TOTAL SYNTHESIS OF (+)-LONGIFOLENE BY AN INTRAMOLECULAR DIELS - ALDER STRATEGY

CENTRE FOR NEWFOUNDLAND STUDIES

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BO LEI, B.Sc.
TOTAL SYNTHESIS OF (+)-LONGIFOLENE BY
AN INTRAMOLECULAR DIELS-ALDER STRATEGY

By

© Bo Lei, B.Sc.

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Doctor of Philosophy

Department of Chemistry
Memorial University of Newfoundland
December 1983

St. John's

Newfoundland
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Department of Chemistry
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December 1989

St. John’s
Newfoundland
TO MY WIFE AND PARENTS
ABSTRACT

The total synthesis of the sesquiterpene (+)-longifolene by an intramolecular Diels-Alder cycloaddition strategy is described. The route utilized an addition initiated ring closure involving methyllithium and epoxyfulvene 80. The cyclopentadienyl anion 81 that resulted cyclized in an exo-tet manner to generate a substituted spiro[2.4]hepta-4,6-diene 82 in which the cyclopropane ring blocked the 1,5-sigmatropic rearrangement and acted as a latent methylene group. Oxidation with active MnO₂ afforded cyclopropyl aldehyde 83, which was condensed with the anion derived from methyl 3,3-dimethylacrylate 97 in the presence of cadmium chloride. These conditions resulted in selective γ substitution and were a consequence of isomerization to the thermodynamically most favored product. This procedure was shown to be general for related systems.

The resulting alcohol-protected triene 100 was cyclized directly to tetracyclic adduct 103 under thermal conditions in a microwave oven. Modification of the functional groups gave cyclopropyl ketone 118, which opened to the longifolene ring system by lithium/ammonia reduction.

The route to optically active material followed a different pathway which involved the Lewis acid catalyzed addition of methanol to the optically active spirocyclopropane-cyclopentadiene 134. The product 137 was capable of rapid sigmatropic rearrangement, which in principle could give rise to several different Diels-Alder adducts. In practice, because of the constrained nature of the cyclic dienophile, the lowest energy path led to the adduct 138 with the tricyclic nucleus required for (+)-longifolene. This was the only product isolated and represented the first successful synthesis of a cycloheptane directly from a cyclopentadiene in a
carbocyclic precursor. In order to complete the synthesis the lactone 138 was reduced and the primary alcohol converted selectively to its acetate 144. Sequential removal of the secondary hydroxyl functions was accomplished under free radical conditions. Pyrolysis of the acetate 146 at 525°C provided (+)-longifolene.
ACKNOWLEDGMENTS

So many people have supported me throughout my graduate career, it is impossible to mention them all by name.

It is a privilege for me to thank Professor Alex G. Fallis for his outstanding supervision, constant enthusiasm, encouragement, and financial support throughout the course of this research project. I thank him not only for teaching me chemistry, but also for helping me to develop an effective scientific work ethic. His assistance and patience in the preparation of this thesis are gratefully acknowledged.

I wish to extend special thanks to Dr. Paul Slowery, Dr. William Brown, Dr. Veejendra Yadav, Dr. Gervais Bérubé, and Dr. John Macaulay for their friendship, unselfish help, and invaluable suggestions, which made my participation in our research group enjoyable. I am also grateful to Mrs. Nola Lee and Mr. Isaac Kennedy for their friendship and assistance, especially during my time at the University of Ottawa.

I would like to thank Dr. J. Burnell for his support, our many stimulating discussions, and his superb teaching of modern NMR spectroscopy.

I am also thankful to all members of the teaching and support staff in the Department of Chemistry at the Memorial University of Newfoundland, especially Dr. J. Bridson for his assistance in the last stage of my graduate studies, Dr. C. Jablonski for NMR service, and Dr. B. Gregory for mass spectrometry service.

I would like to thank Dr. H. Dettman, Mr. R. Capoor, and Dr. C. Kazakoff in the Department of Chemistry at the University of Ottawa for their excellent NMR and mass spectrometry service.
I wish to thank the Memorial University of Newfoundland for their fellowship support, and the University of Ottawa for allowing me to complete this research in the Department of Chemistry.

Finally, I wish to express my deepest appreciation for the understanding, the patience, encouragement, and love provided by my wife, Chen Naijian, my mother, Zhu Yuanhe, and my father, Lei Yongsu. With my love, I dedicate this thesis to them.
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6.7 Conversion of Lactone (138) to (+)-Longifolene

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Part III Experimental

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<td>Ac</td>
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<tr>
<td>AIBN</td>
<td>2,2'-azobisisobutyronitrile</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>n-Bu</td>
<td>n-butyl</td>
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<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
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<tr>
<td>ca.</td>
<td>about, approximately</td>
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<td>cf.</td>
<td>compare</td>
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<td>cm</td>
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<tr>
<td>m-CPBA</td>
<td>m-chloroperoxybenzoic acid</td>
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<tr>
<td>Cy</td>
<td>cyclohexyl</td>
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<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhanced polarization transfer</td>
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<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
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<td>dec.</td>
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<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
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<td>DIPT</td>
<td>diisopropyl tartrate</td>
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<td>DMAP</td>
<td>N,N-dimethyaminopyridine</td>
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<td>DME</td>
<td>1,2-dimethoxyethane (glyme)</td>
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<td>DMF</td>
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<td>HMPA</td>
<td>hexamethylphosphoramide</td>
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<tr>
<td>IR</td>
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<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
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<td>lithium diisopropylamide</td>
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<td>M+</td>
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<td>multiplet</td>
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<td>mp</td>
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<td>nmr (NMR)</td>
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<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<td>Ph</td>
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<td>ppm</td>
<td>parts per million</td>
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<td>psi</td>
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<tr>
<td>q</td>
<td>quartet</td>
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<tr>
<td>RT (R.T.)</td>
<td>room temperature (about 22°C)</td>
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<td>s</td>
<td>singlet</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<td>tetra-n-butylammonium fluoride</td>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TMEDA</td>
<td>N,N,N,N'-tetramethylethylenediamine</td>
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PART I
INTRODUCTION
CHAPTER 1 BACKGROUND

1.1 Structure Elucidation

In 1920 Simonsen demonstrated that the tricyclic sesquiterpene, (+)-longifolene, occurred in the essential oil of *Pinus longifolia*. The (+)-enantiomer is known to occur in higher plants, mainly Gymnospermae, while its antipode has been found in liverworts.

The structure of longifolene was first elucidated in 1923 by Simonsen *et al.* At that time their identification was limited to the tricyclic ring system, vinyl group, tertiary methyl group and geminal dimethyl groups established chemically by degradation. Structures 1 and 2 (Scheme 1) were suggested for longifolene according to its molecular formula, $C_{15}H_{24}$, the isoprene rule and the results of these chemical investigations.

![Scheme 1](image)

The correct structure of longifolene, long an unsolved and complicated chemical problem, was revealed in 1953 by Ourisson and Naffa on the basis of an X-ray crystallographic study of longifolene hydrochloride by Moffet and
and the chemical evidence that upon treatment with hydrogen chloride, longifolene 3 undergoes a Wagner-Meerwein rearrangement to longifolene hydrochloride 6 (Scheme 2).

Scheme 2

Further studies on the molecular rotation of derivatives of longifolene suggested that the proposed structure 3 also represented the absolute configuration of (+)-longifolene. This has since been confirmed by several total syntheses.
1.2 Biosynthesis

It has been established that the actual isoprene unit utilized in the terpene biosynthesis is mevalonic acid 7 (or an appropriately activated simple derivative),\textsuperscript{9,10,11} three of these self-condense with decarboxylation to farnesol 8a and 8b, the simplest acyclic sesquiterpene (Scheme 3).

\begin{center}
\begin{tikzpicture}
    \node[draw,shape=circle,fill=white] (a) at (0,0) {\text{OH}};
    \node[draw,shape=circle,fill=white] (b) at (0,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (c) at (0,-4) {\text{COOH}};
    \node[draw,shape=circle,fill=white] (d) at (0,-6) {\text{OH}};
    \node[draw,shape=circle,fill=white] (e) at (2,0) {\text{COOH}};
    \node[draw,shape=circle,fill=white] (f) at (2,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (g) at (2,-4) {\text{OH}};
    \node[draw,shape=circle,fill=white] (h) at (2,-6) {\text{OH}};
    \node[draw,shape=circle,fill=white] (i) at (4,0) {\text{OH}};
    \node[draw,shape=circle,fill=white] (j) at (4,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (k) at (4,-4) {\text{OH}};
    \node[draw,shape=circle,fill=white] (l) at (4,-6) {\text{OH}};
    \node[draw,shape=circle,fill=white] (m) at (6,0) {\text{OH}};
    \node[draw,shape=circle,fill=white] (n) at (6,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (o) at (6,-4) {\text{OH}};
    \node[draw,shape=circle,fill=white] (p) at (6,-6) {\text{OH}};
    \node[draw,shape=circle,fill=white] (q) at (8,0) {\text{OH}};
    \node[draw,shape=circle,fill=white] (r) at (8,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (s) at (8,-4) {\text{OH}};
    \node[draw,shape=circle,fill=white] (t) at (8,-6) {\text{OH}};
    \node[draw,shape=circle,fill=white] (u) at (10,0) {\text{OH}};
    \node[draw,shape=circle,fill=white] (v) at (10,-2) {\text{OH}};
    \node[draw,shape=circle,fill=white] (w) at (10,-4) {\text{OH}};
    \node[draw,shape=circle,fill=white] (x) at (10,-6) {\text{OH}};

    \draw[->,thick] (a) -- (b);
    \draw[->,thick] (b) -- (c);
    \draw[->,thick] (c) -- (d);
    \draw[->,thick] (d) -- (e);
    \draw[->,thick] (e) -- (f);
    \draw[->,thick] (f) -- (g);
    \draw[->,thick] (g) -- (h);
    \draw[->,thick] (h) -- (i);
    \draw[->,thick] (i) -- (j);
    \draw[->,thick] (j) -- (k);
    \draw[->,thick] (k) -- (l);
    \draw[->,thick] (l) -- (m);
    \draw[->,thick] (m) -- (n);
    \draw[->,thick] (n) -- (o);
    \draw[->,thick] (o) -- (p);
    \draw[->,thick] (p) -- (q);
    \draw[->,thick] (q) -- (r);
    \draw[->,thick] (r) -- (s);
    \draw[->,thick] (s) -- (t);
    \draw[->,thick] (t) -- (u);
    \draw[->,thick] (u) -- (v);
    \draw[->,thick] (v) -- (w);
    \draw[->,thick] (w) -- (x);
    \draw[->,thick] (x) -- (y);
    \draw[->,thick] (y) -- (z);
    \draw[->,thick] (z) -- (aa);
    \draw[->,thick] (aa) -- (ab);
    \draw[->,thick] (ab) -- (ac);
    \draw[->,thick] (ac) -- (ad);
    \draw[->,thick] (ad) -- (ae);
    \draw[->,thick] (ae) -- (af);
    \draw[->,thick] (af) -- (ag);
    \draw[->,thick] (ag) -- (ah);
    \draw[->,thick] (ah) -- (ai);
    \draw[->,thick] (ai) -- (aj);
    \draw[->,thick] (aj) -- (ak);
    \draw[->,thick] (ak) -- (al);
    \draw[->,thick] (al) -- (am);
    \draw[->,thick] (am) -- (an);
    \draw[->,thick] (an) -- (ao);
    \draw[->,thick] (ao) -- (ap);
    \draw[->,thick] (ap) -- (aq);
    \draw[->,thick] (aq) -- (ar);
    \draw[->,thick] (ar) -- (as);
    \draw[->,thick] (as) -- (at);
    \draw[->,thick] (at) -- (au);
    \draw[->,thick] (au) -- (av);
    \draw[->,thick] (av) -- (aw);
    \draw[->,thick] (aw) -- (ax);
    \draw[->,thick] (ax) -- (ay);
    \draw[->,thick] (ay) -- (az);
    \draw[->,thick] (az) -- (ba);
    \draw[->,thick] (ba) -- (bb);
    \draw[->,thick] (bb) -- (bc);
    \draw[->,thick] (bc) -- (bd);
    \draw[->,thick] (bd) -- (be);
    \draw[->,thick] (be) -- (bf);
    \draw[->,thick] (bf) -- (bg);
    \draw[->,thick] (bg) -- (bh);
    \draw[->,thick] (bh) -- (bi);
    \draw[->,thick] (bi) -- (bj);
    \draw[->,thick] (bj) -- (bk);
    \draw[->,thick] (bk) -- (bl);
    \draw[->,thick] (bl) -- (bm);
    \draw[->,thick] (bm) -- (bn);
    \draw[->,thick] (bn) -- (bo);
    \draw[->,thick] (bo) -- (bp);
    \draw[->,thick] (bp) -- (bq);
    \draw[->,thick] (bq) -- (br);
    \draw[->,thick] (br) -- (bs);
    \draw[->,thick] (bs) -- (bt);
    \draw[->,thick] (bt) -- (bu);
    \draw[->,thick] (bu) -- (bv);
    \draw[->,thick] (bv) -- (bw);
    \draw[->,thick] (bw) -- (bx);
    \draw[->,thick] (bx) -- (by);
    \draw[->,thick] (by) -- (bz);
    \draw[->,thick] (bz) -- (ca);
    \draw[->,thick] (ca) -- (cb);
    \draw[->,thick] (cb) -- (cc);
    \draw[->,thick] (cc) -- (cd);
    \draw[->,thick] (cd) -- (ce);
    \draw[->,thick] (ce) -- (cf);
    \draw[->,thick] (cf) -- (cg);
    \draw[->,thick] (cg) -- (ch);
    \draw[->,thick] (ch) -- (ci);
    \draw[->,thick] (ci) -- (cj);
    \draw[->,thick] (cj) -- (ck);
    \draw[->,thick] (ck) -- (cl);
    \draw[->,thick] (cl) -- (cm);
    \draw[->,thick] (cm) -- (cn);
    \draw[->,thick] (cn) -- (co);
    \draw[->,thick] (co) -- (cp);
    \draw[->,thick] (cp) -- (cq);
    \draw[->,thick] (cq) -- (cr);
    \draw[->,thick] (cr) -- (cs);
    \draw[->,thick] (cs) -- (ct);
    \draw[->,thick] (ct) -- (cu);
    \draw[->,thick] (cu) -- (cv);
    \draw[->,thick] (cv) -- (cw);
    \draw[->,thick] (cw) -- (cx);
    \draw[->,thick] (cx) -- (cy);
    \draw[->,thick] (cy) -- (cz);

    \node at (1,1.5) {7};
    \node at (3.5,0) {8a (trans)};
    \node at (3.5,-2) {8b (cis)};
\end{tikzpicture}
\end{center}

It is now clear that cis-farnesol or trans-farnesol are the precursors for the cyclization to all the cyclic sesquiterpenes.

The biosynthesis of longifolene\textsuperscript{12,13} (Scheme 4) starts with the cyclization of cis-farnesol pyrophosphate 9 to give an eleven-membered ring carbocation 11 via
species 10. The "inside" hydrogen at C-1 of 11 undergoes a 1,3-hydride shift. The conformation of 12, as shown 12a, provides considerable overlap of the \( \pi \)-electrons at C-6 with those of the allylic ion at C-1, so that facile collapse gives rise to the cis-fused bicyclic ion 13. The geometry of 13 ensures the close proximity of C-7 to the double bond at C2-C3 and the formation of a C3-C7 bond to give tricyclic carbocation 14, equivalent to 14a. This carbocation undergoes a 1,2-carbon migration to give 15, which affords longifolene 3 by deprotonation.

It should be noted that the mechanism and the intermediates shown in Scheme 4 do not necessarily represent the actual enzymatic processes, but they do provide a useful framework for the rationalization of the biosynthesis process.

Scheme 5

Arigoni and his co-workers have experimentally investigated the biosynthesis of two antinodal forms of longifolene and developed stereochemical models based on their results.\(^4\) Reasonable incorporation of activity (0.1-0.2 %) from radiolabelled mevalonates into (+)-longifolene were achieved using cuttings of the
Pinus ponderosa tree (Scheme 5, also cf. Scheme 4). A 1,2 carbon migration was observed and a labelled hydrogen moved from C-1 to C-10 by 1,3 shift. The mevalonoid (5-pro-R)-hydrogen and the (5-pro-S)-hydrogen migrate in the biosynthesis of (+)-longifolene and (-)-longifolene respectively.\textsuperscript{15}

### 1.3 Addition Initiated Ring Closure

Conjugated addition (Michael) initiated ring closure is an important synthetic strategy although few fulvene examples are known. It includes the nucleophilic addition to an $\alpha$, $\beta$-unsaturated carbonyl compound to produce an enolate anion which subsequently undergoes an intramolecular ring closure\textsuperscript{16, 17}. This type of reaction was termed MIRC (Michael Initiated Ring Closure) by Little,\textsuperscript{18} who showed that three, five, six and seven membered rings could be formed by this method. However, the cyclizations were usually accompanied by some direct $S_N2$ displacement. This is illustrated in Scheme 6.

\[ E = CO_2R \]

\textit{Scheme 6}
The ratio of the MIRC reaction product formed is clearly dependent upon the concentration of the enolate as well as the rate constant for ring closure, $k_c$. The concentration of the enolate depends on $K_{eq}$ which is related to the relative stabilities of the conjugate acid of the nucleophile and the enolate. Therefore, if $K_{eq} < 1$, a MIRC reaction should occur only when $k_c$ is sufficiently large to compensate for the low enolate concentration. The rate of ring closure to three is faster than closure to five or six membered rings. Thus, it is not too surprising that the MIRC reaction has been used more often to construct the cyclopropane ring. Nevertheless, even when considering closure to a cyclopropane, the MIRC and SN$_2$ reactions are competitive. It has been shown$^{19}$ that both the solvent and the nature of the intermediate generated from different nucleophiles exert a remarkable effect on the course of the reaction.

1.4 Diels - Alder Reaction

The Diels-Alder reaction has become one of the most useful methods available to the synthetic organic chemist since its discovery more than 60 years ago.$^{20}$ The ability to generate simultaneously up to four chiral centers in a highly stereoselective and largely predictable fashion has resulted in its application to numerous synthetic targets.$^{21, 22}$ The intramolecular version has become popular more recently and has also been employed in the construction a variety of polycyclic ring systems in the past fifteen years.$^{23}$ Scheme 7 shows a simple example of the intramolecular Diels-Alder reaction. Of the two possible modes of addition, the fused mode usually predominates except with long chain lengths. If the reacting molecules are themselves cyclic, and / or have ring substituents, complex multicyclic compounds are formed in a single step. The Diels-Alder reaction provides a powerful tool for natural product synthesis because these
multicyclic structures are contained in drugs and natural products and the construction of these molecules are often more difficult and lengthy by other routes.

The Diels-Alder reaction proceeds through a highly ordered transition state.\textsuperscript{24} In the intramolecular Diels-Alder reaction some of the ordering has been achieved by joining the reacting functionalities in the same molecule. This leads to increased reaction rates under mild conditions and successful reactions that would fail even under forcing conditions in the intermolecular version. The constraints on the diene and dienophile imposed by the connecting chain generally facilitate the prediction of regio- and stereoselectivity. Side reactions such as dimerization or polymerization can generally be efficiently avoided by using high dilution. All of these advantages account for the great interest in the study and applications of the intramolecular Diels-Alder reaction and suggest that this reaction should be first considered for any synthesis of a molecule containing a six-membered ring fused
to other rings.\textsuperscript{25, 26}

A number of Lewis-acid catalyzed Diels-Alder reactions have also been reported.\textsuperscript{27} The main problem with Lewis-acid catalysts is that they may also cause side reactions. Diels-Alder reactions have large negative activation volumes and in general can be accelerated under high pressure. Some Diels-Alder reactions have also been carried out in the gas phase, under either static or flow conditions.\textsuperscript{28} However, it is not possible to compare their advantages because the corresponding solution reactions are lacking.

The Diels-Alder reaction has been reviewed frequently.\textsuperscript{21, 23-26, 29-37} This indicates the worldwide interest. However, some facets are still imperfectly understood and as our knowledge increases, this cycloaddition will be even more widely employed for synthetic design and methodology.

1.5 Brieger's Work

In principle the complex carbon skeleton of longifolene could be built by an intramolecular Diels-Alder reaction between a cyclopentadiene and an appropriate side-chain. As early as 1963, Brieger attempted to utilize this strategy to synthesize longifolene.\textsuperscript{38} In his investigation, chloride \textsuperscript{22}, obtained from the addition of hydrochloric acid to geranyl acetate, was treated with excess cyclopentadienyl magnesium bromide. The resulting product, actually a mixture of cyclopentadiene isomers \textsuperscript{23-25}, was heated in refluxing pseudocumene (bp 176°C) (Scheme 8).

He hoped that thermal equilibration of these isomers would cause the 5-substituted cyclopentadiene \textsuperscript{24} to undergo an intramolecular Diels-Alder cycloaddition to give the desired alcohol \textsuperscript{27}. However, the reaction gave a nearly quantitative yield of alcohol \textsuperscript{26}, which corresponded to the cyclization via the
Scheme 8
1-substituted cyclopentadiene 23.

This result showed that the substituted cyclopentadiene underwent a facile 1,5-sigmatropic rearrangement and the intramolecular Diels-Alder adduct of the 1-substituted isomer 23 was thermodynamically stable. In addition, it was clear that cycloaddition to yield a cyclohexane from a C-1 substituted cyclopentadiene was preferred to the competing pathway to a cycloheptane. Subsequent studies have confirmed this behavior and C-5 products arise only when the side-chain is shortened to two linking atoms, as other transition states are extremely strained (cf. Grubbs' work discussed below).

In spite of the lack of success of Brieger's synthesis of longifolene, the synthetic plan was concise, and it was possible that the target molecule could be realized with some modifications in the approach.

1.6 Cyclization of Substituted Cyclopentadienes

Cyclopentadiene is useful for the formation of bicyclo[2.2.1]heptane compounds for natural product syntheses. Considerable research work has been done to study the rearrangement of substituted cyclopentadienes and corresponding competitive Diels-Alder cycloadditions. It has been established, as mentioned above, that the 1,5-sigmatropic rearrangement occurs under very mild conditions and a mixture of isomers was usually observed even when the pure C-5 isomer was used initially. The composition of the isomeric mixture depends in part on the nature of the substituent and not on the method of the synthesis.

The intramolecular Diels-Alder reaction of substituted cyclopentadienes has been carefully examined by Grubbs and Still. They employed cyclopentadiene compounds tethered to an α,β-unsaturated ester functionality as the Diels-Alder reaction precursors. Several functionalized cyclopentadienes were prepared with
Scheme 9

1 - (CH₂)ₙ⁻→E

CpMgCl

30 ↔ 31 ↔ 32

n = 2
E = CO₂R

n = 3, 4

33

34

35
different tether lengths. These substrates readily underwent intramolecular Diels-Alder reaction at mild temperatures (Scheme 9). They showed that the cycloaddition proceeded favorably from a transition state in which the tether formed five- or six-membered rings, but products of type 35 were energetically disfavored.

