New approaches to natural products
by Jong-Gab Jun

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:
New approaches to natural products of theoretical and synthetic interest are presented. A methodology for the cleavage of the 6,8-dioxabicyclo[3.2.1]octane skeletal system is explored by using acetyl iodide, magnesium bromide, aluminum iodide, aluminum hydride and triethylsilane. It is found that the fragmentation products reflect the configuration of the ketal isomer; endo-keta Is give cis-alkenes and exo-keta Is give trans-alkenes. The fragmentation of the ketals gives products (dependent on condition. The utility of this fragmentation methodology is demonstrated in the formal synthesis of si renin. Also, a methodology involving vicinal dianions of 1,2-diesters is explored as a rapid entry into a highly functionalized bicyclic diester. The utility of dienolate methodology in organic synthesis is seen in the applications to the synthesis of valerane and synthetic approaches to maleimycin and hirsutene.
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A thesis submitted in partial fulfillment
of the requirements for the degree
of
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in
Chemistry

MONTANA STATE UNIVERSITY
Bozeman, Montana
August 1985
APPROVAL

of a thesis submitted by

Jong-Gab Jun

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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Approved for the College of Graduate Studies

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Date
Graduate Dean
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Signature  
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Aug 2, 1985
To my parents

"Delight yourself in the Lord and he will give you the desires of your heart."

Psalms 37:4
VITA

Jong-Gab Jun, the first son of In-kee Jun and Jun-Ok Kim, was born in Taegu, Korea on May 4, 1953. After receiving a Bachelor of Science degree in chemistry in August, 1979 from Sogang University, he joined the Korea Institute of Science and Technology where he worked as a researcher until August, 1982, when he came to Montana State University to pursue his studies.
I would like to take this opportunity to thank Jesus who gave me a new life and a joy of life.

I extend my appreciation to my parents and to Pastor In-Kyu Kang, for their encouragement and for believing in me. To my fellow researchers, Dan Bruss, Rich Copp, Tim Schram and Joe Sears, I extend my gratitude for their valuable help and advice through this project. I would also like to thank Dr. John H. Cardellina II for the invaluable help of structural identification.

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Finally, I thank my wife, You-Kyung and my son, Se-Young, for being together.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Natural Products Derived from Ketals, Background Work from Our Laboratories</td>
<td>1</td>
</tr>
<tr>
<td>Natural Products Containing 5-Membered Rings</td>
<td>3</td>
</tr>
<tr>
<td>Via Propellanes</td>
<td>3</td>
</tr>
<tr>
<td>Non-propellanes</td>
<td>8</td>
</tr>
<tr>
<td>RESULTS AND DISCUSSION</td>
<td>11</td>
</tr>
<tr>
<td>Ketal Chemistry</td>
<td>11</td>
</tr>
<tr>
<td>Fragmentation</td>
<td>11</td>
</tr>
<tr>
<td>Need for Mechanism</td>
<td>11</td>
</tr>
<tr>
<td>Further Problems</td>
<td>14</td>
</tr>
<tr>
<td>Other Methods of Fragmentation</td>
<td>19</td>
</tr>
<tr>
<td>Other Unique Chemistry of Bicyclic Ketals</td>
<td>25</td>
</tr>
<tr>
<td>Attempt at Making &quot;Coupled&quot; Ketal</td>
<td>30</td>
</tr>
<tr>
<td>Functionalized Bicyclic Ketal Systems</td>
<td>33</td>
</tr>
<tr>
<td>Attempt at Synthesis of Sirenin</td>
<td>35</td>
</tr>
<tr>
<td>Dianion Chemistry</td>
<td>39</td>
</tr>
<tr>
<td>A New Approach to Valerane</td>
<td>39</td>
</tr>
<tr>
<td>Possible Use in Maleimycin Synthesis</td>
<td>49</td>
</tr>
<tr>
<td>Synthesis for Possible Hirsutene Intermediate</td>
<td>54</td>
</tr>
<tr>
<td>Summary</td>
<td>59</td>
</tr>
<tr>
<td>EXPERIMENTARY</td>
<td>60</td>
</tr>
<tr>
<td>NOTES AND REFERENCES</td>
<td>120</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1. Reference of $^1$H, $^{13}$C and coupling constant for Pyridine... 29

Table 2. Assignment of Chemical Shift for axial and equatorial proton of ketal... 34
LIST OF FIGURES

Figure 1. The 6,8-Dioxabicyclo[3.2.1]octane Skeletal System................................. 1
Figure 2. Natural Products Having Ketal Structures or Derived from Ketals............... 2
Figure 3. Synthesis of Brevicomin........................................... 4
Figure 4. Synthesis of the Mouse Pheromone................................... 4
Figure 5. Synthesis of 7,7-Dimethyl-6,8-dioxabicyclo [3.2.1]octane........................ 5
Figure 6. Synthesis of Racemic (cis-6-methyltetrahydropyran-2-yl)acetic acid............. 5
Figure 7. Synthesis of the Tussock Moth Pheromone.................................... 6
Figure 8. Synthesis of Solenopsin A........................................... 7
Figure 9. Modhephene............................................................................ 8
Figure 10. Total Synthesis of Modhephene........................................... 9
Figure 11. Rearrangement of the N-Acyl lactam.......................................... 10
Figure 12. Synthesis of 2-Substituted Oxazolines....................................... 10
Figure 13. Mycobactic Acid........................................................................ 10
Figure 14. Fragmentation of Cis and Trans 6-octen-2-one................................ 12
Figure 15. Proposed Mechanism for Ketal Cleavage with AcI................................. 13
Figure 16. Cleavage of exo/endo-7-Deuteriomethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane... 14
Figure 17. Cleavage of endo-7-isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane............ 15
Figure 18. Cleavage of 5,7,7-Trimethyl-6,8-dioxabicyclo [3.2.1]octane.................... 16
Figure 19. H Transfer in 6-Acetoxy-7-methyl-7-octene-2-one................................. 17
Figure 20. Attempted Further Reaction of 6,7-Diacetoxy-7-methyl-2-octanone.................. 18
Figure 21. Other Fragmentations of Deuteriomethyl Ketal Cleavage............................... 18
Figure 22. Cleavage with Magnesium bromide......................................................... 19
Figure 23. Magnesium bromide Reaction with Tetrahydrofuran.................................. 20
Figure 24. Cleavage with Triethyilsilane............................................................... 22
Figure 25. The Selective Ring Opening by Triethyilsilane.......................................... 23
Figure 26. Isomer of 1,2-Dimethyl-(cis)-6-methyltetrahydropyran-2-ylpropane............. 24
Figure 27. Configurations of Isomer of 1,2-Dimethyl-(cis)-6-methyltetrahydropyran-2-ylpropane 24
Figure 28. Cleavage of 7-Isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane with AlH3....... 25
Figure 29. Cleavage of 7-Isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane with Al13......... 26
Figure 30. NaBH4 Reduction of 2,3-Dimethyl-1-(5,6-dimethylpyridine-2-yl)butanone........ 30
Figure 31. Possibilities of Coupled Bicyclic ketal Fragmentation................................. 31
Figure 32. Preparation of 5-(n-Bromopentyl)-7-methyl-6,8-dioxabicyclo[3.2.1]octane.......... 32
Figure 33. Attempted Coupling Reaction................................................................. 32
Figure 34. Formation of 7-Methyl-4-propanal-6,8 dioxabicyclo[3.2.1]octane.................. 33
Figure 35. Isomers of 7-Methyl-4-propanal-6,8 dioxabicyclo[3.2.1]octane................... 35
Figure 36. Attempted cyclization of 2-(2-Hydroxymethyl)-6-(n-decyl)-3,4-dihydro-2H-pyran.... 36
Figure 37. Bromination of Ketal................................. 36
Figure 38. Grieco's Synthesis of Sirenin......................... 37
Figure 39. Retro Formal Synthesis for Sirenin............... 38
Figure 40. Esterification of 6,10-Dimethyl-5,9-
  nonadienoic acid......................................... 38
Figure 41. Absolute Stereochemistry of 1-Valeranone........ 40
Figure 42. Conformations of 1-Valeranone...................... 40
Figure 43. Rao's Synthesis of Valerane......................... 41
Figure 44. Comparison of Conformation of Valerane........... 42
Figure 45. Baldwin's Synthesis of Valerane.................... 43
Figure 46. Dianion of 4,5-Dimethylcyclohexene
dicarboxylate.................................................. 44
Figure 47. Dianion Mediated Synthesis of cis-9,10-Bis
  (carboxymethyl)-Δ2-decalin................................ 45
Figure 48. Retro Synthesis of cis-9,10-Dimethyl-
  decalin-2-ene................................................ 45
Figure 49. Synthesis of 12-Thia[4.4.3]propell-3-ene...... 47
Figure 50. Synthesis of cis-9,10-Dimethyldecalin-2-one... 47
Figure 51. Attempted Wittig Reaction of cis-9,10-
  Dimethyldecalin-2-one........................................ 48
Figure 52. Synthesis of Valerane............................... 49
Figure 53. Conformational Assignment for Valerane.......... 50
Figure 54. Structure of Maleimycin.............................. 50
Figure 55. N-Substituted-Δ1-cyclopentene-1,2-
  dicarboxylic imides......................................... 51
Figure 56. Weinrab's Synthesis of Maleimycin................ 51
Figure 57. Synthesis of N-Benzylsuccinimide.................. 52
Figure 58. Attempted Synthesis of Cyclopentanones.......... 53
Figure 59. Synthesis of cis-3-(N-Benzyl)-2,4-dioxabicyclo[3.3.0]heptane........................................ 53

Figure 60. Attempted Synthesis of 3-(N-Benzyl)-2,4-dioxobicyclo[3.3.0]hept-Δ1,5-ene.................. 54

Figure 61. 3-(N-Benzyl)-2,4-dioxotricyclo[3.3.3.0]decane and 3-(N-Benzyl)-2,4-dioxotricyclo[3.3.2.0]nonane......................................................... 54

Figure 62. Structure of Hirsutene, Coriolin and Hirsutic acid.................................................. 55

Figure 63. Retro Synthesis of Hirsutene................................................................. 56

Figure 64. Danheiser's Cyclopentene Annulation.................................................. 56

Figure 65. Synthesis of 2,7,7-Trimethyl-cis-1,5-dicarboethoxy-bicyclo[3.3.0]octan-2-ol............. 57

Figure 66. Tautomers of 2-Carboethoxy-4,4-dimethylcyclohexanone...................................... 58
ABSTRACT

New approaches to natural products of theoretical and synthetic interest are presented. A methodology for the cleavage of the 6,8-dioxabicyclo[3.2.1]octane skeletal system is explored by using acetyl iodide, magnesium bromide, aluminum iodide, aluminum hydride and triethylsilane. It is found that the fragmentation products reflect the configuration of the ketal isomer; endo-ketals give cis-alkenes and exo-ketals give trans-alkenes. The fragmentation of the ketals gives products dependent on condition. The utility of this fragmentation methodology is demonstrated in the formal synthesis of sirenin. Also, a methodology involving vicinal dianions of 1,2-diesters is explored as a rapid entry into a highly functionalized bicyclic diester. The utility of dienolate methodology in organic synthesis is seen in the applications to the synthesis of valerane and synthetic approaches to maleimycin and hirsutene.
CHAPTER 1

INTRODUCTION

Our research has, as its focus, the development of new synthesis methodologies, rather than synthesis itself. We choose certain natural products as test molecules for the developing new methodology. Evidence for our past involvement can be found in the research activity of our group.

Natural Products Derived from Ketals. Background Work from Our Laboratories.

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

![Figure 1. The 6,8-Dioxabicyclo[3.2.1]octane Skeletal System](image)

Our group has been committed to developing new approaches to natural products having this skeletal feature or derived from it (Figure 2).
Figure 2. Natural Products Having Ketal Structures or Derived from Ketals.

The pheromone for the western pine bark beetle, Dendroctonus brevicomis, has been isolated, assigned structure 2, and named brevicomin\(^1\). This has been synthesized by Lipkowitz\(^2\) (Figure 3). The isolation and identification of 3 as a pheromone of the mouse Mus musculus, has recently been reported\(^3\). Bornmann\(^4\) synthesized 3 and verified its structure by its conversion to exo-brevicomin 2 (Figure 4). A similar compound 4, has been identified as a constituent of Japanese hop oil isolated from Humulus lupulus\(^5\) (Figure 5).

The glandular secretion of the civet cat (Viverra civetta) is known as civet and is one of the few animal-derived perfume
materials. A recent examination of the constituents of civet resulted in the isolation of a minor component (2 mg from 1 kg) whose constitution was determined by spectral and synthetic means to be (Figure 6).

The Douglas fir tussock moth (Orgyia pseudotsugata) is a pernicious defoliator of the fir trees of the Northwestern United States. The active pheromone constituent has been identified as (Z)-6-heneicosen-11-one, however, in field tests the (E)-isomer has been found to have equivalent bioactivity. In a separate bioassay, others have found that a 60:40 (E)/(Z) mixture of 6 was considerably more active as a pheromone than pure material isolated from female tussock moths. This pheromone has been synthesized by our group (Figure 7).

The fire ant, Solenopsis saevissima, derives its name from the painful effects of the venom delivered in its bite. Of more practical interest is the known hemolytic, insecticidal and antibiotic activity of the venom. There have been determined to be a number of trans-2-methyl-6-alkyl or alkynyl piperidines serving as constituents of the venom; Solenopsin A, (7), (one of these) was synthesized in our group (Figure 8).

Natural Products Containing 5-Membered Rings

The natural propellane, modhephene, was isolated from the rayless goldenrod and has been the target of several innovative syntheses (Figure 9).
Figure 3. Synthesis of Brevicomin

Figure 4. Synthesis of the Mouse Pheromone
Figure 5. Synthesis of 7,7-Dimethyl-6,8-dioxabicyclo[3.2.1]octane

Figure 6. Synthesis of Racemic (cis-6-Methyltetra-hydropyran-2-yl) acetic acid
Figure 7. Synthesis of the Tussock Moth Pheromone

The recent past has witnessed a flourish of interest in cyclopentanoid chemistry\textsuperscript{13}. Much of this interest is attributable to the isolation of biologically important cyclopentanoid and polycondensed cyclopentanoid natural products. The cyclopentanoids represent a complex challenge to the synthetic chemist, as most of these novel compounds are highly substituted in addition to possessing the five membered ring skeleton.

Modhephene was chosen as a target molecule and synthesized in our group\textsuperscript{14}. Critical to the success of this synthesis was a dianion-mediated cyclopentannulation procedure, a heteroatom-assisted stereoselective hydrogenation and a dimethylation of a carbonyl (Figure 10).
Figure 8. Synthesis of Solenopsin A
Figure 9. Modhephene

Non-propellanes

By analogy to the N-acyl lactam rearrangement used in our laboratory for the synthesis of 2-substituted pyrrolines and piperidines\(^1\) (Figure 11), Kim\(^2\) envisioned a new procedure for preparing 2-substituted oxazolines. Thermal rearrangement of the N-acyl-2-oxazolidones in the presence of calcium oxide has been shown to provide a new entry into 2-substituted oxazolines (Figure 12). This initial success suggested the possibility that a similar approach might find eventual application in a synthesis of the natural product, mycobactic acid 4\(^3\) (Figure 13)\(^4\).

Our group has shown the utility of new protocols in the successful completion of a number of specific targets. What remains to be done? What questions need to be answered? In the next portions of this thesis will discuss: a) The mechanism of bicyclic ketal fragmentation, b) Application of this protocol to a formal synthesis of sirenin, c) Extension of the dianion methodology for preparing ring systems, d) A new synthesis of
valerane, e) Approaches to the antibiotic, maleimycin and f) Preliminary studies toward the synthesis of hirsutene.

Figure 10. Total Synthesis of Modhephene
Figure 11. Rearrangement of the N-Acyl lactam

$$\begin{align*}
&\text{Figure 12. Synthesis of 2-Substituted Oxazolines} \\
&\text{( } R = \text{CH}_3, \text{Ph, 2-methoxybenzyl} \text{) }
\end{align*}$$

Figure 13. Mycobactic Acid
CHAPTER 2

RESULTS AND DISCUSSION

Ketal Chemistry

Fragmentation

Need for Mechanism

A series of bicyclic ketal fragmentations using acetyl iodide demonstrated a quite interesting relationship in which the trans alkene was the major product, just as the exo orientation prevailed in the ketal. A useful mechanistic interpretation was generated from the observation that there appeared to be a general trend that endo-ketals gave cis-alkenes and exo-ketals gave trans-alkenes. It has been an observation that Grignard additions or hydride reductions used in the synthesis of the bicyclic ketals always result in the predominance of exo products. In the simplest, and most often repeated experiment, the exo- to endo- ratio of 15 is 60:40. Cleavage of this ketal with NaI/AcCl gave a 65:35 ratio of trans to cis alkenes (Figure 14).

