A novel bicyclic ketal fragmentation reaction
by Michael Gerard Bjorkland

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry
Montana State University

Abstract:
A new methodology for the cleavage of the 6,8-dioxabicyclo[3.2.1] octane skeletal system is examined. The use of acetyl iodide as a reagent to cleave the bicyclic ketals to the corresponding δ,ε-unsaturated ketones is observed. In each cleavage carried out in this study, the trans/cis ratio found in the products correlates directly to the exo/endo ratio of the starting materials and a mechanism for the cleavage reaction based on these findings is proposed. The utility of the methodology is demonstrated in two synthetic pathways; one leading to the sex attractant of the Douglas-fir tussock moth, Orgyia pseudotsugata, and the other to a major constituent of the venom of the Fire Ant, Solenopsis savissima.

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A thesis submitted in partial fulfillment
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Bozeman, Montana

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APPROVAL

of a thesis submitted by

Michael Gerard Bjorklund

This thesis has been read by each member of the thesis committee and has been found to be satisfactory regarding content, English usage, format, citations, bibliographic style, and consistency, and is ready for submission to the College of Graduate Studies.

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Signature Michael G. Bjorklund

Date July 24, 1984

To my grandfather, Delbert Bjorklund

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I would like to take this opportunity to thank those whose contributions helped to make this research possible.

I extend my appreciation to my parents, William and Iola Bjorklund, and to my mother and father-in-law, Lowell and Marcella Nelson, for their encouragement and for believing in me. To my fellow researchers, Dan Bruss, Rich Copp, Jong-Gab Jun and Dave Wilkening, I extend my gratitude for their valuable help and advice throughout this project. I would also like to thank Joe Sears for the invaluable mass spectral information.

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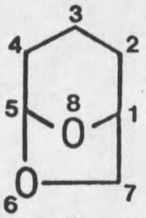
ABSTRACT

A new methodology for the cleavage of the 6,8-dioxabicyclo[3.2.1]octane skeletal system is examined. The use of acetyl iodide as a reagent to cleave the bicyclic ketals to the corresponding δ,ϵ-unsaturated ketones is observed. In each cleavage carried out in this study, the *trans*/*cis* ratio found in the products correlates directly to the *exo*/*endo* ratio of the starting materials and a mechanism for the cleavage reaction based on these findings is proposed. The utility of the methodology is demonstrated in two synthetic pathways; one leading to the sex attractant of the Douglas-fir tussock moth, *Orgyia pseudotsugata*, and the other to a major constituent of the venom of the Fire Ant, *Solenopsis savissima*.

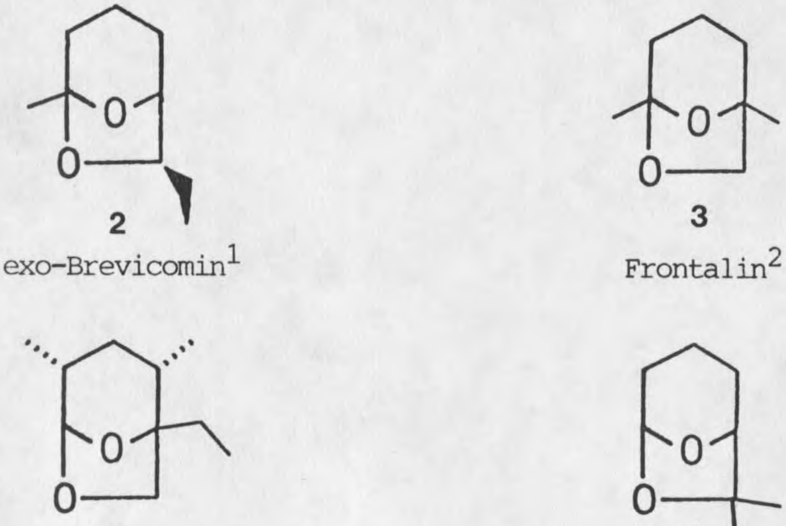
INTRODUCTION

Bicyclic ketals containing the 6,8-dioxabicyclo[3.2.1]octane skeletal system, (<u>1</u>), (Figure 1), several examples of which are illustrated in Figure 2, comprise a group of natural products that has received a substantial amount of attention by chemists in recent years.



1

Figure 1. The 6,8-Dioxabicyclo[3.2.1]octane Skeletal System



2
exo-Brevicomin[1]

3
Frontalin[2]

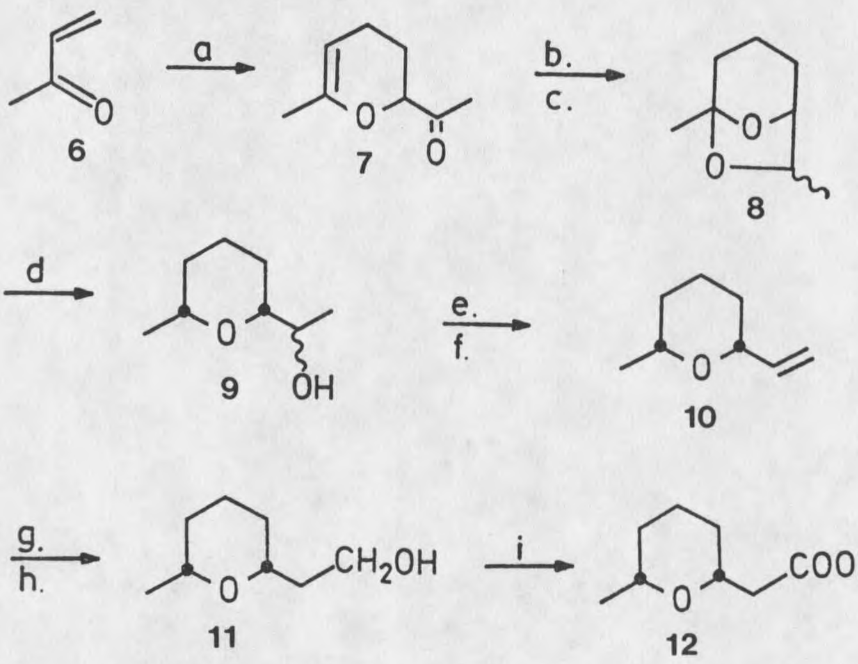
4
Multistriatin[3]

5
7,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane[4]

Figure 2. Natural Products Containing the 6,8-Dioxabicyclo-[3.2.1]octane Skeletal System

As a result of the myriad of different methodologies for synthesizing specifically substituted bicyclic acetals and ketals, the usefulness of such systems as intermediates in the preparation of other natural products became apparent to this group.

In 1982, Kim utilized the hydrogenolysis of <u>8</u> with aluminum hydride as the key step in the synthesis of <u>12</u>, a minor constituent of the glandular secretion from the civet cat (<u>Viverra</u> <u>civetta</u>)[5] (Figure 3).

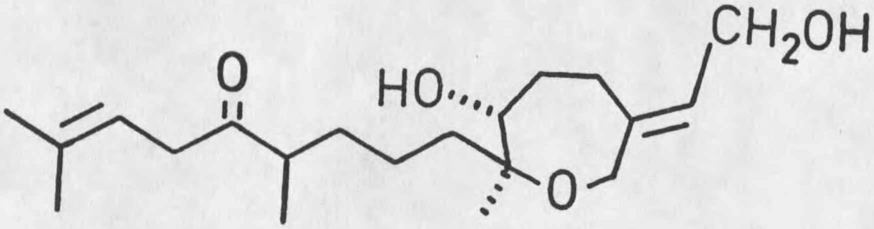


(a) 185°C, 2h; (b) $NaBH_4$/i-PrOH; (c) TSOH/C_6H_6; (d) AlH_3; (e) AcCl/Pyd; (f) 450°C, N_2; (g) B_2H_6; (h) H_2O_2/OH^-; (i) CrO_3/H_2SO_4 or PDC

Figure 3. Kim's Synthesis of (cis-6-Methyl tetrahydropyran-2-yl)-acetic Acid

The observed ring opening of 8 to 9 is readily explained by coordination of the Lewis acid with 0-6, followed by cleavage of the C-5 - 0-6 bond, and is in agreement with similar work done by Brown,[6] Baker[7] and Mundy.[8] It has, in fact, been established that the preferred site of lanthanide interaction during lanthanide - induced shift studies is 0-6.[9] CNDO/2 calculations indicate that the electron density around 0-6 and 0-8 are very similar and suggest that the specificity does not seem to arise from electronic factors.

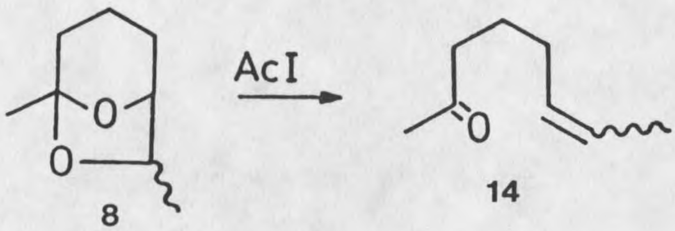
Having observed the specific cleavage of the C-5 - O-6 bond, a question that came to mind was, could a reagent be found that would specifically cleave the C-5 - O-8 bond? Such a cleavage would result in a novel entry into oxepane derivatives and allow for a potential synthesis of zoapatonol, **(13)** (Figure 4), a potent contragestational diterpenoid isolated from the leaves of zoapatle (Montanoa tomentosa) by Levine and co-workers in 1979.[10]



13

Figure 4. Structure of Zoapatanol

In an attempt to find such a reagent, 8 was reacted with acetyl iodide generated in situ.[11] Surprisingly, the elimination of both bridging oxygens was obtained, resulting in the ketone, **(14)**, as shown in Figure 5.



8

14

Figure 5. The Reaction of 5,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane With Acetyl Iodide

The fact that the robust bicyclic system, generally resistant to hydrolysis, is fragmented to give a ketone is interesting in itself; however, the presence of the δ,ϵ - unsaturation in the product made this result even more intriguing. The similarity of the ketone, (**14**), to several insect pheromones was striking.

Unsaturated ketones have been found to be both major and minor constituents in the sex pheromones of various insects. Several examples are illustrated in Figure 6. (Z)-7-nonadecen-11-one, (**15**), and (Z)-7-eicosen-11-one, (**16**), were found by Tamaki et al.[12] to be components of the sex attractant of the peach fruit moth (Carposina niponensis). (Z)-9-tricosen-14-one, (**17**), a stimulant from the female housefly (Musca deomestic L.) was identified by Uebel et al.[13] in 1978.

(Z)-6-Heneicosen-11-one, (**18**), and (Z)-1,6-heneicosadien-11-one, (**19**), are the principle and minor sex pheromone components of the Douglas-fir tussock moth (Orgyia pseudotsugata), as reported by Smith and co-workers.[14,15] The Douglas-fir tussock moth (DFTM) is a severe defoliator of fir forests of western North America.

