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SYNTHETIC APPROACHES TO THE INSIDE-OUTSIDE
BICYCLO[8.2.2]TETRADODECANE SYSTEM

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Andrew Wai-Wah Ho, B.S., M.S.

****

The Ohio State University
1975

Reading Committee:

Professor Paul G. Gassman
Professor Melvin S. Newman
Professor John S. Swenton

Approved By

Paul G. Gassman
Adviser
Department of Chemistry
To Patti
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VITA

May 23, 1945 .......................... Born - Swatow, China

1969 ................................. B.S. in Chemistry, University of Illinois, Urbana, Illinois

1969-1971 ............................ Teaching Assistant, University of Wisconsin, Madison, Wisconsin

1971 ................................. M.S. in Organic Chemistry, University of Wisconsin, Madison, Wisconsin

1971-1972 ............................ Graduate Teaching Assistant, The Ohio State University, Columbus, Ohio

1972-1975 ............................ Graduate Research Associate, The Ohio State University, Columbus, Ohio

PUBLICATION


FIELDS OF STUDY

Major Field: Organic Chemistry

Synthesis and solvolyis of cyclopropylpropanesultone.
Professor Robert M. Coates, University of Illinois.

Synthesis and solvolyis of substituted allyl p-nitrobenzoate.
Professor Harlan L. Goering, University of Wisconsin.

Synthesis of inside-outside bicyclic compounds.
Professor Paul G. Gassman, The Ohio State University.
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INTRODUCTION

Theoretically, bridged bicyclic molecules can exist in two different topological structures: one in which both the bridgehead atoms have the same spatial orientation, and the other in which their spatial orientation is opposite. Assuming that the bicyclic chains have no special label, the bicyclic molecule with similar orientation at the bridgehead, can exist in two different stereoisomers (atropisomers), which are represented as the inside-outside \((i,o)\) (1) and the outside-inside \((o,i)\) (2). Similarly, bicyclic molecules with opposite spatial orientation at the bridgehead can also have two atropisomers: inside-inside \((i,i)\) (3) and outside-outside \((o,o)\) (4).  

![Diagram of bicyclic molecules]

The majority of bicyclic molecules only exist as the structure (4) with both of their bridgeheads in the outside-outside orientation. This is particularly true when the chains of the bicyclic

\[ \text{(1) For a detailed discussion of bicyclic molecules with inverted bridgeheads, see H. E. Simmons, C. H. Park, R. T. Uyeda, and M. F. Habibi, Trans. N.Y. Acad. Sci., 32, 521 (1970).} \]
molecule are short. For example, due to intolerable bond angle deformation and nonbonded compressions, norcamphor can only exist as the structure 5, whereas structures 6, 7, and 8 are 'forbidden' (in terms of our present thinking). However, when the length of the bicyclic chain increase, the degree of such bond angle deformation and nonbonding interaction automatically decreases and the existence of other atropisomers become possible. The earliest examples of inside-outside, outside-inside, and inside-inside bicyclic molecules has been mainly limited to macrobicyclic systems having nitrogen at both bridgeheads.

(2) K. Mislow, 'Introduction to Stereochemistry,' W. A. Benjamin, New York, N.Y., p. 102, 1966.


In 1967, Simmons and Park\textsuperscript{3a} in order to prove the idea that macro-bicyclic diamines with bridgehead nitrogen atoms potentially can exist as conformations in which the lone pairs are both outside and inside the bicyclic cavity, synthesized a series of 1,(k+2)-diazabicyclo-[k,1,m]alkanes with k, l, m > 6 through a relatively simple route as in the following:

They observed the 100 MHz pmr spectrum of 1,10-diazabicyclo[8.8.8]-hexacosane in fluorochloroform, and found out that this compound has resonances at 2.20 (12H) and 1.36 ppm (36H) at 25°, while below -95° the α-CH₂ resonance is split into two broad lines (∼3:2) separated by 45 Hz. This suggests that there is a possible conformational change of (10) as in Figure 1, with an activation energy of 7.7 kcal/mole and 
\[ k = 1.4 \times 10^7 \text{ sec}^{-1} \] 
 at 25°. 
Figure 1

This conformational change was further revealed by protonation of the bicyclo diamines to give the bisammonium salts. 1,10-Diaza-bicyclo[8.8.8]hexacosane bisammonium hydrochloride (12) was isolated as homogeneous crystalline form from water, and it was identified as the outside-outside isomer by pmr spectra. When this outside-outside
bishydrochloride was dissolved in 50% aqueous trifluoroacetic acid, it changed to an isomeric salt over 4 days which was identified as the inside-inside isomer (13). This suggests that the inside-inside ion 13 is thermodynamically more stable than the outside-outside ion 12. Models show that 13 has a very compact structure in which the chains contain a maximum of trans arrangements and are oriented for favorable nonbonded and dispersion interactions. Evidently, the inside-outside isomers are less stable than either the outside-outside or the inside-inside isomers, which is due to the torsional and nonbonded repulsion effects. The inside-outside ion is only detected when \( k, l, m \geq 10 \). For example, 1,12-diazabicyclo[10.10.10]dotriacontane bisammonium hydrochloride exists as an equilibrium of three isomers in 50% trifluoroacetic acid.
This topological isomerization also happens in the cryptates. Lehn and coworkers \textsuperscript{4a} discovered that the potassium cryptate exists in aqueous solution as an equilibrium mixture of three conformations: outside-outside (17), inside-outside (18), and inside-inside (19).

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=0.3\textwidth]{cryptate_diagram.png}};
\end{tikzpicture}
\end{center}

However, in the solid state, the cryptate exists as the inside-inside isomer (19), which has been confirmed by an X-ray crystallographic study of a rubidium cryptate.

Besides those macrobicyclic molecules with nitrogen bridgeheads, macrobicyclic molecules with phosphorus atoms as bridgeheads also can exist in different topological isomers. \textsuperscript{1}1,10-Diposphabicyclo[8.8.8]-hexacosane has been synthesized stereospecifically as the outside-outside isomer (20), which is stable at room temperature. \textsuperscript{1} At 190\textdegree{}C in dichlorobenzene solution, 20 can be equilibrated to give a mixture of two isomers, the outside-outside (20) and the inside-outside (21) in roughly equal amounts. The inside-outside isomers in the phosphine is much more stable as compared with amines, primarily because the interchain crowding is decreased by lengthening the bonds from the bridgehead atoms to the adjacent methylenes (C-N, 1.47 \text\AA \textsuperscript{1} vs C-P, 1.87 \text\AA).
It was not until the late sixties that Park and Simmons synthesized their first macrobicyclic hydrocarbon, bicyclo[8.8.8]hexacosane, and detected all three possible isomers: outside-outside, inside-outside, and inside-inside. They isolated both the inside-outside and inside-inside isomers, and found that the two are not interconvertible even when heated at 200°.

Up to this stage, there was still lack of any general approach for the synthesis of such inside-outside or inside-inside bicyclic molecules. It was only until the last 5 years that the synthesis and study of chemistry of bicyclic molecules with inverted bridgehead(s) draw more attention. This is partly due to recent improvements in synthetic and analytical techniques which have allowed the synthesis and characterization of such compounds to be more possible. However, the most important reason that activated such study is the nature of these molecules, the strain that they might possess, and the relatively unknown chemical behavior.

Strain in a molecule exists when bonds in that molecule are built in such a fashion that they are not able to achieve normal bond angles. These angle distortions result in a higher energy than would occur without such distortions. These bond distortions of a molecule quite
often affect its chemical reactivity. Therefore in the past 15 years, much work has gone into the elucidation of the nature of strained rings and the chemistry of their 'bent' carbon-carbon sigma bonds. This is evidenced by more than 1000 papers on this subject which appeared during this period. However, the investigations of this subject have been limited primarily to the chemistry of compounds containing small rings.

In 1974, Gassman first suggested that highly reactive 'bent' carbon-carbon sigma bonds might exist in aliphatic systems which did not contain any small ring. In fact, this idea can be supported by some unusual reactivity which has been noted for the paracyclophanes. Addition of either dimethyl fumarate or dimethyl maleate to paracyclophane (24) gave a mixture of 25 and 26. Cram and Reich suggested that the paracyclophane underwent homolytic cleavage of the strained carbon-carbon sigma bond to form the p,p'-dimethylene-bibenzyl diradical. Addition of this diradical to the unsaturated ester would give a new diradical, at which stage rotation could occur followed by a radical combination step to give a mixture of 25 and 26.

(6) For more detailed reviews of 'bent' carbon-carbon sigma bond chemistry, see: F. J. Williams, III, Ph.D. Dissertation, The Ohio State University, 1970; E. A. Armour, ibid., 1973; and references cited therein.


Other cyclic trans olefins such as trans-cyclooctene (27) and trans-cycloheptene (28) might also be expected to show some properties of molecules containing 'bent' carbon-carbon sigma bonds. Unfortunately, the reactivity of the olefinic linkage overshadows any chemical
reactivity of the rest of the molecule which might be associated with the strained sigma bonds. As a result of this, Gassman suggested that bicyclic molecules with inverted bridgehead(s) would constitute excellent models for the study of such 'bent' carbon-carbon sigma bond chemistry. In these molecules, if the chains connecting the bridgeheads are small enough, not only the carbon-carbon sigma bonds attached to the inverted bridgehead(s) would be in the 'bent' state, but also the nonbonding steric interaction between the inverted bridgehead(s) with the rest of the molecule would cause significant perturbations in the bonding in certain parts of the molecule.

The concept that macrobicyclic hydrocarbon with inverted bridgehead(s) potentially could be a highly strained molecule was further supported by some theoretical calculations. Schleyer and Chang had done some calculations on the inside-outside bicyclo[6.2.2]-dodecane (29), inside-outside bicyclo[7.2.2]tridecane (30), and inside-outside bicyclo[8.2.2]tetradecane (31) as in Table 1.

\[\text{Diagram of bicyclic hydrocarbons:} \]

\[\text{(CH}_2\text{)}_6\quad\text{(CH}_2\text{)}_7\quad\text{(CH}_2\text{)}_8\]

\[\text{29} \quad \text{30} \quad \text{31}\]

---

(10) P. v. R. Schleyer, private communication to P. G. Gassman.
Table 1. Calculated Strain Energies of 29, 30, and 31.

<table>
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<th>Energy</th>
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<th>30</th>
<th>31</th>
</tr>
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<tr>
<td>Nonbonded Repulsions</td>
<td>9.65</td>
<td>6.88</td>
<td>7.45</td>
</tr>
<tr>
<td>Angle Deformation</td>
<td>17.54</td>
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<td>Torsional Strain</td>
<td>7.16</td>
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<tr>
<td>Total Strain</td>
<td>34.35</td>
<td>24.63</td>
<td>24.31</td>
</tr>
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The energy unit is in kcal/mole at 25°C.

As we can see, the strain energy of the compounds 30 and 31, which have 7- and 8-methylenes on their longer side chain, are about the same, but compound 29, which has only 6-methylenes, has gone up about 10 kcal/mole in the total strain energy. This is due chiefly to an increase in the CCC angle strain.

Therefore in order to do some more intense studies on the chemistry of bicyclic molecules with inverted bridgeheads, Gassman and coworkers began an exploration of synthetic routes to these inside-outside and inside-inside bicyclics, which hopefully would become generalized. They began on a simple and yet very effective approach based on the concept that the concerted \([2\pi + 4\pi]\) Diels-Alder addition of

good dienophiles to cyclic conjugated cis,trans- and trans,trans-dienes such as $32$ and $33$ would occur stereospecifically. This would automatically lead to adducts of the inside-outside structure $34$ and inside-inside structure $35$, respectively. However, a $[2\pi + 2\pi]$ cycloaddition via the formation of diradical intermediates was often observed in this type of reaction. Therefore, in order to minimize such side reactions, they start with perfluoro-2-butyn $36$, which is a powerful dienophile $^{12}$ and yet a relatively poor participant in


free radical cycloadditions. Isomers of 1,3-cyclododecadiene was prepared and used as the diene system. Heating of 2.5:1 mixture of perfluoro-2-butyne (36) and cis,trans-1,3-cyclododecadiene (37) in a sealed tube at 150° for 42 hr gave 78% of the inside-outside bicyclic compound (38) and 16% of 39. Unfortunately, under the same reaction conditions no inside-inside bicyclic adduct could be obtained by using the cis,cis-1,3-cyclododecadiene (40) as diene. This is because it is too strenuous for 40 to achieve a planar cisoid conformation, which is a basic requirement in the \([2\pi + 4\pi]\) cycloaddition. As for the trans-trans-1,3-cyclododecadiene (41), it simply exists in the transoid conformation and is thermally much less stable than the two other isomers.
Two other inside-outside bicyclic compounds had been prepared with the same approach. The crystalline inside-outside bicyclic \( 42 \), and the more strained inside-outside bicyclic \( 43 \).

Some preliminary chemical reactions on \( 38 \) have been studied. Hydrogenation of \( 38 \) yielded 97\% of \( 44 \). The tetrasubstituted double bond remained untouched. Photolysis of \( 38 \) gave 85\% of a tetracyclic photoisomer \( 45 \). One of the more interesting reactions of \( 38 \) was its facile loss of hydrogen fluoride on treatment with base. Compound \( 38 \),

(14) P. G. Gassman and S. R. Korn, unpublished results.

(15) P. G. Gassman and T. Bailey, unpublished results.
when heated with potassium tert-butoxide in tert-butyl alcohol, gave 80% of 46, which was catalytically reduced to 47. It is quite
suprising that \( \text{46} \) failed to aromatize to \( \text{48} \) during the base treatment (and even in acidic conditions). It seems that formation of \( \text{48} \) would provide for a gain of energy both due to aromatization and a relief of strain. Whether this is a result of the inaccessibility of the encapsulated bridgehead hydrogen to proton acceptors still remains a question.

Finally it is worthy of mention that \( \text{38} \) can be converted to the paracyclophane \( \text{42} \) in low yield by treatment of N-bromosuccinimide in the presence of benzoyl peroxide. This was believed to go through an unstable intermediate (50).

\[ \text{38} \xrightarrow{\text{NBS}} \text{50} \xrightarrow{} \text{48} \]

Thus far all the work reported on the subject of bicyclic hydrocarbons with inverted bridgehead(s) is still in a preliminary stage. Only compounds with bridgehead proton(s) captured in the bicyclic cage have been made, and as of yet no bicyclic molecule with caged functional groups has ever been reported. Many physical and chemical properties of such compounds remain to be elucidated. The effects of bond

\( \text{16} \) In the presence of p-toluenesulfonic acid.
distortion on chemical reactivity of this type of molecules are still relatively unknown. The most urgent work that faced us was the development of synthetic approaches to these molecules. Until we can master the skill of such syntheses, there is really not much we can do about elaborating its chemistry. The goal of this thesis work, therefore, was to develop some practical synthetic routes to an inside-outside bicyclic molecule \(^{51}\), with an active functional group such as an aldehyde caged inside the bicyclic rings, and the length of the longer side-chain being adjusted so that no homeomorphic isomerization \(^{17}\) of the molecule could occur. Hopefully one of these synthetic routes would provide enough material so that the chemistry of these new compounds could be investigated.

(17) Homeomorphic isomerization is used here to mean a conformational change in which three-stranded molecules turn inside out by passage of one chain through the ring defined by the other two chains.
RESULTS AND DISCUSSION

PART I. Synthesis of 1-(6-Hydroxyhexyl)bicyclo[2.2.2]oct-2-ene.

As we mentioned previously, our goal was to search for some practical synthetic routes which would lead to the target molecule, the inside-outside bicyclic compound $5_1$. After examining the molecular model of $5_1$, two immediate precursors $5_2$ and $5_3$ were proposed.

![Structures $5_2$ and $5_3$](image)

By looking at the structures of $5_2$ and $5_3$, one would believe that a simple oxidative cleavage of the double bond in either $5_2$ or $5_3$ would automatically lead to the inside-outside bicyclic $5_1$, with an active carbonyl group being caged in the bicyclic rings. In order for this active functional group to exist within the cage, the length of the longer side chain must be adjusted. For example, from the study of models, if the number of methylene groups on the longer side chain is larger than 10, homeomorphic isomerization is definitely a
possibility. On the other hand, if \( n \) is smaller than 6, the molecule is simply too strained to encage such a functional group as a carbonyl, and its probability of existence becomes a question. Therefore the reasonable length for \( n \) would be in the range of 7 to 9, and the shortest possible chain, namely \( n = 7 \) was the initial goal.

Synthetic approaches to the precursor \( \text{52} \) were first investigated. The first idea was that one could start with a bicyclo[3.2.2]nonane

\[ \text{54} \rightarrow \text{55} \rightarrow \text{56} \]

\( X \) = halides, sulfonates, etc.
system with a suitable length of side chain carrying an active leaving group extended from one bridgehead. An intramolecular cyclization would lead to the third ring, and after transformations of a few functional groups, one would expect to obtain 52.

In order to reach compound 54, it seemed that the unknown precursor 1-(6-hydroxyhexyl)bicyclo[2.2.2]oct-2-ene (57) would be an excellent choice. Transformations from 57 to 54 could be done as shown in Scheme I.

First the hydroxy group in 57 must be protected either as a tetrahydropyranyl ether or a dimethyl-5-butyldisilyl ether (58). Both protective groups could be removed in acidic condition or in the case of the latter, by tetra-n-butylammonium fluoride in tetrahydrofuran. A simple hydroboration or oxymercuration on the double bond in 58 would give an alcohol 59, which could be oxidized with Sarrett reagent to a ketone 60. Subsequent oxidation of the ketone 60


Scheme I

R = THP
or
$\text{Si(CH}_3\text{)}_2(\text{t-Bu})$
with selenium dioxide would provide the α-diketone. An alternative route to the α-diketone was also considered to be very attractive.

Oxidation of \( \text{58} \) with m-chloroperbenzoic acid in methylene chloride would lead to an epoxide, \( \text{64} \), which could be catalytically oxidized to a \( \alpha \)-hydroxy ketone \( \text{65} \) with boron trifluoride etherate in dimethyl sulfoxide. \( \text{24} \) Sarreott oxidation of the \( \alpha \)-hydroxy ketone \( \text{65} \) would give the expected \( \alpha \)-diketone \( \text{61} \). Treatment of \( \text{61} \) with ethereal diazomethane would be expected to provide the desired \( \beta \)-diketone \( \text{62} \), which after removal of the hydroxy protective group and treatment with tosyl or mesyl chloride in pyridine would become the anticipated precursor \( \text{54} \).

In order to test the validity of the above proposed scheme, especially the critical transformation of an olefin to a \( \beta \)-diketone, a model compound, the bicyclo[2.2.2]oct-2-ene (67) was chosen for study. Hydroboration of \( \text{67} \) with diborane in tetrahydrofuran gave 90% of 2-hydroxybicyclo[2.2.2]octane (68). The bicyclo[2.2.2]-octan-2-one (69) was obtained in 89% yield by oxidizing \( \text{68} \) with 6

\begin{itemize}
\end{itemize}
equivalents of Sarrett's reagent. The ketone 69 was further oxidized with selenium dioxide in aqueous dioxane at refluxing temperature to give 47% yield of the bicyclo[2.2.2]octan-2,3-dione (70), which on treatment of ethereal diazomethane afforded 34% of crystalline
bicyclo[3.2.2]nonan-2,4-dione (71).28 Even though 70 and 71 were obtained in low yield, this proved that the synthetic route proposed in Scheme I was a possible pathway to the precursor 54.

The main part of the synthesis involved the preparation of compound 57. The construction of structure 57 was started from the bicyclo[2.2.2]octene skeleton substituted with active functional groups at the bridgehead, which later could serve as a stepping stone for the extension of the side chain. It was fortunate that the known 1-carboethoxybicyclo[2.2.2]oct-2-ene (72) met this criteria.27 Compound 72 has been reported by Grob, Roberts, Stock, and Chapman. The synthetic path and procedures to 72 developed by Grob and coworkers was adopted and shown as in Scheme II. Details are presented in the Experimental part. Reaction of crotonaldehyde and diethylamine in benzene with potassium carbonate as catalyst gave a 42% yield of 1-diethylaminobutadiene (73). Diels Alder reaction of 73 and ethyl acrylate in benzene at room temperature for six days provided 71% yield of ethyl-2-diethylamino-3-cyclohexene-1-carboxylate

Yields of 71 and 70 have not been optimized.


