AN INVESTIGATION OF THE EFFECT OF ORGANIC SOIL CONSTITUENTS ON BORON ADSORPTION

by

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ABSTRACT

The preparation and synthetic utility of a number of structurally interesting donor-acceptor reagents is described. It has been found that protonative deconjugations of geometrically isomeric \( \beta \)-trimethylstannyl-\( \alpha,\beta \)-unsaturated esters are highly stereospecific. Thus, treatment of the esters (131) and (137) with lithium diisopropylamide in THF or THF-HMPA followed, in each case, by transfer of the resultant solution to a cold (-98°C) solution of acetic acid in ether, provided exclusively the alkyl 3-trimethylstannyl-3-alkenoates (167) and (173), respectively.

Ethyl (Z) and (E)-3-trimethylstannyl-3-pentenoates were converted into the chlorides (99) and (100), respectively. Transmetalation of (99) afforded (204), which was transformed into the Grignard reagent (218). Both (204) and (218) serve effectively as conjunctive reagents which are synthetically equivalent to the (E)-\( \delta^3,\alpha^5 \)-2-pentene synthon (200). For example, copper(I)-catalyzed conjugate addition of (218) to enones and subsequent intramolecular alkylation of the resultant products form the basis of a new (Z)-ethylidenecyclopentane annulation process [(220) \( \rightarrow \) (222)]. Interestingly, although transmetalation of (100) also occurred smoothly, the resultant lithio reagent (207) self-annihilated rapidly even at low temperatures to give ethylidene-cyclopropane.

The annulation method described above played a key role in short syntheses of (±)-oplopanone (257), (±)-8-epi-oplopanone (323), and
(±)-anhydro-oplopanone (258). Thus, (Z)-ethylidenecyclopentane annulation of 4-isopropyl-2-cyclohexen-1-one provided the bicyclic ketone (307). Suitable functional group manipulations transformed (307) into (±)-(257), (±)-(323), and (±)-(258).

Reaction of 1-alkyn-3-ols with Me₃SnCuMe₂S-MeOH, [Me₃SnZn(t-Bu)₂]Li-CuCN, or [Me₃SnZnEt₂]Li-CuCN provided, in varying ratios, the vinylstannanes (109) and (339). Orthoester Claisen rearrangement of (109) and (339) afforded the esters (357) and (363), respectively. Ethyl (Z)-4-trimethylstannyl-4-hexenoate was transformed into the chloride (370). Compound (370) is a convenient precursor of reagents (371) and (374) which are synthetically equivalent to the (E)-d₃,a₆-2-hexene synthon (379). For instance, the Grignard reagent (374) served as a pivotal species in the development of a new six-membered annulation method [(101) → (380)].
99 \( M = \text{SnMe}_3 \)

204 \( M = \text{Li} \)

218 \( M = \text{MgBr} \)

100 \( M = \text{SnMe}_3 \)

207 \( M = \text{Li} \)

\[
\begin{align*}
\text{R} & \quad \rightarrow \\
\text{R'} & \\
\end{align*}
\]

220

222

307

257 \( R^1 = \text{OH}, R^2 = \text{Me} \)

323 \( R^1 = \text{Me}, R^2 = \text{OH} \)

258
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ABBREVIATIONS

The following abbreviations have been used throughout this thesis:

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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DMAP</td>
<td>dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>glc</td>
<td>gas-liquid chromatography</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>ir</td>
<td>infrared</td>
</tr>
<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MEM</td>
<td>methoxyethoxymethyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
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nmr = nuclear magnetic resonance
PCC = pyridinium chlorochromate
Ph = phenyl
Pr = propyl
PPTS = pyridinium p-toluenesulfonate
Py = pyridine
rt = room temperature
q = quartet
s = singlet
t = triplet
Tf = trifluoromethanesulfonyl
THF = tetrahydrofuran
tlc = thin layer chromatography
TMS = trimethylsilyl
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TO MY PARENTS,

with affection
INTRODUCTION
INTRODUCTION

I. General

The chemical synthesis of organic molecules continues to occupy an increasingly important place in the repertoire of the organic chemist. The achievement of a synthesis of a complex organic molecule involves the development of a synthetic strategy and plan, the selection of specific individual steps and their ordering, and the demanding task of experimental execution of the synthesis. A general approach to the analysis of a complex synthetic target is to work the problem backwards. The target molecule is methodically broken apart in such a way that the fragments can be reassembled with reasonable assurance of success. The purpose of such a retrosynthetic analysis\(^1\) is to generate a tree of synthetic intermediates that terminates with a number of accessible starting materials. The synthesis then involves the stepwise construction of the planned intermediates through the application of established chemical reactions. The success of retrosynthetic analysis depends upon a perception of the structural features of the target molecule. Corey has recently put forward five types of strategies for retrosynthetic analysis.\(^2\)

The planning of a synthesis is greatly facilitated by recognizing within a target molecule certain units which can be synthesized, modified, or joined by known or conceivable synthetic operations. Such units are referred to as synthons.\(^3\) The identification of synthons
provides control over tree branching and helps in carrying out a bidirectional analysis, that is, a combined retrosynthetic and synthetic search. A reagent is a compound or intermediate actually used to carry out a synthetic operation. The reactions most frequently used in organic synthesis are polar in nature, i.e. they involve the use of nucleophilic or donor (d) and electrophilic or acceptor (a) reagents.

In synthetic strategy, central importance is attached to minimizing the number of steps and utilizing primarily construction reactions. In a convergent synthesis, if one plans to combine two previously synthesized components A and B in a key step to form a target molecule, it is usually necessary to activate A and/or B. However, such activation is not necessary if a highly reactive coupling agent is used to join the non-activated A and B. Since such reagents are designed to couple two or more components, they are called multiple coupling reagents (MCR).

Seebach has outlined the following properties as being crucial for the successful deployment of a multiple coupling reagent:

(i) It should furnish the desired carbon skeleton and functionality pattern.
(ii) It must allow for selective, sequential (or simultaneous) inter-molecular formation of two or more new bonds to take place.
(iii) If it has heterotopic sites, they must be well-differentiated.
(iv) If the reactive sites are diastereotopic, no mixtures of diastereomers should be formed.

Bifunctional conjunctive reagents, which are similar in concept and function to multiple coupling reagents, are substances that possess
two reactive sites (e.g. two donor centers, two acceptor centers, or one donor and one acceptor center) and are incorporated in whole or in part into a substrate molecule.

Some bifunctional conjunctive reagents have the ability to undergo cyclizations. Such reagents usually react with a bifunctional substrate by an intermolecular coupling step followed by an intramolecular step. Selected examples of such reagents are given below.*

Sulfur-containing groups acidify adjacent C-H bonds and are relatively easy to remove from organic molecules. These properties allow for the use of 1,3-dithiane\(^8\) \((d^1,d^1)\) and methyl benzenesulfonylacetaate\(^9\) \((d^1,d^1)\) as effective bifunctional reagents. For example, cyclobutanone

\[
\begin{align*}
\text{S} & \quad 1 \quad \text{BuLi}^1 \quad \text{S} \\
\text{S} & \quad 2 \quad \text{Cl(CH}_2\text{)}_3\text{X} \\
\text{H} & \quad n\text{-BuLi} \\
\text{S} & \quad 3
\end{align*}
\]

\[
\begin{align*}
\text{HgCl}_2, \\
\text{H}_2\text{O} & \quad 4
\end{align*}
\]

* This summary is not meant to be exhaustive, but is given to provide the reader with some background regarding the use of bifunctional reagents.
(4) has been synthesized by the reaction of 1,3-dithiane (1) with a 1,3-dihalopropane. After 2-(3-chloro-1-propyl)-1,3-dithiane (2) was produced by the reaction of lithiated 1,3-dithiane with a 1-halo-3-chloropropane, the former substance was again treated with n-butyl-lithium. Compound (3) thus obtained was converted into cyclobutanone (4) by mercuric chloride promoted hydrolysis (equation 1). This example illustrates the utility of 1,3-dithiane (1) as a carbonyl dianion (C=0) equivalent.

Trost has used methyl benzenesulfonylacetate as the equivalent of a key methylene dianion synthon (CH2) in the synthesis of (±)-recifeiolide (9).\textsuperscript{9b} Alkylation of the sodium salt of methyl benzenesulfonylacetate with (5) and reductive hydrolysis of the resultant product gave the acid (6). Conversion of the acid (6) into its acid chloride and reaction of the latter material with the alcohol (7) gave the requisite precursor (8). Refluxing a solution of the sodium salt of (8) with Pd(PPh\textsubscript{3})\textsubscript{4} produced the corresponding twelve-membered lactone, which was converted into (±)-recifeiolide (9) by decarbomethoxylation, followed by reductive desulfonylation (equation 2).

The dichloride (11) was used as the equivalent of a novel a,a synthon in an elegant synthesis of (±)-β-vetivone (13).\textsuperscript{10} The first alkylation was carried out by allowing the lithium enolate of the enol ether of 1,3-cyclohexanedione (10) to react with the dichloride (11). Subsequent addition of two equivalents of lithium diisopropylamide provided the spiroannulation product (12) (equation 3). The stereochemistry of compound (12) was anticipated to be as shown because the first alkylation step would involve displacement of the allylic halide.
Br(CH₂)₄CO₂CCl₃ → PhO₂S⁻CO₂Me → PhO₂S⁻(CH₂)₄CO₂H

5 → 6

1. SOCl₂ → AcO⁻Me₂C⁻SO₂Ph
2. OH⁻Me₂C⁻SO₂Ph → 9

7 → 8 → 9

10 + 11 → MeLi → HCl → 13
In the second, intramolecular alkylation reaction, the new carbon-carbon bond would be expected to form trans to the pseudo-axially oriented methyl group. The validity of this assumption was checked by conversion of (12) into the natural product (13).

Based on the concept of nuclear synthons, Hendrickson has developed a synthesis of dihydrojasmine (18) in which mesyl triflone (14) was used as an olefin polyanion equivalent \( \text{C}_2\text{C}_\text{d}^{\text{d}} \).\(^{11}\) Methylation of the \( \alpha,\alpha' \)-dianion of (14), followed by the generation of a new \( \alpha,\alpha' \)-di-

\[
\begin{align*}
1. & \quad \begin{array}{c}
\text{TF} \\
\text{SO}_2
\end{array} \\
2. & \quad \begin{array}{c}
\text{n-BuLi} \\
\text{Mel}
\end{array} \\
3. & \quad \begin{array}{c}
\text{TF} \\
\text{SO}_2
\end{array} \\
4. & \quad \text{R}
\end{align*}
\]

\[
\begin{align*}
14 & \quad \text{TF} \\
15 & \quad \text{TF} \\
16 & \quad \text{TF} \\
17 & \quad \text{TF} \\
18 & \quad \text{TF}
\end{align*}
\]

\[
\begin{align*}
\text{R=n-C}_5\text{H}_11
\end{align*}
\]

* These are small molecular units capable of initiating multiple constructions in one operation. These units provide a nucleus of reactivity capable of rapidly elaborating around it a large product skeleton and hence the name nuclear synthons.\(^{11a}\)
anion and alkylation of the latter species with 1-iodopentane, afforded the sulfone (15). Slow addition of acrolein to the α,α'-dianion of (15) led to the allylic alcohol (16). Treatment of (16) with active manganese dioxide gave the cyclic keto sulfone (17) via oxidation and spontaneous cyclization. The final step to generate dihydrojasmine (18) from (17) via the Ramberg-Backlund reaction\textsuperscript{11c} was accomplished by treatment of the keto sulfone (17) with potassium carbonate (equation 4).\textsuperscript{11b}

Yamamoto and co-workers have reported a new asymmetric annulation protocol via direct coupling of α,ω-dihalides (a,a) with dianions derived from dialkyl succinates (d,d).\textsuperscript{12} For example, (-)-dimethyl cyclopropane-trans-1,2-dicarboxylate (20) was obtained in 99% enantio-meric excess when the dianion of (-)-dimethyl succinate (19) was allowed to react with 0.5 equivalent of bromochloromethane at low temperature (equation 5).

\[ \text{RO}_2\text{C} \text{CO}_2\text{R} \rightarrow \text{CH}_2\text{BrCl} \rightarrow \text{CO}_2\text{R} \]

\[ \text{R=\text{-L-Menthy}} \]

Yamamoto has also developed a new one-pot construction of function-alized cyclopentanones via direct coupling of β-halo esters and diester dianions.\textsuperscript{13} For example, reaction of the dianion of diisopropyl (E)-3-hexendioate (22) with ethyl 3-bromopropionate (23) led to
formation of the 2,3-disubstituted cyclopentanone (24) as a mixture of geometric isomers. The latter material was transformed into the ketal (25) in good yield. This reaction sequence was used in a short synthesis of 11-deoxyprostaglandin E2 (26) (Scheme 1).\textsuperscript{13b}

\[
\begin{align*}
21 & \xrightarrow{2\text{LDA-HMPA}} [\text{22}] \\
23 & \xrightarrow{\text{Br(CH}_2\text{CO}_2\text{Et)}} 24 \\
\text{25} & \xrightarrow{\text{HO}_2\text{OH, H}^+} \text{26}
\end{align*}
\]

\[\text{R= } i-\text{Pr}\]

Scheme 1

The diene (27) has been used as a formal equivalent to the a,d-synthon (28) in a multiple annulation sequence developed by Trost.\textsuperscript{14} Thus, alkylation of the sodium enolate of the keto sulfone (29) with the diene (27), followed by cyclization of the resultant product (30) with
tetra-n-butylammonium fluoride or ethylaluminum dichloride, afforded the 2,3-disubstituted-1,3-butadiene (31). Facile Diels-Alder reaction of (31) with dimethyl acetylenedicarboxylate gave mainly the adduct (32) (Scheme 2).

Scheme 2

![Chemical Reaction Diagram]
The identification of prostaglandins, polyquinanes, and related natural products as important synthetic targets has sparked an active interest and consequent growth in the development of new methodologies for the synthesis of five-membered carbocycles. Recently, Danheiser has described one such novel [3+2] approach to cyclopentane derivatives.\textsuperscript{15} (Trimethylsilyl)allenes (33) serve as three carbon d,a components (34) in this regioselective one-step annulation leading to (trimethylsilyl)-cyclopentenes. As shown by means of a specific example in equation 6, an $\alpha,\beta$-unsaturated ketone (35) was treated with the (trimethylsilyl)-allene (37) in the presence of titanium tetrachloride to provide the annulation product (39). Initial complexation of the enone (35) and titanium tetrachloride would generate the alkoxy allylic carbocation (36). Regioselectivity of electrophilic substitution of this cation at C-3 of the allene (37) was anticipated to be as shown because the resultant vinyl cation (38) would be stabilized by interaction with the adjacent carbon-silicon bond. A 1,2-shift of the trimethylsilyl group, followed by interception of the isomeric vinyl cation by the titanium enolate, would then generate the new five-membered ring. The scope of this annulation strategy has now been extended to the synthesis of
heterocyclic compounds by using aldehydes and N-acyl imine derivatives as allenophiles.\textsuperscript{15c}

The regioselectivity, stereoselectivity and scope of application associated with the Diels-Alder reaction remains unparalleled for the synthesis of cyclohexane derivatives. Reagents that are equivalent to the a,d-synthon (41), as developed by Trost,\textsuperscript{16} offer the possibility of extending such benefits to the synthesis of five-membered rings.
In compounds such as (40) (X = leaving group, M = Si or Sn), the trialkylsilyl or trialkylstannyl groups are removed to provide carbanion equivalents, whereas the X groups (X = OAc, OSO₂CH₃, halide, etc.) are removed to provide carbocation equivalents. Thus, reaction of these conjunctive reagents with palladium(0) complexes gives a π-allylpalladium intermediate (42) in which the C-M bond is weakened by the proximal positive charge. Attack on the metal center by X⁻ results in formation of the palladium complex (43) as a reactive intermediate (see equation 7). Equations 8 and 9 provide examples of reactions of the "trimethylene methane" equivalent (45) with electron-deficient olefins to form new cyclopentane annulated products.¹⁶ᵃ
A different approach, employing 3-iodo-2-(trimethylsilylmethyl)-1-propene (50) as a bifunctional reagent, has been used effectively in the synthesis of the highly functionalized linear triquinane, (±)-coriolin.
The β-keto sulfide (49) was alkylated cleanly with the iodide (50) to provide (51). Oxidation of (51) to the disulfone, followed by fluoride-induced cyclization, produced (52). With this effective annulation protocol for the β-keto sulfide (49), the stage was set for completion of the synthesis, which mainly required adjustment of the oxidation pattern (Scheme 3).

Boger has recently demonstrated the use of cyclopropenone ketal (54) as equivalents to the bifunctional d,a-synthon (55). For example, treatment of (57) with the cyclopropenone ketal (56) resulted in a regioselective thermal addition reaction to provide the adduct (58) (equation 10). As shown in equation 11, nucleophilic attack of the strained cyclopropene onto the electron-deficient olefin, rearrangement of the cyclopropyl cation to the allyl cation, and subsequent collapse
of the dipole have been proposed to explain the formation of the observed products.

The carbethoxycyclopropylphosphonium salt (59) provides another example of a reagent that is equivalent to a d,a-synthon [see (60)] and is used for cyclopentene annulation. For example, the sodium enolate of the hydroxymethylene ketone (61) underwent clean spiroannulation upon treatment with (59) to produce a single crystalline spiro keto ester (62) (equation 12). The latter substance is a pivotal intermediate in
the synthesis of spirovetivane sesquiterpenes.\textsuperscript{19b}

Recent preparations of stereochemically defined organolithium reagents have provided a most useful approach to the stereospecific construction of carbon-carbon bonds.\textsuperscript{20} In light of the stereoselective preparation\textsuperscript{21-24} and facile transmetalation\textsuperscript{25} of vinylstannanes to the corresponding vinyllithium reagents, it was decided to make use of substituted trialkylstannanyl alkenes as potential precursors of novel donor-acceptor reagents. A brief introduction to the use of vinylstannanes as intermediates in organic synthesis should, therefore, be in order.

The metathesis reaction between an organolithium and an organostannane (or an organic derivative of other heavy metals) is known as transmetalation. Early studies of this reaction demonstrated that it is a reversible process\textsuperscript{26} leading to an equilibrium mixture favoring the
more stable organolithium (equation 13).*

\[ \text{Sn-R} + R'\text{Li} \rightleftharpoons \text{Sn-R'} + R\text{Li} \]  

(13)

Kinetic studies of the lithium-tin exchange have generally been interpreted in terms of a four centered transition state (63). The possible intermediacy of transient or stable "ate" complexes (64) has also been suggested.

Several characteristics of the transmetalation of vinylstannanes make this reaction particularly attractive: (i) the reaction usually proceeds efficiently at low temperatures, (ii) the reaction is stereospecific, and (iii) the by-product of the reaction is a coordinatively saturated compound (e.g. tetramethyltin) that usually does not interfere

* Although organolithiums are often represented as monomeric species, they are known to exist as aggregates whose degree of association may be affected by solvent, concentration, and temperature (see ref. 20). For the sake of pictorial clarity, monomeric species will be used in formulations.
with reactions of the lithiated product. The following two examples are representative of the use of this type of reaction in organic synthesis.

Still's synthesis of the germacranolide eucannabinolide (71) illustrates an elegant use of a functionalized vinylstannane. The desired cyclobutenyl tin reagent (67) was prepared from the ketal (65) by a two step sequence outlined in equation 14. Coupling of (67) and the enone (68) proceeded via transmetalation of (67) and addition of the enone (68) to the resultant solution of the corresponding cyclobutenyl-lithium reagent. The addition occurred trans to the bulky isopropenyl substituent to provide a single diastereomer (69). Oxy-Cope ring expansion of (69) led to formation of the enone (70). Appropriate functional group manipulations converted (70) into the natural product (71) (equation 15).

A total synthesis of brefeldin A (78) by Corey is based on a retrosynthetic plan involving two vinylstannanes. Both of the organotin compounds (72) and (76) were prepared readily by hydrostannylation of the corresponding terminal acetylenes using tri-n-butyltin hydride and azobisisobutyronitrile as initiator.
Transmetalation of (72) with n-butyllithium, followed by addition of 1-pentynylcopper, gave the corresponding cuprate reagent. The latter species reacted stereoselectively with enone (73) to produce the conjugate adduct (74) in good yield (equation 16). Conversion of (74) into the aldehyde (75) was carried out by a series of standard reactions. Transmetalation of (76) and reaction of the resulting lithio species with the aldehyde (75) resulted in efficient carbonyl addition to provide the alcohol (77), which was converted into (±)-brefeldin A (78) in seven steps (equation 17).

Vinylstannanes are usually prepared by hydrostannylation of acetylenic compounds. When this type of reaction is carried out on a 1-alkyne as substrate, the major product of the reaction is normally the corres-
1. $n$-BuLi
2. $n$-Pr-CC=C-Cu
3. Na $\text{C(CO}_2\text{Et)}_2$

\[ \text{n-Bu}_3\text{Sn} + \text{t-BuMe}_2\text{SiO} \rightarrow 72 \]

\[ \begin{array}{c}
\text{CH(CO}_2\text{Et)}_2 \\
\text{HO}
\end{array} \text{t-BuMe}_2\text{SiO} \rightarrow 75 \]

\[ \text{n-Bu}_3\text{Sn} + \text{t-BuMe}_2\text{SiO} \rightarrow 76 \]

\[ \text{n-Bu}_3\text{Sn} + \text{t-BuMe}_2\text{SiO} \rightarrow 78 \]
sponding (E)-1-trialkylstannyl-1-alkene. However, the formation of mixtures of products is not unusual. Other more regio- and stereoselective methods for the preparation of vinylstannanes would enhance their usefulness.

II. Previous Work

Previous work in our laboratories had shown that addition of the elements of Me₃Sn-H across the triple bond of α,β-acetylenic esters (79) by reaction of these substrates with lithium (phenylthio)(trimethylstannyl)cuprate (80) could be controlled experimentally so as to produce, highly stereoselectively, either of the geometrically isomeric β-trimethylstannyl esters (81) and (82). Thus, the conjugate addition of (80) to (79) at low temperature (-78°C) in the presence of methanol produced (>98% stereoselectivity) the (E) ester (81), while the (Z) ester (82) was the major (>96% stereoselectivity) product obtained after hydrolysis when the reaction was performed at higher temperature (-48°C) in the absence of a proton source (Scheme 4).

Further work had shown that the (trimethylstannyl)copper reagent (84) added regioselectively to ω-substituted 1-alkynes (83) (X = leaving group or potential leaving group) at -63°C in the presence of methanol to provide, efficiently, the corresponding 2-(trimethylstannyl)-1-alkenes (85) (equation 18).

The products (85) potentially represented convenient precursors of bifunctional conjunctive reagents which could be conceived as being
Scheme 4

\[
\text{Me}_3\text{SnCu-SnMe}_3
\]

\[
\text{H-C≡C-(CH}_2\text{)_nX } \xrightarrow{84} \text{MeOH, -63°C} \xrightarrow{\text{MeOH, -63°C}} \text{H}_2\text{C=C}(\text{CH}_2\text{)_nX} \quad (18)
\]

83 84 85

86
formally equivalent to the donor-acceptor synthons (86).

Transmetalation of 4-chloro-2-(trimethylstannyl)-1-butene (87) with methyllithium at -78°C, followed by addition of phenylthiocopper\textsuperscript{32} or cuprous cyanide, provided clear solutions of the corresponding cuprate reagents. These reagents proved to be sufficiently stable to allow for their reaction with 2-methyl-2-cyclopenten-1-one (88) to afford a good yield of the corresponding conjugate addition product (89).\textsuperscript{33} Treatment of (89) with potassium hydride provided the bicyclic ketone (90) (equation 19). As delineated in equation 20, this new five-membered ring annulation method was based on the theoretical combination of a d\textsuperscript{2},a\textsuperscript{3}-synthon (91) with the d\textsuperscript{2},a\textsuperscript{4}-synthon (92).

The utility of this methylenecyclopentane annulation process was demonstrated by its application to the synthesis of the sesquiterpenoids (±)-Δ\textsuperscript{9(12)}-capnellene (96)\textsuperscript{34a} and (±)-pentalenene.\textsuperscript{34b} For example, the ketone (90) was transformed into the enone (94) via a sequence of standard reactions. Copper(I)-catalyzed conjugate addition of the Grignard reagent prepared from (87) (MeLi, MgBr\textsubscript{2}) occurred stereoselectively from the convex side of the molecule to produce a single addition
product, which was converted readily into the annulation product (95).
Reduction of the ketone, followed by deoxygenation, afforded (±)-Δ⁹\(^\text{12}\)-capnellene (96) (equation 21).\(^{34a}\)
III. Proposals

It is evident from the results reported above that the vinyl-
stannane (87) is readily prepared and that it is a synthetically viable
equivalent to the 1-butene $d^2,a^4$-synthon (92).

A potentially important extension to the methodology summarized
above involved the possibility of preparing, stereoselectively, anal-
ogous reagents that would be synthetically equivalent to the donor-
acceptor synthons (97) and (98). For example, it was of considerable
interest to determine whether or not one could prepare and employ
synthetically (Z)- and (E)-5-chloro-3-trimethylstannyl-2-pentenes, (99)
and (100) respectively, and the related lithio and Grignard reagents.

![Chemical structures]

Clearly, these materials could serve as synthetic equivalents to the
(E)- and (Z)-2-pentene $d^3,a^5$-synthons [(97) and (98), R = Me] respec-
tively and, if the proposed use of these species were to be successful,
one could perform stereoselective ethylidene cyclopentane annulations
shown in general terms in equation 22. The new annulation method, apart
from being interesting from a strictly methodological point of view,
would exhibit considerable promise for applications to organic syn-
thesis. For example, the annulation product (105) (see equation 23) could potentially serve as a steroid CD-ring synthon.

\[
\begin{align*}
101 & \quad \text{to} \quad 102 \\
102 & \quad R = \text{Me}, R' = \text{H} \\
103 & \quad R = \text{H}, R' = \text{Me}
\end{align*}
\]

It was envisaged that compounds (99) and (100) could be prepared from the corresponding \( \beta \)-trimethylstannyl-\( \alpha, \beta \)-unsaturated esters (81) and (82) \( R = \text{Et} \) by a three step sequence of deconjugation, reduction and conversion of the resulting alcohols to corresponding chlorides (Scheme 5). Although the deconjugation of alkyl \( (E) \)- and \( (Z) \)-2-alkenoates had been reported previously,\(^{35} \) the effect of a C-3 substituent on the stereochemistry of the process had not been investigated prior to our work.

Continuing the general study of the preparation and use of structurally interesting bifunctional reagents, we wished to prepare reagents that might serve as synthetic equivalents to donor-acceptor synthons of
general structure (106). Thus, explicitly, we wished to prepare vinylstannanes of general structure (107). The latter substances were expected to be obtainable from the esters (110) which, in turn, would be accessible from the corresponding allylic alcohols (109) by ortho-acetate-based Claisen rearrangement reactions (Scheme 6).
In summary, the primary objectives of this study were the following:

a) to investigate protonative deconjugation of alkyl 3-trimethylstannyl-2-alkenoates,

b) to synthesize and study the transmetalation of the geometrically isomeric 5-chloro-3-trimethylstannyl-2-pentenes,

c) if possible, to develop stereoselective ethyldiene cyclopentane annulation sequences and apply the methodology to natural product synthesis, and

d) to prepare and investigate the chemistry of alkyl (Z)-4-trimethylstannyl-4-alkenoates with a view to develop a general (Z)-ethyldiene cyclcohexane annulation method.
DISCUSSION
I. Protonative Deconjugation of Alkyl 3-Trimethylstannyl-2-alkenoates

A. Preparation of α,β-Acetylenic Esters

Ethyl 2-pentyanoate (113) and ethyl 6-tert-butyldimethylsiloxy-2-hexynoate (116) were prepared by reaction of the corresponding alkynyl-lithium with ethyl chloroformate (equation 24). The required alkynyl-lithium species were generated by deprotonation of the corresponding 1-alkyne with methylthium.

\[
RCH_2\text{C}≡\text{C}-\text{H} \xrightarrow{\text{MeLi}} RCH_2\text{C}≡\text{C}-\text{Li} \xrightarrow{\text{ClCO}_2\text{Et}} RCH_2\text{C}≡\text{C}-\text{CO}_2\text{Et} \quad \text{(24)}
\]

\[
R=\text{Me} \\
\text{111} \quad \text{112} \quad \text{113}
\]

\[
R=\text{t-BuMe}_2\text{SiOCH}_2\text{CH}_2 \\
\text{114} \quad \text{115} \quad \text{116}
\]

1,1-Dibromo olefins, available by reaction of aldehydes with a carbon tetrabromide-triphenylphosphine reagent were also used as precursors to α,β-acetylenic esters. For example, treatment of 3-methylbutanal (117) with carbon tetrabromide-triphenylphosphine afforded the dibromo olefin (118) which, upon successive treatment with methylthium (2 equiv) and ethyl chloroformate, provided ethyl 5-methyl-2-hexynoate (119) (equation 25). In an essentially identical manner,
3-trimethylsilylpropanal (120)\textsuperscript{38} was converted into the $\alpha,\beta$-acetylenic ester (122) (equation 26).

\[
\begin{align*}
\text{117} & \quad \text{118} & \quad \text{119} \\
\text{120} & \quad \text{121} & \quad \text{122} \\
R = \text{Me}_3\text{SiCH}_2
\end{align*}
\]

Methyl 4-cyclopropyl-2-butynoate (129) could not be prepared via the above-mentioned methods because neither the corresponding terminal alkyne nor cyclopropylacetaldehyde were readily available. It has been reported that Li-C=\text{C}-\text{CO}_2\text{Et} may be derived readily from ethyl propynoate, and that the former reagent adds to aldehydes and ketones to give ethyl 4-hydroxy-2-alkynoates in good yield.\textsuperscript{39} However, no alkylation reactions were reported, presumably because of the normally observed sluggish reactivity of alkali metal acetylides with such electrophiles.\textsuperscript{40} Suzuki and coworkers reported a useful though somewhat cumbersome solution to this problem. These workers described a general synthesis of 2-alkynoates via the reaction of iodine with the "ate" complexes obtained from lithium ethoxycarbonylacetylide and trialkyl-
Successive treatment of ethyl propynoate (123) with LDA (1 equiv) and the required trialkylborane resulted in formation of the complex (124), which reacted with iodine at low temperature to provide the corresponding ethyl 2-alkynoate (125) (equation 27). Recently, Boland reported alkylations of the copper salt of ethyl propynoate with allylic halides, but the methodology was not applicable to other classes of electrophiles.

\[
\text{H-\(\equiv\text{C-C}^2\text{Et}\)} \xrightarrow{\text{LDA}} \text{Li}[(\text{R}_3\text{B-\(\equiv\text{C-C}^2\text{Et}\)}] \xrightarrow{\text{I}_2} \text{R-\(\equiv\text{C-C}^2\text{Et}\)} \quad (27)
\]

In 1974, Carlson reported the preparation of the propynoic acid dianion (127) and its regioselective addition to unsymmetrical epoxides to provide the corresponding \(\delta\)-hydroxyacetylenic acids (128) in moderate yields (equation 28). The dianion (127) was generated at \(-45^\circ\text{C}\) with LDA in a 1:1 THF-HMPA solvent system and was allowed to react with epoxides at room temperature for ca. 2-3 days to form the corresponding hydroxyacetylenic acids (128). The role of HMPA was crucial, since the reactions carried out without HMPA resulted in the formation of little or no addition product.
A modified version of the procedure reported above was used in our "one-pot" synthesis of methyl 4-cyclopropyl-2-butyroate (129). Thus, when a solution of the dianion of propynoic acid (127) in THF-HMPA was allowed to react with cyclopropylmethyl bromide (1.05 equiv, room temperature, 24 h) and subsequently with methyl iodide (4 equiv, room temperature, 24 h), the ester (129) was produced directly in 53% yield (equation 29). The dianion (127) was produced at -10°C in a 1:2 THF-HMPA solvent system, which was necessary to maintain a solution throughout the dianion generation-addition sequence.

\[
\text{Li-C≡C-CO}_2\text{Li} \xrightarrow{1. \text{CH}_2\text{Br}} \xrightarrow{2. \text{MeI}} \text{CH}_2\text{C≡C-CO}_2\text{Me}
\]  

(29)

127 129

The generality of this reaction was not investigated, but it is expected that the reaction sequence can be carried out with other reactive halides. If successful, this "one-pot" procedure could represent an attractive route to the preparation of this class of compounds.

B. Preparation of β-Trimethylstannyl-α,β-unsaturated Esters

Previous work in our laboratories had already established that lithium (phenylthio)(trimethylstannyl)cuprate (80) smoothly transfers one Me₃Sn group to α,β-acetylenic esters (79). Furthermore, it was
established that the stereochemical course of this reaction can be controlled experimentally to provide either the (E)- or the (Z)-

\[
\begin{align*}
R-\text{C} & \equiv \text{C}-\text{CO}_2\text{R}' \\
& \quad \text{79}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{Sn} & \text{R} \equiv \text{CO}_2\text{R}' \\
& \quad \text{81}
\end{align*}
\]

\[
\begin{align*}
\text{[Me}_3\text{SnCuSPh]} & \text{Li} \\
& \quad \text{80}
\end{align*}
\]

\[
\begin{align*}
\text{Me}_3\text{Sn} & \text{R} \equiv \text{CO}_2\text{R}' \\
& \quad \text{82}
\end{align*}
\]

The \(\alpha,\beta\)-acetylenic esters (130) were converted into the corresponding (E) esters (131) via a slightly modified version of the reported procedure. For example, addition of a THF solution of ethyl 2-pentynoate (113) containing 1.7 equivalents of methanol to a solution (THF) of 1.4 equivalents of the cuprate reagent (80)* (-98°C, 15 min; -78°C, 6 h), followed by a workup and chromatography of the crude product, afforded the (E) ester (132) in 79% yield (Table I). The original procedure\textsuperscript{21} required two equivalents of the cuprate reagent (80). We discovered that with 1.4 equivalents of (80) the reaction took a longer time to go to completion (6 h instead of 3 h), but the stereoselectivity and overall efficiency appeared to be unaffected. It was also noticed that addition of petroleum ether (instead of ether as in the original procedure) in the workup procedure caused a faster and more complete

* A bright red solution of this reagent was prepared by addition of 1 equiv of solid (phenylthio)copper\textsuperscript{32} to a cold (-20°C) solution of (trimethylstannyl)lithium\textsuperscript{45} in THF under an argon atmosphere (see ref. 31).
Table I: Preparation of Alkyl (E)-3-Trimethylstannyl-2-alkenoates

\[
\text{RCH}_2\text{C}≡\text{C}-\text{CO}_2\text{R}' \xrightarrow{\text{Me}_3\text{SnCuSPh}Li} \text{R}≡\text{C}-\text{CO}_2\text{R}' \quad \text{Me}_3\text{Sn}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 130</th>
<th>R</th>
<th>R'</th>
<th>Product 131</th>
<th>Yield (%)^b</th>
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<tr>
<td>1</td>
<td>113</td>
<td>Me</td>
<td>Et</td>
<td>132</td>
<td>79</td>
</tr>
<tr>
<td>2</td>
<td>116</td>
<td>t-BuMe₂SiOCH₂CH₂</td>
<td>Et</td>
<td>133</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>122</td>
<td>Me₃SiCH₂</td>
<td>Et</td>
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<td>73</td>
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<td>74</td>
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<td>119</td>
<td>i-Pr</td>
<td>Et</td>
<td>136</td>
<td>74</td>
</tr>
</tbody>
</table>

^a Reaction conditions: [Me₃SnCuSPh]Li (1.4 equiv), MeOH (1.7 equiv), THF, -98°C, 15 min; -78°C, 6 h.

^b Yield of purified, distilled product.
precipitation of (phenylthio)copper.

In essentially identical fashion, other \(\alpha,\beta\)-acetylenic esters (130) could be transformed smoothly into the corresponding \((E)-\beta\)-trimethylstannyl-\(\alpha,\beta\)-unsaturated esters (131) (see Table I). Although the results summarized in the table require little additional comment, it should be emphasized that, in each case, flash column chromatography was performed on the crude material to remove hexamethylditin and a small amount (<3% by glc analysis) of the corresponding \((Z)\) isomer (137) that was formed in the reaction.

In accordance with the reported procedure,\(^{21}\) reaction of ethyl 2-pentynoate (113) with 1.3 equiv of the cuprate reagent (80) at -78°C for 15 min and at -48°C for 4 h, followed by protonation (ethanol), workup, and chromatography of the crude product, provided the \((Z)\) ester (138) in 76% yield (Table II). In similar fashion, other \(\alpha,\beta\)-acetylenic esters (130) were converted into the corresponding \((Z)-\beta\)-trimethylstannyl-\(\alpha,\beta\)-unsaturated esters (137) in good yield. These results are summarized in Table II.

The structures assigned to the products shown in Tables I and II were supported by the spectral data derived from these substances. In particular, the \(^1\text{H}\) nmr spectra of these products fully corroborated the stereochemical assignments. For example, the \(^1\text{H}\) nmr spectrum of the ester (136) exhibited the signals expected for a trimethylstannyl group (a 9-proton singlet at \(\delta\) 0.16 with satellite peaks due to Sn-H coupling, \(J = 56\) Hz), an isopropyl group (a 6-proton doublet at \(\delta\) 0.89, \(J = 7\) Hz and a 1-proton multiplet at \(\delta\) 1.60-1.72), and an ethyl ester moiety (a 3-proton triplet at \(\delta\) 1.27 and a 2-proton quartet at \(\delta\) 4.13, \(J = 7\)
Table II: Preparation of Alkyl (Z)-3-Trimethylstannyl-2-alkenoates

\[ RCH_2\equiv C-CO_2R' \rightarrow R-\begin{array}{c} Me_3Sn \\ CO_2R' \end{array} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 130</th>
<th>R</th>
<th>R'</th>
<th>Product 137</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<td>Et</td>
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<td>Et</td>
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<td>79</td>
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<td>i-Pr</td>
<td>Et</td>
<td>142</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: [Me<sub>3</sub>SnCuSPh]<sub>L</sub> (1.3 equiv), THF, -78°C, 15 min; -48°C, 4 h; quenched with EtOH.

<sup>b</sup> Yield of purified, distilled product.

<sup>c</sup> The reaction mixture was quenched with MeOH.
Hz). In addition, a 2-proton doublet of doublets ($J = 1, 7$ Hz) due to the allylic methylene protons appeared at $\delta$ 2.80, while the olefinic proton gave rise to a triplet ($J = 1$ Hz) at $\delta$ 6.00 (with satellite peaks due to Sn-H coupling, $J = 75$ Hz). The $^1$H nmr spectrum of the geometrically isomeric ester (142) was very similar to that of (136) but differed significantly in three important aspects. The position of the signal ($\delta$ 2.80) due to the allylic methylene protons of (136) was considerably downfield from the signal ($\delta$ 2.27) due to the corresponding protons of the isomeric ester (142). Thus, it is reasonable to assume that the $\gamma$-protons are cis to the ester group in (136) but trans to the ester group in (142). The chemical shifts of the olefinic protons observed in the spectra of (136) and (142) ($\delta$ 6.00 and $\delta$ 6.28, respectively) are in agreement with the observation that olefinic protons in unsaturated organotin compounds are shielded by a cis vicinal trialkylstannyl substituent to the extent of about 0.5 ppm. It is also known that in compounds in which a trialkylstannyl group and a hydrogen atom are vicinal on an olefinic linkage, $J_{\text{Sn-H}}$ is much larger when the two substituents are trans to each other than when they are cis to each other. The values of $J_{\text{Sn-H}}$ associated with the olefinic protons in esters (136) and (142) (75 Hz and 121 Hz, respectively) render further support to the stereochemical assignments. Structural assignments of the other products shown in Tables I and II were confirmed by analogous comparisons.

The course of the reaction of the cuprate reagent (80) with $\alpha,\beta$-acetylenic esters (130) can be rationalized as follows. Addition (cis stereochemistry) of (80) to (130) provides initially the vinyl-
cuprate species (143)* (the "kinetic intermediate") which may rearrange to the copper allenoate (144) at higher temperatures. When the reaction is carried out at low temperatures in the presence of a proton source, protonation of (143) is faster than its rearrangement to (144) and results in stereoselective formation of the (E) ester (131). On the other hand, assuming that the stereochemistry of protonation of the allenoate (144) is influenced by the relative stabilities of the products (i.e. the transition state for protonation has product-like character), reaction of (80) with (130) at higher temperatures and subsequent protonation would provide the (Z) ester (137) stereoselectively (Scheme 7). The ester (137) would be expected to be more stable than (131) because the trimethylstannyl group (A value = 0.94 kcal/mol) is less sterically demanding than an alkyl group (for example, the A value for a methyl group is 1.74 kcal/mol). Of course, this is a rather simplistic "explanation" and does not take into consideration various factors which may affect the stability of the initial intermediate (143), including the nature of the reaction medium (solvent) and the possible oligomeric structures of the intermediates.

