



New synthetic methodologies for natural products
by William Gerard Bornmann

A thesis submitted in partial fulfillment of the requirements for the degree of MASTER OF SCIENCE
in Chemistry

Montana State University

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Abstract:

The orbital symmetry allowed [3.3] sigmatropic rearrangement of enamines derived from 2-acetyl-6-methyl-3,4-dihydro-2H-pyran has allowed for facile entry into highly functionalized cyclohexanone derivatives. This new synthetic methodology offers promise for entry into sesquiterpene natural products. A by-product of this research has led to a symple synthesis of brevicomin, the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*.

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Signature William G. Baumann

Date December 28, 1978

To my wife,

Daria

NEW SYNTHETIC METHODOLOGIES

FOR NATURAL PRODUCTS

by

WILLIAM GERARD BORNMANN

A thesis submitted in partial fulfillment
of the requirements for the degree

of

MASTER OF SCIENCE

in

Chemistry

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December, 1978

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Several people have had a major role in making this research study possible and I would like to take this opportunity to thank them.

I would especially like to thank my parents without whose help the completion of this thesis would not have been made possible. I would like to thank Mr. Chris Evans for the expert glass blowing, and Mrs. Kjestine Carey of the Library for always getting a much needed book. Special thanks are also extended to Mr. Gordon Williamson of Mechanical Engineering for lending me precious equipment and giving helpful advice.

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ABSTRACT

The orbital symmetry allowed [3.3] sigmatropic rearrangement of enamines derived from 2-acetyl-6-methyl-3,4-dihydro-2H-pyran has allowed for facile entry into highly functionalized cyclohexanone derivatives. This new synthetic methodology offers promise for entry into sesquiterpene natural products. A by-product of this research has led to a symple synthesis of brevicomin, the aggregating sex pheromone of the pine bark beetle, *Dendroctonus brevicomis*.

Experimental ideas are often born by chance, with the help of some casual observation. Nothing is more common; and this is really the simplest way of beginning a piece of scientific work. We take a walk, so to speak, in the realm of science, and we pursue what happens to present itself to our eyes.

"Serendipity"
Claude Bernard
1865

Part I:

A NEW SYNTHETIC APPROACH TO SESQUITERPENE INTERMEDIATES

CHAPTER I

HISTORICAL

In recent years, two concepts have emerged in synthetic methodology; that of latent functionality and the use of heterocyclic compounds in organic synthesis. D. Lednicher¹ in 1972 quite aptly verbalized the concept of latent functionality as: "One carries some necessary function through one or more steps of a synthesis in a precursor form; and at the proper stage the precursor is converted to the needed group." One could say that this concept is a more sophisticated use of protecting groups. The second and the most important concept was discussed by A. I. Meyers,² and involves the use of heterocyclic compounds in organic synthesis. By directly applying the principle of latent functionality in a heterocyclic synthesis, one could, in effect, design a heterocycle which could allow for the introduction of a variety of functional groups or carbon skeletons. Thus in short, Meyers' concept was that of using a heterocycle as a precursor or vehicle for the synthesis of a more complex molecule.

These concepts were reflected in the synthetic approach to substituted cyclohexenes taken by Buchi^{3,4} which was based on the previous work by J. D. Roberts⁵ and Lutz that deuterium-labeled 2-formyl-2,5-dimethyl-2,3-dihydro-4H-pyran [1] could thermally isomerize by means of a [3,3] sigmatropic rearrangement. A series of well-planned NMR studies conclusively demonstrated that the aldehydic deuterium CDO label ex-

changed with H-6. It was also noted that the optical activity due to the asymmetric center (*) was not lost.

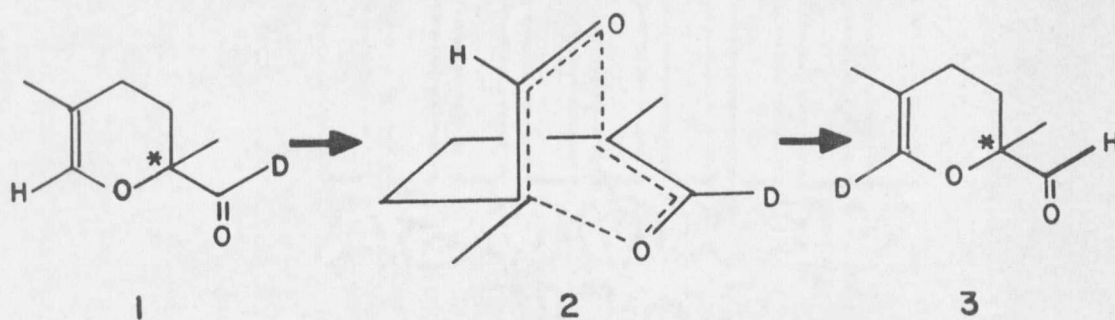


Figure 1. [3,3] Sigmatropic Rearrangement of 2-formyl-2,5-dihydro-4H-Pyran

By dimerizing α,β -unsaturated compounds [4], Büchi was able to obtain acyl dihydropyrans [5] which, when followed by a Wittig condensation, gave 3,4-dihydro-2H-pyranethylenes [5]. These compounds were, in essence, allyl vinyl ethers whose thermal oxy-Cope rearrangement had been previously well documented in the literature. Just as had been expected, these substituted 3,4-dihydro-2H-pyran ethylenes underwent oxy-Cope rearrangements to yield substituted cyclohexene [7] compounds. Such substituted acyl cyclohexenes are not readily obtainable from mixed Diels-Alder reactions and, in fact, are only minor products from these reactions.

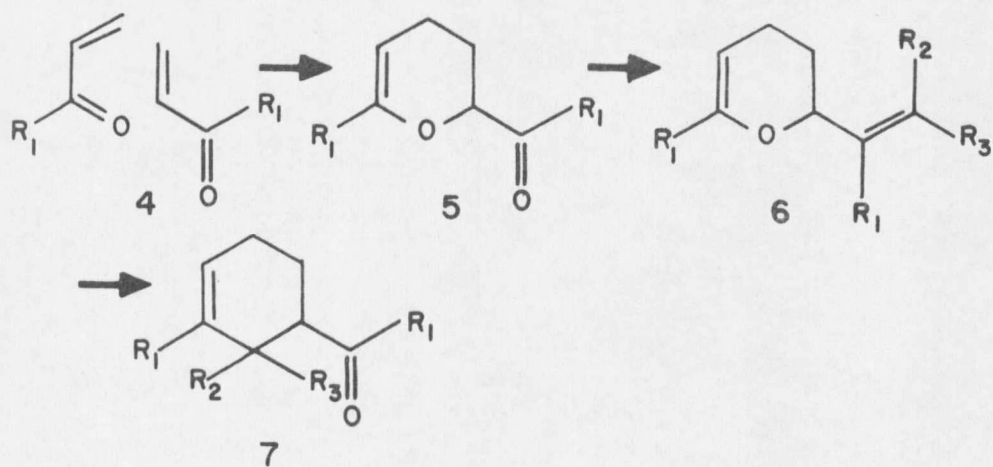


Figure 2. Büchi Synthesis of Substituted 4-Acetylcyclohexenes

Now, in a continuing effort in this laboratory to realize the full implications of this work, it was conceived to substitute different heteroatoms for the carbonyl oxygen and rearrange them into the ring. Thus K. Lipkowitz^{7,8} first made the thiocarbonyl by refluxing 2-acetyl-6-methyl-3,4-dihydro-2H-pyran in pyridine and phosphorous pentasulfide. Sealed tube pyrolysis of the thioacetyl pyran [9] yielded the thiapyranyl system [10].

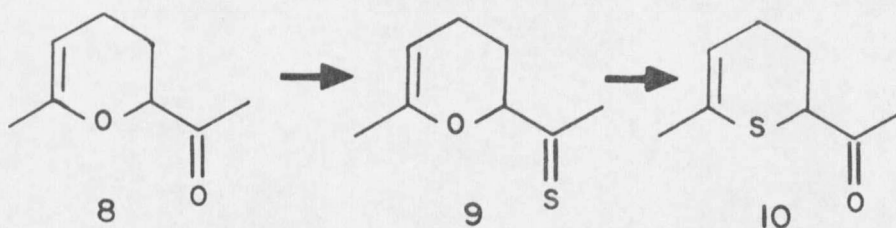


Figure 3. Lipkowitz Synthesis of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Thiapyran

Thus, my objective was to attempt the next heteroatom, nitrogen. The methyl imine of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran [11] was prepared and was subjected to conditions of the Cope rearrangement. The expected product from the pyrolysis was the substituted 1,2-dimethyl-6-acetyl-piperidine [12].

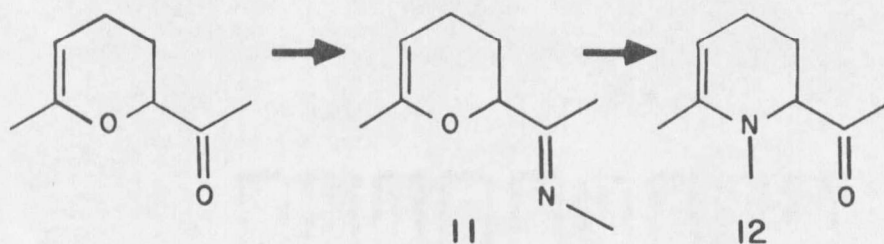
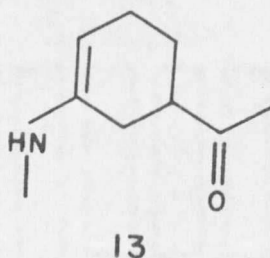


Figure 4. Proposed Synthesis of 1,2-Dimethyl-6-Acetyl-Piperidine

However, this was not observed, and careful analysis of the spectral data from the product led to our assignment for the structure of the

observed compound as 5-acetyl-1-(1-methyl) amino cyclohexene [13].



After consideration of a mechanism for the reaction, it became apparent that an imine-enamine tautomerization had first taken place, followed by a [3,3] sigmatropic shift or Cope rearrangement. This would account for the carbon skeleton of the ring.

Thermal isomerization of imine to enamines have been thoroughly discussed in the literature⁹ for many years. However, the application of such isomerization prior to a [3,3] sigmatropic shift has received very little attention. Some interesting examples can be pointed to, however. Pyrolysis of O-allylhexanolactim¹⁰ [14] gave the 3-allyl-hexanolactam [16] in better than 60% yield.

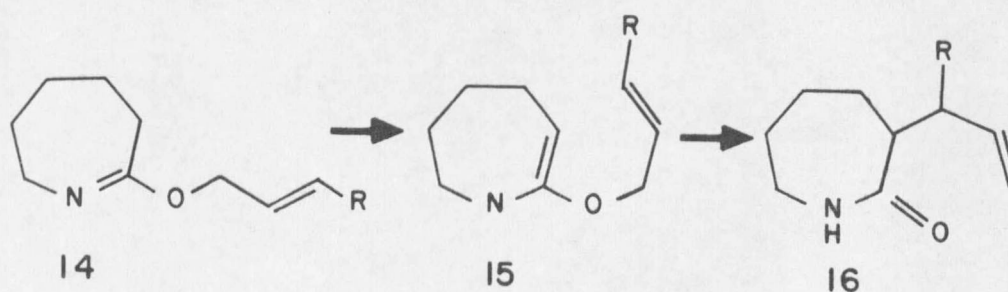


Figure 5. [3,3] Sigmatropic Rearrangement of O-allylhexanolactim

Rationalization of this reaction sequence was that the imine [14] had readily isomerized to the enamine [15]. This intermediate was then set up for a thermally-allowed [3,3] sigmatropic shift.

Hill and Newkom¹¹ demonstrated that when quaternary ammonium salts of imines with an alkyl group in the 2 position were converted to the anhydro base (enamine)[18], they could be then thermally rearranged to [19], presumably by a [3,3] sigmatropic shift.

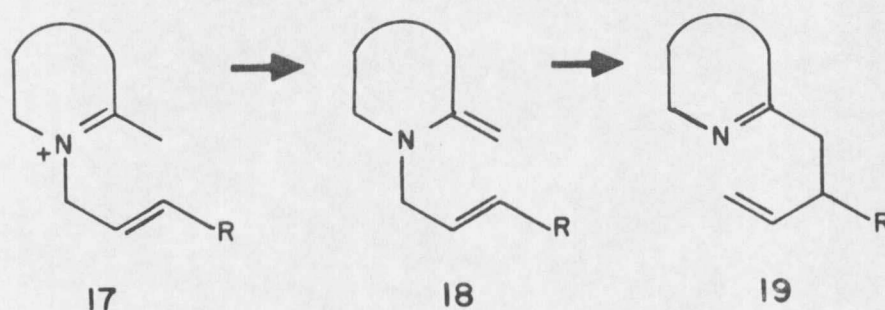


Figure 6. Amino [3,3] Sigmatropic Rearrangement of Hill and Newkom

Based on this work,¹² Bramley and Grigg demonstrated that 4,4-diallyl-3,5-dimethylpyrazole first isomerized to the enamine [21] and then rearranged by way of a [3,3] sigmatropic shift to [22].

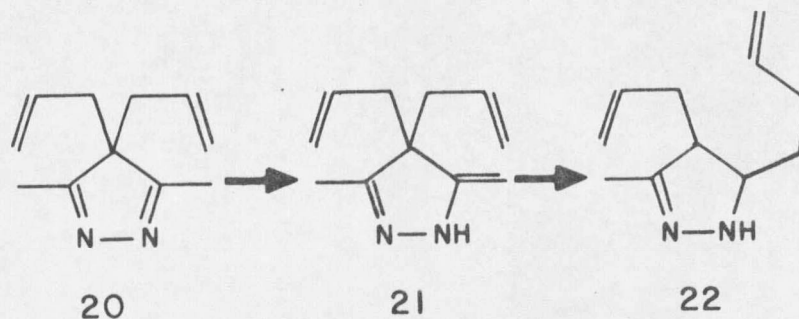
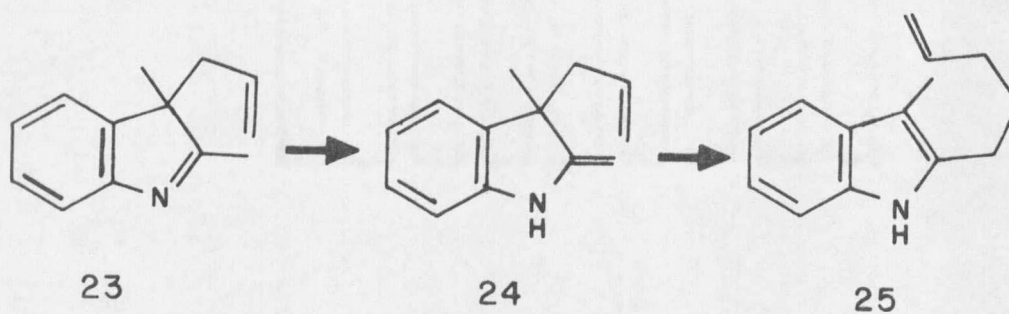
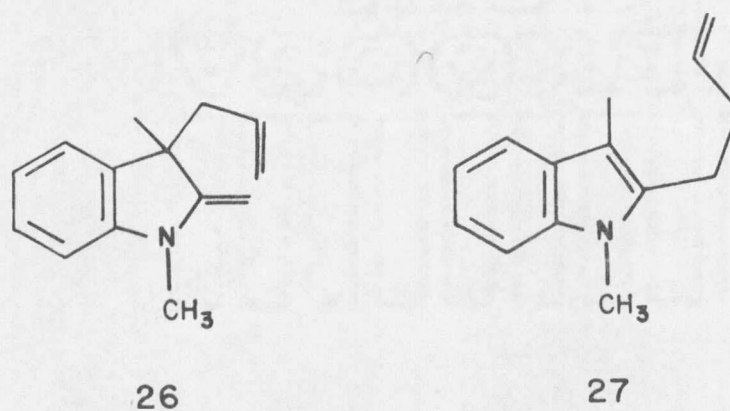


Figure 7. Thermal Sigmatropic Rearrangement of 4-Allyl Isopyrazole to a Pyrazol

Another system investigated by the same authors was that of 3-allylindolemime ketemine [23] which first thermally isomerized to the enamine [24] and then rearranged to [25] by means of a [3,3] sigmatropic shift.



To substantiate this conclusion, the enamine [26] was prepared ($\text{CH}_3\text{I}/\text{NaOH}$), and thermal rearrangement gave the expected product [27].



Eschenmoser has employed the method of transvinyl etherification of 1-dimethylamino-1-methoxy-ethene and the dimethyl acetal of N,N-dimethylacetamide as a vinylating agent. Again note the enamine intermediate [31] which then participates in the actual [3,3] sigmatropic shift.

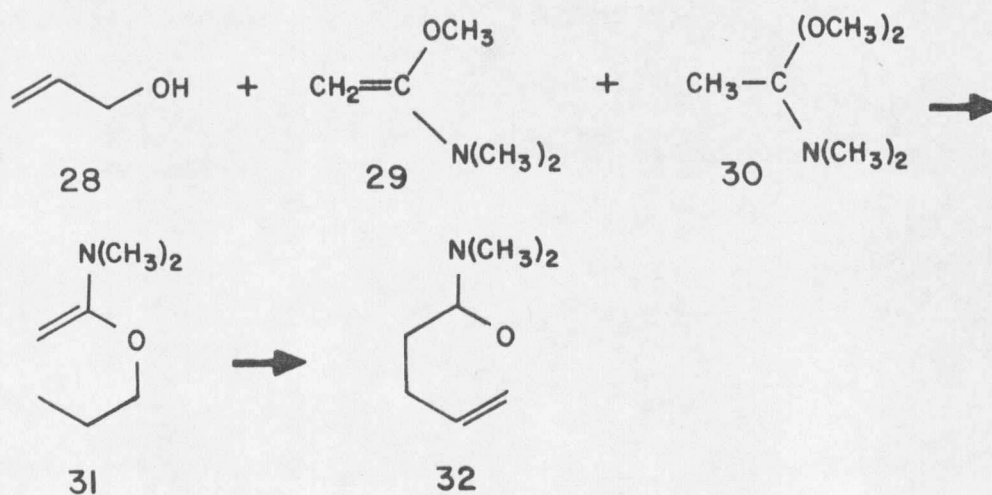


Figure 8. Eschenmoser's Synthesis of γ,δ -Unsaturated Amides

Hill and Gilman have demonstrated that the enamine [33] prepared from N-methyl allylamine and α -disubstituted aldehydes pyrolyzed quantitatively to [34] via a [3,3] sigmatropic shift at 250° C. Mild hydrolysis of [34] gave the aldehyde [35].