1.7 Fallis' Work

It is apparent that a successful intramolecular Diels-Alder approach to a tricyclic skeleton from a 5-substituted cyclopentadiene requires either blocking the 1,5-sigmatropic rearrangement or arranging for the cycloaddition to compete efficiently with the rearrangement. Unfortunately, it has been found that even chlorine does not block the sigmatropic rearrangement and it migrates before the cyclization.\(^4^3\) This means the "blocking" is not necessarily straightforward. Based on this realization a successful approach has been developed in our research group, as shown in Scheme 10. It employs a suitable spiro[2.4]heptadiene of type A to form the desired Diels-Alder adduct of type B. The cyclopropane unit blocks the 1,5-sigmatropic rearrangement and, after the selective cyclopropane ring opening, also serves as latent functionality to provide several types of natural products.

This strategy has been successfully applied to the total synthesis of sinularene.\(^4^5\) Related studies revealed an oxygen substituent (X group) in the sidechain at the carbon adjacent to the cyclopropyl ring was essential for a successful cyclization.\(^4^6\)
Scheme 10

\[
\begin{align*}
\text{Sinularene} \\
\text{Longifolene} \\
\text{Sativene}
\end{align*}
\]
CHAPTER 2
LONGIFOLENE: PREVIOUS SYNTHESSES

The intricate molecular construction of longifolene has attracted a good deal of attention in the past three decades and served as a challenging test for synthetic principles and methods, especially with respect to the construction of ring systems and carbon networks. To date there have been six published total syntheses of longifolene and at least nine unsuccessful attempts.

A brief survey of the reported syntheses of longifolene reveals that each approach employed different strategies and methods for the construction of the tricycloundecane carbon skeleton.

2.1 Corey's Synthesis

The first, well-known, total synthesis of longifolene was reported in 1964 by Corey et al.\textsuperscript{47} The bridged ring system was constructed by an intramolecular Michael cyclization of a homodecalin derivative 39, as shown in Scheme 11.

The Wieland-Miescher ketone 36 was employed as a starting material and converted via tosylate 37 and a pinacol rearrangement, resulting in a ring expansion, to the required homodecalin 39 (41-48%).

Precedent for intramolecular Michael reaction of this type existed in the base-catalyzed cyclization of santonin to santonic acid. Although the transformation of santonin to santonic acid was smooth, the corresponding cyclization of homodecalin 39 to the tricyclodiketone 40 proved to be much less facile and yields of only 10-20% were obtained.
Scheme 11
After the construction of the diketone 40, the α-methylation of the enolate derived from 40 afforded the diketone 41. The cycloheptane carbonyl was reduced by the combination of hydride reduction and Wolff-Kishner reaction of the thio-ketal 42, followed by chromic acid oxidation to give longicamphenylone 43. Addition of methylthiium to 43 followed by dehydration of the resulting tertiary alcohol 44 gave racemic longifolene.

To prepare the optically active product, intermediate 41 was treated with L-(+)-2,3-butanedithiol and the formed diastereomers were resolved. The optically active thiol 42 was then converted to optically active (+)-longifolene 3.

2.2 McMurry’s Synthesis

The second synthesis of longifolene was reported in 1972 by McMurry and Isser. They utilized the same starting material as Corey, but their approach was to form the tricyclic carbon skeleton of longifolene via intramolecular alkylation of a bicyclic keto epoxide as outlined in Scheme 12.

The Wieland-Miescher ketone 36 was converted to the keto epoxide 45, whose enolate underwent an intramolecular epoxide opening to provide the tricyclic keto alcohol 46 in high yield (93%).

Completion of the synthesis required addition of a further methyl group after ring expansion to form the dimethycycloheptane ring of the natural product. Therefore, the alcohol 46 was dehydrated to give the endocyclic olefin 47 which was then treated with bromoform and potassium tert-butoxide, and the dibromo cyclopropane adduct 48 was obtained as the only isomer. Ring expansion was accomplished by solvolysis of 48 with silver perchlorate to yield allylic alcohol 49 quantitatively and 49 was immediately oxidized to give the enedione 50. Introduction of the methyl group by conjugate addition of lithium dimethylcuprate to
Scheme 12
enedione 50 resulted in tetracyclic ketone 51, presumably by intramolecular attack of the enolate generated after conjugate addition. The tricyclic system was regenerated by base catalyzed rearrangement of mesylate 52 to give enone 53 which was easily converted to longifolene.

2.3 Johnson’s Synthesis

The third synthesis of longifolene, reported in 1975 by Johnson et al., utilized the acid-catalyzed rearrangement of an acetylene cyclopentenol to construct the tricyclic ring system of longifolene.

The enol acetate 55 was obtained from conjugate addition of the cuprate derived from 1-iodo-4-hexyne to enone 54 followed by trapping the resulting enolate with acetyl chloride. Further manipulation of this acetate yielded alcohol 56. Treatment of alcohol 56 with trifluoroacetic acid gave the rearranged tricyclic alcohol 57 which constituted a rapid entry to the longifolene framework.

In the presence of acid, the olefin 58 readily isomerized to the exocyclic olefin 59. The ketone 43, an intermediate in both Corey’s and McMurry’s syntheses, was obtained by oxidation and methylation of 59. Methylithium addition and dehydration of 43 provide racemic longifolene in eleven steps from 54, as shown in Scheme 13.

2.4 Oppolzer’s Synthesis

The fourth synthesis of longifolene was reported in 1977 by Oppolzer and Godel. In this synthesis an intramolecular [2 + 2] photoaddition-retroaldol reaction sequence (deMayo reaction) was used to construct the complex longifolene skeleton, as shown in Scheme 14.
Scheme 13
Scheme 14
The key intermediate, enol acetate 63, was obtained from condensation of 1-morpholino-1-cyclopentene 60 with an optically active acid chloride 61 followed by acylation of the resulting diketone 62. Irradiation of 63 gave the cyclobutane 64 which upon hydrogenolysis of the protecting group underwent a spontaneous retroaldol reaction to afford diketone 65. This procedure incorporated the required stereochemistry without disturbance of the chiral center.

Crystallization gave the diketone 65 in 100% optically purity. Introduction of the gem-dimethyl group was accomplished via Wittig olefination of the more reactive cycloheptanone carbonyl, Simmons-Smith cyclopropanation and hydrogenolysis to yield ketone 66, the same intermediate as in the previous syntheses, which was then converted to (+)-longifolene by the literature procedure. The overall yield was 24% from the chiral acid chloride 61.

2.5 Schultz’s Synthesis

The fifth synthesis of longifolene was reported in 1985 by Schultz and Puig. They used an intramolecular diene-carbene cycloaddition, the synthetic equivalent of an intramolecular Diels-Alder reaction between a diene and a carbene, as the key step for construction of the longifolene seven-membered ring, as shown in Scheme 15.

Cyclohexadiene 67 was prepared by Birch reduction–alkylation of methyl 2-methoxybenzoate and alkylated with the dimethyl acetal of 2,2-dimethyl-5-iodopentanal. Conversion of 67 to the key intermediate 69a was accomplished by (1) Treatment of 67 with N-bromoacetamide in methanol to give a diastereomeric mixture of bromoketals 68, (2) dehydrobromination followed ketal hydrolysis during silica gel chromatography, and (3) acetal exchange. The aziridinyl imide 69b generated by reaction of 69a with 1-amino-trans-2,3-diphenylaziridine,
Scheme 15

$$E = \text{CO}_2\text{CH}_3$$
$$R = \text{CH(OCH}_3\text{)}_2$$
on thermolysis gave tricyclic keto-ester 70. The tricyclic compound 70 was converted to 66, an intermediate in Oppolzer's synthesis, by olefin hydrogenation and decarboxylation. Transformation of 66 to racemic longifolene followed the literature procedure.

An enantiospecific synthesis of (-)-longifolene was also achieved, via Birch reduction-alkylation of a chiral benzoic acid derivative to give the chiral cyclohexadiene 67.

2.6 Money's Synthesis

The sixth and the most recent synthesis of longifolene was reported in 1986 by Money and Kuo. In their synthesis, (+)-camphor was employed as the chiral starting material and a titanium tetrachloride promoted cyclization provided the tricyclic intermediate 74 which served as the synthetic precursor of (+)-longifolene.

This enantioselective synthesis began with the conversion of (+)-camphor 71 to (+)-8-bromocamphor 72. The bicyclic trimethylsilyl ether 73, derived from 72 after nine experimental steps, underwent facile intramolecular cyclization when treated with titanium tetrachloride to give a mixture of diastereomeric methoxyketones 74a and 74b. Subsequent reactions provided the ketone 75 and the acetate 76 with the required geminal dimethyl group. Reductive removal of the acetate and oxidation gave (+)-longicamphor 77, which was converted into isolongiborneol 78 by lithium aluminum hydride reduction. Dehydration of 78 yielded (+)-longifolene 3 via a Wagner-Meerwein rearrangement to complete the synthesis.
Scheme 16
CHAPTER 3
SYNTHETIC PLAN

It is fashionable to analyze a target structure by retrosynthetic bond breaking sequences. However, the direct simplistic application of this idea often leads to long, unimaginative synthetic sequences. As described above the direct double disconnection is not suitable, as Briege discovered due to the dominance of the 1,5-sigmatropic rearrangement and the preferred cyclization to 26 (see Scheme 8). Frequently creating a new bond in a target structure allows one to generate a new species which is more amenable to direct synthesis. Longifolene represents such a case. Creation of a new bond (arrow) in 1 (Scheme 17) leads to a new tetracyclic species A. A double disconnection of this synthton leads to the part structure B which can be transformed into a triene C which contains the required functionality for the reverse of the retrosynthetic step via a Diels-Alder cyclization.

To reduce these ideas based on the cyclopropyl concept to practice the strategy outlined in Scheme 18 was envisaged which possesses several interesting synthetic features.

(1) The cyclopropane ring present in the spiro[2.4]hexatetraene 1 will block the generally dominant 1,5-sigmatropic rearrangement of cyclopentadienes under Diels-Alder reaction conditions. This cyclopropyl unit represents a latent methylene group and subsequently undergoes a selective cleavage of the interior cyclopropane bond to provide the tricyclo[5.4.017.06.10]undecane ring system possessed by longifolene.
(2) The Diels-Alder adduct \( ii \) possesses all of the fifteen carbon atoms required and suitable functionality to allow the introduction of the exocyclic double bond of longifolene.

(3) Based on the experience gained from the sinularene synthesis, a bulky C-5 oxygen substituent is essential to ensure that the desired intramolecular cycloaddition will proceed as required.\(^{46}\) In a retrosynthetic sense, the preparation of structure \( iii \) (\( \delta \)-hydroxy \( \alpha,\beta \)-unsaturated ester) could arise from a selective \( \gamma \)-condensation of the spiro-aldehyde \( iv \) with an anion derived from methyl 3,3-dimethylacrylate.

(4) The spiro-aldehyde \( iv \) may be generated by oxidation of the spiro-alcohol \( v \). The latter can be obtained from an addition initiated ring closure involving methyllithium and an epoxyfulvene \( vi \), which in turn may be synthesized from commercially available materials by known methods.\(^{16}\)

A further potential feature of this strategy arises from the geometric constraints imposed by the Diels-Alder transition state. From Scheme 19, it is apparent that only conformation \( Ia \) will permit the cyclization, while conformation \( Ib \) will not undergo adduct formation because the dienophile is not aligned with the diene as required for the cycloaddition. Therefore, if the cyclopropyl unit is chiral, the stereochemistry of the asterisk carbon will control the cyclization to lead to an optically active adduct, from which the chiral longifolene may be synthesized. Interestingly, the chirality of this asterisk carbon will disappear after reductive cyclopropane ring opening. To achieve the chiral heptatriene \( I \), a single enantiomer of spiro-alcohol \( v \) (Scheme 18) is necessary, which may be obtained either from a chiral starting material or by resolution (cf. Scheme 29 in Chapter 6).
Scheme 18

\[ E = \text{CO}_2\text{CH}_3 \]
Scheme 19
In spite of the failure of the Brieger’s approach it might succeed without resorting to a blocking group if direct cyclization from a C-5 substituted cyclopentadiene was the most favorable pathway. In theory this might be accomplished by confining the dienophile to a cyclic system in which the adducts from the C-1 and C-2 substituted cyclopentadienes are excessively strained. This will be discussed in more detail below but structure D (Scheme 17) represents this approach in which X is a functionality that will allow subsequent ring cleavage after cycloaddition. Molecular models reveal that cyclization of D should be preferred over E due to the strain inherent in the cyclohexane adduct. It should however be emphasized that no carbocyclic example of direct cycloheptane formation is known.
PART II

RESULTS AND DISCUSSION
CHAPTER 4
INTRAMOLECULAR DIELS-ALDER REACTION

4.1 Epoxyfulvene Preparation

The epoxidation of methyl vinyl ketone under the basic condition in methanol gave the racemic epoxide 79 (Equation 1) in reasonable yield (60%). The epoxide 79 is quite stable and can be stored in a refrigerator for several months.

\[ \text{H}_2\text{O}_2/\text{OH}^\text{-} \xrightarrow{\text{MeOH}} \]

\[ \text{O} \]

\[ \begin{array}{c}
\text{O} \\
\text{MeOH}
\end{array} \]

Equation 1

The condensation of epoxide 79 with freshly prepared cyclopentadiene was conducted in the presence of a catalytic amount of pyrrolidine to give epoxyfulvene 80 (Equation 2) in a highly efficient manner. Other bases resulted in lower yields and extensive decomposition.\(^\text{16, 54}\) The \(^1\text{H}\) NMR spectrum of 80 displayed a characteristic four proton multiplet at \(\delta 6.35\) for the vinyl protons, a vinyl methyl singlet at 1.91, a multiplet at 2.82 for the methylene hydrogens, and a doublet of doublets \((J = 1.5, 1 \text{ Hz})\) at 3.90 due to the methine hydrogen. These features support the assigned structure.

This bright brown compound is very unstable at room temperature and therefore was used for the next synthetic step as soon as possible. (It may be kept below \(-20^\circ\text{C}\) for up to 48 hours) In one case, a small explosion and production
of a noxious smoke was observed when a large amount (ca. 20g) of frozen epoxyfulvene 80 was allowed to warm to room temperature. The compound became a black mass of polymer-like material. However, it is safe to use this compound immediately after preparation.

\[
\text{Equation 2}
\]

4.2 Epoxyfulvene Cyclization

It is well established that the exocyclic double bond in fulvene is polarized and of reactivity similar to a carbonyl group.\(^5\) This means, in principle, that nucleophilic attack may occur at the exocyclic fulvene double bond or at either end of epoxide in 80. Thus the nucleophilic attack could generate several different products. However, the treatment of epoxyfulvene 80 with methyllithium at -78\(^\circ\)C resulted in the formation of spiro-alcohol 82 as the sole product (55\%) and the recovery of starting material 80 (35\%) after work-up and chromatography. The \(^1\H\) nmr spectrum of the product displayed two methyl singlets at \(\delta 1.40\) and 1.42, the
cyclopropyl hydrogen as a triplet \((J = 7.5 \text{ Hz})\) at 2.39, the methylene protons as a doublet \((J = 7.5 \text{ Hz})\) at 3.78, and the four cyclopentadienyl protons as three overlapping multiplets at 6.30, 6.45 and 6.57, all of which were consistent with the assigned structure. In this case the methyl anion preferentially attacked the C-6 fulvene centre to generate the cyclopentadienyl anion intermediate 81 which cyclized to form the cyclopropane ring by exo-tet cleavage of the epoxide ring (Equation 3).

![Equation 3]

A mixture of product and starting material was always obtained even using a large excess of methyllithium and longer reaction times.

4.3 Cyclopropyl Alcohol Oxidation

The cyclopropyl alcohol 82 was sensitive to chromium based oxidizing reagents. The cyclopropyl aldehyde 83 was prepared with active manganese dioxide oxidation in good yield (86\%) (Equation 4). The \(^1\text{H nmr}\) of 83 showed the aldehyde proton as a doublet \((J = 6 \text{ Hz})\) at 8.56, the disappearance of the methylene protons at 3.78 and the change of the cyclopropyl hydrogen at 2.78
from a triplet to a doublet ($J = 6$ Hz).

![Equation 4](image)

**Equation 4**

The method of preparation of the active manganese dioxide significantly influenced the oxidation. The most effective manganese dioxide for our case was obtained from the reduction of potassium permanganate by charcoal. In practice, a large excess of charcoal was used to prepared the manganese dioxide and the unreacted charcoal remained in the product mixture as a part of the reagent. It was discovered that charcoal from different companies had different levels of effectiveness. The charcoal from the J.T. Baker Company was the best one in our work.

An alternative preparation of aldehyde 83 from alcohol 82, in excellent yield (94 %), employed Swern oxidation using oxalyl chloride and highly dried dimethyl sulfoxide. However, with larger scale reactions (ca. 0.02 mole), the manganese dioxide/charcoal oxidation was preferred due to the convenience of the work-up and product separation.

**4.4 $\alpha$ vs $\gamma$ Condensation**

To prepare a Diels - Alder precursor, such as structure iii (Scheme 18), we required a reliable procedure to introduce directly a conjugated allyl unit to the
spiro-aldehyde. This necessitates a regioselectively controlled condensation of an allyl anion with an aldehyde (Scheme 20).

Scheme 20

Literature methods are available to generate the α-product in a controlled manner but only a few reports describe the regioselective preparation of the γ-product. The control of α vs γ substitution in heteroatom-stabilized allylic anions and resonance-stabilized enolates depends upon the complex interplay between the nature of the atoms, charge delocalization, steric effects, solvation, the type of electrophile, and the counter ion. These difficulties are compounded by the observation that halides and carbonyl systems often exhibit opposite regioselectivities.

Hudlicky and his co-workers found the regioselectivity in the Reformatsky reaction of ethyl 4-bromocrotonate with carbonyl substrates depended on the polarity of solvents and the hardness of metal catalysts. We tested his modified Reformatsky conditions using dry zinc and tetrahydrofuran. It worked well when
either methyl 4-bromocrotonate or methyl 3-bromomethyl-2-butenoate (Table 1, entry 1, p 41) were reacted with benzaldehyde and gave the γ-product exclusively. Unfortunately the reactions (Table 1, entries 5 and 6) with the spiro-aldehyde 83 gave 60:40 and 40:60 α/γ mixtures (Scheme 21), presumably a consequence of the hindered environment of the carbonyl group. Modification of the reaction conditions using an ultrasonic bath or dimethoxyethane (DME) as the solvent provided no significant improvement in the α/γ ratio.

Various lithium anion-salt combinations derived from 2-ethylidene-1,3-dithiane were examined (Scheme 22). Ziegler and Tam demonstrated earlier that allylation of the lithium anion derived from 2-ethylidene-1,3-dithiane afforded the α-product preferentially, while the corresponding copper derivative gave the γ-product exclusively.69 However, in the case of the cuprate derivative with spiro-aldehyde 83 a significant quantity of the α-product was obtained (Table 1, entry 9), although the γ-product dominated. Added zinc salts did not influence the regioselectivity and the α-product dominated in the presence of zinc chloride (Table 1, entry 8).

Except for the reaction of organocadmium reagents with acid chloride, organocadmium species have received relatively little attention.60 Pure, salt free alkyl cadmiums do not react with carbonyl compounds but this reactivity can be altered markedly by the addition of magnesium or lithium salts,61,62 which means that in situ cadmium reagents prepared from organolithium compounds or Grignard reagents can be efficiently used to react with carbonyl compounds. Thus the addition of cadmium chloride powder to the lithium anion at -78°C was examined (Scheme 23). The appropriate carbonyl compound was added to this reagent and the reaction was allowed to warm to 0°C followed by quenching with saturated aqueous ammonium chloride. As summarized in Table 1 all reactions of the lithium anions with added cadmium chloride resulted in γ condensation products.
predominantly with excellent yields (Table 1, entries 2, 4, 10 and 11).

Further studies showed that if the reaction was quenched at -78°C with an acetic acid solution in tetrahydrofuran, the α substituted material was the only product. Equilibration at 0°C for enough time (monitored by TLC) to allow rearrangement to the γ-product was required. Treatment of α-product with lithium diisopropylamide and cadmium chloride at 0°C for one hour resulted in almost same α/γ ratio (88:86 = 10:90, Scheme 24). This proved that the γ substitution observed was a consequence of isomerization to the thermodynamically more stable product. It should be mentioned that a lactone resulting from the γ-product was also found, similar to the case of the chiral materials employed and discussed in Chapter 6.

Lithium amides add in a conjugative manner to methyl crotonate unless hexamethylphosphoramide (HMPA) is present. Thus addition of HMPA was required for complexation and deprotonation of methyl crotonate (Table 1, entry 3). This reduced the influence of the cadmium reagent. The γ selectivity also diminished in the presence of more soluble salts such as cadmium iodide. These results suggest that the solvation effects are of prime importance in establishing the regioselectivity.

Relatively few investigations into the composition and structure of organocadmium reagents have been carried out. "Purified" cadmium reagents, isolated by distillation, have the dialkyl structure, for example, di-n-butylecadmium. However, the structure of in situ alkylcadmiums are complicated and may be markedly different. We found that yields were less and the reactions were incomplete if the ratio of the lithium to cadmium species was not 2:1 molar equivalents. Further work will be required to determine the exact nature of the reactive cadmium reagent.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Substrate</th>
<th>Metal/Salt</th>
<th>$\alpha : \gamma$</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHO</td>
<td>BrCH$_2$$^\text{a}$ = CO$_2$Me</td>
<td>Zn(THF)</td>
<td>0:100</td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>CHO</td>
<td>= CO$_2$Me</td>
<td>LDA/CdCl$_2$</td>
<td>15:85</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>CHO</td>
<td>= CO$_2$Me</td>
<td>LiNC$_2$/CdCl$_2$</td>
<td>50:50</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HMPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CHO</td>
<td></td>
<td>LDA/CdCl$_2$</td>
<td>10:90</td>
<td>95%</td>
</tr>
<tr>
<td>5</td>
<td>CHO</td>
<td>BrCH$_2$$^\text{a}$ = CO$_2$Me</td>
<td>Zn(THF)</td>
<td>60:40</td>
<td>60%</td>
</tr>
<tr>
<td>6</td>
<td>CHO</td>
<td>BrCH$_2$$^\text{a}$ = CO$_2$Me</td>
<td>Zn(THF)</td>
<td>40:60</td>
<td>63%</td>
</tr>
<tr>
<td>Entry</td>
<td>Aldehyde</td>
<td>Substrate</td>
<td>Metal/Salt</td>
<td>$\alpha : \gamma$</td>
<td>Isolated Yield</td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>-----------</td>
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<td>----------------</td>
</tr>
<tr>
<td>7</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>LDA</td>
<td>90:10</td>
<td>96%</td>
</tr>
<tr>
<td>8</td>
<td>&quot;</td>
<td>&quot;</td>
<td>LDA/ZnCl$_2$</td>
<td>60:40</td>
<td>70%</td>
</tr>
<tr>
<td>9</td>
<td>&quot;</td>
<td>&quot;</td>
<td>LDA$_3$</td>
<td>35:65</td>
<td>61%</td>
</tr>
<tr>
<td>10</td>
<td>&quot;</td>
<td>&quot;</td>
<td>LDA/CdCl$_2$</td>
<td>10:90</td>
<td>90%</td>
</tr>
<tr>
<td>11</td>
<td>&quot;</td>
<td><img src="image3.png" alt="Image" /></td>
<td>LDA/CdCl$_2$</td>
<td>15:85</td>
<td>90%</td>
</tr>
</tbody>
</table>
Scheme 21
Reaction Condition:
A: LDA/THF
B: LDA/ZnCl₂
C: LDA/CuL₃P(OMe)₃
D: LDA/CdCl₂

Scheme 22
Scheme 23
Scheme 24

[Chemical reactions and structures depicted in the image]
4.5 Protection of Hydroxy Ester

The direct use of the hydroxy ester 86 for the Diels-Alder reaction was unsuccessful, since even in refluxing benzene the hydroxy ester 86 slowly decomposed. Meanwhile, it was found that a bulky substituent attached to the hydroxyl would encourage this triene precursor to exist in an appropriate conformation for cycloaddition. Therefore, the tert-butyldimethylsilyl group was employed as a suitable protecting group. Surprisingly, the normal methods to convert alcohols to silyl ethers failed in this case, possibly due to the sterically hindered environment of the hydroxyl group. A modified condition for hindered alcohols was employed in which tert-butyldimethylsilyl perchlorate was prepared in situ from alkylsilyl chloride and silver perchlorate. This silyl reagent reacted in acetonitrile with excess pyridine to afford 100 in 93% yield (Equation 5).

\[
\begin{align*}
\text{AgClO}_4, \\
t-	ext{BuMe}_2\text{SiCl} \\
\text{CH}_3\text{CN, Py} \\
\text{R.T., } 12\text{h}
\end{align*}
\]

Equation 5

4.6 Attempted Hydroxy Dithiane Dioxide (102) Preparation

The hydroxy dithiane dioxide was proposed as an alternate Diels-Alder reaction precursor because of the known power of the sulfoxide substituent as the dienophile group. Compound 102 could be obtained from the condensation of
spiro-aldehyde 83 with lithium anion of 2-ethylidene-1,3-dithiane 1,3-dioxide 101 in the presence of cadmium chloride (Equation 5).

\[
\begin{align*}
\text{Equation 6}
\end{align*}
\]

The dithiane dioxide 101 was synthesized from the corresponding dithiane by sodium periodate oxidation\textsuperscript{64} (Equation 6). However, this white crystalline compound was largely insoluble in most organic solvents except in dichloromethane and created difficulties in the subsequent synthetic step. A phase-transfer reaction was tried in a mixture of dichloromethane and aqueous sodium hydroxide solution in the presence of benzyltrimethylammonium hydroxide as a phase-transfer catalyst. Unfortunately, the reaction gave a complicated mixture of products.

\[
\begin{align*}
\text{Equation 7}
\end{align*}
\]
4.7 Intramolecular Diels-Alder Reaction

In spite of the attention the intramolecular Diels-Alder reaction has received some facets are still imperfectly understood. Thus cyclizations that look promising sometimes fail. A series of unsuccessful thermal Diels-Alder reactions related to this work are listed in Table 2 (p. 52). The triene 100, a promising precursor, was unstable in refluxing dichlorobenzene (Table 2, entry 3) and barely cyclized at lower temperature even when heated for a long time (Table 2, entry 1). The reaction in refluxing toluene (Table 2, entry 2) was not complete after 24 hours and gave a low yield of adduct accompanied by decomposition. This lead to the conclusion that for a successful Diels-Alder reaction of the triene 100 a reaction temperature higher than 110°C was necessary but the reaction time should be as short as possible. Therefore, a highly efficient thermal source was required.

