A NEW SYNTHESIS OF ENANTIOMERICALLY PURE BICYCLIC KETONES.
TOTAL SYNTHESIS OF THE DITERPENOIDS
(-)-KOLAVENOL AND (-)-AGELASINE B

By

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ABSTRACT

This thesis describes the synthesis of a series of enantiomerically pure cis-fused bicyclic trimethylstannyl ketones 124, 132 and 133. The bicyclic ketones were prepared by means of a methylenecyclohexane, methylenecyclopentane or an ethylideneclycopentane annulation sequence using the bifunctional conjunctive reagents 12, 110 and 115 and the novel, optically active trimethylstannyl enone 64, in which the trimethylstannyl moiety acts as a readily removable “anchoring” group.

The trimethylstannyl group has a pronounced effect on the circular dichroism of the optically active ketones. A discussion of these effects is presented.

A new, general destannylation procedure was developed and used to prepare a series of enantiomerically pure bicyclic alcohols 165, 175 and 176 from the ketones 124, 132 and 133. The generality of the method was demonstrated with the destannylation (Li, t-BuOH, NH₃) of a series of trimethylstannyl alcohols, ethers and alkenes.

The alcohol 165 was used as an intermediate for the total syntheses of the optically active clerodane diterpenoids (-)-kolavenol (65) and (-)-agelasine B (31). (-)-Kolavenol (65) was prepared in 14 steps and 19.4% overall yield from the enone 64. Thus, the alcohol 165 was oxidized and the resulting ketone 47 was converted to the nitriles 215. The nitriles 215 were stereoselectively alkylated to produce the nitrile 216. Functional group manipulations yielded the iodide 213 via the ether 214. A novel palladium-catalyzed coupling of an organozinc reagent (prepared from 213) with the vinyl iodide 265 produced the ether 282. (-)-Kolavenol (65) was obtained by removal of the silyl protecting group.

(-)-Agelasine B (31) was obtained in three steps from the ether 282. Thus, 282 was converted directly into the bromide 300, and the resulting product was alkylated with the methyl adenine derivative 301 to give the methoxy-protected adenine
derivative 302. A new, mild electrochemical deprotection of 302 was used to prepare (-)-agelasine B (31). This compound was prepared in 16 steps and 5.6% yield from the enone 64.

A new procedure for the synthesis of compound 233, the enantiomer of the active component of the commercially useful perfume Ionoxide® 251, was discovered. The ether 214 was efficiently converted into 233 using acidic reaction conditions.
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<tr>
<td>s</td>
<td>singlet or second</td>
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</table>
$S$ - sinister

$\text{si}$ - stereochemical descriptor

$\text{SEM}$ - 2-trimethylsilylethoxymethyl

$t$ - triplet

$t$ - tertiary

$\text{TBDMS}$ - tert-butyldimethylsilyl

$\text{Th}$ - thienyl

$\text{THF}$ - tetrahydrofuran

$\text{TIPS}$ - triisopropylsilyl

$\text{TLC}$ - thin layer chromatography

$\text{TMP}$ - tetramethylpiperidine

$\text{TMSCl}$ - Trimethylsilyl chloride

$\text{TosMIC}$ - (paratolysufonyl)methyl isocyanide

$p$-$\text{Ts}$ - para-toluenesulfonyl

$\text{uv}$ - ultraviolet

$v$ - very

$V$ - volt

-ve - negative

$w$ - weak

$w_{1/2}$ - peak width at half height (frequency)

$Z$ - zusammen

$\alpha$ - 1,2 relative position

$[\alpha]_D$ or $\lambda^1$ - specific rotation at the sodium D line (589.3 nm) or at the wavelength $\lambda$ and at the temperature $t$ [in \(\text{deg} \cdot \text{cm}^2 / \text{darg}\)]

$\psi$ - ellipticity
<table>
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<th>Symbol</th>
<th>Definition</th>
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<td>$[\psi]_\lambda$</td>
<td>specific ellipticity at the wavelength $\lambda$ at the temperature $t$ in $(\text{deg} \cdot \text{cm}^2 \cdot \text{dag})$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>1,3 relative position</td>
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<tr>
<td>$\delta$</td>
<td>chemical shift in parts per million from TMS</td>
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<td>$\Delta$</td>
<td>heat or reflux</td>
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<td>$\Delta\delta$</td>
<td>chemical shift difference</td>
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<tr>
<td>$\Delta\epsilon$</td>
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<td>$\Delta G^\circ$</td>
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I would like to acknowledge the contributions to this thesis by my research supervisor, Dr. Edward Piers. His excellent teaching, extensive knowledge and high standards imparted to me the science of organic chemistry in its best form. It was both an honor and a privilege to work with him for the last four years. His perseverance at correcting my "frenglish" during the preparation of this manuscript is also acknowledged. Merci very much Ed!

Thanks to the present and past members of the Piers group for creating an excellent research atmosphere, as well as a friendly and stimulating environment. The friendships and the memories of this enjoyable and challenging period of my life will not be forgotten.

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I would like to thank my family and friends for their support during my studies. I express my gratitude to the residents of 4636 West 12th for housing me when the workers started to fall through the ceiling of my apartment. Finally, I would like to express my gratitude to Jana Pika "yetemilio" for outstanding scientific and non-scientific support in my last year of studies at UBC.
A la mémoire de mon père.

"I may, I might, I must
If you will tell me why the fen
Appears impassable, I then
Will tell you why I think that I
Can get across it if I try."

Marianne Moore (1887-1972)
1. INTRODUCTION

1.1. GENERAL

Since Wöhler's serendipitous synthesis of urea from ammonium cyanate in 1828, organic synthesis has progressed enormously in transforming simple raw materials into compounds of elaborated structures.¹ The synthesis of the most toxic non-proteinic compound palytoxin (1) by Kishi and coworkers,² for example, demonstrates the power of contemporary organic chemistry. This progress, however, does not mean that organic synthesis has become a “mature science”. In fact, a lot of progress can still be made in all fields of synthesis to improve the selectivity, the simplicity and the efficiency of a given synthesis.³,⁴ The explosive increase in the number of reactions and methods in recent history has made it necessary for synthetic organic chemists to move from the initial intuitive planning of the synthesis of a single target compound to a systematized retrosynthetic analysis of the general synthesis of a group of compounds. For his contribution in this area of organic chemistry, Corey was awarded the 1990 Nobel Prize for Chemistry, primarily for the elaboration of the theory and the methodology of organic synthesis.⁵,⁶

The development of new reactions relies less on serendipity than on the creativity of the researchers. The new catalytic asymmetric cis dihydroxylation of alkenes by Sharpless and coworkers⁷ is a good example of this kind of progress. It is hoped that the work presented in this thesis will make a contribution to the development of new reactions and new general synthetic methods.
1.2. BACKGROUND AND PROPOSAL

1.2.1. Bifunctional Conjunctive Reagents

An ideal synthesis is one that starts from inexpensive and simple materials and
gives quantitative yield of the desired product with complete control of all the
stereogenic centers, in a single operation. We are still far from this ideal, although
much has been done to get closer to this ultimate goal. The use of organic reagents
that possess more than one reactive site allows for the rapid synthesis of complex
structures. Reagents having two reactive sites are called bifunctional conjunctive reagents\textsuperscript{8} or multiple coupling reagents.\textsuperscript{9} Schematically, the use of bifunctional
conjunctive reagents can be illustrated by examining the synthons 2-4 (Scheme
1.1). These synthons can be simple or complex, having a variety of functionality as
well as different chain lengths.
Synthon 2 with two acceptor sites \( \text{a}^{10} \) can act as an electrophile in a reaction with substrate 5 to give 6. The adduct 6 can also be obtained by nucleophilic attack of the donor site \( \text{d} \) of synthon 3 on an electrophilic center of the substrate 5. General intermediate 7 should be available from attack of a nucleophilic substrate 5 on the acceptor site \( \text{a} \) of synthon 3 or by a nucleophilic attack of the donor site \( \text{d} \) of synthon 4 on an electrophilic center of the substrate 5. The adduct 6 can be intramolecularly cyclized by a nucleophilic reaction of the "S" portion of the species with the acceptor site \( \text{a} \) to give 8. Alternatively, 7 can be cyclized to give 8 by having the donor site \( \text{d} \) attack the "S" portion of the synthon 7.

The acceptor and donor groups have to be selected carefully to avoid unwanted side reactions. It is sometimes necessary to have one of the reactive sites of the synthons (2-4) in a "masked" state to avoid undesired reactions (decomposition, polymerization or self-condensation). A very efficient transformation can be achieved when the reactivity of the functionalized sites of the bifunctional synthons and the substrate are well "tuned". Under these circumstances, the "product" 8 can be obtained in one operation from a combination of one of the synthons 2-4 and the substrate 5 without having to isolate the intermediates 6 or 7.

Our research group has been involved for a number of years in the design of new bifunctional conjunctive reagents and their use in natural products syntheses.\(^{11}\) The total synthesis of (±)-palauolide (9) (Scheme 1.2), a marine natural product, by
Piers and Wai\textsuperscript{12} demonstrates the effectiveness of a bifunctional conjunctive reagent in synthesis. The synthesis starts with the regioselective addition of trimethylstannylcopper(I) dimethyl sulfide complex (11) to 5-chloro-1-pentyne (10) to give bifunctional reagent 12, where the 2-position is the donor site (d) and the 5-position is the acceptor site (a). Transmetallation of the trimethylstannyl function of 12 to give the lithio species 13 can be effected using methyllithium at low temperature. Reagent 13 can be transmetallated with magnesium bromide to give the organomagnesium species 14. The second transmetallation was necessary to produce a more stable, softer nucleophilic reagent. Addition of the organomagnesium reagent 14 to the enone 15 was effected in the presence of copper(I) bromide dimethyl sulfide complex and boron trifluoride etherate to give the adduct 16. Better yields of the cyclized product 17 were obtained when the intermediate 16 was isolated and then cyclized rather than using a direct cyclization method. Intramolecular cyclization was accomplished with potassium tert-butoxide to give the bicyclic ketone 17. The decalin carbon unit of (±)-palauolide (9) is easily recognized in the ketone 17. By varying the substrates and the conjunctive bifunctional reagents employed, many natural products have been successfully prepared in our group. A review of these syntheses is beyond the scope of the thesis and the examples can be found in the literature.\textsuperscript{13}
1.2.2. Isolation and Previous Syntheses of Clerodanes Diterpenoids

Nature has provided us with a multitude of compounds that save or ease the life of millions of people every day. Thanks to progress in chromatography and in spectroscopy, natural product chemists have become very efficient at isolating and characterizing even minor metabolites from biological sources. These improvements are useful because they allow the natural products chemist to collect only a few specimens of a species in order to find and to characterize new compounds. It is often the case, however, that not enough product can be isolated to properly test for the biological activity or even for complete determination of the stereochemistry of the compound.\textsuperscript{14} Also, even if the molecule is relatively abundant in a species, a large demand for a useful compound can endanger the existence of the species.\textsuperscript{15} The total synthesis of a natural product is therefore sometimes necessary to confirm the structure of the natural product, to produce biologically-active synthetic products in convenient amounts and to create new, useful molecules. These new compounds may be helpful against affliction or they may be useful as probes to learn more about the mechanisms of life.\textsuperscript{16}

Our group has been working on the synthesis of natural products of the clerodane family. The clerodanes are a large family of diterpenoids having the carbon skeleton \textsuperscript{18} (equation 1.1). Biosynthetically they are believed to be derived from the indicated rearrangements of the labdane diterpenoid skeleton \textsuperscript{19}. The clerodanes can be divided into two subgroups, the \textit{cis}- and \textit{trans}-clerodanes, according to the two different configurational arrangements of the decalin ring junction between C-5 and C-10. The main interest in the clerodanes resides in their biological activities. They show antimicrobial, antitumoral, cholagogic, cardiotonic, coronadilating and pesticidal activity.\textsuperscript{17} Some of them are also known antifeedants.\textsuperscript{17} A large number of clerodanes have been isolated and only a few \textit{representative} newly-isolated clerodanes are listed
here: **trans-clerodanes**: (+)-cornutin A (20),\(^{18}\) (-)-\(\gamma\)-methoxybutenolide (21),\(^{19}\) grandifolide A (22),\(^{20}\) and (-)-(5R,8R,9S,10R)-12-exo-ent-3,13(16)- clerodien-15-oic acid (23);\(^{21}\) **cis-clerodanes**: the (+)-epoxide 24,\(^{22}\) (-)-linguifolide (25),\(^{23}\) stevisalicionone (26),\(^{24}\) and (-)-ageline B (27).\(^{25}\)
A number of clerodanes have already been synthesized by our group and by others, and many approaches have been studied. A review of the syntheses and the synthetic approaches to the antifeedant clerodanes up to 1986 has already appeared,26 and a retrosynthetic analysis of a few representative syntheses of clerodanes has been done by Fleming.27 All the reported total syntheses of clerodanes completed to date are listed here: \textit{trans-}clerodanes: (±)-annonene (28),28 (±)-avarol (29),29 (±)-ajugarin IV (30),30 (-)-agelasine B (31),31 (±)-ajugarin I (32),32 (±)-palauolide (9),33 (-)-methyl kolavenate (33),34 (±)-maingayic acid (34),35 (±)-isolinaridiol (35) and (±)-isolinaridiol diacetate (36),13b (±)-cascarillone (37),36 (±)-stephalic acid (38);13h \textit{cis-}clerodanes: (±)-linaridial (39),37 (±)-15,16-epoxy-\textit{cis-}\textit{cleroda-3,13(16),14-}triene (40).35,38
1.2.3. Retrosynthetic Analysis for the Synthesis of Enantiomerically Pure Clerodanes

The biological activity of a given compound is often different from that of the corresponding enantiomer. In a racemic mixture, the best one can hope is that the enantiomer of a compound will be inactive. Unfortunately often this is not the case, and the wrong enantiomer might even have toxic effects.\(^{39}\) Our previously-reported syntheses of natural products using bifunctional conjunctive reagents having led to racemic products, we set a goal to devise a general synthetic plan to prepare enantiomerically-pure compounds belonging to the \textit{cis}- and \textit{trans}-clerodane families of diterpenoids.

Retrosynthetically, the bond between C-12 and C-13 of 18 (Scheme 1.3) can be cleaved to give the synthons 42 (nucleophilic) or 43 (electrophilic) and the synthon 41 in which moiety X is a functional group that can either be converted into a leaving group or can be employed to make the carbon 12 nucleophilic. Disconnection of the structure 41 between C-9 and C-11 leads to the synthon 44 having a carbanion-stabilizing group E (nitrile, carbonyl) and the synthon 45 (L = leaving group). Synthon 44 can be seen as being derived from ketone 46 using an appropriate transform. For the synthesis of many \textit{trans}-clerodanes, the \textit{trans}-ketone 17 is the synthetic equivalent of ketone 46. The \textit{exo}-methylene function of ketone 17 can be used as a handle to functionalize at positions 1 to 4 and 18 of the clerodane skeleton. Previous work in our laboratory\(^{12}\) has shown that \textit{trans}-ketone 17 can be easily derived from the \textit{cis}-ketone.
47 by isomerization. Therefore, the cis-ketone 47 was identified as our key intermediate in our synthetic strategy for the synthesis of both cis- and trans-clerodane diterpenoids. Because the cis-ketone 47 is readily epimerized, it was necessary to take measures to preserve the stereochemical integrity of the centers 8 and 10 in cases where cis-clerodanes were the desired targets. It was felt that this could be achieved by having a removable or transformable "anchoring group" "A" at C-7, with the configuration defined as shown in synthon 48.

We reasoned that the anchor "A" would fulfill three major functions. First, the ketone 48 (conformation 49) should be the major product under acid- or base-promoted equilibrating conditions, provided that the group "A" is sufficiently bulky. Each of the isomers 50 and 51 would be disfavored by the severe 1,3-diaxial interaction between the angular methyl and the "A" group. A methylenecyclohexane annulation\(^{40}\) transform related to the ketone 48 would give the bifunctional conjunctive synthon 53 and the optically-active chiron\(^{41}\) 52. Since it is known\(^{42}\) that the stereochemical orientation of a 1,4-addition to an enone of the type 52 is controlled by the presence of a bulky group in the 5 position of 52, the second role of the group "A" is to direct the addition of the synthon 53 to the re-side of carbon 3 in 52. Enone 52 can be synthetically derived from ketone 54, where the anchor "A" serves its last role in preserving the chirality originally present in enone 55. The known enone 55 is readily available from the ketone 56. The enantiomer of 56, the (S)-(−)-3-methylcyclohexanone (57) is also readily available,\(^{43}\) so that it is possible to access both enantiomeric series of clerodanes using this strategy. In addition, a synthetically-useful chiral anchor "A" should be characterized by the following criteria: it should be easily introduced, stable to moist air, heat, and to mild acids and bases, and it should be easy to replace by hydrogen, or to convert into another functional group.
Scheme 1.3
1.2.4. Chiral “Anchors”

A search of the literature revealed that the trimethylsilyl group has been used as a chiral anchor for the synthesis of natural products. 5-Trimethylsilylcyclohex-2-en-1-one (58) (Scheme 1.4) was kinetically resolved to give (R)-(−)-5-trimethylsilylcyclohex-2-en-1-one (59) and (S)-(−)-5-trimethylsilylcyclohex-2-en-1-one (60). Copper(I)-catalyzed addition of an organomagnesium reagent to enone 59 gave the ketone 61 with high stereoselectivity. The silyl group could be removed with copper(II) chloride in hot DMF to give the chiral cyclohexenone 62. The ketone 61 (R = para-tolyl) has been used for the synthesis of (+)-α-curcumene (63).

The trimethylsilyl group fulfills most of the requirement of a synthetically useful anchoring group. It is relatively easy to introduce and is stable to moist air, heat and mild acids and bases. The major drawback of the trimethylsilyl anchor is that the relatively strong carbon-silicon bond [~305 kJ/mol (~73 kcal/mol)] makes it difficult to remove the anchor in the presence of sensitive functional groups.
Based on our experience, we envisaged that the trimethylstannyl group \((\text{Me}_3\text{Sn})\)\(^{47}\) would be able to fulfill all the requirements for a synthetically useful anchoring group. Trimethylstannyl compounds are easily prepared by conjugate addition of a suitable organocuprate to \(\alpha,\beta\)-unsaturated ketones. They are "stable"\(^{48}\) and the weak C-Sn bond \([-188 \text{ kJ/mol} (-45 \text{ kcal/mol})]\)\(^{46}\) should allow the replacement of the Me\(_3\)Sn group by an hydrogen or its transformation into another functional group.

This thesis describes the preparation of the optically active trimethylstannyl-cyclohexenone 64 (Scheme 1.5) from the ketone 56 and demonstrates the use of enone 64 as a substrate in methylenecyclohexane, methylenecyclopentane, and (Z)-ethylidene cyclopentane annulation sequences. The successful syntheses of (-)-kolavenol (65) and (-)-agelasine B (31), two representative, enantiomerically pure trans-clerodanes, are presented to illustrate the synthetic utility of the trimethylstannyl group as an effective anchoring group.
2. DISCUSSION

2.1. METHYLENECYCLOHEXANE, METHYLENECYCLOPENTANE AND (Z)-ETHYLIDENECYCLOPENTANE ANNULATION SEQUENCES

2.1.1. Preparation of (-)-(5R,6R)-3,6-dimethyl-5-trimethylstannyl-2-cyclohexen-1-one (64)

The early stage of our work was aimed at the preparation of the cyclohexenone 64, comprising a trimethylstannyl anchoring group, starting from the known (R)-(−)-5-methyl-2-cyclohexen-1-one 55. In order to prepare enough of the key intermediate 64 and to submit it to a variety of annulation sequences, we needed to access cyclohexenone 55 in large quantities. The optically active enone 55 has been used before in synthesis [(+)-luciduline, (-)-ptilocaulin and (-)-calcimycin] and in chiroptical studies by other researchers. Approaches to enone 55 are summarized in Scheme 2.1, and will be described in the following paragraphs.

\[
\text{\includegraphics[width=0.5\textwidth]{cyclohexenone64.png}}
\]

2.1.1.1. Preparation of (R)-(−)-5-Methyl-2-cyclohexen-1-one (55)

Allinger and Riew have prepared enone 55 from (+)-pulegone (66) (A, Scheme 2.1) using a lengthy and low-yielding procedure. Pulegone (66) was treated with aqueous acid to give the retroaldol product 56 in 66% yield. Ketone 56 was α-brominated to yield the bromoketone 67 (21%). Ketalization of bromoketone
followed by elimination of HBr from bromoketal 68 gave the unsaturated ketal 69 in 65% overall yield. Finally, hydrolysis of the ketal function gave the enone 55 in 9% overall yield from pulegone. Alternatively, bromoketone 67 was transformed into the unsaturated semicarbazone 70 and enone 55 was obtained in 9% overall yield after hydrolysis.

Friedrich and Lutz\cite{49} have prepared the enone 55 using a photosensitized oxidation of the mixture of silyl enol ethers 71 and 72 (B, Scheme 2.1). Their synthesis was shorter and their overall yield (43%) was better than that obtained by Allinger and Riew. Because the enol formation with \( i\)-Pr\(_2\)NLi was not highly regioselective, 3-methyl-2-cyclohexen-1-one (73) was obtained in 22% yield in addition to the desired enone 55. Oppolzer and Petrzilka\cite{50} have trapped the lithium enolate of ketone 56 with diphenyl disulfide (C, Scheme 2.1). The formation of a 2:1 mixture of unspecified diastereomers 74 was observed. Oppolzer and Petrzilka did not observe any of the isomeric sulfides (sulfenylation at the C-2 position of ketone 56).\cite{56} Oxidation of the thioethers 74 and thermolysis of the resulting sulfoxide gave enone 55 in a 43% overall yield. Caine and coworkers\cite{56} have added sodium thiophenolate to a mixture of the known pulegone epoxides 75 to obtain a mixture of sulfides 74 (unknown ratio) (D, Scheme 2.1). Oxidation of the sulfide moieties and a subsequent elimination reaction gave the enone 55 in 49% overall yield. Djerassi and coworkers\cite{55} have prepared enone 55 in 13% overall yield from the ketone 56 by heating the bromoketone 67 in the presence of lithium carbonate and lithium bromide in DMF (E, Scheme 2.1).

These approaches to enone 55 have the disadvantage of low yield and/or long reaction sequences, which make the procedures unsuitable for large scale preparations. We therefore decided to develop an alternative synthesis of enone 55, which will be described in the following pages.
a) H$_3$O$^+$, 66%  b) Br$_2$, H$_2$O, 21%  c) (HOCH$_2$)$_2$, p-TsOH, 92%  d) NaOH, MeOH, 71%  e) H$_3$O$^+$, 96%  f) NH$_2$NHCONH$_2$, AcOH, 65%  g) i-Pr$_2$NLi, THF; TMSCl  

h) hv, O$_2$, Rose Bengal, THF  i) i-Pr$_2$NLi, THF; PhSSPh  j) m-CPBA, CCl$_4$; Δ  
k) H$_2$O$_2$, NaOH  l) PhSNa, THF  m) Li$_2$CO$_3$, LiBr, DMF, Δ.

Scheme 2.1
We had first planned to use the Saegusa oxidation of the silyl enol ether 71 to prepare enone 55. In this method, the silyl enol ether 76 (equation 2.1) is reacted either with palladium(II) acetate in acetonitrile or with palladium(II) acetate and 1,4-benzoquinone in acetonitrile. The corresponding enone 77 is usually obtained in high yield along with a small amount of ketone resulting from hydrolysis of the silyl enol ether.

\[
\begin{align*}
\text{OSiMe}_3 & \quad \text{Pd(OAc)}_2, \text{CH}_3\text{CN} \\
\text{76} & \quad \text{or} \\
\text{Pd(OAc)}_2, \text{O} = \text{O}, \text{CH}_3\text{CN} & \quad \text{77}
\end{align*}
\]

The selective formation of the silyl enol ether 71 over 72 would result in a better yield of the desired Saegusa oxidation product. Addition of the ketone 56 to a solution of \(i\)-Pr\(_2\)NLi and then quenching with TMSCl gives a mixture of distal (71) and proximal (72) enol ethers in a typical ratio of 2-3:1. A modification of the procedure reported by Corey and Gross for the formation of silyl enol ethers was attempted to obtain a more favorable ratio of isomers. Thus, ketone 56 was added to a cold (-78 °C) solution of TMSCl (5 equiv) and \(i\)-Pr\(_2\)NLi (1.1 equiv) to give a quantitative yield of a mixture of the silyl enol ethers 71 and 72, in a slightly improved ratio of 2.5:1. Substitution of the more sterically demanding lithium 2,2,6,6-tetramethylpiperidide (LiTMP) for \(i\)-Pr\(_2\)NLi improved the ratio of 71:72 to 5.7:1 (93% yield). The latter mixture of enol ethers was subjected to the Pd(II) oxidation. A number of solvents and solvent mixtures (acetonitrile, acetonitrile-benzene, acetonitrile-THF) and oxidants (palladium(II) acetate, a mixture of palladium(II) acetate and 1,4-benzoquinone) were investigated, but all reaction conditions were unsuccessful. Even under optimum conditions (palladium(II) acetate, acetonitrile), only 12% of the enone 55 was obtained, along with 18% of \(m\)-cresol as a major side product. In view of these difficulties, alternative oxidation procedures were explored.
Fleming and Paterson\textsuperscript{59} have used 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene to oxidize silyl enol ethers into enones. This approach was applied in an attempt to convert a mixture of the enol ethers 71 and 72 into the enones 55 and 73. Many reaction conditions [i.e., 2,4,6-trimethylpyridine, DDQ, benzene, 12-18\% of 55; 2,4,6-trimethylpyridine, DDQ, dichloromethane, reflux, \textasciitilde 7\% of 55; 2,4,6-trimethylpyridine, DDQ, acetonitrile -20 °C\textsuperscript{60}, 0\% of 55] were tried with little success. This synthetic strategy was abandoned and we turned to alternative procedures to prepare enone 55.

The elimination of a seleninic acid from a keto \(\alpha\)-selenoxide has been reported to be an efficient and mild way to prepare enones.\textsuperscript{61} Since the reaction conditions for the oxidation of the selenide and the elimination reaction are much milder than those necessary to effect the same overall conversion with a sulfide, a better yield of enone 55 than that obtained by Oppolzer and Petrzilka and by Caine and coworkers was expected. The methods involves the trapping of the enolate, the enol, the enol ether or the enol acetate 79 of a ketone 78 (Scheme 2.2) (\(M =\text{Li, H, alkyl or trialkylsilyl, or Ac}\)) with an appropriate arylseleneny1 reagent to give the \(\alpha\)-selenoketone 80. The selenide can be oxidized to the selenoxide 81 with variety of oxidants (NaIO\textsubscript{4}, O\textsubscript{3}, H\textsubscript{2}O\textsubscript{2}, peracids). The selenoxide 81 is not usually isolated, since elimination normally takes place in situ to give the enone 77.
The addition of a THF solution of phenyl selenenyl bromide\textsuperscript{62} (prepared in situ from diphenyl diselenide and bromine) to a mixture of enol ethers \textbf{71} and \textbf{72} in cold (-78 °C) ether (Et\textsubscript{2}O), gave a quantitative yield of a complex mixture of selenides \textbf{82}-\textbf{85} (equation 2.2). This mixture was oxidized with hydrogen peroxide\textsuperscript{63,64} to give the enone \textbf{55} ([\alpha]_D\textsuperscript{30} -86.9°, c = 2.6 in chloroform (lit.\textsuperscript{50}, -90.1° c = 2.55 in chloroform)) in 68% yield, accompanied by ~20% of the enone \textbf{73}. The spectral data of enone \textbf{55} were in agreement with those reported in the literature.\textsuperscript{50} Having established an improved route to prepare enone \textbf{55}, we turned our attention to the 1,4-addition of the trimethylstannyl group to this enone.

\begin{equation}
\textbf{71} + \textbf{72} \xrightarrow{\text{PhSeBr}} \begin{array}{c}
\text{PhSe} \\
\text{O}
\end{array} + \begin{array}{c}
\text{O} \\
\text{SePh}
\end{array} \xrightarrow{\text{H}_2\text{O}_2} \begin{array}{c}
\text{55} \quad 68\% \\
\text{73} \quad \sim 20\%
\end{array}
\end{equation}

\textbf{2.1.1.2. 1,4-Addition of Trimethylstannyl Nucleophiles to the Enone \textbf{55}}

The 1,4-addition of a trimethylstannyl nucleophile to the enone \textbf{55}, followed by trapping\textsuperscript{65} of the resultant enolate \textbf{90} with iodomethane, should afford directly the synthetic equivalent of synthon \textbf{54} ("A" = Me\textsubscript{3}Sn), (2\textit{R},3\textit{R},5\textit{S})-2,5-dimethyl-3-trimethylstannylcyclohexanone (\textbf{91}) (Scheme 2.3). The attack of the Me\textsubscript{3}Sn group on enone \textbf{55} was expected to occur axially from the side opposite to the methyl group for stereoelectronic\textsuperscript{66} reasons to give the enolate \textbf{90}. Studies on 1,4-addition of nucleophiles on cyclohexenones have shown that those reactions, when kinetically controlled, are subject to stereoelectronic effects. The 1,4-addition occurs with stereoelectronic control when the \sigma-orbital of the bond being made is aligned with the \pi-orbitals of the resulting enolate. The axial attack is favored because it goes through the more stable chair-like enolate intermediate \textbf{90} rather than the boat-like enolate intermediate \textbf{91}. Subsequent trapping of the enolate \textbf{90} with iodomethane should take place to give the ketone \textbf{92} with the methyl group on C-2 \textit{trans} to the
trimethylstannyl moiety. For steric reasons, the alkylating agent approaches from the side opposite the bulky Me₃Sn group, and for stereoelectronic reasons, the alkylation takes place via a more stable chair-like transition state with the methyl group becoming attached in an axial orientation.

![Diagram of reaction](image)

Scheme 2.3

We first tried the 1,4-addition-trapping procedure with trimethylstannyllithium (86). A mixture of the ketones 92, 93 and two other compounds having the proposed structures 94 and 95 was obtained in 78% yield. The ratio of the ketone 92 to the other three side products was 7:2 as determined by GLC. The pure ketone 92 ([\( \alpha \)]D²⁸ +134.1°, c = 1.022 in MeOH) was obtained by flash chromatography while 93 was obtained in a pure form via the epimerization of 92 (vide infra). The ketones 94 and 95 were not isolated and their presence in the mixture was suspected.
on the basis of the GLC analysis. The use of the cyanocuprate \(87^{70}\) or the higher order (2-thienyl)(cyano)cuprate \(88^{71}\) gave the same products in a ratio of \(92:8\) \([92:(93+94+95)]\) in 58% and 70% yield, respectively. The best results were obtained when (trimethylstannyl)(phenylthio)cuprate \(89^{70}\) was used. Thus, addition of enone \(55\) to a cold THF solution of lithium (trimethylstannyl)(phenylthio)cuprate (-20 °C, 1 h), followed by the trapping of the resulting enolate with iodomethane dissolved in THF-HMPA (hexamethylphosphoric triamide) (-78 °C, 30 min, -20 °C, 40 min) gave a mixture of ketones \(92, 93, 94\) and \(95\) in a ratio of \(97:3\) \([92:(93+94+95)]\) as determined by GLC] in 78% yield.

The IR spectrum of ketone \(92\) exhibits absorptions at 1708, 768 and 526 cm\(^{-1}\), indicating the presence of a six-membered cyclic ketone and a trimethylstannyl group.\(^{72}\) The \(^1\)H NMR spectrum of \(92\) could be fully assigned using decoupling and \(^1\)H-\(^1\)H homonuclear correlation 2D-NMR (COSY) experiments.\(^{73}\) The COSY homonuclear correlations are listed in Table 2.1. The results of the nuclear Overhauser enhancement difference experiments (NOE)\(^{74}\) on \(92\) supported the predicted stereochemical outcome of the 1,4-addition-trapping procedure. The results are summarized on Figure 2.1 and the enhancements are represented with arrows. The beginning of the arrows represent the irradiated signals while the tips are directed towards the enhanced signals. Irradiation of the signal due to Me-8 (\(\delta\) 0.97) led to the enhancement of the signals corresponding to hydrogens 3, 4e, 5 and 6e; irradiation of the signal due to H-3 led to the enhancement of the resonances due to Me-7 and Me-8. Enhancement of the signal due to H-4e could not be seen because of the proximity of its chemical shift with that of irradiated signal H-3. None of the other products (93 to 95) could show all of these enhancements. The \(^{13}\)C NMR spectrum of the ketone \(92\) could be assigned with the help of the carbon-tin couplings\(^{75}\) and an APT experiment.\(^{76}\)
Further confirmation of the stereochemistry of the ketone 92 was obtained after epimerization of the methyl group in the 2 position (Me-7) by using equilibrating conditions (sodium methoxide in methanol at room temperature). Taking into account the conformational free energy difference (-ΔG°) of a methyl group (1.74 kcal/mol 21
and the trimethylstannyl moiety (1.0 kcal/mol [4.2 kJ/mol]), one should expect ketones 92 and 93 to equilibrate to a mixture in a ratio of approximately of 1:3.5 ($\Delta G^\circ \approx -0.74$ [3.1 kJ/mol]). Molecular mechanics calculations predicted a ratio of 1:5.5 ($\Delta G^\circ \approx -1.02$ [4.3 kJ/mol]). Experimentally, the ketones 92 and 93 had reached an equilibrium ratio of 1:1.1 after 92 had been treated with NaOMe in MeOH for 24 h at room temperature. However, only 68% of the material was recovered due to decomposition of the product or the starting material. The equilibrium ratio suggests that there might be a stabilizing interaction between the carbonyl and the trimethylstannyl group that favors the Me\(_3\)Sn being in the equatorial orientation more than is predicted from the conformational free-energy difference alone. Hudec\(^{53}\) and Kitching and coworkers\(^{80}\) had also observed that the preference for an equatorially oriented trimethylstannyl group of trans-5-methyl-3-trimethylstannylcyclohexanone was greater than expected on the basis of the value of $\Delta G^\circ$. Hudec's explanation for this preference will be discussed later in the circular dichroism section (see section 2.4.3).

Ketones 92 and 93 were separated by flash chromatography to give the pure ketone 93 in 14% yield ([\(\alpha\)]\(_{D}\)\(^{25}\) -44.1°, c = 0.935 in MeOH).

The IR spectrum of ketone 93 exhibits absorptions at 1712, 769 and 524 cm\(^{-1}\), indicating the presence of a six-membered cyclic ketone and a trimethylstannyl group. The \(^1\)H NMR spectrum could be assigned with the assistance of decoupling and COSY experiments. The COSY homonuclear correlations are shown in Table 2.2.
Table 2.2: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Cyclohexanone 93

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, $J$ (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.11 (s, 9H, $^{2}J_{\text{Sn-H}} = 52$)</td>
<td>---</td>
</tr>
<tr>
<td>Me-8</td>
<td>1.01 (d, 3H, 6)</td>
<td>5</td>
</tr>
<tr>
<td>Me-7</td>
<td>1.04 (d, 3H, 6, $^{4}J_{\text{Sn-H}} = 4$)</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>1.75-1.85 (m, 1H)</td>
<td>Me-8, 4e, 4a, 6a,6e</td>
</tr>
<tr>
<td>4a</td>
<td>1.85 (ddd, 1H, 12.5, 12, 5)</td>
<td>3, 4e, 5</td>
</tr>
<tr>
<td>6a</td>
<td>1.97 (ddd, 1H, 13, 12.5, 1)</td>
<td>5, 6e</td>
</tr>
<tr>
<td>3, 4e$^a$</td>
<td>2.00-2.05 (m, 2H)</td>
<td>2,4a, 5</td>
</tr>
<tr>
<td>6e</td>
<td>2.40 (ddd, 1H, 13, 4, 2 )</td>
<td>5, 6a</td>
</tr>
<tr>
<td>2</td>
<td>2.77 (dqd, 1H, 6.5, 6.1, $^{3}J_{\text{Sn-H}} = 132$)</td>
<td>Me-7, 3</td>
</tr>
</tbody>
</table>

$^a$ Overlapping signals.

The stereochemical assignments of 92 and 93 are further confirmed by comparing their $^{13}$C NMR spectral and chiroptical data. Hüdec and Kitching and coworkers have observed that $^{13}$C NMR chemical shifts for axially oriented trimethylstannyl groups are deshielded relative to those of equatorially oriented groups. For example, the $^{13}$C NMR signal for the axial Me$_3$Sn group of 3α-trimethylstannylcholestane 96 appears at $\delta$ -9.3 while the equatorial Me$_3$Sn group of 3β-trimethylstannylcholestane 97 give rise to a $^{13}$C NMR signal at $\delta$ -12.1. The Me$_3$Sn groups of ketones 92 and 93 produce $^{13}$C NMR resonances at $\delta$ -10.13 and $\delta$ -8.80 respectively. The results of these experiments, supports that the Me$_3$Sn group is equatorially oriented in ketone 92 and axially oriented in ketone 93.
The values associated with carbon-tin coupling constants also provide useful information about the stereochemistry of 92 and 93. The two- and three-bond Sn-C couplings have been reported to follow a Karplus-type equation. For example, the cisoid $^3J_{\text{Sn-C}}$ of 7-norbornyltrimethylstannane (98) is 11.9 Hz while the transoid coupling is 67.5 Hz. We observed that the coupling constants $^3J_{\text{Sn-C}}$ between the Me$_3$Sn and Me-7 groups in compounds 92 and 93 were 60 Hz (transoid) and 20 Hz (cisoid), respectively. With the relative stereochemistry of 92 firmly established, the next step of the synthetic sequence was the regioselective introduction of a carbon-carbon double bond to obtain the desired trimethylstannylcyclohexenone 64.

2.1.1.3. Oxidation of the Trimethylstannylcyclohexanone 92

The silyl enol ether 99 (equation 2.3) was prepared in quantitative yield from the ketone 92 following the procedure of Fleming and Paterson. The silyl enol ether 99 was oxidized with DDQ and collidine (2,4,6-trimethylpyridine) in benzene to give the desired enone 64 ($[\alpha]_D^{29} -45.2^\circ$, $c = 1.072$ in MeOH) in 57% overall yield from the ketone 92. Attempts were made to improve the yield of the oxidation step by varying the reaction conditions. No product at all was obtained when acetonitrile was used as
the solvent. Variation in the base from collidine to 2,6-di-tert-butylpyridine (50% yield) or to bis(trimethylsilyl)trifluoroacetamide (45%) also did not improve the yield. Alternatively, selenoxide formation and elimination of selenenic acid gave the same overall yield of the enone 64 as the DDQ oxidation, but the former procedure was less convenient.

The IR spectrum of the cyclohexenone 64 exhibits absorptions at 1669, 768 and 526 cm\(^{-1}\), indicating the presence of a six-membered cyclic enone and a trimethylstannyl group. The \(^1\)H NMR spectrum was fully assigned when the spectrum was taken using C\(_6\)D\(_6\) as a solvent, which gave better dispersion of the signals than CDCl\(_3\). The \(^{13}\)C NMR spectrum was assigned with the assistance of the APT and the heteronuclear \(^1\)H-\(^{13}\)C shift correlation experiments (HSC). The heteronuclear C-H correlations obtained from the HSC experiment are displayed in Table 2.3. The H-H coupling constants of H-5 (12, 9 and 6 Hz) and the \(^3\)J\(_{C-Sn}\) coupling constant of Me-8 (23 Hz, which is correlated to a 50° dihedral angle between the Me\(_3\)Sn and the methyl groups using Kitching and coworkers' Karplus equation) confirm the \textit{trans}-arrangement of the methyl and the trimethylstannyl groups.
Table 2.3: The 400 MHz $^1$H, 75 MHz $^{13}$C, APT and HSC NMR Experiments Data for the Cyclohexenone 64 in C$_6$D$_6$

<table>
<thead>
<tr>
<th>Assignment (C-X)</th>
<th>$^{13}$C and APT $^\delta$ ppm (APT$^a$, $J_{Sn-C}$ (Hz))</th>
<th>$^1$H NMR and HSC $^1$H- $^{13}$C Shift Correlations $^\delta$ ppm (mult, # of H, $J$ (Hz), Assignment [H-X])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>-10.36 (-ve, 340)</td>
<td>0.03 (s, 9H, $^2$$J_{Sn-H} = 52$, Me$_3$Sn)</td>
</tr>
<tr>
<td>Me-8</td>
<td>16.54 (-ve, 23)</td>
<td>1.21 (d, 3H, 7, Me-8)</td>
</tr>
<tr>
<td>Me-7</td>
<td>23.81 (-ve, 6)</td>
<td>1.45 (s, 3H, Me-7)</td>
</tr>
<tr>
<td>5</td>
<td>28.87 (-ve, 400)</td>
<td>1.34 (ddd, 1H, 12, 9, 6, H-5)</td>
</tr>
<tr>
<td>4</td>
<td>35.10 (11)</td>
<td>1.90-2.00 (m, 2H, 4a, 4e)</td>
</tr>
<tr>
<td>6</td>
<td>43.87 (-ve, 16)</td>
<td>2.17-2.26 (m, 1H, H-6)</td>
</tr>
<tr>
<td>2</td>
<td>125.95 (-ve, 9)</td>
<td>5.96 (br s, 1H, H-2)</td>
</tr>
<tr>
<td>3</td>
<td>162.62</td>
<td>b</td>
</tr>
<tr>
<td>1</td>
<td>202.18</td>
<td>b</td>
</tr>
</tbody>
</table>

*a* -ve is reported when a negative peak is observed. The absence of -ve indicates a positive signal.

*b* No correlation

With the synthesis of the enone 64 established, the scope and limitations of the trimethylstannyl moiety as an anchoring group in methylenecyclohexane and methylenecyclopentane annulation sequences could be investigated.

2.1.2. 1,4-Additions to (-)-(5R,6R)-3,6-Dimethyl-5-trimethylstannyl-2-cyclohexen-1-one (64)

2.1.2.1 Conjugate Addition of the 2-(5-Chloro-1-pentenyl) Group

The reactivity of the trimethylstannylcyclohexenone 64 was first tested with the addition of the synthetic equivalent of synthon 53 (see Scheme 1.3). The known$^{87}$ Grignard reagent 14 was prepared from the 5-chloro-2-trimethylstannyl-1-pentene
(12, Scheme 2.4) by transmetallation with methyllithium (small excess) followed by a subsequent transmetallation with magnesium bromide. Reagent 14 was added to the enone 64 in the presence of a catalytic amount of copper(I) bromide-dimethyl sulfide complex and boron trifluoride etherate. Work-up and purification of the crude material gave a mixture of the chloro ketones 100 and 101 varying in ratios from ~4:1 to 5.3:1 by $^1$H NMR. The combined yield of 100 and 101 was ~90%. These ketones could not be separated by flash chromatography on silica gel. Evidence for the structural assignment of epimer 101 was obtained from the $^1$H NMR spectrum of the mixture and from the spectral properties of the products obtained after cyclization of the mixture of chloro ketones (see section 2.1.3.2).
Stereochemically pure chloro ketone 100 was eventually obtained by using a cyanocuprate reagent instead of a Grignard reagent. Thus, transmetallation of vinyl lithium 13 with THF-soluble lithium chloride-copper(I) cyanide\(^{89}\) at -78 °C gave the corresponding cyanocuprate. A mixture of the enone 64 and TMSCl\(^{90}\) was added to the cyanocuprate solution, followed by boron trifluoride etherate.\(^{91}\) The chloro ketone 100 was obtained as a single epimer ([\(\alpha\)]\(_D\)\(^{29}\) +86.4°, c = 1.10 in MeOH), along with a small amount (~4%) of the trimethylstannyl ketone 102 ([\(\alpha\)]\(_D\)\(^{26}\) +134.0°, c = 1.008 in MeOH).

The trimethylstannylcyclohexanone 102\(^{92}\) was isolated in all cases where a cyanocuprate was used, even when the vinylstannane 12 was used in excess relative to the methyllithium in the transmetallation step. This result suggests that vinyl lithium 13 and Me₄Sn are in equilibrium with methyllithium and vinylstannane 12 (equation 2.4). Further support for the existence of such an equilibrium was obtained when butyllithium was added to vinylstannane 12 at -78 °C in THF to give, upon work-up with H₂O, a mixture of 5-chloro-1-butene 103 and a small amount of 2-(butyldimethylstannyl)-5-chloro-1-pentene 104 and 5-chloro-2-(dibutylmethylstannyl)-1-pentene 105 (equation 2.5). The mixture of chloro vinylstannanes 104 and 105 was identified by a combination of \(^1\)H NMR and mass spectroscopy.
The reagents TMSCl and boron trifluoride etherate were both required to obtain high chemical yields. The vinyl cyanocuprate derived from the vinyllithium 13 reacted very slowly to give low yield when added to enone 64 in the absence of boron trifluoride etherate. The low yield was probably due to the decomposition of the cuprate; however, the epimeric selectivity of the addition was complete. With boron trifluoride etherate as the sole additive, the reaction proceeded rapidly, with an identical stereoselectivity but the yields were lower (65%).

The IR spectrum of the chloro trimethylstannylcyclohexanone 100 indicated the presence of a six-membered cyclic ketone (1708 cm\(^{-1}\)), a double bond (1637 cm\(^{-1}\)) and a trimethylstannyl group (768 and 526 cm\(^{-1}\)). The \(^1\)H NMR spectrum of 100 was assigned using homonuclear correlations (COSY) and NOE experiments. The COSY correlations are listed in Table 2.4. The results of the NOE difference experiments of 100 supported the predicted stereochemical outcome of an axial 1,4-addition to the enone 64 based on stereoelectronic arguments (see section 2.1.1.2). The attack occurred axially on the side opposite to the trimethylstannyl moiety. The results of the NOE experiments are summarized on Figure 2.2. Irradiation of the signal due to H-3 led to enhancement of the resonances attributed to Me-7, H-4e, H-3' and H-1'a (\(\delta 4.96\)) (100a); irradiation of the signal due to H-4a led to enhancement of the signals corresponding to Me-8, H-4e, H-2 and H-6a (100b) and irradiation of the signal due to H-1'a led to enhancement of the signals assigned to H-3, H-6e and H-1'b (100c). The reciprocal enhancement between H-1'a and H-3 and the couplings constants of the latter hydrogen (\(J = 14, 13, 2.5\) Hz) clearly demonstrate the \(\text{trans-trans}\) arrangement between the chloropentene, trimethylstannyl and Me-7 moieties of 100.
Table 2.4: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Chloro Ketone 

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR δ ppm (mult., # of H, $J$ (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.10 (s, 9H, $^2J_{Sn-H} = 52$)</td>
<td>---</td>
</tr>
<tr>
<td>Me-7</td>
<td>0.96 (d, 3H, 6.5)</td>
<td>2</td>
</tr>
<tr>
<td>Me-8</td>
<td>1.11 (s, 3H)</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>1.26 (ddd, 1H, 14, 13, 2.5, $^2J_{Sn-H} = 45$)</td>
<td>2, 4a, 4e</td>
</tr>
<tr>
<td>4a</td>
<td>1.63 (dd, 1H, 14, 14, $^3J_{Sn-H} = 21$)</td>
<td>3, 4e</td>
</tr>
<tr>
<td>4'</td>
<td>1.87-1.98 (m, 2H)</td>
<td>3', 5'</td>
</tr>
<tr>
<td>3', 4e</td>
<td>2.03-2.13 (m, 3H)</td>
<td>1'a, 1'b, 3, 4', 4a, 6e (LR)$^a$</td>
</tr>
<tr>
<td>2, 6a</td>
<td>2.17-2.30 (m, 2H)</td>
<td>3, 6e, Me-7</td>
</tr>
<tr>
<td>6e</td>
<td>2.73 (dd, 1H, 14, 3)</td>
<td>4e (LR), 6a</td>
</tr>
<tr>
<td>5'</td>
<td>3.55 (m, 2H)</td>
<td>4'</td>
</tr>
<tr>
<td>1'b</td>
<td>4.88 (br s, 1H)</td>
<td>1'a, 3'</td>
</tr>
<tr>
<td>1'a</td>
<td>4.96 (s, 1H)</td>
<td>1'b, 3'</td>
</tr>
</tbody>
</table>

$^a$ (LR) = Long range or "W" coupling.
The $^{13}$C NMR spectrum of the chloro trimethylstannylcyclohexanone 100 could be assigned using the values of the Sn-C coupling constants and an APT experiment. A coupling constant of 11 Hz ($^3J_{Sn-C}$) was observed between the Me$_3$Sn group and Me-7, indicating a cisoid arrangement between the methyl and trimethylstannyl groups as discussed previously (see structure 98, section 2.1.1.2).

Having demonstrated that a 2-(5-chloro-1-pentenyl) moiety can be stereo-selectively and efficiently added to enone 64, we explored the possibility of adding, in a conjugate sense, other bifunctional reagents to this substrate.

2.1.2.2 Conjugate Addition of the 2-(4-Chloro-1-butenyl) and 3-(5-Chloro-2-pentenyl) Groups

The methylenecyclopentane annulation sequence is also potentially useful for the synthesis of natural products. For example, the rearranged clerodane 6β-hydroxy-incana-pteroniolide (106)$^{93}$ could be synthetically derived from the methylenecyclopentane annulation product 107 (equation 2.6). Compound 107 could be synthetically derived from the 3-methylcyclohexanone 57 (the enantiomer of 56) using the methodology discussed in the preceding pages.
The first part of the methylene- and (Z)-ethylidenecyclopentane annulation sequences, the 1,4-addition of the substituted vinyl moieties to the enone 64, were initially explored with reagents derived from 4-chloro-2-trimethylstannyl-1-butene (110)\(^{94}\) and (Z)-5-chloro-3-trimethylstannyl-2-pentene (115)\(^{13d,95}\) (Scheme 2.5). The chloro butene 110 was prepared in two steps from 3-pentyn-1-ol (108) (equation 2.7). Addition of trimethylstannylcopper(I)-dimethyl sulfide to 3-pentyn-1-ol (108) produced the trimethylstannyl alcohol 109 which was subsequently converted to the chloride 110 by reaction with triphenylphosphine and triethylamine in carbon tetrachloride. (Z)-5-Chloro-3-trimethylstannyl-2-pentene (115) (Scheme 2.5) was prepared from ethyl 2-pentynoate (111). Addition of lithium (trimethylstannyl)-(phenylthio)copper(I) (89) to the alkynoate 111 gave the (E)-trimethylstannyl ester 112.\(^{96}\) Stereoselective deconjugation of the (E)-trimethylstannyl ester 112 with \(i\)-Pr\(_2\)NLi followed by protonation with acetic acid yielded the (Z)-trimethylstannyl ester 113. The (Z)-trimethylstannyl ester 113 was reduced with lithium aluminum hydride in ether to give the (Z)-trimethylstannyl alcohol 114. Finally, the latter compound 114 was converted into (Z)-5-chloro-3-trimethylstannyl-2-pentene (115) using triphenylphosphine and triethylamine in carbon tetrachloride. The overall yield from ethyl 2-pentynoate (111) was 46% and the spectral data of (Z)-5-chloro-3-trimethylstannyl-2-pentene (115) were consistent with those previously reported.\(^{13d,95}\)
The 1,4-addition of the Grignard reagent 116, prepared by the transmetallation of 4-chloro-2-trimethylstannyl-1-butene (110), to enone 64 (Scheme 2.6) produced the trimethylstannyl cyclohexanone 102 (~5% yield) and an inseparable mixture (by flash chromatography) of chloro ketones 117 and 118 in a ratio of 6.7:1 (by $^1$H NMR). The combined yield of 117 and 118 was 55% (73% yield based on recovered starting enone 64). Eventually, the chloro ketone 117 ([$\alpha$]$_D$ $^25 +87.7^\circ$, $c = 1.212$ in MeOH) was prepared, free of the epimer 118, in 69% yield (76% yield based on recovered starting enone 64), through the 1,4-addition of the cyanocuprate 119 to enone 64 in the presence of TMSCl and boron trifluoride etherate. The trimethylstannyl cyclohexanone 102 was also obtained in 10% yield.
The HRMS (M+-Me)_98 and the elemental analysis were consistent with the proposed molecular formula for the chloro ketone 117 and the spectral data (IR, ^1H NMR, ^13C NMR, and circular dichroism) were similar to those obtained for the chloro ketone 100. Those similarities simplified the assignment of all the signals in the ^1H NMR and ^13C NMR spectra of 117.

The 1,4-addition of the organomagnesium species 120 (equation 2.8) to enone 64 gave the chloro ketone 121 ([α]_D^{25} +116.2°, c = 1.036 in MeOH) and some of the starting enone 64. The yield was 65% (84% yield based on recovered enone 64). The more hindered nature of reagent 120 is probably responsible for the complete stereoselectivity of the addition. The same stereoselectivity was also obtained with the corresponding cyanocuprate 122 but the addition was sluggish and the yield was low (16% after 2 h at -78 °C, 70% yield based on recovered starting enone 64). It is interesting to note that in contrast to our previous results, none of the trimethylstannylcyclohexane 102 was isolated. This observation can be understood if we consider the equilibrium between the lithio species 123 (equation 2.9) and the trimethylstannyl species 115. Relief of A(1,3) strain^{100} in 115 by
replacement of the bulky trimethylstannyl group by the relatively small lithium ion will cause the equilibrium to shift completely to the right.

\[
\text{MeLi, THF} \quad 115 \quad \text{MeLi, THF} \\
2) \text{MgBr}_2 \cdot \text{OEt}_2 \quad -78 ^\circ \text{C}, \text{THF} \\
\]\n
\[
\text{BrMg} \quad 120 \quad \text{CuBr} \cdot \text{SMe}_2 \quad 0.05 \text{ equiv} \\
\text{BF}_3 \cdot \text{OEt}_2 \quad 1.1 \text{ equiv} \quad \text{THF}, -78 ^\circ \text{C} \\
\text{65\%} \\
\text{Cl} \quad 121 \\
\text{SnMe}_3 \\
(2.8)
\]

\[
\text{Li(CN)Cu} \quad 122 \\
\]

\[
\text{Me}_3\text{Sn} \quad 115 + \text{MeLi} \quad \text{Me}_4\text{Sn} + \text{Li} \quad 123 \\
(2.9)
\]

The IR spectrum of chloro ketone 121 exhibits absorptions at 1707, 1640, 773 and 525 cm\(^{-1}\), indicating the presence of a six-membered cyclic ketone, a double bond and a trimethylstannyl group. The \(^1\)H NMR and \(^{13}\)C NMR spectra were very similar to those of 100 and 117 and indeed could be assigned with the aid of comparisons with the spectra of the previously prepared trimethylstannylcyclohexanone 102 and the chloro ketones 100 and 117. The presence of signals due to the olefinic proton (\(\delta 5.38 \text{ q, 1H, } J = 7.5 \text{ Hz}\)) and the vinylic methyl group (\(\delta 1.75 \text{ d, 3H, } J = 7.5 \text{ Hz}\)) were consistent with the structural formula 121.\(^{69}\)

In summary, we have described thus far a somewhat improved procedure to prepare the previously reported enone 55 and have shown how this substance can be converted efficiently and stereoselectively into the ketone 92. This ketone was then transformed to the enone 64 by use of straightforward chemistry. The compatibility of the Me\(_3\)Sn function with cuprate additions to the enone 64 was demonstrated with the successful, stereoselective preparation of the chloro ketones 100, 117 and 121. The
next section of this thesis will consist of a description of the exploration of the reaction conditions required for the cyclization of these ketones.

![Chemical structures](image)

2.1.3. Cyclization of the Trimethylstannyl Chloro Ketones 100, 101, 117 and 121

2.1.3.1. Cyclization of the Trimethylstannyl Chloro Ketone 100

The results of our initial attempts to cyclize the chloro ketone 100 were disappointing. Both reported cyclization conditions\(^\text{12}\) using potassium hydride in THF at room temperature or potassium tert-butoxide and 2-methyl-2-propanol in THF gave complex mixtures of ketones. No product could be detected when \(i\)-Pr\(_2\)NLi was used as a base in THF. Small amounts (8 to 47% yield) of the desired cyclized bicyclic ketone 124 were obtained with potassium hexamethyldisilazide (125) in THF at room temperature (equation 2.10). The low yields thus obtained are probably due to the elimination of the trimethylstannyl moiety under the basic conditions. The presence of new olefinic signals in the \(^1\)H NMR spectrum of the crude reaction mixture provided evidence for this proposal. Better results were obtained by replacing the chloride with a better leaving group (e.g. iodide), thus allowing the cyclization to occur at lower temperatures even when using a less readily-equilibrated, more tightly bonded counterion (lithium instead of potassium).
Thus, the chloro ketone 100 was treated with sodium iodide in refluxing acetone for 10 h (Finkelstein reaction) to give the iodo ketone 126 in 95% yield (equation 2.10). The spectral data of this material was consistent with the proposed structure 126. The $^1$H and $^{13}$C NMR signals for the iodomethylene group of 126 appeared at $\delta$ 3.23 and $\delta$ 6.93, respectively, while the equivalent resonances for chloromethylene moiety of 100 appeared at $\delta$ 3.55 and $\delta$ 52.68, respectively.

