SYNTHETIC APPROACH TO THE AGELASIMINES

By

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We accept this thesis as conforming
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The University of British Columbia
Vancouver, Canada

Date 27TH AUGUST 1992
ABSTRACT

Aside from the structural interest and the success achieved in annulation methods as exemplified in schemes 6 and 7 in this laboratory, synthetic work on the agelasimines A and B and their quartenary 9-methyladenine derivative (44) was encouraged by the presence of a variety of biological activities in these natural products. Another aim of this thesis is to confirm the generality of the synthetic method as applied to the total synthesis of ambliol B (48).

Copper(I) mediated conjugate addition of allylmagnesium bromide to 3,4-dimethyl-2-cyclohexen-1-one (63), followed by trapping of the enolate generated with trimethylsilyl chloride, produced the silyl enol ether (62), which was converted to the Mannich base (61). Oxidation of this compound with m-CPBA gave an amine-oxide intermediate which eliminated \( N,N \)-dimethylhydroxylamine to give the enone (60). Conjugate addition of the novel vinylgermane cuprate (19) to this enone and treatment of resultant ketone (80) with iodine gave the iodide (59). This iodide was employed as the cyclization precursor to the \( \text{trans} \)-fused substituted bicyclo[4.4.0]decananol (58). Cyclopropanation of the exocyclic double bond in (58) occurred chemoselectively and gave the cyclopropane (67). The remaining double bond was ozonized and the ozonide cleaved to generate an aldehyde which was reduced to the primary alcohol (93). Hydrogenolysis of the cyclopropane ring of this diol provided the diol (55), which is a possible precursor
for the synthesis of the agelasimines A (42), B (43) and their quartenary 9-methyladenine derivative (44).
Purino-derivative of (42 and 43)

$X = (44)$

Agelasimine A

$X = (42)$

Agelasimine B

$X = (43)$
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>APT</td>
<td>attached proton test</td>
</tr>
<tr>
<td>Aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere(s)</td>
</tr>
<tr>
<td>9-BBN</td>
<td>9-borabicyclo[3.3.1]nonane</td>
</tr>
<tr>
<td>bp</td>
<td>boiling point</td>
</tr>
<tr>
<td>br</td>
<td>broad (spectral)</td>
</tr>
<tr>
<td>Bu</td>
<td>n-butyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>°C</td>
<td>degree Celcius</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>cat</td>
<td>catalytic / catalyst</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionisation (in mass spectrometry)</td>
</tr>
<tr>
<td>cm⁻¹</td>
<td>wave number</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>δ</td>
<td>chemical shift in parts per million downfield from tetramethylsilane</td>
</tr>
<tr>
<td>d</td>
<td>doublet (spectral)</td>
</tr>
<tr>
<td>ED₅₀</td>
<td>dose that is effective in 50% of test subjects</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact (in mass spectrometry)</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent(s)</td>
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<td>Et</td>
<td>ethyl</td>
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<tr>
<td>eV</td>
<td>electron volt(s)</td>
</tr>
<tr>
<td>FT</td>
<td>Fourier transform</td>
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g  - gram(s)
glc - gas-liquid chromatography
h  - hour(s)
HMPA - hexamethylphosphoramide
Hz  - hertz
ir  - infrared
\(J\) - coupling constant (in NMR)
L  - liter(s)
LDA - lithium diisopropylamide
\(\mu\) - micro
M  - moles per liter
m  - multiplet (spectral)
Me  - methyl
mg  - milligram(s)
min - minute(s)
MHz - megahertz
mol - mole(s)
mmol - millimole(s)
MS  - mass spectrometry
\(\text{nmr}\) - nuclear magnetic resonance
Ph  - phenyl
ppm - parts per million
q  - quartet
\(\text{rt}\) - room temperature
s  - singlet (NMR)
soln - solution
t  - triplet (spectral)
Tf$_2$NPh - $N$-phenyltrifluoromethanesulfonimide
THF - tetrahydrofuran
tlc - thin layer chromatography
TMS - trimethylsilyl, tetramethysilane
torr - 1 mm Hg
ACKNOWLEDGMENTS

Gratitude is hereby being expressed to my advisor, Dr. Edward Piers, who was helpful, academically, during the course of this study. His guidance, patience and perfectionistic attitude towards research saw this work to its present stage.

May I say "Thank You" to all other academic staff, technical staff and my colleagues who contributed in one way or the other.

Acknowledgement is made to Ingrid Ellis for the weekend hours spent on my behalf typing most of this thesis.

Finally, thanks are due to my daughter, Selasie and her mum, Empress, who were of constant support, emotionally, and have kept spirits and hopes very high so far.
This thesis is dedicated to the memory
of
my mum,
Celestine Kwasiwor Kuebunya
and
my aunt (guardian),
Margaret Aku Kuebunya
There is excitement, adventure, and challenge, and there can be great art in organic synthesis

R. B. Woodward
In Perspectives in Organic Chemistry
INTRODUCTION

1.1 General

We are now in an era of both the synthesis of new molecules of ever increasing complexity and in the development of new methods which allow more precise control over the formation of new bonds and the stereochemistry of the product. Nature provides the synthetic chemist with a vast array of complex structures whose syntheses are justifiable and well-defined goals. The total synthesis of natural products requires chemists who are able to invent new organic reactions, control relative and absolute stereochemistry in a predictable manner, and realize success in reaching clearly defined targets of research.

Organic reagents possessing two reactive sites (one nucleophilic and one electrophilic, or two nucleophilic or two electrophilic centres) are becoming increasingly important in organic synthesis. These species have been used as reagents by employing the two reactive positions in the novel synthesis of complex and functionalized natural products. They are referred to as "bifunctional conjunctive reagents" or "multiple coupling reagents" and have been used for cyclizations. This involves coupling with bifunctional substrates intermolecularly followed by an intramolecular step. The reactions are usually polar in nature resulting in the reactive sites of the reagents being termed "donor" (d) and "acceptor" (a).
No attempt will be made in this thesis to give examples of the use of these reagents in total synthesis of natural products since such examples are numerous, some of which can be found in the references numbered 4 - 12.

1.2 Background and Proposals

For the past decade, investigations conducted in our research laboratories produced a group of vinylstannanes\textsuperscript{13} and a vinylgermane,\textsuperscript{20} which have been employed as bifunctional conjunctive reagents. Thus, regioselective addition of trimethylstannylcopper-dimethyl sulphide\textsuperscript{14} to 1-alkynes produced $\omega$-chloro-2-trimethylstannyl-1-alkenes (1), where $n = 1, 2$.

As precursors of bifunctional conjunctive reagents, these vinylstannanes possess donor (d) and acceptor (a) sites and as such
are synthetic equivalents of donor-acceptor synthons (2).

These reagents have been utilized in the construction of 5- and 6-membered rings, through conjugate addition to cyclic enones. Thus, 4-chloro-2-trimethylstannylbut-1-ene (3) was converted

Scheme 2
readily into the novel cuprate (4) which added to the cyclic enone (5). A subsequent intramolecular alkylation generated a third cyclopentane ring\textsuperscript{15} to provide the angularly fused triquinane (7), as shown in scheme 2.

5-Chloro-2-trimethylstannyl-1-pentene (8), a homologue of (3) and a synthetic equivalent of the 1-pentene d\textsuperscript{2}, a\textsuperscript{5} synthon (9), has also been employed in annulation.

\[
\begin{align*}
\text{Me}_3\text{Sn} & \quad \equiv \\
(8) & \quad (9)
\end{align*}
\]

For example, 5-chloro-2-lithio-1-pentene (10), obtained by transmetalation of (8), was converted to Grignard and/or organocopper reagents, which added conjugatively to the enone (11). Intramolecular alkylation at the $\alpha$-position of the ketone (12) produced a mixture of the cis- and trans-fused bicyclic compounds (13a) and (13b)\textsuperscript{16} as indicated in scheme 3.

This useful and important methodology was employed in a complementary fashion by reversing the order of deployment of the potential acceptor site (alkyl halide) and the potential donor site (vinylstannane). Such annulation strategies were utilized in the formation of the diene (18), the enone (25), and compounds containing allylic angular hydroxyl groups (eg, (30), (32), (33)).
Thus, cyclic $\alpha$-methoxycarbonyl ketones (14) have been alkylated conveniently with the acceptor site of the iodo analogue (15) of reagent (8). After the conversion of these alkylated products (16) into enol trifluoromethanesulphonates (17), palladium(0)-assisted cyclization afforded the diene systems (18).
The use of the bifunctional conjunctive reagents discussed so far was extended in another useful way by interconverting their donor and acceptor sites. In such a way the activity of the reactive sites themselves have been reversed. This idea was successfully executed by our group in a five-membered ring annulation method involving the use of the vinylgermane cuprate (19) as a synthetic equivalent of the 1-butene $a^2,d^4$ synthon (20).$^{19}$
Thus 1,4-addition of reagent (19) to the cyclic enone (21) produced the 1,4-adduct (22) as an intermediate to the keto vinyl iodide (23). Palladium(0)-catalyzed cyclization produced compound (24) which under the reaction conditions, was isomerized into the enone (25).