Although there are several possible ways to interpret these results, we suggest that a mechanism similar to that used by Goldsmith\textsuperscript{18} for ether cleavage may find application (Figure 15).

This mechanism rationalizes the observations that exo-R gives trans-R, and endo-R gives cis-R. Also, the same results
would be observed if the first acetyl group coordinated with 0-8.

![Chemical structures](image)

Figure 14. Fragmentation of Cis and Trans 6-Octen-2-one

To test this mechanistic hypothesis, we chose a reaction substrate that would not be influenced by the differences in bulk of the exo and endo substituents. The addition of deuteriomethyl Grignard to the dimer of methyl vinyl ketone, (8), gave the isomeric deuterio bicyclic ketal derivatives, (48). The ratio of the exo and endo deuteriomethyl substitution (2:1) was easily derived from the proton NMR spectrum. Cleavage of this ketal (which should experience no steric biases) gave an alkene mixture of 49 as shown in Figure 16. The cis-methyl proton (1.66 ppm) at C-7 is always more downfield than the trans-methyl proton (1.56 ppm).

As a last test of this mechanistic interpretation, we were able to prepare pure endo-7-isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane, (52), in 65% yield by the addition
of isopropylmagnesium chloride to 8. Fragmentation gave only the Z-isomer of 7,8-dimethyl-6-nonen-2-one, (53); however, in only 13% yield. We also obtained 7% of the double bond migrated product 54 (Figure 17).

Figure 15. Proposed Mechanism for Ketal Cleavage with AcI
From these definitive experiments on the mechanism of the ketal fragmentation we can conclude that the fragmentation products reflect the ketal isomer; endo-ketals give cis-alkenes and exo-ketals give trans-alkenes.

Further Problems

Other products appeared in the cleavage reaction of 52 (Figure 17), which gave 64% of very labile and easily decomposed...
product 55. What are they? Do they give additional clues to support the proposed mechanism? We chose the bicyclic ketal 56 as a starting material to solve these problems, because of the simplicity of preparation and lack of stereoisomer problems. After the reaction, the crude material was run through a column of 25 mm x 150 mm silica gel topped with 15 mm of Florisil, using as an eluant, petroleum ether:ethyl acetate (7:3). It was observed that attempting to distill the crude product directly resulted in extensive decomposition and formation of polymeric material. Figure 18 shows the products from the reaction: 7-methyl-6-octene-2-one, 57, (16% yield) and 6-acetoxy-7-methyl-7-octene-2-one, 58, (37% yield) as a major product with 6,7-diacetoxy-7-methyl-2-octanone, 59, (16% yield).

Figure 17. Cleavage of endo-7-isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane
Figure 18. Cleavage of 5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane

The $^{13}$C NMR spectrum of 58 shows 11 carbon resonances; two carbons more than starting material. The data also shows the carbonyl of an ester at 170.2 ppm. The $^1$H NMR spectrum shows methyl proton of acetate at 2.04 ppm and methine proton of C-6 at 5.14 ppm as a triplet which is highly deshielded due to the ester group and adjacent olefin. Also, a methyl proton peak of C-7 at 1.70 ppm is observed. This broad singlet is sharpened when 4.87 and 4.93 ppm are irradiated. A mass 156 amu is
obtained which is amu 42 less than the expected molecular weight. Mass-spectral reaction triggered by intramolecular H transfer involves an initial radical site on a saturated heteroatom such as Figure 19. The unpaired electron is donated to form a new bond to an adjacent (in appropriate conformations) H atom, with concomitant cleavage of another bond to that hydrogen.

Figure 19. H Transfer in 6-Acetoxy-7-methyl-7-octene-2-one

The $^{13}$C NMR spectrum of 59 shows four more carbons than the starting material and indicates two ester carbonyl carbons (170.5 and 170.0 ppm). The $^1$H NMR spectrum also shows two acetate methyl peaks (2.08 and 1.94 ppm). These two products (58 and 59) have a similar structural relationship, and since we did not get any 59 from some reactions, we suspected 59 to be an intermediate precursor of 58. To test this hypothesis, 59 was separated and stirred for two days under the reaction conditions, but we did not get any 58 (Figure 20).
Figure 20. Attempted Further Reaction of 6,7-Diacetoxy-7-methyl-2-octanone

Figure 21. Other Fragmentations of Deuteriomethyl ketal Cleavage
Also, when we carried out the same reaction on 48 we got the same products except deuterated (Figure 21).

From these results, we can conclude that the fragmentation reaction, although a unique way to make δ,ε-unsaturated ketones, has side products, and before it has true synthetic potential, procedures for controlling the reaction will have to be found.

Other Methods of Fragmentation

An interesting result was found during the cleavage reaction of ketal 56 with acetic anhydride and magnesium bromide (prepared by mixing an equimolar amount of 1,2-dibromoethane and magnesium in anhydrous ether). This reaction gave 58 and 59 in a ratio of 2:8 with no trace of 57. Even though this reaction gave a very low yield, the differences in product composition suggest that there are different mechanisms in the two fragmentation processes involved (Figure 22).

![Figure 22. Cleavage with Magnesium bromide](image)

When we used tetrahydrofuran as a solvent to make magnesium bromide, 4-bromobutyl acetate (60) was the major product along
with the starting material, (56). We tried a blank test and found that tetrahydrofuran reacts with magnesium bromide and acetic anhydride to give 60 in 93% yield (Figure 23).

![Figure 23. Magnesium bromide Reaction with Tetrahydrofuran](image)

Gray\textsuperscript{19} reported that reductive cleavage of the carbon-oxygen bond of acetals and ketals can be accomplished by ionic hydrogenation, employing triethylsilane as the reducing agent and boron trifluoride etherate as the acid. We applied this system to our bicyclic ketals, 15, 56 and 52, and found high yield of C\textsubscript{5}-O\textsubscript{6} bond cleavage to form alcohol (Figure 24).

The methyl ketal 15 gave only the cis isomers as a 40:60 mixture of threo alcohol, (61a), and erythro alcohol, (61b), in 85% yield. The formation of cis stereochemistry by this procedure is readily rationalized by considering an intermediate borane complex and S\textsubscript{N}2 hydride displacement\textsuperscript{15} showed in Figure 25\textsuperscript{20}.

The previous work by our group\textsuperscript{21} also showed that aluminum hydride produced exclusively cis-oriented stereoisomers, (61a) and (61b), in a ratio of 60:40 by regioselective attack of the hydride. AlH\textsubscript{3} was prepared by mixing an equimolar amount of
lithium aluminum hydride and aluminum chloride in anhydrous ether solution. Brown's work on the hydrogenolysis of acetals and ketals by mixtures of lithium aluminum hydride and aluminum chloride in ether has indicated that, as in the case for the hydrolysis of dioxabicyclooctanes, the rate controlling step of the hydrogenolysis reaction is the cleavage of the C₅-O₆ bond, weakened by the association of its oxygen atom with the Lewis acid. The association of O₆ with aluminum results in the hydride attacking C₅ from the opposite side of the complex rather than the hindered side.

Another interesting result came from the cleavage of 56 with Et₃SiH, which gave the expected cis alcohol 64 and dehydrated product 62 with unidentified 63 as a 21:45:34 mixture, respectively. Also, the endo-bicyclic ketal, (52), gave the expected cis alcohol, (66a), and dehydrated products, 65a and 65b, as a 74:12:14 ratio, respectively. In contrast to the results of the cleavage reactions of 15, 56 and 52 with Et₃SiH, a more substituted and higher chained compound at C₇ gave more dehydrated product than alcohol. Again, this mechanism requires that boron trifluoride associates with O₆ and weaken the C₅-O₆ bond which is attacked by hydride from the opposite side of the complex to give cis alcohol. Followed by losing H₂O and hydride attacking the carbonium ion by S_N which gave 65a and 65b (Figure 26). The model of this compound indicates the isopropyl group could not get free rotation, which gives the isomer.
The configurational assignments of 65a and 65b are based on the following: (1) The cis isomers, 65a and 65b, should exist at room temperature as two rapidly equilibrating chair conformations, the two protons at C1 and C5 giving rise to an
axial-equatorial time averaged signal in the proton NMR spectrum. Accordingly, the two axial methine protons of the \textit{cis} isomers resonate at higher field (3.10-3.35 ppm) than the corresponding protons of the \textit{trans} isomers (4.01-4.12 ppm)\textsuperscript{23}. 

(2) To determine the configuration of the branched propane, irradiation of the methylene protons at 1.77 ppm gave a doublet of the \(\text{C}_1\) proton, which is coupled with \(\text{H}_A\). Coupling constants of 7 Hz were obtained for \(65\text{a}\) and 9.5 Hz for \(65\text{b}\), indicating 20° and 170° angles between \(\text{C}_1\) proton and \(\text{H}_A\), respectively.

Irradiation of the methyl protons at 0.84 ppm of \(65\text{a}\) gave a doublet of doublet for \(\text{H}_A\), which coupled with the \(\text{C}_1\) proton and \(\text{H}_B\) and indicates \(\text{H}_A\) and \(\text{H}_B\) coupling constant of 10 Hz and corresponds to 180° angle between the two protons. Also, irradiation of \(65\text{b}\) methyl protons at 0.70 ppm gave a doublet for \(\text{H}_A\), which showed a 4 Hz coupling constant between \(\text{H}_A\) and \(\text{H}_B\), corresponding to 45° between these two protons (Figure 27).

![Figure 25. The Selective Ring Opening by Triethylsilane]
Figure 26. Isomer of 1,2-Dimethyl-(cis-6-methyltetrahydro- 
pyran-2-yl) propane

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<th>$J_{H,a}$</th>
<th>$J_{H,b}$</th>
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</thead>
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<tr>
<td>65a</td>
<td>7 Hz (20°)</td>
<td>10 Hz (180°)</td>
</tr>
<tr>
<td>65b</td>
<td>9.5 Hz (170°)</td>
<td>4 Hz (45°)</td>
</tr>
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Figure 27. Configurations of Isomer of 1,2-Dimethyl-(cis-6- 
methyltetrahydropyran-2-yl) propane

When we used aluminum hydride for the endo-isopropyl 
bicyclic ketal, (52), we obtained an 83% yield of cis alcohol
(66a), and trans alcohol (66b), in a 13:87 ratio. As mentioned earlier, aluminum hydride usually gave cis alcohol and no trans alcohol but trans alcohol was the major product in this case (Figure 28).

Figure 28. Cleavage of 7-Isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane with AlH₃

The ¹H NMR spectrum of 66a shows the C₅ proton at 3.43 ppm while 66b shows the C₅ proton at 4.20 ppm. This indicates that 66a has an axial proton and 66b has an equatorial proton at C₅.

In contrasting the results of the cleavage reaction of the bicyclic ketals with AlH₃, Et₃SiH and MgBr₂, we can conclude that fragmentation of the ketals give products dependent on condition.

Other Unique Chemistry of Bicyclic Ketals

While trying to find new reducing agents to cleave bicyclic ketals, we found that aluminum iodide and acetonitrile gave a very novel fragmentation. The AlI₃ was prepared by refluxing one equivalent of dry aluminum foil and 1.6 equivalent of iodine
in ca. 1M acetonitrile solution. We used this system with the endo-isopropyl bicyclic ketal, (52), and found 1,2-dimethyl-(2-cyclohexenone-3-yl) propane, (67), and 2,3-dimethyl-1-(5,6-dimethylpyridine-2-yl) butanone, (68), as a 31:69 ratio. These could be separated by flash chromatography using petroleum ether:ethyl acetate in a 7:3 ratio. When we reacted 2.0 g of the starting material, we obtained 1.7 g of a crude mixture which was analyzed by GLC, 11' x 1/4" of 10% OV-17 column, and showed 67 and 68 as a 31:69 ratio with a few other very minor impurities. However, we were only able to isolate 0.1 g (6% yield) of 67 and 0.15 g (7.3% yield) of 68 and 1.16 g of decomposed product by flash chromatography (Figure 29). TLC chromatography indicates 68 (Rf=0.25) is a more polar compound than 67 (Rf=0.37) in the same solvent system.

Figure 29. Cleavage of 7-Isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane with AlI₃

Structural assignment of 67: (1) The ¹H NMR spectrum shows only 3 methyl peaks, which indicates one methyl group is changed, and shows one alkene proton at 5.84 ppm. A homo
decoupling experiment gave the environment of the substituted 1,2-dimethylpropane; irradiation of the 2.36 ppm signal gave a singlet for 1.04 ppm methyl peak and irradiation of 1.65 ppm gave two singlets at 0.88 and 0.83 ppm as an isopropyl methyl and, the 2.36 ppm methine proton also was coupled with 1.65 ppm methine proton. (2) IR indicates a conjugated carbonyl at 1669 cm\(^{-1}\) and a Gated-\(^{13}\)C NMR spectrum indicates two singlets which include one carbonyl carbon at 199.9 ppm and three doublets, three triplets and three quartets. Finally, HRMS indicates C\(_{11}\)H\(_{18}\)O. All of these data match well with the suggested structure, \(\text{67}\).

Structural assignment of \(\text{68}\): (1) The \(^1\)H NMR spectrum shows that there are 5 methyl peaks, two of them are highly deshielded singlets at 2.63 and 2.54 ppm and three doublets appear at 1.09, 0.92 and 0.85 ppm. Two highly deshielded protons are observed at 7.71 and 7.04 ppm which coupled each other and have a coupling constant of 8 Hz. Irradiation of the 3.04 ppm signal (H\(_A\)) gave a singlet for the 1.09 ppm methyl peak and irradiation of the 2.01 ppm signal (H) gave two singlets at 0.92 and 0.85 ppm as an isopropyl methyl. The 3.04 methine proton was found to be coupled with the 2.01 ppm methine proton.
The above partial structure should relate to electron withdrawing group which deshields $H_A$. The $^1H$ NMR spectrum shows very simple three pieces, but these do not match each other well. The $^{13}C$ spectrum indicates that there are 13 carbons which have 4 highly deshielded singlets, 4 doublets and 5 quartets with no triplets. (2) The IR spectrum shows a conjugated carbonyl at $1681 \text{ cm}^{-1}$ and the UV spectrum gives an absorbance at $274 \text{ nm (} \epsilon_{4140} \text{) and } 239 \text{ nm (} \epsilon_{6640} \text{) in ethanol}; very distinguishable characteristics for 2-carbonyl conjugated pyridine$^{24}$. The HRMS was consistent with the formula C$_{13}$H$_{19}$NO. All of these data indicate that acetonitrile had to react with the ketal to give product 68. Now we have several partial structures that can be put together as follows:

![Partial Structure]

two methyls and two protons

The two protons are coupled to each other with a coupling constant of $8 \text{ Hz}$ which indicates that 7.71 ppm for $C_4$ proton and 7.04 ppm for $C_3$ proton (Table 1).

We can thus put together these pieces to construct the two following possibilities, A and B.
Table 1. Reference of \(^1\)H, \(^{13}\)C and coupling constant for Pyridine

\[
\begin{align*}
\delta(\text{ppm}) & \quad J_{2,3} = 4.0-5.7 \\
7.46(138.7) & \quad J_{3,4} = 6.8-9.1 \\
3.06(125.6) & \quad J_{2,4} = 0-2.5 \\
68.50(149.5) & \quad J_{3,5} = 0.5-1.8 \\
\end{align*}
\]

To find the correct structure we reduced the carbonyl to an alcohol by using sodium borohydride. This gave nice white crystals (m.p. 159-162°C), \(69\), whose \(^1\)H NMR spectrum indicates the carbinol proton at 4.67 ppm as a doublet of doublet, one doublet with tertiary alcohol (\(J=3\) Hz) and the other doublet with adjacent \(H_A\) (\(J=9\) Hz). These clearly indicate that A is the right product (Figure 30).
The mechanisms of these reactions are not yet known.

**Attempt at Making "Coupled" Ketal**

The bicyclic ketal fragmentation with AcI and MgBr$_2$ gave a ketone as a functional group. Figure 31 shows a lot of variety of diketones which can be converted to furans, pyrroles, thiophenes from 1,4-diketone and to pyrans, pyridines from 1,5-diketone, and also, aldol condensation of 1,4-diketone might give prostaglandins.