Scheme II

\[
\begin{align*}
\text{CH}_2=\text{CH}_2 \xrightarrow{\text{HNET}_2, \text{K}_2\text{CO}_3} \quad & \quad \text{CH}_2=\text{CH}_2 \text{N(CH}_2\text{CH}_3)_2 \quad \xrightarrow{\text{EtO}} \quad \text{Benzene} \\
\text{CH}_2=\text{CH}_2 \text{OAc} \quad \xrightarrow{\text{EtO}} \quad & \quad \text{CO}_2\text{CH}_2\text{CH}_3 \\
\text{CH}_2=\text{CH}_2 \text{OAc} \quad \xrightarrow{\text{EtO}} \quad & \quad \text{CO}_2\text{CH}_2\text{CH}_3 \\
\text{H}_2 \xrightarrow{\text{PtO}_2} \quad & \quad \text{CO}_2\text{Et} \\
\text{KHCO}_3, \text{H}_2\text{O} \quad & \quad \text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} \quad \xrightarrow{\text{Pb(OAc)}_4} \quad & \quad \text{CO}_2\text{Et}
\end{align*}
\]
Treatment of \(7_4\) with anhydrous hydrogen chloride in absolute ethanol led to an amine hydrochloride salt, which was pyrolyzed to give 68\% of ethyl 1,3-cyclohexadiene-1-carboxylate (\(7_5\)). An alternative route to the carboxylate \(7_5\) developed by Sayigh and Stock deserves mention here. Reacting crotonaldehyde and acetic anhydride with potassium or sodium acetate as catalyst led to 1-acetoxy-1,3-butadiene (\(7_6\)). The Diels Alder reaction of \(7_6\) with ethyl acrylate afforded the crystalline 1-carboethoxy-2-acetoxy-cyclohex-3-ene (\(7_7\)), which could be pyrolyzed under basic conditions to give the desired ester \(7_5\). Heating \(7_5\) with one equivalent of maleic anhydride gave 1-carboethoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (\(7_8\)) in 95\% yield. Hydrogenation of \(7_8\) in tetrahydrofuran with platinum oxide as catalyst provided a 95\% yield of the 1-carboethoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid anhydride (\(7_9\)), which was hydrolyzed in 20\% aqueous potassium bicarbonate solution to give 97\% yield of the 1-carboethoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid (\(8_0\)). The ethyl ester \(7_2\) was obtained in 55\% yield from an oxidative bisdecarboxylation of the dicarboxylic acid \(8_0\) with lead tetraacetate and pyridine in benzene.

---

The problem of the extension of the side chain from the bridgehead of compound 72 was studied next. The first reaction involved the conversion of compound 72 into compound 81, where X was to be a good leaving group such as halide or sulfonate. It should be possible to replace X in compound 81 with a side chain containing a good leaving and an active functional group protected by the reagent, 1,3-dithiane. The reason that 1,3-dithiane was selected here was because the dithiane group could be conveniently removed through either Raney nickel or dissolving metal reduction (the Birch or

![Chemical Structure](image)

\[ \begin{align*}
\text{CO}_2\text{CH}_2\text{CH}_3 & \quad \rightarrow \quad \text{CH}_2\text{X} \\
72 & \quad 81 \\
X & = \text{Br, I, Ms, or Ts}
\end{align*} \]

---


Benkeser reduction$^{35}$ to the corresponding hydrocarbon in a subsequent transformation.

To test the above idea, compound 72 was converted to 1-hydroxymethylbicyclo[2.2.2]oct-2-ene (82) with lithium aluminum hydride in 86\% yield. Treatment of the alcohol 82 with tosyl chloride in pyridine provided 94\% of crystalline 1-hydroxymethylbicyclo[2.2.2]-oct-2-ene tosylate (83). Displacement of the tosylate 83 with a large excess of sodium bromide in dimethyl sulfoxide gave 88\% of the expected compound, 1-bromomethylbicyclo[2.2.2]oct-2-ene (84). The prospective side chain, 85, was prepared by sodium benzyl oxide with 1,5-dibromopentane in dimethoxy ethane in 46\% yield. The reason that benzyloxy was used as a protective group rather than a tetrahydropyranloxy was because a benzyloxy group would be simultaneously reduced to an alcohol during the step of desulfurization under the dissolving metal reduction condition.

Unfortunately, the alkylation of 84 with 2-lithio-1,3-dithiane in tetrahydrofuran did not materialize. This may have been attributed to the fact that 84 was a neopentyl halide which was sterically quite unfavorable for an $\text{S}_{\text{p}}^{2}$ type alkylation.

A possible solution to this problem was to extend the carboxyl group in 72 one carbon away from the neopentyl center to avoid the steric hindrance. This was successfully achieved as shown in Scheme III.

---

\[
\text{CO}_2\text{CH}_2\text{CH}_3 \xrightarrow{\text{LiAlH}_4} \text{Et}_2\text{O} \rightarrow \text{CH}_2\text{OH} \xrightarrow{\text{TsCl}} \text{CH}_2\text{OTs}
\]

\[
\text{CH}_2\text{Br} \xrightarrow{\text{NaBr}} \text{DMSO} \rightarrow \text{CH}_2\text{Br}
\]

\[
\text{CH}_2\text{OH} + \text{Br-(CH}_2)_5\text{Br} \xrightarrow{\text{Na}} \text{DME} \rightarrow \text{CH}_2\text{-O(CH}_2)_5\text{-Br}
\]

\[
\text{Li} + \text{CH}_2\text{Br} \rightarrow \text{CH}_2\text{Br}
\]

\[
\text{H} + \text{CH}_2\text{Br} \rightarrow \text{H}
\]
Scheme III

1. KOH
2. H₃O⁺

72

83

NaCN
DMSO

86

SOCl₂

87

1. CH₂N₂
2. AgBz
(Et)₃N
MeOH

88

LiAlH₄
Et₂O

91

CH₂CH₂Cl

NaCl
DMSO

92

CH₂CH₂OTs

TsCl

93

CH₂CH₂OH

89

1. KOH
2. H₃O⁺

90

CH₂CO₂H

CH₂CO₂CH₃

CH₂CN

CO₂CH₂CH₃
Bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (86) was obtained in 96% yield from basic hydrolysis of the ester 72 in aqueous methanol. The carboxylic acid 86 was treated with thionyl chloride at room temperature to give 89% of the acid chloride 87. The Wolff rearrangement in this Arndt-Eistert synthesis process was done by adapting Newman's modified procedure. The compound, 1-carbomethoxy-methylbicyclo[2.2.2]oct-2-ene (88) was obtained in 81% yield by treating the acid chloride 87 with diazomethane to give a diazoketone, which was immediately catalytically rearranged in methanol by silver benzoate and triethylamine.

An alternative route for the preparation of the ester 88 was equally successful. Heating the tosylate of 1-hydroxymethylbicyclo[2.2.2]oct-2-ene (83) with excess sodium cyanide in dimethyl sulfoxide for 4 days gave a 94% yield of a low melting 1-cyanomethyl-bicyclo[2.2.2]oct-2-ene (89), which was hydrolyzed with potassium hydroxide in refluxing ethylene glycol for two days to the corresponding carboxylic acid 90 in 85% yield. This carboxylic acid was treated with diazomethane to give the ester 88 in quantitative yield.


(38) See review article by W. E. Bachman and W. S. Stowe, Org. React., Vol. 1, Chapter 2 and references cited therein.

1-(2-Hydroxyethyl)bicyclo[2.2.2]oct-2-ene (91) was obtained in 98% yield from the lithium aluminum hydride reduction of the ester 88 in ether. The alcohol 91 was converted to a tosylate by treatment with tosyl chloride in pyridine. Reaction of the tosylate with sodium chloride in dimethyl sulfoxide provided the 1-(2-chloroethyl)-bicyclo[2.2.2]oct-2-ene (92) in 39% yield (based on the alcohol 91).

Alkylation of the chloride 92 with 2-lithio-1,3-dithiane was still not successful even under long reaction time or high temperature.

Meantime another possible method of the chain extension was taken into consideration. It seemed that the well known fact 40 that reaction of organolithium reagents with either carboxylic acid or the lithium salt of carboxylic acid constituted a simple general method for the synthesis of ketones would be applicable in the present situation.

\[
\begin{align*}
\text{R-} & \text{C=O} + 2 \text{R'Li} \rightarrow \left[ \begin{array}{c} \text{LiO} \\
\text{R-C} \\
\text{R'} \end{array} \right] \\
\text{R-} & \text{C=O} \text{Li} + \text{R'Li} \quad \xrightarrow{\text{H}_2\text{SO}^+} \quad \text{R-C-R'}
\end{align*}
\]

There were two possible ways to apply this reaction: one could either obtain a ketone from the reaction of an organolithium carrying the bicyclo[2.2.2]octene moiety with a straight chain carboxylic acid, or through the reaction of a straight chain alkyllithium with a carboxylic acid of the bicyclo[2.2.2]octene system. Since the chloride 92 was available, it was decided to test the first possibility.

1,4-Butanediol was treated with sodium hydride followed by the addition of benzyl chloride to give 66% yield of 4-benzylxoyl-butanol (93). Oxidation of 93 with Jones reagent in acetone afforded the 4-benzylxybutyric acid (94). The lithium salt of the carboxylic acid 94 was prepared by neutralization of the acid with lithium hydroxide, and dried by heating in a vacuum oven. The alkyllithium was prepared by reacting the chloride 92 with lithium wire (~ 1% Na) in ethyl ether. However, the result of the reaction of lithium benzylxybutyrate (95) with the organolithium 96 was rather disappointing. Two major problems arose, which caused us to abandon this path. First the solubility of the lithium salt 95 in most common solvents for this reaction was so low that reaction was almost impossible. Secondly,


(42) Compound 95 was not soluble in non-polar solvents such as hexane or pentane, and only very slightly soluble in ether or tetrahydrofuran.
the organolithium 96 was too unstable to survive in solvents such as ethyl ether or tetrahydrofuran in reasonable reaction time, and yet due to the low solubility of the lithium salt 95, long reaction times and high temperatures were a necessity. The idea of using the benzyloxybutyric acid instead of its lithium salt was also impractical, because in that case two equivalents of organolithium 96 had to be
used. It was very inefficient to waste one equivalent of alkyl-
lithium which could only be obtained through many step syntheses.

Therefore one had to return to the second alternative route, namely the reaction of a straight chain alkyllithium with a carboxylic acid carrying a bicyclo[2.2.2]octene moiety.

The bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (86), which has been synthesized earlier, was the first choice as the precursor. The first choice of the side chain was the previously mentioned benzyl 5-bromopentyl ether (85). However, attempts to generate the organolithium from the bromide 85 were not successful. This was because immediately after generation of the alkyllithium, an intramolecular cyclization occurred to give the lithium benzyloxide and cyclopentane.

\[
\text{PhCH}_2\text{O} \\
\text{Li} \\
\text{OCH}_2
\]

\[
\text{LiOCH}_2 + \text{pentane}
\]
Fortunately this problem was solved by replacing 85 with 5-bromo-1-pentene (97), which was prepared by selective dehydrobromination of 1,5-dibromopentane with potassium t-butoxide in ether. The organolithium derivative of bromide 97 could be generated by reacting 97 with lithium wire (1% Na) in ether at 0°.

\[
\text{Br(CH}_2)_5\text{Br} \xrightarrow{\text{KOT}} \text{Br} \xrightarrow{\text{Li (1% Na)}} \text{Li}
\]

Reaction of the bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (86) with two equivalents of organolithium 98 provided 78% yield of 1-(2-oxo-5-hexenyl)bicyclo[2.2.2]oct-2-ene (99). Deoxygenation of the ketone in compound 99 by the Wolff-Kishner method was not satisfactory, because under the reaction conditions the terminal olefin was isomerized. However the ketone 99 could be reduced by lithium aluminum hydride to 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]oct-2-ene (100) in 90% yield. The alcohol 100 was treated with methane sulfonyl chloride in pyridine to give the mesylate 101, which was reduced to the hydrocarbon 1-(5-hexenyl)bicyclo[2.2.2]oct-2-ene (102) in 75% yield by lithium

aluminum hydride in ether. The 1-(6-hydroxyhexyl)bicyclo[2.2.2]oct-
2-ene (57) was thus obtained by selective hydroboration with dis-
iamylborane\(^{44}\) in diglyme in 20\% yield.

Although the important precursor 57 to the inside-outside
bicyclic compound 51 has been successfully synthesized, the
synthetic path was lengthy and tedious and the yield of the final
step was far from being satisfactory, therefore, a search for a more
efficient synthetic path was necessary.

\(^{44}\) H. C. Brown and G. Zweifel, J. Amer. Chem. Soc., 81, 1512 (1959);
ibid., 82, 3222, 3223 (1960); ibid., 83, 1241 (1961); G.
Zweifel, K. Nagase, and H. C. Brown, ibid., 84, 190 (1962);
PART II. Diels-Alder cycloaddition on 1-Carboethoxy-1,3-cyclohexadiene and derivatives.

As we mentioned in Part I of this discussion, the precursor 53 was another potential stepping stone to the inside-outside bicyclic compound. After analyzing the structure of 53, it appeared that the tricyclic system could be built from a bicyclic precursor as 103, where
the two side chains with active functional groups could be cyclized to provide the fourth ring. The precursor 103 could arise from a more simplified form 104, which was merely a Diels Alder adduct from the previously synthesized diene ester 75 and a suitable dienophile with suitable sterical orientation. Therefore the study of Diels-Alder reactions on 75 became of immediate interest.

First ethyl α-bromoacrylate (105) was considered as a dienophile. If the diene ester 75 were allowed to react with the dienophile 105,

\[
\text{CO}_2\text{Et} + \text{Br}\text{Et} \xrightarrow{\Delta} \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array} + \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array}
\]

\[
\text{H}_2(\text{Pd/C})
\]

\[
\begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array} \rightarrow \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array} + \begin{array}{c}
\text{CO}_2\text{Et} \\
\text{CO}_2\text{Et}
\end{array}
\]

\[
\text{108} \quad \text{106} \quad \text{107}
\]
hydrogenation of the Diels Alder adduct could be expected to yield a pair of isomers 106 and 107. Dehydrobromination of isomer 106 would lead to the diester 108, which in fact would be the desired precursor 103 in the simplified form.

The preparation of ethyl α-bromoacrylate (105) was quite simple. Ethyl α,β-dibromopropionate (109) was obtained in 95% from bromination of ethyl acrylate. Dehydrobromination of the dibromide 109 with triethylamine in ether gave 86% yield of the desired olefin 105.

\[
\begin{align*}
\text{CH}_2\text{Br}-\text{CHBrCOEt} \\
109
\end{align*}
\]

When the diene 75 was heated with the dienophile 105, no Diels Alder adducts were obtained. Only a small part of diene 75 could be recovered, and the rest turned into polymer. This proved that the rate of polymerization was far greater than the rate of the cycloaddition. Since ethyl α-bromoacrylate (105) is an electron poor dienophile, the rate of cycloaddition would be faster if the diene were an electron rich diene. However, with the carbomethoxy substitution, the diene 75 was a relatively electron poor diene. Therefore in order to have an electron rich diene, the diene 75 was reduced by lithium aluminum hydride in 89% yield to 1-hydroxymethyl-1,3-cyclohexadiene (110).

\[
\text{LiAlH}_4 \quad \text{Et}_2\text{O} \quad \text{CO}_2\text{Et} \quad \text{CH}_2\text{OH}
\]

\[75 \quad 110\]

Reaction of the diene 110 with ethyl α-bromoacrylate (105) did not give any better results. Besides polymer, water and toluene were also among the reaction products. It was believed that dehydration

---

might occur under the reaction conditions.

Another good dienophile\textsuperscript{46} methyl propiolate was also considered in the study. The diene 110 was heated at 80° with one equivalent of methylpropiolate in a sealed Carius tube. A 29% yield of α-hydroxy-o-toluic acid lactone (111)\textsuperscript{47} was obtained. It was believed that a retro-Diels Alder reaction might actually happen under the reaction conditions. The mechanism could be proposed as in the following equation:

\[\begin{align*}
\text{CH}_2\text{OH} & \quad + \quad \text{H}-\text{C} & \quad \text{CO}_2\text{CH}_3 \\
\text{CH}_2\text{OH} & \quad \text{CO}_2\text{CH}_3 \\
\end{align*}\]

\textsuperscript{110}

\textsuperscript{111}

\(\Delta\)

\(\alpha,\beta\)-Unsaturated ketones have long been recognized as good dienophiles, even though extensive studies on the cycloadditions of cyclic \(\alpha,\beta\)-unsaturated ketones have yet to be done. Since the two previous dienophiles did not give any promising results. A study of the cyclic \(\alpha,\beta\)-unsaturated ketones was initiated. The decision
was motivated by the following proposal. If one could successfully work out the Diels-Alder cycloaddition between the diene, 1-carboethoxy-1,3-cyclohexadiene (75) and a cyclic \(\alpha,\beta\)-unsaturated ketone, after hydrogenation of the adducts, a pair of isomers 112 and 113 would be obtained. A Baeyer-Villiger oxidation \(^{48}\) of isomer 112 followed by basic hydrolysis would provide the previously mentioned precursor 105 with built-in functional groups exactly as we desired.

The first two dienophiles which were selected were cyclooct-2-en-1-one (114) and cyclohex-2-en-1-one. The diene ester 75 was heated with cyclooct-2-en-1-one (114) at 160\(^\circ\) in a sealed Carrius tube for 3 days. After hydrogenation of the reaction product, no Diels Alder adducts were detected. Instead a mixture of the Diels Alder dimers of 75 were isolated almost quantitatively. Reaction of 75 with cyclohex-2-en-1-one gave similar results.

These peculiar results required a review of the synthetic plan. The conclusion was reached that the carbonyl group and the double bond in both the cyclooct-2-en-1-one and cyclohex-2-en-1-one would not be able to achieve a planar conformation without disturbing other C-C bonds on the ring, and yet in order to be a good dienophile, the

carbonyl group is preferable to be on the same plane as the double bond. Therefore, if the carbonyl and double bond could be made co-planar, a successful Diels Alder reaction might be expected. The only stable compound that could meet the criteria was cyclopent-2-en-1-one (117). The α,β-unsaturated ketone 117 was prepared by the three-step sequence. Hydrochlorination of cyclopentadiene provided

\[
\text{Cyclopentadiene} \xrightarrow{\text{HCl}} \text{Cyclopentyl chloride} \xrightarrow{\text{NaHCO}_3} \xrightarrow{\text{H}_2\text{O}} \text{Cyclopentanol} \xrightarrow{\text{Na}_2\text{Cr}_2\text{O}_7, \text{H}_2\text{SO}_4} \text{Cyclopentanone}
\]

a 78% yield of 3-chlorocyclopentane (118), which was hydrolyzed immediately in aqueous sodium bicarbonate solution to give 73% of 3-hydroxycyclopentene (119). Oxidation of the alcohol 119 with sodium dichromate and sulfuric acid afforded a 41% yield of the desired ketone 117.
However, reaction of 117 with the diene ester 75 gave the same
discouraging results as the previous case.

Therefore the last resort was limited to the unsubstituted
methyl vinyl ketone as the dienophile, which will be discussed in the
next section.
PART III. Synthesis of 1-(5-Hexenyl)bicyclo[2.2.2]octan-2-one.

As discussed in the previous part of this dissertation, the Diels Alder cycloaddition between the diene, 1-carboethoxy-1,3-cyclohexadiene (75), and cyclic α,β-unsaturated ketones was not promising. Thus, the most reactive dienophile of this system, the acyclic methyl vinyl ketone, was used. Of course it should be realized that by using methyl vinyl ketone, one main advantage which could be provided by using cyclic α,β-unsaturated ketones was lost. According to the proposal in Part II of this discussion, the precursor 104 with two built-in side chains could eventually be obtained if the cycloaddition between diene 75 and a cyclic α,β-unsaturated ketone was successful. However, by using methyl vinyl ketone, only 2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid (120) could be obtained. The side chain at the 3-position which was important for further development would have to be introduced later.

![Diagram](CO2H OH)

120
Fortunately, Buchanan and coworkers had just reported synthesizing the bicyclo[2.2.2]octan-2-one-1-carboxylic acid (121) in their study of the Bredt's rule. Their approach to the synthesis of 121 was based on the concept of a Diels Alder cycloaddition of the diene 75 and methyl vinyl ketone. With such precious information it was decided to develop a synthetic route based on the known compound 121. The synthesis of 121 and its methyl ester 120 were shown as in Scheme IV. The diene ester 75 was heated with methyl vinyl ketone in a sealed Carius tube at 140° for 24 hr to give a 97% yield of a mixture of the isomeric adducts, ethyl 2-acetylbicyclo[2.2.2]-oct-5-ene-1-carboxylate (123) and ethyl 3-acetylbicyclo[2.2.2]-oct-5-ene-1-carboxylate (124).


