



Synthetic studies toward natural products
by Timothy Ryall Schwartz

A thesis submitted in partial fulfillment of the requirements for the degree of DOCTOR OF
PHILOSOPHY in Chemistry
Montana State University
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Abstract:

The importance of the supra-annular effect as a controlling factor in the determination of the exo/endo product ratio of substituted 6,8-dioxabicyclo[3.2.1]octanes was studied through the use of competitive kinetics and nuclear magnetic resonance spectroscopy. It was determined that the supra-annular effect does not exist in the compounds studied and therefore cannot be used to control product stereochemistry. The carbon NMR spectra of these ' bicyclic ketals were examined and the general chemical shift regions of the ring carbons noted. The role of metal ion complexation in determining exo/endo product ratios was also studied and shown to be of minor importance.

The double oxymercuration-demercuration of selected dienes was investigated for potential use in a concurrent synthesis of brevicomin and the sex aggregating pheromone of *Trypodendron lineatum*. Model compounds were synthesized and studied, and progress was made toward the proposed concurrent syntheses.

"A good teacher has been defined as one who makes himself progressively unnecessary."

Thomas J. Carruthers

"I am astonished, disappointed, pleased with myself. I am distressed, depressed, rapturous. I am all these things at once, and cannot add up the sum."

C. G. Jung

"Det henskit af Krig er ta overleve." ("The object of war is to survive it", which struck me as the object of graduate school.)

John Irving

ii

to my wife

Sandy

SYNTHETIC STUDIES TOWARD NATURAL PRODUCTS

by

Timothy Ryall Schwartz

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

of

DOCTOR OF PHILOSOPHY

in

Chemistry

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ABSTRACT

The importance of the supra-annular effect as a controlling factor in the determination of the exo/endo product ratio of substituted 6,8-dioxabicyclo[3.2.1]octanes was studied through the use of competitive kinetics and nuclear magnetic resonance spectroscopy. It was determined that the supra-annular effect does not exist in the compounds studied and therefore cannot be used to control product stereochemistry. The carbon NMR spectra of these bicyclic ketals were examined and the general chemical shift regions of the ring carbons noted. The role of metal ion complexation in determining exo/endo product ratios was also studied and shown to be of minor importance.

The double oxymercuration-demercuration of selected dienes was investigated for potential use in a concurrent synthesis of brevicomin and the sex aggregating pheromone of Trypodendron lineatum. Model compounds were synthesized and studied, and progress was made toward the proposed concurrent syntheses.

CHAPTER ONE

Introduction

The Western pine bark beetle, Dendroctonus brevicornis, has done extensive damage to the coniferous forests of the western United States. Infested trees begin to turn brown and will eventually lose their needles and become dry, lifeless, standing snags. The large number of these dead trees resulting from bark beetle infestation poses a serious fire danger in western forests. This destruction of valuable timber resources has prompted research into methods of controlling bark beetle populations.

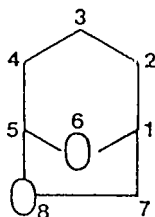
One such method of control involves the use of the beetle's own sex aggregating pheromone. The female produces a pheromone which attracts male beetles and thereby increases the likelihood of mating. Control of beetle populations in small areas is possible by using the aggregating pheromone to lure male beetles into insect traps. A small region can be protected by distributing these traps throughout the area and thus effectively removing most of the male beetles. It is not feasible, however, to protect large areas of forest by this method. Instead, it has been proposed that the pheromone be sprayed aerially over large areas. The ubiquitous presence of the pheromone would severely reduce the chance of a male beetle locating a female, and, again, no mating would occur. Large

quantities of pheromone are required for this type of operation. Seeing this need, synthetic chemists have studied the aggregating pheromone for D. brevicomis, named brevicomin, and many syntheses exist today. The synthesis of brevicomin is complicated by the fact that while brevicomin can exist in several isomeric forms, only one isomer is biologically active. A good synthesis will, therefore, allow the chemist to control the various synthetic reactions which determine the stereochemistry of the product pheromones. We have chosen to study two phenomena which might determine the extent of stereoselectivity possible in two brevicomin syntheses originating in our research group. These two phenomena are the supra-annular effect and metal ion complexation. In addition to evaluating control of stereoselectivity in existing syntheses, we have also explored a new and novel synthesis of two bark beetle pheromones. The proposed scheme will allow the concurrent synthesis of the sex aggregating pheromones for D. brevicomis and Trypodendron lineatum, the Norway spruce bark beetle. A concurrent synthesis would allow the chemist access to two different pheromones using the same reaction sequence and thereby facilitate the synthesis of the pheromones and control of the bark beetles.

CHAPTER TWO

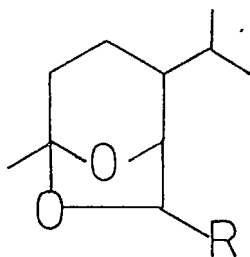
Historical Background

The 6,8-dioxabicyclo[3.2.1]octane ring system (1), a common structural component of sugars, is found in a wide variety of compounds and metabolites.

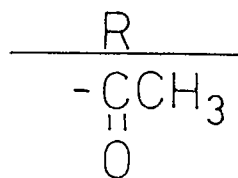


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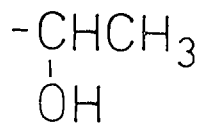
Several compounds, 2-4, containing this skeletal structure have been isolated from tobacco.¹



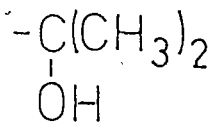
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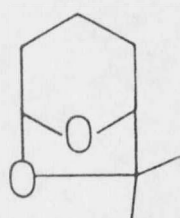
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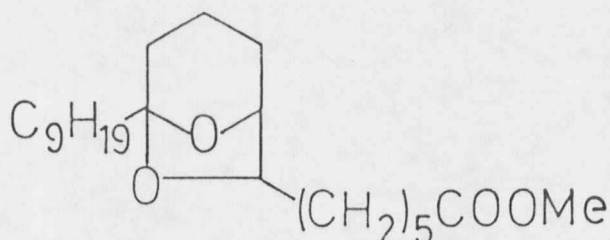
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A similar compound, (5), has been identified as a constituent of Japanese hop oil isolated from Humulus lupulus², and 6 has been shown to occur during fatty acid metabolism in yeast.³

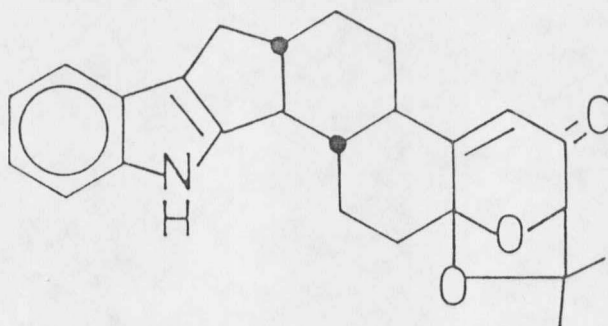


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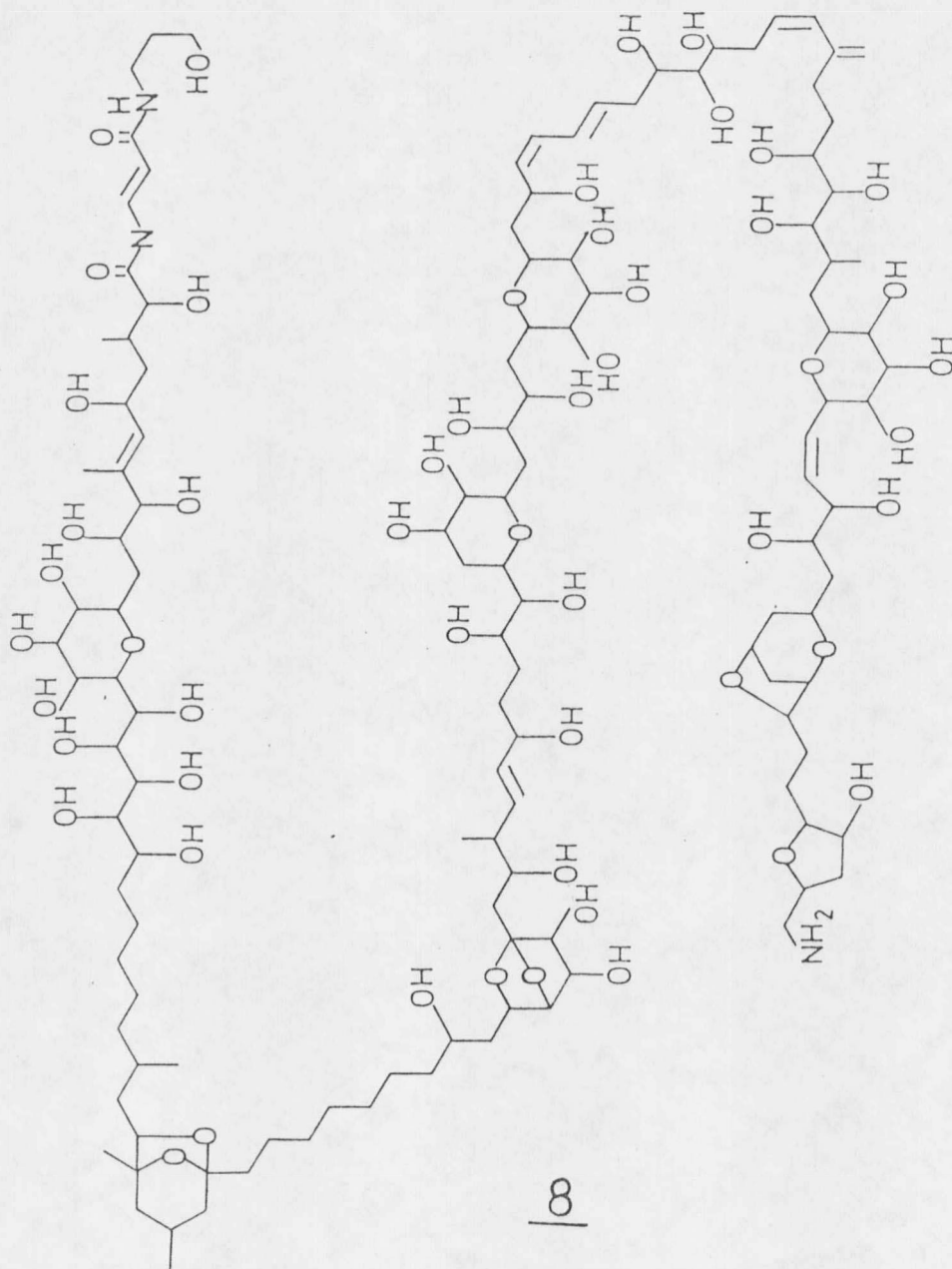
6

A variety of natural products containing this bicyclic ketal structure and exhibiting significant biological activity have been isolated as well. Compound 7, containing a modified bicyclic ketal moiety, has been isolated from Claviceps paspali⁴ and is responsible for a condition in cattle known as the "paspalum staggers". Cattle which have eaten Paspalum dilatatum infected with C. paspali show symptoms of anorexia, tremors, and hyperexcitability.

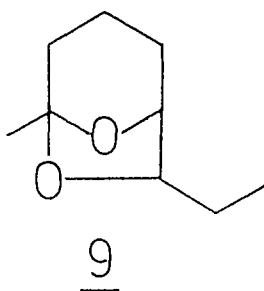


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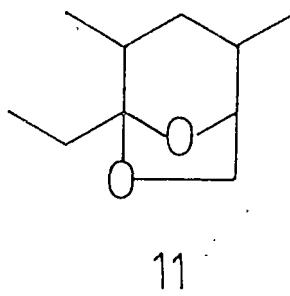
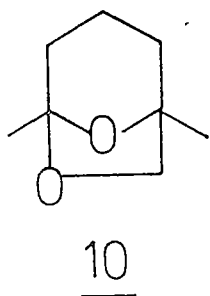
Palytoxin, (8), isolated from several *Palythoa* sp.⁵ is one of the most potent toxins known to man and contains several bicyclic ketal structural fragments.



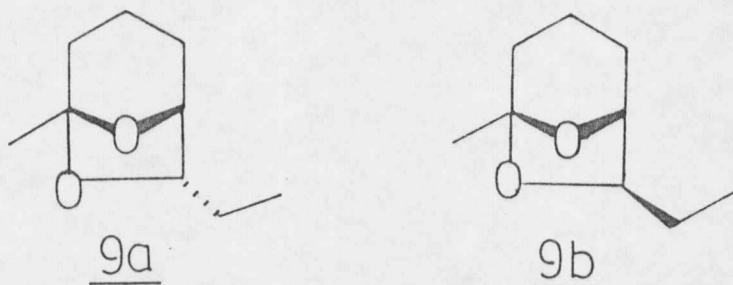
A group of insect sex attractants also contain the 6,8-dioxabicyclo[3.2.1]octane skeleton. The pheromone for the Western pine bark beetle Dendroctonus brevicornis has been isolated, assigned structure (9), and named brevicomin.⁶ The aggregating pheromone for



the Eastern pine bark beetle, Dendroctonus frontalis named frontalin⁷ (10), and the pheromone for the European elm bark beetle, Scolytus multistriatus, named multistriatin⁸ (11), have been isolated and show considerable bioactivity while working in concert with endogenous tree constituents.



Compounds, such as brevicomin, containing the 6,8-dioxabicyclo[3.2.1]octane skeleton and having substitution at C-7 are capable of existing in two isomeric forms, endo (9a) and exo (9b). Generally only one isomer is biologically active. Exo-brevicomin is the only isomer which shows significant pheromone activity.



Our research group has been interested in the synthesis of brevicomin for some time. A good understanding of the mechanism of sexual attraction and aggregation in these beetles and the availability of a high yield stereospecific synthesis of the aggregating pheromone might enable us to effectively control these insect pests.

Exo-brevicomin is produced by the female D. brevicomis as she constructs egg laying galleries in the bark of infested trees. The

aggregating pheromone is detected by male beetles which fly upwind in search of a female with which to mate.

It has been recognized for some time that artificial manipulation of aggregating pheromones can be used as a means of controlling insect pests. Small areas can be protected by baiting insect traps with the aggregating pheromone and distributing the traps throughout the area to be protected. It is not feasible, however, to protect large areas such as national forests using this procedure. An alternative procedure involves broadcasting the pheromone over large areas by the use of airplanes. With the aggregating pheromone evenly distributed over large areas, the males would be unable to locate a female and the beetle population would decline. This control strategy requires the synthesis of large amounts of exo-brevicommin. Our goal, therefore, was to develop and study stereoselective syntheses of brevicomin.

A non-stereoselective reaction sequence directed toward ketals with exo/endo isomers is doomed to produce approximately fifty percent of an isomer with little or no biological activity, and in some cases actually exhibiting anti-pheromone activity. It seemed advantageous, therefore, to examine the current synthetic strategies toward these types of natural products and attempt to explain and be

able to control factors affecting the relative ratio of exo/endo products.

Retrosynthetic analysis of brevicomin suggests two possible synthetic strategies as pointed out by Mundy in a recent review article⁹ and shown in Figure 1.

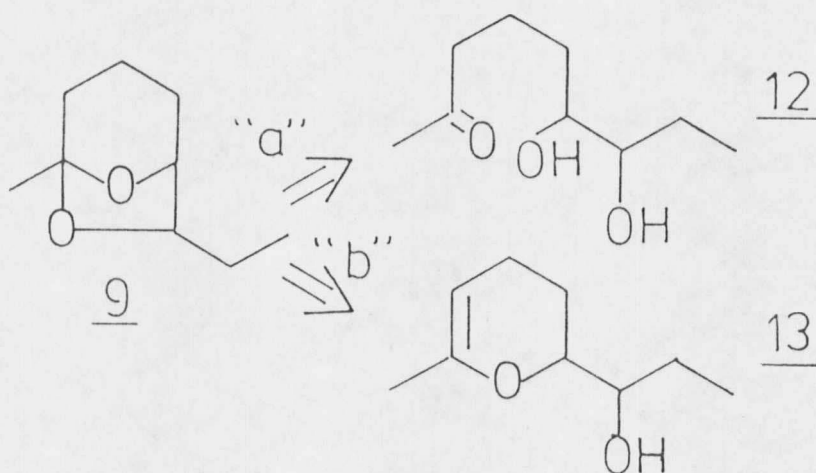
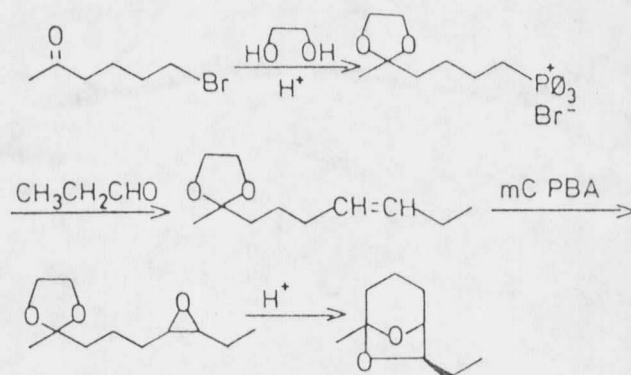


Figure 1. Retrosynthetic Analysis of Brevicommin

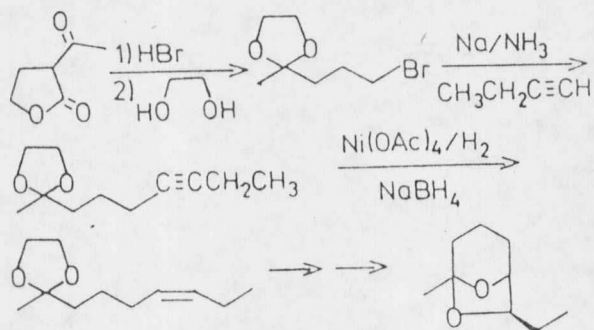
Brevicommin has been synthesized many times utilizing type "a" syntheses (Table 1). Some of these are illustrated on the next few pages (Figure 2). These procedures give a variety of exo/endo ratios, with the biologically active exo-brevicommin generally predominating. The Grigg synthesis is unique in that only the non-biologically active endo-brevicommin is produced.²¹ The Wasserman and Kocienski¹³ syntheses offer the flexibility of synthesizing either exo-brevicommin or endo-brevicommin as the major product.

Table 1. Syntheses of Brevicommin

<u>Type "a" Syntheses</u>	<u>% Exo</u>	<u>% Endo</u>	<u>Ref.</u>
Silverstein's Synthesis	100	0	10
Silverstein's Alternate Synthesis	100	0	10
Wasserman Synthesis	90(9)	10(91)	11
Improved Silverstein Synthesis	95	5	12
Kocienski Synthesis	100(0)	0(100)	13
Coke Synthesis	90	10	14
Meyer Synthesis	100	0	15
Weiler Synthesis	100	0	16
Bernardi Synthesis	60	40	17
Hoffman Synthesis	100	0	18
Fraser-Reid Synthesis	100	0	19
Shafer Synthesis	100	0	20
Grigg Synthesis	0	100	21
<u>Type "b" Syntheses</u>	<u>% Exo</u>	<u>% Endo</u>	<u>Ref.</u>
Mundy Synthesis	9	91	22
Mundy Alternate Synthesis	64	36	22
Kossanji Synthesis	100	0	23
Mundy-Bornmann Synthesis	50	50	24
Cohen Synthesis	43	57	25



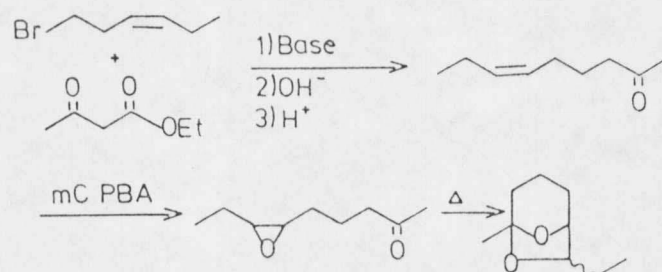
Silverstein's Synthesis



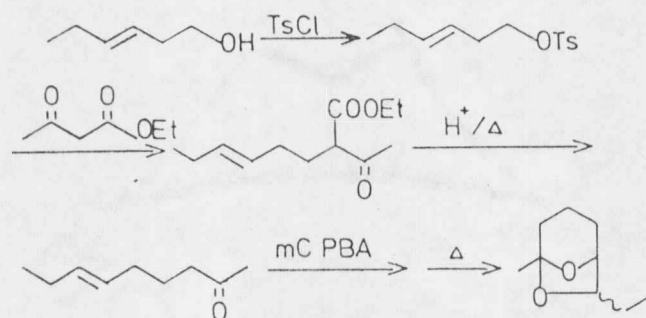
Silverstein's Alternate Synthesis

Figure 2. Some Route "a" Syntheses of Brevicommin

Figure 2 (continued)

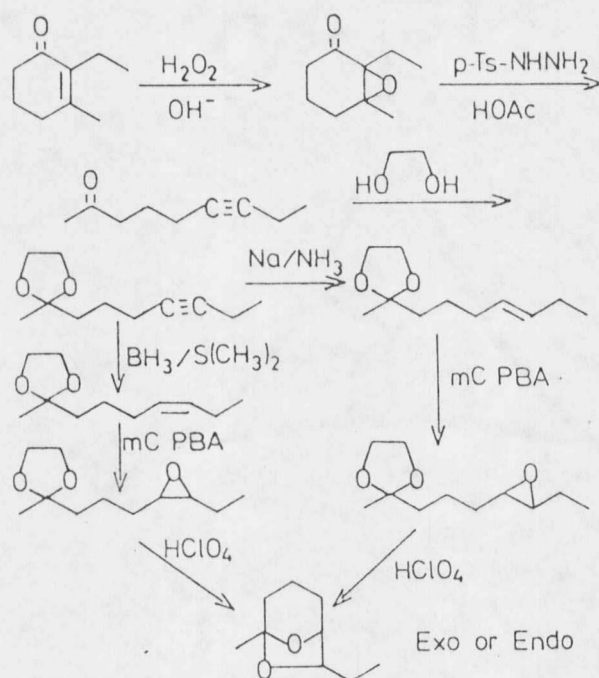


Wasserman Synthesis



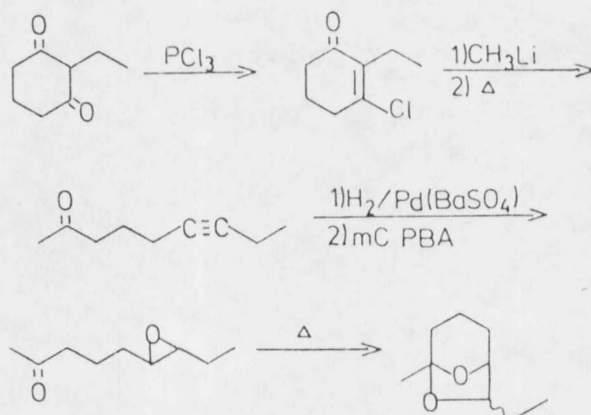
Improved Silverstein Synthesis

Figure 2 (continued)

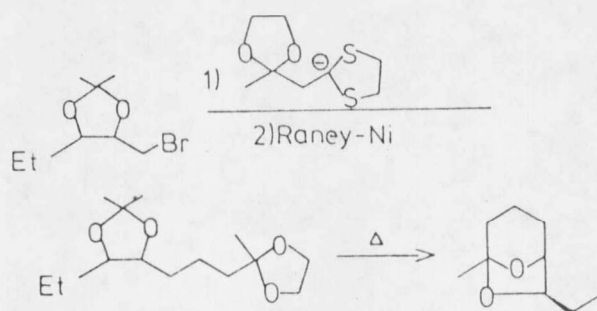


Kocienski Synthesis

Figure 2 (continued)

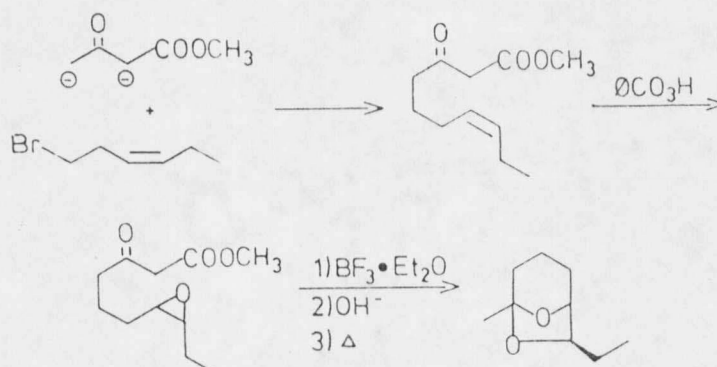


Coke Synthesis

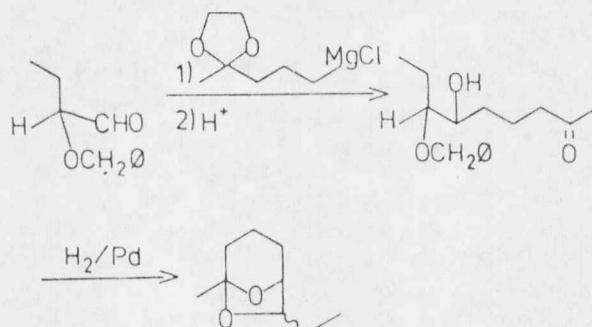


Meyer Synthesis

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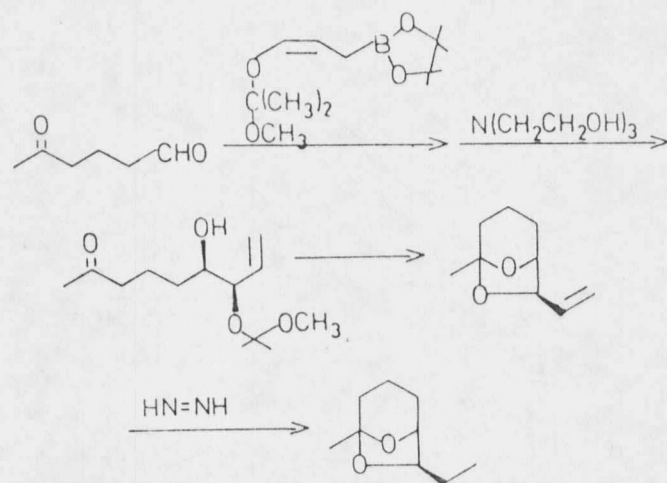


Weiler Synthesis

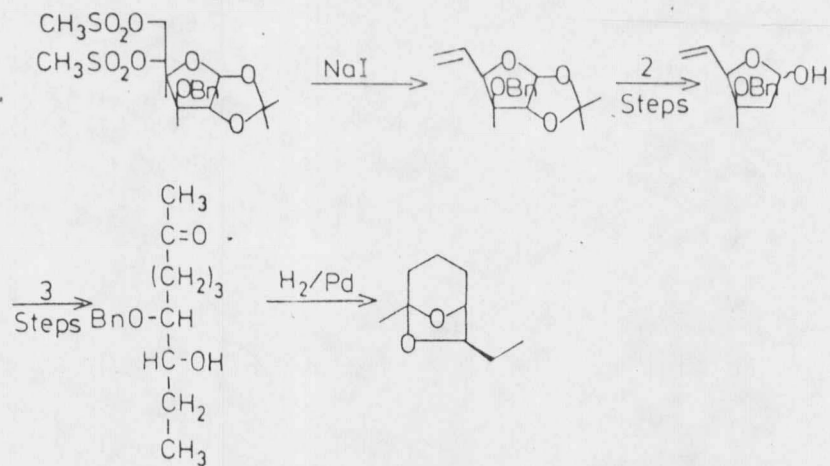


Bernardi Synthesis

Figure 2 (continued)

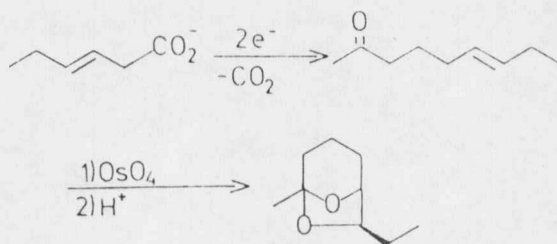


Hoffman Synthesis

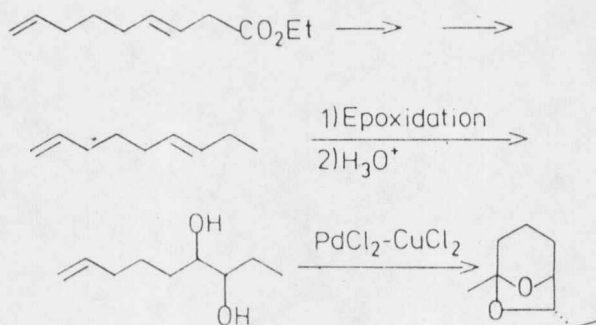


Fraser-Reid Synthesis

Figure 2 (continued)



Shafer Synthesis



Grigg Synthesis

Synthetic route "b" has also been explored by several research groups (Table 1). A recent route "b" synthesis by Cohen (Figure 3) utilizes a Diels-Alder reaction followed by metalation with subsequent attack on propanal and cyclization.²⁵

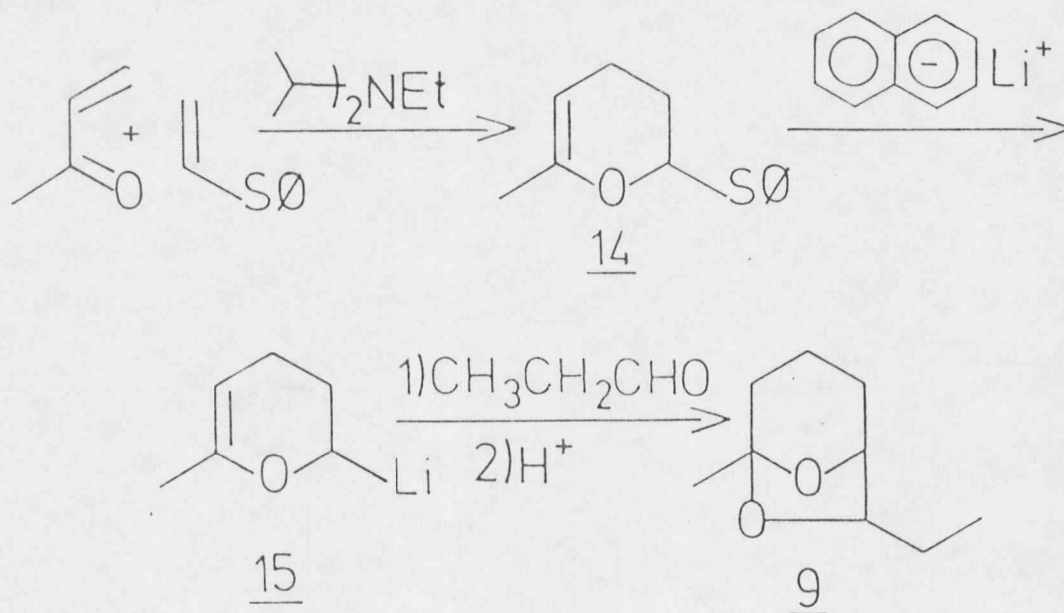


Figure 3. Cohen Synthesis of Brevicomine

A type "b" synthesis of brevicomin utilizing singlet sensitization has been reported by Kossanji and has the advantage of being the one type "b" synthesis to produce only the exo isomer of brevicomin (Figure 4).²³

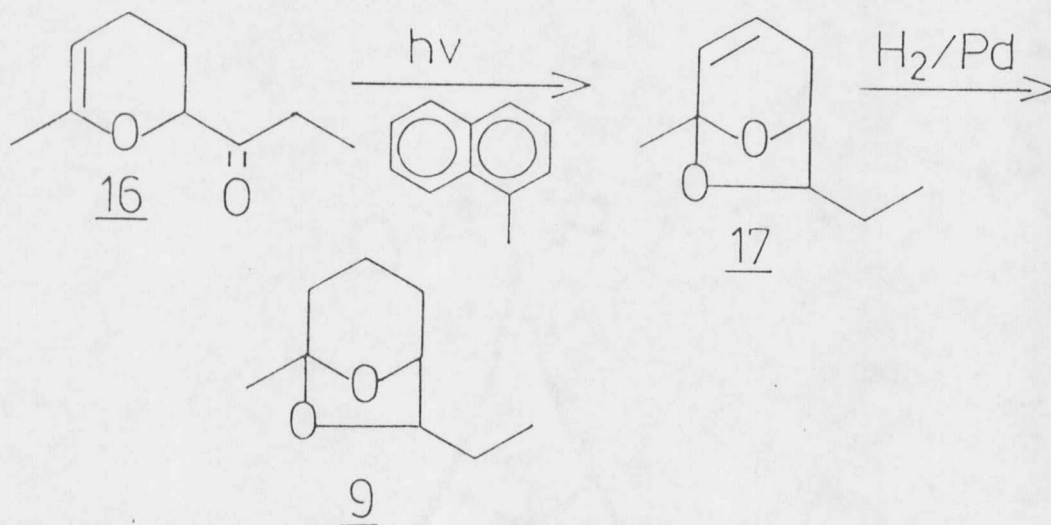


Figure 4. Kossanji Synthesis

Mundy and Bornmann have shown that a route "b" synthesis can be achieved with the use of phenyl selenyl chloride (Figure 5).²⁴

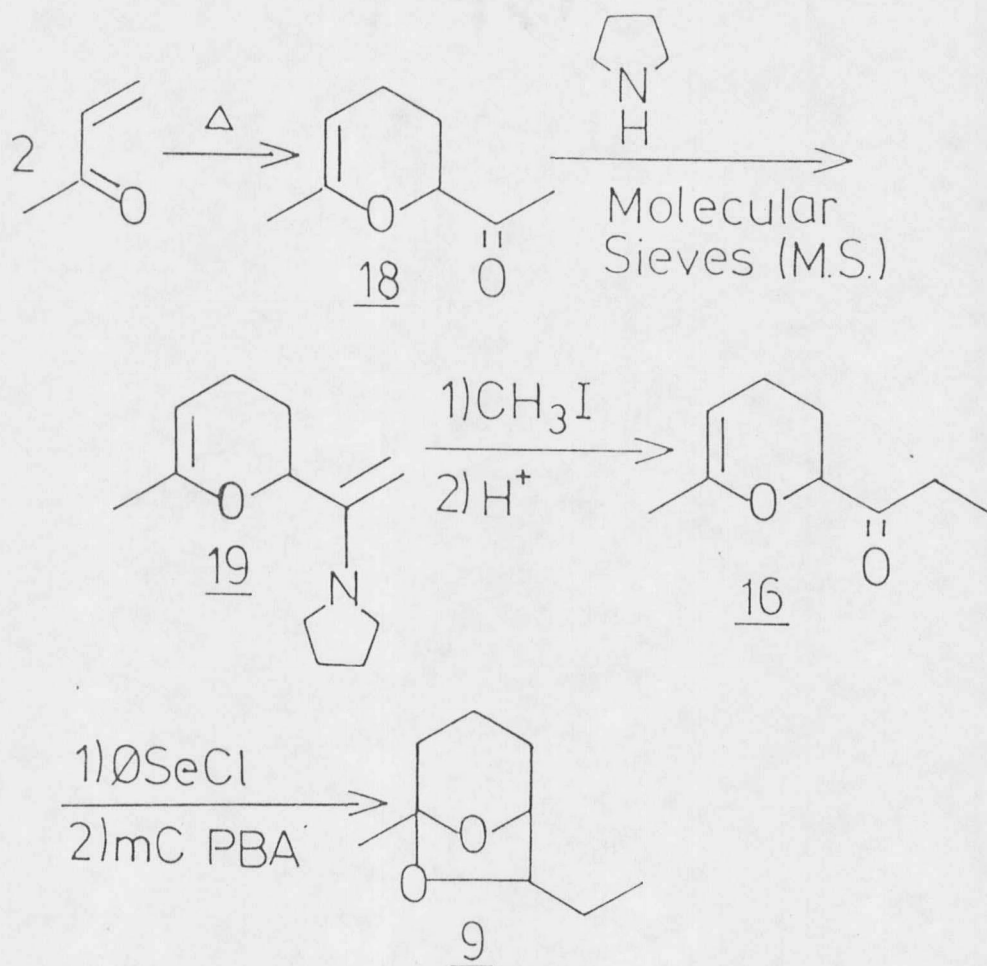


Figure 5. Bornmann Synthesis of Brevicommin

Mundy has also shown that stirring (13) with p-toluene sulfonic acid in the benzene will give brevicomin in an exo/endo ratio of 64/36 (Figure 6).