Regardless of the mechanistic rationale, it is important from a strictly synthetic point of view that each of the isomeric esters (131) and (137) can be prepared readily by reaction of the cuprate reagent (80) with α,β-acetylenic esters (130) under appropriate experimental conditions.

* The initial reaction of α,β-acetylenic esters with (trialkyl-stannyl)cuprates is known to be reversible.52
C. Stereochemical Investigations of Protonative Deconjugation of
$\beta$-Trimethylstannyl-$\alpha,\beta$-unsaturated Esters

With sufficient quantities of (131) and (137) in hand, we turned
our attention to a study of the protonative deconjugation of these
genuinely isomeric $\beta$-trimethylstannyl-$\alpha,\beta$-unsaturated esters.

In 1972, Rathke reported the preparation and reactions of dienolate
anions derived from $\alpha,\beta$-unsaturated esters.\textsuperscript{53} It was well established
by Rathke that treatment of $\alpha,\beta$-unsaturated esters with an excess of a
sterically hindered amide base resulted in the quantitative formation of
the corresponding dienolate anions. The latter species were shown to react with electrophiles predominantly at the alpha carbon. Thus, addition of ethyl crotonate (145) to a solution of lithium N-isopropylcyclohexylamide in THF-HMPA produced the extended enolate anion (146) which could be quenched with dilute hydrochloric acid to provide, in 87% yield, the $\beta,\gamma$-unsaturated ester (147). Alternatively, reaction of (146) with methyl iodide furnished the ester (148) in 87% yield (Scheme 8).

Subsequently, it was shown by Schlessinger that a 1:1 complex of LDA with HMPA represented an essentially non-nucleophilic base for deprotonation of $\alpha,\beta$-unsaturated esters and allowed for the efficient mono- and dialkylation of these esters at the alpha carbon atom. The synthetic potential of this reaction was soon recognized by organic
chemists and is well-reflect ed in the growing number of reports that have appeared on this topic in the past decade. However, most of these reports failed to shed any light on the configurational aspects associated with the double bond migrations in these deconjugative processes. The few examples that did provide some information on the stereochemistry of the carbon-carbon double bond produced in these reactions indicated no clear-cut trend (see citations given in ref. 35).

It was first noted by Krebs,\(^{35a}\) and later supported by Kende\(^{35b}\) with improved results, that protonation of lithium dienoates derived from (Z)-2-alkenoates (149) provided the corresponding (E)-3-enoate products (150) (equation 30), whereas dienolates obtained from (E)-2-enoates (151) gave mainly the (Z)-3-enoate products (152) (equation 31). In the examples cited, the former transformation was shown to be highly stereoselective regardless of the size of the R group.\(^{35b}\) In contrast, however, the stereoselectivity associated with deconjugation of (E)-2-alkenoates (151) was found to decrease significantly with an increase in the size of the R group. For example, although the substrate (153) produced exclusively the ester (154) (equation 32), deconjugation of (155) and (158) provided, in each case, a mixture of the possible isomeric \(\beta,\gamma\)-unsaturated products (equations 33 and 34).\(^{35b}\)

Quite recently, Yamamoto has discovered that the stereoselectivity of protonative deconjugation of (E)-2-alkenoates depends on the size of the ester alkoxy group and on the nature of the base employed for deprotonation.\(^{55}\) Thus, for example, protonative deconjugation of the (E)-2-dodecenoate (161) using potassium hexamethyldisilazide as the base
\[
\begin{align*}
R-\text{CO}_2\text{Et} & \xrightarrow{1) \text{LDA, THF-HMPA, } -78^\circ\text{C}} R-\text{CO}_2\text{Et} \\
149 & \rightarrow 150 \\
2) \text{H}_2\text{O, } -78^\circ\text{C} \\
\end{align*}
\]

\[
R-\text{CO}_2\text{Et} \rightarrow R-\text{CO}_2\text{Et}
\]

\[
151 \rightarrow 152
\]

\[
R-\text{CO}_2\text{Et} \rightarrow R-\text{CO}_2\text{Et}
\]

\[
153 \rightarrow 154
\]

\[
R-\text{CO}_2\text{Et} \rightarrow R-\text{CO}_2\text{Et} + R-\text{CO}_2\text{Et}
\]

\[
155 \rightarrow 156 (81\%) + 157 (13\%)
\]

\[
R-\text{CO}_2\text{Et} \rightarrow R-\text{CO}_2\text{Et} + R-\text{CO}_2\text{Et}
\]

\[
158 \rightarrow 159 (62\%) + 160 (35\%)
\]
produced the (Z)-3-dodecenoate (162) highly stereoselectively (equation 35).

A more complex case ensues when the starting α,β-unsaturated esters have another substituent at C-3.* It has been established that the kinetic deprotonation of β,β-dialkyl-α,β-unsaturated esters using LDA is site-selective and involves a γ C-H bond on the alkyl group that is cis to the ester group. However, stereochemical correspondence between the double bond geometry in the starting 2-alkenoates and in the products has not been reported.

Previous work in our laboratory had demonstrated the feasibility of protonative deconjugation of β-trimethylstannyl-α,β-unsaturated esters. Treatment of compound (164) with two equivalents of LDA at 0°C, followed by inverse quenching of the resulting dienolate anion with glacial acetic acid at -98°C provided a 94:6 mixture of the deconjugated ester (165) and the ester (166) [geometric isomer of the starting material (164)] (equation 36). The conditions used for quenching the dienolate anion were important, since quenching with saturated aqueous

* For examples of stereoselective transformations of 2,4-alkadienoic esters to the corresponding 3,5-dienoic isomers, see ref. 56.
ammonium chloride at -78°C afforded a mixture of the desired product (165) and the ester (166) in a ratio of 2.5:1. The α,β-unsaturated ester (166) was presumed to have been formed via γ-protonation of the extended enolate anion.58b

\[
\text{Me}_3\text{Sn}\text{CO}_2\text{Et} \xrightleftharpoons[1.\text{LDA}][2.\text{AcOH}] \text{Me}_3\text{Sn}\text{CO}_2\text{Et} + \text{Me}_3\text{Sn}\text{H} \quad (36)
\]

164  165(75%)  166(5%)

Protonative deconjugation of the alkyl (E)-3-trimethylstannyl-2-alkenoates (131) was carried out by a procedure very similar to that summarized above. For example, a bright yellow solution of the dienolate anion of ethyl (E)-3-trimethylstannyl-2-pentenoate (132) was prepared by reaction of (132) with 2.3 equiv of LDA in THF (-78°C, 0.5 h; 0°C, 1 h). The solution was cooled to -78°C and then was transferred by means of a cannula to a cold (-98°C) solution of acetic acid in ether to afford, after workup and subsequent distillation of the crude product, ethyl (Z)-3-trimethylstannyl-3-pentenoate (168) as the exclusive product in 82% yield (Table III). In an analogous manner, the (E) esters (133)-(135) were converted cleanly and efficiently into the corresponding (Z)-β,γ-unsaturated esters (169)-(171), respectively. These results are summarized in Table III. Careful analysis of the crude products of these reactions by glc and \(^1\)H nmr spectroscopy showed the complete absence of the geometrically isomeric esters (174)-(177).

Ethyl (E)-5-methyl-3-trimethylstannyl-2-hexenoate (136) exhibited some anomalous behaviour. Deconjugation of (136) by the normal
Table III: Preparation of Alkyl (Z)-3-Trimethylstannyl-3-alkenoates

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 131</th>
<th>R</th>
<th>R'</th>
<th>Product 167</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>132</td>
<td>Me</td>
<td>Et</td>
<td>168</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>133</td>
<td>t-BuMe₂SiOCH₂CH₂</td>
<td>Et</td>
<td>169</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>134</td>
<td>Me₃SiCH₂</td>
<td>Et</td>
<td>170</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>135</td>
<td>cyclopropyl</td>
<td>Me</td>
<td>171</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>136</td>
<td>i-Pr</td>
<td>Et</td>
<td>172³</td>
<td>63</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: LDA (2.3 equiv), THF, -78°C, 0.5 h; 0°C, 1 h; inverse quench, AcOH (excess), ether, -78°C → -98°C.

*b* Yield of purified, distilled product.

*c* LDA-HMPA (2.3 equiv) was used.
procedure was not clean and gave, in addition to the desired $\beta,\gamma$-unsaturated ester (172), a mixture of unidentified products. It seemed possible that the formation of the side-products was due to relatively slow removal of one of the (hindered) $\gamma$ protons in (136). The sluggish nature of the deprotonation could result in condensation of the dienolate anion with unreacted $\alpha,\beta$-unsaturated ester (136). Alternatively, LDA could act as a nucleophile and add conjugatively to the unsaturated ester at a rate competitive with proton abstraction. Indeed, formation of such a Michael adduct from a structurally related substrate has been reported by Schlessinger. In any case, the deconjugation of (136) could be accomplished cleanly by deprotonating this substrate with LDA-HMPA complex. When this modification was employed, the crude product was found to be isomerically pure (glc analysis) and, upon distillation, provided the $\beta,\gamma$-unsaturated ester (172) in 63% yield.

Protonative deconjugation of the (Z) esters (138)-(142) also occurred with complete stereoselectivity, producing exclusively the alkyl (E)-3-trimethylstannyl-3-alkenoates (174)-(178), respectively, in decent yields. Table IV summarizes these results. As expected, none of the geometrically isomeric deconjugated esters (168)-(172) could be detected in the crude products. The procedure employed for these reactions was very similar to that used for the (E) esters, except that deprotonation was done with 1.5 equiv of LDA in THF containing 1.5 equiv of HMPA. This modification was found to be necessary since deprotonation of ethyl (Z)-3-trimethylstannyl-2-pentenoate (138) with LDA alone (2.3 equiv), followed by protonation, provided (glc analysis) a mixture consisting mainly of the starting (Z)-ester (138) (14%) and the
Table IV: Preparation of Alkyl (E)-3-Trimethylstannyl-3-alkenoates$^a$

$$
\text{R-} \quad \text{Me$_3$Sn CO}^' \quad \xrightarrow{137} \quad \text{SnMe$_3$} \quad \text{R-} \quad \text{CO}_2\text{R'}
$$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate 137</th>
<th>R</th>
<th>R'</th>
<th>Product 173</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138</td>
<td>Me</td>
<td>Et</td>
<td>174</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>139</td>
<td>t-BuMe$_2$SiOCH$_2$CH$_2$</td>
<td>Et</td>
<td>175</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>Me$_3$SiCH$_2$</td>
<td>Et</td>
<td>176</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>141</td>
<td>cyclopropyl</td>
<td>Me</td>
<td>177</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>142</td>
<td>i-Pr</td>
<td>Et</td>
<td>178</td>
<td>71</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: LDA-HMPA (1.5 equiv), THF, -78°C, 0.5 h; 0°C, 1 h; inverse quench, AcOH (excess), ether, -78°C → -98°C.

$^b$ Yield of purified, distilled product.
required β,γ-unsaturated ester (174) (80%). The fact that deprotonation of (138) with LDA-HMPA (1.5 equiv) resulted in exclusive formation of (174) after inverse quenching, indicates that the presence of HMPA was essential for rapid and complete formation of the dienolate anion from the (Z) ester (138).

The spectral data of the products shown in Tables III and IV are in complete agreement with the assigned structures. As noted before, the $^1$H nmr spectra of these compounds were very useful in ascertaining their stereochemistry. For example, the $^1$H nmr spectrum of the ester (168) showed a 9-proton singlet at $\delta$ 0.20 (with satellite peaks due to Sn-H coupling, $\mathbf{J} = 54$ Hz), a 3-proton doublet at $\delta$ 1.76 ($\mathbf{J} = 6$ Hz), and a 2-proton doublet at $\delta$ 3.20 ($\mathbf{J} = 1$ Hz), indicating thereby the presence of a trimethylstannyl group, a vinyl methyl group, and an allylic methylene moiety, respectively. A 3-proton triplet at $\delta$ 1.26 ($\mathbf{J} = 7$ Hz) and a 2-proton quartet at $\delta$ 4.12 ($\mathbf{J} = 7$ Hz) showed the presence of an ethyl ester function. More importantly, the signal due to the vinyl proton in (168) appeared at $\delta$ 6.16 as a triplet of quartets ($\mathbf{J} = 1, 6$ Hz) with satellite peaks due to tin-proton coupling ($\mathbf{J}_{\text{Sn-H}} = 131$ Hz). The latter coupling constant indicated a vicinal trans relationship between the trimethylstannyl group and the vinyl proton and hence established the stereochemistry as (Z).

In the $^1$H nmr spectrum of the geometrically isomeric ester (174), the olefinic proton signal appeared at $\delta$ 5.84 (0.32 ppm upfield from the corresponding signal in (168)) and exhibited $\mathbf{J}_{\text{Sn-H}} = 72$ Hz. These data showed that, in (174), there is vicinal cis relationship between the trimethylstannyl group and the vinyl proton.
The infrared spectra of compounds (168) and (174) corroborated the structural assignments. Thus, absorption bands at 1720 and 1725 cm\(^{-1}\) indicated the non-conjugated nature of the ester carbonyl groups in (168) and (174), respectively. The corresponding conjugated esters (132) and (138) showed carbonyl absorptions at 1705 and 1700 cm\(^{-1}\), respectively. The Sn-Me rocking vibration of the trimethylstannyl moiety gave rise to an absorption band at around 770 cm\(^{-1}\) in the infrared spectra of these compounds. Similar analyses of the spectral data of all the other compounds (169)-(172) and (175)-(178) fully supported the structural assignments.

In accord with previous observations,\(^{59}\) the trimethylstannyl compounds did not exhibit molecular ion peaks in their mass spectra. In these cases, the high resolution mass spectrometric measurements were carried out on the m/e = (M\(^{+}\)-15) fragments.

The results summarized above showed that protonative deconjugation of (Z)- and (E)-3-trimethylstannyl-2-alkenoates is highly stereospecific and occurs with inversion of precursor double bond geometry. Recently, Baldwin has made the observation that "in a reaction that involves a formal 1,2-olefin shift, inversion of olefin configuration occurs with migration of the double bond".\(^{60}\) The stereospecific isomerizations discussed above exemplify this generalization.

Krebs found that when the deconjugated esters (150) (R = Me) and (154) [derived from (149) (R = Me) and (153), respectively] were reexposed to deconjugation conditions (LDA-HMPA, -70°C; aq. NH\(_4\)Cl), the esters (150) (R = Me) and (154) were recovered unchanged in good yield.\(^{35a}\) It was, therefore, concluded that the observed stereoselec-
activities associated with the double bond migrations in the deconjugative processes [equations 30 (\(R = \text{Me}\)) and 32] must have their origin in the deprotonation step. Kende and Toder have presented satisfactory mechanistic arguments to explain the observed inversion of stereochemistry in the deconjugation of \(\alpha,\beta\)-unsaturated esters that possess a disubstituted double bond.\(^{35b}\) The proposed rationale is based upon stereoelectronic control (orbital overlap) in formation of the conformationally stable intermediate carbanions and the relative stabilities of these carbanions or the transition states leading to them. A modified version of Kende and Toder's proposed mechanistic rationale is presented below.

The basic stereochemical considerations* for the \((E) \rightarrow (Z)\) and

* For analyses of the transition states proposed in the kinetic deprotonation of esters, ketones, and \(\alpha,\beta\)-unsaturated amides, see ref. 61.
(Z) → (E) deconjugative transformations of the geometrically isomeric 2-alkenoates (149) and (151) are illustrated in Scheme 9. Stereoelectronic considerations require that two conformations for each starting ester be considered as possible arrangements that could lead to transition states for deprotonation. These conformations for (149) and (151) are shown in Scheme 9. In these conformations, the base would approach along the axis of the correctly aligned C-H bond being broken so that deprotonation would occur perpendicular to the plane of the conjugated pi system. Assuming that the transition states for deprotonation have some product-like character, the relative stabilities of the stereo-isomeric carbanions obtained from the two conformations of the starting 2-alkenoates would have a significant influence on the preferred transition-state pathway for deprotonation (product development control). In the case of the (Z) substrates (Scheme 9), the incipient anions (182) derived from the conformation (180) would be destabilized by severe $A^{(1,3)}$ strain between the R and CO$_2$Et groups. For the alternative route, the intermediate anions (181) [derived from conformation (179)] lack the $A^{(1,3)}$ strain present in (182) and are consequently more easily formed from (149). Protonation then occurs at the alpha carbon of (181) to provide the $\beta,\gamma$-unsaturated esters (150) with complete stereoselectivity.

In the absence of major steric interactions, consideration of two opposing factors becomes essential in order to explain the striking preference for the formation of (Z)-3-alkenoates (152) from the corresponding (E)-2-alkenoate precursors (151). The developing anions (186), obtainable from the conformation (184), would be stabilized by the cis
Scheme 9
alkyl substituent R but would be destabilized by $A^{1,3}$ strain between R and H. The stabilizing influence of an alkyl group in a cisoid allylic anion system has been well-documented in the literature.\textsuperscript{63} For example, the potassium salt of the crotlyl anion shows a free energy preference of more than 2 kcal/mol for a cis geometry (187) over a trans form (188) (equation 37).\textsuperscript{63c} Several explanations, including hyperconjugative interaction,\textsuperscript{64a} cyclic conjugation ("aromaticity"),\textsuperscript{64b} intramolecular hydrogen bonding,\textsuperscript{64c} and increase in the CCC angle of the allyl anion unit,\textsuperscript{64d} have been proposed to rationalize the observed preference for the endo- or (Z)-configuration of the crotlyl anion system. In extrapolating these observations and ideas to the deconjugation of the (E)-2-alkenoates (151), one could propose that when R is small, greater stability is expected for the (Z)-carbanions (186) than for their stereoisomers (185). This postulate rationalizes the preferential formation of the (Z)-products (152) starting from the (E)-esters (151).

The above concepts are readily extended to rationalize the results obtained from our study of the deconjugation of $\beta$-trimethylstannyl-$\alpha,\beta$-unsaturated esters. The highly stereoselective transformation of the (E)-esters (131) into the corresponding (Z)-esters (167) can be rationalized by consideration of the two conformations (189) and (190) leading to the transition states (A) and (B), respectively, for
deprotonation (Scheme 10). The severe $A^{(1,3)}$ strain present in (B) easily overrides the benefits of (Z)-substituent stabilization. Thus, despite the presence of steric compression between $R^1$ and $\text{Me}_3\text{Sn}$ in (A), this transition state is still lower in energy content than (B) and is
consequently the preferred transition state leading to the exclusive formation of (167).

The stereoselectivity associated with the deconjugation of alkyl (Z)-3-trimethylstannyl-2-alkenoates (137) (see Table IV) is more consistent and, in most cases, much higher than that connected with deconjugation of the corresponding esters (151) (see equations 32-34) lacking the Me₃Sn group. This difference may be rationalized as follows. Deprotonation of these esters occurs via one or both of two possible transition states, one of which [represented by (D)] would eventually lead to the products (173) and (152), while the other [represented by (C)] would ultimately provide the corresponding geometric isomers (Scheme 11). When R¹ is small (e.g. R¹ = Me) and Y = H, (D) is of lower energy than (C) because of the stabilizing influence of R¹ in the cisoid allylic anion system present in this transition state. Hence, deprotonation occurs solely via transition state (D) and results in the exclusive formation of (152). However, as R¹ becomes relatively more bulky [e.g. R¹ = Et, i-Pr], the non-bonded steric strain between R¹ and H* [see (D)] becomes increasingly important and deprotonation via transition state (C) (Y = H) competes significantly with deprotonation via (D) (Y = H). Therefore, stereoselectivity of the deconjugative process (151) → (152) is highly dependent on the size of the alkyl substituent R¹.

In contrast, when Y = SnMe₃, the A¹,3 steric strain between R¹ and H* in (D) is offset by non-bonded repulsion between R¹ and Y (= SnMe₃) in (C). Thus, apparently, even when R¹ is relatively bulky, deprotonation occurs exclusively by way of transition state (D) (Y =
SnMe$_3$) and substrates (137) are converted cleanly into the corresponding β,γ-unsaturated esters (173).

\[ \begin{align*}
\text{Scheme 11}
\end{align*} \]
II. Synthesis and Transmetalation of (Z)- and (E)-5-Chloro-3-trimethylstannyl-2-pentenes

A. Preparation of (Z)- and (E)-5-Chloro-3-trimethylstannyl-2-pentenes

As described in the previous section, protonative deconjugation of ethyl (E)-3-trimethylstannyl-2-pentenoate (132) and its geometric isomer (138) provided an efficient and highly stereoselective route to the synthesis of ethyl (Z)- and (E)-3-trimethylstannyl-3-pentenoates, (168) and (174), respectively. These esters are, potentially, precursors of structurally interesting donor-acceptor conjunctive reagents. For example, reduction of the ester (168) proceeded smoothly when it was allowed to react with lithium aluminum hydride in dry ether at -20°C (equation 38). The alcohol (193) thus produced in 88% yield showed the diagnostic O-H stretching absorption in its IR spectrum at 3300 cm⁻¹. Treatment of this substance with triphenylphosphine-carbon tetrachloro-

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{CO}_2\text{Et} \\
\text{LiAlH}_4, \text{Et}_2\text{O} & \quad \xrightarrow{\text{Me}_3\text{Sn}} \\
168 & \quad \text{R}^1=\text{Me}, \text{R}^2=\text{H} \\
174 & \quad \text{R}^1=\text{H}, \text{R}^2=\text{Me} \\
\text{Ph}_3\text{P}, \text{CCl}_4, \text{Et}_3\text{N}, \Delta & \quad \xrightarrow{\text{Me}_3\text{Sn}} \\
193 & \quad \text{R}^1=\text{Me}, \text{R}^2=\text{H} \\
194 & \quad \text{R}^1=\text{H}, \text{R}^2=\text{Me} \\
99 & \\
100 & 
\end{align*}
\]
ide\textsuperscript{65} in the presence of triethylamine\textsuperscript{58} afforded (Z)-5-chloro-3-trimethylstannyl-2-pentene (99) in 83\% yield. In similar fashion, the ester (174) was converted, via the alcohol (194), into the chloride (100) in 66\% overall yield. The chemical shifts (\(\delta 6.20\) and \(\delta 5.83\)) and the magnitude of the tin-proton coupling constants (135 Hz and 76 Hz) of the olefinic protons in the \(^1\)H nmr spectra of the geometrically isomeric chlorides (99) and (100), respectively, were consistent with their assigned structures.

B. Transmetalation of (Z)-5-Chloro-3-trimethylstannyl-2-pentene

The mere presence of both a carbon-lithium bond and a primary halide function in a reagent may be regarded as antithetical to its deployment in organic reactions. However, it is occasionally possible to release these thermolabile compounds from the constraint of the fate assigned to them as short-lived intermediates by preparing and using them \textit{in situ} in appropriate solvents at low temperatures. As mentioned in the Introduction, a series of reports\textsuperscript{58a, 33, 34} from our laboratory has described the successful preparation and synthetic utility of the unusual donor-acceptor reagent 4-chloro-2-lithio-1-butene (195) (equation 39). The feasibility of preparing its homologue (197) by transmetalation of 5-chloro-2-trimethylstannyl-1-pentene (196), and its pivotal role in the development of a methylenecyclohexane annulation method was demonstrated in our laboratory by work done concurrently with that outlined in this thesis.\textsuperscript{66} It was also shown that reagent (197)
decomposes slowly even at -50°C. Thus, transmetalation (MeLi, THF, -78°C) of (196) afforded (197) and treatment of the latter reagent with cyclohexanone at -78°C, followed by suitable workup, provided the alcohol (198) in 84% yield (equation 40). However, the yield of (198) decreased to 76%, 58%, and 0% when the reaction mixture was allowed to warm to -63, -48, and -20°C, respectively, prior to addition of the ketone. These results indicated that low temperatures were mandatory for successful deployment of this d,a reagent.

In light of these results, it was of interest to study the possibility of the chlorides (99) and (100) serving as precursors of reagents (199) and (201), which would be synthetically equivalent to the geometrically isomeric d₃,a₅-2-pentene synthons (200) and (202), respectively. Real utility of (199) and (201) as bifunctional conjunctive reagents was necessarily contingent upon the successful transmetalation of (99) and (100), respectively, and upon the stability of the
resulting vinyllithium compounds. There is evidence in the literature to suggest that if there is an alkyl substituent in a vicinal \textit{cis} relationship to a trialkylstannyl group, the transmetalation of that vinylstannane is likely to be slower than that of the corresponding geometric isomer. For example, a THF solution of (203) (3:1 mixture

of \textit{trans} and \textit{cis} isomers, respectively) was treated with one equivalent of \textit{n}-butyllithium (-70°C, 1 h) and then was quenched with water. Separation of the unreacted vinylstannanes (203) (20%) by chromatography and analysis of this material by $^{13}$C nmr spectrum revealed that the \textit{trans}:\textit{cis} ratio of (203) had changed to 2:3. On the basis of these observations, transmetalation of the (Z)-chloride (99) was anticipated to be a challenging task.

It was, therefore, very gratifying to find that compound (99) underwent transmetalation cleanly upon exposure to 1.1 equiv of methyl-lithium at -78°C for 20 min to produce a light brown solution of the
organolithium reagent (204). When this solution was treated with a slight excess (1.1 equiv) of cyclohexanone and was subsequently quenched with saturated aqueous ammonium chloride at -78°C, a mixture of the chloro alcohol (205) (31%) and the cyclic ether (206) (40%) was produced (equation 41). The $^1$H nmr spectrum of the chloro alcohol (205)

![Reaction Diagram]

exhibited a broad triplet at $\delta$ 2.48 (J = 7 Hz) due to the allylic methylene protons while the -CH$_2$Cl protons gave rise to a normal triplet at $\delta$ 3.60 (J = 7 Hz). The one proton triplet of quartets (J = 1, 7 Hz) at $\delta$ 5.36 was indicative of the olefinic proton attached to carbon bearing the methyl group. The ir spectrum of (205) showed the O-H stretching absorption band at 3425 cm$^{-1}$. In the $^1$H nmr spectrum of the spiro ether (206), the signals due to the allylic methylene protons and the -OCH$_2$- protons appeared as a multiplet ($\delta$ 2.35-2.68) and a triplet ($\delta$ 3.75, J = 7 Hz), respectively. The signal at $\delta$ 5.36 (t of q, J = 2, 7 Hz) was assigned to the olefinic proton. The signals due to the vinyl methyl protons could not be located exactly in the $^1$H nmr spectra of (205) and (206) because of the presence of cyclohexane ring protons in the same region. It has been well established that the stereochemical integrity of double bonds is completely preserved in the transmetalation
of vinylstannanes and in reactions of the vinyllithium reagents thus produced.* On this basis, the double bonds in compounds (205) and (206) have been assigned the (Z) configuration.

C. Transmetalation of (E)-5-Chloro-3-trimethylstannyl-2-pentene: Formation of Ethylidene cyclopropane

Encouraged by the findings summarized above, we embarked on the transmetalation of the geometrically isomeric chloro vinylstannane (100). Compound (100) was allowed to react (tetrahydrofuran, -78°C, 20 min) with 1.1 equiv of methyllithium and the resultant solution was treated with cyclohexanone. However, even though all of the starting material (100) had been consumed, no carbonyl addition product could be isolated. Other attempts to trap the expected lithio compound (207) with electrophiles (cyclopentanone, benzaldehyde) failed. Rapid self-annihilation to form ethylidene cyclopropane (208) seemed a plausible pathway for the "disappearance" of (207). In an experiment designed to determine the fate of (207), the reaction mixture obtained by treatment of (100) with methyllithium, as outlined above, was treated with 2,4-dinitrobenzenesulfenyl chloride (209)** and then was allowed to warm to room temperature. In accordance with our expectations, the product

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* For example, see ref. 67 and references cited therein.

** This reagent has been used for the characterization of olefins (see ref. 68).
obtained upon recrystallization (54% yield) proved to be the substituted cyclopropane (210) (equation 42).

The spectral data obtained from this material are in complete agreement with the structural assignment. The mass spectrum of (210) contained prominent peaks corresponding to the molecular ion and \((M^+ - 35Cl)\). The \(^1H\) nmr spectrum showed the signals expected for cyclopropyl protons (a 3-proton multiplet and a 1-proton multiplet at \(\delta 1.20-1.40\) and \(\delta 1.52-1.65\), respectively) and a methyl group (a 3-proton doublet at \(\delta 1.66\), \(J = 7\) Hz). The aromatic protons on the 2,4-dinitrobenzenesulfenyl group gave rise to three 1-proton signals at \(\delta 8.40\) (d, \(J = 10\) Hz), 8.54 (d of d, \(J = 2, 10\) Hz), and 8.98 (d, \(J = 2\) Hz). More importantly, regiochemistry of the addition product was indicated by a 1-proton quartet at \(\delta 4.38\) (\(J = 7\) Hz), assigned to the proton geminal to the chlorine atom. Had the regioisomer been formed, this proton (geminal to the SAr group) would probably have resonated at significantly
Thus, it is evident that, even at -78°C, the lithio compound (207) undergoes facile intramolecular displacement of chloride ion to afford ethylidene cyclopropane (208), which reacts with the sulfenyl chloride (209) to produce the addition product (210). The instability of (207) as compared with its geometric isomer (204) is very surprising. Intermediate (207) may possess higher energy than (204) by virtue of the steric interaction between the cis alkyl substituents. This difference in energy of the intermediates (204) and (207) might be responsible for a lower activation-energy barrier for intramolecular cyclization in the case of (207) relative to that of its geometric isomer (204).

Regardless of the rationale for the difference in stability, it is clear that, in sharp contrast to (E)-5-chloro-3-lithio-2-pentene (204), the (Z)-isomer (207) is very unstable even at -78°C and hence is not a viable reagent for organic synthesis. It seems highly likely that if a substance with structure similar to (207) is to be employed successfully

\* For example, in the $^1$H nmr spectra of (211)\textsuperscript{69a} and (212)\textsuperscript{69b}, the protons $H_A$, $H_B$, and $H_C$ appear at $\delta$ 3.05, 4.36, and 3.54, respectively.

\[
\begin{align*}
\text{\text{\includegraphics[width=0.3\textwidth]{211}}}
\end{align*}
\]

\[
\begin{align*}
\text{\text{\includegraphics[width=0.3\textwidth]{212}}}
\end{align*}
\]
as a donor-acceptor reagent, the chlorine atom will have to be supplanted by a group (e.g., a protected alcohol moiety) which is not easily displaced.

D. Copper(I)-Catalyzed Conjugate Addition of the Grignard Reagent Derived from (204) to Cyclic Enones: Convenient (Z)-Ethylidene-cyclopentane Annulation Sequences

The facility with which organocuprates and organocopper reagents undergo conjugate addition to \( \alpha, \beta \)-unsaturated ketones has attracted a great deal of interest and has been utilized very imaginatively in organic synthesis.\(^7\) An initial report in 1941 by Kharasch and Tawney described the use of catalytic quantities of CuCl in the presence of MeMgBr for effecting 1,4-addition of a methyl group to isophorone.\(^7\) Much work has been performed since then and a plethora of different types of Cu-based reagents are now available to achieve these important transformations.\(^7\)\(^0\)\(^a\) However, the precise composition of these reagents or the identification of the reactive species present in the reaction mixtures are usually not known.\(^*\) The mechanistic details are equally unclear. There is evidence for a pathway involving initial complexation of organocuprates with enones.\(^7\)\(^3\)\(^a\) The intermediacy of a copper(III) \( \beta \)-adduct, which can undergo C-C bond formation by reductive elimination,

\(^*\) For some recent chemical and spectroscopic studies on the composition of organocuprates, see ref. 72.
is widely accepted. An initial coordination of the carbonyl oxygen atom to the cuprate cluster, followed by electron transfer from the cuprate to the enone, to form an anion radical and an electron-deficient metal cluster has also been proposed.

Despite the ability of a number of different reagents of this type to serve as Michael donors, it is often observed that any one combination of cuprous salt and organometallic reagent may not be applicable, in a general sense, to all Michael acceptors. Thus, "the nature of R-Metal (Metal = MgX, Li), the choice of organocopper vs organocuprate, solvent, and the need for additives all contribute to the complexity of determining which reagent is best suited for the substrate in question". In addition, in order to make our annulation process synthetically viable, we were interested in preparing heterocuprates of the general structure (213) rather than bis-homocuprates (214). In view of the likelihood of decomposition of (204) at higher temperatures, it was important to select a proper auxiliary ligand so that the conjugate addition reactions could be performed at low temperatures (below -63°C). In making initial choices regarding the nature of the copper(I) species to use and general reaction conditions to employ, we were guided by past experience in our laboratory with structurally similar reagents.
Thus, addition of solid phenylthiocopper (1 equiv) to a cold (-78°C) solution of (E)-5-chloro-3-lithio-2-pentene (204) in THF [obtained by transmetalation of (99) with 1.1 equiv of MeLi], followed by stirring of the mixture at -78°C for 20 minutes, produced a yellow solution-suspension of the lithium phenylthiocuprate (215). This solution-suspension was treated successively with one equivalent of 2-cyclohexen-1-one (216) (-78°C, 2 h) and 1.4 equiv of HMPA (-78°C, 15 min) and then was allowed to warm to room temperature. Suitable workup and flash chromatography provided the bicyclic olefinic ketone (217) in 30% yield (equation 43).

![Chemical structure](image)

This initial result indicated the feasibility of the desired ethylidenecyclopentane annulation but clearly, the yield left much to be desired. Therefore, we turned our attention to copper(I)-catalyzed conjugate additions of the Grignard reagent (218). This reagent was prepared in a straightforward manner by treatment of a THF solution of the corresponding lithio reagent (204) with 1.2 equivalents of anhydrous magnesium bromide. Conjugate addition of (218) to 2-cyclohexen-1-one (216) in the presence of 0.25 equiv of cuprous bromide-dimethyl sulfide complex,75 followed by treatment of the solution of the resultant enolate anion with HMPA as described above, and suitable workup, provided a 1:5 mixture (by glc analysis) of the cyclized product (217) and
The choice of solvents and the nature of ligands is known to influence dramatically the outcome of organocopper conjugate addition-enolate trapping reactions. However, in the overall process described above, the use of THF as solvent was vital to the success of the initial transmetalation reaction of (99) and to the stability of the lithio species (204) thus produced. An alternative ploy was to quench the enolate anion with a proton source and to isolate the corresponding conjugate addition product. The enolate could then be generated from the latter material under more favorable conditions for the intramolecular cyclization reaction. Thus, the following procedure is representative for the effective use of compound (99) in carrying out (Z)-ethylidenecyclopentane annihilation reactions [generalized in (220) → (222), Table V].

Transmetalation (MeLi, THF, -78°C, 20 min) of the vinylstannane (99) produced the lithio derivative (204), which, upon treatment with 1.2 equivalents of anhydrous MgBr₂, was converted into the Grignard reagent (218). Dilution of the solution (-78°C) with Et₂O, followed by successive addition of CuBrMe₂S (0.3 equiv), 2-cyclohexen-1-one (216) (1 equiv), and BF₃·Et₂O (1.2 equiv) gave, after a reaction time of 2 h and suitable workup, the conjugate addition product (219) in 70% yield.
### Table V: Preparation of (Z)-Ethylidencyclopentane Annulation Products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enone</th>
<th>Conjugate Addition Product (% yield)</th>
<th>Annulation Product (% yield)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Enone 1" /></td>
<td><img src="image2" alt="Conjugate Addition Product 1" /> (79)</td>
<td><img src="image3" alt="Annulation Product 1" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Enone 2" /></td>
<td><img src="image5" alt="Conjugate Addition Product 2" /> (70)</td>
<td><img src="image6" alt="Annulation Product 2" /> (78)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Enone 3" /></td>
<td><img src="image8" alt="Conjugate Addition Product 3" /> (61)</td>
<td><img src="image9" alt="Annulation Product 3" /> (79)</td>
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</tbody>
</table>

- 71 -
Table V (continued)

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<tr>
<td>225</td>
<td>231 (69)</td>
<td>237 (78)</td>
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<td>226</td>
<td>232 (57)</td>
<td>238 (86)</td>
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<tr>
<td>227</td>
<td>233 (56)</td>
<td>239 (79)</td>
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<tr>
<td>228</td>
<td>234 (72)</td>
<td>240 (85)</td>
</tr>
</tbody>
</table>

a Reaction conditions A: 218 (1 equiv), CuBr·Me₂S (0.3 equiv), BF₃·Et₂O (1.2 equiv), THF-Et₂O, -78°C, 2 h; sat. NH₄Cl.
B: KH, THF, r.t., 2.5 h; sat. NH₄Cl.

b Yield of purified, distilled product.
Intramolecular alkylation (KH, THF, r.t.) of the latter material provided the bicyclic olefinic ketone (217) in 78% isolated yield (equation 45).

The generality of this interesting annulation sequence was demonstrated by the conversion of the enones (223)-(228) into the annulation products (235)-(240), respectively (see Table V). In each case, a procedure identical with that outlined above was employed. The overall yields were typically about 50%. Interestingly, even the conjugate additions of the relatively hindered Grignard reagent (218) to the \( \beta,\beta \)-disubstituted enones (223), (226), and (228) were quite efficient.

Two points regarding the procedure employed are noteworthy. Dilution of the THF solution of the Grignard reagent (218) with ether (approximately two times the original volume of the THF solution) was important especially for the reactions involving the substituted enones. For example, 3-methyl-2-cyclohexen-1-one (223) was converted into the addition product (229) in 41% yield when ether was not used. However, the same transformation was achieved in 61% yield by employing the aforementioned procedure. Good donor solvents (e.g. THF, DME) are known to retard the rate of conjugate addition and their admixture with less
polar solvents has been employed successfully to optimize yields of the desired 1,4-addition reactions.\textsuperscript{74a,77} Likewise, the synthetic utility of boron trifluoride-etherate in promoting conjugate additions of organocopper compounds to enones is well-documented.\textsuperscript{76} Recently, a comparative study of the influence of various Lewis acids on reactions of higher order cuprates \textsuperscript{70b} was conducted.\textsuperscript{76a} Special mention was made of BF\textsubscript{3}·Et\textsubscript{2}O for its unique ability to compensate for reduced mixed cuprate reactivity \textit{via} substrate activation. There is evidence to indicate that BF\textsubscript{3}·Et\textsubscript{2}O can act as a strong Lewis acid even in the presence of organolithium species.\textsuperscript{78}

The results of the study of a number of (Z)-ethylidene cyclopentane annulation sequences are summarized in Table V. In all cases studied, the crude product obtained after the copper(I)-catalyzed addition of the Grignard reagent (218) to enones consisted essentially of the conjugate addition product(s) and a small amount of the unreacted enone. In each case, the products were readily separated from the starting material by subjection of the crude mixture to flash chromatography on silica gel. The glc and tlc analyses of the chloro ketones (219), (229), (231), (232) and (234) [see Table V] indicated that they consisted of essentially one component. Their spectral data are in agreement with the assigned structures. For example, the ir spectrum of (229) showed a carbonyl absorption at 1705 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectrum of (229) exhibited signals expected for the tertiary methyl group (a 3-proton singlet at \( \delta \) 1.19), the vinyl methyl group (a 3-proton doublet at \( \delta \) 1.79, \( J = 7 \) Hz), and the olefinic proton (a 1-proton quartet at \( \delta \) 5.38, \( J = 7 \) Hz). Additionally, the -CH\textsubscript{2}Cl protons gave rise to a multiplet at
δ 3.47-3.57 while the signal due to the allylic methylene protons appeared as a multiplet at δ 2.39-2.53. The latter assignments were confirmed by a decoupling experiment. Thus, irradiation of the multiplet at δ 3.47-3.57 (-CH₂Cl) simplified the multiplet at δ 2.39-2.53 (-CH₂-) to a pair of doublets (J = 14 Hz, in each case).

Not surprisingly, the compounds (230) and (233) were, in each case, found to consist of a mixture of epimers. In the ¹H nmr spectrum of (230), the secondary methyl group gave rise to a pair of doublets (ratio ~2:1, J = 7 Hz in each case) at δ 1.06 and 0.90, respectively. Thus, the ratio of the two epimers in (230) was approximately 2:1. Similarly, compound (233) was found by ¹H nmr spectroscopy to consist of an approximately equal proportion of two epimers.

The intramolecular cyclizations of the chloro ketones (221) to yield the ring-annulated products (222) were clean and efficient. In theory, the products initially obtained, except for (236) and (239), could have undergone subsequent epimerization at the bridgehead position adjacent to the carbonyl group. However, all the intramolecular alkylation products (222) were found to be isomerically pure. This observation, initially made on the crude products on the basis of glc analyses, was later confirmed by analyses of the ¹H nmr spectra of these ring-annulated products. The spectral properties of these compounds agreed well with the proposed structures. For example, the ir spectrum of (239) showed an absorption in the region expected for non-conjugated ketone carbonyl groups on a 5-membered ring (1725 cm⁻¹). In the ¹H nmr spectrum of (239), the signals corresponding to the tertiary methyl group and the vinyl methyl group appeared at δ 1.11 (3-proton singlet)
and at $\delta$ 1.66 (3-proton broad doublet, $J = 7$ Hz), respectively. The methine proton gave rise to a one-proton multiplet at $\delta$ 2.88-2.94 whereas the 1-proton broad quartet at $\delta$ 5.35 ($J = 7$ Hz) was attributed to the olefinic proton.