As shown above, if we can make the coupled bicyclic ketals, there are a number of useful applications possible. Acrolein dimer 19 was used as a starting material, and was reacted with methylimagnesium bromide to give a 50:50 ratio of *threo* and *erythro* alcohol 72. Two equivalents of tertiary butyllithium were added to make the dianion, followed by addition of 0.5 equivalent of 1,2-dibromoethane. This reaction did not give the product. We imagined a steric effect might hinder the reaction.
so we changed to 1,5-dibromopentane. This reaction gave an \textit{exo} and \textit{endo} mixture of ketal 73 as a 66:34 ratio in 51% yield without any coupled product. The same reaction with 20 gave ketal 74 (Figure 32).

![Chemical structure diagram](image)

\[
\begin{align*}
71 \ (n=2) \quad & \overset{\text{P}_2\text{O}_5}{\longrightarrow} \quad \text{furan derivatives} \\
71 \ (n=2) \quad & \overset{\text{P}_2\text{S}_5}{\longrightarrow} \quad \text{thiophene derivatives} \\
71 \ (n=2) \quad & \overset{\text{(NH}_4)_2\text{CO}_3}{\longrightarrow} \quad \text{pyrrole derivatives} \\
71 \ (n=2) \quad & \overset{\text{B}}{\longrightarrow} \quad \text{prostaglandin derivatives} \\
71 \ (n=3) \quad & \overset{\text{NH}_3}{\longrightarrow} \quad \text{pyridine derivatives} \\
71 \ (n=3) \quad & \overset{\text{P}_2\text{O}_5}{\longrightarrow} \quad \text{pyran derivatives}
\end{align*}
\]

\textbf{Figure 31.} Possibilities of Coupled Bicyclic ketal Fragmentation

\begin{quote}
Direct coupling did not occur with our conditions; but the reaction gave an alkyl bromide which we thought might be substituted with another anion of bicyclic ketal to give coupled product. Using 72 with two equivalents of tertiary butyllithium and then 73 was added to this dianion reactant, but also this did not give the expected product (Figure 33).
\end{quote}
Figure 32. Preparation of 5-(n-Bromopentyl)-7-methyl-6,8-dioxabicyclo[3.2.1]octane and 5-(n-Bromopentyl)-7-pentyl-6,8-dioxabicyclo[3.2.1]octane

Figure 33. Attempted Coupling Reaction.

At this writing we have not been successful in this coupling of two ketals; however, work continues along these lines.
Functionalized Bicyclic ketal Systems

It is another interesting area to functionalize simple bicyclic ketals. We used mercuric acetate to cyclize the alcohol 72, which gave mercuric complex at C4 of bicyclic ketal. Addition of acrolein under radical conditions gave exo-erythro, exo-threo, endo-threo, and endo-erythro isomers, (75), as a 21:53:9:17 ratio in a 42% yield (Figure 34).

![Chemical structures](image)

Figure 34. Formation of 7-Methyl-4-propanal-6,8-dioxabicyclo[3.2.1]octane

The configurational assignments of isomers of 75 are based on the following: (1) exo and endo methyl groups at C7 are easily identified by their 1H NMR spectra which gives 1.18 ppm of the exo methyl and 1.30-1.34 ppm of endo methyl group. GLC analysis of the product 75 using a 11' x 1/4", 10% OV-17 column shows four isomers (A-D) and 1H NMR of A and B show them to exo isomers while C and D are shown to endo isomers.

(2) Chemical shift of the proton at C4 will tell about axial or equatorial of the proton because equatorial proton is more deshielded than axial proton (Table 2).
Table 2. Assignment of Chemical Shift for axial and equatorial proton of ketal

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>exo-CH₃</td>
<td>1.18 ppm</td>
</tr>
<tr>
<td>endo-CH₃</td>
<td>1.30-1.34 ppm</td>
</tr>
<tr>
<td>H axial</td>
<td>1.50 ppm</td>
</tr>
<tr>
<td>H equatorial</td>
<td>1.63 ppm</td>
</tr>
</tbody>
</table>

Irradiation of the 1.50 ppm signals for B and D gave sharpening at 5.32 ppm for B and 5.27 ppm for D. Also, irradiation of the 1.63 ppm signals of A and C gave sharpening of 5.30 ppm for A and 5.25 ppm for C. This indicates that A and C have equatorial proton and B and D have axial proton at C₄.

Thus, A can be assigned - exo, equatorial (exo-erythro), B - exo, axial (exo-threo), C - endo, equatorial (endo-threo), and D - endo, axial (endo-erythro) (Figure 35).

We tried the same reaction with long chain substituted alcohol, (77), prepared from 76. This reaction did not give the expected product, possibly because of the steric hindrance (Figure 36).

Another simple reaction for halogenation at C₄ of ketal was found in our group. To a solution of ketal 56 in carbon tetrachloride at room temperature was added bromine and the reaction was stirred for 7 hours. This gave an 88% yield of bromo ketal, (78). The same result was obtained from ketal, (48), (Figure 37).
Figure 35. Isomers of 7-Methyl-4-propanal-6,8-dioxabicyclo [3.2.1]octane

**Attempt at Synthesis of Sirenin**

Sirenin (86), is a sperm attractant produced by the female gametes of the water mold *Allomyces*²⁵. This has been synthesized by Grieco²⁶ (Figure 38).
Figure 36. Attempted cyclization of 2-(2-Hydroxymethyl)-6-(n-decyl)-3,4-dihydro-2H-pyran

Figure 37. Bromination of Ketal

We were interested in the synthesis of 81 (R=OH) as a formal synthesis of sirenin. This intermediate might be available from methyl ketone, (88), by haloform reaction and also, 88 is the fragmentation from ketal, (87), (Figure 39).

To make ketal, (87), MVK dimer, (8), was added to a solution of 5-bromo-2-methyl-2-pentene and magnesium in dry ether and cyclized by adding 5% aqueous HCl solution. The exo
Geranyl Chloride $\xrightarrow{a}$ 79 $\xrightarrow{b}$ 80 $\xrightarrow{c}$ 81 $\xrightarrow{d,e}$ 82 $\xrightarrow{f,g,h}$ 83 $\xrightarrow{i}$ 84 $\xrightarrow{j,k}$ 85 $\xrightarrow{l}$ 86

(a) allylmagnesium bromide.  (b) disiamylborane, NaOH-H$_2$O$_2$.
(c) Jones oxidation.  (d) SOCl$_2$.  (e) diazomethane, Cu bronze.
(f) ozonolysis.  (g) dimethyl sulfide.  (h) methyl 2-diethylphosphonopropionate.  (i) sodium hydride, methyl formate.
(j) isopropyl iodide.  (k) NaBH$_4$-NaOH, 3N HCl.  (l) LiAlH$_4$.

Figure 38. Grieco's Synthesis of Sirenin
and endo isomers of 87 were obtained as a 84:16 ratio in a 72% yield. The major exo isomer is the right starting material for making the trans isomer of 88 by fragmentation. AcI cleavage gave the expected fragmentation product, 88 in a 20% yield. This was treated with iodoform reagent to give a positive yellow precipitate. Due to low yield of the iodoform oxidation, we did not obtain a preparatively useful amount of 81, thus, the product was converted to 89 and characterized only by HRMS (Figure 40).

Figure 39. Retro Formal Synthesis for Sirenin

Figure 40. Esterification of 6,10-Dimethyl-5,9-nonadienoic acid
Dianion Chemistry

Dianion chemistry has been shown to be a useful and powerful method for ring annulation. The pioneering work of Wilkening in our group paved the way for our interest in this program. Our group is committed to the concept of developing new approaches to natural products using dianion protocols.

Based on the previous work, we wished to extend our knowledge of the value and limitation of the procedure.

A New Approach to Valerane

The valerane skeleton is a unique and structurally interesting sesquiterpene form. The parent compound is obtained by the reduction of L-valeranone, \( (9) \). Valeranone, isolated from Valeriana officinalis\(^2^7\), is one of the few known nonisoprenoid sesquiterpene ketones\(^2^8\). After a great deal of experimentation by several groups of investigators, its structure and absolute stereochemistry were finally established as shown in Figure 41\(^2^9\). It possesses an unusual carbon skeleton having two angular methyl groups in a cis-fused decalin ring system. The \( C_{14} \) and \( C_{15} \) methyl groups are \( \alpha \)-oriented whereas the \( C_7 \) isopropyl group is \( \beta \)-oriented. The correctness of the proposed structure was substantiated by two different syntheses of \( d \)- and \( l \)-valeranones\(^3^0\). In view of the flexible nature of the cis decalin, valeranone could exist in at least two interchangeable all-chair conformations such as the "steroid" cis conformation or the "nonsteroid" cis conformation (Figure 42). Hartshorn\(^3^1\)
and Hikino\textsuperscript{32} proved that valeranone exists in the steroid cis conformation from a study of its optical rotatory dispersion.

![Figure 41. Absolute Stereochemistry of l-Valeranone](image)

The natural l-valerane, (91), was prepared for comparison from l-valeranone (90) by Rao\textsuperscript{28}. The infrared and NMR spectra of the synthetic 91a (Figure 43) were found to be identical with those of the authentic natural l-valerane, (91), (Figure 44).
Figure 43. Rao's Synthesis of Valerane

(a) dihydropyran, H⁺.  (b) (C₆H₅)₃P=CHCH₃.  (c) B₂H₆, H₂O₂.  
(d) CrO₃.  (e) C₂H₅ONa, EtOH.  (f) H⁺.  (g) dihydropyran, H⁺.  
(h) (C₆H₅)₃P=CH₂.  (i) H₂, Pd/c.  (j) H⁺.  
(k) CrO₃.  (l) HSCH₂CH₂SH, H⁺.  (m) Raney Ni.
Figure 44. Comparison of Conformation of Valerane

The ratio of $91a$ and $91b$ was 40:60 and only $91a$ was found to be identical with natural $91$. Baldwin$^{33}$, also, found the same ratio of $91a$ and $91b$ by using a photoannelation technique with $\alpha$-formyl ketones (Figure 45).
Valerane, with the decalin structure and cis ring juncture, seemed to be well-suited to the stereochemical advantage provided by our dianion ring annulation method. Thus, we decided to make this compound to test the value of dianion chemistry.

(a) hv.  (b) H⁺.  (c) H₂, Pd/c.  (d) (C₆H₅)₃PC(CH₃)₂.
(e) H₂, Pt.  (f) TsNH₂H₂, EtOH.  (g) CH₃Li, Et₂O.
(h) Li, NH₃, t-BuOH.  (i) ClPO(OEt)₂, THF, TMEDA.
(j) Li, EtNH₂.

Figure 45. Baldwin's Synthesis of Valerane
It was postulated that a vicinal ester dianion generated from \( 9_2 \) might be a legitimate intermediate if a disubstituted butane could be found to act as an electrophile in the dianion ring annihilation reaction (Figure 46).

![Dianion of 4,5-Dimethylcyclohexene dicarboxylate](image)

**Figure 46.** Dianion of 4,5-Dimethylcyclohexene dicarboxylate

Additional credence to this approach was gleaned from the anticipated stability of the dianion generated from the vicinal diester, as conjugation of the enolates would serve to stabilize the developing charge. One final bonus this reaction offered was the expected formation of only cis-vicinal diester. The dienolate being presumably planar to permit conjugation, implied that once the first alkylation has occurred the second displacement would proceed from the same face, since formation of the trans ring juncture would require the butano group to twist between the two ester residues. This hypothesis was examined by performing the experiment outlined in Figure 47. When 1.5 equivalents of 1,4-dibromobutane were added to the cooled, bright red THF solution of the dienolate of \( 9_2 \), the bicyclic diester, \( 9_3 \), was obtained in 75% yield.
As expected, exhaustive characterization revealed that only the cis-diester had been formed.

To transfer the diester to the dimethyl group, we proposed to make thiapropellane, (96), (Figure 48).

Figure 48. Retro Synthesis of cis-9,10-Dimethyldecalin-2-ene

Our attention was initially directed toward the synthesis of sulfide, (96). This was accomplished by the reaction sequence shown in Figure 49. The diester, (93) was reduced with
lithium aluminum hydride and treatment of the resulting diol with methanesulfonyl chloride in pyridine gave the dimesylate, (95), in high yield. Heating 95 in dry hexamethylphosphoramide (HMPA) with anhydrous sodium sulfide led to sulfide, (96), in 93% yield. Paquette reported that the use of dry HMPA is essential to the success of this twofold SN₂ displacement-cyclization. In its absence, the capability of sulfide ion to attack at the neopentyl centers is greatly diminished and little or no 96 is produced. Clearly, the high cation-solvating capacity of HMPA, which greatly reduces the effective size of the nucleophile relative to its bulk in other (especially protic) media, causes a marked acceleration of the desired chemical change. Desulfurization of the sulfide, (96), accomplished by Raney-nickel in ethanol solution, gave the dimethyldecalin, (97), in 73% yield and, also, 18% yield of saturated decalin, (97a). This mixture was subjected to hydroboration to give isomeric alcohol, (98), in 95% yield and, at this point, the unreacted 97a was separated by silica gel column chromatography with petroleum ether as a solvent; 98 was isolated with ethylacetate as a solvent. This alcohol, (98), was oxidized with pyridinium dichromate to ketone 99 in 93% yield (Figure 50).

Direct Wittig reaction was attempted to put the isopropyl group at the C₂ position, but this reaction gave 99a instead of the expected product (Figure 51).
Figure 49. Synthesis of 12-Thia[4.4.3]propell-3-ene

Figure 50. Synthesis of cis-9,10-Dimethyldecalin-2-one
Figure 51. Attempted Wittig Reaction of cis-9,10-Dimethyldecalin-2-one

We simply used isopropyl Grignard to put the isopropyl group at C2 and treatment of the product 100 with phosphorous oxychloride gave 101a and 101b as a 45:55 ratio in a 73% yield. This mixture was hydrogenated with 10% palladium on carbon in hexane and gave 91a and 91b as a 45:55 ratio in 80% yield (Figure 52).

As mentioned earlier, Rao and Baldwin synthesized 91a and 91b as a 40:60 ratio and the reported spectral data is identical with ours. Also, we proved the conformation of 91a and 91b by a NOE experiment as follows: Irradiation of the 0.83 ppm resonance in 91a gave a 0.65% positive NOE effect at 1.51 ppm, but irradiation of 0.84 and 0.79 ppm in 91b did not give any positive NOE effect, which indicates 91a is in steroid cis conformation and 91b is in nonsteroid cis conformation (Figure 53).
Possible Use in Maleimycin Synthesis

Maleimycin, a new bicyclic maleimide antibiotic, was isolated from the culture filtrate of *Streptomyces showdoensis* and assigned structure \( \text{102} \) by Suhadolnik\(^3^5\) (Figure 54).

Also, Kasugai\(^3^6\) reported that N-substituted-\(\Delta^1\)-cyclo-pentene-1,2-dicarboxylic imides \( \text{103} \) have fungicidal and herbicidal activities (Figure 55).

Weinrab\(^3^7\) had previously synthesized maleimycin by a longer route than we anticipated (Figure 56). Our interest in making the five-five fused ring system of this molecule using dianion annulation suggested a simpler approach.
Figure 53. Conformational Assignment for Valerane

Figure 54. Structure of Maleimycin
R=halo, lower alkyl, lower alkoxy, cyano, aralkyloxy, haloaralkyloxy, aralkylthio, haloaralkylthio, phenyl napthyl

Figure 55. N-Substituted-\(\Delta^1\)-cyclopentene-1,2-dicarboxylic imides

(a) SOCl\(_2\). (b) Br\(_2\). (c) CH\(_3\)OH. (d) NaH, DMF. (e) acetic anhydride, ammonium hydroxide. (f) trifluoroacetic anhydride. (g) N-bromosuccinimide. (h) silver trifluoroacetate. (i) pH=4

Figure 56. Weinrab's Synthesis of Maleimycin
We chose succinimide as a starting material. This was N-substituted with the benzyl group because imide proton will hinder formation of the needed dianion. Succinimide, (104), benzyl chloride and potassium carbonate were refluxed and gave N-benzylsuccinimide, (105), (Figure 57).

![Figure 57. Synthesis of N-Benzylsuccinimide](image)

When 2.5 equivalents of lithium diisopropyl amide were mixed with 105, a reddish black color of the dienolate was formed; but, this dianion did not react with 3-bromoethylpropionate. Yamamoto reported difficulty in employing 3-bromoethylpropionate in condensations with the dianion of diisopropylsuccinate and he suspected that the proton exchange process was fast (Figure 58).