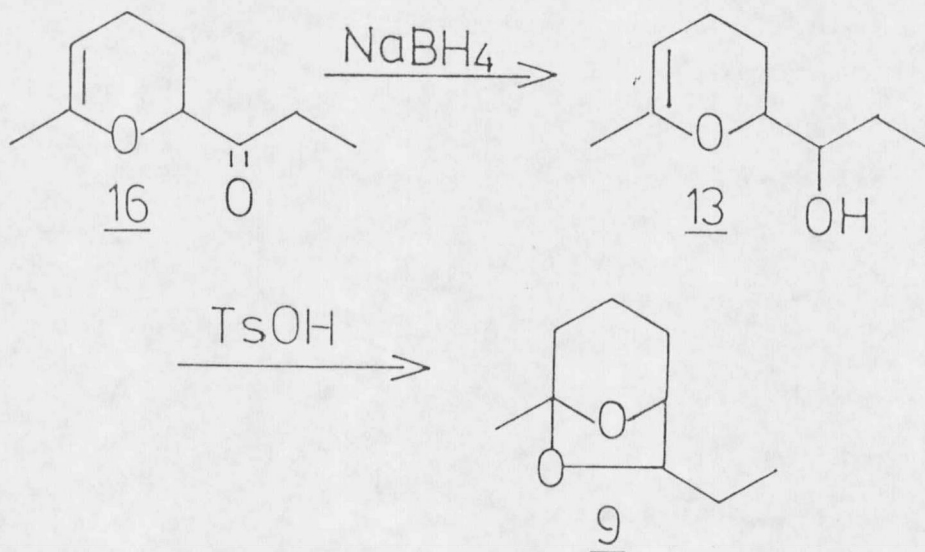


Figure 6. Alternate Mundy Synthesis of Brevicomin

In 1971, Mundy published a short synthesis of brevicomin²² in which the oxymercuration-demercuration reaction sequence, developed by Brown,²⁶ was employed for the final cyclization (Figure 7). Ring closure was induced by the formation of a mercurinium ion on the vinyl ether followed by attack of the hydroxyl group, which acts as an internal nucleophile.

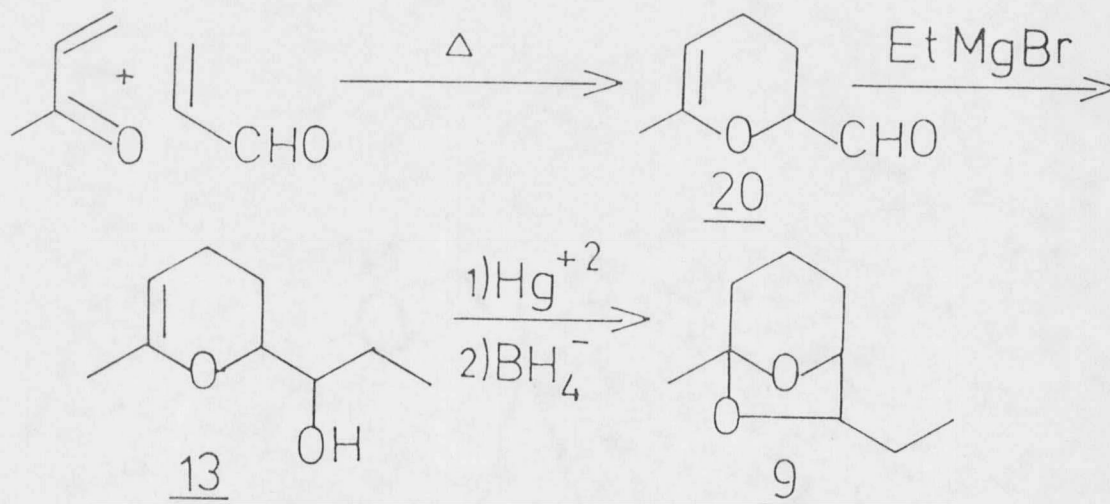


Figure 7. Mundy Synthesis of Brevicomin

The use of mercuric ions to promote ring closures is just one of a variety of organic reactions possible with this reagent. We were prompted, by its use in the Mundy synthesis of brevicomin,²² to review the literature concerning its use in organic synthesis and further encouraged to attempt a novel concurrent synthesis of the aggregating pheromones of D. brevicomis and Trypodendron lineatum, the Norway spruce bark beetle, through the use of mercuric ions.

Mercury compounds have been used for reactions ranging through dehydrogenations, isomerizations, cyclizations involving carbon-carbon and carbon-heteroatom bond formation, and reactions involving addition to olefinic double bonds.

The addition of mercuric salts to olefins, followed by attack of a nucleophile on the mercurinium ion (Figure 8) is commonly called solvomercuration.

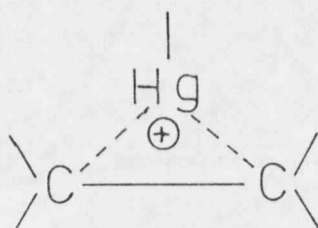


Figure 8. Mercurinium Ion

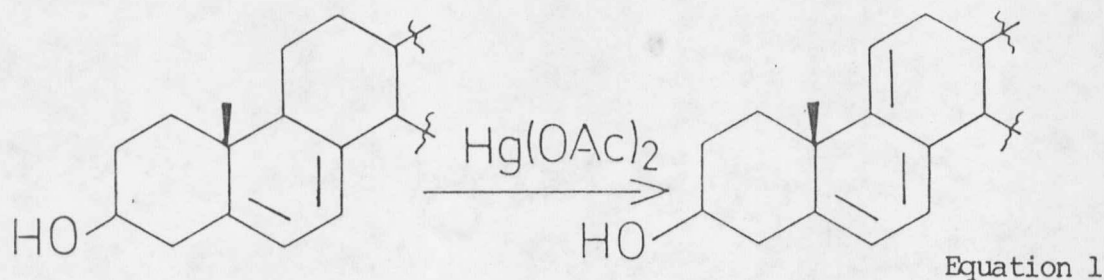
Hydration reactions using mercuric salts and water as the nucleophile have been termed "oxymercuration" reactions. Much of the pioneering work in this area has been done by H. C. Brown,²⁷ who has shown that it is possible to hydrate carbon-carbon double bonds of olefins and dienes selectively. The mercury ion is known to attack from the less hindered side of the double bond, followed by nucleophilic attack at the most highly substituted olefinic carbon to yield the Markovnikov hydration product.

The carbon-mercury bond can then be reduced with a variety of reducing agents. Brown has found that alkaline NaBH_4 is a convenient and efficient method for this reduction.²⁷ This

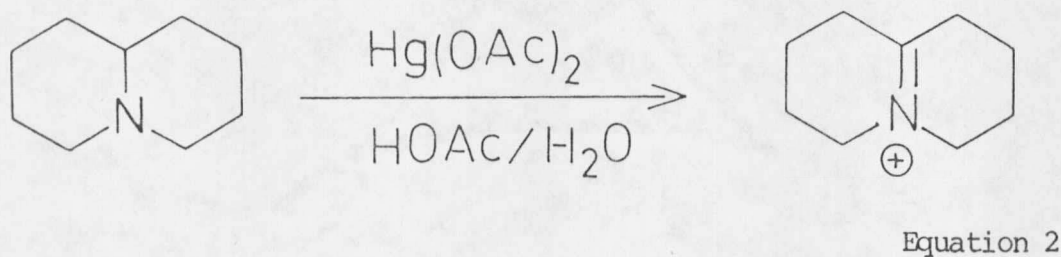
reduction is thought to proceed via a radical mechanism that results in loss of stereochemistry at that carbon center.²⁸

Nucleophiles other than water have been used, and these include acetic acid, methanol, ethanol, hydrogen peroxide, and various organic amines. Common mercury salts used are mercuric acetate, nitrate, perchlorate, sulfate, trifluoroacetate, and mercuric oxide.²⁹

One early use of mercuric acetate is found in the field of steroid chemistry in which a dehydrogenation was accomplished by Windaus (Equation 1).³⁰



It is also possible to dehydrogenate systems containing heteroatoms as shown by the following example (Equation 2).³¹



Isomerizations in systems containing imines or iminium salts are also common (Figure 9).³¹

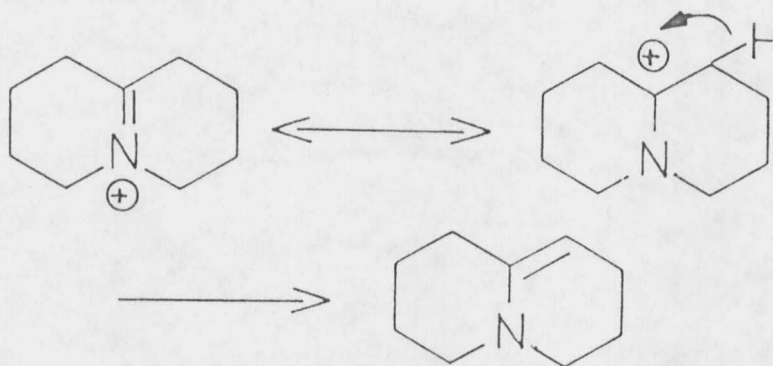


Figure 9. Isomerization of an Iminium Salt

The formation of iminium ions has been used in the synthesis of the Vinca and Iboga alkaloids vincadifformine and coronaridine, respectively. This chemistry is thought to be biomimetic and is also an example of a cyclization utilizing mercuric acetate (Figure 10).³²

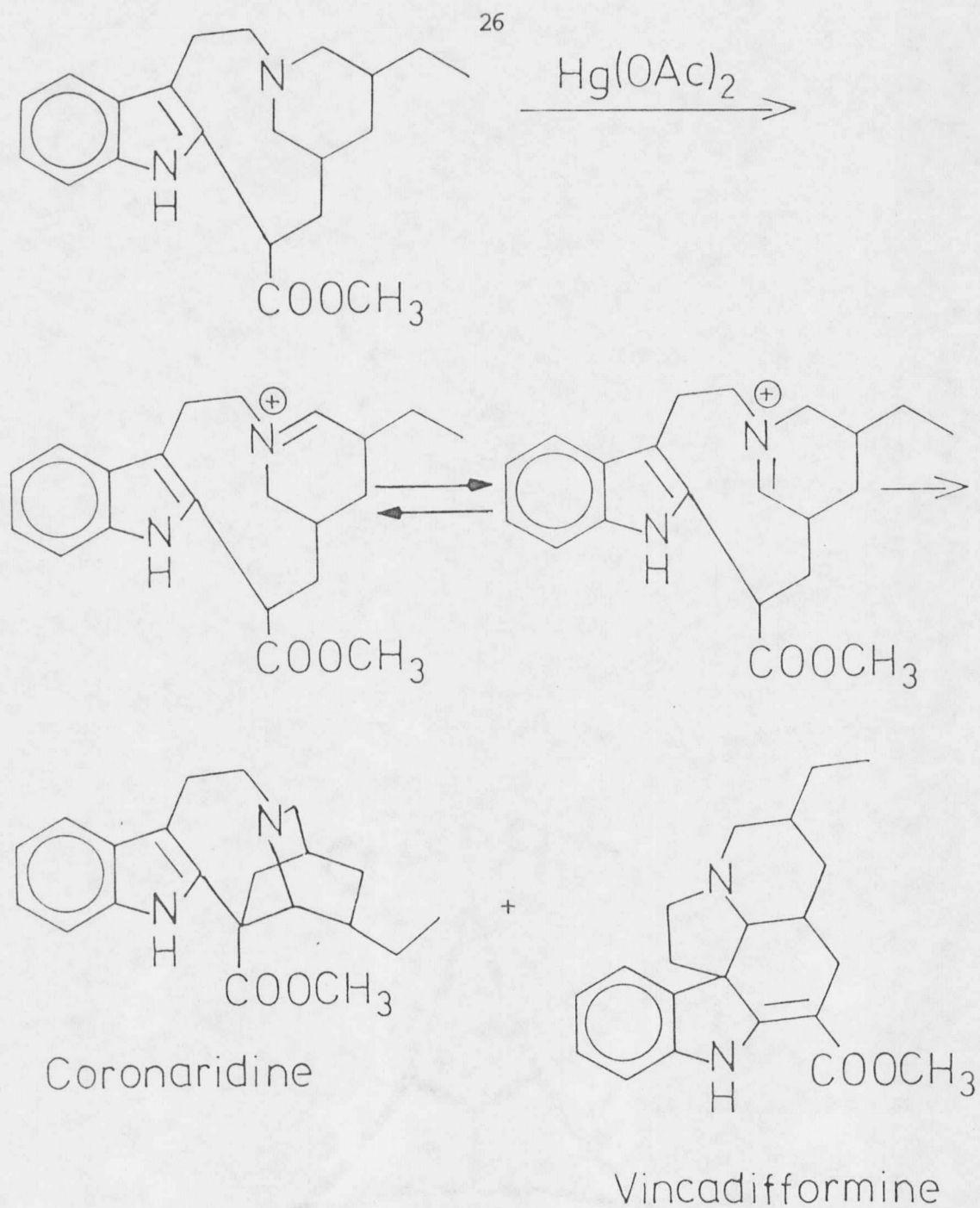


Figure 10. Synthesis of Vincadifformine and Coronaridine

Isomerizations of carbon atoms next to nitrogen are possible through iminium ions as was shown in the conversion of yohimbine to pseudoyohimbine (Figure 11).³³

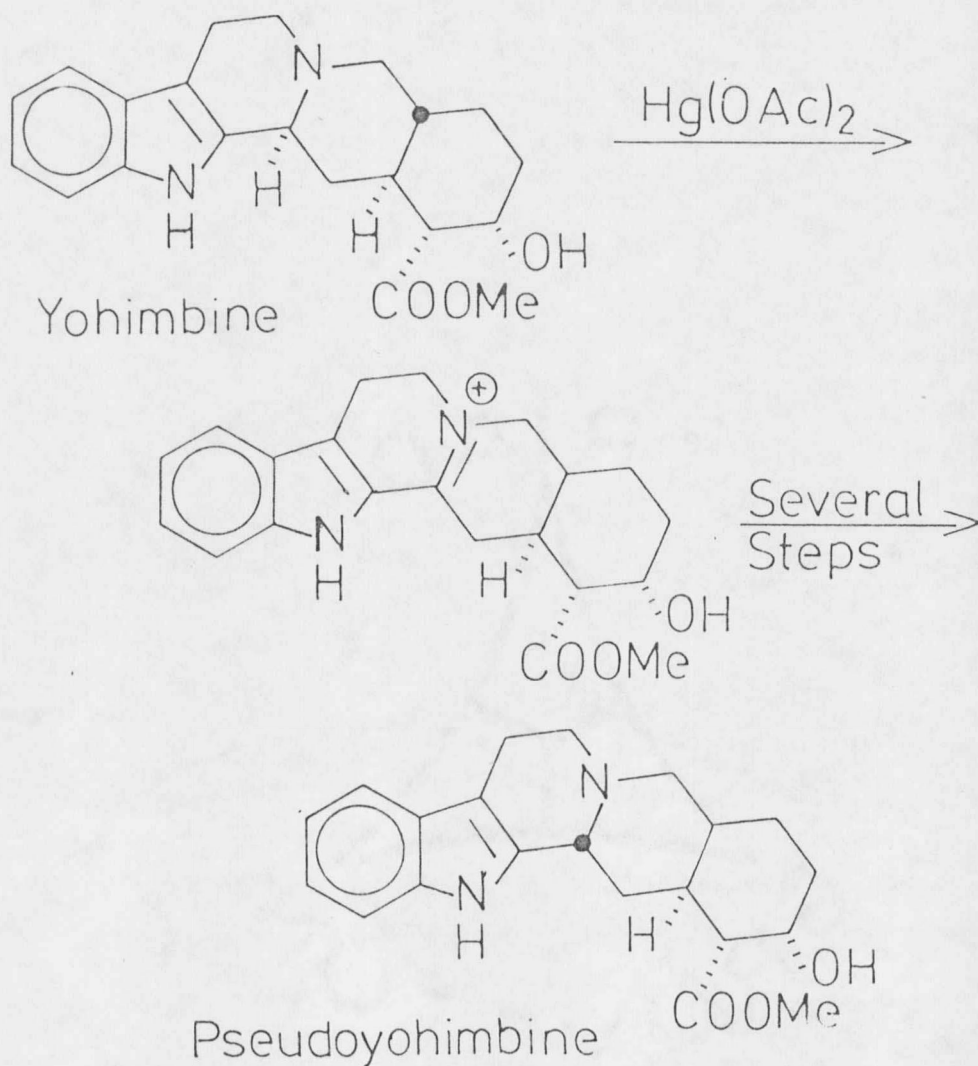
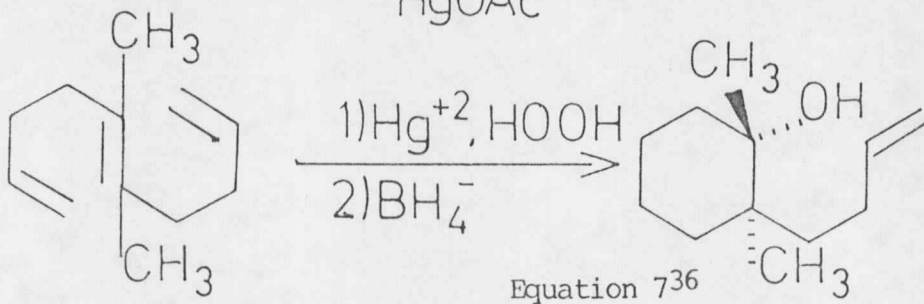
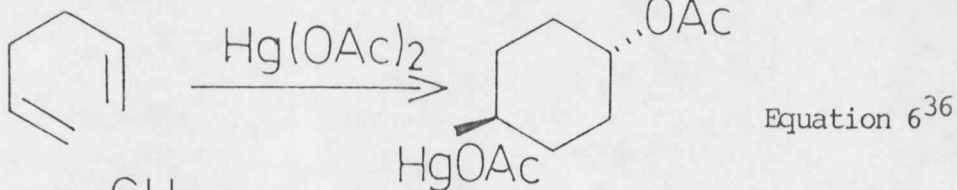
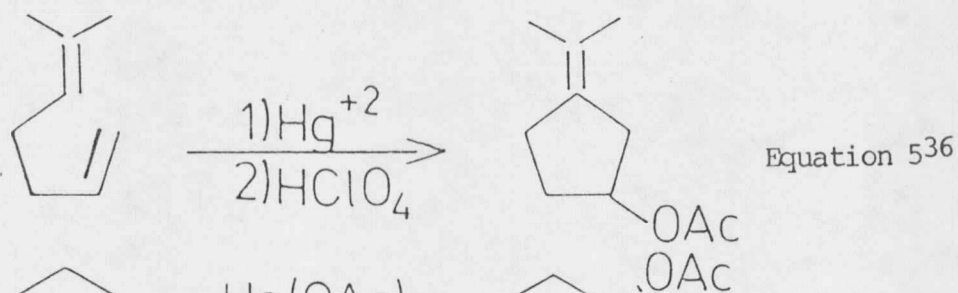
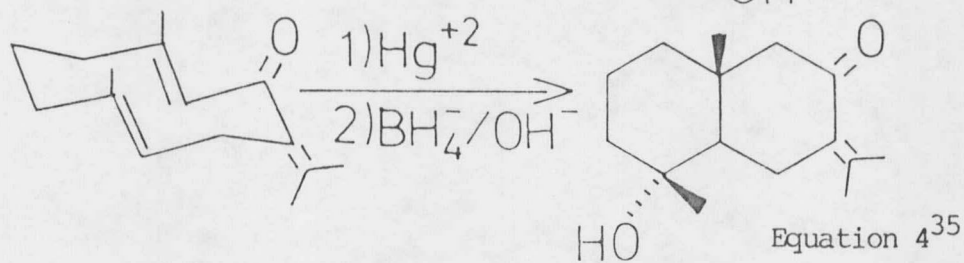
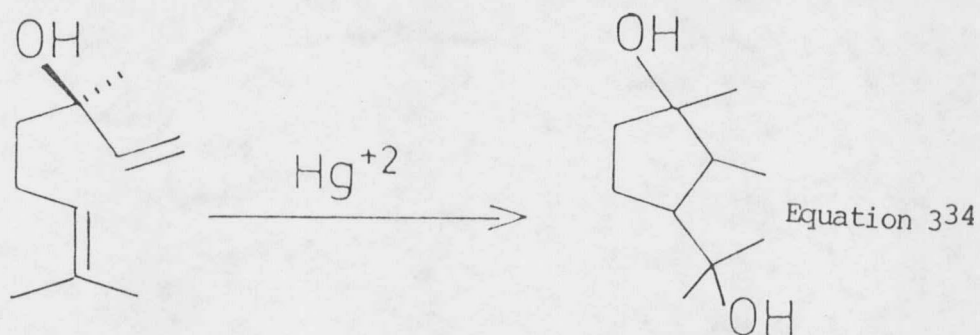
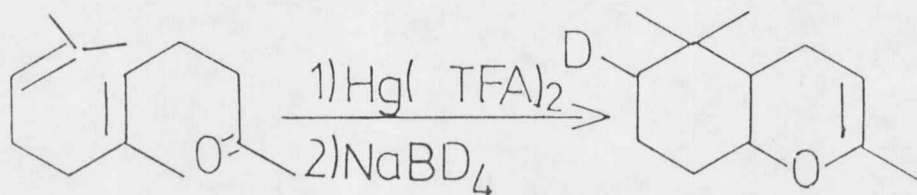


Figure 11. Isomerization of Yohimbine

The use of mercury salts to effect carbon-carbon bond formation is known and has been used in a variety of cyclizations (Equations 3-7).

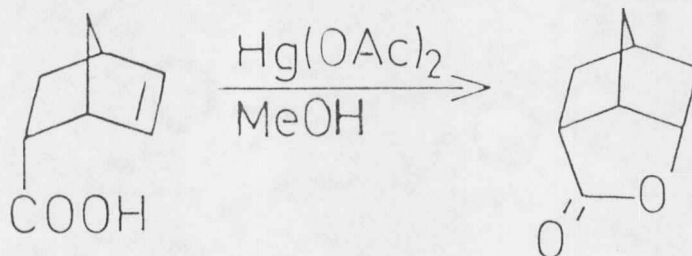


Intramolecular cyclizations have been accomplished using mercury salts through the formation of both carbon-carbon and carbon-heteroatom bonds. These reactions involve the addition of mercury to an olefinic double bond, followed by cyclization. The cyclization of geranylacetone results in the formation of both carbon-carbon and carbon-heteroatom bonds (Equation 8).³⁷



Equation 8

Also within the scope of this reaction is the possibility of using an internal nucleophile rather than a solvent molecule to attack the mercurinium ion. The proximity of the internal nucleophile allows it to compete effectively with solvent in these reactions. Jensen and Miller have used an internal carboxylic acid as a nucleophile as shown in Equation 9.³⁸



Equation 9

Internal cyclizations utilizing a hydroxyl group are perhaps the most common, as illustrated in the following examples (Figure 12).

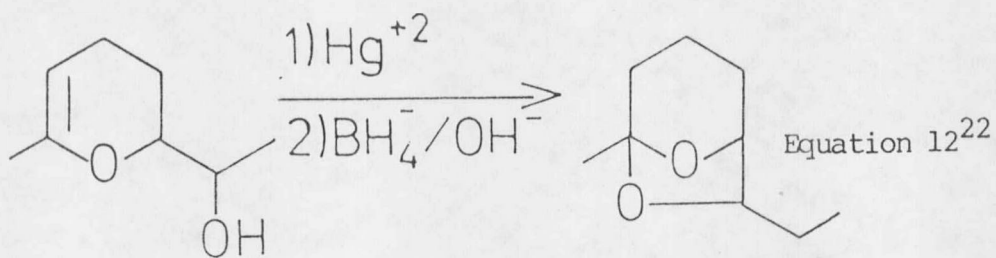
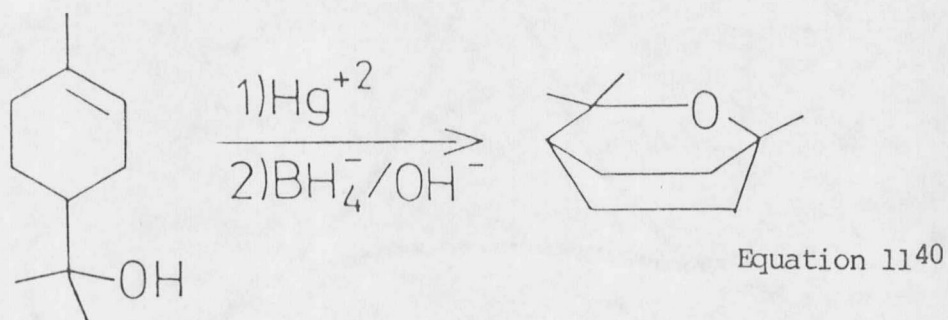
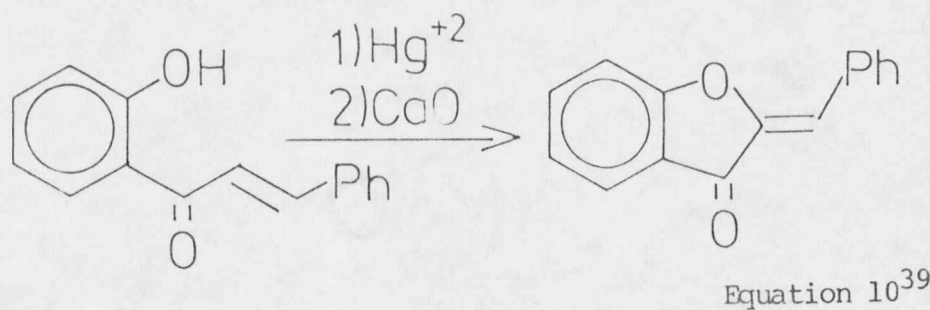


Figure 12. Internal Cyclizations Utilizing a Hydroxyl Group

Recent work by Hoyer demonstrates some of the versatility possible with the use of mercury salts in cyclization reactions (Figure 13).⁴¹

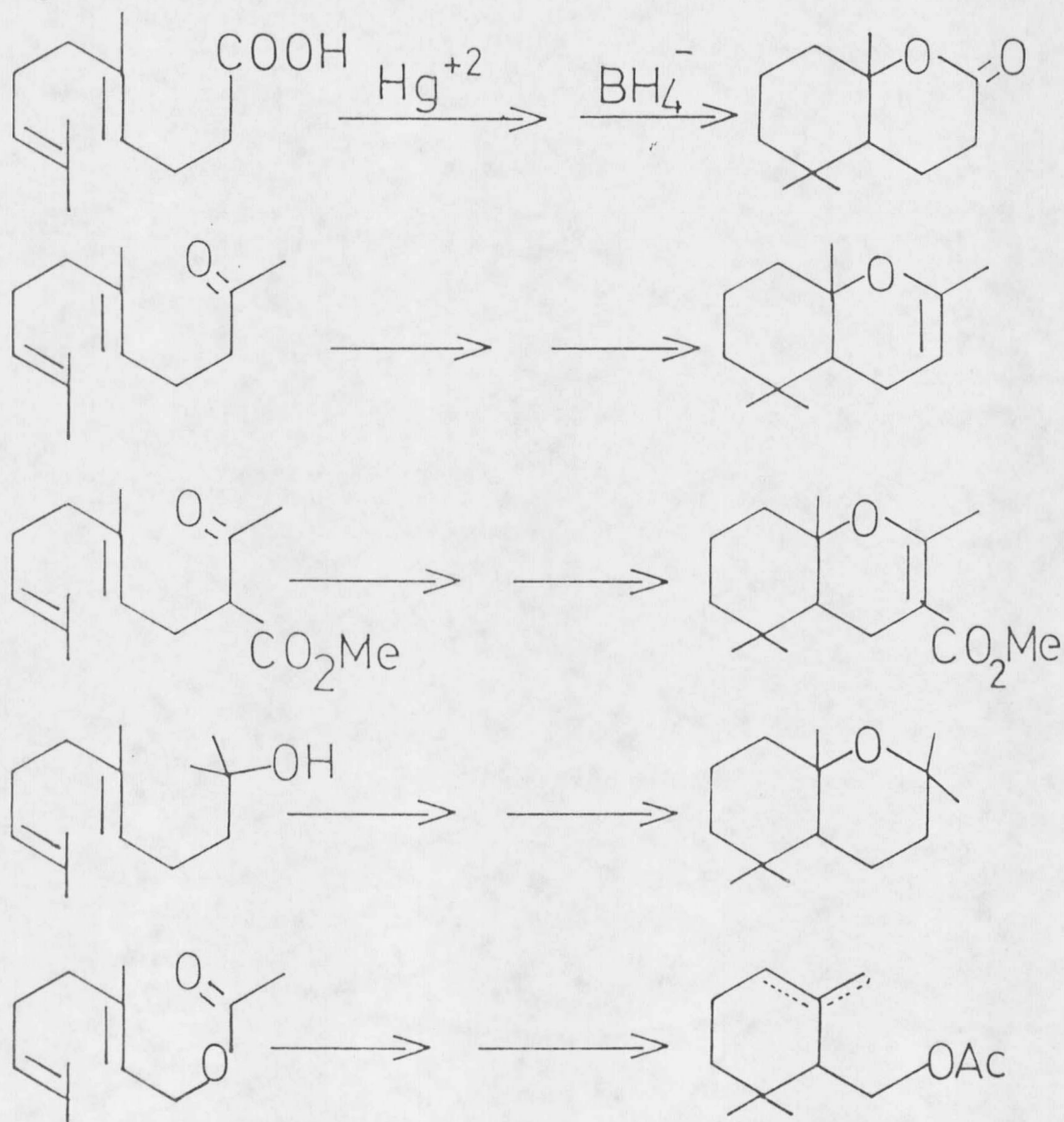
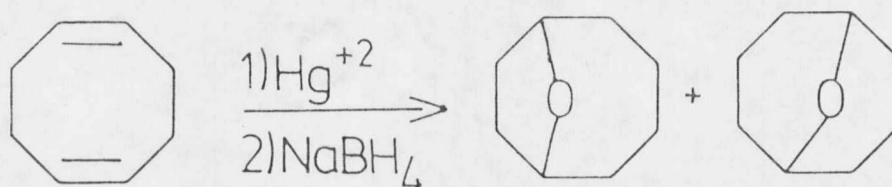