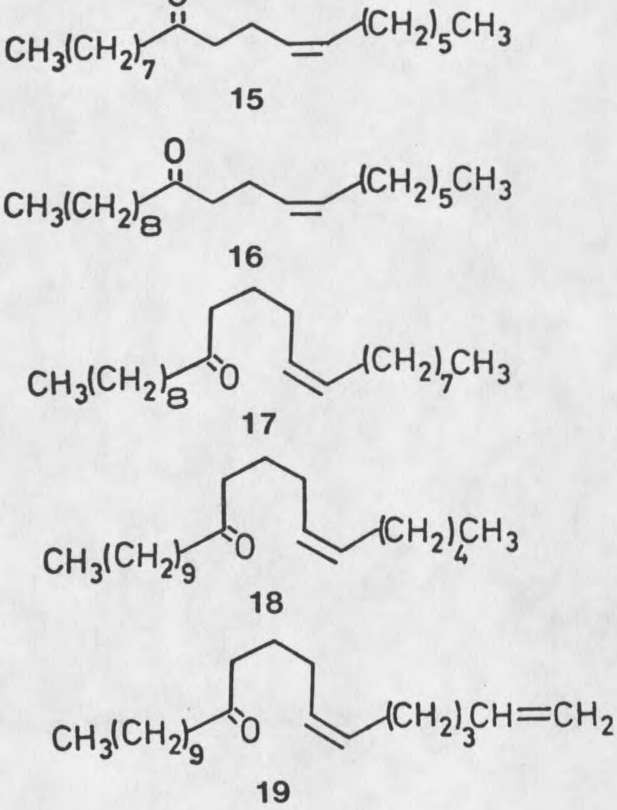


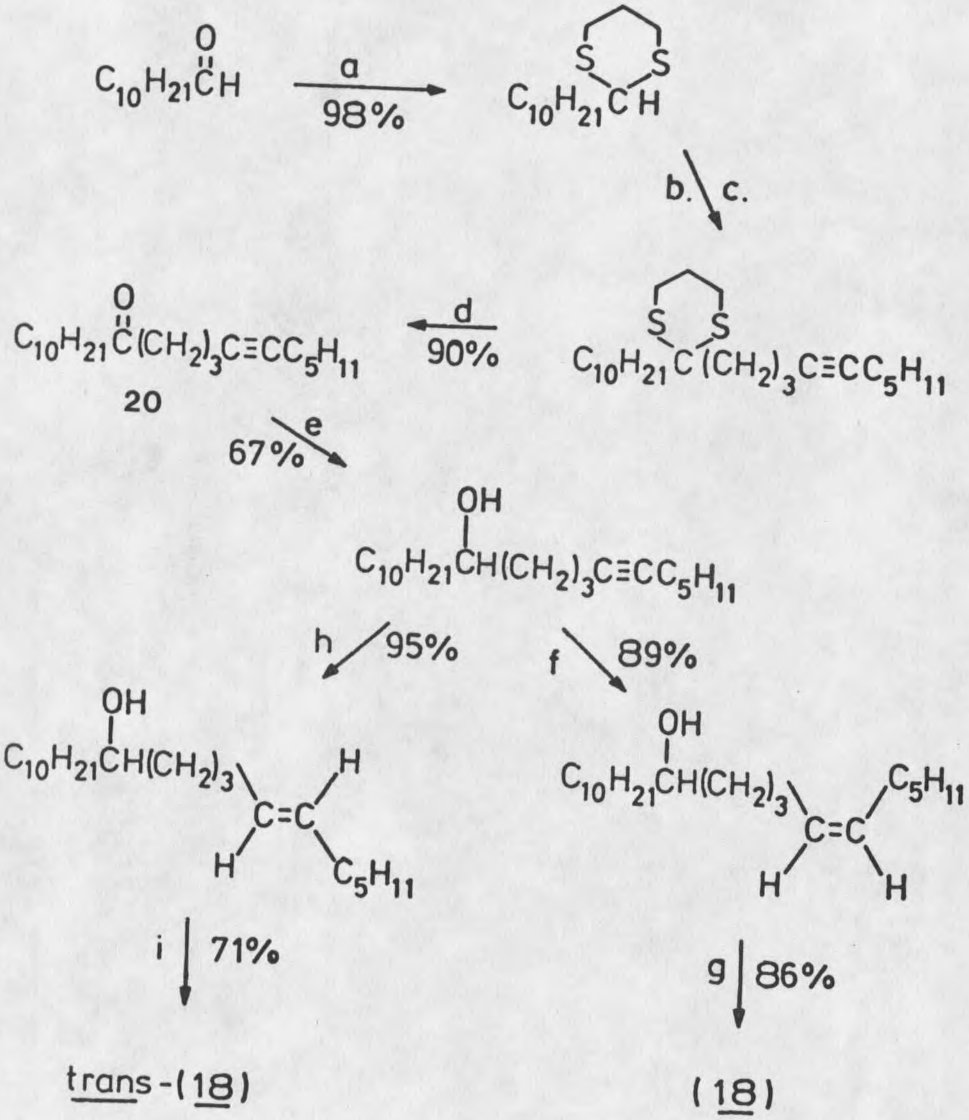
Figure 6. Unsaturated Ketones Found to Be Insect Sex Pheromones

Upon examination of **18**, it can be seen that fragmentation of an appropriate ketal could afford the δ,ϵ- unsaturation present. With this observation, coupled with the fact that **18** may soon be utilized to control the pesky DFTM, we directed our primary efforts toward the synthesis of this pheromone.

Since its isolation and identification in 1975, **18** has been the target of numerous synthetic preparations. In addition to the isolation and characterization of **18**, Smith also performed a total synthesis of the pheromone and its corresponding trans isomer,[16] utilizing the acetylenic ketone intermediate, **(20)**, as shown in Figure 7.

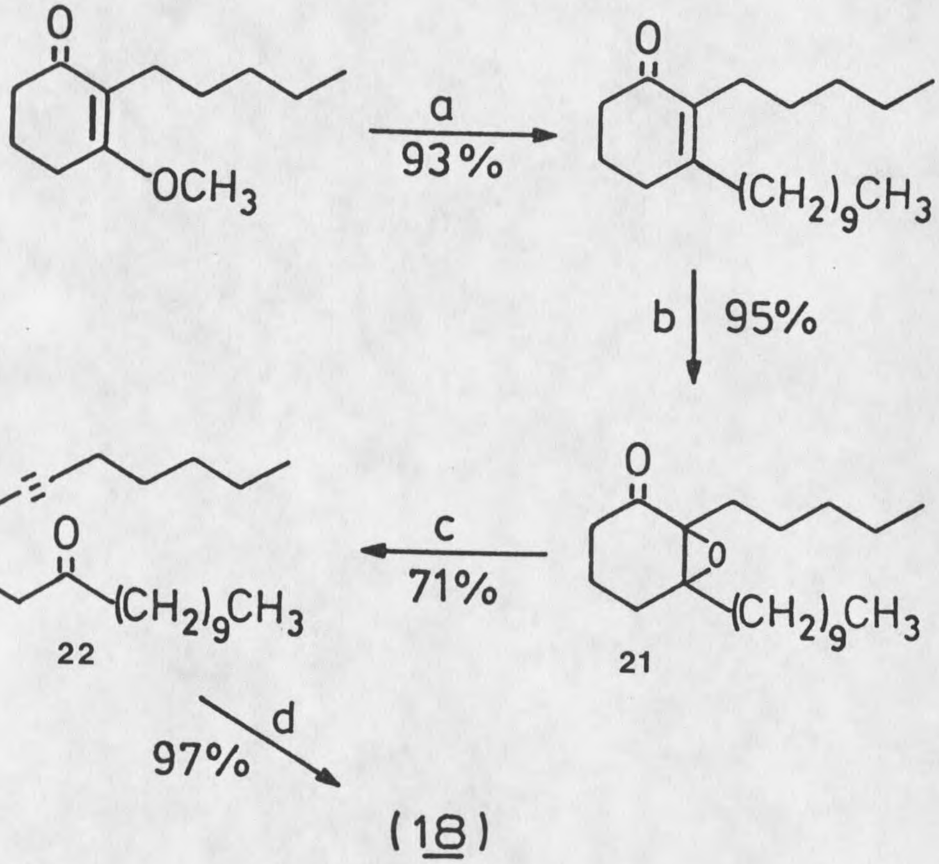
In 1976, Kocienski[17] converted the intermediate epoxide, **(21)**, to the acetylenic ketone, **(22)**, in one step with subsequent hydrogenation over Lindlar's catalyst to give the attractant in 60% overall yield (Figure 8).

An interesting preparation by Zweifel and Pearson[18] in 1980, made use of the mixed thexyldiorganoborane, **(23)**, to achieve their objective with a 74% yield (Figure 9).



(a) BF_3-etherate/$HS(CH_2)_3SH$; (b) C_4H_9Li; (c) $Cl(CH_2)_3C{\equiv}CC_5H_{11}$
(d) CuO, $CuCl_2$, CH_3COCH_3; (e) $LiAlH_4$; (f) H_2/P-2Ni, $H_2N(CH_2)_2NH_2$;
(g) CrO_3/Pyr; (h) Na/NH_3(l); (i) CrO_3/Pyr

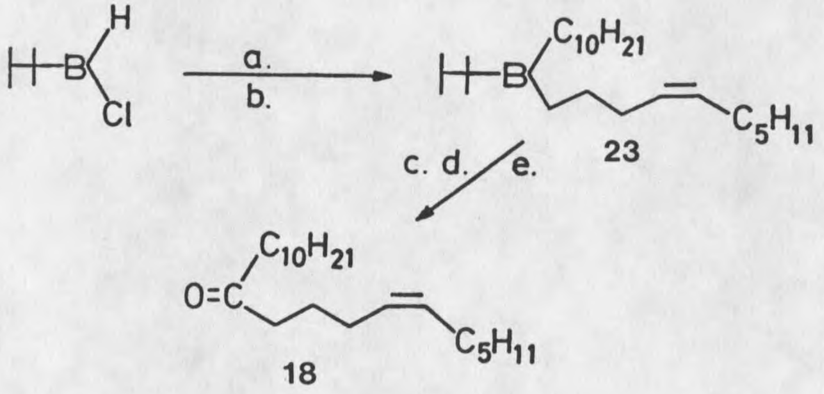
Figure 7. Smith's Synthesis of the DFTM Sex Attractant



(a) n-$C_{10}H_{21}MgBr/Et_2O$, H_3O^+; (b) H_2O_2-NaOH/MeOH;

(c) p-$TsNHNH_2/CH_2Cl_2$-HoAc; (d) H_2-Pd/$BaSO_4$, MeOH-pyridine

Figure 8. Kocienski's Synthesis



(a) $C_8H_{17}CH{=}CH_2$/THF; (b) $H_{11}C_5CH{=}CH(CH_2)_3MgCl/Et_2O$, -78°C; (c) NaCN; (d) C_6H_5COCl; (e) $NaOH/H_2O_2$

Figure 9. Zweifel's Synthesis

Figure 10 shows the approach of Fernández et al.[19] in 1983. With this synthesis, the pheromone was conveniently produced in three steps from δ-valerolactone, **(24)**. In a slightly longer synthesis, Fernández and co-workers[20] reacted furfural, **(26)**, with n-declymagnesium bromide, followed by hydrogenation and Jones oxidation to give the ketol, **(25)**. Duplication of steps used in their previous synthesis afforded **18** in a 24% overall yield (Figure 11).

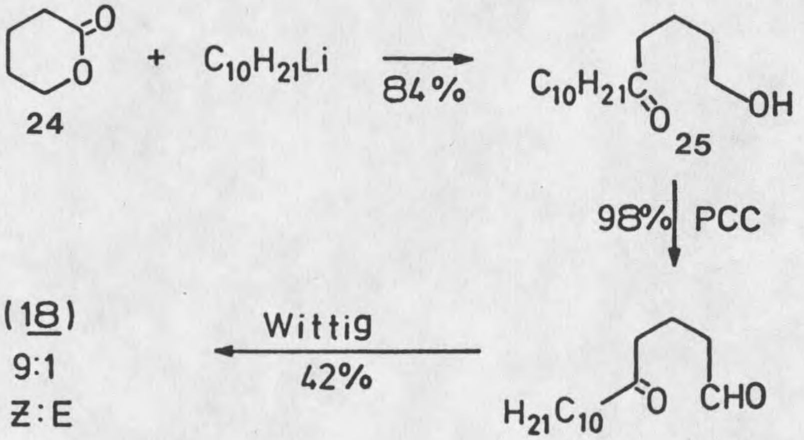
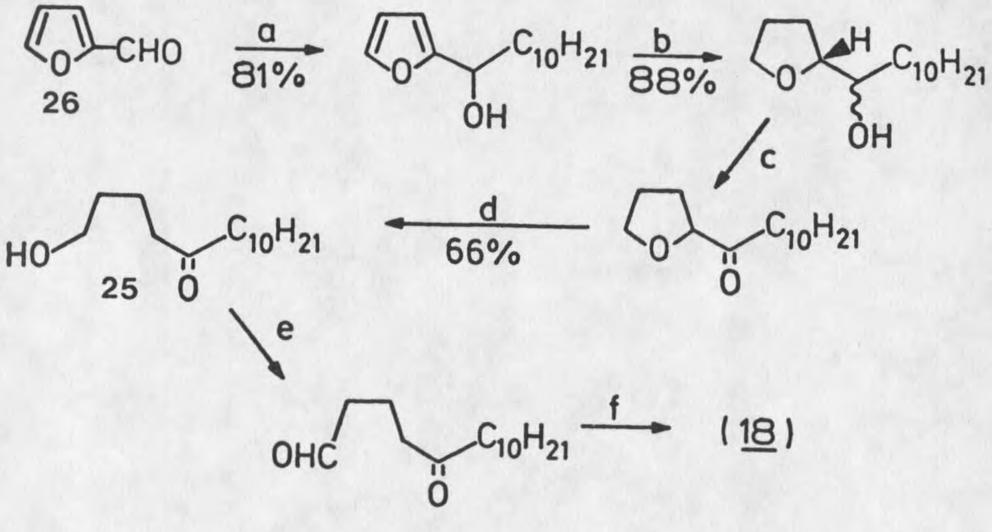


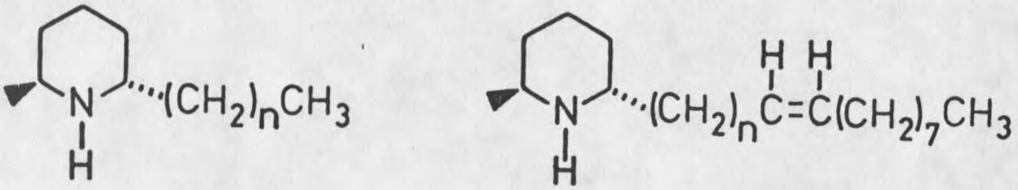
Figure 10. Fernández's Synthesis



(a) $CH_3(CH_2)_9MgBr$; (b) H_2, 5% Rh/c; (c) H_2CrO_4, H_2SO_4, H_2O;
(d) HMPA-Li/THF, $-78^{\circ}C$; (e) PCC; (f) triphenylphosphinehexylide

Figure 11. Fernández's Alternate Synthesis

While assessing the value of the fragmentation reaction depicted in Figure 5 as a means of preparing **18** as well as other δ,ϵ-unsaturated ketones, it did not escape our attention that the reaction might also serve as the key step in the syntheses of other non-ketonoid natural products. One such set of molecules is the venom constituents from the red form of the fire ant, (*Solenopsis saevissima*), identified in 1971 by MacConnell et al.[21] (Figure 12).



