CROSS, John Howland, 1946-
THE SYNTHESSES OF (t)-GRANDISOL,
(t)-DICTYOPTERENE A, AND
(t)-DICTYOPTERENE C'.

Rice University, Ph.D., 1973
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan
RICE UNIVERSITY

THE SYNTHESSES OF (±)-GRANDISOL, (±)-DICHTYOPTERENE A, AND (±)-DICHTYOPTERENE C'

by

John Howland Cross

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Doctor of Philosophy

Thesis Director's Signature

W. E. Billups

Houston, Texas

September, 1973
Acknowledgments

I thank Dr. W. E. Billups for conceiving these projects, and for his timely suggestions during their execution. I value Mr. C. V. Smith's collaboration on several experiments in the grandisol synthesis.

Financial support from an NSF Traineeship and from the Robert A. Welch Foundation is gratefully acknowledged.
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The Synthesis of (±)-Grandisol
ABBREVIATIONS

BWRL  Boll Weevil Research Laboratory, Entomology Research Division, Agricultural Research Service, U. S. D. A., State College, Mississippi

COD  1,5-Cyclooctadiene

DVCB  cis-1,2-Divinylcyclobutane

Lg  An unspecified ligand

Mulheim Group, the
Scientists at the Max Planck Institut für Kohlenforschung, Mulheim-Ruhr who have studied the zero valent nickel catalyzed dimerization of 1,3-dienes

Ni(AcAc)$_2$  Nickel acetylacetonate

Ni(COD)$_2$  Bis-(cyclooctadiene-1,5)-nickel(0)

(Si)$_2$BH  Bis-3-methyl-2-butylborane(Dismethylborane)

t-CHP  Tricyclohexylphosphine

t-PPP  Tri-(2-phenylphenyl) phosphite

VCH  4-Vinylcyclohex-1-ene
This synthesis of grandisol satisfies two often antagonistic aims of Organic Chemistry. It provides an economical route to a chemical important to the lay community and uses new chemistry to do so. As a bonus, it is simple compared to grandisol's complexity. The synthetic objective, 1, is a C\textsubscript{10} terpenoid containing a hydroxyl, a double bond, a cyclobutane, and two asymmetric centers.\textsuperscript{1} The simplicity and novelty spring from the nickel-catalyzed dimerization of isoprene,\textsuperscript{2} which generates the double bond, the cyclobutane, and both asymmetric centers. Selective hydroboration and oxidation add the hydroxyl. The demand for grandisol arises from its potential for controlling America's major cotton pest, the boll weevil \textit{Anthonomus grandis} Boheman. It is one of four compounds, secreted by male boll weevils, that synergistically attract female weevils.\textsuperscript{3} This pheromone, as the four compounds are called, increases the number of females who mate and lay their egg in a square (cotton flower bud) or cotton boll, destroying $200,000,000 worth of cotton yearly.\textsuperscript{4} When this chemical link between males and females is interrupted, the weevil population, according to preliminary experiments, decreases significantly.\textsuperscript{5} One of many schemes envisioned to break the link is saturation of a field with the pheromone. Entomologists at the Boll Weevil Research Laboratory (BWRL) estimate this could be done with 3mg of the pheromone per acre per week.\textsuperscript{4} Such a minute quantity of a naturally occurring pheromone will not poison anyone.
or damage the environment, nor can boll weevils develop an immunity to it. In contrast, insecticidal controls of this creature now account for one-third of all the insecticides used in this country, and immune weevil strains are developing.

Of the four compounds, three are available cheaply, while grandisol sold for $0.70/g, due to a lengthy synthesis, requiring an expensive starting material. Using our synthesis, Chemical Samples Company sells it for $35, and they expect to drop the price to $10/g as they gain experience and improve the synthesis.

The Pheromone

The staff of the BWRL has conducted all the exploration of the boll weevil sex attractant pheromone since they discovered it in 1963. Simultaneously, they have examined other biological controls such as chemosterilants, feeding stimulants, cotton attractants, and larval development inhibitors (juvenile hormones). In 1968, they showed that live males placed in traps effectively controlled boll weevil populations until late summer migrations inundated them. By 1966, they had a laboratory bioassay and could begin to isolate, identify, and synthesize the pheromone. To accomplish these goals, they macerated 4.5 million weevils of both sexes in dichloromethane and extracted 54.7 kg of feces with dichloromethane. Following steam distillation, liquid-liquid partition chromatography on Carbowax 20M coated silica gel separated the extract into five inactive fractions; combining two fractions restored full activity in the bioassay. Separate
chromatography of the two fractions on Adsorbosil-CABN (25% silver nitrate on silica gel) separated each into four fractions; combination of two fractions, one from each original fraction, gave full bioanalytical activity. One of these latter fractions separated into eight peaks upon gas-liquid partition chromatography (GLPC) on Carbowax 4000. The eighth peak, constituting 90% of the fraction, was collected and chromatographed by GLPC on SE-30, giving two peaks. Since no further separation occurred on a Carbowax 20M support coated open tube (SCOT) column, these two peaks were considered to be pure compounds. The other fraction gave six peaks on the Carbowax 4000 column; the sixth was collected, by preparative GLPC, and gave a single peak on the SE-30 column. GLPC on the Carbowax 20M SCOT column gave two peaks, which they considered were pure compounds. These four compounds together have full potency in the bioassay. Mass, proton nuclear magnetic resonance, and infrared spectra provided enough information to assign the structures 1, 2, 3, and 4 to the compounds. They are optically active.

Using an internal standard, they estimated the relative concentrations of each component in the natural pheromone.
No one has studied the pheromone's biosynthesis, but the BWRL staff's observation that males fed fresh cotton squares produce more pheromone than those fed an artificial diet led them to postulate that the weevils convert the two major terpenes in the essential oil of cotton squares, \textit{trans}-\textit{\beta}-ocimene or myrcene, into the pheromone.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{pheromone_structure.png}
\caption{Structure of the pheromone and its precursors.}
\end{figure}

Since female weevils prefer to lay their egg in a square,\textsuperscript{8} this postulate implies that the pheromone does not simply attract females to males, but attracts females to males at a favorable mating spot.

A synthesis of each component confirmed the assigned structures. The syntheses of the cyclohexanes are straightforward and not really pertinent to this work. Since the grandisol synthesis was the sole source of grandisol for three and a half years and is the one ours suppliants, it will be discussed in detail. But first, I wish to close the discussion of the pheromone with the results of its field tests.

In early 1969, the synthetic pheromone, called Grandlure, was ready for testing in the field against the attractive power of square-fed male weevils. The first results were disappointing; no more weevils came to a drop of Grandlure than to an empty trap.\textsuperscript{9} This touched off an intensive effort to formulate Grandlure effectively. It took a year to learn that Grandlure must be combined with a slow release agent, a humectant, a diluent, and water.\textsuperscript{9} But the effort was worth it;
extensive tests showed the synthetic pheromone was 80% as effective as the male weevils. Incidentally, field tests like these show the pheromone is sometimes an aggregating hormone, since in the spring and fall the traps collect equal numbers of males and females. Although refinement of the formulation may increase the potency of the synthetic pheromone, there exists a distinct possibility the natural one consists of five or more components. The limiting factor in finding them or in improving the formulation is the bioassay, which is insensitive. Many times the bioassay showed a formulation was as attractive as the natural pheromone only to have it fail in the field.

The Original Grandisol Synthesis

There was, of course, no hope of obtaining grandisol from natural sources, so the BWRL group modified their structure-proofing synthesis to produce gram quantities of grandisol. This synthesis produced enough grandisol for the field tests, although it would be unserviceable in a nation-wide eradication program.

Beginning with commercially available starting materials, they added acetic acid to methyl vinyl ketone to give 3-oxobutylacetate, which was converted in 80% yield to lactone 11 by Cornforth's 12 and Remizov and Tsetkova's 13 methods. The photochemical [2+2] cycloaddition proceeded quite smoothly, since the yield was good and distillation separated 12(cis and trans) from other products. It was, however, slow and laborious. After addition of 12(cis and trans) to excess methyl lithium, the cis diol 13b, crystallized out, while the trans, 13a, remained in solution. The elimination with acetic anhydride afforded the highest
percentage of acetate 14 of all the methods surveyed. Following LAH reduction, a spinning band distillation separated grandisol and 15. With 3-oxobutylacetate as the starting material, the overall yield was 17%.

\[
\text{AcOH} + \text{CH}_2\text{CO} \xrightarrow{44\%} \text{CH}_2\text{CO} \xrightarrow{2. \text{KOH}} \text{HO} \xrightarrow{1. \text{BF}_3}, \text{CH}_2\text{CO}
\]

PPA 80% for two steps

\[
P_{\text{PA}} \xrightarrow{80\% \text{for two steps}} \text{9}
\]

hν, CH2=CH2 acetophenone (sens) 50%

\[
h\nu, \text{CH}_2=\text{CH}_2 \xrightarrow{50\%} \text{9} + \text{1}
\]

\[
\text{CH}_3\text{Li} \xrightarrow{65\%} \text{11} \xrightarrow{90\%} \text{12}
\]

\[
\text{Ac}_2\text{O} \xrightarrow{90\%} \text{2 parts}
\]

\[
\text{13} + \text{14}
\]

\[
\text{1 part} \xrightarrow{80\%} \text{15}
\]

\[
\text{HO} \xrightarrow{1. \text{LAH}} \text{HO}
\]

\[
\text{HO} \xrightarrow{1. \text{LAH}} \text{HO}
\]
History of this Synthesis

Even before the field testing was satisfactorily completed, grandlure began to receive publicity, owing to a general interest in biological controls and a specific interest in limiting the use of DDT and related insecticides. Part of this publicity was an article in Chemical and Engineering News describing the BWRL synthesis. Many hundreds of persons familiar with the concepts and practices of Organic Chemistry must have seen the structure of grandisol displayed in the article, but only one of these, Professor W. E. Billups, combined a critical analysis of it with a bit of organic chemistry to create a surprisingly simple synthesis. In the course of his analysis, Professor Billups realized that the carbon skeleton of grandisol was one of the several [2+2] cycloadducts of isoprene; furthermore, it was a special one, a "cis-divinyl" isomer. Conversant with cyclobutane chemistry and

![Chemical structures](image_url)

having industrial experience with transition metal catalysis, he was aware of Heimbach's nickel-catalyzed dimerization of 1,3-butadiene to 1,2-cis-divinylcyclobutane (DVCB). Thus, this synthesis is dimerization of isoprene, a cheap starting material, to 5 with a zero-valent nickel-ligand catalyst, then hydration with the selective borohydride, disiamylborane, and hydrogen peroxide. The selective hydroboration
of 2-methyl-1,5-hexadiene to 5-methyl-5-hexen-1-ol boded well for a similar specificity toward the isoprene dimer. That the synthesis was

\[
\begin{align*}
\text{C} & \rightarrow \text{C} \\
\text{C} & \rightarrow \text{O} \\
\text{C} & \rightarrow \text{C} \\
\end{align*}
\]

not immediately reduced to practice resulted from an a priori expectation of three isoprene dimers, \(6\) and \(7\), as well as \(5\).

Two years later, 1972, when Professor Heimbach came to this country to present a talk at the ACS spring meeting in Boston, Professor Billups invited him to give a seminar at Rice. In refusing, Heimbach sent a copy of his ACS paper, in which he reported the dimerization of isoprene to a single cyclobutane, \(5\), with less than 1% of isomers \(6\) and \(7\).