(50) The author would like to thank Professor Buchanan for his generosity in providing the details of the synthesis of compound 121 during his private communication with Professor Gassman. Physical properties of 121 and its precursors in the experimental part of this thesis were compared with those provided by Professor Buchanan and found satisfactory.
Scheme IV

\[ \text{CO}_2\text{Et} + \text{CH}_2=\text{CH}_2 \xrightarrow{\Delta} \text{123} + \text{124} \]

\[ \text{123} \xrightarrow{\text{KOH, EtOH/H}_2\text{O}} \text{125} + \text{126} \]

\[ \text{125} \xrightarrow{\text{CH}_2\text{N}_2, \text{Et}_2\text{O}} \text{127} \]

\[ \text{127} \xrightarrow{\text{CF}_3\text{CO}_2\text{H}, \text{CH}_2\text{Cl}_2, \text{Na}_2\text{HPO}_3} \text{128} \]

\[ \text{128} \xrightarrow{1. \text{KOH}, 2. \text{H}_3\text{O}^+} \text{129} \]

\[ \text{129} \xrightarrow{\text{Jone's Reagent}} \text{121} \]

\[ \text{121} \xrightarrow{\text{CH}_2\text{N}_2} \text{122} \]
Catalytic hydrogenation of the mixture of \(^{123}\) and \(^{124}\) with 5% palladium on carbon in tetrahydrofuran provided a quantitative yield of an isomeric mixture of ethyl 2-acetylbicyclo[2.2.2]octane-1-carboxylate (\(^{125}\)) and ethyl 3-acetylbicyclo[2.2.2]octane-1-carboxylate (\(^{126}\)). The ratio of the keto ester \(^{125}\) to \(^{126}\) was about 4:1. Compound \(^{125}\), which was of interest, could not be separated from \(^{126}\) through distillation. However a mixture of \(^{125}\) and \(^{126}\) was hydrolyzed with potassium hydroxide in aqueous ethanol to a mixture of keto acids, which was fractionally recrystallized from ethanol to give 55% of pure 2-acetylbicyclo[2.2.2]octane-1-carboxylic acid (\(^{127}\)). Esterification of the acid \(^{127}\) with an ethereal solution of diazomethane afforded methyl 2-acetylbicyclo[2.2.2]octane-1-carboxylate (\(^{128}\)) in 93% yield. Methyl 2-acetoxybicyclo[2.2.2]octane-1-carboxylate (\(^{129}\)) was obtained in 94% yield from the Baeyer-Villiger oxidation of the keto ester \(^{128}\) with trifluoroperacetic acid in methylene chloride. Hydrolysis of the ester \(^{129}\) in aqueous ethanolic potassium hydroxide solution gave 96% yield of the 2-hydroxybicyclo[2.2.2]octane-1-carboxylic acid (\(^{120}\)). The hydroxy acid \(^{120}\) was treated with Jones reagent in acetone at 0° to give 81% of the bicyclo[2.2.2]octan-2-one-1-carboxylic acid (\(^{121}\)), which was treated with diazomethane in ether to give 89% of the desired product methylbicyclo[2.2.2]octan-2-one-1-carboxylate (\(^{122}\)).
In order to approach the precursor 104, which was mentioned earlier in Part II of this discussion, from the available compound 122, two side chains must be developed at the bridgehead and the alpha position of the carbonyl. Since it was quite impossible to build both side chains simultaneously, a decision was made to determine the priority of their introduction, so that their synthetic schemes would not conflict with each other, and would not require unnecessary functional group protection. Introduction of the side chain from the bridgehead by taking advantage of the carbomethoxy group required protection of the ketone at the 2 position and subsequent removal of the protective group for the introduction of a second chain at the α-position of the ketone. Alternatively, the first chain was introduced at the α-position of the carbonyl; there was no need to protect the ketone. Therefore at this stage the latter idea was preferred.

There were two problems to consider. First, all reactions or transformations should not influence the bridgehead carbomethoxy group which was necessary for the next chain extension. Secondly, alkylation on the α-position of bicyclic ketones are generally quite difficult because generation of the enolate anion requires very strong base. For example, alkylation of a bicyclo[2.2.1]heptan-2-one required a strong base such as sodium amide or triphenylmethyl sodium. Other conventional strong bases such as sodium hydride

---

and potassium t-butoxide either worked in low yield or simply lead to self-condensation.

\[
\begin{array}{c}
\text{C}_{6}\text{H}_{5} \text{CH} = \text{C} \text{CH} \text{CH} \text{CH} \text{CH} \text{CH}_{2} \text{CH}_{2} \text{CH}_{3} \\
+ \text{NaNH}_{2} \xrightarrow{\text{CH}_{3}\text{I}} \text{C}_{6}\text{H}_{5} \text{CH} = \text{C} \text{CH} \text{CH} \text{CH} \text{CH} \text{CH}_{2} \text{CH}_{2} \text{CH}_{3} \text{CH}_{3}
\end{array}
\]

55%

\[
\begin{array}{c}
\text{C}_{6}\text{H}_{5} \text{CH} = \text{C} \text{CH} \text{CH} \text{CH} \text{CH} \text{CH}_{2} \text{CH}_{2} \text{CH}_{3} \text{CH}_{3} \\
+ \text{Ph}_{3}\text{CNa} \xrightarrow{\text{CH}_{3}\text{I}} \text{C}_{6}\text{H}_{5} \text{CH} = \text{C} \text{CH} \text{CH} \text{CH} \text{CH} \text{CH}_{2} \text{CH}_{2} \text{CH}_{3} \text{CH}_{3}
\end{array}
\]

50%

However, the recently developed lithium dialkyl amide bases such as lithium diisopropyl amide, lithium N-isopropylcyclohexylamide (LiICA), lithium bis(trimethylsilyl)amide, plus a half-dozen


lithium dialkylamides reported by Olofson and Dougherty seemed promising. All of these lithium dialkylamides are very powerful proton-specific, non-nucleophilic bases. They are recognized as excellent bases for abstraction of \( \alpha \)-protons of ester, nitrile, carboxylic acid, ketone, and even halides. By applying these powerful bases, enolate anion of the present bicyclic ketone should be easily generated. Since all of these bases are practically non-nucleophilic, during the alkylation no protection of the bridgehead carbomethoxy groups should be required.

Unfortunately, the attempted alkylation of compound 122 with 5-bromo-1-pentene failed with lithium diisopropylamide, lithium dicyclohexylamide and even lithium 2,2,6,6-tetrapiperidide in tetrahydrofuran, or dimethoxyethane, at various temperatures and reaction times. The starting ketone 122 was always recovered in large

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \quad \xrightarrow{1. \text{LiNR}_2} \quad \xrightarrow{2. \text{Br}} \\
\text{CO}_2\text{CH}_3 & \quad \text{CO}_2\text{CH}_3
\end{align*}
\]

\(122\)


quantity. The exact reason of this failure is still unclear. However, it was not the problem of the generation of an enolate anion, because in later experimental results (to be discussed in Part IV of this thesis) it was found that the bicyclo[2.2.2]octan-2-one system without the bridgehead substitution could be very effectively alkylated at the 3-position by the above method.

Due to the recent success in the development of organocopper reagents, an investigation of the possibility of applying organocopper reagent to the system was started. The carbon-carbon bond formation by selective coupling of alkylcopper reagents with organic halides was well-known. α-Alkylation of ketones through reactions of α-halo ketones with organocopper reagents has also been reported. For example, α-bromo ketone 130 was alkylated with lithium dimethylcuprate to 63% of ketone 131, and ketone 133 was obtained in 60%


yield from alkylation of the α-chloroketone 132 with lithium diisopropenyl cuprate.

\[
\begin{align*}
\text{CH}_3 & \quad \begin{array}{c}
\text{Cl} \\
\end{array} \\
\text{132} & \quad \begin{array}{c}
\text{CH}_3 \\
\end{array}
\end{align*}
\]

Thus the keto ester 122 was brominated with cupric bromide in refluxing ethyl acetate-chloroform to yield 85% of crystalline methyl 3-bromobicyclo[2.2.2]octan-2-one-1-carboxylate (134). The organocopper lithium reagent was generated by reacting one equivalent of tri-n-


butylphosphine-cuprous iodide with two equivalents of 4-pentenyl lithium (98).

\[
2 \overset{\text{Li}}{\text{Li}} + [(\text{Bu})_3\text{P}] \cdot \text{CuI} \xrightarrow{\text{THF}} \overset{-78^\circ}{(\overset{\text{Li}}{\text{Li}})_2\text{CuLi} \cdot (\text{Bu})_n\text{P}}
\]

It was quite disappointing that reaction of the \( \alpha \)-bromoketone \( 134 \) with the organocopper lithium tri-n-butyl phosphine complex (135) did not give any detectable amounts of the desired product. About 60\% of the starting \( \alpha \)-bromoketone \( 134 \) and 14\% of the reduced keto ester \( 122 \) were recovered.

As a result, it was decided to introduce the first side chain of 122 through the bridgehead carbomethoxy group. Naturally, a similar approach to that used in the synthesis of 1-(6-hydroxyhexyl)bicyclo-[2.2.2]oct-2-ene (57), which was discussed in Part I, was attempted.

The ketone 122 was first protected by treating 122 with ethylene glycol and a catalytic amount of p-toluenesulfonic acid in benzene to give 84% of the ethylene ketal of methyl bicyclo[2.2.2]-octan-2-one-1-carboxylate (136). Basic hydrolysis of 136 provided
122 \[\stackrel{\text{TsOH, Benzene}}{\longrightarrow}\] 136 \[\stackrel{\text{KOH, EtOH, H}_2\text{O}}{\longrightarrow}\] 137

1. Li
2. H\(_2\text{O}\)

140 \[\xleftarrow{\text{MsCl}}\] 139 \[\xleftarrow{\text{LiAlH}_4, \text{Et}_2\text{O}}\] 138
77% of the ethylene ketal of bicyclo[2.2.2]octan-2-one-1-carboxylic acid (137). The acid 137 was treated with two equivalents of 4-pentenyl lithium (98) in ether to give 86% of the 1-(1-oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]octane (138). The ketone 138 was reduced with lithium aluminum hydride in ether to give 85% of the ethylene glycol ketal of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one (139). The hydroxy ketal was treated with mesyl chloride in pyridine to give the corresponding mesylate 140.

Due to extreme steric hindrance, lithium aluminum hydride reduction of the mesylate 140 failed to give the expected hydrocarbon 141, instead
it regenerated the alcohol 139 plus some unidentified side products. Presumably the hydride ion must have attacked the sulfur center instead of the carbon center. Equally unfavorable results were obtained when the mesylate 140 was treated with sodium cyanoborohydride in either dimethyl sulfoxide or hexamethylphosphoramide, and lithium triethylborohydride (super hydride) in tetrahydrofuran. Attempts to deoxygenate the ketone 138 directly to the hydrocarbon 141 by treating 138 with tosylhydrazine and reducing with sodium cyanoborohydride in dimethylformamide-sulfolane (1:1) did not prove to be any better; apparently, due to steric hindrance, the tosylhydrazone could not be formed.

It appeared that an extension of one carbon from the bridgehead of the keto ester 122 was necessary to avoid the problem of steric hindrance.


The keto ester 122 was treated with ethane dithiol and boron trifluoride etherate \(^{67}\) to give an 87% yield of the ethylene thio-ketal of methyl bicyclo[2.2.2]octan-2-one-1-carboxylate (142). Lithium aluminum hydride reduction of 142 provided 90% of the ethylene thio-

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \xrightarrow{\text{HSCH}_2\text{CH}_2\text{SH}} \text{BF}_3\cdot\text{OEt}_2 & \text{CO}_2\text{CH}_3 & \xrightarrow{\text{LiAlH}_4} \text{Et}_2\text{O} & \text{CH}_2\text{OH} & \end{align*}
\]

122 142 143

\[
\begin{align*}
\text{CO}_2\text{CH}_3 & \xrightarrow{\text{TsCl}} \text{(O)} & \end{align*}
\]

144 145 146
ketal of 1-hydroxymethylbicyclo[2.2.2]octan-2-one (143). The hydroxy
thioketal was treated with toluenesulfonyl chloride in pyridine
to give the ethylene thioketal of 1-hydroxymethylbicyclo[2.2.2]-
octan-2-one tosylate (144). Reaction of the tosylate 144 with
sodium cyanide in dimethyl sulfoxide unfortunately did not yield the
desired nitrile 145, instead it gave 44% of a peculiar rearrangement
product, 4,7-dithia-tricyclo[7.2.2.0^3,8]tridec-2-ene (146).

However the nitrile 145 was prepared through an alternative
route as shown in Scheme V. The previously mentioned ethylene ketal
ester 136 was reduced with lithium aluminum hydride in ethyl ether to
give an 88% yield of the ethylene ketal of 1-hydroxymethylbicyclo-
[2.2.2]octan-2-one (147). The hydroxy ketal was hydrolyzed in
benzene with a catalytic amount of toluenesulfonic acid to give 91% of
the 1-hydroxymethylbicyclo[2.2.2]octan-2-one (148), which was
treated with tosyl chloride in pyridine to give a 71% yield of the
tosylate 149. Reaction of the tosylate 149 with sodium cyanide in
dimethyl sulfoxide provided a 71% yield of 1-cyanomethylbicyclo[2.2.2]-
octan-2-one (150). The ethylene thioketal of 1-cyanomethylbicyclo-
[2.2.2]octan-2-one (145) was obtained in 82% yield by treating
compound 150 with the ethanedithiol and boron trifluoride etherate.

(67) L. F. Fieser, J. Amer. Chem. Soc., 76, 1945 (1954); ibid., 75,
4386 (1953).

(68) Ethylene thioketal is used here to protect the ketone because
its resistance to weak acid would be advantageous in our later
synthetic conversions.
The ethylene thiketal $^{145}$ was treated with alkyllithium, 98, in ether, and hydrolyzed in dilute hydrochloric acid to give 78% of the $1$-(2-oxo-6-heptenyl)-2,2-ethylenedithiabicyclo[2.2.2]octane ($^{151}$). Reduction of $^{151}$ with lithium aluminum hydride in ether gave 98% of the $1$-(2-hydroxy-6-heptenyl)-2,2-ethylenedithiabicyclo[2.2.2]octane.
Attempts to prepare a tosylate 153 from the alcohol 152 were not successful. Instead of the tosylate 153, a rearranged product, 8-(4-pentenyl)-4,7-dithiatricyclo[8.2.0.0^3,10]tetradec-2-ene (154), was obtained. The tricyclic compound 154 was believed to arise from the following rearrangement.
In fact a similar rearrangement had been reported by Marshall and Roebke. Attempted conversion of the alcohol 155 into the mesylate 156 afforded only a crystalline product 157 in nearly quantitative yield.

With this unexpected rearrangement, a slightly modified version of the synthetic path, which is shown below, was undertaken.

The previously mentioned hydroxy ketal 147 was treated with p-toluenesulfonyl chloride in pyridine to yield 71% of the tosylate 158, which was reacted with sodium cyanide in dimethyl sulfoxide to give 87% yield of the ethylene ketal of 1-carboxyhydroxymethylbicyclo-[2.2.2]octan-2-one (160). The carboxylic acid 160 was reacted with two equivalents of the organolithium reagent 98 in ether to give a 63% yield of 1-(2-oxo-6-heptenyl)-2,2-ethylenedioxybicyclo[2.2.2]octane (161). The ethylene glycol ketal of 1-(2-hydroxy-6-heptenyl)bicyclo-[2.2.2]octan-2-one (162) was obtained in 90% yield from reduction of
with lithium aluminum hydride in ether. However, the reduction of the alcohol to the corresponding methylene through the tosylate was still very sluggish. The hydrocarbon could only be obtained in low yield (20-30%) with many other side products.

Meantime, the application of two recently developed reagents, the chlorodiethylphosphate and the bis(dimethylamino)phosphorochloridate...
It was reported by Ireland and coworkers that treatment of the alcohol 164 with n-butyllithium in tetrahydrofuran and tetra-

\[
\begin{align*}
&\text{OH} \\
&\text{164} \\
&\text{1. nBuLi, THF, TMEDA} \\
&\text{2. ClPO(OEt)₂} \\
&\text{96%} \\
&\text{165} \\
\end{align*}
\]

methylethylenediamine gave the lithium alkoxide which was reacted with chlorodiethylphosphate to give 96% yield of the phosphate 165. Reduction of the phosphate 165 with lithium in ethylamine gave 82% of the corresponding hydrocarbon 166. Similarly, the alcohol 167 was


(71) The author would like to thank Professor Swenton for his helpful information and discussion on these reagents.
reduced to the hydrocarbon 169 through the bis(dimethylamino)phosphate 1168 in excellent yield.

\[ \text{CH}_2\text{OH} \xrightarrow{\text{l. nBuLi, DME}} \text{CH}_2\text{OP(NMe}_2)_2 \]

\[ 167 \rightarrow 168 \]

\[ \text{Li, EtNH}_2, \text{THF, t-BuOH} \downarrow \text{97%} \]

Thus, these reagents were applied to our system, as shown below. The hydroxy ketal 167 was oxidized with chromium trioxide pyridine complex in methylene chloride to the ethylene glycol ketal of 1-formylbicyclo[2.2.2]octan-2-one (170) in 84% yield. Reaction of the aldehyde 170 with 4-pentenyllithium (98) in ether afforded 95% of the alcohol 139. The alcohol 139 was treated with methyllithium and
chlorodiethylphosphate in a mixed solvent of tetrahydrofuran and
tetramethylethylenediamine (4:1) to give a 95% yield of the diethylphosphate of the ethylene glycol ketal of 1-(1-hydroxy-5-hexenyl)bicyclo-
[2.2.2]octan-2-one (171). Reduction of the phosphate 171 with
lithium in liquid ammonia and tetrahydrofuran only gave a 30 to
40% yield of the hydrocarbon 141. However, when the alcohol 139
was treated with n-butyllithium and bis(dimethylamino)phosphoro-
chloridate in tetrahydrofuran and tetramethylethylenediamine, the
N,N,N',N'-tetramethylphosphorodiamidate of the ethylene ketal of 1-
(1-hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one (172) was obtained in
90% yield. Reduction of 172 with excess lithium in liquid ammonia
and tetrahydrofuran gave 89% of the ethylene glycol ketal of 1-(5-
hexenyl)bicyclo[2.2.2]octan-2-one (141). Hydrolysis of the ketal 141
in aqueous hydrochloric acid and tetrahydrofuran provided an 83% yield
of the desired precursor, 1-(5-hexenyl)bicyclo[2.2.2]octan-2-one (173).

(72) Ireland's procedure could not be applied here because with
excess lithium in ethylamine and t-butyl alcohol, the terminal
olefin was also reduced completely.
PART IV. Approaching the Synthesis of the Inside-Outside Bicyclo-
[8.2.2]tetradodecane System.

After succeeding in the synthesis of 1-(5-hexenyl)bicyclo[2.2.2]-
octan-2-one (173), the problem of introducing a second side chain
on compound 173 was studied. As mentioned in Part III of this dis-
cussion, the failure to alkylate at the alpha position of the ketone
122 was a problem. However, the same alkylation condition as had

![Chemical Structure](image)

122

been used for converting 122 into 173, proceeded unbelievably smoothly.
1-(5-Hexenyl)-3-(2-propenyl)bicyclo[2.2.2]octan-2-one (174) was
obtained in 81% yield from the reaction of ketone 173 with lithium
diisopropylamide and allyl bromide in tetrahydrofuran.

It was now necessary to build the fourth ring by connecting the
two side chains in 174. The use of the acyloin condensation for the
closure of medium size rings (8-11 members) still represents the
the method of choice and practically the only choice in most cases. Acyloin condensation became even more reliable when chlorotrimethylsilane was introduced to enable the isolation of the intermediate endiols as trimethylsilyl ether derivatives. Application of the acyloin condensation for the ring closure of 174 required that the terminal olefins in 174 be transformed into esters. This could be done by either converting the olefins to primary alcohols with subsequent oxidation and esterification to the diester, or simply by oxidative cleavage of the olefins to carboxylic acids followed by esterification to the esters. The diester from the former method would eventually lead to a twelve membered ring, whereas diester from


the latter method would cyclize to a ten-membered ring. Since the smallest possible ring was desired, the second path was chosen.

