NEW ANNULATION METHODS.
TOTAL SYNTHESIS OF THE DITERPENOID (±)-AMBLIOL B.

By

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DEPARTMENT OF CHEMISTRY

We accept this thesis as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
April 1990

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The University of British Columbia
Vancouver, Canada

Date May 22, 1990
ABSTRACT

The preparation of bicyclic systems containing an allylic, angular hydroxyl group (general structure 20 and compound 87b) is described. These materials have been prepared via a new annulation sequence involving (a) the alkylation of cyclic ketones with the bifunctional conjunctive reagents 129, 21 and 60, (b) the conversion of the alkylation products into keto vinyl iodides, and (c) cyclization of the keto vinyl iodides via low temperature metal halogen exchange with n-butyllithium.

The cyclization process described in (c) has been employed in the first total synthesis of the diterpenoid (+)-ambliol B (94). Thus, 3,4-dimethyl-2-cyclohexen-1-one (96) was converted, in three steps, into the unstable enone 125. Reaction of this compound with the novel vinylgermane cuprate 110, followed by reaction of the resultant product with iodine, gave the cyclization precursor 106. Cyclization of 106 gave a single, trans-fused product (128) in high yield. The exocyclic methylene function of 128 was cyclopropanated and the vinyl substituent of the resultant cyclopropane was hydroborated to give the cyclopropane diol 149. Hydrogenolysis of the cyclopropane ring of compound 149 provided the required gem-dimethyl moiety. The resultant product was converted into (±)-ambliol B (94) via a four step sequence of reactions involving (a) oxidation of the primary alcohol function, (b) addition of 3-furyllithium to the so-formed unstable aldehyde, (c) acetylation of the secondary alcohol prepared in (b), and (d) reductive removal of the acetoxy function.

A new annulation sequence which utilizes the vinylgermane cuprate 110 as a synthetic equivalent of the 1-butene a\textsuperscript{2},d\textsuperscript{4}-synthon 153 is described. Thus, cyclic enones of the general structure 154 were treated with 110 to provide the keto vinylgermane intermediates 155. The latter materials were transformed into the corresponding keto vinyl iodides 156. Treatment of 156 with a palladium(0) catalyst and a base resulted in cyclization to provide the annulation products 157 or, when R\textsubscript{1} = H, the α,β-unsaturated ketones 185.
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AIBN</td>
<td>azobis(isobutyronitrile)</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>DEG</td>
<td>diethyleneglycol</td>
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<tr>
<td>DIBAL</td>
<td>diisobutylaluminum hydride</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>g</td>
<td>grams</td>
</tr>
<tr>
<td>glc</td>
<td>gas-liquid chromatography</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramidé</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>ir</td>
<td>infrared</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>mg</td>
<td>milligram(s)</td>
</tr>
<tr>
<td>min</td>
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</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
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<tr>
<td>Symbol</td>
<td>Term</td>
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<td>----------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
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<tr>
<td>mmol</td>
<td>millimole(s)</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>nmr</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser enhancement</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
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<td>s</td>
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</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-n-butylammonium fluoride</td>
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<tr>
<td>Tf₂NPh</td>
<td>N-phenyltrifluoromethanesulfonimide</td>
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<td>tetrahydrofuran</td>
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<td>thin layer chromatography</td>
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Finally, I would like to thank my wife, Adri, without whom all of the effort and time invested in these studies would have been pointless.
To the memory of my father
who knew the value of trust

"Maar dis nie te sê nie....."

Breyten Breytenbach
I. INTRODUCTION

1.1 General.

One of the central goals of modern-day synthetic organic chemistry is the design of efficient reagents for the selective and rapid construction of carbon frameworks. A notably successful approach towards the realization of this goal has been the use of "conjunctive reagents" which contain two reactive or potentially reactive sites. The virtue of such "bifunctional conjunctive reagents" is particularly well exploited in the construction of carbocycles, since the two reactive sites can be deployed (either sequentially or in tandem) against a single bifunctional substrate to yield an annulated product. These reactive sites are either nucleophilic or electrophilic in nature and have been respectively termed "donor" (d) and "acceptor" (a) sites.

Although there are far too many reports in the recent literature to be mentioned here, the following pertinent example serves to illustrate how these somewhat theoretical concepts are applied in an annulation sequence in the laboratory.

A key transformation in Paquette’s synthesis of the triquinane 1 (the originally, but incorrectly, proposed structure of the sesquiterpenoid senoxydene) is the attachment of the third ring, as illustrated by the conversion of the bicyclic ketone into the tricyclic enone 4 in Scheme 1. In this annulation sequence the vinylsilane iodide 3 serves as a bifunctional conjunctive reagent. It is synthetically equivalent to the donor-acceptor synthon.

The rapid construction of the required ring in enone 4 is made possible by first utilizing the acceptor site of the synthon in an intermolecular alkylation step, while the donor site is masked as a vinylsilane function. This is followed by unmasking of the donor site via epoxidation and acidification and, finally, a cyclization step to yield the required ring. Manipulation of the
functionality in this ring then leads to the target structure 1. The events referred to above (intermolecular coupling, unmasking and cyclization) are a common feature of the use of bifunctional conjunctive reagents in annulation processes, though not necessarily in this order, and underpin much of the work that will be presented in this thesis.

The next section will describe some previous studies at the University of British Columbia
that are relevant to the ideas delineated above and, in the light of these, will propose some of the questions that the work described in this thesis attempted to answer.

### 1.2 Background and Proposals.

Recent reports\(^6,7\) from our laboratories described, *inter alia*, the preparation of the bifunctional conjunctive reagents 4-chloro-2-trimethylstannyl-1-butene (6) and 5-chloro-2-trimethylstannyl-1-pentene (7) via the reaction of (trimethylstannyl)copper(I)dimethyl sulfide with terminal acetylenes (Scheme 2).

These reagents have subsequently proven to be very useful in annulation procedures in which cyclic enones are the substrates. For example, when the latent donor activity of 6 is unmasked by transmetallation with methyllithium at -78 °C and a copper(I) salt is added, the
so-formed organocuprates 8 and 9 add in a conjugate sense to a variety of cyclic enones (Scheme 3). The acceptor site is next utilized by treatment of the 1,4-adduct with potassium hydride, to give the cyclized product 10. The general applicability of this annulation method has resulted in its use in the total synthesis of a number of natural products. Scheme 4 contains a summary of one such a synthesis.

\[ \text{Me}_3\text{Sn} \quad \text{1)} \text{MeLi, THF, -78}^\circ \text{C} \quad \text{2)} \text{CuSPh or CuCN, -63}^\circ \text{C} \]

\[ \begin{array}{c}
\text{6} \\
\text{8} \text{ M=CuSPh(Li)} \\
\text{9} \text{ M=CuCN(Li)} \\
\end{array} \]

The total synthesis of the sesquiterpenoid (+)-\(\Delta^{9(12)}\)-capnellene (11) commenced with an annulation sequence utilizing 6 in a manner very similar to that shown in Scheme 3. Here, the donor activity of 6 was harnessed in a copper(I)-catalyzed conjugate addition of the Grignard reagent 12 to 2-methyl-2-cyclopenten-1-one. Cyclization of the resultant product gave the cis-fused bicyclic ketone 13. This compound was transformed in several steps into the conjugated enone 14. In its turn, this enone was utilized as a substrate for the now familiar annulation procedure. Thus, the second annulation proceeded via addition of reagent 12 (derived as before from 6) in the presence of a copper(I) salt to 14, followed by potassium hydride-assisted
cyclization as before. Having assembled the entire carbon skeleton in a highly stereoselective way by iterative application of this annulation method, a three step reductive removal of the central carbonyl functionality yielded the target compound 11. In this total synthesis, the bifunctional conjunctive reagent 6 served as a synthetic equivalent of both of the $d^2,a^4$-synthons 15 and 16.
Reagent 7, the one carbon homologue of 6, exhibits similar reactivity under the appropriate reaction conditions, and has been utilized in annulation processes leading to a number of natural products containing a methylenecyclohexane subunit.\textsuperscript{8,9} The example in Scheme 5 suffices to illustrate this analogous procedure.\textsuperscript{10} As before, the donor site of reagent 7 is unmasked by transmetallation with methyllithium. The so formed vinyllithium species was next transformed into a vinylcopper reagent through the agency of copper bromide-dimethyl sulfide and tri-\textit{n}-butylphosphine. Addition of the vinylcopper reagent to 2-methyl-2-cyclohexenone followed by smooth base-promoted cyclization afforded the cis-fused bicyclic product 10a.

In the above examples of annulation procedures utilizing reagents 6 or 7, the vinylic donor site of the reagent was deployed first, while the acceptor site of the reagent was deployed subsequently in an intramolecular alkylation reaction. This order of deployment is shown in a
generalized form in Scheme 6, equation a. Thus, synthon 17, of which reagents 6 or 7 would be the synthetic equivalents, when deployed in this order against a suitable enone, gives annulated products of the general structure 18. A conceivable extension of this methodology would involve

\[
\text{Scheme 6}
\]

the use of these reactive sites in the reversed order. The problem can be stated thus: Would it be possible to use bifunctional conjunctive reagents such as 6 and 7 as synthetic equivalents of the synthon 17 in annulation processes in which the acceptor site is used first, followed by the donor site? If so, the use of such reagents might tolerate not only conjugated enones as substrates, but also ordinary ketones. Equations b and c in Scheme 6 contain generalized examples of two possible annulation sequences based on this idea. The use of synthon 17 as depicted in equation b
has resulted, in our laboratories, in a general method for the preparation of dienes of the type 19.\textsuperscript{11} After a brief discussion of how this is done by way of an example in Scheme 7, we will return to the proposed annulation shown in equation c of Scheme 6 in order to examine the relevance of the part structure 20 in the context of natural product synthesis.

Scheme 7

One of the examples of the "reversed order" annulation process generalized in equation b of Scheme 6 is illustrated in Scheme 7. Central to this procedure is the utilization of an intramolecular variation of the palladium-catalyzed coupling of vinylstannanes and vinyl triflates first reported by Stille and coworkers.\textsuperscript{12} Use was first made of the acceptor site of the iodo analogue (21) of reagent 7 in an alkylation step.\textsuperscript{13} The ketone function present in the so formed
compound 22 was transformed into the required vinyl triflate moiety in 23. In the subsequent coupling step alluded to above, the ability of the vinylstannane moiety of 23 to act as the donor center of reagent 21 was utilized. Thus, palladium-assisted unmasking of both this donor activity and the acceptor activity of the vinyl triflate function resulted in clean formation of the bicyclic diene 24.\textsuperscript{13}

Having seen a practical example in Scheme 7 of the annulation procedure suggested by equation b of Scheme 6, attention can now be turned to the proposed "reverse order" annulation of equation c. It is pertinent to note that the part structure 20 of this equation and part structures 25 and 26 (which are in theory easily derived from 20) are present in a number of natural products. The sesquiterpenoid africanol\textsuperscript{14} (27), for instance, contains the part structure 25. \(\Delta^{9(12)}\)-Capnellene-8\(\beta\),10\(\alpha\)-diol\textsuperscript{15} (28), on the other hand, contains the original part structure 20, while the diterpenoid ambliol B\textsuperscript{16} (29) is clearly related to part structure 26. The derivation of the functionality present in 25 could in principle be performed by hydrogenation of the double bond
in 20, while the \textit{gem}-dimethyl arrangement of 26 could be achieved theoretically by
cyclopropanation of the double bond, followed by hydrogenolysis of the cyclopropane ring.

It was, therefore, of interest to develop a method for the efficient preparation of substances
containing the part structure 20. The first part of the work to be presented in this thesis will be
devoted to the development of an annulation procedure that would yield such materials, using
reactions related to the basic theoretical concepts discussed thus far. It is evident that if such an
annulation process could be developed and shown to be general, the way would be paved towards
attempts at the total synthesis of the natural products shown.

If the use of the bifunctional conjunctive reagents discussed thus far could be extended in
useful ways by reversing the order of deployment of their donor and acceptor sites, it might also
be useful to consider the possibility of reversing the activity of the reactive sites themselves
(Scheme 8). Could one, for instance, achieve reactivity "umpolung"\textsuperscript{17} of both the reactive sites of
the synthon 17 used above to give synthon 30? This would enable a further extension of the usual
annulation process (which produces the structures 18 when enones are used as substrates) to give
structures like 31 from enones. Or, to extend this idea even further, might one be able to prepare
a reagent which would be synthetically equivalent to a synthon containing two donor sites (32),
which, combined with a suitable \(\alpha,\alpha\)-substrate, would yield annulated products such as 33?
Finally, would the spiro-compounds 35, for instance, be accessible via a potential synthon 34
containing two acceptor sites? The exploration of these possibilities was an important motivation
in the synthetic investigations which are to be detailed in the pages that follow.

In summary, the \(\omega\)-halo-2-trimethylstannyl-1-alkene family of bifunctional reagents had
already proven to be useful synthetic equivalents of the donor-acceptor synthons 17 and had, as
such, been applied in two distinct types of annulation procedures (see, for example, Scheme 3 and
Scheme 7). It was the purpose of this work to extend further the use of these and similar reagents
not only in their role as equivalents of the synthons 17, but also to explore some of their
promising potential as reagents in which the donor and acceptor character at the two reactive sites
could be chosen at will.
Scheme 8
II. DISCUSSION

2.1 Annulations Leading to Bicyclic Systems with an Allylic, Angular Hydroxyl Group.

2.1.1 Introductory Remarks.

The starting point of our investigations concerned the development of a general procedure for the preparation of bicyclic systems containing the part structure 36 (Scheme 9; see also equation c of Scheme 6, p.7). Since reagents that are synthetically equivalent to the d,a-synthons 17 were envisaged to play a pivotal role in such an annulation procedure, our thinking was led by the retrosynthetic analysis shown in Scheme 9. A number of methods have been reported for the conversion of vinyl halides into organometallic reagents and bond forming reactions of the latter species by reaction with the carbonyl carbons of aldehydes and ketones are well known.\textsuperscript{18, 19, 20} Consequently, it was felt that the keto vinyl iodides 37 would be rational precursors of 36. In turn, the compounds 37 are easily accessible, in theory, from the corresponding keto vinylstannanes 38.\textsuperscript{21a} Previous work in our laboratories has described the preparation of the compounds 38 via the alkylation of ketones with the iodo vinylstannanes 39\textsuperscript{13}, which are synthetic equivalents of the d,a-synthons 17 (an example is shown in Scheme 7, p.8). Thus, with the compounds 38 in hand, and foreseeing little difficulty in preparing 37, the success of the proposed annulation procedure would depend critically on an effective method to achieve the conversion of 37 into 36.
2.1.2 Preparation of Cyclization Substrates.

With the initial goal of studying the cyclization of compounds of general structure 37, we set out to assemble a set of keto vinylstannane precursors. As was mentioned above, compounds of the general structure 38 have previously been prepared in our laboratories. Specifically, the preparation of the keto vinylstannanes 22, 40, 41 and 42 in equation 1 have, *inter alia*, been reported in connection with a related annulation study. In that study, the methylated compounds
41 and 42 had been prepared via silyl enol ether derivatives of 40 and 22 respectively. In the present case, we chose to prepare 41 and 42 by the method shown in equation 1. For example, treatment of a solution of ketone 22 in THF with potassium tert-butoxide and tert-butyl alcohol, followed by addition of methyl iodide, gave, after workup and flash chromatography of the crude product, a 48% yield of the methylated analogue 42. That this methylation had proceeded with the required site-selectivity was shown by the 400 MHz nmr spectrum of 42, which exhibited a new 3-proton singlet at δ 1.10. Compound 40 could be converted similarly into 41.

In order to allow investigation of the influence of conformational rigidity of the original ring on the stereochemical outcome of the proposed cyclization, two keto vinylstannanes containing the bulky tert-butyl group were also prepared (Scheme 10). Thus, in a manner entirely similar to the preparation of 22 and 40\textsuperscript{13}, the hydrazone 43 could be alkylated with the iodo vinylstannanes 39 to give, after hydrolysis of the hydrazone moiety, a mixture of the epimeric keto vinylstannanes 44 and 45 (n = 1; 63%) or 46 and 47 (n = 2; 59%). In the presence of sodium methoxide in methanol each of these epimeric mixtures could be equilibrated to a mixture containing largely the cis-disubstituted product. The cis compounds 45 and 47 are clearly more stable than their trans counterparts since both substituents occupy an equatorial orientation on the
ring. For example, after equilibration and flash chromatography of the mixture containing 44 and 45, these compounds were isolated in a ratio favouring 45 by 87:13. These epimers could be cleanly separated by chromatography and the overall yield of 45 from the dimethylhydrazone 43 was found to be 54%. Similarly, the ratio of 47 to 46 was 85:15 after the equilibration procedure. Clean chromatographic separation of these epimers could also be achieved and the overall yield of 47 from 43 was 49%.

Preparation of the keto vinyl iodides of general structure 49 from the above array of keto
vinylstannanes (general structure 48) proceeded without incident (Table 1). For example, dropwise addition of a dichloromethane solution of I	extsubscript{2} to a stirred solution of vinylstannane 40 in dichloromethane	extsuperscript{21} at room temperature gave, after workup and distillation of the crude product, the vinyl iodide 50 in 96% yield. The 400 MHz \textsuperscript{1}H nmr spectrum of compound 50 exhibited,

Table 1: Preparation of Keto Vinyl Iodides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>n</th>
<th>R</th>
<th>R	extsubscript{1}</th>
<th>R	extsubscript{2}</th>
<th>Product</th>
<th>Yield \textsuperscript{a}</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>1</td>
<td>H</td>
<td>-OCH\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}O-</td>
<td>50</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>1</td>
<td>Me</td>
<td>-OCH\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}O-</td>
<td>51</td>
<td>48% \textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>2</td>
<td>H</td>
<td>-OCH\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}O-</td>
<td>52</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>42</td>
<td>2</td>
<td>Me</td>
<td>-OCH\textsubscript{2}C(CH\textsubscript{3})\textsubscript{2}CH\textsubscript{2}O-</td>
<td>53</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>1</td>
<td>H</td>
<td>t-Bu</td>
<td>H</td>
<td>54</td>
<td>92%</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>2</td>
<td>H</td>
<td>t-Bu</td>
<td>H</td>
<td>55</td>
<td>95%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Yield of purified, distilled product

\textsuperscript{b} Refers to the yield over two steps: 40 \rightarrow 41 \rightarrow 51.
apart from the other expected resonances, two diagnostic multiplets for the vinyl protons at δ 5.72 and 6.05. These signals are significantly downfield from those of the corresponding resonances for the precursor vinylstannane 40 (δ 5.17 and 5.68) and confirm the replacement of the trimethyltin group at the vinyl carbon with the more electronegative iodine atom.

If a suitable cyclization procedure could be found, all of the above keto vinyl iodides would yield annulated products of the general structure 36 (Scheme 9), in which the newly formed ring would contain an exocyclic double bond. In order to examine briefly whether the proposed annulation sequence could be extended to the preparation of compounds containing an endocyclic double bond, we set out to prepare the keto vinyl iodide substrates 63 and 64 (Scheme 12). In the event that these compounds could be coaxed via appropriate procedures to yield bicyclic products, such products would contain a double bond inside the newly formed ring. Preparation of 63 and 64 could, presumably, be accomplished in a manner similar to that employed for the synthesis of compounds of general structure 49 (see Table 1), provided that a suitable bifunctional reagent could be prepared. Fortunately, previous studies from our laboratories had reported the preparation of vinylstannane alcohols similar in structure to 59 (Scheme 11). Thus, if 59 could be prepared, we needed only to replace the hydroxyl group of this compound with a chloride function in order to have access to a suitable bifunctional reagent (60) needed for the assembly of the keto vinyl iodides 63 and 64. Preparation of 60 (Scheme 11) commenced with the regio- and stereoselective addition of UtWum(phenylthio)(tri-/i-butylstannyl)cuprate to methyl 2-butynoate (57). Flash chromatography of the crude product and distillation of the resultant oil gave methyl (Z)-3-(tri-/i-butylstannyl)-2-butenoate (58) in 67% yield. Reduction of this material with DIBAL produced, in 99% yield, the vinylstannane alcohol 59. The required vinylstannane chloride 60 could now be accessed from 59 by overnight treatment of the latter material with triphenylphosphine in refluxing carbon tetrachloride. After workup and distillation of the crude material, 60 was isolated in 79% yield. The 300 MHz 1H nmr spectrum of this compound contained a 1-proton signal at δ 6.24 (t of q, J = 7.7, 1.6 Hz) attributable to the olefinic proton. Furthermore, associated with this signal were satellite signals characteristic of the three-bond
coupling of this proton with the $^{117}\text{Sn}$ and $^{119}\text{Sn}$ isotopes. That is, the magnitude of the coupling constant associated with this coupling ($^{3}J_{\text{Sn-H}} = 114$ Hz) indicated a trans relationship between this proton and the tin atom$^{24}$, thereby confirming the stereochemistry of the double bond present in 60.

![Scheme 11](image.png)

Preparation of the keto vinyl iodides 63 and 64 (Scheme 12) could now proceed in a manner similar to that used previously for the construction of compounds 50 to 55. Thus, utilization of the vinylstannane chloride 60 in the usual alkylation process$^{13}$ gave the keto vinylstannane 61 in 71% yield. Treatment of 61 with potassium tert-butoxide and tert-butyl alcohol in THF, followed by addition of methyl iodide resulted in a 40% yield of the methylated analogue 62. Compounds 61 and 62, upon brief treatment with iodine in dichloromethane, were smoothly converted into the respective keto vinyl iodides 63 and 64. The spectral characteristics of these materials were in good agreement with their assigned structures. The ir spectrum of 63, for example, exhibited
absorbances at 1715 and 1650 cm$^{-1}$, indicative of a ketone function and an iodo-substituted olefin function, respectively. Comparison of the 400 MHz $^1$H nmr spectra of these compounds revealed a 3-proton singlet ($\delta$ 1.19) in the spectrum of 64 which was not present in that of compound 63, giving evidence of the site-selective installation of the methyl substituent in 64.

![Chemical reactions and structures]

Scheme 12

At this point, the acceptor site of the bifunctional reagents 39 (see Scheme 9 and Scheme 10) and reagent 60 (Scheme 11) had been exploited in the preparation of a range of keto vinyl
iodides. The efficient exploitation of the potential donor site of these reagents was crucial to the success of the cyclization studies that followed.

2.1.3 Cyclization Studies.

As was mentioned in section 2.1.1, there are a number of reports in the literature that deal with the preparation of organometallic reagents from vinyl halides and the subsequent addition of the former species to carbonyl functions. A suitable procedure of this kind would allow the cyclization of the keto vinyl iodides described in the previous section, giving rise to bicyclic structures containing an allylic, angular hydroxyl group.

The first candidate chosen for a practical investigation of these speculations was the keto vinyl iodide 52 (Scheme 13). An initial attempt was made at effecting the desired transformation by an intramolecular Barbier reaction. However, treatment of 52 with magnesium metal in refluxing THF gave, as the major component, the uncyclized product of proto-deiodination (65). Under these reaction conditions reductive processes were clearly favoured over the desired cyclization.

Attention was next turned to the possibility of achieving the cyclization by the simple expedient of using an alkyllithium at low temperature to effect halogen-metal exchange at the vinyl iodide center. Despite fears that the highly nucleophilic character of n-butyllithium might cause unwanted interactions with the carbonyl function of 52, it was gratifying to find that, on addition of ~2.5 equivalents of this reagent to a solution of compound 52 at -78 °C in THF, smooth cyclization had taken place. Workup and flash chromatography of the crude material delivered the bicyclic allylic alcohols 66 and 67 in 79% yield. Careful integration of a ^1H nmr spectrum of the mixture of these two compounds indicated that the ratio of 66 to 67 was 15 : 1. A small amount (~10%) of the uncyclized compound 65 was also isolated.
Evidence that 66 and 67 were indeed materials derived from the desired cyclization came from a variety of spectral data. The ir spectra of both compounds contained absorptions in the range 3610-3440 cm$^{-1}$ attributable to a hydroxyl group, while carbonyl absorptions (1713 cm$^{-1}$ for the starting material 52) were absent. The 400 MHz $^1$H nmr spectra of 66 and 67 each exhibited two broad one-proton singlets for the vinyl protons ($\delta$ 4.75 and 4.80 for 66 and $\delta$ 4.86 and 5.00 for 67). On the other hand, the spectrum of the uncyclized compound 65 contained three vinyl proton resonances ($\delta$ 4.80-4.93 (m, 1H), 4.95-5.15 (m, 1H) and 5.53-6.02 (m, 1H)). Despite this good evidence that the cyclization had indeed been successful, none of the recorded data provided conclusive evidence for the stereochemistry at the ring junction of these compounds. The major product 66, however, proved to be a crystalline solid and could be recrystallized from
hexane/diethyl ether (mp 157-158 °C). A single crystal X-ray analysis\textsuperscript{25a} (Appendix 1) showed conclusively that this material possessed a trans ring fusion (Figure 1). Thus, the cyclization reaction had given rise mainly to a trans-fused bicyclic product while a minor pathway for this reaction had produced the cis-fused compound 67.

Encouraged by this result, the generality of this annulation procedure was investigated by subjecting the remaining keto vinyl iodides to the above reaction conditions.\textsuperscript{26} Table 2 contains a summary of the cyclization results achieved with the compounds 50 to 55 (general structure 49) to give bicyclic products of general structure 68 and/or 69.

It is clear from the results obtained with the keto vinyl iodides 50, 51 and 54 (entries 1, 2 and 5) that five-membered ring annulations are also possible by this method. In the case of substrate 50, for instance, cyclization gave rise (69\% yield) to both cis and trans products
Table 2: Cyclization Reactions of Keto Vinyl Iodides.

\[
\begin{array}{c|cc|cc|cc|c|c}
\text{Entry} & \text{Substrate} & n & R & R_1 & R_2 & \text{Product(s)}^a & \text{Stereochemistry} & \text{Yield(\%)}^b \\
\hline
1 & 50 & 1 & H & -OCH_2C(CH_3)_2CH_2O- & & 70 & \text{trans} & 38 \\
& & & & & & 71 & \text{cis} & 31 \\
2 & 51 & 1 & Me & -OCH_2C(CH_3)_2CH_2O- & & 72 & \text{cis} & 83 \\
3 & 52 & 2 & H & -OCH_2C(CH_3)_2CH_2O- & & 66 & \text{trans} & 71 \\
& & & & & & 67 & \text{cis} & 5 \\
4 & 53 & 2 & Me & -OCH_2C(CH_3)_2CH_2O- & & 73 & \text{cis} & 74 \\
5 & 54 & 1 & H & t-Bu & H & 74 & \text{trans} & 45 \\
& & & & & & 75 & \text{cis} & 33 \\
6 & 55 & 2 & H & t-Bu & H & 76 & \text{trans} & 75 \\
\end{array}
\]

\(^a\) A small amount (between 4% and 13%) of the un cyclized product of proto-deiodination (compare 65 in Scheme 13) was also isolated in each case.