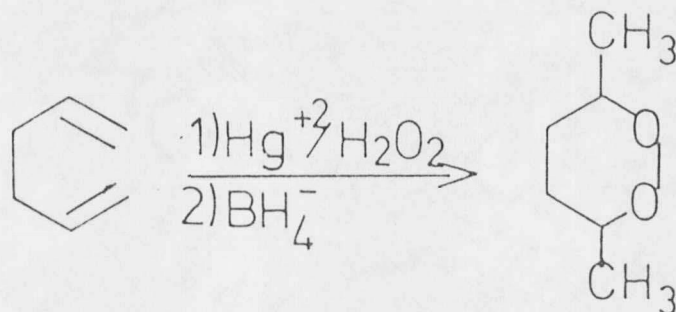
Figure 13. Hoyer's Cyclization Reactions

A further extension of the solvomercuration reaction has been the introduction of the nucleophile into a diene and subsequent cyclization by the use of a double mercuration reaction. Waxman has shown that the oxymercuration of 1,5-octadiene with excess mercuric acetate yields a mixture of the corresponding 1,4 and 1,5 bicyclic ethers (Equation 13).⁴²



Equation 13

Bloodworth has used a double mercuration reaction in the synthesis of endoperoxides (Equation 14).⁴³



Equation 14

Recent work by Barluenga has demonstrated the use of organic amines in the synthesis of a wide variety of nitrogen containing heterocycles (Figure 14).⁴⁴

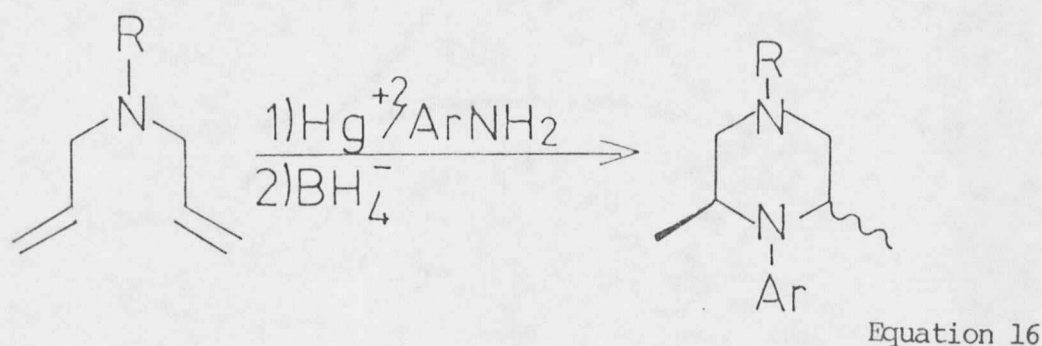
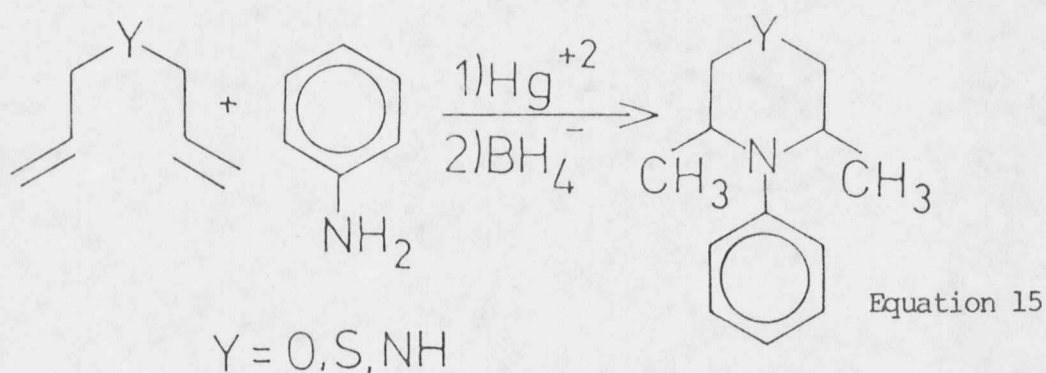


Figure 14. Syntheses of Nitrogen Heterocycles

A logical extension of the use of the double oxymercuration-demercuration reaction was to apply this chemistry to the synthesis of brevicomin. The first solvomercuration reaction would be used to introduce a hydroxyl group and in the second mercuration reaction the hydroxyl group would act as an internal nucleophile and generate the desired bicyclic ketal system. We envisioned a reaction sequence in which the pheromones of *Dendroctonus brevicomis* (9) and

Trypodendron lineatum (22)⁴⁵ might be synthesized concurrently (Figure 15).

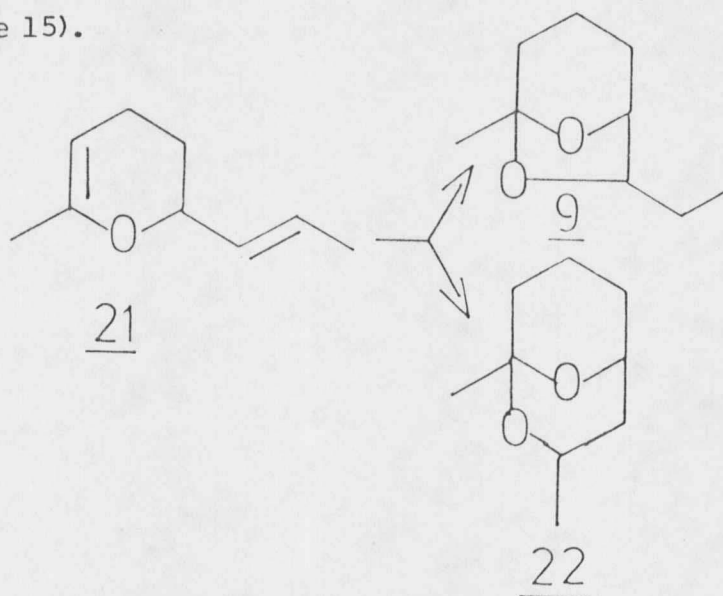


Figure 15. Concurrent Pheromone Syntheses

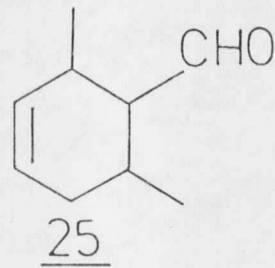
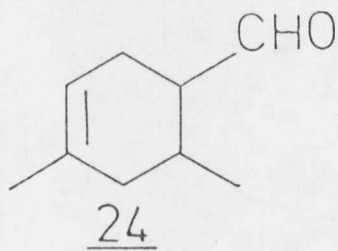
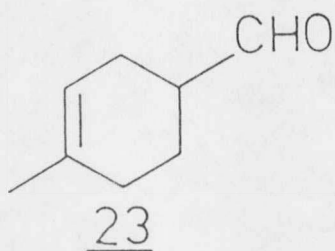
In view of the importance of these pheromones in the potential management of the respective species, their syntheses were undertaken.

CHAPTER THREE

Results and Discussion

Although there is much interesting chemistry involved in the route "a" brevicomin syntheses, we decided to confine our efforts to the evaluation of factors affecting stereoselectivity in route "b" type reaction sequences since the earlier syntheses of brevicomin by our group were of this type.

In a series of papers,^{46b} the first of which was published in 1956, Kugatova noticed specific chemical behavior for cyclohexenes substituted at C-4 with electron-withdrawing groups. It was observed that aldehydes 23, 24, and 25 hydrogenated with great difficulty using a Pd catalyst. Even when the hydrogenation was run at high hydrogen pressures and temperatures of 60–80°C, the yield was only 60–70%. Conversion of the aldehydes to acetals allowed for easy and facile reduction of the olefin under the same conditions.



It was further observed that the ethynylation of aldehydes **26**, **27**, and **28** (Figure 16), was also a difficult and low yield reaction, while the same reaction on the saturated analogs proceeded in a facile manner.

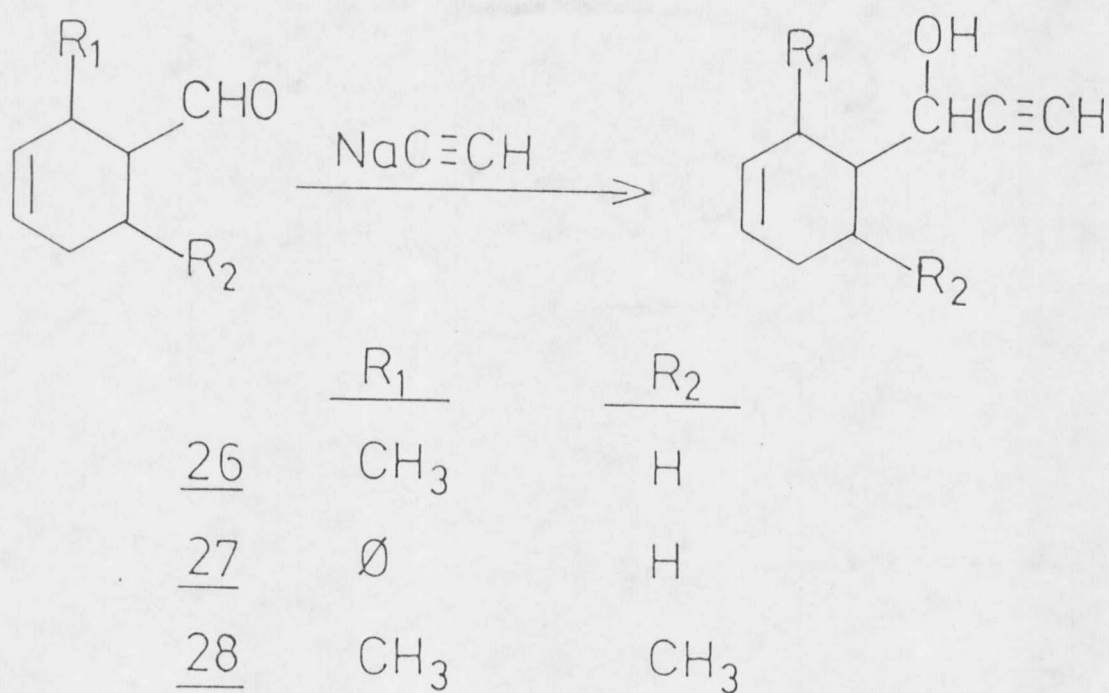
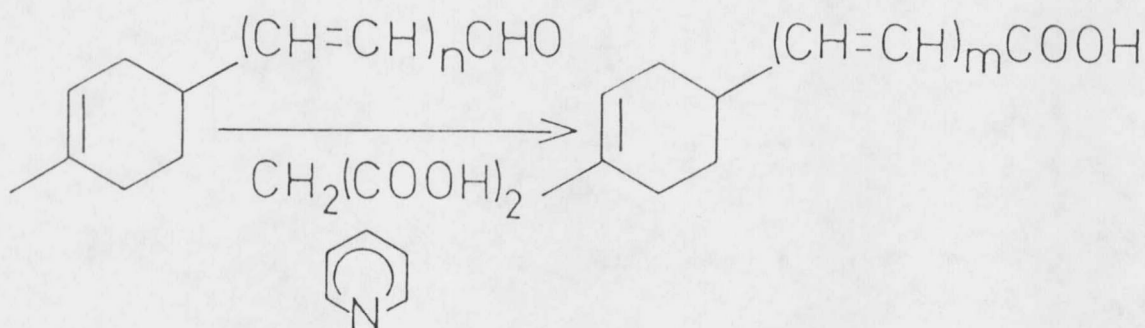


Figure 16. Ethynylation of Cyclohexene Aldehydes

The reaction characteristics of 4-substituted cyclohexenes were further studied by Kugatova⁴⁶ during an investigation of malonic acid condensations with aldehydes **29** and **30**. The reactivity of the carbonyl increased substantially as it was moved away from the ring olefin (Figure 17).



	<u>n</u>	<u>m</u>	<u>Yield</u>
<u>29</u>	0	1	18%
<u>30</u>	1	2	63%

Figure 17. Malonic Acid Condensation of Cyclohexene Aldehydes

In 1962, Kugatova summarized these results and introduced the concept of the "supra-annular effect" to explain the low reactivity of the carbonyl group when it was located in the 4-position relative to a ring olefin.⁴⁶ Reasoning from molecular models, he proposed that cyclohexenes substituted at the 4-position with electron

withdrawing groups might show a preference for the axial orientation of the substituent because the electron density in the double bond could be donated through space into the partially positive carbon of the carbonyl resulting in electron delocalization and, thereby, an increase in the stability of the axial conformation (Figure 18).

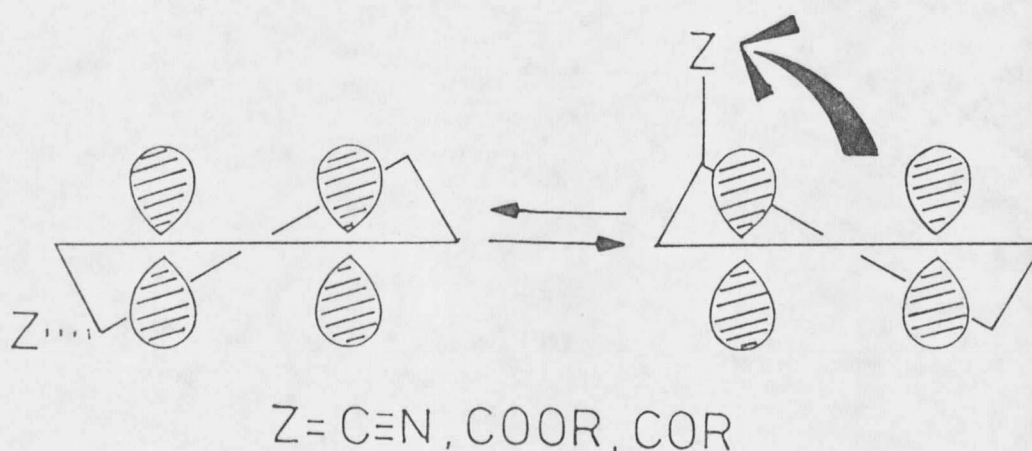
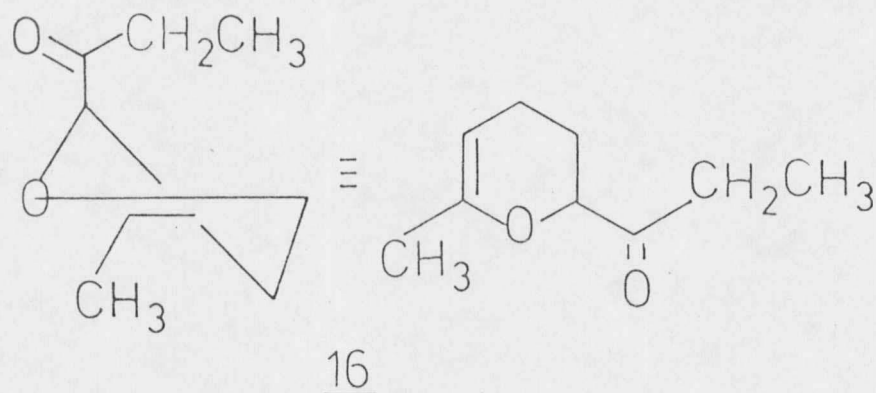


Figure 18. Proposed Supra-Annular Effect

It was argued that if the supra-annular effect was operative, one should see a reduction in the rate of electrophilic attack on the double bond, i.e., hydrogenation, due to a lowered electron density and also a reduction in the rate of nucleophilic attack on the electron withdrawing group, i.e., ethynylation or malonic acid

condensation, due to a lessening of the partial positive charge on the carbonyl carbon.

The concept of a supra-annular effect was of particular interest to us because of the role it might play in controlling exo/endo product ratios in certain brevicomin syntheses. We reasoned that compound **16** might be showing preferential axial orientation of the propionyl group due to the supra-annular effect.



If the axial orientation was preferred, an attacking hydride as in Mundy's alternate synthesis of brevicomin,²² would see two different sides of the molecule and generate either the erythro or the threo alcohol. These alcohols would then cyclize to give endo and exo product ketals (Figure 19).

It seemed reasonable to assume that the carbonyl would be oriented with the oxygen atom as far away from the olefinic electron cloud as was possible (see **16**). This conformation would minimize

electron-electron repulsions between the unshared pairs of electrons on the oxygen and the olefinic pi electron cloud. The steric interaction of the ethyl group lying over the ring should not be large enough to prohibit this conformation.

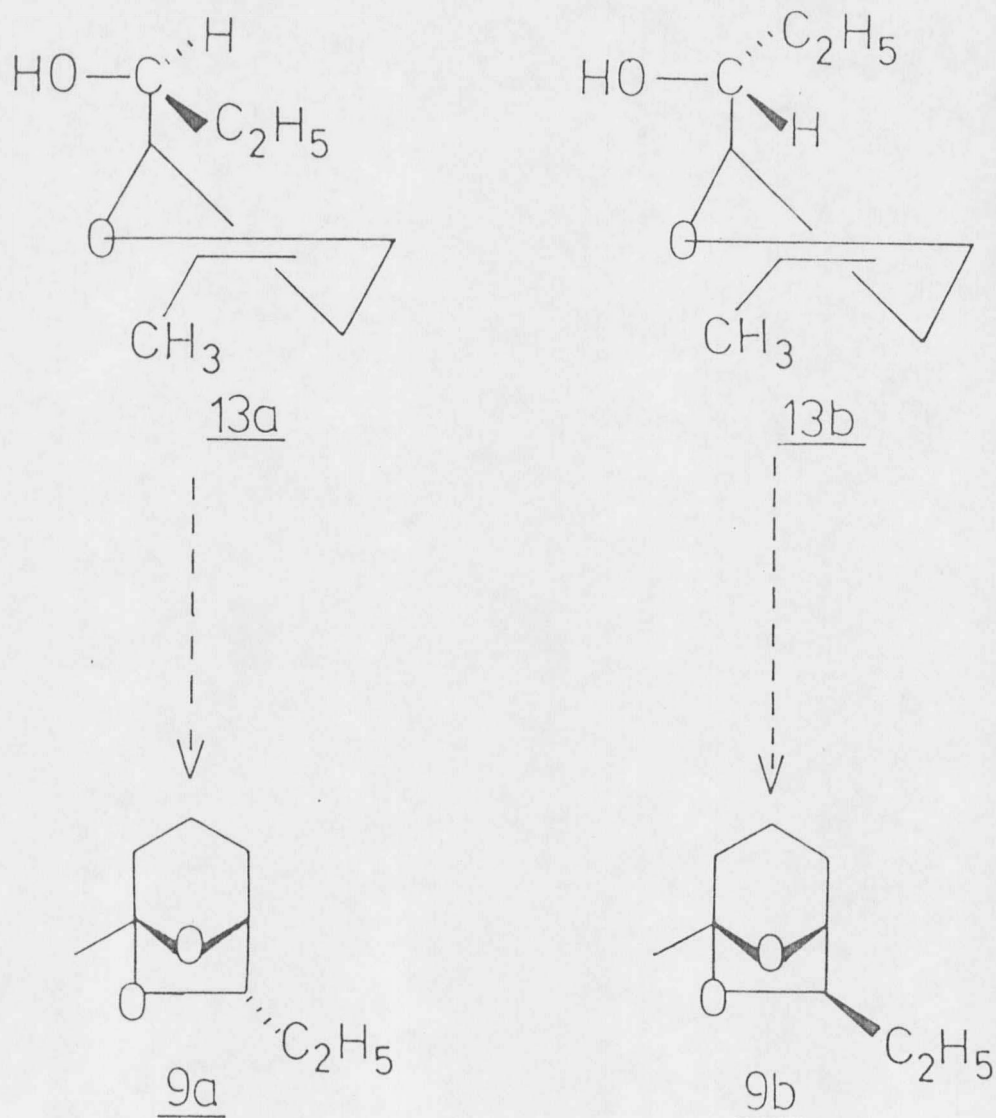


Figure 19. Cyclization of Threo and Erythro Alcohols

If these assumptions are true, the presence of a supra-annular effect would, indeed, have an effect on the exo/endo product ratio as was shown above. We recognized that a clearer understanding of the role of the supra-annular effect in type "b" brevicomin syntheses was necessary so that we could evaluate its potential for controlling stereochemistry in these syntheses.

A further literature search revealed information which cast some doubt on the validity of the supra-annular effect. An NMR study of 4,5-disubstituted cyclohexenes by Viktorova⁴⁷ has shown that these systems prefer the diequatorial conformation in spite of the possibility that the diaxial conformation would have two supra-annular interactions resulting in stabilization due to extensive electron delocalization. These data indicate no significant preference for the axial conformation in these systems (Figure 20). This result directly contradicts the preferred axial conformation which is needed for Kugatova's proposed supra-annular effect.

It has also been shown that electron withdrawing groups at the 4-position are not required for the reduction of alkene reactivity. The addition of bromine to cyclohexene has been observed to be seventeen times faster than the addition of bromine to 4,4-dimethylcyclohexene.⁴⁸ In the dimethyl compound, one methyl must always be in the axial position sterically blocking the incoming

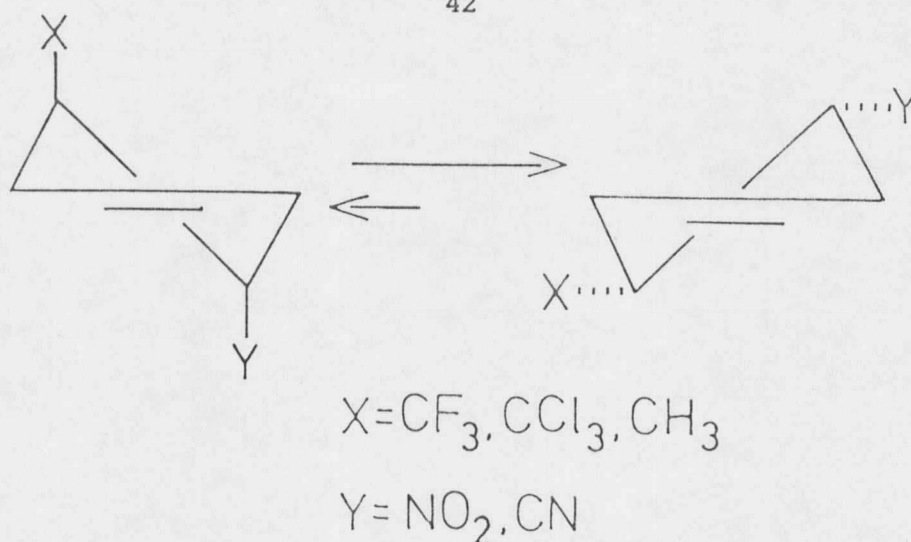


Figure 20. Conformations of 4,5-Disubstituted Cyclohexenes

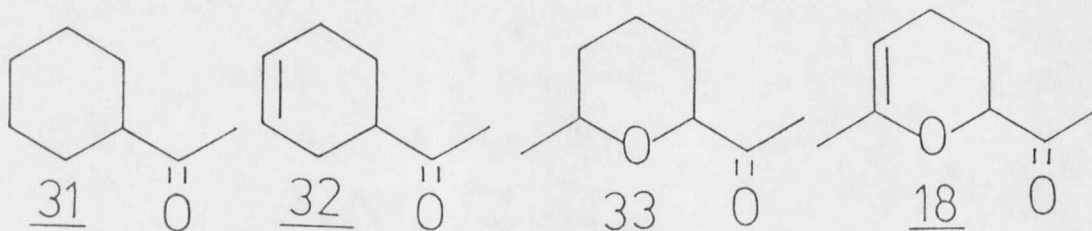
bromine. Furthermore, Rickborn has studied the relative rates of reaction between cyclohexene and 4-methylcyclohexene for epoxidation and cyclopropanation reactions⁵⁰ and has observed similar rate reductions for the 4-methylcyclohexene (Table 2). He has also attributed the

Table 1. Relative Reaction Rates for Cyclohexene and 4-Methylcyclohexene for Simmons-Smith and Epoxidation Reactions

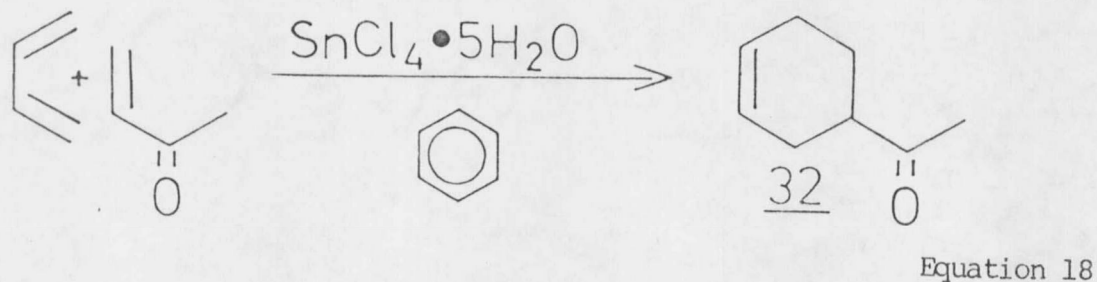
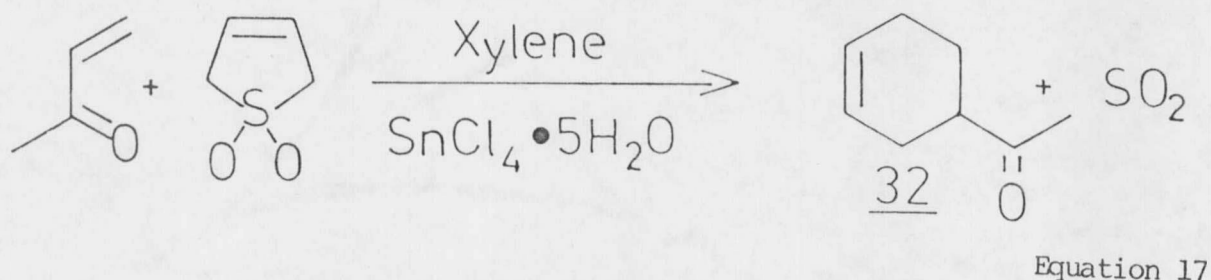
<u>Relative Rates</u>	<u>Cyclohexene</u>	<u>4-Methylcyclohexene</u>
Simmons-Smith	1.00	0.91
Epoxidation	1.00	0.81

slow relative rates of reaction of C₄ substituted cyclohexenes to the steric bulk of the substituent rather than to electronic effects such as the supra-annular effect. There was obviously some controversy over the existence of the supra-annular effect and since it appeared that the supra-annular effect might be useful in controlling the synthesis of bicyclic ketals, we decided to see whether or not the supra-annular effect was operative in our system. The influence of the supra-annular effect on the reduction of carbonyl reactivity was chosen for examination. A convenient reagent for these investigations is NaBH₄. Sodium borohydride does not become less reactive as it sequentially delivers hydride; in contrast to LiAlH₄ which becomes substantially less active with each successive hydride.⁵²

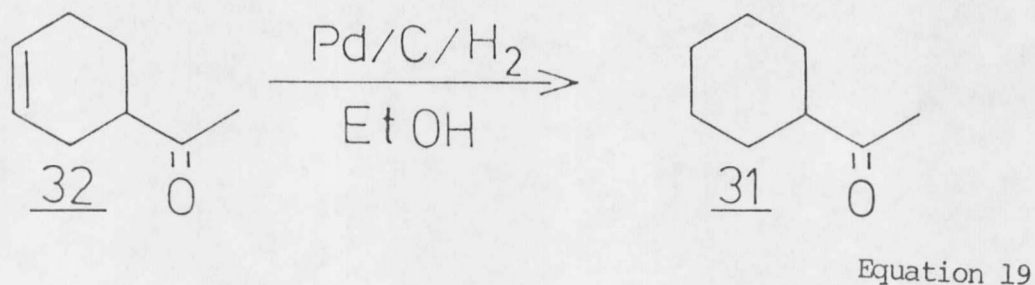
Competitive NaBH₄ reductions were performed on compounds 31, 32, 33, and 18 to determine if the rate of carbonyl reduction was influenced by the presence of the olefin.



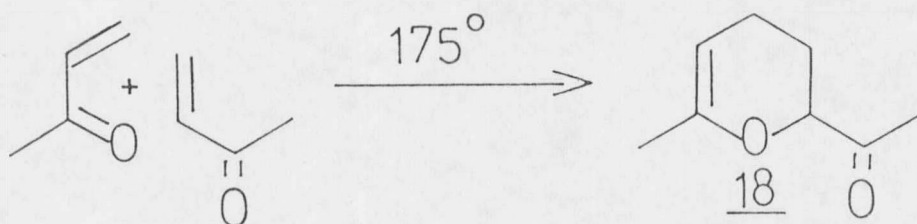
The synthesis of compound 32 was initially attempted by reacting butadiene sulfone with methyl vinyl ketone at reflux with a Lewis acid catalyst (Equation 17). Several attempts gave only low yields, and this method was abandoned. A Lewis acid catalysed Diels-Alder reaction between butadiene and methyl vinyl ketone, however, gave compound 32 in fair yield (22%) as shown in Equation 18.



Ketone 31 was obtained by the catalytic hydrogenation of 32 (Equation 19).



Compound 18, methyl vinyl ketone dimer, was synthesized by the Diels-Alder dimerization of methyl vinyl ketone in a high pressure reaction vessel (Equation 20).



Equation 20

The synthesis of compound 33 proved to be somewhat more difficult than we expected. The vinyl ether proved virtually resistant to attempted reductions with hydrogen using Pd/C and Pt/C as catalysts. As shown in Figure 21, this problem was circumvented by NaBH₄ reduction of the dimer followed by ketalization in the presence of p-toluene sulfonic acid. The ketal was then opened reductively using Pd/C to yield alcohol 36, which was then oxidized with Jones reagent to yield 33. Catalytic reduction of 18 with Rh/alumina also proved to be effective, yielding 90-95% of 33. Unreduced 18 was removed by treating the mixture with a 2% KMnO₄ solution.

Competitive NaBH₄ reductions were performed on compounds 31 and 32 using a three-fold excess of each ketone to hydride.

