A SYNTHETIC APPROACH TO THE VARIECOLIN CLASS OF SESTERTERPENOIDS: TOTAL SYNTHESSES OF (±)-5-DEOXOVARIECOLIN, (±)-5-DEOXYVARIECOLOL AND (±)-5-DEOXYVARIECOLACTONE. A NEW CYCLOHEPTENONE ANNULATION METHOD EMPLOYING THE BIFUNCTIONAL REAGENT (Z)-5-IODO-1-TRIBUTYLSTANNYL-PENT-1-ENE

by

SHAWN DUANE WALKER

B.Sc. (Hons.), McGill University, 1995

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY in THE FACULTY OF GRADUATE STUDIES (Department of Chemistry)

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
July 2002
© Shawn Duane Walker, 2002
In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

Department of Chemistry
The University of British Columbia
Vancouver, Canada
Date July 29, 2002
ABSTRACT

The syntheses of three structurally related substances, (±)-5-deoxovariecolin (204), (±)-5-deoxyvariecolol (93) and (±)-5-deoxyvariecolactone (226) are described as part of a general synthetic strategy toward the variecolin class of sesterterpenoids (48-52). Thus, the known Grignard reagent 99 was combined with 3-methylcyclohex-2-en-1-one (95) in a two step cyclopentene annulation sequence to provide 98. Conjugate addition of cuprate 107 to the enone 98 followed by an epimerization step provided ketone 44 with the correct relative configuration set at three stereogenic centers. Application of a novel cycloheptenone annulation protocol employing the bifunctional reagent 53 furnished the tricyclic intermediate 59. A sequence consisting of dissolving metal reduction and a 1,2-carbonyl transposition provided the ketone 129. A regioselective ring expansion of 129 provided the cyclooctenone 60. The latter was converted to the tetracyclic ketone 61 through an efficient methylenecyclopentane annulation featuring reagent 190. Ketone 61 was further elaborated to the ester 94 through a series of reactions including a palladium-catalyzed methoxycarbonylation. A chemo- and stereoselective double bond hydrogenation and subsequent carbonyl group reduction transformed 94 to the alcohol 203. Oxidation of the alcohol function of 203 provided 204. A key remote functionalization step converted 203 to 93. Chemoselective allylic oxidation of 93 produced 226, a critical intermediate for future synthetic studies.

In the second part of the thesis, the generality of the newly developed cycloheptenone annulation sequence was explored. Thus, alkylation of N,N-dimethylhydrazones of general structure 261 with the bifunctional reagent 53
followed by iododestannylation and hydrolysis of the hydrazone function provided keto alkenyl iodides 262. Butyllithium mediated cyclization of 262 and oxidative rearrangement of the resultant allylic alcohols 57 provided the cycloheptenones 58. The annulation method was also extended to cyclic β-keto ester substrates. The individual reactions involved are experimentally straightforward and the overall yields of the annulation processes are good to excellent.

variecolin (48)
TABLE OF CONTENTS

ABSTRACT............................................................................................................ii

TABLE OF CONTENTS...............................................................................................v

LIST OF TABLES......................................................................................................ix

LIST OF FIGURES...................................................................................................x

LIST OF ABBREVIATIONS..........................................................................................xi

ACKNOWLEDGEMENTS............................................................................................xvi

I. INTRODUCTION....................................................................................................1

1.1 General.............................................................................................................1

1.2 Background.....................................................................................................5

1.3 Proposals.......................................................................................................11
II. DISCUSSION

2.1 A Synthetic Approach to the Variecolin Class of Sesterterpenoids: Total Syntheses of (±)-5-Deoxovariecolin, (±)-5-Deoxyvariecolol and (±)-5-Deoxyvariecolactone

2.1.1 Isolation and Structure determination

2.1.2 Biogenesis

2.1.3 Biological Activity

2.1.4 Previous Synthetic Studies

2.1.5 Retrosynthetic Analysis

2.1.6 Preparation of the Bicyclic Ketone 44

2.1.7 Preparation of the Tricyclic Enone 59: Development of a New Cycloheptenone Annulation Method

2.1.8 Strategic Overview for Assembly of the A- and B-Rings

2.1.9 Preparation of Cyclooctenone 60

2.1.10 An Unsuccessful Attempt to Assemble the A/B Ring System

2.1.11 Completion of the A/B Subunit: Preparation of Tetracyclic Ketone 61

2.1.12 Preparation of Ester 94

2.1.13 Preparation of (±)-5-Deoxovariecolin, (±)-5-Deoxyvariecolol and (±)-5-Deoxyvariecolactone

2.1.14 Conclusion
2.2 Exploration of a New Cycloheptenone Annulation Method: Use of the Bifunctional Reagent (Z)-5-iodo-1-tributylstannylpent-1-ene in Organic Synthesis ........................................ 125

2.2.1 Introductory Remarks .................................................................................................................. 125

2.2.2 Preparation of N,N-Dimethylhydrazone Substrates ................................................................. 126

2.2.3 Preparation of Keto Alkenyl Iodide Substrates ...................................................................... 127

2.2.4 Anionic Cyclizations of the Keto Alkenyl Iodides: Production of Seven-Membered Ring Tertiary Allylic Alcohols ................................................................. 130

2.2.5 Oxidative Rearrangement of the Tertiary Allylic Alcohols: Production of Cycloheptenones ................................................................................................................................. 134

2.2.6 Extension of the Cycloheptenone Annulation to Cyclic β-Keto Ester Substrates .................. 137

2.2.7 A Recent Application to Natural Product Synthesis .............................................................. 140

2.2.8 Conclusion .................................................................................................................................. 141

III. EXPERIMENTAL .............................................................................................................................. 142

3.1 General .......................................................................................................................................... 142

3.1.1 Data Acquisition, Presentation and Experimental Techniques ............................................. 142

3.1.2 Solvents and Reagents .............................................................................................................. 145
3.2 A Synthetic Approach to the Variecolin Class of Sesterterpenoids: Total Syntheses of (±)-5-Deoxovariecolin, (±)-5-Deoxyvariecolol and (±)-5-Deoxyvariecolactone

3.3 Exploration of a New Cycloheptenone Annulation Method: Use of the Bifunctional Reagent (Z)-5-Iodo-1-tributylstannylnpent-1-ene in Organic Synthesis

3.3.1 Preparation of N,N-Dimethylhydrazone Substrates

3.3.2 General Procedure 1: Preparation of keto alkenyl iodides from the corresponding N,N-dimethylhydrazones and (Z)-5-Iodo-1-tributylstannylnpent-1-ene (53)

3.3.3 General Procedure 2: Butyllithium Mediated Anionic Cyclization of Keto Alkenyl Iodides

3.3.4 General Procedure 3: Oxidative Rearrangement of the Tertiary Allylic Alcohols to α,β-Unsaturated Ketones

3.3.5 Extension of the Cycloheptenone Annulation to Cyclic β-Keto Ester Substrates

IV. REFERENCES AND FOOTNOTES

V. APPENDIX

5.1 Appendix 1: X-Ray Crystallographic Data
LIST OF TABLES

Table 1. Immunosuppressive Effects of Compounds 48-52, Azathioprine, Cyclosporin A and FK 506 on the Con A-Induced and LPS-Induced Proliferation of Mouse Splenic Lymphocytes..............20

Table 2. Cuprate Additions to Bicyclo[4.3.0]non-9-en-2-ones and Base-Promoted Equilibration of the Resulting Adducts......................33

Table 3. \(^{1}\)H nmr (400 MHz, CDCl\(_3\)) Data for the Trans-Fused Tricyclic Ketone 130: COSY and NOESY Experiments...............................185

Table 4. \(^{1}\)H nmr (400 MHz, CDCl\(_3\)) Data for the Cis-Fused Tricyclic Ketone 156: NOED Experiments...........................................188

Table 5. \(^{1}\)H nmr (400 MHz, CDCl\(_3\)) Data for the Tricyclic Enone 60: COSY and NOED Experiments...........................................199

Table 6. \(^{1}\)H nmr (400 MHz, CDCl\(_3\)) Data for the Tetracyclic Ketone 61: COSY and NOED Experiments.................................213

Table 7. \(^{1}\)H nmr (500 MHz, CDCl\(_3\)) and \(^{13}\)C nmr (125.8 MHz, CDCl\(_3\)) Data for the Tetracyclic Ketone 61: HMQC and HMBC Experiments..............214

Table 8. \(^{1}\)H nmr (400 MHz, CDCl\(_3\)) Data for the Diene Ester 199: COSY and NOED Experiments...........................................222

Table 9. Preparation of Keto Alkenyl Iodides from N,N-Dimethylhydrazones.................................................................129

Table 10. Butyllithium Mediated Cyclization of Keto Alkenyl Iodides............133

Table 11. PCC Mediated Oxidative Rearrangement of the Tertiary Allylic Alcohols..............................................................136
LIST OF FIGURES

Figure 1. Stereoview of the allylic alcohol 110.................................49
Figure 2. Key $^1$H nmr 2D-NOESY correlations for ketone 130..............69
Figure 3. Key $^1$H nmr NOE enhancements for ketone 156....................71
Figure 4. Key $^1$H nmr NOE enhancements for enone 60........................78
Figure 5. Key $^1$H nmr NOE enhancements for ketone 61.....................98
Figure 6. Key $^1$H nmr NOE enhancements for ester 199....................108
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Å</td>
<td>angstrom</td>
</tr>
<tr>
<td>α</td>
<td>below the plane of a ring or 1,2 relative position</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>amu</td>
<td>atomic mass units</td>
</tr>
<tr>
<td>anal.</td>
<td>analysis</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>ax</td>
<td>axial</td>
</tr>
<tr>
<td>β</td>
<td>above the plane of a ring or 1,3 relative position</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degrees Celcius</td>
</tr>
<tr>
<td>calcd.</td>
<td>calculated</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>COSY</td>
<td>((^1)H-(^1)H)-homonuclear correlation spectroscopy</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>C-x</td>
<td>carbon number x</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million from tetramethylsilane</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Δ</td>
<td>heat</td>
</tr>
<tr>
<td>2D</td>
<td>two-dimensional</td>
</tr>
<tr>
<td>DIBAl-H</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>E</td>
<td>entgegen (configuration)</td>
</tr>
<tr>
<td>ed.</td>
<td>edition</td>
</tr>
<tr>
<td>Ed., Eds.</td>
<td>editor, editors</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia (for example)</td>
</tr>
<tr>
<td>epi</td>
<td>epimeric</td>
</tr>
<tr>
<td>eq</td>
<td>equatorial</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent(s)</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>g</td>
<td>gram</td>
</tr>
<tr>
<td>glc</td>
<td>gas-liquid chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour(s)</td>
</tr>
<tr>
<td>HMBC</td>
<td>$^1$H detected multiple bond heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramid</td>
</tr>
<tr>
<td>HMQC</td>
<td>$^1$H detected heteronuclear multiple quantum coherence</td>
</tr>
<tr>
<td>hv</td>
<td>light energy (from photoirradiation)</td>
</tr>
<tr>
<td>H-x</td>
<td>hydrogen number x</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Meaning</td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz (s^{-1})</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>IC_{50}</td>
<td>inhibitory concentration (for 50% of a biological sample)</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant in hertz</td>
</tr>
<tr>
<td>J_{Sn-H}</td>
<td>n bond coupling for tin and proton nuclei (in hertz)</td>
</tr>
<tr>
<td>KDA</td>
<td>potassium diisopropylamide</td>
</tr>
<tr>
<td>KHMDS</td>
<td>potassium hexamethyldisilazide</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>M^+</td>
<td>molecular ion</td>
</tr>
<tr>
<td>MCPBA</td>
<td>3-chloroperbenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mL</td>
<td>milliliter(s)</td>
</tr>
<tr>
<td>uL</td>
<td>microliter(s)</td>
</tr>
<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole(s)</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOED</td>
<td>nuclear Overhauser effect difference</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>p</td>
<td>page</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
</tr>
<tr>
<td>PDC</td>
<td>pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>i-Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>pyr.</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>R</td>
<td>rectus (configuration)</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>S</td>
<td>sinister (configuration)</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>t</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>tlc</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>uv</td>
<td>ultraviolet</td>
</tr>
<tr>
<td>-ve</td>
<td>negative</td>
</tr>
<tr>
<td>+ve</td>
<td>positive</td>
</tr>
<tr>
<td>Z</td>
<td>zusammen (configuration)</td>
</tr>
<tr>
<td></td>
<td>coordination or complex</td>
</tr>
<tr>
<td>±</td>
<td>racemic</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

I would like to thank my research supervisor, Professor Edward Piers, for his patience, support, and superb guidance throughout the course of these studies. I am grateful to have experienced firsthand his meticulous and insightful approach to the investigation of chemistry. In addition, thanks are extended to both current and former group members for stimulating interactions and discussions, both socially and academically.

A special thanks is extended to Professor Gregory Dake for proof-reading this thesis.

The assistance of the technical staff of the nmr, mass spectrometry, and elemental analysis laboratories is gratefully acknowledged.

Financial assistance in the form of postgraduate scholarships provided by the Natural Sciences and Engineering Research Council of Canada (NSERC) and les fonds pour la formation de chercheurs et l'aide à la recherche (FCAR) as well as through a UBC research fellowship is also acknowledged.

My most sincere thanks and deep appreciation go to Melanie for her continual support and encouragement in all aspects of life.

This thesis is dedicated, with love, to mom and dad.
I. Introduction

1.1 General

Organic synthesis is concerned with the development of new types of chemical transformations or reactions and the use of these reactions to produce target compounds. As the number of reaction types available to the synthetic chemist has increased with time, so too has the structural complexity of the molecular targets (both natural and synthetic). Access to challenging targets, made possible by the development of new synthetic methods and the need for further innovation to generate molecules when current methods fail, synergistically fuel synthetic research. The isolation and structure elucidation of novel natural products continues to provide an important impetus for the study of reaction chemistry. Research programs aimed at the total synthesis of these naturally occurring substances can yield new reaction methods which foster advances in fields as far ranging as drug development, biotechnology, and materials science. Natural products whose elaborate molecular architecture and dense functionalization could scarcely have been anticipated in earlier decades, have now yielded to total synthesis. Yet much remains to be done to increase the efficiency and selectivity of the chemical processes used to synthetically assemble these compounds.

One of the most celebrated achievements of modern synthetic chemistry was the total synthesis of the potent antitumor agent taxol (1). Isolated from the Pacific yew tree in 1971, taxol’s complicated structure resisted intensive efforts toward a laboratory preparation for over two decades. Finally, in 1994, Holton’s group reported the first total synthesis of taxol.\(^1\) Although beautifully imaginative, this work and other approaches to
taxol that followed, were all lengthy, arduous and required large teams of chemists to complete.²

More recently, in 2001, the Japanese group of Hirama reported the first total synthesis of the ciguatoxin CTX3C (2).³ This substance has a ladderlike polyether framework consisting of 13 rings and 30 stereogenic centers and belongs to a family of neurotoxins responsible for seafood poisoning. The poisoning is characterized by gastrointestinal, neurological and cardiovascular disturbances, and in severe cases paralysis, coma and death may occur. Since the content of ciguatoxins in fish is extremely low, detailed biological studies and the preparation of antibodies to detect the toxins had not been completed and a synthetic approach was desirable, in part, to provide a practical supply. After a twelve year effort, an elegant and convergent synthesis of CTX3C was finally achieved.

\[
R = \text{PhCONH(Ph)CH(OH)CO}
\]

\[\text{Taxol} \quad 1\]
Although remarkable, the protracted syntheses of both taxol and CTX3C show the necessity of developing new and sharper tools for bond construction. In particular, these polycyclic targets suggest the need for an expanded pool of useful reagents and expeditious methods for ring formation.

To this end, bifunctional conjunctive reagents have emerged as powerful intermediaries in ring forming processes. These bifunctional reagents possess two potentially reactive sites and have been defined\(^4\) as "simple building blocks which are incorporated in whole, or in part, into a more complex system." The two reactive sites can be either nucleophilic or electrophilic in nature and have been termed "donor" (d) and "acceptor" (a) sites, respectively. The following example illustrates the use of such a reagent in an annulation sequence (Scheme 1). The bifunctional Grignard reagent 3 serves as the synthetic equivalent of the propane d\(^1\),a\(^3\)-synthon 4.\(^5\) The donor site of the reagent is deployed in an intermolecular copper(I)-catalyzed conjugate addition of 3 to cyclohexenone to provide the keto acetal 5. The acetal serves to mask the acceptor site which is revealed by treatment of 5 with aqueous hydrochloric acid. This hydrolysates the
acetal to an aldehyde, which further reacts in an intramolecular aldol condensation-dehydration sequence to generate the bicyclic enone 6.6

Scheme 1
1.2 Background

A continuing program in the Piers laboratories involves the preparation and synthetic uses of structurally diverse bifunctional conjunctive reagents, many of which bear an alkenyltrialkylstannyl moiety. The application of one such reagent to an efficient annulation protocol is illustrated in Scheme 2.
In this method, bromo stannane 7 serves as the synthetic equivalent to the donor-acceptor synthon 8. Reaction of the potassium enolate of a cyclic keto ester of general structure 9 with the bromide (acceptor) portion of reagent 7 provides the alkylated product 10. Treatment of 10 with potassium hydride in the presence of 18-crown-6 effects an intramolecular anionic 1,3 ester shift to produce the rearranged β-keto ester 11. Conversion of the latter compound to the corresponding enol triflate 12 sets the stage for a Pd(0) catalyzed intramolecular Stille coupling with the alkenyltrimethylstannane (donor) function to afford the polycyclic diene ester 13. 

Another valuable annulation protocol developed in our laboratories is illustrated in Scheme 3.

![Scheme 3](image)

In this case, the bifunctional conjunctive reagent 14 serves as the synthetic equivalent to the but-2-ene d²,a⁴-synthon 15. Treatment of a vinylogous ester of general
structure 16 with base followed by addition of reagent 14 provides the alkylated product 17. Reduction of 17 with DIBAL-H followed by acid hydrolysis of the resulting product furnishes the functionalized enone 18. Treatment of 18 with copper(I) chloride in DMF initiates a tin-copper transmetallation and subsequent intramolecular conjugate addition reaction to provide the ketone 19. 

In the preceding two annulation examples, employment of a bromo stannane bifunctional reagent involved a reaction first at the acceptor (bromide) portion of the reagent, followed by later deployment of the donor (stannane) portion. However, this order of deployment may be reversed, as depicted in Scheme 4.

In this cyclization strategy, the bifunctional reagent 20 serves as the synthetic equivalent to a but-1-ene d^2,a^4-synthon 21 and the latent donor ability of the alkenylstannane site in 20 is chemoselectively unmasked by treatment with MeLi. Addition of CuCN generates the cuprate reagent 22 which reacts with enones of general
structure 23 to provide the adduct 24. The methylenecyclopentane annulation sequence is completed by treatment of 24 with potassium hydride to afford the intramolecular alkylation product 25.\(^9\)

Many of the bifunctional reagent mediated annulation processes developed in our laboratories have been featured in natural product syntheses. For example, the total synthesis of the diterpenoid (±)-ambliol B (33)\(^{10}\) employed the iodotrimethylgermane 26 as a synthetic equivalent to the but-1-ene d\(^2\),d\(^4\)-synthon 27 (Scheme 5).

\[ \text{MeMe}_3 \text{Ge} \quad \text{26} \quad \equiv \quad \text{d} \quad \text{d} \quad \text{27} \]

\[ \text{GeMe}_3 \quad \text{I} \quad \text{26} \quad \rightarrow \quad 1) \text{t-BuLi, THF, -78 °C} \quad \text{GeMe}_3 \quad \text{I} \quad \text{26} \quad \rightarrow \quad 2) \text{CuCN} \quad \text{Cu(CN)Li} \quad \text{28} \]

\[ \text{29} \quad \rightarrow \quad 28 \quad \text{Me}_3\text{Ge} \quad \text{30} \quad \rightarrow \quad \text{I}_2 \quad \text{30} \quad \rightarrow \quad 31 \quad \text{BuLi} \quad \text{THF, -78 °C} \quad \text{32} \quad \text{Ambliol B} \quad \text{33} \]

\[ \text{Scheme 5} \]
The cuprate reagent 28, derived from 26, was allowed to react with the enone 29 to furnish the keto trimethylgermane 30. Treatment of 30 with iodine produced the key keto iodide 31. Cyclization of 31 by reaction of this material with n-butyllithium gave the trans-fused product 32. Compound 32, possessing the bicyclic core of ambliol B, was subsequently converted to the target in several steps.10

A similar anionic cyclization approach was used to append the final ring in a synthesis of the tetraquinane diterpenoid (+)-crinipellin B (40) (Scheme 6).
In this synthesis, the iodo allylic bromide 34 served as the equivalent to a prop-1-ene d\(^1\)a\(^3\)-synthon 35. Alkylation of the advanced tricyclic intermediate 36 with reagent 34 afforded the requisite keto iodide 37. Butyllithium mediated anionic cyclization of 37 generated the tetracycle 38. Treatment of this tertiary allylic alcohol with pyridinium chlorochromate effected an oxidative rearrangement to provide the cyclopentenone 39. Further functional group manipulations completed the synthesis of the target compound crinipellin B.\(^{11}\)
1.3 Proposals

A systematic study of the stereochemical outcome of conjugate additions to bicyclo[4.3.0]non-9-en-2-ones has been conducted in our laboratory.\(^{12}\) It was found that addition of cuprate reagents to enones of general structure 41 (Scheme 7) resulted in products 42 and 43, in which the newly introduced group \(R_2\) was \(\text{trans}\) to \(R_1\). Although the \(\text{cis}\)-fused product 42 was predominant, the thermodynamically more stable \(\text{trans}\)-fused epimer 43 was obtained as the major isomer by equilibration with base.

This strategy allows access to compounds such as the 6,5-bicyclic ketone 44 in which the relative configuration of three stereogenic centers can be controlled in a single reaction sequence.
Compound 44 possesses the substitution pattern present in a number of natural products and has been featured in syntheses\textsuperscript{13} of the verrucosane-type diterpenoids (±)-verrucosane-2β-ol (45), (±)-neoverrucosan-5β-ol (46) and (±)-homoverrucosan-5β-ol (47). In the work described herein, it was proposed to utilize 44 in a synthetic route to the class of sesterterpenoids exemplified by variecolin (48),\textsuperscript{14} variecolol (49),\textsuperscript{15} variecolactone (50),\textsuperscript{15} and the variecoacetals A (51)\textsuperscript{16} and B (52)\textsuperscript{16}.
Using ketone 44 as a scaffold for further bond construction, we proposed a sequential annulation approach to assemble the carbocyclic core of the variecolin family. As previously described (Scheme 5 and Scheme 6), anionic cyclizations have proven valuable for the synthesis of 5- and 6-membered carbocyclic rings and it is envisaged that this method could be extended to cycloheptenone construction. The proposed chemistry would involve the theoretical coupling of the two donor-acceptor synthons 54 and 56 to generate substances of general structure 57 (Scheme 8). The iodo stannane 53 and ketone 55 would, presumably, serve as synthetic equivalents to the synthons 54 and 56, respectively. Oxidative rearrangement of the tertiary allylic alcohol 57 would provide the desired cycloheptenone 58. If successful, the generality of this new annulation protocol was to be explored.

Implementation of the proposed cyclization strategy would (in theory) provide cycloheptenone 59 from the ketone 44. Ring expansion studies could then be conducted
to convert 59 to the cyclooctenone 60. The latter compound may be a suitable substrate for application of a methylenecyclopentane annulation (outlined in Scheme 4) to generate compound 61. This advanced intermediate would contain the complete 5,8,6,5-tetracyclic core of the variecolin family and could act as a synthetic entry point to reach the natural products 48-52.
II. Discussion

2.1 A Synthetic Approach to the Variecolin Class of Sesterterpenoids: Total Syntheses of (±)-5-Deoxovariecolin, (±)-5-Deoxyvariecolol and (±)-5-Deoxyvariecolactone.

2.1.1 Isolation and Structure Determination

First isolated in 1991 from fermentation of the fungus Aspergillus variecolor, the sesterterpenoid variecolin (48) has been shown to possess a novel 5,8,6,5-tetracyclic carbon skeleton.\(^{14}\) Its molecular structure contains a total of eight stereogenic centers, including three contiguous stereogenic centers in the A/B ring system and five contiguous stereogenic centers (two of which are quaternary) in the B/C/D ring system. Conformational analysis of the tetracycle, using \(^1\)H-\(^1\)H coupling constants and phase-sensitive NOESY spectra, allowed determination of the relative stereochemistry of 48 and indicated that the cyclooctanoid ring B exists in a boat conformation.
Following the discovery of variecolin, two structurally related sesterterpenoids, variecolol (49) and variecolactone (50), were isolated from the mycelium of *Emericella purpurea*.

Although both variecolol and variecolactone have the same carbon skeleton as variecolin, the carbinol group has formed a 5-membered ring hemiketal with the ketone in 49, and a lactone hemiketal has formed in 50. An X-ray single crystallographic analysis of variecolactone confirmed the assigned structure and relative configurations.

More recently, immunomodulatory guided fractionation of an extract of the fungus *Emericella aurantiobrunnea* afforded the compounds 48-50, along with two new variecolin congeners named variecoacetals A (51) and B (52).
This work also led to the determination of the absolute configuration of variecolin (and presumably its congeners) based on the nmr spectral data of a chiral dimethyl-1,3,5-trioxacycloheptyl derivative 62 (Scheme 9). Careful investigation with molecular models indicates that the NOE observed between H-3' and H-6 is only possible if 62 possesses a 6-R configuration in the conformation shown.
2.1.2 Biogenesis

The novel ring skeleton of the variecolin family (48-52) appears to be a hybrid of the ophiobolin and ceriferene classes of sesterterpenoids. Hensens has proposed a unified biogenetic scheme\textsuperscript{14} from geranylfarnesyl pyrophosphate (63), based on previous biosynthetic studies of the ophiobolins, which links the ophiobolin class\textsuperscript{17} [exemplified by ophiobolin B (65)] and ceriferene class\textsuperscript{17} [exemplified by flocerol (68)] with variecolin (48) (Scheme 10). The intermediate 64 represents the point of divergence. The ophiobolin B core shown in 65 is formed from 64 via a cascade involving a 1,5-hydride shift. Alternatively, a ring expansion of 64 produces the reactive intermediate 66 which further cyclizes to 67. The skeleton of flocerol (68) is reminiscent of the biosynthetic intermediate 67, whereas the variecolin skeleton could be generated from 67 via another hydride shift cascade. It should be noted that variecolin (48) retains the functional group similarity and cis A/B ring junction of ophiobolin B (65), as well as the trans B/C ring junction and relative stereochemistry of rings C and D in flocerol (68).
Scheme 10
2.1.3 Biological Activity

All members of the variecolin family (48-52) have been shown to possess immunosuppressive activity. The IC$_{50}$ values of 48-52 calculated against Con A-(T cells) and LPS-induced (B cells) proliferation of mouse splenic lymphocytes are shown in Table 1. Although the activities of compounds 48-52 are lower than the commonly used immunosuppressive drugs Cyclosporin A or FK 506, they are comparable to or higher than the activity of the drug Azathioprine.

Table 1. Immunosuppressive Effects of Compounds 48-52, Azathioprine, Cyclosporin A and FK 506 on the Con A-Induced and LPS-Induced Proliferation of Mouse Splenic Lymphocytes (from reference 16).

<table>
<thead>
<tr>
<th>Compound</th>
<th>Con A-induced</th>
<th>LPS-induced</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>49</td>
<td>1.7</td>
<td>0.6</td>
</tr>
<tr>
<td>50</td>
<td>8.0</td>
<td>2.5</td>
</tr>
<tr>
<td>51</td>
<td>4.5</td>
<td>1.5</td>
</tr>
<tr>
<td>52</td>
<td>6.5</td>
<td>2.2</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>FK 506</td>
<td>0.000015</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

Interestingly, variecolin (48) and variecolactone (50) have been patented as useful medical and agrochemical fungicides. For example, at a concentration of 10 ppm,
compound 50 displayed 100% antifungal activity against the cucumber fungus *Pseudoperonospora cubensis*, without damaging the cucumber.

Variecolin (48) has also been reported to inhibit angiotensin II binding in rabbit aortic or bovine adrenal cortical membranes with IC$_{50}$ values of 3 ± 1 μM.$^{14}$ As an angiotensin II receptor antagonist, 48 may represent an important structural lead for hypertension lowering therapeutics. Similarly, variecolactone (50) has been patented for treatment of pulmonary hypertension, cardiovascular diseases, cerebrovascular diseases, kidney diseases and asthma.$^{19}$

2.1.4 Previous Synthetic Studies

Despite their impressive biological activity and intriguing molecular architecture, members of the variecolin family of natural products have received little synthetic attention to date. Described in this section are preliminary studies reported by Molander toward the total synthesis of variecolin (48).

2.1.4.1 Approach by Molander

The enantioselective approach to variecolin (48) proposed by Molander$^{20}$ involves a sequenced samarium(II) iodide mediated coupling of the iodo ether 70 with chloro ketone 71, to produce the cyclooctanoid hemiketal 69 *(Scheme 11)*. Further functional group interconversions would then transform compound 69 to the target 48.
Model studies using racemic compounds have demonstrated the general feasibility of the coupling step (Scheme 12). Reaction of the structurally simple iodo ether 72 with chloro ketone 73 provided the adduct 74, which was oxidized to produce the chloro lactone 75. Intramolecular cyclization of 75 with samarium(II) iodide under photochemical conditions yielded the desired cyclic hemiketal 76.
Encouraged by the results of these model studies, efforts were directed toward preparation of the component fragments (70 and 71) required for the synthesis of variecolin (48). The asymmetric syntheses detailed below were conducted before the absolute configuration of variecolin was known, and unfortunately, correspond to the enantiomer of the natural product.

**Synthesis of Enantiopure Lactone 81.**

The commercially available and inexpensive anhydride 77 was subjected to a transesterification reaction and the resulting product was oxidized to afford intermediate 78. A six step sequence from 78 provided the symmetrical diol 79. This compound was desymmetrized via an asymmetric porcine pancreas lipase (PPL) catalyzed acylation to

Scheme 12
generate 80. A five step reaction sequence converted 80 to the lactone 81, which was considered a suitable precursor to iodo ether ent-70 (Scheme 13).

Scheme 13

Synthesis of Chloro Ketone ent-71.

The known, enantiomerically pure Hajos-Parrish ketone 82 was selected as starting material for the synthesis of chloro ketone ent-71 (Scheme 14). Reduction of dione 82 and protection of the crude alcohol as a pivaloate ester furnished 83. Alkylation of indanone 83 provided the product 84. Conjugate reduction of the alkylated indanone 84 with NaBH₄/NiCl₂ gave an unstable trans-fused ketone which was directly hydrogenated to afford ketal 85 in a moderate 52% yield. Reductive removal of the pivaloate ester of 85, and subsequent oxidation of the acquired alcohol with the Dess-Martin periodinane produced the ketone 86. This substance was transformed to the enone 87 using a two step Saegusa protocol. Unfortunately, installation of the D-ring
isopropenyl group by means of an organocuprate addition occurred from the undesired face of the bicyclic enone, to provide ketone 88. To correct the configuration of the isopropenyl group, it was decided to first remove the existing ketone moiety, then cleave the double bond to a methyl ketone and, finally, epimerize the latter material. Reduction of the ketone 88 proved troublesome, furnishing the deoxygenated product 89 in only 52% yield. However, ozonolysis and base catalyzed epimerization proceeded smoothly to afford the thermodynamically favored ketone 90. A Wittig olefination reinstalled the double bond to give 91. Hydrolysis of ketal 91 to the corresponding hemiketal 92 was carried out using catalytic amounts of PdCl2(MeCN)2 in a mixture of acetonitrile and water. Finally, treatment of 92 with Ph3P and CCl4 afforded a 3:1 mixture of the chloro ketone ent-71 and recovered starting material, respectively.

Future Prospects

The Molander group is presently continuing its synthetic studies toward variecolin and efforts are underway to prepare the correct enantiomer of each component fragment. To date, results from the key coupling of fragments 70 and 71 have not been reported.
Scheme 14
2.1.5 Retrosynthetic Analysis.

Our proposed synthetic route to the variecolin class of sesterterpenoids (48-52) involves a sequential annulation approach to establish each of the rings present in these natural products (Scheme 15). It was envisioned that each of the target molecules (48-52) could be derived from 5-deoxyvariecolol (93) through a short sequence of functional group interconversions. Compound 93 contains the complete carbon skeleton and relative configuration present in the variecolin family and could be produced from 94 via a reduction and intramolecular radical etherification protocol. The advanced intermediate 94 may be assembled from 61 through a series of reactions including a Pd(0) catalyzed methoxycarbonylation and subsequent chemo- and stereoselective olefinic double bond hydrogenation. A methylenecyclopentane annulation sequence (as outlined in Scheme 4) employing cuprate 22 could allow access to 61 from tricyclic enone 60. The later compound could be generated by reduction and homologation of the enone 59, which in turn could be produced from combination of bicyclic ketone 44 with the bifunctional reagent 53 in the novel cycloheptenone annulation described in Section 1.3 (page 13). The required ketone 44 can be obtained from commercially available starting materials (including 95 and 96) using methods previously developed in the Piers laboratory.12,13
Scheme 15
2.1.6 Preparation of the Bicyclic Ketone 44.

Helquist and coworkers\textsuperscript{6} have developed a two step cyclopentene annulation sequence employing the Grignard reagent 3. The first step involves a copper(I)-catalyzed conjugate addition of the bifunctional reagent 3 to an enone substrate. In the second step, an acid catalyzed acetal hydrolysis and subsequent intramolecular aldol condensation-dehydration sequence completes the annulation. The application of this method to produce bicyclic enone 98 is illustrated in Scheme 16.\textsuperscript{6}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {95};
\node at (2,0) {3};
\node at (4,0) {97};
\node at (6,0) {98};
\draw[->, thick] (0.5,0.5) -- (2.5,0.5);
\draw[->, thick] (2.5,0.5) -- (4.5,0.5);
\draw[->, thick] (4.5,0.5) -- (6.5,0.5);
\node at (0.25,-0.5) {CuBr·SMe\textsubscript{2}, THF -78 °C, 10 h;}
\node at (0.25,-0.7) {warm to 0 °C over 6 h;}
\node at (0.25,-0.9) {0 °C, 2 h}
\node at (2.25,-0.5) {BrMg, THF -78 °C, 10 h;}
\node at (2.25,-0.7) {warm to 0 °C over 6 h;}
\node at (2.25,-0.9) {0 °C, 2 h}
\node at (4.25,-0.5) {HCl, H\textsubscript{2}O, THF, rt}
\node at (4.25,-0.7) {72 h}
\node at (6.25,-0.5) {74%}
\node at (6.25,-0.7) {77%}
\end{tikzpicture}
\end{center}

Scheme 16

To commence our work we adopted a refined version of this procedure to efficiently prepare compound 98. Based on the work of Stowell,\textsuperscript{21} the bifunctional reagent 3 was replaced with the Grignard reagent 99 derived from bromo acetal 96. Reagent 99 is more conveniently prepared and has greater thermal stability than 3, owing to the propensity of the latter substance to undergo intramolecular attack leading to a cyclopropyl ether (Scheme 17).
The annulation was further modified according to the method of Kuwajima and coworkers. This group has reported that the use of TMSCl and HMPA as additives greatly improved the yields and reduced the reaction times of copper(I)-catalyzed conjugate addition reactions (Scheme 18).

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield of Ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1-2%</td>
</tr>
<tr>
<td>TMSCl (2 equiv.)</td>
<td>30-40%</td>
</tr>
<tr>
<td>TMSCl/HMPA (1-2 equiv. each)</td>
<td>99%</td>
</tr>
</tbody>
</table>
Thus, treatment of 3-methylcyclohex-2-en-1-one (95) with the Grignard reagent 99 in the presence of TMSCl (3.0 equiv.), HMPA (3.0 equiv.) and catalytic CuBr·SMe₂ (15 mol%) afforded, after workup and purification, the keto acetal 100 in 95% yield (equation 1). The spectral properties of compound 100 were identical with those previously reported. For the purpose of comparison it should be noted that the procedure reported by Helquist⁶ provided 97 in 77% yield after a reaction time of 18 h, whereas the modified procedure described above afforded 100 in 95% yield after 2.5 h.

The next step of the annulation sequence required conversion of the keto acetal 100 to the enone 98. The conditions reported by Helquist and coworkers (HCl/H₂O/THF) for the analogous conversion of 97 to enone 98 required a lengthy reaction time (72 h) to reach completion (see Scheme 16). A modified protocol published by Piers and Oballa²⁴ accomplished a similar transformation expeditiously by heating a mixture of 101 in 80% aqueous CF₃CO₂H/dioxane (1:2) at 70 °C for 16 h to provide enone 102 (equation 2).
Piers and Boulet later recommended replacing the relatively high boiling dioxane solvent with THF in this step to facilitate isolation of the product. Following this procedure, a mixture of keto acetal 100 in 80% aqueous CF$_3$CO$_2$H/THF (1:2) was heated at 70 °C for 2.5 h to afford after workup and flash chromatography, the enone 98 in 71% yield. The chromatography column was then flushed with diethyl ether to elute several polar intermediates produced in the cyclization process. The combined eluate was concentrated and the residue obtained was resubjected to acidic reaction conditions (80% aqueous CF$_3$CO$_2$H/THF (1:2), 70 °C) for 16 h to provide after workup and flash chromatography, an additional 12% of the enone 98. The total yield of compound 98 was 83% (Scheme 19). The use of longer reaction times to drive the reaction to completion lead to concomitant formation of by-products that were difficult to separate from the desired enone by flash chromatography.

![Scheme 19](image-url)
The next stage of the synthesis involved conjugate addition of an isopropenyl cuprate reagent to the bicyclic enone 98. Surprisingly, prior to a recent study by Piers and Oballa, little was known about the stereochemical outcome of conjugate addition reactions on bicyclo[4.3.0]non-9-en-2-ones. Table 2 summarizes the results of the study which involved conjugate addition of the organocopper(I) reagent 28 to bicyclo[4.3.0]non-9-en-2-ones 103.

Table 2: Cuprate Additions to Bicyclo[4.3.0]non-9-en-2-ones and Base-Promoted Equilibration of the Resulting Adducts (from reference 12).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Overall Yield (Isolated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cis-Fused</td>
</tr>
<tr>
<td>1</td>
<td>Me</td>
<td>H</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[1 : 3]</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Me</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[99 : 1]</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[1 : 30]</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Me</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>[1 : 5]</td>
</tr>
</tbody>
</table>

-This ratio was obtained upon base equilibration (NaOMe/MeOH/rt) of the cis- and trans-fused epimers.

For each of the substrates, the conjugate addition reaction proceeded completely stereoselectively, with the 3-trimethylgermylbut-3-enyl group being introduced trans to
the angular group R'. In each case, hydrolysis of the resultant silyl enol ether provided a mixture of C-1 epimers with the cis-fused epimer 104 predominating. Each of the adducts in Table 2 was subjected to base-promoted equilibration (NaOMe-MeOH) and the equilibrium ratio of each pair of epimers was determined. For each of the entries 1, 3 and 4 the trans-fused epimer 105 was found to be thermodynamically more stable than the cis-fused epimer 104. In contrast, for entry 2 (R, R' = Me) the cis-fused epimer was found to be more stable. This result was explained in terms of the destabilizing pseudo 1,3-diaxial interaction between the two methyl groups present in the trans-fused epimer (see below).

The overall data was consistent with the equilibrium ratios determined by Dana and coworkers27 for structurally similar compounds. They showed that when a methyl substituent at C-9 is anti to the angular group at C-6 (H or Me), the trans-fused epimer was favored (Scheme 20).
In our work, a sequence involving isopropenyl conjugate addition to the enone \textit{98} followed by base mediated epimerization was envisaged to provide \textit{44}. Addition of 2-bromopropene (\textit{106}) to a solution of \textit{tert}-butyllithium (2.0 equiv.) in THF at -78 °C generated the corresponding isopropenyllithium reagent. Additional of solid copper(I) cyanide (1.0 equiv.) provided a suspension which was stirred at -78 °C for 45 min and then warmed to -45 °C for 15 min to give a pale yellow solution of the cyanocuprate \textit{107} (equation 3).

\begin{equation}
\begin{align*}
\text{Br} & \quad \text{1) } t\text{-BuLi, THF, -78 °C} \\
& \quad \text{2) } \text{CuCN, -78 °C to -45 °C} \\
\end{align*}
\end{equation}

Addition of the bicyclic enone \textit{98} to a solution of the cuprate \textit{107} in the presence of TMSCl\textsuperscript{28} resulted in a rapid conjugate addition. A tlc analysis of the reaction mixture after 5 min indicated complete consumption of the starting material \textit{98} and showed the formation of a non-polar product corresponding to the resultant silyl enol ether. The mixture was warmed to room temperature and was then treated with water. This effected a hydrolysis of the intermediate silyl enol ether to provide, exclusively, the \textit{cis}-fused ketone \textit{108} in 87% yield (equation 4).\textsuperscript{29,30}
The $^1$H nmr spectrum of ketone 108 revealed a singlet for the angular methyl (Me-22, variecolin numbering$^{31}$) at $\delta$ 1.11, a singlet for the isopropenyl methyl (Me-25) at $\delta$ 1.71, a doublet for the angular proton (H-15) at $\delta$ 2.56 ($J = 10.1$ Hz), a signal for H-16 at $\delta$ 2.86 (ddd, $J = 10.1, 10.1, 10.1$ Hz), and two alkenyl proton signals for H-24 and H-24' at $\delta$ 4.78 and $\delta$ 4.83, respectively. The relative stereochemistry was assigned on the basis of NOED experiments. Irradiation of the signal at $\delta$ 1.11 (Me-22) showed enhancements for the signals at $\delta$ 2.56 (H-15) and $\delta$ 2.86 (H-16). Similarly, irradiation of the signal at $\delta$ 2.56 (H-15) showed enhancements for the signals at $\delta$ 1.11 (Me-22) and $\delta$ 2.86 (H-16). Finally, irradiation of the signal at $\delta$ 2.86 (H-16) showed enhancements for the signals at $\delta$ 1.11 (Me-22) and $\delta$ 2.56 (H-15). These results are consistent with addition of the isopropenyl cuprate reagent anti to the angular methyl group and the subsequent generation of a cis ring junction.

