 87 or back into 86 by the symmetry allowed electrocyclic ring-closure. At no point are the enantiomers of 86, 87 or 88 produced in these transformations. Quenching of this mixture of anions will form 85, 89 and 90 (Equation 52),

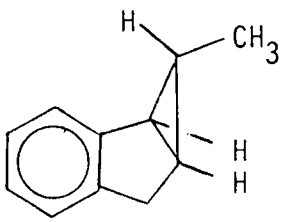


(52)

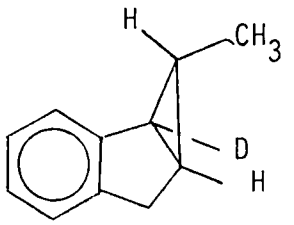
85 89 90

each possessing the same optical purity as the starting material. Thus, if the reaction proceeds via the orbital symmetry controlled routes, total retention of optical activity should be observed. If the transformations proceed by the least motion route for a [1,4] shift, racemization should occur and the only mechanism for epimerization would be via 88. In order to distinguish between the electrocyclic and the sigmatropic processes, since they both will cause epimerization, a label will have to be placed on the five-membered ring of this indene derivative.

Compounds 91 and 91d were chosen as models for the investigation of possible [1,4] shifts in the hydrocarbon framework.



91



91-d

It is anticipated that either the cyclohexadienyl compounds 82—84 or the indene derivatives 91 and 91d will provide an access to the study of anionic [1,4] shifts in a hydrocarbon framework and thus provide a true test of the conservation of orbital symmetry.

CHAPTER II

EXPERIMENTAL SECTION

A. General Considerations

In all experiments involving air-sensitive materials, the glassware was assembled, flame-dried, and maintained under positive nitrogen pressure. A mineral oil bubbler served as a pressure release valve for the system and as a trap to prevent air from entering the apparatus. Syringes and hypodermic needles used in transferring air-sensitive substances were placed in a 120° oven for at least 1 hr prior to use. The syringe and needle were removed and assembled while hot; on cooling the assembled syringe and needle were flushed with dry nitrogen at least three times before using.

The 60 MHz NMR spectra were obtained with either a Varian A-60 or a Varian T-60 A spectrometer. The 100 MHz NMR spectra were obtained with a Varian HA-100 spectrometer. Carbon tetrachloride (CCl_4) was used as solvent, except where noted, and tetramethylsilane (TMS) was used as the internal standard. Chemical shifts were recorded in δ units, ppm downfield from TMS.

The ir spectra were obtained using a Beckmann IR5A spectrometer, calibrated with a polystyrene film. The absorptions were reported as wavelengths in micron units (μ).

Mass spectra were obtained with a Hitachi Perkin Elmer model RMU-6E mass spectrometer.

A Hewlett-Packard model 5750 B gas chromatograph equipped with a Leeds and Northrup Speedomax XL 610 recorder with series 200 Disc Integrator was used for analytical gas-liquid partition chromatography (glpc) work. Helium was the carrier gas with a flow rate of 45 ml/min. A Varian model 920 gas chromatograph equipped with Leeds and Northrup Speedomax H recorder was used for preparative glpc work. Helium was the carrier gas and the flow rate was 75 ml/min. Both gas chromatographs were equipped with thermal conductivity detectors.

The columns used in the HP 5750 B were constructed from 1/8 in. od stainless steel tubing. The columns used in the V920 were constructed from 1/4 in. od stainless steel tubing. The solid support was chromsosorb W, 80-100 mesh except for Column O which used Chromsorb C, 100-120 mesh.

The analytical columns were:

Column A—10 ft, 10% Carbowax 20 M.

Column B—10 ft, 10% Carbowax 20 M Terephthalic Acid Terminated (FFAP).

Column C—10 ft, 10% Silicone Gum Rubber (SE-30).

Column D—6 ft, 10% UCW 9880.

Column E—10 ft, 5% UCON 50 HB 280 K.

Column F—10 ft, 5% β,β'-Oxydipropionitrile.

Column G—10 ft, 5% Diethylene Glycol Succinate (DEGS).

Column H—10 ft, 5% 1,2,3-Tris (2-cyanoethoxy) propane (TCEP).

Column I—5 ft, 5% Carbowax 20 M.

The preparative columns were:

Column J—6 ft, 10% Carbowax 20 M.

Column K—6 ft, 10% SE-30.

Column L—10 ft, 5% DEGS.

Column M—10 ft, 5% TCEP.

Column N—10 ft, 5% Carbowax 20 M.

Column O—10 ft, 1.5% OU-101.

Column P—6 ft, 20% SE-30.

The reagents and solvents which were obtained commercially for this investigation are shown in Table I and Table II with their sources.

All melting points were obtained with a Mel-Temp melting point apparatus and are uncorrected.

B. Preparations

1. Cyclohexadienyl Systems

a. Preparation of 2,2-Dimethyl-1,3-cyclohexanedione.[82]

A solution of 2-methyl-1,3-cyclohexanedione (2.52 g, 20 mmol) in anhydrous ethanol (10 ml) was placed in a 50-ml one-necked round-bottomed flask equipped with side-arm septum and magnetic stirrer. To this stirred solution 1.20 g (22 mmol) of sodium methoxide was added along with 5.0 ml of anhydrous THF. This solution was refluxed for 20 min. To this refluxing solution 1.22 ml (2.78 g, 20 mmol) of methyl iodide was added via syringe. The reaction mixture was refluxed for 12 hr and allowed to cool to room temperature. Water

TABLE I

SOURCE OF COMMERCIAL SOLVENTS

Solvent	Source
Acetone-$\underline{d}_6$	Bio-Rad
Benzene	Fisher Scientific Company
Carbon Tetrachloride	Fisher Scientific Company
Chloroform	Fisher Scientific Company
Chloroform-$\underline{d}$	Aldrich Chemical Company
Deuterium oxide	Bio-Rad
Ethanol	Fisher Scientific Company
Ethyl Ether	Fisher Scientific Company
Ethyl Acetate	Eastman Kodak Company
Hexane	Fisher Scientific Company
Isopropanol	Fisher Scientific Company
Ligroin (30-60°)	Fisher Scientific Company
2,6-Lutidine	Aldrich Chemical Company
Methanol	Fisher Scientific Company
Pentane	Fisher Scientific Company
Pyridine	Fisher Scientific Company
Tetrahydrofuran	Fisher Scientific Company
Toluene	Fisher Scientific Company

TABLE II

SOURCE OF COMMON REAGENTS

Reagent	Source
Aluminum Trichloride	Bahr
Borane Methylsulfide	Aldrich Chemical Company
Boron Trifloride Etherate	Eastman Kodak Company
Bromobenzene	Fisher Scientific Company
n-Butyllithium	Ventron Corporation
t-Butyllithium	Aldrich Chemical Company
Copper	Fisher Scientific Company
Cupric Acetate	Fisher Scientific Company
Cupric Chloride	Fisher Scientific Company
Cupric Sulfate	Fisher Scientific Company
1,1-Dichloroethane	Aldrich Chemical Company
Diethylzinc	Ventron Corporation
Diisopropylamine	Aldrich Chemical Company
Dimedone	Aldrich Chemical Company
Ethyl Iodide	Aldrich Chemical Company
Glycine Ethyl Ester HCl	Aldrich Chemical Company
Indene	Matheson, Coleman and Bell
Isophorone	Fisher Scientific Company
Lithium Aluminum Hydride	Ventron Corporation
Magnesium	Fisher Scientific Company

TABLE II (CONTINUED)

Reagent	Source
Magnesium Sulfate	Fisher Scientific Company
Methanesulfonyl Chloride	Eastman Kodak Company
2-Methylcyclohexa-1,3-diene	Aldrich Chemical Company
Methyl Iodide	Aldrich Chemical Company
Methylene Iodide	Aldrich Chemical Company
Methyllithium	Ventron Corporation
Potassium Carbonate	Fisher Scientific Company
Sodium	Fisher Scientific Company
Sodium Hydroxide	Fisher Scientific Company
Sodium Methoxide	Olin Matheson
Sodium Sulfate	Fisher Scientific Company
Tetramethylethylenediamine	Aldrich Chemical Company
Triphenylmethane	Aldrich Chemical Company
p-Toluenesulfonic Acid	Eastman Kodak Company
p-Toluenesulfonylhydrazide	Aldrich Chemical Company
p-Toluenesulfonyl Chloride	Eastman Kodak Company
Zinc	Fisher Scientific Company

(10 ml) was added and the reaction mixture extracted with one 75-ml and one 25-ml portion of ether. The ether layers were combined and dried over Na_2SO_4. The volatile components of the reaction mixture were removed by use of a rotary evaporator yielding a residue of 0.78 g (30%) of 2,2-dimethyl-1,3-cyclohexanedione. NMR (CCl_4) δ 1.21 (s, 6, C_2 methyls), 1.95 (m, 2, H_5), 2.6 (t, 4, H_4 and H_6, J = 9 Hz); ir (CCl_4) 3.35, 5.75, 7.85, 6.80, 7.20, 7.55, 8.75, 9.68 and 10.0 μ.

b. Preparation of the Bistosylhydrozone of 2,2-Dimethyl-1,3-cyclohexanedione.[83,84] A solution of p-toluenesulfonylhydrazide (2.30 g, 12.3 mmol) and anhydrous ethanol (3 mmol) was added to a solution of 2,2-dimethyl-1,3-cyclohexanedione (0.65 g, 4.6 mmol) and anhydrous ethanol (2 ml). The solution was refluxed for 4 hr, allowed to cool to room temperature and placed in the cold room for 30 min. The volatile components were removed by use of rotary evaporator until a precipitate formed. The precipitate was filtered, washed with cold 95% ethanol, and allowed to air-dry. The yield of product was 1.75 g (82%); mp 192-193° (decomposed); NMR (acetone-d_6) δ 1.20 (s, 6, C_2 methyls), 1.78 (m, 2, H_5), 2.41 (s, 6, aromatic ring methyls), 2.42 (m, 4, H_4 and H_6), 2.75 (s, 2, N-H), 7.30 (d, 2, aromatic), and 7.70 (d, 2, aromatic); ir (nujol) 3.10, 6.80, 7.20, 7.45, 8.50, 9.10, and 9.80 μ.

c. Preparation of 3,3-Dimethyl-1,4-cyclohexadiene.[83,84] A suspension of the bistosylhydrazone of 2,2-dimethyl-1,3-cyclohexanedione (1.60 g, 3.4 mmol) and anhydrous hexane (20 ml) was added to a 100-ml round-bottomed flask equipped with side-arm septum and magnetic

stirrer. To this stirred suspension 1.50 ml of a 1.56 M (23.4 mmol) solution of methyllithium in diethyl ether was added via syringe. No evidence of gas evolution occurred during this addition. The flask was immersed into an oil bath at 40° and stirred for 7 hr; the reaction mixture was then refluxed for 1 hr and allowed to cool to room temperature. Distilled water (6.0 ml) was added slowly and cautiously via a syringe. A very exothermic reaction occurred and a large volume of gas was generated. The reaction mixture was extracted with a 25-ml portion of water and the aqueous layer was extracted with a 20-ml portion of hexane. The organic layers were combined and dried over Na_2SO_4. The material was distilled through a 12-cm Vigreux column and short-path distilling head. The fraction boiling below 100° was examined by NMR which showed a very low yield of olefinic product.

d. Preparation of 2,2-Dideuterio-5,5-dimethyl-1,3-cyclohexanedione. A solution of 5,5-dimethyl-1,3-cyclohexanedione (14.0 g, 100 mmol) and CCl_4 (125 ml) was added to a solution of K_2CO_3 (0.40 g, 2.8 mmol) and deuterium oxide (20 ml, 1.0 mol) and refluxed for 24 hr. The reaction was allowed to cool to room temperature and the layers separated. The organic layer was dried over anhydrous Na_2SO_4 and the volatile components removed by use of rotary evaporator. NMR analysis of the product indicated 85% incorporation of deuterium and showed that the product was a mixture of 2,2-dideuterio-5,5-dimethyl-1,3-cyclohexanedione and 2-deuterio-3-hydroxy-5,5-dimethyl-cyclohex-2-ene-1-one-O-d. A dilution study of the NMR spectrum

of the unlabeled 5,5-dimethyl-1,3-cyclohexanedione showed that the composition of the keto-enol mixture was concentration-dependent. This study also provided evidence that the literature assignments were wrong.

e. Preparation of 2,5,5-Trimethyl-1,3-cyclohexanedione.[85] A solution of NaOH (14.3 g, 358 mmol) and water (250 ml) was added to a solution of 5,5-dimethyl-1,3-cyclohexanedione (50.0 g, 358 mmol) and methyl iodide (44.8 ml, 102.1 g, 720 mmol) and refluxed for 26 hr. The reaction mixture was allowed to cool to room temperature and 50 ml of cold water was added. The bottom layer crystallized and the reaction mixture was placed in the cold room for 2 hr. The precipitate was collected and allowed to air-dry. The product was recrystallized from ethyl acetate and yielded 24.0 g (55.2%) of 2,5,5-trimethyl-1,3-cyclohexanedione. NMR ($CDCl_3$) δ 0.8 (s, 3, C_5 methyl), 1.20 (s, 3, C_5 methyl) 1.22 (d, 3, C_2 methyl, J = 6 Hz), 2.60 (m, 4, H_4 and H_6) and 3.40 (q, 1, H_2, J = 6 Hz).

f. Preparation of the Bistosylhydrazine of 2,5,5-trimethyl-1,3-cyclohexanedione. A solution of p-toluenesulfonylhydrazide (2.30 g, 12.3 mmol) and anhydrous THF (3 ml) was added to a solution of 2,5,5-trimethyl-1,3-cyclohexanedione (0.71 g, 4.6 mmol) and anhydrous THF (3 ml). The solution was refluxed for 4 hr during which a reddish-brown gummy precipitate formed. All attempts to crystallize this material, as well as to characterize it by NMR failed.

