

- I. INVESTIGATIONS ON THE MECHANISM OF THERMAL
DECOMPOSITION OF 1-PYRAZOLINES

- II. THE STEREOCHEMISTRY OF SOLVOLYTIC DISPLACEMENT
AND INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION
BY A DOUBLE BOND AT A VINYL CENTER

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To Millie

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ABSTRACT

I. Two mechanisms have been proposed to account for the net single inversion of stereochemistry observed in the pyrolysis of 3,5-dialkyl-1-pyrazolines. The first, involving initial cleavage of both C-N bonds and formation of a π -cyclopropane intermediate, predicts completely racemic singly inverted product on pyrolysis of an optically active pyrazoline. The sequential C-N bond cleavage proposed in the second mechanism predicts that, to the extent that the rates of initial cleavage of the two C-N bonds are different, some optical activity should be observed in the singly inverted product. In order to resolve this problem, the pyrolysis of (+)-(3R,5R)-trans-3-ethyl-5-methyl-1-pyrazoline was undertaken. Flow pyrolysis of this pyrazoline at 292° and atmospheric pressure led to 71% cis-1-ethyl-2-methylcyclopropane, 27% trans-1-ethyl-2-methylcyclopropane and minor amounts of olefin product. The cis cyclopropane was formed with 0.8% retention of optical purity while the trans product showed 23% retention of optical purity. Correlation of these results with the pyrolyses of this pyrazoline specifically deuterated at C3 and C5 will allow a distinction between the two mechanistic possibilities. This work is currently in progress.

II. In order to determine the stereochemistry of solvolytic displacement and intramolecular nucleophilic substitution by a remote double bond at a vinyl center, the synthesis and solvolysis in trifluoroethanol of (Z)- and (E)-3-methyl-2,6-heptadien-2-yl trifluoromethanesulfonate were undertaken. In addition to 3-methyl-1,2,6-

heptatriene and the products of solvolytic displacement, four cyclized trifluoroethyl ether products were formed. These four products were also generated in the trifluoroethanolysis of 1,2-dimethyl-1-cyclohexen-4-yl tosylate. Net inversion of stereochemistry was observed in both the solvolytic displacement and cyclization processes in the vinyl triflates. Solvolysis of (Z)- and (E)-3-methyl-2-hepten-2-yl trifluoromethanesulfonate also resulted in net single inversion in the vinyl trifluoroethyl ether products. These results are explained in terms of competitive attack on the initially formed ion pairs and on free vinyl cation intermediates.

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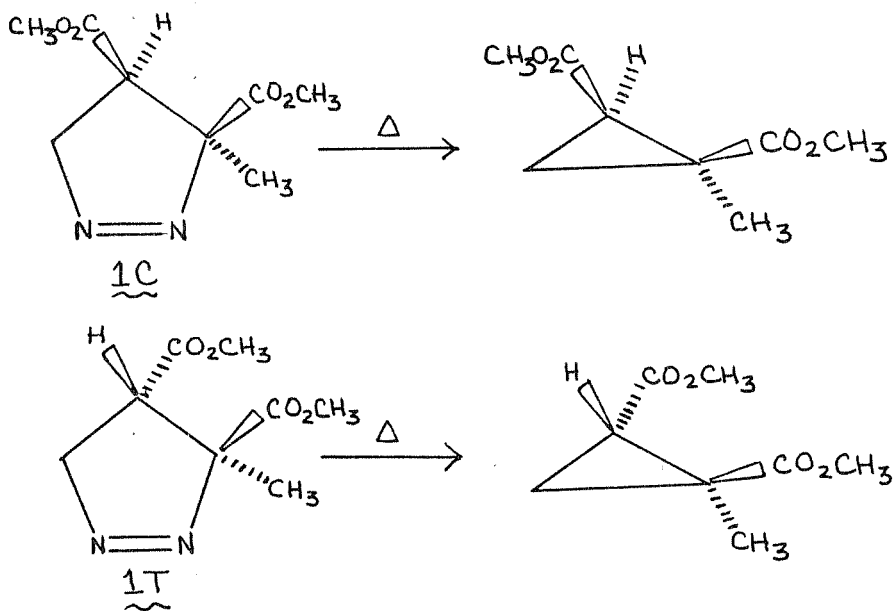
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INVESTIGATIONS ON THE MECHANISM OF THERMAL
DECOMPOSITION OF 1-PYRAZOLINES

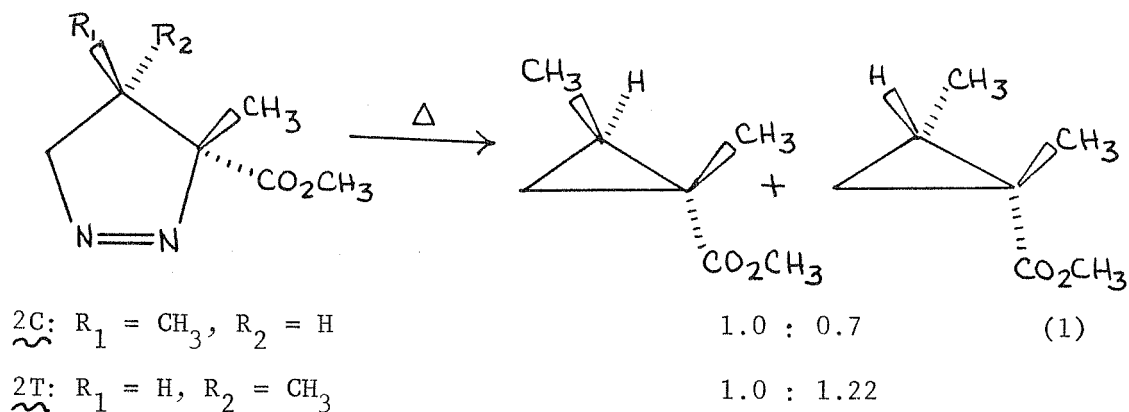
I. INTRODUCTION

Although the thermal decomposition of 1-pyrazolines has long been known to give cyclopropane products,^{1,2} it is only recently that the stereochemical consequences of this reaction have been studied in any detail. The observation in 1932 by von Auwers and König that the relative stereochemistry at C-3 and C-4 in compounds 1C and 1T is preserved in their respective cyclopropane products³ led to the

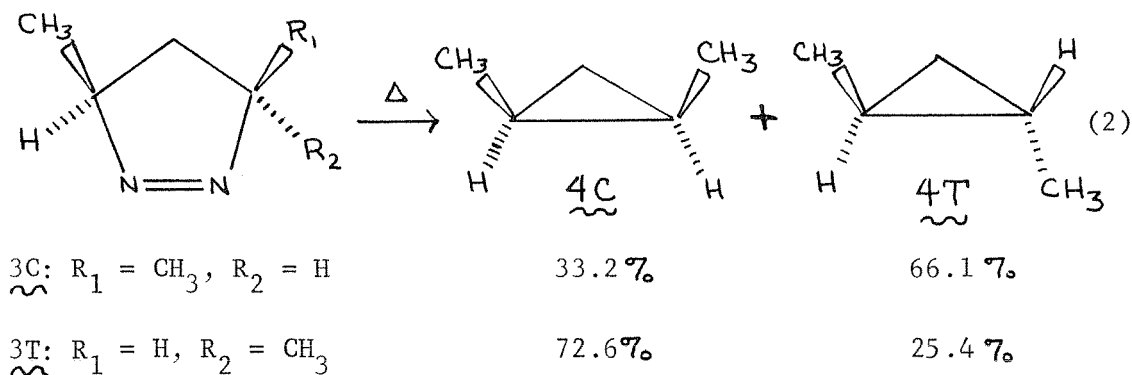


general acceptance of pyrazoline thermolysis as a stereospecific reaction occurring with retention of geometry.⁴ It was not until 1962 that van Auken and Rinehart showed that this high degree of stereospecificity is not necessarily a characteristic of all pyrazoline decompositions.⁵ In particular they showed that although 2C and 2T both exhibit a slight preference for formation of the cyclopropane

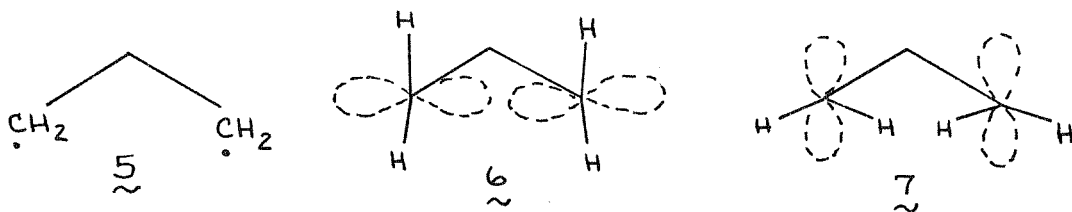
of retained geometry, the reaction is far from stereospecific in this case (eq. 1).



More extensive investigations by the research groups of Overberger,⁶ McGreer,⁷ and Crawford,⁸ have shown that the stereochemical results of pyrazoline pyrolysis are highly dependent upon the degree and types of substitution involved. However, the most unusual results were obtained by Crawford in his studies on the relative stereochemical results at C-3 and C-5 in the simple alkyl substituted pyrazolines 3C and 3T;^{8b,c} here it was found that the cis pyrazoline 3C gave mainly trans cyclopropane 4T while the trans pyrazoline 3T gave predominantly cis cyclopropane 4C (eq. 2).



This curious net single inversion of stereochemistry found a ready explanation in a theoretical study of the trimethylene diradical (5) carried out by Hoffmann.⁹ In these EHT calculations Hoffmann

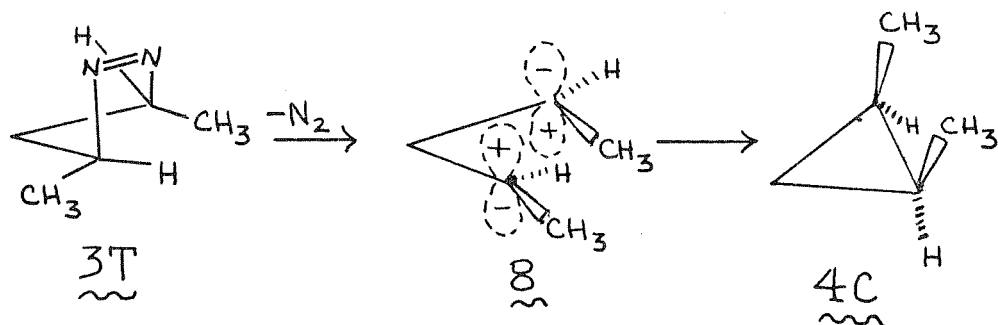


found that although 6 (the "90,90 structure") is the most stable configuration of the trimethylene diradical at small C-C-C angles, there is predicted to be a potential minimum for configuration 7 (the "0,0 structure") at a C-C-C angle of 125°. Furthermore, Hoffmann suggested on the basis of symmetry considerations that the HOMO of 7 (often referred to as the " π -cyclopropane" structure) should contain the antisymmetric (7A) rather than symmetric (7S) contribution from the



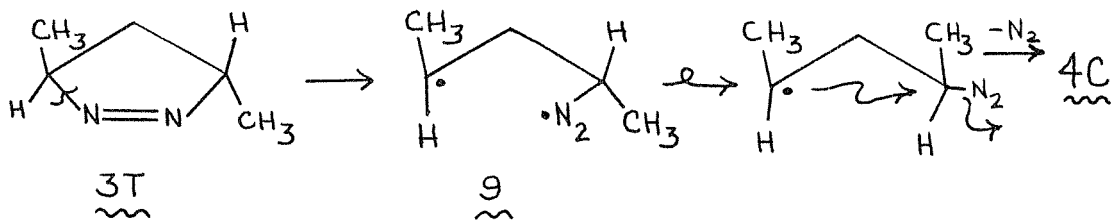
terminal 2pz orbitals. The immediate consequence of this suggestion is that in formation of a cyclopropane product, a π -cyclopropane intermediate should prefer a conrotatory mode of closure.

Thus, using 3T as an example, it was proposed that loss of nitrogen from the "envelope" configuration of the pyrazoline leads directly to the π -cyclopropane 8, which closes in conrotatory fashion to give 4C. Note that because 8 has the antisymmetric ground state, concerted cleavage to give nitrogen and 8 directly is an allowed



process in the Woodward-Hoffmann sense.¹⁰ The minor product 4T must then arise either from a certain amount of the disfavored disrotatory process or from some alternate mechanism.

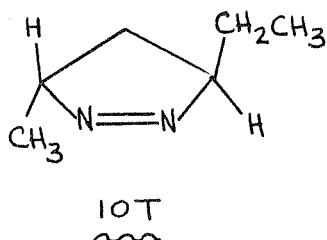
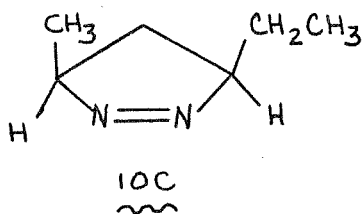
Recently, however, more sophisticated calculations have cast some doubt on the validity of Hoffman's results.¹¹⁻¹³ Perhaps more significantly, a series of experimental results have seriously questioned the π -cyclopropane explanation of the pyrazoline thermolysis stereochemistry.^{8i,14} Instead an alternate mechanism involving sequential rather than simultaneous cleavage of the carbon-nitrogen bonds has been proposed.¹⁴ Again using 3T as an example, this mechanism postulates initial cleavage of a single carbon-nitrogen bond to give the intermediate diradical 9; rotation and backside attack with



expulsion of nitrogen would then lead to the observed major product 4C. As will be discussed below in considerably more detail, both the

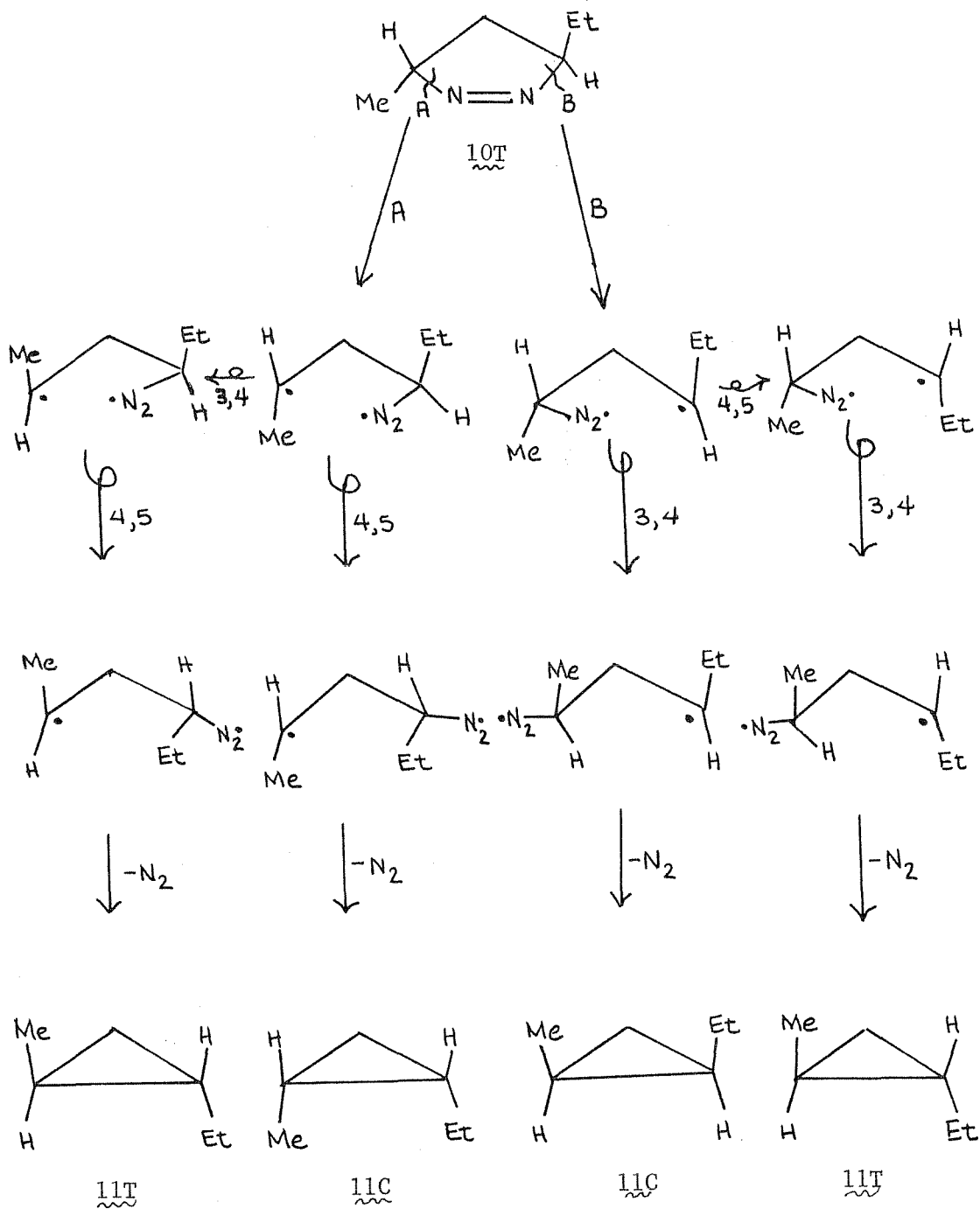
sequential cleavage mechanism and the π -cyclopropane mechanism find support in various experimental results which seem to strongly favor one or the other process.

In an effort to resolve this confusion, I undertook the synthesis and pyrolysis of optically active cis- and trans-3-ethyl-5-methyl-1-pyrazoline (10C and 10T), and here report the preliminary results of this study. Any cyclopropane product (cis or trans) arising from a π -cyclopropane intermediate must of necessity be com-



pletely racemic, since the π -cyclopropane has a plane of symmetry. The predictions of the sequential cleavage mechanism are shown in Scheme 1 for 10T. Cleavage of either bond A or bond B, rotation of the nitrogen containing fragment, and backside attack with loss of nitrogen will lead to the cis cyclopropane product 11C; however cleavage of bond A leads to one enantiomer of 11C, while cleavage of bond B leads to the opposite enantiomer. Thus, to the extent that bonds A and B cleave at different rates, the resulting 11C should retain some optical activity. Also it should be noted that rotation about both the C₃-C₄ and the C₄-C₅ bonds will lead to the minor trans product 11T; however, in this case cleavage of either bond A or bond B leads to the same doubly inverted enantiomer of 11T. Any trans

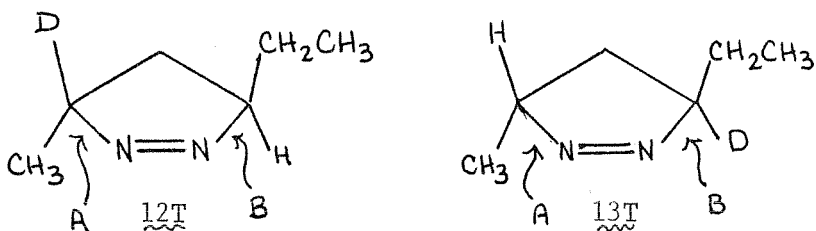
SCHEME 1



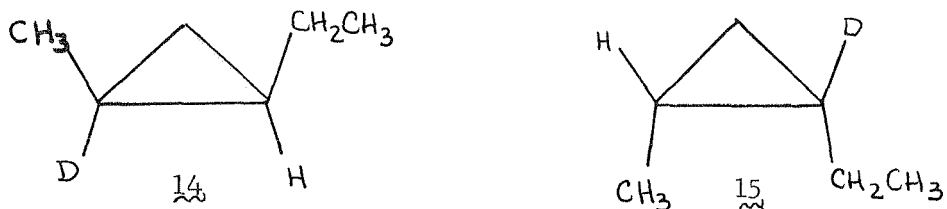
cyclopropane produced by this route should thus be optically active.

Because of their chemical similarity, we would not expect the methyl and ethyl substituted bonds to break at very different rates. The cis cyclopropane produced by the sequential cleavage mechanism should thus be formed with low optical retention, the same result as that predicted by the π -cyclopropane mechanism. Therefore, an experimentally observed lack of optical activity in 11C would not allow a differentiation between the two mechanisms. Similarly, although a lack of optical activity in 11T, the minor product of the reaction, could be taken as evidence for the π -cyclopropane mechanism, it could also indicate that 11T (and presumably a comparable amount of 11C) is arising from a randomly rotating trimethylene diradical; the excess of singly inverted product 11C could still be coming from a competing sequential cleavage mechanism. Thus a lack of optical activity in both products would not by itself allow a mechanistic distinction.

In consideration of the possibility that this ambiguous result might be obtained in the pyrolysis of 10T, a crucial part of this project involves the syntheses and pyrolyses of the optically active deuterated pyrazolines 12T and 13T (and their cis analogs). The secondary deuterium kinetic isotope effect could be expected to slow



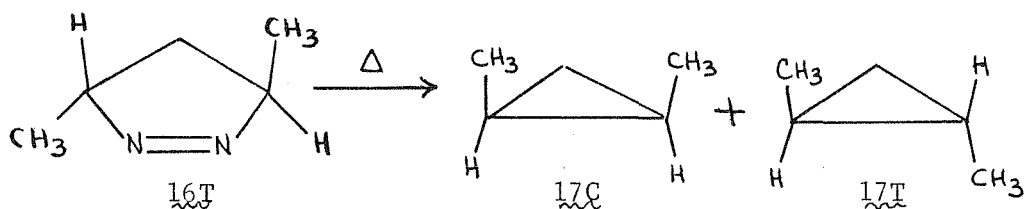
the loss of nitrogen leading directly to a π -cyclopropane,^{15,8g} but again this planar intermediate would have to give racemic products. The effect on the sequential cleavage mechanism should be quite different, however. Deuterium substitution on 12T should slow the cleavage of bond A but not affect the cleavage of bond B while in 13T the effect should be just the opposite. Thus, in the simplest case, if the undeuterated trans pyrazoline gives racemic cis cyclopropane, then the sequential cleavage mechanism predicts that compound 12T of the absolute configuration shown should give an excess of enantiomer 14 of the cis product while 13T should produce an excess of the opposite enantio-



mer 15. Examinations of the isotope effect predicted by the sequential cleavage mechanism ($k_H/k_D \approx 1.2$, vide infra) and of the known maximum rotations of the cis and trans-1-ethyl-2-methylcyclopropanes¹⁶ predict that this shifting of the product optical activity by deuterium substitution should be large enough to be easily detected experimentally. Since the absolute configurations of these cyclopropanes are also known,¹⁶ knowledge of the absolute configuration of the starting pyrazoline would also allow prediction of which enantiomer of product should be enhanced by a given deuterium substitution. This would serve as an additional mechanistic check.

In summary then, the π -cyclopropane mechanism clearly predicts only racemic products from both undeuterated and deuterated optically active pyrazolines; the sequential cleavage mechanism predicts that although the singly inverted cyclopropane product from the undeuterated pyrazoline may or may not be optically active, one can selectively enhance the production of one or the other product enantiomer by appropriate deuteration of the pyrazoline.

A tangentially related experiment has already been carried out independently by Mishra and Crawford,^{8h} who pyrolyzed optically active trans-1,2-dimethyl-1-pyrazoline (16T). Here it was found that

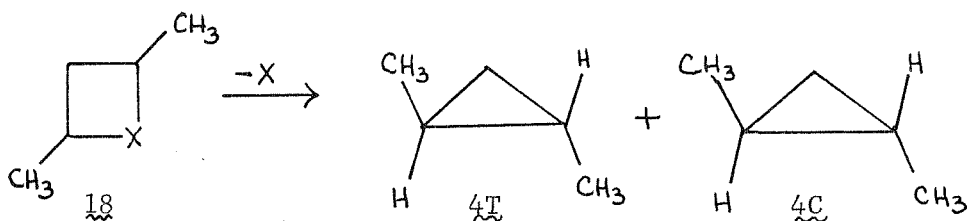


the minor product, trans-1,2-dimethylcyclopropane (17T) was produced with 23% retention of optical purity; the doubly inverted enantiomer being formed in excess. As mentioned above, this result could be arising from a combination of single bond cleavage and freely rotating trimethylene diradical mechanisms, although Crawford preferred to incorporate a "recoil mechanism"¹⁷ (vide infra) into his π -cyclopropane scheme to explain the doubly inverted trans product. No information could be obtained from the major cis product since it is a meso compound. Thus, this experiment does not allow any distinction as to which mechanism is responsible for the predominance of single inversion

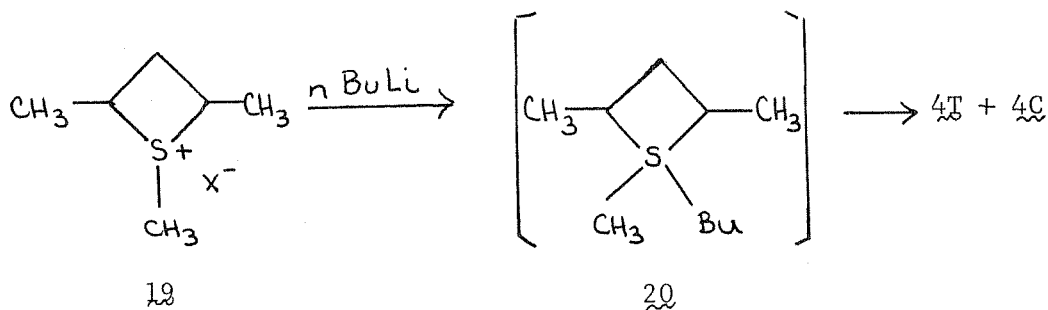
in the cyclopropane products. (Note that neither the freely rotating diradical nor the recoil mechanism alone can explain an excess of singly inverted product.)

II. BACKGROUND

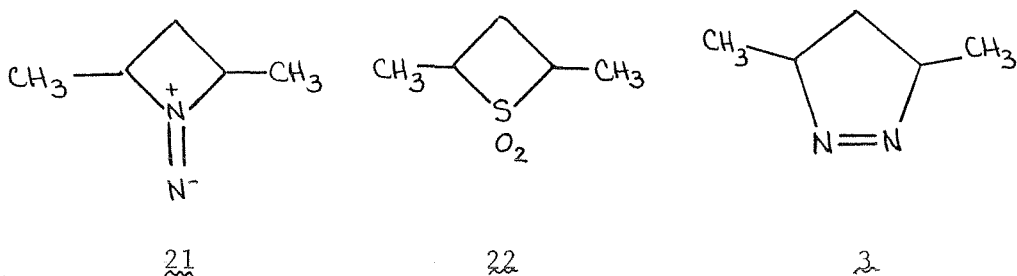
Pyrazolines are by no means the only compounds which form cyclopropanes with net single inversion; several other compounds of the general structure 18 have also been found to exhibit this phenomenon. The reaction of thietanonium salt 19 with n-butyllithium,



presumably proceeding through the neutral intermediate 20 with subsequent loss of dialkyl sulfide, shows the greatest preference for single inversion of any of these systems.¹⁸ Freeman and coworkers have generated diazene 21 by several routes and observed single



inversion,¹⁹ as have Trost et al. in the pyrolysis of sulfone 22.¹⁸



These results are summarized in Table 1; the results in the pyrazoline system (3) are also included.^{8c} Note that selectivity shows a general decrease with increasing temperature.

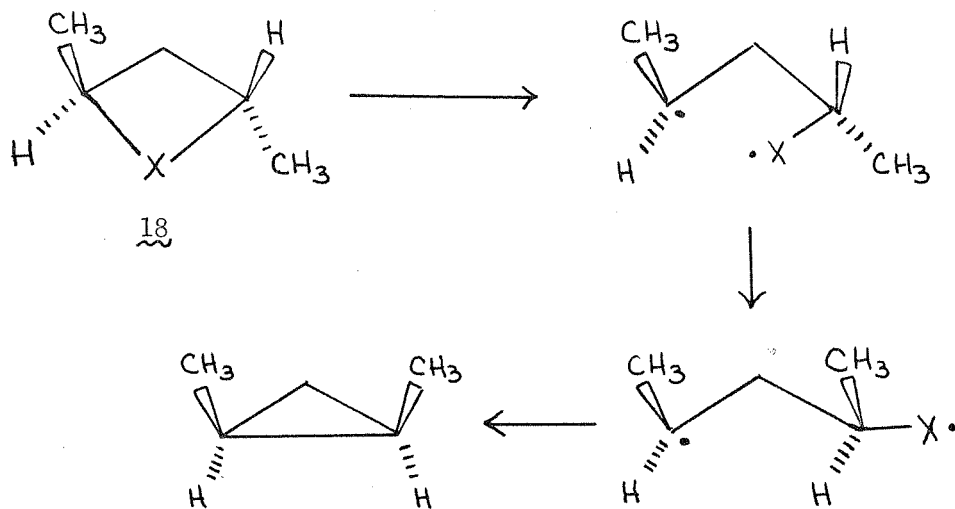
Table 1

Compound	Temperature (°C)	% <u>4C</u>	% <u>4T</u>	% Other Products
cis <u>19</u>	-78°	2.1	22.9	~ 75
trans <u>19</u>	-78°	22.2	2.8	~ 75
cis <u>21</u> ^a	58°	15.6	84.4	< 0.3
trans <u>21</u> ^a	58°	68.5	31.5	< 0.3
cis <u>3</u>	220°	33.2	66.1	0.7 (olefins)
trans <u>3</u>	220°	72.6	25.4	2.0 (olefins)
cis <u>22</u>	350°	33.8	40.1	26.1
trans <u>22</u>	350°	39.2	32.9	27.9

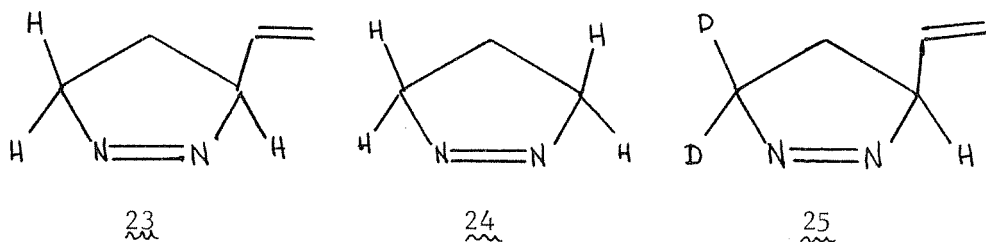
^aValues quoted are for diazene generated from the corresponding N-nitrosoazetidines by reaction with Na₂S₂O₄.

These results have all been interpreted in terms of Hoffmann's π -cyclopropane intermediate (vide supra).^{9,20} In fact, the observation of such similar results from a variety of precursors provides a rather strong argument for the existence of a common intermediate in all of these reactions. In addition, a considerable amount of effort has been expended to rule out the most reasonable alternate mechanism, sequential bond cleavage (Scheme 2):

SCHEME 2

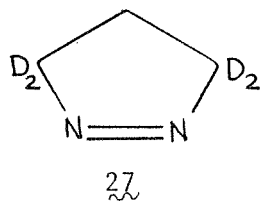
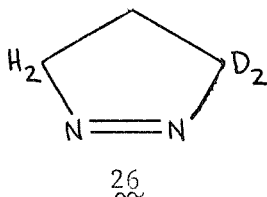
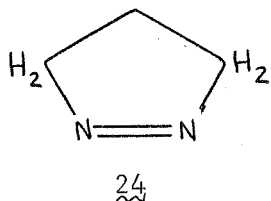


Crawford, in particular, has performed a number of experiments designed to show that both C-N bonds are breaking in the rate determining step of pyrazoline thermolysis. Perhaps the most telling of these was his observation that pyrazoline 23 decomposes with an activation energy 10.2 kcal/mole lower than the parent system (24) and that the deuterated vinylpyrazoline 25 shows a significant secondary deuterium kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} = 1.1$ per D).^{8f} Crawford



quite reasonably interprets these data to mean that both C-N bonds must be breaking in the initial step.

Another attempt to discriminate between the two mechanisms on the basis of kinetic isotope effects proved to be somewhat less revealing. Crawford showed ^{8g} that the systematic decrease in rate observed on substitution of the parent 1-pyrazoline (24) with two (26) and then four (27) deuteria is consistent with the simultaneous cleavage mechanism assuming a k_H/k_D of 1.1 per deuterium. However, as Crawford later



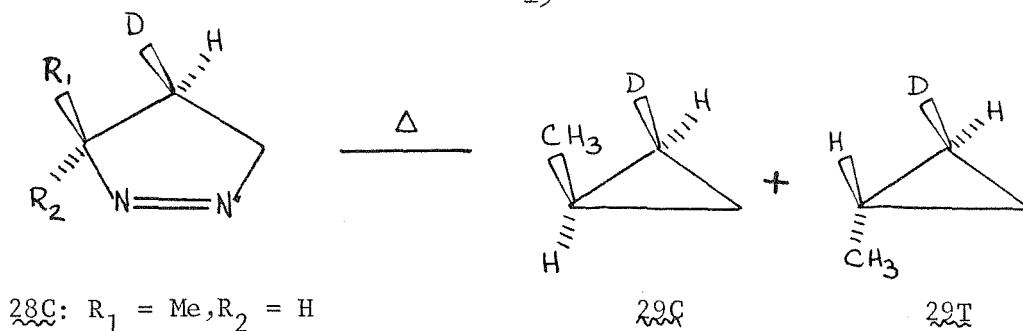
$k \times 10^4 (\text{sec}^{-1})$: 23.86

19.96

17.07

discussed,²¹ these data can also be accommodated by the sequential cleavage mechanism if a k_H/k_D of 1.2 is assumed. Moreover, a similar analysis of the systematic increase in rate caused by methyl substitution in the series 1-pyrazoline (24), 3-methyl-1-pyrazoline, 3,5-dimethyl-1-pyrazoline, shows that the results are actually more consistent with a sequential cleavage mechanism.²²

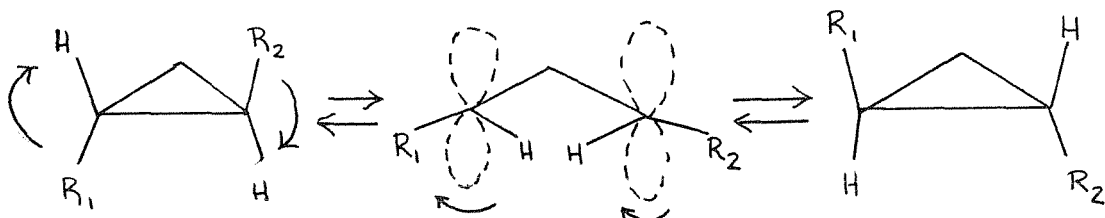
The observation that both cis and trans-4-deuterio-3-methyl-1-pyrazoline (28C and 28T) give rise to an equimolar mixture of cis and trans-1-deuterio-2-methylcyclopropane (29C and 29T)^{8d} seems to require the intermediacy of a π -cyclopropane type intermediate with a plane of symmetry; a randomly rotating diradical would also give these



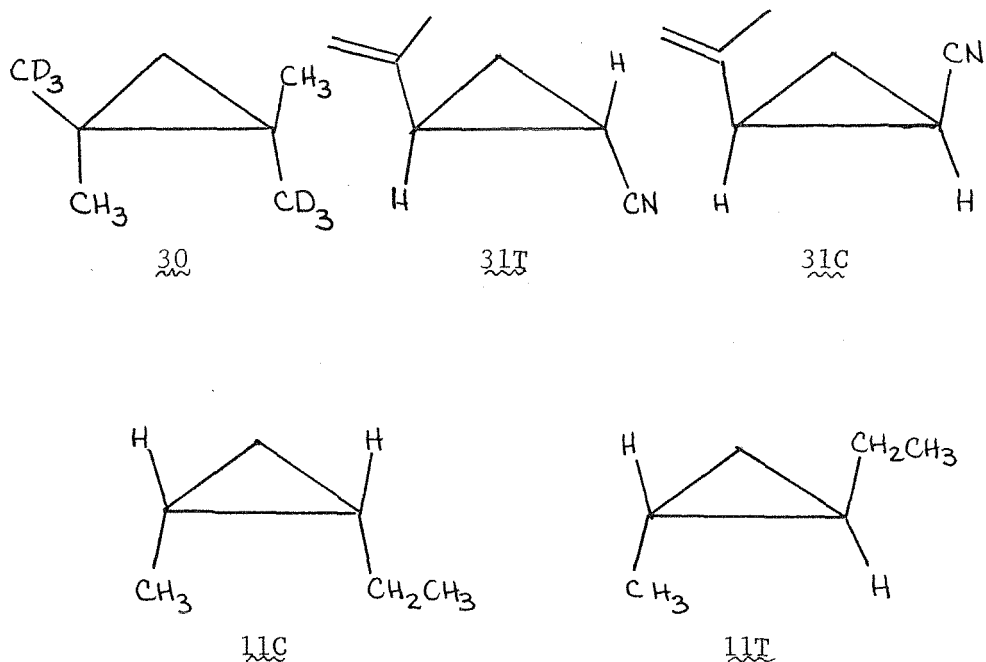
results, but such a species cannot be used to explain single inversion in the dialkyl systems. Assuming a preference for initial cleavage of the methyl substituted C-N bond, the sequential cleavage mechanism would predict a predominance of 29C from 28C and of 29T from 28T.

On the other hand, if one assumes that cyclopropane ring opening is the microscopic reverse of the closure of the trimethylene diradical, then the cyclopropane ring should open in a conrotatory sense. Since successive conrotatory ring opening and closing leads to interconversion of the enantiomers of a given geometric (cis/trans) isomer of cyclopropane without cis-trans isomerization (Scheme 3), the π -cyclopropane mechanism predicts that racemization of an optically active cyclopropane should be much faster than geometric isomerization.

SCHEME 3



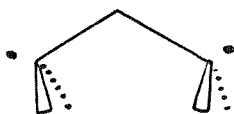
This prediction has been tested both by Berson (compound 30)²³ and by Bergman²⁴ (compounds 11C and 11T). In both cases isomerization was found to be competitive with racemization; no evidence was found to



indicate that the conrotatory process proceeding through a π -cyclopropane played any significant role in the reaction. In fact, the data do not allow more than a minor part of the reaction to be proceeding via planar intermediates or transition states. Both Berson and Bergman favor non-planar diradical intermediates in which ring closure is competitive with rotational processes which interconvert the various diradicals. In a more recent study of compounds 31T and 31C, Doering also found no evidence for a π -cyclopropane intermediate.²⁵ However, Doering did observe a specificity in the geometric isomerization which led him to propose that "continuous" diradicals serve as transition states rather than as barrier-protected intermediates in the above reactions.

This is in agreement with Salem's very detailed calculations on the cyclopropane isomerization mechanism.^{11d} These ab initio SCF-MO calculations suggest that isomerization occurs by extension of the cyclopropane bond followed by a rotation of one terminus until an orthogonal transition state is reached. Reversal of the process then completes the isomerization. In direct contradiction with Hoffmann's original report,⁹ no energy minimum was found for the π -cyclopropane structure.

Using generalized valence bond calculations,¹³ Goddard's group has obtained very similar results. Although the π -cyclopropane structure is predicted to be the most stable diradical conformation if the terminal methylene groups are held planar, relaxation of this requirement shows that the so-called "crab configuration" with both methylene groups canted inward (32) is some 5-6 kcal/mole more stable than the π -cyclopropane structure. There is predicted to be a weak preference

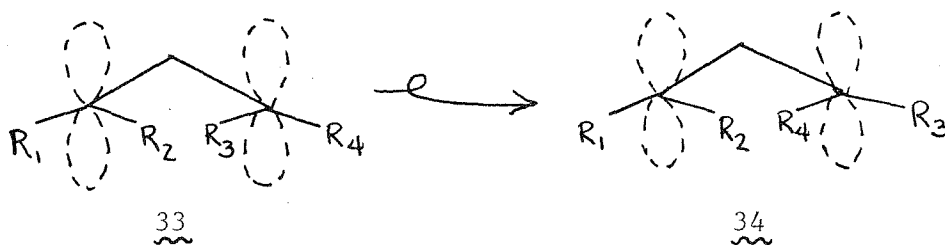


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for conrotation from the forced π -cyclopropane conformation. Neither Salem nor Goddard finds an energy minimum for any of the diradical configurations; thus no barrier is predicted for the closure of a trimethylene diradical to cyclopropane.

These more sophisticated calculations do much to undermine Hoffmann's original EHT predictions, which were all based on planar

terminal methylene groups.⁹ Hoffmann suggested that conrotation from the π -cyclopropane should proceed over a barrier of at most 1 kcal/mole, whereas interconversion of π -cyclopropane structures via rotation of a single methylene groups (33 \rightarrow 34), a process which would



lead to geometrical isomerization in the Berson²³ and Bergman²⁴ systems, should require 10 kcal/mole. The π -cyclopropane structure was also predicted to be stabilized by some 8 kcal/mole over the 90,90 structure 35 at a central C-C-C angle of 125°. Clearly, Hoffmann's



predictions are not consistent with the results discussed above in the optically active cyclopropane pyrolyses.

The question of whether the trimethylene diradical lies in an energy well with a barrier toward ring closure is still open to debate.²⁶ None of the more sophisticated calculations described above finds any evidence for such a barrier.^{11,13} On the other hand, comparison of thermochemical estimates of the heat of formation of the

trimethylene diradical with the heat of formation of cyclopropane and the known activation energy for cyclopropane ring opening (Figure 1) suggest that there should be a 10 kcal/mole barrier to ring closure.²⁶ Recently, Stephenson et al. have mimicked the thermochemical estimates using INDO theoretical calculations,²⁷ and have obtained results which again suggest a sizeable barrier to ring closure. They conclude "that either all present quantum calculations inadequately treat diradical interactions, or that 1,3 and 1,4 diradicals suffer a previously unrecognized destabilizing effect relative to a classical model." This problem may well continue unresolved until some experimental evidence on the existence of the barrier to ring closure is obtained.

The comparison of the results of the pyrazoline pyrolyses and the optically active cyclopropane pyrolyses seems to require that these processes not be the microscopic reverses of one another. Having surmounted this obstacle, several alternatives present themselves for reconciliation of the cyclopropane and pyrazoline results. The simplest answer is that the single inversion in the pyrazoline pyrolysis is arising from some process which does not involve a free trimethylene diradical; this approach will be developed below in more detail. A second explanation was proposed by Stephenson and Brauman who suggested that the excess vibrational energy of the diradicals produced in extrusion reactions might allow these species to explore reaction pathways not accessible to the diradical produced from ground state cyclopropane on simple heating.²⁸ The reactions of the activated diradical would be under entropic control and might then be more stereospecific²⁸ than the reactions of the thermally equilibrated

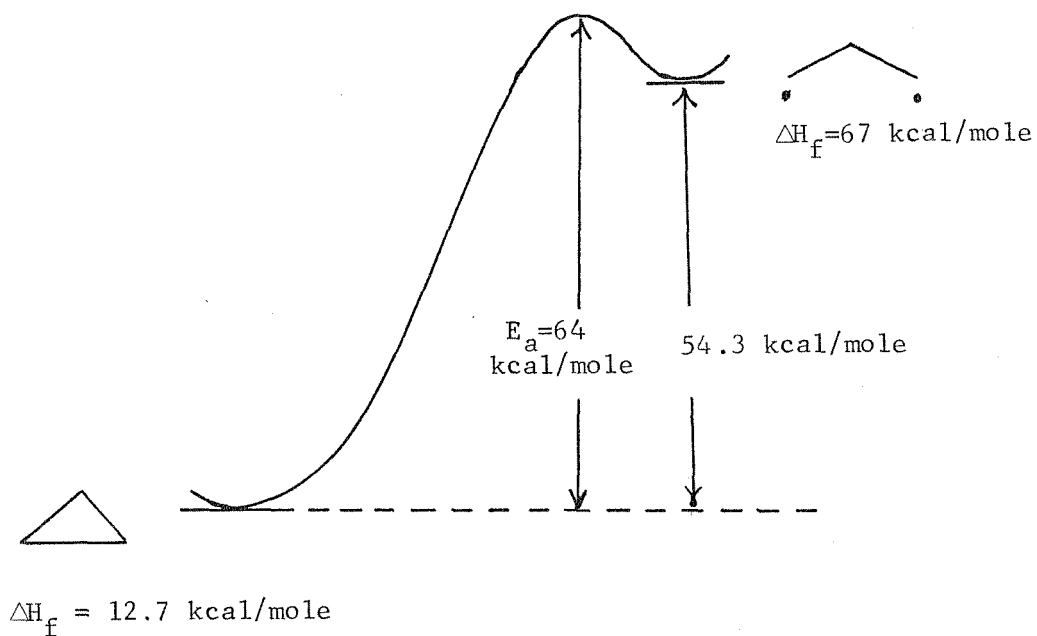


Figure 1

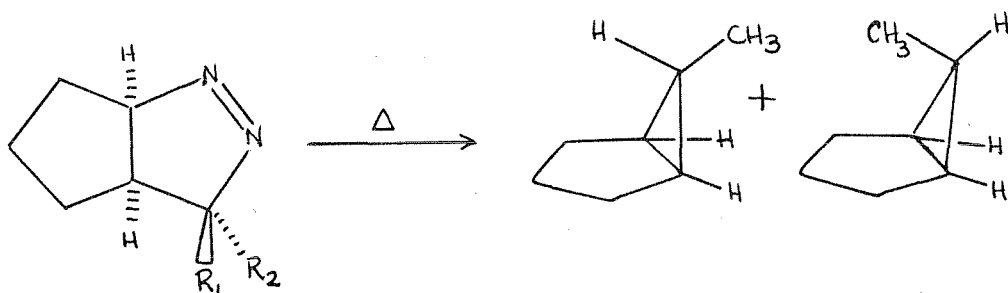
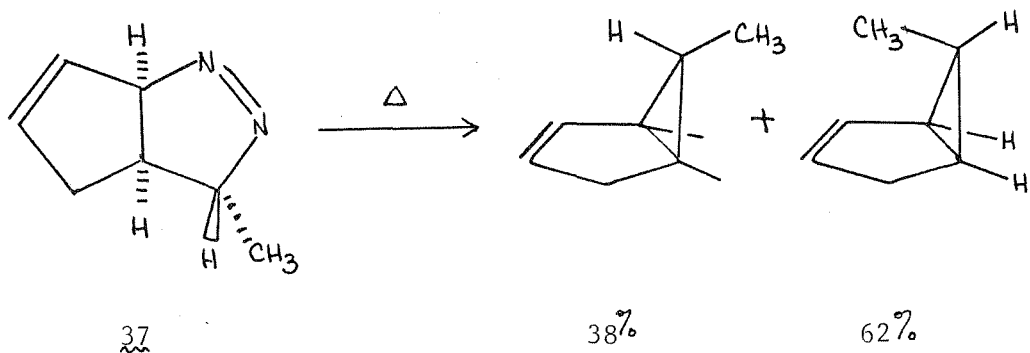
diradical. Aside from the fact that theoretical calculations do not show evidence for any stereospecific behavior of the trimethylene diradical,^{11,13} the extrusion reactions in general do not display the characteristics expected for a "hot molecule" reaction. First, the most stereospecific of these extrusion reactions is the thietanium salt decomposition (Table 3) which occurs in solution at -78°C ;¹⁸ the azetidine deaminations also proceed in solution with a high degree of single inversion.¹⁹ Under these conditions deactivation of hot molecules by collision with solvent would be expected to occur so rapidly as to completely quench any reactions characteristic only of the activated species. Finally, no evidence of chemical activation was observed in the thermolysis of either 3-vinyl-1-pyrazoline or 4-methyl-1-pyrazoline, even at pressures as low as 1.4×10^{-3} torr.²⁹

One of the most convincing experimental arguments against the π -cyclopropane mechanism comes from the pyrolyses of fused bicyclic pyrazolines. Since singly inverted cyclopropane product is at best favored by a factor of 3:1 over the cyclopropane of retained configuration in the simple 3,5-dialkyl pyrazoline pyrolyses, one would predict that by designing a molecule in which strain forces the trimethylene diradical out of the planar conformation of a π -cyclopropane, one could disrupt this rather slight (at most 1.0 kcal/mole) preference for single inversion. The observation of a significant preference for single inversion in such a strained system would tend to rule out the π -cyclopropane mechanism.