Equilibration of the cis-fused ketone 108 with sodium methoxide in methanol provided an 11:1 ratio$^{29}$ of the trans- and cis-fused compounds 44 and 108, respectively, in 95% yield (equation 5). Chromatographic separation of the mixture on silica gel was difficult and provided the pure trans-fused ketone 44 in 64% yield along with mixed fractions containing both 44 and 108. However, the mixed fractions could be resubjected to flash chromatography to provide good overall yields of pure 44.
The $^1$H nmr spectrum of the trans-fused epimer 44 revealed a singlet for the angular methyl (Me-22) at $\delta$ 0.76, a singlet for the isopropenyl methyl (Me-25) at $\delta$ 1.70, a doublet for the angular proton (H-15) at $\delta$ 2.47 ($J$ = 11.1 Hz), a signal for H-16 at $\delta$ 2.84 (ddd, $J$ = 11.1, 11.1, 6.6 Hz), and two alkenyl proton signals for H-24 and H-24' at $\delta$ 4.62 and $\delta$ 4.66, respectively. Confirmation of the trans ring fusion was provided by NOED experiments. Irradiation of the signal at $\delta$ 2.47 (H-15) showed an enhancement for the signal at $\delta$ 1.70 (Me-25). Similarly, irradiation of the signal at $\delta$ 1.70 (Me-25) showed an enhancement for the signal at $\delta$ 2.47 (H-15). This is consistent with H-15 and the isopropenyl Me-25 being on the same face of the molecule. Since it was shown (vide supra) that the isopropenyl group added anti to the angular methyl (Me-22), the ring fusion must be trans.
2.1.7 Preparation of the Tricyclic Enone 59: Development of a New Cycloheptenone Annulation Method.

Over the years, a number of methods for the construction of seven-membered rings have been devised and successfully employed in complex molecule synthesis.\textsuperscript{32} Examples of such methods include the homo-Cope rearrangement of 1,2-divinylcyclopropane systems,\textsuperscript{33} ring expansion reactions,\textsuperscript{34} and cycloaddition processes.\textsuperscript{35} However, new (general) procedures for the expeditious formation of seven-membered carbocycles are desirable. The next stage of the synthesis involved the development of a novel method for appending a seven-membered ring onto the bicyclic ketone 44 as illustrated for the conversion of 44 into the tricycle 59 (Scheme 21).
The production of cycloheptenone 59 was anticipated from a chromium(VI)-mediated oxidative rearrangement of the tertiary allylic alcohol 110. It was hoped that alcohol 110 could be produced from the intramolecular addition of an alkenyl anion to the carbonyl function of 111. For example, treatment of keto iodide 111 with butyllithium should effect a lithium-iodine exchange reaction to generate an alkenyllithium intermediate. This anionic species could then react with the carbonyl group to provide the annulated product 110. The keto alkenyl iodide 111 may be prepared by stereospecific iododestannylation of the corresponding alkenylstannane 112. Alkylation of ketone 44 with the bifunctional reagent 53, followed by a second alkylation with methyl iodide was expected (vide infra) to provide the desired adduct 112.

The proposed cycloheptenone annulation required an efficient preparation of the novel bifunctional reagent (Z)-5-iodo-1-tributylstannylpent-1-ene (53). Although there are a number of reported methods for generating alkenylstannanes, many of these produce mixtures of the (E)- and (Z)-isomers with the more stable (E)-isomer often predominating.36 Fewer general methods are available for the stereoselective preparation of (Z)-alkenylstannanes. For example, the direct method involving catalytic hydrogenation of alkynylstannanes is not an option for preparing (Z)-alkenylstannanes under typical conditions.37 However, an attractive alternative has been devised by Lipshutz and coworkers to allow efficient preparation of these substances (Scheme 22).38

\[
\begin{align*}
&\text{R'} \equiv \equiv \text{SnR}_3 + \text{Cp}_2\text{Zr(H)Cl} \\
&\text{THF} \rightarrow \text{R'} \equiv \equiv \text{SnR}_3 + \text{ZrCp}_2\text{Cl} \\
&\text{H}_2\text{O} \rightarrow \text{R'} \equiv \equiv \text{SnR}_3
\end{align*}
\]

Scheme 22
This group has shown that the hydrozirconation of alkynylstannanes 113 with \( \text{Cp}_2\text{Zr(H)Cl} \) (Schwartz’s reagent\(^{39}\)) proceeds regio- and stereoselectively to afford adducts of general structure 114. Protonolysis of the intermediates 114 generates the corresponding (Z)-alkenylstannanes 115. The interesting regiochemistry of the hydrozirconation, which places the \( \text{Cp}_2\text{ZrCl} \) moiety on the same carbon as the trialkylstannyl group, was rationalized by the long carbon-tin bond (\(-2.2\ \text{Å}\)), the sensitivity of the reaction to steric effects, and the polarizability of the carbon-tin bond.\(^\text{38}\)

On the basis of this account, the (Z)-alkenylstannane 53 required for our work was prepared as shown in Scheme 23.

\[
\begin{align*}
\text{OH} & \quad \text{TBDMS-Cl} \quad \text{imidazole} \quad \text{CH}_2\text{Cl}_2, \text{r.t.} \\
\text{116} & \rightarrow \text{OTBDMS} \\
\text{117} & \quad \text{1)} \text{MeLi, THF, -78 °C} \\
& \quad \text{2)} \text{Bu}_3\text{SnCl, -78 °C to r.t.} \\
& \quad \text{SnBu}_3 \\
\text{118} & \quad >99\% \\
& \downarrow \text{1)} \text{Cp}_2\text{Zr(H)Cl} \\
& \quad \text{THF, r.t.} \\
& \quad \text{2)} \text{H}_2\text{O} \\
\text{120} & \quad \text{90\%} \\
& \downarrow \text{Ph}_3\text{P}\cdot\text{I}_2, \text{imidazole} \\
\text{Bu}_3\text{Sn} & \quad \text{MeCN, Et}_2\text{O} \\
& \quad 0 °\text{C to r.t.} \\
\text{53} & \quad 95\% \\
& \downarrow \text{Bu}_4\text{NF, THF} \\
& \quad \text{r.t.} \\
\text{119} & \quad 92\% \\
\end{align*}
\]

Scheme 23
Treatment of commercial pent-4-yn-1-ol (116) with tert-butyldimethylsilyl chloride in the presence of imidazole\textsuperscript{40} provided the silyl ether 117 in 92% yield. The IR spectrum of 117 showed a sharp alkynyl C-H stretching frequency at 3314 cm\textsuperscript{-1} and a C-C triple bond stretch at 2121 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectrum indicated presence of the tert-butyldimethylsilyl ether by a six proton singlet at $\delta$ 0.02 for the two methyl groups on silicon and a nine proton singlet at $\delta$ 0.93 for the tert-butyl group.

Deprotonation of 117 with methyllithium and reaction of the resultant lithium acetylide with Bu\textsubscript{3}SnCl afforded the crude alkynylstannane 118 in >99% yield. The IR spectrum of 118 exhibited a C-C triple bond absorption at 2151 cm\textsuperscript{-1} and, in agreement with the assigned structure, no alkynyl C-H absorption was observed. The \textsuperscript{1}H nmr spectrum of 118 displayed signals at $\delta$ 0.82-0.99 (m, 15 H), $\delta$ 1.24-1.38 (m, 6H) and $\delta$ 1.49-1.58 (m, 6H) corresponding to the newly introduced tributylstannyl group. Compound 118 was found to be unstable to silica gel chromatography and was used without further purification in the next reaction.

Subjection of 118 to hydrozirconation with Schwartz's reagent\textsuperscript{39} (1.2 equiv.) in THF at room temperature, followed by protonation of the resultant intermediate, produced the (Z)-alkenylstannane 119 in 92% yield. The structure of 119 was confirmed by analysis of the spectroscopic (IR, \textsuperscript{1}H nmr and \textsuperscript{13}C nmr) data. The IR spectrum displayed a C-C double bond stretching frequency at 1599 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr spectrum of 119 indicated the presence of a tert-butyldimethylsilyl ether by the appearance of a six proton singlet at $\delta$ 0.03 for the two methyl groups on silicon and a nine proton singlet at $\delta$ 0.86 for the tert-butyl group. An alkenyl proton signal was observed for H-1 at $\delta$ 5.79 (dt, $J = 12.4, 0.9$ Hz, $^2J_{Sn-H} = 70$ Hz) and for H-2 at $\delta$ 6.50 (dt, $J = 12.4, 7.1$ Hz, $^3J_{Sn-H} = 147$ Hz).
Hz). The coupling constant ($J = 12.4$ Hz) between H-1 and H-2 is consistent with a (Z)-alkene geometry. Also diagnostic is the large tin-proton coupling constant ($^3J_{Sn-H} = 147$ Hz) indicative of a trans relationship between the Sn and H-2. The $^{13}$C nmr spectrum revealed the expected number of signals including two alkenyl carbon resonances at $\delta$ 128.1 and $\delta$ 148.1.

![Diagram of 119](image)

Routine tetrabutylammonium fluoride induced cleavage of the silyl ether of 119 provided the alcohol 120 in 90% yield. This was evidenced in the IR spectrum of 120 by an O-H stretching absorption at 3325 cm$^{-1}$.

The synthesis of the bifunctional reagent was completed by reaction of the alcohol 120 with PPh$_3$I$_2$ and imidazole$^{41}$ in acetonitrile-diethyl ether (3:2) to afford iodide 53 in 95% yield. The overall yield of 53 from pent-4-yn-1-ol (116) was ~70%. Compound 53 was stored in the dark over copper wire and, under these conditions, was found to be stable for over one year at ambient temperature. The spectral data for 53 supported the assigned structure. The IR spectrum of 53 showed an alkenyl absorption at 1598 cm$^{-1}$. The $^1$H nmr spectrum displayed a signal for the alkenyl proton H-1 at $\delta$ 5.85 (d, $J = 12.4$Hz, $^2J_{Sn-H} = 69$ Hz) and a signal for H-2 at $\delta$ 6.45 (dt, $J = 12.4$, 7.0 Hz, $^3J_{Sn-H} = 146$ Hz).
Hz). The coupling constant \( J = 12.4 \, \text{Hz} \) between H-1 and H-2 and the coupling constant \( \langle \delta J_{Sn-H} = 146 \, \text{Hz} \rangle \) between Sn and H-2 revealed that the (Z)-configuration of the double bond remained unchanged.

With the key bifunctional reagent 53 in hand, the annulation sequence could now be explored. The first step would require alkylation of the enolate derived from ketone 44 with the iodide 53. Earlier reports have shown that in the absence of opposing steric interactions, cyclohexanone enolate systems favor the axial introduction of a new alkyl substituent.\(^{42}\) This satisfies the stereoelectronic requirement for perpendicular approach of an electrophile to the enolate, and maintains maximum orbital overlap in a chair-like transition state (Scheme 24). It was expected that similar stereochemical control elements would operate in our synthesis.
Preliminary attempts to alkylate the bicyclic ketone 44 with reagent 53 employing LDA as base failed to afford either of the potential products 121 or 122. Use of KHMDS as the base in this reaction resulted in low yields (<30%) of the alkylated material 121, with predominant recovery of the starting ketone 44. After further experimentation, reproducibly good yields for the alkylation process were obtained under carefully defined reaction conditions. Specifically, treatment of 44 with KDA\textsuperscript{43} in THF at -78 °C, followed by addition of HMPA (4.0 equiv.) and the electrophile 53, and gradual warming of the reaction mixture, gave two products (equation 6).

Monitoring the progress of the reaction by tlc indicated that a single major product was formed in the early stages of the reaction. Over time, the proportion of this
substance decreased with the attendant formation of a less polar spot on the tlc. The initially formed compound was presumed to be an alkylated product 121 in which the newly introduced side chain was in an axial orientation. Under the reaction conditions this material was largely epimerized to the thermodynamically more stable isomer 122, with the side chain in an equatorial orientation. Compounds 121 and 122 were isolated in 9% and 65% yield, respectively. The overall yield of the alkylation reaction was 74%.

Notably, the use of HMPA as an additive was found to be essential for the success of the reaction. The yield enhancing effect of HMPA on enolate alkylations is well known and has been attributed to several factors. The additive can coordinate with the counterion (such as lithium or potassium ion) to enhance the nucleophilic nature of an enolate anion, by diminishing its aggregate state and thereby increasing its reactivity. Moreover, the augmentation of solvent polarity upon addition of HMPA may accelerate the reaction by lowering the activation energy for the $S_N2$ alkylation step.

The spectroscopic data was consistent with the structure of alkylated ketone 121. The $^1$H nmr spectrum of 121 displayed a singlet for the angular methyl (Me-22) at $\delta$ 0.75, a singlet for the isopropenyl methyl (Me-25) at $\delta$ 1.70, a doublet for H-15 at $\delta$ 2.66 ($J$ = 11.1 Hz) and a signal for H-16 at $\delta$ 2.84 (ddd, $J$ = 11.1, 11.1, 6.4 Hz). The expected four alkenyl proton signals were observed at $\delta$ 4.59 (s, H-24), $\delta$ 4.66 (br s, H-24'), $\delta$ 5.78 (d, $J$ = 12.4 Hz, $^2J_{Sn-H}$ = 73 Hz, H-9) and $\delta$ 6.42 (ddd, $J$ = 12.4, 7.0, 7.0 Hz, $^3J_{Sn-H}$ = 143 Hz, H-8). The $^{13}$C nmr spectrum of 121 exhibited alkenyl carbon signals at $\delta$ 108.5, 128.6, 147.5 and 148.3 as well as a carbonyl signal at $\delta$ 213.5.

Similarly, the $^1$H nmr spectrum of 122 displayed a singlet for the angular methyl (Me-22) at $\delta$ 0.69, a singlet for the isopropenyl methyl (Me-25) at $\delta$ 1.69, a doublet for
H-15 at δ 2.48 (J = 11.1 Hz) and a signal for H-16 at δ 2.88 (dd, J = 11.1, 11.1, 6.1 Hz). Alkenyl proton signals were observed at δ 4.61 (s, H-24), δ 4.65 (s, H-24'), δ 5.76 (d, J = 12.3 Hz, 2J_{Sn-H} = 73 Hz, H-9) and δ 6.49 (ddd, J = 12.3, 7.0, 7.0 Hz, 3J_{Sn-H} = 143 Hz, H-8). The ^13C nmr spectrum of 122 exhibited alkenyl carbon signals δ 108.9, 127.8, 147.4 and 148.9 as well as a ketone carbonyl signal at δ 210.5.

To install the quaternary center at C-11 (variecolin numbering) a regio- and stereoselective methylation was now required. Gratifyingly, treatment of a mixture of the ketones 121 and 122 with LDA in THF followed by the addition of methyl iodide provided a single diastereomer 112 in 87% yield (equation 7).

The expectation that the methyl group had been installed in an axial orientation was verified by X-ray single crystallographic analysis of a synthetic intermediate derived from 112 (vide infra). The ^1H nmr spectrum of 112 confirmed that methylation had occurred at C-11. The angular methyl group (Me-22) displayed a singlet at δ 0.69 and the newly introduced methyl group (Me-21) was attributed to a singlet at δ 1.17. The isopropenyl methyl (Me-25) exhibited a singlet at δ 1.69 and H-15 exhibited a doublet at δ 2.76 (J = 11.0 Hz). The regioselectivity of enolate formation in this reaction can be easily understood from an examination of molecular models. Since H-15 is buried within
the bicyclic framework of ketones 121 and 122, it is more difficult to remove by base than the peripherally located, less sterically encumbered H-11.

Treatment of the keto alkenylstannane 112 with iodine (1.1 equiv.) in dichloromethane at room temperature provided the corresponding iodide 111 in 94% yield (equation 8).

![Chemical structure](image)

The $^1$H nmr spectrum of 111 supported the assigned structure. The angular methyl group resonances were observed as singlets at $\delta$ 0.70 and $\delta$ 1.18 while the isopropenyl methyl group displayed a singlet at $\delta$ 1.68. The alkenyl protons for the isopropenyl group were observed as singlets at $\delta$ 4.56 and $\delta$ 4.64, whereas the alkenyl protons of the vinyl iodide moiety appeared as a two proton multiplet at $\delta$ 6.14-6.21.

A pivotal stage had been reached where the decisive anionic cyclization of keto iodide 111 could be attempted. For optimal success, the alkenyllithium intermediate derived from 111 via lithium-iodine exchange would have to favor intramolecular addition to the ketone group over potentially competing intermolecular processes. These competing processes could include intermolecular addition of the transient alkenyllithium species to the carbonyl of a second molecule of 111 or abstraction of the proton on the carbon α to the carbonyl group of 111 to generate a protiodeiodinated product (H in place of I in 111). To promote the desired intramolecular cyclization pathway, dilute reaction
mixtures (~0.02 M in 111) were employed. In the event, treatment of a solution of 111 in THF at 0 °C with a solution of BuLi (2.1 equiv.) in hexanes smoothly furnished a single major product. Workup and recrystallization of the crude product from pentane afforded the allylic alcohol 110 (mp = 118.5-119.5 °C) in 82% yield (equation 9).

\[
\begin{align*}
\text{111} & \quad \text{BuLi} \quad \text{THF, 0 °C} \\
& \quad \text{110} \quad 82%
\end{align*}
\]

The only side product detected in the reaction was a small amount of the uncyclized, protiodeiodinated material. The IR spectrum of the protiodeiodinated compound showed a ketone absorption at 1712 cm\(^{-1}\) and the \(^1\)H nmr spectrum exhibited a complex set of five alkenyl signals. Interestingly, conducting the reaction at lower temperature dramatically increased the proportion of this synthetically unproductive byproduct. For example, glc analysis of a reaction performed at -78 °C indicated a 4:1 ratio of protiodeiodinated material to alcohol 110, respectively.

Evidence that 110 was indeed material derived from the desired cyclization was provided by the spectroscopic data. The IR spectrum of 110 showed a hydroxyl group absorption at 3500 cm\(^{-1}\) while a carbonyl absorption (1708 cm\(^{-1}\) for the starting material 111) was absent. The \(^1\)H nmr spectrum of 110 displayed signals at \(\delta 4.62\) (br s) and \(\delta 4.76\) (d, \(J = 2.0\) Hz) for the alkenyl protons of the isopropenyl group as well as signals at \(\delta 5.70\) (ddd, \(J = 11.9, 4.4, 4.4\) Hz) and \(\delta 5.74\) (d, \(J = 11.9\) Hz) for the alkenyl protons associated with the seven-membered ring. Although the data suggested that the
annulation had been successful, it provided no conclusive evidence for the relative stereochemistry at the new ring junction. However, a single crystal X-ray analysis of the product (Appendix 1) proved that this material possessed a trans-fusion at the newly introduced ring (Figure 1). This structure determination also validated the previously postulated conclusions regarding stereochemical issues in the synthesis. In particular, the earlier alkylation step was verified to have proceeded with axial introduction of the methyl group.

Figure 1. Stereoview of the allylic alcohol 110
The following rationalization for the stereochemical outcome of the anionic cyclization is predicated on the assumption that an alkenyllithium compound 123 (Scheme 25) is a discrete intermediate in the reaction. This intermediate would arise from treatment of 111 with BuLi. Ring closure of 123 could take place by attack of the alkenyllithium carbon on the carbonyl carbon from either the axial or the equatorial direction. Attack from the equatorial direction (pathway i) to provide the trans-fused compound 110 should proceed through a transition state resembling conformer 123A. Conversely, attack from the axial direction (pathway ii) to provide the cis-fused compound 124 should proceed through a transition state resembling conformer 123B. Clearly, the destabilizing 1,3-diaxial interactions between the approaching alkenyllithium moiety and the angular methyl group (Meₐ) and hydrogen atoms (H₉ and H₆) shown in 123B should disfavor the corresponding transition state for axial attack via pathway ii. Since equatorial attack does not suffer from this disadvantage, pathway i is favored and, in practice, only the trans-fused product 110 is produced.
Scheme 25
Completion of the annulation sequence required oxidative rearrangement of the tertiary allylic alcohol moiety of 110 with a Cr(VI) reagent. To this end, treatment of 110 with PCC\(^{48}\) (5.0 equiv.) in the presence of 3 Å molecular sieves\(^{49}\) (0.85 g/mmol 110) in refluxing dichloromethane for 2.5 h provided the desired enone 59 in 72% yield (equation 10). The spectral data obtained for compound 59 were in complete agreement with the assigned structure. The IR spectrum of this material displayed a strong (\(\alpha,\beta\)-unsaturated) carbonyl absorption at 1646 cm\(^{-1}\). The \(^1\)H nmr spectrum of 59 displayed a total of three alkenyl proton resonances including signals at \(\delta 4.63\) and \(\delta 4.68\) for the alkenyl protons of the isopropenyl group and, importantly, a downfield signal at \(\delta 5.61\) for the enone proton. The \(^13\)C nmr spectrum of 59 also exhibited diagnostic signals at \(\delta 125.5\) (C=CH), \(\delta 161.1\) (C=CH) and \(\delta 205.4\) (C=O) for the enone moiety.

The dramatic beneficial effect of using molecular sieves in the PCC oxidation deserves comment. Oxidation of the alcohol 110 under other conditions (PCC, NaOAc, CH\(_2\)Cl\(_2\)\(^{48}\) or PCC adsorbed on alumina\(^{50}\) in CH\(_2\)Cl\(_2\)) was very slow and required a long reaction time (~ 1 week!) with a large excess of PCC to drive the reaction to completion. These forcing conditions were experimentally inconvenient and resulted in diminished yields of the desired enone 59. However, addition of dry, powdered 3 Å molecular sieves greatly accelerated the PCC oxidation and afforded enone 59 in good yield.
A postulated pathway for the oxidative rearrangement is shown in Scheme 26. Since the alcohol function of 110 resides in a sterically hindered environment, formation of the initial chromate ester 125 may be rate determining. This is also supported by the notion that relief of steric strain should promote the subsequent rearrangement step. Furthermore, the rearranged chromate ester 126 appears well disposed for cleavage of the adjacent C-H bond which suggests that this step cannot reasonably account for the remarkably slow oxidation observed in the absence of molecular sieves. Therefore, speculatively, the molecular sieves may accelerate the reaction by facilitating the formation of the intermediate chromate ester 125.
2.1.8 Strategic Overview for Assembly of the A- and B-Rings.

Two general strategies for the homologation of ring-B and appendage of ring-A were considered at this point (Scheme 27). The first approach (strategy 1) would involve conversion of 59 to the isomeric enone 127 followed by application of a methylenecyclopentane annulation sequence (see Scheme 4 on page 7) to generate tetracycle 128. Regioselective ring expansion of the latter substance would provide the advanced intermediate 61 possessing the desired 5,8,6,5-carbocyclic core of the variecolin class of natural products.

A second approach (strategy 2) would involve a series of reactions, including ring expansion, to convert substance 59 to the cyclooctenone 60. Deployment of the methylenecyclopentane annulation sequence would transform 60 to the tetracycle 61.

Clearly, issues of stereocontrol and the effects of molecular topography would be paramount to the success of either synthetic plan. The following sections (2.1.9-2.1.11) will discuss studies involving both strategies which ultimately culminated in the selection of strategy 2 as the most efficient route to compound 61.
Scheme 27

Strategies:
- Strategy 1:
  - 59 -> 127
- Strategy 2:
  - 60 -> 128
  - 128 -> 61

Diagram:
- 59
- 127
- 60
- 128
- 61

Scheme 27
2.1.9 Preparation of Cyclooctenone 60.

It was envisioned that cyclooctenone 60 could be prepared from a selective one-carbon ring expansion of the cycloheptanone 129. The latter substance could be produced from a 1,2-carbonyl transposition of the isomeric ketone 130 which, in turn, could be generated by conjugate reduction of the enone 59 (Scheme 28).

Surprisingly, a survey of the literature revealed little precedent for the stereochemical outcome of 1,4-reduction reactions of cycloheptenones. Moreover, for the 1,4-reduction of cycloheptenone 59, it was expected that the highly hindered environment of the β-carbon would preclude the use of hydride reducing reagents. This expectation was realized when enone 59 failed to undergo a hydridoalkyl cuprate-induced conjugate
reduction under the conditions utilized by Daniewski\textsuperscript{52} for the efficient conversion of indenone 131 to ketone 132. (Scheme 28). To further frustrate matters, generation of the requisite trans 7,6-ring fusion of ketone 130 would require hydride addition to the arguably more sterically encumbered α-face of enone 59.

A dissolving metal reduction of 59 was considered a promising solution to the difficulties delineated above. The results of extensive synthetic and mechanistic studies of dissolving metal reductions have been reviewed by Caine\textsuperscript{53} and only a brief overview will be presented here. On the basis of the available evidence, it appears that there are two possible, perhaps competing, pathways for the conjugate reduction of α,β-unsaturated carbonyl compounds with metals in liquid ammonia (Scheme 29). Addition of an electron from the metal (M = Li, Na, K etc.) to the enone system of 133 yields a radical anion 134. The latter may undergo a rate-limiting protonation\textsuperscript{54} to give the hydroxyallyl radical 135, which can rapidly accept a second electron to generate the anion 136.
Protonation of the hydroxyallyl anion 136 produces an enol 137 which can transfer a proton to a base (before ketonization) to give the enolate 138. Alternatively, addition of a second electron to the radical anion 134 may generate a dianion intermediate 139 which is capable of accepting a proton to directly give the enolate 138. Irrespective of the timing of addition of the first proton and second electron, the enolate ultimately produced can be protonated (often by an alcohol proton donor added to the reaction mixture) to provide the ketone 140. For simplicity of illustration in the subsequent discussion the species undergoing β-protonation is represented as the dianion.

Scheme 30
The stereochemistry of the conjugate reduction is established by the proton transfer to the β-carbon. Based on the results from metal-ammonia reduction of enones with a β-carbon at the fusion of two six-membered rings, Stork has formulated a rule to predict the stereochemistry of the product.\textsuperscript{55} This rule states that the product will be the more stable of the two isomers (\textit{cis} or \textit{trans}) having the newly introduced hydrogen axial to the ketone ring. This reflects the preference for protonation perpendicular to the π-system to maintain continuous orbital overlap of the β-carbon with the enolate double bond. Given that this stereoelectronic requirement is met, the stereochemistry normally corresponds to protonation of the most stable conformation of the anionic intermediate.

For example, the reduction of Δ\textsuperscript{1,9}-2-octalones \textbf{139} invariably generates a preponderance the \textit{trans}-fused product \textbf{145} (Scheme 30).\textsuperscript{56} This can be rationalized by considering the three possible transition states \textbf{140}, \textbf{141} and \textbf{142} involving a half-chair conformation of the anionic intermediate. In two of these conformations (\textbf{140} and \textbf{141}) the orbital of the developing C-H bond overlaps with the remainder of the enolate π-system whereas the alternative conformer \textbf{142} is disfavored because it does not fulfill the overlap requirement. The transition state \textbf{140} leads to an enolate \textbf{143} which is subsequently protonated to afford the \textit{trans}-ketone \textbf{145}. Conversely, the transition state \textbf{141} leads initially to enolate \textbf{144} which is protonated to give the \textit{cis}-ketone \textbf{146}. Since the axial protonation transition state \textbf{140} normally suffers fewer steric interactions than the alternative transition state \textbf{141}, the \textit{trans}-fused product \textbf{145} predominates.
Implicit in the foregoing discussion has been the assumption of considerable tetrahedral character in the β-carbon being protonated. However, it has been noted that the reduction stereoselectivities obtained in octalone systems are often much greater than would be predicted from a simple analysis of the non-bonded interactions in the two stereoelectronically allowed reduction products. For instance, the reduction of
$\Delta^{1,9}$-2-octalone 139 (Scheme 31, $R = H$) yielded a 99:1 mixture of the trans- and cis-products 145 and 146, respectively, whereas analysis of the non-bonded interactions in the corresponding enolates 143 and 144 suggested that the former is only $\sim 1.0$ kcal/mol lower in energy, which should correspond to a trans:cis ratio of $\sim 4:1$. To address this discrepancy an alternative rationale for the reduction stereoselectivity has been proposed by M. J. T. Robinson which presumes that the $\beta$-carbon atom is primarily trigonal in the transition state for protonation.\(^5\) Thus, as a good first approximation the conformation of the intermediate anion may be supposed to be similar in shape to the parent enone. Since the protonation reaction is highly exothermic the corresponding transition state should resemble the reactant more closely than the products. This strongly favors the formation of the trans-fused product as it requires the starting enone to undergo the least deformation of torsional angles and molecular shape during the course of the reaction.

Caine\(^5\) has countered that if a trigonal $\beta$-carbon were involved the stereochemistry of the reduction would be largely controlled by steric hindrance associated with the approach of the proton donor. For the case of enone 139 (where $R = H$) this should lead to at least as much cis- as trans-fused product and thus only a tetrahedral carbanion can adequately account for the observed trans selectively. That the proportion of trans-isomer 135 formed is far greater than would be predicted by analysis of the non-bonded interactions may be accounted for by a kinetic preference for formation of dianion 140 which undergoes protonation more rapidly than equilibration. Presumably, upon addition of a second electron to the radical anion, the torsional strain energy involving movement of atoms and energy changes associated with reorganization of the solvent shell are minimized if the dianion develops in the trans-configuration 140.
Other workers have suggested that the β-carbon atom in the transition state may vary in its degree of trigonal or tetrahedral character depending on the substituents present.\(^{57}\) Delocalization of negative charge by a phenyl group, for instance, may cause the dianion intermediate to adopt a planar geometry. Nevertheless, most reduction results can be readily explained by assuming that the β-carbanion achieves substantial tetrahedral geometry before protonation.

Notably, exceptions to generating the \textit{trans}-fused ketone by axial protonation can result from unfavorable steric interactions in the chair-chair conformation of the anionic intermediate. For example, enone 147 yields almost exclusively the \textit{cis}-decalone 148 on reduction with sodium in liquid ammonia (Scheme 32).\(^{53}\) This result can be traced to the severe 1,3-diaxial interaction between the methyl and \textit{t}-butyl group in the dianion conformer 149 which is relieved in the \textit{cis}-conformer 150.

\begin{align*}
\text{147} & \xrightarrow{\text{Na, NH}_3} \text{148} \\
\text{149} & \xrightarrow{\text{NaO, Na}} \text{150}
\end{align*}

\textbf{Scheme 32}
In contrast to the large volume of data collected for the metal-ammonia reduction of bicyclic 6,6-fused enone substrates, the stereochemical course of the reduction for compounds containing 6,7-fused enones has received relatively little study. An early example involving reduction of bicycle 151 in which the \(\alpha,\beta\)-unsaturated ketone resides within the \textit{six-membered} ring showed rather significant variations in the product stereochemistry depending upon the reducing metal used. Although reactions employing lithium, sodium, or calcium favored formation of the \textit{trans}-fused product 152, the use of barium metal produced an excess of the \textit{cis}-fused product 153 (Scheme 33).\(^5\)  

![Scheme 33](image)

<table>
<thead>
<tr>
<th>M</th>
<th>Product Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li</td>
<td>(76 : 24)</td>
</tr>
<tr>
<td>Na</td>
<td>(87 : 13)</td>
</tr>
<tr>
<td>Ca</td>
<td>(56 : 44)</td>
</tr>
<tr>
<td>Ba</td>
<td>(44 : 56)</td>
</tr>
</tbody>
</table>

In the case of cycloheptenone 59, two low energy conformers of the dianion (154 and 155) in which the orbital of the \(\beta\)-carbon is parallel to the \(\pi\)-system of the enolate can be considered (Scheme 34). The dianion conformer 154 should be the more stable since the alternate conformer 155 experiences a 1,3-diaxial interaction between C-9 and Me-22. Protonation of 154 and 155 would provide the desired \textit{trans}-fused ketone 130 and the \textit{cis}-fused ketone 156, respectively.
Scheme 34

Treatment of 59 with potassium metal in liquid ammonia and THF in the presence of tert-butanol, followed by workup and PCC oxidation of the crude material, afforded a 2.2:1 mixture of ketone products in 89% yield (equation 12). Unfortunately, the diastereomeric products 130 and 156 could not be separated by chromatography on silica gel. However, further chemical transformations (vide infra) permitted the required separation and led to the individual characterization of 130 and 156 at that stage of the synthesis. Importantly, it was also shown that the major epimer was the desired trans-fused ketone 130. Potassium was found to be a better reducing metal than lithium for this process since employment of the latter (in liquid ammonia) lead to an erosion (130:156 = 1.6:1) of the previously observed trans selectivity. Attempted conjugate reductions using
solutions of sodium in HMPA\textsuperscript{59} produced complex mixtures that did not contain either 130 or 156.

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {59};
  \node (B) at (1.5,0) {130};
  \node (C) at (3,0) {156};

  \node (D) at (0,-1) {1) K, NH\textsubscript{3}, THF \textemdash t-BuOH, \(-78^\circ\text{C}\)};
  \node (E) at (1.5,-1) {2) NH\textsubscript{2}Cl \textemdash \text{PCC on Alumina CH\textsubscript{2}Cl\textsubscript{2}}};

  \draw[->] (A) -- (B) node[midway,above] {89\%} node[below] {(2.2 : 1)};

  \node (F) at (0,-2) {OH};
  \node (G) at (1.5,-2) {OSO\textsubscript{2}CH\textsubscript{3}};

  \node (H) at (0,-3) {};\node (I) at (1.5,-3) {};

  \node (J) at (0,-4) {};\node (K) at (1.5,-4) {};

  \node (L) at (0,-5) {};\node (M) at (1.5,-5) {};

\end{tikzpicture}
\end{center}

The 1,2-carbonyl transposition method developed by Trost and his coworkers\textsuperscript{60} was chosen for the next stage of the synthesis. The sequence involves monosulfonylation of a ketone, reduction of the resulting \(\alpha\)-sulfonyl ketone, formation of a mesylate and subsequent base promoted elimination to give an enol thioether. A hydrolysis step completes the sequence to yield the transposed ketone (Scheme 35).

\begin{center}
\textbf{Scheme 35}
\end{center}
An examination of molecular models revealed that the isopropenyl group at C-16 (variecolin numbering\textsuperscript{31}) in \textbf{130} sterically hinders the methylene group at C-9. Thus, it seemed likely that treatment of \textbf{130} with a strong bulky base would result in selective abstraction of a C-7 proton. Molecular models also showed that the angular methyl group (Me-22) in \textbf{156} significantly hinders the methylene group at C-9 and selective abstraction of a C-7 proton would again be expected in this case.

Treatment of the mixture of ketones \textbf{130} and \textbf{156} with LDA in THF followed by addition of diphenyldisulfide provided a mixture of the corresponding sulfenylated products \textbf{157} and \textbf{158} in 81% yield (equation 13). Pleasingly, purification of the crude product mixture by flash chromatography on silica gel permitted easy separation of \textbf{157} and \textbf{158}. A small amount of the starting material mixture (\textbf{130} + \textbf{156}, 18% total) was also recovered.
Compounds 157 were produced as an epimeric mixture of \( \alpha \)-phenylsulfenyl ketones. The ratio of these epimers was approximately 2-3:1 and varied somewhat from experiment to experiment. The \(^1\)H-nmr spectrum of the major diastereomer of 157 exhibited three sharp methyl singlets at \( \delta \) 0.81 (Me-21 or Me-22), \( \delta \) 0.89 (Me-21 or Me-22) and \( \delta \) 1.67 (Me-25) as well as a five proton multiplet at \( \delta \) 7.20-7.40 for the aromatic protons. The well resolved signal for H-9\( \alpha \) at \( \delta \) 2.57 displayed a large geminal coupling constant \((J = 14.0 \text{ Hz})\) to H-9\( \beta \) and a small coupling constant \((J = 2.9 \text{ Hz})\) to H-10 and confirmed that the sulfenylation had selectively occurred at C-7. The signal at \( \delta \) 3.81 (dd, \( J = 11.5, 5.5 \text{ Hz})\) was assigned to H-7. The \(^1\)H-nmr spectrum of the minor diastereomer of 157 was very similar to that described above although in this case the signal at \( \delta \) 3.95 (dd, \( J = 5.5, 5.5 \text{ Hz})\) was assigned to H-7.

Compound 158 was obtained as a single diastereomer of undetermined relative configuration at C-7. The \(^1\)H-nmr spectrum of this material exhibited three sharp methyl singlets at \( \delta \) 0.85 (Me-21 or Me-22), \( \delta \) 0.99 (Me-21 or Me-22) and \( \delta \) 1.62 (Me-25) as well as a five proton multiplet at \( \delta \) 7.20-7.40 for the aromatic protons. The signal for H-9\( \beta \) at \( \delta \) 2.12 (br d, \( J = 12.5 \text{ Hz})\) displayed a large geminal coupling constant which confirmed that the sulfenylation had selectively occurred at C-7. The expected signal for H-7 was observed at \( \delta \) 3.72 (dd, \( J = 6.3, 6.3 \text{ Hz})\).

With compounds 157 and 158 in hand, attention was temporarily directed to securing pure samples of the parent ketones 130 and 156, respectively, for configurational authentication.
Exposure of 157 to zinc-copper couple in methanol in the presence of ammonium chloride smoothly effected a reductive desulfenylation to provide ketone 130 in near quantitative yield (equation 14).

The structure and relative configuration of ketone 130 was unequivocally established from the spectroscopic data. The IR spectrum of 130 revealed a saturated ketone carbonyl absorption at 1699 cm\(^{-1}\). The \(^{13}\)C nmr spectrum displayed a carbonyl carbon signal at \(\delta\) 214.9 as well as two alkenyl carbon signals \(\delta\) 150.1 and 110.6. The \(^1\)H nmr spectrum revealed three methyl group singlets at \(\delta\) 0.82, 0.85 and 1.67 for Me-22, Me-21 and Me-25 (variecolin numbering\(^{31}\)), respectively. Correlation (COSY) experiments permitted the assignment of all remaining protons in the \(^1\)H nmr spectrum of 130 (see Figure 2 and Table 3, experimental, page 185). A small \(W\)-coupling was observed between the angular methyl group Me-22 (\(\delta\) 0.82) and the axial proton H-18\(\beta\) (part of the multiplet at \(\delta\) 1.15-1.28) as well as between Me-21 (\(\delta\) 0.85) and the axial proton H-12\(\alpha\) (part of the multiplet at \(\delta\) 1.29-1.49). The protons H-10, H-9\(\beta\) and H-9\(\alpha\) were found to resonate at \(\delta\) 1.78 (ddd, \(J = 11.7, 11.7, 3.3\) Hz), \(\delta\) 2.20 (dd, \(J = 16.5, 11.7\) Hz) and \(\delta\) 2.68 (dd, \(J = 16.5, 3.3\) Hz), respectively. Preliminary evidence supporting a trans ring fusion was obtained from the magnitude of the H-10 coupling constants. The two large coupling constants indicate axial-axial couplings between H-10 and H-9\(\beta\) and
between H-10 and H-15 and the small coupling constant indicates an axial-equatorial coupling between H-10 and H-9α, all of which is possible only for a trans 7,6-ring fusion.

Additional evidence for the relative configuration shown in 130 was obtained from 2D-NOESY experiments (see Figure 2 and Table 3, experimental, page 185). A key NOE correlation was observed between the signals at δ 0.82 (Me-22) and δ 1.78 (H-10). This requires H-10 and Me-22 to be on the same face of the molecule and verifies the trans ring junction between the six and seven membered rings. The other NOE correlations observed were fully consistent with the assigned stereochemistry. The signal at δ 0.85 (Me-21) showed an NOE correlation with part of the multiplet at δ 1.29-1.49 (H-15) and a correlation with the signal at δ 2.20 (H-9β). An NOE was also observed between the signal at δ 1.67 (Me-25) and the alkenyl signal at δ 4.59-4.63 (H-24). The downfield alkenyl signal at δ 4.71-4.74 (H-24') displayed NOE correlations with part of the multiplet at δ 2.34-2.52 (H-16) and with the signal at δ 2.68 (H-9α).

Figure 2. Key $^1$H nmr 2D-NOESY correlations for ketone 130
Exposure of 158 to zinc-copper couple in methanol in the presence of ammonium chloride provided the cis-fused ketone 156 in 96% yield (equation 15).

The spectroscopic data for compound 156 was fully consistent with the assigned structure. The IR spectrum of this substance showed a saturated ketone carbonyl absorption at 1704 cm\(^{-1}\). The \(^{13}\)C nmr spectrum exhibited a carbonyl carbon signal at \(\delta\) 213.2 as well as two alkenyl carbon signals \(\delta\) 146.4 and 111.3. The \(^1\)H nmr spectrum displayed three methyl singlets at \(\delta\) 0.80, 1.02 and 1.63 for Me-22, Me-21 and Me-25 (variecolin numbering\(^{31}\)), respectively. A signal was observed for H-7\(\alpha\) at \(\delta\) 1.84-1.95, a broad doublet for H-9\(\beta\) at \(\delta\) 2.21 (\(J = 14.1\) Hz), a signal for H-9\(\alpha\) at \(\delta\) 2.40 (dd, \(J = 14.1, 12.0\) Hz), and a multiplet containing H-7\(\beta\) and H-16 at \(\delta\) 2.51-2.59. The two alkenyl proton signals for H-24 and H-24' appeared at \(\delta\) 4.72 and \(\delta\) 4.75, respectively. The following NOED experiments were consistent with the above stereochemical assignments (see Figure 3 and Table 4, experimental, page 188). Irradiation of the multiplet at \(\delta\) 2.51-2.59 (H-7\(\beta\), H-16) showed enhancements for the signals at \(\delta\) 0.80 (Me-22), \(\delta\) 2.21 (H-9\(\beta\)) and \(\delta\) 4.75 (H-24') and vice versa. Of the protons in the irradiated multiplet (H-7\(\beta\), H-16), only H-16 is in close enough proximity to Me-22, H-9\(\beta\) and H-24' to cause an enhancement of these signals. Irradiation of the isopropenyl methyl singlet at \(\delta\) 1.63 (Me-25) enhanced the signal at \(\delta\) 4.72 (H-24) and vice versa, which
confirmed the alkenyl proton assignments. Irradiation of the signal at δ 2.40 (H-9α) caused an enhancement of the singlet at δ 0.80 (Me-22) and vice versa. The observed NOE’s between H-9α and Me-22 and between H-9β and H-16 are only possible if the 7,6-ring junction is cis-fused.