Recent reports in our laboratory documented the successful preparation of bicyclic systems possessing an allylic angular
hydroxyl group,20,26 the double bond being endocyclic or exocyclic. The preparation of the product (30) containing an endocyclic double bond began from the bifunctional reagent (26), which is derivable from the corresponding alcohol.21 The keto vinylstannane (27), resulting from the usual alkylation18 with the vinylstannyl chloride (26), was methylated (28) with t-BuOK in t-BuOH and THF followed by MeI addition. Iodine treatment produced the keto vinyl iodide (29), which was smoothly cyclized to (30) upon treatment with n-BuLi (2.5 equiv).

(Scheme 6)
The exocyclic equivalent of (30) was also accessed using the methodology described above. The bifunctional reagents employed were (15) and its one-carbon lower homologue (81). Hence starting from the alkylated substrates mentioned earlier, the intermediate keto vinyl iodides (31) were cyclized into the products (32) and (33).

\[
\begin{align*}
\text{A} &= -\text{OCH}_2\text{C(CH}_3)_2\text{CH}_2\text{O}^- \\
n &= 1, R = H; \text{both cis and trans,} \\
n &= 2, R = \text{Me}; \text{only cis product.}
\end{align*}
\]

**Scheme 7**

The successful execution of these annulation processes and the fact that the methylenecyclopentane, methylenecyclohexane, their more stable endocyclic isomers and the allylic angular hydroxyl moiety are structural units in the terpenoid family of natural
products, encouraged us in our goal towards the total synthesis of natural products.

In africanol (34), the methylcyclopentane ring could be prepared by hydrogenation of the corresponding methylenecyclopentane moiety, whilst the gem-dimethyl arrangement in 3α,5α-dihydroxychiliolide (41), the agelasimines A (42) and B (43) and their quartenary 9-methyladenine derivative (44) are theoretically achieved by cyclopropanation of the methylenecyclohexane ring, followed by hydrogenolysis of the cyclopropane ring. The other representative natural products of interest are (±)-Δ9(12)-capnellene (35), (±)-pentalenene (36), (±)-axamide-1 (37) and (±)-axisonitrile (38), (-)-methyl kolavenate (39), and Δ9(12)-capnellene-5α,8β,10α-triol (40).
It was in fact an interest in the synthesis of the *trans*-fused bicyclic natural products containing an angular, allylic hydroxyl function that initiated the work described in this thesis.
II DISCUSSION

2.1 Synthetic Approach to the Agelasimines

2.1.1 Introduction

The isolabdane diterpenoids, possessing the general carbon skeleton (45), are a class of terpenoids which biogenetically are derivable from geranylgeraniol (46). Formally (45) could be regarded as being formed via a 1,2-methyl shift involving the migration of the methyl group at C-10 to C-9 followed by 1,2-hydride shift from C-5 to C-10. The clerodane skeleton (47) is formed by methyl group migrations at two positions, from C-4 to C-5 in addition to the C-10 to C-9 migration. There is also the 1,2-hydride shift from C-5 to C-10 following the C-10 to C-9 methyl migration.

A small number of diterpenoids possessing the isolabdane
skeleton have been isolated from terrestrial and marine organisms. Notable examples are ambliols B (48) and C (49) isolated from *Dysidea amblia* (de Laubenfels) samples collected by hand using SCUBA at 20-30 m at Scripps Canyon and Pt. Loma, La Jolla, CA, by Faulkner *et al.*26a,b 3α,5α-Dihydroxychiliolide (41) was isolated from the aerial parts of *Chliotrichium rosmarinifolium* (voucher RMK 9399, U.S. National Herbarium, Washington).23 In 1984, Faulkner *et al.*25 extracted and determined the structure of an unusual purinoditerpene (44), an artifact derived from an unstable base that was the major antimicrobial metabolite of *Agelas mauritiana*. The methanolic extract of this sponge from Enewetak showed significant antimicrobial activity against *Bacillus subtilis* and *Vibrio anguillarum*. Recently,24 Fathi-Afshar and Allen isolated two novel adenine derivatives of a bicyclic diterpenoid, agelasimine A (42) and agelasimine B (43) from the orange sponge *Agelas mauritiana*. This marine sponge was collected from Enewetak Atoll at 15 meter depths.

Aside from the structural interest and the success achieved in annulation methods as exemplified in schemes 6 and 7 in this laboratory, synthetic work on the agelasimines A and B was encouraged by the presence of a variety of biological activities in these natural products. Both compounds have been reported24 to show cell growth inhibition properties when tested against L1210 mouse leukemia cells *in vitro* (ED$_{50}$ = 2-4 μg/mL). Their effect on the smooth muscle relaxation of rabbit gut and beef coronary artery
tissues (ED$_{50}$ = 3-10 μM) was also confirmed. These two compounds also have the ability of inhibiting nucleoside transport into rabbit
erythrocytes (IC\textsubscript{50} = 6-14 µM). The most interesting biological activity tested was the reversal effects on rat aorta ring preparations of various neurotransmitters and other substances. It is anticipated that both agelasimines will be active Ca\textsuperscript{2+}-channel antagonists as well as α\textsubscript{1} adrenergic blockers.

The synthetic aspects of isolabdane diterpenoids had remained unexplored until 1990, when our group reported the first total synthesis of one of these substances, called ambliol B (48).\textsuperscript{26c} Like ambliol B, the agelasimines contain a \textit{gem}-dimethyl moiety adjacent to an angular hydroxyl functionality. Therefore, similar methodology was applied towards our synthetic studies on the agelasimines.

For some background work on clerodane synthesis, the reader is referred to publications describing the synthesis of (+)maingayic acid (50),\textsuperscript{27} (-)-methyl kolavenate (39),\textsuperscript{9} linaridial (51)\textsuperscript{28} and (+)-15,16-epoxy-cis-cleroda-3,13(16),14-triene (52).\textsuperscript{27}
2.1.2 Synthetic Planning

For the synthesis of the substituted \textit{trans}-fused bicyclo[4.4.0]decane (58) by the already documented annulation, the preparation of the \textit{\alpha}-methylene ketone (60) became mandatory. From a synthetic point of view (scheme 8), this substance is derivable from a conjugate addition\textsuperscript{29}-trapping\textsuperscript{30}-alkylation\textsuperscript{31} procedure\textsuperscript{26c,32}, provided that the introduction of the allyl group to 3,4-dimethyl-2-cyclohexen-1-one (63) is stereoselective in the desired sense, that is, \textit{trans} to the 4-methyl group. Fortunately, in this respect, we could utilize the straight-forward result of Piers and Marais\textsuperscript{26c} and also that of Danishefsky.\textsuperscript{32} These authors reported that the conjugate addition of vinylmagnesium bromide and pentenylmagnesium bromide, respectively, generated a metalloenolate species. These were silylated to afford trapped products similar to (62), stereospecifically.
At this stage it was expected that we could take advantage of the reaction of silyl enol ethers with preformed Mannich salts. This occurs regiospecifically to give keto amines (61) as substrates to the α-methylene ketone (60). In this intermediate, the relative configurations of two of the four contiguous stereogenic centres at C-5, C-8, C-9 and C-10 in the natural products have been set up. The allyl moiety and the α-methylene group have been put in place so as to make further side chain manipulations possible.

As already documented in our group by Marais, the bifunctional conjugate reagent (19), the synthetic equivalent of a 1-butene d²,d⁴-synthon (65), is expected to add to the enone (60). A
series of appropriate transformations would then be expected to give

\[ \text{Scheme 9} \]

the \textit{trans}-fused bicyclic product (58) predominantly or exclusively 46a (scheme 9).

Cyclopropanation of the exocyclic double bond in (58) would give (67) (see pages iii and 32), allowing for the manipulation on the remaining double bond to access the ketone (56) or the iodide (54). From the ketone (56), target products (42-44) would be accessible \textit{via} Wadsworth-Emmons-Horner olefination followed by appropriate transformations.
An alternate route would be to couple\textsuperscript{33} the iodide (54) with the vinyl iodide (53), generously supplied by Jacques Roberge, to synthesize an intermediate that would serve as a suitable precursor for the same targets.