This approach has been pursued¹⁴ by the groups of both Bergman

and Crawford⁸ⁱ with similar results. The results of the pyrolyses of 37,⁸ⁱ 38N, 38X, 39N and 39X¹⁴ are shown below in Scheme 4. The bicyclo [3.2.0] system (39) is perhaps the most instructive. Examination of a

SCHEME 4



38N: $R_1 = \text{CH}_3$, $R_2 = \text{H}$

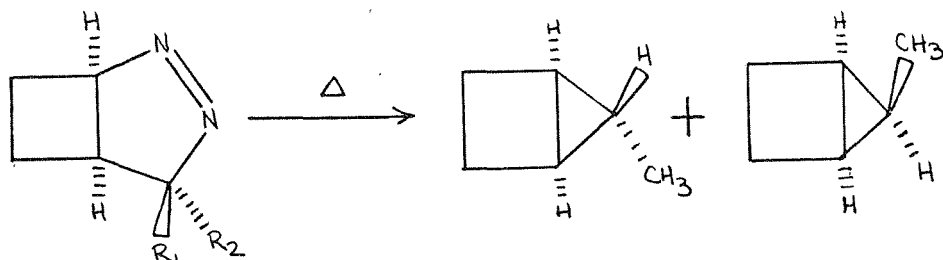
38X: $R_1 = \text{H}$, $R_2 = \text{CH}_2$

67.2%

21.2%

8.1%

72.8%



39N: $R_1 = \text{CH}_3$, $R_2 = \text{H}$

39X: $R_1 = \text{H}$, $R_2 = \text{CH}_3$

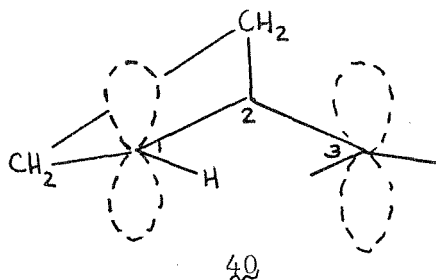
54.5%

31.7%

8.2%

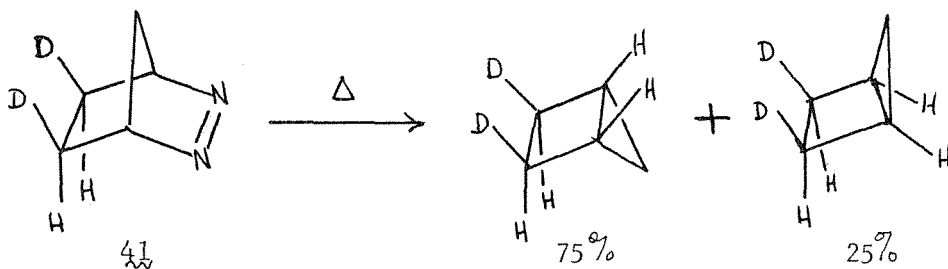
31.3%

π -cyclopropane intermediate in this case (40) shows that C_1 and C_2



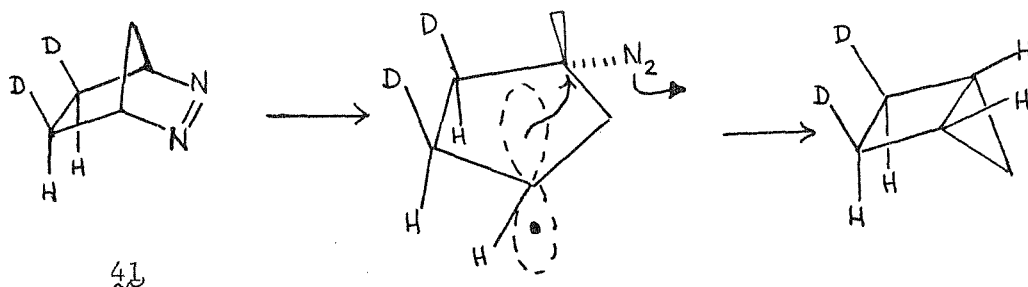
would have to be connected by a two carbon bridge. Even with flexible molecular models this planar conformation of the π -cyclopropane is almost impossible to achieve without introducing severe strain, yet the preference for single inversion is very little changed from that in the monocyclic pyrazoline pyrolyses. This absence of a strain effect on the product distribution has led to the suggestion of alternate mechanisms to account for single inversion.

The most reasonable alternate mechanism is the sequential C-N bond cleavage mechanism described in Section I of this work. This mechanism was first postulated by Roth and Martin to explain the rather unusual stereochemical outcome of the pyrolysis of 41.³⁰ The



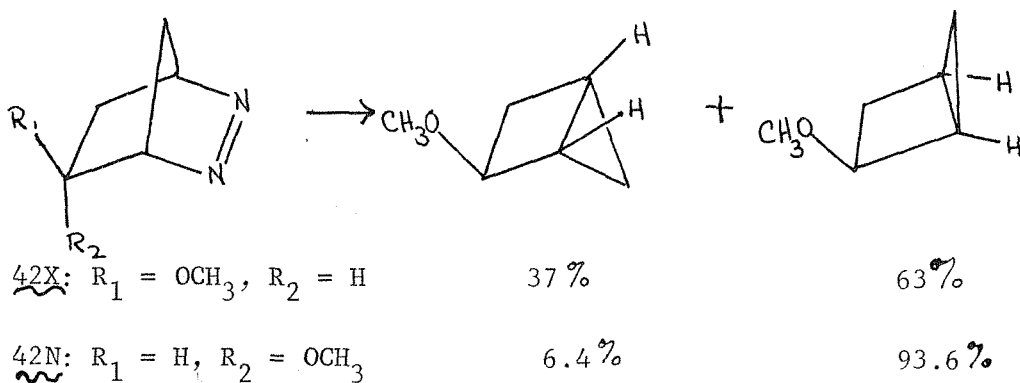
excess of doubly inverted product was assumed to arise from cleavage of one C-N bond followed by radical displacement of nitrogen (Scheme 5).

SCHEME 5



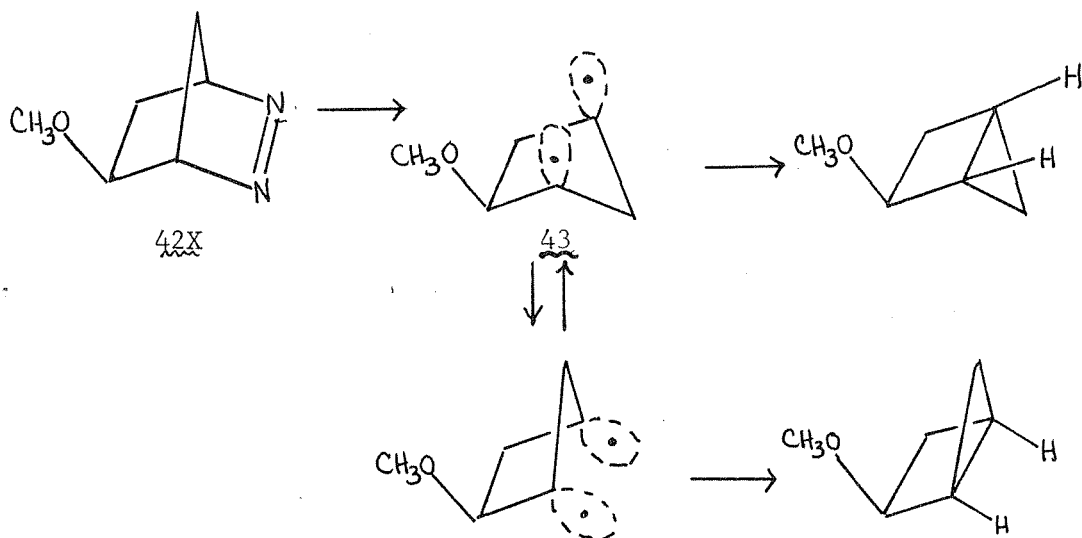
Presumably a competing nitrogen-free diradical with no stereochemical preferences leads to the minor product of retained geometry and a comparable amount (25% absolute yield) of the doubly inverted product.

Allred and Smith have observed a similar result in the pyrolyses of compounds 42X and 42N.¹⁷ The effect is less dramatic here but



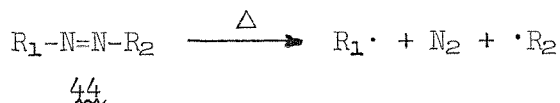
still quite definite. However, Allred prefers to explain his results in terms of a "recoil" effect. Invoking Newton's Third Law, Allred proposes that the inverted pyramidal diradical 43 is formed directly from 42X as "a consequence of recoil from energy released by C-N bond

breaking.^{17b} If ring closure is competitive with inversion of the



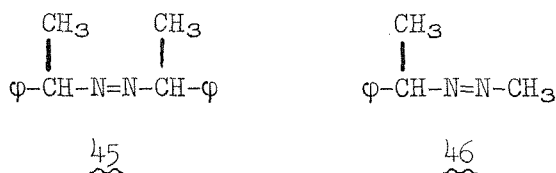
diradical, some excess of the doubly inverted product might be observed. This hypothesis has also been used to explain the excess of double inversion in the minor cyclopropane product in the thermolysis of optically active 3,5-disubstituted pyrazolines (vide supra).^{8h} However, the recoil explanation has recently been disputed on theoretical grounds by Collins et al.³¹ The recoil mechanism is also incapable of explaining the single inversion phenomenon.

The sequential C-N bond cleavage mechanism is not as unreasonable as it might once have seemed. Although it was once commonly accepted that the thermal decomposition of linear azo compounds of the general structure 44 proceeded with simultaneous cleavage of both



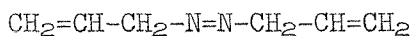
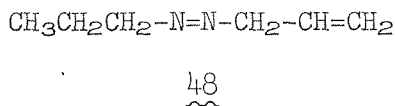
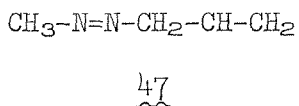
C-N bonds to give molecular nitrogen and two radical fragments, more

recent experiments show that this is not always the case. Seltzer's group has used kinetic isotope effects to show that although 45 decomposes with simultaneous scission of both C-N bonds, 46 must



initially form only two fragments, an α -phenethyl radical and an azo-methane radical.¹⁵ Other groups have used optical activity,^{32,33} CIDNP,³⁴ and solvent viscosity dependences of decomposition rates³⁵ to show that in cases where $\cdot R_2$ is not a particularly stable species, the initial reaction step involves a reversible formation of $R_1\cdot$ and $\cdot N=N-R_2$. Apparently an entire range of mechanisms exists spanning the spectrum from simultaneous through simultaneous but unequal to sequential C-N bond cleavage; which mechanism occurs in a given case apparently depends to a large extent on the stabilities of the $R_1\cdot$ and $R_2\cdot$ radicals.

In this regard, perhaps the most remarkable instance of sequential cleavage in a linear azo compound is found in Crawford's work with compounds 47, 48 and 49.^{21,36}

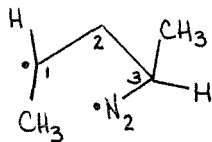


49

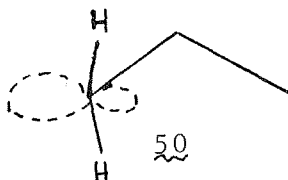
Compounds 47 and 48 both decompose with an activation energy of 35-36 kcal/mole compared with 48.5 kcal/mole for azoethane.³⁷ This difference of 12 kcal/mole reflects the increased stability of the allyl radical relative to the ethyl radical. Compound 49, however, also decomposes with an activation energy of 36.1 kcal/mole suggesting that little or no additional stabilization is achieved by the incorporation of a second allyl group. This suggests that even when simultaneous cleavage could lead to two stabilized allylic radicals, the sequential process is preferred.

In addition to sequential cleavage a second assumption which must be made if this mechanism is to be used to explain single inversion in pyrazoline pyrolyses is that radical displacement of nitrogen would occur with inversion of configuration. The only known examples where the stereochemistry has been determined for radical displacement at a saturated carbon center involve radical openings of cyclopropane rings.³⁸ In all of these cases inversion at the attacked center was observed. Although some care must be taken in generalizing results obtained in cyclopropane systems to reactions involving normal sp^3 centers, these results do make the assumption of inversion in the pyrazoline mechanism a reasonable one.

A third assumption which is critical to the sequential cleavage mechanism is that in intermediate 9 the nitrogen-containing frag-

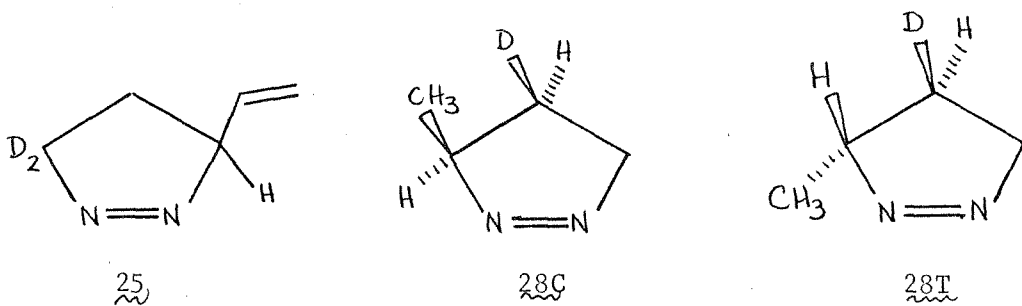


ment must rotate faster about the C2-C3 bond than the radical methylene center rotates about the C1-C2 bond. Free rotation of the methylene center would cause both cis- and trans-pyrazoline isomers to give the same product distribution. While no experimental evidence exists to support this assumption, it can be noted that the calculations of Salem¹¹ suggest that the most stable configuration of the methylene center is as shown in figure 50, with both methylene substituents



canted inward slightly. Additional calculations on the relative rotational barriers in 9 might provide useful insight into this problem.

Although sequential cleavage provides an adequate explanation for the single inversion phenomenon, it is difficult to accommodate all of the pyrazoline data within this mechanism. The kinetic isotope effect in 25^{8f} and the observation of identical product distributions

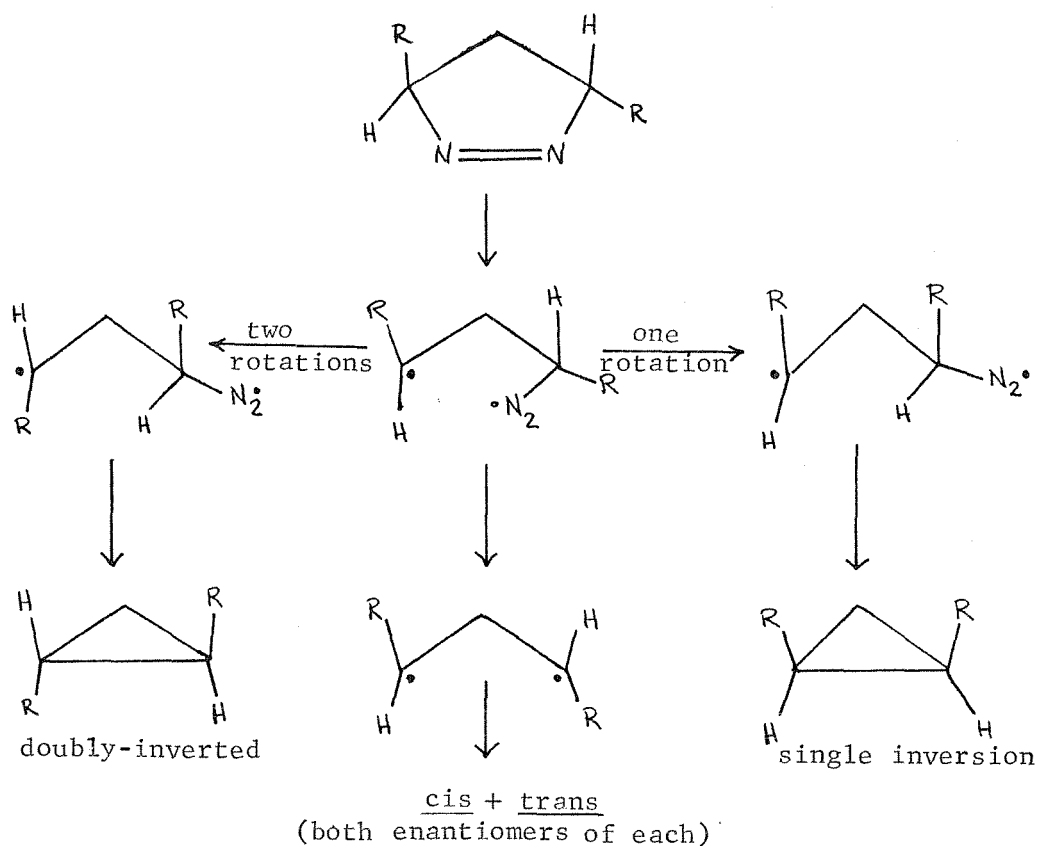


from 28C and 28T^{8d} (vide supra) both suggest that the sequential cleavage mechanism is not operating in these cases. On the other hand, the work of McGreer⁷ and Overberger⁶ has shown that many pyrazolines

do not undergo single inversion.

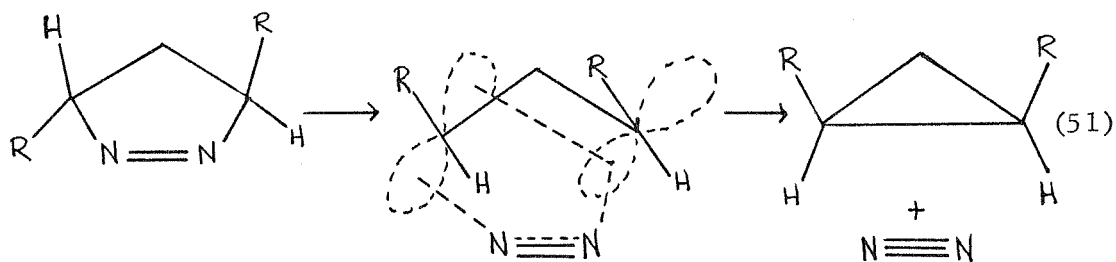
The production of the minor non-singly inverted cyclopropane product obviously complicates the mechanistic problem. Both the π -cyclopropane and the sequential cleavage mechanism were proposed to explain the single inversion phenomenon, and each must be modified to accommodate both the existence of the minor product and the fact that it is partially doubly inverted. Crawford has invoked the recoil effect and a certain amount of less favorable disrotatory closure of the π -cyclopropane to meet this problem. Something like the process shown in Scheme 6 can be used to modify the sequential cleavage mechanism.

SCHEME 6



With these qualifications either mechanism can account for the minor product.

One additional mechanistic suggestion which has been considered and rejected by several workers in the field²⁶ is the possibility that the extrusion of nitrogen and the closure to the singly inverted cyclopropane product occur in a single step in a symmetry allowed¹⁰ $\sigma^2_s + \sigma^2_a$ process (eq. 51). This process can be drawn on paper, but examina-



tion of models shows that the geometric constraints in this system make such a process seem rather improbable. Moreover, Crawford has rather convincingly demonstrated the existence of at least one intermediate after the rate determining step in the pyrolysis of 4-deuterio-4-methyl-1-pyrazoline.^{8c} Here Crawford finds a rather large isotope effect on the cyclopropane/olefin ration, but little effect on the overall rate of pyrazoline decomposition, a finding which indicates that at least some of the cyclopropane must be coming from a reaction intermediate which also gives rise to olefin. This result does not rule out absolutely the possibility that some cyclopropane is coming from a competing concerted process which does not give olefin. However, the acceptance of such an unlikely mechanism would require compelling experimental evidence which necessitated the rejection of the

other more likely mechanisms discussed above and which provided some firm support for the concerted process. Such evidence has clearly not yet been provided.

Thus, the mechanistic question remains unresolved. The π -cyclopropane mechanism has many appealing aspects, but it cannot explain the results of the optically active cyclopropane pyrolyses, nor does it seem to be a reasonable intermediate in the strained bicyclic pyrazoline pyrolyses. The sequential cleavage mechanism does not fit all of the pyrazoline decomposition data either, but it has never been ruled out in a system which is known to undergo single inversion. Of course, there are endless possibilities for speculation as to how the various data might be accommodated to one or the other scheme with a slight modification of mechanism here or a new assumption there, but what is clearly called for is an experiment capable of distinguishing between the two mechanistic possibilities in a system known to undergo single inversion.

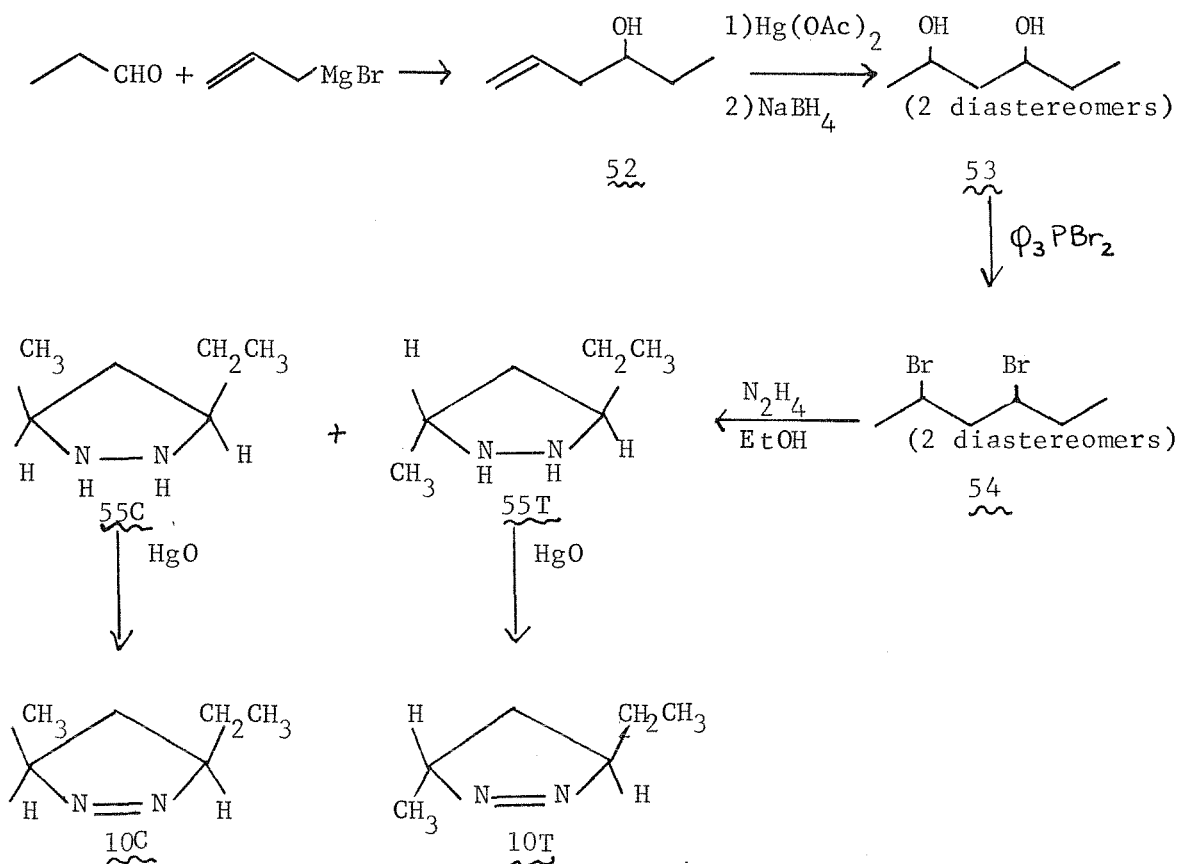
The experiment described in Section I was thus developed to solve this mechanistic problem. The synthetic approaches to the optically active undeuterated and deuterated 3-ethyl-5-methyl-1-pyrazolines and the pyrolysis results to date are described below.

III. RESULTS AND DISCUSSION

Synthesis-Racemic Series

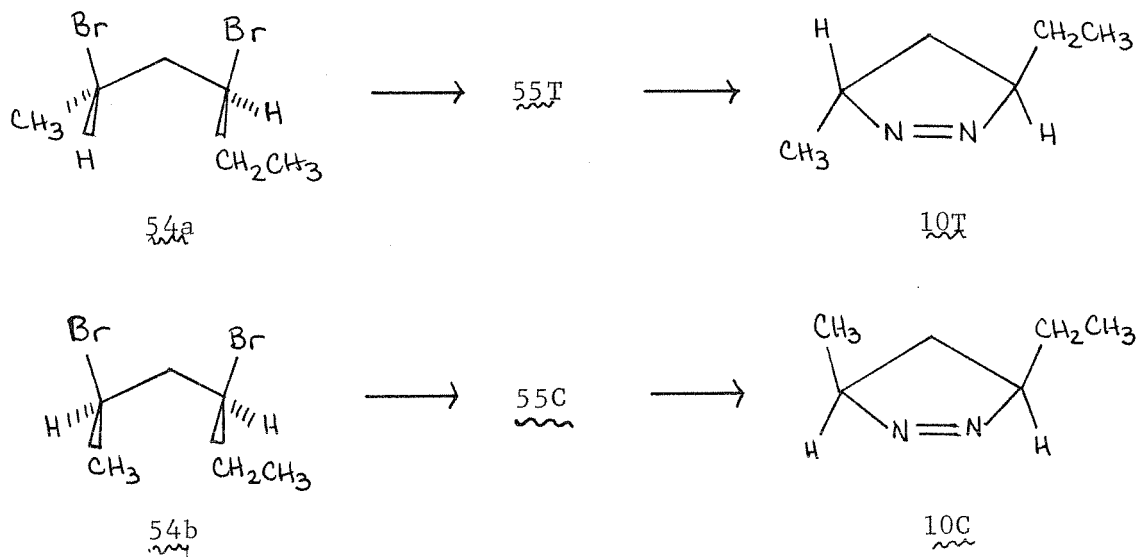
The synthesis of racemic cis- and trans-3-ethyl-5-methyl-1-pyrazoline (10C and 10T) was first carried out to assure the viability of the chosen synthetic scheme and to provide material for preliminary pyrolyses to determine the extent of single inversion in this system. The synthetic approach, outlined in Scheme 7, was based on the general procedure developed by Crawford et al. for the synthesis of 1-pyrazolines.³⁹

SCHEME 7



The Grignard condensation of propionaldehyde and allylmagnesium bromide provided 1-hexen-4-ol (52) in excellent yield. This alcohol was then subjected to Brown's oxymercuration-hydroboration procedure⁴⁰ to provide a mixture of the diastereomers of 2,4-hexanediol (53). This diastereomeric mixture was then converted to a mixture of the diastereomers of 2,4-dibromohexane (54).

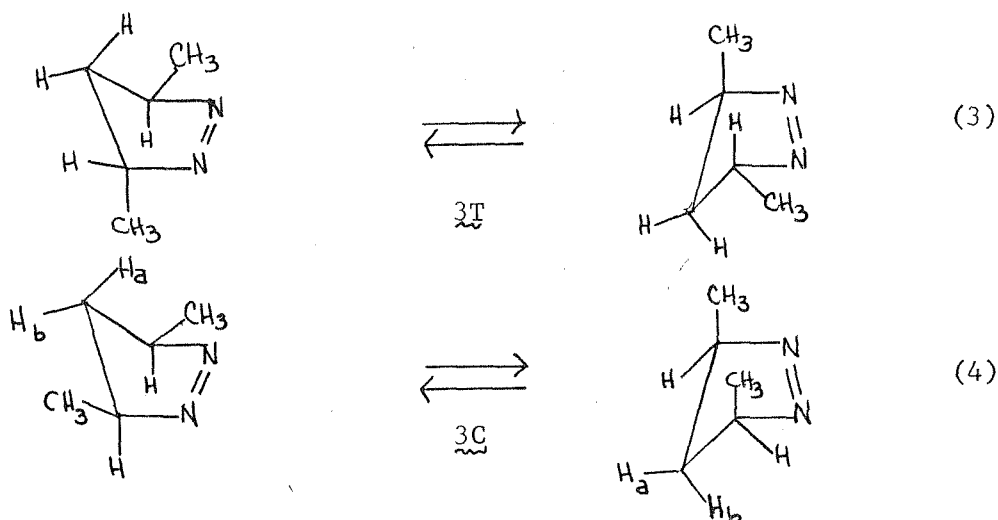
Initially, it was planned that the diastereomeric dibromides would be transformed to a mixture of pyrazolidines 55C and 55T, by the method of Crawford,³⁹ and that separation of the cis-trans isomers would be performed either at this stage, or more likely, at the final pyrazoline stage. Unfortunately, no satisfactory procedure was ever found for the separation of either the pyrazolidine or the pyrazoline isomers. Instead a rather tedious preparative vapor phase chromatography separation of the dibromide diastereomers was resorted to. It was then shown that the (+)-(2R,4R)-2,4-dibromohexane (54a) gave only



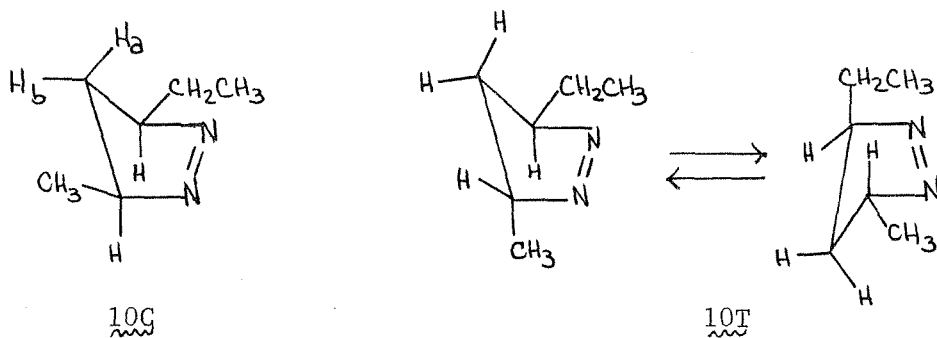
trans pyrazoline and that the (+)-(2S,4R)-2,4-dibromohexane (54b) gave only cis pyrazoline 10C. No crossover in stereochemistry could be observed within the limits of nmr detection.

Thus the dibromide diastereomers were separated and reacted individually with hydrazine in ethanol to give the pyrazolidines, which were in turn oxidized with red mercuric oxide in pentane to provide 10C and 10T. Both the pyrazolidines and the pyrazolines proved to be reasonably stable compounds, but neither survived vapor phase chromatography on metal columns; all vpc work with these compounds was performed with glass columns. Also it should be noted that some difficulty was encountered in attempting to convert the dibromides to the pyrazolidines under the conditions given by Crawford;³⁹ the modifications of this procedure which were found to be necessary are described in the experimental section.

The stereochemistries of pyrazolines 10C and 10T were assigned on the basis of their nmr spectra. Since these assignments are crucial to the interpretation of the pyrolysis results, they will be discussed in some detail: In the case of the cis- and trans-3,5-dimethyl-1-pyrazolines (3C and 3T), Crawford³⁹ was able to resolve the compound identified as the trans pyrazoline; since the cis pyrazoline is a meso compound, this resolution firmly established the identities of 3C and 3T. The nmr of the trans compound showed the methylene hydrogens at C₄ to be equivalent (τ 8.73), presumably because of the facile ring flip which interconverts the two equivalent envelope conformations (eq. 3). In the cis pyrazoline, on the other



hand, the inherent nonequivalence of the two protons at C4 is magnified by the fact that the conformational equilibrium (eq. 4) must lie very heavily toward the configuration where both methyl groups are equatorial. Thus, Crawford found that while H_a absorbed at τ 9.52, proton H_b absorbed at 7.92 τ .⁴¹



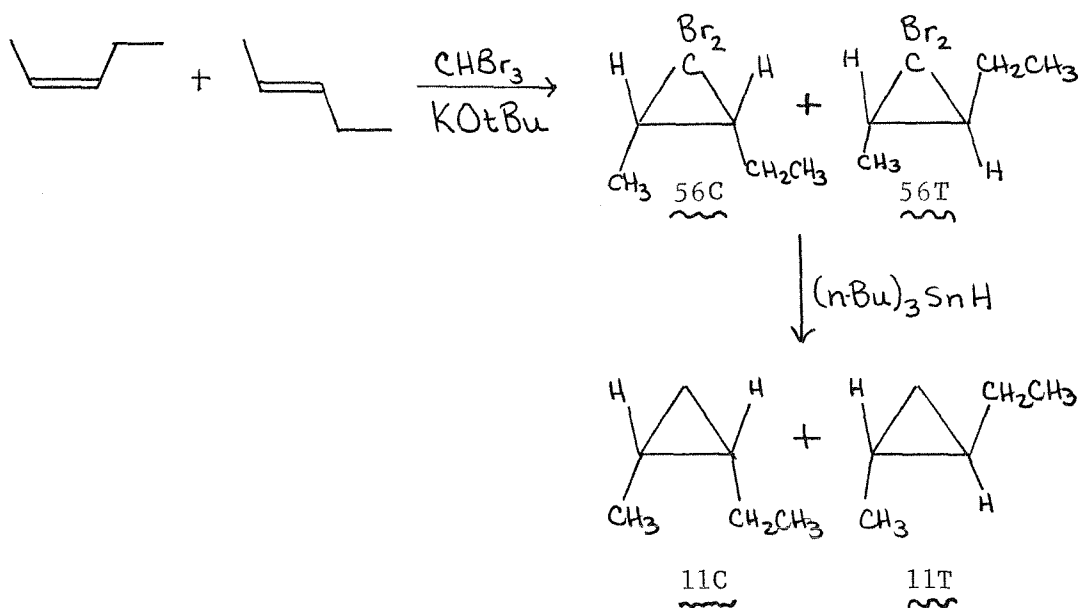
The cis- and trans-1-ethyl-2-methyl-1-pyrazolines (10C and 10T) can thus be readily identified on the basis of their nmr spectra. In 10C proton H_a appears as a doublet of triplets at τ 9.38 while H_b appears at approximately τ 8 (overlap with the methylene protons of the ethyl group obscures the exact location). On the other hand, the very complex spectrum of 10T shows no signals above τ 8.8 other than

the methyl triplet of the ethyl group; the protons at C⁴ (which are not strictly equivalent in this case) absorb at roughly τ 8.6-8.7, overlapping the doublet of the C⁵ methyl group.

Although less definitive, the absorptions of the methine protons at C³ and C⁵ also support the above assignment. In Crawford's case,³⁹ the methine protons of 3T absorb at τ 5.43 while the corresponding protons in 3C are shifted upfield slightly to 5.80 τ . In the present case, the compound assigned as 10T shows the methine protons at τ 5.48 while these protons are again shifted upfield to τ 5.88 in the cis pyrazoline 10C.

Since proper identification of the product cyclopropanes 11C and 11T was also an important consideration, authentic samples of these compounds were prepared by the straightforward route shown in Scheme 8. The cyclopropane products were then separated by preparative

SCHEME 8



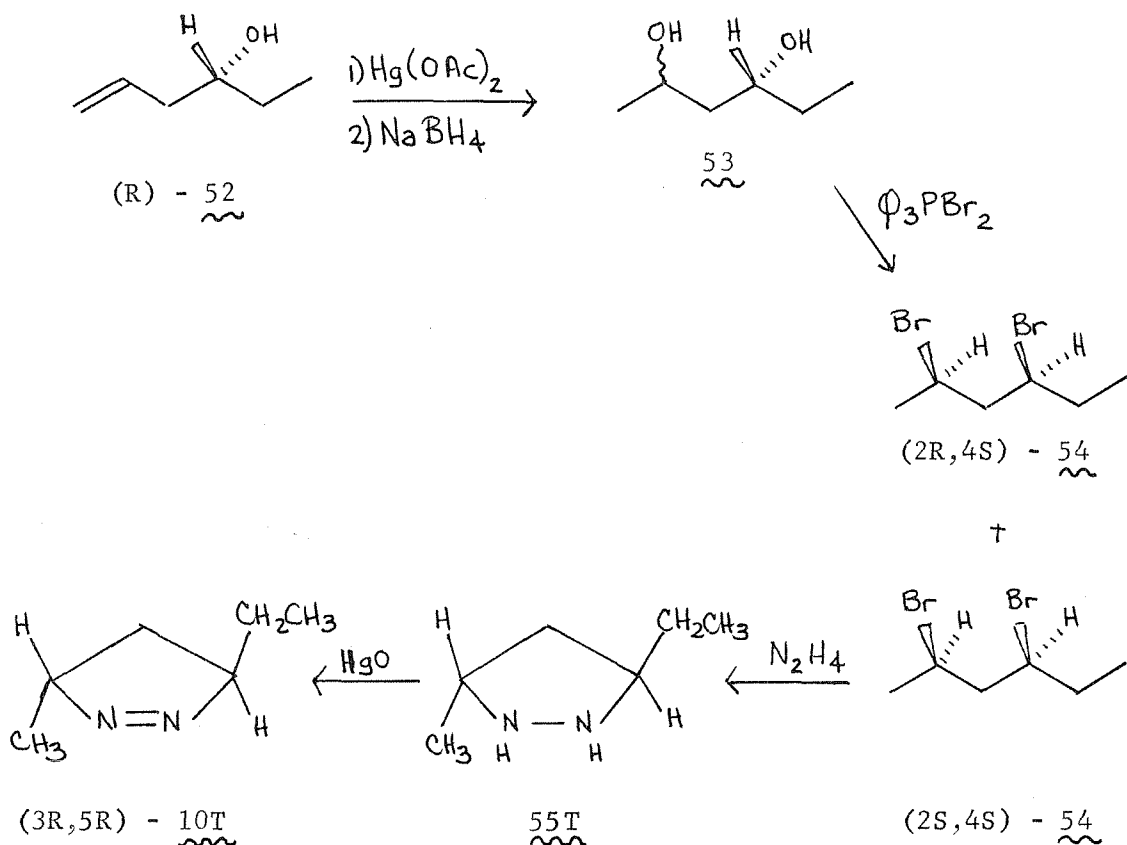
vapor phase chromatography and identified by comparison of their spectra with the known spectra of these compounds.¹⁶

Synthesis-Optically Active Undeuterated Series

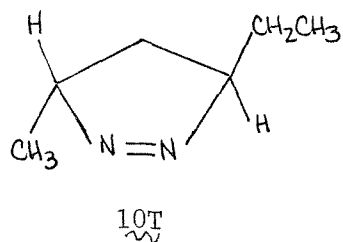
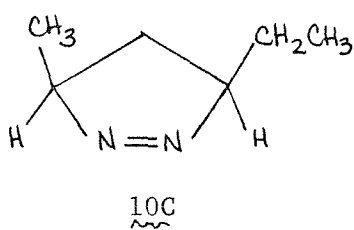
Resolution was accomplished by the conversion of 1-hexen-4-ol (52) to the phthalate half ester (57), whose brucine salt was then recrystallized from ethyl acetate. (The efficiency of the resolution was limited to some extent by the refusal of the phthalate half ester to crystallize at any stage in the sequence.) Alcohol 52 having $[\alpha]_D^{25} - 0.188^\circ$ (neat) was recovered from the recrystallized salt. In order to determine the absolute configuration and maximum rotation of this alcohol, 52 was then hydrogenated to give 3-hexanol, $[\alpha]_D^{25} - 2.74^\circ$. Since (-)-3-hexanol is known to have the R configuration and an $[\alpha]_D^{25} \text{ max.} - 7.13^\circ$,⁴² the sample of (-)-52 produced must also have the R configuration and an optical purity of 38.4%. This alcohol was then carried through as in Scheme 9 to give (+)-(3R,5R)-trans-3-ethyl-5-methyl-1-pyrazoline. In analogy with the results of Crawford,^{8h} the formation of the dibromide and the reaction of the dibromide with hydrazine are each expected to precede with inversion at both reacting centers and with little loss of optical purity.⁴³ The results of the pyrolysis of the optically active pyrazoline are discussed below.

(+)-(S)-1-hexen-4-ol (35.8% optical purity) was recovered from the mother liquor of the resolution and used in the attempted synthesis of the optically active deuterated pyrazolines.

SCHEME 9

Pyrolysis-Racemic Series

The pyrolyses of the racemic cis- and trans-3-ethyl-5-methyl-1-pyrazolines (10C and 10T) were carried out to determine the extent



of single inversion in the cyclopropane products. These pyrolyses were all performed on the glass-lined injection block of a Hewlett-Packard 5750 Research Chromatograph equipped with a Hewlett-Packard 3370A Digital Integrator. (See experimental section for details.) Thus, direct readout of the relative product peak areas was obtained without any of the fractionation problems which may be encountered in the product analysis of normal static or flow pyrolyses. As expected,²⁴ control experiments showed that the products were not interconverting under the reaction conditions. It was also shown that no products arose from pyrazoline decomposition on the vpc column. Cyclopropane products were identified by comparison with the authentic samples produced as described above; olefin products were identified by comparison of retention times with authentic samples procured from Chem Samples Corp. The results of these pyrolyses are summarized in Tables 2 and 3.

The vpc conditions used did not allow separation of the cis cyclopropane llc from cis-3-hexene; the percentages shown for llc thus presumably include a small amount of cis-3-hexene. In analogy with Crawford's findings in the 3,5-dimethyl system (vide infra) this is not expected to change the yield of llc by more than 1% in the case of lot and even less than that in loc, so that no significant error was introduced by this problem. Product percentages at a given temperature were reproducible to $\pm 1\%$.

A comparison shows excellent agreement between these and Crawford's results for the 3,5-dimethyl-1-pyrazolines (3c and 3t) as

Table 2. Percent Product Distributions in the Pyrolysis of
 Racemic trans-3-Ethyl-5-methyl-1-pyrazoline (10T)











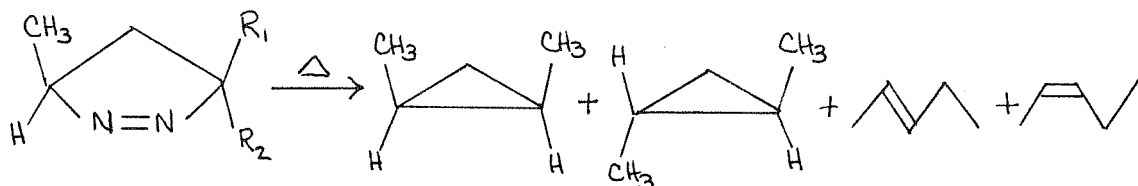
Temp.						1,1C/1,1T
150°C	—	—	—	—	—	—
261°C	25.4	74.5	0.1	trace	trace	2.93
306°C	26.8	71.3	1.2	trace	0.8	2.66
352°C	27.9	69.2	1.6	trace	1.4	2.48
353°C	28.0	69.3	1.6	trace	1.1	2.48
354°C	28.3	69.2	1.3	trace	1.2	2.45

Table 3. Percent Product Distributions in the Pyrolysis of
 Racemic cis-3-Ethyl-5-methyl-1-pyrazoline (LOC)

Temp.	 LLT	 LLC				LLC/LLT
150°C	—	—	—	—	—	—
261°C	70.6	29.4	trace	trace	trace	0.416
300°C	67.0	32.2	0.9	trace	trace	0.481
350°C	65.2	33.3	1.4	trace	0.1	0.511

shown in Scheme 10 (static system, 220°C).^{8c} Both systems show predomi-

SCHEME 10



<u>3C</u> : R ₁ = CH ₃ , R ₂ = H	33.2	66.1	0.68	0.0
<u>3T</u> : R ₁ = H, R ₂ = CH ₃	72.6	25.4	1.08	0.92

nant single inversion, and in both cases the decomposition of the trans pyrazoline is slightly more stereospecific. The present work also reveals a modest temperature dependence in the cyclopropane product ratios; as might be expected the stereospecificity shows a gradual decrease with increasing temperature.

Having thus confirmed the expected predominance of singly inverted cyclopropane product in the pyrolysis of racemic cis- and trans-3-ethyl-5-methyl-1-pyrazoline (10C and 10T), the pyrolysis of the optically active compounds was undertaken.

Optically Active Series

Attention in the optically active series was focused on the trans-pyrazoline 10T for two major reasons, both arising from the fact that the separation of the cis-trans pyrazoline isomers had to be

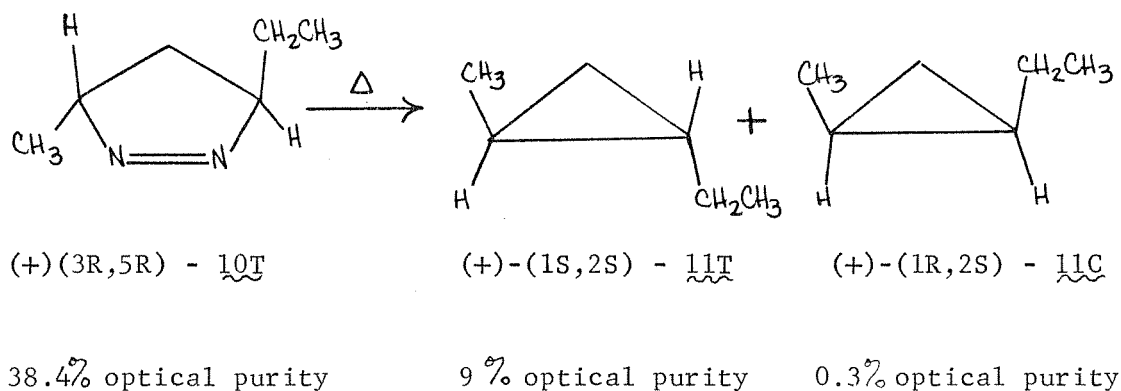
effected at the stage of their dibromide precursors via preparative vapor phase chromatography. First, the dibromides were formed in a (2S,4S):(2R,4S) ratio of 2.8:1, and although clean separation was achieved with small injections, resolution decreased with the size of the injection; thus considerable time was required just to obtain sufficient amounts of the major (2S,4S) isomer to allow synthesis and pyrolysis of the trans-pyrazoline. Second, the (2S,4S) isomer came off the vpc column first and could be cleanly isolated without contamination by the (2R,4S) isomer, whereas the (2R,4S) isomer always contained some small but significant amount of the (2S,4S) isomer. At least one additional pass through the vpc would have been necessary to obtain sufficient pure (2R,4S) dibromide to carry on the reaction sequence. Thus, in the interest of time the trans-pyrazoline was concentrated on. (Note that no essential information was lost here since either the cis or the trans system should provide the information necessary to answer the mechanistic question; however, the cis pyrazoline would serve as a useful check to confirm the results obtained in the trans system.)