We used 1,3-dibromopropane for this dianion reaction and made cis-3-(N-Benzyl)-2,4-dioxobicyclo[3.3.0]-heptane, (107), in 60% yield (Figure 59).

In order to introduce the 1,2-double bond in 107, Wilkening's method was used. The dienolate of 107 was reacted with 1.1 equivalents of iodine in the established
method, but this reaction did not result in formation of the double bond (Figure 60).

\[
\begin{align*}
105 + \text{BrCH}_2\text{IgBr} &\xrightarrow{X} \text{XXD2FPr} \\
\text{CO}_2\text{i-Pr} + \text{BrCH}_2\text{IgBr} &\xrightarrow{X} \text{CO}_2\text{i-Pr}
\end{align*}
\]

Figure 58. Attempted Synthesis of Cyclopentanones

\[
\begin{align*}
105 + \text{Br(CH}_2)_3\text{Br} &\rightarrow \text{107}
\end{align*}
\]

Figure 59. Synthesis of cis-3-(N-Benzyl)-2,4-dioxobicyclo[3.3.0]heptane

In an attempt to test whether we were forming the dienolate of 107, we prepared the propellane of this compound. We have made 5-5-5 (108) and 5-5-4 (109) propellanes in 25% yield of each (Figure 61).
We also tried pyrolysis and photo reaction of 109, but did not form the needed double bond.

Even though we did not get the target maleimycin, this work demonstrated that the dianion reaction could introduce 5-5, 5-4 (110), 5-5-5, 5-5-4 ring annihilation in a convenient way.

Synthesis for Possible Hirsutene Intermediate

Hirsutene, (111), which is the biogenetic precursor of coriolin, (112), and hirsutic acid, (113), is a tricyclic
sesquiterpene hydrocarbon isolated from *Coriolus consers*. Its structure is shown in Figure 62.

In addition to the synthetic interest elicited by the skeletal features of these terpenoids, there exists an array of remarkable physiological properties associated with the coriolin-type sesquiterpenes. The antibiotic and antitumor activities of coriolin and hirsutic acid dictate an efficient synthetic approach to these compounds, particularly in view of their uncertain supply from natural sources. Several interesting syntheses have appeared to date, describing the preparation of coriolin, hirsutic acid and hirsutene.

Our purpose, again, was to construct ring systems by using dianion chemistry. From the structure 111, we can derive retro syntheses for surveying the possible route of dianion chemistry (Figure 63).

*Cis* fused 5-5 configuration of 120 might be a good choice of dianion annulation from the vicinal diester 118. Another ring annulation with *cis* stereochemistry from 121 to 122 might be achieved by Danheiser's annulation method which is
presented in Figure 64.

Figure 63. Retro Synthesis of Hirsutene

Figure 64. Danheiser's Cyclopentene Annulation
We decided to make 120 as a possible intermediate of hirsutene.

As shown in Figure 65, 114 was prepared from aldol condensation of isobutyraldehyde and methyl vinyl ketone with sulfuric acid as a catalyst. Hydrogenation of 114 gave white solid 115 in a 96% yield. Carboethoxylolation of 115 with diethyl carbonate and sodium hydride produced 116 in 68% yield. The NMR chemical shift at 12.22 ppm indicates the presence of enol ester 116a as a more preferable form than keto ester 116 (Figure 66).

Figure 65. Synthesis of 2,7,7-Trimethyl-cis-1,5-dicarboethoxy-bicyclo[3.3.0]octan-2-ol
Figure 66. Tautomers of 2-Carboethoxy-4,4-dimethylcyclohexanone

Favorskii rearrangement of 116 gave the vicinal cyclopentane diester, (118), in a 67% yield. When 1.5 equivalents of 4-chlorobutan-2-one, (119), (prepared from hydrochlorination of methyl vinyl ketone) were added to the dianion generated from the vicinal diester, (60), the desired bicyclic alcohol, (120), was obtained in 21% yield. From this convenient synthesis of 120, we envision the possibility of the preparation of hirsutene, (111), as shown in retro synthesis (Figure 63).
Summary

The work reported in this thesis has made several important contributions to the existing program of synthetic methodology. The mechanism of bicyclic ketal fragmentation has been unambiguously determined. Other side products of the fragmentation reaction provide new entries into pyridine and cyclohexenone derivatives. Details of the stereochemistry of ketal opening have been determined. New methods for ketal functionalization have been developed. The ketal fragmentation protocol was applied to a formal synthesis of sirenin.

Additional studies directed towards determining the range of applicability of dianion annulation have resulted in: a) a stereoselective synthesis of valerane, b) preliminary approaches to maleimycin, and c) a synthesis of a precursor to hirsutene.
CHAPTER 3

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. CDCl₃ 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 analysis were performed using a Varian Aerograph series 2700 gas chromatograph equipped with 11′ x 1/4″, 10% OV-17 column.
Preparation of 2-Acetyl-6-methyl-3,4-dihydro-2H-pyran (8)

A solution of 100 mL (1.20 mole) of methyl vinyl ketone (3-butene-2-one), 0.5 g of hydroquinone and 50 mL of benzene was placed in a steel pressure bomb and heated at 175° C for three hours. After cooling, the solvent was removed via a rotatory evaporator and the product was distilled (water aspirator). Collection from 74° - 77° C gave 56.5 g (0.40 mole) of a clear, colorless liquid (67% yield).

The spectral data were identical to previous work.\textsuperscript{51}

Preparation of exo/endo-5,7-Dimethyl-6,8-dioxabicyclo-[3.2.1]octane (15)

According to the methods of Lipkowitz\textsuperscript{52}, sodium borohydride (0.045 grams, 0.0048 mole) was placed in a flask with 10 mL of 2-propanol and stirred at room temperature. Methyl vinyl ketone dimer (8) (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 methylene chloride and the organics were separated and dried over anhydrous magnesium sulfate. The methylene chloride was removed by rotatory evaporator. The GLC analysis using a 12' x 1/4", 10% OV-210 column indicated an exo/endo ratio of 60:40 (97% yield).

The spectral data was identical to previous work.\textsuperscript{53}
Preparation of 2-Formyl-3,4-dihydro-2H-pyran (19)

A mixture of 84 g (1.5 mole) acrolein (2-propenal), 50 mL of benzene and 0.25 g of hydroquinone was heated in a stainless steel pressure bomb at 175° C for 3 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 (0.28 mole) of a clear, colorless liquid (37.5% yield).

\[ {^1}H \text{ NMR: } 9.71 \text{ (1H, s); 6.51 (1H, d); 4.81 (1H, m); 4.3 (1H, m); 2.03 (4H, m).} \]

Preparation of 2-(1-hydroxyhexyl)-3,4-dihydro-2H-pyran (20)

The n-pentyl magnesium bromide was slowly added to a solution of 17 g (0.15 mole) of 19 stirred in 75 mL of dry ether at 0° C under nitrogen. After 15 hours stirring at room temperature, the reaction was quenched by adding water and extracted with ether, washed with brine, dried over anhydrous magnesium sulfate and reduced in volume. There was obtained 22 g (0.12 mole) of a clear liquid (79% yield).

The spectral data were identical to previous work.

Preparation of cis/trans-6-Octen-2-one (47)

The ketal, (15), (0.50 g; 0.0035 mole) was subjected to the general cleavage procedure by using acetyl chloride and GLC analysis indicated 0.13 g (0.0010 mole) of a 65:35 mixture of trans and cis alkenes, respectively (30% yield).
The spectral data were identical to previous work\textsuperscript{54}.

\textit{\textsuperscript{1}H NMR of trans-47}: 5.38 (2H, m); 2.4 (2H, t); 2.1 (3H, s); 1.98 (2H, q); 1.63 (5H, m).

\textit{\textsuperscript{1}H NMR of cis-47}: 5.45 (1H, m); 5.35 (1H, m); 2.42 (2H, t); 2.15 (3H, s); 2.05 (2H, q); 1.6 (5H, m).

Preparation of exo/endo-7-Deuteriomethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1] octane (48)

Iodomethane-\textsubscript{d\textsubscript{3}} (2.5 g, 0.017 mole) was slowly added to 0.42 g (0.017 mole) of magnesium in 25 mL dry ether under nitrogen. After 2 hours stirring at room temperature, the reaction was cooled to 0\textdegree C and 1.82 g (0.013 mole) of MVK dimer, (8), in 5 mL dry ether was added via a syringe. The reaction mixture was allowed to warm to room temperature and was stirred for 16 hr., after which the reaction was quenched with 25 mL of 5\% aqueous HCl solution. The reaction mixture was extracted with three 30 mL portions of ether which were combined, washed with saturated brine, dried over anhydrous magnesium sulfate and reduced in volume via the rotatory evaporator. This gave 1.48 g (0.0093 mole) of a slight yellow liquid (71.6\% yield).

\textit{\textsuperscript{1}H NMR}: 3.87 (1H, br s); 2.0-1.45 (6H, m); 1.40 (3H, s); 1.36 (2H, s); 1.26 (1H, s).

MS: 159 (M\textsuperscript{+}), 117, 98, 89, 71, 43 (base).

HRMS: Calcd for C\textsubscript{9}H\textsubscript{13}O\textsubscript{2}D\textsubscript{3}: 159.1338. Observed: 159.1339.
Preparations of cis/trans-7-DeuteriromethyI-6-octene-2-one (49); 6-Acetoxy-8,8-dideuterio-7-methyl-7-octene-2-one (50a); 6-Acetoxy-7-deuteriomethyI-7-octene-2-one (50b); 7-DeuteriomethyI-6,7-diacetoxy-2-octanone (51)

(A) Acetyl chloride, (0.2 mL, 2 eq.), was added to a mixture of 0.4 g (2 eq.) of sodium iodide and 0.2 g (0.0013 mole) of 48 in 20 mL of acetonitrile at 0°C under nitrogen. The resulting solution was stirred at room temperature for 24 hours after which time the reaction was quenched by adding 15 mL of 5% aqueous sodium bisulfite and stirring for 30 minutes at room temperature. The reaction mixture was then extracted with three 30 mL portions of ether which were combined, washed with 10% aqueous sodium thiosulfate, 5% aqueous sodium bicarbonate and saturated brine, 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. Reduced volume gave 0.14 g of crude mixture (yield: 49; 15.9%, 50; 37.3%, 51; 15.8%).

(B) The bicyclic ketal; (48) (0.2 g, 0.0013 mole) was subjected to the general cleavage procedure by using magnesium bromide and GLC analysis indicated 0.02 g of a 2:8 mixture of 50;51 and most of the starting material back.
**General Cleavage of the 6,8-Dioxabicyclo[3.2.1]octane System by Using Acetyl Iodide**

Two equivalents of acetyl chloride in 10 mL of clean, dry acetonitrile were slowly added dropwise, via an additional funnel, to a solution of 2 equivalents of sodium iodide and 0.5 g of the bicyclic ketal, stirring at 0°C in 20 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 30 minutes 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.

**General Cleavage of the 6,8-Dioxabicyclo[3.2.1]octane System by Using Magnesium bromide**

One equivalent of 1,2-dibromoethane was added, via syringe, to 1 equivalent of magnesium in 30 mL of dry ether under nitrogen at 0°C. After 3 hours stirring at room temperature, ether was removed via the rotatory evaporator and replaced by 30 mL dry acetonitrile. Then 2 equivalents of acetic anhydride and 0.5 g of the bicyclic ketal were added, successively, to this stirred suspension under nitrogen at 0°C. The resulting solution was stirred at room temperature for 12 hours, after which time the reaction was quenched by adding 20 mL of saturated aqueous sodium bicarbonate. The reaction mixture was then extracted with several 50 mL portions of ether which were combined, washed with brine, dried over anhydrous magnesium sulfate and reduced in volume. The crude material was then separated by flash chromatography using petroleum ether:ethyl acetate in a 7:3 ratio as a solvent system.
General Cleavage of the 6,8-Dioxabicyclo[3.2.1]octane System by Using Aluminum Iodide

In a dry 25 mL two-neck round bottomed flask, 1 equivalent of dry aluminum foil and 1.6 equivalents of iodine in ca. 1M acetonitrile solution was refluxed for 3 hours until the iodine color disappeared. Then 0.5 g of the bicyclic ketal was added to this refluxing reaction mixture and refluxed for 12 hours. After cooling down to room temperature, the reaction mixture was poured into 20 mL of water and extracted with several 30 mL portions of ether which were combined, washed with 5% aqueous sodium hydroxide, 10% aqueous sodium thiosulfate and brine, dried over anhydrous magnesium sulfate and reduced in volume. The crude material was then separated by flash chromatography using petroleum ether:ethyl acetate in a 7:3 ratio as a solvent system.

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

Ten equivalents of triethylsilane and 10 equivalents of boron trifluoride etherate were added sequentially to the 0.5 g of the bicyclic ketal in 10 mL dry methylene chloride at 0°C under nitrogen. After 24 hours stirring at room temperature, the reaction was quenched by adding 20 mL of saturated aqueous sodium bicarbonate. The reaction mixture was then extracted with several 30 mL portions of methylene chloride which were combined, washed with brine, dried over anhydrous magnesium
sulfate and reduced in volume.

**General Cleavage of the 6,8-Dioxabicyclo[3.2.1]octane System by Using Aluminum Hydride**

To a gray suspension of 2 equivalents of aluminum chloride in 20 mL of anhydrous ethyl ether was added dropwise 0.5 equivalent of lithium aluminum hydride in 20 mL of anhydrous ethyl ether in an ice bath under nitrogen. Swirling with ether was repeated several times until all the hydride was added and the gray slurry was stirred for an hour. After this, 0.2 g of the bicyclic ketal in 10 mL ether was added at a rate sufficient for gentle refluxing. The mixture was refluxed for 3 hours. Excess hydride was destroyed by the dropwise addition of ca. 1 mL of water and 2N sulfuric acid was added carefully until no more reaction occurred in an ice bath. The ether layer was separated and the aqueous layer was extracted with ether three times. The combined ether solution was washed with water, brine, dried over anhydrous magnesium sulfate and reduced in volume.

**Preparation of 7-Isopropyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (52)**

To 1.0 g (0.0071 mole) of 8 in 40 mL of anhydrous tetrahydrofuran under nitrogen was added 4.7 mL (1.3 eq.) of 2 M isopropyl magnesium chloride 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 5% aqueous HCl solution and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and reduced in volume. Distillation (water aspirator) and collection of the fraction at 84°C gave 0.86 g (0.0047 mole) of a colorless liquid (65% yield).

^1H NMR: 4.06 (1H, br s); 2.03-1.45 (7H, m); 1.39 (3H, s); 1.18 (3H, s); 0.94 (3H, d, J=7 Hz); 0.80 (3H, d, J=7 Hz).

^13C NMR: 107.0 (s), 85.9 (s), 78.2 (d), 35.1 (d), 34.1 (t), 25.7 (q), 24.2 (t), 19.1 (q), 17.3 (t), 15.9 (q), 12.2 (q).

MS: 184 (M^+), 141, 124, 96, 81, 71, 55, 43 (base).

HRMS: Calcd for C_{11}H_{20}O_{2}: 184.1463. Observed: 184.1466.

IR: 2941, 1385, 1242, 1176, 1040, 917.
Preparations of 7,8-Dimethyl-6-nonen-2-one (53); 7,8-Dimethyl-7-nonen-2-one (54) and unidentified product (55)

(A) The bicyclic ketal (0.50 g, 0.0027 mole), (52), was subjected to the general cleavage procedure by using acetyl iodide to give 0.4 g of reaction product. GLC analysis, using a 5' x 1/4", 20% SE-30 column, indicated a 16:13:7:64 mixture of 52, 53, 54, 55, respectively.

(B) The bicyclic ketal (0.50 g, 0.0027 mole), (52) was subjected to the general cleavage procedure by using magnesium bromide and GLC analysis indicated 2% of 55, and most of starting material, (52) was recovered.

$^1$H NMR of 53:  
5.07 (1H, t, J=5 Hz); 2.39 (2H, t, J=7 Hz); 2.20 (1H, m); 2.11 (3H, s); 1.97 (2H, m); 1.65-1.50 (2H, m); 1.53 (3H, s); 0.95 (6H, d, J=7 Hz).

$^1$H NMR of 54:  
2.41 (2H, t, J=7 Hz); 2.11 (3H, s); 2.00 (2H, t, J=7 Hz); 1.61 (6H, s); 1.59 (3H, s); 1.55 (2H, m); 1.32 (2H, m).