Results

We reproduced Heimbach's work, using \(\text{tris}(2\text{-phenylphenyl})\) phosphite (t-PPP)\(^{16}\) and the nickel atom from \(\text{bis}(1,5\text{-cyclooctadiene})\)-nickel(0) [\(\text{Ni(COD)}_2\)]\(^{17}\) as the nickel-ligand dimerization catalyst. The dimerization will be discussed in detail in the next section. Glpc on Carbowax 20M separated the crude reaction mixture into five dimers. In order of elution, they are: \(5\), \(8\) with the indicated uncertainty in the methyl's position, \(1,5\text{-cyclooctadiene from the catalyst, an unidentified dimer(s), and 9.}\)
9 arises from 5 by both a thermal and a nickel-catalyzed Cope. After collecting a little 5 by preparative glpc, we hydrated it with disiamylborane and $\text{H}_2\text{O}_2/\text{OH}^-$, collected the major peak by glpc, and identified it as grandisol by its NMR. The glpc retention time and NMR of a genuine sample, provided by the BWRL staff, were identical to those of our material. A sample sent to the BWRL showed an activity identical to the natural pheromone in their bioassay. We consulted with Dr. Kenneth Greenlee and Dr. Terry Holton at Chemical Samples Company as they transformed our work into a commercially feasible synthesis. They now dimerize isoprene 11$^4$ at a time and have reduced the cost of grandisol from $\sim 70$/g to $35$/g. A problem has arisen in the commercial synthesis, however, because the boiling points of 5 and 1,5-cyclooctadiene coincide.$^{19}$ As a result, the grandisol resulting from hydroboration of the mixture must be carefully distilled to separate it from 4-cycloocten-1-ol. To solve this problem, we generated the catalyst in situ without using 1,5-cyclooctadiene. Our final pheromone study was the synthesis of (±)-norgrandisol, 10. 1,3-butadiene dimerized under the influence of the same nickel-ligand catalyst to DVCB, which was hydroborated and oxidized to 10. We are awaiting the results of its bioassay.
The Mechanism of the Dimerization \(^2,20-28\)

The experimental ease of this reaction belies its complex mechanism. Shown on the next page are the mechanisms proposed for this reaction. The structures labeled with an \(^i\) have been isolated, and the arrows between them are known reactions, but those between other structures are speculations.

As intimated in the transformation of \(^{16}\) to \(^{17}\) and \(^{17}\) to \(^{18}\), the Mulheim group feels these reactions have several steps that are governed by a set of Woodward-Hoffmann rules modified to account for the nickel atom. \(^2,21,23\) Furthermore, they believe the nickel atom formally changes oxidation states in these intermediates; \(^2\) a generality they stress is the overall constancy of the electron density around the nickel atom. \(^21\) In order for a reaction to work with an electron donating substrate, an electron accepting ligand must be used and vice versa. \(^21\) Coupling, for example \(^{17}\) to \(^{18}\), decreases the electron density and is impelled by the entrance of another ligand. \(^21\)

The discussion above shows how important the ligand is. One cannot yet predict the effect of a particular ligand, although some trends are visible. A nickel atom liganded to only 1,3-dienes, called naked nickel, is a trimerization catalyst affording cyclododecatrienes. \(^21,24\) Liganded to certain phosphines, electron donors, or phosphites, electron acceptors, the nickel, called a dimerization catalyst or a nickel-ligand catalyst, dimerizes 1,3-dienes. \(^21\) Sterically hindered phosphorus atoms bias the reaction towards cyclooctadienes and cyclobutanes rather than vinylcyclohexenes, while increasing the reaction rate. \(^18,21\) Thus, the Mulheim group found tri-(2-phenylphenyl) phosphite to be an excellent
Note: We cannot place the allylic methyl group in 8 from our evidence.

Proof for isolated structures:

\[ \text{17i; pmr} \]
\[ \text{17ai; X-Ray, pmr} \]
\[ \text{19i; the reaction shown} \]
\[ \text{16i, 18i; regeneration of the hydrocarbon with CO} \]

References:

\[ \text{16} \rightarrow \text{17} \rightarrow \text{18} \quad \text{Ref. 2} \]
\[ \text{16i} \rightarrow \text{17i} \leftarrow \text{18i} \quad \text{20} \]
\[ \text{19} \rightarrow \text{19a} \quad \text{21} \]
\[ \text{19i} \rightarrow \text{octane} \quad \text{24} \]
\[ \text{5} \rightarrow \text{18} \rightarrow \text{9} \quad \text{Ref. 21a} \]
\[ \text{17ai} \rightarrow \text{22} \quad \text{22} \]
\[ \text{17i} \rightarrow \text{VCH} \quad \text{20} \]
ligand for the dimerization of isoprene to $\mathfrak{s};^2$ it is a dimerization catalyst, it is quite sterically hindered, and its electron accepting ability offsets the electron donation from isoprene. Variation of the ligand may give a better yield of $\mathfrak{s}$, although we feel t-PPP is nearly the optimum.

An important question about this reaction's synthetic utility is: How does one avoid a mixture of isomers $\mathfrak{s}$, $\mathfrak{6}$, and $\mathfrak{7}$? Upon examining, one sees $\mathfrak{16}$ has a point of inversion. The corresponding complexes for $\mathfrak{6}$ and $\mathfrak{7}$ have a plane of symmetry. This phenomenon is seen in the piperylene dimerization also. Of the six complexes corresponding to $\mathfrak{16}$ that may be written for cis-piperylene and trans-piperylene, the two with a point of inversion give a product, while only one of the four with a plane of symmetry does.$^{21,25}$ $\mathfrak{16a}$, which cannot have a point of inversion, is highly reactive in the dimerization.$^{21}$ No more detailed explanation exists.

A further piece of evidence to bolster the intermediacy of $\mathfrak{16}$ through $\mathfrak{16a}$ is the experimental observation that the reduction of Ni(AcAc)$_2$ to Ni(COD)$_2$ works better when a catalytic amount of butadiene is present. Apparently the butadiene catches the newly-reduced nickel atom before it can precipitate as "Raney" nickel and holds it until it can complex with the 1,5-cyclooctadiene. If isoprene is substituted for butadiene, metallic nickel precipitates,$^{19}$ indicating $\mathfrak{16}$ is less stable than $\mathfrak{16a}$.

Although a fraction of $\mathfrak{17}$ probably cyclizes immediately to $\mathfrak{18}$, the majority of it passes to $\mathfrak{19}$ and $\mathfrak{19a}$. Our contention rests on, first, the existence of such a big-$\pi$-allyl species as shown by the isolation
of \( n \)-octane from the diethyl aluminum hydride reduction of 194. If 174 was the intermediate, the reduction should have given 2-octene. Second, 17ai may result from t-CHP's greater ability to donate electrons, which allows the nickel to release two \( \pi \)-allyl electrons to a double bond.21 Third, the dimerization of isoprene is slower than butadiene,26 which argues that the intermediates are more stable and, hence, have a higher energy of activation in the product-forming reaction. Fourth and last, one cannot get from 17 to 8 directly. When the Mulheim group decomposed 17ai with CO in toluene at -30°, they obtained a 90% yield of d,l-limonene, 22 whereas, in isoprene at 25° with t-PPP, we found exclusively 8: 19 shows a plausible route to 8. Perhaps 17ai's most important contribution is the proof that nickel can form both sigma and \( \pi \)-allyl bonds with the isoprene dimer. In any case, the equilibrium concentrations of 17 and 19 and 19a are unknown. Likewise, the rearrangement of 5 to 9 is unexplored, although under appropriate conditions, the butadiene dimerization yields 40% of DVCB, indicating a large share of the reaction can pass through 5 to 9.18,21,27 On the other hand, 18i and the piperylene cyclobutane dimers decompose to the 1,3-diene when treated with the catalyst at 50mm Hg.21,25

Discussion of Results

For our initial experiments, we decided to reproduce Heimbach's work exactly.2 Accordingly, Ni(AcAc)₂ was reduced with AlEt₃ in the presence of excess 1,5-cyclooctadiene and a catalytic amount of 1,3-butadiene and yellow crystals were obtained.17 Tri-(2-phenylphenyl) phosphite is best made by the Organic Synthesis16 reaction of
phosphorous trichloride and the phenol, in this case, 2-phenylphenol. After the ligand (1 equiv) dissolved, slowly, in deoxygenated isoprene (60-100 equiv), we added the Ni(COD)$_2$ (1 equiv), which dissolved rapidly. We allowed the deep red solution to stir at 25° until gipc indicated the quantity of $\frac{5}{2}$ had reached a steady state, about one week.* The Mulheim group used capillary columns coated with squalene, but by a lucky chance, the column in our chromatograph when we first ran the dimerization was a Carbowax 20M column, and it gave baseline separation of all the products. NMR spectra revealed the structures of four products; a fifth remains unidentified. Pertinent data are shown below.

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Structure</th>
<th>5</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elution time:</td>
<td>8 min</td>
<td>10.5</td>
<td>16</td>
</tr>
<tr>
<td>NMR spectrum:</td>
<td>p. 72</td>
<td>p. 72</td>
<td>-</td>
</tr>
<tr>
<td>IR spectrum:</td>
<td>p. 79</td>
<td>p. 79</td>
<td>-</td>
</tr>
<tr>
<td>% efficiency:</td>
<td>18.8</td>
<td>10.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Knowing the number of moles of 1,5-cyclooctadiene in the reaction and assuming the thermal conductivity detector responded equally to all the dimers and 1,5-cyclooctadiene, we calculated the efficiency, the yield based on isoprene consumed, by weighing the peaks of the gas chromatogram.

* When Chemical Samples runs this reaction in an 114 spherical flask, it warms itself to about 35° and reaches the steady state in two days.19
The unknown compound has proven inordinately difficult to identify; therefore, we think it is two compounds. It is a genuine dimer, since its mass spectrum has a molecular ion at m/e = 136. Other prominent peaks are at m/e = 121, 108, 93, 81, and 68, the base peak. Unlike the other dimers, it is a conjugated diene; the IR shows a double bond absorbance at 1650 cm\(^{-1}\) and another 38 cm\(^{-1}\) below that, the characteristic absorbance pattern of conjugated double bonds;\(^{29}\) the ultraviolet absorbance at 230 nm confirms this and adds that two alkyl substituents are on the double bonds. One is the methyl group that shows a broad singlet in the NMR at 8.4\(\pi\).\(^{30}\) The NMR absorbances at 5.2\(\pi\) and 5.4\(\pi\) and in the IR at 3080 cm\(^{-1}\) and 888 cm\(^{-1}\) indicate a terminal methylene. The IR absorbance at 966 cm\(^{-1}\) indicates a \textit{trans} double bond. Thus, a partial structure is:

![Chemical Structure Image]

This partial structure has the four olefinic protons predicted by integration of the NMR. It suggests the base peak in the mass spectrum is a charged isoprene molecule. Coming from a nickel catalyzed dimerization, this is an unusual partial structure and is worth a deeper exploration.

A small peak, or rather a small elevation, before the cyclobutane peak must represent the presence of some \(\delta\) or \(\zeta\).

The cyclobutane, \(\delta\), is heat sensitive and undergoes a thermal Cope with a half-life estimated at 30 hr at 30\(^\circ\).\(^2\) This affected the attempts to distill \(\delta\), since at the low pressure required to prevent the Cope, the boiling points of \(\delta\) and COD coincided.
We have made two attempts to avoid the use of COD, since on a large scale, distillation is the only way to separate \( \mathbf{5} \) from the other dimers. Hydroboration of the \( \mathbf{5} \) and COD mixture is unnecessarily complicated, as is the distillation of grandisol after hydration. The first attempt was a reduction of Ni(AcAc)\(_2\) in the presence of \( \mathbf{9} \) instead of COD. The nickel precipitated as the metal. In the second, we dissolved Ni(AcAc)\(_2\) and triphenyl phosphite in isoprene and generated the catalyst successfully with triethylaluminum, as is evident from the 15% yield of \( \mathbf{9} \). Triphenyl phosphite was substituted on the chance it might serve as well as t-PPP, but an insignificant steady state concentration of \( \mathbf{5} \) resulted. The \textit{in situ} generation also eliminates the isolation of the pyrophoric catalyst.