g. Preparation of 2,5,5-trimethyl-1,3-cyclohexadiene. A solution of 3-hydroxy-3,6,6-trimethyl-1-cyclohexene[86] (5.7 g, 40.7 mmol) and anhydrous benzene (50 ml) was placed in a 200-ml round-bottomed flask equipped with magnetic stirrer. p-Toluenesulfonic acid (0.02 g, 0.1 mmol) was added and the reaction was refluxed for 6 hr; the water formed was removed by use of a Dean-Stark Trap. The mixture was allowed to cool and was extracted with a 20-ml portion of 5% Na_2CO_3 solution. The organic layer was dried over anhydrous K_2CO_3 and the benzene was removed by distillation through 12-cm vacuum-jacketed Vigreux column. The product was distilled under reduced pressure yielding 2.5 g (50%); bp (ca. 20 mm) 40—42°; NMR (CCl_4) δ 0.95 (s, 6, C_5 methyls), 1.65 (q, 3, C_2 methyl, J = 2 Hz), 2.00 (m, 2, H_6), 5.30 (m, 1, H_1), 5.35 (d, 1, H_4, J = 9 Hz), 5.55 (d, 1, H_3, J = 9 Hz). NMR and glpc (column K, 140°) indicated that product was a ca. 60/40 mixture of 2,5,5-trimethyl-1,3-cyclohexadiene and 4,4-dimethyl-1-methylene-2-cyclohexene; NMR (CCl_4) δ 0.92 (s, 6, C_4 methyls), 1.41 (m, 2, H_5), 2.28 (m, 2, H_6), 4.60 (broad s, 2, methylene CH_2), 5.2—5.4 (m, 2, H_2 and H_3).

h. Preparation of 1,5,5-Trimethyl-1,3-cyclohexadiene. A solution of isophorone (6.90 g, 49.9 mmol) and THF (20 ml) was added to a solution of p-toluenesulfonylhydrazide (9.30 g, 49.9 mmol) in THF (20 ml); three drops of conc HCl were added and the reaction was refluxed for 20 hr. The reaction mixture was allowed to cool and the volatile components removed by use of rotary evaporator leaving an oil, which solidified on standing. An NMR spectrum was

obtained of the crude tosylhydrazone; NMR ($CDCl_3$) δ 0.85 (s, 6, C_5 methyls), 1.80 (broad s, 3, C_1 methyl), 1.95 (broad s, 2, H_6), 2.10 (s, 2, H_4) 2.40 (s, 3, aromatic ring methyl), 6.15 (m, 1, H_2), 7.20 (d, 2, aromatic, J = 8 Hz), 7.80 (d, 2, aromatic, J = 8 Hz). To a suspension of the tosylhydrazone in ether (50 ml), a solution of n-butyllithium (55 ml, 110 mmol) was added in small increments. The addition was carried out at 0° and after the addition was complete, the reaction mixture was allowed to warm to room temperature. Water (20 ml) was added slowly and the quenched reaction mixture was separated. The ether layer was extracted with 50-ml portions of H_2O, 10% HCl, and H_2O, dried over Na_2SO_4, and concentrated by distilling at atmospheric pressure. The residue was distilled at reduced pressure yielding 1.0 g (16.4%) of product; bp 30—32° (ca. 18 mm); NMR suggested a ca. 50:50 mixture of 1,5,5-trimethyl-1,3-cyclohexadiene and 2,6,6-trimethyl-1,3-cyclohexadiene.

i. Preparation of 1-Hydroxy-1-phenyl-4,4-dimethylcyclohex-2-ene. A solution of 4,4-dimethylcyclohex-2-ene-1-one[86,87] (12.60 g, 99.8 mmol) in ether (15 ml) was added to a solution of phenylmagnesium bromide [prepared by reaction of bromobenzene (18.0 g, 114.6 mmol) with magnesium (3.0 g, 123.5 mmol)] and ether (20 ml) at 0°. After the addition was completed, the reaction mixture was allowed to warm to room temperature and was refluxed for 1 hr. The reaction mixture was carefully poured into a separatory funnel containing ice (50 g) and water (50 ml). The reaction mixture was extracted with copious amounts of ether and the ether layers were combined and dried over

$MgSO_4$. The ether was removed by use of rotary evaporator yielding 10.0 g (49.5%) of product; NMR (CCl_4) δ 0.98 (s, 3, C_4 methyl), 1.00 (s, 3, C_4 methyl), 1.10—1.90 (m, 4, H_5 and H_6), 3.0 (s, 1, O -H), 5.40 (s, 2, H_2 and H_3), 6.90—7.40 (m, 5, aromatic).

j. Preparation of 2-Phenyl-5,5-dimethyl-1,3-cyclohexadiene. A solution of 1-hydroxy-1-phenyl-4,4-dimethylcyclohex-2-ene (10.0 g, 49.4 mmol) in benzene (50 ml) was placed in a 200-ml round-bottomed flask equipped with magnetic stirrer. p-Toluenesulfonic acid (0.02 g, 0.1 mmol) was added and the reaction mixture was refluxed until no more evidence of water formation was observed. The water that was formed was removed by use of a Dean-Stark trap. The reaction mixture was allowed to cool and the benzene solution was extracted with a 20-ml portion of 5% $NaHCO_3$, dried over anhydrous K_2CO_3 and the benzene removed by use of rotary evaporator yielding 8.50 g (93.3%) of product; NMR (CCl_4) δ 1.0 (s, 6, C_5 methyls), 2.20 (d, 2, H_6, J = 4 Hz), 5.58 (d of d, 1, H_4, J = 9 Hz and J = 2 Hz), 5.85 (broad t, 1, H_1, J = 4 Hz), 6.10 (d of d, 1, H_3, J = 9 Hz and J = 2 Hz), 7.18 (s, 5, aromatic).

k. Preparation of 1-Hydroxy-1-phenyl-3,5,5-trimethylcyclohex-2-ene. A solution of 3,5,5-trimethylcyclohex-2-ene-1-one (27.64 g, 200 mmol) and ether (30 ml) was added to a solution of phenylmagnesium bromide [prepared by reaction of bromobenzene (36.0 g, 229 mmol) with magnesium (6.0 g, 247 mmol)] and ether (40 ml) at 0°. After addition was completed, the reaction mixture was allowed to warm to room temperature and was refluxed for 1 hr. The reaction mixture was carefully poured into a separatory funnel containing ice (100 g) and water (100 ml).

The quenched reaction mixture was extracted with copious amounts of ether; the ether layers were combined and dried over $MgSO_4$. The ether was removed by use of a rotary evaporator yielding 13.2 g (30.5%); NMR (CCl_4) δ 0.90 (s, 3, C_5 methyl), 0.92 (s, 3, C_5 methyl), 1.80 (broad s, 8, H_4, H_6, C_3 methyl and O-H), 5.40 (broad s, 1, H_2), 7.0—7.4 (m, 5, aromatic).

1. Preparation of 2-Phenyl-4,6,6-trimethyl-1,3-cyclohexadiene. A solution of 1-hydroxy-1-phenyl-3,5,5-trimethylcyclohex-2-ene (13.2 g, 61.3 mmol) in benzene (50 ml) was placed in a 200-ml round-bottomed flask equipped with magnetic stirrer. p-Toluenesulfonic acid (0.02 g, 0.1 mmol) was added and the reaction mixture was refluxed until no more water was removed by Dean-Stark trap. The reaction mixture was allowed to cool to room temperature and the benzene solution was extracted with a 20-ml portion of 5% $NaHCO_3$, dried over anhydrous K_2CO_3, and the benzene removed by use of a rotary evaporator yielding 11.0 g (91%) of product; bp 72—76° (0.15 mm); NMR suggested a mixture of 2-phenyl-4,6,6-trimethyl-1,3-cyclohexadiene, 1-phenyl-3,5,5-trimethyl-1,3-cyclohexadiene and 1-phenyl-3-methylene-5,5-dimethyl-1-cyclohexene.

2. Indenyl Systems

a. Preparation of 1,1-Diiodoethane.[88] A solution of 1,1-dichloroethane (39.6 g, 400 mmol), ethyl iodide (187 g, 1200 mmol) and aluminum chloride (2.0 g, 15 mmol) was placed in an Erlenmeyer flask and heated on a steam bath for 3 hr. The reaction mixture was cooled and poured into water (400 ml), washed with two 100-ml

portions of 5% $NaHSO_3$, and dried over $MgSO_4$. Distillation at reduced pressure yielded 67.3 g (59.7%); bp (25 mm) 75—76°; NMR (CCl_4) δ 2.99 (d, 3, CH_3, J = 7 Hz) and 5.28 (q, 1, CH, J = 7 Hz).

b. Preparation of Zinc-Copper Couple. Method 1.[89] A solution of cupric acetate (0.5 g) and boiling glacial acetic acid (50 ml) was added to 20-mesh granular zinc (35 g) and stirred for three min. The acetic acid was decanted and the couple was washed with a 50-ml portion of glacial acetic acid and three 50-ml portions of anhydrous ether. The couple was kept under ether until ready for use.

Method 2.[90] Zinc powder (25.5 g) and Cu_2Cl_2 (3.9 g) were placed in a round-bottomed flask equipped with magnetic stirrer. Anhydrous ether (40 ml) was added and the suspension was refluxed for 30 min. The couple was then used immediately.

c. Preparation of 2,3-Benzobicyclo[3.1.0]hex-2-ene. Method 1.[89] A suspension of zinc-copper couple (500 mmol, Method 1) and anhydrous ether (50 ml) was placed in a 300-ml three-necked flask equipped with a pressure-equalizing addition funnel, condenser, and magnetic stirrer. To this stirred suspension, a solution of methylene iodide (51.9 g, 193.7 mmol) and indene (46.6 g, 401.4 mmol) was added via the addition funnel. The reaction mixture was refluxed for 4 days and allowed to cool. The organic layer was decanted from the unreacted couple and poured into water (100 ml). The reaction mixture was extracted with copious amounts of ether; the ether layers were combined, dried over $MgSO_4$, and the volatile components were removed

by use of a rotary evaporator. Distillation of the residue at reduced pressure yielded 2.1 g (8.3%); bp 92—94° (ca. 20 mm); NMR (CCl_4) δ 0.1 (q, 1, H_6 endo, J = 4 Hz), 0.95 (t of d, 1, H_6 exo, J = 8 Hz and J = 4 Hz), 1.65 (m, 1, H_5), 2.26 (m, 1, H_1), 2.95—3.10 (m, 2, H_4) and 7.0—7.5 (m, 4, aromatic).

Method 2.[90] A solution of indene (11.9 g, 103 mmol) and carbon tetrachloride (30 ml) was placed in a 200-ml round-bottomed flask equipped with Claisen adapter, condenser, addition funnel, and magnetic stirrer. To this stirred solution, diethylzinc (12.0 g, 97.2 mmol) was added and the mixture was stirred for 30 min. A solution of methylene iodide (53.2 g, 199 mmol) and carbon tetrachloride (30 ml) was added over a 1.0-hr period. The reaction mixture was stirred for an additional 15 min and then poured into 100 ml of 1% HCl. The quenched reaction mixture was extracted with copious amounts of ether; the ether layers were combined, dried over $MgSO_4$, and the volatile components removed by rotary evaporator. The residue was a ca. 50:50 indene: product mixture. The product was isolated by preparation glpc (Column N, 170°) yielding 1.8 g (14.2%) of pure compound whose NMR spectrum was identical to that obtained by Method 1.

d. Preparation of 6-Methyl-2,3-benzo-bicyclo[3.1.0]hex-2-ene. Method 1. A suspension of zinc-copper couple (500 mmol, prepared by Method 1) and anhydrous ether (50 ml) was placed in a 250-ml, three-necked flask equipped with addition funnel, condenser and magnetic stirrer. A solution of indene (34.8 g, 299 mmol) and

1,1-diiodoethane (84.6 g, 300 mmol) was added dropwise over a one-hr period *via* addition funnel. The reaction mixture was worked up in the same manner as in the preparation of 2,3-benzobicyclo[3.1.0]-hex-2-ene (Method 1). The NMR spectrum of isolated material suggested that very little of the desired product was formed.

Method 2. A suspension of zinc-copper couple (prepared by Method 2) was placed in a 250-ml three-necked round-bottomed flask equipped with addition funnel, condenser, and magnetic stirrer. A solution of indene (18.0 g, 155 mmol) and 1,1-diiodoethane (43.3 g, 154 mmol) was added *via* addition funnel at a rate that maintained a gentle reflux. After addition was complete, the reacting mixture was refluxed for 18 hr, allowed to cool, and poured into water (140 ml); the unreacted couple was removed *via* filtration, the layers separated, and the organic layer dried over $MgSO_4$. The volatile components were removed by use of a rotary evaporator. An NMR spectrum of the residue suggested the formation of very little product.