$^1$H NMR of 55:  
5.17 (1H, br s); 4.98 (1H, s); 4.91 (1H, s); 2.65 (1H, m); 2.44 (2H, m); 2.22 (2H, t, J=7 Hz); 2.12 (3H, s); 2.04 (3H, s); 1.06 (3H, d, J=6.5 Hz); 1.03 (3H, d, J=6.5 Hz); 0.90 (3H, d, J=7 Hz).

MS of 53:  
168 (M$^+$), 150, 110, 95 (base), 80, 67, 55, 43.

HRMS:  
Calcd for C$_{11}$H$_{20}$: 168.1514. Observed: 168.1493.
MS of 54: 168 (M+), 150, 135, 121, 110, 95, 83, 67, 55 (base), 43.


MS of 55: 184 (M+ - CH_2CO), 166, 151, 123, 108, 93, 81, 67, 55, 43 (base).

HRMS: Calcd for C_{11}H_{20}O_2: 184.1464. Observed: 184.1464.

TLC: Petroleum ether:ethyl acetate in a 7:3 ratio as a developing solvent on silica gel TLC (H_2SO_4/Cr_2O_7^{2-} visualization).

R_f of (23): 0.51
R_f of (24): 0.51 (UV active)
R_f of (22): 0.40

\[\begin{align*}
53 & \quad \begin{array}{c}
2.39 & 1.65-1.50 & 0.97 \\
2.11 & 2.20 & 1.97 \\
1.53 & 5.07 & 1.97
\end{array} \\
54 & \quad \begin{array}{c}
2.41 & 1.55 \\
2.11 & 2.00 \\
1.32 & 1.59 \\
1.61
\end{array}
\end{align*}\]

Preparation of 5,7,7-Trimethyl-6,8-dioxabicyclo[3.2.1]octane (56)

A solution containing 5.0 g (0.036 mole) of 8 in 70 mL of tetrahydrofuran was stirred under nitrogen while 15 mL (1.3 eq.) of 3.1 M 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 30 mL of 5% aqueous HCl solution and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and reduced in volume. Distillation (water aspirator) and collection of the fraction at 55° C gave 3.9 g (0.025 mole) of a clear, colorless liquid (70% yield).

\[ \text{^1H NMR: } 3.87 (1H, br s); 2.0-1.45 (6H, m); 1.40 (3H, s); 1.36 (3H, s); 1.26 (3H, s). \]

\[ \text{^13C NMR: } 107.2 (s), 81.1 (d), 80.8 (s), 34.2 (t), 29.2 (q), 25.8 (q), 24.2 (t), 20.9 (q), 17.2 (t). \]

\[ \text{MS: } 156 (M^+), 141, 114, 98, 81, 68, 43 (base). \]

\[ \text{HRMS: Calcd for C}_9\text{H}_{16}\text{O}_2: 156.1151. Observed: 156.1149.} \]

\[ \text{IR: } 2857, 1370, 1263, 1214, 1159, 1129, 1098, 1032, 962, 912, 868, 849, 829. \]

Preparations of 7-Methyl-6-octene-2-one (57); 6-Acetoxy-7-methyl-7-octene-2-one (58); 6,7-Diacetoxy-7-methyl-2-octanone (59)

(A) The ketal (0.50 g, 0.0032 mole), (56), was subjected to the general cleavage procedure by using acetyl iodide to give 0.37 g of reaction product. GLC analysis, using a 5' x 1/4'', 20% SE-30 column indicated a 23:54:23 mixture of 57, 58, 59
respectively.

(B) The ketal (2.6 g, 0.017 mole), (56), was subjected to the general cleavage procedure by using magnesium bromide to give 0.4 g of reaction product. GLC analysis indicated a 2:8 mixture of 58 and 59 and most of the starting material back.

**1H NMR of 57:** 5.06 (1H, br t, J=7.5 Hz); 2.39 (2H, t, J=7.5 Hz); 2.11 (3H, s); 1.97 (2H, m); 1.66 (3H, s); 1.56 (3H, s); 1.6-1.5 (2H, m).

**1H NMR of 58:** 5.14 (1H, t, J=5.5 Hz); 4.93 (1H, br s); 4.87 (1H, br s); 2.43 (2H, t, J=7 Hz); 2.12 (3H, s); 2.04 (3H, s); 1.70 (3H, br s); 1.7-1.5 (4H, m).

**1H NMR of 59:** 5.15 (1H, m); 2.43 (2H, m); 2.12 (3H, s); 2.08 (3H, s); 1.94 (3H, s); 1.7-1.5 (4H, m); 1.43 (3H, s); 1.40 (3H, s).

**13C NMR of 57:** 209.5 (s), 132.5 (s), 123.7 (d), 43.1 (t), 29.8 (q), 27.3 (t), 25.6 (q), 23.9 (t), 17.6 (q).

**13C NMR of 58:** 208.3 (s), 170.2 (s), 142.8 (s), 112.8 (t), 76.8 (d), 43.0 (t), 31.9 (t), 29.8 (q), 21.1 (q), 19.4 (t), 18.0 (q).

**13C NMR of 59:** 208.4 (s), 170.5 (s), 170.0 (s), 82.4 (s), 76.2 (d), 42.7 (t), 29.8 (q), 28.1 (t), 22.2 (q), 22.1 (t), 22.0 (q), 20.8 (q), 19.7 (q).

**MS of 57:** 140 (M⁺), 122, 82 (base), 69, 43.

**HRMS:** Calcd for C₉H₁₆O: 140.1201. Observed: 140.1232.

**MS of 58:** 156 (M⁺-CH₂CO), 138, 95, 81, 71, 58, 43 (base).
HRMS: Calcd for C₉H₁₆O₂: 156.1150. Observed: 156.1151.

MS of 59: 157 (M⁺-2CH₂CO-OH), 141, 115, 97, 71, 59, 43 (base).

IR of 57: 1700, 1650 (sh), 1420, 1360,
IR of 58: 1695 (br), 1351, 1225, 1012.
IR of 59: 1690 (br), 1351, 1220, 1130, 1010.

\[ ^1H \quad ^{13}C \]

Preparation of n-Bromobutyl acetate (60)

1,2-Dibromoethane (0.10 g, 0.0054 mole) was added to
0.013 g (1 eq.) of magnesium in 15 mL tetrahydrofuran under
nitrogen. After all the magnesium was dissolved (ca. 2 hrs.),
0.1 mL of acetic anhydride was added in ice bath and then
stirring at room temperature for 24 hrs. Usual work-up gave 1 g
(0.005 mole) of liquid (93% yield).
Preparation of 1-(cis-6-Methyltetrahydropyran-2-yl)ethanol (61a) and (61b)

The exo/endo mixture (0.3 g, 0.002 mole), (15) were subjected to the general cleavage procedure by using triethylsilane to give 0.25 g (0.0017 mole) of reaction product. GLC analysis, using a 11' x 1/4", 10% OV-17 column, indicated a 40:60 mixture of 61a, 61b, respectively (85% yield).

$^1$H NMR of (61a): 3.54 (1H, m); 3.44 (1H, m); 3.05 (1H, m); 2.89 (1H, br s); 1.82 (2H, m); 1.65-1.41 (4H, m); 1.16 (3H, d, J=6.3 Hz); 1.11 (3H, d, J=6.4 Hz).
Preparations of cis-2-Isopropyl-6-methyltetrahydropyran (62); unidentified (63), and 1-Methyl-1-(cis-6-methyltetrahydropyran-2-yl)ethanol (64)

The bicyclic ketal (0.10 g, 0.0064 mole), (56), was subjected to the general cleavage procedure by using triethylsilane to give 70 mg of reaction product. GLC analysis, using a 11' x 1/4', 10% OV-17 column, indicated a 45:34:21 mixture of 62, 63, 64, respectively.
$^1$H NMR of (62): 3.37 (1H, m); 2.93 (1H, m); 1.60 (1H, m); 1.82-1.05 (6H, m); 1.14 (3H, d, J=6 Hz), 0.91 (3H, d, J=6 Hz); 0.84 (3H, d, J=6 Hz).

$^1$H NMR of (63): 4.41 (1H, m); 3.89 (1H, m); 3.75 (1H, m); 2.58 (1H, m); 2.47 (2H, t, J=6.9 Hz); 2.2-1.35 (10H, m); 1.23 (3H, d, J=6.3 Hz); 1.17 (3H, d, J=6.2 Hz), 1.07 (6H, d, J=7 Hz); 1.00 (6H, d, J=7 Hz).

$^1$H NMR of (64): 3.44 (1H, m); 3.11 (1H, dd, J=2, 11 Hz); 2.74 (1H, br s); 1.86-1.05 (6H, m); 1.15 (3H, s); 1.14 (3H, d, J=6 Hz); 1.11 (3H, s).


MS of (64): 158 (M$^+$), 143, 125, 99, 81 (base), 71, 59, 43. HRMS: Calcd for C$_9$H$_{18}$O$_2$: 158.1307. Observed: 158.1328.

$^1$H
Preparations of 1,2-Dimethyl-(cis-6-methyltetrahydropyran-2-yl)propane (65a) and (65b); 1,2-Dimethyl-1-(cis-6-methyltetrahydropyran-2-yl)propanol (66a)

The bicyclic ketal, (0.50 g, 0.0027 mole), (52), was subjected to the general cleavage procedure by using triethysilane to give 0.47 of reaction product. GLC analysis, using a 11' x 1/4", 10% OV-17 column, indicated a 12:14:74 mixture of 65a, 65b, 66a, respectively.

$^1H$ NMR of (65a): 3.35 (1H, m); 3.11 (1H, m); 1.77 (2H, m);
1.70-1.35 (5H, m); 1.22 (1H, m); 1.12 (3H, d, J=6.3 Hz); 0.88 (3H, d, J=6.8 Hz); 0.84 (3H, d, J=6.9 Hz); 0.76 (3H, d, J=6.8 Hz).

$^1H$ NMR of (65b): 3.35 (1H, m); 3.10 (1H, m); 2.00 (1H, m);
1.84-1.45 (6H, m); 1.40 (1H, m); 1.14 (3H, d, J=6.3 Hz); 0.86 (3H, d, J=7 Hz); 0.75 (3H, d, J=7 Hz); 0.70 (3H, d, J=7 Hz).

$^1H$ NMR of (66a): 3.43 (1H, m); 3.30 (1H, dd, J=2, 11 Hz); 1.88 (1H, m); 1.87-1.28 (7H, m); 1.12 (3H, d, J=6.3 Hz); 0.96 (3H, s); 0.90 (3H, d, J=7 Hz); 0.87 (3H, d, J=7 Hz).

MS of (65a): 99 (base, M$^+$-71), 81, 71, 66, 55, 43.

MS of (65b): 170 (M$^+$), 110, 99 (base), 81, 71, 55, 43.
HRMS: Calcd for C$_{11}$H$_{22}$O: 170.1671. Observed: 170.1669.
MS of (66a): 186 (M+), 171, 143, 125, 99, 87 (base), 81, 69, 55, 43.

HRMS: Calcd for C_{11}H_{22}O_{2}: 186.1619. Observed: 186.1617.

Preparation of 1,2-Dimethyl-1-(cis/trans-6-methyltetrahydropyran-2-yl)propanol (66a) and (66b)

The bicyclic ketal (0.20 g, 0.0011 mole), (52), was subjected to the general cleavage procedure by using aluminum hydride to give 0.17 g of reaction product. GLC analysis, using a 11' x 1/4", 10% OV-17 column, indicated a 13:87 mixture of 66a, 66b, respectively (83% yield).

^1H NMR of (66b): 4.20 (1H, m); 3.58 (1H, dd, J=2.8, 11 Hz); 1.89 (1H, m, J=7 Hz); 1.80-1.30 (7H, m); 1.23 (3H, d, J=6.8 Hz); 0.92 (3H, s); 0.90 (3H, d, J=7.9 Hz); 0.84 (3H, d, J=6.9 Hz).
MS of \(66b\): 171 (M\(^{+}-15\)), 143, 125, 99, 87 (base), 81, 69, 55, 43.

HRMS: Calcd for \(C_{11}H_{22}O_2\): 186.1620. Observed: 186.1620.

Preparations of 1,2-Dimethyl-(2-cyclohexanone-3-yl)propane (67) and 2,3-Dimethyl-1-(5,6-dimethylpyridine-2-yl)butanone (68)

General cleavage procedure by using aluminum iodide was introduced to 2.0 g (0.011 mole) of the bicyclic ketal, \((52)\), and this gave 1.73 g of the liquid. GLC analysis of the product using a 11' x 1/4", 10% OV-17 column shows 31:69 ratio of 67 and 68, respectively, but 0.1 g (0.0006 mole) of 67 and 0.15 g (0.00073 mole) of 68 were separated with flash chromatography using petroleum ether:ethyl acetate in a 7:3 ratio as a solvent system.

\[ R_f : 0.48 \quad \text{-----} \quad > \quad 1.16 \text{ g of decomposed product.} \]
\[ R_f : 0.37 \quad \text{-----} \quad > \quad 0.1 \text{ g of 67} \]
\[ R_f : 0.25 \quad \text{-----} \quad > \quad 0.15 \text{ g of 68} \]

\(^1H\) NMR of 67: 5.84 (1H, br s); 2.36 (1H, m); 2.24 (2H, t, \(J=6 \text{ Hz}\)); 2.02-1.88 (4H, m); 1.65 (1H, m); 1.04 (3H, d, \(J=7 \text{ Hz}\)); 0.88 (3H, d, \(J=7 \text{ Hz}\)); 0.83 (3H, d, \(J=7 \text{ Hz}\)).
$^1$H NMR of 68: 7.71 (1H, d, J=8 Hz); 7.04 (1H, d, J=8 Hz); 3.04 (1H, m); 2.63 (3H, s); 2.54 (3H, s); 2.01 (1H, m); 1.09 (3H, d, J=7 Hz); 0.92 (3H, d, J=7 Hz); 0.85 (3H, d, J=7 Hz).

$^{13}$C NMR of 67: 199.9 (s), 170.7 (s), 125.8 (d), 48.8 (d), 37.7 (t), 31.1 (d), 27.4 (t), 22.9 (t), 21.6 (q), 19.5 (q), 15.8 (q).

$^{13}$C NMR of 68: 207.3 (s), 159.9 (s), 157.2 (s), 135.7 (d), 121.2 (s), 119.9 (d), 50.0 (d), 30.2 (d), 24.4 (q), 23.9 (q), 21.4 (q), 18.4 (q), 12.5 (q).

MS of 67: 166 (M$^+$), 151, 148, 124 (base), 109, 96, 81, 67, 55, 41.

HRMS: Calcd for C$_{11}$H$_{18}$O: 166.1358. Observed: 166.1359.

MS of 68: 205 (M$^+$), 190, 163, 134 (base), 106, 79, 63, 53, 41.

HRMS: Calcd for C$_{13}$H$_{19}$NO: 205.1466. Observed: 205.1472.

IR of 67: 2941, 1669 (C=O), 1456, 1376, 1245, 890, 731.

IR of 68: 2941, 1681 (C=O), 1587, 1447, 1370, 1250, 1222, 1190, 1136, 1021, 966, 919, 896, 833, 732.

UV of 68: $\lambda_{max}^{EtOH}$: 274 (4140), 239 (6640).

$^1$H ( $^{13}$C )
Preparation of 2,3 Dimethyl-1-(5,6-dimethylpyridine-2-yl)butanol (69)

To a solution of 0.014 g (0.5 eq.) of sodium borohydride in 10 mL of isopropanol was added 0.015 g (0.00073 mole) of the ketone, (68), and stirred for 1 hour at room temperature. Water (10 mL) was added to hydrolyze the reaction after evaporation of the isopropanol, the reaction mixture was extracted with ether, dried over magnesium sulfate and reduced in volume to yield 0.015 g of slight yellow solid. After washing with pentane 0.0096 g (0.000046 mole) of white solid was obtained (64% yield). (G/C-mass indicates 89:11 ratio of isomer).

M.P. = 159-162°C

$^1$H NMR: 7.60 (1H, d, J=8 Hz); 7.08 (1H, d, J=8 Hz); 4.67 (1H, dd, J=3, 9 Hz); 2.54 (3H, s); 2.49 (3H, s); 2.29 (1H, m); 1.78 (1H, m); 1.67 (1H, d, J=3 Hz); 0.95 (3H, t, J=7 Hz); 0.89 (3H, t, J=7 Hz); 0.51 (3H, t, J=7 Hz).

MS: 207 (M$^+$), 174, 136 (base), 108, 92, 77, 65, 51, 41.