Since the annulation products (222) are produced by kinetically controlled intramolecular alkylations of the corresponding chloro ketones (221), the bridgehead stereochemistry of the initially produced bicyclic ketones would be expected to be cis.$^{33,34,77b}$ Subsequent epimerization is not possible in case of compounds (236) and (239). Hence, these two bicyclic ketones would possess cis-fused ring systems. In the $^1$H nmr spectrum of (236), the methine proton signal appears as a doublet of doublets ($J = 5, 12$ Hz) at $\delta$ 2.63. The coupling constants agree with the speculation that the bridgehead proton would be axially oriented (with respect to the six-membered ring) in the preferred conformation of this molecule.

Trans-fused bicyclo[3.3.0]octane systems are very strained and even under epimerizing conditions, the cis-fused ring systems would be preferred. Therefore, the stereochemistry at the ring junction of each of the compounds (237), (238) and (240) can be (reasonably) assumed to be cis. As expected on the basis of kinetic preference for 5-membered ring formation over 6- or 7-membered ring closures, the site-selectivity with these intramolecular cyclizations [(221) $\rightarrow$ (222), Table V] was found to be excellent. For example, the $^1$H nmr spectrum of the product obtained upon treatment of the chloro ketone (234) with potassium hydride contained a 1-proton doublet of doublets ($J = 9, 18$ Hz) at $\delta$ 2.50. This signal, assigned to the proton $H_A$ in (240), established
unequivocally the structure of the annulated product as (240). No proton in the regioisomeric product (241) would be expected to give rise to such a coupling pattern.

\[
\begin{align*}
\text{240} & \quad \text{241}
\end{align*}
\]

The formation of a single stereoisomer upon intramolecular alkylation of the chloro ketone (219) was somewhat surprising. The free energy difference between cis- and trans-hydrindane [(242) and (243), respectively] has been estimated to be less than 1 kcal/mol.\(^7\) Also,

\[
\begin{align*}
\text{242} & \quad \text{243}
\end{align*}
\]

cyclization of the chloro ketone (244) using potassium hydride has been reported to produce the two stereoisomeric products (245) and (246) in a ratio of 4.9:1, respectively (equation 46).\(^6\) Molecular mechanics

\[
\begin{align*}
\text{244} & \quad \text{KH, THF} & \quad \text{245} + \text{246} \\
\text{244} & \quad \text{KH, THF} & \quad \text{245} + \text{246} \\
\end{align*}
\]
calculations on the two possible products (217) and (247) obtainable from cyclization of (219) indicated that the energy difference between these isomers is quite small.*

The ring-fusion stereochemistry of the cyclization product of (219) was shown to be cis as follows. In addition to the signals due to the olefinic proton (δ 5.29, 1 proton triplet of quartets, J = 2, 7 Hz) and the vinyl methyl group (δ 1.64, 3-proton triplet of doublets, J = 1.5, 7 Hz), the 1H nmr spectrum of the product (217) exhibited four identifiable resonances at δ 3.00-3.06 (1-proton multiplet), δ 2.62-2.70 (1-proton multiplet), δ 1.72 (1-proton doublet of doublet of quartets, J = 4, 5, 13 Hz), and δ 1.40 (1-proton doublet of quartets, J = 4, 13 Hz). These signals were assigned to the protons H_A, H_B, H_C, and H_D, respectively, on the basis of decoupling experiments. Thus, irradiation at δ 2.66 (H_B) simplified the signal at δ 3.00-3.06 (H_A) to a doublet of doublets (J = 6, 13 Hz). On the other hand, saturation of the signal at δ 3.03 (H_A) caused the signal at δ 2.62-2.70 (H_B) and δ 1.40 (H_D) to modify to a doublet of doublets (J = 8, 9 Hz) and a doublet of triplets.

* We thank Prof. Larry Weiler of this department for performing these molecular mechanics calculations.
(J = 4, 13 Hz), respectively. The signal at δ 1.72 (H_C) remained unchanged in both of the experiments. The magnitude of the coupling constants associated with H_A and H_B, as summarized above, along with the fact that the signals due to these protons exhibit width-at-half-height of 26 and 24 Hz, respectively, enabled us to estimate the value of J_{AB} as ≈-7 Hz. The latter value indicated a cis ring-fusion stereochemistry for compound (217). This conclusion was verified by means of a nuclear Overhauser enhancement (nOe) difference experiment. Thus, saturation of the signal at δ 3.03 (H_A) caused a noticeable signal enhancement at δ 2.62-2.70 (H_B). Interestingly, an appreciable enhancement was also observed for the signal at δ 1.64 (vinyl methyl group). This result is in line with the assigned (Z)-configuration of the carbon-carbon double bond in (217). Furthermore, the coupling pattern (d of d of d, J = 6, 7, 13 Hz) of the bridgehead proton H_A in the compound (217) suggests that this substance exists largely in a conformation (A) that holds H_A in an axial orientation with respect to the six-membered ring. This preference is probably because of the severe A^{1,3} steric compression present in the alternative conformation (B) (equation 47).

\[ \text{(47)} \]

![Diagram](image_url)
Unfortunately, the bridgehead proton could not be identified with confidence in case of the compound (235), which was obtained as a single stereoisomer by treatment of the chloro ketone (229) with potassium hydride. The constitution and relative stereochemistry of compound (235), which is structurally related to some recently prepared steroid CD-ring synthons, was shown conclusively by two independent methods. Hydrolysis \((K_2CO_3, \text{MeOH})\) of the acetate \((248)^{80,*}\) (one enantiomer), followed by oxidation \((\text{PCC, NaOAc, CH}_2\text{Cl}_2)^{81}\) of the resultant alcohol \((249)\), provided the ketone \((250)\) which was spectrally different from \((235)\) (equation 48). Thus, the olefinic proton (triplet of quartets, \(J = 2\), 7 Hz), and the bridgehead methyl group (singlet) appeared at \(\delta 5.21\) and \(\delta 0.88\), respectively in the \(^1\text{H} \text{nmr}\) spectrum of \((250)\) while the corresponding signal positions in the \(^1\text{H} \text{nmr}\) spectrum of \((235)\) were \(\delta 5.28\) and \(\delta 1.32\), respectively. Additionally, the axial orientation of the bridgehead proton in \((250)\) was reflected in the coupling pattern associated with it (\(\delta 2.60\), doublet of doublets, \(J = 6\), 12 Hz). In accordance with our expectations, treatment of \((250)\) with potassium hydroxide in EtOH-H\(_2\)O caused complete isomerization at the bridgehead position adjacent to the carbonyl group and produced a ketone which exhibited ir and \(^1\text{H} \text{nmr}\) spectra identical with those of our annulation product \((235)\) (equation 48).

The annulation product \((235)\), obtained by intramolecular alkylation

\* We wish to express our deep appreciation to Dr. Baggiolini, Hoffmann-La Roche, Inc., New Jersey, for a generous sample of compound \((248)\).
of the chloro ketone (229), was reduced with sodium borohydride in methanol to produce, after flash chromatography of the crude product mixture, two epimeric alcohols (251) and (252) in a ratio of 37:63, respectively. Recrystallization from heptane provided needle-shaped crystals of (252) and an X-ray crystallographic study* confirmed the constitution and relative stereochemistry of (252) and, in turn, those of compound (235) (Fig. 1).

In summation, it was found that the stability of the 5-chloro-3-lithio-2-pentenes is dramatically dependent on the geometry of the double bond. Thus, the (Z)-isomer (207), formed by transmetalation of

* We thank Dr. Steven Rettig of this department for performing the X-ray crystallographic analysis.
Figure 1: The perspective view of the alcohol (252)

compound (100), was very unstable and, even at -78°C, was converted rapidly into ethylidencyclopropane (208) (equation 49). In contrast, (E)-5-chloro-3-lithio-2-pentene (204) and the corresponding Grignard reagent (218), readily prepared from (99), were sufficiently stable to serve as pivotal species in the development of a new (Z)-ethylidene-cyclopentane annulation method (equation 50). The latter operation shows considerable promise for applications in organic synthesis. For example, our annulation method may be useful for the preparation of the bicyclo[4.3.0]nonane (hydrindane) fragment widely encountered in nature in a variety of natural products. The ionophore antibiotic X-14547A (253)\textsuperscript{82} and the physiologically active vitamin D\textsubscript{3} metabolite 1α,25-di-hydroxycholecalciferol (254)\textsuperscript{83} are representative examples of such natural products. Indeed, the enantiomerically pure bicyclic acetate
\[
\text{Me}_3\text{SnCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{MeLi, THF, } -78^\circ\text{C}} \text{LiCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{BrMgCl, THF, } -78^\circ\text{C}} \]

(49)

\[
\text{Me}_3\text{SnCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{MeLi, THF, } -78^\circ\text{C}} \text{LiCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{MgBr}_2, \text{THF, } -78^\circ\text{C}} \text{BrMgCH}_2\text{CH}_2\text{Cl}
\]

(99)

\[
\text{CH}_2=\text{CHCl, CuBr•Me}_2\text{S, BF}_3\cdot\text{Et}_2\text{O, THF-Et}_2\text{O, } -78^\circ\text{C}} \xrightarrow{\text{KH, THF}} \]

(50)

\[
\text{253}
\]

\[
\text{254}
\]
(248) was used as a key building block in a totally synthetic route to obtain 1α,25-dihydroxycholecalciferol (254). Thus, ene reaction of (248) with ethyl propynoate afforded (255) and catalytic hydrogenation of the latter substance proceeded stereoselectively from the less hindered face to produce (256) in excellent yield (equation 51). This compound was subsequently converted into the natural product (254).

\[
\begin{align*}
(248) & \xrightarrow{\text{HCCOC₂Et, EtAlCl₂}} (255) \\
(255) & \xrightarrow{\text{H₂, Pd/C}} (256) \\
& \xrightarrow{\text{254 (51)}}
\end{align*}
\]

The ring-fusion stereochemistry of the hydrindane nucleus present in natural products is invariably tran. Therefore, successful application of our methodology demands a plan involving effective epimerization at a bridgehead position at some later stage of the synthesis.

III. Total Synthesis of the Oplopanane-type Sesquiterpenoids

(±)Oplopanone, (±)-8-epi-Oplopanone, and (±)-Anhydro-oplopanone

A. Introduction

*Oplopanax japonicus*, a shrub belonging to Araliaceae, is used as an antipyretic and cough cure in Japan. In 1965, a new type of sesquiter-
Pene ketone, (±)-oplopanone (257), was isolated from the ether extract of this plant and its structure and absolute configuration were reported.\(^8\) Subsequently, it has been detected in many diverse organisms.\(^8\) The olefinic ketones (-)-anhydro-oplopanone (258)\(^8\) and (-)-α-oplopenone (259)\(^9\) are also natural products, having been isolated from *Euryops pedunculatus* and *Santolina oblongifolia*, respectively. The substances (257)-(259) are three members of a small group of oplopanane-type sesquiterpenoids.

\[
\begin{align*}
257 & \quad 258 & \quad 259
\end{align*}
\]

It is interesting to speculate on the biogenetic origin of these sesquiterpene natural products. During their work on the structural elucidation of oplopanone (257), Minato and coworkers converted (257) into the ketone (260).\(^8\) Since ketone (260) was obtainable from α-cadinol (261),\(^8\) the authors suggested that α-cadinol (261) could be

\[
\begin{align*}
257 & \quad 260 & \quad 261
\end{align*}
\]
a precursor of oplopanone (257) in the plant body and that the former substance may be converted into (257) by ring contraction. Cocker has proposed the following two-stage process for the biogenetic formation of the oplopanone carbon skeleton from a cadinane (equation 53).  

\[
\begin{align*}
262 & \rightarrow 263 & \rightarrow 264 & \rightarrow 257 
\end{align*}
\]

Bohlmann's speculation concerning the biogenetic formation of anhydro-oplopanone (258) involves oxidation of bisabolene (265), followed by intramolecular aldol condensation of the resultant keto aldehyde (266), to provide the enone (268). Intramolecular "Michael" addition and subsequent reduction could then occur in a stereoselective manner to afford anhydro-oplopanone (258) (Scheme 12).

B. Previous Synthetic Approaches to (±)-Oplopanone

The bicyclic structure of oplopanone (257), incorporating a trans-fused bicyclo[4.3.0]nonane ring system and five chiral centers, offers an interesting synthetic challenge. The first synthesis of (257) was reported by Caine and Tuller in 1971.  Their approach was based on an elegant photochemical rearrangement of the cross-conjugated cyclohexa-
dienone (274) in glacial acetic acid. Thus, treatment of 1,4-dimethoxy-2-butanone (271) with the potassium enolate of (270) provided a mixture of diketones (272) in 25% yield. Aldol condensation of (272) with alcoholic potassium hydroxide, followed by selenium dioxide oxidation of the resultant enone (273) in tert-butyl alcohol, afforded the required dienone (274) as the major product. The photo-induced rearrangement of (274) in acetic acid proceeded stereoselectively to produce (275) in good yield. The transformation of (275) into the epimeric mixture (276) was accomplished via a two-step sequence involving reduction and acetylation. Cleavage of the allylic acetate and reduction of the tertiary acetate grouping were effected by treatment of (276) with
lithium in ethylamine. Subsequent hydrolysis of the resulting hydroxy enol ether under equilibrating conditions produced the trans-fused bicyclic hydroxy ketone (277). Treatment of (277) with sodium acetylide gave the ethynyl carbinol (278), which was converted into the α-acetoxy ketone (279) by oxymercuration of the triple bond, followed by demercuration with hydrogen sulfide. Reductive removal of the acetoxy group with calcium in liquid ammonia and Jones' oxidation of the diol thus obtained, completed the first total synthesis of (±)-oplopanone (257) (Scheme 13). 90

Taber's strategy for the synthesis 91 of (±)-oplopanone (257) was devised from a "logical" retrosynthetic analysis of the target molecule. As shown in Scheme 14, the synthesis of (257) was accomplished in ten steps from 2-methoxy-5-isopropylbenzoic acid (280). Reductive alkylation of (280) with β-bromophenetole provided the enone (281). Copper(I)-mediated conjugate addition of vinylmagnesium bromide occurred trans to the isopropyl group to produce the desired trisubstituted cyclohexanone (282). Thus, three chiral centers with the required configuration were generated in the key step of this synthesis. Wittig olefination of (282) gave (283), which was treated with boron tribromide to afford the somewhat unstable bromide (284). Chemoselective hydroboration was carried out with disiamylborane and oxidative workup produced the bromo alcohol (285). Oxidation of (285), followed by intramolecular alkylation of the resultant bromo aldehyde under equilibrating conditions, provided the bicyclic aldehyde (286). This compound was converted into (±)-oplopanone (257) by addition of methyllithium to give (287), successive treatment of the latter substance with aqueous
Scheme 13
Scheme 14
mercuric acetate and aqueous basic sodium borohydride, and oxidation of the resulting diol (288) with PCC.

A claimed synthesis of oplopanone (257) by Koster and Wolf\textsuperscript{92} centered around the application of a cationic $\pi$-cyclization of the $\alpha,\beta$-unsaturated ketone (292), as depicted in Scheme 15. Treatment of 4-isopropylphenol (289) with (2-chloroethyl)diethylamine gave the corresponding ether which, upon Birch reduction, provided the dihydrobenzene derivative (290). Site-selective metallation of (290) with $n$-butyllithium, and treatment of the lithio compound with 5-bromo-2-methyl-2-pentene produced (291). Hydrolysis of the enol ether was accomplished with hydrochloric acid and the resulting ketone isomerized under the reaction conditions to afford (292). Direct cation-olefin cyclization was carried out by treatment of the latter material with a mixture of acetic anhydride and acetic acid containing a catalytic amount of perchloric acid at 0°C. The ring-closure was found to be stereoselective, occurring \textit{trans} to the isopropyl group, and hydrolysis of the resulting enol acetate (293) under equilibrating conditions produced a 2:3 mixture of (294) and its epimer (295), respectively. The relative stabilities of (294) and (295) were rationalized on the basis of relative steric compression between the C-3 and C-5 substituents in the two epimers. Epoxidation of this mixture of epimers with dimethylsulfonium methylide (299) or dimethyloxosulfonium methylide (300) was reported to produce all four of the possible stereoisomeric spiro-

\begin{align*}
\text{Me}_2\text{S}^-\text{CH}_2 & \quad \text{Me}_2\text{S}^-\text{CH}_2 \\
299 & \quad 300
\end{align*}
Scheme 15
epoxides. However, under appropriate reaction conditions \text{[(299), KO(t-Bu), DMF, 0°C,]} one isomer was found to predominate. The structure of this isomer was claimed to be as depicted in (296). Reduction of (296), ozonolysis of the resultant olefinic alcohol (297), and equilibration of the ketol (298) thus obtained, was reported to provide a 1:4 mixture of (298) and (±)-oplopanone (257). However, the mp of this synthetic substance "(257)" (63-64°C)\(^92\) was quite different from those reported (101.5-102°C,\(^90\), 97-98°C\(^91\)) previously for (±)-(257).

Recently, Yamamura and coworkers\(^93\) have reported a biomimetic synthesis of (±)-oplopanone (257) from (±)-germacrene-D (301). Treatment of (301) with N-bromosuccinimide in 3:2 THF-H\(_2\)O produced a mixture of seven bromo compounds, from which (302) was isolated in 7% yield. Reduction of the allylic bromide (302) and oxidation of the resultant \(\alpha\)-cadinol (261) with excess osmium tetroxide, afforded the triol (303) which, upon further treatment with methanesulfonyl chloride and DMAP in pyridine, provided (±)-oplopanone (257) (Scheme 16). Thus, this synthesis supports the postulated\(^84,89\) intermediacy of cadinanes (\(\alpha\)-cadinol, in particular) in the biosynthesis of oplopanane-type sesquiterpenoids.

A total synthesis of (±)-anhydro-oplopanone (258) was not reported prior to publication of our work. However, Babkin et al.\(^85a\) have reported that dehydration of (-)-oplopanone (257) with thionyl chloride gives a mixture of two olefinic ketones (258) and (304) (equation 54). The reported (partial) spectral data (ir, \(^1\)H nmr) of the former substance are in agreement with those reported for (-)-anhydro-oplopanone (258) by Bohlmann and Zdero.\(^92\)
C. Total Synthesis of (±)-Anhydro-oplopanone

The synthetic planning for the total synthesis of (±)-anhydro-oplopanone (258) was somewhat simplified by the fact that the target had been chosen with one key step in mind. It was envisaged that the
bicyclo[4.3.0]nonane nucleus could be assembled readily by the general strategy used for the previously developed (Z)-ethyldienecyclopentane annulation process. The ethyldene moiety was contemplated to serve as a convenient precursor for the required α-acetyl side chain. Thus, the former unit could easily be converted into the latter function by a simple hydroboration-oxidation sequence of reactions. The stereochemistry of the acetyl moiety was not critical, since the previous syntheses\textsuperscript{90-92} of (±)-oplopanone (257) had indicated that the required C-3 configuration should be thermodynamically more stable than the corresponding epimer. Hence, the desired substance could be obtained by base-catalyzed equilibration. The proposed synthetic route to (±)-(258) is summarized in Scheme 17.

![Scheme 17](image-url)
Copper(I)-catalyzed conjugate addition of the Grignard reagent (218) to (305) would be expected to take place predominantly (or completely) trans to the isopropyl group.\textsuperscript{91,94} This would generate the desired stereochemistry at C-4 and C-5 [see (258), Scheme 17]. However, the construction of the required trans hydrindane system was a more challenging task, since intramolecular alkylation of (306) was envisioned to provide (307) with cis ring-fusion stereochemistry. We chose to approach this problem in the following manner. Inspection of molecular models led to the conclusion that hydroboration of the ketal of (307) should occur stereoselectively from the more open α-face of the molecule to give (308). It was hoped that deprotection of (308), and base catalyzed epimerization of the resultant ketone, would provide (309) as the major product. Molecular models appear to indicate that the various steric interactions in the trans isomer (309) are, in total, less severe than the steric repulsions in the corresponding cis-fused isomer.

Once the necessary trans-fused ring system was assembled, Wittig olefination, oxidation, and epimerization of the acetyl side chain would furnish (±)-anhydro-oplopanone (258) (Scheme 17).

The starting material chosen for the synthesis, 4-isopropyl-2-cyclohexen-1-one (305), is commercially available from Aldrich Chemical Co., Inc. Infrared and \textsuperscript{1}H nmr spectra of this material indicated that it was essentially pure and devoid of the corresponding β,γ-unsaturated ketone.

The conjugate addition of the Grignard reagent (218) to the enone (305) proceeded in a straightforward manner to provide (306) (equation
Thus, to a cold (-78°C) solution of (Z)-5-chloro-3-trimethylstannyl-2-pentene (99) in THF was added, successively, methyllithium (1.1 equiv), anhydrous magnesium bromide (1.2 equiv), dry ether, copper bromide-dimethylsulfide (0.3 equiv), 4-isopropyl-2-cyclohexen-1-one (305) (1 equiv), and BF₃·Et₂O (1.2 equiv). After the resultant solution had been stirred for 2 h, it was treated with saturated aqueous ammonium chloride. Fractional distillation of the crude product thus obtained, provided the chloro ketone (306) in 70% yield (equation 55). Concordant with expectation, the Michael addition reaction was highly stereoselective and led to exclusive formation of the desired trans-disubstituted cyclohexanone (306).

The spectral data derived from (306) are in complete agreement with the proposed structure. The ¹H nmr spectrum of this material exhibited signals corresponding to the vinyl methyl group (3-proton triplet of doublets at δ 1.64, J = 1.5, 7 Hz) and the olefinic proton (1-proton quartet at δ 5.36, J = 7 Hz). The presence of the isopropyl group was indicated by a pair of 3-proton doublets at δ 0.72 and 0.76 (J = 7 Hz in each case). More importantly, the signal due to the methine proton HA appeared as a doublet of triplets (J = 4.5, 12 Hz) at δ 2.89 while the
proton $H_B$ gave rise to a doublet of doublets of doublets ($J = 2.5, 4.5, 13 \text{ Hz}$) at $\delta 2.17$. The latter assignments were confirmed when saturation of the signal corresponding to $H_B$ ($\delta 2.17$) resulted in simplification of the signal at $\delta 2.89$ ($H_A$) to a simple triplet ($J = 12 \text{ Hz}$). These results showed that $H_A$ is axially oriented on the six-membered ring and that the stereochemistry of the addition product is as shown in (306).

Upon exposure to potassium hydride (2.5 equiv) in tetrahydrofuran at room temperature, compound (306) cyclized smoothly to provide the bicyclic ketone (307) in 92% yield (equation 55). Interestingly, compound (307) was the sole product obtained even when the intramolecular alkylation of (306) was carried out under equilibrating conditions [KO(t-Bu), t-BuOH, 35-40°C, 15 h]. Thus, (307) appears to be the kinetic as well as the thermodynamically favored product of this cyclization reaction.

The stereochemistry of the ring fusion in (307) was established as follows. In the $^1H$ nmr spectrum of (307), the bridgehead protons $H_A$ and $H_B$ gave rise to a broad doublet of doublets ($J = 7, 10 \text{ Hz}$) and a broad quartet ($J = 7 \text{ Hz}$) at $\delta 2.88$ and 2.63, respectively (Fig. 2). Irradiation of the signal at $\delta 2.88$ ($H_A$) simplified the signal at $\delta 2.63$ ($H_B$) to a broad triplet ($J = 7 \text{ Hz}$) whereas saturation of the signal corresponding to $H_B$ ($\delta 2.63$) resulted in simplification of the signal at
Figure 2: The 400 MHz $^1$H nmr spectrum of (307)

$\delta$ 2.88 ($H_A$) to a broad doublet ($J = 10$ Hz). The vicinal coupling constant $J_{AB}$ is, therefore, 7 Hz and suggested a cis-relationship between $H_A$ and $H_B$. Additional, more concrete evidence was obtained by way of a difference nuclear Overhauser enhancement (nOe) experiment. Thus, irradiation at $\delta$ 2.88 ($H_A$) caused signal enhancement at $\delta$ 2.63 ($H_B$) and at $\delta$ 1.63 (vinyl methyl group), supporting thereby the assigned structure (307) for the cyclization product.

In order to allow for hydroboration of the trisubstituted double bond of (307), the ketone (307) was converted into the ketal (311) by Sterzycki's method. Thus, a mixture of the ketone (307) (1 equiv), ethanediol (3 equiv), and pyridinium p-toluenesulfonate (0.3 equiv) in benzene was refluxed with water separation by a Dean-Stark trap to
provide, after suitable workup and distillation, the ketal (311) in 94% yield (equation 56).

\[
\text{307} \xrightarrow{\text{HOCH}_2\text{CH}_2\text{OH}, \text{H}^+} \text{311}
\]  

(56)

The $^1$H nmr spectrum of the ketal (311) (Fig. 3) was consistent with the proposed structure. The signals at $\delta$ 2.61 (1-proton doublet of doublets, $J = 7, 11$ Hz), 2.00-2.09 (1-proton multiplet), 1.33 (1-proton doublet of quartets, $J = 4, 11$ Hz), and 1.11 (1-proton triplet of...
triplets, $J = 3$, 11 Hz), were assigned to the protons $H_A$, $H_B$, $H_X$, and $H_Z$, respectively. Saturation of the signal at $\delta 2.61$ ($H_A$) simplified the signals corresponding to $H_B$ ($\delta$ 2.00-2.09) and $H_Z$ ($\delta$ 1.11) to a broad triplet ($J = 8$ Hz) and triplet of doublets ($J = 3$, 11 Hz), respectively. On the other hand, irradiation at $\delta$ 2.04 ($H_B$) reduced the resonance due to $H_A$ ($\delta$ 2.61) to a simple doublet ($J = 11$ Hz) while the pattern for $H_Z$ ($\delta$ 1.11) remained unaffected. The signal at $\delta$ 1.33 ($H_X$) was unchanged under the conditions of these decoupling experiments. The cis ring-fusion of the hydrindane skeleton in (311) was thus supported by the vicinal coupling constant (7 Hz) between $H_A$ and $H_B$.

It was pleasing to find that compound (311) underwent hydroboration highly stereoselectively upon treatment with borane-methyl sulfide complex (1.5 equiv) to afford, after oxidative workup (3 M NaOH, 30% $H_2O_2$) and flash chromatography of the crude product, the alcohols (308) and (312) in a ratio of 95:5, respectively (equation 57).

\[
\begin{align*}
\text{311} & \xrightarrow{1. \text{BH}_3\cdot \text{Me}_2\text{S}} \text{308} \quad \text{83\%} \\
& \xrightarrow{2. \text{NaOH, H}_2\text{O}_2} \text{312} \quad \text{4\%}
\end{align*}
\]

The spectral data derived from the alcohols (308) and (312) are consistent with the expected regiochemistry of the hydroboration process. However, no firm conclusions could be drawn about the proposed stereochemical assignments. For example decoupling experiments (see Experimental section) suggested that the bridgehead proton $H_A$ exhibited
doublet of doublet of doublets (J = 7, 8, 11 Hz) at δ 2.13 in the ¹H nmr spectrum of (308). Furthermore, the coupling constant between H₈ and HY appeared to be 8 Hz. However, the corresponding protons could not be identified in the ¹H nmr spectrum of (312). Hence, the stereochemical assignments in (308) and (312) were made primarily on the basis of predictions regarding steric approach control in the hydroboration reaction.

The ethylenedioxy group, having served its intended protecting function, was removed by refluxing a solution of compound (308) (1 equiv) and pyridinium p-toluenesulfonate (0.3 equiv) in wet acetone for 2 h. Analysis of the crude product indicated that it consisted of a 2:1* mixture of the epimeric ketols (309) and (313), respectively (equation 58). The fact that a mixture was obtained showed that facile epimerization at the bridgehead position adjacent to the carbonyl group had occurred under the conditions for deprotection.

The mixture of epimers (309) and (313) was treated with a solution of sodium methoxide (0.3 equiv) in methanol at room temperature and the progress of further epimerization was monitored by glc analysis. After

\begin{align*}
\text{308} & \xrightarrow{1. \text{H}_3\text{O}^+} \xrightarrow{2. \text{NaOMe, MeOH}} \text{309} \quad \text{80\%} \quad \text{313} \quad \text{75:25 (58)}
\end{align*}

* This ratio varied slightly from experiment to experiment.
the mixture had been stirred for 3.5 h, the ratio of (309):(313) was found to remain constant. Gas-liquid chromatography as well as $^1$H nmr spectra of the crude mixture suggested that the equilibrium ratio of (309) and (313) was 3:1, respectively. The ir spectrum of this mixture showed absorptions at 3450 and 1700 cm$^{-1}$, indicating the presence of an alcohol function and a carbonyl group, respectively.

The spectral data derived from the mixture of (309) and (313) failed to provide any information regarding the ring-fusion stereochemistry of the two products. The stereochemical assignments in (309) and (313) were based on the equilibration studies and on conformational analyses of these two compounds. The ketal (308) was known to have a cis ring junction. Therefore, deprotection must provide initially the cis-fused ketol. Epimerization of this initially formed cis-fused ketol would then provide the corresponding trans isomer. Since the percentage of (309) was found to increase at the expense of (313) after complete disappearance of the ketal (308) (by glc analysis), compound (309) was assigned the trans ring-junction stereochemistry. The preponderance of the trans-fused ketol (309) at equilibrium may be rationalized on the basis of conformational analyses as depicted in Scheme 18.

Conformer (313B) is obviously less stable than (313A) because of a) the syn-axial interactions between the isopropyl group and the axial hydrogens at C-7 and C-9 and b) the rather severe interactions (1,3-di-axial type) of the C-3 substituent with C-6 and C-8. Of the remaining two configurational isomers (309) and (313A), the former may be envisaged to be more stable because it appears to possess fewer and less severe interactions than those present in (313A). For example, the
Scheme 18

syn-axial interactions involving C-1 and the axial protons on C-5 and C-7, present in (313A), are absent in (309). Furthermore, the steric interaction between the C-3 and C-5 substituents also appears to be less severe in (309) than in (313A). However, there is appreciable angle strain\(^79\) incorporated into the trans-hydrindone (309) relative to its cis epimer (313A). Therefore, on balance, the energy difference between (309) and (313) might be expected to be quite small, with the trans isomer (309) being slightly favored. This small energy difference is reflected in the formation of a 3:1 mixture of (309) and (313), respectively, under equilibrating conditions.

It was gratifying to find that the 3:1 mixture of (309) and (313) was converted primarily into the desired trans-fused olefinic alcohol
(310) upon treatment with three equivalents of methylenetriphenylphosphorane in dimethyl sulfoxide. Thus, the Wittig reaction afforded, after suitable workup and flash chromatography of the crude product on silica gel, the olefinic alcohols (310) and (314) in isolated yields of 76% and 4%, respectively (equation 59). Evidently, equilibration of (309) and (313) occurred under these reaction conditions and the trans isomer (309) preferentially condensed with methylenetriphenylphosphorane. This result may stem from the greater steric hindrance connected with the carbonyl group in the cis- versus trans-hydridone isomers, (313) and (309), respectively. More explicitly, in either isomer, approach of the Wittig reagent from the under side of the carbonyl group is disfavored on steric grounds. However, the β face of the carbonyl is less sterically crowded in (309) than in (313). As a result, the Wittig olefination of (309) would be expected to be faster than that of the cis-isomer (313). The observation of prior epimerization in the Wittig reaction is well-documented in the literature.

The spectral data obtained from compounds (310) and (314) are in complete agreement with the structural assignments. In particular, the $^1$H nmr spectra of (310) and (314) (Fig. 4 and 5, respectively) were very
Figure 4: The 400 MHz $^1$H nmr spectrum of (310)

Figure 5: The 400 MHz $^1$H nmr spectrum of (314)
useful in ascertaining their ring-fusion stereochemistry. In the $^1$H nmr spectrum of (310), the protons $H_A$ and $H_X$ gave rise to a doublet of triplets ($J = 8$, 11 Hz) and a doublet of quartets ($J = 4$, 11 Hz) at $\delta$ 1.20 and 1.05, respectively. In addition, the allylic protons $H_B$ and $H_C$ exhibited a multiplet at $\delta$ 2.30-2.39. Saturation of the signals corresponding to $H_B$ and $H_C$ ($\delta$ 2.30-2.39) modified the signals at $\delta$ 1.20 ($H_A$) and 1.05 ($H_X$) to a doublet of doublets ($J = 8$, 11 Hz) and a simple quartet ($J = 11$ Hz), respectively. This decoupling experiment indicated that the coupling constant between $H_A$ and $H_B$ was 11 Hz, thus suggesting a trans-relationship between these two protons. On the other hand, in the $^1$H nmr of (314), the signals due the bridgehead protons $H_A$ and $H_B$ appeared at $\delta$ 2.06 (1-proton doublet of doublet of doublets, $J = 7$, 8, 10 Hz) and at $\delta$ 2.65-2.71 (1-proton multiplet), respectively. Furthermore, irradiation at $\delta$ 2.68 ($H_B$) led to simplification of the signal at $\delta$ 2.06 ($H_A$) to a doublet of doublets ($J = 7$, 10 Hz). Hence, in the case of compound (314), $J_{AB} = 8$ Hz. This value is certainly within the range expected for a cis ring junction.

Having devised a reasonably efficient route to the olefinic alcohol (310), we began working toward the first of our chosen synthetic objectives, (±)-anhydro-oplopanone (258), as outlined in equation 60. Oxidation of (310) with pyridinium chlorochromate in methylene chloride produced (±)-3-epi-anhydro-oplopanone (315) in 93% yield. The $^1$H nmr spectrum of this material (Fig. 6) established unequivocally the stereochemical assignments of all the chiral centers in (315). Thus, the signals due to the protons $H_X$, $H_A$, and $H_Z$ appeared at $\delta$ 0.98 (1-proton doublet of quartets, $J = 4$, 12 Hz), 1.27 (1-proton doublet of triplets,
\[ J = 7, 12 \text{ Hz}, \] and \[ J = 3, 12 \text{ Hz}, \] respectively. Additionally, the protons \( H_c, H_B, \) and \( H_Y \) gave rise to signals at \( \delta = 2.33 \) (1-proton triplet of doublets, \( J = 4, 13 \text{ Hz}, \) \( J = 2.46-2.57 \) (1-proton multiplet), and \( 3.15 \) (1-proton doublet of doublets of doublets, \( J = 4, 7, 9 \text{ Hz}, \) respectively. Decoupling experiments corroborated these assignments and showed that the magnitude of both of the vicinal coupling constants \( J_{AB} \) and \( J_{AZ} \) is 12 Hz. These values indicate clearly the axial orientation of \( H_B, H_A, \) and \( H_Z \) on the 6-membered ring. In a difference nuclear Overhauser enhancement (nOe) experiment, saturation of the signal at \( \delta = 1.27 \) (\( H_A \)) resulted in signal intensity enhancement at \( \delta = 3.15 \) (\( H_Y \)), suggesting a \textit{cis}-relationship between \( H_A \) and \( H_Y \). This experiment established the configuration of the
fourth chiral center in compound (315).

Base-catalyzed equilibration (NaOMe, MeOH, 60°C) of compound (315) yielded a 7:93 mixture of (315) and (±)-anhydro-oplopanone (258) (equation 60). Fractional crystallization of this mixture from petroleum ether provided pure (±)-(258) which exhibited mp 68°C and gave $^1$H nmr spectrum (400 MHz) identical with that of (-)-anhydro-oplopanone.* Furthermore, ir, ms, and $^{13}$C nmr spectra derived from our synthetic substance are in agreement with those reported for (-)-anhydro-oplopanone.86

In summary, the total synthesis of (±)anhydro-oplopanone (258) was achieved in 24% overall yield from 4-isopropyl-2-cyclohexen-1-one (305).

D. Total Synthesis of (±)-8-epi-Oplopanone and (±)-Oplopanone

The ketol (309) was considered as a good starting point for the synthesis of (±)-oplopanone (257). Stereoselective axial addition of a

* We thank Prof. Bohlmann for a copy of the $^1$H nmr spectrum of (-)-(258).
methyl anion equivalent to the carbonyl group would generate the required C-8 configuration and a straightforward oxidation-epimerization sequence should then provide (±)-oplopanone (257) (Scheme 19).

The availability of reagents for the axial addition of alkyl nucleophiles to substituted cyclohexanones is very limited. The addition of alkyllithiums, Grignard reagents, or organocuprates tend to favor equatorial attack to produce the corresponding axial alcohols. Under specific reaction conditions, trimethylaluminum is known to give predominant axial attack, but the stereoselectivity of this addition is greatly reduced when the cyclohexanones have an α-equatorial substituent.

An alternative approach to this type of conversion involves stereo-

* Very recently, Yamamoto has reported a solution to this problem involving the use of new, bulky organoaluminum compounds (see ref. 100c).
selective epoxidation of (309) followed by reduction to product (316). It was reported by Corey and Chaykovsky that dimethylsulfonium methyldide (299) reacts with cyclohexanones to add methylene across the carbonyl preferentially from the axial side. Thus, when 4-tert-butylcyclohexanone (317) was allowed to react with (299) in THF, the oxiranes (318) and (319) were produced in a ratio of 5:1, respectively (equation 61). This observed selectivity has been rationalized on the basis of kinetic preference for axial addition to the carbonyl group, since the initially formed sulfonium betaines are known to collapse to epoxides faster than they revert to starting materials.

Treatment of the 1:3 mixture of the ketols (313) and (309) with 3 equivalents of dimethylsulfonium methyldide (299) in DMSO-THF gave, after flash chromatography of the crude product and recrystallization of the major product from petroleum ether, the epoxide (320) (mp 92.5-93°C) in 69% yield (equation 62). The ¹H nmr spectrum of (320) exhibited a one-proton doublet of triplets (J = 8, 11 Hz) at δ 2.30. This signal, attributed to Hₐ, established the fact that (320) possesses a trans ring-fusion. In addition, the AB pair of doublets (J = 5 Hz in each case) at δ 2.57 and 2.66 (1H each) correspond to the epoxide protons. However, no conclusion regarding the configuration of the epoxide ring
could be drawn from the spectral data of (320). Lithium aluminum hydride reduction of the epoxide (320) yielded the diol (321) (equation 62). Treatment of (321) with PCC and sodium acetate in methylene chloride afforded the ketol (322) which, upon equilibration (NaOMe, MeOH, 60°C), provided a 7:93 mixture of (322) and (±)-8-epi-oplopanone (323) (equation 63). Pure (323) was obtained from this mixture by flash chromatography, followed by recrystallization of the desired material from hexane-ether. The melting point of (323) (62°C) was quite different from those reported (101.5-102°C, 90 97-98°C) previously for (±)-oplopanone. Furthermore, the 400 MHz $^1$H nmr spectrum of (323) (Fig. 7) is very similar to, but clearly different from, that of authentic (-)-oplopanone (257) (Fig. 8). In the $^1$H nmr spectrum of (323), the
Figure 7: The 400 MHz $^1H$ nmr spectrum of (323)

Figure 8: The 400 MHz $^1H$ nmr spectrum of (-)-oplopanone
bridgehead protons $H_A$ and $H_B$ exhibited signals at $\delta$ 2.02 (1-proton quartet, $J = 11$ Hz) and 1.94 (1-proton doublet of doublet of doublets, $J = 4, 8, 11$ Hz), respectively, whereas the signals due to the protons $H_Y$ and $H_Z$ appeared at $\delta$ 2.60 (1-proton doublet of triplets, $J = 5, 11$ Hz) and 1.07 (1-proton triplet of triplets, $J = 3, 11$ Hz), respectively. These assignments were confirmed by appropriate decoupling experiments. The coupling pattern of $H_A$ (quartet, $J = 11$ Hz) confirmed the assigned stereochemistry at C-3, C-4, C-5 and C-9 in compound (323). Therefore, the only chiral center in (323) which has a configuration different from $(\pm)$-oplopanone (257) is C-8.

At this point it became apparent that, contrary to our "wishes", the addition of dimethylsulfonium methylide (299) to the ketol (309) had occurred predominantly from the equatorial side of the cyclohexane ring. The preference for equatorial attack in this case may be rationalized on the basis of steric hindrance to attack from the $\alpha$ (axial) face of (309). There are examples in the literature which suggest that the incorporation of an $\alpha$-equatorial methyl group in substituted cyclohexanes can reverse the normal (axial) orientation of attack by dimethylsulfonium methylide (299) on these substrates.\(^{102b}\)

As pointed out previously (see Scheme 15), Koster and Wolf\(^{92}\) reported recently an efficient preparation of a mixture of the ketones (294) and (295). Treatment of this mixture with dimethylsulfonium methylide (299) (equilibrating conditions) was reported to give mainly the epoxide (296) which, upon subjection to an appropriate sequence of reactions (lithium aluminum hydride reduction, ozonolysis, and base-promoted epimerization), was claimed to provide $(\pm)$-oplopanone (257)
The melting point of this synthetic material (63-64°C) is significantly different from those reported (101.5-102°C, 90 97-98°C) previously for (±)-(257). Indeed, the mp of Koster and Wolf's synthetic material is very close to that (62°C) of the compound (323) prepared in our work. Moreover, the ketones (295) and (309) are structurally quite similar. Therefore, it appears highly likely that the addition of dimethylsulfonium methylide (299) to (295) had also occurred from the equatorial side of the ketone carbonyl group. It is thus evident from our work that Koster and Wolf had actually prepared, not (±)-(257), but (±)-8-epi-oplopanone (323).