27: n = 10
28: n = 12
29: n = 14

30: n = 3
31: n = 5

Figure 12. Constituents From the Venom of the Fire Ant

This fire ant is found in the southern United States, and has its name derived from the potency of its venom, which has been shown to exhibit pronounced hemolytic,[22] insecticidal and antibiotic[23] activity.

If examined retrosynthetically, it can be seen that the fragmentation reaction mentioned earlier could indeed be used as an important step en route to the heterocyclic venom constituents (Figure 13).

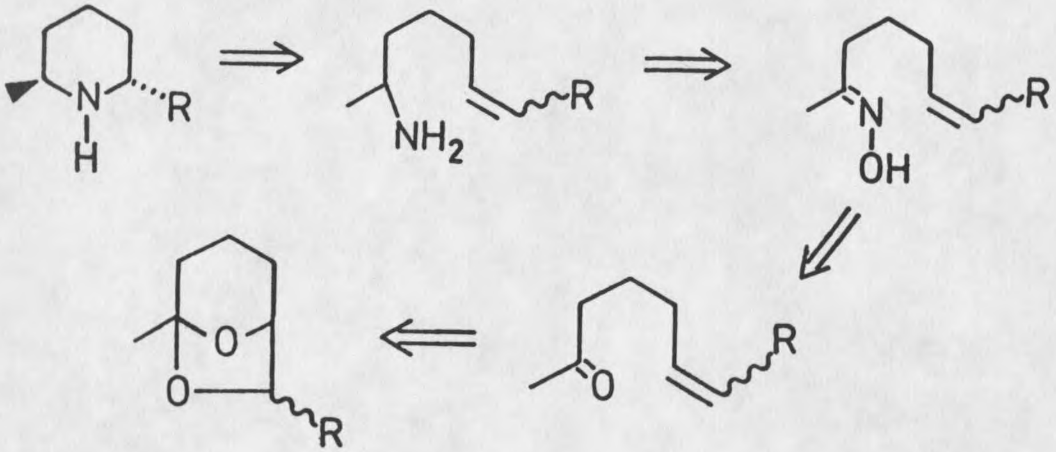
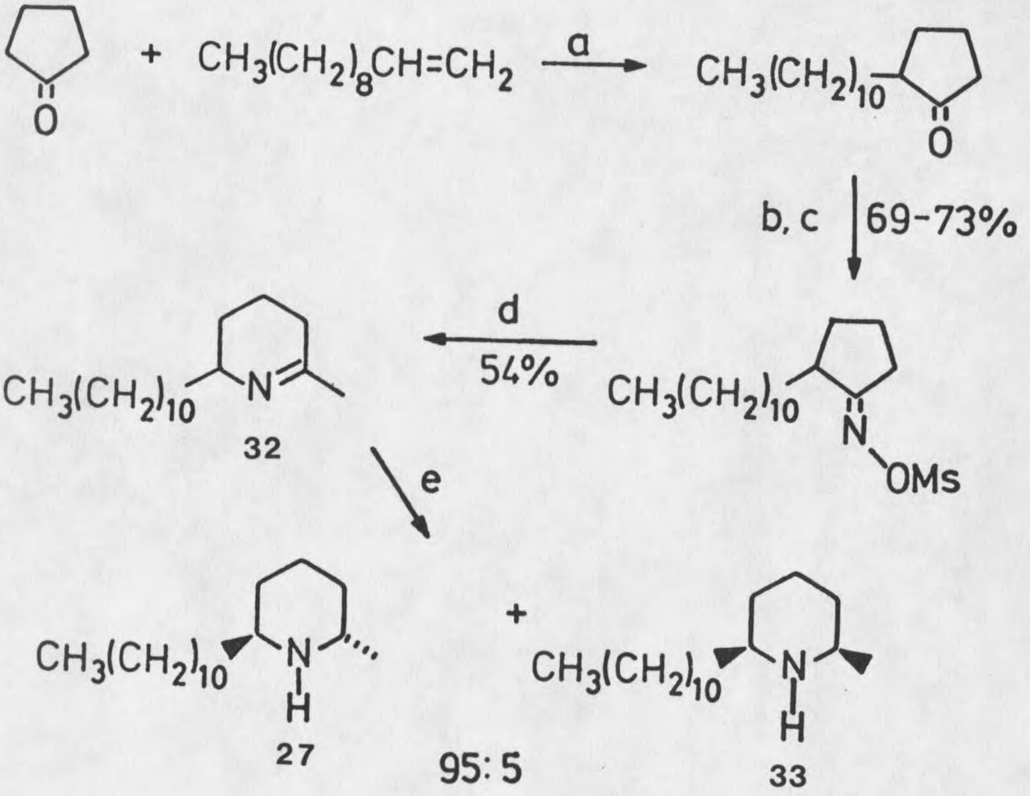


Figure 13. Retrosynthetic Analysis of the Constituents of Fire Ant Venom

An example of a previous synthesis of solenopsin A, (<u>27</u>), by Yamamoto et al.[24] is shown in Figure 14. The crucial step in this preparation was the specific reduction of the double bond in <u>32</u> to give predominantly <u>27</u> with little or no reduction to the undesirable cis product, (<u>33</u>). After much effort, the system which gave the best results was one equivalent each of trimethylaluminum and lithium aluminum hydride added to the reaction mixture slowly at low temperature. This system produced a product mixture 95:5 in favor of the desired isomer, (<u>27</u>).



(a) Ag_2O; (b) $NH_2OH{\cdot}HCl$; (c) CH_3SO_2Cl, Et_3N/CH_2Cl_2;
(d) $(CH_3)_3Al/CH_2Cl_2$; (e) 1:1 - $LiAlH_4:(CH_3)_3Al/THF$

Figure 14. Yamamoto's Synthesis of Solenopsin A

Having carefully considered the significance of the cleavage reaction, it was concluded that it could serve as a useful synthetic tool. The following results therefore attempt to somewhat generalize the reaction, and demonstrate its applicability in novel synthetic routes of <u>18</u> and <u>27</u>.

RESULTS AND DISCUSSION

As was discussed earlier, our desire to procure a novel entry into the oxepane derivatives via the cleavage of the C-5 - O-8 bond in ketals with the 6,8-dioxabicyclo[3.2.1]octane skeletal system, led us to try acetyl iodide generated in situ as a means of bond cleavage. It has been shown by Oku et al.[11] that cyclic ether cleavage with the use of acetyl iodide proceeds as shown in Figure 15, with the product being the iodo-alkylacetate.

Figure 15. Cleavage of Ethers With Acetyl Iodide

It was our hope that we would observe a product similar to that shown in Figure 16, with the reaction proceeding much like that observed for cyclic ethers.

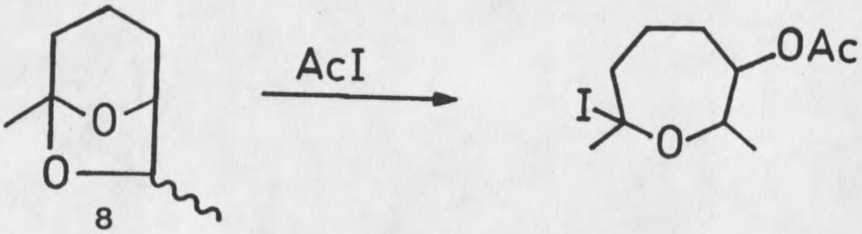


Figure 16. Hypothetical Reaction of 5,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane With Acetyl Iodide

The result that was obtained, shown in Figure 5, clearly did not give the desired result. In fact, the result observed caused us to turn our attention away from oxepane derivatives and toward natural products which might be prepared by using the unique fragmentation reaction. The first task, however, was to see how different bicyclic ketals reacted and if, in fact, all were opened in a similar manner, resulting in their corresponding δ,ϵ-unsaturated ketones.

In addition to 8, a representative sampling of bicyclic ketals including 5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane, **(36)**, 5-methyl-7-ethyl-6,8-dioxabicyclo[3.2.1]octane, (2), and 5-methyl-7-(2-phenylethyl)-6,8-dioxabicyclo[3.2.1]octane, **(42)**, were chosen because of the varying substitution patterns at C-7. A tremendous asset in this endeavor was our group's past experience and expertise in preparing substituted bicyclic ketals.

The preparation of 8 was accomplished by dimerization of methyl vinyl ketone (MVK) to give 7, followed by reduction with sodium borohydride to the alcohol, **(34)**. Cyclization of 34 with tosic acid resulted in a good yield of an exo/endo isomeric mixture of 8 (Figure 17).

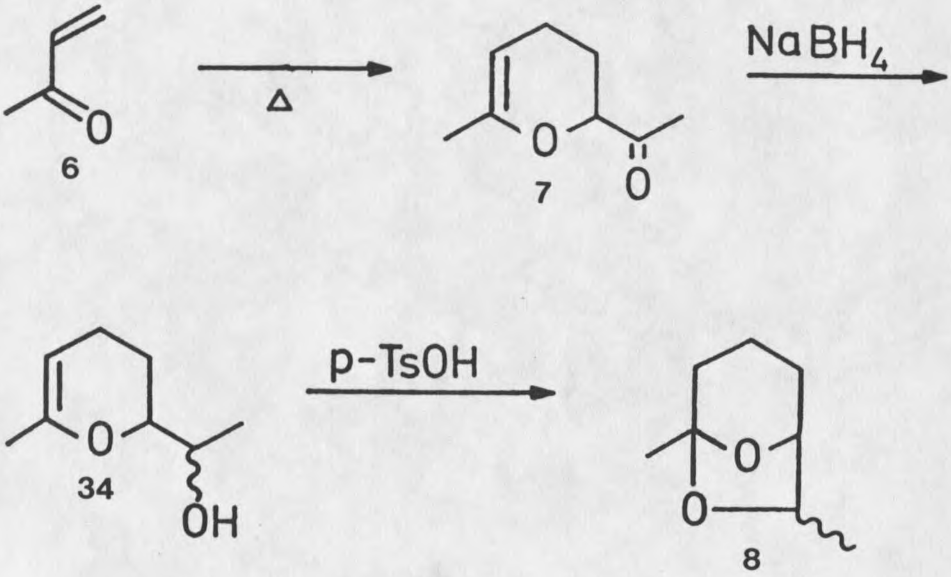


Figure 17. The Preparation of 5,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

A very straightforward scheme was also used in the preparation of <u>36</u>. Starting with MVK dimer, Figure 18 shows how addition of methyl magnesium bromide yielded the alcohol, (<u>35</u>), which upon treatment with tosic acid cyclized to give the desired product in 53% overall yield.

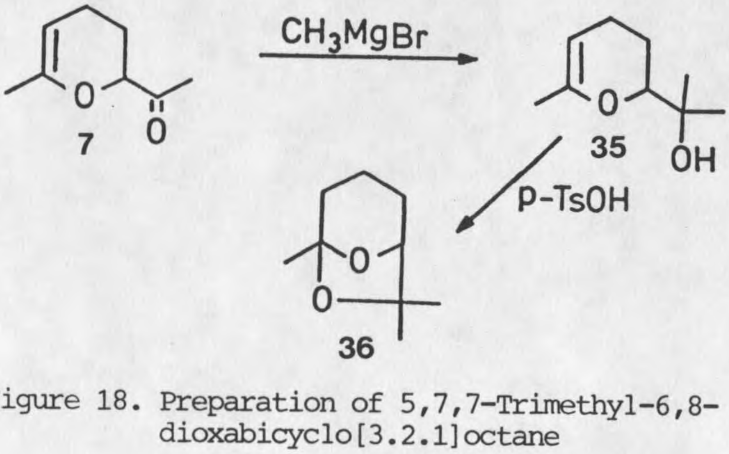


Figure 18. Preparation of 5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane

In order to prepare 2 and 42 from MVK dimer, (7), it was necessary to attach the appropriate side chain to the methyl group alpha to the carbonyl. This was accomplished using a methodology developed by Stork and Dowd.[25] Figure 19 demonstrates how an intermediate enamine salt, (37), was generated by treating MVK dimer with cyclohexyl amine, then reacting the resulting imine with a Grignard reagent. Addition of either iodomethane or α-iodo toluene to the enamine salt, followed by mild hydrolysis, resulted in good yields of 38 and 40, respectively. Reduction of the carbonyl and treatment of the resulting alcohols, (39) and (41), with tosic acid produced the desired bicyclic ketals.

