VINYLCYCLOPROPANATION OF ENONES IN [2+3] CYCLOPENTENE ANNULATION. APPLICATION TO THE TOTAL SYNTHESIS OF (-)-RETIGERANIC ACID

by

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(ABSTRACT)

The addition of the lithium dienolate 161a derived from ethyl 2-bromocrotonate (163) to several enones provided vinylcyclopropanes of type 165 which were converted by thermolysis to the corresponding cyclopentenes in an overall [2+3] annulation process.

The reactions of 161a with other electrophiles such as ketones, α,β-unsaturated esters and α,β-unsaturated aldehydes were also investigated. The possibility of
asymmetric induction utilizing (-)-menthyl 2-bromocrotonate (169) was briefly investigated.

An application of this methodology was expressed in the total synthesis of (-)-retigeranic acid (1), achieved in fifteen steps from menthene (187) in a convergent and enantioselective fashion. The key steps in this synthesis involved the vinylcyclopropanation of bicyclic enone 144 with the lithium dienolate of bromide 180, to provide vinylcyclopropanes 179 and, through their thermolytic rearrangement, the pentacyclic ketone 178, which was converted to the title compound.

![Chemical diagram of the synthesis of (-)-retigeranic acid](image-url)
To my parents.
ACKNOWLEDGMENTS

I want to express my infinite gratitude to Professor Tomas Hudlicky for all his advice and guidance during my career at Virginia Tech. Also, I would like to thank all the members of my committee, Drs. James Wolfe, David Kingston, John Mason and Robert White, for their patience and support.

A special mention is due to my very good friend , with whom I shared so many years of studies and work and who was never too busy to discuss chemistry (or not) with me. I want to include too, for her friendship and continuous support during all these years. I am going to miss them.

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, and for their help in both projects, and Analytical Services and the Glass Shop, without whom the completion of this work would not have been possible.

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I. INTRODUCTION

A large number of natural products have been recognized to contain five-membered rings in their structures.\textsuperscript{1-31} These cyclopentanoids, also termed quinanes,\textsuperscript{6} show a wide diversity in structures, as well as in regio- and stereo-chemistry. (See for example compounds 1 to 2.)

1. Retigeranic acid  
2. Prostaglandin PGF\textsubscript{2α}  
3. Pentalenene

4. Modhephene  
5. Precapnelladiene  
6. Ophiobolin A

7. Verbenalol  
8. Alliacolide  
9. Hirsutic acid

One finds structural types ranging from monocyclic compounds such as prostaglandins,\textsuperscript{12-17} to linear or angularly-fused triquinanes\textsuperscript{6-11} such as hirsutic acid (9) and pentalenene (3) respectively. The iridoids,\textsuperscript{18-26} represented here by verbenalol
(7), 24-26 belong to a cyclopentanoid monoterpene group and have been known for thirty years. However, the need for new methodologies for the construction of five-membered rings did not become evident until the structure elucidation of the prostanoids, represented here by PFG2α (2)27,28 and of the antibiotic triquinane hirsutic acid (2)29-31 in the late sixties. The structural variations found in these groups, as well as their interesting biological activities, stimulated their synthesis, and therefore, the search for synthetic methodologies for the construction of cyclopentanes or their derivatives such as cyclopentanes, cyclopentanones and cyclopentenones. This activity is reflected in the large amount of publications in this area during the last two decades.6·12·32·36 Many approaches to cyclopentanoids have been reported, and these can be divided into several categories: [2+3]37 annulations, [4+1]38 annulations, [2+2+1]39 annulations and [4+2-1]40 annulations (where [2+3], etc., indicates the number of atoms involved in the cyclization).

Unfortunately, none of the existing methodologies available for the construction of five-membered rings, express the regio- and stereo-control in a single step comparable to the applicability of the Diels-Alder reaction for the synthesis of six-membered rings. Hudlicky36 attributes the disadvantage in the synthesis of five- versus six-membered rings to the following factors. First of all the cyclopentanes present what is called charge dissonance41 (two adjacent partial charges of the same sign), which would increase the difficulty of making connections to form the ring. On the other hand, six-membered rings present charge consonance41 (two adjacent charges of opposite sign). Another factor would be the absence of rules to predict stereoelectronic behavior in cyclopentanes, as a result of the strain imparted by the distorted tetrahedral angles. The third problem
would be the lack of synthetic methods to construct cyclopentanes independently of their substitution pattern. In conclusion, more efficient procedures for cyclopentane annulations are necessary in order to complement and improve the ones now available.

The Hudlicky group’s interest in this topic is reflected in the number of linear and angularly-fused triquinanes synthesized in the last decade, such as hirsutene,\textsuperscript{42} isocomenic acid,\textsuperscript{43} isocomene,\textsuperscript{44} pentalenene\textsuperscript{45} and pentalenic acid.\textsuperscript{45} The methodology developed, and successfully utilized in the syntheses mentioned above, consists in a [4+1] cyclopentene annulation, based on the interaction of a carbenoid species (generated by thermolysis of a diazoketone) with a substituted diene. This [4+1] methodology evolved, as Hudlicky indicated,\textsuperscript{36} by examining the biosynthesis of cedranoid sesquiterpenes 10 (Scheme 1). The cyclopentannulation from 11 (Scheme 1) took place, after overall balance, by interaction of two olefins and a cation with the loss of a proton. Following the same reasoning,\textsuperscript{36} and after similar steps, diene 12 would lead to cyclopentene 13, (Scheme 2, route a). If the loss of proton were the first step (route b),
The system originated would be our carbene and two olefins 14 (Scheme 2), which would also lead to cyclopentene 13. The system 14 was also obtained by means of disconnection of 13 in the way showed in Scheme 3.36

Scheme 3

The applicability of this strategy was extended to the heterocyclic field, in particular with nitrogen as the heteroatom (carbenoid was substituted with a nitrene equivalent), allowing the preparation of several pyrrolizidine alkaloids such as supinidine,46 isoretronecanol,47 trachelanthamidine,47 dihydroxyheliotridane,48 hastane,48 platynecine48 and turmeric.48

Unfortunately, the approach to the total synthesis of retigeranic acid (1), another member of the triquinane family, mediated via the [4+1] protocol failed, due to unfavorable electronics of the triquinane acrylate.36 Retigeranic acid (1) 49-52 is a unique molecule for many reasons: it was the first sesterterpene found to occur in lichens,52 also it was the first terpene isolated that contained the angular triquinane system,52 and its pentacyclic structure has no correlation to any other existing sesterterpene.52 Moreover, its structural array with seven chiral centers makes it a very interesting and a challenging target for synthetic organic chemists. No biological activity of 1 has been reported;
however, it is known that other members of the genus *Lobaria* are used as pharmaceuticals and in perfumery.49

The search for a complementary methodology was then justified. In this work, a new [2+3] annulation methodology based on conjugate addition of dienolates containing \( \alpha \)-leaving groups will be described. This approach allowed for the preparation of retigeranic acid (1), and improved other syntheses such as pentalenene (3). In the following sections a review of [2+3] annulations and other anionic cyclizations, as well as the history of retigeranic acid (1), will be presented.
II. HISTORICAL

1. [2+3] Cyclopentannulations

1.1. Introduction

The search for new cyclopentannulation methodologies did not attract the attention of synthetic chemists until the seventies when the full spectrum of natural products with interesting biological activities was discovered to contain either one or more-fused five-membered rings as, for example, prostaglandins\textsuperscript{12-17} and triquinanes\textsuperscript{6-11} respectively. Since that time, active research in this field is reflected in the quantity of publications that were reviewed on several occasions: Paquette\textsuperscript{6-8} in 1979 and 1984, Trost\textsuperscript{32,33} in 1982 and 1986, Santelli-Rouvier\textsuperscript{35} in 1983, Ramaiah\textsuperscript{34} in 1984, Vandewalle\textsuperscript{11} in 1985, Heathcock\textsuperscript{9,10} in 1973 and 1983, Mitra\textsuperscript{12} in 1977, Winterfeldt\textsuperscript{13} in 1982, Ferrier\textsuperscript{14} in 1983 and Hudlicky\textsuperscript{36} in 1988.

These methodologies can be classified into four categories by the number of atoms in each molecule involved in the cyclization: a) [2+3],\textsuperscript{37} b) [4+1],\textsuperscript{38} c) [2+2+1]\textsuperscript{39} and d) [4+2-1]\textsuperscript{40} annulations. The most widely used of these are the [2+3] and the [4+1] protocols. All of these ring closures have been achieved either in a single or in a multiple-step and via radical or ionic intermediates.
1.2. Types of annulations

a) \[2+3\] annulations. In this case, one of the two entities involved in the cyclization provides two of the carbons and the other three. There are several possible combinations, and these are graphically represented in Scheme 4.

An example of one of the radical processes, reported by Little (case i, Scheme 4), is the preparation of the skeleton of linear triquinanes [such as hirsutene (15)] via diradical 16, obtained by thermal decomposition of diazene 16a (Scheme 5).

A methodology that is represented by the anionic reaction v (Scheme 4) would be Mundy's cyclization of dimethylsuccinate dianion (17) with 1,3-dibromopropane (18) (Scheme 6), and by reaction iii, Weiss-Cook's condensation of dimethylacetone-dicarboxylate (19) with an \(\alpha\) diketone 20 at pH 6.8 (Scheme 7).
b) [4+1] annulations. In this case, one molecule provides four of the carbons in the cyclization, and the other, one. The possible interactions, either radical or anionic are represented in Scheme 8.

Reaction i, the interaction of a diene with a carbene species is exemplified by the method of Hudlicky, with a formal [4+1] approach that relies on initial cyclopropanation of the diene, followed by vinylcyclopropane-cyclopentene rearrangement, as explained in the Introduction. Similarly, reaction i is exemplified by the procedure of Danheiser, the carbanion accelerated overall [4+1] cyclopentannulation (Scheme 9). Bromovinylcyclopropane 21 was prepared following Martel's procedure, and transformed into sulfone 22 in two steps, which after base treatment rearranged to
cyclopentene 23 (Scheme 9). This reaction is similar in concept to the alkoxy-accelerated vinylcyclopropane rearrangement reported also by Danheiser.\textsuperscript{38b,c}

\begin{center}
\begin{tikzpicture}

\node at (0,0) (a) {\ce{21}};
\node at (2,0) (b) {\ce{22}};
\node at (4,0) (c) {\ce{23}};

\draw (a) -- (b) node[midway,above] {Br};
\draw (b) -- (c) node[midway,above] {CH\textsubscript{2}SO\textsubscript{2}Ph};
\draw (c) -- (a) node[midway,above] {CH\textsubscript{2}SO\textsubscript{2}Ph};
\end{tikzpicture}
\end{center}

**Scheme 9**

Another example of an anion-based disconnection of type ii (Scheme 8) is Géro's\textsuperscript{38d} cyclization, where cyclopentane 24 was obtained by reaction of epoxide 25 (derived from tartaric acid) with phenylthioacetonitrile (26) in the presence of N-sodiohexamethyldisilazane (Scheme 10).

\begin{center}
\begin{tikzpicture}

\node at (0,0) (a) {\text{Tartaric acid}};
\node at (2,0) (b) {\ce{25}};
\node at (4,0) (c) {\ce{24}};
\node at (1,-1) (d) {\ce{26}};
\node at (3,-1) (e) {NaHMDS};

\draw (a) -- (b) node[midway,above] {\ce{CH\textsubscript{2}CH\textsubscript{2}O}};
\draw (b) -- (c) node[midway,above] {\ce{CN}};
\draw (b) -- (d) node[midway,above] {\ce{PhSCH\textsubscript{2}CN}};
\draw (d) -- (e) node[midway,above] {\ce{NaHMDS}};
\draw (e) -- (c) node[midway,above] {\ce{PhCH\textsubscript{2}O}};
\end{tikzpicture}
\end{center}

**Scheme 10**

c) [2+2+1] annulations.\textsuperscript{39} DeShong's\textsuperscript{39a} carbonyl insertion reaction would serve as a representation of this type of annulation, where two of the carbon atoms belong to an oxirane 27, the other two to an alkyne 28, and the fifth to one of the carbonyl ligands of the organometallic reagent 29 (Scheme 11).

\begin{center}
\begin{tikzpicture}

\node at (0,0) (a) {\ce{27}};
\node at (2,0) (b) {\ce{28}};
\node at (4,0) (c) {\ce{29}};

\draw (a) -- (b) node[midway,above] {\ce{\text{Ph}}};
\draw (b) -- (c) node[midway,above] {\ce{\text{Ph}}};
\draw (a) -- (c) node[midway,above] {\ce{\text{Ph}}};
\end{tikzpicture}
\end{center}

**Scheme 11**

d) [4+2-1] annulations.\textsuperscript{40} In this case a six-membered ring intermediate is generated in the reaction, which later contracts to cyclopentane. An example of this type of reaction is observed in Sworin's\textsuperscript{40a} cationic cyclization of acetals 30 in the presence of
SnCl₄. Intermediate 31 has the ideal conformation for the ring contraction directed by the hydroxy group (Scheme 12).

Similarly, Larsen⁴⁰b utilized a six-membered-ring intermediate, which contained a sulfur atom. The ring contraction was achieved by treatment with LDA or potassium hexamethyldisilazane.

The annulation methodology that will be described in this manuscript corresponds to a [2+3] process. In order to have an overview of this topic, a discussion of the most recent work in this area will be presented in this section. Five categories were found to predominate among the publications: a) radical cyclizations, b) Michael-type additions, c) the reaction of methylenemethane equivalents, d) the use of organometallic intermediates and e) reaction involving zwitterionic intermediates. Most of them have precedents in the literature, and constitute an improvement or slight modification of methodologies already available.
1.3. Radical cyclizations

Addition of free radicals to multiple bonds leads to the generation of a new alkyl radical, which may react with another functional group to form another radical, or with a radical to terminate the process. If a radical is formed at the δ position to a double bond, cyclizations occur readily, and both five and six-membered rings may form. The fact that five-membered rings are usually preferred was surprising for several reasons: a) radicals generally add in an "anti-Markovnikov" fashion (in this case even a five-membered ring with a primary radical intermediate is preferred to a six-membered ring with a secondary radical), b) thermodynamically, formation of six-membered rings would be favored over five-membered rings. Several explanations were proposed in order to rationalize this phenomenon: a) a more favorable entropy when a cyclopentane is formed as compared with a cyclohexane, b) an unfavorable non-bonded interaction between H₁ and H₂ in which was not present in (Scheme 13). This postulate was shown later not to be correct. Beckwith discussed the influence of the steric and stereo-electronic effects that determined the regio and stereo-selectivity of radical processes. He indicated that a more favorable entropy in the formation of a five-membered ring would not have been the most important reason to determine such a selectivity. The new theory supported a dipolar transition complex (with an obtuse angle) as a result of the "nucleophilic-type attack" of the radical to the

![Scheme 13](image-url)
olefin. Consequently, this transition state can be more easily accommodated in 33 than in 32, kinetically favoring the five-membered ring formation.

Based on this precedent (radical additions and cyclizations), in 1987 Curran\textsuperscript{69} reported that a 15:1 mixture of (iodomethylene)-cyclopentane 35 and cyclohexenyl iodide 36 was obtained when butynyl iodide 37 and methyl acrylate (38) were irradiated in benzene with a sunlamp in the presence of hexabutylditin. The ratio of E:Z isomers in 35 was 3:1.

\[
\begin{align*}
   \text{R} \quad & \quad \text{CO}_2\text{Me} \quad \text{Bu}_3\text{SnSnBu}_3, \quad \text{sunlamp} \\
   \text{37a, R=H} \quad & \quad \text{38} \\
   \text{37b, R=TMS} \quad & \quad \text{35} \quad + \quad \text{36}
\end{align*}
\]

A proposed\textsuperscript{69} propagation step is shown in Scheme 14. Radicals 39 and 40 would react rather slowly, but in the absence of an hydrogen atom donor such as Sn-H, no side reactions would be expected. This way of control of the radical reaction by using an halogen atom was referred to as "atom transfer." The driving force of the reaction would be the formation of a more stable alkyl radical 39 from a less stable vinyl radical 40a.

\[
\begin{align*}
   \text{39} \quad + \quad \text{CO}_2\text{Me} & \quad \text{Bu}_3\text{SnSnBu}_3, \quad \text{sunlamp} \\
   & \quad \text{35} \quad + \quad \text{36}
\end{align*}
\]

Scheme 14

Several electron-deficient olefins were investigated. Results are shown in Scheme 15.
<table>
<thead>
<tr>
<th>Iodide</th>
<th>Alkene</th>
<th>Products</th>
<th>5-exo/6-endo</th>
<th>E/Z</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Diagram" /></td>
<td>5-exo</td>
<td>6-endo</td>
<td></td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>R = H, E = CN</td>
<td>7/1</td>
<td>2/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>R = H, E = COCH₃</td>
<td>10/1</td>
<td>1.2/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>R = CH₃, E = CHO</td>
<td>8/1</td>
<td>7.3/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>R = CH₃, E = CO₂CH₃</td>
<td>23/1</td>
<td>10/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>R = H, E = SO₂Ph</td>
<td>9/1</td>
<td>5/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>11/1</td>
<td>3.1/1</td>
</tr>
<tr>
<td>37a</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>9/1</td>
<td>2.4/1</td>
</tr>
<tr>
<td>37b</td>
<td></td>
<td><img src="image" alt="Structure" /></td>
<td>not detected</td>
<td>8/1</td>
<td>45</td>
</tr>
</tbody>
</table>

In all cases a 5-exo over a 6-endo preference was observed. This ratio increased with the use of 1,1-disubstituted olefins and/or TMS-substituted alkyne 37b. With respect to the E/Z ratio of isomers of the 5-exo, the selectivity was modest in the case of monosubstituted electron-deficient olefins and increased with 1,1-disubstituted alkenes. This methodology was applied in the total synthesis of albene⁶⁹ (41) (Scheme 16).
Similarly, Feldman reported the synthesis of functionalized vinylcyclopentanes 42 by reaction of vinylcyclopropane 43 with 10-15 fold excess of an olefin 44 in benzene and in the presence of a phenylthio radical precursor and a Lewis acid (trimethyl aluminum).

![Scheme 16](image)

The results summarized in Scheme 17 show this process to occur with complete regiochemical control, but moderate stereoselectivity. For example, the four possible stereoisomers of 42 are obtained when R and R2 are tert-butyl esters. However, using a

<table>
<thead>
<tr>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>Cond.</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>43a:</td>
<td>CO2-t-Bu</td>
<td>H</td>
<td>CO2-t-Bu</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>43c:</td>
<td>CO2-t-Bu</td>
<td>H</td>
<td>OCO-t-Bu</td>
<td>B</td>
</tr>
<tr>
<td>43d:</td>
<td>OEt</td>
<td>H</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>43e:</td>
<td>Ph</td>
<td>H</td>
<td>CO2Me</td>
<td>A</td>
</tr>
</tbody>
</table>

Condition A: refluxing benzene; condition B: 0.8eq. Me3Al, toluene

Scheme 17
combination of low temperature and trimethyl aluminum (condition B), the stereoselectivity was improved (Scheme 17).

When bulky substituents (i.e., tert-butyl esters) participated in the reaction, the stereoselectivity was higher than with methyl esters, although cyclopentanes were also obtained. The high regioselectivity of this methodology was demonstrated by the double addition of methyl acrylate to cyclopropylcyclopropane to give only regioisomer, even though at least five stereoisomers were formed. The propagation step proposed by the author is shown in Scheme 18.

![Scheme 18](image)

The role of the Lewis acid in these radical additions was not clear. However, it was generally observed that trimethylaluminum increased the rate and improved the stereoselectivity of the reaction.

This reaction was extended by Feldman to the preparation of dihydrofuran derivatives, by using vinyloxiranes instead of vinylcyclopropanes. It also has a precedent on Wender's areneolefin photocyclization leading to polycyclic sesquiterpenes.
1.4. Michael-type additions

An extensively used\textsuperscript{11,34} procedure for the synthesis of five-membered rings relied on the Michael-type addition of reagents 46 to $\alpha,\beta$-unsaturated carbonyl compounds. The subsequent ring closure can then occur if the reagent 46 is equipped with an electrophile that can be trapped by the intermediate enolate anion. Early examples of this kind of chemistry are illustrated by Helquist\textsuperscript{73} and by Pattenden.\textsuperscript{74} Helquist\textsuperscript{73} reported the conjugate addition catalyzed by a cuprous salt, of acetal-containing Grignard reagent 47 to several cyclic enones. Subsequent treatment of 47a with hydrochloric acid produced the cyclization in a "one pot" reaction (Scheme 19). This methodology was utilized by Paquette\textsuperscript{75} and by Tsunoda\textsuperscript{76} in the synthesis of triquinane silphinene (48).