Until recently microwave ovens have not received much attention as controlled thermal sources for conducting routine chemical reactions. However, recent studies indicated that microwave ovens could be safely used to increase dramatically reaction rates. While our work has been in progress reports of the use of microwave ovens for Diels-Alder reactions have appeared. We were interested in the rapid heating capability of the microwave oven and utilized it in our Diels-Alder reaction.

The reaction was carried out in a screw-cap pressure tube (Pyrex vessel) in a commercial Toshiba Model ERS-6630C (720 Watt) or Magnasonic Model MMW3000 (500 Watt) microwave oven. The power setting at 500 watts was used throughout. The pressure tube was placed in the microwave oven through a hole drilled through the top of oven and encased in Teflon. The diameter of the hole should not be larger than 3 cm otherwise serious microwave leakage may occur. The pressure tube was insulated with damp vermiculite to encourage heat transfer...
since the magnetron was tuned to the water frequency (2450 MHz). In addition, all microwave oven experiments were conducted in a fumehood (see Fig. 1, p 53).

The solvents for microwave reactions must have a certain magnitude of dipolar moment otherwise the solvent cannot effectively absorb the microwave energy. However, solvents such as acetone, ethanol, dimethylformamide (DMF) etc. with large dipolar moments explode easily in the pressure tube under microwave oven thermal conditions.\(^{66}\) Reagent solubilities in the solvents available sometimes create difficulties. From our experience, toluene was found to be the best solvent. We have never experienced any difficulty or explosions performing Diels-Alder reactions in toluene but a pressure tube exploded during a Wittig reaction in DMF. In spite of some literature examples DMF should not be employed in microwave experiments.

Thus, the triene \(\text{100}\) was prepared as an approximately 0.05 M solution in toluene and 1% molar equivalent of hydroquinone added to prevent radical polymerization. The time taken for reactions depended on the reaction scale, generally from 0.5 h to 2 h. The adduct \(\text{103}\) was obtained in an excellent yield (92\%\) (Equation 8). The hydroxy ester triene \(\text{86}\) was examined in the Diels-Alder reaction under the same conditions but no cyclization was achieved (Table 2, entry 6). Clearly, the bulky tert-butyldimethylsilyl ether substituent in the side chain assisted the cycloaddition and minimized decomposition. The stereochemistry of the Diels-Alder adduct will be discussed in Chapter 6.

The dithiane triene \(\text{104}\) was prepared as an alternative Diels-Alder reaction precursor. The acylation of the hydroxy group failed and methylation was employed as an alternative protecting method. Again a modified procedure\(^{87}\) was used for this highly sterically hindered hydroxy group (Equation 9). Unfortunately, the Diels-Alder reactions of triene \(\text{104}\), thermally or in the microwave oven, were
unsuccessful (Table 2, entries 7 and 8). We did not investigate the Diels-Alder reaction in the tert-butyldimethylsilyl ether dithiane trienes.

\[
\text{Equation 8}
\]

\[
\text{Equation 9}
\]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Reaction Condition</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>benzene, reflux</td>
<td>N.R.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 days</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>toluene, reflux</td>
<td>10% 103</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>o-dichlorobenzene</td>
<td>decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reflux, 12 h</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image2.png" alt="Image" /></td>
<td>benzene, reflux</td>
<td>partial decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>toluene, reflux</td>
<td>decomposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>toluene, sealed tube</td>
<td>microwave oven</td>
</tr>
<tr>
<td>7</td>
<td><img src="image3.png" alt="Image" /></td>
<td>benzene, reflux</td>
<td>N.R.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>48 h</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>o-xylene, sealed tube</td>
<td>microwave oven, 30 min</td>
</tr>
</tbody>
</table>
Figure 1 Microwave Oven Reaction Apparatus
Desilylation of Diels-Alder adduct 103 afforded the required tetracyclic alcohol 105 (Equation 10). A selective cyclopropane bond cleavage was now required to afford the desired longifolene tricyclic ring system. As illustrated in Scheme 25, there are three possible bond cleavages (a, b, or c) to give different types of products. In general, the cleavage of bond c is least favorable unless activating substituents are present. The following discussion will focus on the series of attempted cyclopropane ring opening approaches summarized in Table 3 (p56).

\[
\text{Equation 10}
\]
Scheme 25
<table>
<thead>
<tr>
<th>Entry</th>
<th>Reactant</th>
<th>Condition</th>
<th>Ring Opened Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Reactant" /></td>
<td>$H_2$, PtO$_2$, EtOAc</td>
<td><img src="image2.png" alt="Product" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Reactant" /></td>
<td>1. $H_2$, Pd/C, EtOAc</td>
<td><img src="image4.png" alt="Products" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. PhOC(=S)Cl, Py</td>
<td><img src="image5.png" alt="Products" /></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Bu$_3$SnH, AIBN</td>
<td><img src="image6.png" alt="Products" /></td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Reactant" /></td>
<td>Cr$_2$(SO$_4$)$_3$, Zn, DMF</td>
<td><img src="image8.png" alt="Products" /></td>
</tr>
<tr>
<td>4</td>
<td><img src="image9.png" alt="Reactant" /></td>
<td>Zn, MeOH/AcOH, reflux</td>
<td><img src="image10.png" alt="Products" /></td>
</tr>
<tr>
<td>5</td>
<td><img src="image11.png" alt="Reactant" /></td>
<td>Li/NH$_3$, Et$_2$O</td>
<td><img src="image12.png" alt="Products" /></td>
</tr>
</tbody>
</table>
5.1 Hydrogenolysis

It is well established that cyclopropanes can be cleaved at the least substituted bond by catalytic hydrogenolysis. Bond "a" and "b" in tetracyclic alcohol 105 are not very different from the viewpoint of substitution, but bond "a" seems less hindered than bond "b". Hydrogenation of tetracyclic alcohol 105 afforded the bond "a" cleavage product cyclohexane alcohol 109 exclusively (Table 3, entry 1). Unexpectedly, under the same reaction conditions (H₂, 60psi, PtO₂, EtOAc / AcOH, 24 h) the tert-butyldimethylsilyl ether 103 did not undergo any ring opening. Apparently the hydroxy group assisted the reaction process through coordination with the catalyst.

5.2 Radical Ring Opening

The physical organic chemistry of radical ring opening reactions has received considerable study, but their synthetic applications are just beginning to be developed. In principle, the reaction shown in Equation 11 could be used for the cyclopropane ring opening of our tetracyclic alcohol 105 although the direction of the ring cleavage is unclear. It was hoped that radical ring opening would give a preference for the desired product.

![Diagram of radical ring opening reaction]

Equation 11
The generation of the initial radical was accomplished stepwise: replacement of the hydroxy group by a radical reaction precursor and then treatment with a stannane. We found the double bond in the tetracyclic alcohol 105 increased the complexity of the products due to the tendency of the radicals to attack the double bond (Scheme 26). Therefore, the tetracyclic alcohol 105 was first hydrogenated and then converted into a phenoxythiocarbonate, a radical precursor as described by Robins.

![Scheme 26](image)

The radical ring opening reaction was carried out on a dilute solution of phenoxy thiocarbonate compound (ca. 0.02 M) in refluxing toluene with slow addition of tributyltin hydride and radical initiator azobis(isobutyronitrile) (AIBN). A (9:1) mixture of cyclopropane ring opened products 111 and 112 was obtained (Table 3, entry 2). Different solvents and reaction times did not significantly influence the composition of the product mixture.
5.3 Reductive Ring Opening

It was established during research on sinularene that chromium (II) salts reduced cyclopropane ketone 113 in DMF/H₂O to give the longifolene type ketone 114 selectively when the double bond was present (Equation 12).71

The same method was examined. The cyclopropane ketone 115 was generated by Swern oxidation of cyclopropane alcohol 105 (Equation 13). A chromium (II) solution was prepared by zinc reduction of chromium (III) sulfate in DMF/H₂O and used immediately. However, the treatment of cyclopropane ketone 115 with the chromium (II) sulfate solution for 36 h at room temperature did not give any ring opened product. Upon heating the reaction solution or in the case of chromium (II) sulfate prepared in situ (an exothermic reaction), the cyclopropane isomerization product 116 was obtained as a sole product (Table 3, entry 3). This was consistent with the observation that the isomerization of the cyclopropane in this strained tetracyclic system was quite facile. In fact, during recrystallization (EtOAc/hexane) of the hydrogenated product from the tetracyclic alcohol 105, isomerization occurred when the solution was warmed (see Experimental).

![Equation 12](image)
The previous work also found that the reduction of cyclopropane ketone 113 with zinc/zinc chloride in methanol afforded 75% of the bridged cycloheptanone 114 (longifolene type) and 25% of the bridged cyclohexanone 117 (sinularene type). (Equation 14)
The application of this method to cyclopropane ketone 115 did not result in a ring opening reaction, but it induced acid catalyzed isomerization of the ester substituent. A modified zinc reduction (Zn, MeOH/AcOH, reflux) of the cyclopropane ketone 118, obtained from hydrogenation of the alkene ketone 115 (Equation 15), resulted in the isomerization of the substituted cyclopropane ring to the isopropyl substituted cyclohexanone 119 (Table 3, entry 4). Hydrogenation was conducted prior to the zinc reduction because the reaction gave a complicated mixture of products when the double bond was present.

Dissolving metal reductions have been applied to the cyclopropane bond cleavage of conjugated cyclopropyl ketones. They are subject to a variety of influences. Lithium/ammonia reduction of cyclopropyl ketone 120 afforded a mixture of 121 and 122, in which the longifolene type product 122 was the minor constituent. To facilitate the analysis resulting diols hydrogenated (Scheme 27).71

\[ \text{H}_2, (20 \text{ psi}) \]
\[ \text{Pd/C, EtOAc, 2h} \]
Lithium/ammonia reduction of cyclopropyl ketone 118 in ether solution at -78°C afforded a 1 : 1 mixture of bond "a" opened product 123 and bond "b" opened product 124 (Table 3, entry 5). Here also the double bond must first be saturated to avoid rearrangement products. The amount of lithium and the reaction time were controlled to prevent the further reduction of the carbonyl groups.

This was the best result obtained for the cyclopropane ring opening, although the 1 : 1 mixture was disappointing. The products could not be separated so the mixture was used directly for further synthesis.

5.4 Attempted Ketone Reduction

The remaining steps are illustrated in Scheme 28. It was anticipated that the unwanted isomer could be successfully separated at one of the synthetic stages before the acetate pyrolysis required to generate the exocyclic double bond.
The formation of tosylhydrazone 125 proceeded without any difficulty but the separation of products still remained a problem. Treatment of this mixture with lithium aluminum hydride provided a complicated mixture of reduced products. From the spectroscopic analysis (IR, NMR), this new mixture contained products at different stages of reduction. This was not satisfactory so the synthesis of racemic longifolene was stopped at this step (cf. Experimental).
CHAPTER 6
ENANTIOSELECTIVE SYNTHETIC APPROACHES

6.1 Initial Approach

As previously discussed in Chapter 3, stereochemical control of the Diels-Alder cyclization should be possible using an optically active spiro-cyclopropane-cyclopentadiene as the precursor (see Scheme 19). Our initial approach to optically active material is shown in Scheme 29.

The cyclopentadienyl anion d cyclizes in an *exo-tet* manner to generate the (1R)-spiro[2.4]hepta-4,6-diene alcohol c. Therefore, once the stereochemistry of the asterisk carbon is constructed in the epoxybutanol g, its chirality will be carried through the whole synthetic sequence and control the stereochemistry of the Diels-Alder reaction. In principle, the optically active epoxide g could be prepared by Sharpless epoxidation of 3-buten-2-ol h.

6.2 Attempted Sharpless Epoxidation

Sharpless and his co-workers reported that the kinetic resolution of secondary allylic alcohols could be achieved by epoxidation with *tert*-butyl hydroperoxide (TBHP) involving a catalytic amount of the titanium tartrate complex in the presence of molecular sieves (Scheme 30).\(^2\) In the case illustrated, the epoxy alcohol product is the type of compound we desired for the enantioselective synthesis.

We followed the same procedure in an attempt to prepare the (2S, 3R) 1,2-epoxy-3-butanol g, the key intermediate, from the racemic 3-buten-2-ol and examined the stoichiometric method as well.\(^3\) Unfortunately, all attempts failed to
Scheme 29
give the desired product in a significant yield. This low molecular weight allylic alcohol seemed unstable under the Sharpless epoxidation conditions.

\[
\begin{align*}
\text{R'} & \text{C} & \text{R} & \quad \text{Ti(OiPr)}_4 \quad \text{(+)-DIPT} \\
& & & \quad \text{TBHP} \\
\text{OH} & \Rightarrow & \text{OH} \\
\text{127} & \leftrightarrow & \text{128} \quad \text{3Å Sieve} \quad -20^\circ C \\
& & \text{129}
\end{align*}
\]

Scheme 30

6.3 Resolution of the Spiro Alcohol (82)

In view of the difficulty experienced preparing optically active epoxy alcohol 8, the possibility of resolving the racemic spiro alcohol 82 was examined since the compound was relatively easy to prepare and fairly stable in storage.

Today it is possible to carry out resolutions of organic compounds with a high probability of success, although resolutions are often still tedious. In general, racemic alcohols are resolved by forming diastereomeric esters, but these methods require acid-catalyzed esterification conditions. Earlier experiments established that spiro-alcohol 82 was unstable in acidic environments and, therefore, a resolution method under basic conditions was required.

(\text{\textit{l}})-Menthyl chloroformate has been used to make carbonates and cabamates for the analytical resolution of alcohols and amines several years ago,\textsuperscript{74} although its preparative application was reported only recently for the resolution of racemic
warfarin. The formation of menthyl carbonates proceeds under basic conditions and thus the stability of the acid sensitive spiro-alcohol 82 will not be influenced.

(-)-Menthyl chloroformate 130 was prepared from (-)-menthol and phosgene solution in toluene at 0°C in the presence of quinoline (Equation 16). Treatment of the racemic spiro-alcohol 82 with this (-)-menthyl chloroformate solution (ca. 1 mmol/mL) in the presence of triethylamine gave a mixture of products. Careful separation by flash chromatography afforded a component 131 (Equation 17). The cyclopropyl hydrogen appeared as a triplet at δ 2.43 (J = 7.2 Hz) in the ¹H nmr spectrum. A series of experiments with increasing concentration of a chiral shift reagent (tris [3-(trifluoromethyl)hydroxymethylene] - (+) -camphorato ]euroium (III) derivative ) caused neither line broadening nor the appearance of a new signal, confirming the presence of a single enantiomer. The other components, including the diastereomer of 131, were difficult to purify by flash chromatography.

\[
\text{ClC(=O)Cl, PhCH}_3 \quad \text{Quinoline, } 0^\circ\text{C} \quad \text{OC(=O)Cl} \\
\text{130}
\]

Equation 16
Equation 17

Scheme 31
Lithium aluminum hydride reduction of (-)-menthylcarbonate 131 in ether solution provided the (+)-R-spiro-alcohol 132 (34% yield from racemic alcohol 82, i.e. 68% of available enantiomer). The stereochemistry of (+)-R-spiro-alcohol 132 was confirmed on the basis of the chemistry of the final product, (+)-longifolene. The manganese dioxide oxidation converted the (+)-R-spiro-alcohol 132 into (+)-R-spiro-aldehyde 133 in the same manner used for the racemic case (Scheme 31).

6.4 γ-Condensation

The condensation of (+)-R-spiro-aldehyde 133 with methyl 3,3-dimethylacrylate anion in the presence of cadmium chloride was carried out under the conditions described previously. Surprisingly, after stirring at 0°C for 2 hours, the δ-hydroxy ester intermediate had cyclized to the (+)-lactone 134 in a yield of 73% (Equation 18).

\[ 	ext{Equation 18} \]
The \textsuperscript{1}H nmr spectrum of 134 (Figure 2, p72) displayed two aliphatic methyl singlets at \( \delta 1.39 \) and 1.43, a vinyl methyl singlet at 1.87, the cyclopropyl hydrogen as a doublet \((J = 4.2 \text{ Hz})\) at 2.31, the methylene protons as multiplets 1.93 to 2.09, a methine proton as double - doublet \((J = 4.2 \text{ and } 10.5 \text{ Hz})\) at 4.48, a vinyl hydrogen as a singlet at 5.76, and the four cyclopentadienyl protons as four multiplets at 6.17, 6.28, 6.49, and 6.58. The COSY spectrum showed that the cyclopropyl hydrogen is adjacent to the methine hydrogen and the latter is adjacent to the methylene protons (Figure 3, p73). The \textsuperscript{13}C and DEPT (Distortionless Enhancement by Polarization Transfer) spectra contained a carbonyl at \( \delta 164.6 \), a quaternary vinyl carbon at 156.0, five CH vinyl carbons at 136.4, 132.3, 131.6, 129.7 and 116.8, two CH carbons at 76.6 and 42.1, a CH\textsubscript{2} carbon at 35.6, three CH\textsubscript{3} carbons at 27.2, 23.0 and 20.4, and two quaternary carbons at 51.1 and 31.9 (Figure 4, p74). The high resolution mass spectrum had a molecular ion at \( m/z \) 230.1303 (Calculated 230.1302). These features support the assigned gross structure.

This condensation can generate two diastereomers (Scheme 32). In principle, the organocadmium compound can approach the carbonyl group from either the "inside" (Re) face or "outside" (Si) face. However, the delocalized \( \pi \) system of the organocadmium compound should align itself preferentially with the \( \pi \) system of the diene, resulting in attack from the "inside" (Re) face to generate the C-5(R)-lactone as the predominant product. This anion approach also avoids the nonbonded interaction with the adjacent geminal dimethyl group. The "outside" (Si) approach gave the C-5(S) diastereomer as a minor product in 12\% isolated yield. Only the Z-olefin can form this six-membered lactone and the E-olefin hydroxy ester was not detected among the products. This is consistent with the thermodynamic features of this reaction discussed earlier: therefore isomerization
occurs until the requisite intermediates are trapped by lactonization.

Scheme 32
Figure 3 COSY spectrum of (134)
Figure 4  $^{13}$C and DEPT nmr spectra of (134)
6.5 Preparation of Triene (137)

The treatment of lactone 134 with boron trifluoride etherate in methanol was expected to convert the lactone into the methyl ester 136 (Equation 19). However, the sole product, isolated in 83% yield, was not the expected compound. Its IR and $^1$H nmr spectra (Figure 5, p77) did not support the presence of a hydroxyl group, but the $^1$H nmr spectrum contained a signal at $\delta$ 3.19 representing 3 hydrogens consistent with a methoxy group. The lactone portion remained and the mass spectrum revealed the molecular weight had increased by 32 mass units. These features were consistent with the addition of methanol. In addition, the signal due to the geminal methyl groups shifted from $\delta$ 1.39 and 1.43 to $\delta$ 1.02 and 1.38, and the cyclopentadienyl portion also changed both position (from $\delta$ 6.17 - 6.58 to $\delta$ 6.21 - 6.65) and pattern (cf. Figure 2). It appeared that the cyclopropane bond had opened to give the isomeric mixture 137 as illustrated in Equation 20, a consequence of the stretched, polarized nature of the cyclopropane bonds in this spiro system. The methanol was added to the least hindered centre as a result of backside attack to generate the C-1'(R) ether.

![Equation 19]

Equation 19
The cyclopentadiene product 137 could be considered a dead end as the desired reaction product 136 had not been obtained. However, we had long suspected that direct cyclization to a cycloheptane should be possible if the dienophile were constrained so that the desired cyclization was the lowest energy pathway. The triene lactone 137 could thus be utilized to test this strategy experimentally.
Figure 5  $^1$H nmr and IR spectra of (137)
Scheme 33
6.6 Diels - Alder Reaction

The C-5(R)C-1(R)-methoxy triene lactone 137, similar to Brieger's precursor but with an activated, geometrically restricted dienophile, was capable of rapid sigmatropic rearrangement. The \(^1H\) nmr spectrum of 137 (Figure 5) showed it was a mixture of rearrangement products although on TLC it appeared as one spot. This mixture could, in principle, give rise to several different Diels-Alder adducts (Scheme 33). The isomers 139a, 139b and 140a, 140b may arise due to cycloaddition to the opposite face of the cyclopentadiene from the C-1 and C-2 substituted series.