The iodo ketone 126 was added to a cold (-78 °C) solution of $i$-Pr$_2$NLi in THF, and the resulting solution of the lithium enolate was rapidly warmed to 35 °C to give the bicyclic ketone 124 ([α]$_D^{28}$ +109.0°, c = 1.014 in MeOH) in 93% yield (equation 2.11). The lithium enolate of 126 is expected to cyclize faster via the transition state 127 (leading to the cis-fused product 124) than via the transition state 128 (leading to a trans-product) for the following reasons: (1) the better antiperiplanar alignment of the orbitals of the enolate with the antibonding orbital of the carbon-iodide bond and (2) the fact that the boat-like transition state 128, necessary in order to maintain an effective orbital overlap through the cyclization, would suffer from angle strain as well as steric interactions involving the methyl group in the 5-position and the iodomethylene moiety.
The IR spectrum of the bicyclic ketone 124 exhibits absorptions at 1702, 1636, 772 and 527 cm⁻¹, indicating the presence of a six-membered cyclic ketone, an exocyclic carbon-carbon double bond and a trimethylstannyl group. A combination of $^1$H NMR, $^1$H decoupling, NOE, COSY, $^{13}$C NMR, APT and HSC experiments was used to determine the structure of the bicyclic ketone 124. The HSC heteronuclear correlations and the APT experiment results (Table 2.5) and the COSY homonuclear correlations (Table 2.6) were used to establish the carbon-hydrogen connectivities. The relative and absolute configurations were established on the basis of NOE experiments, coupling constants and chiroptical properties.⁶⁹
Table 2.5: The 400 MHz $^1$H, 75 MHz $^{13}$C, APT and HSC NMR Experiments Data for the Bicyclic Ketone 124 in C$_6$D$_6$

<table>
<thead>
<tr>
<th>Assignment (C-X)</th>
<th>$^{13}$C and APT $\delta$ ppm (APTa, J$_{Sn-C}$ (Hz))</th>
<th>$^1$H NMR and HSC $^1$H-$^{13}$C Shift Correlations $\delta$ ppm (mult., # of H, J (Hz), Assignment [H-X])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>-10.34 (-ve, 315)</td>
<td>0.05 (s, 9H, $^2$J$_{Sn-H}$ = 51, Me$_3$Sn)</td>
</tr>
<tr>
<td>Me-11</td>
<td>16.37 (-ve, 15)</td>
<td>1.04 (d, 3H, 6.5, Me-11)</td>
</tr>
<tr>
<td>10</td>
<td>21.87</td>
<td>1.40 (dddd, 1H, 14, 14, 5, 5, 10a) and 2.12-2.30 (10e)$_b$</td>
</tr>
<tr>
<td>9</td>
<td>23.75</td>
<td>1.50-1.60 (m, 1H, 9a), and 2.12-2.30 (9e)$_b$</td>
</tr>
<tr>
<td>4</td>
<td>29.24 (-ve, 382)</td>
<td>1.81 (ddd, 1H, 14, 14, 2.5, $^2$J$_{Sn-H}$ = 43, H-4)</td>
</tr>
<tr>
<td>Me-12</td>
<td>30.39 (-ve)</td>
<td>1.07 (s, 3H, Me-12)</td>
</tr>
<tr>
<td>8</td>
<td>33.10</td>
<td>2.00-2.10 (8a)$_c$ and 2.12-2.30 (8e)$_b$</td>
</tr>
<tr>
<td>5</td>
<td>41.55 (13)</td>
<td>1.55 (dd, 1H, 14, 14, $^3$J$_{Sn-H}$ = 24, 5a) and 2.00-2.10 (5e)$_c$</td>
</tr>
<tr>
<td>3</td>
<td>48.12 (-ve, 15)</td>
<td>2.00-2.10 (H-3)$_c$</td>
</tr>
<tr>
<td>6</td>
<td>48.46</td>
<td>.......$_d$</td>
</tr>
<tr>
<td>1</td>
<td>56.06 (-ve, 3)</td>
<td>1.95 (d, 1H, 5, H-1)</td>
</tr>
<tr>
<td>13</td>
<td>107.78</td>
<td>4.58 (br s, 1H, 13a) and 4.78 (br s, 1H, 13b)</td>
</tr>
<tr>
<td>7</td>
<td>150.76</td>
<td>.......$_d$</td>
</tr>
<tr>
<td>2</td>
<td>209.92</td>
<td>.......$_d$</td>
</tr>
</tbody>
</table>

-ve is reported when a negative peak is observed. The absence of -ve indicates positive APT signal.

$^a$ Signals unresolved (8e, 9e and 10e)

$^b$ Signals unresolved (H-3, 5e and 8a)

$^c$ No correlation
Table 2.6: The 400 MHz $^1$H NMR and COSY Data for the Bicyclic Ketone 124 in C$_6$D$_6$

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, $J$ (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.05 (s, 9H, $^2$J$_{Sn-H} = 51$)</td>
<td>----$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>1.04 (d, 3H, 6.5)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.07 (s, 3H)</td>
<td>----$^a$</td>
</tr>
<tr>
<td>10a</td>
<td>1.40 (dddd, 1H, 14, 14, 5, 5)</td>
<td>1, 9a, 9e, 10e</td>
</tr>
<tr>
<td>9a</td>
<td>1.50-1.60 (m, 1H)</td>
<td>8a, 8e, 9e, 10a, 10e</td>
</tr>
<tr>
<td>5a</td>
<td>1.55 (dd, 1H, 14, 14, $^3$J$_{Sn-H} = 24$)</td>
<td>4, 5e</td>
</tr>
<tr>
<td>4</td>
<td>1.81 (dddd, 1H, 14, 14, 2.5, $^2$J$_{Sn-H} = 43$)</td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>1</td>
<td>1.95 (d, 1H, 5)</td>
<td>10a</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>4, Me-11</td>
</tr>
<tr>
<td>5e</td>
<td>2.00-2.10 (m, 3H)</td>
<td>5a</td>
</tr>
<tr>
<td>8a</td>
<td></td>
<td>8e, 9a, 9e</td>
</tr>
<tr>
<td>8e</td>
<td></td>
<td>8a, 9a, 13a (LR)$^b$, 13b (LR)$^b$</td>
</tr>
<tr>
<td>9e</td>
<td>2.12-2.30 (m, 3H)</td>
<td>10a</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13a</td>
<td>4.58 (br s, 1H)</td>
<td>8e (LR)$^b$, 13b</td>
</tr>
<tr>
<td>13b</td>
<td>4.78 (br s, 1H)</td>
<td>8e (LR)$^b$, 13a</td>
</tr>
</tbody>
</table>

$^a$ No correlation.  
$^b$ (LR) = Long range coupling.

Simultaneous irradiation of the signals due to Me-11 and Me-12 produced a NOE enhancement of the signals attributed to H-1, H-3 and H-4, H-5e, and H-8a (see 124a, Figure 2.3). The signal of Me-12 was irradiated and the enhancements are represented on structure 124b. No enhancement of the signal assigned to H-10a could be observed in either of these experiments. Irradiation of the signal corresponding to H-4 (see 124c) enhanced the signals due to Me-11 and the olefinic hydrogen (H-13a). Finally, irradiation of the signal due to H-1 (124d) led to enhancement of the signals attributed to H-5a, H-10a, H-10e and Me-12. The proximity of the signals assigned to H-3 to the irradiated resonance due to H-1
\( \Delta \delta = \sim 0.05 \) precluded the observation of an enhancement of the H-3 signal. The results shown on structures 124a and 124c are in agreement with the cis-cis arrangement on the cyclohexanone ring of the alkene moiety, H-4, and Me-11. The cis ring junction of the decalin skeleton was confirmed by the reciprocal enhancement of the signals due to Me-12 and H-1 (see 124b and 124d).

Figure 2.3 NOE's of Compound 124

2.1.3.2. Cyclization of the Trimethylstannyl Chloro Ketone 101

The structure of the chloro ketone 101 obtained by the addition of the Grignard reagent 14 to the enone 64 (see Scheme 2.4), could be inferred from a series of chemical manipulations. Thus, the mixture of chlorides 100 and 101 (in a ratio of 5.3:1 by \(^1\)H NMR) was treated with sodium iodide in refluxing acetone to give an inseparable mixture of the iodo ketones 126 and 129 in quantitative yield (Scheme 2.7). This mixture was then cyclized with \( i\text{-Pr}_2\text{NLi} \) in THF as described.
earlier to give, after a series of four careful separations by flash chromatography, the bicyclic ketone 124 (68%), a mixture of the bicyclic ketones 124 and 130 (7%) and pure bicyclic ketone 130 (8%) ([α]D25 +209.0°, c = 0.900 in MeOH). The cis-decalin 130 would be expected to be the kinetic product of the cyclization, since the transition state 131 would be predicted to be more stable than alternative arrangements for reasons similar to those described previously in connection with the cyclization of 126.

\[
\begin{align*}
100 + 101 & \xrightarrow{5.3:1} 124 + 130 \\
124 + 130 & \xrightarrow{35^\circ C} 129
\end{align*}
\]

The IR spectrum of the bicyclic ketone 130 exhibited absorptions that indicated the presence of a six-membered cyclic ketone (1698 cm\(^{-1}\)), an exocyclic carbon-carbon double bond (1632 cm\(^{-1}\)), and a trimethylstannyl group (769 and 527 cm\(^{-1}\)). A combination of \(^1\)H NMR, selective decoupling, NOE, COSY, \(^13\)C NMR, and HSC experiments were used to determine the structure of the bicyclic ketone 130. The HSC heteronuclear correlations (Table 2.7) and the COSY homonuclear correlations (Table 2.8) were used to established the carbon and hydrogen connectivities. The stereochemistry of 130 was established by a combination of the NOE experiments, the coupling constants and the chiroptical properties.\(^69\)
Table 2.7: The 400 MHz $^1$H, 75 MHz $^{13}$C, and HSC NMR Experiments Data for the Bicyclic Ketone 130

<table>
<thead>
<tr>
<th>Assignment (C-X)</th>
<th>$^{13}$C NMR $\delta$ ppm ($J_{Sn-C}$ (Hz))</th>
<th>$^1$H NMR and HSC $^1$H-$^{13}$C Shift Correlations $\delta$ ppm (mult., # of H, J (Hz), Assignment [H-X])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>-10.13 (315)</td>
<td>0.11 (s, 9H, $^2J_{Sn-H}$ = 52, Me$_3$Sn)</td>
</tr>
<tr>
<td>Me-11</td>
<td>15.53 (15)</td>
<td>0.99 (d, 3H, 6.5, Me-11)</td>
</tr>
<tr>
<td>Me-12</td>
<td>24.09</td>
<td>1.10 (s, 3H, Me-12)</td>
</tr>
<tr>
<td>9</td>
<td>27.15</td>
<td>1.30 (ddddd, 1H, 14, 14, 13, 4, 4, 9a) and 1.84-1.91 (m, 1H, 9e)</td>
</tr>
<tr>
<td>10</td>
<td>27.73</td>
<td>1.62-1.69 (m, 1H, 10e) and 1.83 (m, 1H, 10a)</td>
</tr>
<tr>
<td>4</td>
<td>29.57 (390)</td>
<td>1.57 (ddd, 1H, 14, 13, 4, H-4)</td>
</tr>
<tr>
<td>8</td>
<td>32.78</td>
<td>2.23 (dm, 1H, 14, 8e) and 2.37-2.45 (m, 1H, 8a)</td>
</tr>
<tr>
<td>5</td>
<td>36.19 (12)</td>
<td>1.18 (ddd, 1H, 14, 4, 1.5, 5e) and 2.43 (dd, 1H, 14, 14, 5a)</td>
</tr>
<tr>
<td>3</td>
<td>42.62 (19)</td>
<td>2.65 (dq, 1H, 13, 6.5, H-3)</td>
</tr>
<tr>
<td>6</td>
<td>45.23 (65)</td>
<td>....b</td>
</tr>
<tr>
<td>1</td>
<td>60.11</td>
<td>2.14 (ddd, 1H, 13, 4, 1.5, H-1)</td>
</tr>
<tr>
<td>13</td>
<td>107.69</td>
<td>4.71 (br s, 1H, 13b) and 4.73 (br s, 1H, 13a)</td>
</tr>
<tr>
<td>7</td>
<td>153.63</td>
<td>....b</td>
</tr>
<tr>
<td>2</td>
<td>216.30</td>
<td>....b</td>
</tr>
</tbody>
</table>

a Overlapping signals (5a and 8a).
b No correlation
Table 2.8: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Bicyclic Ketone 130

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR δ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.11 (s, 9H, $^2$J$_{Sn-H}$ = 52, Me$_3$Sn)</td>
<td>……$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>0.99 (d, 3H, 6.5, Me-11)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.10 (s, 3H, Me-12)</td>
<td>……$^a$</td>
</tr>
<tr>
<td>5e</td>
<td>1.18 (ddd, 1H, 14, 4, 1,5)</td>
<td>4, 5a</td>
</tr>
<tr>
<td>9a</td>
<td>1.30 (ddddd, 1H, 14, 14, 13, 4, 4)</td>
<td>1 (LR)$^b$, 8a, 8e, 9e, 10a, 10e</td>
</tr>
<tr>
<td>4</td>
<td>1.57 (ddd, 1H, 14, 13, 4)</td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>10e</td>
<td>1.62-1.69 (m, 1H)</td>
<td>1, 9a, 9e, 10a</td>
</tr>
<tr>
<td>10a</td>
<td>1.83 (m, 1H)</td>
<td>1, 9a, 9e, 10e</td>
</tr>
<tr>
<td>9e</td>
<td>1.84-1.91 (m, 1H)</td>
<td>8a, 8e, 9a, 10a, 10e</td>
</tr>
<tr>
<td>1</td>
<td>2.14 (ddd, 1H, 13, 4, 1.5)</td>
<td>9a (LR)$^b$, 10a, 10e</td>
</tr>
<tr>
<td>8e</td>
<td>2.23 (dm, 1H, 14)</td>
<td>8a, 9a, 9e</td>
</tr>
<tr>
<td>8a</td>
<td>2.37-2.45 (m, 1H)</td>
<td>8e, 9a, 9e, 13a (LR)$^b$, 13b (LR)$^b$</td>
</tr>
<tr>
<td>5a</td>
<td>2.43 (dd, 1H, 14, 14)</td>
<td>4, 5e</td>
</tr>
<tr>
<td>3</td>
<td>2.65 (dq, 1H, 13, 6.5)</td>
<td>4, Me-11</td>
</tr>
<tr>
<td>13b</td>
<td>4.71 (br s, 1H)</td>
<td>8a (LR)$^b$, 13a</td>
</tr>
<tr>
<td>13a</td>
<td>4.73 (br s, 1H)</td>
<td>8a (LR)$^b$, 13b</td>
</tr>
</tbody>
</table>

$^a$ No correlation.

$^b$ (LR) = Long range coupling or U coupling..

Selective decoupling of the $^1$H NMR signal due to Me-11 (δ 0.99) of compound 130 resulted in a doublet at δ 2.65 (H-3, $J$ = 13 Hz). Irradiation of H-3 produced a doublet of doublets at δ 1.57 (H-4, $J$ = 14, 4 Hz) and a singlet for Me-11. Finally, irradiation of the signal due to H-4 gave a doublet of doublets at δ 1.18 (H-5e, $J$ = 14, 1.5 Hz), a doublet at δ 1.43 (H-5a, $J$ = 14 Hz) and a quartet at δ 2.65 (H-3, $J$ = 6.5 Hz), thus establishing the Me-11, H-3, H-4, H-5e, H-5a spin system and their relative orientations using the values of their coupling constants. The 1,3-diaxial relationship between H-4 and Me-12 and the cis ring junction of the decalin skeleton was confirmed by the NOE experiments. Thus irradiation of the signal due to H-4 led to the
enhancement of the signals due to Me-11, Me-12 and H-5e (see 130a, Figure 2.4) and irradiation of the signal due to Me-12 led to the enhancement of signals due to H-4, H-1 and H-13a\textsuperscript{101} (130b). The elucidation of the structure of compound 130 therefore confirmed our proposed structure for the chloro ketone 101. With the structure of 124 and 130 established, we investigated the annulation sequences of the chloro ketones 117 and 121.

![Figure 2.4 NOE's of Compound 130](image)

2.1.3.3. Cyclization of the Trimethylstannyl Chloro Ketones 117 and 121

The chloro ketones 117 and 121, having one less carbon in the alkenyl side chain than the chloro ketone 100, were expected to cyclize faster than 100. Also, examination of molecular models indicated that the transition state for the cyclization of the enolates of 117 and 121 should involve less angle strain and steric interactions than in the transition state 127, again due to the shorter carbon chain. We were pleased to find that the chloro ketones 117 and 121 readily cyclized upon treatment with \( i\)-Pr\(_2\)NLi, followed by warming to 45 °C. The bicyclic ketone 132 ([\( \alpha \)]\textsubscript{D}\textsuperscript{26} +76.7°, c = 1.14 in MeOH) (equation 2.12) was obtained in 88% yield while the bicyclic ketone 133 ([\( \alpha \)]\textsubscript{D}\textsuperscript{26} +77.1°, c = 0.978 in MeOH) (equation 2.13) was obtained in 83% yield.
The IR spectrum of bicyclic ketone 132 exhibits absorptions at 1687, 1652, 765 and 522 cm\(^{-1}\), indicating the presence of a six-membered cyclic ketone, an exocyclic carbon-carbon double bond and a trimethylstannyl group. A combination of \(^1\)H NMR, NOE, \(^{13}\)C NMR and APT experiments and comparison with the spectra of 124 and 130 were used to confirm the structure of the bicyclic ketone 132. The \(^{13}\)C NMR spectra could be assigned by a combination of the Sn-C coupling constants, the chemical shifts and the APT experiment. The stereochemistry of 132 was established with the assistance of the NOE experiments, the coupling constants and the chiroptical properties.\(^{69}\)

The results of the NOE experiments unambiguously established the cis-ring junction of 132. Thus, irradiation of the signal due to Me-11 (see 132a, Figure 2.5)
led to the enhancement of the signals due to H-9a, H-5a, H-5e, H-1 (δ 2.42, dd, J = 6, 5 Hz) and H-12a. Irradiation of the signal due to H-4 (132b) led to the enhancement of the signals due to Me-10, H-5e and H-8a. Finally, irradiation of the signal due to H-5a (132c) led only to the enhancement of the signal due to Me-11. The enhancement of H-5e could not be seen in the last experiment because its chemical shift was too close to that of the irradiated signal (Δδ = 0.16).

Figure 2.5 NOE's of Compound 132

The IR spectrum of the bicyclic ketone 133 shows absorptions that can be assigned to a six-membered cyclic ketone (1687 cm⁻¹) and a trimethylstannyl group (767 and 527 cm⁻¹). A combination of ¹H NMR, NOE and ¹³C NMR experiments and comparison with the spectra of 124, 130 and 132 were used to determine the structure of the bicyclic ketone 133. The ¹³C NMR spectra could be assigned with the assistance of the Sn-C couplings constants, the chemical shifts and the APT experiment. The stereochemistry of 133 was established with the NOE experiments, the couplings constants and the chiroptical properties.⁶⁹
The results of the NOE experiments established the cis-ring junction of the bicyclic ketone 133. Irradiation of the signal due to Me-11 (see 133a, Figure 2.6) led to enhancement of the signals assigned to Me-13, H-5a, H-1 ($\delta$ 2.30, d, $J = 5$ Hz) and H-5e. Irradiation of the signal due to H-5e (133b) led to the enhancement of the resonances attributed to Me-11, Me-13 and H-5a.

Figure 2.6 NOE's of Compound 133

The preceding work has demonstrated the feasibility of carrying out the methylenecyclopentane, (Z)-ethylidenecyclopentane and methylenecyclohexane annulation sequences on the enantiomerically pure trimethylstannyldicyclohexenone 64 and the usefulness of the Me$_3$Sn group as an anchor to direct and maintain the stereochemistry of the cyclized products. The next objective of the project was to remove the trimethylstannyld anchor, and the results of this portion of the research will be described in the following pages.
2.2. REMOVAL OF THE TRIMETHYLSTANNYL MOIETY

2.2.1. Previous Destannylation Methods

A search of the chemical literature indicated that there were several methods reported to remove a trialkylstannyl moiety. These methods were rarely general and worked only on a few specific substrates. The known destannylation methods can be divided in four classes: oxidation, carbon-carbon bond formation, a combination of carbon-carbon bond formation and fragmentation, and replacement of the R₃Sn moiety by an hydrogen. Examples of each type are presented next.

2.2.1.1. Oxidation

Still⁶⁸ has shown that the tetraalkylstannyl moiety can be oxidized to a carbonyl group in the presence of chromium trioxide. The synthesis of dihydrojasmine (138) illustrates this oxidation (Scheme 2.8). The 1,4-addition of trimethylstannyllithium to 2-cyclopenten-1-one (134), followed by trapping of the resulting enolate with iodopentane, gave the stannyl ketone 135. Reaction of methyllithium with the carbonyl moiety produced the tertiary alcohol 136, which was directly oxidized into the hydroxy ketone 137. The alcohol was then dehydrated to provide dihydrojasmine (138) in an overall yield of 71% from 135. The destannylation method is limited both by the requirement of having a tertiary alcohol in the position γ to the Me₃Sn moiety, and by the necessity of using a large excess of chromium trioxide in order to get good reaction yields. Nevertheless, this type of oxidation might provide access to highly oxidized members of the clerodane family like the (+)-epoxide 24, for example.
2.2.1.2. Carbon-Carbon Bond Formation

Examples of the use of a simultaneous destannylation-carbon bond formation are more common than the oxidation of the trialkylstannyl moiety. Kadow and Johnson\textsuperscript{102} have prepared the bicyclo[3.1.0]hexane 141 in 62% overall yield from the tributylstannyl ketone 139 following the procedure outlined in equation 2.14. The 1,2-addition product 140 was dehydrated with thionyl chloride in pyridine, triggering destannylation and cyclopropanation to give 141. The reaction produced cyclopropyl compounds in good yield only when a good carbocation-stabilizing moiety was on the carbon adjacent to the tertiary alcohol.

In a series of publications, Macdonald and coworkers\textsuperscript{103} have explored the intramolecular destannylation-cyclization of primary alkylstannyl enones, ketones and alkenes. The method is exemplified by equation 2.15. The ketone 142 is cyclized in the presence of diethylaluminum chloride to give the tertiary alcohol 143 in 91% yield.
Although a high yield has been reported for a few specific cases, this method often results in formation of a terminal alkene as the major product by elimination of the Me₃Sn moiety, especially for the formation of rings larger than 5 carbon atoms. For example, ketone 144 (equation 2.16) gave the alkene 145 in 90% yield using acidic conditions identical with those in equation 2.15.

\[
\begin{align*}
\text{O} & \quad \text{SnMe}_3 \\
\text{142} & \quad \text{Et}_2\text{AlCl (2.5 equiv)} \\
\text{CH}_2\text{Cl}_2, 0 \degree \text{C}, 91\% & \quad \text{OH} \\
\text{143} & \\
\end{align*}
\]

(2.15)

\[
\begin{align*}
\text{O} & \quad \text{SnMe}_3 \\
\text{144} & \quad \text{Et}_2\text{AlCl (2.5 equiv)} \\
\text{CH}_2\text{Cl}_2, 0 \degree \text{C}, 90\% & \quad \text{OH} \\
\text{145} & \\
\end{align*}
\]

(2.16)

2.2.1.3. Carbon-Carbon Bond Formation-Fragmentation

Posner and coworkers\textsuperscript{104} have used a “one-pot” annulation sequence involving an oxidative destannylation to prepare macrolides. The total synthesis of phorocantholide I (151) (Scheme 2.9), a natural 10-membered ring lactone isolated from an insect secretion, illustrates the procedure. Thus, tributylstannyllithium was conjugatively added to the cyclohexenone 146, and the resulting enolate was trapped with the iodide 147 to give the ketone 148. The ethoxyethyl protective group was cleaved with aqueous ammonium chloride to give the hemiketal 149. The crude hemiketal was oxidized with lead tetraacetate to yield the macrolide 150. Finally, Wilkinson hydrogenation of 150 produced the natural product 151 in 27% overall yield.
Similarly Baldwin and coworkers\textsuperscript{105} have prepared 10-membered rings by a free radical-promoted cyclization-destannylation method. For example, the iodide \textsuperscript{152} (equation 2.17) was cyclized with tributyltin hydride and AIBN in benzene to give the radical intermediate \textsuperscript{153}, which then fragmented in situ to propagate the radical chain and produce the 10-membered ketone \textsuperscript{154} in 85\% yield.

\textbf{2.2.1.4. Replacement of the R}_3\text{Sn Moiety by an Hydrogen}

To the best of our knowledge only two direct methods exist for the replacement of the R}_3\text{Sn moiety of a tetraalkylstannane by an hydrogen. Except for a few specific examples, the yields of the reactions were generally low because of the very harsh conditions used. Olszowy and Kitching\textsuperscript{106} have destannylated the triisopropylstannane \textsuperscript{155} (equation 2.18) by treatment with deuterated trifluoroacetic acid in dioxane at 100 °C for 10 days! The deuterated cyclohexane \textsuperscript{156} was obtained in only 30\% yield.
Newman-Evans and Carpenter\textsuperscript{107} have successfully destannylation 2-hydroxy-5-tributylstannylbicyclo[2.1.1]hexane 157 (equation 2.19) by the addition of butyl-lithium at \(-78 \, ^\circ C\) followed by deuteration with D\textsubscript{2}O to give the alcohol 159 in 78\% yield. A high yield for the reaction has been reported only when the orientation of the trialkystannyl and hydroxyl groups are \textit{syn} as shown in structure 157. The authors suggested that this arrangement allowed the negative charge on the carbon atom to be stabilized by an intramolecular complexation of the lithium counterions with the oxygen anion as depicted in intermediate 158.

2.2.1.5. A Proposal for the Removal of the Trimethylstannyl Group

With the exception of Still’s oxidation method, none of the known procedures for removal of a Me\textsubscript{3}Sn group would be useful to access the clerodane skeleton using a short reaction sequence. A new destannylation method needed to be developed to achieve our goal. It was proposed that a dissolving metal reduction in either ammonia or amine solvents should result in transfer of an electron to the polarizable tin atom, with the eventual formation of a carbanion. Protonation of the latter species would provide the product where the Me\textsubscript{3}Sn function is replaced by a hydrogen. This proposal is represented in Scheme 2.10. Single electron transfer\textsuperscript{108} to 160 would give the radical 161 and trimethylstannylmetal. This radical could accept another
electron from a second metal atom to form the carbanion 162, which could then either abstract a proton from the solvent or another proton source to produce 163, the desired destannylated product. We set out to verify that this hypothesis could be applied to the destannylation of β-trimethylstannyl ketone substrates.

![Scheme 2.10](image)

2.2.2. Dissolving Metal Reduction of the Bicyclic Trimethylstannyl Ketone 124

Dissolving metal reduction of a carbonyl group with calcium metal in ammonia is a well known method. Wai had previously reported the reduction of the bicyclic ketone 17 to the alcohol 164 (equation 2.20) using this method. We thus proposed to use these conditions to accomplished the desired destannylation.

![Equation 2.20](image)
Using reaction conditions reported by Wai (see equation 2.20), the reduction of the bicyclic ketone 124 with calcium in ammonia (equation 2.21) was attempted. The desired bicyclic alcohol 165 ([α]_D^{24} +37.0°, c = 0.892 in chloroform) was isolated in 9% yield, along with a 26% yield of the bicyclic trimethylstannyl alcohol 166 ([α]_D^{25} -9.52°, c = 1.505 in chloroform). After a series of experiments, effective conditions for the reduction of 124 to 165 were found. Thus, a THF solution of 2-methyl-2-propanol and 124 (equation 2.22) was added to a cold (-78 °C) deep blue solution of lithium in ammonia to produce the alcohol 165 in 89% yield.

The reaction conditions were varied in order to learn about the mechanism of the reduction. By using only 2.2 equivalents of electrons from the metal in the reduction process, only one of the functional groups (ketone or Me₃Sn) should be reduced if there is a significant difference in their reduction rate. In the event, reduction of 124 using 2.2 equivalents of lithium in ammonia gave compounds 124, 165 and 166 in isolated yields of 18%, 31% and 43%, respectively (equation 2.23). The yield of the bicyclic trimethylstannyl alcohol 166 based on the recovered ketone 124 was 52%. The use of calcium metal gave slightly different results. With 1.1 equivalents of calcium, we isolated 31% of 124, only 12% of 165, and 42% of the bicyclic trimethylstannyl alcohol 166 (61% yield based on recovered 124). The lower
reactivity of calcium in the reduction process probably accounts for the greater relative amount of 166 formed during the reduction.\(^{108}\)

The bicyclic trimethylstannyl alcohol 166 was converted to the bicyclic alcohol 165 in 94\% yield using a procedure identical to that described in equation 2.22. In one experiment, the reduction of the ketone 124 with lithium in ammonia in the presence of 2-methyl-2-propanol was quenched with water a minute after the addition of the ketone. From the resulting mixture we isolated a small amount of a ketone that was assigned the structure 17 on the basis of the comparison of its \(^1\)H NMR spectrum with that of Wai.\(^{111}\) It was concluded from the results of the dissolving metal reductions of 124 that the rate of reduction of the carbonyl group is only marginally faster than the reduction of the trimethylstannyl moiety.

The IR spectrum of the bicyclic alcohol 165 exhibits absorptions at 3280, 1637, and 1021 cm\(^{-1}\), indicating the presence of a hydroxyl group and an exocyclic carbon-carbon double bond. A combination of \(^1\)H NMR, selective decoupling, COSY, \(^{13}\)C NMR and APT experiments was used to confirm the structure of the bicyclic alcohol 165.
Selective decoupling of the signal at δ 1.01 (Me-11) simplified the signal due to H-3 at ~δ 1.40. The same signal at ~δ 1.4 (H-3) was simplified along with the appearance of a broad singlet at δ 1.37 (H-1) and a singlet at δ 1.25 (OH) when the signal at δ 3.15 (H-2) was irradiated. The values of the coupling constants of the signal at δ 3.15 (H-2) after D₂O exchange (J = 10, 10 Hz) suggested that H-1 and H-3 are both trans-diaxial to H-2. The homonuclear correlation data (COSY experiment) for the bicyclic alcohol 165 are listed in Table 2.9. The assignment of H-13a and H-13b were based on a comparison of the ¹H NMR spectrum of 165 with that of 124. The ¹³C NMR spectrum was tentatively assigned on the basis of a combination of the chemical shifts and an APT experiment.
Table 2.9: The 400 MHz $^1$H NMR and COSY Data for the Bicyclic Alcohol 165

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-11</td>
<td>1.01 (d, 3H, 7)</td>
<td>2 (LR)$^a$, 3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.15 (s, 3H)</td>
<td>.....$^b$</td>
</tr>
<tr>
<td>OH</td>
<td>1.25 (d, 1H, 6)$^c$</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2, 10a, 10e</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me-11, 2</td>
</tr>
<tr>
<td>4a, 4e</td>
<td>1.20-1.60 (m, 7H)</td>
<td>5e</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a, 9e</td>
<td></td>
<td>8a, 8e</td>
</tr>
<tr>
<td>10a</td>
<td>1.70-1.82 (m, 1H)</td>
<td>1, 8a (LR)$^a$, 9a, 9e, 10e</td>
</tr>
<tr>
<td>5e</td>
<td>1.98-2.07 (m, 2H)</td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td>1, 8e(LR)$^a$, 9a, 9e, 10a</td>
</tr>
<tr>
<td>8e</td>
<td>2.18 (br d, 1H, 13.5)</td>
<td>8a, 9a, 9e, 10e(LR)$^a$</td>
</tr>
<tr>
<td>8a</td>
<td>2.35-2.45 (m, 1H)</td>
<td>8a, 9a, 9e, 10a, 10a(LR)$^a$, 13a and 13b(LR)$^a$</td>
</tr>
<tr>
<td>2</td>
<td>3.15 (ddd, 1H, 10, 10, 6)$^d$</td>
<td>Me-11 (LR)$^a$, OH, 1, 3</td>
</tr>
<tr>
<td>13a</td>
<td>4.60 (dd, 1H, 1.5, 1.5)</td>
<td>8a (LR)$^a$, 13b</td>
</tr>
<tr>
<td>13b</td>
<td>4.79 (dd, 1H, 1.5, 1.5)</td>
<td>8a (LR)$^a$, 13a</td>
</tr>
</tbody>
</table>

$^a$ (LR) = Long range coupling.
$^b$ No correlation.
$^c$ Exchanges with D$_2$O.
$^d$ Becomes dd, J = 10, 10 Hz, with D$_2$O.

The IR spectrum of the bicyclic trimethylstannyl alcohol 166 exhibited absorptions assigned to a hydroxyl group (3290 and 1018 cm$^{-1}$), an exocyclic carbon-carbon double bond (1637 cm$^{-1}$) and a trimethylstannyl groups (764 and 523 cm$^{-1}$). A combination of $^1$H NMR, selective decoupling, COSY, $^{13}$C NMR, APT experiments and comparison with the spectral data of 124 and 165 were used to confirm the structure of the bicyclic trimethylstannyl alcohol 166.

The $^1$H NMR spectrum of 166 was very similar to that of 165. The coupling constants of the signal at $\delta$ 3.16 (H-2) after D$_2$O exchange ($J = 10$, 10 Hz) suggested that H-1 and H-3 are both trans-diaxial to H-2. The homonuclear correlations (COSY experiment) are listed in Table 2.10. The $^{13}$C NMR spectrum of the alcohol 166 was
tentatively assigned on the basis of a combination of the chemical shifts and an APT experiment.

![Chemical structure]

**Table 2.10:** The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Bicyclic Trimethylstanny1 Alcohol 166

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, $J$ (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.08 (s, 9H, $^2$J$_{Sn-H} = 51$)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>1.01 (d, 3H, 6)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.12 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>OH</td>
<td>1.25 (d, 1H, 6)$^b$</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1.26-1.50 (m, 4H)</td>
<td>2, 10a, 10e</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me-11, 2</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>5e</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9a, 9e</td>
<td>1.50-1.60 (m, 2H)</td>
<td>8a, 8e, 10a, 10e</td>
</tr>
<tr>
<td>10a</td>
<td>1.70-1.82 (m, 1H)</td>
<td>1, 9a, 9e, 10e</td>
</tr>
<tr>
<td>10e</td>
<td>2.02 (br d, 1H, 14)</td>
<td>1, 8e(LR)$^c$, 9a, 9e, 10a</td>
</tr>
<tr>
<td>5e</td>
<td>2.07 (br dd, 1H, 14, 1)</td>
<td>4, 5a</td>
</tr>
<tr>
<td>8e</td>
<td>2.17 (br d, 1H, 15)</td>
<td>8a, 9a, 9e, 10e(LR)$^c$</td>
</tr>
<tr>
<td>8a</td>
<td>2.32-2.40 (m, 1H)</td>
<td>8e, 9a, 9e, 13a and 13b(LR)$^c$</td>
</tr>
<tr>
<td>2</td>
<td>3.16 (ddd, 1H, 10, 10, 6)$^d$</td>
<td>OH, 1, 3</td>
</tr>
<tr>
<td>13a</td>
<td>4.51 (dd, 1H, 1.5, 1.5)</td>
<td>8a (LR)$^c$, 13b</td>
</tr>
<tr>
<td>13b</td>
<td>4.80 (dd, 1H, 1.5, 1.5)</td>
<td>8a (LR)$^c$, 13a</td>
</tr>
</tbody>
</table>

$^a$ No correlation.
$^b$ Exchanges with D$_2$O.
$^c$ (LR) = Long range coupling.
$^d$ Becomes dd, $J = 10, 10$ Hz, with D$_2$O.
With a successful destannylation procedure available we wanted to verify the enantiomeric purity of the bicyclic alcohol 165.

2.2.3. Enantiomeric Purity of the Bicyclic Alcohol 165

The enantiomeric purity of the bicyclic alcohol 165 was established by esterification with optically active α-methoxy-α-trifluoromethylphenylacetyl chloride. The formation of Mosher's esters is a well established method for the determination of the optical purity of secondary alcohols. The esters are prepared by the addition of a secondary alcohol to α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl). The diastereomeric purity is easily ascertained by examination of the $^1$H, $^{13}$C or $^{19}$F NMR spectra of the resulting ester. The fluorine-19 NMR spectrum is simpler than $^1$H or $^{13}$C NMR spectra (usually a single peak for each enantiomer is observed in $^{19}$F NMR) and uncongested, making the determination of the enantiomeric purity of the alcohol easier to perform. The method is absolute since the optical purity of a product can be determined without knowing the optical rotation of the pure product. The sensitivity of the determination of optical purity of an alcohol with Mosher's esters is limited by the sensitivity of the NMR technique used.

The (R)-(−)- and (S)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chlorides (168 and 170) (equation 2.24) were prepared from the commercially-available (S)-(−)- and (R)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (167 and 169), respectively, according to the procedure of Mosher and coworkers.

\[
\begin{align*}
\text{(S)-167} & \quad \text{SOCl}_2 \quad \text{NaCl (0.5 equiv)} \quad \text{(R)-168} \\
\text{(R)-169} & \quad \text{SOCl}_2 \quad \text{NaCl (0.5 equiv)} \quad \text{(S)-170} \quad \text{(2.24)}
\end{align*}
\]
The bicyclic alcohol 165 was treated with the acid chlorides 168 and 170 (equation 2.25) separately following the procedure of Dale and Mosher. The crude, isolated product mixture containing the MTPA-esters 171 and 172 was analyzed by NMR spectroscopy. The esters 171 ([α]_D^{28} -23.9°, c = 0.463 in chloroform) and 172 ([α]_D^{30} +31°, c = 0.503 in chloroform) were purified from their respective crude reaction mixtures by chromatography and then characterized. The 1H NMR spectrum of the crude product containing 171 was compared with the spectrum of the purified ester 172 and was shown to be completely devoid of the distinct signals attributed to the enantiomer of 172 thus showing that the alcohol 165 was enantiomerically pure.

The IR spectrum of the bicyclic ester 171 exhibits absorptions at 3084, 1734, 1638 and 723 cm\(^{-1}\) (3079, 1737, 1637 and 725 for the bicyclic ester 172), indicating the presence of an aromatic ring, an ester carbonyl, an exocyclic carbon-carbon double bond and a trifluoromethyl moiety. A combination of 1H NMR, COSY (171), 13C NMR, 19F NMR experiments, chiroptical properties, and comparison with the spectral data of 124 and 165 were used to confirm the structure of the bicyclic esters 171 and 172.
The homonuclear correlations of the COSY experiments are listed in Table 2.11. The assignments for H-13a and H-13b were made by comparison with the $^1$H NMR spectrum of 124. The $^{13}$C NMR spectra of 171 and 172 were tentatively assigned with the assistance of a combination of the chemical shifts and comparison with the spectra of 124, 165 and 166. The characteristic $^1$H NMR signals of 171 are: Me-11 doublet at δ 0.86, Me-12 singlet at δ 1.11, MeO unresolved quartet (long range H-F coupling) at δ 3.56, olefinic protons H-13a and H-13b at δ 4.62 and δ 4.83, H-2 doublet of doublets ($J = 10, 10$ Hz) at δ 4.95 and the aromatic protons at δ 7.35-7.40 and 7.60-7.64. The $^1$H and $^{13}$C NMR spectra of 171 and 172 are very similar, and the assignment of the spectra of 172 can be made by comparison with those of 171. The resolved NMR signals of 172 that have a chemical shift difference greater than δ 0.02 (in absolute value) as compared with those of 171 ($Δδ = δ 172 - δ 171$) are listed in Table 2.12 ($^1$H NMR) and in Table 2.13 ($^{13}$C NMR). None of the signals of 172 were observed in the $^1$H and $^{13}$C NMR spectra of 171 and vice-versa, in either the crude reaction product mixture or in the purified product, thus establishing the enantiomeric excess for the alcohol 165 at a value of at least 98%.$^{115}$

The $^{19}$F NMR (188.3 MHz) spectra were recorded for the esters 171 and 172. The spectrum of the (S)-MTPA ester 171 showed a singlet at δ 4.85 (external trifluoroacetic acid standard) with satellites due to carbon couplings ($^1J_{F-C} = 288$ Hz, $^2J_{F-C} = 44$ Hz and $^3J_{F-C} = 27$ Hz) and a small singlet at δ 5.05. The relative intensity of the two signals was determined to be 157:1 (99.4% pure) in the NMR spectrum. The spectrum of the (R)-MTPA ester 172 showed a singlet at δ 5.02 (external trifluoroacetic acid standard) with $^{13}$C satellites couplings of $^1J_{F-C} = 289$ Hz, $^2J_{F-C} = 44$ Hz and $^3J_{F-C} = 27$ Hz and a small singlet at δ 4.85. The relative intensity of the two signals was 64:1 (98.4% pure). These results clearly show that the bicyclic alcohol 165 is enantiomerically pure (≥96% enantiomeric excess) within the limits of $^1$H, $^{13}$C and $^{19}$F NMR detection.
Table 2.11: The 400 MHz $^1$H NMR and COSY Data for the Bicyclic MTPA-Ester 171

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-11</td>
<td>0.86 (d, 3H, 7)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.11 (s, 3H)</td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>10e</td>
<td>1.16 (br dd, 10, 3)</td>
<td>1, 8e(LR)$^b$, 9a, 9e, 10a</td>
</tr>
<tr>
<td>5a</td>
<td>1.20-1.31 (m, 1H)</td>
<td>4a, 4e, 5e</td>
</tr>
<tr>
<td>9e</td>
<td>1.37-1.45 (m, 1H)</td>
<td>8e, 8a, 9a, 10a, 10e</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2, 10e</td>
</tr>
<tr>
<td>4a,4e</td>
<td></td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>9a</td>
<td>1.50-1.60 (m, 5H)</td>
<td>8a, 8e, 9e</td>
</tr>
<tr>
<td>10a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.60-1.72 (m, 1H)</td>
<td>Me-11, 2, 4a, 4e</td>
</tr>
<tr>
<td>5e</td>
<td>2.03 (ddd, 1H, 13, 4, 4)</td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>8e</td>
<td>2.18 (br dd, 1H, 13, 3)</td>
<td>9a, 9e, 10e(LR)$^b$</td>
</tr>
<tr>
<td>8a</td>
<td>2.30-2.40 (m, 1H)</td>
<td>9a, 9e, 13a and 13b(LR)$^b$</td>
</tr>
<tr>
<td>OMe</td>
<td>3.56 (unresolved q, 3H, $^5J_{F-H} = 1$)</td>
<td>8a(LR)$^b$, 13b</td>
</tr>
<tr>
<td>13a</td>
<td>4.62 (br s, 1H)</td>
<td>8a(LR)$^b$, 13a</td>
</tr>
<tr>
<td>13b</td>
<td>4.83 (br s, 1H)</td>
<td>8a(LR)$^b$, 13a</td>
</tr>
<tr>
<td>2</td>
<td>4.96 (dd, 1H, 10, 10)</td>
<td>1, 3</td>
</tr>
<tr>
<td>$m_-$ and $p$-H’s</td>
<td>7.35-7.40 (m, 3H)</td>
<td>o-H’s</td>
</tr>
<tr>
<td>o-H’s</td>
<td>7.60-7.64 (m, 2H)</td>
<td>$m_-$ and $p$-H’s</td>
</tr>
</tbody>
</table>

a No correlation.

b (LR) = Long range coupling.
Table 2.12: 400 MHz $^1$H NMR Chemical Shift Difference Between the Esters 171 and 172

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR 171 $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>$^1$H NMR 172 $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>$\Delta \delta$ (ppm) $^1$H 172-8 171</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-11</td>
<td>0.86 (d, 3H, 7)</td>
<td>0.77 (d, 3H, 6.5)</td>
<td>-0.09</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.11 (s, 3H)</td>
<td>1.14 (s, 3H)</td>
<td>0.03</td>
</tr>
<tr>
<td>10e</td>
<td>1.16 (br dd, 10, 3)</td>
<td>1.35 (br d, 13)</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>4.96 (dd, 1H, 10, 10)</td>
<td>4.92 (dd, 1H, 10, 10)</td>
<td>-0.04</td>
</tr>
</tbody>
</table>

Table 2.13: $^{13}$C NMR Chemical Shift Difference Between the Esters 171 and 172

<table>
<thead>
<tr>
<th>Assignment (C-X)</th>
<th>171 (75.3 MHz) $\delta$ ppm</th>
<th>172 (125.3 MHz) $\delta$ ppm</th>
<th>$\Delta \delta$ (ppm) $^{13}$C 172-8 171</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-11</td>
<td>18.98</td>
<td>18.56</td>
<td>-0.42</td>
</tr>
<tr>
<td>10</td>
<td>21.31</td>
<td>21.53</td>
<td>0.22</td>
</tr>
<tr>
<td>4</td>
<td>21.57</td>
<td>21.79</td>
<td>0.22</td>
</tr>
<tr>
<td>9</td>
<td>29.14</td>
<td>29.08</td>
<td>-0.06</td>
</tr>
<tr>
<td>Me-12</td>
<td>30.00</td>
<td>30.09</td>
<td>0.09</td>
</tr>
<tr>
<td>8</td>
<td>36.34</td>
<td>36.40</td>
<td>0.06</td>
</tr>
<tr>
<td>3</td>
<td>38.65</td>
<td>38.58</td>
<td>-0.07</td>
</tr>
<tr>
<td>6</td>
<td>41.23</td>
<td>41.30</td>
<td>0.07</td>
</tr>
<tr>
<td>1</td>
<td>48.01</td>
<td>48.15</td>
<td>0.14</td>
</tr>
<tr>
<td>OMe</td>
<td>55.41</td>
<td>55.21</td>
<td>-0.20</td>
</tr>
<tr>
<td>2</td>
<td>79.30</td>
<td>79.68</td>
<td>0.38</td>
</tr>
<tr>
<td>13</td>
<td>108.74</td>
<td>108.70</td>
<td>-0.04</td>
</tr>
<tr>
<td>7</td>
<td>149.82</td>
<td>149.90</td>
<td>0.08</td>
</tr>
</tbody>
</table>

An empirically-derived correlation of configuration with $^1$H NMR chemical shifts for diastereomeric $\alpha$-methoxy-$\alpha$-trifluoromethylphenylacetates has been developed by Dale and Mosher.$^{114}$ Their empirical correlation is described in Scheme 2.11. They
have made a number of (R)- and (S)-MTPA-esters and have observed that a correlation can be made between the theoretical conformations\textsuperscript{116} 173 and 174 and the NMR chemical shift differences between the substituents L\textsuperscript{2} and L\textsuperscript{3}. They discovered that the NMR signal due to L\textsuperscript{3} of 173 was consistently observed at lower field than that of 174 while the reverse trend was observed for the NMR signals due to L\textsuperscript{2} of 173 and 174.

The results obtained with the MTPA esters 171 and 172 were in agreement with those predicted by the model of Dale and Mosher (Scheme 2.11). It was found that the signal due to Me-11 in 172 was shielded relative to that of 171 (\(\Delta\delta = -0.09\)), while the signal due to H-10e in 172 was deshielded relative to the corresponding signal in 171 (\(\Delta\delta = +0.19\)). Examination of the \(^{13}\)C NMR spectra of 171 and 172 revealed the same trend. The signals due to Me-11 and C-3 in 172 were shielded relative those of 171 (\(\Delta\delta = -0.42 \) and -0.07, respectively), while the signals due to C-1 and C-10 in 172 were deshielded relative those of 171 (\(\Delta\delta = +0.14 \) and +0.22, respectively).

Two major objectives of this thesis were realized by the work described in the last section. The development of a new efficient destannylation method for \(\beta\)-trimethylstannyl ketones set the stage for further works towards the synthesis of clerodane-type natural products. Furthermore, the fact that the alcohol 165 had been obtained in enantiomerically pure form confirmed the effectiveness of the trimethylstannyl moiety as a readily removable “chiral anchor”. The next stage of this work involved verification of the generality of the destannylation procedure by carrying out this reduction on a number of trimethylstannyl ketones, alcohols and ethers.
Scheme 2.11
2.2.4. Dissolving Metal Reduction of the Trimethylstannyl Ketones 132, 133 and 102

2.2.4.1. Destannylation of Substituted 4-Trimethylstannylbicyclo[4.3.0]nonan-2-ones

The bicyclic trimethylstannyl ketones 132 and 133 were converted separately into the bicyclic alcohols 175 ([α]_D^{23} -72.4°, c = 0.716 in chloroform) and 176 ([α]_D^{23} -35.2°, c = 0.995 in chloroform) (equation 2.26) in 75% and 66% yield, respectively, using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165.

\[ \text{R = H, 132} \quad \text{R = Me, 133} \]
\[ \text{R = H, 175, 75\%} \quad \text{R = Me, 176, 66\%} \quad (2.26) \]

The IR spectrum of the bicyclic alcohol 175 exhibits absorptions at 3264, 1654, and 1033 cm\(^{-1}\), indicating the presence of a hydroxyl group and an exocyclic carbon-carbon double bond. A combination of \(^1\)H NMR, \(^{13}\)C NMR, APT experiments and comparison with the spectra of 132, 165 and 166 were used to confirm the structure of the bicyclic alcohol 175.

The \(^1\)H NMR spectrum was tentatively assigned from the chemical shifts and comparison with previous spectra. The characteristic \(^1\)H NMR resonances for 175 are due to the Me-10 doublet at δ 0.95, the Me-11 singlet at δ 0.98, a D\(_2\)O exchangeable hydroxyl proton at δ 1.31, the H-2 doublet of doublet of doublets (becomes dd with
D$_2$O, $J = 10, 10$ Hz) at $\delta$ 2.65 and the two broad olefinic signals for H-12a and H-12b at $\delta$ 4.67 and $\delta$ 4.90. The coupling constants of the signal due to H-2 after D$_2$O exchange ($J = 10, 10$ Hz) suggested that the structure and conformation of 175 is as shown below. The chemical shifts and an APT experiment were used to tentatively assign the $^{13}$C NMR spectrum of 175.

![Diagram of 175]

The IR spectrum of the bicyclic alcohol 176 exhibited absorptions due to the presence of a hydroxyl group (3326 and 1015 cm$^{-1}$) and an exocyclic carbon-carbon double bond (1655 cm$^{-1}$). A combination of $^1$H NMR, COSY, $^{13}$C NMR, APT experiments and comparison with the spectra of 132, 133, 165 and 166 were used to confirm the structure of bicyclic alcohol 176. The homonuclear correlations (COSY) are listed in Table 2.14.
Table 2.14: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Bicyclic Alcohol 176

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, $J$ (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-10</td>
<td>0.98 (d, 3H, 6.5)</td>
<td>3</td>
</tr>
<tr>
<td>4a</td>
<td>1.00-1.10 (m, 1H)</td>
<td>3, 4e, 5a, 5e</td>
</tr>
<tr>
<td>Me-11</td>
<td>1.07 (s, 3H)</td>
<td>4a, 5a</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me-10, 2, 4a</td>
</tr>
<tr>
<td>4e</td>
<td>1.25-1.40 (m, 3H)</td>
<td>5e</td>
</tr>
<tr>
<td>5a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OH</td>
<td>1.31 (d, 1H, $J = 6$ Hz)$^b$</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>1.50 (ddd, 1H, 13, 7, 3.5)</td>
<td>2, 9a, 9e</td>
</tr>
<tr>
<td>Me-13</td>
<td>1.62 (ddd, 3H, 7, 2, 2)</td>
<td>8a and 8e (LR)$^c$, 12</td>
</tr>
<tr>
<td>9a, 9e</td>
<td>1.70-1.85 (m, 2H)</td>
<td>1, 8a, 8e</td>
</tr>
<tr>
<td>5e</td>
<td>2.30 (ddd, 1H, 14, 3, 3)</td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>8a, 8e</td>
<td>2.37-2.45 (m, 2H)</td>
<td>Me-13(LR)$^c$, 9a, 9e</td>
</tr>
<tr>
<td>2</td>
<td>2.77 (ddd, 1H, $J = 10, 10, 6$)$^d$</td>
<td>OH, 1, 3</td>
</tr>
<tr>
<td>12</td>
<td>5.25 (br q, 1H, 7)</td>
<td>Me-13, 8a, 8e(LR)$^c$</td>
</tr>
</tbody>
</table>

$^a$ No correlation.
$^b$ Exchanges with D$_2$O.
$^c$ (LR) = Long range coupling.
$^d$ Becomes dd, $J = 10, 10$ Hz, with D$_2$O.

The $^1$H NMR spectrum of 176 was tentatively assigned from the chemical shifts and the homonuclear correlations. The coupling constants of the signal due to H-2
after D$_2$O exchange ($J = 10, 10$ Hz) indicated to us that the conformation of the alcohol 176 is as shown on the previous page. The $^{13}$C NMR spectrum was tentatively assigned with the assistance of the chemical shifts and an APT experiment.

### 2.2.4.2. Trimethylstannyl Cyclohexanone Destannylation

The trimethylstannyl cyclohexanone 102 was converted into the cyclohexanol 177 ([α]$_D^{24}$ +27.6°, $c = 1.125$ in chloroform) (equation 2.27) in 66% yield using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165.

The IR spectrum of cyclohexanol 177 showed absorptions assigned to a hydroxyl group (3351 and 1029 cm$^{-1}$) and a gem-dimethyl$^{117}$ moiety (1387 and 1365 cm$^{-1}$). A combination of $^1$H NMR, selective decoupling (in CDCl$_3$ and D$_2$O), COSY, $^{13}$C NMR, APT experiments, and comparison with the spectra of 102, 165 and 166 were used to confirm the structure of cyclohexanol 177. The homonuclear correlations are listed in Table 2.15.
Table 2.15: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Cyclohexanol 177

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR δ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-9</td>
<td>0.90 (s, 3H)</td>
<td>4a(LR)$^a$, 6a(LR)$^a$</td>
</tr>
<tr>
<td>Me-8</td>
<td>0.94 (s, 3H)</td>
<td>4e(LR)$^a$, 6e(LR)$^a$</td>
</tr>
<tr>
<td>Me-7</td>
<td>1.02 (d, 3H, 6)</td>
<td>2</td>
</tr>
<tr>
<td>3a</td>
<td>1.00-1.05 (m, 1H)</td>
<td>2, 3e, 4a, 4e</td>
</tr>
<tr>
<td>6a</td>
<td>1.10 (dd, 1H, 10, 12.5)</td>
<td>Me-9(LR)$^a$, 1, 6e</td>
</tr>
<tr>
<td>2</td>
<td>1.15-1.25 (m, 2H)</td>
<td>Me-7, 1, 3a, 3e</td>
</tr>
<tr>
<td>4a</td>
<td></td>
<td>Me-9(LR)$^a$, 4e</td>
</tr>
<tr>
<td>OH</td>
<td>1.27 (d, 1H, 5)$^b$</td>
<td>1</td>
</tr>
<tr>
<td>3e</td>
<td>1.28-1.33 (m, 1H)</td>
<td>2, 3a, 4a, 4e</td>
</tr>
<tr>
<td>4e</td>
<td>1.52-1.57 (m, 1H)</td>
<td>Me-8(LR)$^a$, 3a, 3e, 4a</td>
</tr>
<tr>
<td>6e</td>
<td>1.67 (ddd, 1H, 12.5, 4, 2.5)</td>
<td>Me-8(LR)$^a$, 1, 6a</td>
</tr>
<tr>
<td>1</td>
<td>3.30 (m, 1H, $w_{1/2}^c$ = 26)$^d$</td>
<td>OH, 2, 6a, 6e</td>
</tr>
</tbody>
</table>

$^a$ (LR) = Long range coupling.
$^b$ Exchanges with D$_2$O.
$^c$ $w_{1/2}$ is the width at half height of the signal in Hz.
$^d$ $w_{1/2}$ becomes 22 Hz with D$_2$O.

Selective decoupling (mixture of CDCl$_3$ and D$_2$O) of the signals of the alcohol 177 at δ 1.67 (H-6e) simplified the signals for H-6a at δ 1.10 (d, J = 10 Hz) and H-1 at δ 3.30 (br dd, J = 10, 10 Hz), thus confirming the trans, trans-arrangement of H-6a, H-1 and H-2. Irradiation of the signal at δ 3.30 (H-1) produced a doublet at δ 1.10 (H-6a, J = 12.5 Hz), doublet of doublets at δ 1.67 (H-6e, J = 12.5, 2.5 Hz) and simplified the signal at δ 1.15-1.25 (H-2). The $^{13}$C NMR spectrum of 177 was tentatively assigned by comparison with the spectra of 102, 165 and 166 and by use of an APT experiment.
2.2.5. Dissolving Metal Reduction of Trimethylstannyl Alcohols and Ethers

2.2.5.1. Preparation of the Trimethylstannyl Alcohols 178 and 179

The trimethylstannyl alcohols 178 and 179 were prepared by \( i\text{-Bu}_2\text{AlH} \) reduction of the corresponding trimethylstannyl ketones 124 and 102. Thus, treatment of the ketone 124 with \( i\text{-Bu}_2\text{AlH} \) produced the bicyclic alcohol 178 (\( [\alpha]_D^{24} = -68.6^\circ \), \( c = 1.138 \) in chloroform) in 96% yield (equation 2.28), while the reduction of 102 gave the alcohol 179 (\( [\alpha]_D^{28} = -55.0^\circ \), \( c = 1.008 \) in MeOH) in 90% yield. The bulky reducing agent approached the carbonyl moiety selectively from the less hindered face of each of the substrates 124 and 102 (\( si\)-face), as illustrated in Scheme 2.12. Attack on the \( si\)-face of the carbonyl moieties (transition states 180 and 182) suffers from less steric hindrance than the attack on the \( re\)-face (transition states 181 and 183), thus favoring the formation of products with an axial hydroxyl group.

\[
\begin{align*}
1) & \quad i\text{-Bu}_2\text{AlH} (3 \text{ equiv}) \\
& \quad -78^\circ \text{C} \rightarrow 25^\circ \text{C} \\
2) & \quad \text{NH}_4\text{Cl, H}_2\text{O} \\
& \quad 96% \\
\end{align*}
\]

\[
\begin{align*}
1) & \quad i\text{-Bu}_2\text{AlH} (3 \text{ equiv}) \\
& \quad -78^\circ \text{C} \rightarrow 25^\circ \text{C} \\
2) & \quad \text{NH}_4\text{Cl, H}_2\text{O} \\
& \quad 90% \\
\end{align*}
\]
The IR spectrum of the alcohol 178 exhibits absorptions at 3558, 1632, 1081, 764, 523 cm\(^{-1}\), indicating the presence of a hydroxyl group, an exocyclic carbon-carbon double bond and a trimethylstannyl moiety. A combination of \(^1\)H NMR, COSY, \(^{13}\)C NMR, APT experiments and comparison with the spectral data of 162 and 163 were used to confirm the structure of 178. The homonuclear correlations are listed in Table 2.16.
Table 2.16: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Bicyclic Trimethylstannyl Alcohol 178

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.10 (s, 9H, $^2J$ Sn-H = 52)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>0.91 (d, 3H, 6.5)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.10 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>5a</td>
<td>1.32 (dd, 1H, 15, 14, $^3J$ Sn-H = 14)</td>
<td>4, 5e</td>
</tr>
<tr>
<td>1</td>
<td>1.45 (br d, 1H, 5.5)</td>
<td>2, 10a, 10e</td>
</tr>
<tr>
<td>4</td>
<td>1.55 (ddd, 1H, 14, 14, 2.5, $^2J$ Sn-H = 53)</td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>3</td>
<td>1.60-1.75 (m, 3H)</td>
<td>8a, 8e, 9e, 10a</td>
</tr>
<tr>
<td>9a</td>
<td>1.71 (d, 1H, 12)$^b$</td>
<td>2</td>
</tr>
<tr>
<td>10a</td>
<td>2.03-2.16 (m, 1H)</td>
<td>1, 9a, 9e, 10e</td>
</tr>
<tr>
<td>5e</td>
<td>2.17-2.33 (m, 3H)</td>
<td>4, 5a</td>
</tr>
<tr>
<td>8e</td>
<td>2.40-2.53 (m, 1H)</td>
<td>8a, 9a, 10a</td>
</tr>
<tr>
<td>9e</td>
<td>2.40-2.53 (m, 1H)</td>
<td>8a, 9a, 9e, 13a and 13b(LR)$^c$</td>
</tr>
<tr>
<td>8a</td>
<td>3.55 (ddd, 1H, 12, 2.5, 2.5)$^d$</td>
<td>OH, 1, 3</td>
</tr>
<tr>
<td>13a</td>
<td>4.76 (br s, 1H)</td>
<td>8a(LR)$^c$, 13b</td>
</tr>
<tr>
<td>13b</td>
<td>4.83 (br s, 1H)</td>
<td>8a(LR)$^c$, 13a</td>
</tr>
</tbody>
</table>

$^a$ No correlation.  
$^b$ Exchanges with D$_2$O.  
$^c$ (LR) = Long range coupling.  
$^d$ Becomes br s with D$_2$O.