The (+)-(2S,4S)-2,4-dibromohexane was converted as shown in Scheme 9 to (+)-(3R,4R)-trans-3-ethyl-5-methyl-1-pyrazoline, which was then pyrolyzed in a quartz flow system at 292°C and at atmospheric pressure (He carrier gas--see experimental section for details). The observed cis-trans ratio of the cyclopropane products was 2.65, in good agreement with the value obtained in the injection port pyrolysis of the racemic trans pyrazoline. The cyclopropane products were isolated by preparative vapor phase chromatography and their optical

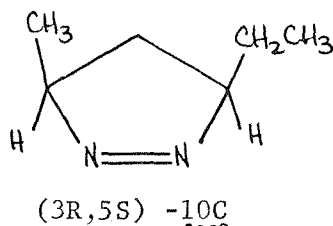
rotations taken: the minor trans cyclopropane product showed $[\alpha]_D^{25} + 3.22^\circ$, $[\alpha]_{365}^{25} + 9.29^\circ$ (n-hexane); the cis cyclopropane product showed $[\alpha]_D^{25} + .058^\circ$, $[\alpha]_{365}^{25} + 0.179^\circ$ (n-heptane).

Based on the maximum rotations and absolute configurations determined by Bergman for the cyclopropane products,¹⁶ the trans cyclopropane produced in the pyrolysis must be 9% optically pure and must have the (1S,2S) absolute configuration. Since the starting (3R,5R) pyrazoline had an optical purity of 38.4%, the trans cyclopropane was thus produced with 23% retention of optical purity and with an excess of double inversion (Scheme 11). This is exactly the result obtained by Crawford for the trans-1,2-dimethylcyclopropane obtained in the pyrolysis of optically active trans-3,5-dimethyl-1-pyrazoline (vide supra).^{8h}

SCHEME 11

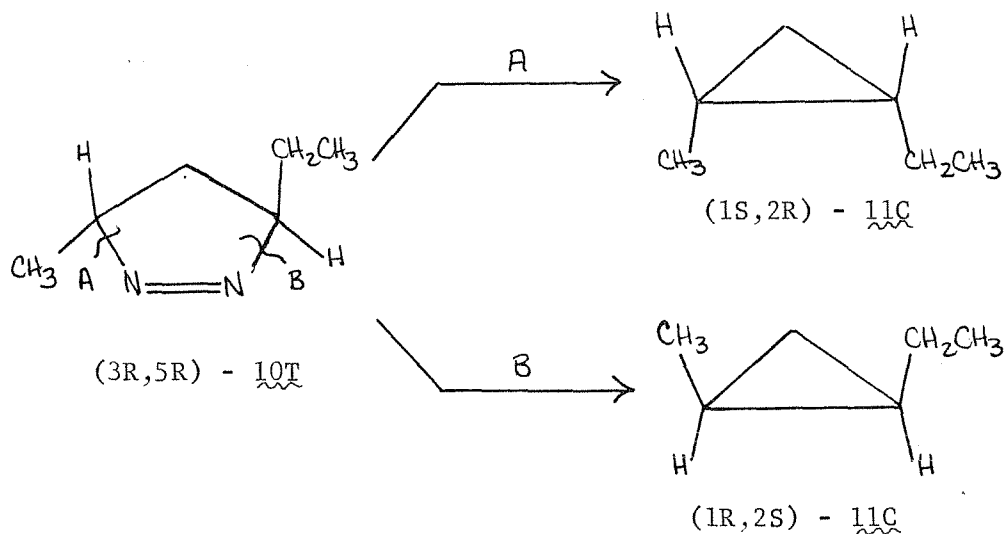


The cis-ethyl-2-methylcyclopropane (11C) was formed with an optical purity of $0.3\% \pm 0.05\%$; thus there was 0.8% retention of optical purity in the process leading to 11C, with a slight preference being shown for the (1R,2S) enantiomer. It is worth noting that any 11C which might have arisen from a cis pyrazoline impurity ((3R,5S)-10C) would have had the (1S,2R) configuration (net double inversion). Thus the small but definite optical activity observed 11C cannot be arising from this source.

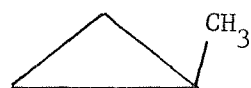
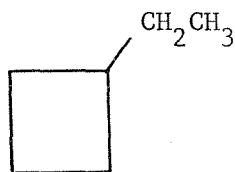
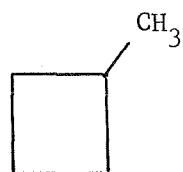


As stated earlier, one cannot base any mechanistic conclusions on the observation of 0.8% retention of optical purity in the singly

SCHEME 12



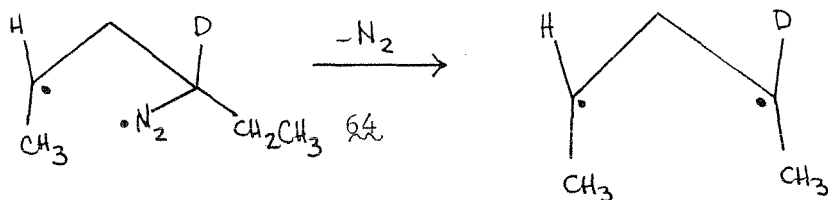
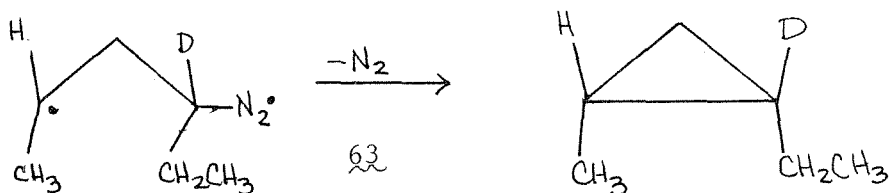
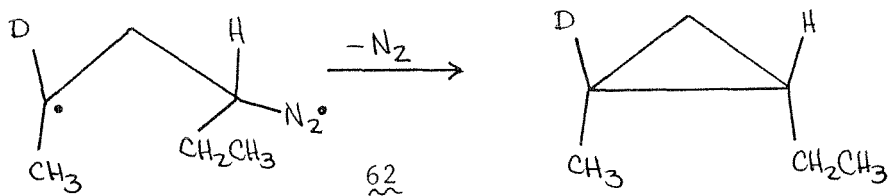
inverted product. However, it is interesting to note that for an excess of the (1R,2S) cis cyclopropane to be produced via the sequential cleavage mechanism, there would have to be a slight preference for initial cleavage of the ethyl substituted C-N bond rather than the methyl substituted bond (Scheme 12). This is consistent with the observation that the thermal decompositions of 58 and 60 occur slightly faster than those of 59 and 61, respectively.^{51,52}

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It is encouraging that detectable optical activity was found in 11C, thus making a quantitative comparison with the results obtained in the deuterated isomers feasible. The combination of these results with those obtained in the pyrolyses of 12T and 13T should provide a definite answer as to which mechanism is involved.

Three further questions must be addressed regarding the deuterated pyrazoline experiments. The first involves the question

of deuterium isotope effects on reaction steps following the rate determining step. Such effects would not, of course, change the prediction of the π -cyclopropane mechanism, since once the racemic intermediate is formed, there is no possibility for an isotope effect to cause a reintroduction of optical activity in a subsequent step. On the other hand, there are few good models for the isotope effects involved in the steps following initial C-N bond breakage in the sequential cleavage mechanism. The ponderal effect on the rotations of the deuterium containing radical groups should be very small, especially in the nitrogen containing fragment. The other steps which might be affected are shown below:



Crawford has shown experimentally that step 62 exhibits little or no kinetic isotope effect;^{8g} this is reasonable since there is very little change in the C-H stretching bond bending force constants on going from an sp^2 (or nearly so) methylene center to the methylene of a cyclopropane. Reaction 63 might be expected to show a positive isotope effect since here the deuterium is on an sp^3 center which is going to cyclopropane product; however, step 64 which is assumed to provide the main competition for 65 will be slowed by a comparable amount for the same reason.^{53,54} Thus, these effects should essentially cancel. This can all be checked experimentally by comparing the product distributions in the deuterated and undeuterated cases.

A second problem is the effect of exchange of deuterium for hydrogen at an optically active center on the maximum rotation of a compound. This problem becomes crucial in the determination of the optical purities of the product cyclopropanes, since the maximum rotations are only known for the protio compounds. Recent calculations by Brewster, however, suggest that such a substitution should cause at most a 1% change in the optical rotation of a compound.⁵⁵ Thus, one can assume with some confidence that any error introduced by calculation of optical purities based on the maximum rotations of the protio compounds will be negligible, although experimental verification of this fact would be desirable.

The final problem in the deuterated cases involves the magnitude of the optical activity which would be introduced by the deuterium isotope effects according to the sequential cleavage mechanism.

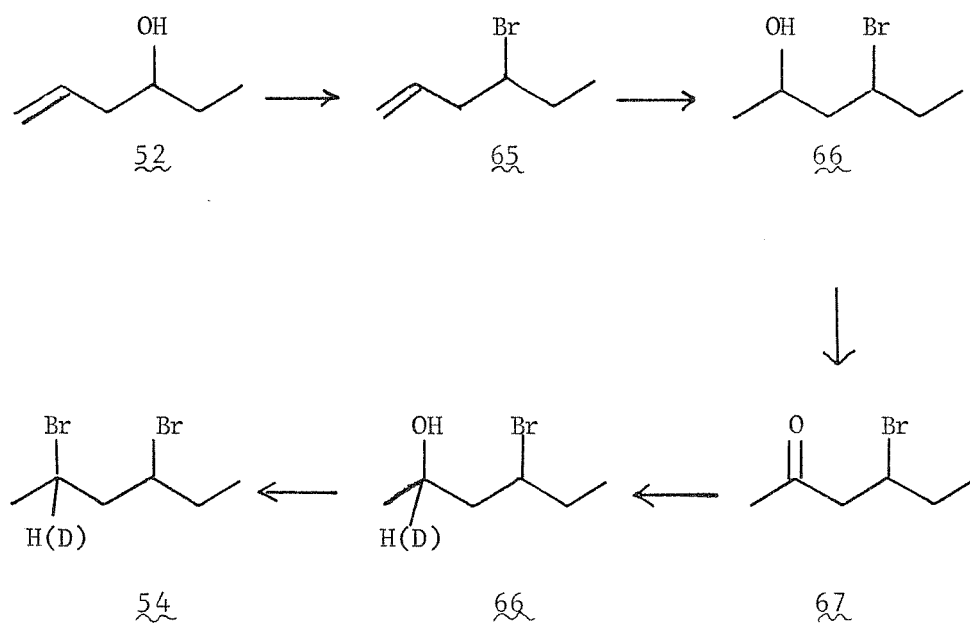
By a conservative estimate, k_H/k_D should be at least 1.1.^{8g,15} (As mentioned previously in the discussion of the 3,3-dideuterio- and 3,3,5,5-tetradeuterio-1-pyrazolines, the actual k_H/k_D is more like 1.2 if the sequential cleavage mechanism is operating; thus 1.1 is definitely a conservative estimate.) A value of 1.1 would lead to a $(1.1-1.0/1.1 + 1.0) = 4.76\%$ retention of optical purity. Even if one assumes that only 60% of the single inversion product arises from the sequential cleavage mechanism and that the rest arises from a randomizing process which also gives the minor cyclopropane isomer, there would still be a 2.85% retention of optical purity. (The 60% value was arrived at as follows: from the trans pyrazoline the cis/trans cyclopropane product ratio at $\sim 300^\circ\text{C}$ is 71/27; thus if equal amounts of cis and trans arise by a randomizing process, then $\frac{71-27}{71} = 62\%$ of the cis would still be coming from the sequential cleavage estimate. This is also a conservative estimate since 23% of the trans product is known to be formed with double inversion in what must be a non-randomizing process.) The difference in the optical purity of the single inversion product from each of the two deuterated pyrazolines should then be at least 5.7%, an easily observable value. It is also important to recognize that this mechanistic test is not based on just the magnitude of the product optical purity, but more important on the ability to shift that optical purity in a predictable way with the deuterium isotope effects.

Thus, these experiments should finally provide a firm experimental basis for distinguishing between the proposed mechanisms for single inversion in pyrazoline pyrolyses.

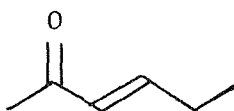
Approaches to the Optically Active Deuterated Series

The synthetic approach outlined for the Scheme 13 was first carried through starting with racemic 1-hexen-4-ol (52) to determine appropriate reaction conditions for the various transformations.

SCHEME 13



Alcohol 52 was converted to the bromide with triphenylphosphine dibromide; oxymercuration-hydroboration then provided a diastereomeric mixture of 4-bromo-2-hexanols (66). A careful Jones oxidation gave bromoketone 67, which, as might be expected, proved to be a rather sensitive compound with a high susceptibility toward HBr elimination to give the α,β unsaturated ketone 68. Reduction of 67 was carried



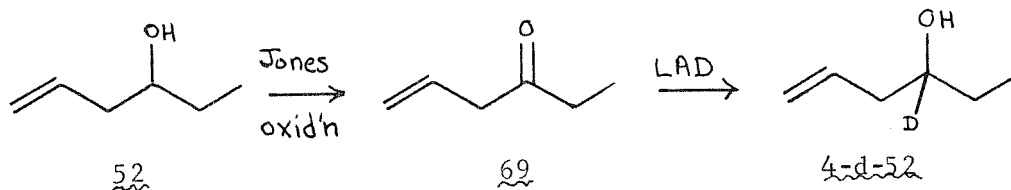
68

out in the racemic case with sodium borohydride and the resulting bromoalcohol diastereomers were then converted to the dibromides with triphenylphosphine dibromide. Conversion of the dibromides to the corresponding pyrazolines (specifically deuterated at C5) would then be carried out as described previously.

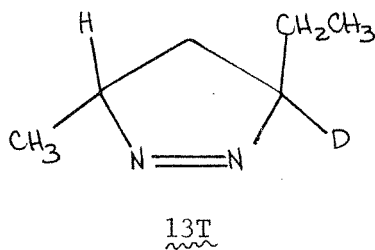
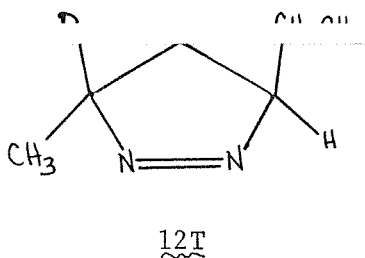
Since no unusual problems were encountered in the above sequence, the entire procedure was then repeated starting with (+)-S-1-hexen-4-ol (35.8% optically pure). Sodium borodeuteride was used in the reduction step to give as the final product 2-d-2,4-dibromohexane. However, the (2R,4R)-2-d-2,4-dibromohexane produced by this route proved to have a specific rotation $[\alpha]_D^{25}$ of only -0.37° ($c = 0.10$ in CHCl_3). Since the (+)-(2S,4S)-2,4-dibromohexane produced from 38.4% optically pure (-)-(R)-1-hexen-4-ol according to Scheme 4 had $[\alpha]_D^{25} + 27.7^\circ$ ($c = 0$ in CHCl_3), it is quite clear that extensive racemization occurred somewhere in Scheme 13, most likely in the final step. Thus, Scheme 13 proved unsuitable for the production of optically active pyrazolines.

The procedure shown in Scheme 14 for the production of optically active pyrazoline deuterated at C3 was also begun. Careful Jones oxidation of alcohol 52 produced ketone 69 with no significant rear-

SCHEME 14

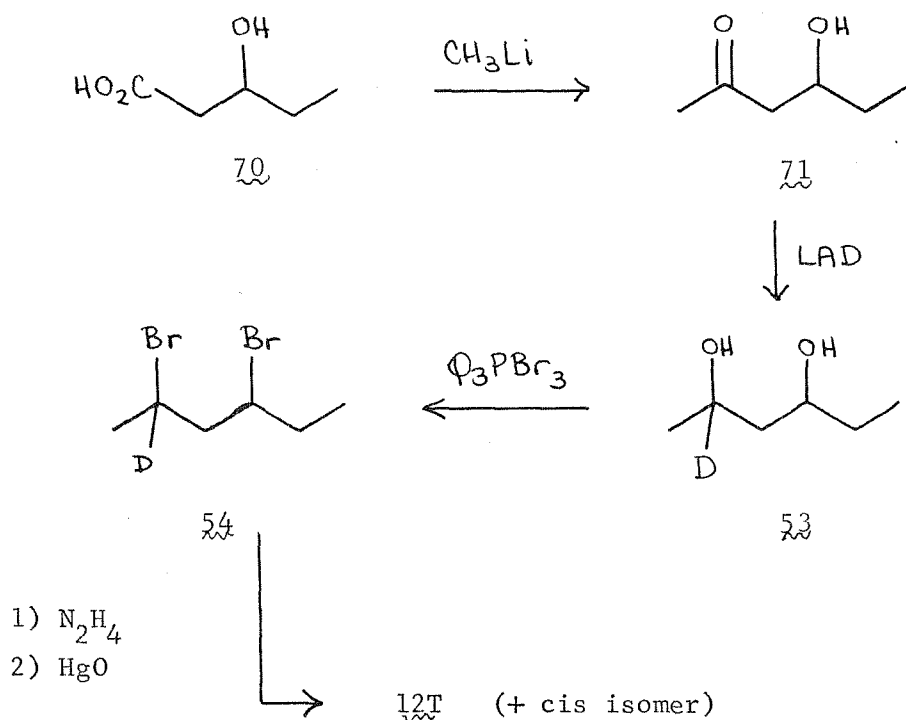


rangement to the corresponding α,β -unsaturated ketone. Low temperature reduction with lithium aluminum deuteride then provided 4-d-1-hexen-4-ol. This alcohol was then converted to the phthalate half ester and resolution was attempted first as in the undeuterated case by fractional crystallization of the brucine salt from ethyl acetate. Unfortunately, the presence of the phthalate half ester of an isopropanol impurity interfered with the crystallization pattern and caused the resolution attempt to be unsuccessful. The deuterated alcohol was recovered and repurified and is currently being subjected to the resolution procedure again. There is no reason why this procedure should not now lead to the optically active deuterated pyrazoline 13T.



In light of the failure of Scheme 5 to produce the optically active deuterated pyrazoline 12T, alternate procedures must be considered. One possibility is shown in Scheme 15.

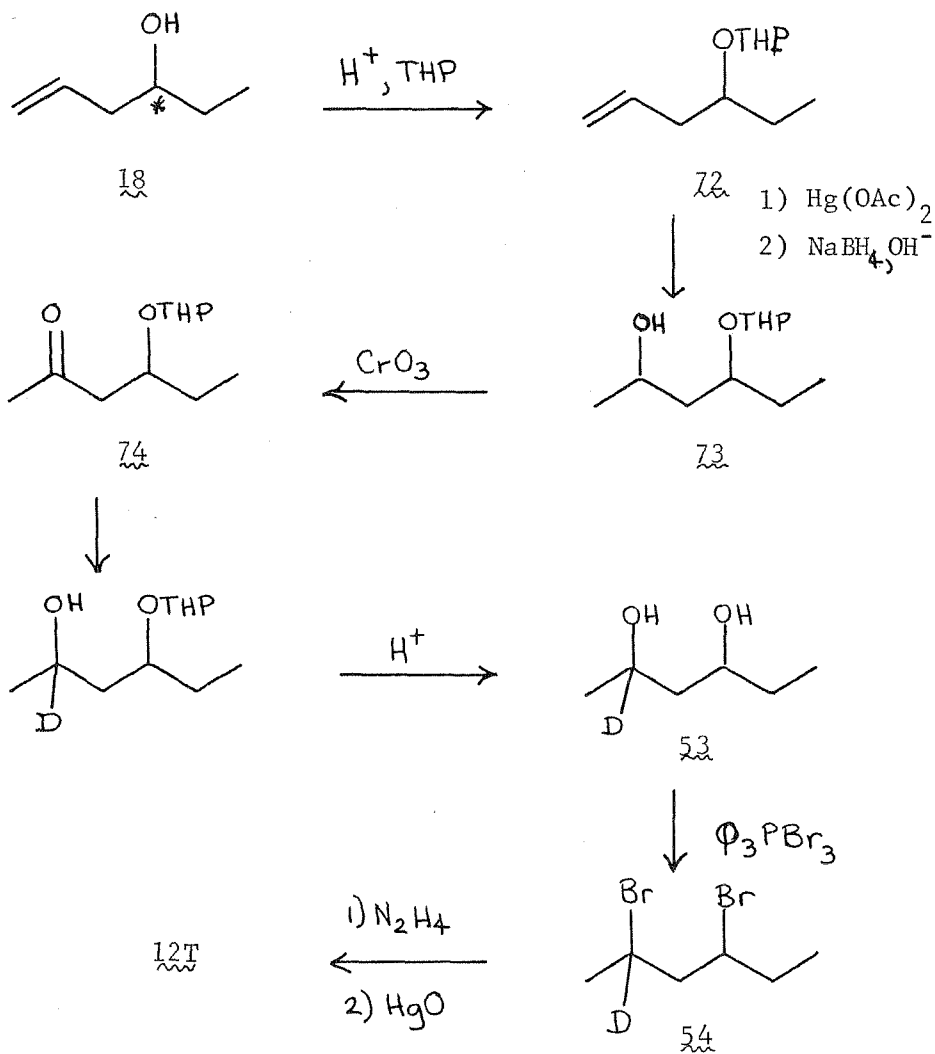
SCHEME 15



Starting with 3-hydroxyvaleric acid (70)⁴⁴ the sequence shown would lead to 12T. Although it has apparently never been attempted, resolution of 70 might be possible through fractional crystallization of its brucine salt. Alternatively, resolution of ketoalcohol 71 might be possible via the phthalate half ester procedure discussed above.

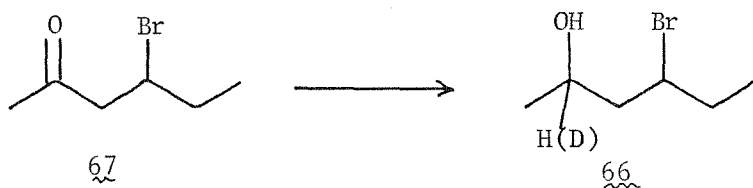
Another possible variation leading to 12T is shown in Scheme 16. Optically active alcohol 52 (vide supra) could be protected as its tetrahydropyranyl ether 72. Oxymercuration-hydroboration followed

SCHEME 16

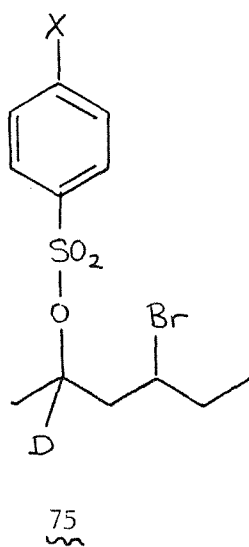


by oxidation under basic conditions would provide $\underline{73}$.⁴⁷ Reduction of the ketone and cleavage of the THP ether would then give diol $\underline{53}$ which was shown in the undeuterated series (Scheme 9) to be a suitable precursor for optically active pyrazoline.

Two additional attempts at the production of optically active pyrazoline deserve mention. The first involved the asymmetric reduction



of ketone 67 (Scheme 13) with diisopinocampheylborane. This procedure has met with some success in the past,^{45,46} but difficulty was encountered in the present case in the separation of the diastereomers of 66 from the products arising from the α -pinene, and the extent of asymmetric induction in this reaction was never determined. Also, some alternate to the procedure used in Scheme 13 would have been necessary to avoid the extensive racemization which occurred there on conversion of 66 to dibromide. One possibility might be the conversion of the alcohol center in 66 directly to a good leaving group as in 75. Reaction of 75 with hydrazine might then lead directly to pyrazolidine.



Care would have to be taken in the choice of leaving group to avoid the intervention of any S_N1 process which might cause stereochemical scrambling. Competition from an elimination process might also be a problem in this system.

A second approach to an optically active pyrazoline precursor involved the recent report of Skell et al. of the partial resolution (65.4% optical purity) of *d,l*-2,3-dibromobutane by successive vacuum distillations of the dibromide from a brucine paste.⁴⁸ Although previous authors had attributed less successful versions of this resolution to selective destruction of one of the dibromobutane enantiomers,⁴⁹ Skell et al. were able to also recover this other enantiomer by workup of the brucine paste residue after distillation. They attribute the success of this resolution to the formation of an asymmetric inclusion complex. The failure of this procedure in the attempted resolution of 2,3-dichlorobutane has shown that the process is not generally applicable to dihalides,⁵⁰ but it was hoped in the present case that the partial resolution of 2,4-dibromohexane might be achieved. Among other advantages, this would have allowed the rescue of the 2-d-2,4-dibromohexane produced in racemic form by Scheme 13 (vide supra). Unfortunately no success was obtained in this attempted resolution.

IV. EXPERIMENTAL

General

Infrared spectra were obtained on a Perkin-Elmer 257 Grating Infrared Spectrophotometer as CCl_4 solutions. Nmr spectra were obtained on either an A-60-A or a T-60 Varian Associates Analytical nmr Spectrometer as carbon tetrachloride or deuteriochloroform solutions with tetramethylsilane (TMS) internal standard. Nmr spectra are reported as: chemical shift (in order of increasing δ), multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, splitting, integration in units of H, assignment.

Vapor phase chromatography (vpc) was performed on the following columns using He carrier gas:

Column A: 10' \times 1/4", 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; Column B: 5' \times 1/4", 5% DEGS on 60/80 Chromosorb P-NAW, stainless steel; Column C: 10' \times 1/4", 8% TCEP on 60/80 Chromosorb P-NAW aluminum; Column D: 5' \times 1/4", 3% SE30 on 100/120 Varaport 30, stainless steel; Column E: 10' \times 1/4", 5% Carbowax on 60/80 Chromosorb P-NAW, aluminum; Column F: 10' \times 1/4", 10% UCC-W98 on 60/80 Chromosorb W-AWDMCS, glass; Column G: 20' \times 1/4" 20% Carbowax on 60/80 Chromosorb P-NAW, aluminum; Column H: 25' \times 1/8", 25% $\beta\beta$ -ODNP on 100/120 Chromosorb W-AWDMCS, stainless steel; Column I: 10' \times 1/4", 10% Carbowax 1500 on 60/80 Chromosorb P-NAW, stainless steel; Column J: 10' \times 1/4", 12% WCC-W98 on 60/80 Chromosorb P-NAW, stainless steel;

Column K: 12' \times 1/4", 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; Column L: 10' \times 1/4", 10% DEGS on 60/80 Chromosorb W-AWDMCS, glass.

Analytical work using the 1/8" columns was performed on a Hewlett-Packard 5750 instrument equipped with flame ionization detector and Hewlett-Packard 3370A Integrator. Except when chromatographing sensitive materials, the injector temperature was maintained at approximately 200°C and the detector at approximately 340°C; the following gas pressures were used (lb/in²): He, 40; Hz, 14; air 30. Analytical and preparative work using 1/4" columns was performed on a Varian Aerograph 90-P3 instrument equipped with thermal conductivity detector using He carrier gas. Except when chromatographing sensitive materials, injector and detector temperatures were maintained at approximately 200°C.

Optical rotations were taken on a Perkin-Elmer 141 digital readout Polarimeter using a 1 ml microcell with 10 cm pathlength. Concentrations shown are in g/ml.

Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

All boiling and melting points are uncorrected.

Syntheses

I. Racemic undeuterated series

(+)-1-Hexen-4-ol (52) was prepared by a procedure similar to that of Hwa and Sims⁵⁶ for reaction of allylmagnesium bromide with acrolein. Into a 5ℓ three-necked flask fitted with mechanical stirrer,

reflux condenser and addition funnel was placed 153.0g (6.28 g.atoms) Mg turnings. The flask was then flamed out under N_2 , after which 360 ml anhydrous ether and three iodine crystals were added. Several ml of a solution of 351g (2.90 mol) allyl bromide in 2.6l anhydrous ether were then added, at which point spontaneous reflux began. The rest of the allyl bromide solution was then added slowly over $6\frac{1}{2}$ hours at a rate sufficient to maintain a gentle reflux. Upon completion of the addition, the dark brown solution was stirred for 2 hrs. at room temperature. Then 108g (1.86 mol) propionaldehyde was added over 3 hrs. again at a rate sufficient to promote a mild reflux. The reaction was then stirred 1 hr. at RT and left overnight under N_2 .

The reaction mixture was decanted slowly off of the excess Mg turnings into 2l of an ice-water mixture. The remaining Mg turnings were rinsed with ether which was also added to the ice water. To this mixture was then added slowly a solution of 120 ml conc. H_2SO_4 in 400 ml H_2O . The aqueous layer of the resulting mixture was washed with ether after which the combined ether layers were dried over $MgSO_4$.

The ether was slowly distilled off through a 24" tantalum wire column. The product was distilled at reduced pressure through a 6" Vigreux column to give 161.6g of 52 (86.6% yield; b.p. 63-65°C at 50 mm); ir: 3570, 3400 (broad), 3075, 2960, 2920, 2880, 1640, 1440, 1000, 995, 920 cm^{-1} ; nmr (CCl_4): δ 0.93 (t, $J = 6.5$ Hz, 3H, $-CH_2CH_3$); 1.38 (q, 2H, $-CHOH-CH_2-CH_3$); 1.73 (s, 1H, OH); 2.0-2.3 (m, 2H, $=CH-CH_2-$); 3.48 (quintuplet, 1H, $-CHOH$); 4.8-5.2 (m, 2H, vinyl CH_2); 5.4-6.2 (m, 1H, vinyl CH). Anal. calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08; found: C, 72.01; H, 12.11.

(+)-2,4-Hexanediol (53). The procedure used was based on that of Brown and Geoghegan.⁴⁰ Into a 3l three-necked flask fitted with mechanical stirrer, addition funnel, and room temperature water bath were placed 159.5g (0.5 mol) mercuric acetate in 500 ml H₂O. 500 ml THF was added to give a yellow suspension, to which was added 50g (0.5 mol) 52 over a period of eight minutes. During this time the yellow color disappeared. The reaction was allowed to stir for 17 min., after which 500 ml of a 3N aqueous NaOH solution was added. A 500 ml solution 0.5M in NaBH₄ and 3N in NaOH was then added slowly (25 min.) to give a black suspension.

After 15 min. of stirring, the solution was saturated with NaCl, and the two resulting layers separated. The aqueous layer was extracted with THF and the combined organic layers were then washed with saturated aqueous NaCl and dried over K₂CO₃.

After removal of solvent by distillation through a Vigreux column, the product was distilled at reduced pressure (b.p. 73-74°C at 1.2 mm) to give 51.5g of 53 as a viscous colorless liquid (87.3% yield). Vpc analysis of this compound could only be performed well on column E (150°C, 100 ml/min), since it either did not come off at all or tailed unacceptably under all other conditions tried. No conditions were ever found under which the diol diastereomers separated. Ir: 3650-3040 (very broad), 2980, 2960, 2940, 1465, 1380, 1330, 1150, 1115, 1080, 1060, 1040, 1010, 965, 930, 900, 855, and 830 cm⁻¹; nmr (CDCl₃): δ 0.75-2.7, overlapping multiplets, 10H, containing 0.94 (perturbed triplet, J = 6.5 Hz, 3H, -CH₂CH₃); and a pair of doublets

(J = 6.0) at 1.20 and 1.23 (CHOH-CH₃ of each of diastereomeric diols); 2.86 (s, 2H, -OH); 3.6-4.4 (m, 2H, -CHOH-).

(+)-2,4-Dibromohexane (54). Bromination was accomplished by a modification of the procedure of Schaefer et al.⁵⁷ Into a flamed out 1ℓ three-necked flask fitted with mechanical stirrer, reflux condenser, addition funnel, and N₂ inlet was placed 205.3 g (0.778 mol) triphenylphosphine in 340 ml acetonitrile (distilled from P₂O₅). With the reaction flask cooled to 0° C, 121.5 g (0.76 mol) of bromine was added dropwise with stirring. The reaction was then returned to room temperature and 45.0 g of the diastereomeric diol mixture 53 in 47.5 ml acetonitrile was added over 10 minutes, during which time the reaction warmed to 50-60°C and all solids dissolved. The reaction was cooled to room temperature and stirred for 3/4 hr.

Most of the acetonitrile was removed at aspirator pressure, leaving a semi-solid white residue in the reaction flask. As this material was then heated to 120-140°C at 0.5 mm, the dibromide product distilled off leaving behind a white solid triphenylphosphine oxide residue. (Liquid nitrogen traps must be used in this procedure to protect the vacuum pump from the large quantities of HBr evolved.) The crude product was dissolved in 120 ml ether, washed in succession with saturated aqueous sodium bicarbonate and sodium chloride solutions, and dried over magnesium sulfate.

The ether was distilled off at atmospheric pressure, after which the mixture of dibromide diastereomers was distilled quickly at

reduced pressure (b.p. 43-45°C at 1 mm) to give 64.9g of product (69.7% yield). Extensive heating was avoided since this is known to cause diastereomeric interconversion, which would lead to racemization in the active series.⁶⁶

The two diastereomeric dibromides were found to separate cleanly on several vpc columns: e.g., column E (160°C, 100 ml/min), column A (140°C, 100 ml/min). Later column K (150°C, 100 ml/min) was found to give the best separation. The two diastereomers, which were formed in a (2R,4R):(2R,4S) ratio of 2.8:1, were separated by preparative vpc, and the following spectra were obtained: ir of (+)-(2R,4R): 3000, 2940, 1467, 1459, 1419, 1384, 1298, 1240, 1213, 1168, 1135, 1176, 982, 974 and 889 cm^{-1} ; nmr of (+)-(2R,4R): δ 1.08 (perturbed triplet, $J = 7.0$, 3H, $-\text{CH}_2\text{CH}_3$); 1.6-2.24 (m, 4H, $-\text{CH}_2$); 1.78 (d, $J = 7.0$, 3H, $-\text{CHBr}-\text{CH}_3$); 3.90-4.56 (m, 2H, $-\text{CHBr}-$). Ir of (+)-(2R,4S): 3000, 2940, 2960, 1467, 1459, 1384, 1294, 1270, 1242, 1208, 1179, 1132, 1009(ω), 999(ω), 987(ω), 907, and 871 cm^{-1} ; nmr of (+)-(2R,4S): δ 1.07 (perturbed triplet, $J = 7.0$, 3H, $-\text{CH}_2\text{CH}_3$); 1.53-2.05 (m, 2H, $-\text{CH}_2-$); 1.72 (d, $J = 7.0$, 3H, $-\text{CH}_3$); 2.05-2.76 (m, 2H, $-\text{CH}_2-$); 3.8-4.4 (m, 2H, $-\text{CHBr}-$).

(+)-Trans-3-ethyl-5-ethylprazolidine (55T). After conversion of the dibromide diastereomer mixture to a cis-trans mixture of pyrazolidines by the general procedure described below, many attempts were made to effect separation of the cis and trans isomers. Similar attempts were made in the next step to separate the cis and trans pyrazoline isomers. These attempts were uniformly unsuccessful, in

part due to the extreme sensitivity of both the pyrazolidines and pyrazolines to metal vpc columns; all work with these compounds was performed on glass vpc columns using injector and detector temperatures of 100°C. In order to produce the individual cis and trans products, separation of the dibromide diastereomers was accomplished first by preparative vpc (column A, 140°C, 100 ml/min) and then each dibromide diastereomer was carried on to pyrazolidine (and pyrazoline) separately.

Although attempts were made to follow Crawford's procedure³⁹ for conversion of 1,3-dibromides to pyrazolidines, no significant extent of reaction was observed in the present case under Crawford's conditions. The following procedure was finally found to be effective:

Into a 10 ml round bottomed flask fitted with two rubber serum caps and magnetic spinbar and flushed with Ar were placed 1.64 ml 98% aqueous ethanol and 0.5 ml (15.8 mmol) 97⁺% anhydrous hydrazine. The reaction flask was cooled in an ice bath and 1.02g (4.18 mmol) (+)(2R,4R)-54 syringed in slowly with stirring. The reaction was then heated to 60°C with continued rapid stirring and checked by vpc (column F, 100°C, 100 ml/min) at regular intervals. After 5 days, the reaction was essentially complete although a small amount of starting material was still visible in vpc trace. During the course of the reaction, an oily lower layer was observed to separate out ($N_2H_4 \cdot HBr$); the reaction flask was cooled to 0°C and stirring continued until this oily lower layer crystallized.

The reaction mixture was filtered and the residual solid washed twice with small portions of ethanol. The combined ethanol

solutions were placed over 0.5g crushed KOH in the refrigerator for 2-3 hours during which time a KBr precipitate formed and settled. The solution was again filtered and the solid washed with small portions of ethanol.

Most of the ethanol was distilled off at 40 mm pressure and the remaining solution was vacuum transferred to leave behind a white solid residue. (+)-55T was isolated from the solution by preparative vpc (column F, 100°C, 100 ml/min); 158 mg (33.5% yld) of product was collected. Ir: 3660, 3300 (v. broad); 2970, 2930, 2890, 1620(ω), 1455, 1440, 1410, 1380, 1320, 1065, 1025, 805 cm^{-1} ; nmr (CDCl_3): δ 1.08 (t, 3H, ethyl CH_3); 1.67 (five line pattern, 2H, ethyl- CH_2 -), 1.08-1.67 (m, 5H, $-\text{CH}_2-$, $-\text{CH}_3$); 3.19 (seven line pattern, 2H, $-\text{CH}-$); 3.93 (s, 2H, $-\text{NH}$).

(+)-Trans-3-ethyl-5-methyl-1-pyrazoline (10T). It was observed that the bubbling of oxygen through the nmr solution of (+)(55T) caused gradual conversion of the pyrazolidine to the corresponding pyrazoline. This procedure was used for a small scale preparation of the trans pyrazoline. (For a procedure more suitable in larger scale reactions: see the preparation of (+)-10T below). The nmr solution was thus left stirring overnight in a stoppered container under O_2 atmosphere. The product (+) 10T was then isolated by preparative vpc (column F, 100°C, 100 ml/min). Ir: 2970, 2950, 2890, 1710, 1460, 1385, 1380, 1315, 1190, 1140, 1130, 970, and 895 cm^{-1} ; nmr (CDCl_3): δ 1.01-2.2 (m, 4H, $-\text{CH}_2-$); 1.01 (t, $J = 7.0$, 3H, ethyl CH_3); 1.34 (d, $J = 7.0$, 3H, $-\text{CH}_3$);

4.52 (seven line pattern, 2H, -CH-). The nmr showed no detectable amount of the cis pyrazoline (10C) described below.

(+)-Cis-3-ethyl-5-methylpyrazolidine (55C). The cis pyrazolidine was prepared from (+)(2R,4S)-54 using the same procedure as in the trans case. Into a dry, Ar flushed 10 ml round bottomed flask fitted with two rubber serum caps and a magnetic spinbar were placed 0.9 ml 98% aqueous ethanol and 0.275 ml (8.18 mmol) 97+% anhydrous hydrazine. The reaction flask was cooled to 0°C and 0.553g (2.27 mmol) (+)(2R,4S)-54 syringed in. The reaction was stirred at 60°C for 4 days, by which time it was essentially complete, although small amounts of starting material could still be seen in the vpc trace.

Workup was accomplished as in the trans case and preparative vpc (column F, 105°C, 100 ml/min) afforded a sample of pure (+) 55C: ir: 3400 (v. broad), 2960, 2920, 2870, 1630(?), 1450, 1375, 1330, 1235, 1220, 970 and 900 cm^{-1} ; nmr (CDCl_3): δ 0.7-3.4, series of badly split multiplets, 12H; 3.7 (s, 2H, -NH).

(+)-Cis-3-methyl-5-ethyl-1-pyrazoline (10C). The cis pyrazolidine proved less amenable to the oxygen oxidation used in the trans case. In this case, $\text{Cu}(\text{OAc})_2$ was added a few mg at a time to the stirred nmr solution of (+)(55C) until vpc analysis (column F, 100°C, 100 ml/min) showed reaction to be essentially complete. Product pyrazoline was vacuum transferred off of the solid residue and (+)-10C isolated from the resulting solution by preparative vpc (column F, 105°C, 100 ml/min). (This procedure was not very satisfactory; for a

better procedure more applicable to larger scale reactions, see the preparation of (+)-10T below.) Nmr (CDCl₃): δ 0.37-0.87 (d of t, J = 12.5, 9.0, 1H, one C⁴ H); 1.07 (t, J = 7.0, 3H, ethyl CH₃); 1.53 (d, J = 7.0, 3H, CH₃); 1.65-2.30 (m, 3H, ethyl CH₂ and one H from C⁴); 4.12 (seven line pattern, 2H, -CH). The nmr showed no detectable amount of the trans pyrazoline (10T) described above. See the text for a discussion of the assignment of shifts and stereochemistries of the pyrazoline isomers.

(+)-Cis- and trans-1,1-dibromo-2-ethyl-3-methylcyclopropane
(56C and 56T).

A. Preparation of potassium-t-butoxide. 100 ml of t-butanol (distilled from potassium onto molecular sieves) and 4.04g of potassium (oxide surface layer cutoff immediately prior to weighing) were placed in a flame dried 250 ml round bottomed flask fitted with a reflux condenser and N₂ inlet. The potassium was allowed to react slowly with the alcohol, and toward the end of the reaction external heating was applied to complete the reaction, giving a clear colorless solution. The t-butanol was then slowly pulled off with a dry ice protected vacuum pump to leave a white powder which was heated gently with a heat gun at 0.01 mm to drive off any remaining alcohol.

B. Addition of dibromocarbene to cis- and trans-2-pentene.
 A flame dried 200 ml three-necked flask was fitted with magnetic stirrer, dry ice condenser, N₂ inlet, and thermometer and connected with a teflon "gouch tube" to a flask containing 10.4g (0.093 mol) potassium t-butoxide. The reaction flask was charged with 23.4g

(0.0927 mol) bromoform (redistilled and dried under Na_2SO_4) and 21.4g (0.3 mol) Phillips Petroleum "2-pentene" (roughly a 1.6:1 cis:trans mixture). The reaction flask was cooled to -20°C and the potassium t-butoxide added in portions over a two hour period, during which time the reaction mixture turned a progressively darker brown color. (Some difficulty was encountered in the stirring; a mechanical stirrer would have provided better mixing.) The reaction was then allowed to warm to 10°C over 3 hrs.

The reaction mixture was taken up in 150 ml pentane and the resulting solution washed in succession with water, 0.1 N aqueous HCl, and saturated aqueous NaCl solution, and dried over magnesium sulfate. Most of the pentane and unreacted pentenes were distilled off through a 20 cm Vigreux column. A crude fractionation was performed at 7 mm pressure to separate the remaining C_5 material and unreacted bromoform from the dibromocyclopropane products (b.p. $55-58^\circ\text{C}$ at 7 mm). Vpc analysis (column D, 100°C , 75 ml/min) of the 15.89g of clear colorless product showed it to contain 10% bromoform and 90% of a 5:1 mixture of cis and trans 56. This crude product was used in the reduction step without further purification.

(+)-Cis- and trans-1-ethyl-2-methylcyclopropane (11C and 11T).

Reduction of the dibromocyclopropane was carried out using a modification of the procedures of Bergman¹⁶ and of Seyferth et al.⁵⁸ Tri-n-butyltin hydride was prepared by the method of Kuivila⁵⁹ in 93% yield.

Into a 25 ml three-necked flask fitted with magnetic stirrer, N_2 inlet and serum cap was placed 6.0g (20.6 mmol) tri-n-butyltin

hydride. The reaction was then cooled to 0°C and 2.04g (8.43 mmol) of the mixture of 56C and 56T (with approximately 10% bromoform) was syringed in dropwise. The reaction was stirred for 1 hr. at 0°C and for 3 days at room temperature.

After 3 days, vpc analysis (column A, 100°C, 75ml/min) showed traces of bromoform but no remaining dibromocyclopropanes. The reaction flask was connected to a -78°C trap and gradually warmed to 60°C at aspirator pressure to give 0.35g (49.4% yield) of a 4.7:1 mixture of 11C and 11T, respectively. The two isomers were separated by preparative vpc (column G, 60°C, 75 ml/min; cis has longer retention time) and the following spectra obtained. Comparison with spectra of authentic samples⁵ confirms the identification of these compounds.

11T: ir: 3070, 3000, 2960, 2930, 2880, 1467, 1458, 1381, 1309 - 1080, 1025, 931, 885, 869 cm⁻¹; nmr (CCl₄): δ 0-0.53, complex multiplet, 4H (cyclopropyl protons); 0.77 to 1.38, complex multiplet, 8H (Me,Et).

11C: ir: 3070, 3000, 2970, 2950, 2890, 1470, 1459, 1395, 1379, 1310, 1175, 1110, 1080, 1025, 990, 970, 920, 895, 850 cm⁻¹; nmr (CCl₄): δ, -0.35, complex multiplet, 1H; 0.62, complex multiplet, 3H; 1.18, complex multiplet, 8H.

II. Optically active undeuterated pyrazoline synthesis.

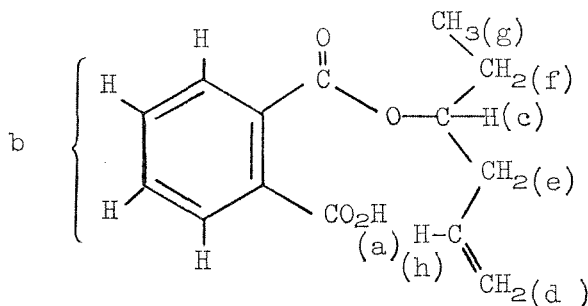
(-)(R)-1-Hexen-4-ol (52)

A. 1-Hexen-4-yl phthalate(57). The procedure followed was essentially that described by Ingersoll⁶⁰ with some modifications. Into a 500 ml round bottomed flask fitted with reflux condenser, large magnetic stirring bar, and a nitrogen inlet were placed 82.2g (0.83 mol)

of racemic 52 and 120g of phthalic anhydride. The reaction was heated for 18 hrs. at 105-110°C to give a viscous yellow oil, the nmr of which indicated the presence of unreacted starting material. 5g more of phthalic anhydride was added, and the reaction was stirred for an additional 8 hrs.