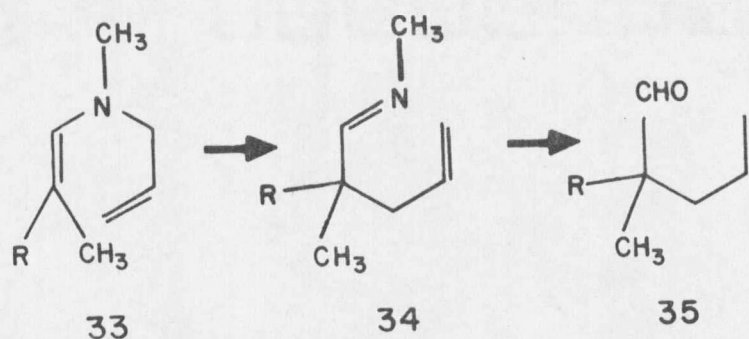
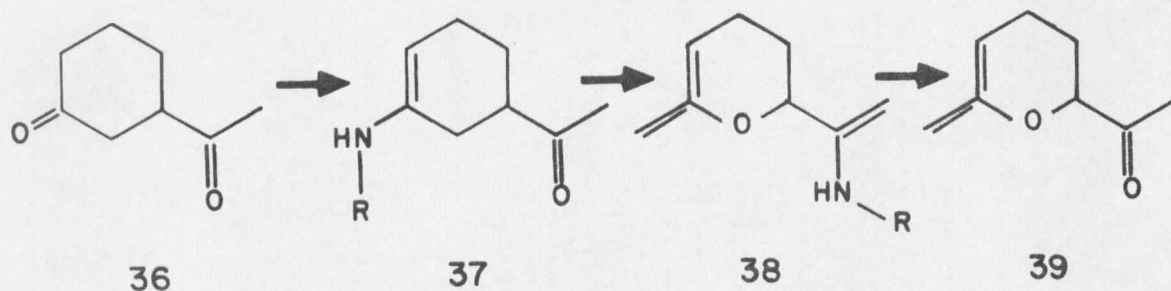


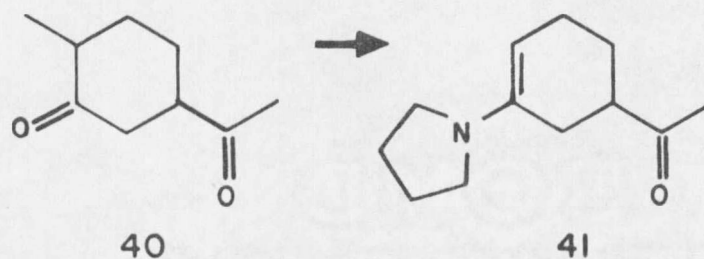
Figure 9. Hill and Gilman Synthesis of N-Methyl-2,2 Dimethyl Pent-4-Enamine

We now could view our enamine sigmatropic rearrangement in terms of E. J. Corey's¹⁵ retro-synthetic analysis as:



From such analysis of the synthetic tree, it seems obvious that the enamine transform is the key intermediate. Thus, the direct preparation and rearrangement of the enamine was undertaken. The pyrrolidine en-

amine of 2-acetyl-6-methyl-3,4-dihydro pyran rearranged quite easily under the pyrolysis conditions as before. Retrosynthetic analysis yields the obvious conclusion that the new enamine [41] is also quite a useful synthetic intermediate:



The only literature analogy to our system was reported by Birkofer¹⁶ and Daum in 1962. Here the pyrrolidino enamine of acetyl furan [43] was prepared and Cope rearranged to the corresponding o-amino phenol [44].

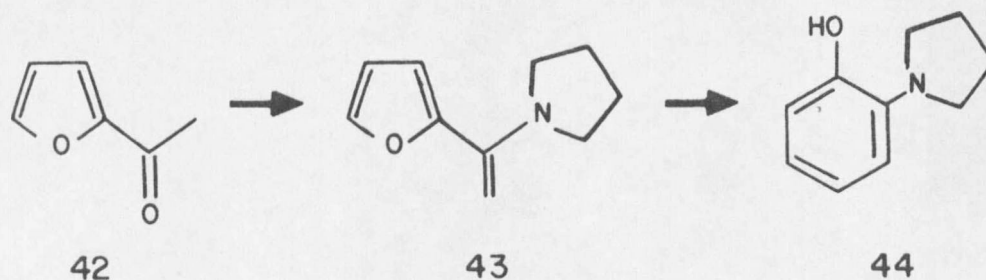


Figure 10. [3,3] Sigmatropic Rearrangement of the Pyrrolidino Enamine of Acetyl Furan to o-Amino Phenol

CHAPTER 2

RESULTS AND DISCUSSION

The N-methyl imine of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran was prepared by passing methyl amine into a cold solution of ether containing 2-acetyl-6-methyl-3,4-dihydro-2H-pyran and molecular sieves. Following isolation and purification, the methyl imine [11] was vacuum pyrolyzed at 250° C to yield [15] in 66% yield after distillation. The product of the pyrolysis was assigned the structure [13] based on the following spectroscopic evidence (Table 1): The infrared spectra shows the imine C=N stretch 1667 cm^{-1} and the ether C-O-C stretch 1053 cm^{-1} for [11]; however, the product does not exhibit a C-O-C stretch nor a C=N stretch; however an N-H stretch 3413 cm^{-1} was observed as well as a C=C stretch 1645 cm^{-1} which is also characteristic of a carbonyl. Secondary enamines C=C stretch at 1695 cm^{-1} was observed. The ultraviolet absorption spectra shows the distinct $n \rightarrow \pi^*$ band 231 nm for the imine [11]; however, the pyrolysis product has an absorption at 220 nm as well as 284 nm. This is indicative of both a secondary enamine and a carbonyl group present as well. NMR spectroscopy confirmed the structure as that of [13] by the observation of the vinyl hydrogen as a triplet at 4.48 δ which is in excellent agreement with the observed chemical shift of the vinyl hydrolysis of 1-N-piperidinocyclohex-1-ene at 4.56 δ , which is also observed as a triplet. Also the methyl group adjacent to the carbonyl was observed at 2.16 δ . Further structural

analysis was done by chemical degradation as follows. Simple catalytic hydrogenation of [13] with Pd/C produces the saturated amine [45] in 82% yield. The quaternary ammonium salt of [45] was prepared in ether and excess methyl iodide, and this, when followed by a Hoffman elimination with potassium tert-butoxide¹⁷ gave 4-acetylcyclohexene [47] in 62% yield. Acid hydrolysis of [13] gave 3-acetylcyclohexanone [36] in 72% yield.

A temperature versus product study (Table 2) was then carried out with the results that 250° C was the optimum pyrolysis temperature. Temperatures any higher usually gave extensive polymerization and a marked decrease in product yield.

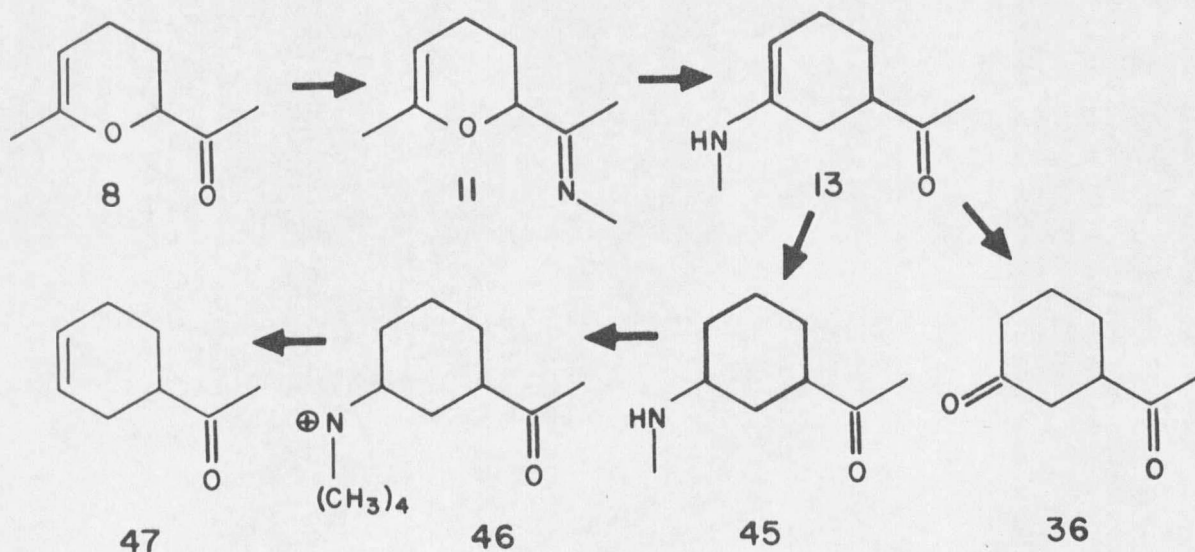


Figure 11. Preparation of 4-Acetyl Cyclohexene and 3-Acetyl Cyclohexanone By the Enamine Cope Rearrangement

Table 1. Principle Spectroscopic Characteristics of Reactant and Products

Infrared Spectroscopy			NMR Spectroscopy		
11		13	11		13
1667 cm^{-1}	C=N stretch of imine	-----	3.07 δ	$\text{C}=\text{N}-\text{CH}_3$	-----
1053 cm^{-1}	C-O-C stretch of the ether	-----	-----	$\text{CH}=\text{C}-\text{N}$	4.48 δ
-----	N-H stretch of secondary enamine	3413 cm^{-1}	-----	CH_3-NH	2.68 δ
-----	C=C stretch of secondary enamine	1645 cm^{-1}	-----	$\text{CH}_3-\text{C}-$ $\parallel$ O	2.16 δ
-----	C=O stretch	1695 cm^{-1}			

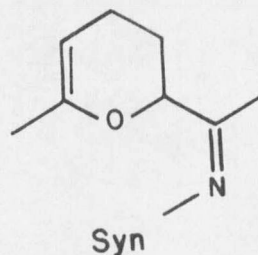
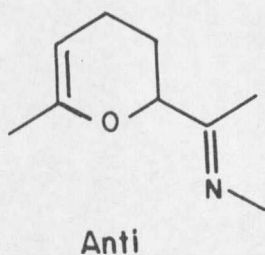
Table 2. Temperature Study of The Pyrolysis Conditions of The Methyl Imine of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran

11	T (°C)	% 11*	% 13*
5.0 grams	150° C	100%	----
5.0 grams	175° C	100%	----
5.0 grams	200° C	81.6%	18.4%
5.0 grams	225° C	29.0%	71.0%
5.0 grams	250° C	----	100%
5.0 grams	275° C	----	73.0%**
5.0 grams	300° C	----	48.2%**

*Relative glc peak areas of material isolated, analysis was done on 10% SE-30 Chromosorb W at 160° C and peak areas were measured by triangulation.

**Extensive polymerization was observed in the pyrolysis tube.

In considering the reaction mechanism for our plan it was of interest to establish the configuration of the N-methyl imine as syn or anti. Careful evaluation of the NMR¹⁸ data established the C-methyl group was observed at a higher field for the anti isomer than for the syn. This is also observed for the N-methyl group for the anti as well; however, the C-H proton is observed at a lower field for the anti isomer than for the syn. The coupling constant for the C-methyl group and the N-methyl group is smaller ($J = 8.9$ Hertz) for the anti isomer than for the syn isomer ($J = 1.6$ Hertz). The coupling constant between CH and N-methyl is larger for the anti ($J = 8.9$ Hertz) than for the syn ($J = 0.5$ Hertz). We can conclude that our N-methyl imine is 92% anti and 8% syn.



The first critical step in the rearrangement is the thermal isomerization¹⁹ of the N-methyl ketimine [11] to the N-methyl enamine [11A].

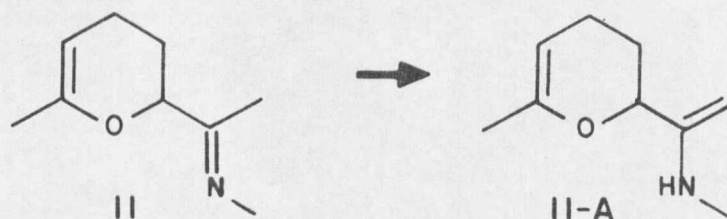


Figure 12. Thermal Isomerization of the Imine to the Corresponding Enamine

The mechanism for this isomerization can be postulated to be a [1,3] sigmatropic hydrogen shift. For such a shift to be thermally allowed an antarafacial migration^{20a-c} of the hydrogen on C₁, would have to be accomplished (Figure 13).

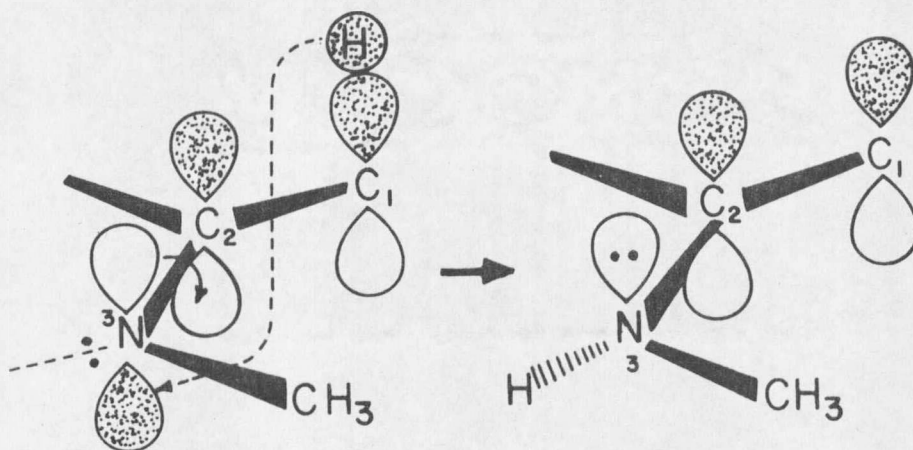


Figure 13. Proposed [1,3] Sigmatropic Hydrogen Shift

From the orbital topology diagram, we can see that as the nitrogen atom rehybridizes from sp^2 to sp^3 there is a simultaneous rehy-

bridization of C-1 from an sp^3 configuration to sp^2 . Thus as the hydrogen is being transferred from carbon to the nitrogen there is a synchronous isomerization of the double bond from $C_2=N$ to $C_2=C_1$. Thus the non-bonding pair of electrons on the nitrogen now becomes available for overlap with the π -system of the double bond, and could be the driving force for the reaction. Klopman^{20f} has suggested that keto-enol tautomerism could possibly be a [1,3] sigmatropic shift system involving a heteroatom (oxygen) possessing an occupied p-orbital perpendicular to the p- π -plane.

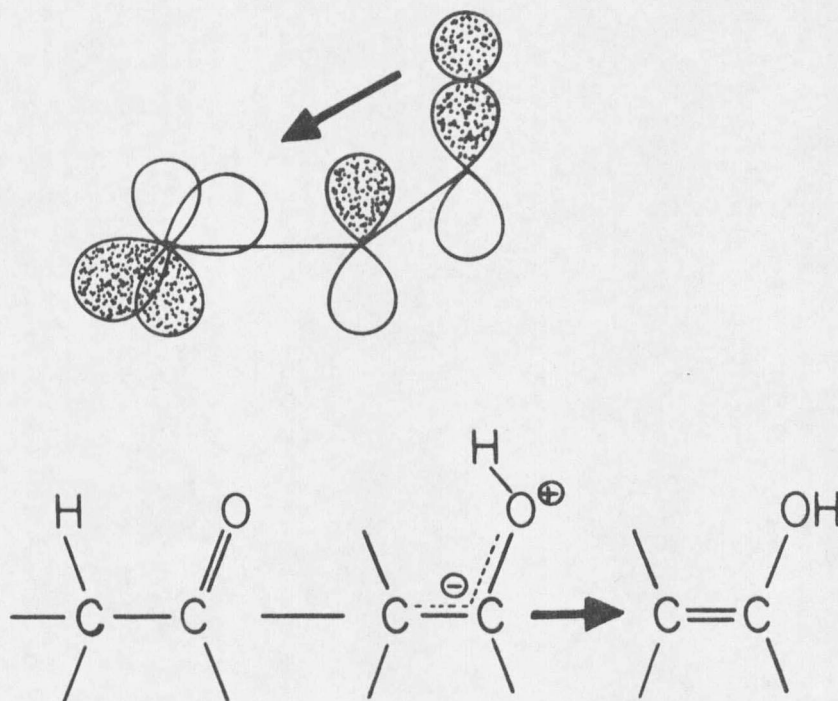


Figure 14. Klopman's Proposed Keto-Enol Tautomerization

One can note that in the geometry of IA severe steric interactions between the enamine and the methyl group are at a minimum and that coplanarity has been maintained between the nitrogen and the carbon of the double bond.

The second step of the rearrangement is a concerted [3,3] sigmatropic migration.^{20,22} For this rearrangement to be thermally allowed, there must be a suprafacial-suprafacial overlap of the p-orbital lobes (Figure 15). An orbital topology diagram clearly shows this in the cyclic six-membered transition state [IIB].

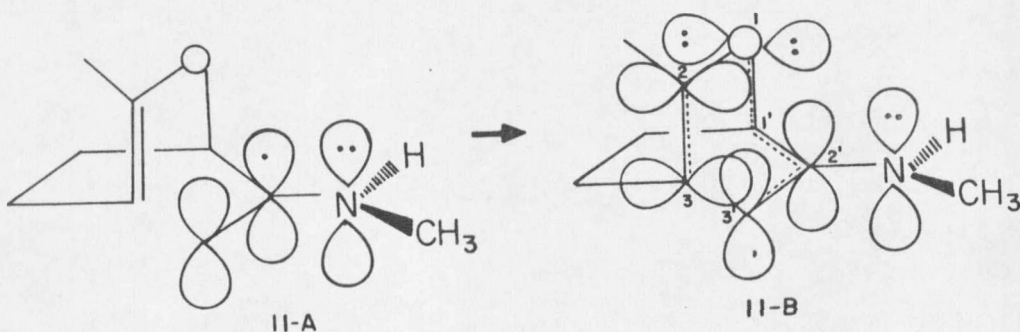


Figure 15. Proposed [3,3] Sigmatropic Migration

We will also note that in both [IIA] and [IIB] that the overlap between the unpaired electrons on the nitrogen and the π -system of the double bond are at a maximum due to the coplanarity of the N and carbon atoms. Thus in a concerted fashion, as the carbons 3 and 3' are rehy-

bridizing to form the σ -bond, carbon 1' and are also rehybridizing from sp^3 to sp^2 which will form the π -system between 1' and 2'. The interaction of the central p-lobes of C-2' and oxygen slightly destabilize the system and contribute to the extreme pyrolysis conditions.²²

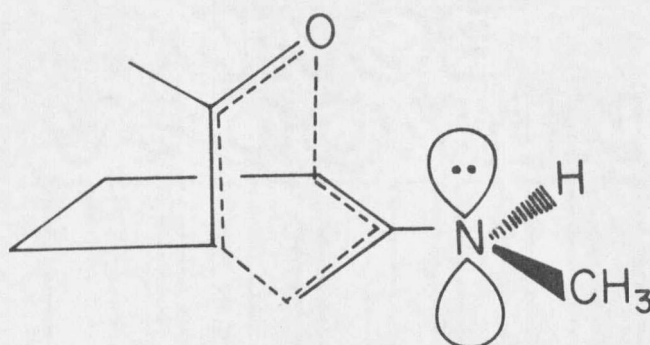


Figure 16. Boat Transition State Geometry

Even though the chair-like transition state geometry is lower in energy due to the quasi-planar arrangement of the six p-lobes, it is also sterically impossible to be attained.^{22,3} Thus the only accessible transition state geometry is that of the boat.

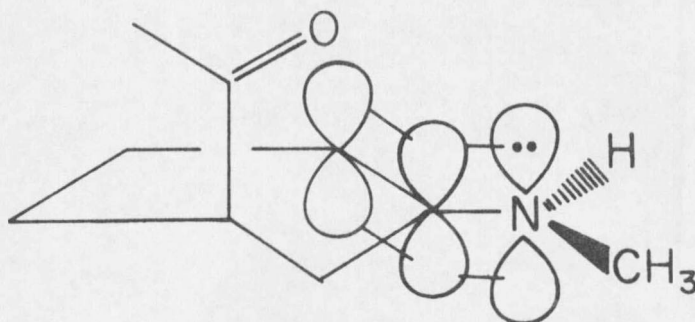
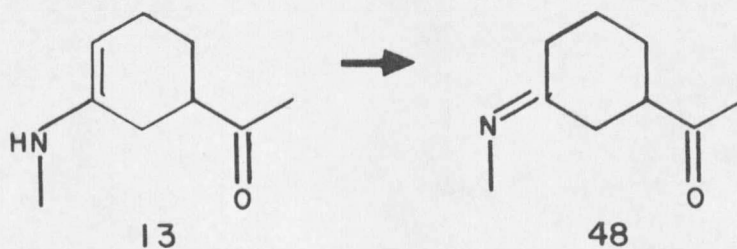


Figure 17. Geometry of 5-Acetyl-1-(1-Methyl) Amino Cyclohexene

Again in the product, 5-acetyl-1-(1-methyl) amino cyclohexene coplanarity has been maintained between the nitrogen atom and the carbons, hence, the overlap between the unpaired electrons of the nitrogen and the π -system of the double atom is at a maximum.²³

One would expect that the product [13] would isomerize again from the enamine to the imine [48]. However, NMR data does not show [48] to be present in appreciable amounts (less than 1%).