Before starting to cleave the olefins of 174, the protection of the carbonyl was required because it would be unwise to expose the carbonyl during the ring closure step of the acyloin condensation. There were two pathways which could be used. Either protect the ketone before cleaving the double bonds, or vice versa. Theoretically, it did not seem to make any difference. In reality, it was learned that there was a great difference.

Compound 174 was first ozonized in methanol and treated with methanolic sodium iodide solution to give the dialdehyde, which was oxidized with Jones reagent to the dicarboxylic acid. After treatment with diazomethane, the dicarboxylic acid was converted to 83% of 1-(5-carboxymethoxypentyl)-3-(2-carboxymethoxethyl) bicyclo[2.2.2]octan-2-one (175). However, an attempt to protect the ketone in 175 as the ethylene glycol ketal was not successful at this stage because the carbonyl was extremely hindered, and high reaction temperatures and long reaction times, which was necessary for the ketalization only led to ester exchange and polymerization. However, when compound 174 was treated with ethylene glycol and a catalytic amount of toluenesulfonic acid in refluxing toluene for three days, it gave 80% of the ethylene glycol ketal of 1-(5-hexenyl)-3-(2-propenyl)bicyclo[2.2.2]octan-2-one (176). Oxidative cleavage of the terminal olefins in 176 with ruthenium tetroxide and sodium metaperiodate in carbon tetrachloride and acetone
gave the dicarboxylic acid, which was treated with diazomethane to give an 80% yield of the ethylene ketal of 1-(5-carbomethoxypentyl)-3-(2-carbomethoxyethyl)bicyclo[2.2.2]octan-2-one (177).
The acyloin condensation of the ketal diester 177 was accomplished by reacting 177 with sodium and chlorotrimethylsilane in refluxing toluene to give about 70-80% of the ethylene ketal of 4,5-bis(trimethylsilyloxy)tricyclo[8.2.2.12,10]pentadec-4-en-15-one (178).

Attempts to convert the bis(trimethylsilyl)ether 178 to its corresponding acyloin by refluxing in methanol or treatment with various alkyllithium reagents in glyme were all unsuccessful. However, by applying a recently developed procedure, the acyloin 179 was obtained in about 50 to 60% yield simply by treating 178 with six equivalents of potassium t-butoxide and four equivalents of potassium hydroxide in tetrahydrofuran at room temperature.

(75) P. G. Gassman, unpublished experimental result.
In order to remove the acyloan, compound 179 was heated with hydrazine and potassium hydroxide in diethylene glycol. The result was quite discouraging; less than 10% of the desired Wolff-Kishner elimination product 180 was obtained plus more than five unidentified side products including starting material.

However compound 179 was reduced with lithium aluminum hydride in refluxing tetrahydrofuran to the diol 181, which on treatment

with $n$-butyllithium and bis(dimethylamino)chlorophosphoridate, followed by reduction with lithium in ethylamine should provide the corresponding hydrocarbon $182$. A few subsequent transformations would lead to the desired inside-outside bicyclo[8.2.2]system as shown below.

\[
\begin{align*}
1. \text{nBuLi, THF, TMEDA} \\
2. \text{ClOP(Me}_2) \\
3. \text{Li, EtNH}_2 \\
\text{tO}_H
\end{align*}
\]
EXPERIMENTAL

Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. Melting points and boiling points are uncorrected. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord or Model 457 Grating Infrared Spectrometer as neat liquids, solutions, or powdered solids in potassium bromide discs. Nuclear magnetic resonance spectra were obtained on Varian Associates A-60, A-60A, or Jeolco MH-100 spectrometers and reported in tau (τ) units relative to tetramethylsilane (τ = 10.00) as the internal standard. Exact mass determinations were obtained on an AEI MS-9 High Resolution Mass Spectrometer.

2-Hydroxybicyclo[2.2.2]octane (68). A 1.4 ml sample of diborane in tetrahydrofuran solution (1.1 N) was added dropwise to a solution of 1.0 g (9.25 mmol) of bicyclo-[2.2.2]oct-2-ene in 10 ml of tetrahydrofuran at 0°C. After the reaction mixture was stirred at room temperature for 24 hrs, a 1.6 ml sample of 3 N aqueous sodium hydroxide was added slowly, followed by 1.6 ml of 30% aqueous hydrogen peroxide. The mixture was poured into 50 ml of cold water and the
aqueous solution was extracted four times with 50-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give a white solid, which was re-crystallized from pentane-ether to give 1.05 g (90%) of white crystals, mp 210-212° [lit 77 mp 210°]; ir (KBr) 2.98, 3.34, and 9.71 μ; nmr (CDCl₃), δ 9.00-7.70 (13H, m) and 6.25-5.80 (1H, broad m).

Bicyclo[2.2.2]octan-2-one (69). Chromium trioxide (19 g, 0.19 mole) was added to a well stirred solution of pyridine (30 g) in 300 ml of methylene chloride. The deep burgundy solution was stirred at room temperature for 15 min, and then 4.0 g (31.7 mmol) of 2-hydroxy-bicyclo[2.2.2]octane was added. The reaction mixture was stirred for 12 hr. The methylene chloride solution was decanted, and the residue was rinsed with 200 ml of methylene chloride. The combined methylene chloride solution was washed with 200 ml of 3% aqueous hydrochloric acid solution, two times with 200-ml portions of 10% aqueous sodium hydroxide, and with 200 ml of saturated sodium chloride solution.

The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated to give a crude brownish solid, which was sublimed at

80° (0.1 mm) to give 3.5 g (89%) of white crystals, mp 174° [lit mp 176°]; ir (KBr) 3.34 and 5.78 μ (ν= 0); nmr (CDCl₃), τ 8.30 (8H, broad s) and 7.85 (4H, broad s).

Bicyclo[2.2.2]octan-2,3-dione (70). A 1.8 g (16.2 mmol) sample of selenium dioxide in a solution of 18 ml of dioxane and 1 ml of water was brought to reflux for 30 min. To this well-stirred refluxing mixture was added at once a solution of 2.0 g (16.1 mmol) of bicyclo-[2.2.2]octan-2-one in 2 ml of dioxane. The reaction mixture was allowed to reflux for 4 hrs. During this period, black precipitates appeared gradually, and finally the brown yellow solution became clear. The reaction mixture was cooled down to room temperature, filtered, and the filtrate was poured into 50 ml of cold water. The aqueous solution was extracted five times with 30 ml portions of ether. The organic layers were washed with 30 ml of 5% aqueous sodium bicarbonate solution, and 50 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give 2.1 g of brown yellow solid, which was chromatographed on 50 g of 60-200 mesh silica gel with 20% ether-pentane as solvent to give 1.05 g

(47\%) of yellow crystal, mp 168-170° [lit mp 168°]; ir (KBr), 3.34, 5.71, 5.78, 6.80, 6.90, 8.00, and 10.99 μ; nmr (CDCl₃), τ 8.00 (8H, m) and 7.30 (2H, m).

Bicyclo[3.2.2]nonan-2,4-dione (71). Into a 20 ml of a solution of 0.1 M diazomethane in ether solution at 0°, was added 200 mg (1.45 mmol) of bicyclo[2.2.2]octan-2,3-dione. The solution was maintained at 0° for 4 hr while nitrogen evolved. The reaction mixture was allowed to stand at room temperature overnight. The solvent and excess diazomethane were evaporated at reduced pressure. The thick oily residue was heated on the steam bath with 5 ml of hydrochloric acid (4N) for 4 hr. The aqueous solution was extracted four times with 30 ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated to give a thick yellowish oil, which was then sublimed at 100° (0.23 mm) to give 80 mg of a white solid, mp 165-172°. This was recrystallized from benzene-petroleum ether to give 75 mg (34\%) of needle-shaped crystals, mp 172-174°; ir (CHCl₃), 2.85-4.17 (broad), 5.81, 5.94, and 6.25 μ; nmr (CDCl₃), τ 8.15 (8H, m), 7.28 (2H, br), and 6.48 (2H, s).

Anal. Calcd for C₉H₁₂O₂: C, 71.03; H, 7.95.  
Found: C, 70.90; H, 8.12.

1-N,N-Diethylaminobutadiene (73). A 290 g (4.15 mol) sample of diethyl-amine and 80 g of potassium carbonate was allowed to react with 140 g (2 moles) of freshly distilled crotonaldehyde in 200 ml of benzene at -5° to -10° for one hour. The mixture was allowed to stand at room temperature for 6 hr. The solution was decanted from the potassium carbonate. A 1.2 g sample of hydroquinone was added to the clear solution, which was condensed under reduced pressure. The remaining golden oil was fractionated with a one-foot Vigreux column. Approximately 105 g (42%) of pure product was collected, bp 70-72° (35-40 mm) [lit 64-66° (10 mm)]; ir (film), 3.34, 6.10, and 11.9 μ; nmr (CCl₄), δ 8.90 (6H, t), 7.92 (4H, q), 5.35 (3H, m), and 3.82 (2H, m).

Ethyl-2-diethylamino-3-cyclohexene-1-carboxylate (74). A solution of 75 g (0.6 mol) of freshly distilled 1-diethylaminobutadiene in 145 ml of dry benzene was allowed to react with 96.7 ml of freshly distilled ethyl acrylate at room temperature

(80) Siegfried Hunig and Herbert Kahanek, Chem. Ber., 90, 238 (1957); See also C.A., 51, 12049f (1957).
in the dark for six days. The reaction mixture was acidified with 2N aqueous hydrochloric acid solution and extracted with two 200-ml portions of ethyl ether. The aqueous solution was neutralized with aqueous sodium hydroxide solution. A layer of golden oil appeared, which was isolated by extracting with ethyl ether. The ethereal solution was dried over anhydrous sodium sulfate and filtered. After removing the solvent under reduced pressure, the residual oil was vacuum distilled to give a 98g (71%) of light yellow liquid, bp 63-64° (0.06-0.07 mm) [lit 80-83° (0.2 mm)]; ir (film), 3.34, 5.75, 8.70, and 9.62 μ; nmr (CDCl₃), T 9.04 (6H, t), 8.75 (5H, t), 8.10 (4H, m), 7.70-7.30 (4H, 2 quartets), 7.30 (1H, m), 6.40 (1H, m), 5.90 (2H, q), and 4.20 (2H, m).

**Ethyl 1,3-cyclohexadiene-1-carboxylate (75).** A slow stream of hydrogen chloride was passed into a mixture of 110 g (0.49 mole) of ethyl-2-diethylamino-3-cyclohexene-1-carboxylate in 400 ml of absolute ethanol until the solution was acidic to pH paper. The acidic solution was first distilled at atmospheric pressure to remove the ethanol, and then heated up to 170-180° for 2 hr. A colorless oil was then distilled at 130-135° (45 mm). At the end of the distillation, the temperature was elevated to 190-195° (20 mm) for a very short time. The distillate was diluted with 200 ml of ether and the organic layer was washed twice with 2% aqueous hydrochloric acid solution, once with
water, and once with brine. After drying over anhydrous sodium sulfate and filtration, the solvent was removed in vacuo and the residue was distilled to give 50.5 g (68%) of a colorless liquid, bp 105-106° (30 mm) [lit 90-92° (11 mm)]; ir (film), 3.28, 3.34, 5.88, 6.10, 6.33, 7.93, 8.13, 9.35, and 14.49 μ; nmr (CCl₄), τ 8.75 (3H, t), 7.70 (4H, m), 5.87 (2H, q), 3.98 (2H, m), and 6.88 (1H, m).

1-Carboethoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (76). A mixture of 33.2 g (0.34 mole) of maleic anhydride and 49 g (0.322 mole) of ethyl 1,3-cyclohexadiene-1-carboxylate was stirred at 100° for 30 min, and at 170-175° for 40 min. After cooling to room temperature, the crude solid was recrystallized twice from benzene-petroleum ether (low boiling) solvent. After drying in a vacuum oven (40°) for 2 days, the product weighted 75 g (93%), mp 85-86° [lit 86.5-87°]; ir (KBr), 3.34, 5.18, 5.62, 5.78, 8.13, 9.26, 13.51, and 14.28 μ; nmr (CCl₄), τ 8.63 (3H, t), 8.80-7.90 (4H, m), 6.78 (2H, m), 6.30 (1H, d), 5.68 (2H, q), and 3.50 (2H, m).

1-Carboethoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid anhydride (79).

A solution of 36 g (0.144 mole) of 1-carboethoxybicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride in 100 ml of tetrahydrofuran and 250 mg of platinum oxide was hydrogenated at 60 lb pressure. After a drop of 13 lb of pressure, the reaction was complete. The solution was filtered through Celite. After removal of the solvent in vacuo, the crude solid residue was crystallized from benzene-petroleum ether.

This gave 36.5 g (95%) of product as white crystals, mp 81-82.5° \[^{81}\text{lit mp} 82.5-83.0°\]; ir (KBr), 3.39, 5.40, 5.62, 5.81, 8.00, 9.35, and 10.87 μ; nmr (CDCl₃), τ 8.70 (3H, t), 8.50-8.00 (8H, br s), 6.74 (1H, dd), 6.26 (1H, d), and 5.75 (2H, q).

1-Carboethoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid (80). A 67 g (0.266 mole) sample of 1-carboethoxybicyclo[2.2.2]octan-2,3-dicarboxylic acid anhydride was heated on a steam bath with 266 ml of 20% potassium bicarbonate solution until a completely clear solution was obtained. The solution was acidified with 56 ml of concentrated hydrochloric acid. The precipitated white solid was collected by filtration and recrystallized from acetone-water solution. The product was dried in a
vacuum oven (60°) for 3 days. A 69.9 g (91%) yield of the dicarboxylic acid was obtained, mp 132-143° [lit mp 135-147°]; ir (KBr), 3.12-4.00 (broad), 5.74, 5.81, 8.00, and 8.20 μ.

1-Carboethoxybicyclo[2.2.2]oct-2-ene (72). A mixture of 5.4 g (0.2 mole) of 1-carboethoxybicyclo[2.2.2]octane-2,3-dicarboxylic acid and 31.6 g (0.4 mole) of pyridine in 400 ml dry benzene was reacted with 96 g (0.2 mole) of lead tetraacetate. The mixture was heated on a steam bath until carbon dioxide started to evolve. It was allowed to stay at room temperature for 24 hr. The precipitated lead acetate was removed by filtration, and the filtrate was washed successively with water, 2N aqueous hydrochloric acid, and water. After drying over anhydrous sodium sulfate and filtration, the solvent was removed in vacuo. The oily residue was distilled through a one-foot Vigreux column to give 19.78 g (55%) of colorless product, bp 84-85° (2.4 mm) [lit bp 95-96° (10 mm)]; ir (film), 3.40, 5.77, 6.25, 8.13, 9.43, 13.42, and 14.43 μ; nmr (CCl4), τ 8.76 (3H, t), 9.00-8.00 (8H, m), 5.87 (2H, q), and 3.70 (2H, m).

l-Hydroxymethylbicyclo[2.2.2]oct-2-ene (§2). In a 250-ml, 3-necked, round-bottomed flask, equipped with mechanical stirrer and condenser, was placed a slurry of 2.4 g (0.063 mole) of lithium aluminum hydride in 100 ml of anhydrous ether. A 15 g (0.083 mole) sample of l-carboethoxybicyclo[2.2.2]oct-2-ene in 30 ml of ether was added drop-wise while the reaction mixture was stirred in an ice bath. The reaction was allowed to stir overnight at room temperature. To the reaction mixture was then slowly added 2.4 ml of water, 2.4 ml of 15% aqueous sodium hydroxide solution, and 7.2 ml of water, successively. The white precipitates were removed by filtration, and washed with 50 ml of ether. The combined ether solution was dried over anhydrous magnesium sulfate and filtered. After the solvent was removed in vacuo, the oily residue was distilled to give 9.9 g (86%) of a very viscous colorless liquid, bp 84-85° (2.6 mm) [lit bp 104° (10 mm)]; n_D^21 1.5092; ir (film), 2.94, 3.29, 3.45, 6.21, 9.52, and 14.49 μ; nmr (CDCl_3), τ 8.75 (8H, m), 7.50 (1H, br), 7.25 (1H, s), 6.45 (2H, s), and 3.80 (2H, m).


1-Hydroxymethylbicyclo[2.2.2]oct-2-ene tosylate (83). A 4.0 g (29 mmole) sample of 1-hydroxymethylbicyclo[2.2.2]oct-2-ene in 40 ml of dry pyridine was treated with 6 g (31.6 mmole) of p-toluenesulfonyl chloride at room temperature for 48 hr. The mixture was poured into 100 ml of cold 3% aqueous hydrochloric acid solution. A solid soon precipitated, which was isolated by extraction with four 50-ml portions of ether. The combined ether extracts were washed with 50 ml of 3% aqueous hydrochloric acid, 50 ml of 10% sodium carbonate solution, and 50 ml of saturated sodium chloride solution, dried over anhydrous sodium sulfate, and filtered. After removal of solvent under reduced pressure, 8.2 g of crude solid remained. This was recrystallized from ether-petroleum ether to give 8.0 g (94%) of white crystals, mp 95-96° [lit mp 94.5-96°]; ir (KBr), 3.23, 3.34, 6.02, 6.78, 7.41, 7.75, 10.53, 12.05, 12.35, 12.66, and 14.49 μ; nmr (CDCl3), ν 9.00-8.30 (8H, m), 7.55 (3H, s), 7.65, 7.35 (1H, br), 6.05 (2H, s), 3.90-3.35 (2H, m), and 2.60-1.90 (4H, dd).

1-Bromomethylbicyclo[2.2.2]oct-2-ene (84). A 10 g (0.34 mole) sample of 1-hydroxymethylbicyclo[2.2.2]-oct-2-ene tosylate and 17.6 g (0.17 mole) of sodium bromide was dissolved in 200 ml of dimethyl sulfoxide. The mixture was heated on the steam
bath for 2 days and then allowed to stand at room temperature for 3 days. The reaction mixture was poured into 300 ml of cold water. The aqueous solution was extracted with four 100-ml portions of pentane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude oily residue was distilled to give 6.0 g (88%) of colorless bromide, bp 71-73° (2.8 mm); ir (film), 3.28, 3.39, 3.48, 8.06, 8.13, and 14.49 μ; nmr (CDCl₃), 7 8.90-8.20 (8H, m), 7.50 (1H, br), 6.60 (2H, s), and 3.90 (2H, m).

Anal. Calcd for C₉H₁₃Br: C, 53.75; H, 6.52; Br, 39.73.
Found: C, 53.75; H, 6.66; Br, 39.37.

Bicyclo[2.2.2]oct-2-ene-1-carboxylic acid (86). 1-Carboethoxybicyclo-[2.2.2]oct-2-ene (4 g, 0.022 mole) was dissolved in a solution of 2.5 g of potassium hydroxide in 2.5 ml of water and 15 ml of methanol. The reaction mixture was heated at reflux on a steam bath for 4 hr, and then poured into 50 ml of ice water. The aqueous solution was acidified with concentrated hydrochloric acid. The separated organic layer was extracted three times with 100-ml portions of ether. The combined ether extracts were washed with 50 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent in vacuo gave 3.5 g of a crude solid (mp 85-101°), which was sublimed at 70° (0.5-0.6 mm) to give 3.2 g (96%) of pure
product, mp 110-114°; ir (KBr), 2.86, 3.34, 3.57 (broad), 5.80, 7.00, 7.57, 10.53, and 14.29 μ; nmr (CDCl₃), τ 8.90-7.90 (8H, m), 7.45 (1H, m), 3.70 (2H, m), and -1.85 (1H, s).

Anal. Calcd for C₉H₁₂O₂: C, 71.02; H, 7.95.

Found: C, 70.85; H, 8.18.

Bicyclo[2.2.2]oct-2-ene-1-carboxylic acid chloride (87). A 1.88 g (15.8 mmol) sample of distilled thionyl chloride was added to 2 g (13.2 mmol) of bicyclo[2.2.2]oct-2-ene-1-carboxylic acid. The reaction mixture was stirred at room temperature for 6 hr and distilled at reduced pressure (35-40 mm) to remove excess thionyl chloride. The remaining oil was vacuum distilled to give 2.0 g (89%) of a colorless acid chloride, bp 75-76° (2.8 mm); nD 1.5055; ir (film), 3.22, 3.34, 5.48, 10.87, 12.50 and 14.49 μ; nmr (CDCl₃) τ 9.00-7.80 (8H, m), 7.35 (1H, m), and 3.65 (2H, m).