The $^1$H NMR spectrum of 178 had many similarities to that of 166. The doublet of doublet of doublets at $\delta$ 3.55 (H-2) ($J = 12, 2.5, 2.5$ Hz) collapsed to a broad singlet after D$_2$O exchange, thus establishing that H-1 and H-3 are both cis to H-2. The $^{13}$C NMR spectrum of 178 was tentatively assigned by comparison with the spectra of 165 and 166 and with the aid of an APT experiment.

The trimethylstannyl cyclohexanol 179 exhibited IR absorptions attributed to a hydroxyl group (3482 and 1071 cm$^{-1}$) and gem-dimethyl (1386 and 1363 cm$^{-1}$) and trimethylstannyl (763 and 523 cm$^{-1}$) moieties. A combination of $^1$H and $^{13}$C NMR
(C₆D₆), APT experiments and comparison with the spectral data of 177, 165, 166 and 178 were used to confirm the structure of the alcohol 179.

The width at half height (8 Hz) of the signal due to H-1 suggested a cis,cis-arrangement of the hydrogens H-2, H-1 and H-6a. The ¹³C NMR spectrum was tentatively assigned by comparison with the spectra of 177, 165, 166 and 178 and with the aid of an APT experiment.

2.2.5.2. Preparation of the Bicyclic Trimethylstannyl Methyl Ether 184

The potassium salt of the bicyclic alcohol 178 was treated with iodomethane in DMF to give the ether 184 ([α]D²⁴ +3.9°, c = 0.98 in chloroform) (equation 2.29) in 91% yield.¹¹⁸

The IR spectrum of the bicyclic ether 184 exhibits absorptions at 1640, 1461, 1093, 764 and 523 cm⁻¹, indicating the presence of an ether function, an exocyclic carbon-carbon double bond and a trimethylstannyl moiety. A combination of ¹H NMR, selective decoupling, COSY, ¹³C NMR, APT experiments and comparison with the spectral data of 165, 166 and 178 were used to confirm the structure of the ether 184. The homonuclear correlations are listed in Table 2.17.
Table 2.17: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Ether 184

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me$_3$Sn</td>
<td>0.05 (s, 9H, $^2$J$_{Sn-H}$ = 51)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>0.96 (d, 3H, 6.5)</td>
<td>3</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.06 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>5a</td>
<td>1.21 (dd, 1H, 15, 14, $^3$J$_{Sn-H}$ = 14)</td>
<td>4, 5e</td>
</tr>
<tr>
<td>1</td>
<td>1.45 (br dd, 1H, 2.5, 2.5)</td>
<td>2, 10a, 10e</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me-11, 2</td>
</tr>
<tr>
<td>4</td>
<td>1.52-1.80 (m, 4H)</td>
<td>5a, 5e</td>
</tr>
<tr>
<td>9a</td>
<td>1.90-2.12 (m, 2H)</td>
<td>8a, 8e, 9a, 10a</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>9e</td>
<td>2.15-2.25 (m, 2H)</td>
<td>4, 5a</td>
</tr>
<tr>
<td>8e</td>
<td></td>
<td>8a, 9a, 9e</td>
</tr>
<tr>
<td>8a</td>
<td>2.42 (dddd, 1H, 15, 12.5, 6, 2.5, 2.5)</td>
<td>8e, 9a, 9e, 13a and 13b(LR)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>3.12 (dd, 1H, 3.5, 2.5, $^4$J$_{Sn-H}$ = 18)</td>
<td>1, 3</td>
</tr>
<tr>
<td>MeO</td>
<td>3.38 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>13a</td>
<td>4.55 (br s, 1H)</td>
<td>8a(LR)$^b$, 13b</td>
</tr>
<tr>
<td>13b</td>
<td>4.68 (br s, 1H)</td>
<td>8a(LR)$^b$, 13a</td>
</tr>
</tbody>
</table>

$^a$ No correlation.

$^b$ (LR) = Long range coupling.
The main differences between the $^1$H NMR spectrum of 184 and that of 178 was the absence of the hydroxyl signal, the upfield shift of the signal due to H-2 to δ 3.12 from δ 3.55, and the appearance of the methoxy singlet at δ 3.38. The assignments of the $^1$H NMR spectrum were confirmed by selective decoupling experiments of the signals due to Me-11, H-5a, H-8a, and H-2, respectively. The $^{13}$C NMR spectrum of 184 was tentatively assigned by comparison with the spectra of 165 and 178, and with the aid of an APT experiment.

2.2.5.3. Preparation of the Trimethylstannylcyclohexyl SEM-Ether 185

Following a procedure reported by Lipshutz and Pegram, the trimethylstannyl alcohol 179 was treated with (2-trimethylsilyl)ethoxy)methyl chloride (SEM-Cl) and diisopropylethylamine to give the SEM-protected product 185 ($\left[\alpha\right]_D$ -68.9°, c = 1.008 in MeOH) (equation 2.30) in 88% yield.

The IR spectrum of the SEM-ether 185 indicated absorptions due to gem-dimethyl (1459 and 1364 cm$^{-1}$), ether (1101 cm$^{-1}$), trimethylsilyl (1250 and 836 cm$^{-1}$) and trimethylstannyl (764 and 523 cm$^{-1}$) moieties. A combination of $^1$H, $^{13}$C, APT NMR experiments (all in C$_6$D$_6$) and comparison with the spectral data of 102, 179 and 184 were used to corroborate the structure of the SEM-ether 185.

The main differences between the $^1$H NMR spectra of 185 and 179 was the absence of a signal due to a hydroxyl proton and the appearance of the signals due to the SEM moiety [δ 0.03 (Me$_3$Si), δ 0.99 (H-2'), δ 3.62-3.70 (H-1, H-1'), and δ 4.59 and 4.76 (two d, OCH$_2$O)] in the spectrum of 185. The $^{13}$C NMR spectrum was tentatively assigned by comparison with the spectra of 102, 179 and 184 and with the assistance of an APT experiment.
2.2.5.4. Destannylation of the Alcohol 178 and the Ether 184

When the trimethylstannyl alcohol 178 was treated with lithium in ammonia using conditions identical with those described for the transformation of 124 to 165, none of the expected bicyclic alcohol 187 was produced. The only product obtained (91% yield) was assigned the structure 186 ([α]_D^{25} -13.9°, c = 0.985 in chloroform) (equation 2.31), based on the following spectral data.

The IR spectrum of the saturated bicyclic alcohol 186 exhibits absorptions at 3515 and 1013 cm\(^{-1}\), indicating the presence of a hydroxyl moiety. A combination of \(^1\)H NMR, selective decoupling, NOE, COSY, \(^{13}\)C NMR, APT experiments and comparison with the spectral data of 124, 178 and 184 were used to confirm the structure of the saturated bicyclic alcohol 186. The homonuclear correlations are listed in Table 2.18.

The absence of signals due to olefinic protons in the \(^1\)H NMR spectrum and the presence of a second methyl doublet at higher field indicated that the carbon–carbon double bond in 178 had been reduced in addition to the carbon–tin bond.
Table 2.18: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Saturated Bicyclic Alcohol 186

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR δ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-13</td>
<td>0.74 (d, 3H, 7)</td>
<td>7</td>
</tr>
<tr>
<td>Me-12</td>
<td>0.83 (s, 3H)</td>
<td>7(LR)$^a$</td>
</tr>
<tr>
<td>Me-11</td>
<td>0.94 (d, 3H, 6)</td>
<td>3</td>
</tr>
<tr>
<td>5a</td>
<td>0.98 (ddd, 1H, 13.5, 13, 3)</td>
<td>4a, 4e, 5e</td>
</tr>
<tr>
<td>1</td>
<td>1.13-1.26 (m, 2H)</td>
<td>2, 10a, 10e</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Me-11, 4a, 4e</td>
</tr>
<tr>
<td>OH</td>
<td>1.30 (d, 1H, 4.5)$^b$</td>
<td>2</td>
</tr>
<tr>
<td>8a</td>
<td>1.35 (dddd, 1H, 13, 13, 13, 4.5)</td>
<td>7, 8e, 9a, 9e</td>
</tr>
<tr>
<td>4a, 4e</td>
<td></td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>8e</td>
<td>1.40-1.55 (m, 5H)</td>
<td>7, 8a, 9e</td>
</tr>
<tr>
<td>9a</td>
<td></td>
<td>10e</td>
</tr>
<tr>
<td>10a</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5e</td>
<td></td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>7</td>
<td>1.83-2.13 (m, 4H)</td>
<td>Me-12(LR)$^a$, Me-13, 8a</td>
</tr>
<tr>
<td>9e</td>
<td></td>
<td>8e, 9a, 10a</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>3.73 (br s, 1H)$^c$</td>
<td>OH, 1, 3</td>
</tr>
</tbody>
</table>

$^a$ (LR) = Long range coupling.
$^b$ Exchanges with D$_2$O.
$^c$ Almost no change with D$_2$O.
The results of the NOE experiments confirmed the proposed structure for 186, and the enhancements are summarized in Figure 2.7. Most importantly, irradiation of the signal assigned to Me-13 enhanced the resonances due to H-8a and H-8e, a phenomenon which could only happen if Me-13 is in the equatorial orientation (see 186a). The $^{13}$C NMR spectrum was tentatively assigned by comparison with the spectra of 124, 178 and 184 and with the aid of an APT experiment.

It is known that isolated double bonds can be reduced by dissolving metals in the presence of a good proton source at higher temperatures. When the reduced unsaturation is part of a methylenecyclohexane ring, it would be expected that the resulting methyl group would occupy the more stable, normally equatorial, orientation.$^{121}$ For example, Wai$^{121}$ reported that reduction of the phosphorodiamidate 188 (Scheme 2.13) with lithium in diethylamine in the presence of
2-methyl-2-propanol at 0 °C gave a 1:1 mixture of the desired alkene 189 and the saturated compound 190. When the temperature was decreased to -10 °C, the ratio of 189:190 was 2:1. Complete chemoselectivity was finally obtained at -20 °C in the absence of 2-methyl-2-propanol.

\[
\text{Li, EtNH}_2 \quad \text{t-BuOH} \\
\begin{align*}
0 °C, 10 \text{ min} & \quad \text{188} \\
-10 °C, 5 \text{ min} & \quad \text{189:190 2:1} \\
-20 °C, 10 \text{ min} & \quad \text{189}
\end{align*}
\]

Scheme 2.13

In our case, the ease of reduction of the carbon-carbon double bond of the bicyclic alcohol 178 is probably due to the proximity of the hydroxyl group to the double bond which could increase the rate of reduction by intramolecular protonation,\textsuperscript{122} thus permitting the reduction to occur even at -78 °C. Support for this hypothesis was obtained by destannylation of the methyl ether 184, which was treated under conditions identical with those used for 178. Thus, the expected unsaturated ether 191 ([\(\alpha\)]\textsubscript{D}\textsuperscript{24} +4.4°, c = 0.69 in chloroform) was obtained in 52% yield (equation 2.32).
The IR spectrum of the unsaturated ether 191 exhibited absorptions attributed to an ether function (1461 and 1101 cm\(^{-1}\)) and an exocyclic carbon-carbon double bond (1640 cm\(^{-1}\)). A combination of \(^1\)H NMR, selective decoupling, COSY, \(^13\)C NMR, APT experiments and comparison with the spectral data of 124, 178, 184 and 186 were used to confirm the structure of the unsaturated ether 191. The homonuclear correlations are listed in Table 2.19.
Table 2.19: The 400 MHz $^1$H NMR and COSY Data for the Bicyclic Unsaturated Ether 191

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-11</td>
<td>0.97 (d, 3H, 7)</td>
<td>3</td>
</tr>
<tr>
<td>5a</td>
<td>0.90-1.08 (m, 1H)</td>
<td>4a, 4e, 5e</td>
</tr>
<tr>
<td>Me-12</td>
<td>1.13 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>9a</td>
<td>1.35-1.45 (m, 1H)</td>
<td>8a, 8e, 9e, 10a, 10e</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>2, 10e</td>
</tr>
<tr>
<td>4a, 4e</td>
<td>1.45-1.62 (m, 4H)</td>
<td>3, 5a, 5e</td>
</tr>
<tr>
<td>10a</td>
<td></td>
<td>9a, 9e</td>
</tr>
<tr>
<td>3</td>
<td>1.75-1.85 (m, 1H)</td>
<td>Me-11, 2, 4a, 4e</td>
</tr>
<tr>
<td>9e</td>
<td>1.85-2.02 (m, 2H)</td>
<td>8a, 8e, 9a, 10a</td>
</tr>
<tr>
<td>10e</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>5e</td>
<td>2.06 (ddd, 1H, 14.5, 7.5, 4)</td>
<td>4a, 4e, 5a</td>
</tr>
<tr>
<td>8e</td>
<td>2.18-2.26 (m, 1H)</td>
<td>8a, 9a, 9e</td>
</tr>
<tr>
<td>8a</td>
<td>2.29-2.38 (m, 1H)</td>
<td>8e, 9a, 9e, 13a and 13b(LR)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>3.29-3.38 (m, 1H)</td>
<td>1, 3</td>
</tr>
<tr>
<td>OMe</td>
<td>3.33 (s, 3H)</td>
<td>.....$^a$</td>
</tr>
<tr>
<td>13a, 13b</td>
<td>4.67 (s, 2H)</td>
<td>8a(LR)$^b$</td>
</tr>
</tbody>
</table>

$^a$ No correlation.

$^b$ (LR) = Long range coupling.

Selective decoupling experiments involving signals due to Me-11, H-5a, H-3, H-5e and H-2 confirmed the $^1$H NMR assignments of 191. The $^{13}$C NMR spectrum was tentatively assigned by comparison with the spectra of 124, 178, 184 and 186 and with the assistance of an APT experiment.

2.2.5.5. Destannylation of the Trimethylstannyl Cyclohexanol 179

Treatment of the alcohol 179 with lithium in ammonia, using conditions identical with those described for the transformation of 124 to 165, produced the cyclohexanol 192 ([\(\alpha\)]$_{D}^{25}$ +2.6°, c = 1.080 in chloroform) (equation 2.33) in 70% yield. Preparation of the enantiomer of 192 (i. e. 195) has been reported by
Kergomard and coworkers.\textsuperscript{123} It was prepared in 20\% yield along with the ketone \textbf{194} by microbiological reduction (\textit{Beauveria sulfurescens}) of 2,5,5-trimethylcyclohex-2-en-1-one \textbf{193} (equation 2.34). The optical rotation of \textbf{195} was \([\alpha]_{578}^2 -11^\circ\), \(c = 0.027\) in chloroform.\textsuperscript{123} The alcohol \textbf{192} had the same magnitude of rotation with the opposite sign (\([\alpha]_{578}^2 +11^\circ\), \(c = 0.040\) in chloroform),\textsuperscript{124} thus supporting our assignment.

\[\begin{align*}
\text{OH} & \quad \text{"Li"} \quad 70\% \quad \text{OH} \\
179 & \quad \downarrow \quad \downarrow \\
\text{SnMe}_3 & \quad 192
\end{align*}\]  
(2.33)

\[\begin{align*}
\text{Beauveria sulfurescens} & \quad 10\text{ days} \quad \text{193} \\
\downarrow & \\
33\% & \quad + & \quad 47\% \quad + \quad 20\%
\end{align*}\]  
(2.34)

The IR spectrum of the cyclohexanol \textbf{192} exhibits absorptions at 3367, 1387, 1366 and 1068 cm\(^{-1}\), indicating the presence of a hydroxyl group and a \textit{gem}-dimethyl moiety. A combination of \(^1\text{H} \text{NMR}, \text{COSY}, \ ^{13}\text{C} \text{NMR}, \text{APT} \text{experiments and comparison with the spectral data of 102, 177 and 179} \text{ were used to establish the structure of cyclohexyl alcohol 192. The homonuclear correlations of 192 are listed in Table 2.20.}
Table 2.20: The 400 MHz $^1$H NMR and 200 MHz COSY Data for the Cyclohexyl Alcohol 192

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR (400 MHz) $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-8$^a$</td>
<td>0.97 (s, 3H)</td>
<td>.....$^b$</td>
</tr>
<tr>
<td>Me-7</td>
<td>0.93 (d, 3H, 7)</td>
<td>2</td>
</tr>
<tr>
<td>Me-9$^a$</td>
<td>0.99 (s, 3H)</td>
<td>.....$^b$</td>
</tr>
<tr>
<td>4a</td>
<td>1.07-1.15 (m, 1H)</td>
<td>3a, 3e, 4e</td>
</tr>
<tr>
<td>OH</td>
<td>1.21 (d, 1H, 4.5)$^c$</td>
<td>1</td>
</tr>
<tr>
<td>3a, 3e</td>
<td></td>
<td>2, 4a</td>
</tr>
<tr>
<td>4e</td>
<td>1.33-1.60 (m, 5H)</td>
<td></td>
</tr>
<tr>
<td>6a, 6e</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.82 (m, 1H)</td>
<td>Me-7, 3a, 3e</td>
</tr>
<tr>
<td>1</td>
<td>3.88 (dddd, 7, 4.5, 4, 4, 1H)$^d$</td>
<td>OH, 6a, 6e</td>
</tr>
</tbody>
</table>

$^a$ Me-8 and Me-9 can be interchanged.
$^b$ No correlation.
$^c$ Exchanged with D$_2$O.
$^d$ Becomes ddd, $J = 7, 4, 4$ Hz with D$_2$O.

The examination of the $^1$H NMR spectrum of 192 (with D$_2$O) revealed that H-1 had the expected equatorial orientation. The $^{13}$C NMR spectrum was tentatively assigned by comparison with the spectra of 102, 177 and 179 and with the aid of an APT experiment.

2.2.5.6. Destannylation of the Trimethylstannylcyclohexyl SEM-Ether 185

Reaction of the SEM-ether 185 with lithium in ammonia under conditions identical with those described for the transformation of 124 to 165 provided the cyclohexyl SEM-ether 196 ([α]$_D^{25}$ -4.8°, c = 1.005 in chloroform) (equation 2.35) in 85% yield.
The SEM-ether 196 displayed IR absorptions due to a gem-dimethyl function (1462 and 1366 cm\(^{-1}\)), an ether group (1103 cm\(^{-1}\)) and a trimethylsilyl moiety (1250 and 836 cm\(^{-1}\)). A combination of \(^1\)H NMR, COSY, \(^{13}\)C NMR, APT experiments and comparison with the spectral data of 102, 179 and 185 were used to confirm the structure of 196. The homonuclear correlations are listed in Table 2.21.

Table 2.21: The 400 MHz \(^1\)H NMR and 200 MHz COSY Data for the Cyclohexyl SEM-Ether 196

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>(^1)H NMR (400 MHz) δ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me(_3)Si</td>
<td>0.01 (s, 9H)</td>
<td>b</td>
</tr>
<tr>
<td>Me-8(^a)</td>
<td>0.89 (s, 3H)</td>
<td>b</td>
</tr>
<tr>
<td>Me-7</td>
<td>0.90 (d, 3H, 7)</td>
<td>2</td>
</tr>
<tr>
<td>2(^')</td>
<td>0.90-0.95 (m, 2H)</td>
<td>1(^')</td>
</tr>
<tr>
<td>Me-9(^a)</td>
<td>0.95 (s, 3H)</td>
<td>b</td>
</tr>
<tr>
<td>4a</td>
<td>1.03-1.12 (m, 1H)</td>
<td>3a, 3e, 4e</td>
</tr>
<tr>
<td>6e</td>
<td>1.25 (dd, 1H, 13.5, 4)</td>
<td>6a, 1</td>
</tr>
<tr>
<td>3a</td>
<td>1.35 (ddd, 1H, 13.5, 10, 4)</td>
<td>2, 3e, 4a, 4e</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>2, 3a, 4a</td>
</tr>
<tr>
<td>4e</td>
<td>1.40-1.56 (m, 3H)</td>
<td></td>
</tr>
<tr>
<td>6a</td>
<td></td>
<td>1, 6e</td>
</tr>
<tr>
<td>2</td>
<td>1.83-1.93 (m, 1H)</td>
<td>Me-7, 3a, 3e</td>
</tr>
<tr>
<td>1(^')</td>
<td>3.58-3.67 (m, 2H)</td>
<td>2(^')</td>
</tr>
<tr>
<td>1</td>
<td>3.74 (ddd, 8, 4, 4, 1H)</td>
<td>6a, 6e</td>
</tr>
<tr>
<td>OCH(_2)O</td>
<td>4.62-4.70 (two d, 8, 1H)</td>
<td>b</td>
</tr>
</tbody>
</table>

\(^a\) Me-8 and Me-9 can be interchanged.
\(^b\) No correlation.
The $^{13}$C NMR spectrum of 196 was tentatively assigned by comparison with the spectra of 102, 177, 179 and 185 and with the assistance of an APT experiment.

The generality of the dissolved metal destannylation reaction was successfully demonstrated in this last section. Trimethylstannyl compounds containing alkene, carbonyl, hydroxy, methyl ether and SEM-ether functions have been efficiently destannylationed. Having disclosed both the usefulness and the generality of the use of the trimethylstannyl anchor for the formation of enantiomerically-pure compounds, we set out to prepare the synthetically useful bicyclic trans-fused and cis-fused bicyclic ketones 17 and 47, respectively.
2.3. PREPARATION OF *trans*-FUSED AND *cis*-FUSED KETONES 17 AND 47

2.3.1. Oxidation of the Bicyclic Alcohol 165

Following a procedure reported by Ley and coworkers,\textsuperscript{125} the bicyclic alcohol 165 was oxidized to the *cis*-fused ketone 47 ([\(\alpha\])\textsubscript{D}\textsuperscript{25} -32.6°, c = 1.175 in chloroform) (equation 2.36) with N-methylmorpholine N-oxide (NMO) in the presence of a catalytic amount of tetrapropylammonium perruthenate (TPAP). The product 47 was obtained in 96% yield, free of any detectable amount of isomers resulting from epimerization.

A combination of IR, \(^1\)H NMR, \(^{13}\)C NMR, APT experiments and comparison with the spectral data of the racemic ketone 47 reported by Wai\textsuperscript{126} was used to confirm the structure of the optically active ketone 47.\textsuperscript{69}

The spectral data of the enantiomerically pure bicyclic ketone 47 were consistent with those reported by Wai.\textsuperscript{127} The \(^{13}\)C NMR spectrum was tentatively assigned by comparison with the spectra of 124 and 165 and with the assistance of an APT experiment.

Following a procedure of Wai,\textsuperscript{127} the ketone 47 was treated with potassium tert-butoxide in 2-methyl-2-propanol to give a mixture (73% yield) of the *trans*-fused ketone 17 and the *cis*-fused ketone 47, in a ratio of 94:6, respectively, as established by \(^1\)H NMR spectroscopy (equation 2.37). The two ketones were separated by means of radial chromatography.\textsuperscript{128}
A combination of IR, $^1$H NMR, $^{13}$C NMR, and APT experiments was used to confirm the structure of the trans-fused ketone 17. The spectral data of the bicyclic ketone 17 agreed very well with those reported by Wai. The $^{13}$C NMR spectrum was tentatively assigned by comparison with the spectra of 124, 165 and 47 and with the assistance of an APT experiment.

The next step in this research program was to demonstrate the synthetic utility of the enantiomerically pure ketones 17 and 47 for the synthesis of trans- and cis-clerodane diterpenoids. Before discussing the syntheses, we will discuss and summarize the circular dichroism (CD) spectra of the CD-active compounds obtained in the course of our work.
2.4. CIRCULAR DICHROISM

2.4.1. General

Circular dichroism (CD) is a powerful chiroptical method that can, if used properly, give valuable information about the absolute configuration of a compound or its conformation. The subject of CD has been reviewed,\textsuperscript{129} and therefore only the basic principles will be described.

A circular dichroism spectrum is the plot of the difference in absorption by a chromophore of left and right polarized electromagnetic radiation versus the wavelength of the radiation. A non-zero signal is observed when the chromophore is located in an asymmetric environment, and such a chromophore is called a chirophore. This phenomenon of differential absorption is also called a Cotton effect, and was first observed in optical rotatory dispersion (ORD) spectra. The CD spectrum of a chirophoric compound will have the same magnitude but the opposite sign to that of its enantiomer. The most studied chirophores by CD are carbonyl groups, probably because they absorb in an accessible wavelength range,\textsuperscript{130} and because of their widespread occurrence in natural products. The absolute stereochemistry of new carbonyl compounds can be assigned with a very good level of certainty on the basis of the comparison of their CD data with the data available in the voluminous literature on the subject.\textsuperscript{131}

A set of empirical rules has been developed for the determination of the absolute stereochemistry of ketones, enones and esters.\textsuperscript{131} The rules were first developed to predict accurately the absolute stereochemistry of cyclohexanone derivatives. The analysis of the CD spectra of the ketones 17 and 47 will serve to illustrate the use of the octant rule for the confirmation of absolute stereochemistry.
2.4.2. Circular Dichroism and Structure Relationships: The Octant Rule

The octants are divisions of the space around the π-orbitals of the carbonyl moiety based both on experimental results and theoretical considerations of the interaction of polarized electromagnetic radiation with the charge distribution of the interacting orbitals. The octants for a cyclohexanone derivative are shown in Figure 2.8. The carbonyl group is centered along the z axis where the x and y axes intersect. The C1, C2 and C6 carbon atoms of the cyclohexanone lie in the yz plane, while C3, C4 and C5 sit above the yz plane. When one or more of the hydrogens attached to C2, C3, C5 or C6 are replaced by a substituent that creates an asymmetric molecule, the octant rule is stated as: "The sign of the 300-nm Cotton effect for chiral ketones is positive if the bulk of the dissymmetric environment of the carbonyl chromophore lies in the far lower right or far upper left octants, and negative if in the far lower left and far upper right octants." Since the front four octants are almost never occupied, the octant rule can be redrawn as in Figure 2.9. The point of view is now along the z-axis through the carbonyl group. The orientations of the substituents on the cyclohexanone are indicated with the markers ax (axial orientation) and eq (equatorial orientation). The substituents on the x and y axes (C2-eq, C4-ax, C4-eq and C6-eq) are generally considered to make no contribution to the Cotton effect.
Exceptions to the octant rule are known.\textsuperscript{133} Normally a substituent contributes to the Cotton effect in a manner that is in a direct relationship to the sign of the octant where the substituent is located. Such a substituent is called consignate. Some substituents, such as fluorine and Me$_3$N$^+$, show antiocquant behavior and are therefore called dissinate.
2.4.3. **Circular Dichroism Measurements and Absolute Stereochemistry of Ketones**

2.4.3.1. **The Circular Dichroism Spectrum of the trans-Fused Bicyclic Ketone 17**

Redrawing of the *trans*-fused ketone 17 according to the rules of the simplified octant (Figure 2.10), one can predict that the sign of the Cotton effect should be positive, since the bulk of the molecule lies in a positive octant. Experimentally, the CD absorption of 17 measured in chloroform was in good agreement with this prediction. The specific ellipticity, $\left[\psi\right]_{299.5}^{25}$, was measured to be $+5194$ (DE = +3.0) for the ketone 17.\textsuperscript{134,135} The CD spectrum of the ketone 17 is shown in Figure 2.12.

![Figure 2.10](image)

**Figure 2.10** Representation of the Rear Octants of the Ketone 17

2.4.3.2. **The Circular Dichroism Spectrum of the cis-Fused Bicyclic Ketone 47**

The octant rule prediction for the bicyclic ketone 47 is complicated by the existence of two possible chair-chair conformations 47\textsuperscript{a} and 47\textsuperscript{b} (equation 2.38). Both conformations must be examined to determine their relative populations, and thus their contributions to the Cotton effect. The conformation 47\textsuperscript{a}, with two sp\textsuperscript{3}-sp\textsuperscript{3}, two gauche sp\textsuperscript{2}-sp\textsuperscript{3} and one sp\textsuperscript{2}-sp\textsuperscript{2} carbon-carbon interactions ($2 \times 0.9 - 3 \times 0.5$ kcal/mol\textsuperscript{136} = $-3.3$ kcal/mol [13.8 kJ/mol]), is more stable than the conformation 47\textsuperscript{b} with one gauche sp\textsuperscript{2}-sp\textsuperscript{3}, three gauche sp\textsuperscript{3}-sp\textsuperscript{3} and one 1,3-diaxial Me-CH\textsubscript{2} (sp\textsuperscript{3}-sp\textsuperscript{3}) carbon-carbon interactions ($-0.5 + 3 \times 0.9 + 3.7$ kcal/mol = $-6.9$ kcal/mol [28.9 kJ/mol]).
With a free energy difference ($\Delta G^\circ$) calculated to be approximately 3.6 kcal/mol [15.1 kJ/mol], conformer 47a should be the major contributor to the Cotton effect. Thus, the sign of the Cotton effect was predicted to be negative, as shown in Figure 2.11. In accordance with the prediction, the CD of 47 in chloroform was found to be $\left\langle \Psi \right\rangle_{302.825} = -477.1 (\Delta \varepsilon = -0.28)$. The CD spectra of the ketone 47 is shown in Figure 2.12. The amplitude of the specific ellipticity of the ketone 47 was multiplied by a factor of ten (10) for better comparison with that of the ketone 17.

Figure 2.11 Representation of the Rear Octants of the Ketone 47
Figure 2.12 Circular Dichroism Spectra of the trans-Fused and cis-Fused Ketones 17 and 47 (amplitude X 10) in CHCl₃
2.4.3.3. The Reported Circular Dichroism of β-Trimethylstannyl Cyclohexanones

Hudec reported the first CD spectra of cyclic β-trimethylstannyl ketones.\(^{53}\) Hudec prepared (3\(R\),5\(S\))-5-methyl-3-trimethylstannylcylohexanone (197) [from (-)-(\(R\))-5-methyl-2-cyclohexen-1-one (55)] and (1\(R\),5\(R\),6\(S\))-6-methyl-5-trimethylstannylbicyclo[4.4.0]decan-3-one (199) [from (1\(R\),6\(R\))-6-methylbicyclo[4.4.0]dec-4-en-3-one (198)] (equation 2.39), and then studied the CD spectra of those compounds.

![Chemical structures](image)

Two major CD absorption bands were observed for the ketones 197 and 199. A strong absorption at 294–298 nm, and a weaker one of opposite sign, at 220–229 nm were supposedly due to a \(n\rightarrow\pi^\ast\) transition. Because the symmetry of the transitions are opposite (\(n_\alpha\rightarrow\pi^\ast\) at ~225 nm, \(n_\sigma\rightarrow\pi^\ast\) at ~296 nm), the signs of their respective Cotton effects are also opposite. Hudec assumed that ketone 197 exists mainly in the conformation 197\(a\) and not 197\(b\). He predicted that the sign of the Cotton effect would be positive since the bulk of the molecule (Me\(3\)Sn moiety) was in a positive octant (Figure 2.13). Kitching and coworkers have shown,\(^{80}\) using C-Sn coupling constants and by LiAlH\(_4\) reduction, that the ketone 197 actually exists as a mixture of the conformers 197\(a\) and 197\(b\) in a 3:2 ratio. Thus, the conformation 197\(b\), having a negative Cotton effect (because the Me\(3\)Sn group occupies a negative octant) (Figure 2.14) should decrease the value of the specific ellipticity of 197. The observed specific ellipticity of ketone 197 was positive at 298 nm and
negative at 220 nm thus confirming Hudec's prediction. Surprisingly, the Cotton effects were quite strong \([ \Psi ]_{298} = +7813 (\Delta \varepsilon = +6.51)\) and \([ \Psi ]_{220} = -10873 (\Delta \varepsilon = -9.06)\). This observation was more fully understood by the study of the CD spectrum of the ketone 199.

![Figure 2.13](image1.png) **Figure 2.13** Representation of the Rear Octants of the Conformer 197a

![Figure 2.14](image2.png) **Figure 2.14** Representation of the Rear Octants of the Conformer 197b

The ketone 199 (R = Me3Sn) was predicted to have a positive Cotton effect because the Me3Sn moiety, the most polarizable group on 199, lies in a positive octant (**Figure 2.15**).\(^{137}\) The experimental results were not in agreement with those predicted: the specific ellipticities were \([ \Psi ]_{294} = -1504 (\Delta \varepsilon = -1.50)\) and \([ \Psi ]_{229} = +552 (\Delta \varepsilon = +0.55)\). The structurally related ketone 200 (with R = H) had a slightly smaller Cotton effect than 199 \([ \Psi ]_{289} = -2461, \Delta \varepsilon = -1.24\). Hudec concluded from these results, and from his previous results with nitrogen derivatives, that the \(\beta\)-trimethylstannyl moiety on a cyclohexanone is strongly consignate when equatorially-oriented and weakly dissignate when axially-oriented. This conclusion explains why the Cotton effect of the trimethylstannyl cyclohexanone 197 is relatively strong, since both conformers might be contributing, in a positive sense, to the Cotton effect.
Hudec explained the unusual consignate-dissignate behavior of the trimethylstannyl moiety by the existence of a strong through-bond coupling of the carbon-tin σ-bond orbital with the π-orbitals of the carbonyl group. Our results from conformationally and stereochemically less ambiguous models support Hudec's reports on the strongly consignate equatorial and weakly dissigane axial CD behavior of the Me₃Sn group in β-trimethylstannyl cyclo-hexanones.

![Figure 2.15](image)

**Figure 2.15** Representation of the Rear Octants of the Ketones 199 and 200

### 2.4.3.4. The Circular Dichroism of β-Trimethylstannyl Cyclohexanones

The CD measurements of the β-trimethylstannyl cyclohexanones prepared during the studies described in this thesis are listed in Table 2.22. The CD spectrum of the trimethylstannyl cyclohexanone 92 is representative of the CD spectra of the trimethylstannyl ketones obtained during the work presented in this thesis and the spectrum is shown in Figure 2.16. As in Hudec's pioneering work, two Cotton effects of opposite sign were observed in all cases; a positive low energy transition at 298–308 nm and a negative higher energy transition at 221–236 nm. The value of the long wave circular dicroism (Δε) of the substrates with an equatorially-oriented trimethylstannyl moiety is strong, with values ranging from +12.84 to +16.48. The circular dicroisms of the ketones 92 and 102 (+15.79 and +16.48) demonstrates, as suggested by Hudec, that the equatorially-oriented trimethylstannyl group is strongly consignate. The comparatively low intensity of Δε of 197 (+6.51) can be accounted for since 40% of its ellipticity contribution comes from the conformation 197b, with a weakly dissigane axial trimethylstannyl group.
The circular dicroism of the conformationally unambiguous ketone 93 (see discussion in section 2.1.1.2) is +0.85 (Table 2.22) while the circular dichroism of the corresponding ketone 201 with the Me₃Sn moiety replaced by a hydrogen is +0.62. Because the value of the circular dichroism of the ketone 93 is greater than that of ketone 201, the weakly dissinate character of the axial trimethylstannyl moiety as stated by Hudec is confirmed.

The circular dicroism of each of the ketones 100, 126, 117 and 121 (Table 2.22) is smaller than that of either 92 and 102. This result can be explained by the negative contribution to the Cotton effect of the halo alkene side chain, which probably resides in a negative octant. When the steric bulk of the alkene side chain is reduced (removal of a halogen atom), as in the cyclized products 124, 132 and 133, the magnitude of the circular dicroisms are increased. The ketone 130, with both negatively and positively contributing side chains, has a stronger Cotton effect than the corresponding cyclized ketone 124 (Δε = +16.08 vs. +15.04).

The intensities of the high energy transitions varied more than those of the low energy transitions. This variability of the short wave values may be attributed to the fact that in this area of the spectrum, there is a high level of noise due to the UV absorption of the substrates and the solvent (e.g. see the increase in absorbance in the region of 220–225 nm of the ketone 92 in Figure 2.16).
Table 2.22: Circular Dichroism of β-Trimethylstannyl Cyclohexanones

<table>
<thead>
<tr>
<th>Structure</th>
<th>Rear Octants Representation</th>
<th>Substituents Structure #</th>
<th>Long Wave $\Psi \lambda$</th>
<th>Short Wave $\Psi \lambda$</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Rear Octants Representation 1" /></td>
<td>R = H: 92</td>
<td>+18030 (+15.79)</td>
<td>-6789 (-5.95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R = Me: 102</td>
<td>+17950 (+16.48)</td>
<td>-7454 (-6.84)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Structure 2" /></td>
<td><img src="image4.png" alt="Rear Octants Representation 2" /></td>
<td>n = 2, X = Cl, R = H 100</td>
<td>+10820 (+12.84)</td>
<td>-2666 (-3.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 2, X = I, R = H 126</td>
<td>+9034 (+13.22)</td>
<td>-8814 (-12.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 1, X = Cl, R = H 117</td>
<td>+11630 (+13.30)</td>
<td>-6780 (-7.76)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 1, X = Cl, R = Me 121</td>
<td>+11310 (+13.42)</td>
<td>-7568 (-8.98)</td>
</tr>
<tr>
<td><img src="image5.png" alt="Structure 3" /></td>
<td><img src="image6.png" alt="Rear Octants Representation 3" /></td>
<td>n = 2, R = H 124</td>
<td>+13980 (+15.04)</td>
<td>-9123 (-9.82)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 1, R = H 132</td>
<td>+14980 (+15.48)</td>
<td>-6307 (-6.52)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 1, R = Me 133</td>
<td>+13329 (+14.34)</td>
<td>-4821 (-5.19)</td>
</tr>
<tr>
<td><img src="image7.png" alt="Structure 4" /></td>
<td><img src="image8.png" alt="Rear Octants Representation 4" /></td>
<td>130</td>
<td>+14946 (+16.08)</td>
<td>-8015 (-8.60)</td>
</tr>
<tr>
<td><img src="image9.png" alt="Structure 5" /></td>
<td><img src="image10.png" alt="Rear Octants Representation 5" /></td>
<td>93</td>
<td>+973 (+0.85)</td>
<td>-2127 (-1.86)</td>
</tr>
</tbody>
</table>

a The exact value of the wavelength of the absorption maxima is in the Experimental Section. The absorption maxima ranged between 298-308 nm.

b The exact value of the wavelength of the absorption maxima is in the Experimental Section. The absorption maxima ranged between 221-236 nm.
Figure 2.16 Circular Dichroism Spectrum of the Trimethylstannyl Ketone 92 in Methanol
2.4.4. The Circular Dichroism of Enones

Rules have been derived to infer the absolute stereochemistry of α,β-unsaturated ketones from the sign of their Cotton effect.\textsuperscript{131} The application of these rules is complicated by the difficulty in assessing the precise conformation of enones, the weakness of the carbonyl $n\rightarrow\pi^*$ absorption (normally between 320–350 nm), the fact that the CD curve often shows vibrational fine structure and is sometimes of a bisignate form.\textsuperscript{139} A modified octant rule can be applied to the CD spectra of simple enones, and it is based on the helicity of the enones. An optically active enone having the helicity illustrated in (A) (Figure 2.17) is expected to have a positive Cotton effect for the $n\rightarrow\pi^*$ absorption at 320–350 nm. The helicity rule representation (A) for an enone in a half-chair conformation can be translated into the octant representation (B). The sign of the 320–350 nm transition is fixed by the antioctant behavior (dissignate) of the double bond. The enantiomeric relationship is illustrated by (C) and (D).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{helicity规则和反向八面体代表法.png}
\caption{Helicity Rule and Rear Octants Representations for Enones}
\end{figure}
2.4.4.1. The Circular Dichroism of (-)-(R)-5-methyl-2-cyclohexen-1-one (55)

A bisignate CD curve was observed for the enone 55 for the n→π* transition with specific ellipticities values of -428 at 353 nm (Δε = -0.14) and +377 at 316 nm (Δε = +0.13). A negative Cotton effect could be inferred by the application of the modified octant rule to the half-chair conformation 55 (Figure 2.18). The experimental results are therefore consistent with the predicted absolute configuration.

![Figure 2.18 Rear Octants Representation for the Enone 55](image)

2.4.4.2. The Circular Dichroism of (-)-(5R, 6R)-3,6-Dimethyl-5-trimethylstannyl-2-cyclohexen-1-one (64)

Analysis of the CD spectrum of the trimethylstannyl cyclohexenone 64 by means of the modified octant rule (Figure 2.19) predicts a positive Cotton effect because the dissignate double bond is present in the negative octant. The experimental value of the specific ellipticity of 64 was positive as expected, but was unusually large ([Ψ]290nm = +2365, Δε = +2.06). The magnitude of the measured ellipticity probably results from the contribution of the dissignate enone double bond and the strongly consignate contribution of the trimethylstannyl moiety to the Cotton effect.

![Figure 2.19 Rear Octants Representation for the Enone 64](image)
2.4.5. The Circular Dichroism of the MTPA-Esters 171 and 172

The CD spectrum of methyl (S)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoate (202) has been studied by Djerassi and coworkers. It was found that the specific ellipticity (or $\Delta\varepsilon$) values were very dependent on solvent and temperature, while the wavelength of the absorption varied only slightly. The sign of the Cotton effect was independent of the measurement conditions. The transitions between 253–280 nm were assigned to the phenyl ring, and the transition at 230–250 nm was attributed to the ester carbonyl.

![Chemical Structure of 202](image)

The specific ellipticities of the MTPA-esters are listed in Table 2.23. The sign and the amplitude of the Cotton effects of the bicyclic ester 171 correlate well with those of the methyl ester 202.

An almost enantiomeric relationship is observed between the sign of the Cotton effects of the methyl ester 202 and the bicyclic ester 172 (Table 2.23). The wavelength of absorption due to the carbonyl moiety of 172 is longer than expected and the value of the circular dicroism is weaker than expected. It is obvious that the contribution of the asymmetric bicyclic moiety to the Cotton effect of the carbonyl group is responsible for this observed difference.
Table 2.23: Specific Ellipticity and Circular Dichroism of the MTPA-Esters 171, 172 and 202

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ester Absorption</th>
<th>Phenyl Ring Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 171" /></td>
<td>[ \Psi ]_{233} = -1867&lt;sup&gt;a&lt;/sup&gt; [ \Delta \varepsilon ] = -2.32</td>
<td>[ \Psi ]_{256} = +235 [ \Delta \varepsilon ] = +0.29</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Structure 202" /></td>
<td>[ \Psi ]_{263} = +400 [ \Delta \varepsilon ] = +0.50</td>
</tr>
<tr>
<td></td>
<td>[ \Psi ]_{269} = +307 [ \Delta \varepsilon ] = +0.38</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ester Absorption</th>
<th>Phenyl Ring Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 172" /></td>
<td>[ \Psi ]_{230} = -2981&lt;sup&gt;b&lt;/sup&gt; [ \Delta \varepsilon ] = -2.24</td>
<td>[ \Psi ]_{256} = +161&lt;sup&gt;c&lt;/sup&gt; [ \Delta \varepsilon ] = +0.12</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Structure 202" /></td>
<td>[ \Psi ]_{261} = +268&lt;sup&gt;b&lt;/sup&gt; [ \Delta \varepsilon ] = +0.20</td>
</tr>
<tr>
<td></td>
<td>[ \Psi ]_{269} = +157&lt;sup&gt;c&lt;/sup&gt; [ \Delta \varepsilon ] = +0.12</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Structure</th>
<th>Ester Absorption</th>
<th>Phenyl Ring Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 172" /></td>
<td>[ \Psi ]_{240} = +585&lt;sup&gt;a&lt;/sup&gt; [ \Delta \varepsilon ] = +0.73</td>
<td>[ \Psi ]_{256} = -139 [ \Delta \varepsilon ] = -0.17</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Structure 202" /></td>
<td>[ \Psi ]_{262} = -241 [ \Delta \varepsilon ] = -0.30</td>
</tr>
<tr>
<td></td>
<td>[ \Psi ]_{269} = -155 [ \Delta \varepsilon ] = -0.19</td>
<td></td>
</tr>
</tbody>
</table>

- Measured in chloroform at 29 °C.
- Measured in cyclohexane at 20 °C.
- Extrapolated from the CD curve of 202 in ether:isopentane:ethanol (5:5:2). See Figure 5 in ref 140.

The circular dichroism studies of our trimethylstannyl ketones provided confirmation, with unambiguous models, of Hudec’s report of the consignate-dissignate behavior of the trimethylstannyl moiety in \( \beta \)-trimethylstannyl-cyclohexanones. The CD results also provided supplementary evidence for the stereochemical assignments of the substances prepared during the course of our
work. The following sections of this thesis will describe the use of the optically active, stereodefined bicyclic ketones 17 and 47 as precursors for the total syntheses of the trans-clerodane diterpenoids (–)-kolavenol (65) and (–)-agelasine B (31).

2.5. TOTAL SYNTHESIS OF trans-CLERODANE DITERPENOIDS

2.5.1. Total Synthesis of (–)-Kolavenol (65)

2.5.1.1. Isolation of (–)-Kolavenol (65)

(–)-Kolavenol (65) (equation 2.40) was isolated by Misra and coworkers\textsuperscript{141} from the oleoresin of an Asian plant called \textit{Hardwickia pinata} Roxb. The structure and the absolute stereochemistry of 65 were elucidated by means of spectroscopic methods (\textsuperscript{1}H NMR, IR, MS) and chemical degradations and correlations.\textsuperscript{142} It was postulated that kolavenol is biosynthetically related to the geranylgeraniol precursor 203 (\(X = \text{P}_2\text{O}_6^{3-}\)) by rearrangement of the cation 204 (equation 2.40). Compound 65 was shown by Hubert and Wiemer\textsuperscript{143} to repel the leafcutter ant \textit{Atta cephalotes}. 

\begin{equation}
\text{203} \xrightarrow{\text{H}^+} \text{204} \xrightarrow{\text{H}} \text{65}
\end{equation}
2.5.1.2. Previous Total Synthesis of (-)-Kolavenol (65)

(-)-Kolavenol (65) has been prepared by the reduction of (-)-methyl kolavenate (33) (equation 2.41) which is available from the esterified extracts of the roots of the *Solidago* species. A formal total synthesis of (-)-kolavenol (65) has been done by Tokoroyama and coworkers who have synthesized (-)-methyl kolavenate (33) according to Scheme 2.14.

Tokoroyama's synthesis started with Ender's asymmetric alkylation of the (S)-hydrazone 205 to produce the enone 206 (Scheme 2.14). Methyllithium was added to the enone 206, and the tertiary alcohol intermediate was oxidized to yield the transposed enone 207. Compound 207 was converted into the bicyclic enone 208 using a previously reported sequence of reactions. The cyano alcohol 209 was prepared from 208 in 83% overall yield by means of a stereoselective hydrocyanation followed by reduction of the carbonyl moiety with L-Selectride® (LiB[CH(Me)C2H5]3H). At this point, all the chiral centers necessary to construct the clerodane carbon skeleton had been introduced with the required stereochemistry. The vinyl moiety of 209 was elaborated by a hydroboration reaction to install the required primary hydroxyl group. The resulting primary alcohol function was converted into the corresponding pivaloate and then the secondary alcohol was dehydrated with phosphorus oxychloride to give the bicyclic pivaloate 210. The nitrile group was reduced (i-Bu2AlH) to the imine with simultaneous removal of the pivaloate.
After acid hydrolysis of the imine, the resulting aldehyde was further reduced under Wolff-Kishner conditions to produce the angular quaternary methyl group. The primary alcohol was transformed into a mesylate and then displaced with bromide ion to give the primary bromide 211. The alkylation of the bromide 211 with lithium acetylide-ethylene diamine complex gave the acetylene derivative 212 in 71% yield. Finally, Negishi's zirconium-catalyzed carboalumination, followed by the trapping of the organoaluminum intermediate with methyl chloroformate, produced the desired (-)-methyl kolavenate (33) in 31% yield.

2.5.1.3. Synthetic Plan

As described in Scheme 1.3, it was planned to produce the clerodane skeleton 18 through the coupling of substances equivalent to synthons such as 42 or 43 with an intermediate of the type 41 (Scheme 2.15). A synthetic equivalent of 41 is the bicyclic primary iodide 213, since the iodide can be displaced by a nucleophile (like 42) or can be subjected to a lithium-iodine exchange to give an alkyl lithium species suitable for addition to an electrophile (like 43). The bicyclic iodide 213 could be prepared from the bicyclic methoxymethyl ether 214 by means of functional group manipulations. The preparation of the racemic bicyclic methoxymethyl ether 214 had been reported previously by Piers and Wai.13b
The racemic bicyclic ether 214 was synthesized from the trans-fused bicyclic ketone 17 in six steps and in an overall yield of 28% (Scheme 2.16). The conversion of the ketone 17 to the mixture of nitriles 215 (85:15 α-CN:β-CN) was effected by reaction of 17 with the potassium anion of (p-tolylsulfonyl)methyl isocyanide in 2-methyl-2-propanol and HMPA. The mixture 215 was deprotonated with i-Pr₂NLi and the resultant anion was alkylated with 2-iodo-1-methoxymethoxy ethane to produce exclusively the nitrile 216 (steric approach control). The required quaternary methyl group was prepared by a stepwise reduction of the nitrile moiety. The nitrile 216 was first transformed to the an aldehyde by reaction with i-Bu₂AlH and hydrolysis of the resulting imine. The aldehyde was then reduced with LiAlH₄ and the alcohol was converted to a phosphorodiamidate. The ether 214 was finally obtained by reduction of the amidate with lithium in methylamine.
Scheme 2.16

2.5.1.4. Synthesis of the (+)-Bicyclic Methoxymethyl Ether 214

The optically active bicyclic methoxymethyl ether 214 was prepared in four steps from the cis-fused ketone 47 using a sequence of reactions significantly modified from that reported by Piers and Wai.13b Because the reaction conditions used to convert the ketone 17 into the nitrile 215 (Scheme 2.16) were similar to those used to isomerize the ketone 47 into the ketone 17 (see equation 2.37), it was decided to convert 47 directly into the mixture of nitriles 215 (equation 2.42). It was also discovered that use of N,N-dimethylpropyl urea (DMPU) in place of the more toxic HMPA improved the yield of the reaction from 64% to 82%.
The identity of the mixture 215 was confirmed by comparison of the spectral
data of the nitriles (IR, $^1$H NMR, HRMS) with the reported data,$^{145}$ and by TLC and GLC comparison with an authentic sample of the racemic 215. The ratio of $\alpha$- and $\beta$-nitriles was determined by GLC and $^1$H NMR spectroscopy.

The mixture of nitriles 215 was not separated but was alkylated, following the
procedure described by Wai,$^{145}$ with 2-iodo-1-methoxymethoxy ethane to produce the
dicyclic ether 216 ([$\alpha$]$_D^{25}$ +56.9°, c = 1.06 in chloroform) in 94% yield (see
Scheme 2.16, vide supra). The spectral data of the ether 216 (IR, $^1$H NMR, HRMS) was in agreement with that reported by Wai. The main features of the $^{13}$C NMR spectrum were the signals assigned to the methoxy group (-ve, $\delta$ 55.37), the acetal methylene ($\delta$ 95.50), the exocyclic carbon-carbon double bond ($\delta$ 157.85 and $\delta$ 104.18) and the nitrile moiety ($\delta$ 122.32).

The bicyclic nitrile 216 was reduced with $i$-Bu$_2$AlH to afford the aldehyde 218 in 89% yield after the hydrolysis of the imine 217 (equation 2.43).$^{146}$ It was found that the yield of the aldehyde 218 was greatly reduced if the pH was too low during the hydrolysis of the aluminium salts. It was also observed that the aldehyde 218 was very unstable in chloroform that had not been filtered through flame-dried basic alumina. This acid lability of the aldehyde 218 and the imine 217 was subsequently found to be a general property of the trans-clerodanes, and will be discussed later.

The spectral data obtained for the aldehyde 218 was consistent with the
previously reported data.$^{147}$ The $^{13}$C NMR spectrum was recorded and showed characteristic signals for the methoxy group ($\delta$ 55.16), acetal methylene ($\delta$ 96.35),
exocyclic carbon-carbon double bond (δ 103.84 and δ 158.32) and aldehyde moiety (δ 206.52). The specific rotation ([α]_D^25) of the aldehyde 218 was +69.2°, c = 1.035 in chloroform, and a positive Cotton effect was observed at 311 nm ([Ψ]_311^25 = +854, Δε = +0.76). It is difficult to produce an octant representation of the aldehyde 218 that leads to an acceptable rationale for the sign of the Cotton effect.

It was proposed that the deoxygenation of the aldehyde 218 to the desired bicyclic methoxymethyl ether 214 could be effected directly using either a Wolff-Kishner or a Huang-Minlon deoxygenation reaction. Our first attempts to form the hydrazone using the Huang-Minlon reaction conditions were unsuccessful. We attributed this failure to the very hindered nature of the aldehyde moiety (see Figure 2.20). Eventually, the hydrazone 219 was prepared by heating the aldehyde 218 with anhydrous hydrazine in anhydrous diethylene glycol (equation 2.44). [DANGER, hot anhydrous hydrazine might detonate on exposure to oxygen.] The excess hydrazine and the water produced by the reaction were removed by distillation, and the resulting hydrazone was then converted to the deoxygenated ether 214 ([α]_D^25 +75.7°, c = 1.165 in chloroform) under the Huang-Minlon reaction conditions.

Figure 2.20 Representation of the Steric Hindrance of the Aldehyde 218
The spectral data of the (+)-bicyclic methoxymethyl ether 214 was in agreement with that reported by Wai. The following characteristic $^{13}$C NMR signals for the ether 214 were recorded: methoxy group ($\delta$ 55.05), acetal methylene ($\delta$ 96.38) and exocyclic carbon-carbon double bond ($\delta$ 102.75 and $\delta$ 160.35).

The (+)-bicyclic methoxymethyl ether 214 could thus be obtained optically pure, using our improved procedure, in four steps and in an overall yield of 56%. Our next goal towards the total synthesis of (-)-kolavenol (65) was the preparation of the primary iodide 213.

2.5.1.5. Preparation of the (-)-Bicyclic Primary Iodide 213

The first step in the preparation of the iodide 213 was the removal of the methoxymethyl group from the ether 214 using dimethylboron bromide. A discussion of the deprotection mechanism at this point will simplify the interpretation of our results. Guindon and coworkers have proposed the mechanism illustrated in Scheme 2.17 for the hydrolysis of methoxymethyl ethers with dimethylboron bromide. The first step of the deprotection is believed to be the complexation of the Lewis acid Me$_2$BBr with the oxygen atoms of the ether 220 to produce the complex 221. The reaction can then proceed following either pathway (A) or (B). Route (A) should lead to the oxonium salt 224 and the boron ether 225 via the complex 222. The oxonium salt 224 is probably in equilibrium with the bromomethyl ether 226; however, either compound should yield the free alcohol 227 and HBr upon treatment with water. Similarly, pathway (B) would produce the boron ether 229 and the oxonium salt 228 via the complex 223. Reaction of the ether 229 and the bromomethyl ether 230 with
water would give the same products as those produced in path (A). Guindon and coworkers have observed the bromomethyl ether 226 by $^1$H NMR spectroscopy, and they also succeeded in trapping 226 with nucleophiles (e. g. 226 + MeOH $\rightarrow$ 220). From the ratio of the free alcohol to the trapped ether, they have established that the preference for the pathway (A) over (B) for a primary methoxymethyl ether is on the order of 25:1.\textsuperscript{152}
Using Guindon’s procedure, Wai observed that the methoxymethyl moiety of the ether 214 could be hydrolyzed along with the isomerization of the exo-methylene moiety to give the alcohol 231 in high yield, free of the alcohol 232 (equation 2.45). The isomerization of the carbon-carbon double bond was probably catalyzed by the presence of traces of HBr in the dimethylboron bromide or by the HBr produced by the hydrolysis of the excess Me₂BBr.