Reuse of the catalyst is another important goal for the commercial synthesis. Currently, after a maximum quantity of \( \mathbf{5} \) forms, the nickel is precipitated by addition of four equivalents of triphenyl phosphite. The Mulheim group, however, has made DVCB by evaporating the butadiene and dimers from the nickel-ligand catalyst, and then redissolving it in fresh butadiene. They used the catalyst four times this way.\(^{18}\) One of the difficulties here is that as the dimers evaporate, the nickel finds itself in an increasing concentration of an unacceptable ligand, \( \mathbf{9} \). Metallic nickel will precipitate, unless the t-PPP alone can ligand it. Another problem is what effect distilling the unreacted isoprene will have on the nickel-catalyzed Cope. Given the unpredictability of this reaction, our only course is to attempt this work-up.

I discussed on page 12 why t-PPP is an excellent ligand. Throughout this project, we made no effort to improve upon it, but
it has some imperfections. Though 2-phenylphenol is plentifully available, its reaction with PCl$_3$ gives, after recrystallization, only a moderate yield of t-PPP. With a molecular weight of 536amu, it requires many grams for every reaction. For this reason also, we must attempt to reuse the catalyst. If one could selectively precipitate the nickel, as NiO or NiCl$_2$, the ligand would be recovered after distilling all the dimers. Is there a better ligand? Balancing the reasonable increase in 5's yield against the availability of another ligand, the answer is no.

The disiamylborane/H$_2$O$_2$ hydration is a standard procedure developed by H. C. Brown and co-workers. Using it, they hydrated 2-methyl-1,5-hexadiene to 5-methyl-5-hexen-1-ol in 68% yield.

\[
\begin{align*}
\text{5} & \quad \text{\rightarrow} \quad \text{1} \\
\end{align*}
\]

We collected milligram quantities of 95% pure 5 by preparative glpc. 8 was the only contaminant. Slow addition of 1 equiv of disiamylborane to an ice-cold THF solution of 5 insured selective addition. After oxidation, work-up, and vacuum evaporation, a viscous, colorless liquid remained. Glpc on SE-30 or a non-polar UCON showed a significant amount of low boiling material, but only one major peak, which proved to be grandisol, as its glpc retention time and NMR was identical with that of an authentic sample from the BWRL. Simultaneous chromatography of a known amount of the grandisol reaction mixture and
geraniol showed the yield was 50%. Preparative chromatography, which I thank Mr. C. V. Smith for performing, afforded pure grandisol for a bioassay, which rated our material as active as the natural alcohol. Chemical Samples developed the reactions from our 100mg scale to a 100g scale.

As a model system for the hydroboration, we used DVCB. The alcohol so obtained is demethylated grandisol or norgrandisol, $^{10}$. This molecule differs from grandisol only in its volume; the functional groups and their relative placement are identical. We have submitted a sample to EWRL for bioassay. The results promise to be amusing, since inactivity will indicate an exceedingly specific response to grandisol's volume. Degrees of activity mean little in this insensitive

\[
\begin{array}{c}
\text{HO} \\
\text{C}
\end{array}
\]

bioassay, so any response will warrant some field testing, because norgrandisol is easier to make than grandisol. Under selected conditions, the Mulheim group converts butadiene to DVCB in 40% efficiency. $^{18}$ Due to the absence of the methyl group, the reaction is perhaps ten times faster than that of isoprene. $^{18,21d}$ DVCB is less thermally labile than 5 and boils lower than COD, so we distilled it easily to 90% purity. The hydroboration is simpler since the alcohol cannot be contaminated with another isomer.
The Synthesis of Dictyopterene A and C
The Dictyopterenes are a class of $C_{11}$ hydrocarbons isolated by Moore, Pettus, and Doty$^{31a,b,c}$ from the essential oil of algae of the genus Dictyopteris. The hydrocarbons found in the oil so far are shown on the facing page. Jaenicke, Donike, Akintobi, and Müller$^{32a}$ independently discovered $D'$, which they called Sirenin, in the female gametes of the marine brown alga Ectocarpus siliculosus (Dillw.) Lyngb. For reasons to be developed shortly, we wished to synthesize $A$, $B$, $C'$, and $D'$ and isolate $D$ and $D$ for the first time. The asymmetric compounds are optically active in nature, but since our syntheses dealt only with racemic compounds, I will refer to the enantiomeric pair unless otherwise stated.

Biologically, they are interesting, because they are the only compounds besides dimethyl sulfide isolated from wet, undecomposed seaweed to possess odor.$^{1a}$ Moreover, naturally occurring cyclopropanes are still rather rare. Jaenicke and co-workers$^{32a,b}$ are indubitably pursuing the precise nature of $D'$'s chemotactic action during the mating of E. siliculosus. With two exceptions, their biosynthetic origins are unknown and unexplored. Pettus and Moore$^{31c}$ observed that naturally occurring $A$ pyrolyzed to the enantiomer of naturally occurring $C'$; therefore, $C'$ must arise from $C$. They also observed that naturally occurring $B$ pyrolyzed to the enantiomer of naturally occurring $D'$; therefore, $D'$ must arise from $D$. Unfortunately, Jaenicke and co-workers$^{32a}$ did not publish the specific rotation of Sirenin.

Commercially, A's characteristic "odor of the sea"$^{33}$ aroused the interest of several flavor and fragrance companies, resulting in the synthesis of $A$, $D$, their double bond isomers $28$ and $29$ and $C'$.$^{34}$
Chemically, they are quite simple, as far as natural products go; yet the monocyclic ones represent the relatively unstudied specialty of divinylcyclopropanes (DVCP's). When we undertook these syntheses, cis-1,2-divinylcyclopropane was known only as a reactive intermediate unisolable at -40°C, causing much interest in its rearrangement to 1,4-cycloheptadiene. During the course of our work, Brown, Golding, and Stofko finally isolated and characterized cis-1,2-divinylcyclopropane after a craftsmanlike synthesis. An alkyl substituent forming a cis double bond greatly stabilizes a cis-1,2-DVCP, because of steric hinderance in the conformation required to yield 6-alkyl-cis, cis-1,4-cycloheptadiene, the only isomer allowed by Bredt's rule; for instance, is believed to Cope in 1 hr. at 15°C, while its double bond isomer requires heating for 5 hr. at 75°C.

\[ \begin{align*}
\text{H} & \quad \xrightarrow{\Delta} \\
R & \quad \equiv \\
\end{align*} \]

\text{cis-Divinylcyclopropane and its rearrangement at 190°C to 1,4-cycloheptadiene were known}^{37} \text{ and Pettus and Moore}^{31c} \text{ had measured the activation energies as well as the stereoselectivities of the rearrangements of A to C' and B to D', but only Baldwin}^{38} \text{ had studied the mechanism. He concluded that the rearrangement proceeded in two steps; epimerization to the cis-DVCP is followed by a concerted Cope. The epimerization is sluggish below 150°C. Our interest stemmed from the desire to gain experience with DVCP's, with a view to synthesizing cis-1,2-divinylcyclopropane, and from the existence of the reaction developed by Billups and Shields}^{39} \text{ to make vinylalkylidenecyclopropanes.}
The reaction is elimination by potassium t-butoxide in dimethyl sulfoxide (DMSO) of two moles of HCl from a 1,1-dichlorocyclopropane, readily available by addition of dichlorocarbene to an olefin; its crux is the ability of the base-solvent system to generate allylic anions, allowing rapid rearrangement of the initially formed cyclopropanes. One of several possible mechanisms is shown on the next page. I am indebted to Mr. Stanley Chow, who synthesized compound 27.

Although the DVCP's are thermodynamically more stable by 7 kcal/mole, the vinylalkylidene cyclopropanes are the exclusive product, if the reaction is worked up in about a half-hour. Billups and co-workers did an experiment which is particularly pertinent here; dichloride eliminated to 31 exclusively, although 32 might well have formed. To

\[
\begin{align*}
\text{31} & \quad \text{Cl} \quad \text{Cl} \\
\text{30} & \quad \text{cis} \\
\text{32} & \quad \rightarrow
\end{align*}
\]

migrate the double bond, we stirred equal weights of potassium t-butoxide and 27 for 15 hr. in DMSO at 25°C. The NMR of the crude product showed a doublet of triplets at 9.35 ppm caused by the cyclopropane proton cis to the double bonds. No 3' was detected.

Following pyrolysis at 100°C, we separated the products by preparative gas-liquid partition chromatography (glpc) on Apiezon J. The first peak had the same retention time as trans-3-decene. The next peak was identified as 28 from Ohloff and Pickenhagen's NMR and IR data; a smaller peak close behind proved to be A; the major peak was clearly 3'. Assuming the thermal conductivity detector responds equally
to A, 28, and C' and assuming little A and 28 pyrolyzed at 100° C, the relative yields are: 28, 32%; A, 11%; C', 57%. The retention time of 33, the major product from pyrolysis of 27, proved that no 27 remained after the base catalyzed double bond migration.

In an attempt to separate A, C, 28, and 29, we eluted them with pentane from 25% silver nitrate on silica gel. The trans-3-decene came off first followed by a little C'; finally came several fractions of DVCP's. Their gas chromatograms showed enrichment in the cis isomers, but always contaminated with some of the trans. The allylic methylene protons of 29 are a quartet centered on 7.89τ, while those of 28 are at 7.86τ. The methylene protons allylic to the trans double bond in A, however, appear at 8.05τ. By analogy, those of C should be at 8.1τ. All the DVCP fractions had adsorptions at 7.89τ.

A 1g sample of 27 was subjected to base for 11 hr., worked up, and pyrolyzed in CCl₄ at 170° C for 3.5 hr. Removal of the CCl₄ afforded 95% pure C' in 50% yield. The overall yield from 3-decene to C' was 30%.

Our yield of DVCP's (41%) compares favorably with other current dictyopterene syntheses,²²b,³³,³⁴ which rely on a Wittig reaction between the appropriate phosphonium ylide and cis or trans-vinylcyclopropanecarbaldehyde, which is available in only 16% yield by reduction
of the product from addition of ethyl diazoacetate to butadiene.42
One group's overall yield was 13%,34 although their yield of A (5.2%)
was better than ours. On the other hand, our process is potentially
a two-step one.

Although the elimination-isomerization sequence was to be used
again in the synthesis of Dictyopterenes B, D, and D', we had to decide
how and when to incorporate the other double bond. Incorporating it
early would lead to 34, which would give the diallylic anion 35 upon
treatment with potassium t-butoxide in DMSO. Although thermodynamically
35 should yield the DVCP's, kinetically it might yield 38. Incorpo-

\[ \text{Kot-Bu} \quad \text{DMSO} \]

\[ 34 \rightarrow [ \quad 35 \quad ] \rightarrow B + D \]

\[ 36 \quad + \quad 37 \]

\[ 38 \]

rating the double bond later would require a base-inert functionality
convertible to a double bond. Two other considerations were brevity
and stability towards addition of dichlorocarbene. Assuming the double
bond is incorporated early, one works backwards through the two steps
to 39.

\[ \text{Kot-Bu} \quad \text{DMSO} \]

\[ 34 \quad \text{Cl} \quad \text{Cl} \]

\[ 39 \]

\[ \text{CHCl}_3 \quad \text{Kot-Bu} \quad 68\% \]

\[ 40 \]
Now, a moment's reflection reveals that $39$ is symmetrical, if both double bonds are cis or trans; this is good, because dichlorocarbene is not selective between disubstituted double bonds and because construction of symmetrical molecules involves one reaction with two moles of a reagent rather than two reactions with two reagents. $39$'s symmetry committed us to a synthesis incorporating the double bond early. Continuing backwards, the cis double bonds are simply, but elegantly, introduced by the hydrogenation over Lindlar's catalyst$^{43}$ of acetylene $41$, whose preparation from 1,5-hexadiyne and ethyl iodide is in the literature.$^{44}$ Although coupling two pentyl fragments to form $39$ or $41$

\[
39 \xrightarrow{\text{H}_2/\text{Pd}/\text{CaCO}_3/\text{Quinoline}/100\%} \quad 41 \xleftarrow{\text{NaNH}_2/\text{NH}_3/78\%} \quad \text{CH}_3\text{CH}_2\text{I}
\]

appeared feasible, we never found a trustworthy reagent, and finding the preparation of $41$ settled the matter.