1-Carbomethoxymethylbicyclo[2.2.2]oct-2-ene (88). To about 0.25 moles of an ice cold ether solution of diazomethane, prepared from N-nitrosomethylurea, was added 9 g (52.5 mmol) of bicyclo[2.2.2]oct-2-ene-1-carboxylic acid chloride. After standing overnight, the solvent
and excess diazomethane was removed under reduced pressure to give a yellow solid α-diazoketone, which was not purified, but immediately placed into a flask with 60 ml of absolute methanol. To this well stirred diazoketone solution, 15 ml of catalyst prepared from 1.5 g of silver benzoate and 15 ml of triethylamine (distilled from barium oxide) was added slowly at room temperature. Nitrogen evolved immediately and the reaction was complete in about 2 hr. The resulting dark reaction mixture was filtered through Celite, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in 200 ml of ether and washed with 100 ml of water and with 50 ml of saturated sodium chloride solution, dried over sodium sulfate, filtered, and the filtrate was evaporated to give a yellow oil, which was vacuum distilled to give 7.7 g (82%) of a colorless ester, bp 96.5-98.5° (4.4 mm); $n_D^{25.6}$ 1.4803; ir (neat), 3.28, 3.39, 5.75, 7.00, 8.00, 8.27, 8.51, 8.77, and 14.39 μ; nmr (CDCl$_3$), τ 9.00-8.30 (8H, m), 7.60 (2H, s), 7.50 (1H, br), 6.38 (3H, s), and 3.80 (2H, m).

**Anal.** Calcd for C$_{11}$H$_{16}$O$_2$: C, 73.30; H, 8.95.

**Found:** C, 73.05; H, 8.97.

1-Cyanomethylbicyclo[2.2.2]oct-2-ene (89). A mixture of 11 g (37.6 mmol) of 1-hydroxymethylbicyclo-

\[
\text{CH}_2\text{CN}
\]

[2.2.2]oct-2-ene tosylate and 9.2 g (188 mmol) of sodium cyanide in 200 ml of dry dimethyl sulfoxide was heated on the steam bath for 4 days.
The reaction mixture was poured into three times its volume of ice water, and the aqueous solution was extracted with four times of 100 ml portions of pentane. The combined pentane extracts were washed once with 100 ml of 20% ferrous sulfate solution, once with 100 ml of water, and once with 100 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed to give a crude oily solid (5.8 g). Sublimation of the crude solid at 30° (0.1 mm) gave 5.2 g (94%) of colorless crystals, mp 31-33°; ir (CHCl₃), 3.28, 3.34, 3.39, 4.44 (C=O), 6.15, and 14.49 μ; nmr (CDCl₃), τ 8.55 (8H, m), 7.55 (2H, s), 7.45 (1H, br), and 4.20-3.40 (2H, m).


Found: C, 81.42; H, 8.93; N, 9.55.

α-Bicyclo[2.2.2]oct-2-enyl acetic acid (20). A mixture of 1-cyano-
methylbicyclo[2.2.2]oct-2-ene (2 g, 13.6 mmol) and potassium hydroxide (5 g) in 20 ml of ethylene glycol was heated at 170° for 2 days. The mixture was poured into 100 ml of cold water and extracted with two 50-ml portions of ethyl ether to remove any unreacted starting compound or organic impurity. The resulting aqueous layer was acidified with 6 N hydrochloric acid. The acidic aqueous solution was extracted with three 50-ml portions of ethyl ether. The organic layer
was dried over anhydrous sodium sulfate, and filtered. After removal of
the solvent under reduced pressure, the solid residue was sublimed at
30-40° (2.5 mm) to give 1.92 g (85%) of product, mp 58-60°; ir (KBr),
2.86-4.00 (broad), 5.88, 6.94, 7.14, 10.58, and 14.39 μ; nmr (CDCl₃),
τ 8.80-8.10 (8H, m), 7.60 (2H, s), 7.50 (1H, br), 2.80 (2H, m), and
-1.25 (1H, s).

**Anal.** Calcd for C₁₀H₁₄O₂: C, 72.26; H, 8.49.

Found: C, 72.30; H, 8.53.

l-(2-Hydroxyethyl)bicyclo[2.2.2]oct-2-ene (91). A sample of 7.36 g
(40.9 mmol) of the ester (88) was
added dropwise into an ice cold
solution of 1.55 g of lithium
aluminum hydride in 100 ml of dry
ether. After the addition of the
methyl ester, the reaction mixture
was allowed to remain at room temperature for 12 hr. The resulting
complex was hydrolyzed by slowly adding 1.55 ml of water, followed by
1.55 ml of 15% aqueous sodium hydroxide solution, and 4.65 ml of water.
The white inorganic precipitates were removed by filtration, and the
filtrate was dried over anhydrous sodium sulfate. After filtration and
removal of solvent, the viscous oil was vacuum distilled to give 6.2 g
(98%) of a colorless oil, bp 110-112° (4.3 mm); nD²⁵ 1.5030; ir (neat),
2.98, 3.28, 3.36, 9.62, and 14.49 μ; nmr (CDCl₃), τ 9.00-8.30 (8H, m),
8.28 (2H, t), 7.90 (1H, s), 7.50 (1H, br), 6.25 (2H, t), and 3.85 (2H, m).

**Anal.** Calcd for C₁₀H₁₆O: C, 78.90; H, 10.59.

Found: C, 78.74; H, 10.65.
1-(2-Chloroethyl)bicyclo[2.2.2]oct-2-ene (22). A mixture of 5.8 g (3.81 mmol) of 1-(2-hydroxyethyl)bicyclo[2.2.2]oct-2-ene and 8.0 g (42 mmol) of p-toluenesulfonyl chloride in 50 ml of dry pyridine was allowed to react at 0° for 48 hr. The reaction mixture was then poured into 200 ml of cold water, and the aqueous solution was extracted four times with 50-ml portions of ether. The combined ether layers were washed with 50 ml of 5% aqueous hydrochloric acid, 50 ml of water, and 50 ml of brine, dried over anhydrous sodium sulfate, and filtered. After removal of solvent in vacuo, 5.0 g of crude tosylate was obtained. This crude tosylate was dissolved in a solution of sodium chloride (15 g) in 100 ml of dry dimethyl sulfoxide. The reaction mixture was stirred at room temperature for 24 hr, and poured into 200 ml of cold water. The aqueous solution was extracted four times with 50-ml portions of pentane. The organic layers were dried over anhydrous sodium sulfate, and filtered. After removal of pentane under reduced pressure, the residue was vacuum distilled to give 2.54 g (39% based on the starting alcohol) of colorless product, bp 89-91° (4.1 mm). An analytical sample was collected from a preparative vpc (10% FS-1265 on Chrom W, t = 120°), nD22.3 1.5034; ir (film), 3.28, 3.39, 3.46, 6.90, 13.33, and 14.49 μ; nmr (CDCl3), τ 9.00-8.20 (8H, m), 8.10 (2H, m), 7.50 (1H, br), 6.40 (2H, m), and 3.85 (2H, m).

Anal. Calcd for C10H15Cl: C, 70.37; H, 8.86; Cl, 20.77.

Found: C, 70.46; H, 8.90; Cl, 20.64.
Benzyl 5-Bromopentyl Ether (85). Benzyl alcohol (32.4 g, 0.3 mol) was added dropwise to a flask containing sodium metal (7.1 g, 0.31 mol) in dry dimethoxyethane (250 ml). The reaction mixture was refluxed at 80° for 24 hr. Then 98 g (0.3 mol) of 1,5-dibromopentane was added very carefully, and the reaction mixture was refluxed for 24 hr. It was then poured into one liter of ice water and extracted four times with 200-ml portions of pentane. The pentane extracts were dried over anhydrous magnesium sulfate, filtered, and condensed. The resulting crude oil was fractionated through a one-foot Vigreux column to give 35.65 g (46%) of colorless product, bp 100-103° (0.07 mm); n_D^24 1.5240 [lit bp 105-109° (0.15 mm)]; ir (film), 3.28, 3.39, 6.25, 9.09, 13.61, and 14.49 μ; nmr (CDCl_3), δ 8.70-7.85 (6H, m), 6.65 (4H, m), 5.58 (2H, s), and 2.79 (5H, s).

4-Benzylxyloxy-1-butanol (92). Sodium hydride (57% in mineral oil, 21 g, 0.5 mole) was added in small batches to excess 1,4-butanediol (90 g, 1 mol) covered with a layer of 200 ml of dry benzene. After the addition was completed, the reaction mixture was refluxed for

4 hr, and benzyl chloride (63.3 g, 0.5 mol) was added slowly and reflux was continued for 18 hr. The solution was cooled, 500 ml of water was added, and the resultant mixture was extracted four times with 300-ml portions of ether. The ether extracts were washed with 200 ml of water and 200 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure. The resultant viscous oil was vacuum distilled to give the product (59.5 g, 66%) as a colorless oil, bp 100-105° (0.3 mm) [lit bp 95-105° (0.5 mm)], \(n_d^{25.5} = 1.5093\); ir (neat), 2.94, 3.28, 3.39, 9.17, 13.61, and 14.39 \(\mu\); nmr (CDCl₃), 8 8.40 (4H, m), 7.10-6.30 (5H, m), 5.59 (2H, s), and 2.80 (5H, s).

4-Benzylloxybutyric acid (94). Jones reagent (40 ml, 8N) was added dropwise to an ice cold solution of 18 g (0.1 mol) of 4-benzylloxybutanol in 500 ml of acetone. After the addition of the Jones reagent, the reaction mixture was poured into 2 l of cold water and the aqueous solution was extracted four times with 500-ml portions of ether. The combined ethereal solutions were washed with 200 ml of saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solution was filtered and the ether solvent was removed.

under reduced pressure. The oily residue was vacuum distilled to give
13.05 g (67%) of pure acid, bp 132-134° (0.12 mm) [lit bp 133-134°
(0.5 mm)], n^25_D 1.5091; ir (neat), 2.86-4.00 (broad), 5.88, 9.09,
13.51, and 13.39 μ; nmr (CDCl₃), τ 8.10 (2H, m), 7.55 (2H, t, J =
6 Hz), 6.53 (2H, t, J = 6 Hz), 5.58 (2H, s), 2.80 (5H, s), and -0.95
(1H, s).

5-Bromo-1-pentene (97). Into a suspension of 23 g (0.205 mole) of
potassium t-butoxide in 400 ml of
anhydrous ether at 0°, a 46 g
(0.2 M) of 1,5-dibromopentane was
added in one portion. The reaction
mixture was stirred for 12 hr,
and poured into 500 ml of cold
water. The organic layer was separated and the aqueous layer was
extracted twice with 150-ml portions of ether. The combined ether
layers were dried over anhydrous magnesium sulfate and filtered.
The filtrate was fractionally distilled through a one-foot packed
helix glass column. A 10.4 g (35% yield) sample of pure bromide was
collected, bp 124-127° (760 mm); n^23_D 1.4590 [lit bp 126-129°; n^20_D
1.4640]; ir (neat), 3.21, 3.38, 6.09, and 10.91 μ; nmr (CDCl₃), τ
8.50-7.50 (4H, m), 6.63 (2H, t), 5.12-4.70 (2H, m), and 4.50-3.80
(1H, m).

(87) V. N. Drozd, Y. A. Ustynyuk, M. A. Tsel'eva, and L. B. Dmitriew,
1-(2-Oxo-5-hexenyl)bicyclo[2.2.2]oct-2-ene (99). Into a 3-necked, round-bottomed flask equipped with mechanical stirrer, condenser, and argon gas inlet, was placed a solution of 44 g (296 mmole) of 5-bromo-1-pentene in 150 ml of dry ether. To this well-stirred solution (cooled at -20°) was added slowly 4.15 g (0.592 mole) of lithium wire (containing 1% of sodium) in small pieces. After about one hr, the reaction subsided, and the purple alkylaluminium solution was transferred through a thin intrametic plastic tube (by applying an argon gas pressure) into another 3-necked flask containing a solution of 15 g (98.5 mmole) of the carboxylic acid (86) in 100 ml of dry ether at 0°. After the addition of the alkylaluminium, the reaction mixture was stirred at room temperature for 48 hr, and it was poured as slow as possible into a liter of vigorously stirred ice-water. The aqueous solution was extracted four times with 200-ml portions of ether. The combined ether extracts were washed with 200 ml of 10% sodium bicarbonate solution and 200 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give a light yellow oil, which was vacuum distilled to give 15.66 g (78%) of a colorless oil, bp 95-98° (0.25 mm); n^23.6 1.4969; ir (neat), 3.28, 3.39, 5.85 (C=O), 6.10, 10.99, and 14.49 μ; nmr (CDCl₃), 7.89-7.70 (12H, m), 7.40 (2H, t), 7.60-7.20 (1H, br), 5.00 (2H, m), 4.60-3.90 (1H, m), and 3.70 (2H, m).
A nal. Calcd for C_{14}H_{20}O: C, 82.30; H, 9.87.

Found: C, 82.05; H, 9.97.

1-(1-Hydroxy-5-hexenyl)bicyclo[2.2.2]oct-2-ene (100). Into a flask containing a suspension of 3 g (79 mmole) of lithium aluminum hydride in 500 ml of dry ether, 15.6 g (76.4 mmole) of 1-(2-oxo-5-hexenyl)bicyclo[2.2.2]oct-2-ene was added dropwise at 0°. After the addition, the reaction mixture was stirred at room temperature for 18 hr. It was then hydrolyzed by successive addition of 3 ml of water, 3 ml of 15% aqueous sodium hydroxide solution, and 9 ml of water. The white solid precipitates were collected by filtration, and the ether filtrate was dried over anhydrous magnesium sulfate, filtered, and the solvent was evaporated to give a thick oil, which was vacuum distilled to give 14.11 g (90%) of the alcohol, bp 97-99° (0.3 mm), n_d^20 1.5036; ir (neat), 2.90, 3.28, 3.34, 6.10, 10.99, and 14.49 μ; nmr (CDCl_3), δ 9.00-8.15 (12H, m), 7.95 (2H, br), 7.50 (1H, br), 6.55 (1H, m), 5.00 (2H, m), and 4.70-3.60 (3H, m).

A nal. Calcd for C_{14}H_{22}O: C, 81.50; H, 10.75.

Found: C, 81.24; H, 10.74.

1-(5-Hexenyl)bicyclo[2.2.2]oct-2-ene (102). Into a solution of 5 g (24.2 mmol) of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]oct-2-ene in 40 ml of dry pyridine at 0°, 3.06 g (26.6 mmol) of methanesulfonyl
chloride was added slowly. The reaction mixture remained at 0° for 8 hr. It was then poured into one liter of ice-cold 5% aqueous hydrochloric acid. The aqueous solution was extracted four times with 200 ml portions of ether. The combined ether extracts were washed with 100 ml of saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and the solvent was removed in vacuo to give 7.35 g of crude oily mesylate. This crude mesylate was added slowly into a suspension of 0.91 g (24 mmol) of lithium aluminum hydride in 150 ml of dry ether. The reaction was stirred at room temperature for 24 hr, and then hydrolyzed by the successive addition of 0.91 ml of water, 0.91 ml of 15% aqueous sodium hydroxide solution, and 2.73 ml of water. The white precipitates were removed by filtration and the ethereal filtrate was dried over anhydrous magnesium sulfate, filtered, and evaporated to give an oil which was vacuum distilled to give 3.41 g (75%) of a colorless liquid, bp 108-109° (3.5-3.6 mm); nD^25 1.4873; ir (film), 3.28, 3.34, 6.10, 6.89, 10.10, 10.64, 10.99, and 14.49 μ; nmr (CDCl₃), τ 9.10-8.30 (14H, m), 8.20-7.80 (2H, m), 7.55 (1H, br), 5.10 (2H, m), and 4.70-3.60 (3H, m).


Found: C, 88.31; H, 11.57.
1-(6-Hydroxyhexyl)bicyclo[2.2.2]oct-2-ene (57). Into a mixture of 0.81 g (11.6 mmole) of 2-methyl-2-butene and 0.165 g (4.35 mmol) of sodium borohydride in 5 ml of freshly distilled diglyme was added dropwise a 0.82 g (5.8 mmol) of boron trifluoride etherate at 0°.

After the addition, the reaction mixture was stirred at room temperature for 2.5 hr. To this reaction mixture, a solution of 1.0 g (5.25 mmol) of 1-(5-hexyl)bicyclo[2.2.2]oct-2-ene in 5 ml of diglyme was added. The white reaction mixture was stirred at room temperature under nitrogen for 24 hr. It was hydrolyzed by the addition of 6 ml of 3N aqueous sodium hydroxide solution followed by 4 ml of 30% hydrogen peroxide. The mixture was stirred for 2 hr, and poured into a 50 ml of saturated sodium bicarbonate solution. The aqueous solution was extracted five times with 50 ml portions of ether. The combined ether layers were washed with 100 ml of 10% aqueous sodium bisulfite solution, 100 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to give 1.1 g of crude oil. The crude oil was chromatographed on 50 g of 60-200 mesh silica gel with 10% ether-hexane as solvent to give 0.43 g of the starting olefin and 220 mg (20%) of the product. An analytical sample of the product was prepared via preparative vpc (10' x 2/8" 10% SE-30), \( n_D^{25} 1.4952; \) ir (film), 3.01, 3.29, 3.40, 3.50, 6.19, 9.43, and 14.45 \( \mu \); nmr (CDCl\(_3\)), \( \tau \)
9.00-8.70 (1H, m), 8.20 (1H, s), 7.55 (1H, br), 6.40 (2H, t), and 4.20-3.60 (2H, m).

**Anal.** Calcd m/e for C_{14}H_{24}O: 208.18270. C, 80.71; H, 11.61.

**Found:** 208.18307. C, 80.66; H, 11.66.

1-Hydroxymethyl-1,3-cyclohexadiene (110). To a well stirred suspension of 6.0 g (0.16 mole) of lithium aluminum hydride in 300 ml of dry ether, was added a solution of 25.2 g (0.165 mol) of 1-carbomethoxy-1,3-cyclohexadiene in 50 ml of ether at 0°. The reaction mixture was stirred for 45 min and refluxed for another 30 min. After cooling to room temperature, it was hydrolyzed through the addition of 6 ml of water, 6 ml of 15% aqueous sodium hydroxide solution, and 18 ml of water, successively. The precipitated white solid was removed by filtration and washed with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The oily residue was vacuum distilled to give 16.1 g (89%) of product, bp 67.5-68.5° (2.15 mm) [lit bp 85-87° (12 mm)]; ir (film), 2.99, 3.28, 3.39, and 6.25 μ; nmr (CDCl₃), 7.85 (4H, s), 6.68 (1H, br s), 5.92 (2H, s), and 4.10 (3H, m).

α-Hydroxy-o-toluic Acid Lactone (**111**). A mixture of 1.53 g (18.2 mmol) of methyl propiolate and 2.0 g (18.2 mmol) of 1-hydroxymethyl-1,3-cyclohexadiene sealed in a 10 ml Carius tube was heated at 80° for 15 days. The thick brownish oily mixture was recrystallized three times from benzene-petroleum ether to give 0.71 g (29%) of white solid. Thin layer chromatography (silica gel) analysis of the mother liquid indicated the presence of the unreacted starting 1-hydroxymethyl-1,3-cyclohexadiene. The structure of the white solid was proposed as the α-hydroxy-o-toluic acid lactone based on the following facts, mp 72° [lit mp 73°]; ir (KBr), 5.70, 6.25, 6.82, 6.95, 9.50, 10.00, and 13.52 μ; nmr (CDCl₃), 4.65 (2H, s), 2.65-1.95 (4H, m); molecular ion, m/e 134.

3-Hydroxycyclopentene (**119**). Into 454 g (6.9 mol) of freshly distilled cyclopentadiene was introduced under cooling with an ice-salt bath, a stream of dry hydrogen chloride until a volume increase of 90 to 95 ml had occurred. The reaction mixture was vacuum distilled to give 555 g (78.5%) of the 3-chlorocyclopentene, bp 30° (20 mm). This 3-chlorocyclopentene was added dropwise over 2 hr under intense stirring to a solution of 450 g of sodium bicarbonate
in 2 l of water at 0°. The reaction mixture was stirred for an additional hour, saturated with sodium chloride, and extracted with four 500-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, evaporated, and vacuum distilled to give 2.58 g (73%) of cyclopenten-3-ol (119), bp 42° (3.5 mm); n_D^20 1.4716 [lit 1.4717]; ir (film), 2.86, 3.22, 3.34, 6.25, 9.52, and 10.36 μ; nmr (CDCl₃), τ 8.60-7.20 (4H, m), 6.85 (1H, br s), 5.20 (1H, m), and 4.12 (2H, m).