![Structural diagram](image)

**Figure 3.** Key $^1$H nmr NOE enhancements for ketone 156

With the relative stereochemistry of both 130 and 156 now firmly established, the carbonyl transposition sequence was continued using the required trans-fused α-phenylsulfenyl ketones 157.

Reduction of the ketone function of 157 with sodium borohydride provided a mixture of alcohols which were converted to the corresponding mesylates upon treatment with methanesulfonyl chloride in triethylamine-dichloromethane. Exposure of the crude mixture of mesylates to a solution of potassium tert-butoxide in DMSO-THF provided the alkenyl thioether 159 in 79% overall yield (equation 16). In accordance with the assigned structure, the $^1$H nmr spectrum of 159 displayed three alkenyl proton signals for H-8, H-24 and H-24' at δ 6.02-6.07, δ 4.59-4.60 and δ 4.70, respectively, as well as a signal for the five aromatic protons at δ 7.15-7.30.
Hydrolysis of the alkenyl thioether 159 with mercuric chloride in acetonitrile-water (3:1) at reflux for 5 h provided the ketone 129 in 99% yield (equation 17). The spectroscopic data for compound 129 was fully consistent with the assigned structure. The IR spectrum of this substance showed a saturated ketone carbonyl absorption at 1703 cm\(^{-1}\). The \(^{13}\)C nmr spectrum exhibited a carbonyl carbon signal at \(\delta\) 215.6 and two alkenyl carbon signals \(\delta\) 150.5 and 109.7. The \(^1\)H nmr spectrum displayed three methyl group singlets at \(\delta\) 0.83, 0.85 and 1.64 and two alkenyl proton resonances at \(\delta\) 4.58-4.60 and \(\delta\) 4.67-4.68.
Saegusa and coworkers\textsuperscript{61} have reported that reaction of 1-trimethylsilyloxybicyclo[\(n.1.0\)]alkanes 160 with ferric chloride, followed by treatment of the intermediate \(\beta\)-chloroketones 161 with sodium acetate, leads to the corresponding conjugated cycloalkenones 162. This process constitutes a novel one-carbon ring homologation method (Scheme 36).

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme36}
\caption{Scheme 36}
\end{figure}

Booker-Milburn and Thompson have proposed the following mechanism\textsuperscript{62} to account for the regioselectivity of the cyclopropane bond cleavage in the presence of ferric chloride (Scheme 37). In the first step, a Lewis acid catalyzed ring opening of the cyclopropyl silyl ether 160 gives an iron(III) homoenolate\textsuperscript{63} 163. Homolytic fission of the iron-carbon bond generates a primary carbon radical 164 which undergoes rapid rearrangement to the more stable secondary carbon radical 166 via a cyclopropyl alkoxy radical intermediate 165. The secondary carbon radical 166 subsequently abstracts a chlorine atom from FeCl\(_3\) to provide the chloroketone 161.
An examination of molecular models suggested that the methylene group at C-8 (variecolin numbering\textsuperscript{31}) in ketone 129 (Scheme 38) should experience greater steric shielding relative to the methylene group at C-2. This is a consequence of the internal location of the C-8 methylene in the angularly fused tricycle 129 and steric shielding influences from the C-16 isopropenyl group versus the essentially unhindered peripheral location of the C-2 methylene. Thus, it seemed reasonable that treatment of 129 with a strong bulky base would result in selective abstraction of a C-8 proton. In the event, kinetic deprotonation of ketone 129 with KHMDS in THF at -78 °C, followed by addition of trimethylsilyl chloride and warming of the reaction mixture to 0 °C produced a trimethylsilyl enol ether\textsuperscript{64} with >95% site selectivity (by $^1$H nmr analysis). Chemoselective cyclopropanation of the later material using the conditions reported by Miyano and coworkers\textsuperscript{65} (ZnEt\textsubscript{2}, ClCH\textsubscript{2}I, O\textsubscript{2}) afforded the silyl cyclopropyl ether 167 as
a major diastereomer (configuration undetermined) in ~95% crude yield (Scheme 38). In agreement with prior reports, the cyclopropanation was found to be accelerated by the presence of oxygen.\(^6\) However, in the present case the rate at which oxygen was introduced to the reaction mixture was crucial to the success of the procedure. Rapid introduction of dry oxygen (from a gas cylinder or balloon) to the reaction mixture lead to low yields of cyclopropanation with predominant recovery of the unreacted silyl enol ether starting material. On the other hand, slow diffusion of air (through a drying tube) into the reaction mixture resulted in complete consumption of the starting material and efficiently provided the desired product 167 after 4 h. In contrast, in the absence of oxygen the cyclopropanation reaction required overnight (20-24 h) reaction times. Since the silyl cyclopropyl ether 167 was found to be unstable to silica gel chromatographic purification the crude compound was used immediately in the Saegusa homologation.\(^6\)

Slow addition (dropwise over 2 h) of a solution of 167 and pyridine (1.0 equiv.) in dry THF to a cold (0 °C) DMF solution of anhydrous ferric chloride (3.0 equiv.) was followed by warming of the reaction mixture to room temperature and additional stirring for 12 h. The crude mixture of β-chloroketones so produced was dissolved in methanol containing sodium acetate (20 equiv.) and the resulting mixture was heated at reflux for 6 h. Workup and flash chromatography of the crude product mixture provided two enones, 60 and 168, in a combined overall yield of 86% from 129.
Happily, the desired cyclooctenone 60 was obtained as the major product in 64% overall yield from ketone 129. The spectral data derived from 60 were in complete agreement with the assigned structure. The IR spectrum of this material exhibited an enone carbonyl absorption at 1663 cm\(^{-1}\). The \(^{13}\)C nmr spectrum of 60 also confirmed the presence of the enone moiety since signals due to the C=C=C=O carbon resonances were observed at \(\delta\) 137.4, \(\delta\) 142.7 and \(\delta\) 202.7. The \(^1\)H nmr spectrum of 60 revealed three methyl group singlets at \(\delta\) 0.69, 1.01 and 1.65 for Me-22, Me-21 and Me-25 (variecolin numbering\(^{31}\)), respectively. Correlation (COSY) experiments permitted the assignment of all remaining protons in the \(^1\)H nmr spectrum (see Table 5, experimental, page 199).

Proton resonances at \(\delta\) 1.49 (dd, \(J = 11.1, 11.1\) Hz), \(\delta\) 1.59-1.71 (m), \(\delta\) 2.11 (dd, \(J = 13.7, 11.1\) Hz),
9.5 Hz) and δ 2.31 (ddd, J = 11.1, 11.1, 5.3 Hz) were assigned to H-15, H-10, H-1α and H-16, respectively. A two proton multiplet at δ 2.87-2.92 was attributed to H-1β and H-8β. Importantly, the expected alkenyl proton resonances were observed at δ 4.56 (s) for H-24, δ 4.65 (s) for H-24', δ 6.26 (d, J = 11.9 Hz) for H-6 and δ 6.50 (ddd, J = 11.9, 9.5, 9.5 Hz) for H-2. In NOED experiments (see Figure 4), irradiation of the signal at δ 0.69 (Me-22) showed enhancements for the signals at δ 1.59-1.71 (H-10) and δ 2.31 (H-16). Similarly, irradiation of the signal at δ 1.59-1.71 (H-10) showed enhancements for the signals at δ 0.69 (Me-22) and δ 2.31 (H-16). Irradiation of the signal at δ 2.31 (H-16) showed enhancements for the signals at δ 0.69 (Me-22), δ 1.59-1.71 (H-10) and δ 4.65 (H-24'). Irradiation of the signal at δ 1.01 (Me-21) showed an enhancement for the signal δ 1.49 (H-15) and vice versa, as well as key enhancements for the signals at δ 2.11 (H-1α) and the H-1β part of the signal at δ 2.87-2.92. Irradiation of the signal at δ 2.11 (H-1α) showed enhancements for the signals at δ 1.01 (Me-21) and δ 6.50 (H-2). Irradiation of the signal at δ 6.26 (H-6) showed an enhancement for the signal δ 6.50 (H-2). Likewise, irradiation of the signal at δ 6.50 (H-2) showed enhancements for the signals at δ 2.11 (H-1α) and δ 6.26 (H-6). The NOE enhancements observed between Me-21 and each of the C-1 protons and between H-2 and H-1α are only possible for the cyclooctenone isomer represented by 60 in which the eight-membered ring exists in a tub-like conformation (see below). Significantly, the acquisition of 60 verifies the structure of the preceding intermediates in the homologation sequence and, in particular, validates the earlier expectations regarding regiocontrol in the enolate formation step.
The cycloheptenone 168 (Scheme 38) was obtained as the minor reaction product in 22% yield. The IR spectrum of this material exhibited an enone carbonyl absorption at 1693 cm\(^{-1}\). The \(^{13}\)C nmr spectrum of 168 indicated the presence of an enone moiety since signals due to the C=C–C=O carbon resonances were observed at \(\delta\) 124.1, \(\delta\) 144.6 and \(\delta\) 203.1. Alkenyl carbon resonances for the isopropenyl group were also observed at \(\delta\) 109.8 and \(\delta\) 150.4. All five of these carbon signals displayed a positive amplitude in an APT experiment. The \(^1\)H nmr spectrum of 168 revealed three methyl group singlets at \(\delta\) 0.70, \(\delta\) 0.84 and \(\delta\) 1.63 and two alkenyl proton singlets for the isopropenyl group were observed at \(\delta\) 4.56 and \(\delta\) 4.65. The two exocyclic enone protons exhibited downfield singlets at \(\delta\) 5.15 and \(\delta\) 6.00.
Formation of the minor enone product 168 can be accounted for mechanistically if the ferric chloride mediated cyclopropane cleavage of 167 provides (by equilibration via a cyclopropyl alkoxy radical) the primary methylcycloheptanone radical 169 in addition to the expected cyclooctanone radical 170 (Scheme 39). Intermediates 169 and 170 further react with ferric chloride to produce the β-chloroketones 171 and 172, respectively. Dehydrochlorination of the acquired β-chloroketones leads to the enones 60 and 168. Evidently, in this case the greater thermodynamic stability normally associated with a secondary carbon radical relative to a primary carbon radical is partially offset by the increased strain present in the eight-membered ring of 170 compared to the seven-membered homologue 169. Although the balance of these effects favors formation of the ring expanded intermediate 170 to the extent that the desired cyclooctenone 60 is ultimately produced in good (64%) overall yield, the significant (22%) yield of an isomeric cycloheptenone 168 is nevertheless an uncommon result. For example, Saegusa ring expansion of the related, yet structurally simpler 1-trimethylsilyloxy bicyclo[5.1.0]octane (160, n = 3) was reported to afford exclusively the cyclooctenone 162 (n = 3) in excellent yield (Scheme 36).
Scheme 39
Saegusa and coworkers\textsuperscript{61} have recommended the use of DMF as solvent for optimum yields in the ferric chloride mediated ring expansion reaction and further noted that yields were dramatically attenuated in diethyl ether. However, in the present synthesis it was discovered that the highly nonpolar nature of 167 hampered its dissolution in DMF at room temperature. This difficulty was largely circumvented without affecting the efficiency of the homologation process by adding a THF solution of 165 to a solution of ferric chloride in DMF. The resulting DMF-THF (5:1) solvent mixture maintains the yield enhancing effects of the former solvent in the silyloxydicyclopropane fragmentation as well as improved solubility of 167 due to the latter solvent.
2.1.10 An Unsuccessful Attempt to Assemble the A/B Ring System.

In concert with the preceding work, a synthesis of the cycloheptenone 127 from ketone 130 was conducted. Thus, reaction of the lithium enolate of ketone 130 with trimethylsilyl chloride generated the corresponding trimethylsilyl enol ether which was directly treated with phenylselenenyl chloride to provide an epimeric mixture of the α-phenylselenides 173 in 88% yield (Scheme 40). Unfortunately, oxidation of 171 and elimination of the resulting selenoxide under typical conditions \(^{66}\) (NaIO\(_4\), MeOH-H\(_2\)O-THF, with or without added NaHCO\(_3\) or H\(_2\)O\(_2\), CH\(_2\)Cl\(_2\), pyridine) afforded poor yields (28-45%) of the desired enone 127. However, after further experimentation an effective protocol to produce 127 was found. Accordingly, treatment of 173 with purified \(^{67}\) meta-chloroperbenzoic acid (MCPBA) (1.2 equiv.) in dichloromethane at -78 °C for 2 h followed by addition of diisopropylamine (3.0 equiv.) and tetrachloromethane and heating of the resulting mixture at reflux for 20 min furnished enone 127 in 90% yield (Scheme 40).

![Scheme 40](image-url)
The IR spectrum of 127 displayed an enone carbonyl absorption at 1656 cm\(^{-1}\). The \(^1\)H-nmr spectrum of this substance exhibited the expected three methyl group singlets at \(\delta\) 0.80, \(\delta\) 0.99 and \(\delta\) 1.68. The two alkenyl protons of the isopropenyl group were observed at \(\delta\) 4.65 (m) and \(\delta\) 4.75 (m) and the two alkenyl protons of the enone system were observed downfield at \(\delta\) 5.85 (dd, \(J = 12.3, 1.4\) Hz) \(\delta\) 6.24 (ddd, \(J = 12.3, 5.8, 5.8\) Hz).

With the tricyclic enone 127 in hand, assembly of the fourth ring via a methylenecyclopentane annihilation sequence was investigated. Previous syntheses in our laboratory have successfully employed cyanocuprate 22 as the key reagent for this process. In this work, transmetallation of alkenyltrimethylstannane 20 with methyllithium generated an intermediate alkenyllithium species 174 which was subsequently treated with CuCN to provide the requisite cuprate 22 (Scheme 41).

![Scheme 41](image)

Interestingly, it has been noted that in reactions of cuprate 22 with enone substrates, a small amount of product resulting from 1,4-addition of a methyl group is often obtained along with the expected product of alkenyl cuprate addition. For example, in a study by Piers and Roberge, cuprate 22 was allowed to react with enone 175 to provide the expected ketone product 176 in 69% yield along with \(~10\)% yield of the undesired 3-methylketone 177 (equation 18).
The product 177 was observed even when alkenyltrimethylstannane 20 was used in excess relative to methyllithium in the transmetallation step during preparation of cyanocuprate 22. After further investigation, it was reasonably suggested that the alkenyllithium 174 and tetramethylstannane are in equilibrium with methyllithium and the alkenyltrimethylstannane 20 (equation 19).

Clearly, the presence of this equilibrium has a deleterious effect on the yield of the desired conjugate addition product and may also complicate purification procedures. In an attempt to circumvent any such difficulties in the present synthesis it was proposed to generate the requisite alkenyllithium species 174 via transmetallation of alkenyltributylstannane 178 with butyllithium (equation 20). The expectation was that the bulky tributylstannyl group should shift the equilibrium farther to the right than in the previous case involving a trimethylstannyl group. In addition, the lower volatility and reduced toxicity of tributylstannane 178 make it an attractive alternative to the trimethylstannane 20.
The first step in the preparation of reagent 178 involved the stannylcupration of terminal alkyne 179 followed by in situ protonation of the resulting alkenylcopper species according to a general procedure previously developed in our laboratory. Thus, treatment of 3-butyln-1-ol (179) with tributylstannylcopper(I)-dimethyl sulfide (180) in THF-MeOH produced a mixture of alkenylstannanes, 181 and 182, which were readily separated by flash chromatography on silica gel (equation 21).

The desired alkenylstannane 181 was produced as the major regioisomer in 67% yield. The $^1$H nmr spectrum of 181 displayed an alkenyl proton signal for H-4 at $\delta$ 5.27 (d, $J = 2.8$ Hz, $^3J_{Sn-H} = 60$ Hz) and for H-4' at $\delta$ 5.77-5.78 (m, $^3J_{Sn-H} = 133$ Hz). The H-4 and H-4' assignments were based on the large tin-proton coupling constant ($^3J_{Sn-H} = 133$ Hz) indicative of a trans relationship between the Sn and H-4' and the smaller tin-proton coupling constant ($^3J_{Sn-H} = 60$ Hz) indicative of a cis relationship between the Sn and H-4.

\[
\begin{align*}
\text{SnBu}_3 \quad \text{BuLi} & \quad \text{Li} \\
+ & \rightarrow \\
\text{Cl} \quad \text{Cl} & \quad \text{SnBu}_4
\end{align*}
\]
The minor regioisomer 182 was produced in 15% yield. The $^1$H nmr spectrum of 182 displayed an alkenyl proton signal for H-3 at $\delta$ 5.91 (dt, $J = 18.9$, 6.2 Hz) and a signal for H-4 at $\delta$ 6.04 (dt, $J = 18.9$, 1.1 Hz). The large coupling constant ($J = 18.9$ Hz) between the vicinal protons H-3 and H-4 confirmed the (E)-alkene geometry.

The synthesis of the bifunctional reagent was completed by reaction of the alcohol 181 with PPh$_3$ and CCl$_4$ in the presence of triethylamine to afford the chloro stannane 178 in 99% yield (equation 22).

![Equation 22](image)

The results of the annulation sequence applied to enone 127 are illustrated in Scheme 42. Treatment of alkenylstannane 178 with BuLi at -78 $^\circ$C followed by addition of CuCN provided the cyanocuprate 22. Exposure of the enone 127 to cuprate 22 in the presence of TMSBr at -78 $^\circ$C for 2.5 h provided a mixture of the addition products 183 and 184 in 98% combined yield. The ratio of these products varied slightly from one experiment to another, but the stereoselectivity was disappointingly low in all cases (183: 184 ~1.0-1.7:1.0). In agreement with our expectations, no product resulting from the conjugate addition of a butyl moiety was observed. Adduct 183, easily separated from its epimer 184 by flash chromatography, underwent smooth intramolecular cyclization when treated with potassium hydride in THF. The identity of the tetracyclic ketone 128 so
produced was convincingly established by means of $^1$H-nmr COSY and NOED experiments.

In the $^1$H-nmr spectrum of ketone 128, the protons $H_a$, $H_b$ and $H_c$ were found to resonate at $\delta$ 3.32 (ddd, $J = 11, 8.0, 8.0$ Hz), $\delta$ 2.95-3.00 (m) and $\delta$ 2.19-2.32 (m), respectively. In NOED experiments, irradiation of the signal at $\delta$ 3.32 ($H_a$) caused an enhancement of the signals at $\delta$ 2.95-3.00 ($H_b$) and $\delta$ 2.19-2.32 ($H_c$). Similarly, irradiation of the signal at $\delta$ 2.95-3.00 ($H_b$) caused an enhancement of the signals at $\delta$ 3.32 ($H_a$) and
δ 2.19-2.32 (Hₖ). The observed NOE enhancements are only possible if Hₐ, Hₕ and Hₑ reside in close proximity on the same face of the molecule. Hence, ketone 128 must possess a cis-fused 7,5 ring junction with the relative stereochemistry shown.

A recent report from the Rigby group⁷³ has described the regioselective homologation of cycloheptanone 185 to the cyclooctanone 186 during a synthesis of the ophiobolane ring system (equation 23).
Mindful of this result, we investigated a similar ring expansion approach to convert ketone 128 to the cyclooctanone 61 (Scheme 43). Unfortunately, treatment of 128 with trimethylsilyldiazomethane (1.2 equiv.) in the presence of boron trifluoride-diethyletherate (4.0 equiv.) at -45 °C lead to the formation of a complex mixture of products which were not separated or individually characterized. Recourse to milder Lewis acid additives (MgBr$_2$·OEt$_2$ or ZnCl$_2$) in the hopes of minimizing unwanted side-reactions failed to induce the homologation reaction and led solely to the recovery of starting material 128.

![Scheme 43](image)

In light of the unsuccessful homologation attempts to provide 61 from ketone 128 as well as the poor selectivity observed in the earlier cuprate addition step, this strategy to establish the A/B ring system was abandoned.
2.1.11 Completion of the A/B Subunit: Preparation of Tetracyclic Ketone 61.

Attention was now focused on further elaboration of the cyclooctenone 60 to the tetracyclic ketone 61 via a methylenecyclopentane annulation. For this method to succeed, the substituents adorning the 8-membered ring of 60 would have to induce sufficient conformational bias to permit a stereoselective conjugate addition.

\[ \text{Ketone 60} \rightarrow \text{Ketone 61} \]

In a pertinent study of medium and large ring compounds, Still and Galynker demonstrated that even a single (remote) methyl substituent can provide enough conformational bias to allow highly stereoselective conjugate additions to be carried out. As shown in Scheme 44, addition of lithium dimethylcuprate to 8-methylcyclooct-2-en-1-one (187) resulted in the clean formation of a single adduct 188. The authors accounted for the observed stereoselection by suggesting peripheral attack of the cuprate on either (or both) of the two lowest energy conformers of the cyclooctenone (187A and/or 187B).
An examination of molecular models, supported by key $^1$H-nmr NOED experiments \textit{(vide supra)}, suggested that the 8-membered ring of enone 60 exists predominantly in a tub-like conformation. Consequently, this ground state topography should provide more open access to the entry of a cuprate reagent from the direction \textit{cis} to the angular methyl group, Me-22 (Scheme 45). If the stereocontrol elements outlined above are in operation, peripheral attack of a cuprate reagent on this low energy conformation of 60 should lead directly to a product enolate in which the relative configuration at C-2 has been correctly installed.
In contrast to many previous enone substrates \(^9,68\) (including cycloheptenone 127 from the preceding section) which smoothly yielded adducts upon exposure to the lower order cyanocuprate 22, cyclooctenone 60 was recalcitrant, even in the presence of the powerful facilitator \(^28\) trimethylsilyl bromide (equation 24).

The attenuated reactivity of enone 60 towards conjugate addition prompted a search for a more reactive cuprate/facilitator system. To this end, the higher order cyanocuprate 189 (containing the nontransferable 2-thienyl ligand \(^75\)) and the homocuprate 190 were prepared for evaluation (Scheme 46). Thus, alkenylstannane 178 was allowed to react with BuLi (1.0 equiv.) in THF at \(-78\) °C. The corresponding
alkenyllithium reagent so obtained was treated with a solution of lithium 2-thienylcyanocuprate (1.0 equiv.) in THF at -78 °C to provide a yellow solution of the cyanocuprate 189. Similarly, transmetallation of alkenylstannane 178 with BuLi (1.0 equiv.) in THF at -78 °C, was followed by sequential addition of solid copper(I) bromide-dimethyl sulfide (0.5 equiv.), brief warming (~ 5 min) of the mixture to -50 °C, and recooling to -78 °C provided an orange solution of the homocuprate 190.

![Scheme 46](image)

After considerable experimentation, it was discovered that treatment of enone 60 with a large excess of the higher order cyanocuprate 189 (10 equiv.) in the presence of boron trifluoride-diethyletherate 76 (10 equiv.) in THF at -78 °C provided a single adduct 191. Unfortunately, the yields (0-73%) of 191 obtained in this reaction varied greatly from experiment to experiment, presumably due to poor stability of the cyanocuprate.
On the other hand, employment of the homocuprate 190 (3.0 equiv.) under similar conditions, reproducibly furnished the ketone 191 in high yield (89%) (equation 25).

\[ \begin{array}{c}
\text{60} \\
\text{BF}_3\cdot\text{OEt}_2 \\
\text{THF, -78 °C} \\
\text{191} \\
89\%
\end{array} \]

The IR spectrum of chloro ketone 191 exhibited a carbonyl absorption at 1702 cm\(^{-1}\). The \(^1\text{H-nmr}\) spectrum of this substance displayed four distinct alkenyl proton singlets at \(\delta\) 4.59, \(\delta\) 4.73, \(\delta\) 4.77 and \(\delta\) 4.88 as well as a two proton multiplet for the chloromethylene group at \(\delta\) 3.59-3.65. However, at this point, conclusive evidence for the relative configuration of 191 was not obtained. Rather, it was recognized that the heightened conformational rigidity expected for the product(s) of the ensuing cyclization step would be particularly conducive to detailed spectroscopic analysis.

Intramolecular alkylation of the chloro ketone 191 by treatment with KH (5 equiv.) in THF for 3 h at room temperature lead to a mixture of two products, 61 and 192, in a ratio of ~ 2:1, respectively (equation 26). Although the \(cis\)-fused ketone 61 was expected\(^{77}\) to be the kinetic product of the cyclization, it was apparent that competitive epimerization of this material to the \(trans\)-fused ketone 192 was occurring during the reaction. Monitoring the progress of the reaction by gc supported this notion as did the observation that over longer reaction times the relative proportion of ketone 192
increased. To further complicate matters, the products 61 and 192 were found to be completely inseparable by chromatography on silica gel. Moreover, varying the reaction time, temperature, or the number of equivalents of KH employed failed to provide the desired cis ketone 61 without accompanying formation of significant quantities of the trans ketone 192.

To alleviate these difficulties, a number of experimental modifications were considered. It was anticipated that replacing the chloride with a better leaving group (e.g. iodide) would increase the rate of cyclization relative to the rate of product equilibration. Replacement of KH with a lithium base (e.g. LiOr-Bu) to provide a less readily equilibrated, more tightly bonded enolate counterion (e.g. lithium instead of potassium) was also expected to promote the desired transformation. Finally, it was proposed that switching to a less polar solvent (e.g. benzene) might further suppress the undesired equilibration process.

Thus, the chloro ketone 191 was treated with sodium iodide in refluxing acetone for 50 h (Finkelstein reaction) to give the iodo ketone 193 in 99% yield (equation 27). The success of the substitution was readily confirmed from the $^1$H-nmr spectrum of 193 which exhibited a well resolved signal for the iodomethylene group at $\delta$ 3.27-3.59.
Gratifyingly, reaction of the iodo ketone 193 with lithium tert-butoxide (3.0 equiv.) in refluxing benzene for 1.5 h provided the cis-fused ketone 61 as the exclusive product, along with recovered starting material (equation 28). The mass balance for the reaction was essentially quantitative and, in practice, the cyclization was allowed to reach 50-60% completion to avoid formation of the trans-fused isomer. The required cis-fused ketone 61 was easily separated from the remaining starting material by flash chromatography on silica gel.

Under the same reaction conditions (LiOt-Bu, benzene) at room temperature, neither the intramolecular alkylation of 193 nor the epimerization of 61 occurred appreciably. Thus, a 'thermal trigger' could be used to control the extent of the reaction.
By simply cooling the mixture to room temperature, the reaction could be effectively stalled at any point to permit analysis of an aliquot. In this manner, the extent of the conversion was closely monitored to maximize the formation of isomerically pure product. When the cyclization reaction was allowed to reach more than ~60% completion the relative proportion of the undesired isomer 192 was observed to rise rapidly. In an experiment in which the reaction was allowed to reach completion (reflux, 3 h), an ~ 5:1 mixture of 61 : 192 was obtained in >99% yield.

The IR spectrum of pure ketone 61 exhibited a carbonyl absorption at 1702 cm\(^{-1}\). A combination of \(^1\)H nmr, homonuclear COSY, NOED, \(^{13}\)C nmr, heteronuclear HMBC, and HMQC experiments fully corroborated the assigned structure of tetracycle 61. These experiments allowed the assignment of all protons in the \(^1\)H nmr spectrum (see Table 6, experimental, page 213) and all carbons in the \(^{13}\)C nmr spectrum (see Table 7, experimental, page 214) of ketone 61 and unambiguously established the relative configuration of this substance. In the \(^1\)H nmr spectrum, the protons H-19', H-19, H-6, H-2 and H-10 (variecolin numbering\(^{31}\)) were found to resonate at \(\delta 4.89\) (br d, \(J = 2.0\) Hz), \(\delta 4.78\) (br d, \(J = 2.0\) Hz) \(\delta 3.23\) (ddd, \(J = 7.1, 7.1, 7.1\) Hz), \(\delta 2.86-2.90\) (m) and \(\delta 1.74-1.78\) (m), respectively. In NOED experiments (see Figure 5), irradiation of the signal at \(\delta 4.89\) (H-19') caused an enhancement of the signal at \(\delta 4.78\) (H-19). Irradiation of the signal at \(\delta 4.78\) (H-19) caused an enhancement of the signals at \(\delta 4.89\) (H-19') and \(\delta 2.86-2.90\) (H-2). Irradiation of the signal \(\delta 3.23\) (H-6) caused an enhancement of the signals at \(\delta 2.86-2.90\) (H-2) and \(\delta 1.74-1.78\) (H-10). Similarly, irradiation of the signal at \(\delta 2.86-2.90\) (H-2) caused an enhancement of the signals at \(\delta 3.23\) (H-6), \(\delta 1.74-1.78\) (H-10) and \(\delta 4.78\) (H-19). Finally, irradiation of the signal at \(\delta 1.74-1.78\) (H-10) caused an enhancement
(inter alia) of the signals at $\delta$ 3.23 (H-6) and $\delta$ 2.86-2.90 (H-2). The observed NOE enhancements between H-2 and H-6 confirmed the cis fusion of the newly generated A/B ring junction. Furthermore, the NOE's between the angular proton H-10 and each of methine protons H-6 and H-2 are only possible if all three protons reside in close proximity on the same (concave) face of the molecule. Since the configuration at C-10 is known with certainty (vide supra) the relative configuration of the A-ring is thus also established. This structure determination also confirms the identity of the previous intermediates (191 and 193) and validates the earlier expectations regarding remote stereochemical induction via medium-ring conformational preferences.

Figure 5. Key $^1$H nmr NOE enhancements for ketone 61
Base mediated equilibration (NaOMe, MeOH) of the pure cis-fused ketone 61 at room temperature for 16 h provided, exclusively, the trans-fused ketone 192 in 99% yield (equation 29). The IR spectrum of 192 displayed a carbonyl absorption at 1703 cm⁻¹. The ¹H nmr spectrum of 192 exhibited three methyl group singlets at δ 0.70, δ 0.88 and δ 1.70. Four well resolved alkenyl proton signals were also observed at δ 4.57-4.58 (m), δ 4.75 (br s), 4.79 (br s) and 4.92-4.93 (m) as well as a signal for H-6 at δ 2.68-2.75 (m).
2.1.12 Preparation of Ester 94.

To complete the carbon skeleton common to the variecolin family of sesterterpenoids, a final one-carbon homologation was required. At this point, conversion of tetracylic ketone 61 to the α,β-unsaturated ester 94 was considered to be a particularly judicious strategy. Aside from installing both C-20 (variecolin numbering\textsuperscript{31}) and the olefinic double bond between C-7 and C-8, the ester function produced in 94 would readily serve as a handle for further synthetic transformations.

Cacchi and coworkers\textsuperscript{78} have reported a general palladium-catalyzed methoxycarbonylation of alkenyl triflates 194 to provide the corresponding α,β-unsaturated esters 195. According to this method, the desired esters 195 are produced by exposure of the alkenyl triflates 194 to a Pd(0) catalyst under an atmosphere of carbon monoxide in the presence of methanol and a tertiary amine base (equation 30).
The postulated pathway\textsuperscript{79} for this transformation is illustrated in Scheme 47. The first step consists of oxidative addition of the triflate 194 to a palladium(0) species to generate an alkenyl palladium(II) complex 196. Rapid insertion of carbon monoxide into the C-Pd bond of 196 produces an acyl palladium(II) species 197. Finally, the intermediate 197 reacts with methanol (or other alcohol) solvent in the presence of amine base to regenerate the palladium(0) catalyst and furnish the desired ester 195.
The homologation of ketone 61 to the ester 94 was accomplished as outlined in Scheme 48. Kinetically controlled deprotonation of ketone 61 with KHMDS in THF, followed by addition of N-phenyltrifluoromethanesulfonimide, produced the alkenyl triflate 198. This substance proved remarkably susceptible to hydrolysis and attempts at chromatographic purification on silica gel resulted, predominantly, in reversion to the starting ketone 61. In subsequent experiments, a non-aqueous workup was shown to be the most effective method for isolating the desired triflate 198. Thus, concentration of the crude reaction mixture, trituration of the acquired residue with pentane - diethyl ether (95:5), filtration to remove insoluble impurities, and concentration of the resulting filtrate provided, in >95% yield, the crude triflate 198. Treatment of a solution of the triflate 198 in DMF - MeOH (2:1) with a catalytic amount of Pd(PPh₃)₄ and N,N-diisopropylethylamine under an atmosphere of carbon monoxide smoothly furnished the ester 94 in 68% overall yield from ketone 61.
The spectral data obtained for compound 94 was in complete agreement with the assigned structure. The IR spectrum of this material displayed a strong (α,β-unsaturated) ester carbonyl absorption at 1719 cm$^{-1}$. The $^1$H nmr spectrum of 94 displayed methylidene and isopropenyl alkenyl proton signals at $\delta$ 4.57 (s, 1H), $\delta$ 4.69 (br s, 2H) and $\delta$ 4.82 (s, 1H) as well as the expected downfield signal at $\delta$ 6.62 (dd, 1H, $J = 7.5, 2.8$ Hz) for the alkenyl portion of the unsaturated ester. A methyl ester singlet at $\delta$ 3.61 further corroborated the assigned structure.

With the acquisition of tetracycle 94, the complete carbocyclic core of the variecolin family had been assembled and further studies could now be directed towards key functional group interconversions.
2.1.13. Preparation of (±)-5-Deoxovariecolin, (±)-5-Deoxyvariecolol and (±)-5-Deoxyvariecolactone.

In order to establish the correct relative configuration at C-3 (variecolin numbering\textsuperscript{31}) in 199, a stereoselective reduction of the exocyclic methyldiene double bond of triene ester 94 was required. An examination of molecular models suggests that the C-3 double bond is sterically less hindered than the alkene function of the C-16 isopropenyl group, since the later is somewhat buried within the B/C ring system. Furthermore, the concave nature of the A/B subunit (imparted by the cis ring fusion) should favor reduction of the C-3 methylene of 94 from the more accessible \( \alpha \) face.

The reduction of 94 with the transitory diimide (H-N=N-H) species was considered a particularly promising approach. Since diimide reductions are believed to proceed through a cyclic six-membered transition state, the addition is therefore stereospecifically syn and generally takes place from the less hindered side of the double bond (equation 31).\textsuperscript{80}
Reaction of acids with potassium azodicarboxylate is reported to be a convenient and effective method of generating diimide.\textsuperscript{81} For example, in Corey's synthesis of ovalicin, generation of diimide in this manner resulted in the chemoselective reduction of 200 to provide the important intermediate 201 in good yield (equation 32).\textsuperscript{82}

Unfortunately, several attempts to reduce 94 with diimide generated by acidification of potassium azodicarboxylate met with disappointing results (equation 33). Analysis of the crude reaction mixtures by tlc confirmed the consumption of starting material 94 and indicated the concomitant formation of numerous (unidentified) by-products. Since only minor amounts of the expected reduction product(s) could be detected in the $^1$H nmr spectrum of the crude reaction mixture, it was presumed that the triene ester 94 was unstable under the acidic reaction conditions. However, performing the reaction in the presence of pyridine (used in excess relative to the acetic acid) and
varying the reaction solvent (dichloromethane, methanol, or benzene) failed to significantly ameliorate these difficulties.

In light of the results obtained, as summarized above, alternative reduction methods were investigated. As shown in Scheme 49, both homogeneous hydrogenation of 94 using Rh(PPh₃)₃Cl (Wilkinson’s catalyst)⁸³ as well as heterogeneous hydrogenation using PtO₂ (Adam’s catalyst)⁸⁴ rapidly effected reduction of both non-conjugated olefinic double bonds to provide a single diastereomer 202. Although the chemoselectivity of this hydrogenation was unsatisfactory, the high facial selectivity related to the reduction of the exocyclic double bond was nevertheless quite encouraging.
Further experimentation revealed that careful catalytic hydrogenation of 94 using 5% platinum on alumina in methanol smoothly furnished the desired monoreduction product 199 in 94% yield (equation 34).

\[
\text{94} \xrightarrow{\text{H}_2, \text{Pt/Al}_2\text{O}_3, \text{MeOH, r.t.}} \text{199} \quad (34)
\]

The structure and relative configuration of 199 was fully corroborated by the spectroscopic data. The IR spectrum of this material displayed a strong (\(\alpha,\beta\)-unsaturated) ester carbonyl absorption at 1718 cm\(^{-1}\). The \(^1\)H nmr spectrum of 199 exhibited a methyl group doublet (\(J = 7.0\) Hz) at \(\delta\) 0.80 for the newly generated Me-19 (variecolin numbering\(^{31}\)), as well as methyl group singlets at \(\delta\) 0.81 and \(\delta\) 0.87 for Me-22 and Me-21, respectively. The presence of the isopropenyl group was confirmed by resonances at \(\delta\) 1.67 (s), \(\delta\) 4.56 (br s) and \(\delta\) 4.69 (br s) for Me-25, H-24 and H-24', respectively. A signal for the methoxycarbonyl group was observed at \(\delta\) 3.65 (s) and a signal for the alkenyl proton H-8 was present at \(\delta\) 6.43 (ddd, \(J = 5.3, 5.3, 1.6\) Hz). Correlation (COSY) experiments allowed the assignment of all remaining signals in the \(^1\)H nmr spectrum of 199 (see Table 8, experimental, page 222). In particular, one-proton resonances at \(\delta\) 1.99-2.07 (m), \(\delta\) 2.13-2.19 (m) and \(\delta\) 3.23-3.30 (m) were assigned to H-3, H-2 and H-6, respectively. In NOED experiments (see Figure 6 below, and Table 8, experimental,
irradiation of the signal at δ 0.80 (Me-19) caused an enhancement of the signal at δ 1.99-2.07 (H-3). Irradiation of the signal at δ 1.99-2.07 (H-3) caused an enhancement of the signals at δ 0.80 (Me-19), δ 2.13-2.19 (H-2) and δ 3.23-3.30 (H-6). Irradiation of the signal at δ 2.13-2.19 (H-2) caused an enhancement of the signals at δ 1.99-2.07 (H-3) and δ 3.23-3.30 (H-6). Similarly, irradiation of the signal at δ 3.23-3.30 (H-6) caused an enhancement of the signals at δ 1.99-2.07 (H-3) and δ 2.13-2.19 (H-2). The observed NOE enhancements confirmed the expectation that hydrogenation of the C-3-C-19 double bond should occur from the (convex) α-face of 94.

Figure 6. Key $^{1}$H nmr NOE enhancements for ester 199

The ester function of 199 was reduced with diisobutylaluminum hydride (DIBAL-H) in diethyl ether to afford the allylic alcohol 203 in 99% yield (Scheme 50). This was evidenced in the IR spectrum of 203 by a hydroxyl group absorption at 3850 cm$^{-1}$. In addition, the $^{1}$H nmr spectrum displayed the required C-20 methylene proton signals at δ 3.90 (dd, $J = 12.2$, 5.2 Hz, H-20) and δ 4.08 (dd, $J = 12.2$, 6.9 Hz, H-20').
Oxidation of the allylic alcohol 203 with manganese dioxide in diethyl ether provided (±)-5-deoxovariecolin (204) in 75% yield. The IR spectrum of 204 displayed a strong (α,β-unsaturated) aldehyde carbonyl absorption at 1691 cm⁻¹. The ¹H nmr spectrum of 204 exhibited the four expected methyl group signals at δ 0.81 (s), δ 0.85 (d, J = 6.4 Hz), δ 0.89 (s) and δ 1.71 (s) for Me-22, Me-19, Me-21 and Me-25, respectively. The two alkenyl protons of the isopropenyl group were observed at δ 4.63-4.64 (m, H-24) and δ 4.74 (d, J = 2.4 Hz, H-24') and the alkenyl proton of the unsaturated aldehyde moiety was present at δ 6.57-6.61 (m, H-8). The aldehyde proton was found to resonate at δ 9.22 (s, H-20). Importantly, 204 possesses the complete carbocyclic core and relative configuration of (±)-variecolin and differs from (±)-variecolin only in the oxidation level at C-5.
An exciting and challenging junction in the synthesis had been reached. Since all members of the variecolin family are oxygenated at C-5, the daunting task at hand was to oxidize (or suitably functionalize) the corresponding unactivated C-5 methylene group in the advanced synthetic intermediate 203.