2.1.3 Synthetic Studies on the Agelasimines

The studies started from the preparation of 3,4-dimethyl-2-cyclohexen-1-one (63) according to standard methods,\textsuperscript{34} which were
modified to give an optimum yield of 81%. This compound has spectral properties identical to those reported by Dauben et. al.\textsuperscript{35}

A copper(I)-catalyzed conjugate addition of allylmagnesium bromide (64) to the enone (63) in the presence of HMPA/Me\textsubscript{3}SiCl\textsuperscript{30} did not produce the required 1,4-adduct but rather the 1,2-addition product (68) in 83% yield. The presence of the OH group was indicated by a strong absorption peak in the ir spectrum at 3366 cm\textsuperscript{-1}. This was confirmed by a peak at $\delta$ 69.9 in the 50 MHz $^{13}$C nmr spectrum. The vinyl proton in the ring appeared at $\delta$ 5.31 as a broad singlet in the $^1$H nmr spectrum (400 MHz, CDCl\textsubscript{3}). This result is not unexpected, since earlier reports\textsuperscript{29a,b} have documented this. Good donor solvents such as THF have been known to retard or inhibit conjugate addition.

The dienol (68) could serve as a viable precursor to the silyl enol ether (62) via an anionic oxy-Cope rearrangement\textsuperscript{36,37,38} followed by trapping\textsuperscript{37a} of (69) with trimethylsilyl chloride as shown in Scheme 10.

\begin{align*}
\begin{array}{c}
\text{(68)} \\
\text{K}^+ \text{O}^- \\
\text{(69)} \\
\text{TMSO} \\
\text{(62)}
\end{array}
\end{align*}

\textbf{Scheme 10}
Having failed to effect the conjugate addition by Cu(I)-catalysis, attention was drawn to earlier experiments whereby 0.5 equivalent\(^{39a}\) of a Cu(I) species was employed to improve the yields of the 1,4-adducts when 3-methyl-2-cyclohexen-1-one (71) and 1-acetylcyclohexene (72) were substrates.\(^{39b}\) The usual 0.25 equivalent of Cu(I) gave significant amounts of 1,2-addition to the carbonyl group.

When this approach was extended to our system, both 1,2- and 1,4-addition products were obtained in the ratio of 1:1. However, it was found that use of 1.0 equivalent of CuBr\(_2\).Me\(_2\)S gave exclusively 1,4-addition, and the silyl enol ether (62) was produced and purified\(^{40}\) in 86% yield (scheme 11). The silyl enol ether and terminal olefin frequencies appeared at 1668 cm\(^{-1}\), 1252 cm\(^{-1}\) and 1641 cm\(^{-1}\), 910 cm\(^{-1}\), respectively, in the ir spectrum. The presence of one tertiary and one secondary methyl group was indicated at \(\delta\) 0.80 (s, 3H) and 0.82 (d, 3H, \(J = 7\) Hz), respectively, in the \(^1\)H nmr spectrum (400 MHz, CDCl\(_3\)). The presence of four vinyl protons was also indicated by signals at \(\delta\) 4.65 (br s, 1H), \(\delta\) 4.92-5.05 (m, 2H) and 5.68-5.84 (m, 1H). According to literature precedence,\(^{26c,29c,32}\) the relative configuration of the two chiral centres present in the (62)
could be assigned with confidence and were correct for the eventual synthesis of the target natural products (42-44).

Due to the unstable nature of the silyl enol ether (62), its hydrolysis product, the ketone (70) is always isolated as a side product. This ketone was fully characterized. The ir spectrum showed peaks at 1714 cm$^{-1}$, 1640 cm$^{-1}$ and 916 cm$^{-1}$. $^1$H nmr spectroscopy (400 MHz, CDCl$_3$) showed the presence of one tertiary and one secondary methyl group at $\delta$ 0.71 (s, 3H) and 0.88 (d, 3H, $J = 8$ Hz), respectively. The vinyl protons resonated as multiplets in the region $\delta$ 4.94-5.10 (2H) and 5.68-5.81 (1H). The keto carbon-atom was confirmed in the $^{13}$C nmr spectrum (100 MHz, CDCl$_3$) at $\delta$ 212.1. The exact mass determined for C$_{11}$H$_{18}$O was 166.1358 and compares well with the calculated value of 166.1361. Microanalysis gave C 78.80 and H 10.80 as against the theoretical value of C 79.47 and H 10.91.

Now that we had successfully prepared the silyl enol ether (62), its reaction with methyllithium at room temperature for 30
min, according to the procedure of Stork and Hudrlik,\textsuperscript{41} generated the enolate (73) with positional specificity (scheme 11). This enolate was then allowed to react with dimethyl(methylene) ammonium iodide (74, Eschenmoser's salt\textsuperscript{42}) following Danishefsky's method.\textsuperscript{31,32} This was followed by acidic (1N HCl) work-up and basification (5% aq. Na\textsubscript{2}CO\textsubscript{3}) to afford a 96% yield of the Mannich base (61), which consisted of an epimeric mixture at the C-2 position. The ir (neat) spectrum of the keto amine (61) revealed peaks at 1715 cm\textsuperscript{-1} for keto group and at 1639 cm\textsuperscript{-1} for olefin group. The \textsuperscript{1}H nmr spectrum (400 MHz, CDCl\textsubscript{3}) showed that the correct product had been isolated. Prominent peaks in the spectrum at \( \delta \) 2.15 and 2.20 (s, s, ratio 2.2:1, 6H) are assignable to the methyl
groups of the Me₂N moiety. The chemical ionization (CI) mass spectrum of this compound gave prominent fragments at 224 (M⁺ + 1, 2.3%), 223 (M⁺, 4.3%), and 58 (CH₂=N+Me₂, 100%).

Because of its instability, the crude keto amine mixture (61) was oxidized without further purification with m-chloroperoxybenzoic acid in dichloromethane to form the corresponding labile N-oxide (75). This material was passed through a short column of silica gel to produce the α-methylene ketone (60) in 85% yield, after purification and distillation (scheme 12). Surprisingly, this biselectrophile was stable compared to its lower homolog (vinyl in place of allyl), prepared in our group by Marais. Resonance frequencies in the ir spectrum at 1695 cm⁻¹ and 1610 cm⁻¹ indicated the presence of the α,β-unsaturation. The terminal olefin gave rise to an absorption at 1640 cm⁻¹. The ¹H nmr spectrum (400 MHz, CDCl₃) of this enone showed resonance peaks at δ 5.15 (br s, 1H) and 5.84 (br s, 1H) due to the two methylene protons β to the carbonyl group. Other assignments were as expected. The ¹³C nmr spectrum (50 MHz, CDCl₃) indicated the carbonyl carbon at δ 203.7.

![Diagram](image-url)

Scheme 12
A minor compound, exhibiting a higher retention time on glc as compared to (60), was also isolated. This material exhibited spectral properties similar to those of (60), except that its α-methylene protons resonated at δ 4.76 (br s, 1H) and 4.97 (br s, 1H) in its $^1$H nmr spectrum (400 MHz, CDCl$_3$). The structure (76)$^{44}$ was assigned to this minor side product.

\[
\begin{align*}
\text{(60)} & \\
\text{(76)} & 
\end{align*}
\]

In order to prepare the novel cuprate (19)$^{26c}$ a cold (-98°C) THF solution of (77), (0.05 M)$^{26c}$ was treated with 2.00-1.95 equivalents of tert-butyllithium and the resultant solution was warmed to -78°C whereupon 1.1 equivalents of copper(I) cyanide was added. Brief warming to -35°C gave the cyanocuprate (19) as a

\[
\begin{align*}
\text{(77)} & \xrightarrow{(1) \text{t-BuLi (2 eq.), THF, -98°C}} \text{Me}_3\text{Ge} & \\
& \xrightarrow{(2) \text{CuCN, -78°C}} \text{Cu(CN)Li} & \text{(19)}
\end{align*}
\]
The enone (60) was allowed to react with 1.6 equivalents of the cuprate (19) in the presence of three equivalents of trimethylsilylbromide at \(-78^\circ C\) in THF for 2 hours (scheme 13, page 28). The resulting silyl enol ether intermediate (78) was hydrolyzed and the reaction mixture was worked up. The crude 1,4-adduct (79), which consisted of two epimers in the ratio of 1:2.5, was epimerized with 0.5 equivalents of potassium tert-butoxide in tert-butanol and THF to give the more stable isomer. Purification and distillation of the crude oil gave a 50% yield of the keto vinylgermane (80). Evidence that the desired compound was indeed formed came from the ir spectrum. The ketone function gave rise to an absorption at 1713 cm\(^{-1}\), while the olefin function produced peaks at 1639 cm\(^{-1}\) and 916 cm\(^{-1}\). The \(^1\)H nmr spectrum (400 MHz, CDCl\(_3\)) of (80) exhibited a nine-proton singlet at \(\delta\) 0.18 for the Me\(_3\)Ge group and three-proton signals at \(\delta\) 0.55 (s) and 0.89 (d, \(J = 8\) Hz) due to the tertiary and secondary methyl groups, respectively. Three vinyl protons can be found in the region \(\delta\) 5.02-5.18 (m). The vinyl proton \(trans\) to the Me\(_3\)Ge moiety appeared at \(\delta\) 5.47 (m, 1H) whilst the fifth vinyl proton gave a peak at \(\delta\) 5.73-5.88 (m). Compound (80) exhibited expected \(^{13}\)C nmr spectral (50 MHz, CDCl\(_3\)) characteristics.