The crude phthalate half ester 57 was then added to a solution of 122g (1.135 mol) of sodium carbonate in 2.5l of water and stirred without warming until all the oil had dissolved. This slightly cloudy solution was extracted in succession with benzene and hexane to remove any unreacted starting materials. 200 ml of conc. HCl (2.32 mol) were added slowly with stirring, causing the phthalate half ester to precipitate as a light yellow oil.

The oil was then taken up in chloroform, washed with saturated aqueous NaCl solution and dried over Na₂SO₄. The chloroform was then stripped off on a rotovap and the resulting pale yellow oil pumped on at 2 mm for 45 min. In this and other preliminary runs, no successful way of inducing this oil to crystallize was ever found. Nmr (CCl₄):
 δ 0.97 (t, J = 6.5, 3H, H_g); 1.66 (q, J = 6.5 Hz, 2H, H_f); 2.44 (t, J = 6.0 Hz, 2H, H_e); 4.8-5.3 (m, 3H, H_c and H_d); 5.4-6.2 (m, 1H, H_h); 7.3-7.9 (m, 4H, H_b); 11.76 (s, 1H, H_a).



B. Brucine salt formation and recrystallization. 111.8g (0.45 mol) of the above oil was dissolved in 200 ml warm ethyl acetate. To this was slowly added a slurry of 177.2g brucine (0.45 mol) in 400 ml hot ethyl acetate. The resulting mixture was placed on a steam bath and ethyl acetate was added until all solids had dissolved. The solution was allowed to cool gradually to room temperature, during which time light tan mushroom shaped crystal formations were observed to form. After several hours at room temperature, the solution was placed in the refrigerator overnight. The crystals were filtered, crushed, and washed quickly with cold ethyl acetate. This recrystallization was repeated twelve more times to give 139.8 of brucine salt (0.218 mol).

C. Decomposition of brucine salt. The brucine salt was dissolved in the minimum amount of hot ethanol and added to 698 ml of 0.725 N HCl (0.505 mol). The phthate ester separated from the solution as a pale yellow oil, which again resisted all attempts at crystallization. The aqueous solution was extracted with ether, which was added to the original oil, causing brucine dissolved in the oil to precipitate. Sufficient 1N HCl was added to dissolve the brucine, after which this aqueous solution was itself extracted with ether. The combined organic layers were washed in succession with 1N HCl and saturated aqueous NaCl solution and dried over Na_2SO_4 . The ether was removed under aspirator pressure, and the resulting oil was pumped on for 1 hr. at 10 mm and $\frac{1}{2}$ hr. at 2 mm.

Saponification and isolation of 52 were accomplished using

the "most beautiful steam distillation setup" Ben-Avi Weissman has ever seen.⁶¹ The active phthalate half ester was placed in a 500 ml 3N flask to which was added a solution of 21.76g (0.544 mol) sodium hydroxide in 65.3 ml water. The solution was placed in an oil bath preheated to 95-100°C and steam was introduced to effect the steam distillation. A lighter organic layer was soon observed to form. The distillation was continued until no organic layer remained in the reaction flask and the distillate in the condenser had lost its characteristic milky appearance. The lower layer of the distillate was saturated with NaCl; the organic layer was then separated and dried over K₂CO₃ to give 19.46g (0.195 mol) of alcohol > 99% pure by vpc (column A, 105°C, 100 ml/min). The following rotations were obtained: $[\alpha]_D^{25} - 0.188^\circ$, $[\alpha]_{436}^{25} - 0.873^\circ$, $[\alpha]_{365}^{25} - 2.11^\circ$ (neat); $[\alpha]_D^{25} + 1.57$ (c=0.084 in CHCl₃).

Hydrogenation to optically active 3-hexanol (vide infra) shows that this sample of 52 is 38.4% optically pure and has the R configuration. Attempts at an alternate determination of optical purity using optically active shift reagent were unsuccessful.⁶²

(+)-3-Hexanol (76). Since the only literature values for $[\alpha]_D$ max for 3-hexanol involve neat readings, and since the smallest polarimeter cells available had a capacity of approximately 1 ml, it was necessary to dilute the optically active 76 produced by the hydrogenation of (-)-52 (vide infra) with a known amount of racemic 76 in order to obtain a neat reading (which could then be corrected for the dilution factor). This racemic 3-hexanol was produced by a conven-

tional LAH reduction of a 3-hexanone sample (Aldrich) already on hand.

Into a dried 500 ml flask fitted with addition funnel, mechanical stirrer, and nitrogen inlet, was placed 3.83g (0.40 equivalents) of LAH in 116 ml anhydrous ether (fresh can). The flask was cooled to -20°C and 15.94g (0.16 mol) 3-hexanone in 32 ml anhydrous ether was added dropwise over $\frac{1}{2}$ hr. The reaction was allowed to stir at -20°C for an additional 45 min. and then for 2 hrs. at room temperature. The reaction was cooled to 0°C , diluted with 400 ml anhydrous ether and quenched with saturated aqueous Na_2SO_4 solution. The solution was filtered and dried over Na_2SO_4 .

The ether was distilled off at atmospheric pressure through a 24" Vigreux column; the product was then distilled through a 6" Vigreux column at reduced pressure (b.p. $59-60^{\circ}\text{C}$ at 30 mm) to give 15.08g of (+)-76 (92.6% yield). Polarimeter readings showed that this material was, as expected, completely racemic.

(-)-(R)-3-Hexanol (76). (-)-(R)-52 was subjected to atmospheric pressure hydrogenation to give 3-hexanol, whose absolute configuration and maximum rotation are known.¹¹ In a 10 ml flask were placed 0.2225g (2.225 mmol) (-)-52 ($[\alpha]_{\text{D}}^{25} - 0.188$, neat) and 48 mg PtO_2 in 3 ml ethyl acetate. The reaction was stirred at room temperature until hydrogen uptake ceased (70 min.), at which point vpc analysis (column A, 80°C , 60 ml/min) showed the reaction to be complete. The product 3-hexanol was purified by preparative vpc (column A) to give 0.1695g of optically active product.

This material was placed in a 1 ml volumetric flask and

sufficient racemic 3-hexanol (vide supra) was added to total 1.00 ml (0.6216g racemic 3-hexanol). The following optical rotations were obtained for this material: $[\alpha]_D^{25} - 0.588^\circ$; $[\alpha]_{436}^{25} - 1.114$, $[\alpha]_{365}^{25} - 1.666$. When these values are then corrected for the dilution with racemic 3-hexanol, the following values are obtained for the original active sample derived from the (-)-52: $[\alpha]_D^{25} - 2.74^\circ$, $[\alpha]_{436}^{25} - 5.20^\circ$, $[\alpha]_{365}^{25} - 7.76^\circ$. Based on $[\alpha]_D^{18}$ max $- 7.13^\circ$ for (R)-3-hexanol,⁴² this sample of (-)-76, and thus the (-)-52 produced above, must have optical purities of 38.4% and must have the R configuration.

(+)-(S)-1-hexen-4-ol (52). The ethyl acetate was stripped off the mother liquor from the above brucine salt recrystallizations to give approximately 120g (0.187 mol) of brucine salt. This salt was decomposed to the phthalate half ester, which was in turn subjected to saponification and steam distillation as described above to give 14.92g of (+)-52. Subsequent hydrogenation to (+)-(S)-3-hexanol showed this material to be 35.8% optically pure.

(+)-(S)-3-hexanol (76). (+)-52 (243.5 mg) was hydrogenated as described above to give, after vpc purification, 166.2 mg of (+)-76, whose rotation was obtained as described for (-)-76 above: $[\alpha]_D^{25} + 2.55^\circ$, $[\alpha]_{436}^{25} + 4.96$, $[\alpha]_{365}^{25} + 7.40$. Based on $[\alpha]_D^{18}$ max $- 7.13^\circ$ for (-)-(R)-3-hexanol,⁴² this material, and the (+)-1 from which it was derived, must be 35.8% optically pure and must have the S configuration.

Optically active 2,4-hexanediol (53). A diastereomeric mixture of the optically active 2,4-hexanediols having the R configuration at the C-4 position was produced by the oxymercuration-hydroboration procedure described above for the racemic series. Since no simple means was ever found for separation of the diastereomers, no rotations were obtained for the individual diastereomers.

(+)-(2S,4S)-2,4-Dibromohexane (54) and (-)-(2R,4S)-2,4-dibromohexane (54). The above mixture of optically active diol diastereomers (53) was converted to the corresponding mixture of dibromide diastereomers by the procedure described above in the racemic series. The dibromide diastereomers were separated by careful preparative vpc (column A, 10'10% DEGS, 40°C, 100 ml/min). About 3g of the (2S,4S) and 1g of the (2R,4S) isomer were collected, providing a sufficient amount of (2S,4S) to carry on the reaction sequence. Vpc analysis showed the (2S,4S) to be free of any (2R,4S) contamination, while the (2R,4S) sample contained several percent (2S,4S). The following rotations were obtained: (2S,4S) - $[\alpha]_D^{25} + 27.7^\circ$ (neat); (2R,4S) - $[\alpha]_D^{25} - 0.632^\circ$ (c=0.0372 in CHCl₃).

(+)-(3R,5R)-Trans-3-ethyl-5-methyl-1-pyrazoline (10T). The 3.2g of vpc pure (+)-(2S,4S)-54 was then converted to (3R,5R)-trans-3-ethyl-5-methylpyrazolidine (55T) by the procedure described above in the racemic series, except that in this case the reaction was allowed to proceed for 9 days 18 hrs. to ensure complete reaction. The workup was also done as above up to the distillation of the final workup

solution. Here the pressure was reduced to the point where the boiling point of ethanol was roughly 30°; ethanol was distilled off under these conditions until vpc analysis (column F, 100°C, 75 ml/min) showed the solution remaining in the pot to be roughly 30% pyrazolidine and 70% ethanol. This mixture was then vacuum transferred at 0.02 mm and the resulting solution used directly in the oxidation step.

A 100 ml flask was next fitted with a magnetic stirring bar and an addition funnel protected with a drying tube. The flask was charged with 5.97g (2.75 mmol) red mercuric oxide and 3.9g anhydrous Na₂SO₄ (2.74 mmol) in 27 ml reagent grade pentane. The flask was cooled to 0°C and, with rapid stirring, the above pyrazolidine-ethanol solution (theoretically 1.31 mmol pyrazolidine) was added dropwise over 5 min. The mercuric oxide quickly blackened as the pyrazolidine was added. The reaction was allowed to stir for an additional 30 min at 0°C.

The reaction mixture was then filtered and the solid residue triturated twice with pentane. Most of the pentane was then distilled off at atmospheric pressure through a 20 cm Vigreux column, and the pure pyrazoline was isolated from the remaining solution by preparative vpc (column F, 100°C, 75 ml/min) in an overall yield of 31.9% based on (+)-(2S,4S)-54. The following optical rotations were obtained for this material (c=.019 in n-heptane): $[\alpha]_D^{25} + 140.5^\circ$, $[\alpha]_{436}^{25} + 331^\circ$, $[\alpha]_{365}^{25} + 763^\circ$. Based on the 38.4% optical purity of (-)-(R)-52, this suggests that for (+)-(3R,5R)-10T, $[\alpha]_D^{25} \text{ max} = + 366^\circ$. Nmr analysis shows no detectable contamination of this material with the cis pyra-

zoline isomer; vpc also shows no detectable contamination.

III. An approach to optically active 3-d-3-ethyl-5-methyl-1-pyrazoline (12)

(+)-4-d-1-Hexen-4-ol (4-d-52)

A. (+)-1-Hexen-4-one (63). Jones reagent was prepared by dissolving 100g CrO₃ in 714 ml H₂O, cooling to 0°C and adding slowly with stirring 90 ml of conc. H₂SO₄; this solution was then placed in the refrigerator. A 6l three-necked flask equipped with overhead stirrer, addition funnel, thermometer to measure solution temperature, and a 10-15°C cooling bath was charged with 75g (0.75 mol) 52 in 1800 ml acetone. To this solution was added dropwise with vigorous stirring 650 ml of the precooled Jones reagent. The course of the reaction was followed by vpc (column A, 110°C, 100 ml/min) during the addition, and the reaction appeared to be complete after 20 min. of additional stirring.

The excess Jones reagent was quenched by gradual addition of isopropanol (more than 10 ml required for disappearance of the orange color; solution may not have been acidic enough)⁶³ after which the organic layer was decanted off the Cr salts. The solution was diluted with 2.3l saturated aqueous NaCl solution, and sufficient NaCl was added to saturate the aqueous layer. The aqueous layer was extracted thoroughly with pentane (total ~ 1100 ml), and the combined organic layers washed with cold saturated aq. NaHCO₃ solution (in turn extracted with pentane) and saturated aqueous NaCl solution. The combined organic layers were dried over Na₂SO₄.

Distillation was accomplished at as low a temperature as possible, since previous work had shown that prolonged heating tended to cause gradual formation of a new product, presumably the α,β -unsaturated ketone. The pentane and much of the acetone were boiled off through a Vigreux column; with the pot never higher than 45°C , the pressure was gradually lowered to distill off the remaining acetone. After a rather large forerun, the product was rapidly distilled (b.p. $56\text{--}57^\circ\text{C}$ at 55 mm). The forerun, which contained large amounts of product, was redistilled at reduced pressure to recover more product. Because of the rapid distillation procedure, the combined distillates proved to contain a large amount of isopropanol. Based on vpc analysis and correction for response factors, the final mixture contained roughly 38.5g 69 (52.5% yield) and 10.6g isopropanol, but only traces of the starting material (52). This mixture was subjected to LiAlD_4 reduction without further purification.

A sample of 69 was purified by preparative vpc (column A, 105°C , 75 ml/min) for spectral purposes: ir: 3090, 2990, 2920, 2890, 1720, 1640, 1475, 1430, 1415, 1385, 1355, 1145, 1110, 1050, 1030, 995 and 925 cm^{-1} ; nmr (CCl_4): δ 1.01, triplet ($J = 7.5$), $3\text{H}(-\text{CH}_2\text{CH}_3)$; 2.36, quartet ($J = 7.5$), $2\text{H}(-\text{CH}_2\text{CH}_3)$; 3.06, doublet ($J = 7.0$) with further fine splitting (approximately doublet of triplets), $2\text{H}(\text{CH}_2=\text{CH}-\text{CH}_2-)$; 4.8-5.25, complex multiplet, $2\text{H}(\text{CH}_2=\text{C}-)$; 5.6-6.25, complex multiplet, $1\text{H}(\text{CH}_2=\text{CH}-)$.

B. LiAlD_4 reduction. This procedure was first carried

out using LAH to show that no double bond migration occurs during the reduction.

Into a 1ℓ three-necked flask equipped with overhead stirrer, reflux condenser, addition funnel, and N₂ inlet was placed 7.0g (0.1667 mol, 0.667 equiv.) IAlD₄ in 250 ml anhydrous ether (distilled from LAH). The reaction flask was cooled to -25°C and a solution of 49.1g of the above 69 isopropanol mixture (roughly 0.57 mol total, 0.39 mol 69) in 75 ml anhydrous ether was added dropwise over 85 min. The reaction was allowed to warm slowly to 0°C over 3 hrs. with stirring. The reaction was diluted with 100 ml additional anhydrous ether, and 25 ml of saturated aqueous Na₂SO₄ solution was added dropwise. Toward the end of this process, the solid aluminum salts separated out as a white granular precipitate. The solution was then filtered, the solid residue washed twice with ether, and the combined ether solutions dried overnight over Na₂SO₄.

The bulk of the ether was distilled off at atmospheric pressure through a 24 cm Vigreux column. The residue was fractionated at 60 mm to give 44.0g of a mixture containing roughly 87% by weight 4-d-52 (b.p. 68°C) and 13% isopropanol. A sample of 4-d-52 purified by vpc (column K, 125°C, 100 ml/min) showed the following nmr: 0.93 (t, J = 6.5, 3H, ethyl CH₃); 1.43 (perturbed triplet, 2H, ethyl CH₂); 1.97-2.36 (m, 2H, allylic CH₂); 5.4-6.2(m, 1H, vinyl CH); nmr shows no detectable signal at δ 3.48 corresponding to -CHOH.

Attempted resolution of 4-d-1-hexen-4-ol (4-d-52). Resolution of 4-d-52 was attempted using the same procedure as described above for the undeuterated material. An initial attempt was made using the 4-d-52 isopropanol mixture produced in the previous step. Unfortunately, the brucine salt phthalate half ester of the isopropanol which was also formed in this process proved not only to be very much less soluble than the brucine salt of the phthalate half ester of 4-d-52, but also to alter the entire pattern of crystallization. No satisfactory resolution was obtained in this procedure, although it was possible to separate most of the brucine salt of the phthalate half ester of isopropanol by successive fractional crystallizations. The 4-d-52 was recovered from the mother liquor salts by decomposition of the brucine salt and saponification-steam distillation as described above in the undeuterated series; this 4-d-52 still contained approximately 3% isopropanol, which will be completely removed before the deuterated alcohol is resubjected to the resolution procedure.

IV. Approaches to 5-d-3-ethyl-5-methyl-1-pyrazoline (13)

The following sequence was first carried out using racemic starting material and NaBH_4 reduction to show that the diastereomers of 2,4-dibromohexane could be produced by this route.

(+)-(R)-4-Bromo-1-hexene (65). Again the procedure of Schaefer et al.⁵⁷ was followed. Into a dry 300 ml three-necked flask equipped with overhead stirrer, addition funnel, N_2 inlet and reflux, condenser was placed 39.9g (0.154 mol) triphenylphosphine in 131 ml acetonitrile

(dried over molecular sieves). The flask was cooled to 0°C and 24g (0.15 mol) bromine was added dropwise over 20 minutes. The reaction was then returned to room temperature and a solution of 14.92g (0.149 mol) of (+)-(S)-1-hexen-4-ol (35.8% optically pure, vide supra) in 18.75 ml dry acetonitrile was added over 10 min., during which time the reaction warmed to 50-60°C and all solid dissolved to give a clear yellow solution. The reaction was cooled to room temperature and allowed to stir for an additional 30 min.

Most of the acetonitrile was evaporated at reduced pressure and collected in a 0°C receiver. The reaction flask was slowly heated to 100°C at 0.07 mm to drive a second fraction containing the remaining acetonitrile and the product into a dry ice cooled receiver. (Liquid nitrogen traps must be used in this process to protect the vacuum pump from the HBr evolved in the distillation.) The acetonitrile first fraction was saturated with water and extracted with 7 × 5 ml pentane washes to allow recovery of the relatively small amount of product in this fraction.

The second fraction was dissolved in 50 ml pentane. The combined pentane solutions were washed three times with water and once with saturated aqueous NaCl solution, a procedure which effectively removed acetonitrile from the pentane with little loss of product. The pentane was distilled off at atmospheric pressure and the product 65 distilled at reduced pressure (b.p. 59-61°C at 48 mm) to give 17.25g (70.8% yield) of clear colorless liquid: $[\alpha]_D^{25} + 0.33^\circ$ (neat). Ir: 3085, 2945, 2895, 2855, 1642, 1463, 1457, 1435, 1383, 1293, 1226, 1193, 1143,

1057, 995, 922 and 891 cm^{-1} ; nmr: δ 1.04, triplet ($J=7$), $3\text{H}(-\text{CH}_2\text{CH}_3)$; 1.82, multiplet (approximately doublet of quartets), $2\text{H}(-\text{CH}_2\text{CH}_3)$; 2.57, triplet ($J=7$), $2\text{H}(\text{H}_2\text{C}=\text{CH}-\text{CH}_2-)$; 3.88, 5 line pattern ($J \sim 7$), $1\text{H}(-\text{CHBr}-)$; 4.8-5.25, multiplet, $2\text{H}(\text{CH}_2=)$; and 5.4-6.2, multiplet, $1\text{H}(\text{CH}_2=\text{CH}-)$.

Optically active 4-bromo-2-hexanol (66). Hydration of the double bond of (+)-(R)-65 to give a diastereomeric mixture of bromoalcohols having the R configuration at the C-4 position was accomplished by Brown's oxymercuration-hydroboration procedure.⁴⁰ Into a 1ℓ three-necked flask fitted with mechanical stirrer and addition funnel was placed 33.2g (10⁴ mmol) mercuric acetate in 10⁴ ml water. To this was added 10⁴ ml THF causing the formation of a bright yellow suspension. Then 16.9g (10⁴ mmol) of (+)-(R)-65 was added dropwise, during which time (~ 1 min.) the yellow color of the solution disappeared. The reaction was allowed to stir for an additional 35 minutes at room temperature, after which it was cooled to 0°C and 10⁴ ml 3N NaOH was slowly added. Finally 10⁴ ml of a solution 0.5M in NaBH_4 and 3N in NaOH was added dropwise causing the solution immediately to turn black. The solution was allowed to stir for 15 min. more at 0°C.

The reaction mixture was saturated with NaCl and the organic layer separated; the aqueous solution was extracted with THF and these washings were added to the original organic layer and dried over Na_2SO_4 . Vpc inspection (column E, 165°C, 100 ml/min.) showed the

presence of some diol (53) in the product mixture. This was removed by the following procedure. THF was distilled off at reduced pressure (b.p. THF $\sim 32^{\circ}\text{C}$) until 75 ml of solution remained. This solution was diluted with 75 ml pentane and washed with 150 ml H_2O . The aqueous solution was extracted twice with 20 ml pentane and the combined organic solutions, which were now shown by vpc to be free of diol, were dried over Na_2SO_4 . Most of the pentane and THF was then distilled off and the residue subjected to a crude fractionation to give 11.7g of the diastereomeric diol mixture (b.p. $40\text{--}45^{\circ}\text{C}$ at 0.4 mm) which still contained small amounts of solvent and other low boiling impurities. This mixture was subjected to oxidation without further purification; no attempt was made to separate the diastereomers.

(R)-4-Bromo-2-hexanone (67). Oxidation of the optically active mixture of bromoalcohol diastereomers was carried out by a combination of the methods of Djerassi⁶⁴ and Meinwald.⁶⁵ Djerassi's standard solution of oxidizing agent was made by dissolving 26.72g CrO_3 in 23 ml conc. H_2SO_4 and diluting with water to a final volume of 100 ml. This solution was then precooled in the refrigerator before use.

A 200 ml three-necked flask equipped with addition funnel, mechanical stirrer and rubber serum cap was charged with a solution of 11.7g of the optically active diastereomeric bromoalcohol mixture (66) produced above dissolved in 39 ml acetone. The flask was cooled to 0°C and 18.8 ml of the precooled Jones reagent solution was added

dropwise with vigorous stirring; stirring was continued for an additional 15 min. Vpc analysis of an aliquot at this point⁶⁵ showed complete disappearance of starting material (column A, 145°C, 100 ml/min.). (Vigorous stirring is necessary to ensure complete reaction.)

The reaction was allowed to come to room temperature and sodium bisulfite was added in small portions until the orange color characteristic of chromic acid had completely disappeared from the upper layer of the reaction mixture. This upper layer was decanted and the viscous residual dark green chromium salts were extracted once with 30-60 petroleum ether. Addition of this pet ether wash to the upper layer caused separation of more chromium salts, which were combined with the original salts, diluted with an equal volume of water, and extracted three times with pet ether. The combined organic solutions were then washed with saturated aqueous NaCl, cold saturated aqueous NaHCO₃, and saturated aqueous NaCl before being dried over Na₂SO₄.

The acetone and pet ether were stripped off at reduced pressure and the crude product was subjected to NaBD₄ reduction without further purification. Vpc analysis of compound 67 proved to be very difficult due to its instability on vpc columns, presumably due to the facile loss of HBr to give an α,β -unsaturated ketone. Extensive heating of this compound was avoided to reduce the possibility of such decomposition on a larger scale.

2-d-4-Bromo-2-hexanol (2-d-66). Into a 250 ml flask fitted with magnetic stirrer, addition funnel, and N₂ inlet was placed the sample

of optically active 67 produced in the preceding step (theoretical max 65 mmol) in 119 ml absolute EtOH. The flask was then cooled to 0°C and a solution of 1.0g sodium borodeuteride (23.9 mmol) in 23.5 ml absolute EtOH was added dropwise with stirring. The reaction was then stirred for 70 min. at 0°C, at which point vpc analysis (column A, 160°C, 100 ml/min) shows no remaining starting material.

The reaction was quenched by dropwise addition of 2.41 ml glacial acetic acid. The reaction mixture was concentrated by the distillation of EtOH through a 20 cm Vigreux column at reduced pressure (b.p. EtOH 30-35°C). When approximately 20 ml of solution remained, the reaction mixture was dissolved in 75 ml pentane and washed in turn with water, saturated aqueous NaHCO₃, and saturated aqueous NaCl solutions. The aqueous washes were then saturated with NaCl and extracted with small portions of pentane until vpc showed no more product appearing in the pentane washes. The combined pentane solutions were dried over sodium sulfate, and the pentane distilled off at atmospheric pressure through a 20 cm Vigreux column. The residue was pumped on briefly at 0.5 mm at room temperature to remove low boiling volatiles and then vacuum transferred to give 7.069 of a 44:56 mixture (in order of increasing retention time) of the diastereomers of 4-d-66, which was carried on to the next step without further purification.

2-d-2,4-Dibromohexane (2-d-54). Again the basic procedure of Schaefer et al.⁵⁷ was used. Into a 200 ml RB3N flask fitted with overhead stirrer, addition funnel, reflux condenser, and N₂

inlet was placed 10.32g (39.3 mmol) triphenylphosphine in 34 ml acetonitrile (dried over mol sieves). The flask was cooled to 0°C and 6.2g (38.8 mmol) bromine was added dropwise. The reaction was returned to room temperature and a solution of 7.06g (38.8 mmol) of the mixture of diastereomers of 4-d-66 produced in the previous step in 4.9 ml acetonitrile was added over 2 minutes, during which time the reaction flask grew warm and all solid dissolved. The reaction was cooled to room temperature and allowed to stir for an additional 30 min.

Most of the acetonitrile was distilled at aspirator pressure leaving behind a semi-solid paste. This residue was then heated to 120-140°C at 0.2 mm to drive over the dibromide product; subsequent heating to 160°C produced no more product. (Liquid N₂ traps are necessary in this distillation to protect the vacuum pump from the HBr evolved.) The crude product was dissolved in 50 ml ether, washed with saturated aqueous NaHCO₃ and NaCl solutions, and dried over Na₂SO₄. The solution was then concentrated by distillation of the ether through a 20 cm Vigreux column at atmospheric pressure.

A sample of 2d-(2R,4R)-54 was then isolated by preparative vpc (column A, 140°C, 100 ml/min). Optical rotations taken on this material gave the following results (c=0.10 in CHCl₃): $[\alpha]_D^{25} - 0.37^\circ$, $[\alpha]_{365}^{25} - 1.24^\circ$. Since the previously prepared undeuterated (2S,4S)-54 of approximately 38.4% optical purity had $[\alpha]_D^{25} + 27.7^\circ$ (c=0.10 in CHCl₃), it was clear that somehow extensive racemization had occurred somewhere in the reaction sequence leading from the 35.8% optically pure (+)-(S)-1-hexen-4-ol to this 2-d-(2R,4R)-2,4-dibromohexane. In

any event, this sample of 54 was not of sufficient optical purity for the reaction to be carried on further.

Attempted reduction of (+)-67 with (+)-diisopinocampheylborane. Following the procedure of Varma and Caspi⁴⁵ the reduction of racemic 4-bromo-2-hexanone (67) was carried out with (+)-diisopinocampheylborane in the hope of observing asymmetric induction of optical activity in the product alcohol diastereomers (66). Had this procedure proved successful and practical, the procedure would have been repeated using a deuterated borane.

Into a flame dried 100 ml RB3N flask fitted with rubber septum, magnetic stirrer, thermometer, and N₂ inlet were placed 0.464g (12.25 mmol) sodium borohydride and 4.91g (36.2 mmol) (+)- α -pinene (Hercules) in 25.8 ml THF (distilled from LAH). The flask was cooled to 0°C and 2.03 ml (16.1 mmol) of boron trifluoride etherate was syringed in over 10 min. The reaction was then stirred for 9 hrs. at 0-2°C to produce a milky white suspension. Ketone 67 (16.1 mmol) was added via syringe over 10 min. after which the reaction was stirred for 22 hrs. at 0-2°C to give a cloudy green solution. 0.7 ml water was then added to destroy the excess hydride after which 6.44 ml of 3N NaOH was added over 15 min., during which time the solution first went clear and then clouded again. Following this, 6.44 ml 30% aqueous hydrogen peroxide was added, causing the temperature of the solution in the flask to rise to 6-7°C. The reaction mixture was then stirred for 90 min. at 40°C. The THF layer was separated and the aqueous solution was extracted with several small portions of

ether, after which the combined organic solutions were washed twice with saturated aqueous NaCl and dried over sodium sulfate.

Vpc analysis was attempted on several columns (column D, 100°C, 100 ml/min.; column J, 120°C, 100 ml/min.; column A, 145°C, 100 ml/min.; and column I, 150°C, 100 ml/min.). Only on column J could adequate separation of the diastereomers of 66 from the alcohol derived from α -pinene be achieved, and this column did not provide separation of the diastereomers themselves. Predicted boiling points suggested that separation by distillation would be extremely difficult and any contamination by α -pinene derived products would ruin attempts at determination of optical rotations.

A portion of the mixture of product alcohols was converted to the corresponding bromides by the procedure described above for (2R,4R)-54. However, no conditions could be found which would separate the α -pinene derived product(s) from the desired dibromide diastereomers. Since the procedure described above for the formation of optically active 2-d-(2R,4R)-54 seemed to be proceeding well at the time, this asymmetric reduction technique was not investigated further.

V. Attempted resolution of 54 by distillation from brucine paste

In light of the success of Skell et al.⁴⁸ in partially resolving d, l-2,3-dibromobutane (65.4% optical purity) by vacuum distillation from a brucine paste, the analogous resolution of 2,4-dibromohexane (54) was attempted as described below.

Into a 250 ml RBSN flask was placed 24.4g (0.10 mol) of a 2.8:1 mixture of racemic (2R,4R)- and (2R,4S)-2,4-dibromohexane (54); to this was slowly added with stirring 13.6g (29.3 mmol) brucine powder to give a thick paste, which was allowed to sit for three hrs. The reaction flask was then connected to a -78° trap and pumped on for 10 hrs. at 0.5 mm, during which time 8.72g of dibromide was collected. The reaction flask was then placed in a 35°C oil bath and pumped on overnight at 0.8 mm to give 11.94g more dibromide. Finally, the brucine residue was dissolved in 10% H_2SO_4 and extracted with ether to recover the remaining dibromide. No significant optical rotation was observed in any of these samples, and this approach was not pursued any farther.

Pyrolyses

Injection port pyrolyses. The pyrolyses of the individual cis and trans isomers of racemic 3-ethyl-5-methyl-1-pyrazoline (10) were performed on the injection port of a Hewlett-Packard 5750 Research Chromatograph equipped with flame ionization detector and a Hewlett-Packard 3370A Digital Integrator which provided direct read-out of peak areas. Fresh clean glass injection port liners were used in each pyrolysis. The injector port area was surrounded with glass wool to maintain temperature stability, and injector septa were changed frequently since it was observed that prolonged exposure of the rubber septa to high temperatures ($> 300^{\circ}\text{C}$) caused them to become brittle and crack. Product analyses were performed on column H (25°C , 10 ml/min.); adequate separation of all product peaks was

observed except for cis-3-hexene, which had the same retention time as cis-1-ethyl-2-methylcyclopropane; however, since cis-3-hexene is undoubtedly only a very minor product of this reaction, little error was introduced by this problem.

As expected, injection of authentic samples of the reaction products showed that no product interconversion occurred at the injector temperatures used. Each of the pyrazoline pyrolyses was carried out by injection of 1 μ l of a 10% solution of the pyrazoline in n-octane at several temperatures. Also, injection of each of the pyrazolines at an injector temperature of 100°C (well below the temperatures necessary for pyrolysis) was carried out to show that no products were arising from some sort of catalytic decomposition of the pyrazoline on the column walls or packing. Reproducibility of the product distribution at a given temperature was well within 1%. (See text for results and discussion.)

Flow pyrolyses. Flow pyrolysis of (+)-(3R,5R)-trans-3-ethyl-5-methyl-1-pyrazoline (10T, 38.4% optical purity) was carried out in an oven heated quartz tube (1.2 cm ID; 32 cm oven length; volume contained in heated section of pyrolysis tube roughly 36 cc). Auxilliary heating wires covered with asbestos wrapping were used on the quartz tube on either side of the oven to prevent condensation between the sample flask and the oven and between the oven and the collecting traps. Helium carrier gas was introduced into the bottom of the sample flask by means of a tapered capillary tube. Products were collected in a series of two glass helices filled

traps; it was found that by keeping the first trap at -78°C and the second at -196°C efficient trapping of products could be obtained without aerosol formation.

In the pyrolysis of (+)-(3R,5R)-10T 450 mg of vpc purified pyrazoline (nmr show no detectable contamination with cis pyrazoline) was carried through the oven at 292°C over a period of 7 hrs. 45 min.; the helium carrier flow rate was 60 ml/min. The pyrolysis product was then vacuum transferred out of the glass helices filled traps. Vpc analysis (column F, 100°C , 75 ml/min) showed complete reaction of starting material and (column G, 60°C , 75 ml/min.) formation of trans- and cis-1-ethyl-2-methylcyclopropane in 1:2.65 ratio with about 2% additional total yield of the cis- and trans-2- and 3-hexenes. The cyclopropanes were then separated by preparative vpc (column G, 60°C , 75 ml/min.) to give trans product: $[\alpha]_{\text{D}}^{25} + 3.22^{\circ}$ and $[\alpha]_{365}^{25} + 9.29^{\circ}$ ($c=0.061$ in n-hexane), and cis product: $[\alpha]_{\text{D}}^{25} + 0.058$ and $[\alpha]_{365}^{25} + 0.179^{\circ}$ ($c=0.184$ in n-heptane); the cis product contained roughly 1% hexene impurities, but these can make no contribution to the optical rotation. See text for a full discussion of these results.

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THE STEREOCHEMISTRY OF SOLVOLYTIC DISPLACEMENT
AND INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION
BY A DOUBLE BOND AT A VINYL CENTER

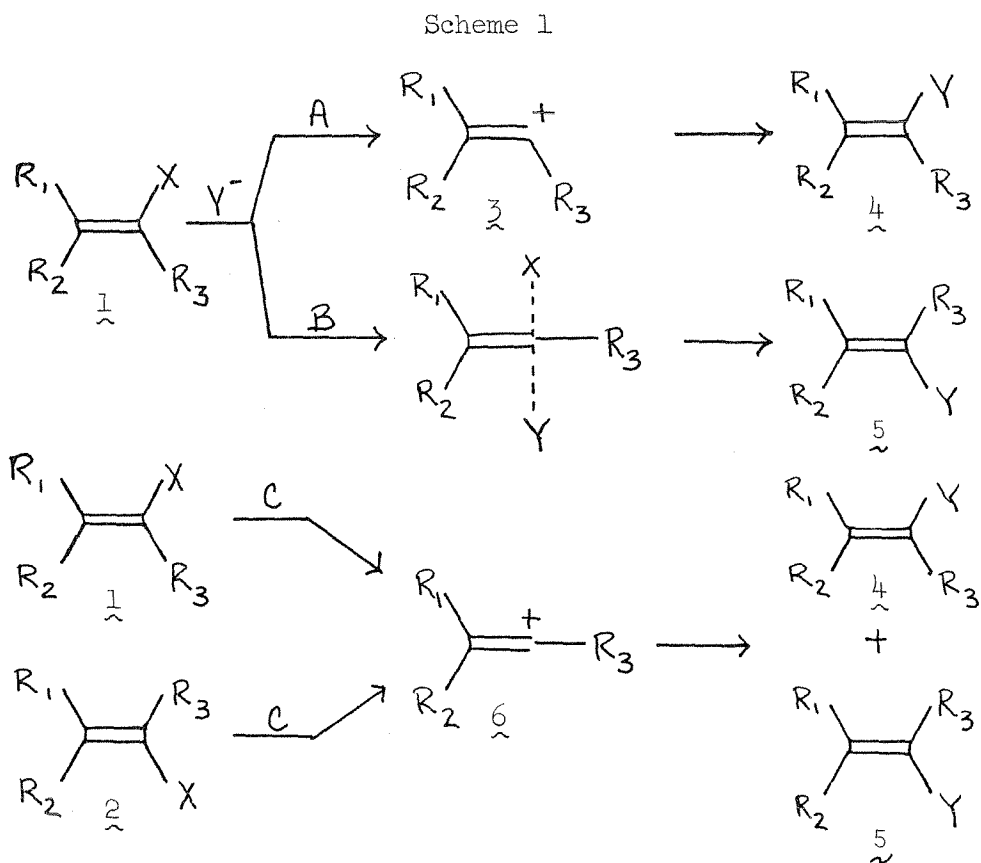
I. INTRODUCTION

The stereochemistry of solvolytic displacement at a saturated (sp^3) carbon center has been the subject of extensive research over the past four decades. One of the more important tools in the demonstration of the importance of the S_N1 mechanism^{2a} in many of these displacements has been the use of optically active substrates whose absolute configuration could be correlated with the configurations of the solvolytic products. In the solvolyses of optically active substrates which would be expected to lead to highly stabilized carbonium ions on ionization, the observation of racemic products provided striking confirmation of the predictions of the simple S_N1 mechanism.² However, the reactions of substrates leading to less stable carbonium ions have played an even more important role in the evolution of a more detailed understanding of the ionization process. The observation of significant amounts of inversion at the carbon center in the solvolyses of these substrates prompted the elaboration of the S_N1 mechanism to include such features as solvent participation and ion pair formation.^{2b,c}

The expectation that comparable experiments might provide valuable insight into the nature of solvolytic displacement at a vinyl (sp^2) center has only recently begun to be realized. Undoubtedly, this delay in the investigation of vinyl systems was due in large part to the presumed inaccessibility of dicoordinated carbonium ions (vinyl cations) under reasonable solvolytic conditions. However,

beginning with the demonstration by Grob and Cseh in 1964 that certain α -bromostyrenes solvolyze via vinyl cations in 80% aqueous ethanol at 100°C,³ a convincing body of evidence has been presented to show that vinyl cations can be generated under relatively mild conditions from a variety of precursors.⁴ The S_N1 nature of these processes has been established quite conclusively.^{4,5}

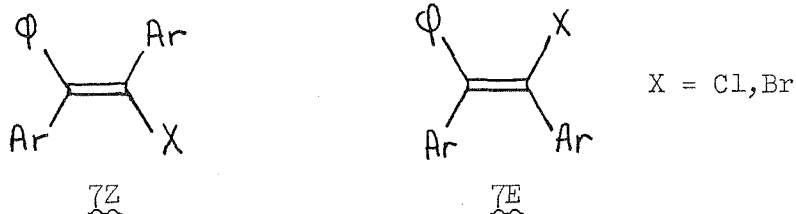
The planar nature of the ethylenic system of course rules out the use of chirality as a tool in the investigation of the displacement stereochemistry at a vinyl center. Instead, the relationships of the leaving group and the displacing nucleophile to the remote substituents on the double bond must be employed. Scheme 1 depicts the three



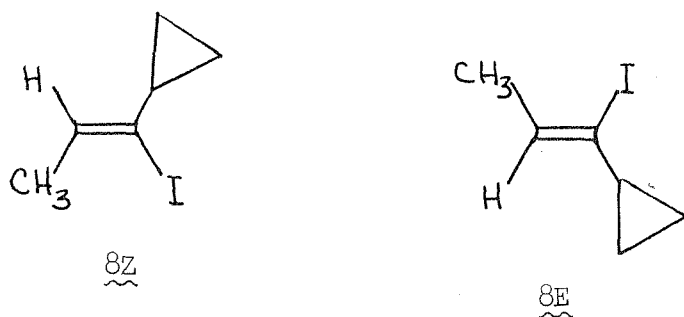
extreme possibilities for the stereochemical outcome of displacement at a vinyl center. Retention of configuration, shown as path A, could presumably arise by the formation and trapping of a configurationally stable bent vinyl cation $\underline{3}$. Direct backside participation by the nucleophile or backside attack on an ion pair formed by the initial ionization of $\underline{1}$ would lead to the inverted product $\underline{5}$ (path B). The stereochemical randomization shown in path C would result from the intermediacy of either a linear vinyl cation ($\underline{6}$) or a rapidly equilibrating pair of bent vinyl cations. The observation of the same ratio of products $\underline{4}$ and $\underline{5}$ from either starting isomer becomes the vinyl equivalent of the racemization process observed at tetrahedral centers.

The results in saturated systems suggest, of course, that the above scheme is an oversimplification.² Combinations of the various possibilities would lead to varying amounts of retention and inversion from each starting isomer. In particular, formation of a bent cation which loses its configuration at a rate competitive with trapping would produce net retention of configuration, that is, an excess of product $\underline{4}$ from $\underline{1}$ and an excess of $\underline{5}$ from $\underline{2}$. Net inversion could result from competitive solvent trapping of both the initial ion pair and a free linear cation.

The results of such stereochemical studies at vinyl centers have been reported for substrates leading to highly stabilized vinyl cations. Rappoport and Apeloig have shown that both $\underline{7Z}$ and $\underline{7E}$ give rise to identical product distributions under a variety of solvolytic



conditions.⁶ Initial results suggested that the cyclopropyl stabilized systems $\underline{8A}$ and $\underline{8E}$ also lead to the same product distribution on ioniza-



tion.⁷ Thus, in direct analogy with the results in saturated systems, highly activated vinyl substrates are found to undergo extensive or complete "racemization" on solvolysis. Extension of this comparison with saturated systems, however, suggests that the above results cannot be generalized to less activated vinyl systems, and that the examination of substrates leading to less stable vinyl cations should, in fact, provide additional insight into the detailed nature of the S_N1 process at an sp^2 center.

The examination of reactions where a remote double bond within the substrate acts as a nucleophile, either in concert with the initial ionization or in a subsequent step, has also led to an increased understanding of the fundamental processes involved in the

S_N1 reaction at saturated carbon centers.⁸ Moreover, these cyclizations have proved to have great synthetic value, as evidenced by the now familiar biogenetically patterned cyclizations of polyolefinic substrates to give multicyclic products.⁹ Stereochemically one would expect a high degree of inversion at the ionizing center in those cases where participation of the double bond has been shown to be important in the ionization step; surprisingly, experimental verification of this prediction has so far been reported in only one case.⁸ⁱ Similar experiments in vinyl systems have again been hampered until recently by the lack of suitable vinyl cation precursors.

In this work we present an investigation of the stereochemistry of displacement at a simple alkyl substituted center both by solvent and, potentially more useful synthetically, by a remote double bond.

II. RESULTS

Synthesis and Solvolysis of (Z)- and (E)-3-Methyl-2,6-heptadien-2-yl Trifluoromethanesulfonate (9Z and 9E). Use of the very reactive¹⁰ trifluoromethanesulfonate (triflate) leaving group has been shown to be the method of choice for the generation of alkyl substituted vinyl cations under solvolytic conditions.^{6,11} Thus, in order to study both the stereochemistry of solvolytic displacement and the preferences for cyclization at a vinyl center, vinyl triflates 9Z and 9E were chosen for our initial studies. The inclusion of the methyl group at C3 was prompted by the observation



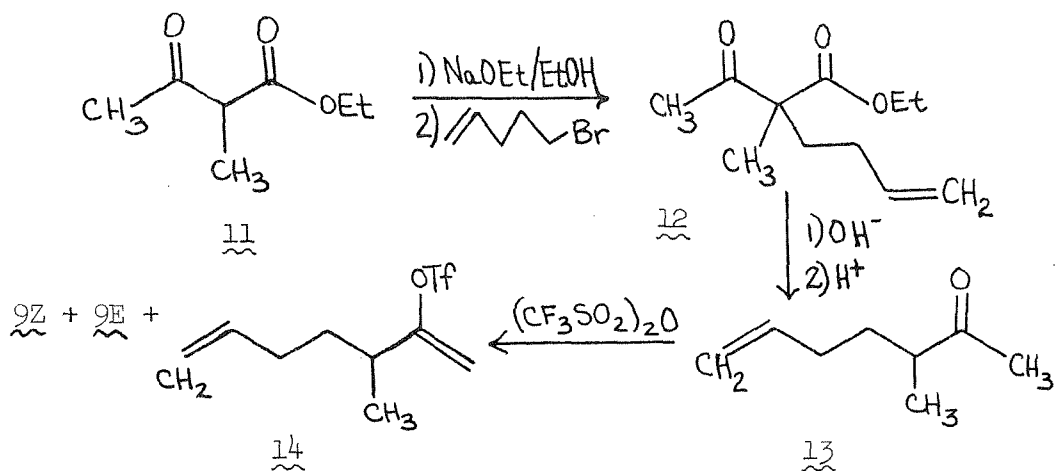
of Stang and Summerville that although 10E solvolyzes via a vinyl cation mechanism in 80% aqueous ethanol at 76°, 10Z undergoes a con-



certed trans elimination to give dimethylacetylene as the only product. Since the acetylene product obviously provides no stereochemical information, the methyl group was used to block the elimination process in 9Z.