In 1961, Barton and coworkers\(^\text{86}\) disclosed a remarkable radical translocation approach to allow remote functionalizations (Scheme 51). The method involves photolysis of a nitrite ester 205 to generate an oxygen radical 206 which subsequently abstracts a hydrogen atom from a 5-carbon to give a translocated radical 207. Capture of nitric oxide (liberated in the original homolysis) by the carbon radical 207 provides an intermediate 208 which tautomerizes to the oxime 209.
For example, in the key step of Barton and Beaton's synthesis of aldosterone acetate, photolysis of the nitrite ester \(210\) afforded a 21% yield of the oxime \(211\) which was subsequently converted to the target compound by treatment with aqueous acid (Scheme 52). 87
Since an examination of molecular models indicated that the hydroxyl moiety of 203 and a hydrogen atom (H-5β) on C-5 were in close spatial proximity, it was anticipated that this localized environment within the rigid framework of the compound would be amenable to a Barton remote functionalization. Significantly, conversion of 203 to the oxime 212 via a Barton reaction would allow direct access to variecolol (49) in a subsequent hydrolysis step (Scheme 53).
Treatment of the alcohol 203 with nitrosyl sulfuric acid in pyridine furnished the corresponding nitrite ester 213 in nearly quantitative yield (Scheme 54). This transformation was confirmed by the absence of a hydroxyl group absorption in the IR spectrum of 213. Furthermore, the $^1$H nmr spectrum of 213 displayed two downfield methylene proton signals at $\delta$ 4.90-4.98 (m, H-20) and $\delta$ 5.09-5.17 (m, H-20'). However, photolysis of 213 under a variety of conditions (e.g. sun lamp, dichloromethane, 50 °C; medium pressure mercury arc lamp, benzene, 5-10 °C) produced very complex mixtures of products which, disappointingly, did not contain significant quantities of oxime 212.
In light of the singularly unsuccessful attempts to effect a Barton reaction, consideration was given to alternative radical translocation strategies. At this point, an oxidative radical etherification of the alcohol 203 to generate 5-deoxyvariecolol (93) was deemed a potentially viable approach. Notably, the C-5 configuration shown in 93 can be expected since the alternative cyclization pathway to produce 214 would require the formation of a highly strained trans-fused bicyclo[3.3.0] system.
In a recent synthesis of (+)-epoxydictymene, Paquette and coworkers\textsuperscript{89} irradiated a solution of 215 in the presence of (diacetoxyiodo)benzene\textsuperscript{90} and iodine to provide the crucial cyclization product 216 in 95\% yield (Scheme 55).

With this result in mind, a solution of 203 in cyclohexane containing (diacetoxyiodo)benzene (3.0 equiv.) and iodine (1.0 equiv.) was irradiated with a 200 W tungsten filament for 30 min (equation 35). Unfortunately, the major product isolated from this reaction was the iodo epoxide\textsuperscript{91} 217 (relative configuration undetermined) and none of the desired ether 93 was observed.
Another powerful method for the oxidative cyclization of alcohols 218 to tetrahydrofuran derivatives 222 involves the use of lead tetraacetate (with or without added iodine). Although the mechanism of this process is complicated, a simplified view is presented in Scheme 56. Thus, an initial ligand exchange generates the lead (IV) alkoxide 219. Preferential cleavage of the (RO)-Pb bond provides the alkoxy radical 206 which abstracts a H-atom to form 207. Recapture of a lead radical provides the organolead intermediate 220 which may produce the cyclized product 222 via the intermediacy of a carbocation 221.

Scheme 56
Fortunately, when a mixture of the alcohol 203 and lead tetraacetate in the presence of calcium carbonate was heated at reflux for 20 min, the aldehyde (±)-5-deoxovariecolin (204) and the desired ether (±)-5-deoxyvariecolol (93) were produced in a 3:2 ratio (by glc analysis), respectively (Scheme 58). Treatment of the crude product mixture with sodium borohydride, followed by chromatography of the resultant material on silica gel, provided a 58% yield of the alcohol 203 and a 39% overall yield of the cyclized product 93. The recovered starting material 203 could be recycled for subsequent reactions.

Scheme 58
The structure and relative configuration of (+)-5-deoxyvariecolol (93) was confirmed by the spectroscopic data. The IR spectrum of this material displayed no absorption for a hydroxyl group. The $^1$H nmr spectrum of 93 exhibited a methyl group doublet ($J = 9.2$ Hz) at $\delta$ 0.83 (Me-19), two methyl group singlets at $\delta$ 0.84 (Me-22) and $\delta$ 0.90 (Me-21) and an isopropenyl methyl group singlet at $\delta$ 1.67 (Me-25). The isopropenyl alkenyl protons resonated at $\delta$ 4.58 (br s, H-24) and $\delta$ 4.69 (br s, H-24') and the alkenyl proton H-8 resonated at $\delta$ 5.38-5.43 (m). The allylic ether proton signals were present at $\delta$ 4.19 (br d, $J = 11.3$ Hz, H-20) and $\delta$ 4.34 (br d, $J = 11.3$ Hz, H-20'). Signals at $\delta$ 3.42-3.50 (m) and $\delta$ 4.61-4.63 (m) were assigned to H-6 and H-5, respectively. In NOED experiments, irradiation of the signal at $\delta$ 3.42-3.50 (H-6) caused an enhancement of the signal at $\delta$ 4.61-4.63 (H-5) and vice versa. Importantly, the mutual NOE enhancements observed between H-5 and H-6 indicate that they must reside on the same side on the molecule. Since the configuration at H-6 is known (vide supra), the configuration at C-5 is therefore verified as indicated in structure 93.
The acquisition of ether 93 fully validates the previously proposed remote functionalization strategy to oxygenate C-5. Furthermore, this result is significant since successful lead tetraacetate mediated cyclizations of allylic alcohols are rare. For example, it has been reported\(^9^4\) that treatment of the allylic alcohol 223 with lead tetraacetate in benzene gave as the principal product the corresponding aldehyde 224, with no indication of tetrahydrofuran products 225 (Scheme 59).

\[
\begin{align*}
\text{223} & \xrightarrow{\text{Pb(OAc)}_4, \text{CaCO}_3, \text{benzene reflux}} \text{224} \\
\text{80\%}
\end{align*}
\]

\textbf{Scheme 59}

The stage was now set to pursue a chemoselective oxidation of the C-20 methylene group of 93. Although PCC\(^4^8\) has been reported\(^9^5\) to oxidize allylic ether functions to the corresponding \(\alpha,\beta\)-unsaturated lactones, it failed to oxidize 93. On the other hand, attempted oxidation with Jones’ reagent\(^9^6\) resulted in the rapid decomposition of ether 93. However, treatment of 93 with chromium trioxide-pyridine (Collins’ reagent\(^9^7\)) prepared according to the procedure of Ratcliffe\(^9^8\) smoothly furnished (\(\pm\))-5-deoxyvariecolactone (226) in 95% yield (equation 36).
The spectral data derived from 226 were in complete agreement with the assigned structure. The IR spectrum of this substance displayed a strong carbonyl absorption at 1751 cm\(^{-1}\), characteristic of an unsaturated \(\gamma\)-lactone moiety.\(^9\) The \(^{13}\)C nmr spectrum of 226 exhibited a carbonyl carbon signal at \(\delta\) 176.5 and four alkenyl carbon signals at \(\delta\) 150.5, \(\delta\) 143.3, \(\delta\) 125.3, and \(\delta\) 110.3. The \(^1\)H nmr spectrum of 226 exhibited a methyl group doublet \((J = 7.3 \text{ Hz})\) at \(\delta\) 0.69 (Me-19), two methyl group singlets at \(\delta\) 0.84 (Me-22) and \(\delta\) 0.91 (Me-21) and an isopropenyl methyl group singlet at \(\delta\) 1.68 (Me-25). The isopropenyl alkenyl protons resonated at \(\delta\) 4.62 (br s, H-24) and \(\delta\) 4.69 (br s, H-24'), the methine proton H-5 resonated at \(\delta\) 4.94-4.99 (m) and the alkenyl proton H-8 resonated downfield at \(\delta\) 6.90-6.93 (m).
With the arrival at (±)-5-deoxyvariecolactone (226) sufficient functionality is now present to allow rapid synthetic access to all members (48-52) of the variecolin family. Although material constraints have precluded the realization of these syntheses in the present work, studies relating to the conversion of 226 to 48-52 are in progress.

![Diagram showing chemical structures and reactions]
2.1.14 Conclusion.

The work described in this part of the thesis involved a general synthetic strategy toward the variecolin class of sesterterpenoids which culminated in the total syntheses of (±)-5-deoxovariecolin (204), (±)-5-deoxyvariecolol (93) and (±)-5-deoxyvariecolactone (226) (Scheme 60). A sequential annulation approach was employed to establish each of the rings present in these structurally related substances and the complete carbocyclic framework of the variecolin family was successfully assembled. Highlights of the approach include the use of bifunctional reagents for expedient ring formation as well as the exploitation of conformational effects and molecular topography for stereoselective bond construction.

The known Grignard reagent 99 was deployed in a two step cyclopentene annihilation sequence to provide bicycle 98. Conjugate addition of cuprate 107 to the enone 98 followed by an epimerization step provided ketone 44 with the correct relative configuration set at three stereogenic centers. Application of a novel cycloheptenone annihilation protocol employing the bifunctional reagent 53 furnished the tricyclic intermediate 59. The generality of this new annihilation method is investigated in the second part of the thesis. A homologation sequence was developed to transform 59 to the cyclooctenone 60. The latter was converted to the tetracyclic ketone 61 in an efficient methylenecyclopentane annulation featuring reagent 190. Methoxycarbonylation of 61 followed by further functional group interconversions afforded the alcohol 94 which was subsequently converted to each of 204, 93, and 226. Production of 93 and 226 involved a key remote functionalization step. Efforts to prepare 48-52 from 226 are ongoing.
(a) BrMg(CH$_2$)$_2$CH(O(CH$_2$)$_3$O) (99), CuBr·Me$_2$S, TMSCl, HMPA, THF, -78 °C, 95%;
(b) CF$_3$CO$_2$H, THF, 70 °C, 83%; (c) reagent 107, TMSCl, THF, -78 °C; H$_2$O, rt, 87%;
(d) NaOMe, MeOH, r.t., 95%; (e) KDA, THF, -78 °C; HMPA, reagent 53, -78 °C to -48 °C to rt, 74%;
(f) LDA, THF, 0 °C; Mel, -78 °C to 0 °C, 87%; (g) I$_2$, CH$_2$Cl$_2$, rt, 94%;
(h) BuLi (2.1 equiv.), THF, 0 °C; NaHCO$_3$, H$_2$O, 82%; (i) PCC, 3 Å molecular sieves,
CH$_2$Cl$_2$, reflux, 72%; (j) K, NH$_3$, THF, t-BuOH, -78 °C; NH$_4$Cl (solid); PCC on alumina,
CH$_2$Cl$_2$, 89%; (k) LDA, THF, 0 °C; PhSSPh, 81%; (l) NaBH$_4$, MeOH, CH$_2$Cl$_2$, rt; (m)
MsCl, NEt$_3$, CH$_2$Cl$_2$, rt; (n) KOt-Bu, DMSO, THF, 0 °C to rt, 79% from 157; (o) HgCl$_2$,
MeCN, H$_2$O, reflux, 99%; (p) KHMDS, THF, -78 °C; TMSCl, -78 °C to 0 °C; (q) Et$_2$Zn,
ClCH$_2$I, cyclohexane, O$_2$, 0 °C to rt; (r) FeCl$_3$, DMF, THF, 0 °C to rt; (s) NaOAc, MeOH,
reflux, 64% from 129.

Scheme 60
(t) reagent 190, BF$_3$OEt$_2$, THF, -78 °C, 89%; (u) NaI, acetone, reflux, 99%; (v) LiO-t-Bu, benzene, reflux, 50-60% (+ 40-50% recovered 193); (w) KHMDS, THF, -78 °C to 0 °C; PhN(SO$_2$CF$_3$)$_2$; non-aqueous workup; (x) Pd(PPh$_3$)$_4$ (10 mol %), CO (1 atmosphere), MeOH, DMF, i-Pr$_2$NEt, rt, 68% from 61; (y) H$_2$ (1 atmosphere), 5%-Pt-on-alumina, MeOH, rt, 94%; (z) DIBAl-H, Et$_2$O, 0 °C, 99%; (aa) MnO$_2$, Et$_2$O, rt, 75%; (bb) Pb(OAc)$_4$, CaCO$_3$, cyclohexane, reflux; NaBH$_4$, MeOH, CH$_2$Cl$_2$, rt, 39% (+ 58% recovered 203); (cc) CrO$_3$·2Pyr, CH$_2$Cl$_2$, rt, 95%.

Scheme 60 (continued)
2.2 Exploration of a New Cycloheptenone Annulation Method: Use of the Bifunctional Reagent (Z)-5-iodo-1-tributylstannylpent-1-ene in Organic Synthesis.

2.2.1 Introductory Remarks.

In connection with a synthetic study toward the variecolin family of sesterterpenoids, a concise seven-membered ring annulation method was proposed (see Scheme 8, page 13) and successfully employed (see Section 2.1.7, pages 38-53) in the conversion of bicyclic ketone 44 to the cycloheptenone 59. The novel bifunctional reagent (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (prepared as shown in Scheme 23, page 40) played a pivotal role in the elaboration of this method. Contemporaneously with the synthetic work described in the first part of this thesis, the generality of this new cycloheptenone annulation protocol was explored. The following sections detail the extension of this process to the efficacious appendage of a seven-membered ring onto a variety of functionalized cyclic ketones (or suitable derivatives thereof).
2.2.2 Preparation of $N,N$-Dimethyhydrazone Substrates.

In the preceding work, an efficient monoalkylation of ketone 44 with the iodide 53 had been accomplished. However, subsequent experiments employing structurally simpler ketone and $N,N$-dimethylhydrazone substrates indicated that the latter generally afforded higher yields of monoalkylated product in the alkylation step. Thus, for use in the annulation sequence described herein, the known hydrazones 227-231 were prepared. This was achieved by refluxing the corresponding commercially available ketones in neat dimethylhydrazine or by treating the ketones with dimethylhydrazine in refluxing benzene with azeotropic removal of water. In this manner, the hydrazones 227, 228, 229, 230 and 231 were isolated in yields of 98%, 99%, 99%, 99% and 100%, respectively.

The formation of each of the $N,N$-dimethyhydrazones was indicated by glc analysis and spectroscopic data was obtained to fully confirm the identity of each substrate. For example, the $^1$H nmr spectrum of 229 exhibited a diagnostic six proton singlet at $\delta$ 2.40 for the two methyl groups on nitrogen. The remaining hydrazone substrates provided similar spectroscopic data.
2.2.3 Preparation of Keto Alkenyl Iodide Substrates.

The first step in the annulation protocol is illustrated by the transformation of hydrazone 227 into the keto alkenyl iodide 234, as summarized in Scheme 60. Treatment of 227 with LDA in THF at -78 °C and then at 0 °C, followed by addition of HMPA, cooling to -78 °C, addition of the electrophile 53, and warming of the reaction mixture to room temperature, provided the alkylated102 hydrazone 232. In order to avoid the possibility of protiodestannylation of the alkenylstannane function during hydrolysis of the hydrazone moiety, the intermediate 232 was subjected to iododestannylation, which provided, stereospecifically, the iodide 233. At this stage, hydrolysis103 of the hydrazone unit by treatment of 233 with acetic acid-sodium acetate in aqueous THF at room temperature produced the ketone 234. The three-step conversion of 227 into 234, which was easily and conveniently performed without purification of the intermediates 232 and 233, was highly efficient and produced 234 in an overall yield of 90%. The IR spectrum of 234 displayed a strong carbonyl group absorption at 1713 cm$^{-1}$ and a carbon-carbon double bond absorption at 1610 cm$^{-1}$. The $^{13}$C nmr spectrum of 234 also confirmed the presence of the ketone function by a signal at δ 211.5. The $^1$H nmr spectrum of this substance indicated the required signals for the ketal moiety including two methyl group singlets at δ 0.96 and δ 1.00 as well as a pair of two proton singlets at δ 3.52 and δ 3.54. The two side-chain alkenyl proton signals were observed at δ 6.12-6.18 (m, 2H).
Subjection of the dimethylhydrazones 228, 229, 230 and 231 to the alkylation-iododestannylation-hydrolysis protocol described above provided the iodo ketones 235, 236, 237 and 238, respectively, in overall yields ranging from 69-98% (Table 9). Notably, entry 4 includes an additional step since the initial iodo ketone product (derived from hydrazone 230), which consisted of three diastereomers, was equilibrated with sodium methoxide in methanol at room temperature. Purification of the resultant material by flash chromatography on silica gel afforded the most stable diastereomer 237.
Table 9: Preparation of Keto Alkenyl Iodides from $N,N$-Dimethylhydrazones

1) LDA, THF, $-78 \, ^\circ\text{C}$ to 0 $^\circ\text{C}$

2) HMPA, $-78 \, ^\circ\text{C}$ to rt

3) I$_2$, CH$_2$Cl$_2$, rt

4) AcOH, NaOAc, THF, H$_2$O, rt

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazone</th>
<th>Keto Iodide</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image1" alt="image" /></td>
<td><img src="image2" alt="image" /></td>
<td>98%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="image" /></td>
<td><img src="image4" alt="image" /></td>
<td>93%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image5" alt="image" /></td>
<td><img src="image6" alt="image" /></td>
<td>69%$^a$</td>
</tr>
<tr>
<td>5</td>
<td><img src="image7" alt="image" /></td>
<td><img src="image8" alt="image" /></td>
<td>80%</td>
</tr>
</tbody>
</table>

$^a$-an additional equilibration step (NaOMe, MeOH, rt) was performed.
2.2.4 Anionic Cyclizations of the Keto Alkenyl Iodides: Production of Seven-Membered Ring Tertiary Allylic Alcohols.

The next step in the annulation sequence involved a lithium-iodine exchange, induced by treatment of a keto alkenyl iodide with butyllithium, followed by intramolecular attack of the resultant alkenyllithium species on the carbonyl carbon to provide a cyclic tertiary allylic alcohol\(^\text{47,104}\) (e.g. see equation 9, page 48 and Scheme 25, page 50). Since this is formally a 7-exo-trig cyclization it is stereoelectronically favorable according to Balwin’s rules.\(^\text{105}\) However, for the method to be generally useful, the desired intramolecular addition to the ketone function would have to be favored over potentially competing intra- and intermolecular processes such as proton abstraction by the alkenyllithium intermediate. Thus, dilute reaction conditions (~ 0.02 M in keto iodide) were employed to promote the desired intramolecular cyclization. Furthermore, an excess of butyllithium (>2 equiv) was required to achieve optimal results since the use of lesser quantities led to incomplete lithium-iodine exchange.\(^\text{47}\) The reaction of butyllithium with an alkenyl iodide generates butyl iodide in addition to an alkenyllithium species. Apparently, the reaction of butyllithium with butyl iodide to afford octane is competitive with the initial lithium-iodine exchange making at least two equivalents of butyllithium necessary to ensure complete consumption of the alkenyl iodide. Although the anionic cyclization is likely quite rapid, a standard procedure was employed which involved stirring the reaction mixtures for 1 h at -78 °C followed by quenching with saturated aqueous NaHCO\(_3\). In contrast to the earlier described cyclization of keto iodide 111 (see Section 2.1.7, equation 9, page 48), which was
conducted at 0 °C, it was found that the keto alkenyl iodides employed in this study were more efficiently annulated at lower temperature (-78 °C).

An example of the ring closure process is shown in equation 37. Treatment of a cold (-78 °C) THF solution of 234 with BuLi (2.1 equiv.) produced, after a suitable workup procedure, the cyclized product 239 in 84% yield as a single diastereomer of undetermined configuration. The IR spectrum of 239 displayed a strong hydroxyl group absorption at 3495 cm⁻¹ and a carbon-carbon double bond absorption at 1654 cm⁻¹. The 

As summarized in Table 10, butyllithium-induced ring closure of 235, 236 and 237 furnished the tertiary allylic alcohols 240, 241 and 242, respectively, in good-to-excellent yields (entries 2-4). Although 240 was produced as a mixture of diastereomers (~5:1), the alcohols 241 and 242 were obtained in diastereomerically pure form. The
relative configurations at the newly formed ring junctions of these materials are of no consequence to the overall annulation processes and, consequently, were not determined. The only other product detected in each of these reactions was uncyclized material in which the iodine of the starting material was replaced by a hydrogen. In each case, this (minor) product was readily separated from the requisite alcohol by flash chromatography of the mixture on silica gel. Interestingly, THF was found to be a better solvent than diethyl ether for the cyclization, since conducting the reaction in the latter solvent led to a dramatic rise in the proportion of protiodeiodinated material at the expense of the desired annulation product. Addition of a polar cosolvent (HMPA) failed to improve reaction yields. Attempted anionic cyclizations of 238 (entry 5) led to very low yields of (impure) alcohol 243 and a poor mass balance for the reaction. Presumably, this is due to the labile nature of the alcohol moiety of 243 which is both allylic and benzylic and, as such, is relatively susceptible to ionization to form a stabilized carbocation.
Table 10: Butyllithium Mediated Cyclization of Keto Alkenyl Iodides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Keto Iodide</th>
<th>Allylic Alcohol</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image_url" alt="Image 234" /></td>
<td><img src="image_url" alt="Image 239" /></td>
<td>84%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image_url" alt="Image 235" /></td>
<td><img src="image_url" alt="Image 240" /> (5:1)</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image_url" alt="Image 236" /></td>
<td><img src="image_url" alt="Image 241" /></td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image_url" alt="Image 237" /></td>
<td><img src="image_url" alt="Image 242" /></td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image_url" alt="Image 238" /></td>
<td><img src="image_url" alt="Image 243" /></td>
<td>trace</td>
</tr>
</tbody>
</table>
2.2.5 Oxidative Rearrangement of the Tertiary Allylic Alcohols: Production of Cycloheptenones.

The final step in the annulation sequence involved oxidative rearrangement\textsuperscript{51} of the tertiary allylic alcohols to the corresponding enones. An example of the oxidation process is shown in equation \textbf{38}. Treatment of \textbf{239} with PCC\textsuperscript{48} (2 equiv.) in the presence of 3 Å molecular sieves\textsuperscript{49} in dichloromethane at room temperature for 2 h provided the enone \textbf{244} in 85\% yield. The spectral data obtained for compound \textbf{244} were in agreement with the assigned structure. The IR spectrum of this material displayed a strong (\(\alpha,\beta\)-unsaturated) carbonyl absorption at 1636 cm\textsuperscript{-1}. The \(^{13}\text{C}\) nmr spectrum of \textbf{244} also exhibited diagnostic signals at \(\delta 126.8\) (C=CH), \(\delta 158.9\) (C=CH) and \(\delta 204.3\) (C=O) for the enone moiety. The \(^1\text{H}\) nmr spectrum of \textbf{244} displayed signals attributable to the ketal function and, importantly, a downfield signal at \(\delta 5.89\) (s) for the enone alkenyl proton.

![Equation 38]

Typically, in this and subsequent conversions of tertiary allylic alcohols to the corresponding cycloheptenones, \(~0.85\) g of molecular sieves per mmol of substrate was
employed. The sieves were powdered and flame-dried under reduced pressure (vacuum pump) prior to use. In general, the oxidative conversions in the presence of the molecular sieves were superior (i.e., faster and more efficient) than those carried out in the absence of the sieves.

The results of the oxidation process are summarized in Table 11. Exposure of each of the compounds 240, 241, and 242 to PCC\textsuperscript{48} in the presence of 3 Å molecular sieves\textsuperscript{49} provided the enone annulation products 245 (74%), 246 (82%) and 247 (86%), respectively.
Table 11: PCC Mediated Oxidative Rearrangement of the Tertiary Allylic Alcohols.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allylic Alcohol</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="239" alt="Image" /> <img src="244" alt="Image" /></td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td><img src="240" alt="Image" /> <img src="245" alt="Image" /></td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td><img src="241" alt="Image" /> <img src="246" alt="Image" /></td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td><img src="242" alt="Image" /> <img src="247" alt="Image" /></td>
<td>86%</td>
</tr>
</tbody>
</table>
2.2.6. Extension of the Cycloheptenone Annulation to Cyclic β-Keto Ester Substrates.

Application of the annulation method was also extended to cyclic β-keto ester substrates (Scheme 61). Reaction of iodide 53 with the potassium enolates of the keto esters 248 and 249 in refluxing THF led to excellent yields of the alkylated products 250 and 251. Treatment of each of these substances with a solution of iodine in dichloromethane smoothly effected iododestannylation to produce the iodides 252 and 253 in 99% and 94% yields, respectively. The spectral data derived from these materials were in complete agreement with the assigned structures. For example, the IR spectrum of 253 displayed two carbonyl group absorptions at 1713 cm\(^{-1}\) and 1735 cm\(^{-1}\). The \(^1\)H nmr spectrum of 253 displayed two alkenyl proton signals at δ 6.14 (ddd, \(J = 7.1, 7.1, 7.1\) Hz) and δ 6.19 (ddd, \(J = 7.1, 0.9, 0.9\) Hz) and a methyl ester singlet at δ 3.71.

![Scheme 61](image-url)
Experimentation showed that, compared with the substrates (234, 235, 236, 237) examined previously, the butyllithium-mediated cyclizations of the iodides 252 and 253 were more efficiently carried out at 0 °C than at -78 °C. Thus, treatment of 252 and 253 with butyllithium in THF at 0 °C for 45 min provided very good yields of the corresponding bicycles 254 and 255 (Scheme 62). In each case, the desired alcohol (a single diastereomer, configuration undetermined) was accompanied by minor amounts of uncyclized protiodeiodinated material. At -78 °C, the amount of these synthetically unproductive by-products increased. It should be noted that, with respect to the cyclization process, the reactions were highly chemoselective. No products that would have resulted from ring closure involving the ester carbonyl functions could be detected in the crude product mixture. Since any uncyclized by-products produced in the reactions were difficult to separate chromatographically from the required tertiary allylic alcohols 254 and 255, the crude products were subjected directly to oxidation with PCC\textsuperscript{48} (2-3 equiv.) in refluxing dichloromethane containing 3Å molecular sieves\textsuperscript{49} (reaction time: 5.5 h for 254; 2.5 h for 255). Subsequent purification of the crude products by chromatography on silica gel gave the enones 256 and 257 in moderate overall yields from 252 and 253, respectively.

Although the beneficial effect of using molecular sieves in the PCC oxidation has been previously noted\textsuperscript{49} (see section 2.1.7, equation 10, page 51) it deserves further emphasis at this point. Oxidations of the (crude) allylic alcohols 254 and 255 under a variety of other conditions (e.g. PCC, NaOAc, CH\textsubscript{2}Cl\textsubscript{2};\textsuperscript{48} PCC adsorbed on alumina\textsuperscript{50} in refluxing CH\textsubscript{2}Cl\textsubscript{2} or refluxing benzene) were very slow and required long reaction times (~2 days) with a large excess of PCC (>10 equiv.) to drive the reaction to completion.
Unfortunately, these forcing conditions led to concomitant formation of polar by-products and gave low yields of the enones. These difficulties were largely circumvented when the protocol outlined in Scheme 62 was employed.

Scheme 62

Evidence that the desired annulations had been successful was provided by the spectroscopic data derived from the products. For example, the IR spectrum of 257 displayed a strong (α,β-unsaturated) carbonyl absorption at 1666 cm⁻¹ as well as an ester carbonyl absorption at 1728 cm⁻¹. The ¹³C nmr spectrum of 257 also exhibited diagnostic signals at δ 133.3 (C=CH), δ 160.7 (C=CH) and δ 203.1 (C=O) for the enone moiety and a signal for the ester carbonyl carbon at δ 175.5. The ¹H nmr spectrum of 257 displayed a methyl ester singlet at δ 3.70 and a downfield signal at δ 6.08 (s) for the enone alkene proton.
2.2.7 A Recent Application to Natural Product Synthesis.

Following its initial disclosure, the cycloheptenone annulation method was quickly adopted by Dudley and Danishefsky in an efficient synthesis of the hydroazulene core of the antibacterial diterpene guanacastepene (Scheme 63). Thus, butyllithium mediated reductive cyclization of the keto iodide 258 provided the key bicyclic alcohol 259 as a single diastereomer (relative stereochemistry undetermined) in yields ranging between 62-65%. Oxidative rearrangement of 259 furnished the desired hydroazulene 260 in yields ranging between 71-92%.

Scheme 63
2.2.8 Conclusion.

In summary, the bifunctional reagent 53 has been successfully employed in the development of a new cycloheptene annulation method. The individual reactions involved are experimentally straightforward and the overall yields of the annulation processes are good to excellent. Of particular note are the high yields associated with the butyllithium-mediated ring closure of seven membered rings in the transformations of 234, 235, 236, 237, 252, and 253 into 239, 240, 241, 242, 254, and 255, respectively.
III. Experimental

3.1 General.

3.1.1 Data Acquisition, Presentation and Experimental Techniques.

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air-bath temperatures of Kugelrohr (bulb-to-bulb) distillations and are uncorrected. The removal of residual traces of solvent or moisture from a compound under reduced pressure (vacuum pump), refers to submitting the sample to a pressure of ~0.25 Torr, at room temperature for a period of 30-60 minutes.

Infrared (IR) spectra were recorded as either films between sodium chloride plates (liquid samples) or as potassium bromide pellets (solid samples) employing a Perkin-Elmer 1710 FT-IR spectrophotometer with internal calibration.

Proton nuclear magnetic resonance (\(^1H\) nmr) spectra were recorded on Bruker models AMX-500 (500 MHz), WH-400 (400 MHz), AV-400 (400 MHz) or AV-300 (300 MHz) spectrometers using deuteriochloroform (CDCl₃) or deuteriobenzene (C₆D₆) as solvents, as indicated. Signal positions (δ values) are given in parts per million (ppm) from tetramethysilane (δ 0) and were measured relative to the signals for chloroform (δ 7.24) or benzene (δ 7.15). Coupling constants (J values) are given in Hertz (Hz). The tin-proton coupling constants (\(J_{Sn-H}\)) are reported as an average of the \(^{117}\)Sn and \(^{119}\)Sn values. The spectral data are given in the following format: chemical shift (ppm), multiplicity, number of protons, coupling constant(s), and assignments (when known). The
abbreviations used for the multiplicities are: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). In the \(^1\text{H}\) nmr spectra, H-x and H-x' have been used to designate protons on the same carbon, with H-x' being the proton resonating at lower field. In some cases, the proton assignments were supported by COSY (\(^1\text{H}-\text{H}\) homonuclear correlation spectroscopy) and/or 1D-NOE (nuclear Overhauser enhancement) difference experiments or 2D-NOESY (nuclear Overhauser effect spectroscopy) experiments.

Carbon nuclear magnetic resonance (\(^{13}\text{C}\) nmr) spectra and the attached proton test experiments (APT) were recorded on a Varian XL-300 spectrometer at 75.3 MHz or on Bruker models AV-300 (75.5 MHz), AM-400 (100.4 MHz) or AMX-500 (125.8 MHz) spectrometers, using deuteriochloroform as the solvent. Signal positions (\(\delta\) values) are given in parts per million (ppm) from tetramethylsilane (\(\delta\) 0) and were measured relative to the signals for chloroform (\(\delta\) 77.0). The APT experiments were used to differentiate methyl and methine (negative phase signals) from methylene and quaternary carbons (positive phase signals). Signals with negative phase or positive phase in the attached proton test are so indicated in brackets (-ve) or (+ve) respectively, following the chemical shift. In some cases, the proton and carbon assignments were supported by (\(^1\text{H}, ^{13}\text{C}\)) heteronuclear multiple quantum coherence experiments (HMQC) and heteronuclear multiple bond correlation experiments (HMBC), which were carried out using a Bruker AMX-500 spectrometer.

Low and high resolution electron impact mass spectra were recorded on a Kratos MS 80 or on a Kratos Concept II HQ mass spectrometer. The molecular ion (\(M^+\)) masses are given unless otherwise noted. For some compounds containing the tributylstannyl
(SnBu₃) group, the high resolution mass spectrometry molecular mass determinations were made based on the (M – Bu)⁺ peak. All compounds subjected to high resolution mass measurements were homogeneous by glc and/or tlc analyses.

Elemental analyses were performed on a Carlo Erba CHN model 1106 or on a Fisons EA model 1108 elemental analyzer, by the UBC Microanalytical Laboratory.

Gas-liquid chromatography (glc) analyses were performed on a Hewlett-Packard model 5890 gas chromatograph equipped with a flame ionization detector and fused silica capillary column (~25 m x 0.20 mm coated with 5% phenylmethyl silicone).

Thin layer chromatography (tlc) was carried out on commercially available aluminum-backed silica gel 60 F₂₅₄ plates (E. Merck, type 5554, thickness 0.2 mm). Visualization was accomplished by using uv light (254 nm) and/or iodine followed by heating the plates after staining with an appropriate reagent. The stains used were: (a) phosphomolybdic acid (PMA) in EtOH (20% w/v, Aldrich Chemical Co.), (b) ammonium molybdate (5% w/v) and cerium(IV) sulfate (0.1% w/v) in 10% aqueous sulfuric acid, (c) vanilin (6% w/v) in sulfuric acid (4% v/v) - EtOH (10% water v/v in ethanol), (d) anisaldehyde (5% v/v) in a sulfuric acid - EtOH mixture (5% H₂SO₄ v/v in EtOH). Flash Chromatography was performed with 230-400 mesh silica gel (E. Merck, Silica Gel 60 or Silacycle, Silica Gel) or with tlc-grade Sigma type H silica gel 10-40 μm, no binder, using the technique described by Still.¹⁰⁷

Unless otherwise stated, all reactions were carried out under an atmosphere of dry Argon using glassware that had been thoroughly flame and/or oven (~140 °C) dried. The glass syringes, Teflon® cannulae and stainless steel needles used for handling anhydrous solvents and reagents were oven dried, cooled in a dessicator, and flushed with dry argon.
prior to use. Plastic syringes were flushed with dry argon before use. The small and large Teflon® cannulae were purchased from Canlab (Mississauga, ON.) and have the following dimensions: the small cannulae have an inner diameter of 0.38 mm and a wall thickness of 0.23 mm, and the large cannulae have an inner diameter of 0.97 mm and a wall thickness of 0.30 mm.

Concentration, evaporation, or removal of solvent under reduced pressure (water aspirator) refers to solvent removal via a Büchi rotary evaporator at ~25 Torr.

Cold temperatures were maintained by the use of the following baths: 0 °C, ice/water; -20 °C, -30 °C and -48 °C, aqueous calcium chloride/dry ice (27, 35, and 47 g CaCl₂/100 mL H₂O, respectively); -65 °C, acetone-acetonitrile/dry ice; -78 °C, acetone/dry ice.

3.1.2 Solvents and Reagents.

All solvents and reagents were purified and dried using established procedures. Benzene and dichloromethane were distilled from calcium hydride. Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. All four of these solvents were distilled under an atmosphere of dry argon and used immediately.

Acetonitrile, carbon tetrachloride, cyclohexane, N,N-diisopropylamine, N,N-diisopropylethylamine, N,N-dimethylformamide, dimethyl sulfoxide, ethanol, hexamethylphosphoramid (HMPA), 2-methyl-2-propanol (t-BuOH), pyridine, and triethylamine were distilled from calcium hydride under an atmosphere of dry argon.
Magnesium was added to methanol and after refluxing the mixture, the methanol was distilled from the resulting magnesium methoxide solution under an atmosphere of dry argon. The aforementioned solvents and reagents were stored under an atmosphere of dry argon in bottles sealed with a SureSeal® (Aldrich Chemical Co.). All other solvents were obtained commercially and used without further purification.

Petroleum ether refers to a hydrocarbon mixture with a boiling point range of 30-60 °C.

Solutions of methyl lithium in diethyl ether, n-butyllithium in hexanes or t-butyllithium in pentane were obtained from the Aldrich Chemical Co. and were standardized using the procedure of Kofron and Baclawski.\textsuperscript{109}

A solution of NaOMe in dry methanol was prepared in the following manner. To a cold (-78 °C) flask containing sodium metal and a Teflon\textsuperscript{®} coated stir bar was added the appropriate amount of dry MeOH. The mixture was warmed to room temperature with stirring and the resultant solution was stored under an atmosphere of dry argon in a bottle sealed with a SureSeal\textsuperscript{®} (Aldrich Chemical Co.).

Trimethylsilyl chloride, tributylstannyl chloride and boron trifluoride-etherate were purified by distillation from calcium hydride under an atmosphere of dry argon and were used immediately.

Lithium diisopropylamide (LDA) was prepared by adding a solution of butyllithium (1.0 equiv.) in hexanes to a solution of diisopropylamine (1.1 equiv.) in dry THF at -78 °C followed by warming to 0 °C for 20 min prior to use.

Potassium hydride was obtained as a 35% suspension in mineral oil from the Aldrich Chemical Co. and was rinsed free of the oil with dry diethyl ether under an
atmosphere of dry argon. The residual solvent was then removed from the potassium hydride under reduced pressure (vacuum pump).

Aqueous ammonium chloride-ammonia (NH₄Cl-NH₃) (pH 8) solution was prepared by the addition of 50 mL of concentrated (28-30%) aqueous ammonia to 950 mL of saturated aqueous ammonium chloride solution.

Iodine was purified via sublimation by warming (~70 °C) the iodine under reduced pressure (~25 Torr).

Methyl iodide, chloroiodomethane and deuteriochloroform were passed through a short column of dry basic alumina (activity I) prior to use. The basic alumina was dried by oven heating (~140 °C) for at least 12 h and cooled in a desiccator.

Argon was dried by bubbling it through concentrated sulfuric acid, and then passing it through a Drierite® and potassium hydroxide (KOH) filled drying tube.

All other reagents were commercially available and were used without further purification.
3.2. A Synthetic Approach to the Variecolin Class of Sesterterpenoids:
Total Syntheses of (±)-5-Deoxovariecolin (±)-5-Deoxyvariecolol (±)-5-
Deoxyvariecolactone.

Preparation of 3-[2-(2,6-Dioxan-1-yl)ethyl]-3-methylcyclohexanone (100).

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

\[
\begin{align*}
1) \text{Mg, THF} \\
2) \text{cat. CuBr·Me}_2\text{S} \\
3) \text{3-methylcyclohex-2-en-1-one} & \quad \text{TMSCl, HMPA, -78 °C}
\end{align*}
\]

To a stirred suspension of freshly ground magnesium turnings (1.32 g, 55.5 mmol, 3.0 equiv.) and iodine (a few crystals) in dry THF (10 mL), at room temperature, was added via cannula a solution of 2-(2-bromoethyl)-1,3-dioxane (96) (8.50 g, 43.6 mmol, 2.4 equiv.) in dry THF (3 mL). The bromide solution was added at such a rate that reflux of the reaction mixture was maintained. After the addition was complete (~ 30 min), the mixture was heated at reflux for an additional 1 h and then allowed to cool to room temperature and diluted with dry THF (50 mL). The mixture was cooled to -78 °C, solid CuBr·Me₂S (1.40 g, 6.80 mmol, 15 mol% with respect to the Grignard reagent) was added in one portion and the cloudy mixture stirred for 1 h. Dry HMPA (9.48 mL, 54.5 mmol, 3.0 equiv.) was added dropwise via syringe and the mixture was stirred at -78 °C for 10 min. A solution of 3-methylcyclohex-2-en-1-one (2.00 g, 18.2 mmol, 1.0 equiv.) and trimethylsilyl chloride (6.91 mL, 54.5 mmol, 3 equiv.) in dry THF (4 mL) was added
dropwise via cannula over 15 min. The resultant pale yellow mixture was stirred at -78 °C for 2.5 h and was then allowed to warm to room temperature. Water (12 mL) was added and the mixture stirred for 5 min before adding aqueous NH₄Cl-NH₃ (pH 8, 40 mL) and diethyl ether (50 mL). The mixture was opened to the atmosphere and stirred vigorously overnight, at which point the aqueous layer was a deep blue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed successively with water (2 x 40 mL), aqueous 10% CuSO₄ solution (2 x 40 mL), brine (2 x 40 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (140 g of silica gel, 2:1 petroleum ether - ethyl acetate). The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 99-108 °C/0.25 torr) to afford the keto acetal \textbf{100} (3.92 g, 95%) as a colorless oil. The spectral data for keto acetal \textbf{100} are identical with those previously reported.\cite{6}
Preparation of 6-Methylbicyclo[4.3.0]non-9-en-2-one (98).

To a stirred solution of the keto acetal 100 (1.11 g, 4.90 mmol, 1.0 equiv.) in THF at room temperature was added a solution of 80% aqueous trifluoroacetic acid (15 mL, prepared by diluting 12 mL of neat CF₃CO₂H with 3 mL water). The reaction mixture was heated at 70 °C in an oil bath for 2.5 h, and was then allowed to cool to room temperature. The mixture was neutralized by the careful addition of saturated aqueous NaHCO₃ (20 mL) followed by addition of solid NaHCO₃. Water (20 mL) and Et₂O (25 mL) were added, the layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 40 mL). The combined organic extracts were washed with brine (1 x 40 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g of silica gel, 2:1 petroleum ether - diethyl ether) to afford the enone 98 (523 mg, 71%) as a colorless oil. After recovery of the enone 98 the column was flushed with diethyl ether (800 mL). The eluate was concentrated, the residue obtained was dissolved in a mixture of THF (15 mL) and 80% aqueous trifluoroacetic acid (7.6 mL) and the mixture was heated at 70 °C for 16 h. The reaction mixture was cooled to room temperature, carefully neutralized by addition of saturated aqueous NaHCO₃ (10 mL) followed by addition of solid NaHCO₃. Water (10 mL) and diethyl ether (15 mL) were added, the layers were separated, and the
aqueous phase was extracted with diethyl ether (2 x 20 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (40 g of silica gel, 2:1 petroleum ether - diethyl ether) to afford a further 91 mg (12%) of compound 98. The total yield of the enone 98 was 614 mg (83%). The spectral data for the enone 98 are identical with those previously reported.\(^6\)

**Preparation of Lithium Isopropenyl(cyano)cuprate (107).**

\[
\begin{align*}
\text{Br} & \quad 1) \text{t-BuLi, THF, } -78^\circ \text{C} \\
\text{106} & \quad 2) \text{CuCN, } -78^\circ \text{C to } -45^\circ \text{C} \\
\text{Cu(CN)Li} & \quad 107
\end{align*}
\]

To a stirred solution of tert-butyllithium (6.66 mL, 1.7 M in pentane, 11.3 mmol, 2.0 equiv.) in dry THF (17 mL) at -78 °C was added 2-bromopropene (106) (0.503 mL, 5.66 mmol, 1.0 equiv.), dropwise via syringe over 45 min. After the mixture had been stirred for another 15 min, solid CuCN (507 mg, 5.66 mmol, 1.0 equiv.) was added in a single portion and the resulting mixture was stirred at -78 °C for 45 min and then at -45 °C for 15 min, to provide a clear, pale yellow solution of the cuprate 107. The solution was recooled to -78 °C prior to use.
Preparation of (1S*, 6R*, 9S*)-9-Isopropenyl-6-methylbicyclo[4.3.0]nonan-2-one (108).