During the epimerization of the crude mixture (79) (scheme 13, page 28), the less stable isomer (82) was converted under thermodynamic conditions into the relatively more stable compound (81). It can be seen from the two conformational formulas that (82)
has two axial and two equatorial substituents whereas (81) has only one axial and three equatorial substituents.

\[ \text{(82)} \quad \rightarrow \quad \text{(81)} \]

It should be noted that the exact equivalents of reagents utilized in the preparation of (19) and subsequently (80) are necessary for best results. Deviations from these amounts gave the coupling product (84) and the \( t \)-butyl conjugate addition product (83)

\[ \text{(83)} \quad \text{(84)} \]

The keto vinylgermane (80) (scheme 13, page 28) was expediently transformed into the corresponding keto vinyl iodide (59) by treatment with 1.1 equivalents of iodine in dichloromethane at room temperature. After work-up and
purification, the keto vinyl iodide (59), homogeneous by tlc and glc, was obtained in 91\% yield (scheme 13). The compound (59) exhibited all the expected resonances in both its ir (neat) and $^1$H nmr

Scheme 13

(400 MHz, CDCl$_3$) spectra. Ir absorptions for the ketone group and
the vinyl group were observed at 1712 cm\(^{-1}\) and 1638 cm\(^{-1}\), respectively. That for the iodo-substituted double bond appeared at 1617 cm\(^{-1}\). In the \(^1\)H nmr spectrum, two diagnostic multiplets for the iodovinyl protons appeared at \(\delta\) 5.67-6.02. These signals are significantly downfield from those of the corresponding resonances for the precursor vinylgermane (80), thus confirming that the germane moiety had been replaced by the more electronegative iodine atom. The \(^{13}\)C nmr (50 MHz, CDCl\(_3\)) spectrum confirmed the types and the total number of carbon atoms present.

As discussed previously, the keto vinyl iodide (59) is the precursor to the required substituted trans-fused bicyclo[4.4.0]decananol (58) (scheme 14). Attention was therefore turned to achieving this transformation by the addition of 2.4 equivalents of \(n\)-butyllithium at \(-78^\circ\text{C}\) to a THF solution of (59). Within 15 min, smooth cyclization had occurred. Work-up, chromatographic purification and distillation provided the alcohol (58) in 87% yield as a single product.

Evidence that (58) was indeed produced came from a variety of spectral data. The ir spectrum of this compound exhibited an O-H stretching absorption at 3426 cm\(^{-1}\). The olefin absorption appeared at 1639 cm\(^{-1}\). The 400 MHz \(^1\)H nmr spectrum of (58) revealed the presence of two methyl groups resonating at \(\delta\) 0.85 (d, 3H, secondary Me, \(J = 8\) Hz) and 0.88 (s, 3H, tertiary Me). The protons on the exocyclic double bond showed resonance absorptions at \(\delta\) 4.65 (br s, 1H) and 4.73 (br s, 1H), whilst the vinyl protons of the allyl group
gave rise to resonances in the region δ 4.90-5.05 (m, 2H) and 5.62-5.75 (m, 1H). In the 13C nmr spectrum, the tertiary carbinol carbon of (58) produced a signal at δ 73.6.

Despite the highly nucleophilic character of n-butyllithium, it is interesting to note that direct reaction of this reagent with the carbonyl group did not occur. Thus the reaction of n-butyllithium to effect iodine-metal exchange at the low temperature was faster than its reaction with the nonconjugated ketonic carbonyl group present in (59).\(^{46b}\)

(Scheme 14)

The spectroscopic data derived from the cyclization product
(58) did not provide conclusive evidence regarding the stereochemistry at the ring junction of this material. However, precedence has been set by cyclization studies by Marais\textsuperscript{26c} that such systems yield products of the desired stereochemistry. Cyclization is expected to take place \textit{via} conformer (85). For steric reasons, attack on the carbonyl atom by the vinyllithium moiety will take place from the equatorial face to give the transient \textit{trans}-fused lithium alkoxide (86). This species, upon protonation, would give (58). In the case of axial facial attack by the approaching vinyllithium moiety on the carbonyl carbon, a 1,3-diaxial interaction with the axially oriented methyl would be experienced, destabilizing the transition state.

The annulation sequence was, therefore, highly stereoselective and in view of the stability ascribed to conformer (85), the desired stereochemical relationships at the four diastereomeric carbon atoms in (58) can reasonably be assigned, though the ultimate confirmation of this will be made after the completion of the total syntheses of the natural products. The \textit{trans}-fused bicyclic skeleton of the agelasimines (42-44) had also been correctly installed.

Before any synthetic manipulations of the allyl group of (58) could be carried out, it was necessary to convert the exocyclic double bond into a relatively unreactive cyclopropane moiety.

The use of diethylzinc\textsuperscript{47a} instead of zinc-copper couple\textsuperscript{48} for the cyclopropanation of olefins was reported by Furukawa \textit{et. al.} In
1972, Miyano documented evidence that the presence of oxygen greatly accelerates the cyclopropanation.\textsuperscript{49} Thus, treatment of a dry benzene solution of (58) with diiodomethane-diethylzinc in the presence of dry oxygen gave a 90% yield of the cyclopropane (67) as a colourless oil. The ir spectrum of (67) indicated absorptions at 3075 cm\(^{-1}\), 3001 cm\(^{-1}\) and 1015 cm\(^{-1}\) characteristic of the cyclopropane ring. The O-H stretch and the olefin absorptions were indicated between 3599-3514 cm\(^{-1}\) and at 1637 cm\(^{-1}\), respectively. This compound exhibited four characteristic high field multiplets in its 400 MHz \(^1\)H nmr spectrum at \(\delta\) 0.00-0.10, 0.15-0.24, 0.48-0.58 and 0.60-0.69, indicative of the protons on the cyclopropane ring. The protons attached to the vinyl moiety showed resonances in the region \(\delta\) 4.95-5.05 (m, 2H) and 5.68-5.84 (m, 1H), confirming that the cyclopropanation was site-selective.

As reported by Marais\textsuperscript{20,26c} in a related reaction, longer reaction times gave poor yields of (67) and an unwanted side reaction, possibly involving cyclopropanation of the allyl group double bond. Additionally, in our hands, quenching of the reaction
mixture with the usual aqueous NH₄Cl-NH₄OH (pH 8) provided the desired product (67) and another compound (87) in the ratio of 1:6. Evidence for the structure of compound (87) came from the absence of the hydroxyl and cyclopropane groups as indicated by its ir and 400 MHz ¹H nmr spectra. The multiplet in the region δ 2.50-2.72, integrating for two protons, is attributable to the allylic protons of the newly generated side chain. The two CH₂I protons are observable in the region δ 3.01-3.19 as a multiplet and are coupled to the adjacent protons as indicated in a COSY experiment. All other resonances are as expected. The CI mass spectrum revealed peaks and their fragments as follows: 358 (M⁺, 1.6%), 317 (M⁺-allyl, 80.8%), 316 (M⁺-42, 78.9%), 231 (M⁺-I, 10.4%), 189 [M⁺-(I + allyl), 100%].

With some experimentation on the method of quenching the reaction mixture, it was found that the use of a 0.1 M aqueous
solution of sodium thiosulphate effectively eliminated the by-product (87) formation.

The next steps of the planned syntheses were to involve hydroboration of the double bond of (67), hydrogenolysis of the cyclopropane ring into a gem-dimethyl moiety and oxidation of the primary alcohol group into an aldehyde (90). These conversions were to be followed by reaction of the aldehyde with methyllithium and the oxidation of the intermediate secondary alcohol (91) to provide (56), our targeted Wadsworth-Emmons-Horner substrate (scheme 15).
Hence, treatment of \((67)\) with 2.0 equivalents of 9-BBN in THF gave an organoborane intermediate. Unfortunately, during the oxidative work-up\(^\text{51}\), all the solvent was lost from the reaction mixture, leaving an intractable (gummy) material. All attempts to isolate the desired product \((88)\) proved futile.

It was at this stage of the synthesis that Jacques Roberge generously supplied a quantity of the vinyl iodide \((53)\). The synthetic pathway \((54\longrightarrow 42-44)\) outlined on page 19 became more appealing compared to the one in Scheme 15. The preparation of the compound \((55)\) therefore became mandatory. This could, in theory, be conveniently accessed via a sequence of reactions involving initially the reductive cleavage of the ozonide intermediate derived from \((67)\),\(^\text{52}\) followed by reduction\(^\text{53}\) of the aldehyde \((92)\) to produce the diol \((93)\).\(^\text{54}\)

It was to the double bond in \((67)\) that attention was directed (scheme 16). Ozonolysis\(^\text{52}\) of this double bond generated an ozonide which was cleaved by dimethyl sulphide into the aldehyde \((92)\). The crude aldehyde was then reduced with sodium boronhydride to give the diol \((93)\) in 52% yield.