\(^b\) Refers to yields of isolated, purified products.

containing new five-membered rings (70 and 71), with the trans compound 70 being slightly favoured. A similar result was obtained with the conformationally biased substrate 54 (entry 5), which gave the corresponding trans- (74) and cis-fused (75) bicyclic products in a combined yield.
of 78%. When the R substituent is a methyl group (entry 2), only the cis-fused product 72 (83%) was obtained.

It is pertinent to note explicitly that, for the formation of both five- and six-membered rings \((n = 1 \text{ or } 2)\), cyclization of the substrates in which \(R = \text{Me} (51 \text{ and } 53)\) produced the corresponding cis-fused products 72 and 73 exclusively. On the other hand, ring closure of substances in which \(R = \text{H}\) showed varying degrees of preference for the trans-fused product. When \(n = 1\) (50 and 54) this preference was rather small (70 over 71 and 74 over 75). With \(n = 2\), however, (52 and 55) the trans product was either greatly favoured (66 over 67, see Scheme 13) or formed exclusively (76).

The stereochemistry of the cyclized products was assigned by use of a variety of methods.
The stereochemistry of products 70 and 71, for instance, was determined on the basis of the transformations shown in Scheme 14. Conversion of compound 50 into the corresponding enol silyl ether 77 was achieved by use of a standard method. Treatment of 77 with $n$-Bu$_3$SnH and azobisisobutyronitrile (AIBN) in refluxing benzene, followed by reaction of the resultant crude mixture with $n$-Bu$_4$NF (TBAF) in THF, gave a radical cyclization product (56% yield after workup and column chromatography of the crude product) that was spectroscopically identical with 71. On the basis of literature precedents and examination of molecular models, there is little doubt that the radical cyclization of 77 would produce a cis-fused bicyclo[4.3.0]nonane system and, therefore, the stereochemical assignments with respect to compounds 70 and 71 were secure.

Figure 2: Stereoview of the Allylic Alcohol 72.

Compound 72, the single cyclized product obtained in 83% yield from treatment of 51 with 2.5 equivalents of $n$-BuLi in THF (-78 °C), could be recrystallized from hexane/diethyl ether and
exhibited mp 99-102 °C. This crystalline material was subjected to a single crystal X-ray analysis\textsuperscript{25a} (Figure 2), which showed that 72 contains a cis-fused bicyclic structure.

The cis stereochemistry of product 73 could be established from an interesting $^1$H nmr experiment conducted on its methyl ether derivative 78. The latter material was easily obtained by treatment of a THF solution of 73 with sodium hydride, followed by reaction of the resultant alkoxide with methyl iodide. In the $^1$H nmr spectrum of 78 recorded at room temperature, the signals due to the olefinic protons, the -OMe function, the angular methyl group and other resonances appeared as broad, unresolved peaks (Figure 3). However, when the spectrum was recorded at -10 °C (Figure 4) and then again at -30 °C (Figure 5), a progressively better resolved spectrum was obtained and at -30 °C, it was clear that two conformational isomers, in a ratio of $\sim 3 : 2$, were present. The conformationally mobile cis-fused compound 78 could give rise to these peculiar spectral characteristics via conformational "flipping" between the conformational isomers 78a and 78b. A careful inspection of molecular models shows that the observed 3 : 2 ratio of these isomers seems reasonable on the basis of conformational analysis. Thus, in terms of

![Figure 3: The 300 MHz $^1$H nmr Spectrum of Methyl Ether 78 at 20 °C in CDCl$_3$.](image)
Figure 4: The 300 MHz $^1$H nmr Spectrum of Methyl Ether 78 at -10 °C in CDCl$_3$.

Figure 5: The 300 MHz $^1$H nmr Spectrum of Methyl Ether 78 at -30 °C in CDCl$_3$. 
steric interactions, conformer 78a contains one 1,3 diaxial interaction, five 1,3 syn-axial interactions and two interactions between an axial methylene group and the sp$^2$ center. A quite similar pattern of steric interactions is present in 78b, namely, one 1,3 diaxial interaction, six 1,3 syn-axial interactions and one interaction between an axial methyl group and the sp$^2$ center. It is therefore reasonable to assume that the observed isomer ratio is indeed due to the two chairlike conformers of the cis-fused methyl ether 78.

At room temperature, the conformational flipping apparently takes place at a rate which closely approaches the nmr time scale. This causes broadening of the signals since the spectrometer records an average of the signal positions for the two conformational isomers present in solution. At lower temperatures, conformational flipping is slowed to a rate which is significantly slower than the nmr time scale, causing broadening to disappear, and the resolution of signals due to both of the conformational isomers 78a and 78b. It is highly unlikely that such
features could be derived from the conformationally much more rigid trans-fused isomer 73a, which cannot undergo the above conformational flipping. Consequently, the stereochemistry of the sole product obtained from cyclization of 53 could be assigned with confidence as being cis (compound 73, table 2).

The cyclization reaction of 54 gave rise to the compounds 74 and 75. The ring-fusion stereochemistry of the latter materials could be assigned due to the similarity of their $^1$H nmr spectra to those of the analogous trans/cis pair 70 and 71. For example, the chemical shifts of the broad triplets ($J \approx 2$ Hz) due to the olefinic protons of the trans-fused compound 70 and those of compound 74 ($\delta$ 4.85, 4.99 and 4.84, 4.99, respectively) are very similar. Furthermore, this same pair of resonances for the cis compound 71 and compound 75 ($\delta$ 5.01, 5.10 and 5.01, 5.07, respectively) are similarly alike. Compounds 74 and 75 can therefore confidently be assigned as possessing, respectively, trans and cis ring junction stereochemistry.

The last entry in Table 2 reports the cyclization of compound 55 to give the trans bicyclo[4.4.0]decane derivative 76 in a yield of 75%. Comparison of the $^1$H nmr spectrum of this material with that of the only other trans bicyclo[4.4.0]decane derivative in the table (compound 66) shows the following significant correlations:

66: $\delta$ 2.16 (br d, 1H, $J = 12$ Hz), 2.50 (t of d, 1H, $J = 14$, 5 Hz), 4.75 and 4.80 (br s, br s, 1H each, vinyl protons).

76: $\delta$ 2.15 (br d, 1H, $J = 13$ Hz), 2.52 (t of d, 1H, $J = 15$, 5 Hz), 4.74 and 4.79 (br s, br s, 1H each, vinyl protons).
Since the trans geometry of compound 66 had been established by X-ray analysis, the above similarities no longer left the stereochemistry of 76 in doubt.

An interesting observation concerning the cyclization of the t-butyl-substituted substrates 54 and 55 is that these reactions required only slightly more than one equivalent of n-BuLi in order to go to completion. In contrast, the reactions of the ketal containing substrates required just over two equivalents of this reagent. Thus, in the case of substrates 50, 51, 52 and 53, use of less than 2 equivalents of n-BuLi gave back some starting material. Presumably, reaction of n-BuLi with these substrates gives the corresponding vinyl lithium species (which cyclizes) and n-BuI. Apparently, in these cases, the rate of the reaction of n-BuLi with n-BuI (to give octane) is competitive with that of the initial lithium iodine exchange process. On the other hand, since substrates 54 and 55 required only one equivalent of n-BuLi, the lithium iodine exchange in these cases must be considerably faster than the reaction of n-BuLi with n-BuI. The reasons for this presumed difference in the rate of exchange of iodine for lithium at the vinyl site as a function of the substrate substituents (t-butyl vs. spiroketal) are not clear.

An alternative explanation (which subsequent work showed to be tenuous at best, see p. 66) is that, in the case of the ketal containing cyclization substrates, the first equivalent of n-BuLi is complexed by the two oxygen atoms of the ketal moiety, making it unavailable for the lithium-iodine exchange process. A second equivalent of this reagent is thus necessary for the exchange reaction and subsequent cyclization to proceed. The absence of oxygen containing functionalities in the substrates with tert-butyl substituents therefore means that only one equivalent of n-BuLi is required in these cases.

A rationalization of the stereochemical outcome of the cyclization reactions summarized in Table 2 would be best served by starting with the reaction leading to the product 76 (Table 2, entry 6). An assumption throughout this discussion will be that conformers such as 79a (Scheme 15) are discrete intermediates in the cyclization reactions. Thus, substrate 55 should give rise to the intermediate 79 upon treatment with n-BuLi. In this case, the stericly demanding t-butyl substituent precludes the existence of the diaxially substituted conformer 79b. Cyclization should
thus take place only from the conformer 79a in which both substituents are equatorially disposed. When the intermediate is in the favoured conformation 79a, the vinyllithium moiety may attack the carbonyl carbon from either the axial or the equatorial direction. Axial attack from this conformer would yield the cis-fused compound 80 (pathway ii). Axial attack is disfavoured, however, since the transition state (which should resemble structure A in Scheme 15) in this case would be destabilized by 1,3 steric interactions with the indicated hydrogen atoms oriented
axially on the ring. Since equatorial attack does not suffer from this disadvantage, pathway i in the scheme is favoured exclusively, giving the trans-fused compound 76 as the only product. Axial attack via pathway ii does, therefore, not occur.

The results summarized above have interesting implications for the cyclization of compound 52 (Scheme 16). In this reaction both a trans-fused product (66) and a cis-fused product (67) were formed. It will be recalled that 66 was favoured over 67 by a ratio of 15 : 1. If, by analogy to the above discussion, conformer 81a does not cyclize via pathway ii, then the

Scheme 16
minor product 67 could only have been formed from conformer 81b via pathway iii (equatorial attack, Scheme 16). This, in turn, implies that the ratio of the products formed from this reaction (66 : 67, 15 : 1) reflects to some extent the equilibrium ratio of the conformers 79a and 79b under the given reaction conditions. Such a result correlates well with the reasonable assumption that the conformation in which the vinyllithium-containing substituent occupies an equatorial orientation (81a) will be favoured to a significant extent over the alternative conformation in which this substituent is axially oriented and therefore experiences a 1,3 diaxial interaction with a ketal oxygen substituent (81b).

In summary, some general conclusions for the two above systems are:

1) When the vinyllithium containing substituent is equatorially oriented, equatorial attack (giving a trans-fused product) proceeds to the exclusion of axial attack (which would yield a cis-fused product).

2) From this follows that when a cis-fused product is observed, it is a consequence of equatorial attack from a conformation in which the vinyllithium containing substituent is oriented axially.

When a methyl group is appended to the α-position of the cyclization substrate (compound 53 in Table 2), it is no longer possible to predict with confidence which of the two chairlike conformations (82a and 82b, Scheme 17) of the vinyllithium intermediate will be favoured. This is because both conformations now have two axial and two equatorial substituents. The cyclization reaction of 53, however, gave the cis-fused compound 73 as the sole cyclization product. If conclusions 1) and 2) above are taken to be valid also for the cyclization of 53, this result would indicate the sole operation of cyclization pathway iii (Scheme 17). It would also demand an explanation of the non-operation of pathway i. Equatorial attack from conformation 82a is disfavoured because the incoming nucleophile must approach the carbonyl carbon from the same side of the ring as that on which the axially oriented methyl group is located. If the angle of approach of the nucleophile to the plane of double bond is taken to be ~109° 30, molecular models show that a large gauche interaction develops during this approach (dihedral angle = <30°).
Although a gauche interaction is also implicated between the incoming nucleophile and the (equatorially oriented) methyl group during attack from conformation \textit{82b}, molecular models demonstrate convincingly that this interaction is now rather small (dihedral angle >90°). Due to this significant difference in the steric demands encountered by the nucleophile during its approach to the carbonyl group, pathway iii is favoured over pathway i. The cis-fused compound \textit{73} is thus the only bicyclic product isolated from the cyclization reaction of \textit{53}. 

\textbf{Scheme 17}
In the cyclization reactions which yield new five-membered rings, the effects of ring strain, in addition to the steric effects discussed above, must be considered. A rationale regarding the stereochemical outcome of the cyclization of the substrate 54 is similar to that discussed earlier for the ring closure of 55 (see Scheme 15). Thus, treatment of the keto vinyl iodide 54 with n-BuLi produces a vinyl lithium intermediate for which the conformer 84b is precluded by the bulky tert-butyl substituent (Scheme 18). Thus, it is highly likely that cyclization can occur only
from conformer $84a$ via pathway i and/or pathway ii in Scheme 18. Since product $74$ was isolated in 45% yield and $75$ in 33% yield (ratio of $1.4 : 1$), it is clear that some preference for pathway i does indeed exist. It will be recalled from Scheme 15, however, that in the cyclization of compound $55$ only the trans-fused product $76$ was formed and thus cyclization proceeded only via pathway i. In the present case both pathways i and ii are clearly operative, despite the fact that axial attack via pathway ii suffers the axial interactions with the indicated hydrogen atoms (see B) that were invoked for the ring closure of $55$. This difference in behaviour is explicable by taking into account the developing ring strain which is present when the vinyllithium nucleophile approaches the carbonyl carbon during the formation of a new five-membered ring, but not in the case of a six-membered ring. Explicitly, molecular models show that, for cyclization from conformer $84a$, the transition state for approach of the nucleophile to the equatorial face of the carbonyl carbon suffers from considerable angle strain within the forming five-membered ring. Such strain is largely absent in the transition state for approach to the axial face. The strain in the former partly offsets the previously mentioned preference for equatorial attack and causes both pathways i and ii to operate in this case. Apparently, the effect of this difference in developing ring strain is not quite as large as the effect of the steric 1,3 axial interactions associated with axial attack, and pathway i is therefore still slightly favoured. Product $74$ is thus favoured over product $75$ by a ratio of $1.4 : 1$.

In light of the above observations, the cyclization results achieved with compound $50$ are easily understood. Cyclization of $50$ gave the trans-fused product $70$ and the cis-fused product $71$ in a ratio of $1.2 : 1$. Here the conformation in which the vinyllithium-containing substituent occupies an equatorial orientation ($85a$) will be favoured to a significant extent over the alternative conformation $85b$ in which this substituent is axially oriented (Scheme 19). If only pathways i and ii were operating, the ratio of $70$ to $71$ would be expected (from the discussion of the cyclization of $54$, Scheme 18) to be about $1.4 : 1$. That the actual ratio is $1.2 : 1$ appears to indicate that $71$ is also formed via pathway iii. If the $15 : 1$ ratio of conformers $81a$ to $81b$ in Scheme 16 is taken also as the ratio of conformers $85a$ to $85b$ in the present case, a simple
calculation reveals that the contribution of conformer 85b (via pathway iii) to the relative yield of compound 71 should change the 1.4 : 1 ratio observed for trans- to cis-fused products in Scheme 18, to a ratio of 1.2 : 1 in the present case. This is precisely what is experimentally observed and provides some vindication of the arguments presented so far. In this case, therefore, it appears that all three pathways are operative.

A discussion of the cyclization of the last remaining substrate in Table 2, compound 51, will benefit from some of the conclusions that have been drawn so far (Scheme 20). Firstly, as in
Scheme 17, the addition of an α-methyl group makes both conformers 86a and 86b more or less equally favoured. Since a trans-fused product was not isolated in this case, pathway i was not followed. This is not surprising, since two quite severe impediments would be operational. The

first is the same type of strong gauche interaction invoked in pathway i of Scheme 17, due to the axial methyl substituent. The second is the developing ring strain equivalent to that mentioned for pathway i of Scheme 18 and which is characteristic of the formation of trans-fused five-membered ring systems of this type. Pathway ii, on the other hand, experiences less...
pronounced developing ring strain, just as in pathway ii of Scheme 18. Although no gauche interaction is present here, this pathway is destabilized by the 1,3 axial interactions also seen to make pathway ii in Schemes 15 and 16 untenable. Although this pathway was still invoked (despite the 1,3 axial interactions) in the cyclizations leading to five-membered rings in Schemes 18 and 19, a more favourable option is now available via the significantly populated conformer 86b. Pathway iii via this conformer suffers a much less severe gauche interaction than that encountered in pathway i (see Scheme 17) as well as the lesser of the two types of developing ring strain (i.e. cis ring formation rather than trans ring formation; see Scheme 18). Pathway iii thus seems to be principally responsible for the sole formation of the cis-fused product 72 in this cyclization reaction.

The methodology described above could also be applied, albeit with diminished success, to the preparation of substances in which the carbon-carbon double bond of the product is endocyclic rather than exocyclic. In Scheme 12 (p. 19) the preparation of two keto vinyl iodide precursors required for such a process had been illustrated. Substrates 63 and 64 were subjected to reaction conditions similar to those required for cyclization of the substrates listed in Table 2 (Scheme 21). However, treatment of 63 with 2.5 equiv. of n-BuLi in THF at -78 °C resulted in a complex mixture of products. Use of other alkyllithiums such as t-BuLi, different solvents (pentane, diethyl ether) or additives (HMPA, BF₃·Et₂O) did not prove to be helpful in producing clean cyclization to give the desired product (87a). In contrast, the methyl substituted analogue 64 could be cleanly cyclized to produce a single bicyclic allylic alcohol 87b. Use of a reaction temperature slightly higher than that used in the previous studies served to raise the isolated yield of the product from 53% (at -78 °C) to 76% (at -63 °C). Successful cyclization was evidenced by the presence of an O-H stretch in the ir spectrum of compound 87b at 3460 cm⁻¹, as well as by the absence of a carbonyl absorbance (the starting material 64 contained a carbonyl stretch at 1710 cm⁻¹). Furthermore, while the protons of the vinyl methyl group in the 400 MHz ¹H nmr spectrum of 64 appeared at δ 2.51 as a broad three-proton singlet, these protons in the ¹H nmr spectrum of the cyclized product 87b were evidenced as a doublet at δ 1.71 (J = 2 Hz).
Since the carbon-carbon double bond in this product is now inside the five-membered ring, the cis-fused nature of 87b was never in doubt. Molecular models show convincingly that, for this system, approach of the vinyllithium moiety to the face of the carbonyl double bond which would cause formation of a trans-fused bicyclic system is severely constrained by developing ring strain. Approach of the nucleophile to the alternative face, on the other hand, is relatively strain-free. A single, cis-fused bicyclic product therefore resulted from this reaction.

The failure of the cyclization of compound 63 requires some comment. It can be speculated that the lithium iodine exchange reaction of 63 and 64 is somewhat slower than the corresponding reaction involving the substrates listed in Table 2. This is reasonable since, for 63 and 64, the exchange takes place at a 1,1,2-trisubstituted double bond, while the substrates in Table 2 contain 1,1-disubstituted double bonds. The higher substitution pattern thus causes greater steric hindrance in the approach of the reagent to the substrate and, consequently, a reduction in reaction
rate. At this slower rate, other processes involving the n-BuLi reagent may compete with the exchange process, such as addition of this reagent to the carbonyl carbon. In the case of substrate 63, for instance, this addition reaction might be at the root of the failure to observe the desired cyclization. Compound 64, on the other hand, can still undergo successful cyclization because the competition of the above two processes is once again tilted in favour of the desired exchange reaction. In this instance the rate of addition of n-BuLi to the carbonyl carbon is slowed by the presence of a sterically demanding quarternary center adjacent to the carbonyl site. The lithium-iodine exchange process thus wins out, and cyclization proceeds. In contrast, since the position adjacent to the carbonyl carbon in 63 is merely tertiary and thus sterically less crowded, the addition reaction now wins out, and cyclization fails.
2.2 Total Synthesis of the Diterpenoid (+)-Ambliol B.

2.2.1 Introduction.

It is highly likely that the clerodane diterpenoids (general carbon skeleton 91) are biogenetically derived from the labdanes (carbon skeleton 89). While 89 retains the "original" isoprenoid arrangement present in geranylgeraniol (88), 91 can be formally obtained from 89 via a series of 1,2-shifts. Thus, the methyl group attached to carbon 10 in 89 is shifted to carbon 9 in 91, while one of the methyl groups on carbon 4 in 89 is shifted to carbon 5 in 91. Interestingly,
there are a small number of diterpenoids$^{32,16}$ that possess a carbon framework (general carbon skeleton 90) which, in terms of biogenetic rearrangement, lies between the labdane and clerodane skeletons. Compounds which possess this carbon skeleton (for which the name "isolabdanes" has been suggested$^{32c}$) have thus undergone only one 1,2 methyl shift when compared with the labdanes, namely from carbon 10 to carbon 9.

A number of natural products with the isolabdane carbon skeleton are illustrated on this page. It is most interesting that these materials, despite the relative rarity of the isolabdane skeleton, originate from both terrestrial and marine sources. Koanophyllic acid A (93), for example, was isolated from the aerial parts of Koanophyllon conglobatum, a plant indigenous to Brazil.$^{32d}$ Agelasimine A and B (92a and 92b), on the other hand, were isolated recently$^{32a}$ from...
an orange marine sponge, *Agelas mauritiana*, which was collected from Enewetak Atoll at 15-m depths. The *Dysidea* species of marine sponges have proven to be a rich source of a variety of secondary metabolites, including chlorinated and brominated materials and sulfur-containing sesquiterpenes.\(^{16a}\) Recently, Faulkner reported the first isolation of diterpenes from a *Dysidea* species.\(^{16}\) Ambliol B and C (94 and 95) were isolated from *Dysidea amblia*, which had been collected at 30-m depth at Scripps Canyon, La Jolla, CA. Ambliol B was one of the major metabolites obtained from a methanolic extract of the sponge.

From a synthetic viewpoint, the fact that ambliol B contains a tertiary, angular hydroxy group adjacent to a quarternary centre is particularly noteworthy. It was hoped that the new annulation sequence discussed in section 2.1 of this thesis could be instrumental in assembling this arrangement of functionality during an attempted synthesis of this interesting diterpenoid. As far as could be ascertained from a perusal of the literature, none of the natural products possessing an isolabdane carbon skeleton had yielded to total synthesis prior to our efforts. It is nevertheless important to take careful note of synthetic precedents that may have been set by others during the construction of materials that are similar in structure to ambliol B. A recent report by Tokoroyama detailing the synthesis of (+)-maingayic acid (a member of the clerodane diterpenoids, which differ from the isolabdanes by the position of a single methyl substituent, *vide supra*) provided such an opportunity.\(^{33}\) As can be seen, maingayic acid (104, Scheme 22) and ambliol B (94) have the same relative stereochemistry at their four respective chiral centres, as well as having the position of two methyl substituents and a furan-containing side chain in common. A brief review of the total synthesis of 104 (Scheme 22) would therefore be instructive.

Tokoroyama’s synthesis commenced with a copper(I)-catalyzed 1,4-addition of vinylmagnesium bromide to 3,4-dimethyl-2-cyclohexen-1-one (96) (Scheme 22). This installed, with the correct relative stereochemistry, the two-carbon appendage onto which the furan ring was to be attached later. The enolate anion intermediate formed by the above procedure was captured with formaldehyde, giving the hydroxy ketone 97 as a diastereomeric mixture. A key
Scheme 22
part of Tokoroyama’s synthetic strategy now followed, namely the assembly of the second ring, followed by the installation of the remaining quarternary stereocenter. Thus, the labile mesylates 98 derived from 97 were allowed to react with methyl 3-oxopentanoate in the presence of sodium methoxide. The so-formed product underwent hydrolysis, decarboxylation and aldol condensation upon exposure to hydrochloric acid in refluxing methanol, producing the bicyclic enone 99 in 79% yield from 98. At this point, three of the four chiral centres of the target compound had been installed with the required relative stereochemistry. The fourth chiral centre was installed by treatment of the enone 99 with diethylaluminum cyanide. It is noteworthy that the transfer of the cyano moiety to the β-carbon of the fully substituted enone functionality proceeded with complete stereoselectivity and in a yield of 83%. The cyano ketone thus produced was converted into the cyano ketal 100. Standard techniques were employed for the transformation of the vinyl group into the CH₂CHO moiety. Attachment of the required furan ring was accomplished by treatment of compound 101 with 3-furyllithium in diethyl ether. The resulting secondary alcohol was deoxygenated via reductive cleavage of the acetate derivative, giving the cyano furan 102. The full carbon skeleton of (+)-maingayic acid had now been assembled with the correct stereochemistry and only standard manipulation of functionality remained. Hydrolysis of the ketal group, followed by ketone reduction with L-Selectride, produced an α-axial secondary alcohol, which underwent regioselective dehydration in the presence of POCl₃ to yield the cyano olefin 103. The cyano group in 103 was converted into an aldehyde through the reductive action of diisobutylaluminum hydride followed by hydrolysis of the resulting imine. Finally, oxidation of the aldehyde was accomplished with a buffered solution of sodium chlorite containing 2-methyl-2-butene as a chlorine scavenger, giving (+)-maingayic acid in 21% yield from the aldehyde.
2.2.2 Retrosynthetic Analyses and Model Studies.

The basis of the synthetic plan that we wished to implement for a total synthesis of (+)-ambliol B (94) was rooted in the annulation method discussed in section 2.1 of this thesis. Against this background, even a cursory glance at the structure of this interesting marine diterpenoid made it clear that, in a retrosynthetic sense, one of the first tasks would be the

functional group interconversion of the gem-dimethyl moiety into an exocyclic carbon-carbon double bond. Furthermore, replacement of the furan-containing side-chain with some suitable substituent R gives the simplified bicyclic structure 105 which contains an allylic, angular
hydroxyl group (Scheme 23). Disconnection of the indicated bond in 105 leads to the key keto vinyl iodide 106. It will be recalled from the results of the cyclization reactions discussed in section 2.1.3, that cyclizations of keto vinyl iodides leading to new six-membered rings (n = 2) in which the substituent R = H (cf. substrates 52 and 55 in Table 2, p. 24) gave the trans-fused product predominantly (cf. product 66) or exclusively (cf. product 76). It was therefore with some confidence that the cyclization, under similar conditions, of a compound such as 106 was foreseen to produce a trans-fused bicyclo[4.4.0]decane 105. A conformational representation of 106 reveals that the vinyl iodide-containing side-chain attached to the ring with the required stereochemistry would occupy an equatorial orientation. In this conformation, the six-membered ring has three equatorially oriented substituents and one axially oriented substituent, which is a more stable than the alternative conformation which would have, conversely, three axially oriented and one equatorially oriented substituent. Since this substituent is adjacent to a ketone function, one could presume that the required stereochemistry would be accessible via an acid- or base-catalyzed equilibration procedure. A compound with the alternative stereochemistry at carbon two (epimer of 106) would clearly be less stable than 106, since the six-membered ring would then contain two axially oriented and two equatorially oriented substituents.

If all of the foregoing strategies were destined for success, the requirements of the synthesis would be reduced to a practicable preparation of a synthetic intermediate such as 106. Two possible approaches towards this goal are illustrated in retrosynthetic form in Scheme 24. The most obvious simplifying disconnection of 106 that represented itself is shown by route a), by which one arrives at an enolate of the type 107 and the bifunctional alkylating agent 21, previously encountered in Scheme 7 on p. 8. Thus, in the annulation sequence leading from 107 in Scheme 24 to 105 in Scheme 23, the the bifunctional reagent 21 would serve as a synthetic equivalent of the 1-pentene d2,a5-synthon 108. A foreseeable problem with the route a) disconnection, however, was that it required alkylation to take place at a centre which is adjacent to a quarternary centre in 107. Steric interactions might prevent the successful alkylation of 107 with a relatively unreactive alkylating agent such as 21.
An alternative disconnection (route b) yields the enone 109. Since the β-carbon of the α,β-unsaturated ketone moiety in 109 is now an acceptor center, a bifunctional reagent containing two donor centres would be required for the overall annulation process leading to 105. A new
bifunctional conjunctive reagent, the vinylgermane cuprate 110, was developed expressly for this purpose (*vide infra*). It is a synthetic equivalent of the 1-butene $d^2,d^4$-synthon 111.