Generally, cycloadditions of substituted cyclopentadienes favor incorporation of the tether linkage into a five- or six-membered ring if allowed by the steric constraints. As mentioned the triene 137 contained a constrained cyclic dienophile and molecular models indicated that of the five possible tetracyclic adducts, compound 138 was least constrained tether and the requisite transition state geometry was the most readily achieved. The cycloaddition of triene 137 was conducted in a microwave oven, as described in Chapter 4, and afforded only one product after chromatography. The intramolecular Diels-Alder reaction of 137 was expected to afford preferentially the adduct 138 (Equation 21). Table 4 (p 81) lists the \(^13C\) nmr spectral characteristics for the possible products. The \(^1H\) nmr of the product (Figure 6, p 82) contained two olefinic protons at δ 6.24 and 6.32, excluding the possibility of adducts 140a and 140b, and the DEPT and \(^13C\) nmr spectra (Figure 7, p 83) contained one CH\(_2\) carbon at δ 41.5, eight CH carbons at 138.7, 136.5, 76.3, 74.2, 58.5, 52.9, 51.0 and 49.9, and two quaternary carbons at 56.3 and 40.4, excluding the possibility of adducts 139a and 139b. Therefore, the Diels-Alder adduct must be the tetracyclic lactone 138. This compound possessed the tricyclic carbon skeleton required for (+)-longifolene and represented the first...
successful synthesis of a cycloheptane directly from the cycloaddition of a substituted cyclopentadiene.

As the spectrum on page 82 indicates the C-5 proton falls at δ 4.62 but the related proton on the methoxyl bearing carbon is hidden. This is a consequence of its orientation with respect to the carbonyl group. It is shielded and shifted upfield due to the anisotropic effect of the carbonyl falling coincidently under the methoxyl signal at δ 3.11. (Unfortunately the integration is not very reliable since the strongest signals were run well off the page.) Consistent with analysis once the lactone is reduced this signal falls as part of a multiplet at δ 3.95 (cf Figure 32, p169).

\[ \text{PhCH}_3, \text{Sealed Tube} \]
\[ \text{Microwave Oven} \]
\[ 30 \text{ min.} \]

\[ 137 \]

\[ 138 \]

Equation 21

In accord with the experimental result, theoretical calculations by an Alchemy II molecular Model Program gave the following relative energies: 1 : 4.7 : 7.4 : 3.6 : 4.1 for 138 : 139a : 139b : 140a : 140b. These numbers reflect in part the relative difficulties of their formation and the relative strain of the different transition states. They indicate that the adduct 138 is the least strained.

The enantioselectivity of this Diels-Alder cycloaddition was controlled by the stereochemistry of C-5 of the triene 137. The restricted geometry of the
dienophile allowed only the C₅-7-exo adduct 138, which leads to (+)-longifolene. The epimeric adduct 142 which would lead to (-)-longifolene, would have to arise from the (4S)-triene 141 (Scheme 34, p 84).

**Table 4 Proton and Carbon Types of Possible Diels-Alder Adducts**

<table>
<thead>
<tr>
<th>Olefinic H CH₂</th>
<th>CH₂</th>
<th>CH</th>
<th>Quat. C</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>139a</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>139b</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>140a</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>140b</td>
<td>1</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
Figure 7  $^{13}$C and DEPT nmr spectra of (138)
Scheme 34
6.7 Conversion of Lactone 151 into (+)-Longifolene

The remaining steps to convert the Diels-Alder adduct 138 into (+)-longifolene are shown in Scheme 35.

To remove any likelihood of a retro Diels-Alder reaction, the tetracyclic lactone 138 was hydrogenated under mild conditions (10 psi, EtOAc, 5 % Pd/C, 22°C). Attempts to convert the methyl ether to a secondary hydroxyl group using trimethylsilyl iodide\(^{76,77}\) failed. Thus, the lactone ring was opened by lithium aluminum hydride reduction to give the methoxy diol 143.

In general a primary hydroxy is more active than a secondary one in esterifications. Therefore, the treatment of the diol 143 with acetic anhydride in the presence of pyridine under carefully controlled conditions at 0°C selectively produced the desired acetate 144 in 74% yield. This was accompanied by the diacetate (15 % yield) as a by-product which could be reduced to diol 143 and recycled.

A free radical deoxygenation via the Robins procedure\(^{70}\) removed the secondary hydroxy group. Next the methoxy group was converted into a secondary hydroxyl by treatment with sodium iodide and trimethylsilyl chloride in the presence of triethylamine. This is a modification of the standard procedure\(^{78}\) and was developed to avoid acetate hydrolysis. The new hydroxyl function was also removed under free radical conditions to afford the acetate 146.

Pyrolysis of the acetate 146 at 525°C provided (+)-longifolene in 55 % yield. The pyrolysis apparatus is illustrated in Figure 8 (p 88). The yield is somewhat lower than for sinularene (76 %), probably a result of the scale (30 mg), but the hydrocarbon was generated cleanly. The synthetic conditions of the pyrolysis were examined at 500°C and 550°C. The former resulted in the mostly recovered starting material whereas the latter gave additional decomposition.
Scheme 35
Figure 8 Pyrolysis Apparatus
The purified sesquiterpene was compared by spectroscopy and optical rotation with an authentic sample. This confirmed the structure and the successful completion of the synthesis from the chiral spiro-alcohol 133 via eleven steps in 11.2% overall yield to give (+)-longifolene, \( [\alpha]^{22} = +47.04^\circ \) (c 1.7, CHCl₃); authentic sample from Aldrich, \( [\alpha]^{22} = +51.2^\circ \) (c 1.9, CHCl₃); lit\(^{1,2} \) \( [\alpha]^{22} = +45.71^\circ \) (neat). The \(^1\)H, \(^13\)C, IR and MS spectra of the synthetic longifolene are displayed in Figure 9 (p90), Figure 10 (p91), Figure 11 (p92), and Figure 12 (p93) respectively. The \(^1\)H and \(^13\)C nmr spectra of the authentic longifolene are displayed in Figure 13 (p94) and Figure 14 (p95).

6.8 An Alternative Route To (145) From (138)

We mentioned earlier that the Diels-Alder adduct 138 was hydrogenated first to remove any likelihood of retro Diels-Alder reaction. However, it was later discovered that this adduct was quite stable, so an alternative synthetic sequence from adduct 138 to the methoxy acetate 145 was examined (Scheme 36). The double bond of the acetate was hydrogenated before the conversion of the methoxy group to a secondary alcohol because the double bond interfered with this reaction to give a complicated product mixture. Thus both routes are adequate but it is easier to handle the compounds in the saturated series.
Scheme 36
Figure 10 $^{13}$C and DEPT nmr spectra of (3)
Figure 11  IR spectrum of (3)
Figure 13: 'H nmr spectrum of Authentic Longifolene (Aldrich)
Figure 14 $^{13}$C nmr spectrum of Authentic Longifolene (Aldrich)
**General:**

Infrared (IR) spectra were recorded on a Perkin-Elmer 1320 or 783 grating spectrophotometer, and were calibrated with the 1601 cm⁻¹ band of polystyrene film. Proton magnetic resonance (¹H NMR) spectra were measured at 60 MHz with a Varian EM 360 spectrometer or at 80 MHz with a Bruker WP80 spectrometer or at 200 MHz with a Varian Gemini spectrometer or at 300 MHz with a General Electric GN 300 or a Varian XL 300 spectrometer. Carbon magnetic resonance (¹³C NMR) spectra were measured at 50 MHz with a Varian Gemini spectrometer or at 75 MHz with a General Electric GN 300 or a Varian ZL 300 spectrometer. The residual solvent signal was used as an internal standard CDCl₃; ¹H: δ 7.262, ¹³C: δ 77.00 and signal positions are reported in ppm downfield from tetramethylsilane (δ scale) as an internal standard, the numbers of protons, multiplicities, coupling constants, and proton assignments are indicated in parentheses. Mass spectra were determined on a V.G. Micromass 7070 HS instrument using an ionization energy of 70 eV, or on a Hewlett-Packard 5890A gas chromatograph 5970B mass selective detector equipped with a 12.5 m capillary column (0.2 mm ID) coated with crosslinked dimethyl silicone (0.33 µm). Optical rotations were measured using a Perkin-Elmer 241 polarimeter (sodium light, cell length = 10 cm, c = g / 100 mL).

Gas-liquid chromatographic analyses were conducted on a Hewlett Packard 402B gas chromatograph equipped with a column (3 m × 6 mm i.d.) containing 1.5 % OV-17 supported on Gas Chrom Q using helium as the carrier gas. Analytical thin layer chromatography (TLC) was carried out on commercial precoated silica gel plates with fluorescent indicator (Eastman Kodak silica gel 13181) or on aluminum sheets precoated (0.2 mm layer thickness) with silica gel 60 F₂₅₄ (E. Merck). Flash
column chromatography using E. Merck silica 60 (230-400 mesh) was employed for all column chromatography.

Petroleum ether refers to a fraction with boiling range 30-60°C. Anhydrous diethyl ether (ether), tetrahydrofuran (THF), dimethoxyethane (DME), and dioxane were obtained by distillation from LiAlH₄ or potassium/benzophenone. Methanol and absolute ethanol were dried by distillation from magnesium. Dry hexamethylphosphoramid (HMPA), dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and diisopropylamine were prepared by distillation from calcium hydride. Solutions in organic solvents were dried over anhydrous magnesium sulfate and stripped of solvent with a Büchi rotary evaporator connected to a water aspirator. Unless otherwise indicated, all reactions were conducted under an atmosphere of dry nitrogen.

1,2-Epoxy-3-butane (79)

3-Buten-2-one (56 g, 0.8 mol, Aldrich) was dissolved in methanol (400 mL) containing 30% hydrogen peroxide (230 ml) and the solution cooled to 0°C with an external ice bath. Aqueous sodium hydroxide (2M, 200 ml) was added dropwise to the stirred solution (caution: initially the reaction is very exothermic) maintaining the temperature below 20°C. Stirring was continued for further 8 h at 22°C after the addition was completed. The reaction was extracted with dichloromethane (5 x 100 mL), the extracts dried, filtered, concentrated, and the product was purified by distillation to give the epoxy-ketone 79 (42 g, 60%, the yield was 71% on a small scale); bp 45-46°C/12 Torr; 1R (film): 1715 (C=O), 1260, 865 (C-O) cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ: 1.99 (s, 3H, CH₃), 2.92 (m, 2H, CH₂-O), 3.28 (dd, 1H, J = 1.5, 1 Hz, O=C-CH-O). Exact mass calcd. for C₄H₆O₂: 86.0368; found: 86.0352.
6-Methyl-6-oxiranylfulvene (80)

A stirred absolute methanol solution (12 mL) of cyclopentadiene (3.30 g, 0.05 mol, freshly distilled) and 1,2-epoxy-3-butanone (4.30 g, 0.05 mol) was cooled to 0°C and pyrrolidine (0.25 mL) was added. The yellow color due to the fulvene was immediately observed and stirring was continued for 2 h at 0°C, then 2 h at 22°C. The reaction was poured into ice water and extracted with petroleum ether (2 x 20 mL). The combined organic layers were washed with 5% aqueous HCl, 5% aqueous sodium bicarbonate, followed by brine, dried, filtered and concentrated to give the epoxy fulvene 80 (5.8 g, 86%). The epoxy fulvene 80 was sufficiently pure for direct use. Upon storage at -20°C it formed yellow crystals and it was kept anhydrous by addition and evaporation of anhydrous benzene; IR (film): 3060 (H-C=), 1635 (s, C=) cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ: 1.91 (s, 3H, CH₃), 2.82 (m, 2H, CH₂-O), 3.90 (dd, 1H, J = 1.5, 1 Hz, CH-O), 6.35 (m, 4H, H-C=C). Exact mass calcd. for C₁₀H₁₁O: 134.0732; found: 134.0708.

2,2-Dimethyl-1-hydroxymethylspiro[2.4]hepta-4,6-diene (82)

Methyl lithium (1.5 M in ether, 10.5 mL, 16 mmol, Aldrich) was added dropwise to a stirred anhydrous THF solution (50 mL) containing the epoxy fulvene 80 (2.01 g, 15 mmol) maintained at -78°C by an external solid CO₂/acetone bath. After stirring for 30 min at -78°C, the reaction mixture was allowed to warm to 0°C and quenched with aqueous ammonium chloride. The mixture was extracted with ether (2 x 20 mL). The combined ether extracts were dried, filtered and concentrated. The crude product was purified by flash chromatography (20% ethyl acetate/petroleum ether) to give the spiro-alcohol 82 (1.24 g, 55%); IR
(film): 3350 (br, OH), 3090, 3060 (H-C=), 1650 (s, C=C) cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ: 1.40 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 1.71 (br s, 1H, OH), 2.39 (t, 1H, J = 7.5 Hz, cyclopropyl H), 3.78 (m, 1H, CH₂-O), 3.94 (m, 1H, CH₂-O), 6.30 (m, 2H, H-C=C), 6.45 (m, 1H, H-C=C), 6.57 (m, 1H, H-C=C); ¹³C NMR (CDCl₃) δ: 138.4, 133.0, 131.8, 129.2, 62.0, 52.3, 43.4, 35.3, 27.5, 20.4. Exact mass calcd. for C₁₀H₁₄O: 150.1044; found: 150.1025.

(2',2' - Dimethylspiro [2.4] hepta-4', 6'- diene - 1'-yl) carboxaldehyde (83)

Active MnO₂ Oxidation:

The spiro alcohol 82 (3.0 g, 0.02 mmol) in 25 mL of dichloromethane was added dropwise to a stirred and refluxed suspension of active MnO₂· (30 g, or 40 g as a mixture with charcoal) in 250 mL of dichloromethane. The mixture was stirred under reflux for 12 h, cooled to room temperature and filtered through a band of Celite and anhydrous MgSO₄. The solid was washed thoroughly with dichloromethane (200 mL) and the combined filtrate was concentrated. The crude product was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to afford the spiro-aldehyde 83 (2.5 g, 84 %) as a pale yellow liquid; IR (film): 2825 (H·CO), 2720 (H·CO), 1704 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 1.42 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 2.78 (d, 1H, J = 6 Hz, cyclopropyl H), 6.17 (m, 1H, cyclopentadienyl H), 6.53 (m, 2H, cyclopentadienyl H), 6.60 (m, 1H, cyclopentadienyl H), 9.56 (d, 1H, J = 6 Hz, H-C=O); ¹³C nmr (CDCl₃) δ: 198.0, 135.5, 132.4, 131.6, 131.4, 56.8, 49.4, 37.1, 26.8, 20.7. Exact mass calcd. for C₁₀H₁₂O: 148.0888; found: 148.0888.

*Preparation of Active Manganese Dioxide

1. A solution of manganese sulfate (111 g) in water (150 mL) and a solution
of sodium hydroxide (40%, 117 mL) were added simultaneously to a hot solution of potassium permanganate (96 g) in water (600 mL) over a period of 1 h. Manganese dioxide was precipitated as a fine brown solid. After stirring for 1 h, the solid was collected by filtration and washed thoroughly with water until the washings were colorless. The solid was dried in an oven at 100-120 °C and ground to a fine powder (85 g) for use. (Based on the literature method of reference 56)

2 A mixture of potassium permanganate (40 g) and charcoal (20 g, J. T. Baker) in 500 mL of water was stirred under heating (70-80 °C) until the purple color discharged. After cooling to room temperature, the solid was collected by filtration, washed thoroughly with water, and dried in an oven at 100-120 °C. The final product was a mixture of manganese dioxide and charcoal as fine powder. (After considerable experimentation we found this material was best provided Baker charcoal was used. This procedure is based on reference 57.)

**Swern Oxidation:** 79, 80

Dimethylsulfoxide (DMSO) (1.76 mL, 25 mmol, dried over CaH₂) in anhydrous dichloromethane (5 mL) was added dropwise to a stirring solution of oxalyl chloride (1.13 mL, 13 mmol, Aldrich) in anhydrous dichloromethane (25 mL) at -78 °C with solid CO₂ / acetone cooling bath. After 10 minutes, this was followed by the addition of spiro-alcohol 82 (1.6508 g, 11 mmol) in anhydrous dichloromethane (10 mL) over a period of 5 min. A foamy white precipitate developed. The suspension was stirred for further 15 minutes and triethylamine (8.35 mL, 60 mmol) was added slowly. After the precipitate disappeared, the external cooling bath was removed, the reaction was allowed to gradually warm to
room temperature, cold water (30 mL) was added, and the mixture was stirred for another 15 minutes. The resulting mixture was separated and the aqueous layer was extracted with dichloromethane (30 mL). The organic layers were combined, washed with 5% HCl, 5% NaHCO₃ and brine (20 mL each time). The washed organic solution was dried, filtered and evaporated to remove solvent. Flash chromatography (5% ethyl acetate/petroleum ether) of the crude product afforded afforded the spiro-aldehyde 82 (1.50 g, 92%) as a pale yellow liquid.

*Methyl 4-bromo-3-methyl-2-butenonate (84)*

Methyl 3,3-dimethylacrylate 97 (5.4 g, 47 mmol) was dissolved in a carbon tetrachloride solution (50 mL) containing N-bromosuccinimide (NBS) (8.7 g, 49 mmol, Aldrich) and AIBN (0.078 g). The mixture was stirred under reflux for 8 h, cooled and filtered to remove the precipitate. The filtrate was concentrated and purified by distillation under reduced pressure to afford the bromo-ester 84 (6.9 g, 68%) as a mixture of Z,E-isomers, b.p range: 45-70 °C / 0.6 Torr. ¹H nmr (80 MHz, CDCl₃) shows two sets of peaks, A: δ: 1.99 (d, J = 2 Hz, 3H, CH₃-C=C), 3.65 (s, 3H, OCH₃), 4.47 (m, 2H, CH₂Br), 5.68 (d, J = 2 Hz, 1H, H-C=C); B: δ: 2.21 (d, J = 2 Hz, 3H, CH₃-C=C), 3.65 (s, 3H, OCH₃), 3.86 (d, J = 1 Hz, 2H, CH₂Br), 5.87 (m, 1H, H-C=C). The integration of the two sets of peaks was almost 1:1.

*Methyl 3,3-dimethylacrylate (97)*

A solution of 3,3-dimethylacrylic acid (11.0 g, 0.11 mol, Aldrich) and boron trifluoride etherate (14.3 g, 0.10 mol, Aldrich) in 40 mL of absolute methanol was stirred under reflux for 12 h, cooled to 0 °C, and quenched with 5% aqueous sodium carbonate solution. The mixture was extracted with ether (2 × 30 mL)
and the combined extracts were dried, filtered, and concentrated. Fractional distillation under reduced pressure gave the methyl ester 97 (6.6 g, 54%) as a colorless liquid; b.p: 30 °C / 0.6 Torr; 1H nmr (200 MHz, CDCl₃) δ: 1.88 (d, 3H, J = 1.2 Hz, CH₃), 2.16 (d, 3H, J = 1.5 Hz, CH₃), 3.67 (s, 3H, OCH), 5.67 (m, 1H, H-C=C); Exact mass calcd. for C₇H₁₀O₂: 114.0680; found: 114.0687.

General Procedure for Reformatsky Reaction:

Active zinc powder* (five molar equivalent) suspended in anhydrous THF (2 mL) was placed in a three necked flask equipped with a condenser and a dropping funnel. The reactant aldehyde (benzaldehyde or 83, ca. 2 mmol) and bromoesters (84 or 89, 1.5 molar equivalent) in anhydrous THF (10 mL) were placed in the dropping funnel. A few drops of THF solution containing the starting materials were added to the stirred suspension. Next a small crystal of iodine was added and the reaction was heated. After the reaction began refluxing and the iodine color discharged, the rest of the THF solution was added dropwise to the reaction while stirring under reflux. After the addition was complete, the reaction was continued for another 1 hour, cooled to room temperature, quenched with saturated aqueous ammonium chloride, and filtered to remove zinc solid. The filtrate was extracted with ether (2 × 10 mL) and the combined extracts were washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (20% ethyl acetate/petroleum ether). This is related to the method of Hudlický.⁸¹ ⁸²

*Preparation of Active Zinc Powder ⁸¹

The commercially available zinc dust (Aldrich) was quickly washed with 50% acetic acid and filtered (done in fume hood). The washed zinc dust was rinsed
thoroughly with water and DME, and dried under vacuum at 110 °C for 12 h. The treated zinc powder can be stored under N₂ but should be re-dried for at least 2 h before use.

*Methyl 5-hydroxy-3-methyl-5-phenyl-2-butoatoate (85)*

IR (film): 3450 (OH), 1725 (C=O), 1640, 1600 (C=C) cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 1.57 (s, 3H, CH₃), 3.02 (d, 1H, J = 4.4 Hz, CH₂), 3.40 (d, 1H, J = 8.8 Hz, CH₂), 3.74 (s, 3H, OCH₃), 4.83 (s, 1H, H·C=C), 4.85 (s, 1H, OH), 5.05 (dd, 1H, J = 4.4, 8.8 Hz, H·C-OH), 7.33 (s, 5H, phenyl H). Low resolution mass spectrum found 220 (C₁₃H₁₆O₃, M⁺).

*Methyl 5-hydroxy-5-(2',2'-dimethylspiro[2.4]hepta-4',6'-dien-1'-yl)-2-pentenoate (90)*

IR (film): 3450 (OH), 1720 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 2.05 (d, J = 3.5 Hz, 1H, cyclopropyl H), 2.25 (br. s, 1H, OH), 2.30 - 2.60 (m, 2H, CH₂), 3.72 (s, 3H, OCH₃), 4.55 (m, 1H, H·C-OH), 5.76 (d, J = 6 Hz, 1H, C=CH-CO₂Me), 6.18 (m, 2H, cyclopentadienyl H), 6.43 (m, 2H, cyclopentadienyl H), 6.88 (m, 1H, H·C=CH₂ CO₂Me). Low resolution mass spectrum found 248 (C₁₃H₂₀O₃, M⁺).

*Methyl 2-vinyl-3-hydroxy-3-(2',2'-dimethylspiro[2.4]hepta-4',6'-dien-1'-yl)propanoate (91)*

IR (film): 3490 (OH), 1730 (C=O), 1640 (C=C) cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 2.80 (d, J = 3 Hz, 1H, OH), 3.25 (dd, J = 6, 12 Hz, 1H, H·C-CO₂Me), 3.65 (s, 3H, OCH₃), 4.52 (m, 1H, H·C-OH), 5.25 (m, 2H, CH₂=C), 5.60 - 5.90 (m, 1H, H·C=CH₂), 6.22 (m, 1H, cyclopentadienyl H), 6.45 (m, 1H,
cyclopentadienyl H). Low resolution mass spectrum found 248 (C$_{15}$H$_{20}$O$_{3}$, M$^+$.)