One may be able to rationalize this by the fact that in certain systems hydrogen bonding may stabilize the enamine tautomer²⁴ through inter-

molecular chelate formation between the carbonyl oxygen and the NH proton (Figure 18). This could also account for the high boiling point of the rearranged product [48].

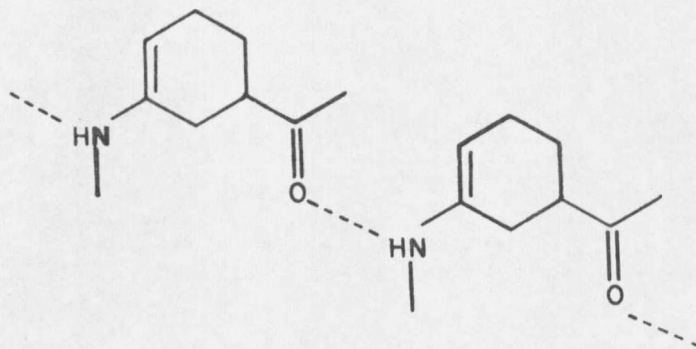


Figure 18. Proposed Hydrogen Bonding

An alternative explanation could be attributed to the supraannular effect.²⁵ In our system, the π -electrons of the enamine double bond could interact with the carbonyl group. Thus we would not see the reversion back to the methyl imine but rather the stabilized enamine form.

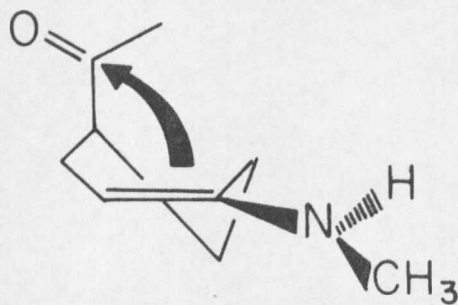
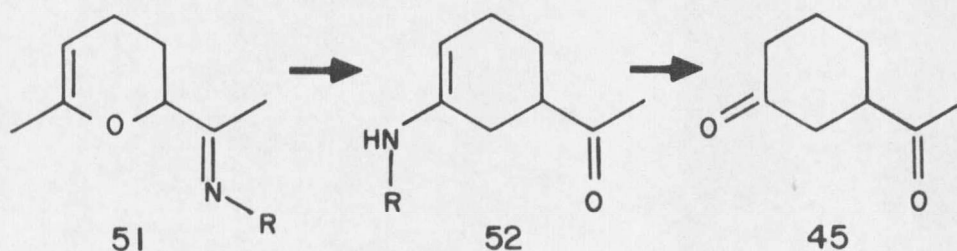


Figure 19. Proposed Supraannular Effect

To test the validity of this rearrangement, other examples were examined. The ethyl [51A], propyl [51B], and butyl [51C] imines were prepared in the manner previously described and pyrolyzed under the same conditions to yield the corresponding alkylamino-5-acetylcyclohexene in every case. Acid hydrolysis also yielded the 5-acetylcyclohexanone. The severe disadvantage of synthetically using these compounds would be that all the alkylamino-5-acetylcyclohexenes are extremely air sensitive and have to be stored under nitrogen.



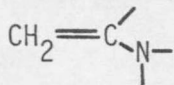
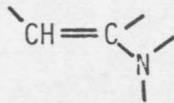
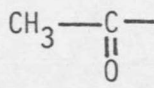
Based on the data already discussed, the specificity of pyrolysis could be furthered by the direct preparation of the enamine, thus eliminating the initial imine-enamine tautomerization. Also, it would unambiguously establish that the formation of the enamine is the key step in the thermal rearrangement. The pyrrolidino enamine of 2-acetyl-6-methyl-3,4-dehydro-2H-pyran [53] was formed by gently warming a mixture of the pyran and pyrrolidine over molecular sieves. The vacuum pyrolysis of the resulting enamines [53] under the same conditions previously described provided an excellent yield of the desired product

[41]. Instrumental analysis again verified the structure (Table 3).

The infrared spectra of the initial enamine [8] exhibited a C=C stretch of enamine at 1672 cm^{-1} and an ether C-O-C stretch at 1070 cm^{-1} . The rearranged product [41] did not exhibit the ether C-O-C stretch, however the C=C stretch of enamine was observed at 1639 cm^{-1} as well as the C=O stretch of carbonyl at 1698 cm^{-1} . The ultraviolet absorption spectra showed an absorption at 228 nm for [8], however the rearranged product [41] gives two: 227 nm (characteristic of enamine) and 281 nm (characteristic of the transition of a carbonyl). The nuclear magnetic resonance spectrum confirmed the stretch as [41] by the observation of the methyl group adjacent to the carbonyl at 2.14 δ and also the vinyl hydrogen as a triplet at 4.28 δ . Simple acid hydrolysis of [41] gave acetylcyclohexanone [36] in 73% yield. Alkylation of [41] with methyl-iodide followed by acid hydrolysis yield 2-methyl-5-acetylcyclohexanone [40] in 76% yield.

Note: *Both isomers were observed.

Table 3. Principle Spectroscopic Characteristics of Reactants and Products

Infrared Spectroscopy			NMR Spectroscopy		
53		41	53		41
1070 cm^{-1}	C-O-C stretch of the ether	-----	3.64 δ	$\text{CH}_2=\text{C}-\text{N}-$ 	-----
1672 cm^{-1}	C=C stretch of the enamine	1639 cm^{-1}	-----	$\text{CH}=\text{C}-\text{N}-$ 	4.28 δ
-----	C=O stretch of the carbonyl	1698 cm^{-1}	-----	$\text{CH}_3-\text{C}-$ 	2.14 δ

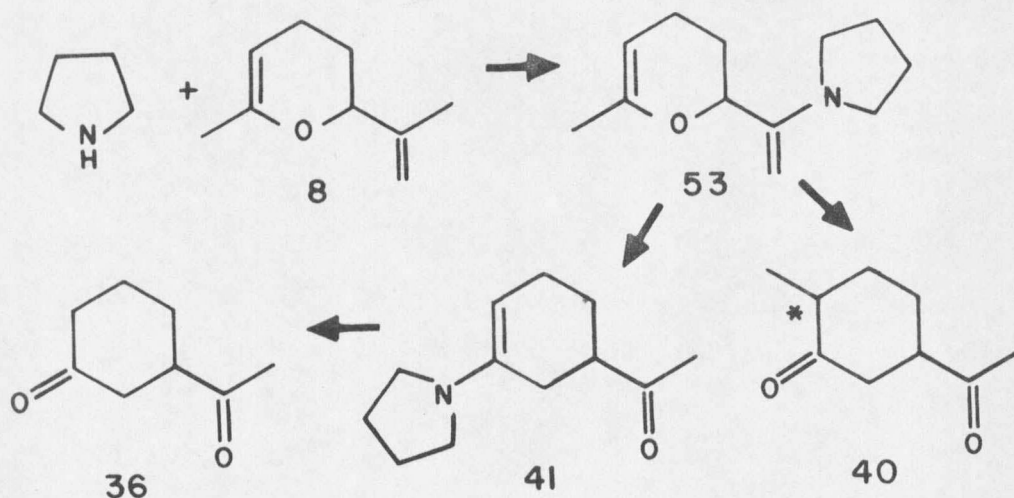


Figure 20. Preparation of 5-Acetyl-1-(1-Pyrrolidinyl)Cyclohexene by the Enamine Cope Rearrangement Proceeded by Ether Alkylation or Acid Hydrolysis

Again, a temperature versus product study (Table 4) was undertaken with the results that 250° C was the optimum pyrolysis temperature which concurs with that of the imine rearrangement. Temperatures any higher gave extensive polymerization and a marked decrease in product just as we observed in the previous imine pyrolysis (Table 1, p. 13).

The initial formation of the pyrrolidino enamine could, in theory, yield two isomers [53A] and [53B]; however, only [53A] was observed.

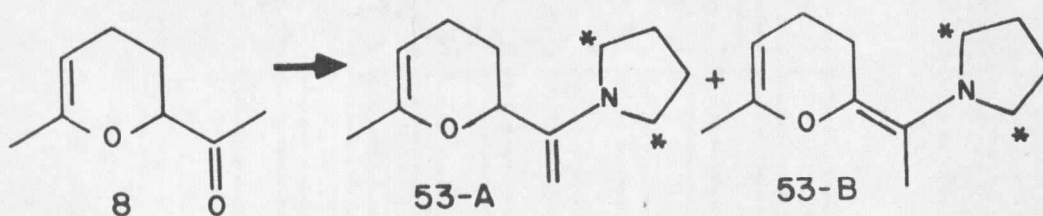


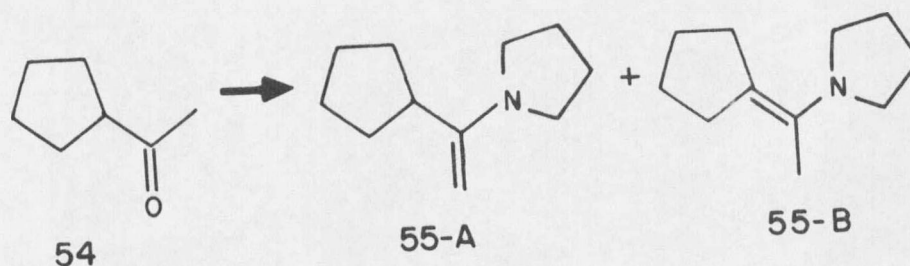
Table 4. Temperature Study of the Pyrolysis Conditions of the Pyrrolidine Enamine of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran

53	T (°C)	% 53*	% 41*
5.0 grams	150° C	100%	----
5.0 grams	175° C	100%	----
5.0 grams	200° C	79.0%	21.0%
5.0 grams	225° C	31.0%	69.0%
5.0 grams	250° C	----	100%
5.0 grams	275° C	----	70.0%**
5.0 grams	300° C	----	55.0%**

*Relative glc peak areas of material isolated; analysis was done on 10% SE-30 Chromosorb W at 160° C peak areas were measured by triangulation.

**Extensive polymerization was observed in the pyrolysis tube.

This could be rationalized by the severe steric interactions between the methylene groups (*) adjacent to the nitrogen atom and the coplanar pyran ring in [53B]. Such interactions are minimized in [53A] while overlap of the electron pair on the nitrogen and the π -electrons of the double bond are maximized by the required coplanarity of the nitrogen of the nitrogen and carbon atoms.^{23,28} Thus, severe destabilizing non-bonded repulsion arises from the more substituted isomer. This can be further substantiated by the reported preparation of the pyrrolidino enamine of acetylcyclopentane [53] [54] exclusively in the less substituted isomer [55A].²⁹



The mechanism for the thermal rearrangement of the pyrrolidino enamine of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran to 5-acetyl-1-(1-pyrrolidinyl)cyclohexene was again envisioned as a concerted [3,3] sigmatropic shift of oxy-Cope rearrangement.^{20,22} For such a rearrangement to be thermally allowed, there must be a suprafacial-suprefacial overlap of the interacting p-orbital lobes which can be seen from the orbital topology of [53C].

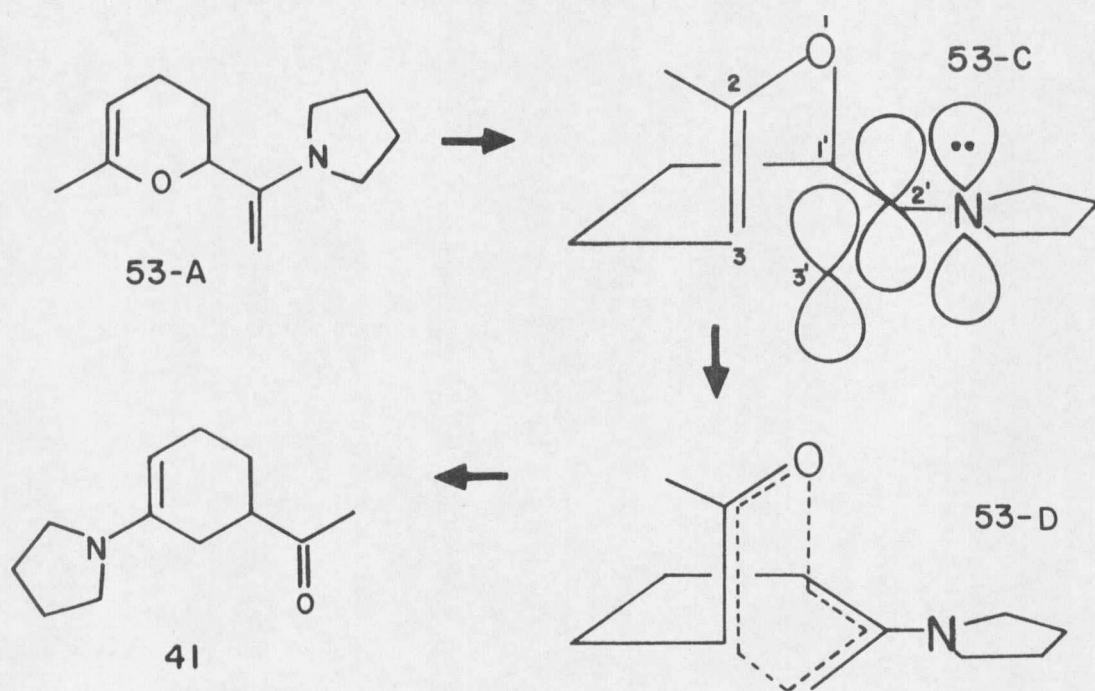


Figure 21. Proposed [3,3] Sigmatropic Rearrangement of the Pyrrolidino Enamine of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran

Again, even though the chair-like transition state geometry^{22,3a,b} is clearly favored over the boat, it is also clear once again that the chair transition state is sterically impossible to be attained in [53C], hence the boat transition state represents the only accessible pathway.

One must note that in the rearranged product [41], the overlap between the electron pair on the nitrogen and the electrons of the π -system are at a maximum due to the coplanarity of the nitrogen and the 2,3,28 cyclohexene carbons. Steric hindrance between the methylene hydro-

gens adjacent to the nitrogen (*) and the 4 acetylcyclohexene ring are at a minimum, which significantly contributes to the stability of the molecule.

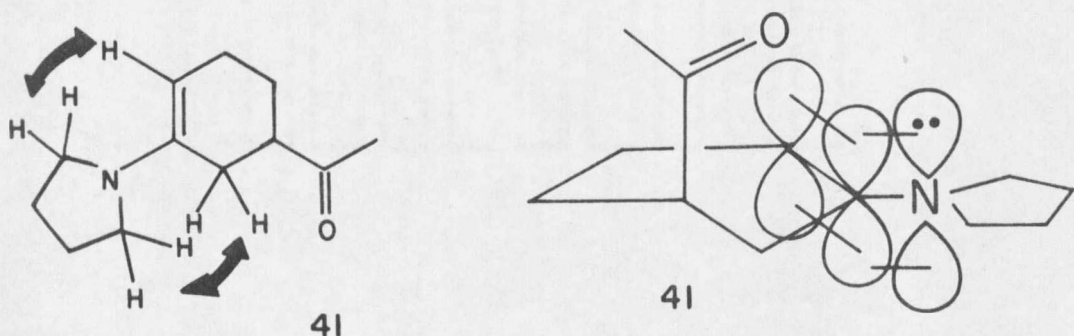


Figure 22. Geometry of 5-Acetyl-1-(1-pyrrolidinyl)cyclohexene

In conclusion, of the two systems investigated, the imine and enamine; the 5-acetyl-1-(1-pyrrolidinyl)cyclohexene is easier to work with, air stable for short periods of time and the yields are much better. In synthetic strategies this would be the intermediate compound of choice.

Another plausible synthetic strategy would be the Diels-Alder reaction between 2-methoxy butadiene-5,6 and methyl-3-butene-2-one [57]; however, there would be two products from this reaction [58A] and [58B] and whether or not one could separate these is unknown. However, if one could separate these two components, mild acid hydrolysis of [58A] would give the 5-acetylcyclohexanone [59]. Now the preparation of the pyrrolidino enamine of 5-acetylcyclohexanone will yield five compounds

[60A,B], of which only one will be the target compound [60A]. Therefore one can conclude that the enamine-Cope rearrangement would be the method of choice for preparing compounds of the nature because of the fact that the enamine functionality will be in the correct configuration for additional work. It has been also suggested that the acetyl enol [61] derivative could also possibly be Cope rearranged to give [62], which then could be alkylated in the 2 position. The shortcomings to this could be the fact that upon acid hydrolysis to the ketone [63], enamine formation will be indiscriminate and yield 6 compounds [64A-F].

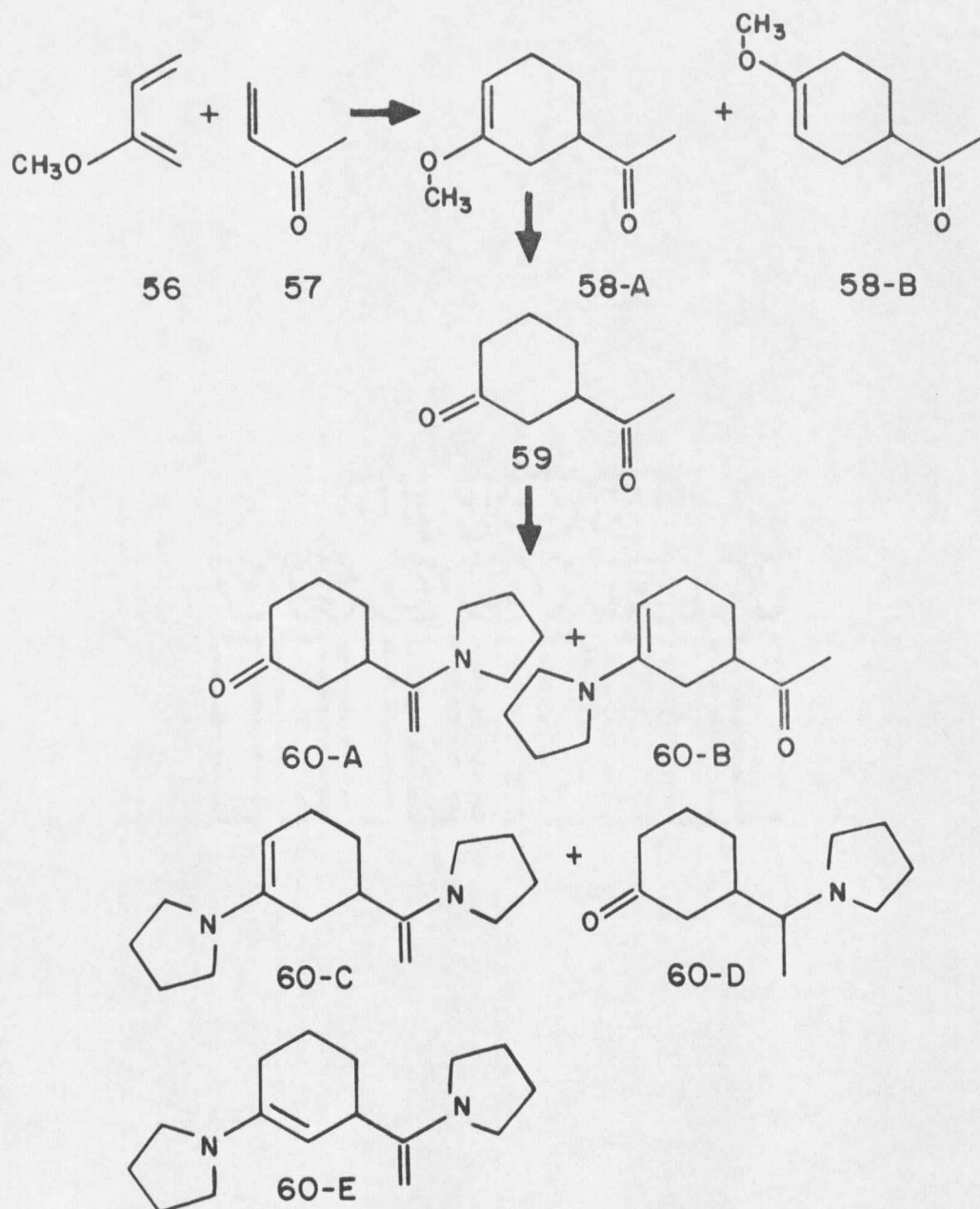


Figure 23. Proposed Synthesis of 3-Acetylcyclohexanone By Diels-Alder Reaction And the Formation of the Corresponding Pyrrolidino Enamines