The above retrosynthetic simplifications have thus led to the monocyclic structures 109 and/or 107. Enone 109 may, however, conceivably be derived from 107 by the reaction of the latter species with a reactive one-carbon electrophile. Such an electrophile would have to be sufficiently reactive to overcome the severe steric constraints mentioned previously. Ultimately, therefore, the retrosynthetic analysis indicates the preparation of an enolate such as 107. If a vinyl group is chosen as the substituent $R$ and a silyl enol ether as the precursor of the enolate function, the initial task in the synthesis of (+)-ambliol B is seen to be the preparation of compound 112.

Model studies were performed to test the feasibility of some of the transformations suggested by the retrosynthetic plan outlined in Schemes 23 and 24. It was especially important to gain some experience of the chemistry that was planned for the later stages of the synthesis. Firstly, we were interested in investigating the preparation of a model compound containing the *gem*-dimethyl moiety adjacent to an angular hydroxyl group from a bicyclic model with an allylic, angular hydroxyl function. This is one of the transformations suggested in Scheme 23 in going from 105 to the target compound 94. The trans-fused bicyclic allylic alcohol 66 (see Scheme 13, p. 22), prepared during the annulation studies (section 2.1), seemed an appropriate candidate for such an investigation (Scheme 25).

More than twenty years ago, Furukawa and co-workers published an improved, modified variation of the classic Simmons-Smith procedure$^{34}$ for the cyclopropanation of olefins.$^{35}$ In this variation, diethylzinc substitutes for the usual zinc-copper couple required for this procedure. A few years later, investigations by Miyano gave evidence of the striking rate acceleration of this reaction in the presence of oxygen.$^{36}$ Thus, treatment of a dichloromethane solution of 66 with diiodomethane-diethylzinc in an oxygen atmosphere afforded (69%) the cyclopropane 113. This crystalline material (mp 113-114 °C) exhibited four characteristic high field multiplets in its 400 MHz $^1$H nmr spectrum ($\delta$: 0.05-0.13, 0.20-0.29, 0.51-0.63 and 0.63-0.70), indicative of the
protons on the cyclopropane ring. It was gratifying to find that cleavage of the cyclopropane moiety in 113 could be achieved in the presence of the other potentially reactive functional groups (tertiary alcohol, ketal). Thus, hydrogenolysis of 113\textsuperscript{7,37} under carefully controlled conditions ($H_2$ (1.5 atm.), $PtO_2$, dry acetic acid, room temp., 55 min.) provided (60\%) the alcohol 114, mp 76-78 °C. The $^1H$ nmr spectrum (400 MHz, CDCl$_3$) of 114 exhibited four three-proton singlets ($\delta$ 0.91, 0.94, 0.97 and 0.99) for the the four tertiary methyl substituents present in this material.

Importantly, use of higher hydrogen pressures and/or longer reaction times gave mixtures of the desired product 114 and the diol ether 115. For example, treatment of 113 with three atmospheres of $H_2$ for two hours but under otherwise similar conditions to those given above, gave 114 and 115 in a ratio of ~1 : 2, respectively. The structure of 115 was evident from its 400 MHz $^1H$ nmr spectrum which exhibited the resonances of five protons in that region of the spectrum indicating the presence of protons adjacent to an oxygen function: $\delta$ 3.12-3.23 (m, 1H,
H, \( w_{1/2} = 26 \text{ Hz} \), 3.33 (s, 2H), 3.44 (d, 2H, \( J = 5 \text{ Hz} \)). Additionally, a broad one-proton triplet at \( \delta 3.01 \), which disappeared on addition of \( D_2O \), confirmed the presence of a primary hydroxyl group. Interestingly, compound 115 was isolated as a single diastereomer with the indicated stereochemistry at the ring carbon atom adjacent to the ether oxygen function. The relative stereochemistry at this site was readily deduced from the width at half height of the \( ^1H \) nmr signal of the proton labelled H\( _a \) in the sketch. The \( w_{1/2} \) value of this multiplet is 26 Hz (vide supra), indicating the presence of (a) diaxial coupling(s). This proton must therefore be axially oriented on the ring.

Having thus shown the viability of this part of the synthetic strategy, attention was turned to a model study of what was envisioned to be the final stage in the synthesis, namely the attachment of the furan ring. Part of the synthetic plan during this stage called for the R group in the structure 105 (Scheme 23) to be a hydroxyethyl substituent. Compound 116\(^{38} \) (Scheme 26) was therefore chosen as a suitable model for this investigation. Oxidation of 116 proceeded without incident, giving the aldehyde 117 in good yield (91\%). This compound was, however, quite unstable and was thus used without delay in the next step. Tokoroyama's protocol\(^{33,39} \) could now be followed. Thus, treatment of 117 with 3-lithiofuran\(^{40} \) in diethyl ether (\(-78 ^0\text{C}\)) gave the secondary alcohol 118 (70\%). The presence of an alcohol function was indicated by an absorbance at 3389 cm\(^{-1}\) in the ir spectrum of 118. Furthermore, the presence of the furan ring was confirmed by the appearance of signals (\( \delta 6.43 \text{ (m, 1H)} \) and 7.38 (m, 2H)) in the vinyl/aromatic region of the 400 MHz \( ^1H \) nmr spectrum of this material. Conversion of 118 into
the acetate 119 proceeded in high yield (92%). Reductive removal of the acetoxy function from the latter material was achieved with lithium in liquid ammonia and THF at -78 °C. The yield of the desired furan 120, after workup and distillation of the crude oil, was an encouraging 86%. The $^1$H nmr spectrum (400 MHz, CDCl$_3$) of 120 exhibited resonances at δ 0.91 (s, 3H, -Me) and 2.33-2.41 (m, 2H, protons adjacent to the furan ring). The protons on the furan ring were individually resolved and appeared at δ 6.28 (br s, 1H), 7.22 (br s, 1H) and 7.35 (t, 1H, $J = 1.5$ Hz).

Attempts to effect attachment of the furan ring to the two-carbon side chain of 116 in a
more direct way met with failure. For example, treatment of the tosylate derived from 116 with higher order\textsuperscript{41} or lower order cuprates\textsuperscript{42} prepared from 3-lithiofuran returned the starting material, even after prolonged reaction times. The primary iodide derived from the alcohol 116 gave the same result upon exposure to a higher order cyanocuprate\textsuperscript{41} derived from 3-lithiofuran.

Having thus gained confidence that the synthetic operations in the latter part of the planned synthesis were to some extent preceded, the construction of the natural product could begin.

2.2.3 The Total Synthesis of (±)-Ambliol B.

As was indicated by the retrosynthetic analysis discussed above, the first synthetic task was the preparation of the silyl enol ether 112 (Scheme 24). Using 3,4-dimethyl-2-cyclohexen-1-one\textsuperscript{43}(96) as the starting material, a copper(I)-catalyzed 1,4-addition of vinyl magnesium bromide in the presence of trimethylsilyl chloride was performed\textsuperscript{44} (Scheme 27). Workup and distillation of the crude oil gave the silyl enol ether 112 in 90% yield. The \textsuperscript{1}H nmr spectrum (400 MHz, CDCl\textsubscript{3}) of 112 indicated the presence of one secondary and one tertiary methyl group at \(\delta\) 0.84 (d, 3H, J = 7 Hz) and 0.93 (s, 3H), respectively. Also present were signals indicative of the presence of four vinyl protons at \(\delta\) 4.59 (br s, 1H), 4.95 (br d, 1H, J = 12 Hz), 4.95 (br d, 1H, J = 16 Hz) and 5.77 (d of d, 1H, J = 18, 10 Hz). The relative stereochemistry of the two asymmetric centres in 112 could be confidently assigned as indicated, based on ample literature precedent for the stereoselectivity of addition of copper(I)-based reagents to 96.\textsuperscript{45,46,33} Thus, in this reaction, the relative stereochemistry of two of the four asymmetric centers present in ambliol B (94) had been correctly installed.

Attention was now turned to the preparation of the compound 122. This would require the site-selective alkylation of the lithium enolate 121 with the bifunctional reagent 21. In a landmark paper in 1968, Stork and Hudrlik had reported the generation of metal enolates from
silyl enol ethers. Furthermore it was shown that the structural integrity of the enolates was retained in subsequent alkylation processes, since the alkylation products were formed site-selectively. The latter point was particularly important to our purposes, since enolate equilibration would almost certainly result in alkylation at the sterically less hindered $\alpha'$-site of ketone 123. Thus, following the Stork procedure, a solution of the silyl enol ether 112 in DME was treated with methyllithium at room temperature for 30 min to generate the enolate 121. The
vinylstannane iodide 21 was subsequently added at 0 °C and the solution was allowed to warm slowly to room temperature overnight. After workup, an examination of the crude product mixture revealed none of the desired product 122. Instead, the ketone 123 was isolated, along with unreacted 21. It was clear that the steric demands of the adjacent quarternary center were preventing carbon-carbon bond formation at the required enolate carbon atom in 121. This view was confirmed when the above reaction was attempted using THF and HMPA as co-solvents. Again, none of the desired product 122 was formed, but the O-alkylated compound 124 was isolated as the major product. Recourse to an alternative reagent/solvent combination (lithium amide, THF/liquid ammonia) again returned the ketone 123 and unreacted 21. These failures prompted the search for an alternative protocol for the assembly of the key keto vinyl iodide 106 (Scheme 24, equation 2) and culminated in the discovery of the novel vinylgermane cuprate 110 and its use, in conjunction with enone 125, in a solution to this problem.

Even though the experiments described above failed to provide the desired alkylation product, it was speculated that the lithium enolate 121 might yet undergo reaction at the required carbon center, provided that a sufficiently reactive electrophile were chosen. In this regard, a report in 1982 by Danishefsky had shown that a lithium enolate very similar in structure to 121 could be made to undergo site-selective reaction with dimethyl(methylene)ammonium chloride.49 We chose to investigate this procedure using the iodo analogue (126, Eschenmoser's salt50) of this highly reactive electrophile (Scheme 28). Thus, treatment of the silyl enol ether 112 with methyllithium in THF gave a solution of the lithium enolate 121. To this solution (at -78 °C) was added Eschenmoser's salt. Gratifyingly, workup of the reaction mixture gave the crude Mannich
Scheme 28

base 127 as a mixture of epimers in ~84% yield. The ir spectrum of this material indicated the presence of a ketone (1713 cm\(^{-1}\)) and an olefin (1637 cm\(^{-1}\)). The \(^1H\) nmr spectrum (400 MHz, CDCl\(_3\)) showed the expected resonances, among which were two signals (for the two epimers) at \(\delta 2.17\) and 2.24 (s, s, ratio 2:1, 6H) attributable to the methyl substituents on the nitrogen atom. Since the site-selectivity of the reaction of the enolate 121 could not have been corrupted\(^{46,47}\), the structure of 127 could be assigned with confidence.

Treatment of the Mannich base with \(m\)-CPBA in dichloromethane\(^{46}\) caused the formation of
the corresponding N-oxide from which, during filtration of the crude reaction mixture through a small plug of silica gel, was eliminated the elements of N,N-dimethylhydroxylamine to give the enone 125 (76%). This compound proved to be extremely unstable, and therefore, had to be used immediately in the subsequent step of the synthesis. Nevertheless, if a freshly prepared sample was transferred swiftly to an ir spectrometer, evidence for structure 125 could be witnessed. Thus, the ir spectrum contained absorbances at 1697 and 1636 cm\(^{-1}\), typical of an \(\alpha,\beta\)-unsaturated ketone. The presence of the vinyl substituent was corroborated by an absorbance at 1615 cm\(^{-1}\).

The successful preparation of 125 made it imperative that a bifunctional reagent equivalent to the \(d^2,d^4\)-synthon 111 be found. Thus, 125 contains two acceptor sites which, when combined with the donor sites of the appropriate synthetic equivalent of 111 in an annulation sequence, would lead ultimately to the bicyclic nucleus (128) of the natural product.

Since a synthetic equivalent of the synthon 111 would have to be a bifunctional four-carbon reagent, attention was turned to the vinylstannane chloride 6 (Scheme 29). This reagent had been used quite extensively in our laboratories\(^7\) (see, for instance, Scheme 4, p. 5) as a synthetic equivalent of the \(d^2,a^4\)-synthon 15. Comparison of 15 with 111 illustrates that, formally, "umpolung"\(^17\) at carbon four of synthon 15 would yield the desired synthon 111. In practice, the desired umpolung would be achieved if reagent 6 or its iodo-analogue 129\(^13\) were to undergo metal-halogen exchange at carbon four without affecting the carbon-metal bond already present at carbon two of these reagents. Put in another way, metal-halogen exchange at carbon four was desired without concomitant transmetallation of the carbon-tin bond at carbon two.

First attempts were directed at the preparation of the Grignard reagent 130a from 129. Thus, treatment of 129 with magnesium in refluxing THF, followed by addition of a suitable electrophile such as cyclohexanone gave no evidence for the formation of an addition product. Therefore, this avenue was not pursued further. The possible preparation of the lithio-derivative 130b of reagent 6 was also investigated. Treatment of 6 with lithium 4,4\(^{-}\)-di-\(\text{tert}\)-butylbiphenyl\(^5\), however, apparently failed to produce 130b in appreciable quantities. This failure was evident after the addition of cyclohexanone, since a GC analysis of the crude
Scheme 29
reaction mixture revealed a host of products. At this point, it was felt that the inability to perform these rather standard metal-halogen exchange procedures might be due to unwanted side reactions caused by the presence of the vinylstannane moiety. It was therefore decided to replace the tin atom with an element that would yield a vinylmetal moiety with similar but somewhat diminished reactivity.

Since the average carbon-tin bond is known to be longer than the average carbon-germanium bond\textsuperscript{52}, and since longer bonds are associated with lower bond dissociation energies\textsuperscript{53}, it was felt that the replacement of the trimethylstannyl function in 6 with a trimethylgermyl function might prove to be helpful. Since previous work in our laboratories had shown that reagent 6 could undergo transmetallation in the presence of methyllithium\textsuperscript{7} (see Scheme 3, p. 4) without the interference of metal-halogen exchange processes, the vinylolithium reagent 131 was prepared. It was gratifying to find that addition of trimethylgermanium bromide to a cold solution of 131 in THF produced, after 1.5 hr at -78 °C, the vinylgermane chloride 132. The $^1$H nmr spectrum (400 MHz, CDCl$_3$) of the starting material 6 exhibited, for the methyl substituents on tin, a nine-proton singlet at $\delta$ 0.18 which, additionally, contained the characteristic satellite peaks due to two-bond coupling with the $^{117}$Sn and $^{119}$Sn isotopes ($^{2}J_{\text{Sn-H}} = 53$ Hz). In contrast, compound 132 exhibited a nine-proton singlet at $\delta$ 0.24, devoid of satellite peaks, for the methyl substituents on germanium. Furthermore, the vinyl proton resonances of 132 appeared as one-proton multiplets at $\delta$ 5.33 and 5.61, while the corresponding resonances for the starting material appeared at $\delta$ 5.31 and 5.72.

Due to the volatility of compound 132, the crude oil recovered from the transmetallation-substitution process reaction was immediately subjected to a Finkelstein procedure. Thus, exposure of the crude 132 to NaI in refluxing acetone for 48 hrs, followed by workup and distillation of the crude oil, gave the vinylgermane iodide 133 in 72% overall yield from 6.

The crucial halogen-metal exchange procedure needed for the generation of a synthetic equivalent of the d$^2$d$^4$-synthon 111 could now be investigated. After many trials, a procedure
was discovered for the preparation of the vinylgermane cuprate 110 from 133. Thus, treatment of a cold (-95 °C) THF solution of 133 with two equivalents of tert-butyllithium (rapid addition), followed by addition of 1.1 to 1.2 equivalents of CuCN and brief warming to -35 °C, gave a homogenous, light brown solution of the cyanocuprate 110. Use of less than two equivalents of the alkyllithium or slow addition of this reagent produced varying amounts of the Wurtz-type coupling product 135 (equation 3). Thus, if the tert-butyllithium reagent was added too slowly,

\[
\begin{align*}
\text{Me}_3\text{Ge} & \quad + \quad \text{Me}_3\text{Ge} \\
\text{I} & \quad + \quad \text{Li} \\
\rightarrow & \\
\text{Me}_3\text{Ge} & \quad \text{Me}_3\text{Ge} \\
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2
\end{align*}
\]  

(3)

\[
\begin{align*}
\text{I} & \quad + \quad \text{Li} \\
\rightarrow & \\
\text{Me}_3\text{Ge} & \quad \text{Me}_3\text{Ge} \\
\text{CH}_3 & \quad \text{CH}_2 & \quad \text{CH}_2
\end{align*}
\]  

(4)

the iodide 133 and the alkyllithium species 134 produced by halogen-metal exchange from 133 are present together in solution for a sufficient period of time so that coupling occurs. This situation can also come about if an insufficient amount of tert-butyllithium to convert 133 fully to 134 is added. Ordinarily, one equivalent of tert-butyllithium would suffice. It appears, however, that the reaction of tert-butyllithium (136) with tert-butyl iodide (137, formed from the halogen-metal exchange along with 134) is competitive with the exchange process, probably giving 2-methylpropane (138), 2-methylpropene (139) and lithium iodide (equation 4). Since this reaction consumes one equivalent of tert-butyllithium, a second equivalent is needed in order for the halogen-metal exchange to proceed to completion.

Evidence that cuprate 110 was indeed present in solution came from the 1,4-addition reaction illustrated in Scheme 30. Thus, the cuprate 110 was allowed to react, in the presence of
trimethylsilyl chloride with 2-cyclohexen-1-one (140) at -78 °C. After hydrolysis of the intermediate silyl enol ether 141, workup of the reaction mixture and distillation of the crude oil, the 1,4-adduct 142 was isolated in pure form (73% yield from 140). Spectroscopic evidence for this structure came from an ir spectrum which indicated the presence of a ketone (1715 cm⁻¹) and the \(^1\)H nmr spectrum (400 MHz, CDCl₃) of 142 which exhibited a nine-proton singlet at \(\delta 0.21\) for the methyl substituents on germanium and two one-proton multiplets in the vinylic region at \(\delta 5.19\) and 5.51.

Since it was hoped that the above methodology could be used subsequently towards the preparation of the keto vinyl iodide cyclization precursor 106 (equation 2), it was gratifying to find that the vinylgermane 142 was smoothly converted to the corresponding vinyl iodide 143 upon treatment of the former substance with iodine in dichloromethane\(^{21a}\) (90%). Interestingly, 142 required exposure to iodine for 24 hrs for the reaction to proceed to completion. In contrast, the conversion of the vinylstannanes shown in Table 1 (p. 16) into the corresponding iodides was
essentially complete after dropwise addition of a solution of iodine in dichloromethane to the former. The slower rate of conversion in the present case is perhaps an indication of the greater strength of the carbon-germanium bond in comparison with the carbon-tin bond. The conversion of 142 into 143 was confirmed by the expected spectral characteristics for 143, including a high resolution mass spectrum which gave an exact mass of 278.0161 mass units. The calculated exact mass for 143 (C_{10}H_{15}OI) is 278.0169.

The newly developed cuprate 110 could now be deployed against the unstable enone 125 in a bid to gain access to the key keto vinyl iodide 106 (Scheme 31). Thus, to a cold (-78 °C) THF solution of the cuprate 110 containing five equivalents of trimethylsilyl chloride was added a THF solution of the freshly prepared enone 125. The reaction was complete after 1 hour at -78 °C, and the resultant silyl enol ether 144 was hydrolyzed by adding aqueous ammonium chloride to the
reaction flask. Workup and distillation of the resultant crude oil gave a mixture of compounds which consisted largely (78% by glc analysis) of the vinylgermane ketone 145. Attempts to purify the sample further by means of flash chromatography or drip column chromatography were unsuccessful. It was nevertheless clear from the $^1$H nmr spectrum of the mixture (vide infra) that compound 145 was present as a single diastereomer. In the hydrolysis step a new asymmetric center was created at the carbon adjacent to the carbonyl group. Conformational analysis shows that of the two possible diastereomers, 145 should be the more stable since it contains three equatorially and one axially oriented substituents on the six-membered ring. The other diastereomer (not shown) would have two equatorially and two axially oriented substituents. The stereochemistry of 145 was thus assigned without difficulty. The $^1$H nmr spectrum (400 MHz, CDCl$_3$) of the mixture containing 145 exhibited the following diagnostic resonances: $\delta$ 0.18 (s, 9H, -GeMe$_3$), 0.67 (s, 3H, tertiary Me) and 0.82 (d, 3H, secondary Me, $J = 7$ Hz) for the five methyl substituents present in this compound, $\delta$ 4.92 (d, 1H, $J = 18$ Hz), 5.13 (d, 1H, $J = 12$ Hz) and 5.62 (d of d, 1H, $J = 18$, 12 Hz) for the protons on the vinyl substituent, and $\delta$ 5.13 (m, 1H) and 5.47 (m, 1H) for the vinyl protons of the vinylgermanium moiety.

The cyclization precursor 106 could now be accessed by overnight treatment of the vinylgermane ketone 145 with iodine in dichloromethane. Flash chromatography of the crude oil obtained after workup gave, in 42% overall yield from enone 125, the key keto vinyl iodide 106. This material exhibited all the expected spectral characteristics including, in its ir spectrum, a ketone carbonyl stretch at 1713 cm$^{-1}$ and two carbon-carbon double bond stretches at 1637 and 1618 cm$^{-1}$ for the vinyl substituent and the iodo-substituted double bond, respectively. Replacement of the germane moiety with an iodo group was clearly witnessed by the downfield shift of the signals for the adjacent vinyl protons in the 400 MHz $^1$H nmr spectrum of 106. Thus, while these signals appeared at $\delta$ 5.13 (m, 1H) and 5.47 (m, 1H) for 145 (vide supra), they could now be witnessed at $\delta$ 5.67 (m, 1H) and 6.01 (m, 1H).

With substrate 106 in hand, the previously developed cyclization reaction$^{26}$ (section 2.1.3) could now be utilized. It was anticipated that the vinyllithium intermediate generated for this
purpose would possess the conformation depicted by 146a (Scheme 32) which has only one axially oriented and three equatorially oriented substituents. The other possible conformer (146b) has three axially oriented substituents, two of which would be engaged in a destabilizing 1,3 diaxial interaction. On the basis of our earlier studies involving cyclization of compounds 52 and 55 (Table 2 (p. 23)), it was expected that, from conformation 146a, attack on the carbonyl carbon by the vinyl lithium moiety would proceed from the equatorial face to give the trans-fused lithium alkoxide intermediate 147. Clearly, attack on the axial face is disfavoured by a 1,3 diaxial interaction of the "incoming" vinyl lithium center with the axially disposed tertiary methyl substituent located on carbon three.

It was gratifying to find that, upon treatment of 106 with two equivalents of \( n \)-butyllithium
at -78 °C, followed by hydrolysis, a single cyclized product was formed in 88% yield. Based on the conformational analysis discussed above and the precedents provided by the earlier studies, the trans ring fusion stereochemistry of the product (128) was assigned with confidence, despite a lack of direct spectroscopic evidence. The collected spectral data of 128 did, however, provide ample evidence of the other structural features of this material. For example, the ir spectrum exhibited an O-H stretch at 3493 cm\(^{-1}\) and a carbon-carbon double bond stretch at 1636 cm\(^{-1}\). An absorption in the carbonyl region was no longer in evidence. The \(^1\)H nmr spectrum (400 MHz, CDCl\(_3\)) indicated the presence of two methyl groups by resonances at \(\delta\) 0.77 (d, 3H, secondary Me, \(J = 8\) Hz) and 0.99 (s, 3H, tertiary Me). The protons of the vinyl substituent were indicated by three resonances at \(\delta\) 4.96 (d of d, 1H, \(J = 18, 1.5\) Hz), 5.05 (d of d, 1H, \(J = 11, 1.5\) Hz) and 5.41 (d of d, 1H, \(J = 18, 11\) Hz). Finally, the vinyl protons of the exocyclic double bond were in evidence at \(\delta\) 4.69 and 4.79 (br s, br s, 1H each).

In this cyclization reaction, some starting material was returned unless at least two equivalents of \(n\)-butyllithium were employed. The reader is referred to p. 30 of section 2.1.3 where two possible arguments were advanced to explain this phenomenon. The current observation seems to lend greater credibility to the first of these arguments. Thus, despite the fact that no oxygen-containing function other than the carbonyl group is present in the substrate 106, two equivalents of this reagent are still necessary for the reaction to go to completion. The first argument, which invokes the competitive reaction of \(n\)-butyllithium with \(n\)-butyl iodide, therefore seems more likely.

At this point, attention should be drawn to the fact that, in compound 128, the trans-fused bicyclic nucleus of ambliol B (94) had been assembled, with the relative stereochemistry of all four asymmetric centres present in the natural product correctly installed. It remained for the furan ring to be attached and for the exocyclic methylene function in 128 to be converted into a gem-dimethyl moiety.

Toward this end, the effort invested in the model studies performed previously (see Schemes 25 and 26) was handsomely rewarded. Thus, treatment of 128 with diethylzinc and
diiodomethane in a dry oxygen atmosphere gave the cyclopropane 148 (Scheme 33). A number of factors were crucial to the success of this procedure. Firstly, it was important that the reaction be performed with benzene as a solvent. Use of more polar solvents such as dichloromethane or diethyl ether led to the recovery of varying amounts of starting material, even when an excess of each of the reagents was employed. Additionally, if benzene was not used, clean conversion to 148 could not be achieved since a number of side products were invariably formed. Secondly, the time of exposure of the starting material to the reagents was crucial for the prevention of the formation of side products. For instance, if a benzene solution of 128 was allowed to react with diethylzinc and diiodomethane for 90 minutes at 0 °C, the desired product was obtained in a yield
of 60% after workup and flash chromatography of the crude material. The same procedure, but with a reaction time of 30 min, gave a 91% yield of 148. This observation is perhaps not surprising if it is remembered that there are two potential sites of reaction in the starting material. It is believed, however, that oxygen-containing functional groups in the vicinity of a double bond exert an accelerating and directing effect on the cyclopropanation reaction.\footnote{57} Therefore, under the appropriate, carefully controlled reaction conditions, the double bond of the allylic alcohol function in 128 could be chemoselectively cyclopropanated in the presence of the vinyl substituent.