2 - Ethylene-1,3-dithiane (92)

Preparation of Propanethioic acid: The Grignard reagent was prepared from bromoethane (21.8 g, 0.20 mmol, Aldrich) and magnesium turnings (6.0 g, 0.25 mmol, J. T. Baker) in anhydrous THF (200 mL). A solution of carbon disulfide (15.2 g, 0.20 mmol, Aldrich) in anhydrous THF (20 mL) was added dropwise to the reagent decanted from the remaining magnesium and maintained at -10 °C. The brown solution that formed was allowed to warm to room temperature overnight and then quenched with 10 % hydrochloric acid at -10 °C. The mixture was extracted with ether (2 x 100 mL) and the combined ether layers were washed with brine, dried, filtered, and concentrated at 0 °C. Distillation under reduced pressure gave 13.9 g (65.5 %) of the thioic acid as a brown liquid with a very nasty smell; bp 38 °C / 0.2 Torr; $^1$H nmr (80 MHz, CDCl$_3$) δ: 1.37 (t, 3H, J = 7.4 Hz, CH$_3$), 2.63 (s, 1H, SH), 3.06 (q, 2H, J = 7.4 Hz, CH$_2$-C=S). This is a modification of the literature method.$^8$

Preparation of Dithiane (92): A LDA solution was prepared from diisopropylamine (13 g, 128 mmol) and n-butyllithium (2.5 M in hexane, 44 mL, 110 mmol, Aldrich) in anhydrous THF (250 mL) at 0 °C. HMPA (27.0 mL, 150 mmol) was added to the solution at 0 °C, followed by a solution of propanethioic acid (5.3 g, 50 mmol) in anhydrous THF (5 mL) over a period of 10 min. After stirring the golden yellow solution at room temperature for 2 h, it was cooled to -78 °C, followed by the dropwise addition of a anhydrous THF solution (5 mL) of 1-bromo-3-chloropropane (7.9 g, 50 mmol, Aldrich). The solution was allowed to warm to room temperature overnight. The reaction mixture was poured into
hexane (100 mL) and washed with 5% sodium bicarbonate (50 mL) and water (2 x 50 mL), and the combined aqueous layers were backwashed with hexane (50 mL). The combined hexane extracts were washed with brine, dried, filtered and concentrated. The residue was distilled to yield 3.81 g (52%) of dithiane 92 as a pale yellow liquid with an unpleasant smell; bp 61 - 62°C / 0.3 Torr (lit. bp 43 - 44°C / 0.1 Torr); ¹H nmr (80 MHz, CDCl₃) δ: 1.76 (d, 3H, J = 7 Hz, CH₃), 2.18 (m, 2H, CH₂), 2.87 (m, 4H, SCH₂), 6.00 (q, 1H, J = 7 Hz, H-C=C). Low resolution mass spectrum found 146 (M⁺).

General Procedure for Condensation of Aldehydes and Dithiane (92):
A: LDA

A LDA solution was prepared from diisopropylamine (0.232 g, 2.3 mmol, Aldrich) and n-butyllithium (2.5 M in hexane, 0.9 mL, 2.2 mmol, Aldrich) in anhydrous THF (5 mL) at -25°C. Dithiane 92 (0.321 g, 2.2 mmol) in anhydrous THF (2 mL) was added to the solution, forming a yellow solution. After stirring at -25°C for 30 minutes, the solution was cooled to -78°C, followed by dropwise addition of spiro-aldehyde 83 (0.220 g, 1.5 mmol) in anhydrous THF (10 mL). The resulting solution was stirred at -78°C for further 30 minutes, warmed to 0°C, and quenched with saturated aqueous ammonium chloride. The mixture was extracted with ether (2 x 20 mL) and the combined ether extracts were washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (20% ethyl acetate / petroleum ether) to give 0.349 g (86%) of α-hydroxy dithiane 94 and 0.051 g (10%) of γ-hydroxy dithiane 96, α : γ = 90 : 10, total yield 96%.

B: LDA / ZnCl₂
2-Ethylidene-1,3-dithiane 92 (0.2044 g, 1.4 mmol) in anhydrous THF (2 mL) was added dropwise to a LDA solution prepared from diisopropylamine (0.152 g, 1.5 mmol) and n-butyllithium (2.5 M in hexane, 0.6 mL, 1.5 mmol, Aldrich) in anhydrous THF (5 mL) at -40°C. The yellow solution was stirred at -40°C for 40 minutes and zinc chloride (0.2031 g, 1.5 mmol, Aldrich) was added. After stirring at -40°C for additional 30 minutes, the reaction solution was cooled to -78°C, followed by dropwise addition of spiro-aldehyde 83 (0.1924 g, 1.3 mmol) in anhydrous THF (10 mL). The reaction was continued for a further hour at -78°C, warmed to 0°C, and quenched with saturated aqueous NH₄Cl. The mixture was extracted with ether (2 x 20 mL) and the combined ether extracts were washed with brine, dried, filtered, concentrated, and purified by flash chromatography (15% ethyl acetate/petroleum ether) to give 0.1626 g (43%) of triene 96 (α-product) and 0.1037 g (27%) of triene 94 (γ-product), α:γ = 60:40, total yield 70%.

C: LDA / CuI · P(MeO)₃

A LDA solution was prepared from diisopropylamine (0.36 mL, 2.6 mmol) and n-butyllithium (2.7 M in hexane, 0.96 mL, 2.6 mmol, Aldrich) in anhydrous THF at -25°C. Dithiane 92 (0.3650 g, 2.5 mmol) in anhydrous THF (1 mL) was added to the solution. The reaction solution was stirred at -25°C for 30 minutes, cooled to -78°C, followed by addition of trimethylphosphite cuprous iodide complex * (0.9058 g, 2.8 mmol) in anhydrous THF (2 mL). A yellow precipitate gradually formed during one hour of stirring. The spiro-aldehyde 83 (0.3703 g, 2.5 mmol) in anhydrous THF (10 mL) was added dropwise to the yellow suspension over a period of 30 minutes, resulting in a greenish solution. The solution was stirred at -78°C for an hour, warmed to 0°C, stirred at 0°C for 30 min, and quenched with saturated aqueous NH₄Cl. A minimum amount of water was added to just
dissolve the white precipitate and the mixture was stirred at 0°C for 10 min and extracted with ether (3 × 15 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (20% ethyl acetate /petroleum ether) gave 0.1591 g (22%) of 96 (α-product) and 0.2892 g (39%) of 94 (γ-product), α : γ = 35 : 65, total yield 61%. This procedure is related to the method of Ziegler. \(^\text{59}\)

*Preparation of CuI-(MeO)\(_3\)P Complex:* \(^\text{59}\)

A mixture of trimethyl phosphite (1.61 g, 13 mmol, Aldrich) and cuprous iodide (2.5 g, 13 mmol, Aldrich) in anhydrous benzene (20 mL) was refluxed for 8 hours with stirring. The hot suspension was filtered from the remaining insoluble materials and the filtrate was concentrated to give a white solid. Recrystallization from ether / chloroform mixture afforded 1.94 g (47.5%) of trimethylphosphite-cuprous iodide complex as white needles, which were kept in freezer until required.

**D: LDA / CdCl\(_2\)**

The dithiane 92 (2.2 mmol) in anhydrous THF (5 mL) was added dropwise to a LDA solution prepared from diisopropylamine (2.3 mmol) and n-butyllithium (2.5 M in hexane, 2.3 mmol) in anhydrous THF (10 mL) at -40°C. After stirring at -40°C for 30 min, the reaction was cooled to -78°C and cadmium chloride powder (1.5 mmol, Aldrich, gold label, ground and dried in vacuum at 110°C) was added in one portion. The white suspension was stirred at -78°C for 30 minutes and a anhydrous THF solution (10 mL) containing aldehyde (benzaldehyde or spiro-aldehyde 83, 1.0 mmol) was added over a period of 30 minutes. After the addition was complete, the reaction was conducted at -78°C for a further hour,
warmed to 0°C, stirred at 0°C for 0.5 hour, and quenched with saturated aqueous 
NH₄Cl. The mixture was filtered through Celite and the filtrate was extracted with 
ether (2 × 15 mL). The combined ether layers were washed with brine, dried, 
filtered, and concentrated. The oily residue was purified by flash chromatography 
(15% ethyl acetate/petroleum ether) to give α-product (95 or 96) and γ-product 
(93 or 94) in total yield of 90-95%, γ-product dominated (cf. Table 1).

2 - (3-Hydroxy-3-phenylpropyldiene)-1,3-dithiane (93)

IR (film): 3410 (br, OH), 1605, 1585 (C=O), 705 (s, C=S) cm⁻¹; ¹H nmr 
(80 MHz, CDCl₃) δ: 2.01 - 2.27 (m, 3H), 2.60 - 2.93 (m, 6H), 4.74 (t, 1H, J = 6.4 
Hz, HC-O), 5.97 (t, 1H, J = 7.4 Hz, H-C=C), 7.37 (m, 5H, phenyl H). Exact mass 
calcd. for C₁₃H₁₆O₂S₂: 252.0642; found: 252.0647.

2 - (3-Hydroxy-3-(2',2'-dimethylspiro[2.4]hepta-4',6'-dien-1'-yl) 
propyldiene)-1,3-dithiane (94)

IR (film): 3410 (OH), 1600 (C=O) cm⁻¹, ¹H nmr (300 MHz, CDCl₃) δ: 
1.39 (s, 3H, CH₃), 1.41 (s, 3H, CH₃), 2.03 (d, 1H, J = 9.6 Hz, cyclopropyl H), 
2.18 (m, 2H, -SCH₂CH₂-SCH₂-), 2.58 (dd, 2H, J = 5.7, 7.5 Hz, CH₂-C=C), 2.88 
(t, 4H, J = 6.0 Hz, SCH₂), 2.97 (s, 1H, OH), 3.41 (m, 1H, H-C=O-H), 6.07 (t, 1H, 
J = 7.5 Hz, H-C=C), 6.37 (m, 1H, cyclopentadienyl H), 6.44 (m, 1H, 
cyclopentadienyl H), 6.49 (m, 2H, cyclopentadienyl H). Exact mass calcd. for 
C₁₆H₂₂OS₂: 294.1111; found: 294.1119.

2 - Vinyl-2-(1-hydroxy-1-phenyl)-1,3-dithiane (95)

IR (film): 3450 (br, OH), 3080, 3060, 3025 (phenyl H), 1625 (C=O) cm⁻¹; 
¹H nmr (80 MHz, CDCl₃) δ: 1.94 (m, 2H, CH₂), 2.80 (m, 4H, SCH₂), 2.94 (d,
1H,  J = 3.2 Hz, OH), 4.90 (d,  1H,  J = 3.2 Hz, H-C=O), 5.35 - 6.00 (m, 3H, H-C=C), 7.26 - 7.48 (m, 5H, phenyl H).  Exact mass calcd. for C_{12}H_{16}O_{2}: 252.0642; found: 252.0657.

2-Vinyl-2-[1-hydroxy-1-(2', 2'-dimethylspiro[2.4]hepta-4', 6'-dien-1'-yl)]-1,3-dithiane (96)

$^1$H nmr (80 MHz, CDCl$_3$) δ: 1.39 (s, 3H, CH$_3$), 1.45 (s, 3H, CH$_3$), 1.89 (m, 2H, -SCH$_2$-CH$_2$-SCH$_2$), 2.35 (d, 1H,  J = 9.9 Hz, OH), 2.53 (d, 1H,  J = 4.5 Hz, cyclopropyl H), 2.83 (m, 4H, SH$_2$), 3.89 (dd, 1H,  J = 4.5, 9.9 Hz, H-C=OH), 5.11 - 5.59 (m, 3H, H-C=C), 6.15 - 6.50 (m, 4H, cyclopentadienyl H).  Exact mass calcd. for C$_{16}$H$_{22}$O$_2$: 294; found: 294 (low resolution).

**General Procedure of LDA/CdCl$_2$ Reaction with methyl3,3-dimethylacrylate (97)**

A LDA (2.1 equiv) solution was prepared from diisopropylamine and n-butyllithium in anhydrous THF at -78°C. A THF solution of methyl ester 97 (2.0 equiv.) was added dropwise to the solution, yielding a pale yellow solution. After stirring for 30 minutes at -78°C, cadmium powder (Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion and the resulting suspension was stirred for further 30 minutes, followed by addition of aldehyde (benzaldehyde or spiro-aldehyde 83) in THF with a syringe pump (0.1 mL/min). After the addition was complete, the reaction was continued for an additional hour, then allowed to warm to 0°C, stirred for 30 minutes at 0°C, and quenched by saturated aqueous NH$_4$Cl. The mixture was filtered through Celite and the filtrate was extracted with ether (2 × 20 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (20 % ethyl acetate / petroleum ether) afforded the hydroxyester 85 or 86.
(γ-product) and the hydroxyester 87 or 88 (α-product), α/γ ratios and yields see Table 1 in Chapter 4.

**Methyl 5-hydroxy-3-methyl-5-(2',2' -dimethylspiro [2.4] hepta - 4', 6' - dien - 1'-yl )-2-pentenoate (86)**

IR (film): 3480 (OH), 3060 (H-C=C), 1720 (C=O), 1635 (C=C) cm⁻¹;

¹H nmr (300 MHz, CDCl₃) δ: 1.38 (s, 3 H, CH₃), 1.43 (s, 3 H, CH₃), 1.71 (s, 3 H, CH₃), 1.95 (d, 2 H, J = 6.5 Hz, CH₂-C=C), 2.15 (d, 1 H, J = 10.6 Hz, cyclopropyl H), 3.35 (br. s, 1 H, OH), 3.62 (s, 3 H, OCH₃), 4.22 (m, 1 H, CH-O), 5.15 (s, 1 H, H-C=C), 6.15 (m, 2 H, cyclopentadienyl H), 6.38 (m, 2 H, cyclopentadienyl H), 6.50 (m, 2 H, cyclopentadienyl H); ¹³C nmr (CDCl₃) δ: 164.4, 138.7, 137.8, 132.5, 131.3, 128.9, 127.7, 70.5, 56.3, 52.1, 51.2, 42.9, 34.5, 27.1, 22.5, 19.9. Low resolution mass spectrum found 262 (C₁₆H₂₁O₃, M⁺), 244 (C₁₆H₂₀O₂, M⁺-H₂O).

**Methyl 2-isopropylidenyl-3-hydroxy-3-(2',2' -dimethylspiro [2.4] hepta - 4', 6' - dien - 1'-yl ) propanoate (88)**

IR (CHCl₃): 3660 (OH), 1730 (C=O), 1650 (C=C) cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: 1.41 (s, 3 H, CH₃), 1.48 (s, 3 H, CH₃), 1.68 (s, 3 H, CH₃-C=C), 2.28 (d, 1 H, J = 10.5 Hz, cyclopropyl H), 2.82 (br s, 1 H, OH), 3.47 (d, 1 H, J = 7.5 Hz, CH-CO₂Me), 3.69 (s, 3 H, OCH₃), 4.02 (m, 1 H, CH-O), 4.76 (s, 1 H, H-C=C), 4.83 (s, 1 H, H-C=C), 6.18 (m, 2 H, cyclopentadienyl H), 6.41 (m, 1 H, cyclopentadienyl H), 6.50 (m, 1 H, cyclopentadienyl H); ¹³C nmr (CDCl₃) δ: 172.9, 139.1, 137.9, 132.5, 132.2, 129.0, 115.6, 71.0, 59.8, 51.9, 51.5, 46.8, 35.7, 26.4, 22.0, 21.0. Low resolution mass spectrum found 262 (C₁₆H₂₂O₃, M⁺), 244 (C₁₆H₂₀O₂, M⁺-H₂O).
LDA / CdI₂ Reaction of Benzaldehyde with methyl 3,3-dimethylacrylate (97)

An anhydrous THF solution (5 mL) of methyl 3,3-dimethylacrylate 97 (1.026 g, 9 mmol) was added dropwise to a LDA solution prepared from diisopropylamine (1.3 mL, 9 mmol) and n-butyllithium (2.6 M in hexane, 3.5 mL, 9 mmol, Aldrich) in anhydrous THF (30 mL) at -78°C. The solution was stirred for 30 min after the addition was complete, followed by addition of cadmium iodide (1.649 g, 4.5 mmol, Aldrich, gold label, dried under vacuum for 2 h at 110°C) in one portion. Cadmium iodide slowly dissolved and formed a light yellow solution.

Benzaldehyde (0.424 g, 4 mmol, Aldrich, re-distilled) in anhydrous THF (5 mL) was added dropwise to this solution. The resulting solution was stirred for an hour at -78°C, for 30 min at 0°C, and quenched with saturated aqueous NH₄Cl. The mixture was extracted with ether (2 × 20 mL) and the organic layers combined, washed with brine, dried, filtered, and concentrated. Flash chromatography (20% ethyl acetate/petroleum ether) gave hydroxy-ester 85 (γ-product, 0.519 g, 59%) and hydroxy-ester 87 (α-product, 0.051 g, 6%), α : γ = 10 : 90, 65% total yield.

Thermodynamic Study of LDA / CdCl₂ Reaction:

1. Methyl 3,3-dimethylacrylate 97 (0.114 g, 1.0 mmol) in anhydrous THF (5 mL) was added dropwise into a LDA solution prepared from diisopropylamine (0.15 mL, 1.1 mmol) and n-butyllithium (2.5 M in hexane, 0.44 mL, 1.1 mmol) in anhydrous THF (5 mL) at -78°C. After stirring for 30 min, cadmium chloride powder (0.0916 g, 0.5 mmol, Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion. The suspension was stirred for 30 min at -78°C and an anhydrous THF solution (10 mL) containing the spiro-aldehyde 83 (0.074 g, 0.5 mmol) was added dropwise over a period of 45 min. The reaction
was stirred for an hour at -78°C and then quenched by slowly adding acetic acid (1 mL) in anhydrous THF (2 mL). The mixture was filtered with the help of Celite and the filtrate was extracted with ether (2 x 20 mL). The combined ether layers were washed with brine, dried, filtered, and concentrated. Flash chromatography (20% ethyl acetate/petroleum ether) yielded hydroxy-ester 88 (0.1034 g, 79%) as the dominant product.

2. An LDA (0.8 mmol) solution was prepared in anhydrous THF (5 mL) at -78°C and a THF solution (2 mL) of methyl 3,3-dimethylacrylate (0.0456 g, 0.4 mmol) was added dropwise. After stirring for 30 min, cadmium chloride powder (0.0732 g, 0.4 mmol, Aldrich, treated as described above) was added in one portion, followed by a solution of hydroxy-ester 88 (0.1034 g, 0.39 mmol) in anhydrous THF (10 mL). The suspension was stirred for an hour at -78°C, warmed to 0°C, stirred for an hour at 0°C, and then quenched with saturated aqueous NH₄Cl. The mixture was filtered and the filtrate was extracted with ether (2 x 20 mL). The ether extracts were combined, washed with brine, dried, filtered, and concentrated. Flash column chromatography (15% ethyl acetate/petroleum ether) gave hydroxy-ester 86 (0.0755 g, 73%) and recovered starting material 88 (0.0139 g, 13.4%), α:γ = 16:84.

**LiNCY₂/CdCl₂ Reaction of Benzaldehyde with Methyl crotonate**

A THF (2 mL) solution of HMPA (1.79 g, 10 mmol) was added to a lithium dicyclohexylamide (LiNCY₂) solution prepared from dicyclohexylamine (1.63 g, 9 mmol) and n-butyllithium (2.6 M in hexane, 3.5 mL, 9 mmol) in anhydrous THF (20 mL) at 0°C. The solution was stirred for 30 min at 0°C, then cooled to -78°C, followed by the addition of methyl crotonate (0.905 g, 9 mmol, Aldrich) in
anhydrous THF (5 mL). After stirring for 30 min at -78°C, cadmium powder (0.825 g, 4.5 mmol, Aldrich, gold label, ground and dried under vacuum at 110°C overnight) was added in one portion. The resulting suspension was stirred for 30 min at -78°C and a solution of benzaldehyde (0.424 g, 4 mmol, Aldrich, re-distilled) in anhydrous THF (5 mL) was added dropwise into the suspension. The reaction was continued at -78°C for an hour, at 0°C for 30 min, and quenched with saturated aqueous NH₄Cl. The mixture was filtered through Celite, and the filtrate was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine, dried, filtered, concentrated, and purified by flash chromatography (20% ethyl acetate/petroleum ether) to give 98 (γ-product, 0.338 g, 41%) and 99 (α-product, 0.328 g, 40%), α : γ = 50 : 50, 81% total yield.

*Methyl 5-hydroxy-5-phenyl-2-pentenoate (98)*

IR (film): 3490 (OH), 3080, 3060, 3030 (phenyl C-H), 1715 (C=O), 1600 (C=C) cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 2.13 (m, 2 H, CH₂), 2.80 - 3.15 (m, 2 H, H-C-O, OH), 3.69 (s, 1 H, OCH₃), 5.81 (m, 1 H, C=CH-CO₂Me), 6.85 (m, 1 H, H-C=H-CO₂Me), 7.25 (m, 5 H, phenyl H). Low resolution mass spectrum found 206 (C₁₂H₁₄O₃, M⁺).

*Methyl 2-vinyl-3-hydroxy-3-phenylpropanoate (99)*

IR (film): 3490 (OH), 1725 (C=O), 1460 (C=C) cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 2.89 (d, J = 2.6 Hz, 1 H, OH), 3.35 (dd, J = 2.6, 5.8 Hz, 1 H, H-C=CO₂Me), 3.61 (s, 3 H, OCH₃), 5.05 (m, 1 H, H-C-OH), 5.32 (m, 2 H, C=CH₂), 5.96 (m, 1 H, H-C=CH₂), 7.32 (m, 5 H, phenyl H). Exact mass calcd. for C₁₂H₁₄O₃: 206.0942; found: 206.0968.
2 - Ethyldiene - 1, 3 - dithiane 1, 3 - dioxide (101) \(^{64}\)

Sodium periodate (5.39 g, 25.2 mmol) in water (40 mL) was added dropwise with stirring to 2-ethyldiene-1,3-dithiane 92 (1.22 g, 8.4 mmol) in THF (30 mL). A white precipitate was formed in a mildly exothermic reaction. The suspension was stirred for 12 h. The reaction mixture was extracted with dichloromethane (5 × 25 mL), the combined extracts were dried, filtered, and concentrated under vacuum to give a yellow, oily solid. The latter was washed with THF and recrystallized from a mixture of THF and dichloromethane to give the dioxide 101 (0.98 g, 65%), mp 164 - 165.6 °C, \(^1\)H nmr (80 MHz, CDCl\(_3\)) \(\delta\): 2.16 (d, 3H, \(J = 3.5\) Hz, CH\(_3\)-C=C), 2.2 - 2.9 (m, 4H), 3.06 (m, 1H, H-CHS=O), 3.13 (m, 1H, H-CHS=O), 6.16 (q, 1H, \(J = 3.5\) Hz, H-C=C). Exact mass calcd. for C\(_8\)H\(_{10}\)O\(_2\)S\(_2\): 178.0122; found: 178.0121. This structure was confirmed by X-ray crystallography.

**Procedure of Phase - Transfer Catalyst Reaction: \(^{85}\)**

The spiro-aldehyde 83 (0.1314 g, 0.9 mmol) in dichloromethane (3 mL) was added dropwise at 22 °C to a vigorously stirring mixture of dithiane dioxide 101 (0.14466 g, 0.8 mmol) and benzyltriethylammonium chloride (0.0192 g, 0.08 mmol) in dichloromethane (10 mL) and 10% aqueous NaOH (2 mL) at room temperature. After stirring for 10 min, the reaction solution was diluted with ice-cold water and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NH\(_4\)Cl, dried, filtered, and concentrated to give a brown liquid. TLC (3% MeOH/CHCl\(_3\)) and \(^1\)H nmr indicated it was a mixture of products.

3 - [ Nethoxy - 3 - ( 2', 2' - dimethylspiro [ 2. 4 ] hepta - 4', 6' - dien - 1' - yl ) - ]
Commercially available potassium hydroxide was placed in a round bottomed flask and heated under vacuum with Bunsen burner to remove water. The resulting potassium hydroxide was ground quickly and re-dried under vacuum at 110°C to obtain a fine white powder.