Pattenden\textsuperscript{74} synthesized ring A of $\Delta^9(12)$-capnellene-8$\alpha,10\alpha$-diol (49) by first, addition of cuprate 50 to 3-methylcyclopentenone and then, cyclization by treatment of the enol acetate 51 with stannic chloride (Scheme 20).
Many reactions of this type have been reported in the last five years, and they will be briefly described in this section. Methylene-cyclopentane derivatives 52 were prepared by Piers\textsuperscript{77} in 1983, by reaction of cuprates 53 or 54 with cyclic enones, and subsequent ring closure of intermediate 55 with potassium hydride (Scheme 21).

\begin{equation}
\begin{array}{ccc}
53: M = \text{Cu(SPh)Li} \\
54: M = \text{Cu(CN)Li}
\end{array}
\end{equation}

<table>
<thead>
<tr>
<th>enone</th>
<th>55 (% w/53)</th>
<th>55 (% w/54)</th>
<th>52 (%)</th>
</tr>
</thead>
</table>
| \text{cyclohexanone} | 83 | 80 | R^1=H \\
& | & R^2=H (75) |
| \text{cinnamaldehyde} | 77 | 78 | R^1=CH_3 \\
& | & R^2=H (75) |
| \text{cinnamaldehyde} | 75 | 77 | R^1=H \\
& | & R^2=H (68) |
| \text{cinnamaldehyde} | 77 | 75 | R^1=CH_3 \\
& | & R^2=H (75) |
| \text{cinnamaldehyde} | 80 | 78* | R^1=H \\
& | & R^2=CH_3 (70) |
| \text{cinnamaldehyde} | 70 | 72 | (65) |

* BF\textsubscript{3}·OEt\textsubscript{2} catalyzed the reaction.
In all cases the stereochemistry of the ring junction was cis. Compounds 53 and 54 were prepared by transmetallation of 4-chloro-2-trimethylstannylbut-1-ene with MeLi, followed by addition of phenylthiocopper or copper cyanide respectively.

Danheiser reported in 1985 the reaction of α,β-unsaturated acyilsilanes with allenylsilanes in the presence of TiCl₄ to produce five-membered carboxylic compounds 58. Results are summarized in Scheme 22. The reaction could be controlled to produce either five or six-membered rings when 2-alkylacylsilanes were used (Scheme 22a).

<table>
<thead>
<tr>
<th></th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>56</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-BuMe₂Si</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>72</td>
</tr>
<tr>
<td>t-BuMe₂Si</td>
<td>CH₃</td>
<td>CH₃</td>
<td>CH₃</td>
<td>55</td>
</tr>
<tr>
<td>Me₃Si</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>66</td>
</tr>
<tr>
<td>t-BuMe₂Si</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>78</td>
</tr>
<tr>
<td>Me₃Si</td>
<td>CH₃</td>
<td>H</td>
<td>H</td>
<td>74</td>
</tr>
</tbody>
</table>

Scheme 22
To avoid the [3+3] mode of the reaction, t-BuMe₂Si acylsilane was used, the reaction time was minimized, and the reaction temperature was not permitted to exceed -78 °C. Adducts 58 were oxidized to the corresponding carboxylic acids with 10% aqueous sodium hydroxide and 30% hydrogen peroxide.

In 1986, Ghosez\textsuperscript{83} prepared ketals of cyclopentanone 59 by addition of a compound containing a stabilized 1,3-dipole such as 60 to an enone. The equivalent for compound 60 was found in 3-phenylsulfonyl ortho-propionate (60a) which presented the potential carbanion at C-3 and the cationic character of the orthoester at C-1.

The addition of cyclohexenone to the lithium anion of 60a afforded a complex mixture of 1,2- and 1,4-adducts along with several unidentified products. However, in
the presence of HMPA, the 1,4-adduct constituted the major product of the reaction. This was proved by the isolation of compound 61 (Scheme 23).

Scheme 23

The lithium enolate anion 62 was trapped with trimethylsilyl chloride to give 63, which was treated with a catalytic amount of trimethylsilyl triflate to furnish 64 as a single diastereomer in 68% overall yield (Scheme 23). Other examples of this method are shown in Scheme 24.

<table>
<thead>
<tr>
<th>enone</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>H</td>
<td>50</td>
</tr>
<tr>
<td>O</td>
<td>H</td>
<td>65</td>
</tr>
</tbody>
</table>

Scheme 24
In all cases the stereochemistry at the ring junction was cis and the phenylsulfonyl substituent was oriented in the exo position. The reaction proved to be independent of the ring size, as well as substitution pattern at C-2 and C-4. However, when the enone was substituted at C-3, a mixture of several products was obtained (Scheme 24).

Similarly, Beak\textsuperscript{84} reported in 1986 an anionic [3+2] cyclization-elimination reaction, that consisted of the addition of an allylic anion 65 to an electron-deficient olefin to provide cyclopentene ring 66.

No vinylcyclopropanes were observed, and only very small amount of the alternative regioisomer was present. The reaction was believed to occur in a stepwise fashion by analogy with Kauffman's\textsuperscript{85} 1,1-diphenyl-2-azaallyl-lithium system, although this supposition has not been proved. The results are summarized in Scheme 25.

<table>
<thead>
<tr>
<th>olefin</th>
<th>product</th>
<th>% yield</th>
<th>olefin</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CO}_2\text{Me})</td>
<td>(\text{CON}\text{(I-Pr)}\text{_2})</td>
<td>59</td>
<td>(\text{Me}_3\text{Si}\text{CO}_2\text{Me})</td>
<td>(\text{CON}\text{(I-Pr)}\text{_2})</td>
<td>57</td>
</tr>
<tr>
<td>(\text{CONPhMe})</td>
<td>(\text{CON}\text{(I-Pr)}\text{_2})</td>
<td>65</td>
<td>(\text{HCONPhMe})</td>
<td>(\text{CONPhMe})</td>
<td>33</td>
</tr>
<tr>
<td>(\text{CONPhMe})</td>
<td>(\text{CO}_2\text{Me})</td>
<td>66b</td>
<td>(\text{CON}\text{(I-Pr)}\text{_2})</td>
<td>(\text{CN})</td>
<td>66f</td>
</tr>
</tbody>
</table>

Scheme 25
Poor yields of cyclopentanes were realized when olefins unsubstituted at the α-position were employed, as illustrated by 66e (Scheme 25). However, an alternative synthesis was accomplished by treatment of 66d with tetrabutylammonium fluoride in THF-H2O, obtaining 67 in 68%.

Another report of cyclopentene annulation methodology involving a tandem Michael-carbene insertion reaction was published in 1986 by Ochiai. Conjugated addition of an anion (Nu') to an alkyne lithiodonium salt 68, produced lithiodonium ylide 69, which by reductive elimination may have formed the highly reactive allcylidene carbene 70. Intramolecular 1,5-carbon-hydrogen insertion reaction of 70, regioselectively gave compound 71. When all carbon atoms of the cyclopentene ring, as in 71a, were contained in the substituted ethynyl group of 68, the reaction could be considered a [5+0]
cyclopentene annulation. On the other hand, when the carbon atoms in $71b$ were contributed from the nucleophile and the ethynyl group, the reaction also became a [2+3] cyclopentene annulation. This type of vinyl insertion reaction is similar to Dreiding's α-alkynone cyclization leading to triquinanes. In Scheme 27 only the [2+3] annulations are included.

<table>
<thead>
<tr>
<th>Nu</th>
<th>$71b$</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>[5+0]</td>
<td>79:21</td>
<td>[2+3]</td>
</tr>
<tr>
<td>[5+0]</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>[5+0]</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>[5+0]</td>
<td>74</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 27

Ikegami reported in 1986 a LiI-promoted vinylcyclopropane-cyclopentene rearrangement. Diquinane $72$ was prepared in seven steps from 2-methoxycarbonyl-2-cyclopentenone $73$. The key-steps were the palladium-catalyzed cyclopropanation of $74$,

Scheme 28

\[ a) \text{Et}_2\text{AICCH}_2\text{OSi(t-Bu)Me}_2; \quad b) \text{H}_2, \text{Lindlar cat.}; \quad c) \text{HF-Py}; \quad d) \text{PhOCOCl}; \quad e) \text{Pd(PPh}_3)_4; \quad f) \text{LiI or LiBr, DMF}; \quad g) 135 \, ^\circ\text{C} \]
and then lithium iodide mediated $S_N2'$ nucleophillic opening of 75 to give 76 via intermediate allylic iodides 77. Decarboxylation of 76 finally led to 72 (Scheme 28).

The vinylcyclopropane-cyclopentane rearrangement took place by heating a mixture of 75 and LiI in DMF at 110 °C. Under the same conditions compound 78 did not react, suggesting that the presence of a methoxycarbonyl group was essential for the rearrangement to occur. The reaction took place also using LiBr, but other salts such as LiCl, NaI or NaBr gave complex mixtures. The corresponding thermal rearrangement of vinylcyclopropanes has been extensively used by Cohen,90 Danheiser,38b,c,56 Hudlicky,91 Monti,92 Paquette,93 Piers94 and Trost95 in approaches to the synthesis of cyclopentenes.

In 1986, Boger96 described a highly functionalized-cyclopentene formation as a result of an allylcarbene [2+3] cycloaddition to an electron-deficient olefin. The reactive intermediate 79 (characterized as a nucleophilic and $\pi$-delocalized singlet allylcarbene) was thermally generated from cyclopropenone ketal 80,97 and in the presence of an olefin bearing two geminal electron withdrawing substituents, cyclopentenes 81 were formed (Scheme 29). No other reactive intermediates were detected.

This reaction proved to be insensitive to the polarity of the solvents utilized. The relative rate for a given substrate was DMF (2)>CH$_3$CN (1.4)>C$_6$H$_6$ (1.0)>C$_5$H$_5$N.
On the other hand, it was found to be sensitive to olefin substitution. β,β-Disubstituted olefins bearing two geminal electron-withdrawing groups failed to react with cyclopropenone ketal 80.

Highly functionalized five-membered rings of type 82 were also prepared by Bunce\textsuperscript{98} in 1987 by means of a tandem Michael-Michael ring closure reaction. This

<table>
<thead>
<tr>
<th>EWG</th>
<th>EWG</th>
<th>solvent</th>
<th>81</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>53</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>57</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>95-100</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>82</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td>benzene</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>61</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>O</td>
<td>CO\textsubscript{2}Et</td>
<td>benzene</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Scheme 29
methodology has a precedent in the Michael-Michael ring closures for the synthesis of functionalized six-membered rings.99 The reagent 83 was designed to contain a Michael donor and acceptor in the same molecule. To avoid intramolecular cyclizations these two entities had to be separated by less than three carbons. In this case anion 83 would be in equilibrium with a less stable anion 84, disfavoring the ring closure. Schemes 30 and 31 summarize the results of addition of 83 to acyclic and cyclic enones respectively. Both acyclic and cyclic enones react well, although acyclic ones gave slightly better results. As with the standard Michael reaction, the success of this reaction depends on the environment of the β-position of the enone, as a result of the sterically hindered approach or the facile competing retro-Michael reaction.100
<table>
<thead>
<tr>
<th>enone</th>
<th>R</th>
<th>R'</th>
<th>82a:82b</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>H</td>
<td></td>
<td>&gt;50:1</td>
<td>65</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td></td>
<td>5:2</td>
<td>73</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td></td>
<td>&gt;50:1</td>
<td>81</td>
</tr>
<tr>
<td>Ph</td>
<td>CH₃</td>
<td></td>
<td>18:1</td>
<td>83</td>
</tr>
</tbody>
</table>

Scheme 30

Examination of the results in Scheme 30, reveals that the stereochemistry of the cyclized products reflected the thermodynamic conditions under which the reactions were performed. While 2-unsubstituted enones gave almost exclusively the trans product, α-methyl enones gave a mixture of stereoisomers (reduced steric differentiation between acyl and methyl groups). On the other hand, the stereochemistry of the products derived from cyclic enones (Scheme 31) depended on the ring sizes of the fused bicyclic compounds formed. Evaluation of other carbanion-stabilizing functionalities on the Michael donor moiety, like -CN and -COR, allowed the conclusion that, in general, the malonate-derivative reagents provided the best results under conditions employing alkoxide base.

The methodology that will be described in this manuscript belongs to this section. A vinylcyclopropane is formed via Michael addition to an enone, which can be rearranged to the cyclopentene.
1.5. The reaction of trimethylenemethane equivalents

In search for cyclopentannulation methodologies equivalent to the Diels-Alder reaction for six-membered rings, Trost developed a [2+3] process, which involved the interaction of a zwitterion equivalent of trimethylenemethane with an electron-deficient olefin. The carbanion equivalents in were represented by silyl or stannyl groups, and the carbocations, by leaving groups such as acetate, methanesulfonate, iodide, etc. Palladium (0) complexes were needed as activators (intermediate) in the reactions with electron-deficient olefins in order to obtain cyclopentanes (Scheme 32).

\[
\begin{align*}
\text{Si(CH}_3)_3 \quad \text{OAc} & \quad \xrightarrow{\text{PdL}_{n+m}} \\
\quad & \quad \xrightarrow{\text{PdL}_n} \\
\quad & \quad \xrightarrow{\text{Z}}
\end{align*}
\]

The geometry was usually retained in the product with E-olefins, but not with Z-olefins, which produced trans:cis ratios of 1:1.3 to 1:2. As an extension of his methodology, and in contrast to the earlier observations, Trost described in 1986 a stereospecific palladium mediated cycloaddition of (X = OAc, MR3 = SiMe3) to methyl (Z) (R)-4,5-di-O-isopropylidene-pent-2-enoate (ratio of diastereomers >50:1) in 69% yield. The (E)-enoate gave two products in 76:24 ratio and 78% yield (Scheme 33). These results led to considerations of a possible concerted mechanism, instead of a stepwise one as it was originally interpreted.
Based on these antecedents, Molander reported in 1986 a stereocontrolled [2+3] cyclopentannulation methodology, by reaction of trimethylenemethane equivalents (in this case dianionic synthons), and 1,2-diones (dielectrophilic species).

The success of this process relied on the activation of the remaining carbonyl in intermediate by metal alkoxide. The addition of the allylsilane led stereospecifically to cis diols. Zn was the first reducing agent tried, but ring closure was not achieved. When SnF was used instead two advantages over Zn surfaced: 1) Sn was a stronger Lewis acid than Zn, and induced cyclization, and 2) the fluoride increased the nucleophilicity of the allylsilane. Reaction of compound with different 1,2 diones was investigated, and the results are summarized in Scheme 34.
<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>% yield</th>
<th>diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>72</td>
<td>&gt;75:1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃CH₂</td>
<td>88</td>
<td>&gt;32:1</td>
</tr>
<tr>
<td>CH₃</td>
<td>C₆H₅</td>
<td>72</td>
<td>&gt;28:1</td>
</tr>
<tr>
<td>CH₃(CH₂)₂</td>
<td>CH₃(CH₂)₂</td>
<td>68</td>
<td>&gt;25:1</td>
</tr>
<tr>
<td>CH₃(CH₂)₃</td>
<td>Cl(CH₂)₄</td>
<td>73</td>
<td>&gt;50:1</td>
</tr>
<tr>
<td>-(CH₂)₄-</td>
<td></td>
<td>41</td>
<td>one diastereomer</td>
</tr>
<tr>
<td>CH₃</td>
<td>(CH₃)₂CH</td>
<td>24</td>
<td>one diastereomer</td>
</tr>
<tr>
<td>Ph</td>
<td>Ph</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 34
1.6. The use of organometallic intermediates

In 1984, Rosenblum\textsuperscript{111} reported the cycloaddition of $\eta^1$-allyl, propargyl or allenyl Fp complexes ($\text{Fp} = \eta^5\text{C}_5\text{H}_5\text{Fe(CO)}_2$) \textit{26}, \textit{27} and \textit{28} respectively, with troponeiron tricarbonyl \textit{99a} activated by either trimethylsilyl triflate or n-butylboryl triflate.

![Chemical Structures](image)

Results are shown in Scheme 35.

<table>
<thead>
<tr>
<th>nucleophile</th>
<th>$R$</th>
<th>activator</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>H</td>
<td>TMSOTf</td>
<td>![Product Image]</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>Bu$_2$BOTf</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Bu$_2$BOTf</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>27</td>
<td>Me</td>
<td>TMSOTf</td>
<td>![Product Image]</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Me</td>
<td>Bu$_2$BOTf</td>
<td></td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>SiMe$_3$</td>
<td>Bu$_2$BOTf</td>
<td></td>
<td>62*</td>
</tr>
<tr>
<td>28</td>
<td>TMSOTf</td>
<td>Bu$_2$BOTf</td>
<td>![Product Image]</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Bu$_2$BOTf</td>
<td></td>
<td></td>
<td>55</td>
</tr>
</tbody>
</table>

* $R=$H, the TMS group was lost during the reaction

Scheme 35

These reactions can be explained by an initial attack of the nucleophile \textit{26} at C-1 of \textit{99a}, which is the least hindered carbon atom of the pentadienyl ligand. Ring closure is assisted by the uncomplexed enol double bond (Scheme 36). In all cases a single
regioisomer was obtained. The same author,\textsuperscript{112} in 1985, extended this reaction to tropylium salt 100 which gave 101 (\( \beta: \alpha = 2.2:1, 64\% \)) when treated with 96 (R=H), or 102 (61\%) when treated with 97 (Scheme 37). Similarly, 103 reacted with 96 (R=H), to give compound 104 in 41\% yield (Scheme 38).

In 1985 Binger\textsuperscript{113} reported the [2+3] cycloaddition of methylenecyclopropane 105 with several electron-deficient olefins, catalyzed by Ph\(_3\)P/Ni(COD)\(_2\) to give 106, 107 or 108 depending on R (Scheme 39). The regio and stereo-chemistry of the products was found dependent on the nature of substituents R, as well as on the olefin geometry.
A speculation about the reaction mechanism presented by the author is shown in Scheme 41.

* 6% of cis/trans 108 was obtained
** 4% of cis/trans 108 was obtained
In 1988, Hayashi\textsuperscript{114} reported the preparation of optically active vinylcyclopropanes and vinylidihydrofurans when Pd$_2$(dba)$_3$•CHCl$_3$ and (R)-N,N-dimethyl-1-[(S)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine were used as catalysts in the reaction of (Z)-2-butenylene dicarbonate with dimethyl malonate. The enantiomeric purity of the product proved to be very sensitive to the reaction time. For example, in a two-hour reaction the enatiomeric excess was 67\%, and in twenty-four hours, it diminished to 30\%. The racemization could be explained by a reversible pathway during the closure of the cyclopropane.
1.7. Reaction involving zwitterionic intermediates

Snider described a process in which cyclopentanedicarboxylates were obtained by treatment of diethyl cyclopropane-1,1-dicarboxylate (109) with 1,1-di-, tri- and tetra-substituted alkenes in the presence of EtAlCl₂ (2 equivalents). A zwitterionic system was proposed as an intermediate. These results are shown in Scheme 42 (E=ethyl ester).

```
\[ \text{EtO}_2\text{C} \text{CO}_2\text{Et} + \text{R}' \text{R''} \text{EtAlCl}_2 \rightarrow \text{ EtO}_2\text{C} \text{CO}_2\text{Et} \]
```

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Product(s)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Product(s)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reaction led to complex mixtures when 2-methyl- or 2,6-dimethylmethylene cyclohexane was used, due to a facile 1,2-hydride shift from 111a to give 112, which closed to give isomeric decalin derivatives (Scheme 43). Substituted cyclopropanedicarboxylates were also studied, leading to diastereomeric mixtures in most of the cases.115
2. Dienolate addition to enones

The generation of a carbon-carbon bond by means of a 1,2-addition of an enolate to a carbonyl compound (aldol condensation) has been known for more than 100 years,\textsuperscript{116} and constitutes one of the most important and useful tools in organic synthesis. This reaction has been extensively studied and reviewed,\textsuperscript{117} and in the last two decades, a special emphasis in the study of control of the regio-, stereo-\textsuperscript{118} and, more recently enantio-selection,\textsuperscript{119} materialized.

Unfortunately, such complete information is not available for systems of increased complexity, such as those involving the addition of an enolate to an enone,\textsuperscript{120} or of a dienolate to a simple electrophile\textsuperscript{121} or to an enone.\textsuperscript{122} This is understandable considering the increased complexity of the variables in any of the above situations. For example, with the additions of enolate species to enones instead of carbonyls, 1,4-addition is also possible. Similarly, when a dienolate is the nucleophile, its geometry will have an important role in the final stereochemistry of the product, and the question of \(\alpha\)-versus \(\gamma\)-mode of addition will become important. The situation is even more aggravated when the reaction takes place between a dienolate and an enone. Very little is known in this area save isolated reports by Oppolzer,\textsuperscript{123} Hudlicky\textsuperscript{124a,b} and Heathcock.\textsuperscript{125} This is the case that will be described later in this dissertation: addition of an ambident nucleophile, itself equipped with a leaving group, to an enone with concomitant formation of two carbon-carbon bonds. The work reported in addition of dienolates to enones in the last eleven years will be briefly described in this section.