Method 3.[91] A solution of indene (19.8 g, 170 mmol) and dry hexane was added to a 250-ml three-necked round-bottomed flask equipped with addition funnel, septum, and magnetic stirrer. Diethylzinc (12.0 g, 97.2 mmol) was added very carefully *via* a syringe to the stirred solution. A solution of 1,1-diiodoethane (62.5 g, 222 mmol) and hexane (5 ml) was placed in the addition funnel and added dropwise over a 40-min period. A water bath (20°) as well as rate of addition was used to control the reaction. After

addition was complete, the septum and addition funnel were removed and the reaction mixture was stirred as rapidly as possible for 20 min. After the 20-min contact with air, a slow stream of O_2 (ca. 10 ml/min) was blown across the surface of the reaction mixture as the stirring was continued for 10 min. The solution was then transferred to a 600-ml beaker containing 100 ml of 10% HCl and stirred. The two layers were separated, the aqueous layer extracted with two 50-ml portions of ether, the ether extracts combined with the organic layer, and dried over $MgSO_4$. The volatile components were removed by use of a rotary evaporator and an NMR spectrum was taken of the residue. The NMR suggested the formation of 6-methyl-2,3-benzobicyclo[3.1.0]hex-2-ene. Distillation of the residue at reduced pressure yielded ca. 4.0 g (28%) of product; bp 118—122° (20 mm); NMR (CCl_4) δ 0.55 (d, 3, endo methyl, J = 6 Hz), 0.8—1.3 (m, 1, H_6), 1.4—1.9 (m, 1, H_5), 2.40 (t, 1, H_1, J = 8 Hz), 2.7—3.3 (m, 2, H_4) and 6.9—7.2 (broad s, 4, aromatic).

e. Preparation of 1,1,3-Trideuterioindene. A solution of indene (24.8 g, 213 mmol) in CCl_4 (25 ml) was added to a solution of ca. 10% NaOD/D_2O (prepared by addition of 5.0 g of sodium metal to 50 ml of D_2O) and refluxed for 72 hr. The organic layer was separated and added to a fresh 10% NaOD/D_2O solution (50 ml) and refluxed for an additional 72 hr. The organic layer was separated, dried over anhydrous K_2CO_3, and distilled at reduced pressure yielding 22.3 g (92%); bp 81° (ca. 20 mm); NMR (CCl_4) δ 6.50 (s, 1, H_2) and 7.10—7.55 (m, 4, aromatic); greater than 98% incorporation of 3 deuterium atoms.

f. Preparation of 1,4,4-Trideuterio-2,3-benzobicyclo[3.1.0]-hex-2-ene. A solution of 1,1,3-trideuterioindene (3.0 g, 25.2 mmol) and hexane (5 ml) was placed in a 50-ml round-bottomed flask equipped with side-arm septum, condenser, and magnetic stirrer. Diethylzinc (3 g, 24.3 mmol) was added via a syringe to the stirred solution. Methylene iodide (6.8 g, 47.9 mmol) was added over a five-min period via a syringe and the reaction mixture was stirred for 8 hr. The reaction mixture was poured into 10% HCl (20 ml) and washed with water (10 ml), 5% $NaHCO_3$ (10 ml), dried over anhydrous Na_2SO_4, and the volatile components removed by use of a rotary evaporator. Distillation at reduced pressure yielded 1.6 g (49.4%); bp 40° (0.1 mm); NMR (CCl_4) δ -0.1 (m, 1, endo H_6), 0.9 (m. 1, exo H_6), 1.65 (m, 1, H_5), and 7.10 (m, 4, aromatic).

g. Preparation of 6-Methyl-1,4,4-trideuterio-2,3-benzobicyclo-[3.1.0]hex-2-ene. A solution of 1,1,3-trideuterioindene (6.0 g, 50.4 mmol), diethylzinc (5 g, 40.5 mmol), and hexane (5 ml) was placed in a 50-ml round-bottomed flask equipped with Claisen adapter, addition funnel, condenser, and magnetic stirrer. A solution of 1,1-diiodoethane (2.3 g, 75.6 mmol) and hexane (5 ml) was added dropwise via the addition funnel at a rate that maintained a gentle reflux. After the addition was completed, the reaction mixture was stirred for 1.5 hr, poured into 10% HCl (25 ml), washed with water (10 ml), 5% $NaHCO_3$ (10 ml), and dried over anhydrous Na_2SO_4. The product was isolated by preparative glpc (Column N, 180°); NMR (CCl_4) δ 0.55 (d, 3, endo methyl, J = 6 Hz), 0.8—1.5 (m, 1, H_6), 1.73 (d, 1, H_5, J = 8 Hz) and 7.05—7.40 (m, 4, aromatic).

h. Preparation of Ethyl Diazoacetate.[92] A solution of glycine ethyl ester-hydrochloride (279.0 g, 2.0 mol), sodium acetate (1.4 g, 17.1 mmol), and distilled water (550 ml) was placed in a 4-l beaker and the solution was cooled to -15°. Low boiling ligroine was added and a mechanical stirrer was used to stir the two-phase system. A HONO solution (prepared from 70 ml of 2N H_2SO_4, 220 g of $NaNO_2$, and 300 ml of distilled water) was cooled to +10° C and added as rapidly as possible which maintained the reaction temperature below -10°. After addition was complete, the reaction was allowed to warm to +10° and was extracted with two 300-ml portions of 5% $NaHCO_3$ and two 100-ml portions of water; the organic layer was dried over $MgSO_4$ and concentrated by use of a rotary evaporator. This yielded 181 g (79.3%) of ethyl diazoacetate; NMR (CCl_4) δ 1.00 (t, 3, CH_3, J = 6 Hz), 3.95 (q, 2, CH_2, J = 6 Hz), and 4.75 (s, 1, CH).

i. Preparation of Ethyl 2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylate. A suspension of powdered copper (100 mg) and anhydrous cupric sulfate (100 mg) in indene (29.7 g, 256 mmol) and hexane (2 ml) was placed in a 250-ml round-bottomed flask equipped with Claisen adapter, pressure-equalizing addition funnel, condenser with oil bubbler at top, and magnetic stirrer. The flask was immersed in an oil bath at 100° and a solution of ethyl diazoacetate (45.0 g, 394 mmol) and hexane (16 ml) was added over a two-hr period and allowed to stir for an additional one hr. The reaction flask was removed from the oil bath, allowed to cool, and the catalyst removed

by vacuum filtration. The product was distilled at reduced pressure yielding 28.3 g (54.7%); bp 92—94° (0.15 mm); NMR and glpc analysis suggested a ca. 55:45 (exo:endo) mixture of ethyl exo-2,3-benzobicyclo-[3.1.0]hex-2-ene-6-carboxylate and endo-2,3-benzobicyclo[3.1.0]hex-2-ene-6-carboxylate.

j. Preparation of Ethyl endo-2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylate. The epimeric mixture was separated by preparative glpc (Column P, 180°), retention time 10 min; NMR (CCl_4) δ 0.87 (t, 3, O-CH_2-CH_3, J = 7 Hz), 1.83 (t, 1, H_6, J = 8 Hz), 2.09 (m, 1, H_5), 2.83 (broad t, 1, H_1, J = 8 Hz), 3.0—3.4 (m, 2, H_4), 3.80 (q, 2, O-CH_2-CH_3, J = 7 Hz), and 7.00—7.40 (m, 4, aromatic).

k. Preparation of Ethyl exo-2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylate. The epimeric mixture was separated by preparative glpc (Column P, 180°) retention time 14 min; NMR (CCl_4) δ 1.12 (t, 1, H_6, J = 3 Hz), 1.21 (t, 3, -O-CH_2 CH_3, J = 7 Hz), 2.32 (m, 1, H_5), 2,85 (d of d, 1, H_1, J = 7 Hz and J = 3 Hz), 3.00—3.20 (m, 2, H_4), 4.10 (q, 2, O-CH_2-CH_3, J = 7 Hz), and 7.05—7.50 (m, 4, aromatic).

l. Preparation of Ethyl 1,4,4-Trideuterio-2,3-benzobicyclo-[3.1.0]hex-2-ene-6-carboxylate. A suspension of powdered copper (20 mg) and anhydrous cupric sulfate (20 mg) in 1,1,3-trideuterioindene (6.0 g, 50.4 mmol) and hexane (2 ml) was placed in a 50-ml round-bottomed flask equipped with Claisen adapter, addition funnel, condenser with oil bubbler at trap, and magnetic stirrer. The flask was immersed in an oil bath at 100° and a solution of ethyl diazoacetate

(8.8 g, 77.1 mmol) and hexane (4 ml) was added over a 45-min period; the solution was allowed to stir for an additional 30 min. The reaction flask was removed from oil bath, allowed to cool, organic material taken up in hexane (50 ml), the catalyst removed by vacuum filtration, and the volatile components removed by use of a rotary evaporator yielding 5.0 g (48%) of crude product.

m. Preparation of Ethyl endo-1,4,4-Trideuterio-2,3-benzobicyclo-[3.1.0]hex-2-ene-6-carboxylate. The crude epimeric mixture was separated by preparative glpc (Column P, 180°), retention time 10 min; NMR (CCl_4) δ 0.88 (t, 3, O-CH_2-CH_3, J = 7 Hz), 1.86 (d, 1, H_6, J = 8 Hz), 2.16 (d, 1, H_5, J = 8 Hz), 3.78 (q, 2, O-CH_2 CH_3, J = 7 Hz), and 7.00—7.45 (m, 4, aromatic).

n. Preparation of Ethyl exo-1,4,4-Trideuterio-2,3-benzobicyclo-[3.1.0]hex-2-ene-6-carboxylate. The crude epimeric mixture was separated by preparative glpc (Column P, 180°), retention time 14 min; NMR (CCl_4) δ 1.11 (d, 1, H_6, J = 3 Hz), 1.24 (t, 3, O-CH_2-CH_3, J = 7 Hz), 2.35 (d, 1, H_5, J = 3 Hz), 4.15 (q, 2, O-CH_2 CH_3, J = 7 Hz), and 7.10—7.50 (m, 4, aromatic).

o. Preparation of 2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylic Acid. A solution of the epimeric (55:45) ethyl esters (12.0 g, 59.3 mmol) and 10% NaOH (50 ml) was placed in a 200-ml round-bottomed flask equipped with condenser and magnetic stirrer. Ethyl alcohol (35 ml) was added and the reaction mixture was refluxed for 24 hr, allowed to cool, acidified with 10% HCl (60 ml), and extracted with two 50-ml portions of ether. The ether layers were combined,

dried over $MgSO_4$, and the volatile components were removed by use of a rotary evaporator yielding 10.0 g (96.8%) of the epimeric acids; NMR ($CDCl_3$) δ 1.10 (t, 1, endo H_6, $\underline{J}$ = 3 Hz), 1.90 (t, 1, exo H_6, $\underline{J}$ = 8 Hz), 2.10—2.70 (m, 1, H_5), 2.75-3.40 (m, 3, H_1 and H_4), 7.00—7.40 (m, 4, aromatic) and 11.8 (s, 1, -COO$\underline{H}$).

p. Preparation of Isopropyl 2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylate. A solution of isopropyl alcohol (250 ml), the epimeric (55:45) 2,3-benzobicyclo[3.1.0]hexane-6-carboxylic acids (62.4 g, 35.8 mmol), and concentrated H_2SO_4 (2 ml) was placed in a 500-ml round-bottomed flask equipped with condenser and magnetic stirrer, and refluxed for 4 hr. The reaction mixture was cooled, transferred to a separatory funnel containing ether (100 ml) and extracted with 10% Na_2CO_3 (100 ml). The aqueous layer was extracted with ether (100 ml); the ether layers were combined, dried over K_2CO_3 and the volatile components removed by use of a rotary evaporator yielding the epimeric isopropyl esters which were distilled at reduced pressure, 50.0 g (64.6%); bp 90—95° (150 μ); NMR (CCl_4) δ 0.75 (d, 3, endo $CH(\underline{CH_3})_2$, $\underline{J}$ = 6 Hz), 0.95 (d, 3, endo $CH(\underline{CH_3})_2$, $\underline{J}$ = 6 Hz), 1.10 (m, 1, endo H_6), 1.21 (d, 6, exo $CH(\underline{CH_3})_2$, $\underline{J}$ = 6 Hz), 1.85 (m, 1, exo H_6), 2.35 (m, 1, H_5), 2.60—3.30 (m, 5, H_2 and H_4), 4.52 (m, 1, endo $C\underline{H}(CH_3)_2$, $\underline{J}$ = 6 Hz), 4.90 (m, 1, exo $C\underline{H}(CH_3)_2$, $\underline{J}$ = 6 Hz), and 6.90—7.30 (m, 4, aromatic). The aqueous layer was acidified with 10% HCl (150 ml) and extracted with ether (100 ml). The ether solution was dried over $MgSO_4$ and concentrated by use of a rotary evaporator yielding 5.8 g (33 mmol) of unreacted acid.

NMR and glpc (Column C, 200°) analysis of the isopropyl ester suggested a 70:30 (exo:endo) mixture of epimers.

q. Preparation of exo-2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylic Acid. A solution of NaOH (2.4 g, 60 mmol) in 75% methanol-water (60 ml) was placed in a 250-ml round-bottomed flask equipped with magnetic stirrer. A solution of the epimeric (70:30) isopropyl esters (18.6 g, 86 mmol) and methanol (25 ml) was added and refluxed for 14 hr. The reaction solution was allowed to cool, transferred to a separatory funnel containing water (200 ml), and extracted with three 100-ml portions of ether; the ether layers were combined, dried over K_2CO_3, and volatile components removed by use of a rotary evaporator yielding 6.5 g of unreacted ester. NMR suggested that the unreacted ester was a 15:85 (exo:endo) mixture. The aqueous layer was acidified with excess 10% HCl and extracted with three 100-ml portions of ether. The ether layers were combined and dried over Na_2SO_4; the volatile components were removed by use of a rotary evaporator yielding 9.8 g of essentially pure exo acid; mp 141—142°; NMR ($CDCl_3$) δ 1.16 (t, 1, endo H_6, J = 3 Hz), 2.50 (m, 1, H_5), 2.85—3.30 (m, 3, H_1 and H_4), 7.0—7.4 (m, 4, aromatic), and 11.1 (s, 1, COOH).

r. Preparation of endo-2,3-Benzobicyclo[3.1.0]hex-2-ene-6-carboxylic Acid. A solution of recovered (15:85) isopropyl esters (6.5 g, 30 mmol) and 95% ethanol was placed in a 100-ml round-bottomed flask equipped with magnetic stirrer. A 10% NaOH solution (30 ml) was added and the solution was refluxed for 2 days. The reaction

solution was allowed to cool, transferred to a separatory funnel containing 100 ml of water, and extracted with a 100-ml portion of ether. The aqueous layer was acidified with excess 10% HCl and extracted with 100 ml of ether; the ether layer was dried over Na_2SO_4, the volatile components removed by use of a rotary evaporator, and the recovered acid recrystallized from chloroform yielding 3.7 g of endo acid; mp 169—170°; NMR ($CDCl_3$) δ 1.91 (t, 1, exo H_6, J = 8 Hz), 2.22 (m, 1, H_5), 2.85—3.40 (m, 3, H_1 and H_4), and 7.00—7.40 (m, 5, aromatic and COOH).

s. Preparation of exo-6-Hydroxymethyl-2,3-benzobicyclo[3.1.0]-hex-2-ene. A suspension of $LiAlH_4$ (2.3 g, 61 mmol) and anhydrous ether (10 ml) was placed in a 200-ml round-bottomed flask equipped with Claisen adapter, condenser with drying tube, pressure-equalizing addition funnel, and magnetic stirrer. The round-bottomed flask was cooled to 0° by immersion in an ice-salt bath. A solution of exo-2,3-benzobicyclo[3.1.0]hex-2-ene-6-carboxylic acid (8.2 g, 47 mmol) and anhydrous ether (20 ml) was added slowly via the addition funnel; after addition was completed, the reaction mixture was refluxed for 12 hr. The solution was cooled to room temperature and a saturated solution of Na_2SO_4 in H_2O (10 ml) was added cautiously. The solution was extracted with two 25-ml portions of ether, the ether layers were combined, dried over Na_2SO_4 and the volatile components removed by use of a rotary evaporator. Distillation at reduced pressure yielded 7.3 g (97%); bp 122° (0.2 mm); NMR (CCl_4) δ 0.60 (m, 1, endo H_6), 1.65 (m, 1, H_5), 2.20 (m, 1, H_1),