HRMS: Calcd for C$_{13}$H$_{21}$NO: 207.1623. Observed: 207.1622.
Preparation of threo/erythro-2-(1-Hydroxyethyl)-3,4-dihydro-2H-pyran (72)

Acrolein dimer (19) (0.50 g, 0.0045 mole) was placed in 30 mL of tetrahydrofuran and stirred at 0°C under nitrogen. Methyllithium (5.2 mL of 1.3 M solution) was then added via a syringe and the reaction was stirred for seven hours. The reaction was hydrolyzed by the addition of 25 mL of water and was stirred an additional half an hour. The mixture was then extracted three times with ether and the organics were combined and dried over anhydrous magnesium sulfate. Evaporation gave 0.40 g (0.0031 mole) of erythro alcohol (69% yield).

If 1.5 equivalents of methyImagnesium bromide are used instead of methyllithium, one can get a 50:50 mixture of threo and erythro isomer57.

$^1$H NMR of threo-72: 6.37 (1H, br d, J=6 Hz); 4.68 (1H, br s); 3.72 (1H, m); 3.55 (1H, m); 2.38 (1H, d, J=4.7 Hz); 2.15-1.50 (4H, m); 1.19 (3H, d, J=6.5 Hz).
\[ ^1\text{NMR of erythro-72: } 6.37 (1H, br d, J=6 \text{ Hz}); 4.68 (1H, br s); 3.92 (1H, m); 3.70 (1H, m); 2.15-1.50 (4H, m); 1.89 (1H, d, J=4.7 \text{ Hz}); 1.19 (3H, d, J=6.5 \text{ Hz}). \]

\[ \text{MS of threo-72: } 128 (M^+), 110, 95, 83 (\text{base}), 71, 55, 43. \]

\[ \text{HRMS: Calcd for } C_7H_{12}O: 128.0837. \text{ Observed: } 128.0840. \]

\[ \text{MS of erythro-72: } 128 (M^+), 110, 95, 83 (\text{base}), 71, 55, 43. \]

\[ \text{HRMS: Calcd for } C_7H_{12}O_2: 128.0837. \text{ Observed: } 128.0832. \]

\[ \text{IR: } 3305, 2843, 1644, 1253, 1088, 751. \]

\[ ^1\text{H} \]

\[ \text{threo-72 } \quad \text{ erythro-72 } \]

\[ \]

Preparation of exo/endo-5-(n-Bromopentyl)-7-methyl-6,8-dioxabicyclo-[3.2.1]octane (73)

The mixture of 0.5 g (0.0039 mole) of the alcohol, (72), 4.4 mL (2 eq.) tertiary butyllithium and 0.27 mL (0.5 eq.) of 1,5-dibromopentane were subjected to the same procedure of (74), and which gave 0.65 g (0.0024 mole) of a yellow liquid (51% yield). GLC analysis shows the exo/endo isomeric ratio to be 66:34.
Attempted Coupling Reaction of exo/endo-5-(n-Bromopentyl)-7-methyl-6,8-dioxabicyclo[3.2.1]octane, (73), with 2-(1-Hydroxyethyl)-3,4-dihydro-2H-pyran (72).

Tertiary butyllithium (0.44 mL, 2 eq.) was added to a solution of 0.05 g (0.00039 mole) of the alcohol, (72) in 10 mL of tetrahydrofuran at -78°C under nitrogen. After 10 minutes, the reaction mixture was warmed up to 0°C for 1 hour and room temperature for 30 minutes, then again cooled down to 0°C. The resulting solution was added to 0.11 g (1 eq.) of the bicyclic
ketal, (73), in 5 mL tetrahydrofuran at 0°C, then stirred for 1 hour at 0°C and 2 hours at room temperature. GLC analysis showed only starting materials.

**Preparation of exo/endo-5-(n-Bromopentyl)-7-pentyl-6,8-dioxabicyclo[3.2.1]octane (74)**

To a solution of 0.50 g (0.0027 mole) of the alcohol, (20), stirring in 10 mL of tetrahydrofuran at -78°C under an argon atmosphere was slowly added 3 mL (2 eq.) of 1.8 molar tertiary butyllithium. 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 to 0°C, the resulting solution was added to 0.37 mL (0.0027 mole) of 1,5-dibromopentane in 10 mL tetrahydrofuran via a syringe at 0°C and the solution mixture was stirred for 1 hour at 0°C and then 2 hours at room temperature. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride solution, extracted with 30 mL ether three times and washed with 5% aqueous HCl, brine, dried over anhydrous magnesium sulfate and reduced in volume gave 0.3 g (0.0009 mole) of a yellow liquid (33% yield). GLC analysis of the product using a 25' x 1/4", 10% OV-17 column shows the exo/endo isomeric ratio to be 26:74.

**1H NMR of exo-74**: 4.17 (1H, br s); 3.96 (1H, m); 3.39 (2H, t, J=7 Hz); 1.9-1.2 (22H, m); 0.88 (3H, br t).
\textbf{1H NMR of endo-74:} 4.08 (1H, br s); 3.96 (1H, m); 3.39 (2H, t, J=7 Hz); 1.9-1.2 (22H, m); 0.87 (3H, br t).

\textbf{MS of exo-74:} 334, 332 (M⁺), 263, 261, 234, 232, 179, 177, 156 (base), 127, 114, 100, 69.

\textbf{HRMS:} Calcd for C_{16}H_{29}O_{2}Br: 332.1350. Observed: 332.1355.

\textbf{MS of endo-74:} 334, 332 (M⁺), 277, 275, 253, 234, 232, 211, 179, 177, 156 (base), 135, 113, 69.

\textbf{HRMS:} Calcd for C_{16}H_{29}O_{2}Br: 332.1350. Observed: 332.1372.

\textbf{Preparations of exo/endo-7-MethyI-4-propanal-6,8-dioxabicyclo[3.2.1]octane (75)}

To a solution of 0.1 g (0.00078 mole) of the alcohol, (72), stirring in 20 mL of tetrahydrofuran at room temperature was added 0.3 g (1.2 eq.) of mercuric acetate. After overnight stirring at room temperature, the solution was reduced in volume via a rotatory evaporator, then 20 mL of methylene chloride and 0.44 g (10 eq.) of acrolein were added successively. 0.09 g (3 eq.) of sodium borohydride was dissolved in 2.5 mL water and then added to the reaction mixture very slowly. After stirring at room temperature for 2 hours, the reaction mixture was quenched with dropwise addition of 20 mL of saturated aqueous sodium bicarbonate solution, and extracted with chloroform, washed with brine, dried over anhydrous magnesium sulfate and reduced in volume gave 0.060 g (0.00033 mole) of a slight yellow liquid
(42% yield). GLC analysis of the product using a 11' x 1/4", 10% OV-17 column shows the exo-erythro, exo-threo, endo-threo, endo-erythro isomeric ratio to be 21:53:9:17.

$^1$H NMR of exo-erythro-75: 9.73 (1H, br s); 5.30 (1H, br s); 4.11 (1H, q, J=6 Hz); 4.02 (1H, br s); 2.42 (2H, t, J=7 Hz); 1.90-1.25; (6H, m); 1.18 (3H, d, J=6.1 Hz).

$^1$H NMR of exo-threo-75: 9.75 (1H, br s); 5.32 (1H, br s); 4.19 (1H, q, J=6.4 Hz); 3.99 (1H, br s); 2.48 (2H, t, J=7 Hz); 1.95 (2H, m); 1.78 (2H, m); 1.50 (1H, m); 1.34 (2H, br t); 1.18 (3H, d, J=6.6 Hz).

$^1$H NMR of endo-threo-75: 9.74 (1H, br s); 5.25 (1H, br s); 4.11 (2H, br d); 2.42 (2H, t, J=7 Hz); 1.90-1.39 (6H, m); 1.30 (3H, d, J=6 Hz).

$^1$H NMR of endo-erythro-75: 9.77 (1H, br s); 5.27 (1H, br s); 4.10 (2H, br d); 2.48 (2H, t, J=7 Hz); 2.15-1.40 (6H, m); 1.34 (3H, d, J=6.2 Hz).

MS of exo-erythro-75: 184 (M$^+$), 138, 128, 112, 94 (70%), 83, 79, 71, 67, 55 (base), 43 (60%).

MS of exo-threo-75: 184 (M$^+$), 141, 138, 128, 120, 94 (83%), 83, 79, 71, 67, 55 (base), 43 (40%).
MS of **endo-threo**-75: 184 (M+), 140, 120, 110, 94 (58%), 83, 78, 71, 67, 55 (base), 43 (86%).

MS of **endo-erythro**: 184 (M+), 140, 120, 112, 94 (76%), 83, 79, 71, 67, 55 (base), 43 (63%).

**HRMS**: Calcd for C_{10}H_{16}O_{3}: 184.1099. Observed: 184.1095.

### **exo-erythro**

\[
\begin{align*}
9.73 & \quad H-C-O \\
2.42 & \quad H \\
1.63 & \quad H \\
5.30 & \quad H \\
4.11 & \quad CH_3
\end{align*}
\]

### **exo-threo**

\[
\begin{align*}
9.75 & \quad H-C-O \\
2.48 & \quad H \\
1.78 & \quad H \\
1.34 & \quad H \\
5.32 & \quad CH_3
\end{align*}
\]

### **endo-threo**

\[
\begin{align*}
9.74 & \quad H-C-O \\
2.42 & \quad H \\
1.63 & \quad H \\
5.25 & \quad CH_3 \\
1.30 & \quad 4.11
\end{align*}
\]

### **endo-erythro**

\[
\begin{align*}
9.77 & \quad H-C-O \\
2.48 & \quad H \\
1.50 & \quad H \\
2.48 & \quad H \\
5.27 & \quad CH_3 \\
1.34 & \quad 4.10
\end{align*}
\]
Preparation of 2-(2-Hydroxymethyl)-3,4-dihydro-2H-pyran (76)

Acrolein dimer (19) (1 g, 0.009 mole) was placed in 20 mL of isopropanol and cooled to O°C. 0.17 g (0.5 eq.) of sodium borohydride was added slowly with stirring and the resulting solution was stirred for 1 hour at room temperature. 10 mL of water was then added and the resulting solution was extracted with ether, dried over magnesium sulfate and reduced in volume. The alcohol was not purified, but used directly for the next step.

Preparation of 2-(2-Hydroxymethyl)-6-(n-decy l)-3,4-dihydro-2H-pyran (77)

To the crude alcohol, (76), in 20 mL dry tetrahydrofuran was added dropwise 10 mL (2 eq.) of 1.8 M tertiary butyllithium at -78°C under nitrogen. The mixture was stirred 1 hour at O°C, 30 minutes at O°C and then 3.8 mL (0.018 mole) of n-decyl iodide was added at O°C and stirred for 1 hour at O°C, for 2 hours at room temperature 20 mL of water was slowly added to the reaction mixture and extracted with ether. After drying and evaporation of solvent there was obtained 1.0 g (0.0039 mole) of liquid (44% yield from 19).

\[ \text{H NMR: } 4.48 \text{ (1H, br s); } 3.85 \text{ (1H, m); } 1.86-1.23 \text{ (25H, m); } 0.85 \text{ (3H, t, J=6 Hz).} \]

\[ \text{MS: } 254 \text{ (M+), 187, 169 (base), 141, 128, 113, 100, 85, 70, 55, 41.} \]
Preparation of 4-Bromo-5,7,7-trimethyl-6,8-dioxabicyclo[3.2.1]octane (78), and 4-Bromo-7-deuteriomethyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane (78a)

To a solution of 0.20 g (0.0013 mole) of the bicyclic ketal, (56), stirring in 20 mL of carbon tetrachloride at room temperature, was added 0.066 mL (1 eq.) of bromine via syringe. The solution was stirred for 7 hours, after which time 20 mL of water were added and the resulting solution was extracted with three 20 mL portions of methylene chloride which were combined, washed with 10% aqueous sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and reduced in volume to give 0.270 g (0.00115 mole) of slight yellow liquid (88% yield). 78a was prepared from 48.

$^1$H NMR of 78: 4.01 (1H, dd); 3.95 (1H, br d); 2.4-2.15 (2H, m); 2.0-1.64 (2H, m); 1.59 (3H, s); 1.41 (3H, s); 1.30 (3H, s).

$^1$H NMR of 78a: Same as 78 except 1.41 (2H, s), (1.30 1H, s).

$^{13}$C NMR of 78: 107.3, 82.2, 80.6, 54.2, 30.1, 28.7, 27.4, 24.6, 20.9.

MS of 78: 154 (M$^+$-HBr), 111, 93, 83, 77, 67, 55 (base), 41.

MS of 78a: 239, 237 (M$^+$), 197, 195, 179, 177, 149, 131, 115, 97, 89, 71, 43 (base).

Preparation of exo/endo-5,7-Dimethyl-7-(4-methyl-3-pentene)-6,8-dioxabicyclo[3.2.1]octane (87)

5-bromo-2-methyl-2-pentene (2.0 g, 0.012 mole) was slowly added to 0.30 g (0.012 mole) of magnesium in 30 mL of dry ether at room temperature under nitrogen. The reaction mixture was stirred at 0°C for 2 hours until a dark gray solution formed, at which point 1.4 g (0.010 mole) of MVK dimer, (8), in 10 mL dry ether was slowly added via syringe and stirred 10 hours at room temperature. 20 mL of 5% aqueous HCl was added and the reaction mixture was extracted with ether. The extracts were washed with brine, dried over anhydrous magnesium sulfate and reduced in volume to give 1.6 g (0.0070 mole) of liquid (72% yield). GLC analysis of the product using a 11' x 1/4", 10% OV-17 column shows the exo:endo isomeric ratio is 84:16.

\[ ^1H \text{ NMR of exo-87: } 5.09 \text{ (1H, br t, } J=7 \text{ Hz); 3.92 (1H, br d, } J=3.4 \text{ Hz); } 2.15-1.45 \text{ (10H, m); 1.66 (3H, s); 1.59 (3H, s); 1.40 (3H, s); 1.33 (3H, s).} \]

\[ ^1H \text{ NMR of endo-87: } 5.11 \text{ (1H, br t); 3.88 (br d); 2.15-1.45 (10H, m); 1.67 (3H, s); 1.60 (3H, s); 1.41 (3H, s); 1.26 (3H, s).} \]
$^{13}$C NMR of mixture: 131.3 (s), 124.4 (d), 107.1 (s), 82.9 (s), 79.9 (d), 41.3 (t), 34.2 (t), 25.7 (t), 25.6 (q), 24.2 (t), 23.1 (q), 17.9 (q), 17.5 (t), 17.3 (q).

MS of exo-87: 224 (M$^+$), 164, 142, 121, 113, 98, 93, 82, 69, 55, 43 (base).

HRMS: Calcd for C$_{14}$H$_{24}$O$_2$: 224.1776. Observed: 224.1764.

MS of endo-87: 224 (M$^+$), 182, 164, 141, 135, 121, 107, 98, 93, 81, 67, 55, 43 (base).

HRMS: Calcd for C$_{14}$H$_{24}$O$_2$: 224.1776. Observed: 224.1766.

IR (mixture): 2907, 1379, 1241, 1198, 1176, 1105, 1041.

$^1$H ($^{13}$C)

Preparation of cis/trans-7,11-Dimethylododeca-6,10-diene-2-one

A solution of 0.17 g (0.00076 mole) of the bicyclic ketal, (87), in 10 mL acetonitrile was subjected to the general
cleavage procedure by using acetyl iodide to give 0.032 g (0.00015 mole) of reaction product. GLC analysis, by using capillary column (SE-30), indicated the product, but it was difficult to separate of pure 88 (20% yield).

MS: 208 (M+), 193, 175, 150, 135, 123, 119, 107, 95, 79, 67, 43 (base).

HRMS: Calcd for C_{14}H_{24}O: 208.1827. Observed: 208.1822.

Preparation of 6,10-Dimethyl-5,9-nonadienoic acid (81) and Methyl 6,10-dimethyl-5,9-nonadinoate (89)

The crude mixture (0.11 g) of 88 was dissolved in 2 mL of water with 1 mL of dioxane to produce a homogeneous solution. Addition of 1 mL of 10% NaOH and the KI-I_{2} reagent dropwise was followed by shaking until a definite dark color of iodine persisted. The mixture was heated in water bath (60° C) for 2 minutes. Excess iodine was removed by the addition of few drops of NaOH solution then dilute with water and allowed to stand 15 minutes. The yellow precipitate (CHI_{3}) was filtered and shown to have 119-121° as a M.P. The filtrate was acidified and extracted with ether. Evaporation of the solvent gave a crude acid which was not purified; but was refluxed in 10 mL methanol with 10 drops of sulfuric acid for 1 hour. The methanol was evaporated and 20 mL of water and 20 mL of ether was added for extraction. After drying over MgSO_{4}, evaporation of solvent gave 15 mg of crude product.
MS of 89: 224 (*M*^+^), 209 (base), 168, 135, 123, 95, 69, 55, 41.