The synthesis of 9Z and 9E is shown in Scheme 2. Alkylation of ethyl 2-methylacetoacetate (11) with 4-bromo-1-butene and subsequent saponification and decarboxylation of the product 12 provided 3-methyl-6-hepten-2-one (13) in an overall yield of 24% based on 11. Treatment of ketone 13 with trifluoromethanesulfonic anhydride and

Scheme 2



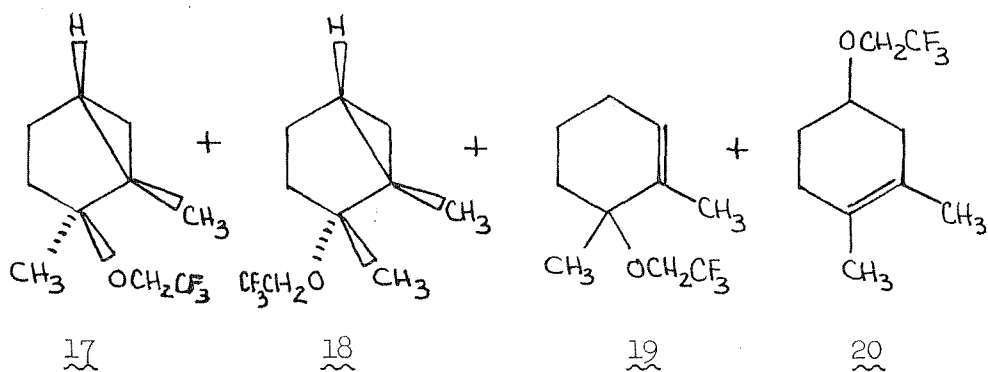
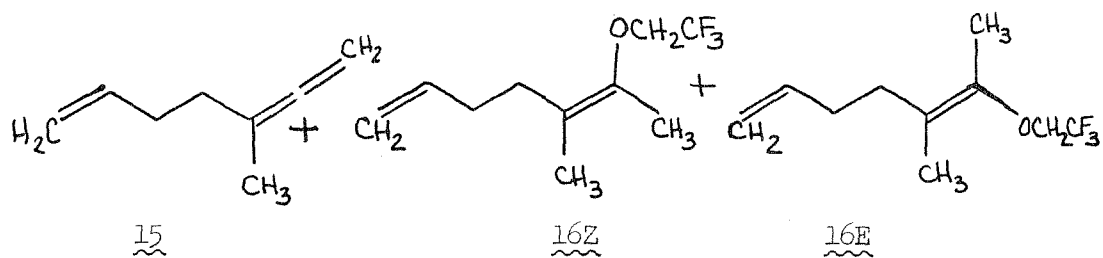
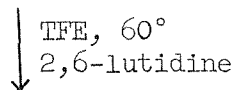
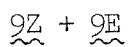
2,6-lutidine in methylene chloride at -20° gave a mixture of vinyl triflates 9Z, 9E, and 14.¹² Careful preparative vapor phase chromatography (vpc) on a diethyleneglycolsuccinate (DEGS) column allowed isolation of both 9Z and 9E in $> 96\%$ purity.

The stereochemical assignments of 9Z and 9E were based primarily on their respective proton nmr spectra. The β -methyl signal in 9Z appears at δ 1.76 while the β -methyl signal on 9E is shifted downfield to δ 1.83 ppm. This change is consistent with the observed deshielding of the β -methyl by a cis triflate function in the 2-buten-2-yl triflates 10Z and 10E; in 10E the β -methyl trans to the triflate is found at δ 1.22, but the β -methyl cis to the triflate in 10Z appears downfield at δ 1.31.¹¹ The long range "homoallylic" coupling between the two methyl groups confirms the assignments shown for 9Z and 9E. The magnitude of this coupling constant has been shown to be consistently larger for the trans configuration of interacting hydrogens than for the cis configuration.¹³ Thus, the coupling between the two methyls in 9Z is 1.1 ± 0.1 Hz while the coupling in 9E is 1.5 ± 0.1 Hz.

A preliminary solvolysis of a mixture of 9Z and 9E in 80% aqueous ethanol at 70° produced only ketone 13 and a product identified as 3-methyl-1,2,6-heptatriene (15) on the basis of its characteristic allene infrared absorption at 1958 cm⁻¹. Since these results provided no stereochemical information, the reaction was next attempted in 2,2,2-trifluoroethanol, a solvent of high ionizing power but low nucleophilicity which has been shown in the past to provide enhanced cyclization in other systems.^{8e,f,14} Solvolysis of a mixture of 9Z and 9E in absolute trifluoroethanol buffered with 2,6-lutidine provided a mixture of products including allene 15, the solvolytic displacement products 16Z and 16E, and the cyclized trifluoroethyl ethers 17, 18, 19, and 20 (Scheme 3). These products were all identified on the basis of their infrared and proton nmr spectra.

The stereochemistries of the isomeric vinyl trifluoroethyl ethers 16Z and 16E were again assigned on the basis of the chemical shifts of the β-methyl groups and on the homoallylic coupling constants for the methyl groups (vide supra). In accord with the general observation that $J_{\text{trans}} > J_{\text{cis}}$ for homoallylic coupling,¹³ the compounds assigned structures 16Z and 16E show methyl-methyl coupling constants of 0.9 ± 0.1 and 1.3 ± 0.1 Hz, respectively. In addition the β-methyl in 16Z occurs at δ 1.56, but the β-methyl in 16E is shifted downfield to δ 1.63. This deshielding by a cis trifluoroethoxy group has been observed in other similar systems.¹⁵

Scheme 3



The identification of the isomeric bicyclo[3.1.0] hexane derivatives 17 and 18 was also accomplished by nmr. In compound 17

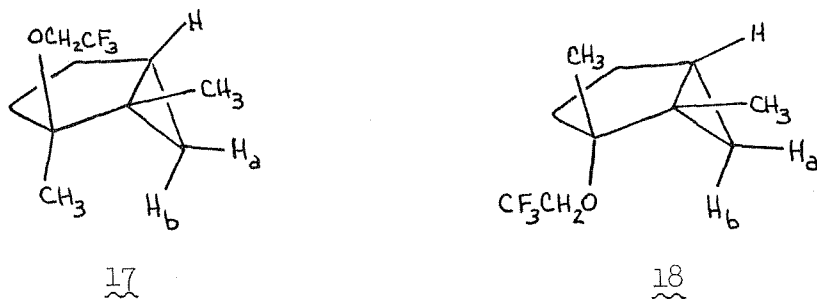


Table 1. Products Formed in Trifluoroethanolysis^a of (Z)- and (E)-3-Methyl-2,6-heptadien-2-yl Trifluoromethanesulfonates (9Z and 9E) at 60°C

Substrate	Reaction time, hrs.	Products % ^b					
		<u>15</u>	<u>16E</u>	(<u>16Z</u> + <u>18</u>) ^c	<u>17</u>	<u>19</u>	<u>20</u>
<u>9Z</u>	36.5	12.7	51.3	15.0	7.4	8.2	5.4
<u>9Z</u>	48	14.1	50.5	14.0	7.0	7.9	6.4
<u>9Z</u>	71	14.6	48.6	14.2	6.8	9.1	6.6
<u>9E</u>	24	12.9	33.8	23.4	11.3	10.6	8.0
<u>9E</u>	37.5	11.8	32.7	22.2	11.0	12.2	10.2
<u>9E</u>	49	9.8	33.2	22.8	10.9	13.0	10.6
<u>9E</u>	72	8.4	33.4	22.6	10.2	13.7	12.0

^a Solvolyses buffered with 2 equiv. of 2,6-lutidine. Substrate concentration normally ca. 0.095M. ^b Product percentages determined by direct integration of solvolysis vpc traces (Hewlett-Packard Model 5750 gas chromatograph equipped with HP 5370A digital integrator). Absolute yields determined by vpc using internal standard to be > 95%. ^c Eluted as single peak; see Table 2 for relative amounts of 16Z and 18 after 72 hours as estimated by nmr.

Table 2. Product Distribution on Trifluoroethanolysis^a of (Z)- and (E)-3-Methyl-2,6-heptadien-2-yl Trifluoromethanesulfonate (9Z and 9E) after 72 hrs. at 60°C

Substrate	Products % ^b						16E/16Z	% Cyclized Products	
	<u>15</u>	<u>16E</u>	<u>16Z</u>	<u>17</u>	<u>18</u>	<u>19</u>			<u>20</u>
<u>9Z</u>	14.6	48.6	9.9	6.8	4.3	9.1	6.6	4.9	0.27
<u>9E</u>	8.4	33.4	16.2	10.2	6.4	13.7	12.0	2.1	0.42

^aSolvolyzes buffered with 2 equiv. of 2,6-lutidine. Substrate concentration normally ca. 0.095M. ^bSee footnotes b and c, Table 1. ^cSum of 17, 18, 19, and 20.

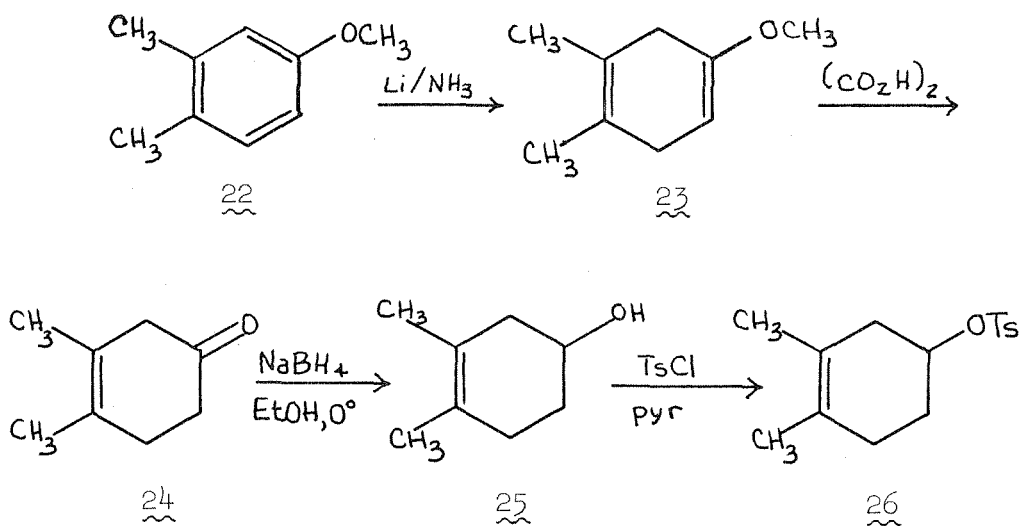
both of the methylene hydrogens at C6 appear as a complex multiplet at δ 0-0.4, but in compound 18 the trifluoroethoxy group causes these protons to be distinctly nonequivalent with H_a appearing as a doublet of doublets at δ 0.34 while H_b appears as a doublet of doublets at δ 0.84. This deshielding of the syn C6 hydrogen by an electron withdrawing cis substituent at C2 has been observed before in both the 2-methoxy- and 2-chlorobicyclo[3.1.0] hexanes as well as in the parent alcohols.¹⁶ Table 1 shows the resulting product distributions as a function of time. Products 16Z and 18 eluted as a single peak under the analytical conditions chosen and the sum of these compounds is shown as a single entry in Table 1. Vpc isolation and nmr examination of this peak after completion of the solvolyses allowed the complete product distribution analysis shown in Table 2; the ratio of the two vinyl ether products and the percentage of cyclized products from each starting isomer are also shown.¹⁷

No interconversion of the vinyl triflates could be detected, although the contamination of each starting material with approximately 4% of the other isomer might have masked a small degree of interconversion. In particular, no accumulation of the slower reacting isomer 9Z was observed during the solvolysis of 9E. The apparent interconversion of the cyclized products was confirmed in the solvolysis of 1,2-dimethyl-1-cyclohexen-4-yl tosylate (36) described below.

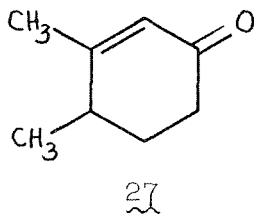
Synthesis and Solvolysis of 1,2-Dimethyl-1-cyclohexen-4-yl tosylate (36). The independent preparation of the cyclized products

obtained in the trifluoroethanolyses of 9Z and 9E was accomplished by the solvolysis of tosylate 26, whose synthesis is shown in Scheme 4.

Scheme 4



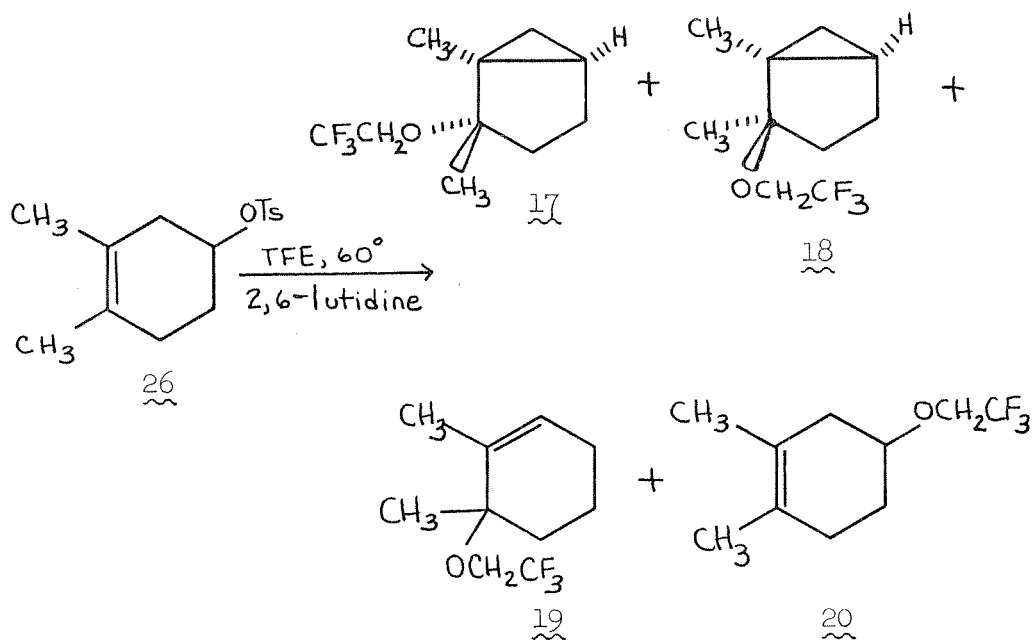
Birch reduction of commercially available 3,4-dimethylanisole (22) gave the sensitive vinyl ether 23, which was then hydrolyzed with oxalic acid to provide the β,γ -unsaturated ketone 24. Under the conditions used, 24 was always contaminated with a small amount of the rearranged α,β -unsaturated ketone 27. To circumvent this problem,



ketone 24 was reduced to alcohol 25 under the conditions developed by Heathcock et al.,¹⁸ for reduction of a β,γ -unsaturated ketone in the presence of an α,β -unsaturated ketone. Ketone 27 proved totally unreactive under these conditions, and after reaction of 25 with tosyl chloride in pyridine this ketone impurity was easily removed in the recrystallization of the product tosylate 26.

Tosylate 26 was then solvolyzed in buffered trifluoroethanol at 60°C. In addition to traces of unidentified olefinic products the same trifluoroethyl ethers were obtained as in the cyclizations of 9Z and 9E (Scheme 5). Although reaction of the tosylate was over

Scheme 5



well within the first hour, the reaction was allowed to stir for an additional 65 hours at 60°C to provide information on the product stabilities under the reaction conditions. The change of the product distribution with time is shown in Table 3. The mass balance suggests

Table 3. Product Distribution in the Trifluoroethanolysis^a of 1,2-Dimethyl-1-cyclohexen-4-yl Tosylate (26) at 60°C

Time	Product % ^b			
	<u>17</u>	<u>18</u>	<u>19</u>	<u>20</u>
3 hrs.	37.6	13.7	19.5	29.2
66 hrs.	14.6	11.4	32.4	41.6

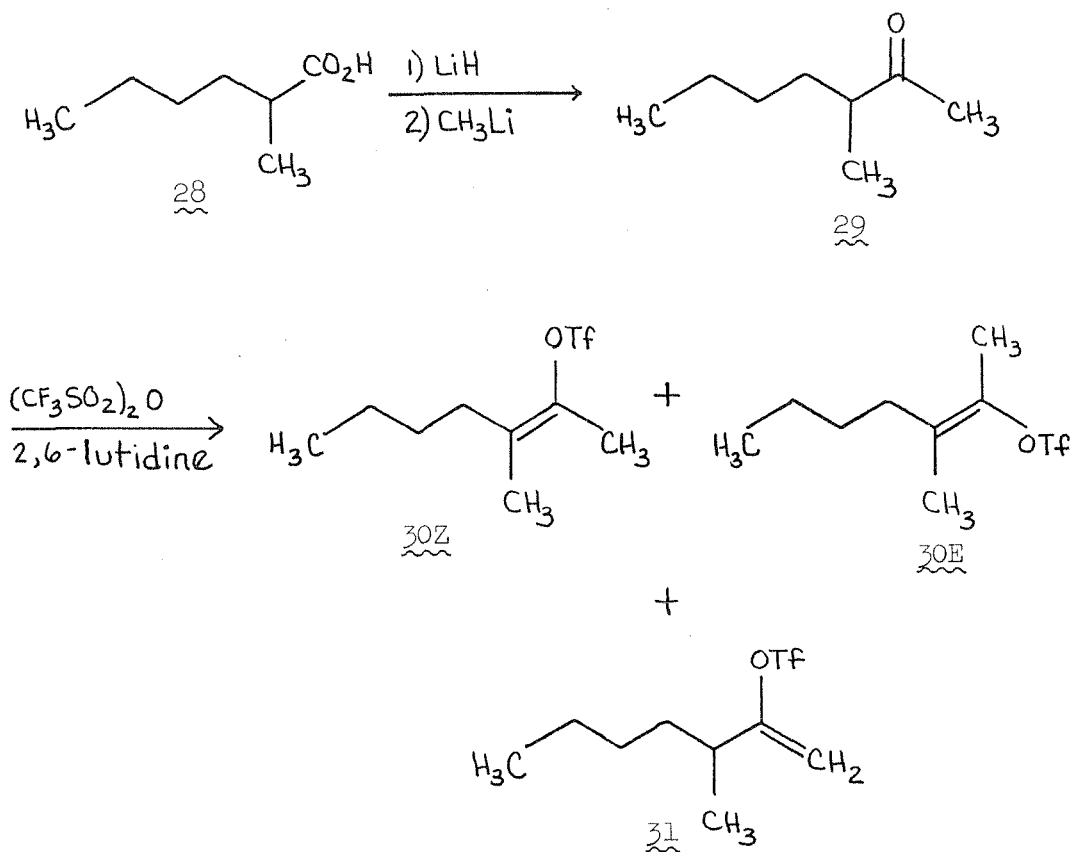
^aSolvolyses buffered with 2 equiv. 2,6-lutidine. Substrate concentration 0.1 M. ^bProduct percentages determined by direct integration of solvolyses vpc traces.

that these changes are due to interconversion of the product isomers rather than selective destruction of products 17 and 18. Thus 17 and to a lesser extent 18 are gradually converted to 19 and 20 during the course of the reaction.

Synthesis and Solvolysis of (Z)- and (E)-3-Methyl-2-hepten-2-yl Trifluoromethanesulfonate (30Z and 30E). In order to determine whether the different product ratios observed in the reactions of 9Z and 9E were generally characteristic of the solvolyses of isomeric alkyl substituted vinyl triflates, or whether the differences were in fact due to some selective interaction with the remote double

bond, the solvolyses of triflates 30Z and 30E were also undertaken. The synthetic route to these compounds is shown in Scheme 6. Since

Scheme 6

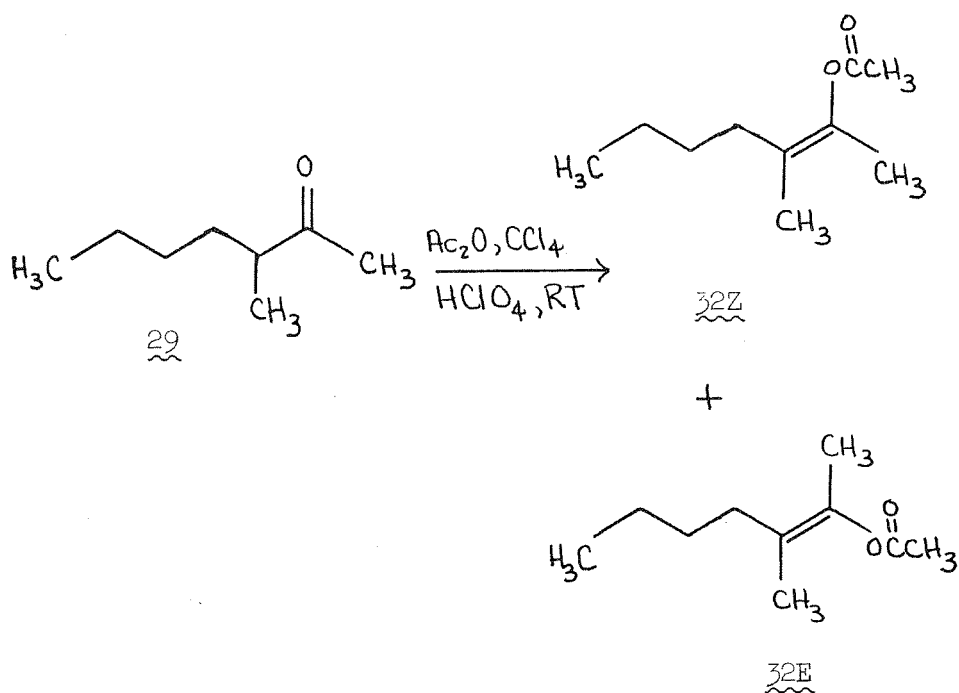


commercial samples of 3-methyl-2-heptanone (29) proved to be highly contaminated with isomeric ketones,¹⁹ the reaction of methyllithium with 2-methylhexanoic acid (28) was instead employed for the generation of 29. A mixture of vinyl triflates 30Z, 30E, and 31 was then obtained by reaction of 29 with trifluoromethanesulfonic anhydride;

30Z and 30E were isolated in > 96% purity by preparative vpc.

The stereochemistries of 30Z and 30E were assigned in the same manner as those of 9Z and 9E (vide supra). The β -methyl signal of 30Z appears as a finely split quartet at δ 1.72 while the β -methyl quartet of 30E is shifted downfield to δ 1.78. The homoallylic methyl-methyl coupling constants for 30Z and 30E are 0.9 ± 0.1 and 1.3 ± 0.1 Hz, respectively. As discussed previously in the case of 9Z and 9E, these data are completely consistent with the assignments shown.

Attempts to provide corroborative information on the stereochemistries of the vinyl triflates by use of the europium shift reagent $\text{Eu}(\text{fod})_3$ ^{20,21} failed, apparently because of a lack of complexation between the shift reagent and the vinyl triflates. However, an alternate approach did provide additional evidence for the stereochemical assignments of 30Z and 30E. Vinyl acetates 32Z and 32E were prepared from ketone 29 by the procedure of House *et al.*²² The stereochemical assignments of the vinyl acetates were again based on the homoallylic coupling constants: $J = 0.9 \pm 0.1$ Hz for 32Z and $J = 1.4 \pm 0.1$ Hz for 32E. The β -methyl of 32E showed a slight upfield shift (δ 1.48) relative to the β -methyl of 32Z (δ 1.65), in accord with the observations of Parnham and Dooley in the 2-buten-2-yl acetates.²³ The stereochemistries of 32Z and 32E were then confirmed by the use of $\text{Eu}(\text{fod})_3$ according to the method of Kelsey.²⁴ When the shift of the acetoxy methyl protons, $\Delta_{\text{obsd}}^{\text{Ac}}$, is plotted versus the shift of the α - and β -methyl and β -methylene protons, $\Delta_{\text{obsd}}^{\text{i}}$, at



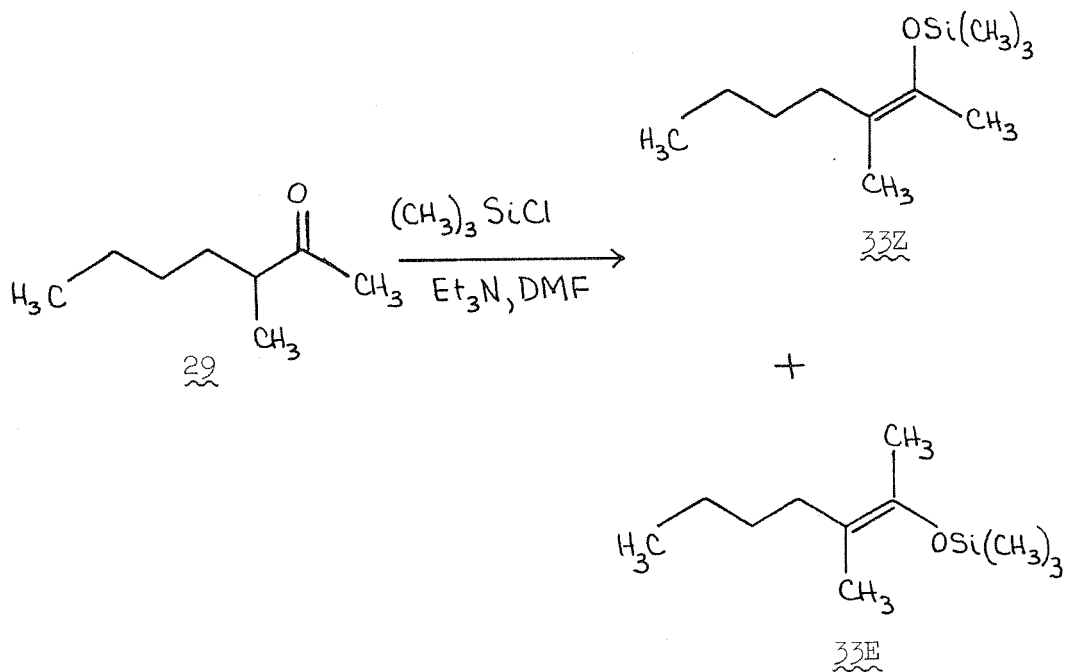
varying concentrations of shift reagent, straight lines are obtained whose slopes are equal to $\Delta_{\text{max}}^{\text{Ac}}/\Delta_{\text{max}}^{\text{i}}$, the ratio of the theoretical maximum shifts of the acetoxy methyl and the proton in question.²⁴ Kelsey has shown that these slope values are characteristic for a proton in a given geometrical relation to the acetoxy. Thus, for example, since a β -methyl cis to the acetoxy will be shifted to a greater extent than a β -methyl trans to the acetoxy at any given concentration of shift reagent,²⁴ the value of $\Delta_{\text{max}}^{\text{Ac}}/\Delta_{\text{max}}^{\text{i}}$ will be smaller for the cis β -methyl than for the trans β -methyl. The values of $\Delta_{\text{max}}^{\text{Ac}}/\Delta_{\text{max}}^{\text{i}}$ for the α - and β -methyls and the β -methylene of 32Z and 32E are shown in Table 4. These results, which are in good agreement with those obtained by Kelsey in similar vinyl acetates,

Table 4. $\Delta_{\max}^{A_c}/\Delta_{\max}^i$ for Vinyl Acetates 32Z and 32E

H_i	Compound	$\Delta_{\max}^{A_c}/\Delta_{\max}^i$
α -CH ₃	<u>32Z</u>	1.60
	<u>32E</u>	1.62
β -CH ₃	<u>32Z</u>	4.15
	<u>32E</u>	2.09
β -CH ₂	<u>32Z</u>	1.88
	<u>32E</u>	3.91

confirm the stereochemical assignments of 32Z and 32E.

The trimethylsilyl enol ethers 33Z and 33E were then prepared from ketone 29 by another of House's procedures.²⁵

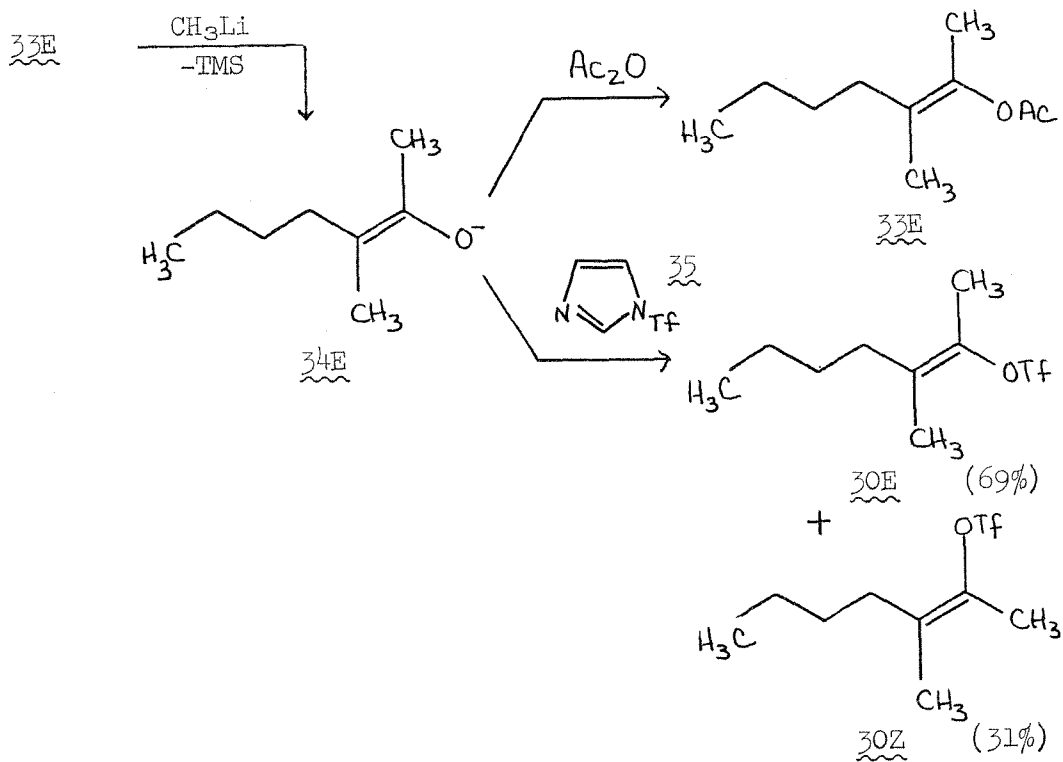
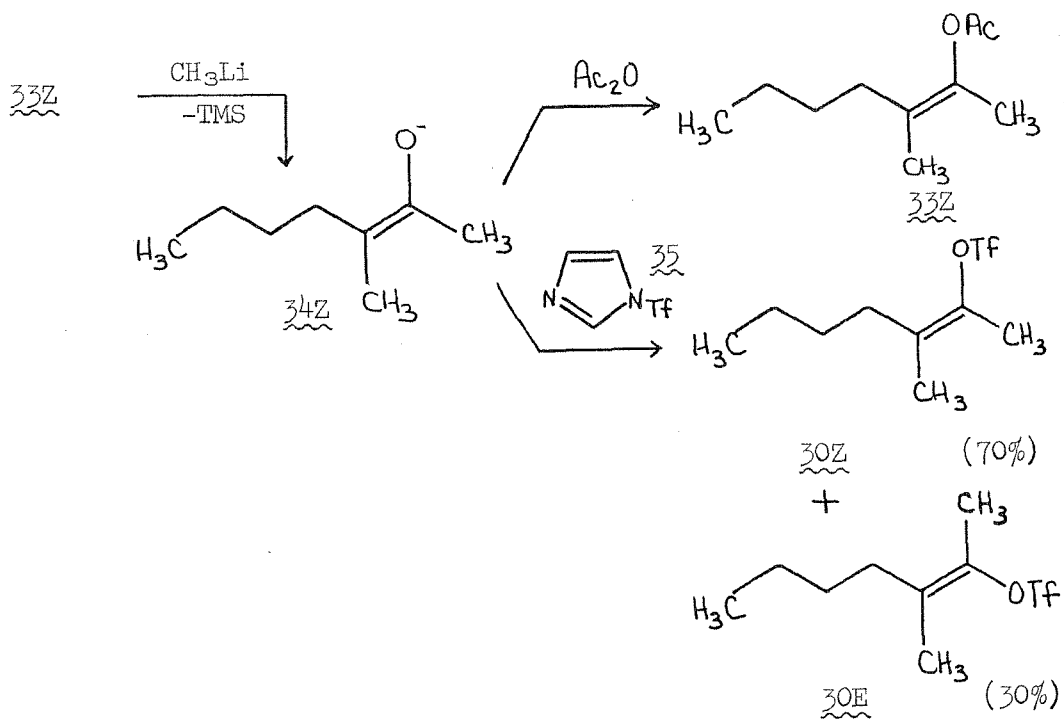


The initial stereochemical assignments of 33Z and 33E based on the homoallylic coupling constants ($J = 1.0 \pm 0.1$ Hz for 33Z, $J = 1.5 \pm 0.1$ Hz for 33E) were confirmed by conversion of 33Z to vinyl acetate 32Z and of 33E to vinyl acetate 32E. In each case the stereospecific transformation was accomplished by quenching in acetic anhydride enolates 34Z and 34E formed respectively by the cleavage of silyl ethers 33Z and 33E with methyllithium (Scheme 7). (The trimethylsilyl enol ethers also failed to show any interaction with the $\text{Eu}(\text{fod})_3$ shift reagent).

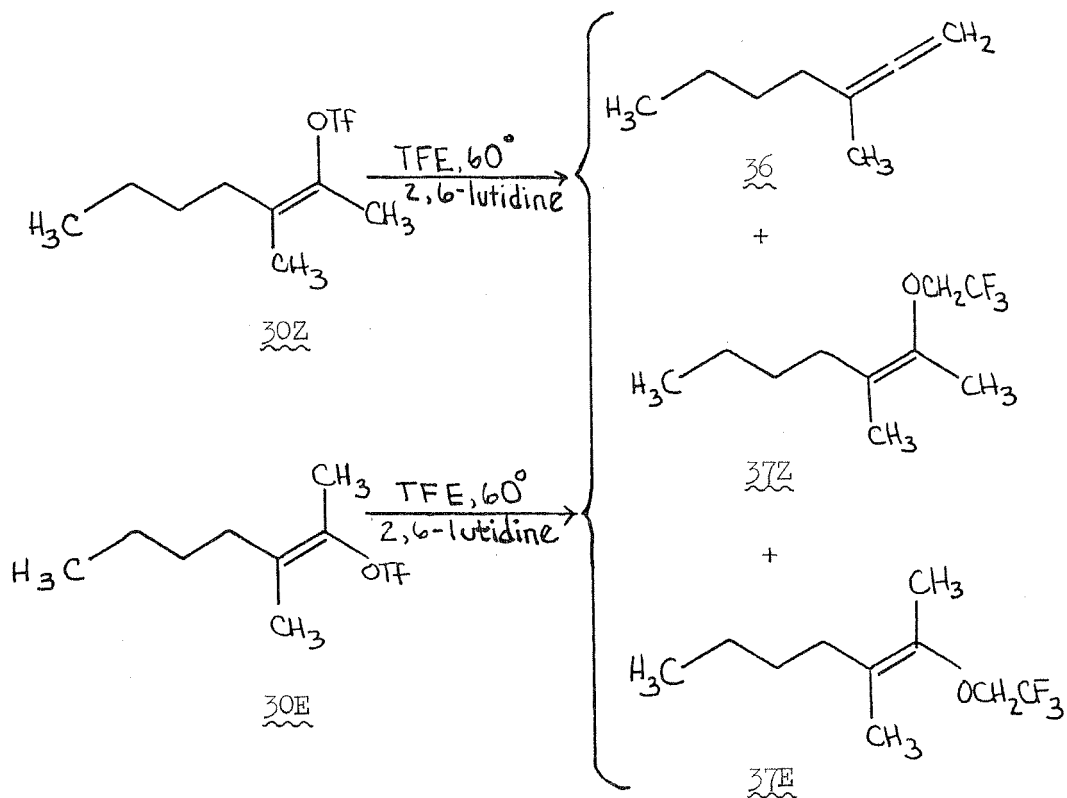
The enolates were treated with trifluoromethanesulfonic imidazole²⁶ (35) in an attempt to generate the vinyl triflates 30Z and 30E. Unfortunately, this procedure was not as stereospecific as the acetate formation. 34Z gave a 70:30 mixture of 30Z and 30E, respectively, and 34E led to a 31:69 mixture of 30Z and 30E; the source of the stereochemical crossover is not clear. Although the lack of complete stereospecificity makes these results less definitive than might have been hoped, the observed stereoselectivity in the formation of 30Z and 30E does support the assigned stereochemistries.

Vinyl triflates 30Z and 30E were then subjected individually to solvolysis at 60°C in trifluoroethanol buffered with 2,6-lutidine. Only three products were formed in these reactions: allene 36 and the two solvolytic displacement products 37Z and 37E (Scheme 8). The products were identified on the basis of their infrared and nmr spectra. Product 36 exhibited a characteristic allene ir absorption at 1960 cm^{-1} and an nmr consistent with the structure shown. Vinyl

Scheme 7



Scheme 8



trifluoroethyl ether 37Z showed a β -methyl quartet at δ 1.58 with a homoallylic coupling of 0.8 ± 0.1 Hz; the β -methyl quartet of 37E was shifted downfield to δ 1.62 with a homoallylic coupling of 1.3 ± 0.1 Hz. As discussed previously in the case of 16Z and 16E, these data lead to the stereochemical assignments shown. Once again, vinyl-trifluoroethyl ethers 37Z and 37E fail to form complexes with $\text{Eu}(\text{fod})_3$.

The product distributions in the solvolysis of 30Z and 30E are shown in Table 5 as a function of time. Aside from some irreproducibility in the percentages of allene 36, it can be seen that the product distributions do not change significantly with time; in

Table 5. Product Distributions in the Trifluoroethanolysis^a of (Z)- and (E)-3-Methyl-2-hepten-2-yl Trifluoromethanesulfonate (30Z and 30E) at 60°C as a Function of Time

Substrate	Reaction time, hrs.	Product % ^b			Ratio (<u>37E</u> / <u>37Z</u>) ^c
		<u>36</u>	<u>37Z</u>	<u>37E</u>	
<u>30Z</u>	12.5	14.9	14.8	70.4	4.8
<u>30Z</u>	85	13.3	15.4	71.4	4.6
<u>30Z</u> ^d	72	15.0	15.3	69.6	4.5
<u>30E</u>	12.5	18.9	23.5	57.6	2.4
<u>30E</u>	85	14.4	24.9	60.8	2.4
<u>30E</u> ^d	72	15.1	24.6	60.4	2.5

^aSolvolyses buffered with 2 equiv. 2,6-lutidine. Substrate concentration normally ca. 0.09 M. ^bProduct percentages determined by direct integration of solvolysis vpc traces (Hewlett-Packard Model 5750 gas chromatograph equipped with HP 5370A digital integrator). ^cSome irreproducibility in the percentages of 30 increases the error in the product percentages to $\pm 3\%$; however, the trifluoroethyl ether ratio is accurate to ± 0.1 . ^dDuplicate runs; absolute yields determined by vpc using an internal standard to be $> 95\%$.

particular, the constancy of the ratios of 37E to 37Z suggests that no interconversion of the trifluoroethyl ether products occurs. The ratio of 37E to 37Z has also been shown to be insensitive to variations in the concentrations of substrate and buffer (Table 6). Again no interconversion of vinyl triflate isomers 30Z and 30E could be detected.

Table 6. Product Distributions in the Trifluoroethanolysis^a of (Z)-3-Methyl-2-hepten-2-yl Trifluoromethanesulfonate (30Z) at 60°C at Varying Concentrations

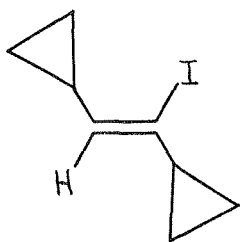
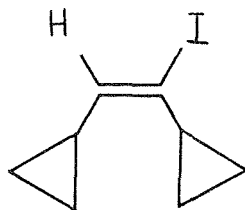
<u>30Z</u> concn. M	Buffer ^b concn. M	Product %			<u>(37E/37Z)</u>
		<u>36</u>	<u>37Z</u>	<u>37E</u>	
0.09	0.18	13.3	15.4	71.4	4.6
0.023	0.046	12.5	15.9	71.6	4.5
0.09	0.36	12.1	16.2	71.7	4.4

^aSee footnotes b-d, Table 4. ^b2,6-Lutidine.

III. DISCUSSION

As mentioned earlier, previous studies in more activated vinyl systems showed stereochemical randomization on solvolysis of either of the geometrically isomeric starting materials.^{6,7} These results are best explained by the assumption that both reactions proceed through a common vinyl cation intermediate. Examination of the data presented above, however, suggests that the case is more complex for solvolyses proceeding through simple alkyl substituted vinyl cations.²⁷ In particular, systems 9 and 30 both show significant amounts of inversion at the vinyl center in the solvolytic displacement process. Although the (E)/(Z) trifluoroethyl ether ratio is always greater than unity in both systems, considerably more (Z) trifluoroethyl ether is produced from the (E) vinyl triflate than from the (Z) triflate.

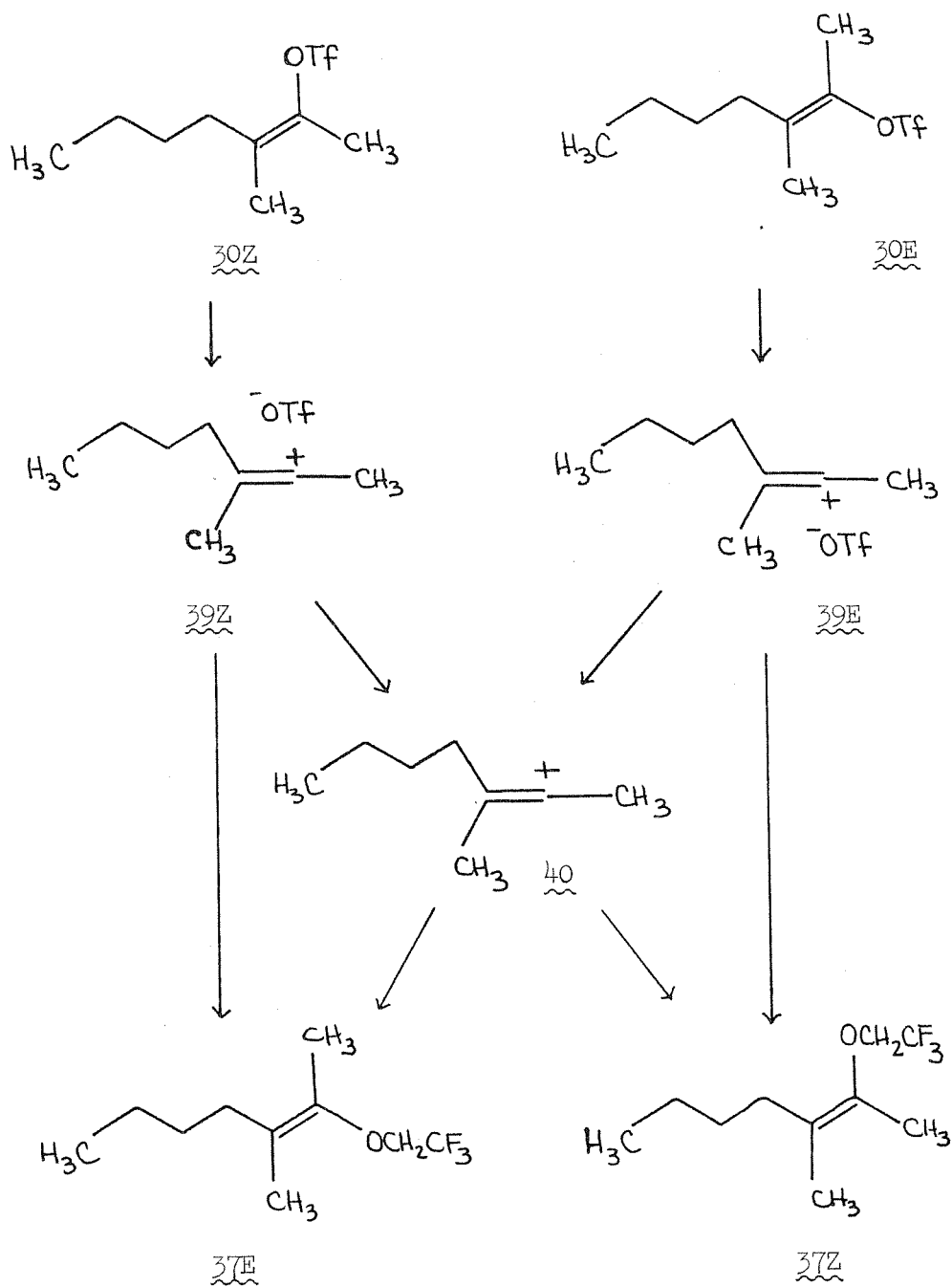
In light of the above observations Kelsey has reexamined the stereochemistry of the silver acetate catalyzed ionization of the (Z)- and (E)-isomers of 1-cyclopropyl-1-iodopropene (8Z and 8E) using more sophisticated analytical techniques than were previously available.^{1a} Earlier results had suggested that both isomers gave rise to the same distribution of solvolytic products.⁷ The more precise measurements, however, revealed the presence of an inversion component in these systems as well. Moreover, investigation of the dicyclopropyliodethylenes 38Z and 38E demonstrated that these compounds also show a small but detectable preference for inversion.^{1a} Thus, even in these

38Z38E

systems leading to highly stabilized vinyl cations net inversion of stereochemistry may be observed on solvolysis. These results suggest that careful investigation of other activated systems⁶ may reveal a similar stereochemical preference.

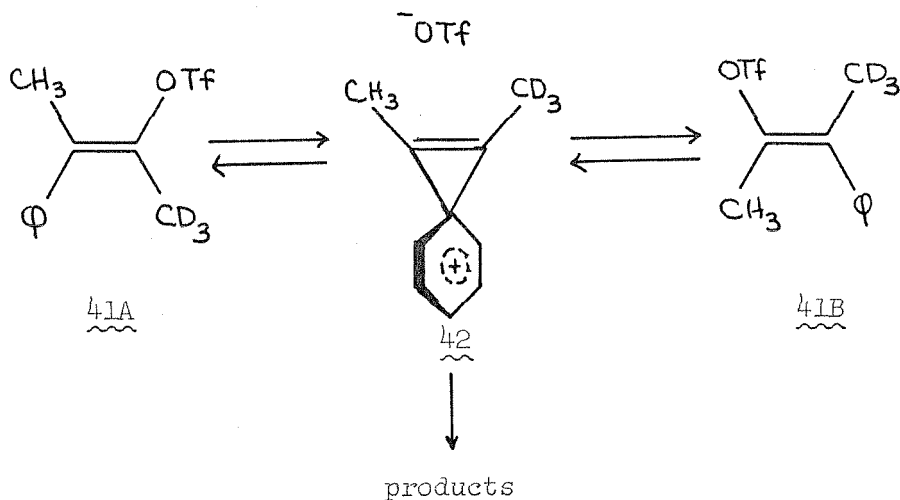
The observation of partial but not complete inversion of stereochemistry obviously rules out the exclusive involvement of either free vinyl cations or direct S_N2 -displacement by solvent in these systems. Although we have obtained no direct evidence for their involvement,^{27a} we presently feel that these results are best rationalized by the intervention of ion pairs as shown for vinyl triflates 30Z and 30E in Scheme 9. In analogy to the results in displacements at saturated carbon centers,² the presence of the triflate counterion in ion pairs 39Z and 39E would be expected to shield the side of the molecule from which the triflate departed. Competition between solvent trapping of ion pairs 39Z and 39E and the free vinyl cation 40 would lead to the net inversion of configuration observed.

Scheme 9



There is no reason to suspect that ion pairing should play a less important role in these ionizations than in comparable reactions at saturated centers. Other authors have also invoked ion pairs to explain results observed in vinyl systems.²⁷ In a recent paper, Stang and Dueber suggested that internal return from the intimate ion pair 42 is responsible for the presence of some of the rearranged isomer 41B in reisolated samples of partially solvolyzed 41A (Scheme 10).¹⁵ Again, however, no definitive proof for the existence of 42 was offered.