A solution of the cuprate 107 (5.66 mmol, 2.0 equiv.) was prepared as described above. To this cold (-78 °C), stirred solution was added trimethylsilyl chloride (1.08 mL, 8.49 mmol, 3.0 equiv.) dropwise via syringe. A solution of the enone 98 (425 mg, 2.83 mmol, 1.0 equiv.) in dry THF (2 mL) was added via cannula and the reaction mixture was stirred at -78 °C for 15 min. The mixture was allowed to warm to room temperature, water (15 mL) was added and the mixture was stirred for an addition 1 h. Aqueous NH₄Cl-NH₃ (pH 8, 40 mL) was added and air was bubbled through the mixture until the aqueous layer became deep blue. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (50 g of silica gel, 90:10 petroleum ether - diethyl ether) to afford the ketone 108 (444 mg, 87%) as a colorless oil. The spectral data for ketone 108 are identical with those previously reported, including:
$^{1}$H nmr (CDCl$_3$, 400 MHz) $\delta$: 1.11 (s, 3H, Me-10), 1.41-1.51 (m, 2H), 1.61-1.73 (m, 1H), 1.71 (br s, 3H, Me-13), 1.71-1.91 (m, 4H), 1.91-2.03 (m, 1H), 2.13-2.30 (m, 2H), 2.56 (br d, 1H, $J = 10.1$ Hz, H-1), 2.86 (dddd, 1H, $J = 10.1, 10.1, 10.1$ Hz, H-9), 4.78 (br s, 1H, H-12), 4.83 (m, 1H, H-12').

In NOED experiments, irradiation of the signal at $\delta$ 1.11 (Me-10) showed enhancements for the signals at $\delta$ 2.56 (H-1) and $\delta$ 2.86 (H-9). Similarly, irradiation of the signal at $\delta$ 2.56 (H-1) showed enhancements for the signals at $\delta$ 1.11 (Me-10) and $\delta$ 2.86 (H-9). Irradiation of the signal at $\delta$ 2.86 (H-9) showed enhancements for the signals at $\delta$ 1.11 (Me-10) and $\delta$ 2.56 (H-1).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 21.7, 24.0, 28.7, 29.5, 35.1, 38.9, 41.1, 46.6, 49.0, 62.7, 109.8, 146.4, 214.0.
Preparation of ($1R^*$, $6R^*$, $9S^*$)-9-Isopropenyl-6-methylbicyclo[4.3.0]nonan-2-one (44).

To the neat ketone 108 (1.00 g, 5.25 mmol, 1.0 equiv.) was added a solution of NaOMe in dry MeOH (5.25 mL, 2.0 M, 10.5 mmol, 2.0 equiv.) and the resulting mixture was stirred at room temperature for 70 h. The MeOH was removed by rotary evaporation and brine (50 mL) and diethyl ether (50 mL) were added to the residue. The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. $^1$H nmr spectroscopic analysis of the oil thus obtained indicated an 11:1 ratio of the trans and cis-fused compounds, 44 and 108, respectively, as determined by the integration of their vinyl proton signals. The crude product was purified by flash chromatography (100 g of tlc grade silica gel, 90:10 petroleum ether - diethyl ether). The appropriate fractions were collected to afford mixed fractions containing compounds 44 and 108 (311 mg, 31%) as well as pure trans-fused ketone 44 (641 mg, 64%). The total yield of compounds 44 and 108 was 952 mg (95%). The first compound that eluted was the cis-fused ketone 108 and
the mixed fractions were resubjected to flash chromatography to allow the separation of a pure sample of the *trans*-fused epimer 44.

The spectral data for the *trans*-fused ketone 44 are identical with those previously reported,12 including:

\[ ^1\text{H} \text{nmr (CDCl}_3, 400 \text{ MHz}) \delta: 0.76 (s, 3\text{H}, \text{Me-10}), 1.40-1.78 (m, 4\text{H}), 1.70 (s, 3\text{H}, \text{Me-13}), 1.78-2.08 (m, 4\text{H}), 2.22-2.30 (m, 2\text{H}), 2.47 (d, 1\text{H}, J = 11.1 \text{ Hz}, \text{H-1}), 2.84 (\text{ddd}, 1\text{H}, J = 11.1, 11.1, 6.6 \text{ Hz}, \text{H-9}), 4.62 (\text{br s}, 1\text{H}, \text{H-12}), 4.66 (\text{br s}, 1\text{H}, \text{H-12'}). \]

In NOED experiments, irradiation of the signal at \( \delta 2.47 \) (H-1) showed an enhancement for the signal at \( \delta 1.70 \) (Me-13). Similarly, irradiation of the signal at \( \delta 1.70 \) (Me-13) showed an enhancement for the signal at \( \delta 2.47 \) (H-1).

\[ ^{13}\text{C} \text{nmr (CDCl}_3, 75.3 \text{ MHz}) \delta: 18.6, 21.1, 24.4, 27.3, 38.5, 39.8, 41.3, 41.5, 49.4, 63.3, 108.8, 147.5, 210.6. \]
Preparation of 5-(tert-Butyldimethylsiloxy)pent-1-yne (117).

\[
\begin{align*}
\text{HO} & \quad \text{TBDMS-Cl} \\
\text{116} & \quad \text{imidazole} \\
\text{CH}_2\text{Cl}_2, \text{ r.t.} & \quad \text{TBDMSO} \\
\text{117} & \quad \text{211} \\
\end{align*}
\]

To a stirred solution of the alcohol 116 (9.50 g, 113 mmol, 1.0 equiv.) and imidazole (9.50 g, 136 mmol, 1.2 equiv.) in dry CH\textsubscript{2}Cl\textsubscript{2} (150 mL), at room temperature, was added tert-butyldimethylsilyl chloride (17.5 g, 116 mmol, 1.03 equiv). The reaction mixture was stirred at room temperature for 2.5 h and then was concentrated to ~100 mL by rotary evaporation. The mixture was filtered through flash silica gel (90 g, elution with 50:1 petroleum ether - diethyl ether) and the combined eluate was concentrated by rotary evaporation. The residual material was distilled (air-bath temperature 50-60 °C/0.25 torr) to afford compound 117 (20.6 g, 92%) as a colorless oil.

IR (neat): 3314, 2955, 2859, 2121, 1473, 1390, 1257, 1108, 835 cm\textsuperscript{-1}.

\(^1\)H nmr (CDCl\textsubscript{3}, 400 MHz) δ: 0.02 (s, 6H, SiMe\textsubscript{2}), 0.93 (s, 9H, CMe\textsubscript{3}), 1.70 (m, 2H, H-4), 1.90 (t, 1H, J = 2.7 Hz, H-1), 2.25 (dt, 2H, J = 2.7, 7.0 Hz, H-3), 3.67 (t, 2H, J = 6.0 Hz, H-5).
\[ ^{13}\text{C} \text{ nmr (CDCl}_3, 75.3 \text{ MHz}) \delta: -5.4 \text{ (SiMe}_2), 14.8, 18.3, 25.9 \text{ (CMMe}_3), 31.5, 61.3 \text{ (C-5)}, 68.2 \text{ (C-1)}, 84.1 \text{ (C-2)}. \]

Exact Mass calcd. for \( \text{C}_{10}\text{H}_{19}\text{OSi} \text{ (M – Me)}^+ \): 183.1205; found: 183.1203.

Anal. calcd. for \( \text{C}_{11}\text{H}_{22}\text{OSi} \): C 66.60, H 11.18; found: C 66.55, H 11.32.
Preparation of 1-(Tributylstannyl)-5-(tert-butyldimethylsiloxy)pent-1-yne (118).

To a cold (-78 °C), stirred solution of alkyne 117 (18.9 g, 95.1 mmol, 1.0 equiv.) in dry THF (300 mL) was added MeLi (67.9 mL, 1.4 M in diethyl ether, 95.1 mmol, 1.0 equiv.) dropwise via syringe over 10 min. The reaction mixture was stirred at -78 °C for 2 h. Tributyltin chloride (25.8 mL, 95.1 mmol, 1.0 equiv.) was added and the mixture was allowed to warm to room temperature overnight. The mixture was concentrated to ~150 mL by rotary evaporation, 5% aqueous NaHCO₃ (100 mL) was added and the layers were separated. The aqueous phase was extracted with 1:1 diethyl ether - petroleum ether (3 x 100 mL). The combined organic extracts were washed with brine (1 x 100 mL), dried over anhydrous magnesium sulfate with stirring for 1 h, and concentrated under reduced pressure. After removal of traces of solvents (vacuum pump), the alkynylstannane 118 (46.2 g, 99.7%) was obtained as a clear, colorless oil and was used immediately in the next reaction.
IR (neat): 2956, 2857, 2151, 1524, 1464, 1255, 1107 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 0.04 (s, 6H, SiMe$_2$), $\delta$: 0.82-0.99 (m, 15 H), 0.86 (s, 9H, CMe$_3$), 1.24-1.38 (m, 6H), 1.49-1.58 (m, 6H), 1.65-1.75 (m, 2H, H-4), 2.30 (t, 2H, $J = 7.1$ Hz, H-3), 3.69 (t, 2H, $J = 6.4$ Hz, H-5).

$^{13}$C nmr (CDCl$_3$, 50.3 MHz) $\delta$: -5.3, 10.9, 13.7, 16.6, 18.3, 26.0, 27.0, 28.3, 32.2, 61.7, 81.6, 111.3.

Exact Mass calcd. for C$_{19}$H$_{39}$O$^{120}$SnSi (M – Bu)$^+$: 431.1792; found: 431.1801.
Preparation of (Z)-5-(tert-butyldimethylsiloxy)-1-tributylstannylpent-1-ene (119).

\[
\text{118} \xrightarrow{1) \text{Cp}_2\text{Zr(H)}\text{Cl}} \xrightarrow{\text{THF, r.t.}} \text{119}
\]

To a stirred suspension of the Schwartz reagent (29.4 g, 114 mmol, 1.2 equiv.) in dry THF (700 mL) at room temperature was added neat alkynylstannane 118 (46.2 g, 95.0 mmol, 1.0 equiv.) via cannula, over 20 min. The reaction mixture was stirred for 2 h at room temperature. To the resulting dark red mixture was added water (6 mL) adsorbed on basic alumina (40 g). The mixture was concentrated to ~150 mL by rotary evaporation and filtered through flash silica gel (200 g, elution with 900 mL of pentane). The combined filtrate was concentrated under reduced pressure and the acquired oil was purified by flash chromatography (200 g of silica gel, 50:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), alkenylstannane 119 (43.0 g, 92%), a pale yellow oil.
IR (neat): 2928, 2857, 1599, 1464, 1255, 1104, 838 cm⁻¹.

\(^1\)H nmr (CDCl₃, 400 MHz) δ: 0.03 (s, 6H, SiMe₂), 0.82-0.98 (m, 15 H), 0.86 (s, 9H, CMe₃), 1.25-1.34 (m, 6H), 1.39-1.58 (m, 6H), 1.58-1.62 (m, 2H, H-4), 2.07-2.11 (m, 2H, H-3), 3.61 (t, 2H, J = 6.6 Hz, H-5), 5.79 (dt, 1H, J = 12.4, 0.9 Hz, \(^2\)J\(_{Sn-H}\) = 70 Hz, H-1), 6.50 (dt, 1H, J = 12.4, 7.1 Hz, \(^3\)J\(_{Sn-H}\) = 147 Hz, H-2).

\(^13\)C nmr (CDCl₃, 75.3 MHz) δ: -5.3 (-ve, SiMe₂), 10.2 (+ve), 13.7 (+ve), 18.3 (-ve), 25.9 (-ve), 27.4 (+ve), 29.2 (+ve), 33.1 (+ve), 33.6 (+ve), 63.0 (+ve), 128.1 (-ve), 148.6 (-ve).

Exact Mass calcd. for C\(_{19}\)H\(_{41}\)OSi\(^{120}\)Sn (M – Bu)+: 433.1949; found: 433.1948.

Anal. calcd. for C\(_{23}\)H\(_{50}\)OSiSn: C 56.44, H 10.30; found: C 56.49, H 10.47.
Preparation of (Z)-5-tributylstannylpent-4-en-1-ol (120).

\[
\text{TBDMSO} - \text{SnBu}_3 \quad \xrightarrow{\text{Bu}_4\text{NF, THF}} \quad \text{HO} - \text{SnBu}_3
\]

To a stirred solution of silyl ether 119 (8.60 g, 17.6 mmol, 1.0 equiv.) in THF (40 mL) at room temperature was added Bu$_4$NF (20.0 mL, 1.0 M in THF containing 5% water, 20.0 mmol, 1.1 equiv.). The reaction mixture was stirred for 2 h at room temperature. Saturated aqueous NaHCO$_3$ (40 mL) and diethyl ether (40 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (130 g of silica gel, 60:40 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the alcohol 120 (5.90 g, 90%) as a pale yellow oil.
IR (neat): 3325, 2960, 2923, 1464, 1070, 837 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 0.82-0.98 (m, 15 H), 1.24-1.33 (m, 6H), 1.39-1.59 (m, 6H),
1.61-1.68 (m, 2H, H-2), 2.09 (qd, 2H, $J = 7.0$, 0.9 Hz, H-3), 3.64 (td, 2H, $J = 6.6$, 5.6 Hz, H-1),
5.81 (dt, 1H, $J = 12.4$, 0.9 Hz, $^2J_{Sn-H} = 70$ Hz, H-5), 6.50 (dt, 1H, $J = 12.4$, 7.0 Hz, $^3J_{Sn-H} = 149$ Hz, H-4).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 10.2 (+ve), 13.7 (-ve), 27.3 (-ve), 29.2 (+ve), 32.8 (+ve),
33.6 (+ve), 62.6 (+ve), 128.7 (-ve), 148.2 (-ve).

Exact Mass calcd. for C$_{13}$H$_{27}$O$^{120}$Sn (M – Bu)$^+$: 319.1084; found: 319.1080.

Anal. calcd. for C$_{17}$H$_{36}$O$^-$Sn: C 54.43, H 9.67; found: C 54.72, H 9.58.
Preparation of (Z)-5-iodo-1-tributylstannylpent-1-ene (53).

To a cold (0 °C), stirred solution of triphenylphosphine (5.22 g, 19.9 mmol, 1.3 equiv.) and imidazole (2.71 g, 39.8 mmol, 2.6 equiv.) in dry acetonitrile (60 mL) and dry diethyl ether (100 mL) was added solid iodine (4.97 g, 19.6 mmol, 1.28 equiv.). The reaction mixture was allowed to warm to room temperature and vigorously shaken by hand until the color of the iodine disappeared. The mixture was recooled to 0 °C and a solution of alcohol 120 (5.70 g, 15.3 mmol, 1.0 equiv.) in dry diethyl ether (20 mL) was added via cannula. The mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. Saturated aqueous NaHCO₃ (60 mL) and water (40 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (1 x 80 mL) and petroleum ether (1 x 80 mL). The combined organic extracts were washed with water (1 x 80 mL) and brine (1 x 80 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The resulting oil/salt mixture was filtered through a pad of flash silica gel (60 g, elution with diethyl ether) and the combined filtrate was concentrated. The acquired oil was passed through a thin pad of flash silica gel (25 g, elution with petroleum ether) to afford, after concentration of the filtrate under reduced pressure, iodide 53 (7.00 g, 95%) as a colorless oil.
IR (neat): 2925, 1598, 1463, 1376, 1338, 1205, 1072, 598 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.82-0.98 (m, 15 H), 1.25-1.34 (m, 6H), 1.39-1.59 (m, 6H), 1.87-1.94 (m, 2H, H-4), 2.09-2.14 (m, 2H, H-3), 3.17 (t, 2H, J = 7.0 Hz, H-5), 5.85 (d, 1H, J = 12.4 Hz, \(^2\)J\(_{\text{Sn-H}}\) = 69 Hz, H-1), 6.45 (dt, 1H, J = 12.4, 7.0 Hz, \(^3\)J\(_{\text{Sn-H}}\) = 146 Hz, H-2).

\(^{13}\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 6.1 (+ve), 10.3 (+ve), 13.7 (-ve), 27.4 (+ve), 29.2 (+ve), 33.6 (+ve), 37.7 (+ve), 129.9 (-ve), 146.6 (-ve).

Exact Mass calcd. for C\(_{13}\)H\(_{26}\)\(^{120}\)Sn (M – Bu\(^+\)): 429.0101; found: 429.0101.

Anal. calcd. for C\(_{17}\)H\(_{35}\)Sn: C 42.10, H 7.27; found: C 42.29, H 7.12.
Preparation of \((1R^*, 3R^*, 6S^*, 9S^*)\)-9-Isopropenyl-6-methyl-3-[\((Z)\)-5-(tributylstannyl)pent-4-en-1-yl]bicyclo[4.3.0]nonan-2-one (121) and \((1R^*, 3S^*, 6S^*, 9S^*)\)-9-Isopropenyl-6-methyl-3-[\((Z)\)-5-(tributylstannyl)pent-4-en-1-yl]bicyclo[4.3.0]nonan-2-one (122).

To a cold (-78 °C), stirred solution of \(t\)-BuOK (380 mg, 3.38 mmol, 1.2 equiv.) in dry THF (14 mL) was added dry diisopropylamine (474 \(\mu\)L, 3.38 mmol, 1.2 equiv.) followed by BuLi (2.14 mL, 1.58 M in hexanes, 3.38 mmol, 1.2 equiv.). The reaction mixture was stirred at -78 °C for 40 min. The neat ketone 44 (540 mg, 2.82 mmol, 1.0 equiv.) was added via cannula [addition flask rinsed with cold (-78 °C) dry THF (2 mL)] and the reaction mixture was stirred at -78 °C for 2.5 h. Dry HMPA (1.96 mL, 11.3 mmol, 4.0 equiv.) was added and the reaction mixture was stirred at -78 °C for an additional 30 min. A cold (-78 °C) solution of \((Z)\)-5-iodo-1-tributylstannylpent-1-ene (53) (2.50 g, 5.16 mmol, 1.8 equiv.) in dry THF (3 mL) was added via cannula and stirring was continued at -78 °C for 30 min. The reaction mixture was then stirred at -48 °C for 2 h and allowed to slowly warm to room temperature overnight. Saturated aqueous NaHCO\(_3\) (70 mL) and diethyl ether (40 mL) were added and the layers were separated.
The aqueous phase was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with 10% aqueous CuSO₄ solution (2 x 60 mL), brine (1 x 60 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (200 g of silica gel, 97:3 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), two compounds. The first compound to be eluted was the keto alkenylstannane 122 (1.01 g, 65%) as a colorless oil.

IR (neat): 2927, 1718, 1598, 1458, 1376, 1182, 1071, 881 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.69 (s, 3H, Me-15), 0.84-0.89 (m, 15 H), 1.11-1.67 (m, 20 H), 1.69 (s, 3H, Me-18), 1.74-1.83 (m, 2H), 1.94-2.06 (m, 3H), 2.07-2.15 (m, 1H), 2.16-2.24 (m, 1H), 2.48 (d, 1H, J = 11.1 Hz, H-1), 2.88 (ddd, 1H, J = 11.1, 11.1, 6.1 Hz, H-9), 4.61 (s, 1H, H-17), 4.65 (s, 1H, H-17'), 5.76 (d, 1H, J = 12.3 Hz, ²JSn-H = 73 Hz, H-14), 6.49 (ddd, 1H, J = 12.3, 7.0, 7.0 Hz, ³JSn-H = 143 Hz, H-13).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 10.1 (+ve), 13.6 (-ve), 18.7 (-ve), 20.9 (-ve), 27.3 (+ve), 27.6 (+ve), 27.65 (+ve), 28.6 (+ve), 29.1 (+ve), 31.8 (+ve), 37.2 (+ve), 38.6 (+ve), 39.7 (+ve), 41.3 (-ve), 50.0 (+ve), 50.2 (-ve), 63.5 (-ve), 108.9 (+ve), 127.8 (-ve), 147.4 (+ve), 148.9 (-ve), 210.5 (+ve).

Exact Mass calcd. for C₂₆H₄₅O₁²₀Sn (M – Bu)⁺: 493.2492; found: 493.2498.
Anal. calcd. for C$_{30}$H$_{54}$OSn: C 65.58, H 9.91; found: C 65.58, H 10.00.

The second compound to be eluted was the keto alkenylstannane 121 (146 mg, 9%) as a colorless oil.

IR (neat): 2926, 1714, 1600, 1458, 1381, 1071, 881 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 0.75 (s, 3H, Me-15), 0.84-0.89 (m, 15 H), 1.22-1.80 (m, 23H), 1.70 (s, 3H, Me-18), 1.97-2.08 (m, 3H), 2.28 (ddd, 1H, $J = 7.1, 7.1, 7.1$ Hz, H-3), 2.66 (d, 1H, $J = 11.1$ Hz, H-1), 2.84 (ddd, 1H, $J = 11.1, 11.1, 6.4$ Hz, H-9), 4.59 (s, 1H, H-17), 4.66 (br s, 1H, H-17'), 5.78 (d, 1H, $J = 12.4$ Hz, $^2J_{Sn-H} = 73$ Hz, H-14), 6.42 (ddd, 1H, $J = 12.4, 7.0, 7.0$ Hz, $^2J_{Sn-H} = 143$ Hz, H-13).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 10.2 (+ve), 13.7 (-ve), 18.7 (-ve), 21.3 (-ve), 27.3 (+ve), 27.6 (+ve), 27.8 (+ve), 28.8 (+ve), 29.2 (+ve), 32.4 (+ve), 35.1 (+ve), 36.7 (+ve), 39.8 (+ve), 40.9 (-ve), 49.5 (+ve), 50.6 (-ve), 59.1 (-ve), 108.5 (+ve), 128.6 (-ve), 147.5 (+ve), 148.3 (-ve), 213.5 (+ve).

Exact Mass calcd. for C$_{26}$H$_{45}$O$^{120}$Sn (M – Bu)$^+$: 493.2492; found: 493.2492.

The total yield of ketones 121 and 122 was 1.15 g (74%)
To a cold (-78 °C), stirred solution of diisopropylamine (352 µL, 2.51 mmol, 1.3 equiv.) in dry THF (6 mL) was added BuLi (1.47 mL, 1.58 M in hexanes, 2.31 mmol, 1.2 equiv.). The reaction mixture was stirred at -78 °C for 5 min, warmed to 0 °C for 30 min and was then recooled to -78 °C. A solution of ketones 121 and 122 (1.06 g combined, 1.93 mmol, 1.0 equiv.) in dry THF (4 mL) was added via cannula and the reaction mixture was warmed to 0 °C for 3 h to afford a pale yellow mixture. The reaction mixture was recooled to -78 °C, methyl iodide (1.20 mL, 19.3 mmol, 10 equiv.) was added neat via syringe and the mixture was allowed to slowly warm to room temperature overnight. Saturated aqueous NaHCO₃ (40 mL) and diethyl ether (80 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 80 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (100 g of silica gel, 99:1 petroleum ether - diethyl ether) to afford, after
concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), ketone **112** (951 mg, 87%) as a colorless oil.

IR (neat): 2956, 1713, 1456, 1382, 1073, 880 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 0.69 (s, 3H, Me-16), 0.84-0.89 (m, 15 H), 1.17 (s, 3H, Me-15), 1.23-1.55 (m, 20 H), 1.61-1.65 (m, 1H), 1.69 (s, 3H, Me-19), 1.79-1.83 (m, 2H), 1.97-2.06 (m, 3H), 2.76 (d, 1H, $J = 11.0$ Hz, H-1), 2.82 (ddd, 1H, $J = 11.0$, 11.0, 6.2 Hz, H-9), 4.57 (br s, 1H, H-18), 4.64 (br s, 1H, H-18'), 5.75 (d, 1H, $J = 12.4$ Hz, $^2J_{Sn-H} = 72$ Hz, H-14) 6.51 (ddd, 1H, $J = 12.4$, 7.0, 7.0 Hz, $^3J_{Sn-H} = 143$ Hz, H-13).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 10.2 (+ve), 13.7 (-ve), 18.5 (-ve), 21.1 (-ve), 24.2 (-ve), 24.3 (+ve), 27.4 (+ve), 27.9 (+ve), 29.2 (+ve), 35.8 (+ve), 36.0 (+ve), 37.7 (+ve), 37.9 (+ve), 39.6 (+ve), 41.4 (-ve), 47.8 (+ve), 49.4 (+ve), 58.7 (-ve), 108.5 (+ve), 127.9 (-ve), 147.7 (+ve), 149.1 (-ve), 214.0 (+ve).

Exact Mass calcd. for C$_{27}$H$_{47}$O$_{120}$Sn (M − Bu)$^+$: 507.2649; found: 507.2656.

Anal. calcd. for C$_{31}$H$_{56}$OSn: C 66.08, H 10.02; found: C 66.15, H 10.06.
Preparation of (1R*, 3S*, 6S*, 9S*)-9-Isopropenyl-3,6-dimethyl-3-[(Z)-5-iodopent-4-en-1-yl]bicyclo[4.3.0]nonan-2-one (111).

To a stirred solution of the keto alkenylstannane 112 (929 mg, 1.65 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (16.5 mL), at room temperature, was added a solution of iodine in dry CH$_2$Cl$_2$ (18 mL, 0.10 M, 1.8 mmol, 1.1 equiv.). The reaction mixture was stirred at room temperature for 15 min, and then saturated aqueous Na$_2$S$_2$O$_3$ (30 mL) was added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (70 g of tlc grade silica gel, 99:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the keto alkenyl iodide 111 (618 mg, 94%) as a colorless oil.
IR (neat): 3076, 2937, 1708, 1646, 1455, 1383, 882 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.70 (s, 3H, Me-16), 1.18 (s, 3H, Me-15), 1.36-1.91 (m, 11H), 1.68 (s, 3H, Me-19), 1.97-2.05 (m, 1H), 2.10-2.14 (m, 2H), 2.76 (d, 1H, \(J = 10.9\) Hz, H-1), 2.81 (ddd, 1H, \(J = 10.9, 6.4, 6.4\) Hz, H-9), 4.56 (s, 1H, H-18), 4.64 (s, 1H, H-18'), 6.14-6.21 (m, 2H, H-13, H-14).

\(^{13}\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 18.5 (-ve), 21.1 (-ve), 22.1 (+ve), 24.3 (-ve), 27.9 (+ve), 35.4 (+ve), 35.6 (+ve), 36.1 (+ve), 37.4 (+ve), 39.6 (+ve), 41.3 (-ve), 47.9 (+ve), 49.4 (+ve), 58.6 (-ve), 82.3 (-ve), 108.5 (+ve), 141.3 (-ve), 147.6 (+ve), 213.9 (+ve).

Exact Mass calcd. for C\(_{19}\)H\(_{29}\)IO: 400.1263; found: 400.1261.

Anal. calcd. for C\(_{19}\)H\(_{29}\)IO: C 57.00, H 7.30; found: C 56.86, H 7.40.
To a cold (0 °C), stirred solution of keto alkenyl iodide 111 (300 mg, 0.749 mmol, 1.0 equiv.) in dry THF (45 mL) was added BuLi (983 μL, 1.6 M in hexanes, 1.57 mmol, 2.1 equiv), via syringe, in a single rapid injection. The reaction mixture was stirred at 0 °C for 2 h. Saturated aqueous NaHCO$_3$ (30 mL) was added, the layers were separated and the aqueous phase was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude solid product was purified by recrystallization from cold (0 °C) pentane and the acquired mother liquor was concentrated and recrystallized twice more from cold (0 °C) pentane. The yield of the allylic alcohol 110 obtained after collection of three crops of crystals was 264 mg (71%). The residue obtained from concentration of the remaining mother liquor was twice recrystallized from cold (-78 °C) pentane to afford a further 41 mg of alcohol 110. The total yield of the allylic alcohol 110 obtained was 305 mg (82%) as a colorless solid (mp = 118.5-119.5 °C).
IR (KBr): 3500, 2932, 1640, 1458, 1138, 885 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.99 (s, 3H), 1.03 (s, 3H), 1.18-1.54 (m, 9H), 1.62 (ddd, 1H, J = 13.5, 2.5, 2.5 Hz), 1.69 (d, 1H, J = 11.6 Hz, H-2), 1.72 (s, 3H, Me-17), 1.74-1.85 (m, 1H), 1.89-1.96 (m, 1H), 1.98-2.06 (m, 1H), 2.23 (ddd, 1H, J = 13.5, 3.2, 3.2 Hz), 2.33-2.42 (m, 1H), 2.71-2.84 (m, 1H), 4.62 (br s, 1H, H-16), 4.76 (d, 1H, J = 2.0 Hz, H-16'), 5.70 (ddd, 1H, J = 11.9, 4.4, 4.4 Hz, H-13), 5.74 (d, 1H, J = 11.9 Hz, H-14).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 20.8 (-ve), 22.0 (-ve), 23.2 (+ve), 27.2 (+ve), 29.4 (br, 2C), 35.0 (+ve), 35.9 (+ve), 38.7 (+ve), 41.4 (+ve), 41.5 (+ve), 42.7 (+ve), 44.0 (-ve), 51.9 (br, 2C), 79.4 (+ve), 111.2 (+ve), 131.4 (-ve), 138.6 (-ve).

Exact Mass calcd. for C₁₉H₃₀O: 274.2297; found: 274.2296.

Anal. calcd. for C₁₉H₃₀O: C 83.15, H 11.02; found: C 83.19, H 11.13.

The relative configuration shown for the allylic alcohol 110 was determined by X-ray crystallographic analysis.¹¹⁰
Preparation of $(2R^*, 3S^*, 6S^*, 9S^*)$-3-Isopropenyl-6,9-dimethyltricyclo[7.5.0.0^{2,6}]tetradec-1(14)-en-13-one (59).

To a stirred solution of the allylic alcohol 110 (78.1 mg, 0.284 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (3 mL) was added sequentially dry, powdered 3 Å molecular sieves (241 mg, 0.85 g / mmol alcohol) and pyridinium chlorochromate (306 mg, 1.42 mmol, 5.0 equiv). The brown mixture was heated at reflux for 2.5 h. The mixture was cooled to room temperature, diethyl ether (9 mL) was added and the mixture was stirred vigorously at room temperature for 1 h. The mixture was filtered through a column of Florisil® (~2 g) and the column was eluted with diethyl ether (~300 mL) and then ethyl acetate (~100 mL) until no uv active product was detected in the eluate. The eluate was concentrated under reduced pressure and the crude product purified by flash chromatography (2 g of silica gel, 85:15 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), enone 59 (55.9 mg, 72%) as a colorless oil.
IR (neat): 3073, 2932, 1646, 1455, 1381, 1206, 888 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.70 (s, 3H, Me-18), 1.23 (s, 3H, Me-19), 1.32 (dm, 1H, \(J = 13.5\) Hz), 1.38-1.72 (m, 7H), 1.63 (s, 3H, Me-17), 1.73-1.86 (m, 3 \(H\)), 2.00-2.09 (m, 1H), 2.41 (dd, 1H, \(J = 11.2, 1.3\) Hz, H-2), 2.52 (ddd, 1H, \(J = 17.4, 6.4, 6.4\) Hz), 2.59-2.67 (m, 2H), 4.63 (d, 1H, \(J = 0.7\) Hz, H-16), 4.68 (m, 1H, H-16'), 5.61 (d, 1H, \(J = 1.3\) Hz, H-14).

In NOED experiments, irradiation of the signal at \(\delta 2.41\) (H-2) showed an enhancement for the signal at \(\delta 1.23\) (Me-19). Similarly, irradiation of the signal at \(\delta 1.23\) (Me-19) showed an enhancement for the signal at \(\delta 2.41\) (H-2).

\(^{13}\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 17.5 (+ve), 18.4 (-ve), 20.1 (-ve), 26.0 (-ve), 28.6 (+ve), 36.1 (+ve), 38.5 (+ve), 39.1 (+ve), 42.4 (+ve), 43.2 (+ve), 44.3 (+ve), 44.4 (-ve), 46.1 (+ve), 52.9 (-ve), 110.2 (+ve), 125.5 (-ve), 146.6 (+ve), 161.1 (+ve), 205.4 (+ve).

Exact Mass calcd. for C\(_{19}\)H\(_{28}\)O: 272.2140; found: 272.2135.

Anal. calcd. for C\(_{19}\)H\(_{28}\)O: C 83.77, H 10.36; found: C 84.00, H 10.42.
Preparation of (1S*, 2S*, 3S*, 6S*, 9S*)-3-Isopropenyl-6,9-dimethyltricyclo[7.5.0.0^2,6]tetradecan-13-one (130) and (1R*, 2S*, 3S*, 6S*, 9S*)-3-Isopropenyl-6,9-dimethyltricyclo[7.5.0.0^2,6]tetradecan-13-one (156).

A cold (-78 °C) mixture of liquid ammonia (10 mL, distilled from NaNH₂) and potassium wire (87.8 mg, 2.25 mmol, 6.0 equiv.) was stirred at -78 °C for 30 min, during which time the potassium dissolved. A solution of enone 59 (102 mg, 0.374 mmol, 1.0 equiv.) and dry tert-butyl alcohol (143 μL, 1.50 mmol, 4.0 equiv.) in dry THF (8 mL) was added via cannula. The blue, biphasic mixture was stirred at -78 °C for 30 min. Excess potassium metal was destroyed by the addition of isoprene (374 μL, 3.74 mmol, 10 equiv). After the mixture had been stirred at -78 °C for 5 min, solid NH₄Cl (~1 g) was added and, after a further 10 min, the mixture was opened to the atmosphere via an air cooled condenser and was warmed to room temperature to allow the ammonia to evaporate. Diethyl ether (10 mL) and water (10 mL) were added to the residue and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (1 x 25 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue
obtained was dissolved in dry CH$_2$Cl$_2$ (3.0 mL), pyridinium chlorochromate on basic alumina (385 mg, 21.5 wt % PCC, 0.374 mmol, 1.0 equiv.) was added and the mixture was stirred at room temperature for 1 h. Diethyl ether (10 mL) was added and the mixture was stirred for a further 1 h. The mixture was filtered through a column of Florisil® (~ 2 g) and the column was eluted with diethyl ether (~100 mL). The eluate was concentrated under reduced pressure and the crude product purified by flash chromatography (10 g of tlc grade silica gel, 90:10 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), a mixture of ketones 130 and 156 (91 mg total, 89%) as a colorless oil.

$^1$H-nmr and gc analyses indicated a 2.2:1 ratio of the trans- and cis-fused compounds, 130 and 156, respectively. Although these diastereomeric ketones could not be separated by flash chromatography on silica gel, they were separated and individually characterized at a later stage of the synthesis (vide infra).

To a cold (-78 °C), stirred solution of diisopropylamine (163 µL, 1.16 mmol, 3.1 equiv.) in dry THF (4.5 mL) was added BuLi (703 µL, 1.60 M in hexanes, 1.13 mmol, 3.0 equiv.). The mixture was stirred for at -78 °C for 5 min, warmed to 0 °C for 30 min and was then recooled to -78 °C. A solution of ketones 130 and 156 (103 mg, 0.375 mmol, 1.0 equiv.) in dry THF (1 mL) was added via cannula and the reaction mixture was stirred at -78 °C for 5 min and then was warmed to 0 °C for 1 h. A solution of diphenyldisulfide (246 mg, 1.13 mmol, 3.0 equiv.) in dry THF (1.5 mL) was added via cannula, the resulting mixture was stirred at 0 °C for 3 h and then was warmed to room temperature for 5 h. Saturated aqueous NH₄Cl (30 mL) and diethyl ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (14 g of tlc grade silica gel, 96:4
petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), two fractions along with recovered starting material.

The first fraction to elute was the cis-fused α-phenylsulfonyl ketone 158 (34 mg, 24%) as a white solid (mp = 54-55 °C).

IR (KBr): 3073, 2927, 1704, 1584, 1378, 1266, 890, 738, 690 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.85 (s, 3H, Me-18 or Me-19), 0.99 (s, 3H, Me-18 or Me-19), 1.11 (dm, 1H, J for the doublet = 14.3 Hz), 1.24-1.94 (m, 12H), 1.62 (s, 3H, Me-17), 2.06-2.13 (m, 1H), 2.12 (br d, 1H, J = 12.5 Hz, H-14β), 2.54-2.61 (m, 1 H), 2.82 (dd, 1H, J = 12.5, 12.5 Hz, H-14α), 3.72 (dd, 1H, J = 6.3, 6.3 Hz, H-12), 4.72 (m, 1H, H-16), 4.76 (s, 1H, H-16'), 7.20-7.40 (m, 5H, aromatic protons).

¹³C nmr (CDCl₃, 75.5 MHz) δ: 18.7, 20.0, 23.7, 26.4, 26.8, 29.7, 31.4, 35.5, 36.6, 38.7, 40.3, 41.2, 41.6, 44.9, 48.6, 56.3, 111.5, 127.4, 129.0, 131.5, 133.7, 146.2, 207.5.

Exact Mass calcd. for C₂₅H₃₄OS: 382.2330; found: 382.2337.

Anal. calcd. for C₂₅H₃₄OS: C 78.48, H 8.96; found: C 78.24, H 9.03.
The second fraction to elute was a mixture of the diastereomeric trans-fused α-phenylsulfenyl ketones 157 (82 mg, 57%) as a sticky white solid. An approximate ratio for these diastereomers was 2-3:1. The data given below for the compounds 157 refers to the inseparable mixture of diastereomers, unless otherwise noted.

IR (KBr): 3073, 2922, 1584, 1439, 1384, 887, 740, 691 cm⁻¹.

¹H nmr (CDCl₃, 300 MHz) δ: 0.81 (s, 3H, Me-18 or Me-19, major diastereomer), 0.82 (s, 3H, Me-18 or Me-19, minor diastereomer), 0.89 (s, 3H, Me-18 or Me-19, major diastereomer), 0.90 (s, 3H, Me-18 or Me-19, minor diastereomer), 1.15-1.77 (m, 11H), 1.67 (s, 3H, Me-17), 1.90-2.20 (m, 3 H), 2.39-2.49 (m, 2H), 2.57 (dd, 1H, J = 14.0, 2.9 Hz, H-14α, major diastereomer), 2.94 (dd, 1H, J = 17.0, 4.2 Hz, H-14α, minor diastereomer), 3.81 (dd, 1H, J = 11.5, 5.5 Hz, H-12, major diastereomer), 3.95 (dd, 1H, J = 5.5, 5.5 Hz, H-12, minor diastereomer), 4.57 (m, 1H, H-16, minor diastereomer), 4.63 (s, 1H, H-16, major diastereomer), 4.71 (d, 1H, J = 1.8 Hz, H-16', minor diastereomer), 4.73 (s, 1H, H-16', major diastereomer), 7.20-7.40 (m, 5H, aromatic protons).

¹³C nmr (CDCl₃, 75.5 MHz) δ: (major diastereomer only) 17.2, 18.0, 19.4, 25.8, 29.8, 35.1, 37.9, 38.5, 39.9, 40.9, 43.4, 43.8, 43.9, 47.5, 48.5, 56.8, 110.6, 127.3, 128.9, 131.7, 134.0, 149.9, 209.2.
Exact Mass calcd. for C_{25}H_{34}OS: 382.2330; found: 382.2334.

Anal. calcd. for C_{25}H_{34}OS: C 78.48, H 8.96; found: C 78.33, H 8.82.

The fraction that eluted last was the recovered starting material (130 + 156) (19 mg, 18%). The total yield of the ketones 157 and 158 was 116 mg (81%, >95% based on recovered starting material).
Preparation of (1S*, 2S*, 3S*, 6S*, 9S*)-3-Isopropenyl-6,9-dimethyl tricyclo[7.5.0.0\(^{2,6}\)]tetradecan-13-one (130).

To a stirred solution of the \(\alpha\)-phenylsulfenyl ketones 157 (33.4 mg, 0.0873 mmol, 1.0 equiv.) in dry methanol (2.0 mL) at room temperature was added sequentially, ammonium chloride (94 mg, 1.7 mmol, 20 equiv.) and zinc-copper couple (143 mg, 2.18 mmol, 25 equiv.). The reaction mixture was stirred at room temperature for 16 h. Diethyl ether (10 mL) was added and the mixture was filtered through a thin pad of Celite.\(^{5}\) The collected material was washed with diethyl ether (15 mL), and the combined filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (5 g of silica gel, 90:10 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the ketone 130 (23.7 mg, 99%) as a colorless oil.
IR (neat): 3071, 2922, 1699, 1456, 1383, 884 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.82 (s, 3H, Me-18), 0.85 (s, 3H, Me-19), 1.15-1.28 (m, 2H, H-5β, H-7β), 1.29-1.49 (m, 5H, H-2, H-4β, H-5α, H-7α, H-8α), 1.51-1.74 (m, 5H, H-8β, H-10α, H-10β, H-11α, H-11β), 1.67 (s, 3H, Me-17), 1.78 (ddd, 1H, J = 11.7, 11.7, 3.3 Hz, H-1), 1.91-2.04 (m, 1H, H-4α), 2.20 (dd, 1H, J = 16.5, 11.7 Hz, H-14α), 2.34-2.52 (m, 3H, H-3, H-12α, H-12β), 2.68 (dd, 1H, J = 16.5, 3.3 Hz, H-14β), 4.59-4.63 (m, 1H, H-16), 4.71-4.74 (m, 1H, H-16').

Detailed ¹H nmr data (CDCl₃) derived from COSY and NOESY experiments are given in Table 3.