The 400 MHz $^1$H nmr spectrum of compound 148 confirmed that chemoselective cyclopropanation had indeed taken place. Four one-proton multiplets were observed at high field in the spectrum of 148, at $\delta$ 0.02-0.10, 0.19-0.27, 0.50-0.59 and 0.64-0.71, indicating the protons on the cyclopropane ring. That the vinyl substituent was still intact was shown by three one-proton resonances at $\delta$ 4.88 (d of d, 1H, $J = 17, 1.5$ Hz), 5.05 (d of d, 1H, $J = 11, 1.5$ Hz) and 5.43 (d of d, 1H, $J = 17, 11$ Hz).

It was to the latter functional group that attention was now turned. Since it was clear that the planned hydrogenolysis of the the cyclopropane ring in 148 would cause concomitant hydrogenation of the double bond, the latter function was first transformed into a primary alcohol. Thus, treatment of 148 (Scheme 33) with diborane in THF followed by an oxidative workup\footnote{58}, gave, after flash chromatography of the crude material, the primary alcohol 149 in 73% yield. A small amount (11%) of the regioisomeric secondary alcohol 149a was also isolated. That the major product of this reaction was indeed the primary alcohol 149 was readily shown by a two-proton multiplet at $\delta$ 3.56-3.72 in the 400 MHz $^1$H nmr spectrum of this compound. The chemical shift value of this two-proton signal indicated that these protons are adjacent to an oxygen function, thereby establishing the primary nature of the alcohol group. The $^1$H nmr spectrum of the minor compound (149a), on the other hand, contained a one-proton signal in this region of the spectrum ($\delta$ 3.94), indicating that only one proton is adjacent to the oxygen function and, therefore, the presence of a secondary alcohol. Interestingly, this nmr spectrum also
indicated that 149a is a single diastereomer. The borane reagent must therefore have attacked the double bond of the starting material (148) preferentially from one face. The origin of this diastereofacial selectivity is not clear from inspection of a molecular model of 148.

Hydrogenolysis of the cyclopropane ring in the alcohol 149 was next examined. The experience gained during efforts to achieve this type of transformation on the model cyclopropane 113 (see Scheme 25) was valuable. Thus, using the optimized reaction conditions developed for the hydrogenolysis of 113 (H₂ (1.5 atm.), PtO₂, dry acetic acid, room temp., 55 min.), the hydrogenolysis of the cyclopropane ring in 149 to give compound 150 could be achieved in 87% yield. In the ¹H nmr spectrum (400 MHz, CDCl₃) of 150, four resonances attributable to the four methyl groups present in this compound could be discerned at 0.86 and 0.87 (s, s, 3H each, tertiary Me), 0.88 (d, 3H, secondary Me, J = ~7 Hz) and 0.98 (s, 3H, tertiary Me). Furthermore, the methylene protons adjacent to the primary hydroxyl group were in evidence as a two-proton multiplet at 3.58-3.74.

The final stage of the synthesis had now been reached. All that remained was the attachment of the furan ring (Scheme 34). This was achieved by a sequence of steps similar to that which had been used for the model compound 116 (Scheme 26).³³,³⁹ Thus, oxidation of the diol 150 with PCC in dichloromethane in the presence of sodium acetate⁵⁹ gave an unstable aldehyde that was used directly in the next step. A solution of the crude unstable aldehyde was added directly to a cold solution of 3-lithiofuran.⁴⁰ The addition product 151, a diastereomeric mixture, was isolated in 71% yield from the diol 150, after workup and filtration of the crude material through a small plug of silica gel.

The ir spectrum of 151 exhibited a strong O-H stretch at 3469 cm⁻¹. The presence of the gem-dimethyl moiety was indicated by a characteristic pair of bands at 1381 and 1368 cm⁻¹.⁶⁰ Most importantly, the presence of a 3-substituted furan ring was confirmed by diagnostic absorptions⁶¹ at 1504, 1025 and 874 cm⁻¹.

Treatment of 151 with acetic anhydride in pyridine and dichloromethane for 24 hrs supplied the corresponding acetate 152 (59% yield). The ir spectrum of 152 confirmed that
mono-acetylation of the diol 151 had taken place. Thus, an O-H stretch was in evidence at 3550 cm\(^{-1}\), while an ester carbonyl stretch at 1732 cm\(^{-1}\) was also present. Proof that it was the secondary hydroxyl function of 151 (a diastereomeric mixture of diols) that had been acetylated was supplied by the chemical shift values of the protons adjacent to the acetoxy function in the 400 MHz \(^1\)H nmr spectrum of 152. These protons gave rise to two signals (for the two
Figure 6: The 400 MHz $^1$H nmr Spectrum of Natural (-)-Ambliol B in CDCl$_3$.

Figure 7: The 400 MHz $^1$H nmr Spectrum of Synthetic (+)-Ambliol B in CDCl$_3$.
diastereomers), integrating for one proton, at δ 5.95 (t, $J = 6 \text{ Hz}$) and 6.00 (d of d, $J = 9, 2.5 \text{ Hz}$).

The final step in the synthesis was the reductive removal of the acetoxy function in 152. Treatment of this material with lithium in liquid ammonia$^{62}$ and THF at -78 °C for 15 minutes supplied, after workup and chromatography of the resultant crude material, (+)-ambliol B (94) in 76% yield. The spectral characteristics of the synthetic compound (ir, $^1\text{H}$ and $^{13}\text{C}$ nmr spectra) were identical with those of a sample of the natural material.$^{16a,63}$ The 400 MHz $^1\text{H}$ nmr spectra of the synthetic and natural materials are illustrated in Figures 6 and 7.

In summary, the first total synthesis of the marine diterpenoid ambliol B was achieved in 13 steps and 4% overall yield from the enone 96.$^{64}$ A key transformation was the cyclization of the keto vinyl iodide 106 to form the bicyclic nucleus of the natural product (Scheme 32). The high yield and correct stereochemical outcome of this step was preceded by the cyclization studies performed during development of a new annulation method (Section 2.1).$^{26}$ Central to the preparation of 106 was the development of the novel vinylgermane cuprate 110 (Scheme 31).
2.3 Five-membered Ring Annulations Based on Palladium(0)-catalyzed Intramolecular Coupling.

2.3.1 Introductory Remarks.

In the total synthesis of ambliol B (discussed in Section 2.2 of this thesis) the vinylgermane cuprate 110 had served as a synthetic equivalent of the 1-butene d²,d⁴-synthon 111 (equation 5). In this role, it had been used in the annulation sequence which served to prepare the bicyclic compound 128 from the enone 125 (see Scheme 28). The question arose whether the utility of reagent 110 could be expanded so that it would also find application as a synthetic equivalent of the 1-butene a²,d⁴-synthon 153 in annulation sequences. For example, if 110 (in its role as a synthetic equivalent of 153) could be successfully combined with an α,β-unsaturated ketone of general structure 154, a novel annulation sequence leading to bicyclic compounds of general structure 157 will have been developed (Scheme 35). It was envisioned that such an annulation sequence would commence with the 1,4-addition of reagent 110 to a suitable α,β-unsaturated ketone. The 1,4-adduct 155 would then be transformed into the keto vinyl iodide 156. These steps are entirely similar in kind to those in which reagent 110 had been used during the synthesis...
of the natural product, and required only that they be applicable to a variety of enone substrates.
In fact, during the development of suitable reaction conditions for the use of 110, a keto vinyl iodide such as 156 had been prepared (see compound 143 in Scheme 30). The crucial step in the sequence depicted in Scheme 35 would clearly be the cyclization reaction, in which the potential acceptor site of the vinyl iodide moiety in 156 would have to be combined with the potential donor site located α to the ketone function. The conditions under which such a cyclization became possible are described in Section 2.3.3. First, in section 2.3.2, the preparation of a number of cyclization substrates like 156 are delineated.
2.3.2 Preparation of Cyclization Substrates.

In order to prepare keto vinyl iodide cyclization substrates, the enones 96, 140 and 161-163 in Table 3 were chosen as starting materials. The enones 140, 162 (isophorone) and 163 ((R)-(−)-carvone) are commercially available. Enone 96 was the starting material for the synthesis of (+)-ambliol B and was prepared as described earlier. The bicyclic enone 161 was prepared as illustrated in Scheme 36. Thus, treatment of the dimethylhydrazone derivative of cyclopentanone 158 with LDA in THF (0 °C) was followed by addition of 1,2-epoxybutane (-78 °C). The mixture was allowed to warm to room temperature overnight. Workup gave a crude product which was treated immediately with sodium periodate in THF and water. The crude

![Scheme 36](image-url)
Table 3: Preparation of Cyclization Substrates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents</th>
<th>Enone</th>
<th>Keto Vinylgermane (Yield, %)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Keto Vinyl Iodide (Yield, %)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{R}_1 - \text{R}_4 = H$</td>
<td>140</td>
<td>142 (73%)</td>
<td>143 (97%)</td>
</tr>
<tr>
<td>2</td>
<td>$\text{R}_1, \text{R}_2 = \text{Me}$  \hspace{1cm} $\text{R}_3, \text{R}_4 = H$</td>
<td>96</td>
<td>164 (74%)</td>
<td>168 (87%)</td>
</tr>
<tr>
<td>3</td>
<td>$\text{R}_1, \text{R}_3, \text{R}_4 = \text{Me}$  \hspace{1cm} $\text{R}_2 = H$</td>
<td>162</td>
<td>165 (35%)</td>
<td>169 (83%)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>163</td>
<td>166 (88%)</td>
<td>170 (80%)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>161</td>
<td>167 (63%)</td>
<td>171 (70%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 110, $\text{Me}_3\text{SiCl}$, THF, -78°C; then $\text{H}_2\text{O}$, $\text{NH}_4\text{Cl}$, overnight.

<sup>b</sup> Reaction conditions: $\text{I}_2$, $\text{CH}_2\text{Cl}_2$, overnight.

<sup>c</sup> HMPA was added and the reaction mixture was allowed to warm slowly to rt overnight.

<sup>d</sup> The reaction mixture was allowed to warm slowly to rt over 5 hrs.
material obtained from this reaction was distilled to give the keto alcohol 159 (41% from 158). Compound 159 was oxidized with pyridinium chlorochromate, affording the diketone 160 (59%). The ir spectrum of this material exhibited two carbonyl stretching absorptions at 1740 and 1714 cm\(^{-1}\) for the five-membered ring ketone and the side chain ketone, respectively. Intramolecular aldon condensation of 160 was achieved in the presence of potassium hydroxide in refluxing methanol. The resultant enone 161 was isolated, after workup and flash chromatography of the crude material, in a yield of 68% from 160. That an \(\alpha,\beta\)-unsaturated ketone moiety was indeed present in this compound was indicated by its ir spectrum, which exhibited the characteristic pair of strong absorptions at 1705 and 1669 cm\(^{-1}\). The presence of a vinylic methyl substituent was indicated by a broad three-proton singlet at \(\delta\) 1.71 in the \(^1\)H nmr spectrum (400 MHz, CDCl\(_3\)) of 161.

Table 3 contains a summary of the preparation of a number of keto vinyl iodide cyclization precursors. The preparation of compound 143 (entry 1) was described in section 2.2.3 (Scheme 30). The remaining keto vinyl iodides 168 - 171 were prepared analogously. For instance, treatment of a THF solution of the enone 96 (-78 °C) with the vinylgermane cuprate 110 in the presence of trimethylsilyl chloride, followed by \textit{in situ} hydrolysis of the silyl enol ether intermediate, gave the keto vinylgermane 164. Flash chromatography of the crude product afforded 164 in 74% yield. The \(^1\)H nmr spectrum (300 MHz, CDCl\(_3\)) of this material revealed the following diagnostic resonances: \(\delta\) 0.23 (s, 9H, -GeMe\(_3\)), 0.78 (s, 3H, tertiary Me), 0.93 (d, 3H, secondary Me, \(J = 7\) Hz), 5.19 and 5.52 (m, m, 1H each, vinyl protons). Treatment of compound 164 with a solution of iodine (1.5 equiv) in dichloromethane\(^{21b}\) for 21 hrs gave, after workup and flash chromatography of the crude material, the keto vinyl iodide 168 (87%). The \(^1\)H nmr (300 MHz, CDCl\(_3\)) resonances of the vinyl protons of 168 appeared at \(\delta\) 5.69 (m, 1H) and 6.04 (m, 1H), significantly downfield from the values for the corresponding protons in the starting material 164 (\textit{vide supra}). Thus, it was evident that the replacement of the trimethylgermane moiety with the more electronegative iodine atom had taken place.

The general success of the two step conversion of enones into the corresponding keto vinyl
iodides is evident from the data presented in Table 3. While the second step (the conversion of the vinyl germanes to vinyl iodides) proceeded without incident, the first step (addition of the vinylgermane cuprate 110 to the enones) requires a few additional comments.

The highly hindered enone isophorone (162) underwent reaction with the cuprate 110 if HMPA was added and the reaction mixture was allowed to warm slowly to room temperature. The reluctance of isophorone to undergo 1,4-additions is well known. In this light, the low yield (35%) of compound 165 is understandable.

The addition of cuprate 110 to enone 163 ((R)-(-)-carvone) proceeded in the precedented stereoselective way, trans to the substituent at carbon five. The stereoselectivity of this addition was indicated by the 400 MHz $^1$H nmr spectrum of the product 166, which exhibited the presence of a pair of diastereomers (epimers at carbon two, in a ratio of ~2.5 : 1). Thus, the signals for the secondary methyl substituents appeared at $\delta$ 1.02 and 1.14 (d, d, ratio of ~2.5 : 1, 3H, $J = 7$ Hz). Additionally, the vinyl protons of the isopropenyl substituent appeared at $\delta$ 4.71, 4.75, 4.79 and 4.82 (all br s, ratio of 1 : 2.5 : 2.5 : 1, 2H). The presence of the vinylgermane moiety was assured by a nine-proton signal at $\delta$ 0.20 and 0.21 (s, s, ratio undetermined).

The production of the keto vinylgermane 167 (63%) from the $\alpha,\beta$-unsaturated enone 161 was gratifying. This yield could be achieved despite the fact that the double bond of the enone function in 161 is fully substituted (and therefore sterically crowded). As in the case of 166, a pair of diastereomers was evident from the 400 MHz nmr spectrum of 167. For example, the vinyl protons present in this mixture appeared at $\delta$ 5.17 and 5.21 (m, m, ratio of 1 : 1.5, 1H), and 5.50 and 5.55 (m, m, ratio of 1:1.5, 1H). Since it is well known that conjugate additions of cuprate reagents to bicyclo[3.3.0]oct-1-en-3-ones proceed to give cis-fused products highly stereoselectively, the ring fusion stereochemistry of this material could be confidently assigned.
2.3.3 Cyclization Studies.

Although there seem to be no known general methods, to date, for achieving direct carbon-carbon bond formation between the vinylic carbon atom of a vinylic halide function and the α-carbons of a ketone, the use of palladium catalysis in a related intramolecular coupling process has been reported. In 1987, Ciufolini and Brown described the preparation of the Fredericamycin A model compound 173 via the palladium-assisted intramolecular coupling of the β-diketo aryl iodide 172 (equation 6). Sodium hydride served to generate the enolate anion of the β-diketone function. A catalytic amount of the palladium reagent was subsequently added, effecting coupling of the enolate anion (which acts as a donor) with the potential acceptor site of the aryl iodide substituent. This cyclization method was later extended to include a number of "soft" enolates (pKₐ < 15) and an aryl bromide.

We were intrigued by the possibility that a similar combination of an appropriate base and a zerovalent palladium catalyst might effect the desired cyclization of the keto vinyl iodide precursors shown in Table 3. A number of important differences from the example given above need to be made explicit. For each of the substrates 143 and 168 - 171, an enolate anion can be formed at two possible sites (the α- and α'-positions). Provision would have to be made (in the form of a proton donor) for the equilibration of these enolate anions, since only one of them (formed by proton abstraction from carbon two of each substrate) possesses the regiochemistry
required for the proposed cyclization reaction. Furthermore, these enolates would be of the "hard" ($pK_a = 20$) type. A sufficiently strong base would therefore have to be employed. On the other hand, the propensity of vinyl halides for elimination (to form acetylenes) in the presence of strong bases is well documented. The use of vinyl iodides rather than aryl iodides as the acceptor partners in such a cyclization might thus be untenable. Fully aware of potential problems such as these, the general viability of the proposed cyclization technique was examined using the keto vinyl iodide 143.

An initial experiment was conducted by adding a THF solution of 143 to a cold ($0 \, ^\circ \text{C}$), stirred solution of potassium tert-butoxide (1.1 equivalents) in THF and tert-butyl alcohol (Scheme 37, route i). The resulting solution was stirred at this temperature for 5 mins and 50
mole % of tetrakis(triphenylphosphine) palladium was added. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hrs. Workup and flash chromatography of the crude product delivered, to our delight, the bicyclic enone 175 (62%). The presence of the conjugated enone moiety in 175 was confirmed by the presence of strong absorptions at 1678 and 1621 cm⁻¹ in the ir spectrum of this compound. Additionally, the ¹H nmr spectrum of 175 exhibited a broad three-proton singlet at δ 2.08 for the vinylic methyl substituent. It was apparent that the desired coupling reaction had taken place to give, initially, the non-conjugated enone 174. Under the basic reaction conditions, this material had isomerized to the more stable conjugated enone 175. Later experiments (vide infra) were to give confirmation of this rationalization of events.

With the knowledge that the coupling reaction was a viable method for achieving the desired cyclization, optimization of the reaction conditions could be investigated. It would be desirable, for instance, to achieve satisfactory yields of cyclized products with smaller molar quantities of the (expensive) catalyst. Route ii of Scheme 37 illustrates the result obtained when the reaction was repeated exactly as before (route i), but with only 10 mole % of catalyst rather than 50 mole %. Base promoted elimination of HI from the vinyl iodide moiety now predominated to give almost exclusively the uncyclized keto acetylene 176. (The glc-determined ratio of the products 176 and 175 obtained from this reaction was >27 : 1). The ir spectrum of 176 exhibited the absorbances characteristic of a terminal acetylene at 3290 and 2116 cm⁻¹, while a carbonyl stretch was in evidence at 1709 cm⁻¹.

In order to check whether or not the acetylene 176 might be an intermediate in the reaction that delivered 175 from 143, compound 176 was resubmitted to the reaction conditions used in route ii, but with 20 mole % of the catalyst. After a reaction time of 3 hrs, no change was detected and the acetylene 176 was recovered unchanged.

Under the reaction conditions outlined in route ii, 10 mole % of catalyst was clearly insufficient to prevent unwanted elimination from competing successfully with the desired palladium-catalyzed cyclization. If, however, these results can be understood in terms of an
adjustment of the relative rates of the two processes under discussion (cyclization and elimination), it seemed possible that reaction conditions could be chosen such that the desired cyclization would be favoured without the need to resort to high molar quantities of catalyst. Thus, if the contact time of the base and the substrate could be kept to a minimum, while the catalyst and the substrate were constantly in contact, the desired cyclization might again be favoured, even with relatively small molar quantities of catalyst. In practice, this would translate into adding the catalyst to the substrate first, followed by slow, dropwise addition of the base. Route iii in Scheme 37 illustrates the specific conditions under which this protocol succeeded in restoring the cyclization reaction to prominence, while requiring only 16 mole % of the palladium(0) catalyst. Following this method, the ratio of 175 to 176 was >60 : 1, as indicated by glc analysis of a sample of the crude reaction mixture.

Confident that suitable conditions for cyclization had been uncovered, attention was turned to the cyclization of the remaining keto vinyl iodides that had been prepared (168 - 171, Table 3). Table 4 contains a summary of the cyclization reactions that were performed. For instance, treatment of the keto vinyl iodide 168 under the conditions discussed above (route iii, Scheme 37) gave the bicyclic enone 177 (58%). The ir spectrum of the latter compound revealed the presence of a conjugated enone (1678, 1626 cm⁻¹). The ¹H nmr spectrum (300 MHz, CDCl₃) of 177 showed signals due to a tertiary methyl group (δ 0.89 (s, 3H)), a secondary methyl group (δ 0.94 (d, 3H, J = 7 Hz)) and a vinylic methyl group (δ 2.02 (br s, 3H)). In a similar fashion, substrates 169 - 171 were transformed into the annulation products 178 - 180, respectively.

A number of comments relevant to the results summarized in Table 4 need to be made. It is clear from the cyclization of compounds 170 and 171 that the reaction can be performed on compounds which contain a substituent at the position α to the ketone function. In these cases, of course, base-promoted isomerization of the carbon-carbon double bonds of the products (179 and 180) into conjugation with the ketone double bonds cannot take place. On the other hand, the initially formed products which do not contain an α-substituent undergo this isomerization under the reaction conditions, to give the corresponding conjugated cyclized products (175, 177 and
Table 4: Palladium(0)-catalyzed Cyclization Reactions of Keto Vinyl Iodides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substituents</th>
<th>Keto Vinyl Iodide</th>
<th>Product (Yield, %)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$R_1 - R_4 = H$</td>
<td><img src="image1" alt="Image" /></td>
<td>175 (59%)</td>
</tr>
<tr>
<td>2</td>
<td>$R_1, R_2 = Me$ $R_3, R_4 = H$</td>
<td><img src="image2" alt="Image" /></td>
<td>177 (58%)</td>
</tr>
<tr>
<td>3</td>
<td>$R_1, R_3, R_4 = Me$ $R_2 = H$</td>
<td><img src="image3" alt="Image" /></td>
<td>178 (74%)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td><img src="image4" alt="Image" /></td>
<td>179 (65%)</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td><img src="image5" alt="Image" /></td>
<td>180 (65%)</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: ~20 mole % (Ph$_3$P)$_4$Pd, THF, room temperature, 5 min; then addition of $t$-BuOK, THF/$t$-BuOH, room temperature, dropwise, over 3 h.
Evidence that the newly formed rings in compounds 179 and 180 are cis-fused came from $^1$H nmr nOe difference experiments that were performed on these substances. For instance, irradiation of the three-proton singlet (δ 1.25) due to the tertiary methyl group of 179 resulted in enhancement of the signal due to one of the vinyl protons (δ 4.84) present on the exocyclic methylene group. Inspection of molecular models showed convincingly that such an enhancement is likely for either of the two conformers (179a and 179b) of a cis-fused bicyclic product, since the indicated protons are spatially quite close together. A model of the trans-fused bicyclic product (179c), on the other hand, indicates that the protons of the angular methyl group and the protons on the exocyclic methylene group are spatially remote. A bicyclic product with this configuration is, therefore, highly unlikely to produce the observed nOe result. The stereochemistry of 179 was thus unambiguously established.

A similar $^1$H nmr nOe difference experiment performed on compound 180 (Table 3) also
showed enhancement of a vinyl proton resonance (δ 4.93) when the signal due to the tertiary methyl group (δ 1.08) was irradiated. Inspection of molecular models of compound 180 reveals that the methyl protons and Ha are spatially quite close together. However, when rings B and C are trans-fused, the methyl group and Ha are in a spatially remote relationship. The stereochemical assignment of compound 180 was therefore also secure.

Although no studies were undertaken to probe the mechanism of the cyclization reaction, a catalytic cycle based on literature precedents can be proposed. Four basic processes are postulated, labelled A through D in Scheme 38. In step A (oxidative addition), the palladium(0) catalyst inserts into the carbon-iodine bond of the cyclization substrate 156. The so-formed organopalladium(II) species 181 reacts with potassium tert-butoxide in the presence of tert-butyl alcohol (step B, enolate anion formation). Under these conditions two possible potassium enolates (182 and 183) can be formed, but these species are in equilibrium with each other. Only 182 participates in the next step, however, and the equilibrium between these species is continually shifted to the left as 182 is consumed in step C. In step C, the six-membered palladocycle 184 is formed from the enolate 182. This process is formally a transmetallation, since the potassium enolate is replaced by a "palladium enolate" in which the palladium(II) is bonded to the α-carbon atom rather than the oxygen atom. When the cyclization experiment is performed, potassium iodide can be seen to start precipitating from the reaction mixture shortly after the dropwise addition of the base is commenced. The final step in the catalytic cycle (step D) is the reductive elimination of palladium(0) from the palladocycle 184. In this step, carbon-carbon bond formation between the vinyl carbon and the carbon α to the ketone takes
Scheme 38
place to form the cyclized product \textbf{157}. Palladium(II) is concomitantly reduced to palladium(0), and the next cycle of the catalytic process commences. As was mentioned previously, if the product \textbf{157} has $R_1 = H$, isomerization of the double bond into conjugation with the ketone function takes place under the basic reaction conditions, to give products of general structure \textbf{185}.

In summary, a new annulation method for the construction of five-membered rings had been developed. The use of the vinylgermane cuprate \textbf{110} as a synthetic equivalent of the $a^2,d^4$-synthon \textbf{153}, as well as the use of a new palladium(0)-catalyzed coupling method were central to the success of this procedure. The application of the annulation sequence to the construction, \textit{inter alia}, of the triquinane model compound \textbf{180} in seven-steps from cyclopentanone N,N-dimethylhydrazone (\textbf{158}) illustrates the potential use of this method as a tool in natural product synthesis.
2.4 Conclusion.

The bifunctional conjunctive reagents 4-iodo-2-trimethylstannyl-1-butene (129), 5-iodo-2-trimethylstannyl-1-pentene (21)\textsuperscript{13,26} and the related 2-trimethylgermyl-1-butene cuprate 110\textsuperscript{64} are versatile reagents in organic synthesis. The principal part of the work discussed in this thesis has illustrated their use in the development of a number of novel annulation procedures.

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \text{Me}_3\text{Ge} \\
\begin{array}{c}
\text{Me}_3\text{Sn} \\
(\text{C}_2\text{H}_5)_n \quad \text{I}
\end{array} & \quad \begin{array}{c}
\text{Me}_3\text{Ge} \\
(\text{C}_2\text{H}_5)_n \quad \text{Cu(CN)Li}
\end{array} \\
129 \text{ (n = 1)} & \quad 110
\end{align*}
\]

The reagents 129 and 21, for example, are synthetic equivalents of the d,a-synths 17 (Scheme 39). In this capacity, they have been shown to enter into annulations with ketones to yield products containing an allylic, angular hydroxyl group (20, Scheme 39; see section 2.1). Use of reagent 129 yields products in which the new ring is five-membered, while 21 yields products with new six-membered rings. The cyclization step in these annulations involves an experimentally simple procedure (low temperature metal halogen exchange) and delivers the cyclized products cleanly, in high yield and with predictable ring fusion stereochemistry.

The discovery of the vinylgermane cuprate 110 facilitated the key transformation in the total synthesis of the diterpenoid ambliol B. In the annulation depicted in equation b of Scheme 39, the synthetic equivalence of cuprate 110 to the 1-butene d\textsuperscript{2},d\textsuperscript{4}-synthon 111 was exploited. Thus, 110 could be combined with the enone 125, which contains two acceptor sites, to give, stereoselectively, the required bicyclic intermediate 128. On the basis of the stereochemical
Scheme 39

(a) 

(b) 

(c)
precedents uncovered during the development of the annulations schematized in equation \(a\), the trans-fused nature of \(128\) was confidently predicted. With the preparation of the latter compound, the relative stereochemistry of all four asymmetric centres present in the natural product had been installed correctly.