Our attempts to reproduce Wai’s results with the optically-active ether 214 were unsuccessful. Treatment of the (+)-bicyclic methoxymethyl ether 214 with dimethylboron bromide in cold (-78°C) dichloromethane, followed by a work-up in the presence of base produced a colorless oil that turned black and released white fumes if left for too long (~1 h) at room temperature before chromatography. None of the desired alcohol was isolated from the black mixture; however a small amount of a less polar compound was observed. The same non-polar compound was isolated in 69% yield when we attempted to remove the methoxymethyl ether protecting group of 214 by heating it at 50 °C in aqueous HCl-THF for 20 h. The structure 233 was proposed for this non-polar product on the basis of the spectral data analysis and was latter confirmed by comparison with results from the literature.
IR absorptions at 1386 and 1365 cm\(^{-1}\) indicated the presence of a gem-dimethyl moiety, while absorptions at 1064 and 912 cm\(^{-1}\) were consistent with the presence of a tetrahydrofuran ring.\(^{156}\) The molecular formula of compound 233 was found to be C\(_{16}\)H\(_{28}\)O from the interpretation of the HRMS (calcd 236.2140, found 236.2147) and the elemental analysis (calcd C 81.29\%, H 11.94\%, found C 81.00\%, H 12.10\%). The \(^1\)H NMR spectrum (Figure 2.21) displayed 3 methyl singlets (\(\delta\) 0.81, 0.87 and 0.92), 1 methyl doublet that was assigned to Me-15 (\(\delta\) 0.81 \(J = 6\) Hz), and two doublet of doublet of doublets assigned to H-3a and H-3b (\(\delta\) 3.71, \(J = 3, 8.5, 10\) Hz and \(\delta\) 3.82, \(J = 8.5, 8.5, 8.5\) Hz).

The \(^{13}\)C NMR spectrum of 233 displayed 16 distinct signals in agreement with the proposed molecular formula (Table 2.24). The signals were divided into four groups based on the interpretation of the APT and the HMOC\(^{157}\) experiments. The signals of four methyl moieties were found and among them, the \(^{13}\)C NMR signal at \(\delta 17.44\) was assigned to Me-15 from analysis of the HMOC experiment. Seven methylenic carbons were identified, with the \(^{13}\)C NMR resonance at \(\delta 62.44\) assigned to C-3 on the basis of the HMOC experiment and the chemical shift. Two methines and three quaternary carbons were also observed. The \(^{13}\)C NMR signal at \(\delta 85.10\) was attributed to C-1 on the basis of its chemical shift.
### Table 2.24: Assignment of the NMR Data for the Tricyclic Ether

<table>
<thead>
<tr>
<th>Assignment (C-X)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>&lt;sup&gt;13&lt;/sup&gt;C Spectrum δ (APT)</th>
<th>HMOC&lt;sup&gt;1&lt;/sup&gt;H NMR Correlations δ (mult., # of H, J (Hz), Assignment)</th>
<th>Long Range&lt;sup&gt;1&lt;/sup&gt;H-&lt;sup&gt;13&lt;/sup&gt;C HMBC&lt;sup&gt;158&lt;/sup&gt; Correlations C-X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-14</td>
<td>13.47 (-ve)</td>
<td>0.81 (s, 3H, Me-14)</td>
<td>1, 4, 5, 6</td>
</tr>
<tr>
<td>Me-15</td>
<td>17.44 (-ve)</td>
<td>0.81 (d, 3H, 6, Me-15)</td>
<td>5, 6, 7</td>
</tr>
<tr>
<td>12</td>
<td>18.44</td>
<td>1.30-1.40 (m, 3H, H-12e)</td>
<td>1, 10, 11, 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.70 (dddd, 1H, 3, 3.5, 13, 13, 13, H-12a)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>22.10</td>
<td>1.30-1.40 (m, 3H, H-8a)</td>
<td>1, 6, 7, 9, 10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.41-1.51 (m, 3H, H-8e)</td>
<td></td>
</tr>
<tr>
<td>Me-17</td>
<td>22.37 (-ve)</td>
<td>0.94 (s, 3H, Me-17)</td>
<td>Me-16, 9, 10, 11</td>
</tr>
<tr>
<td>7</td>
<td>31.28&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00-1.20 (m, 4H, H-7a)</td>
<td>6, 8, 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.41-1.51 (m, 3H, H-7e)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>31.42&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.00-1.20 (m, 4H, H-13e)</td>
<td>9, 11, 12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.52-1.65 (m, 2H, H-13a)</td>
<td></td>
</tr>
<tr>
<td>Me-16</td>
<td>32.27 (-ve)</td>
<td>0.87 (s, 3H, Me-16)</td>
<td>Me-17, 9, 10, 11</td>
</tr>
<tr>
<td>10</td>
<td>34.09</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>35.37</td>
<td>1.52-1.65 (m, 2H, H-4b)</td>
<td>1, 3, 5, 6, Me-14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.77 (ddd, 1H, 3, 8.5, 12.5, H-4a)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>35.46 (-ve)</td>
<td>1.41-1.51 (m, 3H, H-6)</td>
<td>4, 5, 7, Me-14, Me-15</td>
</tr>
<tr>
<td>11</td>
<td>42.70</td>
<td>1.00-1.20 (m, 4H, H-11a)</td>
<td>9, 10, 12, 13, Me-16, Me-17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.30-1.40 (m, 2H, H-11e)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>47.03</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>47.91 (-ve)</td>
<td>1.00-1.20 (m, 4H, H-9)</td>
<td>7, 8, 10, 13, Me-16, Me-17</td>
</tr>
<tr>
<td>3</td>
<td>62.44</td>
<td>3.71 (ddd, 1H, 3, 8.5, 10, H-3b)</td>
<td>1, 4, 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.82 (ddd, 1H, 8.5, 8.5, 8.5, H-3a)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>85.10</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-----&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> The table reads from left to right. The assignment and the chemical shifts of the <sup>13</sup>C NMR spectrum (with the results of the APT experiments in brackets) are in the first and second columns, respectively. The third column shows the <sup>1</sup>H NMR signal(s) which correlates with the carbon of the first two columns, as obtained from the HMOC experiment (1 bond correlation). The last column lists the carbons which correlate with the <sup>1</sup>H NMR signal(s) of the third column as obtained from the HMBC experiment (2 and 3 bonds correlation).

<sup>b</sup> The assignment can be interchanged.

<sup>c</sup> No correlation.
Figure 2.21 500 MHz $^1$H NMR Spectrum of Compound 233 in CDCl$_3$
A series of selective homonuclear decouplings of the ether 233 in relation to the HMQC data provided evidence for the assignment of a few more $^{13}$C NMR signals (Table 2.24). Thus, irradiation of the signal at $\delta$ 3.82 and 3.71 induced a modification of the signals at $\delta$ 1.77 and 1.52-1.65. The two latter signals were assigned to H-4 and consequently, the $^{13}$C NMR signal for C-4 was observed at $\delta$ 35.37. Decoupling of the signals due to Me-15 simplified the resonance due to H-6 at $\delta$ 1.41-1.51 resulting in the assignment of the $^{13}$C NMR signal at $\delta$ 35.46 to C-6. The other methine carbon signal at $\delta$ 47.91 was assigned to C-9 by default and the attached hydrogen was found at $\delta$ 1.00-1.20.

Analysis of the spectral data provided the correlation of each $^{13}$C NMR signal with its respective attached proton(s). The connectivity of the carbons was established with the help of an HMBC experiment (Table 2.24). The doublet at $\delta$ 0.81 ($^1$H NMR) was correlated to a quaternary carbon at $\delta$ 47.03 (C-5), a methylene carbon at $\delta$ 31.28 (C-7) (or $\delta$ 31.42, C-13) and the methine due to C-6, thus confirming the initial assignment of C-6. The remaining quaternary carbon signal (at $\delta$ 34.09) was assigned to C-10. The methyl singlet at $\delta$ 0.81 ($^1$H NMR) showed correlations with C-1, C-4, C-5 and C-6 thus providing enough evidence to assign the methyl singlet at $\delta$ 0.81 to Me-14. The methyls at $\delta$ 0.87 and 0.94 ($^1$H NMR) both correlated to C-10, C-9 and the methylene carbon at $\delta$ 42.70 (C-11). The methyl at $\delta$ 0.87 ($^1$H NMR) had an HMBC correlation with the carbon at $\delta$ 22.37, which also had an HMQC correlation with the methyl at $\delta$ 0.94 ($^1$H NMR), thus establishing the gem-dimethyl relationship of these two groups. The hydrogen at $\delta$ 1.70 ($^1$H NMR) correlated (HMBC) with C-11 and a carbon at $\delta$ 31.42 (C-13). This hydrogen showed NOE enhancement giving a doublet of doublet of doublet of doublet of doublets (dddddd, $J$ = 3, 3.5, 13, 13, 13 Hz) when the signal at $\delta$ 0.94 was irradiated. The signal at $\delta$ 1.70 was assigned to H-12a (233) on the basis of the observed coupling constants since no other hydrogen of 233 can have three large (13 Hz) and two small (3 and 3.5 Hz) coupling constants. The preceding NOE enhancement was also used to distinguished between C-16 and C-17.
since only the axial methyl will be close enough to H-12a to show an enhancement. At this point, the $^{13}$C NMR spectrum of 233 was confidently assigned (C-8 was assigned by default) and its $^{13}$C NMR chemical shift data was compared with a series of reported examples to determine whether the ring junction was cis or trans.

The $^{13}$C NMR spectra of trans-fused compounds 234–241$^{159}$ and the cis-fused compounds 242–246$^{160}$ were assigned and reported in the literature. The average chemical shifts of the signals assigned to C-7–13 and C-16 and C-17 for both the trans and cis compounds are compared with the assigned $^{13}$C NMR signals for the ether 233 in Table 2.25.

Table 2.25: Comparison of Selected $^{13}$C NMR Signals of trans- and cis-Decalins Related to the Ether 233

<table>
<thead>
<tr>
<th>C-X</th>
<th>$^{13}$C NMR Chemical Shifts (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Trans (234–241)</strong></td>
</tr>
<tr>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>7</td>
<td>33.2–39.9</td>
</tr>
<tr>
<td>8</td>
<td>17.6–21.0</td>
</tr>
<tr>
<td>*9</td>
<td>54.3–54.9</td>
</tr>
<tr>
<td>10</td>
<td>33.0–33.3</td>
</tr>
<tr>
<td>*11</td>
<td>42.4–42.5</td>
</tr>
<tr>
<td>12</td>
<td>18.4–18.7</td>
</tr>
<tr>
<td>*13</td>
<td>42.1–42.9</td>
</tr>
<tr>
<td>Me-16</td>
<td>33.1–33.5</td>
</tr>
<tr>
<td>*Me-17</td>
<td>21.1–21.6</td>
</tr>
</tbody>
</table>
There is a significant difference between the chemical shifts of the trans- and cis-fused models at the carbon centers marked with a star (*) in Table 2.25. Two of these pairs (C-9 and C-13) were rejected because, in compound 233, these centers were close to the tetrahydrofuran ring oxygen and thus were not similar enough to be compared with those of the set of known compounds we had. However, the measured chemical shifts of C-11 and Me-17 of 233 (δ 42.7 and 22.4 respectively) had almost the same values as those of the corresponding carbons in the models compounds of the trans series. On this basis, the ring junction of the ether 233 was assigned the trans stereochemistry.

It may be proposed that 233 is formed from the acid-catalyzed rearrangement of the alcohol 231 or 232 (Scheme 2.18). Protonation of the double bond of 231 or 232 would lead to the same tertiary carbocation 247. Rearrangement of this carbocation would produce the decalin 248 with a tetrasubstituted double bond. This bond can be protonated and the new tertiary carbocation trapped with the alcohol oxygen acting as an internal nucleophilic terminator to produce 233.
A Chemical Abstract Service Structure Search® resulted in the discovery of a Russian patent by Vlad and coworkers\textsuperscript{162} for the preparation and use of compound 249 as a less expensive substitute for whale’s ambergris in the perfume industry (equation 2.46). This ether was prepared in 24% yield by the dehydration of bicyclohomofarnesane-8α,12-diol 250 catalyzed by the acidic ion exchange resin KG-23. The same workers later reported the preparation of 251 under the same reaction conditions.\textsuperscript{163} The spectral data reported for 251 were identical with those of 249 reported in the previous patent. Vlad and coworkers corrected their previous assignment of the ether 249 by a chemical correlation to the previously known ester 252. The spectral data for the ether 233 is compared with those for the ether 251 in Table 2.26, and from this comparison it can be concluded that the ether prepared by treatment of 214 with aqueous acid (\textit{vide supra}) is enantiomeric with the ether 251.

\[ 250 \xrightarrow{\text{KG-23, MeC_6H_5, reflux, 1.5 h}} 249 + \text{other products} \]  

(2.46)
Table 2.26: Comparison of the Reported Spectral Data of Ether 251 with the Data of Ether 233

<table>
<thead>
<tr>
<th>Data</th>
<th>Ether 233</th>
<th>Ether 251</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR</td>
<td>1386</td>
<td>1383</td>
</tr>
<tr>
<td></td>
<td>1365</td>
<td>1368</td>
</tr>
<tr>
<td></td>
<td>1039</td>
<td>1044</td>
</tr>
<tr>
<td></td>
<td>1023</td>
<td>1030</td>
</tr>
<tr>
<td>1H NMR CCl4</td>
<td>0.80, s, Me</td>
<td>0.80, s, Me</td>
</tr>
<tr>
<td></td>
<td>0.81, d, J = 6 Hz, Me</td>
<td>0.82, d, J = 6 Hz, Me</td>
</tr>
<tr>
<td></td>
<td>0.86, s, Me</td>
<td>0.87, s, Me</td>
</tr>
<tr>
<td></td>
<td>0.91, s, Me</td>
<td>0.92, s, Me</td>
</tr>
<tr>
<td></td>
<td>3.66, ddd, J = 3, 8.5, 10 Hz, OCH2</td>
<td>3.76, ddd, J = 8.5, 8.5, 8.5 Hz, OCH2</td>
</tr>
<tr>
<td>LRMS Analysis</td>
<td>M⁺(236), 6%</td>
<td>M⁺(236), 11%</td>
</tr>
<tr>
<td>calcd. for C₁₆H₂₈O , C 81.29%, H 11.94%</td>
<td>C 81.00%, H 12.10%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>+39.1° (18°C)</td>
<td>+39.1° (18°C)</td>
</tr>
<tr>
<td>Concentration</td>
<td>1.77</td>
<td>6.3</td>
</tr>
<tr>
<td>g/100 mL in chloroform</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The cleavage of the ether 214 with dimethylboron bromide, using the procedure of Wai, was repeated and the crude product was immediately subjected to column chromatography on silica gel. The major homogeneous fraction appeared to be unstable on TLC. The resulting oil was distilled (Kugelrohr), yielding a mixture of the alcohols 231 and 232 and a non-polar still-pot residue (see equation 2.45). The latter material, the amount of which was dependent on the work-up procedure used, was purified by flash chromatography. The molecular formula of the acquired material was found to be C₃₃H₅₆O₂ by HRMS (calcd: 484.4280, found: 484.4276) and elemental analysis (calcd: C 81.76%, H 11.64%, found: C 81.92%, H 11.72%). The analysis of the IR spectrum indicated the presence of a carbon-carbon double bond (1636 cm⁻¹) and an ether moiety (1109, 1080, 1038 and 891 cm⁻¹). The ¹H NMR spectrum displayed three dioxomethylene singlets at δ 4.55, 4.57 and 4.60, showing that the residue was not homogeneous. With the exception of the dioxomethylene...
singlets and the presence of a broad multiplet at δ 3.30–3.50, the ¹H NMR spectrum of the mixture was very similar to that of the mixture of alcohols 231 and 232. Thus, the structures 253–255 were proposed on the basis of the spectral data for the non-polar residue. The formaldehyde acetals 253–255 were probably formed by the reaction of the deprotected, partially-isomerized alcohol mixture 231 and 232 with some non-hydrolyzed bromomethylene derivatives 256 or 257 (equation 2.47) (see 226 to 220 Scheme 2.17, vide supra). The observation that the bromomethylene compounds 256 and 257 were not hydrolyzed during work-up with aqueous sodium bicarbonate-THF and chromatography was very surprising, since, according to Guindon and coworkers, no bromomethylene substances should be left after the aqueous work-up!¹⁶⁶ The mixture of formaldehyde acetals 253–255 was converted into a 1:1 mixture of the alcohols 231 and 232 in 84% yield using the reaction conditions described in equation 2.48 (DME is the acronym of 1,2-dimethoxyethane).
Attempts to minimize the formation of side products during the hydrolysis of the methoxymethyl ether moiety of 214 led to an effective procedure. Thus, treatment of 214 with dimethylboron bromide in dichloromethane at -78 °C produced a 1:4 mixture of the alcohols 231 and 232 in 86% yield, after careful work-up with sodium carbonate and sodium bicarbonate in aqueous DME (equation 2.49). The spectral data of the mixture of alcohols 231 and 232 were compared with those obtained by Wai and were found to be acceptable.167

The exocyclic carbon-carbon double bond of the remaining amount of 231 in the mixture of alcohols 231 and 232 was isomerized by treatment of the mixture with anhydrous \( p \)-TsOH in dry chloroform. The material obtained, in 93% yield, consisted of a mixture of the alcohols 231 and 232, in ratios varying from 1:52 to 1:107, as determined by integration of \( ^1H \) NMR spectra. The observed ratios of exo- and endocyclic carbon-carbon double bonds is consistent with the expected ratio calculated\(^{79}\) from the difference in energy between the two isomers 231 and 232 (\( \Delta G^\circ = -2 \text{kcal/mol} \ [8.4 \text{kJ/mol}] \)). The specific rotation ([\( \alpha \])\( _D^{25} \)) of the mixture of alcohols 231 and 232 (ratio 1:107) was -48.7° (c = 1.04 chloroform).
The alcohol 232 was converted into the iodide 213 using a modification of the procedure developed by Garregg and Samuelsson. Thus, the iodide 213 ([α]_D^{25} -45.7°, c = 1.75 in chloroform) was obtained in 90% yield after stirring a solution of the alcohol 232 with a mixture of iodine, triphenylphosphine and imidazole (equation 2.50).

Absorptions for the primary iodide moiety of compound 213 were observed in the IR spectrum at 1158 and 530 cm\(^{-1}\). A characteristic upfield signal for the iodomethylene group was observed at \(\delta 1.09\) in the \(^{13}\)C NMR spectrum of compound 213. The \(^1\)H NMR spectrum of 213 was characterized by the presence of two methyl singlets (\(\delta 0.70, \delta 0.97\)), a methyl doublet (\(\delta 0.82, J = 6\) Hz), a methyl doublet of doublet of doublets (\(\delta 1.56, J = 1.5, 1.5, 1.5\) Hz), two iodomethylene hydrogen signals (ddd, \(1H, \delta 3.02, J = 5.5, 9, 12.5\) Hz and ddd, \(1H, \delta 3.11, J = 5, 9, 12.5\) Hz) and a broad olefinic singlet (1H, \(\delta 5.18\)). The iodide 213 was free of the isomeric exo-olefin product since no other olefinic signals were observed in the \(^1\)H NMR spectrum. Having devised an efficient route for the preparation of the iodide 213 we set out to prepare the synthetic equivalents of the donor synthon 42 and the acceptor synthon 43 (see Scheme 2.15).

### 2.5.1.6. Preparation of the Synthetic Equivalent of the Synthons 42 and 43

The vinyl iodides 264 or 265 (Scheme 2.19) can be viewed as being the synthetic equivalents of both synthons 42 and 43. Thus, lithium-iodine exchange, effected by treatment of 264 and 265 with an alkyllithium reagent, would produce the corresponding nucleophilic vinyllithium species. Alternatively, 264 and 265 could be
coupled directly with a suitable nucleophilic organometallic reagent. The vinyl iodides 264 and 265 were easily prepared in four steps from ethyl 2-butynoate (258).

The first step in the synthesis was the 1,4-addition of the (trimethylstannyl)-(cyano)cuprate 87 to the butynoate 258 in the presence of ethanol (Scheme 2.19). The E-trimethylstannyl ester 259 was obtained in 79% yield, along with a small amount of the Z-trimethylstannyl ester 260.

The IR spectrum of the E-ester 259 displayed absorptions for the ester carbonyl (1715 cm\(^{-1}\)), carbon-carbon double bond (1604 cm\(^{-1}\)) and trimethylstannyl moiety (772 and 530 cm\(^{-1}\)). Similar absorptions were observed for the Z-isomer 260. Characteristic \(^1\)H NMR signals for the E-ester 259 were observed at \(\delta \) 0.17 (s, Me\(_3\)Sn) and at \(\delta \) 5.97 (q, \(J = 2 \text{ Hz, } ^3J_{\text{Sn-H}} = 74 \text{ Hz}\)) while those of the Z-ester 260 were observed at \(\delta \) 0.19 (s, Me\(_3\)Sn) and at \(\delta \) 6.40 (q, \(J = 2 \text{ Hz, } ^3J_{\text{Sn-H}} = 117 \text{ Hz}\)). The stereochemical assignments of E-ester 259 and Z-ester 260 were obtained from the \(^3J_{\text{Sn-H}}\) coupling constants between the tin atoms (average of \(^{117}\)Sn and \(^{119}\)Sn couplings) and the olefinic protons. The \(^3J_{\text{Sn-H}}\) coupling for an olefinic proton trans to
a trimethylstannyl group is in the range 87–139 Hz while the cis arrangement gives coupling in the range 47–74 Hz.\textsuperscript{171}

The E-ester 259 was reduced with \textit{i}-Bu\textsubscript{2}AlH and the resulting alcohol 261 was allowed to react with either \textit{tert}-butyldimethylsilyl chloride (TBDMSCl)\textsuperscript{172} or triisopropylsilyl chloride (TIPSCI)\textsuperscript{173} to give the TBDMS-ether 262 or the TIPS-ether 263. The ethers 262 and 263 were each treated with iodine\textsuperscript{174} to give the iodides 264 and 265 in 94% and 88% overall yield from the alcohol 261, respectively. The spectral data (IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, APT, LRMS and HRMS) and the elemental analyses were consistent with the structures proposed for compounds 261–265.

The alcohol 261 had characteristic IR absorptions at 3303 and 1006 cm\textsuperscript{-1} (hydroxyl group) and at 768 and 526 cm\textsuperscript{-1} (Me\textsubscript{3}Sn moiety). The \textsuperscript{1}H NMR spectrum displayed an olefinic signal as a quartet of triplets at \(\delta\) 5.78 (1H, \(J = 2, 6.5\) Hz) with tin-hydrogen coupling of 76 Hz, indicating that this hydrogen was \textit{cis} to the trimethylstannyl group.

The silyl ethers 262 and 263 had characteristic absorptions for the trimethylstannyl (775, 528 and 766, 528 cm\textsuperscript{-1}, respectively) and trialkylsilyl groups (1256, 838 and 1256, 883 cm\textsuperscript{-1}, respectively). The \textsuperscript{1}H NMR spectra of 262 and 263 displayed expected resonances for the olefinic hydrogens (\(\delta\) 5.68, qt, 1H, \(J = 2, 6.5\) Hz, \(3J_{\text{Sn-H}} = 76\) Hz and \(\delta\) 5.69, qt, 1H, \(J = 2, 6.5\) Hz, \(3J_{\text{Sn-H}} = 76\) Hz, respectively).

The IR spectra of the vinyl iodides 264 and 265 exhibited signals at 1639 and 1640 cm\textsuperscript{-1} (C–C double bond, respectively) and 1257, 838 cm\textsuperscript{-1} and 1255, 883 cm\textsuperscript{-1} (trialkylsilyl group, respectively). The olefinic signals for the iodides 264 and 265 were observed at \(\delta\) 6.28 (qt, 1H, \(J = 2, 6.5\) Hz) and \(\delta\) 6.31 (qt, 1H, \(J = 2, 6.5\) Hz) in their respective \textsuperscript{1}H NMR spectra.

With the vinylic iodides 264 and 265 and the vinylstannyl compounds 262 and 263 in hand, investigations into the coupling of these substances with the iodide 213 were carried out.
2.5.1.7. Attempted Coupling with the Iodide 213 Acting as an Electrophile

It was initially planned to carry out the transmetallation of the trimethylstannyl ether 262 with methyllithium and to use the resulting vinyl lithium species 266 to displace the primary iodide function in compound 213 (equation 2.51).\(^{175}\) Model studies for the coupling reaction were made with the ether 262 and the primary iodide 267. No significant amount of the coupled product 268 was obtained from the reaction of the vinyl lithium 266 with the iodide 267, and neither of the starting materials were recovered.

![Chemical structure diagram]

The vinyl iodide 264 was treated with \textit{tert}-butyllithium and coupling of the resultant lithium species with 267 in THF-HMPA was attempted (equation 2.52). Again, the reaction did not give any of the desired product 268. It was suspected that the failure of the coupling reaction was due to an unsuccessful lithiation step. This hypothesis was tested by trapping the product of the lithium-halogen exchange with TMSCl to give a mixture of compounds in only \(\sim 25\%\) yield after addition of pentane and filtration through Florisil\textsuperscript{®} (equation 2.53). Analysis of the product by \(^1\)H NMR spectroscopy showed that a mixture of the silylated compounds 269 and 270 and smaller amounts of the compounds 271 and 272 were obtained. Compound 270 is possibly formed by a lithium halogen exchange of 264 and a TBDMS hydrogen abstraction with the alkyllithium (\textit{t}-BuLi or the vinyl lithium species) followed by the trapping of the corresponding dianion with TMSCl. The vinyl hydrogen in compounds 271 and 272 may be introduced by intermolecular proton abstraction (of the TBDMS group hydrogen) or by protonation with traces of moisture. Crich and Ritchie\(^{176}\) have
reported that a methyl group attached to a silicon atom can be lithiated with tert-butyllithium. For example, compound 273 gives a mixture of the sulfides 274 and 275 upon treatment with tert-butyllithium and diphenyl disulfide (equation 2.54). To avoid this side reaction, the TIPS-ether 265 was used for the coupling, since isopropyl groups are not as readily metallated with tert-butyllithium as compared to the methyl moiety of the TBDMS group of 264. When the TIPS-ether 265 was treated with tert-butyllithium and the resulting vinyllithium species 276 was trapped with TMSCl, the vinyl silane 277 was obtained in 75% yield (equation 2.55).
The use of cuprates rather than vinyllithium reagents has been reported to effect coupling with alkyl iodides. In the course of the synthesis of maytansine, for example, Corey and coworkers\(^{177}\) have coupled the cuprate 278 with the benzylic iodide 279 to give compound 280 in 90% yield (equation 2.56). It was hoped that similar methodology could be applied to the primary iodide 213, although it must be pointed out that 213 is not as reactive as Corey’s benzylic iodide 279.

![Chemical structure](image)

The vinyllithium species 276 (equation 2.55, *vide supra*) was used to prepare nucleophilic reagents that were coupled with the iodide 213. The results of the attempted coupling of 213 with higher order cyano cuprates [obtained by adding two equivalents of 276 to CuCN or one equivalent of 276 to (2-thienyl)Cu(CN)Li (88)] were not encouraging. Alternatively, the coupling reaction was attempted with the Grignard reagent 281 in the presence of a copper(I) catalyst (CuCN or CuI)\(^{178}\) (see equation 2.57) but the yields of the desired product were unacceptable. The best results were obtained when the Grignard reagent 281 was added in an inverse fashion\(^{179}\) to a mixture of the iodide 213, tributylphosphine, tributylphosphine-copper(I) iodide complex\(^{180}\) and HMPA in THF. A mixture of non-polar products and the pure, desired TIPS-ether of (-)-kolavenol 282 (45% yield) ([α]_D^25 -39.7°, c = 1.60 in chloroform) were obtained after work up and purification (equation 2.57). The non-polar mixture was purified by TLC grade chromatography and was found to consist of recovered starting iodide 213 (70% of the non-polar mixture by GLC) and smaller amounts of the olefin 283 and the dimer 284.
Key IR absorptions for the TIPS ether 282 were observed at 1669 cm\(^{-1}\) (carbon-carbon double bond) and at 1257 and 883 cm\(^{-1}\) (triisopropylsilyl group). Five signals due to methyl groups were observed in the \(^1\)H NMR spectra of 282: three singlets at \(\delta\) 0.71, \(\delta\) 0.99 and \(\delta\) 1.61 (Me-20, 19 and 16, respectively), a doublet at \(\delta\) 0.80 \((J = 6.5\) Hz, Me-17) and a doublet of doublets at \(\delta\) 1.59 \((J = 1.5, 2\) Hz, Me-18). The signals due to the isopropyl groups and the methylene-15 (Figure 2.22) were observed between \(\delta\) 1.00-1.20 \((21\)H, m) and at \(\delta\) 4.25 \((d, J = 6\) Hz), respectively. Two olefinic protons were detected at \(\delta\) 5.20 \((br\ s, H-3)\) and \(\delta\) 5.31 \((qt, J = 1.5, 6\) Hz, H-14). The stereochemistry of olefinic chain of 282 was confirmed by the use of NOE difference experiments (Figure 2.22). Irradiation of the signal due to Me-18 led to the enhancement of the signal due to H-3 (a). Reciprocal enhancements were observed between the resonances assigned to Me-16 and the methylene-15 (b\leftrightarrow c) and the latter methylene and H-14 (d\leftrightarrow e).
The alkene 282 exhibited an IR absorption due to a carbon-carbon double bond at 1663 cm\(^{-1}\). The characteristic \(^1\)H NMR signals were: two methyl singlets (\(\delta 0.68\), Me-20 and \(\delta 0.98\), Me-19), a methyl triplet (\(\delta 0.69, J = 8.5\) Hz, Me-12), a methyl doublet (\(\delta 0.75, J = 6.5\) Hz, Me-17), a methyl doublet of doublets (\(\delta 1.55, J = 2, 2.5\) Hz, Me-18) and an olefinic hydrogen (br m, \(\delta 5.19\), H-3). The \(^{13}\)C NMR spectrum indicated the presence of 16 carbons which is in agreement with the assigned structure.

The IR and \(^1\)H NMR spectra of the dimer 284 were similar to those of 283. The major difference was the absence of the methyl triplet. The \(^{13}\)C NMR spectrum displayed only 16 resonances but the HRMS was consistent with a dimeric compound.

Although the copper-catalyzed Grignard coupling gave the desired product, the low yield of the reaction along with problems in the scaling up the reaction prompted us to use another approach to the synthesis of (-)-kolavenol (65).

2.5.1.8. Coupling with the Iodide 213 Acting as a Precursor of a Nucleophilic Reagent

Tokoroyama and coworkers\(^{181}\) have reported the total synthesis of (±)-ageline A (285), a marine natural product extracted from sponges of the genus Agelast, using a Pd(0)-catalyzed coupling of the organozinc reagent 286 with the vinyl bromide 287.
(equation 2.58). The coupled product 289 was obtained in 66% yield using PdCl$_2$dpff$^{182}$ (288) as the source of palladium(0). The resulting compound 289 was subsequently converted into (±)-ageline A (285).

An approach similar to that of Tokoroyama was envisaged for the coupling of the primary iodide 213 with vinyl iodide 265. The formation of the zinc reagents from butyl iodide 290 and the iodide 267 was studied initially. Knochel and coworkers$^{183}$ have used the reaction of primary iodides with activated zinc (Zn dust, BrCH$_2$CH$_2$Br, TMSCl, THF) ("Zn", 291) to prepare organozinc reagents. This method was applied to the iodides 290 and 267 (equation 2.59). We observed no formation of homocoupled products as described by Knochel and coworkers$^{183}$ but a variable amount of iodide was converted to the corresponding alkane. Better results were obtained using a
stepwise procedure. Thus, lithium-iodide exchange\textsuperscript{184} of the iodides 290 or 267 with \textit{t}-BuLi in ether-hexane\textsuperscript{185} followed by addition of zinc bromide prepared in situ with zinc dust and dibromoethane in THF gave the desired zinc reagents 294 and 295 (equation 2.60).

\[
\begin{align*}
\text{Bu} & + \text{"Zn"} \rightarrow \text{BuZnI} \\
290 & 291 & 292
\end{align*}
\]

\[
\begin{align*}
\text{I} & + \text{"Zn"} \rightarrow \text{ZnI} \\
267 & 291 & 293
\end{align*}
\]

\[
\begin{align*}
1) \text{t-BuLi} \\
\text{Ether-Pentane} \\
\text{BuZnI} & 292
\end{align*}
\]

\[
\begin{align*}
2) \text{ZnBr}_2 \\
\text{BuZnBr} & 294
\end{align*}
\]

\[
\begin{align*}
1) \text{t-BuLi} \\
\text{Ether-Pentane} \\
\text{ZnBr} & 295
\end{align*}
\]

\[
\begin{align*}
2) \text{ZnBr}_2
\end{align*}
\]

The same palladium(0) catalyst as the one used by Tokoroyama, PdCl\textsubscript{2}dpff (288) (equation 2.58), was tested to couple the organozinc species 293 with the iodide 265 but none of the desired product was obtained. With palladium(0) bis-(dibenzylidene)acetone [Pd(dba)\textsubscript{2}]\textsuperscript{186} and triphenylphosphine\textsuperscript{187} the coupled product was obtained in yields up to 60%. The best yield was attained using Pd(dba)\textsubscript{2} and triphenylarsine.\textsuperscript{188} Triphenylarsine has been found to be the ligand of choice for palladium(0) catalyzed coupling reactions. It was found to increase the rate of the Stille coupling of vinylstannane compounds with vinyl iodides by a factor of 100–1000 compared to the rates measured with phosphine ligands like triphenylphosphine.\textsuperscript{188} The faster reaction rates can be attributed to the lower dissociation energy of triphenylarsine from the palladium(0) compared with that of triphenylphosphine.

The zinc reagent 296 was prepared as shown in equation 2.61. The solution of this reagent was then carefully transferred to a solution/suspension of Pd(dba)\textsubscript{2} and
triphenylarsine in THF. The iodide 265 was added immediately and the mixture was stirred overnight. The TIPS-ether 282 was obtained in 77% yield. Also isolated were small amounts of the alkane 283 and the dimer 284. The next step of the projected work was the conversion of 282 into (-)-kolavenol (65).

2.5.1.9. Preparation of Synthetic (-)-Kolavenol (65)

Synthetic (-)-kolavenol (65) was produced in 96% yield by cleavage of the silyl ether linkage 282 with tetrabutylammonium fluoride\(^ {189} \) (equation 2.62). The spectral data of this material was in agreement with that reported for natural (-)-kolavenol (65) (see section 2.5.1.11).\(^ {142} \)
2.5.1.10. Preparation of the Semi-Synthetic (-)-Kolavenol (65) from Natural (-)-Methyl Kolavenate (33)

A small sample of (-)-methyl kolavenate (33) (4.7 mg, from esterified natural kolavenic acid) was obtained from Dr. Tokoroyama.\textsuperscript{190} It was reduced with \textit{i}-Bu\textsubscript{2}AlH to give (-)-kolavenol (65) in 47\% yield (equation 2.63). This semi-synthetic (-)-kolavenol and the synthetic (-)-kolavenol obtained as described above (2.5.1.9) were identical by TLC analysis. A comparison of the spectral data of synthetic, semi-synthetic and natural (-)-kolavenol (65) is made in section 2.5.1.11.

2.5.1.11. Comparison of the Spectral Data of the Natural, Semi-Synthetic and Synthetic (-)-Kolavenol (65)

Comparison of the spectral data of our synthetic kolavenol, the semi-synthetic kolavenol derived from methyl kolavenate and the reported data for (-)-kolavenol is presented in \textbf{Table 2.27}. This comparison confirmed that we had realized the total
synthesis of (-)-kolavenol, in 14 steps and 19.4% overall yield from the optically active trimethylstannyl cyclohexenone 64. The identity of the synthetic kolavenol can also be confirmed by the examination of the D_2O exchanged 400 MHz ¹H NMR spectra of synthetic (Figure 2.23) and semi-synthetic (Figure 2.24) (-)-kolavenol (65).

In summary, the synthesis of enantiomerically pure (-)-kolavenol (65) was accomplished by means of a novel methylenecyclohexane annulation-destannylation sequence. We also improved on and shortened the procedure of Piers and Wai for the preparation of the methoxymethyl ether 214. The acid sensitivity of this compound was illustrated by its acid-catalyzed rearrangement to give the tricyclic ether 233. This acid lability of the trans-clerodane skeleton should be considered when planning the synthesis of other clerodanes. The elucidation of the structure of the rearrangement product 233 was unambiguously accomplished using two dimensional NMR techniques and NOE experiments. This assignment corrected the erroneous published assignment of the structure of the enantiomer of 233. The acid catalyzed rearrangement leading to 233 should be explored to produce the commercially important perfume Ionoxide® 251. Finally, a new efficient palladium-catalyzed coupling procedure of the zinc reagent 296 with the iodide 265 yielded the protected precursor of (-)-kolavenol 282. The next section will be concerned with the use of the TIPS-ether 282 as a precursor for the total synthesis of (-)-agelasine B (31).
Figure 2.23 400 MHz $^1$H NMR Spectrum of Synthetic (-)-Kolavenol (65) in CD$\text{Cl}_3$-D$_2$O
Figure 2.24 400 MHz $^1$H NMR Spectrum of the Semi-synthetic (-)-Kolavenol (65) in CDCl$_3$-D$_2$O
Table 2.27: Comparison of the Reported Spectral Data for (-)-Kolavenol with that of the Synthetic and Semi-Synthetic (-)-Kolavenol (65)

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</table>

a Reference 141; b Reference 142b; c Reference 191; d Reference 144; e 400 MHz, CDCl₃; f 60 MHz, CCl₄; g 125.8 MHz, CDCl₃; h Not enough material; i 25 MHz, CDCl₃; j Calculated value for C₂₀H₃₄O.
2.5.2. Synthetic Studies Toward (-)-Agelasine B (31)

2.5.2.1. Isolation of (-)-Agelasine B (31)

(-)-Agelasine B (31) is a structurally unusual marine natural product isolated from the Okinawan sponge *Agelas nakamura* Hoshino. This substance possesses a 9-methyl-7-adeninium moiety attached to C-15 of a trans-clerodane diterpenoid skeleton and, interestingly, has been shown to display a variety of biological activities, including antimicrobial activity and inhibitory effects on Na, K-ATPase. In addition to their interesting biological activity, biologists have used the compounds isolated from the *Agelas* sponges to establish the chemotaxonomy of the otherwise difficult to identify monogenic family of sponges.

![Structural formula of (-)-Agelasine B (31)](image)

The first partial structural elucidation of the agelasines was reported by Cullen and Devlin working with an extract from the sponge *Agelas dispar* Duchessaing and Michelotti. They showed, using spectroscopic techniques and chemical degradation, that the agelasines were composed of a diterpenoid skeleton (C$_{20}$H$_{33}$) and a 9-methyl-7-adeninium moiety (see 297).
The full structural elucidation of agelasine B (31) was accomplished by Nakamura and coworkers\textsuperscript{192} by use of spectroscopic methods and chemical degradation. It was found that agelasine B (31) was sensitive to both strong acids and weak bases. Thus, when agelasine B (31) was treated with HCl in acetic acid\textsuperscript{192b} the rearranged product 298 was obtained in 75\% yield (equation 2.64), while treatment of the agelasines 297 with aqueous sodium carbonate\textsuperscript{196} or aqueous ammonium hydroxide\textsuperscript{25} produced the formamides 299 (equation 2.65). The rearrangement of 31 to 298 is another example of the acid sensitivity of the trans-clerodane skeleton.

\begin{equation}
31 \xrightarrow{\text{HCl-CH}_3\text{COOH}} 298 \quad \text{(70\%)}
\end{equation}

\begin{equation}
297 \xrightarrow{\text{Na}_2\text{CO}_3\cdot\text{H}_2\text{O} \text{ or } \text{NH}_4\text{OH-}\text{H}_2\text{O-MeOH}} 299 \quad \text{(2.65)}
\end{equation}

2.5.2.2. Previous Synthesis of (−)-Agelasine B (31)

Tokoroyama and coworkers\textsuperscript{31} have prepared (−)-agelasine B (31) from (−)-methyl kolavenate (33) obtained from esterification of natural (−)-kolavenic acid (Scheme 2.20). This synthesis constitute a formal total synthesis of (−)-agelasine B (33) since they have already synthesized (−)-kolavenate (33) (see section 2.5.1.2). Reduction of the ester moiety of 33 gave (−)-kolavenol (65), which was converted into the bromide 300. The bromide was displaced with the known adenine derivative 301.
to give the desired methoxy adenine derivative 302 and the hydrobromide adduct 303 in a ratio of 4.3:1. The N-methoxy group of 302 was removed using zinc in acetic acid, and the counterion was then exchanged with chloride to give (-)-agelasine B (31).

Scheme 2.20
2.5.2.3. Preparation of the Kolavenyl Bromide (300)

It was initially planned to carry out the total synthesis of (-)-agelasine B (31) via an approach similar to that of reported by Tokoroyama and coworkers. A report by Palomo and coworkers indicated that a silyl ether can be transformed directly into an alkyl bromide using triphenylphosphine dibromide. For example, the silyl ether 304 was converted into the primary bromide 305 in 91% yield using the triphenylphosphine dibromide reagent (equation 2.66).

\[
\begin{align*}
\text{TBDMSO(CH}_2\text{)}_{13}\text{CH}_3 & \xrightarrow{(C}_6\text{H}_5\text{)}_3\text{PBr}_2 \quad 2.2 \text{ equiv} \quad \text{CH}_2\text{Cl}_2, \quad 10 \text{ min} \quad \text{BrCH}_2(\text{CH}_2)_{12}\text{CH}_3 \\
304 & \quad 91\% \quad 305 \quad (2.66)
\end{align*}
\]

Low yields of the bromide 300 were obtained when Palomo's procedure was applied to the TIPS-ether 282. It was suspected that the low yields might be due to the instability of the allylic bromide 300 during chromatography on common (acidic) silica gel. Indeed, compound 300 was obtained in 85% yield when purification of the crude product was done with neutral silica gel (latrobeads®) (equation 2.67). A small amount of (-)-kolavenol (65) was isolated as a side product (~10%) in the reaction.
Because of its instability, the bromide 300 was not fully characterized and only its $^1$H NMR spectrum was recorded. The spectrum of 300 displayed three methyl singlets (δ 0.72, 0.98 and 1.71), one methyl doublet (δ 0.81, $J = 6$ Hz) and one methyl multiplet (δ 1.58). A doublet was observed at δ 4.00 (2H, $J = 8.5$ Hz), it was attributed to the hydrogen of the bromomethylene moiety. The signals for the olefinic hydrogens appeared as a broad singlet at δ 5.19 (1H) and a broad triplet at δ 5.50 (1H, $J = 8.5$ Hz).

2.5.2.4. Preparation of the Adenine Derivative 301

The adenine derivative 301 was prepared in five steps from adenine (306) using a previously reported procedure (Scheme 2.21).\textsuperscript{198} Adenine (306) was oxidized with hydrogen peroxide in acetic acid to give the $N^1$-oxide 307 (mp 295–300 °C dec, lit.\textsuperscript{198a} 297–307 °C dec), which was alkylated with iodomethane to produce the salt 308 (mp 223–227 °C, lit.\textsuperscript{198b} 222°C). Compound 308 was neutralized using an ion exchange resin to afford the methoxyaminopurine 309 (mp 250–260 °C dec, lit.\textsuperscript{198b} 255–257 °C dec), which yielded the quaternary ammonium salt 310 (mp 205–215 °C dec, lit.\textsuperscript{198b} 214–215 °C dec) upon treatment with iodomethane. The air-sensitive adenine derivative 301 (mp 230–235 °C dec, lit.\textsuperscript{198c} 239 °C dec) was obtained by neutralization of the ammonium salt 310, followed by a thermal Dimroth rearrangement.
2.5.2.5. Preparation of the Methoxy-Protected Adenine Derivative 302 and The $N^6$-Alkylated Adenine Derivative 303

Kolavenyl bromide (300) was treated with the adenine derivative 301 using reaction conditions identical to those reported by Tokoroyama and coworkers (see Scheme 2.20). The methoxy adenine derivative 302 ([$\alpha$]$_D$\textsuperscript{25} -24.4°, $c = 1.02$ in MeOH [lit.$^{31}$ [$\alpha$]$_D$\textsuperscript{21} -26.2°, $c = 1.00$ in MeOH]) and the $N^6$-alkylated adenine derivative 303 (isolated as the free base) ([$\alpha$]$_D$\textsuperscript{25} -38.7°, $c = 2.96$ in MeOH) were isolated in 42% and 32% yield, respectively, after purification. The ratio of the isolated products 302 to 303 (1.3:1) was different from that reported by Tokoroyama for the same reaction (4.4:1!). It had also been reported that the reaction could be performed at room temperature for an extended period of time without loss of selectivity or yields.$^{31}$ The alkylation was repeated at room temperature and the products 302 and 303 were obtained in 29% and 23%, respectively. Thus, the ratio of the two products was, again, 1.3:1! The best yields were obtained when kolavenyl bromide 300 was
treated with 301 in the presence of a catalytic amount of Bu₄NI (equation 2.68). The products 302 and 303 were obtained in 52% and 38% yields respectively, giving a ratio of 1.4:1 of isolated products. The ratio of the crude reaction products 302 to 303 as obtained by integration of the ¹H NMR spectrum was even worse at 1.25:1! The reason for the discrepancy between our results and those of Tokoroyama is not clear.

Compound 302 exhibited IR absorptions due to the NH group at 3414, 1595 and 881 cm⁻¹, the carbon-carbon and carbon-nitrogen double bonds at 1672 and 1556 cm⁻¹ and the N–O bond at 1058 cm⁻¹ (lit.31 3360, 1670, 1590, 1550, 1050, 880 cm⁻¹). Analysis of the ¹H NMR spectrum confirmed the formation of 302. Seven methyl groups were observed: 5 singlets at δ 0.70, δ 0.98, δ 1.89 (Me-16), δ 3.92 (Me-N), and δ 4.04 (Me-O), one doublet at δ 0.78 (J = 6 Hz, Me-17), and one multiplet at δ 1.55 (Me-18). The other relevant ¹H NMR signals were: a doublet at δ 5.15 (2H, J = 8 Hz, H’s-15), a broad singlet at δ 5.15 (H-3) and a broad triplet at δ 5.43 (J = 8 Hz, H-14) and the signals attributed to the adeninium moiety at δ 7.82 (d, 1H, J = 4 Hz, H-2’ [becomes a singlet with D₂O])¹⁹⁹, δ 9.90 (H-8’) and δ 10.49 (br s, NH [exchanged with
D$_2$O)] (lit.\textsuperscript{31} two singlets at $\delta$ 7.97 and $\delta$ 9.83, 1H each). The $^{13}$C NMR spectrum was consistent with the proposed structure. The UV spectrum of 302 had a maximum at 294 nm ($\varepsilon$ 4452, 9.0 x 10$^{-5}$ M in MeOH) characteristic of a $N$-methoxy methyl adeninium moiety.\textsuperscript{200}

The neutral adenine derivative 303 exhibited IR absorptions consistent with the reported data.\textsuperscript{31} In contrast to the IR spectrum of 302, no NH absorptions were observed. The $^1$H NMR spectrum of 303 was differentiated from the spectrum 302 by the absence of exchangeable protons, and by the more shielded nature of the signals assigned to Me-16 (\$\Delta$\$\delta$\textsuperscript{201} 0.11), N-Me (\$\Delta$\$\delta$ 0.11), O-Me (\$\Delta$\$\delta$ 0.12), H's-15 (\$\Delta$\$\delta$ 0.38) and H-8' (\$\Delta$\$\delta$ 1.42) due to the neutrality of the molecule. The $^{13}$C NMR spectrum was consistent with the proposed structure. The UV spectrum of 303 had a maximum at 278 nm ($\varepsilon$ 14498, 1.8 x 10$^{-5}$ M in MeOH) characteristic of a $N$-methoxy methyl adenine moiety.\textsuperscript{200}

2.5.2.6. Reduction of the Methoxy-Protected Adenine Derivative 302 with Zinc in Acetic Acid

The methoxy-protected agelasine B 302 was treated with zinc in acetic acid as described by Tokoroyama and coworkers (equation 2.69).\textsuperscript{31} No agelasine B (31) or starting material were observed in the $^1$H NMR spectrum of the crude reaction mixture (equation 2.69). After three unsuccessful attempts, it was decided to investigate the reduction using a less valuable model compound.
2.5.2.7. Preparation of the Methoxy-Protected Adenine Derivative 313

The geranyl derivative 313 was prepared in two steps from geraniol (311) using a procedure similar to that reported by Tokoroyama and coworkers. Geraniol (311) was treated with triphenylphosphine dibromide to give the known geranyl bromide (312). The allyl bromide 312 was treated with the methoxy methyl adenine derivative 301 to give the alkylated adenine derivative 313 after purification by selective precipitation and centrifugation, while the compound 314 was obtained by chromatography over basic alumina of the material derived from the supernatant solutions.

The spectral data for the compounds 313 and 314 were consistent with the proposed structures. The assignment of the spectra (IR, $^1$H NMR, $^{13}$C NMR, LRMS, HRMS and UV) was based on comparison with that of 302 and 303.
2.5.2.8 Reduction of the Methoxy-Protected Methyl Adenine Derivative 313 with Zinc in Acetic Acid

Removal of the methoxy protecting group of compound 313 was attempted using reaction conditions identical to those reported by Tokoroyama and coworkers (equation 2.71). The desired product 315 (mp 154-157 °C [lit. 145-150 °C]) was obtained in 33% yield after purification of the crude reaction mixture.

![Diagram](image)

The IR spectrum of the dialkyl adeninium 315 displayed absorptions assigned to the NH₂ group (3322 and 3131 cm⁻¹) and to the carbon-nitrogen and carbon-carbon double bonds (1651, 1613 and 1590 cm⁻¹). The ¹H NMR spectra exhibited signals consistent with the structure 315. The presence of the adeninium moiety was confirmed by the occurrence of the signals at δ 4.07 (s, 3H, N-Me), δ 6.78 (br s, 2H, NH₂ [exchanged with D₂O]), δ 8.49 (s, 1H, H-2') and δ 10.95 (s, 1H, H-8' [slowly exchanged with D₂O]). The ¹H and ¹³C NMR spectra could be assigned completely by mean of the off-resonance proton decoupled ¹³C, APT, HMQC and HMBC NMR experiments. The UV spectrum of 315 was characteristic of a compound having a 7,9-dialkyl adeninium moiety with a maximum at 273 nm (ε 6777, 2.78 x 10⁻⁴ M in MeOH).

Because the isolated yield of 315 was low it was decided to test the stability of (-)-agelasine B (31) to the zinc in acetic acid reduction procedure. The opportunity to do this test was given to us when Dr. R. Andersen generously gave us a sample of the extract of the sponge Agelas species (probably nakamura) containing (-)-agelasine B (31).
2.5.2.9. Isolation of Natural (-)-Agelasine B (31) from the Crude Extract of the Sponge Agelas Species

The initial extraction and purification steps of (-)-agelasine B (31) from the sponge Agelas were carried out by Ms. Jana Pika (Ph. D. student with Dr. R. Andersen). The purified extract obtained by Ms. Pika was passed through a SepPak® C18 reverse phase chromatographic column and was then further purified either by high pressure liquid chromatography (HPLC) to give a sample of pure (-)-agelasine B (31) or by TLC grade silica chromatography to give a sample enriched in (-)-agelasine B (31) (>25% of the mixture as established by the integration of the 1H NMR spectrum of the mixture, the remaining 75% was composed of the agelasines A, C, D and E). The latter sample was used to test the stability of (-)-agelasine B (31) with zinc in acetic acid. The HPLC-purified sample (mp 170-175 °C) exhibited spectral data consistent to that reported for (-)-agelasine B (31) (lit. 31,192 b 167-170 °C) (see Table 2.28, vide infra).

2.5.2.10. Treatment of the Enriched Sample of Natural (-)-Agelasine B (31) with Zinc in Acetic Acid

A sample containing (-)-agelasine B (>25% pure, vide supra, 93 mg) was treated with zinc in acetic acid using reaction conditions similar to those described previously (see equation 2.71). After work-up, no (-)-agelasine B (31) was observed in the 1H NMR spectrum of the crude reaction mixture. Purification of this material by TLC grade silica chromatography produced only a very small amount of agelasine B.

The reason(s) for the failure of effecting reduction of 302 with zinc in acetic acid or for the destruction of (-)-agelasine B (31) under the same conditions are unclear, particularly when one takes into account the reports of Tokoroyama and coworkers. In our hands, both processes gave a large number of products that differed widely in polarity (TLC analyses). One can speculate that the adeninium moiety may have been reduced and/or that some of the observed side products may have been due to the established rearrangement of the acid sensitive trans-clerodane.
skeleton. The difficulties encountered with Tokoroyama's demethoxylation method prompted the development of another reaction procedure for the demethoxylation of compound 302.

2.5.3. Electrochemical Demethoxylation: Total Synthesis of (-)-Agelasine B (31)

2.5.3.1. Introduction

It has been proposed that zinc in acidic solution reduces a substrate by acting as an electron donor (single or two electron donor).\textsuperscript{210} The reduction potential of the transferred electron from the metal to the substrate will often dictate which products are formed in the reaction. The reduction potential has to be sufficiently large in order to transfer electrons to the substrate and produce an anion. The resulting anion is rapidly protonated by the acid present in the reaction medium to give the reduced product. If the reduction potential is not correctly adjusted, either a reduction does not take place at all or the reduction products can be further reduced. When the yields obtained by reduction with metals in the presence of acids are not acceptable, the only way to avoid side product formation is by changing the acid, the acid concentration, the metal or by using an amalgam of different metals in order to adjust the reduction potential of the transferred electron to the desired level. Optimization is difficult and requires a large amount of material to do all the trials, because the products have to be isolated in order to obtain the yield of the reactions. Both the adjustment of the electron transfer potential and the need for a smaller amount of substrate to find the appropriate reaction conditions can be met by the use of an electrochemical process.

An example of the electrolysis of a nitrogen-oxygen bond has been reported. Lund and Kwee\textsuperscript{211} have demethoxylated 1-methoxybenzotriazole (316) to give the benzotriazole (317) in an unreported yield (equation 2.72) by means of a reduction at a controlled potential of -0.75 V versus a saturated calomel electrode (SCE) in 1 N aqueous HCl. The reduction of 316 was shown to be a two electron process by polarography.
Single electron transfer reactions are easy to control with an electrode since the potential of the transferred electron can be accurately determined by adjusting the power supply potential. The number of electrons donated can be measured and controlled in a more reliable way than in the case of reduction with metals in the presence of acids. The major advantage of electrochemistry over metal-acid reductions is that the use of electroanalytical methods (e.g. cyclic voltammetry or polarography) require only very small amounts of the substrate to rapidly investigate and optimize the reaction conditions.\textsuperscript{212} Since cyclic voltammetry was used to solve our synthetic problem, a short discussion of the method will be included.

\textbf{2.5.3.2. Cyclic Voltammetry}\textsuperscript{213}

Cyclic voltammetry is a relatively simple experiment that can provide valuable information about the electrochemical behavior of a compound. This electrochemical technique is similar to linear sweep voltammetry (LSV) where the potential (E) between the electrodes is scanned linearly towards a more negative or positive potential until a reduction or an oxidation takes place and a current (i) is observed. In cyclic voltammetry, the voltage is scanned towards a preset potential and then back to its initial point. A schematic representation of a voltammograph and the three-electrode electrochemical cell necessary for cyclic voltammetry are shown in (A) (Figure 2.25).
The cell is composed of a work electrode (W) where the reaction of interest takes place, a counter electrode (C), and a reference electrode (RE) against which the potential of the working electrode is measured. The electrodes are immersed in a solution of the electroactive substance and a support electrolyte that provides sufficient electrical conductivity through the solution. The reference electrode is a half-cell that has a known and constant potential as long as the current going through it is negligible. The voltammograph generates a triangular potential wave that scans between two preset limits and records the current variations between the work and the counter electrodes. The speed of the scanning can be varied to yield information about the kinetics of the electrochemical reaction.

The voltammogram (B) (Figure 2.25)\textsuperscript{214} is typical of a reversible process. The resulting second half is symmetrical with the first wave. An irreversible process is characterized by a returning wave that follows the residual current (C).\textsuperscript{215} An electrochemical step followed by a chemical step is called an EC process (D), and has a returning wave showing a non-symmetrical minimum due to the transfer of electrons from the newly-formed species. The maximum at high potential of curve (E) represents the point were the solvent or the electrolyte becomes electroactive and gets reduced. The potential at which the current rapidly rises is called the solvent discharge, breakdown or decomposition potential.
2.5.3.3 Voltammograms of the Geranyl Derivative 313, the Methoxy-Protected Adenine Derivative 302 and (-)-Agelasine B (31)

The reduction of the geranyl derivative 313 was investigated under conditions similar to those reported for the demethoxylation of 1-methoxybenzotriazole (316) (equation 2.72). Although the choice of a mercury work electrode was suitable for our substrates, we could not use aqueous HCl as the reaction medium because it could trigger the rearrangement of the trans-clerodane skeleton. Instead, a 0.1 M aqueous sodium acetate buffer solution at a pH of 4.5 was selected. This choice was based on the availability of the buffer and the necessity of having a mildly acidic reaction medium for the reduction to take place.

The voltammetric measurements were made using a hanging mercury drop electrode (HMDE) as the work electrode, a platinum wire as the counter electrode, and a Ag/AgCl electrode in a saturated solution of AgCl in saturated aqueous KCl.
(separated from the reaction solution by a porous glass [Vicor®]) as the reference electrode \((E = 0.197 \text{ V vs. normal hydrogen electrode NHE}, -0.045 \text{ V vs. SCE})\). The scanning speed was set at 100 mV/s and the reaction solution was purged of oxygen with dry nitrogen.