Cyclopenten-3-one (117). A sample of 42 g (0.5 mole) of 3-hydroxy-cyclopentene was added dropwise to a vigorously stirred solution of 75 g (0.25 mole) of sodium dichromate, 12.5 ml of 50% sulfuric acid in 250 ml of water at 0°. The reaction mixture remained at 0° for 1/2 hr, then was saturated with sodium chloride, and extracted four times with 200-ml portions of ethyl ether. The combined ether extracts were washed with 100 ml of saturated sodium bicarbonate solution and 100 ml of brine, dried over anhydrous magnesium sulfate, filtered, and vacuum distilled through a one-foot Vigreux column to give 16.8 g (41%) of pure cyclopenten-3-one, bp 74° (40 mm); n_D^24.3 1.4794 [lit bp 42° (11 mm), n_D^20 1.4814].

A mixture of 3 g (19.7 mmol) of 1-carboethoxy-1,3-cyclohexadiene and 2.94 g (23.7 mmol) of cyclooct-2-ene-1-one sealed in a Carius tube under argon was heated at 170° for 48 hr, and then at 160° for 36 hr. The reaction product was distilled through a short path distillation apparatus to give 2.7 g of a thick yellow oil, bp 115-145° (0.2-0.1 mm) and 2.5 g of tar which was non-distillable. The yellow oil was catalytically hydrogenated at 60 lb/in² pressure in tetrahydrofuran with 200 mg of 5% palladium on carbon. After filtration and removal of solvent in vacuo, the hydrogenated product was chromatographed on 100 g of 60-200 mesh of silica gel with 5% ether-petroleum ether as solvent. A 2.6 g yield of colorless thick oil was obtained. The structure of this product was proposed as the dimer of 1-carboethoxy-1,3-cyclohexadiene based on the following facts: \( \text{IR (neat), } 3.34, 5.80, 5.85, 6.10, 8.00, \text{ and } 9.35 \mu \text{m; } \text{NMR (CDCl}_3\text{), } \tau 8.70 (6H, t, } J = 7 \text{ Hz), } 8.90-7.00 (15H, m), 5.80 (4H, q, } J = 7 \text{ Hz), and } 3.22 (1H, m). \)

**Anal. Calcd m/e for C\(_{18}\)H\(_{26}\)O\(_4\): 306.18308.**

**Found:** 306.18359.
Ethyl 2-Acetyl\(\text{bicyclo[2.2.2]oct-5-ene-1-carboxylate (125)}\), and Ethyl 3-Acetyl\(\text{bicyclo[2.2.2]oct-5-ene-1-carboxylate (126)}\).  

![Diagram: Ethyl 2-Acetyl\(\text{bicyclo[2.2.2]oct-5-ene-1-carboxylate (125)}\)](image)

1-Carboethoxy-1,3-cyclohexadiene
(30 g, 0.197 mole), methyl vinyl ketone (28 g, 0.4 mole), and hydroquinone (15 mg) were placed in a Carius tube which was flushed with nitrogen and sealed. The reaction mixture was heated in an oil bath at \(140^\circ\) for 24 hr. The light yellow clear oil was vacuum distilled to give 41.2 g (93\%) of a colorless mixture of acetyl esters, bp 125-133\(^\circ\) (2.2 mm); ir (neat), 3.23, 3.34, 3.45, 5.73, 5.85, 8.00, 8.59, 9.30, and 13.99 \(\mu\); nmr (CDCl\(_3\)), \(\tau\) 8.76 and 8.73 (3H altogether, t, \(J = 7 \text{ Hz for both, ratio } \approx 4:1\)), 8.90-7.60 (6H, m), 7.99, 7.91 and 7.88 (3H altogether, singlets), 7.30 (1H, m), 6.75 (1H, dd, \(J = 11\) and 6 Hz), 5.80 and 5.84 (2H total, quartets, \(J = 7 \text{ Hz for both, ratio } \approx 4:1\)), 3.85 (1H, m), and 3.38 (1H, br d, \(J = 8 \text{ Hz}\)).

Ethyl 2-Acetyl\(\text{bicyclo[2.2.2]octane-1-carboxylate (125)}\) and Ethyl 3-Acetyl\(\text{bicyclo[2.2.2]octane-1-carboxylate (126)}\). The mixture of ethyl 2-acetyl\(\text{bicyclo[2.2.2]oct-5-ene-1-carboxylate and ethyl 3-acetyl-\(\text{bicyclo[2.2.2]oct-5-ene-1-carboxylate (40.5 g)}\) was dissolved in tetra-
hydrofuran (40 ml) with 5% palladium on carbon (500 mg) added. The mixture was hydrogenated with a Parr Hydrogenator for about one hour until the hydrogen pressure became constant (initial pressure was set at 60 lb/in²). After filtration and removal of solvent in vacuo it gave a mixture of products (41 g, 100%) as a colorless liquid; ir (film) 3.34, 3.45, 5.71, 5.81, 8.00, and 9.43 μ; nmr (CDCl₃), τ

8.80 and 8.78 (3H total, triplets, J = 7 Hz for both, ratio ~ 4:1), 8.70-7.80 (11H, m), 7.90 and 7.89 (3H total, singlets), 7.10-6.70 (1H, m), 5.95 and 5.93 (2H, total, quartets, J = 7 Hz for both).

2-Acetyl bicyclo[2.2.2]octane-1-carboxylic Acid (127). A sample of 41 g (0.183 mole) of the mixture of ethyl 2-acetyl bicyclo[2.2.2]octane-1-carboxylate and ethyl 3-acetyl bicyclo[2.2.2]octane-1-carboxylate was refluxed in a solution of 30 g of potassium hydroxide in 330 ml of 10% aqueous ethanol for 4 hr. After cooling, the reaction mixture was acidified with 6N concentrated hydrochloric acid and extracted four times with 200-ml portions of ether. The combined ether end extracts
were dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give a crude solid, which was fractionally recrystallized from absolute ethanol to give 19.6 g (55%) of pure 2-acetyl bicyclo[2.2.2]octane-1-carboxylic acid as prisms, mp 163-166° [lit mp 164-167°]; ir (CCl₄), 3.30-4.00 (broad), 5.78, 5.81, and 7.75 μ; nmr (CDCl₃), τ 8.70-7.50 (11H, m), 7.87 (3H, s), 6.90 (1H, m), and -1.17 (1H, br s). The minor isomer, 3-acetyl bicyclo[2.2.2]-octane-1-carboxylic acid, was left as a mixture with 2-acetyl bicyclo-[2.2.2]octane-1-carboxylic acid in the mother liquid.

Methyl 2-Acetyl bicyclo[2.2.2]octane-1-carboxylate (128). 2-Acetyl bicyclo[2.2.2]octane-1-carboxylic acid (17.6 g, 89.6 mmol) was dissolved in 100 ml of ether. To this well-stirred solution at 0° was added dropwise an ethereal solution of diazomethane (100 ml, 0.1 mole). After the evolution of nitrogen subsided, the solution was allowed to remain at room temperature for 0.5 hr, and the solvent was removed under vacuum to give 17.6 g (93%) of a clear liquid; ir (film), 3.36, 3.45, 5.71, 5.81, 7.94, and 9.35 μ; nmr (CDCl₃), τ 8.70-7.50 (11H, m), 7.90 (3H, s), 7.20-6.70 (1H, m), and 6.40 (3H, s).

Methyl 2-Acetoxybicyclo[2.2.2]octane-1-carboxylate (129). Trifluoroacetic anhydride (35 ml) was added over 30 min to a well-stirred solution of methylene chloride (35 ml) and 90% hydrogen peroxide
vigorous stirring over 1.5 hr, the solution of trifluoroperacetic acid prepared as above. The reaction mixture was stirred at 0° for 2 hr, and was allowed to warm to room temperature overnight. Methylene chloride (200 ml) was then added and the solution was washed carefully with three 100-ml portions of saturated sodium bicarbonate solution (carbon dioxide given off). The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give a clear product (12.5 g, 94%, purity checked with analytical vpc on a 3% SF-1265 column showed > 98%); ir (film), 3.36, 3.45, 5.73, and 8.00 μ; nmr (CDCl₃), τ 8.80-7.50 (11H, m), 8.02 (3H, s), 6.40 (3H, s), and 4.80 (1H, dd, J = 11 and 3 Hz).

2-Hydroxybicyclo[2.2.2]octane-1-carboxylic Acid (120). A solution of methyl 2-acetoxybicyclo[2.2.2]-octane-1-carboxylate (7.5 g, 33.2 mmol) and potassium hydroxide (7.5 g) in 10% aqueous ethanol (120 ml) was refluxed on the steam bath for 4 hr. After cooling,
most of the ethanol was removed under reduced pressure. The residue was dissolved in 50 ml of water and extracted with 100 ml of ether. The aqueous phase was separated and acidified with 6 N hydrochloric acid. The liberated organic acid was extracted with three 50-ml portions of ethyl acetate. The combined ethyl acetate solutions were washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give a crystalline hydroxy acid (5.4 g, 96%). A sample was purified by sublimation at 70° (0.1 mm), mp 109-111° (lit mp 110-111.5°); ir (KBr), 2.86-4.20 (broad), 5.86, 8.00, and 9.70 μ; nmr (CDCl₃), 7.8.90-7.60 (1H, m), 5.80 (1H, dd, J = 9 and 3 Hz), and 3.10 (2H, br s).

Bicyclo[2.2.2]octan-2-one-1-carboxylic Acid (121). Jones reagent (8N) was added dropwise to a solution of 5.0 g (29.4 mmol) of 2-hydroxy-
bicyclo[2.2.2]octane-1-carboxylic acid in 100 ml of acetone at 0° (until a permanent orange color persisted). The solution was then concentrated in vacuo and diluted with 100 ml of water. The aqueous solution was extracted with ether and the combined ether extracts were washed with 50 ml of brine, dried over anhydrous magnesium sulfate and filtered. On removal of the ether in vacuo, the filtrate afforded 3.8 g (81%) of the keto acid. A pure sample was sublimed at 80° (0.1 mm), mp 144-146° [lit mp 146°]; ir (KBr), 2.86-4.00 (broad),
5.73, 5.83, 7.81, 7.91, and 10.53 \mu; \text{nmr (CDCl}_3\text{), } \tau 8.50-7.50 (9H, m),
7.60 (2H, d, J = 3 Hz), and -0.50 (1H, s).

\text{Methylbicyclo[2.2.2]octane-2-one-l-carboxylate (122). Diazomethane in}
\text{ether solution (30 ml, 0.03 mole)}
\text{was added dropwise to a solution of}
3.0 g (17.9 mmol) of bicyclo[2.2.2]-
\text{octan-2-one-l-carboxylic acid in}
25 ml of ether at 0^\circ. \text{After the}
evolution of nitrogen subsided,}
\text{the solution was allowed to remain at room temperature for 1 hr. On}
\text{removal of the ether, an oily solid was obtained, which was sublimed}
at 50^\circ (0.1 mm) to give 2.9 g (89\%) of the product as needles, mp
62-64^\circ [\text{lit mp } 62.5-64.5^\circ]; \text{ir (KBr), } 3.39, 3.45, 5.75, 5.83, 8.07,
9.52, \text{and } 9.71 \mu; \text{nmr (CDCl}_3\text{), } \tau 8.60-7.50 (9H, m), 7.70 (2H, d, J =
3 Hz), \text{and } 6.30 (3H, s).

\text{Methyl 3-Bromobicyclo[2.2.2]octan-2-one-l-carboxylate (134). A sample}
of 0.5 g (2.73 mmol) of methyl-
bicyclo[2.2.2]octan-2-one-l-
carboxylate was added to a suspension
of 1.22 g (5.50 mmol) of cupric
bromide in 10 ml of one-to-one
mixture of ethyl acetate and
chloroform. The dark reaction mixture was refluxed for 10 hr, and
the reaction solution gradually turned green. At the same time,
white precipitates appeared with the liberation of hydrogen bromide. The white cuprous bromide was removed by filtration and washed with chloroform. The organic filtrate was washed with 10 ml of saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give a white solid, which was recrystallized from chloroform and low boiling petroleum ether to give 0.61 g (85%) of needle shape crystals, mp 102.0-103.5°; ir (CCl₄), 3.34, 5.72, 5.75, 6.85, 6.95, 7.93, and 9.52 μ; nmr (CDCl₃), τ 8.60-7.40 (9H, m), 6.27 (3H, s), and 5.64 (1H, m).

Anal. Calcd for C₁₀H₁₃BrO₃: C, 46.00; H, 5.02; Br, 30.60. Found: C, 45.88; H, 5.02; Br, 30.68.

Ethylene Ketal of Methylbicyclo[2.2.2]octan-2-one-1-carboxylate (136).

A mixture of 12 g (66 mmol) of methylbicyclo[2.2.2]octan-2-one-1-carboxylate, 31 g (0.5 mole) of ethylene glycol, and 0.5 g of toluenesulfonic acid in 300 ml of benzene was placed in a flask equipped with a Dean Stark trap. The reaction mixture was heated at reflux for 24 hr. Water was continuously removed from the Dean Stark trap during this period. The reaction mixture was then poured into 200 ml of 5% aqueous sodium bicarbonate solution, and extracted four times with 200-ml portions of ethyl ether. The combined ether extracts were washed with 200 ml of saturated sodium
chloride solution, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give 14.5 g (96%) of crude thick oil, which was vacuum distilled at 93-94° (0.42 mm) to give 12.5 g (84%) of pure semisolid product. An analytical sample was collected via preparative vpc (on a 10' x 3/8" 10% SE-30 column), mp 42-43°; ir (film), 3.34, 5.78, 6.99, and 8.00 μ; nmr (CDCl₃), 7.89-7.40 (1H, m), 6.36 (3H, s), and 6.15 (4H, m).

Anal. Calc'd for C₁₂H₁₉O₄: C, 63.70; H, 8.02.

Found: C, 63.63; H, 7.98.

Ethylene Ketal of Bicyclo[2.2.2]octan-2-one-1-carboxylic Acid (137).

A mixture of 14 g of the ethylene ketal of methyl bicyclo[2.2.2]-octan-2-one-1-carboxylate, 14 g of potassium hydroxide, in 150 ml of 10% aqueous ethanol was heated at reflux for 12 hr. After removal of ethanol in vacuo, the residue was diluted with 100 ml of ice water and carefully acidified to pH 5 with 10% aqueous hydrochloric acid. The aqueous solution was extracted five times with 100 ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give a crude solid, which was recrystallized from pentane-ether to yield 10.1 g (77%) of pure carboxylic acid, mp 117-119°; ir (CCl₄), 2.86-4.17 (broad), 5.88, and 7.81 μ; nmr (CDCl₃), 7.80-7.50 (1H, m),
6.05 (4H, s), and -0.45 (1H, s).

Anal. Calcd for C_{11}H_{16}O: C, 62.25; H, 7.60.

Found: C, 62.13; H, 7.57.

1-(1-Oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]octane (138). A sample of 17.4 g (0.116 mol) of 5-bromo-1-pentene was added slowly under argon to a suspension of 1.63 g (0.232 mol) of lithium wire (1% Na) in 120 ml of anhydrous ether at 0°. The mixture was vigorously stirred until the reaction subsided. The alkyllithium solution thus prepared was added slowly under argon to a solution of 9.5 g (44.7 mmol) of the ethylene ketal of bicyclo[2.2.2]octan-2-one-l-carboxylic acid in 150 ml of dry ether at 0°. White precipitates appeared immediately and soon redissolved again. The cloudy solution was allowed to remain at room temperature for 24 hrs, and slowly poured into 500 ml of 5% ice-cold aqueous ammonium chloride solution buffered to pH 8 with ammonium hydroxide. The aqueous solution was extracted with four 200-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to give an oil, which was vacuum distilled to yield 10.2 g (86%) of colorless product, bp 133.5-135.0° (0.58 mm).

An analytical sample was collected via preparative vpc (on a 10' x 3/8" 10% SE column, temperature 180°), n\textsubscript{D}^25.2 1.4981; ir (film), 3.28, 3.34,
Reduction of 1-(Oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]-octane (138). A solution of 9.7 g (36.6 mmol) of 1-(oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]-octane in 20 ml of ether was added to a suspension of 1.39 g (36.6 mmol) of lithium aluminum hydride in 200 ml of ether at 0°. The reaction mixture was stirred at room temperature for 24 hr, and hydrolyzed by adding successively 1.39 ml of water, 1.39 ml of 15% aqueous sodium hydroxide solution, and 4.17 ml of water. The white precipitates were removed by filtration and washed with 50 ml of ether. The ether filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was vacuum distilled to give 8.3 g (85%) of colorless ethylene ketal of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]-octan-2-one (139), bp 130-135° (0.1-0.15 mm); n_D26 1.4998; ir (film), 2.82, 3.28, 3.34, 6.08, 9.09, 9.80, and 11.05 μ; nmr (CDCl_3), τ 8.90-7.70 (17H, m), 6.20 (1H, s), 6.35-6.00 (1H, m), 6.05 (4H, m), 5.25-4.80 (2H, m), and 4.50-3.80 (1H, m).

Anal. Calcd for C_{16}H_{24}O: C, 72.69; H, 9.15.

Found: C, 72.68; H, 9.22.

Reduction of 1-(Oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]-octane (138). A solution of 9.7 g (36.6 mmol) of 1-(oxo-5-hexenyl)-2,2-ethylenedioxybicyclo[2.2.2]-octane in 20 ml of ether was added to a suspension of 1.39 g (36.6 mmol) of lithium aluminum hydride in 200 ml of ether at 0°. The reaction mixture was stirred at room temperature for 24 hr, and hydrolyzed by adding successively 1.39 ml of water, 1.39 ml of 15% aqueous sodium hydroxide solution, and 4.17 ml of water. The white precipitates were removed by filtration and washed with 50 ml of ether. The ether filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was vacuum distilled to give 8.3 g (85%) of colorless ethylene ketal of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]-octan-2-one (139), bp 130-135° (0.1-0.15 mm); n_D26 1.4998; ir (film), 2.82, 3.28, 3.34, 6.08, 9.09, 9.80, and 11.05 μ; nmr (CDCl_3), τ 8.90-7.70 (17H, m), 6.20 (1H, s), 6.35-6.00 (1H, m), 6.05 (4H, m), 5.25-4.80 (2H, m), and 4.50-3.80 (1H, m).

Anal. Calcd for C_{16}H_{24}O: C, 72.69; H, 9.15.

Found: C, 72.68; H, 9.22.
Ethylene Thioketal of Methyl Bicyclo[2.2.2]octan-2-one-1-carboxylate

(142). A solution (10 ml) of freshly distilled boron trifluoride etherate was added to a mixture of 10 g (55 mmol) of methyl bicyclo-[2.2.2]octan-2-one-1-carboxylate and 10 ml of ethanedithiol. The reaction mixture was stirred at room temperature for 2 hr, and diluted with 300 ml of ether. The ethereal solution was washed three times with 100-ml portions of 5% aqueous potassium hydroxide solution, 100 ml of water, and 100 ml of saturated sodium chloride solution. The ether layer was dried over anhydrous potassium carbonate, filtered, and concentrated in vacuo to give an oily solid, which was recrystallized from a minimum amount of methanol to yield 12.4 g (87%) of white crystals, mp 64-66°; ir (CHC13), 3.42, 5.81, 8.00, 8.20, and 9.35 μ; nmr (CDCl3), τ 8.70-7.40 (11H, m), 6.80 (4H, m), and 6.38 (3H, s).

Anal. Calcd for C12H16O2S2: C, 55.76; H, 7.02; S, 24.82.

Found: C, 55.83; H, 6.98; S, 24.72.

Ethylene Thioketal of 1-Hydroxymethylbicyclo[2.2.2]octan-2-one (143).