HRMS: Calcd for C\textsubscript{14}H\textsubscript{24}O\textsubscript{2}: 224.1776. Observed: 224.1805.

**Preparation of 4,5-Dimethylcyclohexene dicarboxylate (92)**

A solution of 15 g (0.099 mole) of cis-1,2,3,6-tetrahydrophthalic anhydride was mixed with 100 mL of methanol, and 0.1 mL of concentrate sulfuric acid at room temperature. After 3 hours at reflux, the reaction mixture was cooled to room temperature and methanol was evaporated via a rotatory evaporator. 100 mL of ether was added to the reaction mixture and washed with 50 mL of 5% aqueous sodium bicarbonate solution followed by saturated brine. The organic layer was dried over anhydrous magnesium sulfate and reduced in volume followed by distillation (0.4 mm Hg). Collection from 85°-88° C gave 16.4 g (0.0828 mole) of a clear, colorless liquid (84% yield).

\(^1\text{H NMR: } 5.65 (2\text{H, s})\); 3.66 (6\text{H, s})\); 3.02 (2\text{H, t, } J=5 \text{ Hz})\); 2.53 (2\text{H, dd, } J=6, 16 \text{ Hz})\); 2.33 (2\text{H, dd, } J=6, 16 \text{ Hz}).

\(^{13}\text{C NMR: } 173.6 \text{ (s), 124.8 (d), 51.6 (q), 39.4 (d), 25.4 (t).}


HRMS: Calcd for C\textsubscript{10}H\textsubscript{14}O\textsubscript{4}: 198.0891. Observed: 198.0887.

IR: 2941, 1736 (C=O), 1445, 1212, 1036.
Preparation of cis-9,10-Bis(Carboxymethyl)-Δ2-decalin (93)

A solution of 150 mL of dry tetrahydrofuran, 75 mL of 2.7 M n-buthyllithium, and 26.1 mL of diisopropylamine was stirred under nitrogen at -78° C for 15 minutes; then 13.5 g (0.0682 mole) of the diester, (92), was injected via a syringe and the bright red solution was stirred for an additional 10 minutes. At this time 22 g (1.5 eq.) of 1,4-dibromobutane in 30 mL dry tetrahydrofuran was added to the reaction mixture. This resulted in a lightening of the color of the reaction to a pale yellow. After stirring for 3 hours at room temperature, the reaction was quenched by pouring it into excess dilute HCl. The phases were separated and the aqueous phase was extracted three times with 50 mL portions of methylene chloride. The combined organics were dried, evaporated and distilled (0.4 mm Hg). Collection from 115°-120° C gave 12.9 g (0.0512 mole) of a clear, colorless liquid (75% yield).
Preparation of cis-9,10-Bis(hydroxymethyl)-Δ²-decalin (94)

A solution of 12.9 g (0.0512 mole) of the diester, (93), in 20 mL of dry tetrahydrofuran was slowly added (exothermic) to a stirred mixture of 4 g (0.1 mole) of LiAlH₄ and 100 mL of dry tetrahydrofuran. After 10 hours stirring at room temperature, the reaction mixture was hydrolyzed by slowly adding 60 mL of ether and 20 mL of water. The inorganic salts were filtered off and the ether layer was washed with 5% aqueous HCl followed by saturated brine. Evaporation gave 9.79 g (0.0499 mole) of white solid (98% yield).
M.P. (without recrystallization) : 143-145° C (Ref. 147-149° C).34.

$^1$H NMR:  5.56 (2H, s); 3.68 (2H, d, J=10 Hz); 3.56 (2H, d, J=10 Hz); 3.12 (2H, br s); 2.04 (4H, br s); 1.73-1.35 (8H, m).

$^{13}$C NMR (pyridine + CDCl$_3$): 123.8 (d), 65.9 (t), 38.1 (t), 30.7 (t), 29.6 (t), 20.3 (t).

MS:  178 (M$^+$-H$_2$O), 160, 147, 105, 91 (base), 79, 67, 41.

HRMS: Calcd for C$_{12}$H$_{18}$O: 178.1356. Observed: 178.1355.

IR:  3226 (-CH), 2899, 1471, 1087, 1058, 1020, 1000, 980, 658.

Preparation of cis-9,10-Bis(methanesulfonyloxymethyl)-Δ²-decalin (95)

To an ice-cold stirred solution of 12.5 mL (0.162 mole) of methanesulfonyl chloride in 20 mL of pyridine was added dropwise a solution of 9.5 g (0.048 mole) of the diol, (94), in 40 mL of pyridine at 0-5° C. After an additional 2 hours stirring in the cold ice bath, the reaction was poured into ice-5% HCl solution and extracted with three 50 mL portions of chloroform, washed with 5% aqueous sodium bicarbonate, saturated brine and dried.
over anhydrous magnesium sulfate. Evaporation gave 16.7 g (0.0474 mole) of white solid (98% yield).

M.P. (from methanol): 121-123°C (Ref. 124.5-125.5)34

\[ ^1H \text{ NMR: } 5.59 \text{ (2H, s); 4.29 (2H, d, J=10 Hz); 4.13 (2H, d, J=10 Hz); 3.01 (6H, s); 2.21 (2H, br d, J=17 Hz); 2.02 (2H, br d, J=17 Hz); 1.58-1.52 (8H, m). } \]

\[ ^{13}C \text{ NMR: } 123.3 \text{ (d), 72.8 (t), 37.8 (s), 37.2 (q), 30.6 (t), 28.5 (t), 20.2 (t). } \]

MS: 178 (M+Mg2O), 160, 147, 123, 105, 91 (base), 79, 67, 41.


IR: 2890, 1468, 1340 (asymmetric SO2 stretching) 1180 (symmetric SO2 stretching), 943, 850, 763, 670.

\[ ^1H \text{ (} ^{13}C \text{ )} \]

Preparation of 12-Thia[4.4.3]propell-3-ene (96)

The dimesylate (15.4 g; 0.0438 mole), (95), was mixed with 12 g (0.15 mole) of sodium sulfide (sodium sulfide·9 hydrate was treated with benzene azeotrope to remove water) and 150 mL of dry hexamethylphosphoramide, and heated to 120°C for 24 hours. The brownish-colored contents were cooled to room temperature
and treated with 150 mL of water, extracted with ether. The ether layer was washed with water, saturated brine, dried over magnesium sulfate and reduced in volume to give 7.9 g (0.041 mole) of white solid (93% yield).

M.P. (from methanol): 84-86° (Ref. 85-87°)

$^1$H NMR: 5.51 (2H, s); 2.81 (2H, br s); 2.68 (2H, br s); 2.11 (2H, d, J=7 Hz); 1.97 (2H, d, J=7 Hz); 1.59-1.33 (8H, m).

$^{13}$C NMR: 123.5 (d), 44.3 (s), 41.2 (t), 32.5 (t), 31.0 (t), 21.6 (t).

MS: 194 (M$^+$), 147, 133, 119, 105, 91 (base), 79, 67, 41.

HRMS: Calcd for C$_{12}$H$_{18}$S: 194.1129. Observed: 194.1161.

IR: 2890, 1453, 909, 734, 661.

Preparation of cis-9,10-Dimethyldecalin-2-ene (97)

The propellane (2.95 g; 0.0152 mole), (96), was dissolved in 80 mL of ethanol and stirred at reflux with 20 g of Raney-nickel for 12 hours. After cooling to room temperature, the Raney-nickel was filtered and the filtrate was evaporated. Saturated brine (50 mL) was added and the reaction was
extracted with ether, dried over anhydrous magnesium sulfate and reduced in volume. 1.8 g (0.011 mole) of liquid were obtained (73% yield) and 0.45 g (0.0027 mole; 18% yield) of cis-9,10-dimethyldecalin, (97a), was obtained which are separated after hydroboration.

\[
\text{H NMR of 97: } 5.53 (2H, s); 1.98-1.28 (12H, m); 0.85 (6H, s).
\]

\[
\text{C NMR of 97: } 124.5 (d), 35.1 (s), 34.4 (t), 34.1 (t), 23.9 (t), 21.7 (q).
\]

\[
\text{MS of 97: } 164 (M^+), 149 \text{ (base), 135, 109, 93, 81, 67, 55, 41.}
\]

\[
\text{HRMS: Calcd for C_{12}H_{20}: 164.1564. Observed: 164.1562.}
\]

\[
\text{IR of 97: } 2907, 1449, 1374, 909, 735.
\]

Preparation of cis-9,10-Dimethyl-2-hydroxydecalin (98)

A solution of the decalin mixture (1 g of 97; 0.0061 mole, 0.25 g of 97a) in 40 mL of dry tetrahydrofuran at 0°C was connected to the borane generator (0.3 g of sodium borohydride in 10 mL of diglyme was slowly added to 2 mL of boron trifluoride etherate in 10 mL of diglyme at room temperature) with slight
flow of nitrogen. After 1 hour, the reaction mixture was heated an hour to 70-80° C, then stirred for 2 hours at room temperature, 3 mL of water was carefully added to the reaction mixture, then oxidized at 30-50° C by adding 5 mL of 3N NaOH, followed by 5 mL of 30% hydrogen peroxide. After 1 hour stirring, the reaction mixture was extracted with ether and washed with 5% aqueous HCl and saturated brine, dried over anhydrous magnesium sulfate and reduced in volume. At this point, unreacted 97a (0.25 g) was separated by silica gel column with petroleum ether as a solvent, then 1.05 g (0.00577 mole) of liquid, (98), was isolated with ethyl acetate as a solvent (95% yield).

$^1$H NMR: 3.85 (1H, br s); 2.0-1.0 (15H, m); 0.87 (3H, s); 0.85 (3H, s).

$^{13}$C NMR: 67.9 and 66.9 for the isomers of the hydroxyl-bearing carbon. Several peaks were found at 37-31 and 25-21.

MS: 182 (M$^+$), 164, 149 (base), 135, 121, 109, 95, 82, 67, 55, 42.

HRMS: Calcd for C$_{12}$H$_{22}$O: 182.1671. Observed: 182.1670.

IR: 3289 (-CH), 2915, 1449, 1370, 1242, 1040.

$^1$H ( $^{13}$C )
Preparation of cis-9,10-Dimethyldecalin-2-one (99)

The hydroxydecalin (0.79 g; 0.0043 mole), (98), was stirred with 2.5 g (1.5 eq.) of pyridinium dichromate in 60 mL of methylene chloride for 24 hours at room temperature under nitrogen. 50 mL of ether was added with 3 g of magnesium sulfate and filtered to magnesium sulfate-florisil-magnesium sulfate column several times until the dark brown color disappeared. From this reaction, 0.73 g (0.0041 mole) of slight yellow liquid was obtained (93% yield).

$^1$H NMR: 2.35 (2H, br s); 1.7-1.2 (12H, m); 1.02 (3H, s); 0.89 (3H, s).

$^{13}$C NMR: 199.8, 40.6, 38.0, 35.2, 34.8, 33.7, 23.4, 22.9, 21.7, 21.3 (two carbons are hindered).

MS: 180 (M$^+$), 165, 137, 123, 109 (base), 95, 82, 67, 55, 42.

HRMS: Calcd for C$_{12}$H$_{20}$O: 180.1514. Observed: 180.1514.

IR: 2899, 1709 (C=O), 1447, 705.

Preparation of cis-9,10-Dimethyl-2-hydroxy-2-isopropyldecalin (100)

To a solution of 0.5 g (0.003 mole) of ketone, (99), in 20 mL of dry tetrahydrofuran was added 2.1 mL (1.5 eq.) of 2 M isopropylmagnesium chloride at 0°C under nitrogen. After 2
hours reflux, the reaction mixture was hydrolyzed by adding 10 mL of water and extracted with ether, dried over anhydrous magnesium sulfate and reduced in volume to give 0.55 g (0.0025 mole) of liquid (88% yield).

$^1$H NMR: 2.0-1.3 (16H, m); 1.01 (3H, s); 0.88 (3H, d, J=6 Hz); 0.86 (3H, d, J=10 Hz); 0.77 (3H, s).

$^{13}$C NMR: 74.6 and 74.2 for the isomeric hydroxycarbon.

MS: 206 (M$^+$-H$_2$O), 181 (base), 163, 123, 107, 69, 55, 44.

HRMS: Calcd for C$_{15}$H$_{28}$O: 224.2140. Observed: 224.2136.

IR: 3390 (-CH), 2933, 1449.

Preparations of cis-9,10-Dimethyl-2-isopropyldecalin-1-ene (101a), cis-9,10-Dimethyl-2-isopropyldecalin-2-ene (101b)

To a solution of 0.49 g (0.0022 mole) of hydroxydecalin, (100), in 10 mL of pyridine was added 1.0 mL of phosphorous oxychloride. The reaction mixture was heated to 90° C and maintained at this temperature for 15 minutes, then allowed to cool to room temperature. After a total reaction time of 2 hours, the solution was poured into 40 g of ice-water very slowly and extracted with three 30 mL portions of ether. The combined ether extracts were washed with 50 ml of 5% aqueous
HCl, 50 mL of 5% sodium bicarbonate, 50 mL of saturated brine and dried over anhydrous magnesium sulfate and reduced in volume to give 0.33 g (0.0016 mole) of liquid. This was shown by GLC analysis to be a 73% yield of a 45:55 mixture of \(101a\) and \(101b\).

\(^1\)H NMR of \(101a\): 4.95 (1H, t, \(J=1.5\) Hz); 1.9-1.2 (14H, m); 0.96 (6H, d, \(J=7\) Hz); 0.83 (3H, s); 0.80 (3H, s).

\(^1\)H NMR of \(101b\): 5.23 (1H, t, \(J=2\) Hz); 1.9-1.2 (14H, m); 0.96 (6H, d, \(J=7\) Hz); 0.83 (6H, s).

\(^1^3\)C NMR of mixture: 140.4, 121.3, 115.5 for sp\(^2\) carbon.

MS of \(101a\): 206 (M\(^+\)), 191, 163, 150, 135, 107 (base), 95, 81, 67, 55, 42.


MS of \(101b\): 206 (M\(^+\)), 191, 163, 110 (base), 95, 81, 67, 55, 42.


IR of mixture: 2907, 1449.

\(^1\)H (\(^{13}\)C)

\(101a\)

\(101b\)
Preparation of 2α-Isopropyl-cis-9β, 10β-dimethyldecalin (racemic valerane) (91a), and 2β-Isopropyl-cis-9β, 10β-dimethyldecalin (dl-7-Isovalerane) (91b)

To a solution of 0.30 g (0.0015 mole) of olefin mixture, (101a), (101b), in 20 mL of hexane was added 0.1 g of 10% palladium on carbon. The mixture was hydrogenated for 12 hours at 60 psi. The catalyst was removed by filtration and the solvent was evaporated to yield 0.242 g (0.00116 mole) of a 45:55 mixture of 91a, and 91b, respectively (80% yield).

$^1$H NMR of 91a: 1.86-1.03 (16H, m); 0.84 (6H, d, J=10 Hz); 0.83 (3H, s); 0.82 (3H, s).

$^1$H NMR of 91b: 1.95-1.04 (16H, m); 0.84 (3H, s); 0.83 (6H, d, J=6 Hz); 0.79 (3H, s).

MS of 91a: 208 (M$^+$), 193, 165, 149, 137, 123, 109, 95, 83. (base), 69, 55, 41.

HRMS: Calcd for C$_{15}$H$_{28}$: 208.2191. Observed: 208.2180.

MS of 91b: 208 (M$^+$), 193 (base), 165, 151, 137, 123, 109, 95, 83, 69, 55, 41.

HRMS: Calcd for C$_{15}$H$_{28}$: 208.2191. Observed: 208.2180.
Attempted Wittig Reaction of (99)

n-Buthyllithium (0.1 mL; 10.2 M) was added to a solution of 0.385 g (0.001 mole) of isopropyltriphenylphosphonium bromide in 25 mL of dry ether at 0°C under nitrogen. The orange-red colored reaction mixture was stirred for 15 minutes and 0.144 g (0.0008 mole) of keton, (47), in 5 mL of ether was slowly added to the reaction mixture. After 2 hours reflux, the solid was filtered and filtrate was extracted with petroleum ether, washed with saturated brine, dried over magnesium sulfate and reduced in volume. GLC and GC-MS analysis indicate 60% yield of 2-butyl-cis-9,10-dimethyl-2-hydroxydecalin (99a).