With $33g$ of $40$ in hand, we added $10g$ to $2.2$ equivalents of potassium t-butoxide in DMSO. Fearing the effects of strong base on this unfamiliar system, we kept the reaction time short, but upon working up the reaction, we found not a clear yellow liquid but a deep red one, although the $95\%$ yield was consistent with our experience with this reaction. The NMR was also disquieting, showing too few protons, some of which were too far downfield. However, we proceeded as if nothing was awry. From our experience with $27$'s pyrolysis to $33$, we expected $34$ to yield mainly $42$, easily identified by the two broad pmr absorbances at $5.2\tau$ and $5.39\tau$ of the terminal methylene protons. After
heating an aliquot 5hr. at 100° C these peaks appeared, but 42 obviously represented only a small fraction of the total mass.

Concurrently, we attempted to form DVC's by treating another aliquot in base and DMSO, although for a relatively short time and with half the base used in the A and C series. Pyrolysis failed to generate any of the peaks associated with D'. Foiled in our attempt to gain B and D' easily, we ceased experimental work, until we could decide how to proceed.

To aid our planning, we obtained and analyzed the gas chromatograms of these reactions. The elimination product contained six major compounds in four well resolved peaks of comparable area; the second and third peaks consisted of two partially resolved peaks. By comparison with known material, the fourth peak was dichloride 40. The product from base-catalyzed bond migration and pyrolysis showed five unresolved peaks, one of which was about 40% of the total. No 40 was present.

Desiring to start at one end of the problem and knowing starting material remained, we subjected 40 to normal elimination and bond migration conditions. The gas chromatogram of the elimination was little changed, except now the second peak appeared to be one compound and the starting material was almost consumed; that from the bond migration was also quite unchanged, although the large peak was better resolved. Simultaneously, we ran the reaction at 0° C, hoping to obtain a single product. A solution of 1.3g potassium t-butoxide in
2.7ml THF and 3.5ml DMSO froze just below 0°. Elimination of 1g 40 in it for 45hr gave after work-up a deep red liquid in 81% yield. The gas chromatogram had the same peaks as the normal elimination; a significant amount of starting material remained.

When we became convinced the reaction was reproducible, we began separating the products by preparative glpc on Apiezon J. Obtaining a pmr of the first peak, we assigned it structure 43 on the basis of the characteristic terminal methylene absorption, the presence of six olefinic protons, and the 1H multiplet centered at 6.757. The ultraviolet absorption maximum at 237nm (ε ~ 1.27 x 10^4) is consistent with the methylenecyclopentene structure. 43 must arise from pyrolysis of 38 in the chromatograph's injection block and column. If we have located the alkenyl double bond correctly, we have again demonstrated this reaction's preference for vinylalkylidenecyclopropanes.

During this flurry of work, it occurred to us to try addition of base to the dichlorocyclopropane 40, the inverse of the ordinary procedure. Adding it in 35min gave the lightest colored product yet, although a gas chromatogram revealed the usual four products plus starting material. Extension of the addition and reaction times in several steps led finally to the predominance of the peak containing two compounds. Since the pure compound polymerized readily, we did
not obtain a yield. *

The pmr spectrum contains the low field absorptions observed earlier, indicating these compounds are direct products of the elimination, but it is not that of \( \overline{40} \) or any dictyopterene or \( \overline{36} \) or \( \overline{37} \). An ultraviolet maximum at 277nm (\( \epsilon \sim 31,400 \)) suggests three or four conjugated double bonds. Hydrogenation of these two compounds gave a pmr and gas chromatogram similar to those obtained from hydrogenation of \( \overline{27} \), while those from \( \overline{C'} \) were different. The data from the hydrogenations corresponded well with that reported by Ohloff and Pickenhagen. 34 We have made no structure assignment.

The large peak from the base-catalyzed bond migration was not a dictyopterene, and we did not pursue its analysis further.

* The previous reaction in this series gave a 50% yield.
VINYLUCYCLOPROANONE

Vinylcyclopropanone is a convenient term for a field of experiments that, though vinylcyclopropanone still eludes us, is sufficiently interesting to warrant a place in this thesis. Our objective was the synthesis of vinylmethylene cyclopropane\textsuperscript{39} with an oxygen atom replacing the methylene carbon. We wanted this molecule both for comparison with vinylmethylene cyclopropane itself and for its own merits. On their own merits, cyclopropanones are especially interesting, because this class of simple chemicals escaped chemists until 1965\textsuperscript{45} and many studies are wanted to discover how well they fit the predictions made about them from the numerous theories guiding organic chemists today.

Although cyclopropanone is best described as \textsuperscript{44}, vinylcyclopropanone could be \textsuperscript{45}, \textsuperscript{46}, \textsuperscript{47}, or \textsuperscript{48}.\textsuperscript{45} By analogy to vinylmethylene cyclopropane,\textsuperscript{46} it will rearrange to \textsuperscript{49}, perhaps by an electrocyclic ring closure of \textsuperscript{46}. Nevertheless, \textsuperscript{50} is also possible. \textsuperscript{46} may also undergo a [4+2] cycloaddition with an olefin.\textsuperscript{47}
The only general synthesis of vinylmethylenecyclopropanes, that of Billups, Shields, Chow, and Deno,\textsuperscript{39} was unsuitable for vinylcyclopropanone until R. V. Stevens\textsuperscript{48} pointed out the [2+2] addition of singlet oxygen to "electron rich olefins"\textsuperscript{49a}. The most active olefin then available to Billups and his co-workers was \textsuperscript{51}, whose methyl groups provided insufficient activation. Since singlet oxygen adds well to di- and tetra-alkoxy substituted double bonds\textsuperscript{49a,b,59} became the favored objective. The synthesis required olefin \textsuperscript{53} as starting material and is shown on the following page. Having no prior experience to draw on, we took a let's-try-it-and-see attitude towards the possibility of elimination of alkoxide. Anyway, using the ethylene acetal might make the elimination reversible.

Since 2-pentenal dimethyl acetal, \textsuperscript{53}, has been synthesized several times\textsuperscript{50a,b,c,56}, our problem was to find a preparation that would yield the pure compound in adequate quantities for unrestricted exploration of the succeeding steps. We perused six approaches and reduced three to practice. The most effective was the Bodoux-Tschitschibabin reaction, using an acetylenic grignard\textsuperscript{51a,b,c,d}, followed by reduction over Lindlar's catalyst\textsuperscript{43}. Addition of dichlorocarbene by the micellar technique\textsuperscript{52a,b,c} afforded a lower boiling mixture and a single (glpc on Apiezon J) higher boiling compound, which we assigned structure \textsuperscript{54} on the basis of its pmr. A cursory examination of the former disclosed that it contained an aldehyde(s), resulting, probably, from hydrolysis of "C-H bond insertion" products \textsuperscript{60} and \textsuperscript{61}.

\[
\text{HCl}_2C\text{OCH}_3 \quad \text{HCl}_2C\text{OCH}_3
\]
\[
\text{OCH}_3 \quad \text{OCH}_3
\]
\[
\text{60} \quad \text{61}
\]
1. EtMgBr
2. CH(OCH₃)₃ → 50%

1-butyne

H₂
Pd/BaSO₄
Quinoline 100%

OCH₃

53

OCH₃

Cl
Cl

54

KOC-Bu
DMSO

OCH₃

55

OCH₃

OCH₃

Cl

56

Cl

OCH₃

-2 HCl → polymer

57

OCH₃

58

38%

56 →

OCH₃

OCH₃

59

OCH₃
Addition of potassium t-butoxide in DMSO to a solution of 54 in DMSO did not yield 59, but the reaction was reproducible and seemed to give a single product (decomposition occurred on the GC column), whose pmr, IR, and mass spectra furnished enough data to assign it structure 58. The mass spectrum showed the molecule contained no chlorine and had a molecular ion at m/e = 172, which corresponds to 59 plus one molecule of methanol; the pmr did show three methoxyl peaks, two practically identical to those in 52 and 54, while the third appeared .55ppm downfield. In good agreement with the ones in 52 and 53, the dimethyl acetal proton appeared as a singlet at 4.97. A 3H triplet at 9.17 and a 2H multiplet at 8.67 showed the ethyl group was intact. A strong, broad IR absorbance at 1880cm⁻¹ was so unusual that it was relatively simple to assign it to the C = C stretch of a disubstituted cyclopropene. 53a,b This datum and the absence of olefinic protons in the pmr spectrum argued that the ethyl, dimethyl acetal, and the methoxyl were bonded to different cyclopropene carbons. The collapse of the 1H triplet at 7.757 upon irradiation of the methylene group picked out the cyclopropene carbon bearing a proton. Therefore, the double bond is between the dimethyl acetal and the methoxyl.

A mechanism for the formation of 58 is easily written, since Shields and Gardner 54 studied the reaction of dichlorocyclopropanes with NaOCH₃ in DMSO. It is shown on page 37. Although cyclopropanes must be intermediates in the elimination reaction of dichlorocyclopropanes and although the base-catalyzed rearrangement of methylcyclopropanes to methylenecyclopropanes is well known, 55 58's isolation is unprecedented. As one may see on page 37, 56 is the normal intermediate
in the formation of 59. Even though 56 (and 58) could lose 10 kcal/mol strain energy by migrating the bond, it endures long enough to be attacked by methoxide, because the dimethyl acetal proton is virtually inaccessible. This inaccessibility is in accord with Davis and Brown's study on the elimination of HBr from numerous α-bromoacetals that had one or more beta protons. The relative yields of α,β-unsaturated acetals and ketene acetals correlate well with the steric requirements of the acetal group. Alkyl acetals become predominantly α,β-unsaturated acetals, because the alkyl groups sweep freely through a large volume. The ethylene acetal restrains this movement and leads to ketene acetals. Substitution on the ethylene acetal leads back to α,β-unsaturated acetals, since the steric bulk increases. So the trail to vinylcyclopropanone passes through 54 with an ethylene acetal.

\[ \text{CHCl}_3, 50\% \text{ NaOH} \rightarrow \text{Cl} \rightarrow \text{Kt-Bu, DMSO} \rightarrow \text{or} \]

The usual acetal formation reaction converted 52 to 62, although the usual Lindlar hydrogenation failed to give 63 until 5% Pd/C, a more active catalyst, was substituted. Addition of dichlorocarbene to 63
yielded 64 in 41% yield; in this case, no aldehyde was detected. The elimination, both by normal and inverse addition, failed. The pmr showed no vinyl protons, so the product was not 65; it was not 66.

58 itself has some potentials. It is an incipient heteroatom vinylmethylene cyclopropane, since hydrolysis of the enol ether and the acetal would place carbonyls where double bonds exist in vinylmethylene cyclopropane. The great strain energy of the cyclopropene makes it likely that the enol ether will hydrolyze first. Since the energy of activation for the rearrangement to 68 will be small, the hydrolysis must be conducted at low temperatures. Furthermore, 58, 67, and 68 will all polymerize readily, so the catalyst used must be mild. The rearrangement of 67 to 68 is identical to that of the vinylmethylene cyclopropanes.\(^\text{46}\) The yield of 58 might be increased by addition of methoxide to the potassium t-butoxide, thereby suppressing or reversing the formation of 57. Excess methoxide should add to the cyclopropene to give 69, which is a 67 precursor that is less likely to polymerize than 58. Finally, the parent compound in this series, 70, can be synthesized from acrolein.
EXPERIMENTAL

All reactions, save hydrogenations, were carried out in a nitrogen atmosphere. Proton magnetic resonance (pmr) spectra were recorded on a Varian A-56/60 spectrometer in CCl₄ solutions with TMS as an internal standard. Infrared spectra were made from liquid films between NaCl plates on a Beckman IR-20 or IR-8 spectrophotometer. The ultraviolet spectra were made from heptane solutions on a Cary Model 14MS recording spectrophotometer;* Mass spectra were obtained from a Consolidated Electrodynamics Corp. 21-110 high resolution mass spectrometer. Glpc analyses were carried out on Model 700 or 5700A Hewlett Packard gas chromatographs. A Varian Areograph Model A-700 Autoprep was used for preparative glpc. All three had thermal conductivity detectors (TCD); the carrier gas was always helium.