At this juncture, we turned our attention to epoxidation of the alkene function in compound (310). It was envisioned that if the axial approach of a reagent at C-8 is disfavored, as indicated by the reaction of dimethylsulfonium methylide (299) with (309), then the epoxidation of (310) should occur preferentially from the equatorial side to provide the desired epoxy alcohol (324). Treatment of (310) with m-chloroperbenzoic acid resulted in formation of the epoxides (324) and (320) in approximately equal proportions. However, epoxidation of (310) via the corresponding bromohydrins proved to be reasonably stereoselective.
Thus, treatment of the olefinic alcohol (310) with N-bromosuccinimide in DMSO-water (3:1), followed by immediate treatment of the resulting crude bromohydrin mixture with methanolic potassium carbonate, provided, after chromatographic separation of the resultant products, the desired epoxide (324) (63%, mp 91°C) along with a small amount (12%) of the epimeric substance (320) (equation 65). In the $^1$H nmr spectrum of (324), the signals due to the two epoxide protons appeared at $\delta$ 2.48 (1-proton doublet, $J$ = 5 Hz), and 2.86 (1-proton doublet of doublets, $J$ = 2, 5 Hz). The small coupling constant (2 Hz) associated with the latter resonance was attributed to a long range $W$ coupling between one of the oxirane protons and the bridgehead proton $H_B$. This observation provided strong support for the assigned stereochemistry of the epoxide moiety in (324). Examination of molecular models shows that $W$ coupling of one of the oxirane protons with $H_B$ is possible only if the epoxide methylene protons are on the alpha face of the molecule.

The stereoselectivity observed in the bromohydrin-based epoxidation reaction may be rationalized as follows. Studies on bromohydrin formation in aqueous DMSO have shown that in the case of an unsymmetrical bridged bromonium ion, the nucleophile (DMSO) reacts at the carbon atom with the more pronounced carbonium-ion character.$^{103a}$ However, the
reaction is known to exhibit a high degree of stereoselectivity with predominant anti addition, ruling out a discrete carbonium-ion intermediate. Therefore, assuming the formation of the bridged bromonium ion from the alkene function in compound (310) to be reversible, preferential nucleophilic attack from the more open β-face of the molecule should provide the bromohydrin (325). Base-promoted intramolecular ring closure would then produce the required epoxy alcohol (324) (equation 66).

Reduction of the compound (324) produced the corresponding diol (316) (96%, mp 117-118°C) which, upon oxidation, afforded (±)-3-epi-oplopanone (326) (94%, mp 68°C) (equation 67). Equilibration of the latter material with sodium methoxide in methanol gave a 6:94 mixture of (326) and (±)-oplopanone (257). Fractional crystallization of this mixture from hexane-ether provided pure (±)-(257) (mp 99-100°C) in 84% yield. This material exhibited tlc properties and gave 1H nmr spectrum (400 MHz) identical with those of natural (-)-oplopanone.84,*

* We are very grateful to Dr. M. Matsumoto, Shionogi Research Laboratory, for a sample of (-)-(257) and for copies of its ir and 1H nmr spectra and to Professor Taber for copies of ir, 1H nmr, and mass spectra of (±)-(257).
In summation, the total synthesis of (±)-oplopanone (257) was accomplished in 15% overall yield from 4-isopropyl-2-cyclohexen-1-one (305). The synthetic sequence used in this synthesis demonstrated the viability of employing the newly developed (Z)-ethylidenecyclopentane annulation method in organic synthesis.

IV. Hydrostannylation of 1-Alkyn-3-ols Via Stannylmetalation.

Preparation of (E)-6-Chloro-3-lithio-2-hexene and the Related Grignard Reagent

A. Preparation of 1-Alkyn-3-ols

Having established the feasibility of preparing (Z)-5-chloro-3-trimethylstannyl-2-pentene (99) and having demonstrated the synthetic
utility of the corresponding lithio (204) and Grignard (218) reagents, we turned our attention to the possibility of preparing trimethylstannanes of general structure (107). As mentioned in the Introduction, it was envisaged that the desired bifunctional reagents (107) could be obtained stereoselectively via orthoester-based Claisen rearrangement of the corresponding vinylstannanes (109) (Scheme 6). The efficiency of this route was contingent upon the regioselective hydrostannylation of 1-alkyn-3-ols (108) to provide the vinylstannanes (109).

The requisite ethynyl carbinols (108) were readily prepared* by reaction of monolithium acetylide with the appropriate aldehydes.\(^{104}\)

* 3-Butyn-2-ol (336) was obtained from the Aldich Chemical Co., Inc.
The monolithium acetylide was, in turn, generated by addition of n-butyl-lithium to acetylene in THF at -78°C. A summary of the preparation of a number of 1-alkyn-3-ols from the corresponding aldehydes is given in Table VI.

B. Addition of the (Trimethylstannyl)copper Reagent to 1-Alkyn-3-ols

It had been shown earlier that reaction of the (trimethylstannyl)copper reagent \(84\) with various \(\omega\)-substituted 1-alkynes \(83\) in the presence of methanol afforded high yields of the corresponding 2-trimethylstannyl-1-alkenes \(85\) (equation 18). We have investigated the reaction of reagent \(84\) with 3-butyn-2-ol \(336\). The regioselectivity of addition was found to be critically dependent on various reaction parameters. In general, it was found that the presence of an \textit{in situ} proton source (MeOH) and low reaction temperatures (-63°C to -78°C) favored the formation of the desired product \(337\) (equation 68). Under optimum conditions, the isomeric vinylstannanes \(337\) and \(338\) were produced in a ratio of 3:1, respectively. Thus, reaction of 3-butyn-2-ol \(336\) with 1.5 equivalents of \(\text{Me}_3\text{SnCu.Me}_2\text{S}\) \(84\) in the
Table VI: Preparation of 1-Alkyn-3-ols from Aldehydes\textsuperscript{a}

\[
\begin{align*}
\text{R-CHO} & \rightarrow \text{R-C=C-H} \\
327 & \quad 108
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde 327</th>
<th>R</th>
<th>Product 108</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>328 n-hexyl</td>
<td></td>
<td>332</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>329 CH\textsubscript{3}OCH\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}</td>
<td></td>
<td>333</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>330 H\textsubscript{2}C-CH(CH\textsubscript{2})\textsubscript{2}</td>
<td></td>
<td>334</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>331 cyclopropyl</td>
<td></td>
<td>335</td>
<td>74</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: Li-C=C-H (1.1 equiv), THF, -78°C, 30 min; r.t., 1 h; H\textsubscript{2}O.

\textsuperscript{b} Yield of purified, distilled product.
presence of methanol (50 equiv) at -78°C for 2.5 h and at 0°C for 1 h afforded the trimethylstannanes (337) and (338) in isolated yields of 52% and 17%, respectively. In similar fashion, other acetylenic alcohols (108) were converted into mixtures of the corresponding vinylstannanes (109) and (339) (see Table VII). In each case, a procedure identical with that outlined above was employed. The isomeric allylic alcohols (109) and (339) were, in each case, readily separable by flash column chromatography on silica gel. The ratio of (109) and (339) formed in each reaction (Table VII) refers to isolated yields of purified products.

The regio- and stereochemical assignments of these products were based primarily on \( ^1H \) nmr spectroscopy. In the \( ^1H \) nmr spectra of the 2,2-disubstituted vinylstannanes (109), the olefinic protons produced very similar and characteristic signal patterns. Typically, the protons \( H_A \) and \( H_X \) gave rise to signals at around \( \delta 5.2 \) and 5.8, respectively, with \( J_{AX} \approx 2 \) Hz. Each resonance was split further by coupling with the allylic methine proton (\( J \approx 0-3 \) Hz). The magnitude of the tin-proton coupling constants gave an additional indication that \( H_A \) was cis to the trimethylstannyl group (\( J_{Sn-H} \approx 72 \) Hz) while \( H_X \) was trans to \( Me_3Sn \) (\( J_{Sn-H} \approx 146 \) Hz) and hence the two protons must have been geminal to
Table VII: Reaction of the (Trimethylstannyl)copper Reagent with 1-Alkyn-3-ols$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Products</th>
<th>Ratio$^b$</th>
<th>Combined Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>336</td>
<td>Me</td>
<td>337:338</td>
<td>75:25</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>332</td>
<td>n-hexyl</td>
<td>340:344</td>
<td>66:34</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>333</td>
<td>CH$_3$OCH$_2$(CH$_2$)$_2$</td>
<td>341:345</td>
<td>58:42</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>334</td>
<td>H$_2$C=CH(CH$_2$)$_2$</td>
<td>342:346</td>
<td>60:40</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>335</td>
<td>cyclopropyl</td>
<td>343:347</td>
<td>55:45</td>
<td>64</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: reagent (84) (1.5 equiv), MeOH (50 equiv), THF, -78°C, 2.5 h, 0°C, 1 h; sat NH$_4$Cl.

$^b$ Based on isolated yields of purified products.
each other.

On the other hand, in the $^1$H nmr spectra of the isomeric (E)-vinyl-stannanes (339), the olefinic protons $H_L$ and $H_M$ typically exhibited an AB pattern around $\delta 6.1$ with $\Delta \delta \approx 0.15$ and $J_{LM} \approx 19$ Hz. Each line in this AB pattern was further split by coupling with the allylic methine proton. The upfield doublet ($H_L$) was further split into two doublets ($J \approx 5$ Hz) by vicinal coupling whereas the downfield doublet ($H_M$) was further split into two doublets by allylic coupling ($J \approx 0.1$ Hz). The magnitude of $J_{LM} (\approx 19$ Hz) indicated that the olefinic protons were trans and, therefore, that the alkene (339) possessed the (E) configuration. In addition, $J_{Sn-H}$ associated with $H_L$ and $H_M$ were $\approx 75$ Hz and $\approx 80$ Hz, respectively. These values also indicated that $H_L$ was cis to the Me$_3$Sn moiety while $H_M$ was geminal to it. Thus, interpretation of the olefinic proton signals in the $^1$H nmr spectra of the products (109) and (339) unequivocally ascertained the regio- and stereochemical assignments.

The chromatographic behavior of the isomeric vinylstannanes (109) and (339) was also quite useful in making preliminary speculations regarding the regiochemical outcome of these hydrostannylation reactions. More explicitly, the desired 2-trimethylstannyl-1-alken-3-ols (109) consistently showed greater mobilities on tlc analyses (silica gel, development with petroleum ether-ethyl acetate mixtures) and shorter retention times on glc analyses than the corresponding (E)-vinylstannanes (339). Thus, one may make reasonably confident tentative assignments of regiochemistry of the isomeric vinylstannanes (109) and (339) simply by glc or tlc.
It is evident that, in contrast to similar transformations\textsuperscript{23} involving 1-alkynes that contain a polar functional group (e.g. OH, OR) further removed from the triple bond, reaction of the acetylenic alcohols (108) with Me\textsubscript{3}SnCu·Me\textsubscript{2}S does not exhibit notable regioselectivity. It is not immediately obvious why a hydroxy group adjacent to the alkyne function should noticeably influence the regioselectivity of the trimethylstannylcupration and result in the production of relatively greater amounts of the vinylstannanes (339). There is evidence that suggests that the reaction of Me\textsubscript{3}SnCu·Me\textsubscript{2}S with 1-alkynes is reversible.\textsuperscript{23} Therefore, it is possible that the relative thermodynamic stability of the intermediate vinylcopper species (348) and (349) is, at least partially, responsible for the final product distribution. When $Y = H$, the inductive effect of the alkyl group would destabilize the intermediates (349) relative to (348). Protonation of (348) would then provide the 2-trimethylstannyl-1-alkenes regioselectively. However, when $Y = OH$, the electron-withdrawing effect of oxygen may provide additional stability to (349) relative to (348) because of the proximity of oxygen to the anionic center in the former intermediate. Thus, one may rationalize the observed decrease of regioselectivity as a consequence of comparable stabilities of the intermediates (348) and (349) ($Y = OH$). Alternatively, an initial coordination of the hydroxy...
group with the organometallic reagent may result in preferential formation of the intermediate (349) \((Y = OH)\) \textit{via} internal delivery of the reagent.

C. Reaction of (Trimethylstannyl)zinc Reagents with 1-Alkyn-3-ols

In 1984, Oshima and coworkers reported that the reaction of terminal acetylenes with \((n\text{-Bu}_3\text{Sn})_2\text{Zn}\) in the presence of various transition-metal catalysts provides the corresponding 2-tri-\textit{n}-butylstannyl-2-alkenes preferentially.\(^{105}\) Thus, treatment of 4-benzyloxy-1-butyn (350) with \((n\text{-Bu}_3\text{Sn})_2\text{Zn-CuCN}\) and \((n\text{-Bu}_3\text{Sn})_2\text{Zn-Pd(PPh}_3)_4\) gave a mixture of the vinylstannanes (351) and (352) in ratios of 26:74 and 14:86, respectively (equation 69). The organozinc reagent \((n\text{-Bu}_3\text{Sn})_2\text{Zn}\) was prepared by mixing tri-\textit{n}-butylstannyllithium (2 equiv) with zinc bromide (1 equiv).\(^{105}\)

\[
R-C \equiv C-H \xrightarrow{\text{catalyst}} \frac{(n\text{-Bu}_3\text{Sn})_2\text{Zn}}{R-Sn-Bu_3 \quad n\text{-Bu}_3\text{Sn}} + \quad (69)
\]

\[
R = \text{PhCH}_2\text{O(CH}_2)_2
\]

Subsequently, it was discovered that the silylzinc compound \([\text{PhMe}_2\text{SiZnR}_2]\text{Li}\), derived from dimethylphenylsilyllithium and the required dialkylzinc, readily add to alkynes in the presence of copper(I) cyanide to produce, after suitable workup, the corresponding
vinylsilanes with good control of regio- and stereochemistry. The regioselectivity of this effective hydrosilylation was found to be critically dependent on the nature of the dialkylzinc employed. For instance, the reaction of \([\text{PhMe}_2\text{SiZnEt}_2]\)Li with 4-benzyloxy-1-butyne (350) provided a mixture of the (E)-alkene (353) and its regioisomer (354) in a ratio of 67:33, whereas compound (354) was the predominant product (95% regioselectivity) obtained when \([\text{PhMe}_2\text{SiZn(tBu)}_2]\)Li was employed (equation 70). Among the various transition metal catalysts employed, CuCN was found to be the most effective in catalyzing these silylzincation reactions.

We have prepared the analogous (trimethylstannyl)zinc reagents and investigated their reactions with 1-alkyn-3-ols. The reagents (355)*

\[
\begin{align*}
R'\text{C≡C} - & \xrightarrow{\text{CuCN}} \text{PhMe}_2\text{SiZnR}_2\text{Li} & \text{R'}\text{SiMe}_2\text{Ph} + \text{PhMe}_2\text{Si} \\
\end{align*}
\]

\(350 \quad 353 \quad 354\)

\(R' = \text{PhCH}_2\text{O(CH}_2)_2\)

<table>
<thead>
<tr>
<th>(R)</th>
<th>Ratio 353:354</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>67:33</td>
</tr>
<tr>
<td>i-Pr</td>
<td>33:67</td>
</tr>
<tr>
<td>t-Bu</td>
<td>5:95</td>
</tr>
</tbody>
</table>

* These formulations are not meant to imply actual structures, but are used to show stoichiometry and for convenience.
and (356) were prepared by reaction of equimolar amounts of Me$_3$SnLi and the required dialkylzinc in THF at -20°C for 20 min (equations 71 and 72). As with most cuprates and analogous reagents, these organozincates

$$\text{Me}_3\text{SnLi} + (\text{t-Bu})_2\text{Zn} \rightarrow [\text{Me}_3\text{SnZn(t-Bu)}_2]\text{Li} \quad (71)$$

$$\text{Me}_3\text{SnLi} + \text{Et}_2\text{Zn} \rightarrow [\text{Me}_3\text{SnZnEt}_2]\text{Li} \quad (72)$$

are likely to be thermally unstable and sensitive to oxygen. Therefore, these reagents were always prepared immediately prior to their use and maintained under an atmosphere of dry argon. For the preparation of (355), it is best to use relatively fresh (< 2 weeks old) di-tert-butyl-zinc solution.

In nearly all the cases studied, higher regioselectivities (relative to those provided by reactions involving Me$_3$SnCu·Me$_2$S) were obtained when the acetylenic alcohols (108) were subjected to CuCN-catalyzed stannylzincation reactions. For example, when 3-butyn-2-ol (336) was allowed to react with 2 equivalents of the reagent (355) in the presence of a catalytic amount of copper(I) cyanide, the isomeric vinylstannanes (337) and (338) were produced in a ratio of 4:1 (Table VIII, Entry 1). It may be recalled that the reaction of 3-butyn-2-ol (336) with Me$_3$SnCu·Me$_2$S had provided a 3:1 mixture of (337) and (338), respectively (Table VII, Entry 1). Similar (minor) improvements in regioselectivity were obtained with the alkynes (332)-(334) (compare Tables VII and VIII). However, in the case of 1-cyclopropyl-2-propyn-ol (335), direct stannylcupration and CuCN-catalyzed stannylzincation with
the reagent (355) gave essentially identical proportions of (343) and (347).

In analogy with the findings of Oshima and coworkers, we have found that the regiochemistry of these reactions is governed by the nature of the dialkylzinc employed. Thus, when the stannylzincations of substrates (108) were carried out with the reagent (356) in the presence of CuCN, the mixtures of reaction products consisted largely of the (E)-vinylstannanes (339) (Table VIII). In each case, a procedure identical with that outlined above for reagent (355) was employed.

It is clear that a rather simple change in the constitution of the organozincate reagent \([\text{Me}_3\text{SnZnR}_2]\text{Li}\) has a profound effect on the regiochemistry of the overall transformation (compare, for example, Entries 1 and 2, Table VIII). A closer examination of the results summarized in Table VIII reveals that higher, more consistent regioselectivities (>85%) were obtained in the reactions of acetylenic alcohols (108) with reagent (356). On the other hand, in the reactions of (108) with reagent (355), the regioselectivity of the overall transformation decreased as the size of the R group increased (compare Entries 1, 3, 9, Table VIII). Further experimentation is needed to understand the reasons underlying these observed results.

From a synthetic point of view, it is important that the attainable regioselectivities of the CuCN-catalyzed stannylzincation reactions of ethynyl carbinols (108) made the acquisition of reasonable yields of either (109) or (339) quite straightforward.
Table VIII: Reaction of the (Trimethylstannyl)zinc Reagents with 1-Alkyn-3-ols

\[
\begin{align*}
R\ \overset{C=C-H}{\underset{OH}{\longrightarrow}}
& \quad \text{Me}_3\text{Sn} \quad \overset{H_A}{\underset{H_x}{\longrightarrow}}
& \quad \text{Hi SnMe}_3 \quad \overset{H_L}{\underset{H_M}{\longrightarrow}}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Conditions\textsuperscript{a}</th>
<th>Products \textsuperscript{b}</th>
<th>Ratio \textsuperscript{b}</th>
<th>Combined Yield (%) \textsuperscript{b}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>336</td>
<td>Me</td>
<td>A</td>
<td>337:338</td>
<td>82:18</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>336</td>
<td>Me</td>
<td>B</td>
<td>337:338</td>
<td>11:89</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>332</td>
<td>n-hexyl</td>
<td>A</td>
<td>340:344</td>
<td>75:25</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>332</td>
<td>n-hexyl</td>
<td>B</td>
<td>340:344</td>
<td>2:98</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>333</td>
<td>CH\textsubscript{3}OCH\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}</td>
<td>A</td>
<td>341:345</td>
<td>74:26</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>333</td>
<td>CH\textsubscript{3}OCH\textsubscript{2}O(CH\textsubscript{2})\textsubscript{2}</td>
<td>B</td>
<td>341:345</td>
<td>6:94</td>
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</tr>
<tr>
<td>7</td>
<td>334</td>
<td>H\textsubscript{2}C=CH(CH\textsubscript{2})\textsubscript{2}</td>
<td>A</td>
<td>342:346</td>
<td>68:32</td>
<td>63</td>
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<td>8</td>
<td>334</td>
<td>H\textsubscript{2}C=CH(CH\textsubscript{2})\textsubscript{2}</td>
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<td>A</td>
<td>343:347</td>
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<td>cyclopropyl</td>
<td>B</td>
<td>343:347</td>
<td>15:85</td>
<td>68</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions. A: reagent (355) (2.0 equiv), CuCN (0.04 equiv), THF, -20°C, 1 h; 0°C, 1 h; sat. NH\textsubscript{4}Cl. B: reagent (356) (2.0 equiv), CuCN (0.04 equiv), THF, -20°C, 1 h; 0°C, 1 h; sat. NH\textsubscript{4}Cl.

\textsuperscript{b} Based on isolated yields of purified products.
D. The Orthoester Claisen Rearrangement of 2-Trimethylstannyl-1-alken-3-ols and (E)-1-Trimethylstannyl-1-alken-3-ols

With sufficient quantities of the isomeric allylic alcohols (109) and (339) in hand, we embarked on the orthoester Claisen rearrangement of these compounds. When 3-trimethylstannyl-3-buten-2-ol (337) was heated with 7 equivalents of triethyl orthoacetate and 0.06 equivalent of propanoic acid at 135-138°C for 2.5 h under conditions allowing for distillative removal of ethanol, the ester (358) was produced cleanly and efficiently in 82% yield (Table IX). In similar fashion, the alcohols (340)-(342) were readily transformed into the corresponding esters (359)-(361), respectively (Table IX). Interestingly, orthoacetate-based Claisen rearrangement of the isomeric allylic alcohols (338) and (344)-(346) also proceeded cleanly to provide, in good yields, the structurally interesting and potentially useful allylic trimethylstannanes (364)-(367), respectively. These results are summarized in Table X.

Two comments should be made regarding the data given in Table IX and X. Firstly, treatment of the crude product mixture with aqueous potassium dihydrogen phosphate (5%) hydrolyzed the excess triethyl orthoacetate and thus made the workup cleaner and more efficient. Even the allylic vinylstannanes (363) were found to be stable under these workup conditions. Secondly, the reactions of the cyclopropyl derivatives (343) and (347) were found to be sluggish and gave rise to several by-products (glc and tlc analyses). When 15 equivalents of triethyl orthoacetate and 0.2 equivalent of propanoic acid were employed, the
Table IX: Preparation of Ethyl (Z)-4-Trimethylstannyl-4-alkenoates

\[
\begin{align*}
\text{Me$_3$Sn} & \quad \text{R} & \quad \text{CO$_2$Et} \\
109 & \quad 357 & \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>337</td>
<td>Me</td>
<td>358</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>n-hexyl</td>
<td>359</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>341</td>
<td>CH$_3$OCH$_2$O(CH$_2$)$_2$</td>
<td>360</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>342</td>
<td>H$_2$C=CH(CH$_2$)$_2$</td>
<td>361</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>343</td>
<td>cyclopropyl</td>
<td>362$^c$</td>
<td>58</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: CH$_3$C(OEt)$_3$ (7 equiv), CH$_3$CH$_2$CO$_2$H (0.06 equiv), 135-140°C, 2.5 h; aqueous KH$_2$PO$_4$ (5%), r.t., 30 min.

$^b$ Yield of purified, distilled product.

$^c$ CH$_3$C(OEt)$_3$ (15 equiv) and CH$_3$CH$_2$CO$_2$H (0.2 equiv) were used.
Table X: Preparation of Ethyl (E)-3-Trimethylstannyl-4-alkenoates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R</th>
<th>Product</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>338</td>
<td>Me</td>
<td>364</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>344</td>
<td>n-hexyl</td>
<td>365</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>345</td>
<td>CH$_3$OCH$_2$O(CH$_2$)$_2$</td>
<td>366</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>346</td>
<td>H$_2$C=CH(CH$_2$)$_2$</td>
<td>367</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>347</td>
<td>cyclopropyl</td>
<td>368&lt;sup&gt;c&lt;/sup&gt;</td>
<td>62</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: CH$_3$C(0Et)$_3$ (7 equiv), CH$_3$CH$_2$CO$_2$H (0.06 equiv), 135-140°C, 2.5 h; aqueous KH$_2$PO$_4$ (5%), r.t., 30 min.

<sup>b</sup> Yield of purified, distilled product.

<sup>c</sup> CH$_3$C(0Et)$_3$ (15 equiv) and CH$_3$CH$_2$CO$_2$H (0.2 equiv) were used.
reactions appeared to be faster and relatively clean. Subjection of the crude mixtures to flash chromatography on silica gel afforded the desired esters (362) and (368) in yields of 58 and 62%, respectively.

Thus, in accord with the well-established stereoselectivity of the orthoester Claisen rearrangement, the secondary allylic alcohol substrates (109) and (339) were converted solely into the corresponding \( \gamma,\delta \)-unsaturated esters (357) and (363), respectively. The spectral data derived from these compounds are in complete agreement with the assigned structures. For example, the ir spectrum of (358) contained the appropriate bands for an ester (1736 cm\(^{-1}\)) containing an alkene function (1624 cm\(^{-1}\)) and a trimethylstannyl group (770 cm\(^{-1}\)). In addition, in the \( ^{1}\text{H} \) nmr spectrum of (358), the vinyl methyl group and the olefinic proton gave rise to signals at \( \delta \) 1.70 (a 3-proton doublet, \( J = 6 \) Hz) and 6.10 (a 1-proton quartet, \( J = 6 \) Hz, \( J_{\text{Sn-H}} = 140 \) Hz), respectively. The magnitude of the tin-proton coupling constant (140 Hz) associated with the vinyl proton clearly indicated its \textit{trans} relationship with the trimethylstannyl group and thus confirmed the stereochemical assignments.

The ir spectrum of the isomeric trimethylstannane (364) was also indicative of the presence of an ester moiety (1729 cm\(^{-1}\)), an alkene function (1654 cm\(^{-1}\)), and a trimethylstannyl group (767 cm\(^{-1}\)). Furthermore, in the \( ^{1}\text{H} \) nmr spectrum of compound (364), the two olefinic protons gave rise to signals at \( \delta \) 5.14 (1-proton doublet of quartet of doublets, \( J = 1, 6, 16 \) Hz) and 5.49 (1-proton quartet of doublet of doublets, \( J = 1.5, 8, 16 \) Hz). The magnitude of the coupling constant between the two vinylic protons (16 Hz) was clearly in the range
expected for a trans disubstituted double bond. Analogous spectral analyses were made in assigning the structures of the other products shown in Tables IX and X.

E. Preparation and Reactions of (E)-6-Chloro-3-lithio-2-hexene.

(Z)-Ethylidenecyclohexane Annulation Sequences

Having devised a reasonably efficient and stereoselective route to ethyl (Z)-4-trimethylstannyl-4-hexenoate (358), we turned our attention to the preparation of the corresponding chloro vinylstannane (370). Treatment of (358) with lithium aluminum hydride in ether at 0°C produced the olefinic alcohol (369) in good yield (equation 73).

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{CO}_2\text{Et} \\ \\
\text{358} & \quad \xrightarrow{\text{LAH, Et}_2\text{O}} \\
\text{Me}_3\text{Sn} & \quad \text{OH} \\ \\
\text{369} & \quad \xrightarrow{\text{Ph}_3\text{P} \cdot \text{CCl}_4, \text{Et}_3\text{N}} \\
\text{370} & \quad \text{Cl}
\end{align*}
\]

Reaction of the alcohol (369) with triphenylphosphine-carbon tetrachloride in the presence of triethylamine afforded (Z)-6-chloro-3-trimethylstannyl-2-hexene (370) (equation 73). The spectral data of compounds (369) and (370) corroborated fully the assigned structures.

Surprisingly, successive treatment of a cold (-78°C) THF solution of compound (370) with methyllithium (2 h) and cyclohexanone (1 h),
followed by aqueous workup, did not provide any of the expected chloro alcohol (372) and/or the spiro ether (373). To the contrary, tlc and glc analyses of the recovered material showed the presence of unconsumed vinylstannane (370). It may be recalled that the analogous compound (Z)-5-chloro-3-trimethylstannyl-2-pentene (99) had undergone complete transmetalation upon exposure to 1.1 equiv of methyllithium in THF at -78°C for 20 min. These two results seem to indicate that the chloride function in (99) plays some role in the transmetalation reaction of that compound.

Higher reaction temperatures (e.g. -48°C) and use of DME as solvent failed to provide better results for the desired transmetalation reaction of (370). Eventually, it was found that compound (370) underwent complete transmetalation when treated with methyllithium (1.1 equiv) and HMPA (1.1 equiv) in THF at -78°C for 1 h. The addition of cyclohexanone to the solution of (E)-6-chloro-3-lithio-2-hexene (371) thus obtained, followed by warming of the reaction mixture to room temperature, produced the spiro ether (373) in 68% yield (equation 74). This result established clearly that the vinyllithium species (371) is stable at low temperatures and is a viable donor-acceptor reagent for synthesis.

It was gratifying to find that the Grignard reagent (374), obtained by treatment of (371) with anhydrous MgBr₂ (1.2 equiv), reacted cleanly with 2-cyclopenten-1-one (225) and 2-methyl-2-cyclohexen-1-one (224) in the presence of CuBr·Me₂S (0.3 equiv) and BF₃·Et₂O (1.2 equiv) to provide the conjugate addition products (375) and (376), respectively, in good yields (equations 75 and 76). Intramolecular alkylation of the chloro ketones (375) and (376) occurred smoothly upon treatment of these
substances with potassium hydride in THF. The \((Z)\)-ethylidene-cyclohexane annulation products (377) and (378), respectively, were formed in excellent yields.

Not unexpectedly, the chloro ketone (376) was found to consist of a 2:1 mixture of epimers. Accordingly, in the \(^1\text{H} \text{nmr} \) spectrum of (376),
the secondary methyl groups of the two epimers gave rise to a pair of doublets (ratio 2:1, $\Delta = 7$ Hz in each case) at $\delta$ 0.89 and 1.06, respectively. However, kinetically controlled intramolecular alkylation of both the epimers should provide the same cis-fused bicyclic ketone (378). Indeed, glc analysis of the crude product and the $^1$H nmr spectrum of (378) indicated that a single olefinic ketone was obtained when the epimeric mixture (376) was treated with potassium hydride.

The cis bicyclic ketone (377), produced by intramolecular alkylation of (375), could have undergone subsequent epimerization at the bridgehead position adjacent to the carbonyl group. However, the $^1$H nmr spectrum of (377) showed that the cyclization product of (375) consisted of a single bicyclic olefinic ketone possessing a cis ring-fusion stereochemistry. Thus, the $^1$H nmr spectrum of (377) contained a resonance at $\delta$ 3.22 (1-proton broad quartet, $\Delta = 7$ Hz), attributed to one of the bridgehead protons. This signal indicated a 7 Hz coupling constant between the bridgehead protons and hence a cis-fused bicyclic hydrindane unit in compound (377).

In summary, it was found that addition of the elements of $\text{Me}_3\text{Sn-H}$ across the triple bond of acetylenic alcohols (108) by reaction of these substrates with $\text{Me}_3\text{SnCu-Me}_2\text{S-MeOH}$, $[\text{Me}_3\text{SnZn(}t\text{-Bu)}_2]\text{Li-CuCN}$, or $[\text{Me}_3\text{SnZnEt}_2]\text{Li-CuCN}$ provides, in varying ratios, the trimethylstannyl alkenes (109) and (339). Orthoacetate-based Claisen rearrangement of compounds (109) and (339) was shown to afford the esters (357) and (363), respectively (equations 77 and 78). These esters are, potentially, precursors of structurally interesting donor-acceptor conjunc-
tive reagents. For example, the ester (358) was converted into the chloride (370), which, upon transmetalation (MeLi, THF-HMPA, -78°C) produced the vinyllithium (371). Compound (371) and the corresponding Grignard reagent (374) serve as synthetic equivalents to the (E)-d$_3$-a$_6$-2-hexene synthons (379) in the newly developed (Z)-ethylidenebicyclohexane annihilation method [(101) → (380)]. The allylic trimethylstannanes (363) are also potentially useful reagents and the chemistry of these substances is currently under investigation in our laboratory.

\[
\begin{align*}
R\text{C≡C-H} & \rightarrow R\text{C≡C-H} & & \rightarrow R\text{SnMe}_3 \\
\text{OH} & & & \text{CO}_2\text{Et} \\
108 & & & 370 \\
357 & & & 358 \text{ R= Me} \\
\end{align*}
\]

\[
\begin{align*}
R\text{C≡C-H} & \rightarrow R\text{C≡C-H} & & \rightarrow R\text{SnMe}_3 \\
\text{OH} & & & \text{Me}_3\text{Sn} \text{CO}_2\text{Et} \\
108 & & & 363 \\
339 & & & 379 \\
\end{align*}
\]
EXPERIMENTAL
General

Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected. Boiling points were recorded as air-bath temperatures required for bulb-to-bulb (Kugelrohr) distillations and are also uncorrected. Infrared (ir) spectra were obtained on liquid films, KBr pellets, or chloroform solutions, employing a Perkin-Elmer model 1710 spectrophotometer (internal calibration) or a Perkin-Elmer model 710B spectrophotometer calibrated using the 1601 cm\(^{-1}\) band of a polystyrene film. Proton and carbon-13 nuclear magnetic resonance (\(^{1}\)H and \(^{13}\)C nmr) spectra were recorded on deuterochloroform solutions using Bruker models WP-80, HXS-270 or WH-400 spectrometers or a Varian model XL-300 instrument. Signal positions are given in \(\delta\) units and were measured relative to tetramethysilane (TMS) as the internal standard or to the chloroform signal (\(\delta\) 7.25).\(^{109}\) The multiplicity, number of protons, coupling constants, and assignments (where possible) are indicated in parenthesis. The tin-proton coupling constants (\(J_{\text{Sn-H}}\)) are given as an average of the \(^{117}\)Sn and \(^{119}\)Sn values. Low and high resolution mass spectra were recorded with Varian/MAT CH4B and/or Kratos/AEI MS 50 mass spectrometers. In cases of compounds with trimethylstannyl groups the molecular weight determinations (high resolution mass spectrometry) were based on \(^{120}\)Sn and were made on the \((M^+\cdot\text{CH}_3)\) peak.\(^{59}\)
Gas-liquid chromatography (glc) analyses were performed on Hewlett-Packard models 5880 or 5890 capillary gas chromatographs using 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54 and flame ionization detectors.

Thin layer chromatography (tlc) analyses were done on commercial aluminum-backed silica gel plates (E. Merck, Type 5554). Visualization was accomplished with ultraviolet light, iodine, and/or by spraying the plate with 5% ammonium molybdate - 10% aqueous sulfuric acid. Conventional column chromatography was done on 70-230 mesh silica gel (E. Merck) while flash chromatography was done on 230-400 mesh silica gel (E. Merck).

All compounds that were subjected to mass spectrometric determinations were homogeneous by tlc and glc analyses.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame-dried.

Cold temperatures used for various reactions were obtained as follows: ice-acetone (-10°C), 27 g CaCl₂/100 ml H₂O/CO₂ (-20°C), 46 g CaCl₂/100 ml H₂O/CO₂ (-48°C), chloroform/CO₂ (-63°C), acetone/CO₂ (-78°C) and methanol/N₂ (-98°C).

Solvents and reagents were purified and dried using established procedures. Ether and THF were distilled from sodium benzophenone ketyl. Triethylamine, diisopropylamine, HMPA, DMSO and DMF were distilled from calcium hydride. Methylene chloride and carbon tetrachloride were distilled from P₂O₅. Petroleum ether refers to the fraction boiling between 30-60°C.
Hexamethylditin was obtained from Organometallics, Inc. and was used without further purification.

Solutions of methyllithium (low halide) in ether and n-butyllithium in hexane were obtained from Aldrich Chemical Co., Inc. and were standardized using the procedure of Kofron and Baclawski.¹¹²

Cuprous bromide-dimethyl sulfide complex was prepared by the method of House,⁷⁵a after washing the commercial cuprous bromide with methanol.⁷⁵b

Phenylthiocopper was prepared by the method of Posner.³²

Cuprous cyanide was purchased from Aldrich Chemical Co., Inc. and was used without further purification.

Saturated aqueous ammonium chloride (pH 8) was prepared by the addition of ≈50 ml of aqueous ammonium hydroxide (58%) to 1 L of saturated aqueous ammonium chloride.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of methyllithium in ether to a solution of diisopropylamine (1 equiv) in dry THF at -78°C. The resulting colorless solution was then stirred at 0°C for 10 min before being used.

Anhydrous magnesium bromide was prepared by the dropwise addition of a solution of 1,2-dibromoethane in dry ether to a suspension of magnesium (0.5 equiv) in dry ether. The ether was removed under high vacuum.

A stock solution of anhydrous zinc chloride was prepared by melting the solid under vacuum, crystallizing from dry THF under argon, and dissolving in dry THF.¹¹³

A stock solution of di-tert-butylzinc was prepared by the dropwise
addition of a solution of anhydrous zinc chloride in dry THF to tert-
butyl magnesium chloride (2 equiv) in dry THF at 0°C. After the 
addition was complete the reaction mixture was stirred for 24 h at room 
temperature and then was stored under argon.

A solution of diethylzinc in toluene was obtained from Aldrich 
Chemical Co., Inc.

Preparation of Trimethylstannyllithium

To a cold (-20°C), stirred solution of hexamethylditin in dry THF 
(≈10 mL per mmol) was added a solution of methyllithium in ether (1 
equiv). The resulting yellow solution was stirred at -20°C for 20 min 
to afford a solution of trimethylstannyllithium.

Preparation of Lithium(Phenylthio)(trimethylstanny)cuprate (80)

$$\text{[Me}_3\text{SnCuSPh]}\text{Li}$$

To a cold (-20°C), stirred solution of trimethylstannyllithium in 
dry THF was added solid phenylthiocopper (1 equiv). The resulting 
slurry was stirred at -20°C for 20 min to afford a bright red solution 
of lithium(phenylthio)(trimethylstanny)cuprate (80).
Preparation of the (Trimethylstannyl)copper Reagent (84)

\[
\text{Me}_3\text{SnCu} \cdot \text{Me}_2\text{S}
\]

To a cold (-78°C), stirred solution of trimethylstannylolithium in dry THF was added solid cuprous bromide-dimethyl sulfide (1 equiv). The resulting slurry was stirred at -78°C for 10 min and at -63°C for 15 min to afford a dark red solution of (84).

Preparation of the (Trimethylstannyl)zinc Reagent (355)

\[
\left[\text{Me}_3\text{SnZn(}t\text{-Bu})_2\right] \text{Li}
\]

To a cold (-20°C), stirred solution of trimethylstannyllithium in dry THF was added a solution of di-\textit{tert}-butylzinc in THF (1 equiv). The resulting solution was stirred at -20°C for 20 min to afford a pale yellow solution of (355).
Preparation of the (Trimethylstannyl)zinc Reagent (356)

\[
\text{[Me}_3\text{SnZnEt}_2\text{]} \text{Li}
\]

To a cold (-20°C), stirred solution of trimethylstannylolithium in dry THF was added a solution of diethylzinc in toluene (1 equiv). The resulting solution was stirred at -20°C for 20 min to afford a pale yellow solution of (356).

Preparation of Ethyl 6-tert-Butyldimethylsiloxy-2-hexynoate (116)

\[
\text{t-BuMe}_2\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{-C} \equiv \text{C- CO}_2\text{Et}
\]

To a cold (-78°C), stirred solution of 5-tert-butyldimethylsiloxy-1-pentyne (114)\textsuperscript{115} (2.0 g, 10 mmol) in 35 mL of dry THF was added a solution of methyllithium in ether (7.1 mL, 10 mmol). The resulting clear solution was stirred at -78°C for 15 min, warmed to -20°C and stirred at this temperature for 1 h. Ethyl chloroformate (1.0 mL, 10 mmol) was added and the yellow solution was stirred at -20°C for 1 h and at room temperature for 1 h. Saturated aqueous sodium bicarbonate and ether were added. The organic layer was separated, washed (water, brine) and dried (MgSO\textsubscript{4}). Solvent removal (rotary evaporation), followed by distillation (air-bath temperature 105-115°C/0.3 Torr) of
the residual oil, afforded 2.43 g (89%) of the ester (116) as a colorless oil. This material exhibited IR (film): 2210, 1705, 1250, 1110, 1060, 840 cm\(^{-1}\); \(\text{\textsuperscript{1}H}\) NMR (80 MHz, CDCl\(_3\)) \(\delta\): 0.03 (s, 6H, Me\(_2\)Si-), 0.88 (s, 9H, Me\(_3\)CSi-), 1.28 (t, 3H, -OCH\(_2\)CH\(_3\), \(J = 7\) Hz), 1.80 (m, 2H, -CH\(_2\)CH\(_2\)CH\(_2\)-), 2.40 (t, 2H, -CH\(_2\)-C=O-, \(J = 7\) Hz), 3.65 (t, 2H, -OCH\(_2\)-, \(J = 6\) Hz), 4.18 (q, 2H, -OCH\(_2\)CH\(_3\), \(J = 7\) Hz). **Exact Mass** calcd. for C\(_{13}\)H\(_{23}\)O\(_3\)Si (M\(^+\)-CH\(_3\)): 255.1417; found: 255.1419.