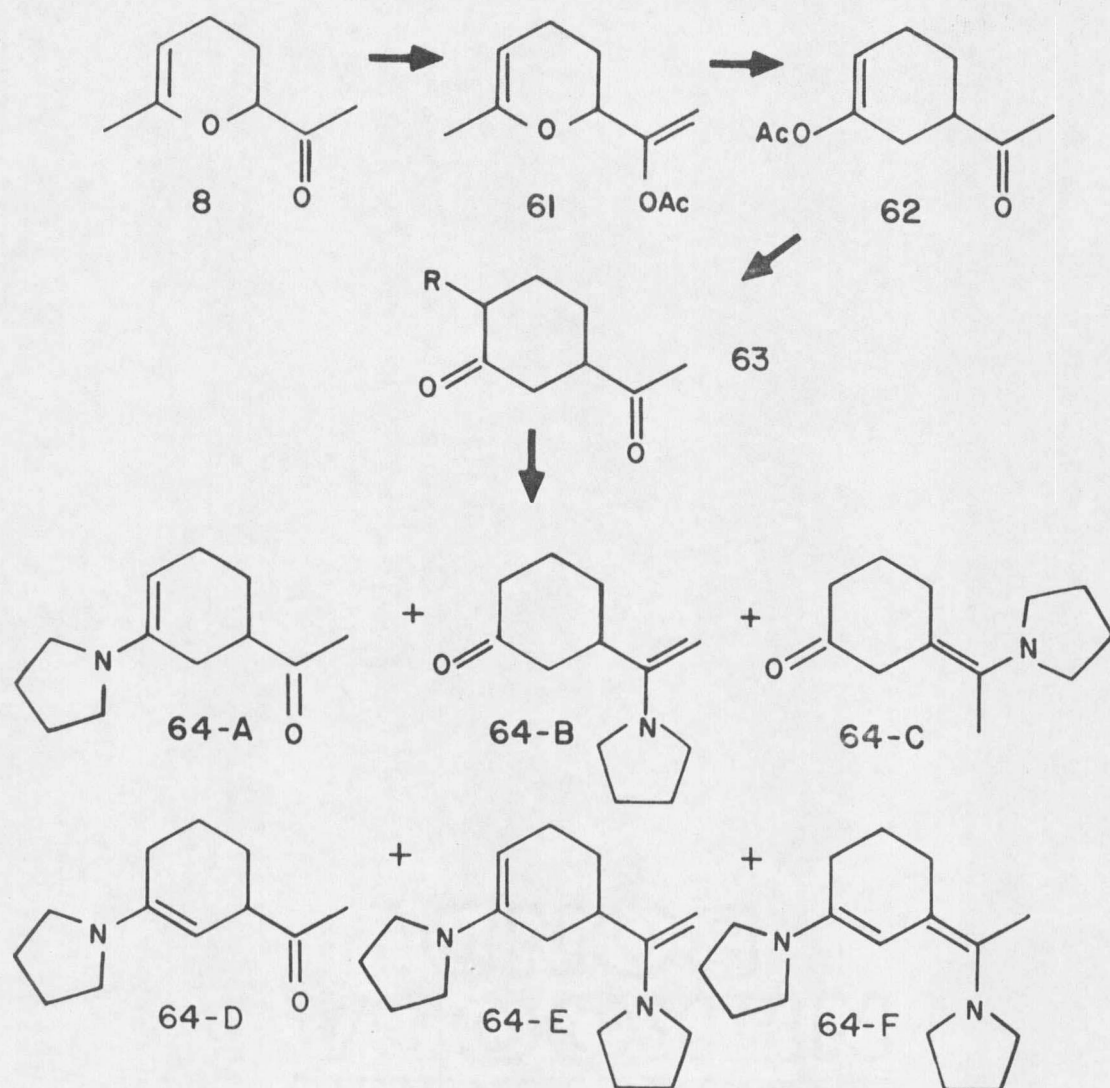
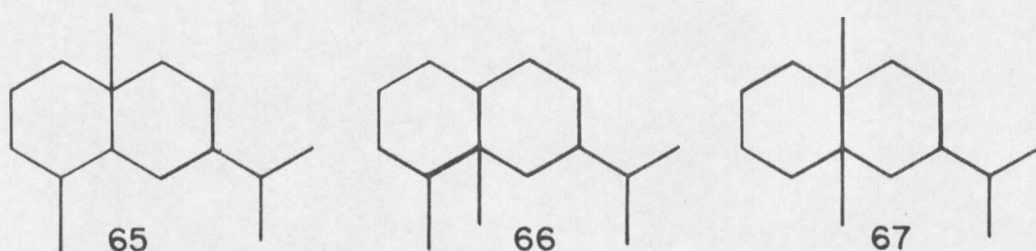


Figure 24. Proposed Cope Rearrangement of the Acetyl Enol of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran

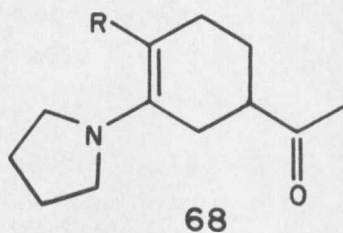
CHAPTER 3

APPLICATION OF THE ENAMINE COPE REARRANGEMENT

Retrosynthetic analysis¹⁵ of the bicyclic sesquiterpenes skeletons^{30a,b} of the eudesmanes [65], eremophilanes [66], and valeranes [67]



reveal one key intermediate [68] which might serve as a common precursor.



For eudesmanes ($R = \text{CH}_3$), and for eremophilane ($R = \text{H}$), Robinson annelation of [68] with ethylvinyl ketone will allow for the construction of the basic octalene skeleton essential for the total synthesis³¹ of compounds related to the abovementioned carbon skeletons. Thus, application of the enamine Cope rearrangement can best be demonstrated

by the proposed synthesis of α -cyperone [74]. Robinson annelation^{32a,b} of the resulting enamine [71] would give [72]. Selective ketalization of α,β -unsaturated ketones such as [72] with other ketones present is well-known. Thus the product [73] followed by a Wittig condensation would convert the acetyl carbonyl to a methylene group. Hydrolysis of the ketal would once again regenerate our α,β -unsaturated ketone and thus complete the total synthesis of α -cyperone [74]. Note that the synthesis is accomplished in five high-yield steps as compared to the synthesis developed by Piers³³ which was accomplished in eight steps. Another synthesis of α -cyperone by J. K. Roy³⁴ consisted of the Robinson annelation of dehydrocarvone which gave a reported 3% yield.

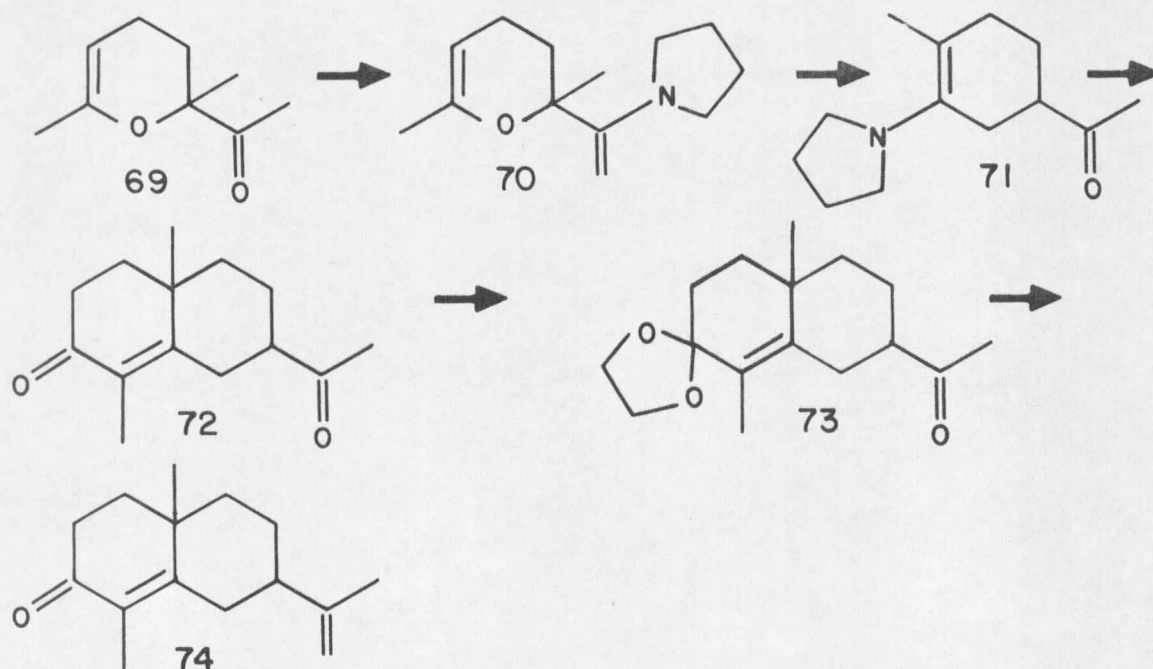


Figure 25. Proposed Synthesis of α -Cyperone

Another demonstration of the enamine Cope rearrangement as a useful synthetic tool could be in the proposed synthesis of $7\beta,10\beta$ selina-4,11-diene. Again Robinson annelation³² of [71] with ethylvinyl ketone would give [72]. Preferential ketalization with ethanedithiol³³ of the α,β -unsaturated ketone in [72], followed by Raney nickel desulfurization, would yield the unsaturated compound [75]. Subsequent Wittig condensation of [76] would give [77].

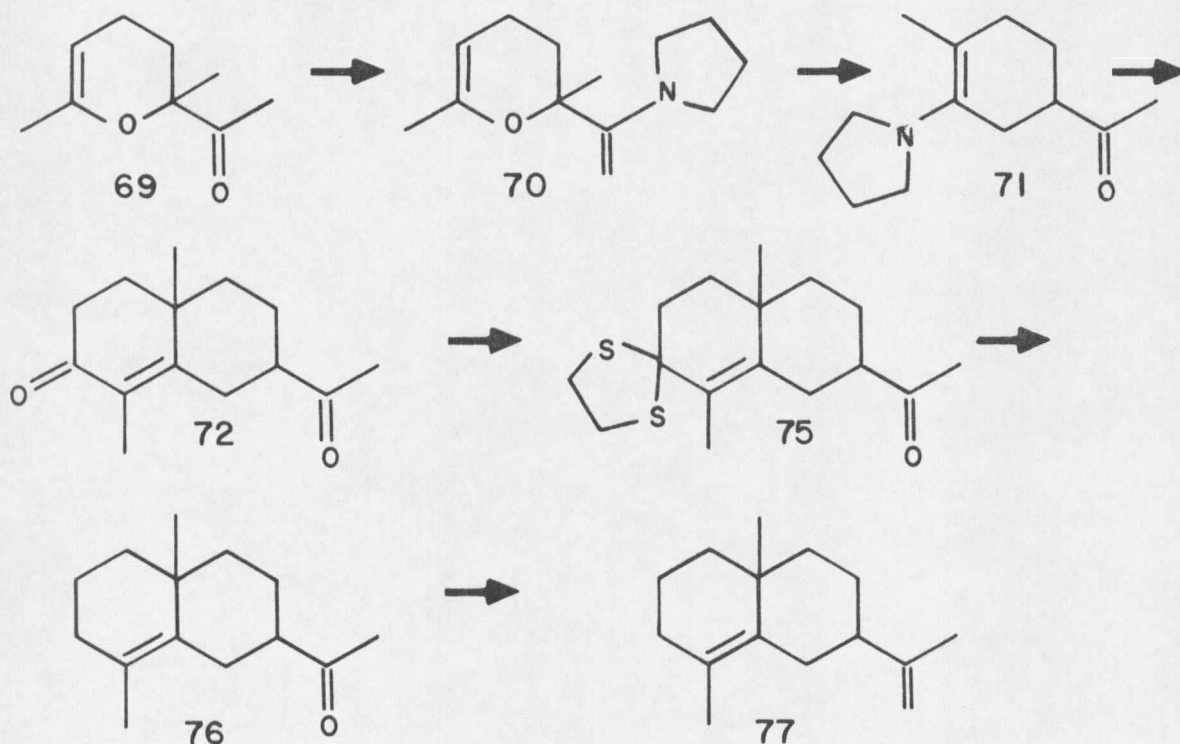
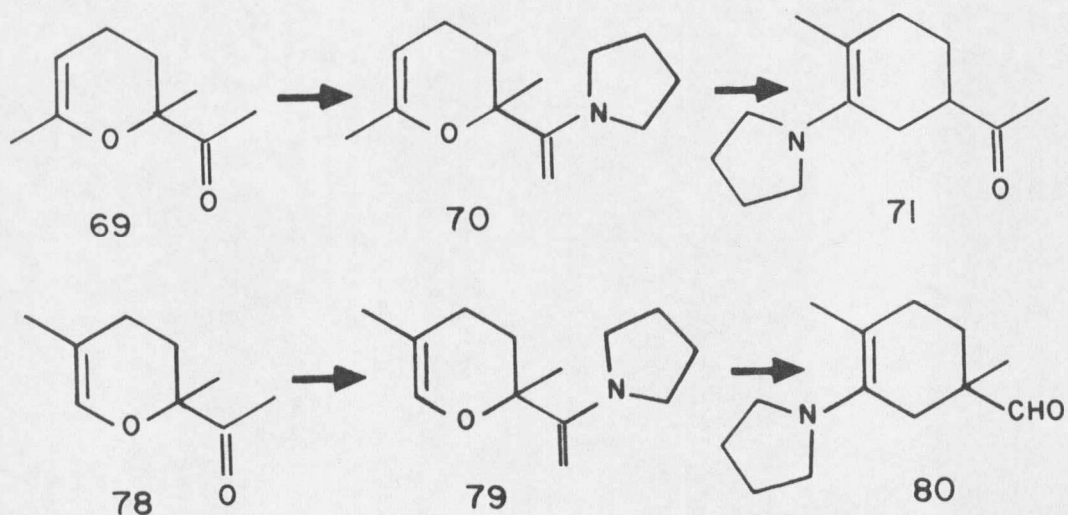


Figure 26. Proposed Synthesis of $7\beta,10\beta$ Selina-4,11-Diene

CHAPTER 4

FUTURE RESEARCH

Future research in the area of the enamine-oxy-Cope rearrangement will have to depend on the synthesis of various substituted 2-acetyl-3,4-dihydro-2H-pyrans.³⁶⁻³⁹ We can easily see that a specifically substituted pyran precursor will give a specifically substituted 5-acetyl-1-(1-pyrrolidinyl)cyclohexene.



Thus we could generalize the substitution pattern in both starting pyran [81] and rearranged enamine [83] as:

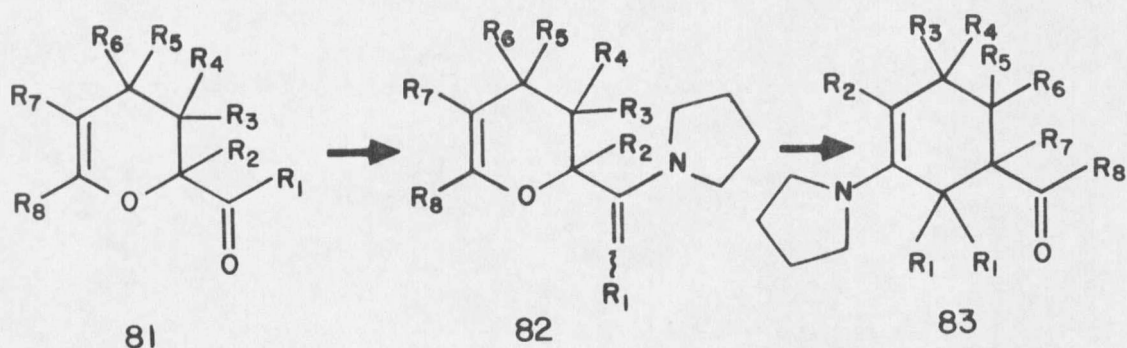


Figure 27. General Substitution Pattern of Reactants and Products in the Enamine Cope Rearrangement

Therefore, one could synthesize a specifically substituted pyran which would in turn give a specific enamine [85].

Several excellent reviews^{36,37} have been published which deal with the Diels-Alder reactions of α,β -unsaturated carbonyl compound giving 3,4-dihydro-2H-pyrans and various other functional groups in the 2-position as acetyl or carbomethoxy. One must keep in mind that an acetyl group (methyl ketone) in the 2-position is a prerequisite for pyrrolidino enamine formation and subsequent rearranged product. As we can see, the full potential of this synthetic technique can only be realized by the proper development of the initial pyran ring precursor.

CHAPTER 5

EXPERIMENTAL

Proton nuclear magnetic resonance spectra were recorded on Varian A-60 or Varian T-60 nuclear magnetic resonance spectrometers. Peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra for both liquid and solid compounds were obtained from a Varian Model CH-5 mass spectrometer.

Glc analyses were carried out using a Varian Aerograph series 2700 instrument and all work was done using a 10' x 3/8' copper column packed with 1.5% OV-101 on Chromosorb G. Gas flow was maintained at 18 ml/sec. Infrared spectra were obtained with Beckman IR 5A or IR20 infrared spectrophotometers. UV spectra were recorded on a Cary 14 recording spectrophotometer or on a Varian series 634 UV-visible spectrophotometer.

Melting points were performed on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Boiling points are uncorrected and reported in mm of mercury (b.p. (10) 75° C indicates the boiling point was 75° C at 10 mm of mercury). Solvents were generally removed under reduced pressure via Buchi rotatory evaporator.

General Procedure for the Pyrolysis of Imines and Enamines

The vacuum pyrolysis conditions for either the imines or enamines were the same. A 15 ml round bottom flask was charged with the

imine or enamine to be pyrolyzed and was placed on the Pyrex pyrolysis tube (Pyrex helices) and the entire system was evacuated (0.3 mm of mercury). The heating element (18 feet of resistant nichrome wire) for the pyrolysis tube was controlled by a Variable Powerstat Transformer. The internal temperature of the column was monitored with an iron-constantan thermocouple fused into the wall of the column and the temperature was recorded with an Omega Type 2809 Digital Thermometer. When the internal temperature reached 250° C the heating mantle was activated and the imine or enamine was allowed to reflux.

The crude pyrolyzed product was collected in a pyrex U-tube filled with pyrex helices and externally cooled in a Dewar flask containing either isopropyl alcohol/dry ice or ice/salt mixtures. When either the imine or enamine was no longer present in the 15 ml round bottom flask, both transformers were shut off and the system was allowed to cool down to room temperature. At this point the vacuum was broken, and the contents of the U-tube were removed by flushing with dry hexane. Removal of this solvent under reduced pressure yields the product. (Refer to diagram on following page.)