An anhydrous THF / DMSO solution (20 mL, 1 : 2 v/v) of the cyclopentadiene-dithiane 94 (0.729 g, 2.4 mmol) was added dropwise to a suspension of dried KOH powder (1.120 g, 20 mmol) in anhydrous THF / DMSO (50 mL, 1 : 2 v/v) maintained at 0°C, followed by iodomethane (1.14 g, 8.0 mmol, Aldrich). After the addition was complete, the reaction was slowly warmed to room temperature and stirred overnight. The resulting solution was quenched with ice-cold water and the mixture was extracted with ether (3 x 10 mL). The combined ether extracts were dried over anhydrous Na₂SO₄, filtered, and concentrated. The black residue was purified by flash chromatography (5% ethyl acetate / petroleum ether) to afford the methyl ether dithiane 104 (0.569 g, 77%) as an oily liquid; $^1$H nmr (300 MHz, CDCl₃) δ: 1.36 (s, 3 H, CH₃), 1.38 (s, 3 H, CH₃), 2.03 (d, 1 H, $J = 9.6$ Hz, cyclopropyl H), 2.18 (m, 2 H, CH₂), 2.58 (dd, 2 H, $J = 5.7$, 7.5 Hz, CH₂-C=C), 2.89 (t, 4 H, $J = 6$ Hz, SCH₂), 2.97 (s, 3 H, OCH₃), 3.41 (m, 1 H, CH-O), 6.07 (t, 1 H, $J = 7.5$ Hz, H-C=C), 6.22 (m, 1 H, cyclopentadienyl H), 6.35 (m, 1 H, cyclopentadienyl H), 6.46 (m, 1 H, cyclopentadienyl H), 6.50 (m, 1 H, cyclopentadienyl H).

*Methyl 5-tert-butyldimethylsiloxy-3-methyl-5-(2',2'-dimethylspiro[2,4']hepta-4',6'-dien-1'-yl)-2-pentenoate (100)*

tert-Butyldimethylsilyl chloride (1.2995 g, 8.6 mmol, Aldrich) was added to a
stirring suspension of silver perchlorate (1.7433 g, 8.5 mmol) in anhydrous acetonitrile (25 mL) at room temperature. The white suspension formed (silver chloride and tert-butylidimethylsilyl perchlorate) was stirred for 30 min and pyridine (2 mL, excess) was added, followed by a solution of hydroxy-ester 80 (1.100 g, 4.2 mmol) in anhydrous acetonitrile (5 mL). The resultant mixture was stirred overnight, diluted with ether (30 mL), and then filtered. The filtrate was washed with 5% aqueous NaHCO₃ and brine, dried, filtered, and concentrated. Flash chromatography (5% ethyl acetate/petroleum ether) afforded the silyl ether product 100 (1.429 g, 91%) as a colorless liquid. GC-MS analysis indicated it was a mixture of two major components with M⁺/z 376, IR spectroscopy indicated the hydroxyl group had disappeared, and ¹H nmr confirmed the existence of tert-butylidimethylsilyl group. Therefore, the product was used directly for Diels-Alder reaction without further purification.

5 - tert - Butyldimethylsiloxy - 3, 3, 7, - trimethyl - 8 - methoxycarbonyltetracyclo (5.4.0²₄. 0₂₉) undecane (103)

An anhydrous toluene solution (25 mL) containing silyl ether triene 100 (0.6185 g, 1.6 mmol) and hydroquinone (2 mg, Aldrich) was placed in a thick-walled glass pressure tube (Pyrex), flushed with nitrogen, and then sealed. The pressure tube was placed in a microwave oven and surrounded with damp vermiculite. The reaction was conducted for 2 h, the pressure tube was completely cooled, and the solution transferred to a round bottomed flask and concentrated. The residue was purified by flash chromatography (5% ethyl acetate/petroleum ether) to yield the Diels-Alder adduct 103 (0.5535 g, 92%) as a colorless liquid; IR (film): 1715 (C=O), 1565 (C=C) cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: -0.23 (S, 3 H, SiCH₃), 0.15 (S, 3 H, SiCH₃), 0.21 (d, J = 8.4 Hz, 1 H, cyclopropyl H), 0.83
(S, 3 H, CH₃), 0.84 (S, 9 H, t-butyl H), 1.09 (S, 3 H, CH₃-cyclopropane), 1.16 (S, 3 H, CH₃-cyclopropane), 1.95 (dd, J = 4.2, 11.4 Hz, 1 H, CH₂, another H hidden in CH₃ peak), 2.42 (m, 2 H, bridgehead CH), 2.90 (d, J = 8.7 Hz, H-C-CON₂Me), 3.66 (S, 3 H, OCH₃), 3.94 (m, 1 H, H-C-OTBDMSi), 5.89 (m, 1 H, H-C=C), 6.17 (m, 1 H, H-C=C); ¹³C nmr (CDCl₃) δ: 175.5 (C=O), 136.6 (C=C), 131.5 (C=C), 71.5 (CH), 65.5 (CH), 56.4 (quaternary C), 51.1 (CH₃), 49.0 (CH₂), 46.2 (CH), 43.8 (CH), 43.4 (quaternary C), 32.4 (CH), 25.6 (3 C, CH₃), 25.0 (quaternary C), 23.7 (CH₃), 22.7 (CH₃), 17.9 (quaternary C), 17.2 (CH₃), -4.6 (CH₃), -5.2 (CH₃). Exact mass calcd. for C₁₈H₃₇O₃Si (M⁺- t-butyl): 319.1728; found: 319.1726.

5 - Hydroxy - 3, 3, 7 - trimethyl - 8 - methoxycarbonyltetracyclo [5. 4. 0 1.7. 0 2.4. 0 2.9] - 10 - undecene (105) ⁸⁷

Tetra-n-butylammonium fluoride (1.0 M in THF, 2.5 mL, 2.5 mmol, Aldrich) was added to a stirred solution of the silyl ether ester 103 (0.4718 g, 1.25 mmol) in anhydrous THF (5 mL) at room temperature. The reaction solution was stirred for a further 2 h and then evaporated to remove the solvent. The black residue was dissolved in ether (15 mL) and washed with water (20 mL). The aqueous layer was extracted with ether (10 mL) and the organic layers were combined, washed with saturated aqueous NH₄Cl, dried, filtered, and concentrated. The crude product was purified by flash chromatography (20 % ethyl acetate/petroleum ether) to give 0.2448 g (75 %) of tetracyclic alcohol 105 as a pale yellow oil; IR (film): 3440 (OH), 1720 (C=O), 1570 (C=C) cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: 0.23 (d, 1 H, J = 8.8 Hz, cyclopropyl H), 0.83 (s, 3 H, CH₃), 1.11 (s, 3 H, CH₃), 1.15 (d, 1 H, J = 11.5 Hz, CH₂-CH-O), 1.17 (s, 3 H, CH₃), 1.95 (dd, 1 H, J = 4.1, 11.5 Hz, CH₂-CH-O), 2.03 (br. s, 1 H, OH), 2.42 (m, 2 H, CH₂-C=C), 2.89 (d, 1
H, J = 9 Hz, CH-CO₂Me), 3.72 (s, 3 H, OCH₃), 4.03 (dd, 1 H, J = 8.8, 9 Hz, CH-O), 5.88 (m, 1 H, H-C=C), 6.16 (m, 1 H, H-C=C); ¹³C nmr (CDCl₃) δ: 175.5, 136.6, 131.8, 70.9, 67.3, 64.7, 56.8, 51.5, 49.0, 46.3, 43.8, 32.0, 25.4, 23.4, 22.6, 17.1; DEPT (CDCl₃) δ: 136.6 (CH), 131.8 (CH), 70.9 (CH), 64.7 (CH), 51.5 (CH₃), 49.0 (CH₂), 46.3 (CH), 43.8 (CH), 32.0 (CH), 23.4 (CH₃), 22.6 (CH₃), 17.1 (CH₃). Exact mass calcd. for C₁₆H₂₀O₂ (M⁺- H₂O): 244.1458; found: 244.1462. Low resolution mass spectrum found 262 (C₁₆H₂₂O₃, M⁺).

4 - Hydroxy - 2 - isopropyl - 6 - methyl - 7 - methoxycarbonyltricyclo [5.3.0.¹6.0₂.⁸] - decane (109)

Tetracyclic alcohol 105 (0.057 g, 0.2 mmol) was dissolved in ethyl acetate (15 mL) and a catalytic amount of PtO₂ (ca. 10 mg, Alfa Products) was suspended in the solution. The reaction was carried out in a Parr apparatus under hydrogen (60 psi) for 24 h. The resulting mixture was filtered and the filtrate was concentrated to give a yellow solid. Recrystallization (ethyl acetate / hexane) of the crude product yielded the tricyclic alcohol 109 (0.049 g, 86%) as a white solid; IR (CHCl₃): 3610, 3450 (OH), 1725 (C=O) cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: 0.81 (d, 3 H, J = 6.8 Hz, isopropyl CH₃), 0.90 (d, 3 H, J = 6.8 Hz, isopropyl CH₃), 0.96 (s, 3 H, CH₃), 1.00 - 1.93 (overlaped 9 H), 2.01 (br. s, 1 H, CH), 2.10 (br. s, 1 H, OH), 2.22 (d, 1 H, J = 9.0 Hz, CH-CO₂Me), 3.69 (s, 3 H, OCH₃), 4.16 (m, 1 H, CH-O); ¹³C nmr (CDCl₃) δ: 175.6, 70.5, 63.9, 55.0, 51.4, 49.6, 43.7, 41.9, 41.8, 31.3, 27.8, 27.0, 22.6, 20.7, 18.0, 17.4; DEPT (CDCl₃) δ: 70.5 (CH), 63.9 (CH), 51.4 (CH₃), 49.6 (CH₂), 43.7 (CH), 41.8 (CH), 31.3 (CH₂), 27.8 (CH), 27.0 (CH₂), 22.6 (CH₃), 20.7 (CH₂), 18.0 (CH₃), 17.4 (CH₃). Exact mass calcd. for C₁₆H₂₄O₂ (M⁺- H₂O) 248.1770; found 248.1722. Low resolution mass spectrum found 266 (C₁₆H₂₆O₃, M⁺).
Pyridine (160 µL, 2.0 mmol, Aldrich, dried with 4 Å molecular sieves) was added to a stirred solution of tetracyclic alcohol 105 (0.1968 g, 0.75 mmol) in anhydrous dichloromethane (5 mL) maintained at room temperature, followed by phenyl chlorothioformate (118 µL, 0.85 mmol, Aldrich). The resulting yellow solution was stirred for 1 h at room temperature, concentrated, and the residue was dissolved in 20 mL of ether. The ether solution was washed with 5% aqueous HCl (5 mL), 5% aqueous NaHCO₃ (5 mL), and brine (10 mL), dried, filtered, concentrated, and purified by Chromatotron (2% ethyl acetate/petroleum ether) to give the thiocarbonate product 110 (0.1662 g, 56%) as a yellow solid; ¹H nmr (300 MHz, CDCl₃) δ: 0.42 (d, 1 H, J = 8.4 Hz, cyclopropyl H), 0.88 (s, 1 H, CH₃), 1.19 (d, 1 H, J = 11.6 Hz), 1.22 (s, 3 H, CH₃), 2.00 (dd, 1 H, J = 4.2, 11.6 Hz, CH₂), 2.49 (br. s, 1 H, CH-C=C), 2.54 (m, 1 H, CH-C=C), 3.26 (d, 1 H, J = 9 Hz, CH-CO₂Me), 3.72 (s, 3 H, CH₃), 5.44 (t, 1 H, J = 8.7 Hz, CH-O), 5.94 (m, 1 H, H-C=C), 6.21 (dd, 1 H, J = 2.7, 5.7 Hz, H-C=C), 7.09 (d, 2 H, J = 8.2 Hz, phenyl H), 7.27 (m, 1 H, phenyl H), 7.40 (m, 2 H, phenyl H); ¹³C nmr (CDCl₃) δ: 193.5, 173.7, 153.4, 136.5, 131.2, 129.4 (2 C), 126.4, 121.9 (2 C), 83.0, 61.3, 56.5, 48.5, 46.3, 43.9, 43.8, 29.4, 26.2, 23.4, 22.6, 17.9; APT (CDCl₃), (CH₂, C=O, quaternary C) δ: 193.5, 173.7, 153.4, 56.5, 48.5, 43.9, 26.2; (CH₃, CH) δ: 136.5, 131.2, 129.4, 126.4, 121.9, 83.0, 61.3, 51.6, 46.3, 43.8, 29.4, 23.4, 22.6, 17.9. Low resolution mass spectrum found 398 (C₂₃H₂₆O₄S, M⁺), 366 (M⁺- S), 338 (M⁺- AcOH), 244 (M⁺- PhO(C=S)OH).

2 - Isopropyl - 6 - methyl - 7 - methoxycarbonyltricyclo [ 5. 3. 0₁.₆, 0².₈ ] - 3 - decene ( 111 )
1. Tetracyclic alcohol 105 (0.0583 g, 0.22 mmol) was dissolved in ethyl acetate (20 mL) and a catalytic amount (ca. 10 mg) of 10 % Pd / activated carbon (Alfa Products) was suspended in the solution. The reaction was carried out in Parr apparatus under hydrogen (10 psi) for 10 h. The reaction mixture was then filtered and the filtrate was concentrated to give the hydrogenated tetracyclic alcohol (0.0564 g, 96 %) as a pale yellow liquid. This product was used directly for the next synthetic step.

2. The hydrogenation product was dissolved in anhydrous dichloromethane (5 mL) and pyridine (65 μL, 0.8 mmol, Aldrich, dried over 3 Å molecular sieves) was added at room temperature, followed by phenyl chlorothioformate (53 μL, 0.6 mmol, Aldrich). The yellow solution was stirred for 1 h at room temperature and concentrated to remove the solvent. The residue was dissolved in ether (20 mL) and the ether solution was washed with 5 % aqueous HCl (5 mL), 5 % aqueous NaHCO₃ (5 mL), and brine (10 mL). The washed organic solution was dried, filtered, and concentrated to give a dark-brown oily material. The crude product passed through a short silica gel column (eluted with 2 % ethyl acetate/petroleum ether) to afford thiocarbonate product (0.0522 g, 61 %), which was used directly for the radical reaction without further purification.

3. A solution of tributyltin hydride (81 μL, 0.3 mmol, Aldrich) and AIBN (5 mg, recrystallized, from Aldrich) in anhydrous toluene (5 mL) was added with a syringe pump (0.25 mL/h) to a stirred solution of thiocarbonate compound (0.0522 g, 0.13 mmol) in refluxing anhydrous toluene (10 mL). After the addition was complete, the reaction mixture was stirred and refluxed for a further 4 h, cooled to room temperature, and concentrated to remove the solvent. The residue was applied
overnight to the top of a silica gel column (saturated with petroleum ether), eluted first with petroleum ether to wash out the tin compound (nasty odor), and then eluted with 2% ethyl acetate/petroleum ether to yield 0.0255 g (70.4%) of a colorless liquid. GC-MS analysis indicated it was a mixture of cyclopropane ring opened products 111 and 112 (approximately 9:1). Isopropyl tricyclic alkene 111; 

$^1$H nmr (300 MHz, CDCl$_3$) δ: 0.86 (d, 3 H, $J = 6.9$ Hz, isopropyl CH$_3$), 0.92 (d, 3 H, $J = 6.9$ Hz, isopropyl CH$_3$), 1.09 (s, 3 H, CH$_3$), 1.26 (m, 2 H, CH$_2$), 1.58 - 1.76 (overlapped 4 H, CH$_2$), 1.89 (sextet, 1 H, $J = 6.9$ Hz, isopropyl H), 2.04 (m, 1 H, CH), 2.23 (m, 1 H, CH), 2.65 (d, 1 H, $J = 4.5$ Hz, CH-CO$_2$Me), 3.65 (s, 3 H, OCH$_3$), 5.56 (dd, $J = 4.5$, 9.8 Hz, H-C=C), 5.90 (d, 1 H, $J = 9.8$ Hz, H-C=C); 

$^{13}$C nmr (CDCl$_3$) δ: 173.3, 133.2, 123.6, 57.5, 56.8, 51.3, 46.0, 45.8, 44.0, 41.3, 28.8, 26.5, 22.8, 20.3, 19.0, 17.4.

* A attempt to purify the hydrogenation product by recrystallization (ethyl acetate/hexane) caused an isomerization of the cyclopropane ring to yield a sinularene-type product: 4-hydroxy-2-isopropenyl-6-methyl-7-methoxycarbonyltricyclo[5.3.0.1$^6$.0$^2$.8]-decane; IR (film): 3605 (OH), 1725 (C=O), 1640 (C=C) cm$^{-1}$; $^1$H nmr (300 MHz, CDCl$_3$) δ: 0.97 (s, 3 H, CH$_3$), 1.15 (m, 1 H), 1.48 (m, 2 H, CH$_2$), 1.53 (br. s, 2 H, CH$_2$), 1.73 (s, 3 H, CH$_3$-C=C), 1.66 - 1.87 (overlap 3 H), 2.01 (br. s, 1 H, CH), 2.22 (d, 1 H, $J = 8.7$ Hz, CH-CO$_2$Me), 2.23 (br. s, 1 H, OH), 3.69 (s, 3 H, OCH$_3$), 4.32 (m, 1 H, CH-O), 4.71 (m, 2 H, CH$_2$=C); $^{13}$C nmr (CDCl$_3$) δ: 175.5, 148.4, 109.6, 69.5, 63.5, 56.9, 51.5, 48.7, 43.9, 42.0, 41.7, 38.1, 27.5, 22.5, 21.1, 19.8; DEPT (CDCl$_3$) δ: 109.2 (CH$_2$), 69.5 (CH), 63.5 (CH), 48.7 (CH$_2$), 43.9 (CH), 42.0 (CH), 38.1 (CH$_2$), 27.5 (CH$_2$), 22.5 (CH$_3$), 21.1 (CH$_2$), 19.8 (CH$_3$). Low resolution mass spectrum found 264 (C$_{16}$H$_{24}$O$_3$, M$^+$), 246 (M$^+$-H$_2$O).
**3,3,7-Trimethyl-8-methoxycarbonyltetracyclo[5.4.0.1^7.0^2.4.0^2.9]-10-undecene-5-one (115)**

1. A solution of dimethyl sulfoxide (210 µL, 3.0 mmol, dried over CaH₂) in anhydrous CH₂Cl₂ (2 mL) was added dropwise to a solution of oxalyl chloride (130 µL, 1.5 mmol, Aldrich) in anhydrous CH₂Cl₂ (5 mL) maintained at -78°C with an external solid CO₂/acetone bath. After stirring for 10 min, alcohol 105 (0.3369 g, 1.3 mmol) in anhydrous CH₂Cl₂ (3 mL) was added dropwise, forming a white precipitate. The suspension was stirred for 15 min at -78°C and triethylamine (0.8 mL, excess) in anhydrous CH₂Cl₂ (2 mL) was added dropwise to form a clear yellow solution. The solution was allowed to warm to 0°C with external ice/water bath, cold water (15 mL) was added, and the mixture was stirred for 10 min at 0°C. The resulting mixture was separated and the aqueous layer was re-extracted with CH₂Cl₂ (10 mL). The combined organic layers were washed with 5% hydrochloric acid (5 mL), 5% aqueous NaHCO₃ (5 mL), and brine, dried, filtered, and concentrated to afford crude ketone product 115 as a yellow solid (0.3118 g, 93%). This product was further purified by recrystallization (ethyl acetate/hexane) to give white crystals (0.2527 g, 75.4%); mp 37-38.5°C; ¹H nmr (300 MHz, CDCl₃) δ: 0.87 (s, 1 H, cyclopropyl H), 0.90 (s, 3 H, CH₃), 1.12 (s, 3 H, CH₃), 1.16 (s, 3 H, CH₃), 1.30 (d, 1 H, J = 12 Hz, H-CH-C=O), 2.13 (dd, 1 H, J = 4, 12 Hz, H-CH-C=O), 2.68 (m, 1 H, CH-C=C), 2.70 (m, 1 H, CH-C=C), 3.58 (s, 1 H, CH-C=O), 3.72 (s, 3 H, OCH₃), 6.06 (m, 1 H, H-C=C), 6.27 (m, 1 H, H-C=C); ¹³C nmr (CDCl₃) δ: 205.0, 170.7, 136.9, 131.9, 69.9, 57.9, 51.6, 48.3, 47.4, 44.7, 44.6, 35.4, 30.9, 23.1, 22.9, 19.5. *Exact mass* calcd. for C₁₆H₂₀O₃ 260.1407; found 260.1420.
Trifluoroacetic anhydride (0.56 mL, 4.0 mmol, Aldrich) was added to a solution of dimethylsulfoxide (0.32 mL, 4.5 mmol, dried over CaH₂) in anhydrous CH₂Cl₂ (5 mL) maintained at -78°C with an external solid CO₂/acetone bath, to form a white precipitate. After stirring for 15 min, a solution of alcohol 105 (0.2018 g, 0.77 mmol) in anhydrous CH₂Cl₂ (5 mL) was added dropwise over a period of 10 min; 30 min later, a solution of triethylamine (1.4 mL, excess) in anhydrous CH₂Cl₂ (2 mL) was added dropwise to give a clear yellow solution. The solution was allowed to warm slowly to 0°C, stirred for 30 min at 0°C, diluted with CH₂Cl₂ (20 mL), and quenched with cold water. The mixture was separated and the aqueous layer was extracted with CH₂Cl₂ (20 mL). The combined organic layers were washed with an equal volume of water, 5% hydrochloric acid, 5% aqueous NaHCO₃ and saturated aqueous NH₄Cl, dried, filtered, and concentrated. Flash chromatography (10% ethyl acetate / petroleum ether) afforded the ketone ester 115 (0.1714 g, 86%) as a pale yellow oil. The ¹H nmr spectrum of this product was consistent with the product obtained by the method described above. However isomerization of the methyl ester group had occurred at C-8. The most obvious evidence was the presence of a minor OCH₃ peak (δ 3.71) and a major one (δ 3.72) with a combined total integration of three protons.

Unsuccessful Jones' Oxidation to Prepare (115) ⁸⁹

Jones' reagent was prepared according to the literature method from CrO₃ (7 g) and concentrated H₂SO₄ (6 mL) in water (50 mL). A stirred solution of alcohol 105 (48 mg) in 10 mL of acetone/THF (10:1) at room temperature was treated with the Jones' reagent. The resulting mixture was concentrated and the residue was extracted in a separatory funnel with a mixture of 1:1 ether/water
(30 mL). The ether layer was dried, filtered, and concentrated to give a yellow liquid. The \(^1\)H nmr spectrum indicated it was a mixture of complicated products.