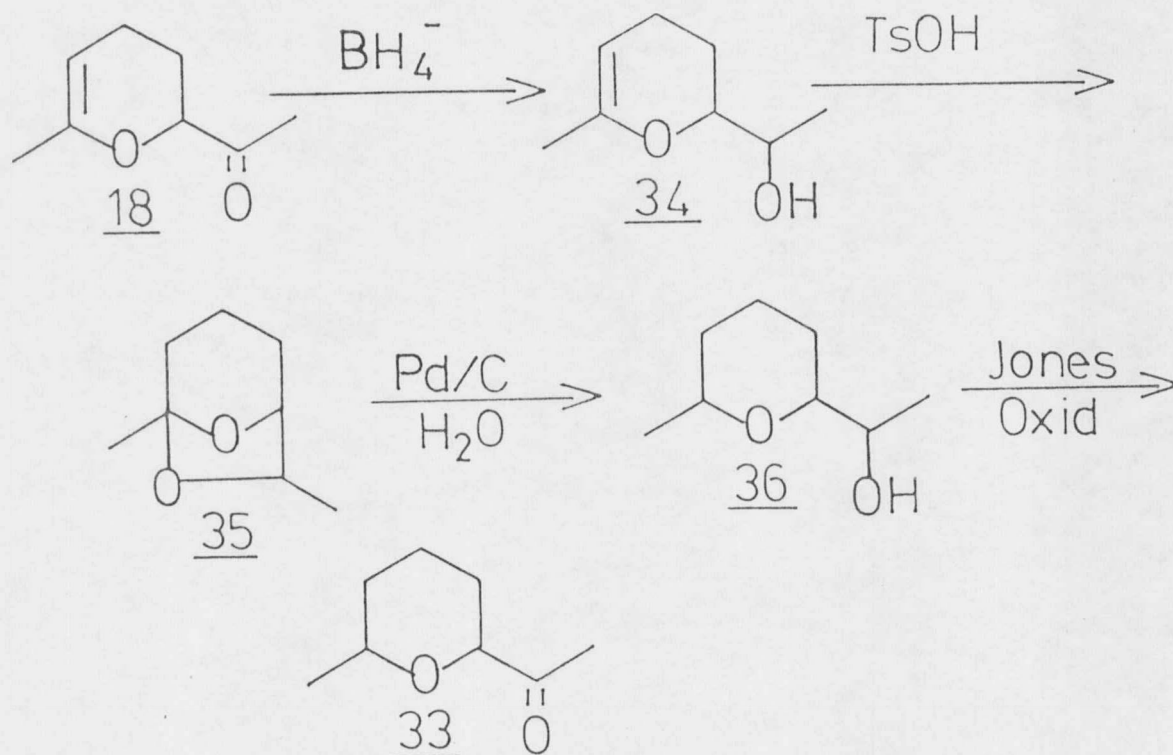


Figure 21. Synthesis of 2-Acetyl-6-methyl-tetrahydropyran

The reductions were analysed with GLC and the extent of the reaction was measured by electronic integration of the peak areas for the remaining amount of ketones and an internal standard, o-dibromobenzene. This was chosen as the internal standard because

it gave a symmetrical GLC peak and its retention time placed it in a region of the chromatogram distant from either the reactant ketones or the alcohol products. The alcohols were monitored but were not characterized. The ratio of each ketone peak area to the area of the internal standard was compared to standard curves (moles ketone vs. ketone peak area/internal standard peak area), and the results were used to determine relative rates according to Equation 21.⁵²

$$\text{Relative Rates} = \frac{\ln(\text{fraction of A remaining})}{\ln(\text{fraction of B remaining})}$$

Equation 21

One would expect 32 to show a relatively slower reduction rate due to the potential supra-annular interaction. The results, however, show a relative rate = $k_{31}/k_{32} = 0.76 \pm 0.04$, indicating that 31 is being reduced more slowly. This would seem to indicate that the supra-annular effect is not present in these compounds. Indeed, the rate ratio is actually the opposite of what would be predicted.

Similar competitive reductions were performed on compounds 33 and 18, which more closely resemble the compounds in Mundy's

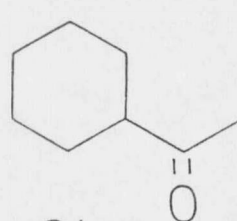
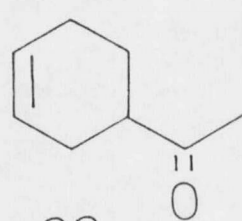
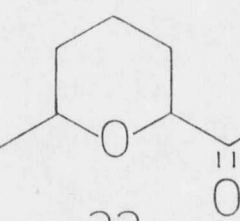
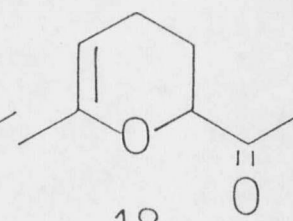
brevicommin synthesis.²² The competitive reductions of 33 and 18 gave a relative rate = $k_{33}/k_{18} = 0.58$. Again we see the opposite of the predicted relative rates and thus we are forced to discount the supra-annular effect for these molecules.

One might postulate a reverse supra-annular effect, in which electrons would flow from the carbonyl to the olefin, in an attempt to explain the observed rates. This does not seem likely, however, because it would require electrons to flow away from the partially positive carbonyl carbon toward the electron cloud of the olefin. Conversely, because of the objectionable nature of the reverse supra-annular effect, these data may indicate that the ketones prefer the more expected equatorial conformation of the C₄ substituent in which a supra-annular interaction would be impossible.

While discounting the supra-annular effect, the presence of an oxygen atom does seem to influence the relative reaction rates. A look at the overall normalized relative rates shows a rate retarding effect of the oxygen heteroatom in (33) and (18) (Table 3).

Since the rate differences were small, we decided to check the validity of our experimental procedures. Equation 21 is valid so long as neither ketone is limiting in concentration.⁵² The effect of ketone concentration on relative rates was determined by running the

Table 3. Normalized Relative Reaction Rates for Competitive Kinetic Experiments

				
<u>31</u>	<u>32</u>	<u>33</u>	<u>18</u>	
<u>31</u>	<u>32</u>	<u>33</u>	<u>18</u>	
Rel. Rates	1.00	1.26	0.33	0.57

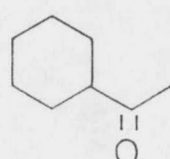
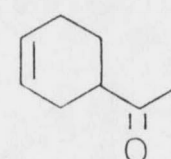
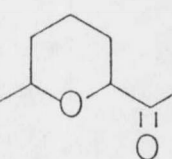
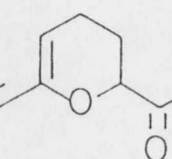
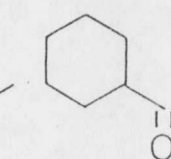
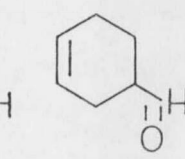
competitive reductions with a 2:1 molar ratio of ketones, instead of the usual 1:1 molar ratio. As one can see from Table 4, this ratio produced no significant change in relative rates, thereby confirming the accuracy of our experimental approach.

Table 4. Reactant Ratio versus Relative Rates

<u>Molar Ratio 33/18</u>	<u>Relative Rate</u>
1:1	0.58
1:2	0.61
Average = $0.59 \pm .02$	

To further determine if electron density was being delocalized from the olefin into the carbonyl, we examined the ^{13}C NMR carbon chemical shifts. Delocalization should result in shielding of the carbonyl carbon and an upfield shift. Carbon NMR data for these compounds are shown in Table 5. It can be seen that there are no correlations between the chemical shift of the carbonyl carbon and relative reactivity.

Table 5. ^{13}C Chemical Shift Data (ppm)

						
	<u>31</u>	<u>32</u>	<u>33</u>	<u>18</u>	<u>37</u>	<u>38</u>
	<u>31</u>	<u>32</u>	<u>33</u>	<u>18</u>	<u>37</u>	<u>38</u>
$\text{C}=\text{O}$	212.5	211.7	249.5	209.5	205.1	204.6
$\alpha\text{-C}$	51.6	47.4	83.3	80.4	50.1	46.2

A trend was noted for the alpha carbon, however (Figure 22). It can be seen that in each related pair of molecules, the alpha

carbon of the compound containing the olefin resonates at a higher field than the alpha carbon of the saturated compound. Six-membered cyclic olefins are known to exist in a twisted half-chair.⁵³ Given this half-chair conformation, it is quite possible that the alpha carbon is positioned within the shielding cone of the olefinic bond which would account for the slight upfield shift of the alpha carbon in these unsaturated compounds.

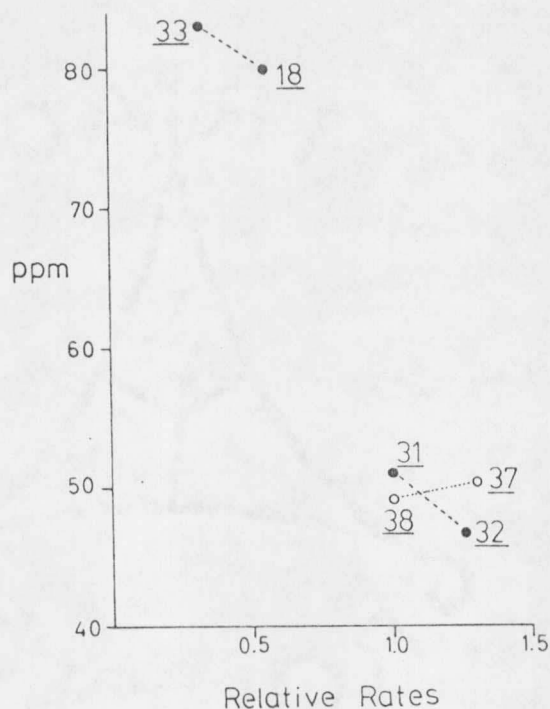


Figure 22. Chemical Shift Correlations for the Alpha Carbons

Compounds 37 and 38, purchased from Aldrich Chemical Co., were also included to determine if aldehydes and ketones reacted in a similar manner. A reverse trend was observed for these aldehydes. More aldehydes need to be run to establish a definite trend.

Having ruled out the supra-annular effect as a controlling factor in determining exo/endo ratios, we next considered the possibility of metal ion complexation during the reduction step. We reasoned that, in the NaBH_4 reduction of 16, the sodium ion might be capable of forming a complex between the oxygen in the pyran ring and the carbonyl oxygen in the propionyl group. This type of complexation might fix the propionyl group in the axial conformation. An in-coming nucleophile, i.e. a hydride, would then see two stereotopically different sides of the planar carbonyl and result in stereoselectivity in the reduced products in accordance with Cram's Rule.⁵⁴

Metal complexation is well known for its effects on the stereoselectivity of enolate formation⁵⁵ and we considered the possibility that complexation might be controlling the stereoselectivity of our NaBH_4 reduction in a similar manner. The idea of sodium ion complexation is supported in a recent paper by Glass⁵⁶ in which it was noticed that complexation occurred in the NaBH_4 reduction of α -alkoxy- β -keto esters (Figure 23). He

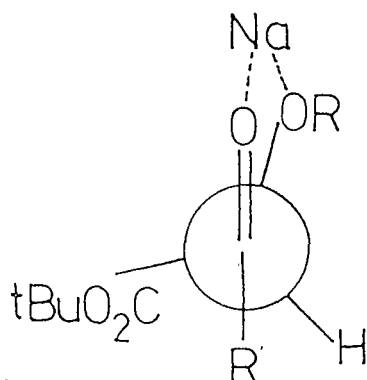


Figure 23. Sodium Ion Complexation of α -Alkoxy- β -keto Esters

reported that the addition of 15-crown-5 ether, which chelates sodium ions, removes any stereoselectivity due to cation complexation; a diastereomeric 7:1 ratio was reduced to a 1:1 ratio.

Cation complexation was also noted by Pierre⁵⁷ during the NaBH_4 and LiAlH_4 reductions of N-tert-butyl 2-acetyl aziridine (Figure 24). Diastereomeric ratios as high as 98:2 were obtained from a postulated Na or Li chelate. Here, too, stereoselectivity was eliminated by the addition of crown ethers.

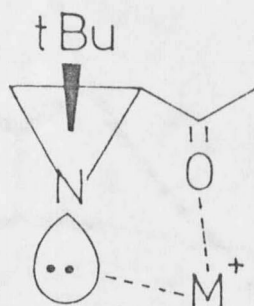
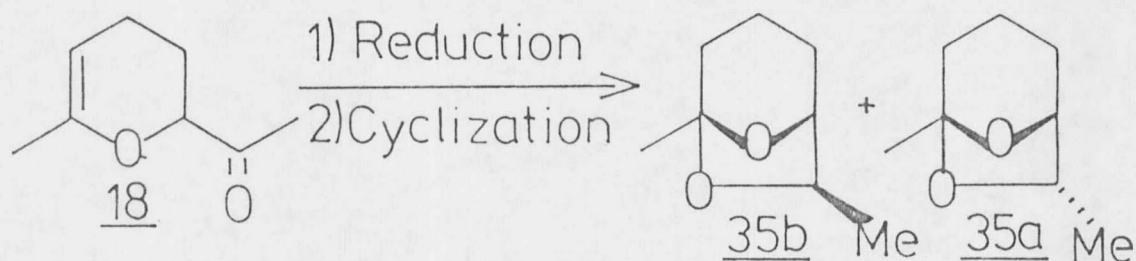


Figure 24. Metal Ion Chelation of N-tert-Butyl-2-acetyl Aziridine

In light of these reports, reduction of **18** was attempted with several hydride reducing agents containing different cations. The relative amounts of products were determined by the integration of the respective GLC chromatograms.

As shown in Table 6, a small trend paralleling the reactivity of these reagents was noticed. The differences are too small, however, to be a major factor in controlling the stereoselectivity of these reactions.

Table 6. Reduction and Cyclization of 2-Acetyl-6-methyl-3,4-dihydro-2H-pyran with Various Reducing Agents



<u>Reducing Agent</u>	<u>Percent Yield</u>	
L-Selectride	80	20
LiBH ₄	60	40
NaBH ₄	57	43
KBH ₄	49	51
LiAlH ₄	51	49

As a final check, these same reductions were performed on compound **16** to determine any effects in the actual brevicomin synthesis. Compound **16** was synthesized (Figure 25) via the methyl iodide alkylation of the pyrrolidino enamine obtained from methyl

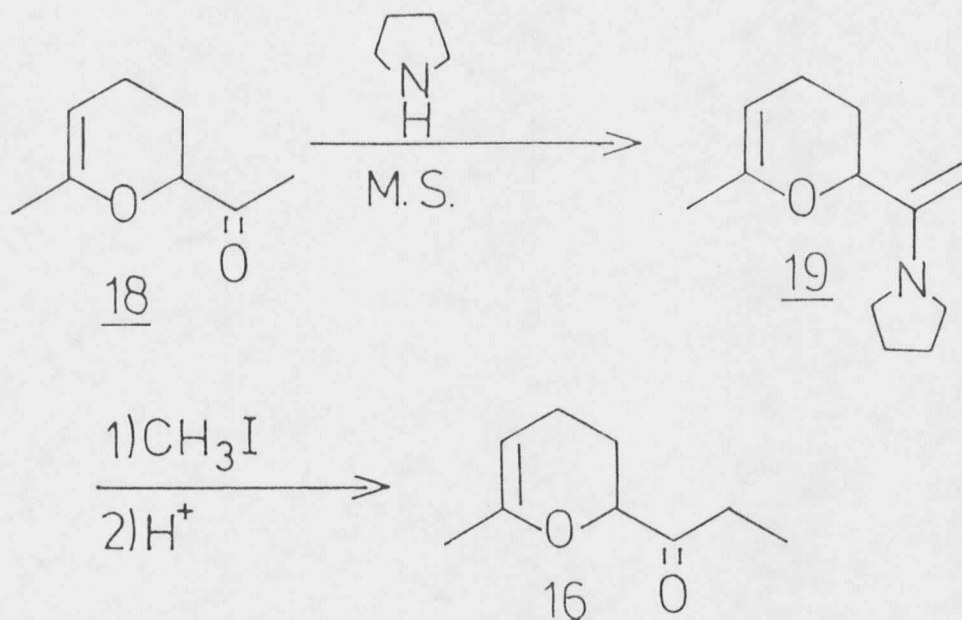
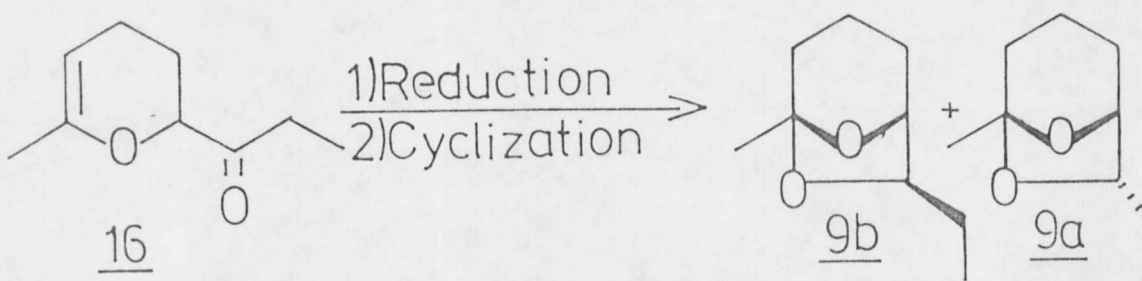


Figure 25. Synthesis of 2-Propionyl-6-methyl-3,4-dihydro-2H-pyran vinyl ketone dimer (**18**).²³ The pyrrolidine and dimer were placed in anhydrous ether and allowed to react while standing over 3 Å molecular sieves. The crude enamine **19** was then directly alkylated with methyl iodide. Hydrolysis yielded a 60:40 mixture of unreacted dimer and the desired ethyl ketone. Separation was attempted by standard silica gel and Florisil chromatography, with minimal effectiveness. It was decided at this point to attempt the reduction of the mixture without separation. An excess of NaBH_4 was used and the ketals resulting from cyclization of the alcohols were easily separated and identified by GLC (20% SE-30).

The same trend as observed for 18, paralleling reagent reactivity, was noticed (Table 7). The KBH_4 results appeared to be out of sequence. This reduction was repeated with the same result. At the present time there is no apparent explanation for this anomaly.

Table 7. Reduction of 2-Propionyl-6-methyl-3,4-dihydro-2H-pyran with Various Reducing Agents



<u>Reducing Agent</u>	<u>Percent Yield</u>	
LiBH_4	65	35
NaBH_4	55	45
KBH_4	65	35
LiAlH_4	51	49

Metal complexation has also been reported for the magnesium ion in Grignard reactions. Colonge has shown that size of the nucleophile and magnesium ion complexation play an important role in

product formation on the reaction of various Grignard reagents with acrolein dimer⁵⁸ (Figures 26 and 27). Colonge postulated that

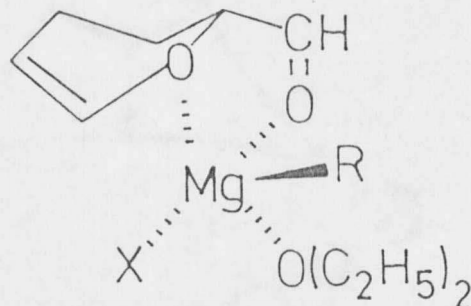


Figure 26. Magnesium Ion Complexation with Acrolein Dimer

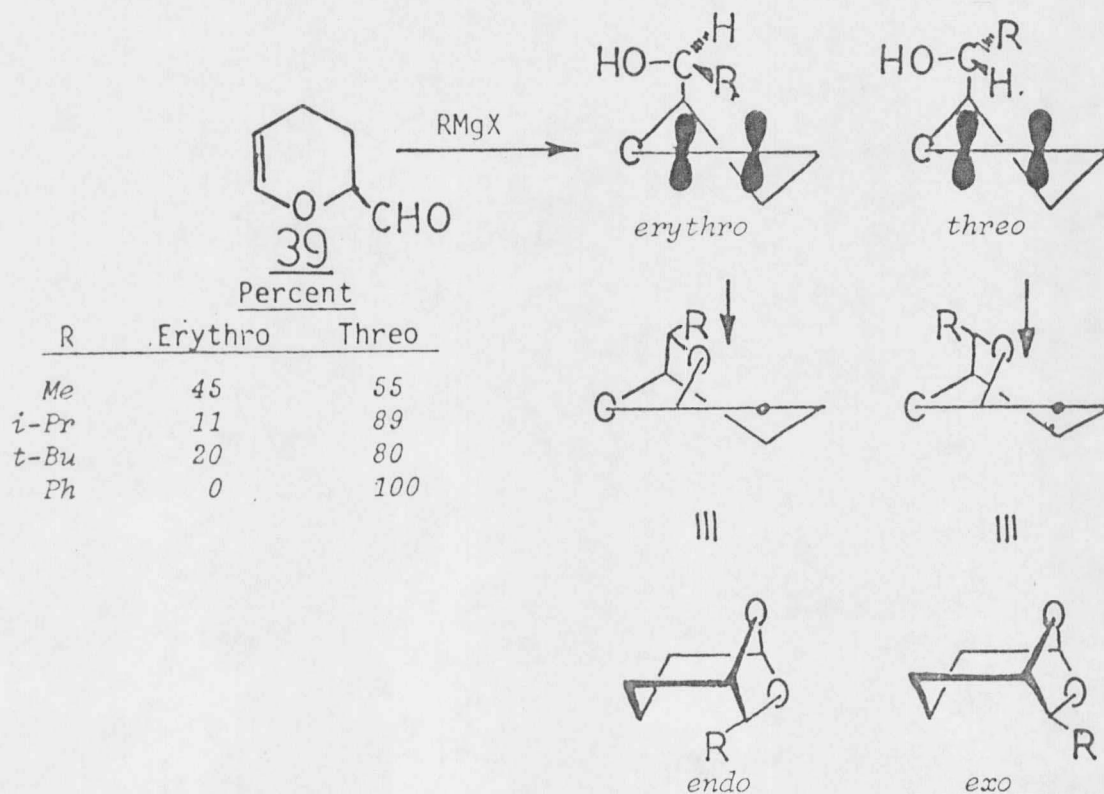


Figure 27. Reaction of Acrolein Dimer with Various Grignard Reagents

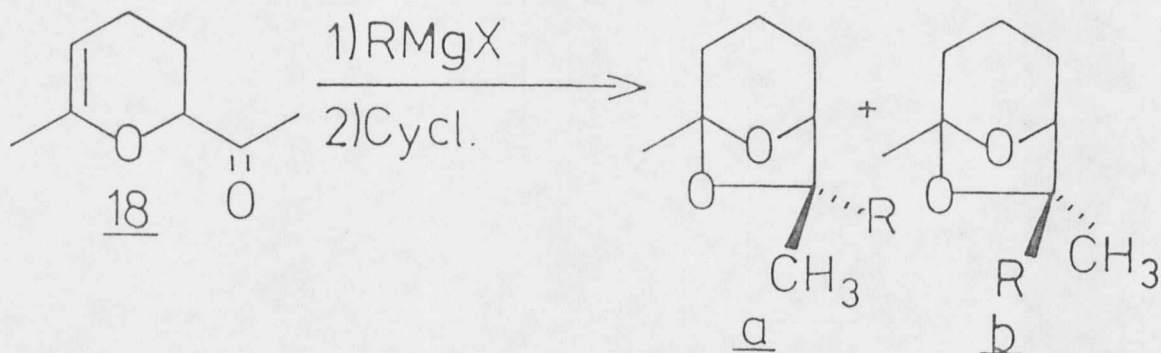
because of the magnesium ion complexation, the Grignard reagent was delivered stereoselectively to give predominantly the threo isomer which subsequently cyclized to the exo bicyclic ketal.

Because the original Mundy brevicomin synthesis utilized a Grignard reaction,²² a study analogous to that of Colonge was undertaken using methyl vinyl ketone dimer 18 as the substrate. Dimer 18 was reacted with methyl, ethyl, phenyl, isopropyl, and tert-butyl magnesium bromides. The resultant alcohols were cyclized by stirring in dry benzene with a trace amount of p-toluene sulfonic acid. The relative amounts of bicyclic ketals were determined by GLC and are given in Table 8.

The results for this system are parallel to those found in the acrolein dimer series (Figure 27). The only notable exception is the case of the phenyl magnesium bromide. It would appear that the same type of complexing is occurring with 18 as occurred in the acrolein dimer (39).

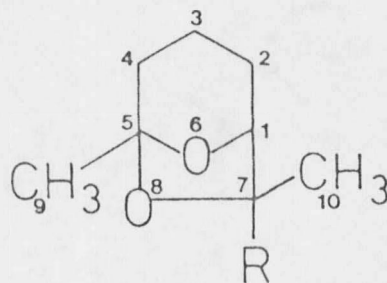
Having synthesized ketals 31 - 34, ¹³C NMR spectra were taken of both endo and exo ketals from the Grignard reactions to see if predictive correlations could be obtained for the ring carbons. Chemical shift data for these ketals are shown in Table 9.

Table 8. Reaction of 2-Acetyl-6-methyl-3,4-dihydro-2H-pyran with Several Grignard Reagents

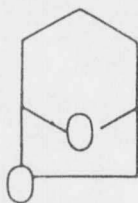


R	Percent Yield	
(40) Methyl	--	--
(41) Ethyl	*	*
(42) i-Propyl	89	11
(43) tert-Butyl	84	16
(44) ϕ	75	25

*unable to separate exo/endo isomers by GLC

Table 9. ^{13}C Chemical Shift Data for Endo and Exo Bicyclic Ketals

R	C ₁	C ₂	C ₃	C ₄	C ₅	C ₇	C ₉	C ₁₀	
H- <u>exo</u>	75.5	23.6	17.3	34.2	107.1	77.4	24.9	13.7	<u>35a</u>
H- <u>endo</u>	75.8	25.3	17.1	27.7	108.0	80.1	34.9	21.9	<u>35b</u>
CH ₃	81.3	24.3	17.2	34.3	107.4	80.9	29.3	25.9	<u>40</u>
i-Pr- <u>exo</u>	80.9	23.7	17.8	34.3	107.3	86.7	30.5	25.9	<u>42b</u>
i-Pr- <u>endo</u>	78.4	24.3	17.4	34.2	107.2	86.1	25.8	19.2	<u>42a</u>
- <u>exo</u>	82.1	25.0	16.2	34.8	108.3	85.6	32.0	25.9	<u>44b</u>
- <u>endo</u>	82.6	24.7	17.4	35.5	108.4	84.9	23.6	25.2	<u>44a</u>
t-bu- <u>exo</u>	77.1	25.2	17.4	34.5	107.4	87.4	24.6	17.0	<u>43b</u>
t-bu- <u>endo</u>	—	—	—	—	—	—	—	—	



73.8 29.1 15.7 31.6 102.3 68.4 — — 1

The relative endo vs. exo position of an alkyl substituent at C-7 has only a small effect on the chemical shift of the ring carbons. It is possible, however, to assign general chemical shift regions for the ring carbons as shown in Figure 28 (page 63). The general regions may have some predictive value for these bicyclic ketal systems.

It is also possible to qualitatively predict dihedral bond angles (ϕ) (Figure 29) and ring conformations by using proton-

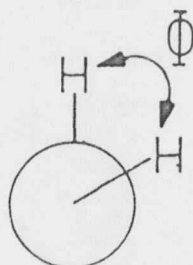


Figure 29. Dihedral Angle (ϕ)

proton coupling constants and the Karplus equation (Equation 22).⁵⁹

$$J_{HH} = J^{\circ} \cos \phi - .28$$

Equation 22

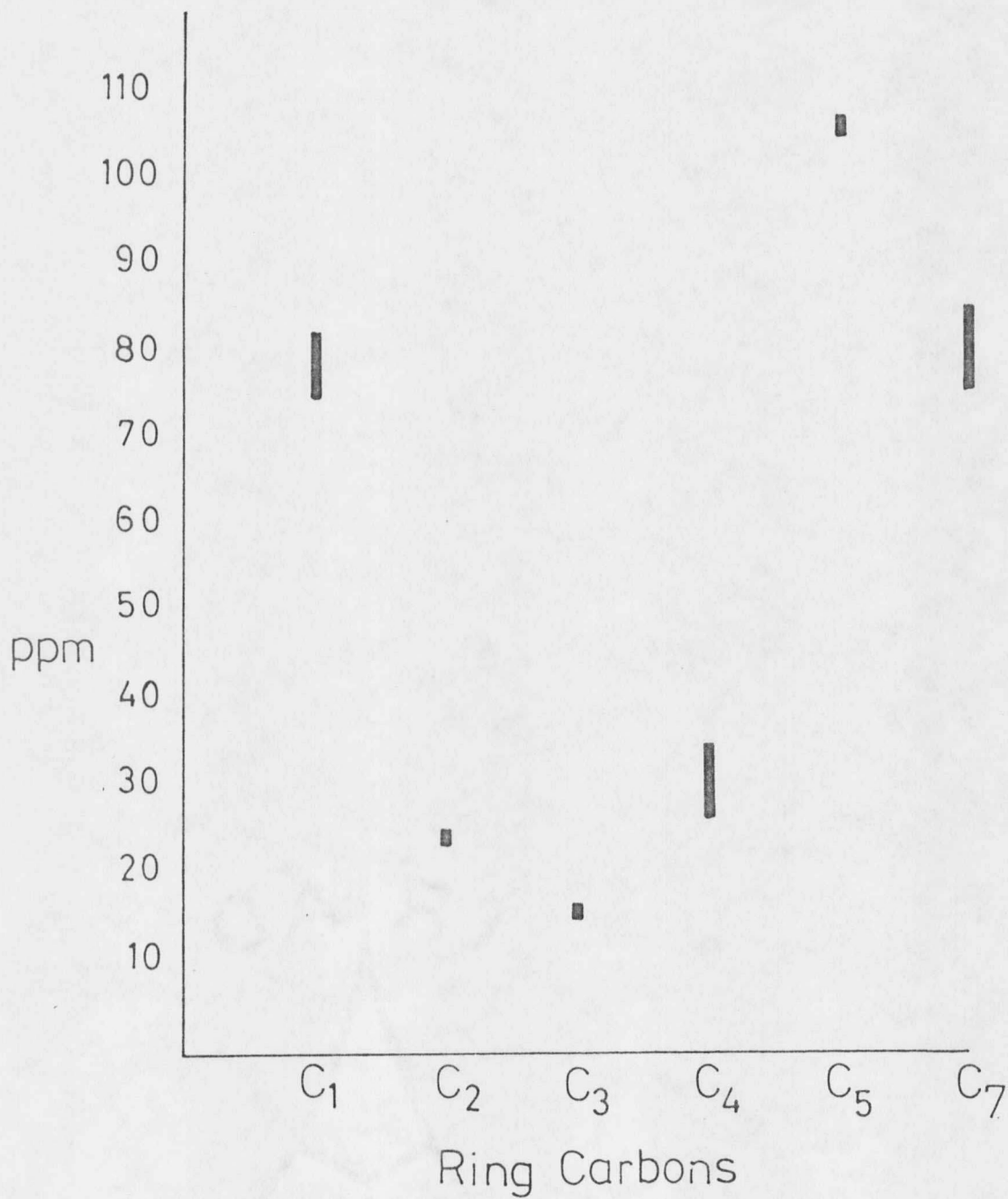
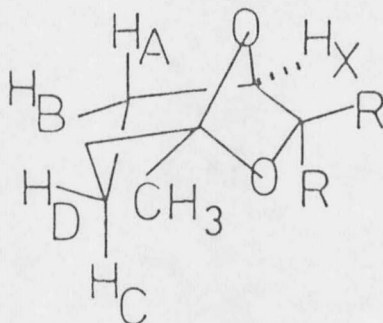


Figure 28. General Chemical Shift Regions

Proton NMR spectra were taken of the available bicyclic ketals and the coupling constants measured (Table 10). In some spectra the determination of coupling constants was not possible due to overlap with other proton resonances.

Table 10. Proton-Proton Coupling Constants for Endo and Exo 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octanes

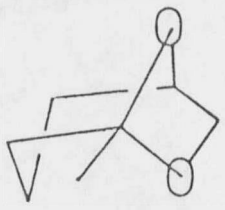
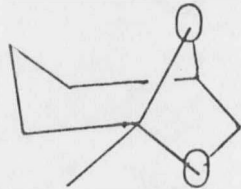


	J_{AB}	J_{AX}	J_{BX}	J_{AC}	J_{AB}	J_{BC}	J_{BD}
<u>35b</u>	11.9	3.0	3.3	4.6	—	—	4.62
<u>35a</u>	12.6	4.0	—	5.9	1.3	—	—
<u>40a</u>	14.0	4.0	—	5.9	—	—	—
<u>42b</u>	13.9	4.0	2.0	5.9	—	—	—
<u>44b</u>	14.2	3.8	—	5.9	—	—	—

A Dreiding model of the 6,8-dioxabicyclo[3.2.1]octane skeleton was constructed and the dihedral angles between protons $H_A - H_X$ and $H_A - H_C$ were measured (Table 11). Dihedral angles were then

calculated from the measured coupling constants and compared to the values obtained from the model measurements. From a comparison of these two sets of data, a determination can be made as to whether the six-membered ring portion of the bicyclic system exists in a chair or in a boat conformation and approximate bond angles can be calculated.