That the expected product was formed was shown by the presence of a two-proton multiplet in the region \(\delta\) 3.54-3.73 of the \(^1\text{H}\) nmr spectrum of \((93)\). These signals can be attributed to the \(\text{CH}_2\text{OH}\) protons. Other proton signals in the 400 MHz \(^1\text{H}\) nmr spectrum are as expected.
Scheme 16

Hydrogenolysis of the cyclopropane ring of the diol (93) was achieved by the use of H₂ (1.0 atm), PtO₂, and dry acetic acid at room temperature for 90 min to yield (55), (60%).
This compound exhibited spectral properties identical with those of the same compound prepared by Marais\textsuperscript{20,26c} as an intermediate towards the total synthesis of ambliol B. In particular, its IR (CDCl\textsubscript{3}) spectrum exhibited O-H absorption in the region 3690-3609 cm\textsuperscript{-1}. The \textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) spectrum indicated the four methyl groups at \(\delta 0.85, 0.86, 0.95\) (s, s, s, 3H each) for the tertiary ones and \(0.87\) (d, 3H, \(J = 7\) Hz) for the secondary one. The two protons attached to the oxygen atom have chemical shift values in the region \(\delta 3.55-3.70\) (m), confirming the primary nature of the alcohol.

Due to time constraints, the total synthesis of the natural products, agelasimines A and B and their 9-methyl quartenary purino derivative, could not be fully carried out. However, the stage had been rightly set towards the achievement of such a goal.

2.2 Conclusion

The bifunctional conjunctive reagents, the lower order cuprate (19)\textsuperscript{26c} and the \(\alpha\)-methylene ketone (94),\textsuperscript{20,26c,31,32,44} are novel reagents employed in the total synthesis of natural products.
During our synthetic studies towards the total synthesis of the agelasimines (42-44), (19) was combined stereoselectively with (94, R = allyl) to produce the trans-fused bicyclic intermediate (58). This compound has the four contiguous stereocentres present in the agelasimines (42-44). A series of transformations gave the known diol (55),\textsuperscript{20,26c} a possible precursor to the target natural products.

It was anticipated that the diol (55) would be transformed into the iodide (54) which upon palladium(0)-catalyzed coupling with the vinyl iodide, followed by appropriate transformations would produce the agelasimines (42 - 44),
where $X$ is defined as

$$X = (42; R^i = \text{NMe}, \ R^{ii} = \text{H})$$

$$= (44; R^i = \text{O}, \ R^{ii} = \text{Me})$$

$$X = (43)$$
III EXPERIMENTAL

3.1.0 General Procedure, Solvents and Reagents

Proton nuclear magnetic resonance ($^1$H nmr) spectra were obtained on deuteriochloroform solutions (unless stated otherwise) using a Varian XL-300 or Bruker models AC-200E or WH-400 spectrometers. Signal positions are given in parts per million (δ) from tetramethylsilane (TMS) as the internal standard. For those compounds containing trimethylstannyl, trimethylgermyl and/or trimethylsilyl group, the resonance positions were determined relative to the deuteriochloroform signal (δ 7.25).\(^{57}\) Coupling constants ($J$-values) are reported in Hz and were measured on spectral spacings judged to be first order.\(^{58}\) The spectra listed follow the order: chemical shift (ppm); (multiplicity, number of protons, assignment (where possible), coupling constants (Hz)). The tin-proton coupling constants ($J_{\text{Sn-H}}$) are given as an average of the $^{117}\text{Sn}$ and $^{119}\text{Sn}$ values.

Carbon nuclear magnetic resonance ($^{13}$C nmr) spectra were recorded on a Varian model XL-300 spectrometer at 75.3 MHz or on Bruker models AC-200E at 50.3 MHz or WH-400 at 100.6 MHz, using deuteriochloroform as the solvent. Signal positions are given in parts per million (δ) relative to the deuteriochloroform signal (δ 77.0).\(^{59}\) Signals with negative intensities in an attached proton test (APT) are so indicated in brackets (-ve) following the chemical shift.
Infrared (ir) spectra were obtained on liquid films (neat, sodium chloride plates), chloroform solutions (0.1 mm sodium chloride cells) or potassium bromide discs, employing a Perkin-Elmer model 1710 Fourier transform IR spectrophotometer (internal calibration), a Perkin-Elmer model 7108 spectrophotometer calibrated using the 1601 cm⁻¹ band of a polystyrene film or a Bomem Michelson 100 FT-IR spectrometer using internal calibration. Peak intensities are indicated by the following letters: vs = very strong, s = strong, m = medium and w = weak.

Low resolution and high resolution mass spectra were recorded with a Kratos MS 50/DS 55 SM, and low resolution one with AEI M59/DS 55 SM, 70 eV, employing electron ionization (EI). The desorption chemical ionisation (DCI) spectra were recorded with a Delsi Nermag R10-10C and 10B mass spectrometer. The DCI data are generally accompanied by a chromatogram-like page which is the evaporation profile of the sample during heating of the DCI filament. All compounds which were subjected to high resolution mass measurements were homogeneous 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 $^{120}\text{Sn}$ or $^{74}\text{Ge}$ respectively and were made on the (M⁺-Me) peak. Determinations for compounds containing tributylstannyl groups were made on the (M⁺-Bu) peak.
Microanalyses were performed in the Microanalytical Laboratory, University of British Columbia using a Carlos Erba Elemental Analyser 1106.

Analytical gas-liquid chromatography (glc) analyses were performed on either a Hewlett-Packard model 5880 or a 5890 capillary gas chromatograph, employing 25 m x 0.21 mm fused silica columns coated with cross-lined SE-54, both using flame ionization detectors.

Thin-layer chromatography (tlc) was performed on commercially available aluminium backed sheets, precoated with silica gel 60 to a thickness of 0.2 mm (E. Merck, type 5554). Visualization of the chromatogram was accomplished using one or more of the following techniques: (a) ultraviolet light (254 nm tube); (b) iodine vapour stain; (c) heating with a hot gun a chromatogram that had been stained with (i) a 5% aqueous solution of ammonium molybdate in 10% aqueous sulfuric acid (w/v) or (ii) a 5% solution of anisaldehyde in 95% ethanol that had been acidified with 5 ml conc. sulphuric acid or (iii) a 7% ethanol solution of vanillin that had been acidified with 18.4 ml of 40% aqueous sulphuric acid (w/v). Conventional column (drip) chromatography, medium pressure chromatography, and flash chromatography, as well as separations with radial chromatography on Harrison Chromatotron™ models 7924T and 7924C were done with 230-400 mesh silica gel (E. Merck, silica gel 60 PF-254 with calcium sulphate).
Distillation temperatures (uncorrected) were recorded as air-bath temperatures required for short path bulb-to-bulb (Kugelrohr) distillations.

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected.

All pure and dry solvents and reagents were obtained by using established procedures. Diethyl ether and tetrahydrofuran were dried with and distilled from sodium benzophenone ketyl. Dichloromethane and carbon tetrachloride were dried over and distilled from phosphorus pentoxide. Diisopropylamine, hexamethylphosphoramid, triethylamine, benzene, trimethylsilyl chloride and trimethylsilyl bromide were dried over and distilled from calcium hydride. The petroleum ether used was the fraction with boiling point between 35-60°C.

Hexamethylditin was obtained from Organometallics, Inc. and was used without further purification unless coloured, in which case it was distilled under aspirator vacuum (bp approximately 80°C) prior to use.

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 and Suffert. Solutions of potassium t-
butoxide in tetrahydrofuran and diethylzinc in toluene were also obtained from Aldrich Chemical Co., Inc.

Cuprous bromide-dimethyl sulfide complex was prepared by the method of House\textsuperscript{65} and Townsend.\textsuperscript{66} Old stocks of this material were purified by the method of Wuts\textsuperscript{67} after they had been washed with methanol.

Commercially available dimethyl(methylene)ammonium iodide (Eschenmoser's salt)\textsuperscript{42} was recrystallized from tetramethylenesulphone and dried under vacuum (vacuum pump) at 50°C before use.

Aqueous NH\textsubscript{4}Cl-NH\textsubscript{4}OH (pH 8) was prepared by the addition of \(\approx\) 100 ml of aqueous ammonium hydroxide (29-30\%) to \(\approx\) 1 L of saturated aqueous ammonium chloride.

Lithium diisopropylamide (LDA) was prepared by the addition of a solution of methyllithium in ether (1.0 equivalent) to a solution of diisopropylamine (1.6 equivalents) in dry THF at -78°C. The resulting solution was stirred at 0°C for 10 mins before use.