2.90 (m, 2, H_4), 3.40 (d, 2, -CH_2-OH), 3.62 (s, 1, -CH_2 O-H), and 6.90—7.20 (m, 4, aromatic).

t. Preparation of endo-6-Hydroxymethyl-2,3-benzobicyclo-[3.1.0]hex-2-ene. A solution of endo-2,3-benzobicyclo[3.1.0]hex-2-ene-6-carboxylic acid (0.5 g, 2.9 mmol) and anhydrous ether (10 ml) were placed in a 50-ml round-bottomed flask equipped with Claisen adapter, addition funnel, condenser, and magnetic stirrer. A suspension of $LiAlH_4$ (0.11 g, 2.9 mmol) and anhydrous ether (10 ml) was placed in the addition funnel and added slowly; after addition was complete the reaction mixture was refluxed for 48 hr, allowed to cool to room temperature, and a saturated solution of Na_2SO_4-H_2O (10 ml) was added. The layers were separated and the aqueous layer was extracted with ether (30 ml). The ether layers were combined, dried over Na_2SO_4 and the volatile components removed by use of a rotary evaporator yielding ca. 0.4 g of the endo alcohol; NMR (CCl_4) δ 1.15 (quintuplet, 1, exo H_6, J = 8 Hz), 1.72 (q of d, 1, H_5, J = 6 Hz and J = 3 Hz), 2.40 (t, 1, H_1, J = 6 Hz), 2.60—3.0 (m, 2, H_4), 2.90 (d, 2, -CH_2OH, J = 8 Hz), 3.35 (s, 1, -CH_2O-H), and 6.80—7.20 (m, 4, aromatic).

u. Preparation of the Tosylate of exo-6-Hydroxymethyl-2,3-benzobicyclo[3.1.0]hex-2-ene. Method 1.[93] A solution of the exo alcohol (0.80 g, 5.0 mmol) and anhydrous pyridine (4 ml) was placed in a 10-ml round-bottomed flask equipped with magnetic stirrer and septum; the flask was cooled to 5° by placement in ice water. p-Toluenesulfonyl chloride (1.14 g, 5.5 mmol) was added in small

portions (ca. 0.2 g) and the flask was placed in the cold room (ca. 4°) for 14 hr. After standing for 14 hr, the solution was poured into a separatory funnel containing ice (10 g) and ether (10 ml); the layers were separated, the aqueous layer extracted with ether (10 ml), the ether layers combined, dried over Na_2SO_4 and the ether removed by use of a rotary evaporator, maintaining the water bath at 18°. An NMR spectrum taken of the residue showed that no apparent reaction had taken place.

Method 2. A solution of p-toluenesulfonyl chloride (0.43 g, 2.3 mmol) and anhydrous pyridine (0.18 ml, 2.2 mmol) was placed in a 10-ml round-bottomed flask equipped with magnetic stirrer and septum. A solution of the exo alcohol (0.36 g, 2.3 mmol) and dry toluene (3 ml) was added and allowed to stir overnight. The reaction mixture was transferred to a separatory funnel containing cold water (0.5 ml) and ether (10 ml). The layers were separated, the organic layer was dried over Na_2SO_4, and the ether removed by use of a rotary evaporator. An NMR spectrum of the residue was consistent with the presence of desired product but it also indicated that some olefinic contaminents were present.

v. Preparation of exo-6-Methyl-2,3-benzobicyclo[3.1.0]hex-2-ene. Method 1. The exo-tosylate, prepared by method 2, was taken up in ether and cooled to 0°. A suspension of $LiAlH_4$ (0.5 g, 13.2 mmol) and anhydrous ether (10 ml) was placed in a 100-ml round-bottomed flask equipped with side-arm septum and condenser with drying tube. The chilled tosylate-ether solution was added to

the $LiAlH_4$-ether suspension and allowed to stir for 1 hr at room temperature, refluxed for 2 hr, and allowed to cool. A saturated solution of Na_2SO_4 and H_2O (20 ml) was added, the layers were separated, the aqueous layer extracted with ether (10 ml), the ether layers combined, dried over Na_2SO_4, and the ether removed by use of a rotary evaporator. An NMR spectrum was taken of the crude residue. The appearance of a doublet at δ 1.20 suggested formation of the desired product. Analysis of the residue *via* glpc (Column D, 150°) showed the presence of a 2:1 mixture; an attempt to purify product by preparative glpc (Column P, 150°) failed.

Method 2. The exo alcohol (1.0 g, 6.2 mmol) was placed in a 10-ml round-bottomed flask equipped with septum and magnetic stirrer. A solution of *n*-butyllithium in hexane (3.0 ml, 6.5 mmol) was added and the reaction mixture was allowed to stir at room temperature for 15 min. TMEDA (0.73 g, 6.3 mmol) was added *via* a syringe. *p*-Toluenesulfonyl chloride (1.3 g, 6.8 mmol) was added carefully (exothermic reaction) while cooling with an ice bath. The solution was stirred for 30 min at room temperature and worked up as in Method 1. The isolated residue was taken up in anhydrous ether and added to a suspension of $LiAlH_4$ (0.24 g, 6.3 mmol) and anhydrous ether (10 ml). This mixture was refluxed for 14 hr and worked up as in Method 1. An NMR spectrum was taken of the residue obtained after volatile components were removed by use of a rotary evaporator. NMR suggested that some product was formed, but that the residue consisted largely of olefinic products.

Method 3. A solution of the exo alcohol (1.6 g, 10 mmol) and benzene (10 ml) was placed in a 25-ml round-bottomed flask equipped with side-arm septum and magnetic stirrer. The solution was cooled to 0° and anhydrous 2,6-lutidine (1.1 g, 10.3 mmol) was added *via* syringe. p-Toluenesulfonyl chloride (3.3 g, 17.3 mmol) was added, and the solution allowed to warm to room temperature; a precipitate formed and was filtered. The filtrate was added to a cold suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) and ether (25 ml); the mixture was allowed to warm to room temperature and then refluxed for 3 hr. The reaction mixture was allowed to cool to room temperature and was carefully poured into a stirred mixture of ice water (10 ml) and ether (30 ml). The ether layer was separated, dried over Na_2SO_4 and the volatile components removed by use of a rotary evaporator. NMR analysis of the residue suggested very little product formed.

Method 4. A solution of the exo carboxylic acid (0.626 g, 3.59 mmol) and anhydrous THF (15 ml) was placed in a 50-ml round-bottomed flask equipped with septum adapter, condenser with oil bubbler, and magnetic stirrer. A solution of BF_3-Et_2O (4.7 ml, 38 mmol) was added *via* syringe and the solution was stirred for 2 min. The flask was then immersed in an ice bath and the contents were stirred for 5 min. A solution of BH_3-DMS (9.5 ml, 9.5 mmol) was added dropwise to the cold solution *via* syringe, the reaction was allowed to warm to room temperature and stirred for 4 hr. Water (2 ml) was added and the reaction mixture was extracted with ether (15 ml); the ether layer was dried over K_2CO_3 and volatile components

were removed by use of rotary evaporator. NMR analysis of the residue indicated very little product formed.

Method 5.[94] A solution of the exo alcohol (1.6 g, 10 mmol) and anhydrous 2,6-lutidine (10 ml) was placed in a 25-ml round-bottomed flask equipped with side-arm septum and magnetic stirrer. The flask was immersed in an ice-salt bath and methanesulfonyl chloride (2.6 g, 22.7 mmol) was slowly added *via* syringe to the cold alcohol-lutidine solution. The solution was stirred, maintaining the temperature below 0°, for 3 hr. The solution was poured into a mixture of ice (30 g) and concentrated HCl (5 ml) and extracted with cold ether (50 ml). The ether layer was transferred to a 125-ml Erlenmeyer flask containing anhydrous Na_2SO_4 and allowed to dry for 30 min at 0°; the ether layer was decanted into another 125-ml Erlenmeyer flask and the volume was reduced to *ca*. 25 ml by use of a rotary evaporator. The Erlenmeyer flask was placed in a Dry Ice-acetone bath; after standing for *ca*. 15 min at -78° crystals formed. These crystals were collected by use of a cold Büchner funnel. The crystals were transferred, in small portions, to a suspension of $LiAlH_4$ (3.0 g, 79 mmol) and anhydrous ether (20 ml). The reaction mixture was refluxed for 24 hr and poured into an 800-ml beaker containing wet ether (100 ml). The ether layer was washed with 10% HCl (100 ml), dried over K_2CO_3 and the volatile components removed by use of a rotary evaporator. The residue was purified by preparative glpc (Column K, 180°) for NMR analysis; NMR (CCl_4) δ 0.32 (m, 1, endo H_6), 1.10 (d, 3, exo CH_3, J = 6 Hz), 1.20—2.60 (m, 1, H_5), 1.90—2.15

(m, 1, H_1), 2.70—3.10 (m, 2, H_4), and 6.90—7.20 (m, 4, aromatic). NMR also indicated the presence of olefinic contaminents.

C. Reactions

1. Reactions of 2-Phenyl-5,5-dimethyl-1,3-cyclohexadiene with n-Butyllithium

Method 1. A solution of 30-60° ligroin (5 ml) and 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.55 g, 3.0 mmol) was treated with a solution of n-butyllithium in hexane (1.5 ml, 3.0 mmol) at 0° for 3 hr. The reaction mixture was quenched with water (5 ml), poured into a separatory funnel containing 30-60° ligroin (20 ml), and washed with two 20-ml portions of water; the organic layer was separated and dried over Na_2SO_4. The volatile components were removed by use of a rotary evaporator yielding 0.55 g of product whose NMR spectrum was identical with starting material.

Method 2. A solution of 30-60° ligroin (5 ml) and 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.55 g, 3.0 mmol) was treated with a solution of n-butyllithium in hexane (1.5 ml, 3.0 mmol) at room temperature for 8 hr. The reaction was worked-up as in Method 1. NMR analysis of the product showed that it was identical with starting material.

Method 3. A solution of 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.3 g, 1.6 mmol) and anhydrous THF (0.3 ml) was placed in an NMR tube and cooled to -78°. A solution of n-butyllithium in hexane (1 ml, 2 mmol) was added, the tube was shaken and a deep-red color

appeared. NMR spectra were taken after the temperature reached 24°, and after standing for 48 hr at 24°. The reaction mixture was quenched by pouring into water (5 ml) and extracted with 30-60° ligroin (3 ml); the organic layer was separated, dried over Na_2SO_4, and the volatile components were removed by use of a rotary evaporator. NMR analysis of the product suggested incorporation of a butyl group. Analysis of the product by glpc (Column C, 220°) indicated a high (79%) conversion to a two-component mixture of higher boiling materials.

2. Reaction of 2-Phenyl-5,5-dimethyl-1,3-cyclohexadiene with t-Butyllithium

A solution of 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.37 g, 2 mmol) and 30-60° ligroin (10 ml) was cooled to 0° and a solution of t-butyllithium in pentane (1.5 ml, 2.1 mmol) was added. TMEDA (0.23 g, 2 mmol) was slowly added via a syringe; the reaction solution was allowed to warm to room temperature and stirred for 24 hr. The solution was quenched with water (5 ml), extracted with two 10-ml portions of 10% acetic acid, dried over K_2CO_3, and the volatile components were removed by use of a rotary evaporator. Analysis of the product by NMR and glpc indicated quantitative addition of t-butyllithium to the substrate. The glpc indicated only one product.

3. Reaction of 2-Phenyl-5,5-dimethyl-1,3-cyclohexadiene with Lithium Diisopropylamide

Method 1. A solution of diisopropylamine (0.30 g, 3 mmol) and anhydrous THF (5 ml) was cooled to -78° and a solution of

n-butyllithium in hexane (1.5 ml, 3.0 mmol) was added and stirred for 15 min. A solution of 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.55 g, 3 mmol) and anhydrous THF (2 ml) was added via syringe maintaining the temperature below -65° during addition. The reaction mixture was allowed to warm to room temperature and was stirred for 10 hr. The reaction mixture was quenched with water (5 ml), extracted with two 5-ml portions of 10% acetic acid, dried over K_2CO_3, and the volatile components removed by use of a rotary evaporator. NMR analysis indicated partial conversion of 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene into 6-phenyl-3,3-dimethyl-1,4-cyclohexadiene.

Method 2. The above procedure was repeated exactly, except that the reaction mixture was quenched with D_2O instead of H_2O. NMR analysis indicated partial conversion of the 1,3-cyclohexadiene into the 1,4-cyclohexadiene but gave no evidence of deuterium incorporation.

4. Reaction of 2-Phenyl-5,5-dimethyl-1,3-cyclohexadiene with Lithium Triphenylmethide

A solution of triphenylmethane (0.48 g, 2 mmol) and THF (5 ml) was treated with a solution of n-butyllithium in hexane (1 ml, 2 mmol). A solution of 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene (0.37 g, 2 mmol) was added and the resulting solution was stirred at room temperature for 12 hr. The reaction mixture was quenched with water (5 ml) and extracted with hexane (10 ml); the organic layer was separated, dried over Na_2SO_4 and the volatile components removed by use of a rotary evaporator. NMR analysis of the residue

indicated a partial conversion of the 1,3-cyclohexadiene into the 1,4-cyclohexadiene.

5. Reaction of 3-Phenyl-1,5,5-trimethyl-1,3-cyclohexadiene with n-Butyllithium

Method 1. A solution of 30-60° ligroin (5 ml) and 3-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene (0.59 g, 3 mmol) was treated with a solution of n-butyllithium in hexane (1.5 ml, 3 mmol) at 0° for 3 hr. The reaction mixture was quenched with water (5 ml), poured into a separatory funnel containing 30-60° ligroin (20 ml), and washed with two 20-ml portions of water; the organic layer was separated, dried over Na_2SO_4, and the volatile components removed by use of a rotary evaporator. NMR analysis of the residue indicated that it was identical to the starting material.

Method 2. A solution of 30-60° ligroin (5 ml) and 3-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene (0.59 g, 3 mmol) was treated with a solution of n-butyllithium in hexane (1.5 ml, 3 mmol) at room temperature for 8 hr. The reaction was worked-up as in Method 1. The NMR spectrum of the product was identical with that of starting material.