Table 11. Measured Dihedral Angles for Chair and Boat Conformations of 6,8-dioxabicyclo[3.2.1]octanes

	$J_{HA} - J_{HX}$	$J_{HA} - J_{HC}$
	55°	120°
	10°	75°

Karplus, in his original paper,⁵⁹⁷ suggested the use of $J^\circ = 8.5$ for $0^\circ \leq \phi \leq 90^\circ$ and $J^\circ = 9.5$ for $90^\circ \leq \phi \leq 180^\circ$. Modified J° values have been suggested for use with carbohydrates⁶⁰ in an attempt to minimize error due to the electronegativity of the oxygen atom, different bond lengths, etc. The suggested values are $J^\circ = 9.3$ for $0^\circ \leq \phi \leq 90^\circ$ and $J^\circ = 10.4$ for $0^\circ \leq \phi \leq 180^\circ$. Both sets of J°

values were used and the dihedral angles calculated for compounds 35b and 35a (Table 12).

Table 12. Calculated Dihedral Angles for Endo and Exo 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octanes

	$J_{H_A-H_X}$	$J_{H_A-H_C}$	$J_{H_A-H_X}$	$J_{H_A-H_C}$
$J^\circ = 8.5, 9.5$	52°	136°	45°	144°
$J^\circ = 9.3, 10.4$	54°	133°	47°	140°

35b

35a

It is immediately obvious from a comparison of the calculated angles (Table 12) and the measured angles (Table 11) that the six-membered ring has adopted the chair conformation. Furthermore, compound 35a in which the methyl group is endo to the ring system, shows a decreased dihedral angle between protons $H_A - H_X$. This result agrees with current concepts of steric bulk. An endo methyl would cause C-3 to swing up resulting in a slightly flattened chair conformation (Figure 30). This movement results in a decrease in the dihedral angle between H_A and H_X (Figure 31).

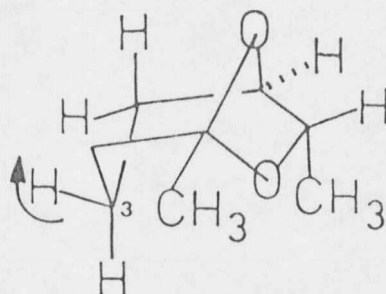


Figure 30. Deformation of the Chair Conformation

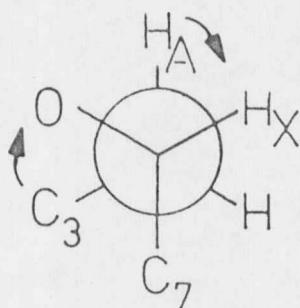


Figure 31. Decrease in H_A-H_X Dihedral Angle

While these results are qualitative, they are in agreement with conformational theory and give some indication of ring deformations.

During the course of the supra-annular investigation, it was noticed that the alcohols resulting from hydride reduction cyclized spontaneously over a period of time. It was recognized that the overall exo/endo ratio may be affected by the different rates of

cyclization for the two isomeric alcohols derived from the reduction step (Figure 32). An analysis of the relative rates of cyclization for the alcohols **34a** and **34b** was undertaken to investigate this possible effect.

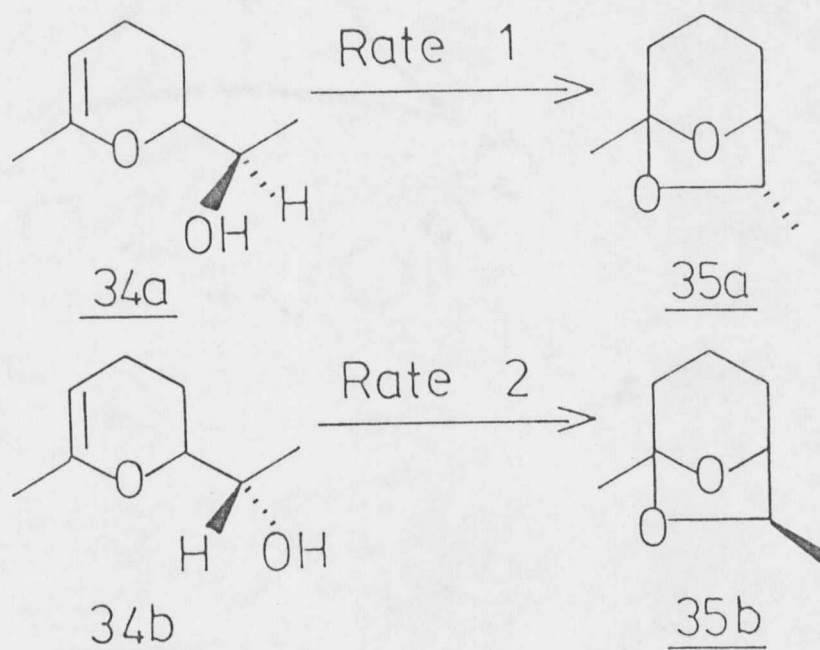


Figure 32. Cyclization of Isomeric Alcohols

Mixtures of isomeric alcohols were synthesized by the NaBH_4 reduction of **18**. These alcohols were allowed to spontaneously cyclize over a period of sixty hours. The progress of the cyclization was followed by GLC. After normalizing the integrated peak areas, the decrease in alcohol was plotted vs. time. This

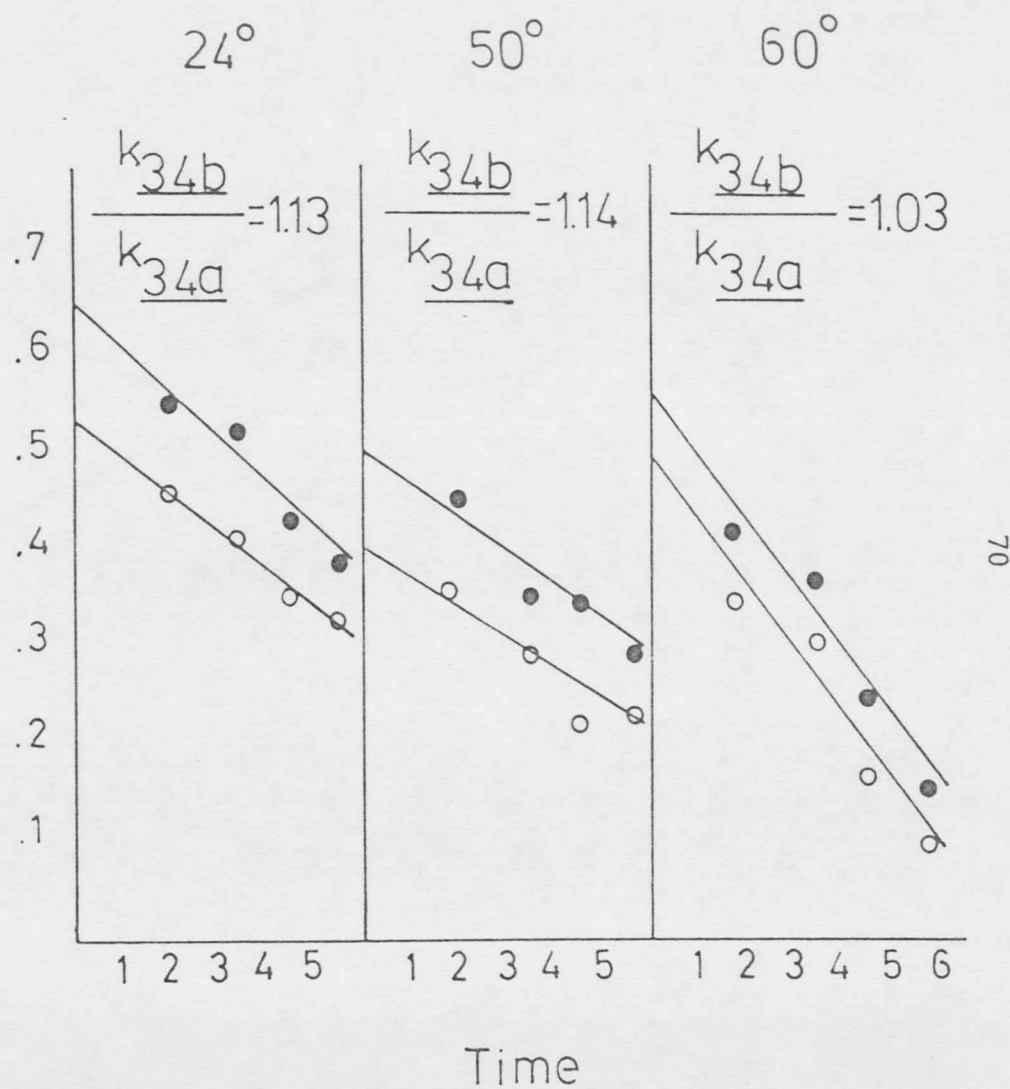
experiment was performed at three temperatures; 25°C, 50°C and 60°C. The change in relative rates of cyclization for the two alcohols is within the range of experimental error and is essentially negligible even over a range of 36°C. The different rates of cyclization for the threo and erythro alcohols appears not to be a major factor in the overall endo/exo product ratio (Figure 33).

Having determined that neither the supra-annular effect nor metal ion complexation were important factors in controlling the stereochemical outcome of the brevicomin syntheses developed by our research group, we decided to explore the use of a double oxymercuration-demercuration reaction sequence in the synthesis of pheromones possessing a bicyclic ketal structure. To determine the range and scope of the double oxymercuration reaction in these systems, some model compounds were first studied.

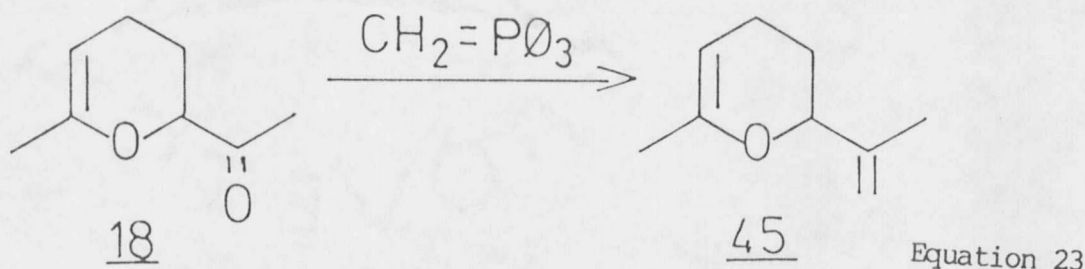
Figure 33. Relative Rates of Cyclization

$$\frac{\%alc}{\%alc + \%ketal}$$

○ = 34a
● = 34b



Compound **45** was synthesized from methyl vinyl ketone dimer (**18**) via a Wittig reaction as shown in Equation 23. The Wittig reagent



was made by reacting methyl triphenylphosphonium bromide with tert-butyllithium. Ketone **18** was then added slowly and stirred overnight to give **45** in 91% yield. Diene **45** was identified by the presence of a molecular ion at $m/e = 138$ in its mass spectrum and by the proton NMR spectrum which showed two broad singlets at $\delta 4.83$ and $\delta 4.72$ for the protons on the terminal olefin, a broad singlet at $\delta 4.31$ for the proton on C_4 , and two methyl singlets at $\delta 1.71$ and $\delta 1.69$. Infrared analysis confirmed the enol ether by an absorption at 1680 cm^{-1} .

It was postulated that **45** might undergo double oxymercuration-demercuration to yield **40** as shown in Figure 34. The oxymercuration should proceed in a Markovnikov manner to give 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane **40**. It has been shown in several cases that attack by an internal nucleophile can compete favorably with an external nucleophile.^{22,37-44}

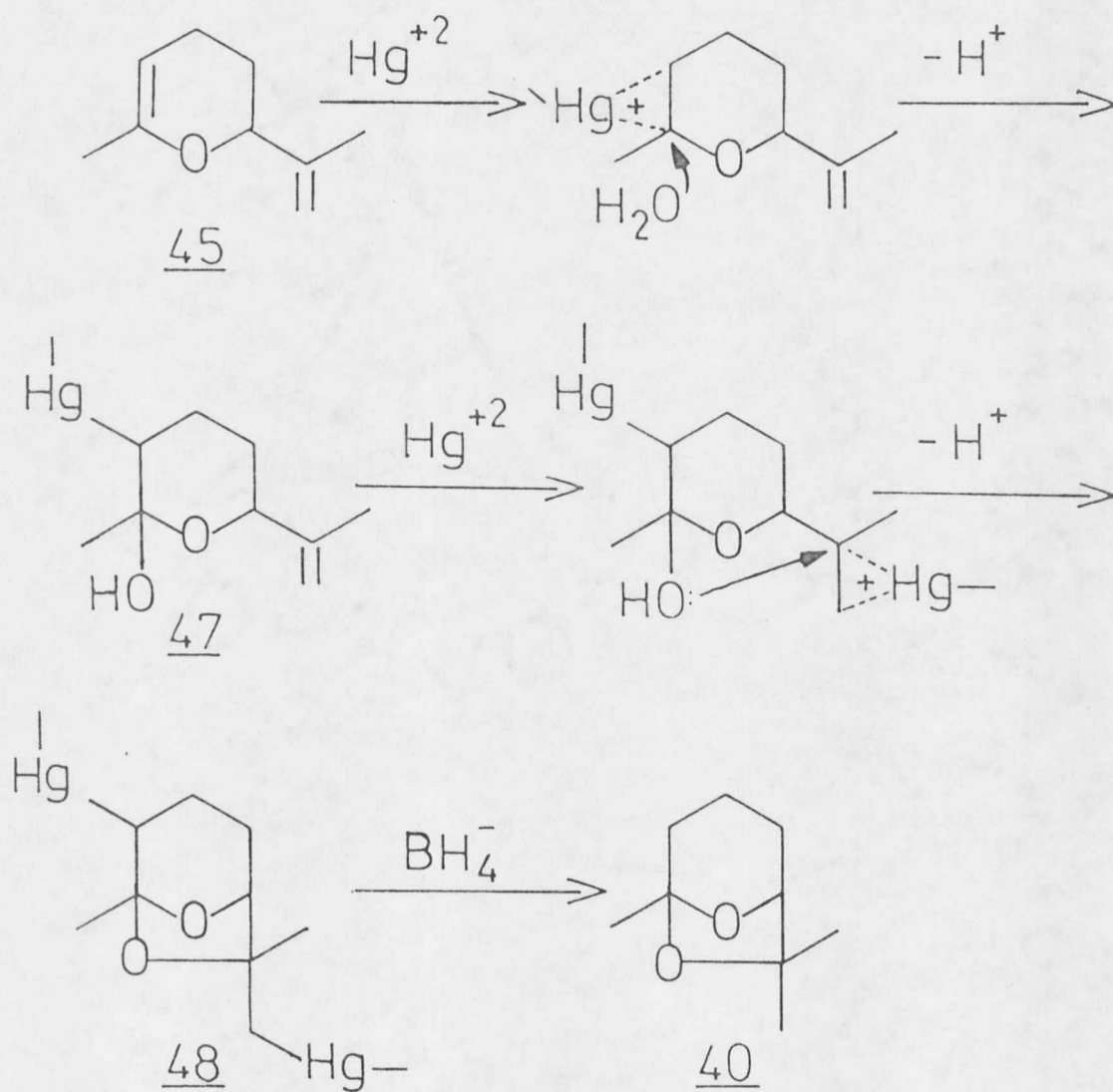
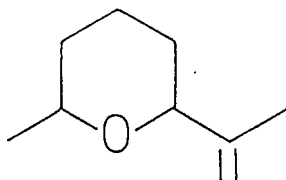


Figure 34. Double Oxymercuration-Demercuration Cyclization Mechanism

The double oxymercuration-demercuration was performed by reacting 45 with two equivalents of mercuric acetate in THF/water. GLC analysis revealed one major product peak, which was shown to be an alcohol by its infrared spectrum and presumed to be alcohol 47. The crude reaction mixture was then placed in dry benzene with a trace of p-toluene sulfonic acid and stirred overnight. By GLC examination, three new products appeared at short retention times and were identified as starting material (45), the expected bicyclic ketal (40), and compound 46.



46

Proton NMR of 42 revealed the presence of a vinyl methyl at δ 1.85, a methyl doublet at δ 1.32, and the appearance of a one-proton multiplet at δ 3.95, as well as two broad singlets for the terminal olefin.

Bicyclic ketal 40 was identified, in part, by GLC coinjection with 40 synthesized by the reaction sequence shown in Figure 35.

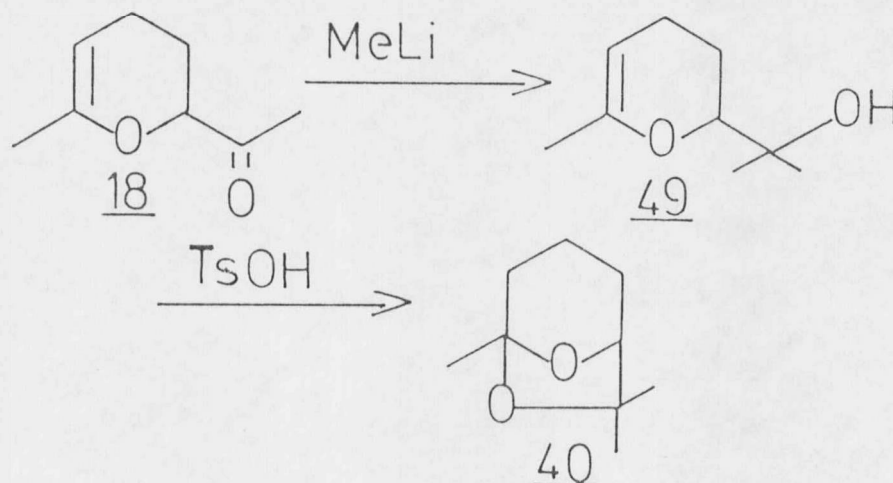


Figure 35. Synthesis of 5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane

The presence of water droplets in the reaction with p-toluene sulfonic acid suggested that 46 might have been formed from a dehydration reaction. The reduction of bicyclic ketal 40 with NaBH_4 followed by a dehydration was considered as a possible mechanism (Figure 36).

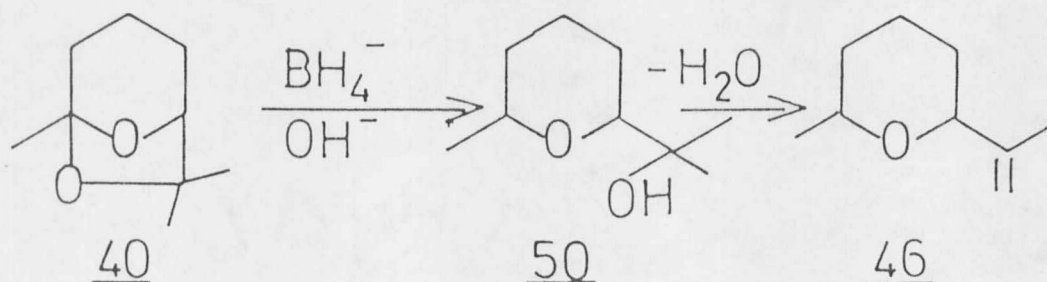
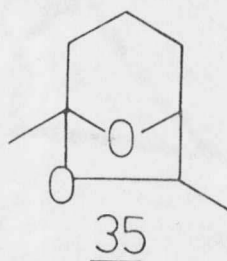


Figure 36. Possible Dehydration Mechanism

While NaBH_4 is not known to reduce ketals, it was decided to check this possibility by placing the readily available ketal 35 under the same reaction conditions.



Ketal 35 was synthesized by a NaBH_4 reduction of ketone 18 followed by spontaneous cyclization in the acid workup. GLC analysis indicated the presence of both *endo* and *exo* isomers (Figure 37).

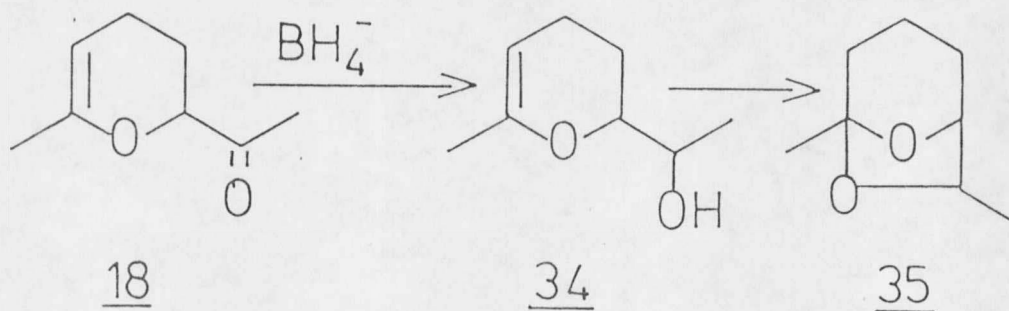
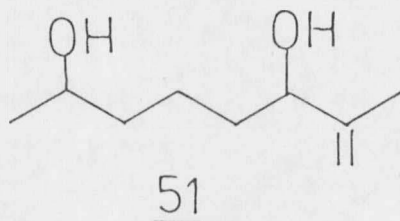


Figure 37. Synthesis of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

Compound 35 was placed in a 3 M NaOH, 0.5 M NaBH₄ solution and stirred overnight. GLC analysis revealed only the starting material present.

At this time the original alcohol we had presumed to be 47 was reisolated and shown to be a diol with structure 51. Compound 51



exhibited a mass spectral pattern typical of alcohols; a small molecular ion at $m/e = 158$ and peaks at $m/e = 140$ ($M - H_2O$) and $m/e = 125$ ($M - H_2O - CH_3$). Also seen were peaks at $m/e = 71$ and 45 , corresponding to fragmentation alpha to the hydroxyl groups. Other spectral data included a strong -OH absorption in the infrared spectrum and a 1H NMR consistent with an open chain structure (see Experimental).

A ring opening of this type might be plausible given the basic conditions of the demercuration reaction. A possible mechanism for the formation of 51 is shown in Figure 38.

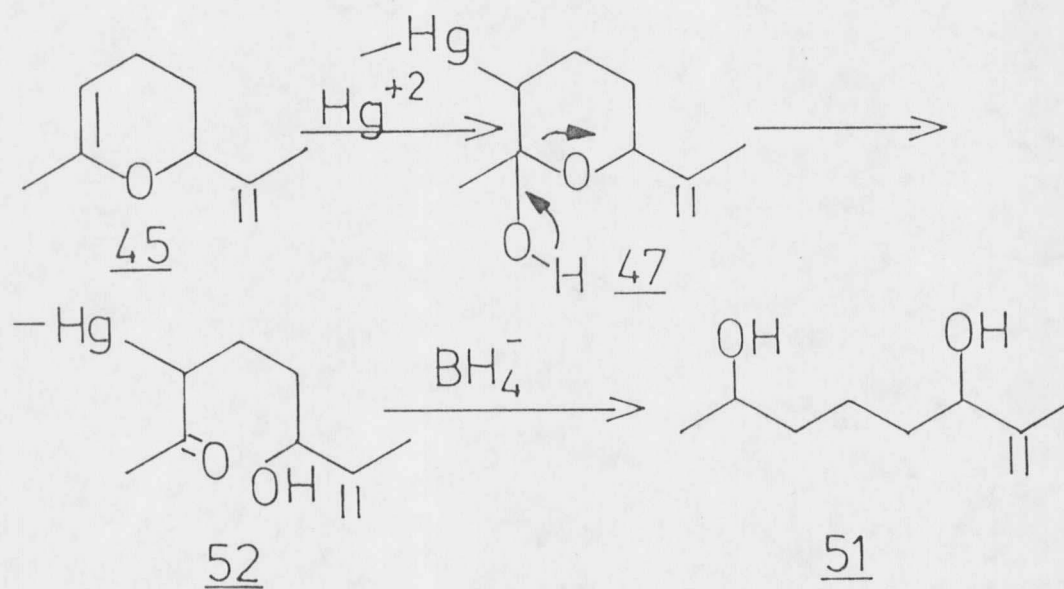


Figure 38. Proposed Mechanism for the Formation of 3,7-Dihydroxy-2-methyl-1-octene

In the presence of acid, diol **51** could recyclize with the loss of a molecule of water to yield **46** as shown in Figure 39.

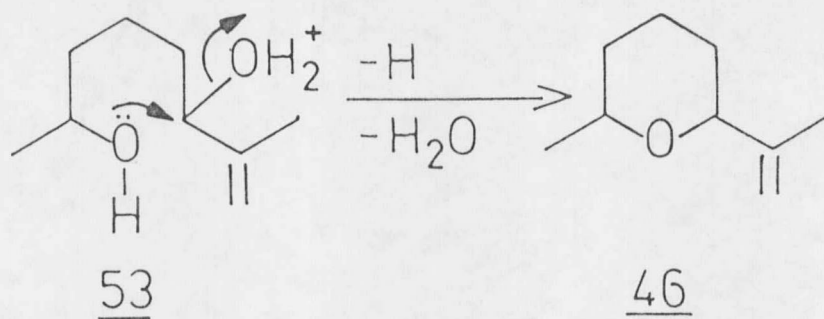


Figure 39. Proposed Cyclization of 3,7-Dihydroxy-2-methyl-1-octene

Figure 40 summarizes these chemical transformations. Compounds 54 and 55, although never isolated, might be present in small amounts and would produce starting diene 45 or 40 upon loss of water.

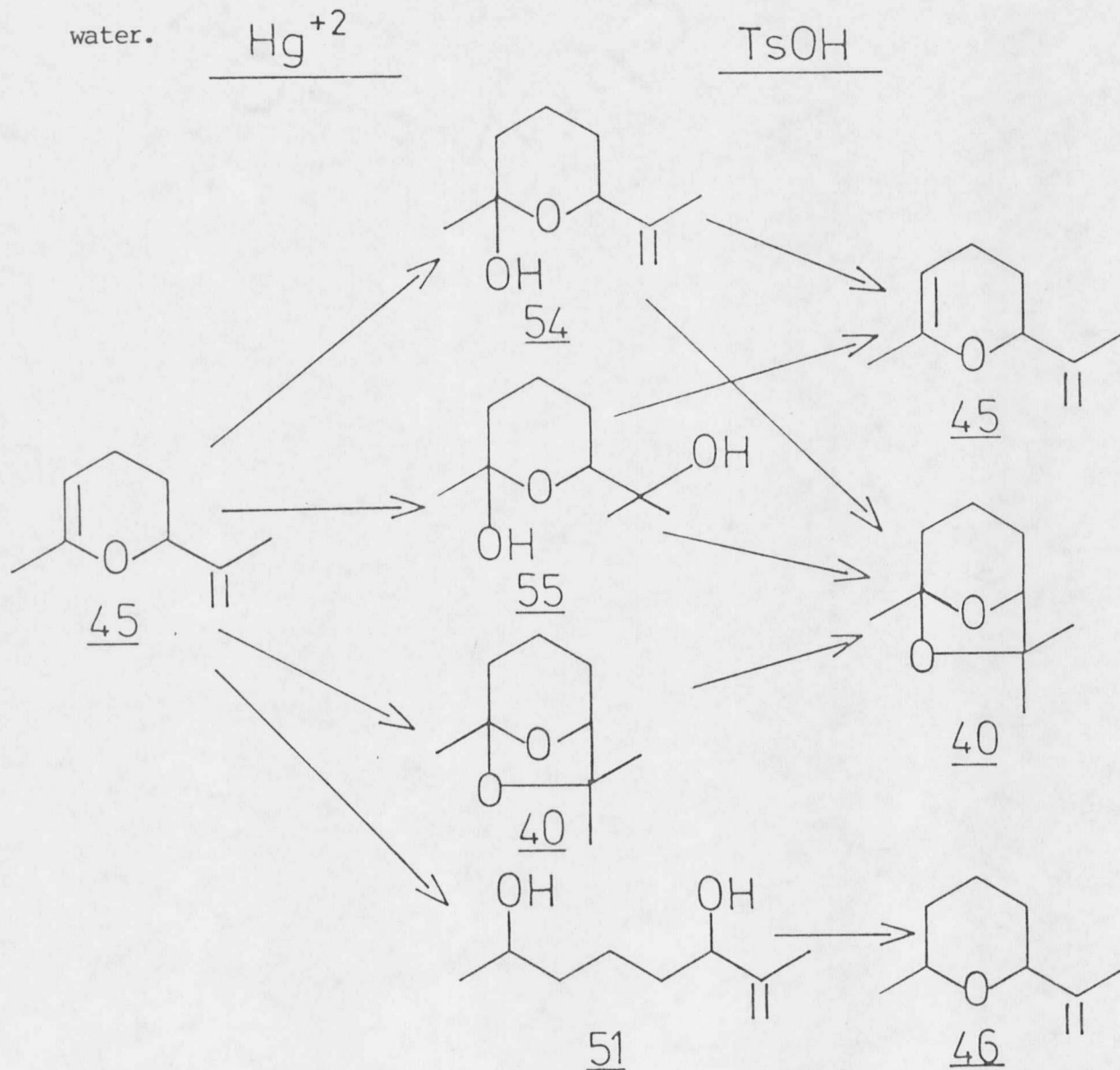


Figure 40. Summary of Reactions

It is interesting to note that the first mercurinium ion formed, and the most stable one, will occur on the enol ether because of the resonance stabilization available from the oxygen atom. There are, however, two isomeric mercurinium ions possible (Figure 41).

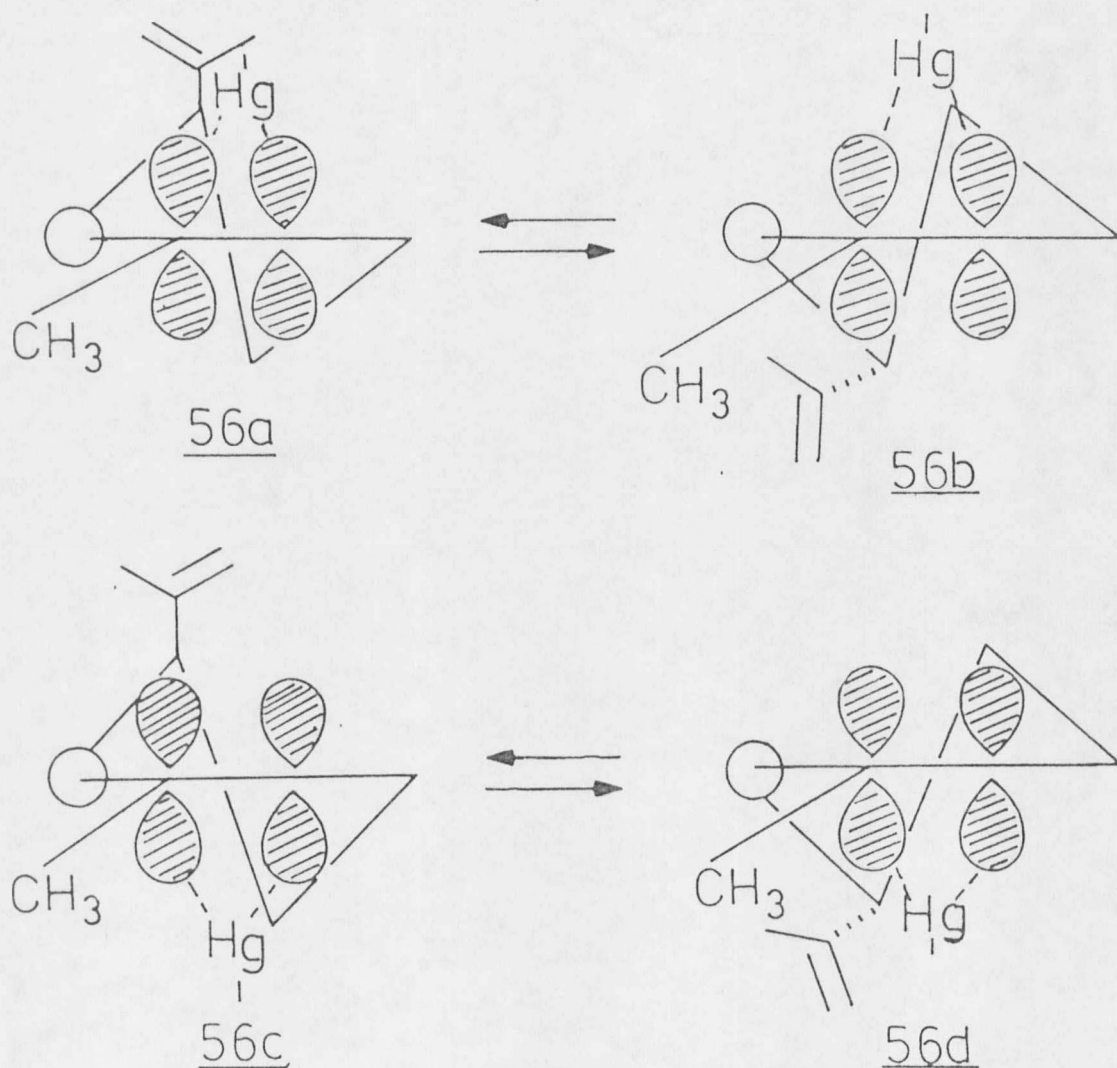
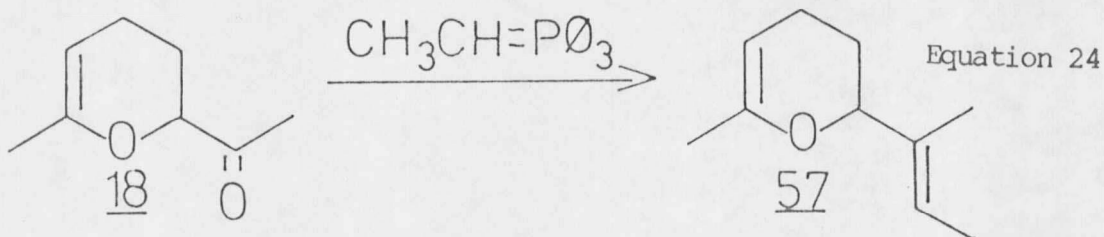


Figure 41. Isomeric Mercurinium Ions

If a water molecule attacks anti to the mercurinium ion and attacks the carbon alpha to the oxygen atom, only conformations 56c and 56d will result in cyclization to a ketal. Hence, there is a fifty percent chance that the alcohol formed will not be capable of cyclizing. It is possible that alcohols formed from conformations 56a and 56b could give rise to starting diene through dehydration and to pyran 46 through ring opening and recyclization.