**Preparation of Methyl 4-Cyclopropyl-2-butynoate (129)**

![Structure of 4-Cyclopropyl-2-butynoate](attachment:structure.png)

To a cold (-20°C), stirred solution of diisopropylamine (140 \(\mu\)L, 1 mmol), and propynoic acid (616 \(\mu\)L, 10 mmol) in 7.5 mL of dry THF was added a solution of \(\pi\)-butyllithium in hexane (14.5 mL, 21 mmol). After the light yellow solution had been stirred at -20°C for 10 min, 15 mL of HMPA was added and stirring was continued at -20°C for 15 min and at -10°C for 1.5 h. Cyclopropylmethyl bromide\(^{44}\) (1.42 g, 10.5 mmol) was added. The solution was allowed to warm to room temperature. After 24 h, methyl iodide (2.5 mL, 40 mmol) was added and stirring was continued for a further 24 h at room temperature. Cold water and ether were added. The aqueous layer was extracted thoroughly with ether. The combined organic extract was washed (water, brine) and dried (MgSO\(_4\)). Solvent removal afforded a yellow oil which was subjected to flash.
chromatography on silica gel (30 g, elution with petroleum ether-ether, 25:1). Concentration of the appropriate fractions and distillation (air-bath temperature 50-65°C/0.3 Torr) of the residual material afforded 735 mg (53%) of the ester (129) as a colorless oil. This material exhibited IR (film): 3050, 2210, 1710, 1260 cm\(^{-1}\); \(^1\)H NMR (80 MHz, CDC\(_3\)) \(\delta\): 0.50-1.50 (m, 5H, cyclopropyl protons), 2.30 (d, 2H, \(-\text{CH}_2\)-C\(=\), \(J = 7\) Hz), 3.78 (s, 3H, -OCH\(_3\)). **Exact Mass** calcd. for C\(_8\)H\(_{10}\)O\(_2\): 138.0681; found: 138.0680.

General Procedure 1: Preparation of 1,1-Dibromoolefins (381)

\[
\begin{align*}
\text{H} & \quad \text{Br} \\
\text{R} & \quad \text{Br}
\end{align*}
\]

To a reagent\(^{37}\) prepared by stirring a mixture of zinc dust (3.3 g, 50 mmol), triphenylphosphine (13.1 g, 50 mmol), carbon tetrabromide (16.6 g, 50 mmol), and 80 mL of dry dichloromethane at room temperature for 24 h was added the appropriate aldehyde (25 mmol). The resulting tan suspension was stirred at room temperature for 2 h. Petroleum ether (400 mL) was added and the supernatant solution was decanted from the oil. The oil was taken up in 80 mL dichloromethane, petroleum ether (400 mL) was added and the supernatant solution was again decanted. Concentration of the combined supernatant solutions, followed by flash distillation (0.1 Torr, receiving bulb cooled to -78°C), afforded the corresponding dibromoolefin (381).
General Procedure 2: Preparation of $\alpha,\beta$-Acetylenic Esters (130)

$$RCH_2^+C\equiv C-CO_2Et$$

A solution of the appropriate 1,1-dibromoolefin (381) (20 mmol) in 50 mL of dry THF at -78°C was treated with a solution of methyllithium in ether (42 mmol). After being stirred at -78°C for 1 h and at room temperature for 1 h, the solution was cooled to -20°C. Ethyl chloroformate (28 mmol) was added and the solution was stirred at -20°C for 1 h and at room temperature for 1 h. Saturated aqueous sodium bicarbonate and ether were added. The organic layer was washed (water, brine), dried (MgSO$_4$), and concentrated. Distillation of the residual oil afforded the corresponding $\alpha,\beta$-acetylenic ester (130).

**Preparation of Ethyl 5-Methyl-2-hexynoate (119)**

Following general procedure 1 outlined above, 3-methylbutanal (117) (2.7 mL, 25 mmol) afforded 5.68 g (94%) of the dibromoolefin (118) as a colorless oil (flash distillation temperature <50°C/0.1 Torr). This
material exhibited ir (film): 1610, 1460, 1380, 1365, 860, 790 cm\(^{-1}\); \(^1H\) nmr (80 MHz, CDCl\(_3\)) \(\delta\): 0.93 (d, 6H, -CHMe\(_2\), \(J = 7\) Hz), 1.50-1.85 (m, 1H, -CHMe\(_2\)), 2.00 (t, 2H, -CH\(_2\)CHMe\(_2\), \(J = 7\) Hz), 6.41 (t, 1H, olefinic proton, \(J = 7\) Hz).

Following general procedure 2, 1,1-dibromo-4-methyl-1-pentene (118) (5.57 g, 23 mmol) in 60 mL of dry THF was treated successively with a solution of methyllithium in ether (30.9 mL, 48 mmol) and ethyl chloroformate (3.1 mL, 32.2 mmol). Normal workup, followed by distillation (air-bath temperature 85-100°C/20 Torr), afforded 2.622 g (74%) of the ester (119) as a clear, colorless oil. This material exhibited ir (film): 2234, 1713, 1388, 1367, 1251 cm\(^{-1}\); \(^1H\) nmr (80 MHz, CDCl\(_3\)) \(\delta\): 1.00 (d, 6H, Me\(_2\)CH-, \(J = 7\) Hz), 1.32 (t, 3H, -OCH\(_2\)CH\(_3\), \(J = 7\) Hz), 1.60-2.10 (m, 1H, Me\(_2\)CH-), 2.23 (d, 2H, -CH\(_2\)-C=C, \(J = 6\) Hz), 4.20 (q, 2H, -OCH\(_2\)CH\(_3\), \(J = 7\) Hz). Exact Mass calcd. for C\(_9\)H\(_{11}\)O\(_2\) (M\(^+\)-CH\(_3\)): 139.0759; found: 139.0757.

Preparation of Ethyl 5-Trimethylsilyl-2-pentyonoate (122)

\[
\text{Me}_3\text{Si} \quad \text{H} \quad \text{Br} \quad \text{Me}_3\text{SiCH}_2\text{CH}_2\text{C}≡\text{C-CO}_2\text{Et}
\]

Following general procedure 1, 3-trimethylsilyl-1-propanal (120)\(^{38}\) (3.25 g, 25 mmol) afforded 6.60 g (92%) of 1,1-dibromo-4-trimethylsilyl-
1-butene (121) as a colorless oil (flash distillation temperature <50°C/0.1 Torr). This material was used directly in the next reaction. Compound (121) (6.60 g, 23 mmol) was dissolved in 130 mL of dry THF and the solution was treated successively with a solution of methylithium in ether (34.9 mL, 48 mmol) and ethyl chloroformate (2.7 mL, 28 mmol) as outlined in general procedure 2. Normal workup, followed by distillation (air-bath temperature 70-85°C/19 Torr), afforded 3.33 g (73%) of the ester (122) as a colorless liquid. This material exhibited ir (film): 2239, 1713, 1251 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.24 (s, 9H, Me₃Si⁻), 1.05 (t, 2H, Me₃SiCH₂⁻, J = 7 Hz), 1.48 (t, 3H, -OCH₂CH₃, J = 7 Hz), 2.53 (t, 2H, Me₃SiCH₂CH₂⁻, J = 7 Hz), 4.40 (q, 2H, -OCH₂CH₃, J = 7 Hz). Exact Mass calcd. for C₉H₁₅O₂Si (M⁺-CH₃): 183.0842; found: 183.0848.

General Procedure 3: Preparation of Alkyl (E)-3-Trimethylstannyl-2-alkenoates (131)

To a cold (-98°C), stirred solution of lithium (phenylthio)(trimethylstannyl)cuprate (80) (1.4 mmol) in 14 mL of dry THF was added, dropwise, a solution of the appropriate α,β-acetylenic ester (130) (1.0 mmol) in ~1.0 mL of dry THF containing dry methanol (1.7 mmol). The reaction mixture was stirred at -98°C for 20 min, warmed to -78°C, and
stirred for a further 6 h. After successive addition of methanol or ethanol (~2 mL) and petroleum ether (~30 mL), the mixture was allowed to warm to room temperature with vigorous stirring. The resulting yellow slurry was filtered through a short column of Florisil. The column was eluted with a further 30 mL of petroleum ether and the combined eluate was concentrated. The residue was subjected to flash chromatography on silica gel (18 g, petroleum ether-ether mixture as eluant). Concentration of the appropriate fractions, followed by distillation of the crude product, afforded the corresponding alkyl (E)-3-trimethylstannyl-2-alkenoate (131).

General Procedure 4: Preparation of Alkyl (Z)-3-Trimethylstannyl-2-alkenoates (137)

\[
\text{Me}_3\text{Sn} \quad \begin{array}{c}\text{CO}_2\text{R'} \\
\end{array}
\]

To a cold (-78°C), stirred solution of lithium (phenylthio)-(trimethylstannyl)cuprate (80) (1.3 mmol) in 13 mL dry THF was added the appropriate \( \alpha,\beta \)-acetylenic ester (130) (1.0 mmol) as a solution in \( \approx 1.0 \) mL of dry THF. The reaction mixture was stirred at -78°C for 15 min, warmed to -48°C, and stirred at that temperature for 4 h. After successive addition of methanol or ethanol (~ 2 mL) and petroleum ether (~30 mL), the mixture was allowed to warm to room temperature with vigorous stirring. Normal workup (as in general procedure 3), followed
by distillation of the crude product gave the corresponding alkyl (Z)-3-
trimethylstannyl-2-alkenoate (137).

Preparation of Ethyl (E)-3-Trimethylstannyl-2-pentenoate (132)

Following general procedure 3, ethyl 2-pentynoate (113) (126 mg, 1 mmol) was converted into the \( \beta \)-trimethylstannyl-\( \alpha,\beta \)-unsaturated ester (132). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 200:3), followed by distillation (air-bath temperature 55-70°C/0.2 Torr) of the material thus obtained, afforded 229.8 mg (79%) of the (E)-pentenoate (132) as a colorless oil. This material exhibited ir (film): 1705, 1600, 1175, 770 cm\(^{-1}\); \(^1\)H nmr (CDCl\(_3\), 80 MHz) \( \delta \): 0.20 (s, 9H, -SnMe\(_3\), \( J_{\text{Sn-H}} \) = 54 Hz), 1.05 (t, 3H, CH\(_3\)CH\(_2\)-, \( J = 7 \) Hz), 1.30 (t, 3H, CH\(_3\)CH\(_2\)O-, \( J = 7 \) Hz), 2.90 (broad q, 2H, CH\(_3\)CH\(_2\)C-, \( J = 7 \) Hz), 4.15 (q, 2H, CH\(_3\)CH\(_2\)O-, \( J = 7 \) Hz), 5.95 (t, 1H, olefinic proton, \( J = 1 \) Hz, \( J_{\text{Sn-H}} = 73 \) Hz). Exact Mass calcd. for C\(_9\)H\(_{17}\)O\(_2\)Sn (M\(^+\)-CH\(_3\)): 277.0250; found: 277.0250.
Preparation of Ethyl (Z)-3-Trimethylstannyl-2-pentenoate (138)

Following general procedure 4, ethyl 2-pentynoate (113)\textsuperscript{36} (126 mg, 1 mmol) was converted into the ester (138). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 200:3), followed by distillation (air-bath temperature 55-65°C/0.2 Torr) of the material thus obtained, afforded 220.9 mg (76%) of the (Z)-pentenoate (138) as a colorless oil. This material exhibited ir (film): 1700, 1600, 1195, 770 cm\(^{-1}\); \textsuperscript{1}H nmr (CDCl\textsubscript{3}, 80 MHz) \(\delta\): 0.18 (s, 9H, -SnMe\textsubscript{3}, \(J_{\text{Sn-H}}\) = 54 Hz), 1.02 (t, 3H, CH\textsubscript{3}CH\textsubscript{2}O-, \(J\) = 7 Hz), 1.28 (t, 3H, CH\textsubscript{3}CH\textsubscript{2}C-, \(J\) = 7 Hz), 2.30 (broad q, 2H, CH\textsubscript{3}CH\textsubscript{2}C-, \(J\) = 7 Hz), 4.18 (q, 2H, CH\textsubscript{3}CH\textsubscript{2}O-, \(J\) = 7 Hz), 6.35 (t, 1H, olefinic proton, \(J\) = 1 Hz, \(J_{\text{Sn-H}}\) = 121 Hz). \textbf{Exact Mass} calcd. for C\textsubscript{9}H\textsubscript{17}O\textsubscript{2}Sn (M\textsuperscript{+}-CH\textsubscript{3}): 277.0250; found: 277.0252.

Preparation of Ethyl (E)-6-tert-Butyldimethylsiloxy-3-trimethylstannyl-2-hexenoate (133)
Following general procedure 3, ethyl 6-tert-butyldimethylsiloxy-2-hexynoate (116) (270 mg, 1 mmol) was converted into the ester (133). Subjection of the crude mixture to flash chromatography on silica gel (18 g, elution with petroleum ether-ether, 30:1) provided a colorless liquid which upon distillation (air-bath temperature 150-160°C/0.3 Torr) gave 309.5 mg (71%) of pure (E)-hexenoate (133) as a colorless oil. This material exhibited ir (film): 1695, 1580, 1175, 840, 770 cm⁻¹; H nmr (400 MHz, CDCl₃) δ: 0.04 (s, 6H, -SiMe₂), 0.20 (s, 9H, -SnMe₃, J.Sn-H = 56 Hz), 0.89 (s, 9H, -SiCMe₃), 1.27 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.60-1.66 (m, 2H, -CH₂CH₂CH₂-), 2.89-2.94 (m, 2H, -CH₂C=), 3.64 (t, 2H, -SiOCH₂-, J = 6 Hz), 4.15 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.96 (broad s, 1H, olefinic proton, J.Sn-H = 73 Hz). Exact Mass calcd. for C₁₆H₃₃O₃SiSn (M⁺-CH₃): 421.1221; found: 421.1208.

Preparation of Ethyl (Z)-6-tert-Butyldimethylsiloxy-3-trimethylstannyl-2-hexenoate (139)

Following general procedure 4, ethyl 6-tert-butyldimethylsiloxy-2-hexynoate (116) (270 mg, 1 mmol) was converted into the ester (139). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 50:1), followed by distillation (air-bath temperature 145-155°C/0.3 Torr), provided 344.5 mg (79%) of the
(Z)-hexenoate (139) as a colorless oil. This material exhibited ir (film): 1695, 1585, 1200, 835, 770 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.05 (s, 6H, -SiMe₂), 0.19 (s, 9H, -SnMe₃, J.Sn-H = 56 Hz), 0.91 (s, 9H, -SiCMe₃), 1.29 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.57-1.64 (m, 2H, -CH₂CH₂CH₂₂), 2.46-2.51 (m, 2H, -CH₂C=), 3.61 (t, 2H, -OCH₂CH₃, J = 6 Hz), 4.18 (q, 2H, -OCH₂CH₃, J = 7 Hz), 6.37 (broad s, 1H, olefinic proton, J.Sn-H = 120 Hz). Exact Mass calcd. for C₁₆H₃₃O₃SiSn (M⁺-CH₃): 421.1221; found: 421.1240.

Preparation of Methyl (E)-4-Cyclopropyl-3-trimethylstannyl-2-butenoate (136)

Following general procedure 3, methyl 4-cyclopropyl-2-butenoate (129) (138 mg, 1 mmol) was converted into the ester (136). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 50:1), followed by distillation (air-bath temperature 60-75°C/0.3 Torr) of the material thus obtained, afforded 225.0 mg (74%) of the (E)-butenoate (136) as a colorless oil; ir (film): 3050, 1710, 1590, 1170, 770 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.23 (s, 9H, -SnMe₃, J.Sn-H = 56 Hz), 0.15-0.20 and 0.45-0.50 (m, m, 2H each, cyclopropyl methylene protons), 0.73-0.82 (m, 1H, cyclopropyl methine proton), 2.83 (d of d, 2H, -CH₂C=, J = 1, 7 Hz), 3.68 (s, 3H, -OCH₃),
5.99 (t, 1H, olefinic proton, $J = 1$ Hz, $J_{Sn-H} = 76$ Hz). **Exact Mass**
calcd. for C$_{10}$H$_{17}$O$_2$Sn (M$^+$-CH$_3$): 289.0250; found: 289.0238.

Preparation of Methyl (Z)-4-Cyclopropyl-3-trimethylstannyl-2-
butenoate (142)

Following general procedure 4, methyl 4-cyclopropyl-2-butynoate (129) (138 mg, 1 mmol) was converted into the ester (142). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 200:3), followed by distillation (air-bath temperature 60-80°C/0.3 Torr) of the oil thus obtained, afforded 203.7 mg (67%) of the (Z)-butenoate (142) as a colorless oil; ir (film): 3060, 1705, 1600, 1200, 770 cm$^{-1}$; $^{1}$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.19 (s, 9H, $-SnMe_3$, $J_{Sn-H} = 56$ Hz), 0.06-0.12 and 0.46-0.53 (m, m, 2H each, cyclopropyl methylene protons), 0.77-0.85 (m, 1H, cyclopropyl methine proton), 2.34 (d of d, 2H, $-CH_2C=, J = 1$, 7 Hz), 3.73 (s, 3H, $-OCH_3$), 6.53 (t, 1H, olefinic proton, $J = 1$ Hz, $J_{Sn-H} = 120$ Hz). **Exact Mass**
calcd. for C$_{10}$H$_{17}$O$_2$Sn (M$^+$-CH$_3$): 289.0250; found: 289.0250.
Preparation of Ethyl (E)-5-Methyl-3-trimethylstannyl-2-hexenoate (134)

Following general procedure 3, ethyl 5-methyl-2-hexynoate (119) (154 mg, 1 mmol) was converted into the ester (134). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 200:3), followed by distillation (air-bath temperature 85-95°C/0.3 Torr) of the resultant oil, provided 236.7 mg (74%) of the (E)-hexenoate (134) as a colorless oil; ir (film): 1719, 1597, 1385, 1367, 1177, 771 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.16 (s, 9H, -SnMe₃, Jₘₙ-H = 56 Hz), 0.89 (d, 6H, -CHMe₂, J = 7 Hz), 1.27 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.60-1.72 (m, 1H, -CHMe₂), 2.80 (d of d, 2H, -CH₂C=, J = 1, 7 Hz), 4.13 (q, 2H, -OCH₂CH₃, J = 7 Hz), 6.00 (t, 1H, olefinic proton, J = 1 Hz, Jₘₙ-H = 75 Hz). Exact Mass calcd. for C₁₁H₂₁O₂Sn (M⁺-CH₃): 305.0563; found: 305.0566.

Preparation of Ethyl (Z)-5-Methyl-3-trimethylstannyl-2-hexenoate (140)

Following general procedure 4, ethyl 5-methyl-2-hexynoate (119)
(154 mg, 1 mmol) was converted into the ester (140). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 100:1), followed by distillation (air-bath temperature 70-80°C/0.3 Torr) of the material thus obtained, afforded 243.0 mg (76%) of the (Z)-hexenoate (140) as a colorless oil; ir (film): 1704, 1599, 1385, 1369, 1196, 772 cm\(^{-1}\); \(^1\)H nmr (270 MHz, CDCl\(_3\)) \&: 0.15 (s, 9H, \(-\text{SnMe}_3\), J\text{Sn-H} = 56 Hz), 0.87 (d, 6H, \(-\text{CHMe}_2\), J = 7 Hz), 1.27 (t, 3H, \(-\text{OCH}_2\text{CH}_3\), J = 7 Hz), 1.60-1.72 (m, 1H, \(-\text{CHMe}_2\)), 2.27 (d of d, 2H, \(-\text{CH}_2\text{C}=\), J = 1, 7 Hz), 4.16 (q, 2H, \(-\text{OCH}_2\text{CH}_3\), J = 7 Hz), 6.28 (t, 1H, olefinic proton, J = 1 Hz, J\text{Sn-H} = 121 Hz). Exact Mass calcd. for C\(_{11}\)H\(_{21}\)O\(_2\)Sn (M\(^+\)-CH\(_3\)): 305.0563; found: 305.0554.

Preparation of Ethyl (E)-5-Trimethylsilyl-3-trimethylstannyl-2-pentenoate (135)

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{Me}_3\text{Sn} \\
& \quad \text{H} \\
& \quad \text{CO}_2\text{Et}
\end{align*}
\]

Following general procedure 3, ethyl 5-trimethylsilyl-2-pentynoate (122) (198 mg, 1 mmol) was converted into the ester (135). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 40:1), followed by distillation (air-bath temperature 85-95°C/0.2 Torr) of the oil thus obtained, provided 265.4 mg (73%) of the (E)-pentenoate (135) as a colorless oil; ir (film): 1710, 1600, 1240, 1180, 840, 760 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \&: 0.03 (s, 9H,
Preparation of Ethyl (Z)-5-Trimethylsilyl-3-trimethylstannyl-2-pentenoate (141)

Following general procedure 4, ethyl 5-trimethylsilyl-2-pentynoate (122) (198 mg, 1 mmol) was converted into the ester (141). Flash chromatography of the crude product on silica gel (18 g, elution with petroleum ether-ether, 50:1), followed by distillation (air-bath temperature 70-80°C/0.2 Torr) of the material thus obtained, afforded 283.6 mg (78%) of the (Z)-pentenoate (141) as a colorless oil; ir (film): 1703, 1600, 1201, 861, 769 cm\(^{-1}\); \(^1\)H nmr (270 MHz, CDCl\(_3\)) \(\delta\): 0.01 (s, 9H, -SiMe\(_3\)), 0.16 (s, 9H, -SnMe\(_3\)), \(J_{Sn-H} = 56\) Hz), 0.50-0.58 (m, 2H, -CH\(_2\)SiMe\(_3\)), 1.28 (t, 3H, -OCH\(_2\)CH\(_3\)), \(J = 7\) Hz), 2.33-2.40 (m, 2H, -CH\(_2\)C=), 4.15 (q, 2H, -OCH\(_2\)CH\(_3\)), \(J = 7\) Hz), 6.33 (t, 1H, olefinic proton, \(J = 1\) Hz, \(J_{Sn-H} = 120\) Hz). \textbf{Exact Mass} calcd. for C\(_{12}\)H\(_{25}\)O\(_2\)SiSn (M\(^+\)-CH\(_3\)): 349.0645; found: 349.0634.
General Procedure 5: Preparation of Alkyl (Z)-3-Trime thylstannyl-3-alkenoa tes (167). Protonative Deconjugation of Alkyl (E)-3-Trimethyl stannyl-2-alkenoates (131).

To a cold (-78°C), stirred solution of LDA (1.15 mmol) in 5 mL of dry THF was added a solution of the appropriate alkyl (E)-3-trimethylstannyl-2-alkenoate (131) (0.5 mmol) in 0.5 mL of dry THF. The bright yellow solution was stirred at -78°C for 30 min and at 0°C for 1 h. The solution was cooled to -78°C and transferred into a cold (-98°C), vigorously stirred solution of glacial acetic acid (0.3 mL) in 5 mL of ether, using either a syringe or a cannula. The solution was allowed to warm to room temperature and saturated aqueous sodium bicarbonate and ether were added. The organic layer was separated and the aqueous layer was extracted thoroughly with ether. The combined extract was washed (water, brine), dried (MgSO₄), and concentrated. The residual oil was distilled to afford pure deconjugated ester (167).

Preparation of Ethyl (Z)-3-Trime thylstannyl-3-pentenoate (168)
Following general procedure 5, ethyl (E)-3-trimethylstannyl-2-pentenoate (132) (145.5 mg, 0.5 mmol) was converted into the ester (168). Analysis of the crude product by glc showed the complete absence of the geometrically isomeric ester. Distillation (air-bath temperature 65-80°C/0.2 Torr) of the crude product afforded 119 mg (82%) of the pure \( \beta,\gamma \)-unsaturated ester (168) as a colorless oil; ir (film) 1720, 1160, 770 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \( \delta \): 0.20 (s, 9H, -SnMe\(_3\), \( J_{Sn-H} = 54 \) Hz), 1.26 (t, 3H, -OCH\(_2\)CH\(_3\), \( J = 7 \) Hz), 1.76 (d, 3H, CH\(_3\)C=, \( J = 6 \) Hz), 3.20 (d, 2H, -CCH\(_2\)-, \( J = 1 \) Hz), 4.12 (q, 2H, -OCH\(_2\)CH\(_3\), \( J = 7 \) Hz), 6.16 (t of q, 1H, olefinic proton, \( J = 1 \), 6 Hz, \( J_{Sn-H} = 131 \) Hz). Exact Mass calcd. for C\(_9\)H\(_{17}\)O\(_2\)Sn (M\(^+\)-CH\(_3\)): 277.0250; found: 277.0246.

Preparation of Ethyl (Z)-6-\( \text{tert} \)-Butyldimethylsiloxyl-3-trimethylstannyl-3-hexenoate (169)

Following general procedure 5, ethyl (E)-6-\( \text{tert} \)-butyldimethylsiloxyl-3-trimethylstannyl-2-hexenoate (133) (217.5 mg, 0.5 mmol) was subjected to protonative deconjugation. Analysis of the crude product by glc indicated the exclusive formation of one isomer. Distillation (air-bath temperature 155-165°C/0.3 Torr) of the crude product provided 180.1 mg (83%) of the pure \( \beta,\gamma \)-unsaturated ester (169) as a colorless oil; ir (film) 1720, 1110, 840, 775 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \( \delta \):
0.04 (s, 6H, -SiMe₂), 0.16 (s, 9H, -SnMe₃, J_Sn-H = 54 Hz), 0.91 (s, 9H, -SiCMe₃), 1.20 (t, 3H, -OCH₂CH₃, J = 7 Hz), 2.24 (q, 2H, -CH₂CH₂C=, J = 7 Hz), 3.17 (s, 2H, -CH₂CO₂Et), 3.51 (t, 2H, -SiOCH₂-, J = 7 Hz), 4.10 (q, 2H, -OCH₂CH₃, J = 7 Hz), 6.05 (t, 1H, olefinic proton, J = 7 Hz, J_Sn-H = 129 Hz). \textbf{Exact Mass} calcd. for C₁₆H₃₃O₃SiSn (M⁺-CH₃): 421.1221; found: 421.1204.

\textbf{Preparation of Methyl (Z)-4-Cyclopropyl-3-trimethylstannyl-3-butenoate (172)}

Protonative deconjugation of methyl (E)-4-cyclopropyl-3-trimethylstannyl-2-butenoate (136) (151.5 mg, 0.5 mmol) was carried out as outlined in general procedure 5. Analysis of the crude product by glc showed the exclusive formation of one isomer. Distillation (air-bath temperature 60-75°C/0.3 Torr) of this material gave 119.3 mg (79%) of the pure β,γ-unsaturated ester (172) as a colorless oil; ir (film): 3060, 1730, 1615, 1180, 770 cm⁻¹; \textsuperscript{1}H nmr (400 MHz, CDCl₃) δ: 0.22 (s, 9H, -SnMe₃, J_Sn-H = 56 Hz), 0.38-0.44 and 0.72-0.78 (m, m, 2H each, cyclopropyl methylene protons), 1.26-1.36 (m, 1H, cyclopropyl methine proton), 3.18 (s, 2H, -CCH₂-), 3.66 (s, 3H, -OCH₃), 5.42 (d, 1H, olefinic proton, J = 8 Hz, J_Sn-H = 128 Hz). \textbf{Exact Mass} calcd. for C₁₀H₁₇O₂Sn (M⁺-CH₃): 289.0250; found: 289.0253.
Preparation of Ethyl (Z)-5-Methyl-3-trimethylstannyl-3-hexenoate (170)

Compound (170) was prepared via a modified version of general procedure 5. Thus, HMPA (23.6 μL, 0.14 mmol) was added dropwise to a solution of LDA (0.14 mmol) in 0.5 mL of dry THF at -78°C. After the clear solution had been stirred at -78°C for 15 min, a solution of ethyl (E)-5-methyl-3-trimethylstannyl-2-hexenoate (134) (18.9 mg, 0.06 mmol) in 0.5 mL of dry THF was added slowly and stirring was continued at -78°C for 30 min and at 0°C for 1 h. The solution was recooled to -78°C and transferred (syringe) into a cold (-98°C), vigorously stirred solution of glacial acetic acid (0.1 mL) in 1 mL of dry ether. Normal workup yielded a crude yellow product which, on the basis of a glc analysis, was isomerically pure. The crude material was passed through a short column of silica gel (3 g, elution with petroleum ether-ether, 100:1). Concentration of the eluate and distillation (air-bath temperature 85-95°C/0.3 Torr) of the residual oil gave 11.9 mg (63%) of the β,γ-unsaturated ester (170) as a colorless oil; ir (film): 1731, 1584, 1399, 1369, 1180, 760 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.20 (s, 9H, -SnMe₃, JSn-H = 56 Hz), 0.98 (d, 6H, -CHMe₂, J = 7 Hz), 1.25 (t, 3H, -OCH₂CH₃, J = 7 Hz), 2.16-2.26 (m, 1H, -CHMe₂), 3.16 (s, 2H, -CCH₂-), 4.12 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.84 (d, 1H, olefinic proton, J = 9 Hz, JSn-H = 128 Hz). **Exact Mass** calcd. for C_{11}H_{21}O₂Sn (M⁺-CH₃): 305.0563; found: 305.0559.
Preparation of Ethyl (E)-5-Trimethylsilyl-3-trimethylstannyl-3-
pentenoate (171)

Following general procedure 5, ethyl (E)-5-trimethylsilyl-3-trimethylstannyl-2-pentenoate (135) (181.5 mg, 0.5 mmol) was subjected to protonative deconjugation. Analysis of the crude product by glc showed the complete absence of the geometrically isomeric ester. Distillation (air-bath temperature 85-95°C/0.2 Torr) of the crude product provided 129.9 mg (72%) of the pure β,γ-unsaturated ester (171) as a colorless oil. This material exhibited ir (film): 1730, 1615, 1245, 1170, 845, 760 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.02 (s, 9H, -SiMe₃), 0.18 (s, 9H, -SnMe₃, JₜSn-H = 54 Hz), 1.25 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.54 (d, 2H, Me₃SiCH₂-, J = 8 Hz), 3.17 (s, 2H, -CH₂CO₂Et), 4.11 (q, 2H, -OCH₂CH₃, J = 7 Hz), 6.10 (t, 1H, olefinic proton, J = 8 Hz, JₜSn-H = 131 Hz). Exact Mass calcd. for C₁₂H₂₅O₂SiSn (M⁺-CH₃): 349.0645; found: 349.0651.
General Procedure 6: Preparation of Alkyl (E)-3-Trimethylstannyl-3-alkenoates (173). Protonative Deconjugation of Alkyl (Z)-3-Trimethylstannyl-2-alkenoates (137)

\[
\begin{align*}
\text{Hexamethylphosphoramide} & \quad (130.5 \ \mu\text{L}, \ 0.75 \ \text{mmol}) \quad \text{was added to a} \\
& \text{solution of LDA (0.75 mmol) in 5 mL of dry THF at } -78^\circ\text{C}. \ \text{After the} \\
& \text{clear solution had been stirred at } -78^\circ\text{C for 15 min, a solution of the} \\
& \text{appropriate alkyl (Z)-3-trimethylstannyl-2-alkenoate (137) (0.5 mmol) in} \\
& 0.5 \ \text{mL of dry THF was added dropwise and stirring was continued at } -78^\circ\text{C} \\
& \text{for 30 min and at } 0^\circ\text{C for 30 min. The solution was cooled to } -78^\circ\text{C} \ \text{and} \\
& \text{then was transferred into a cold (-98°C), vigorously stirred solution of} \\
& \text{glacial acetic acid (0.3 mL) in 5 mL of ether, using either a syringe or} \\
& \text{a cannula. The solution was allowed to warm to room temperature and} \\
& \text{saturated aqueous sodium bicarbonate and ether were added. The organic} \\
& \text{layer was separated and the aqueous layer was extracted thoroughly with} \\
& \text{ether. The combined extract was washed (water, brine), dried (MgSO}_4\text{),} \\
& \text{and concentrated. The residual oil was distilled to afford pure decon-} \\
& \text{jugated ester (173).}
\end{align*}
\]
Preparation of Ethyl (E)-3-Trimethylstannyl-3-pentenoate (174)

Following general procedure 6, ethyl (Z)-3-trimethylstannyl-2-pentenoate (138) (145.5 mg, 0.5 mmol) was subjected to protonative deconjugation. Analysis of the crude product by glc showed the exclusive formation of one isomer. Distillation (air-bath temperature 50-70°C/0.2 Torr) of this material afforded 125.9 mg (87%) of the pure deconjugated ester (174) as a colorless oil; ir (film): 1725, 1125, 770 cm⁻¹; ¹H nmr (400 MHz, CDCl₃), δ: 0.14 (s, 9H, -SnMe₃, Jₜ Sn-H = 54 Hz), 1.27 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.75 (d, 2H, CH₃C=, J = 7 Hz), 3.24 (d, 2H, -CCH₂, J = 2 Hz), 4.13 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.84 (t of q, 1H, olefinic proton, J = 2, 7 Hz, Jₜ Sn-H = 72 Hz). Exact Mass calcd. for C₉H₁₇O₂Sn (M⁺-CH₃): 277.0250; found: 277.0250.

Preparation of Ethyl (E)-6-tert-Butyldimethylsiloxy-3-trimethylstannyl-3-hexenoate (175)

Following general procedure 6, ethyl (Z)-6-tert-butyldimethylsiloxy-3-trimethylstannyl-2-hexenoate (139) (217.5 mg, 0.5 mmol) was
subjected to protonative deconjugation. Analysis of the crude product by glc indicated the exclusive formation of one isomer. Distillation (air-bath temperature 150-160°C/0.3 Torr) of the crude oil provided 175.8 mg (81%) of the pure \(\beta,\gamma\)-unsaturated ester (175) as a colorless oil; ir (film): 1720, 1100, 840, 770 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)), \(\delta\): 0.05 (s, 6H, -SiMe\(_2\)_), 0.12 (s, 9H, -SnMe\(_3\)_), 0.89 (s, 9H, -SiCMe\(_3\)_), 2.38 (q, 2H, -CH\(_2\)CH\(_2\)_), 3.29 (d, 2H, -SiOCH\(_2\)_), 4.12 (q, 2H, -OCH\(_2\)CH\(_3\)_), 5.77 (t, 1H, olefinic proton), Exact Mass calcd. for C\(_{16}\)H\(_{33}\)O\(_3\)SiSn (M\(^+\)-CH\(_3\)_): 421.1221; found: 421.1218.

Preparation of Methyl (E)-4-Cyclopropyl-3-trimethylstannyl-3-butenoate (178)

[Diagram]

Protonative deconjugation of methyl (Z)-4-cyclopropyl-3-trimethylstannyl-2-butenoate (142) (151.5 mg, 0.5 mmol) was carried out as outlined in general procedure 6. Analysis of the crude product by glc showed the exclusive formation of one isomer. Distillation (air-bath temperature 65-80°C/0.3 Torr) of the crude product gave 116.4 mg (77%) of the pure \(\beta,\gamma\)-unsaturated ester (178) as a colorless oil; ir (film): 3060, 1730, 1605, 1170, 770 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.11 (s,
9H, -SnMe₃, J_{Sn-H} = 56 Hz), 0.37-0.45 and 0.75 to 0.83 (m, m, 2H each, cyclopropyl methylene protons), 1.60-1.70 (m, 1H, cyclopropyl methine proton), 3.43 (d, 2H, -CCH₂-, J = 2 Hz), 3.68 (s, 3H, -OCH₃), 6.04 (t of d, 1H, olefinic proton, J = 2, 9 Hz, J_{Sn-H} = 72 Hz). **Exact Mass** calcd. for C₁₀H₁₇O₂Sn (M⁺-CH₃): 289.0250; found: 289.0253.

**Preparation of Ethyl (E)-5-Methyl-3-trimethylstannyl-3-hexenoate (176)**

![Chemical Structure](image)

Protonative deconjugation of ethyl (Z)-5-methyl-3-trimethylstannyl-2-hexenoate (140) (159.5 mg, 0.5 mmol) was carried out as outlined in general procedure 6. Analysis of the crude product by glc showed the complete absence of the geometrically isomeric ester. The crude product was passed through a short column of silica gel (8 g, elution with petroleum ether-ether, 100:1). Concentration of the eluate and distillation (air-bath temperature 70-80°C/0.2 Torr) of the oil thus obtained afforded 112.6 mg (71%) of the β,γ-unsaturated ester (176) as a colorless oil; ir (film): 1734, 1369, 1327, 1180, 769 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.10 (s, 9H, -SnMe₃, J_{Sn-H} = 56 Hz), 0.95 (d, 6H, -CHMe₂, J = 7 Hz), 1.25 (t, 3H, -OCH₂CH₃, J = 7 Hz), 2.66-2.74 (m, 1H, -CHMe₂), 3.26 (d, 2H, -CCH₂-, J = 1.5 Hz), 4.10 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.50 (t of d, 1H, olefinic proton, J = 1.5, 9 Hz, J_{Sn-H} = 75 Hz). **Exact Mass** calcd. for C₁₁H₂₁O₂Sn (M⁺-CH₃): 305.0563; found: 305.0568.
Preparation of Ethyl (E)-5-Trimethylsilyl-3-trimethylstanny1-3-pentenoate (177)

Following general procedure 6, ethyl (Z)-5-trimethylsilyl-3-trimethylstanny1-2-pentenoate (141) (181.5 mg, 0.5 mmol) was subjected to protonative deconjugation. Analysis of the crude product by glc showed the complete absence of the geometrically isomeric ester. Distillation (air-bath temperature 85-95°C/0.2 Torr) of the crude product afforded 140.8 mg (78%) of the pure /S,7-unsaturated ester (177) as a colorless oil; ir (film): 1733, 1601, 1249, 1178, 855, 766 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.02 (s, 9H, -SiMe₃), 0.12 (s, 9H, -SnMe₃, J_{Sn-H} = 52 Hz), 1.22 (t, 3H, -OCH₂CH₃, J = 7 Hz), 1.67 (d, 2H, Me₃SiCH₂-, J = 8 Hz), 3.23 (d, 2H, -CH₂CO₂Et, J = 1.5 Hz), 4.12 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.77 (t of t, 1H, olefinic proton, J = 1.5, 8 Hz, J_{Sn-H} = 75 Hz). Exact Mass calcd. for C₁₂H₂₅O₂SiSn (M⁺-CH₃): 349.0645; found: 349.0642.

General Procedure 7: Reduction of Esters to Alcohols

To a cold (-20°C), stirred solution-suspension of lithium aluminum hydride (247 mg, 6.5 mmol) in 50 mL of dry ether was added dropwise a solution of the appropriate ester (10 mmol) in 10 mL of dry ether. The reaction mixture was stirred at -20°C for 1.5 h. The cold bath was
removed and the reaction mixture was treated cautiously with sodium sulfate decahydrate. After complete precipitation of the aluminum salts, the resulting slurry was filtered through a short column of Florisil (30 g, elution with ether). Concentration of the eluate and distillation of the residual oil afforded the corresponding alcohol.

Preparation of (Z)-3-Trimethylstannyl-3-penten-1-ol (193)

\[
\text{Me}_3\text{Sn} - \overset{\text{OH}}{\text{CH}} - \text{CH}_2 - \text{CH}_3
\]

General procedure 7 was followed. From 2.91 g (10 mmol) of ethyl (Z)-3-trimethylstannyl-3-pentenoate (168) there was obtained, after distillation (air-bath temperature 60-75°C/0.2 Torr) of the crude product, 2.181 g (88%) of the alcohol (193) as a colorless oil. This material exhibited IR (film): 3300, 1600, 1040, 770 cm\(^{-1}\); \(^1\)H NMR (80 MHz, CDCl\(_3\) \(\delta\): 0.23 (s, 9H, -SnMe\(_3\), \(J_{\text{Sn-H}}\) = 52 Hz), 1.60 (broad s, 1H, exchanges with D\(_2\)O, -CH\(_2\)OH), 1.77 (broad d, 3H, CH\(_3\)C\(-\), \(J\) = 7 Hz), 2.48 (broad t, 2H, -CH\(_2\)\(-\), \(J\) = 7 Hz), 3.56 (t after addition of D\(_2\)O, 2H, -CH\(_2\)OH, \(J\) = 7 Hz), 6.20 (t of q, 1H, olefinic proton, \(J\) = 2.5, 7 Hz, \(J_{\text{Sn-H}}\) = 138 Hz). Exact Mass calcd. for C\(_7\)H\(_{15}\)OSn (M\(^+\)-CH\(_3\)): 235.0144; found: 235.0146.
Preparation of (E)-3-Trimethylstannyl-3-penten-1-ol (194)

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{OH} \\
\end{align*}
\]

Reduction of ethyl (E)-3-trimethylstannyl-3-pentenoate (174) (2.91 g, 10 mmol) was accomplished via general procedure 7. Distillation (air-bath temperature 75-90°C/0.3 Torr) of the crude product afforded 2.158 g (87%) of the alcohol (194) as a clear, colorless oil. This material exhibited ir (film): 3300, 1600, 1040, 770 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDC\(_3\)) \(\delta\): 0.13 (s, 9H, -SnMe\(_3\), \(J_{\text{Sn-H}} = 52 \text{ Hz}\)), 1.45 (t, 1H, exchanges with D\(_2\)O, -OH, \(J = 7 \text{ Hz}\)), 1.75 (d, 3H, CH\(_3\)C=, \(J = 7 \text{ Hz}\)), 2.58 (t, 2H, -CCH\(_2\)-, \(J = 7 \text{ Hz}\)), 3.62 (q, 2H, -CH\(_2\)OH, \(J = 7 \text{ Hz}\)), 5.87 (t of q, 1H, olefinic proton, \(J = 2.5, 7 \text{ Hz}\), \(J_{\text{Sn-H}} = 77 \text{ Hz}\)). Exact Mass calcd. for C\(_7\)H\(_{15}\)OSn (M\(^+-\text{CH}_3\)): 235.0144; found: 235.0156.