Method 3. The procedure in Method 2 was followed exactly, except the reaction mixture was refluxed for 2 hr. The NMR spectrum of recovered product was identical to that of starting material.

Method 4. The procedure in Method 2 was followed exactly, except that the reaction mixture was refluxed for 9 hr. The NMR spectrum of the recovered product was identical to that of starting material.

Method 5. A solution of n-butyllithium in hexane (1.5 ml, 3 mmol) was added to a solution of TMEDA (5 ml) and 3-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene and the resulting solution was stirred at room temperature for 12 hr. The reaction mixture was quenched with water (5 ml), and extracted with 30-60° ligroin (30 ml); the organic layer was extracted with three 15-ml portions of 10% acetic acid and two 15-ml portions of water. The organic layer was dried over Na_2SO_4, and the volatile components removed by use of a rotary evaporator. Analysis of the product by NMR indicated addition of n-butyllithium to 3-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene.

Method 6. A solution of 3-phenyl-1,5,5-trimethyl-1,3-cyclohexadiene (0.3 g, 1.5 mmol) and THF (0.3 ml) was placed in an NMR tube, cooled to -78°, and a solution of n-butyllithium in hexane (1.0 ml, 2 mmol) was added. The NMR tube was shaken and allowed to warm to room temperature. NMR spectra were taken over a 45-min interval. The reaction mixture was allowed to remain in the NMR tube for 24 hr, quenched with water (5 ml) and worked up as in Method 2. The NMR spectrum of the recovered residue indicated addition of n-butyllithium to the substrate. Analysis of the product by glpc (Column C, 220°) indicated a high conversion (79%) into a two-component mixture similar to the mixture formed in the reaction of n-butyllithium with 2-phenyl-5,5-dimethyl-1,3-cyclohexadiene.

6. Reaction of 2,5,5-Trimethyl-1,3-cyclohexadiene with n-Butyllithium

A solution of TMEDA (5 ml) and 2,5,5-trimethyl-1,3-cyclohexadiene (0.37 g, 3 mmol) was treated with a solution of n-butyllithium in

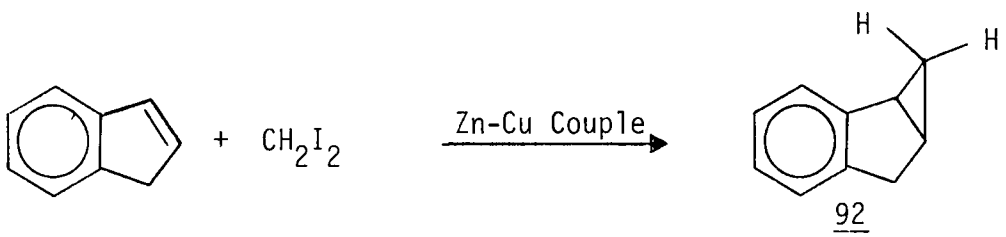
hexane (1.5 ml, 3 mmol), and the resulting solution was stirred for 12 hr at room temperature. The reaction mixture was quenched with water (5 ml) and extracted with hexane (15 ml). The organic layer was extracted with three 15-ml portions of 10% acetic acid, two 15-ml portions of water, dried over Na_2SO_4, and the volatile components removed by distillation through a short-path distilling head at atmospheric pressure. The NMR spectrum of the residue was identical to that of starting material.

CHAPTER III

RESULTS AND DISCUSSION

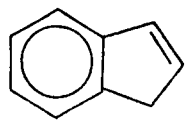
The investigation of possible [1,4] anionic sigmatropic shifts began with the synthesis of exo-6-methyl-2,3-benzobicyclo-[3.1.0]hex-2-ene (91) (p 45).

The possibility of preparing this substrate in one step by an extension of the Simmons-Smith reaction[95,96] was examined. Cyclopropanation by the addition of methylene iodide to a mixture of indene and zinc-copper couple[89] produced 2,3-benzobicyclo[3.1.0]-hex-2-ene (92) (Equation 53) in 8.3% yield.



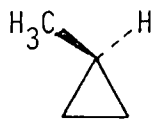
92 (53)

Numerous attempts to extend this method, using ethylidene iodide in place of methylene iodide, to prepare 91 (p 45) resulted only in the formation of intractable tars and provided no evidence for product formation. The more reactive zinc-copper couple described by Effenberger and Wurtz[90] was also tried several times and produced the same results.

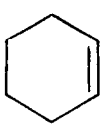
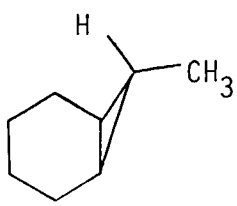


+ CH_3CHI_2 $\xrightarrow{\text{Zn-Cu Couple}}$ "Tars" (54)

The formation of these tars was not unexpected owing to the tendency of indene to polymerize, but the complete absence of any evidence of product formation was somewhat surprising. For example, Setser and Rabinovitch[97] reported the formation of methylcyclopropane, in 25% yield, by the addition of ethylidene iodide to ethylene (Equation 55). Simmons and coworkers[98] reported the

$H_2C{=}CH_2$ + CH_3CHI_2 $\xrightarrow{\text{Zn-Cu Couple}}$  (55)

synthesis of exo-7-methylbicyclo[4.1.0]heptane (93) (Equation 56) in 3.6% yield from the reaction of ethylidene iodide and cyclohexene, in the presence of zinc-copper couple.

 + CH_3CHI_2 $\xrightarrow{\text{Zn-Cu Couple}}$  (56)

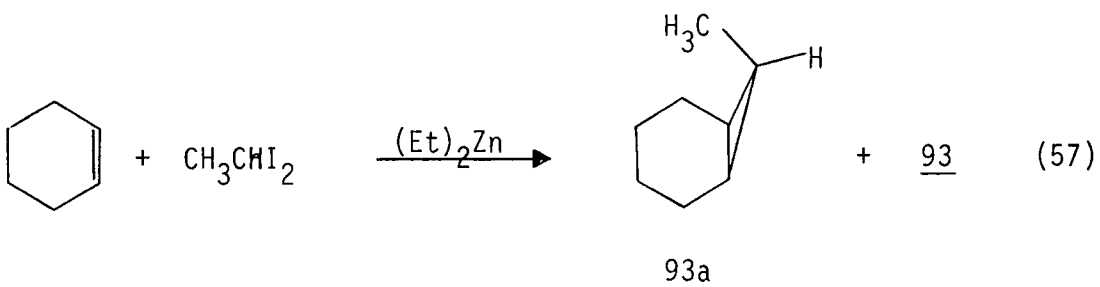
93

Because of the above-mentioned failures, the preparation of compound 91 (p 45) by use of the Simmons-Smith reaction was

abandoned in favor of the recently developed procedure for cyclopropanation by Furukawa and coworkers.[91,99] The Furukawa method allows the conversion of polymerizable olefins into the corresponding cyclopropanes in yields far superior to those obtained by use of the Simmons-Smith reaction. This procedure is essentially a Simmons-Smith reaction except that the zinc-copper couple is replaced by diethylzinc. To test this method, the synthesis of 2,3-benzobicyclo[3.1.0]hex-2-ene (92) was attempted and was found to succeed.

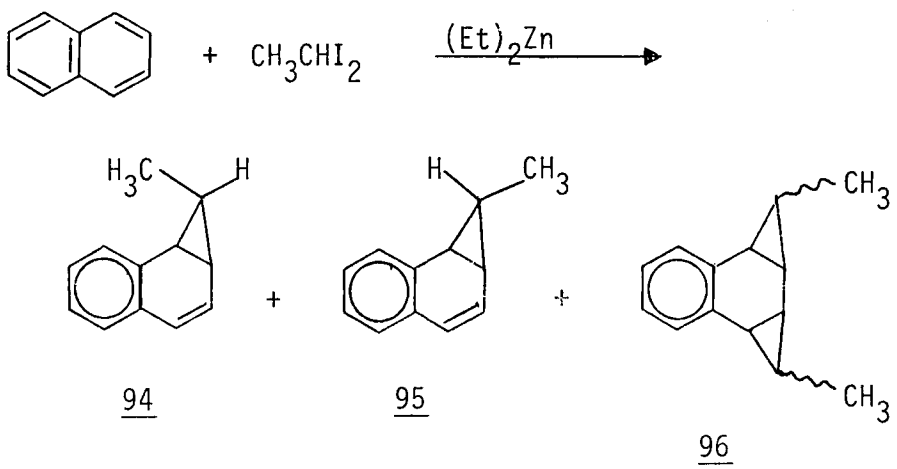
Miyano and Hashimoto[100] reported an improved yield of compound 92 by passing a stream of dry oxygen over the surface of the reaction mixture. This result was extremely surprising in view of the fact that diethylzinc reacts violently (very nice blue flames) when exposed to air.

Furukawa and coworkers[101,102] have extended the diethylzinc reaction to the formation of methylcyclopropanes by the reaction of ethylidene iodide, olefin, and diethylzinc. For example, the reaction of cyclohexene under these conditions produced a 1.5:1 mixture of endo- and exo-7-methylbicyclo[4.1.0]heptane (93a) and (93) (p 82), respectively, in 66% yield[101] (Equation 57).



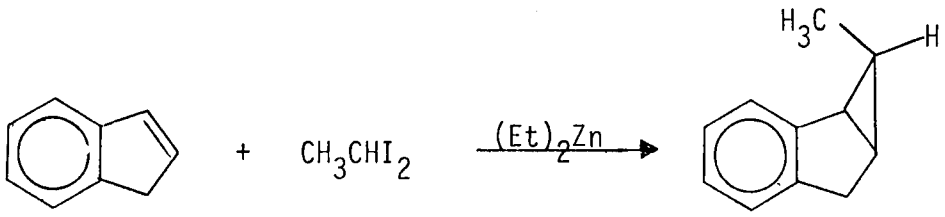
(57)

The reaction of naphthalene with ethylidene iodide and diethylzinc yielded a mixture of five products.[102] These products consisted of a 14% yield (glpc) of a 1:3.5 mixture of endo- and exo-7-methyl-2,3-benzobicyclo[4.1.0]hepta-2,4-diene (94) and (95) and a 7% yield (glpc) of a 1:9.6:3.9 mixture of exo, exo-, exo, endo-, and endo, endo-5,8-dimethyl-2,3-benzotricyclo[5.1.0.$0^{4,6}$]oct-2-ene (96) (Equation 58).



94 95 96 (58)

Furukawa and coworkers were able to separate the mixture of isomers of compound 96 but were unable to separate compound 94 from 95. The composition of this mixture was determined by NMR spectroscopy. These workers also reported that the reaction of indene with ethylidene iodide and diethylzinc produced only endo-6-methyl-2,3-benzobicyclo-[3.1.0]hex-2-ene (97) in 28% yield (glpc).[102]



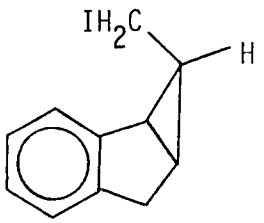
(59)

97

The exclusive formation of 97 was based on NMR and glpc analysis of the product. Compound 97 was accompanied by higher boiling components in ca. 10% yield. The apparent preparation of compound 97 without formation of compound 91 (p 45) by this method was a surprising but pleasing result and it appeared that the synthesis portion of this study was nearing its end.

The reaction of ethylidene iodide with a mixture of indene and diethylzinc by the modified procedure of Miyano and Hashimoto[100] provided a 28% yield (isolated) of what appeared to be pure endo-6-methyl-2,3-benzobicyclo[3.1.0]hex-2-ene (97). The NMR spectrum of this product appeared to be identical to the reported spectrum,[102] but the integrated areas were not consistent with pure 97. The total area of the aliphatic region was consistent with structure 97, but the area under the methyl doublet at δ0.55 was one proton too small. The possibility of a mixture of 97 and 91 (p 45) was at first dismissed, because glpc analysis of the product on all available analytical columns showed only the presence of one component accompanied by a small amount of higher boiling material. No evidence

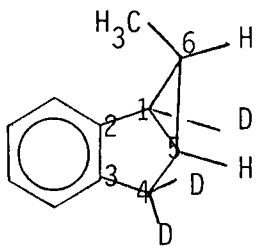
of the formation of a compound similar to structure 98 could be found.



98

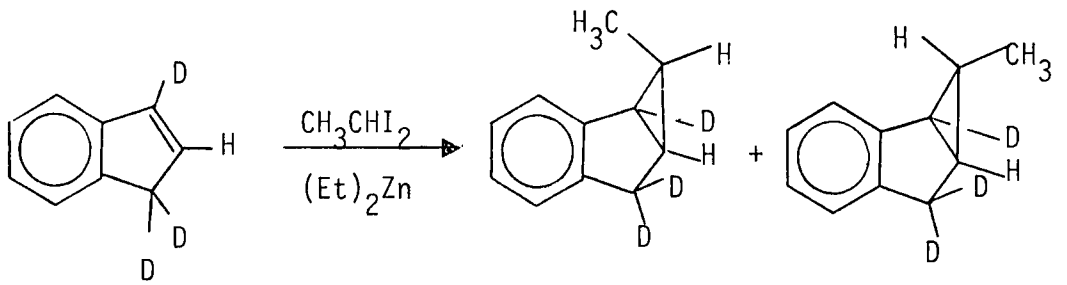
The only reasonable explanation for the NMR spectrum was that the product was, in fact, a mixture of compounds 91 (p 45) and 97, and that the exo-methyl doublet was buried beneath some other proton's resonance.

In order to demonstrate this, 1,1,3-trideuterioindene was prepared and transformed, using the above procedure, into methylcyclopropane 99. Both the 60 MHz and 100 MHz NMR spectra were examined. Comparison of the area of the methyl doublet with the area of the H_5 doublet again indicated that the methyl area was ca. one proton too small.



99

Comparison of the area of H_5 with the area of exo H_6 indicated ca. a one proton excess and a possible doublet with J = 6 Hz at δ 1.10. These results suggested that the reaction of 1,1,3-trideuterio-indene with ethylidene iodide and diethylzinc produced a mixture of endo-and exo-6-methyl-1,4,4-trideuterio-2,3-benzobicyclo[3.1.0]-hex-2-ene (99) and (100) (Equation 60) in a ratio of ca. 3:1.