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

Cold bath temperatures were obtained by using the following combination of solvents and coolants\textsuperscript{68}: 27 g CaCl\textsubscript{2}/100 ml H\textsubscript{2}O/dry
ice (-20°C), 39 g CaCl\textsubscript{2}/100 ml H\textsubscript{2}O/dry ice (-35°C), acetone-dry ice (-78°C) and methanol-liquid N\textsubscript{2} (-98°C).

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

3.2.1 Synthetic Studies on Agelasinines. Experimental.

Preparation of 3,4-dimethyl-2-cyclohexen-1-one (63).

\[
\begin{align*}
\text{Ha} & \\
\text{K} & \\
\end{align*}
\]

3,4-Dimethylanisole (10.08 g, 73.5 mmol), dissolved in absolute ethanol\(^{34a}\) (50 mL), was added to cold (-78°C) liquid ammonia (250 mL, freshly distilled over sodium). Lithium (3.0 g, 432 mmol) was added in small pieces and the blue solution was stirred for 2 h\(^{34b}\) at -78°C. Ammonium chloride (13 g, 243 mmol) was added carefully in small portions and the mixture was left at ambient temperature until all the ammonia had evaporated. Water (100 mL) was added to the residue and the aqueous phase was extracted with Et\(_2\)O (50 x 3 mL). Due to the very high volatility of the intermediate 4,5-dimethyl-1-methoxy-1,4-cyclohexadiene,\(^{34c}\) solvent removal was carefully and partially done (rotary evaporator, 35°C). The residual solution was treated with 50% hydrochloric acid (100 mL) and the resultant mixture was refluxed for 45 min.\(^{34d}\) The mixture was cooled to room temperature, extracted with ether (3 x 50 mL), washed with brine (2 x 20 mL), dried (MgSO\(_4\)) and the solvent removed (rotary evaporator). The residual oil was purified by flash chromatography
(300 g silica gel, elution with 70:30 hexanes-diethyl ether) and distilled (air-bath temperature 90-95°C/11 torr) as a colourless oil to give 7.43 g (81%) of the enone (63); ir (neat): 2966 (m), 1674 (vs), 1627 (m), 1255 (m), 861 (w) cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 1.15 (d, 3H, secondary Me, \(J = 8\) Hz), 1.65-1.77 (m, 1H), 1.90 (s, 3H, Me), 2.01-2.12 (m, 1H), 2.20-2.31 (m, 1H), 2.32-2.48 (m, 2H), 5.78 (br s, 1H, \(H_a\)); \(^13\)C nmr (50 MHz, CDCl\(_3\)) \(\delta\): 17.7(-), 22.7(-), 30.3, 34.3(-), 34.5, 126.3(-), 166.5, 204.1.

**Preparation of 1- Allyl-3,4-dimethyl-2-cyclohexen-1-ol (68)**

![Chemical structure](image)

To a cold (-78°C), stirred solution of allylmagnesium bromide (0.75 mL of a 1.0 M solution in THF, 1.5 equiv) in dry THF (2.2 mL) was added copper(I) bromide-dimethyl sulfide (5.2 mg, 5 mole %) and dry HMPA (0.21 mL, 2.4 equiv).\(^{30a-f}\) To this mixture was added, dropwise over 10 min, a solution of 3,4-dimethyl-2-cyclohexen-1-one (63, 61.4 mg, 1 equiv) and trimethylsilyl chloride (0.13 mL, 2.0 equiv) in dry THF (0.4 mL). The reaction mixture turned orange during this addition. Stirring was continued for 4 h at -78°C. Dry triethylamine (0.14 mL, 2.03 equiv) and hexanes (2.0 mL) were added sequentially. The reaction mixture was allowed to warm to room temperature and was poured into water (3.0 mL). The layers were separated and the organic phase was washed with water (5
mL). The organic solution was dried (MgSO₄) and the solvent was evaporated to give after flash chromatography (3.0 g silica gel, CH₂Cl₂, 0.5% Et₃N), 68.4 mg (83%) of (68) as a colourless oil; ir (neat): 3366 (s), 3075 (m), 2935 (vs), 1665 (w), 1640 (m), 1439 (s), 1377 (m), 1131 (m), 989 (s), 913 (s), 845 (m) cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 1.04 (d, 3H, secondary Me, J = 8 Hz), 1.35-1.90 (m, 4H), 1.69 (s, 3H, Me), 1.52 (s, 1H, OH), 1.95-2.15 (m, 1H), 2.26 (d, 2H, allylic CH₂, J = 7 Hz), 5.05-5.15 (m, 2H, Hb and Hc), 5.31 (br s, 1H, Ha) 5.79-5.95 (m, 1H, Hd); ¹³C nmr (50 MHz, CDCl₃) δ: 19.0(-), 21.5(-), 28.4, 34.0(-), 34.3, 46.9, 69.9, 118.4, 127.3(-), 134.0(-), 142.2; Exact Mass calcd for C₁₁H₁₈O: 166.1357; found: 166.1352.

Preparation of 3-allyl-cis-3,4-dimethyl-1-trimethylsiloxycyclohexene (62)

To a cold (-78°C), stirred solution of allylmagnesium bromide (15 mL of a 1.0 M solution in THF, 1.5 equiv) in dry THF (44 mL) was added copper(I) bromide-dimethyl sulphide (2.08 gm, 1.0 equiv).³⁹ After the mixture had been stirred for 30 min, dry HMPA (4.2 mL, 2.4 equiv) was added and the mixture stirred for 10 min. A solution
of 3,4-dimethyl-2-cyclohexen-1-one (63) (1.23 g, 1 equiv) and trimethylsilyl chloride (2.56 mL, 2.0 equiv) in dry THF (8 mL) was added dropwise, over 10 min, to the mixture, during which time it turned deep red. Stirring was continued for 2 h at -78°C. Dry triethylamine (2.8 mL, 2.03 equiv) and hexanes (40 mL) were successively added. The reaction mixture was allowed to warm to room temperature and then was poured into cold water (0°C, 60 mL). After separating the layers, the organic phase was washed with cold water (2 x 30 mL), dried (MgSO₄) and concentrated. Flash chromatography (75 g silica gel CH₂Cl₂, 0.5% Et₃N), followed by distillation (130-145°C/11 torr), provided 1.636 g (69%) of the silyl enol ether (62) as a colourless oil; ir (neat): 3076 (w), 2961 (s), 1668 (s), 1641 (m), 1252 (vs), 1207 (s), 910 (s), 844 (vs) cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.15 (s, 9H, SiMe₃), 0.80 (s, 3H, tertiary Me), 0.82 (d, 3H, secondary Me, J = 7 Hz), 1.40-1.65 (m, 3H), 1.75-2.15 (m, 4H), 4.65 (br s, 1H, Ha), 4.92-5.05 (m, 2H, Hb and Hc), 5.68-5.84 (m, 1H, Hd); ¹³C nmr (50 MHz, CDCl₃) δ: 0.0 (-), 14.9 (-), 22.3 (-), 27.2, 29.4, 34.0 (-), 37.3, 45.7, 114.3 (-), 116.2, 135.7 (-), 149.2; Exact mass calcd for C₁₄H₂₆O₃Si: 238.1753; found: 238.1752.
A second compound isolated (135 mg) alongside the desired product was distilled (air-bath temp., 120-130°C/11 torr) and analyzed for a hydrolysis product of the silyl enol ether (63). This was characterized as 3-allyl-3,4-dimethylcyclohexanone (70); ir (neat): 2963 (vs), 1714 (vs), 1640 (w), 1458 (m), 1244 (s), 916 (s) cm\(^{-1}\); \(^1\)H nmr (400 MHz, CDCl\(_3\)) \(\delta\): 0.71 (s, 3H, tertiary Me), 0.88 (d, 3H, secondary Me, \(J = 8\) Hz), 1.49-1.63 (m, 1H), 1.70-1.85 (m, 2H), 1.86-2.00 (m, 2H), 2.03-2.15 (m, 1H), 2.19-2.35 (m, 3H), 4.94-5.10 (m, 2H, \(H_a\) and \(H_b\)), 5.68-5.81 (m, 1H, \(H_c\)); \(^{13}\)C nmr (100 MHz, CDCl\(_3\)) \(\delta\): 14.7 (-), 18.8 (-), 30.5, 36.4 (-), 38.4, 39.9, 40.7, 45.6, 51.2, 52.2, 118.2, 133.5 (-), 212.1; Exact mass calc’d for C\(_{11}\)H\(_{18}\)O: 166.1358; C, 79.47; H, 10.91; found: 166.1361; C, 78.80; H, 10.80.