Scheme 10

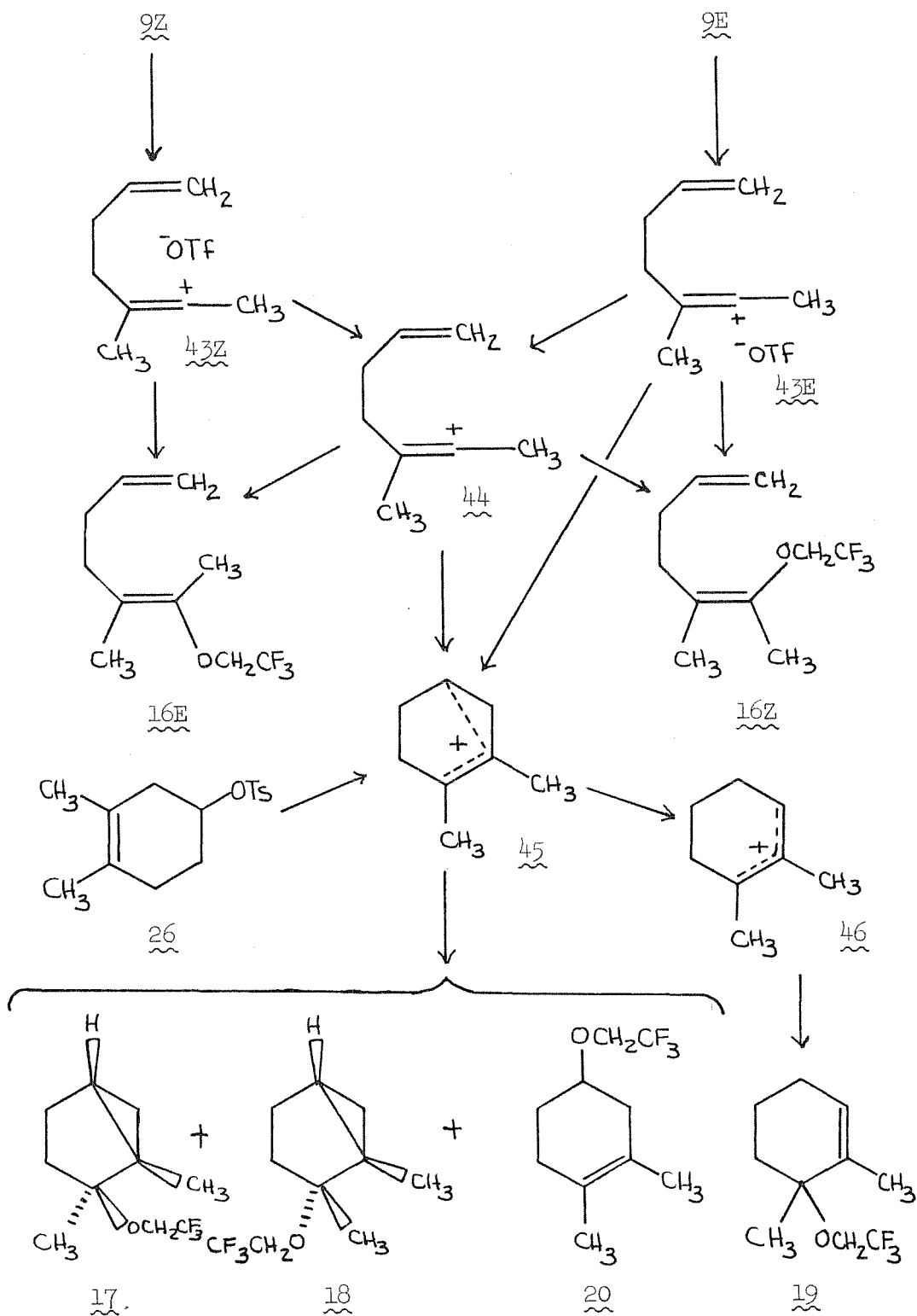


An alternate mechanistic possibility which would also result in net inversion involves direct ionization to the free vinyl cation 40 and competitive $\text{S}_{\text{N}}2$ attack by solvent on the vinyl triflates. Although considerable evidence has been presented elsewhere for the $\text{S}_{\text{N}}1$ nature of the reaction of vinyl substrates under the solvolytic

conditions employed here,^{4,11} the distinction between solvent trapping of an ion pair and direct backside attack by solvent on the starting material is not easily determined experimentally. Indeed, this problem has still not been fully resolved in saturated systems.²⁹ However, there are some considerations which mitigate against the S_N2 reaction at a vinyl center. In recent theoretical calculations, Kelsey and Bergman have demonstrated the unfavorableness of S_N2 attack at a vinyl carbon relative to a saturated carbon.³⁰ The observation of extensively rearranged products in certain vinyl triflate solvolyses has been taken as evidence for the ionic nature of the reaction.³¹ Also, cycloheptenyl and cyclooctenyl triflates do not show any substantial rate depression over cis-2-buten-2-yl triflate at 100°C in 50% aqueous ethanol.³² In both of these systems backside attack would be expected to be severely hindered. Although none of these results strictly precludes the possibility of S_N2 attack by solvent in the present system, they do make it seem less plausible than the ion pair explanation.

It is interesting to note that not only the solvolytic displacement process but also the cyclization reactions of vinyl triflates 9Z and 9E show a preference for inversion. More cyclized product is obtained from 9E where the remote double bond is trans to the triflate function than from 9Z where they are cis (Table 2). This can again be explained by the intervention of ion pairs as shown in Scheme 11. In ion pair 43Z the vinyl cation is shielded by the triflate counterion from nucleophilic attack by the remote double bond; thus the

Scheme 11



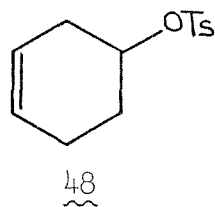
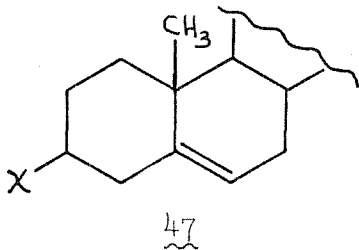
cyclized products from 9Z must arise from the free vinyl cation 44. In the reaction of 9E, however, both ion pair 43E and the free ion 44 may undergo cyclization.

The observation of more cyclization from 9E than 9Z raises the question of direct double bond participation in the ionization process, a phenomenon which has been shown to be important in cyclization reactions at saturated centers.⁸ One criterion for such participation in the present case would be the observation of a kinetic acceleration in 9E relative to its 6,7-dihydro analog 30E. Qualitative estimates of the relative reaction rates show, however, that all four vinyl triflates react at very similar rates and that 30E in fact reacts somewhat faster than 9E; the estimated relative rates for 9Z, 9E, 30Z, and 30E are 1.0, 1.8, 1.8, and 3.0, respectively. This lack of evidence for concerted cyclization is consistent with the mechanism outlined in Scheme 11.

The cyclized products may all be explained in a relatively straightforward manner. Cyclization of vinyl cation 44 (or 43E) would lead to cation 45, which for the sake of convenience is represented here as having a "homoallylic" structure. Solvent trapping of 45 would lead directly to products 17, 18, and 20, while hydride shift to give allylic cation 46 followed by trapping at the tertiary center gives product 19. The observation of the same products on solvolysis of tosylate 26, which would be expected to lead to ion 45 directly, provides additional evidence for the proposed pathway.

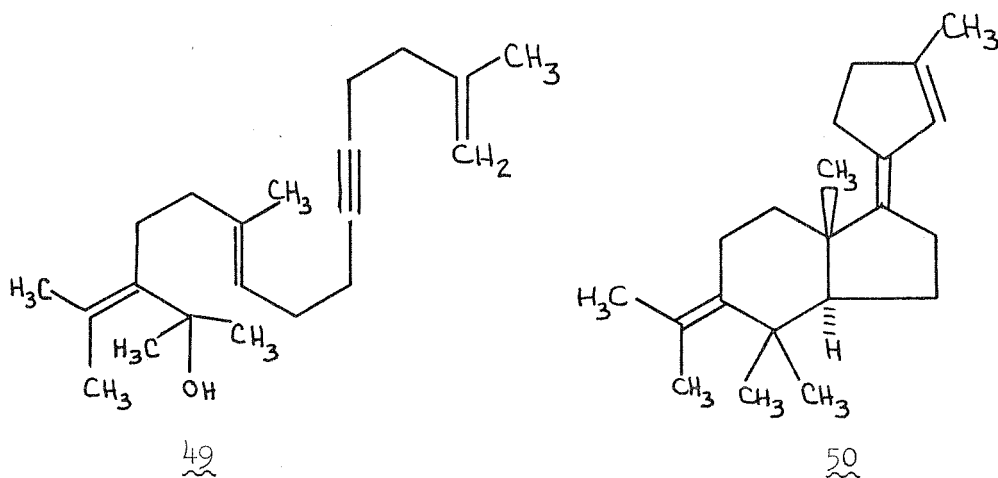
Although it would be interesting to compare the ratios of

cyclic products arising from the vinyl triflate cyclizations and from tosylate 26, the gradual conversion of 17 and 18 to 19 and 20 during the course of the reaction make a quantitative comparison of product distributions somewhat difficult. Also since under the analytical conditions used, product 17 appears in the end of the solvent tail while product 18 is coeluted with 16Z (vide supra), complete analysis of product distributions at low conversion was not possible. However, it is clear that throughout the reaction the product distribution from tosylate 26 contains relatively more of product 20 than does the distribution from the triflate cyclizations. This excess of direct displacement product might be attributable to a small amount of backside participation by the weakly nucleophilic^{3e,f} trifluoroethanol solvent in the ionization of 26. It may be noted that to the extent that cation 45 does have homoallylic character arising from direct participation of the double bond in the initial ionization step, product 20 would be expected to be formed with retention of configuration at the displacement center in analogy with the results obtained by Shoppee in the solvolyses of Δ^5 -cholestene derivatives (47).³³ No suitable stereochemical test of this possibility has yet been made, although



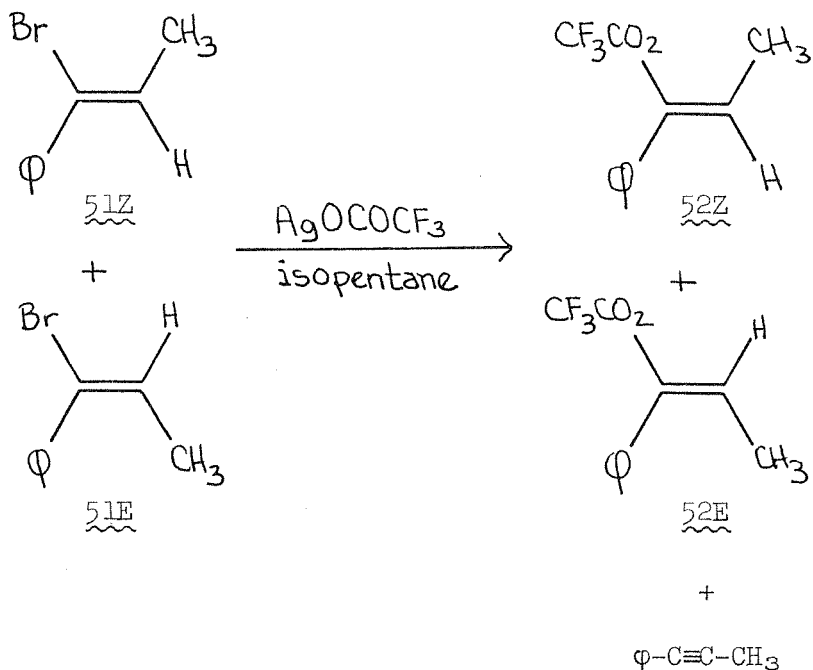
direct participation by the double bond has been implicated in the parent system 48 by the moderate acceleration of the solvolysis rate of 48 relative to its saturated analog.³⁴

The synthetic possibilities of cyclization to a vinyl cation center have already been exploited in one instance by Johnson et al.^{35c} The trifluoroacetic acid catalyzed cyclization of trienynol 49 to the tricyclic triene 50 in methylene chloride at -70°C presumably proceeds



through an intermediate vinyl cation, although the possibility that the entire cyclization is concerted has not been ruled out. Several other examples of acetylene participation in polyolefinic cyclizations have also been presented.³⁵

Finally, it is of interest to compare the results of the present study with those obtained by Kernaghan and Hoffmann for the silver trifluoroacetate catalyzed ionization of the (Z) and (E) isomers of 1-bromo-1-phenylpropene (51Z and 51E) in isopentane at 25°C .³⁶ Under these heterogeneous conditions, the trifluoroacetate substitution products 52Z and 52E are formed with net retention of



configuration. It was suggested by the authors that interactions with the surface of the silver salt might be responsible for these results. In any event it is clear that these reactions are fundamentally different from the true solvolyses of vinyl triflates such as those carried out here in trifluoroethanol; thus it is not particularly surprising that different stereochemical outcomes are observed.

The reaction of 51E with silver trifluoroacetate under homogeneous conditions in diethyl ether at 25°C was also reported to proceed with net retention of configuration.³⁶ Kernaghan and Hoffmann chose to explain this observation by a double inversion mechanism involving nucleophilic participation by solvent to form an intermediate oxonium ion. However, this mechanism does not easily explain the lack of reactivity under these conditions of 51Z, which would be expected to

show less steric hindrance to backside attack by solvent than 51E. The alternate possibility of nucleophilic trapping of ion pairs by aggregated silver salts has been suggested previously to account for the small degree of ion pair return product in the homogeneous silver acetate catalyzed solvolyses of cyclopropyl substituted vinyl iodides 8Z and 8E in acetic acid.⁷ The lack of reactivity of 43Z is still puzzling however.

IV. EXPERIMENTAL

General. Infrared spectra were obtained as CCl₄ solutions on a Perkin-Elmer 257 Grating Infrared Spectrophotometer. Nmr spectra were obtained on either an A-60-A or a T-60 Varian Associates Analytical nmr Spectrometer as carbon tetrachloride or deuteriochloroform solutions with tetramethylsilane (TMS) internal standard. Nmr spectra are reported as: chemical shift (in order of increasing δ); multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; splitting; integration in units of H; and assignment. Qualitative and preparative vapor phase chromatography (vpc) was performed on a Varian Aerograph 90-P3 instrument equipped with a thermal conductivity detector and helium carrier gas. Except when chromatographing sensitive materials, injector and detector temperatures were maintained at 200-210°C. Analytical vpc was carried out on a Hewlett-Packard 5750 instrument with a flame ionization detector and Hewlett Packard 3370A Integrator. The injector temperature was maintained at approximately 200°C and the detector at 340°C; the following gas pressures were used (lb/

in²): He, 40; H₂, 14; air, 30. The following vpc columns were used: column A, 10' × 1/4" 10% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column B, 5' × 1/4" 5% DEGS on 60/80 Chromosorb P-NAW, stainless steel; column C, 5' 3% SE30 on 100/120 Varaport 30, stainless steel; column D, 15' × 1/8" 10% DEGS on 100/120 Chromosorb P-NAW, stainless steel; column E, 10' × 1/4" UCC-W98 on 60/80 Chromosorb W-AWDMCS, glass; column F, 10' × 1/4" 20% DEGS on Chromosorb P-NAW, stainless steel; column G, 10' × 1/4" 20% Carbowax on Chromosorb P-NAW, stainless steel; column H, 7' × 1/4" 8% FFAP on Chromosorb P-NAW, stainless steel; column I, 10' × 1/4" 20% SE30 on Chromosorb W-AWDMCS, glass. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan, 48106. All boiling points are uncorrected.

Trifluoromethanesulfonic acid anhydride (53). 53 (b.p. 83-84°C) was prepared in 77.6% yield by treatment of trifluoromethanesulfonic acid (3M Co.) with fresh phosphorus pentoxide according to the procedure of Gramstad and Haszeldine.³⁷ The anhydride was found to be stable indefinitely when opened only under an inert atmosphere and stored in the refrigerator in a glass bottle with a teflon lined cap.

3-Carboethoxy-3-methyl-6-hepten-2-one (12). Into a dry 500 ml three-necked flask fitted with a mechanical stirrer, an addition funnel, and a reflux condenser protected with a calcium sulfate drying tube were placed 85 ml absolute ethanol and 3.95g (172 mmol) freshly cut sodium. The mixture was stirred for 3 hours to allow complete

reaction of the sodium. To this solution was added dropwise with vigorous stirring 22.2g (154 mmol) ethyl 2-methylacetoacetate (Aldrich Chem. Co.) to give a viscous reaction mixture. This mixture was heated to reflux and 25g (185 mmol) 4-bromo-1-butene (J. T. Baker Chem. Co.) was added dropwise. The solution was stirred at reflux for 7 hours. After cooling, the reaction mixture was decanted off of the sodium bromide salt, which was rinsed with a small portion of ethanol. Most of the ethanol was distilled off through a 40 cm Vigreux column at atmospheric pressure.

In the most successful procedure the remaining solution was subjected directly to saponification and decarboxylation to give 3-methyl-6-hepten-2-one (13 vide infra). However, in one instance 12 was isolated by the following procedure. The concentrated reaction mixture was dissolved in 150 ml ether and washed with 50 ml water and 2.50 ml saturated aqueous sodium chloride solution. After drying over calcium sulfate the ether solution was subjected to fractional distillation to give 7.2g of 12 (23.6% yield); ir: 3070, 2970, 2920, 2860, 1735, 1710, 1640, 1450 (br.), 1375, 1350, 1255, 1225, 1190, 1145, 1100, 1020, 990, 915, 860 cm^{-1} ; nmr: δ 1.26 (s, 3H, CH_3 , and t, 3H, $-\text{CH}_3$ of ethyl group), 1.9 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.07 (s, 3H, $-\text{COCH}_3$); 4.16 (q, 2H, $-\text{CH}_2$ of ethyl group), 4.75-5.15 (m, 2H, vinyl CH_2), and 5.3-5.9 (m, 1H, vinyl CH).

3-Methyl-6-hepten-2-one (13). In the most efficient procedure the concentrated reaction mixture described above was stirred for 22 hrs. at 50°C with 246g of a 5% sodium hydroxide solution (308 mmol

NaOH). This mixture was washed with ether to remove the small amount of 13 already formed. The aqueous solution was then acidified to pH < 2 with concentrated hydrochloric acid causing the vigorous evolution of carbon dioxide. After stirring for $\frac{1}{2}$ hr., the solution was extracted with ether; the aqueous portion was stirred overnight at room temperature and again extracted with ether. The combined ether solutions were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride solutions and dried over magnesium sulfate. The ether was then removed by distillation through a 20 cm Vigreux column and the residue subjected to fractional distillation to give 4.7g 13, b.p. 54°C at 15 mm (24% yield based on ethyl 2-methylacetoacetate). Anal. calcd. for 13: C, 76.14; H, 11.18. Found: C, 75.87; H, 11.45; ir: 3070, 2960, 2915, 1710, 1640, 1460, 1355, 1170, 995, 915 cm^{-1} ; nmr: δ 1.05 (d, 3H, -CH₃), 2.03 (s, 3H, -COCH₃), 2.45 (m, 1H, -CH-), 1.2-2.2 (m, 4H, -CH₂CH₂-), 5.0 (m, 2H, vinyl CH₂), 5.7 (m, 1H, vinyl CH).

(Z)- and (E)-3-Methyl-2,6-heptadien-2-yl trifluoromethanesulfonate (9Z and 9E). Into an oven dried 50 ml round bottomed flask equipped with a magnetic stirring bar was placed 20 ml methylene chloride (dried over magnesium sulfate) and 1.71g (16 mmol) 2,6-lutidine (dried over molecular sieves). The reaction flask was flushed with argon, sealed with a rubber serum cap, and cooled to -78°. In a glove bag under a nitrogen atmosphere 4.23g (15 mmol) trifluoromethanesulfonic acid anhydride was taken up into a syringe;

the syringe needle was quickly inserted through the reaction flask septum, and the anhydride was slowly added to the reaction mixture over 10 minutes. During this time the solution turned a light yellow color and a small denser second layer was formed. The mixture was stirred for 15 minutes after which 0.631g (5.0 mmol) 3-methyl-6-hepten-2-one (13) was added dropwise. The reaction was stirred for 15 minutes at -78° and was then allowed to warm to -30° , during which time the two phase solution became cloudy (-55°) and cleared again as a single layer (-35°). Aliquots were taken at regular intervals, quenched in a mixture of pentane and saturated aqueous sodium bicarbonate solution and examined by vpc (column B, 100°C , 100 ml/min.). After stirring at -30° to -20° for 15 hours the reaction was found to be complete.

The reaction was warmed to 0°C and 10 ml saturated aqueous sodium bicarbonate added dropwise. This mixture was extracted with 30 ml ether. The organic solution was washed rapidly three times with cold 0.5 normal hydrochloric acid followed by saturated aqueous sodium chloride solution. After drying over sodium sulfate most of the ether was distilled at atmospheric pressure. The remaining solution was then vacuum transferred off of the polymeric residue typical of this reaction. Vpc analysis showed formation of 9Z and 9E in a roughly 1:1 ratio in addition to a smaller amount of the isomeric terminal double bond triflate (14). In small scale reactions, estimates based on vpc comparison with an internal standard suggest a combined yield of 12-13% for 9Z and 9E.

9Z and 9E were then separated by preparative vpc (column A,

115°; 100 ml/min); each product was contaminated with approximately 2-4% of the other isomer. Ir of 9Z: 3080, 2990, 3050, 2970, 1691, 1642, 1415, 1380, 1255, 1235, 1215, 1150, 1095, 1023, 995, 920 cm^{-1} ; nmr of 9Z. δ 1.83 (q, $J = 1.1$ Hz, 3H, $\beta\text{-CH}_3$), 2.06 (m, 3H, $\alpha\text{-CH}_3$), 2.14-2.35 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 4.82-5.32 (m, 2H, vinyl CH_2), 5.45-6.2 (m, 1H, vinyl CH). Ir of 9e: 3080, 2990, 3050, 2970, 1691, 1642, 1415, 1380, 1255, 1235, 1215, 1150, 1095, 995, 920; nmr of 9E: δ 1.98 (q, $J = 1.5$ Hz, 3H, $\beta\text{-CH}_3$), 2.05 (m, 3H, $-\text{CH}_3$), 2.2 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 4.82-5.23 (m, 2H, vinyl CH_2), 5.45-6.2 (m, 1H, vinyl CH).

3-Methyl-2-heptanone (29). Reaction of 2-methylhexanoic acid (22, Eastman Organic Chemicals) with methyllithium was accomplished by a modification³⁸ of the procedure of Bare and House.³⁹ A 300 ml three-necked flask equipped with a reflux condenser, a nitrogen inlet, a pressure equalizing addition funnel, and a mechanical stirrer, was charged with 430 mg (54.1 mmol) lithium hydride in 90 ml ether (distilled from LAH). A solution of 5.81g (44.6 mmol) 2-methylhexanoic acid in 20 ml ether was added dropwise over a period of 30 minutes with rapid precipitation of a white salt. The viscous reaction mixture was heated to reflux and stirred overnight, after which it was cooled to 10° and 22.7 ml methyllithium (2.2 M., 49.9 mmol) was added dropwise over 25 minutes with vigorous stirring, causing all the solid to dissolve. After stirring an additional four hours at room temperature, the reaction mixture was siphoned under a positive pressure of nitrogen into a vigorously stirred 0°C solution of 6.83 ml concentrated hydrochloric acid in 100 ml water. The aqueous layer was extracted with

ether and the combined organic solutions washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. After drying over magnesium sulfate, the ether was distilled off through a 20 cm Vigreux column at atmospheric pressure and the residue subjected to fractional distillation at reduced pressure to give 4.75g 29, yield 83%, b.p. 63-64° at 25 mm (lit.⁴⁰ b.p. 162°C at 760 mm). Anal. calcd. for 29: C, 74.94; H, 12.58; found: C, 75.13; H, 12.80; ir: 2952, 2922, 2867, 2852, 1706, 1462, 1455, 1374, 1349, 1169, 1132 and 947 cm^{-1} ; nmr: δ 0.8 - 1.55 (m, 12H, including doublet, $J=6.5$, $-\text{CH}_3$), 2.02 (s, 3H, $-\text{COCH}_3$), and 2.4 (m, 1H, $-\text{CH}-$).

(Z)- and (E)-3-Methyl-2-hepten-2-yl trifluoromethanesulfonate (30Z and 30E). The procedure described above for the production of 9Z and 9E was followed using 3-methyl-2-heptanone, except that the reaction was instead run at -10° for 16 hours. After workup preparative vapor phase chromatography (column A, 100°C , 100 ml/min) provided 30Z and 30E, each contaminated with approximately 2-4% of the other isomer. Nmr of 30Z: δ 0.92 (t, $J = 6.5$ Hz, 3H, $-\text{CH}_3$), 1.1-1.55 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.72 (q, $J = 0.9$ Hz, 3H, $\beta\text{-CH}_3$), 2.02 (m, 3H, $\alpha\text{-CH}_3$), 2.15 (m, 2H, allylic CH_2); nmr of 30E: δ 0.93 (t, 3H, $-\text{CH}_3$), 1.1-1.6 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.78 (q, $J = 1.3$ Hz, 3H, $\beta\text{-CH}_3$), 2.02 (m, 5H, $\alpha\text{-CH}_3$ and allylic CH_2).

(Z)- and (E)-3-Methyl-2-hepten-2-yl acetate (32Z and 32E). The vinyl acetates were prepared according to the procedure of House et al.²² A 10 ml round bottomed flask with a magnetic stirring bar was charged with 0.4g (3.13 mmol) 3-methyl-2-heptanone (29), 1.44g acetic

anhydride and 3.76 ml carbon tetrachloride. A catalytic amount of 70% aqueous perchloric acid ($\sim 2\mu\text{l}$) was added causing the solution to turn yellow immediately. The reaction was stirred at room temperature and followed by vpc (column A, 110°C , 100 ml/min.); aliquots were shaken with a pentane/saturated aqueous sodium bicarbonate solution before vpc injection. After 3.5 hrs. the reaction was complete. The reaction mixture was then poured into a cold ($0-5^\circ\text{C}$) mixture of 15 ml pentane and 15 ml saturated aqueous sodium bicarbonate solution. Solid sodium bicarbonate was added until the solution had been neutralized. The aqueous layer was extracted with pentane and the combined pentane solutions were washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. The pentane was distilled off at atmospheric pressure through a 20 cm Vigreux column; the residue was subjected to fractionation at reduced pressure to give 3.7g (70% yield) of a 1:1 mixture of 32Z and 32E. Several vpc columns were used in an effort to obtain clean separation of the two isomers: columns F and G provided very little separation, but column A (100°C , 100 ml/min.) provided adequate separation when small injections were used. Enough 32Z and 32E were isolated to obtain their spectra and to conduct the shift reagent studies (see text). Ir of 32Z: 2970, 2930, 2870, 1750, 1697, 1470, 1460, 1450, 1390, 1370, 1265, 1225, 1200, 1140, 1050, 1020, 940 and 865 cm^{-1} ; nmr of 32Z: δ 0.9 (t, 3H, CH_3), 1.1-1.55 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.65 (q, $J = 0.9\text{ Hz}$, 3H, CH_3 trans to OAc), 1.81 (m, 3H, CH_3 gem to OAc), 1.91 (m, 2H, allylic CH_2), 2.04 (s, 3H, $-\text{COCH}_3$). Ir of 32E: 2970, 2930, 2870, 1750, 1699, 1470, 1460, 1445, 1370, 1260,

1200, 1140, 1050, 1020, 940, 930 and 865 cm^{-1} ; nmr of 32E 0.93 (t, 3H, CH_3), 1.1-1.55 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.48 (q, $J = 1.4$ Hz, 3H, CH_3 cis to OAc), 1.81 (m, 3H, CH_3 gem to OAc), 2.0 (m, 2H, allylic CH_2), 2.05 (s, 3H, $-\text{COCH}_3$). Shift reagent studies were carried out with $\text{Eu}(\text{fod})_3$ (Norell Chemical Co.) as a 0.2-0.5 M solution in carbon tetrachloride according to the procedure of Kelsey.²⁴

(Z)- and (E)-2-Trimethylsilyloxy-3-methyl-2-heptene (33Z and 33E). The procedure of House *et al.*²⁵ was used to prepare the trimethylsilyl enol ethers of 3-methyl-2-heptanone (29). To a solution of 1.81g (16.7 mmol) chlorotrimethylsilane (distilled immediately prior to use) and 3.38g (33.3 mmol) triethylamine (dried over molecular sieves) in 6.3 ml dimethylformamide (dried over molecular sieves) was added 2.0g (15.8 mmol) 29. The solution turned a brown-orange color almost immediately with formation of a light yellow salt (triethylamine hydrochloride). The reaction was refluxed for 72 hours, then cooled to room temperature, diluted with 15 ml pentane and washed rapidly with 3×20 ml cold saturated aqueous sodium bicarbonate solution. The aqueous solution was extracted with pentane, and the combined pentane solutions were washed rapidly in succession with cold 1N hydrochloric acid, cold saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. After drying over magnesium sulfate, the solution was concentrated by distillation of the pentane through a 20 cm Vigreux column. Vpc analysis (column I, 120°C, 100 ml/min.) showed large amounts of terminal double bond silyl enol ether and

smaller amounts the 2,3-double bond isomers. Pure 33Z and 33E were isolated by preparative vpc (column I, 110°C, 100 ml/min). Ir of 33Z: 2967, 2927, 2867, 1677, 1468, 1456, 1446, 1387, 1265, 1251, 1217, 1182, 1012, 948, and 852 (broad) cm^{-1} ; nmr of 33Z: δ 0.15 (s, 9H, -SiMe₃), 0.92 (m, 3H, -CH₃), 1.1-1.55 (m, 4H, -CH₂CH₂-), 1.55 (q, J = 1.0 Hz, 3H, CH₃ trans to silyloxy group), 1.75 (m, 3H, CH₃ gem to silyloxy group), 1.75-2.2 (m, 2H, allylic CH₂). Ir of 33E: 2950, 2870, 1679, 1470, 1385, 1372, 1263, 1252, 1188, 1050, 1009, 956, and 855 cm^{-1} ; nmr of 33E: δ 0.13 (s, 9H, -SiMe₃), 0.92 (m, 3H, CH₃), 1.1-1.15 (m, 4H, -CH₂CH₂-), 1.51 (q, J = 1.5 Hz, 3H, CH₃ cis to silyloxy group), 1.74 (m, 3H, CH₃ gem to silyloxy group); 1.94 (m, 2H, allylic CH₂).

Conversion of (Z)- and (E)-2-trimethylsilyloxy-3-methyl-2-heptene (33Z and 33E) to vinyl acetates 32Z and 32E. Using the procedure of House *et al.*²⁵ 103 mg (0.515 mmol) of silyl ether 33Z in 0.5 ml dimethoxyethane (distilled from LAH) was reacted under nitrogen with 0.26 ml (0.507 mmol) 1.95M methyllithium in diethyl ether. The reaction was allowed to stir at room temperature for one hour and then diluted with 3 ml dry dimethoxyethane. 1.8 ml of this reaction mixture was transferred into 2 ml of rapidly stirring acetic anhydride. (The remainder of the enolate solution was used in the vinyl triflate synthesis described below.) After stirring for 15 minutes the acetic anhydride solution was added to 0°C mixture of pentane, saturated aqueous sodium bicarbonate, and excess sodium bicarbonate. After complete hydrolysis of the acetic anhydride, the aqueous layer was

extracted with pentane and the combined pentane layers were washed with water and saturated aqueous sodium chloride before being dried over sodium sulfate. Vpc analysis (column A, 105°C, 100 ml/min.) and comparison of retention times showed formation of vinyl acetate 32Z as the only major product. In addition a few percent of 3-methyl-2-heptanone (29) was observed.

Using the same procedure silyl ether 33E was reacted with methylolithium and quenched with acetic anhydride. In this case vinyl acetate 32E and a few percent of ketone 29 were the only significant products.

Conversion of (Z)- and (E)-2-trimethylsilyloxy-3-methyl-2-heptane (33Z and 33E) to vinyl triflates 30Z and 30E. To the remaining 1.7 ml of the enolate solution produced from 33Z as described above was added 150 mg (0.75 mmol) of trifluoromethanesulfonic imidazolide.²⁶ The reaction was stirred for one hour at room temperature before being diluted with 5 ml pentane and quenched with 2 ml water. The aqueous layer was extracted with pentane and the combined pentane layers were washed with saturated aqueous sodium chloride and dried over sodium sulfate. Vpc analysis (column A, 105°C, 100 ml/min.) showed that the reaction was only 10-20% complete at this point resulting in the formation of large amounts of ketone 29. However, the only additional products were vinyl triflates 30Z and 30E, which were formed in a 70:30 ratio, respectively.

In a similar procedure the enolate derived from silyl ether 33E

gave, in addition to large amounts of ketone 29, a 29:71 mixture of 30Z and 30E, respectively. The vinyl triflate products were identified by comparison of retention times with authentic samples of 30Z and 30E (column A, 120°C, 100 ml/min.).

1,2-Dimethyl-3-methoxy-1,4-cyclohexadiene (23). Birch reduction of 3,4-dimethylanisole (22), Aldrich Chem. Co.) was carried out by the method of Wilds and Nelson.⁴¹ A 250 ml three-necked flask equipped with a glass covered magnetic stirring bar, gas inlet, pressure equalizing addition funnel, and a dry ice condenser with a soda lime drying tube was charged with 6.25g (46 mmol) 22 in 25 ml ether (distilled from LAH), 100 ml ammonia was condensed into the flask and 1.61g (230 mmol) lithium wire was added in small pieces over five minutes. The deep blue solution was stirred for ten minutes after which 12.4g (270 mmol) absolute ethanol was added dropwise over twenty minutes. The reaction was stirred for an additional half hour during which time the blue color disappeared. The ammonia was allowed to evaporate slowly through a Vigreux column, and a mixture of 50 ml ether and 80 ml water was added to the remaining solution. The aqueous layer was extracted with 3 x 25 ml ether and the combined ether layers were washed with saturated aqueous sodium chloride and dried over potassium carbonate.

Vpc analysis of the reaction workup proved to be difficult due to the decomposition of the vinyl ether; however, treatment of column B (100°C, 100 ml/min.) with ammonia before each injection made successful analysis possible: reaction of starting material was complete and 23

proved to be the only significant product. Vinyl ether 23 was kept in the freezer as a dilute ether solution until immediately prior to use, at which point the solvent was removed on a rotary evaporator and the crude 23 used without further purification.

1,2-Dimethyl-1-cyclohexen-4-one (24). The 1,2-dimethyl-3-methoxy-1,4-cyclohexadiene (23) produced above (theoretical: 46 mmol) was added slowly to a solution of 7.57g (60 mmol) oxalic acid dihydrate in 100 ml methanol and 5 ml water. The reaction was stirred at room temperature and followed by vpc (column B, 100°C, 100 ml/min.); after 1.5 hr. the reaction was complete. The solution was diluted with 15 ml water and neutralized with 6.34g sodium bicarbonate. After stirring for 15 minutes this solution was added to a mixture of 75 ml pentane and 150 ml water. The aqueous layer was extracted with pentane and the combined pentane solutions were washed with water and saturated aqueous sodium chloride and dried over sodium sulfate. The pentane was distilled off at atmospheric pressure and the resulting crude product subjected directly to sodium borohydride reduction. Vpc analysis of the crude product showed in addition to solvent residue an 87:13 mixture of 24 and the rearrangement product 3,4-dimethyl-2-cyclohexen-1-one (27). Small amounts of these two compounds were isolated via preparative vpc (column B, 100°C, 100 ml/min.) for spectral purposes: ir of 24: 2975, 2915, 2865, 2855, 1718, 1445, 1425, 1404, 1385, 1355, 1296, 1255, 1225, 1195, 1138, 1117, 1022, and 921 cm^{-1} ; nmr of 24: δ 1.68 (broad singlet, 6H, $-\text{CH}_3$), 2.36 (m, 4H, $=\text{CCH}_2\text{CH}_2\text{CO}-$), 2.68 (m, 2H,

=CCH₂CO-); ir of 27: 3030, 2970, 2935, 2880, 1670, 1625, 1460, 1450, 1440, 1425, 1375, 1340, 1325, 1305, 1290, 1245, 1200, 1175, 1140, 1040, 1005, 950, 925, 860, and 690 cm⁻¹; nmr of 27: δ 1.19 (d, 3H, CH₃), 1.91 (m, 3H, allylic CH₃), 1.5-2.5 (m, 5H, -CHCH₂CH₂-), 5.65 (m, 1H, vinyl CH).

1-2,Dimethyl-1-cyclohexen-4-ol (25). The method of Heathcock et al.¹⁸ for reduction of a β-γ unsaturated ketone in the presence of an α,β-unsaturated ketone was used. A solution of the crude mixture of 24 and 27 described above in 61.8 absolute ethanol was placed in a dry 250 ml flask equipped with a magnetic stirring bar, a pressure equalizing addition funnel, and a Drierite drying tube. The flask was cooled to 0°C and a solution of 4.76g (12.6 mmol) sodium borohydride in 103 ml absolute ethanol was added dropwise over 35 minutes. The light yellow reaction mixture was stirred at 0°C for an additional 30 min. before being quenched with 1.15 ml glacial acetic acid. The resulting solution was added to a mixture of 100 ml pentane and 200 ml water. The aqueous layer was extracted with several small portions of pentane, and the combined pentane solutions were washed with water and saturated aqueous sodium chloride and dried over sodium sulfate.

The pentane was distilled off through a 40 cm Vigreux column and the residue subjected to fractional distillation at reduced pressure to give 1.45g of an 85:15 mixture (b.p. ~ 76° at 6 mm) of 1,2-dimethyl-1-cyclohexen-4-ol (25) and unreacted α,β-unsaturated ketone 27. The overall yield of 25 based on 3,4-dimethylanisole (32) was 21.6%. A sample of 25 isolated via preparative vpc (column B, 120°C, 100 ml/min.)

gave the following analytical data: Anal. calcd. for $C_8H_{14}O$: C, 76.14; H, 11.18; found: C, 75.85; H, 11.41; ir of 25: 3610, 3355, 2990, 2920, 2870, 2855, 1445, 1440, 1385, 1365, 1130, 1045, and 950 cm^{-1} ; nmr of 25: 1.57 (broad singlet, 6H, $-CH_3$), 1.4-1.8 (m, 2H), 1.8-2.2 (m, 4H); 2.8 (shift dependent on concentration, s, 1H, $-OH$), 3.76 (m, 1H, carbinol CH).

1,2-Dimethyl-1-cyclohexen-4-yl tosylate (26). Into a 10 ml pear-shaped flask was placed 1.0g (6.74 mmol of 25) of the 85:15 mixture of 25 and 27 described above in 4.15 ml pyridine (dried over molecular sieves). A solution of 1.33g (6.98 mmol) recrystallized p-toluenesulfonyl chloride in 2.8 ml pyridine was added with stirring. The reaction mixture was placed in a refrigerator for 3 days, during which time white needles of pyridine hydrochloride formed in the pale yellow solution. The mixture was added to 30 ml cold water and the aqueous solution was extracted with ether, which was in turn washed in succession with cold 0.5N hydrochloric acid, water, and saturated aqueous sodium chloride solution before being dried over sodium sulfate.

After removal of the ether on a rotary evaporator, the residual oil was crystallized twice from pentane at -80° to give the white crystalline tosylate 26. Vpc analysis (column C, 120°C , 100 ml/min.) of the pentane solution (column C, 120°C , 60 ml/min.) showed 27 and a small amount of unreacted 25, but vpc analysis of an ether solution of tosylate 26 (which did not survive the vpc conditions) showed no contamination with 27 or 25. Ir of 26: 2965, 2925, 2875, 1600, 1445, 1395, 1192, 1181, 1100, 1014, 946, 925, and 855 cm^{-1} ; nmr of 26: δ 1.55 (broadened

singlet, 6H, $-\text{CH}_3$), 1.65-2.3 (m, 6H, $-\text{CH}_2$), 2.43 (s, 3H, $\underline{\text{p-Me}}$), 4.65 (five line pattern, $J = 6.5$ Hz, 1H, $-\text{CHPTs}$), 7.5 (AB quartet, 4H, aromatic protons).

Solvolysis of (Z)- and (E)-3-methyl-2,6-heptadien-2-yl trifluoromethanesulfonate ($\underline{9Z}$ and $\underline{9E}$) in 80% aqueous ethanol. Into 11.4 ml aqueous ethanol was placed 58.8 mg (0.227 mmol) of a roughly 1:1 mixture of $\underline{9Z}$ and $\underline{9E}$ purified by preparative vpc (column E, 120°C, 100 ml/min.). To this solution was added 33.2 mg (0.30 mmol) 2,6-lutidine (distilled before use). The reaction was stirred at 70-75° for 22 hrs., at which time reaction of the triflates was essentially complete. The reaction mixture was diluted with 70 ml pentane; washed with cold 0.5N HCl, water, and saturated aqueous sodium chloride solution. Most of the pentane was distilled off through a 20 cm Vigreux column at atmospheric pressure. Vpc analysis of the remaining solution (column B, 100°, 75°, 100 ml/min.; column C, 80°, 100 ml/min.) showed only two products in a 3:4 ratio in order of increasing retention time. The first product was isolated by preparative vpc (column B, 80°, 100 ml/min.) and identified as 3-methyl-1,2,6-heptatriene ($\underline{15}$) on the basis of its ir: 3090, 2990, 2920, 2860, 1958 (allene), 1642 ($\text{CH}_2=\text{CH}-$), 1448, 1432, 1373, 1292, 1202, 1173, 1154, 1000, 968, and 853 cm^{-1} . (See trifluoroethanol solvolysis below for the nmr of $\underline{15}$). The second product was identified as 3-methyl-6-hepten-2-one ($\underline{13}$) by comparison with an authentic sample of $\underline{13}$ (vide supra).

Solvolysis of (Z)- and (E)-3-methyl-2,6-heptadiene-2-yl trifluoromethanesulfonate (9Z and 9E) in trifluoroethanol. I. Preparative Solvolyses. Trifluoroethanol (Aldrich "Gold Label" 99+%) was dried over molecular sieves and distilled through a molecular sieve packed column before use. 2,6-Lutidine was dried over molecular sieves before use. Failure to follow these procedures led to formation of significant amounts of 3-methyl-2-hepten-6-one (13) in the solvolyses of 9Z and 9E.

Into an oven-dried 10 ml pear shaped flask with a magnetic stirring bar was placed 126.2 mg (0.49 mmol) of a roughly 1:1 mixture of 9Z and 9E (purified by preparative vpc-column B, 90°C, 100 ml/min.) and 105 mg (0.98 mmol) 2,6-lutidine in 4.9 ml trifluoroethanol. The reaction was stoppered and stirred at 70°C for 31 hours, after which it was added to a mixture of 15 ml water and 10 ml pentane. The aqueous layer was extracted with pentane and the combined pentane solutions were washed with cold saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride before being dried over potassium carbonate. The pentane was distilled off at atmospheric pressure through a 20 cm Vigreux column and the reaction products were then isolated via preparative vpc (column A, 120°C, 100 ml/min.).

The following spectral data were obtained for the product compounds (in order of increasing retention time): ir of 3-methyl-1,2,6-heptatriene (15): 3090, 2990, 2920, 2860, 1958, 1642, 1448, 1432, 1373, 1292, 1202, 1173, 1154, 1000, 968, and 853 cm^{-1} ; nmr of 15: δ 1.67 (t, J = 3, 3H, -CH₃), 2.06 (m, 4H, -CH₂CH₂-), 4.55 (sextet, J = 3, 2H, allene CH₂), 4.75-5.17 (m, 2H, vinyl CH₂), 5.33-6.17 (m, 1H, vinyl CH);

ir of 1,2-dimethyl-2-anti-(2',2',2'-trifluoroethoxy)-bicyclo [3.1.0] hexane (17): 3070, 3035, 2945, 2885, 1460, 1420, 1377, 1342, 1285 (broad), 1165 (broad), 1130, 1050, 1025, 1005, 977, 908, 888, 848, 690, and 655 cm^{-1} ; nmr of 17: δ 0-0.4 (m, 2H, cyclopropyl CH_2), \sim 0.9-1.43 (m, 1H, cyclopropyl CH), 1.13 (s, 3H, CH_3 gem to OCH_2CF_3), 1.23 (s, 3H, cyclopropyl CH_3), 1.43-2.0 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 3.66 (q, $J = 8.5$ Hz, $-\text{CH}_2\text{CF}_3$), ir of 1,2-dimethyl-2-syn-(2',2',2'-trifluoroethoxy)-bicyclo [3.1.0] hexane (18): 3070, 3035, 2945, 2885, 1479, 1456, 1417, 1389, 1377, 1282, 1163 (broad), 1128 (broad), 1048, 1020, 1011, 975, 910, 879, 848, and 689 cm^{-1} ; nmr of 18: δ 0.34 (d of d, 1H, C6 cyclopropyl H); 0.84 (d of d, 1H, cyclopropyl H), \sim 0.8-1.1 (m, 1H, C5 cyclopropyl H), 1.15 (s, 3H, CH_3 gem to $-\text{OCH}_2\text{CF}_3$), 1.31 (s, 3H, cyclopropyl CH_3), 1.62 (m, 4H, $-\text{CH}_2\text{CH}_2$), 3.77 (q, $J = 8.5$ Hz, CH_2CF_3); ir of (Z)-3-methyl-2-(2',2',2'-trifluoroethoxy)-2,6-heptadiene (16Z); 3080, 2955, 2875, 1683, 1640, 1463, 1415, 1388, 1375, 1283, 1160 (broad), 1120, 1088, 998, 970, 913, 850, and 665 cm^{-1} ; nmr of 16Z: δ 1.56 (q, $J = 0.9$ Hz, 3H, CH_3 trans to OCH_2CF_3), 1.79 (m, 3H, CH_3 gem to OCH_2CF_3), 2.10 (m, 2H, CH_2), 2.14 (\sim s, 2H, CH_2), 3.90 (q, $J = 8.5$ Hz, 2H, CH_2CF_3), 4.14-5.15 (m, 2H, vinyl CH_2), 5.25-6.0 (m, 1H, vinyl CH); ir of (E)-3-methyl-2-(2',2',2'-trifluoroethoxy)-2,6-heptadiene (16E), 3080, 2990, 2930, 2870, 1683, 1641, 1444, 1419, 1388, 1377, 1312, 1287, 1160 (broad), 1088, 971, 919, 852, and 661 cm^{-1} ; nmr of 16E: δ 1.64 (q, $J = 1.3$, 3H, CH_3 cis to OCH_2CF_3), 1.79 (m, 3H, CH_3 gem to OCH_2CF_3), 2.03 (\sim s, 2H, CH_2), 2.08 (m, 2H, CH_2), 3.90 (q, $J = 8.5$ Hz, 2H, $-\text{CH}_2\text{CF}_3$), 4.74-5.17 (m, 2H, vinyl CH_2), 5.31-6.2 (m, 1H, vinyl CH); ir of 2,3-dimethyl-3-(2',2',2'-trifluoro-

ethoxy)-1-cyclohexene (19): 2980, 2930, 2855, 1449, 1440, 1379, 1357, 1276, 1160, 1122, 978, 880, 849, 679, 659 cm^{-1} ; nmr of 19: δ 1.18 (s, 3H, CH_3 gem to OCH_2CF_3), 1.65 (m, 5H, allylic CH_3 and CH_2), 2.00 (m, 4H, allylic CH_2 and CH_2 alpha to OCH_2CF_3), 3.69 (q, $J = 8.5$, 2H, CH_2CF_3), 5.33 (m, 1H, vinyl CH); ir of 1,2-dimethyl-4-(2',2',2'-trifluoroethoxy)-1-cyclohexene (20): 2925, 2875, 2850, 1447, 1373, 1280, 1160, 1133, 1000, 972, 868, 672 cm^{-1} ; nmr of 20: δ 1.58 (s, 6H, CH_3), 1.58-2.2 (m, 6H, CH_2), 3.77 (q, $J = 8.5$, 2H, CH_2CF_3). Compounds 18 and 16Z were collected as a single peak containing roughly 70% 16Z and 30% 18. Pure 18 was isolated as a product of the solvolysis of 1,2-dimethyl-1-cyclohexen-4-yl tosylate (37) (vide infra). The nmr of 17 also showed traces of what may have been o-xylene (δ 2.24 and 7.0 in a ratio of 3:2); an authentic sample of o-xylene had the same retention time as the impurity in 17. No o-xylene was present in any of the starting materials.