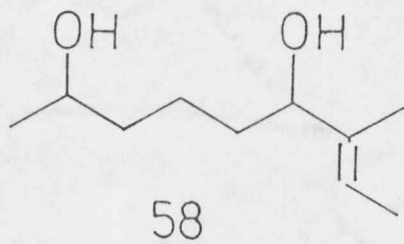
The oxymercuration-demercuration of diene 57 was attempted next. It was synthesized by a Wittig reaction on ketone 18 as shown in Equation 24. Ethyl triphenylphosphonium bromide was prepared by



reacting ethyl bromide and triphenylphosphine for 24 hours at 135°C in a pressure bomb. After recrystallization from water, the Wittig salt was reacted with methyllithium to produce the active Wittig reagent. Dimer 18 was then added slowly to give a 95% yield of 57 by GLC.

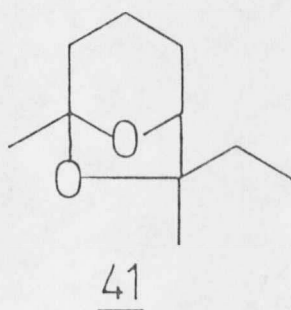
A mass spectrum of 57 showed a molecular ion at $m/e = 152$ (18% of base peak) and the enol ether was again confirmed by an infrared absorption at 1680 cm^{-1} . Proton NMR indicated the presence of three vinyl methyl groups.

Oxymercuration-demercuration of 57 produced an alcohol which was identified as compound 58 and several minor uncharacterized products.

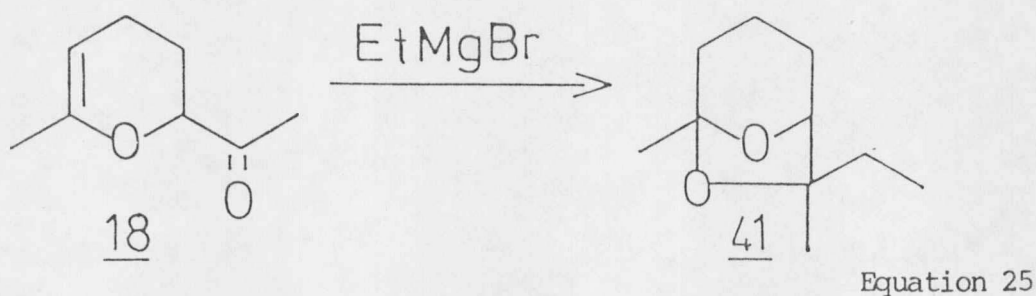


Compound 58 was characterized by the presence of a molecular ion at $m/e = 172$ and major fragmentation ions at $m/e = 154$ ($M - H_2O$), 139 ($M - H_2O - CH_3$), 85, 69, 55, and 45. Proton NMR confirmed the presence of two vinyl methyl groups. A methyl doublet at $\delta 1.20$ was also seen for the protons on C_9 .

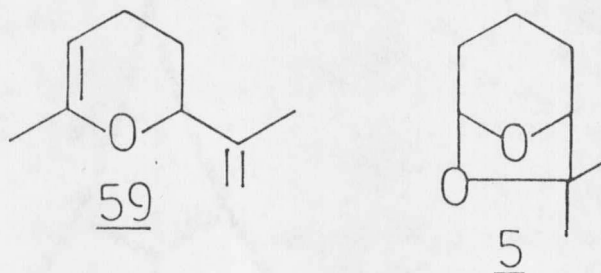
After stirring the crude mixture in benzene with *p*-toluene sulfonic acid, starting material (57) and compound 41 were isolated.



The identity of ketal 41 was established by coinjection with material obtained by unambiguous synthesis (Equation 25). These results are consistent with the data from the oxymercuration of 45.



The oxymercuration-demercuration of diene 59 was next investigated in an attempt to synthesize ketal 5, a constituent of Japanese hop oil made from *Humulus lupulus*.²



Diene 59 was synthesized by a series of reactions starting with acrolein dimer (39), as shown in Figure 42.

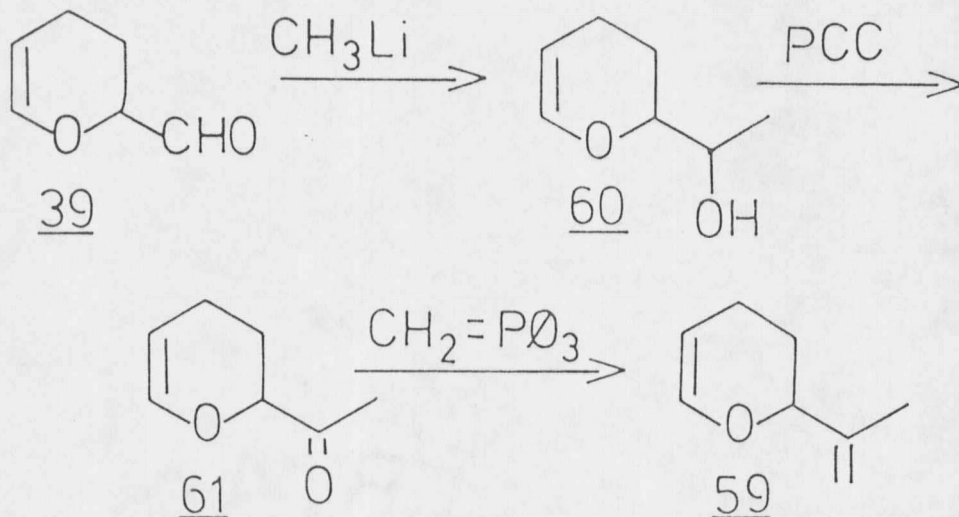


Figure 42. Synthesis of 2-Isopropenyl-3,4-dihydro-2H-pyran

Aldehyde **39** was reacted with methyllithium to give alcohol **60** in 93% purity. Alcohol **60** was then oxidized with pyridinium chlorochromate (PCC)⁶² to give **61** in 63% yield. Ketone **61** was reacted with the methylene Wittig reagent to produce diene **59** in 70% yield. The proton NMR spectrum of **59** showed the expected methyl singlet at $\delta 1.78$ and one-proton resonances at $\delta 5.01$ and $\delta 4.91$ for the terminal olefinic protons. Three additional resonances at $\delta 4.21$, $\delta 4.69$, and $\delta 6.43$ correspond to protons on C_2 , C_5 , and C_6 , respectively.

Oxidation of 60 was also attempted with Jones Reagent and pyridinium dichromate (PDC).⁶³ The presence of acid in the Jones reagent caused preferential cyclization of 60 to ketal 62 (Figure 43). PDC oxidation, while not acidic, gave 61 in lower yields.

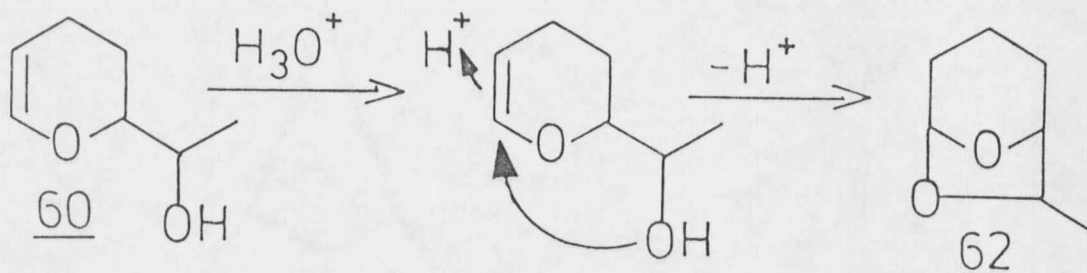
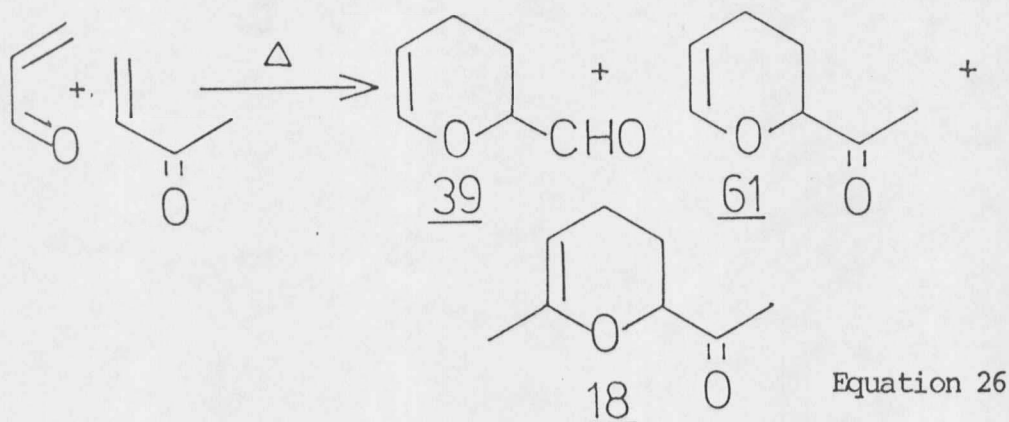


Figure 43. Cyclization by Jones Reagent

An alternative synthesis of 61 was also tried (Equation 26).



Equation 26

When equal amounts of acrolein and methyl vinyl ketone are mixed and heated in a bomb for two hours, 61 was produced in 60-65% yield.

Mundy has shown, however, that **20** is the product predicted by Frontier Molecular Orbital Theory.⁹ (See Appendix B.) Under the reaction conditions, compound **20** is unstable and undergoes a Claisen rearrangement to produce **61** (Figure 44).

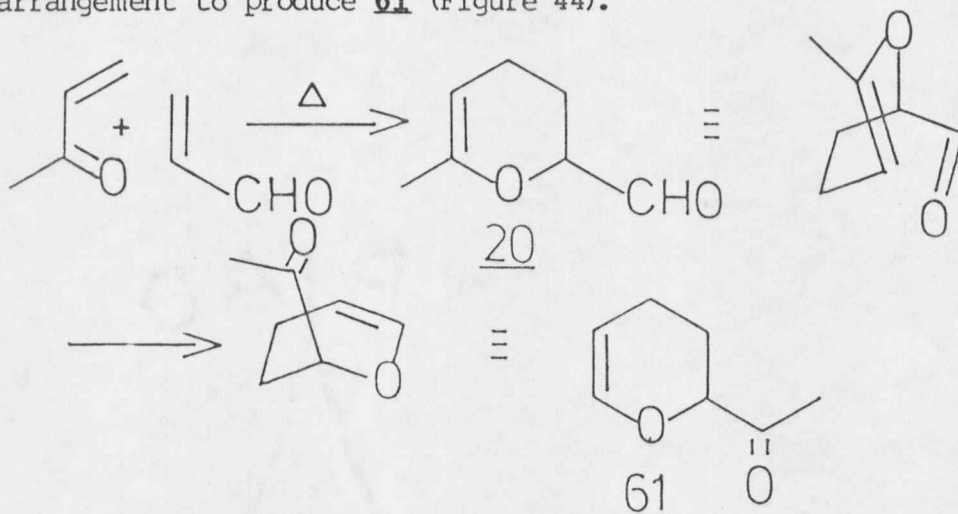


Figure 44. Claisen Rearrangement

Oxymercuration-demercuration of **59** followed by stirring in benzene/p-toluene sulfonic acid produced ketal **5** in 22% yield. The formation of this ketal by oxymercuration was confirmed by the independent synthesis of **5**, as shown in Figure 45.

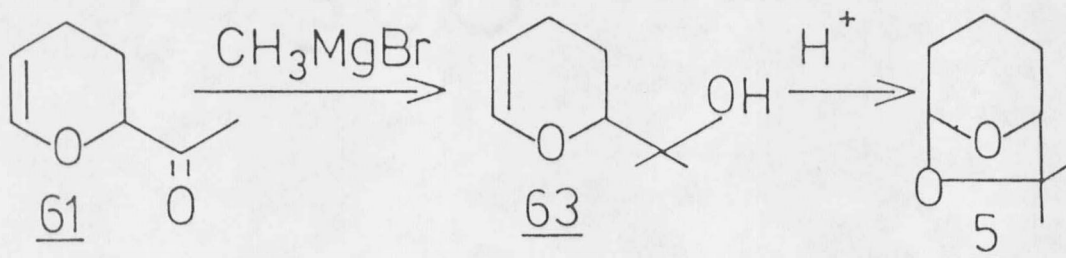


Figure 45. Synthesis of 7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

In the oxymercuration of 45, 57, and 59, Markovnikov addition to the mercurinium ion allows for an accurate prediction of the cyclized ketal products. These three compounds each contain a tertiary cationic mercurinium ion 64 into which an internal nucleophile might attack (Figure 46).

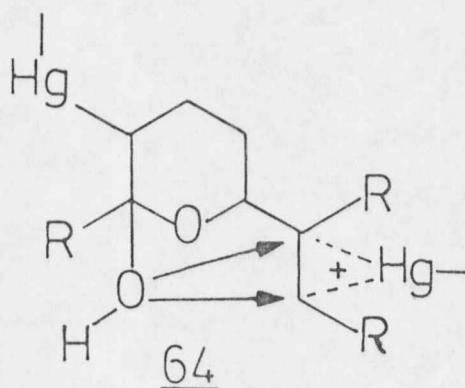


Figure 46. Tertiary Mercurinium Ions

The cyclization of diene 65 was attempted next to determine whether a five- or six-membered ring would form from the attack of a nucleophile on one of two secondary mercurinium ions (Figure 47). On the basis of entropy arguments, one would predict the preferential formation of the five-membered ring over the less probable formation of a six-membered ring.

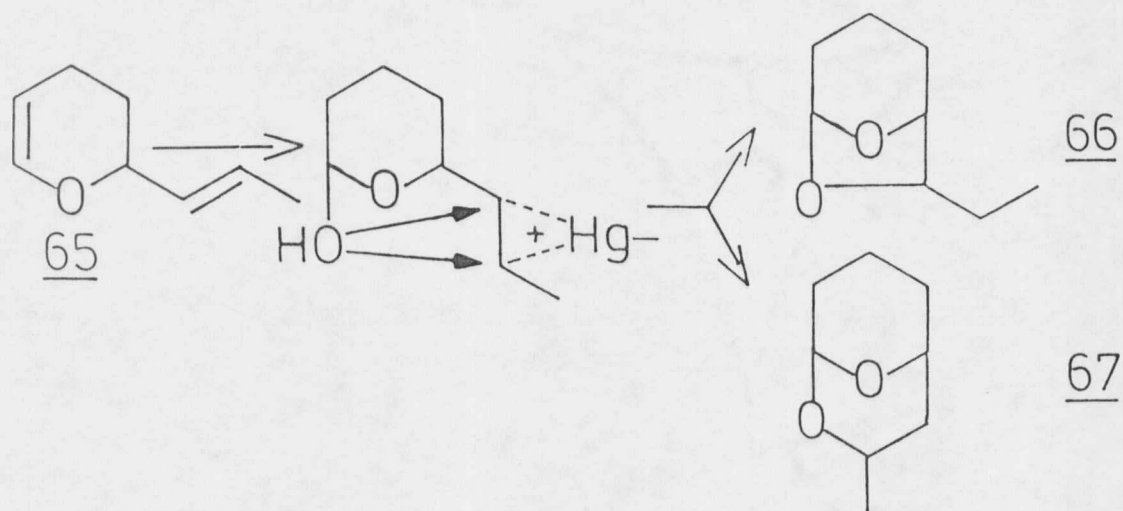
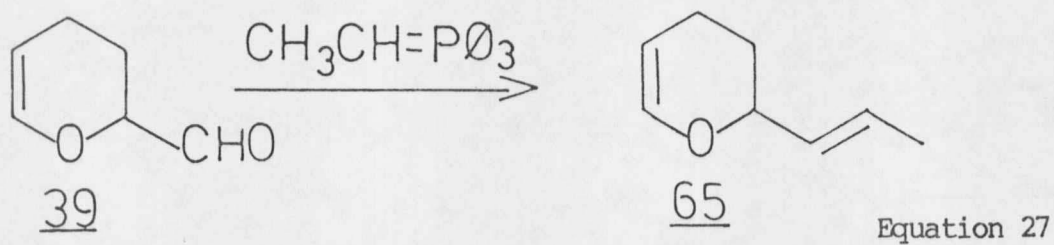


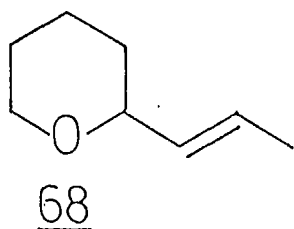
Figure 47. Nucleophilic Attack on Secondary Mercurinium Ions

Compound 65 was synthesized by a Wittig reaction on acrolein dimer (39). The ethyl triphenylphosphonium bromide was reacted with methyl lithium to produce the Wittig reagent. Dimer 39 was then added slowly to give a 95% yield of 65 by GLC (Equation 27).



Spectral data confirming the structure of diene 65 included a molecular ion at $m/e = 124$, infrared absorptions at 3010 and 1650 cm^{-1} (enol ether), and the appearance of proton NMR absorptions for a vinyl methyl group at $\delta 1.70$ and five downfield protons resonating at $\delta 6.39$, $\delta 5.55$ (two protons), and $\delta 4.64$ (two protons).

Oxymercuration-demercuration of diene 65 was attempted using several different mercury salts. All reactions were run for half an hour at room temperature, followed by standard demercuration. All the reactions produced uncharacterized alcohols and compound 68. No ketals could be identified.



The proton NMR spectrum of 68 suggested a mixture of cis and trans isomers; however, a separation of these isomers was not attempted. The results of the oxymercuration-demercuration reaction using various mercury salts are shown in Table 13.

Table 13. Oxymercuration with Several Mercury Salts

<u>Salt</u>	<u>Percent of 68</u>
Hg(OAc)	45-49
HgSO ₄	61
HgNO ₃	39
Hg(TFA) ₂	17

The absence of ketal formation seems to indicate a preference for base catalysed ring opening in this system (Figure 48). The

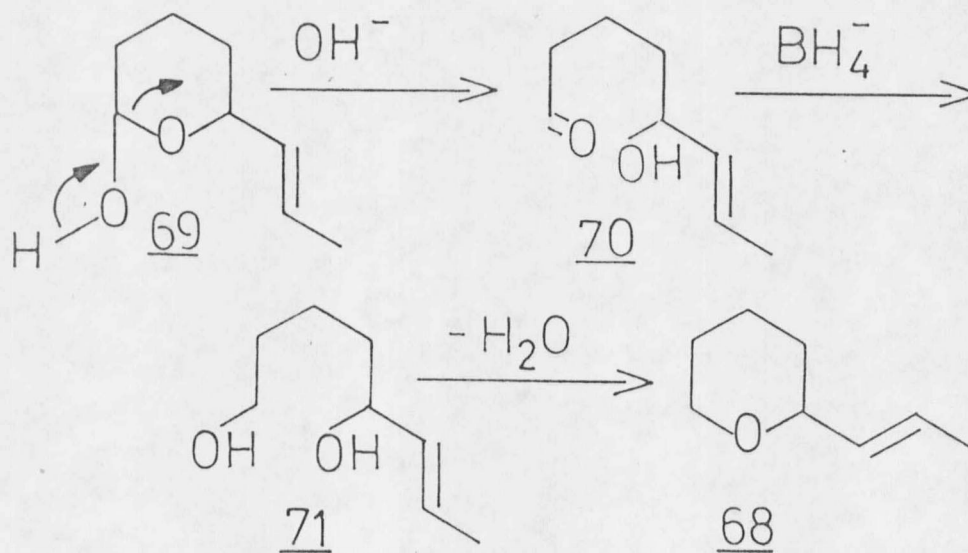


Figure 48. Base Catalysed Ring Opening

lack of ketal formation from the oxymercuration of 65 may be the result of a slower rate of cyclization of alcohol 69 as compared to the rate of ring opening. The absence of ketal formation in this last model system cast some doubt on the success of the planned pheromone synthesis.

Having investigated several model systems, an attempt was made to synthesize diene 21, the precursor to the desired pheromones 2 and 22 (Figure 49). The direct approach, the synthesis of aldehyde 20 from acrolein and methyl vinyl ketone followed by reaction of

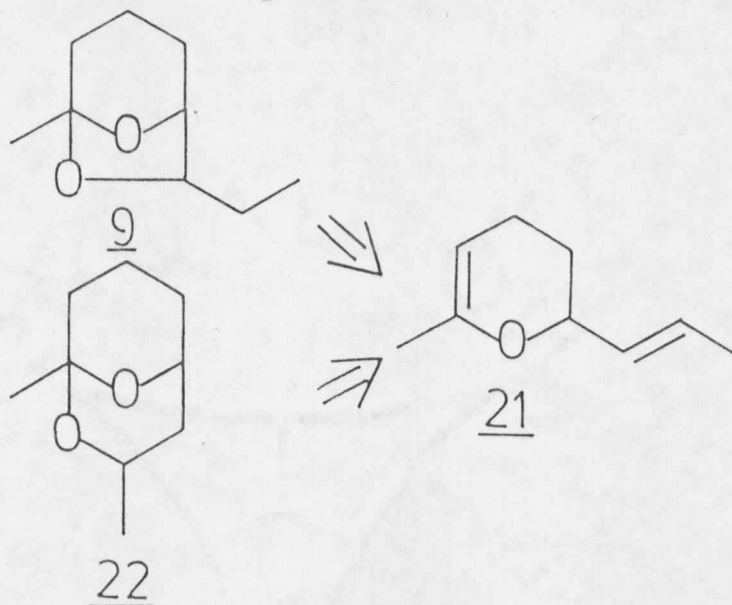
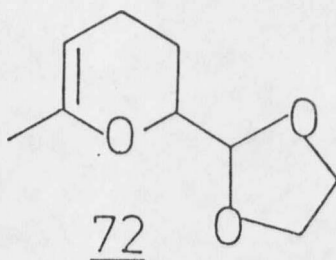


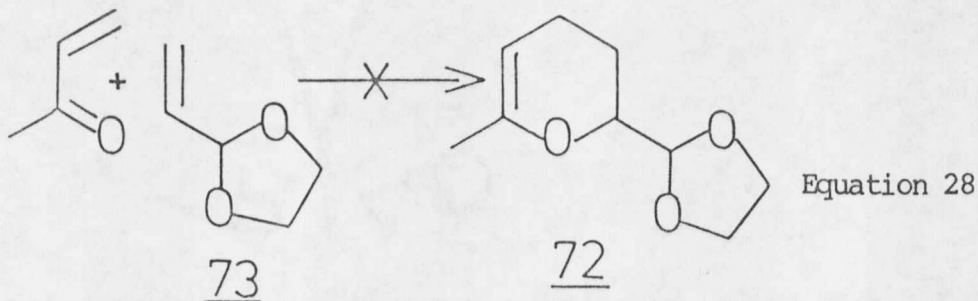
Figure 49. Precursor to Desired Pheromones

26 with the ethyl Wittig reagent, is not feasible due to the thermal rearrangement to 61, as we have seen earlier. It was thought that

if the aldehyde functionality in acrolein could be protected as an acetal, it might be possible to synthesize compound 72. Aldehyde 20 could then be regenerated by mild acid treatment of 72.



The acrolein acetal 73 was synthesized according to the method of Fischer and Smith⁶⁴ with a yield of 85–89% by reacting acrolein, ethylene glycol and p-toluene sulfonic acid in benzene using a Dean-Stark water separator. The subsequent reaction of 73 with methyl vinyl ketone failed to give the desired Diels-Alder product after heating for two hours at 175°C, despite several attempts (Equation 28).



Synthesis of **21** was next attempted through the series of reactions shown in Figure 50. The synthesis of enamine **19** and

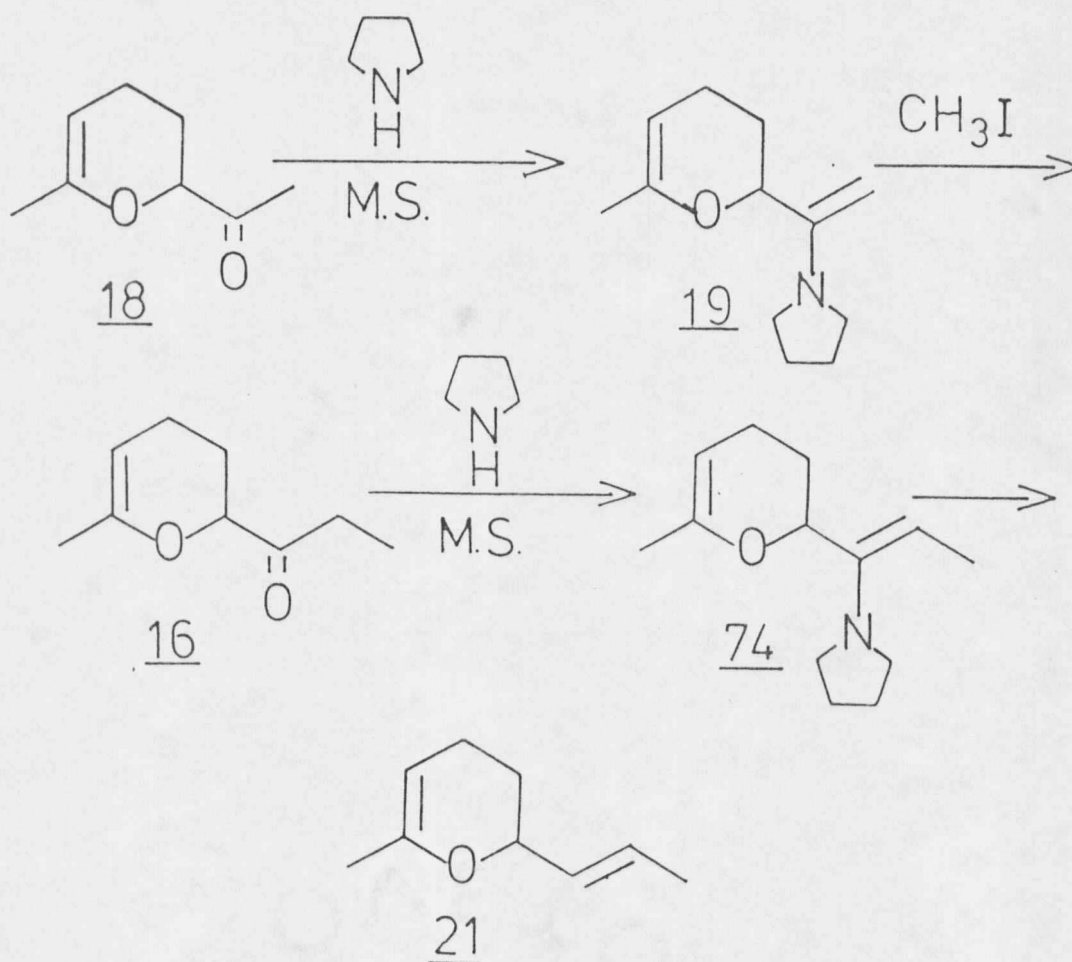
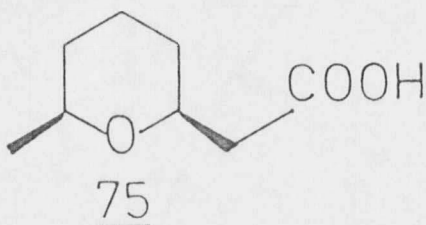


Figure 50. Proposed Synthesis of 2-(1-Propenyl)-6-methyl-3,4-dihydro-2H-pyran

ketone **16** have been demonstrated by Bornmann²³ and the reduction of enamines to olefins has been used successfully in the synthesis of **75**, a Civet cat constituent.⁶⁵



Reaction of **18** with pyrrolidine over 3 Å molecular sieves or by the use of a Dean-Stark apparatus produced **19** with an isolated yield of 31-60%. The reaction of **19** with methyl iodide at room temperature for twenty-four hours produced only 9% of ketone **16**. By refluxing the reaction for twenty-four hours, yields of 15-45% were achieved. Fifty five to 85% of ketone **18** was recovered. The separation of compounds **18** and **16** was attempted using silica gel and Florisil column chromatography. No significant separation was achieved. Because of the inability to separate **18** and **16** and the low yields obtained, this method was temporarily abandoned.

A synthesis of **21** was next envisioned in which the Diels-Alder reaction between methyl vinyl ketone and methyl acrylate would produce ester **76**. Compound **76** could then be reduced with diisobutyl

aluminum hydride (DIBAL) at low temperature to give aldehyde 20 (Figure 51).

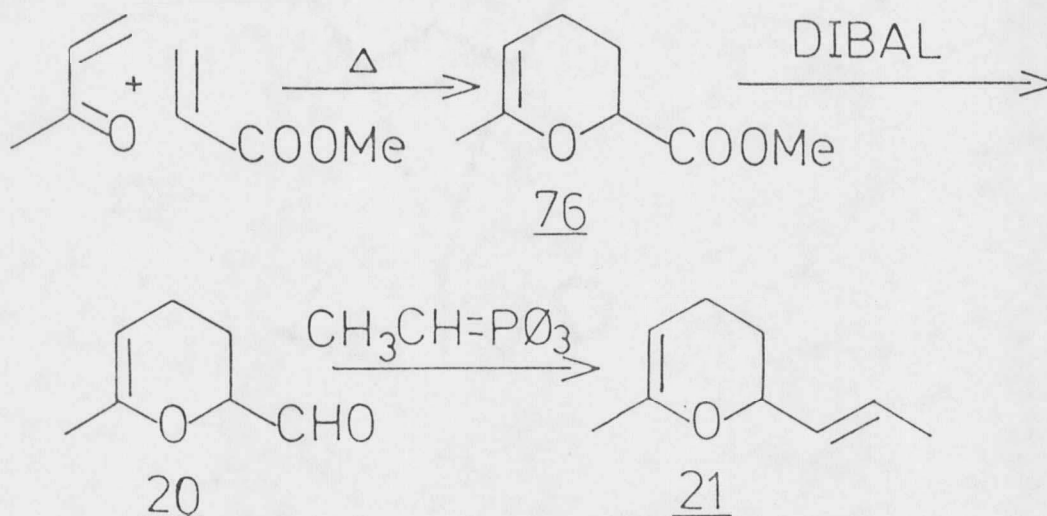


Figure 51. Alternate Synthesis of 2-(1-Propenyl)-6-methyl-3,4-dihydro-2H-pyran

When one equivalent of methyl vinyl ketone was reacted with four equivalents of methyl acrylate for two hours at 175°C, a 60:40 mixture of 18:76 was obtained after distillation. Increasing the ratio of methyl vinyl ketone to methyl acrylate to 1:10 resulted in the formation of intractable tar. Separation of 18 and 76 could not be achieved by standard column chromatography or by using reverse phase (C₁₈) flash chromatography. An attempt was then made to reduce the mixture of 18 and 76 with an excess of LiAlH₄ in the hope that the alcohols produced might be separable. Workup in the

absence of acid resulted in ketals 35b and 35a from the reduction and cyclization of 18. Analysis of relative GLC retention times suggested that alcohol 77 had also cyclized (Figure 52).