In 1977 Kraus\textsuperscript{125} examined a new annulation reaction as a result of condensation of a dienolate \textit{112} (obtained by treatment of \textit{112a} with n-butyllithium) to a carbonyl-type
compound 113. Adduct 114 was obtained after trapping with TMSCl. These results are shown in Scheme 44.

Several interesting observations were noted: a) the site of attack was the γ instead of the α position of the dienolate, b) compound 112 did not react with ketones, and c) 1,2-addition to the carbonyl compound did not occur.

Oppolzer\textsuperscript{127} reported in 1982 the regio- and stereo-selective synthesis of (±)-khusimone 115 by addition of the dienolate of 116\textsubscript{a} to cyclopentenone. An 88:12 stereoselection of C-6/C-5 was obtained in compounds 117. One year later the second generation synthesis was published\textsuperscript{128} using an asymmetric Michael methodology to
introduce chirality to the system. In this case the chiral 116b was used, expecting a high
dienolate-π-facial differentiation to control the chirality of both C-6 and C-5.

When chiral 116b was added to cyclopentenone, a 63:21:9:7 mixture of
diastereomers 117 (70% yield) was obtained. X-ray-diffraction of the major Michael
adduct showed (5S,6S)-chirality. Similar aprotic Michael addition of the dienolate of
116b to cyclopentenone and in situ trapping of the intermediate enolate with allyl
bromide, gave a 48:5:9:9 diastereomer mixture 118 in 55% yield. The major isomer was
also assigned (5S,6S), and was converted into enantiomerically pure (-)-khusimone
115128 in nine steps and 14% overall yield.

A selective γ Michael addition of tin (II) dienolates 119 to acyclic enones was
described by Stevens129 in 1985. Compounds 120 were obtained when the reaction was
carried out at -45 °C, and the results are summarized in Scheme 45.

α-Michael-mode of dienolate addition was not observed, and neither was the 1,2-
addition product to the carbonyl group. Moreover, if the reaction was carried out at 0 °C,
cyclohexenols 121 (R= t-Bu) and elimination products 122 (R= i-Pr) and 123 (R= Et) were
obtained with high stereoselectivity, as a result of an intramolecular Aldol condensation reaction (Scheme 46). The author speculated that a stepwise mechanism was taking place.

\[
\begin{array}{ccc}
R & R^1 & R^2 & \% \text{ yield of 120} \\
\hline
t-Bu & CH_3 & Ph & 83 \\
t-Bu & CH_3 & H & 75 \\
t-Bu & Ph & Ph & 81 \\
t-Bu & -CH=CHPh & Ph & 71 \\
t-Bu & -CH_2CH_2CH_2 & - & - \\
i-Pr & CH_3 & Ph & 72 \\
i-Pr & CH_3 & H & 55 \\
Et & CH_3 & Ph & 60 \\
Et & CH_3 & H & 38 \\
\end{array}
\]

**Scheme 45**

Method A: enone was added at 0 °C after dilution.
Method B: after addition of the enone, the mixture was diluted and the temperature raised to 0 °C.

(γ-selective 1,4-conjugate addition to enone, followed by aldol-type cyclization), instead of a Diels-Alder type reaction.
Mestres (1985) prepared compound 124 with high regio- and stereo-selectivity by reaction of the lithium dienolate derived from 2-butenoic acid 125, with enone 126

\[
\text{125} + \text{126} \xrightarrow{\text{LIO}_2} \text{127} \xrightarrow{[3,3]} \text{124} \text{ with base} \text{124} \xrightarrow{\text{H}_2\text{O}} \text{125}
\]

\(\text{R=Ph} \) at 66 °C in 81% yield. The author remarked that the high stereoselectivity would not be expected from a reversible 1,4 addition, but rather from an oxy-Cope rearrangement of the 1,2 adduct 127, which was obtained by γ-attack of dienolate 125 to enone 126 (R=Ph) (Scheme 47).

\[
\begin{array}{c}
\text{125} + \text{126} \\
\text{R=Ph}
\end{array} \xrightarrow{\text{R=Ph}} \text{127} \xrightarrow{[3,3]} \text{124}
\]

Scheme 47

Effectively, when the reaction was carried out at -95 °C, only the protonated form of 127 was obtained, which was converted into 124 by treatment with two equivalents of base for 2 hours and at 25 °C. The regiochemistry of the reaction was highly dependent upon the substituent R on enone 126 as it is represented by ratio 124:128 in Scheme 48.

<table>
<thead>
<tr>
<th>R in 126</th>
<th>crude % yield</th>
<th>124:128</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>81</td>
<td>100:0</td>
</tr>
<tr>
<td>t-Bu</td>
<td>92</td>
<td>85:15</td>
</tr>
<tr>
<td>i-Bu</td>
<td>71</td>
<td>55:45</td>
</tr>
<tr>
<td>i-Pr</td>
<td>70</td>
<td>47:53</td>
</tr>
<tr>
<td>n-Pr</td>
<td>87</td>
<td>36:61</td>
</tr>
<tr>
<td>Me</td>
<td>93</td>
<td>20:80</td>
</tr>
</tbody>
</table>

Scheme 48

Hudlicky studied in 1985 the regioselectivity of the vinylogous Reformatsky reaction with ambident electrophiles. α-Adducts were obtained when "polar conditions"
were utilized [Zn/Cu (AcOH) in ether]. On the other hand, when "non-polar conditions" were used, γ-adducts were formed.

In 1986, Yamaguchi examined the stereochemistry of the Michael addition products of several dienolates of tertiary amides (129a, 129b) to 2-decenoate 130. The ratio threo 131a to erythro 131b is presented in Scheme 49.

The best selectivity for the threo adduct (>10:1) was obtained from the pyrrolidine amide and in the presence of HMPA (Scheme 49). On the other hand, erythro selectivity
was enhanced in the absence of HMPA, and the best result (1:5) was obtained from the methyl valinol amide (Scheme 49).

The addition of pyrrolidine amides dienolates to several esters in the presence of HMPA was also investigated and it is shown in Scheme 50. Selectivity for the threo adduct was exclusively observed.

\[
\text{R} \quad \text{R'} \quad \% \text{ yield} \quad \text{threo:erythro}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>% yield</th>
<th>threo:erythro</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CH₃</td>
<td>62</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td></td>
<td>59</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>n-C₇H₁₅</td>
<td></td>
<td>65</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>81</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>n-C₄H₉</td>
<td></td>
<td>84</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>n-C₇H₁₅</td>
<td></td>
<td>91</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td>87</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

Scheme 50

Holton¹³³ described in 1986 the stereospecific addition of lithium dienolate 132 to α-thiophenyl butenolide 133 to give adduct 134 as a single diastereomer in 96% yield. This result was obtained during studies toward the synthesis of aphidicolin 135. This reaction has a precedent in the addition of compounds of type 132 to ethyl 2-cyano-3-methylcrotonate.¹³⁴
3. Retigeranic acid

3.1. Isolation, structure and biogenesis

Among foliose lichens, *Lobaria* is a genus found mainly in tropic and temperate zones,\textsuperscript{51} and at more than 8,000 ft. of altitude.\textsuperscript{49} Of the 215 reported species, 83 were first described in East Asia;\textsuperscript{51} many of them are known for their use in perfumery and as pharmaceuticals.\textsuperscript{49} The lichens of the *Lobaria retigera* group contain four species:\textsuperscript{51} 1) *Lobaria isidiosa*, 2) *Lobaria subisidiosa*, 3) *Lobaria retigera* and 4) *Lobaria subretigera*.

In 1965 Seshadri\textsuperscript{49} isolated a terpenoid acid, "compound B" by light petroleum ether Soxhlet extraction of the powdered lichens of *L. retigera* (collected in the western Himalayas) and subsequent crystallization in dioxane-acetone. Absence of "compound B" was reported in *L. isidiosa*. In 1966 the same authors\textsuperscript{50} isolated this "compound B", now called retigeranic acid, from *L. subretigera*. At that time retigeranic acid was thought to be a tetracyclic $\alpha,\beta$-unsaturated terpenic acid.\textsuperscript{50}

In 1972, Shibata\textsuperscript{52} isolated a compound, tentatively named "L-A", from the lichens of *L. isidiosus*, but in this case collected in the eastern Himalayas. It was obtained from the chloroform-soluble fraction of the ethereal extract of the lichens. This "compound L-A" was proved to be identical to Seshadri's retigeranic acid by mixed fusion and comparisons of TLC and IR spectra. Retigeranic acid was also found in *L. subretigera*.\textsuperscript{52} It was not until 1972 that the molecular formula was proved to be $C_{25}H_{38}O_2$, and the structure and absolute configuration \textsuperscript{1} determined by Shibata.\textsuperscript{52}

\[ \text{\textsuperscript{1} Retigeranic acid} \]
These results were accomplished by X-ray crystallography of the para-bromoanilide derivative of the carboxylic acid functionality, obtained by recrystallization from acetone.

The biosynthetic pathways of retigeranic acid 1 were proposed by Shibata to be the cyclization of geranylgeranyl pyrophosphate as shown in Scheme 51.

With the first total synthesis of 1, achieved by Corey in 1985, it was demonstrated that natural retigeranic acid was actually a mixture of two isomeric acids, of which 1 was called retigeranic acid "A" and was the minor isomer. These results were confirmed by Shibata at the same time. Evidently, compound "A" was separated by fractionation of the mixture during recrystallization of the p-bromoanilide derivative. At that time, the structure of compound "B" remained unknown, although there were some speculations about the location of the C-epimer. Paquette synthesized retigeranic acid methyl ester in 1987, together with its epimers 136 and 137. However, neither of them was identified with compound "B". Before their synthesis was even accomplished, the structure of compound "B" was elucidated, and identified as the C-9 epimer of 1 (the isopropyl β instead of α).
3.2. Synthetic approaches

The first published attempt toward retigeranic acid 1, was reported by Hudlický\textsuperscript{91d} with the synthesis of the triquinane residue 138 (right half, 8% overall yield) in 1982. (+) Pulegone 139 was the starting material. After Favorski rearrangement and ozonolysis, the known\textsuperscript{138} ketoester 140 was obtained in 76% yield (Scheme 52). The key intermediate 141 was prepared in six steps from 140 (39% overall) by alkylation, decarboxylation, Reformatski and formation of the diazoketone. Cyclopropanation (75\%) and pyrolysis (60\%) gave the desired tricyclic skeleton 142, that after deoxygenation, afforded the triquinane residue 138 (Scheme 53).
Unfortunately all the attempts for the union of 138 with the left half 138a, to give intermediate 138b (Diels-Alder approach), were unsuccessful. Several acyl anion equivalents derived from 138a did not add to acrylate 138, probably due to the lack of orbital overlap in the \(\alpha,\beta\)-unsaturated system, preventing the conjugation. A second approach involved the reaction of 138c, but it was abandoned when 138c was realized to have the wrong stereochemistry.

Another synthesis of the right half, in this case compound 143, was achieved by Paquette, in 1984 in eleven steps and 3% overall yield (some modifications were introduced recently to increase the optical purity of the products). The starting material was also optically active pulegone 139. Enone 144 was prepared in four steps from ketoester 140 in 18% yield, and as a 5:1 mixture of separable epimers. Enone 143 was

Scheme 54
obtained together with 143a (as a 7:3 mixture), and purification involved reduction of the mixture, separation of the alcohols, and reoxidation of the major alcohol to give pure 143 (Scheme 54).

The left half of retigeranic acid, racemic trans-hydrindanone 145, was obtained by Fallis\textsuperscript{140} in 1985, in a stereoselective manner. Aldehyde 146 was prepared in three steps by alkylation of the dianion of 3-methylbutyric acid. Two different routes to hydrindanone 145 were described: one was through the intramolecular Diels-Alder of triene 147, and the second one was through the internal Michael-aldol of enone-aldehyde 148 (routes a and b respectively). Both sequences are shown in Scheme 55.
The most productive route was b. In route a there was lack of reproducibility of the results (60% yield was initially reported) when a "fresh bottle" of solvent was used for the Diels-Alder of triene 147.

The first total synthesis of racemic retigeranic acid 1 was achieved by Corey in 1985. The starting material was the known hydridenone 148 (prepared in two steps from 2,6-dimethyl-5-heptenal). Intermediate 149 was obtained in six steps (Scheme 56) from 148 in 65% overall yield. Diels-Alder reaction of 149 with methyl 3-formyl-cis crotonate gave compound 150 in 61% yield, which was converted into 151 in four steps (Scheme 56). After treatment of 151 with oxalyl chloride and triethylamine, cyclobutanone 152 was formed. Ring expansion took place, and in four steps compound 153 was obtained in 65% overall yield. Hydrogenation of 153, epimerization to the most
stable isomer and deoxygenation afforded olefin 154 in 61% yield. Ring C was cleaved by osmium tetroxide, and then reclosed to give retigeranic aldehyde in 48% yield. Finally, oxidation of the aldehyde lead to retigeranic acid (1) (85%). Corey, with his twenty-five-step synthesis and 2% overall yield, demonstrated that natural retigeranic acid was a mixture of two isomeric carboxylic acids, of which 1 constituted the minor isomer.

In 1987 Paquette completed the synthesis of the methyl ester of the natural enantiomer of retigeranic acid 1, together with two other epimers 136 and 137 (see Section 3.1), as a result of lack of selectivity in some of the steps. The synthesis was convergent; however it had twenty-two steps, only three steps less than Corey’s linear one. The left half, compound 155 was prepared from (-)-limonene 156 in fifteen steps and in 2.3% overall yield (Scheme 57).

![Scheme 57](image)

The coupling reaction took place between 155 and 143 giving in 53% a 74:26 mixture of 157a and 157b (favoring the wrong isomer), that was separated after the ozonolysis
Isomer 158a was converted to 5b-epiretigeranic acid methyl ester 136 in seven steps (Scheme 59).

Isomer 158b was subjected to the same sequence obtaining finally retigeranic acid methyl ester (less than 0.05% overall yield); however, some problems were created. The ring closure to 159 needed to be done in piperidine-AcOH, thus producing a mixture of epimers (159), which was not separated until the end of the sequence (Scheme 60).

No conditions were found to epimerize compound 136 to the natural isomer of retigeranic acid methyl ester, which structure was favored over isomer 136 in 2.4 Kcal-
Paquette attributed the lack of acidity to a misalignment of the proton at C-5b, preventing conjugation with the unsaturated ester.

The synthesis of \( 1 \) that will be described in this work constitutes a fourteen-step enantiocontrolled one, and it was completed in 1988.\textsuperscript{124b,c} Wender's\textsuperscript{142} preceded this synthesis, but it has not yet been published. Wender's approach was successful in the preparation of intermediate \( 138b \) by meta photocycloaddition.
III. DISCUSSION

1. Introduction

A new full spectrum of natural products containing either one or more-fused five-membered rings, as for example prostaglandines and triquinanes, was discovered in the early seventies.\textsuperscript{1-31} As a consequence, an increased interest in the development of cyclopentannulation methodologies was observed since then, and it continues to the present time.\textsuperscript{6-12,32-36} The reason for such a long-term research could be attributed to the lack of versatility in any of the existing methods and to the difficulty in controlling and predicting the stereochemistry of the product. In other words, a methodology equivalent to the Diels-Alder for the construction of six-membered rings does not exist for five-membered rings. New procedures for the synthesis of cyclopentane rings are thus necessary in order to complement the existing ones.

As mentioned in section I, the interest of the Hudlicky group in the synthesis of linear- and angularly-fused triquinanes started with the development of an overall intramolecular [4+1] cyclopentannulation.\textsuperscript{91a,b} This was the result of the decomposition of a diazoketone into a vinylcyclopropane, which was thermolytically rearranged to the corresponding cyclopentene ring.\textsuperscript{38b,c,56,90-95} The evolution of this methodology\textsuperscript{36} can be easily visualized by the following disconnection of diquinane 160, where "±" would represent a carbenoid species 160a (Scheme 61). As a result of this new procedure, several triquinanes were prepared,\textsuperscript{42-45} and furthermore, this methodology was extended
to the heterocyclic field allowing for the preparation of many pyrrolizidine alkaloids.\textsuperscript{46-48} The triquinane residue \textsuperscript{138} (p. 46) of retigeranic acid, was also prepared\textsuperscript{91d} using this methodology. Unfortunately, the coupling with the left half was not achieved due to unfavorable electronics of the triquinane acrylate \textsuperscript{138}.\textsuperscript{36,124b} At this time, the need of a complementary methodology became evident, and observing\textsuperscript{36} the disconnection (shown by the arrows) in Scheme 62, the idea of an intermolecular reaction arose. In this approach, synthon \textsuperscript{161} would be provided with a nucleophilic and an electrophilic group at C-2. This new methodology would have the advantage of facilitating the synthesis of starting materials, but it would have the disadvantage of a lesser reactivity (inter- versus intramolecular reaction).

An equivalent of compound \textsuperscript{161} was found in enolate \textsuperscript{161a}, that contained bromine as a leaving group. This enolate would be generated from ethyl 2,4-dibromobutenoate (\textsuperscript{162}), by treatment with zinc (Reformatsky reaction),\textsuperscript{143} or from ethyl 2-bromobutenoate\textsuperscript{144} (\textsuperscript{163}) with a base. The Reformatsky reaction had a precedent in Hudlicky's group,\textsuperscript{131,145} but the reagent used was ethyl 4-bromobutenoate. The reaction was run with different enones,\textsuperscript{131} the regiocontrol being possible by correct manipulation of the catalysts and solvents. Once the enolate \textsuperscript{161a} was formed, subsequent addition to an enone would be expected to give intermediate \textsuperscript{164} which would have two options for the ring closure in a Darzen-type\textsuperscript{146} reaction: 1) allylic S\textsubscript{N}2' displacement of the bromine
to give directly the five-membered ring 160 (Scheme 63) and 2) a direct SN2 displacement of the bromine to furnish vinylcyclopropane 165 (Scheme 63a).

By examination of Baldwin's cyclization rules, the ring closure leading to a five-membered ring would constitute a 5-Endo-Trig, that is unfavored, while the second one would be a 3-Exo-Tet, that is favored. Vinylcyclopropane 165 would then be expected, but unfavored cyclopentannulation does not mean it cannot be done. With this in mind, the investigation of the Reformatsky approach to cyclopentenes was initiated.
2. Investigations of the chemistry of dibromocrotonates

Dibromide 162 was prepared in three steps from commercially available ethyl crotonate. First, treatment with NBS gave the 4-bromo ester 166;\(^{148}\) bromination of 166 with a solution of bromine in CCl\(_4\) at 0 °C afforded tribromide 166a, and 162 was obtained by dihydrobromination with 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)\(^{149}\) in DME, also at 0 °C (Scheme 64).

![Scheme 64](image)

The zinc enolate was prepared in ethyl ether by addition of 162 to the zinc/copper (acetic acid) catalyst\(^{145}\) at room temperature, in the presence of an initiator (a crystal of iodine). Reactions with carbonyl compounds such as cyclopentanone and benzaldehyde were investigated. Very complex mixtures were obtained in both cases, as indicated by either thin layer chromatography (more than five spots) or \(^1\)H-NMR spectroscopy (very crowded vinyl region). Purification of the different fractions indicated the presence of both \(\alpha\)- and \(\gamma\)-addition products 167a-e (Scheme 65). These results were surprising because similar studies with 4-bromocrotonate\(^{145}\) 166 afforded exclusively \(\alpha\)-addition.

![Scheme 65](image)
with zinc/copper (acetic acid) as the catalyst, and γ-addition when dried zinc was present. Other unexpected results were the partial exchange of the bromine at C-2 (proved by the isolation of compound 167d), and the presence of dimer 167e (Scheme 65). This methodology proved not to be useful in the synthesis of cyclopentene rings due to the complexity of the mixtures obtained. Attempts to carry out this reaction with enones instead of simple carbonyl compounds were not done, as the complexity of the systems would have been even higher. As these results appeared too complex, we turned to the simpler system ethyl 2-bromobutenoate (163).
3. Vinylcyclopropanation with ethyl 2-bromocrotonate

The second approach involved lithium enolate 161a prepared by treatment of ethyl 2-bromobutenoate144,150 (163) with lithium diisopropylamide. Bromo ester 163 was obtained using a similar procedure (Scheme 66) to that for the synthesis of 162. Bromination of ethyl crotonate with bromine in CCl₄ at 0 °C, and then dehydrobromination with DBU also at 0 °C, afforded a 1:1 mixture of E and Z isomers 163, which were easily identified by ¹H-NMR.