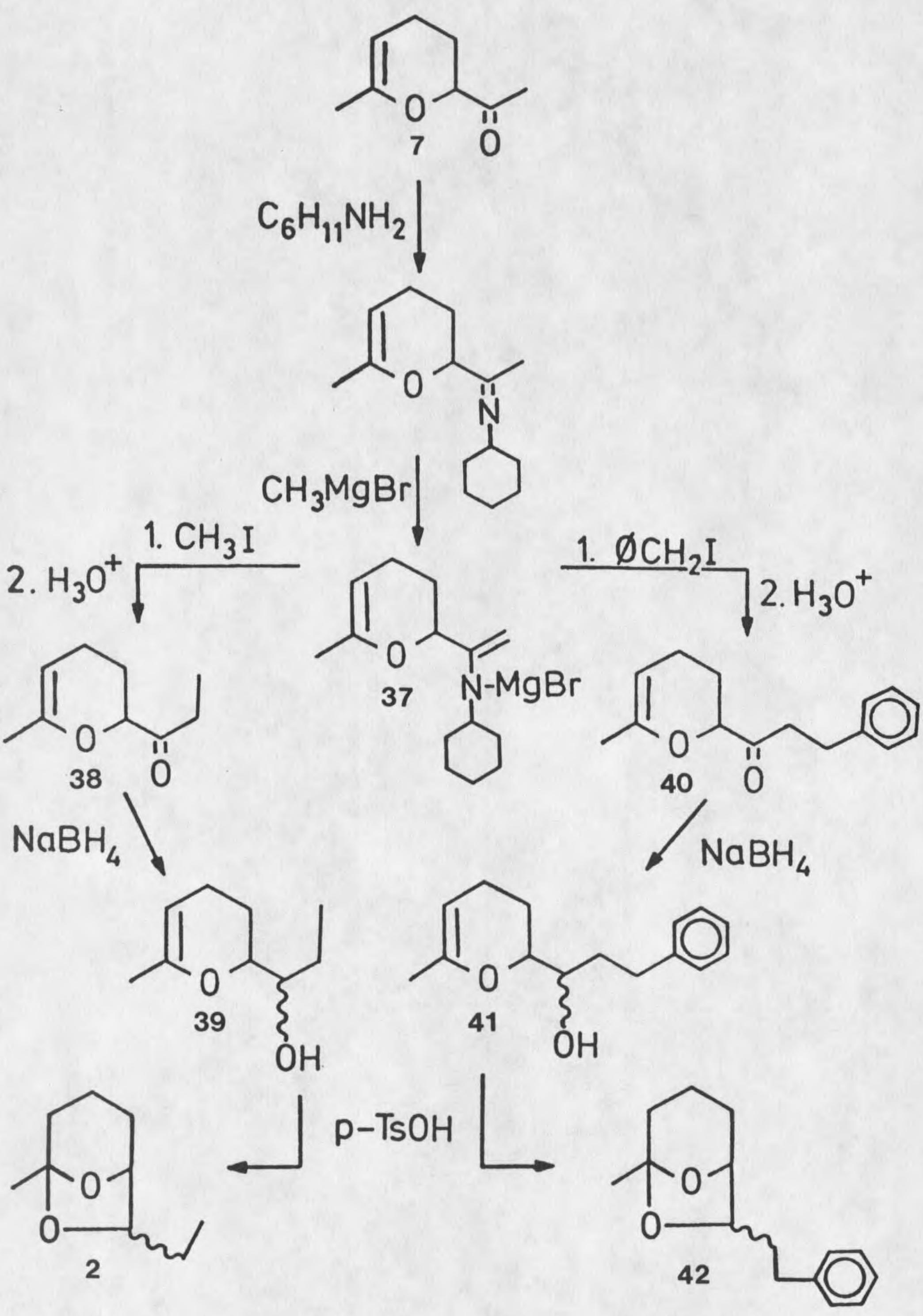


Figure 19. Preparation of 5-Methyl-7-ethyl and 5-Methyl-7-(2-phenylethyl)-6,8-dioxabicyclo[3.2.1]octane

It is noteworthy to mention that in addition to cyclization via tosic acid, we also observed cyclization upon injection of any of the alcohols, (34), (35), (39), or (41), into the gas chromatograph. That is, when GLC collections were done and the products were identified, it was always found that the alcohols had been converted to their corresponding bicyclic ketals.

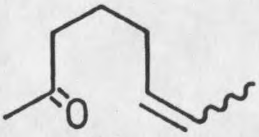
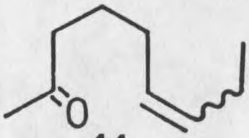
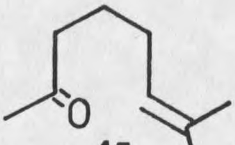
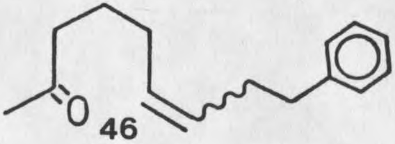
Having successfully prepared the bicyclic ketals (8), (36), (2) and (42), the series of cleavages was undertaken.

All four ketals were fragmented under identical conditions, which involved the generation of acetyl iodide in situ by slowly adding an acetonitrile[26] solution of acetyl chloride to a solution of the ketal and sodium iodide stirring in acetonitrile at 0°C. After continuous stirring at ambient temperature for 24 hours, the reaction mixtures were subjected to workup which included aqueous washings of sodium thiosulfate, sodium bicarbonate and brine. Initial cleavages were carried out using one equivalent each of the reagents and the ketals; however, considerable amounts of ketal remained unreacted. This problem was easily circumvented by using two equivalents of the reagents for each equivalent of ketal. Attempts to purify the products by vacuum distillation were unsuccessful because substantial decomposition occurred during even mild heating.

Following workup, the products were cleaned by passing them through a pad of silica gel. GLC integration was then used to determine the percent yields, which are listed in Table 1, along with ratios of exo/endo isomers in the starting materials, and ratios of trans/cis isomers in the resulting ketones.

Table 1

Acetyl Iodide Fragmentation of Bicyclic Ketals

Ketal	% exo/endo	Product	% trans/cis	Yield
(8)	60/40	 **14**	65/35	30%
(2)	60/40	 **44**	71/29	31%
(36)	---	 **45**	---	24%
(42)	60/40	 **46**	70/30	33%

The results of the fragmentations proved to be very intriguing. A trend which presented itself was that in each fragmentation the ratio of trans/cis products closely corresponded to the exo/endo isomeric ratio observed for the starting materials. Although this result can be interpreted in more than one way, we proposed a mechanism similar to that used Goldsmith[27] for ether cleavage (Figure 20).

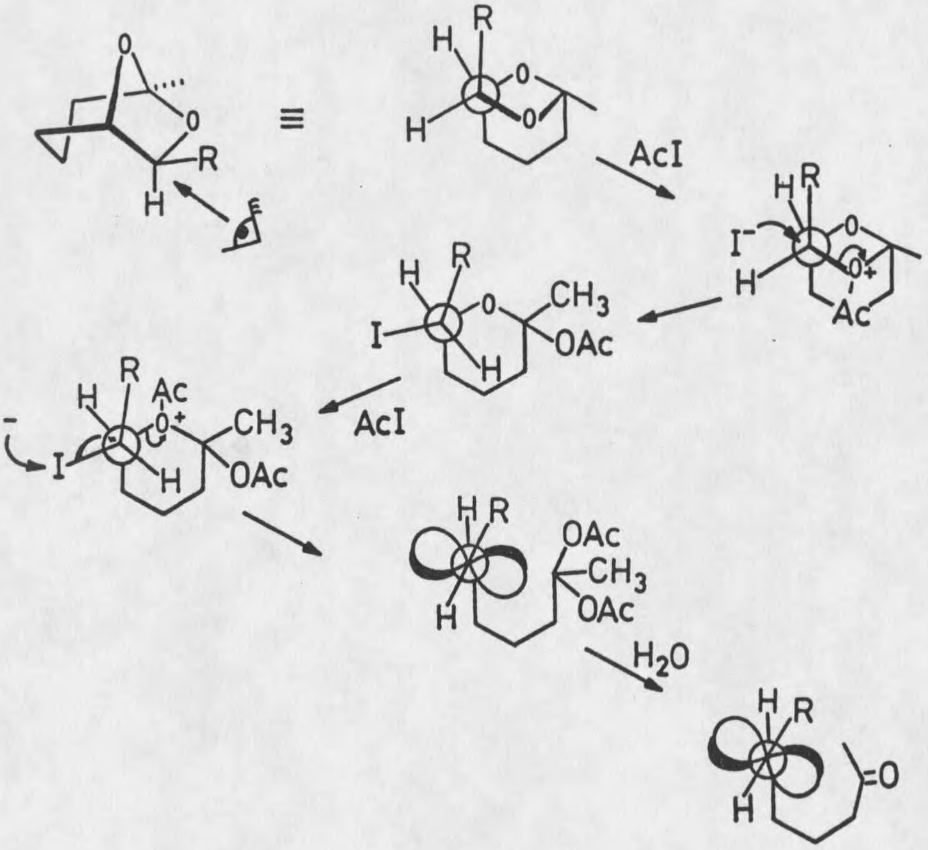


Figure 20. Proposed Mechanism for Bicyclic Ketal Cleavage

With this mechanism, it follows that exo-ketals give trans-ketones, and endo-ketals give only cis-ketones. Although the same results would be observed should the first acetate coordinate with O-8, the propensity of the first coordination to occur at O-6, as discussed earlier, led us to propose the mechanism above.

Having shown the generality of the fragmentation reaction toward several different bicyclic ketals, it was our desire to demonstrate its value as a practical synthetic tool.

(Z)-6-Heneicosen-11-one, (**18**), the sex pheromone of the Douglas-fir tussock moth, is a δ,ϵ-unsaturated ketone and served as an excellent subject for our initial synthetic efforts.

A retrosynthetic analysis of the pheromone reveals that it could be obtained by cleaving the bicyclic ketal, (**47**), as shown in Figure 21. Unlike the previous bicyclic ketals, which all contained a methyl group at C-5, **47** must incorporate a ten carbon chain at C-5. Therefore, in order to prepare **47**, it was necessary to employ different chemistry than that used to prepare the previous ketals.

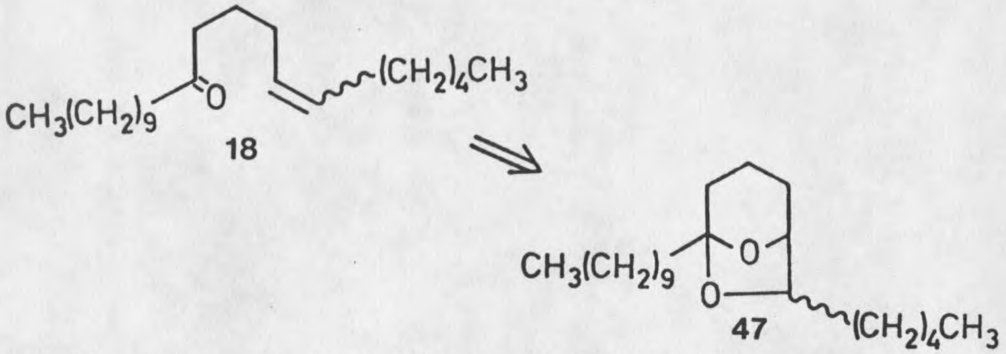


Figure 21. Retrosynthetic Analysis of (E) and (Z)-6-Heneicosen-11-one

Our first consideration as an approach to **47** was to take advantage of the ability of substituted dihydropyrans to undergo oxy-Cope rearrangement. Studies done by Lutz and Roberts[28] in 1971 showed how deuterium labeled 2-formyl-2,5-dimethyl-3,4-dihydro-2H-pyran, (**48**), could thermally isomerize to give **49** (Figure 22).

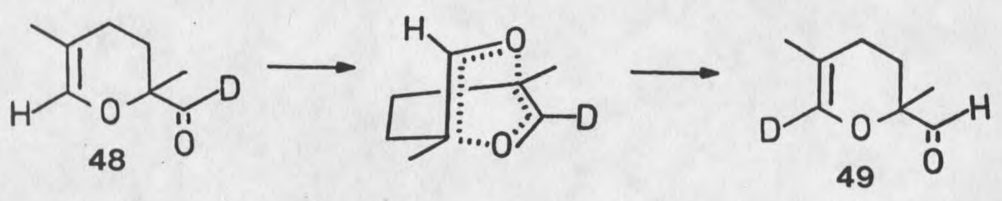


Figure 22. Oxy-Cope Rearrangement of Deuterium Substituted 2-Formyl-2,5-dimethyl-3,4-dihydro-2H-pyran

This knowledge, coupled with our ability to α-alkylate 7, led us to propose a tandem alkylation rearrangement approach to **47** as shown in Figure 23.