The Grandisol Synthesis

Ni(COD)₂ and, hence, the dimerization reaction are uncommonly sensitive to oxygen; we handled them in a dry box and took pains in deoxygenating our solvents.

Bis-[cyclooctadiene-(1,5)]-nickel(0). This preparation differs only in details from Wilke's.¹⁷ It begins with dehydration of nickel acetylacetonate hydrate (Ni(ACAc)₂·H₂O)** (55g, .2 moles, lequiv) at

* I thank Mr. P. Scott Glaspie for recording them.

** That supplied by Aldrich Chemical Co., Inc. was used without further purification. According to Charles and Pawlikowski,¹⁸ it may also be made from Ni(OH)₂ and 2,4-dioxopentane.
80-90° in vacuo overnight in a three-necked, 500ml, round bottomed flask equipped with a serum stopper, a pressure equalizing dropping funnel closed with a serum stopper, a gas adapter, and a magnetic stirring bar. The funnel must have a teflon lined stopcock, as AlEt₃ in toluene dissolves stopcock grease and leaks out into the air and jams the stopcock when it hydrolyzes. As it dehydrates, the turquoise monohydrate becomes a darker green. The flask is brought to atmospheric pressure with nitrogen and left attached to the nitrogen system. 250ml of toluene, freshly distilled under nitrogen, is introduced. Vacuum distilled* 1,5-cyclooctadiene (119g, 1.1 moles, 5.5 equiv) is also added now. Stirring and heating dissolve the Ni(AcAc)₂·OH₂O shortly.** The emerald green solution is cooled to -5° to -10° in an ice-salt bath. When the solution is cold, some 1,3-butadiene is bubbled in through the serum stopper on the flask. A 12″ needle attached to the lower half of a 1ml syringe barrel wired into a length of tygon tubing pushed onto the nipple of the valve on the gas cylinder works fine. Triethyl aluminum in toluene (86.6ml of a 26.3 wt/vol % solution,*** .2 moles, 1 equiv) is added dropwise in 5hr.

After about one-half of the AlEt₃ is added, a fine yellow precipitate appears in the green solution. Afterwards the solution becomes brown. The reaction is allowed to stir overnight and to warm to room

* It bumps excessively.
** More toluene may be added without detriment.
*** 25 wt/vol % AlEt₃ in toluene is manufactured by Texas Alkyls and sold through Stauffer Chemical Corp. It is pyrophoric, but can be transferred safely in a syringe equipped with a stopcock to isolate the contents from air. The barrel and plunger should be sealed with mineral oil.
temperature, then it is filtered on a Büchner funnel with a paper disc, because the smallness of the crystals prohibits use of a fritted glass filter. The crystals may be washed with toluene, but it is not necessary. They should be bright yellow. The last of the toluene is evaporated under vacuum. The compound decomposes rapidly in oxygen to give an olive drab powder. The yield is about 80%.

**Tri-(2-phenylphenyl) phosphite.** This preparation derives from that of triethyl phosphite in *Organic Syntheses.* 16 2-Phenylphenol (100g, .59 moles, 3 equiv; Aldrich Chemical Co., used as received) is dissolved in 1½ anhydrous ether in a 1L, three-necked flask equipped with an addition funnel, a mechanical stirrer, and a gas adapter leading to a nitrogen source. N,N-diethylaniline (88g, .59 moles, 3 equiv; freshly distilled from zinc dust) is added, the flask cooled to 0°, and PCl₃ (27g, .197 moles, 1 equiv; refluxed for several hours and distilled) is dripped in over an hour. The suspension must be vigorously stirred; otherwise, HCl may be liberated locally in concentrations sufficient to form other products. 16 The ice bath is removed, and the reaction is allowed to stir 4hr before filtering the N,N-diethylaniline hydrochloride and evaporating most of the ether on a rotary evaporator. Should a small quantity of insoluble material separate now, dilute the solution with ether and filter. The ether is again evaporated. Crystallization should occur on cooling in a freezer. It is somewhat difficult to make the phosphite crystallize. The yield is about 42g, 43% based on PCl₃; concentration of the mother liquor yields a second crop, which brings the yield to 50%. The entire batch is recrystallized in a 200ml pressure bottle filled about 3cm above the solid with
isoprene and heated on a steam bath. The hygroscopic crystals melt at 95°-98°: mass spectrum \( P^+ = 538 \).

The **Dimerization Reaction**. A single-necked, 1L, round bottomed flask closed with a serum stopper and containing isoprene (420g, 6.16 moles, 77 equiv; distilled under nitrogen) is placed in a dry box. Tri-(2-phenylphenyl) phosphate (43g, 0.080 moles, 1 equiv) is dissolved by swirling at 25°. Its solution is moderately slow. \( \text{Ni(COD)}_2 \) (21.9g, 0.080 moles, 1 equiv) is added in one portion; no precautions are necessary. The solution should be red with little or no precipitate. A 3µl aliquot may be withdrawn daily and analyzed on a 6ft 1/8in 20% Carbowax 20M on 80/100 Chromsorb W (acid washed) column heated to 60° with a carrier gas flow of 30ml/min. COD emerges in about 16min, but is easily located by injecting some. The peak preceding it is 8, and the peak preceding 5, the first peak after isoprene, is the cyclobutane 7. A further very small peak that may precede 5 is probably the symmetrical cyclobutanes 6 and 7. The structure of the first peak after COD is unknown. The largest peak, emerging 16min after this, is 9 (see page 17). The reaction's progress is determined by weighing the peaks and calculating the ratio of 5 to COD. This ratio will reach about 1.8 after 5-7 days at 25°.** The yields are shown on p. 17.

Work-up begins with addition of triphenyl phosphite (100g, 0.320 moles, 4 equiv). Cooling for 2hr at -22° precipitates most of the

---

* It also recrystallizes from benzene/ethanol, but one must be careful to completely remove the ethanol, since it is an efficient nickel ligand.

** But see the footnote on p. 17.
catalyst, which is then filtered. By carefully lowering the pressure, the isoprene is distilled at 25° through a short column into a dry-ice cooled receiving flask. At about 5mm enough dimer is distilling to collect. The earliest fractions contain mostly isoprene, then the concentration of 5 increases, and finally falls off as the concentration of 9 grows in the later fractions. I thank Mr. C. V. Smith for working out the details of this distillation. Preparative glpc affords pure 5, 8, the unknown, and 9. The column is a 3/8in, 6ft 20% Carbowax 20M on 80/100 mesh Chromsorb P heated to 60° with the injector and detector blocks at 65°. The gas flow is 50 ml/min. The identification of the dimers rests on the following data.

**cis-[2-Isopropenyl-1-vinyl]-1-methylocyclobutane (5).** pmr τ 8.75 (sharp s, 3H) 8.45 (s, 3H) 8.17 (m, 4H) 7.5 (t, 1H) 5.46 (unresolved m, 1H) 5.11-5.35 (m, 2H) 4.98 (B of ABC, 1H) 4.0 (A of ABC, 1H).

IR: 3090, 1645, 1000, 910, and 888cm⁻¹.

PMR: p. 72 IR: p. 79

**1-Vinyl-1,3or4-dimethylocyclohex-3-ene (8).** pmr τ 9.02 (sharp s, 3H) 8.4 (s+m, 5H) 8.16 (m, 4H) 5.28 (C of an ABC system, 1H) 5.05 (B of an ABC system, 1H) 4.73 (unresolved m, 1H) 4.25 (A of an ABC system, 1H).

IR: 3090, 3010, 1645, 910, and 805cm⁻¹.

PMR: p. 72 IR: p. 79

**An Unidentified Isoprene Dimer.** pmr τ 8.27 (s+d, 6H) 8.09 (m, 3H) 7.87 (s?, 2H) 5.33 (broad s, 2H) 5.20 (broad s, 1H) 4.70 (unresolved m, 1H) 4.01 (s) and 3.78 (s).
IR: 3090, 3010, 1650, 1615, 965, and 890 cm\(^{-1}\).

Mass spectra: m/e=136 (P\(^+\)), 121, 108, 107, 93, 81, 79, 68 (base),
67, 53, 41, 39.

UV \(\lambda_{max}^{\text{heptane}}=230\text{nm}, (\epsilon=9390)\). The extinction coefficient is
inaccurate, since the spectra was made on a solution containing 1mg of
the unknown; this mass is at the limit of the balance's accuracy.

PMR: p. 73 IR: p. 79

\underline{1,5-Dimethyl-1,5-cyclooctadiene (9)}. pmr \(\tau\) 8.36 (broad s, 6H)
7.73 (s+d, 8H) 4.75 (unresolved m, 2H).

IR: 3000, 1445, and 835 cm\(^{-1}\).

PMR: p. 72 IR: p. 79

For conformation, a PMR was made on some COD prepped from the
dimerization reaction. 7.65 \(\tau\) (broad s, 8H) 4.5 \(\tau\) (unresolved m, 4H)
are the two peaks, which are identical to the PMR of authentic COD.

\underline{Grandisol (1)}. 5 (449mg, 3.3mmoles, 1 equiv) was syringed into
a 6in test tube containing a magnetic stirring bar and closed with a
rubber serum stopper. 4.5ml dry THF (distilled from LAH) was added.
1ml of .75M disiamylborane in THF was added dropwise at 0\(^\circ\). A total
of 5ml (3.75mmoles, 1.15 equiv) of the borohydride was added in 1ml
aliquots at 1hr intervals. 1hr after the last ml was added, I added
3N NaOH (.42ml, 1.26mmoles, .33 equiv) and then added 30% H\(_2\)O\(_2\) (1.43g,
11.25mmoles, 3 equiv) in 45min. Addition of NaCl (s) caused the
aqueous and organic layers to separate. The THF was evaporated, and
the residue dissolved in benzene, which was washed three times with
water, dried once with a saturated sodium chloride solution, dried
over CaSO₄, and evaporated under a stream of nitrogen. Some of the 3-methyl-2-butanol was removed by vacuum. Pure grandisol was separated by preparative glpc on a 6ft-² in 10% UCON LB550X PM-719 on 80/100mesh Chromsorb W (acid washed) column heated to 130°. The injector was at 150°, and the detector at 200°. A sample of this material proved as active as the natural material in the BWRL's bioassay. The sample for bioassay was obtained by Mr. C. V. Smith, to whom I am indebted.

**PMR** τ 8.82 (sharp s, 3H)  [7.9-8.5 (m) 8.36 (s), 1OH] 7.5 (t, 1H) 6.45 (t, J=7Hz, 2H) 5.41 (unresolved m, 1H) 5.22 (unresolved m, 1H). This spectrum agrees with one supplied us by the BWRL. See p. 74 for our spectrum.

The Yield of Grandisol was determined by a glpc comparison of the crude grandisol with a known quantity of geraniol. First, however, we found the TCD's response to both alcohols by weighing the peaks formed by a mixture of authentic grandisol from the BWRL and geraniol.