The vinylcyclopropanation took place in THF at -78 °C, and in the presence of hexamethyolphosphoramide (HMPA). Five minutes after the addition of cyclopentenone was completed, total disappearance of the starting materials was observed. Two compounds were formed as demonstrated by thin layer chromatography (TLC), gas chromatography and ¹H-NMR analysis, in a ratio 3:2 (more polar:less polar in TLC). The crude product was purified by column chromatography and the compounds identified as the exo and endo isomer of vinylcyclopropanes 165 (n=1, exo and endo refer to the vinyl group). The exo compound was the most polar isomer by TLC, and also the major one. No cyclopentene was observed, only direct displacement of the bromide occurred, as expected following Baldwin's ring closure rules. It is interesting to mention that 1,4-addition leading to exo and endo 165 was exclusively obtained, and no 1,2-addition product was present.

In order to understand the mechanism of the reaction, attempts were made to isolate the protonated form of enolate 164 (p. 55). Several attempts, such as lowering the
reaction temperature and/or changing the bromide for a poorer leaving group as chloride or -SO₂Ph were tried. Unfortunately, in all cases efforts at trapping 164 were unsuccessful; lowering the temperature of the enone addition did not change the composition of the reaction mixture. The vinylcyclopropanes were the sole products, even by quenching the reaction immediately after completion of the enone addition. When bromide was substituted by chloride or -SO₂Ph, more complex mixtures were obtained, and therefore lower reaction yields. The effect of the substituent at C-2 is shown in Scheme 67. It is interesting to note the selection for the endo isomer when -SO₂Ph was the leaving group.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Crotonate</th>
<th>Yield of cyclopropanes* (exo/endo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br</td>
<td>CO₂Et</td>
<td>93% (60/40)</td>
</tr>
<tr>
<td>Cl</td>
<td>CO₂Et</td>
<td>70% (59/41)</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>CO₂Et</td>
<td>18% (0/100)</td>
</tr>
</tbody>
</table>

*: by NMR or GC

Scheme 67

The order of addition of reagents was very important in determining the nature of the products. Hagiwara¹⁴⁴ reported in 1976 the preparation of tricyclic ketone 166 by enolization of cyclohexenone with lithium diisopropylamide, and then addition of methyl 2-bromobutenoate (inverse order of addition, see Scheme 68). This tricyclic ketone was used later in the syntheses of eremophilane sesquiterpenes.¹⁵⁰a

![Scheme 68]
<table>
<thead>
<tr>
<th>Enone</th>
<th>Products</th>
<th>Yield*</th>
<th>Exo/Endo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>100%</td>
<td>70/30</td>
</tr>
<tr>
<td></td>
<td></td>
<td>93%</td>
<td>60/40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%</td>
<td>50/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12%</td>
<td>35/65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td>50/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15%, 45%</td>
<td>70/30**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>45%</td>
<td>50/50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70%</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35%, 20%</td>
<td>—</td>
</tr>
</tbody>
</table>

* NMR and GC yields  
** trans vinylacetyl/cis vinylacetyl, 70/30

Scheme 69
The regio and stereochemistry of this new reaction with a variety of enones was investigated (Scheme 69). No attempts were made at this time to optimize the conditions.

The best yields were achieved when commercially available cyclopentenone and cyclohexenone were the starting materials. Increasing the steric bulk of the reagents, as in the $\beta,\beta$-dimethyl substituted enones $168a$ and $168b$, gave more complex mixtures. Moreover, in the case of $168a$ a trace of $\gamma$-addition product was generated. The yield of the reaction with isophorone $168b$ was slightly increased by activation of the carbonyl group with boron trifluoride etherate.\textsuperscript{152} In the case of bicyclic enone $168c$,\textsuperscript{153} an alleviation of the strain imposed by the double bond to the system would occur when the cyclopropane was formed. This situation predicted a good yield of the corresponding vinylcyclopropane $168d$, which was the key intermediate in Hudlicky's synthesis of pentalenene $3$.\textsuperscript{45b,c} By using this methodology, intermediate $168d$ was prepared in a much shorter sequence leading to a second generation of pentalenene $3$.

Beside enones, other electrophiles were investigated. Cyclopentanone gave the corresponding vinylloxirane $168e$ in good yield, which can be rearranged to the dihydrofurans. This constituted very good news considering the large number of natural products that contains this residue. Ethyl acrylate afforded a 1:1 mixture of the vinylcyclopropanes in very good yield. On the other hand, acrolein reacted in a different manner from the rest of the $\alpha,\beta$-unsaturated carbonyl compounds. The major isomers isolated in this reaction were trans divinyloxirane $168b$ and oxepine $168c$ (obtained by Cope rearrangement of the cis divinyloxirane), formed by means of 1,2-addition to the carbonyl group.

With the success of this methodology, a vinylcyclopropanation with optical induction attracted our attention. An optically active bromocrotonate was designed, in
which the ester contained a menthyl residue as the chiral auxiliary. The synthesis of menthyl 2-bromocrotonate (169) proved to be troublesome and it is shown in Scheme 70.

Treatment of commercially available crotonyl chloride with (-)-menthol in a basic solvent (triethylamine) afforded the non-conjugated ester 170. This result was explained by participation of the ketene intermediate 171,154 formed in the presence of triethylamine. Ketene 171 reacted with menthol to give 170.

The double bond was then isomerized to position 2 by stirring 170 with DBU155 in THF at room temperature for three hours. The conjugated ester was then subjected to the standard procedure of bromination with a solution of bromine in CCl₄ and dehydrobromination to afford the desired 2-bromo ester 169 in 88% overall yield. The formation of the non-conjugated ester 170 was, after all, very convenient because it provided a simple procedure to prepare the 4-bromo isomer 172, that could not be
obtained by the standard procedure of bromination with N-bromosuccinimide (Scheme 70). This compound constituted a potential chiral reagent for the Reformatsky reaction.

Vinylcyclopropanation took place by treatment of menthyl ester 169 with lithium diisopropylamide-HMPA in THF at -78 °C, and then addition of cyclopentenone. After ten minutes two spots were detected by TLC and no starting material was left, indicating the completion of the reaction. The crude mixture was purified by column chromatography and the isolated compounds identified as endo and exo vinylcyclopropanes 173. However the 1H-NMR spectra of both isomers presented a crowded area of vinyl groups at 5-6 ppm, indicating the presence of either diastereomers or rotamers. Both compounds were hydrolyzed separately to the corresponding acids by treatment with potassium hydroxide in CH3OH-water and reesterified with diazoethane.

The isomer 173-endo afforded the vinylcyclopropane 165-endo (n=1) as a sole product.

However, the isomer 173-exo gave a mixture of variable composition of two compounds (Scheme 71). One was identified as 165-exo (n=1) vinylcyclopropane (identical to that obtained directly from ethyl 2-bromobutenoate), and the other one was unknown. The
only satisfactory explanation of this situation was the formation of a side product during the cyclopropanation, and this side product would not separate from 173-exo until reesterification. Following this reasoning, cyclobutane 174 was a strong candidate to be the side product. Data obtained from ¹H- and ¹³C-NMR spectra of the transesterified product, matched the values expected for 174a. The menthyl ester 174 would have been formed due to the large size of the menthyl group, allowing enolate 175 to have enough time to equilibrate with enolate 175a. Ring closure of 175a would occur by attack at C-5 to displace the bromide. The protonated form of 175 was not isolated in this case.

Examining these results, the question arose as to what would happen in the hydrolysis of the 165-exo vinylcyclopropane (prepared directly from ethyl 2-bromobutenoate). The reaction was performed, and the results were completely unexpected. The hydrolysis product of 165-exo was exactly the same of that of the "173-exo mixture". This indicated that the side product was generated during hydrolysis of the ester of the vinylcyclopropane, and not during the vinylcyclopropanation reaction. Following this reasoning the product would be 176 and not the cyclobutane 174. The structure of 176 was proposed by examination of the most probable mechanism during the hydrolysis reaction (Scheme 72).

In the presence of a base the enolate of the ketone would form, which may compete with the hydroxide ions in attack on the ester carbonyl leading to intermediate 177. At this stage, the hydroxide may attack 177 at either carbonyl, but only bonds a or c can cleave (the resulting negative charge would be conjugated to the adjacent carbonyl).
When the attack is done through path A, the vinylcyclopropane 165-exo would be obtained after reesterification. When the attack is through path B, compound 176 would be the product. The structure of 176 was later confirmed by heteronuclear J-resolved experiments. The transesterified cyclopropanes were then subjected to chiral NMR shift reagent experiments showing almost no optical induction (5% ee).

A new methodology for the preparation of vinylcyclopropanes, and therefore for cyclopentene rings was developed. This reaction has the advantage over other vinylcyclopropanations in terms of versatility and simplicity provided by the good reactivity of several enones and other electrophiles. As the asymmetric induction appeared poor, the best way of enantiocontrol in applications (at least for the moment) seemed to be the utilization of optically pure synthons until better results are obtained. With these results in mind, we turned to the preparation of two chiral residues for retigeranic acid (I).
4. Retigeranic Acid Synthesis

Among the terpenes that contain either an angular or a linear triquinane, retigeranic acid (1)\textsuperscript{49-52} was the molecule selected for synthesis as an application of this new cyclopentannulation methodology. The reason for the selection of this molecule was its interesting structural array with seven chiral centers, that makes it a most challenging target.

The retrosynthetic analysis for retigeranic acid started with the location of the diquinane residue 160. This synthon can be seen in rings C and D where there is a carbonyl at C-5 (ring D, compound 178). The diquinane in 178 may be prepared from the corresponding vinylcyclopropane 179, and this in turn, from enone 144 and bromo

\[ \text{Retigeranic Acid, } 1 \]
ester 180 by application of the [2+3] methodology described before (Scheme 73).

Enone 144 is a known compound. It was synthesized by Paquette\textsuperscript{139} in 1984, in optically pure form (see Section II.3). Bromide 180 can be prepared from ketone 145, which is known in the literature\textsuperscript{135,140} but in both cases was synthesized as the racemate (see Section II.3). The synthesis of optically active bromide 180 would require a reasonable amount of effort, and therefore in this case, it seemed advantageous to conduct a model study of the key reaction, the vinylcyclopropanation. The system selected for the model reaction requires similarity with the real one, but at the same time it needs to be simpler. The model vinylcyclopropanation was carried out with bromo ester 181\textsuperscript{158} and enone 144. Bromo ester 181 was prepared in three steps from cyclohexanone (Scheme 74). First treatment of cyclohexanone with ethyl trimethylsilylacetate/lithium dicyclohexylamide (Peterson olefination) afforded \( \alpha,\beta \)-unsaturated ester 182\textsuperscript{159} in 85% yield. Standard bromination and dehydrobromination afforded bromo ester 181 in 90% yield (from 182). Enone 144 was synthesized following Paquette’s\textsuperscript{139} procedure. The lithium enolate of bromo ester 181 was prepared with LDA and HMPA at -78 °C. Enone 144 was added at -78 °C, and after 30 minutes, the reaction was quenched. Two compounds, different from the starting materials were detected by TLC. After purification by column chromatography, they were identified as the desired endo and exo...
vinylcyclopropanes 183 obtained in 40% yield. The endo-exo assignment was done by careful comparison of both the 1H-NMR spectra and molecular models. Comparing with a simpler system such as vinylcyclopropanes 165 (n=1) for example, some differences were found. The ratio endo:exo in this case was 4:1, with the endo being the major isomer. Another difference was that the exo compound was the less polar isomer.

With these antecedents, the synthesis of chiral bromide 180 was initiated. It seemed possible that this bromide could be obtained from ketone 145 (p. 48), following a procedure identical to that used for the preparation of 181 from cyclohexanone. The immediate goal was then to prepare optically active ketone 145. Since the procedure for the synthesis of this racemic ketone was known in the literature,140 it was reasonable to follow it to prepare the optically active one by using chiral starting materials. Fallis140 reported two different routes to ketone 145 (Scheme 55, Section II.3) starting from racemic aldehyde 146. In order to select the route to follow, the protection of the purity of the chiral center at C-2 in 146 had to be taken into account. Fallis indicated route b to be the most productive. However, compound 148 obtained by this route, was in great disadvantage with respect to compound 147. In residue 148 the chiral center at C-5 would be conjugated to an α,β-unsaturated ketone. On the other hand, in compound 147 the chiral center was conjugated to an α,β-unsaturated ester. It is well known that protons adjacent to ketones are at least 100 times more acidic than protons adjacent to esters.160 Route a thus appeared to be much safer for the chiral center.

After the selection was done, it was necessary to prepare compound 146 in a chiral fashion. As shown in the retrosynthesis in Scheme 75, the aldehyde would be obtained from the selective ozonolysis of the most electron-rich double bond in enol ether 184.161 This enol ether would be prepared either from acetal 185 or from aldehyde 186.
Synthesis of acetals 185 and 188 and aldehyde 186. Acetal 185 was prepared in three steps from commercially available (+)-limonene 156 (Scheme 76): hydrogenation of the exocyclic double bond in 156 gave menthene 187 in 92% yield. Subsequent ozonolysis in MeOH-CH$_2$Cl$_2$ (2:1) and reductive work-up with ten equivalents of dimethylsulfide and catalytic amounts of p-toluenesulfonic acid, gave acetal 188 in 87% yield (from 187). Wittig reaction on the ketone carbonyl of 188 with methyltriphenylphosphonium bromide led to acetal 185 in 72% yield. Aldehyde 186 was obtained in 85% yield by hydrolysis of acetal 185 with 3% aqueous HClO$_4$ in THF (Scheme 76).
Aldehyde 186 was dissolved in pentane and hexamethyldisilazane and trimethylsilyl iodide were added. The reaction product mixture was very complex and no TMS enol ethers 184 were observed. All the efforts were then directed to the synthesis of methyl enol ethers from acetal 185.

The neat acetal was distilled in the presence of p-TsOH, and no enol ethers were observed. It was also refluxed in 1,1,2-trichlorotrifluoroethane (bp. 47-48 °C), in the presence of an acid catalyst, using a Soxhlet extractor with molecular sieves, which would trap the MeOH, and again no enol ethers were observed. Another method that was tried was the activation of one of the methoxy groups of the acetal with TMSI and then displacement of MeOH with a base like HMDS. In this case there was formation of enol ethers, but the mixture was too complex to consider this a good methodology. By this time keto aldehyde 189 was considered an equally useful intermediate. Again it was assumed that 189 could be prepared from acetal 188 or aldehyde 190 (Scheme 77).

\[
\text{Scheme 77}
\]

Synthesis of aldehyde 190. Aldehyde 190 was prepared in 84% yield by ozonolysis of menthene (156) in an identical procedure to that for acetal 188, except that no catalyst was used during the work-up. This aldehyde proved to be unstable to prolonged storage as it polymerized easily. However it was freshly obtained by
hydrolysis of keto acetal \textit{188} (stable to storage) in 3% aqueous HClO$_4$ and THF in 88% yield (Scheme 78).$^{164}$

\begin{equation}
\begin{array}{c}
\text{187} \\
1. \text{O}_3, \text{MeOH-CH}_2\text{Cl}_2 \\
2. \text{Me}_2\text{S} \\
\text{CHO} \quad 84\%
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{188} \\
3\% \text{HClO}_4, \text{THF-H}_2\text{O} \quad 88\%
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{190} \\
\text{CHO}
\end{array}
\end{equation}

\textbf{Scheme 78}

\textbf{Synthesis of aldehyde \textit{189}.} As the synthesis of enol ethers proved troublesome, enamine \textit{191a} was prepared (92% yield) by stirring keto aldehyde \textit{190} and piperidine in ethyl ether.$^{162}$ Ozonolysis of the enamine$^{169}$ in dichloromethane gave the desired keto aldehyde \textit{189} in 30% yield (Scheme 79). The reason for this low yield was the difficult purification of the product due to the presence of polymers derived from oxidation of N-formylpiperidine. Lowering the temperature of the work-up (-20 °C) did not avoid polymerization, but decreased decomposition of aldehyde \textit{189}, which proved very unstable to storage. With aqueous work-up used to separate dimethylsulfoxide, no product was obtained because of an increase in the polymerization. Aldehyde \textit{189} was isolated by distillation and column chromatography, after reductive work-up with dimethylsulfide for 24 hours and negative test of peroxides (potassium iodide).

On the other hand, an "old bottle" of keto acetal \textit{188} was found contaminated with the E isomer of enol ether \textit{191b} (R=OMe), suggesting that the conversion occurred upon standing. Several acid catalysts were tried either during pyrolysis of acetal \textit{188}, or by
stirring at different temperatures (room temperature-50 °C) under 18 mmHg of pressure to displace the methanol. p-Toluenesulfonic acid and diisopropylethylammonium tosylate\textsuperscript{170} did not afford the enol ethers \textit{191b}, but they gave the aldol condensation product, enone \textit{192} as the sole isomer. The acid catalyst that finally gave the enol ethers \textit{191b} was potassium hydrogen sulfate (Scheme 80).\textsuperscript{171} Distillation of neat acetal \textit{188} over this salt (freshly dried at 400 °C) at 1.5 mmHg, gave 44% of a 1.2:1 mixture of E and Z enol ethers \textit{191b} and 17% of starting material back. The reaction mixture was heated to 120 °C for no longer than 10 minutes, otherwise the amount of polymer formed would have been much higher. Also, the pressure could not be lower than 1.5 mmHg, because the conversion of the acetal to the enol ethers would have been less. The distillate was purified by column chromatography to give an inseparable mixture (even by fractional distillation) of enol ethers \textit{191b} and the starting material, which was recycled.

Ozonolysis of enol ethers \textit{191b} in MeOH-CH\textsubscript{2}Cl\textsubscript{2} (2:1) and reductive work-up with dimethylsulfide gave the desired ketoaldehyde \textit{182} in 80% isolated yield, in a very clean reaction. The quality of the product was better when the solvent was a mixture of methanol-dichloromethane than when it was only dichloromethane. For the ozonolysis, it was necessary to use acid-free methanol (distilled from magnesium). When spectroscopic grade methanol was used without further purification, a 2:1 mixture of

\begin{center}
\begin{tabular}{lll}
\hline
\text{CATALYST} & \text{Cat.} & \text{Δ} \\
\hline
\text{p·TsOH} & 100 & 0 \\
\text{Diisopropylethylammonium tosylate} & 100 & 0 \\
\text{Potassium hydrogen sulfate} & 0 & 100 \\
\hline
\end{tabular}
\end{center}
acetals 193a and 193b were obtained, and no keto aldehyde 189 was formed (Scheme 81). This reaction was undesired because the recovery of the keto aldehyde 189 from these acetals would have involved stirring with an acid catalyst for more than five hours, constituting a risk for racemization of the chiral center next to the aldehyde. It is interesting to note that no acetal 193b was formed when keto aldehyde 189 was stirred overnight in MeOH with p-TsOH, and only starting material was recovered with less than 10% of 193a. This suggested that acetals 193 were obtained directly from the ozonide under acid-catalyzed conditions, and not from aldehyde 189 (Scheme 81).

Of the two methodologies available to obtain keto aldehyde 189, the preferred route to be followed in the sequence to retigeranic acid (1), was the one that utilized enol ethers 191b. The reason of this selection was the higher quality of the aldehyde obtained, and the simplicity of the purification, even when the overall yields were similar.

Synthesis of left half of retigeranic acid. The immediate target was triene 147 (Scheme 55), which Fallis140 prepared from racemic aldehyde 146. Optically active keto aldehyde 189 was the one available here, and it was transformed first to keto diene 194 in 80% yield by treatment with ethyl 4-dimethoxyphosphonyl-3-methoxy-2-
butenoate and LDA in a Horner Emmons reaction (Scheme 82). As expected, only the carbonyl group of the aldehyde reacted with one equivalent of the reagent at -78 °C (it was not necessary to warm to 0 °C as Fallis reported). The Horner Emmons reagent was selected considering the target triene 147. The reason for the presence of the methoxy group as a substituent in the diene was the better stereoselectivity of the Diels Alder, as Fallis indicated. The known desired triene 147 was finally obtained by a Wittig reaction of keto diene 194 with methyltriphenylphosphonium bromide in 80% yield. At this point there was some concern about the optically purity of the chiral center. To prove that no racemization had occurred during the Wittig-type reactions, triene 147 was ozonized to keto aldehyde 189. Optical rotations of the aldehydes, before and after the Wittig reactions were compared, and they had the same value.