The voltammogram of the compound 313 (2.5 \(\times\) \(10^{-3}\) M in NaOAc buffer) was recorded from 0 to -1.2 V and an expansion of the voltammogram is shown in **Figure 2.26**.\(^{216}\) The resulting curve has the shape typical of an irreversible process with a maximum at -1.06 V (2.4 \(\mu\)A) and a minimum at -1.12 V (2.0 \(\mu\)A). Solvent decomposition is observed at -1.2 V. Without the substrate, the solvent decomposition is not observed until a potential of at least -1.4 V is reached. The observed difference in the solvent decomposition potential is probably due to the reduction of the solvent with the substrate 313 acting as the catalyst, transferring electrons from the electrode to the solvent and producing hydrogen gas. This phenomenon is called catalytic hydrogen reduction and has been reported by Janik and Elving,\(^{217}\) who have observed the low potential solvent reduction while studying the polarographic behavior of purines, pyrimidines, pyridine and flavins at pH's more acidic than 5.

![Figure 2.26 Voltammogram of Compound 313](image)
The voltammogram of the methoxy-protected adenine derivative 302 was recorded, and showed features similar to those of 313. Two irreversible waves were seen in the expansion at -1.01 V (1.5 μA, 1.3 x 10^{-3} M in NaOAc buffer) and -1.18 V (0.7 μA) (Figure 2.27). Solvent decomposition was observed at -1.29 V.

Natural agelasine B (31) was also studied by cyclic voltammetry (2.4 x 10^{-3} M in NaOAc buffer) (Figure 2.28). A small maximum was observed at -1.02 V although the current was very small at 0.08 μA. Catalytic hydrogen reduction occurred at -1.2 V. The small maximum at -1.02 V may be due either to the reduction of (-)-agelasine B (31) or to the reduction of a contaminant present in trace amounts.

From the results of the voltammograms of compounds 302, 313 and 31, it was concluded that the methoxy-protected adeninium derivatives 302 and 313 may be reduced at constant potential of ~-1 V in the aqueous sodium acetate buffer. Even if a reduction wave is observed at -1.02 V for (-)-agelasine B (31), its amplitude is small enough (32 times smaller than that of compounds 302 and 313) that the methoxy adenine derivative 302 will be reduced faster than the desired demethoxylated product. In all cases the substrates were recovered unchanged from the analytical cell in good yield (70-90%), showing that the buffer is not harmful to the compounds 302, 313 and 31. Verification of the electroanalytical predictions based on cyclic voltammetry was made with the electrolysis of compound 313.
Figure 2.27 Voltammogram of Compound 302
2.5.3.4. Electrolysis of the Methoxy-Protected Adeninium Derivative 313

The electrochemical reductions were all performed in a mercury electrochemical cell made by the UBC glass and mechanical shops. The electrochemical cell used is shown diagrammatically in Figure 2.29. A constant potential of -1.0 V was maintained for the duration of the electrolysis, and the amount of current that passed through the solution was monitored with an electrometer hooked into a voltage-time integrator made by the UBC electronics shop.

The electrolysis of the suspension of the adeninium derivative 313 was stopped after 1.9 equivalents of electrons had passed through the solution/suspension. The expected product 315 was obtained in 41% yield (57% based on recovered 313) after exchange of the counterion with chloride ion (equation 2.73). The spectral data derived from 315 were identical with those described earlier. The addition of cosolvents to solubilize the adeninium salt 313 [methanol, ethylene carbonate, poly(dimethylsiloxane)] did not improve the yields of 315.
Figure 2.29 Electrochemical Mercury Cell (Actual Size)
2.5.3.5. Electrolysis of the Methoxy-Protected Adeninium Derivative 302

The electrolysis of the methoxy-adeninium derivative 302 was effected using reaction conditions similar to those described for the demethoxylation of the geraniol derivative 313 (see equation 2.73). Synthetic (-)-agelasine B (31) was obtained in 53% yield (57% yield based on recovered 302) after purification by chromatography with TLC grade silica gel using a mixture of methanol and dichloromethane as solvent (equation 2.74). Even though a relatively large difference in polarity exists between 31 and 302, the separation of these salts by chromatography was very difficult. Repetitive chromatographies and filtration through a microporous membrane (to remove any residual silica particles [Nylon membrane 0.2 μm, # C619000 from Chromatographic Specialties Inc. Brockville, Ont.]) had to be done in order to obtain pure (-)-agelasine B (31). The physical data of the synthetic (-)-agelasine B (31) was in good agreement with that reported for the natural (-)-agelasine B (31) and with the natural (-)-agelasine B (31) isolated from the Agelas sponge obtained from the research group of Dr. Andersen (see Table 2.28).218 The natural and synthetic (-)-agelasine B (31) had identical behavior by TLC. The $^1$H NMR spectra of (-)-agelasine B (31) are presented in Figures 2.30 (synthetic 31, 400 MHz), 2.31 (natural 31, 400 MHz), 2.32 (Tokoroyama’s synthetic 31, 100 MHz), and 2.33 (Tokoroyama's natural 31, 100 MHz).
Table 2.28: Comparison of the Reported Spectral Data for (-)-Agelasine B (31) and the Spectral Data for the Synthetic and Natural (-)-Agelasine B (31)

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In summary, the total synthesis of enantiomerically pure (-)-agelasine B (31) was accomplished in 23% yield from the TIPS-ether 282. A new, direct preparation of the allyl bromide 300 from the TIPS-ether 282 was used in conjunction with a modification of Tokoroyama's coupling procedure of the bromide 300 with \( N^6 \)-methoxy-9-methyl adenine (301) to give the methoxy-protected adenine derivative 302 in acceptable yields. Finally, a new electrolytic process was developed to remove the methoxy protecting group in a mild, controllable fashion to yield the desired (-)-agelasine B (31). The identity of the synthetic (-)-agelasine B (31) was confirmed by comparison of its spectral data with that reported in the literature, and with a sample of natural (-)-agelasine B (31) isolated from an *Agelas* species sponge.
Figure 2.30 400 MHz $^1$H NMR Spectrum of the Synthetic (-)-Agelasine B (31)
Figure 2.31 400 MHz $^1$H NMR Spectrum of the Natural (-)-Agelasine B (31)
Figure 2.32 100 MHz $^1$H NMR Spectrum of Tokoroyama's Synthetic (-)-Agelasine B (31)
Figure 2.33 100 MHz $^1$H NMR Spectrum of Tokoroyama's Natural (-)-Agelasine B (31)
3. CONCLUSION

In summary, we have prepared the enantiomerically pure trimethylstannyl enone 64 and have demonstrated that it serves as an effective substrate for methylenecyclohexane, methylenecyclopentane and (Z)-ethyldiene cyclopentane annulation sequences. The resulting bicyclic ketones 124, 132 and 133 were conveniently destannylated using lithium in ammonia to give the alcohols 165, 175 and 176. The scope and the compatibility of the destannylation procedure with other functional groups was demonstrated by carrying out the destannylation of a series of compounds containing hydroxyl, olefinic, and ether functions.

The β-trimethylstannyl cyclohexanones obtained during the course of the work described in this thesis were studied by circular dichroism. The results obtained confirmed unambiguously Hudec’s conclusion that, in β-trimethylstannyl cyclohexanones, an equatorially oriented Me₃Sn group is strongly consignate and an axially oriented Me₃Sn moiety is weakly dissignate.

The alcohol 165 was used as an intermediate for the total syntheses of the trans-clerodane diterpenoids (-)-kolavenol (65) and (-)-agelasine B (31) (Scheme 3.1). The alcohol 165 was converted efficiently in five steps to the ether 214. This compound was transformed into the iodide 213, which was converted into the organozinc species 318. Palladium(0)-catalyzed coupling of 318 with the vinyl iodide 265 gave 282, which was easily transformed into (-)-kolavenol (65). (-)-Kolavenol (65) was thus prepared in 14 steps and an overall yield of 19.4% from the enantiomerically pure cyclohexenone 64.
The TIPS ether 282 was converted directly into the allylic bromide 300, which, upon reaction with the adenine derivative 301, gave 302 (Scheme 3.1). A new, mild electrochemical reduction of 302 was developed to yield (-)-agelasine B (31) in a total of 16 steps and 5.6\% overall yield from the enone 64.
Scheme 3.1
4. EXPERIMENTAL

4.1. GENERAL

4.1.1. Data Acquisition and Presentation

Proton nuclear magnetic resonance (\( ^1\text{H} \) NMR) spectra were recorded on either a Varian XL-300 spectrometer or on Bruker AC-200, WH-400 or AMX-500 spectrometers using deuteriochloroform (CDCl\(_3\)) as the solvent and tetramethylsilane or chloroform (δ 7.25) as the internal standard, unless otherwise noted. Signal positions are given in parts per million (δ) from tetramethylsilane. Coupling constants (\( J \)) are given in Hertz (Hz). The multiplicity, number of protons, coupling constant(s), and assignments (when known) are given in parentheses. Abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. When a hydrogen was observed to be coupled with the same coupling constant to two, three, four or five protons which are chemically and magnetically non-equivalent, the designation dd, ddd, dddd and dddt are used instead of using t, q, quintet and sextet, respectively. For compounds exhibiting AB and ABX type spin systems, the quoted values for chemical shifts and coupling constants are measured as if they were first order systems, although these values only approximate the real values.\(^{219}\) Selective decoupling experiments refer to \( ^1\text{H} - ^1\text{H} \) spin decoupling experiments. Tin-hydrogen coupling constants (\( J_{\text{Sn-H}} \)) are given as an average of the \( ^{117}\text{Sn} \) and \( ^{119}\text{Sn} \) values.

The nuclear Overhauser enhancement difference experiments (NOE)\(^{220}\) were recorded on a Bruker WH-400 NMR spectrometer.

\( ^1\text{H} - ^1\text{H} \) Homonuclear correlation experiments (COSY)\(^{73}\) were recorded on Bruker WH-400 or AC-200 spectrometers. The heteronuclear \( ^1\text{H} - ^{13}\text{C} \) shift correlation
experiments (HSC)\textsuperscript{221} were recorded on a Varian XL-300 spectrometer. \textsuperscript{1}H-\textsuperscript{13}C heteronuclear multiple quantum coherence experiments (HMQC),\textsuperscript{222} the \textsuperscript{1}H-\textsuperscript{13}C heteronuclear multiple bonds connectivity experiments (HMBC)\textsuperscript{222} (2–3 bonds correlations) and (ROESY)\textsuperscript{223} were recorded on Bruker AMX-500 spectrometer.

Carbon nuclear magnetic resonance (\textsuperscript{13}C NMR) spectra and the attached proton test experiments (APT)\textsuperscript{76} were recorded on a Varian XL-300 spectrometer at 75.3 MHz or on Bruker AM-200 (50.3 MHz), AM-400 (100.4 MHz) or AMX-500 (125.8 MHz) spectrometers, using deuteriochloroform as the solvent, unless otherwise noted. Signal positions are given in parts per million (\(\delta\)) from tetramethylsilane, measured relative to the chloroform signal at \(\delta\) 77.0.\textsuperscript{117} Signals with negative intensity in the attached proton test are so indicated in brackets (-ve) following the chemical shift.

Fluorine nuclear magnetic resonance (\textsuperscript{19}F NMR) spectra were recorded on a Bruker AM-200 (188.3 MHz) spectrometer, using deuteriochloroform as the solvent. Signal positions are given in parts per million (\(\delta\)) from the spectrometer with an external trifluoroacetic acid reference.

Infrared (IR) spectra were recorded from liquid films between sodium chloride plates or from potassium bromide pellets using a Perkin-Elmer 1710 Fourier Transform Spectrophotometer with internal calibration.

Low and high resolution electron impacts mass spectra (LRMS, HRMS and FABMS respectively) were recorded on a Kratos MS50 mass spectrometer (70 eV). The ion type is presented followed by its relative intensity (ex.: LRMS: \(M^+(110),\textsuperscript{98} 55\%\)) Desorption chemical ionization mass spectra (DCIMS) were recorded with a Delsi Nermag R-10-10 C mass spectrometer. The following atomic mass were used to calculate the mass of the fragments observed in the HRMS: \textsuperscript{1}H 1.007825; \textsuperscript{12}C 12.0000; \textsuperscript{14}N 14.00307; \textsuperscript{16}O 15.99491; \textsuperscript{19}F 18.99840; \textsuperscript{28}Si 27.97693; \textsuperscript{32}S 31.97207; \textsuperscript{35}Cl 34.96885; \textsuperscript{120}Sn 119.9021; \textsuperscript{127}I 126.9044.

Elemental analyses were performed on a CARLO ERBA CHN elemental analyzer, Model 1106, by the UBC Microanalytical Laboratory.
Circular dichroism spectra (CD), optical rotatory dispersion spectra (ORD) and specific rotations at the sodium D line (589.3 nm) or at the wavelength λ and the temperature t ([α]D or λ induce where deg = degree (°) and dag = decagram.) were measured on a JASCO J710 spectropolarimeter. The specific ellipticity at the wavelength λ and the temperature t ([Ψ]λ, t in deg cm^-2 dag^-1) and the peak width at half height (λ_1/2) are reported in the following manner: λ (specific ellipticity, λ_1/2).

Ultraviolet spectra (UV) were recorded on a Perkin Elmer Lambda 2 UV/VIS spectrophotometer. The λ_max and the extinction coefficient are reported.

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Distillation temperatures refer to air-bath temperatures of Kugelrohr distillations and are uncorrected.

Gas-liquid chromatography (GLC) analyses were performed on Hewlett-Packard Model 5880A or 5890 capillary gas chromatographs, each having a flame ionization detector and a fused silica column, either ~20 m x 0.21 mm coated with cross-linked SE-54 or ~25 m x 0.20 mm coated with 5% phenyl-methyl silicone, respectively.

Thin layer chromatography (TLC) was carried out on commercial aluminium backed silica gel 60 plates (E. Merck, type 5554, 0.2 mm). Reverse phase TLC was performed on commercially available, glass backed plates (Whatman, type KC_18/KC_18F). Visualization was accomplished with ultraviolet light (254 nm), a solution of phosphomolybdic acid (PMA) in EtOH (20% w/v, Aldrich), a solution of vanillin in a sulfuric acid-EtOH mixture (vanillin: 6% vanillin w/v, 4% sulfuric acid and 10% water, v/v, in EtOH), iodine or Dragendorff reagent. Flash chromatography was done on 230-400 mesh silica gel (E. Merck, Silica Gel 60). "TLC grade silica chromatography" was done on 10-50 μm Type H silica (S-6628, Sigma). Radial chromatography was done on a Chromatotron® Model 7924 using 1 and 2 mm thick radial plates (silica gel 60, PF 254, with calcium sulfate, E. Merck #7749).
All compounds that were subjected to high resolution mass spectrometry and elemental analysis were homogeneous by TLC analyses and >95% pure by GLC analyses.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame or oven (~140 °C) dried. The glass syringes for handling anhydrous solvent and reagents were oven dried while the plastic syringes, the needles and the Teflon® cannulae were flushed with a stream of dry argon prior to use.

Concentration, evaporation or removal of the solvent under reduced pressure (water aspirator) refer to solvent removal via a Büchi rotary evaporator at ~15 torr.

Cold temperatures were maintained by use of the following baths: 0 °C, ice/water; -10 °C, ice/acetone; -20 °C, -30 °C, -40 °C and -48 °C, aqueous calcium chloride/CO₂ (27, 35, 43 and 47 g CaCO₃/100 ml H₂O, respectively)²²⁶; -60 °C, chloroform/CO₂; -78 °C, acetone/CO₂; -98 °C, MeOH/liquid nitrogen.

This thesis was prepared on a Macintosh® computer using the word processor Microsoft Word 4.0 and 5.0. The drawings were done using the chemical drawing program ChemDraw™ version 2.1.3 from Cambridge Scientific Computing.

4.1.2. Solvents and Reagents

Solvents and reagents were purified and dried using known procedures.²²⁷ Petroleum ether refers to a hydrocarbon mixture with bp 30-60 °C. Ether refers to diethyl ether. Ether and THF were distilled from sodium benzophenone ketyl. DME was distilled from the sodium/potassium benzophenone ketyl. Carbon tetrachloride was refluxed and then distilled from phosphorus pentoxide. Benzene, dichloromethane, diisopropylamine, N,N-diisopropylethylamine, DMA, DMF, DMPU, DMSO, HMPA (WARNING: carcinogenic), TMP, acetonitrile, 1,2-dibromoethane,
pyridine, toluene and triethylamine were refluxed over and then distilled from calcium hydride. HMPA, DMF, DMPU and pyridine were stored over 4Å molecular sieves.

Magnesium was added to MeOH and, after refluxing the mixture, the MeOH was distilled from the resulting solution of magnesium methoxide. EtOH, diethylene glycol, triethylene glycol and ammonia were treated with sodium and distilled. 2-Methyl-2-propanol was passed through a short column of flame dried 4Å molecular sieves.

Trimethylsilyl chloride (TMSCl) was dried by refluxing over calcium hydride and was distilled before use.

Solutions of methyllithium (LiBr complex in ether), butyllithium and tert-butyllithium (both in hexane) were obtained from Aldrich Chemical Co., Inc. and were standardized using either the procedure of Kofron and Baclawski\textsuperscript{228} or the one of Suffert.\textsuperscript{229}

Lithium diisopropylamide (i-Pr\textsubscript{2}NLi) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) solutions were prepared by the addition of a solution of butyllithium (1.0 equiv) in hexane to a solution of diisopropylamine or TMP (1.1 equiv) in THF at -78 °C. The resulting colorless or faintly yellow solution was stirred at 0 °C for ten minutes before use.

Copper(I) cyanide was washed sequentially with anhydrous MeOH and anhydrous ether and then was kept under vacuum (0.1 torr, vacuum pump) overnight at room temperature. Copper(I) bromide-dimethyl sulfide complex was prepared by the method described by Wuts.\textsuperscript{230}

Iodomethane, chloroform and deuteriochloroform were dried by passing through a short column of oven dried basic alumina (activity I).

Aqueous ammonium chloride solution (pH 9) was prepared by addition of 50 mL of aqueous ammonium hydroxide (58%) to 950 mL of saturated aqueous ammonium chloride.
4.2. EXPERIMENTAL PROCEDURES

4.2.1. Methylene cyclohexane, Methylene cyclopentane and (Z)-Ethylidene cyclopentane Annulation Sequences

4.2.1.1. Preparation of (-)-(R)-5-Methyl-2-cyclohexen-1-one (55) and 3-Methyl-2-cyclohexen-1-one (73)\(^{50,51,58,62,64}\)

A) Preparation of the Silyl Enol Ethers 71 and 72

A cooled (-78 °C) solution of TMSCI (59 mL, 470 mmol, 5 equiv) in THF (180 mL) was added over a period of 20 min to a stirred solution of LTMP (110 mmol, 1.2 equiv) in THF (180 mL) at -78 °C via a wide bore Teflon® cannula. A cold (-78 °C) solution of (R)-(+)-3-methylcyclohexanone (10.5 g, 94 mmol) in THF (180 mL) was added via a Teflon® cannula over a period of 30 min. The mixture was stirred at -78 °C for 15 min. Triethylamine (79 mL, 564 mmol, 6.0 equiv) was added, the mixture was stirred 5 min and then was poured into a stirred mixture of saturated aqueous sodium bicarbonate (1.5 L) and petroleum ether (600 mL). The two layers were separated and the aqueous layer was extracted twice with petroleum ether (1.5 L total volume). The combined organic layer was washed with 1 M aqueous citric acid until it was neutral. The organic layer was dried over anhydrous sodium sulfate and then carefully removed under reduced pressure (~25 °C bath). The resultant colorless oil was fractionally distilled (76-82 °C/18 torr) to give 16.0 g (93%) of a 4:1 mixture of silyl enol ethers 71 and 72, respectively. The mixture gave the following selected spectral data: IR (neat): 2956, 2926, 2844, 1671, 1457, 1370, 1252, 1186, 894, 846 cm\(^{-1}\); \(^1\)H NMR (300 MHz) \(\delta\): 0.12 and 0.18 (two s, 9H, Me\(_3\)Si), 0.92 and 0.95 (two d,
3H, $J = 6$ Hz), 4.72 (m, 0.16 H, H-a, 72), 4.82 (m, 0.84 H, H-a, 71); LRMS: $M^+(184)$ 21.2%; HRMS calcd for C$_{10}$H$_{20}$OSi: 184.1283, found: 184.1288; TLC: 9:1 hex:ether, PMA.

B) Preparation of the $\alpha$-Seleno Ketones 82, 83, 84, and 85

![Chemical Structures](image)

Bromine (2.45 mL, 48 mmol, 0.55 equiv) was slowly added via an addition funnel to a cold (0 °C) solution of diphenyldiselenide (15.9 g, 50 mmol, 0.57 equiv) in ether (180 mL). The resultant solution of phenylselenenyl bromide was transferred via Teflon® cannula to a cold (-78 °C) solution of the silyl enol ether mixture (71, 72, 16 g, 87 mmol) in ether (90 mL). The dark red mixture was stirred for 10 min at -78 °C and for 10 min at 0 °C. The solution was cooled to -78 °C and then was poured into a vigorously stirred mixture of saturated aqueous sodium bicarbonate (1 L) and ether (200 mL). The layers were separated and the aqueous layer was extracted twice with ether (2 x 200 mL). The combined yellow organic layers were dried with sodium sulfate. The solvent was removed under reduced pressure and the dark orange oil was stirred under vacuum (vacuum pump, 0.1 torr) for 1 h to remove the residual 3-methylcyclohexanone. The excess diphenyldiselenide was removed by flash chromatography (600 g silica gel, 9:1 petroleum ether:ether) to give a mixture of isomeric $\alpha$-phenylseleno ketones 82, 83, 84 and 85 (23 g, ~100% yield). TLC: 9:1 hex:ether, UV, PMA.
C) Preparation of the Cyclohexenones 55 and 73

Aqueous hydrogen peroxide (30%, 24 g, ~200 mmol, 4.6 equiv in 25 mL of water) was added slowly to a solution of the \( \alpha \)-phenylseleno ketone mixture (11.6 g, 43 mmol) in dichloromethane (200 mL). (WARNING: there is an induction period). An exothermic reaction took place and the flask was cooled with a -10 °C bath. The internal temperature of the reaction mixture was kept below 42 °C. The mixture was stirred an additional 10 min at room temperature and was poured into a mixture of saturated aqueous sodium bicarbonate (1.5 L) and dichloromethane (400 mL). The layers were separated and the top layer was extracted twice with dichloromethane (2 x 200 mL). The combined organic layers were washed with water (1 L) and dried over sodium sulfate. The solvent was removed by distillation through a 50 cm Vigreux column. The residual oil was purified by flash chromatography (160 g of silica gel, 9:1 petroleum ether:ether). The most polar fractions were concentrated to give ~1 g (~20%) of 3-methylcyclohex-2-enone (73). The less polar fractions were combined and the solvents were distilled using a 50 cm Vigreux column to give a slightly yellow oil. The oil was distilled (50-90 °C/15 torr) to give 3.3 g (68%) of (-)-(\(R\))-5-methyl-2-cyclohexen-1-one (55), a colorless oil which exhibited IR (neat): 3037, 2959, 1680, 1618, 1458, 1429, 1392, 735 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \( \delta \): 1.07 (d, 3H, \( J = 5.6 \) Hz, Me), 2.01-2.30 (m, 3H, H-4a, H-5, H-6a), 2.38-2.54 (m, 2H, H-4e, H-6e), 6.04 (m, 1H, H-2), 6.96 (m, 1H, H-3); \(^13\)C NMR (50.3 MHz) \( \delta \): 20.87 (-ve, Me), 30.02 (-ve, C-5),
33.69, 45.95 (C-4, C-6), 129.23 (-ve, C-3), 149.58 (-ve, C-2), 199.57 (C-1); LRMS: M+(110) 51.5%; HRMS calcd for C₇H₁₀O: 110.0732, found: 110.0741; [α]D° -86.9°, c = 2.6 in chloroform (lit., -90.1° c = 2.55 chloroform); CD: c = 2.6 chloroform: [Ψ]ₜ₃₀: 316.0 nm (+377.4, 32.2 nm), 352.6 nm (-428.1, 25.6 nm).

4.2.1.2. Preparation of (+)-(2R,3R,5S)-2,5-Dimethyl-3-trimethylstannylcyclohexan-1-one (92)

A solution of methyllithium (1.63 M, 100 mL, 163 mmol, 2 equiv) was added to a cold (-20 °C) solution of hexamethylditin (33.7 mL, 163 mmol, 2 equiv) in THF (500 mL). The mixture was stirred for 20 min at -20 °C, for 5 min at 0 °C, and then was cooled back to -20 °C to give a faint yellow solution of trimethylstannyllithium (86). Solid copper(I) phenyl sulfide (28.2 g, 163 mmol, 2 equiv) was added in one portion to the trimethylstannyllithium (86) solution and the mixture was stirred at -20 °C for 20 min to give a dark red solution of the (trimethylstannyl)(phenylthio)cuprate (89). A solution of freshly distilled enone 55 (9 g, 82 mmol) in THF (80 mL) was added, via cannula, over a period of 10-20 min. The mixture was stirred 1 h at -20 °C and was then cooled to -78 °C. Iodomethane (51 mL, 817 mmol, 10 equiv) and HMPA (WARNING: carcinogenic, 28.5 mL, 163 mmol, 2 equiv) were successively added and the mixture was stirred 30 min at -78 °C. The solution was warmed to -20 °C and mixed at this temperature for an additional 40 min. Florisil® (500 g) and ether (500 mL) were mixed together and the mixture was packed into a chromatographic column. The cold reaction mixture was poured into the ether layer at the top of the
column. The solvents were eluted and the Florisil® was washed with an additional 500 mL of ether. The combined eluants were concentrated and the dark oil was passed through a column of Florisil® (200 g) and the column was washed with 500 mL of ether. The combined eluants were concentrated and the residue was stirred under vacuum (vacuum pump, 0.1 torr) for 2 h to remove the thioanisole. The mixture was purified by flash chromatography (1 kg silica gel, 9:1 petroleum ether:ether) and the acquired oil was distilled (80-110 °C/0.07 torr) to give 18.4 g (78%) of 92, a colourless oil which exhibited IR (neat): 2960, 2909, 1708, 768, 526 cm⁻¹; ¹H NMR (400 MHz) δ: 0.11 (s, 9H, ²J Sn-H = 52 Hz, Me₃Sn), 0.97 (d, 3H, J = 7 Hz, Me-8), 1.02 (d, 3H, J = 6.5 Hz, Me-7), 1.62 (ddd, 1H, J = 12, 12, 3.5 Hz, H-3), 1.71 (ddddd, 1H, J = 14, 3.5, 3.5, 2 Hz, H-4e), 2.01 (ddd, 1H, J = 14, 12, 4 Hz, H-4a), 2.17 (ddd, 1H, J = 13, 3.5, 2 Hz, H-6e), 2.41-2.51 (m, 2H, H-2, H-5), 2.57 (dd, 1H, J = 13, 6 Hz, H-6a); COSY: see Table 2.1; ¹H NMR decoupling experiments (400 MHz): irradiation of the signal at δ 0.97 (Me-8) led to simplification of the signal at δ 2.41-2.51 (H-5); irradiation at δ 1.02 (Me-7) produced a doublet at δ 2.45 (J = 12 Hz, H-2); NOE difference experiments: Irradiation at δ 0.97 (Me-8) led to the enhancement of signals at δ 1.62 (H-3), δ 1.71 (H-4e), δ 2.17 (H-6e), δ 2.47 (H-5); irradiation at δ 1.62 (H-3) led to the enhancement of signals at δ 0.97 (Me-8), δ 1.02 (Me-7) [Note, H-4e is too close to H-3 to see an enhancement]; ¹³C NMR (75.3 MHz) δ: -10.13 (-ve, ¹J Sn-C = 320 Hz, Me₃Sn), 15.94 (-ve, ³J Sn-C = 60 Hz, Me-7), 18.66 (-ve, Me-8), 29.22 (-ve, ¹J Sn-C = 375 Hz, C-3), 35.07 (-ve, C-5), 35.41 (²J Sn-C = 40 Hz, C-4), 48.28 (C-6), 48.32 (-ve, C-2), 214.14 (C-1); LRMS: M⁺(290) 5.9%; HRMS calcld for C₁₁H₂₂OSn: 290.0692, found: 290.0693; Anal. calcld for C₁₁H₂₂OSn: C 45.72, H 7.67, found: C 45.89, H 7.59; [α]D²⁸ +134.1°, c = 1.022 in MeOH; CD: c = 1.022 in MeOH: [Ψ]λ²⁸: 299.7 nm (+18030, 34.5 nm), 232.6 nm (-6789, 6.0 nm).
4.2.1.3. Preparation of (-)-(2S,3R,5S)-2,5-Dimethyl-3-trimethylstannylcyclohexan-1-one (93)

Sodium hydride (5 mg, 0.13 mmol, 0.3 equiv, 60% in oil) was added to a solution of the cyclohexanone 92 (121 mg, 0.42 mmol) in MeOH (2.5 mL). After the mixture had been stirred at room temperature for 26 hours, the ratio between 92 and 93 became constant at 1:1.1 (GLC) and some decomposition was observed. Brine (10 mL) was added and the mixture was extracted with ether (3 x 10 mL). The ether extracts were dried with magnesium sulfate and concentrated to give 105 mg of colourless oil. The oil was purified by flash chromatography (10 g silica gel, 30:67.5:0.5 dichloromethane:hex:ether). The more polar fraction (65 mg, 54%) was a mixture of 92 and 93. The less polar fraction was distilled (85-95 °C/0.1 torr) to give 16.6 mg (14%) of pure cyclohexanone 93, a colourless oil which exhibited IR (neat): 2963, 2924, 2824, 1712, 769, 524 cm⁻¹; ¹H NMR (400 MHz) δ: 0.11 (s, 9H, 2J_{Sn-H} = 52 Hz, Me₃Sn), 1.01 (d, 3H, J = 6 Hz, Me-8), 1.04 (d, 3H, J = 6 Hz, 4J_{Sn-H} = 4 Hz, Me-7), 1.75-1.85 (m, 1H, H-5), 1.85 (ddd, 1H, J = 12.5, 12, 5 Hz, H-4a), 1.97 (ddd, 1H, J = 13, 12.5, 1 Hz, H-6a), 2.00-2.05 (m, 2H, H-3, H-4e), 2.40 (ddd, 1H, J = 13, 4, 2 Hz, H-6e), 2.77 (dqd, 1H, J = 6.5, 6, 1 Hz, 3J_{Sn-H} = 132 Hz, H-2); COSY: see Table 2.2; Selective decoupling experiments: irradiation of the signal at δ 1.04 (Me-7) produced a doublet of doublets at δ 2.77 (J = 6.5, 1 Hz, 3J_{Sn-H} = 132 Hz, H-2); irradiation at δ 2.77 (H-2) simplified the signals at δ 1.04 (s, 4J_{Sn-H} = 4 Hz, Me-7), 1.97 (dd, J = 13, 12.5 Hz, H-6a), 2.00-2.05 (H-3); ¹³C NMR (75.3 MHz) δ: -8.8078 (-ve, 1J_{Sn-C} = 315 Hz, Me₃Sn), 15.78 (-ve, 3J_{Sn-C} = 20 Hz, Me-7), 22.32 (-ve, Me-8), 33.54 (-ve, 1J_{Sn-C} = 367 Hz, C-3), 35.43 (-ve, 3J_{Sn-C} = 20 Hz, C-5), 38.44
\( 2J_{\text{Sn-C}} = 10 \text{ Hz, C-4), 48.37 (-ve, C-2), 49.90 (C-6), 212.08 (C-1); LRMS: M^+(290) 8.7\%; \) HRMS calcd for \( \text{C}_{12}\text{H}_{22}\text{OSn} \): \( 290.0692 \), found: 290.0684; Anal. calcd for \( \text{C}_{12}\text{H}_{22}\text{OSn} \): C 45.72, H 7.67, found: C 45.78, H 7.49; \([\alpha]_D^{25} -44.1^\circ, c = 0.935 \) in MeOH; CD: \( c = 0.935 \) in MeOH: \([\Psi]_\lambda^{25} : 300.0 \text{ nm (+973.2, 35.5 nm), 221.2 nm (-2127, 27.0 nm).}

4.2.1.4. Preparation of (−)-(5R,6R)-3,6-Dimethyl-5-trimethylstanny1-2-cyclohexen-1-one (64)

A) Preparation of the Trimethylstanny1 Silyl Enol Ether 99

A solution of the 3-trimethylstanny1cyclohexanone 92 (8.83 g, 30.6 mmol) in THF (18 mL) was added over a period of 15 min, via cannula, to a freshly prepared solution of \( t\)-Pr\( \text{NLi} \) (36.6 mmol, 1.2 equiv) in THF (60 mL) at -78 °C. The mixture was stirred for 1.5 h at -78 °C and TMSCI (7.8 mL, 61 mmol, 2 equiv) was added. The solution was warmed to room temperature and the white suspension was concentrated. Dry pentane (200 mL) was added and the suspension was triturated and then was filtered through Celite\textsuperscript{®} and the Celite\textsuperscript{®} was washed with pentane. The pentane was removed under reduced pressure and the pentane/Celite\textsuperscript{®} treatment was repeated. The residual oil was distilled (85-95 °C/0.5 torr) to give ~11 g (~100%) of the silyl enol ether 99 as a colourless oil. No further purification was done and the silyl enol ether was used directly for the next step. The oil gave the following selected spectral data: IR (neat): 2958, 2869, 2840, 1660, 1455, 898, 847, 760, 524 cm\(^{-1}\); \( ^1\text{H NMR (400 MHz)} \delta: 0.07 (s, 9H, 2J_{\text{Sn-H}} = 30 \text{ Hz, Me}_3\text{Sn}), 0.19 (s, 9H, Me}_3\text{Si}, 0.97 \)
(d, 3H, J = 7.6 Hz, Me), 1.09 (d, 3H, J = 7.6 Hz, Me), 1.37-1.43 (m, 1H), 1.52-1.58 (m, 1H), 1.79-1.87 (m, 1H), 2.14-2.21 (m, 2H), 4.68 (d, 1H, J = 2.6 Hz, H-2).

B) Preparation of the Trimethylstannylcyclohexenone 64

A solution of DDQ (13.87 g, 61.1 mmol, 2 equiv) in benzene (330 mL) was added over a period of 1.5 h, via cannula, to a mixture of collidine (8.5 mL, 64.1 mmol, 2.1 equiv) and the silyl enol ether 99 (11 g, 30.5 mmol) in benzene (90 mL) at room temperature. The black mixture was stirred for an additional 1.5 h after the end of the addition. The suspension was filtered through a loose plug of cotton wool directly into a mixture of saturated aqueous sodium bicarbonate (1.5 L) and ether (1 L) and the phases were separated. The aqueous layer was extracted with ether (3 x 250 mL). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (200 mL) and brine (300 mL). The ether extract was dried over sodium sulfate and concentrated. The residual material was purified by flash chromatography (275 g silica gel, 85:15 hex:ether). The resulting oil was distilled (70–110 °C/0.07 torr) to give 5.0 g (57%) of the enone 64 as a low melting solid (mp: 22–24°C). The compound exhibited IR (neat): 2976, 2911, 1669, 1437, 1377, 1227, 768, 526 cm⁻¹; ¹H NMR (400 MHz) δ: 0.08 (s, 9H, 2J_Sn-H = 52 Hz, Me₃Sn), 1.16 (d, 3H, J = 7 Hz, Me-8), 1.69 (ddd, 1H, J = 12, 10, 6 Hz, H-5), 1.94 (s, 3H, Me-7), 2.35-2.50 (m, 3H, H-6, H-4a, H-4e), 5.86 (br s, 1H, H-2); ¹H NMR (400 MHz, C₆D₆) δ: 0.03 (s, 9H, 2J_Sn-H = 52 Hz, Me₃Sn), 1.21 (d, 3H, J = 7 Hz, Me-8), 1.34 (ddd, 1H, J = 12, 9, 6 Hz, H-5), 1.45 (s, 3H, Me-7), 1.90-2.00 (m, 2H, H-4a, H-4e), 2.17-2.26 (m, 1H, H-6), 5.96 (br s, 1H, H-2); ¹³C NMR (75.3 MHz) δ: -10.36 (-ve, ¹J_Sn-C = 340 Hz, Me₃Sn),
16.54 (-ve, $^3J_{Sn-C} = 23$ Hz, Me-8), 23.81 (-ve, $^4J_{Sn-C} = 6$ Hz, Me-7), 28.87 (-ve, $^1J_{Sn-C} = 400$ Hz, C-5), 35.10 ($^2J_{Sn-C} = 11$ Hz, C-4), 43.87 (-ve, $^2J_{Sn-C} = 16$ Hz, C-6), 125.95 (-ve, $^4J_{Sn-C} = 9$ Hz, C-2), 162.62 (C-3), 202.18 (C-1); HSC: see Table 2.3; LRMS: M$^+$ (288) 7.0%; HRMS calcd for C$_{11}$H$_{20}$O$^+$Sn: 288.0535, found: 288.0543; Anal. calcd for C$_{11}$H$_{20}$O$^+$Sn: C 46.04, H 7.02, found: C 46.23, H 7.12; $[\alpha]_D^{29}$ -45.2°, c = 1.072 in MeOH; CD: c = 1.072 in MeOH: $[\psi]_x^{29}$: 329.5 nm (+2365, 44 nm), 264.3 nm (+2666, ~8.5 nm).

4.2.1.5. Preparation of the 5-Chloro-2-trimethylstannyll-1-pentene (12)$^{87a-c,233}$

A solution of methyl lithium (1.27 M, 245 mL, 311 mmol, 1 equiv) was added to a cold (-20 °C) solution of hexamethylditin (64 mL, 311 mmol, 1 equiv) in THF (1.3 L). The mixture was stirred for 30 min at -20 °C to give a faint yellow solution of trimethylstannyllithium (86). The solution was cooled to -78 °C (15 min) and solid copper(I) bromide-dimethyl sulfide complex (63.9 g, 311 mmol, 1 equiv) was added in one portion. The dark red solution was stirred at -78 °C for 30 min and 5-chloro-1-pentyne (32.9 mL, 311 mmol) was added over a period of 30 min, via a Teflon® cannula. The mixture was stirred for 8 h at -78 °C and then glacial acetic acid (88.9 mL, 1.55 mol, 5 equiv) was added. The solution was stirred for 15 min at -78 °C and aqueous ammonium chloride (pH 9, 100 mL) was added and the mixture was warmed to room temperature (30 min). The content of the flask was poured into a 4 L Erlenmeyer flask containing a mixture of aqueous ammonium chloride (pH 9, 1 L) and ether (1 L) and the mixture was efficiently stirred overnight. The layers were separated and the dark blue layer was extracted with ether (2 x 1 L). The combined ether extracts were washed successively with ammonium chloride pH 9 solution (1 L) and
brane (1 L). The organic layer was dried with magnesium sulfate and concentrated to give a colourless oil (75 g). The oil was purified by a slow (7 h) chromatography on silica gel (2.25 kg, petroleum ether) to give 66.2 g (68%) of 5-chloro-2-trimethylstannyl-1-pentene (12) as colourless oil after distillation (100-105 °C/30 torr). The spectral data derived from this compound were identical with those reported previously. 87c

4.2.1.6. Preparation of (+)-(2R,3R,5S)-5-(5-Chloro-2-pent-1-enyl)-2,5-dimethyl-3-trimethylstannylcyclohexanone (100) and (2R,3R,5R)-5-(5-Chloro-2-pent-1-enyl)-2,5-dimethyl-3-trimethylstannylcyclohexanone (101) and (+)-(2R,3R)-2,5,5-Trimethyl-3-trimethylstannylcyclohexanone (102)

A) Preparation of the Chloro Ketone 100

A solution of methyllithium (1.5 M, 607 µL, 0.91 mmol, 1.8 equiv) was added to a cold (-78 °C) solution of 5-chloro-2-trimethylstannyl-1-pentene (12, 257 mg, 0.96 mmol, 1.9 equiv) in THF (10 mL) and the mixture was stirred at this temperature for 20 min. A cold (-78 °C) solution of lithium chloride-copper(I) cyanide89,234,235 (LiCl: 77 mg, 1.82 mmol, 3.6 equiv; CuCN: 82 mg, 0.9 mmol, 1.8 equiv) in THF (2 mL) was transferred, via cannula, to the resultant solution. A mixture of the enone 64 (144 mg, 0.5 mmol) and TMSCI (320 µL, 2.5 mmol, 5 equiv) in THF (2 mL) was added via cannula and the orange solution was stirred for 2 h at -78 °C. Boron trifluoride etherate91 (68 µL, 0.55 mmol, 1.1 equiv) was added and the mixture was stirred at -78 °C for 2 h. Aqueous ammonium chloride (pH 9, 15 mL) was added and the reaction mixture was opened to the air and was then warmed to room temperature.
Ether (15 mL) was added and the mixture was stirred until the aqueous layer turn deep blue. The layers were separated and the aqueous blue layer was extracted with ether (3 x 15 mL). The combined organic extracts were washed successively with aqueous ammonium chloride (pH 9, 15 mL) and brine (15 mL) and then the ether extracts were dried with magnesium sulfate. The solvents were removed under reduced pressure and the resulting oil was purified by flash chromatography (10 g silica gel, 9:1 hex:ether, 80 mL). The less polar fraction was composed mostly of the ketone 102 (9 mg, ~4% yield). The more polar, major fraction gave, after distillation (120–130 °C/0.1 torr), 170 mg (86 %) of the pure chloro ketone 100, which exhibited IR (neat): 2965, 1708, 1637, 1456, 1377, 768, 526 cm⁻¹; ¹H NMR (400 MHz) δ: 0.10 (s, 9H, 2J_SN-H = 52 Hz, Me₃Sn), 0.96 (d, 3H, J = 6.5 Hz, Me-7), 1.11 (s, 3H, Me-8), 1.26 (ddd, 1H, J = 14, 13, 2.5 Hz, 2J_SN-H = 45 Hz, H-3), 1.63 (dd, 1H, J = 14, 14 Hz, 3J_SN-H = 21 Hz, H-4a), 1.87-1.98 (m, 2H, H-4'), 2.03-2.13 (m, 3H, H-4e, H-3'), 2.17-2.30 (m, 2H, H-2, H-6a), 2.73 (dd, 1H, J = 14, 3 Hz, H-6e), 3.55 (m, 2H, H-5'), 4.88 (br s, 1H, H-1'b), 4.96 (s, 1H, H-1'a); COSY: see Table 2.4; NOE difference experiments: irradiation of the signal at δ 1.26 (H-3) led to enhancement of the signals at δ 0.96 (Me-7), δ 2.03-2.13 (H-4e, H-3'), δ 4.96 (H-1'a); irradiation of the signal at δ 1.63 (H-4a) led to enhancement of the signals at δ 1.11 (Me-8), δ 2.06 (H-4e), δ 2.17-2.30 (H-2, H-6a); irradiation of the signal at δ 4.96 (H-1'a) led to enhancement of the signals at δ 1.26 (H-3), δ 2.73 (H-6e), δ 4.88 (H-1'b); ¹³C NMR (50.3 MHz) δ: -10.15 (-ve, 1J_SN-C = 366 Hz, Me₃Sn), 15.47 (-ve, 3J_SN-C = 11 Hz, Me-7), 27.39 (C-4'), 28.92 (-ve, 1J_SN-C = 376 Hz, C-3), 29.34 (-ve, Me-8), 31.32 (C-3'), 40.04 (2J_SN-C = 12 Hz, C-4), 44.71 (C-6), 47.87 (-ve, 2J_SN-C = 18 Hz, C-2), 48.38 (C-5), 52.68 (C-5'), 112.11 (C-1'), 150.66 (C-2'), 204.17 (C-1); DCIMS(NH₃): MH⁺(393); HRMS calcd for C₁₆H₂₉ClOSn: 392.0928, found: 392.0927; Anal. calcd for C₁₆H₂₉ClOSn: C 49.08, H 7.47, found: C 49.28, H 7.64; [α]D²⁹ +86.4°, c = 1.10 in MeOH; CD: c = 1.10 in MeOH; [Ψ]D²⁹: 299.7 nm (+10820, 35 nm), 230.9 nm (-2666, 7.5 nm).
B) (+)-(2R,3R)-2,5,5-Trimethyl-3-trimethylstannylcyclohexanone (102)

Distilled (90-100 °C/0.1 torr); IR (neat): 2959, 1708, 1455, 1367, 764, 525 cm⁻¹; ¹H NMR (400 MHz) δ: 0.11 (s, 9H, ²J Sn-H = 52 Hz, Me₃Sn), 0.89 (s, 3H, Me-8), 2³ 0.99 (d, 3H, J = 7 Hz, Me-7), 1.05 (s, 3H, Me-9), 1.51 (ddd, 1H, J = 13.5, 13.5, 3.5 Hz, ²J Sn-H = 42 Hz, H-3), 1.53-1.60 (m, 1H, H-4e), 1.73 (dd, 1H, J = 14.5, 13.5 Hz, ³J Sn-H = 26 Hz, H-4a), 2.13 (dd, 1H, J = 12.5, 2 Hz, H-6e), 2.28 (d, 1H, J = 12.5 Hz, H-6a), 2.35 (dq, 1H, J = 13.5, 7 Hz, H-2); ¹³C NMR (50.3 MHz) δ: -10.14 (-ve, ¹J Sn-C = 315 Hz, Me₃Sn), 15.27 (-ve, ³J Sn-C = 11 Hz, Me-7), 24.83 (-ve, Me-8), 30.03 (-ve, ¹J Sn-C = 378 Hz, C-3), 31.84 (-ve, Me-9), 40.00 (³J Sn-C = 69 Hz, C-5), 43.43 (²J Sn-C = 14 Hz, C-4), 47.41 (-ve, ²J Sn-C = 19 Hz, C-2), 55.06 (C-6), 213.50 (³J Sn-C = 65 Hz, C-1); LRMS: M⁺(304) 3.1%; HRMS calcd for C₁₂H₂₄O₃Sn: 304.0848, found: 304.0854; Anal. calcd for C₁₂H₂₄O₃Sn: C 47.57, H 7.98, found: C 47.71, H 7.95; [α]D²⁶ +134.0°, c = 1.008 in MeOH; CD: c = 1.008 in MeOH: [Ψ]λ²⁶: 298.4 nm (+17950, 39 nm), 232.3 nm (-7454, 7 nm).

C) Preparation of the Mixture of Chloro Ketones 100 and 101

A solution of methylthium (1.44 M, 2.4 mL, 3.46 mmol, 1.4 equiv) was added to a cold (-78 °C) solution of the chloro vinylstannane 12 (923 mg, 3.45 mmol,
1.38 equiv) in THF (25 mL) and the mixture was stirred at this temperature for 20 min. Solid magnesium bromide etherate (907 mg, 3.51 mmol, 1.4 equiv) was added in one portion and the white suspension was stirred at -78 °C for 20 min. Solid copper(I) bromide-dimethyl sulfide (26 mg, 0.13 mmol, 0.05 equiv), a solution of the trimethylstannylcyclohexenone 64 (719 mg, 2.51 mmol) in THF (4 mL) and boron trifluoride etherate (340 µL, 2.76 mmol, 1.1 equiv) were successively added. The yellow suspension was stirred at -78 °C for 4 h. Aqueous ammonium chloride (pH 9, 25 mL) was added and the mixture was warmed to room temperature and was poured into ether (30 mL) in an Erlenmeyer flask. The mixture was vigorously stirred in the presence of air until the aqueous layer became deep blue. The layers were separated and the aqueous blue layer was extracted with ether (3 x 30 mL). The combined organic layers were successively washed with aqueous ammonium chloride (pH 9, 25 mL) and brine (25 mL) and the ether extracts were dried with sodium sulfate. The solvents were removed under reduced pressure to give 1.2 g of a colourless oil. The oil was purified by flash chromatography (35 g silica gel, 85:15 petroleum ether:ether, 400 mL) to give 884 mg (90%) of a colourless oil after distillation (120-150 °C/0.08 torr). The oil was a 5.3:1 mixture of chloro ketones 100 and 101 by GLC analysis and was inseparable by flash chromatography on silica gel. The 1H NMR (400 MHz) spectrum of the mixture showed, in addition to the signals derived from 100, δ: 0.12 (s, 9H, Me3Sn), 1.01 (d, 3H, J = 6.5 Hz, Me-7), 1.02 (s, 3H, Me-8), 2.35 (m, 1H, H-2), 4.79 (br s, 1H, H-1′b).
4.2.1.7. Preparation of (+)-(2R,3R,5S)-5-(5-lodo-2-pent-1-enyl)-2,5-dimethyl-3-trimethylstannylcyclohexanone (126) and (2R,3R,5R)-5-(5-lodo-2-pent-1-enyl)-2,5-dimethyl-3-trimethylstannylcyclohexanone (129)

A) Preparation of the Iodo Ketone 126

The chloro ketone 100 (4.11 g, 10.5 mmol) was added, neat, to a solution of sodium iodide (flame dried under vacuum, vacuum pump, 0.1 torr, 25.2 g, 168 mmol, 16 equiv) in dry acetone (120 mL) and the flask was rinsed with acetone (~2 mL). The stirred mixture was protected from light with aluminium foil and was refluxed for 10 h. Water (120 mL) was added to the yellow suspension and the mixture was extracted with ether (4 x 200 mL). The ether extracts were dried with magnesium sulfate, filtered and concentrated to give 8 g of crude oil. The oil was purified by flash chromatography (150 g silica gel, 9:1 hex:ether, 1.2 L) to give 4.84 g (95%) of the iodo ketone 126. An analytical sample, obtained by distillation of the oil (200-210 °C/0.07 torr), exhibited IR (neat): 2965, 1707, 1636, 1456, 1376, 768, 526 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.13 (s, 9H, \(^2\)J \(\text{Sn-H} = 52\) Hz, Me\(_3\)Sn), 0.98 (d, 3H, \(J = 6.5\) Hz, Me-7), 1.13 (s, 3H, Me-8), 1.28 (ddd, 1H, \(J = 14, 14, 2.5\) Hz, \(^2\)J \(\text{Sn-H} = 48\) Hz, H-3), 1.65 (dd, 1H, \(J = 14, 14\) Hz, \(^3\)J \(\text{Sn-H} = 21\) Hz, H-4a), 1.87-2.01 (m, 2H, H-4'), 2.02-2.07 (m, 2H, H-3'), 2.10 (ddd, 1H, \(J = 14, 3, 2.5\) Hz, H-4e), 2.21 (dd, 1H, \(J = 14, 1\) Hz, H-6a), 2.25 (m, 1H, H-2), 2.74 (dd, 1H, \(J = 14, 3\) Hz, H-6e), 3.23 (m, 2H, H-5'), 4.89 (br s, 1H, H-1'b), 4.97 (s, 1H, H-1'a); \(^1\)C NMR (75.3 MHz) \(\delta\): -10.06 (-ve, \(^1\)J \(\text{Sn-C} = 316\) Hz, Me\(_3\)Sn), 6.93 (C-5'), 15.33 (-ve, \(^3\)J \(\text{Sn-C} = 11\) Hz, Me-7), 28.87 (-ve, \(^1\)J \(\text{Sn-C} = 376\) Hz, C-3), 29.41 (-ve, Me-8), 31.09 (\(^2\)J \(\text{Sn-C} = 12\) Hz, C-4), 32.03 (C-3'), 40.02 (C-6), 47.97
(-ve, $^2J_{\text{Sn-C}} = 18$ Hz, C-2), 48.35 (C-5), 52.64 (C-4'), 112.20 (C-1'), 150.32 (C-2'), 212.26 (C-1); DCIMS(NH$_3$): MH$^+$ (485); HRMS calcld for C$_{15}$H$_{26}$O$_2$Sn (M$^+$-Me): 469.0049, found: 469.0044; Anal. calcld for C$_{16}$H$_{29}$O$_2$Sn: C 39.79, H 6.05, found: C 39.74, H 6.12; $[\alpha]_D^{26} +76.6^\circ$, c = 1.014 in MeOH; CD: c = 1.014 in MeOH: $[\Psi]_\lambda^{26}$: 300.1 nm (+9034, 35 nm), 227.9 nm (-8814, 9 nm).

B) Preparation of the Mixture of Iodo Ketones 126 and 129

The 5.3:1 mixture of chloro ketones 100 and 101 (884 mg, 2.26 mmol) was converted into the mixture of iodo ketones 126 and 129 (5.3:1, 1.1 g, 100%) using a procedure identical with that described above. The $^1$H NMR (400 MHz) spectrum of the mixture showed in addition to the signals due to 126, $\delta$: 0.14 (s, 9H, Me$_3$Sn), 1.02 (d, 3H, $J = 6.5$ Hz, Me-7), 1.03 (s, 3H, Me-8), 4.79 (br s, 1H, H-1'b).

4.2.1.8. Preparation of (+)-(1R,3R,4R,6R)-3,6-Dimethyl-7-methylene-4-trimethylstannylbicyclo[4.4.0]decan-2-one (124) and (+)-(1S,3R,4R,6S)-3,6-Dimethyl-7-methylene-4-trimethylstannylbicyclo[4.4.0]decan-2-one (130)

A) Preparation of the Bicyclic Ketone 124
A solution of the iodo ketone 126 (5.73 g, 11.9 mmol) in THF (20 mL) was added over a period of 20 min, via a small bore Teflon® cannula, to a cold (-78 °C) solution of i-Pr₂NLi (0.5 M, 26.1 mL, 13 mmol, 1.1 equiv) in THF (50 mL). The mixture was stirred at -78 °C for 1 h and then was warmed for 20 min (water bath, 35 °C). Aqueous citric acid (0.1 M, 50 mL) and ether (100 mL) were added. The layers were separated and the aqueous layer was extracted with ether (3 x 100 mL). The combined organic extracts were washed with brine (50 mL) and then were dried with magnesium sulfate. The solvents were removed under reduced pressure and the residual solid was purified by flash chromatography (180 g silica gel, 97:3 petroleum ether:ether) to give 3.84 g (93%) of the bicyclic ketone 124 as a white solid after distillation (120-150 °C/0.06 torr). The product was recrystallized from MeOH to afford colourless needles, mp 55.5-56 °C. The product exhibited IR (2% KBr): 2976, 2937, 1702, 1636, 1452, 1380, 527 cm⁻¹; ¹H NMR (400 MHz) δ: 0.14 (s, 9H, ²J_SN-H = 51 Hz, Me₃Sn), 0.95 (d, 3H, J = 6.5 Hz, Me-11), 1.28 (s, 3H, Me-12), 1.56-1.66 (m, 2H), 1.69-1.87 (m, 3H), 2.06-2.18 (m, 2H), 2.23-2.47 (m, 4H), 4.51 (br s, 1H, H-13), 4.77 (br s, 1H, H-13); ¹H NMR (400 MHz, C₆D₆) δ: 0.05 (s, 9H, ²J_SN-H = 51 Hz, Me₃Sn), 1.04 (d, 3H, J = 6.5 Hz, Me-11), 1.07 (s, 3H, Me-12), 1.40 (ddddd, 1H, J = 14, 14, 5, 5 Hz, H-10a), 1.50-1.60 (m, 1H, H-9a partially buried under H-5a), 1.55 (dd, 1H, J = 14, 14 Hz, ³J_SN-H = 24 Hz, H-5a), 1.81 (dddd, 1H, J = 14, 14, 2.5 Hz, ²J_SN-H = 43 Hz, H-4), 1.95 (d, 1H, J = 5 Hz, H-1), 2.00-2.10 (m, 3H, H-3, H-5e, H-8a), 2.12-2.30 (m, 3H, H-8e, H-9e, H-10e), 4.58 (br s, 1H, H-13a)4.78 (br s, 1H, H-13b); HSC: see Table 2.5; COSY: see Table 2.6; Selective decoupling experiments (C₆D₆): irradiation of the signal at δ 1.04 (Me-11) led to a doublet at δ 2.08 (H-3, J = 14 Hz); irradiation at δ 1.40 (H-10a) simplified the signals at δ 1.50-1.60 (H-9a), 1.95 (s, H-1), 2.12-2.30 (H-9e, H-10e); irradiation at δ 1.81 (H-4) simplified the signals at δ 1.55 (dd, J = 14, 2.5 Hz, H-5a), 2.00-2.10 (H-3, H-5e); irradiation at δ 1.95 (H-1) simplified the signals at δ 1.40 (dddd, J = 14, 14, 5 Hz, H-10a), 2.12-2.30 (H-10e); NOE difference experiments (C₆D₆): irradiation of the signal at δ 1.04 (Me-11, [NOTE: the signal at
δ 1.07 (Me-12) was also irradiated]) led to the enhancement of signals at δ 1.81 (H-4), δ 1.95 (H-1), δ 2.00-2.10 (H-3, H-5e, H-8a); irradiation of the signal at δ 1.07 (Me-12) led to the enhancement of the signals at δ 1.55 (H-5a), δ 1.95 (H-1), δ 2.05 (H-5e, H-8a); irradiation of the signal at δ 1.81 (H-4) led to the enhancement of signals at δ 1.04 (Me-11) and δ 4.58 (H-13a); irradiation of the signal at δ 1.95 (H-1) led to the enhancement of signals at δ 1.07 (Me-12), δ 1.40 (H-10a), δ 1.55 (H-5a), δ 2.22 (H-10e); ^13C NMR (75.3 MHz, C₆D₆) δ: -10.34 (-ve, 1J_Sn-C = 315 Hz, Me₃Sn), 16.37 (-ve, 3J_Sn-C = 15 Hz, Me-11), 21.87 (C-10), 23.75 (C-9), 29.24 (-ve, 1J_Sn-C = 382 Hz, C-4), 30.39 (-ve, Me-12), 33.10 (C-8), 41.55 (2J_Sn-C = 13 Hz, C-5), 48.12 (-ve, 2J_Sn-C = 15 Hz, C-3), 48.46 (C-6), 56.06 (-ve, 4J_Sn-C = 3 Hz, C-1), 107.78 (C-13), 150.76 (C-7), 209.92 (C-2); LRMS: M⁺(356) 3.2%; HRMS calcd for C₁₆H₂₈O₂Sn: 356.1161, found: 356.1164; Anal. calcd for C₁₆H₂₈O₂Sn: C 54.12, H 7.95, found: C 54.22, H 8.03; [α]D²⁸ +109.0°, c = 1.014 in MeOH; CD: c = 1.014 in MeOH: [Ψ]λ²⁸: 307.5 nm (+13980, 36 nm), 234.5 nm (-9123, 6.5 nm).