The versatility of reagent \(110\) became apparent with the development of a third annulation procedure (equation \(c\), Scheme 39). Here, \(110\) was utilized as a synthetic equivalent of the 1-butene \(\text{a}^2,\text{d}^4\)-synthon \(153\). Suitable enones of general structure \(154\) were combined with \(110\) to give annulated products of the type \(157\), or \(185\) (when \(R_1 = H\)). The cyclization step in this sequence involves the palladium(0)-catalyzed intramolecular coupling of a potassium enolate and a vinyl iodide (section 2.3.3).

The synthetic utility of the novel vinylgermane cuprate \(110\) (as well as its potential higher carbon homologues) has not yet been fully explored. The possible application of reagents such as these to other novel annulation methods and natural product synthesis is currently being pursued in our laboratories.
III. EXPERIMENTAL

3.1 General.

Infrared (ir) spectra were recorded on liquid films, chloroform solutions or potassium bromide discs, using a Perkin-Elmer model 1710 Fourier transform spectrophotometer (internal calibration) or a Perkin-Elmer model 710B spectrophotometer calibrated with the 1601 cm$^{-1}$ band of a polystyrene film.

Proton nuclear magnetic resonance ($^1$H nmr) spectra were recorded on deuteriochloroform solutions (unless otherwise stated) using a Varian model XL-300 or Bruker models WP-80 or WH-400 spectrometers. Signal positions are given in parts per million (δ) from tetramethylsilane (TMS) as the internal standard. Coupling constants (J-values) are reported in Hz and were measured on spectral spacings judged to be first order. Data are reported in the format: chemical shift in ppm (multiplicity, number of protons, assignment (if possible), coupling constants). Tin-proton coupling constants ($J_{\text{Sn-H}}$) are given as an average of the values for $^{117}$Sn and $^{119}$Sn.

Carbon nuclear magnetic resonance ($^{13}$C nmr) spectra were recorded on deuteriochloroform solutions at 75.3 MHz using the Varian spectrometer noted above. Signal positions are given in parts per million (δ) relative to deuteriochloroform (δ 77.0). Signals with negative intensities in an attached proton test (APT) are indicated by (-ve) following the chemical shift.

Low resolution mass spectra were recorded with a Varian/MAT CH4B mass spectrometer. High resolution mass spectra were recorded with a Kratos/AEI MS 50 or MS 902 mass spectrometer. All compounds subjected to high resolution mass measurements were homogenous by glc and/or tlc analysis. For those compounds containing trimethylstannyl or trimethylgermyl groups, the high resolution mass spectrometry molecular weight determinations were based on
$^{120}$Sn or $^{74}$Ge respectively and were made on the (M$^+\text{-Me}$) peak. Determinations for compounds containing tributylstannyl groups were made on the (M$^+\text{-Bu}$) peak.$^{74}$

Microanalyses were performed in the Microanalytical Laboratory, University of British Columbia.

Gas-liquid chromatography (glc) analyses were performed on Hewlett-Packard models 5880 or 5890 capillary gas chromatographs, employing 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54 and equipped with flame ionization detectors.

Thin-layer chromatography (tlc) analyses were done on commercial aluminum-backed silica gel plates (E. Merck, type 5554). Visualization was accomplished with ultraviolet light, iodine vapour and/or heating the chromatogram under a hot gun after immersion in 5% ammonium molybdate in 10% aqueous sulfuric acid. Conventional (drip) and flash column chromatography$^{75}$ were performed on 230-400 mesh silica gel (E. Merck, Silica gel 60).

Distillation temperatures (uncorrected) were recorded as air-bath temperatures required for short-path bulb-to-bulb (Kugelrohr) distillation. Melting points were measured on a Fisher-Johns apparatus and are uncorrected.

Solvents and reagents were purified and dried using established procedures.$^{76}$ THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane and carbon tetrachloride were distilled from $\text{P}_2\text{O}_5$. Diisopropylamine, triethylamine, HMPA, benzene, trimethylsilyl chloride and pyridine were distilled from calcium hydride. Petroleum ether refers to the fraction boiling between 30-60 °C.

Solutions of methyllithium in diethyl ether, $n$-butyllithium in hexane and $t$-butyllithium in pentane were obtained from the Aldrich Chemical Co., Inc. and were standardized using the method of Kofron and Baclawski.$^{77}$

Phosphate buffer, pH 7.2 (prepared from monobasic potassium phosphate and sodium hydroxide in reagent grade I water) was obtained from the Aldrich Chemical Co., Inc.

Cuprous bromide-dimethyl sulfide complex was prepared by the method of House.$^{78}$ Phenylthiocopper was prepared by the method of Posner.$^{79}$
Commercially available N,N-dimethylmethyleneammonium iodide (Eschenmoser’s salt) was sublimed at 140 °C and 0.07 mm Hg and stored under argon prior to use.

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

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

All other reagents and solvents were commercially available and were utilized without purification unless stated otherwise.

Cold bath temperatures were obtained by the following mixtures of solvents and coolants: -20 °C: 27 g CaCl2/100 ml H2O/dry ice; -48 °C: 46 g CaCl2/100 ml H2O/dry ice; -63 °C: chloroform/dry ice; -78 °C: acetone/dry ice; -98 °C: methanol/liquid N2.

All reactions were carried out under an atmosphere of dry argon using flame dried glassware unless stated otherwise.
3.2 Experimental Procedures.

3.2.1 Bicyclic Systems with an Allylic, Angular Hydroxyl Group.

3.2.1.1 Preparation of Cyclization Substrates.

Methyl (Z)-3-(Tri-n-butylstannyl)-2-butenoate (58).22

\[
\text{MeO} \quad \text{SnBu}_3
\]

To a cold (-20 °C), stirred solution of hexa-n-butylditin (6.96 g, 12 mmol) in 100 mL of dry THF was added a solution of n-butyllithium in hexane (7.50 mL, 1.60 M, 12 mmol). The resultant yellow solution was stirred at -20 °C for 20 min. Phenylthiocopper (2.06 g, 12 mmol) was added and the deep red-brown solution which formed after ~5 min was stirred (-20 °C) for an additional 20 min. After the reaction mixture had been cooled to -78 °C, a solution of methyl 2-butynoate (57) (0.98 g, 10 mmol) in 5 mL of dry THF was added and the resulting solution was stirred at -78 °C for 15 min and at -48 °C for 4 h. Methanol (1 mL) and diethyl ether (100 mL) were added, the mixture was allowed to warm to room temperature, and was then stirred overnight. During this time a flocculent yellow precipitate formed. The slurry was treated with anhydrous magnesium sulfate and was then suction filtered. Removal of the solvent from the filtrate gave a yellow oil which was flash chromatographed (14 x 5 cm column, elution with petroleum ether). The resultant clear oil was distilled (air-bath temperature 95 - 101 °C/0.04
Torr) to give 2.62 g (67%) of the unsaturated ester 58 as a colourless oil; ir (film): 1708, 1601, 1204, 862 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.83-1.63 (diffuse m, 27H), 2.15 (d, 3H, vinylic methyl group, \(J = 1.5\) Hz, \(^3J_{\text{Sn-H}} = 40\) Hz), 3.72 (s, 3H, -OCH\(_3\)), 6.42 (q, 1H, vinyl proton, \(J = 1.5\) Hz, \(^3J_{\text{Sn-H}} = 107\) Hz). Exact Mass calcd. for C\(_{13}\)H\(_{25}\)O\(_2\)Sn (M\(^+\)-Bu): 333.0877; found: 333.0874.

(Z)-3-(Tri-\(\pi\)-butylstannyl)-2-buten-1-ol (59).\(^{22}\)

\[
\text{SnBu}_3
\]
\[\text{HO} - \text{SnBu}_3\]

To a cold (-78 °C), stirred solution of the ester 58 (2.60 g, 6.7 mmol) in dry diethyl ether (80 mL) was added, dropwise, a solution of diisobutylaluminum hydride in hexane (16.7 mL, 1 M, 16.7 mmol). The solution was stirred at -78 °C for 1 h and at 0 °C for 2.5 h. After 8 mL of saturated aqueous ammonium chloride had been added, the mixture was allowed to warm to room temperature. The resultant slurry was treated with anhydrous magnesium sulfate and was then filtered through a short column of Florisil. The column was washed with ether and the solvent was removed \textit{in vacuo} from the combined eluate. The resultant crude product was flash chromatographed (14 x 5 cm column, elution with 9:1 petroleum ether - diethyl ether) to give a colourless product which was distilled (air-bath temperature 105 - 110 °C/0.04 Torr) to provide 2.38 g (99%) of the alcohol 59 as a clear oil; ir (film): 3319, 999, 875 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.82-1.66 (diffuse m, 28H), 1.95 (d, 3H, vinylic methyl group, \(J = 1.5\) Hz, \(^3J_{\text{Sn-H}} = 42\) Hz), 4.02 (m, 2H, -CH\(_2\)OH), 6.27 (m, 1H, vinyl proton, \(^3J_{\text{Sn-H}} = 120\) Hz). Exact Mass calcd. for C\(_{12}\)H\(_{25}\)OSn (M\(^+\)-Bu): 305.0928; found: 305.0922.
(Z)-1-Chloro-3-(tri-n-butylstannyl)-2-butene (60).

To a stirred solution of the allylic alcohol 59 (1.10 g, 3.05 mmol) in dry carbon tetrachloride (6 mL) was added triphenylphosphine (0.94 g, 3.58 mmol) and the resulting clear solution refluxed for 24 h. During this time, triphenylphosphine oxide slowly precipitated from the solution. The bulk of the solvent was removed and the remaining slurry was triturated with hexane (~10 mL). The precipitated solids were removed by filtration through a short column of Florisil. The column was washed with hexane. Removal of the solvent from the combined eluate, followed by distillation (air-bath temperature 98 - 105 °C/0.04 Torr) of the residual oil, yielded 909 mg (79%) of the chloride 60 as a colourless oil; ir (film): 1247, 875, 688 cm⁻¹; ¹H nmr (300 MHz, CDCl₃) δ: 0.83-1.66 (diffuse m, 27H), 1.96 (dt, 3H, vinylic methyl group, J = 1.6, 0.8 Hz, ³J_{Sn-H} = 41 Hz), 3.97 (dq, 2H, -CH₂Cl, J = 7.7, 0.8 Hz), 6.24 (tq, 1H, vinyl proton, J = 7.7, 1.6 Hz, ³J_{Sn-H} = 114 Hz). Exact Mass calcd. for C₁₂H₂₄ClSn (M⁺-Bu): 323.0588; found: 323.0591.

General Procedure 1: Preparation of Keto Vinylstannanes.¹³

To a cold (0 °C), stirred solution of LDA (1.1 - 1.3 equiv) in dry THF (2 mL per mmol of LDA) was added, dropwise, a solution of the appropriate N,N-dimethylhydrazone⁸⁰ (1 equiv) in dry THF (1.5 mL per mmol). The reaction mixture was stirred at 0 °C for 2 h. After the mixture
had been cooled to -78 °C, a solution of the appropriate vinylstannane halide (1.2 - 1.6 equiv) in dry THF (~1 mL per mmol) was added dropwise. The resulting reaction mixture was allowed to warm slowly to room temperature and was then stirred overnight. Water (6 mL per mmol of hydrazone) and dichloromethane (15 mL per mmol of hydrazone) were added. The layers were separated and the aqueous phase was extracted thoroughly with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent afforded a crude oil which was dissolved in THF (9 mL per mmol of hydrazone). To this solution were added phosphate buffer (pH 7.2, 4 mL per mmol of hydrazone), water (4 mL per mmol of hydrazone) and sodium periodate (5 equiv). The reaction mixture was stirred overnight and was then gravity filtered. The bulk of the THF was removed from the filtrate and the remaining mixture was thoroughly extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent afforded a yellow oil which was flash chromatographed. Distillation of the resultant oil gave the desired keto vinylstannane.

Preparation of the Keto Vinylstannanes 44 and 45.

Following general procedure 1, a solution of LDA (1.3 equiv) was treated successively with the \( N,N \)-dimethylhydrazone of 4-\textit{tert-}butylocyclohexanone\textsuperscript{80} (43, 217 mg, 1.11 mmol) and 4-ido-2-trimethylstannyl-1-butene\textsuperscript{13} (129, 607 mg, 1.6 equiv). The crude oil thus obtained was
treated with a buffered THF/water solution of sodium periodate. Flash chromatography (14 x 3 cm column, elution with 97 : 3 petroleum ether - diethyl ether) of the crude material, followed by distillation (air-bath temperature 113 - 120 °C/0.1 Torr) of the oil thus obtained, provided 258 mg (63%) of a mixture of the keto vinylstannanes 44 and 45. Tlc analysis indicated that the trans-disubstituted compound 44 predominated in the mixture.

Equilibration of 44 and 45 was accomplished by adding a solution of the mixture epimers (285 mg, 0.77 mmol) in methanol (5 mL) to a solution of sodium methoxide (~ 0.15 mmol) in methanol (20 mL). The reaction mixture was stirred overnight and the solvent was removed. The residue was partitioned between dichloromethane (25 mL) and water (15 mL) and the layers were separated. The aqueous phase was extracted thoroughly with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent and flash chromatography (14 x 3 cm column, elution with 97 : 3 petroleum ether - diethyl ether) of the resulting oil gave two fractions. The first compound to be eluted was the cis keto vinylstannane 45. Concentration of the appropriate fractions provided a colourless oil which was distilled (air-bath temperature 107 - 114 °C/0.1 Torr) to give 45 (241 mg, 85%); ir (film): 3033, 1714, 914, 769 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, J_{Sn-H} = 53 Hz), 0.90 (s, 9H, -CMe₃), 1.06-1.27 (m, 2H), 1.36-1.50 (m, 1H), 1.53-1.63 (m, 1H), 1.88-2.00 (m, 1H), 2.05-2.17 (m, 2H), 2.20-2.43 (m, 5H), 5.15 (m, 1H, Hₐ, J_{Sn-H} = 70 Hz), 5.65 (m, 1H, Hₐ, J_{Sn-H} = 149 Hz).

Exact Mass calcd. for C₁₆H₂₉OSn (M⁺-Me): 357.1240; found: 357.1243.

The second compound to be eluted was the trans keto vinylstannane 44. Concentration of the appropriate fractions provided a colourless oil which was distilled (air-bath temperature 113 - 120 °C/0.1 Torr) to give 44 (37 mg, 13%) as a colourless oil; ir (film): 3035, 1714, 916, 769 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.14 (s, 9H, -SnMe₃, J_{Sn-H} = 53 Hz), 0.91 (s, 9H, -CMe₃), 1.39-1.89 (m, 6H), 1.96-2.05 (m, 1H), 2.14-2.47 (m, 5H), 5.18 (m, 1H, Hₐ, J_{Sn-H} = 70 Hz), 5.68 (m, 1H, Hₐ, J_{Sn-H} = 153 Hz). Exact Mass calcd. for C₁₆H₂₉OSn (M⁺-Me): 357.1240; found: 357.1241.
Preparation of the Keto Vinylstannanes 46 and 47.

Following general procedure 1, a solution of LDA (1.1 equiv) was treated successively with the \( N,N \)-dimethylhydrazone of 4-tert-butylcyclohexanone\(^{80}\) (43, 365 mg, 1.86 mmol) and 5-iodo-2-trimethylstannyl-1-pentene\(^{13}\) (21, 827 mg, 1.2 equiv). The crude oil thus obtained was treated with a buffered THF/water solution of sodium periodate. Flash chromatography (14 x 3 cm column, elution with 97:3 petroleum ether - diethyl ether) of the crude material, followed by distillation (air-bath temperature 122 - 130 °C/0.1 Torr) of the oil thus obtained, provided 426 mg (59%) of a mixture of the keto vinylstannanes 46 and 47. Tlc analysis indicated that the trans-disubstituted compound 46 predominated in the mixture.

Equilibration of 46 and 47 was accomplished by adding a solution of the mixture epimers (292 mg, 0.76 mmol) in methanol (5 mL) to a solution of sodium methoxide (\(~0.15\) mmol) in methanol (18 mL). The reaction mixture was stirred overnight and the solvent was removed. The residue was partitioned between dichloromethane (25 mL) and water (15 mL) and the layers were separated. The aqueous phase was extracted thoroughly with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent and flash chromatography (14 x 3 cm column, elution with 97:3 petroleum ether - diethyl ether) of the resulting oil gave two fractions. The first compound to be eluted was the cis keto vinylstannane
47. Concentration of the appropriate fractions provided a colourless oil which was distilled (air-bath temperature 122 - 130 °C/0.1 Torr) to give 47 (243 mg, 83%); ir (film): 3033, 1716, 913, 768 cm⁻¹; \(^1\)H nmr (400 MHz, CDCl₃) 8: 0.14 (s, 9H, -SnMe₃, \(^2\)J\(_{Sn-H} = 54\) Hz), 0.92 (s, 9H, -CMe₃), 1.06-1.19 (m, 2H), 1.32-1.50 (m, 3H), 1.54-1.64 (m, 1H), 1.74-1.85 (m, 1H), 2.05-2.43 (m, 7H), 5.14 (m, 1H, H\(_a\), \(^3\)J\(_{Sn-H} = 70\) Hz), 5.66 (m, 1H, H\(_b\), \(^3\)J\(_{Sn-H} = 153\) Hz). Exact Mass calcd. for C\(_{17}\)H\(_{31}\)OSn (M⁺-Me): 371.1397; found: 371.1401.

The second compound to be eluted was the trans keto vinylstannane 46. Concentration of the appropriate fractions provided a colourless oil which was distilled (air-bath temperature 122 - 130 °C/0.1 Torr) to give 46 (43 mg, 15%); ir (film): 3040, 1714, 914, 769 cm⁻¹; \(^1\)H nmr (400 MHz, CDCl₃) 8: 0.14 (s, 9H, -SnMe₃, \(^2\)J\(_{Sn-H} = 54\) Hz), 0.92 (s, 9H, -CMe₃), 1.24-1.75 (m, 8H), 1.80-2.06 (m, 1H), 2.24-2.48 (m, 4H), 5.16 (m, 1H, H\(_a\), \(^3\)J\(_{Sn-H} = 70\) Hz), 5.66 (m, 1H, H\(_b\), \(^3\)J\(_{Sn-H} = 153\) Hz). Exact Mass calcd. for C\(_{17}\)H\(_{31}\)OSn (M⁺-Me): 371.1397; found: 371.1398.

Preparation of the Keto Vinylstannane 61.

Following general procedure 1, a solution of LDA (1.3 equiv) was treated successively with the N,N-dimethylhydrazone of 1,4-cyclohexanedione mono-2-2-dimethyltrimethylene ketal\(^8\) (365 mg, 1.52 mmol) and (Z)-1-chloro-3-(tri-n-butylstannyl)-2-butene (60, 873 mg, 1.5 equiv). The
crude oil thus obtained was treated with a buffered THF/water solution of sodium periodate. Flash chromatography (16 x 4 cm column, elution with 90 : 10 petroleum ether - diethyl ether) of the crude material, followed by distillation (air-bath temperature 150 - 160 °C/0.04 Torr) of the oil thus obtained, provided 581 mg (71%) of the keto vinylstannane 61; ir (film): 1718, 1623, 1121, 875 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.80-1.68 (diffuse m, 30H), 0.90, 1.01 (s, s, 3H each, CH\(_3\)CCH\(_3\)), 1.90 (br s, 3H, vinylic methyl group, \(^3\)J\(_{\text{Sn-H}}\) = 42 Hz), 2.24-2.37 (m, 1H), 2.40-2.60 (m, 5H), 3.55, 3.57 (s, s, 2H each, -OCH\(_2\)CCH\(_2\)O-), 5.99 (m, 1H, vinyl proton, \(^3\)J\(_{\text{Sn-H}}\) = 132 Hz). Exact Mass calcd. for C\(_{23}\)H\(_{41}\)O\(_3\)Sn (M\(^+\)-Bu): 485.2078; found: 485.2086.

General Procedure 2: Preparation of \(\alpha\)-Methylated Keto Vinylstannanes.

To a cold (0 °C), stirred solution of potassium tert-butoxide (1.5 - 5 equiv) in dry THF (16 mL per mmol) and dry tert-butyl alcohol (8 mL per mmol) was added, dropwise, a solution of the appropriate keto vinylstannane (1 equiv) in dry THF (2 - 3 mL per mmol). The resulting solution was stirred at 0 °C for 20 min. Methyl iodide (1.5 equiv, filtered through basic alumina prior to use) was added neat and the reaction mixture was allowed to warm slowly to room temperature and was then stirred overnight. Saturated aqueous ammonium chloride (pH 8) (~10 mL per mmol of the keto vinylstannane) and diethyl ether (~15 mL per mmol of the keto vinylstannane) were added. The layers were separated and the aqueous phase was thoroughly extracted with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. When the crude material thus obtained was flash chromatographed and distilled, the desired methylated product was furnished in pure form, or as a constituent of an inseparable mixture of compounds.
Preparation of the α-Methylated Keto Vinylstannane 41.\textsuperscript{13}

\[
\begin{align*}
\text{Me} & \quad \text{SnMe}_3 \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{SnMe}_3 \\
\end{align*}
\]

Following general procedure 2, a solution of potassium tert-butoxide (139 mg, 1.5 equiv) was treated successively with the keto vinylstannane 40\textsuperscript{13} (337 mg, 0.81 mmol) and methyl iodide (173 mg, 1.5 equiv). Flash chromatography (14 x 3 cm column, elution with 85 : 15 petroleum ether - diethyl ether) of the crude product mixture, followed by distillation (air-bath temperature 120 - 170 °C/0.04 Torr) of the resulting oil, gave 292 mg of an inseparable mixture of compounds containing the desired product 41. This mixture was used without further purification in the preparation of the keto vinyl iodide 51 (\textit{vide infra}, p. 105).

Preparation of the α-Methylated Keto Vinylstannane 42.\textsuperscript{13}

\[
\begin{align*}
\text{Me} & \quad \text{Hb} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{Me} \\
\text{Me} & \quad \text{Hb} \\
\text{Ha} & \quad \text{SnMe}_3 \\
\end{align*}
\]

Following general procedure 2, a solution of potassium tert-butoxide (159 mg, 3.3 equiv) was treated successively with the keto vinylstannane 22\textsuperscript{13} (184 mg, 0.43 mmol) and methyl iodide
(91 mg, 1.5 equiv). Flash chromatography (14 x 2 cm column, elution with 85 : 15 petroleum ether - diethyl ether) of the crude product mixture, followed by distillation (air-bath temperature 153 - 160 °C/0.04 Torr) of the resulting oil, gave 92 mg (48%) of the desired methylated product; ir (film): 3040, 1712, 1109, 769 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.13 (s, 9H, -SnMe₃, ²J_sn-H = 52 Hz), 0.98, 1.02, 1.10 (s, s, s, 3H each, -CH₃ groups), 1.12-1.42 (m, 3H), 1.49, 1.67 (td, td, 1H each, J = 14, 5 Hz in each case), 1.90 (d, 1H, J = 16 Hz), 2.02-2.30 (m, 4H), 2.38-2.56 (m, 2H), 3.45-3.60 (m, 4H, -OCH₂CCH₂O-), 5.13 (m, 1H, Hₐ, ³J_sn-H = 72 Hz), 5.63 (m, 1H, Hₐ, ³J_sn-H = 153 Hz). Exact Mass calcd. for C₁₉H₃₅O₃Sn (M⁺-Me): 429.1451; found: 429.1456.

Preparation of the α-Methylated Keto Vinylstannane 62.

Following general procedure 2, a solution of potassium tert-butoxide (634 mg, 5 equiv) was treated successively with the keto vinylstannane 61 (580 mg, 1.13 mmol) and methyl iodide (685 mg, 4 equiv). Flash chromatography (15 x 3 cm column, elution with 93 : 7 petroleum ether - diethyl ether) of the crude product mixture, followed by distillation (air-bath temperature 155 - 165 °C/0.04 Torr) of the resulting oil, gave 240 mg (40%) of the desired methylated product; ir (film): 1713, 1621, 1108 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.81-1.68 (diffuse m, 26H), 0.97, 1.02, 1.12 (s, s, s, 3H each, -CH₃ groups), 1.79-2.59 (m, 9H), 1.89 (br d, 3H, vinylic methyl group, J = 2 Hz, ³J_sn-H = 44 Hz), 3.46-3.62 (m, 4H, -OCH₂CCH₂O-), 5.84-5.92 (m, 1H, vinyl proton, ³J_sn-H = 136 Hz). Exact Mass calcd. for C₂₄H₄₃O₃Sn (M⁺-Bu): 499.2234; found: 499.2230.
**General Procedure 3: Preparation of Keto Vinyl Iodides**

To a stirred solution of the appropriate keto vinylstannane (1 equiv) in dry dichloromethane (22 mL per mmol) was added, dropwise, a solution of iodine in dry dichloromethane (slightly over 1 equiv, 0.04 M) until the purple colour of the iodine persists in the reaction mixture. Aqueous sodium thiosulfate (~0.1 M, ~ the same volume as that of dichloromethane) was added and the organic layer was separated. The aqueous phase was extracted with an additional aliquot of dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent provided the crude keto vinyl iodide which was distilled to yield the required product. In some cases, the crude product was chromatographed prior to distillation.

**Preparation of the Keto Vinyl Iodide 50.**

Following general procedure 3, the keto vinylstannane 40\(^{13}\) (748 mg, 1.80 mmol) was converted into the keto vinyl iodide 50. The crude product was distilled (air-bath temperature 153 - 158 °C/0.04 Torr) to provide 657 mg (96%) of the required iodide 50 as a light yellow oil; ir (film): 1714, 1617, 1120 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.01, 1.03 (s, s, 3H each, -CMe\(_2\)), 1.36-1.48 (m, 1H), 1.54 (t, 1H, \(J = 14\) Hz), 1.71-1.84 (m, 1H), 1.95-2.08 (m, 1H), 2.25-2.35 (m,
1H), 2.37-2.63 (m, 6H), 3.55, 3.57 (s, s, 2H each, -OCH₂CCH₂O-), 5.72 (m, 1H, Hₐ) 6.05 (m, 1H, Hₖ). *Exact Mass* calcd. for C₁₅H₂₃I₃O₄: 378.0694; found: 378.0694.

**Preparation of the Keto Vinyl Iodide 51.**

Following general procedure 3, a mixture of compounds containing the keto vinylstannane 4₁₃ (344 mg) was converted into a mixture of products containing the keto vinyl iodide 5₁. The crude mixture was drip column chromatographed (50 g of silica gel, elution with 90 : 10 petroleum ether - diethyl ether) to give a fraction which, after distillation (air-bath temperature 145 - 153 °C/0.04 Torr), provided 203 mg (48% from the keto vinylstannane 4₀) of the required iodide 5₁ as a light yellow oil; ir (film): 1709, 1617, 1108 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.01, 1.02, 1.15 (s, s, s, 3H each, -CH₃ groups), 1.74 (td, 1 H, J = 12, 5 Hz), 1.90-2.02 (m, 2H), 2.05-2.27 (m, 4H), 2.35-2.61 (m, 3H), 3.42-3.65 (m, 4H, -OCH₂CCH₂O-), 5.68 (m, 1H, Hₐ), 6.03 (m, 1H, Hₖ). *Exact Mass* calcd. for C₁₆H₂₅I₃O₄: 392.0850; found: 392.0848.
Preparation of the Keto Vinyl Iodide 52.