Triene 147 was then subjected to the reaction conditions reported in the literature to obtain bicyclic system 195. In our hands reflux in p-dichlorobenzene (bp.: 173 °C) or 1,2,3-trichlorobenzene (bp.: 218-219 °C) did not lead to either isomer 195a (Δ^3.4) or 195b (Δ^4.5). Fallis obtained a 60% yield of compounds 195 under these conditions, but the results were irreproducible when a "fresh bottle" of solvent was used.
Several different conditions (temperature, reaction time and solvents) were then investigated. The "best" results were obtained using toluene as solvent, in sealed tubes at 300 °C for 8 hours. Under these conditions the reaction yield was 23%, but 36% of starting material was recovered, which was recycled (Scheme 83). Higher temperatures (350 °C in an autoclave) did not improve the yield of the reaction, but the undesired cis-fused isomer started to form (trans:cis = 4:1 non separable mixture). Higher reaction times did not improve the yields either. When the tubes where allowed to cool outside the sand (faster cooling), better reaction yields were obtained, suggesting the possibility of an equilibrium process. High pressure was not enough for the reaction to work. When 10,000 psi were applied to the system at room temperature only starting material was recovered. Flash vacuum pyrolysis did not afford the desired product either. It was interesting to note that when "wet" p-dichlorobenzene was used as solvent in a sealed tube reaction, at 280 °C for 12 hours, ketone 145 was obtained directly (the intermediates were hydrolized and decarboxylated under this conditions). This procedure is not recommended because the unreacted starting material was also hydrolyzed and could not be recovered.

The reaction product under the conditions described above (300 °C, 8h, sealed tubes) showed three spots by TLC: one was the pure conjugated bicyclic ester-enol ether 195a (yellow upon development with anisaldehyde solution). The second one was an inseparable unidentified mixture of compounds suspected to contain the non conjugated bicyclic ester-enol ether 195b (yellowish when developed with anisaldehyde solution).
The third one was starting material in 80% purity, which was recycled. The conjugated isomer 195a was quantitatively hydrolyzed to the bicyclic ester-enol 196 with concentrated HCl in THF. The second spot was subjected to the same conditions, and the same enol 196 was separated from the rest of the mixture, confirming the presence of 195b. The combined ester-enol 196 was then decarboxylated in 99% yield by refluxing with lithium iodide in DMF for 2 hours (Scheme 84). These conditions were different from the ones reported by Fallis (LiI, DMSO-H2O, reflux, 12h!). Proton NMR spectra and chromatographic properties of ketone 145 were identical to the sample sent by Profs. Fallis and Corey. This ketone was found to be optically active with [\(\alpha\)]D = -62.5° (c 1.0, MeOH).

Ketone 145 was subjected to a Peterson olefination and transformed to \(\alpha,\beta\)-unsaturated esters 197 (75%) by following an identical procedure to that for the

Scheme 84

Scheme 85
preparation of 182 (Scheme 85). Then bromination (Br₂, CCl₄, 0 °C) and dehydrobromination (DBU, DME, 0 °C) gave a 3:1 mixture (more polar:less polar) of bicyclic bromides 180 in 70% yield from ketone 145. The E and Z isomers were not assigned because of the similarity of the chemical shifts in the ¹H-NMR. Different NOE experiments were also unable to distinguish between the isomers.

**Synthesis of exo and endo vinylcyclopropanes 179.** Bromides 180 and enone 144 were now ready for the key reaction. The mixture of bromo esters 180 was treated with LDA in THF at -78 °C. There was some concern related to this enolization product. Protons at C-3 were the most available ones, but would protons at C-5 also be abstracted? If that happened, the vinylcyclopropane formed would lead to the wrong pentacyclic skeleton. The enolate was formed at -78 °C in 1.5 hours and in the presence of HMPA (Scheme 86). The enone was then added, and the reaction stirred for 0.5 hours at -78 °C. Only two spots were observed by TLC that were isolated and identified as the vinylcyclopropanes 179-exo and endo in a 1:1.5 ratio (56% isolated yield). With this result there was no need for a more hindered base than LDA, as lithium cyclohexylisopropyl- or dicyclohexyl-amide, to avoid abstraction of protons at C-5. The vinylcyclopropanes were assigned as endo or exo (with respect to the double bond) by ¹H-NMR spectroscopy.
Looking at the molecular models of 179, in the endo isomer, the vinylic proton (at C-3') would be toward the ring, therefore it would be expected to be at lower fields than in the exo; the methyl group at C-1' would be in the shielding cone of the ketone carbonyl group, so it was expected at higher fields than in the exo. In the exo isomer methyl group at C-3 was cis with respect to the bulky group, so it would be expected at lower fields than in the endo isomer. Comparing this reasoning with the data obtained, the exo isomer was the least polar, and the endo, the most polar. There are two other observations to add which agreed with the assignment. In the least polar isomer, the methylene group of the ethyl ester appeared more crowded than in the other isomer, which is characteristic of the exo compounds (the methylene is located toward the ring, so the protons are no longer equivalents). Also, in the endo isomer the ester group (most polar group) was more exposed, and therefore this isomer should be more polar.

**Synthesis of pentacyclic esters 178 and 201.** Both vinylcyclopropanes, separately or as a mixture, were thermolyzed\textsuperscript{91e,173} in an horizontal Vycor tube covered with a thing layer of lead carbonate at 585 °C and 10^{-4}.10^{-5} \text{mmHg} (diffusion pump). In almost all cases a 1:1 mixture of pentacyclic ketone 178 and its epimer at C-5b 198 was obtained. These two isomers were separable by chromatography, and their structure and stereochemistry was determined by \textsuperscript{1}H- and \textsuperscript{13}C-NMR spectroscopy, and by comparison with the \textsuperscript{1}H-NMR spectrum of the methyl ester of retigeranic acid sent by Prof. Paquette.
In order to try to improve the selectivity for the natural isomer, a temperature profile for the rearrangement was carried out (Scheme 87). Even if the values did not drastically change, the tendency of an increase in the selectivity for isomer 178 was observed.

![Scheme 87](image)

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>179-exo</th>
<th>179-endo</th>
<th>178</th>
<th>198</th>
</tr>
</thead>
<tbody>
<tr>
<td>500</td>
<td>0.6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>endo</td>
<td>585</td>
<td>1.7</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>exo</td>
<td>585</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>625</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>655</td>
<td>1.2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

**Scheme 87**

Molecular mechanics calculations predicted the natural isomer to be 3.1 Kcal more
stable than the epimer (Scheme 88). A more strained structure for the epimer can be easily seen, even in molecular models. For this reason, such a similar selectivity in the rearrangement was unexpected.

Pentacyclic ketone 178 was reduced at room temperature to the corresponding mixture of alcohols 199 with sodium borohydride in methanol in 98% yield (Scheme 89). The reduction did not take place when a mixture of ethyl ether and methanol was used as solvent. The alcohols were deoxygenated to retigeranic acid ethyl ester 201 following Barton’s procedure. Xanthates 200 were obtained from the alcohols 199 by treatment with NaH in THF, then carbon disulfide and finally methyl iodide. The crude xanthates were purified through a plug of silica gel. After the solvent was removed, reduction with n-tributyltinhydride was carried out in refluxing toluene and in the presence of the radical initiator, AIBN (47% yield from alcohols 199, Scheme 89). The solution of tinhydride was added in portions to the refluxing xanthates in toluene over 10 minutes, otherwise a very complex mixture of products was obtained. Purification consisted of column chromatography with several elutions in hexane to eliminate the tin compounds. The molecular formula was corroborated by $^{13}$C-NMR, and the
stereochemistry by comparison of \(^1\)H-NMR spectra. The spectrum corresponding to the purified product was very similar to the one of retigeranic acid methyl ester sent to us by Prof. Paquette. It also had the same patterns as the spectrum of natural retigeranic acid A, with some of them shifted a fraction of ppm.

**Retigeranic acid and comparison with authentic sample.** Retigeranic acid 1 was finally obtained by hydrolysis of the ethyl ester 201 with potassium hydroxide in refluxing ethanol (45% yield) (Scheme 90). There was a second product which was not identified, probably obtained by cleavage of ring C. Reaction performed under milder conditions, such as refluxing methanol did not afford retigeranic acid (1), only starting material was recovered.

Following the same procedure as that for the preparation of 201, pentacyclic ketone 198 was converted to retigeranic acid ethyl ester epimer at C-5b 202 (Scheme 91).
Epimerization studies. Looking at the structure of epimer 202 and knowing that it is unfavorable in 3.1 Kcal with respect to the natural isomer, it seemed reasonable to think that the proton at C-5b would be easily isomerized by treatment with a base. With sodium methoxide in refluxing MeOH or with potassium tert-butoxide in tert-butanol no reaction was observed after 5 hours. After 12 hours the compound decomposed. Stirring with silica gel or with alumina the C-5b center did not epimerize either. At the same time, Paquette\(^\text{137}\) had the same results, and he attributed this lack of acidity to a misalignment of the proton at C-5b, which would make the conjugation with the ester carbonyl difficult.

After the failure of a base- or acid-catalyzed epimerization and the selectivity in the pyrolysis by control of the temperature, a radical reaction was the only alternative left. Epimer 202 was then treated with an excess of N-bromosuccinimide in CCl\(_4\) and in the presence of a catalytic amount of benzoyl peroxide. Four compounds were formed by TLC, which were assigned tentatively as 203a-d. Then treatment with n-butylltinhydride in THF gave one product, which was purified by preparative TLC, in order to separate the tin compounds. This product was co-injected in a GC column with epimer 201, and it had the same retention time. \(^1\)H-NMR showed the same pattern for the C-5b proton, but at 3.0 ppm instead of 3.25 ppm. It is important to mention that at this stage, only 0.6 mg of substance was available, and the difference in the chemical shift could be attributed to the presence of non polar impurities derived from (Bu\(_3\)Sn)\(_2\).

Retigeranic acid was thus prepared in 0.6% overall yield in a short, stereo and enantiocontrolled manner by utilization of both isomeric pentacyclic esters 201 and 202.
It was obtained in fifteen steps from (+)-limonene, which contributed the chiral center necessary for the synthesis of optically pure ketone 145. The crucial reaction occurred smoothly, and the corresponding vinylcyclopropanes were thermolyzed to furnish the pentacyclic skeleton of retigeranic acid.
5. Conclusions

A new methodology consisting of an overall [2+3] annulation for the construction of five-membered rings was developed. This new methodology complemented the already existing [4+1] procedure in Hudlicky's group, and allowed for a second generation synthesis of pentalenene, as well as for the total synthesis of (-)-retigeranic acid.

This simple reaction proved to have good versatility as demonstrated by the high reactivity of not only several enones, but also other electrophiles such as ketones, $\alpha,\beta$-unsaturated esters and aldehydes. A very interesting result of this work was the possibility of the preparation of vinyloxiranes via this methodology. These species can be readily converted into the corresponding dihydrofurans, a very common residue in a large number of natural products.

The asymmetric induction of the reaction with menthyl esters appeared poor. However, the best way of enantiocontrol (at least for the moment) was the utilization of optically pure synthons (enone and ester bromide).

Future work in this area would include the optimization of the reaction conditions, in order to improve the yields. The investigation of the reactivity of several carbonyl compounds in this reaction and the corresponding application for the synthesis of natural products containing the dihydrofuran residue would be considered. Finally, the study of different chiral auxiliaries in the bromocrotonate should also be included in order to obtain chiral induction.

The synthesis of the pentacyclic sesterterpene retigeranic acid was carried out in a regio and enantiocontrolled fashion, constituting the shortest synthesis performed up to the present time. The complete sequence of this synthesis is shown in Scheme 92.
Future work would include a second generation that takes into account the formation of epimer 198.

Scheme 92
IV. EXPERIMENTAL

All nonhydrolytic reactions were carried out in a nitrogen or argon atmosphere, using standard techniques for the exclusion of air and moisture. Glassware used for moisture-sensitive reactions was flame-dried with an internal inert gas sweep. All solvents were distilled from appropriate drying agents prior to use.

Infrared spectra were recorded on neat samples (NaCl plates), unless otherwise specified, on a Perkin-Elmer 283B or 710B spectrometer. $^1$H NMR spectra were obtained on a Bruker WP-270 instrument, using CDCl$_3$ as solvent and TMS as internal reference. Chemical shifts are expressed in δ units and the coupling constants indicated in parentheses and expressed in hertz; multiplicities of the signals are indicated as follows: s for singlet, d for doublet, t for triplet, q for quartet, m for multiplet, and any combinations as appropriate. The abbreviation br next to signal multiplicity connotes broad. $^{13}$C NMR spectra were recorded on Bruker WP-270 or NR-80 instruments, using CDCl$_3$ as solvent and TMS as internal reference. Chemical shifts are in δ units and multiplicities are as specified. Optical rotations were recorded on a Perkin Elmer 241 polarimeter. Mass spectra were recorded on a double focusing Dupont 21-110C or VG 70-70E-HF (exact mass) mass spectrometer or on a Dupont 20-491 instrument (low resolution).

Flash chromatography was performed by the procedure of Still and co-workers, using Kiesel gel 60 (230-400 mesh) by EM reagents. MM2 calculations were performed on a Mac II Apple computer using MMX program from Serena Software (Bloomington, Indiana).
**l-Menthyl 3-Butenoate (110).** l-Menthol (25 g, 0.16 mol) was dissolved in Et$_3$N (45 mL) and it was mechanically stirred. Crotonyl chloride (25.1 g, 0.24 mol) was added dropwise at 0 °C. A very thick white paste was formed. The reaction was quenched with 3N HCl (until acidic) and diluted with ethyl ether (100 mL). The organic layer was washed with 3N HCl (20 mL), and the combined aqueous layers were extracted with ethyl ether (2 x 100 mL). The organic layer was washed with 10% KOH, 3N HCl, brine, dried (Na$_2$SO$_4$), and the solvent was evaporated to give 36 g (100%) of crude ester 110 which was used in the next step without further purification. 110: \( R_f = 0.60 \) (hex/Et$_2$O, 9:1); \( \text{bp. (Kugelrohr temp.)} 150 \degree \text{C (10^{-3} \text{ mmHg})} \); \( [\alpha]_D -76.2 \degree \) (c 6.76, EtOH); \( \text{IR (neat, NaCl)} \ 3100, 2970, 2880, 1740, 1650 \text{ cm}^{-1} \); \( ^1\text{H-NMR (CDCl}_3) \delta 0.75 \) (d, 3H, J=8.0 Hz), 0.80-1.15 (m, 9H), 1.30-1.60 (m, 2H), 1.60-1.70 (br d, 2H), 1.75-1.90 (m, 1H), 1.90-2.05 (br d, 1H), 3.05 (dd, 2H, J$_1$=7.0, J$_2$=2.0 Hz), 4.7 (dt, 1H), 5.15 (br d, 1H), 5.20 (br d, 1H), 5.9 (m, 1H); \( ^{13}\text{C-NMR (CDCl}_3) \delta 16.4 \) (CH$_3$), 20.7 (CH$_3$), 22.0 (CH$_3$), 23.6 (CH$_2$), 26.3 (CH), 31.4 (CH), 34.3 (CH$_2$), 39.5 (CH$_2$), 40.9 (CH$_2$), 47.0 (CH), 74.4 (CH), 118.2 (CH$_2$), 130.5 (CH), 171.0 (C); \( \text{Mass spectrum (70 eV, m/e (rel. int.))} 224 (18, M^+), 138 (80), 123 (35), 95 (70), 83 (100), 69 (94). \)

**d-Menthy1 3-buten0ate:** \( [\alpha]_D +74.9 \degree \) (c 1.17, EtOH).

**l-Menthy1 3,4-dibromobutanoate (110a).** l-Methyl-3-buten0ate (110) (30 g, 0.134 mol) was dissolved in CCl$_4$ (50 mL) at 0 °C, and it was mechanically stirred. Bromine (34 g, 0.214 mol) was added dropwise at 0 °C. After the addition was complete the solvent was evaporated and the resulting dibromide 110a used without further purification. 110a: \( R_f = 0.60 \) (hex/Et$_2$O, 9:1); \( \text{bp. (Kugelrohr temp.)} 200 \degree \text{C (10^{-3} \text{ mmHg})} \); \( [\alpha]_D -35.3 \degree \) (c 5.61, EtOH); \( \text{IR (neat, NaCl)} \ 2960, 2880, 1730 \text{ cm}^{-1} \); \( ^1\text{H-NMR (CDCl}_3) \delta 0.75 \) (dd, 3H, J$_1$=7.0, J$_2$=2.0 Hz), 0.80-1.15 (m, 9H), 1.30-1.60 (m,
2H), 1.60-1.75 (br d, 2H), 1.85-2.10 (m, 2H), 2.80 (m, 1H), 3.30 (m, 1H), 3.70 (m, 1H), 3.90 (dd, 1H, J=7.3 Hz), 4.5 (m, 1H), 4.75 (m, 1H); **^13^C-NMR** (CDCl₃) δ 16.3 (CH₃), 20.7 (CH₃), 21.9 (CH₃), 23.4 (CH₂), 26.2 (CH), 31.3 (CH), 34.1 (CH₂), 35.4 (CH₂), 40.7 (CH₂), 42.0 (CH₂), 45.1 (CH), 46.9 (CH), 75.3 (CH), 169.1 (C); Mass spectrum (Cl, m/e (rel. int.)) 385 (6, (M + 1)+), 289 (3), 247 (10), 225 (10), 139 (100).

**d-Menthyl 3.4-dibromobutanoate:** [α]D +32.9° (c 1.32, EtOH).

**l-Menthyl 4-bromobutenoate (172).** The crude dibromide 170a was dissolved in DME (50 mL), and DBU (30.5 g, 0.20 mol) was added dropwise at 0 °C. When the addition was finished, the reaction was quenched with 3N HCl (until acidic) and ethyl ether (70 mL). The organic layer was washed with 3N HCl (20 mL). The combined aqueous layer was extracted with ethyl ether (3 x 80 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and the solvent was evaporated. Ester 172 (36.5 g, 90% from menthyl 3-butenolate 170) was obtained after filtration through silica gel. **172:** Rf = 0.4 (hex/Et₂O, 9:1); mp. 35-36 °C; bp. (Kugelrohr temp.) 200 °C (10⁻³ mmHg); [α]D -60.2° (c 3.32, EtOH); IR (neat, NaCl) 2980, 2880, 1730, 1655 cm⁻¹; **^1H-NMR** (CDCl₃) δ 0.75 (d, 3H, J=7 Hz), 0.85-1.15 (m, 9H), 1.35-1.60 (m, 2H), 1.60-1.75 (br d, 2H), 1.80-1.90 (m, 1H), 1.95-2.10 (br d, 1H), 4.0 (dd, 2H, J₁=8.0, J₂=2.0 Hz), 4.75 (dt, 1H), 6.05 (br d, 1H, J=16.0 Hz), 7.0 (m, 1H); **^13^C-NMR** (CDCl₃) δ 16.4 (CH₃), 20.6 (CH₃), 21.9 (CH₃), 23.5 (CH₂), 26.3 (CH), 29.1 (CH₂), 31.3 (CH), 34.2 (CH₂), 40.8 (CH₂), 47.0 (CH), 74.6 (CH), 125.1 (CH), 141.3 (CH), 165.0 (C); Anal Calcd for C₁₄H₂₃BrO₂: C, 55.46; H, 7.59; Br, 26.37. Found: C, 55.00; H, 7.59; Br, 26.64.

**d-Menthyl 4-bromobutenoate:** [α]D +57.0° (c 0.50, EtOH).
**l-Menthyl 2-butenoate (169a).** l-Menthol (25 g, 0.16 mol) was dissolved in Et₃N (45 mL), and the mixture was mechanically stirred. Crotonyl chloride (25.1 g, 0.24 mol) was added dropwise at 0 °C. A very thick white paste was formed. Freshly distilled THF (50 mL) was added to wash the walls of the flask, and then DBU (30.5 g, 0.20 mol) was added dropwise at 0 °C. Workup of the reaction mixture prior to the addition of DBU resulted in quantitative isolation of deconjugated ester 170. The mixture was allowed to warm up to room temperature and stirred for 3 h. The reaction mixture was diluted with ethyl ether and washed with 10% HCl (until acidic), and the combined aqueous layer was extracted with ethyl ether (3 x 80 mL). The combined organic layer was washed with 10% KOH, 10% HCl, and brine. It was then filtered through a plug of silica gel, dried (Na₂SO₄), and the solvent was evaporated to yield 35.1 g (98%) of crude ester 169a as a mixture of E:Z isomers (5:1). **169a-E:** Rᵣ = 0.54 (hex/Et₂O, 9:1), **169a-Z:** Rᵣ = 0.67 (hex/Et₂O, 9:1); bp. (Kugelrohr temp.) 150 °C (10⁻³ mmHg); [α]ᵣ -85.3° (c 1.73, EtOH); IR (neat, NaCl) 2930, 2880, 1710, 1660 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.75 (d, 3H, J=8.0 Hz), 0.90 (m, 6H), 0.95-1.20 (m, 4H), 1.35-1.60 (m, 2H), 1.60-1.75 (br d, 2H), 1.85 (dd, 3H, J₁=7.0, J₂=2 Hz), 1.95-2.10 (br d, 1H), 4.75 (dt, 1H, J₁=12, J₂=6 Hz), 6.80 (dd, 1H J₁=15, J₂=2 Hz), 6.95 (m, 1H); ¹³C-NMR (CDCl₃) δ 16.3 (CH₃), 17.7 (CH₃), 20.6 (CH₃), 21.9 (CH₃), 23.5 (CH₂), 26.2 (CH), 31.3 (CH), 34.2 (CH₂), 40.9 (CH₂), 47.1 (CH), 73.6 (CH), 123.2 (CH₂), 143.7 (CH), 165.9 (C); Mass spectrum (Cl, m/e (rel. int.)) 225 (3.7, (M+1)⁺), 139 (100).