Preparation of (Z)-5-Chloro-3-trimethylstannyl-2-pentene (99)

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{Cl} \\
\end{align*}
\]

To a stirred solution of the alcohol (193) (2.490 g, 10 mmol) in 50 mL of dry carbon tetrachloride was added triethylamine (1.5 mL, 11 mmol) and triphenylphosphine (5.25 g, 20 mmol). The resultant solution was refluxed for 24 h. Petroleum ether (75 mL) was added and the
resulting slurry was filtered through a column of Florisil (40 g, elution with petroleum ether). Evaporation of the solvent from the combined eluate, followed by distillation of the residue (air-bath temperature 40-50°C/0.3 Torr), afforded 2.207 g (83%) of the chloride (99) as a colorless oil; ir (film): 1610, 770, 740 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 0.20 (s, 9H, -SnMe₃, J₃Sn-H = 52 Hz), 1.75 (broad d, 3H, CH₃C=, J = 7 Hz), 2.60 (broad t, 2H, -CCH₂-, J = 7 Hz), 3.45 (t, 2H, -CH₂Cl, J = 7 Hz), 6.20 (t of q, 1H, olefinic proton, J = 2, 7 Hz, J₃Sn-H = 135 Hz). Exact Mass calcd. for C₇H₁₄³⁵ClSn (M⁺-CH₃): 252.9806; found: 252.9807.

Preparation of (E)-5-Chloro-3-trimethylstannyl-2-pentene (100)

\[
\text{Me₃Sn} - \overset{\text{Cl}}{\text{C}} \quad \text{Me₃Sn}
\]

To a stirred solution of the alcohol (194) (1.245 g, 5 mmol) in 30 mL of dry carbon tetrachloride was added triethylamine (765 μL, 5.5 mmol) and triphenylphosphine (2.62 g, 10 mmol). The resultant solution was refluxed for 24 h. Petroleum ether (50 mL) was added and the resulting slurry was filtered through a column of Florisil (25 g, elution with petroleum ether). Evaporation of the solvent from the combined eluate, followed by distillation of the residue (air-bath temperature 40-55°C/0.3 Torr), afforded 1.013 g (76%) of the chloride (100) as a colorless oil; ir (film): 1600, 770, 740 cm⁻¹; ¹H nmr (80
MHz, CDCI3) δ: 0.18 (s, 9H, -SnMe3, J_{Sn-H} = 52 Hz), 1.75 (d, 3H, CH3-CH, J = 7 Hz), 2.75 (broad t, 2H, -CH2-, J = 7 Hz), 3.45 (t, 2H, -CH2Cl, J = 7 Hz), 5.83 (t of q, 1H, olefinic proton, J = 2, 7 Hz, J_{Sn-H} = 76 Hz).

Exact Mass calcd. for C7H1435ClSn (M+CH3): 252.9806; found: 252.9814.

Transmetalation of (E)-5-Chloro-3-trimethylstannyl-2-pentene (100).

Preparation of the Chloro Sulfide (210)

To a cold (-78°C), stirred solution of (E)-5-chloro-3-trimethylstannyl-2-pentene (100) (200 mg, 0.75 mmol) in 2 mL of dry THF was added a solution of methyllithium in ether (0.57 mL, 0.82 mmol). After the light yellow solution had been stirred at -78°C for 20 min, a solution of 2,4-dinitrobenzenesulfenyl chloride (209) (160 mg, 0.91 mmol) in 4 mL of dry methylene chloride was added and the reaction mixture was allowed to warm slowly to room temperature. After 16 h, the solvent was evaporated and the crude product was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 85:15). The yellow solid thus obtained was recrystallized from hexane-acetone. There was obtained 111.3 mg (54%) of the chloro sulfide (210) as a yellow solid, which had mp 128-130°C and exhibited ir (KBr): 3050, 1570, 1500, 1330, 1040, 910, 830, 730 cm⁻¹; ¹H nmr [80 MHz, (CD3)2CO] δ:
1.20-1.40 and 1.52-1.65 (m, m, 3H and 1H, cyclopropyl protons), 1.66 (d, 3H, CH$_3$CH-, $J$ = 7 Hz), 4.38 (q, 1H, CH$_3$CH-, $J$ = 7 Hz), 8.40 (d, 1H, H$_A$, $J_{AB}$ = 10 Hz), 8.54 (d of d, H$_B$, $J_{BX}$ = 2 Hz, $J_{AB}$ = 10 Hz), 8.98 (d, 1H, H$_X$, $J_{BX}$ = 2 Hz). Exact Mass calcd. for C$_{11}$H$_{11}$N$_2$O$_4^{35}$ClS: 302.0129; found: 302.0123.

Transmetalation of (Z)-5-Chloro-3-trimethylstannyl-2-pentene (99).

Preparation of (Z)-5-Chloro-3-(1-hydroxycyclohexyl)-2-pentene (205) and (Z)-4-Ethylidene-1-oxaspiro[4.5]undecane (206)

![Diagram of molecules 205 and 206]

To a cold (-78°C), stirred solution of (Z)-5-chloro-3-trimethylstannyl-2-pentene (99) (133.6 mg, 0.5 mmol) in 2 mL of dry THF was added a solution of methyllithium in ether (0.43 mL, 0.55 mmol). The resulting light yellow solution was stirred at -78°C for 20 min. Cyclohexanone (57 µL, 0.55 mmol) was added and the reaction mixture was stirred at -78°C for 45 min. Saturated aqueous ammonium chloride (0.5 mL) and ether (10 mL) were added and the mixture was allowed to warm to room temperature. The aqueous layer was extracted with ether. The combined organic extract was washed (water, brine), dried (MgSO$_4$), and concentrated. The resulting oil was subjected to flash chromatography on silica gel (10 g, elution with petroleum ether-ether, 93:7).

The less polar product was isolated by removal of the solvent from
the appropriate fractions, followed by distillation (air-bath temperature 40-55°C/0.2 Torr) of the residual material. The colorless oil obtained (33.2 mg, 40%) was identified as the spiro ether (206), which exhibited IR (film): 1060, 910 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ: 1.18-1.80 (m, 13H), 2.35-2.68 (m, 2H, -CCH₂-), 3.75 (t, 2H, -CH₂O-, J = 7 Hz), 5.36 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Exact Mass calcd. for C₁₁H₁₈O: 166.1358; found: 166.1359.

The more polar product was isolated by concentration of the appropriate column fractions, followed by distillation (air-bath temperature 70-85°C/0.2 Torr) of the residual oil. The colorless oil obtained (31.4 mg, 31%) was identified as the alcohol (205), which exhibited IR (film): 3425, 1120, 960 cm⁻¹; ¹H NMR (80 MHz, CDCl₃) δ: 1.05-2.20 (m, 14H), 2.48 (broad t, 2H, -CCH₂-, J = 7 Hz), 3.60 (t, 2H, -CH₂Cl, J = 7 Hz), 5.36 (t of q, 1H, olefinic proton, J = 1, 7 Hz). Exact Mass calcd. for C₁₁H₁₉O₃₅Cl: 202.1126; found: 202.1126.

General Procedure 8: Transmetalation of (Z)-5-Chloro-3-trimethyl-stannyl-2-pentene (99) and Conjugate Addition of the Grignard Reagent (218) to Cyclic Enones (220)

\[ \text{BrMg} \quad 218 \quad \text{O} \quad 220 \quad \text{Cl} \quad 221 \]

To a cold (-78°C), stirred solution of (Z)-5-chloro-3-trimethyl-
stannyl-2-pentene (99) (133.6 mg, 0.5 mmol) in 2 mL of dry THF was added
a solution of methyllithium in ether (0.45 mL, 0.55 mmol). The color-
less solution was stirred at -78°C for 20 min. Anhydrous magnesium
bromide (110.5 mg, 0.6 mmol) was added and the resultant milky solution
was stirred for 10 min. The solution was then diluted by dropwise
addition of 4 mL of dry ether and stirring was continued at -78°C for a
further 10 min. After successive addition of copper bromide-dimethyl-
sulfide complex (30.8 mg, 0.15 mmol), the appropriate cyclic enone (220)
(0.5 mmol), and boron trifluoride-etherate (74 μL, 0.6 mmol), the yellow
solution was stirred at -78°C for 2 h. Saturated aqueous ammonium
chloride (pH 8) (3 mL) and ether (10 mL) were added successively and the
mixture was allowed to warm to room temperature with vigorous stirring.
Stirring was maintained until the aqueous phase became deep blue. The
layers were separated and the aqueous layer was extracted with ether.
The combined ether extract was washed (water, brine), dried (MgSO₄), and
concentrated. The resulting oil was subjected to flash chromatography
on silica gel, if necessary. Distillation of the oil thus obtained
provided the conjugate addition product (221).

Preparation of (Z)-3-[3-(5-Chloro-2-pentenyl)]cyclohexanone (219)
Following general procedure 8, 2-cyclohexen-1-one (216) (48 mg, 0.5 mmol) was converted into the chloro ketone (219). Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 75-90°C/0.2 Torr) of the oil thus obtained, yielded 70.5 mg (70%) of (219) as a colorless oil; ir (film): 1710, 1230, 885, 740 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.63 (broad d, 3H, -CCH₃, J = 7 Hz), 1.67-1.79 (m, 3H), 2.10-2.53 (m, 7H), 2.88-2.98 (m, 1H, H₆A), 3.50-3.63 (m, 2H, =CCH₂CH₂Cl), 5.32 (q, 1H, olefinic proton, J = 7 Hz). Exact Mass calcd. for C₁₁H₁₇O₃Cl: 200.0969; found: 200.0966.

Preparation of (Z)-3-[3-(5-Chloro-2-pentenyl)]-3-methylcyclohexanone (229)

Following general procedure 8, 3-methyl-2-cyclohexen-1-one (223) (55 mg, 0.5 mmol) was converted into the chloro ketone (229). Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 90-105°C/0.2 Torr) of the crude oil thus obtained, afforded 65.1 mg (61%) of (229) as a colorless oil; ir (film): 1705,
1230, 740 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.19 (s, 3H, CH₃C-), 1.72-1.78 (m, 1H), 1.79 (d, 3H, CH₃C-, J = 7 Hz), 1.83-1.92 (m, 2H), 2.07-2.16 (m, 1H), 2.26-2.35 (m, 3H), 2.39-2.53 (m, 2H, -CCH₂-), 2.68 (d, 1H, J = 14 Hz), 3.47-3.57 (m, 2H, -CH₂Cl), 5.38 (q, 1H, olefinic proton, J = 7 Hz). Irradiation at δ 3.52 (-CH₂Cl) simplified the multiplet at δ 2.39-2.53 (-CCH₂-) to a pair of doublets (J = 14 Hz each). Exact Mass calcd. for C₁₂H₁₉O³⁺Cl: 214.1126; found: 214.1125.

Preparation of the Chloro Ketone Mixture (230)

Following general procedure 8, 2-methyl-2-cyclohexen-1-one (224) (48 mg, 0.5 mmol) was converted into the chloro ketone (230). Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 105-120°C/0.3 Torr) of the crude material thus obtained, provided 68.2 mg (64%) of (230) as a colorless oil. This material showed one spot on tlc analysis (petroleum ether-ether, 3:1). The ¹H nmr spectrum indicated that it consisted of a 2:1 mixture of two epimers. This material exhibited ir (film): 1700, 1230, 730 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.90 and 1.06 (d, d, ratio 2:1, 3H, CH₃CH₂, J =
7 Hz each), 1.55-2.66 (m, 12H), 3.02-3.12 (m, 1H, HA), 3.49-3.70 (m, 2H, -CH₂Cl), 5.32-5.48 (m, 1H, olefinic proton). **Exact Mass** calcd. for C₁₂H₁₉O₃5Cl: 214.1126; found: 214.1127.

**Preparation of (Z)-3-[3-(5-Chloro-2-pentenyl)]cyclopentanone (231)**

![Chemical Structure](image)

Following general procedure 8, 2-cyclopenten-1-one (225) (41 mg, 0.5 mmol) was converted into the chloro ketone (231). Normal workup, followed by flash chromatography on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 85-100°C/0.3 Torr) of the oil thus obtained afforded 63.9 mg (69%) of (231) as a colorless oil; ir (film): 1730, 1160, 740 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.69 (broad d, 3H, CH₃C-), J = 7 Hz), 1.72-1.85 (m, 1H), 2.01-2.50 (m, 7H), 3.25-3.35 (m, 1H, HA), 3.50-3.59 (m, 2H, -CH₂Cl), 5.42 (q, 1H, olefinic proton, J = 7 Hz). **Exact Mass** calcd. for C₁₀H₁₅O₃5Cl: 186.0813; found: 186.0816.
Preparation of (Z)-3-[3-(5-Chloro-2-pentenyl)]-3-methylcyclopentanone (232)

Following general procedure 8, 3-methyl-2-cyclopenten-1-one (226) (46.6 mg, 0.5 mmol) was converted into the chloro ketone (232). Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 85-95°C/0.2 Torr) of the oil thus obtained, provided 56.9 mg (57%) of (232) as a colorless oil; ir (film): 1730, 1165, 745 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.22 (s, 3H, CH\(_3\)-CH\(_2\)-), 1.73 (d, 3H, CH\(_3\)-), 2.11-2.18 (m, 2H), 2.25-2.33 (m, 2H), 2.45 (s, 2H, O-C-CH\(_2\)-C-), 2.48-2.55 (m, 2H), 3.57 (t, 2H, -CH\(_2\)Cl, \(J = 7\) Hz), 5.34 (q, 1H, olefinic proton, \(J = 7\) Hz). Exact Mass calcd. for C\(_{11}\)H\(_{17}\)O\(^{35}\)Cl: 200.0969; found: 200.0966.

Preparation of the Chloro Ketone Mixture (233)
Following general procedure 8, 2-methyl-2-cyclopenten-1-one (227) \(^{117}\) (46.6 mg, 0.5 mmol) was converted into the chloro ketone mixture (233). Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 90-100°C/0.2 Torr) of the crude oil thus obtained, afforded 56.4 mg (56%) of (233) as a colorless oil. This material showed one spot on tlc analysis (petroleum ether-ether, 3:1). The \(^1\)H nmr spectrum indicated that it consisted of a 1:1 mixture of two epimers. This material exhibited ir (film): 1725, 1155, 735 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.92 and 1.00 (d, d, ratio 1:1, 3H, CH\(_3\)CH-, \(\ integrated\) 7 Hz each), 1.65 and 1.68 (d, d, ratio 1:1, 3H, CH\(_3\)C-, \(\ integrated\) 7 Hz each), 1.70-2.49 (m, 7H), 2.85 and 3.45 (d of t and q, ratio 1:1, 1H, H\(_A\), \(\ integrated\) 6, 11 Hz and 8 Hz), 3.50-3.63 (m, 2H, -CH\(_2\)Cl), 5.45 and 5.52 (q, q, ratio 1:1, 1H, olefinic proton, \(\ integrated\) 7 Hz each). Exact Mass calcd. for C\(_{11}\)H\(_{17}\)O\(_3\)Cl: 200.0969; found: 200.0963.

Preparation of cis, (Z)-1-[3-(5-Chloro-2-pentenyl)]bicyclo[3.3.0]-octan-3-one (234)

Following general procedure 8, bicyclo[3.3.0]oct-1-en-3-one (228) \(^{118}\) (61 mg, 0.5 mmol) was converted into the chloro ketone (234).
Normal workup, followed by flash chromatography of the crude product on silica gel (10 g, elution with petroleum ether-ether, 3:1) and distillation (air-bath temperature 115-130°C/0.3 Torr) of the oil thus obtained, provided 81.3 mg (72%) of (234) as a colorless oil; ir (film): 1725, 1170, 745 cm\(^{-1}\); \(\text{H}^\text{nmr}\) (400 MHz, CDCl\(_3\)) \(\delta:\) 1.43-1.58 (m, 3H), 1.69 (d, 3H, CH\(_3\)C=, \(J = 7\) Hz), 1.65-1.78 (m, 1H), 1.92-2.04 (m, 3H), 2.10 (d of d, 1H, \(J = 5, 18\) Hz), 2.46-2.59 (m, 4H), 2.84-2.91 (m, 1H), 3.46-3.57 (m, 2H, -CH\(_2\)Cl), 5.36 (q, 1H, olefinic proton, \(J = 7\) Hz). Exact Mass calcd. for C\(_{13}\)H\(_{19}\)O\(^{35}\)Cl: 226.1126; found: 226.1121.

General Procedure 9: Cyclization of the Chloro Ketones (221).

Preparation of the (Z)-Ethylidenecyclopentane Annulation Products

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222

To a stirred suspension of potassium hydride (30 mg, 0.75 mmol) in 2 mL of dry THF was added, dropwise, a solution of the appropriate chloro ketone (221) (0.30 mmol) in 1 mL of dry THF. The resultant yellow mixture was stirred at room temperature for 2.5 h. Saturated aqueous ammonium chloride (3 mL) and ether (8 mL) were added and the mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted thoroughly with ether. The combined ether extract was washed (water, brine) and dried (MgSO\(_4\)). Solvent removal
under reduced pressure, followed by distillation of the residual oil, afforded the corresponding annulated product (222).

Preparation of cis,(Z)-7-ethylidenebicyclo[4.3.0]nonan-2-one (217)

Following general procedure 9, the chloro ketone (219) (60.2 mg, 0.3 mmol) was converted into the bicyclic ketone (217). Normal workup, followed by distillation (air-bath temperature 45-60°C/0.2 Torr) of the crude product, afforded 38.3 mg (78%) of (217) as a colorless oil; ir (film): 1700, 1230, 890 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.40 (d of q, 1H, J = 4, 13 Hz), 1.64 (t of d, 3H, CH₃C=, J = 1.5, 7 Hz), 1.72 (d of d of q, 1H, J = 4, 5, 13 Hz), 1.83-2.05 (m, 4H), 2.25-2.55 (m, 4H), 2.62-2.70 (m, 1H, H_B), 3.00-3.06 (m, 1H, H_A), 5.29 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Irradiation at δ 2.66 (H_B): signal at δ 3.03 (H_A) simplified to a d of d (J = 6, 13 Hz), multiplet at δ 1.83-2.05 simplified. Irradiation at δ 3.03 (H_A): signal at δ 2.66 (H_B) simplified to a d of d (J = 8, 9 Hz), signal at δ 1.40 simplified to a d of t (J = 4, 13 Hz), multiplet at δ 1.83-2.05 simplified. In a difference nuclear Overhauser enhancement (nOe) experiment, irradiation at δ 3.03 (H_A) caused signal enhancement at δ 2.66 (H_B) and at δ 1.64 (CH₃C=). Exact Mass calcd. for C₁₁H₁₆O: 164.1202; found: 164.1196.
Preparation of cis, (Z)-6-Methyl-7-ethylidenebicyclo[4.3.0]nonan-2-one (235)

Following general procedure 9, the chloro ketone (229) (64.2 mg, 0.3 mmol) was converted into the bicyclic ketone (235). Normal workup, followed by distillation (air-bath temperature 45-60°C/0.2 Torr) of the crude product, provided 41.9 mg (79%) of (235) as a colorless oil; ir (film): 1700, 1240 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.32 (s, 3H, CH₃C-), 1.67 (t of d, 3H, CH₃CH=, J = 2, 7 Hz), 1.70-1.79 (m, 2H), 1.83-2.05 (m, 4H), 2.25-2.32 (m, 1H), 2.36-2.45 (m, 4H), 5.28 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Exact Mass calcd. for C₁₂H₁₈O: 178.1358; found: 178.1358.
Preparation of cis, (Z)-6-Methyl-7-ethylidenebicyclo[4.3.0]nonan-2-one (235) from the Bicyclic Acetate (248)

To a stirred solution of potassium carbonate (264 mg, 1.6 mmol) in 4 mL of aqueous methanol was added a solution of the enantiomerically pure bicyclic acetate (248)\(^{80}\) (88.8 mg, 0.4 mmol) in 2 mL of methanol. The resulting clear solution was stirred at room temperature for 24 h. The solution was diluted with water and extracted thoroughly with ether. The combined extract was washed (water, brine) and dried (MgSO\(_4\)). Solvent removal and distillation (air-bath temperature 80-90°C/0.4 Torr) of the residual oil, afforded 63.3 mg (88%) of the alcohol (249) as a colorless oil; \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.90 (s, 3H, CH\(_3-C\)), 1.09-1.78 (m, 10H), 1.82-1.90 (m, 1H), 1.99-2.08 (m, 1H), 2.13-2.30 (m, 2H), 2.38-2.48 (m, 1H), 3.64 (d of t, 1H, -CHOH, J = 5, 11 Hz), 5.14 (t of q, 1H, olefinic proton, J = 2, 7 Hz).

To a stirred solution-suspension of pyridinium chlorochromate (PCC) (97 mg, 0.45 mmol) and sodium acetate (7.4 mg, 0.09 mmol) in 2 mL of dry methylene chloride was added a solution of the bicyclic alcohol (249) (54
mg, 0.3 mmol) in 0.5 mL of dry CH₂Cl₂. The black reaction mixture was stirred at room temperature for 2 h. Dry ether (10 mL) was added and the supernatant was decanted from the black gum. The latter residue was stirred with a further 5 mL of dry ether and the organic solution was again decanted. The combined organic solution was passed through a short column of Florisil (3 g, elution with ether). The combined eluate was concentrated to afford a clear pale yellow oil. This oil was distilled (air-bath temperature 50-65°C/0.2 Torr) to afford 42.0 mg (79%) of (250) as a colorless oil; ¹H nmr (400 MHz, CDCl₃) δ: 0.88 (s, 3H, CH₃C-), 1.61-1.85 (m, 5H), 1.89-2.15 (m, 3H), 2.22-2.34 (m, 3H), 2.37-2.48 (m, 2H), 2.60 (d of d, 1H, H₆, J = 6, 12 Hz), 5.21 (t of q, 1H, olefinic proton, J = 2, 7 Hz).

A mixture of 1% aqueous potassium hydroxide (1 mL) and ethanol (15 mL) was stirred for 5 min. To 5 mL of this solution was added a solution of the bicyclic ketone (250) (25 mg, 0.14 mmol) in 0.5 mL of ethanol. The resulting clear solution was stirred at room temperature for 3.5 h. The solution was diluted with water and extracted thoroughly with ether. The combined extract was washed (water, brine) and dried (MgSO₄). Solvent removal and distillation (air-bath temperature 50-60°C/0.2 Torr) of the residual oil gave 19.7 mg (79%) of a colorless oil. This compound was spectrally identical with the annulation product (235); ir (film): 1700, 1240 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.32 (s, 3H, CH₃C-), 1.67 (t of d, 3H, CH₃C-), J = 2, 7 Hz), 1.70-1.79 (m, 2H), 1.83-2.05 (m, 4H), 2.25-2.32 (m, 1H), 2.36-2.45 (m, 4H), 5.28 (t of q, 1H, olefinic proton, J = 2, 7 Hz).
Preparation of the Bicyclic Alcohols (251) and (252)

To a cold (0°C), stirred solution of the bicyclic ketone (235) (178 mg, 1 mmol) in 15 mL of dry methanol was added a solution of sodium borohydride (45.5 mg, 1.2 mmol) in 2 mL of dry methanol. After the resulting solution had been stirred at 0°C for 15 min, glacial acetic acid (1 mL) and ether (25 mL) were added. The layers were separated and the aqueous layer was extracted with ether. The combined organic extract was washed (aqueous NaHCO₃, water, brine), dried (MgSO₄) and concentrated under reduced pressure. The crude oil thus obtained was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 85:15).

The less polar product was isolated by removal of the solvent from the appropriate fractions, followed by distillation (air-bath temperature 55-70°C/0.2 Torr) of the residual material. There was thus obtained 54.7 mg (30%) of the alcohol (251) as a colorless oil which exhibited ir (film): 3300, 1020 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.20 (s, 3H, CH₃-), 1.26-1.53 (m, 6H), 1.65 (t of d, CH₃C=, J = 2, 7 Hz), 1.60-1.90 (m, 3H), 2.09-2.14 (m, 1H), 2.38-2.44 (m, 2H), 3.40-2.48 (m, 1H, -CH₂OH-), 5.25 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Exact Mass calcd. for C₁₂H₂₀O: 180.1515; found: 180.1513.

The more polar product was isolated by concentration of the appro-
appropriate column fractions, followed by distillation (air-bath temperature 75-90°C/0.2 Torr) of the residual oil. There was obtained 92.1 mg (51%) of compound (252) as a white solid. Recrystallization of this material from heptane provided a crystalline compound which exhibited mp 83.5-84°C; ir (KBr): 3300, 1020 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.32 (s, 3H, CH₃C-), 1.26-1.44 (m, 3H), 1.52-1.75 (m, 9H), 2.00-2.06 (m, 1H), 2.28-2.44 (m, 2H), 3.92-3.98 (m, 1H, -CH₃OH-), 5.21 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Irradiation at δ 3.95 simplified the signal at δ 2.03 to a d of d (J = 6, 12 Hz); the multiplets at δ 1.26-1.44 and δ 1.52-1.75 were also changed. The constitution and relative stereochemistry of (252) was confirmed by an X-ray crystallographic study. Exact Mass calcd. for C₁₂H₂₀O: 180.1515; found: 180.1512. Anal. calcd. for C₁₂H₂₀O: C, 80.00; H, 11.11; found: C, 79.70; H, 11.26.

Preparation of cis,(Z)-1-Methyl-7-ethylidenebicyclo[4.3.0]nonan-2-one (236)

Following general procedure 9, the chloro ketone mixture (230) (64.2 mg, 0.3 mmol) was converted into the bicyclic ketone (236). Normal workup, followed by distillation (air-bath temperature 45-60°C/0.2 Torr) of the crude product, provided 44.0 mg (83%) of 236 as a
colorless oil; ir (film): 1710, 1440 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\):
1.06 (s, 3H, CH\(_3\)C-), 1.40-1.50 (m, 2H), 1.64 (t of d, CH\(_3\)C=, \(J = 2, 7\) Hz), 1.71 (t of q, 1H, \(J = 5, 12\) Hz), 1.80-1.88 (m, 1H), 1.92-2.00 (m, 1H), 2.09-2.17 (m, 1H), 2.31-2.42 (m, 2H), 2.43-2.54 (m, 2H), 2.63 (d of d, 1H, \(J = 5, 12\) Hz), 5.29 (t of q, 1H, olefinic proton, \(J = 2, 7\) Hz).

Exact Mass calcd for C\(_{12}\)H\(_{18}\)O: 178.1358; found: 178.1359.

Preparation of cis,\((Z)\)-6-Ethylidenebicyclo[3.3.0]octan-2-one (237)

Following general procedure 9, the chloro ketone (231) (56 mg, 0.3 mmol) was converted into the bicyclic ketone (237). Normal workup, followed by distillation (air-bath temperature 40-50°C/0.2 Torr) of the crude product, provided 35.0 mg (78%) of (237) as a colorless oil; ir (film): 1730, 1130 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.68 (t of d, 3H, CH\(_3\)C=, \(J = 1.5, 7\) Hz), 1.75-1.95 (m, 3H), 2.15-2.37 (m, 5H), 2.64-2.71 (m, 1H), 3.32-3.40 (m, 1H), 5.36 (t of q, 1H, olefinic proton, \(J = 1.5, 7\) Hz). Exact Mass calcd for C\(_{10}\)H\(_{14}\)O: 150.1045; found: 150.1044.
Preparation of \textit{cis},(Z)-5-Methyl-6-ethylidenebicyclo[3.3.0]octan-2-one (238)

Following general procedure 9, the chloro ketone (232) (60.2 mg, 0.3 mmol) was converted into the bicyclic ketone (238). Normal workup, followed by distillation (air-bath temperature 40-50°C/0.2 Torr) of the crude product, afforded 42.4 mg (86%) of (238) as a colorless oil; ir (film): 1730, 1140 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.30 (s, 3H, CH\(_3\)C-), 1.74 (t of d, 3H, CH\(_3\)C-, \(J\) = 2, 7 Hz), 1.81-1.88 (m, 2H), 1.92-2.01 (m, 1H), 2.18-2.29 (m, 3H), 2.34-2.43 (m, 3H), 5.36 (broad q, 1H, olefinic proton, \(J\) = 7 Hz). \textit{Exact Mass} calcd for C\(_{11}\)H\(_{16}\)O: 164.1202; found: 164.1202.

Preparation of \textit{cis},(Z)-1-Methyl-6-ethylidenebicyclo[3.3.0]octan-2-one (239)

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Preparation of \textit{cis},(Z)-5-Methyl-6-ethylidenebicyclo[3.3.0]octan-2-one (238)

Following general procedure 9, the chloro ketone (232) (60.2 mg, 0.3 mmol) was converted into the bicyclic ketone (238). Normal workup, followed by distillation (air-bath temperature 40-50°C/0.2 Torr) of the crude product, afforded 42.4 mg (86%) of (238) as a colorless oil; ir (film): 1730, 1140 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.30 (s, 3H, CH\(_3\)C-), 1.74 (t of d, 3H, CH\(_3\)C-, \(J\) = 2, 7 Hz), 1.81-1.88 (m, 2H), 1.92-2.01 (m, 1H), 2.18-2.29 (m, 3H), 2.34-2.43 (m, 3H), 5.36 (broad q, 1H, olefinic proton, \(J\) = 7 Hz). \textit{Exact Mass} calcd for C\(_{11}\)H\(_{16}\)O: 164.1202; found: 164.1202.

Preparation of \textit{cis},(Z)-1-Methyl-6-ethylidenebicyclo[3.3.0]octan-2-one (239)
Following general procedure 9, the chloro ketone mixture (233) (60.2 mg, 0.3 mmol) was converted into the bicyclic ketone (239). Normal workup, followed by distillation (air-bath temperature 45-60°C/0.2 Torr) of the crude product, afforded 38.9 mg (79%) of (239) as a colorless oil; ir (film): 1725, 1105 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.11 (s, 3H, CH₃C-), 1.41-1.49 (m, 1H), 1.66 (broad d, 3H, CH₃C-, J = 7 Hz), 1.69-1.79 (m, 1H), 1.87-1.94 (m, 1H), 2.14-2.39 (m, 5H), 2.88-2.94 (m, 1H), 5.35 (broad q, 1H, olefinic proton, J = 7 Hz). Exact Mass calcd. for C₁₁H₁₆O: 164.1202; found: 164.1200.

Preparation of the Tricyclic Ketone (240)

Following general procedure 9, the chloro ketone (234) (68 mg, 0.3 mmol) was converted into the tricyclic ketone (240). Normal workup, followed by distillation (air-bath temperature 65-80°C/0.2 Torr) of the crude product, afforded 48.3 mg (85%) of (240) as a colorless oil; ir (film): 1725, 1135 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.39-1.47 (m, 1H), 1.70-1.80 (m, 6H), 1.89-2.00 (m, 2H), 2.10-2.23 (m, 4H), 2.28-2.35 (m, 2H), 2.50 (d of d, 1H, Hₐ, J = 9, 18 Hz), 2.75-2.82 (m, 1H), 5.37 (t of q, 1H, olefinic proton, J = 2, 7 Hz). Exact Mass calcd. for C₁₃H₁₈O: 190.1358; found: 190.1358.
Preparation of trans,(Z)-4-Isopropyl-3-[3-(5-chloro-2-pentenyl)]
cyclohexanone (306)

Following general procedure 8, 4-isopropyl-2-cyclohexen-1-one (305) (690 mg, 5 mmol) was converted into the chloro ketone (306). Fractional distillation of the crude material obtained on workup gave initially a small amount of the starting enone (305), followed by 845.1 mg (70%) of the chloro ketone (306) (air-bath temperature 140-155°C/0.3 Torr), as a colorless oil; {\textit{ir}} (film): 1710, 1200, 730 cm\(^{-1}\); \(^1{}\text{H} \text{nmr (400 MHz, CDCl}_3\text{)}\)
\[\delta: \ 0.72 \text{ and } 0.96 (d, d, 3H each, -CHMe}_2\text{, } J = 7 \text{ Hz each}), \ 1.44 (d of q, 1H, } J = 4.5, 13 \text{ Hz}), 1.64 (t of d, 3H, CH}_3\text{C=, } J = 1.5, 7 \text{ Hz}), \ 1.67-1.78 \text{ (m, 2H), 1.98-2.05 (m, 1H), 2.17 (d of d of d, 1H, } H_B\text{, } J = 2.5, 4.5, 13 \text{ Hz), 2.30-2.49 (m, 5H), 2.89 (d of t, 1H, } H_A\text{, } J = 4.5, 12 \text{ Hz), 3.55-3.65 (m, 2H, -CH}_2\text{Cl), 5.36 (q, 1H, olefinic proton, } J = 7 \text{ Hz}). \] Irradiation at \(\delta 2.17 \text{ (} H_B\text{)}\) simplified the signal at \(\delta 2.89 \text{ (} H_A\text{)}\) to a t (\( J = 12 \text{ Hz}) \) and modified the multiplets at \(\delta 2.30-2.49\) and \(\delta 1.98-2.05\). \textit{Exact Mass calcd. for C}_{14}H_{23}O_{35}Cl: 242.1449; found: 242.1444.\]
Preparation of the Bicyclic Ketone (307)

Following general procedure 9, the chloro ketone (306) (824.5 mg, 3.4 mmol) was converted into the bicyclic ketone (307). Normal workup, followed by distillation (air-bath temperature 70-80°C/0.2 Torr) of the crude product, afforded 644.5 mg (92%) of (307) as a colorless oil; ir (film): 1705, 1245 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.86 and 0.98 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.43-1.53 (m, 2H), 1.63 (q of d, 3H, CH₃C=, J = 1.5, 7 Hz), 1.84-2.01 (m, 4H), 2.22-2.37 (m, 2H), 2.49-2.58 (m, 2H), 2.63 (broad q, 1H, H₆, J = 7 Hz), 2.88 (broad d of d, 1H, H₆, J = 7, 10 Hz), 5.33 (t of q, 1H, olefinic proton, J = 1.5, 7 Hz). Irradiation at δ 2.88 (H₆): signal at δ 2.63 (H₆) simplified to a broad t (J = 7 Hz), multiplets at δ 2.49-2.58 and δ 1.43-1.53 also changed. Irradiation at δ 2.63 (H₆): δ 2.88 (H₆) simplified to a broad d (J = 10 Hz), multiplets at δ 2.22-2.33 and δ 2.49-2.58 also changed. In a difference nuclear Overhauser enhancement (nOe) experiment, irradiation at δ 2.88 (H₆) caused signal enhancement at δ 2.63 (H₆), δ 1.63 (CH₃C=) and at δ 0.86 (-CHMe-). Exact Mass calcd. for C₁₄H₂₂O: 206.1672; found: 206.1666.
Preparation of the Ketal (311)

To a stirred solution of the bicyclic ketone (307) (1.00 g, 4.85 mmol) in 55 mL of benzene was added successively ethanediol (903.9 mg, 14.55 mmol) and pyridinium p-toluenesulfonate (365.5 mg, 1.46 mmol). The mixture was refluxed under a Dean-Stark water trap for 2.5 h. Benzene was removed under reduced pressure and 60 mL of ether was added to the residue. The resultant mixture was washed (saturated aqueous sodium bicarbonate, brine) and dried (MgSO\textsubscript{4}). Solvent removal under reduced pressure and distillation (air-bath temperature 115-125°C/0.3 Torr) of the residual oil afforded 1.140 g (94%) of (311) as a colorless oil; \textit{ir} (film): 1440, 1145, 1105 cm\textsuperscript{-1}; \textit{\textsuperscript{1}H nmr} (400 MHz, CDCl\textsubscript{3}) \delta: 0.84 and 0.90 (d, d, 3H each, \textit{-CHMe\textsubscript{2}}, \textit{J} = 7 Hz each), 1.11 (t of t, 1H, \textit{H\textsubscript{Z}}, \textit{J} = 3, 11 Hz), 1.33 (d of q, 1H, \textit{J} = 4, 11 Hz), 1.55-1.85 (m, 9H), 2.00-2.09 (m, 1H, \textit{H\textsubscript{B}}), 2.14-2.23 (m, 1H), 2.41-2.50 (m, 1H), 2.61 (d of d, 1H, \textit{H\textsubscript{A}}, \textit{J} = 7, 11 Hz), 3.94 (broad s, 4H, \textit{-OCH\textsubscript{2}CH\textsubscript{2}O-}), 5.24 (q, 1H, olefinic proton, \textit{J} = 7 Hz). Irradiation at \textit{\delta} 2.61 (\textit{H\textsubscript{A}}): signal at \textit{\delta} 2.00-2.09 (\textit{H\textsubscript{B}}) simplified to a broad t (\textit{J} = 8 Hz), signal at \textit{\delta} 1.11 (\textit{H\textsubscript{Z}}) simplified to a t of d (\textit{J} = 3, 11 Hz). Irradiation at \textit{\delta} 2.04 (\textit{H\textsubscript{B}}): signal at \textit{\delta} 2.61 (\textit{H\textsubscript{A}}) simplified to a d (\textit{J} = 11 Hz), the multiplet at \textit{\delta}
1.55-1.85 was also simplified. Exact Mass calcd. for C₁₆H₂₆O₂:
250.1934; found: 250.1938.

Preparation of the Tricyclic Alcohol (308)

To a cold (0°C), stirred solution of the ketal (311) (500 mg, 2.0 mmol) in 8 mL of dry THF was added, dropwise, borane-methyl sulfide complex (300 μL, 3.0 mmol). The resulting colorless solution was stirred at 0°C for 30 min and at room temperature for 3.5 h. Sufficient water was added to quench the excess borane. Aqueous 3M sodium hydroxide (1.0 mL, 3.0 mmol) was added slowly to this solution. After the solution had been cooled to 0°C, 30% hydrogen peroxide (1.0 mL, 8.8 mmol) was added dropwise and the resulting solution was heated at 40-50°C for 1 h. Saturated aqueous ammonium chloride (4 mL) and ether (10 mL) were added and the layers were separated. The aqueous layer was extracted thoroughly with petroleum ether-ether, 1:1. The combined organic extract was washed (water, brine), dried (MgSO₄), and concentrated. The resulting oil was subjected to flash chromatography on silica gel (28 g, elution with petroleum ether-ether 11:9).
The major, less polar product was isolated by removal of the solvent from the appropriate fractions, followed by distillation (air-bath temperature 148-158°C/0.3 Torr) of the residue. The colorless oil thus obtained (444.2 mg, 83%) was identified as the tricyclic alcohol (308); ir (film): 3450, 1380, 1120 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.79 and 0.94 (d, d, 3H each, -CH\(_2\)Me, \(\jmath = 7\) Hz each), 1.20 (d, 3H, -CH(OH)Me, \(\jmath = 7\) Hz), 1.25-1.36 (m, 1H), 1.49 (t of t, 1H, H\(_Z\), \(\jmath = 3\), 11 Hz), 1.59-1.85 (m, 8H), 1.89-1.96 (m, 1H, H\(_Y\)), 2.13 (d of d of d, H\(_A\), \(\jmath = 7\), 8, 11 Hz), 2.24-2.31 (m, 1H), 2.99 (broad s, 1H, exchanges with D\(_2\)O, -OH), 3.90-3.99 (m, 4H, -OCH\(_2\)CH\(_2\)O-), 3.99-4.05 (m, 1H, H\(_M\)). Irradiation at \(\delta\) 4.02 (H\(_M\)): multiplet at \(\delta\) 1.89-1.96 (H\(_Y\)) simplified to a q (\(\jmath = 8\) Hz), d at \(\delta\) 1.20 (-CH(OH)Me) simplified to a s. Irradiation at \(\delta\) 1.92 (H\(_Y\)): the multiplet at \(\delta\) 3.99-4.05 (H\(_M\)) simplified to a q (\(\jmath = 7\) Hz), the multiplet at \(\delta\) 2.24-2.31 changed and the signal at \(\delta\) 2.13 (H\(_A\)) became a d of d (\(\jmath = 7\), 11 Hz). Irradiation at \(\delta\) 2.13 (H\(_A\)): the multiplet at \(\delta\) 1.89-1.96 (H\(_Y\)) changed and the signal at \(\delta\) 1.49 (H\(_Z\)) became a t of d (\(\jmath = 3\), 11 Hz). Exact Mass calcd. for C\(_{13}\)H\(_{28}\)O\(_3\): 268.2039; found: 268.2033.