Following general procedure 3, the keto vinylstannane 22\textsuperscript{13} (190 mg, 0.44 mmol) was converted into the keto vinyl iodide 52. The crude product was distilled (air-bath temperature 158 - 166 °C/0.04 Torr) to provide 165 mg (95%) of the required iodide 52 as a pale yellow oil which solidified on standing. Recrystallization from hexane afforded light yellow crystals, mp 66 - 68 °C; ir (CHCl\textsubscript{3}): 1713, 1618, 1120 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) \delta: 0.99, 1.06 (s, s, 3H each, -CMe\textsubscript{2}), 1.14-1.29 (m, 1H), 1.47-1.62 (m, 3H), 1.71-1.84 (m, 2H), 2.26-2.35 (m, 1H), 2.36-2.43 (m, 2H), 2.46-2.60 (m, 4H), 3.55, 3.58 (s, s, 2H each, -OCH\textsubscript{2}CCH\textsubscript{2}O-), 5.70 (m, 1H, H\textsubscript{a}), 6.04 (m, 1H, H\textsubscript{b}). \textit{Exact Mass} calcd. for C\textsubscript{16}H\textsubscript{25}I\textsubscript{3}: 392.0850; found: 392.0853.

Preparation of the Keto Vinyl Iodide 53.

Following general procedure 3, the keto vinylstannane 42\textsuperscript{13} (82 mg, 0.19 mmol) was converted into the keto vinyl iodide 53. The crude product was distilled (air-bath temperature 142 - 150 °C/0.04 Torr) to provide 72 mg (96%) of the required iodide 53 as a colourless oil; ir (film):
1710, 1617, 1107 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.00, 1.02, 1.14 (s, s, s, 3H each, -CH\(_3\) groups), 1.27-1.59 (m, 3H), 1.59-1.70 (m, 1H), 1.95 (dd, 1H, \(J = 15, 2\) Hz), 2.05-2.23 (m, 3H), 2.36 (br t, 2H, \(J = 7\) Hz), 3.46-3.62 (m, 4H, -OCH\(_2\)CCH\(_2\)O-), 5.70 (br d, 1H, H\(_a\), \(J = 1.5\) Hz), 6.02 (dd, 1H, H\(_b\), \(J = 3, 1.5\) Hz). Exact Mass calcd. for C\(_{17}\)H\(_{27}\)I\(_3\): 406.1007; found: 406.1002.

Preparation of the Keto Vinyl Iodide S4.

Following general procedure 3, the keto vinylstannane 45 (225 mg, 0.61 mmol) was converted into the keto vinyl iodide S4. The crude product was flash chromatographed (14 x 2 cm column, elution with 97 : 3 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 109 - 118 °C/0.1 Torr) to provide 165 mg (73%) of the required iodide S4 as a light yellow oil; ir (film): 1714, 1618, cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.92 (s, 9H, -CM\(_3\)), 1.18 (q, 1H, \(J = 12\) Hz), 1.33-1.51 (m, 2H), 1.60 (tt, 1H, \(J = 12, 3\) Hz), 1.95-2.06 (m, 1H), 2.07-2.17 (m, 2H), 2.26-2.55 (m, 5H), 5.71 (m, 1H, H\(_a\)), 6.03 (m, 1H, H\(_b\)). Anal. calcd. for C\(_{14}\)H\(_{23}\)I\(_2\): C 50.31, H 6.94, I 37.97; found: C 50.26, H 6.85, I 37.79.
Preparation of the Keto Vinyl Iodide 55.

Following general procedure 3, the keto vinylstannane 47 (114 mg, 0.30 mmol) was converted into the keto vinyl iodide 55. The crude product was distilled (air-bath temperature 140 - 148 °C/0.1 Torr) to provide 98 mg (95%) of the required iodide 55 as a pale yellow oil; ir (film): 1714, 1618 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.93 (s, 9H, -CMe₃), 1.08-1.24 (m, 2H), 1.37-1.64 (m, 4H), 1.72-1.84 (m, 1H), 2.05-2.19 (m, 2H), 2.23-2.46 (m, 5H), 5.69 (m, 1H, Hₐ), 6.04 (m, 1H, Hₖ). Exact Mass calcd. for C₁₃H₂₅IO: 348.0952; found: 348.0952.

Preparation of the Keto Vinyl Iodide 63.

Following general procedure 3, the keto vinylstannane 61 (260 mg, 0.48 mmol) was converted into the keto vinyl iodide 63. The crude product was flash chromatographed (14 x 2 cm column, elution with 90 : 10 petroleum ether - diethyl ether) and the oil thus obtained was
distilled (air-bath temperature 130 - 134 °C/0.04 Torr) to provide 137 mg (76%) of the required iodide 63 as a light yellow oil; ir (film): 1715, 1650, 1122 cm⁻¹; ^1^H nmr (400 MHz, CDCl₃) δ: 1.00, 1.04 (s, s, 3H each, CH₃CCH₃), 1.51-1.66 (m, 1H), 1.69-1.83 (m, 1H), 2.08-2.20 (m, 1H), 2.26-2.74 (m, 6H), 2.50 (br s, 3H, vinylic methyl group), 3.55, 3.57 (s, s, 2H each, -OCH₂CCH₂O-), 5.42-5.51 (m, 1H, vinyl proton). Exact Mass calcd. for C₁₅H₂₃IO₃: 378.0693; found: 378.0692.

**Preparation of the Keto Vinyl Iodide 64.**

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\text{Following general procedure 3, the keto vinylstannane 62 (232 mg, 0.42 mmol) was converted into the keto vinyl iodide 64. The crude product was flash chromatographed (14 x 2 cm column, elution with 87 : 13 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 127 - 134 °C/0.04 Torr) to provide 130 mg (79%) of the required iodide 64 as a light yellow oil; ir (film): 1710, 1645, 1104 cm⁻¹; ^1^H nmr (400 MHz, CDCl₃) δ: 0.99, 1.04, 1.19 (s, s, s, 3H each, -CH₃ groups), 2.00-2.65 (m, 8H), 2.51 (br s, 3H, vinylic methyl group), 3.45-3.65 (m, 4H, -OCH₂CCH₂O-), 5.26-5.34 (m, 1H, vinyl proton). Exact Mass calcd. for C₁₆H₂₅IO₃: 392.0850; found: 392.0848.}
3.2.1.2 Cyclization Studies.

General Procedure 4: Cyclization Reactions of Keto Vinyl Iodides.$^{26}$

To a cold (-78 °C) solution of the appropriate keto vinyl iodide in THF (7 mL per 0.1 mmol) was added a solution of n-butyllithium in hexane (1.2 - 1.6 M, 1.2 or 2.5 equiv) and the reaction mixture was stirred for 10 - 15 min. Water (~5 mL per mmol of starting material) was added and the reaction mixture was allowed to warm to room temperature. Diethyl ether (~10 mL per mmol of starting material) was added and the layers were separated. The aqueous layer was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the crude material thus obtained was flash chromatographed. Concentration of the appropriate fractions and removal of traces of solvent under reduced pressure (vacuum pump) provided the corresponding cyclized product(s) containing an allylic, angular hydroxyl group.

Preparation of the Allylic Alcohols 70 and 71.

Following general procedure 4, the keto vinyl iodide 50 (40 mg, 0.11 mmol) was treated with n-butyllithium (2.5 equiv). The crude product mixture was flash chromatographed (12 x 1
cm column, elution with 60 : 40 petroleum ether - diethyl ether) to give two fractions. The first compound to be eluted was the trans-fused allylic alcohol 70. Concentration of the appropriate fractions provided 10.2 mg (38%) of 70, a white crystalline solid (recrystallized from hexane/diethyl ether, mp 103 - 104 °C; ir (CHC\(_3\)): 3604, 3073, 1658, 1095 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.97, 0.99 (s, s, 3H each, -CMe\(_2\)), 1.48-1.79 (m, 6H), 1.81-1.94 (m, 2H), 2.17-2.39 (m, 3H), 2.57 (ddq, 1H, \(J = 18, 9, \sim 2\) Hz), 3.42-3.61 (m, 4H, -OCH\(_2\)CCH\(_2\)O-), 4.85, 4.99 (br t, br t, 1H each, vinyl protons, \(J = \sim 2\) Hz); \(^{13}\)C nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): 22.7 (-ve), 22.8 (-ve), 25.8, 28.1, 29.4, 29.7, 30.2, 31.3, 44.2 (-ve), 70.0, 70.2, 77.4, 98.8, 105.3, 155.8. Exact Mass calcd. for C\(_{15}\)H\(_{24}\)O\(_3\): 252.1726; found: 252.1723.

The second compound to be eluted was the cis-fused allylic alcohol 71. Concentration of the appropriate fractions provided 8.3 mg (31%) of 71, a colourless oil; ir (film): 3419, 3070, 1656, 1113, 1093 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.96, 0.98 (s, s, 3H each, -CMe\(_2\)), 1.30-1.40 (m, 2H), 1.42-1.54 (m, 2H), 1.80 (td, 1H, \(J = 12, 4\) Hz), 1.89-2.14 (m, 5H), 2.35-2.60 (m, 2H), 3.40-3.58 (m, 4H, -OCH\(_2\)CCH\(_2\)O-), 5.01, 5.10 (br t, br t, 1H each, vinyl protons, \(J = \sim 2\) Hz). \(^{13}\)C nmr (75.3 MHz, CDCl\(_3\)) \(\delta\): 22.7 (-ve), 22.8 (-ve), 26.1, 28.2, 29.4, 29.7, 30.1, 33.0, 44.5 (-ve), 69.9, 70.2, 79.4, 97.5, 107.1, 154.5. Exact Mass calcd. for C\(_{15}\)H\(_{24}\)O\(_3\): 252.1725; found: 252.1726.

Preparation of the Allylic Alcohol 72.

Following general procedure 4, the keto vinyl iodide 51 (104 mg, 0.27 mmol) was treated
with n-butyllithium (2.5 equiv). The crude product was flash chromatographed (12 x 1 cm column, elution with 75 : 25 hexane - diethyl ether) to give 58.5 mg (83%) of the cis-fused allylic alcohol 72, a white crystalline solid (recrystallized from hexane/diethyl ether, mp 99 - 102 °C). X-ray crystallographic analysis confirmed the structure of this solid\textsuperscript{25a}; ir (film): 3620, 1665, 1121 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) \(\delta\): 0.92, 0.96, 0.98 (s, s, s, 3H each, \(-\text{CMe}_2\) and angular Me), 1.35 (br s, 1H, OH), 1.38-1.46 (m, 1H), 1.56-2.06 (m, 7H), 2.29-2.51 (m, 2H), 3.41 (dd, 1H, H\textsubscript{a} or H\textsubscript{b}, \(J = 12, 1.3\) Hz), 3.46 (dd, 1H, H\textsubscript{a} or H\textsubscript{b}, \(J = 11, 1.3\) Hz), 3.52 (d, 1H, H\textsubscript{c} or H\textsubscript{d}, \(J = 12\) Hz), 3.57 (d, 1H, H\textsubscript{c} or H\textsubscript{d}, \(J = 11\) Hz), 4.95, 5.10 (br t, br t, 1H each, vinyl protons, \(J = 2.1\) Hz, \(J = 2.5\) Hz). \textsuperscript{13}C nmr (75.3 MHz, CDCl\textsubscript{3}) \(\delta\): 22.1 (ve), 22.6 (ve), 22.9 (ve), 26.2, 30.1, 30.3, 32.6, 36.8, 44.4, 70.0, 70.0, 80.3, 98.0, 106.4, 156.8. \textit{Exact Mass} calcd. for C\textsubscript{16}H\textsubscript{26}O\textsubscript{3}: 266.1882; found: 266.1878.

Preparation of the Allylic Alcohols \textbf{66} and \textbf{67}.

Following general procedure 4, the keto vinyl iodide 52 (79 mg, 0.20 mmol) was treated with n-butyllithium (2.2 equiv). The crude product mixture was flash chromatographed (12 x 1 cm column, elution with 75 : 25 petroleum ether - diethyl ether) to give two fractions. The first compound to be eluted was the trans-fused allylic alcohol 66. Concentration of the appropriate
fractions provided 38 mg (71%) of 66, a white crystalline solid (recrystallized from hexane/diethyl ether, mp 157 - 158 °C). X-ray crystallographic analysis confirmed the structure of this solid25a; ir (CHCl₃): 3602, 3087, 1645, 1095 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.96, 1.05 (s, s, 3H each, -CMe₂), 1.05 (br s, 1H, -OH), 1.28-2.00 (m, 10H), 2.16 (br d, 1H, J = 12 Hz), 2.20-2.30 (m, 1H), 2.50 (td, 1H, J = 14, 5 Hz), 3.41-3.61 (m, 4H,-OCH₂CCH₂O-), 4.75, 4.80 (br s, br s, 1H each, vinyl protons). ¹³C nmr (75.3 MHz, CDCl₃) δ: 22.7 (-ve), 22.7 (-ve), 27.3, 27.4, 28.2, 30.2, 31.6, 32.4, 34.9, 41.3 (-ve), 70.0, 70.1, 71.2, 97.8, 106.8, 153.1. Exact Mass calcd. for C₁₆H₂₆O₃: 266.1882; found: 266.1875.

The second compound to be eluted was the cis-fused allylic alcohol 67. Concentration of the appropriate fractions provided 3 mg (5%) of 67, a colourless oil; ir (film): 3447, 3085, 1643, 1102 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.93, 1.01 (s, s, 3H each, -CMe₂), 1.16-2.00 (m, 10H), 2.04-2.22 (m, 3H), 2.36-2.46 (m, 1H), 3.43-3.61 (m, 4H,-OCH₂CCH₂O-), 4.86, 5.00 (br s, br s, 1H each, vinyl protons). Exact Mass calcd. for C₁₆H₂₆O₃: 266.1882; found: 266.1886.

Preparation of the Allylic Alcohol 73.

Following general procedure 4, the keto vinyl iodide 53 (60 mg, 0.14 mmol) was treated with n-butyllithium (2.5 equiv). The crude product was flash chromatographed (12 x 1 cm column, elution with 65 : 35 hexane - diethyl ether) to give 31 mg (74%) of the cis-fused allylic
alcohol 73; ir (film): 3493, 3084, 1643, 1108 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.89 (s, 6H, -CMe\(_2\)), 1.06 (s, 3H, Me), 1.22 (br d, 1H, \(J = 14\) Hz), 1.33 (dt, 1H, \(J = 14, 4\) Hz), 1.41 (s, 1H, OH), 1.46-1.57 (m, 2H), 1.61 (d, 1H, \(J = 15\) Hz), 1.87-2.12 (m, 3H), 2.17-2.47 (m, 4H), 3.38-3.65 (m, 4H, -OCH\(_2\)CCH\(_2\)O-), 4.81, 4.98 (br s, br s, 1H each, vinyl protons). Exact Mass calcd. for C\(_{17}\)H\(_{28}\)O\(_3\): 280.2039; found: 280.2043.

Preparation of the Allylic Alcohols 74 and 75.

Following general procedure 4, the keto vinyl iodide 54 (153 mg, 0.46 mmol) was treated with n-butyllithium (1.2 equiv). The crude product mixture was flash chromatographed (14 x 1 cm column, elution with 93 : 7 to 88 : 12 petroleum ether - diethyl ether) to give two fractions. The first compound to be eluted was the trans-fused allylic alcohol 74. Concentration of the appropriate fractions provided 43 mg (45%) of 74, a colourless oil; ir (film): 3470, 3071, 1658, cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.89 (s, 9H, -CMe\(_2\)), 1.06 (tt, 1H, \(J = 12, 4\) Hz), 1.19-1.75 (m, 9H), 2.02 (dt, 1H, \(J = 13, 3\) Hz), 2.28 (dtt, 1H, \(J = 18, 9, \sim 2\) Hz), 2.56 (ddq, 1H, \(J = 18, 9, \sim 2\) Hz), 4.84, 4.99 (br t, br t, 1H each, \(J = \sim 2\) Hz, vinyl protons). Exact Mass calcd. for C\(_{17}\)H\(_{28}\)O: 208.1827; found: 208.1820.

The second compound to be eluted was the cis-fused allylic alcohol 75. Concentration of the appropriate fractions provided 31 mg (33%) of 75, a colourless oil; ir (film): 3397, 3072,
1657, cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.83 (s, 9H, -CMe$_3$), 0.83-0.94 (m, 1H), 1.06 (tt, 1H, $J$ = 12, 3 Hz), 1.23-1.40 (m, 3H), 1.55-1.73 (m, 3H), 1.90 (dt, 1H, $J$ = 13, 7 Hz), 2.07-2.21 (m, 2H), 2.43 (dtt, 1H, $J$ = 18, 9, ~2 Hz), 2.58 (ddq, 1H, $J$ = 18, 10, ~2 Hz), 5.01, 5.07 (br t, br t, 1H each, $J$ = ~2 Hz, vinyl protons). *Exact Mass* calcd. for C$_{14}$H$_{24}$O: 208.1827; found: 208.1824.

**Preparation of the Allylic Alcohol 76.**

Following general procedure 4, the keto vinyl iodide 55 (199 mg, 0.57 mmol) was treated with $n$-butyllithium (1.2 equiv). The crude product was flash chromatographed (14 x 2 cm column, elution with 96 : 4 petroleum ether - diethyl ether) to give 95 mg (75%) of the trans-fused allylic alcohol 76 as colourless crystals (recrystallized from ethanol/water, mp 78 -79 $^\circ$C); ir (KBr disk): 3460, 3100, 1650, 900 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.88 (s, 9H, -CMe$_3$), 1.01-1.11 (m, 2H), 1.22-1.74 (m, 9H), 1.77-1.91 (m, 2H), 2.15 (br d, 1H, $J$ = 13 Hz), 2.52 (td, 1H, $J$ = 15, 5 Hz), 4.74, 4.79 (br s, br s, 1H each, vinyl protons). *Exact Mass* calcd. for C$_{15}$H$_{26}$O: 222.1984; found: 222.1980.
Preparation of the Allylic Alcohol 87b.

Following general procedure 4, the keto vinyl iodide 64 (87 mg, 0.22 mmol) was treated with n-butyllithium (2.5 equiv) at -63 °C. The crude product was flash chromatographed (14 x 1 cm column, elution with 70 : 30 petroleum ether - diethyl ether) to give 45 mg (76%) of the trans-fused allylic alcohol 87b as white crystals (recrystallized from hexane/diethyl ether, mp 75 -77 °C); ir (film): 3460, 3035, 1107, 819 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) s: 0.91, 1.01, 1.16 (s, s, s, 3H each, -CH\(_3\) groups), 1.30-1.40 (m, 1H), 1.43 (d, 1H, J = 14 Hz), 1.60-1.85 (m, 3H), 1.71 (d, 3H, vinylic methyl group, J = 2 Hz), 1.94-2.05 (m, 2H), 2.08-2.19 (m, 2H), 3.37-3.59 (m, 4H, -OCH\(_2\)CCH\(_2\)O-), 5.48 (br s, 1H, vinyl proton). Exact Mass calcd. for C\(_{16}\)H\(_{28}\)O\(_3\): 266.1882; found: 266.1885.

Preparation of the Silyl Enol Ether 77.\(^{27}\)
To a cold (-78 °C), stirred solution of LDA (1.3 equiv) in dry THF (0.5 mL) was added, dropwise, a solution of the keto vinyl iodide 50 (79 mg, 0.21 mmol) in dry THF (0.5 mL). The reaction mixture was stirred for 1 h and trimethylsilyl chloride (39 mg, 1.7 equiv) was added dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 1.5 h. The solvent was removed and the crude product thus obtained was flash chromatographed (14 x 1 cm column, elution with 95 : 5 petroleum ether - diethyl ether). The resultant clear oil was distilled (air-bath temperature 125 - 132 °C/0.04 Torr) to provide 66 mg (70%) of the silyl enol ether 77; ir (film): 3050, 3030, 1666, 1617, 1252, 1200, 1121 cm⁻¹; ¹H nmr (300 MHz, CDCl₃) 8: 0.20 (s, 9H, SiMe₃), 0.96, 1.00 (s, s, 3H each, -CMe₂), 1.38-1.60 (m, 2H), 1.85-2.00(m, 1H), 2.15-2.60 (m, 6H), 3.44-3.63 (m, 4H, -OCH₂CCH₂O-), 4.63-4.70 (m, 1H, H₅), 5.71 (br s, 1H, H₆), 6.04 (br s, 1H, H₇). Exact Mass calcd. for C₁₈H₃₁IO₃Si: 450.1089; found: 450.1087.

Alternative Preparation of the Allylic Alcohol 71.

To a solution of the silyl enol ether 77 (64 mg, 0.14 mmol) in dry benzene (7.1 mL) was added tri-n-butyltin hydride (52 mg, 1.25 equiv) and AIBN (2 mg, 0.1 equiv). The reaction mixture was refluxed for 1 h and the solvent was removed. The crude oil thus obtained was filtered through a short silica gel column (5 x 2 cm, elution with petroleum ether) and the solvent was removed from the filtrate. The remaining crude material was dissolved in dry THF (0.6 mL) and TBAF (0.43 mL of a 1 M solution in THF, 3 equiv) was added. The reaction mixture was
stirred for 0.5 h at room temperature. Diethyl ether (5 mL) and water (3 mL) were added and the layers were separated. The aqueous phase was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent and flash chromatography (12 x 1 cm column, elution with 65 : 35 petroleum ether - diethyl ether) of the resulting oil gave, after removal of traces of solvent (vacuum pump), 20 mg (56%) of a colourless oil. This material exhibited a \(^1\)H nmr spectrum (400 MHz, CDCl\(_3\)) identical with that of the allylic alcohol 71 prepared previously (vide supra, p. 109).

**Preparation of the Methyl Ether 78.**

To a warm (55 °C), stirred suspension of NaH (∼2 equiv, twice washed with 2 mL of dry THF) in dry THF (2 mL) was added a solution of the allylic alcohol 73 (34 mg, 0.12 mmol) in dry THF (1.5 mL). Methyl iodide (1.5 equiv, filtered through basic alumina prior to use) was added dropwise over 15 min and the reaction mixture was stirred at 55 °C for 4.5 h. Diethyl ether (7 mL) and water (5 mL) were added to the cooled mixture and the layers were separated. The aqueous phase was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent and flash chromatography (12 x 1 cm column, elution with 90 : 10 hexane - diethyl ether) of the resulting crude product, followed by distillation (air-bath temperature 120 - 125 °C/0.04 Torr) of the clear oil thus obtained, gave 24 mg (67%) of the methyl ether 78; ir (CHCl\(_3\)): 3089, 1641, 1108, 1081 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)):
CDCl₃, 20 °C) s: 0.85, 1.02, 1.07 (s, br s, s, 3H each, -CH₃ groups), 1.36-2.32 (m, 12H), 1.12 (br s, 3H, -OCH₃), 3.34-3.66 (m, 4H, -OCH₂CCH₂O-), 4.87, 5.05 (br s, br s, 1H each, vinyl protons);

¹H nmr (300 MHz, CDCl₃, -30 °C) s: 0.78, 0.80, 0.83, 1.10 (s, s, s, s, 9H, -CH₃ groups), 1.34-2.46 (m, 12H), 2.94, 3.24 (s, s, 3H, ratio 4:3, -OCH₃), 3.28-3.71 (m, 4H, -OCH₂CCH₂O-), 4.74, 4.86, 4.92, 5.15 (br s, br s, br s, br s, 2H, ratio 3:3:4:4, vinyl protons). Exact Mass calcd. for C₁₈H₃₀O₃: 294.2195; found: 294.2198.
3.2.2  (4)-Ambliol B (94) Experimental.

Preparation of the Silyl Enol Ether 112.

To a cold (-78 °C), stirred solution of vinylmagnesium bromide (3.8 mL of a 1 M solution in THF, 1.5 equiv) in dry THF (11 mL) was added dry HMPA (1.04 mL, 2.4 equiv) and copper(I) bromide·dimethyl sulfide (26 mg, 5 mole %). To this mixture was added, dropwise over 25 min, a solution of 3,4-dimethyl-2-cyclohexen-1-one (307 mg, 1 equiv) and trimethylsilyl chloride (543 mg, 2 equiv) in dry THF (2 mL). The reaction mixture turned deep red during this addition. Stirring was continued for 6 h at -78 °C. Dry triethylamine (0.7 mL) and hexane (10 mL) were added successively. The reaction mixture was allowed to warm to room temperature and was poured into water (15 mL). The layers were separated and the organic phase was washed with water (~15 mL). The organic material was dried over anhydrous magnesium sulfate and the solvent was removed. Distillation (air-bath temperature 117 - 125 °C/13 Torr) of the crude material thus obtained provided 420 mg, (90%) of the silyl enol ether 112 as a colourless oil; ir (film): 3083, 1677, 1632, 1252, 1190, 887, 844 cm⁻¹; H nmr (400 MHz, CDCl₃) δ: 0.19 (s, 9H, SiMe³), 0.84 (d, 3H, secondary Me, J = 7 Hz), 0.93 (s, 3H, tertiary Me), 1.40-1.74 (m, 3H), 1.90-2.14 (m, 2H), 4.59 (br s, 1H, H₄), 4.95 (m, 2H, H₂ and H₆), 5.77 (m, 1H, H₄). Exact Mass calcd. for C₁₃H₂₄OSi: 224.1597; found: 224.1593.
Preparation of the Keto Amine 127.

To a cold (0 °C), stirred solution of the silyl enol ether 112 (613 mg, 2.73 mmol) in dry THF (12 mL) was added a solution of methyllithium in diethyl ether (1.5 M, 1.1 equiv). The reaction mixture was allowed to warm to room temperature and was stirred for 1 h. The so-formed solution of the lithium enolate\textsuperscript{47} 121 was cooled (-78 °C) and added via cannula to a rapidly stirred, cold (-78 °C) slurry of Eschenmoser's salt\textsuperscript{50} (126, 1.01 g, 2 equiv) in dry THF (18 mL).\textsuperscript{85,86} The reaction mixture was allowed to warm to room temperature and was stirred for 2.5 h. Aqueous HCl (1 N, 30 mL) and diethyl ether (20 mL) were added and the layers were separated. The organic phase was extracted thoroughly with 1 N HCl and the combined extracts were carefully neutralized with sodium carbonate. The neutralized mixture was extracted with dichloromethane (3 x 30 mL) and the combined extracts were washed with brine (30 mL). The layers were separated and the organic phase was dried over anhydrous magnesium sulfate. Removal of the solvent gave 478 mg (~84%) of the crude keto amine 127 as a ~2 : 1 mixture of epimers; ir (film): 3083, 1713, 1637 cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) \delta: 0.63, 0.97 (s, s, ratio 1:2, 3H, tertiary Me), 0.81, 0.88 (d, d, ratio 1:2, 3H, secondary Me, J = 8 Hz), 1.50-2.70 (m, 7H), 2.17, 2.24 (s, s, ratio 2:1, 6H, NMe\textsubscript{2}), 2.97 (t, 1H, J = 12 Hz), 4.92-5.25 (m, 2H, H\textsubscript{a} and H\textsubscript{b}), 5.67-5.82 (m, 1H, H\textsubscript{c}). The CI mass spectrum gives a base peak at 210 (M\textsuperscript{+} +1) for C\textsubscript{13}H\textsubscript{23}NO. Glc analysis indicated that this material consisted very largely (90%) of the epimers 127. Since the
epimeric stereocenter would be removed in the next step, this mixture was used without further purification in the next step.