**d-Menthyl 2-butenoate:** [α]ᵣ +79.4° (c 0.77, EtOH).

**l-Menthyl 2,3-dibromobutanoate (169b).** l-methyl 2-butenoate (169a) (34.5 g, 0.15 mol) was dissolved in CCl₄ (50 mL), and it was mechanically stirred. Bromine
(39 g, 0.25 mol) was added dropwise at 0 °C. After the addition was complete, the excess bromine and the solvent were evaporated to afford ester 162b, which was used immediately without further purification. 162b: Rf = 0.67 (hexane/ether, 9:1); bp. (Kugelrohr temp.) 200 °C (10⁻³ mmHg); [α]D -32.1° (c 6.73, EtOH); IR (neat, NaCl) 2960, 2880, 1740 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.75 (dd, 3H, J₁=8.0, J₂=2.5 Hz), 0.90-1.00 (m, 7H), 1.00-1.15 (m, 2H), 1.40-1.60 (m, 2H), 1.60-1.80 (br d, 2H), 1.90 (d, 3H, J=6.0 Hz), 2.00-2.10 (m, 2H), 4.30-4.60 (m, 2H), 4.70-4.80 (m, 1H); ¹³C-NMR (CDCl₃) δ 16.1 (CH₃), 20.6 (CH₃), 21.9 (CH₃), 23.2 (CH₂), 23.8 (CH₃), 26.0 (CH), 31.3 (CH), 34.1 (CH₂), 39.8 (CH₂), 45.6 (CH), 46.9 (CH), 50.0 (CH), 76.4 (CH), 167.2 (C); Mass Spectrum (CI, m/e (rel. int.)) 385 (5.7, (M+1)⁺), 225 (12), 139 (100).

**d-Menthyl 2,3-dibromobutanoate:** [α]D +32° (c 0.59, EtOH)

**l-Menthyl 2-bromobutenoate (169).** Crude dibromide 169b was dissolved in DME (100 mL) and DBU (30.5 g, 0.20 mol) was added dropwise at 0 °C with mechanical stirring. After addition was complete, the reaction was quenched with 3N HCl (until acidic) and ethyl ether (100 mL). The organic layer was washed with 3N HCl (20 mL). The combined aqueous layer was extracted with ethyl ether (2x80 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and the solvent evaporated in vacuo. After filtration through a bed of silica gel, 41.0 g (88% from menthyl 2-butenoate 169a) of ester 169 was obtained as a 50:50 mixture of Z and E isomers. 169-E: Rf = 0.43 (hexane/ether, 95:5); 169-Z: Rf = 0.34 (hexane/ether, 95:5); bp. (Kugelrohr temp. of the 1:1 mixture) 200 °C (10⁻³ mmHg); [α]D -74.3° (c 5.57, EtOH); IR (neat, NaCl) 2900, 2850, 1710, 1630 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.75 (d, 3H, J=7.0 Hz), 0.85-1.00 (m, 7H), 1.00-1.20 (m, 2H), 1.40-1.60
(m, 2H), 1.65-1.75 (br d, 2H), 2.05 (d, 3H, J=8 Hz), 2.00 (m, 2H), 4.75 (dt, 1H),
6.70 (q, 1H, J=8.0 Hz); 13C-NMR (CDCl3) δ 16.2 (CH3), 17.7 (CH3), 20.7 (CH3),
21.9 (CH3), 23.4 (CH2), 26.1 (CH), 31.4 (CH), 34.1 (CH2), 40.6 (CH2), 47.0 (CH),
76.2 (CH), 112.3 (C), 140.5 (CH), 162.4 (C); 1H-NMR (CDCl3) δ 0.75 (d, 3H, J=7.0 Hz), 0.85-1.00 (m, 7H); 1.00-1.20 (m, 2H), 1.40-1.60 (m, 2H), 1.95 (d, 3H, J=6 Hz), 2.00 (m, 2H), 4.75 (dt, 1H), 7.35 (q, 1H, J=6.0 Hz); 13C-NMR (CDCl3) δ 16.4 (CH3), 17.2 (CH3), 20.7 (CH3), 21.9 (CH3), 23.5 (CH2), 26.3 (CH),
31.4 (CH), 34.1 (CH2), 40.6 (CH2), 47.0 (CH), 76.4 (CH), 118.3 (C), 142.2 (CH)
161.7 (C).

d-Menthyl 2-bromobutenoate: 60:40 mixture, [α]D +72.9° (c 1.23, EtOH)

6-Carbomenthyloxy-6-vinylbicyclo[3.0.1]hexane-2-one, 173-exo and
173-endo isomers. A solution of lithium diisopropylamide prepared from
diisopropylamine (0.95 g, 9.4 mmol) and n-BuLi (3.80 mL, 9.4 mmol, 2.5 M in hexane)
in THF (9.4 mL), was cooled to -78 °C. HMPA (1.8 mL, 10.4 mmol) was added, and
the mixture stirred for 20 min. Menthyl 2-Bromo-crotonate (169) (2.84 g, 9.4 mmol)
was then added dropwise, and the mixture stirred at -78 °C for 0.5 h. Cyclopentenone
(0.84 g, 10.3 mmol) was then added, and the reaction quenched at -78 °C after 0.5 h with
saturated NH4Cl solution (6 mL) and ethyl ether (10 mL). The organic layer was washed
once with 3N HCl (5 mL) and the combined aqueous layer was extracted with ethyl ether
(3 x 10 mL). The organic layer was then washed with brine (3 x 10 mL), dried
(Na2SO4) and the solvents removed under vacuo to yield the vinylcyclopentanes 173
(exo:endo= 2:3) that were separated by column chromatography to give 550 mg (19%) of
exo isomer and 390 mg (14%) of the endo isomer. 173-exo: Rf = 0.23 (hexane/ether,
7:3); 1H-NMR (CDCl3) δ 0.69 (m, 3H, J=7.5 Hz), 0.78-1.10 (m, 8H), 1.30-1.55 (m,
2H), 1.62 (m, 2H), 1.78-2.05 (m, 3H), 2.05-2.35 (m, 6H), 4.65 (qd, 1H, J₁=4.0, J₂=11.6 Hz), 4.99 (d, 1H, J=17.4 Hz), 5.03 (d, 1H, J=11.0 Hz), 5.85 (m, 1H); Mass Spectrum (70 eV, m/e (rel. int.)) 166 (100), 148 (20), 138 (18), 124 (18), 110 (20), 97 (15), 91 (10), 83 (62), 77 (12), 69 (27), 55 (28). Calcd. for C₉H₁₂O₃: 166.0630. Found: 166.0620. 173-endo: Rf = 0.33 (hexane/ether, 7:3); ¹H-NMR (CDCl₃) δ 0.65 (m, 3H), 0.80 (m, 6H), 0.85-1.00 (m, 3H), 1.20-1.50 (m, 2H), 1.55 (m, 2H), 1.70(m, 1H), 1.78-2.30 (m, 5H), 2.40-2.55 (m, 2H), 4.50 (dt, 1H, J₁=10.0, J₂=4.0 Hz), 5.22 (d, 1H, J=15.5 Hz), 5.32 (dd, 1H, J₁=10.1, J₂=3.0 Hz), 5.88 (m, 1H); ¹³C-NMR (CDCl₃) δ 16.5 (CH₃), 19.7 (CH₂), 20.6 (CH₃), 21.8 (CH₃), 23.2 (CH₂), 25.9 (CH), 31.2 (CH), 34.1 (CH₂), 35.3 (CH), 36.2 (CH₂), 40.6 (CH₂), 41.2 (CH), 47.1 (CH), 75.6 (CH), 122.9 (CH₂), 128.8 (CH), 170.0 (C), 212.9 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 166 (100), 148 (25), 138 (20), 124 (35), 95 (18), 67 (83) 77 (13), 69 (25), 55 (28). Calcd. for C₉H₁₂O₃: 166.0630. Found: 166.0615.

1S-(1α,3β,6α,7α)-2-Carbethoxy-2-cyclohexenyl-3,7-dimethyl-4-oxo bicyclo[4.3.0.1₁.₃]nonane, 183-exo and 183-endo. A solution of lithium diisopropylamide prepared from diisopropylamine (41.0 mg, 0.4 mmol) and n-BuLi (0.16 mL, 0.4 mmol, 2.5 M in hexane) in THF (1 mL), was cooled to -78 °C. HMPA (80 mg, 0.44 mmol) was added, and the mixture stirred for 20 min. 1-Bromo-1-carboxyethylmethylidencyclohexane (181) (100.0 mg, 0.4 mmol) dissolved in 1 mL of THF was then added dropwise via cannula, and the mixture stirred at -78 °C for 0.5 h. The enone 144 (70. mg, 0.44 mmol) was then added and the reaction quenched at -78 °C after 0.5 h with saturated NH₄Cl solution (4 mL) and ethyl ether (6 mL). The organic layer was washed once with 3N HCl (3 mL) and the combined aqueous layer was extracted with ethyl ether (3 x 5 mL). The organic layer was then washed with brine (3 x
4 mL), dried (Na₂SO₄) and the solvents removed under vacuo to yield vinylcycloporpanes (183) (endo:exo = 4.5:1) that were separated by column chromatography to give 10.2 mg (8%) of exo isomer and 41.0 mg (32%) of the endo isomer. **183-exo:** Rf = 0.5 (hexane/ether, 3:1); **1H-NMR** (CDCl₃) δ 1.00 (d, 3H, J=7.0 Hz), 1.12 (s, 3H), 1.20 (t, 3H, J=7.5 Hz), 1.25-1.45 (m, 2H), 1.45-1.75 (m, 6H), 1.75-2.10 (m, 6H), 2.10-2.27 (m, 1H), 2.38 (m, 1H), 4.10 (q, 2H, J=7.5 Hz), 5.68 (bs, 1H); **13C-NMR** (CDCl₃) δ 9.2 (CH₃), 14.1 (CH₃), 17.6 (CH₃), 22.0 (CH₂), 22.9 (CH₂), 24.7 (CH₂), 25.4 (CH₂), 28.0 (CH₂), 33.6 (CH₂), 41.1 (CH₂), 41.8 (CH), 42.5 (C), 45.1 (C), 47.5 (CH), 54.0 (C), 60.7 (CH₂), 129.0 (CH), 132.6 (C), 169.4 (C), 215.6 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 316 (80, M⁺), 287 (28), 243 (45), 199 (32), 173 (32), 159 (50), 84 (100). **Calcd. for C₂₀H₂₈O₃:** 316.2038. **Found:** 316.1992. **183-endo:** Rf = 0.3 (hexane/ether, 3:1); **1H-NMR** (CDCl₃) δ 0.98 (d, 3H, J=7.0 Hz), 1.02 (s, 3H), 1.17 (t, 3H, J=7.5 Hz), 1.28-1.65 (m, 6H), 1.70-2.20 (m, 10H), 4.05 (m, 2H), 5.82 (bs, 1H); **13C-NMR** (CDCl₃) δ 9.8 (CH₃), 13.9 (CH₃), 18.4 (CH₃), 21.9 (CH₂), 22.9 (CH₂), 24.5 (CH₂), 25.7 (CH₂), 27.6 (CH₂), 33.3 (CH₂), 41.2 (CH₂), 42.1 (CH), 44.6 (C), 47.1 (CH), 48.6 (C), 52.3 (C), 61.1 (CH₂), 131.2 (CH), 131.2 (C), 169.9 (C), 214.7 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 316 (100, M⁺), 288 (25), 243 (90), 219 (48), 199.30), 173 (30) 159 (58), 84 (52). **Calcd. for C₂₀H₂₈O₃:** 316.2038. **Found:** 316.2029.

**(R)-7,7-Dimethoxy-5-isopropylheptan-2-one (188).** A solution of menthene (187) (27 g, 0.20 mol) in CH₂Cl₂ (50 mL) was added to 100 mL of methanol contained in a glass gas-washing bottle equipped with a glass fritt-terminated inlet tube, and the solution cooled to -78 °C (dry-ice/acetone). Ozone was bubbled through this solution until a lavender blue color persisted (saturated solution) which usually took 1.5
h. After purging with N2 to displace residual ozone, p-toluenesulfonic acid (0.5 g) was added and the mixture transferred to a round bottom flask. Methyl sulfide (120 g, 1.93 mol) was added slowly at 0 °C to avoid any boiling over, and the mixture was stirred at room temperature for 24 h. The reaction mixture was concentrated, diluted with 50 mL of ethyl ether, poured into cold saturated NaHCO3 and the aqueous layer extracted with ether (3x50 mL). The organic layers were combined, washed with brine (3x50 mL), dried and evaporated to give 37 g (87%) of essentially pure acetal, suitable for use in the next step. **188**: Rf = 0.18 (hexane/ether=7:3); bp (Kugelrohr temp.) 80-100 °C (0.2 mmHg); [α]D +3.2° (c 5.50, MeOH); IR (neat) 2950, 2830, 1720, 1190, 1160, 1125, 1050 cm⁻¹; 1H-NMR (CDCl3) δ 0.80 (d, 3H, J=7.0 Hz), 0.82 (d, 3H, J=7.0 Hz), 1.20-1.30 (m, 1H), 1.30-1.38 (m, 1H), 1.40-1.73 (m, 4H), 2.10 (s, 3H), 2.40 (t, 2H, J=7.0 Hz), 3.25 (s, 3H), 3.29 (s, 3H), 4.39 (t, 1H, J=5.8 Hz); 13C-NMR (CDCl3) δ 18.5 (CH3), 19.2 (CH3), 24.8 (CH2), 29.5 (CH), 29.8 (CH3), 33.4 (CH2), 39.1 (CH), 41.8 (CH2), 52.3 (CH3), 53.2 (CH3), 103.9 (CH), 208.9 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 215 (18, (M-1)⁺), 199 (23), 185 (9), 141 (22), 81 (78), 69 (100). Calcd. for C12H23O3: 215.1647. Found : 215.1653.

(R)-6-Oxo-3-isopropylheptanal (**190**). a) From (R)-7,7-Dimethoxy-5-isopropyl-heptan-2-one (**188**). (R)-7,7-Dimethoxy-5-isopropylheptan-2-one (**188**) (35.1 g, 0.163 mol) was dissolved in THF (200 mL), and the solution was cooled to 0 °C. 3% aq. HClO₄ (200 mL) was added dropwise and the mixture stirred under nitrogen at 0 °C for 3 h, and then at room temperature for 3 h. The reaction mixture was diluted with ethyl ether (150 mL), the organic layer was separated and the aqueous layer was extracted with ether (2x80 mL). The organic layers were combined and washed with saturated NaHCO₃ (100 mL), brine (3x100 mL), dried (Na₂SO₄) and solvent removed in vacuo.
The crude product was distilled using a Kugelrohr apparatus to yield 24.3 g (88%) of pure aldehyde. 190: Rf = 0.12 (hexane/ether, 7:3); bp (Kugelrohr temp.) 120-130 °C (0.05 mmHg); [α]D +5.4° (c 2.3, MeOH); 1H-NMR (CDCl3) δ 0.80 (d, 3H, J=7.0 Hz), 0.82 (d, 3H, J=7.0 Hz), 1.35-1.50 (m, 1H), 1.52-1.70 (m, 2H), 1.78-1.88 (m, 1H), 2.10 (s, 3H), 2.12-2.24 (m, 1H), 2.32-2.42 (m, 3H), 9.72 (t, 1H, J=2.0 Hz).

From menthene (187), using a procedure identical to that for the preparation of 188, menthene (187) (27 g, 0.196 mol) in CH2Cl2 (50 mL) and CH3OH (100 mL) was ozonized and the reaction work-up done in the absence of p-toluenesulfonic acid to give 28 g (84%) of 190 after Kugelrohr distillation.

E and Z (S)-7-Methoxy-5-isopropyl-6-hepten-2-one (191b). (R)-7,7-Dimethoxy-5-isopropylheptan-2-one (188) (17.6 g, 81.5 mmol) was distilled over potassium hydrogen sulfate (0.2 g) at 90-100 °C (1.5 mmHg). The distillate (11.5 g) was purified by column chromatography on silica gel to give 6.65 g (44%) of an inseparable mixture of enol ethers (E:Z = 1.2:1) and 3.0 g (17%) of starting ketoacetal. The mixture of enol ethers was used in the next step. 191b: Rf = 0.38 (hexane/ether, 7:3). 1H-NMR of the mixture (CDCl3) δ 0.78-0.85 (four doublets, 12H), 1.21-1.78 (m, 6H), 2.10 (s, 6H), 2.15-2.50 (m, 6H), 3.48 (s, 3H, E isomer), 3.50 (s, 3H, Z isomer), 4.03 (dd, 1H, J1=10.5, J2=5.8 Hz, Z isomer), 4.36 (dd, 1H, J1=12.8, J2=10.5 Hz, E isomer), 5.95 (d, 1H, J=5.8 Hz, Z isomer), 6.15 (d, 1H, J=12.8 Hz, E isomer). 13C-NMR (CDCl3) δ E isomer: 18.6 (CH3), 20.5 (CH3), 26.9 (CH2), 29.7 (CH3), 32.3 (CH), 41.8 (CH2), 44.4 (CH), 55.6 (CH3), 103.5 (CH), 147.6 (CH), 208.3 (C). Z isomer: 18.4 (CH3), 20.3 (CH3), 26.5 (CH2), 29.7 (CH3), 31.9 (CH), 39.7 (CH), 41.8 (CH2), 59.0 (CH3), 108.3 (CH), 147.0 (CH), 208.3 (C); Mass
Spectrum (70 eV, m/e (rel. int.)) 184 (8, M+), 167 (20), 141 (30), 126 (60), 81 (100). Calcd. for C_{11}H_{20}O_{2}: 184.1463. Found: 184.1469.

1-Methylcarboxy-4-isopropylcyclopent-1-ene (192). (R)-7,7-Dimethoxy-5-isopropylheptan-2-one (188) (12 g, 0.156 mol) was heated to 120 °C in the presence of diisopropylethylammonium tosylate and in a distillation apparatus. After the methanol was collected, the Vigreux column was removed and the residue was distilled in vacuo at 47 °C (0.05 mmHg). Pure enone 192 (7.8 g, 92%) was obtained, which solidified when room temperature was reached. 192: Rf = 0.34 (hexane/ether, 85:15); IR (neat) 2970, 2930, 1660, 1610 cm^{-1}; ^{1}H-NMR (CDCl_{3}) δ 0.89 (d, 3H, J=7.0 Hz), 0.90 (d, 3H, J=7.0 Hz), 1.55 (m, 1H), 2.03 (m, 1H), 1.10-2.28 (m, 2H), 2.28 (s, 3H), 2.52-2.70 (m, 2H), 6.65 (br s) 1H; ^{13}C-NMR (CDCl_{3}) δ 20.6 (CH_{3}, double intensity), 26.1 (CH_{3}), 33.1 (CH), 34.6 (CH_{2}), 38.0 (CH_{2}), 45.4 (CH), 143.5 (CH), 145.5 (C), 196.4 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 152 (20, M+), 137 (30), 125 (50), 109 (90). Calcd. for C_{10}H_{16}O: 152.1201. Found: 152.1215.