Preparation of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran [8]

As described in the literature,⁴⁰ methyl-3-butene-2-one 100 grams (1.42 moles) was placed in a steel pressure vessel and dimerized at 185° C for four hours. After cooling, the contents were removed and vacuum distilled (water aspirator) to give a colorless liquid, b.p. (10)

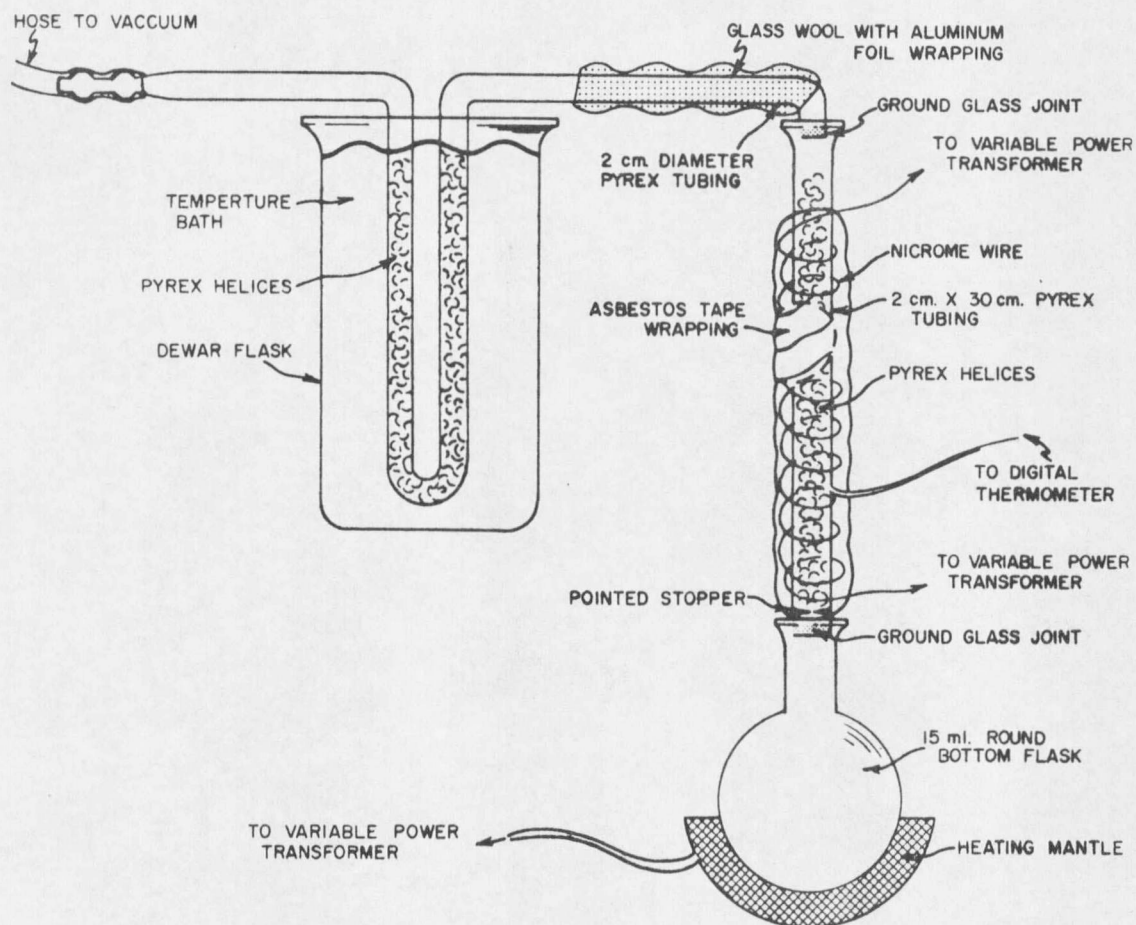
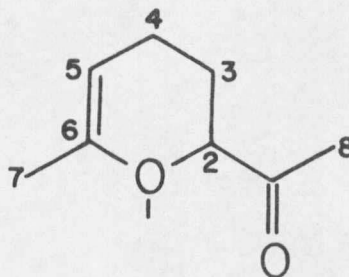


Figure 28. Vacuum Pyrolysis Apparatus

74° C, 42.5 grams (85% yield).

nmr data



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2	4.17	1	broad triplet
3,4	2.03-1.56	4	multiplet
5	4.48	1(7 cps)	multiplet
7	1.78	3	singlet
8	2.17	3	singlet

I.R. (film) cm^{-1}

2874 (C-H stretch); 1712 (C=O stretch); 1675 (C=C stretch); 1429;
1385; 1351; 1279; 1232 (C-O-C stretch); 1163; 1103; 1070 (C-O-C
stretch); 917.4; 894.5; 758.7 (CH=CH stretch).

U.V. (hexane)

208 nm (ϵ 3.32) 281 (ϵ 1.59)

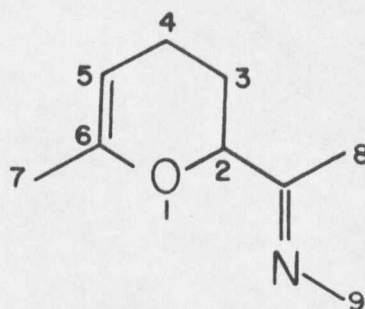
Mass Spectrum m/e (relative intensity)

140 (37%); 97 (100%); 79 (5.3%); 69 (9.0%); 55 (7.5%); 53 (4.5%);
43 (2.5%); 41 (15.1%).

General Preparation of N-Alkyl Imines of 2-Acetyl-6-Methyl-3,4-Dihydro
Pyrans

For the sake of brevity we will only consider in detail the preparation of the N-methyl imine of 2-acetyl-6-methyl-3,4-dehydro pyran [11]. All other imines were prepared in the same manner with the identical results. Only their spectral characteristics will be given.

A solution of 2-acetyl-6-methyl-3,4-dihydro pyran (19 grams, 0.071 mole) and 100 ml of diethyl ether containing 15 grams of Linde 4 Å molecular⁴¹ sieves was cooled to 0° C in an ice/salt bath. Into this solution was bubbled 2.48 grams (8.085 moles) of methyl amine (a 20% excess). The resulting solution was allowed to come to room temperature and stir overnight, at the end of which time the molecular sieves were filtered from the reaction mixture and washed twice with 25 ml portions of anhydrous diethyl ether. The solvent was then removed from the combined ether fractions under reduced pressure and the remaining residue was vacuum distilled (water aspirated) to give 9.72 grams (0.068 mole) 97% b.p. (0.25) 37° C, a 97% yield. Analysis by glc indicated only one component.



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2	4.18	1	multiplet
3,4	1.44-2.23	4	multiplet
5	4.42	1	multiplet
7	1.74	3	singlet
8	1.87	3	singlet
9	3.07	3	singlet

I.R. (film) cm^{-1}

2857; 1667 (C=N stretch); 1429; 1379; 1299; 1282; 1235 (C-O-C stretch); 1163; 1053 (C-O-C stretch); 917.4; 873.4; 754.7

U.V. (hexane)

231 nm (ϵ 3.70) λ_{max} .

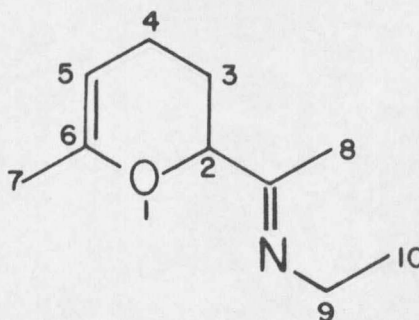
Mass Spectrum m/e (relative intensity)

153 (28.2%); 124 (13.6%); 97 (100%); 70 (16.1%); 56 (32.1%); 29

(12.4%)

N-Ethyl Imine of 5-Methyl-2-Acetyl-3,4-Dihydro-2H-Pyran [51A]

B.P. (0.25) 48° C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2	4.16	1	multiplet
3,4	1.29-2.26	4	multiplet
5	4.37	1	multiplet
7	1.70	3	singlet
8	2.15	3	singlet
9	3.09	2	quartet
10	0.91	3	triplet

I.R. (film) cm^{-1}

2902; 1678 (C=N stretch); 1660 (C=C stretch); 1440; 1386; 1238;

1170 (C—O—C stretch); 1072 (C—O—C stretch); 923; 754

U.V. (hexane)

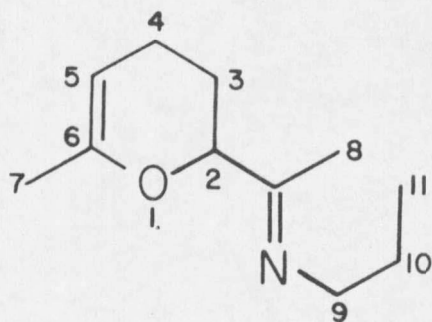
230 nm (ϵ 3.47) λ_{max} .

Mass Spectrum m/e (relative intensity)

167 (29.3%); 124 (16.1%); 97 (100%); 70 (56.1%); 43 (16.2%)

N-Propyl Imine of 5-Methyl-2-Acetyl-3,4-Dihydro-2H-Pyran [51B]

b.p. (0.25) 54° C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2	4.14	1	multiplet
3,4,10	1.32-2.24	6	multiplet
5	4.39	1	multiplet
7	1.71	3	singlet
8	2.14	3	singlet
9	2.15	3	broad triplet
11	0.93	3	triplet

I.R. (film) cm^{-1}

2899; 1675 (C=N stretch); 1664 (C=C stretch); 1440; 1383; 1236;
1168 (C-O-C stretch); 1070 (C-O-C stretch); 920.8; 753.0

U.V. (hexane)

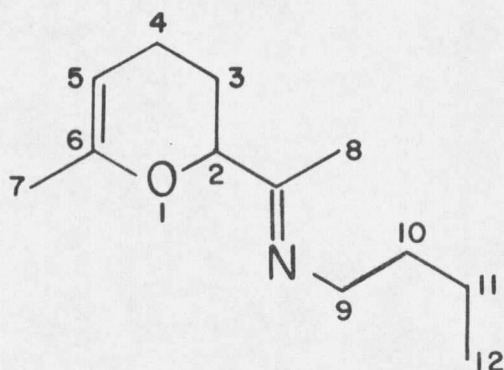
232 nm (ϵ 3.44) λ_{max} .

Mass Spectrum m/e (relative intensity)

181 (31.1%); 124 (14.6%); 97 (100%); 84 (40.1%); 57 (18.8%)

N-Butyl Imine of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran [51C]

b.p. (0.25) 67°C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2	4.12	1	multiplet
3,4,10,11	1.30-2.25	8	multiplet
5	4.36	1	multiplet
7	1.76	3	singlet
8	2.18	3	singlet
9	3.19	2	triplet
12	0.96	3	triplet

I.R. (film) cm^{-1}

2892; 1674 (C-N stretch); 1665 (C=C stretch); 1446; 1380; 1236;
1167 (C-O-C stretch); 1070 (C-O-C stretch); 921; 756

U.V. (hexane)

236 nm (ϵ 3.40) λ_{max} .

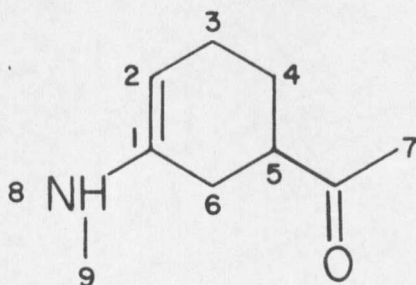
Mass Spectrum m/e (relative intensity)

195 (28.6%); 98 (51.2%); 97 (100%); 71 (26.1%)

General Preparation of 5-Acetyl-1-(1-Alkyl)Amino Cyclohexene

Again we will only describe in detail the preparation of 5-acetyl-1-(1-methyl)amino cyclohexene [13]. The other imines which were also investigated (ethyl [52B], propyl [52B] and butyl [52C]) were accomplished in exactly the same manner, only the spectral data will be given for these compounds.

Using the general pyrolysis procedure, 5.0 grams (0.035 mole) of [11] were placed in the 15 ml round bottom flask and following the conditions previously described, pyrolysis was initiated. After three hours, the apparatus was cooled and the crude pyrolysis product was removed, yielding 4.7 grams of an air-sensitive compound which had to be stored under nitrogen. Analysis by glc suggested only one compound present. Distillation under high vacuum gave 3.3 grams (0.023 mole) of [13], b.p. (0.3) 125° C, 66% yield. (Note: 1.4 grams of polymerized residue remained in the distillation flask.)



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
3,4,5,6	0.84-2.41	7	unresolved multiplet
2	4.48	1	triplet
7	2.16	3	singlet
8	3.40	1	broad multiplet
9	2.68	3	doublet

I.R. (film) cm^{-1}

3413 (NH stretch); 2857; 3268; 1645 (C=C stretch); 1563; 3086
(C=C-H stretch); 1695 (C=O stretch); 1429; 1342; 840.3; 751.9 (C=C)

U.V. (hexane)

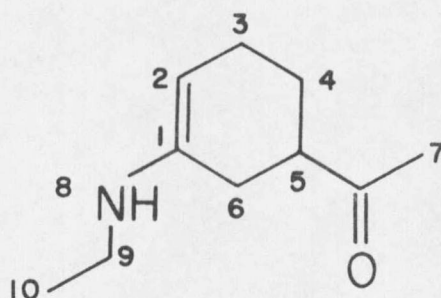
220 nm (ϵ 3.79) 284 nm (ϵ 1.77) λ_{max} .

Mass Spectrum m/e (relative intensity)

153 (28.6%); 123 (16.3%); 110 (100%); 83 (12.6%); 80 (98.2%); 70
(11.8%); 43 (26.8%)

5-Acetyl-1-(1-Ethyl)Amino Cyclohexene [52A]

b.p. (0.8) 132° C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
3,4,5,6	1.02-2.50	7	multiplet
2	4.44	1	triplet
7	2.14	3	singlet
8	3.44	1	multiplet
9	2.74	2	multiplet
10	0.87	3	triplet

I.R. (film) cm^{-1}

3421 (N-H stretch); 3254; 2850; 1697 (C=O stretch); 1637 (C=C stretch of enamine); 1558; 1428; 134; 844.6; 750.1

U.V. (hexane)

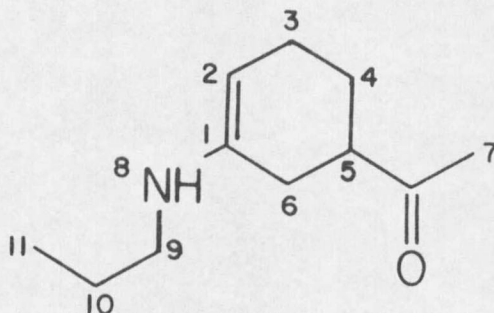
222 nm (ϵ 3.80) 283 nm (ϵ 1.71) λ_{max} .

Mass Spectrum m/e (relative intensity)

167 (41.6%); 123 (27%); 80 (100%); 70 (21.7%); 44 (33.4%)

5-Acetyl-1-(1-Propyl)Amino Cyclohexene [52B]

b.p. (0.8) 140° C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
3,4,5,6,10	1.08-2.56	9	multiplet
9	2.70	2	multiplet
2	4.45	1	multiplet
7	2.16	3	singlet
8	3.38	1	multiplet
11	0.91	3	triplet

I.R. (film) cm^{-1} 3405 (N-H stretch); 3259; 3094 ($=\text{C}-\text{H}$ stretch); 2890; 1704 ($\text{C}=\text{O}$)

stretch); 1643 (enamine C=C); 1408; 1351; 986; 892; 740.9

U.V. (hexene)

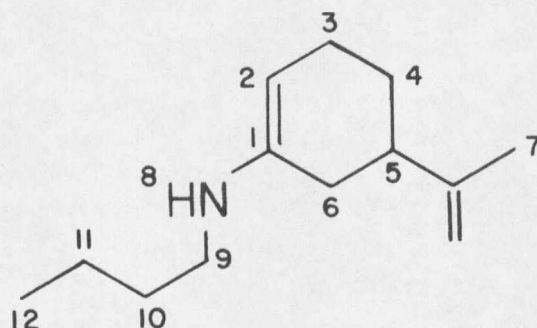
223 nm (ϵ 3.77); 2.81 nm (ϵ 1.68), $\lambda_{\max}$.

Mass Spectrum m/e (relative intensity)

181 (30.6%); 138 (17.2%); 123 (22%); 80 (100%); 70 (15%); 58 (21.2%); 43 (39.1%)

5-Acetyl-1-(1-Butyl)Amino Cyclohexene [52C]

b.p. (0.8) 146° C



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
3,4,5,6,10,11	1.1-2.51	11	multiplet
2	4.42	1	multiplet
7	2.15	3	singlet
8	3.31	1	multiplet
9	2.67	2	multiplet
12	0.92	3	triplet

I.R. (film) cm^{-1}

3400 (NH stretch); 3261; 3089 ($=\text{C}_{\text{H}}$ stretch); 1649 ($\text{C}=\text{C}$ stretch of enamine); 1562; 1423; 1353; 852; 746.1

U.V. (hexane)

229 nm (ϵ 3.76); 282 nm (ϵ 1.88), λ_{max} .

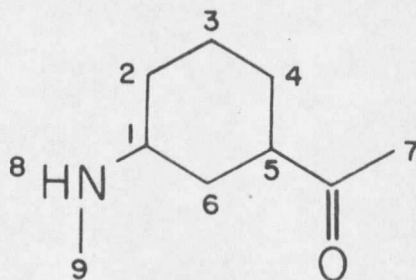
Mass Spectrum m/e (relative intensity)

195 (36.4%); 152 (16.9%); 123 (21.3%); 80 (100%); 72 (20.6%); 70 (14.2%); 43 (33.2%)

Hydrogenolysis of 5-Acetyl-1-(1-Methyl)Amino Cyclohexene [45]

3.0 grams (0.021 mole) of 5-acetyl-1-(1-methyl)amino cyclohexene were dissolved in a 50 ml of dry ethanol, to which was added 1.5 grams of 10% Pd/C. This entire mixture was placed in a Parr Catalytic Hydrogenation apparatus under a hydrogen atmosphere of 25 lbs. with shaking at room temperature. At the end of 24 hours, the contents were removed,

and the Pd/C was filtered and washed twice with 25 ml portions of dry ethanol. The ethanol fractions were combined and the solvent removed under reduced pressure. The remaining residue was vacuum distilled (water aspirator) to give 2.46 grams (0.017 mole), b.p. (0.8) 123° C (82% yield); glc analysis on 10% SE-30 150° C indicated only one component.



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
7	2.16	3	singlet
1,2,3,4,5,6	0.84-2.14	10	unresolved multiplet
9	2.42	3	singlet

I.R. (film) cm^{-1}

3333 (NH stretch); 2857; 1701 (C=O stretch); 1445; 1346

U.V. (hexane)

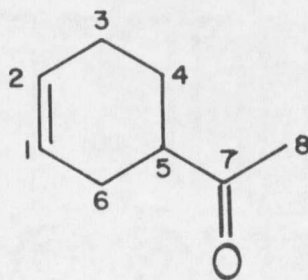
284 nm (ϵ 1.92); 201 nm (ϵ 3.8), λ_{max} .

Mass Spectrum m/e (relative intensity)

155 (22.4%); 140 (12.3%); 125 (9.6%); 112 (100%); 97 (14%); 82 (13.3%); 43 (26.1%)

Preparation of 4-Acetylcyclohexene [47]

2.0 grams (0.013 mole) of [45] was added to a solution of 50 ml of anhydrous diethyl ether and 2.3 grams (0.016 mole) of 25% excess methyl iodide. The solution was allowed to stir under N_2 atmosphere for four hours at room temperature, at the end of which time the quaternary ammonia salt was collected by vacuum filtration and washed three times with 25 ml portions of anhydrous ether. The salts were then added to a solution of 1.45 grams (0.013 mole) of potassium tert-butoxide in 50 ml of tert-butyl alcohol at 80° C with stirring. After five hours, the solution was cooled and extracted with 50 ml portions of anhydrous ether, dried over anhydrous magnesium sulfate, and the solvent removed under reduced pressure. The remaining residue was vacuum distilled (water aspirator) to give a clear liquid 1.0 grams, b.p. (10) 75° C, a yield of 62%. Analysis by glc indicated only one compound present.



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
3,4,5,6	1.12-2.84	7	unresolved multiplet
1,2	5.64	2	broadened singlet
8	2.14	3	singlet

strong peaks at 2.19 and 2.06.

I.R. (film) cm^{-1}

2857; 1724; 1429; 1351; 1220; 716.3; 651.6

U.V. (hexane)

180 nm (ϵ 4.03); 284 nm (ϵ 3.380), λ_{max} .

Mass Spectrum m/e (relative intensity)

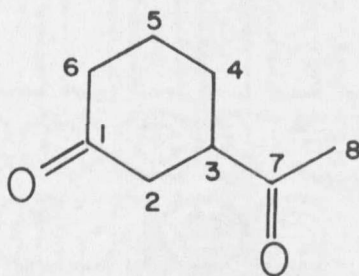
124 (22.6%); 81 (59.3%); 70 (33.8%); 54 (29.2%); 43 (100%)

General Preparation of 3-Acetylcyclohexanone [36]

Since all of the 5-acetyl-1-(1-alkyl)amino cyclohexenes were acid hydrolyzed to the same product, 3-acetylcyclohexanone [36], only the acid hydrolysis of 5-acetyl-1-(1-methyl)amino cyclohexene will be described in full detail.