2 - Isopropenyl - 6 - methyl- 7 - methoxycarbonyltricyclo [ 5. 3. 0 \(^{1.6}. 0^{2.8} \) dec - 9 - en - 4 - one \(116\)

1. Crystalline \(\text{Cr}_2(\text{SO}_4)_2.15\text{H}_2\text{O}\) (2.35 g, Aldrich) and zinc powder (1.6 g, Aldrich) were added in portions to a stirred solution of tetracyclic ketone \(115\) (0.1735 g, 0.67 mmol) in a 2:1 mixture of DMF / \(\text{H}_2\text{O}\) (50 mL) at room temperature. The reaction was exothermic and formed a deep blue solution with zinc powder suspended in it. The mixture was stirred for 1 h at R.T., diluted with ether (20 mL), and filtered. The filtrate was separated and the aqueous layer was extracted with ether (15 mL). The combined organic layers were washed with water (20 mL), dried, and concentrated. Flash chromatography (10 % ethyl acetate / petroleum ether) yielded cyclopropane ring isomerization product \(116\) (0.1045 g, 60 %) as a pale yellow liquid; IR (film): 1730 (C=O), 1710 (C=O), 1645 (C=C), 1560 (C=C) cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 1.04 (s, 3 H, CH\(_3\)), 1.13 (m, 1 H, CH\(_2\)), 1.62 (m, 1 H, CH\(_2\)), 1.65 (s, 3 H, CH\(_3\)-C=C), 2.47 (m, 1 H, CH=C=C), 2.81 (m, 2 H, CH\(_2\)-C=O), 3.02 (m, 1 H, CH=C=C), 3.40 (d, 1 H, J = 1.1 Hz, CH-CO\(_2\)Me), 3.72 (s, 3 H, OCH\(_3\)), 4.69 (m, 1 H, terminal CH\(_2\)=C), 4.77 (m, 1 H, terminal CH\(_2\)=C), 5.97 (m, 1 H, H-C=C), 6.17 (m, 1 H, H-C=C); \(^{13}\)C nmr (CDCl\(_3\)) \(\delta\): 205.7, 169.2, 148.0, 137.5, 131.0, 111.8, 68.1, 66.7, 52.1, 50.9, 50.1, 47.4, 41.9, 40.3, 24.4, 21.9; DEPT (CDCl\(_3\)) \(\delta\): 137.5 (CH), 131.0 (CH), 111.8 (CH\(_2\)), 66.1 (CH), 52.1 (CH\(_3\)), 50.9 (CH), 50.1 (CH), 47.4 (CH\(_2\)), 40.3 (CH\(_2\)), 24.4 (CH\(_3\)), 21.9 (CH\(_3\)). Exact mass calcd. for C\(_{16}\)H\(_{20}\)O\(_3\): 260.1407; found: 260.1411.
2. A Cr(II) solution was prepared as follows: crystalline Cr₂(SO₄)₃·15H₂O (5 g) and zinc powder (1.3 g) were mixed in distilled water (30 mL) and the mixture was stirred overnight at room temperature under nitrogen. Decanted from the precipitates, a clear blue solution of Cr(II)SO₄ (ca. 0.5 M) was obtained. This prepared Cr(II) solution (2 mL) and zinc powder (0.1 g) were added to a solution of cyclopropane ketone 115 (8 mg, 0.03 mmol) in DMF (6 mL). The reaction was stirred for 36 h at room temperature and no reaction was observed (GC-MS monitoring). Then the reaction mixture was refluxed for 12 h. After cooling to room temperature, the resulting mixture was filtered and the filtrate was extracted with ether (2 × 15 mL). The combined ether extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (5 % ethyl acetate / petroleum ether) yielded a single product (7 mg), whose ¹H nmr spectrum was consistent with that of cyclopropane ring isomerization product 116.

3,3,7-Trimethyl-8-methyoxycarbonyltetracyclo [5.4.0.1⁵.0².4.0².9] undecan-5-one (118)

Alkene ketone 115 (0.2210 g, 0.85 mmol) was dissolved in ethyl acetate (10 mL) and a catalytic amount of 10 % Pd / activated carbon (ca. 20 mg, Alfa Product) was suspended in the solution. The hydrogenation was carried out in a Parr apparatus under hydrogen (15 psi) for 12 h. The resulting mixture was filtered through a band of Celite and the filtrate was concentrated to give a yellow solid. Recrystallization (ethyl acetate / hexane) gave the ketone ester 118 (0.2071 g, 93 %) as a white crystal; IR (CHCl₃): 1732 (C=O), 1715 (C=O) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ: 0.94 (s, 1 H, cyclopropyl H), 1.03 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃), 1.20 (s, 3 H, CH₃), 1.36 (d, 1 H, J = 12 Hz, H-CH-C=O), 1.75 - 1.80 (overlaped m, 3 H), 1.95 - 2.15 (overlaped m, 4 H), 3.24 (s, 1 H, CH-C=O), 3.71
(OCH₃); ¹³C nmr (CDCl₃) δ: 205.4, 170.1, 72.6, 51.5, 50.6, 47.5, 43.0, 39.9, 33.3, 30.9, 29.0, 22.9, 22.6, 21.4, 19.3. Exact mass calcd. for C₁₆H₂₂O₃: 262.1563; found: 262.1544.

2 - Isopropenyl - 6 - methyl - 7 - methoxycarbonyltricyclo [5.3.0] 15.3.0 2.1 decan - 4 - one (119)

A methanol (1 mL) solution of cyclopropane ketone 118 (6 mg, 0.02 mmol) was added to a stirred mixture of zinc powder (0.5 g) and zinc chloride (0.5 g) in methanol (5 mL) at room temperature. A few drops of glacial acetic acid were added and the mixture was refluxed with stirring overnight. After cooling to room temperature, the mixture was filtered and the filtrate was extracted with ether (2 x 10 mL). The combined ether layers were washed with 5% aqueous NaHCO₃ (5 mL) and brine (15 mL), dried, filtered, and concentrated. Flash chromatography (10% ethyl acetate / petroleum ether) afforded the cyclopropane ring isomerization product 119 (5 mg, 83%) as a colorless liquid; ¹H nmr (300 MHz, CDCl₃) δ: 1.11 (s, 3 H, CH₃), 1.07 - 1.22 (overlap 3 H), 1.72 (s, 3 H, CH₃-C=C), 1.58 - 1.89 (overlap 3 H), 2.16 (m, 2 H, CH₂), 2.34 (m, 1 H, CH), 2.49 (m, 1 H, CH), 3.10 (br. s, 1 H, CH-CO₂Me), 3.71 (s, 3 H, OCH₃), 4.73 (m, 1 H, H-C=C), 4.84 (m, 1 H, H-C=C). Low resolution mass spectrum found 262 (C₁₆H₂₂O₃, M⁺).

Li / NH₃ Reductive Cyclopropane Ring Opening

Ammonia gas from a cylinder was condensed into a flask through a solid CO₂ / acetone cooling condenser and the flask was also maintained at -78°C with an external solid CO₂ / acetone bath. After the liquid ammonia volume was ca. 3 mL, a small piece of lithium metal (ca. 8 mg) was added and a blue solution
formed. A solution of cyclopropane ketone 118 (0.2091 g, 0.79 mmol) and tert-butanol (0.0805 g, 1.1 mmol) in anhydrous ether (10 mL) was added dropwise to the Li/NH₃ solution. After the addition was complete, stirring was continued for 10 min at -78°C. The reaction was quenched with ammonium chloride, and the solid CO₂/acetone bath was removed. The reaction mixture was allowed to warm to 0°C with an external ice/water bath and the ammonia was allowed to evaporate under a stream of N₂. Water (10 mL) was added, the resulting mixture was separated, and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic layers were washed with saturated aqueous NH₄Cl (20 mL), dried, filtered, and concentrated. Flash chromatography (5% ethyl acetate/petroleum ether) afforded a pale yellow oil (0.2019 g, 97%). GC-MS established it was a mixture of two components with $M^+/z$ 264, and the ratio was almost 1:1.

This mixture and p-toluenesulfonohydrazide (0.1843 g, 1.0 mmol, Aldrich) were mixed in absolute methanol (5 mL), and the solution was refluxed and stirred for 1 h. After cooling to room temperature, CH₂Cl₂ (10 mL) was added and the mixture was washed with water (10 mL), dried, filtered, and concentrated to give a yellow solid. Recrystallization (ethanol/water) gave a pale yellow solid, which was a mixture of two tosylhydrazone products. Efforts to separate the mixture by flash chromatography were unsuccessful.

The mixture of tosylhydrazone products were dissolved in anhydrous THF (5 mL) and LiAlH₄ (0.1 g) was added in portions at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. After work-up by adding ice-cold water, the mixture was filtered, and the filtrate was extracted with CH₂Cl₂ (2 x 15 mL). The combined CH₂Cl₂ extracts were washed with brine (30 mL), dried, filtered, and concentrated to give an oily liquid. Flash chromatography (25% ethyl acetate/petroleum ether) afforded a colorless liquid (0.091 g), which
still was a mixture of reduction products. This mixture was kept in freezer for further purification.

**Attempt to Prepare (2S, 3R) 1,2 - Epoxy - 3 - butanol (g)**

1. Activated 3 Å molecular sieves (2 g, 30 % w/w to alcohol, Fisher, ground and dried overnight in vacuo at 110°C) were added to a stirred solution of 3-buten-2-ol (7.21 g, 100 mmol, Aldrich) and (+)-diisopropyl tartrate [(+)-DIPT] (3.52 g, 15 mmol, Aldrich) in anhydrous CH₂Cl₂ (400 mL). The suspension was cooled to -20°C and titanium tetraisopropoxide (3 mL, 10 mmol, Aldrich, re-distilled) was added dropwise. After stirring for 30 min at -20°C, a solution of anhydrous tert-butyl hydroperoxide* (3.3 M in toluene, 21.2 mL, 70 mmol) was added dropwise and the reaction mixture was stirred for 6 days in a freezer (ca. -20°C). A freshly prepared aqueous solution (100 mL) of ferrous sulfate heptahydrate (33 g) and citric acid monohydrate (11 g) was cooled to 0°C with an external ice / water bath and the reaction mixture was poured into it. The two-phase mixture was stirred for 15 min and filtered. The filtrate was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were treated with an aqueous solution (100 mL) of NaCl (5 g) and NaOH (30 g) by vigorously stirring for 1 h at 0°C. The mixture was separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 50 mL). The combined organic layers were dried and then concentrated at 0°C. None of the desired product was found in the residue. (Based on the method of Sharpless.73)

2. Titanium tetraisopropoxide (30 mL, 100 mmol, Aldrich, re-distilled) was added dropwise to a stirred solution of 3-buten-2-ol (7.2 g, 100 mmol, Aldrich) and (+)-diisopropyl tartrate (28.1 g, 120 mmol, Aldrich) in anhydrous CH₂Cl₂ (400 mL)
maintained at -20°C. After stirring for 30 min at -20°C, a solution of anhydrous tert-butyl hydroperoxide* (3.3 M in toluene, 18 mL, 60 mmol) was added dropwise and then the reaction mixture was stirred for 3 days in a freezer (ca. -20°C). The resulting mixture was poured into a cooled (-20°C) solution of acetone (300 mL) and water (30 mL). The viscous mixture was stirred while warming to R.T. and then filtered. The filtrate was concentrated to ca. 50 mL and mixed with an aqueous solution (100 mL) of NaCl (5 g) and NaOH (30 g) at 0°C. The two-phase mixture was vigorously stirred for 1 h at 0°C and separated. The aqueous layer was extracted with CH2Cl2 (2 x 50 mL) and the combined organic layers were washed with brine (100 mL), dried, filtered, and concentrated at 0°C to give a milky liquid, which did not contain the desired product. (Based on the method of reference 94.)

3. 3-Buten-2-ol (3.6 g, 50 mmol, Aldrich), 3 Å molecular sieves (3.5 g, Aldrich, ground and dried overnight in vacuo at 110°C) and (+)-diethyl tartrate (2.5 mL, 15 mmol, Aldrich) were mixed in anhydrous CH2Cl2 (200 mL). The mixture was stirred and cooled to -10°C with an external ice/salt bath. Titanium tetraisopropoxide (2.5 mL, 8 mmol, Aldrich, re-distilled) was added dropwise, followed by anhydrous tert-butyl hydroperoxide* (3.3 M in toluene, 20 mL, 60 mmol), and the reaction mixture was stirred for 24 h at -20°C. GC-MS did not indicate any of the desired reaction product. (Based on the method of reference 93.)

* tert-Butyl hydroperoxide (70% in H2O, 325 mL, Aldrich) and reagent-grade toluene (400 mL) were mixed in a 1 L separatory funnel by swirling (do not shake), and then separated. The organic layer was transferred to a 1 L
round-bottom flask equipped a Dean-Stark trap and a condenser. The solution was refluxed under N₂, about 20 mL of water was collected, and then a further 20 mL of distillate was removed through the side arm to ensure removal of the last trace of water. After cooling to room temperature, the remaining solution (ca. 600 mL) was transferred to a brown glass bottle and stored over 4 Å molecular sieves in a cold-room (ca. 4°C). The concentration of tert-butyl hydroperoxide was approximately 3.3 M.

(-)-Menthyl chloroformate (130)

Phosgene gas was bubbled through toluene (100 mL, pre-weighed with container) at 0°C for an hour and the container was weighed to establish the amount of phosgene dissolved in toluene. This work must be done in the fumehood.

A solution of (-)-menthol (15.6 g, 0.1 mol, Fisher) and quinoline (14.2 g, 0.11 mol, Aldrich, re-distilled) was prepared in toluene (100 mL) and cooled to 0°C. A stock toluene solution of phosgene (20 g, 0.2 mol) was added dropwise to the solution and slowly formed a white precipitate. The mixture was stirred at 0°C and monitored by TLC until the reaction was complete. The resulting mixture was filtered to remove the precipitate, and the filtrate was flushed with nitrogen in fumehood at 21°C to remove the excess phosgene. The flushed solution was transferred to an Erlenmeyer flask and a few grams of calcium carbonate were added as the stabilizer. This (-)-menthyl chloroformate 130 solution in approximately 1 mmol/mL concentration was stored in refrigerator before use.

(Based on the method of reference 74.)
(1R') (2', 2'-Dimethylspiro [2. 4] - 4', 6' - dien - 1' - yl) methyl (-) menthyl carbonate (131)

The stock solution of (-)-menthyl chloroformate 130 (1.2 equimolar to spiro-alcohol 82) was concentrated and the residue was re-dissolved in anhydrous benzene to prepare a 0.5 mmol/mL solution. To the solution was added dropwise a solution of racemic spiro-alcohol 91 and triethylamine (equimolar) in anhydrous benzene (1 mmol/mL). The reaction mixture was filtered to remove the precipitate formed, and the filtrate was concentrated to give a thick brown liquid. This mixture was separated by flash chromatography (2% ethyl acetate/petroleum) to afford the spiro-heptadienyl (-)-menthyl carbonate 131 as a white solid; mp 29-31°C; 1H nmr (300 MHz, CDCl₃) δ: 0.79 (d, 3 H, J = 7 Hz, CH₃), 0.91 (t, 6 H, J = 6.5 Hz, isopropyl CH₃), 1.05 (m, 2 H, CH₂), 1.41 (s, 6 H, CH₃-cyclopropane), 1.36 - 1.46 (m, 2 H, CH₂), 1.66 (m, 2 H, CH₂), 1.94 (m, 1 H, CH), 2.03 (m, 1 H, CH), 2.43 (t, 1 H, J = 7.2 Hz, cyclopropyl H), 4.38 (d, 2 H, J = 7.2 Hz, CH₂-O), 4.52 (dt, 1 H, J = 4.4, 10.9 Hz, CH-O), 6.25 (m, 2 H, cyclopentadienyl H), 6.45 (m, 1 H, cyclopentadienyl H), 6.53 (m, 1 H, cyclopentadienyl H); 13C nmr (CDCl₃) δ: 158.8, 137.4, 132.5, 131.2, 129.3, 78.4, 66.3, 51.2, 47.0, 40.7, 37.8, 34.1, 33.9, 31.4, 26.8, 26.1, 23.3, 21.9, 20.6, 19.8, 16.3.

Chiral shift reagent, tris[3-(trifluoromethyhydroxymethylene)-(+)-camphorato], europium(III) derivative, was added to a CDCl₃ solution (0.5 mL) containing the (-)-menthyl carbonate 131 (6.7 mg, 0.02 mmol) in the following molar ratios (1:1, 1:2, 1:3, 1:4) and 1H nmr spectra were recorded. No new signals were observed, and there was no line broadening except for the isopropyl methyl resonances (δ 0.91) which were isolated into two doublets.
(+)(1R) 2, 2'-Dimethyl-1'-hydroxymethylspiro[2.4]hepta-4,6'-diene (132)

Spiroheptadienyl (-)-menthyl carbonate 131 (3.98 g, 12 mmol) was dissolved in anhydrous THF (50 mL) and cooled to 0°C with an external ice-water bath. Lithium aluminum hydride (1.14 g, 30 mmol) was added in several small portions. The reaction suspension was allowed to warm slowly to room temperature, and the suspension was stirred until the reaction was complete by TLC monitoring. The reaction mixture was re-cooled to 0°C and the excess LiAlH₄ was destroyed with careful addition of cold water. The resulting mixture was filtered and the filtrate was neutralized with 5% aqueous hydrochloric acid. This solution was extracted with ether (3 x 25 mL) and the combined ether layers were dried, filtered and concentrated. Flash chromatography (20% ethyl acetate/petroleum ether) afforded (+)-R-spiro-alcohol 133 (1.762 g, 98%) as a colorless liquid; [α]²² = +21.4° (c 4.6, CHCl₃); IR (film): 3350 (br, OH), 3090, 3060 (H-C=C), 1650 (S, C=C) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 1.41 s, 3H, CH₃), 1.43 s, 3H, CH₃), 1.71 (br s, 1H, OH), 2.41 (dd, 1H, J = 7.5, 8.1 Hz, cyclopropyl H), 3.80 (dd, 1H, J = 8.1, 11.7 Hz, CH₂-O), 3.99 (dd, 1H, J = 7.5, 11.7 Hz, CH₂-O), 6.30 (m, 2H, cyclopentadienyl H), 6.45 (m, 1H, cyclopentadienyl H), 6.57 (m, 1H, cyclopentadienyl H); ¹³C NMR (CDCl₃) δ: 138.4, 133.0, 131.8, 129.2, 62.0, 52.3, 43.4, 35.3, 27.5, 20.4. Exact mass calcd. for C₁₀H₁₄O: 150.1044; found: 150.1032.

(+)(1'R) 2', 2'-Dimethylspiro[2.4]hepta-4', 6'-diene-1'-yl) carboxaldehyde (133)

The spiro-alcohol 145 (2.25 g, 15 mmol) in dichloromethane (25 mL) was added dropwise to a stirring, refluxing suspension of activated MnO₂/charcoal (40 g as a prepared mixture) in dichloromethane (250 mL). The mixture was stirred
under reflux for 12 h, cooled to room temperature, filtered through Celite and anhydrous MgSO₄, and washed thoroughly with dichloromethane. The combined filtrates were concentrated and the crude product was purified by flash chromatography (5 % ethyl acetate / petroleum ether) to yield the (+)-R-spiro-aldehyde 133 (1.90 g, 86 %) as a pale yellow liquid; [α]²² = +23.0° (ε 2.9, CHCl₃); IR (film): 2825 (H-CO), 2720 (H-C-H), 1704 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 1.42 (s, 3H, CH₃), 1.56 (s, 3H, CH₃), 2.78 (d, 1H, J = 6 Hz, cyclopropyl H), 6.17 (m, 1H, cyclopentadienyl H), 6.53 (m, 2H, cyclopentadienyl H), 6.60 (m, 1H, cyclopentadienyl H), 9.56 (d, 1H, J = 6 Hz, H-C=O); ¹³C nmr (CDCl₃) δ: 198.0, 135.5, 132.4, 131.6, 131.4, 56.8, 49.4, 37.1, 26.8, 20.7. Exact mass calcd. for C₁₉H₁₂O: 148.0888; found: 148.0888.

(+)-SR, 1'R) 3'-Methyl-5'-{(2', 2'-dimethylspiro[2.4]hepta-4', 6'-dien-1'-yl)-6-oxa-2-cyclohexenone (134)

An LDA solution was prepared from diisopropylamine (0.32 mL, 2.3 mmol) and n-butyllithium (2.5 M, 0.9 mL, 2.3 mmol, Aldrich) in anhydrous THF (5 mL) at -40°C, and a solution of 3,3-dimethylacrylate 97 (0.2510 g, 2.2 mmol) in anhydrous THF (2 mL) was added dropwise. After stirring for 20 min, cadmium chloride powder (0.3660 g, 2.0 mmol, Aldrich, gold label, ground and dried overnight under vacuum at 110°C) was added in one portion. The suspension was stirred for 30 min at -40°C, and a solution of (+)-spiro-aldehyde 133 (0.1586 g, 1.1 mmol) in anhydrous THF (5 mL) was added by syringe pump (0.1 mL / min). After the addition was complete, stirring was continued for a further 30 min at -40°C. The reaction was allowed to warm to 0°C, stirred for 2 hours at 0°C, and then quenched with saturated aqueous NH₄Cl. The mixture was filtered through Celite and the filtrate was extracted with ether (2 x 15 mL). The combined organic layers
were dried, filtered and concentrated. Flash chromatography (15 % ethyl acetate / petroleum ether) afforded (+)-triene lactone 134 (0.1846 g, 73 %) as a colorless liquid and α-product 88 (0.0387 g, 15 %). (+)-Triene-lactone 134; [α]_D^22 = +17.7° (c 3.4, CHCl_3); IR (film): 1710 (C=O), 1650 (C=C) cm⁻¹; ^1H nmr (200 MHz, CDCl₃) δ: 1.39 (s, 3 H, CH₃), 1.43 (s, 3 H, CH₃), 1.87 (s, 3 H, CH₃-C=C), 1.93 - 2.09 (m, 2 H, CH₂-C=C), 2.31 (d, 1 H, J = 4.2 Hz, cyclopropyl H), 4.48 (m, 1 H, H-C-O), 5.76 (s, 1 H, H-C=C), 6.17 (m, 1 H, cyclopentadienyl H), 6.28 (m, 1 H, cyclopentadienyl H), 6.49 (m, 1 H, cyclopentadienyl H), 6.58 (m, 1 H, cyclopentadienyl H); ^13C nmr and DEPT (CDCl₃) δ: 164.6 (C=O), 156.0 (C=C), 136.4 (C=CH), 132.3 (C=CH), 131.6 (C=CH), 129.7 (C=CH), 116.8 (C=CH), 76.6 (CH), 51.1 (quaternary C), 42.1 (CH), 35.6 (CH₂), 31.9 (quaternary C), 27.2 (CH₃), 23.0 (CH₃), 20.4 (CH₃). Exact mass calc. for C₁₅H₁₈O₂: 230.1302; found: 230.1303.

(5R, 1'R) 5 -(2'-Cyclopentadienyl - 1' - methoxy - 2', 2'-dimethyl ethyl) -3-methyl-6-oxa-2-cyclohexenone (137)

Boron trifluoroethersate (92 μL, 0.75 mmol, Aldrich) was added to a solution of spiro-heptadiene lactone 134 (0.1652 g, 0.72 mmol) in absolute methanol (10 mL) at room temperature. The reaction solution was stirred for 4 h and quenched with 5 % aqueous NaHCO₃. The mixture was extracted with ether (2 × 25 mL) and the ether extracts were combined, washed with brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (15 % ethyl acetate / petroleum ether) to give the cyclopropane ring - opened product 137 (0.1573 g, 83 %) as a pale yellow liquid. This product was a mixture of substituted cyclopentadienes from the rapid 1,5-sigmatropic rearrangement. IR (film): 1730 (C=O), 1575 (C=C) cm⁻¹; ^1H nmr (200 MHz, CDCl₃) δ: 1.11, 1.12
Cyclopentadiene 137 (0.1378 g, 0.6 mmol) and hydroquinone (5 mg) were dissolved in anhydrous toluene (10 mL). The solution was placed in a Pyrex pressure tube and flushed with nitrogen for 2 hours and sealed. The pressure tube was placed in a microwave oven (Toshiba ERS-6630C) and surrounded with damp vermiculite. The power level was set to 500 watts and the reaction was conducted for an hour. After cooling to room temperature, the pressure tube was opened and concentrated. The residue was purified by flash chromatography (10% ethyl acetate/petroleum ether) to give the Diels-Alder adduct 138 (0.1335 g, 97%) as a colorless liquid; IR (film): 1725 (C=O), 1575 (C=C) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ: 0.95 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.18 (s, 3 H, CH₃), 1.82 - 2.19 (m, overlap 4 H), 2.53 (s, 1 H, CH₂-C=C), 2.72 (s, 1 H, bridge head CH₃), 3.11 (s, 4 H, OCH₃, one H-C-O hidden), 4.62 (s, 1 H, H-C-O), 6.44 (m, 1 H, H-C=C), 6.32 (m, 1 H, H-C=C); ¹³C nmr (CDCl₃) δ: 174.9, 138.7, 136.5, 76.3, 74.2, 58.5, 56.3, 52.9, 51.0, 49.9, 48.5, 41.5, 40.4, 24.6, 23.6, 23.0; DEPT (CDCl₃) δ: 138.7 (CH), 136.5 (CH), 76.3 (CH), 58.5 (CH), 52.9 (CH), 51.0 (CH), 49.9 (CH), 48.5 (CH₂), 41.5 (CH₂), 24.6 (CH₃), 23.6 (CH₃), 23.0 (CH₃).