(S)-5-Oxo-2-isopropylhexanal (189) a) from enol ethers 191b. A mixture of E and Z (S)-7-methoxy-5-isopropyl-6-hepten-2-one (191b) (16.2 g, 88.0 mmol) (E:Z = 1.2:1) was dissolved in 2:1 MeOH/CH_{2}Cl_{2} (150 mL), cooled to -78 °C, and O_{3} was bubbled through it until the appearance of a blue color. Nitrogen was then bubbled through the solution at -78 °C until the excess O_{3} was eliminated. Dimethylsulfide (65 mL, 885 mmol) was added at 0 °C, and the reaction mixture was stirred overnight at room temperature. The solvent was removed in vacuo, the crude product dissolved in ethyl ether (50 mL), and washed with brine (3x30 mL). The organic layer was then dried, concentrated in vacuo, and distilled using a Kugelrohr apparatus. Pure ketoaldehyde
(11.0 g, 80%) was obtained. 189: \( R_f = 0.17 \) (hexane/ether, 4:1); bp = (Kugelrohr temp.) 125 °C (0.25 mmHg); [\( \alpha \)]D +40° (c 1.72, CDCl₃); \( ^1\text{H-NMR} \) (CDCl₃) \( \delta \) 0.95 (d, 3H, J=7.0 Hz), 0.98 (d, 3H, J=7.0 Hz), 1.70-1.90 (m, 2H), 2.00-2.08 (m, 2H), 2.10 (s, 3H), 2.25-2.55 (m, 2H), 9.60 (d, 1H, J=3.1 Hz); \( ^{13}\text{C-NMR} \) (CDCl₃) \( \delta \) 19.5 (CH₃), 19.5 (CH₂), 20.2 (CH₃), 28.4 (CH), 29.9 (CH₃), 41.3 (CH₂), 57.5 (CH), 205.1 (CH), 207.8 (C). b) from (S)-3-Isopropyl-6-oxo-1-piperidinohept-1-ene (191a). (S)-3-Isopropyl-6-oxo-1-piperidinohept-1-ene \( ^{162} \) (9.7 g, 45 mmol) was dissolved in CH₂Cl₂ (150 mL), cooled to -78 °C, and ozone bubbled through it until the appearance of a permanent blue color. Dimethyl sulfide (28 g, 450 mmol) was added dropwise at -20 °C, and the mixture stirred at room temperature for 24 h. Solvent was evaporated in vacuo, and the residue distilled in vacuo (70-90 °C, 0.25 mmHg) and chromatographed on silica gel (hexane/ether, 4:1) to yield 2.1 g (30%) of ketoaldehyde 189.

2,6-Dimethoxy-2-methyl-5-isopropylpirane \( ^{193\text{a}} \) and 6,6-Dimethoxy-5-isopropylhexan-2-one \( ^{193\text{b}} \). In an identical procedure for that to the preparation of keto aldehyde 189, except that using spectroscopical grade methanol without further purification, acetals \( ^{193\text{a}} \) and \( ^{193\text{b}} \) were obtained as a 2:1 mixture in 75% yield. \( ^{193\text{a}} \): \( R_f = 0.53 \) (hexane/ether, 4:1); \( ^1\text{H-NMR} \) (CDCl₃) \( \delta \) 0.80 (d, 3H,J=7.0 Hz), 0.87 (d, 3H, J=7.0 Hz), 1.20-1.30 (m, 1H), 1.30 (s, 3H), 1.40-1.60 (m, 3H), 1.65-1.80 (m, 1H), 1.98 (m, 1H), 3.26 (s, 3H), 3.48 (s, 3H), 4.33 (d, 1H, J=8.1 Hz); \( ^{13}\text{C-NMR} \) (CDCl₃) \( \delta \) 17.3 (CH₃), 18.2 (CH₂), 20.5 (CH₃), 23.6 (CH₃), 26.7 (CH), 35.6 (CH₂), 45.0 (CH), 47.8 (CH₃), 56.0 (CH₃), 99.4 (C), 100.8 (CH); Mass Spectrum (70 eV, m/e (rel. int.)) 170 (23.8 (M-32)+), 155 (7.5), 113 (20), 97 (50), 85 (100). Calcd. for C₁₀H₁₈O₂: 170.1307. Found: 170.1301. \( ^{193\text{b}} \): \( R_f = 0.21 \) (hexane/ether, 4:1); \( ^1\text{H-}
NMR (CDCl₃) δ 0.80 (d, 3H, J=7.0 Hz), 0.87 (d, 3H, J=7.0 Hz), 1.33-1.45 (m, 1H), 1.45-1.58 (m, 2H), 1.75-1.88 (m, 1H), 2.08 (s, 3H), 2.35-2.65 (m, 2H), 3.23 (s, 3H), 3.30 (s, 3H), 4.12 (d, 1H, J=7.0 Hz); ¹³C-NMR (CDCl₃) δ 18.4 (CH₃), 20.0 (CH₂), 20.6 (CH₃), 27.8 (CH), 29.7 (CH₃), 43.2 (CH₂), 45.4 (CH), 53.4 (CH₃), 55.0 (CH₃), 108.0 (CH), 209.2 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 170 (21 (M-32)+), 155 (45), 113 (20), 100 (35), 85 (100). Calcd. for C₁₀H₁₈O₂: 170.1307. Found: 170.1301.

Ethyl (S)-3-methoxy-9-oxo-6-isopropyl-2,4-decadienoate (194). A solution of lithium diisopropylamide prepared from diisopropylamine (7.20 g, 71.2 mmol) and n-butyllithium (32 mL, 2.4 M in hexane) in THF (50 mL), was cooled to -78 °C; HMPA (13.5 mL) was added and the mixture stirred for 20 min. A solution of ethyl 4-dimethoxyphosphonyl-3-methoxy-2-butenoate (17.1 g, 68.0 mmol) in THF (80 mL) at -78 °C was added dropwise via cannula. The mixture was stirred for 15 min, and a solution of (S)-5-oxo-2-isopropylhexanal (182) (10.10 g, 64.7 mmol) in THF (50 mL) was added. The reaction mixture was stirred at -78 °C for 15 min, and quenched with water (50 mL) and diethyl ether (100 mL). The aqueous layer was extracted with ether (3x50 mL), the organic layers were combined and washed with 3N HCl (3x30 mL), brine (3x30 mL), dried (Na₂SO₄), concentrated and distilled using a Kugelrohr apparatus to give 14.62 g (80%) of 194: Rf = 0.25 (hexane/ether, 4:1); bp (Kugelrohr temp.) 220 °C (0.05 mmHg); [α]D +50° (c 2.08, EtOH); IR (neat) 3080, 2960, 2860, 1660, 1590 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.80 (d, 3H, J=7.0 Hz), 0.85 (d, 3H, J=7.0 Hz), 1.24 (t, 3H, J=7.0 Hz), 1.40-1.65 (m, 2H), 1.70-1.90 (m, 2H), 2.07 (s, 3H), 2.31 (m, 2H), 3.65 (s, 3H), 4.10 (q, 2H, J=7.0 Hz), 4.95 (s, 1H), 6.18 (dd, 1H, J₁=16.0, J₂=10.0 Hz), 7.23 (d, 1H, J=17.0 Hz); ¹³C-NMR (CDCl₃) δ 14.4 (CH₃), 19.3
(CH$_3$), 20.5 (CH$_3$), 25.8 (CH$_2$), 30.0 (CH$_3$), 32.2 (CH$_3$), 41.9 (CH$_2$), 49.4 (CH$_2$), 55.3 (CH$_3$), 59.4 (CH$_2$), 91.0 (CH), 123.8 (CH), 140.6 (CH), 166.5 (C), 167.3 (C), 208.8 (C); Mass Spectrum (70 eV, m/e (rel. int.)). 282 (20, M$^+$), 237 (17), 225 (28), 209 (18), 151 (45), 127 (50), 109 (100), 91 (42). Calcd. for C$_{19}$H$_{25}$O$_4$: 282.1831. Found: 282.1838.

**Ethyl (S)-3-methoxy-9-methyl-6-isopropyl-2,4,9-decatrionate (147).**

Methyltriphenylphosphonium bromide (19.7 g, 55 mmol) was suspended in THF (20 mL), cooled to 0 °C, and n-butyllithium (25 mL, 60 mmol; 2.4 M in hexane) was added dropwise. The orange-brown solution was slowly warmed to room temperature, and a solution of ethyl (S)-3-methoxy-9-oxo-6-isopropyl-2,4-decadienoate (1%) (14.2 g, 50 mmol) in THF (20 mL) was added dropwise. The reaction was quenched after two hours with brine (50 mL), and diluted with ethyl ether (100 mL). The organic layer was washed with water (6 x 50 mL), dried (Na$_2$SO$_4$), and the solvent removed in vacuo. The crude product was distilled using a Kugelrohr apparatus at 210 °C (0.05 mmHg) to yield 11.3 g (80%) of triene 147: R$_f$ = 0.70 °C (hexane/ether=4:1); bp (Kugelrohr temp.) 210 °C (0.05 mmHg); [α]$_D$ +43° (c 1.2, MeOH). $^1$H-NMR (CDCl$_3$) δ 0.79 (d, 3H, J=7.0 Hz), 0.81 (d, 3H, J=7.0 Hz), 1.21 (t, 3H, J=8.0 Hz), 1.28-1.42 (m, 1H), 1.48-1.62 (m, 2H), 1.62 (s, 3H), 1.88-2.00 (m, 3H), 3.61 (s, 3H), 4.09 (q, 2H, J=8.0 Hz), 4.60 (bd, 2H), 4.95 (s, 1H), 6.21 (dd, 1H, J$_1$=15.0, J$_2$=9.0 Hz), 7.20 (d, 1H, J=15.0 Hz).

**1R,6S,7S)-3-Carbethoxy-4-methoxy-1-methyl-7-isopropylbicyclo [4.3.0] nonene, Δ$^3$ and Δ$^4$ isomers, 195a and 195b.**

Ethyl (S)-3-methoxy-9-methyl-6-isopropyl-2,4,9-decatrionate (147) (1.47 g, 5.25 mmol) was dissolved in
toluene (25 mL), sealed, and heated to 300 °C for 8 h. The tubes were opened, rinsed with dichloromethane; the solvent was removed in vacuo and the crude product chromatographed on flash silica gel to yield 266.5 mg (18%) of the conjugated isomer (195a), 196.3 mg of an inseparable mixture that contained 40% by GC of the non conjugated isomer (195b) (5% yield), and 535.7 mg of starting material. 195a: Rf = 0.22 (hexane/ether = 4:1)*; [α]D -95° (c 0.54, MeOH); IR (neat) 2980, 2900, 1715, 1620 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.75 (s, 3H), 0.82 (d, 3H, J=6.0 Hz), 0.88 (d, 3H, J=6.0 Hz), 1.25 (t, 3H, J=6.0 Hz), 1.30-1.50 (m, 2H), 1.50-1.70 (m, 3H), 1.70-2.15 (m, 3H), 2.25 (m, 2H), 3.70 (s, 3H), 4.15 (q, 2H, J=6.0 Hz). ¹³C-NMR (CDCl₃) δ 14.3 (CH₃), 17.7 (CH₃), 18.9 (CH₃), 21.6 (CH₃), 25.4 (CH₂), 28.7 (CH₂), 30.5 (CH), 38.6 (CH₂), 39.7 (CH₂), 40.1 (C), 46.4 (CH), 47.5 (CH), 55.7 (CH₃), 59.7 (CH₂), 107.7 (C), 162.1 (C), 168.2 (C). 61b: Rf = 0.60 (hexane/ether = 4:1)*

*(yellow when developed with anisaldehyde solution)

(1R,6S,7S)-3-Carbethoxy-4-hydroxy-1-methyl-7-isopropylbicyclo[4.3.0]non-3-ene (196). (1R,6S,7S)-3-Carbethoxy-4-methoxy-1-methyl-7-isopropyl bicyclo[4.3.0]non-3-ene (195b) (1.68 g, 6.0 mmol) was dissolved in THF (45 mL). Concentrated hydrochloric acid (2 mL) was added. After stirring at room temperature for 30 min, the reaction was diluted with ethyl ether; the organic layer was washed with water (7x10 mL), dried (Na₂SO₄) and the solvent removed in vacuo. The crude product (1.59 g) was used without further purification. 196: Rf = 0.6 (hexane/ether, 95:5); bp (Kugelrohr temp.) 150-160 °C (0.05 mmHg); IR (neat) 2950, 2875, 1645, 1610 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.74 (s, 3H), 0.82 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 1.28 (t, 3H, J=7.0 Hz), 1.20-1.40 (m, 3H), 1.45-1.65 (m, 3H), 1.70-1.85 (m, 1H), 1.90-2.10 (m, 2H), 2.23-2.55 (m, 2H), 4.18 (q, 2H, J=7.0
(1R,6S,7S)-7-Isopropyl-1-methylbicyclo[4.3.0]nonan-4-one (145).

Lithium iodide (3.4 g, 30 mmol) was dissolved in DMF (30 mL) and a solution of (1R,6S,7S)-3-carbethoxy-4-hydroxy-1-methyl-7-isopropyl bicyclo[4.3.0]nonan-3-ene (196) (1.59 g, 6.0 mmol) in DMF (5 mL) was added dropwise. The reaction was heated under reflux for 2 h, quenched with 3N HCl (10 mL), and diluted with ethyl ether (20 mL). The aqueous layer was extracted with ethyl ether (3x15 mL), the combined organic layer washed with brine (3x15 mL), dried (Na2SO4), and the solvent removed in vacuo. The crude product was distilled using a Kugelrohr apparatus at 120 °C (0.025 mmHg) to yield 1.15 g (99%) of ketone 145: Rf = 0.20 (hexane/ether = 95:5); bp (Kugelrohr temp.) 120 °C (0.025 mmHg); [α]D -62.5° (c 1.0, MeOH); 1H-NMR (CDCl3) δ 0.78 (d, 3H, J=7.0 Hz), 0.86 (d, 3H, J=7.0 Hz), 0.98 (s, 3H), 1.18 (m, 2H), 1.40-1.70 (m, 5H), 1.75-1.90 (m, 2H), 2.13 (t, 1H, J=14.0 Hz), 2.25-2.48 (m, 3H).

E and Z (1R,6S,7S)-4-(1-Bromo-1-carbethoxymethylidene)-1-methyl-7-isopropylbicyclo[4.3.0]nonane (180). Ethyl trimethyl-silylacetate (1.93 g, 12.06 mmol) in THF (10 mL), was added dropwise to a solution of lithium dicyclohexylamide prepared from dicyclohexylamine (2.19 g, 12.06 mmol) and n-butyllithium (4.8 mL, 12.06 mmol; 2.5 M in hexane) in THF (10 mL) at -78 °C. After stirring for 30 min, a solution of (1R,6S,7S)-7-isopropyl-1-methylbicyclo[4.3.0]nonan-
4-one (145) (1.17 g, 6.03 mmol) in THF (10 mL) was added dropwise. The reaction mixture was then slowly warmed to room temperature and, after one hour, quenched with cold 3N HCl (10 mL) and ethyl ether (20 mL). The organic layer was washed with 3N HCl (5 mL) and the combined aqueous layer extracted with ethyl ether (3x8 mL). The organic layers were combined, washed with brine (3x20 mL), dried (Na₂SO₄) and concentrated in vacuo. The crude product was filtered through a plug of silica gel to yield 1.19 g (75%) of α, β-unsaturated esters. These esters were dissolved in CCl₄ (20 mL), cooled to 0 °C, and a solution of bromine (1.08 g, 6.8 mmol) in CCl₄ (3 mL) was added dropwise at 0 °C. The solvent was removed and 1,8-Diazaacyclo[5.4.0]undec-7-ene (0.76 g, 5 mmol) was added dropwise at 0 °C. The reaction was quenched with cold 3N HCl (5 mL) and ethyl ether (10 mL). The aqueous layer was extracted with ethyl ether (3x10 mL). The combined organic layer was washed with brine (3x10 mL), dried (Na₂SO₄) and evaporated under vacuo. The crude product was filtered through a plug of silica gel to yield 1.45 g (70 % from ketone 145) of a 3:1 (more polar:less polar) mixture of E and Z bromides. **180-less polar:** Rf = 0.57 (hexane/ether = 95:5); bp (Kugelrohr temp.) 200 °C (0.025 mmHg); IR (neat) 2950, 2810, 1720 cm⁻¹; **¹H-NMR** (CDCl₃) δ 0.78 (d, 3H, J=7.0 Hz), 0.85 (s, 3H), 0.88 (d, 3H, J=7.0 Hz), 1.00-1.20 (m, 2H), 1.30 (t, 3H, J=7.0 Hz), 1.20-1.80 (m, 7H), 1.85 (t, 1H, J=13.9 Hz), 2.20 (dt, 1H, J=13.9, 5.8 Hz), 2.93 (m, 2H), 4.25 (q, 2H, J=7.0 Hz); **¹³C-NMR** (CDCl₃) δ 14.1 (CH₃), 17.3 (CH₃), 18.0 (CH₃), 21.7 (CH₃), 24.4 (CH₂), 29.5 (CH), 30.8 (CH₂), 31.9 (CH₂), 38.5 (CH₂), 41.3 (C), 46.1 (CH), 50.6 (CH), 61.7 (CH₂), 106.0 (C), 149.9 (C), 164.8 (C). **180-more polar:** Rf = 0.47 (hexane/ether = 95:5); bp (Kugelrohr temp.) 200 °C (0.025 mmHg); IR (neat) 2950, 2810, 1720 cm⁻¹; **¹H-NMR** (CDCl₃) δ 0.80 (d, 3H, J=7.0 Hz), 0.84 (s, 3H), 0.90 (d, 3H, J=7.0 Hz), 1.00-1.20 (m, 2H), 1.20-1.35 (m, 1H), 1.30 (t, 3H, J= 6.0 Hz), 1.35-1.78 (m, 6H), 1.82 (t, 1H,
J=15.0 Hz), 2.25 (dt, 1H, J=15.0, 6.0 Hz), 2.90 (bd, 1H, J=15.0 Hz), 3.00 (bd, 1H, J=15.0 Hz), 4.25 (q, 2H, 6.0 Hz); $^{13}$C-NMR (CDCl$_3$) $\delta$ 14.0 (CH$_3$), 17.5 (CH$_3$), 18.3 (CH$_3$), 21.7 (CH$_3$), 24.4 (CH$_2$), 28.7 (CH$_2$), 29.7 (CH), 34.6 (CH$_2$), 38.4 (CH$_2$), 39.0 (CH$_2$), 41.4 (C), 46.4 (CH), 50.3 (CH), 61.7 (CH$_2$), 106.0 (C), 150.5 (C), 164.8 (C).

$\text{1S-(1α,3β,6α,7α)-2-Carbethoxy-3,7-dimethyl-2-{4-[(1β,6α,7α)-1-methyl-7-isopropylbicyclo[4.3.0]non-3-enyl]}-4-oxobicyclo[4.3.0]01,3]}$ nonane, $\text{179}-\text{exo}$ and $\text{179}-\text{endo}$ isomers. Lithium diisopropylamide, prepared from diisopropylamine (77.0 mg, 0.76 mmol) and n-butyllithium (0.30 mL, 0.76 mmol, 2.5 M in hexane) was dissolved in THF (3 mL) and cooled to -78 °C. I—IMPA (149 mg, 0.83 mmol) was added, and the mixture stirred for 20 min. A solution of E and Z (1R,6S,7S)-4-(1-bromo-1-carbethoxymethyliden)-1-methyl-7-isopropylbicyclo[4.3.0] nonane (180) (237.1 mg, 0.69 mmol) in THF (3 mL) was then added dropwise via cannula. Stirring was continued at -78 °C for 1.5 h. Enone 144 (103.7 mg, 0.69 mmol) in THF (2 mL) was added, and the reaction quenched at -78 °C after 0.5 h with saturated NH$_4$Cl solution (4 mL) and ethyl ether (6 mL). The organic layer was washed with 3N HCl (3 mL), and the combined aqueous layer was extracted with ethyl ether (3 x 5 mL). The organic layer was then washed with brine (3 x 4 mL), dried (Na$_2$SO$_4$) and the solvents removed in vacuo to yield vinylcyclopropanes $\text{179}-\text{exo}$ and $\text{179}-\text{endo}$ (endo:exo = 3:2) that were separated by column chromatography (hexane/ether, 4:1) to give 63.4 mg (22%) of exo isomer and 97.4 mg (34%) of the endo isomer. $\text{179}-\text{exo}$: $R_f = 0.47$ (hexane/ether, 4:1); IR (neat) 2950, 2870, 1720 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 0.70 (s, 3H), 0.80 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=7.0 Hz), 1.15 (s, 3H), 1.20 (t, 3H, J=7.0 Hz), 1.05-2.30 (m, 18H), 2.39 (m, 1H), 4.08(m, 2H), 5.57
(bs, 1H); $^{13}$C-NMR (CDCl$_3$) $\delta$ 9.1 (CH$_3$), 14.2 (CH$_3$), 17.8 (CH$_3$, double intensity), 18.7 (CH$_3$), 21.6 (CH$_3$), 24.8 (CH$_2$, double intensity), 30.5 (CH), 33.8 (CH$_2$, double intensity), 38.9 (CH$_2$), 40.3 (C), 41.1 (CH$_2$, double intensity), 41.1 (CH), 42.3 (C), 45.6 (C), 46.9 (CH), 47.3 (CH, double intensity), 53.9 (C), 60.7 (CH$_2$), 128.9 (CH), 132.2 (C), 169.1 (C), 215.7 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 412.2 (30, M$^+$), 384.3 (8), 339.3 (10), 315.2 (9), 159.1 (7), 123.1 (22). Calcd. for C$_{27}$H$_{40}$O$_3$: 412.2977. Found: 412.2976. 179-endo: R$_f$ = 0.19 (hexane/ether, 4:1); IR (neat) 2970, 2890, 1730, 1710 cm$^{-1}$; $^1$H-NMR (CDCl$_3$) $\delta$ 0.65 (s, 3H), 0.79 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 1.00 (d, 3H, J=7.0 Hz), 1.02 (s, 3H), 1.20 (t, 3H, J=7.0 Hz), 1.10-1.88 (m, 10H), 1.88-2.28 (m, 9H), 4.09 (q, 2H, J=7.0 Hz), 5.80 (bs, 1H); $^{13}$C-NMR (CDCl$_3$) $\delta$ 9.8 (CH$_3$), 14.0 (CH$_3$), 18.3 (CH$_3$), 18.7 (CH$_3$, double intensity), 21.7 (CH$_3$), 24.7 (CH$_2$, double intensity), 30.4 (CH), 30.7 (CH$_2$), 33.3 (CH$_2$), 38.7 (CH$_2$), 39.9 (C), 41.0 (CH$_2$), 41.8 (CH$_2$), 42.1 (CH), 42.3 (C), 44.5 (C), 47.1 (CH, double intensity), 47.2 (CH), 52.5 (C), 61.1 (CH$_2$), 131.0 (CH), 131.1 (C), 169.9 (C), 214.8 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 412 (100, M$^+$), 384 (18), 366 (12), 339 (35), 159 (15), 123 (30) 95 (35), 55 (62). Calcd. for C$_{27}$H$_{40}$O$_3$: 412.2977. Found: 412.2991.