A solution of 11.6 g (45 mmol) of the ethylene thioetetal of methyl-bicyclo[2.2.2]octan-2-one-1-carboxylate in 50 ml of ether was added slowly to a suspension of 1.7 g (45 mmol) of lithium aluminum
hydride in 100 ml of ether at 0°. The reaction mixture was stirred at
room temperature for 6 hr, and hydrolyzed by adding successively
1.7 ml of water, 1.7 ml of 15% aqueous sodium hydroxide solution, and
5.1 ml of water. The white precipitate was collected by filtration
and washed with ether. The filtrate was dried over anhydrous potassium
carbonate and filtered. After removal of solvent in vacuo, the solid
residue was recrystallized from chloroform and pentane to give 9.5 g
(90%) of needle-like crystals, mp 85-87°; ir (CHCl₃), 2.86, 3.42,
6.90, 7.15, and 9.80 μ; nmr (CDCl₃), τ 8.70-8.00 (9H, m), 7.58 (2H, d,
J = 3 Hz), 6.95 (1H, br), 6.73 (4H, s), and 6.35 (2H, br s).

Anal. Calcd for C₁₁H₁₈O₂S₂: C, 57.35; H, 7.87; S, 27.83.
Found: C, 57.43; H, 7.78; S, 27.57.

Ethylene Thioketal of 1-Hydroxymethylbicyclo[2.2.2]octan-2-one
Tosylate (144). A mixture of 9 g (39.1 mmol) of the ethylene ketal of
1-hydroxymethylbicyclo[2.2.2]octan-2-one and 9.15 g (48 mmol) of tosyl
chloride in 50 ml of dry pyridine
was stored in the refrigerator for
48 hr. The mixture was poured
into 200 ml of ice water, and the
aqueous mixture was extracted four times with 100-ml portions of ether.
The combined ether extracts were washed with ice water, saturated
sodium bicarbonate solution, and brine, dried over anhydrous magnesium
sulfate, and filtered. After removal of solvent from the filtrate in
vacuo, it afforded 14 g of a red-brown thick oil; ir (neat), 3.34, 6.25, 6.90, 7.46, 8.44, and 8.51 μ. This tosylate was used immediately in other reactions without further purification.

Reaction of the Ethylene Thioketal of 1-Hydroxymethylbicyclo[2.2.2]-octan-2-one Tosylate with Sodium Cyanide. A mixture of 14 g (37 mmol) of the ethylene thioketal of 1-hydroxymethylbicyclo[2.2.2]-octan-2-one tosylate and 10 g (0.2 mol) of sodium cyanide in 50 ml of dimethyl sulfoxide was heated at 120° for seven days. The brown mixture was poured into 250 ml of cold water, and the aqueous solution was extracted four times with 200-ml portions of ether. The combined ether extracts were washed with saturated sodium bicarbonate solution, water, and brine, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent from the filtrate in vacuo afforded 6.5 g of crude brown thick oil, which was chromatographed on 200 g of 60-200 mesh silica gel with 10% ether-hexane as solvent. The first fractions gave 3.48 g (44%) of a white solid, mp 60-62°; ir (CHCl₃), 3.33, 3.39, 3.44, 6.06 (w), 7.09, 11.49, and 12.05 μ; nmr (CDCl₃), 7 8.90-8.10 (8H, m), 7.40 (1H, br d, J = 7 Hz), 7.10 (6H, s), and 3.32 (1H, d, J = 7 Hz); exact mass analysis: calcd m/e 212.0693900; obs. m/e 212.0696984; diff., 0.0004. The structure of this product was proposed as the 4,7-dithia-tricyclo[7.2.2.0⁵,⁹]tridec-2-ene (146).
Anal. Calcd for C_{11}H_{16}S_{2}: C, 62.21; H, 7.59; S, 30.20.

Found: C, 62.28; H, 7.62; S, 29.78.

The second fractions gave 1.38 g of an unidentified white solid, mp 65-65°; ir (CHCl₃), 3.40, 3.48, 4.49 (C≡N), 6.90, and 7.04 μ; nmr (CDCl₃), τ 8.50-7.60 (11H, m), 7.45 (2H, s), and 7.30-6.40 (4H, m).

Ethylene Ketal of 1-Hydroxymethylbicyclo[2.2.2]octan-2-one (147).

A solution of 17 g (75 mmol) of the ethylene ketal of methyl-bicyclo[2.2.2]octan-2-one-1-carboxylate in 50 ml of dry ether was added slowly to a suspension of 2.85 g (75 mmol) of lithium aluminum hydride in 150 ml of dry ether. After the addition of the ester, the reaction mixture was stirred at room temperature for 24 hrs, and hydrolyzed by adding 2.85 ml of water, 2.85 ml of 15% aqueous sodium hydroxide solution and 8.85 ml of water, successively. The white precipitate was removed by filtration and the filtrate was concentrated in vacuo to give 13 g (88%) of colorless viscous oil (purity > 98%; checked by analytical vpc on a 10', 10% SE-30 column). An analytical sample was collected via preparative vpc (10' x 3/8" 10% SE-30 column), n_D^{19} 1.5050; ir (neat), 2.86, 3.45, 9.09, and 10.00 μ; nmr (CDCl₃), τ 8.90-7.90 (11H, m), 7.20 (1H, t, J = 5 Hz), 6.52 (2H, d, J = 5 Hz), and 6.05 (4H, s).
1-Hydroxymethylbicyclo[2.2.2]octan-2-one (148). A mixture of 9.8 g (49.4 mmol) of the ethylene ketal of 1-hydroxymethylbicyclo[2.2.2]octan-2-one, 1 g of p-toluenesulfonic acid monohydrate, 10 ml of water, and 50 ml of benzene was refluxed at 80° for 24 hr. The mixture was poured into 100 ml of 10% aqueous potassium bicarbonate solution. The aqueous layer was extracted three times with 100 ml portions of ether. The combined ether extracts were washed with 50 ml of saturated sodium bicarbonate solution, and 50 ml of brine, dried over anhydrous magnesium sulfate, and filtered. After removing the solvent under reduced pressure a 6.9 g (91%) of crude oil was obtained. This was distilled at 95-98° (0.4 mm) to give 6.1 g (80%) of colorless viscous oil; ir (neat), 2.86, 3.40, 3.47, 5.81, and 9.62 μ; nmr (CDCl₃), δ 8.90-7.90 (8H, m), 7.80 (3H, br), 7.30 (1H, t, J = 6.5 Hz), and 6.55 (2H, d, J = 6.5 Hz).

1-Hydroxymethylbicyclo[2.2.2]octan-2-one Tosylate (149). A sample of 4.9 g (25.8 mmol) of freshly recrystallized tosyl chloride was added to a solution of 3.2 g (20.8 mmol) of 1-hydroxymethylbicyclo[2.2.2]-
octan-2-one in 20 ml of dry pyridine. The reaction mixture was allowed to remain at 0°C for 48 hr. It was then poured into 200 ml of 2N aqueous hydrochloric acid. The aqueous layer was extracted five times with 50-ml portions of ether. The ether extracts were washed twice with 50-ml portions of 2N aqueous hydrochloric acid, 50 ml of saturated sodium bicarbonate solution, and 50 ml of brine. After drying over anhydrous magnesium sulfate, filtration, and removal of the solvent, 5.5 g of crude solid was obtained, which was recrystallized with ether and hexane to give 4.6 g (71%) of pure tosylate, mp 112-113°C; IR (CHCl₃), 3.23, 3.40, 5.81, 6.25, 7.33, 8.51, and 11.98 μm; NMR (CDCl₃), δ 8.70-8.00 (9H, m), 7.80 (2H, br s), 7.58 (3H, s), 6.05 (2H, s), and 2.80-2.10 (4H, dd, J = 8 Hz).

**1-Cyanomethylbicyclo[2.2.2]octan-2-one (150)**. A mixture of 3.75 g (12.1 mmol) of the tosylate 149, and 3.6 g (60 mmol) of sodium cyanide in 15 ml of dry dimethylosulfoxide was heated at 80°C for three days. The mixture was poured into 100 ml of water. The aqueous layer was extracted four times with 100-ml portions of ether. The combined ether extracts were washed twice with 50 ml portions of saturated
sodium bicarbonate solution, and twice with 50 ml portions of brine, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 1.8 g of crude solid. This crude solid was recrystallized from ether-chloroform to give 1.4 g (71%) of pure nitrile, mp 108-110°; ir (CHCl₃), 3.40, 3.48, 4.46 (C-N), 5.81, and 6.67 μ; nmr (CDCl₃), τ 8.80-7.80 (9H, m), 7.65 (2H, br s), and 7.56 (2H, s).

Anal. Calcd for C₁₀H₁₃NO: C, 73.60; H, 8.03; N, 8.58.
Found: C, 73.59; H, 8.10; N, 8.89.

**Ethylene Thioketal of 1-Cyanomethylbicyclo[2.2.2]octan-2-one (145).**

A 1.0 ml of freshly distilled boron trifluoride etherate was added slowly to a mixture of 1.0 g (6.12 mmol) of 1-cyanomethylbicyclo[2.2.2]-octan-2-one in 1.5 ml of ethane-dithiol. The reaction mixture was stirred at room temperature for 12 hr and poured into 50 ml of 5% aqueous potassium hydroxide solution. The aqueous layer was extracted five times with 30 ml portions of ether. The ether extracts were washed with 5% aqueous potassium hydroxide solution, water and brine, dried over anhydrous magnesium sulfate, and filtered. After removal of the solvent, the solid residue was recrystallized from chloroform and pentane to give 1.2 g (82%) of prismatic crystals, mp 88-90°; ir (CHCl₃), 3.40, 3.47, 4.46 (C-N), and 9.09 μ; nmr (CDCl₃), τ 8.50-7.90 (9H, m), 7.45 (2H, br d, J = 2 Hz), 7.20 (2H, s), and 7.00-6.40 (4H, m).
Anal. Calcd for C$_{12}$H$_{17}$NS$_2$: C, 60.21; H, 7.16; N, 5.85.

Found: C, 60.54; H, 7.22; N, 5.93.

1-(2-Oxo-6-heptenyl)-2,2-ethylenedithiabicyclo[2.2.2]octane (151).

A 0.04 g (5.8 mmol) piece of lithium wire was added to a solution of 0.43 g (29 mmol) of 5-bromo-1-pentene in 20 ml of dry ether in a 50-ml, 3-necked flask equipped with a Herzberg stirrer. The reaction mixture was stirred at -20° until the lithium metal almost disappeared. The greyish solution was transferred under argon into a solution of 0.5 g (2.08 mmol) of the ethylene thioketal of 1-cyano-methylbicyclo[2.2.2]octan-2-one in 10 ml of anhydrous ether at 0°. The slight yellowish clear solution was then allowed to remain at room temperature for 24 hr. To this solution, a 10-ml portion of 10% aqueous hydrochloric acid was added, and the mixture was stirred vigorously for 2 hr at room temperature, and poured slowly into 20 ml of saturated sodium bicarbonate solution. The aqueous solution was extracted four times with 50 ml portions of ether. The combined ether extracts were washed with 50 ml of brine, dried over anhydrous magnesium sulfate, and filtered. After removal of solvent in vacuo, the brown residue was molecularly distilled at 140-150° (pot temperature) (0.4 mm) to give 0.50 g (78%) of the ketone; ir (neat), 3.24, 3.41, 3.49, 5.85, 6.10, 6.86, 7.30, and 10.49 μ; nmr (CDCl$_3$), τ
8.80-7.60 (15H, m), 7.50 (2H, br s), 7.25 (2H, s), 6.80 (4H, m), 5.18 (1H, m), 4.95 (1H, m), and 4.60-3.80 (1H, m).

Anal. Calcd m/e for C_{17}H_{20}OS_{2}: 310.14248.

Found: 310.14313.

1-(2-Hydroxy-6-heptenyl)-2,2-ethylene dithiabicyclo[2.2.2]octane (152).

A solution of 2.4 g (7.7 mmol) of 1-(2-oxo-6-heptenyl)-2,2-ethylene dithiabicyclo[2.2.2]octane in 10 ml of dry ether was added to a suspension of 0.3 g of lithium aluminum hydride in 30 ml of dry ether at 0°. The reaction mixture was stirred at room temperature for 18 hr and hydrolyzed by adding 0.3 ml of water, 0.3 ml of 15% aqueous sodium hydroxide solution, and 0.9 ml of water, successively. The white precipitates were removed by filtration and washed with ether. The ethereal filtrate was concentrated in vacuo to give 2.4 g (98%) of colorless viscous oil; ir (neat), 2.94, 3.25, 3.40, 3.49, 6.10, 6.88, 7.80, and 10.50 μ; nmr (CDCl₃), δ 9.00-7.00 (18H, m), 7.50 (2H, br s), 6.78 (4H, m), 6.35 (1H, m), 5.20-4.80 (2H, m), and 4.50-3.80 (1H, m).

Anal. Calcd m/e for C_{17}H_{20}OS_{2}: 312.15813.

Found: 312.15867.
Attempted Preparation of the Tosylate of 1-(2-Hydroxy-6-heptyl)-2,2-ethylenedithiabicyclo[2.2.2]octane (153). A mixture of 2.1 g (6.7 mmol) of 1-(2-hydroxy-6-heptyl)-2,2-ethylenedithiabicyclo[2.2.2]-octane and 1.53 g (8.0 mmol) of tosyl chloride in 10 ml of dry pyridine was stored in the refrigerator for 36 hr. The reaction mixture was poured into 100 ml of 5% ice-cold aqueous hydrochloric acid. The aqueous solution was extracted with four 50-ml portions of ether, and the ether extracts were washed with 50 ml of 5% aqueous hydrochloric acid, 50 ml of water, and 50 ml of brine, dried over anhydrous magnesium sulfate, and filtered. After removal of solvent in vacuo, 2.05 g of a viscous oil was obtained, which was chromatographed on 80 g of 60-200 mesh silica gel with 5% ether-hexane as solvent to give 1.52 g of a colorless oil; ir (neat), 3.24, 3.29, 3.40, 3.49, 6.10, 6.88, 7.80, 10.49, and 12.15 μ; nmr (CDCl₃), 7 9.00-7.20 (17H, m), 7.25 (4H, s), 6.80 (1H, m), 5.25-4.80 (2H, m), 4.50-3.80 (1H, m), and 3.22 (1H, d, J = 6.5 Hz). The structure of this product was proposed as the 8-(4-pentenyl)-4,7-dithiatriocycl[8.2.2.0³,1⁰]tetradec-2-ene (154).

Anal. Calcd m/e for C₁₇H₂₆S₂: 294.14757.

Found: 294.14815.
Ethylene Ketal of 1-Hydroxymethylbicyclo[2.2.2]octan-2-one Tosylate (158). A mixture of 13 g (65 mmol) of the ethylene ketal of 1-hydroxymethylbicyclo[2.2.2]octan-2-one and 14 g (73 mmol) of tosyl chloride in 50 ml of dry pyridine was stirred at room temperature for 48 hr under nitrogen. The mixture was poured into 300 ml of 10% ice cold citric acid solution. The aqueous solution was extracted three times with 100-ml portions of ether. The ether extracts were washed with 10% sodium bicarbonate solution, water, and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and evaporated under reduced pressure to give 16.2 g (71%) of a light yellow viscous oil; ir (neat), 3.45, 6.25 (w), 7.41, 8.44, 8.51, and 10.53 μ; nmr (CDCl₃), 7.10-8.10 (11H, m), 7.60 (3H, s), 6.05-6.05 (4H, m), 6.05 (2H, s), and 2.80-2.10 (4H, dd, J = 8 Hz). The tosylate failed to crystallize from benzene, petroleum ether or chloroform even at low temperature (−78°C), and was used in other reactions without further purification.

Ethylene Ketal of 1-Cyanomethylbicyclo[2.2.2]octan-2-one (159). A vigorously stirred mixture of 16 g (45.4 mmol) of the ethylene ketal of 1-hydroxymethylbicyclo[2.2.2]-octan-2-one tosylate and 12 g of sodium cyanide in 100 ml of dry
Dimethyl sulfoxide was heated at 120° for seven days. After cooling, the mixture was poured into 500 ml of cold water, and the aqueous solution was extracted with four 200-ml portions of ether. The ether extracts were washed with 10% sodium bicarbonate solution and brine, dried over anhydrous magnesium sulfate, and filtered. After removal of solvent in vacuo, the oily residue was vacuum distilled to give 8.5 g (91%) of a colorless oil, bp 101.5-102.0° (0.15-0.1 mm). This viscous oil soon solidified. An analytical sample was prepared via preparative vpc (10' x 3/8", 10% SE-30 column, temperature 150°), mp 43-45°; ir (CHCl₃), 3.34, 4.46 (C-N), 8.93, 9.71, and 10.70 μ; nmr (CDCl₃), τ 8.60-7.90 (11H, m), 7.70 (2H, s), and 6.10 (4H, m).

Anal. Calcd for C₁₂H₁₇NO₂: C, 69.54; H, 8.27; N, 6.76.
Found: C, 69.70; H, 8.42; N, 6.72.

Base Hydrolysis of the Ethylene Ketal of 1-Cyanomethylbicyclo[2.2.2]-octan-2-one (159). To a solution of 10 g of potassium hydroxide in 50 ml of ethyl glycol was added a 8.3 g (40 mmol) of the ethylene ketal of 1-cyanomethylbicyclo[2.2.2]octan-2-one. The mixture was refluxed at 180° for 24 hr. After cooling, the solution was poured into 300 ml of ice water with two drops of 1% phenolphthalein solution added. The aqueous solution was vigorously stirred and neutralized with 10% aqueous
hydrochloric acid. The cloudy solution was extracted with four 200-ml portions of ether, and the ether extracts were washed with 150 ml of brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to give 7.9 g (87%) of a very viscous oil (ethylene ketal of 1-carbohydroxymethylbicyclo[2.2.2]octan-2-one) (160), which failed to crystallize even at low temperature (-78°). A one-gram of the crude carboxylic acid was treated with diazomethane in ether solution.

After removal of solvent, the residue was vacuum distilled to give 0.9 g of the ethylene ketal of 1-carbomethoxybicyclo[2.2.2]octan-2-one (160), bp 98-100° (0.3 mm) as a colorless liquid; n_D^19 1.4911; ir (neat), 3.40, 5.78, 8.70, and 9.76 μ; nmr (CDCl₃), τ 8.60-7.90 (11H, m), 7.80 (2H, s), 6.40 (3H, s), and 6.15 (4H, s).

Anal. Calcd for C₁₃H₂₀O₄: C, 64.98; H, 8.39.

Found: C, 64.97; H, 8.55.

1-(2-Oxo-6-heptenyl)-2,2-ethylenedioxybicyclo[2.2.2]octane (161). To a suspension of 1.16 g (166 mmol) of lithium wire (1% Na) in 80 ml of dry ether at 0° was added drop-wise, while stirring, 12.4 g (83 mmol) of 5-bromo-1-pentene under argon. After the reaction subsided, the alkyllithium solution thus prepared was added through intramatic tubing to a solution of 7.8 g (34.4 mmol) of the carboxylic acid 160 in 100 ml of dry ether at 0°. A white precipitate appeared immediately and redissolved again after the complete addition of the alkyl-
lithium solution. The reaction mixture was stirred at room temperature overnight, and poured slowly into 400 ml of vigorously stirred 5% aqueous ammonium chloride solution buffered at pH 8 with ammonium hydroxide at 0°. The aqueous mixture was extracted with four 200-ml portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, and filtered. After removal of the solvent, the oily residue was vacuum distilled to give 5.78 g (63%) of a colorless ketone, bp 127-128° (0.1 mm), n\textsubscript{D}^20 1.4993; ir (neat), 3.28, 3.34, 5.88, 6.08, 8.89, 9.76, and 10.99 μ; nmr (CDCl\textsubscript{3}), δ 8.80-7.40 (17H, m), 7.65 (2H, s), 6.12 (4H, m), 5.00 (2H, m), and 4.60-3.50 (1H, m).

Anal. Calcd for C\textsubscript{17}H\textsubscript{26}O\textsubscript{3}: C, 73.35; H, 9.42.

Found: C, 73.49; H, 9.49.

Ethylene Ketal of 1-(2-Hydroxy-6-heptenyl)bicyclo[2.2.2]octan-2-one (162). A solution of 3.3 g (12.3 mmol) of 1-(2-oxo-6-heptenyl)-2,2-ethylenedioxybicyclo[2.2.2]octane in 10 ml of ether was added dropwise to a suspension of 0.47 g (12.3 mmol) of lithium aluminum hydride in 100 ml of ether at 0°. The mixture was stirred at room temperature overnight and hydrolyzed by adding successively 0.47 ml of water, 0.47 ml of 15% aqueous sodium hydroxide solution, and 1.41 ml of water. The white precipitate was removed by filtration and washed with ether. The ether filtrate was concentrated \textit{in vacuo} to give 3.5 g of a crude oil,
which was vacuum distilled to give 3.0 g (90%) of a viscous oil, bp 130-132° (0.1 mm); ir (neat), 2.91, 3.26, 3.41, 3.50, 6.10, 8.93, 9.71, and 10.99 μ; nmr (CDCl₃), τ 9.00-7.70 (19H, m), 6.60-6.10 (2H, m), 6.08 (4H, s), 5.20-4.80 (2H, m), and 4.50-3.80 (1H, m).