B) Preparation of the Bicyclic Ketones 124 and 130

The ketones 124 and 130 were prepared from the mixture of iodo ketones 126 and 129 (5.3:1, 1.11 g, 2.3 mmol) using a procedure identical with that described above except for the purification. An initial flash chromatography (75 g silica gel, 9:1
petroleum ether:ether) of the crude product gave the ketone 124 (74 mg, 9%) and a mixture of the ketones 124 and 130 (620 mg, 76%). Three additional, careful flash chromatographies (silica gel [100-150:1 silica gel:mixture w:w], 95:5 petroleum ether:ether) were performed and the appropriate fractions were combined to give the ketone 124 (559 mg, 68%), a mixture of the ketones 124 and 130 (54 mg, 7%) and the ketone 130 (62 mg, 8%). The ketone 130 was distilled (110–120 °C/0.1 torr) to give a white solid. The solid was recrystallized from MeOH to afford small prisms, mp 69.5-70.5 °C. The solid exhibited IR (2% KBr): 2960, 2940, 2864, 1698, 1632, 1450, 1379, 900, 769, 527 cm⁻¹; ¹H NMR (400 MHz) δ: 0.11 (s, 9H, ²J Sn-H = 52 Hz, Me₃Sn), 0.99 (d, 3H, J = 6.5 Hz, Me-11), 1.10 (s, 3H, Me-12), 1.18 (dd, 1H, J = 14, 4, 1.5 Hz, H-5e), 1.30 (dddd, 1H, J = 14, 14, 13, 4 Hz, H-9a), 1.57 (dd, 1H, J = 14, 13, 4 Hz, H-4), 1.62-1.69 (m, 1H, H-10e), 1.83 (m, 1H, H-10a), 1.84-1.91 (m, 1H, H-9e), 2.14 (ddd, 1H, J = 13, 4, 1.5 Hz, H-1), 2.23 (dm, 1H, J = 14 Hz, H-8e), 2.37-2.45 (m, 1H, H-8a), 2.43 (dd, 1H, J = 14, 14 Hz, H-5a), 2.65 (dq, 1H, J = 13, 6.5 Hz, H-3), 4.71 (br s, 1H, H-13b), 4.73 (br s, 1H, H-13a); HSC: see Table 2.7; COSY: see Table 2.8; Selective decoupling experiments: irradiation of the doublet at δ 0.99 (Me-11) led to simplification of the signal at δ 2.65 (d, J = 13 Hz, H-3); irradiation at δ 1.57 (H-4) simplified the signals at δ 1.18 (dd, J = 14, 1.5 Hz, H-5e), 2.43 (d, J = 14 Hz, H-5a), 2.65 (q, J = 6.5 Hz, H-3); irradiation at δ 2.65 (H-3) simplified the signals at δ 1.00 (s, Me-11), δ 1.57 (dd, J = 14, 4 Hz, H-4); NOE difference experiments: irradiation at δ 1.10 (Me-12) led to the enhancement of signals at δ 1.57 (4%,H-4), δ 2.14 (3%, H-1), δ 4.73 (3%, H-13a); irradiation at δ 1.57 (H-4) led to the enhancement of signals at δ 1.00 (Me-11), δ 1.10 (5%, Me-12), δ 1.18 (H-5e); ¹³C NMR (50.3 MHz) δ: -10.13 (¹J Sn-C = 315 Hz, Me₃Sn), 15.53 (³J Sn-C = 15 Hz, Me-11), 24.09 (Me-12), 27.15 (C-9), 27.73 (C-10), 29.57 (¹J Sn-C = 390 Hz, C-4), 32.78 (C-8), 36.19 (²J Sn-C = 12 Hz, C-5), 42.62 (²J Sn-C = 19 Hz, C-3), 45.23 (³J Sn-C = 65 Hz, C-6), 60.11 (C-1), 107.69 (C-13), 153.63 (C-7), 216.30 (C-2); LRMS: M⁺(356) 2.8%; HRMS calcd for C₁₆H₂₈OSn: 356.1161, found: 356.1161; Anal. calcd for C₁₆H₂₈OSn: C 54.12, H 7.95, found:
C 54.32, H 7.92; [α]D<sup>25</sup> +209.0°, c = 0.900 in MeOH; CD: c = 0.900 in MeOH: 
[Ψ]λ<sup>25</sup>: 304.5 nm (+14946, 36 nm), 236.2 nm (-8015, 9 nm).

4.2.1.9. Preparation of (+)-(2R,3R,5S)-5-(4-Chloro-2-but-1-enyl)-2,5-dimethyl-3-
trimethylstannylcyclohexanone (117)

A solution of methyllithium (1.47 M, 930 µL, 1.37 mmol, 1.2 equiv) was added to
a solution of freshly distilled 4-chloro-2-trimethylstannyl-1-pentene (110, generously
supplied by Johanne Renaud, 318 mg, 1.26 mmol, 1.1 equiv) in THF (3 mL) at -78 °C. The
colourless mixture was stirred for 30 min at -78 °C and then a cold (-78 °C)
solution of lithium chloride-copper(I) cyanide complex (LiCl: 107 mg, 2.52 mmol, 2.2 equiv; 
CuCN: 113 mg, 1.26 mmol, 1.1 equiv) in THF (3.6 mL) was added via 
cannula. The bright yellow solution was stirred for 15 min at -78 °C and then a mixture
of the enone 64 (331 mg, 1.15 mmol) and TMSCI (365 µL, 2.88 mmol, 2.5 equiv) in 
THF (1 mL) was added. Boron trifluoride etherate (155 µL, 1.26 mmol, 1.1 equiv) was
added to the orange solution and the mixture was stirred for 3 h at -78 °C. Aqueous
ammonium chloride (pH 9, 10 mL) and ether (10 mL) were added, the mixture was
warmed to room temperature and was stirred in the presence of air until the bottom
layer turned dark blue. The layers were separated and the aqueous layer was
extracted with ether (3 x 20 mL). The combined organic extracts were washed with 
brine (10 mL) and dried with magnesium sulfate. The solvents were removed under
reduced pressure to give 409 mg of a colourless oil. The oil was purified by flash 
chromatography (50 g silica gel, 95:5 petroleum ether:ether). The least polar fraction
gave 36 mg (10%) of the ketone 102 while the most polar fraction gave 33 mg (10%) of the starting enone 64. The major fraction gave 300 mg (69%, 76% based on recovered starting material) of the chloro ketone 117 as a colourless oil after distillation (110-120 °C/0.04 torr). The chloro ketone 117 exhibited IR (neat): 2966, 2929, 2872, 1707, 1636, 1456, 1377, 776, 525 cm⁻¹; ¹H NMR (400 MHz) δ: 0.11 (s, 9H, ²Jₘ-H = 52 Hz, Me₃Sn), 0.97 (d, 3H, ²Jₘ-H = 6.5 Hz, Me-7), 1.12 (s, 3H, Me-8), 1.29 (ddd, 1H, ²Jₘ-H = 46 Hz, H-3), 1.66 (dd, 1H, ²Jₘ-H = 14, 14 Hz, ³Jₘ-H = 21 Hz, H-4a), 2.04 (ddd, 1H, ²Jₘ-H = 14, 3, 3 Hz, ³Jₘ-H = 24 Hz, H-4e), 2.22 (d, 1H, ²Jₘ-H = 15 Hz, H-6a), 2.20-2.30 (m, 1H, H-2), 2.30-2.50 (m, 2H, H-3'), 2.72 (dd, 1H, ²Jₘ-H = 15, 3 Hz, H-6e), 3.61 (m, 2H, H-4'), 4.94 (br s, 1H, H-1'b), 5.04 (s, 1H, H-1'a); ¹³C NMR (50.3 MHz) δ: -10.18 (-ve, ¹Jₘ-C = 317 Hz, Me₃Sn), 15.29 (-ve, ³Jₘ-C = 11 Hz, Me-7), 28.79 (-ve, ¹Jₘ-C = 373 Hz, C-3), 29.10 (-ve, Me-8), 33.96 (C-3'), 39.88 (²Jₘ-C = 12 Hz, C-4), 43.19 (C-6), 47.68 (-ve, ²Jₘ-C = 17 Hz, C-2), 48.22 (C-5), 52.43 (C-4'), 113.67 (C-1'), 148.60 (C-2'), 212.50 (C-1); LRMS: M⁺-Me(363); HRMS calcd for C₁₄H₂₄ClO₃Sn: 363.0537, found: 363.0533; Anal. calcd for C₁₅H₂₇ClO₃Sn: C 47.72, H 7.21, found: C 47.89, H 7.26; [α]D²⁵ +87.7°, c = 1.212 in MeOH; CD: c = 1.212 in MeOH: [Ψ]D²⁵: 299.8 nm (+11630, 35 nm), 231.7 nm (-6780, 7 nm).

4.2.1.10. Preparation of (Z)-5-Chloro-3-trimethylstannyl-2-pentene (115)¹³d,⁹⁵

A) Preparation of Ethyl (Z)-3-Trimethylstannyl-3-pentenoate (113)

A solution of ethyl (E)-3-trimethylstannyl-2-pentenoate (112, generously supplied by Timothy Wong, 1.09 g, 3.73 mmol) in THF (4 mL) was slowly added (5–10 min) to a solution of i-Pr₂NLi (0.27 M in THF, 48 mL, 13.1 mmol, 3.5 equiv) at
-78 °C. The mixture was stirred for 30 min at -78 °C and for 1 h at 0 °C. The mixture was recooled to -78 °C and was transferred, via a wide bore Teflon® cannula, to a solution of glacial acetic acid (2.25 mL, 39.3 mmol, 10.5 equiv) in ether (38 mL) at -98 °C. The mixture was warmed to room temperature, saturated aqueous sodium bicarbonate (40 mL) was added and the layers were separated. The aqueous fraction was extracted with ether (2 x 20 mL). The combined ether extracts were washed with brine and were dried over magnesium sulfate. The solvents were removed under reduced pressure to give 1.25 g of a yellow oil. The oil was purified by flash chromatography (30 g silica gel, 98:2 petroleum ether:ether, 400 mL) to give 887 mg (82%) of ethyl (Z)-3-trimethylsilyl-3-pentenoate (113) as a colourless oil after distillation (50–70 °C/0.08 torr). The spectral data derived from this compound were identical with those reported previously.13d,95

B) Preparation of (Z)-3-Trimethylstannyl-3-penten-1-ol (114)

A solution of ethyl (Z)-3-trimethylstannyl-3-pentenoate (113, 997 mg, 3.42 mmol) in ether (4 mL) was slowly added to a cold (-20 °C) solution-suspension of lithium aluminium hydride (85 mg, 2.24 mmol, 0.65 equiv) in ether (20 mL). The mixture was stirred for 3 h at -20 °C and then powdered sodium sulfate decahydrate (0.5 g) was added and the mixture was warmed to room temperature. The suspension was filtered through a column of Florisil® (10 g) and the Florisil® was washed with ether (120 mL). The solvent was removed to give 879 mg of a colourless oil. The oil was purified by flash chromatography (25 g silica gel, 3:2 petroleum ether:ether, 200 mL) to give 620 mg (73%) of (Z)-3-trimethylstannyl-3-penten-1-ol (114) as a colourless oil after distillation (60–70 °C/0.1 torr). The spectral data derived from this compound were identical with those reported previously.13d,95
C) Preparation of (Z)-5-Chloro-3-trimethylstannyl-2-pentene (115)

Solid triphenylphosphine (1.31 g, 4.98 mmol, 2 equiv) was added to a mixture of triethylamine (382 µL, 2.74 mmol, 1.1 equiv) and (Z)-3-trimethylstannyl-3-penten-1-ol (114, 620 mg, 2.49 mmol) in dry carbon tetrachloride (15 mL). The mixture was refluxed for 24 h and then was cooled to room temperature. Petroleum ether (25 mL) was added and the suspension was filtered through a column of Florisil® (15 g) and the Florisil® was washed with petroleum ether (75 mL). The solvents were carefully removed under reduced pressure to give 731 mg of oil. The oil was distilled (40–60 °C/0.1 torr) to yield 612 mg (92%) of (Z)-5-chloro-3-trimethylstannyl-2-pentene (110) as a colourless oil. The spectral data derived from this compound were identical with those reported previously.¹³d,⁹⁵

4.2.1.11. Preparation of (+)-(2R,3R,5S)-5-[(Z)-5-Chloro-3-pent-2-enyl]-2,5-dimethyl-3-trimethylstannylcyclohexanone (121)⁹⁹

A solution of methyllithium (1.47 M, 300 µL, 0.44 mmol, 1.26 equiv) was added to a cold (-78 °C) solution of freshly distilled (Z)-5-chloro-3-trimethylstannyl-2-pentene (115, 107 mg, 0.4 mmol, 1.14 equiv) in THF (2 mL). The mixture was stirred for 20 min at -78 °C and solid magnesium bromide etherate (140 mg, 0.54 mmol, 1.5 equiv) was
added in one portion. The milky suspension was stirred for 25 min at -78 °C and then
ether (4 mL) was slowly added (4 min). The mixture was stirred for 10 min at -78 °C
and then solid copper(I) bromide-dimethyl sulfide (27 mg, 0.13 mmol, 0.38 equiv),
a solution of the trimethylstannylocyclohexenone 64 (100 mg, 0.35 mmol) in ether
(1 mL) and boron trifluoride etherate (45 μL, 2.76 mmol, 1.1 equiv) were successively
added. The yellow suspension was stirred at -78 °C for 3 h [NOTE: the yellow colour
persisted only for 1 h]. Aqueous ammonium chloride (pH 9, 3 mL) and ether (10 mL)
were added and the mixture was warmed to room temperature. The mixture was
vigorously stirred in the presence of air until the aqueous layer became deep blue.
The layers were separated and the aqueous blue layer was extracted with ether (2 x
10 mL). The combined organic layers were successively washed with water (3 mL)
and brine (3 mL) and the extracts were dried with magnesium sulfate. The solvents
were removed under reduced pressure to give 136 mg of a colourless oil. The oil was
purified by flash chromatography (10 g silica gel, from 9:1 to 7:3 petroleum ether:ether)
to give 23 mg (23%) of recovered starting material 64 and 88 mg (65%, 84% based on
recovered starting material) of the chloro ketone 121 as a colourless oil after
distillation (120-150 °C/0.08 torr). The chloro ketone 121 exhibited IR (neat): 2968,
1707, 1640, 1455, 1378, 773, 525 cm⁻¹; ¹H NMR (400 MHz) δ: 0.15 (s, 9H,
²J_{Sn-H} = 52 Hz, Me₃Sn), 1.02 (d, 3H, J = 6.5 Hz, Me-7), 1.22 (s, 3H, Me-8), 1.39
(dddd, 1H, J = 14, 13, 2.5 Hz, ²J_{Sn-H} = 44 Hz, H-3), 1.64 (dd, 1H, J = 14, 14 Hz,
³J_{Sn-H} = 19 Hz, H-4a), 1.75 (d, 3H, J = 7.5 Hz, Me-1'), 2.11 (d, 1H, J = 14 Hz
H-6a), 2.30-2.42(m, 2H, H-4'), 2.50-2.60 (m, 2H, H-2, H-4e), 2.85 (dd, 1H, J = 14, 3 Hz, H-6e),
3.54 (m, 2H, H-5'), 5.38 (q, 1H, J = 7.5 Hz, H-2'); ¹³C NMR (50.3 MHz) δ: -10.22 (-ve,
¹J_{Sn-C} = 316 Hz, Me₃Sn), 15.30 (-ve, ³J_{Sn-C} = 11 Hz, Me-7), 15.73 (-ve, Me-1'), 29.68
(-ve, Me-8), 29.89 (-ve, ¹J_{Sn-C} = 374 Hz, C-3), 39.27 (C-4'), 42.19 (²J_{Sn-C} = 12 Hz,
C-4), 44.59 (C-6), 48.07 (-ve, ²J_{Sn-C} = 18 Hz, C-2), 48.65 (C-5), 53.81 (C-5'), 124.63
(-ve, C-2'), 139.05 (C-3'), 212.30 (C-1); LRMS: M⁺-Me(377); HRMS calcd for
C₁₅H₂₆ClO₃Sn: 377.0693, found: 377.0696; Anal. calcd for C₁₆H₂₉ClO₃Sn: C 49.08,
H 7.47, found: C 49.26, H 7.57; [α]D\textsuperscript{25} +116.2°, c = 1.036 in MeOH; CD: c = 1.036 in MeOH: [Ψ]λ\textsuperscript{25}: 302.5 nm (+11310, 37 nm), 233.5 nm (-7568, 7 nm).

4.2.1.12. Preparation of (+)-(1R,3R,4R,6R)-3,6-Dimethyl-7-methylene-4-trimethylstannylbicyclo[4.3.0]nonan-2-one (132)

A solution of the chloro ketone 117 (327 mg, 0.87 mmol) in THF (3 mL) was added over a period of 20 min, via a small bore Teflon\textsuperscript{®} cannula, to a cold (-78 °C) solution of i-Pr\textsubscript{2}NLi (0.5 M in THF, 2.1 mL, 1.05 mmol, 1.2 equiv). The mixture was stirred at -78 °C for 1 h and then was warmed for 45 min (water bath, 45 °C). Aqueous citric acid (0.1 M, 3 mL) and ether (5 mL) were added. The layers were separated and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic extracts were washed with brine (5 mL) and then were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 308 mg of a faint yellow oil that crystallized at room temperature. The solid was purified by flash chromatography (8 g silica gel, 7:3 hex:dichloromethane, 100 mL) to give 260 mg (88%) of the bicyclic ketone 132 as a white solid after distillation (80-100 °C/0.15 torr). The product was sublimed (70 °C/0.1 torr) to afford colourless needles, mp 59.9-60.2 °C. The product exhibited IR (2% KBr): 2979, 2918, 1687, 1652, 1460, 1378, 883, 765, 522 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz) δ: 0.11 (s, 9H, \textsuperscript{2}J\textsubscript{Sn-H} = 52 Hz, Me\textsubscript{3}Sn), 0.95 (d, 3H, \textsuperscript{3}J = 6.5 Hz, Me-10), 1.13 (s, 3H, Me-11), 1.42 (ddd, 1H, \textsuperscript{3}J = 14, 13.5, 3 Hz, \textsuperscript{2}J\textsubscript{Sn-H} = 42 Hz, H-4), 1.53-1.65 (m, 2H, H-8e, H-9a), 1.90 (dd, 1H, \textsuperscript{3}J = 14, 14 Hz, \textsuperscript{3}J\textsubscript{Sn-H} = 24 Hz, H-5a),
2.06 (dd, 1H, J = 14, 3 Hz, 3J_{Sn-H} = 20 Hz, H-5e), 2.23 (m, 1H, H-3), 2.38-2.44 (m, 3H, H-1, H-8a, H-9e), 4.60 (dd, 1H, J = 2.5, 2 Hz, H-12a), 4.82 (dd, 1H, J = 2, 2 Hz, H-12b); NOE difference experiments: Irradiation at δ 1.13 (Me-11) led to the enhancement of signals at δ 1.53-1.65 (2%, H-9a), δ 1.90 (3%, H-5a), δ 2.06 (1.5%, H-5e), δ 2.42 (4%, dd, J = 6, 5 Hz, H-1), δ 4.60 (1%, H-12a); irradiation at δ 1.42 (H-4) led to the enhancement of signals at δ 0.95 (2%, Me-10), δ 2.06 (3%, H-5e), δ 2.38-2.44 (9%, H-8a); irradiation at δ 1.90 (H-5a) led to the enhancement of signals at δ 1.13 (4%, Me-11); 13C NMR (50.3 MHz) δ: -10.11 (-ve, 1J_{Sn-C} = 315 Hz, Me3Sn), 16.06 (-ve, 3J_{Sn-C} = 16 Hz, Me-10), 20.98 (C-9), 29.96 (-ve, 1J_{Sn-C} = 378 Hz, C-4), 30.15 (C-8), 31.20 (-ve, Me-11), 38.63 (2J_{Sn-C} = 13 Hz, C-5), 47.89 (-ve, 2J_{Sn-C} = 19 Hz, C-3), 54.84 (3J_{Sn-C} = 72 Hz, C-6), 59.97 (-ve, C-1), 103.74 (C-12), 155.60 (C-7), 222.30 (3J_{Sn-C} = 65 Hz, C-2); LRMS: M+ (342) 4%; HRMS calcd for C_{15}H_{26}OSn: 342.1005, found: 342.1013; Anal. calcd for C_{15}H_{26}OSn: C 52.83, H 7.68, found: C 52.90, H 7.74; [α]_D^{26} +76.7°, c = 1.14 in MeOH; CD: c = 1.14 in MeOH: [Ψ]_x^{26}: 301.8 nm (+14980, 37 nm), 233.2 nm (-6307, 6 nm).

4.2.1.13. Preparation of (+)-(1R,3R,4R,6R)-3,6-Dimethyl-7-(Z)-ethylidene-4-trimethylstannylbicyclo[4.3.0]nonan-2-one (133)
The chloro ketone 121 (145 mg, 0.37 mmol) was converted into the bicyclic ketone 133 using a procedure identical with that described for the preparation of the bicyclic ketone 132. The ketone 133 was obtained in 83% yield (109 mg) after chromatography (4 g silica gel, 95:5 hex:ether) and distillation (120-130 °C/0.15 torr). The ketone 133 was recrystallized from MeOH to afford colourless plates, mp 56.4–57.3 °C. The product exhibited IR (2% KBr): 2967, 1687, 1458, 1376, 767, 527 cm⁻¹; ¹H NMR (400 MHz) δ: 0.12 (s, 9H, ²Jₛₚ-H = 52 Hz, Me₃Sn), 1.01 (d, 3H, J = 6.5 Hz, Me-10), 1.25 (s, 3H, Me-11), 1.38 (ddd, 1H, J = 14, 13.5, 2 Hz, ²Jₛₚ-H = 45 Hz, H-4), 1.55(m, 1H, H-9a), 1.62 (ddd, 3H, J = 7.5, 2, 2 Hz, Me-13), 1.85 (dd, 1H, J = 14, 14 Hz, ³Jₛₚ-H = 21 Hz, H-5a), 2.19-2.45 (m, 5H, H-1, H-3, H-8a, H-8e, H-9e), 2.59 (dd, 1H, J = 14, 2 Hz, ³Jₛₚ-H = 24 Hz, H-5e), 5.27 (ddq, 1H, J = 2, 2, 7.5 Hz, H-12); NOE difference experiments: Irradiation at δ 1.25 (Me-11) led to the enhancement of signals at δ 1.62 (1%, Me-13), δ 1.85 (1.5%, H-5a), δ 2.30 (3%, d, J = 5 Hz, H-1), δ 2.59 (2%, H-5e); irradiation at δ 2.59 (H-5e) led to the enhancement of signals at δ 1.25 (1.5%, Me-11), δ 1.62 (3.6%, Me-13), δ 1.85 (27%, H-5a); ¹³C NMR (50.3 MHz) δ: -10.23 (-ve, ¹Jₛₚ-C = 315 Hz, Me₃Sn), 13.26 (-ve, Me-13), 16.23 (-ve, ³Jₛₚ-C = 15 Hz, Me-10), 22.76 (C-9), 28.67 (-ve, Me-11), 29.55 (-ve, ¹Jₛₚ-C = 380 Hz, C-4), 33.79 (C-8), 39.16 (²Jₛₚ-C = 14 Hz, C-5), 48.44 (-ve, ²Jₛₚ-C = 18 Hz, C-3), 53.92 (³Jₛₚ-C = 80 Hz, C-6), 62.42 (-ve, C-1), 115.24 (-ve, C-12), 145.35 (C-7), 213.20 (C-2); LRMS: M⁺(356) 18%; HRMS calcd for C₁₆H₂₈O₃Sn: 356.1161, found: 356.1154; Anal. calcd for C₁₆H₂₈O₃Sn: C 54.12, H 7.95, found: C 54.26, H 8.06; [α]D²⁶ +77.1°, c = 0.978 in MeOH; CD: c = 0.978 in MeOH: [Ψ]D²⁶: 303.4 nm (+13329, 37 nm), 234.6 nm (-4821, 6 nm).
4.2.2. Dissolved Metal Reductions of Trimethylstannylcyclohexane Derivatives

4.2.2.1. Preparation of (+)-(1R,2R,3S,6R)-3,6-Dimethyl-7-methylenebicyclo[4.4.0]-decan-2-ol (165)

A mixture of the bicyclic ketone 124 (144 mg, 0.4 mmol) and 2-methyl-2-propanol (770 μL, 8.1 mmol, 20 equiv) in THF (5 mL) was transferred, via cannula, to a cold (-78 °C), deep blue solution of lithium (28 mg, 4.1 mmol, 10 equiv) in ammonia (30 mL). The mixture was stirred for 1 h at -78 °C and was refluxed for 1 h. Solid ammonium chloride (400 mg) was added and the color of the suspension turned from deep blue to yellow and then became colorless. Ether (10 mL) was added and the ammonia was evaporated. Water (10 mL) and ether (20 mL) were added to the residual material and the layers were separated. The aqueous layer was extracted with ether (2 x 20 mL) and the combined ether extracts were washed with brine (10 mL) and then dried with magnesium sulfate. The solvents were removed under reduced pressure to give 91 mg of a colorless oil. The oil was purified by flash chromatography (4 g silica gel, 47:48:5 hex:dichloromethane:ether, 100 mL) to give 71 mg (89%) of the bicyclic alcohol 165 as a white solid after distillation (80–110 °C/0.1 torr). The product was recrystallized from acetonitrile to afford colourless needles, mp 87.5-88 °C. The product exhibited IR (2% KBr): 3280, 3084, 2982, 2930, 1637, 1460, 1374, 1078, 1021, 892 cm⁻¹; ¹H NMR (400 MHz) δ: 1.01 (d, 3H, J = 7 Hz, Me-11), 1.15 (s, 3H, Me-12), 1.25 (d, 1H, J = 6 Hz, OH [exchanged with D₂O]),
1.20-1.60 (m, 7H, H-1, H-3, H-4a, H-4e, H-5a, H-9a, H-9e), 1.70-1.82 (m, 1H, H-10a),
1.98-2.07 (m, 2H, H-5e, H-10e), 2.18 (br d, 1H, J = 13.5 Hz, H-8e), 2.35-2.45 (m, 1H,
H-8a), 3.15 (ddd, 1H, J = 10, 10, 6 Hz, H-2 [becomes dd, J = 10, 10 Hz, with D2O]),
4.60 (dd, 1H, J = 1.5, 1.5 Hz, H-13a), 4.79 (dd, 1H, J = 1.5, 1.5 Hz, H-13b); COSY: see
Table 2.9; Selective decoupling experiments: irradiation of the signal at δ 1.00
(Me-11) led to simplification of the signal at δ 1.40 (H-3); irradiation at δ 1.70-1.82
(H-10a) simplified the signals at δ 1.37 (br s, H-1), δ 1.59 (H-9a, H-9e), δ 2.05 (H-10e);
irradiation at δ 2.18 (H-8e) simplified the signals at δ 1.59 (H-9a, H-9e), δ 2.05 (H-10e),
δ 2.40 (H-8a); irradiation at δ 2.40 (H-8a) simplified the signals at δ 1.59 (H-9a, H-9e),
δ 2.18 (H-8e), δ 4.60 (d, J = 1.5 Hz, H-13a), δ 4.79 (d, J = 1.5 Hz, H-13b); irradiation at
δ 3.15 (H-2) simplified the signals at δ 1.25 (s, OH), δ 1.37 (br s, H-1), δ 1.40 (H-3);
^13C NMR (50.3 MHz) δ: 18.95 (-ve, Me-11), 21.55 (C-10), 21.58 (C-4), 29.20 (C-9),
30.27 (-ve, Me-12), 32.99 (C-5), 36.76 (C-8), 40.75 (-ve, C-3), 41.10 (C-6), 50.68 (-ve,
C-1), 73.56 (-ve, C-2), 107.80 (C-13), 151.07 (C-7); LRMS: M+(194) 5%; HRMS calcd
for C_{13}H_{22}O: 194.1671, found: 194.1662; Anal. calcd for C_{13}H_{22}O: C 80.36,
H 11.41, found: C 80.20, H 11.37; [α]_D^{24} +37.0°, c = 0.892 in chloroform.

4.2.2.2. Preparation of (-)-(1R,2S,3R,4R,6R)-3,6-Dimethyl-7-methylene-4-trimethyl-
stannylbicyclo[4.4.0]decan-2-ol (166)

Calcium metal (15 mg, 0.37 mmol, 1.1 equiv) was added to a cold (-78 °C)
solution of the bicyclic ketone 124 (121 mg, 0.34 mmol) and 2-methyl-2-propanol
(161 μL, 1.7 mmol, 5 equiv) in THF:ammonia (13 mL:25 mL). The mixture was stirred for 15 min at -78 °C and was refluxed for 1.5 h. During that period, the suspension became colorless. Solid ammonium chloride (400 mg) and ether (15 mL) were added and the ammonia was evaporated. Water (10 mL) and ether (15 mL) were added and the layers were separated. The aqueous layer was extracted with ether (2 x 15 mL) and the combined ether extracts were washed with brine (10 mL) and then dried with magnesium sulfate. The solvents were removed under reduced pressure to give 123 mg of a colorless oil. The oil was purified by flash chromatography (14 g silica gel, 35:60:5 hex:dichloromethane:ether, 200 mL) to give 38 mg (31%) of the starting material 124, 8 mg (12%) of the bicyclic alcohol 165 and 52 mg (42%) of the bicyclic trimethylstannyl alcohol 166 as a white solid after distillation (110-120 °C/0.1 torr). The product was recrystallized from acetonitrile to afford colourless cubes, mp 59–60 °C. The product exhibited IR (2% KBr): 3290, 3078, 2981, 2928, 1637, 1450, 1374, 1084, 1044, 1018, 893, 764, 523 cm⁻¹; ¹H NMR (400 MHz) δ: 0.08 (s, 9H, \(^2J_{Sn-H} = 51\) Hz, Me₃Sn), 1.01 (d, 3H, J = 6 Hz, Me-11), 1.12 (s, 3H, Me-12), 1.25 (d, 1H, J = 6 Hz, OH [exchanged with D₂O]), 1.26-1.50 (m, 4H, H-1, H-3, H-4, H-5a), 1.50-1.60 (m, 2H, H-9a, H-9e), 1.70-1.82 (m, 1H, H-10a), 2.02 (br d, 1H, J = 14 Hz, H-10e), 2.07 (br dd, 1H, J = 14, 1 Hz, H-5e), 2.17 (br d, 1H, J = 15 Hz, H-8e), 2.32-2.40 (m, 1H, H-8a), 3.16 (ddd, 1H, J = 10, 10, 6 Hz, H-2 [become dd, J = 10, 10 Hz, with D₂O]), 4.51 (dd, 1H, J = 1.5, 1.5 Hz, H-13a), 4.80 (dd, 1H, J = 1.5, 1.5 Hz, H-13b), COSY: see Table 2.10; Selective decoupling experiments: irradiation of the signal at δ 1.01 (Me-11) led to simplification of the signal at δ 1.42 (H-3); irradiation at δ 1.70-1.82 (H-10a) simplified the signals at δ 1.32 (br d, J = 10 Hz, H-1), δ 1.50-1.60 (H-9a, 9e), δ 2.02 (br s, H-10e); irradiation at δ 2.17 (H-8e) simplified the signals at δ 1.50-1.60 (H-9a, H-9e), δ 2.02 (H-10e), δ 2.32-2.40 (H-8a); irradiation at δ 2.32-2.40 (H-8a) simplified the signals at δ 1.50-1.60 (H-9a, H-9e), δ 2.17 (br s, H-8e); irradiation at δ 3.16 (H-2) simplified the signals at δ 1.25 (s, OH), δ 1.35 (br s, H-1), δ 1.42 (H-3); ¹³C NMR (50.3 MHz) δ: -10.32 (-ve, \(^1J_{Sn-C} = 306\) Hz, Me₃Sn), 19.94 (-ve,
$^{3}J_{\text{Sn-C}} = 16 \text{ Hz, Me-11}), 21.49 \text{ (C-10), 21.70 (C-9), 27.43 (-ve, }^{1}J_{\text{Sn-C}} = 399 \text{ Hz, C-4), 30.09 (-ve, Me-12), 32.97 \text{ (C-8), 41.47 (}^{2}J_{\text{Sn-C}} = 14 \text{ Hz, C-5), 42.50 \text{ (C-6), 44.32 (-ve, }^{2}J_{\text{Sn-C}} = 19 \text{ Hz, C-3), 50.66 (-ve, C-1), 74.35 (-ve, C-2), 107.89 \text{ (C-13), 150.99 \text{ (C-7); LRMS: M+}(358) \text{ 6.1%; HRMS calcd for } C_{16}H_{30}OSn: 358.1318, \text{ found: 358.1317; Anal. calcd for } C_{16}H_{30}OSn: C 53.81, H 8.46, \text{ found: C 53.66, H 8.47; } [\alpha]_{D}^{25} = -9.52^\circ, c = 1.505 \text{ in chloroform.}

4.2.2.3. Transformation of the Bicyclic Trimethylstannyl Alcohol 166 Into the Bicyclic Alcohol 165

The bicyclic trimethylstannyl alcohol 166 (142 mg, 0.4 mmol) was converted into the bicyclic alcohol 165 (73 mg, 94%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1).

4.2.2.4. Preparation of (-)-(1R,2R,3a6R)-3,6-Dimethyl-7-methylenebicyclo[4.3.0]-nonan-2-ol (175)

![Chemical structure of 175](image)

The bicyclic trimethylstannyl ketone 132 (90 mg, 0.26 mmol) was converted into the bicyclic alcohol 175 (36 mg, 75%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the reduction was purified by repetitive flash chromatography (5 g silica gel, 20:3:2 hex:dichloromethane:ethyl acetate) and by distillation (70-75 °C/0.09 torr). The product was recrystallized from acetonitrile to afford colourless needles, mp 68.5–}
69 °C. The product exhibited IR (2% KBr): 3264, 3069, 2953, 2917, 1654, 1457, 1372, 1058, 1033, 1019, 877 cm⁻¹; ¹H NMR (400 MHz) δ: 0.95 (d, 3H, J = 6.5 Hz, Me-10), 0.98 (s, 3H, Me-11), 1.08 (dddd, 1H, J = 14.5, 14, 14, 3 Hz, H-4a), 1.22-1.33 (m, 1H, H-3), 1.31 (d, 1H, J = 6 Hz, OH [exchanged with D₂O]), 1.37-1.49 (m, 3H, H-1, H-4e, H-5a), 1.78-1.90 (m, 3H, H-5e, H-9a, H-9e), 2.35-2.45 (m, 1H, H-8a), 2.48-2.57 (m, 1H, H-8e), 2.65 (ddd, 1H, J = 10, 10, 6 Hz, H-2 [become dd, J = 10, 10 Hz, with D₂O]), 4.67 (br s, 1H, H-12a), 4.80 (br s, 1H, H-12b), ¹³C NMR (50.3 MHz) δ: 18.57 (-ve, Me-10), 23.34 (C-4), 28.84 (C-9), 29.28 (C-5), 30.67 (-ve, Me-11), 33.34 (C-8), 39.22 (-ve, C-3), 47.42 (C-6), 54.98 (-ve, C-1), 76.96 (-ve, C-2), 102.91 (C-12), 156.50 (C-7); LRMS: M⁺(180) 18.6%; HRMS calcd for C₁₂H₂₀O: 180.1514, found: 180.1520; Anal. calcd for C₁₂H₂₀O: C 79.94, H 11.18, found: C 80.07, H 11.04; [α]D²³ -72.4°, c = 0.716 in chloroform.

4.2.2.5. Preparation of (-)-(1R,2R,3S,6R)-3,6-Dimethyl-7-[(Z)-ethylidene]bicyclo[4.3.0]-nonan-2-ol (176)

The bicyclic trimethylstannyl ketone 133 (111 mg, 0.31 mmol) was converted into the bicyclic alcohol 176 (40 mg, 66%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the dissolved metal reduction was purified by flash chromatography (8 g silica gel, 20:3:2 hex:dichloromethane:ethyl acetate, 100 mL) and by distillation (90-105 °C/0.08 torr). The product was recrystallized from
acetonitrile to afford colourless needles, mp 52.5-53.5 °C. The product exhibited IR (2% KBr): 3326, 2965, 2918, 2851, 1655, 1375, 1352, 1061, 1015, 862 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.98 (d, 3H, \(J = 6.5\) Hz, Me-10), 1.00-1.10 (m, 1H, H-4a), 1.07 (s, 3H, Me-11), 1.25-1.40 (m, 3H, H-3, H-4e, H-5a), 1.31 (d, 1H, \(J = 6\) Hz, OH [exchanged with D\(_2\)O]), 1.50 (ddd, 1H, \(J = 13, 7, 3.5\) Hz, H-1), 1.62 (ddd, 3H, \(J = 7, 2, 2\) Hz, Me-13), 1.70-1.85 (m, 2H, H-9a, H-9e), 2.30 (ddd, 1H, \(J = 14, 3, 3\) Hz, H-5e), 2.37-2.45 (m, 2H, H-8a, H-8e), 2.77 (ddd, 1H, \(J = 10, 10, 6\) Hz, H-2 [becomes dd, \(J = 10, 10\) Hz, with D\(_2\)O]), 5.25 (br q, 1H, \(J = 7\) Hz, H-12); COSY: see Table 2.14; \(^{13}\)C NMR (50.3 MHz) \(\delta\): 12.93 (-ve, Me-13), 18.80 (-ve, Me-10), 23.97 (C-4), 28.10 (-ve, Me-11), 29.75 (C-9), 31.65 (C-5), 34.36 (C-8), 39.28 (-ve, C-3), 47.62 (C-6), 57.38 (-ve, C-1), 76.93 (-ve, C-2), 114.77 (-ve, C-12), 145.52 (C-7); LRMS: M\(^{+}\)(194) 33.2%; HRMS calcd for C\(_{13}\)H\(_{22}\)O: 194.1671, found: 194.1670; Anal. calcd for C\(_{13}\)H\(_{22}\)O: C 80.36, H 11.41, found: C 80.10, H 11.47; [\(\alpha\)]\(^{23}\)D = -35.2°, c = 0.995 in chloroform.

4.2.2.6. Preparation of (+)-(1S,2S)-2,5,5-Trimethylcyclohexanol (177)

The trimethylstannyl ketone 102 (124 mg, 0.41 mmol) was converted into the alcohol 177 (39 mg, 66%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the reduction was purified by flash chromatography (5 g silica gel, 8:1:1 hex:dichloromethane:ethyl acetate) and by distillation (90-110 °C/15 torr). The product exhibited IR (neat): 3351, 2916, 1456, 1387, 1365, 1080, 1048, 1029, 921 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.90 (s, 3H, Me-9), 0.94 (s, 3H, Me-8), 1.02 (d, 3H, \(J = 6\) Hz, Me-7), 1.00-1.05 (m, 1H, H-3a), 1.10 (dd, 1H, \(J = 10, 12.5\) Hz, H-6a), 1.15-1.25 (m, 2H,
H-2, H-4a), 1.27 (d, 1H, J = 5 Hz, OH [exchanged with D$_2$O]), 1.28-1.33 (m, 1H, H-3e), 1.52-1.57 (m, 1H, H-4e), 1.67 (ddd, 1H, J = 12.5, 4, 2.5 Hz, H-6e), 3.30 (m, 1H, $w_{1/2} = 26$ Hz, H-1 [$w_{1/2}$ becomes 22 Hz with D$_2$O]); COSY: see Table 2.15; Selective decoupling experiments (CDCl$_3$ and D$_2$O): irradiation of the signal at $\delta$ 1.03 (Me-7, H-3a and maybe H-6a at 1.10 $\delta$) led to simplification of the signal at $\delta$ 1.15-1.25 (H-2, H-4a), $\delta$ 1.28-1.33 (H-3e), $\delta$ 1.52-1.57 (H-4e), 1.67 (H-6e), 3.30 (H-1); irradiation of the signal at $\delta$ 1.10 (H-6a and H-2) led to simplification of the signal at $\delta$ 1.02 (s, Me-7), $\delta$ 1.28-1.33 (H-3e), $\delta$ 1.52-1.57 (H-4e), 1.67 (br s, H-6e), $\delta$ 3.30 (H-1); irradiation of the signal at $\delta$ 1.67 (H-6e) led to simplification of the signal at $\delta$ 1.10 (d, J = 12 Hz, H-6a), $\delta$ 3.30 (br dd, J = 10, 10 Hz, H-1); irradiation of the signal at $\delta$ 3.30 (H-1) led to simplification of the signal at $\delta$ 1.10 (d, J = 12.5 Hz, H-6a), $\delta$ 1.67 (dd, J = 12.5, 2.5 Hz, H-6e), $\delta$ 1.15-1.25 (H-2); $^{13}$C NMR (50.3 MHz) $\delta$: 18.26 (-ve, Me-7), 25.09 (-ve, Me-8), 29.97 (C-3), 32.53 (C-5), 32.99 (-ve, Me-9), 38.70 (C-4), 40.54 (-ve, C-2), 48.44 (C-6), 73.47 (-ve, C-1); LRMS: M$^+$ (142) 3.4%; HRMS calcd for C$_9$H$_{18}$O: 142.1358, found: 142.1348; Anal. calcd for C$_9$H$_{18}$O: C 76.00, H 12.75, found: C 75.77, H 12.85; $[\alpha]_D^{24} +27.6^\circ$, c = 1.125 in chloroform.

4.2.2.7. Preparation of (-)-(1R,2R,3R,4R,6R)-3,6-Dimethyl-7-methylene-4-trimethylstannylbicyclo[4.4.0]decan-2-ol (178)
A solution of diisobutylaluminum hydride (1M hex, 2.24 ml, 2.24 mmol, 3 equiv) was added to a cold (-78 °C) solution of the ketone 124 (265 mg, 0.75 mmol) in THF (5 mL). The solution was stirred at -78 °C for 50 min and then at room temperature for 10 min. The reaction mixture was recooled to -78 °C and then MeOH (250 µL), saturated aqueous ammonium chloride (4 drops) and ether (10 mL) were added. The mixture was stirred at room temperature for 1 h and magnesium sulfate (0.5 g) was added. The milky white suspension was filtered through a column containing Florisil® (2 g) and a layer of Celite® (0.5 g) on top. The solids were triturated and washed with ether (25 mL) and the solvents were removed under reduced pressure to give a colourless oil. The oil was purified by flash chromatography (10 g silica gel, 95:5 hex:ether, 65 mL) to give 254 mg (96%) of the bicyclic trimethylstannyl axial alcohol 178 as a colourless oil after distillation (120-130 °C/0.05 torr). The product exhibited IR (neat): \(3558, 3080, 2918, 1632, 1441, 1396, 1376, 1188, 1081, 980, 895, 764, 523\) cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.10 (s, 9H, \(J_{\text{Sn-H}} = 52\) Hz, Me\(_3\)Sn), 0.91 (d, 3H, \(J = 6.5\) Hz, Me-11), 1.10 (s, 3H, Me-12), 1.32 (dd, 1H, \(J = 15, 14\) Hz, \(J_{\text{Sn-H}} = 14\) Hz, H-5a), 1.45 (br d, 1H, \(J = 5.5\) Hz, H-1), 1.55 (ddd, 1H, \(J = 14, 14, 2.5\) Hz, \(J_{\text{Sn-H}} = 53\) Hz, H-4), 1.60-1.75 (m, 3H, H-3, H-9a, H-10e), 1.71 (d, 1H, \(J = 12\) Hz, OH [exchanged with D\(_2\)O]), 2.03-2.16 (m, 1H, H-10a), 2.17-2.33 (m, 3H, H-5e, H-8e, H-9e), 2.40-2.53 (m, 1H, H-8a), 3.55 (ddd, 1H, \(J = 12, 2.5, 2.5\) Hz, H-2 [becomes br s with D\(_2\)O]), 4.76 (br s, 1H, H-13a), 4.83 (br s, 1H, H-13b); COSY: see Table 2.16; \(^{13}\)C NMR (50.3 MHz) \(\delta\): -10.41 (-ve, \(J_{\text{Sn-C}} = 307\) Hz, Me\(_3\)Sn), 20.06 (-ve, \(J_{\text{Sn-C}} = 16\) Hz, Me-11), 21.71 (-ve, \(J_{\text{Sn-C}} = 400\) Hz, C-4), 24.58 (C-10), 27.05 (C-9), 30.09 (-ve, Me-12), 32.13 (C-8), 38.86 (C-5), 41.66 (-ve, C-3), 41.85 (C-5), 47.99 (-ve, C-1), 79.76 (-ve, \(J_{\text{Sn-C}} = 56\) Hz, C-2), 106.28 (C-13), 155.49 (C-7); LRMS: M\(^+\) (358) 5.1%; HRMS calcd for C\(_{16}\)H\(_{30}\)OSn: 358.1318, found: 358.1322; Anal. calcd for C\(_{16}\)H\(_{30}\)OSn: C 53.81, H 8.46, found: C 53.96, H 8.52; \([\alpha]_D^{24} -68.6^\circ\), c = 1.138 in chloroform.
4.2.2.8. Preparation of (-)-(1R,2R,3R)-2,5,5-Trimethyl-3-trimethylstannylcyclohexanol (179)

The trimethylstanny1 ketone 102 (283 mg, 0.934 mmol) was converted into the trimethylstanny1 alcohol 179 (257 mg, 90%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 178 (4.2.2.7). The product of the reduction was purified by flash chromatography (7 g silica gel, 4:1 hex:ether) and by distillation (70-80 °C/0.09 torr). The product exhibited IR (neat): 3482, 2950, 2900, 1458, 1386, 1363, 1188, 1071, 1020, 1007, 932, 763, 523 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ: 0.09 (s, 9H, ²J_{Sn-H} = 50 Hz, Me₃Sn), 0.74 (m, 1H, OH), 0.84 (s, 3H, Me-8), 0.87 (d, 3H, J = 7 Hz, Me-7), 1.18 (dd, 1H, J = 14, 3 Hz, H-6a), 1.19 (s, 3H, Me-9), 1.27 (dd, 1H, J = 14, 13.5 Hz, H-4a), 1.36 (ddq, 1H, J = 14, 3, 7 Hz, H-2), 1.48-1.58 (m, 2H, H-4e, H-6e), 1.69 (dd, 1H, J = 14, 13.5, 3 Hz, ²J_{Sn-H} = 48 Hz, H-3), 3.51 (m, 1H, w_{1/2} = 7.8 Hz, H-1); ¹³C NMR (75.3 MHz, C₆D₆) δ: -10.33 (-ve, ¹J_{Sn-C} = 310 Hz, Me₃Sn), 20.13 (-ve, ³J_{Sn-C} = 8 Hz, Me-7), 22.95 (-ve, Me-8), 27.68 (-ve, ¹J_{Sn-C} = 338 Hz, C-3), 30.16 (³J_{Sn-C} = 56 Hz, C-5), 34.23 (-ve, Me-9), 40.20 (²J_{Sn-C} = 14 Hz, C-2), 44.88 (²J_{Sn-C} = 8 Hz, C-4), 46.11 (⁴J_{Sn-C} = 3 Hz, C-6), 72.20 (-ve, ³J_{Sn-C} = 59 Hz, C-1); LRMS: M⁺(306) 0.3%; HRMS calcd for C₁₂H₂₆O.Sn: 306.1005, found: 306.1006; Anal. calcd for C₁₂H₂₆O.Sn: C 47.25, H 8.59, found: C 47.40, H 8.53; [α]D ²⁸ -55.0°, c = 1.008 in MeOH.
4.2.2.9. Preparation of (+)-(1R,2R,3R,4R,6R)-3,6-Dimethyl-2-methoxy-7-methylene-4-trimethylstannylbicyclo[4.4.0]decane (184)

DMSO (5 μL, 0.07 mmol, 1 equiv) was added to a suspension of potassium hydride (23 mg, 35% in oil, washed with ether [3 x 1 mL] using a syringe to add and removed the ether and dried under vacuum [vacuum pump], 0.2 mmol, 3 equiv) in DMF (300 μL). The mixture was stirred for 10 min at room temperature and a solution of the bicyclic trimethylstannyl axial alcohol 178 (24 mg, 0.07 mmol) in DMF (1 mL) was added via cannula. Some bubbling was observed. The grayish suspension was stirred for 10 min at room temperature and then was cooled to 0 °C. Iodomethane (42 μL, 0.7 mmol, 10 equiv) was added and the mixture was stirred at room temperature for 1 h. Water (4 mL) and hex (4 mL) was added and the layers were separated. The aqueous layer was extracted with hex (3 x 5 mL). The combined organic layers were washed with brine (5 mL) and then dried with magnesium sulfate. The solvents were removed under reduced pressure to give 25 mg of oil. The oil was purified by flash chromatography (2.5 g silica gel, 9:1 hex: dichloromethane) to give 23 mg (91%) of the bicyclic trimethylstannyl ether 184 after distillation (95–110 °C/0.1 torr). The product exhibited IR (neat): 3079, 2908, 1640, 1461, 1375, 1192, 1093, 884, 764, 523 cm⁻¹; ¹H NMR (400 MHz) δ: 0.05 (s, 9H, 2J_{Sn-H} = 51 Hz, Me₃Sn), 0.96 (d, 3H, J = 6.5 Hz, Me-11), 1.06 (s, 3H, Me-12), 1.21 (dd, 1H, J = 15, 14 Hz, 3J_{Sn-H} = 14 Hz, H-5a), 1.45 (br dd, 1H, J = 3.5, 3.5 Hz, H-1), 1.52-1.80 (m, 4H, H-3, H-4, H-9a, H-10e), 1.90-2.12 (m, 2H, H-9e, H-10a), 2.15-2.25 (m, 2H, H-5e, H-8e),
2.42 (dddd, 1H, \( J = 15, 12.5, 6, 2.5, 2.5 \) Hz, H-8a), 3.12 (dd, 1H, \( J = 3.5, 2.5 \) Hz, \( ^4J_{\text{Sn-H}} = 18 \) Hz, H-2), 3.38 (s, 3H, OMe), 4.55 (br s, 1H, H-13a), 4.68 (br s, 1H, H-13b);

COSY: see Table 2.17; Selective decoupling experiments: irradiation of the signal at \( \delta 0.96 \) (Me-11) led to simplification of the signal at \( \delta 1.61 \) (dd, \( J = 12.5, 2.5 \) Hz, H-3); irradiation of the signal at \( \delta 1.21 \) (H-5a) led to simplification of the signal at \( \delta 1.73 \) (dd, \( J = 14, 5 \) Hz, H-4), \( \delta 2.20 \) (d, \( J = 5 \) Hz, H-5e); irradiation of the signal at \( \delta 2.42 \) (H-8a) led to simplification of the signal at \( \delta 1.60 \) (H-9a), \( \delta 2.00 \) (H-9e), \( \delta 1.98 \) (H-8e); irradiation of the signal at \( \delta 3.12 \) (H-2) led to simplification of the signal at \( \delta 1.45 \) (br d, \( J = 3.5 \) Hz, H-1), \( \delta 1.61 \) (H-3); \( ^{13}\text{C} \) NMR (50.3 MHz) \( \delta: -10.51 \) (-ve, \( ^1J_{\text{Sn-C}} = 303 \) Hz, Me\(_3\)Sn), 20.30 (-ve, \( ^3J_{\text{Sn-C}} = 19 \) Hz, Me-11), 23.19 (-ve, \( ^1J_{\text{Sn-C}} = 405 \) Hz, C-4), 23.54 (C-10), 26.75 (C-9), 30.95 (-ve, Me-12), 32.46 (C-8), 38.92 (C-6), 42.25 (\( ^3J_{\text{Sn-C}} = 15 \) Hz, C-5), 42.76 (-ve, \( ^2J_{\text{Sn-C}} = 19 \) Hz, C-3), 48.01 (-ve, C-1), 61.56 (-ve, OMe), 89.55 (-ve, \( ^3J_{\text{Sn-C}} = 54 \) Hz, C-2), 104.49 (C-13), 153.22 (C-7); LRMS: M\(^+\)(372) 3.6%;

HRMS calcd for C\(_{17}\)H\(_{32}\)OSn: 372.1474, found: 372.1481; Anal. calcd for C\(_{17}\)H\(_{32}\)OSn: C 55.02, H 8.69, found: C 55.20, H 8.75; \([ \alpha ]\)\(_D\)\(^{24}\) +3.9°, c = 0.98 in chloroform.

4.2.2.10. Preparation of \((-\)-(1\(R\),2\(R\),3\(R\))-2,5,5-Trimethyl-1-(2'-'trimethylsilylethoxy)-methoxy-3-trimethylstannylcyclohexane (185)\(^{19}\)

SEM-Cl (201 \( \mu \)L, 1.13 mmol, 3 equiv) was added to a solution of the trimethylstannyl alcohol 179 (115 mg, 0.38 mmol) and N,N-diisopropylethylamine
(329 µL, 1.89 mmol, 5 equiv) in dry dichloromethane (200 µL). The mixture was stirred for 1.5 h and then saturated aqueous ammonium chloride (1 mL) was added. The mixture was extracted with dichloromethane (2 x 10 mL) the combined organic extracts were washed with brine (2 mL) and then dried with magnesium sulfate. The solvents were removed under reduced pressure to give 326 mg of oil. The oil was purified by flash chromatography (3 g silica gel, 95:5 hex: ether) to give 145 mg (88%) of the trimethylstannyl SEM ether 185 after distillation (130-140 °C/0.03 torr). The product exhibited IR (neat): 2952, 1459, 1364, 1250, 1101, 1033, 861, 836, 764, 523 cm⁻¹; ¹H NMR (400 MHz, C₆D₆) δ: 0.03 (s, 9H, Me₃Si), 0.12 (s, 9H, ²Jₜ-Sn-H = 50 Hz, Me₃Sn), 0.89 (s, 3H, Me-8), 0.99 (two dd’s, 2H, J = 1.5, 7 Hz, H-2’), 1.08 (d, 3H, J = 7 Hz, Me-7), 1.09-1.13 (m, 1H, H-6a), 1.22 (s, 3H, Me-9), 1.33 (dd, 1H, J = 14, 13.5 Hz, ³Jₜ-Sn-H = 16 Hz, H-4a), 1.49 (ddq, 1H, J = 14, 7, 3 Hz, H-2), 1.62 (ddd, 1H, J = 13.5, 3, 3 Hz, ³Jₜ-Sn-H = 14 Hz, H-4e), 1.75-1.90 (m, 2H, H-3, H-6e), 3.62-3.70 (m, 2H, H-1, H-1’), 3.72-3.81 (m, 1H, H-1’), 4.59 (d, 1H, J = 7 Hz, OCH₂O), 4.76 (d, 1H, J = 7 Hz, OCH₂O); ¹³C NMR (75.3 MHz, C₆D₆) δ: -10.32 (⁻ve, ¹Jₗ-Sn-C = 298 Hz, Me₃Sn), -1.18 (⁻ve, ¹Jₗ-Si-C = 51 Hz, Me₃Si), 18.37 (C-2’), 20.44 (⁻ve, ³Jₗ-Sn-C = 23 Hz, Me-7), 23.88 (⁻ve, ¹Jₗ-Sn-C = 411 Hz, C-3), 27.07 (⁻ve, Me-8), 30.39 (³Jₗ-Sn-C = 62 Hz, C-5), 34.17 (⁻ve, Me-9), 40.26 (⁻ve, ²Jₗ-Sn-C = 18 Hz, C-2), 41.94 (C-6), 44.93 (²Jₗ-Sn-C = 14 Hz, C-4), 65.14 (C-1’), 76.96 (⁻ve, ³Jₗ-Sn-C = 58 Hz, C-1), 93.65 (OCH₂O); LRMS: M⁺-Me(421) 6%; HRMS calcld for C₁₈H₄₀O₂SiSn: 421.1584, found: 421.1588; Anal. calcld for C₁₈H₄₀O₂SiSn: C 49.67, H 9.26, found: C 49.88, H 9.21; [α]D²⁸ -68.9°, c = 1.008 in MeOH.
4.2.2.11. Preparation of (-)-(1R,2S,3S,6S,7R)-3,6,7-Trimethylbicyclo[4.4.0]decan-2-ol (186)

The bicyclic trimethylstannyl alcohol 178 (137 mg, 0.38 mmol) was converted into the alcohol 186 (68 mg, 91%) using a procedure identical with that described for the transformation of the bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the reduction was purified by flash chromatography (5 g silica gel, 95:5 hex:ether) and by distillation (75-90 °C/0.15 torr). The product was a low melting (25–30 °C) colourless solid. The product exhibited IR (neat): 3515, 2920, 1446, 1382, 1371, 1170, 1044, 1013, 975, 951 cm⁻¹; ¹H NMR (400 MHz) δ: 0.74 (d, 3H, J = 7 Hz, Me-13), 0.83 (s, 3H, Me-12), 0.94 (d, 3H, J = 6 Hz, Me-11), 0.98 (ddd, 1H, J = 13.5, 13, 3 Hz, H-5a), 1.13-1.26 (m, 2H, H-1, H-3), 1.30 (d, 1H, J = 4.5 Hz, OH [exchanged with D₂O]), 1.35 (ddd, 1H, J = 13, 13, 13, 4.5 Hz, H-8a), 1.40-1.55 (m, 5H, H-4a, H-4e, H-8e, H-9a, H-10a), 1.83-2.13 (m, 4H, H-5e, H-7, H-9e, H-10e), 3.73 (br s, 1H, H-2 [almost no change with D₂O]); COSY: see Table 2.18; Selective decoupling experiments: irradiation of the signal at δ 0.74 (Me-13) led to simplification of the signal at δ 2.08 (dd, J = 11, 3.5 Hz, H-7); irradiation at δ 0.94 (Me-11 and H-5a) simplified the signals at δ 1.15-1.20 (H-3), δ 1.50-1.55 (H-4a, H-4e), δ 1.91 (H-5e); NOE difference experiments: Irradiation at δ 0.74 (Me-13) led to the enhancement of signals at δ 1.35 (H-8a), δ 1.40-1.55 (H-8e), δ 1.92 (H-5e), δ 2.09 (H-7); irradiation at δ 0.83 (Me-12) led to the enhancement of signals at δ 1.22 (H-1), δ 1.35 (H-8a), δ 1.92 (H-5e); irradiation at δ 0.94 (Me-11 and H-5a) led to the enhancement of signals at
\[ \delta 1.30 (\text{OH}), \delta 1.50-1.55 (H-4a, H-4e), \delta 1.92 (H-5e), \delta 3.73 (H-2) \]; irradiation at \( \delta 0.98 \) (H-5a) led to the enhancement of signals at \( \delta 1.15 \) (-NOE, H-3), \( \delta 1.24 \) (-NOE, H-1), \( \delta 1.30 \) (-NOE, OH), \( \delta 1.92 \) (H-5e); irradiation at \( \delta 1.35 \) (H-8a and OH) led to the enhancement of signals at \( \delta 0.74 \) (Me-11), \( \delta 0.83 \) (Me-12), \( \delta 0.94 \) (Me-13), \( \delta 2.08 \) (H-9e), 3.75 (H-2); irradiation at \( \delta 3.73 \) (H-2) led to the enhancement of signals at \( \delta 1.24 \) (H-1), \( \delta 1.30 \) (OH), \( \delta 1.45-1.55 \) (H-10e); \( ^{13}\text{C} \) NMR (50.3 MHz) \( \delta \): 16.09 (-ve, Me-12), 17.98, (-ve, Me-11), 22.44 (-ve, Me-13), 23.54, 23.72, 26.89, 30.31 (C-4, 8, 9, 10), 31.51 (-ve, C-7), 35.51 (C-6), 37.18 (C-5), 38.30 (-ve, C-3), 46.74 (-ve, C-1), 78.52 (-ve, C-2); LRMS: M\(^+\)(196) 0.2%; HRMS calcd for C\(_{13}\)H\(_{24}\)O: 196.1827, found: 196.1820; Anal. calcd for C\(_{13}\)H\(_{24}\)O: C 79.53, H 12.32, found: C 79.50, H 12.42; \( [\alpha]_D^{25} \) -13.9\(^\circ\), c = 0.985 in chloroform.