Preparation of 3-allyl-2-(Dimethylamino)methyl-cis-3,4-dimethyl-cyclohexanone (61)

![Structural diagram](https://via.placeholder.com/150)

To a cold (0°C), stirred solution of the silyl enol ether (62) (325.1 mg, 1.37 mmol) in dry THF (6 mL) was added a solution of methyllithium in diethyl ether (1.1 mL, 1.4M, 1.1 equiv). After allowing the reaction mixture to warm to room temperature, it was
stirred for 1 h. The solution of lithium enolate\textsuperscript{41} so-formed was cooled (-78°C) and added \textit{via} cannulation to a rapidly stirred, cold (-78°C) slurry of dimethyl(methylene)ammonium iodide, (74, 505 mg, 2 equiv)\textsuperscript{42} in dry THF (9 mL).\textsuperscript{31,32,44} After allowing the reaction mixture to warm to room temperature, stirring was continued for 2.5 h. Hydrochloric acid (1 N, 15 mL) and diethyl ether (10 mL) were added and the layers were separated. Thorough extraction of the organic phase with 1 N hydrochloric acid and careful neutralization of the combined aqueous extracts with 5% sodium carbonate was followed by CH\textsubscript{2}Cl\textsubscript{2} (5 x 20 mL) extraction of the neutralized mixture. The combined extracts were washed with brine (20 mL). The layers were separated and the organic phase was dried (MgSO\textsubscript{4}). The solvent was removed to give 291.1 mg (96%) of the crude keto amine (61) as a 2.2:1 mixture of epimers contaminated with the subsequently desired elimination enone product (60) (16% by glc); ir (neat): 3075 (w), 2966 (vs), 2821 (m), 2768 (m), 1715 (vs), 1639 (w), 916 (m) cm\textsuperscript{-1}; \textsuperscript{1}H nmr (400 MHz, CDCl\textsubscript{3}) \delta: 0.54, 0.81 (s, s, ratio 1:2.2, 3H, tertiary Me), 0.88, 0.92 (d, d, ratio 1:2.2, 3H, secondary Me, J = 8 Hz), 1.49-1.65 (m, 1H), 1.79-2.45 (m, 7H), 2.15, 2.20 (s, s, ratio 2.2:1, 6H, NMe\textsubscript{2}), 2.50-2.63 (m, 1H), 2.85-3.04 (t, 1H, J = 12 Hz), 5.01-5.18 (m, 2H, H\textsubscript{a} and H\textsubscript{b}), 5.67-5.95 (m, 1H, H\textsubscript{c}). The CI mass spectrum gave prominent peaks at 224 (M\textsuperscript{+} + 1, 2.3%), 223 (M\textsuperscript{+}, 4.3%), 58 (100%). Because of its instability and the subsequent removal of the epimeric stereocentre, this mixture was used without further purification in the next step.
Preparation of 3-allyl-cis-3,4-dimethyl-2-methylene cyclohexanone (60)

To a solution of the keto amine (61) (1.46 g, 6.54 mmol) in dry CH$_2$Cl$_2$ (27.5 mL) was added $m$-chloroperoxybenzoic acid (3.39 g, 1.5 equiv). The reaction mixture was stirred for 20 min at 25°C and was then filtered rapidly through a short column of silica gel, eluting with 80:20 hexanes-diethyl ether. The solvent was removed from the combined eluate and the crude sample chromatographed on the chromatotron model 7924T (silica gel 60 PF - 254 with CaSO$_4$, E. Merck). Concentration of the appropriate fractions, followed by distillation (100-120°C/11 torr), afforded 989.6 mg (85%) of the α-methylene ketone (60) as a colourless oil; ir (neat): 3076 (s), 1695 (s), 1640 (s), 1610 (s) cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 0.97 (d, 3H, secondary Me, $J = 7$ Hz), 1.00 (s, 3H, tertiary Me), 1.59-1.70 (m, 1H), 1.80-19.2 (m, 1H), 1.99-2.18 (m, 2H), 2.19-2.28 (m, 1H), 2.29-2.54 (m, 2H), 4.99-5.10 (m, 2H, H$_c$ and H$_d$), 5.15 (br s, 1H, H$_b$), 5.60-5.78 (m, 1H, H$_e$), 5.84 (br s, 1H, H$_a$); $^{13}$C nmr (50 MHz, CDCl$_3$) δ: 15.0 (-), 22.0 (-), 26.4, 35.1, 37.1 (-), 43.9, 109.9, 117.8, 118.7, 133.8 (-),
153.1, 203.7; Exact mass calcd for $\text{C}_{12}\text{H}_{18}\text{O}$: 178.1357; found: 178.1361.

A minor compound of higher retention time on glc was also isolated and analyzed to be the isomeric $\alpha$-methylene ketone (76); ir (neat): 2927 (vs), 1759 (vs), 1646 (vs), 1575 (w), 1527 (w), 1462 (s), 1379 (s), 1254 (s), 1132 (s), 997 (s), 917 (s) cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) $\delta$: 0.94 (d, 3H, secondary Me, $J = 8$ Hz), 0.98 (s, 3H, tertiary Me), 1.5-1.61 (m, 1H), 1.71-1.92 (m, 2H), 2.04-2.15 (m, 1H), 2.31-2.48 (m, 2H), 2.65-2.79 (m, 1H), 4.76 (br s, 1H H$_b$), 4.97 (br s, 1H, H$_a$), 4.99-5.10 (m, 2H, H$_c$ and H$_d$), 5.65-5.80 (m, 1H, H$_e$).

**Preparation of lithium (3-trimethylgermyl-3-butenyl)(cyano) cuprate (19)**
To a cold (-98°C), rapidly stirred solution of freshly distilled 4-iodo-2-trimethylgermyl-1-butene (77) (318 mg, 1.07 mmol) in dry THF (13.3 mL, 0.05 M) was rapidly added a solution of tert-butyl lithium in pentane (1.21 mL, 1.72 M, 1.95 equiv). The resulting yellow and cloudy solution was stirred at -98°C for 10 min and was then warmed to -78°C. Copper(I) cyanide (104.9 mg, 1.1 equiv) was added and the so-formed yellowish suspension was stirred at -78°C for 5 min. Brief warming of the reaction mixture to -35°C provided a clear pale tan solution of the lower order vinylgermane cuprate (19), which was recooled to -78°C and used immediately.

Preparation of (2S*, 3R*, 4S*)-3-allyl-3,4-dimethyl-2-(4-trimethylgermyl-4-pentenyl)cyclohexanone (80)

To a cold (-78°C), stirred solution of the cuprate reagent (19) (1.6 equiv, prepared as described above) in dry THF (26.5 mL, 0.05 M) was added, dropwise and successively, trimethylsilyl bromide (597 mg, 3 equiv) and a solution of 3-allyl-cis-3,4-dimethyl-2-methylene cyclohexanone (60) (236.2 mg, 1.0 equiv) in
dry THF (1 mL). The so-formed orange solution was stirred at -78°C for 2 h. Water (2 mL) was added and the reaction mixture was allowed to warm to room temperature (30 min). Aqueous NH₄Cl-NH₄OH (pH 8, 10 mL) and diethyl ether (10 mL) were added and the mixture was stirred open to the atmosphere overnight. The layers were separated and the aqueous phase was extracted thoroughly with diethyl ether. The combined extracts were dried (MgSO₄) and the solvent removed to give 377.9 mg (78%) of the keto vinylgermane (79) that consisted of a 1:2.5 mixture of epimers at C-2, as determined by glc. This mixture was epimerized using potassium tert-butoxide (0.33 mL, 1.0 M, 0.5 equiv) in THF. Flash chromatography (20 g silica gel, CCl₄-CH₂Cl₂ 1:1.5) and then distillation (160-180°C/1.0 torr) of the crude oil gave 241.3 mg (50%) of a single product (80); ir (neat): 2968 (vs), 1713 (vs), 1639 (w), 916 (w), 825 (m), 740 (m), 600 (m) cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.18 (s, 9H, -GeMe₃), 0.55 (s, 3H, tertiary Me), 0.89 (d, 3H, secondary Me, J = 8 Hz), 1.01-1.15 (m, 1H), 1.18 (m, 1H), 1.40-1.64 (m, 2H), 1.65-1.78 (m, 1H), 1.79-1.88 (m, 1H), 1.89-2.20 (m, 1H), 2.05-2.21 (m, 4H), 2.21-2.39 (m, 3H), 5.02-5.18 (m, 3H, Hₐ, Hₖ and Hₜ), 5.47 (m, 1H, Hₜ), 5.73-5.88 (m, 1H, Hₜ); ¹³C nmr (50 MHz, CDCl₃) δ: -1.9 (-), 15.3 (-), 22.5, 28.3, 31.8, 36.4 (-), 37.6, 41.1, 42.5, 45.4, 56.8 (-), 102.9, 118.3, 121.1, 133.6, 144.1, 212.2; Exact mass calcd for C₁₈H₃₁OGe (M⁺): 337.1587; found: 337.1585.