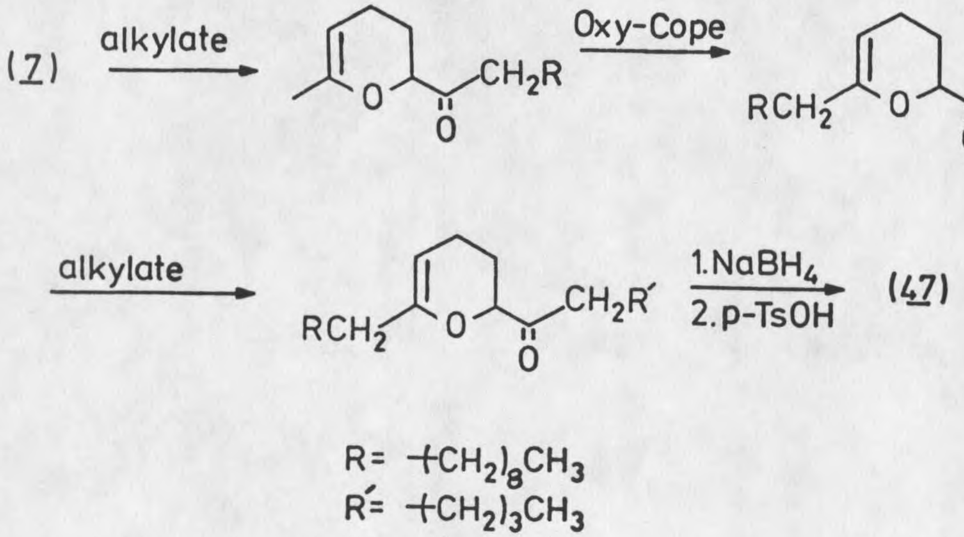


Figure 23. Proposed Preparation of 5-Decyl-7-pentyl-6,8-dioxabicyclo[3.2.1]octane

However, before any attempts at such a scheme were undertaken, a preparation of brevicomin, (2), by Cohen and Bhupathy[29] came to our attention. In a one flask synthesis, brevicomin was synthesized from acrolein dimer, (50). Sequential treatment of 50 with excess ethyllithium and methyl iodide, followed by aqueous acidic workup afforded 2 in 69% yield as a 4:1 mixture of endo and exo isomers as shown in Figure 24.

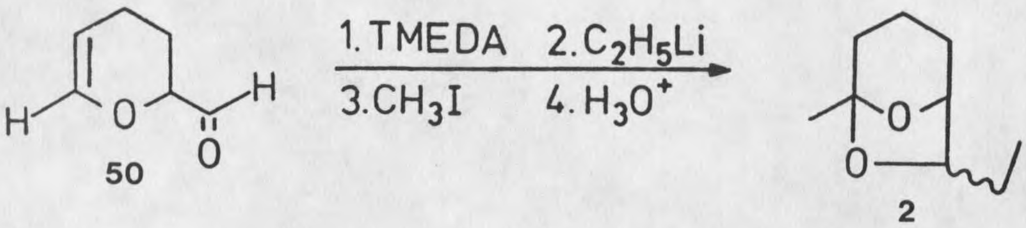


Figure 24. One Flask Synthesis of Brevicomin

Our interest in this preparation lay in the fact that by substituting n-pentyllithium for ethyllithium, and using n-decyl iodide rather than methyl iodide, 47 might be readily obtained.

Figure 25 illustrates the mechanism of the reaction. Upon addition of the first equivalent of alkyllithium, the threo and erythro isomers, (51), are formed. The remaining alkyllithium then deprotonates the 6-position, resulting in the dilithium salt, (52), which upon addition of the alkyl iodide is converted to (53). Upon treatment with acid 53 is cyclized to give the corresponding bicyclic ketal.

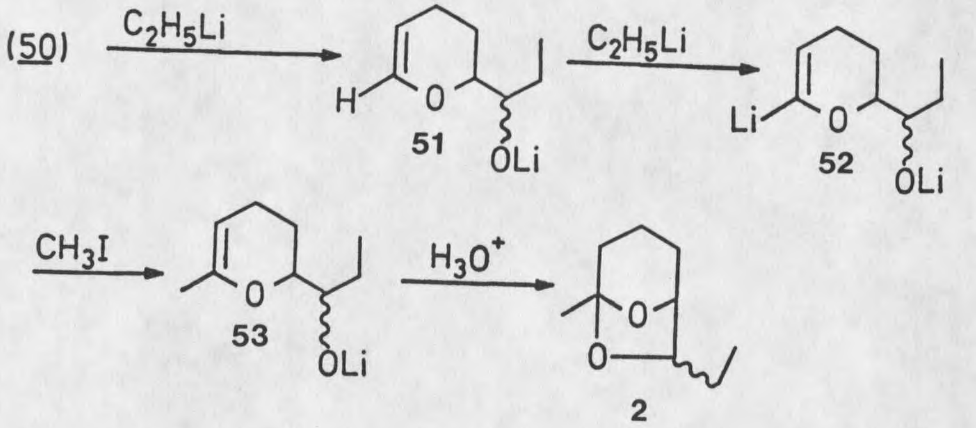


Figure 25. Mechanism for the Cohen-Bhupathy Synthesis of Brevicomin

Much to our dismay, attempts to duplicate the reaction sequence using n-pentyllithium and n-decyl iodide under a variety of reaction conditions resulted in failure. Not only was **47** not generated, but the only molecules that could be detected following workup were starting materials. Because of this observation, we concluded that the n-pentyllithium was not properly generated.

A second method for the preparation of the isomeric brevicomins was also mentioned in the Cohen paper. This method involved the addition of ethyl magnesium bromide to **50**, yielding the conjugate acids of **51**. These were isolated and subjected to treatment with two equivalents of an alkyllithium to generate **52**. Alkylation of **52** was followed by cyclization as before. Our first attempt having been futile, we chose to pursue the latter method.

The Grignard reagent, n-pentyl magnesium bromide, was generated by adding n-pentyl bromide to magnesium filings in dry ether. The Grignard reagent was added to an ethereal solution of **50** at 0°C. After an aqueous workup, a 79% yield of the isomeric alcohols, **(54)**, was obtained (Figure 26).

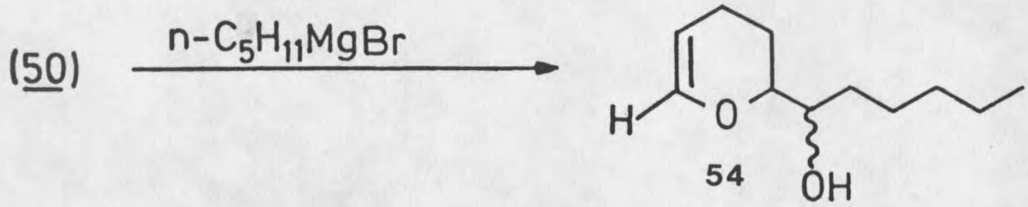


Figure 26. Preparation of 2-(1-Hydroxyhexyl)-3,4-dihydro-2H-pyran

Optimistic with success to this point, the alcohol was treated with two equivalents of tertiary butyllithium at -78°C. After addition of the n-decyl iodide, the reaction mixture was stirred for 16 hours at room temperature. An acidic workup gave a flocculent white solid, which to our consternation, was revealed by mass spectral analysis to be eicosane.

An explanation for this came upon considering the reaction conditions used. At -78°C, and with a short time lapse between the addition of the tertiary butyllithium and that of the n-decyl iodide, insufficient deprotonation of the 6-position of **54** occurred. Instead, exchange between the tertiary butyllithium and some of the n-decyl iodide resulted in the formation of n-decyllithium; the n-decyllithium then executed S_N2 attack on the remaining n-decyl iodide, resulting in the formation of eicosane. However, when the tertiary butyllithium was stirred with **54** for many hours at room temperature before the addition of n-decyl iodide, the product, **(47)**, still eluded us as once again only starting materials were obtained.

Somewhat frustrated, we sought a different set of conditions to use. In 1981, Boeckman and Bruza[30] published work describing the generation of cyclic vinyl ether carbanions. Their procedure called for the addition of the alkyllithium at -78°C, warming to 0°C and stirring for thirty minutes. The alkyl iodide was then added at 0°C and the resulting solution was stirred for one hour. They commented that little or no reaction occurred until the temperature was warmed to 0°C, and the anion generated was stable for at least several hours at room temperature. Using conditions similar to Boeckman and Bruza, a 70:30 *exo*:*endo* isomeric mixture of the ketal, **(47)**, was at last obtained in 25% yield from **54** (Figure 27). It might also be noted that a small amount of eicosane was present as an impurity.

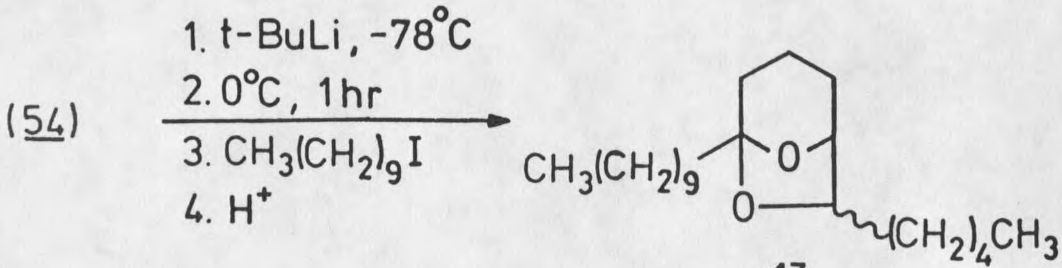
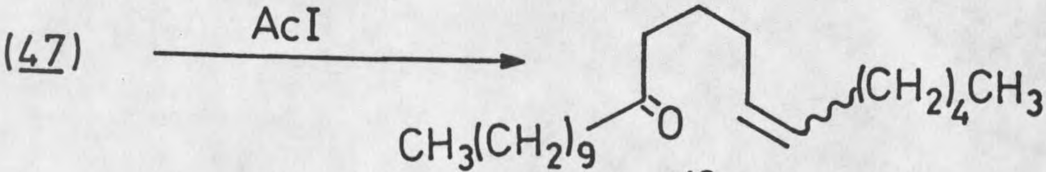


Figure 27. Preparation of 5-Decyl-7-pentyl-6,8-dioxabicyclo[3.2.1]octane

The final step was to cleave the bicyclic ketal, **(47)**, to the corresponding *trans* and *cis*-δ,ϵ-unsaturated ketones, **(18)**. Though only ketals with a methyl group at C-5 had been fragmented to this point, the mechanism proposed indicates that other C-5 substituted ketals should react as well. This was, in fact, the case and **47** was successfully cleaved to give a 23% yield of a 78:22 mixture of the *trans*:*cis* isomers of **18**, respectively (Figure 28).



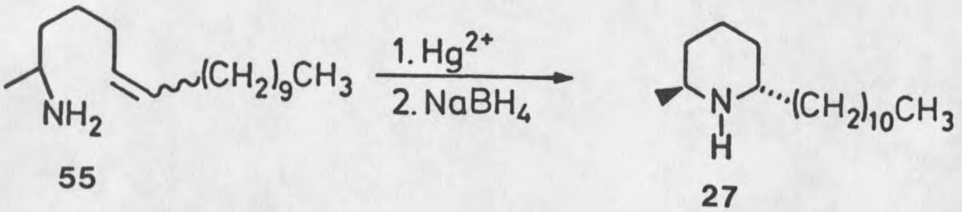
18

Figure 28. Cleavage of *exo*/*endo*-5-Decyl-7-pentyl-6,8-dioxabicyclo-[3.2.1]octane to *trans*/*cis*-6-Heneicosen-11-one

A question that may come to mind is why did we pursue the total synthesis of the pheromone, **(18)**, if our previous work demonstrated that the major isomer would be the non-natural *trans* isomer? The answer lies in the fact that though it is true the *cis* form is the isomer isolated from the female DFTM, the *trans* isomer has also been found to be a highly active sex attractant. In fact, in a laboratory and field bioassay,^{31} a 60:40 mixture of *trans*:*cis* isomers proved to be considerably more attractive to male DFTM than actual female extract!

To further demonstrate the utility of the novel fragmentation reaction, an effort to synthesize 2-methyl-6-undecylpiperidine, solenopsin A, **(27)**, was put forth.

Our target in this synthesis was the unsaturated amine, **(55)**. In a previous synthesis of solenopsin A, Khuong-Huu et al.[32] prepared 27 in one step with an amino-mercuration of 55 as shown in Figure 29. Thus, by procuring 55 we would thereby accomplish a new formal synthesis of 27.