The preparation of 3-acetylcyclohexanone was achieved in the following manner. 3.0 grams (0.019 mole) of freshly distilled [13] were dissolved in 50 ml of a 5% aqueous sulfuric acid. This entire solution was refluxed under a nitrogen atmosphere for 24 hours and the resulting orange-colored solution was cooled and the benzene layer

separated. The aqueous layer was extracted twice with 25 ml portions of benzene. The combined benzene portions were washed three times with 50 ml portions of saturated sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure left a residue which was vacuum distilled (water aspirator), b.p. 124° C, to yield 1.97 grams of a colorless liquid, a yield of 72%. Analysis by glc showed only one compound present.



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
8	2.16	3	singlet
2,3,4,5,6	1.16-2.48	9	multiplet

I.R. (film) cm^{-1}

2857; 1701 (C=O stretch); 1721; 1429; 1351; 1255; 1220; 1163

U.V. (hexane)

288 nm (ϵ 3.70)

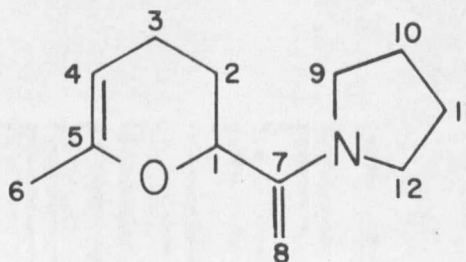
Mass Spectrum m/e (relative intensity)

140 (10%); 97 (61.25%); 69 (37.5%); 55 (40%); 43 (100%); 41 (71.25%); 39 (33.5%)

General Preparation of Pyrrolidino Enamine of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran [53]

10 grams (0.071 mole) of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran were added to 5.5 grams (0.077 mole) of pyrrolidine and 15 grams of Linde 4A molecular sieves. This mixture was then warmed to 35° C and maintained at this temperature, while stirring under a nitrogen atmosphere for 24 hours. After this time the reaction mixture was cooled, the molecular sieves were filtered from the mixture and were washed twice with 25 ml portions of anhydrous ether. The ether was combined with the filtrate and removed under reduced pressure. The residue was vacuum distilled to give a colorless liquid, b.p. (0.8) 83° C, 12.45 grams, a yield of 91%. Glc analysis suggested that only one compound was present.

nmr data



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
6	1.82	3	singlet
2,3,10,11	1.42-2.26	8	unresolved multiplet
4	4.49	1	multiplet
1	4.24	1	multiplet
8	2.64	2	doublet
9,12	2.94	4	unresolved multiplet

I.R. (film) cm^{-1}

3078 (C-H stretch); 2857; 1672 (C=C stretch of enamine); 1613; 1287; 1250; 1235; 1166; 1070 (C-O-C stretch); 950.6; 754.7 (C=C stretch)

U.V. (hexane)

228 nm (ϵ 3.78) λ_{max} .

Mass Spectrum m/e (relative intensity)

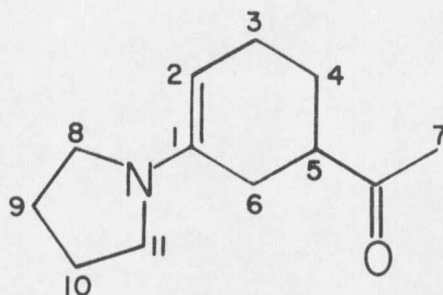
193 (32.3%); 123 (22.1%); 122 (32%); 97 (100%); 96 (51.2%); 70 (23%)

Anal: Calc'd for $\text{C}_{12}\text{H}_{19}\text{ON}$; C 74.56; H 9.90. Found: C 76.90; H 10.26.

Preparation of 5-Acetyl-1-(1-Pyrrolidiny)Cyclohexene [41]

Using the general pyrolysis procedure, 5.0 grams (0.025 mole) of pyrrolidine enamine was placed in the 15 ml round bottom flask and following the conditions previously described, pyrolysis was initiated.

After three hours the apparatus was cooled and the crude pyrolysis product was removed, yielding 5 grams of an air sensitive product which had to be stored under nitrogen. Glc analysis indicated a homogeneous compound, and high vacuum distillation gave 4.3 grams of a clear yellow liquid, b.p. (0.8) 135°C , a yield of 86% after distillation. (Note: 0.61 grams of polymerized residues remained in the distillation flask.)



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
3,4,5,6,9,10	1.08-2.46	11	multiplet
2	4.28	1	multiplet
7	2.14	3	singlet
8,11	2.89	4	multiplet

I.R. (film) cm^{-1}

2890; 1698 (C=O stretch); 1639 (C=C stretch); 1395; 1351; 1163;

754.7; 2082 $C=C-H$ stretch)

U.V. (hexane)

227 nm (ϵ 3.81); 281 nm (ϵ 1.62), λ_{max} .

Mass Spectrum m/e (relative intensity)

193 (21%); 178 (8.2%); 150 (100%); 108 (6.3%); 123 (42.6%); 80 (8.9%); 70 (44%); 43 (57.6%)

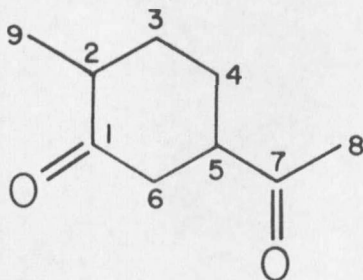
Anal: Calc'd for $C_{12}H_{19}NO$; C 74.58; H, 9.90. Found: C 74.68; H, 9.68

Preparation of 3-Acetylcyclohexanone [36]

4.0 grams (0.020 mole) of freshly-distilled 5-acetyl-1-pyrrolidine-1-cyclohexene were dissolved in 50 ml of dry benzene. The resulting solution was placed under a nitrogen atmosphere to which was added 10 ml of a 5% aqueous sulfuric acid and refluxed for a period of 24 hours, after which the solution was cooled and extracted three times with 100 ml portions of ether. The combined ether extracts were washed three times with 100 ml portions of saturated sodium bicarbonate, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The remaining residue was vacuum distilled (water aspirator) to give a colorless liquid, b.p. $124^{\circ}C$, 2.11 grams, a yield of 73%. Spectra was identical to that previously discussed.

Preparation of 2-Methyl-5-Acetylcyclohexanone [40]

3.0 grams (0.015 mole) of 5-acetyl-1-pyrrolidine-1-cyclohexene were dissolved in 50 ml of dry benzene, and the entire solution was placed under a nitrogen atmosphere. While stirring, 2.12 grams (0.015 mole) of methyl iodide were injected over a period of 1/2 hour. The resulting mixture was then allowed to reflux for 24 hours, at the end of which time 10 ml of aqueous 5% sulfuric acid was added. The resulting solution was further refluxed for an additional five hours to affect hydrolysis. The resulting orange-colored solution was cooled and extracted three times with 100 ml portions of ether. The combined ether extracts were washed three times with 100 ml portions of saturated sodium bicarbonate, dried over anhydrous magnesium sulfate and the ether removed under reduced pressure. The resulting residue was vacuum distilled to yield a colorless liquid, b.p. (10) 131-132° C, 1.81 grams (76%). Glc analysis indicates only one compound present.



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	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
8	2.18	3	singlet
9	0.92	3	multiplet (both isomers present)
3,4,5,6,2	1.12-2.55	8	multiplet

I.R. (film): cm^{-1}

2924; 1712-1689 (C=O stretch); 1456; 1429; 1359; 1266; 1176;
965.3

U.V. (hexane)

290 nm (ϵ 3.72) λ_{max} .

Mass Spectrum m/e (relative intensity)

43 (100%); 55 (72%); 96 (65.6%); 111 (57.8%); 139 (15.6%); 154
(19.6%)

Anal: Calc'd for $\text{C}_9\text{H}_{14}\text{O}_2$; C, 70.10; H, 9.14. Found: C, 69.82; H, 8.53

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REFERENCES

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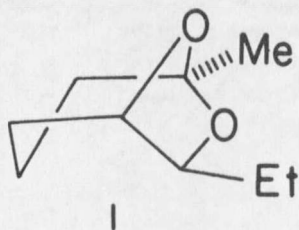
Part II:
A NEW SYNTHESIS OF BREVICOMIN

Chapter 1

HISTORICAL

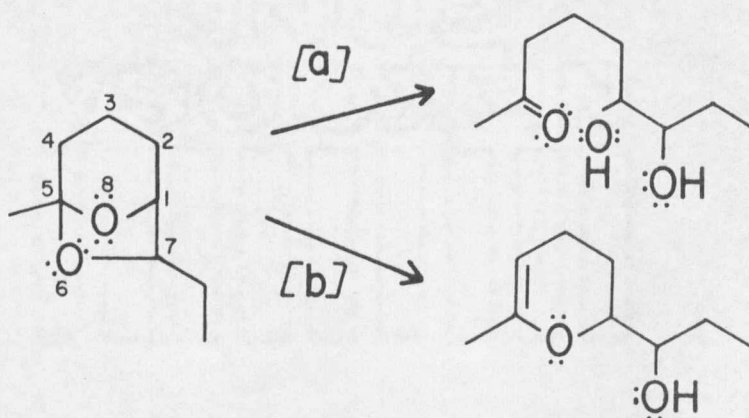
The western pine bark beetle, *Dendrocotonus brevicomis*, has been responsible for mass destruction of the ponderosa pine in both the United States and Canada. The invasion and eventual destruction of the tree by *D. brevicomis* occurs in two phases. In the first, an initial attack is made by a few beetles which bore into the tree and construct a nuptial chamber. In this period of activity, they expel frass, a mixture of fecal pellets and wood fragments. The frass contains a third component, a sex pheromone¹ which in turn triggers the secondary massive invasion which undoubtedly kills the tree.

In 1968, Silverstein² and coworkers isolated 2 mg of the aggregating sex pheromone of *D. brevicomis* from 1.6 kg. of frass and reported the structure as exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane (1) or exo-brevicomine.



Because one could actually use *exo-brevicomin* for the manipulation of the mating habits of *D. brevicomis* one could potentially provide the Forest Service with an ecologically advantageous means of population control for this specific insect. It is interesting to note that there are no effective means of controlling *D. brevicomis* up to this point. Thus, attention was then turned toward the total synthesis of brevicomin because of the obvious isolation problems, especially in large quantities.

As Mundy³ has pointed out in a recent review, retro-synthetic analysis of the 7-ethyl-5-methyl-6,8-dioxabicyclo [3.2.1] octane ring skeleton reveals two possible routes for the construction of the ketal moiety of this molecule.



In route [a], the synthetic strategy demands the construction

of a molecule with ketone and glycol functionality, while route [b] consists of the construction of a dihydropyran carbinol.

In 1969, Silverstein⁴ published the first synthesis of brevicomin in which the synthetic strategy consisted of the preparation of the ethylene ketal (3) of 6-bromohexane-2-one (2), followed by treatment with triphenyl phosphine to yield the phosphonium salt (4). Condensation of (4) with propionaldehyde yielded a mixture of cis and trans non-6-ene-2-one ethylene ketal (5), which upon treatment with m-chloroperbenzoic acid gave the cis and trans epoxides (6) which were separated by glc. Hydrolysis gave the intermediate diol (7) which closed to the bicyclic ketal.

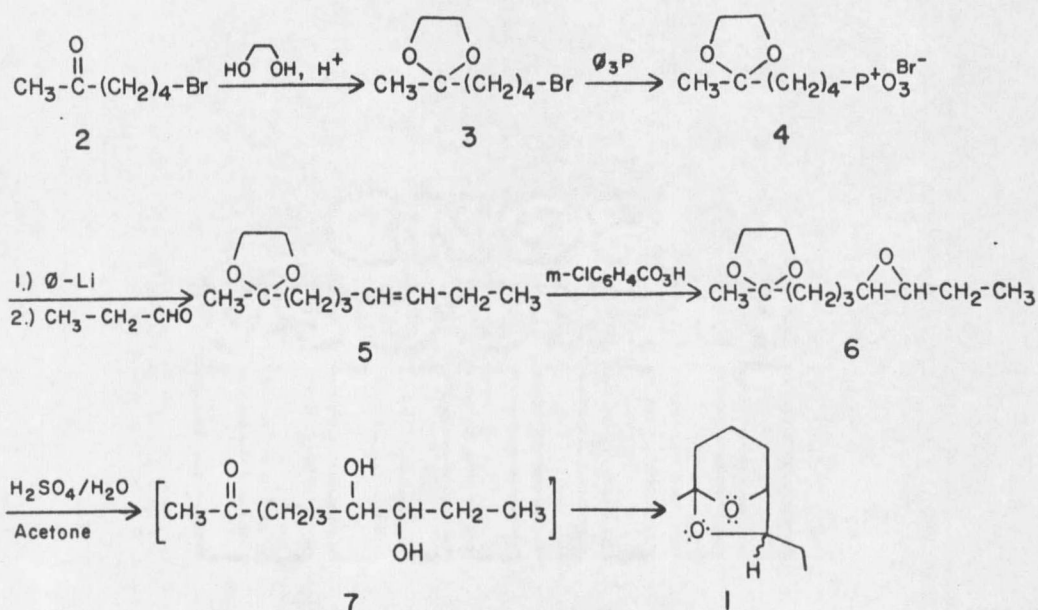


Figure 29. Silverstein's Brevicommin Synthesis.

An alternative approach taken by Silverstein involved the acid hydrolysis of 2-acetyl butyrolactone (8), which when followed by ketalization gave 5-bromopentan-2-one, ethylene ketal (9) in 60% yield. Treatment of 9 with Na/NH₃ and 1-butyne gave the non-6-yn-2-one ethylene ketal (10) in 16.7% yield. This was reduced with nickel tetraacetate and sodium borohydride to give cis-non-6-ene-2-one ethylene ketal (5) in 80% yield.

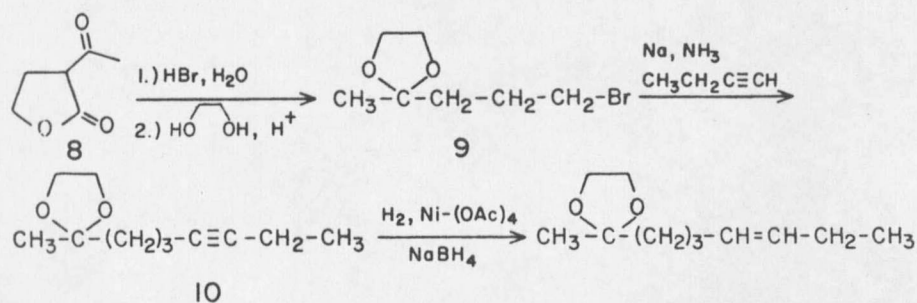
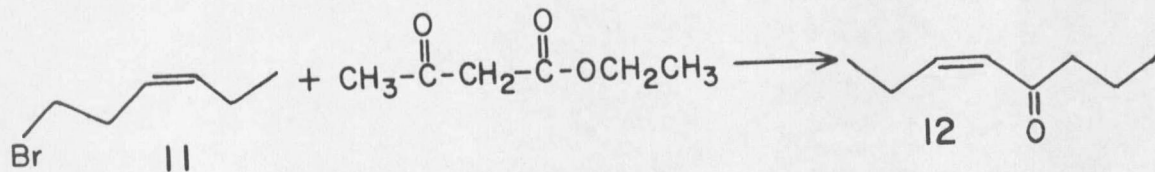


Figure 30. Silverstein's Alternate Scheme.

Working along the same lines, Wasserman⁵ and coworkers alkylated acetoacetic ester with *cis*-1-bromo-3-hexene (11) which, followed by saponification and decarboxylation, gave *cis*-non-6-ene-2-one (12). The ketone (12) was treated with *m*-chloroperbenzoic acid to give the *cis*-epoxide (13) which upon sealed tube pyrolysis at 210°C gave brevicomin in a 95% yield: with an *exo/endo* ratio of 90:10.



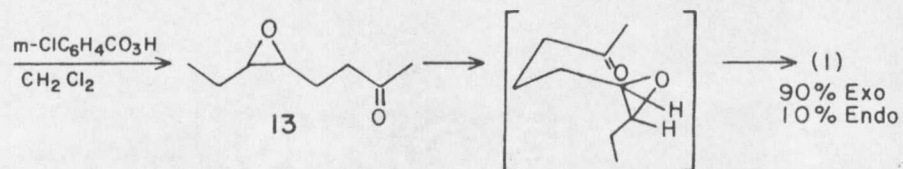


Figure 31. Wasserman Synthesis of Brevicomine.

Silverstein⁶ and coworkers, in 1971, were able to greatly improve their original synthesis by the conversion of *cis*-3-hexene-1-ol (14) to its tosylate ester (15), which was used to alkylate ethyl acetoacetate. This, followed by acid hydrolysis and decarboxylation yielded (12), *cis*-6-nonene-2-ol, in 37% yield. Treatment of 12 with *m*-chloroperoxybenzoic acid in benzene at 15°C gave *cis*-6,7-oxedononan-2-one, which in turn was refluxed in benzene to give 1 a 55% yield (95% of which was exo and 5% endo).

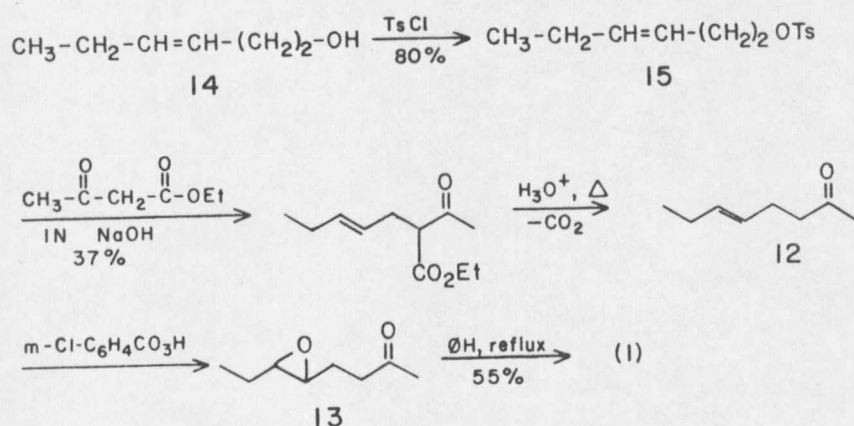


Figure 32. Improved Silverstein Synthesis of Brevicomin.

In 1976, P. L. Kocienski and R. W. Ostrow⁷ published yet another synthesis of brevicomin based on the ketone diol synthon developed by Silverstein. The Eschenmoser fragmentation of the epoxy ketone (15) yielded 16. Ketalization of 16 gave the Silverstein intermediate, 6-nonyl-2-one ethylene ketal, (10). Reduction of the acetylenic ketal (10) by $\text{BH}_3 \cdot \text{Me}_2\text{S}$ followed by protonation gave the Silverstein intermediate, cis-non-6-ene-2-one, (5). Stereospecific acid cleavage of the cis epoxide (6) with concomitant hydrolysis of the ketal gave the keto diol intermediate, (7).