II. Analytical solvolyses. In a typical procedure 24.5 mg (0.95 mmol) of 9Z, 20.4 mg (0.190 mmol) dry 2,6-lutidine, and 1.0 ml trifluoroethanol were placed with a magnetic stirring bar in an oven-dried 2 ml vial, which was then sealed with a rubber serum cap. The solution was stirred in an oil bath at $60 \pm 2^\circ$ for 72 hours. 1-2 μl aliquots were withdrawn at regular intervals and injected directly onto column D (130°) for analysis and direct digital integration using the Hewlett-Packard 3370A Integrator. Products were identified by comparison of retention time with the samples obtained in the preparative scale reaction described above. Compounds 18 and 16Z eluted as a

single peak; the relative amounts of 18 and 16Z at the end of the solvolysis run were determined in a somewhat larger scale comparable reaction by preparative vpc isolation of this peak (column A, 120°C, 100 ml/min.) and nmr analysis of this mixture. Solvolyses of 9E were performed in a similar manner. In each case estimation of overall yield was made by comparison with an internal standard; after correction for relative response factors (all trifluoroethyl ethers were assumed to have the same relative response as 37E) the overall yield was found to be > 95%. No interconversion of 9Z and 9E could be detected during the course of the reaction.

Solvolysis of (Z)- and (E)-3-methyl-2-hepten-2-yl trifluoromethanesulfonate (30Z and 30E) in trifluoroethanol. Analytical solvolyses were performed in the same manner as for 9Z and 9E above, except that the vpc analyses were carried out at 110° on column D. In addition to the experiments carried out using 0.09 M 30E or 30E and 0.18M 2,6-lutidine concentrations, runs were made using 0.9 M 30Z with 0.364M 2,6-lutidine and 0.23M 30Z with 0.46M 2,6-lutidine. No significant change in the vinyl ether product ratio was observed under any of these conditions (see text). Again overall product yield was > 95% and no interconversion of 30Z and 30E was detected.

For identification of products, the final reaction mixtures of six of the analytical solvolyses were combined and added to a mixture of 10 ml pentane and 15 ml water. The aqueous layer was extracted with pentane, and the combined pentane solutions were washed with cold

0.5N hydrochloric acid, saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride before being dried over magnesium sulfate. Most of the pentane was removed by distillation through a 20 cm Vigreux column at atmospheric pressure. The three reaction products were then isolated via preparative vpc (column A, 110°C, 100 ml/min.); ir of 36: 3050, 2930 (broad), 2880, 2865, 1960, 1470, 1460, 1448, 1430, 1380, 1371, 1290, 1250, 1205, 1180, 1102, 968, 850 cm^{-1} ; nmr of 36: δ 0.92 (m, 3H, CH_3), 1.15-1.7 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.66 (t, $J = 3\text{Hz}$, 3H, allenic CH_3), 1.92 (m, 2H, allylic methylene), 4.53 (sextet?, $J=3$, 2H, allenic CH_2); ir of (Z)-37Z: 2960, 2930, 2870, 1685, 1470, 1460, 1450, 1422, 1390, 1285 (broad), 1165, 1088, 970, 850, 660 cm^{-1} ; nmr of 37Z: δ 0.92 (m, 3H, CH_3), 1.1-1.55 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.58 (q, $J = 0.8\text{ Hz}$, 3H, CH_3 trans to OCH_2CF_3), 1.80 (m, 3H, CH_3 gem to OCH_2CF_3), 2.08 (~ broadened triplet, 2H, allylic methylene), 3.90 (q, $J = 8.5$, 2H, CH_2CF_3); ir of (E)-37E: 2960, 2930, 2870, 1686, 1470, 1460, 1420, 1376, 1310, 1285 (broad), 1165 (broad), 1085, 970, 907, 850, 660 cm^{-1} ; nmr of 37E. δ 0.92 (m, 3H, CH_3), 1.1-1.55 (m, 4H, $-\text{CH}_2\text{CH}_2-$), 1.62 (q, $J = 1.3\text{ Hz}$, 3H, CH_3 cis to OCH_2CF_3), 1.80 (m, 3H, CH_3 gem to OCH_2CF_3), 1.93 (broadened triplet, 2H, allylic CH_2), 3.90 (q, $J = 8.5$, 2H, $-\text{CH}_2\text{CF}_3$).

Estimates of the half lives for reaction of 9Z, 9F, 30Z, and 30E at 60° were made by monitoring the disappearance of starting material in each solvolysis. Because the vinyl triflates are known to give

somewhat irreproducible results from injection to injection (variances of up to 10-15%) and because the oil bath temperature was subject to $\pm 2^\circ$ fluctuations, these numbers are at best very rough estimates. The approximate half lives of 21, 11.4, 11.6, and 7 hrs. for 9Z, 9E, 30Z, and 30E, respectively, lead to relative rate estimates of 1:1.8:1.8:3 for these compounds.

Solvolysis of 1,2-dimethyl-1-cyclohexen-4-yl tosylate (26) in trifluoroethanol. I. Preparative solvolysis. Into a 10 ml pear-shaped flask with magnetic stirring bar and rubber serum cap was placed 150 mg (0.54 mmol) 26 and 112 mg (1.07 mmol) 2,6-lutidine (dried over molecular sieves) in 5.4 ml trifluoroethanol (dried over molecular sieves and distilled through a molecular sieve packed column). The reaction mixture was stirred in an oil bath at $60 \pm 2^\circ$ for three hours and then added to a mixture of 10 ml pentane and 15 ml water. The aqueous layer was extracted with pentane and the combined pentane solutions were washed with cold 0.5N hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. After drying over magnesium sulfate the pentane was distilled off at atmospheric pressure. The reaction products were then isolated by preparative vpc (column A, 100°C , 100 ml/min.). Products 17, 19, and 20 gave spectra identical to those of the samples of these compounds obtained above in the preparative scale solvolysis of 9Z and 9E. In addition, 18 was obtained in pure form and shown to have the same spectra as the minor product isolated with 16Z in that experiment (vice supra). Three very minor products showing olefinic ir and nmr

absorptions were collected together but were not further characterized due to lack of material.

II. Analytical solvolyses. Into a 2 ml vial with magnetic stirring bar and a rubber serum cap were placed 28.3 mg (0.1 mmol) tosylate (26) and 21 mg (0.2 mmol) 2,6-lutidine in 1.0 ml trifluoroethanol. The reaction mixture was stirred at $60 \pm 2^\circ$ and aliquots were analyzed directly as in the above solvolyses. Although the reaction was complete within the first hour, it was then allowed to stir for an additional 65 hours at 60°C to determine the stabilities of the cyclic trifluoroethyl ethers to the reaction conditions (see text for discussion). Although no formal studies of overall product yield were performed, the total integrated areas of the products for the same size injection at 3 and 66 hours did not differ significantly, suggesting that the changes in product ratios with time were indeed due to interconversion of the products and not to selective decomposition of 17 and 18.

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PROPOSITIONS

ABSTRACT OF PROPOSITIONS

- I. A synthetic approach to the theoretically interesting butalene molecule from a spirohexadiene precursor is proposed.
- II. It is suggested that rhodium (I) catalysts might provide a mild, efficient process for the conversion of acid chlorides to aldehydes.
- III. The possible intramolecular trapping of a 1,3-diradical by a sulfhydryl group is proposed.
- IV. A means of distinguishing between the possible mechanisms of participation of acetylenes in cyclizations, and of solvolyses of five- and six-membered ring vinyl triflates is suggested.
- V. It is proposed that an investigation be undertaken of cyclic dialkoxy carbenes which could lead to cyclopropanes and cyclobutanes on extrusion of carbon dioxide.

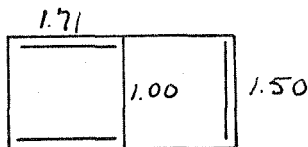
PROPOSITION I

1,3,5- Bicyclo [2.2.0] hexatriene (1), or "butalene" as it is more commonly named, belongs to a rather select class of fused bicyclic compounds. Although each of the four membered rings is cyclobutadiene-

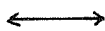
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like in nature, the π -system around the perimeter of the molecule, like benzene, contains six electrons. Thus, this fusion of two antiaromatic¹ rings creates a molecule with potential aromatic character.

Simple Hückel (HMO) calculations² on butalene predict a delocalization energy of 1.66β (compared to 2β for benzene and 0 for cyclobutadiene) and the bond orders shown in 2. This structure may

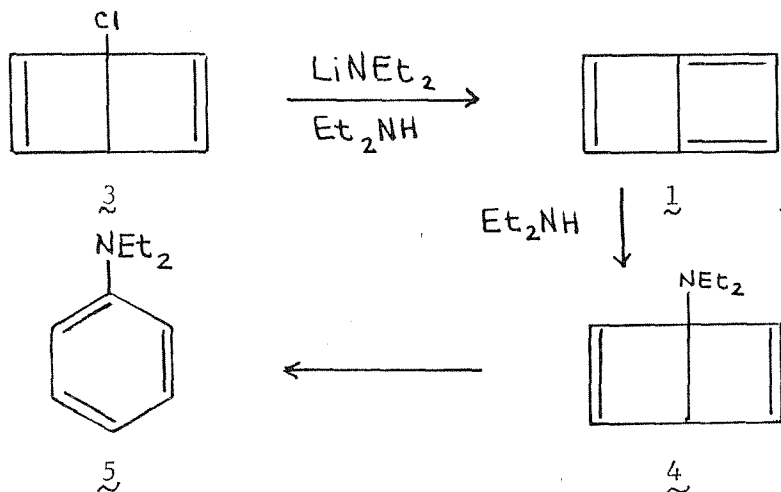
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best be interpreted in terms of equal contributions from resonance forms 1a and 1b with little or no contribution from 1c.

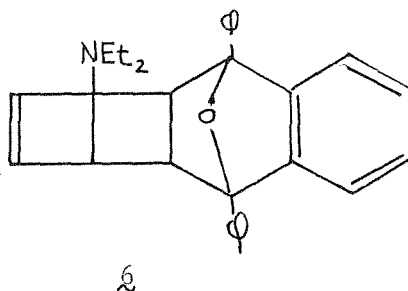
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Using more sophisticated semiempirical SCF MO calculations Dewar has calculated a resonance energy of -6.7 kcal/mole for butalene, indicating that this compound should be somewhat antiaromatic.³ For comparison Dewar calculates the resonance energies of benzene and cyclobutadiene to be 20 and -18 kcal/mole, respectively. It should be noted here that the Hückel and Dewar resonance energies are not directly comparable since the Hückel value is based on the isolated ethylene double bond as a reference state while the Dewar values use a hypothetical conjugated linear polyene as a model. A more direct comparison between the Hückel and Dewar resonance energies can be obtained by the method of Hess and Schaad⁴, who use HMO calculations but a reference state similar to Dewar's. This approach gives resonance energies of -0.4β , $+0.39\beta$, and -1.07β for butalene, benzene, and cyclobutadiene. Thus, although butalene is predicted to be somewhat antiaromatic, it is considerably less destabilized than cyclobutadiene.

Two experimental approaches to butalene have thus far been reported. Breslow has shown that 1-chloro-2,5-bicyclo [2.2.0] hexadiene (3) reacts with lithium diethylamide in diethylamine to give

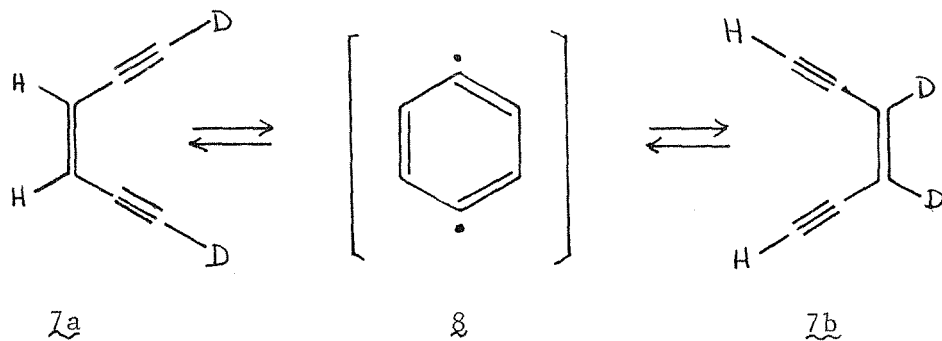


diethylaniline (5)¹. The intermediacy of Dewar benzene 4 in this reaction is suggested by the formation of the Diels-Alder adduct 6 when the reaction is run in the presence of diphenylisobenzofuran⁵. Breslow has proposed that the mechanism of this reaction involves initial dehydro-



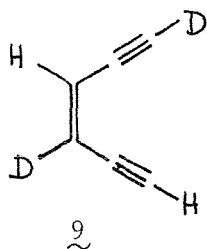
halogenation of 3 to form butalene which then adds diethylamine to give 4; however, if butalene is formed, it is clearly highly reactive under these conditions.

In a different experiment, Jones and Bergman have shown that deuterated cis-1,5-hexadiyn-3-ene (7a) undergoes a degenerate thermal



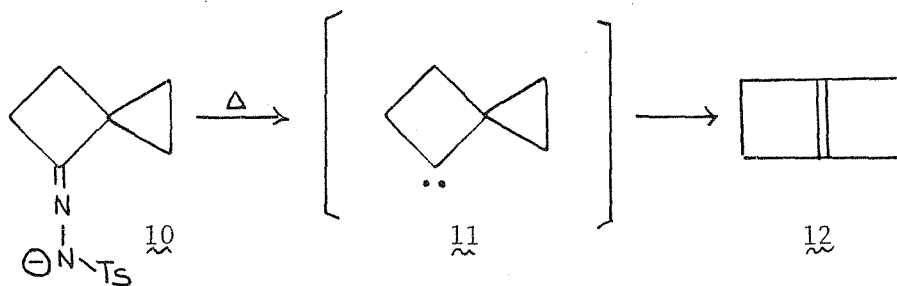
rearrangement which exchanges the vinyl and acetylenic hydrogens^{6,7}.

None of the single exchange product 9 is observed, indicating that the

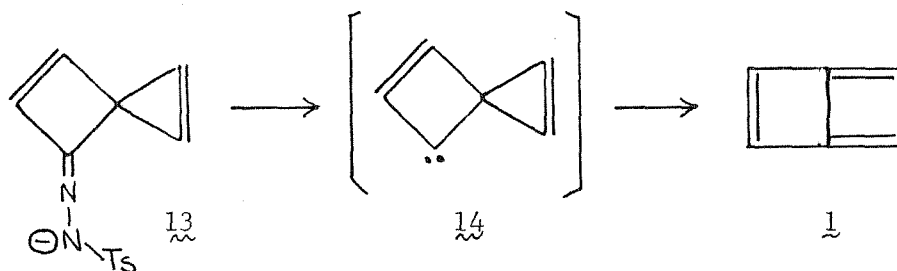


reaction must proceed via an intermediate or transition state in which C1, C3, C4, and C6 become chemically equivalent. Although butalene was considered as a possible intermediate, the observation of typical free radical trapping products when the reaction was run in solution prompted the suggestion that the reaction was actually proceeding via the 1,4-benzene diradical (8), often referred to as p-benzyne.

An alternate synthetic approach which, if successful, would allow the examination of both the spectroscopic and chemical properties of butalene would clearly be desirable. One promising approach is suggested by the recent report of Wiberg, et al.,⁸ that pyrolysis of the



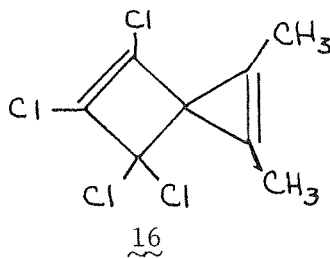
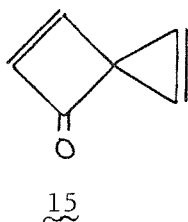
sodium salt of spiro [2.3] hexanone-4 tosylhydrazone (10) gives $\Delta^{1,4}$ -bicyclo [2.2.0] hexene (12), presumably via carbene 11. A comparable rearrangement in carbene 14 would lead directly to the butalene system.



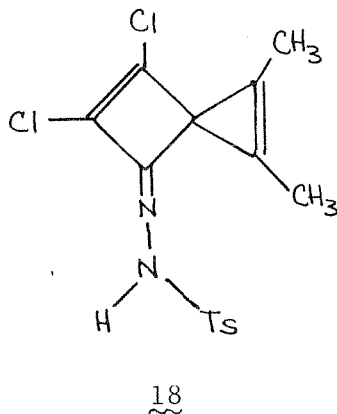
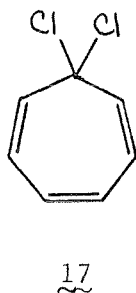
The tosylhydrazone salt 13 would be a suitable precursor for 14.

The parent spiro [2.3] hexa-1,5-dien-4-one (15) is not a known compound. The only spiro [2.3] hexadiene reported to date is compound 1.

16⁹. Although studies on the parent compound would, of course, be



desirable, 16 represents an excellent candidate for preliminary investigations of the proposed synthetic route. Jones and Ennis have found that the most efficient synthesis of the tosylhydrazone of tropone involves treatment of the gem dichloride 17 with tosylhydrazine¹⁰. In

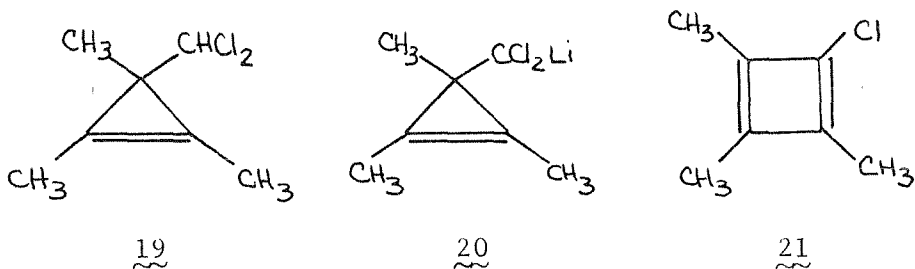


analogy, treatment of 16 with tosylhydrazine should lead directly to the desired tosylhydrazone 18.

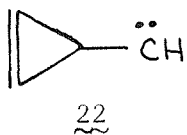
Conversion of 18 to the diazo compound followed by photolysis in an argon matrix at 8°K might then provide butalene under conditions where it could be examined spectroscopically. The recent success of Chapman in generating and studying cyclobutadiene under these

conditions¹¹ demonstrates the usefulness of this technique in the study of highly reactive compounds. Pyrolysis of the salt of 18 or the diazo compound in the presence of suitable Diels-Alder trapping agents might also provide chemical evidence for the intermediacy of butalene in this reaction.

The rearrangement suggested for carbene 14 would not be entirely without precedent. Closs has suggested that the cyclobutadiene dimers observed on treatment of 19 with n-butyllithium at -20° arise from ring expansion of the carbenoid 20 to give 21.¹² On the other hand, cyclobutadiene formation from diazo compound precursors of cyclopropenylcarbene 22 has not been reported, apparently because the major



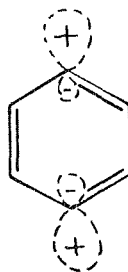
pathway for thermal decomposition of carbene 22 is fragmentation to



two acetylenes.¹³ However, the comparable fragmentation in carbene 14 appears to be effectively blocked since one of the acetylene fragments would have to be contained in a four membered ring.

The possibility that once formed butalene might rearrange to p-benzyne can also be considered. Theoretical calculations suggest that the highest occupied molecular orbital of p-benzyne should involve

the antisymmetric combination of the two radical lobes ($\underline{8A}$); the symmetric combination $\underline{8S}$ is calculated to lie somewhat higher in energy.

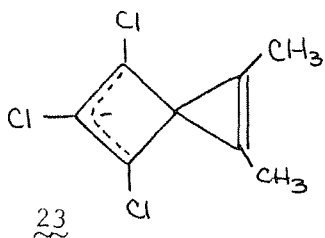
 $\underline{8A}$  $\underline{8S}$

This leads to the prediction^{14a} that the interconversion of butalene and p-benzyne should be forbidden in the Woodward Hoffman sense.¹⁵

This does not mean that the reaction will not occur, but it does suggest that there will be some barrier to the interconversion.

It would thus be of interest to perform trapping experiments similar to those of Jones and Bergman⁶ to see whether the products suggested to arise from p-benzyne are also formed in the pyrolysis of the salt of tosylhydrazone 18 or of the corresponding diazo compound. The diazo compound would clearly be preferable if it can be obtained since the salt will undoubtedly be insoluble in the solvents used in the p-benzyne experiment (CCl_4 , toluene, and pristane). If butalene is converted to p-benzyne then one would also predict the observation of cis-1,5-hexadiyn-3-ene(7) in the pyrolysis of the salt in vacuo.

Finally, it should be noted that in their studies on the possibility of spiroaromaticity in anion 23 Semmelhack, et.al.,¹⁶ have proposed that the kinetic instability of this species is due to loss of



chloride ion and reaction of the resulting carbene. No evidence was provided in support of this hypothesis, however, nor was any information or speculation given as to the nature of the products arising from

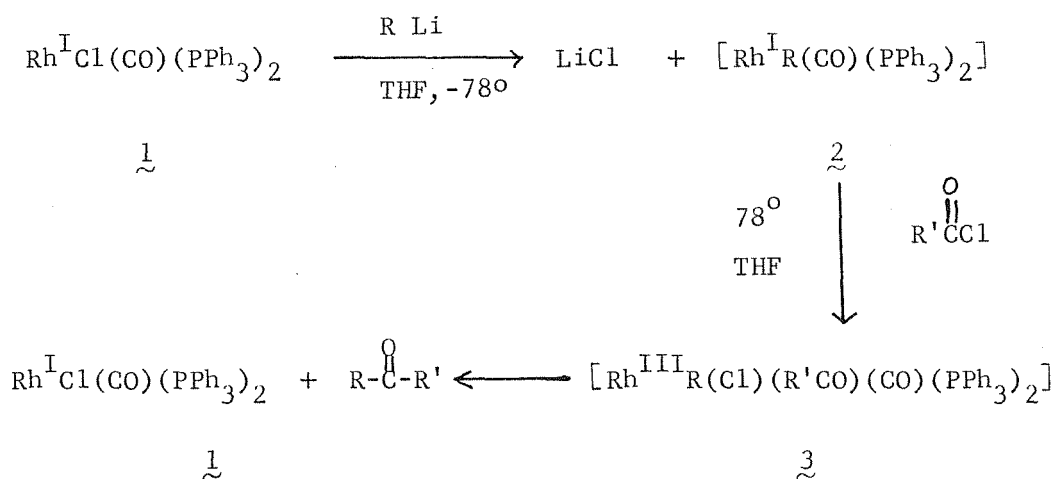
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PROPOSITION II

Recently Hegedus, et al. reported the convenient synthesis of unsymmetrical ketones from acyl chlorides using the rhodium catalyst 1.¹ Treatment of 1 with an organolithium or Grignard reagent leads

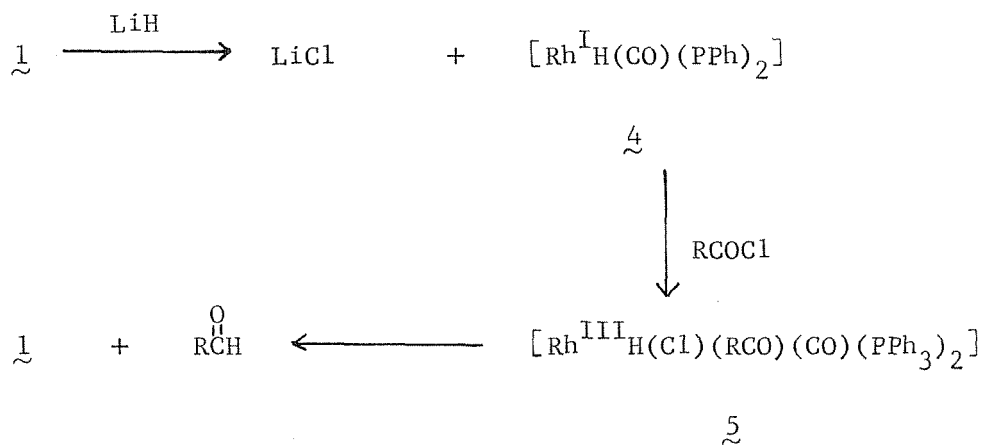


presumably to the alkyrhodium(I) complex 2. Oxidative addition² of an acid chloride to 2 is then proposed to generate the unstable alkylacylrhodium(III) complex 3, which undergoes spontaneous reductive elimination² to form the ketone product and regenerate the original chlororhodium complex 1. The proposed processes all find some precedent in previous work with rhodium complexes. Although spectroscopic evidence for the intermediacy of 2 was obtained, 3 could not be detected suggesting that the reductive elimination is a rapid step.

This reaction sequence presents several distinct advantages. Aryl, α,β -unsaturated, and simple aliphatic acid chlorides are all suitable substrates for this procedure, and in each case high yields of ketone product are obtained under extremely mild conditions. The

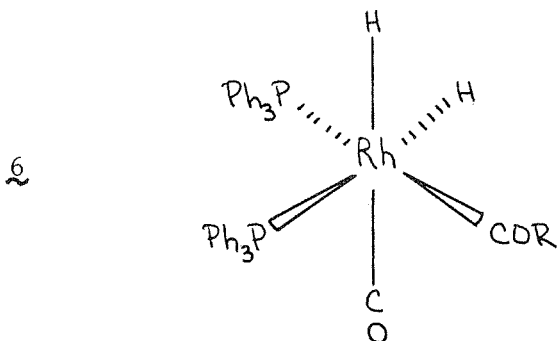
reaction can also be safely carried out in the presence of a large variety of functional groups including aldehydes, esters, nitriles, and obviously ketones. Finally, the initial rhodium catalyst is generated in reuseable form in the final reaction step. Since cost is usually an important consideration in the use of transition metal complexes in organic synthesis, this last consideration makes this synthetic approach particularly attractive.

The Hegedus procedure also suggests a modification which might transform this sequence into a means of converting acid chlorides to the corresponding aldehyde under very mild conditions. By analogy, treatment of $\underline{1}$ with a suitable hydride donor might be expected to provide the rhodium(I) complex $\underline{4}$. Lithium hydride would be the



simplest of the various hydride donors which might be used. Treatment of $\underline{4}$ with an acid chloride would then provide the rhodium(III) complex $\underline{5}$ by oxidative addition. Complex $\underline{5}$ is very similar to the dihydridoacylrhodium(III) complex $\underline{6}$

which has been proposed as an intermediate in the rhodium catalyzed hydroformylation of terminal alkenes to aldehydes.^{3,4} As in the

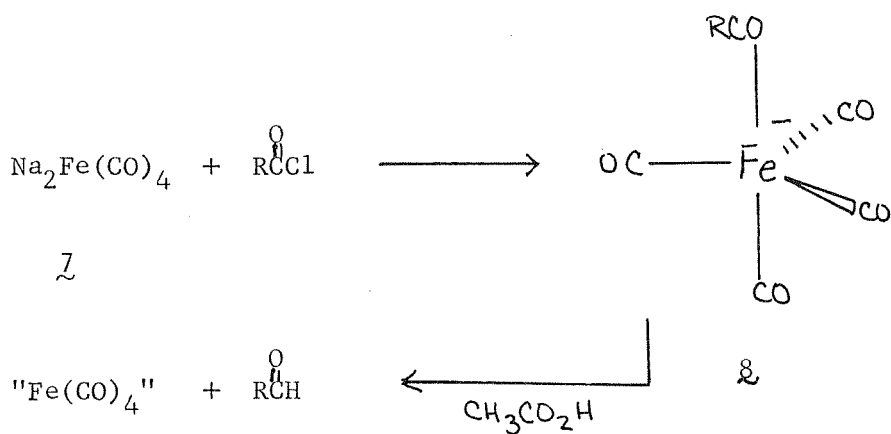


hydroformylation reactions 5 would be expected to undergo rapid reductive elimination to form the desired aldehyde and regenerate the initial rhodium complex. It has already been shown that the product aldehydes would be stable to the reaction conditions.¹

The advantages of this aldehyde synthesis would be the same as those discussed for the Hegedus ketone synthesis¹: mild conditions, the reduction of the acid chloride in the presence of a variety of sensitive functional groups, and no net consumption of the transition metal catalyst 1. This approach would provide a useful alternative to the existing procedures for reduction of acid derivatives directly to aldehydes, many of which either are of limited applicability or require protection of the sensitive functional groups which are unaffected in the rhodium reaction.⁵

This process would be comparable in scope to the procedure developed by Collman⁶ and Cooke⁷ (Scheme 1) for the conversion of acid chlorides to aldehydes using sodium tetracarbonylferrate (7).

SCHEME 1



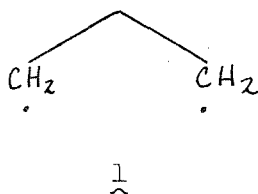
Reaction of an acid chloride with 7 provides the isolable intermediate 8 which can be cleaved with acetic acid to give the product aldehyde and an iron species which trimerizes to $\text{Fe}_3(\text{CO})_{12}$ in the absence of excess carbon monoxide. Although a complete study of the sensitivities of various other organic functional groups toward 7 was not reported, esters at least are stable to the reaction conditions. Collman has not yet attempted to recycle the iron containing products⁸, although this should in principle be feasible since 7 is initially produced from iron pentacarbonyl. Failure to obtain efficient recovery and recycling of the iron species would represent a serious drawback in this procedure compared to the proposed rhodium catalyzed process, since in that reaction sequence the initial rhodium complex 1 would be recovered directly in re-useable form.¹

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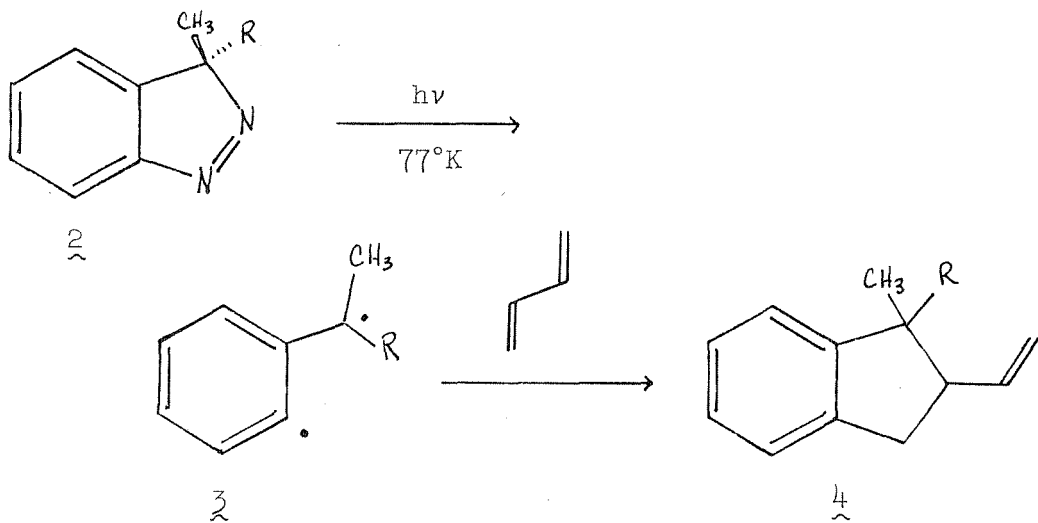
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PROPOSITION III

The formation of the trimethylene diradical (1) as a reactive



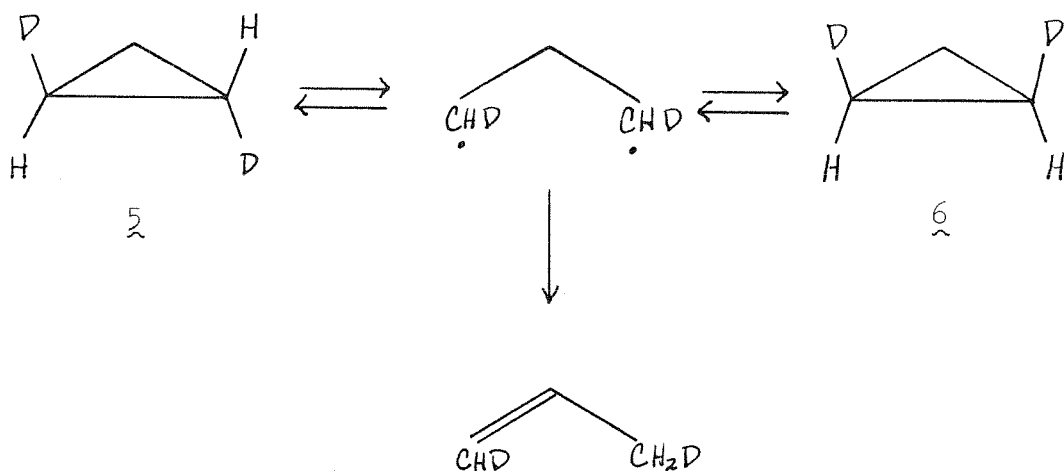
intermediate in the pyrolysis of cyclopropanes was first proposed by Chambers and Kistiakowsky in 1934.¹ Since that time considerable evidence has been advanced for the intermediacy of 1 in this and other reactions.² In only one instance, however, has definite spectroscopic evidence for the existence of a 1,3-diradical been reported. In that



case Closs et al. observed an esr signal attributable to the triplet diradical 3 on irradiation of indazole 2 at 77°K.³ On irradiation of 2 in butadiene, adduct 4 was formed, presumably by addition of butadiene

to diradical 2. This is also the only instance in which trapping of a 1,3-diradical has been achieved by chemical means.

In spite of the lack of spectroscopic and chemical trapping evidence for their existence, 1,3-diradicals have remained attractive intermediates in a variety of reactions. The results observed in cyclopropane pyrolyses in particular seem best understood on the basis of diradical intermediates. Thus, in addition to propylene formation by a hydrogen shift process, trans-1,2-dideuterocyclopropane (5) is found to undergo a faster isomerization to the cis isomer 6 on pyrolysis.⁴ Intuitively, this seems to require an intermediate in which one



of the cyclopropane ring bonds has been broken, and which has a sufficient lifetime for rotation around one of the remaining C-C bonds to occur before hydrogen shift or ring closure takes place. This argument is typical of those advanced for diradical intermediates in that the experimental results are explained on the basis of what is essentially

an intuitive expectation of how a diradical species ought to behave. Because predictions based on expected diradical behavior have been substantiated in a large number of experiments, diradicals have achieved widespread acceptance as reaction intermediates.

The designation of a 1,3-diradical as an intermediate implies the existence of energy barriers toward ring closure and hydrogen shift in this species. In other words, the diradical must lie in a well on the energy surface of the reaction as in Figure 1(a). This is in contrast to the alternate possibility that the diradical might correspond to a transition state in the reaction as in Figure 1(b). The

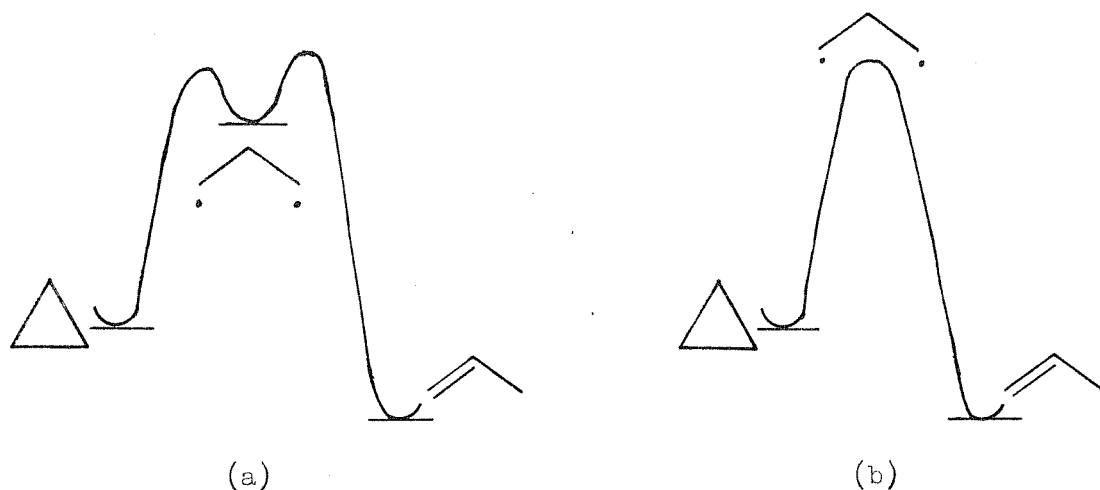


Figure 1

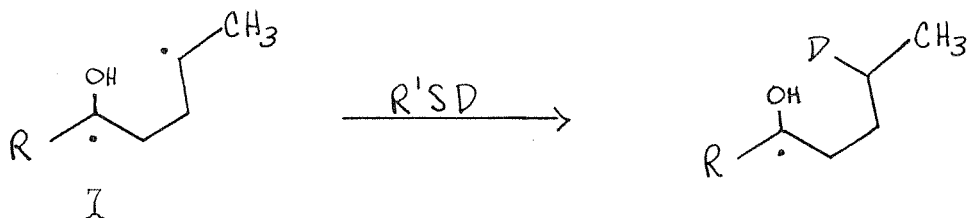
feeling that cyclopropane cleavage reactions are best explained by a barrier protected 1,3-diradical intermediate has been supported by thermochemical estimates which predict that the trimethylene diradical should lie in a 9-10 kcal/mole energy well.⁵ Recently, however,

theoretical calculations have been presented which suggest that there is no dip in the energy surface corresponding to a diradical intermediate.^{6,7} In fact, no secondary energy minimum is found along the reaction coordinate for cis-trans isomerization of a cyclopropane. At best, the transition state for this reaction could be thought of as having diradical character. Although the discrepancy between the theoretical and thermochemical calculations has not yet been explained,⁸ the theoretical results clearly challenge the traditional mechanism of cyclopropane ring cleavage.

The failure to intercept proposed 1,3-diradical intermediates in chemical trapping experiments performed to date is, of course, ambiguous. Although this could be taken as evidence that the reaction does not involve a discrete 1,3-diradical intermediate, it could also be taken to indicate that the trapping reactions attempted were not fast enough to compete with ring closure and hydrogen migration in the diradical. Thus, increasingly faster trapping experiments serve to define the limits of the energy well in which a possible 1,3-diradical could lie. In addition, of course, there is the possibility that by an improved technique one could actually trap the diradical, if it is a true intermediate, thereby solving the mechanistic problem.

One approach to such 1,3-diradical trapping experiments is suggested by a recent report of Wagner and Zepp.⁹ Although it has long been suspected that triplet 1,4-diradicals of the general structure $\text{[} \dots \text{]}$ were intermediates in the type-II photoelimination of ketones,^{10,11} no attempts to trap these species with agents like dienes proved successful. However, Wagner and Zepp were able to successfully intercept

these intermediates with alkyl mercaptans. This suggests that it might



prove interesting to attempt the trapping of a 1,3-diradical with a mercaptan.

For successful trapping, the rate of reaction of the mercaptan with the diradical would have to be competitive with the rate of the irreversible hydrogen migration process. Using Benson's thermochemical calculations, one can estimate that in the parent trimethylene diradical the rate of hydrogen migration should be on the order of 10^8 - 10^9 sec^{-1} at 300-400°C, the approximate temperature necessary for ring cleavage in a disubstituted cyclopropane (vide infra).⁵ Estimates of the rate of reaction of mercaptans with a radical center under these conditions prove to be more difficult. In addition to the lack of activation parameters necessary for the correction of rates to the higher temperatures involved in a cyclopropane pyrolysis, values reported for the rate of bimolecular trapping of simple radicals with mercaptans¹² vary from 10^6 to $10^8 \text{ M}^{-1} \text{ sec}^{-1}$ at room temperature in hydrocarbon solvents.

A variety of intramolecular reactions have been shown in the past to proceed at considerably faster rates than their intermolecular counterparts.¹³ Rate increases of several orders of magnitude are not

uncommon. Thus, it is reasonable to suppose on the basis of the estimated rates presented above that intramolecular trapping by a sulfhydryl group might be able to compete successfully with the hydrogen migration process in a 1,3-diradical at 300-400°C. (The large uncertainties in the numbers involved suggest that it would be easier to settle the question by running the reaction than by continuing to speculate on what might happen.)

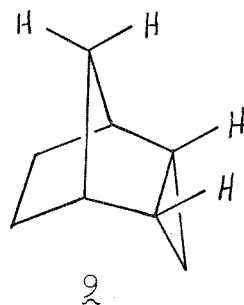
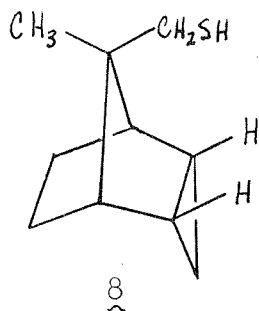
Unfortunately, the use of the alkyl mercaptan functionality introduces a rather severe limitation on the cyclopropane ring cleavages which can be investigated. Ethanethiol ($\text{C}_2\text{H}_5\text{SH}$) is found to undergo a rather facile elimination of H_2S ($\log A = 13.0$, $E_a = 51.2$ kcal/mole)¹⁴ which



at 400°C (the temperature necessary for reasonable rates of ring opening of disubstituted cyclopropanes) would be roughly twice as fast as the ring opening process in cis-1,2-dimethylcyclopropane ($\log A = 15.08$, $E_a = 58.87$)^{15a} and 180 times faster than the overall process leading to the hydrogen migration product ($\log A = 13.92$, $E_a = 61.4$ for cis-2-pentene formation).^{15b} Thus, even if trapping were competitive with the irreversible hydrogen migration process in the diradical, elimination of H_2S might remove the thiol group before trapping could take place. (It should be noted that the two other possible thermal reactions of the mercaptan group, homolytic cleavage of the R-S and the

S-H bonds, are considerably higher energy processes which should not interfere with these experiments.)^{14,16}

One way to circumvent this problem, of course, would be to block the H₂S elimination process as in compound 8 (or its exo isomer).

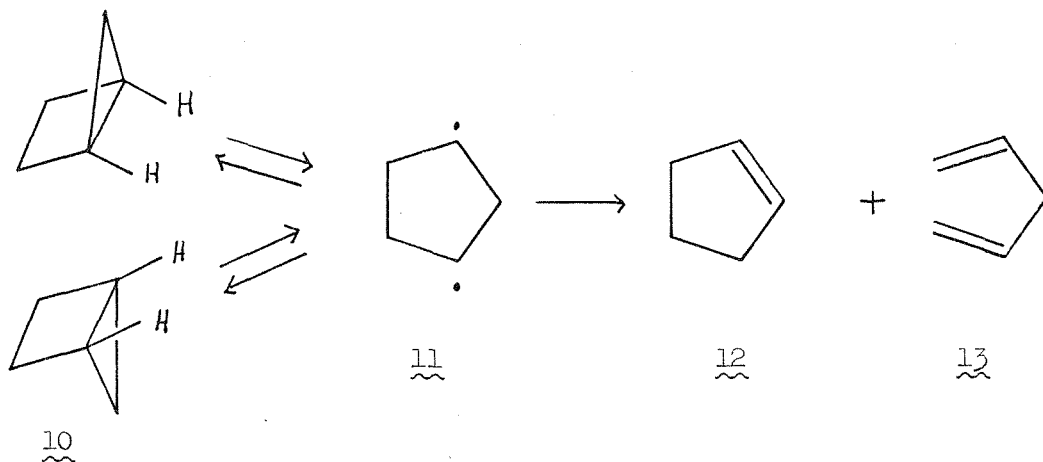


A second way to avoid the elimination of H₂S, even in systems where this process is not blocked, is to fuse the cyclopropane ring into a strained bi- or tricyclic system. In this way the activation energy for the cleavage reaction will be lowered relative to that of a simple cyclopropane due to the increased relief of strain achieved on opening the three-membered ring. This would allow the carrying out of the trapping experiments at lower temperatures where the loss of H₂S would not occur. Obviously, compound 8 also incorporates this feature.

Unfortunately, kinetic studies on even the parent tricyclococ-tane system 9 have not been reported. Thus, no information is available on the relative rates of ring inversion and hydrogen migration, nor is there any data to indicate how deep a well the possible diradical intermediate might lie in. Thus, it might prove more profitable to

first attempt the trapping experiments on a simpler system which has already been studied in some detail.