¹³C nmr (CDCl₃, 75.3 MHz) δ: 17.5 (-ve), 17.7 (-ve), 19.0 (-ve), 19.7 (+ve), 29.8 (+ve), 35.3 (+ve), 38.0 (+ve), 39.1 (+ve), 39.8 (+ve), 41.6 (-ve), 43.1 (+ve), 43.4 (+ve), 44.3 (+ve), 46.2 (+ve), 48.3 (-ve), 49.1 (-ve), 110.6 (+ve), 150.1 (+ve), 214.9 (+ve).

Exact Mass calcd. for C₁₉H₃₀O: 274.2297; found: 274.2290.

Anal. calcd. for C₁₉H₃₀O: C 83.15, H 11.02; found: C 83.27, H 11.12.
Table 3: $^1$H nmr (400 MHz, CDCl$_3$) Data for the Trans-Fused Tricyclic Ketone 130:

COSY and NOESY Experiments.

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$^1$H-nmr (400 MHz) $\delta$ (mult., $J$ (Hz))</th>
<th>COSY Correlations$^b$</th>
<th>NOESY Correlations$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>1.78 (ddd, $J = 11.7, 11.7, 3.3$)</td>
<td>H-2, H-14a, H-14$\beta$</td>
<td>Me-18</td>
</tr>
<tr>
<td>H-2</td>
<td>part of the m at 1.29-1.49</td>
<td>H-1, H-3</td>
<td>Me-19</td>
</tr>
<tr>
<td>H-3</td>
<td>part of the m at 2.34-2.52</td>
<td>H-2, H-4a, H-4$\beta$</td>
<td>H-4a, H-16', Me-18</td>
</tr>
<tr>
<td>H-4a</td>
<td>1.91-2.04 (m)</td>
<td>H-3, H-4$\beta$, H-5a, H-5$\beta$</td>
<td>H-3, H-4$\beta$, H-5a, Me-18</td>
</tr>
<tr>
<td>H-4$\beta$</td>
<td>part of the m at 1.29-1.49</td>
<td>H-3, H-4a, H-5a, H-5$\beta$</td>
<td>H-4a</td>
</tr>
<tr>
<td>H-5a</td>
<td>part of the m at 1.29-1.49</td>
<td>H-4a, H-4$\beta$, H-5$\beta$</td>
<td>H-4a, H-5$\beta$</td>
</tr>
<tr>
<td>H-5$\beta$</td>
<td>part of the m at 1.15-1.28</td>
<td>H-4a, H-4$\beta$, H-5a, Me-18</td>
<td></td>
</tr>
<tr>
<td>H-7a</td>
<td>part of the m at 1.29-1.49</td>
<td>H-7$\beta$, H-8a, H-8$\beta$,</td>
<td></td>
</tr>
<tr>
<td>H-7$\beta$</td>
<td>part of the m at 1.15-1.28</td>
<td>H-7a, H-8$\beta$, H-8$\beta$, Me-19</td>
<td></td>
</tr>
<tr>
<td>H-8a</td>
<td>part of the m at 1.29-1.49</td>
<td>H-7a, H-7$\beta$, H-8$\beta$, Me-19</td>
<td></td>
</tr>
<tr>
<td>H-8$\beta$</td>
<td>part of the m at 1.51-1.74</td>
<td>H-7a, H-7$\beta$, H-8a</td>
<td></td>
</tr>
<tr>
<td>H-10a</td>
<td>part of the m at 1.51-1.74</td>
<td>H-10$\beta$, H-11a, H-11$\beta$, Me-19</td>
<td></td>
</tr>
<tr>
<td>H-10$\beta$</td>
<td>part of the m at 1.51-1.74</td>
<td>H-10a, H-11a, H-11$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-11a</td>
<td>part of the m at 1.51-1.74</td>
<td>H-10a, H-10$\beta$, H-11$\beta$, H-12a, H-12$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-11$\beta$</td>
<td>part of the m at 1.51-1.74</td>
<td>H-10a, H-10$\beta$, H-11a, H-12a, H-12$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-12a</td>
<td>part of the m at 2.34-2.52</td>
<td>H-11a, H-11$\beta$, H-12$\beta$</td>
<td>H-12$\beta$</td>
</tr>
<tr>
<td>H-12$\beta$</td>
<td>part of the m at 2.34-2.52</td>
<td>H-11a, H-11$\beta$, H-12a</td>
<td>H-12a, Me-19</td>
</tr>
<tr>
<td>H-14a</td>
<td>2.68 (dd, $J = 16.5, 3.3$)</td>
<td>H-1, H-14$\beta$</td>
<td>H-14$\beta$, H-16'</td>
</tr>
<tr>
<td>H-14$\beta$</td>
<td>2.20 (dd, $J = 16.5, 11.7$)</td>
<td>H-1, H-14a</td>
<td>H-14a, Me-19</td>
</tr>
<tr>
<td>H-16</td>
<td>4.59-4.63 (m)</td>
<td>H-16', Me-17</td>
<td>H-16', Me-17</td>
</tr>
<tr>
<td>H-16'</td>
<td>4.71-4.74 (m)</td>
<td>H-16, Me-17</td>
<td>H-3, H-14$\alpha$, H-16</td>
</tr>
<tr>
<td>Me-17</td>
<td>1.67 (s)</td>
<td>H-16, H-16'</td>
<td>H-16</td>
</tr>
<tr>
<td>Me-18</td>
<td>0.82 (s)</td>
<td>H-5$\beta$, H-7$\beta$</td>
<td>H-1, H-3, H-4$\alpha$</td>
</tr>
<tr>
<td>Me-19</td>
<td>0.85 (s)</td>
<td>H-8a</td>
<td>H-2, H-12$\beta$, H-14$\beta$</td>
</tr>
</tbody>
</table>

a- $^1$H$^\prime$ indicates the hydrogen of a pair which is more downfield ($H-16'$ is more downfield than $H-16$).
b-Only the COSY and NOESY data which could be unambiguously assigned are recorded.
Preparation of \((1R^*, 2S^*, 3S^*, 6S^*, 9S^*)\)-3-Isopropenyl-6,9-dimethyl tricyclo[7.5.0.0^{2,6}]tetradecan-13-one (156).

To a stirred solution of the \(\alpha\)-phenylsulfenyl ketone 158 (9.4 mg, 0.025 mmol, 1.0 equiv.) in dry methanol (1.0 mL) at room temperature was added sequentially, ammonium chloride (27 mg, 0.49 mmol, 20 equiv.) and zinc-copper couple (40 mg, 0.61 mmol, 25 equiv.). The reaction mixture was stirred at room temperature for 15 h. Diethyl ether (5 mL) was added and the mixture was filtered through a thin pad of Celite.\(^\circledR\) The collected material was washed with diethyl ether (10 mL), and the combined filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (2 g of silica gel, 90:10 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the ketone 156 (6.5 mg, 96%) as a colorless oil.
IR (neat): 3073, 2927, 1704, 1644, 1461, 1378, 8896 cm⁻¹.

¹H nmr (CDCl₃, 300 MHz) δ: 0.80 (s, 3H, Me-18), 1.02 (s, 3H, Me-19), 1.15 (dm, 1H, J for doublet = 14.1 Hz) 1.24-1.71 (m, 12 H), 1.63 (s, 3H, Me-17), 1.84-1.95 (m, 1H, H-12α), 2.18-2.30 (m, 1H), 2.21 (br d, 1H, J = 14.1 Hz, H-14β), 2.40 (dd, 1H, J = 14.1, 12.0 Hz, H-14α), 2.51-2.59 (m, 2H, H-3, H-12β), 4.72 (d, 1H, J = 1.2 Hz, H-16), 4.75 (s, 1H, H-16').

Detailed ¹H nmr data (CDCl₃) derived from NOED experiments are given in Table 4.

¹³C nmr (CDCl₃, 75.3 MHz) δ: 17.3 (+ve), 18.6 (-ve), 20.0 (-ve), 25.3 (-ve), 26.9 (+ve), 29.7 (+ve), 32.6 (+ve), 35.6 (+ve), 36.5 (+ve), 38.1 (-ve), 40.6 (+ve), 41.3 (+ve), 41.6 (+ve), 43.5 (+ve), 44.8 (-ve), 48.3 (-ve), 111.3 (+ve), 146.4 (+ve), 213.2 (+ve).

Exact Mass calcd. for C₁₉H₃₀O: 274.2297; found: 274.2299.

Anal. calcd. for C₁₉H₃₀O: C 83.15, H 11.02; found: C 83.30, H 11.07.
Table 4: $^1$H nmr (400 MHz, CDCl$_3$) Data for the Cis-Fused Tricyclic Ketone 156: NOED Experiments.

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$^1$H-nmr (400 MHz)</th>
<th>NOED Correlations$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-3</td>
<td>part of the m at 2.51-2.59</td>
<td>H-14$\beta$, H-16', Me-18</td>
</tr>
<tr>
<td>H-12$\alpha$</td>
<td>1.84-1.95 (m)</td>
<td>H-12$\beta$, H-14$\alpha$</td>
</tr>
<tr>
<td>H-12$\beta$</td>
<td>part of the m at 2.51-2.59</td>
<td>H-12$\alpha$</td>
</tr>
<tr>
<td>H-14$\alpha$</td>
<td>2.40 (dd, $J = 14.1$, 12.0)</td>
<td>H-12$\alpha$, H-14$\beta$, Me-18</td>
</tr>
<tr>
<td>H-14$\beta$</td>
<td>2.21 (br d, $J = 14.1$)</td>
<td>H-3, H-14$\alpha$</td>
</tr>
<tr>
<td>H-16</td>
<td>4.72 (d, $J = 1.2$)</td>
<td>Me-17</td>
</tr>
<tr>
<td>H-16'</td>
<td>4.75 (s)</td>
<td>H-3</td>
</tr>
<tr>
<td>Me-17</td>
<td>1.63 (s)</td>
<td>H-16</td>
</tr>
<tr>
<td>Me-18</td>
<td>0.80 (s)</td>
<td>H-3, H-14$\alpha$</td>
</tr>
</tbody>
</table>

$^a$- H' indicates the hydrogen of a pair which is more downfield (H-16' is more downfield than H-16).

$^b$- Only the NOED data which could be unambiguously assigned are recorded.
Preparation of (1S*, 2S*, 3S*, 6S*, 9R*)-3-isopropenyl-6,9-dimethyl-12-phenylthiotricyclo[7.5.0.0²₆]tetradec-12-ene (159).

To a stirred solution of the α-phenylsulfenyl ketones 157 (199 mg, 0.520 mmol, 1.0 equiv.) in dry CH₂Cl₂ (3.0 mL) and dry methanol (3.0 mL) was added sodium borohydride (39.3 mg, 1.04 mmol, 2.0 equiv.) and the resulting mixture stirred at room temperature for 2 h. Saturated aqueous NH₄Cl (20 mL) was added and the mixture was stirred for 20 min. Diethyl ether (25 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with brine (1 x 20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford a sticky, pale yellow oil. The oil was dissolved in dry CH₂Cl₂ (5.0 mL), triethylamine (725 µL, 5.20 mmol, 10.0 equiv.) was added and the mixture was cooled to 0 °C. Methanesulfonyl chloride (201 µL, 2.60 mmol, 5.0 equiv.) was added dropwise via syringe and the reaction mixture was stirred at 0 °C for 5 min and then was warmed to room temperature for 1 h. Saturated aqueous NaHCO₃ (30 mL) and diethyl ether (20 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 20 mL) and pentane (2 x 20
mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to afford a yellow solid residue (240 mg). The residue was dissolved in a mixture of dry THF (5.0 mL) and dry DMSO (5.0 mL) and the resulting solution was cooled to 0 °C with stirring. A solution of potassium tert-butoxide (175 mg, 1.56 mmol, 3.0 equiv.) in dry DMSO (2.5 mL) was added via cannula and the resulting mixture was stirred for 5 min at 0 °C and then was warmed to room temperature for 25 min. Saturated aqueous NH₄Cl (30 mL), water (10 mL) and petroleum ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with petroleum ether (1 x 30 mL) and diethyl ether (1 x 30 mL). The combined organic extracts were washed with brine (3 x 25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (20 g of silica gel, petroleum ether), to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the alkenyl thioether 159 (151 mg, 79% overall) as a colorless oil.
IR (neat): 3072, 2917, 1640, 1477, 1439, 1382, 1025, 885 cm\textsuperscript{-1}.

\textsuperscript{1}H nmr (CDCl\textsubscript{3}, 400 MHz) \(\delta\): 0.84 (s, 3H), 0.94 (s, 3H), 1.09 (ddd, 1H, \(J = 13.4, 3.1, 3.1\) Hz), 1.22 (ddd, 1H, \(J = 10.5, 10.5, 10.5\) Hz), 1.30-1.64 (m, 9H), 1.67 (s, 3H, Me-17), 1.92-2.04 (m, 2H), 2.12 (br dd, 1H, \(J = 16.5, 6.6\) Hz), 2.33 (ddd, 1H, \(J = 16.5, 9.0, 1.5\) Hz), 2.41 (ddd, 1H, \(J = 11.0, 11.0, 5.5\) Hz), 2.44-2.51 (m, 1H), 4.59-4.60 (m, 1H, H-16), 4.70 (br s, 1H, H'-16'), 6.02-6.07 (m, 1H, H-13), 7.15-7.30 (m, 5H, aromatic protons).

\textsuperscript{13}C nmr (CDCl\textsubscript{3}, 75.5 MHz) \(\delta\): 17.6 (-ve), 18.1 (-ve), 19.5 (-ve), 27.7 (+ve), 30.1 (+ve), 30.2 (+ve), 35.5 (+ve), 38.4 (+ve), 38.6 (+ve), 40.1 (+ve), 43.3 (+ve), 43.5 (+ve), 44.5 (-ve), 47.6 (-ve), 48.1 (-ve), 109.5 (+ve), 126.1 (-ve), 128.8 (-ve), 129.9 (-ve), 136.0 (+ve), 136.1 (+ve), 136.2 (-ve), 151.0 (+ve).

Exact Mass calcd. for C\textsubscript{25}H\textsubscript{34}S: 366.2381; found: 366.2381

Anal. calcd. for C\textsubscript{25}H\textsubscript{34}S: C 81.91, H 9.35; found: C 81.73, H 9.36.
Preparation of \((1S^*,\ 2S^*,\ 3S^*,\ 6S^*,\ 9R^*)\)-3-Isopropenyl-6,9-dimethyl tricyclo[7.5.0.0^{2,6}]tetradecan-12-one (129).

To a stirred mixture of the alkenyl thioether 159 (311 mg, 0.851 mmol, 1.0 equiv.) in acetonitrile (9.0 mL) and water (3.0 mL) was added mercuric chloride (1.16 g, 4.25 mmol, 5.0 equiv.). The reaction mixture was heated at reflux for 5 h and then was cooled to room temperature. Saturated aqueous NH₄Cl (40 mL) and diethyl ether (40 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 50 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ (2 x 40 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (30 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the ketone 129 (232 mg, 99%) as a white solid (mp = 57-58 °C).
IR (KBr): 3071, 1703, 1641, 1455, 1382, 883 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) δ: 0.83 (s, 3H, Me-18 or Me-19), 0.85 (s, 3H, Me-18 or Me-19), 1.13-1.77 (m, 12H), 1.64 (s, 3H, Me-17), 1.91-2.04 (m, 2H), 2.26-2.55 (m, 5H), 4.58-4.60 (m, 1H, H-16), 4.67-4.68 (m, 1H, H-16').

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 15.9 (-ve), 17.9 (-ve), 19.3 (-ve), 23.7 (+ve), 30.1 (+ve), 35.4 (+ve), 38.0 (+ve), 38.3 (+ve), 38.9 (+ve), 39.4 (+ve), 40.0 (+ve), 43.4 (+ve), 43.5 (+ve), 47.5 (-ve), 48.5 (-ve), 49.1 (-ve), 109.7 (+ve), 150.5 (+ve), 215.6 (+ve).

Exact Mass calcd. for C$_{19}$H$_{30}$O: 274.2297; found: 274.2290.

Anal. calcd. for C$_{19}$H$_{30}$O: C 83.15, H 11.02; found: C 83.25, H 11.11.
Preparation of (1S*, 2S*, 3S*, 6S*, 9R*)-3-Isopropenyl-6,9-dimethyl tricyclo[7.6.0.0^{2,6}]pentadec-11-en-13-one (60) and (1S*, 2S*, 3S*, 6S*, 9R*)-3-Isopropenyl-6,9-dimethyl-11-methylidenetricyclo[7.5.0.0^{2,6}]tetradecan-12-one (168).

To a cold (-78 °C), stirred solution of KHMDS (3.13 mL, 0.50 M in toluene, 1.57 mmol, 2.0 equiv.) in dry THF (3 mL) was added a solution of ketone 129 (215 mg, 0.783 mmol, 1.0 equiv.) in dry THF (4 mL), via cannula, and the reaction mixture was stirred at -78 °C for 3h. Trimethylsilyl chloride (298 µL, 2.35 mmol, 3.0 equiv.) was added dropwise via syringe and the mixture was stirred at -78 °C for 5 min and then was warmed to 0 °C for 1 h. Cold (0 °C), saturated aqueous NaHCO₃ (20 mL) and diethyl ether (20 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 20 mL) and pentane (1 x 20 mL). The combined organic
extracts were washed with cold (0 °C) saturated aqueous NaHCO₃ (20 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The clear, colorless oil obtained was further dried under vacuum (vacuum pump) for 10 h. The oil was dissolved in dry cyclohexane (9 mL) and the resulting solution was cooled to 0 °C with stirring. Diethylzinc (744 μL, 0.744 mmol, 0.95 equiv.) was added dropwise via syringe and the reaction mixture was stirred at 0 °C until the white fumes dissipated (~ 5 min). Chloroiodomethane (54 μL, 0.744 mmol, 0.95 equiv.) was added via syringe and the mixture was stirred at 0 °C for 30 min. The reaction mixture was then stirred under an air atmosphere (Drierite® filled drying tube) at 0 °C for 3 h and at room temperature for 1 h. Saturated aqueous NH₄Cl (30 mL) and diethyl ether (20 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 20 mL) and pentane (1 x 20 mL). The combined organic extracts were washed with aqueous NaHCO₃ (5%, 1 x 20 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure to provide the crude cyclopropane silyl ether 167 (282 mg, ~95% yield) as a white solid. Since this product was unstable to silica gel chromatographic purification the crude compound was used immediately in the next reaction.

To a cold (0 °C), stirred solution of dry ferric chloride (381 mg, 2.35 mmol, 3.0 equiv.) in dry DMF (10 mL) was added, dropwise via syringe over 2 h, a solution of the cyclopropane silyl ether 167 and pyridine (63 μL, 0.783 mmol, 1.0 equiv.) in dry THF (2 mL). The yellow reaction mixture was warmed to room temperature and stirred for 12 h. Aqueous HCl (5%, 30 mL) and diethyl ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL) and the
combined organic extracts were washed successively with aqueous HCl (5%, 1 x 25 mL),
brine (1 x 25 mL) and aqueous NaHCO₃ (5%, 1 x 25 mL). The organic extracts were
then dried over anhydrous magnesium sulfate and concentrated under reduced pressure.
The residual oil obtained was dissolved in dry methanol (5 mL), sodium acetate (1.28 g,
15.7, mmol, 20 equiv.) was added and the reaction mixture was heated at reflux for 6 h.
The mixture was cooled to room temperature, water (25 mL) and diethyl ether (25 mL)
were added and the layers were separated. The aqueous phase was extracted with diethyl
ether (2 x 25 mL). The combined organic extracts were washed with aqueous NaHCO₃
(5%, 1 x 25 mL), dried over anhydrous magnesium sulfate and concentrated under
reduced pressure. The crude product was purified by flash chromatography (20 g of tlc
grade silica gel, 96:4 petroleum ether - diethyl ether), to afford, after concentration of the
appropriate fractions and removal of traces of solvent (vacuum pump), two products.
The first compound that eluted was the enone 168 (47 mg, 22%), a colorless oil:

IR (neat): 3071, 2917, 1693, 1610, 1456, 1144, 941, 884 cm⁻¹.

¹H nmr (CDCl₃, 300 MHz) δ: 0.70 (s, 3H, Me-18 or Me-19), 0.84 (s, 3H, Me-18 or Me-19), 1.11-1.66 (m, 11H), 1.63 (s, 3H, Me-17), 1.90-2.01 (m, 2H), 2.20 (d, 1H, J = 14.4 Hz, H-10 or H-10'), 2.40 (ddd, 1H, J = 10.8, 10.8, 5.4 Hz, H-3), 2.47-2.52 (m, 2H), 4.56 (s, 1H, H-16), 4.65 (s, 1H, H-16'), 5.15 (s, 1H, H-20), 6.00-6.01 (m, 1H, H-20').

¹³C nmr (CDCl₃, 75.3 MHz) δ: 17.1 (-ve), 18.1 (-ve), 19.4 (-ve), 24.4 (+ve), 30.1 (+ve), 35.5 (+ve), 38.5 (+ve), 38.8 (+ve), 40.0 (+ve), 43.4 (+ve), 43.6 (+ve), 47.4 (-ve), 48.6, (-ve) 48.7 (+ve), 49.6 (-ve), 109.8 (+ve), 124.1 (+ve), 144.6 (+ve), 150.4 (+ve), 203.1 (+ve).

Exact Mass calcd. for C₂₀H₃₀O: 286.2297; found: 286.2295.

Anal. calcd. for C₂₀H₃₀O: C 83.86, H 10.56; found: C 83.70, H 10.69.
The second compound that eluted was the enone 60 (137 mg, 64%), a colorless oil:

IR (neat): 3071, 2933, 1663, 1455, 1384, 1175, 883 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.69 (s, 3H, Me-19), 1.01 (s, 3H, Me-20), 1.12-1.44 (m, 8H, H-4β, H-5α, H-5β, H-7α, H-7β, H-8α, H-8β, H-15β), 1.49 (dd, 1H, J = 11.1, 11.1 Hz, H-2), 1.59-1.71 (m, 1H, H-1), 1.65 (s, 3H, Me-18), 1.77-1.86 (m, 1H, H-15α), 1.89-2.00 (m, 1H, H-4α), 2.11 (dd, 1H, J = 13.7, 9.5 Hz, H-10α), 2.31 (ddd, 1H, J = 11.1, 11.1, 5.3 Hz, H-3), 2.42 (br dd, 1H, J = 12.6, 6.9 Hz, H-14α), 2.87-2.92 (m, 2H, H-10β, H-14β), 4.56 (s, 1H, H-17), 4.65 (s, 1H, H-17'), 6.26 (d, 1H, J = 11.9 Hz H-12), 6.50 (ddd, 1H, J = 11.9, 9.5, 9.5 Hz, H-11).

Detailed ¹H nmr data (CDCl₃) derived from COSY and NOED experiments are given in Table 5.

¹³C nmr (CDCl₃, 75.3 MHz) δ: 17.9 (-ve), 19.7 (-ve), 20.5 (-ve), 23.5 (+ve), 30.3 (+ve), 35.5 (+ve), 37.1 (+ve), 37.5 (+ve), 38.2 (-ve), 40.0 (+ve), 42.6 (+ve), 42.9 (+ve), 43.4 (+ve), 47.4 (-ve), 48.4 (-ve), 109.7 (+ve), 137.4 (-ve), 142.7 (-ve), 150.4 (+ve), 202.7 (+ve).

Exact Mass calcd. for C₂₀H₃₀O: 286.2297; found: 286.2291.

Anal. calcd. for C₂₀H₃₀O: C 83.86, H 10.56; found: C 83.61, 10.60.
Table 5: $^1$H nmr (400 MHz, CDCl$_3$) Data for the Tricyclic Enone **60**: COSY and NOED Experiments.

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$^1$H-nmr (400 MHz) $\delta$ (mult., $J$ (Hz))</th>
<th>COSY Correlations$^b$</th>
<th>NOED Correlations$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-1</td>
<td>1.59-1.71 (m)</td>
<td>H-2, H-15$\beta$</td>
<td>H-3, Me-19</td>
</tr>
<tr>
<td>H-2</td>
<td>1.49 (dd, $J$ = 11.1, 11.1)</td>
<td>H-1, H-3</td>
<td>Me-20</td>
</tr>
<tr>
<td>H-3</td>
<td>2.31 (ddd, $J$ = 11.1, 11.1, 5.3)</td>
<td>H-2, H-4$\alpha$, H-4$\beta$</td>
<td>H-1, H-17', Me-19</td>
</tr>
<tr>
<td>H-4$\alpha$</td>
<td>1.89-2.00 (m)</td>
<td>H-3, H-4$\beta$, H-5$\alpha$, H-5$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-4$\beta$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-3, H-4$\alpha$, H-5$\alpha$, H-5$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-5$\alpha$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-4$\alpha$, H-4$\beta$, H-5$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-5$\beta$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-4$\alpha$, H-4$\beta$, H-5$\alpha$</td>
<td></td>
</tr>
<tr>
<td>H-7$\alpha$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-7$\beta$, H-8$\alpha$, H-8$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-7$\beta$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-7$\alpha$, H-8$\alpha$, H-8$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-8$\alpha$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-7$\alpha$, H-7$\beta$, H-8$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-8$\beta$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-7$\alpha$, H-7$\beta$, H-8$\alpha$</td>
<td></td>
</tr>
<tr>
<td>H-10$\alpha$</td>
<td>2.11 (dd, $J$ = 13.7, 9.5)</td>
<td>H-10$\beta$</td>
<td>H-10$\beta$, H-11, Me-20</td>
</tr>
<tr>
<td>H-10$\beta$</td>
<td>part of the m at 2.87-2.92</td>
<td>H-10$\alpha$</td>
<td>H-10$\alpha$, Me-20</td>
</tr>
<tr>
<td>H-11</td>
<td>6.50 (ddd, $J$ = 11.9, 9.5, 9.5)</td>
<td>H-10$\alpha$, H-10$\beta$, H-12</td>
<td>H-10$\alpha$, H-12</td>
</tr>
<tr>
<td>H-12</td>
<td>6.26 (d, $J$ = 11.9)</td>
<td>H-11</td>
<td>H-11</td>
</tr>
<tr>
<td>H-14$\alpha$</td>
<td>2.42 (br dd, $J$ = 12.6, 6.9)</td>
<td>H-14$\beta$, H-15$\alpha$</td>
<td></td>
</tr>
<tr>
<td>H-14$\beta$</td>
<td>part of the m at 2.87-2.92</td>
<td>H-14$\alpha$, H-15$\alpha$, H-15$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-15$\alpha$</td>
<td>1.77-1.86 (m)</td>
<td>H-14$\alpha$, H-14$\beta$, H-15$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-15$\beta$</td>
<td>part of the m at 1.12-1.44</td>
<td>H-1, H-14$\beta$, H-15$\alpha$</td>
<td></td>
</tr>
<tr>
<td>H-17</td>
<td>4.56 (s)</td>
<td>H-17'</td>
<td>Me-18</td>
</tr>
<tr>
<td>H-17'</td>
<td>4.65 (s)</td>
<td>H-3, H-17</td>
<td></td>
</tr>
<tr>
<td>Me-18</td>
<td>1.65 (s)</td>
<td>H-17</td>
<td></td>
</tr>
<tr>
<td>Me-19</td>
<td>0.69 (s)</td>
<td>H-1, H-3</td>
<td></td>
</tr>
<tr>
<td>Me-20</td>
<td>1.01 (s)</td>
<td>H-2, H-10$\alpha$, H-10$\beta$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ - H' indicates the hydrogen of a pair which is more downfield (H-17' is more downfield than H-17).

$^b$ - Only the COSY and NOED data which could be unambiguously assigned are recorded.
Preparation of Tributylstannylcopper(I)-dimethyl sulfide (180).

\[ \text{Bu}_3\text{SnCu-SMe}_2 \]

180

To a cold (-78 °C), stirred solution of hexabutylditin (50.0 g, 86.2 mmol, 1.0 equiv.) in dry THF (70 mL) was added butyllithium (56.7 mL, 1.52 M in hexanes, 86.2 mmol, 1.0 equiv.) via syringe. The reaction mixture was stirred at -78 °C for 30 min, warmed to -45 °C for 1 h and recooled to -78 °C. Solid CuBr-SMe\(_2\) (17.7 g, 86.2 mmol, 1.0 equiv.) was added in a single portion. The resulting yellow slurry was stirred at -78 °C for 30 min and then warmed to -45 °C for 30 min, to provide a dark red solution of tributylstannylcopper(I)-dimethyl sulfide (180).
Preparation of 3-Tributylstannylbuto-3-en-1-ol (181) and (E)-4-Tributylstannylbuto-3-en-1-ol (182).

![Chemical Structures]

A solution of tributylstannylcopper(I)-dimethyl sulfide (180) (86.2 mmol, 2.3 equiv.) was prepared as described above. To this cold (-78 °C), stirred solution was added a solution of 3-butyn-1-ol (179) (2.63 g, 37.5 mmol, 1.0 equiv.) in dry THF (10 mL) via cannula. Dry MeOH (80 mL) was added via syringe and the reaction mixture was allowed to slowly warm to room temperature over 8 h. Aqueous NH₄Cl-NH₃ (pH 8, 150 mL) and diethyl ether (100 mL) were added and air was bubbled through the mixture until the aqueous layer became deep blue. The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 75 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (200 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), two products.
The first compound that eluted was the alkenylstannane 181 (9.10 g, 67%), a colorless oil:

IR (neat): 3369, 2933, 1463, 1048, 875 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.83-0.91 (m, 15H), 1.25-1.36 (m, 7H), 1.43-1.52 (m, 6H), 2.50 (t, 2H, J = 6.2 Hz, H-2), 3.62 (dt, 2H, J = 6.2, 6.2 Hz, H-1), 5.27 (d, 1H, J = 2.8 Hz, ³J_{Sn-H} = 60 Hz, H-4), 5.77-5.78 (m, 1H, ³J_{Sn-H} = 133 Hz, H-4').

¹³C nmr (CDCl₃, 75.3 MHz) δ: 9.5 (+ve), 13.6 (-ve), 27.3 (+ve), 29.0 (+ve), 44.2 (+ve), 61.3 (+ve), 128.3 (+ve), 151.4 (+ve).

Exact Mass calcd. for C₁₂H₂₅O¹²⁰Sn (M – Bu)⁺: 305.0927; found: 305.0925.

Anal. calcd. for C₁₆H₃₄OSn: C 53.21, H 9.49; found: C 53.12, H 9.45.
The second compound that eluted was the alkenylstannane 182 (1.98 g, 15%), a colorless oil:

IR (neat): 3360, 2922, 1463, 1046, 991, 874 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.84-0.92 (m, 15H), 1.26-1.37 (m, 7H), 1.43-1.52 (m, 6H), 2.37-2.42 (tdd, 2H, J = 6.2, 6.2, 1.1 Hz, H-2), 3.66 (q, 2H, J = 6.2 Hz, H-1), 5.91 (dt, 1H, J = 18.9, 6.2 Hz, H-3), 6.04 (dt, 1H, J = 18.9, 1.1 Hz, H-4).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 9.3 (+ve), 13.6 (-ve), 27.2 (+ve), 29.0 (+ve), 41.1 (+ve), 61.4 (+ve), 131.9 (-ve), 144.8 (-ve).

Exact Mass calcd. for C₁₂H₂₅O¹²⁰Sn (M – Bu)⁺: 305.0927; found: 305.0933.

The total yield of the alkenylstannanes 181 and 182 was 11.1 g (82%).
Preparation of 4-Chloro-2-tributylstannylbut-1-ene (178).

To a stirred solution of triphenylphosphine (2.18 g, 8.31 mmol, 1.5 equiv.) and triethylamine (1.16 mL, 8.34 mmol, 1.5 equiv.) in dry CCl₄ (10 mL) was added a solution of the alcohol 181 (2.00 g, 5.54 mmol, 1.0 equiv.) in dry CCl₄ (4 mL) via cannula. The reaction mixture was heated at reflux for 24 h. The mixture was cooled to room temperature, petroleum ether (30 mL) was added and the mixture was stirred at room temperature for 1 h. The mixture was filtered through a pad of Florisil® (50 g, elution with pentane) and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (200 g of silica gel, petroleum ether). The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 170-174 °C/0.80 Torr) to afford the chloride 178 (2.09 g, 99%), as a colorless oil.

IR (neat): 3036, 2854, 1464, 1377, 1072, 923, 662 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.85-0.93 (m, 15H), 1.27-1.35 (m, 6H), 1.44-1.52 (m, 6H), 2.61-2.72 (m, 2H, H-3), 3.51 (t, 2H, J = 7.6 Hz, H-4), 5.23-5.24 (m, 1H, ³J₈₁ = 61 Hz, H-1), 5.74-5.76 (m, 1H, ³J₈₁ = 132 Hz, H-1').
\[^{13}\text{C nmr (CDCl}_3, 75.3 \text{ MHz)} \delta: 9.6 \text{ (+ve)}, 13.7 \text{ (-ve)}, 27.4 \text{ (+ve), 29.1 (2C, +ve), 43.9 (+ve), 128.0 (+ve), 150.8 (+ve).}\]

Anal. calcd. for C\text{\textsubscript{16}}H\text{\textsubscript{33}}ClSn: C 50.63, H 8.76; found: C 50.94, 8.76.

\section*{Preparation of the homocuprate (190).}

\begin{center}
\begin{tikzpicture}
\node (178) [text width=2cm] {178};
\node (190) [text width=3cm, right of=178] {190};
\node (buLi) [above of=178] {1) BuLi, THF, -78 °C};
\node (CuBrSMe) [above of=190] {2) CuBr\textcdot SMe\textsubscript{2}, THF};
\node (temp1) [right of=buLi] {-78 °C, 30 min;}
\node (temp2) [right of=temp1] {-50 °C, 5 min}
\end{tikzpicture}
\end{center}

To a cold (-78 °C), stirred solution of 4-chloro-2-tributylstannylbut-1-ene (178) (269 mg, 0.708 mmol, 2.0 equiv.) in dry THF (8.0 mL) was added butyllithium (443 μL, 1.60 M in hexane, 0.708 mmol, 2.0 equiv.) dropwise via syringe (allowing the BuLi solution to run down the side of the cold flask) over 15 min. The resulting clear, colorless solution was stirred at -78 °C for 30 min. Solid CuBr\textcdot SMe\textsubscript{2} (73.0 mg, 0.354 mmol, 1.0 equiv.) was added in a single portion. The resulting mixture was stirred at -78 °C for 30 min, warmed to -50 °C for 5 min, and then recooled to -78 °C to provide an orange solution of the homocuprate 190.

A solution of the homocuprate 190 (0.354 mmol, 3.0 equiv.) was prepared as described above. To this cold (-78 °C), stirred solution was added boron trifluoride-diethyl etherate (146 μL, 1.18 mmol, 10.0 equiv.) dropwise via syringe. A solution of the enone 60 (33.8 mg, 0.118 mmol, 1.0 equiv.) in dry THF (2 mL) was added via cannula and the reaction mixture was stirred at -78 °C for 1 h. Aqueous NH₄Cl-NH₃ (pH 8, 25 mL) and diethyl ether (25 mL) were added and the mixture was allowed to warm to room temperature. Air was bubbled through the mixture until the aqueous layer became deep blue. The layers were separated and the aqueous phase was extracted with diethyl ether (2 x 25 mL). The combined organic extracts were washed with saturated aqueous NH₄Cl (1 x 25 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (8 g of silica gel, 95:5 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the chloro ketone 191 (39.5 mg, 89%) as a colorless oil.
IR (neat): 3074, 2929, 1702, 1641, 1455, 1383, 889 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.78 (s, 3H), 0.90 (s, 3H), 1.12-1.60 (m, 12H), 1.61-1.79 (m, 1H), 1.68 (s, 3H, Me-18), 1.88-2.01 (m, 2H), 2.20-2.32 (m, 2H), 2.38 (d, 1H, \(J = 12\) Hz), 2.41-2.62 (m, 4H), 3.59-3.65 (m, 2H), 4.59 (s, 1H), 4.73 (s, 1H), 4.77 (s, 1H), 4.88 (s, 1H).

\(^{13}\)C nmr (CDCl\(_3\), 75.5 MHz) \(\delta\): 17.9 (-ve), 18.9 (-ve), 20.8 (-ve), 22.2 (+ve), 30.0 (+ve), 35.4 (+ve), 35.6 (+ve), 36.9 (+ve), 38.5 (2C), 39.8 (-ve), 39.9 (+ve), 42.6 (+ve), 43.4 (+ve), 43.8 (+ve), 47.5 (-ve), 48.5 (-ve), 49.6 (+ve), 51.7 (+ve), 109.7 (+ve), 110.0 (+ve), 149.9 (+ve), 152.0 (+ve), 214.8 (+ve).

Exact Mass calcd. for C\(_{24}\)H\(_{37}\)O\(^{35}\)Cl: 376.2533; found: 376.2527.

Anal. calcd. for C\(_{24}\)H\(_{37}\)OCl: C 76.46, H 9.89; found: C 76.74, 10.00.
Preparation of (1S*, 2S*, 3S*, 6S*, 9R*, 11R*)-11-(1-(2-Iodoethyl)vinyl)-3-isopropenyl-6,9-dimethyltricyclo[7.6.0.0^{2,6}]pentadecan-13-one (193).

A stirred mixture of the chloro ketone 191 (56.6 mg, 0.150 mmol, 1.0 equiv.) and anhydrous NaI (1.10 g, 7.50 mmol, 50 equiv.) in dry acetone (3 mL) was heated at reflux for 50 h. The mixture was cooled to room temperature, water (20 mL) and diethyl ether (15 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 15 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (10 g of silica gel, 95:5 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the iodo ketone 193 (70.1 mg, 99%) as a colorless oil.
IR (neat): 3074, 2920, 1701, 1642, 1454, 1381, 889 cm⁻¹.

\(^1\)H nmr (CDCl₃, 400 MHz) δ: 0.78 (s, 3H), 0.90 (s, 3H), 0.90-1.01 (m, 1H), 1.12-1.80 (m, 12H), 1.69 (s, 3H, Me-18), 1.88-2.02 (m, 2H), 2.20-2.31 (m, 2H), 2.37 (d, 1H, J = 12 Hz), 2.39-2.46 (m, 1H), 2.52-2.64 (m, 3H), 3.21-3.29 (m, 2H), 4.58 (s, 1H), 4.72 (s, 1H), 4.77 (s, 1H), 4.88 (s, 1H).

\(^13\)C nmr (CDCl₃, 100.4 MHz) δ: 18.0 (-ve), 18.9 (-ve), 20.8 (-ve), 22.2 (+ve), 29.7 (+ve), 30.0 (+ve), 35.4 (+ve), 35.7 (+ve), 38.19 (-ve), 38.24 (+ve), 38.5 (+ve), 39.8 (-ve), 39.9 (+ve), 43.4 (+ve), 43.7 (+ve), 47.5 (-ve), 48.5 (-ve), 49.6 (+ve), 51.8 (+ve), 109.4 (+ve), 110.0 (+ve), 149.5 (+ve), 154.2 (+ve), 214.8 (+ve).

Exact Mass calcd. for C\(_{24}\)H\(_{37}\)OI: 468.1889; found: 468.1896.

Anal. calcd. for C\(_{24}\)H\(_{37}\)OI: C 61.53, H 7.96; found: C 61.64, 8.00.

A stirred solution of the iodo ketone 193 (80.1 mg, 0.171 mmol, 1.0 equiv.) and lithium tert-butoxide (500 µL, 1.0 M in hexanes, 0.50 mmol, 3.0 equiv.) in dry benzene (12 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, saturated aqueous NaHCO₃ (15 mL) was added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ (1 x 15 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (25 g of silica gel, 97:3 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), one product along with recovered starting material.
The first compound that eluted was the tetracyclic ketone 61 (31.4 mg, 55%), a colorless oil.

IR (neat): 3071, 2927, 1702, 1641, 1384, 882 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 500 MHz) \(\delta\): 0.84 (s, 3H, Me-19), 0.86 (s, 3H, Me-24), 1.02 (dm, 1H, J for the doublet = 13.7 Hz, H-18\(\beta\)), 1.17-1.54 (m, 9H, H-2, H-2', H-10, H-12, H-14, H-15, H-15', H-17, H-17'), 1.64-1.71 (m, 1H, H-6), 1.67 (s, 3H, Me-23), 1.74-1.78 (m, 1H, H-11), 1.88-2.02 (m, 4H, H-6', H-10', H-14', H-18\(\alpha\)). 2.24-2.32 (m, 2H, H-5, H-9), 2.35-2.40 (m, 1H, H-9'), 2.46 (ddd, 1H, J = 11.1, 11.1, 5.6 Hz, H-13), 2.51-2.57 (m, 1H, H-5'), 2.86-2.90 (m, 1H, H-3), 3.23 (ddd, 1H, J = 7.1, 7.1, 7.1 Hz, H-7), 4.57-4.58 (m, 1H, H-22), 4.71 (d, 1H, J = 2.2 Hz, H-22'), 4.78 (d, 1H, J = 2.0 Hz, H-20), 4.89 (d, 1H, J = 2.0 Hz, H-20').

Detailed \(^1\)H nmr data (CDCl\(_3\)) derived from COSY and NOED experiments are given in Table 6.

\(^{13}\)C nmr (CDCl\(_3\), 100.4 MHz) \(\delta\): 18.2 (-ve), 19.0 (-ve), 21.5 (-ve), 23.4 (+ve), 27.2 (+ve), 29.9 (+ve), 32.0 (+ve), 34.4 (+ve), 35.2 (+ve), 38.0 (+ve), 39.8 (+ve), 41.0 (-ve), 42.0 (-ve), 43.4 (+ve), 44.7 (+ve), 45.6 (+ve), 48.2 (-ve), 48.7 (-ve), 57.1 (-ve), 105.2 (+ve), 110.0 (+ve), 150.6 (+ve), 157.5 (+ve), 216.6 (+ve).
Detailed $^{13}$C nmr data (CDCl$_3$) derived from HMQC and HMBC experiments are given in Table 7.