55

27

Figure 29. Aminomercuration of 2-Amino-6-heptadecene

Using the enamine chemistry previously described, the ketone, **(56)**, was routinely generated in good yield from MVK dimer, **(7)**. Reduction of **56** with sodium borohydride afforded the alcohol, **(57)**, which upon treatment with tosic acid cyclized to give a 60:40 ratio of the exo:endo isomers of **(58)** in a 69% yield from **56**. Subsequent cleavage of **58** with acetyl iodide afforded a fair yield of a predominantly trans mixture of the cis and trans isomers of **59** (Figure 30).

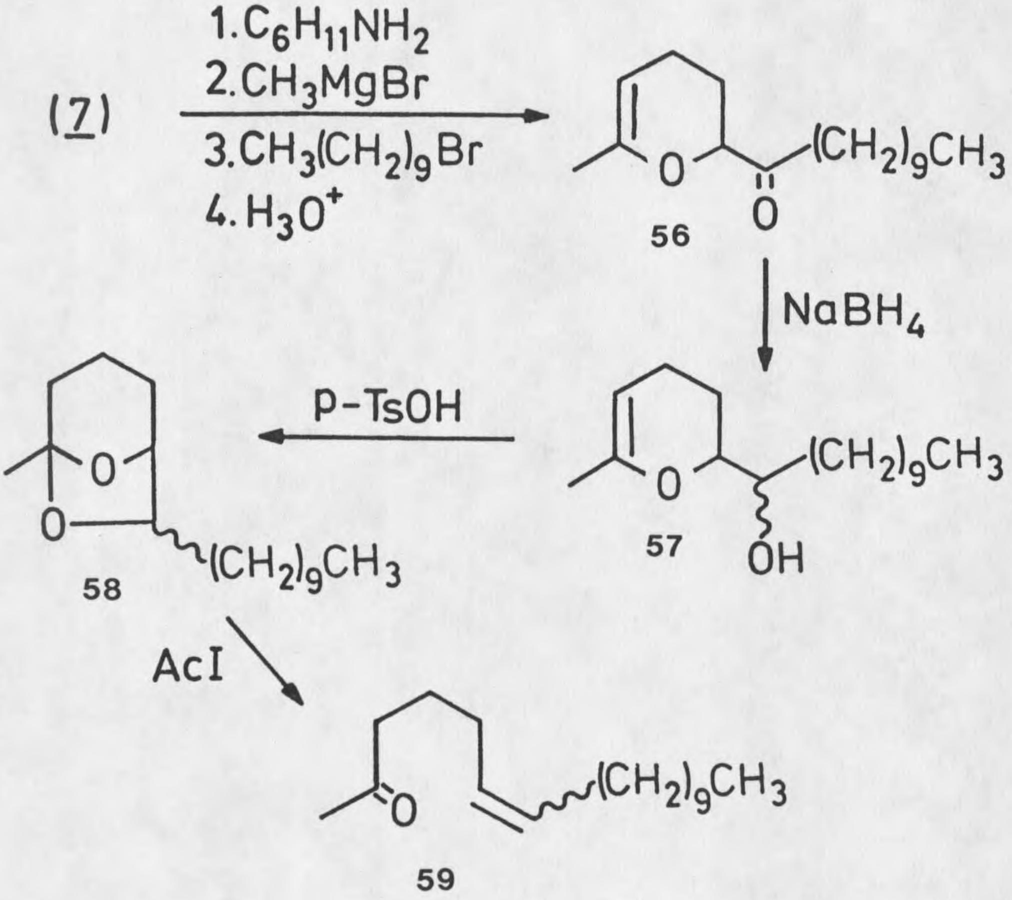
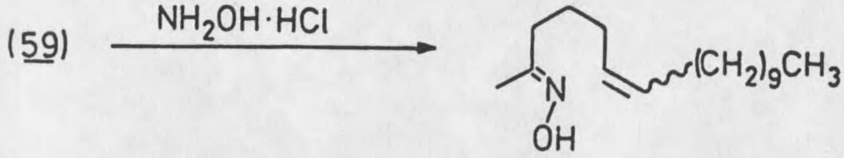


Figure 30. Preparation of trans/cis-Heptadecen-2-one

In order to attain 55, we first needed to prepare the intermediate oxime, **(60)**. This was readily accomplished by simply stirring the ketone, **(59)**, with two equivalents each of hydroxylamine hydrochloride and sodium acetate for a few hours at room temperature (Figure 31).



60

Figure 31. Oxime Formation From 6-Heptadecen-2-one

Reduction of the oxime, **(60)**, a seemingly straightforward reaction, was one that caused us some vexation. Since the preservation of the double bond was essential, catalytic hydrogenation was ruled out. Another method, described in some detail by Smith, Maienthal and Tipton,[33] was that of using lithium aluminum hydride to reduce the oxime. However, attempts at reduction with the hydride reagent under different reaction conditions failed to produce the amine, **(55)**.

In a recent paper by Ipaktschi,[34] the use of Molybdenum trioxide and sodium borohydride was reported as a means of reducing unsaturated oximes with the preservation of the double bond. The reaction conditions consisted of adding sodium borohydride to a solution of the oxime and molybdenum trioxide in methanol at 0°C, and stirring for one hour. Using conditions similar to these to reduce **60**, we obtained a product mixture shown by GC-MS to consist of 81% of the desired amine. Interestingly enough, an additional 10% of the product mixture gave a mass spectrum identical to that reported for the cyclized product, **(27)**[32]! Additional work to understand this novel cyclization is in progress.

SUMMARY

The results contained in this thesis represent an effort to generalize the reaction of bicyclic ketals with acetyl iodide. The reaction is significant in that it proceeds to cleave the bicyclic ketals to δ,ϵ-unsaturated ketones, which in several cases may serve as key intermediates in the syntheses of natural products. Indeed, the synthetic schemes presented have demonstrated the usefulness and consistency of the novel fragmentation.

Although the fragmentation has thus far only given fair yields, both the ease with which substituted bicyclic ketals can be prepared from inexpensive, readily available starting materials, and the convenience of directly obtaining the unsaturated ketones, serve as offsetting factors.

EXPERIMENTAL

Reported boiling points and melting points are uncorrected. All NMR spectra were recorded on a Bruker 250 MHz FT-NMR, with the chemical shifts reported in parts per million relative to TMS. $CDCl_3$ was used as a solvent and an internal standard. Mass spectra were obtained using a VG MM16 mass spectrometer and accurate mass data were obtained using a VG 7070 high resolution mass spectrometer. Infrared spectra were recorded using a Beckman IR-5 spectrometer with absorption frequencies being reported in reciprocal centimeters.

GLC analyses were performed using either a Varian Aerograph series 2700 (1/4") or series 1400 (1/8") gas chromatograph. Unless otherwise stated, all integrative analyses were obtained using the Varian 1400, equipped with a 8' x 1/8" 13% DEGS column and interfaced with a Spectra Physics - Autolab Minigrator.

Preparation of 2-Acetyl-6-Methyl-3,4-Dihydro-2H-Pyran, (**7**)

A solution of 84 g (1.20 moles) of methyl vinyl ketone (3-buten-2-one), .5 g of hydroquinone and 50 ml of benzene was placed in a steel pressure bomb and heated at 175°C for 3 hours. After cooling, the solvent was removed via a rotatory evaporator and the product was distilled (water aspirator). Collection from 65-75°C gave 56.5 g (.40 moles) of a clear, colorless liquid (67% yield).

The spectral data was identical to previous work.[35]

Preparation of 2-(1-Hydroxyethyl)-6-Methyl-3,4-Dihydro-2H-Pyran, (**34**)

10 g (.071 moles) of methyl vinyl ketone dimer, (**7**), was placed in 75 ml of methanol and cooled to 0°C. 1.0 g (.026 moles) of sodium borohydride was added slowly with stirring and the resulting solution was stirred for 1 hour at room temperature. 75 ml of water was then added and the resulting solution was extracted with three 75 ml portions of methylene chloride which were combined, dried over magnesium sulfate and reduced in volume via the rotatory evaporator.

The alcohol was not purified, but used directly for the next step.

Preparation of exo/endo-5,7-Dimethyl-6,8-Dioxabicyclo[3.2.1] octane, (**8**)

The crude alcohol, (**34**), was added to a solution of a catalytic amount of tosic acid stirring in 100 ml of benzene. The resulting solution was stirred at room temperature for 30 minutes, at the end of which time the solution was washed with two 50 ml portions of aqueous sodium bicarbonate and two 50 ml portions of water, dried over magnesium sulfate and reduced in volume via the rotatory evaporator.

Distillation of the crude product, and collection of the fraction at 55-65°C (water aspirator), yielded 6.9 g (.05 moles) of a clear, colorless liquid [68% yield from **7**].

The exo:endo isomeric ratio was 60:40 as determined by GLC analysis and the spectral data was identical to previous work.[36]

Preparation of 2-(1-Hydroxy-1-Methylethyl)-6-Methyl-3,4-Dihydro-2H-Pyran, (35)

14 g (.1 moles) of 7 was stirred in 200 ml of tetrahydrofuran under nitrogen while 40 ml (.128 moles) of 3.2 molar methyl magnesium bromide was added via a syringe over a period of 10 minutes. The reaction mixture was stirred at room temperature for 16 hours, after which the reaction was quenched with 25 ml of water and stirred for 10 minutes. The organic layer was poured off, dried over anhydrous magnesium sulfate and reduced in volume. 12.5 g (80% crude yield) of the crude alcohol was obtained as a clear, slightly yellow liquid.

The alcohol was not purified, but used directly for the next step.

Preparation of 5,7,7-Trimethyl-6,8-Dioxabicyclo[3.2.1]octane, (36)

11 g (.07 moles) of the crude alcohol, (35), was placed in a solution of a catalytic amount of tosic acid in 100 ml of benzene. The solution was stirred at room temperature for 3 hours, after which time it was washed with two portions each of aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate and reduced in volume. Distillation (water aspirator) and collection of the fraction at 63-65°C gave 7.2 g (.046 moles) of a clear, colorless liquid (53% yield from 7).

^{1}H-NMR: 3.87 (1H, br s); 2.0-1.45 (6H, m); 1.41 (3H, s);
1.37 (3H, s); 1.27 (3H, s)

Preparation of 2-Propionyl-6-Methyl-3,4-Dihydro-2H-Pyran, (38)

7 g (.05 moles) of (7) and 5 g (.05 moles) of cyclohexylamine were placed in 100 ml of dry benzene and refluxed using a Dean-Stark water trap for 24 hours, after which the reaction mixture was reduced in volume and the crude imine placed in a solution of a slight excess of methyl magnesium bromide stirring in 150 ml of dry tetrahydrofuran under a nitrogen atmosphere. This mixture was refluxed for 4.5 hours, cooled to 0°C, and 7.1 g (.05 moles) of methyl iodide was added slowly. The resulting solution was warmed for 24 hours with stirring. The solution was once again cooled to 0°C and 1 equivalent of 5% aqueous acetic acid was added slowly and stirred for 30 minutes. The resulting mixture was extracted with three 75 ml portions of ether which were combined, washed with two portions of aqueous sodium bicarbonate, two portions of water, dried over anhydrous magnesium sulfate and reduced in volume via the rotatory evaporator. Distillation (water aspirator) and collection of the fraction at 85°C gave 4.6 g (.03 moles) of a clear liquid (60% yield).

The spectral data was identical to previous work.[37]

Preparation of 2-(1-Hydroxypropyl)-6-Methyl-3,4-Dihydro-2H-Pyran, (39)

An excess of sodium borohydride was slowly added to a solution of 4.0 g (.026 moles) of 38 stirring in 50 ml of methanol at 0°C. The solution was stirred for 45 minutes at room temperature, after which time 50 ml of water were added and the resulting solution extracted with three 50 ml portions of methylene chloride which were combined, dried over anhydrous magnesium sulfate and reduced in volume via the rotatory evaporator.

The alcohol (3.3 g, 81% crude yield) was not purified, but used directly for the next step.

Preparation of exo/endo-5-Methyl-7-Ethyl-6,8-Dioxabicyclo[3.2.1] octane, **(2)**

2.8 g (.018 moles) of the crude alcohol, **(39)**, was stirred with a catalytic amount of tosic acid in 50 ml of benzene at room temperature. After 2 hours the solution was washed with two 50 ml portions of aqueous sodium bicarbonate, two 50 ml portions of water, dried over anhydrous magnesium sulfate and reduced in volume. Distillation (water aspirator) and collection of the fraction at 78°C gave 2.3 g (.015 moles) of a clear, colorless liquid (68% yield from 38).

The exo:endo isomeric ratio was 60:40 as determined by GLC analysis and the spectral data was identical to previous work.[38]

Preparation of 2-(1-Oxo-3-Phenylpropyl)-6-Methyl-3,4-Dihydro-2H-Pyran, **(40)**

The same procedure utilized to prepare 2-propionyl-6-methyl-3,4-dihydro-2H-pyran, **(38)**, was employed. 7.7 g (.055 moles) of 7, 5.5 g (.055 moles) of cyclohexylamine and 12 g (.055 moles) of benzyl iodide were used. Workup as before, distillation and collection of the fraction at 156-158°C (1.5 mm Hg) gave 9.0 g (.039 moles) of a clear, slightly yellow liquid (71% yield).