<table>
<thead>
<tr>
<th></th>
<th>Weight</th>
<th>Wt/Wt</th>
<th>Peak Weights and Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>grandisol</td>
<td>1.907mg</td>
<td>1.063</td>
<td>74.8mg 183.1</td>
</tr>
<tr>
<td>geraniol</td>
<td>1.794mg</td>
<td></td>
<td>69.7 177.3</td>
</tr>
</tbody>
</table>

\[
\frac{wt/\text{wt}}{(\text{peak wt}/\text{peak wt})} = \frac{1.063}{1.073} = 0.99
\]

\[
1.063 \div 1.0327 = 1.02
\]

The TCD responded equally to grandisol and geraniol. Two samples were chromatographed on a 6ft-² in 30% SE-30 on 80/100mesh Chromsorb W (acid washed) column operated at 120° with a gas flow of 150ml/min.
SAMPLE A:

\[ \frac{\text{geraniol wt}}{\text{geraniol peak wt}} = \frac{1.19 \text{mg}}{106.7} = \frac{x}{72.0} = \frac{\text{grandisol wt}}{\text{grandisol peak wt}} \]

\[ x = 0.7953 \text{mg of grandisol} \]

SAMPLE B:

\[ \frac{\text{geraniol wt}}{\text{geraniol peak wt}} = \frac{1.01 \text{mg}}{102.1} = \frac{x}{66.7} = \frac{\text{grandisol wt}}{\text{grandisol peak wt}} \]

\[ x = 0.6561 \text{mg of grandisol} \]

The total weight of the crude reaction mixture was 1713.7mg. SAMPLE A is 5.993mg of the crude mixture.

There are, therefore, \( (1713.7/5.993) \times 0.7953 = 227.42 \text{mg of grandisol in the crude reaction mixture.} \)

SAMPLE B was 5.924mg.

\[ (1713.7/5.924) \times 0.6561 = 190.\text{mg} \]

Since 3.3mmoles of 5 were used, the theoretical yield of grandisol, MW = 154, was 446.15mg.

SAMPLE A: \((227.42/446.15) \times 100 = 51\%\)

SAMPLE B: \((190./446.15) \times 100 = 42.5\%\)

A third sample was chromatographed on the UCON column described on p. 47, after most of the volatiles had been removed \textit{in vacuo}.

SAMPLE C:

\[ \frac{\text{geraniol wt}}{\text{geraniol peak wt}} = \frac{1.76 \text{mg}}{145.7} = \frac{x}{52.1} = \frac{\text{grandisol wt}}{\text{grandisol peak wt}} \]

\[ x = 0.63 \text{mg of grandisol} \]

The total weight of the crude reaction mixture was now 1487.9mg.

Sample C was 4.00mg of it.
\[(1487.9/4.00) \times 0.63 = 233.\text{mg}\]
\[(233./446.15) \times 100 = 52\%

In summary, the three yields are 51%, 42.5%, and 52%, which average to 48.5%.

**Attempted Preparation of Bis-(1,5-dimethylcyclooctadiene-1,5)-nickel(0).** I followed the procedure for making Ni(COD)_2 precisely; the solution turned black after the first few drops of AlEt_3 were added, and no precipitate formed.

**In situ Catalyst Generation.** Examine the preparation of Ni(COD)_2 on pp.41-3. In the flask (250ml) described for preparation of Ni(COD)_2, Ni(AcAc)_2 \cdot H_2O (5g, 18.2mmoles, 1 equiv) was dehydrated in vacuo at 90° for 6hr. The dark green powder dissolved after heating in 17ml toluene and triphenyl phosphite (5.62g, 18.2mmoles, 1 equiv). It remained in solution when isoprene (60g, 81 moles, 44.5 equiv) was added to the warm toluene solution. The clear, light-green solution was cooled in an ice-salt bath and a catalytic amount of 1,3-butadiene added. AlEt_3 (8ml of a 26.3% solution, 18.2mmoles, 1 equiv) was added slowly drop-wise, causing a heavy colorless precipitate to form after 2 or 3ml. As the addition continued, the reaction's color lightened and then began to turn red. After all the AlEt_3 was added, the reaction was rust colored, the usual color of the dimerization reaction. Glpc analysis showed formation of 5, 8, the unknown dimer, and 9. The reaction was stopped with 3 equiv of triphenyl phosphite, filtered, the isoprene evaporated, and 9 distilled in 15% yield, 8.25g. bp=137-138° (reflux ratio=1/1).
cis-1,2-Divinylcyclobutane (DVCB). Typically, Ni(COD)$_2$ (.625g, 2.28mmoles, 1 equiv) and t-PPP (1.22g, 2.28mmoles, 1 equiv) were placed in a 200ml pressure bottle. 1,3-Butadiene (56.5g, 1.05 moles, 500 equiv) was poured in, and the reaction heated to 50º for 4hr, cooled, stopped with triphenyl phosphite (3 equiv), and the diene allowed to evaporate. 4.7g of DVCB, 4-vinylcyclohex-1-ene (VCH), and COD remained. The dimers accumulated from several runs were distilled on a spinning band column. An oil bath heated the distilling flask to 30º. The reflux ratio was 15-20/1. The DVCB was 90% pure; VCH was the only impurity: bp=16-17º/9mm. pmr $\tau$ 8.0 (complex m, 4H) 6.96 (unresolved m, 2H) 5.2 (4 peaks, 2H) 4.98 (s, 2H) 3.83-4.45 (d of the A proton of an ABC system, 2H).

IR: 3060, 1630, 980, and 898cm$^{-1}$.

PMR: p. 73 IR: p. 80

Norgrandisol (10). DVCB was hydroborated, oxidized, and worked up just as 5 was. A pure sample for bioassay was obtained by preparative glpc on a 6ft-$\frac{1}{4}$in 30% SE-30 on 80/100mesh Chromsorb W (acid washed) column heated to 100º. The injector was at 135º, the detector at 150º, and the gas flow at 150ml/min. PMR: $\tau$ 7.75-8.66 (very complex multiplets+OH, s, 9H) 6.55 (t, $J=6.5$Hz, 2H) An ABC system: 5.18 (4 peaks, 1H) 4.95 (broad s, 1H) 3.75-4.35 (complex m, 1H).

IR: 3150-3600 (broad OH), 3080, 2950 (broad, strong) 1240,1035 (broad) 990 and 905cm$^{-1}$, CCl$_4$ solution.

PMR: p. 73
The Dictyopterenes Syntheses

The DMSO used was dried over CaH₂ and distilled immediately prior to use. The potassium t-butoxide came from MSA Research Corp. and was used without further purification, except where noted.

1,1-Dichloro-2-ethyl-3-hexylcyclopropane (26). Mr. Stanley Chow performed this reaction. trans-3-Decene (35g, .25 moles, 1 equiv; Chemical Samples Co.) was dissolved in 200ml pentane contained in a three-necked, 1L flask. Causing the solution to turn yellow, potassium t-butoxide (29g, .258 moles, 1.03 equiv) was added. While stirring at a moderate pace, ethanol-free CHCl₃ (35g, .294 moles, 1.17 equiv) was dripped in at 0°. After 1hr, the reaction was poured into water, and the product extracted with pentane, which was washed and dried over sodium sulfate. After evaporation of the pentane on a rotary evaporator, distillation afforded the unreacted olefin at 42°/2.5mm and the dichlorocyclopropane at 99°/2.5mm. Using recovered olefin, the carbenation was repeated twice more, resulting in a 43.1g, 77%, yield based on trans-3-decene consumed: bp=99°/2.5mm. PMR: τ 9.10 (t+m) 8.60 (broad unresolved m)

IR: No IR was recorded for this compound.

syn and anti-1-Hexylidene-2-vinylcyclopropane (27). This reaction was also done by Mr. Stanley Chow. 26 (43.1g, .193 moles, 1 equiv) was dripped into a mechanically stirred solution of potassium t-butoxide (54g, .481 moles, 2.5 equiv) dissolved in 100ml of DMSO and maintained at 25° with a water bath. One-half hour after the addition was
completed, the black reaction mixture was poured into ice and water and extracted with pentane, which was washed with water, dried over sodium sulfate, and evaporated on a rotary evaporator. Since the pmr integral showed too few olefinic protons, the product was resubjected to elimination by an amount of base estimated to be 2.5 equiv of the remaining dichlorocyclopropane. The product, with an acceptable pmr, weighed 22.3g, 78%: pmr τ 9.1 (t+m, 4H) 8.68 (broad, unresolved multiplets, 7H) 7.6-8.25 (broad, unresolved m, 3H) 4-5.4 (ABC+m, 4H).

IR: 3080, 2929, 1628, 975, and 885 cm⁻¹.

PMR: p. 75 IR: p. 80

1-(2-Hexenyl)-2-vinylcyclopropane (A, C, 28, and 29). All four geometrical isomers of this compound were generated by stirring 27 (1.5g, 10mmoles, 1 equiv) suspended in a solution of sublimed potassium t-butoxide (1.5g, 13.4mmoles, 1.3 equiv) and 15ml DMSO for 15hr at 25°. The dark reaction was poured onto ice and pentane, and the water extracted twice more with pentane, which was washed, dried with a saturated sodium chloride solution and sodium sulfate, and evaporated by a stream of N₂, leaving a dark red liquid, 1.3g, 86%: pmr: A multiplet centered at 9.5τ indicated the reaction was successful.

Pyrolysis of A, C, 28, and 29. The crude product from the previous reaction was diluted with CCl₄, sealed in an NMR tube, and heated at 80° in an oil bath overnight. The reaction was followed by observing the growth of a broad peak in the pmr at 4.45τ.

Gas Chromatographic Analysis of the Dictyopterenes. A 10ft, 1/8in, 10% Apiezon J on 80/100mesh Chromsorb W (acid washed) column, programmed
from 75°-150° at 2°/min beginning 2 min after the injection and with
a gas flow of 21 ml/min, separated the pyrolysate into 13 peaks; four of
these, however, comprised 85% of the product. The first, eluted after
24.5 min, was trans-3-decene, identified by comparison of its retention
time with a genuine sample. Second (32.6 min) comes 28, whose identity
is proven below, along with that of the next two products. A appeared
third, after 34.9 min. A minor peak then appeared that had the retention
time of 33 (37.2 min). The fourth and major peak was C', eluted in
44.6 min.

Preparative glpc was carried out like the analyses, except a 12 ft-
column was used.

\[(\pm)\text{-trans-1-(cis-2'-Hexenyl)-2-vinylcyclopropane}\, (28)\] . pmr τ
9.1 (t, 3H) 9.2-9.45 (m, 2H) 8.4-8.8 (complex, 5H) 7.88 (quartet,
2H) 5.3 (m, 1H) 5.2 (s and d, 1H) 4.5-5 (m, 3H).

IR: 3080, 3010, 1638, 1030, 985, and 895 cm\(^{-1}\).

PMR: p. 75 IR: p. 80

Dictyopterene A [\((\pm)-\text{trans-1-(trans-2'-hexenyl)-2-vinylcyclopro-
pane}\) . pmr τ 9.1 (t+5, 5H) 8.4-8.9 (unresolved multiplets, 7H) 8.05
(quartet, J=6 Hz, 2H) 5.1-5.4 (BC of ABC, 2H) 4.35-5.02 (A of ABC+m,
3H).

IR: 3080, 3010, 2960, 2930, 2870, 1632, 1460, 1030, 980, 955,
and 895 cm\(^{-1}\).

PMR: p. 75 IR: p. 80

Dictyopterene C' [\((\pm)-\text{6-butylocyclohepta-1,4-diene}\) . pmr τ 9.1
(t, J ~ 5, 3H) 8.69 (unresolved multiplets, 6H) 7.85 (broad m, 3H)
Column Chromatography of A, C, 28, and 29. Note: Preparation of the solid phase and the chromatography were done in the dark.