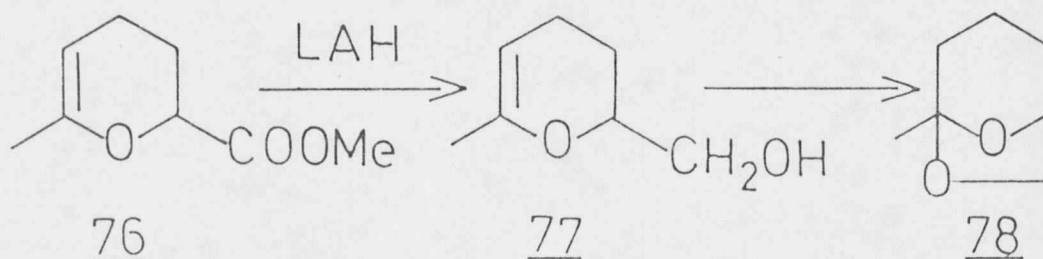


Figure 52. LiAlH_4 Reduction of Mixture

Reduction of the mixture of 18 and 76 was next tried with NaBH_4 in 2-propanol with the intention of reducing and cyclizing 18 but leaving 76 unreacted (Figure 53).

Product analysis revealed the presence of 35b and 35a as expected, but ester 76 was not found. Further examination showed that ester 76 had been transesterified to 79 during the reaction. Transesterifications mediated by NaBH_4 are a documented

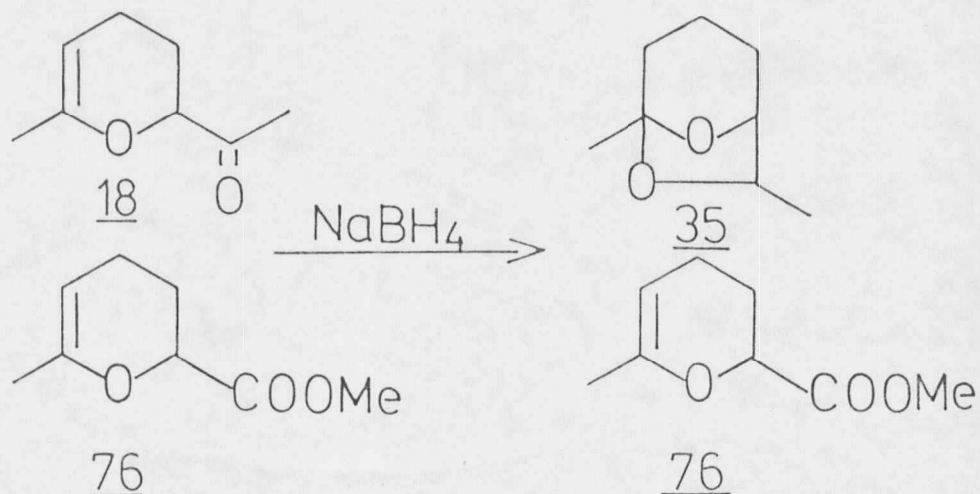
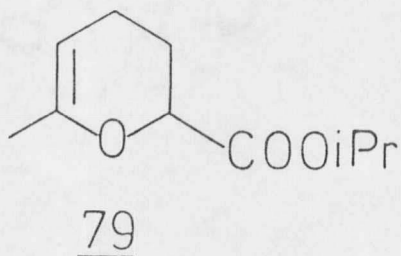


Figure 53. NaBH_4 Reduction of Mixture

phenomenon.⁶¹ Separation of ketals 35b and 35a from ester 79 was attempted using silica gel chromatography with minimal success.



Although the synthesis of the target compounds 9 and 22 was not achieved, the parameters of oxymercuration-demercuration reactions in these systems have been clarified and progress made toward the synthesis of pheromones 9 and 22.

CHAPTER FOUR

Conclusion

This work has revealed several points worth emphasizing. It has been established through the use of competitive reactions that the supra-annular effect does not exist in the compounds studied and therefore is not a significant factor in controlling stereochemistry in the brevicomin syntheses we have examined. Carbon NMR studies have supported this conclusion by showing no evidence of increased electron density on the carbonyl carbon of these compounds. The carbon NMR studies did provide, however, general information which will be useful in identifying ring carbons in substituted 6,8-dioxabicyclo[3.2.1]octanes by the use of chemical shift data.

Metal ion complexation in brevicomin syntheses utilizing metal hydride reductions was shown to play a minor role in influencing the exo/endo product ratio. Related studies involving magnesium ion complexation in Grignard reactions support and confirm earlier observations found in the literature that the steric size of the organomagnesium reagent does have an effect on product stereochemistry.

Following the study of model compounds, several unsuccessful attempts were made to synthesize the precursor for a concurrent

pheromone synthesis. These studies led us to an interesting base catalysed ring opening that was observed to produce open-chain alcohols which subsequently recyclize to tetrahydroyrans. The results obtained from the double oxymercuration-demercuration of model compounds suggest that the major product of a concurrent synthesis of the two desired pheromones will result from this base catalysed ring opening and that this reaction sequence will probably not produce useful pheromones.

Our study of the double oxymercuration-demercuration reaction sequence has, however, shown that this sequence will indeed produce bicyclic ketals. Bark beetle analogs were successfully synthesized, although more work needs to be done to optimize yields. The use of properly functionalized starting dienes will allow the synthesis of a variety of bicyclic ketals and open-chain diols.

CHAPTER FIVE

Experimental

General

Proton and carbon nuclear magnetic resonance spectra were recorded on a Bruker 250 FT-NMR spectrometer. Chemical shifts are given in parts per million and referenced to tetramethylsilane (TMS) at zero ppm or to the center peak of chloroform at 77.27 ppm. Mass spectra were taken using a Varian Model CH-5 mass spectrometer.

GLC analyses were performed using a Varian Aerograph series 1000 interfaced with a Spectra Physics-Autolab Minigrator. The GLC was fitted with a 15-ft by 1/8-in column of 15% Carbowax on Chromosorb G or a 15-ft by 1/4-in column of 20% SE-30.

Infrared spectra were obtained as neat films on NaCl discs using a Beckman IR-5 instrument.

Elemental analyses were obtained from Galbraith Laboratories, Knoxville, TN.

Preparation of Standard Curves for Competitive Kinetics

A standard curve was made for each reactant for each competitive kinetic experiment to insure accurate determination of reactant concentrations. 0.50 grams of each reactant was placed in a 10.0 ml volumetric flask and sufficient 2-propanol added to bring

the contents to mark. A 5.0 ml sample of this solution was mixed with 1.0 ml of a standard o-dibromobenzene solution (5.0 ml o-dibromobenzene diluted to 25.0 ml with 2-propanol) and the total adjusted to 10.0 ml. Two 5- μ l injections of this sample were made into the GLC apparatus. Electronic integration of peak areas provided the first calibration points on graphs plotting the reactant area/standard area vs. moles of reactant.

The remaining 5.0 ml were adjusted to 10.0 ml and the procedure was repeated. Five such sequential dilutions resulted in a standard curve for each reactant. Standard curve parameters were obtained by the use of a linear regression program with the calibration points obtained as stated above. Standard curve parameters for each reactant are given in Table 14.

Procedure for Competitive Kinetics Experiments

To about 0.50 grams of each reactant ketone was added sufficient 2-propanol to bring the volume to 25.0 ml. Five ml of this solution was mixed with 1.0 ml of the standard o-dibromobenzene stock solution. GLC analysis for this solution (area of ketone peak/area o-dibromobenzene peak) provided the data for the determination of moles of unreacted ketone. The remaining 20 ml of solution were placed in a small round bottom flask and a limiting amount of NaBH_4 (about 3 moles ketone/mole hydride) was added. The reaction mixture

Table 14. Standard Curve Parameters for Competitive Kinetics Experiments

Reactant	$\frac{\text{y-Intercept}}{\text{area of reactant}} \div \text{area of standard}$	slope	R
(18)	1.15×10^{-5}	1.18×10^{-3}	.9999
(33)	8.01×10^{-6}	9.07×10^{-4}	.9998
(18)	4.56×10^{-5}	2.12×10^{-3}	.9998
(37)	3.42×10^{-5}	1.55×10^{-3}	.9998
(36)	-6.27×10^{-5}	5.76×10^{-4}	.9997
(37)	4.52×10^{-5}	2.14×10^{-4}	.9999
(35)	-1.27×10^{-4}	6.28×10^{-4}	.9979
(39)	-4.15×10^{-5}	3.66×10^{-4}	.9993

was stirred for half an hour at room temperature. After the reaction was quenched with water, the solvent was removed under vacuum and the residue was made up to 20.0 ml with 2-propanol. Five ml of this solution was withdrawn and added to 1.0 ml of standard o-dibromobenzene solution. GLC analysis was performed in duplicate and each experiment was run in duplicate. Relative reactivities were calculated using Equation 21 and the concentrations established by the use of GLC areas and standard curves.

$$\text{Relative Rate} = \frac{k_A}{k_B} = \frac{\ln \frac{[A]_t}{[A]_0}}{\ln \frac{[B]_t}{[B]_0}} = \frac{\ln(\text{fraction of A remaining})}{\ln(\text{fraction of B remaining})}$$

Equation 21

Attempted Synthesis of 4-Acetylcyclohexene (32) Using Butadiene Sulfone

Butadiene sulfone (17.7 grams, 0.15 mole) was placed in a flask with 100 ml of xylene, methyl vinyl ketone (7.0 grams, 0.1 mole) and $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ (7.0 grams, 0.02 mole). The reaction was stirred magnetically and refluxed for one hour. During the reflux the reaction turned black and gave off a white gas. The reaction was cooled and 50 ml H_2O and 50 ml Et_2O were added. The layers were separated and the organic layer was washed twice with water and then dried over MgSO_4 . GLC analysis showed only a small amount of 4-acetylcyclohexene (32) formed.

Preparation of 4-Acetylcyclohexene (32)

Following the method of Fray and Robinson,⁶⁷ 21.0 grams (0.06 mole) of $\text{SnCl}_4 \cdot 5\text{H}_2\text{O}$ was placed in a two necked flask fitted with reflux condenser and bubbler. Fifty ml of benzene and 21.0 grams

(0.30 mole) methyl vinyl ketone dimer (18) were added and the reaction stirred at room temperature. Butadiene (21.6 grams, 0.40 mole) was then bubbled slowly into the solution over the course of an hour. The reaction was then stirred for an additional hour at room temperature. Benzene was removed by roto-evaporation at reduced pressure and the residue distilled. Isolated yield = 21.6%.

^1H NMR:	3.73	t	1H
	2.93	t	1H
	2.60	m	1H
	2.18	s	3H
	2.12	m	2H
	1.98	m	2H
	1.57	m	2H

^{13}C NMR: 211.7 (ppm), 126.9, 125.5, 47.4, 28.0, 26.8, 24.7, 24.6

IR: 3080 (cm^{-1}), 2900, 1720, 1440, 1360, 1170, 618, 655

MS: 124 (M^+), 109, 99, 71, 80, 79, 77, 55, 53, 43, 41, 39

Preparation of Acetylcyclohexane (31)

4-Acetylcyclohexene (32) (2.85 grams, 0.023 mole) was dissolved in 50 ml of absolute ethanol and this solution placed in a hydrogenation bottle with a small amount of Pd/C. This solution was shaken with a hydrogen pressure of 50 psi in a Paar hydrogenation apparatus for five hours. The reaction was filtered through Hyflo Super Cel and the ethanol was removed under vacuum. GLC analysis showed only one peak with a quantitative yield.

^1H NMR: 2.33 m 1H
 2.13 s 3H
 1.79 br m 5H
 1.26 br m 5H

^{13}C NMR: 212.5 (ppm), 51.6, 28.5, 27.9, 26.0, 25.7

IR: 2930 (cm^{-1}), 1710, 1455, 1360, 1245, 1170, 970, 890

MS: 126 (M^+), 111, 83, 71, 68, 67, 55, 43, 41, 39

Preparation of 2-Acetyl-6-methyl-4,5-dihydro-2H-pyran (18)

Methyl vinyl ketone (69.1 grams, 0.99 mole) was placed in a steel high pressure bomb and shaken for two hours at 175°C according to the procedure of Alder.⁶⁸ After cooling, the contents of the bomb were distilled under vacuum to give 40.9 grams of a colorless liquid distilling at 50–55°C at 1.3 mm Hg (59% yield).

^1H NMR: 4.53 t 1H
 4.27 dd 1H
 2.25 s 3H
 1.97 m 4H
 1.79 s 3H

^{13}C NMR: 209.1 (ppm), 149.3, 96.2, 80.2, 25.6, 23.3, 19.7, 19.0

IR: 3060 (cm^{-1}), 2960, 1725, 1680, 1440, 1395, 1360, 1285, 1240, 1170, 1110, 1075, 920, 900, 765

MS: 140 (M^+), 97, 69, 55, 43, 41

Attempted Reduction of Methyl Vinyl Ketone Dimer (18) with Pt/C

Methyl vinyl ketone dimer (18) (1.0 gram) was dissolved in 25 ml of absolute ethanol and placed in a hydrogenation bottle, Pt/C (0.0262 grams) was added and the bottle was placed in a Paar hydrogenator under 55 psi hydrogen. After shaking for four hours, the catalyst was filtered off and the ethanol was removed under vacuum. GLC analysis showed less than 10% reduction.

Attempted Reduction of Methyl Vinyl Ketone Dimer (18) with Pd/C

Methyl vinyl ketone dimer (18) (1.0 gram) was dissolved in 25 ml absolute ethanol and placed in a hydrogenation bottle. A trace amount of Pd/C was added and the bottle placed in a Paar hydrogenator under 55 psi hydrogen and shaken for several hours. After being filtered, the ethanol was removed under vacuum and GLC analysis showed only starting ketone.

Synthesis of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octanes (35a) and (35b)

According to the methods of Lipkowitz,⁶⁸ NaBH₄ (0.045 grams, 0.0048 mole) was placed in a flask with 10 ml 2-propanol and stirred at room temperature. Methyl vinyl ketone dimer (18) (0.50 grams, 0.0036 mole) was added dropwise and the reaction stirred for two

hours. Hydrolysis was accomplished by the addition of 10 ml water. The reaction was extracted three times with CH_2Cl_2 and the organics were separated and dried over MgSO_4 . The CH_2Cl_2 was removed by rotoevaporation. The GLC trace showed two peaks corresponding to exo/endo isomers. Yield = 97%.

^1H NMR (35b):

4.20	q	1H
4.06	br s	1H
1.70-1.90	m	2H
1.62	m	4H
1.46	s	3H
1.20	d ($J = 6.4$ Hz)	3H

^1H NMR (35a):

4.16-4.28	m	2H
1.73-2.00	m	2H
1.52-1.67	m	4H
1.44	s	3H
1.33	d ($J = 6.1$ Hz)	3H

MS: 142 (M^+), 100, 98, 81, 72, 71, 67, 58, 57, 55, 54, 43, 41

Preparation of 2-(1-Hydroxyethyl)-6-methyltetrahydropyran (36)

5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (35) (15.8 grams, 0.11 mole) was dissolved in absolute ethanol and placed in a hydrogenation bottle with about 0.10 grams Pd/C and shaken in a Paar hydrogenator until the hydrogen uptake ceased. The solution was filtered followed by removal of the ethanol under vacuum. GLC

analysis indicated 98% yield. Two isomers were detected by NMR spectroscopy. No attempt was made to separate them.

^{13}C NMR: 82.5 (ppm), 81.1, 80.4, 74.1, 73.9, 70.6, 69.7, 33.6, 33.3, 27.0, 24.6, 23.3, 22.2, 18.3, 17.9

(See also page 108.)

^1H NMR: (See page 109.)

IR: 3420 (cm^{-1}), 2940, 1445, 1368, 1135, 1085, 1050, 913, 895, 910

MS: 144 (M^+) (not seen), 99, 81 (base peak), 71, 57, 55, 45, 43, 42, 41, 39

Calculated: C, 67.61 H, 11.11

Found: C, 66.50 H, 10.98

Preparation of 2-Acetyl-6-methyltetrahydropyran (33)

Following the procedure of Brown,⁶⁹ 2.1 grams (0.015 mole) of 2-(1-hydroxyethyl)-6-methyltetrahydropyran (36) were dissolved in 20 ml of Et_2O and Jones reagent (1.5 grams $\text{Na}_2\text{Cr}_2\text{O}_7$, 2.04 grams H_2SO_4 , and 15 ml water) was added dropwise. After being stirred for two hours at 25°C , the reaction was stopped by separating the Et_2O layer. The aqueous layer was extracted with Et_2O and the organic layers were combined and washed with sodium bicarbonate solution. The ether was then dried over MgSO_4 and the ether was removed under vacuum.

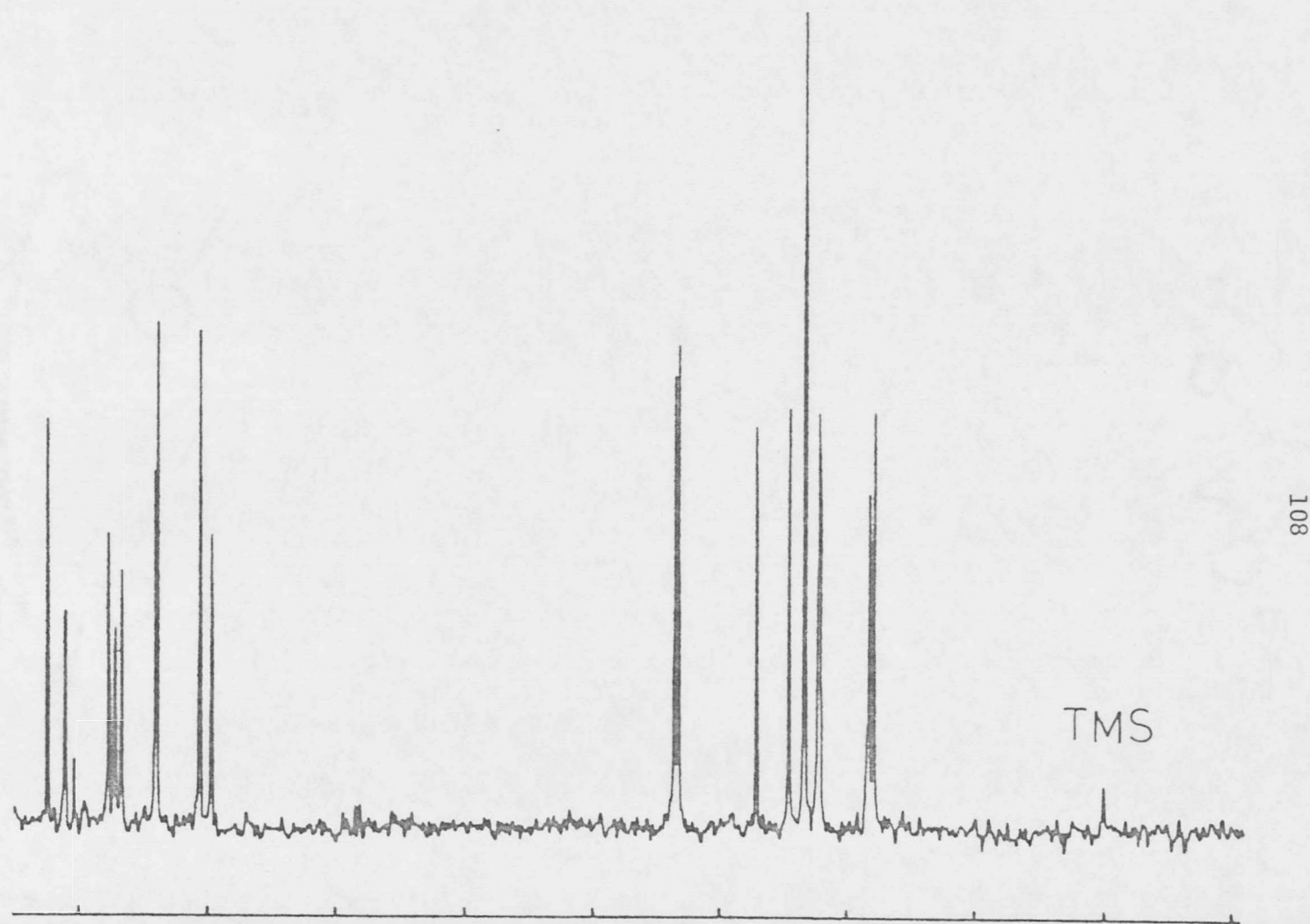


Figure 54. ^{13}C NMR of 2-(1-Hydroxyethyl)-6-methyltetrahydropyran (36)

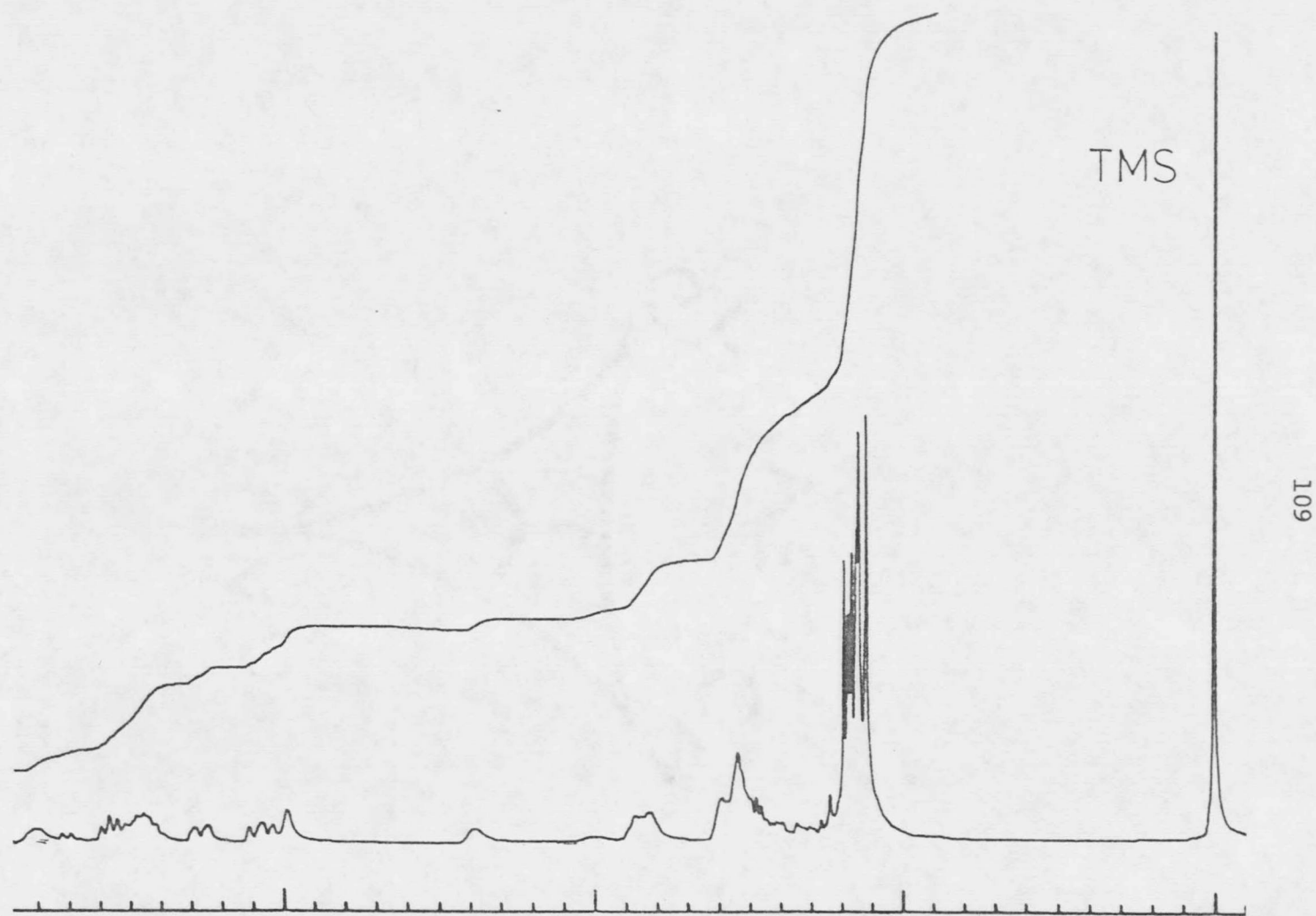


Figure 55. ^1H NMR of 2-(1-Hydroxyethyl)-6-methyltetrahydropyran (36)

¹H NMR:

3.73	dd	1H
3.10	m	1H
2.11	s	3H
1.79	m	3H
1.50	m	3H
1.14	d	3H

¹³C NMR: 209.9 (ppm), 83.3, 74.1, 32.8, 27.6, 25.7, 23.4, 22.1

IR: 2940 (cm⁻¹), 1730, 1455, 1362, 1098, 1055, 885

MS: 142 (M⁺), 99, 81, 71, 70, 57, 55, 45, 44, 43 (base peak), 42, 41, 39

Calculated: C, 67.61 H, 9.86

Found: C, 67.61 H, 10.07

Reduction of Methyl Vinyl Ketone Dimer (18) with Rh/Alumina

Ketone 18 (1.0 gram) was dissolved in 25 ml of absolute ethanol in a hydrogenation bottle. Powdered Rh/alumina (0.047 grams) was added and the bottle placed under 55 psi hydrogen and shaken for 135 minutes. The catalyst was filtered through Hyflo Super Cel and the ethanol was removed under vacuum. GLC analysis revealed a 91% conversion of dimer 18 to ketone 33. The remaining 9% of dimer 18 was removed by oxidation. The reaction mixture was placed in 50 ml of benzene and was stirred at 0°C. One hundred ml of 2% KMnO₄ was added dropwise and the reaction was stirred for one and one-half hours at 0°C. The reaction was then extracted three times with

25 ml Et₂O and was dried over MgSO₄. GLC analysis showed only compound, 33, remaining.

Reduction of Methyl Vinyl Ketone Dimer (18) with Various Reducing Agents

All reductions utilizing a solid reducing agent (NaBH₄, LiAlH₄, LiBH₄, KBH₄) were performed using the same procedure. This procedure is delineated for NaBH₄ below.

Sodium borohydride (0.095 grams, 0.0025 mole) was placed in a flask with 25 ml of dry THF and stirred at room temperature. Methyl vinyl ketone dimer (18) (1.40 grams, 0.01 mole) was added dropwise and stirring was continued for one hour. The reaction was hydrolysed with 50 ml of water and the reaction was then extracted twice with 25 ml CH₂Cl₂. GLC analysis with electronic integration of peak areas allowed a determination of the relative amounts of products.

Reduction with L-Selectride was accomplished by the addition of 10.0 ml of a 1.0 M solution of L-Selectride in THF to a stirred solution of 1.4 grams methyl vinyl ketone dimer (18) in 50 ml of dry THF under a N₂ atmosphere. The reaction was stirred for one hour and then hydrolysed by the addition of 50 ml water. After extraction two times with 25 ml Et₂O, the organic layer was dried over MgSO₄ and the solvent was removed under vacuum.

Reduction of 2-Propionyl-6-methyl-3,4-dihydro-2H-pyran (16) with
Various Reducing Agents

Reductions were performed on a reactant mixture composed of 13% ketone **16** and 87% ketone **18**. Reductions with LiBH_4 , NaBH_4 , KBH_4 were done using the same procedure. This procedure will be illustrated for the reaction with NaBH_4 .

Excess NaBH_4 was combined with 25 ml of dry THF and the mixture was stirred at room temperature. The reactants (1.0 gram) were added dropwise and the reaction was stirred for 30 minutes. Hydrolysis was accomplished by the addition of 2 ml of water followed by stirring for half an hour. Extraction with three volumes Et_2O and drying over MgSO_4 completed the workup. The Et_2O was removed under vacuum and the product ratios determined by GLC analysis.

Synthesis of the Pyrrolidino Enamine of 2-Acetyl-6-methyl-3,4-dihydro-2H-pyran (19)²⁴

Methyl vinyl ketone dimer (**18**) (10.0 grams) was added to pyrrolidine (5.5 grams, 0.077 mole) and 15 grams of 4 Å molecular sieves and the reaction was placed under a nitrogen atmosphere. The reaction was warmed to 35°C and swirled occasionally for 24 hours. After the reaction had cooled, the molecular sieve was filtered off

and washed with two portions of Et₂O. Distillation under high vacuum gave a light yellow liquid. B.P. = 89-94°C (0.8 mm Hg). Isolated yield was equal to 31%. Literature B.P. (0.8) = 83°C.

Synthesis of 2-Propionyl-6-methyl-3,4-dihydro-2H-pyran (16)²⁴

Compound 19 (3.0 grams, 0.016 mole) was mixed with 50 ml of dry benzene in a flask fitted with a reflux condenser and was placed under nitrogen. Methyl iodide (2.8 grams, 0.020 mole) was added dropwise with stirring at 0°C. After being stirred for one hour, the reaction was refluxed for 24 hours. After cooling to 0°C, the reaction was hydrolysed by the careful addition of one equivalent of 5% acetic acid (0.96 grams acetic acid in 19.2 ml water). The reaction was stirred for half an hour, followed by extraction three times with 50 ml Et₂O, washing twice with saturated NaHCO₃ solution, and drying over MgSO₄. GLC analysis indicated a 40% yield of 16. The reaction was also attempted with stirring at room temperature for 24 hours. This reaction showed only a 9% yield of 16 by GLC.

Synthesis of 7-Alkyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octanes
(40)-(44)

The substituted bicyclic ketals were all made via Grignard reactions with the appropriate alkyl magnesium halides on methyl

vinyl ketone dimer (18). Compounds made in this manner include the C₇-phenyl, -ethyl, -isopropyl, -methyl, and -tert-butyl substituted ketals. A representative procedure will be given for the C₇ phenyl substituted bicyclic ketal.

Magnesium metal (0.38 grams, 0.016 mole), bromobenzene (2.5 grams, 0.016 mole), and 50 ml anhydrous Et₂O were placed in a two necked flask fitted with serum cap, reflux condenser, and CaCl₂ drying tube and the mixture stirred magnetically for 90 minutes. Methyl vinyl ketone dimer (18) (2.0 grams, 0.014 mole) was added slowly via syringe. The reaction was then stirred at room temperature for 24 hours and was subsequently hydrolysed by the addition of a solution made by mixing 2 ml glacial acetic acid, 6 ml water, and 6 grams ice. The ether layer was separated and the aqueous layer was extracted three times with ether. The ether fractions were combined, washed with saturated NaHCO₃ solution and dried over MgSO₄.

Without purification, this crude mixture was placed in 50 ml dry benzene with a trace of p-toluene sulfonic acid and stirred overnight. To this solution was added 50 ml Et₂O and the resulting solution was washed twice with saturated NaHCO₃, dried over MgSO₄, and the solvents were removed under vacuum.

GLC analysis on a 20% SE-30 column allowed separation of endo and exo isomers which were identified by their proton and carbon NMR spectra. The isomers of the C₇ ethyl bicyclic ketal could not be separated by this method.

(35a)

¹³C NMR: 107.1, 77.4, 75.5, 34.2, 24.9, 23.6, 13.7, 17.3

¹ H NMR:	4.19	q	1H
	4.05	s	1H
	1.94-1.09	m	6H
	1.44	s	3H
	1.20	d (J = 6.1)	3H

(35b)

¹³C NMR: 108.0, 80.1, 75.8, 34.9, 27.7, 25.3, 21.9, 17.1

¹ H NMR:	4.28-4.16	m	2H
	2.00-1.52	m	6H
	1.44	s	3H
	1.33	d (J = 6.1)	3H

(40)

¹³C NMR: 107.4, 81.3, 80.9, 34.3, 29.3, 25.9, 24.3, 20.9, 17.2

¹ H NMR:	3.75	d (J = 3.3)	1H
	1.92-1.48	m	6H
	1.37	s	3H
	1.34	s	3H
	1.24	s	3H

(42b)

^{13}C NMR: 107.3, 86.7, 80.9, 34.3, 30.5, 26.2, 23.7, 19.3,
19.0, 17.8

^1H NMR:	3.80	d	1H
	2.24-1.56	m	7H
	1.38	s	3H
	1.12	s	3H
	1.02	d ($J = 6.7$)	3H
	.85	d ($J = 6.7$)	3H

(42a)

^{13}C NMR: 107.2, 86.1, 78.4, 35.2, 34.2, 25.8, 24.3, 19.2,
17.4, 16.0, 12.3

^1H NMR:	4.08	d ($J = 3.6$)	1H
	2.06-1.55	m	7H
	1.41	s	3H
	1.21	s	3H
	.97	d ($J = 7.2$)	3H
	.84	d ($J = 7.2$)	3H

(44b)

^{13}C NMR: 143.9, 128.0, 126.5, 125.6, 108.3, 82.1, 34.7, 32.0,
25.9, 24.9, 16.2

(44b)

^1H NMR:	7.42-7.21	m	5H
	4.42	s	1H
	1.73-1.15	m	6H
	1.56	s	3H
	1.53	s	3H

(44a)

^{13}C NMR: 143.9, 127.9, 126.4, 125.5, 108.3, 82.0, 34.6, 31.9, 25.9, 24.9, 16.1

^1H NMR:	7.45-7.18	m	5H
	4.48	s	1H
	2.19-1.64	m	6H
	1.61	s	3H
	1.53	s	3H

Synthesis of 2-Formyl-3,4-dihydro-2H-pyran (39)⁶⁸

One hundred ml of acrolein (84.0 grams, 1.5 mole) was combined with 100 ml of benzene and placed in a high pressure bomb reactor. The reaction was heated at 175°C for two hours with continuous shaking. Distillation provided 31.9 grams of a colorless liquid. B.P. (asp) = 69-75°C. Yield = 38%.