The minor, more polar product was isolated by concentration of the appropriate column fractions, followed by distillation (air-bath temperature 150-160°C/0.3 Torr) of the residual crude material. The colorless oil thus obtained (20.3 mg, 4%), was identified as the tricyclic alcohol (312); ir (film): 3450, 1370, 1100 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.89 and 0.94 (d, d, 3H each, -CH\(_2\)Me, \(\jmath = 7\) Hz each), 1.05 (t of t, 1H, H\(_Z\), \(\jmath = 3\), 11 Hz), 1.18 (d, 3H, -CH(OH)Me, \(\jmath = 7\) Hz), 1.26-1.38 (m, 2H), 1.52-1.64 (m, 5H), 1.77-1.89 (m, 5H), 1.99 (d of d, 1H, \(\jmath \))
- 6, 11 Hz), 3.64-3.71 (m, 1H, H_M), 3.88-4.00 (m, 4H, -OCH_2CH_2O-).

Exact Mass calcd. for C_{16}H_{28}O_3: 268.2039; found: 268.2043.

Preparation of the Hydroxy Ketone Mixture (309) and (313)

A stirred solution of the ketal (308) (402 mg, 1.5 mmol) in 13.5 mL of acetone containing 1.5 mL of water and pyridinium p-toluenesulfonate^96 (113 mg, 0.45 mmol) was refluxed for 2 h. Most of the solvent was removed under reduced pressure and 45 mL of ether was added to the residue. The resultant mixture was washed with aqueous sodium bicarbonate and brine and then was dried (MgSO_4). Removal of the solvent under reduced pressure gave 311.5 mg (93%) of a yellow oil. Analysis of this material by glc indicated that it consisted of a 2:1* mixture of (309) and (313) respectively.

A solution of sodium methoxide (0.42 mmol) in 2 mL of dry methanol was added to a stirred solution of the crude product in 3 mL of dry methanol. The yellow solution was stirred at room temperature for 3.5 h. Saturated aqueous ammonium chloride (2 mL) and ether (10 mL) were

* This ratio varied slightly from experiment to experiment.
added. The aqueous layer was extracted thoroughly with ether. The combined organic extract was washed (brine), dried (MgSO₄), and concentrated. Distillation (air-bath temperature 140-150°C/0.3 Torr) of the residual oil afforded 269.8 mg (80%) of a colorless oil which was a 3:1 mixture of the hydroxy ketones (309) and (313); ir (film): 3450, 1700, 1370, 1110 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.79 and 0.92 (d, d, ratio 3:1, 3H, -CHMe₂, J = 7 Hz each), 1.00 and 1.02 (d, d, ratio 1:3, 3H, -CHMe₂, J = 7 Hz each), 1.15 and 1.17 (d, d, ratio 1:3, 3H, -CH(OH)Me, J = 7 Hz each), 1.05-2.55 (m, 13H), 2.69-2.76 and 2.99-3.07 (m, m, ratio 1:3, 1H), 3.90-3.97 and 4.19-4.27 (m, m, ratio 1:3, 1H, -CH(OH)Me).

Exact Mass calcd. for C₁₄H₂₄O₂: 224.1777; found: 224.1774.

Preparation of the Olefinic Alcohol (310)

A stirred suspension of sodium hydride (74 mg, 3 mmol) in 12 mL of dry dimethyl sulfoxide was heated at 80°C for 35 min, during which time hydrogen evolution ceased. The resulting solution of methylsulfinyl carbanion₉⁷ was cooled to room temperature and a solution of methyltriphenylphosphonium bromide (1.11 g, 3.1 mmol) in 5 mL of dry DMSO was added by syringe. The yellow slurry of the ylide was stirred for 10 min at room temperature and a solution of the 3:1 mixture of ketols (309)
and (313), respectively, (224 mg, 1 mmol) in 5 mL of dry DMSO was added. After the resulting solution had been stirred at room temperature for 16 h, it was poured into ice-water and the mixture was extracted thoroughly with pentane. The combined extract was washed (1:1 dimethyl sulfoxide-water, water, and brine), dried (MgSO₄), and concentrated. The residual yellow oil was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ether, 4:1).

The major, less polar product was isolated by removal of the solvent from the appropriate fractions, followed by distillation (air-bath temperature 75-90°C/0.1 Torr) of the remaining oil. The colorless oil thus obtained (167.9 mg, 76%) was identified as the olefinic alcohol (310), which exhibited IR (film): 3350, 1635, 890 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.76 and 0.97 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.00 (d, 1H, exchanges with D₂O, -OH, J = 6 Hz), 1.05 (d of q, 1H, Hₓ, J = 4, 11 Hz), 1.14 (d, 3H, -CH(OH)CH₃, J = 7 Hz), 1.20 (d of t, 1H, Hₐ, J = 8, 11 Hz), 1.49 (broad t, 1H, J = 8 Hz), 1.65-2.03 (m, 8H), 2.30-2.39 (m, 2H, Hₐ and Hₜ), 4.15-4.22 (m, 1H, Hₘ), 4.51 (d, 1H, olefinic proton, J = 2 Hz), 4.61 (d, 1H, olefinic proton, J = 2 Hz). Irradiation at δ 2.34 (Hₐ, Hₜ): signal at 1.05 (Hₓ) simplified to a q (J = 11 Hz), signal at δ 1.20 (Hₐ) simplified to a d of d (J = 8, 11 Hz), multiplet at δ 1.65-2.03 was also changed. Irradiation at δ 4.19 (Hₘ): signal at δ 1.14 (-CH(OH)CH₃) simplified to a s, signal at δ 1.00 (-OH) became a s, multiplet at δ 1.65-2.03 was simplified. Exact Mass calcd. for C₁₅H₂₅O: 222.1985; found: 222.1981.

The minor, more polar product was isolated by concentration of the appropriate column fractions, followed by distillation (air-bath tem-
perature 80-90°C/0.1 Torr) of the remaining crude material. The colorless oil thus obtained (9.7 mg, 4%) was identified as the olefinic alcohol (314); ir (film): 3350, 1635, 880 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.79 and 0.93 (d, d, 3H each, -CHMe\(_2\), \(J = 7\) Hz each), 1.12-1.19 (m, 1H), 1.20 (d, 3H, -CH(OH)Me, \(J = 7\) Hz), 1.31-1.39 (m, 2H), 1.63-1.85 (m, 6H), 1.92-1.99 (m, 1H, H\(Y\)), 2.06 (d of d of d, 1H, H\(A\), \(J = 7, 8, 10\) Hz), 2.14-2.33 (m, 2H), 2.65-2.71 (m, 1H, H\(B\)), 3.92-4.00 (m, 1H, H\(M\)), 4.69 (broad s, 1H, olefinic proton), 4.71 (broad s, 1H, olefinic proton). Irradiation at \(\delta 3.96\) (H\(M\)): signal at \(\delta 1.92-1.99\) (H\(Y\)) simplified to a q (\(J = 8\) Hz), \(\delta 1.20\) (-CH(OH)Me) became a s. Irradiation at \(\delta 2.68\) (H\(B\)): signal at \(\delta 2.06\) (H\(A\)) simplified to a d of d (\(J = 7, 10\) Hz), multiplet at \(\delta 1.63-1.85\) was also changed. \textbf{Exact Mass} calcd. for C\(_{17}\)H\(_{26}\)O: 222.1985; found: 222.1983.

\begin{center}
\textbf{Preparation of (±)-3-\textit{epi}-Anhydro-oplopanone (315)}
\end{center}

To a stirred solution-suspension of pyridinium chlorochromate (PCC) (233 mg, 1.08 mmol) in 2 mL of dry methylene chloride was added a solution of the olefinic alcohol (310) (120 mg, 0.54 mmol) in 2 mL of dry
CH₂C₁₂. The black reaction mixture was stirred at room temperature for 2 h, 10 mL of dry ether was added, and the supernatant was decanted from the black gum. The latter material was stirred with a further 10 mL of dry ether and the ether solution was again decanted. The combined organic solution was passed through a short column of Florisil (8 g, elution with ether). The combined eluate was concentrated to afford a clear pale yellow oil. Distillation (air-bath temperature 100-115°C/0.3 Torr) of the crude oil afforded 110.7 mg (93%) of (315) as a colorless oil; IR (film): 3060, 1710, 1645, 885 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.76 and 0.90 (d, d, 3H each, -CHMe₂, /= 7 Hz each), 0.98 (d of q, 1H, Hₓ,  /= 4, 12 Hz), 1.27 (d of t, 1H, Hₐ,  /= 7, 12 Hz), 1.54-1.77 (m, 4H), 1.81 (t of t, 1H, H₂,  /= 3, 12 Hz), 1.87-1.94 (m, 1H), 1.98-2.07 (m, 2H), 2.17 (s, 3H, CH₃C⁻), 2.33 (t of d, 1H, Hc,  /= 4, 13 Hz), 2.46-2.57 (m, 1H, Hₜ), 3.15 (d of d of d, 1H, Hy,  /= 4, 7, 9 Hz), 4.53 (d, 1H, olefinic proton,  /= 2 Hz). Irradiation at δ 3.15 (Hy): signal at δ 1.27 (Hₐ) simplified to a t (/= 12 Hz) and the multiplet at δ 1.98-2.07 was changed. Irradiation at δ 2.52 (Hₜ): multiplet at δ 1.87-1.94 simplified to a t (/= 9 Hz) and the signal at δ 1.27 (Hₐ) became a d of d (/= 7, 12 Hz). Irradiation at δ 1.27 (Hₐ): δ 3.15 (Hy) simplified to a d of d (/= 4, 9 Hz), δ 2.46-2.57 (Hₜ) became a broad t (/= 9 Hz), and δ 1.81 (H₂) changed into a t of d (/= 3, 12 Hz). Irradiation at δ 0.98 (Hₓ): δ 2.33 (Hc) simplified to a d of d (/= 4, 13 Hz) and δ 1.81 (H₂) changed into a t of d (/= 3, 12 Hz). In a difference nuclear Overhauser enhancement (nOe) experiment, irradiation at δ 1.27 (Hₐ) caused signal enhancement at δ 3.15 (Hy), δ 0.98 (Hₓ) and δ 0.76 (-CHMe₂). Exact mass
Preparation of (±)-Anhydro-oplopanone (258)

A solution of sodium methoxide (0.17 mmol) in 2 mL of dry methanol was added to a stirred solution of the olefinic ketone (315) (98 mg, 0.45 mmol) in 2 mL of dry methanol. The yellow solution was stirred at 60°C for 24 h. The solution was cooled to room temperature and 2 mL of saturated aqueous ammonium chloride and 10 mL of ether were added. The aqueous layer was extracted with ether. The combined organic extract was washed (brine), dried (MgSO₄) and concentrated. Analysis of the crude product by glc indicated that it consisted of a 93:7 mixture of (±)-anhydro-oplopanone (258) and the starting epimeric ketone (315). Recrystallization of this mixture from petroleum ether provided 81.4 mg (83%) of pure (258) which exhibited mp 68°C; ir (CHCl₃): 3060, 1705, 1645, 885 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.66 and 0.91 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.11 (d of q, 1H, Hₓ, J = 4, 11 Hz), 1.27 (t of t, 1H, H₂, J = 3, 11 Hz), 1.50-1.76 (m, 5H), 1.81 (d of d of d, 1H, Hₜ, J = 5, 7, 11 Hz), 1.87-2.04 (m, 3H), 2.18 (s, 3H, CH₃C-), 2.37 (d of d
of $d$, 1H, $H_C$, $\delta = 3, 4, 13$ Hz), 2.71 ($d$ of $t$, 1H, $\delta = 5, 11$ Hz), 4.57 ($d$, 1H, olefinic proton, $\delta = 2$ Hz), 4.67 ($d$, 1H, olefinic proton, $\delta = 2$ Hz). Irradiation at $\delta$ 2.71 ($H_Y$): multiplets at $\delta$ 1.50-1.76 and $\delta$ 1.87-2.04 simplified. Irradiation at $\delta$ 2.37 ($H_C$): the signal at $\delta$ 1.11 ($H_X$) simplified to a $q$ ($\delta = 11$ Hz) and multiplet at $\delta$ 1.87-2.04 was changed. Irradiation at $\delta$ 1.27 ($H_Z$): the signal at $\delta$ 1.11 ($H_X$) became a $d$ of $t$ ($\delta = 4, 11$ Hz), and multiplet at $\delta$ 1.50-1.76 simplified. $^{13}$C nmr (75.6 MHz, CDCl$_3$) $\delta$: 15.7 ($q$), 22.0 ($q$), 26.6 ($t$), 27.4 ($t$), 28.5 ($t$), 28.9 ($q$), 29.6 ($d$), 35.3 ($t$), 49.3 ($d$), 51.8 ($d$), 52.1 ($d$), 56.1 ($d$), 103.6 ($t$), 150.9 ($s$), 211.7 ($s$). The chemical shifts and the multiplicities reported above were derived from the proton noise decoupled and the off-resonance decoupled $^{13}$C nmr spectra, respectively. Exact Mass calcd. for C$_{15}$H$_{24}$O: 220.1828; found: 220.1828. These spectral data are in agreement with those reported for (-)-anhydro-oplopanone.

Preparation of the Epoxy Alcohol (320)

\begin{center}
\includegraphics[width=0.3\textwidth]{epoxy_alcohol.png}
\end{center}

A stirred solution-suspension of sodium hydride (28.8 mg, 1.2 mmol) in 2 mL of dry DMSO was heated at 80°C for 35 min, during which time
hydrogen evolution ceased. The resulting solution of methylsulfinyl carbanion was cooled to room temperature, diluted with 4 mL of dry THF, and then was cooled with an ice-salt bath. A solution of trimethylsulfonium iodide \(^{119}\) (244.8 mg, 1.2 mmol) in 3 mL of dry DMSO was added over a period of three minutes. After the solution had been stirred for an additional minute, a solution of the 3:1 mixture of the ketols (309) and (313), respectively, (89.6 mg, 0.4 mmol) in 3 mL of dry DMSO was added in one single portion and stirring was continued at ice-salt temperature for 30 min and then for 8 h with the bath removed. Saturated aqueous ammonium chloride (3 mL) and pentane (15 mL) were added successively and the aqueous layer was extracted thoroughly with ether. The combined extract was washed (water, brine), dried (MgSO\(_4\)), and concentrated. The residual oil was subjected to flash chromatography on silica gel (10 g, elution with petroleum ether-ether, 2:1). Concentration of the appropriate column fractions gave a pale yellow solid, which was recrystallized from petroleum ether to afford 65.6 mg (69\%) of white, needle shaped crystals (mp 92.5-93°C) of the epoxide (320); \(\text{IR (CHCl}_3\) : 3590, 3350, 3000, 1240, 900 cm\(^{-1}\); \(\text{H NMR (300 MHz, CDCl}_3\) \(\delta: 0.81\) and 0.97 (d, d, 3H each, \(-\text{CHMe}_2\), \(J = 7\) Hz each), 1.14 (d, 3H, \(-\text{CH(OH)}\text{Me}, J = 7\) Hz), 1.10-1.72 (m, 10 H), 1.80-2.05 (m, 3H), 2.30 (d of t, 1H, \(H_A\), \(J = 8, 11\) Hz), 2.57 and 2.66 (d, d, 1H each, AB pair of doublets, epoxide protons, \(J = 5\) Hz each), 4.16 (broad q, 1H, \(H_M\), \(J = 7\) Hz). \(\text{Exact Mass} \text{ calcd. for } C_{15}H_{26}O_2: 238.1934; \text{ found: 238.1935.}\)
Preparation of the Diol (321)

To a cold (0°C), stirred solution-suspension of lithium aluminum hydride (6 mg, 0.15 mmol) in 2 mL of dry ether was added a solution of the epoxy alcohol (320) (33.7 mg, 0.14 mmol) in 2 mL of dry ether. The reaction mixture was stirred at room temperature for 1 h. Normal workup (as outlined in general procedure 7), followed by distillation (air-bath temperature 95-110°C/0.3 Torr) of the crude product, afforded 30.95 mg (91%) of (321) as a glassy, low melting solid. This material exhibited ir (CHCl₃): 3600, 3450, 1370, 880 cm⁻¹; ¹H nmr (300 MHz, CDCl₃) 6: 0.81 and 0.93 (d, d, 3H each, -CHMe₂, J = 7 Hz), 1.13 (d, 3H, -CH(OH)Me, J = 7 Hz), 1.18 (s, 3H, CH₃C-), 1.20-2.05 (m, 15H), 4.11 (broad q, 1H, -CH(OH)Me, J = 7 Hz). Exact Mass calcd. for C₁₄H₂₅O₂ (M⁺-CH₃): 225.1856; found: 225.1859.
Preparation of the Hydroxy Ketone (322)

![Structure of compound 322](image)

To a stirred solution-suspension of PCC (52.6 mg, 0.24 mmol) and sodium acetate (5.0 mg, 0.06 mmol) in 2 mL of dry methylene chloride was added a solution of the diol (321) (29.3 mg, 0.12 mmol) in 2 mL of dry CH$_2$Cl$_2$. The black reaction mixture was stirred at room temperature for 2 h, 10 mL of dry ether was added, and the supernatant solution was decanted from the black gum. The latter material was stirred with a further 10 mL of dry ether and the organic solution was again decanted. The combined organic solution was passed through a short column of Florisil (3 g, elution with ether). The combined eluate was concentrated to obtain a pale yellow oil. Distillation (air-bath temperature 95-110°C/0.3 Torr) afforded 26.5 mg (91%) of (322) as a colorless oil; ir (film): 3450, 1700, 1360 cm$^{-1}$; $^1$H nmr (300 MHz, CDCl$_3$) $\delta$: 0.82 and 0.89 (d, d, 3H each, -CHMe$_2$, $J = 7$ Hz each), 1.08 (broad s, exchanges with D$_2$O, 1H, -OH), 1.20 (s, 3H, CH$_3$C(OH)-), 1.16-2.00 (m, 12H), 2.16 (s, 3H, CH$_3^-$), 3.14 (d of d of d, 1H, H$_Y$, $J = 4$, 7, 9 Hz). **Exact Mass** calcd. for C$_{15}$H$_{26}$O$_2$: 238.1934; found: 238.1922.
Preparation of (±)-8-epi-Oplopanone (323)

A solution of sodium methoxide (0.04 mmol) in 0.5 mL of dry methanol was added to a stirred solution of the ketol (322) (22.5 mg, 0.095 mmol) in 2 mL of dry methanol. The yellow solution was stirred at 60° C for 24 h. The solution was cooled to room temperature and 1 mL of saturated ammonium chloride and 5 mL of ether were added. The aqueous layer was extracted with ether. The combined organic extract was washed (brine), dried (MgSO₄), and concentrated. Analysis of the crude product by glc indicated that it consisted of a 93:7 mixture of (±)-8-epi-oplopanone (323) and the starting epimeric ketol (322). The yellow oil was subjected to flash chromatography on silica gel (6 g, elution with petroleum ether-ether, 11:9). Removal of the solvent from the appropriate fractions, followed by recrystallization of the residue from hexane-ether, afforded 18.8 mg (84%) of pure (323) which exhibited mp 62° C; IR (CHCl₃): 3590, 3450, 1705, 1465, 1390, 1375, 1360 cm⁻¹; H (nmr) (400 MHz, CDCl₃) 6: 0.72 and 0.90 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.07 (t of t, 1H, Hz, J = 3, 11 Hz), 1.22 (s, 3H, CH₃C(0H)-), 1.29-1.37 (m, 4H), 1.43-1.63 (m, 4H), 1.70-1.77 (m, 2H), 1.94 (d of d of d, 1H, H₈, J = 4, 8, 11 Hz), 2.02 (q, 1H, HA, J = 11 Hz), 2.19 (s, 3H, CH₃C⁻)
2.60 (d of t, 1H, H_y, J = 5, 11 Hz). Irradiation at δ 2.60 (H_y): δ 2.02 (H_A) simplified to a t (J = 11 Hz), multiplet at δ 1.43-1.63 was also simplified. Irradiation at δ 1.07 (H_z): δ 2.02 (H_A) simplified to a t (J = 11 Hz), multiplets at δ 1.29-1.37, δ 1.43-1.63 and 1.70-1.77 were also changed. \(^{13}\)C nmr (75.6 MHz, CDCl\(_3\)) δ: 15.8 (q), 20.7 (t), 21.9 (q), 24.5 (t), 28.2 (q), 28.7 (t), 29.0 (q), 29.7 (d), 40.0 (t), 44.8 (d), 49.4 (d), 55.7 (d), 56.1 (d), 70.4 (s), 212.1 (s). The chemical shifts and the multiplicities reported above were derived from the proton noise decoupled and the off-resonance decoupled \(^{13}\)C nmr spectra, respectively. Exact Mass calcd. for C\(_{15}\)H\(_{26}\)O\(_2\): 238.1934; found: 238.1929.

Preparation of the Epoxy Alcohol (324)

To a stirred solution of the olefinic alcohol (310) (53.5 mg, 0.24 mmol) in 3 mL of DMSO and 1 mL of water was added N-bromosuccinimide (NBS) (85.8 mg, 0.48 mmol) in one portion. After 45 min, the reaction mixture was treated with 2 mL of saturated aqueous sodium bicarbonate and 2 mL of water. The resulting mixture was extracted thoroughly with
ether and the combined ether extract was washed (water, brine), dried (MgSO₄), and concentrated to afford a clear pale yellow liquid which was used directly in the next reaction.

The above product, a mixture of bromohydrins, was stirred vigorously for 1.5 h with a suspension of potassium carbonate (66.6 mg, 0.48 mmol) in 3 mL of methanol. The reaction mixture was diluted with water and extracted with ether. The ether extract was washed (water, brine), dried (MgSO₄), and concentrated to give a pale yellow liquid. This liquid was subjected to flash chromatography on silica gel (12 g, elution with petroleum ether-ether, 7:3).

The minor, less polar product was isolated by removal of solvent from the appropriate fractions, followed by recrystallization of the residue from petroleum ether. The long, needle-shaped crystals thus obtained (6.6 mg, 12%), exhibited spectra and mp identical with those of the epoxy alcohol (320).

The major, more polar product was obtained by concentration of the appropriate column fractions followed by recrystallization of the residue from petroleum ether. The substance thus obtained as long, needle-shaped crystals (36.1 mg, 63%) was identified as the epoxy alcohol (324) which exhibited mp 91°C; ir (CHCl₃): 3590, 3450, 3040, 840 cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: 0.79 and 0.98 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.14 (d, 3H, CH₃CH(OH)-, J = 7 Hz), 1.18-1.45 (m, 4H), 1.58-2.05 (m, 9H), 2.34 (d of t, 1H, H_A, J = 7, 11 Hz), 2.48 (d, 1H, H_G, J = 5 Hz), 2.86 (d of d, 1H, H_F, J = 2, 5 Hz), 4.16 (broad q, 1H, H_M, J = 7 Hz). Exact Mass calcd. for C₁₅H₂₆O₂: 238.1934; found: 238.1933.
Preparation of the Diol (316)

To a cold (0°C), stirred solution-suspension of lithium aluminum hydride (6 mg, 0.15 mmol) in 2 mL of dry ether was added a solution of the epoxy alcohol (324) (33.3 mg, 0.14 mmol) in 2 mL of dry ether. The reaction mixture was stirred at room temperature for 1 h. Normal workup (as outlined in general procedure 7), followed by recrystallization of the white solid from petroleum ether-ether, gave 32.2 mg (96%) of (316) in the form of needle shaped crystals which exhibited mp 117-118°C; ir (CHCl₃): 3590, 3400, 1370, 1120, 890 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.78 and 0.94 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.07 (d of q, 1H, J = 4, 11 Hz), 1.08 (s, 3H, CH₃C(OH)-), 1.12 (d, 3H, CH₃CH(OH)-, J = 7 Hz), 1.24-1.41 (m, 4H), 1.51 (t of t, 1H, J = 3, 11 Hz), 1.60-2.00 (m, 8H), 4.11 (d of q, 1H, -CH(OH)Me, J = 1, 7 Hz). Exact Mass calcd. for C₁₄H₂₅O₂ (M⁺-CH₃): 225.1856; found: 225.1852.
Preparation of (±)-3-epi-Oplopanone (326)

![Chemical Structure](image)

To a stirred solution-suspension of PCC (50.5 mg, 0.23 mmol) in 2 mL of dry methylene chloride was added a solution of the diol (316) (28.1 mg, 0.12 mmol) in 2 mL of dry CH₂Cl₂. The black reaction mixture was stirred at room temperature for 2 h, 10 mL of dry ether was added, and the supernatant solution was decanted from the black gum. The latter material was stirred with a further 10 mL of dry ether and the ether layer was again decanted. The combined organic solution was passed through a short column of Florisil (3 g, elution with ether). The combined eluate was concentrated and distilled (air-bath temperature 85-95°C/0.2 Torr) to afford 26.2 mg (94%) of (326) as a white solid which exhibited mp 68°C; ir (CHCl₃): 3590, 3450, 1700, 1385, 1370, 1360 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.79 and 0.89 (d, d, 3H each, -CHMe₂, J - 7 Hz each), 1.01 (d of q, 1H, Hₓ, J = 4, 11 Hz), 1.09 (s, 3H, CH₃C(OH)⁻), 1.33-1.49 (m, 4H), 1.57-1.73 (m, 4H), 1.77 (t of d, 1H, Hₐ, J - 3, 13 Hz), 1.83-2.00 (m, 2H), 2.08 (d of t, 1H, Hₐ, J = 7, 11 Hz), 2.16 (s, 3H, CH₃(­)), 3.13 (d of d of d, 1H, Hₚ, J = 4, 7, 9 Hz). **Exact Mass** calcd. for C₁₅H₂₆O₂: 238.1934; found: 238.1945.
Preparation of (±)-Oplopanone (257)

A solution of sodium methoxide (0.04 mmol) in 0.5 mL of dry methanol was added to a stirred solution of the ketol (326) (10 mg, 0.042 mmol) in 2 mL of dry methanol. The yellow solution was stirred at 40-45°C for 36 h. The solution was cooled to room temperature and 1 mL of saturated ammonium chloride and 3 mL of ether were added. The aqueous layer was extracted with ether. The combined organic extract was washed (brine), dried (MgSO₄), and concentrated. Analysis of the crude solid by glc indicated that it consisted of a 94:6 mixture of (±)-oplopanone (257) and the starting epimeric ketol (326). Fractional crystallization of the pale yellow solid from hexane-ether provided 8.43 mg (84%) of needle-shaped crystals (mp 99-100°C) of (±)-oplopanone (257), which exhibited IR (CHCl₃): 3590, 3450, 1710, 1465, 1385, 1370, 1360 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.70 and 0.90 (d, d, 3H each, -CHMe₂, J = 7 Hz each), 1.04-1.17 (m, 2H), 1.20 (s, 3H, CH₃C(OH)-), 1.35-1.63 (m, 7H), 1.77-1.87 (m, 3H), 1.96 (broad q, 1H, H₆, J = 11 Hz), 2.19 (s, 3H, CH₃C-), 2.66 (d of d of d, 1H, H₇, J = 6, 9, 11 Hz). ¹³C nmr (75.6 MHz, CDCl₃) δ: 15.6 (q), 20.3 (q), 22.0 (q), 23.0 (t), 25.3 (t), 28.6 (t), 29.6 (q), 29.7 (d), 42.1 (t), 46.7 (d), 49.5 (d), 55.8
(d), 57.0 (d), 73.1 (s), 211.5 (s). The chemical shifts and the multiplicities reported above were derived from the proton noise decoupled and the off-resonance decoupled $^{13}$C nmr spectra, respectively. Exact Mass calcd. for C$_{15}$H$_{26}$O$_2$: 238.1934; found: 238.1932. Compound (257) exhibited tlc properties and spectra [$^1$H nmr (400 MHz), ir] in agreement with those reported for (-)-oplopanone. Also, the mp of our synthetic material was very close to those reported (101.5-102°C$_{90}$, 97-98°C$_{91}$) for (±)-(257).

General Procedure 10: Preparation of 1-Alkyn-3-ols (108)

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

To a cold (-78°C), stirred solution of acetylene (≈ 1.6 g, 60 mmol) in 100 mL of dry THF was added a solution of n-butyllithium in hexane (35.3 mL, 55 mmol) over a 10 min period. The resulting pale yellow solution was stirred at -78°C for 15 min and a solution of the appropriate aldehyde (50 mmol) in 8 mL of dry THF was added dropwise over a 5 min period. Stirring was continued at -78°C for 30 min and then for 1 h with the bath removed. Water (40 mL) was added, followed by anhydrous potassium carbonate until the aqueous phase became pasty. The organic phase was decanted and the aqueous layer was extracted thoroughly with ether. The combined organic extract was dried (MgSO$_4$) and concentrated. The remaining oil was distilled under reduced pressure to afford the
corresponding ethynyl carbinol (108).

Preparation of 1-Nonyn-3-ol (332)

Following general procedure 10, heptanal (328) (5.71 g, 50 mmol) was converted into 1-nonyn-3-ol. Normal workup, followed by distillation (air-bath temperature 85-95°C/17 Torr) of the crude oil, afforded 4.86 g (69%) of (332) as a colorless oil; ir (film): 3312, 2200, 1125, 628 cm⁻¹; ¹H nmr (300 MHz, CDC₁₃) δ: 0.90 (t, 3H, CH₃CH₂-, J = 7 Hz), 1.20-1.50 (m, 8H), 1.60-1.85 (m, 3H), 2.47 (broad s, 1H, =CH), 4.34 (broad s, 1H, -CHOH). Exact Mass calcd for C₉H₁₆O: 140.1202; found: 140.1194.

Preparation of 1-Cyclopropyl-2-propyn-1-ol (335)

Following general procedure 10, cyclopropanecarbaldehyde (331) (1.0 g, 14.3 mmol) was allowed to react with a solution of monolithium acetylde (16 mmol) in 40 mL of dry THF. Distillation
(air-bath temperature 35-50°C/19 Torr) of the oil obtained after workup afforded 1.014 g (74%) of (335) as a colorless oil; ir (film): 3305, 3086, 2116, 1030, 652 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.40-0.63 (m, 4H), 1.18-1.30 (m, 1H, cyclopropyl methine proton), 2.06 (broad s, 1H, exchanges with D₂O, -OH), 2.43 (d, 1H, =CH, J = 3 Hz), 4.20 (d of d, 1H, -CH(OH), J = 3, 7 Hz). Exact Mass calcd. for C₉H₁₁O (M⁺-H): 95.0497; found: 95.0494.

Preparation of 5-Methoxymethoxy-1-pentyn-3-ol (333)

Following general procedure 10, 3-(methoxymethoxy)propanal (329)* (5.9 g, 50 mmol) was converted into 5.371 g (75%) of the carbinol (333) (air-bath distillation temperature 90-100°C/17 Torr) as a colorless oil; ir (film): 3290, 2114, 1151, 1039, 667 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 2.00 (q, 2H, -CH₂CH₂O-, J = 7 Hz), 2.48 (d, 1H, =CH, J = 2 Hz), 3.05 (d, 1H, exchanges with D₂O, -OH, J = 7 Hz), 3.40 (s, 3H, -OCH₃), 3.78 (broad t, 2H, -CH₂CH₂O-, J = 7 Hz), 4.45-4.60 (m, 1H, -CH(OH)), 4.65 (s, 2H, -OCH₂O-). Exact Mass calcd. for C₇H₁₁O₃ (M⁺-H): 143.0708; found: 143.0706.

* We are grateful to Mr. Peter Marrs for a generous supply of (329).
Preparation of 6-Hepten-1-yn-3-ol (334)

![Chemical Structure](image)

Following general procedure 10, 4-pentenal (330)\(^{121}\) (1.0 g, 12 mmol) was allowed to react with a solution of monolithium acetylide (18 mmol) in 40 mL of dry THF. Distillation (air-bath temperature 45-65°C/19 Torr) of the crude product obtained after workup provided 964.9 mg (74%) of (334) as a colorless oil; ir (film): 3304, 3079, 2116, 1642, 1025, 916, 655 cm\(^{-1}\); ^1H nmr (80 MHz, CDCl\(_3\)) \(\delta\): 1.75-1.95 (m, 2H, -CH\(_2\)CH(0H)-), 2.12-2.32 (m, 3H), 2.48 (d, 1H, =CH, \(J = 2\) Hz), 4.40 (d of t, 1H, -CH(OH)-, \(J = 2, 7\) Hz), 5.01 (t of d, 1H, HA, \(J = 1, 10\) Hz), 5.07 (t of d of d, 1H, HB, \(J = 1, 17\) Hz), 5.85 (t of d of d of d, 1H, HX, \(J = 7, 10, 17\) Hz). Exact Mass calcd. for C\(_7\)H\(_9\)O (M\(^+\)-H): 109.0654; found: 109.0657.

General Procedure 11: Addition of the (Trimethylstannyl)copper Reagent (84) to 1-Alkyn-3-ols (108) in the Presence of Methanol. Preparation of 2-Trimethylstannyl-1-alken-3-ols (109) and (E)-1-Trimethylstannyl-1-alken-3-ols (339)

![Chemical Structures](image)

To a cold (-78°C), stirred solution of the (trimethylstannyl)copper
reagent (84) (3 mmol) in 24 mL of dry THF was added a THF solution (1 mL) of the appropriate 1-alkyn-3-ol (108) (2 mmol) followed by anhydrous methanol (4.05 mL, 100 mmol). The dark red solution was stirred at -78°C for 2.5 h and at 0°C for 1 h. Saturated aqueous ammonium chloride (pH 8) (5 mL) and ether (20 mL) were added and the mixture was allowed to warm to room temperature with vigorous stirring. Stirring was maintained until the aqueous phase became deep blue and the organic phase became clear. The layers were separated and the aqueous phase was extracted thoroughly with ether. The combined organic solution was washed with saturated aqueous ammonium chloride (pH 8), dried (MgSO₄), and concentrated. Subjection of the residue to flash chromatography on silica gel, concentration of the appropriate fractions and bulb-to-bulb distillation of the crude products thus obtained afforded the corresponding 2-trimethylstannyl-1-alken-3-ol (109) and (E)-1-trimethylstannyl-1-alkene-3-ol (339).

General Procedure 12: Addition of the (Trimethylstannyl)zinc Reagent (355) or (356) to 1-Alkyn-3-ols in the Presence of Cuprous Cyanide.

Preparation of 2-Trimethylstannyl-1-alken-3-ols (109) and/or (E)-1-Trimethylstannyl-1-alken-3-ols (339)

\[
\text{[Me}_3\text{SnZn(}-\text{Bu})_2\text{]} \text{Li} \quad \text{[Me}_3\text{SnZnEt}_2\text{]} \text{Li}
\]

355 356

Solid cuprous cyanide (3.6 mg, 0.04 mmol) and a THF (1.5 mL)
solution of the appropriate 1-alkyn-3-ol (108) (1 mmol) were added successively to a cold (-20°C), stirred solution of the (trimethylstannyl)zinc reagent (355) or (356) (2 mmol) in 10 mL of dry THF. The resulting orange solution was stirred at -20°C for 1 h and at 0°C for 1 h. Saturated aqueous ammonium chloride (pH 8) (4 mL) and ethyl acetate (15 mL) were added and the mixture was allowed to warm to room temperature with vigorous stirring. Stirring was maintained until the aqueous phase became deep blue and the organic phase became clear. The layers were separated and the aqueous phase was extracted thoroughly with ethyl acetate. The combined organic extract was washed (water, brine), dried (MgSO₄), and concentrated. Subjection of the residue to flash chromatography on silica gel, concentration of the appropriate fractions and distillation of the crude products thus obtained provided the corresponding 2-trimethylstannyl-1-alken-3-ol (109) and (E)-1-trimethylstannyl-1-alkene-3-ol (339).

Preparation of 3-Trimethylstannyl-3-buten-2-ol (337) and (E)-4-Trimethylstannyl-3-buten-2-ol (338)

\[ \text{337} \quad \text{Me}_3\text{Sn} \]
\[ \text{338} \quad \text{SnMe}_3 \]

a) **Via** General Procedure 11, Reagent (84) (Me₃SnCuMe₂S)

Following general procedure 11, 3-butyn-2-ol (336) (140 mg, 2 mmol)
was converted into a mixture of the vinylstannanes (337) and (338). The
crude mixture was subjected to flash chromatography on silica gel (18 g,
elution with petroleum ether-ethyl acetate, 19:1). The major, less
polar product was isolated by removal of solvent from the appropriate
fractions, followed by distillation (air-bath temperature 65-75°C/17
Torr) of the residue. The colorless oil thus obtained (244.2 mg, 52%)
was identified as the olefinic alcohol (337); ir (film): 3353, 3040,
1067, 923, 770 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 0.20 (s, 9H, -SnMe₃,
J_{Sn-H} = 54 Hz), 1.25 (d, 3H, CH₃CH-, J = 7 Hz), 1.62 (d, 1H, exchanges
with D₂O, -OH, J = 6 Hz), 4.30-4.55 (m, 1H, -CH(OH)-), 5.20 (d of d, 1H,
Hₐ, J = 2, 3 Hz, J_{Sn-H} = 72 and 79 Hz). Exact Mass calcd. for C₆H₁₃OSn (M⁺-CH₃): 220.9989; found: 221.0001.

The minor, more polar product was obtained by distillation (air-
bath temperature 80-90°C/17 Torr) of the oil derived from concentration
of the appropriate column fractions. This material (81.4 mg, 17%), a
colorless oil, was identified as the alcohol (338); ir (film): 3339,
1605, 1059, 989, 769 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 0.15 (s, 9H,
-SnMe₃, J_{Sn-H} = 56 Hz), 1.25 (d, 3H, -CH₃, J = 7 Hz), 1.83 (broad s, 1H,
exchanges with D₂O, -OH), 4.10-4.35 (m, 1H, -CH(OH)-), 5.85-6.37 (m, 2H,
olefinic protons, J_{Sn-H} = 72 and 79 Hz). Exact Mass calcd. for C₆H₁₃OSn
(M⁺-CH₃): 220.9989; found: 220.9990.
b) Via General Procedure 12, Reagent (355) \([(\text{Me}_3\text{SnZn(t-Bu)}_2)\text{Li}]\)

Following general procedure 12, 3-butyn-2-ol (336) (70 mg, 1 mmol) was allowed to react with the (trimethylstannyl)zinc reagent (355) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol). Workup, product separation, and distillations as described above yielded 129.3 mg (55%) of (337) and 28.4 mg (12%) of (338). These materials exhibited \text{ir} and $^1\text{H}$ nmr spectra identical with those described above.

c) Via General Procedure 12, Reagent (356) \([(\text{Me}_3\text{SnZnEt}_2)\text{Li}]\)

General procedure 12 was followed. Thus, treatment of 3-butyn-2-ol (336) (70 mg, 1 mmol) with the (trimethylstannyl)zinc reagent (356) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 18.9 mg (8%) of (337) and 152.9 mg (65%) of (338). The identity of these materials was confirmed by analysis (glc and tlc) and spectra (ir, $^1\text{H}$ nmr).
Preparation of 2-Trimethylstannyl-1-nonen-3-ol (340) and (E)-1-Trimethylstannyl-1-nonen-3-ol (344)

\[
\begin{align*}
&\text{Me}_3\text{Sn} \quad \text{H}_A \\
n-C_6\text{H}_3 \quad \text{H}_X \quad \text{OH} \\
&\text{SnMe}_3 \quad \text{H}_M \\
n-C_6\text{H}_3 \quad \text{OH}
\end{align*}
\]

a) Via General Procedure 11, Reagent (84) (Me$_3$SnCu.Me$_2$S)

Following general procedure 11, 1-nonyl-3-ol (332) (280 mg, 2 mmol) was converted into a mixture of the vinylstannanes (340) and (344). The crude mixture was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 19:1).

The major, less polar product was purified by distillation (air-bath temperature 75-90°C/0.2 Torr) of the residual material derived from concentration of the appropriate column fractions. This material (262.9 mg, 43%), a colorless oil, was identified as the olefinic alcohol (340); ir (film): 3373, 1039, 925, 769 cm$^{-1}$; $^1$H nmr (270 MHz, CDCl$_3$) δ: 0.18 (s, 9H, -SnMe$_3$, J$_{Sn-H}$ = 54 Hz), 0.87 (broad t, 3H, CH$_3$CH$_2$-, J = 7 Hz), 1.23-1.33 (m, 7H), 1.38-1.60 (m, 3H), 4.16-4.25 (m, 1H, -CH(OH)-), 5.23 (d of d, 1H, H$_A$, J = 2, 2 Hz, J$_{Sn-H}$ = 71 Hz), 5.73 (d of d, 1H, H$_X$, J = 2, 2 Hz, J$_{Sn-H}$ = 145 Hz). **Exact Mass** calcd. for $C_{11}H_{23}OSn$ (M$^+$-CH$_3$): 291.0771; found: 291.0752.