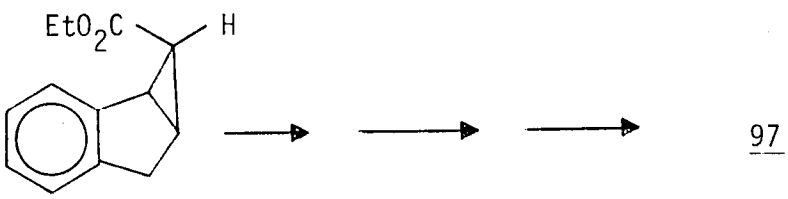


(60)

99 100

The inability to separate these two epimers resulted in the abandonment of this synthetic scheme and the investigation of another method of preparation of these compounds.

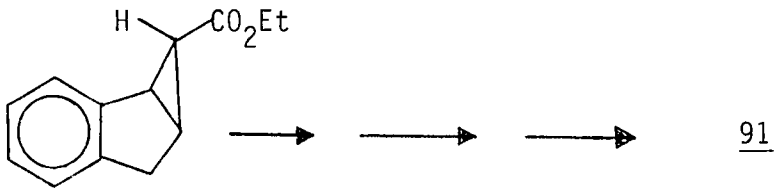
The synthesis of ethyl endo- and exo-2,3-benzobicyclo[3.1.0]-hex-2-ene-6-carboxylate, (101) and (102) respectively, and the conversion of these compounds into 97 (p 85) and 91 (p 45) Equation 61 was attempted.



97

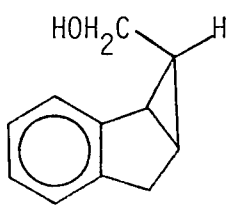
101

(61)

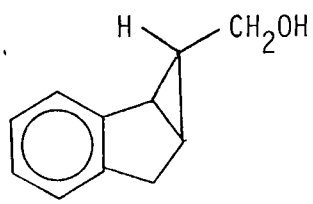


102

This method possessed two advantages over the diethylzinc reaction: (1) separation of epimers before conversion into compounds 91 and 97, and (2) resolution and preparation of optically active compounds 91 and 97. This method also had disadvantages: (1) it is a multistep synthesis and (2) eventually the 6-hydroxymethyl-2,3-benzobicyclo[3.1.0]hex-2-ene must be converted into its tosylate, and the tosylate must be reduced to the final product. This conversion of the alcohol into the tosylate and then into product was anticipated to be a poor yielding reaction and consequently necessitated the ability to prepare and separate large quantities of either the endo and exo-6-hydroxymethyl-2,3-benzobicyclo[3.1.0]hex-2-ene (103) and (104) or their precursors.



103

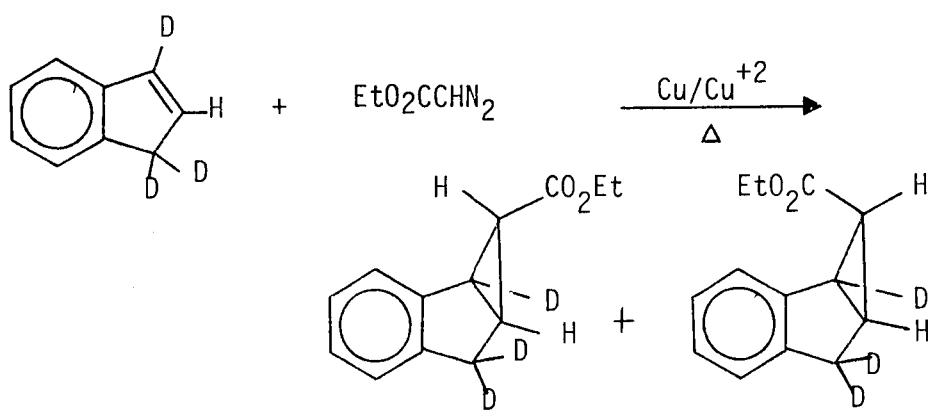


104

The exo and endo ethyl esters 102 and 101 were prepared by the addition of ethyl diazoacetate to a solution of indene and

hexane containing a $Cu°/CuSO_4$ catalyst. This reaction produced a 55:45 (exo:endo) mixture of esters in ca. 55% yield. Samples for NMR spectra were obtained by preparative glpc. The assignment of stereochemistry to the epimers was based on the chemical shift and coupling constant for H_6. The chemical shift of H_6 for the exo ethyl ester was δ 1.12 (J = 3 Hz) and the chemical shift of H_6 for the endo ethyl ester was δ 1.83 (J = 8 Hz). The chemical shift of the endo H_6 was expected to be at higher field than that of the exo H_6 owing to the shielding effect of the aromatic ring. It is also known that cis coupling constants are greater than trans coupling constants in cyclopropanes.

In order to firmly establish the stereochemistry at C_6, ethyl diazoacetate was added to a solution of 1,1,3-trideuterioindene and hexane containing a $Cu°/CuSO_4$ catalyst. The reaction produced a mixture of ethyl exo- and endo-1,4,4-trideuterio-2,3-benzobicyclo-[3.1.0]hex-2-ene carboxylates 105 and 106 (Equation 62). Samples for NMR spectra were obtained by preparative glpc.



(62)

105 106

The structural assignments based on the unlabeled compounds were confirmed. Because the H_6 resonance in the exo ethyl ester was partially obscured by the methyl triplet making the determination of the coupling constant difficult, the transesterification of the ethyl esters to the methyl esters was investigated.

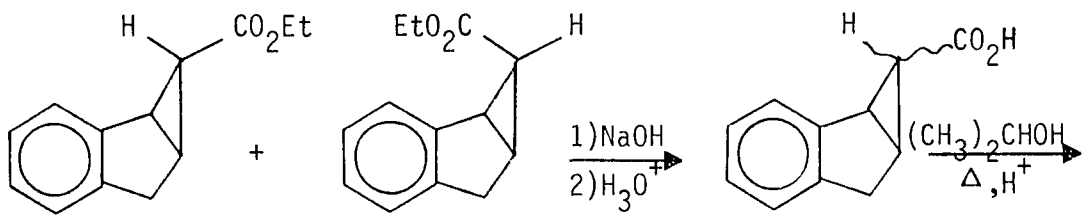
The epimeric mixture of unlabeled ethyl esters was refluxed in the presence of a trace of p-toluenesulfonic acid and excess methanol. The progress of this reaction was monitored by glpc and the observation was made that the exo ethyl ester was reacting at a faster rate than the endo. This observation was the basis for the eventual large-scale separation of the epimers in this system. Various transesterification methods were attempted in a search for a method in which one epimer would react exclusively; all of these investigations failed to provide a suitable method for the separation of the epimers.

The possibility of separating the ethyl esters by a stereoselective hydrolysis of the exo ester was examined.[103] This study indicated that there was a difference in the rate of hydrolysis of the exo and endo ethyl ester but again the difference was not great enough to use as a separation technique.

The possibility that a more hindered ester would provide an adequate difference was examined by the conversion of the epimeric ethyl esters into the carboxylic acids and then into the isopropyl esters. The hydrolysis of a 55:45 (exo:endo) mixture of ethyl esters into a mixture of epimeric carboxylic acids of unchanged

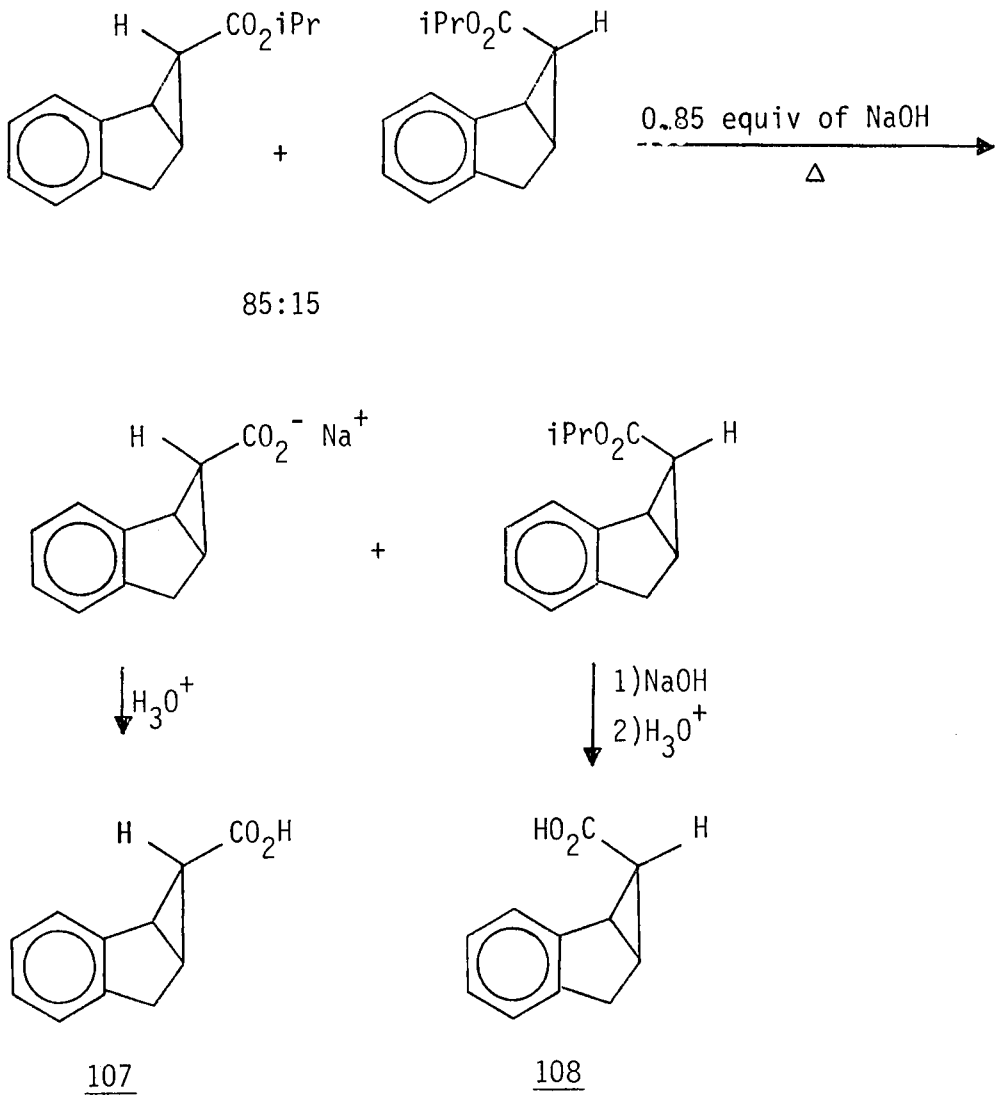
composition was accomplished by refluxing a solution of the ethyl esters in aqueous ethanol containing an excess of NaOH. The carboxylic acids were partially converted into an epimeric mixture of isopropyl esters of changed composition (85:15, exo:endo). The NMR spectrum of this mixture was very interesting in that the methyls of the endo isopropyl group, instead of appearing as a doublet as in the exo epimer, appeared as two doublets. This observation was quite troublesome for some time until it was realized that this was an example of the chemical shift nonequivalence of the methyl groups of the isopropyl moiety caused by an asymmetric center.[104]

The epimeric isopropyl esters were then successfully stereoselectively hydrolyzed. This was accomplished by treating a solution of the esters and 75% ethanol-water with an equivalent amount (equivalent to the amount of exo isopropyl ester) of NaOH. This method provided pure exo-2,3-benzobicyclo[3.1.0]hex-2-ene-6-carboxylic acid 107 and unreacted endo isopropyl ester (Equation 63)



102 101

55:45 55:45



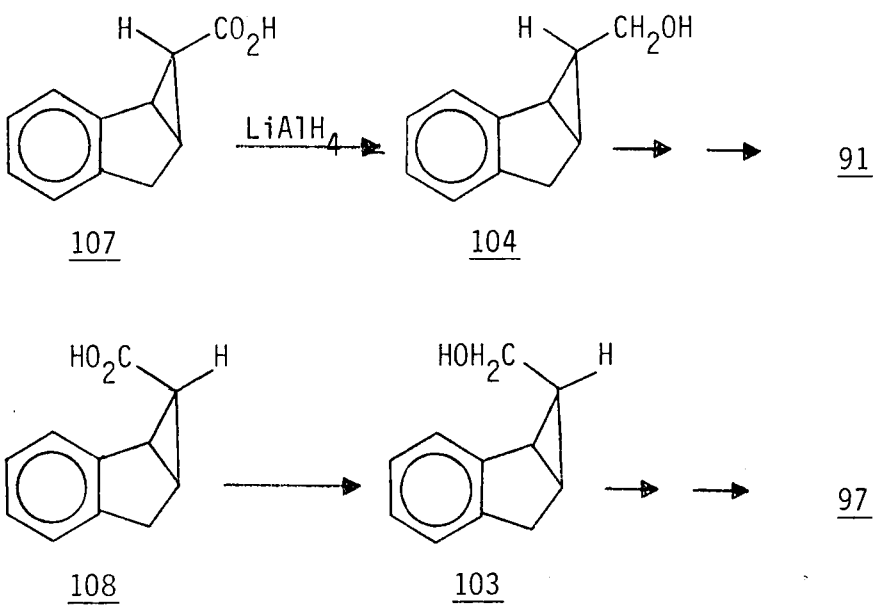
(63)

107 108

which was converted into the endo acid by hydrolysis with excess NaOH, acidification, and recrystallization from $CHCl_3$. This rather circuitous route provided a method of synthesizing exo- and endo-2,3-benzobicyclo[3.1.0]-hex-2-ene-6-carboxylic acid (107) and (108), respectively, in quantities that could not be obtained by the

traditional separation methods of either preparative glpc, or column chromatography.[105]

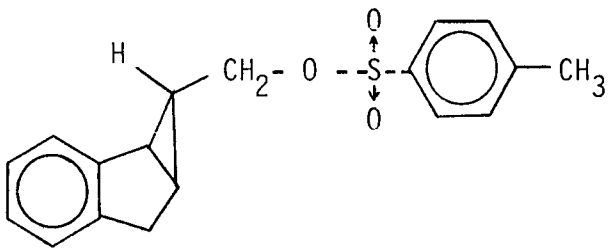
The next step in the preparation of either 91 (p 45) or 97 (p 85) was the conversion of the corresponding acid, 107 or 108, respectively, into the alcohols 104 or 103 by treatment with $LiAlH_4$ (Equation 64).