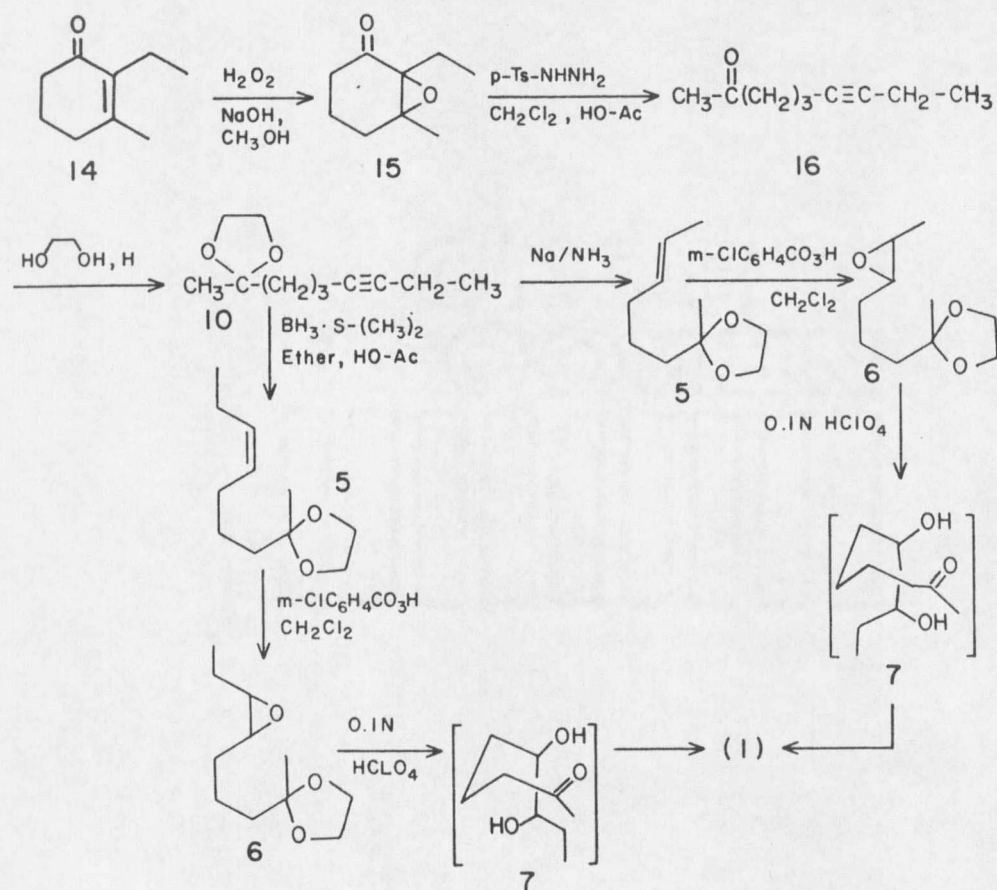


Figure 33. Kocienski Synthesis of Brevicommin.

The Silverstein intermediate was still to be used in another

synthesis of brevicomin in 1977 by Coke⁸, which consisted of the alkylation of 1,3-cyclohexanedione with ethyl iodide to give 2-ethyl-1,3-cyclohexanedione, which when followed by treatment with phosphorous trichloride yielded the chloride (17). Treatment of 17 with methyl-lithium, followed by pyrolysis, gives 16. This acetylenic ketone was reduced to the cis olefin with 10% palladium on barium sulfate. Treatment of 12 with m-chloroperbenzoic acid yielded the Silverstein intermediate, (13); which, when heated at 210°C gave both exo and endo brevicomin in a 9:1 ratio.

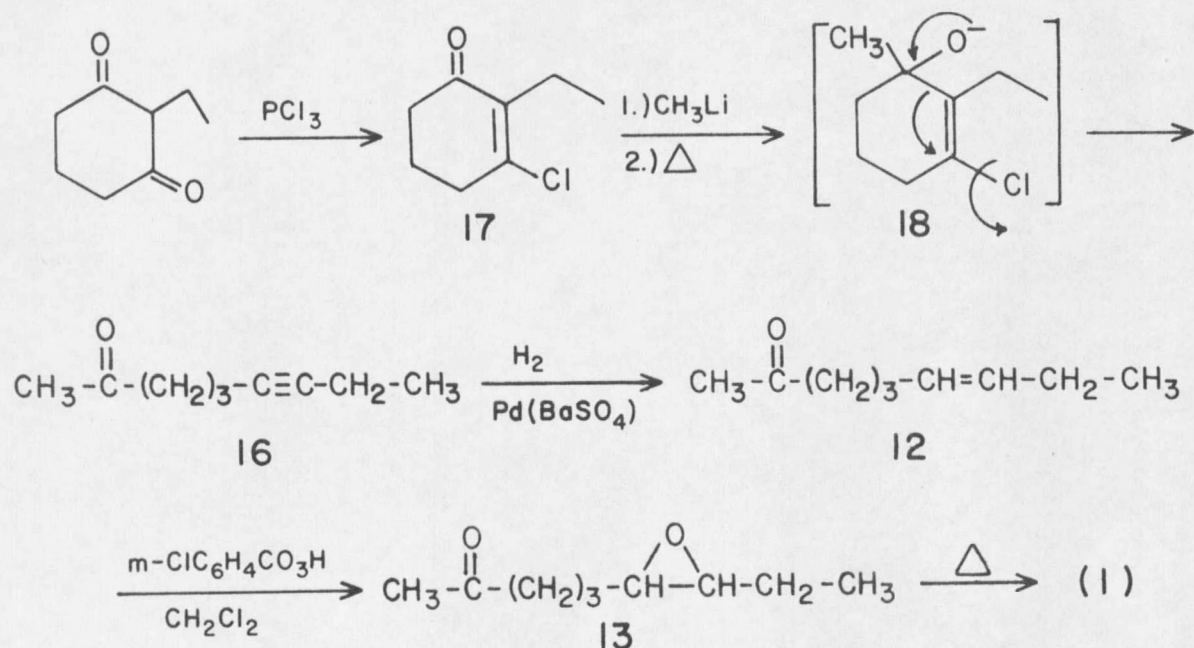
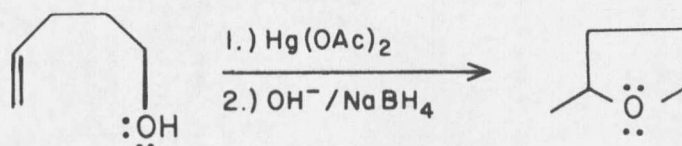


Figure 34. Coke Synthesis of Brevicomin.

Now turning our attention to the second retrosynthetic route, b, H. C. Brown⁹ provided the initial synthetic impetus in a paper published in 1970, in which cyclic ethers were constructed from unsaturated alcohols via oxymercuration/demercuration.



The mechanism for this reaction was thought to proceed along the lines of first electrophilic attack by the mercuriacetate cation to form the intermediate cyclic mercurinium ion which then undergoes subsequent intramolecular nucleophilic attack of the hydroxyl group. Demercuration and deprotonation gave a five-membered cyclic ether.

In a series of papers first published in 1971 Mundy¹⁰ demonstrated a three-step synthesis of brevicomin. The synthetic strategy developed from the $\pi_s^{4s} + \pi_s^2$ cycloaddition of methylvinyl ketone and acrolein to yield 2-formyl-6-methyl-2,3-dihydro-2H-pyran, (19). The Grignard reaction of ethylmagnesium bromide with 19 gave both isomers of 2-(2-hydroxyethyl)-6-methyl-2,3-dihydro-2H-pyran, (20). Cyclization of the pyranyl carbinol, (20), via the oxymercuration/demercuration

method of Brown gave exo/endo brevicomin in a 1:1 ratio.

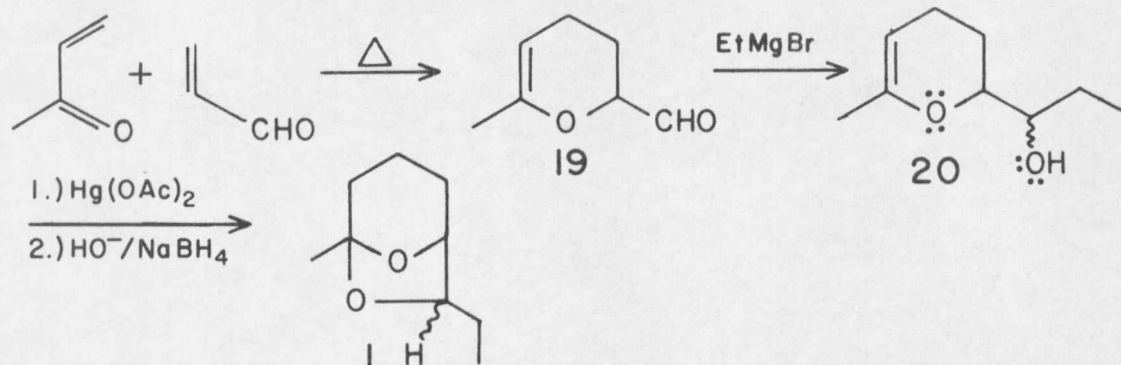


Figure 35. Mundy Synthesis of Brevicomin.

Mundy has also demonstrated that treatment of **20** with *p*-toluenesulfonic acid in benzene gives brevicomin in 87% yield with a 64:36 ratio of exo to endo isomers.

It is also worthwhile to mention that unlike any of the before-mentioned syntheses, Kossanye¹¹ reported a quite novel synthesis of brevicomin in 1977. Here the selective irradiation of 2-propionyl-6-methyl-2,3-dihydro-4H-pyran, (**21**), by singlet sensitization and triplet quenching by 1-methylnaphthalene gave the stereoselective exo-isomers of 1-methyl-6-exo-ethyl-7,8-dioxabicyclic[3.2.1]oct-2-ene, (**22**), in 23% yield. Catalytic hydrogenation of **22** gave exo brevicomin, (**1**), in 95% yield.

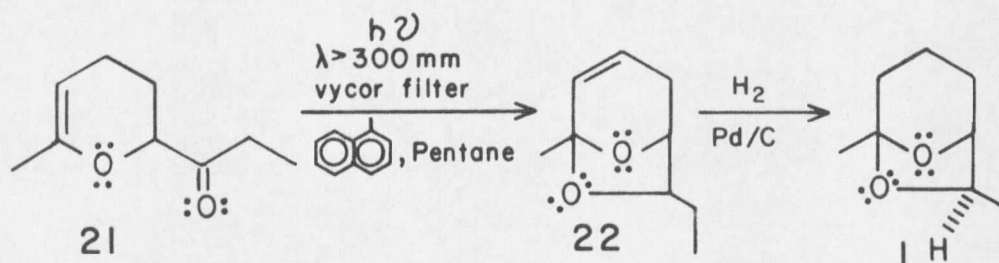


Figure 36. Kassanye Synthesis of Brevicomin.

Thus, in a continuing effort in our laboratory to improve the original Mundy synthesis of brevicomin, a search for a better electrophilic reagent was begun. Careful investigation of the literature revealed such an electrophile in phenylselenenyl chloride. In 1974, K. B. Sharpless¹² reported a new route for the synthesis of allylic ethers by the electrophilic addition of various ϕSe_χ reagents (where $\chi = \text{Cl}$, Br or oAc) to alkenes. These reagents always undergo trans-1,2 additions to give the adduct, (23), which is quite stable when $\chi = \text{oAc}$, but is both thermally and solvolytically unstable when $\chi = \text{Cl}$ or Br. Addition of an alcohol gave the phenylselenoether, (24), which when oxidized with 30% H_2O_2 in THF at room temperature gave 25. This underwent syn elimination via 26 to give the allylic ether, (27), in 93% yield.

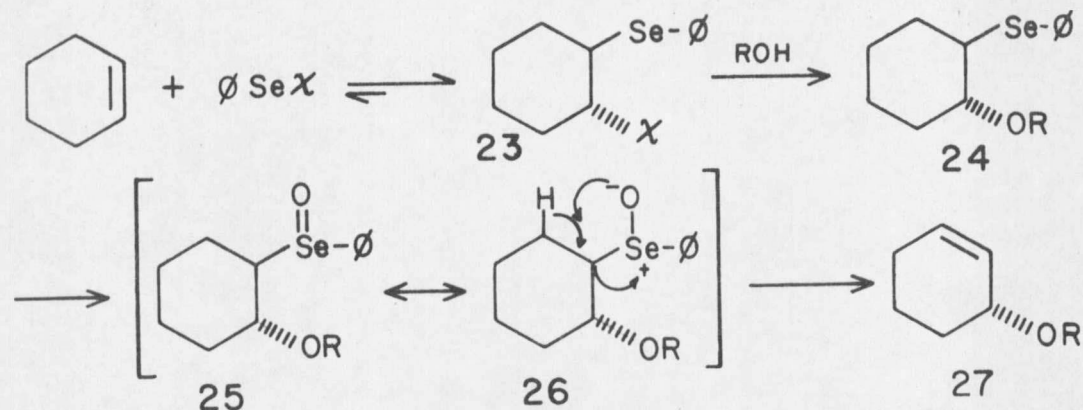


Figure 37. Sharpless Synthesis of Cyclic Ethers.

Based on this work of Vemura¹³, Nicolaou¹⁴ reported in 1977 that treatment of unsaturated alcohols such as **28** with phenylselenenyl chloride in methylene chloride at -78°C afforded the phenylseleno ethers, (**30**). Oxidation of **30** with 30% $\text{H}_2\text{O}_2/\text{THF}$ gave the allylic ether, (**32**), in 87% yield. Treatment of the phenylseleno ether with Raney nickel in THF at 25°C reductively removed the phenylseleno group to give the bicyclic ether, (**31**), in 95% yield.

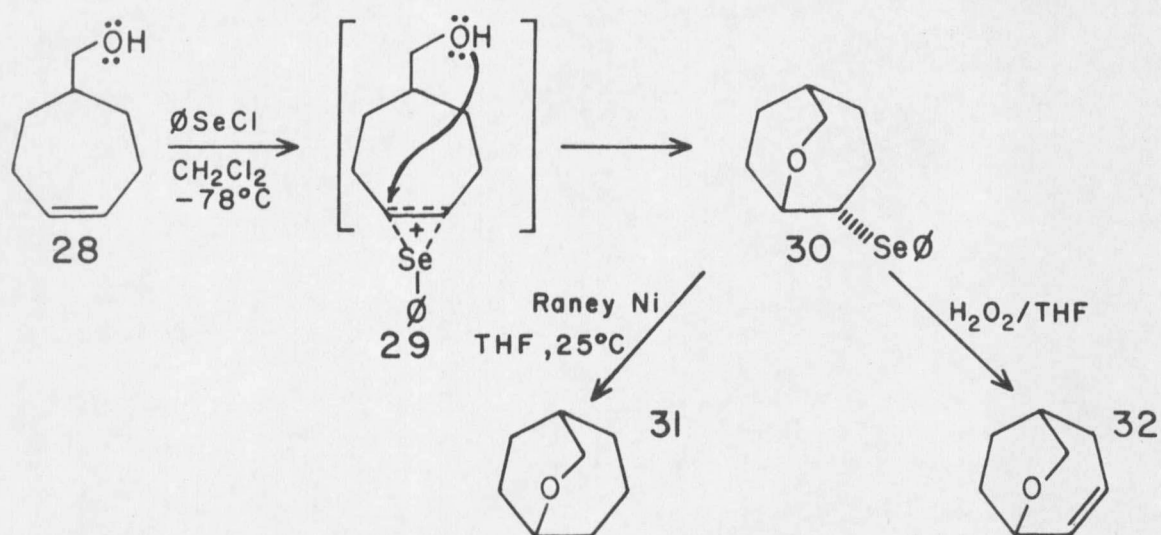


Figure 38. Nicolaou Synthesis of Bicyclic Ethers.

The mechanism for this reaction was again postulated to proceed via an initial attack of the highly electrophilic ϕSeCl on the double bond followed by the intramolecular nucleophilic attack by the hydroxyl group, via **29**. Realizing the importance of these experimental findings, the question we addressed ourselves to was, can the addition of ϕSeCl to dihydropyran carbinols produce a bicyclic ketal, and, if so, can we in fact synthesize brevicomin.

Chapter 2

RESULTS AND DISCUSSION

The Diels-Alder reaction¹⁶ of 1-butene-3-one gave 2-acetyl-6-methyl-3,4-dihydro-2H-pyran in 85% yield. The actual preparation of 2-propionyl-6-methyl-3,4-dihydro-2H-pyran²¹ was accomplished in two ways with approximately equal efficiency. The first method was that of Stork and Doud¹⁷ which consisted of the formation of the cyclohexylimine of 23, followed by the addition of ethylmagnesium bromide which yields the enamine, (23a). Alkylation of 23a with methyl iodide at 0°C, followed by hydrolysis with one equivalent of 5% aqueous acetic acid gave 21 in 81% yield. The second method involved the direct alkylation of the pyrrolidino enamine, (24), at 0°C with methyl iodide, again followed by careful hydrolysis with one equivalent of 5% aqueous acetic acid to give 21 in 88% yield. One must be careful in the acid hydrolysis, otherwise the 2-propionyl-6-methyl-3,4-dihydro-2H-pyran, (21), ring will open.¹⁸

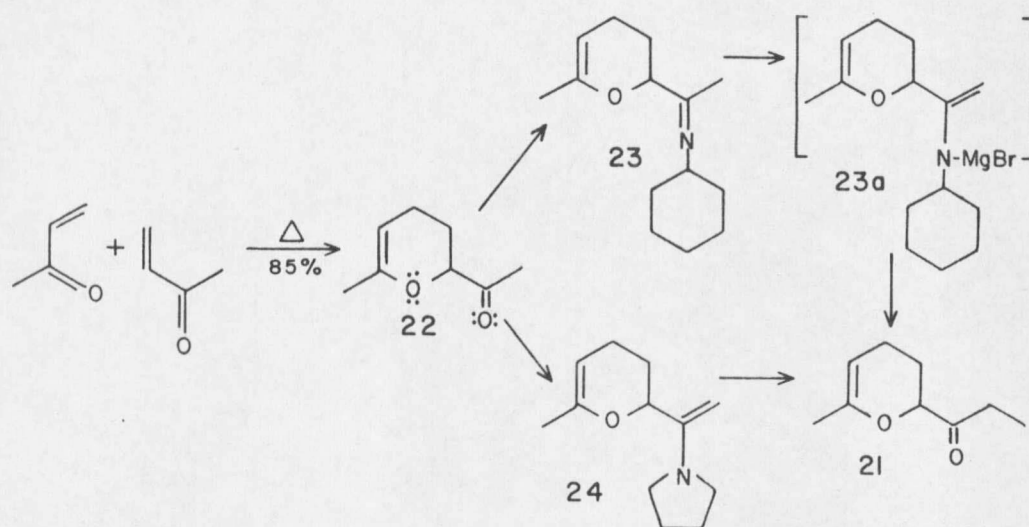


Figure 39. Synthesis of 2-Propionyl-5-Methyl-3,4-Dihydro-2H-Pyran.

The non-stereospecific reduction¹⁹ of 2-propionyl-6-methyl-3,4-dihydro-2H-pyran, (21), by sodium borohydride in isopropyl alcohol at 0°C gave both isomers 2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-pyran, (20), in a 1:1 ratio; determined by glc on 15% OV-101 at 110°C. Treatment of 20 with 1 equivalent of phenylselenenyl chloride at -78°C in

methylene chloride containing two equivalents of potassium carbonate gave 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane (38) in quantitative yield. Ketalization was evidenced by the appearance of four infrared absorptions in the $1200\text{--}1050\text{ cm}^{-1}$ regions, characteristic of cyclic ketals. Both nuclear magnetic resonance and mass spectral data supported this conclusion. Treatment of 38 with activated Raney Nickel in THF at room temperature gave both endo and exo isomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane, (1), in 92% yield. The exo and endo isomer ratio was determined to be in 1:1 by glc analysis on 5% SE-30. Oxidation of 38 with 30% hydrogen peroxide in THF at room temperature with periodic cooling gave the expected product, 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene, (22), in only 29% yield. The major product of the reaction was 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane-4-one, (39), in 71% yield. Catalytic hydrogenation of 22 with 10% Pd/C in ethyl acetate gave a 91% yield of 1 with a 1:1 isomer ratio.