**Preparation of the Enone 125.**

![Enone 125](image)

To a solution of the keto amine 127 (79 mg, 0.38 mmol) in dry dichloromethane (1.6 mL) was added \( m \)-chloroperoxybenzoic acid (1.5 equiv). The reaction mixture was stirred for 15 min and was then filtered rapidly through a short column of silica gel (5 x 2 cm column, elution with 80:20 petroleum ether - diethyl ether). Removal of the solvent from the eluate (the last traces of solvent were removed on a vacuum pump) afforded 47 mg (76%) of the enone 125 as a colourless oil that was homogenous by glc analysis; ir (film): 3083, 1697, 1636, 1615 cm\(^{-1}\). This compound was extremely unstable and, therefore, was used without delay in the preparation of the keto vinylgermane 145.
4-Chloro-2-trimethylgermyl-1-butene 132.

![Chemical structure of 4-Chloro-2-trimethylgermyl-1-butene 132.]

To a cold (-78 °C), stirred solution of 4-chloro-2-trimethylstannyl-1-butene (6)\(^7\) (2.13 g, 8.41 mmol) in dry THF (40 mL) was added a solution of methyllithium in diethyl ether (1.5 M, 1.1 equiv). The reaction mixture was stirred at -78 °C for 5 min, trimethylgermyl bromide (1.99 g, 1.2 equiv) was added dropwise and the resulting mixture was stirred at this temperature for 1.5 h. Saturated aqueous ammonium chloride (pH 8, 30 mL) and diethyl ether (50 mL) were added and the mixture was allowed to warm to room temperature. The layers were separated and the organic phase was washed with saturated aqueous ammonium chloride. The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed (rotary evaporator, bath temperature ~35 °C) to yield the crude vinylgermane chloride 132 as a light yellow oil which was homogenous by glc analysis; ir (film): 3051, 826, 601 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.24 (s, 9H, GeMe\(_3\)), 2.64 (br t, 2H, allylic methylene protons, \(J = 8\) Hz), 3.56 (t, 2H, -CH\(_2\)Cl, \(J = 8\) Hz), 5.33 (m, 1H, H\(_a\)), 5.61 (m, 1H, H\(_b\)). Due to the high volatility of 132, the crude product was utilized without further purification in the following step.
4-Iodo-2-trimethylgermyl-1-butene 133.

\[ \text{Me}_3\text{Ge} \quad \begin{array}{c}
\text{H}_a \\
\text{I} \\
\text{H}_b
\end{array} \]

To a solution of the crude vinylgermane chloride 132 (the sample prepared as described above) in acetone (35 mL) was added sodium iodide (19 g, 15 equiv based on 6). The reaction mixture was refluxed for 48 h and was then cooled to room temperature. The bulk of the solvent was removed and diethyl ether (~60 mL) and water (~50 mL) were added to the residual material. The layers were separated and the organic phase was washed with water (2 x 30 mL). The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed. The crude oil thus obtained was distilled (air-bath temperature 85 - 92 °C/15 Torr) to provide 1.80 g (72% from 6) of the vinylgermane iodide 133 as a colourless oil; ir (film): 3050, 825, 600 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.24 (s, 9H, GeMe\(_3\)), 2.77 (br t, 2H, allylic methylene protons, \(J = 8\) Hz), 3.21 (t, 2H, \(-\text{CH}_2\text{I}, J = 8\) Hz), 5.33 (m, 1H, H\(_a\)), 5.59 (m, 1H, H\(_b\)). \text{Exact Mass} \text{ calcd. for C}_6\text{H}_{12}\text{IGe} (M^+\text{-Me}): 284.9197; \text{found: 284.9191.}

Preparation of the Cuprate 110.
To a cold (-95 °C) rapidly stirred solution of 4-iodo-2-trimethylgermyl-1-butene (133) (159 mg, 0.53 mmol) in dry THF (6 mL) was rapidly added a solution of tert-butyllithium in pentane (1.9 M, 2 equiv). The resultant yellow solution was stirred at -95 °C for 7 min and was then warmed to -78 °C. Copper(I) cyanide (57 mg, 1.2 equiv) was added and the so-formed yellowish suspension became colourless after ~5 min. Brief warming of the reaction mixture to ~-35 °C provided a light tan solution of the vinylgermane cuprate 110 which was recooled to -78 °C and used immediately.

Preparation of the Keto Vinylgermane 145.

![Diagram of molecular structure]

To the cold (-78 °C), stirred solution of the cuprate 110 prepared as described above was added, dropwise and successively, trimethylsilyl chloride (289 mg, 2.66 mmol), and a solution of the unstable enone 125 (47 mg, 0.29 mmol) in dry THF (1 mL). After addition of each drop of the latter, the reaction mixture turned yellow briefly. Stirring was continued at -78 °C for 1 h and saturated aqueous ammonium chloride (4 mL) and diethyl ether (10 mL) were added. The reaction mixture was allowed to warm to room temperature and was stirred overnight, open to the atmosphere. The layers were separated and the organic phase was washed successively with saturated aqueous ammonium chloride (5 mL) and brine (5 mL). The organic phase was dried over anhydrous magnesium sulfate and the solvent was removed. The material thus obtained was
distilled (air-bath temperature 110 - 118 °C/0.1 Torr) to provide 47 mg of a mixture of compounds that consisted largely (78% by glc analysis) of the keto vinylgermane 145, which was accompanied by small amounts of unidentified materials. $^1$H nmr analysis (vide infra) of the mixture indicated that 145 was present as a single diastereomer. Attempts to purify this material further by means of flash chromatography or drip column chromatography were unsuccessful. This material exhibited ir (film): 3082, 3045, 1714, 1638, 825, 599 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.18 (s, 9H, -GeMe$_3$), 0.67 (s, 3H, tertiary Me), 0.82 (d, 3H, secondary Me, $J = 7$ Hz), 1.00-1.77 (m, 5H), 1.84-2.01 (m, 2H), 2.08-2.23 (m, 3H), 2.33-2.50 (m, 2H), 4.92 (d, 1H, $H_a$, $J = 18$ Hz), 5.13 (d, 1H, $H_b$, $J = 12$ Hz), 5.13 (m, 1H, $H_c$), 5.47 (m, 1H, $H_d$), 5.62 (dd, 1H, $H_e$, $J = 18$, 12 Hz). Exact Mass calcd. for C$_{17}$H$_{29}$OGe (M$^+$-Me): 323.1430; found: 323.1430.

**Preparation of the Keto Vinyl Iodide 106.**

To a solution of the mixture containing largely the keto vinylgermane 145 (152 mg, ~0.45 mmol) in dry dichloromethane (9 mL) was added a solution of iodine in dry dichloromethane (12.5 mL of a 0.04 M solution, 0.5 mmol) and the resulting deep red solution was stirred for 17 h.$^{21b}$ Aqueous sodium thiosulfate (~0.1 M, ~ the same volume as that of dichloromethane) was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal
of the solvent provided the crude keto vinyl iodide which was flash chromatographed (14 x 2 cm column, elution with 97 : 3 petroleum ether - diethyl ether). The colourless oil thus obtained was distilled (air-bath temperature 134 - 140 °C/0.1 Torr) to give 103 mg (42% from the enone 125) of the keto vinyl iodide 106. This material was homogenous by tlc and glc analyses and exhibited ir (film): 3082, 1713, 1637, 1618 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.67 (s, 3H, tertiary Me), 0.82 (d, 3H, secondary Me, \(J = 8\) Hz), 1.05-1.32 (m, 2H), 1.46-1.78 (m, 3H), 1.84-2.01 (m, 2H), 2.20 (d, 1H, \(J = 10\) Hz), 2.27-2.51 (m, 4H), 4.93 (d, 1H, \(H_a\), \(J = 18\) Hz), 5.15 (d, 1H, \(H_b\), \(J = 11\) Hz), 5.63 (dd, 1H, \(H_c\), \(J = 18, 11\) Hz), 5.67 (m, 1H, \(H_d\)), 6.01 (m, 1H, \(H_e\)). \textit{Exact Mass} calcd. for C\(_{15}\)H\(_{23}\)O\(_I\): 346.0795; found: 346.0794.

Preparation of the Allylic Alcohol 128.

![Diagram](attachment:image.png)

To a cold (-78 °C), stirred solution of the keto vinyl iodide 106 (59 mg, 0.17 mmol) in dry THF (10 mL) was added a solution of \(n\)-butyllithium in hexane (1.3 M, 2.4 equiv). The reaction mixture was stirred at -78 °C for 10 min and water (4 mL) was added. After allowing the reaction mixture to warm to room temperature, diethyl ether (15 mL) was added. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The resulting crude product was flash chromatographed (12 x 1 cm column, elution with 97 : 3
petroleum ether - diethyl ether). The colourless oil thus obtained was distilled (air-bath temperature 105 - 112 °C/0.1 Torr) to provide 33 mg (88%) of the required trans-fused allylic alcohol 128; ir (film): 3493, 3082, 1636, 908 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) s: 0.73-1.89 (m, 11H), 0.77 (d, 3H, secondary Me, $J$ = 8 Hz), 0.99 (s, 3H, tertiary Me), 2.14 (br d, 1H, $J$ = 13 Hz), 2.49 (br td, 1H, $J$ = 14, 5 Hz), 4.69 (br s, 1H, $H_a$ or $H_b$), 4.79 (br s, 1H, $H_a$ or $H_b$), 4.96 (dd, 1H, $H_c$, $J$ = 18, 1.5 Hz), 5.05 (dd, 1H, $H_d$, $J$ = 11, 1.5 Hz), 5.41 (dd, 1H, $H_e$, $J$ = 18, 11 Hz). Exact Mass calcd. for C$_{15}$H$_{24}$O: 220.1827; found: 220.1822.

Preparation of the Model Cyclopropane 113.

To a cold (0 °C), stirred solution of the allylic alcohol 66 (96 mg, 0.36 mmol) in dry dichloromethane (4 mL) was added a solution of diethylzinc in toluene (1.1 M, 1.1 equiv). Dry diiodomethane (44 µL, 1.5 equiv) was added dropwise. The argon flow was turned off and dry oxygen was introduced into the space above the reaction mixture through a septum cap by means of an oxygen filled balloon containing a hypodermic needle as outlet. The reaction mixture was stirred under an oxygen atmosphere at 0 °C for 30 min.$^{36}$ Saturated aqueous ammonium chloride (pH 8, 5 mL) and dichloromethane (15 mL) were added and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted thoroughly with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed. The resulting crude product was flash chromatographed (14
x 2 cm column, elution with 70 : 30 petroleum ether - diethyl ether) to give 70 mg (69%) of the cyclopropane 113 as colourless crystals (recrystallized from hexane/diethyl ether, mp 113 - 114 °C); ir (CHCl₃): 3604, 3080 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) s: 0.05-0.13, 0.20-0.29, 0.51-0.63, 0.63-0.70 (m, m, m, m, 1H each, protons on cyclopropane ring), 0.95, 0.98 (s, s, 3H each, -CMe₂), 1.05-1.30 (m, 5H), 1.36-1.78 (m, 6H), 1.93 (dt, 1H, J = 13, 3 Hz), 2.09 (dq, 1H, J = 13, 3 Hz), 2.16-2.28 (m, 1H), 3.46, 3.54 (s, s, 2H each, -OCH₂CCH₂O-). Exact Mass calcd. for C₁₇H₂₈O₃: 280.2038; found: 280.2044.

Preparation of the Cyclopropane 148.

To a stirred solution of the allylic alcohol 126 (37 mg, 0.17 mmol) in dry benzene (1 mL) was added a solution of diethylzinc in toluene (1.1 M, 2.4 equiv). Dry diiodomethane (41 µL, 3.0 equiv) was added dropwise. The reaction mixture was cooled to 0 °C. The argon flow was turned off and dry oxygen was introduced into the space above the reaction mixture through a septum cap by means of an oxygen filled balloon containing a hypodermic needle as outlet. The reaction mixture was stirred under an oxygen atmosphere at 0 °C for 30 min. Saturated aqueous ammonium chloride (pH 8, 2 mL) and benzene (7 mL) were added and the reaction mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted thoroughly with benzene. The combined extracts were dried over anhydrous
magnesium sulfate and the solvent was removed. The resulting crude product was flash chromatographed (12 x 1 cm column, elution with 96 : 4 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 105 - 112 °C/0.1 Torr) to yield 36 mg (91%) of the cyclopropane 148 as a colourless oil; ir (film): 3506, 3078, 1635, 908 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.02-0.10, 0.19-0.27 (m, m, 1H each, protons on cyclopropane ring), 0.50-0.59 (m, 2H, one proton on cyclopropane ring, one proton not assigned), 0.64-0.71 (m, 1H, proton on cyclopropane ring), 0.74 (d, 3H, secondary Me, J = 8 Hz), 0.95 (s, 3H, tertiary Me), 1.00-1.11 (m, 2H), 1.15-1.73 (m, 9H), 2.21 (tdd, 1H, J = 13, 4, 2 Hz), 4.88 (dd, 1H, Hₐ, J = 17, 1.5 Hz), 5.05 (dd, 1H, Hₐ, J = 11, 1.5 Hz), 5.43 (dd, 1H, Hc, J = 17, 11 Hz). Exact Mass calcd. for C₁₆H₂₆O: 234.1984; found: 234.1978.

Preparation of the Diol 149.

To a cold (0 °C), stirred solution of the cyclopropane 148 (33 mg, 0.14 mmol) in dry THF (1 mL) was added a THF solution of borane-THF complex (0.22 M, 0.21 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 3 h. Water (0.5 mL) was added and the reaction mixture was cooled to 0 °C. Aqueous sodium hydroxide (1 mL of a 3 M solution) was added rapidly, the cooling bath was removed, and aqueous hydrogen peroxide (1
mL of a 30% solution) was added dropwise. The reaction mixture was stirred at 50 °C for 1 h and at room temperature for 12 h. The aqueous phase was saturated with sodium chloride and diethyl ether (3 mL) was added. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The crude product mixture thus obtained was drip column chromatographed (16 x 1 cm column, elution with 70 : 30 petroleum ether - diethyl ether) to provide two fractions. The first compound to be eluted was the minor alcohol 149a. Concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) from the oil thus obtained gave 4 mg (11%) of 149a as a single diastereomer; 1H nmr (400 MHz, CDCl₃) δ: 0.00-0.07, 0.19-0.27, (m, m, 1H each, protons on cyclopropane ring), 0.47-0.58 (m, 2H, one proton on cyclopropane ring, one proton unassigned), 0.64-0.73 (m, 1H, proton on cyclopropane ring), 0.77-1.77 (m, 12H), 0.99 (d, 3H, secondary Me on ring, J = 8 Hz), 1.04 (s, 3H, tertiary Me), 1.20 (d, 3H, secondary Me adjacent to OH group, J = 7 Hz), 2.19-2.30 (m, 1H), 3.94 (br q, 1H, Hₐ, J = 7 Hz).

The second compound to be eluted was the desired diol 149. Concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) from the oil thus obtained, provided 26 mg (73%) of 149; ir (film): 3414, 3077 cm⁻¹; 1H nmr (400 MHz, CDCl₃) δ: 0.00-0.08, 0.19-0.27 (m, m, 1H each, protons on cyclopropane ring), 0.48-0.59 (m, 2H, one proton on cyclopropane ring, one proton unassigned), 0.62-0.70 (m, 1H, proton on cyclopropane ring), 0.81-1.79 (m, 14H), 0.87 (partly obscured d, 3H, secondary Me, J = ~7 Hz), 0.88 (s, 3H, tertiary Me), 2.16-2.28 (m, 1H), 3.56-3.72 (m, 2H, Hₐ and H₃). Exact Mass calcd. for C₁₆H₂₈O₂: 252.2089; found: 252.2097.
Preparation of the Model Alcohol 114.

To a solution of the model cyclopropane 113 (15 mg, 0.05 mmol) in dry acetic acid (2 mL) was added platinum(IV) oxide (Adams' catalyst, ~10 mole %). The reaction mixture was stirred under an atmosphere of hydrogen (1.5 atmospheres) for 55 min and was then added slowly to a cold (0 °C), stirred, saturated aqueous solution of sodium bicarbonate (10 mL). Diethyl ether (15 mL) was added and the layers were separated. The aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The crude product mixture thus obtained was flash chromatographed (10 x 1 cm column, elution with 70 : 30 petroleum ether - diethyl ether) to provide 9 mg (60%) of the required alcohol 114 as colourless crystals (recrystallized from hexane, mp. 76 - 78 °C); \textit{ir} (CHCl$_3$): 3617, 1124 cm$^{-1}$; \textit{H} nmr (400 MHz, CDCl$_3$) $\delta$: 0.91, 0.94, 0.97, 0.99 (s, s, s, s, 3H each, two -CMe$_2$ groups), 1.09-1.71 (m, 11H), 1.82-1.94 (m, 2H), 2.12-2.21 (m, 1H), 3.42-3.60 (m, 4H, -OCH$_2$CCH$_2$O-). \textit{Exact Mass} calcd. for C$_{17}$H$_{30}$O$_3$: 282.2194; found: 282.2188.

When the hydrogenolysis of 113 (44 mg) was carried out in acetic acid under 3 atmospheres of hydrogen for 2h, workup and flash chromatography (12 x 1 cm column) as described above gave two fractions. The first compound to be eluted was the alcohol 114 (9 mg, 20%). The second compound to be eluted was the diol ether 115. Concentration of the appropriate fractions, followed by removal of traces of solvent (vacuum pump) gave 17 mg (38%) of 115 as a single diastereomer. This compound, a colourless oil, exhibited \textit{H} nmr (400 MHz, CDCl$_3$) $\delta$: 0.91, 0.95
(s, s, 3H, 9H, two -CMe₂ groups), 1.12 (br d, 1H, J = 13 Hz), 1.20 (br s, 1H, tertiary -OH, disappears on addition of D₂O), 1.24-1.77 (m, 11 H), 1.82-1.91 (m, 1H), 3.01 (br t, 1H, primary -OH, disappears on addition of D₂O, J = 5 Hz), 3.12-3.23 (m, 1H, Hₐ, w½ = 26 Hz), 3.33 (s, 2H, Hₜ), 3.44 (d, 2H, H₂, J = 5 Hz). Exact Mass calcd. for C₁₇H₃₂O₃: 284.2351; found: 284.2359.

Preparation of the Diol 150.

To a solution of the cyclopropane diol 149 (25 mg, 0.10 mmol) in dry acetic acid (2 mL) was added platinum(IV) oxide (Adams’ catalyst, ~10 mole %). The reaction mixture was stirred under an atmosphere of hydrogen (1.5 atmospheres) for 55 min and was then added slowly to a cold (0 °C), stirred, saturated aqueous solution of sodium bicarbonate (30 mL). Diethyl ether (15 mL) was added and the layers were separated. The aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The crude product mixture thus obtained was flash chromatographed (10 x 1 cm column, elution with 70 : 30 petroleum ether - diethyl ether) to provide, after removal of traces of solvent (vacuum pump), 22 mg (87%) of the diol 150; ir (film): 3414, 1386, 1375 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.86, 0.87 (s, s, 3H each, tertiary Me groups), 0.88 (partly obscured d, 3H, secondary Me, J = ~7 Hz), 0.98 (s, 3H, tertiary Me), 1.00-1.74 (m, 16H), 3.58-3.74 (m, 2H, H₂). Exact Mass calcd. for C₁₆H₃₀O₂: 254.2246; found: 254.2241.
Preparation of the Model Furan Alcohol 118.

To a solution of the alcohol 116 (284 mg, 2.0 mmol) in dry dichloromethane (7 mL) was added pyridinium chlorochromate (647 mg, 1.5 equiv). The resulting solution was stirred for 1.5 h. Dry diethyl ether (10 mL) was added and the reaction mixture was filtered through a column (15 x 3 cm) of Florisil. The column was washed with diethyl ether. The solvent was removed from the combined eluate (rotary evaporator, bath temperature ~40 °C) to give 256 mg (91%) of the aldehyde 117; ir (film): 2730, 1721 cm$^{-1}$. This volatile compound was unstable and was therefore used without delay in the next step.

To a cold (-78 °C), stirred solution of n-butyllithium in hexane (2.35 mL of a 1.56 M solution, 1 equiv) was added, dropwise, a solution of 3-bromofuran (537 mg, 3.66 mmol, 1 equiv) in dry diethyl ether (10 mL). The reaction mixture was stirred at -78 °C for 30 min and a solution of the freshly prepared aldehyde 117 (247 mg, 1.83 mmol, 0.5 equiv) in dry diethyl ether (2 mL) was added dropwise over 5 min. The reaction mixture was stirred at -78 °C for 80 min and saturated aqueous ammonium chloride (pH 8, 5 mL) was added. The two-phase mixture was allowed to warm to room temperature and the layers were separated. The organic phase was washed with brine (5 mL) and dried over anhydrous magnesium sulfate. The solvent was
removed and the crude product mixture was flash chromatographed (14 x 2 cm column, elution with 88 : 12 petroleum ether - diethyl ether). Distillation of the oil thus obtained (air-bath temperature 95 - 100 °C/0.1 Torr) provided 258 mg (70%) of the furan alcohol 118 as a colourless oil; ir (film): 3389, 1504, 1025, 875 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.00 (s, 3H, -Me), 1.25-1.57 (m, 11H), 1.68 (dd, 1H, Hₐ or Hₖ, J = 15, 4 Hz), 1.79 (dd, 1H, Hₐ or Hₖ, J = 15, 8 Hz), 4.87 (dt, 1H, Hₜ, J = 8, 4 Hz), 6.43 (m, 1H, Hₜ), 7.38 (m, 2H, Hₑ and Hₚ). Exact Mass calcd. for C₁₃H₂₀O₂: 208.1463; found: 208.1455.

Preparation of the Furan Diol 151.

To a solution of the diol 150 (10 mg, 0.04 mmol) in dry dichloromethane (0.5 mL) was added pyridinium chlorochromate⁵⁹ (13 mg, 1.5 equiv) and anhydrous sodium acetate (0.9 mg, 0.3 equiv) and the resulting solution was stirred for 1.5 h. Dry diethyl ether (1 mL) was added and the reaction mixture was filtered through a column (5 x 1 cm) of Florisil. The column was washed with diethyl ether. The solvent was removed from the combined eluate to give 9 mg of an unstable aldehyde which was dissolved in dry diethyl ether (0.5 mL) and used without delay in the next step.

To a cold (-78 °C), stirred solution of n-butyllithium in hexane (0.24 mL of a 1.56 M
solution, 0.38 mmol) was added, dropwise, a solution of 3-bromofuran (57 mg, 0.39 mmol) in dry
diethyl ether (1 mL). The reaction mixture was stirred at -78 °C for 30 min and the solution of
the freshly prepared crude aldehyde was added dropwise over 5 min. The reaction mixture was
stirred at -75 - -70 °C for 1 h and was allowed to warm to room temperature over 5 min.
Saturated aqueous ammonium chloride (pH 8, 2 mL) was added. The layers were separated and
the organic phase was washed with brine (5 mL). The organic material was dried over anhydrous
magnesium sulfate. Tlc analysis indicated the presence of two compounds (ratio ~1 : 1) which,
after preparation of their corresponding mono-acetates (vide infra), were shown to be the
diastereomeric pair of furan diols 151. The solvent was removed and the crude product mixture
was chromatographed (6 x 0.7 cm column, elution with diethyl ether). Concentration of the
appropriate fractions and removal of traces of solvent (vacuum pump) provided, as a colourless
oil, 9 mg (71%) of the required addition product 151; ir (film): 3469, 1504, 1381, 1368, 1025, 874
cm⁻¹.

Preparation of the Model Acetate 119.

To a stirred solution of the furan alcohol 118 (55 mg, 0.26 mmol) in dry dichloromethane (1
mL) was added dry pyridine (0.25 mL) and acetic anhydride (0.25 mL). The reaction mixture
was stirred overnight. Water (2 mL) and diethyl ether (3 mL) were added and the layers were
separated. The aqueous phase was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the crude product was flash chromatographed (12 x 1 cm column, elution with 95 : 5 petroleum ether - diethyl ether). The colourless oil thus obtained was distilled (air-bath temperature 100 - 110 °C/0.1 Torr) to provide 61 mg (92%) of the acetate 119; ir (film): 3137, 1739, 1504, 1240, 1024, 875 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.93 (s, 3H, -Me), 1.20-1.60 (m, 10H), 1.68 (dd, 1H, Hₐ or Hₐ, J = 15, 4 Hz), 2.01 (partly obscured dd, 1H, Hₐ or Hₐ, J = 15, 8 Hz), 2.01 (s, 3H, -OC(O)CH₃), 5.97 (dd, 1H, Hₐ, J = 8, 4 Hz), 6.40 (br s, 1H, Hₐ), 7.36 (br s, 1H, Hₐ or Hₐ), 7.41 (br s, 1H, Hₐ or Hₐ). Exact Mass calcd. for C₁₅H₂₂O₃: 250.1569; found: 250.1570.

Preparation of the Acetate 152.

To a stirred solution of the furan diol 151 (9 mg, 0.028 mmol) in dry dichloromethane (0.5 mL) was added dry pyridine (0.25 mL) and acetic anhydride (0.25 mL). The reaction mixture was stirred for 24 h. Water (3 mL) and diethyl ether (5 mL) were added and the layers were separated. The aqueous phase was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the crude
product was chromatographed (5 x 0.7 cm column, elution with 90 : 10 petroleum ether - diethyl ether). Concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) provided, as a mixture of diastereomers, 6 mg (59%) of the acetate 152 (a colourless oil); ir (film): 3550, 1732, 1505, 1241, 1023, 875 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) (selected signals) δ:
0.77, 0.93 (d, d, ratio undetermined, 3H, secondary Me, J = 7 Hz), 0.82, 0.85, 0.86, 0.97 (s, s, s, s, ratio undetermined, 9H, three tertiary Me groups), 1.90 (dd, 1H, J = 7, 3 Hz), 2.01, 2.06 (s, s, ratio of 1 : 0.7, 3H, -OC(0)CH₃), 5.95, 6.00 (t, dd, ratio undetermined, 1H, H₃, J = 6 and 9, 2.5 Hz), 6.39, 6.43 (br s, br s, 1H, ratio of 0.7 : 1, H₄), 7.36, 7.39, 7.44 (t, m, br s, ratio undetermined, 2H, H₅ and H₆, J = 1.5 Hz). Exact Mass calcd for C₂₂H₃₄O₄: 362.2457; found: 362.2451.