(64)

The preparation of either endo- or exo-6-methyl-2,3-benzobicyclo-[3.1.0]hex-2-ene, (97) or (91) was now only two steps away. Because of the anticipated difficulty in completing these last two steps only the exo-hydroxymethyl compound 104 was used in this attempted conversion.

The first step required the synthesis of tosylate 109 of the exo alcohol. Many attempts to prepare this tosylate by the



109

standard methodology all resulted in the formation of a pale blue solution and the failure to observe the appearance of a pyridine hydrochloride precipitate. Only unreacted alcohol was recovered when these preparations were worked up. The possibility that pyridine was displacing the tosylate led to a variation of this method.[106]

This variation of the standard method involved the reaction of a solution of the exo alcohol in toluene with one equivalent of pyridine and a slight excess of p-toluenesulfonyl chloride at room temperature. This procedure produced a precipitate which was filtered and found to be water soluble. The filtrate was examined by NMR spectroscopy and the spectrum was found to be consistent with that expected for the tosylate. The NMR spectrum also exhibited resonances suggesting the presence of an olefinic compound(s).

The filtrate was dissolved in ether, cooled to 0° and added to a suspension of $LiAlH_4$ (four-fold molar excess) in ether. The reaction was worked-up after refluxing for 2 hr. An NMR spectrum was taken of the isolated residue and it indicated the formation

of methyl compound 91 (p 45) as the minor component of the products obtained. The major component was an olefin of undetermined structure. Attempts to isolate compound 91 were unsuccessful. This sequence was attempted several additional times and each trial provided the same results.

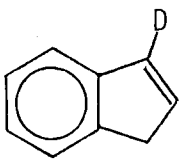
Another procedure that was attempted involved the treatment of alcohol 104 with one equivalent each of n-butyllithium and TMEDA followed by the addition of p-toluenesulfonyl chloride and warming to room temperature. This reaction mixture was taken up in ether as before, and added to a suspension of $LiAlH_4$ in ether. An NMR spectrum of the residue obtained after work-up indicated that the product was a gross mixture of olefins and provided very little evidence for the formation of compound 97. The possibility that the tosylate was decomposing after isolation suggested that the preparation of compound 91 might succeed if the isolation of tosylate 109 were omitted.

This procedure involved the reaction of exo alcohol 104 with an equivalent of 2,6-lutidine and excess p-toluenesulfonyl chloride at 0°. The reaction was allowed to warm to room temperature, and the precipitate that formed (presumably 2,6-lutidine hydrochloride) was filtered. The filtrate was added to a cold suspension of $LiAlH_4$ and ether and refluxed. The residue obtained after work-up indicated the formation of compound 91 in low yield as well as a considerable amount of starting material.

In an act of complete desperation the exo carboxylic acid 107 (p 92) was treated with a 10-fold excess of BF_3-Et_2O followed by addition of a 3-fold excess of BH_3-DMS (borane-dimethyl sulfide complex). This procedure produced a residue of uncharacterizable material. It had been hoped that this method would produce compound 91 (p 45) in one step.[107]

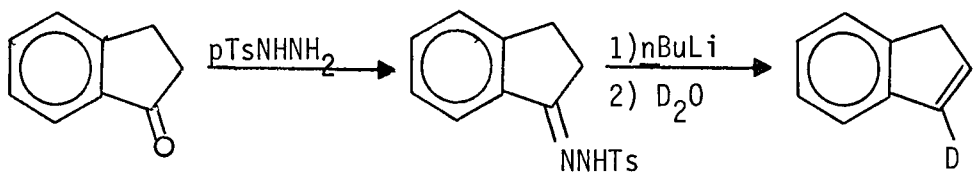
One final attempt was made to synthesize compound 91 (p 45). This method involved the treatment of the exo alcohol 104 with a two-fold excess of methanesulfonyl chloride using 2,6-lutidine as the solvent. The temperature of the reaction was never allowed to exceed 0°. The mesylate was isolated from an ethereal solution at -78° and added to a suspension of $LiAlH_4$ and ether at 0°. This method provided the best preparation of 91 although the sample obtained by preparative glpc still contained an olefinic component.

The preparation of 91d (p 45) by the preceding method required the synthesis of 3-deuterioindene (110). The procedure of Stamke and Bond[108] appeared to provide the best and least expensive pathway to 110. Their method was an extension of the work of Shapiro and



110

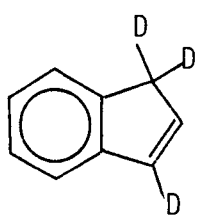
and Heath[83] on the conversion of tosylhydrazones, by reaction with alkyllithiums, into olefins. The tosylhydrazone 111 of 1-indanone was prepared and dissolved in TMEDA. Treatment of this solution with 4 equivalents of n-butyllithium in hexane followed by quenching of the reaction by addition of D_2O should have provided 3-deuterioindene (Equation 65).



(65)

111 110

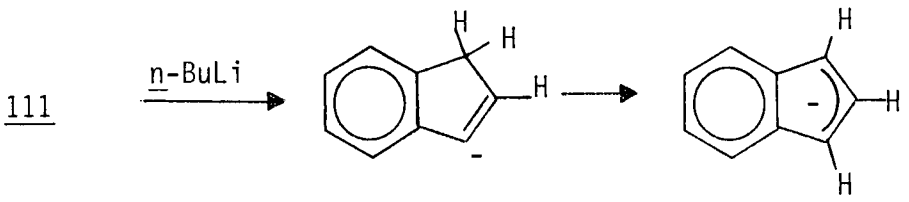
After work-up, the NMR spectrum of the isolated product indicated not the formation of 110, but rather the partially trideuterated 1,1,3-trideuterioindene 112. Comparison of the NMR spectra obtained



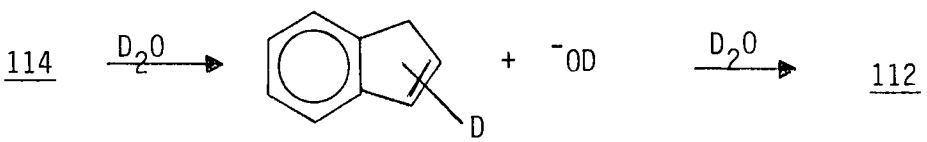
112

from previous synthesis of 112, as well as glpc comparison confirmed this result. Treatment of tosylhydrazone 111 with two equivalents of n-butyllithium resulted in formation of partially deuteriated

1,1,3-trideuterioindene, but deuterium incorporation was not as complete as in the reaction with 4 equivalents.[107] This formation of 1,1,3-trideuterioindene might proceed by the conversion of the intermediate vinyl anion 113 into allylic anion 114 before quenching with D_2O (Equation 66).



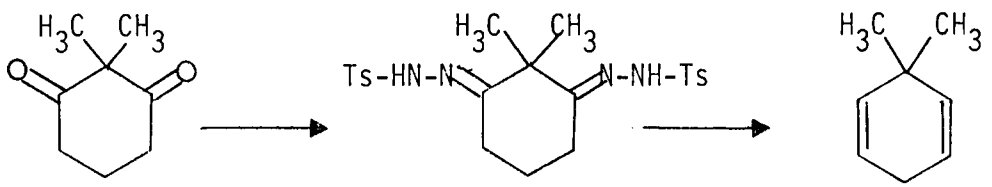
113 114 (66)



These observations, along with the difficulty in preparing compound 91 (p 45), resulted in the abandonment of this particular scheme for the examination of possible anionic [1,4] sigmatropic shifts of an alkyl group. In hopes of finding evidence for the anionic [1,4] sigmatropic shift of an alkyl group, a series of cyclohexadienes was prepared and an attempt was made to generate an anion capable of undergoing a [1,4] shift.

This area of research was begun with the attempted synthesis of compound 76a by the extension of the Shapiro reaction[83] for the preparation of alkenes from ketones. The diketone 115 was

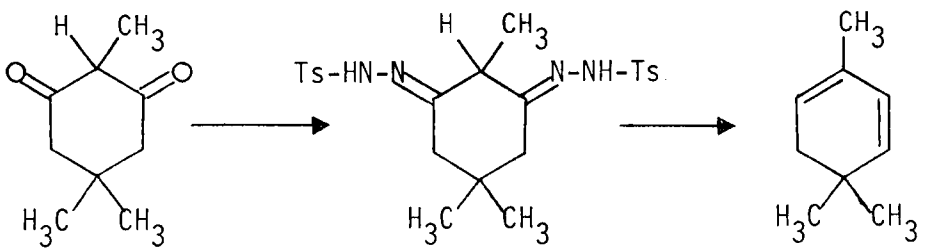
prepared by the method of Magid and Wilson.[76] The bistosylhydrazone 116 was prepared and treated with four equivalents of n-butyllithium yielding an olefinic product which displayed an NMR spectrum similar to, but not identical to the NMR spectrum of the compound prepared by Wilson[82] (Equation 67).



115 116 76a (67)

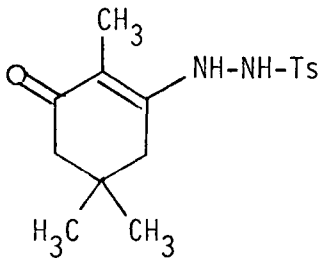
Although this method possessed synthetic possibilities, the preparation of 76 (p 36) was dropped in favor of the more suitably labeled compounds 82, 83 and 84 (p 40).

The preparation of compound 82 by formation of the bistosylhydrazone 117 of compound 118 followed by treatment with four equivalents of n-butyllithium was investigated (Equation 68).



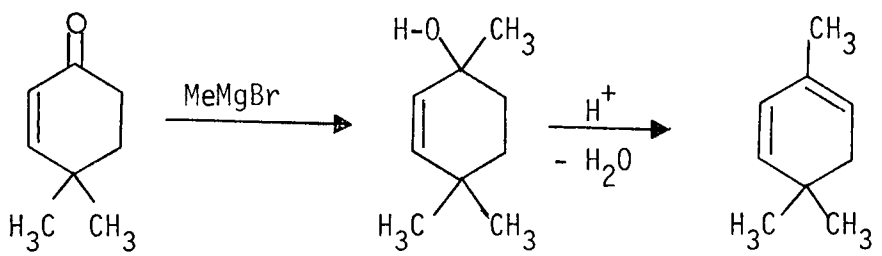
118 117 82 (68)

Attempts to prepare compound 117 failed, resulting in the formation of an uncharacterizable red-gummy substance, possibly the vinylogus amide 119. Similar results have been reported in the attempted



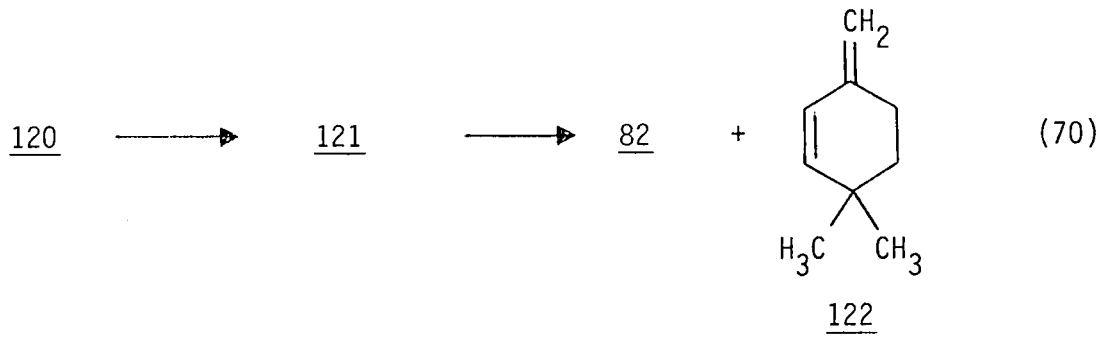
119

preparation of the bistosylhydrazone of cyclopentane-1,3-dione.[109] This method was abandoned in favor of the reaction of ketone[86,87] 120 with methylmagnesium bromide followed by dehydration to form diene 82 (Equation 69).



120 121 82 (69)

The reaction of ketone 120 with methylmagnesium bromide yielded alcohol 121. Dehydration of this alcohol produced a 60:40 mixture of diene 82 and methylenecyclohexene 122 (Equation 70).



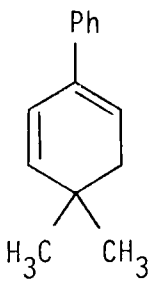
(70)

A preliminary investigation was made using this mixture. Treatment of this 60:40 mixture in TMEDA with n-butyllithium at room temperature for 2 hr followed by quenching with water provided no evidence of any type of rearrangement or change in the composition of the mixture of 82 and 122. Apparently higher temperatures and longer reaction times would be needed for the observation of anionic [1,4] shifts.

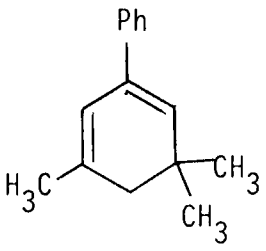
This apparent need for higher temperatures necessitated the ability to separate the three isomers of xylene by glpc. Attempts to separate these isomers on all available columns failed, although the ortho isomer could be separated from the meta and para. In another act of desperation, a sulfuric acid packed column was used in an unsuccessful effort to separate the three isomers.[110] This inability to separate the xylenes ended the investigation of this substrate for an anionic [1,4] shift.

Two possible reasons can be given for the failure to observe the anionic [1,4] shift in the system examined by Wilson and Magid;[76] these are : (1) the equilibrium between the monocyclic anion and

bicyclic anion might not exist (p 37) and (2) if the equilibrium between the monocyclic and the bicyclic anions does exist, then there might not be sufficient driving force for the [1,4] shift to occur in the bicyclic anion. The dienes 84 and 83 (p 40) were designed and synthesized in an effort to provide systems in which: (1) a driving force for the equilibrium between the monocyclic and bicyclic anions, and (2) a driving force for the rearrangement were present, respectively.