Preparation of 6,8-Dioxabicyclo[3.2.1]octane (1)

Sodium borohydride (0.76 grams, 0.02 mole) was placed in 40 ml of 2-propanol and the mixture was stirred magnetically. Acrolein dimer (39) (7.6 grams, 0.068 mole) was added dropwise and the stirring continued for one hour. After hydrolysis by the addition of 25 ml water, the reaction mixture was extracted three times with Et₂O and the ether layer dried over MgSO₄. The ether was removed under vacuum. Infrared analysis indicated that the product was an alcohol.

The crude alcohol was placed in dry benzene and the mixture was stirred overnight with a trace of p-toluene sulfonic acid. The benzene solution was then washed with water and dried over MgSO_4 . GLC analysis showed quantitative conversion to the cyclized ketal 1.

^1H NMR:	5.52	s	1H
	4.50	s	1H
	3.97	d	1H
	3.79	t	1H
	1.93-.144	m	6H

^{13}C NMR: 102.3 (ppm), 73.8, 68.4, 31.6, 299.1, 15.7

MS: 114 (M^+), 86, 84, 68, 67, 58, 57, 55, 43, 41, 39

Procedure for the Determination of Cyclization Rates of 2-(1-Hydroxyethyl)-6-methyl-3,4-dihydro-2H-pyrans 35a and 35b

A mixture of isomeric alcohols (35a) and (35b) was made by placing NaBH_4 (0.045 grams, 0.00479 mole) and 10 ml 2-propanol in a flask equipped with a magnetic stirrer. Methyl vinyl ketone dimer (18) (0.50 grams, 0.00357 mole) was added dropwise and the reaction stirred for 30 minutes. After extracting the reaction with Et_2O , the organic layer was dried over MgSO_4 and the solvent was removed under vacuum.

The alcohols were dissolved in 2-propanol and placed in a constant temperature bath. Analysis was performed by GLC with electronic integration. Analyses were performed at regular intervals of twelve hours over a period of sixty hours. Three GLC injections were made per analysis. The ratio of alcohol percent to the sum of alcohol and bicyclic ketal percentages was calculated for each isomer and averaged over the three injections.

Relative rates of cyclization for the two isomeric alcohols were obtained by plotting the ratio of alcohol percent to the sum of alcohol and ketal percentages versus time. The slopes of the lines so generated were determined using a linear regression program. All correlation coefficients exceeded 0.944.

Preparation of 2-Isopropenyl-6-methyl-3,4-dihydro-2H-pyran (45)⁶¹

Methyl triphenylphosphonium bromide (19.64 grams, 0.055 mole) and 200 ml of anhydrous Et₂O were placed in a three necked flask equipped with mechanical stirrer, reflux condenser, and rubber septum. The flask was evacuated and placed under nitrogen. tert-Butyllithium (26.2 ml of a 2.1 M solution) was then added via syringe and the mixture was stirred for three hours. Methyl vinyl ketone dimer (**18**) (7.0 grams, 0.055 mole) was added via syringe and the reaction stirred twelve hours. The reaction was hydrolysed by the addition of 100 ml of water and overnight stirring. The Et₂O

layer was separated and the aqueous layer extracted twice with 50 ml Et₂O. The organic fractions were combined, dried over MgSO₄, and the Et₂O removed under vacuum. GLC analysis showed 91% yield. Distilled yield = 16%.

¹ H NMR:	4.83 (ppm)	s	1H
	4.72	s	1H
	4.31	br s	1H
	4.06	dd	1H
	1.96	m	2H
	1.71	s	3H
	1.69	s	3H
	1.67	m	2H

¹³C NMR: 151.1 (ppm), 145.4, 111.6, 95.4, 78.8, 26.5, 20.7, 20.3, 18.6

IR: 3070 (cm⁻¹), 2920, 1680, 1440, 1390, 1245, 1175, 1075, 1055, 902, 760

MS: 138 (M⁺), 95, 68, 67, 53, 43, 41, 39

Oxymercuration-Demercuration of 2-Isopropenyl-6-methyl-3,4-dihydro-2H-pyran (45)

Mercuric acetate (4.6 grams, 0.0145 mole) was dissolved in 5 ml water and the mixture stirred magnetically at room temperature. Forty-five ml of THF were added and the solution turned into a bright yellow suspension. Compound (45) (1.0 grams, 0.00725 mole) was added rapidly and the mixture was stirred for half an hour.

Hydrolysis was performed by adding sequentially 10 ml of 3 M NaOH and 10 ml of 3 M NaOH, 0.5 M NaBH₄ solutions. After filtering through Hyflo Super Cel, the mixture was extracted three times with 25 ml Et₂O and the organics were combined and dried over anhydrous MgSO₄. The solvents were removed under vacuum. The products were then placed in dry benzene with a trace of p-toluene sulfonic acid and the mixture was stirred twelve hours. The reaction was washed twice with saturated NaHCO₃ and dried over MgSO₄. The benzene was then removed and the products analyzed by GLC on a 20% SE-30 column. The products were identified as 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane (40), 2-isopropenyl-6-methyl-tetrahydropyran (46), and 3,7-dihydroxy-2-methyl-1-octene (51).

5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane (40):⁶⁸

¹ H NMR:	3.76	d	1H
	1.45-1.95	m	6H
	1.37	s	3H
	1.34	s	3H
	1.24	s	3H

MS: 156 (M⁺), 114, 98, 96, 86, 81, 71, 69, 68, 55, 43 (base peak)

2-Isopropenyl-6-methyl-tetrahydropyran (46):

¹ H NMR:	5.38	br s	1H
	4.96	dd	1H
	4.89	br s	1H
	3.95	m	1H
	1.85	s	3H
	1.61	m	6H
	1.32	d	3H

Calculated: C, 77.089 H, 11.501

3,7-Dihydroxy-2-methyl-1-octene (51):

¹ H NMR:	4.93	br s	1H
	4.82	br s	1H
	4.06	t	1H
	3.79	sext	1H
	1.71	s	3H
	1.63-1.37	m	6H
	1.18	d	3H

¹³C NMR: 148.0 (ppm), 111.2, 76.7, 68.3, 39.4, 35.3, 23.8, 22.1, 17.8

IR: 3330 (cm⁻¹), 2910, 1630, 884

MS: 158 (M⁺), 140 (M - H₂O), 125 (M - H₂O - CH₃), 97, 71 (base peak)

Calculated: C, 68.313 H, 11.466

Attempted Reduction of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane
(35) with NaBH₄/OH⁻

Ketal 35 (0.03 grams) was placed in 10 ml THF and was stirred magnetically. Ten ml of 3 M NaOH, 0.50 M NaBH₄ were added and the

reaction was stirred for 48 hours. GLC analysis on 20% SE-30 at 160°C showed only starting material to be present.

Synthesis of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane (35)

Ketal 35 was synthesized according to the method of Lipkowitz.⁶⁸ Sodium borohydride (0.045 grams, 0.00479 mole) was mixed with 10 ml of 2-propanol and stirred at room temperature. Methyl vinyl ketone dimer (18) (0.50 grams, 0.00357 mole) was added dropwise and the reaction was stirred for two hours. Hydrolysis was accomplished by adding 10 ml of water. After being extracted three times with Et₂O, the organics were combined and dried over anhydrous MgSO₄. Spectral data for this compound is found on page 116.

Preparation of 2-(1-Methyl-1-propenyl)-6-methyl-3,4-dihydro-2H-pyran (57)⁶¹

Ethyl triphenylphosphonium bromide (14.0 grams, 0.0377 mole) and 100 ml anhydrous Et₂O were placed in a three necked flask fitted with mechanical stirrer, reflux condenser, and septum. The flask was evacuated and placed under a nitrogen atmosphere. tert-Butyllithium (18 ml of a 2.1 M solution) was added slowly via syringe and the reaction was stirred for several hours, until the reaction was clear and red in color. Methyl vinyl ketone dimer (18)

(5.0 grams, 0.0357 mole) was then added via syringe and the reaction was stirred sixteen hours at room temperature. The reaction was hydrolysed by the addition of 50 ml water and further stirring for two hours, after which time the Et₂O layer was separated. The aqueous layer was extracted twice with 50 ml Et₂O and the organic layers were combined, dried over MgSO₄, and the ether was removed.

¹ H NMR:	5.19	q	1H
	4.50	dd	1H
	4.30	br d	1H
	1.60-2.10	br m	4H
	1.66	m	6H
	1.57	m	3H

MS: 152 (M⁺), 109, 82, 881, 79, 67, 55, 53, 43, 41, 39

IR: 3020 (cm⁻¹), 2960, 1680, 1440, 1384, 1300, 1242, 1170, 1080, 1042, 932, 878, 810, 756

Preparation of Ethyl Triphenylphosphonium Bromide

Ethyl triphenylphosphonium bromide was prepared by the method of House and Rasmusson.⁷⁰ Triphenylphosphine (78.7 grams, 0.30 mole) and ethyl bromide (38.7 grams, 0.35 mole) were combined with 75 ml benzene and placed in a high pressure bomb equipped with a mechanical stirrer. The reaction was heated at 135°C for twenty-four hours with stirring. After cooling, the crystals were washed with CH₂Cl₂ and recrystallized from water. Yield = 64%.

Oxymercuration-Demercuration of 2-(1-Methyl-1-propenyl)-6-methyl-3,4-dihydro-2H-pyran (57)

Mercuric acetate (2.1 grams, 0.0066 mole) was dissolved in 5 ml of water. Fifteen ml THF were added while stirring to produce a yellow suspension. Diene 57 (0.5 grams, 0.0033 mole) was then added in one portion to the yellow suspension and stirring continued for half an hour. Ten ml of 3 M NaOH were added followed by 10 ml of 3 M NaOH, 0.5 M NaBH₄ and the reaction was stirred another 30 minutes. After we had filtered off the solids, the reaction was extracted with Et₂O and the ether dried over anhydrous MgSO₄. The solvents were removed under vacuum. The residual products were then placed in dry benzene and were stirred with a trace of p-toluene sulfonic acid for twelve hours. The reaction was washed with saturated NaHCO₃ and dried over MgSO₄. GLC analysis indicated three major products identified as starting diene (57), 4,8-dihydroxy-3-methyl-2-nonene (58), and 7-ethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (41).

4,8-Dihydroxy-3-methyl-2-nonene (58):

¹ H NMR:	5.34	q	1H
	4.61	t	1H
	3.81	m	1H
	1.66	d	3H
	1.61	s	3H
	1.31-1.57	m	6H
	1.20	d	3H

MS: 172 (M⁺), 154 (M - H₂O), 139 (M - H₂O - CH₃), 85, 69, 55, 45,
43

Calculated: C, 69.723 H, 11.703

Preparation of 7-Ethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane
(41)

7-ethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (41) was synthesized according to the method of Lipkowitz, Mundy and Geeseman.²² Ethyl bromide (6.4 grams, 0.0596 mole), magnesium powder (1.4 grams, 0.0576 mole), and 50 ml of anhydrous Et₂O were placed in a two necked flask equipped with a reflux condenser and a dropping funnel and were stirred for two hours under a nitrogen atmosphere. Methyl vinyl ketone dimer (18) was then added dropwise and the reaction was stirred another two hours. Hydrolysis was accomplished by pouring the reaction over a mixture of 12 grams ice, 12 ml water, and 4 ml glacial acetic acid. The Et₂O layer was separated and the aqueous layer was extracted twice with Et₂O. The

ether fractions were combined and dried over MgSO_4 . GLC analysis indicated a quantitative yield. B.P. (asp.) = 72°C .

Synthesis of 2-(1-Hydroxyethyl)-3,4-dihydro-2H-pyran (60)

Acrolein dimer (39) (4.6 grams, 0.041 mole) was placed in 50 ml of dry Et_2O and stirred at 0°C under nitrogen in a two necked flask equipped with a reflux condenser and serum cap. Methylolithium (40 ml of a 1.2 M solution) was then added via syringe and the reaction was stirred for seven hours. The reaction was hydrolysed by the addition of 25 ml water and was stirred an additional half an hour. The mixture was then extracted three times with Et_2O and the organics were combined and dried over anhydrous MgSO_4 .

MS: 128 (M^+), 95, 84, 83, 81, 71, 70, 57, 55, 45, 43, 41, 39

IR: $3400\text{ (cm}^{-1}\text{)}$, 2900, 1650, 1375, 1240, 1071, 925, 871, 728

Synthesis of 2-Acetyl-3,4-dihydro-2H-pyran (61)⁹

Pyran 60 (0.3 grams, 0.00237 mole) was placed in 25 ml CH_2Cl_2 and was stirred in a two necked flask fitted with a reflux condenser. Pyridinium chlorochromate (0.83 grams, 0.0036 mole) was then added and the reaction was stirred eight hours. One hundred fifty ml of Et_2O were added and the black residue was washed twice with 50 ml Et_2O . The Et_2O was then passed through a short pad of

Florisil and the ether was removed under vacuum. GLC analysis indicated a 68% purity. Isolated yield = 0.1 gram (33%).

¹ H NMR:	6.44	d	1H
	4.76	m	1H
	4.27	m	1H
	2.26	s	3H
	1.84-2.13	m	4H

IR: 3050 (cm⁻¹), 2950, 1720, 1650, 1425, 1360, 1235, 1072, 930, 905, 72 9

MS: 126 (M⁺), 83, 55, 43, 39

Synthesis of 2-Isopropenyl-3,4-dihydro-2H-pyran (59)

For this reaction a mixture of acrolein dimer (39) (26%), 2-acetyl-3,4-dihydro-2H-pyran (61) (60%), and methyl vinyl ketone dimer (18) (14%) was used. Methyl triphenylphosphonium bromide (60.1 grams, 0.168 mole) was placed in 200 ml of anhydrous Et₂O and the slurry was stirred mechanically under a nitrogen atmosphere. tert-Butyllithium (76.2 ml of a 2.1 M solution) was added slowly via syringe and the reaction was stirred two hours. The ketone mixture (16.8 grams) was then added and the reaction was stirred overnight. One hundred ml of water were then added and the stirring continued until the reaction was transparent. The ether layer was separated and the aqueous layer then extracted three times with

Et₂O. The organic portions were combined and dried over MgSO₄. GLC analysis indicated 70% purity. Isolated yield = 38%.

¹ H NMR:	6.43	d	1H
	5.01	br s	1H
	4.91	br s	1H
	4.69	br t	1H
	4.21	br d	1H
	1.68-2.20	m	4H
	1.78	s	3H

MS: 124 (M⁺), 109, 95, 93, 91, 81, 79, 77, 69, 68, 67, 66, 55, 53, 51, 41

IR: 3080 (cm⁻¹), 2920, 1650, 1430, 1240, 1070, 1041, 902, 728

Attempted Oxidation of 2-(1-Hydroxyethyl)-3,4-dihydro-2H-pyran (60)
with Jones Reagent

The Jones reagent was prepared according to the method of Brown.⁶⁹ For 1.0 mole of secondary alcohol, the reagent is prepared by mixing 100 grams Na₂Cr₂O₇, 136 grams concentrated H₂SO₄, and 800 ml water.

Hydroxy pyran 60 (3.44 grams, 0.027 mole) was dissolved in 25 ml Et₂O and placed in a two necked flask fitted with a reflux condenser, dropping funnel, and stir bar. Jones reagent was prepared according to the above instructions and added dropwise to the stirring solution, maintaining the temperature at 25°-30°C. After the addition was complete, the reaction was stirred for

another two hours. The ether layer was then separated and the aqueous layer was extracted twice with Et₂O. The ether layers were combined and were washed first with saturated NaHCO₃ and then with water. The organics were then dried over MgSO₄ and the solvent was removed under vacuum. GLC analysis indicated an 87% yield of cyclized ketals (62a) and (62b).⁶²

¹H NMR (62b) (exo):

5.55	s	1H
4.25	q	1H
4.03	br s	1H
1.75-1.96	m	2H
1.43-1.73	m	4H
1.20	d	3H

¹H NMR (62a) (endo):

5.50	s	1H
4.13	m	2H
1.78-2.03	m	2H
1.45-1.76	m	4H
1.36	d	3H

Oxidation of 2-(1-Hydroxyethyl)-3,4-dihydro-2H-pyran (60) with
Pyridinium Dichromate (PDC)

Alcohol 60 (0.3 grams, 0.00237 mole) was placed in 25 ml of CH₂Cl₂ and was stirred magnetically. PDC (1.34 grams, 0.00355 mole) was added to the stirred solution and the reaction was stirred at room temperature for 24 hours. One hundred fifty ml of Et₂O were

then added and the reaction mixture was passed through a column of silica gel. After the solvents were removed under vacuum, GLC analysis showed a 38% yield of 2-acetyl-3,4-dihydro-2H-pyran (61).

Oxymercuration-Demercuration of 2-Isopropenyl-3,4-dihydro-2H-pyran
(59)

For this reaction a mixture containing 70% 2-isopropenyl-3,4-dihydro-2H-pyran (61) and 20% 2-isopropenyl-6-methyl-3,4-dihydro-2H-pyran (43) was used. Mercuric acetate (6.0 grams, 0.019 mole) was dissolved in 15 ml water. Forty-five ml of THF were added and the resulting yellow suspension was stirred magnetically. One gram of the mixture containing diene 59 was then added in one portion and stirring continued for 30 minutes. Fifteen ml of 3 M NaOH were added followed by 15 ml of 3 M NaOH, 0.5 M NaBH₄ solution. The solution was then stirred for an additional half an hour. After being filtered, the reaction was extracted three times with Et₂O. The ether fractions were combined and dried over MgSO₄. The solvents were removed under vacuum and the solid triphenylphosphine oxide was filtered off. The crude mixture was then placed in dry benzene with a trace of p-toluene sulfonic acid and was stirred overnight. This reaction was washed with saturated NaHCO₃ and then dried over MgSO₄. GLC analysis showed one major product peak (55%)

which was shown by NMR to be composed of 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane (40) (61%) and 39% of the desired 7,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (5).

¹H NMR:

5.51	s	1H
3.90	d	1H
1.51-2.12	m	6H
1.44	s	3H
1.29	s	3H

These values are in good agreement with the literature values.²

Synthesis of 2-(2-Hydroxyisopropyl)-3,4-dihydro-2H-pyran (63)

Magnesium (0.43 grams, 0.018 mole) and 50 ml anhydrous Et₂O were placed in a two necked flask equipped with reflux condenser and an addition funnel and stirred at 0°C under a nitrogen atmosphere. Methyl iodide (2.84 grams, 0.020 mole) was added dropwise and the reaction was stirred two hours. Two grams of a mixture of 60% ketone 61 and 14% ketone 18 were then added to the grey, cloudy solution. After being stirred an additional hour, the reaction was hydrolysed with a solution of 1.1 ml glacial acetic acid in 25 ml water. The ether layer was separated and dried over MgSO₄. GLC analysis showed two major peaks, the second of which was shown by proton NMR to be alcohol 63. The first peak was identified as a mixture of ketals 5 and 40 by proton NMR.

¹ H NMR:	6.41	d	1H
	4.70	m	1H
	3.58	dd	1H
	1.51-2.17	m	4H
	1.25	s	3H
	1.20	s	3H

Alternative Synthesis of 2-Acetyl-3,4-dihydro-2H-pyran (61)

Acrolein (42.0 grams, 0.75 mole) was combined with methyl vinyl ketone (43.0 grams, 0.61 mole), placed in a high pressure bomb and heated at 175°C for two hours with continuous shaking. After distillation, 30.3 grams of clear liquid were obtained which was shown by GLC to contain 65% of ketone 61.

Preparation of 2-(1-Propenyl)-3,4-dihydro-2H-pyran (65)

Ethyl triphenylphosphonium bromide (40.4 grams, 0.11 mole) and 200 ml of anhydrous Et₂O were placed in a three necked flask fitted with mechanical stirrer, reflux condenser, and septum. The flask was evacuated and filled with nitrogen. Methyllithium (91.7 ml of a 1.2 M solution) was added via syringe and the reaction was stirred at room temepature for five hours. Acrolein dimer (39) (12.4 grams, 0.11 mole) was added dropwise to this clear red solution and the mixture was then stirred overnight after which it appeared a chalky yellow color. Addition of 100 ml water followed by stirring for four hours effected hydrolysis. The Et₂O layer was separated and

the aqueous layer extracted twice with 50 ml Et₂O. The organics were combined, dried over MgSO₄ and the ether was removed by rotoevaporator. Distillation afforded a clear liquid boiling at 67°C under aspirator vacuum.

¹H NMR: 6.39 d 1H
 5.55 m 2H
 4.64 m 2H
 1.90 br m 4H
 1.70 dd 3H

¹³C NMR (cis and trans isomers):

144.0 (ppm), 130.5, 127.4, 100.4, 71.0, 28.1, 19.5, 17.8,
 13.3

IR: 3010 (cm⁻¹), 2920, 1650, 1445, 1240, 1060, 975, 900, 760, 730

MS: 124 (M⁺), 95, 93, 83, 81, 70, 69, 68 (base peak), 67, 66, 55,
 53, 41, 39

Oxymercuration-Demercuration of 2-(1-Propenyl)-3,4-dihydro-2H-pyran (65)

Oxymercuration-demercuration of diene 6A was performed using two equivalents of mercuric acetate, mercuric trifluoroacetate, mercuric nitrate, and mercuric sulfate. A sample procedure will be given for the reaction done with mercuric acetate.

Mercuric acetate (2.6 grams, 0.0082 mole) was dissolved in 5 ml water and was stirred magnetically while 15 ml THF were added, producing a yellow suspension. Diene 65 (0.5 grams, 0.0040 mole) was then added to the rapidly stirred suspension in one portion. The reaction was stirred 30 minutes at room temperature and then 10 ml 3M NaOH was added followed by 10 ml of a 3M NaOH, 0.5 M NaBH₄ solution. After filtering, the reaction was extracted three times with Et₂O and the organics were combined and dried over MgSO₄. GLC analysis was used to determine yields (see Table 13) of compound 68.

¹H NMR (cis and trans isomers):

5.77-5.35	m	4H
4.12	t	1H
4.00	dd	2H
3.74	dd	1H
3.48	m	2H
2.85	m	2H
2.68	m	6H
2.61-2.34	m	10H

MS: 126 (M⁺), 111 (M - CH₃), 69, 55, 41

IR: 2940 (cm⁻¹), 2850, 1450, 1090, 1040, 960, 895, 704

Calculated: C, 76.14 H, 11.18

Synthesis of Acrolein Ethylene Glycol Acetal (73)⁶⁴

Acrolein (84.0 grams, 1.5 mole), ethylene glycol (90.0 grams, 1.45 mole), 130 ml benzene, and 70 ml anhydrous Et₂O, and p-toluene sulfonic acid (7.13 grams, 0.0375 mole) were placed in a one liter flask with a Dean-Stark trap and the mixture was refluxed for 14 hours. Eighteen and one-half ml of water were recovered. The solvents in the distilling flask were removed under vacuum and the remaining material carefully distilled to give 85-89% isolated yield of a clear liquid. B.P.(asp) = 24°-30°C. Rapid distillation at higher temperatures resulted in decomposition of the acetal back to the starting materials.

¹ H NMR:	5.85	m	1H
	5.49	d (J = 17 Hz)	1H
	5.36	d (J = 10 Hz)	1H
	5.24	d (J = 6 Hz)	1H
	3.96	m	4H

Attempted Diels-Alder Synthesis of 2-Formyl-6-methyl-3,4-dihydro-2H-pyran Ethylene Glycol Acetal (72)

Methyl vinyl ketone (2.03 grams, 0.029 mole), acetal **73** (8.6 grams, 0.086 mole) and 10 ml benzene were placed in a pressure bomb and the mixture was heated at 175°C for two hours with continuous shaking. After the reaction mixture had cooled, GLC analysis showed only starting material to be present.

Synthesis of 2-(Carboxymethyl)-6-methyl-3,4-dihydro-2H-pyran (76)⁶⁸

Methyl vinyl ketone (14.0 grams, 0.20 mole) and methyl acrylate (68.8 grams, 0.80 mole) were placed in a high pressure bomb and heated at 175°C for two hours. Distillation gave 4.2 grams of a 60:40 mixture of 18:76.

¹ H NMR:	4.53	d	2H
	3.78	s	3H
	2.13-1.90	m	4H
	1.80	s	3H

MS: 156 (M⁺), 124, 113, 97, 96, 82, 81, 69, 66, 55, 53, 43 (base peak)

IR: 2950 (cm⁻¹), 2850, 1740, 1695, 1445, 1395, 1290, 1215, 1174, 1115, 1080, 1040, 764

Separation of the product mixture was attempted using silica gel column chromatography with petroleum ether as the mobile phase. Although some separation was noticed, both compounds were found in each collected fraction. Reverse phase flash chromatography was attempted on a C₁₈ column eluting with 50:50 acetonitrile/water. Again, inadequate separation was achieved.

Reduction of the 60:40 18:76 Mixture with LiAlH₄

Lithium aluminum hydride (1.0 grams, 0.0264 mole) and 100 ml dry THF were placed in a two necked flask fitted with a reflux

condenser and dropping funnel and were stirred at 0°C. The 60:40 mixture (3.7 grams) was added dropwise to the stirring solution and the reaction was stirred overnight. Twenty-five ml of water were then added slowly to the reaction and the mixture was stirred an additional 30 minutes. The reaction was extracted three times with Et₂O and the organics were combined and dried over MgSO₄. GLC coinjection established the presence of ketals 35a and 35b. A third product peak was seen at a shorter GLC retention time than 35a and 35b and assumed to be ketal 78. No alcohols were found.

Reduction of the 60:40 18:76 Mixture with NaBH₄

Sodium borohydride (0.10 grams, 0.00265 mole) was placed in 10 ml of 2-propanol and was stirred magnetically. The 18:76 mixture (0.53 grams) was then added dropwise and the reaction was stirred for one hour. Ten ml of water were added and the reaction stirred for an additional 30 minutes. The reaction was then extracted three times with 10 ml Et₂O. The ether portions were combined and dried over MgSO₄. GLC coinjection confirmed the presence of ketals 35a and 35b. A third product peak was identified by ¹H NMR as 2-(carboxyisopropyl)-6-methyl-2H-pyran (77).

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¹ H NMR:	5.10	m	1H
	4.52	br s	1H
	4.48	m	1H
	1.91-2.12	m	4H
	1.80	br s	3H
	1.27	d	6H

IR: 2960 (cm⁻¹), 2910, 1730, 1690, 1380,, 1285, 1205, 1178, 1100,
1078

MS: 184 (M⁺), 143, 142, 124, 99, 97, 82, 81, 69, 55, 43, 41

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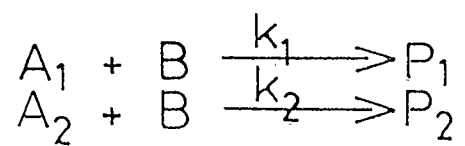
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APPENDICES

APPENDIX A. Derivation of Equation 21



$$-\frac{d[A_1]}{dt} = k_1[A_1][B]$$

$$-\frac{d[A_2]}{dt} = k_2[A_2][B]$$

$$\frac{d[A_1]}{d[A_2]} = \frac{k_1}{k_2} \frac{[A_1]}{[A_2]}$$

$$\frac{d[A_1]}{[A_1]} = \frac{k_1}{k_2} \frac{d[A_2]}{[A_2]}$$

APPENDIX A (continued)

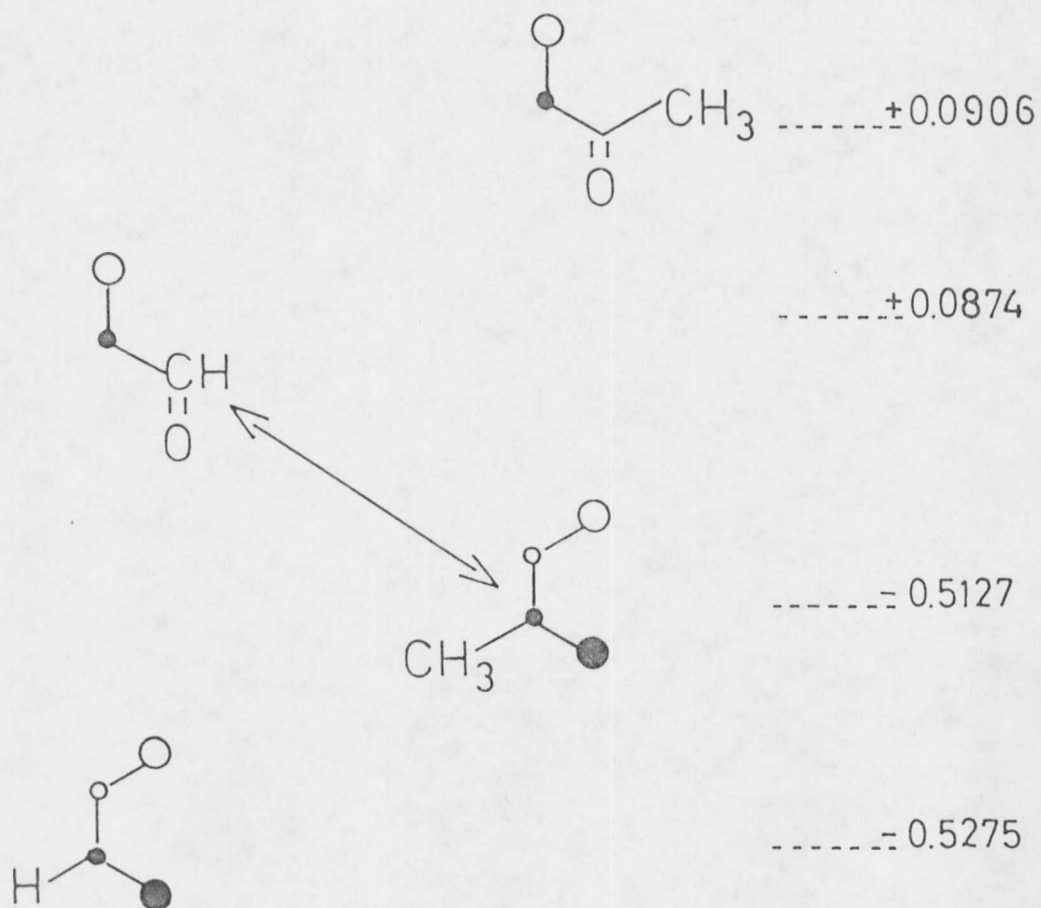
$$\ln \frac{[A_1]}{[A_1]_0} = \frac{k_1}{k_2} \ln \frac{[A_2]}{[A_2]_0}$$

$$\text{Ratio} = \frac{k_1}{k_2} = \frac{\ln \frac{[A_1]}{[A_1]_0}}{\ln \frac{[A_2]}{[A_2]_0}} = \frac{\ln(\text{fraction } A_1)}{\ln(\text{fraction } A_2)}$$

APPENDIX B. Prediction of (55) by Frontier
Molecular Orbital Theory

Acrolein

Methyl vinyl
ketone



MONTANA STATE UNIVERSITY LIBRARIES
 stks D378.Sch96@Theses RL
 Synthetic studies toward natural product
 3 1762 00113709 8

D378
 Sch96 Schwartz, T. R.
 cop.2 Synthetic studies
 toward natural products

DATE	ISSUED TO

— D378
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