12.5g of AgNO₃ was dissolved in 150ml of acetonitrile, 37.5g silica gel (powder, J. T. Baker) were added, and the acetonitrile distilled on a rotary evaporator and in vacuo overnight at 25°. The column was made using pentane. 800mg of the mixture, decolorized by passage through a short silica gel column, was placed on the column and chromatographed with pentane flowing at about 1ml/min. The first two fractions were 3-3-decene, then some C appeared mixed with the decene; these fractions totaled 88mg. The next 9 fractions were mixtures having two peaks in their gas chromatogram; the largest was C, which from the peak shape must have resulted from pyrolysis on the column. The smaller was never identified. From this and the clarity of the cyclopropane proton cis to the cis-divinyl groups (See the pmr on p. 78, which is Fraction 12), we conclude these fractions are enriched in the cis-divinyl isomers, C and 29. The mass of these fractions is 207mg.

(±)-Dictyopterene C'. An Alternate Synthesis. 27 (1g) was subjected to sublimed potassium t-butoxide (1g) in 15ml of DMSO for 11hr, then worked up as described on p. 52, diluted with CCl₄, sealed in an NMR tube, and heated at 175° in the oven of a gas chromatograph for 2.5hr. Decolorization of the product on a short silica gel column
provided 500mg of pure C', a 50% yield. A gas chromatogram showed a single major peak comprising at least 95% of the mass. The pnr was identical to that described on p. 53 and shown on p. 76. (The yield might have been higher had I not broken the NMR tube containing the sample and lost about 100mg.)

3,7-Decadiyne (41). The procedure is that of Brune, Wolff, and Hüther. 44 800ml of anhydrous ammonia were condensed into a three-necked, 31, round-bottom flask fitted with a glass stopper, mechanical stirrer, and cold-finger condenser. Alternate addition of a small crystal of Fe(NO₃)₃·9H₂O and a chunk of sodium established a rate of conversion to sodium amide such that the blue color of dissolved sodium was confined to the vicinity of the dissolving chunk. One mole, 3 equiv, of sodium was added. When the first drops of a solution of 1,5-hexadiyne (25g, .32 moles, 1 equiv; Chemical Samples Co., used without further purification) in 40ml dry ether hit the ammonia, the black, metallic-looking suspension turned to a gray slurry. After refluxing 2.5hr, the reaction was cooled to -78°, and ethyl iodide (178g, 1.14 moles, 3.5 equiv) in 100ml dry ether added in 1.5hr with rapid stirring. The solution warmed to -33° overnight. By morning the gray color was completely discharged, leaving a clear solution tinged with black, finely-divided iron. The reaction was recooled to -78° and kept there for 36hr, when it was allowed to warm up and the ammonia to distill. The residue was diluted with 100ml ether, washed twice with water, and dried with a saturated sodium chloride solution and sodium sulfate. The ether was evaporated, and the diyne distilled to give 33.6g, 78%: bp=52-70°/5mm. pnr τ 8.91 (t, J=7Hz, 6H) [7.88 (quartet, J=7Hz)
7.71 (s), 8H].

IR: 2980, 1450, 1320, 1260, and 1060 cm\(^{-1}\). This data agrees with Brune, et al.\(^{44}\)

cis,cis-3,7-Decadiene (39). The reaction was carried out in a Parr hydrogenation apparatus with a 2-3\(\text{g}\) pressure above the following solution: 200ml pentane, decadiyne 41 (33.6g, .252 moles, 1 equiv), distilled, synthetic quinoline (.672g, 2 wt%), and 5% Pd/CaCO\(_3\) (.672g, 2wt%). The hydrogen (2 equiv) was absorbed in about 2hr, with the rate slowing appreciably toward the end. The Pd/CaCO\(_3\) was removed by filtration through Celite. The majority of the solution was used directly in the next reaction; a small sample was removed to obtain spectra.

\[\text{PMR} \quad \tau \quad 9.05 \text{ (t, J=7Hz, 6H) [7.98 (unresolved m) 8.05 (unresolved doublet of quartets) 8H]} \quad 4.7 \text{ (m, 4H).}\]

IR: 3020, 2970, 2940, 2880, 1460, and 1070 cm\(^{-1}\).

1,1-Dichloro-2-(cis-3-hexenyl)-3-ethylcyclopropane (40).
Potassium t-butoxide (28g, .25 moles, 1 equiv) was put in a three-necked, 1L flask, and the pentane solution of cis,cis-3,7-decadiene was poured in. (Enough pentane should be used to keep the base from sticking to the sides of the flask.) The suspension was stirred at a moderate rate at 0\(^\circ\), while alcohol-free CHCl\(_3\) (30g, .25 moles, 1 equiv) was added dropwise in about 1hr. After one-half hour, the reaction was poured into water, the pentane layer separated and washed with water, and dried with saturated sodium chloride solution and sodium sulfate. The pentane was evaporated, the unreacted olefin distilled at 40mm, and the black residue set aside. Using this olefin, the carbenation was repeated twice more, and the combined residues distilled to
give a pure (glpc) product in 68% yield, 33.6g: bp=65-70°/0.25mm

PMR τ 9.08 (t, J=7Hz, 6H) 8.58 (unresolved m, 6H) 8.4 (unresolved quartets, 4H) 4.68 (m, 2H).

IR: 3010, 2970, 1460, 810, and 750cm⁻¹.

PMR: p. 76 IR: p. 81

Note: The gas chromatographies performed in the next reactions utilized the same analytical and preparative Apiezon J columns and the same conditions set forth on p. 52.

Attempted Elimination of 40 (Short Contact Time). Potassium t-butoxide (11.3g, .1 mole, 2.2 equiv) was dissolved in 30ml DMSO at 25°. With mechanical stirring, 40 (10g, .045 moles, 1 equiv) was added drop-wise in 15min, and the reaction stirred for 10min before it was poured onto ice and pentane. The layers were separated, and the aqueous layer was vigorously extracted twice with pentane. The combined extracts were washed, dried with saturated sodium chloride solution and sodium sulfate, and the pentane evaporated. A deep red liquid remained that weighed 6.4g. Glpc showed a large peak with a retention time of 63min, which was identified as 40. Five other compounds with retention times of 26.8, 35.4, 36.4, 40.4, and 41.2min appeared, as well as numerous tiny ones. Pyrolysis of the crude mixture resulted in an insignificant conversion to 42, since the terminal methylene peaks at 5.1τ and 5.4τ appeared only weakly.

Stirring 1g of this mixture with .5g potassium t-butoxide for 4hr, and working it up as above, gave 697mg of liquid. Its pyrolysis produced no 42 nor D'. The pyrolysate's gas chromatogram had a single
peak at 35.6min and three moderate sized, unresolved peaks immediately following.

**Normal Elimination of 40.** The dichlorocyclopropane 40 (1.5g, 6.85mmoles, 1 equiv) was added dropwise in 20min to potassium t-butoxide (1.7g, 15.3mmoles, 2.3 equiv) dissolved in 10ml DMSO. The reaction was stirred for 30min and poured into water and pentane, the aqueous phase extracted twice more with pentane, which was washed twice with water, dried with a saturated sodium chloride solution and over sodium sulfate, and finally evaporated at 28°. The gas chromatogram showed 5 peaks, that of 40 and four of the others mentioned on p. 57. The peak with a retention time of 35.4min had disappeared. The NMR derivative trace was undefined, but the integral showed only 4.65 olefinic protons to 11.35 aliphatic, although it should have been 6 to 10. The product weighed 917mg, 91%.

809mg of this product was suspended in a solution of 700mg of potassium t-butoxide in 10ml DMSO, contained in a single-necked flask sealed with a wired-on serum stopper and stirred magnetically. The reaction was deep blue or black. In 12hr, it was poured into water and pentane and worked up as above. The gas chromatogram was different; it showed 2 large peaks, one of which was eluted in 35.6min and had a single large peak immediately followed by three smaller ones, and the other of which was eluted in 40.4 and 41.2min. The pnr derivative recording was complex and the integral showed only 3.5 olefinic protons to 12.5 aliphatic, although it should have been 7 to 9. The product weighed 143mg, 18%.
### Summary of Gas Chromatograms

<table>
<thead>
<tr>
<th>Eliminations</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short contact time</td>
<td>26.8 (43) 35.4 36.4 40.4 &amp; 41.2 (X &amp; Y) 63 (40)</td>
</tr>
<tr>
<td>Normal procedure</td>
<td>26.6 &quot; 36.2 40.2 &amp; 41.0 &quot; 63 &quot;</td>
</tr>
<tr>
<td>Inverse addition</td>
<td>tr &quot; tr 41.2 &quot; tr &quot;</td>
</tr>
<tr>
<td>Low temperature p. 31</td>
<td>26.6 &quot; 36.2 40.2 &amp; 41.2 &quot; 63 &quot;</td>
</tr>
<tr>
<td>Bond migration</td>
<td>35.4 40.4 41.2 + 37.0 37.6 38.8 (little resolution)</td>
</tr>
<tr>
<td>Bond migration + pyrolysis</td>
<td>35.4 36.5 37.6 38.8</td>
</tr>
</tbody>
</table>

**Inverse-Addition Elimination of 40.** Four experiments were run by this procedure with only the time of addition varying. This one produced the purest product, mostly X and Y.  

$\underline{40}$ (1g, 4.52mmoles, 1 equiv) was poured into a 50ml flask, whose single neck held a pressure equalizing addition funnel connected to a nitrogen source. It was suspended in 15ml DMSO. Potassium t-butoxide (1.493g, 13.3mmoles, 2.94 equiv) was dissolved in another 10ml and poured into the funnel. With magnetic stirring, the basic solution was added dropwise at 25° in 6hr and the reaction stirred a further 8hr. Then it was poured into water and pentane and worked up as in the normal elimination (p. 58) except 2-3ml of pentane was not evaporated, because the product in the previous experiment had polymerized. The products from the inverse addition reactions were yellow instead of dark red, as those from all the other eliminations had been. The gas chromatogram showed predominantly the two peaks at 41.2min. No starting material remained. The yield in the previous reaction was 52%. 
Identification of the Products

5-(1-Pentenyl)-3-methylenecyclopent-1-ene (43). GC retention time: 26.6 min.

\[ \text{pmr } \tau \begin{bmatrix} 9.01 \text{ (t, J=7)} & 8.91 \text{ (s)} & 8.80 \text{ (s), 6H} \end{bmatrix} 7.9 \text{ (quintet+m, 3H)} \\
6.76 \text{ (unresolved m, 1H)} \quad 5.37 \text{ (unresolved m, 1H)} \quad 5.2 \text{ (doublet of unresolved multiplets, 1H)} \\
4.5-5.0 \text{ (complex m, 2H)} \quad 4.28 \text{ (m, 1H)} \quad 3.93 \text{ (doublet of doublets?, 1H)}. \]

\[ \lambda_{\text{heptane}}^{\text{max}} = 237 \text{nm} \quad \varepsilon = 12,7000 \]

The extinction coefficient is inaccurate, since the spectrum was made on a solution of 100 ml heptane containing 74 \( \mu \)g of 43; this weight is at the limit of the balance's accuracy.

Since this compound was not seen in the pmr spectra of the crude reactions, it arose by pyrolysis of 38 in the GC.

PMR: p. 76

Peak #2. GC retention time: 36.2 min.

\[ \text{pmr } \tau \ 9.0 \text{ (t, J=7Hz)} \]

The remainder of the derivative is undefined. Assuming this is a \( C_{11}H_{16} \) compound, the pmr integral shows 5 olefinic protons and 11 aliphatic ones.

Compounds X and Y. GC retention time: 40.2 and 41.2 min

\[ \text{pmr } \tau \begin{bmatrix} 9.4 \text{ (m)} & 8.5-9.25 \text{ (m), 7H} \end{bmatrix} 8.12 \text{ (unresolved AB quartet?, 1H)} \\
7.76 \text{ (quintet, 2H)} \quad 6.98 \text{ (broad, unresolved m, 1H)} \quad 4.55-5.21 \text{ (complex, 2H)} \\
3.68-4.27 \text{ (m, 3H)}. \]

IR: 3080, 3020, 2970, 2940, 2880, 1640, 1630, 1590, 1460, 1380, 1010, 970, 895, and 740 cm\(^{-1}\).