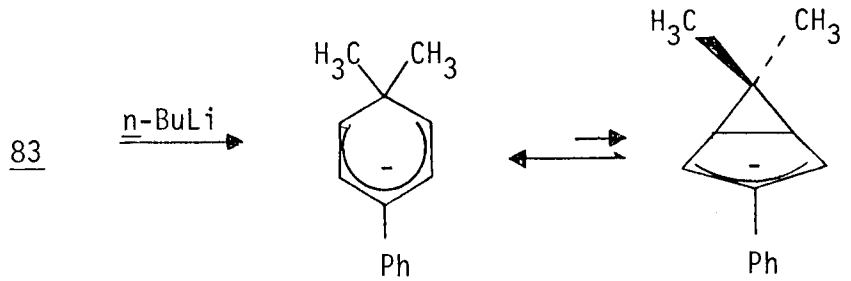


83



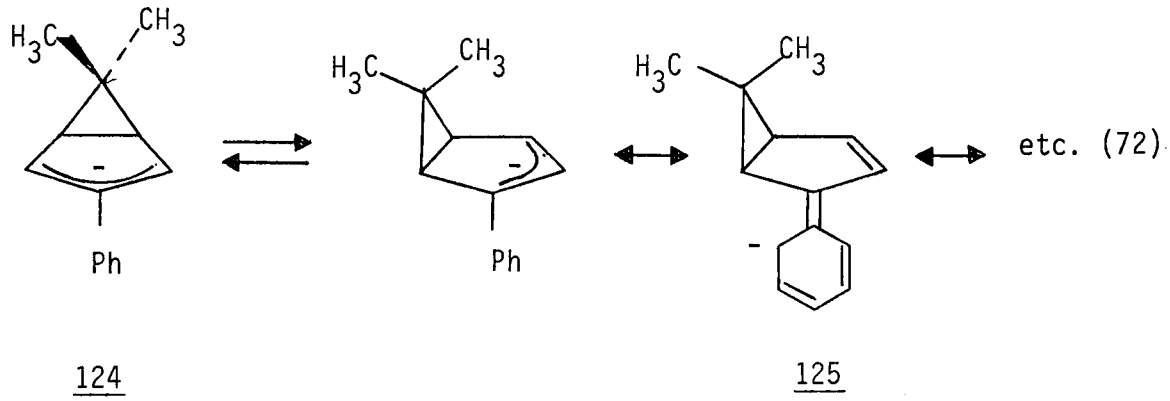
84

Treatment of diene 83 with n-butyllithium should provide the anion 123 which should be in equilibrium with anion 124 (Equation 71).



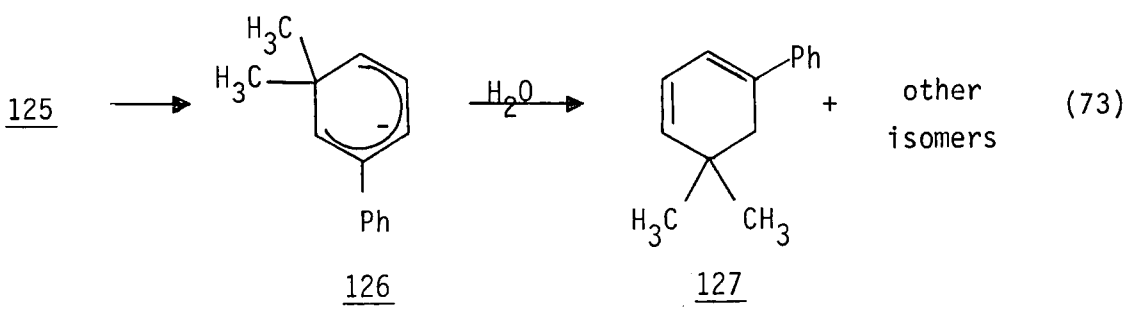
123 124 (71)

It should be noted that anion 124 is not only destabilized by the ring strain of the cyclopropane, but also it has lost the stabilizing effect of resonance with the phenyl ring. It was hoped that this loss of resonance stability would provide the necessary driving force for the [1,4] shift, for if the [1,4] shift occurs anion 125 would be generated, and although it is still bicyclic, the resonance is reestablished (Equation 72).



124 125

Ring-opening of anion 125 should produce anion 126 and, after quenching, diene 127 (Equation 73).

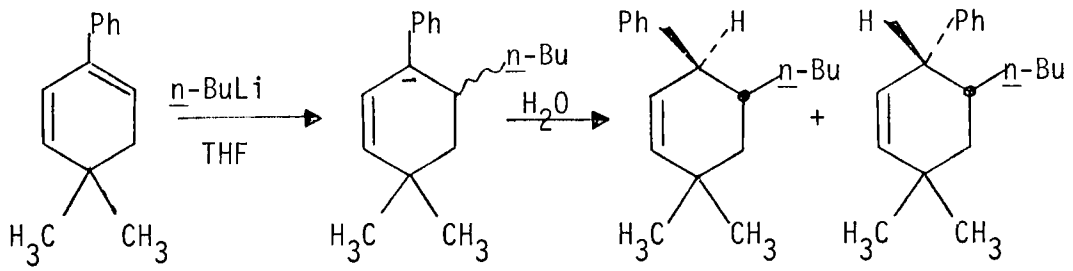


126 127

This occurrence of events would result in the changing of the label (the phenyl group) in the starting material. All attempts to generate

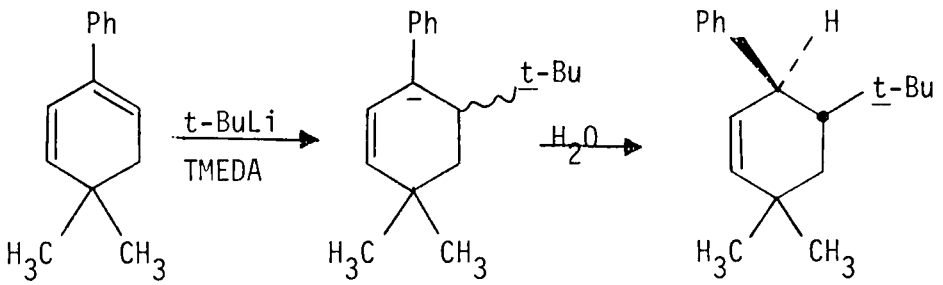
anion 123 failed in the absence of THF or TMEDA, as was evidenced by no apparent change in the NMR spectrum of the product (unreacted starting material) recovered after quenching with water. This failure to abstract a proton from compound 83 by n-butyllithium was at first not expected. However, Burley and Young[111] reported similar deviant behavior in the reaction of n-butyllithium and 1,3-diphenylpropene; the only reaction observed in hexane was the addition of n-butyllithium to the substrate double bond and that process took three months to occur.

An attempt to generate anion 124 and observe its NMR spectrum was made by the use of the procedure of Bates and coworkers.[80] An NMR spectrum was obtained of the anion although a complete interpretation could not be made. This anion was quenched and an NMR spectrum obtained of the isolated material. The NMR suggested that a reaction had taken place and it indicated that n-butyllithium had added to the substrate. Glpc analysis of the product also indicated the conversion (>90%) into a two-component mixture of higher boiling compounds. It was assumed that these compounds were the cis and trans isomers of the addition product (Equation 74).



83 (74)

The treatment of diene 83 with t-butyllithium in TMEDA produced an even more surprising result. NMR and glpc analysis indicated an almost quantitative addition of t-butyllithium to the substrate forming only one isomer, presumably the trans isomer (Equation 75).

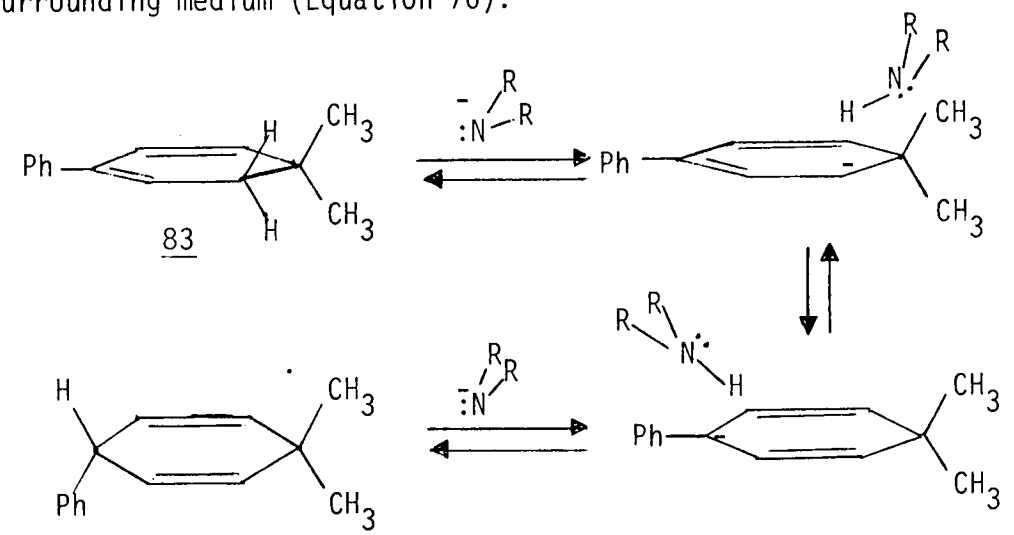


83 (75)

Only when compound 83 was treated with either lithium diisopropylamide or lithium triphenylmethide did proton abstraction appear to be occurring. This was suggested by the appearance of the NMR spectrum of the product on quenching by water. The spectrum indicated conversion of the 1,3-cyclohexadiene into a mixture of the 1,3- and 1,4-cyclohexadienes by lithium diisopropylamide. Analogous results were obtained by the use of lithium triphenylmethide except that conversion had not proceeded as far as in the lithium diisopropylamide reaction.

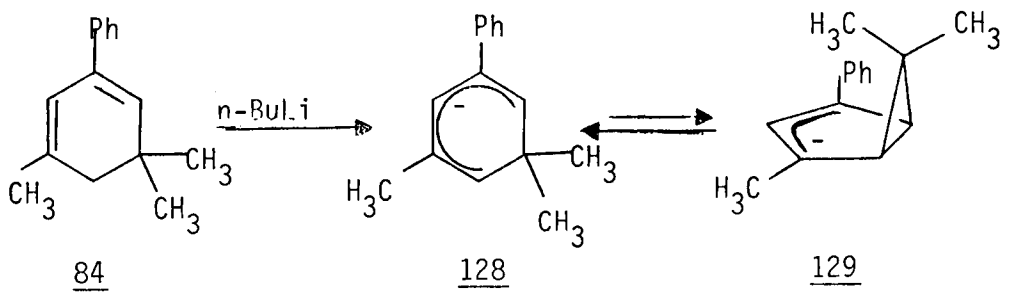
When the reaction of 83 and lithium diisopropylamide was quenched with D_2O instead of H_2O, the NMR spectrum of the recovered product indicated no incorporation of deuterium. This result was unexpected but may be an example of a "conducted proton tour"[112,113] across the face of anion 123. This "conducted tour" involves the

abstraction and delivery of a proton from 83 by the base from one bonding site to the next without the proton's ever wandering into the surrounding medium (Equation 76).



(76)

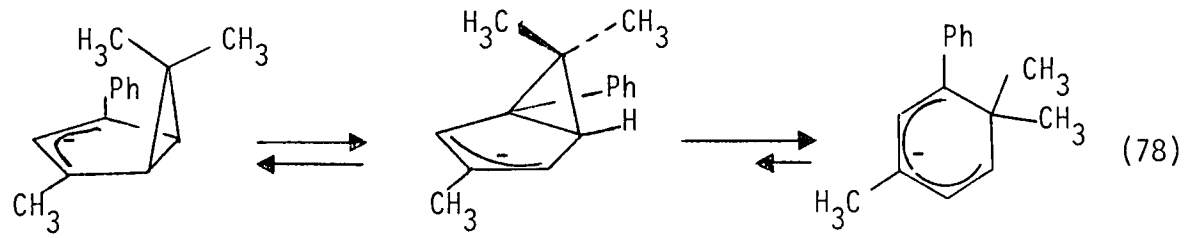
The reaction of diene 84 with n-butyllithium should provide the anion 128 which is not stabilized by resonance with the phenyl



(77)

group. However ring-closure to 129 would provide resonance stabilization of the anion, and it is this stabilization that hopefully would provide sufficient driving force for the ring-closure to occur (Equation 77). The occurrence of a [1,4] shift from anion 129

would produce an anion that has had the stabilizing effect of the phenyl ring removed, but ring-opening of this anion would restore this resonance stabilizing effect (Equation 78).



(78)

129

This combination of effects hopefully would provide the anionic [1,4] sigmatropic shift of an alkyl group.

The same reactions as performed on diene 83 were applied to compound 84 and analogous results were obtained. No reaction was detected in hexane solution, and n-butyllithium in the presence of THF added to 84 in a similar manner to that reported for compound 83. Further study of this substrate was discontinued because of its aberrant behavior.

The search for the anionic [1,4] sigmatropic shift of an alkyl group in these systems came to an inconclusive and, for this author, a disappointing end. The difficulty in wanting to either become or remain a physical organic chemist is that the system that hopefully will provide beautiful results must first be synthesized and the species of interest successfully generated. The problem outlined in this dissertation is one of interest and importance in the continuing effort to further our understanding of the concept of orbital symmetry, and the search should be continued.

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LIST OF REFERENCES

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VITA

Julian Everette Parker, III was born May 16, 1949 at 11:35 P.M. in Pinehurst, North Carolina. He graduated from Fayetteville Senior High School of Fayetteville, North Carolina on June 2, 1967. In August of 1967, he entered Pfeiffer College in Misenheimer, North Carolina and started the long journey toward becoming an organic chemist. On May 16, 1971, he received from Pfeiffer College his B.A. degree in Chemistry, "Thank the Laude." He also received, on this day in May: (1) his acceptance to the U.S. Air Force Officer Flight Program; (2) his acceptance to the U.S. Army R.O.T.C. Program; and (3) a letter of induction from his local Selective Service Board. Shortly thereafter he chose to become an officer and a gentleman and he reported to Fort Knox, Kentucky on June 24, 1971.

In the fall of 1971 he entered the Graduate School of the University of Tennessee, where he held a graduate teaching assistantship in the Department of Chemistry from 1971 to 1976. On June 2, 1973 he lost the sight in his right eye and received a medical discharge from the U.S. Army. He received the Outstanding Graduate Teaching Award 1974-1975 and in December of 1976 received the coveted Ph.D. degree in Chemistry.

On August 26, 1972, he married Brenda Kay Walker of Casar, North Carolina and on August 26, 1976 he became Visiting Assistant Professor of Organic Chemistry, The College of Charleston, Charleston, South Carolina.

The author is a member of the American Chemical Society.