Exact Mass calcd. for C$_{24}$H$_{36}$O: 340.2766; found: 340.2764.

Anal. calcd. for C$_{24}$H$_{36}$O: C 84.65, H 10.66; found: C 84.55, 10.80.

The second compound that eluted was the recovered starting material 193 (36 mg, 45% recovered). The yield of the tetracyclic ketone 61 based on recovered starting material is >95%.
Table 6: $^1$H nmr (400 MHz, CDCl$_3$) Data for the Tetracyclic Ketone 61: COSY and NOED Experiments.

![Chemical Structure of 61]

<table>
<thead>
<tr>
<th>Assignment H-x(^a)</th>
<th>$^1$H-nmr (400 MHz) $\delta$ (mult., $J$ (Hz))</th>
<th>COSY Correlations(^b)</th>
<th>NOED Correlations(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-2</td>
<td>part of the m at 1.17-1.54</td>
<td>H-2', H-3,</td>
<td></td>
</tr>
<tr>
<td>H-2'</td>
<td>part of the m at 1.17-1.54</td>
<td>H-2, H-3</td>
<td></td>
</tr>
<tr>
<td>H-5</td>
<td>part of the m at 2.24-2.32</td>
<td>H-5', H-6, H-6', H-20, H-20'</td>
<td></td>
</tr>
<tr>
<td>H-5'</td>
<td>2.51-2.57 (m)</td>
<td>H-5, H-6, H-6',</td>
<td></td>
</tr>
<tr>
<td>H-6</td>
<td>1.64-1.71 (m)</td>
<td>H-5, H-5', H-6', H-7</td>
<td></td>
</tr>
<tr>
<td>H-6'</td>
<td>part of the m at 1.88-2.02</td>
<td>H-5, H-5', H-6, H-7</td>
<td></td>
</tr>
<tr>
<td>H-7</td>
<td>3.23 (ddd, $J = 7.1, 7.1, 7.1$)</td>
<td>H-3, H-6, H-6'</td>
<td>H-3, H-11</td>
</tr>
<tr>
<td>H-9</td>
<td>part of the m at 2.24-2.32</td>
<td>H-9', H-10, H-10'</td>
<td></td>
</tr>
<tr>
<td>H-9'</td>
<td>2.35-2.40 (m)</td>
<td>H-9, H-10, H-10'</td>
<td></td>
</tr>
<tr>
<td>H-10</td>
<td>part of the m at 1.17-1.54</td>
<td>H-9, H-9', H-10', H-11</td>
<td></td>
</tr>
<tr>
<td>H-10'</td>
<td>part of the m at 1.88-2.02</td>
<td>H-9, H-9', H-10</td>
<td></td>
</tr>
<tr>
<td>H-11</td>
<td>1.74-1.78 (m)</td>
<td>H-10, H-12</td>
<td>H-3, H-7, H-13, Me-24</td>
</tr>
<tr>
<td>H-12</td>
<td>part of the m at 1.17-1.54</td>
<td>H-11, H-13</td>
<td></td>
</tr>
<tr>
<td>H-14</td>
<td>part of the m at 1.17-1.54</td>
<td>H-13, H-14', H-15, H-15'</td>
<td></td>
</tr>
<tr>
<td>H-14'</td>
<td>part of the m at 1.88-2.02</td>
<td>H-13, H-14, H-15, H-15'</td>
<td></td>
</tr>
<tr>
<td>H-15</td>
<td>part of the m at 1.17-1.54</td>
<td>H-14, H-14', H-15'</td>
<td></td>
</tr>
<tr>
<td>H-15'</td>
<td>part of the m at 1.17-1.54</td>
<td>H-14, H-14', H-15,</td>
<td></td>
</tr>
<tr>
<td>H-17</td>
<td>part of the m at 1.17-1.54</td>
<td>H-17', H-18$\alpha$, H-18$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-17$\beta$</td>
<td>part of the m at 1.17-1.54</td>
<td>H-17, H-18$\alpha$, H-18$\beta$</td>
<td></td>
</tr>
<tr>
<td>H-18$\alpha$</td>
<td>part of the m at 1.88-2.02</td>
<td>H-17, H-17', H-18$\beta$, Me-19</td>
<td></td>
</tr>
<tr>
<td>H-18$\beta$</td>
<td>1.02 (dm, $J = 13.7$)</td>
<td>H-17, H-17', H-18$\alpha$</td>
<td></td>
</tr>
<tr>
<td>Me-19</td>
<td>0.84 (s)</td>
<td>H-18$\alpha$</td>
<td></td>
</tr>
<tr>
<td>H-20</td>
<td>4.78 (d, $J = 2.0$)</td>
<td>H-3, H-5</td>
<td>H-3, H-20'</td>
</tr>
<tr>
<td>H-20'</td>
<td>4.89 (d, $J = 2.0$)</td>
<td>H-3, H-5</td>
<td>H-20</td>
</tr>
<tr>
<td>H-22</td>
<td>4.57-4.58 (m)</td>
<td>Me-23</td>
<td>H-22', Me-23</td>
</tr>
<tr>
<td>H-22$\beta$</td>
<td>4.71 (d, $J = 2.2$)</td>
<td>Me-23</td>
<td>H-13, H-22</td>
</tr>
<tr>
<td>Me-23</td>
<td>1.67 (br s)</td>
<td>H-22, H-22$\beta$</td>
<td>H-22</td>
</tr>
<tr>
<td>Me-24</td>
<td>0.86 (s)</td>
<td>H-11, H-13</td>
<td></td>
</tr>
</tbody>
</table>

\(a\) H' indicates the hydrogen of a pair which is more downfield (H-17' is more downfield than H-17).

\(b\) Only the COSY and NOED data which could be unambiguously assigned are recorded.
Table 7: $^1$H nmr (500 MHz, CDCl$_3$) and $^{13}$C nmr (125.8 MHz, CDCl$_3$) Data for the Tetracyclic Ketone 61: HMQC and HMBC Experiments.

![Diagram of compound 61]

<table>
<thead>
<tr>
<th>Assignment C-x</th>
<th>$^{13}$C-nmr (125.8 MHz) $\delta$ (ppm)</th>
<th>HMQC $^1$H-$^{13}$C Correlations$^{a,b}$ H-x$^c$</th>
<th>HMBC $^1$H-$^{13}$C Long Range Correlations$^{a,b}$ H-x</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-1</td>
<td>38.0</td>
<td>H-2 (2 bond), Me-19 (2 bond)</td>
<td></td>
</tr>
<tr>
<td>C-2</td>
<td>45.6</td>
<td>H-7 (3 bond), Me-19 (3 bond)</td>
<td></td>
</tr>
<tr>
<td>C-3</td>
<td>41.0</td>
<td>H-3</td>
<td>H-6 (3 bond), H-7 (2 bond), H-20 (3 bond)</td>
</tr>
<tr>
<td>C-4</td>
<td>157.5</td>
<td>H-5 (2 bond), H-6' (3 bond), H-7 (3 bond)</td>
<td></td>
</tr>
<tr>
<td>C-5</td>
<td>32.0</td>
<td>H-5, H-5'</td>
<td>H-7 (3 bond), H-20' (3 bond)</td>
</tr>
<tr>
<td>C-6</td>
<td>27.2</td>
<td>H-6, H-6'</td>
<td>H-7 (2 bond)</td>
</tr>
<tr>
<td>C-7</td>
<td>57.1</td>
<td>H-7</td>
<td>H-6' (2 bond), H-10' (4 bond)</td>
</tr>
<tr>
<td>C-8</td>
<td>216.6</td>
<td></td>
<td>H-6 (3 bond), H-7 (2 bond), H-9'' (2 bond)</td>
</tr>
<tr>
<td>C-9</td>
<td>44.7</td>
<td>H-9, H-9'</td>
<td>H-11 (3 bond)</td>
</tr>
<tr>
<td>C-10</td>
<td>23.4</td>
<td>H-10, H-10'</td>
<td>H-9 (2 bond), H-9' (2 bond)</td>
</tr>
<tr>
<td>C-11</td>
<td>42.0</td>
<td>H-11</td>
<td>H-9 (3 bond), H-9'' (3 bond), H-13 (3 bond)</td>
</tr>
<tr>
<td>C-12</td>
<td>48.7</td>
<td>H-12</td>
<td>H-11 (2 bond), H-13 (2 bond), Me-24 (3 bond)</td>
</tr>
<tr>
<td>C-13</td>
<td>48.2</td>
<td>H-13</td>
<td>H-22' (3 bond), Me-23 (3 bond)</td>
</tr>
<tr>
<td>C-14</td>
<td>29.9</td>
<td>H-14, H-14'</td>
<td>H-13 (2 bond)</td>
</tr>
<tr>
<td>C-15</td>
<td>39.8</td>
<td>H-15, H-15'</td>
<td>Me-24 (3 bond)</td>
</tr>
<tr>
<td>C-16</td>
<td>43.4</td>
<td></td>
<td>H-10 (4 bond), Me-24 (2 bond)</td>
</tr>
<tr>
<td>C-17</td>
<td>35.2</td>
<td>H-17, H-17'</td>
<td>Me-19 (4 bond), Me-24 (3 bond)</td>
</tr>
<tr>
<td>C-18</td>
<td>34.4</td>
<td>H-18, H-18'</td>
<td>H-2 (3 bond)</td>
</tr>
<tr>
<td>C-19</td>
<td>21.5</td>
<td>Me-19</td>
<td>H-11 (3 bond)</td>
</tr>
<tr>
<td>C-20</td>
<td>105.2</td>
<td>H-20, H-20'</td>
<td></td>
</tr>
<tr>
<td>C-21</td>
<td>150.6</td>
<td></td>
<td>H-13 (2 bond), Me-23 (2 bond)</td>
</tr>
<tr>
<td>C-22</td>
<td>110.0</td>
<td>H-22, H-22'</td>
<td>H-13 (3 bond), Me-23 (3 bond)</td>
</tr>
<tr>
<td>C-23</td>
<td>19.0</td>
<td>Me-23</td>
<td>H-13 (3 bond), H-22 (3 bond), H-22' (3 bond)</td>
</tr>
<tr>
<td>C-24</td>
<td>18.2</td>
<td>Me-24</td>
<td>H-18'' (4 bond)</td>
</tr>
</tbody>
</table>

$^a$ The assignment and the chemical shifts of the $^{13}$C nmr spectrum are listed in the first and second columns, respectively. The third column shows the hydrogen(s) which correlate with the carbon of the first two columns, as obtained from the HMQC experiment (1 bond correlation). The last column lists the hydrogen(s) which correlate with the $^{13}$C nmr signal of the first two columns as obtained from HMBC experiments (2, 3 and 4 bond correlations).

$^b$ Only the HMQC and HMBC data which could be unambiguously assigned are recorded.

$^c$ H' indicates the hydrogen of a pair which is more downfield (H-17' is more downfield than H-17).
Preparation of (1R*, 3R*, 7S*, 11S*, 12S*, 13S*, 16S*) 13-Isopropenyl-1,16-dimethyl-4-methylidenetetracyclo[9.7.0.0.3.7.0.12.16]octadecan-8-one (192).

To a solution of the ketone 61 (10.1 mg, 0.0268 mmol, 1.0 equiv.) in dry methanol (0.5 mL) was added a solution of NaOMe (536 μL, 0.50 M in methanol, 0.27 mmol, 10 equiv.) via syringe and the resulting mixture was stirred at room temperature for 16 h. Saturated aqueous NaHCO₃ (10 mL) and diethyl ether (10 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. ¹H nmr analysis (400 MHz, CDCl₃) of the crude reaction mixture showed complete consumption of the starting material 61 and indicated the formation of a single epimeric product 192. The crude product was purified by flash chromatography (2 g of silica gel, 97:3 petroleum ether - diethyl ether). After concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the ketone 92 (10.0 mg, 99%) was obtained as a colorless oil which slowly crystallized to a white solid (mp = 94.0-94.5 °C).
IR (KBr): 3071, 2926, 1703, 1464, 1381, 887 cm⁻¹.

¹H nmr (CDCl₃, 500 MHz) δ: 0.70 (s, 3H), 0.88 (s, 3H), 1.03 (ddd, 1H, J = 13.7, 4.0, 4.0 Hz), 1.16 (ddd, 1H, J = 11.0, 11.0, 11.0 Hz), 1.32-1.74 (m, 10H), 1.70 (s, 3H, Me-23), 1.85-1.98 (m, 2H), 2.01-2.11 (m, 1H), 2.21-2.36 (m, 3H), 2.40-2.44 (m, 1H), 2.45-2.53 (m, 2H), 2.68-2.75 (m, 1H, H-7), 4.57-4.58 (m, 1H), 4.75 (br s, 1H), 4.79 (br s, 1H), 4.92-4.93 (m, 1H).

¹³C nmr (CDCl₃, 125.8 MHz) δ: 17.9 (-ve), 18.5 (-ve), 19.3 (+ve), 20.5 (-ve), 27.5 (+ve), 29.7 (+ve), 32.6 (+ve), 34.8 (+ve), 35.4 (+ve), 38.5 (+ve), 39.9 (+ve), 41.1 (-ve), 43.5 (+ve), 45.1 (-ve), 46.1 (+ve), 47.3 (-ve), 48.1 (-ve), 50.2 (+ve), 60.0 (-ve), 105.3 (+ve), 110.2 (+ve), 149.5 (+ve), 157.1 (+ve), 215.6 (+ve).

Exact Mass calcd. for C₂₄H₃₆O: 340.2766; found: 340.2765.

Anal. calcd. for C₂₄H₃₆O: C 84.65, H 10.66; found: C 84.81, 10.81.
Preparation of (1R*, 3R*, 7R*, 11S*, 12S*, 13S*, 16S*)-13-Isopropenyl-8-methoxycarbonyl-1,16-dimethyl-4-methylidenetetracyclo[9.7.0.0.3.7.12.16]octadec-8-ene (94).

To a cold (-78 °C), stirred solution of KHMDS (782 μL, 0.50 M in toluene, 0.39 mmol, 4.0 equiv.) in dry THF (1.2 mL) was added a solution of ketone 61 (33.3 mg, 0.0978 mmol, 1.0 equiv.) in dry THF (1.0 mL) via cannula. The reaction mixture was stirred at -78 °C for 15 min and then was warmed to 0 °C for 2 h. A solution of N-phenyltrifluoromethanesulfonimide (175 mg, 0.489 mmol, 5.0 equiv.) in dry THF (1.0 mL) was added via syringe and the reaction mixture was stirred at 0 °C for 3 h. The mixture was concentrated under reduced pressure. The residue obtained was triturated (95:5 pentane - diethyl ether) and filtered. The filtrate was concentrated and the trituration was repeated with cold (0 °C) pentane. Filtration and concentration of the
combined filtrate under reduced pressure afforded the crude alkenyl triflate 198 (45.9 mg, >95%) as a white solid. This triflate proved to be susceptible to hydrolysis and attempts at chromatographic purification on silica gel resulted, predominantly, in reversion to the starting ketone 61. The non-aqueous workup outlined proved to be the most effective method of isolating the desired triflate 198, which was used immediately in the next reaction.

To a stirred solution of the alkenyl triflate 198 (1.0 equiv.) and N,N-diisopropylethylamine (170 μL, 0.978 mmol, 10 equiv.) in a mixture of dry DMF (2.0 mL) and dry methanol (1.0 mL) at room temperature was added tetrakistriphenylphosphine palladium(0) (11.7 mg, 10 mol% based on 198). The reaction mixture was stirred under an atmosphere of carbon monoxide (balloon) at room temperature for 3 h. Water (10 mL) and diethyl ether (10 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (3 x 10 mL). The combined organic extracts were washed with water (2 x 10 mL) and brine (2 x 10 mL), dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (10 g of silica gel, 98:2 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the ester 94 (25.4 mg, 68% overall) as a colorless oil.
IR (neat): 3072, 1719, 1640, 1434, 1383, 1246, 1085, 881 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) δ: 0.84 (s, 3H), 0.89 (s, 3H), 1.03 (ddd, 1H, $J = 14.0, 3.2, 3.2$ Hz), 1.21 (m, 1H), 1.29-1.50 (m, 7H), 1.68 (s, 3H, Me-25), 1.78-2.01 (m, 5H), 2.32 (ddd, 1H, $J = 12.0, 12.0, 4.2$ Hz, H-13), 2.38-2.61 (m, 4H), 2.72 (m, 1H, H-3), 3.61 (s, 3H, Me-22), 3.66 (m, 1H, H-7), 4.57 (s, 1H), 4.69 (br s 2H), 4.82 (s, 1H), 6.62 (dd, 1H, $J = 7.5, 2.8$ Hz, H-9).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 18.1, 19.0, 21.9, 26.7, 30.1, 30.3, 31.9, 35.5, 36.3, 38.9, 40.0, 42.0, 42.8, 43.2, 43.4, 44.4, 48.5, 49.4, 51.3, 103.3, 110.2, 133.6, 141.3, 150.6, 157.0, 169.1.

Exact Mass calcd. for C$_{26}$H$_{38}$O$_2$: 382.2872; found: 382.2868.
Preparation of \((1R^*, 3S^*, 4S^*, 7R^*, 11S^*, 12S^*, 13S^*, 16S^*)-13\text{-isopropenyl} 1,4,16\text{-trimethyl-8-methoxycarbonyl-tetracyclo[9.7.0.0^{3,7}.0^{12,16}]octadec-8-ene-8-carboxylate}\) (199).

To a stirred solution of the triene ester 94 (9.2 mg, 0.024 mmol, 1.0 equiv.) in dry methanol (2.5 mL) at room temperature was added 5\% platinum on alumina (18 mg, 0.0047 mmol, 20 mol \%). The flask was purged with hydrogen gas and the mixture was vigorously stirred under a hydrogen atmosphere (balloon) for 2 h. The reaction mixture was filtered through a thin pad of Celite®, the collected material was washed with diethyl ether (30 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified by flash chromatography (2 g of silica gel, 98:2 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the diene ester 199 (8.7 mg, 94\%) as a colorless oil.
IR (neat): 3071, 1718, 1639, 1434, 1382, 1233, 884 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.80 (d, 3H, \(J = 7.0\) Hz, Me-20), 0.81 (s, 3H, Me-26), 0.87 (s, 3H, Me-19), 0.94 (ddd, 1H, \(J = 13.9, 3.7, 3.7\) Hz, H-18), 1.08 (d, 1H, \(J = 14.4\) Hz, H-2), 1.15-1.50 (m, 8H, H-2', H-5, H-12, H-14, H-15, H-15', H-17, H-17'), 1.62-1.98 (m, 7H, H-5', H-6, H-6', H-10, H-11, H-14', H-18'), 1.67 (s, 3H, Me-25), 1.99-2.07 (m, 1H, H-4), 2.13-2.19 (m, 1H, H-3), 2.39 (ddd, 1H, \(J = 11.0, 11.0, 5.4\) Hz, H-13), 2.41-2.48 (m, 1H, H-10'), 3.23-3.30 (m, 1H, H-7), 3.65 (s, 3H, Me-22), 4.56 (br s, 1H, H-24), 4.69 (br s, 1H, H-24'), 6.43 (ddd, 1H, \(J = 5.3, 5.3, 1.6\) Hz, H-9).

Detailed \(^1\)H nmr data (CDCl\(_3\)) derived from COSY and NOED experiments are given in Table 8.

\(^{13}\)C nmr (CDCl\(_3\), 100.4 MHz) \(\delta\): 15.4, 18.1, 19.0, 21.9, 28.9, 21.1, 30.0, 31.8, 35.0, 35.4, 38.4, 38.6, 39.3, 40.0, 40.8, 42.1, 42.6, 43.4, 48.4, 48.7, 51.5, 110.1, 134.7, 138.7, 150.6, 170.9.

Exact Mass calcd. for C\(_{26}\)H\(_{40}\)O\(_2\): 384.3028; found: 384.3022.
**Table 8:** $^1$H nmr (400 MHz, CDCl$_3$) Data for the Diene Ester **199**: COSY and NOED Experiments.

![Diagram of molecule 199]

<table>
<thead>
<tr>
<th>Assignment</th>
<th>$^1$H-nmr (400 MHz) $\delta$ (mult., $J$ (Hz))</th>
<th>COSY Correlations$^b$</th>
<th>NOE Correlations$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H-2</td>
<td>1.08 (d, $J = 14.4$)</td>
<td>H-2'</td>
<td>H-4, H-7, Me-26</td>
</tr>
<tr>
<td>H-2'</td>
<td>part of the m at 1.15-1.50</td>
<td>H-2, H-3</td>
<td></td>
</tr>
<tr>
<td>H-3</td>
<td>2.13-2.19 (m)</td>
<td>H-2', H-7</td>
<td></td>
</tr>
<tr>
<td>H-4</td>
<td>1.99-2.07 (m)</td>
<td>H-5, H-5', Me-20</td>
<td>H-3, H-7, Me-20</td>
</tr>
<tr>
<td>H-5</td>
<td>part of the m at 1.15-1.50</td>
<td>H-4, H-5', H-6, H-6'</td>
<td></td>
</tr>
<tr>
<td>H-5'</td>
<td>part of the m at 1.62-1.98</td>
<td>H-4, H-5, H-6, H-6'</td>
<td></td>
</tr>
<tr>
<td>H-6</td>
<td>part of the m at 1.62-1.98</td>
<td>H-5, H-5', H-6', H-7</td>
<td></td>
</tr>
<tr>
<td>H-6'</td>
<td>part of the m at 1.62-1.98</td>
<td>H-5, H-5', H-6, H-7</td>
<td></td>
</tr>
<tr>
<td>H-7</td>
<td>3.23-3.30 (m)</td>
<td>H-3, H-6, H-6', H-9</td>
<td>H-3, H-4</td>
</tr>
<tr>
<td>H-9</td>
<td>6.43 (ddd, $J = 5.3, 5.3, 1.6$)</td>
<td>H-7, H-10, H-10'</td>
<td></td>
</tr>
<tr>
<td>H-10</td>
<td>2.41-2.48 (m)</td>
<td>H-9, H-10', H-11</td>
<td></td>
</tr>
<tr>
<td>H-11</td>
<td>part of the m at 1.62-1.98</td>
<td>H-9, H-10</td>
<td></td>
</tr>
<tr>
<td>H-12</td>
<td>part of the m at 1.15-1.50</td>
<td>H-10, H-12</td>
<td></td>
</tr>
<tr>
<td>H-13</td>
<td>2.39 (ddd, $J = 11.0, 11.0, 5.4$)</td>
<td>H-12, H-14, H-14'</td>
<td></td>
</tr>
<tr>
<td>H-14</td>
<td>part of the m at 1.15-1.50</td>
<td>H-13, H-14', H-15, H-15'</td>
<td></td>
</tr>
<tr>
<td>H-14'</td>
<td>part of the m at 1.62-1.98</td>
<td>H-13, H-14, H-15, H-15'</td>
<td></td>
</tr>
<tr>
<td>H-15</td>
<td>part of the m at 1.15-1.50</td>
<td>H-14, H-14', H-15'</td>
<td></td>
</tr>
<tr>
<td>H-15'</td>
<td>part of the m at 1.15-1.50</td>
<td>H-14, H-14', H-15</td>
<td></td>
</tr>
<tr>
<td>H-17</td>
<td>part of the m at 1.15-1.50</td>
<td>H-17', H-18, 18'</td>
<td></td>
</tr>
<tr>
<td>H-17'</td>
<td>part of the m at 1.15-1.50</td>
<td>H-17, H-18, H-18'</td>
<td></td>
</tr>
<tr>
<td>H-18</td>
<td>0.94 (ddd, $J = 13.9, 3.7, 3.7$)</td>
<td>H-17, H-17', H-18'</td>
<td></td>
</tr>
<tr>
<td>H-18'</td>
<td>part of the m at 1.62-1.98</td>
<td>H-17, H-17', H-18</td>
<td></td>
</tr>
<tr>
<td>Me-19</td>
<td>0.87 (s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me-20</td>
<td>0.80 (d, $J = 7.0$)</td>
<td>H-4</td>
<td></td>
</tr>
<tr>
<td>Me-22</td>
<td>3.65 (s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H-24</td>
<td>4.56 (br s)</td>
<td>Me-25</td>
<td></td>
</tr>
<tr>
<td>H-24'</td>
<td>4.69 (br s)</td>
<td>Me-25</td>
<td></td>
</tr>
<tr>
<td>Me-25</td>
<td>1.67 (s)</td>
<td>H-24, H-24'</td>
<td></td>
</tr>
<tr>
<td>Me-26</td>
<td>0.81 (s)</td>
<td>H-3, H-13, H-11</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ H' indicates the hydrogen of a pair which is more downfield (H-24' is more downfield then H-24).

$^b$ Only the COSY and NOE data which could be unambiguously assigned are recorded.

To a cold (0 °C), stirred solution of the ester 199 (20.3 mg, 0.0263 mmol, 1.0 equiv.) in dry diethyl ether (3.0 mL) was added DIBAl-H (400 μL, 1.0 M in hexane, 0.20 mmol, 7.6 equiv.) via syringe. The reaction mixture was stirred at 0 °C for 30 min. Saturated aqueous NH₄Cl (40 μL) was added to destroy the excess DIBAl-H and the resulting mixture was stirred at r.t. for 30 min. The mixture was treated with anhydrous magnesium sulfate and stirred for a further 30 min. The mixture was filtered through a thin pad of Celite®, the collected material was washed with diethyl ether (40 mL) and the combined filtrate was concentrated under reduced pressure. The crude product obtained was purified by flash chromatography (2 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the alcohol 203 (18.5 mg, 99%) as a colorless oil.
IR (neat): 3850, 2924, 2854, 1454, 1380, 884 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.69 (d, 3H, \(J = 7.3\) Hz, Me-20), 0.83 (s, 3H), 0.86 (s, 3H), 0.88-0.97 (m, 1H), 1.03 (d, 1H, \(J = 15.0\) Hz), 1.13-1.46 (m, 8H), 1.55 (dd, 1H, \(J = 14.0\), 11.3 Hz, H-12), 1.65-2.04 (m, 7H), 1.68 (s, 3H, Me-24), 2.14 (ddd, 1H, \(J = 12\), 12, 4 Hz), 2.22 (ddd, 1H, \(J = 10.4\), 10.4, 7.0 Hz), 2.37-2.44 (m, 2H), 3.25-3.32 (m, 1H, H-7), 3.90 (dd, 1H, \(J = 12.2\), 5.2 Hz, H-21), 4.08 (dd, 1H, \(J = 12.2\), 6.9 Hz, H-21'), 4.55-4.57 (m, 1H, H-23), 4.68 (d, 1H, \(J = 2.5\) Hz, H-23'), 5.74-5.76 (m, 1H, H-9).

\(^13\)C nmr (CDCl\(_3\), 100.4 MHz) \(\delta\): 15.4, 18.1, 19.1, 21.9, 27.0, 30.0, 30.3, 33.4, 35.7, 36.3, 38.8, 38.9, 40.1, 40.8, 41.1, 41.7, 43.4, 43.6, 48.5, 49.5, 68.2, 109.8, 130.8, 138.3, 151.0.

Exact Mass calcd. for C\(_{25}\)H\(_{40}\)O: 356.3079; found: 356.3079
Preparation of (±)-5-Deoxovariecolin (204).

To a stirred solution of the alcohol 203 (5.5 mg, 0.015 mmol, 1.0 equiv.) in dry diethyl ether (1.0 mL) at room temperature was added solid MnO₂ (20 mg, 0.23 mmol, 15 equiv.). The resulting brown mixture was stirred at room temperature for 4 h. The mixture was filtered through a thin pad of Celite®, the collected material was washed with diethyl ether (40 mL) and the combined filtrate was concentrated under reduced pressure. The crude product obtained was purified by flash chromatography (2 g of silica gel, 9:1 petroleum ether - diethyl ether), to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the aldehyde 204 (4.1 mg, 75%) as a thick, colorless oil.
IR (neat): 3070, 1691, 1628, 1456, 1382, 885 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.81 (s, 3H, Me-22), 0.85 (d, 3H, \(J = 6.4\) Hz, Me-19), 0.89 (s, 3H, Me-21), 0.98 (m, 1H), 1.11 (br d, 1H, \(J = 15.0\) Hz, H-1), 1.16-1.32 (m, 3H), 1.36-1.53 (m, 5H), 1.66-1.82 (m, 3H), 1.71 (s, 3H, Me-25), 1.89-2.08 (m, 6H), 2.11-2.19 (m, 1H), 2.40 (ddd, 1H, \(J = 11.0, 11.0, 5.5\) Hz, H-16), 2.57 (dd, 1H, \(J = 18.3, 6.7\) Hz, H-9), 3.10-3.16 (m, 1H, H-6), 4.63-4.64 (m, 1H, H-24), 4.74 (d, 1H, \(J = 2.4\) Hz, H-24'), 6.57-6.61 (m, H-8), 9.22 (s, 1H, H-20).

\(^{13}\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 15.7, 18.2, 18.9, 22.0, 28.1, 28.6, 29.7, 30.5, 34.0, 35.3, 36.7, 38.3, 39.5, 39.9, 40.8, 41.8, 42.6, 43.5, 48.2, 48.4, 110.4, 144.5, 150.5, 157.8, 197.4.

Exact Mass calcd. for C\(_{25}\)H\(_{38}\)O: 354.2923; found: 354.2918
Preparation of (±)-5-Deoxyvariecolol (93).

To a stirred solution of the alcohol 203 (6.2 mg, 0.017 mmol, 1.0 equiv.) in dry cyclohexane (2.0 mL) at room temperature, was added sequentially, anhydrous calcium carbonate (30 mg, 0.30 mmol, 18 equiv.) and lead tetraacetate (30 mg, 0.068 mmol, 4.0 equiv., dried at vacuum pump pressure for 2 h prior to use). The reaction mixture was heated at reflux for 20 min. The mixture was cooled to room temperature, diluted with dry diethyl ether (4.0 mL) and stirred for 30 min to precipitate the lead and calcium salts. The mixture was filtered through a pad of flash silica gel (~1 g, elution with 30 mL of diethyl ether) and the filtrate was concentrated under reduced pressure. $^1$H nmr analysis (400 MHz, CDCl$_3$) of the crude reaction mixture showed complete consumption of the starting material 203 and indicated the formation of the desired cyclic ether 93 and the aldehyde 204 (previously characterized, vide supra) in a ratio of 2:3, respectively.
To a stirred solution of the crude products 93 and 204 (prepared above) in dry methanol (1.0 mL) and dry CH2Cl2 (1.0 mL), at room temperature, was added sodium borohydride (4.0 mg, 0.11 mmol). The reaction mixture stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure and the residue obtained was purified by flash chromatography (2 g of silica gel, 99:1 to 95:5 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), two compounds.

The first compound that eluted was (±)-5-deoxyvariecolol 93 (2.4 mg, 39%), as a colorless amorphous solid.

IR (KBr): 2923, 2854, 1458, 1379, 1075, 884 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.83 (d, 3H, J = 9.2 Hz, Me-19), 0.84 (s, 3H, Me-22), 0.90 (s, 3H, Me-21), 1.09 (d, 1H, J = 14.3 Hz), 1.16-1.48 (m, 9H), 1.67 (s, 3H, Me-25), 1.70-2.06 (m, 5H), 2.17-2.23 (m, 1H), 2.30-2.48 (m, 3H), 3.42-3.50 (m, 1H, H-6), 4.19 (br d, 1H, J = 11.3 Hz, H-20), 4.34 (br d, 1H, J = 11.3 Hz, H-20), 4.58 (br s, 1H, H-24), 4.61-4.63 (m, 1H, H-5), 4.69 (br s, 1H, H-24), 5.38-5.43 (m, 1H, H-8).

In NOED experiments, irradiation of the signal at δ 4.61-4.63 (H-5) showed an enhancement for the signal at δ 3.42-3.50 (H-6). Similarly, irradiation of the signal at δ 3.42-3.50 (H-6) showed an enhancement for the signal at δ 4.61-4.63 (H-5).
$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 16.9, 18.1, 19.5, 22.0, 29.0, 30.3, 34.6, 35.5, 38.78, 38.80, 38.9, 40.0, 40.1, 40.9, 41.1, 43.5, 48.16, 48.24, 48.6, 73.8, 89.3, 109.5, 119.5, 137.5, 151.2.

Exact Mass calcd. for C$_{25}$H$_{38}$O: 354.2923; found: 354.2922

The second compound that eluted was the recovered starting alcohol 203 (3.6 mg, 58%). The yield of the cyclic ether 93 based on recovered starting material is >95%.
Preparation of (±)-5-Deoxyvariecolactone (226).

To a stirred solution of the ether 93 (2.1 mg, 0.0059 mmol, 1.0 equiv.) in dry CH₂Cl₂ (0.80 mL) at room temperature was added Collins' reagent (200 μL, 0.42 M in CH₂Cl₂, 0.084 mmol, 14 equiv.). The resulting mixture was stirred at room temperature for 1.5 h. Diethyl ether (3 mL) was added and the mixture was stirred for 30 min to precipitate the chromium salts. The mixture was filtered through a thin pad of Florisil® (~0.5 g, elution with 20 mL of diethyl ether) and the combined filtrate was concentrated under reduced pressure. The crude product purified by flash chromatography (0.5 g of silica gel, 85:15 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the lactone 226 (2.1 mg, 95%) as a colorless oil.
IR (neat): 2924, 1751, 1457, 1376, 1201, 1027, 950 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.69 (d, 3H, J = 7.3 Hz, Me-19), 0.84 (s, 3H, Me-22), 0.91 (s, 3H, Me-21), 0.99 (dm, 1H, J for the doublet = 11 Hz, H-1), 1.02-1.59 (m, 10H), 1.68 (s, 3H, Me-25), 1.86-2.27 (m, 5H), 2.37 (ddd, 1H, J = 11.6, 11.6, 5.8 Hz, H-16), 2.42-2.52 (m, 1H), 2.69-2.77 (m, 1H), 3.81-3.89 (m, 1H, H-6), 4.62 (br s, 1H, H-24), 4.69 (br s, 1H, H-24'), 4.94-4.99 (m, 1H, H-5), 6.90-6.93 (m, 1H, H-8).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 17.1, 18.1, 19.3, 21.8, 29.4, 30.0, 34.3, 35.2, 37.9, 38.8, 39.1, 39.6, 39.9, 40.5, 41.1, 43.5, 45.0, 48.0, 48.1, 84.8, 110.3, 125.3, 143.3, 150.5, 176.5.

Exact Mass calcd. for C₂₅H₃₆O₂: 368.2715; found: 368.2714.
3.3 Exploration of a New Cycloheptenone Annulation Method: Use of the Bifunctional Reagent \((Z)-5\text{-Iodo-1-tributylstannylpent-1-ene}\) in Organic Synthesis.

3.3.1 Preparation of \(N,N\)-Dimethylhydrazone Substrates.

The hydrazone substrates (227,\textsuperscript{101} 228,\textsuperscript{25} 229,\textsuperscript{25} 230\textsuperscript{25}) were prepared from the corresponding commercially available ketones and exhibited spectral data identical with those previously reported.
Preparation of 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one $N,N$-dimethylhydrazone (227).\textsuperscript{101}

To a stirred mixture of 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one (690 mg, 3.48 mmol, 1.0 equiv.) in dry benzene (10 mL), at room temperature, was added $N,N$-dimethylhydrazine (2.5 mL, 35 mmol, 10 equiv.) The reaction mixture was heated at reflux for with azeotropic removal of water for 20 h. The mixture was allowed to cool to room temperature and was then dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was distilled (air-bath temperature 125-130 °C / 0.04 Torr) to afford the $N,N$-dimethylhydrazone 227 (817 mg, 98%) as colorless oil which crystallized upon standing.
Preparation of Cyclohexanone \( N,N \)-dimethylhydrazone (228).\(^{25}\)

\[
\begin{align*}
\text{N} \quad \text{N(Me)}_2 \\
\text{N-} & \quad \text{N-} \nonumber \\
\text{228} & \nonumber
\end{align*}
\]

A mixture of cyclohexanone (5.00 mL, 48.2 mmol, 1.0 equiv.) and \( N,N \)-dimethylhydrazine (20 mL, 264 mmol, 5.5 equiv.) containing dry 4 Å molecular sieves (6 g) and a few crystals of \( p \)-toluenesulfonic acid was stirred at room temperature for 48 h. The mixture was filtered and the filtrate so obtained was diluted with diethyl ether and water. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was distilled (air-bath temperature 105-110 °C / 20 Torr) to afford the \( N,N \)-dimethylhydrazone 228 (6.9 g, 99%) as a colorless oil.
Preparation of Cycloheptanone $N,N$-dimethylhydrazone (229)$^{25}$

A mixture of cycloheptanone (3.00 mL, 25.4 mmol, 1.0 equiv.) and $N,N$-dimethylhydrazine (10 mL, 127 mmol, 5.0 equiv.) containing dry 4 Å molecular sieves (5 g) and a few crystals of $p$-toluenesulfonic acid was stirred at room temperature for 48 h. The mixture was filtered and the filtrate so obtained was diluted with diethyl ether and water. The layers were separated and the aqueous phase was extracted three times with diethyl ether. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was distilled (air-bath temperature 50-60 °C / 0.10 Torr) to afford the $N,N$-dimethylhydrazone 229 (3.9 g, 99%) as a colorless oil.
Preparation of bicyclo[4.4.0]decan-2-one \(N,N\)-dimethylhydrazone (230).

To a stirred mixture of bicyclo[4.4.0]decan-2-one (4.0 g, 26 mmol, 1.0 equiv.) in dry benzene (40 mL), at room temperature, was added \(N,N\)-dimethylhydrazine (4.0 mL, 53 mmol, 2.0 equiv.) The reaction mixture was heated at reflux with azeotropic removal of water for 15 h. The mixture was allowed to cool to room temperature, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude yellow product was distilled (air-bath temperature 160-180 °C / 8 Torr) to afford the \(N,N\)-dimethylhydrazone 230 (5.05 g, 99%) as a pale yellow oil.
3.3.2 General Procedure 1: Preparation of keto alkenyl iodides from the corresponding 
$N,N$-dimethylhydrazones and (Z)-5-iodo-1-tributylstannylpent-1-ene (53).

\[ \text{261} \quad \xrightarrow{1)} \text{LDA, THF, -78 °C to 0 °C} \quad \xrightarrow{2)} \text{HMPA, SnBu}_{3} \quad \xrightarrow{3)} \text{I$_{2}$, CH$_{2}$Cl$_{2}$, rt} \quad \xrightarrow{4)} \text{AcOH, NaOAc, THF, H$_{2}$O, rt} \quad \text{262} \]

To a cold (-78 °C), stirred solution of LDA (2.0 equiv.) in dry THF (2.5 mL/mmol LDA) was added, via cannula, a solution of dimethylhydrazone 261 (2.0 equiv.) in dry 
THF (0.6 mL/mmol hydrazone). The resulting mixture was stirred for 5 min at -78 °C and 
then 2 h at 0 °C. Dry HMPA (4.0 equiv.) was added via syringe and the mixture was 
stirred at 0 °C for 10 min, and then was cooled to -78 °C. A solution of (Z)-5-iodo-1-
tributylstannylpent-1-ene (53) (1.0 equiv.) in dry THF (1.0 mL/mmol iodide) was added 
dropwise via cannula. The mixture was stirred at -78 °C for 2 h and was then allowed to 
warm slowly to room temperature overnight. Saturated aqueous NaHCO$_{3}$ (10 mL/mmol 
iodide), diethyl ether (20 mL/mmol iodide) and water (10 mL/mmol iodide) were added 
and the layers were separated. The aqueous phase was extracted three times with diethyl 
ether and the combined organic extracts were washed four times with brine, dried over 
anhydrous magnesium sulfate, and concentrated under reduced pressure.
The crude material obtained as described above was dissolved in dry CH₂Cl₂ (10 mL/mmol iodide) and a 0.1 M solution of iodine in dry CH₂Cl₂ (1.1 equiv.) was added dropwise via syringe with vigorous stirring at room temperature. After stirring for an addition 15 min, the solution was treated with saturated aqueous Na₂S₂O₃ (10 mL/mmol iodide), the layers were separated, and the aqueous phase was extracted three times with diethyl ether. The combined organic extracts were washed once with 5% aqueous NaHCO₃, twice with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure.

To the material obtained as described above, was added sequentially THF (1.3 mL/mmol iodide), water (0.3 mL/mmol iodide), sodium acetate (0.6 g/mmol iodide), and acetic acid (1.9 mL/mmol iodide). The reaction mixture was stirred at room temperature for the specified length of time, at which point tlc analysis indicated complete consumption of the starting material. The mixture was carefully neutralized by addition of solid NaHCO₃. Diethyl ether and water were added and the layers were separated. The aqueous phase was extracted three times with diethyl ether and the combined organic extracts were washed once with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel) and the oil thus obtained was either distilled or traces of solvent were removed (vacuum pump) to afford the keto alkenyl iodide 262.
Preparation of 8-[(Z)-5-Iodopent-4-enyl]-3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one (234).

Following general procedure 1, a solution of LDA (5.83 mmol, 2.0 equiv.) in dry THF (15 mL) was treated with a solution of 3,3-dimethyl-1,5-dioxaspiro[5.5]undecan-9-one \(N,N\)-dimethylhydrazone (227) (1.40 g, 5.83 mmol, 2.0 equiv.) in dry THF (3.5 mL), followed by sequential addition of dry HMPA (2.03 mL, 11.7 mmol, 4.0 equiv.) and a solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (1.41 g, 2.91 mmol, 1.0 equiv.) in dry THF (3.0 mL). To a solution of the alkylation product in dry \(\text{CH}_2\text{Cl}_2\) (30 mL) was added a solution of iodine in dry \(\text{CH}_2\text{Cl}_2\) (30 mL, 0.10 M, 1.1 equiv.). The material obtained from the iododestannylation reaction was treated sequentially with THF (3.8 mL), water (0.85 mL), sodium acetate (1.7 g) and acetic acid (5.4 mL), and the reaction mixture was stirred for 15 min. The crude product was purified by flash chromatography (100 g of tlc silica gel, 9:1 then 4:1 petroleum ether - diethyl ether). The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature
220-230 °C/0.50 Torr) to afford the keto alkenyl iodide 234 (1.03g, 90%) as a pale yellow oil.