Exact mass calcd. for C₁₅H₁₈O₂ (M⁺-CH₃OH): 230.1302; found: 230.1321. Low resolution mass spectrum found 262 (C₁₆H₂₂O₃, M⁺).
(1R, 2R, 4R, 5R, 7S, 8R, 9S) 5-hydroxy-8-hydroxymethyl-4-methoxy-3,3,7-
trimethyltricyclo[5.4.0.0^2,9]undecane (143) 

Tetracyclic lactone 138 (0.0792 g, 0.3 mmol) was dissolved in ethyl acetate (10 mL) and a catalytic amount (ca. 10 mg) of 5% Pd/C activated carbon was suspended in the solution. Hydrogenation was conducted in a Parr apparatus under hydrogen (30 psi) for 4 h at room temperature. The resulting mixture was filtered through a bed of Celite and the filtrate was concentrated to give a pale yellow liquid. This crude product was checked by nmr to make sure the double bond was completely hydrogenated, and used directly for the next step.

The hydrogenated lactone was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice/water bath. Lithium aluminum hydride (50 mg, Aldrich) was added to the cold solution and the reaction was allowed to warm to room temperature. After stirring for 4 h at room temperature, the reaction was cooled to 0°C and quenched with cold water. The mixture was filtered and the filtrate was extracted with ether (2 x 10 mL). The combined organic layers were washed with brine, dried, filtered, and concentrated. Flash chromatography (40% ethyl acetate/petroleum ether) yielded 0.0652 g (92% from 138) of the diol 143 as a colorless liquid; IR (film): 3460 (OH) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ:

0.94 (s, 3 H, CH₃), 1.10 (s, 3 H, CH₃), 1.13 (s, 3 H, CH₃), 1.19 - 1.85 (m, 9 H, CH₂, CH), 2.10 (br. s, 2 H, OH), 3.18 (s, 3 H, OCH₃), 3.73 (m, 2 H, CH₂-O), 3.95 (m, 1 H, CH-O), 4.60 (s, 1 H, CH-O); ¹³C nmr (200 MHz, CDCl₃) δ: 81.3, 66.1, 63.2, 55.6, 49.2, 48.7, 48.1, 45.7, 44.9, 42.3, 39.7, 31.5, 25.8, 22.9, 21.6, 17.6. Low resolution mass spectrum found 236 (M⁺-CH₃OH), 218 (236-H₂O), these peaks were too weak for a high resolution mass spectrum.
(1R, 2R, 4R, 5R, 7S, 8R, 9S) 8-Acetoxymethyl - 5-hydroxy - 4-methoxy - 3, 3, 7-trimethyltricyclo [5.4.0.1^7.0^{2.9}] undecane (144)

Diol 143 (0.4820 g, 1.8 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice-water bath. To the solution was added pyridine (0.3 mL), followed by acetic anhydride (0.2 mL, 2.0 mmol, Aldrich). The reaction solution was stirred for 6 h at 0°C, diluted with ether (20 mL), and then quenched with cold water. The mixture was separated and the aqueous layer was re-extracted with ether (15 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ and brine, dried, filtered, and concentrated. Flash chromatography (10% ethyl acetate / petroleum ether) afforded 0.0724 g (15%) of recovered starting material and 0.4127 g (74%) of the hydroxy acetate 144 as an oily liquid; IR (film): 3460 (br, OH), 1740 (C=O) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ: 0.77 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃), 1.27 (s, 3 H, CH₃), 1.40 - 2.10 (overlapped m, 9 H), 2.03 (s, 3 H, CH₃-C=O), 2.25 (m, 1 H, CH-CH₂-O), 2.73 (br. s, 1 H, OH), 3.20 (s, 3 H, OCH₃), 4.05 - 4.20 (overlapped m, 3 H, CH₂-O and CH-O), 5.50 (dd, 1 H, J = 7.5, 10 Hz, CH-O).

(1R, 2R, 4R, 7S, 8R, 9S) 8-Acetoxymethyl - 4-methoxy - 3, 3, 7-trimethyltricyclo [5.4.0.1^7.0^{2.9}] undecane (145)

1. Pyridine (0.16 mL, 2.0 mmol), followed by phenyl chlorothioformate (0.14 mL, 1.0 mmol) were added to a stirred anhydrous dichloromethane solution (5 mL) containing hydroxy acetate 144 (0.2016 g, 0.65 mmol) at room temperature. After the reaction was complete (TLC monitoring), the solvent was evaporated under reduced pressure. The residue was dissolved in ether (30 mL) and the ether solution was washed with 5% aqueous NaHCO₃ and brine. This ether solution was dried, filtered, and concentrated. The residue was passed through a short
silica gel column with 10% ethyl acetate/petroleum ether as elute. The chromatographed material (0.2395 g) was used directly for the radical reduction. This thiocarbonate radical precursor was stirred and refluxed in anhydrous toluene (5 mL) while a solution of tributyltin hydride (0.22 mL, 0.8 mmol) and a catalytic amount of AIBN (6 mg) in anhydrous toluene (2 mL) was added with a syringe pump at a speed of 0.5 mL/h. After the addition was complete, the reaction solution was stirred and refluxed for further 4 h, cooled to room temperature, and evaporated under reduced pressure to remove the solvent. The crude product was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane until the tin compound (with a very nasty odor) was washed over, and then eluted with 5% ethyl acetate/petroleum ether to afford the methoxy acetate 145 (0.1356 g, 71%) as a colorless liquid; IR (film): \( \tilde{\nu} \) (C=O) cm\(^{-1}\); \(^1\)H nmr (200 MHz, CDCl\(_3\)) \( \delta \): 0.83 (s, 3 H, CH\(_3\)), 1.05 (s, 3 H, CH\(_3\)), 1.11 (s, 3 H, CH\(_3\)), 1.10 - 1.40 (m, 8 H, CH\(_2\)), 1.56 - 2.15 (m, 4 H, CH), 2.00 (s, 3 H, CH\(_3\)C=O), 2.40 (dd, 1 H, \( J = 8, 10.5 \) Hz, CH-O), 3.14 (s, 3 H, OCH\(_3\)), 3.98 (d, 2 H, \( J = 8 \) Hz, CH\(_2\)-O); \(^1^3\)C nmr (CDCl\(_3\)) \( \delta \): 171.4, 65.8, 60.0, 49.5, 48.8, 48.4, 47.4, 47.3, 45.9, 37.2, 24.5, 25.6, 24.6, 22.4, 20.8, 17.7. Low resolution mass spectrum found 294 (C\(_{18}\)H\(_{30}\)O\(_3\), M\(^+\)), 262 (M\(^+\)-MeOH), these peaks were too weak for high resolution Mass spectrum.

2. Alkene acetate 150 (0.0646 g, 0.22 mmol) was dissolved in ethyl acetate (15 mL) and a catalytic amount (ca. 10 mg) of 5% Pd/activated carbon was suspended in the solution. Hydrogenation was conducted in a Parr apparatus under H\(_2\) (20 psi) for two hours. The resultant mixture was filtered through Celite and concentrated. The residue was purified by flash chromatography (5% ethyl acetate/petroleum ether) to give methoxy acetate 145 (0.0627 g, 97%) as a colorless liquid, the
spectral data were identical with those of the compound obtained by the other synthetic route.

\((-\) (1R, 2R, 7S, 8R, 9S) 8 - Acetoxymethyl - 3, 3, 7 - trimethyltricyclo \{5.4.0 \cdot 1.0 \cdot 2.9\} undecane \) (146)

Methoxy acetate (0.0650 g, 0.22 mmol) and sodium iodide (0.045 g, 0.30 mmol) were mixed in anhydrous dichloromethane (5 mL). Triethylamine (56 \mu L, 0.40 mmol) was added to this solution, followed by chlorotrimethylsilane (38 \mu L, 0.30 mmol, Aldrich), forming a yellow solution. After stirring for an hour, the reaction was stopped by adding saturated aqueous NH₄Cl. The mixture was extracted with dichloromethane (2 \times 20 mL) and the extracts were combined, washed with 10% aqueous sodium thiosulfate (to remove iodine) and brine, dried, and concentrated to give a pale yellow liquid.

The resulting crude alcohol product was dissolved in anhydrous dichloromethane (2 mL) and pyridine (32 \mu L, 0.40 mL, Aldrich, re-distilled) was added, followed by phenyl chlorothioformate (42 \mu L, 0.30 mmol) in anhydrous dichloromethane (1 mL). The reaction mixture was stirred for 3 h at room temperature and then concentrated to remove solvent. The residue was dissolved in ether (20 mL) and the ether solution was washed with water (2 \times 20 mL), dried, filtered, and concentrated. The residue was passed through a short silica column to give the crude thiocarbonate product for direct use in the radical reaction.

To a stirring, refluxing solution of thiocarbonate in anhydrous toluene (2 mL) was added a solution of tributyltin hydride (54 \mu L, 0.2 mmol) and AIBN (5 mg) in anhydrous toluene (2 mL) by syringe pump at a speed of 0.5 mL/h. After the addition was complete, the reaction solution was stirred and refluxed for
a further five hours, cooled to room temperature, and concentrated. The crude product was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane until the tin compounds (nasty odor) were washed out, and then eluted with 5% ethyl acetate/petroleum ether to afford the acetate 146 (0.0291 g, 50% from 145) as a colorless liquid; \( [\alpha]^{22}_D = -11.8^\circ \) (c 3.7, CHCl_3); IR (film): 1745 (C=O), 1240 (C-O) cm\(^{-1}\); \(^1\)H nmr (200 MHz, CDCl_3) \&:

- 0.88 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 1.00 - 1.65 (m, 13 H, CH_2 and CH), 1.95 (m, 1 H, CH-CH_2-O), 2.00 (s, 3 H, CH_3C=O), 4.19 (d, 2 H, J = 7.9 Hz, CH_2-O);
- \(^{13}\)C nmr (CDCl_3) \&: 171.1, 66.2, 64.3, 54.8, 44.9, 44.5, 41.3, 38.9, 36.6, 33.5, 32.7, 32.1, 31.7, 30.8, 24.6, 20.9, 20.8. 

Exact mass calcd. for C_{15}H_{24} (M^+-AcOH): 204.1872; found: 204.1884. Low resolution mass spectrum found 264 (M^+).

\( (+) \) Longifolene (3)

A pyrolysis apparatus was assembled as shown in Figure 8. The quartz tubing filled with quartz-wool was preheated to 525°C under a flow of nitrogen. A solution of acetate 146 (0.0261 g, 0.0984 mmol) in anhydrous benzene (2 mL) was added dropwise in order to pass through the hot quartz tubing at a rate that permitted the hot vapor to condense completely in the cold (-78°C) receiving flask.

To prevent the acetic acid formed in pyrolysis from interfering with the product a small amount of solid NaHCO_3 was placed in the receiving flask. After the reaction solution was pyrolyzed, additional anhydrous benzene (3 mL) was added in the same manner to wash the quartz-wool. The apparatus was cooled to room temperature under nitrogen. Then the cold receiving flask was removed from the apparatus and warmed to room temperature. Ether (15 mL) was added and the ether solution was transferred to a separatory funnel by filtration. Th
solution was washed with saturated aqueous NH₄Cl (15 mL), dried, filtered, and concentrated. The yellow residue was purified by flash chromatography (petroleum ether) to yield 0.0110 g (55%) of (+)-longifolene as a colorless liquid; \([\alpha]^{22}_D = +47.0^\circ\) (c 1.7, CHCl₃), (authentic commercial sample \([\alpha]^{22}_D = +51.2^\circ, c\ 1.9, CHCl₃\); IR (film): 1658 (C=C) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ: 0.88 (s, 3 H, CH₃), 0.93 (s, 3 H, CH₃), 0.98 (s, 3 H, CH₃), 1.10 (m, 1 H), 1.35 - 1.70 (m, 10 H), 2.04 (d, 1 H, 2.5 Hz), 2.58 (d, 1 H, 25.3 Hz, CH=CH), 4.45 (s, 1 H, H-C=C), 4.71 (s, 1 H, H-C=CH); ¹³C nmr (300 MHz, CDCl₃) δ: 168.0, 99.0, 62.0, 47.7, 44.9, 43.8, 43.2, 36.2, 33.4, 30.4, 30.3, 29.9, 29.5, 25.3, 20.9; DEPT (300 MHz, CDCl₃) δ: 99.0 (CH₂), 62.0 (CH), 47.7 (CH), 44.9 (CH), 43.2 (CH₂), 36.2 (CH₂), 30.4 (CH₃), 30.3 (CH₃), 29.9 (CH₃), 29.5 (CH₂), 25.2 (CH₂), 20.9 (CH₂). Exact mass calc. for C₁₃H₂₄: 204.1872; found: 204.1870.

(1R, 2R, 4R, 5R, 7S, 8R, 9S) 5-Hydroxy-8-hydroxymethyl-4-methoxy-3,3,7-trimethyltricyclo[5.4.0]¹7.0²₉] -10-undecene (147)

Tetracyclic lactone 138 (0.1574 g, 0.6 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice-water bath. LiAlH₄ (100 mg, excess) was added in several small portions and the resulting suspension was allowed to warm slowly to room temperature. The suspension was stirred with monitoring by TLC until the reaction was complete. The reaction mixture was then cooled to 0°C, diluted with ether (15 mL), and quenched with cold water to destroy the excess LiAlH₄. The resulting mixture was filtered, and the filtrate was separated. The aqueous layer was re-extracted with ether (2 × 15 mL), the organic phases were combined, washed with saturated aqueous NH₄Cl, dried, filtered, and concentrated to give a very pure diol 147, which was used directly for further synthetic work. IR (film): 3410 (br, OH), 3060 (H-C=C), 1585 (C=C), cm⁻¹;
1H nmr (200 MHz, CDCl₃) δ: 0.94 (s, 3 H, CH₃), 1.10 (s, 3 H, CH₃), 1.13 (s, 3 H, CH₃), 1.28 (t, 1 H, J = 8 Hz, CH), 1.43 (br s, 1 H, OH), 1.66 - 1.73 (m, 2 H, CH₂), 1.89 (br s, 1 H, OH), 1.96 (dd, 1 H, J = 9.5 Hz, CH), 2.29 (br s, 1 H, CH-C=C), 2.39 (br s, 1 H, CH-C=C), 3.19 (s, 3 H, OCH₃), 3.77 - 4.10 (overlap m, 3 H, CH₂-O and CH-O), 4.56 (s, 1 H, H-C-O), 5.93 (m, 1 H, H-C=C), 6.31 (m, 1 H, H-C=C); 13C nmr (CDCl₃) δ: 140.6, 132.8, 66.9, 62.3, 58.4, 53.2, 50.8, 50.4, 49.5, 48.6, 40.0, 38.5, 37.0, 28.4, 22.8, 17.4. Low resolution mass spectrum found 248 (C₁₆H₂₄O₂, M⁺-H₂O).

(IR, 2R, 4R, 5R, 7S, 8R, 9S) 8-Acetoxymethyl-5-hydroxy-4-methoxy-3,3,7-trimethyltricyclo[5.4.01.7,02.9]-10-undecene (148)

Diol 147 (0.3052 g, 1.15 mmol) was dissolved in anhydrous ether (5 mL) and cooled to 0°C with an external ice/water bath. Pyridine (0.2 mL) was added to this solution, followed by acetic anhydride (0.2 mL, 2.0 mmol, Aldrich). The reaction solution was stirred overnight at 0°C, diluted with ether (20 mL), and then quenched with cold water. The mixture was separated and the aqueous layer was extracted with ether (15 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ and brine, dried, filtered, and concentrated. The crude product was purified by flash chromatography (10% ethyl acetate/petroleum ether) to afford 0.2610 g (74%) of acetate 161 and 0.0772 g (15%) of the diacetate. Subsequently, the latter material was treated with LiAlH₄ to recover the starting material. Acetate 148; IR (film): 3460 (OH), 1740 (C=O), 1560 (C=C) cm⁻¹; 1H nmr (200 MHz, CDCl₃) δ: 0.72 (s, 3 H, CH₃), 1.05 (s, 3 H, CH₃), 1.17 (s, 3 H, CH₃), 1.48 (m, 1 H, CH), 1.60 - 2.10 (overlap m, 3 H), 2.05 (s, 3 H, CH₃-C=O), 2.25 (m, 1 H, CH-C=C), 2.72 (m, 1 H, CH-C=C), 3.08 (br s, 1 H, OH), 3.25 (s, 3 H, OCH₃), 3.35 (d, 1 H, J = 7.5 Hz, CH-O), 4.25 (overlap d, 2
H, CH₂-O), 5.52 (m, 1 H, CH-OH), 5.88 (m, 1 H, H-C=C), 6.42 (d, J = 6 Hz, H-C=C).

(1R, 2R, 4R, 5R, 7S, 8K, 9S) 8 - Acetoxymethyl - 4 - methoxy - 5 - phenoxythiocarbonyloxy - 3, 3, 7 - trimethyltricyclo [5.4.0 1,7.0 2.9] - 10 - undecene (149)

Pyridine (0.16 mL, 2 mmol), followed by phenyl chlorothioformate (0.14 mL, 1 mmol, Aldrich), was added to a stirred solution of alcohol 148 (0.2016 g, 0.65 mmol) in anhydrous CH₂Cl₂ (5 mL) at room temperature. The reaction was stirred for 3 h at room temperature and then concentrated to remove the solvent. The residue was extracted with ether (30 mL), and the ether solution was washed with 5% aqueous NaHCO₃ and brine, dried, filtered, and concentrated. Flash chromatography (5% ethyl acetate/petroleum ether) gave recovered starting material (0.0413 g, 20.5%) and the thiocarbonate 149 (0.1936 g, 67%); IR (film): 1745 (C=O), 1595 (C=C), 1490 (phenyl) cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ: 0.77 (s, 3 H, CH₃), 1.24 (s, 3 H, CH₃), 1.27 (s, 3 H, CH₃), 1.54 (m, 2 H, CH₂), 1.70 - 2.00 (overlapped m, 4 H), 2.04 (s, 3 H, CH₃-C=O), 2.33 (d, 1 H, J = 7.5 Hz, CH-C=C), 2.54 (m, 1 H, CH-C=C), 2.79 (br s, 1 H, CH-O), 3.20 (s, 3 H, OCH₃), 4.28 (dd, 2 H, J = 3.6, 7.1 Hz, CH₂-O), 5.94 (dd, 1 H, J = 2.3, 5.5 Hz, H-C=C), 6.07 (dd, 1 H, J = 7.5, 10.1 Hz, CH-OC(=S)OPh), 6.35 (d, 1 H, J = 5.9 Hz, H-C=C), 7.03 (m, 1 H, phenyl H), 7.06 (m, 1 H, phenyl H), 7.25 (m, 1 H, phenyl H), 7.35 (m, 2 H, phenyl H); ¹³C nmr (CDCl₃) δ: 194.1, 172.0, 153.5, 138.2, 133.1, 129.5 (2 C), 126.5, 121.9 (2 C), 90.6, 74.9, 64.3, 63.6, 58.4, 55.6, 52.3, 48.9, 48.8, 43.7, 41.1, 23.3, 22.6, 20.9, 20.1. Low resolution mass spectrum found 291 (C₁₈H₂₇O₃, M⁺- PhOC(=S)O), 259 (C₁₇H₂₅O₂, M⁺ - PhOC(=S)O - MeOH).

These peaks were too weak for a high resolution mass spectrum.
(1R, 2R, 4R, 7S, 8R, 9S) 8-Acetoxymethyl-4-methoxy-3, 3, 7-trimethyltricyclo[5.4.0\textsuperscript{1,2}, 0\textsuperscript{2,9}]-10-undecene (150)

A solution of tributyltin hydride (0.22 mL, 0.8 mmol, Aldrich) and AIBN (16 mg) in anhydrous toluene (2 mL) was added to a stirred, refluxing solution of phenoxythiocarbonate 149 (0.1396 g, 0.31 mmol) in anhydrous toluene (5 mL) at a rate of 0.5 mL/h with a syringe pump. After the addition was complete, the reaction solution was stirred and refluxed for a further 6 h. It was cooled to room temperature, and concentrated to remove the solvent. The residue was applied (overnight) to the top of a silica gel column (saturated with hexane), eluted first with hexane to wash out the tin compounds, and then eluted with 5% ethyl acetate/petroleum ether to afford methoxy acetate (0.0806 g, 89%) as a colorless liquid; IR (film): 3060 (H-C=C), 1735 (C=O), 1574 (C=C) cm\(^{-1}\); \(^1\)H nmr (200 MHz, CDCl\(_3\)) \(\delta\): 0.66 (s, 3 H, CH\(_3\)), 1.10 (s, 3 H, CH\(_3\)), 1.16 (s, 3 H, CH\(_3\)), 1.31 (m, 2 H, CH\(_2\)), 1.56-2.17 (overlapped m, 5 H), 2.00 (s, 3 H, CH\(_3\)-C=O), 2.52 (m, 1 H, CH-C=C), 2.70 (br s, 1 H, CH-C=C), 3.15 (s, 3 H, OCH\(_3\)), 4.04 (d, 2 H, \(J = 7.3\) Hz, CH\(_2\)-O), 5.91 (dd, 1 H, \(J = 3, 5.7\) Hz, H-C=C), 6.35 (d, 1 H, \(J = 5.7\) Hz, H-C=C); \(^13\)C nmr (CDCl\(_3\)) \(\delta\): 171.2, 138.9, 133.0, 75.6, 66.5, 66.4, 58.1, 50.8, 49.4, 48.7, 46.4, 43.7, 41.1, 33.7, 23.3, 23.0, 20.7, 18.9. Low resolution mass spectrum found 292 (C\(_{18}\)H\(_{28}\)O\(_3\), M\(^+\)), 260 (C\(_{17}\)H\(_{24}\)O\(_2\), M\(^+\) - MeOH).
REFERENCES


SPECTRA

$^1$H nmr, $^{13}$C nmr, IR and / or MS spectra of some key intermediates are listed here.
Figure 16 $^{13}$C – $^1$H correlation spectrum of (132)
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**Figure 17** $^1$H nmr spectrum of (133)
Figure 19  IR spectrum of (134)
Figure 20  Mass spectrum of (134)
Figure 31. IR spectrum of (146).