^{1}H-NMR: 7.2-7.4 (5H, m); 4.55 (1H, br s); 4.32 (1H, m); 2.85-3.1 (4H, m); 1.85-2.1 (4H, m); 1.81 (3H, s)

^{13}C-NMR: 210.28 (s), 149.90 (s), 141.26 (s), 128.43 (2C, meta); 128.36 (2C, ortho); 126.04 (para), 96.35 (d), 80.22 (d), 39.71 (t), 29.21 (t), 23.65 (t), 19.94 (q), 19.19 (t)

MS: 230(M^+), 187, 139, 105, 97 (base peak), 91, 77, 43

Calculated for $C_{15}H_{18}O_2$: 230.1307

Observed: 230.1295

IR: 3025, 1725, 1690, 1600, 1500, 1445, 1245, 1070, 925, 750, 695

Preparation of 2-(1-Hydroxy-3-Phenylpropyl)-6-Methyl-3,4-Dihydro-2H-Pyran, (**41**)

To a solution of 4 g (.017 moles) of **40** stirring in 50 ml of methanol at 0°C was slowly added an excess of sodium borohydride. The solution was stirred for 1 hour at room temperature, after which time 50 ml of water were added and the resulting solution was extracted with three 50 ml portions of methylene chloride which were combined, dried over anhydrous magnesium sulfate and reduced in volume.

The alcohol was not purified, but used directly for the next step.

IR: 3450

Preparation of *exo/endo*-5-Methyl-7-(2-Phenylethyl)-6,8-Dioxabicyclo-[3.2.1]octane, **(42)**

The crude alcohol, **(41)**, was added to a solution of a catalytic amount of tosic acid in 60 ml of benzene. The solution was stirred for 72 hours at room temperature, after which time it was washed with two portions each of aqueous sodium bicarbonate and water, dried over anhydrous magnesium sulfate and reduced in volume. The product was purified using Kugelrohr distillation (.6 mm Hg). Collection from 130-160°C afforded 2.5 g of a clear, colorless liquid (63% yield from 40).

GLC integration using a 10' x 1/4" 20% SE-30 column indicated an *exo/endo* ratio of 60:40.

^{1}H-NMR of *exo*-**42**: 7.25 (5H ,m); 4.14 (1H, br s); 4.04 (1H, t); 2.68 (2H, br m); 1.82 (4H, m); 1.65 (4H, br d); 1.45 (3H, s)

^{1}H-NMR of *endo*-**42**: 7.23 (5H, m); 4.18 (1H, br s); 4.10 (1H, br q); 2.85 (1H, m); 2.65 (1H, m); 2.12 (1H, m); 1.85 (3H, m); 1.7-1.5 (4H, m); 1.45 (3H, s)

^{13}C-NMR of *exo*-**42**: 142.06 (s), 128.49 (2C, meta); 128.48 (2C, ortho); 125.84 (para), 107.94 (s), 79.14 (d), 78.74 (d), 37.38 (t), 34.94 (t), 31.76 (t), 27.79, 25.07 (q), 17.14 (t)

^{13}C-NMR of endo-**42**: 141.77, 128.55 (2C, meta); 128.48 (2C, ortho); 126.07 (para), 107.11, 79.58, 34.39, 33.19, 30.78, 24.95, 23.78, 17.46
(one peak buried under solvent peaks 76-78)

MS of exo-**42**: 232 (M^+), 190, 172, 161, 129, 104, 91, 43 (base peak)
Calculated for $C_{15}H_{20}O_2$: 232.1463
Observed: 232.1461

MS of endo-**42**: 232 (M^+), 190, 172, 143, 129, 104, 99, 98, 91, 43 (base peak)
Calculated for $C_{15}H_{20}O_2$: 232.1463
Observed: 232.1451

IR of exo-**42**: 3030, 1600, 1500, 1455, 1380, 1350, 1330, 1240, 1120, 750, 700

IR of endo-**42**: Identical to the exo isomer

General Cleavage of the 6,8-Dioxabicyclo[3.2.1]octane System

2 equivalents of acetyl chloride in 10 ml of clean dry acetonitrile were slowly added dropwise, via an addition funnel, to a solution of 2 equivalents of sodium iodide and 1 equivalent of the bicyclic ketal stirring at 0°C in 25 ml of acetonitrile. The resulting solution was stirred at room temperature for 24 hours, after which time the reaction was quenched by adding 15 ml of aqueous sodium bisulfite and stirring for 2 hours at room temperature. The

reaction mixture was then extracted with several 50 ml portions of ether which were combined, washed with aqueous sodium thiosulfate, aqueous sodium bicarbonate, brine and water, dried over anhydrous magnesium sulfate and reduced in volume.

The crude material was then run through a column of 25 mm x 150 mm silica gel topped with 15 mm of florisil using petroleum ether: ethyl acetate in a 7:3 ratio as a solvent system. Volume was again reduced and GLC integrative analysis was used to determine the amount of desired product present.

cis/trans-6-Octen-2-one, (**14**)

.5 g (3.52 mmoles) of **8** were subjected to the general cleavage conditions and GLC analysis indicated .132 g (1.05 mmoles) of a 65:35 mixture of trans/cis-6-octen-2-one, respectively (30% yield).

^{1}H-NMR of trans-**14**: 5.38 (2H, m); 2.4 (2H, t); 2.1 (3H, s); 1.98 (2H, q); 1.63 (5H, m) (Irradiation of the multiplet at 1.63 collapsed the multiplet at 5.38 into a recognizable dd, J = 15 Hz).

^{1}H-NMR of cis-**14**: 5.45 (1H, m); 5.35 (1H, m); 2.42 (2H, t); 2.15 (3H, s); 2.05 (2H, q); 1.6 (5H, m) (Irradiation of the multiplet at 1.60 collapsed the multiplets at 5.45 and 5.35 into a recognizable dd, J = 11 Hz).

^{13}C-NMR of trans-**14**:	209.00, 130.50, 125.80, 42.95, 31.84, 29.75, 23.57, 17.71
^{13}C-NMR of cis-**14**:	208.96, 129.66, 124.72, 43.00, 29.77, 26.09, 23.55, 12.64
MS of trans-**14**:	126 (M^+), 108, 68 (base peak), 58, 55, 43 Calculated for $C_8H_{14}O$: 126.1044 Observed: 126.1046
MS of cis **14**:	126 (M^+), 108, 68 (base peak), 58, 55, 43 Calculated for $C_8H_{14}O$: 126.1045 Observed: 126.1078
IR of trans-**14**:	3010, 1720, 1690 (sh), 1440, 1420, 1360, 1165, 970
IR of cis-**14**:	3005, 1720, 1675 (sh), 1440, 1410, 1360, 1160, 695

cis/trans-6-Nonen-2-one, (**44**)

1.0 g (6.4 mmoles) of **2** were subjected to the general cleavage conditions and GLC analysis indicated .28 g (2.0 mmoles) of a 71:29[39] mixture of trans/cis-6-nonen-2-one, respectively (31% yield).

All spectral data was taken on the cis/trans mixture.

^{1}H-NMR: 5.40 (2H, m); 2.41 (2H, t); 2.13 (3H, s); 1.99 (4H, m); 1.63 (2H, m); .96 (3H, t)
(Irradiation of the multiplet at 1.99 gave a dd at 5.4, J = 15.3 Hz).

^{13}C-NMR: (only trans isomer peaks are reported), 209.35 (s), 133.11 (d), 128.16 (d), 42.94 (t), 31.80 (t), 29.86 (q), 25.48 (t), 23.53 (t), 13.82 (q)

MS: 140 (M^+), 122, 82, 67, 58, 55, 43 (base peak), 41, 39
Calculated for $C_9H_{16}O$: 140.1201
Observed: 140.1195

IR: 1710, 1650 (sh), 1430, 1360, 1225, 1165, 965

7-Methyl-6-Octen-2-one, (**45**)

1.0 g (6.4 mmoles) of **36** were subjected to the general cleavage reaction and GLC analysis indicated .22 g (1.57 mmoles) of product (24% yield).

^{1}H-NMR: 5.08 (1H, br t); 2.41 (2H, t); 2.13 (3H, s); 2.05 (2H, m); 1.69 (3H, s); 1.65-1.5 (5H, m)
(Irradiation of the multiplet at 2.05 produced a singlet at 5.08).

^{13}C-NMR: 209.46 (s), 132.46 (s), 123.74 (d), 43.12 (t), 29.81 (q), 27.26 (t), 25.63 (q), 23.90 (t), 17.61 (q)

MS: 140 (M^+), 122, 83, 82 (base peak), 69, 67, 43, 41

Calculated for $C_9H_{16}O$: 140.1201

Observed: 140.1232

IR: 1700, 1650 (sh), 1420, 1360, 1160

cis/trans-9-Phenyl-6-Nonen-2-one, (**46**)

.5 g (2.2 mmoles) of **42** were subjected to the general cleavage reaction and GLC analysis using a 10' x 1/4" 20% SE-30 column indicated .154 g (.7 mmoles) of a 70:30[40] mixture of trans/cis-9-phenyl-6-nonen-2-one, respectively (33% yield).

All spectral data was taken on the cis/trans mixture.

^{1}H-NMR: 7.3-7.1 (5H, m); 5.4 (2H, m); 2.67 (2H, m); 2.34 (4H, m); 2.11 (3H, s); 1.98 (2H, q); 1.57 (2H, m)

^{13}C-NMR: (only trans isomer peaks are reported), 208.78, 141.91, 130.36, 129.94, 128.38 (2C, meta); 128.16 (2C, ortho); 125.64 (para), 42.80, 35.92, 34.16, 31.75, 29.76, 23.44

MS: 216 (M^+), 198, 158, 143, 104, 91 (base peak), 77, 67, 65, 43, 41

Calculated for $C_{15}H_{20}O$: 216.1514

Observed: 216.1523

IR: 1710, 1680 (sh), 1440, 1355, 1155, 1020, 970, 740, 695

Preparation of 2-Formyl-3,4-Dihydro-2H-Pyran, (**50**)

A mixture of 84 g (1.5 moles) acrolein (2-propenal), 50 ml of benzene and .25 g hydroquinone was heated in a stainless steel pressure bomb at 175°C for 2.5 hours, after which time the solution was cooled and the benzene and unreacted acrolein were removed. Distillation and collection of the fraction at 40°C (water aspirator) gave 31.5 g (.28 moles) of a clear, colorless liquid (37.5% yield).

^{1}H-NMR: 9.71 (1H, s); 6.51 (1H, d); 4.81 (1H, m); 4.3 (1H, m); 2.03 (4H, m)

IR: 3020, 2825, 2700, 1725, 1640, 1440, 1375, 1235, 1065, 900, 725

Preparation of n-Pentyl Magnesium Bromide

11 g (.45 moles) of magnesium filings were crushed using a mortar and pestel and transferred to a three necked, 250 ml round bottom flask equipped with a nitrogen trap and addition funnel. 50 ml of dry ether were added to the filings. A solution of 68 g (.45 moles) of n-pentyl bromide in 100 ml of dry ether was added slowly without stirring via the addition funnel and an exothermic reaction ensued which lasted throughout the addition process. The resulting dark solution was allowed to stand for one hour at room temperature before being used.

Preparation of 2-(1-Hydroxyhexyl)-3,4-Dihydro-2H-Pyran, **(54)**

The n-pentyl magnesium bromide was slowly added (via a syringe) to a solution of 17 g (.15 moles) acrolein dimer, **(50)**, stirring in 75 ml of dry ether at 0°C under a nitrogen atmosphere. The solution was stirred for 15 hours at room temperature, at which point only enough water needed to quench the excess Grignard was added. The ether layer was then separated from the magnesium salts which had formed and the salts were washed with several 50 ml portions of ether. The ether layers were combined, washed with two 100 ml portions each of brine and water, dried over anhydrous magnesium sulfate and reduced in volume. 22 g of a clear liquid were obtained (79% yield).