The minor, more polar product was obtained by removal of solvent from the appropriate fractions, followed by distillation (air-bath temperature 80-95°C/0.2 Torr) of the residual material. The colorless oil obtained (135.6 mg, 22%) was identified as the olefinic alcohol
(344); ir (film): 3338, 990, 769 cm\(^{-1}\); \(^1\)H nmr (270 MHz, CDCl\(_3\)) \(\delta\): 0.15 (s, 9H, -SnMe\(_3\), \(J_{\text{Sn-H}}\) = 56 Hz), 0.87 (broad t, 3H, CH\(_3\)CH\(_2\)-, \(J = 7\) Hz), 1.25-1.35 (m, 7H), 1.47-1.54 (m, 3H), 4.02-4.08 (m, 1H, -CH(OH)-), 6.01 (d of d, 1H, \(H_L\), \(J = 5\), 19 Hz, \(J_{\text{Sn-H}}\) = 73 Hz), 6.18 (d of d, 1H, \(H_M\), \(J = 1\), 19 Hz, \(J_{\text{Sn-H}}\) = 81 Hz). Exact Mass calcd. for C\(_{11}\)H\(_{23}\)OSn (M\(^+\)-CH\(_3\)):
291.0771; found: 291.0771.

b) Via General Procedure 12, Reagent (355) ([Me\(_3\)SnZn(t-Bu)\(_2\)]Li)

General procedure 12 was followed. Thus, treatment of 1-nonyl-3-ol (332) (140 mg, 1 mmol) with the (trimethylstannyl)zinc reagent (355) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 161.5 mg (53%) of (340) and 53.4 mg (17%) of (344). These materials were identified on the basis of their glc and tlc properties and their spectra (ir and \(^1\)H nmr).

c) Via General Procedure 12, Reagent (356) ([Me\(_3\)SnZnEt\(_2\)]Li)

General procedure 12 was followed. Thus treatment of 1-nonyl-3-ol (332) (140 mg, 1 mmol) with the (trimethylstannyl)zinc reagent (356) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 3.9 mg (1%) of (340) and 192.7 mg (63%) of (344). These
materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, $^1$H nmr).

Preparation of 1-Cyclopropyl-2-trimethylstannyl-2-propen-1-ol (343) and (E)-1-Cyclopropyl-3-trimethylstannyl-2-propen-1-ol (347)

![Diagram](image)

343

347

a) Via General Procedure 11, Reagent (84) ($\text{Me}_3\text{SnCuMe}_2\text{S}$)

Following general procedure 11, 1-cyclopropyl-2-propyn-1-ol (335) (192 mg, 2 mmol) was converted into a mixture of the vinylstannanes (343) and (347). The crude mixture was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 9:1).

The major, less polar product was purified by distillation (air-bath temperature 45-55°C/0.2 Torr) of the residual material derived from concentration of the appropriate fractions. This material (183.0 mg, 35%), a colorless oil, was identified as the olefinic alcohol (343); ir (film): 3413, 3080, 3006, 1028, 925, 770 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 0.20 (s, 9H, $-\text{SnMe}_3$, $J_{\text{Sn-H}} = 52$ Hz), 0.24-0.30 (m, 1H), 0.36-0.42 (m, 1H), 0.52-0.60 (m, 2H), 0.92-1.01 (m, 1H), 1.68 (s, 1H, exchanges with D$_2$O, -OH), 3.48 (d of d of d, 1H, $-\text{CH(OH)}$-, $J = 1$, 1, 8 Hz), 5.26 (d of d, 1H, $H_A$, $J = 1$, 2 Hz, $J_{\text{Sn-H}} = 71$ Hz), 5.83 (d of d, 1H, $H_X$, $J = 1$, 2
Hz, J_{Sn-H} = 143 Hz). \textbf{Exact Mass} calcd. for C_{8}H_{15}OSn (M^{+}-CH_{3}): 247.0144; found: 247.0147.

The minor, more polar product was obtained by removal of solvent from the appropriate fractions, followed by distillation (air-bath temperature 55-65°C/0.2 Torr) of the residual material. The colorless oil obtained (151.6 mg, 29%) was identified as the olefinic alcohol (347); ir (film): 3337, 3080, 1024, 990, 764 cm\(^{-1}\); \(^{1}\)H nmr (400 MHz, CDC\(_{3}\)) \(\delta\): 0.10 (s, 9H, -SnMe\(_{3}\), J_{Sn-H} = 56 Hz), 0.24-0.38 (m, 2H), 0.51-0.60 (m, 2H), 0.92-1.03 (m, 1H), 1.65 (d, 1H, exchanges with D\(_{2}\)O, -OH, J = 6 Hz), 3.42-3.50 (m, 1H, -CH(OH)-), 6.09 (d of d, 1H, H\(_{L}\), J = 5, 19 Hz, J_{Sn-H} = 72 Hz), 6.25 (d of d, 1H, H\(_{M}\), J = 1, 19 Hz, J_{Sn-H} = 80 Hz). \textbf{Exact Mass} calcd. for C_{8}H_{15}OSn (M^{+}-CH_{3}): 247.0144; found: 247.0140.

b) \textbf{Via} General Procedure 12, Reagent (355) ([Me_{3}SnZn(t-Bu)_{2}]Li)

General procedure 12 was followed. Thus treatment of 1-cyclopropyl-2-propyn-1-ol (335) (96 mg, 1 mmol) with the (trimethylstannyl)-zinc reagent (355) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 100.3 mg (38%) of (343) and 89.1 mg (34%) of (347). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, \(^{1}\)H nmr).
c) Via General Procedure 12, Reagent (356) [(Me₃SnZnEt₂)Li]

General procedure 12 was followed. Thus treatment of 1-cyclopropyl-2-propyn-1-ol (335) (96 mg, 1 mmol) with the (trimethylstannyl)-zinc reagent (356) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 26.9 mg (10%) of (343) and 151.2 mg (58%) of (347). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, ¹H nmr).

Preparation of 5-Methoxymethoxy-2-trimethylstannyl-1-penten-3-ol (341) and (E)-5-Methoxymethoxy-1-trimethylstannyl-1-penten-3-ol (345)

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{H}^\text{A} \\
\text{MOMOCH}_2\text{CH}_2 & \quad \text{H}^\text{x} \\
\text{OH} & \\
341 \\
\text{Me}_3\text{Sn}^\text{SnMe}_3 & \\
\text{MOMOCH}_2\text{CH}_2 & \quad \text{H}^\text{L} \\
\text{OH} & \quad \text{H}^\text{M} \\
345
\end{align*}
\]

a) Via General Procedure 11, Reagent (84) (Me₃SnCu.Me₂S)

Following general procedure 11, 5-methoxymethoxy-1-pentyn-3-ol (333) (288 mg, 2 mmol) was converted into a mixture of the vinylstannanes (341) and (345). The crude mixture was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 4:1).

The major, less polar product was purified by distillation (air-bath temperature 75-85°C/0.2 Torr) of the residual material derived from
concentration of the appropriate fractions. This material (255.1 mg, 41%), a colorless oil, was identified as the olefinic alcohol (341); ir (film): 3474, 1150, 1044, 921, 771 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, J_{Sn-H} = 55 Hz), 1.67-1.74 (m, 2H, -CH₂CH₂O⁻), 2.64 (d, 1H, exchanges with D₂O, -OH, J = 6 Hz), 3.33 (s, 3H, -OCH₃), 3.60-3.73 (m, 2H, -CH₂CH₂O⁻), 4.36-4.46 (m, 1H, -CH(OH)⁻), 4.58 (s, 2H, -OCH₂O⁻), 5.22 (broad s, 1H, H₆, J_{Sn-H} = 72 Hz), 5.74 (broad s, 1H, H₇, J_{Sn-H} = 146 Hz). Exact Mass calcd. for C₉H₁₉O₃Sn (M⁺-CH₃): 295.0356; found: 295.0360.

The minor, more polar product was obtained by removal of solvent from the appropriate fractions, followed by distillation (air-bath temperature 90-100°C/0.2 Torr) of the residual material. The colorless oil obtained (186.7 mg, 30%) was identified as the olefinic alcohol (345); ir (film): 3428, 1151, 1044, 990, 921, 769 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, J_{Sn-H} = 55 Hz), 1.70-1.90 (m, 2H, -CH₂CH₂O⁻), 2.46 (d, 1H, exchanges with D₂O, -OH, J = 5 Hz), 3.35 (s, 3H, -OCH₃), 3.60-3.77 (m, 2H, -CH₂CH₂O⁻), 4.22-4.32 (m, 1H, -CH(OH)⁻), 3.60 (s, 2H, -OCH₂O⁻), 6.02 (d of d, 1H, H₆, J = 5, 19 Hz, J_{Sn-H} = 74 Hz), 6.25 (broad d, 1H, H₇, J = 19 Hz, J_{Sn-H} = 80 Hz). Exact Mass calcd. for C₉H₁₉O₃Sn (M⁺-CH₃): 295.0356; found: 295.0353.

b) Via General Procedure 12, Reagent (355) ([Me₃SnZn(t-Bu)₂]Li).

General procedure 12 was followed. Thus treatment of 5-methoxy-methoxy-1-pentyn-3-ol (333) (144 mg, 1 mmol) with the (trimethylstannyl)-
zinc reagent (355) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 157.8 mg (51%) of (341) and 55.5 mg (18%) of (345). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, 1H nmr).

c) Via General Procedure 12, Reagent (356) [(Me₃SnZnEt₂)Li]

General procedure 12 was followed. Thus treatment of 5-methoxy-methoxy-1-pentyn-3-ol (333) (144 mg, 1 mmol) with the (trimethylstannyl)-zinc reagent (356) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 12.5 mg (4%) of (341) and 195.2 mg (63%) of (345). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, 1H nmr).

Preparation of 2-Trimethylstannyl-1,6-heptadien-3-ol (342) and (E)-1-Trimethylstannyl-1,6-heptadien-3-ol (346)
a) Via General Procedure 11, Reagent (84) \((\text{Me}_3\text{SnCu.Me}_2\text{S})\)

Following general procedure 11, 6-hepten-1-yn-3-ol (334) (220 mg, 2 mmol) was converted into a mixture of the vinylstannanes (342) and (346). The crude mixture was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 9:1).

The major, less polar product was purified by distillation (air-bath temperature 50-60°C/0.2 Torr) of the residual material derived from concentration of the appropriate fractions. This material (238.0 mg, 43%), a colorless oil, was identified as the olefinic alcohol (342); ir (film): 3387, 3078, 1014, 913, 769 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.20 (s, 9H, -SnMe\(_3\), J\(_{\text{Sn-H}}\) = 54 Hz), 1.50-1.72 (m, 3H), 2.05-2.21 (m, 2H, -CH\(_2\)C=), 4.28 (broad t, 1H, -CH(OH)-, J = 7 Hz), 5.00 (q of d, 1H, H\(_G\), J = 2, 10 Hz), 5.06 (q of d, 1H, H\(_F\), J = 2, 18 Hz), 5.27 (d of d, 1H, H\(_A\), J = 1, 2 Hz, J\(_{\text{Sn-H}}\) = 76 Hz), 5.78 (d of d, 1H, H\(_X\), J = 1, 2 Hz), J\(_{\text{Sn-H}}\) = 152 Hz), 5.86 (t of d of d, 1H, H\(_T\), J = 7, 10, 18 Hz). Exact Mass calcd. for C\(_9\)H\(_{17}\)OSn (M\(^+\)-CH\(_3\)): 261.0301; found: 261.0309.

The minor, more polar product was obtained by removal of solvent from the appropriate fractions, followed by distillation (air-bath temperature 65-75°C/0.2 Torr) of the residual material. The colorless oil obtained (158.9 mg, 29%) was identified as the olefinic alcohol (346); ir (film): 3335, 3078, 991, 911, 769 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.14 (s, 9H, -SnMe\(_3\), J\(_{\text{Sn-H}}\) = 52 Hz), 1.58-1.69 (m, 3H), 2.08-2.23 (m, 2H), 4.05-4.17 (m, 1H, -CH(OH)-), 4.98 (broad d, 1H, H\(_G\), J = 10 Hz), 5.07 (broad d, 1H, H\(_F\), J = 17 Hz), 5.85 (t of d of d, 1H, H\(_T\), J = 7, 10, 17 Hz), 6.02 (d of d, 1H, H\(_L\), J = 6, 18 Hz, J\(_{\text{Sn-H}}\) = 75 Hz),
6.18 (d, 1H, H₃, J = 18 Hz, J₈Sn-H = 80 Hz). **Exact Mass** calcd. for C₉H₁₇OSn (M⁺-CH₃): 261.0301; found: 261.0306.

b) **Via** General Procedure 12, Reagent (355) ([Me₃SnZn(t-Bu)₂]Li)

General procedure 12 was followed. Thus treatment of 6-hepten-1-yn-3-ol (334) (110 mg, 1 mmol) with the (trimethylstannyl)zinc reagent (355) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 118.0 mg (43%) of (342) and 55.7 mg (20%) of (346). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, ¹H nmr).

c) **Via** General Procedure 12, Reagent (356) ([Me₃SnZnEt₂]Li)

General procedure 12 was followed. Thus treatment of 6-hepten-1-yn-3-ol (334) (110 mg, 1 mmol) with the (trimethylstannyl)zinc reagent (356) (2 mmol) in the presence of cuprous cyanide (3.6 mg, 0.04 mmol), followed by workup, flash chromatography, and distillations as described above, afforded 17.4 mg (6%) of (342) and 175.8 mg (64%) of (346). These materials were identified on the basis of their chromatographic properties (tlc, glc) and their spectra (ir, ¹H nmr).
General procedure 13: Orthoacetate-Based Claisen Rearrangements.

Preparation of Ethyl (Z)-4-Trimethylstannyl-4-alkenoates (357) or Ethyl (E)-3-Trimethylstannyl-4-alkenoates (363)

\[ R\text{SnMe}_3\xrightarrow{-OAc} \text{CO}_2\text{Et} \]  

357

\[ R\text{H} \xrightarrow{-SnMe}_3\text{H} \xrightarrow{-OAc} \text{CO}_2\text{Et} \]  

363

A mixture of the appropriate 2-trimethylstannyl-1-alken-3-ol (109) [or (E)-1-trimethylstannyl-1-alken-3-ol (339)] (0.5 mmol), triethyl ortho-acetate (642 µL, 3.5 mmol) and propanoic acid (2.3 µL, 0.03 mmol) was heated at 135-140°C for 2.5 h with distillative removal of ethanol. After the mixture had been cooled to room temperature, it was treated with 25 mL of aqueous potassium dihydrogen phosphate (5%) and then stirring was continued for 30 min. The mixture was extracted thoroughly with ether. The ether extract was washed (saturated aqueous sodium bicarbonate, water, brine) and dried (MgSO₄). Solvent removal and distillation of the residual material afforded the corresponding Claisen rearrangement product (357) [or (363)].

Preparation of Ethyl (Z)-4-Trimethylstannyl-4-hexenoate (358)

Following general procedure 13, 3-trimethylstannyl-3-buten-2-ol
(337) (236 mg, 1 mmol) was heated with triethyl orthoacetate (1.28 mL, 7 mmol) and propanoic acid (4.5 µL, 0.06 mmol) at 135-140°C for 2.5 h under conditions for distillative removal of ethanol. Normal workup and distillation (air-bath temperature 55-65°C/0.2 Torr) of the residual oil provided 250.0 mg (82%) of a colorless oil which was identified as the ester (358); ir (film): 1736, 1624, 1371, 1163, 1044, 770 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 0.23 (s, 9H, -SnMe₃, J_{Sn-H} = 52 Hz), 1.25 (t, 3H, -CH₂CH₃, J = 7 Hz), 1.70 (d, 3H, CH₃C=, J = 6 Hz), 2.20-2.55 (m, 4H), 4.10 (q, 2H, -CH₂CH₃, J = 7 Hz), 6.10 (q, 1H, olefinic proton, J = 6 Hz, J_{Sn-H} = 140 Hz). Exact Mass calc'd. for C₁₀H₁₉O₂Sn (M⁺-CH₃): 291.0407; found: 291.0416.

Preparation of Ethyl (Z)-4-Trimethylstannyl-4-undecanoate (359)

Following general procedure 13, 2-trimethylstannyl-1-nonen-3-ol (340) (306 mg, 1 mmol) was heated with triethyl orthoacetate (1.28 mL, 7 mmol) and propanoic acid (4.5 µL, 0.06 mmol) at 135-140°C for 2.5 h with distillative removal of ethanol. Normal workup, followed by distillation (air-bath temperature 95-105°C/0.2 Torr) of the crude material, afforded 302.3 mg (80%) of (359) as colorless oil; ir (film): 1740, 1621, 1371, 1160, 1040, 770 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.18 (s, 9H, -SnMe₃, J_{Sn-H} = 54 Hz), 0.87 (broad t, 3H, -CH₂CH₂CH₃, J = 7 Hz),
Preparation of Ethyl (Z)-5-Cyclopropyl-4-trimethylstannyl-4-pentenoate (362)

General procedure 13 was used with some modification. A mixture of 1-cyclopropyl-2-trimethylstannyl-2-propen-1-ol (343) (131 mg, 0.5 mmol), triethyl orthoacetate (1.37 mL, 7.5 mmol) and propanoic acid (7.5 µL, 0.1 mmol) was heated at 135-138°C for 3 h, as ethanol was removed by distillation. The crude product obtained after normal workup was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ethyl acetate, 19:1). Distillation (air-bath temperature 75-85°C/0.2 torr) of the residual material derived from concentration of the appropriate fractions afforded 96.8 mg (58%) of (362) as a colorless oil; ir (film): 3082, 1737, 1619, 1181, 1043, 770 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.23 (s, 9H, -SnMe₃, J.Sn-H = 52 Hz), 0.34-0.38 and 0.67-0.73 (m, m, 2H each, cyclopropyl methylene protons), 1.19-1.25 (m, 1H, cyclopropyl methine proton), 1.23 (t, 3H, -CH₃, J = 7 Hz), 2.29 (t,
2H, J = 8 Hz), 2.47 (t, 2H, J = 8 Hz), 4.11 (q, 2H, -CH₂CH₃, J = 7 Hz), 5.39 (broad d, 1H, olefinic proton, J = 8 Hz, Jₜₜ = 135 Hz). **Exact Mass** calcd. for C₁₂H₂₁O₂Sn (M⁺-CH₃): 317.0563; found: 317.0566.

Preparation of Ethyl (Z)-7-Methoxymethoxy-4-trimethylstannyl-4-heptenoate (360)

![Chemical Structure](image)

Following general procedure 13, 5-methoxymethoxy-2-trimethylstannyl-1-penten-3-ol (341) (155 mg, 0.5mmol) was heated with triethyl orthoacetate (642 µL, 3.5 mmol) and propanoic acid (2.3 µL, 0.03 mmol) at 135-138°C, for 2.5 h, as ethanol was removed by distillation. Normal workup, followed by distillation (air-bath temperature 100-110°C/0.2 Torr) of the crude product, afforded 144.5 mg, (76%) of (360) as a colorless oil; ir (film): 1735, 1622, 1152, 1044, 920, 772 cm⁻¹; ¹H nmr (270 MHz, CDCl₃)  δ: 0.18 (s, 9H, -SnMe₃, JₜSn-H = 55 Hz), 1.20 (t, 3H, -CH₂CH₃, J = 7 Hz), 2.23-2.30 (m, 4H), 2.40-2.50 (t, 2H, J = 7 Hz), 3.30 (s, 3H, -OCH₃), 3.46 (t, 2H, -OCH₂CH₂, J = 7 Hz), 4.06 (q, 2H, -OCH₂CH₃, J = 7 Hz), 4.56 (s, 2H, -OCH₂O-), 5.98 (t, 1H, olefinic proton, J = 7 Hz, Jₜₜ = 137 Hz). **Exact Mass** calcd. for C₁₃H₂₅O₄Sn (M⁺-CH₃): 365.0774; found: 365.0772.
Preparation of Ethyl (Z)-4-Trimethylstannyl-4,8-nonadienoate (361)

Following general procedure 13, 2-trimethylstannyl-1,6-heptadien-3-ol (342) (138 mg, 0.5 mmol) was heated with triethyl orthoacetate (642 μL, 3.5 mmol) and propanoic acid (2.3 μL, 0.03 mmol) at 135-140°C for 2.5 h, as ethanol was removed by distillation. Normal workup, followed by distillation (air-bath temperature 85-95°C/0.2 Torr) of the crude product, afforded 136.5 mg (79%) of (361) as a colorless oil; ir (film): 3078, 1739, 1641, 1620, 1159, 1040, 913, 770 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.14 (s, 9H, -SnMe₃, JₜSn-H ~ 56 Hz), 1.23 (t, 3H, -CH₂CH₃, J = 7 Hz), 2.03-2.13 (m, 4H), 2.28 (t, 2H, J = 7 Hz), 2.47 (t, 2H, J = 7 Hz), 4.10 (q, 2H, -OCH₂CH₃, J = 7 Hz), 4.93 (broad d, 1H, Hₐ, J = 10 Hz), 4.98 (broad d, 1H, Hₐ, J = 16 Hz), 5.70-5.84 (m, 1H, Hₜ), 6.00 (m, 1H, Hₚ, JₜSn-H = 136 Hz). Exact Mass calcd. for C₁₃H₂₃O₂Sn (M⁺-CH₃): 331.0720; found: 331.0716.

Preparation of Ethyl (E)-3-Trimethylstannyl-4-hexenoate (364)

Following general procedure 13, (E)-4-trimethylstannyl-3-buten-2-ol
(338) (236 mg, 1 mmol) was heated with triethyl orthoacetate (1.28 mL, 7 mmol) and propanoic acid (4.5 μL, 0.06 mmol) at 135-140°C for 2.5 h, under conditions for distillative removal of ethanol. Normal workup and distillation (air-bath temperature 55-65°C/0.2 Torr) of the residual material afforded 228.9 mg (75%) of a colorless oil that was identified as the ester (364); ir (film): 1729, 1654, 1371, 1186, 1035, 967, 767 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.04 (s, 9H, -SnMe₃, J_{Sn-H} = 56 Hz), 1.21 (t, 3H, -CH₂CH₃, J = 7 Hz), 1.61 (d of d, 3H, CH₃C=, J = 1.5, 6 Hz), 2.20-2.32 (m, 1H, Me₃SnCH-), 2.53 (d of d, 1H, -CH₂CO₂Et, J = 6, 16 Hz), 2.55 (d of d, 1H, -CH₂CO₂Et, J = 8, 16 Hz), 4.09 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.14 (d of q of d, 1H, H_A, J = 1, 6, 16 Hz), 5.49 (q of d of d, 1H, H_B, J = 1.5, 8, 16 Hz). Exact Mass calcd. for C₁₁H₂₂O₂Sn: 306.0642; found: 306.0651.

Preparation of Ethyl (E)-3-Trimethylstannyl-4-undecenoate (365)

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{CO}_2\text{Et} \\
\text{H}_A & \quad \text{H}_B \\
\text{C}_6\text{H}_{13} \quad \text{C}_6\text{H}_{13}
\end{align*}
\]

Following general procedure 13, (E)-1-trimethylstannyl-1-nonene-3-ol (344) (153 mg, 0.5 mmol) was heated with triethyl orthoacetate (642 μL, 3.5 mmol) and propanoic acid (2.3 μL, 0.03 mmol) at 135-140°C for 2.5 h, as ethanol was removed by distillation. Normal workup, followed by distillation (air-bath temperature 95-105°C/0.2 Torr) of the crude product, afforded 144.2 mg (77%) of (365) as a colorless oil; ir (film):
1734, 1650, 1466, 1372, 1186, 1035, 966, 767 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.06 (s, 9H, -SnMe₃, JSn-H = 52 Hz), 0.88 (broad t, 3H, -CH₂CH₂CH₃, J = 7 Hz), 1.21-1.35 (m, 11H), 1.97 (broad q, 2H, -CH₂C=, J = 7 Hz), 2.32 (broad d of t, 1H, Me₃SnCH-, J = 7, 8 Hz), 2.58 (d of d, 1H, -CH₂CO₂Et, J = 7, 16 Hz), 2.60 (d of d, 1H, -CH₂CO₂Et, J = 8, 16 Hz), 4.12 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.18 (d of t of d, 1H, Hₓ, J = 1, 7, 15 Hz), 5.51 (t of d of d, 1H, Hᵧ, J = 1, 8, 15 Hz). **Exact Mass**
calcd. for C₁₅H₂₉O₂Sn (M⁺-CH₃) 361.1190; found: 361.1188.

**Preparation of Ethyl (E)-5-Cyclopropyl-3-trimethylstannyl-4-pentenoate (368)**

General procedure 13 was used with some modification. A mixture of (E)-1-cyclopropyl-3-trimethylstannyl-2-propen-1-ol (347) (131 mg, 0.5 mmol), triethyl orthoacetate (1.37 mL, 7.5 mmol) and propanoic acid (7.5 µL, 0.1 mmol) was heated at 135-140°C for 3 h, as ethanol was removed by distillation. The crude product obtained after normal workup was subjected to flash chromatography on silica gel (18 g, elution with petroleum ether-ether, 97:3). Distillation (air-bath temperature 75-85°C/0.2 Torr) of the material derived from concentration of the appropriate fractions afforded 102.3 mg (62%) of (368) as a colorless oil; ir (film): 3080, 1733, 1649, 1371, 1186, 1035, 959, 767 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.06 (s, 9H, -SnMe₃, JSn-H = 52 Hz), 0.88 (broad t, 3H, -CH₂CH₂CH₃, J = 7 Hz), 1.21-1.35 (m, 11H), 1.97 (broad q, 2H, -CH₂C=, J = 7 Hz), 2.32 (broad d of t, 1H, Me₃SnCH-, J = 7, 8 Hz), 2.58 (d of d, 1H, -CH₂CO₂Et, J = 7, 16 Hz), 2.60 (d of d, 1H, -CH₂CO₂Et, J = 8, 16 Hz), 4.12 (q, 2H, -OCH₂CH₃, J = 7 Hz), 5.18 (d of t of d, 1H, Hₓ, J = 1, 7, 15 Hz), 5.51 (t of d of d, 1H, Hᵧ, J = 1, 8, 15 Hz). **Exact Mass**
calcd. for C₁₅H₂₉O₂Sn (M⁺-CH₃) 361.1190; found: 361.1188.
MHz, CDCl₃) δ: 0.07 (s, 9H, -SnMe₃, JSn-H = 56 Hz), 0.23-0.28 and 0.58-0.65 (m, m, 2H each, cyclopropyl methylene protons), 1.25 (t, 3H, -CH₂CH₃, J = 7 Hz), 1.26-1.34 (m, 1H, cyclopropyl methine proton), 2.31 (broad, overlapped d of d of d, 1H, Me₃SnCH-, J = 7, 8, 8 Hz), 2.56 (d of d, 1H, -CH₂CO₂Et, J = 7, 16 Hz), 2.59 (d of d, 1H, -CH₂CO₂Et, J = 8, 16 Hz), 4.12 (q, 2H, -CH₂CH₃, J = 7 Hz), 4.81 (d of d of d, 1H, HA, J = 2, 8, 15 Hz), 5.57 (d of d of d, 1H, HB, J = 1, 8, 15 Hz). Irradiation at δ 5.57 (HB): δ 4.81 (HA) simplified to a d of d (J = 2, 8 Hz) and δ 2.31 (Me₃SnCH-) became a broad d of d of d (J = 2, 7, 8 Hz). Irradiation at δ 4.81 (HA): signal at δ 5.57 (HB) simplified to a d of d (J = 1, 8 Hz) and δ 1.26-1.34 (cyclopropyl methine proton) was changed.

Exact Mass calcd for C₁₂H₂₁O₂Sn (M⁺-CH₃): 317.0563; found: 317.0564.

Preparation of Ethyl (E)-7-Methoxymethoxy-3-trimethylstannyl-4-heptenoate (366)

Following general procedure 13, (E)-5-methoxymethoxy-1-trimethylstannyl-1-penten-3-ol (345) (155 mg, 0.5mmol) was heated with triethyl orthoacetate (642 µL, 3.5 mmol) and propanoic acid (2.3 µL, 0.03 mmol) at 135-138°C, for 2.5 h, as ethanol was removed by distillation. Normal workup, followed by distillation (air-bath temperature 100-110°C/0.2 Torr) of the crude product, afforded 150.0 mg, (79%) of (366) as a
colorless oil; ir (film): 1733, 1650, 1372, 1039, 960, 920, 769 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.06 (s, 9H, -SnMe₃, J_{Sn-H} = 55 Hz), 1.24 (t, 3H, -OCH₂CH₃, J = 7 Hz), 2.23-2.27 (m, 3H), 2.57 (d of d, 1H, -CH₂CO₂Et, J = 7, 18 Hz), 2.60 (d of d, 1H, -CH₂CO₂Et, J = 8, 18 Hz), 3.34 (s, 3H, -OCH₃), 3.48 (t, 2H, -OCH₂CH₂-, J = 7 Hz), 4.10 (q, 2H, -OCH₂CH₃, J = 7 Hz), 4.59 (s, 2H, -OCH₂O-), 5.16 (t of d, 1H, HA, J = 7, 15 Hz), 5.62 (d of d, 1H, HB, J = 8, 15 Hz). Exact Mass calcd. for C₁₄H₂₈O₄Sn: 380.1009; found: 380.1005.

Preparation of Ethyl (E)-3-Trimethylstannyl-4,8-nonadienoate (367)

Following general procedure 13, (E)-1-trimethylstannyl-1,6-heptadien-3-ol (346) (138 mg, 0.5 mmol) was heated with triethyl orthoacetate (642 µL, 3.5 mmol) and propanoic acid (2.3 µL, 0.3 mmol) at 135-140°C for 2.5 h, as ethanol was removed by distillation. Normal workup, followed by distillation (air-bath temperature 90-100°C/0.2 Torr) of the crude product, afforded 133.6 mg (77%) of (367) as a colorless oil; ir (film): 3077, 1733, 1641, 1186, 1035, 967, 912, 768 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 0.07 (s, 9H, -SnMe₃, J_{Sn-H} = 52 Hz), 1.24 (t, 3H, -CH₂CH₃, J = 7 Hz), 2.03-2.10 (m, 4H), 2.30 (d of t, 1H, Me₃SnCH-, J = 7, 8 Hz), 2.56 (d of d, 1H, -CH₂CO₂Et, J = 7, 16 Hz), 2.59 (d of d, 1H, -CH₂CO₂Et, J = 8, 16 Hz), 4.10 (q, 2H, -OCH₂CH₃, J = 7 Hz), 4.92 (broad
d, 1H, H_F, J = 10 Hz), 4.98 (broad d, 1H, H_G, J = 16 Hz), 5.09-5.23 (m, 1H, H_A), 5.53 (broad d of d, 1H, H_B, J = 8, 15 Hz), 5.70-5.84 (m, 1H, H_T). **Exact Mass** calcd. for C_{14}H_{26}O_{2}Sn: 346.0955; found: 346.0961.

Preparation of (Z)-4-Trimethylstannyl-4-hexen-1-ol (369)

![Structure of (Z)-4-Trimethylstannyl-4-hexen-1-ol (369)](image)

General procedure 7 was followed. To a cold (0°C), stirred solution-suspension of lithium aluminum hydride (85.5 mg, 2.25 mmol) in 15 mL of dry ether was added, dropwise, a solution of ethyl (Z)-4-trimethylstannyl-4-hexenoate (358) (918 mg, 3 mmol) in 8 mL of dry ether. The reaction mixture was stirred at 0°C for 1 h. Normal workup, followed by distillation (air-bath temperature 55-65°C/0.2 Torr) of the crude product, provided 758.7 mg (96%) of the olefinic alcohol (369) as a colorless oil; ir (film): 3333, 1624, 1449, 1055, 769 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDCl\(_3\)) \(\delta\): 0.20 (s, 9H, -SnMe\(_3\), \(J\_\text{Sn-H} = 52 \text{ Hz}\)), 1.33 (t, 1H, exchanges with D\(_2\)O, -OH, \(J = 7 \text{ Hz}\)), 1.48-1.78 (m, 5H), 2.28 (broad t, 2H, =CH\(_2\)_2, \(J = 7 \text{ Hz}\)), 3.60 (q, 2H, -CH\(_2\)CH\(_2\)OH, \(J = 7 \text{ Hz}\)), 6.10 (t of q, 1H, olefinic proton, \(J = 1.5, 7 \text{ Hz, } J\_\text{Sn-H} = 144 \text{ Hz}\)). **Exact Mass** calcd. for C\(_8\)H\(_{17}\)OSn (M\(^+\)-CH\(_3\)): 249.0301; found: 249.0306.
Preparation of (Z)-6-Chloro-3-trimethylstannyl-2-hexene (370)

\[
\text{Cl} \\
\text{Me}_3\text{Sn}
\]

To a stirred solution of the alcohol (369) (660 mg, 2.5 mmol) in 20 mL of dry carbon tetrachloride was added triethylamine (383 µL, 2.75 mmol) and triphenylphosphine (1.31 g, 5 mmol). The resultant solution was refluxed for 24 h. Petroleum ether (50 mL) was added and the resulting slurry was filtered through a column of Florisil (15 g, elution with petroleum ether). Evaporation of the solvent from the combined eluate, followed by distillation (air-bath temperature 60-70°C/0.2 Torr) of the residual oil, afforded 510.6 mg (72%) of the chloride (370) as a colorless oil; ir (film): 1623, 981, 769, 720 cm\(^{-1}\); \(^1\)H nmr (80 MHz, CDCl\(_3\)) \(\delta\): 0.23 (s, 9H, -SnMe\(_3\)), \(J_{\text{Sn-H}} = 52\) Hz, 1.63-1.95 (m, 5H), 2.33 (broad t, 2H, -CCH\(_2\)-, \(J = 7\) Hz), 3.50 (t, 2H, -CH\(_2\)Cl, \(J = 7\) Hz), 6.10 (t of q, 1H, olefinic proton, \(J = 1.5, 6\) Hz, \(J_{\text{Sn-H}} = 142\) Hz). \textbf{Exact Mass} calcd. for C\(_8\)H\(_{16}\)\(^{35}\)Cl\(^{118}\)Sn (M\(^+\)-CH\(_3\)): 264.9957; found: 264.9944.
Transmetalation of (Z)-6-Chloro-3-trimethylstannyl-2-hexene (370).
Preparation of (Z)-5-Ethylidene-1-oxaspiro[5.5]dodecane (373)

To a cold (-78°C), stirred solution of (Z)-6-chloro-3-trimethylstannyl-2-hexene (370) (141.2 mg, 0.5 mmol) in 2 mL of dry THF was added successively a solution of methyllithium in ether (0.33 mL, 0.55 mmol) and HMPA (95.7 μL, 0.55 mmol). After the light yellow solution had been stirred for 1 h, cyclohexanone (57 μL, 0.55 mmol) was added and stirring was continued for 1 h at -78°C and for 10 h with the cooling bath removed. Saturated aqueous ammonium chloride (0.5 mL) and ether (10 mL) were added and the layers were separated. The aqueous layer was extracted with ether. The combined organic extract was washed (water, brine), dried (MgSO₄), and concentrated. Distillation (air-bath temperature 30-40°C/0.2 Torr) of the crude product provided 61.5 mg (68%) of the spiro ether (373) as a colorless oil; ir (film): 1659, 1445, 1088, 998 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 1.45-2.05 (m, 15H), 2.23 (broad t, 2H, -CCH₂-, J = 7 Hz), 3.70 (t, 2H, -CH₂O-, J = 7 Hz), 5.18 (t of q, 1H, olefinic proton, J = 1.5, 7 Hz). Exact Mass calcd. for C₁₂H₂₀O: 180.1515; found: 180.1514.
Preparation of (Z)-3-[3-(6-Chloro-2-hexenyl)]cyclopentanone (375)

To a cold (-78°C), stirred solution of (Z)-6-chloro-3-trimethylstannyl-2-hexene (370) (141.2 mg, 0.5 mmol) in 2 mL of dry THF was added successively a solution of methyllithium in ether (0.33 mL, 0.55 mmol) and HMPA (95.7 μL, 0.55 mmol). The resulting light yellow solution was stirred at -78°C for 1 h to obtain the corresponding vinyllithium intermediate (371). Following general procedure 8, this solution was treated with anhydrous magnesium bromide (110.5 mg, 0.6 mmol) and then was diluted with 4 mL of dry ether. Cuprous bromide-dimethylsulfide complex (30.8 mg, 0.15 mmol), 2-cyclopenten-1-one (225) (41 mg, 0.5 mmol), and boron trifluoride-etherate (74 μL, 0.6 mmol) were added. General conditions and workup (general procedure 8) provided the chloro ketone (375). Fractional distillation of the crude material obtained on workup gave initially a small amount of the starting enone, followed by 59.0 mg (59%) of the chloro ketone (375) (air-bath temperature 90-100°C/0.2 Torr), as a colorless oil; ir (film): 1743, 1153, 978, 722 cm⁻¹; ¹H nmr (80 MHz, CDCl₃) δ: 1.68 (broad d, 3H, CH₃C=, J = 7 Hz), 1.75-2.75 (m, 10H), 3.05-3.45 (m, 1H, HA), 3.58 (t, 2H, -CH₂Cl, J = 7 Hz), 5.35 (broad q, 1H, olefinic proton, J = 7 Hz). Exact Mass calcd. for C₁₁H₁₇OCl: 200.0969; found: 200.0967.
Preparation of the Chloro Ketone Mixture (376)

To a cold (-78°C), stirred solution of (Z)-6-chloro-3-trimethylstannyl-2-hexene (370) (141.2 mg, 0.5 mmol) in 2 mL of dry THF was added successively a solution of methyllithium in ether (0.33 mL, 0.55 mmol) and HMPA (95.7 μL, 0.55 mmol). The light yellow solution was stirred at -78°C for 1 h, to obtain the corresponding vinyllithium intermediate (371). Following general procedure 8, this solution was treated with anhydrous magnesium bromide (110.5 mg, 0.6 mmol), and then was diluted with 4 mL of dry ether. Cuprous bromide-dimethylsulfide complex (30.8 mg, 0.15 mmol), 2-methyl-2-cyclohexen-1-one (224)¹¹⁶ (48 mg, 0.5 mmol), and boron trifluoride-etherate (745 μL, 0.6 mmol) were added. General conditions and workup (general procedure 8) provided the chloro ketone mixture (376). Fraction distillation of the crude product obtained on workup gave initially a small amount of the starting enone, followed by 69.7 mg (61%) of (376) (air-bath temperature 105-115°C/0.2 Torr), as a colorless oil; ir (film): 1709, 1313, 1017, 965, 730 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.89 and 1.06 (d, d, ratio 2:1, 3H, CH₃CH₂−, J = 7 Hz each), 1.59-2.85 (m, 14H), 3.06-3.11 (m, 1H, H_A), 3.53-3.61 (m, 2H, -CH₂Cl), 5.29-5.37 (m, 1H, olefinic proton). Exact Mass calcd. for C₁₃H₂₁O₃⁵Cl: 228.1282; found: 228.1282.
Preparation of cis, (Z)-2-Ethylidenebicyclo[4.3.0]nonan-7-one (377)

Following general procedure 9, the chloro ketone (375) (60.2 mg, 0.3 mmol) was allowed to react with a stirred suspension of potassium hydride (30 mg, 0.75 mmol) in 2 mL of dry THF. Normal workup, followed by distillation (air-bath temperature 45-55°C/0.2 Torr) of the crude product, provided 39.7 mg (81%) of the bicyclic ketone (377) as a colorless oil; ir (film): 1741, 1133, 877 cm⁻¹; ¹H nmr (270 MHz, CDCl₃) δ: 1.26-1.35 (m, 2H), 1.64 (d of d, 3H, CH₃CH=, J = 1.5, 7 Hz), 1.66-2.50 (m, 9H), 3.22 (broad q, 1H, J = 7 Hz), 5.32 (broad q, 1H, olefinic proton, J = 7 Hz). Exact Mass calcd. for C₂₀H₂₂O: 296.1458; found: 296.1457.

Preparation of cis, (Z)-1-Methyl-7-ethylidenebicyclo[4.4.0]decan-2-one
(378)

Following general procedure 9, the chloro ketone mixture (376) (68.6 mg, 0.3 mmol) was allowed to react with a stirred suspension of
potassium hydride (30 mg, 0.75 mmol) in 2 mL of dry THF. Normal workup, followed by distillation (air-bath temperature 50-60°C/0.2 Torr) of the crude product, afforded 49.4 mg (86%) of (378) as a colorless oil; ir (film): 1703, 1451, 924 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.06 (s, 3H, -C-CH₃), 1.18-1.20 (m, 2H), 1.47-1.76 (m, 3H), 1.55 (d of d, 3H, CH₃CH=, J = 2, 7 Hz), 2.00-2.15 (m, 4H), 2.25-2.39 (m, 2H), 2.60-2.70 (m, 2H), 5.28 (t of q, 1H, olefinic proton, J = 2, 7 Hz). **Exact Mass** calcd. for C₁₃H₂₀O: 192.1515; found: 192.1513.
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