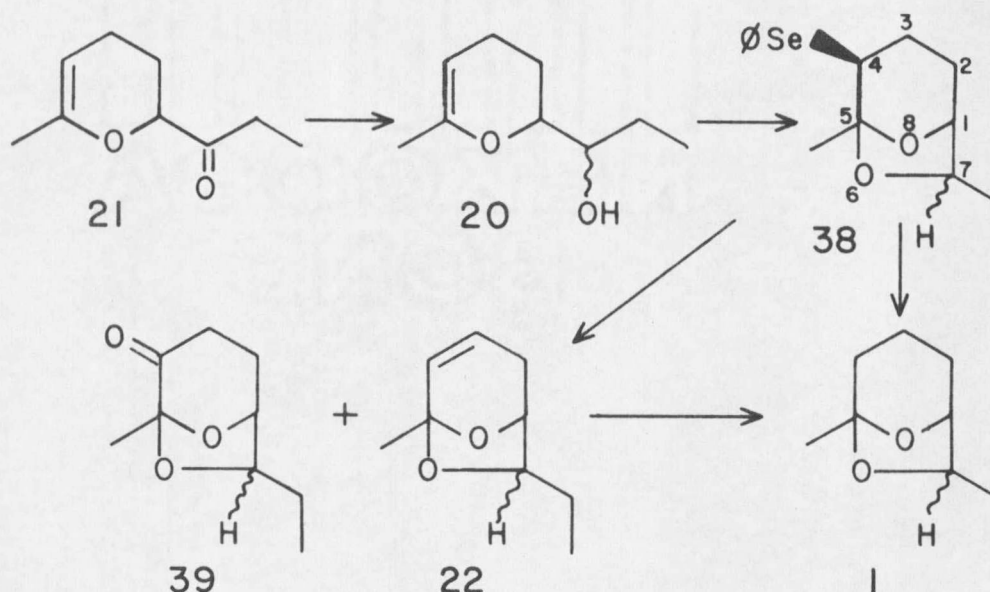


Figure 40. Navel Synthetic Approach to Brevicomin.

Oxidation of **38** with *m*-chloroperbenzoic acid in methylene chloride at 25°C gave **22** in 86% yield with an exo/endo isomer ratio of 1:1.

In the oxidation reaction of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane with 30% hydrogen peroxide, we can rationalize the formation of 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene by the syn elimination of the selenoxide, (**40**), in the same fashion as those reported by Reich²⁰ with concomitant formation of phenylselenic acid.

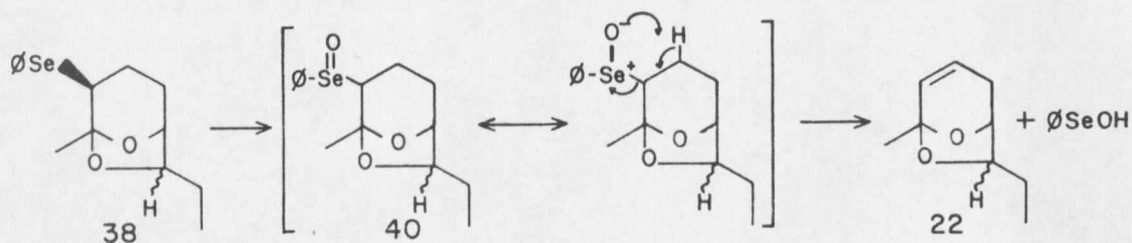


Figure 41. Reaction Mechanism for the Formation of 5-Methyl-7-Ethyl-6,8-Dioxabicyclo[3.2.1]oct-3-ene.

The formation of the major product of the reaction 39, was postulated to be derived from a Pummer-like²⁰ rearrangement. Protonation of the selenoxide giving 41 which upon elimination of water gives the Pummer intermediate (43). Hydrolysis of this intermediate, followed by a hydrogen transfer to the phenylselenide gives a species²⁰ which eventually leads to 39.

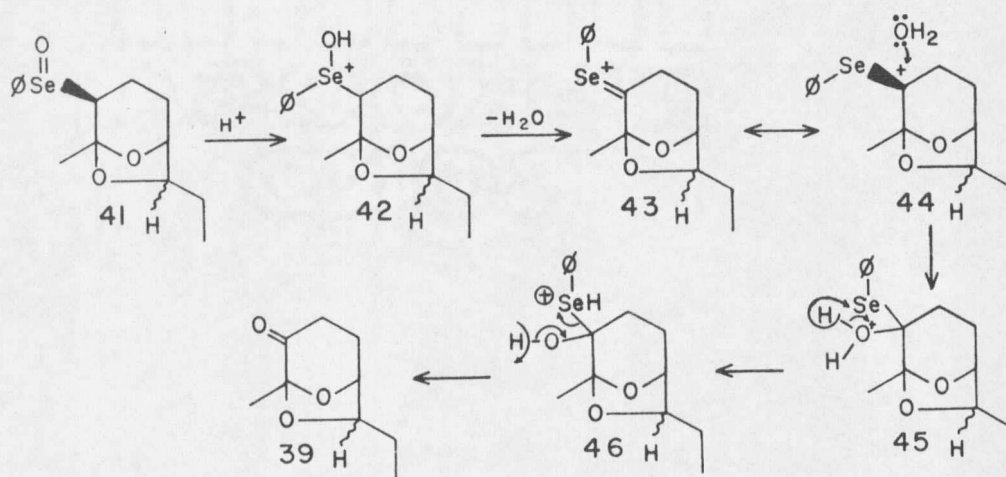


Figure 42. Reaction Mechanism for the Formation of 5-Methyl-7-Ethyl-6,8-Dioxabicyclo[3.2.1]oct-4-one.

The role of the water hydrolysis in the Pummer rearrangement was confirmed with the oxidation of 38 with one equivalent of m-chloropero-benzoic acid which only gave one product, 22, in 86% yield.

Chapter 3

EXPERIMENTAL

Preparation of 2-propionyl-5-methyl-3,4-dihydro-2H-pyran

This compound was prepared by two methods outlined below.

Method A

15.0 grams (0.077 mole) of the pyrrolidino enamine of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran was placed in dry benzene and cooled to 0°C. While the mixture was stirring under a nitrogen atmosphere, 11.00 grams (0.077 mole) of methyl iodide were added over a period of thirty minutes. After stirring for one hour at 0°C, the mixture was refluxed for twenty-four hours; at the end of which time the solution was cooled to 0°C and hydrolyzed by one equivalent of a 5% aqueous solution of acetic acid (4.62 grams of acetic acid in 87.9 ml of water.) This mixture was then allowed to stir for 45 minutes at the end of which time the solution was extracted with four 100 ml portions of ether which was washed with two 15 ml portions of sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and the ether removed under vacuum via a rotatory evaporator. The residue was vacuum distilled to give 10.44 grams of a colorless liquid, b.p. 84°C, 88% yield.

Method B

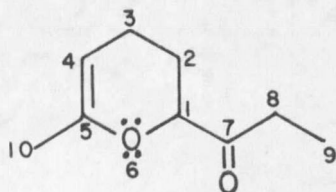
20 grams (0.142 mole) of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran and 14.1 grams (0.142 mole) of cyclohexyl amine was placed in 200 ml of

dry benzene and refluxed with a Dean-Stark water separator for twenty-four hours at the end of which time the benzene was removed under reduced pressure via rotatory evaporator and the residue was vacuum distilled to yield 29.2 g of a clear liquid, b.p. (.8) 95-96°C.

14 grams (0.063 mole) of the cyclohexylimine of 2-acetyl-6-methyl-3,4-dihydro-2H-pyran were added to a solution of 150 ml of dry THF and 9.23 grams (0.069 moles) of ethylmagnesium bromide. This solution was refluxed for five hours, at the end of which time the solution was cooled to 0°C and 8.94 grams (0.063 moles) of methyl iodide were added over a period of one hour. This mixture was then allowed to stir at room temperature for twenty-four hours. The mixture was then cooled to 0°C and hydrolyzed with 1 equivalent of 5% aqueous acetic acid (3.78 grams, in 71.87 ml) for thirty minutes. The mixture was extracted with four 100 ml portions of ether, washed twice with 50 ml portions of 5% sodium bicarbonate dried over magnesium sulfate filter and the ether was removed under vacuum via rotatory evaporator. The residue was vacuum distilled to yield 81% of a colorless liquid, b.p. 84°C.

Products from both reactions were identified by IR, NMR, UV and mass spectra data. Analysis by glc on 15% SE-30 at 130°C showed the compounds to be identical.

NMR Data



	Chemical Shift (δ)	Number of Protons	Nature of Peaks
10	1.7	3	singlet
4	4.44	1	multiplet
2,3	1.92	4	multiplet
1	4.16	1	multiplet
8	2.5	2	quartet ($J=7.2 \text{ Hz}$)
9	1.03	3	triplet ($J=7.2 \text{ Hz}$)

I.R. (thin film) cm^{-1}

2882, 1712, 1678; 1449; 1385; 1355; 1299; 1241; 1190; 1167; 1111; 1071;
929.4; 999.3; 815.7; 751.9.

U.V. Data (cyclohexane) 208(=2100) 281(=38) 155(4.2); 154(28.1); 112
(3.4); 111(28.6); 98(11.1); 97(100); 95(18.2); 93(10.1); 83(11.4); 81
(13.4); 79(16.2); 71(11.1); 70(16.0); 69 (32.1); 67(14.6); 57(16.6); 55
(36.2); 53(19.1); 43(42.6); 41(29.3).

Calculated: C 70.10%; H 9.14%

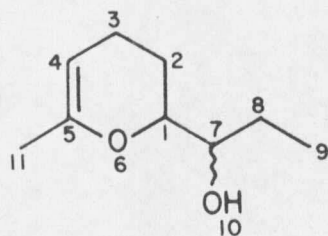
Found: C 70.07%; H 9.35%

Preparation of 2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-pyran (20)

To a stirred solution of 100 ml of isopropyl alcohol and 14.0 grams (0.090 mole) of 2-propionyl-5-methyl-3,4-dihydro-2H-pyran, which was externally cooled to 0°C , was added 3.45 grams (0.090 mole) of

sodium borohydride over a period of one hour. The reaction mixture was allowed to stir for two hours at 0°C at the end of which time 15 ml of 20% aqueous sodium hydroxide were added. Stirring was continued for an additional two hours after which the solution was poured into 200 ml of distilled water and extracted with four 100 ml portions of ether, which were combined, dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure to yield a residue which was vacuum distilled to yield 12.19 grams (86%) of a clear colorless liquid, b.p. (10) 84°C. Glc analysis on 15% OV-101 at 110°C showed the two alcohol isomers in a ratio of 1:1.

NMR Data



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
11	1.7	3	singlet
4	4.40	1	multiplet
2,3,8	1.1-2.2	6	multiplet
1,7	3.18-3.71	2	multiplet
9	1.02	3	triplet
10	2.98	1	broad singlet

I.R. Data (thin film) cm^{-1}

3367; 2890; 1678; 1449; 1385; 1292; 1241; 1171; 1064; 980.4; 943.3;
877.2; 758.7

Mass Spectrum m/e (relative intensity)

156(18.3); 141(1.6); 127(2.1); 123(1.2); 114 (11.3); 109(2.3); 99(31.2);
98(91.2); 97(100); 95(33); 86(21.3); 85(42.6); 84(52.3); 83(10.4);
81(13.3); 79(6.3); 72(12.3); 71(34.3); 70(7.3); 69(41.3); 67(8.6);
57(13.9); 55(10.33); 43(61.4); 41(12.9)

Calculated: C 69.2%; H 10.31%

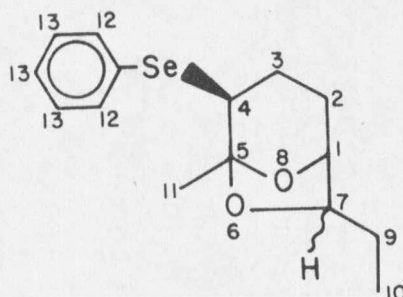
Found: C 69.01%; H 10.61%

Preparation of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]-octane (38)

A solution of 100 ml of dry methylene chloride and 8.2 grams (0.052 mole) of 2-(2-hydroxyethyl)-6-methyl-3,4-dihydro-2H-pyran, (20), and 20 grams of anhydrous potassium carbonate was prepared and placed in a 200 ml, three-necked, round-bottom flask equipped with an injection septum, mechanical stirrer and reflux condenser. The entire apparatus was evacuated and placed under a nitrogen atmosphere surrounded by a temperature bath of acetone and dry ice (-78°C). While stirring, a solution of 10 ml of dry methylene chloride and 10 grams (0.052 mole) of phenylselenenyl chloride was injected. The resulting orange-colored solution was allowed to stir at -78°C for four hours and then at room

temperature for 24 hours at the end of which time the reaction mixture was removed and filtered. The methylene chloride was removed under reduced pressure via the rotatory evaporator and then column chromatographed on a 2.5 cm x 48 cm silica gel column which had been prepacked with methylene chloride. The column was eluted with methylene chloride. Collection of the compound and removal of the methylene chloride under reduced pressure via rotatory evaporator left a red oil. Thin layer chromatography on silica gel IB/CH₂Cl₂ showed only one compound present, R_f 0.712. The yield was quantitative.

NMR Data



	<u>Chemical Shift (δ)</u>	<u>Number of Peaks</u>	<u>Nature of Peaks</u>
2,3,9	1.1-2.01	6	multiplet
1	3.99	1	multiplet
7	3.80	1	multiplet
10	0.88	3	triplet
11	1.35	3	singlet
12	7.48	2	multiplet
13	7.19	3	multiplet
4	3.26	1	multiplet

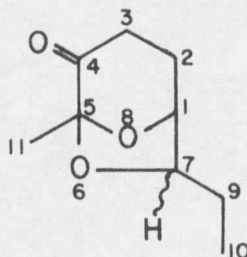
Mass Spectrum m/e (relative intensity)

311(12.3%); 269(6.3%); 268(3.2%); 253(16.3%); 156(55.2%); 155(12.3%);
126(6.7%); 113(26%); 112(19.3%); 97(32%); 84(19.3%); 83(42.3%); 66
(36.2%); 43(100%); 41(17.4%)

Oxidation of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]-
octane with 30% Hydrogen Peroxide

In a 125 ml Erlenmeyer flask equipped with a magnetic stirrer, was placed 75 ml of dry THF and 4.0 grams (0.012 moles) of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane. To this was added over a period of 20 minutes 1.36 ml (0.408 grams, 0.012 mole) of 30% H_2O_2 . External cooling became necessary during the reaction to maintain 25°C. After four hours of stirring, the mixture was added to 250 ml of distilled water and potassium carbonate was added until a basic pH was maintained. The resulting solution was then extracted with three 150 ml portions of ether, dried over anhydrous magnesium sulfate, filtered and ether removed under reduced pressure via rotatory evaporator. The residue was vacuum distilled to yield two fractions: (I) b.p. (10) 64°C, which corresponds to 22 (29%); and (II) b.p. (10) 68°C, which corresponds to 39 (71%).

NMR Data: 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-4-one



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
2,3,9	1.1-2.04	6	multiplet
1	3.97	1	multiplet
7	3.70	1	multiplet
10	0.90	3	triplet
11	1.35	3	singlet

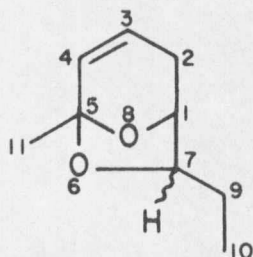
I.R. Data (thin film) cm^{-1}

2899; 1767; 1453; 1381; 1351; 1241; 1176; 1111; 1075; 1033; 970.9;
927.6; 881.1; 847.5

Mass Spectrum m/e (relative intensity)

170(6.8%); 154(7.1%); 142(5.3%); 128(6.33%); 114(37.2%); 99(8.4%);
98(22.3%); 86(21.3%); 85(100%); 72(6.1%); 71(12.3%); 69(44.2%);
68(39.2%); 58(13.1%); 57(24%); 55(12.3%); 43(91.2%); 42(20%); 41(6.3%)

NMR Data: 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (22)



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
3,4	5.66	2 (vinyl)	multiplet
2,9	1.30-2.81	4	multiplet
1	4.08	1	broad singlet
7	3.64	1	multiplet
10	0.90	3	triplet
11	1.40	3	singlet

I.R. Data (thin film) cm^{-1}

3050; 1642; 1385; 1194; 1179; 1109; 1036; 1014; 974.4; 932.6; 880.8;
712

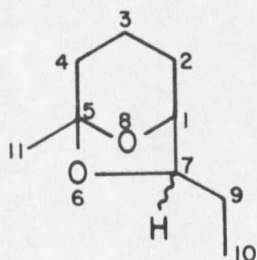
Mass Spectrum m/e (relative intensity)

154(3.2%); 127(3.6%); 98(18.4%); 86(32.4%); 85(39.2%); 66(19.4%);
114 (36.1%); 43(100%)

Preparation of exo/endo-7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane
[1]

In 200 ml of dry THF was dissolved 4.0 grams (0.012 mole) of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane to which was added 25 grams of activated Raney nickel catalyst which was stirred under nitrogen for 24 hours at the end of which time the catalyst was removed from the reaction mixture by filtration, and the THF was then removed under reduced pressure via the rotatory evaporator. The residue was then chromatographed on a 46 cm x 2.5 cm silica gel column prepacked with methylene chloride of which solvent was used to elute the column. The purpose of the column chromatography was to remove the phenylselenol which remains behind in the silica gel. The methylene chloride was then removed under reduced pressure via the rotatory evaporator leaving a light yellow residue which upon distillation gave 1.72 g of clear colorless liquid, b.p. (10mm) 64°C, a yield of 91.3%. Glc analysis on 15% SE-10 demonstrated the two isomers of 7-ethyl-5-methyl-6,8-dioxabicyclo[3.2.1]octane in a 1:1 ratio.

NMR Data



	<u>Chemical Shift (δ)</u>	<u>Number of Protons</u>	<u>Nature of Peaks</u>
1	3.98	1	multiplet
7	3.79	1	multiplet
10	0.88	3	triplet
11	1.38	3	singlet
2,3,4,9	1.1-1.98	8	multiplet

I.R. Data (thin film) cm^{-1}

2899; 1462; 1383; 1333; 1238; 1190; 1176; 1109; 1032; 1006; 970.9;
927.6; 900.9; 880.3; 851.8; 782.5

Mass Spectrum m/e (relative intensity)

156(4.7%); 127(4.3%); 114(28%); 99(6.3%); 98(14.8%); 86(10.3%); 85
(32%); 72(3.4%); 71(7.8%); 68(14.1%); 57(10%); 55(6.3%); 43(100%);
41(13.4%)

Calculations: C, 69.20; H, 10.31

Found: C, 69.17; H, 10.45

Oxidation of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane with m-chloroperbenzoic acid

To a solution of 1.0 grams (0.0032 mole) of 4-phenylseleno-5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane in 25 ml of dry methylene chloride was slowly added while stirring a solution of 0.63 grams (0.0032 mole) of m-chloroperbenzoic acid over a period of 30 minutes,

with periodic cooling to maintain the reaction temperature at 25°C. After one hour the reaction was stopped with the addition of 20 ml of 10% aqueous sodium sulfite. Separation of the methylene chloride layer followed by washing with three 50 ml portions of 5% aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate and removal of the methylene chloride under reduced pressure via the rotatory evaporator left a residue which upon distillation gave 0.42 grams of a clear, colorless liquid b.p. (10) 64°C which corresponds to the previously isolated 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene in 86% yield by NMR, IR and mass spectral data.

Hydrogenolysis of 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene (22)

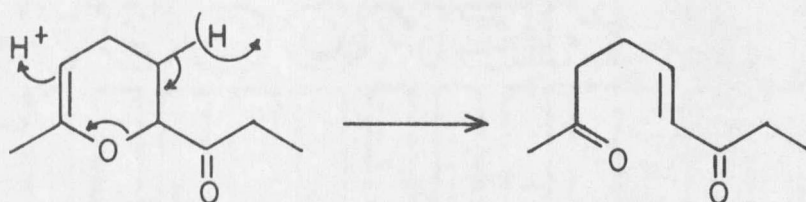
0.5 grams (0.0032 mole) of 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]oct-3-ene was placed in 50 ml of redistilled ethyl acetate with 0.5 grams of 10% Pd/C. This was then placed in a Parr Catalytic Hydrogenation apparatus under a hydrogen atmosphere of 45 lbs. After shaking at room temperature for 24 hours, the reaction was stopped and the catalyst filtered from the reaction mixture and the ethyl acetate removed under reduced pressure. The remaining residue was distilled under vacuum to yield 0.46 grams of a clear colorless liquid, b.p. (10) 64°C which was identical in NMR, IR, glc and mass spectral data (1).

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18. Ring opening may proceed in the following manner



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