IR (neat): 2953, 1713, 1472, 1121, 918 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.96 (s, 3H), 1.00 (s, 3H), 1.17-1.86 (m, 6H), 2.09-2.15 (m, 2H), 2.24-2.31 (m, 1H), 2.45-2.55 (m, 4H), 3.52 (s, 2H), 3.54 (s, 2H), 6.12-6.18 (m, 2H).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 22.5 (-ve), 22.6 (-ve), 25.2 (+ve), 28.1 (+ve), 30.1 (+ve), 31.5 (+ve), 34.6 (+ve), 37.0 (+ve), 38.1 (+ve), 44.6 (-ve), 70.3 (+ve), 70.6 (+ve), 82.6 (-ve), 96.3 (+ve), 140.8 (-ve), 211.5 (+ve).

Exact Mass calcd. for C₁₆H₂₅O₃I: 392.0848; found: 392.0850.

Preparation of 2-[(Z)-5-Iodopent-4-enyl]cyclohexanone (235).

Following general procedure 1, a solution of LDA (4.45 mmol, 2.0 equiv.) in dry THF (10 mL) was treated with a solution of cyclohexanone \(N,N\)-dimethylhydrazone (228) (623 mg, 4.45 mmol, 2.0 equiv.) in dry THF (2.0 mL), followed by sequential addition of dry HMPA (1.55 mL, 8.90 mmol, 4.0 equiv.) and a solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (1.10 g, 2.27 mmol, 1.0 equiv.) in dry THF (5.0 mL). To a solution of the alkylation product in dry \(\text{CH}_2\text{Cl}_2\) (20 mL) was added a solution of iodine in dry \(\text{CH}_2\text{Cl}_2\) (25 mL, 0.10 M, 1.1 equiv.). The material obtained from the iododestannylation reaction was treated sequentially with THF (2.7 mL), water (0.60 mL), sodium acetate (1.2 g) and acetic acid (3.6 mL), and the reaction mixture was stirred for 19 h. The crude product was purified by flash chromatography (50 g of tlc silica gel, 9:1 petroleum ether - diethyl ether). The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 149-160 °C/0.04 Torr) to afford the keto alkenyl iodide 235 (660 mg, 98%) as a pale yellow oil.
IR (neat): 3069, 2928, 1708, 1448, 1128, 883 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 1.17-1.25 (m, 1H), 1.34-1.45 (m, 3H), 1.61-1.72 (m, 2H), 1.75-1.86 (m, 2H), 1.98-2.14 (m, 4H), 2.23-2.31 (m, 2H), 2.34-2.39 (m, 1H), 6.12-6.18 (m, 2H, H-10, H-11).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 24.8 (+ve), 25.4 (+ve), 27.9 (+ve), 28.7 (+ve), 33.9 (+ve), 34.6 (+ve), 41.9 (+ve), 50.3 (-ve), 82.5 (-ve), 140.9 (-ve), 213.0 (+ve).

Exact Mass calcd. for C$_{11}$H$_{17}$OI: 292.0324; found: 292.0330.

Anal. calcd. for C$_{11}$H$_{17}$OI: C 45.22, H 5.86; found: C 45.45, H 5.76.
Preparation of 2-[(Z)-5-Iodopent-4-enyl]cycloheptanone (236).

Following general procedure 1, a solution of LDA (8.26 mmol, 2.0 equiv.) in dry THF (20 mL) was treated with a solution of cycloheptanone $N,N$-dimethylhydrazone (229) (1.27 g, 8.26 mmol, 2.0 equiv.) in dry THF (5.0 mL), followed by sequential addition of dry HMPA (2.87 mL, 16.5 mmol, 4.0 equiv.) and a solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (2.00 g, 4.13 mmol, 1.0 equiv.) in dry THF (5.0 mL). To a solution of the alkylation product in dry CH$_2$Cl$_2$ (40 mL) was added a solution of iodine in dry CH$_2$Cl$_2$ (45 mL, 0.10 M, 1.1 equiv.). The material obtained from the iodoestannylation reaction was treated sequentially with THF (5.4 mL), water (1.2 mL), sodium acetate (2.4 g) and acetic acid (7.6 mL), and the reaction mixture was stirred for 24 h. The crude product was purified by flash chromatography (85 g of silica gel, 93:7 petroleum ether - diethyl ether). The appropriate fractions were concentrated and the oil thus obtained was distilled (air-bath temperature 178-184 °C/0.20 Torr) to afford the keto alkenyl iodide 236 (1.17 g, 93%) as a pale yellow oil.
IR (neat): 2926, 1703, 1455, 1278, 935, 693 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 1.28-1.42 (m, 6H), 1.57-1.74 (m, 2H), 1.80-1.86 (m, 3H), 2.07-2.13 (m, 2H), 2.39-2.50 (m, 4H), 6.14 (ddd, 1H, \(J = 7, 7, 7\) Hz, H-11) 6.17 (br d, 1H, \(J = 7\) Hz, H-12).

\(^13\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 24.4 (+ve), 25.5 (+ve), 28.5 (+ve), 29.4 (+ve), 31.3 (+ve), 31.5 (+ve), 34.5 (+ve), 42.7 (+ve), 51.8 (-ve), 82.6 (-ve), 140.8, (-ve), 216.0 (+ve).

Exact Mass calcd. for C\(_{12}\)H\(_{19}\)O: 306.0481; found: 306.0484.

Anal. calcd. for C\(_{12}\)H\(_{19}\)O: C 47.07, H 6.25; found: C 47.33, H 6.22.
Preparation of (1S*, 3R*, 6R*)-3-[(Z)-5-Iodopent-4-enyl]bicyclo[4.4.0]decan-2-one (237).

Following general procedure 1, a solution of LDA (4.96 mmol, 2.0 equiv.) in dry THF (15 mL) was treated with a solution of bicyclo[4.4.0]decan-2-one N,N-dimethylhydrazone (230) (963 mg, 4.96 mmol, 2.0 equiv.) in dry THF (3.0 mL), followed by sequential addition of dry HMPA (1.73 mL, 9.92 mmol, 4.0 equiv.) and a solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (1.20 g, 2.48 mmol, 1.0 equiv.) in dry THF (3.0 mL). To a solution of the alkylation product in dry CH₂Cl₂ (25 mL) was added a solution of iodine in dry CH₂Cl₂ (27 mL, 0.10 M, 1.1 equiv.). The material obtained from the iododestannylation reaction was treated sequentially with THF (3.2 mL), water (0.74 mL), sodium acetate (1.5 g) and acetic acid (4.6 mL), and the reaction mixture was stirred for 3 h. The crude product was purified by flash chromatography (40 g of silica gel, 7:3 petroleum ether - diethyl ether). The appropriate fractions were concentrated and the three epimers 263 obtained were dissolved in dry methanol (10 mL). To this stirred solution, at room temperature, was added a solution of sodium methoxide in dry methanol (14.9 mL, 0.50 M, 7.44 mmol, 3 equiv.) and the reaction mixture was stirred for
15 h. Saturated aqueous NaHCO₃ (10 mL), water (10 mL) and diethyl ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (100 g of tlc silica gel, 97:3 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the keto alkenyl iodide 237 (589 mg, 69% overall) as a colorless oil.

IR (neat): 3076, 2926, 1703, 1446, 1235, 894, 695 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.10-1.53 (m, 8H), 1.62-1.85 (m, 5H), 1.89-1.96 (m, 1H), 2.06-2.15 (m, 6H), 2.23-2.31 (m, 1H), 6.12-6.18 (m, 2H, H-14, H-15).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 25.2 (+ve), 25.3 (+ve), 25.6 (+ve), 25.7 (+ve), 28.7 (+ve), 33.2 (+ve), 33.8 (+ve), 34.4 (+ve), 34.8 (+ve), 45.9 (-ve), 50.1 (-ve), 55.2 (-ve), 82.4 (-ve), 141.2 (-ve), 213.5 (+ve).

Exact Mass calcd. for C₁₅H₂₃OI: 346.0794; found: 346.0784.

Anal. calcd. for C₁₅H₂₃OI: C 52.03, H 6.70; found: C 51.90, H 6.72
3.3.3 General Procedure 2: Butyllithium Mediated Anionic Cyclization of Keto Alkenyl Iodides.

To a cold (-78 °C), stirred solution of the keto alkenyl iodide 262 (1.0 equiv.) in dry THF (60 mL/mmol of keto alkenyl iodide) was added, in a single rapid injection with a syringe, a solution of BuLi in hexanes (~1.6 M, 2.1 equiv.). The reaction mixture was stirred at -78 °C for 1 h and then was treated with saturated aqueous NaHCO₃ (20 mL/mmol keto alkenyl iodide). The mixture was warmed to rt, water (20 mL/mmol of keto alkenyl iodide) and diethyl ether (40 mL/mmol of keto alkenyl iodide) were added and the layers were separated. The aqueous phase was extracted three times with diethyl ether. The combined organic extracts were washed once with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the allylic alcohol 57.
Preparation of the Tertiary Allylic Alcohol 239.

Following general procedure 2, a solution of the keto alkenyl iodide 234 (475 mg, 1.21 mmol, 1.0 equiv.) in dry THF (68 mL) was treated with BuLi (1.60 mL, 1.60 M in hexanes, 2.42 mmol, 2.1 equiv.). The crude product was purified by flash chromatography (30 g of tlc silica gel, 3:2 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the allylic alcohol 239 (271 mg, 84%) as a colorless oil which slowly crystallized to a white solid (mp = 69-70 °C).

IR (KBr): 3495, 2932, 1449, 1363, 1094, 966 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.90 (s, 3H), 1.00 (s, 3H), 1.24 (s, 1H), 1.45-1.91 (m, 10H), 2.09-2.23 (m, 3H), 3.40 (dd, 1H, J = 11, 1 Hz), 3.46 (dd, 1H, J = 11, 1 Hz), 3.47 (d, 1H, J = 11 Hz), 3.56 (d, 1H, J = 11 Hz), 5.48 (d, 1H, J = 12 Hz, H-2), 5.78 (ddd, 1H, J = 12, 6, 6 Hz, H-3).
$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 22.6, 22.8, 25.8, 27.5, 27.6, 30.2, 32.8, 37.8, 37.9, 39.4, 70.0, 70.1, 72.0, 97.6, 133.4, 138.2.

Exact Mass calcd. for C$_{16}$H$_{20}$O$_3$: 266.1882; found: 266.1875.

Anal. calcd. for: C 72.14, H 9.84; found: C 72.02, H 9.96.

**Preparation of Bicyclo[5.4.0]undec-2-en-1-ol (240).**

Following general procedure 2, a solution of the keto alkenyl iodide 235 (198 mg, 0.679 mmol, 1.0 equiv.) in dry THF (35 mL) was treated with BuLi (897 µL, 1.59 M in hexanes, 1.43 mmol, 2.1 equiv.). The crude material was purified by flash chromatography (10 g of tlc silica gel, 95:5 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) two alcohol products.
The first product that eluted was the major diastereomer of the allylic alcohols 240 (68 mg, 60%), a white solid (mp = 26-26.5 °C).

IR (KBr): 3443, 2926, 1448, 1142, 948 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.24-1.54 (m, 10H), 1.65-1.81 (m, 4H), 2.09-2.14 (m, 2H), 5.44 (d, 1H, J = 11.8 Hz, H-2), 5.77 (ddd, 1H, J = 11.8, 6.0, 6.0 Hz, H-3).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 21.3 (+ve), 25.9 (+ve), 27.8 (2C, both +ve), 31.1 (+ve), 33.6 (+ve), 41.7 (+ve), 43.3 (-ve), 72.7 (+ve), 132.9 (-ve), 139.5 (-ve).

Exact Mass calcd. for C₁₁H₁₈O: 166.1358; found: 166.1353.

Anal. calcd. for C₁₁H₁₈O: C 79.46, H 10.91; found: C 79.38, H 10.84. (Determined for the mixture of alcohols 240.)

The second product that eluted was the minor diastereomer of the allylic alcohols 240 (13.5 mg, 12%), a white solid (mp = 69.2-69.8 °C).

IR (KBr): 3269, 2930, 1443, 1045, 955 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.23-1.67 (m, 12H), 2.05-2.26 (m 4H), 5.45 (dd, 1H, J = 11.9, 2.4 Hz, H-2), 5.81 (ddd, 1H, J = 11.9, 7.6, 4.3 Hz, H-3).
$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 22.8 (+ve), 23.8 (+ve), 25.6 (+ve), 29.2 (+ve), 29.8 (+ve), 31.6 (+ve), 42.0 (+ve), 44.9 (-ve), 75.6 (+ve), 133.3 (-ve), 137.0 (-ve).

Anal. calcd. for C$_{11}$H$_{18}$O: C 79.46, H 10.91; found: C 79.38, H 10.84. (Determined for the mixture of alcohols 240.)

The combined total yield of the alcohols 240 was 81.5 mg (72%).

**Preparation of Bicyclo[5.5.0]dodec-2-en-1-ol (241).**

Following general procedure 2, a solution of the keto alkenyl iodide 236 (300 mg, 0.980 mmol, 1.0 equiv.) in dry THF (58 mL) was treated with BuLi (1.50 mL, 1.35 M in hexanes, 1.96 mmol, 2.1 equiv.). The crude product was purified by flash chromatography (10 g of tlc silica gel, 9:1 petroleum ether - diethyl ether) to afford, after
concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the allylic alcohol 241 (118 mg, 68%) as a white solid (mp = 43-44 °C).

IR (KBr): 3426, 2923, 1446, 1052, 957 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.14-1.93 (m, 14H), 2.01-2.11 (m, 2H), 2.17-2.25 (m, 2H), 5.58 (br d, 1H, J = 11.4 Hz, H-2), 5.86 (ddd, 1H, J = 11.4, 7.0, 4.4 Hz, H-3).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 22.1 (+ve), 26.9 (+ve), 27.4 (+ve), 30.19 (+ve), 30.23 (+ve), 31.4 (+ve), 33.5 (+ve), 44.9 (+ve), 46.0 (-ve), 76.2 (+ve), 135.0 (-ve), 140.5 (-ve).

Exact Mass calcd. for C₁₂H₂₀O: 180.1514; found: 180.1511.

Anal. calcd. for C₁₂H₂₀O: C 79.94, H 11.18; found: C 79.61, H 11.05.
Preparation of (2S*, 7R*, 10R*)-Tricyclo[8.5.0.0\textsuperscript{2,7}]pentadec-14-en-1-ol (242).

Following general procedure 2, a solution of the keto alkenyl iodide 237 (412 mg, 1.19 mmol, 1.0 equiv.) in dry THF (60 mL) was treated with BuLi (1.56 mL, 1.60 M in hexanes, 2.38 mmol, 2.1 equiv.). The crude product was purified by flash chromatography (26 g of silica gel, 95:5 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the allylic alcohol 242 (236 mg, 90%) as a white solid (mp = 54-54.8 °C).

IR (KBr): 3481, 2927, 1450, 1112, 898 cm\textsuperscript{-1}.

\(^{1}\text{H} \text{nmr (CDCl}_3, 400 \text{ MHz)} \delta: 0.89-1.89 \text{ (m, 20H)}, 1.98-2.09 \text{ (m, 1H)}, 2.19-2.32 \text{ (m, 1H)}, 5.68 \text{ (dd, 1H, } J = 11.7, 1.8 \text{ Hz, H-15)}, 5.87 \text{ (ddd, 1H, } J = 11.7, 7.8, 5.7 \text{ Hz, H-14}).
\( ^{13}\text{C nmr (CDCl}_3,\ 75.3\ \text{MHz)} \delta: 25.4\ (+ve), 26.4\ (+ve), 26.7\ (+ve), 27.0\ (+ve), 27.5\ (+ve), 31.3\ (+ve), 33.9\ (+ve), 34.0\ (+ve), 34.8\ (+ve), 37.1\ (-ve), 43.2\ (-ve), 52.5\ (-ve), 74.8\ (+ve), 133.6\ (-ve), 137.6\ (-ve).\)

Exact Mass calcd. for \( \text{C}_{15}\text{H}_{24}\text{O} \): 220.1827; found: 220.1823.

Anal. calcd. for \( \text{C}_{15}\text{H}_{24}\text{O} \): C 81.76, H 10.98; found: C 81.94, H 11.00.
3.3.4 General Procedure 3: Oxidative Rearrangement of the Tertiary Allylic Alcohols to \( \alpha,\beta \)-Unsaturated Ketones.

To a stirred solution of the allylic alcohol 57 (1.0 equiv.) in dry \( \text{CH}_2\text{Cl}_2 \) (10 mL/mmol of alcohol) at room temperature was added sequentially dry, powdered 3 Å molecular sieves (0.85 g/mmol of alcohol) and pyridinium chlorochromate (2.0 equiv.). The brown mixture was stirred at room temperature for the specified amount of time, at which point tlc analysis indicated complete consumption of the starting material. Diethyl ether (five times the volume of \( \text{CH}_2\text{Cl}_2 \)) was added and the mixture was stirred vigorously at room temperature for 1 h. The mixture was filtered through a pad of Florisil\textsuperscript{®} (~50 times the weight of the alcohol) and the collected material was washed with diethyl ether and then ethyl acetate until no uv-active product was detected in the eluate. The combined eluate was concentrated under reduced pressure and the crude product purified by flash chromatography (tlc silica gel) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the enone 58.
Preparation of the enone 244.

Following general procedure 3, a solution of the tertiary allylic alcohol 239 (136 mg, 0.511 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (2.0 mL) containing 3 Å molecular sieves (434 mg, 0.85 g/mmol alcohol) was treated with pyridinium chlorochromate (220 mg, 1.02 mmol, 2.0 equiv.). The reaction mixture was stirred for 2 h. The crude product was purified by flash chromatography (13 g of tlc silica gel, 6:4 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the enone 244 (115 mg, 85%) as a colorless oil which slowly crystallized to a white solid (mp = 94.5-95 °C).

IR (KBr): 2940, 1636, 1456, 1281, 1114, 1085, 893 cm$^{-1}$.

$^1$H-nmr (CDCl$_3$, 400 MHz) δ: 0.91 (s, 3H), 1.00 (s, 3H), 1.37-1.48 (m, 3H), 1.63-1.73 (m, 1H), 1.78-1.87 (m, 1H), 1.91-1.98 (m 1H), 2.17-2.23 (m, 2H), 2.37-2.46 (m, 2H),
2.50-2.64 (m, 3H), 3.46 (d, 2H, J = 11.5 Hz), 3.52 (d, 1H, J = 11.4 Hz), 3.54 (d, 1H, J = 11.4 Hz), 5.89 (s, 1H, H-2).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 20.1 (+ve), 22.5 (-ve), 22.7 (-ve), 30.2 (+ve), 32.0 (+ve), 32.4 (+ve), 34.8 (+ve), 40.7 (-ve), 41.5 (+ve), 44.3 (+ve), 70.2 (+ve), 70.3 (+ve), 96.8 (+ve), 126.8 (-ve), 158.9 (+ve), 204.3 (+ve).

Exact Mass calcd. for C$_{16}$H$_{24}$O$_3$: 264.1726; found: 264.1718.

Anal. calcd. for: C 72.69, H 9.15; found: C 72.61, H 9.36.

Preparation of Bicyclo[5.4.0]undec-1-en-3-one (245).

Following general procedure 3, a solution of the tertiary allylic alcohols 240 (43.5 mg, 0.262 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (1.0 mL) containing 3 Å molecular sieves (223 mg, 0.85 g/mmol alcohol) was treated with pyridinium chlorochromate (113 mg, 0.524 mmol, 2.0 equiv.). The reaction mixture was stirred for 23 h. The crude product
was purified by flash chromatography (3 g of tlc silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the enone 245 (32 mg, 74%) as a colorless oil.

IR (neat): 2929, 1651, 1450, 1268, 872 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.21-2.03 (m, 11H), 2.26-2.38 (m, 2H), 2.49-2.64 (m, 2H), 5.87 (s, 1H, H-2).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 20.0 (+ve), 25.9 (+ve), 28.4 (+ve), 34.1 (+ve), 36.1 (+ve), 39.8 (+ve), 44.5 (+ve), 46.1 (-ve), 126.0 (-ve), 161.2 (+ve), 205.1 (+ve).

Exact Mass calcd. for C₁₁H₁₆O: 164.1201; found: 164.1203.

Anal. calcd. for C₁₁H₁₆O: C 80.44, H 9.82; found: C 80.27, H 10.00.
Preparation of Bicyclo[5.5.0]dodec-1-en-3-one (246).

Following general procedure 3, a solution of the tertiary allylic alcohol 241 (48.2 mg, 0.268 mmol, 1.0 equiv.) in dry CH$_2$Cl$_2$ (1.0 mL) containing 3 Å molecular sieves (230 mg, 0.85 g/mmol alcohol) was treated with pyridinium chlorochromate (116 mg, 0.536 mmol, 2.0 equiv.). The reaction mixture was stirred for 1 h. The crude product was purified by flash chromatography (1 g of tlc silica gel, 8:2 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the enone 246 (39 mg, 82%) as a colorless oil.

IR (KBr): 2927, 1661, 1443, 1263, 958 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) δ: 1.20-1.90 (m, 12H), 2.29-2.42 (m, 3H), 2.48-2.54 (m, 1H), 2.67-2.72 (m, 1H), 5.88 (s, 1H, H-2).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) δ: 19.8 (+ve), 28.2 (+ve), 29.8 (+ve), 30.0 (+ve), 31.8 (+ve), 33.4 (+ve), 37.4 (+ve), 41.3 (+ve), 41.6 (-ve), 129.5 (-ve), 164.8 (+ve), 206.2 (+ve).
Exact Mass calcd. for C_{12}H_{18}O: 178.1358; found: 180.1358.

Anal. calcd. for C_{12}H_{18}O: C 80.85, H 10.18; found: C 80.65, H 10.12.

Preparation of (2S*, 7R*, 10R*)-Tricyclo[8.5.0.0^{2,7}]pentadec-1(15)-en-14-one (247).

Following general procedure 3, a solution of the tertiary allylic alcohol 242 (100 mg, 0.454 mmol, 1.0 equiv.) in dry CH_{2}Cl_{2} (2.0 mL) containing 3 Å molecular sieves (386 mg, 0.85 g/mmol alcohol) was treated with pyridinium chlorochromate (196 mg, 0.908 mmol, 2.0 equiv.). The reaction mixture was stirred for 3 h. The crude product was purified by flash chromatography (12 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump), the enone 247 (85 mg, 86%) as a colorless oil.
IR (neat): 2917, 1646, 1448, 1266, 1112, 904 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 1.03-1.47 (m, 8H), 1.61-1.85 (m, 9H), 1.95 (ddd, 1H, \(J = 14.3, 9.7, 4.8\) Hz), 2.25-2.32 (m, 1H), 2.57-2.61 (m, 2H), 5.75 (s, 1H, H-15).

\(^{13}\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 19.6 (+ve), 25.8 (+ve), 26.2 (+ve), 29.2 (+ve), 33.5 (+ve), 34.1 (+ve), 34.9 (+ve), 35.6 (+ve), 44.7 (+ve), 45.0 (-ve), 47.5 (-ve), 49.6 (-ve), 122.5 (-ve), 163.4 (+ve), 206.1 (+ve).

Exact Mass calcd. for C\(_{15}\)H\(_{22}\)O: 218.1671; found: 218.1670.

Anal. calcd. for C\(_{15}\)H\(_{22}\)O: C 82.52, H 10.16; found: C 82.31, H 10.14.
3.3.5 Extension of the Cycloheptenone Annulation to Cyclic \( \beta \)-Keto Ester Substrates.

Preparation of Ethyl 1-[(Z)-5-tributylstannylpent-4-enyl]-2-oxocyclohexane carboxylate (250).

To a stirred suspension of potassium hydride (96 mg, 2.4 mmol, 1.2 equiv.) in dry THF (8.0 mL) at room temperature was added neat ethyl 2-oxocyclohexanecarboxylate (248) (320 \( \mu \)L, 2.00 mmol, 1.0 equiv.) via syringe and the resulting mixture was stirred for 45 min. A solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (1.94 g, 4.00 mmol, 2.0 equiv.) in dry THF (5.0 mL) was added via cannula and the reaction mixture was heated at reflux for 17 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting oil-salt mixture was purified by flash chromatography (100 g of silica gel, 97:3 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the keto alkenyl stannane 250 (1.03 g, 98\%) as a colorless oil.
IR (neat): 2930, 1717 (br), 1459, 1202, 1070, 866 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 0.85-0.89 (m, 15 H), 1.22-1.33 (m, 6H), 1.24 (t, 3H, J = 7.1 Hz, H-9), 1.38-1.75 (m, 13H), 1.85 (dd, 1H, J = 13.2, 5.0 Hz), 1.94-2.04 (m, 3H), 2.40-2.51 (m, 3H), 4.17 (qd, 2H, J = 7.1, 2.1 Hz, H-8), 5.77 (d, 1H, J = 12.4 Hz, J_Sn-H = 75 Hz, H-14), 6.45 (dt, 1H, J = 12.4, 7.0 Hz, J_Sn-H = 140 Hz, H-13).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 10.2 (+ve), 13.7 (-ve), 14.2 (-ve), 22.6 (+ve), 24.4 (+ve), 27.3 (+ve), 27.6 (+ve), 29.2 (+ve), 34.3 (+ve), 35.9 (+ve), 37.2 (+ve), 41.1 (+ve), 60.7 (+ve), 61.1 (+ve), 128.5 (-ve), 148.3 (-ve), 171.9 (+ve), 207.9 (+ve).

Exact Mass calcd. for C₂₂H₃₉O₃¹²⁰Sn (M – Bu)⁺: 471.1921; found: 471.1927.

Preparation of Ethyl 1-[(Z)-5-tributylstannylpent-4-enyl]-2-oxo-cycloheptane carboxylate (251).

To a stirred suspension of potassium hydride (106 mg, 2.6 mmol, 1.2 equiv.) in dry THF (8.0 mL) at room temperature was added neat methyl 2-oxocycloheptanecarboxylate (249) (343 µL, 2.20 mmol, 1.0 equiv.) via syringe and the resulting mixture was stirred for 45 min. A solution of (Z)-5-iodo-1-tributylstannylpent-1-ene (53) (1.60 g, 3.31 mmol, 1.5 equiv.) in dry THF (5.0 mL) was added via cannula and the reaction mixture was heated at reflux for 17 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting oil-salt mixture was purified by flash chromatography (70 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the keto alkenyl stannane 251 (1.08 g, 94%) as a colorless oil.
IR (neat): 2928, 1714 (br), 1457, 1150, 879 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 0.85-0.89 (m, 15H), 1.24-1.35 (m, 6H), 1.43-1.75 (m, 16H), 1.92-2.16 (m, 4H), 2.42-2.48 (m, 1H), 2.56-2.62 (m, 1H), 3.70 (s, 3H, H-9), 5.77 (d, 1H, \(J = 12.4\) Hz, \(^2J_{Sn-H} = 72\) Hz, H-14), 6.44 (dt, 1H, \(J = 12.4, 7.0\) Hz, \(^3J_{Sn-H} = 141\) Hz, H-13).

\(^13\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 10.2 (+ve), 13.6 (-ve), 24.8 (+ve), 25.6 (+ve), 27.3 (+ve), 29.1 (+ve), 29.9 (+ve), 32.7 (+ve), 35.0 (+ve), 37.2 (+ve), 41.9 (+ve), 52.1 (-ve), 62.9 (+ve), 128.5 (-ve), 148.2 (-ve), 172.9 (+ve), 209.4 (+ve).

Exact Mass calcd. for C\(_{22}H_{39}O_3^{120}\)Sn (M – Bu\(^+\)): 471.1921; found: 471.1922.

Anal. calcd. for C\(_{26}H_{48}O_5\)Sn: C 59.22, H 9.17; found: C 59.27, H 9.17.
Preparation of Ethyl 1-[(Z)-5-iodopent-4-enyl]-2-oxocyclohexanecarboxylate (252).

To a stirred solution of the alkenyl stannane 250 (984 mg, 1.87 mmol, 1.0 equiv.) in dry CH₂Cl₂ (20 mL) at room temperature, was added a solution of iodine in dry CH₂Cl₂ (18.7 mL, 0.10 M, 1.87 mmol, 1.0 equiv.) via syringe. The reaction mixture was stirred for 15 min at room temperature. Saturated aqueous Na₂S₂O₃ (40 mL) and diethyl ether (60 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ (1 x 40 mL) and brine (1 x 60 mL), and then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (75 g of silica gel, 95:5:1 petroleum ether - diethyl ether - triethylamine) to afford, after concentration of the appropriate fractions and removal of traces of solvents (vacuum pump) the keto alkenyl iodide 252 (677 mg, 99%) as a colorless oil.
IR (neat): 3073, 2939, 1713 (br), 1450, 1202, 695 cm\(^{-1}\).

\(^1\)H nmr (CDCl\(_3\), 400 MHz) \(\delta\): 1.23-1.46 (m, 3H), 1.24 (t, 3H, \(J = 7.1\) Hz, H-9), 1.52-1.73 (m, 4H), 1.87 (ddd, 1H, \(J = 12.8, 12.8, 4.4\) Hz), 1.95-2.00 (m, 1H), 2.11 (ddd, 2H, \(J = 7.1, 7.1\) Hz), 2.38-2.50 (m, 3H), 4.18 (q, 2H, \(J = 7.1\) Hz, H-8), 6.11-6.19 (m, 2H, H-13, H-14).

\(^13\)C nmr (CDCl\(_3\), 75.3 MHz) \(\delta\): 14.2 (-ve), 22.6 (+ve), 22.8 (+ve), 27.6 (+ve), 34.2 (+ve), 34.9 (+ve), 36.2 (+ve), 41.1 (+ve), 60.8 (+ve), 61.2 (+ve), 82.9 (-ve), 140.7 (-ve), 172.0 (+ve), 208.0 (+ve).

Exact Mass calcd. for C\(_{14}\)H\(_{21}\)O\(_3\)I: 364.0536; found: 364.0540.

Anal. calcd. for C\(_{14}\)H\(_{21}\)O\(_3\)I: C 46.17, H 5.81; found: C 46.46, H 5.82.
Preparation of Methyl 1-[(Z)-5-iodopent-4-enyl]-2-oxocycloheptanecarboxylate (253).

To a stirred solution of the alkenyl stannane 251 (983 mg, 1.87 mmol, 1.0 equiv.) in dry CH₂Cl₂ (20 mL) at room temperature, was added a solution of iodine in dry CH₂Cl₂ (19.0 mL, 0.10 M, 1.90 mmol, 1.0 equiv.) via syringe. The reaction mixture was stirred for 15 min at room temperature. Saturated aqueous Na₂S₂O₃ (40 mL) and diethyl ether (60 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were washed with 5% aqueous NaHCO₃ (1 x 40 mL) and brine (1 x 60 mL), and then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The crude product was purified by flash chromatography (60 g of silica gel, 85:15:2 petroleum ether - diethyl ether - triethylamine). The appropriate fractions were concentrated, and the oil thus obtained was distilled (air-bath temperature 266-270 °C/10 Torr) to afford the keto alkenyl iodide 253 (634 mg, 94%) as a pale yellow oil.
IR (neat): 2932, 1735, 1713, 1456, 1228, 1162, 697 cm$^{-1}$.

$^1$H nmr (CDCl$_3$, 400 MHz) $\delta$: 1.31-1.75 (m, 10H), 1.94-2.02 (m, 1H), 2.08-2.15 (m, 3H), 2.43-2.49 (m, 1H), 2.57-2.63 (m, 1H), 3.71 (s, 3H, H-9), 6.14 (ddd, 1H, $J = 7.1, 7.1, 7.1$ Hz, H-13), 6.19 (ddd, 1H, $J = 7.1, 0.9, 0.9$ Hz, H-14).

$^{13}$C nmr (CDCl$_3$, 75.3 MHz) $\delta$: 23.0 (+ve), 24.8 (+ve), 25.5 (+ve), 29.8 (+ve), 32.8 (+ve), 34.8 (2C, both +ve), 41.9 (+ve), 52.1(-ve), 62.7 (+ve), 82.9 (-ve), 140.5 (-ve), 172.8 (+ve), 209.3 (+ve).

Exact Mass calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_3\text{I}$: 364.0536; found: 364.0539.

Anal. calcd. for $\text{C}_{14}\text{H}_{21}\text{O}_3\text{I}$: C 46.17, H 5.81; found: C 46.09, H 5.89.
Preparation of Ethyl 5-oxobicyclo[5.4.0]undec-6-enecarboxylate (256).

To a cold (0 °C), stirred solution of the keto alkenyl iodide 252 (173 mg, 0.475 mmol, 1.0 equiv.) in dry THF (28 mL) was added, in a single rapid injection with a syringe, a solution of BuLi in hexanes (683μL, 1.46 M, 0.998 mmol, 2.1 equiv.). The reaction mixture was stirred at 0 °C for 45 min and then was treated with saturated aqueous NaHCO₃ (10 mL). Water (10 mL) and diethyl ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The residue obtained as described above was dissolved in dry CH₂Cl₂ (2.5 mL). To this stirred solution was added sequentially dry, powdered 3 Å molecular sieves (375 mg, 0.85 g/mmol alcohol) and pyridinium chlorochromate (307 mg, 1.43 mmol, 3.0 equiv.). The resulting brown reaction mixture was heated at reflux for 5.5 h. The mixture was cooled to room temperature, diethyl ether (12 mL) was added and the mixture was stirred vigorously for 1 h. The mixture was filtered through a pad of Florisil® (2 g) and the collected material was washed with diethyl ether (200 mL) and then ethyl acetate
(100 mL) until no uv-active product was detected in the eluate. The combined eluate was concentrated under reduced pressure and the crude product was purified by flash chromatography (6 g of tic silica gel, 7:3 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the enone 256 (74 mg, 70% overall) as a colorless oil.

IR (neat): 2937, 1724, 1649, 1451, 1181, 1097, 890 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.27 (t, 3H, J = 7.1 Hz, H-14), 1.31-1.40 (m, 3H), 1.54-1.83 (m, 4H), 2.08-2.13 (m, 1H), 2.26-2.35 (m, 4H), 2.43-2.52 (m, 1H), 2.64-2.70 (m, 1H), 4.16 (q, 2H, J = 7.1 Hz, H-13), 5.98 (s, 1H, H-6).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 14.2 (-ve), 18.1 (+ve), 23.2 (+ve), 27.6 (+ve), 37.7 (+ve), 39.1 (+ve), 39.5 (+ve), 43.5 (+ve), 55.7 (+ve), 61.1 (+ve), 129.2 (-ve), 156.8 (+ve), 173.9 (+ve), 203.6 (+ve).

Exact Mass calcd. for C₁₄H₂₀O₃: 236.1413; found: 236.1406.

Anal. calcd. for C₁₄H₂₀O₃: C 71.16, H 8.53; found: C 71.46, H 8.62.
Preparation of Methyl 5-oxobicyclo[5.4.0]dodec-6-ene-1-carboxylate (257).

To a cold (0 °C), stirred solution of the keto alkenyl iodide 253 (128 mg, 0.351 mmol, 1.0 equiv.) in dry THF (20 mL) was added, in a single rapid injection with a syringe, a solution of BuLi in hexanes (467 µL, 1.58 M, 0.737 mmol, 2.1 equiv.). The reaction mixture was stirred at 0 °C for 1 h and then was treated with saturated aqueous NaHCO₃ (10 mL). Water (10 mL) and diethyl ether (30 mL) were added and the layers were separated. The aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

The residue obtained as described above was dissolved in dry CH₂Cl₂ (1.5 mL). To this stirred solution was added sequentially dry, powdered 3 Å molecular sieves (298 mg, 0.85 g / mmol alcohol) and pyridinium chlorochromate (151 mg, 0.702 mmol, 2.0 equiv.). The resulting brown reaction mixture was heated at reflux for 2.5 h. The mixture was cooled to room temperature, diethyl ether (8 mL) was added and the mixture was stirred vigorously for 1 h. The mixture was filtered through a pad of Florisil® (1 g) and the collected material was washed with diethyl ether (200 mL) and then ethyl acetate
(150 mL) until no uv-active product was detected in the eluate. The combined eluate was concentrated under reduced pressure and the crude product was purified by flash chromatography (8 g of silica gel, 9:1 petroleum ether - diethyl ether) to afford, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the enone 257 (44 mg, 53% overall) as a colorless oil.

IR (neat): 2928, 1728, 1666, 1447, 1245, 1089, 892 cm⁻¹.

¹H nmr (CDCl₃, 400 MHz) δ: 1.32-1.46 (m, 3H), 1.59-1.92 (m, 8H), 1.99-2.05 (m, 1H), 2.18-2.51 (m, 4H), 3.70 (s, 3H, H-14), 6.08 (s, 1H, H-6).

¹³C nmr (CDCl₃, 75.3 MHz) δ: 19.2 (+ve), 23.8 (+ve), 29.7 (+ve), 30.5 (+ve), 37.7 (+ve), 38.2 (+ve), 40.3 (+ve), 41.9 (+ve), 52.3 (-ve), 56.0 (+ve), 133.3 (-ve), 160.7 (+ve), 175.5 (+ve), 203.1 (+ve).

Exact Mass calcd. for C₁₄H₂₀O₃: 236.1413; found: 236.1403.

Anal. calcd. for C₁₄H₂₀O₃: C 71.16, H 8.53; found: C 71.00, H 8.60.
IV. References and Footnotes


5. Synthons have been defined by Corey as "structural units within a molecule which are related to possible synthetic operations". Corey, E. J.; Cheng, X.-M. in The logic of Chemical Synthesis; John Wiley & Sons: New York, 1989.


(b) Piers, E.; Renaud, J.; Rettig, S. J. Synthesis 1998, 590.


29. The ratio of isomers was determined by integration of the respective alkenyl signals in the $^1$H nmr (400 MHz) spectrum.

30. The other epimer could not be detected in the $^1$H nmr (400 MHz) spectrum.

31. The variecolin numbering system (see page 15) reported in the original isolation paper (see reference 14) is used throughout the Discussion and differs from the IUPAC based numbering system used in the Experimental section.


35. For [4 + 3] cycloaddition processes, see:

For [5 + 2] cycloaddition processes, see:


44. The ratio of compounds 121 and 122 varied depending on the reaction conditions and the extent of epimerization.

(b) Jackman, L. M.; Lange, B. C. Tetrahedron 1977, 33, 2737.
(c) Liotta, C. L.; Caruso, T. C. Tetrahedron Lett. 1985, 26, 1599.
The methyl iodide was purified immediately prior to use by passing it through a short plug of oven-dried basic alumina.


Formation of hydroxyallyl radicals may be favored when a stronger proton donor than ammonia is present in the reaction mixture. However, the acidity of ammonia can be significantly increased by coordination with metal cations and thus in the absence of a better proton donor, the solvent ammonia may still protonate the intermediate radical anion. (see ref. 53)

(b) Stork, G.; Darling, S. D. J. Am. Chem. Soc. 1964, 86, 1761.


63. This is in analogy with the known TiCl₄ and SnCl₄ mediated ring opening of
cyclopropyl ethers to give titanium and tin homoenoates, respectively. For an
excellent review of metal homoenoates generated from silyloxy- cyclopropanes

64. House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. J. Org. Chem. 1969, 34,
2324.


67. Commercially available (40-50%) MCPBA was dissolved in dichloromethane
and the resulting solution was washed three times with pH 7.4 phosphate buffer,
dried (MgSO₄) and concentrated under reduced pressure. The pure MCPBA thus
obtained was stored in a plastic bottle in the fridge (~5 °C) and used shortly after
preparation.

(c) Piers, E.; Orellana, A. Synthesis, 2001, 2138.


71. Leusink, A. J.; Budding, H. A.; Marsman, J. W. J. Organomet. Chem. 1967, 9,
285.


75. Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E.

1984, 25, 5959.

(b) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. J.


In agreement with the results derived from catalytic hydrogenation of structurally related verucosane-type terpenoids (see ref. 25), utilization of palladium on carbon resulted in extensive isomerization of the olefinic double bonds.


For an excellent review on remote intramolecular free radical functionalizations see: Majetich G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095.


The cyclization of an allylic alcohol to give an iodo epoxide under similar conditions has been previously noted (see Galatisis, P.; Millan, S. D. *Tetrahedron Lett.* **1991**, *32*, 7493.):

\[
\text{PhI(OAc)}_2, I_2 \rightarrow \text{O} \\
\text{CH}_2\text{Cl}_2, \text{hv} \rightarrow \text{I} \\
72\%
\]

93. A base is commonly added to sequester the acetic acid formed during the course of the reaction (see ref. 92).


100. A preliminary account of this work has been reported: Piers, E.; Walker, S. D.; Armbrust, R. *J. Chem. Soc, Perkin Trans. 1*, 2000, 635.


110. The X-ray structure determination was performed on racemic material by Dr. S. Rettig.
Appendix 1: X-ray Crystallographic Data

X-ray Data for Allylic Alcohol 110

Formula: C_{19}H_{30}O

Crystal Color, Habit: colorless, irregular

Crystal system: orthorhombic

Lattice type: primitive

Lattice Parameters:

\[ a = 9.9581(12) \, \text{Å} \]
\[ b = 17.1158(6) \, \text{Å} \]
\[ c = 18.6741(5) \, \text{Å} \]
\[ V = 3182.8(3) \, \text{Å}^3 \]

Space group: Pbca(#61)

Z value: 8

Number of reflections used in refinement: 4370

Residuals:

\[ R = 0.040 \]
\[ R_w = 0.039 \]