MS: 220 (M+-H₂O), 205, 195, 181 (base), 163, 123, 107, 95, 81, 69, 55, 41, 28.


Preparation of N-Benzylsuccinimide (105)

Succinimide (30 g, 0.30 mole) was mixed with benzyl chloride (52 mL, 0.45 mole) and potassium carbonate (21 g, 0.15 mole), and then the mixture was heated to reflux for 2 hours.
70 mL of 5% aqueous HCl was added to the reaction mixture and extracted with chloroform, washed with saturated brine and reduced in volume to give 32 g (0.17 mole) of white solid (57% yield).

M.P.: 101-103\(^\circ\) C

\(^1\)H NMR: 7.39-7.25 (5H, m); 4.64 (2H, s); 2.69 (4H, s).

\(^{13}\)C NMR: 177.0 (s), 135.8 (s), 129.0 (d), 128.7 (d), 128.0 (d), 42.4 (t), 28.1 (t).


HRMS: Calcd for C\(_{11}\)H\(_{14}\)NO\(_2\): 189.0789. Observed: 189.0787.

Preparation of cis-3-(N-Benzyl)-2,4-dioxobicyclo[3.3.0]heptane (107)

A solution of 5.0 g (0.026 mole) of N-benzylsuccinimide, in 40 mL of dry tetrahydrofuran was added to a stirred solution of 2.5 equivalents of lithium diisopropylamide (8.5 mL of diisopropylamine was added to 6.5 mL of 10.2 M n-butyllithium in 200 mL of dry tetrahydrofuran at \(-10^\circ\) C under nitrogen) at \(-78^\circ\) C. The reaction mixture was stirred for 10 minutes at \(-78^\circ\) C and then 4 mL (1.5 eq.) of 1,3-dibromopropane was added and
stirred overnight at room temperature. 100 mL of 5% aqueous HCl solution was added to the reaction mixture and extracted with three 60 mL portions of ether, washed with 5% sodium bicarbonate, saturated brine and reduced in volume. After separation of 1,3-dibromopropane via a silica gel column using ether as a solvent, 3.64 g (0.0159 mole) of liquid was obtained (60% yield).

1H NMR: 7.31-7.26 (5H, m); 4.6 (2H, s); 3.13 (2H, br d, J=8.9 Hz); 2.15-1.60 (4H, m); 1.19 (2H, m).

13C NMR: 180.0 (s), 136.0 (s), 128.6 (d), 128.5 (d), 127.8 (d), 45.1 (d), 42.3 (t), 30.4 (t), 24.7 (t).


IR: 2915, 1695 (C=O), 1389, 1340, 1176, 697.

Preparation of 3-(N-Benzyl)-2,4-dioxotricyclo[3.3.3.0]decane

To a stirred solution of 2.5 equivalents of lithium diisopropylamide in 30 mL of dry tetrahydrofuran was added 0.33
g (0.0014 mole) of J in 5 mL of dry tetrahydrofuran at -78° C under nitrogen. After 10 minutes, 0.22 mL (1.5 eq.) of 1,3-dibromopropane was added to the reaction mixture and stirred overnight at room temperature. Work-up as usual gave 0.093 g (0.00035 mole) of liquid (24% yield).

\( ^1H \text{ NMR: } 7.27 \ (5H, \text{ br s}); \ 4.60 \ (2H, \text{ s}); \ 2.06 \ (4H, \text{ m}); \ 1.70 \ (4H, \text{ m}); \ 1.50 \ (4H, \text{ m}). \)

\( ^{13}C \text{ NMR: } 181.7 \ (s), \ 136.3 \ (s), \ 128.6 \ (d), \ 128.2 \ (d), \ 127.7 \ (d), \ 63.4 \ (s), \ 42.4 \ (t), \ 36.4 \ (t), \ 27.4 \ (t). \)

MS: 269 (M\(^+\), base), 241, 229, 213, 200, 185, 172, 145, 132, 109, 91, 79, 66.

HRMS: Calcd for C\(_{17}\)H\(_9\)NO\(_2\): 269.1413. Observed: 269.1403.

IR: 2941, 1709 (C=O), 1399, 1353, 1147, 969, 701.

\( ^1H \) \( ^{13}C \)

\[
\begin{array}{c}
1.50(27.4) \\
2.06,1.70(36.4) \\
4.60(42.4)
\end{array}
\]
Preparation of 3-(N-Benzyl)-2,4-dioxotricyclo[3.3.2.0]nonane (109)

To a stirred solution of 2.5 equivalents of lithium diisopropylamide in 100 mL of dry tetrahydrofuran was added 1.5 g (0.0066 mole) of 107 in 20 mL of dry tetrahydrofuran at -78° C under nitrogen. After 10 minutes, 0.9 mL (1.5 eq.) of 1,3-dibromoethane was added to the reaction mixture and stirred overnight at room temperature. Work-up as usual yielded 0.42 g (0.0017 mole) of the product (25% yield).

\[ \text{H NMR: } 7.6-7.25 (5H, m); \ 4.63 (2H, s); \ 2.32-1.53 (1OH, m). \]


Preparation of cis-3-(N-Benzyl)-2,4-dioxobicyclo[3.2.0]hexane (110)

To a stirred solution of 2.5 equivalents of lithium diisopropylamide in 200 mL dry tetrahydrofuran was added 2.5 g (0.013 mole) of benzylsuccinimide, (105), in 30 mL of dry tetrahydrofuran at -78° C under nitrogen. After 10 minutes, 1.71 mL (1.5 eq.) of 1,2-dibromoethane was added to the reaction mixture and stirred overnight at room temperature. After the usual work-up, there was obtained 1.3 g (0.0060 mole) of product (46% yield).
1H NMR: 7.38-7.25 (5H, m); 4.68 (2H, s); 2.75 (2H, s); 1.44 (2H, dd, J=4, 7 Hz); 1.01 (2H, dd, J=4, 7 Hz).


Preparation of 4,4-Dimethyl-2-cyclohexenone (114)

A solution of 27.2 mL (0.30 mole) of isobutyraldehyde and 16.2 mL (0.20 mole) of methyl vinyl ketone was mixed at room temperature with 0.2 mL of concentrated sulfuric acid. The solution was warmed cautiously to 45-50° C and maintained at that temperature by means of occasional cooling with a cold-water bath. (Caution: A violent reaction may result if the temperature is allowed to exceed 65° C). The exothermic reaction subsided within about 1 hour. The solution was then refluxed through a Dean-Stark trap until water removal ceased (ca. 3 hours). Distillation (1.6 mm Hg) of the mixture gave 14.9 g (0.12 mole) of clear liquid at 35-41° C (60% yield)

1H NMR: 6.63 (1H, d, J=10 Hz); 5.80 (1H, d, J=10 Hz); 2.42 (2H, t, J=7 Hz); 1.83 (2H, t, J=7 Hz); 1.13 (6H, s).
\(^{13}\)C NMR: 199.3 (s), 159.6 (d), 126.6 (d), 35.9 (d), 34.2 (d), 32.6 (s), 27.5 (q).

MS: 124 (M\(^+\)), 109, 96 (base), 82, 81, 77, 67, 53, 41.


IR: 2933, 1681 (\(\alpha,\beta\)-unsaturated C=O), 1464, 1383, 1239, 1125, 805.

\(^1\)H (\(^{13}\)C )

\[ \begin{align*}
&2.42(35.9) & 5.80(126.6) \\
&1.83(34.2) & 6.63(159.6) \\
&(32.6) & 1.13(27.5)
\end{align*} \]

Preparation of 4,4-Dimethylcyclohexanone (115)

Six grams (0.05 mole) of 4,4-dimethyl-2-cyclohexenone, (114), were dissolved in 40 mL of glacial acetic acid and 0.2 g of 10% palladium on carbon was added. The mixture was shaken overnight under 60 atmosphere of hydrogen. The mixture was filtered twice through florisil, and then poured into a mixture of 200 mL of water and 150 mL of ether. The acetic acid was neutralized by slow addition of solid sodium bicarbonate. The aqueous layer was separated and washed twice with ether. The ether layers were combined and dried. Concentration gave 6.0 g (0.048 mole) of prism-like needles, M.P. 37-39°. Sublimation removed a small amount of residual oil and raised the melting point to 39-41° (96% yield).
**1H NMR:** 2.31 (4H, t, J=7 Hz); 1.63 (4H, t, J=7 Hz); 1.06 (6H, s).

**13C NMR:** 212.0 (s), 38.9 (d), 37.7 (d), 29.7 (s), 27.3 (q).

**MS:** 126 (M+), 111, 83, 71 (base), 55, 43.

**HRMS:** Calcd for C₈H₁₄O: 126.1045. Observed: 126.1049.

**IR:** 2933, 1715 (C=O).

Preparation of 2-Carboxethoxy-4,4-dimethyl-l-cyclohexenol (116a)

Into a 250 mL three-necked flask was placed 5.1 g (0.11 mole) of 50% sodium hydride-oil suspension. While under nitrogen, the solid was washed 3 times with dry toluene and 3 times with anhydrous tetrahydrofuran (solvent removed by syringe). A solution of diethyl carbonate (12.1 mL, 0.1 mole) in dry tetrahydrofuran (25 mL) was added dropwise and the stirred mixture was heated to reflux. A solution of 4,4-dimethylcyclohexanone (5 g, 0.04 mole), (115), in 10 mL of tetrahydrofuran was slowly added over 45 minutes (fast stirring was required to remove foaming). Heating was continued for 8 hours and the flask was cooled in an ice bath. A solution of acetic acid (40 mL) and saturated brine (50 mL) was slowly added, followed by ether (125 mL) and solid sodium bicarbonate.
The layers were separated, and the aqueous phase was extracted with ether (2 x 50 mL). The combined organic layers were washed with brine, dried and evaporated. Distillation (0.63 mm Hg) gave 5.3 g (0.027 mole) of clear, colorless liquid at 74-80° C (68% yield).

**1H NMR:** 12.22 (1H, s); 4.18 (2H, q, J=7 Hz); 2.26 (2H, t, J=7 Hz); 2.00 (2H, br s); 1.42 (2H, t, J=7 Hz); 1.28 (3H, t, J=7 Hz); 0.93 (6H, s).

**13C NMR:** 172.7 (s), 171.0 (s), 96.3 (s), 60.0 (t), 35.9 (t), 34.3 (t), 28.8 (s), 27.7 (q), 26.4 (t), 14.1 (q).

**MS:** 198 (M⁺), 183, 170, 152, 142 (base), 137, 124, 113, 109, 96, 81, 68, 55, 41.


**IR:** 2915 (br), 1653, 1616, 1282, 1235, 1205, 1070, 820.

Preparation of 6-Bromo-2-carboethoxy-4,4-dimethylcyclohexanone (117)

To a solution of 4.2 g (0.021 mole) of the keto ester, (116), in 15 mL of methylene chloride was added dropwise 3.4 g
(0.021 mole) of bromine at 0° C and stirred 8 hours at room temperature. The α-Bromo product was isomerized to the γ-bromo by bubbling a stream of moisture through the solution for 1 hour. Excess hydrogen bromide was removed by rinsing with 5% aqueous sodium bicarbonate and water. The organic solvent was dried over anhydrous magnesium sulfate and reduced in volume. The resulting yellow oil (6.1 g) was used directly for the next step.

**Preparation of 1,2 Dicarboethoxy-4,4-dimethylcyclopentane (118)**

To a solution of 4 g (0.1 mole) of sodium hydroxide in 25 mL of ethanol and 25 mL of water was added dropwise 6.1 g of crude bromoketo ester, (117), at 0° C and stirred for 1.5 hours at 0° C, then reflux for 1 hour. The yellow slurry which resulted was diluted with water, the ethanol evaporated at reduced pressure and then the resulting solution was acidified by adding HCl, extracted with ether, washed with saturated brine, dried over magnesium sulfate and reduced in volume. Distillation (0.67 mm Hg) gave 3.4 g (0.014 mole) of the clear, colorless liquid at 84-90° C (67% yield from 116a).

**1H NMR:** 4.12 (4H, q, J=7 Hz); 3.25 (2H, m); 1.85 (2H, m); 1.66 (2H, m); 1.23 (6H, t, J=7 Hz); 1.02 (6H, s).

**13C NMR:** 174.4 (s), 60.1 (t), 46.3 (d), 44.1 (t), 38.9 (s), 28.6 (q), 13.8 (q).

**MS:** 242 (M⁺), 227, 197, 196, 168, 153, 139, 123, 95 (base), 81, 67, 55, 41.
Preparation of 4-Chlorobutan-2-one (119)

A methylene chloride solution of 20 g (0.28 mole) of methyl vinyl ketone was stirred at 0°C while 10.2 g of gaseous HCl were bubbled into the flask at a rate such that little or no HCl was detected by wet litmus paper at the exit port of the reaction flask. The reaction was deemed complete when HCl was evidenced above the reaction (ca. 2 hours). The reaction was worked up by transferring the methylene chloride solution to a separatory funnel and rinsing repeatedly with saturated sodium bicarbonate solution. If this rinse procedure was omitted, the distilled product became highly colored and rapidly polymerized. After removal of the methylene chloride in vacuo, the reddish residue was distilled (40-41°C at 18 mm Hg) to provide 23.7 g (0.224 mole) of colorless liquid (80% yield).
\[ ^1\text{H NMR: } 3.71 (2H, t, J=6.5 \text{ Hz}); 2.90 (2H, t, J=6.5 \text{ Hz}); 2.18 (3H, s). \]
\[ ^{13}\text{C NMR: } 204.8 (s), 45.5 (t), 38.0 (t), 30.0 (q). \]
\[ \text{MS: } 108 (M^+ + 2), 106 (M^+), 91, 71, 63, 43 (\text{base}). \]
\[ \text{HRMS: Calcd for } C_{9}H_{17}OCl: 106.0185. \text{ Observed: } 106.0189. \]
\[ \text{IR: } 1718 (\text{C=O}), 1368, 1163, 727, 649. \]

Preparation of 2,7,7-Trimethyl-(cis)-1,5-dicarboethoxy-bicyclo[3.3.0]octan-2-ol (120)

A solution of 2.5 equivalents of lithium diisopropylamide in 50 mL of dry tetrahydrofuran was stirred while cooled to \(-78^\circ\) C and 0.70 g (0.0029 moIe) of the diester, (118), was added slowly via syringe under nitrogen. After stirring 30 minutes, 0.46 g (1.5 eq.) of 119 was added at \(-78^\circ\) C. The reaction was then stirred for 24 hours at room temperature and quenched by cautiously adding 10% aqueous HCl solution, extracted with ether, washed with saturated brine and then dried over magnesium sulfate. This gave 0.89 g of an orange syrup which was passed through a silica gel column (5 cm x 45 cm, 9:1 hexane:ethyl acetate) to provide 0.19 g (0.0061 mole) of the product (21% yield).
$^1$H NMR: 4.09 (2H, q, $J=7$ Hz); 4.07 (2H, q, $J=7$ Hz); 2.9-1.4 (9H, m); 1.51 (3H, s); 1.24 (3H, t, $J=7$ Hz); 1.21 (3H, t, $J=7$ Hz); 1.09 (3H, s); 1.04 (3H, s).

$^{13}$C NMR: 178.9 (s), 173.8 (s), 83.1 (s), 73.0 (s), 63.6 (s), 61.4 (t), 60.6 (t), 50.5 (t), 49.7 (t), 40.5 (t), 36.9 (s), 36.8 (t), 32.7 (q), 31.2 (q), 23.7 (q), 14.0 (q), 13.9 (q).

MS: 312 (M+), 266, 241, 221, 195 (base), 167, 149, 121, 107, 93, 79, 65, 43.

HRMS: Calcd for C$_{17}$H$_{28}$O$_5$: 312.1936. Observed: 312.1938.

IR: 3333 (-OH), 2924, 1712 (C=O), 1674 (C=O), 1368, 1277, 1212, 1186, 1026, 911, 730.

$^1$H ($^{13}$C)


pyridine-2-carbaldehyde

\[ \lambda_{\text{max}}^{\text{Heptane}} = 231 \ (10,000) \]
\[ 238 \ (7,800) \]
\[ 268 \ (3,750) \]


36. H. Kasugai, *Japan Kokai*, 75, 121, 433 (Cl, AOIN, CO7D), 23 Sep 1975; *Chem. Abstr.*, 84, P26862S.


New approaches to natural products