Ethyl 3R-(3$\alpha$,3$\alpha$,5$\alpha$,5$\beta$,6$\alpha$,$\beta$,9$\alpha$,9$\alpha$,a$_{11}$a$_{S\alpha}$)-5-Oxo-2,3,3a,4,5,5a, 5b,6,6a,7,8,9,9a,10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate 178 and 5b epimer 198. Vinylcyclopropane 179 (55.6 mg, 0.14 mmol) was evaporated (10$^{-4}$ mmHg) through a horizontally situated Vycor tube (41 cm, 5 mm i. d.) which was heated to 585 °C after being thoroghly cleaned (nitric acid, 50% KOH) and preheated with a slurry of PbCO$_3$. The apparatus was rinsed with CH$_2$Cl$_2$; the solution was filtered to remove inorganic
impurities, and the solvent evaporated to yield 44.5 mg of a 1:1 mixture (75% by GC) of 178 and 198. This mixture was separated by chromatography on silica gel (hexane/ether, 9:1) to give 13.3 mg (24%) of 178 and 15.2 mg (27%) of 198. 178: RF = 0.58 (hexane/ether, 4:1); [α]D +75º (c 0.27, CDCl3); IR (neat) 2930, 2850, 1725, 1700, 1625 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.78 (d, 3H, J=7.0 Hz), 0.80 (s, 3H), 0.88 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=7.0 Hz), 1.05 (s, 3H), 1.30 (t, 3H, J=7.0 Hz), 1.15-2.08 (m, 15H), 2.20 (m, 2H), 2.42 (dd, 1H, J₁=12.0, J₂=7.2 Hz), 2.55 (dd, 1H, J₁=12.0, J₂=4.8 Hz), 3.38 (dd, 1H, J₁=15.0, J₂=4.8 Hz), 4.21 (dq, 2H, J₁=7.0, J₂=3.0 Hz); ¹³C-NMR (CDCl₃) δ 14.3 (CH₃), 17.3 (CH₃), 18.2 (CH₃), 18.3 (CH₃), 21.8 (CH₃), 22.1 (CH₃), 24.6 (CH₂), 27.9 (CH₂), 29.7 (CH), 30.8 (CH₂), 34.4 (CH₂), 38.5 (CH₂), 40.6 (CH), 41.8 (CH₂, double intensity), 42.1 (C), 46.3 (CH), 50.4 (CH, double intensity), 55.2 (CH), 56.7 (C), 59.7 (CH₂), 69.2 (C), 129.4 (C), 156.5 (C), 165.8 (C), 221.6 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 412 (30, M⁺), 384 (15), 366 (5), 339 (20), 223 (9), 149.(100), 123 (50), 57 (45). Calcd. for C₂₇H₄₀O₃: 412.2977. Found: 412.2931. 198: RF = 0.47 (hexane/ether, 4:1); IR (neat) 2930, 2840, 1725, 1700 1625 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.68 (s, 3H), 0.82 (d, 3H, J=6.0 Hz), 0.85 (d, 3H, J=6.0 Hz), 0.96 (s, 3H), 1.02 (d, 3H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz), 1.00-1.94 (m, 12H), 1.94-2.70 (m, 7H), 3.12 (t, 1H, J=9.0 Hz), 4.20(m, 2H); ¹³C-NMR (CDCl₃) δ 14.3 (CH₃), 16.1 (CH₃), 18.9 (CH₃), 19.2 (CH₃), 21.5 (CH₃), 23.0 (CH₃), 26.2 (CH₂), 30.9 (CH), 31.2 (CH₂), 32.1 (CH₂), 35.2 (CH₂), 39.2 (CH₂), 39.4 (CH₂), 40.3 (CH₂), 42.7 (C), 43.3 (CH), 45.4 (CH), 47.3 (CH), 49.9 (CH), 50.2 (CH), 58.4 (C), 59.5 (CH₂), 68.4 (C), 131.1 (C), 163.0 (C), 165.0 (C), 226.1 (C); Mass Spectrum (70 eV, m/e (rel. int.)) 412.3 (25, M⁺), 338.3 (100), 296.2 (42), 271.2.(40), 123.1 (72), 95.1 (50). Calcd. for C₂₇H₄₀O₃: 412.2977. Found: 412.2972.
Ethyl 3R-(3α,3αα,5β,5βα,6αβ,9α,9αα,11αS*)-2,3,3α,4,5,5α,5β,6,6α,7,8,9a,10-tetradecahydro-3,5α,6α-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate (101). Pentacyclic ketone 178 (27.5 mg, 0.067 mmol) was dissolved in MeOH (1 mL) and NaBH₄ (10 mg, 0.27 mmol) was added at room temperature. The reaction was stirred for 20 min, quenched carefully with water (0.5 mL) and ethyl ether (1 mL), and acidified with 3N HCl (0.5 mL). The aqueous layer was extracted with ethyl ether (3x0.5 mL); the combined organic layer was washed with brine (3x0.5 mL), dried (Na₂SO₄), and the solvents were evaporated in vacuo to yield a mixture of alcohols (27 mg, 98%). 122: Rf = 0.48 and 0.28 (hexane/ether, 4:1); IR (neat) 3410, 2930, 2850, 1690, 1620 cm⁻¹. The alcohols were dissolved in 1 mL of THF, NaH (30 mg) (previously washed with 3 mL of THF) and one crystal of imidazole was added. The mixture was refluxed for 1 h, then CS₂ (1 mL) was added, and the mixture was refluxed for 30 min. Finally methyl iodide (1 mL) was added, and the mixture refluxed for 30 min. The reaction was quenched very carefully with water (0.5 mL) and CH₂Cl₂ (1 mL). The aqueous layer was extracted with CH₂Cl₂ (3x1 mL). The organic layer was washed with brine (3x1 mL), dried (Na₂SO₄), and the solvents removed in vacuo. The crude xanthates were filtered through a plug of silica gel using hexane/ether (9:1) as the eluant. Rf = 0.77 (hexane/ether, 9:1). The xanthates were dissolved in toluene (1 mL), and the mixture was heated to reflux. n-Tributyltinhydride (27 mL) dissolved in 1 mL of toluene was added in portions (4x0.25 mL of solution); then AIBN (2 mg), and the mixture refluxed for 20 min. The solvent was evaporated in vacuo and the crude mixture chromatographed in hexane to give 12.4 mg (47% from alcohols 199) of 201: Rf = 0.61 (hexane/ether, 95:5); [α]D -84° (c 0.17, CDCl₃); IR (neat) 2920, 2850, 1700, 1620 cm⁻¹; ¹H-NMR...
(CDCl₃) δ 0.80 (d, 3H, J=7.0 Hz), 0.81 (s, 3H), 0.88 (d, 3H, J=6.0 Hz), 0.98 (d, 3H, J=6.0 Hz), 1.00 (s, 3H), 1.05-1.15 (m, 2H), 1.30 (t, 3H, J=7.0 Hz), 1.15-1.50 (m, 6H), 1.50-1.90 (m, 11H), 2.28 (dd, 1H, J₁=15.6, J₂=6.0 Hz), 2.45 (dd, 1H, J₁=12.0, J₂=6.0 Hz), 3.25 (dd, 1H, J₁=15.6, J₂=4.8 Hz), 4.15(q, 2H, J=7.0 Hz); ¹³C-NMR (CDCl₃) δ 13.6 (CH₃), 17.7 (CH₃), 18.4 (CH₃), 20.0 (CH₃), 21.8 (CH₃, double intensity), 24.7 (CH₂), 28.0 (CH₂), 29.8 (CH), 30.9 (CH₂, double intensity), 36.2 (CH₂), 38.2 (CH₂), 38.8 (CH₂), 39.1 (CH₂), 42.1 (C), 43.7 (CH), 46.7 (CH), 49.6 (CH), 52.0 (CH), 52.6 (C), 56.9 (CH), 59.4 (CH₂), 71.8 (C), 133.5 (C), 153.5 (C), 167.2 (C). Mass Spectrum (70 eV, m/e (rel. int.)) 398 (12, M⁺), 369 (6), 325 (100), 231 (15), 221 (20), 188 (20), 177 (20), 158 (80). Calcd. for C₂₇H₄₂O₂: 398.3184. Found: 398.3149.

Ethyl 3R-(3α,3αa,5αb,5βa,6aβ,9α,9αa,11αS*)-2,3,3α,4,5,5α,5β,6,6a,7,8,9α,10-tetradecahydro-3,5α,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate (202). Using a procedure identical to that for the preparation of 201, pentacyclic ketone epimer 198 (25.3 mg, 0.06 mmol) was converted to retigeranic acid ethyl ester epimer in 44% overall yield. 202: Rf = 0.61 (hexane/ether, 95:5); IR (neat) 2940, 2860, 1705, 1630 cm⁻¹; ¹H-NMR (CDCl₃) δ 0.69 (s, 3H), 0.82 (d, 3H, J=7.0 Hz), 0.88 (d, 3H, J=7.0 Hz), 0.93 (s, 3H), 0.98 (d, 3H, J=7.0 Hz), 1.30 (t, 3H, J=7.0 Hz), 1.00-1.85 (m, 18H), 2.10 (m, 1H), 2.55 (m, 2H), 2.75 (t, 1H, J=8.7 Hz), 4.19 (m, 2H); ¹³C-NMR (CDCl₃) δ 13.6 (CH₃), 14.4 (CH₃), 18.9 (CH₃), 19.2 (CH₃), 21.6 (CH₃), 26.2 (CH₂), 30.0 (CH₂), 31.0 (CH₂, double intensity), 33.1 (CH), 36.7 (CH₂), 38.2 (CH₂, double intensity), 40.4 (CH₂), 42.6 (C), 42.8 (CH), 45.6 (CH), 47.6 (CH), 51.7 (CH), 52.6 (C), 58.0 (CH), 58.0 (CH₂), 71.3 (C), 134.3 (C), 150.0 (C), 167.1 (C); Mass Spectrum (70
eV, m/e (rel. int.)) 398 (20, M+), 384 (5), 369 (4), 325 (100), 135 (50), 57 (40). 
Calcd. for C\textsubscript{27}H\textsubscript{42}O\textsubscript{2}: 398.3184. Found: 398.3087.

Retigeranic acid (1). Retigeranic acid ethyl ester (201) (6.0 mg, 1.5x10^{-2} mmol) was dissolved in EtOH (1 mL) and 35 μL of a 5% aqueous KOH solution was added. The mixture was refluxed for 2 h, then the solvent was removed in vacuo, and the residue dissolved in 0.5 mL of ethyl ether and 0.5 mL of 5% HCl. The aqueous layer was extracted with ether (2x0.5 mL). The combined organic layer was washed with brine, dried (Na\textsubscript{2}SO\textsubscript{4}) and concentrated. The residue was purified by preparative TLC to give 2.5 mg (45%) of retigeranic acid (1) identical in spectral and chromatographic properties with the natural sample. (We thank Profs. Paquette and Shibata for providing \textsuperscript{1}H-NMR and natural sample respectively.) 1: R\textsubscript{f} = 0.54 (hexane/EtOAc, 4:1); [\alpha]D - 98° (c 0.125, CDCl\textsubscript{3}). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}) \delta 0.78 (d, 3H, J=6.6 Hz), 0.83 (s, 3H), 0.88 (d, 3H, J=6.7 Hz), 0.99 (s, 3H), 0.99 (d, 3H, J=6.2 Hz), 1.00-1.92 (m, 19 H), 2.37 (dd, 1H, J\textsubscript{1}=14.6, J\textsubscript{2}=6.9 Hz), 2.47 (dd, 1H, J\textsubscript{1}=11.5, J\textsubscript{2}=6.3 Hz), 3.33 (dd, 1H, J\textsubscript{1}=16.0, J\textsubscript{2}=3.5 Hz), 8.69 (s, 1H).

Epimerization of 202 to 201. Epimer 202 (1.5 mg, 3.8x10^{-3} mmol) was dissolved in CCl\textsubscript{4} (0.5 mL) and N-bromosuccinimide (2 mg, 11.3x10^{-3} mmol) and benzoylperoxide (less than one crystal) were added. The reaction mixture was refluxed for 30 min, it was then filtered through a plug of cotton, and the solvent removed. Absence of the starting epimer was demonstrated by GC analysis. The residue was dissolved in toluene (0.5 mL), and a solution of n-tributyltinhydride in toluene (36 μL of a 100 mg/mL solution, 12.4x10^{-3} mmol) was added dropwise. The reaction was refluxed for 20 min, then the toluene was removed in vacuo. The crude reaction mixture
was purified by preparative TLC (hexane, 3 elutions). The compound obtained was co-
injected with epimer 201, and it had the same retention time. $^1$H-NMR showed the same
pattern for the C-5b proton, but at 3.0 ppm instead.
V. REFERENCES


31. Hashimoto, H.; Tsuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. 


36. Hudlicky, T.; Rulin, F.; Lovelace, T. C.; Reed, J. "Synthesis of Natural Products 
   Containing Five-Membered Rings. An Evolution of General Methodology", in 


38. [4+1] approach: (a) ref. 26; (b) Danheiser, R. L.; Martínez-Dávila, C.; Auchus, R. 
   Martínez-Dávila, C.; Morin, J. M. *J. Org. Chem.* **1980**, *45*, 1340; (d) Barrière, 
   F.; Barrière, J.-C.; Barton, D. H. R.; Cleophax, J.; Gateaux-Olesker, A.; Géro, S. 
   Maqvi, S. M. *Organic Reactions* **1985**, *33*, 247; (f) ref 46; (g) ref. 36; (h) ref. 56.

   4892; (b) Hashimoto, H.; Furuichi, K.; Miwa, T. *J. Chem. Soc., Chem. 


41. Evans, D. A. "Consonant and Dissonant Relationships: An Organizational Model 


88. For reviews on intramolecular carbon-hydrogen insertion reactions of carbenes see:


102. For reviews see: (a) Trost, B. M. *Tetrahedron* 1977, 33, 2615; (b) Trost, B. M. *Acc. Chem. Res.* 1980, 13, 385; (c) Trost, B. M.; Verhoeven, T. R.;


122. see references 126-134.


156. We want thank Graciela Barbieri for running this experiments.

157. An investigation of optical induction utilizing different auxiliary groups is being performed at the present time.


163. (a) Johnson, A. W. "Ylid Chemistry", Academic Press, New York, 1966; (b) Bestmann, H. J.; Vostrowsky, O. Top. Curr. Chem. 1983, 109, 85; (c) Pommer,


172. We thank Prof. Weinreb and coworkers (Penn. State Univ.) for performing this experiment.


VI. APPENDIX

SELECTED SPECTRA

1. 1S-(1α,3β,6α,7α)-2-Carbethoxy-2-cyclohexenyl-3,7-dimethyl-4-oxo bicyclo[4.3.0]nonane, 183-endo.
   \( ^1\)H-NMR ................................................................. 129
   \( ^13\)C-NMR, MS ......................................................... 130

2. 1S-(1α,3β,6α,7α)-2-Carbethoxy-2-cyclohexenyl-3,7-dimethyl-4-oxo bicyclo[4.3.0]nonane, 183-exo.
   \( ^1\)H-NMR ................................................................. 131
   \( ^13\)C-NMR, MS ......................................................... 132

3. (R)-7,7-Dimethoxy-5-isopropylheptan-2-one (188).
   \( ^1\)H-NMR ................................................................. 133
   \( ^13\)C-NMR, IR, MS ..................................................... 134

4. (R)-6-Oxo-3-isopropylheptanal (190).
   \( ^1\)H-NMR ................................................................. 135

5. (S)-3-Isopropyl-6-oxo-1-piperidinohept-1-ene (191a)
   \( ^1\)H-NMR ................................................................. 136

   \( ^1\)H-NMR ................................................................. 137
   \( ^13\)C-NMR of mixture and pure E isomer ......................... 138
   IR, MS ................................................................. 139

7. (S)-5-Oxo-2-isopropylhexanal (189)
   \( ^1\)H-NMR ................................................................. 140
8. Ethyl (S)-3-methoxy-9-oxo-6-isopropyl-2,4-decadienoate (194).

\[ ^{1}H\text{-NMR} \]

\[ ^{13}C\text{-NMR, IR, MS} \]

9. Ethyl (S)-3-methoxy-9-methyl-6-isopropyl-2,4,9-decatrionate (147).

\[ ^{1}H\text{-NMR} \]

10. (1R,6S,7S)-3-Carbethoxy-4-methoxy-1-methyl-7-isopropylbicyclo[4.3.0]non-3-ene 195a.

\[ ^{1}H\text{-NMR} \]

\[ ^{13}C\text{-NMR, IR} \]

11. (1R,6S,7S)-3-Carbethoxy-4-hydroxy-1-methyl-7-isopropylbicyclo[4.3.0]non-3-ene (196).

\[ ^{1}H\text{-NMR} \]

\[ ^{13}C\text{-NMR, IR, MS} \]

12. (1R,6S,7S)-7-Isopropyl-1-methylbicyclo[4.3.0]nonan-4-one (145).

\[ ^{1}H\text{-NMR} \]


\[ ^{1}H\text{-NMR} \]

\[ ^{13}C\text{-NMR, IR, MS} \]

14. 1S-(1α,3β,6α,7α)-2-Carbethoxy-3,7-dimethyl-2-{4-[[1β,6α,7α]-1-methyl-7-isopropyl bicyclo[4.3.0]non-3-enyl]-4-oxobicyclo[4.3.0.0^{1,3}] nonane, 179-endo.

\[ ^{1}H\text{-NMR} \]
15. 1S-(1α,3β,6α,7α)-2-Carbethoxy-3,7-dimethyl-2-{4-[(1β,6α,7α)-1-methyl-7-isopropyl bicyclo[4.3.0]non-3-enyl]-4-oxobicyclo[4.3.0.01,3]nonane, 179-exo.

1H-NMR ............................................................................. 156

13C-NMR, IR, MS ....................................................................... 157

16. Ethyl 3R-(3α,3αα,5αβ,5bβ,6αβ,9α,9αα,11αS*)-5-Oxo-2,3,3a,4,5,5a,5b,6,6a,7, 8,9,9a,10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate 178.

1H-NMR ............................................................................. 158

13C-NMR, IR, MS ....................................................................... 159

17. Ethyl 3R-(3α,3αα,5αβ,5bβ,6αβ,9α,9αα,11αS*)-5-Oxo-2,3,3a,4,5,5a,5b,6,6a,7, 8,9,9a,10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate 198.

1H-NMR ............................................................................. 160

13C-NMR, IR, MS ....................................................................... 161

18. Ethyl 3R-(3α,3αα,5αβ,5bβ,6αβ,9α,9αα,11αS*)-2,3,3a,4,5,5a,5b,6,6a,7,8,9,9a, 10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate (201).

1H-NMR ............................................................................. 162

13C-NMR, IR, MS ....................................................................... 163

19. Ethyl 3R-(3α,3αα,5αβ,5bα,6αβ,9α,9αα,11αS*)-2,3,3a,4,5,5a,5b,6,6a,7,8,9,9a, 10-tetradecahydro-3,5a,6a-trimethyl-9-isopropyl-1H-pentaleno[1,6a-a]-s-indacene-11-carboxylate (202).

1H-NMR ............................................................................. 164

13C-NMR, IR, MS ....................................................................... 165
20. Retigeranic acid (1).

$^1$H-NMR .......................................................... 166


$^1$H-NMR .......................................................... 167
180 less polar
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