### 4.2.2.12. Preparation of (+)-(1R,2S,3S,6R)-3,6-Dimethyl-2-methoxy-7-methylene-bicyclo[4.4.0]decane (191)

The bicyclic trimethylstannyl methyl ether 184 (56 mg, 0.15 mmol) was converted into the alcohol 191 (16 mg, 52\%) using a procedure identical with that described for the transformation of the trimethylstannyl bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the reduction was purified by flash chromatography (4 g silica gel, 4:1 hex:dichloromethane) and by distillation (70–80 °C/0.2 torr). The product exhibited IR (neat): 3084, 2931, 1640, 1461, 1381, 1195, 1123, 1101, 1056, 1039, 914, 886 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \( \delta \): 0.97 (d, 3H, \( J = 7 \) Hz,
Me-11), 0.90-1.08 (m, 1H, H-5a), 1.13 (s, 3H, Me-12), 1.35-1.45 (m, 1H, H-9a), 1.45-1.62 (m, 4H, H-1, H-4a, H-4e, H-10a), 1.75-1.85 (m, 1H, H-3), 1.85-2.02 (m, 2H, H-9e, H-10e), 2.06 (ddd, 1H, J = 14.5, 7.5, 4 Hz, H-5e), 2.18-2.26 (m, 1H, H-8e), 2.29-2.38 (m, 1H, H-8a), 3.29-3.38 (m, 1H, H-2), 3.33 (s, 3H, OMe), 4.67 (s, 2H, H-13a, H-13b); COSY: see Table 2.19; Selective decoupling experiments: irradiation of the signal at δ 0.97 (Me-11 and H-5a) led to simplification of the signal at δ 1.45-1.62 (H-4a, H-4e), δ 1.75-1.85 (H-3), δ 2.06 (H-5e); irradiation at δ 1.05 (H-5a) simplified the signals at δ 1.45-1.62 (H-4a, H-4e), δ 2.06 (dd, J = 7.5, 4, H-5e); irradiation at δ 1.80 (H-3) simplified the signals at δ 0.97 (s, Me-11), δ 1.45-1.62 (H-1, H-4a, H-4e), δ 3.29-3.38 (H-2); irradiation at δ 2.06 (H-5e) simplified the signals at δ 0.90-1.08 (H-5a), δ 1.45-1.62 (H-4a, H4e); irradiation at δ 3.33 (H-2) simplified the signals at δ 1.45-1.62 (H-1), δ 1.85-2.02 (H-3); 13C NMR (75.3 MHz) δ: 16.90 (-ve, Me-11), 25.24 (C-10), 25.59 (C-4), 26.03 (C-9), 27.89 (-ve, Me-12), 30.75 (C-5), 32.90 (C-8), 35.10 (-ve, C-3), 39.15 (C-6), 46.83 (-ve, C-1), 59.03 (OMe), 84.74 (-ve, C-2), 105.35 (C-13), 155.20 (C-7); LRMS: M+(208) 6.2%; HRMS calcd for C14H24O: 208.1827, found: 208.1827; Anal. calcd for C14H24O: C 80.71, H 11.61, found: C 80.20, H 11.78; [α]D24 +4.4°, c = 0.69 in chloroform.

4.2.2.13. Preparation of (+)-(1R,2S)-2,5,5-Trimethylcyclohexan-1-ol (192)

The trimethylstannylicyclohexanol 179 (123 mg, 0.40 mmol) was converted into the alcohol 192 (40 mg, 70%) using a procedure identical with that described for the transformation of the trimethylstannylicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The volatile product of the reduction was purified by flash chromatography.
(6 g silica gel, 9:1 pentane:ether) and by distillation (85-95 °C/17 torr). The product exhibited IR (neat): 3367, 2927, 1465, 1387, 1366, 1176, 1068, 1037, 1011 cm⁻¹; ¹H NMR (400 MHz) δ: 0.90 (s, 3H, Me-8), 0.93 (d, 3H, J = 7 Hz, Me-7), 0.99 (s, 3H, Me-9), 1.07-1.15 (m, 1H, H-4a), 1.21 (d, 1H, J = 4.5 Hz, OH [exchanged with D₂O]), 1.33-1.60 (m, 5H, H-3a, H-3e, H-4e, H-6a, H-6e), 1.82 (m, 1H, H-2), 3.88 (dddd, 1H, J = 7, 4.5, 4, 4 Hz, H-1 [becomes ddd, J = 7, 4, 4 Hz with D₂O]); COSY: see Table 2.20; ¹³C NMR (50.3 MHz) δ: 13.20 (-ve, Me-7), 26.42 (C-3), 28.72 (-ve, Me-8), 30.86 (-ve, Me-9), 31.10 (C-5), 34.74 (-ve, C-2), 35.14 (C-4), 43.44 (C-6), 70.37 (-ve, C-1); LRMS: M⁺(142) 1.5%; HRMS calcd for C₉H₁₈O: 142.1358, found: 142.1366; [α]₅₇⁸⁺²⁵ +11°, c = 0.040 in chloroform (for the enantiomer (195): [α]₅₇⁸⁻²⁵ -11°, c = 0.027 in chloroform)¹²³; [α]₅₇⁸⁺²⁵ +16.3°, c = 1.080 in chloroform; [α]₁⁻²⁵ +2.6°, c = 1.080 in chloroform.

4.2.2.14. Preparation of (-)-(1R,2S)-2,5,5-Trimethyl-1-(2-trimethylsilylethoxy)methoxy-cyclohexane (196)

The trimethylstannyl SEM-ether 185 (137 mg, 0.31 mmol) was converted into the alcohol 196 (73 mg, 85%) using a procedure identical with that described for the transformation of the trimethylstannyl bicyclic ketone 124 into the bicyclic alcohol 165 (4.2.2.1). The product of the reduction was purified by flash chromatography (6 g silica gel, 9:1 hex:dichloromethane) and by distillation (70-80 °C/0.15 torr). The product exhibited IR (neat): 2954, 1462, 1366, 1250, 1195, 1175, 1145, 1103, 1056, 937, 920, 836 cm⁻¹; ¹H NMR (400 MHz) δ: 0.01 (s, 9H, Me₃Si), 0.87 (s, 3H, Me-8), 0.90 (d, 3H, J = 7 Hz, Me-7), 0.90-0.95 (m, 2H, H-2'), 0.95 (s, 3H, Me-9), 1.03-1.12 (m, 1H, H-4a),
1.25 (dd, 1H, J = 13.5, 4 Hz, H-6e), 1.35 (ddd, 1H, J = 13.5, 10, 4 Hz, H-3a), 1.40-1.56 (m, 3H, H-3e, H-4e, H-6a), 1.83-1.93 (m, 1H, H-2), 3.58-3.67 (m, 2H, H-1'), 3.74 (ddd, 1H, J = 8, 4, 4 Hz, H-1), 4.62-4.70 (two d, 2H, J = 8 Hz, OCH2O); COSY see Table 2.21; 13C NMR (50.3 MHz) δ: -1 18 (-ve, 1J Si-C = 50 Hz, Me3Si), 13.58 (-ve, Me-7), 18.08 (C-2'), 26.72 (-ve, C-3), 28.58 (-ve, Me-8), 30.74 (-ve, Me-9), 31.12 (C-5), 33.14 (-ve, C-2), 35.16 (C-4), 40.31 (C-6), 64.75 (C-1'), 74.95 (-ve, C-1), 92.81 (OCH2O); LRMS: M+-Me3Si(199) 6.4%; DCIMS(NH3): MNH4+(290); HRMS calcd for C12H25O2Si: 229.1624, found: 229.1621; Anal. calcd for C15H32O2Si: C 66.11, H 11.84, found: C 66.35, H 11.89; [α]D25 -4.8°, c = 1.005 in chloroform.

4.2.3. Mosher's Esters

4.2.3.1. Preparation of (-)-(1R,2R,3S,6R)-3,6-Dimethyl-7-methylenebicyclo[4.4.0]-decan-2-yl (2S)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoate (171)

(R)-(−)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride (168) (26 μL, 0.14 mmol, 1.4 equiv) was added to a solution of the bicyclic alcohol 165 (19.5 mg, 0.1 mmol) in pyridine (300 μL) and carbon tetrachloride (300 μL). The mixture was stirred at room temperature for 4 days. During that period the solution turned slightly yellow and a small amount of white precipitate was observed. 3-Dimethylamino-
propylamine (24 µL, 0.19 mmol, 1.9 equiv), ether (5 mL) and cold (0 °C) aqueous hydrochloric acid (1 M, 3 mL) were added and the layers were separated. The organic layer was washed successively with cold (0 °C) saturated aqueous sodium bicarbonate (3 mL) and brine (3 mL). The ether extract was dried with magnesium sulfate and the solvent was removed under reduced pressure to give 29 mg of solid. A 1H NMR (400 MHz) of the crude product was recorded. The mixture was purified by flash chromatography (2 g silica gel, in gradient from 95:5 to 2:3 hex:ether) to give 8 mg (40%) of the starting alcohol 165 and 17 mg (41%, 69% based on recovered starting alcohol) of the Mosher's ester 171 as a white solid. The ester was recrystallized from hex to afford colourless prisms, mp 99.5-100 °C. The product exhibited IR (2% KBr): 3084, 2985, 2936, 2873, 1734, 1638, 1493, 1451, 1376, 1301, 1264, 1190, 1159, 1104, 1082, 1026, 971, 906, 723 cm⁻¹; 1H NMR (400 MHz) δ: 0.86 (d, 3H, J = 7 Hz, Me-11), 1.11 (s, 3H, Me-12), 1.16 (br dd, J = 10, 3 Hz, H-10e), 1.20-1.31 (m, 1H, H-5a), 1.37-1.45 (m, 1H, H-9e), 1.50-1.60 (m, 5H, H-1, H-4a, H-4e, H-9a, H-10a), 1.60-1.72 (m, 1H, H-3), 2.03 (ddd, 1H, J = 13, 4, 4 Hz, H-5e), 2.18 (br dd, 1H, J = 13, 3 Hz, H-8e), 2.30-2.40 (m, 1H, H-8a), 3.56 (unresolved q, 3H, 5J_F-H = 1 Hz, OMe), 4.62 (br s, 1H, H-13a), 4.83 (br s, 1H, H-13b), 4.96 (dd, 1H, J = 10, 10 Hz, H-2), 7.35-7.40 (m, 3H, aromatic H's), 7.60-7.64 (m, 2H, aromatic H's); COSY: see Table 2.11; 19F NMR (188.3 MHz); δ: 4.85 (intensity: 469.8, 1J_F-C = 288.3 Hz, 2J_F-C = 43.7 Hz, 3J_F-C = 27.4 Hz, (1R,2R,2'S,3S,6R)-isomer), 5.05 (intensity: 2.9, other isomer); 13C NMR (75.3 MHz) δ: 18.98 (Me-11), 21.31 (C-10), 21.57 (C-4), 29.14 (C-9), 30.00 (Me-12), 32.68 (C-5), 36.34 (C-8), 38.65 (C-3), 41.23 (C-6), 48.01 (C-1), 55.41 (OMe), 79.30 (C-2), 108.74 (C-13), 127.47, 128.18, 128.23 (2C's), 128.31, 129.52, 149.82 (C-7), 166.20 (C-1'); LRMS: M⁺(410) (saturated); HRMS calcd for C_{23}H_{29}F_{3}O_3: 410.2063, found: 410.2069 (peak matched); Anal. calcd for C_{23}H_{29}F_{3}O_3: C 67.30, H 7.12, found: C 67.50, H 7.20; [α]_D^{28} -23.9°, c = 0.463 in chloroform; [Ψ]_D^{28} 268.9 nm (+306.8, 4 nm), 262.5 nm (+400.0, 4 nm), 256.4 nm (+235.1, 3.5 nm), 233.3 nm (-1867, 15 nm), 226.9 nm (+1486, 2 nm).
4.2.3.2. Preparation of (+)-(1R,2R,3S,6R)-3,6-Dimethyl-7-methylenebicyclo[4.4.0]-
decan-2-yl (2R)-2-Methoxy-2-phenyl-3,3,3-trifluoropropanoate (172)

The bicyclic alcohol 165 (19.5 mg, 0.1 mmol) was converted into the Mosher's
ester 172 (17 mg, 41% {60 % based on recovered starting alcohol 165, 6 mg}) using
a procedure identical with that described for the transformation of the bicyclic alcohol
165 into the Mosher's ester 171 (4.2.3.1) using (S)-(+)2-methoxy-2-phenyl-3,3,3-
trifluoropropanoyl chloride (170) (26 µL, 0.14 mmol, 1.4 equiv). The ester was
recrystallized from hex at -20 °C to afford colourless prisms, mp 105-105.5 °C. The
product exhibited IR (2% KBr): 3079, 2982, 2957, 2926, 1737, 1637, 1455, 1301,
1265, 1181, 1159, 1027, 972, 725 cm⁻¹; ¹H NMR (400 MHz) δ: 0.77 (d, 3H, J = 6.5 Hz,
Me-11), 1.14 (s, 3H, Me-12), 1.20-1.30 (m, 1H, H-5a), 1.35 (br d, J = 13 Hz, H-10e),
1.45-1.75 (m, 7H, H-1, H-3, H-4a, H-4e, H-9a, H-9e, H-10a), 2.02 (ddd, 1H, J = 14, 3,
3 Hz, H-5e), 2.17 (br d, 1H, J = 14 Hz, H-8e), 2.30-2.40 (m, 1H, H-8a), 3.56 (m, 3H,
OMe), 4.63 (br s, 1H, H-13a), 4.83 (br s, 1H, H-13b), 4.92 (dd, 1H, J = 10.5, 10.5 Hz,
H-2), 7.36-7.42 (m, 3H, aromatic H's), 7.55-7.62 (m, 2H, aromatic H's); ¹⁹F NMR
(188.3 MHz); δ: 4.85 (intensity: 20, other isomer); 5.02 (intensity: 1274, ¹J F-C =
289.3 Hz, ²J F-C = 43.9 Hz, ³J F-C = 27.0 Hz, (1R,2R,2'S,3S,6R)-isomer); ¹³C NMR
(125.8 MHz) δ: 18.56 (Me-11), 21.53 (C-10), 21.79 (C-4), 29.08 (C-9), 30.09 (Me-12),
32.68 (C-5), 36.40 (C-8), 38.58 (C-3), 41.30 (C-6), 48.15 (C-1), 55.21 (OMe), 79.68
(C-2), 108.70 (C-13), 127.80, 128.30 (3 C's), 129.5, 131.80, 149.90 (C-7), 166.20 (C-1'); LRMS: M+\cdot C_{14}H_{21}O_2(189) 14.4\%, M+\cdot OOC(Ph)(OMe)CF_3(177) 100\%;
DCIMS(NH_3): MNH_4^+(428); HRMS calcd for C_{9}H_{8}F_3O: 189.0527, found: 189.0523;
calcd for C_{13}H_{21}: 177.1643, found: 177.1645; Anal. calcd for C_{23}H_{29}F_3O_3: C 67.30,
H 7.12, found: C 67.39, H 7.26; [ \alpha ]_D^{30} +31^\circ, c = 0.503 in chloroform; [ \Psi ]_\lambda^{25}: 268.9 nm (-155.4 3 nm), 262.4 nm (-240.7, 4 nm), 256.2 nm (-138.5, 3 nm), 240.4 nm (+584.9, 11 nm).
4.2.4. Total Synthesis of (-)-Kolavenol (65)

4.2.4.1. Preparation of (-)-(1R,3S,6R)-3,6-Dimethyl-7-methylenebicyclo[4.4.0]decan-2-one (47)\textsuperscript{238}

Solid TPAP (73 mg, 0.21 mmol, 0.05 equiv) was added to a solution-suspension of molecular sieves (powdered then flame dried under vacuum (vacuum pump), 2.1 g), 4-methylmorpholine-N-oxide (732 mg, 6.25 mmol, 1.5 equiv) and the bicyclic alcohol 165 (810 mg, 4.17 mmol) in dry dichloromethane (8.5 mL).\textsuperscript{125} [NOTE: Efficient stirring was done with a large magnetic stirrer plate and a 2 cm hexagonal bar]. The mixture was initially dark green and after 1 min became black. The suspension was stirred for 50 min at room temperature and was then filtered through a column of silica gel (10 g). The silica was washed with ethyl acetate (100 mL), the solvents were removed under reduced pressure. The resulting oil was purified by flash chromatography (20 g silica gel, 9:1 petroleum ether:ether, 200 mL) and by distillation (80-90 °C/0.3 torr) to give 765 mg (96%). The product exhibited IR (neat): 3085, 2934, 2869, 1708, 1639, 1456, 1376, 1080, 1043, 897, 874 cm\textsuperscript{-1} (3084, 1708, 1639, 894 and 874 cm\textsuperscript{-1})\textsuperscript{239}; \textsuperscript{1}H NMR (400 MHz) δ: 0.98 (d, 3H, J = 6 Hz, Me-17 [NOTE: Clerodane numbering system]), 1.28 (s, 3H, Me-19), 1.52-1.80 (m, 6H), 2.06-2.14 (m, 2H), 2.18-2.35 (m, 4H), 4.60 (br s, 1H, H-18a), 4.73 (br s, 1H, H-18b); [δ: 0.98 (d, 3H, J = 6 Hz), 1.31 (s, 3H), 1.55-1.92 (m, 6H), 2.08-2.17 (m, 2H), 2.25-2.39 (m, 4H), 4.63 (br s, 1H), 4.74 (br s, 1H)]\textsuperscript{247}; \textsuperscript{13}C NMR (75.3 MHz) δ: 14.81 (-ve, Me-17), 21.41
(C-1), 23.36 (C-2), 30.71 (-ve, Me-19), 30.85, 32.75, 36.38 (C-3, C-6, C-7), 44.70 (-ve, C-8), 45.50 (C-5), 56.22 (-ve, C-10), 107.66 (C-18), 150.38 (C-4), 212.51 (C-9); LRMS: M+(192) 77.6%; HRMS calcd for C13H20O: 192.1514, found: 192.1521; Anal. calcd for C13H20O: C 81.20, H 10.48, found: C 81.20, H 10.59; [α]_D^{25} -32.6°, c = 1.175 in chloroform; CD: c = 1.175 in chloroform: [Ψ]_D^{25}: 302.8 nm (-477.1, 45 nm, with shoulders at 310.9, 298.0, 293.9 and 287.5 nm).

4.2.4.2. Preparation of (+)-(1S,3aR,6R)-3,6-Dimethyl-7-methylenebicyclo[4.4.0]decan-2-one (17)

The bicyclic ketone 47 (70 mg, 0.36 mmol) was stirred with potassium tert-butoxide (82 mg, 0.73 mmol, 2 equiv) in 2-methyl-2-propanol for 48 h at room temperature. Cold (0 °C) aqueous hydrochloric acid (1 N, 2.5 mL) was added and the mixture was extracted with hex (3 x 2.5 mL). The combined organic extracts were washed with brine (2.5 mL) and then, were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 77 mg of oil. The oil was purified by flash chromatography (7 g silica gel, 95:5 hex:ether) to give 51 mg (73%) of a mixture (94:6 by 1H NMR) of the ketones 17 and 47 respectively. The mixture was purified by two radial chromatographies (A: 1 mm silica gel, 95:5 hex:ether; B: 1 mm silica gel, 3:1:1 chloroform:carbon tetrachloride:hex) to give an analytical sample of the ketone 17 after distillation (70-80 °C/0.25 torr). The product exhibited IR (neat): 3087,
2935, 2868, 1713, 1639, 1447, 1377, 1079, 1034, 895, 882 cm\(^{-1}\) \([3086, 1713, 1638, 895 \text{ and } 876 \text{ cm}^{-1}]^{241}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.88 (s, 3H, Me-19 [NOTE: Clerodane numbering system]), 0.99 (d, 3H, \(J = 6.5\) Hz, Me-17), 1.20-1.32 (m, 1H), 1.52-1.68 (m, 3H), 1.80-1.90 (m, 2H), 1.97 (dddd, \(J = 13.5,13, 4\) Hz, 1H), 2.05-2.40 (m, 5H), 4.69 (br s, 2H, H-18); [0.87 (s, 3H), 0.99 (d, 3H, \(J = 6\) Hz), 1.15-1.32 (m, 1H), 1.50-1.69 (m, 3H), 1.78-1.90 (m, 2H), 1.96 (dt, 1H, \(J = 4, 13\) Hz), 2.04-2.40 (m, 5H), 4.70 (br s 2H)]\(^{249}\); \(^{13}\)C NMR (100.6 MHz) \(\delta\): 14.42 (Me-17), 18.94 (C-1), 21.05 (C-2), 26.60 (Me-19), 31.75, 32.19, 35.90 (C-3, C-6, C-7), 44.55 (C-8), 45.22 (C-5), 57.99 (C-10), 105.62 (C-18), 155.88 (C-4), 213.26 (C-9); LRMS: \(M^+\) (192) 62.8\%; HRMS calcd for C\(_{13}\)H\(_{20}\)O: 192.1514, found: 192.1519; Anal. calcd for C\(_{13}\)H\(_{20}\)O: C 81.20, H 10.48, found: C 81.04, H 10.34; \([\alpha]_D^{25} +144.4^\circ\), \(c = 1.38\) in chloroform; CD: \(c = 1.38\) in chloroform: \([\Psi]_\lambda^{25}\): 299.5 nm (+5194, 37 nm, with shoulders at 309.8, 292.6 and 283.7 nm).

4.2.4.3. Preparation of (1R,2S,3R,6R)- and (1R,2R,3R,6R)-2-Cyano-3,6-dimethyl-7-methylenebicyclo[4.4.0]decane (215)\(^{242,243}\)

Solid potassium tert-butoxide (3.61 g, 32.2 mmol, 7.2 equiv) was added to a cold (0 °C) solution of TosMIC\(^{244}\) (2.62 g, 13.4 mmol, 3 equiv) in DMPU (15 mL). The thick dark yellow paste was stirred for 30 min at 0 °C and then a solution of the bicyclic ketone 47 (848 mg, 4.4 mmol) and 2-methyl-2-propanol (422 μL, 4.47 mmol,
1.01 equiv) in DMPU (2 mL) was added. The mixture was stirred 1 h at room temperature and then 95 h at 45 °C (oil bath temperature). The solution was poured into a cold (0 °C), stirred mixture of aqueous hydrochloric acid (1N, 30 mL) and hex (30 mL). The layers were separated and the aqueous layer was extracted with hex (2 x 30 mL). The combined organic extracts were successively washed with water (30 mL), saturated aqueous copper(II) sulfate (2 x 30 mL) and brine (2 x 30 mL). The extracts were dried with magnesium sulfate and the solvents were removed under reduced pressure to give 900 mg of yellow oil. The oil was purified by flash chromatography (50 g silica gel, 15:1 petroleum ether:ether) to give 733 mg of a mixture of the bicyclic nitriles 215 after distillation (60-70 °C/0.1 torr) (85:15, 82%, 88% based on 56 mg of recovered starting material). The identity of the mixture was confirmed by comparison of its data (IR, 1H NMR, TLC and GLC) with that of an authentic sample of the racemic mixture (prepared by John Wai). The product exhibited IR (neat): 3086, 2932, 2863, 2235, 1640, 1447, 1379, 893 cm⁻¹; 1H NMR (400 MHz) δ: 0.96 (s, 3H, Me-19, 215 β-CN, [NOTE: Clerodane numbering system]), 1.12 (d, 3H, J = 6 Hz, Me-17, 215 α-CN), 1.15 (d, 3H, J = 6 Hz, Me-17, 215 β-CN), 1.24 (s, 3H, Me-19, 215 α-CN), 1.25-1.78 (m, 8H, 215 β-CN, 215 α-CN), 1.85-2.00 (m, 2H, 215 β-CN, 215 α-CN), 2.03-2.10 (dd, 1H, J = 10, 10 Hz, H-9, 215 β-CN), 2.10-2.20 (m, 1H, H-3e, 215 β-CN, 215 α-CN), 2.30-2.45 (m, 1H, H-3a, 215 β-CN, 215 α-CN), 2.60 (dd, 1H, J = 4.5 Hz, H-9, 215 α-CN), 4.56 (br s, 1H, H-18a, 215 α-CN), 4.61 (br s, 1H, H-18b, 215 α-CN), 4.62 (br s, 1H, H-18a, 215 β-CN), 4.68 (br s, 1H, H-18b, 215 β-CN); LRMS: M⁺(203) 84.1%; HRMS calcd for C₁₄H₂₁N: 203.1674, found: 203.1672; Anal. calcd for C₁₄H₂₁N: C 82.70, H 10.41, found: C 82.64, H 10.36.
4.2.4.4. Preparation of (+)-(1S,2R,3R,6R)-2-Cyano-3,6-dimethyl-2-(3,5-dioxahexyl)-7-methylenebicyclo[4.4.0]decane (216)²⁴⁵

A solution of the bicyclic mixture of nitriles (215: 707 mg, 3.5 mmol) and HMPA (WARNING: carcinogenic, 1.2 mL, 7 mmol, 2 equiv) in THF (5 mL) was slowly added, via cannula, to a cold (0 °C) solution of i-Pr₂NLi (0.13 M in THF, 40 mL, 5.2 mmol, 1.5 equiv). The mixture was stirred for 30 min at 0 °C. 2-Iodo-1-methoxy-methoxyethane (319: 620 μL, 4.9 mmol, 1.4 equiv)²⁴⁶ was added neat to the yellow solution. The resulting colourless solution was stirred at 0 °C for 30 min and at room temperature for 3.5 h. The solution was diluted with petroleum ether (100 mL) and was washed successively with cold (0 °C) aqueous hydrochloric acid (1N, 40 mL), saturated aqueous copper(II) sulfate (2 x 40 mL), aqueous sodium thiosulfate (10%, 30 mL) and brine (40 mL). The extracts were dried with magnesium sulfate and the solvents were removed under reduced pressure to give 1.2 g of oil. The oil was purified by TLC grade silica chromatography (31 g H type silica, 8:2 hex:ether, 100 mL and 3:1 hex:ether, 200 mL) to give 950 mg (94%) of the bicyclic alkylated nitrile 216. The product exhibited IR (neat): 3087, 2930, 2228, 1639, 1448, 1381, 1213, 1153, 1110, 1042, 894 cm⁻¹; ¹H NMR (400 MHz) δ:  1.12 (d, 3H, J = 6 Hz, Me-17, [NOTE: Clerodane numbering system]), 1.24 (s, 3H, Me-19), 1.25-1.35 (m, 2H), 1.45-1.75 (m, 6H), 1.82 (dm, 1H, J = 14.5 Hz), 1.94 (dm, 1H, J = 12 Hz), 2.04-2.16 (m, 3H, two of them H-11), 2.38 (dddd, 1H, J = 14, 14, 5.5, 1.5, 1.5 Hz, H-3a), 3.32 (s, 3H, OMe), 3.48 (m, 2H, H-12), 4.53 (br s, 1H, H-18a), 4.54 (s, 2H, OCH₂O), 4.57 (dd, 1H, J = 1.5, 1.5 Hz,
H-18b); $^{13}$C NMR (50.3 MHz) $\delta$: 17.65 (-ve, Me-17), 19.00 (-ve, Me-19), 23.08, 27.65, 28.42, 32.20, 33.81, 36.24 (C-1, C-2, C-3, C-6, C-7, C-11), 37.57 (-ve, C-8), 40.10 (C-5), 43.58 (C-9), 48.50 (-ve, C-10), 55.37 (-ve, OMe), 62.56 (C-12), 95.50 (OCH$_2$O), 104.18 (C-18), 122.32 (CN, C-20), 157.85 (C-4); LRMS: $M^+$ (291) 1.2%; HRMS calcd for C$_{18}$H$_{29}$NO$_2$: 291.2198, found: 291.2202; Anal. calcd for C$_{18}$H$_{29}$NO$_2$: C 74.18, H 10.03, N 4.81; found: C 74.13, H 10.14, N 4.88; $\left[ \alpha \right]_D^{25} +56.9^\circ$, c = 1.06 in chloroform.

4.2.4.5. Preparation of (+)-(1S,2R,3R,6R)-3,6-Dimethyl-2-(3,5-dioxahexyl)-2-methanoyl-7-methylenebicyclo[4.4.0]decane (218)

A solution of i-Bu$_2$AlH (1 M in hex, 13 mL, 13 mmol, 4 equiv) was added to a solution of the nitrile 216 (943 mg, 3.4 mmol) in freshly distilled DME (32 mL) and the mixture was stirred at 50-60 °C for 6 h. The reaction mixture was cooled and was carefully poured into degassed water (32 mL) under a blanket of argon. Ether (100 mL) and aqueous hydrochloric acid (1 N, 10 mL) were added to the thick paste. The layers were separated and aqueous hydrochloric acid (1 N, 4 mL) and ether (50 mL) were added to the aqueous layer and the layers were separated. The last procedure was repeated until the aqueous layer become acidic (10 times, 600 mL total volume of ether). The combined organic layers were dried with magnesium sulfate and concentrated to give 894 mg of a greenish oil. The oil was dissolved in a mixture of THF (39 mL), glacial acetic acid (39 mL) and water (6 mL) and the solution was
stirred at room temperature for 12 h. The solvents were removed under vacuum (0.2 torr, vacuum pump) and the residue was dissolved in ether (150 mL) and successively washed with saturated aqueous sodium bicarbonate (30 mL) and brine (2 x 20 mL) and the ether layer was dried with magnesium sulfate. The solvent was removed under reduced pressure and the colorless residual oil was kept under vacuum (vacuum pump) overnight to give 851 mg (89%) of the aldehyde 218 (the aldehyde decompose rapidly in chloroform if the chloroform is not passed through flame dried basic alumina). The product exhibited IR (neat): 3085, 2928, 2768, 1713, 1637, 1448, 1377, 1212, 1153, 1044, 894 cm⁻¹; ¹H NMR (400 MHz) δ: 0.97 (s, 3H, Me-19, [NOTE: Clerodane numbering system]), 1.03 (d, 3H, J = 7 Hz, Me-17), 1.20-1.95 (m, 11H), 2.10-2.30 (m, 3H), 3.33 (s, 3H, OMe), 3.47 (m, 2H, H's-12), 4.55 (m, 2H, H's-18), 4.56 (s, 2H, OCH₂O), 9.96 (s, 1H,CHO); ¹³C NMR (50.3 MHz) δ: 16.89 (-ve, Me-17), 21.26 (-ve, Me-19), 22.20, 27.42, 28.35, 28.55, 32.63, 36.77 (C-1, C-2, C-3, C-6, C-7, C-11), 36.04 (-ve, C-8), 39.92 (C-5), 50.50 (-ve, C-10), 53.64 (C-9), 55.16 (-ve, OMe), 62.75 (C-12), 96.35 (OCH₂O), 103.84 (C-18), 158.32 (C-4), 206.52 (-ve, CHO, C-20); LRMS: M⁺(294) 0.5%; HRMS calcd for C₁₈H₃₀O₃: 294.2195, found: 294.2202 (matched peak); Anal. calcd for C₁₈H₃₀O₃: C 73.43, H 10.27, found: C 73.62, H 10.40; [α]D²⁵ +69.2°, c = 1.035 in chloroform; CD: c = 1.035 in chloroform; [ψ]λ²⁵: 310.7 nm (+853.5, 44 nm).

4.2.4.6. Preparation of (+)-(1R,2S,3R,6R)-2-(3,5-Dioxahexyl)-7-methylene-2,3,6-trimethylbicyclo[4.4.0]decane (214)¹⁴⁸,²⁴⁷
Anhydrous hydrazine [DANGER, ARGON ATMOSPHERE] \(^{248,249,250}\) (3.15 mL, 98 mmol, 100 equiv) was added via syringe to a solution of the aldehyde \(218\) (284 mg, 0.96 mmol) in anhydrous diethylene glycol (4 mL) and the mixture was heated between 120-140 °C (sand bath temperature) for 7 h. The mixture was cooled to room temperature and the excess hydrazine was distilled under vacuum (vacuum pump, 0.2 torr, 70-80 °C sand bath temperature). Powdered potassium hydroxide (552 mg, 9.8 mmol, 10 equiv) was added and the mixture was heated at 230 °C (sand bath temperature) for 1.5 h. The mixture was cooled to room temperature and then water (15 mL) and ether (50 mL) were added. The layers were separated and the aqueous layer was extracted with ether (4 x 30 mL). The combined organic layers were washed with brine (15 mL) and dried with magnesium sulfate. The solvents were removed under reduced pressure to give 292 mg of oil. The oil was purified by flash chromatography (4 g silica gel, 95:5 hex:ether) to give 221 mg (82%) of the ether \(214\) as a colourless oil after distillation (110-140 °C/0.2 torr). The product exhibited IR (neat): 3086, 2928, 1636, 1448, 1385, 1213, 1149, 1078, 1041, 892 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.75 (s, 3H, Me-19, [NOTE: Clerodane numbering system]), 0.85 (d, 3H, \(J = 6\) Hz, Me-17), 1.04 (s, 3H, Me-20), 1.20-1.70 (m, 11H), 1.88 (br d, 1H, \(J = 12\) Hz, H-2e), 2.10 (br dd, 1H, \(J = 4\), 13.5 Hz, H-3e), 2.29 (br tdt, 1H, \(J = 1.3\), 5, 13.5 Hz, H-3a), 3.34 (s, 3H, OMe), 3.38 (ddd, 1H, \(J = 5\), 10, 11 Hz, H-12b), 3.47 (ddd, 1H, \(J = 6\), 10, 11 Hz, H-12a), 4.49 (br s, 2H, H's-18), 4.57 (s, 2H, OCH\(_2\)O); \(^{13}\)C NMR (50.3 MHz) \(\delta\): 16.19 (-ve, Me-17), 17.86 (-ve, Me-20), 20.84 (-ve, Me-19), 22.00, 27.47, 28.55, 33.04, 37.25 (2 x CH\(_2\)) (C-1, C-2, C-3, C-6, C-7, C-11), 37.57 (-ve, C-8), 39.09 (C-5), 40.11 (C-9), 49.50 (-ve, C-10), 55.05 (-ve, OMe), 63.50 (C-12), 96.38 (OCH\(_2\)O), 102.75 (C-18), 160.35 (C-4); LRMS: M'-MeOH(248) 12.2%; HRMS calcd for C\(_{18}\)H\(_{32}\)O\(_2\): 280.2402, found: 280.2396; Anal. calcd for C\(_{18}\)H\(_{32}\)O\(_2\): C 77.09, H 11.50, found: C 77.20, H 11.46; \([\alpha]\)\(_D\)\(^{25}\) +75.7°, c = 1.165 in chloroform.
4.2.4.7. Preparation of (1R,2S,3R,6R)-2-(2-Hydroxyethyl)-7-methylene-2,3,6-trimethylbicyclo[4.4.0]decane (232). (-)-(1R,6R,7S,8R)-7-(2-Hydroxyethyl)-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (231), the Acetals 253-255 and (-)-(1R,5S,6R,9S)-5,6,10,10-Tetramethyl-2-oxatricyclo[7.4.0.0^{1,5}]tridecane (233).

A) Preparation of the Mixture of Alcohols 231 and 232

A solution of dimethylboron bromide (2 M in dichloromethane, 460 µL, 0.92 mmol, 3 equiv) was added to a cold (-78 °C) solution of the ether 214 (86 mg, 0.3 mmol) in dry dichloromethane (4 mL). The mixture was stirred for 4.5 h at -78 °C and was carefully transferred via cannula into a rapidly stirred mixture of DME (9 mL), saturated aqueous sodium bicarbonate (4 mL) and saturated aqueous sodium carbonate (5 mL). The reaction flask was rinsed with a small amount of DME (~3 mL) and the DME was added, via cannula, to the work-up mixture and the mixture was efficiently stirred for 6 h at room temperature. Ether (20 mL) was added and the layers were separated. The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed successively with 10% (w/v) aqueous sodium
thiosulfate (6 mL) and brine (2 x 10 mL) and the ether extracts were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 101 mg of oil. The oil was purified by flash chromatography (6 g silica gel, 7:3 to 3:1 hex:ether, 100 mL) to give 62 mg (86%) of the isomeric alcohols 232 and 231 (1:4 by $^1$H NMR) after distillation (100-120 °C/0.15 torr). The mixture exhibited $^1$H NMR (400 MHz) $\delta$: 0.73 (s, 3H, Me-19, 231, [NOTE: Clerodane numbering system]), 0.75 (s, Me-19, 232), 0.86 (d, 3H, $J$ = 6 Hz, Me-17, 232 and 231), 1.00 (s, 3H, Me-20, 231), 1.04(s, Me-20, 232), 1.10-2.35 (m, 16H, 232 and 231 including $\delta$ 1.57 [m, 3H, Me-18, 231]), 3.45-3.70 (m, 2H, H-12, 232 and 231), 4.49 (d, in a ratio 1:2 with the signal at $\delta$ 5.18, $J$ = 1.6 Hz, H-18, 232$^{251}$, 5.18 (m, 1H, H-3, 231).

B) Preparation of the Acetals 253-255

If the work-up time in (A) is shorter or if only sodium bicarbonate is employed, as suggested by Guindon and coworkers,$^{152b}$ we observed the formation of varying amounts (0%-30%) of the acetals 253-255 (mixture of exo-exo, endo-endo and exo-endo double bonds; the ratio of the double bonds exo:endo was 2.5:1 by $^1$H NMR)$^{252}$ A pure sample of this material was obtained by TLC grade silica chromatography (2 g H type silica, 98:2 hex:ether). The product exhibited IR (neat): 2963, 2921, 1636, 1448, 1384, 1109, 1080, 1038, 891 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$: 0.72 and 0.74 (two s, 3H, Me-19, [NOTE: Clerodane numbering system]), 0.83 (d, 3H, $J$ = 6 Hz, Me-17), 0.95 and 1.02 (two s, 3H, Me-20), 1.10-2.35 (m, 15H, including $\delta$ 1.57 [m, 3H, endo Me-18]),
3.30-3.50 (m, 2H, H-12), 4.49 (d, 2H, J = 1.6 Hz, H-18), 4.55-4.60 (three s, 2H, OCH2O), 5.18 [m, H-3 (endo double bond) in a ratio 1:5 with the signal of the exo-methylene at δ 4.49]; LRMS: M+-C16H26O(248) 4.4%; DCIMS(NH3): MNH4+(502); DCIMS(i-Bu): M+(484); HRMS calcd for C33H56O2: 484.4280, found: 484.4276; Anal. calcd for C33H56O2: C 81.76, H 11.64, found: C 81.92, H 11.72

C) Preparation of the Alcohol 231

Anhydrous p-TsOH (12 mg, 0.07 mmol, 0.16 equiv) was added to a solution of the alcohols 232 and 231 (1:2.2, 103 mg, 0.44 mmol) in dry chloroform (10 mL, dried by passing through 5 g of flame dried basic alumina) at room temperature. The mixture was stirred for 24 h and the solvent was removed under reduced pressure. The resulting oil was immediately purified by flash chromatography (6 g silica gel, 7:3 hex:ether) to give 96 mg (93%) of a mixture of alcohols 232 and 231 (1:52 by 1H NMR) after distillation (100-120 °C/0.2 torr). The product exhibited IR (neat): 3354, 2962, 1461, 1383, 1028, 980 cm⁻¹; 1H NMR (400 MHz) δ: 0.73 (s, 3H, Me-19, [NOTE: Clerodane numbering system]), 0.86 (d, 3H, J = 6 Hz, Me-17), 1.00 (s, 3H, Me-20), 1.10-1.80 (m, 14H, including δ 1.54 [m, 1H, OH exchanges with D2O] and δ 1.58 [m, 3H, Me-18]), 1.95-2.10 (m, 2H, H's-2), 3.55-3.67 (m, 2H, H's-12), 4.49 (d, very small, 232), 5.18 (m, 1H, H-3); 13C NMR (50.3 MHz) δ: 16.19 (-ve, Me-17), 17.93 (-ve, Me-20), 18.02 (-ve, Me-19), 19.96 (-ve, Me-18), 18.54, 26.80, 27.47, 36.67, 38.24, 38.75 (C-1, C-2, C-5, C-6, C-7, C-11), 37.30 (-ve, C-8), 40.92 (C-9), 47.96 (-ve, C-10), 56.63 (C-12), 120.41 (-ve, C-3), 144.23 (C-4); LRMS: M+-236) 0.9%; DCIMS(NH3): M+(236) 3 %; HRMS calcd for C16H28O: 236.2140, found: 236.2147; Anal. calcd for C16H28O: C 81.29, H 11.94, found: C 81.49, H 12.13; [α]D²⁵ -48.7°, c = 1.035 in chloroform.
A solution of the ether 214 (15 mg, 0.05 mmol) in THF (1 mL) and aqueous hydrochloric acid (6 N, 1 mL) was heated at 50 °C for 20 h. Water (1 mL) was added and the mixture was extracted with ether (2 x 10 mL). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate (2 x 1.5 mL) and brine (2 x 1.5 mL) and the ether extracts were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 8.6 mg (69%) of the tricyclic ether 233 after flash chromatography (0.3 g silica gel, 95:5 hex:dichloromethane) and distillation (75-85 °C/0.07 torr). The product exhibited IR (neat): 2947, 1464, 1386, 1365, 1064, 1039, 1023, 1001, 950, 912 cm⁻¹ [lit.¹⁶² (CCl₄): 1383, 1368, 1044, 1030 cm⁻¹]; ¹H NMR (400 MHz, CCl₄, TMS) δ: 0.80 (s, 3H), 0.81 (d, 3H, J = 6 Hz, Me-15), 0.86 (s, 3H), 0.91 (s, 3H), 0.95-1.20 (m, 4H), 1.20-1.60 (m, 8H), 1.60-1.80 (m, 2H), 3.66 (ddd, 1H, J = 3, 8.5, 10 Hz, H-3), 3.76 (ddd, 1H, J = 8.5, 8.5, 8.5 Hz, H-3); [lit.¹⁶², ¹H NMR (CCl₄, TMS) δ: 0.80 (s, 3H), 0.82 (d, 3H, J = 6 Hz, Me-15), 0.87 (s, 3H), 0.92 (s, 3H), 3.72 (center m, CH₂O)]; ¹H NMR (400 MHz) δ: 0.81 (s, 3H, Me-14), 0.81 (d, 3H, J = 6 Hz, Me-15), 0.87 (s, 3H, Me-16), 0.94 (s, 3H, Me-17), 1.00-1.20 (m, 4H, H-8a, H-9, H-11a, H-13a), 1.30-1.40 (m, 3H, H-7e, H-11e, H-12e), 1.41-1.51 (m, 3H, H-6, H-7a, H-8e), 1.52-1.65 (m, 2H, H-4a, H-13e), 1.70 (dddd, 1H, J = 3, 3.5, 13, 13 Hz, 12a), 1.77 (ddd, 1H, J = 3, 8.5, 12.5 Hz, H-4b), 3.71 (ddd, 1H, J = 3, 8.5, 10 Hz, H-3a), 3.82 (ddd, 1H, J = 8.5, 8.5, 8.5 Hz, H-3b); COSY: see Table 4.1.
Table 4.1: The 400 MHz $^1$H NMR and COSY Data for the Tricyclic Ether 233

<table>
<thead>
<tr>
<th>Assignment (H-X)</th>
<th>$^1$H NMR $\delta$ ppm (mult., # of H, J (Hz))</th>
<th>COSY Correlation (H-X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-14</td>
<td>0.81 (s, 3H)</td>
<td>.....a</td>
</tr>
<tr>
<td>Me-15</td>
<td>0.81 (d, 3H, 6)</td>
<td>6</td>
</tr>
<tr>
<td>Me-16</td>
<td>0.87 (s, 3H)</td>
<td>.....a</td>
</tr>
<tr>
<td>Me-17</td>
<td>0.94 (s, 3H)</td>
<td>9(LR), 11a(LR)</td>
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<td>7a</td>
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<td></td>
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<td>9</td>
<td>1.00-1.20 (m, 4H)</td>
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<tr>
<td>11a</td>
<td></td>
<td>Me-17(LR)</td>
</tr>
<tr>
<td>13a</td>
<td></td>
<td>11e, 12a, 12e</td>
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<td>13a</td>
<td></td>
<td>13e</td>
</tr>
<tr>
<td>8a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11e</td>
<td>1.30-1.40 (m, 3H)</td>
<td>6, 7a, 7e, 8e, 9</td>
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<td>11a, 12a</td>
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<td>13a, 13e</td>
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</tr>
<tr>
<td>7e</td>
<td>1.41-1.51 (m, 3H)</td>
<td>Me-15, 7a</td>
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<td>8a</td>
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<tr>
<td>4b</td>
<td>1.52-1.65 (m, 2H)</td>
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<td>13e</td>
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<td>12a, 12e, 13a</td>
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<td>12a</td>
<td>1.70 (dddddd, 1H, 3, 3.5, 13, 13, 13)</td>
<td>11a, 11e, 12e, 13a, 13e</td>
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<tr>
<td>4a</td>
<td>1.77 (ddd, 1H, 3, 8.5, 12.5)</td>
<td>3a, 3b, 4b</td>
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<td>3b</td>
<td>3.71 (ddd, 1H, 3, 8.5, 10)</td>
<td>3a, 4a, 4b</td>
</tr>
<tr>
<td>3a</td>
<td>3.82 (ddd, 1H, 8.5, 8.5, 8.5)</td>
<td>3b, 4a, 4b</td>
</tr>
</tbody>
</table>

*a No correlation.

*b (LR) = Long range correlation.

HMBC: see Table 2.24, HMQC: see Table 2.24; Selective decoupling experiments: irradiation of the signal at $\delta$ 0.81 (Me-15) led to simplification of the signal at $\delta$ 1.41-1.51 (H-6); irradiation of the signal at $\delta$ 1.41-1.51 (H-6, H-7e, H-8a) led to simplification of the signal at $\delta$ 0.81 (s, Me-15), $\delta$ 1.00-1.20 (H-7a, H-9) and 1.30–1.40 (H-8e); irradiation of the signal at $\delta$ 1.70 (H-12a) led to simplification of the signal at $\delta$ 1.00-1.20 (H-11a, H-13a), $\delta$ 1.30-1.40 (H-11e, H-12e) and $\delta$ 1.52-1.65 (H-13e);
irradiation at $\delta$ 3.71 (H-3a or b) simplified the signal at $\delta$ 1.53-1.65 (H-4a or b), produced a doublet of doublets at $\delta$ 1.77 ($J = 8.5, 12.5$ Hz, H-4a or b) and a doublet of doublets at $\delta$ 3.82 ($J = 8.5, 8.5$ Hz, H-3b or a); irradiation at $\delta$ 3.82 (H-3b or a) simplified the signal at $\delta$ 1.53-1.65 (H-4a or b), produced a doublet of doublets at $\delta$ 1.77 ($J = 3.5, 12.5$ Hz, H-4b or a) a doublet of multiplets at $\delta$ 3.71 ($J = 10$ Hz, H-3a or b); NOE difference experiments: Irradiation of the signals at $\delta$ 0.81 (Me-14 and Me-15) enhanced the signals at $\delta$ 1.00-1.20 (H-7a, H-13a), $\delta$ 1.41-1.51 (H-6, H-7e), $\delta$ 1.52-1.65 (H-13e, H-4b), $\delta$ 1.77 (H-4a, ddd, $J = 3, 8.5, 12.5$ Hz): Irradiation of the signals at $\delta$ 0.83 (mostly Me-15) enhanced the signals at $\delta$ 1.00-1.20 (H-7a), $\delta$ 1.41-1.51 (H-6, H-7e), $\delta$ 1.77 (H-4a, ddd, $J = 3, 8.5, 12.5$ Hz): Irradiation of the signal at $\delta$ 0.87 (Me-16) enhanced the signals at $\delta$ 1.30-1.40 (dm, $J = 11$ Hz, H-11e), $\delta$ 1.41-1.51 (dm, $J = 13.5$ Hz, H-8e): Irradiation of the signal at $\delta$ 0.94 (Me-17) enhanced the signals at $\delta$ 1.30-1.40 (dm, $J = 11$ Hz, H-11e and m, H-8a), $\delta$ 1.41-1.51 (dm, $J = 13.5$ Hz, H-8e): Irradiation of the signal at $\delta$ 1.15 (mostly H-11a) enhanced the signals at $\delta$ 0.87 (Me-16), $\delta$ 1.30-1.40 (H-11e, H-12e), $\delta$ 1.52-1.65 (H-13e negative NOE), $\delta$ 1.70 (ddddd, negative NOE, H-12a): Irradiation of the signal at $\delta$ 1.70 (H-12a) enhanced the signals at $\delta$ 0.94 (Me-17), $\delta$ 1.30-1.40 (H-11e, H-12e), $\delta$ 3.71 (ddd, $J = 3, 8.5, 10$ Hz, H-3b): Irradiation of the signal at $\delta$ 1.77 (H-4a) enhanced the signals at $\delta$ 1.41-1.51 (H-6), $\delta$ 1.52-1.65 (H-4b), $\delta$ 3.82 (H-3a): Irradiation of the signal at $\delta$ 3.71 (H-3b) enhanced the signals at $\delta$ 1.52-1.65 (H-4b), $\delta$ 3.82 (H-3a): Irradiation of the signal at $\delta$ 3.82 (H-3a) enhanced the signals at $\delta$ 1.77 (H-4a), $\delta$ 3.71 (H-3b); $^{13}$C NMR (50.3 MHz) $\delta$: 13.47 (-ve, Me-14), 17.44 (-ve, Me-15), 18.44 (C-12), 22.10 (C-7), 22.37 (-ve, Me-17), 31.28 (C-8), 31.42 (C-13), 32.27 (-ve, Me-16), 34.09 (C-10), 35.37 (C-4), 35.46 (-ve, C-6), 42.70 (C-11), 47.03 (C-5), 47.91 (-ve, C-9), 62.44 (C-3), 85.10 (C-1); LRMS: $M^+$(236) 6.4%; HRMS calcd for $C_{16}H_{28}O$: 236.2140, found: 236.2147; Anal. calcd for $C_{16}H_{28}O$: C 81.29, H 11.94, found: C 81.00, H 12.10; $[^\alpha]D^{25}$ +39.1°, c = 1.77 in chloroform [lit.$^{162}$ $[^\alpha]D^{25}$ for the enantiomer +39.1°, c = 6.3 in chloroform].
4.2.4.8. Preparation of (-)-(1R,6R,7S,8R)-7-(2-idoethyl)-1,2,7,8-tetramethylbicyclo-[4.4.0]dec-2-ene (213)\(^{168}\)

Solid iodine (217 mg, 0.84 mmol, 2.4 equiv) was added to a cold (0 °C) mixture of triphenylphosphine (230 mg, 0.88 mmol, 2.5 equiv) and imidazole (60 mg, 0.88 mmol, 2.5 equiv) in dry dichloromethane (5 mL). The mixture was stirred for 20 min at 0 °C and for 10 min at room temperature to give a yellow precipitate in a bright yellow solution. The mixture was cooled back to 0 °C and a solution of the bicyclic alcohol 231 (83 mg, 0.35 mmol) in dry dichloromethane (3 mL) was slowly added. The mixture was stirred at room temperature for 24 h and then saturated aqueous sodium bicarbonate (10 mL) and ether (20 mL) were added. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were dried with magnesium sulfate and were passed through a column of Florisil® (10 g) and the Florisil® was washed with ether (50 mL). The combined eluants were concentrated and the resulting oil was purified by TLC grade silica chromatography (10 g H type silica, hex) to give 109 mg (90%) of the bicyclic iodide 213 as a low melting solid (mp 29-30 °C) after distillation (90-130 °C/0.1 torr). The product exhibited IR (neat): 2963, 1664, 1437, 1383, 1158, 797, 621, 530 cm\(^{-1}\); \(^1\)H NMR (400 MHz) δ: 0.70 (s, 3H, Me-19, [NOTE: Clerodane numbering system]), 0.82 (d, 3H, J = 6 Hz, Me-17), 0.97 (s, 3H, Me-20), 1.15 (dd, 1H, J = 8, 12.5 Hz), 1.29 (dd, 1H, J = 2, 12 Hz), 1.35-1.60 (m, 8H, including δ 1.56 [d, 3H, J = 1.5 Hz, Me-18]), 1.69 (ddd, 1H, J = 2.5, 3, 13 Hz), 1.94-2.13 (m, 4H), 3.02 (ddd, 1H, J = 5.5, 9, 12.5 Hz, H-12a), 3.11 (ddd, 1H, J = 5.0, 9, 12.5 Hz, H-12b), 5.18 (m, 1H, H-3); \(^13\)C NMR
(75.3 MHz) δ: 1.09 (C-12), 16.21 (-ve, Me-17), 17.81 (-ve, Me-20), 18.00 (-ve, Me-19), 19.97 (-ve, Me-18), 18.45, 26.80, 27.28, 36.63, 43.86 (C-1, C-2, C-6, C-7, C-11), 36.40 (-ve, C-8), 38.06, 42.33 (C-5, C-9), 46.45 (-ve, C-10), 120.42 (-ve, C-3), 144.14 (C-4); LRMS: M+(346) 17.8%; HRMS calcd for C16H27I: 346.1157, found: 346.1155; Anal. calcd for C16H27I: C 55.49, H 7.86, found: C 55.84, H 7.83; [α]D25 -45.7°, c = 1.75 in chloroform.