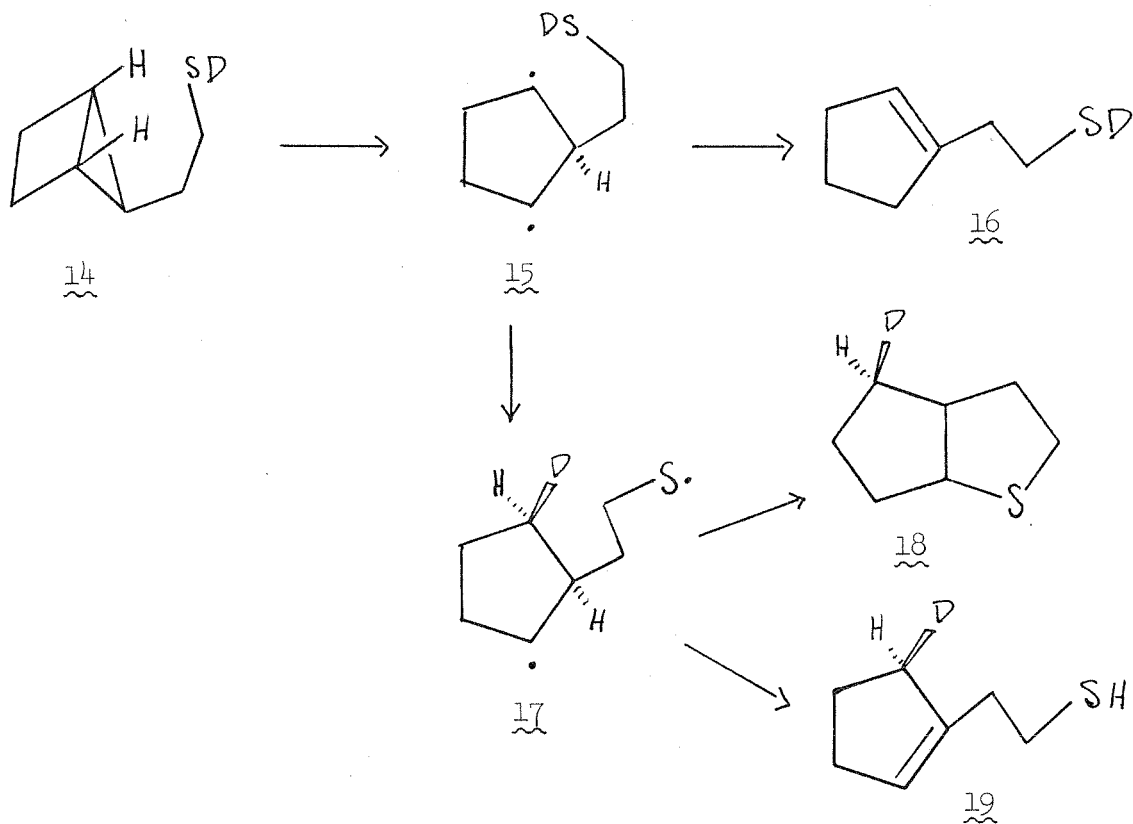
One possibility is the bicyclo[2.1.0] pentane system (10).



This system is known to undergo a facile ring inversion process in addition to the slower hydrogen migration to give 12.¹⁷ Diene 13 is also detected as a very minor product. The rearrangement to give cyclopentene ($\log A = 14.1$, $E_a = 45.6$ kcal/mole)^{17a} proceeds readily at 300°C; at this temperature the elimination of H₂S from an alkyl mercaptan would be expected to proceed at a rate $\sim 10^3$ slower than cyclopentene formation based on the activation parameters for decomposition of ethanethiol given above. Benson predicts that there should be an 8 kcal/mole barrier to ring closure from diradical 11, and a 14.4 kcal/mole barrier toward hydrogen migration, although the latter value appears somewhat high.¹⁸

Thus, deuterated bicyclopentane 14 (or its endo isomer) might prove an interesting system in which to attempt the trapping experiments. (5-Substituted bicyclo-pentane systems still undergo preferential cleavage of the ring fusion bond¹⁹ and give products derived from

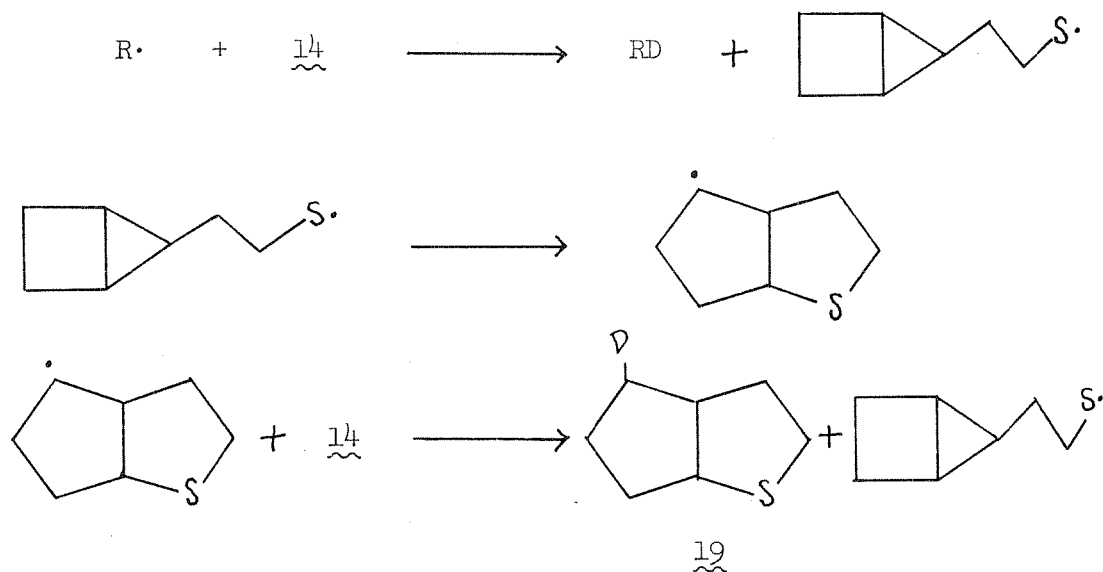
hydrogen rather than alkyl shift.²⁰⁾ As discussed previously, observation of product 16 would not allow a decision as to whether diradical 15



was an intermediate or a transition state in this reaction. Trapping of 15, however, would lead to 16. It is not completely clear what course the subsequent reaction of 16 would take in the gas phase. Closure to 18 is probably not unreasonable; hydrogen abstraction to give 19 also seems possible. Of course, the less likely possibility of reversal of 17 to 15 with eventual formation of only 16 would not be detectable.

In the event that products other than 16 are observed, several control reactions would be necessary to assure that these products are

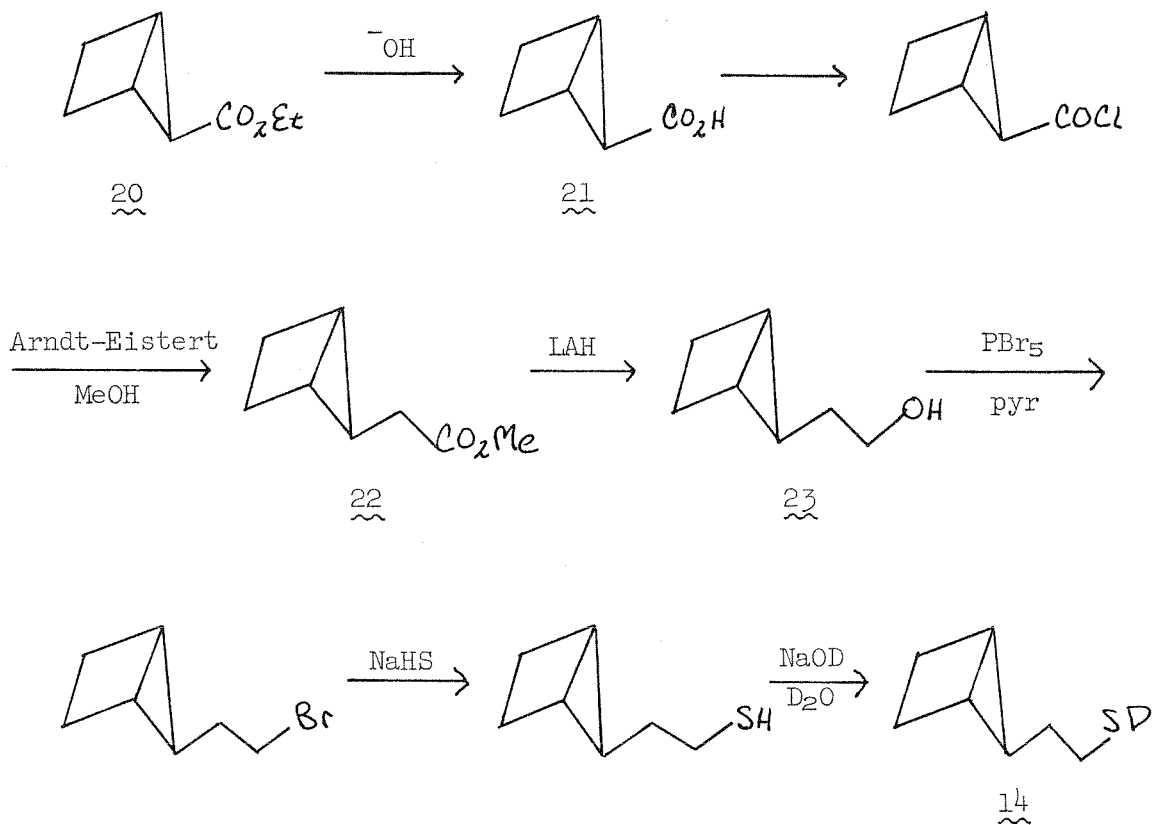
arising from interception of an intermediate diradical. Obviously, the stability of 13 to the reaction conditions would have to be checked to determine that no products were arising from subsequent reactions of 16. The most important alternative to rule out would be the radical chain process which also leads to 19 as shown in Scheme 1. Presumably rate data could be used to rule out this possibility since the chain process would show different kinetics than the unimolecular decomposition of 14. It would also be necessary to show that direct reaction of thiols with cyclopropane rings do not occur under the reaction conditions. If it can be demonstrated through control experiments that



products like 18 and 19 do not arise from some extraneous source, then one would have good reason to suggest that the trapping of an actual diradical intermediate was involved.

Synthesis of 14 could be accomplished by the route shown in

Scheme 2 starting with ester 20.²¹ (The exo isomer of 14 is available by a similar route.) Conversion of acid 21 to the acid chloride²² under



mild conditions (e.g., triphenylphosphine in carbon tetrachloride²² or oxalyl chloride in benzene²³) followed by an Arndt-Eistert reaction²⁴ and lithium aluminum hydride reduction would provide alcohol 23 which might be converted to the thiol as shown.²⁵

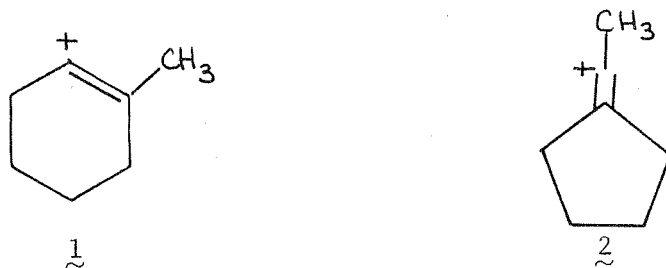
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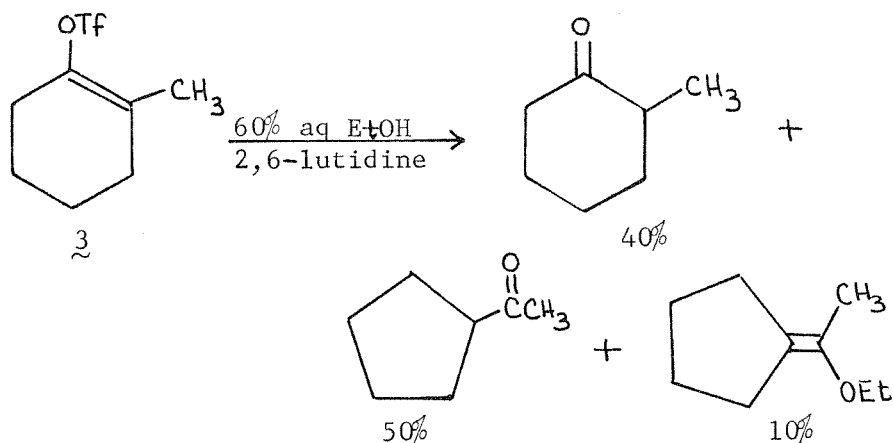
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PROPOSITION IV

The facile interconversion of the bent vinyl cation 1 and linear vinyl cation 2 has been postulated by Pfeiffer, et al. to explain the

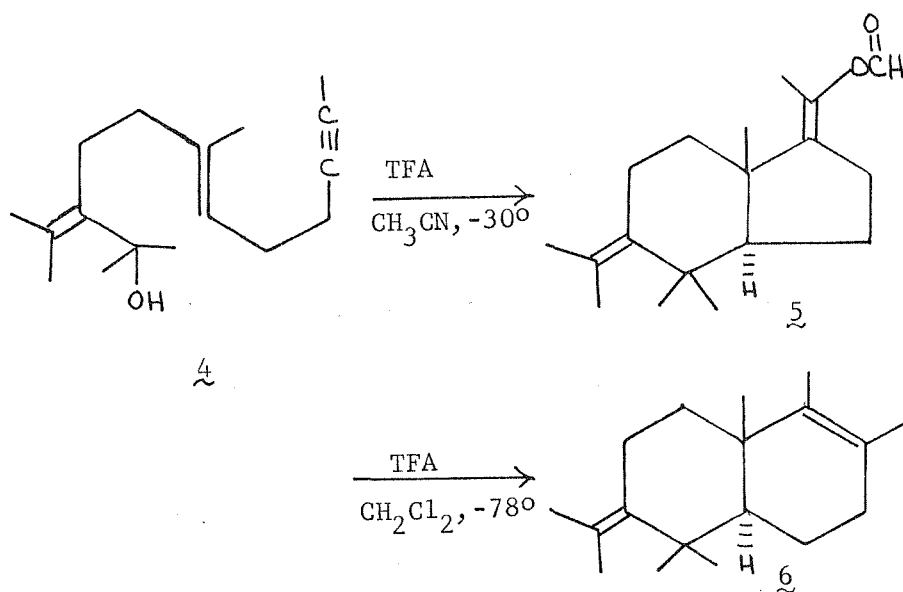


products observed in the solvolysis of 2-methyl-1-cyclohexenyl triflate (3).¹ Based on the comparable amounts of five- and six-membered ring products these authors have suggested that 1 and 2 are of comparable energy, with the increased stability of the linear over the bent cation being balanced by the 5 kcal/mole increase in ring strain of a methylene cyclopentane relative to a 1-methylcyclohexene.²



A similar explanation has been used by Johnson, et al. to explain their observations in the cyclization of dienynol 4. In the presence of a nucleophilic solvent (e.g., acetonitrile) 4 reacts to form the bicyclic product 5; in the presence of trifluoroacetic acid

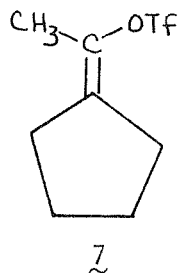
in methylene chloride at -78° , however, 4 gives product 6, presumably by abstraction of chloride from the solvent. Johnson attributes these



results to the initial formation of a five-membered ring cation (a substituted version of 2) which either reacts directly with solvent or, in a less nucleophilic medium, equilibrates with the six-membered ring cation before being trapped.

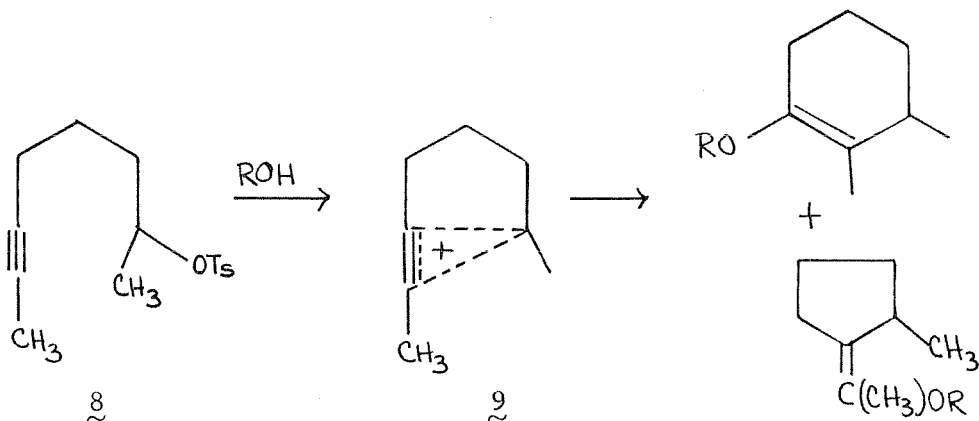
In both of the above cases the authors either implicitly or explicitly suggest the reversibility of the interconversion of cations of type 1 and 2. Strictly the results of Pfeiffer, *et al.*, require only that the rates of solvent trapping of 1 and of rearrangement of 1 to 2 be comparable¹. Johnson's observations do seem to provide evidence for the rearrangement of a cation of type 2 to one similar to 1.³ However, in this case the increased stability of a 6/6 fused ring system over a 6/5 ring system may provide the driving force for the rearrangement. The solvolysis of vinyl triflate 7 would do much to clarify this question; observation of six-membered ring products in the

solvolysis of 7 would provide confirmatory evidence for the 2 to 1



interconversion suggested in systems 3 and 4. This argument assumes, of course, that vinyl cations 1 and 2 (and their analogs in system 4) are discrete intermediates in the above reactions.

Peterson and Kamat have, however, proposed an alternate explanation for the observation of both five- and six-membered ring products in the solvolysis of tosylate 8.⁴ Based on the differences in



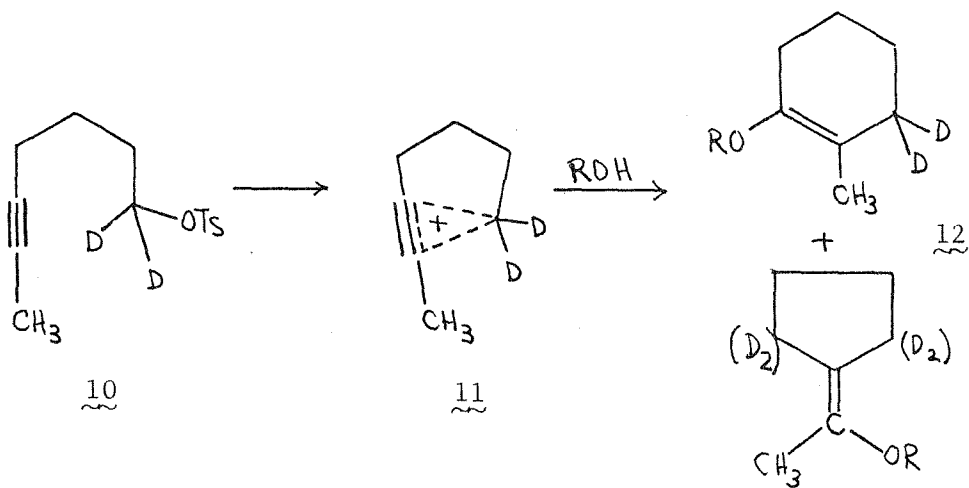
hybridization and the energies of the electron containing orbitals, these authors suggest that the energy difference between bent and linear vinyl cations should be on the order of 77 kcal/mole. Since such a difference would rule out the intermediacy of a bent cation in these reactions, they propose instead, albeit reluctantly, that the bridged ion 9 is involved in this cyclization, thus avoiding the

the necessity of invoking a bent vinyl cation to explain the six-membered ring product.

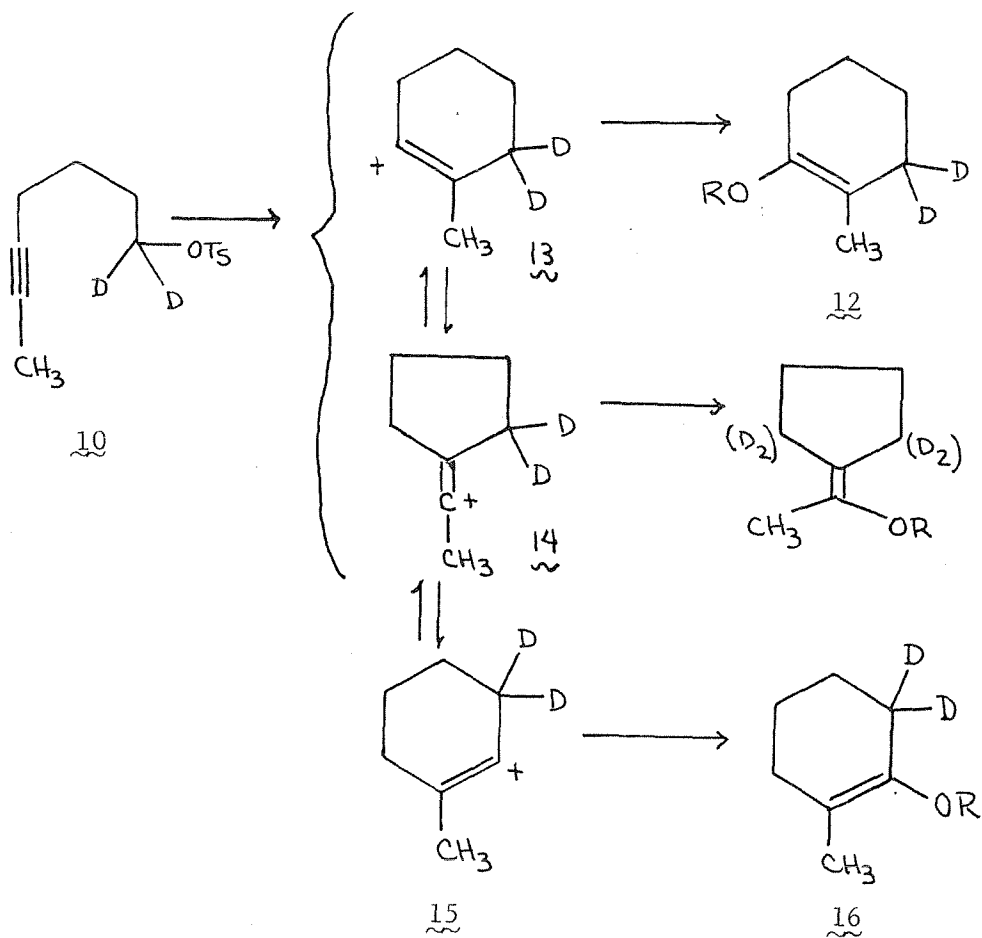
Although the value of 77 kcal/mole is undoubtedly too high, Peterson's and Kamat's proposal is not without merit. Theoretical calculations have estimated the difference in energy of bent and linear vinyl cations at anywhere from 28.9 kcal/mole (EHT calculations)⁴ to 47 kcal/mole (non-empirical LCAO MO SCF calculations)^{5c}. In addition Pfeiffer et al.¹, have considered the intervention of a bridged species to explain the rate and product distributions observed in the solvolyses of substituted cyclohexenyl triflates (vide supra), although they point out that theoretical calculations predict a linear vinyl cation to be more stable than the corresponding bridged cation.⁶ In their review of vinyl cations⁷ Modena and Tonellato also suggest the intermediacy of bridged species in the solvolyses of cyclohexenyl derivatives.

Assuming that as predicted vinyl triflate 7 does indeed give some six-membered ring product (indicating either that the $7 \rightarrow 8$ rearrangement does occur or that 7 also solvolyzes via bridged ion 9 depending on the choice of mechanism), a fairly simple test can be used to distinguish between the intermediacy of discrete vinyl cations 1 and 2 and bridged ion 9. Solvolysis of tosylate 10 deuterated as shown would lead by the bridge ion mechanism to intermediate 11 (Scheme 1). The only six-membered ring product predicted from 11 is 12. The discrete vinyl cation mechanism predicts the initial formation of 13 and/or 14; however, Wagner-Meerwein shift in 14 leads not only back to 13 but also to 15. Thus this mechanism predicts the observation of both 12 and 16 as six-membered ring products (Scheme 2). Compounds 12 and

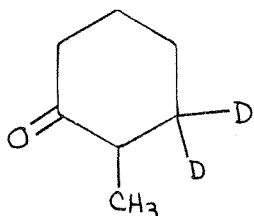
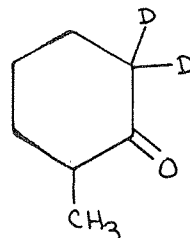
SCHEME 1



SCHEME 2

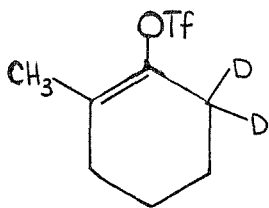
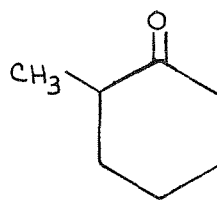


16 may be distinguishable by nmr. Also hydrolysis of 12 and 16 yields ketones 17 and 18, respectively. Although the deuteria in 17 are not

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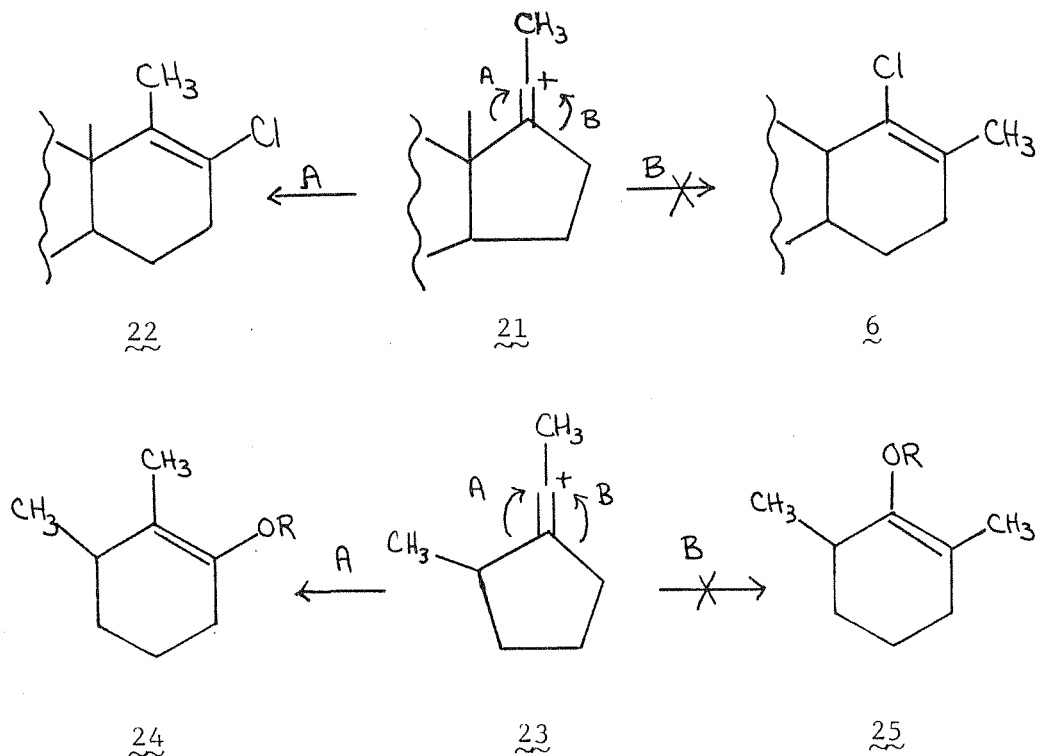
labile, the deuteria in 18 should be easily exchanged out by aqueous base since they are α to the carbonyl. Mass spectral or nmr analysis would then provide definite values for the relative amounts of 12 and 16 formed in the above reactions. (The above solvolyses would best be carried out in a non-nucleophilic solvent like trifluoroethanol⁸ to avoid products of direct solvent displacement on tosylate 10.)

The same experiment can be carried out on triflate 19, produced from the parent ketone 20 by base catalyzed exchange of the α -protons

1920

in NaOD/D₂O and conversion of the deuterated ketone to 19 in the usual manner.⁹ Note that with this substrate the bridged ion mechanism predicts only product 16 while the discrete vinyl cation mechanism again predicts formation of both 12 and 16.

In connection with the above experiment it is of interest to note that Johnson does not see any of product 22, which could also be produced in addition to 6 from the other possible Wagner-Meerwein



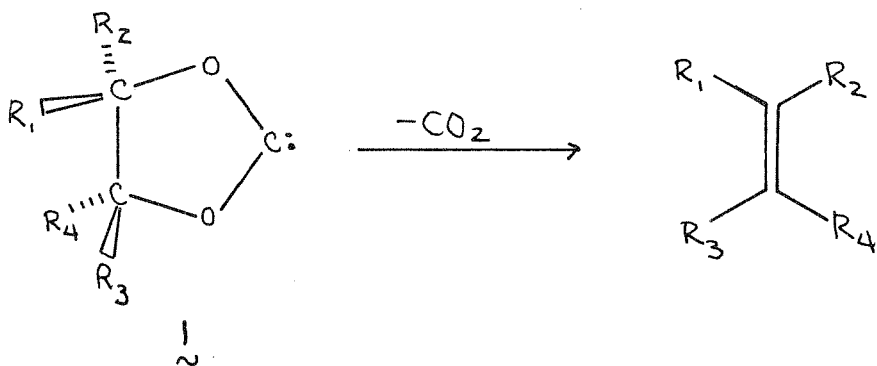
shift in ion $\underline{21}$.^{3a} Similarly, Peterson and Kamat see only $\underline{24}$ and no $\underline{25}$. Compounds $\underline{22}$ and $\underline{24}$ are of course the exclusive products predicted by the bridged ion mechanism; however, selective Wagner-Meerwein migration of the tertiary substituted substituent in both cases (path A) also explains the observed results. The more symmetrical cation $\underline{14}$ should provide less ambiguous results.

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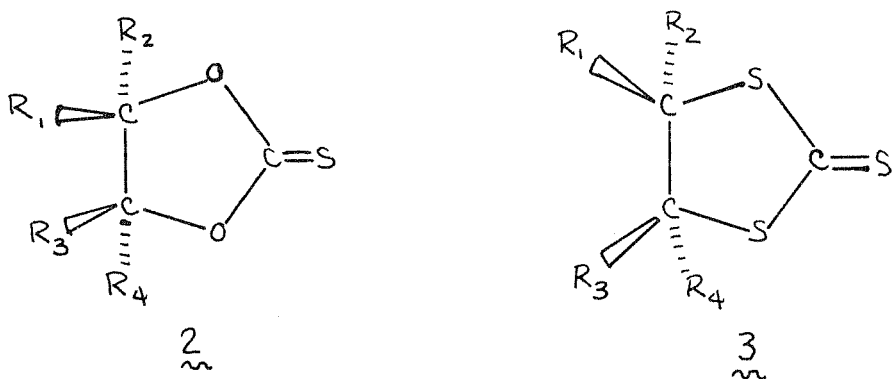
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PROPOSITION V

In 1963 Corey suggested that the decomposition of carbenes of type 1 should lead stereospecifically to the corresponding olefin by



loss of carbon dioxide.¹ The desulfurization of thioncarbonates of the general structure 2 was chosen as a synthetic approach to carbene 1.

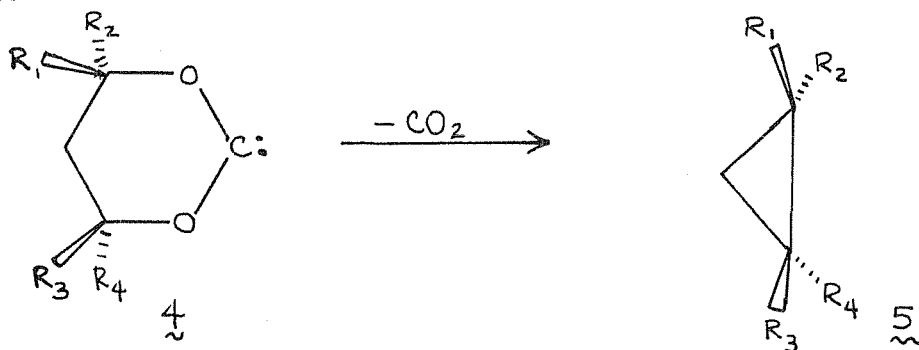


In fact, treatment of a variety of thioncarbonates with trimethylphosphite led to the stereospecific formation of the predicted olefin in high yield. Since 2 can be readily prepared from a 1,2-diol, this sequence provided a simple procedure for conversion of diols to the corresponding olefins. Perhaps the most striking success of this procedure was the generation of trans-cyclooctene from

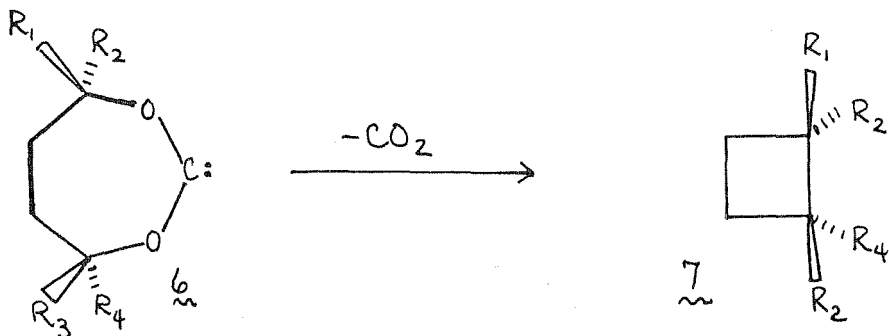
trans-1,2-cyclooctanediol. The corresponding trithiocarbonate 3 was also found to give trans cyclooctene on treatment with trimethyl phosphite.² Moreover, trapping studies suggested that trans-cycloheptene could be produced as a transient intermediate by this route.²

Corey's proposal was made before the development of the Woodward-Hoffmann rules for the prediction of stereochemistry in concerted reactions.³ Several years after the fact, however, Woodward and Hoffmann were able to predict on the basis of orbital symmetry considerations that the linear extrusion of carbon dioxide from 1 should be accompanied by disrotatory closure to the observed olefin of retained stereochemistry.⁴

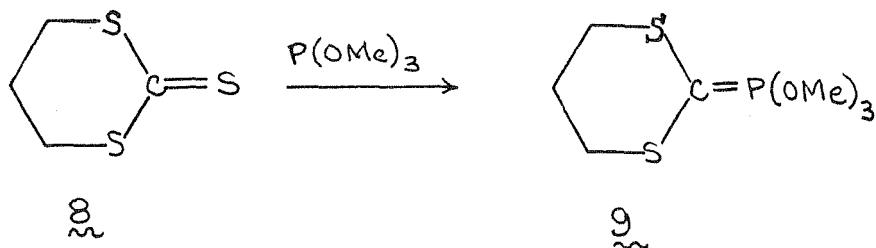
Based on the Woodward-Hoffmann rules one can also predict that the linear extrusion of carbon dioxide from carbenes of general structure 4 could lead in an allowed process to the cyclopropane of retained



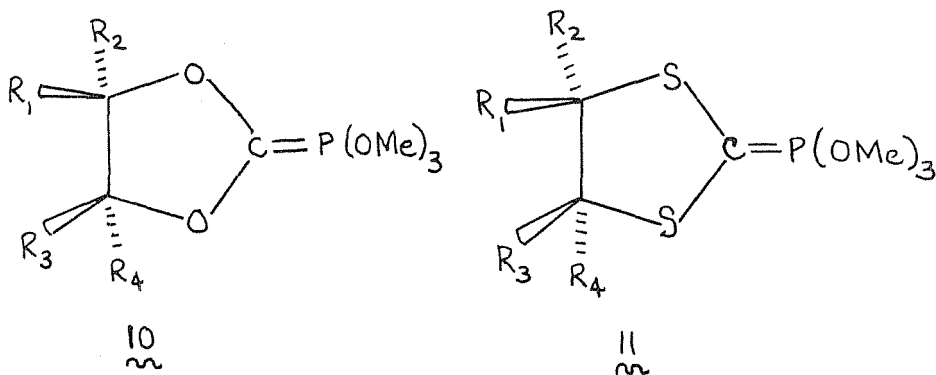
configuration (5). This would represent an efficient synthesis of cyclopropanes from 1,3-diol precursors. Similarly, the conversion of 6 to 7 by linear extrusion of carbon dioxide is predicted to be an allowed process.



This idea obviously also occurred to Corey, who later attempted the desulfurization of the trithiocarbonate 8.⁵ However, in this case ylide 9 was the only product formed. Corey was able to show that the

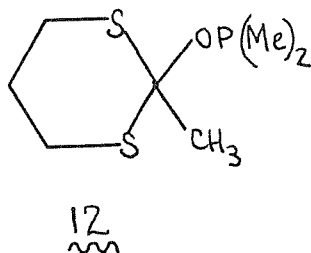


desulfurization of the thiono- and trithiocarbonates 2 and 3 also proceeded via phosphorous ylides by trapping some of these intermediates (e.g., 10, 11) with benzaldehyde in a Wittig reaction.⁵ Thus, it is

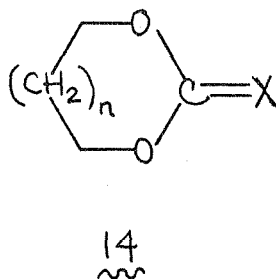
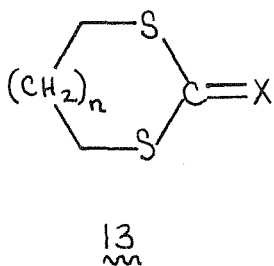


quite reasonable to assume that in the olefin syntheses Corey was not observing decomposition of a discrete carbene intermediate but rather

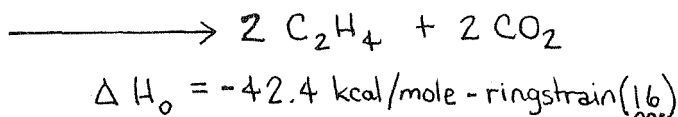
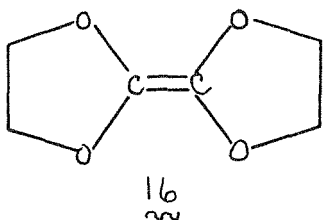
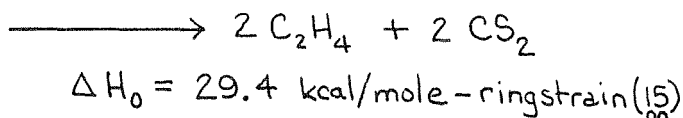
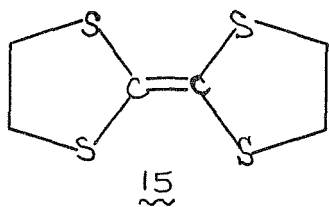
concerted thermal decomposition of the phosphorous ylide to reform trimethylphosphite in addition to the carbon dioxide and olefin. Attempts at thermal decomposition of ylide 9 yielded the rearranged phosphite ester 12.



No other investigations of more promising precursors to carbenes 4 and 6 have apparently been reported. Before considering such precursors, however, the question must be raised as to whether dithio compounds (13) or their oxygen analogs (14) are more likely substrates for the desired fragmentation. Although the heats of formation of the possible precursors and the corresponding carbenes are rather difficult to

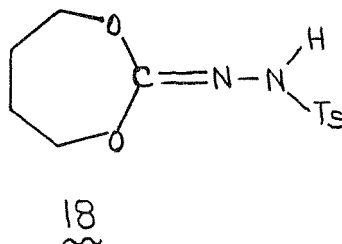
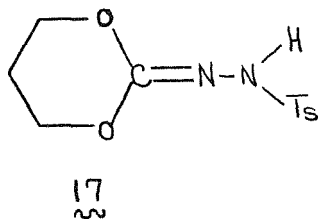


calculate because of the lack of necessary information, some insight into this question can be obtained by calculation of the enthalpies of reaction for the fragmentation of carbene dimers 15 and 16 to ethylene and carbon disulfide or carbon dioxide, respectively. Using Benson's group equivalent technique⁶ and assuming that the ring strain



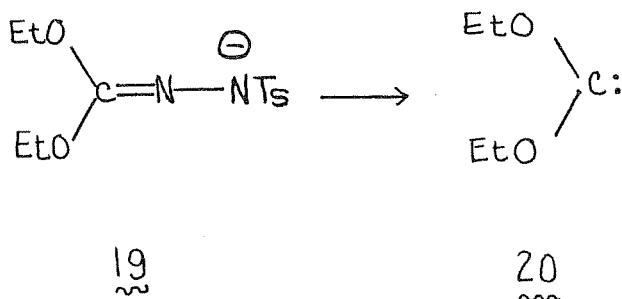
values for 15 and 16 are not too different,⁷ it can be shown that the fragmentation of 16 is some 72 kcal/mole more favorable than the fragmentation of 15. The formation of carbon dioxide obviously provides considerably more driving force for fragmentation than does the formation of carbon disulfide. Thus, the oxygen containing precursors (14) should definitely prove superior to those containing sulfur (13).

The most obvious compounds for study would of course be the salts of tosylhydrazones 17 and 18. There is apparently only one

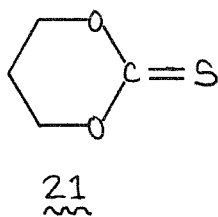


published report of the thermal decomposition of the tosylhydrazone salt of a carbonate diester. In that case Crawford and Raap pyrolyzed

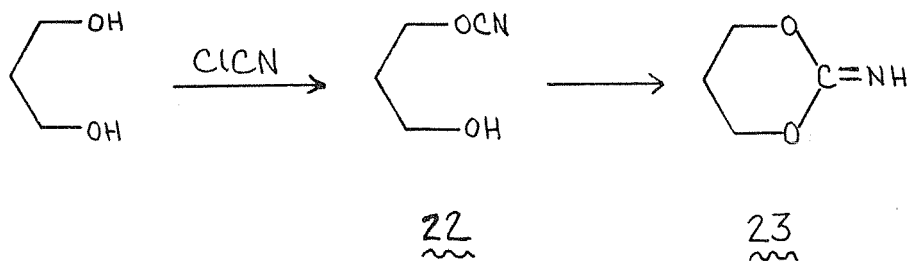
19 and, encouragingly, obtained products which apparently arise from decomposition of carbene 20.⁸



One straightforward approach to 17 would be by treatment of the thiocarbonate 21 with tosylhydrazine; 21 would be obtained from the reaction of 1,3-propanediol with the thiocarbonyldiimidazole reagent used by Corey in his olefin syntheses.^{1,2} Alternatively, under the proper conditions the reaction of 1,3-propanediol with cyanogen chloride



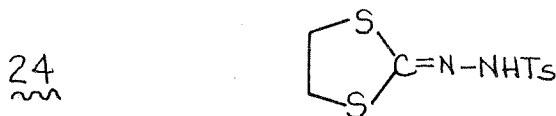
might provide imine 23 via the initially formed cyanate 22.⁹ Treatment



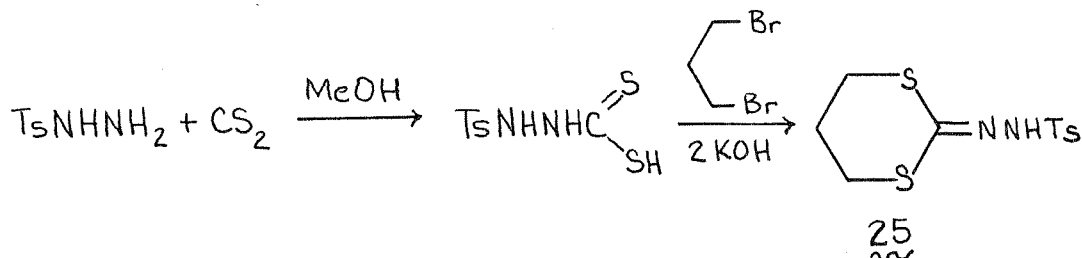
of imine 23 with tosylhydrazine under the conditions used by Crawford and Raap in their synthesis of 19⁸ would then provide 17. Treatment

of 21 or its carbonate analog directly with ammonia might also lead to 23. Similar approaches to 18 can be envisioned.

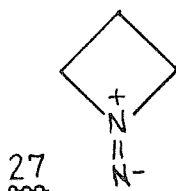
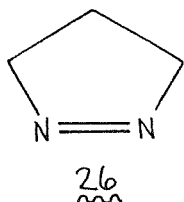
The synthesis of the less desirable (vide supra) dithiohydrazone 25 could certainly be achieved by the method used by Lemal in the synthesis of 24.¹⁰ This approach is outlined below using 1,3-dibromo-



propane rather than the 1,2-dibromoethylene used by Lemal. Use of 1,4-dibromobutane would provide the dithio analog of 18.

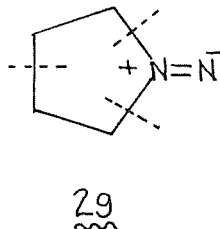
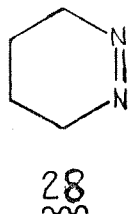


Examination of the pyrolysis products of the salts of these various tosylhydrazones would then reveal whether these precursors are suitable sources of cyclopropanes and cyclobutanes (and perhaps larger rings). If this should prove to be the case the synthetic value of these reactions would be obvious. However, some interesting mechanistic opportunities would also be provided. In all of the previously examined extrusion processes leading to cyclopropanes, for example the thermal decomposition of 1-pyrazolines (26) and diazenes of general structure 27, the fragmentation was essentially a four electron process. To give cyclopropane and nitrogen in a single concerted step these reactions would be required by orbital symmetry³ to proceed via a highly strained $\sigma_s^2 + \sigma_a^2$ process. Rather than undergo such contortions,



26 and 27 apparently react by a diradical mechanism, the nature of which is not yet completely clear.¹¹ On the other hand, the conversion of carbene 4 (or the diazo compound precursor) to carbon dioxide and the cyclopropane of retained geometry in a concerted six electron process is predicted to be allowed. It would thus be quite interesting to examine the products of the stereochemically labelled carbene 4 to determine whether this prediction is fulfilled or whether this reaction also proceeds via a diradical mechanism.

The proposed cyclobutane synthesis would also provide some interesting mechanistic insight. Although tetrahydropyridazenes (28) have proved to be rather elusive, diazene 29 is observed to fragment directly to nitrogen and two ethylenes.¹² In this case the linear extrusion of nitrogen and simultaneous ethylene formation is an allowed



process. However, in carbene 6 the concerted formation of ethylene is allowed only if the extrusion of carbon dioxide is a nonlinear cheletropic process,¹² i.e., the carbon dioxide must come out with a twisting motion. (This nonlinear process is apparently avoided in the case of diazene 27.) One alternate possibility open to 6 is the direct formation of a cyclobutane of retained stereochemistry with linear extrusion of

of carbon dioxide, an allowed process for $\underline{6}$, but forbidden for $\underline{29}$. Finally $\underline{6}$ might decompose via a diradical process which would presumably lead to both ethylene and cyclobutane of somewhat scrambled stereochemistry. Determination of which of these possibilities is actually the lowest energy process would provide useful information on the nature of concerted and diradical mechanisms.

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