PMR: p. 77 IR: p. 81
UV \( \lambda_{\text{max}} = 278 \text{nm} \) \( \epsilon = 31,800 \) \( \epsilon \) is inaccurate for the reason given on p. 60.

**Hydrogenation Studies on Compounds X and Y.** 27, C', and compounds X and Y were hydrogenated at 40psi over 10%Pd/C in pentane for 3.5hr on a Parr apparatus. The alkanes were chromatographed on the 1/8in Apiezon J column at 155° and a gas flow of 21ml/min.

<table>
<thead>
<tr>
<th>Hydrogenation Of</th>
<th>Retention Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X and Y</td>
<td>6.20</td>
</tr>
<tr>
<td>3</td>
<td>6.00</td>
</tr>
<tr>
<td>C'(^{**})</td>
<td>5.75*</td>
</tr>
</tbody>
</table>

PMR's: \( \tau \)

Hydrogenation of

X and Y 9.13 (t?, 25% of integral) 8.8 (unresolved m, 53% of integral) 7.5-8.3 (low, broad absorbance, 22%) 27 9.11 (t, J=5Hz, 8-9H) 8.7 (s+m, 15-16H) C'(butylcycloheptane) 9.12 (t, 3H) 8.78 (unresolved m, 10H) 8.49 (unresolved m, 9H).

Vinylcyclopropanone

2-Pentynal dimethyl acetal (52). Ethyl magnesium bromide (2 moles) in THF was prepared by the method of Skattebøl, Jones, and Whiting, 59

* Trace amount

** The C' was obtained by pyrolysis of fraction 11 from the column chromatography described on p. 54; a trace of the cyclopropanes must have remained after the pmr indicated complete conversion.
except a cold-finger condenser was substituted for the reflux one. After the magnesium had disappeared, the dropping funnel was replaced with another cold-finger condenser whose upper arm pointed towards the inner tube. A Pasteur pipet was mounted in this arm so that its tip was 1 mm from the inner tube. The other end of the pipet was connected by tygon tubing to the nipple on a cylinder of 1-butyne (100g, 1.85 moles, 1 equiv; Farchan Research Laboratories). The inner tubes of both condensers were charged with dry ice and acetone. With the Grignard at 25°, the 1-butyne was condensed on the cold-finger at such a rate that the addition took 7 hr. Ethane evolved vigorously after each drop, and occasionally a drop of 1-butyne formed on the other condenser. The solution stood 15 hr. Trimethyl orthoformate (244g, 2.3 moles, 1.24 equiv) washed with 5% NaOH and distilled from LAH, was added quickly. Remaining transparent throughout, the brown reaction was heated with stirring to about 50° for 5 days, then 1% of THF was distilled off. 1% CuCl was added, and the reaction refluxed for 1 hr. The remaining THF was distilled until the stillhead temperature was 95°. The black reaction mixture was cooled and diluted with 500 ml ether, and the magnesium salts filtered. The salts were thoroughly washed with a further 500 ml of ether. A 38 wt/vol% solution of NH₄Cl destroyed any remaining Grignard. The ethereal solution was decanted from the resulting salts, dried through a cone of MgSO₄ and over Na₂SO₄ and distilled on a rotary evaporator. The product distilled at 77-78°/47 mm. The yield was 122.4 g, 50.1%: \[ \text{pmr} \tau \] 8.8 (t, J=7 Hz, 3H) 7.72 (quartet, J=7 Hz, 2H) 6.75 (s, 6H) 5.05 (narrow triplet, J=1 Hz, 1H).
IR: 2830, 2250, 1190, 1150, 1090, and 1055 cm\(^{-1}\).

cis-2-Pentenal dimethyl acetal (53). 52 (40g, .312 moles, 1 equiv), distilled, synthetic quinoline (800mg, 2% by wt), 5% Pd/CaCO\(_3\) (800mg, 2% by wt), and 200ml of pentane were hydrogenated at 54b using a Parr apparatus until 1 equiv of hydrogen was absorbed. The catalyst was filtered by celite, and the pentane evaporated on a rotary evaporator. The light-yellow product, containing the quinoline, weighed 40.8g, a 99% yield. Glpc on a 10ft-\(\frac{1}{2}\)in 10% Apiezon J on 80/100 Chromsorb W (acid washed) column at 100\(^{\circ}\) showed only a single peak.

\[
\begin{align*}
\text{pmr} & : 9.0 (t, J=7Hz, 3H) & 7.85 (quintet, J=7Hz, 2H) & 6.8 (s, 6H) & 5.0 (d, J=5Hz, 1H) & 4.1-4.85 (m, 2H).
\end{align*}
\]

IR: 3040, 2830, 1665, 1190, 1112, and 1050 cm\(^{-1}\).

2,2-Dichloro-3-ethylecyclopropane carboxaldehyde dimethyl acetal (54). Olefin 53 (40.8g, .314 moles, 1 equiv), ethanol-free CHCl\(_3\) (94g, .785 moles, 2.5 equiv), and hexadecyltrimethylammonium bromide (1.7g, .00475 moles, .015 equiv) were stirred rapidly in a 1l Morton flask. 50% aqueous NaOH was added; the reaction quickly warmed to 60\(^{\circ}\) and turned black. More NaOH was added when the reaction had cooled to 50\(^{\circ}\) until a total of 110g (1.37 moles, 4.38 equiv) was so added. When the reaction had cooled to 45\(^{\circ}\), about 2hr, the reaction was poured into a separatory funnel, ether added, the aqueous layer separated, and the ethereal solution washed three times with water. The ether was dried with a saturated sodium chloride solution and sodium sulfate and evaporated on a rotary evaporator. Distillation afforded a fraction weighing 10.5g that boiled at 50\(^{\circ}\)/40mm. Among other peaks the pmr shows a doublet at .5\(\tau\) and the IR has a strong band at 1695 cm\(^{-1}\) and
a weak band at 2740 cm\(^{-1}\). These data suggest an aldehyde.

The cyclopropane 54 boiled at 60°/4 mm. The yield was 12.9 g, 19.3% based on 53. The product gave a single peak on the Apiezon J glpc column described above. \(\text{pmr}\) \(\tau\) 8.91 (t, \(J=6\) Hz, 3H) 8.1-8.7 (m, 4H) 6.73 (s, 3H) 6.63 (s, 3H) 5.82 (d, \(J=7\) Hz, 1H).

IR: 2980, 1450, 1195, 1142, 1110, 1065, and 810 cm\(^{-1}\).

PMR: p. 77  IR: p. 81

2-Methoxy-3-ethylcycloprop-1-enecarboxaldehyde dimethyl acetal (58). The dichloride 54 (1g, 4.96 mmoles, 1 equiv) was placed in a 50 ml flask containing a magnetic stirring bar and having a pressure equalizing addition funnel in its single neck. 7 ml of DMSO, which was freshly distilled from CaH\(_2\), dissolved it, and another 10 ml aliquot dissolved the potassium t-butoxide (1.2 g, 10.7 mmoles, 2.16 equiv), and this solution was poured into the addition funnel. Dropwise addition of the base rapidly produced a dark solution, but required 2.25 hr to complete. After stirring for 1 hr, the reaction was poured into water and pentane, shaken energetically to extract the product, and the aqueous layer saturated with NaCl to break the emulsion. The three pentane extracts were washed twice with water and twice with a saturated sodium chloride solution and evaporated at 25° on a rotary evaporator. A red liquid weighing 330 mg, 38%, remained. It decomposed upon glpc on the Apiezon J column as evidenced by a multiplicity of peaks, although one peak was much larger. \(\text{pmr}\) \(\tau\) 9.15 (t, \(J=7\) Hz, 3H) 8.6 (m, 2H) 7.75 (t, \(J=4.5\) Hz, 1H) 6.75 (s, 6H) 6.16 (s, 3H) 4.9 (s, 1H).

IR: 2980, 2850, 1880, 1450, 1350, 1280, 1190, 1150, 1095, 1050, and 970 cm\(^{-1}\).
mass spectrum m/e=172 (²⁺) 157 141 (the base peak) 127 111 109
99 75.

PMR: p. 77 IR: p. 78

2-Pentenal ethylene acetal (62)⁵⁷ 2-Pentenal dimethyl acetyl (52)
(43.5g, .338 moles, 1 equiv) was added to ethylene glycol (28g, .45
moles, 1.33 equiv), benzene (90ml), and a few crystals of p-toluenesul-
fonic acid monohydrate in a flask equipped for distillation. The
benzene-methanol azeotrope distilled at 65°. The theoretical amount
of methanol distilled. When the stillhead temperature reached 72°, the
brown contents of the distilling flask were cooled, diluted with ether,
washed with water, and dried with a saturated sodium chloride solution
and sodium sulfate. Distillation afforded a colorless liquid in 76%
yield, 28.5g: bp=79°/10mm pmr τ 8.84 (t, 3H) 7.75 (quartet, 2H)
6.15 (m, 4H) 4.55 (narrow triplet, 1H).

cis-2-Pentenal ethylene acetal (63). Alkyne 62 (28.5g, .226 moles,
1 equiv), synthetic quinoline (570mg, 2% by wt), 5% Pd/CaCO₃ (570mg,
2% by wt), and 150ml pentane were subjected to 5 lb hydrogen pressure
in a Parr apparatus, but no hydrogen was absorbed until the pressure
was increased to 20 lb. Therefore, the reaction was interrupted and 5%
Pd/C (570mg, 2% by wt) was added. Hydrogen was then absorbed at 2-4 lb.
Absorbtion ceased after 1 equiv was taken up. The catalyst was fil-
tered, the pentane was evaporated, and the product used directly in
the next reaction. pmr τ 8.97 (t, 3H) 7.80 (quintet, 2H) 6.15 (m,
4H) 4.1-4.85 (m, 3H)
IR: 2980, 2900, 1660, 1110, 1030, and 950cm⁻¹.
2,2-Dichloro-3-ethylcyclopropanecarboxaldehyde ethylene acetal

(64). Olefin 63, (29g, .226 moles, 1 equiv), ethanol-free CHCl₃
(74.4g, .621 moles, 2.75 equiv), and hexadecyltrimethylammonium bromide
(1.235g, .00339 moles, .015 equiv) were stirred vigorously in a 1l
Morton flask. 50% aqueous NaOH (136g, 1.7 moles, 7.5 equiv) was added
dropwise in 2.25hr at 25°. The reaction was allowed to stir for 8hr,
during which it warmed itself to 35°. The reaction was poured into
water and ether, but a third layer of heavy tars separated. The ether
was isolated, washed until the water was neutral to litmus, and dried
with a saturated sodium chloride solution and sodium sulfate. Distil-
lation gave a fraction boiling at 79-83°/21mm, which appeared to be the
olefin 63. The dichlorocyclopropane weighed 19.5g, 41%: bp=79-82°/1mm

pmr τ 8.88 (t, 3H) 8.35 (unresolved, m, 4H) 6.08 (m, 4H) 5.35 (unre-
solved, m, 1H)

IR: 2980, 2900, 1430, 1380, 1100, 810, and 760cm⁻¹.

Attempted Elimination of 64. The reaction was run as on p. 58
and p. 59. The times of reaction were: normal addition, 51min and
9min; inverse addition, 3hr and 5.5hr. The pmr showed no vinyl protons.
The intense C=C absorption of ketene acetals at 1720cm⁻¹ and the band
at 895cm⁻¹, which is associated with methylenecyclopropanes, were both
missing from the IR.
LITERATURE CITED


4. R. C. Gueldner, personal communication.


8. M. M. Butler, personal communication.


   a) *ibid.*, p. 57.
   b) *ibid.*, p. 82.
   c) *ibid.*, p. 54.
   d) *ibid.*, p. 69.


26. P. Heimbach, G. Schomburg, and G. Wilke, unpublished results reported in Ref. 21, p. 69.


48. R. V. Stevens, personal communication.


Spectra