Anal. Calcd m/e for C₁₇H₂₈O₃: 280.20382.

Found: 280.20435.
Bis(dimethylamino)phosphorochloridate (163). Anhydrous dimethylamine (300 g) in dry ether (990 ml) was cooled to -78° with dry ice acetone solution in a 3-4 3-necked flask. A solution of phosphorus oxychloride (256 g) in ether (990 ml) was added dropwise and a vigorous reaction took place. After the addition the reaction mixture was kept overnight and the dimethylamine hydrochloride which had separated was removed by filtration. The ether solvent was removed under reduced pressure, and the clear residue fractionated with a one-foot Vigreux column. The fraction, bp 92-94° (2.5 mm) [lit 79-82° (0.6 mm) and 98° (15 mm)] (186 g, 65%) was collected.

Ethylene Ketal of 1-Formylbicyclo[2.2.2]octan-2-one (170). A 15.7 g sample (157 mmole) of fresh chromium trioxide was added slowly to a solution of 24.8 g (314 mmol) of dry pyridine in 160 ml of methylene chloride under nitrogen. The burgundy color chromium trioxide pyridine complex solution was stirred at room temperature for 20 min and was cooled to 0°. To this cooled solution was added in one portion a solution of 5.2 g (26.2 mmole) of


the ethylene ketal of 1-hydroxymethylbicyclo[2.2.2]octan-2-one in 15 ml of methylene chloride. A black precipitate appeared immediately. The reaction mixture was allowed to stay at room temperature for 1.5 hr. The methylene chloride solution was decanted into a flask and the black residue was washed several times with 200-ml portions of ether. The combined organic solution was condensed under reduced pressure to give a brown oil, which was then diluted with 200 ml of ether. The ether solution was washed twice with 100-ml portions of saturated sodium bicarbonate solution, twice with 100-ml portions of water, and with 100 ml of brine, dried over anhydrous magnesium sulfate and filtered. After removing the solvent, the light yellow oil was distilled at 74° (0.15 mm) to give 4.3 g (84%) of colorless product, n°D 1.4962. An analytical sample was collected from vpc (10' x 3/8", 10% SE-30) which shows the following spectral properties: ir (film) at 3.40, 3.50, 3.64, 5.81 (-CH), 8.45, 8.88, 9.70, and 10.70 µ; nmr (CDCl₃) at τ 8.80-7.60 (1H, m), 6.10 (4H, m), and 0.28 (1H, s).

**Anal.** Calcd for C₁₁H₁₆O₃: C, 67.33; H, 8.22. Found: C, 67.22; H, 8.37.

**Ethylene Ketal of 1-(1-Hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one (139).**

A solution of 4.5 g (30 mmole) of 5-bromo-1-pentene in 10 ml of dry ether was added dropwise to a well-stirred suspension of 0.42 g (60 mmole) of lithium wire in 50 ml of dry ether at -20 to -30° under argon.
After the lithium metal dissolved completely (purple-gray solution), it was added to a solution of 4.3 g (21.9 mmol) of the ethylene ketal of 1-formylbicyclo[2.2.2]octan-2-one in 10 ml of ether. A white precipitate appeared after 1 hr, and the reaction mixture was allowed to stay at room temperature overnight. The reaction mixture was poured into 200 ml of cold saturated ammonium chloride solution. The aqueous solution was extracted with four 100-ml portions of ether. The combined ether extracts were washed with 100 ml of saturated aqueous sodium bicarbonate solution and 100 ml of brine, dried over anhydrous magnesium sulfate, and filtered. After removing solvent under vacuum, it gave 5.6 g (95.5%) of colorless crude oil, which was pure enough for further reaction. An analytical sample was prepared from vpc (10' x 3/8", 10% SE-30) which shows the following spectral properties: ir (film), 2.83, 3.24, 3.42, 3.49, 6.10, 8.60, 8.90, and 11.00 μ; nmr (CDCl₃), δ 8.80-7.60 (17H, m), 6.20 (2H, m), 6.05 (4H, s), 5.00 (2H, m), and 4.40-3.60 (1H, m).


Found: C, 72.07; H, 9.87.

Diethylphosphate of the Ethylene Ketal of 1-(1-Hydroxy-5-hexenyl)-bicyclo[2.2.2]octan-2-one (171). A 14 ml (29.4 mmole) sample of methyllithium in ether was added dropwise to a solution of 5.6 g (21 mm) of the ethylene ketal of 1-(1-hydroxy-5-hexenyl)bicyclo-[2.2.2]octan-2-one in 40 ml of dry tetrahydrofuran at 0°. The reaction mixture was stirred for 1 hr and 10 ml of tetramethylethlenediamine
was added. The reaction mixture was warmed to room temperature and a 7.25 g (42 mmole) of chloro-diethylphosphate was added in one portion. After standing at room temperature for 24 hr, the reaction mixture was poured into 200 ml of cold saturated aqueous sodium bicarbonate solution. The aqueous solution was extracted with four 150-ml portions of ether and the combined ether extracts were washed with water until the aqueous layer became neutral. The organic layer was washed with 150 ml of brine, dried over anhydrous magnesium sulfate, and filtered. Removal of solvent under reduced pressure gave 8.0 g (95%) of light yellow oil; ir (film), 3.24, 3.40, 6.10, 7.90, 8.80, and 10.0 μ; nmr (CDCl₃), τ 8.70 (6H, t, J = 7 Hz), 9.10-7.60 (17H, m), 6.15 (4H, m), 5.90 (4H, q, J = 7 Hz), 5.70 (1H, m), 5.10 (2H, m), and 4.50-3.70 (1H, m).

N,N,N',N'-Tetramethylphosphorodiamidate of the Ethylene Ketal of 1-(1-Hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one (172). A 15 ml (30 mmole) aliquot of n-butyllithium in hexane was added dropwise to a solution of 7 g (26.2 mmole) of the ethylene ketal of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one in 40 ml of dry tetrahydrofuran at

0° under argon. After stirring of the reaction mixture for 1 hr, was added 10 ml of tetramethylethylene-diamine followed by 22.3 g (131 mmole) of bis(dimethylamino)phosphorochloridate. The reaction mixture was allowed to stay at room temperature for 24 hr. It was then poured into 200 ml of cold 10% aqueous potassium bicarbonate solution. The aqueous solution was extracted with four 200-ml portions of ether. The combined ether extracts were washed with 100 ml of saturated sodium bicarbonate solution, twice with 200-ml portions of water, and once with 200 ml of brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent gave 9.6 g (90%) of a yellow oil; ir (film), 3.25, 3.40, 6.10, 7.66, 8.17, 10.10, and 10.70 μ; nmr (CDCl₃), δ 8.90-7.70 (17H, m), 7.35 (12H, dd, J = 9 Hz), 6.10 (4H, m), 5.60 (1H, m), 5.10 (2H, m), and 4.50-3.70 (1H, m).

Ethylene Ketal of 1-(5-Hexenyl)bicyclo[2.2.2]octan-2-one (141). A 800 ml sample of liquid ammonia was distilled into a solution of 20 g (49.7 mmole) of the N,N,N',N'-tetramethylphosphorodiamidate of the ethylene ketal of 1-(1-hydroxy-5-hexenyl)bicyclo[2.2.2]octan-2-one in 200 ml of dry tetrahydrofuran. To this liquid ammonia solution was
added 1.75 g (0.25 mole) of lithium wire in 1/4 in. size. The purple-blue reaction mixture was maintained at -36° for 72 hr. Then most of the liquid ammonia was allowed to evaporate. The blue-gray residue was hydrolyzed very carefully with 200 ml of saturated aqueous ammonium chloride solution. The aqueous solution was extracted with five 200-ml portions of ether. The combined ether extracts were washed with two 100-ml portions of saturated aqueous sodium bicarbonate solution, 200 ml of water, and two 200-ml portions of brine. The organic layer was dried over anhydrous magnesium sulfate, and filtered. Removal of the solvent under reduced pressure gave 11.1 g (89%) of a colorless oil. An analytical sample was prepared via vpc (10' x 3/8", 10% SE-30, temperature = 160°), shows nD^24.6 1.4906; ir (film), 3.24, 3.40, 3.49, 6.10, 8.90, 9.65, and 11.00 μ; nmr (CDCl₃), δ 8.80-7.70 (19H, m), 6.12 (4H, m), 5.05 (2H, m), and 4.50-3.80 (1H, m).

Anal. Calcd for C₁₆H₂₆O₂: C, 76.75; H, 10.47.
Found: C, 76.47; H, 10.67.

1-(5-Hexenyl)bicyclo[2.2.2]octan-2-one (173). A 11.0 g (44 mmole)

sample of the ethylene ketal of 1-(5-hexenyl)bicyclo[2.2.2]octan-2-one was added to a solution of 20 ml of 20% aqueous hydrochloric acid in 100 ml of tetrahydrofuran. The reaction mixture was heated at
reflux for 18 hr, and poured into 200 ml of ice-water. The aqueous solution was saturated with sodium chloride and extracted with four 200-ml portions of ether. The combined ether extracts were washed with 150 ml of saturated sodium bicarbonate solution and with 200 ml of brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent gave 9.5 g of crude oil with a fragrant smell. Chromatography (200 g, 60-200 mesh silica gel) with 5% ether-hexane gave 7.5 g (83%) of a colorless oil, \( n_D^{21} 1.4905 \). An analytical sample was collected via vpc (10' x 3/8", 10% SE-30), which shows the following spectral properties; ir (film), 3.24, 3.40, 5.80 (s = 0), 6.10, and 11.00 \( \mu \); nmr (CDCl\(_3\)), \( \tau 8.80-7.70 \) (19H, m), 5.30-4.80 (2H, m), and 4.60-3.85 (1H, m).

**Anal. Calcd for C\(_{14}\)H\(_{22}\O:** C, 81.50; H, 10.75.

**Found:** C, 81.46; H, 10.73.

\( 1-(5\text{-Hexenyl})-3-(2\text{-propenyl})\text{bicyclo}[2.2.2]octan-2\text{-one (174)} \). A 24.5 ml (41.6 mmole) sample of methyl-lithium in ether was added slowly under argon into a solution of 4.6 g (45.5 mmole) of diisopropylamine in 20 ml of freshly purified tetrahydrofuran at 0°. This reaction mixture was held at 0° for 0.5 hr and cooled down to -78°. To this lithium diisopropoxylamide solution was added dropwise a solution of 7.8 g (37.8 mmole) of \( 1-(5\text{-hexenyl})\text{bicyclo}[2.2.2]octan-2\text{-one in 15 ml of} \)
tetrahydrofuran. After the addition of the ketone, the solution was allowed to be warmed to -30 to -40°C for 2 hr. To this cold reaction mixture 23 g (0.19 mole) of freshly distilled allyl bromide was added in one portion. The reaction mixture was stirred at room temperature for 48 hr, and poured into 200 ml of cold 10% aqueous hydrochloric acid. The aqueous solution was extracted with four 150-ml portions of ether. The combined ether extracts were washed with 50-ml of 10% aqueous hydrochloric acid, 100 ml of water, 100 ml of saturated aqueous sodium bicarbonate solution, and 100 ml of brine. The organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent under reduced pressure gave 9.0 g of crude oil. The crude oil was chromatographed on 200 g of 60-200 mesh silica gel with 5% ether-hexane as solvent. The first fraction gave 7.5 g (81%) of a colorless product, and the second fraction gave 300 mg of unreacted starting ketone. An analytical sample was prepared via vpc (10' x 3/8", 10% SE-30 column, temperature 170°C), which shows the following spectral properties: ir (film), 3.24, 3.42, 3.50, 5.84, 6.10, 10.10, and 11.00 μ; mmr (CDCl₃), δ 8.80-7.10 (20H, m), 5.30-4.80 (2H, m), and 4.55-3.80 (1H, m).

**Anal. Calcd for C₁₇H₂₆O: C, 82.87; H, 10.64.**

**Found: C, 82.77; H, 10.87.**

1-(5-Carbomethoxypentyl)-3-(2-carbomethoxyethyl)bicyclo[2.2.2]octan-2-one (175). Ozone (generated by a Welsbach T-408 Ozonizer) was passed through a solution of 1 g (4.06 mmole) of 1-(5-hexenyl)-3-(2-propenyl)-
bicyclo[2.2.2]octan-2-one in 50 ml of absolute methanol at -78° for 15 min. The cold solution was poured into a mixture of 2 g of sodium iodide, 4 ml of acetic acid, and 100 ml of methanol. After stirring at room temperature for 2 hr, the solution was treated with saturated aqueous sodium thiosulfate to give a colorless solution. Most of the methanol was removed under reduced pressure and the residue was diluted with 100 ml of water. The mixture was extracted with five 50-ml portions of ether and the organic layer was washed with 50 ml of 10% sodium bicarbonate solution, 50 ml of water, and 50 ml of brine. After drying over anhydrous magnesium sulfate and filtration, the solvent was removed in vacuo, giving a clear oil. This crude aldehyde was dissolved in 100 ml of reagent grade acetone and the mixture was cooled to 0°. To this mixture, Jones reagent (8 N) was added dropwise until the solution turned brown (permanently). Most of the acetone was removed under reduced pressure, and the residue was diluted with 100 ml of water. The aqueous solution was extracted with five 50-ml portions of ether and the organic layer was extracted with four 50-ml portions of 10% aqueous sodium hydroxide solution. The basic solution was neutralized with concentrated hydrochloric acid and extracted with five 50-ml portions of ether. The ether layer was washed with 50 ml of brine and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent gave a thick gummy
solid. This crude acid was dissolved into 20 ml of ether and treated with diazomethane solution. After removal of solvent, a 1.05 g (83%) of the diester was obtained as a clear oil. An analytical sample was prepared via vpc (10' x 3/8", 10% SE-30 column, temperature = 170°), which shows the following spectral data: ir (film), 3.40, 3.49, 5.75, 5.85, 7.90, and 8.55 μ; nmr (CDCl₃), δ 8.90-6.90 (20H, m), 6.36 (3H, s), and 6.32 (3H, s).

Anal. Calcd for C₁₇H₂₆O₅: C, 65.78; H, 8.44. Found: C, 65.82; H, 8.53.

Ethylene Ketal of 1-(5-Hexenyl)-3-(2-propenyl)bicyclo[2.2.2]octan-2-one (176). A mixture of 7.2 g (29.3 mmole) of 1-(5-hexenyl)-3-(2-propenyl)bicyclo[2.2.2]octan-2-one, 50 ml of ethylene glycol, 400 mg of p-toluenesulfonic acid, and 150 ml of toluene was heated at reflux for 72 hr. Water was continuously withdrawn from a Dean Stark trap during this refluxing period. The solution was cooled to room temperature and poured into 200 ml of 10% potassium bicarbonate solution. The toluene solution was separated and the aqueous solution was extracted with four 150-ml portions of ether. The ether layer and toluene layer were combined and washed with two 100-ml portions of water and 100 ml of brine. After drying over anhydrous magnesium sulfate and filtration, the solvent was removed in vacuo, yielding 8.5 g of crude oil. This oil was chromatographed on 200 g of 60-200 mesh
silica gel with 5% ether-hexane as solvent to give 6.7 g (79.5%) of the ketal as a colorless oil, \( n_D^{25.4} = 1.4987 \). An analytical sample was prepared by vpc (10% SE-30 column) which gave the following spectral data: ir (film), 3.25, 3.40, 3.49, 6.10, 8.80, 9.00, and 11.00 \( \mu \); nmr (CDCl\(_3\)), \( \tau \) 8.90, 7.60 (20H, m), 6.12 (4H, s), 5.25-4.85 (4H, m), and 4.60-3.80 (2H, m).

**Anal.** Calcd for C\(_{19}\)H\(_{30}\)O\(_2\): C, 78.57; H, 10.41.

**Found:** C, 78.72; H, 10.50.

**Ethylene Ketal of 1-(5-Carbomethoxypentyl)-3-(2-carbomethoxyethyl)-bicyclo[2.2.2]octan-2-one (177).** A suspension of 0.4 g of ruthenium dioxide in 50 ml of carbon tetrachloride was stirred at 0\(^\circ\) and treated with a solution of 3.2 g of sodium metaperiodate in 50 ml of water. The black oxide dissolved in about 1 hr. The clear carbon tetrachloride layer was separated and filtered through glass wool. The clear yellow filtrate of ruthenium tetroxide was added to a solution of 2 g (6.9 mmole) of the ethylene ketal of 1-(5-hexenyl)-3-(2-propenyl)bicyclo[2.2.2]octan-2-one in 100 ml of acetone. A black precipitate appeared immediately, and the reaction mixture was


added to a solution of 2 g of sodium metaperiodate in 50 ml of water. When precipitation of the black ruthenium dioxide seemed complete, 3 g of periodate was added to dissolve it. The addition was repeated twice more in the course of 12 hr. Isopropyl alcohol was added to destroy the excess reagent, the mixture was filtered to remove black ruthenium dioxide, and the solvent was removed by evaporation. The oily residue was diluted with 200 ml of ether and washed with 100 ml of water, and with 100 ml of brine. After drying over anhydrous magnesium sulfate, the organic solution was condensed to about 20 ml, and treated with diazomethane solution. Removal of ether solvent in vacuo gave 1.93 g (80%) of a thick oil; ir (film), 3.40, 3.49, 5.75, and 8.50 \mu m; nmr (CDCl$_3$), \texttau 9.00-8.10 (17H, m), 8.00-7.10 (4H, m), 6.40 (6H, s), and 6.20 (4H, m).

**Anal. Calcd m/e for C$_{18}$H$_{30}$O$_6$:** 354.20421. C, 64.39; H, 8.53.

**Found:** 354.20469. C, 65.54; H, 8.48.

**Ethylene Ketal of 4,5-Bis(trimethylsilyloxy)tricyclo[8.2.2.1$^2$,10$^7$]-pentadec-4-en-5-one (178).** Sodium (6.0 g) was dispersed in 125 ml of dry toluene under nitrogen. Trichloromethylsilane (20 ml) was slowly added to this dispersion. A solution of 2.25 g (6.35 mmol) of the ethylene ketal of diester 177 in 25 ml of dry toluene was added dropwise to the rapidly stirred refluxing solution over a 12 hr period. Reflux was continued for
another 12 hr. The solution was allowed to cool and then filtered through Celite. The solvent was removed under reduced pressure. The residue oil (3.05 g) was chromatographed on 100 g of 60-200 mesh silica gel with chloroform as solvent. A 2.15 g of compound 178 was obtained; ir (film), 3.39, 3.49, 6.00, 8.00, 8.95, 11.90, and 13.40 μ; nmr (CDCl₃), δ 9.80 (18H, br), 8.90-7.00 (20H, m), and 6.10 (4H, br m).

**Anal.** Calcd m/e for C₂₃H₄₂Si₂O₄: 438.26213.

**Found:** 438.26308.
REFERENCES


10. P. v. R. Schleyer, private communication to P. G. Gassman.


16. In the presence of p-toluenesulfonic acid.

17. Homeomorphic isomerization is used here to mean a conformational change in which three-stranded molecules turn inside out by passage of one chain through the ring defined by the other two chains.


26. Yields of 71 and 70 have not been optimized.


42. Compound 95 was not soluble in non-polar solvents such as hexane or pentane, only very slightly soluble in ether or tetrahydrofuran.


50. The author would like to thank Professor Buchanan for his generosity in providing the details of the synthesis of compound 121 during his private communication with Professor Gassman. Physical properties of 121 and its precursors in the experimental part of this thesis were compared with those provided by Professor Buchanan and found satisfactory.


68. Ethylene thioketal is used here to protect the ketone because its resistance to weak acid would be advantageous in our later synthetic scheme.


71. The author would like to thank Professor Swenton for his helpful information and discussion on these reagents.

72. Ireland's procedure could not be applied here because with excess lithium in ethylamine and t-butanol, the terminal olefin was also reduced completely.


75. P. G. Gassman, unpublished experimental result.


80. Siegfried Hünig and Herbert Kahaneck, Chem. Ber., 90, 238 (1957); see also C.A., 51, 12049f (1957).