Preparation of the Model Furan 120.

To a cold (-78 °C), stirred solution of lithium (16 mg, 2.32 mmol) in liquid ammonia (~6 mL) was added, dropwise, a solution of the acetate 119 (29 mg, 0.12 mmol) in dry THF (1 mL).³³ The reaction mixture was stirred at -78 °C for 1 h. Saturated aqueous ammonium chloride (pH 8, 2 mL) was added rapidly, followed by diethyl ether (10 mL). The reaction mixture was allowed to warm to room temperature and the ammonia was allowed to evaporate. The layers were separated. The aqueous phase was extracted thoroughly with diethyl ether and the combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed and the crude oil thus obtained was distilled (air-bath temperature 88 - 93 °C/0.1 Torr) to provide 19 mg (86%)
of the furan 120 as a colourless oil; ir (film): 1502, 1026, 874 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) s:
0.91 (s, 3H, -Me), 1.24-1.57 (m, 12H), 2.33-2.41 (m, 2H, Hₐ and Hₖ), 6.28 (br s, 1H, H₇), 7.22 (br
s, 1H, H₉), 7.35 (t, 1H, H₈, J = 1.5 Hz). Exact Mass calcd. for C₁₃H₂₀O: 192.1514; found:
192.1512.

(±)-Ambliol B (94).

To a cold (-78 °C), stirred solution of lithium (5.5 mg, 0.79 mmol) in liquid ammonia (~5
mL) was added, dropwise, a solution of the acetate 152 (5.0 mg, 0.014 mmol) in dry THF (0.5
mL). The reaction mixture was stirred at -78 °C for 15 min. Saturated aqueous ammonium
chloride (pH 8, 2 mL) was added rapidly, followed by diethyl ether (5 mL). The reaction mixture
was allowed to warm to room temperature and the ammonia was allowed to evaporate. The
layers were separated. The aqueous phase was extracted thoroughly with diethyl ether and the
combined extracts were dried over anhydrous magnesium sulfate. The solvent was removed and
the crude oil thus obtained was chromatographed (4 x 0.7 cm column, elution with 93 : 7
petroleum ether - diethyl ether) to provide, after removal of traces of solvent (vacuum pump), 3.2
mg (76%) of (±)-ambliol B (94), a colourless oil; ir (film): 3544, 1503, 1383, 1365, 1026, 873
$^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.84 (d, 3H, secondary Me, $J = 6.5$ Hz), 0.86, 0.87, 1.00 (s, s, s, 3H each, tertiary Me groups), 1.12 (br d, 1H, $J = 13$ Hz), 1.18 (s, 1H, -OH), 1.29-1.73 (diffuse m, 13H), 2.26 (td, 1H, $H_a$ or $H_b$, $J = 14$, 5.3 Hz), 2.36 (td, 1H, $H_a$ or $H_b$, $J = 14$, 5 Hz), 6.28 (br s, 1H, $H_c$), 7.22 (br s, 1H, $H_d$), 7.35 (t, 1H, $H_e$, $J = 1.5$ Hz); $^{13}$C nmr (75 MHz, C$_6$D$_6$) $\delta$: 16.2, 17.7, 18.5, 21.9, 22.5, 24.1, 24.7, 26.7, 32.4, 36.7, 37.1, 38.2, 39.0, 39.1, 41.2, 75.9, 111.3, 125.9, 138.8, 143.0. Exact Mass calcd. for C$_{20}$H$_{32}$O$_2$: 304.2402; found: 304.2399. Compound 94 exhibited $^1$H nmr and $^{13}$C nmr spectra identical with those derived from natural (-)-ambliol B.$^{16,63}$
3.2.3 1,4-Additions of the Cyanocuprate (110) to Enones. Palladium(0)-catalyzed Cyclizations.

3.2.3.1 Preparation of Cyclization Substrates.

Preparation of the Diketone 160.

To a cold (0 °C), stirred solution of LDA (8.89 mmol, 1.1 equiv) in dry THF (25 mL) was added, dropwise, a solution of cyclopentanone N,N-dimethylhydrazone\(^{66}\) (158, 1.02 g, 8.08 mmol) in dry THF (2 mL).\(^{67}\) The reaction mixture was stirred at 0 °C for 2 h. After the mixture had been cooled to -78 °C, 1,2-epoxybutane (1.17 g, 16.2 mmol, 2 equiv) was added dropwise. The resulting reaction mixture was allowed to warm slowly to room temperature and was stirred overnight. Water (20 mL) and diethyl ether (30 mL) were added. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded a crude oil which was dissolved in methanol (100 mL). To this solution were added phosphate buffer (pH 7.2, 20 mL), water (30 mL) and sodium periodate (3.8 g, 17.8 mmol).\(^{80}\) The reaction mixture was stirred overnight and was then gravity filtered. The bulk of the methanol was removed from the filtrate and the remaining mixture was thoroughly extracted with dichloromethane. The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed. Distillation
(air-bath temperature 71 - 78 °C/0.1 Torr) of the resultant oil gave 447 mg (41%) of the keto alcohol 159, a colourless oil; ir (film): 3415, 1729 cm⁻¹.

To a stirred solution of the keto alcohol 159 (3.1 g, 19.8 mmol) in dry dichloromethane (65 mL) was added pyridinium chlorochromate (8.6 g, 39.7 mmol). The resulting solution was stirred for 4 h. Dry diethyl ether (70 mL) was added and the reaction mixture was filtered through a column (50 x 16 cm) of Florisil. The column was washed with diethyl ether and the solvent was removed from the combined eluate. The crude oil thus obtained was flash chromatographed (16 x 5 cm column; elution with 75 : 25 petroleum ether - diethyl ether) to give a colourless oil which was distilled (air-bath temperature 111 - 119 °C/15 Torr) to provide 1.8 g (59%) of the diketone 160; ir (film): 1740, 1714 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.07 (t, 3H, -CH₃, J = 8 Hz), 1.47-1.60 (m, 1H), 1.74-1.89 (m, 1H), 2.00-2.11 (m, 1H), 2.15-2.59 (m, 7H), 2.85-2.95 (m, 1H). *Exact Mass* calcd. for C₉H₁₄O₂: 154.0994; found: 154.0994.

**Preparation of the Enone 161.**

To a solution of potassium hydroxide in ethanol (5% w/v, 40 mL) was added a solution of the diketone 160 (800 mg, 5.19 mmol) in ethanol (5 mL). The reaction mixture was refluxed for 17 h and was allowed to cool to room temperature. Aqueous HCl (0.1 N, 40 mL) and diethyl ether (50 mL) were added. The layers were separated and the aqueous phase was thoroughly extracted with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The crude oil thus obtained was flash chromatographed (14 x 3 cm column; elution with 88 : 12 petroleum ether - diethyl ether) to give a colourless oil which
was distilled (air-bath temperature 113 - 119 °C/15 Torr) to provide 483 mg (68%) of the enone 161; ir (film): 1705, 1669 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.00-1.15 (m, 1H), 1.71 (br s, 3H, vinylic Me group), 1.93-2.23 (m, 4H), 2.43-2.59 (m, 2H), 2.65 (dd, 1H, J = 18, 7 Hz), 2.72-2.83 (m, 1H). Exact Mass calcd. for C₇H₁₂O: 136.0888; found: 136.0890.

General Procedure 5: Preparation of Keto Vinylgermanes.

To a cold (-78 °C), stirred solution of the cuprate 110 (1.4 - 2 equiv, prepared as described on p. 124) in dry THF (10 mL per mmol of cuprate) was added, dropwise and successively, trimethylsilyl chloride (3 equiv based on the amount of cuprate) and a solution of the appropriate enone (1 equiv) in dry THF (2 mL per mmol). The so-formed yellow solution was stirred at -78 °C until the reaction was determined to have reached completion (by glc and/or tlc analysis), usually after ~3 h. Water (~0.5 mL per mmol of enone) was added and the reaction mixture was allowed to warm to 0 °C. Saturated aqueous ammonium chloride (~6 mL per mmole of enone) and diethyl ether (~10 mL per mmol of enone) were added and the mixture was stirred open to the atmosphere at room temperature overnight. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate. Removal of the solvent afforded the crude product which was flash chromatographed and/or distilled to give the desired keto vinylgermane.
Preparation of the Keto Vinylgermane 142.

Following general procedure 5, a solution of the cuprate 110 (2 equiv) was treated with 2-cyclohexen-1-one (140, 21 mg, 0.22 mmol). The crude product thus obtained was distilled (air-bath temperature 110 - 118 °C/0.1 Torr) to provide 43 mg (73%) of the keto vinylgermane 142 as a colourless oil; ir (film): 3044, 1715, 825, 598 cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.21 (s, 9H, -GeMe$_3$), 1.25-2.10 (m, 8H), 2.17-2.49 (m, 5H), 5.19 (m, 1H, H$_a$), 5.51 (m, 1H, H$_b$). Exact Mass calcd. for C$_{12}$H$_{21}$GeO (M$^+$-Me): 255.0804; found: 255.0799.

Preparation of the Keto Vinylgermane 164.

Following general procedure 5, a solution of the cuprate 110 (1.9 equiv) was treated with 3,4-dimethyl-2-cyclohexen-1-one (140, 80 mg, 0.64 mmol). The crude product was flash chromatographed (14 x 2 cm column, elution with 95 : 5 petroleum ether - diethyl ether). The
colourless oil thus obtained was distilled (air-bath temperature 127 - 133 °C/0.1 Torr) to provide 142 mg (74%) of the keto vinylgermane 164; ir (film): 3055, 1718, 825, 598 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.23 (s, 9H, -GeMe\(_3\)), 0.78 (s, 3H, tertiary Me), 0.93 (d, 3H, secondary Me, \(J = 7\) Hz), 1.29-1.50 (m, 2H), 1.54-1.70 (m, 1H), 1.77-1.94 (m, 2H), 2.03-2.20 (m, 3H), 2.28-2.39 (m, 3H), 5.19 (m, 1H, H\(_a\)), 5.52 (m, 1H, H\(_b\)). *Exact Mass* calcd. for \(\text{C}_{14}\text{H}_{25}\text{GeO} (\text{M}^+\text{-CH}_3)\): 283.1117; found: 283.1111.

**Preparation of the Keto Vinylgermane 165.**

![Diagram of the keto vinylgermane 165]

Following general procedure 5, a solution of the cuprate 110 (1.6 equiv) was treated with isophorone (162, 76 mg, 0.55 mmol). HMPA (0.46 mL, 2.65 mmol) was added and the reaction mixture was allowed to warm slowly to room temperature and was then stirred overnight. The crude product was flash chromatographed (14 x 2 cm column, elution with 95 : 5 petroleum ether - diethyl ether). The colourless oil thus obtained was distilled (air-bath temperature 129 - 136 \(^0\)C/0.1 Torr) to provide 56 mg (35%) of the keto vinylgermane 165; ir (film): 3043, 1715, 825, 599 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.21 (s, 9H, -GeMe\(_3\)), 1.04, 1.05, 1.07 (s, s, s, 3H each, tertiary Me groups), 1.31-1.50 (m, 2H), 1.55, 1.64 (d, d, 1H each, H\(_a\) and H\(_b\), \(J = 14\) Hz), 2.10-2.26 (m, 6H), 5.18 (m, 1H, H\(_c\)), 5.51 (m, 1H, H\(_d\)). *Exact Mass* calcd. for \(\text{C}_{15}\text{H}_{27}\text{GeO} (\text{M}^+\text{-CH}_3)\): 297.1274; found: 297.1272.
Preparation of the Keto Vinylgermane 166.

Following general procedure 5, a solution of the cuprate 110 (1.4 equiv) was treated with (R)-(-)-carvone (163, 174 mg, 1.16 mmol). The crude product was distilled (air-bath temperature 130 - 137 °C/0.1 Torr) to provide 329 mg (88%) of the keto vinylgermane 166 as a colourless oil that consisted of an ~2.5 : 1 mixture of epimers at carbon two and exhibited ir (film): 3045, 1713, 1646, 825, 599 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.20, 0.21 (s, s, ratio undetermined, 9H, -GeMe₃), 1.02, 1.14 (d, d, ratio ~2.5:1, 3H, secondary Me, J = 7 Hz), 1.74, 1.76 (br s, br s, ratio undetermined, 3H, vinylic methyl protons), 1.98-2.72 (m, 9H), 4.71, 4.75, 4.79, 4.82 (br s, br s, br s, br s, ratio of ~1:2.5:2.5:1, 2H, Hₐ and Hₐ), 5.18 (m, 1H, Hₗ), 5.50 (m, 1H, Hₔ). **Exact Mass** calcd. for C₁₆H₂₇GeO (M⁺-CH₃): 309.1273; found: 309.1273; **Anal** calcd. for C₁₇H₃₀GeO: C 63.21, H 9.36; found: C 63.18, H 9.48.
Preparation of the Keto Vinylgermane 167.

Following general procedure 5, a solution of the cuprate 110 (2 equiv) was treated with the enone 161 (41 mg, 0.30 mmol). The crude product was distilled (air-bath temperature 115 - 123 °C/0.1 Torr) to provide 59 mg (63%) of the keto vinylgermane 167 as a colourless oil that consisted of an ~1.5 : 1 mixture of epimers at carbon two and exhibited ir (film): 3046, 1741, 825, 600 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.20, 0.23 (s, s, ratio undetermined, 9H, -GeMe\(_3\)), 1.00, 1.02 (d, d, ratio undetermined, 3H, secondary Me, \(J = 7\) Hz), 1.30-2.25 (diffuse m, 11H), 2.31-2.47 (m, 2H), 2.58-2.68 (m, 1H), 5.17, 5.21 (m, m, ratio ~1:1.5, 1H, \(H_a\)), 5.50, 5.55 (m, m, ratio ~1:1.5, 1H, \(H_b\)). Exact Mass calcd. for C\(_{16}\)H\(_{28}\)GeO: 310.1351; found: 310.1347; Anal calcd. for C\(_{16}\)H\(_{28}\)GeO: C 62.19, H 9.13; found: C 62.08, H 9.24.

General Procedure 6: Preparation of Keto Vinyl Iodides.\(^{21b}\)

To a stirred solution of the appropriate keto vinylgermane (1 equiv) in dry dichloromethane (22 mL per mmol) was added a solution of iodine in dry dichloromethane (1.5 equiv, 0.04 M). The reaction mixture was stirred at room temperature until the reaction was determined to have reached completion (by glc and/or tlc analysis), usually after ~20 h. Aqueous sodium thiosulfate
(~0.1 M, ~ the same volume as that of dichloromethane) was added and the organic layer was separated. The aqueous phase was extracted with dichloromethane and the combined extracts were dried over anhydrous sodium sulfate. Removal of the solvent provided the crude product which was flash chromatographed. Removal of traces of solvent (vacuum pump) from, or distillation of, the resultant oil yielded the required keto vinyl iodide.

**Preparation of the Keto Vinyl Iodide 143.**

Following general procedure 6, the keto vinylgermane 142 (55 mg, 0.21 mmol) was converted into the keto vinyl iodide 143. The crude product was distilled (air-bath temperature 120 - 128 °C/ 0.1 Torr) to provide 55 mg (97%) of the required iodide 143 as a light yellow oil; ir (film): 1713, 1617 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.30-1.44 (m, 1H), 1.46-1.74 (m, 3H), 1.76-1.97 (m, 2H), 1.99-2.12 (m, 2H), 2.21-2.53 (m, 5H), 5.71 (m, 1H, H₆), 6.05 (m, 1H, H₆). *Exact Mass* calcd. for C₁₀H₁₅I: 278.0169; found: 278.0161
Preparation of the Keto Vinyl Iodide 168.

Following general procedure 6, the keto vinylgermane 164 (92 mg, 0.31 mmol) was converted into the keto vinyl iodide 168. The crude product was flash chromatographed (12 x 1 cm column, elution with 88 : 12 pentane - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 135 - 142 °C / 0.1 Torr) to provide 83 mg (87%) of the required iodide 168 as a colourless oil; ir (film): 1714, 1617 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.80 (s, 3H, tertiary Me), 0.97 (d, 3H, secondary Me, \(J = 7\) Hz), 1.42-1.72 (m, 3H), 1.75-1.96 (m, 2H), 2.10 (d, 1H, \(J = 14\) Hz), 2.23-2.48 (m, 5H), 5.69 (m, 1H, \(H_a\)), 6.04 (m, 1H, \(H_b\)). Exact Mass calcd. for C\(_{12}\)H\(_{19}\)IO: 306.0482; found: 306.0479.

Preparation of the Keto Vinyl Iodide 169.

Following general procedure 6, the keto vinylgermane 165 (55 mg, 0.18 mmol) was
converted into the keto vinyl iodide 169. The crude product was distilled (air-bath temperature 135 - 140 °C/ 0.1 Torr) to provide 47 mg (83%) of the required iodide 169 as a colourless oil; ir (film): 1713, 1618 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.04, 1.05, 1.07 (s, s, s, 3H each, tertiary Me groups), 1.46-1.69 (m, 4H), 2.11-2.26 (m, 4H), 2.36-2.48 (m, 2H), 5.68 (m, 1H, H\(_c\)), 6.02 (m, 1H, H\(_b\)). *Exact Mass* calcd. for C\(_{12}\)H\(_{18}\)I\(_2\) (M\(^+\) - Me): 305.0405; found: 305.0401; Anal calcd. for C\(_{13}\)H\(_{21}\)I: C 48.76, H 6.61; found: C 48.58, H 6.67.

**Preparation of the Keto Vinyl Iodide 170.**

Following general procedure 6, the keto vinylgermane 166 (117 mg, 0.36 mmol) was converted into the keto vinyl iodide 170. The crude product was flash chromatographed (14 x 2 cm column, elution with 93 : 7 pentane - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 137 - 142 °C/ 0.1 Torr) to provide 94 mg (80%) of the required iodide 170 as a light yellow oil that consisted of an ~1.3 : 1 mixture of epimers at carbon two and exhibited ir (film): 1709, 1646, 1617, 894 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.02-1.29, 1.44-1.84, 1.89-2.74 (m, m, m, aliphatic protons on cyclohexane ring and side chain), 1.06, 1.15 (d, d, ratio ~1 : 1.3, 3H, secondary Me, \(J = 7\) Hz), 1.74, 1.76 (br s, br s, ratio undetermined, 3H, vinylic methyl protons), 4.71, 4.76, 4.80, 4.83 (br s, br s, br s, br s, ratio ~1.3 : 1 : 1 : 1.3, 2H, H\(_a\) and H\(_b\)), 5.71 (m, 1H, H\(_c\)), 6.04 (m, 1H, H\(_d\)). *Exact Mass* calcd. for C\(_{14}\)H\(_{21}\)I: 332.0639; found: 332.0630.
Preparation of the Keto Vinyl Iodide 171.

Following general procedure 6, the keto vinylgermane 167 (57 mg, 0.18 mmol) was converted into the keto vinyl iodide 171. The crude product was flash chromatographed (12 x 1 cm column, elution with 92 : 8 petroleum ether - diethyl ether). Concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) from the oil thus obtained provided 41 mg (70%) of the required iodide 171 as a colourless oil that consisted of an ~1.5 : 1 mixture of epimers at carbon two and exhibited ir (film): 1738, 1617, 894 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \&: 1.02, 1.03 (d, d, ratio undetermined, 3H, secondary Me, \(J = 7\) Hz), 1.33-2.50 (diffuse m, 13H), 2.58-2.69 (m, 1H), 5.66, 5.70 (m, m, ratio ~1:1.5, 1H, \(H_a\)), 6.01, 6.06 (m, m, ratio ~1:1.5, 1H, \(H_b\)).

*Exact Mass* calcd. for C\(_{13}\)H\(_{19}\)IO: 318.0483; found: 318.0486.
3.2.3.2 Cyclization Studies.

**General Procedure 7: Palladium(0)-catalyzed Cyclization Reactions of Keto Vinyl Iodides.**

To a solution (room temperature) of the appropriate keto vinyl iodide (1 equiv) in dry THF (1 mL per 0.1 mmol) was added tetrakis(triphenylphosphine) palladium (~20 mole % based on the starting material). The reaction mixture was stirred for 5 min and a solution of potassium tert-butoxide in a 4:1 mixture of dry THF and dry tert-butyl alcohol (0.24 M, 1.1 equiv) was added via a syringe pump over 3 h. During this time potassium iodide precipitated slowly from the reaction mixture. After the reaction mixture had been stirred for an additional hour, diethyl ether (~2.5 mL per 0.1 mmol of starting material) and brine (the same volume as that of diethyl ether) were added. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed. The crude material was flash chromatographed and/or distilled to give the desired cyclized product.

**Preparation of the Bicyclic Enone 175.**

Following general procedure 7, the keto vinyl iodide 143 (82 mg, 0.30 mmol) was converted into the bicyclic enone 175. The crude product was flash chromatographed (12 x 1 cm column, elution with 90:10 petroleum ether - diethyl ether) and the oil thus obtained was distilled (air-bath temperature 120 - 128 \(^\circ\)C/15 Torr) to provide 26 mg (59%) of the required
enone 175 as a colourless oil; ir (film): 1678, 1621, 1261 cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.18-1.33 (m, 1H), 1.40-1.55 (m, 1H), 1.68-1.84 (m, 1H), 1.94-2.36 (m, 5H), 2.08 (br s, 3H, -CH\(_3\)), 2.38-2.53 (m, 2H), 2.83-2.96 (m, 1H). Exact Mass calcd. for C\(_{10}\)H\(_{14}\)O: 150.1044; found: 150.1043.

Preparation of the Bicyclic Enone 177.

Following general procedure 7, the keto vinyl iodide 168 (65 mg, 0.21 mmol) was converted into the bicyclic enone 177. The crude product was distilled (air-bath temperature 127 - 134 \(^\circ\)C/15 Torr) to provide 22 mg (59%) of the required enone 177 as a colourless oil; ir (film): 1678, 1626 cm\(^{-1}\); \(^1\)H nmr (300 MHz, CDCl\(_3\)) \(\delta\): 0.89 (s, 3H, tertiary Me), 0.94 (d, 3H, secondary Me, \(J = 7\) Hz), 1.60-1.85 (m, 5H), 2.02 (br s, 3H, vinylic Me), 2.13-2.64 (m, 4H). Exact Mass calcd. for C\(_{12}\)H\(_{18}\)O: 178.1357; found: 178.1364; Anal. cald. for C\(_{12}\)H\(_{18}\)O: C 80.85, H 10.18; found: C 80.82, H 10.06.
Preparation of the Bicyclic Enone 178.

Following general procedure 7, the keto vinyl iodide 169 (83 mg, 0.26 mmol) was converted into the bicyclic enone 178. The crude product was distilled (air-bath temperature 133 - 140 °C/15 Torr) to provide 37 mg (74%) of the required enone 178 as a colourless oil; ir (film): 1682, 1624 cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.93, 1.03, 1.10 (s, s, s, 3H each, tertiary Me groups), 1.59-1.91 (m, 4H), 2.10 (br s, 3H, vinylic Me), 2.13 (d, 1H, J = 17 Hz), 2.20-2.28 (m, 1H), 2.29 (d, 1H, J = 17 Hz), 2.51-2.64 (m, 1H). Exact Mass calcd. for C₁₃H₂₀O: 192.1514; found: 192.1519.

Preparation of the Bicyclic Ketone 179.

Following general procedure 7, the keto vinyl iodide 170 (60 mg, 0.18 mmol) was converted into the bicyclic ketone 179. The crude product was flash chromatographed (12 x 1 cm column, elution with 80 : 20 pentane - dichloromethane). Concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) from the oil thus obtained provided 24
mg (65%) of the bicyclic ketone 179 as a colourless oil; ir (film): 3078, 1703, 1646, 892 cm⁻¹; H nmr (400 MHz, CDCl₃) δ: 1.25 (s, 3H, angular Me), 1.46-1.57 (m, 1H), 1.71-1.94 (m, 3H), 1.76 (br s, 3H, vinylic Me), 2.17 (dt, 1H, J = 12.6 Hz), 2.37-2.59 (m, 4H), 2.61-2.70 (m, 1H), 4.70 (br s, 1H, Ha or Hb), 4.84 (m, 2H, Ha or Hb and Hc), 5.02 (t, 1H, Ha, J = 2 Hz); H nmr (400 MHz, CDCl₃) nOe difference: irradiation at δ 1.25 (angular Me) causes enhancement at δ 4.84 (Hc); C nmr (50.3 MHz, CDCl₃) δ: 21.4, 23.1, 28.2, 29.7, 30.3, 40.8, 42.8, 46.9, 59.1, 108.1, 110.9, 147.0, 154.5, 212.6. Exact Mass calcd. for C₁₄H₂₀O: 204.1514; found: 204.1519.

Preparation of the Tricyclic Ketone 180.

Following general procedure 7, the keto vinyl iodide 171 (39 mg, 0.12 mmol) was converted into the tricyclic ketone 180. The crude product was flash chromatographed (12 x 1 cm column, elution with 98 : 2 pentane - diethyl ether). Concentration of the appropriate fractions and removal of traces of solvent (vacuum pump) from the oil thus obtained provided 15 mg (65%) of the tricyclic ketone 180 as a colourless oil; ir (film): 3080, 1735, 1645, 893 cm⁻¹; H nmr (400 MHz, CDCl₃) δ: 1.08 (s, 3H, Me), 1.34-1.76 (m, 6H), 1.80-1.90 (m, 2H), 1.98-2.09 (m, 1H), 2.17-2.26 (m, 1H), 2.38-2.55 (m, 2H), 2.73 (dd, 1H, J = 19, 11 Hz), 4.93 (t, 1H, Ha, J = 2 Hz), 4.96 (t, 1H, Hb, J = 2 Hz); H nmr (400 MHz, CDCl₃) nOe difference: irradiation at δ 1.08 (Me) causes enhancement at δ 4.93 (Ha). Exact Mass calcd. for C₁₃H₁₈O: 190.1358; found: 190.1359; Anal. calcd. for C₁₃H₁₈O: C 82.06, H 9.53; found: C 82.24, H 9.62.
IV. REFERENCES

1. Following Trost, "conjunctive reagents" are defined as "reagents which are simple building blocks that are incorporated in whole or in part into a more complex system and to differentiate them from reagents that operate on but are not normally incorporated into a substrate." See: B.M. Trost, Acc. Chem. Res., 11, 453 (1978).


5. Synthons are defined as "structural units within a molecule which are related to possible synthetic operations". See: E.J. Corey, Pure Appl. Chem., 14, 19 (1967).


17. "Umpolung" is "any process by which donor and acceptor reactivity of an atom are interchanged". See ref. 3.


25. a) We thank Dr. S. Rettig for performing the X-ray structure determinations.; b) All X-ray structure determinations were performed on racemic materials. The compound depicted in the figure is the mirror image of the structure indicated.
38. Miguel Romero is thanked for a generous sample of the alcohol 116.
63. Professor D.J. Faulkner is thanked for a sample of (-)-ambliol B.


V. APPENDIX

5.1 Appendix 1: X-Ray Crystallographic Data.

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