Preparation of (2S*, 3R*, 4S*)-3-allyl-3,4-dimethyl-2-(4-iodo-4-pentenyl)cyclohexanone (59)
To a solution of the keto vinylgermane (80) (257 mg, 0.73 mmol) in dry CH$_2$Cl$_2$ (14.6 mL) was added a solution of iodine in dry dichloromethane (20.3 mL of a 0.04 M solution, 0.81 mmol) and the resulting deep red solution was stirred at room temperature for 20 h. Aqueous sodium thiosulphate (0.1 M, 14.64 mL, 1.46 mmol) was added and the organic layer was separated. The aqueous phase was extracted with CH$_2$Cl$_2$ and the combined extracts were dried (Na$_2$SO$_4$). Solvent removal provided the crude keto vinyl iodide (59) (240.9 mg, 91%), homogeneous by tlc and glc analyses. This was filtered (15 g silica gel, CH$_2$Cl$_2$) and the solvent removed (rotary evaporator) to give pure (59) as a colourless oil (198.4 mg, 75%); ir (neat): 3074 (w), 2962 (s), 1712 (vs), 1638 (w), 1617 (m), 893 (m) cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 0.56 (s, 3H, tertiary Me), 0.90 (d, 3H, secondary Me, $J = 8$ Hz), 1.15-1.35 (m, 3H), 1.48-1.75 (m, 3H), 1.80-1.90 (m, 1H), 1.90-2.02 (m, 1H), 2.12 (d, 2H, $J = 9$ Hz), 2.22-2.50 (m, 4H), 5.09-5.20 (m, 2H, Ha and Hb), 5.67 (m, 1H, Hc), 5.75-5.90 (m, 1H, He), 6.02 (m, 1H, Hd); $^{13}$C nmr (50 MHz, CDCl$_3$) δ: 1.0 (-), 15.3 (-), 21.3, 28.4, 31.7, 36.3 (-), 41.0, 42.5, 45.5, 45.8, 56.7 (-), 112.4, 118.6,
Preparation of the trans-fused Bicyclo Allylic Alcohol (58)

To a cold (-78°C), stirred solution of the keto vinyl iodide (59) (60 mg, 0.17 mmol) in dry THF (10 mL) was added a solution of n-butyllithium in hexane (0.25 mL, 1.6 M, 2.4 equiv). The reaction mixture was stirred at -78°C for 15 min and water (4 mL) was added. The reaction mixture was allowed to warm to room temperature, and diethyl ether (15 mL) was added. The layers were separated and the aqueous phase was extracted several times with diethyl ether. The combined extracts were dried (MgSO$_4$), the solvent was removed and the resulting oil distilled (145-160°C/1.0 torr) to give 33.8 mg (87%) of the desired trans-fused allylic alcohol (58); ir (neat): 3426 (m), 3075 (w), 2931 (vs), 1639 (m), 912 (s) cm$^{-1}$; $^1$H nmr (400 MHz, CDCl$_3$) δ: 0.80-1.10 (m, 2H), 0.85 (d, 3H, secondary Me, $J = 8$ Hz), 0.88 (s, 3H, tertiary Me), 1.14-1.80 (m, 8H),
1.85 (m, 1H, possibly Hf or Hg) 1.96-2.20 (m, 3H, allylic CH₂ protons, and Hg or Hf), 2.49 (m, 1H), 4.65 (br s, 1H, Hc), 4.73 (br s, 1H, Hd), 4.90-5.05 (m, 2H, Ha and Hb), 5.62-5.75 (m, 1H, He); ¹³C nmr (50 MHz, CDCl₃) δ: 15.9 (-), 17.1 (-), 21.6, 26.5, 27.9, 32.7, 36.4, 36.8 (-), 40.1, 41.7, 48.6 (-), 73.6 (OH), 105.8, 116.9, 134.8 (-), 155.1.

**Preparation of the Cyclopropane (67)**

To a stirred solution of the allylic alcohol (58) (21.6 mg, 0.09 mmol) in dry benzene (1 mL) at 25°C was added a solution of diethylzinc in toluene (0.24 mL, 1.1 M, 2.4 equiv). Dry diiodomethane (22 µL, 3.0 equiv) was added dropwise, and the reaction mixture cooled to 0°C. After turning off the argon flow, dry oxygen was introduced into the space above the reaction mixture through a septum cap by means of an oxygen filled baloon containing a hypodermic needle as an outlet. Stirring was continued under the oxygen atmosphere at 0°C for 30 min. An aqueous solution of sodium thiosulphate (0.1 M, 2 mL) and benzene (5 mL) was 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 (MgSO₄) and the solvent was removed. The remaining crude oil was flash chromatographed (1.0 g silica gel, pet. ether-diethyl ether 95:5) to give 20.5 mg (90%) of the cyclopropane (67) as a colourless oil; ir (neat): 3599 (w), 3514 (w), 3075 (m), 3001 (m), 2926 (vs), 1637 (w), 911 (s) cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.00-0.10, 0.15-0.24 (m, m, 1H each, protons on cyclopropane ring). 0.48-0.58 [m, 2H, one (or two) proton(s) on the cyclopropane ring, one proton un-assigned], 0.60-0.69 (m, 1H, proton on cyclopropane ring). 0.78-0.90 (d, partly superimposed by s, 6H, secondary and tertiary Me groups), 1.11-1.45 (m, 7H), 1.5-1.75 (m, 4H), 1.95-2.25 (m, 3H, Hₗ and allylic CH₂ protons), 4.95-5.05 (m, 2H, Hₐ and Hₐ), 5.68-5.84 (m, 1H, Hₗ).

**Preparation of the Cyclopropane Diol (93)**

![Cyclopropane Diol](image)

Ozone was bubbled through a cold (-78°C), stirred solution of the alkene (67) (33.8 mg, 0.14 mmol) in methanol (7.0 mL)⁵²ᵃ until a blue colour developed.⁵²ᵇ The solution was allowed to stand at
-78°C for 5 min. The excess ozone was removed by passing a stream of argon through the reaction mixture. Dimethyl sulfide (0.28 mL) was added and the colourless solution was warmed to room temperature. Stirring was continued for 2 h. The solution was concentrated under reduced pressure. The crude aldehyde so formed was redissolved in CH₂Cl₂ (10 mL) and absolute ethanol (10 mL). This solution was cooled to 0°C and then was treated with NaBH₄ (21.37 mg, 4.14 equiv). The mixture was stirred at 0°C for 30 min, after which ether (40 mL) was added and the mixture was filtered through a plug of silica gel. The filtrate was concentrated and the residue was chromatographed on the chromatotron model 7924C (hexanes-diethyl ether 3:1) to give 17.9 mg (52%) of the diol (93) as a colourless oil; ¹H nmr (400 MHz, CDCl₃) δ: 0.00-0.06, 0.18-0.26 (m, m, 1H each, protons on cyclopropane ring). 0.47-0.58[m, 2H, one (or two) cyclopropane ring proton(s), the other not assigned], 0.59-0.72 (m, 1H, cyclopropane ring proton). 0.75-1.80 (m, 14H), 0.85 (partly obscured d, 3H, secondary Me, J = 7 Hz), 0.86 (s, 3H, tertiary Me), 2.19 (m, 1H), 3.54-3.73 (m, 2H, Hₐ).

**Preparation of the Diol (55)**

![Diagram of the diol molecule]
To a solution of the cyclopropane diol (93) (17.9 mg, 0.07 mmol) in dry acetic acid (1.5 mL) was added platinum (IV) oxide (Adam's catalyst, ~10 mole %). The reaction mixture was stirred for 2 h, under an atmosphere of hydrogen (1.0 atmosphere), and then slowly and cautiously neutralized with a cold (0°C), stirred, saturated aqueous solution of NaHCO₃ (20 mL). After adding diethyl ether (10 mL), the layers were separated and the aqueous phase thoroughly extracted with diethyl ether. The combined extracts were dried (MgSO₄) and the solvent removed to give a crude product which was flash chromatographed (1.0 g silica gel, hexanes-diethyl ether, 7:3). The product, (55) (60%), exhibited the following characteristics: ir (CDCl₃ soln): 3690 (w), 3609 (w), 2839 (vs), 1602 (m), 1460 (w), 1147 (m) cm⁻¹; ¹H nmr (400 MHz, CDCl₃) δ: 0.85, 0.86 (s, s, 3H each, tertiary Me groups), 0.87 (d, partly obscured, 3H, secondary Me, J = 7 Hz), 0.95 (s, 3H, tertiary Me), 1.02-1.80 (m, 16H), 3.55-3.70 (m, 2H, Hₐ). This substance was found to be spectroscopically identical with the same compound prepared previously in our laboratory via a related synthetic sequence.²⁶c
IV REFERENCES