^{1}H-NMR (major isomer): 6.39 (1H, br d); 4.7 (1H, br s); 3.8-3.6 (2H, m); 2.18 (1H, d); 2.05 (2H, m); 1.80 (2H, m); 1.6-1.2 (8H, m); .89 (3H, br t)

^{13}C-NMR (major isomer): 143.26 (d), 100.72 (d), 77.84 (d), 73.25 (d), 31.8 (t), 25.08 (t), 24.06 (t) 22.57 (t), 22.49 (t), 19.51 (t), 13.93 (q)

MS: 184 (M^+), 166, 127, 109, 95, 84, 83 (base peak), 81, 70, 67, 57, 56, 55, 43, 41, 29, 27

Calculated for $C_{11}H_{20}O_2$: 184.1464

Observed: 184.1464

IR: 3350, 3030, 1650, 1460, 1380, 1240, 1070, 725

Preparation of exo/endo-5-Decyl-7-Pentyl-6,8-Dioxabicyclo[3.2.1]-octane, (**47**)

To a solution of 3.75 g (.02 moles) of the alcohol, (**54**), stirring in 10 ml of tetrahydrofuran at -78°C under an argon atmosphere was slowly added 22 ml (.04 moles) of 1.8 molar tertiary butyl lithium. The resulting solution was transferred to an ice bath and stirred at 0°C for 1 hour, after which time the ice bath was removed and the solution stirred at room temperature for 30 minutes. After again cooling the solution to 0°C, 5.3 g (.02 moles) of n-decyl iodide were added dropwise via an addition funnel and the solution was stirred for 1 hour at 0°C and then for 2 hours at room temperature. The reaction mixture was quenched with 25 ml of saturated aqueous ammonium chloride solution, diluted with 50 ml of diethyl ether, reduced in volume and added to a solution of a catalytic amount of tosic acid stirring in 50 ml of benzene. The resulting solution was stirred for 45 minutes at room temperature, after which time it was washed with two 75 ml portions of aqueous sodium bicarbonarte, dried over anhydrous magnesium sulfate and reduced in volume. Kugelrohr distillation and collection of the fraction from 140-190°C (.6 mm Hg) gave 1.7 g (.0052 moles) of a clear, slightly yellow liquid (26% yield).

GLC analysis of the product using a 10' x 1/4", 20% SE-30 column showed the exo/endo isomeric ratio to be 70:30.

^{1}H-NMR of exo-**47**: 4.09 (1H, s); 3.98 (1H, br t); 1.9-1.2 (32H, m);
.88 (6H, br d)

^{1}H-NMR of endo-**47**: 4.18 (1H, br s); 3.98 (1H, m); 1.95-1.15 (32H, m); .88 (6H, br d)

^{13}C-NMR of exo-**47**: 109.32, 79.79, 78.68, 37.93, 35.57, 33.88, 31.87, 31.75, 29.87, 29.55 (3C), 29.27, 28.28, 25.30, 23.03, 22.60, 22.76, 17.15, 13.97, 13.88

^{13}C-NMR of endo-**47**: 108.50, 80.50, 38.29, 33.11, 31.99, 31.86, 29.89, 29.55 (3C), 29.26, 28.83, 26.43, 24.11, 22.94, 22.60, 22.48, 17.48, 13.98, 13.89
(1 peak buried in $CDCl_3$ peaks)

MS of exo-**47**: 324 (M^+), 295, 253, 225, 211, 169, 156 (base peak), 127, 114, 100, 85, 84, 71, 69, 68, 57, 55, 43, 41, 29
Calculated for $C_{21}H_{40}O_2$: 324.3028
Observed: 324.3016

MS of endo-**47**: 324 (M^+), 295, 281, 267, 253, 224, 211, 169, 156 (base peak), 155, 113, 99, 98, 95, 85, 71, 69, 67, 57, 55, 43, 41, 29
Calculated for $C_{21}H_{40}O_2$: 324.3028
Observed: 324.3036

IR: (Taken on the exo/endo mixture) 1460, 1380, 1340, 1240, 1170, 1120, 1020, 935, 860, 725

Preparation of (Z)/(E)-Heneicosen-11-one, **(18)**

.5g (1.54 mmoles) of the ketal, **(47)**, were subjected to the general cleavage conditions; however, the crude product was cleaned using flash chromatography with a 9:1, petroleum ether: ether solvent system. GLC analysis using a 10' x 1/4", 10% SE-30 column indicated .107 g (3.47 mmoles) of a 78:22 isomeric mixture of trans/cis-heneicosen-11-one, respectively (23% yield).[40]

^{1}H-NMR: 5.37 (2H, m); 2.38 (4H, t); 1.97 (4H, br m); 1.61 (4H, m); 1.26 (20H, br s); .88 (6H, distorted t)

^{13}C-NMR: (trans isomer), 211.46, 131.50, 129.19

MS: (trans isomer), 308 (M^+), 251, 237, 197, 169, 124 (base peak), 96, 82, 81, 69, 68, 67, 55, 54, 43, 41, 29

Calculated for $C_{21}H_{40}O$: 308.3078

Observed: 308.3057

(cis isomer), 308 (M^+), 251, 237, 197, 169, 124, 96, 95, 82, 69, 68, 67, 55, 54, 43, 41, 29

Calculated for $C_{21}H_{40}O$: 308.3078

Observed: 308.3062

Preparation of 2-(1-Oxoundecyl)-6-Methyl-3,4-Dihydro-2H-Pyran, **(56)**

Again, the same procedure utilized to prepare 2-propionyl-6-methyl-3,4-dihydro-2H-pyran, **(38)**, was employed. 20 g (.143 moles) of **7**, 14.2 g (.143 moles) of cyclohexylamine and 29.7 g (.143 moles) of n-bromononane were used. Workup as before, Kugelrohr distillation and collection of the fraction at 165-180°C (1.2 mm Hg) gave 20.5 g (.077 moles) of a clear, yellowish liquid (54% yield).

^{1}H-NMR: 4.52 (1H, br s); 4.28 (1H, dd); 2.61 (2H, m); 1.99 - 1.85 (4H); 1.79 (3H, s); 1.57 (2H, br t); 1.26 (14H, br s); .88 (3H, t)

^{13}C-NMR: 211.26 (s), 149.71 (s), 96.05 (d), 79.91 (d), 37.74 (t), 31.66 (t), 29.34, 29.25, 29.19, 29.08, 28.99, 23.42, 22.81, 22.42 (t), 19.71 (q), 18.94, 13.81 (q)

MS: 266 (M^+), 223, 169, 140, 97 (base peak), 69, 57, 43, 41

Calculated for $C_{17}H_{30}O_2$: 266.2245

Observed: 266.2220

IR: 3030, 1715, 1680, 1455, 1385, 1240, 1170, 1105, 1070, 925, 765, 735

Preparation of 2-(1-Hydroxyundecyl)-6-Methyl-3,4-Dihydro-2H-Pyran, (**57**)

To a solution of 10.5 g (.039 moles) of the ketone, (**56**), stirring in 100 ml of methanol at 0°C was slowly added an excess of sodium borohydride. The solution was stirred for 1 hour at room temperature, after which time 100 ml of water were added and the resulting solution was extracted with three 100 ml portions of methylene chloride which were combined, dried over anhydrous magnesium sulfate and reduced in volume.

The alcohol (10.0 g, 94% crude yield) was not purified but used directly for the next step.

IR: 3350

Preparation of exo/endo-5-Methyl-7-Decyl-6,8-Dioxabicyclo[3.2.1]-octane, **(58)**

19.0 g (.071 moles) of the crude alcohol, **(57)**, was added to a solution of a catalytic amount of tosic acid stirring in 100 ml of benzene at room temperature. The solution was allowed to stir for 2 hours, after which time the solvent was removed and the crude product was directly distilled using a Kugelrohr distillation apparatus. Collection of the fraction at 140-180°C (1.0 mm Hg) gave 14.0 g (.052 moles) of a clear, yellowish liquid (69% yield from **56**).

The exo:endo isomeric ratio was 60:40 as determined by GLC analysis.

^{1}H-NMR of exo-**58**: 4.11 (1H, br s); 3.98 (1H, br t); 1.9-1.5 (8H, m); 1.41 (3H, s); 1.25 (16H, br s); .87 (3H, t)

^{1}H-NMR os endo-**58**: 4.19 (1H, br s); 4.04 (1H, m); 2.0-1.5 (10H, m); 1.43 (3H, s); 1.26 (14H, br s); .88 (3H, t)

^{13}C-NMR of exo-**58**: 107.67 (s), 79.96 (d), 78.71 (d), 35.82 (t), 35.00 (t), 31.91, 29.59 (4C), 29.32 (t), 27.97 (t), 25.56 (t), 25.12 (q), 22.67 (t), 17.21 (t), 14.07 (q)

^{13}C-NMR of *endo*-**58**: 106.92, 80.32, 77.21, 34.49, 31.89, 29.86, 29.58 (3C), 29.31, 28.93, 26.88, 25.04, 23.81, 22.67, 17.57, 14.07

MS of *exo*-**58**: 268 (M^+), 226, 197, 169, 100, 98, 81, 55, 43 (base peak)
Calculated for $C_{17}H_{32}O_2$: 268.2402
Observed: 268.2389

MS of *endo*-**58**: 268 (M^+), 226, 183, 98, 81, 67, 55, 43 (base peak)
Calculated for $C_{17}H_{32}O_2$: 268.2402
Observed: 268.2369

IR of *exo*-**58**: 1450, 1380, 1240, 1190, 1178, 1110, 1035, 1005, 915, 847, 730

IR of *endo*-**58**: Identical to the *exo* isomer.

Preparation of *cis*/*trans*-6-Heptadecen-2-one, (**59**)

.5 g (1.87 mmoles) of the ketal, (**58**), were cleaved using the general cleavage conditions and GLC analysis indicated .13 g (.52 mmoles) of a predominantly *trans* mixture of *cis*/*trans*-6-heptadecen-2-one (28% yield).

All spectral data was taken on the *cis*/*trans* mixture.

^{1}H-NMR: 5.36 (2H, m); 2.40 (2H, m); 2.13 (3H, s); 1.98 (4H, m); 1.62 (2H, m); 1.26 (16H, br s); .88 (3H, s)
(Irradiation of the multiplet at 1.98 gave a dd at 5.36, J = 15.2 Hz).

^{13}C-NMR: 209.23 (s), 131.65 (d, trans); 129.11 (d, trans); 131.14 (cis), 128.60 (cis)

MS: 252 (M^+), 234, 194, 125, 96, 81, 68, 67, 55, 54, 43 (base peak), 41
Calculated for $C_{17}H_{32}O$: 252.2453
Observed: 252.2452

IR: 1700 (br), 1440, 1350, 1160, 965, 720

Preparation of the Oxime of 6-Heptadecen-2-one, **(60)**

.13 g (.52 mmoles) of the ketone, **(59)**, was placed in 25 ml of ethanol along with .08 g (1.2 mmoles) of hydroxylamine hydrochloride, and .08 g (1.0 mmoles) sodium acetate. The resulting solution was stirred at room temperature for 6 hours, after which time the ethanol was removed and the residue was diluted with 50 ml of ether. The ether solution was then washed with 2 portions each of brine and water, dried over magnesium sulfate and reduced in volume. Flash chromatography using 8:2, petroleum ether: ether as a solvent system yielded 78 mg of pure anti oxime as a yellowish oil, which crystallized upon refrigeration (57% yield).

All spectral data was taken on the cis/trans mixture.

^{1}H-NMR: 8.88 (1H, broad); 5.30 (2H, m); 2.19 (2H, t); 1.99 (4H, m); 1.88 (3H, s); 1.56 (2H, m); 1.26 (16H, br s); .88 (3H, t)

^{13}C-NMR: (trans isomer reported), 158.57 (s), 131.44 (d), 129.22 (d), 35.25 (t), 32.53 (t), 31.99, 31.85, 29.59 (3C), 29.32, 29.27, 29.11, 26.10 (t), 22.62 (t), 14.0 (q), 13.29 (q)

MS: 267 (M^+), 250, 140, 124, 110, 96, 73 (base peak), 57, 41

Calculated for $C_{17}H_{33}NO$: 267.2562

Observed: 267.2562

IR: 3200, 1715, 1670, 1460, 1370, 1270, 965, 713

Preparation of 2-Amino-6-Heptadecene (55)

25 mg (9.63 x 10^{-5} moles) of the oxime **(60)** was dissolved in 10 ml of ethanol. 0.02 g (1.4 x 10^{-4} moles) of molybdenum trioxide and 0.04 g (1.1 x 10^{-3} moles) of sodium borohydride were added at 0°C and the resulting solution was stirred at room temperature for 2 hours. The ethanol was then removed, and the residue was diluted with 10 ml of ether and 20 ml of water. The layers were separated and the aqueous layer was extracted with two 10 ml portions of ether. The ether layers were then combined, washed with brine and water, dried over magnesium sulfate and reduced in volume.

GC-MS analysis of the product revealed it to consist of 81% of the desired amine, **(55)**, 10% **(27)**, and 9% unidentified products.[41]

MS: 253 (M^+), 238, 126, 98, 95, 82, 70, 57, 55, 44 (base peak), 41, 29

MS of (**27**): 253 (M^+), 252, 238, 111, 99, 98 (base peak), 70, 55, 41

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40. Separation of the isomers was obtained using a 30 m x .25 mm ID Durabond 1 capillary column, .25 µm film thickness.

41. Analysis was carried out using a 30 m x .25 mm ID Durabond 5 capillary column, .25 µm film thickness.