4.2.4.9. Preparation of (E)-3-Trimethylstanny1-2-buten-1-ol (261)

A) Preparation of Ethyl (E)- and (Z)-3-Trimethylstanny1-2-butenoate (259 and 260)

A solution of methyllithium (1.4 M, 32 mL, 44.7 mmol, 1.3 equiv) was slowly added to a cold (-20 °C) solution of hexamethylditin (9.3 mL, 44.7 mmol, 1.3 equiv) in THF (250 mL). After 20 min, the solution was faintly yellow and the stir bar was blue. The solution was cooled to -78 °C and stirred at this temperature for 10 min. Solid copper(I) cyanide (4.0 g, 44.7 mmol, 1.3 equiv) was added, in one portion, to the almost colorless solution. The yellow-red solution/suspension was stirred 6 min at -78 °C and 15 min at -48 °C. The clear orange solution of the cuprate 87 was cooled to -78 °C and was stirred at this temperature for 10 min. Anhydrous EtOH (2.6 mL, 44.7 mmol, 1.3 equiv) was added dropwise and a solution of ethyl 2-butynoate (258, 4.0 mL, 34.3 mmol) in THF (30 mL) was added via a small bore Teflon® cannula over a period of 40 min at -78 °C. The pale yellow solution was stirred at -78 °C for 3 h. A stopper was removed and aqueous ammonium chloride (pH 9, 50 mL) was rapidly added via a 50 mL disposable plastic syringe to the efficiently stirred reaction mixture. The red-brown mixture was warmed to room temperature and aqueous ammonium chloride (pH 9, 15 mL) was added and the mixture was poured into a large Erlenmeyer
flask. Ether (800 mL) was added and the mixture was efficiently stirred overnight. The layers were separated and the deep blue aqueous layer was reextracted with ether (100 mL). The combine organic layers were dried with magnesium sulfate and the solvents were removed under reduced pressure. The resulting oil was purified by TLC grade silica chromatography (160 g H type silica, 200:3 petroleum ether:ether, 2 L) to give 17.48 g (79%) of ethyl (E)-3-trimethylstannyl-2-butenoate (259) after distillation (50-70 °C/0.1 torr) and 1.33 g (14%) of a 1:1 mixture of the ester 259 and ethyl (Z)-3-trimethylstannyl-2-butenoate (260). A pure sample of the ester 260 was obtained by further chromatography. The (E)-ester 259 exhibited IR (neat): 2981, 2912, 1715, 1604, 1447, 1367, 1340, 1179, 1039, 865, 772, 530 cm⁻¹; ¹H NMR (400 MHz) δ: 0.17 (s, 9H, ²J_Sn-H = 54 Hz, Me₃Sn), 1.28 (t, 3H, J = 7 Hz, OCH₂Me), 2.38 (d, 3H, J = 2 Hz, ³J_Sn-H = 50 Hz, Me-4), 4.15 (q, 2H, J = 7 Hz, OCH₂Me), 5.97 (q, 1H, J = 2 Hz, ³J_Sn-H = 74 Hz, H-2); ¹³C NMR (75.3 MHz) δ: -10.07 (-ve, ¹J_Sn-C = 340 Hz, Me₃Sn), 13.31 (-ve, OCH₂Me), 21.39 (-ve, ²J_Sn-C = 34 Hz, Me-4), 59.51 (OCH₂Me), 127.84 (-ve, ²J_Sn-C = 40 Hz, C-2), 164.43 (C-3), 168.05 (C-1); LRMS: M+-Me(263) 46.6%; DCIMS(NH₃): MH⁺(279); HRMS calcd for C₈H₁₅O₂Sn (M+-Me): 263.0093, found: 263.0094; Anal. calcd for C₉H₁₈O₂Sn: C 39.03, H 6.55, found: C 38.37, H 6.47.

The (Z)-ester 260 exhibited IR (neat): 2981, 1703, 1604, 1445, 1369, 1318, 1202, 1103, 1044, 864, 773, 535 cm⁻¹; ¹H NMR (400 MHz) δ: 0.19 (s, 9H, ²J_Sn-H = 56 Hz, Me₃Sn), 1.29 (t, 3H, J = 7 Hz, OCH₂Me), 2.15 (d, 3H, J = 2 Hz, ³J_Sn-H = 44 Hz, Me-4), 4.17 (q, 2H, J = 7 Hz, OCH₂Me), 6.40 (q, 1H, J = 2 Hz, ³J_Sn-H = 117 Hz, H-2); LRMS: M+-Me(263) 58.5%; DCIMS(NH₃): M⁺(278); HRMS calcd for C₈H₁₅O₂Sn (M⁺-Me): 263.0093, found: 263.0092; Anal. calcd for C₉H₁₈O₂Sn: C 39.03, H 6.55, found: C 38.88, H 6.59.

B) Preparation of (E)-3-Trimethylstannyl-2-buten-1-ol (261)
A solution of \(i-\text{Bu}_2\text{AlH}\) (1 M hex, 43.3 mL, 43.3 mmol, 3 equiv) was added to a cold (-78 °C) solution of the (E)-ester 259 (4.0 g, 14.4 mmol) in ether (350 mL). The mixture was stirred for 50 min at -78 °C and for 2 h at 0 °C. Saturated aqueous ammonium chloride (10 mL) was added and the mixture was stirred for 1 h at room temperature. Magnesium sulfate (10 g) was added and the white suspension was stirred for 2 h. The gel was filtered through Florisil® (190 g) and the Florisil® was washed with ether (1.75 L). The ether was removed under reduced pressure and the oil was purified by distillation (60-90 °C/0.25 torr) to give 3.27 g (97%) of the (E)-alcohol 261. The (E)-alcohol 261 exhibited IR (neat): 3303, 2981, 2907, 1435, 1189, 1117, 1061, 1006, 768, 526 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.13 (s, 9H, \(^{2}J_{\text{Sn-H}} = 55\) Hz, Me\(_3\)Sn), 1.32 (t, 1H, \(J = 6\) Hz, OH [exchanged with D\(_2\)O]), 1.90 (d, 3H, \(J = 2\) Hz, \(^{3}J_{\text{Sn-H}} = 52\) Hz, Me-4), 4.28 (dd, 2H, \(J = 6\), 6.5 Hz, H's-1 [became a d, \(J = 6.5\) Hz, with D\(_2\)O]), 5.78 (qt, 1H, \(J = 2\), 6.5 Hz, \(^{3}J_{\text{Sn-H}} = 76\) Hz, H-2); \(^{13}\)C NMR (50.3 MHz) \(\delta\): -10.26 (-ve, Me\(_3\)Sn), 18.56 (-ve, Me-4), 58.84 (C-1), 138.67 (-ve, C-2), 142.70 (C-3); LRMS: M+\(-\text{Me}(221)\) 100%; HRMS calcd for C\(_6\)H\(_{13}\)OSn (M+\(-\text{Me}\)): 220.9987, found: 220.9994; Anal. calcd for C\(_7\)H\(_{16}\)OSn: C 35.79, H 6.87, found: C 35.52, H 6.89.

4.2.4.10. Preparation of (E)-1-(tert-Butyldimethylsilyloxy)-3-trimethylstannyl-2-butene (262) and (E)-1-(Tri-[iso-propyl]silyloxy)-3-trimethylstannyl-2-butene (263)

A) Preparation of the TBDMS-Ether 262

Solid TBDMS\(_2\)I (2.37 g, 15.7 mmol, 2 equiv) was added to a solution of the (E)-alcohol 261 (1.85 g, 7.86 mmol) and imidazole (1.61 g, 23.6 mmol, 3 equiv) in dry dichloromethane (125 mL). The white solution/suspension was stirred at room temperature for 3.5 h. Saturated ammonium chloride (100 mL) was added and the
layers were separated. The aqueous layers was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with brine (100 mL). The organic extracts were dried with magnesium sulfate and the solvent was removed under reduced pressure. The resulting oil was filtered through silica gel (11 g) and the silica was washed with a mixture of hex and dichloromethane (95:5, 125 mL). The solvents were removed under reduced pressure to give 2.72 g (99%) of the (E)-TBDMS ether 262 after distillation (80-90 °C/0.06 torr). The (E)-TBDMS ether 262 exhibited IR (neat): 2980, 2956, 1473, 1373, 1256, 1190, 1093, 1042, 1007, 838, 775, 528 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.09 (s, 6H, Me\(_2\)Si), 0.11 (s, 9H, Me\(_3\)Sn), 0.91 (s, 9H, t-Bu), 1.84 (d, 3H, J = 2 Hz, 3\(J\)\(_{Sn-H}\) = 51 Hz, Me-4), 4.29 (d, 2H, \(J\) = 6.5 Hz, 4\(J\)\(_{Sn-H}\) = 16 Hz, H’s-1), 5.68 (qt, 1H, \(J\) = 2, 6.5 Hz, 3\(J\)\(_{Sn-H}\) = 76 Hz, H-2); \(^13\)C NMR (50.3 MHz) \(\delta\): -10.29 (-ve, 1\(J\)\(_{Sn-C}\) = 347 Hz, Me\(_3\)Sn), -5.06 (-ve, 1\(J\)\(_{Si-C}\) = 50 Hz, Me\(_2\)Si), 18.42 (SiCMe\(_2\)), 18.56 (-ve, Me-4), 26.01 (-ve, SiCMe\(_3\)), 59.95 (3\(J\)\(_{Sn-C}\) = 60 Hz, C-1), 139.52 (C-3), 140.12 (-ve, C-2); LRMS: M\(^+\)-Me(335) 45.8%; HRMS calcd for C\(_{12}\)H\(_{27}\)OSiSn (M\(^+\)-Me): 335.0852, found: 335.0857 (peak matched); Anal. calcd for C\(_{13}\)H\(_{30}\)OSiSn: C 44.72, H 8.66, found: C 44.90, H 8.76.

B) Preparation of the TIPS-Ether 263

TIPSCI\(^{173}\) (2.7 mL, 12.6 mmol, 1.1 equiv) was added to a solution of the (E)-alcohol 261 (2.7 g, 11.5 mmol) and imidazole (1.6 g, 23 mmol, 2 equiv) in dry dichloromethane (100 mL). The white solution/suspension was stirred at room temperature for 22 h. Saturated ammonium chloride (85 mL) was added and the layers were separated. The aqueous layers was extracted with dichloromethane (3 x 50 mL) and the combined organic layers were washed with brine (85 mL). The organic extracts were dried with magnesium sulfate and the solvent was removed under reduced pressure. The resulting oil was filtered through silica gel (20 g) and the silica was washed with a mixture of hex and dichloromethane (95:5, 200 mL). The solvents were removed under reduced pressure to give 4.3 g (96%) of the (E)-TIPS
ether 263 after distillation (110-130 °C/0.15 torr). The product exhibited IR (neat):
2962, 2944, 2867, 1464, 1366, 1256, 1190, 1042, 1014, 996, 883, 766, 683, 528 cm⁻¹;
¹H NMR (400 MHz) δ: 0.10 (s, 9H, ²J Sn-H = 53 Hz, Me₃Sn), 1.02-1.15 (m, 21H, [i-Pr]₃Si), 1.82 (td, 3H, J = 0.8, 2 Hz, ³J Sn-H = 51 Hz, Me-4), 4.35 (qd, 2H, J = 0.8,
5.5 Hz, ⁴J Sn-H = 19 Hz, H's-1), 5.69 (qt, 1H, J = 2, 5.5 Hz, ³J Sn-H = 77 Hz, H-2);
¹³C NMR (50.3 MHz) δ: -10.27 (-ve, ¹J Sn-C = 327 Hz, Me₃Sn), 12.05 (-ve, ²J Sn-C =
60 Hz, C-4), 18.00 (-ve, Si(CHMe₂)₃), 18.63 (-ve, Si(CHMe₂)₃), 60.20 (³J Sn-C = 80 Hz,
C-1), 138.84 (C-3), 140.59 (-ve, ³J Sn-C = 25 Hz, C-2); LRMS: M⁺-Me(377) 23.5%;
DCIMS(NH₃): M⁺(391) 5.96%; HRMS calcd for C₁₅H₃₃O₂Sn: 377.1322, found: 377.1329; Anal. calcd for C₁₆H₃₆O₂Sn: C 49.12, H 9.27, found: C 49.22,
H 9.29.

4.2.4.11. Preparation of (E)-1-(tert-Butyldimethylsilyloxy)-3-iodo-2-butene (264) and
(E)-3-Iodo-1-(tri-iso-propylsilyloxy)-2-butene (265)¹⁷⁴

A) Preparation of the TBDMS-Iodide 264

A solution of iodine (1.19 g, 4.68 mmol, 1.1 equiv) in dry dichloromethane
(30 mL) was added, dropwise via a Teflon® cannula, to a solution of the (E)-TBDMS ether 262 (1.48 g, 4.25 mmol) in dry dichloromethane (30 mL), at room temperature,
until a yellow coloration persisted. The mixture was stirred for 30 min and was washed
with aqueous sodium thiosulfate (10% w/v, 5 mL) and brine (5 mL). The dichloromethane solution was dried with magnesium sulfate and the solvent was
removed under reduced pressure to give 2.27 g of a colorless oil. The oil was purified
by flash chromatography (60 g silica gel, 95:5 hex:ether [note: the trimethylstannyl iodide decomposes on the top of the column to give a yellow band]) to give 1.27 g
(95 %) of the (E)-TBDMS iodoether 264 after distillation over copper(0) (60-80 °C,
0.1 torr). The product was kept over copper(0) and was protected from the light. The 
\((E)\)-TBDMS iodoether 264 exhibited IR (neat): 2956, 2711, 1639, 1472, 1381, 1257, 
1092, 1042, 1007, 939, 838, 777, 669 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.06 (s, 6H, 
\(\text{Me}_2\text{Si}\)), 0.89 (s, 9H, \(\text{t-Bu}\)), 2.40 (dt, 3H, \(J = 2, 1\) Hz, Me-4), 4.11 (dd, 2H, \(J = 1, 6.5\) Hz, 
H's-1), 6.28 (qt, 1H, \(J = 2, 6.5\) Hz, H-2); \(^{13}\)C NMR (50.3 MHz) \(\delta\): -5.22 (Me\(_2\)Si), 18.32 
(Si\(_3\)Me\(_3\)), 25.87 (-ve, SiCMe\(_3\)), 28.08 (Me-4), 60.67 (C-1), 95.97 (C-3), 140.64 (C-2).

B) Preparation of the TIPS-Iodide 265

A solution of iodine (3.45 g, 13.6 mmol, 1.05 equiv) in dry dichloromethane 
(100 mL) was added, dropwise via a Teflon® cannula, to a solution of the \((E)\)-TIPS 
ether 263 (5.06 g, 12.9 mmol) in dry dichloromethane (100 mL), at room temperature, 
until a yellow coloration persisted. The mixture was stirred for 1.6 h and was washed 
with aqueous sodium thiosulfate (10% w/v, 20 mL) and brine (20 mL). The 
dichloromethane solution was dried with magnesium sulfate and the solvent was 
removed under reduced pressure to give a colorless oil. The oil was purified by flash 
chromatography (200 g silica gel, 95:5 hex:ether, 1.75 L, [note: the trimethylstannyl 
iodide decomposes on the top of the column to give a yellow band]) to give 4.2 g 
(92%) of the \((E)\)-TIPS iodoether 265 after distillation over copper(0) 
(85-110 °C/0.1 torr). The product was kept over copper(0) and was protected from 
the light. The \((E)\)-TIPS iodoether 265 exhibited IR (neat): 2943, 2867, 1640, 1463, 
1382, 1255, 1110, 1043, 1014, 996, 883, 772, 684 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.95– 
1.25 (m, 21H, \([\text{i-Pr}]_3\text{Si}\)), 2.40 (td, 3H, \(J = 1, 2\) Hz, Me-4), 4.20 (qd, 2H, \(J = 1, 6.5\) Hz, 
H's-1), 6.31 (qt, 1H, \(J = 2, 6.5\) Hz, H-2); \(^{13}\)C NMR (50.3 MHz) \(\delta\): 11.97 (-ve, 
Si\(_3\)CHMe\(_2\)_3), 17.90 (-ve, Si\(_3\)CHMe\(_2\)_3), 28.15 (-ve, C-4), 60.96 (C-1), 95.42 (C-3), 
140.96 (-ve, C-2); LRMS: \(M^+(354)\) 0.2%; HRMS calcd for C\(_{13}\)H\(_{27}\)I\(_3\)Si: 354.0875, 
found: 354.0877; Anal. calcd for C\(_{13}\)H\(_{27}\)I\(_3\)Si: C 44.06, H 7.68, found: C 44.28, 
H 7.53.
4.2.4.12. Preparation of \((1R,6R,7S,8R)-7\text{-Ethyl-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene}\) (283), the Dimer 284 and \((-\)-(1\text{-}R\text{-}6\text{-}R\text{-}7\text{-}S\text{-}8\text{-}R)-7\{-3\text{-}Methyl\text{-}5\{-\text{-}tri\{isopropyl\}silyloxy\}-3\{-E\text{-pentenyl}\}\}\text{-}1,2,7,8\text{-}tetramethylbicyclo[4.4.0]dec-2-ene\) (282)

A) Copper(I) Catalyzed Vinylmagnesium-alkyl Iodide Coupling

A solution of tert-butyl lithium (1.7 M in hex, 450 µL, 0.76 mmol, 7.1 equiv) was slowly added to a cold (-78 °C) solution of the \((E)\text{-TIPS iodoether 265}\) (135 mg, 0.38 mmol, 3.5 equiv) in THF (1.5 mL). The yellow solution was stirred at -78 °C for 20 min and solid magnesium bromide etherate (98 mg, 0.38 mmol, 3.5 equiv) was added. The white suspension/solution was stirred for 15 min at -78 °C and 10 min at room temperature. The clear, colourless solution was added via cannula, in 15 min, to a cold (7 °C) solution of tributylphosphine (freshly distilled, 19 µL, 0.07 mmol, 0.7 equiv), tributylphosphine-copper(I) iodide complex (21 mg, 0.053 mmol, 0.5 equiv), HMPA (WARNING: carcinogenic, 107 µL, 0.54 mmol, 5 equiv) and the bicyclic iodide 213 (37 mg, 0.11 mmol) in THF (0.5 mL). During the addition, the initially bright yellow solution became pale yellow after 7 min, colorless after 12 min,
pale yellow after 15 min and again bright yellow after 25 min. After 1 h the temperature had risen to 12 °C and the solution was bright yellow. At 15 °C (after 2 h), the solution turned dark green. Then as the temperature increased to room temperature, the solution became pale green (20 °C, 4.3 h) and then colorless (26 °C, 7.3 h). After 20 h, the flask was opened and aqueous ammonium chloride (pH 9, 5 mL) and ether (3 mL) were added to the reaction mixture. The mixture was vigorously stirred until the aqueous layer became bright blue and then was extracted with ether (3 x 10 mL). The combined organic layers were washed successively with saturated aqueous copper(II) sulfate (2 x 5 mL), brine (5 mL), aqueous sodium thiosulfate (10%, 5 mL) and brine (5 mL). The organic extracts were dried with magnesium sulfate and the solvents were removed under reduced pressure to give 131 mg of oil. The oil was purified by TLC grade silica chromatography (3.2 g H type silica, hex, 50 mL; 95:5, 30 mL and 9:1, 20 mL, hex:dichloromethane) to give: -less polar fraction: 5.5 mg of a mixture consisting of the bicyclic iodide 213 (~70%) and smaller amounts of the reduced bicyclic compound 283 and the dimer 284; -more polar fraction: 21.5 mg (45%, 53% based on recovered starting material) of the desired TIPS ether of (-)-kolavenol 282.

The (1R,6R,7S,8R)-7-ethyl-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (283) (distilled: 65-75 °C/0.08 torr) exhibited IR (neat): 2964, 1663, 1460, 1382, 1242, 1176, 1003, 980, 797 cm\(^{-1}\); \(^1\)H NMR (400 MHz) \(\delta\): 0.68 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.69 (t, 3H, \(J = 8.5\) Hz, Me-12), 0.75 (d, 3H, \(J = 6.5\) Hz, Me-17), 0.98 (s, 3H, Me-19), 1.10-1.50 (m, 12H, including \(\delta\) 1.55 [dd, 3H, \(J = 2, 2.5\) Hz, Me-18]), 1.68 (ddd, 1H, \(J = 2.5, 4, 12.5\) Hz), 1.95-2.05 (br m, 2H, H's-2), 5.19 (br m, 1H, H-3); \(^{13}\)C NMR (50.3 MHz) \(\delta\): 7.21 (-ve, Me-12), 15.93 (-ve, Me-17), 18.00 (-ve, Me-20), 18.36 (-ve, Me-19), 19.90 (-ve, Me-18), 18.17, 26.88, 27.52, 30.42 (C-1, C-6, C-7, C-11), 35.47 (-ve, C-8), 36.86, 38.09, 38.27 (C-2, C-5, C-9), 46.69 (-ve, C-10), 120.49 (-ve, C-3), 144.62 (C-4); LRMS: \(M^+(220)\) 22.6%; HRMS calcd for \(C_{16}H_{28}\): 220.2191, found: 220.2183.
The dimer 284 (mp: 129-130 °C, pumped overnight [vacuum pump]) exhibited IR (2% KBr): 2933, 1636, 1457, 1382, 1174, 1000, 798 cm⁻¹; ¹H NMR (400 MHz) δ: 0.69 (s, 6H, 2 x Me-20 [NOTE: Clerodane numbering system]), 0.79 (d, 6H, J = 6.5 Hz, 2 x Me-17), 0.98 (s, 3H, 2 x Me-19), 1.00-1.30 (m, 8H, 2 x H's-12,?), 1.30-1.60 (m, 20 H, including [δ 1.57, dd, 6H, J = 2, 2.5 Hz, 2 x Me-18]), 1.69 (ddd, 2H, J = 2.5, 4, 12.5 Hz), 1.95-2.05 (br m, 4H, 2 x H's-2), 5.15 (br m, 2H, 2 x H-3); ¹3C NMR (100.6 MHz) δ: 13.11 (-ve, Me-17), 18.01 (-ve, Me-20), 18.40 (-ve, Me-19), 19.90 (-ve, Me-18), 23.47, 26.90, 27.56 (C-1, C-6, C-7, C-11), 36.21 (-ve, C-8), 36.85, 38.13, 38.54, 38.56 (C-2, C-5, C-9, C-12), 46.41 (-ve, C-10), 144.62 (C-4); LRMS: M⁺(438) 2.8%; HRMS calcd for C₃₂H₅₄: 438.4226, found: 432.4225.

The (-)-(1R,6R,7S,8R)-7-[3-methyl-5-(tri-[iso-propyl]silyloxy]-3-(E-pentenyl)]-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (282) exhibited IR (neat): 2942, 2866, 1669, 1463, 1382, 1257, 1107, 1062, 1014, 883, 777, 682 cm⁻¹; ¹H NMR (400 MHz) δ: 0.71 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.80 (d, 3H, J = 6.5 Hz, Me-17), 0.99 (s, 3H, Me-19), 1.00-1.20 (m, 22H, [i-Pr]₃Si (21H)), 1.25-1.50 (m, 8H), 1.59 (dd, 3H, J = 1.5, 2 Hz, Me-18)), 1.61 (s, 3H, Me-16), 1.70 (ddd, 1H, J = 2.5, 3, 13 Hz), 1.79 (ddd, 1H, J = 5, 13, 13 Hz, H-12a), 1.86 (ddd, 1H, J = 5, 13, 13 Hz, H-12b), 2.00-2.05 (m, 2H, H's-11), 4.25 (d, 2H, J = 6 Hz, H-15), 5.20 (br s, 1H, H-3), 5.31 (qt, 1H, J = 1.5, 6 Hz, H-14); NOE difference experiments: Irradiation at δ 1.59 (Me-18) led to the enhancement of signals at δ 5.20 (H-3, 2.3%); irradiation at δ 1.61 (Me-16) led to the enhancement of signals at δ 4.25 (H-15, 2%); irradiation at δ 4.25 (H-15) led to the enhancement of signals at δ 1.61 (Me-16), δ 5.31 (dd, H-14, 2%); irradiation at δ 5.20 (H-3) led to the enhancement of signals at δ 2.00-2.10 (H-2?); irradiation at δ 5.31 (H-14) led to the enhancement of signals at δ 4.25 (H-15, 2.5%); ¹³C NMR (50.3 MHz) δ: 12.09 (-ve, Si[CHMe₂]₃), 15.97 (-ve, Me-17), 16.62 (-ve, Me-20), 18.03 (-ve, Si[CHMe₂]₃), 18.26 (-ve, Me-19), 18.38 (-ve, Me-16), 19.95 (-ve, Me-18), 26.89, 27.54, 32.83, (C-1, C-6, C-7, C-11), 36.23 (-ve, C-8), 36.68, 36.86,
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38.18, 38.58 (C-2, C-5, C-9, C-12), 46.39 (-ve, C-10), 60.58 (C-15), 120.48 (-ve, C-3), 124.35 (-ve, C-14), 137.32 (C-13), 144.53 (C-4); LRMS: MH+(447) 0.3%; HRMS calcd for C_{29}H_{54}SiO: 446.3944, found: 446.3942; Anal. calcd for C_{29}H_{54}SiO: C 77.95, H 12.18, found: C 78.20, H 12.23; [α]D^{25} = -39.7°, c = 1.60 in chloroform.

B) Palladium-catalyzed Alkyl/zinc-vinyl Iodide Coupling

A solution of the bicyclic iodide 213 (freshly distilled, 91.3 mg, 0.26 mmol) in dry ether in a Kugelrohr bulb (0.2 mL) was added, via a small bore Teflon® cannula, to a cold (-78 °C) solution of t-BuLi (1.67 M in hex, 363 µL, 0.61 mmol, 2.3 equiv) and the bulb was rinsed with dry ether (3 x 100 µL) into the t-BuLi solution. The colourless suspension/solution was stirred for 20 min at -78 °C and for 10 min at room temperature. The clear, slightly yellow solution was cooled to -78 °C and a solution of freshly prepared zinc dibromide^{254,255} (0.4 mmol, 2 equiv) in THF (0.7 mL) was added using the same cannula. The resulting solid mass became, upon warming to room temperature for 10 min, a colourless, slightly cloudy solution. A beige solution/suspension of palladium(0)bis(dibenzylidene)acetone (Pd(dba)₂, 4.5 mg, 0.008 mmol, 0.03 equiv) and triphenylarsine (9.7 mg, 0.032 mmol, 0.12 equiv) in THF (0.5 mL, prepared 10 min before) was added via a wide bore Teflon® cannula to the solution of the zinc reagent. The (E)-TIPS iodoether 265 (freshly distilled over Cu(0), 140 mg, 0.4 mmol, 1.5 equiv) was added immediately, via syringe, to the red-brown solution/suspension. The solution/suspension became a clear yellow solution within one min, then the color gradually changed to a brown-yellow. The mixture was stirred at room temperature for 21 h and ether (3 mL) and saturated aqueous ammonium chloride (3 mL) were added. The mixture was extracted with ether (3 x 15 mL) and the ether layers were washed with aqueous sodium thiosulfate (10% w/v, 2 x 3 mL) and brine (5 mL). Magnesium sulfate (~1 g) and Florisil® (~1 g) were added to the organic layer and the mixture was stirred for a few minutes. The solids were filtered and the solvents were removed under reduced pressure to give 222 mg of oil. The residue
was purified by TLC grade silica chromatography (8.5 g H type silica, hex, 60 mL; 98:2 hex:dichloromethane, 60 mL; 95:5 hex:dichloromethane, 30 mL; 9:1 hex:dichloromethane, 60 mL) to give 6.2 mg (11%) of (1R,6R,7S,8R)-7-ethyl-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (283), 5.1 mg (9%) of the dimer 284 and 90 mg (77% after removal of traces of solvent by pumping overnight under vacuum [vacuum pump]) of the TIPS ether of (-)-kolavenol 282.

4.2.4.13. Preparation of (-)-(1R,6R,7S,8R)-7-[3-Methyl-5-hydroxy-3-(E-pentenyl)]-1,2,7,8-tetramethylbicyclo[4.4.0]dec-2-ene (65) [(-)-Kolavenol]

A) Synthetic (-)-Kolavenol (65)

A solution of Bu₄NF (1 M in THF, 0.5 mL, 0.5 mmol, 2.5 equiv) was added to a solution of the TIPS ether of (-)-kolavenol 282 (82 mg, 0.184 mmol) in THF (3 mL). The mixture was stirred at room temperature for 2 h. Water (6 mL) and brine (3 mL) were added to the slightly yellow solution and the mixture was extracted with ethyl acetate (4 x 20 mL). The combine organic layers were dried with magnesium sulfate and the solvents were removed under reduced pressure to give a pale yellow oil. The oil was purified by flash chromatography (4.5 g silica gel, 5:3:2 hex:ether:dichloromethane, 60 mL) to give 51 mg (96%) of synthetic (-)-kolavenol (65) after distillation (140-150 °C/0.1 torr). The product exhibited IR (neat): 3319, 2938, 1668, 1451, 1382, 1305, 1241, 1172, 1131, 1100, 1075, 1001, 851, 797 cm⁻¹ [lit.¹⁴²b (neat): 3333, 1665, 1240, 1175, 1133, 1100, 1080, 1006, 865, 800 cm⁻¹]; ¹H NMR
(400 MHz) δ: 0.70 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.79 (d, 3H, J = 6 Hz, Me-17), 0.99 (s, 3H, Me-19), 1.09 (t, 1H, J = 5.5 Hz, OH [exchanged with D₂O]), 1.17 (ddd, 1H, J = 4, 13, 13 Hz), 1.30-1.60 (m, 11H, including δ 1.58 [m, 3H, Me-18]), 1.66 (s, 3H, Me-16), 1.70 (ddd, 1H, J = 2.5, 3, 13 Hz), 1.81 (ddd, 1H, J = 5, 13, 13 Hz, H-12a), 1.88 (ddd, 1H, J = 5, 13, 13 Hz, H-12b), 1.95-2.05 (m, 2H), 4.13 (dd, 2H, J = 5.5, 6.5 Hz, H-15 [becomes d, J = 6.5 Hz with D₂O]), 5.18 (br s, 1H, H-3), 5.38 (br t, 1H, J = 6.5 Hz, H-14) [lit.¹⁴²b (CCl₄) for H-15: δ 3.98 (d, 2H, J = 6.5 Hz)]; ¹³C NMR (125.8 MHz) δ: 15.93 (Me-17), 16.48 (Me-20), 17.94 (Me-19), 18.33 (Me-16), 19.90 (Me-18), 18.22, 26.85, 27.47, 32.79, (C-1, C-6, C-7, C-11), 36.22 (C-8), 36.70, 36.81 (C-2, C-12), 38.14, 38.58 (C-5, C-9), 46.39 (C-10), 59.40 (C-15), 120.44 (C-3), 122.80 (C-14), 140.80 (C-13), 144.53 (C-4); LRMS: M⁺(290) 7.8%; HRMS calcd for C₂₀H₃₄O: 290.2610, found: 290.2619; Anal. calcd for C₂₀H₃₄O: C 82.70, H 11.80, found: C 82.47, H 11.70; [α]D²⁵ -56.3°, c = 3.55 in chloroform [lit.¹⁴²b [α]D²⁵ -45.7°, c = 4.2 in chloroform].

B) Semi Synthetic (-)-Kolavenol (65)

An authentic sample of (-)-methyl kolavenate (33) (~24 mg) was obtained from Dr. Tokoroyama. The sample showed the presence of impurities by GLC and TLC and was purified by flash chromatography (1.5 g silica gel, 4:1 to 3:2 hex:ether) to give three major fractions: the least polar fraction (A) (4.7 mg), the middle fraction (B)
(5.8 mg) and the most polar fraction (C) (4.8 mg). The three fractions were treated with \(i\text{-}Bu_2\text{AlH}\) but only the fraction (A) gave (-)-kolavenol (65). The following procedure was used. A solution of \(i\text{-}Bu_2\text{AlH}\) (1 M in hex, 70 μL, 0.07 mmol, 4 equiv) was added to a cold (-78 °C) solution of methyl kolavenate (4.7 mg, 0.015 mmol) in dry ether (1 mL). The mixture was stirred for 15 min at -78 °C and for 2 h at room temperature. Three drops of saturated aqueous ammonium chloride were added and the mixture was stirred for 15 min. Magnesium sulfate (~0.2 g) was added and the mixture was filtered through a column of Florisil® (0.5 g) and the Florisil® was washed with ether (15 mL). The solvents were removed under reduced pressure to give 5.3 mg of an oil. The oil was purified by flash chromatography (0.2 g silica gel, 5:3:2 hex:ether:dichloromethane, 10 mL) to give 2 mg (47%) of natural kolavenol after distillation (140-150 °C/0.1 torr). This product was identical by GLC and TLC with the synthetic (-)-kolavenol. The product exhibited IR (neat): 3319, 2927, 1668, 1455, 1382, 1305, 1242, 1172, 1131, 1100, 1075, 1000, 851, 797 cm\(^{-1}\); \(^1\)H NMR (400 MHz) δ: 0.70 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.79 (d, 3H, \(J = 7\) Hz, Me-17), 0.99 (s, 3H, Me-19), 1.09 (m, 1H, [exchanged with D\(_2\)O]), 1.17 (ddd, 1H, \(J = 4, 13, 13\) Hz), 1.30-1.60 (m, 11H, including δ 1.58 [m, 3H, Me-18]), 1.66 (s, 3H, Me-16), 1.70 (ddd, 1H, \(J = 2.5, 3, 13\) Hz), 1.81 (ddd, 1H, \(J = 5, 13, 13\) Hz, H-12a), 1.88 (ddd, 1H, \(J = 5, 13, 13\) Hz, H-12b), 1.95–2.05 (m, 2H), 4.13 (br d, 2H, \(J = 6.5\) Hz, H-15 [becomes d, \(J = 6.5\) Hz with D\(_2\)O]), 5.18 (br s, 1H, H-3), 5.38 (br t, 1H, \(J = 6.5\) Hz, H-14); LRMS: \(M^+(290)\) 0.1%; HRMS calcd for C\(_{20}\)H\(_{34}\)O: 290.2610, found: 290.2602
4.2.5. Total Synthesis of (-)-Agelasine B (31)

4.2.5.1. Preparation of 6-Methoxyamino-9-methylpurine (N\textsuperscript{6}-Methoxy-9-methyladenine 301)

![Chemical structure of 6-Methoxyamino-9-methylpurine](image)

A) Preparation of 6-Aminopurine N\textsuperscript{1}-Oxide (Adenine N\textsuperscript{1}-Oxide 307)

6-Aminopurine (adenine, 306, 10 g, 74 mmol) was dissolved in hot glacial acetic acid (60 mL). The mixture was cooled to room temperature and aqueous hydrogen peroxide (30 %, 37 mL, ~326 mmol, ~4.4 equiv) was slowly added. The solution was stirred for 5 days at room temperature. The crystals were filtered and were washed with a small amount of cold acetic acid. The product was recrystallized from hot water to give 7.1 g (63%) of 6-aminopurine N\textsuperscript{1}-oxide (adenine N\textsuperscript{1}-oxide 307), mp 295–300 °C, dec. (lit.\textsuperscript{198a} 297–307, dec.). The product exhibited IR (2% KBr): 3397, 3105, 3020, 2515, 1877, 1661, 1594, 1448, 1411, 1376, 1328, 1241, 1158, 1092, 1027, 904, 648, 554, 531 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, D\textsubscript{2}O) δ: 8.25 (s, 1H); 8.55 (s, 1H); LRMS: M\textsuperscript{+}(151) 7.2%; HRMS calcd for C\textsubscript{5}H\textsubscript{5}N\textsubscript{5}O: 151.0494, found: 151.0491; Anal. calcd for C\textsubscript{5}H\textsubscript{5}N\textsubscript{5}O: C 39.74, H 3.33, N 46.34, found: C 39.81,
B) Preparation of N\textsuperscript{1}-Methoxy-6-aminopurinium Iodide (N\textsuperscript{1}-Methoxyadeninium Iodide \textsuperscript{308})\textsuperscript{198c}

Iodomethane (passed through a small plug of flame dried basic alumina, 7.3 mL, 117 mmol, 2.5 equiv) was added to a suspension of powdered 6-aminopurine N\textsuperscript{1}-oxide (adenine N\textsuperscript{1}-oxide \textsuperscript{307}, 7.1 g, 47 mmol) in DMA (63 mL). The suspension was stirred for 22 h at room temperature and the precipitate was filtered and was washed with cold EtOH (2 x 5 mL). The solvents were removed from the combined filtrate under reduced pressure and the solid residue was washed with EtOH (2 x 5 mL). The solids were combined and recrystallized from EtOH:water (7:3) to give 8.41 g (61%) of N\textsuperscript{1}-methoxy-6-aminopurinium iodide (N\textsuperscript{1}-methoxyadeninium iodide \textsuperscript{308}) mp 223–227 °C, lit.\textsuperscript{198c} 222 °C. The unstable product exhibited IR (1% KBr): 3200, 3000, 2564, 1669, 1599, 1537, 1417, 1384, 1343, 1268, 1237, 1148, 1113, 961, 923, 808, 721, 654, 582, 544 cm\textsuperscript{-1}; LRMS: M\textsuperscript{+}-HI(165) 0.8%; HRMS calcd for C\textsubscript{6}H\textsubscript{7}N\textsubscript{5}O (M\textsuperscript{+}-HI): 165.0650, found: 165.0656.

C) Preparation of N\textsuperscript{1}-Methoxy Adenine Derivative \textsuperscript{309}\textsuperscript{198c}
A solution of the $N_1$-methoxy-6-aminopurinium iodide ($N_1$-methoxyadeninium iodide 308, 2.88 g, 9.8 mmol) in warm water (125 mL) was passed through a column of ion exchange resin (Amberlite® IRA-402-HCO$_3^-$, 30 mL). The Amberlite® was washed with deionized water (300 mL) and the water was removed from the combined eluant under reduced pressure. The remaining solid was recrystallized from water (50 mL) and the derived material was kept under vacuum (vacuum pump) overnight to give 1.51 g (93%) of $N_1$-methoxy adenine derivative 309 as white crystals (mp: 250–260 °C, dec, lit. $^{198c}$ 255–257 °C, dec). The air-unstable product exhibited IR (1% KBr): 3220, 3105, 3020, 2563, 1669, 1599, 1417, 1384, 1268, 1237, 1148, 1113, 923, 808, 654, 582, 544 cm$^{-1}$; LRMS: M+(165) 44.3%; HRMS calcd for C$_6$H$_7$N$_5$O: 165.0650, found: 165.0650.

D) Preparation of $N^1$-Methoxy-9-methyl Adeninium Iodide Derivative 310$^{198c}$

Iodomethane (passed through a small plug of flame dried basic alumina, 2.4 mL, 37 mmol, 2.5 equiv) was added to a suspension of powdered $N^1$-methoxy adenine derivative 309 (2.5 g, 15 mmol) in DMA (48 mL). The suspension was stirred for 108 h at room temperature. The reaction mixture was cooled to 0 °C and the precipitate was filtered and was washed with cold EtOH (2 x 15 mL). The colourless solid was kept under reduced pressure (vacuum pump) overnight to give 1.61 g (35%) of the $N^1$-methoxy-9-methyl adeninium iodide derivative 310: (mp: 205–215 °C, dec,
lit.\textsuperscript{198c} 214-215 °C, dec). The product exhibited IR (1% KBr): 3220, 3025, 1678, 1581, 1524, 1395, 1239, 959, 688, 529 cm\textsuperscript{-1}; Anal. calcd for C\textsubscript{7}H\textsubscript{10}IN\textsubscript{5}O: C 27.38, H 3.28, N 22.81, found: C 27.17, H 3.28, N 22.68.

E) Preparation of 6-Methoxyamino-9-methyl Adenine Derivative 301\textsuperscript{198a}

![Chemical Structure](image)

A solution of the N\textsuperscript{1}-methoxy-9-methyl adeninium iodide derivative 310 (1.0 g, 3.25 mmol) in warm water (55 mL) was passed through a column of ion exchange resin (Amberlite\textsuperscript{©} IRA-402-HCO\textsubscript{3} \textsuperscript{-}, 10 mL)\textsuperscript{198a}. The Amberlite\textsuperscript{©} was washed with deionized water (360 mL) and the combined eluants were concentrated to ~60 mL under reduced pressure. The concentrate was refluxed for 3 h, cooled to room temperature and then the water was removed under reduced pressure. The yellow solid was washed with cold EtOH (10 mL). The remaining solid was pumped under reduced pressure (vacuum pump) overnight to give 333 mg (57%) of 6-methoxyamino-9-methyl adenine derivative 301 as pinkish crystals (becomes red upon standing in air) (mp: 230-235 °C dec., lit.\textsuperscript{198a} 239 °C dec.). The product exhibited IR (2% Nujol\textsuperscript{©} mull): 1654, 1594, 1208, 1182, 1136, 1057, 870 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, D\textsubscript{2}O) \(\delta\): 1.50-3.00 (very br s, 1H, MeONH, exchange with D\textsubscript{2}O), 3.82 (s, 3H, Me), 4.02 (s, 3H, OMe), 7.80 (s, 1H, H-2), 8.20 (br s, 1H, H-8); LRMS: M\textsuperscript{+}-HI(179) 15%; HRMS calcd for C\textsubscript{7}H\textsubscript{9}N\textsubscript{5}O : 179.0807, found: 179.0807.
4.2.5.2. Preparation of Geranyl Bromide (312). 7-Geranyl-6-methoxyamino-9-methyl Adeninium Bromide Derivative 313 and 6-(Geranylmethoxyamino)-9-methyl Adenine Derivative 314

A) Preparation of Geranyl Bromide (312)

A solution of geraniol (311, 465 μL, 2.68 mmol) in dichloromethane (4 mL) was added to a cold (0 °C) suspension of triphenylphosphate dibromide (1.36 g, 3.2 mmol, 1.2 equiv) in dichloromethane (7.3 mL). The mixture was stirred at room temperature for 1 h and was then filtered rapidly through a column of silica (latrobead® GRS-8060, 10 g) and the silica was washed with hex:dichloromethane (9:1 100 mL). The fractions were combined and the solvents were removed under reduced pressure to give 580 mg (~100%) of the unstable (on silica) geranyl bromide (312). The product was used directly for the next step. The product exhibited $^1$H NMR (400 MHz) δ: 1.65 (s, 3H, Me), 1.73 (s, 3H, Me), 1.78 (s, 3H, Me), 2.00-2.15 (m, 4H, H's-4 and H's-5), 4.02 (d, 2H, $J = 8$ Hz, H's-1), 5.06 (br m, 1H, H-6), 5.51 (t, 1H, $J = 8$ Hz, H-2).

B) Reaction of 6-Methoxyamino-9-methyl Adenine Derivative 301 with Geranyl Bromide (312)

A mixture of geranyl bromide (312, 361 mg, 1.66 mmol) and 6-methoxyamino-9-methyl adenine derivative 301 (375 mg, 2.1 mmol, 1.3 equiv) in DMA (10 mL) was stirred at 55 °C for 2.5 h. The mixture was cooled to room temperature and ether
(45 mL) was added. The mixture was centrifuged, the supernatant was decanted and the solid was triturated with ether (32 mL). The mixture was centrifuged and the supernatants, containing mostly 6-(geranylmethoxyamino)-9-methyl adenine derivative 314, were combined. The solvents were removed under reduced pressure and the residue was put aside. The residual solid from the centrifugation was triturated with dichloromethane (40 mL), the mixture was centrifuged and the supernatant was removed. The last procedure was repeated once more with dichloromethane (24 mL). The residual solid (211 mg, 56%) was composed mainly of 6-methoxyamino-9-methyl adenine derivative 301. The dichloromethane of the supernatants was removed under reduced pressure to give a white solid. The solid was dissolved in dichloromethane (12 mL) and ether (24 mL) was added and the mixture was centrifuged. The liquid was removed and the last procedure was repeated. The solid was kept under reduced pressure (vacuum pump) overnight to give 248 mg (38% based on the geranyl bromide 312) of 7-geranyl-6-methoxyamino-9-methyl adeninium bromide derivative 313, mp 185-186 °C. The product exhibited IR (1% KBr): 3493, 3123, 2980, 1673, 1597, 1557, 1455, 1398, 1351, 1146, 1056, 881, 744 cm⁻¹; ¹H NMR (400 MHz) δ: 1.60 (s, 3H, Me), 1.68 (s, 3H, Me), 1.89 (s, 3H, Me), 2.12 (s, 2H, H's-4 or H's-5), 2.13 (s, 2H, H's-4 or H's-5), 3.91 (s, 3H, N-Me), 4.11 (s, 3H, O-Me), 5.05 (br m, 1H, H-6), 5.09 (d, 2H, J = 8 Hz, H-1), 5.50 (t, 1H, J = 8 Hz, H-2), 7.87 (br s, 1H, H-2' [becomes sharp s with D₂O]), 9.67-9.78 (br m, 1H, H-8' [becomes sharp s with D₂O]), 10.60-10.90 (br m, 1H, NH [exchanges with D₂O]); ¹³C NMR (50.3 MHz) δ: 17.12 (-ve, C-10), 17.70 (-ve, C-9), 25.62 (-ve, C-8), 26.04 (C-5), 32.19 (-ve, NMe), 39.45 (C-4), 48.25 (C-1), 62.36 (-ve, OMe), 110.48, 115.42 (-ve, C-6), 123.30 (-ve, C-2), 132.12, 135.98, 137.03 (-ve), 141.36, 146.27, 149.02 (-ve); FABMS (3-nitrobenzyl alcohol matrix): M⁺-Br(316); HRMS calcd for C₁₇H₂₆N₅O (M⁺-Br): 316.2137, found: 316.2130; UV (5.3 x10⁻⁵ M in MeOH): 291.0 nm, ε 7630.
The fraction containing 6-(geranylmethoxyamino)-9-methyl adenine derivative 314 was purified by flash chromatography (basic alumina activity (I), 40 g, from 100% dichloromethane to 95:5 dichloromethane:MeOH) to give 59 mg (11%) of the product 314. The product exhibited IR (neat): 3493, 2980, 2927, 1665, 1577, 1456, 1377, 1328, 1297, 1235, 1052, 839, 736 cm⁻¹; ¹H NMR (400 MHz) δ: 1.55 (s, 3H, Me), 1.62 (s, 3H, Me), 1.79 (s, 3H, Me), 2.00-2.15 (m, 4H, H's-4 and H's-5), 3.83 (s, 3H, N-Me), 3.95 (s, 3H, O-Me), 4.72 (d, 2H, J = 8 Hz, H-1), 5.05 (t, 1H, J = 6.5 Hz, H-6), 5.44 (t, 1H, J = 8 Hz, H-2), 7.89 (s, 1H, H-2'), 8.48 (s, 1H, H-8'); LRMS: M⁺(315) 0.3%; HRMS calcd for C₁₇H₂₅N₅O: 315.2059, found: 315.2059.

4.2.5.3. Preparation of Kolavenyl Bromide 300. (-)-7-Kolavenyl-N⁶-methoxy-9-methyl Adeninium Bromide Derivative 302 and (-)-N⁶-Kolavenyl-N⁶-methoxy-9-methyl Adenine Derivative 303

A) Preparation of Kolavenyl Bromide (300)

Triphenylphosphine dibromide¹⁹⁷ (55.4 mg, 0.13 mmol, 1.5 equiv) was added to a suspension of the TIPS ether of (-)-kolavenol 282 (39.3 mg, 0.088 mmol) in dichloromethane (2 mL). The colourless mixture was stirred for 1 h at room temperature and was filtered rapidly through a column of silica (Iatrobead® GRS-8060, 0.8 g) and the silica was washed with hex:dichloromethane (9:1, 30 mL). Two
fractions were collected: the more polar fraction was concentrated and repurified by TLC grade silica chromatography (0.2 g, 7:2:1 hex:ether:dichloromethane) to give 2.6 mg (10%) of (-)-kolavenol; the less polar fraction contained 26.1 mg (85%, 94% based on recovered (-)-kolavenol) of kolavenyl bromide 300. The product exhibited $^1$H NMR (400 MHz) δ: 0.72 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.81 (d, 3H, $J = 6$ Hz, Me-17), 0.98 (s, 3H, Me-19), 1.18 (ddd, 1H, $J = 4$, 12.5, 12.5 Hz), 1.20-1.60 (m, 11H, including δ 1.58 [m, 3H, Me-18]), 1.69 (m, 1H), 1.71 (s, 3H, Me-16), 1.83 (ddd, 1H, $J = 5$, 13, 13 Hz, H-12a), 1.90 (ddd, 1H, $J = 5$, 13, 13 Hz, H-12b), 1.95-2.10 (m, 2H), 4.00 (d, 2H, $J = 8.5$ Hz, H's-15), 5.19 (br s, 1H, H-3), 5.50 (br t, 1H, $J = 8.5$ Hz, H-14). The kolavenyl bromide was used without further purification.

B) Reaction of 6-Methoxyamino-9-methyl Adenine Derivative 301 with Kolavenyl Bromide (300)

Solid 6-methoxyamino-9-methyl adenine derivative (301, 27 mg, 0.15 mmol, 2 equiv) was added to a solution of kolavenyl bromide (300, 26.1 mg, 0.074 mmol) in DMA (1 mL). One small crystal of dry Bu$_4$NI was added and the mixture was stirred at 60 °C for 3 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure (vacuum pump). $^1$H NMR analysis of the crude material showed that the products 302 and 303 were obtained in a ratio of 1.25:1. The residual solid was purified by TLC grade silica chromatography (2.5 g H type silica, 95:5, 35 mL, 9:1, 35 mL, 8:2, 20 mL, dichloromethane:MeOH) to give two fractions. The less polar fraction (16.5 mg) was repurified by TLC grade silica chromatography (1 g H type silica, 95:5, dichloromethane:MeOH, 15 mL) to give 12.6 mg (38%) of (-)-$N^6$-kolavenyl-$N^6$-methoxy-9-methyl adenine derivative 303 as a very sticky oil. The product exhibited IR (neat): 2960, 2928, 1660, 1577, 1455, 1382, 1328, 1235, 1074, 957, 644 cm$^{-1}$ [lit. $^{31}$ IR (chloroform): 2690(sic?), 1630, 1580, 1380, 1330, 950 cm$^{-1}$]; $^1$H NMR (400 MHz) δ: 0.68 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.75 (d, 3H, $J = 6$ Hz, Me-17), 0.97 (s, 3H, Me-19), 1.12 (ddd, 1H, $J = 4$, 12.5, 12.5 Hz), 1.20-1.60 (m, 11H, including δ 1.54 [m, 3H, Me-18]), 1.68 (dm, 1H,
\( J = 13.5 \text{ Hz} \), 1.78 (s, 3H, Me-16), 1.75-1.90 (m, 2H, H's-12), 1.95-2.05 (m, 2H), 3.81 (s, 3H, N-Me), 3.92 (s, 3H, O-Me), 4.72 (d, 2H, \( J = 8 \text{ Hz} \), H's-15), 5.15 (br s, 1H, H-3), 5.40 (br t, 1H, \( J = 8 \text{ Hz} \), H-14), 7.89 (s, 1H, H-2'), 8.48 (s, 1H, H-8') \[ \text{lit.}^{31} \] 1H NMR (CDCl\(_3\)) \( \delta \): 7.73 (s, 1H), 8.39 (s, 1H)\(^{259}\); 13C NMR (125.8 MHz) \( \delta \): 15.94 (-ve, Me-17), 16.72 (-ve, Me-16), 17.92 (-ve, Me-20), 18.31 (-ve, Me-18), 19.88 (Me-19), 18.20, 26.82, 27.46, 32.94 (C-1, C-2, C-7, C-11), 29.71 (-ve, NMe), 39.16 (-ve, C-8), 36.57, 36.79, 38.11, 38.54 (C-5, C-6, C-9, C-12), 46.33 (-ve, C-10), 48.27 (C-15), 62.50 (-ve, OMe), 117.95 (-ve, C-14), 119.22, 120.43 (-ve, C-3), 140.90 (C-13), 141.49, 144.46 (C-4), 151.70, 152.34, 155.96; LRMS: \( M^+ (451) \) 0.9%; HRMS calcd for C\(_{27}\)H\(_{41}\)N\(_5\)O: 451.3311, found: 451.3313; \([ \alpha ]^D_{25} \) -38.7°, c = 2.96 in MeOH; UV (1.8 x10\(^{-5}\) M in MeOH): 277.5 nm, \( \varepsilon \) 14498.

The most polar fraction (27 mg) was repurified by TLC grade silica chromatography (2.5 g H type silica, 95:5, 35 mL, 9:1, 35 mL, 8:2, 20 mL, dichloromethane:MeOH) to give 20.5 mg (52%) of the (−)-7-kolavenyl-N\(_6\)-methoxy-9-methyl adeninium bromide derivative 302 after the product has been kept overnight under reduced pressure (vacuum pump) mp 198-199 °C \[ \text{lit.}^{31} \] 192-196 °C]. The product exhibited IR (1% KBr): 3414, 2960, 1672, 1595, 1556, 1438, 1384, 1058, 881 cm\(^{-1}\) \[ \text{lit.}^{31} \] IR (chloroform): 3360, 2960, 1670, 1590, 1550, 1050, 880 cm\(^{-1}\)]; 1H NMR (400 MHz) \( \delta \): 0.70 (s, 3H, Me-20) \[ \text{NOTE: Clerodane numbering system}\], 0.78 (d, 3H, \( J = 6 \text{ Hz} \), Me-17), 0.98 (s, 3H, Me-19), 1.14 (ddd, 1H, \( J = 4, 12.5, 12.5 \text{ Hz} \), 1.20-1.60 (m, 11H, including \( \delta \) 1.55 [m, 3H, Me-18]), 1.69 (dm, 1H, \( J = 12 \text{ Hz} \)), 1.89 (s, 3H, Me-16), 1.85-2.05 (m, 4H, H's-12,?), 3.92 (s, 3H, N-Me), 4.04 (s, 3H, O-Me), 5.10 (d, 2H, \( J = 8 \text{ Hz} \), H's-15), 5.15 (br s, 1H, H-3), 5.43 (br t, 1H, \( J = 8 \text{ Hz} \), H-14), 7.82 (d, 1H, \( J = 4 \text{ Hz} \), H-2' [becomes s with D\(_2\)O]), 9.90 (s, 1H, H-8'),\(^{181}\) 10.49 (br s, 1H, NH [exchanged with D\(_2\)O] \[ \text{lit.}^{31} \] 1H NMR (CDCl\(_3\)) \( \delta \): 7.97 (s, 1H), 9.83 (s, 1H)); 13C NMR (125.8 MHz) \( \delta \): 16.01 (Me-17), 17.50 (Me-16), 17.94 (Me-20), 18.31 (C-1), 19.89 (Me-19), 18.28 (Me-18), 26.86, 27.43, 33.02 (C-2, C-7, C-11), 32.20 (NMe), 36.23, 36.35, 36.76, 38.14, 38.65 (C-5, C-6, C-8, C-9, C-12), 46.39 (C-10), 48.36 (C-15),
62.40 (OMe), 110.40 (C-5'), 115.10 (C-14), 120.30 (C-3), 136.00 (C-8'), 137.10 (C-4'), 141.30 (C-6'), 144.40 (C-4), 147.30 (C-13), 148.90 (C-2'); LRMS: M+-HBr(451) 1.3%; HRMS calcd for C_{27}H_{41}N_{8}O (M+-HBr): 451.3311, found: 451.3310 (peak matched); Anal. calcd for C_{27}H_{42}N_{8}O_{1/2}H_{2}O: C 59.88, H 8.00, N 12.93, found: C 60.07, H 8.00, N 12.66.; [α]_{D}^{25} -24.4°, c = 1.02 in MeOH [lit.\textsuperscript{31} [α]_{D}^{21} -26.2°, c = 1.00 in MeOH]; UV (9.0 x 10^{-5} M in MeOH): 293.5 nm, ε 4452.

**4.2.5.4. Isolation of Natural (-)-Agelasine B (31) from an Extract of a Papua-New Guinea Sponge Agelas species (Likely Agelas nakamura)**

A mixture of agelasines (1.3 g) was obtained from Ms. Jana Pika, a Ph D student in Dr. R. Andersen's research group.\textsuperscript{260} A portion of the dark yellow extracts (100 mg, dissolved in a minimum amount of MeOH) was applied on top of 3 SepPak\textsuperscript{®} columns (Waters) in series (3 x 0.8 g reverse phase C\textsubscript{18} columns, prewashed with 20 mL MeOH and then with 20 mL of water) and the agelasines were eluted with portions (10 mL) of a mixture of water and MeOH in the following proportions 1:0, 4:1, 3:2, 2:3, 1:4 and 0:1. The fractions were monitored by reverse phase TLC (4:1 acetonitrile:0.2 M aqueous sodium chloride, visualized with UV and Dragendorff's reagent\textsuperscript{261}). The two middle fractions (3:2 and 2:3 water-methanol elution) were combined and the solvents were removed under reduced pressure to give 80 mg of a slightly yellow mixture of agelasines. The three SepPaks\textsuperscript{®} columns were washed with dichloromethane (10 mL), hex (10 mL), MeOH (10 mL) and water (10 mL). The above
chromatographic procedure was repeated on three additional fractions (100 mg each) of the dark yellow extracts yielding a total of 300 mg of slightly yellow mixture of agelasines.

The agelasines mixture was dissolved in a minimum amount of MeOH:water (4 mL, 1:1), the solution was filtered through a 0.22 μm membrane filter (Millex-GV®) and was purified by reverse phase preparative HPLC\textsuperscript{192b} (Waters Radial-Pak\textsuperscript{TM} cartridge, 10 x 250 mm, C\textsubscript{18} on 10μm Porasil\textsuperscript{®} silica). The HPLC system used was composed of a System Controller model 600E and Tunable Absorbance Detector model 486 [tuned at 272 nm], both from Waters. The Controller and the Detector were supervised by an IBM clone computer running a Chromatography Workstation Maxima 825 version 3.30 program from Dynamic Solution (Millipore). The agelasines were purified (11 x ~350 μL injections) with a MeOH:0.2 M aqueous sodium chloride eluant (flow: 10 mL/min, gradient curve #4, 30 min from 7:3 to 85:15 and 15 min at 85:15 then reequilibrated at 7:3 for 20 min). The fractions were monitored by reverse phase analytical HPLC (Waters Radial-Pak\textsuperscript{TM} cartridge, 8 x 100 mm, C\textsubscript{18}, type 8MBC18 on 10μm Porasil\textsuperscript{®} silica). The analytical HPLC hardware was almost the same system as the preparative HPLC except that the detector was a Waters Programmable Photodiode Array Detector model 994 [tuned at 272 and 254 nm]. The eluant used was MeOH:0.2 M aqueous sodium chloride at a flow of 2.5 mL/min (gradient curve #4, 15 min from 7:3 to 85:15 and 5 min at 85:15 then reequilibrated 10 min at 7:3). The fractions derived from the preparative HPLC system were pooled into four groups according to their composition, purity and retention time. Each pool was separately concentrated under reduced pressure (30 °C bath) until a white precipitate appeared. Each concentrate was extracted with ethyl acetate (3 x 100 mL) and each aqueous fraction was passed through three C\textsubscript{18} reverse phase SepPaks\textsuperscript{®} (in series) in order to recover any traces of agelasine left in the water after the extractions. In each case air (3 x 20 mL) was pushed through the SepPaks\textsuperscript{®} to removed the excess water and then MeOH (30 mL) was passed through the SepPaks\textsuperscript{®}. The MeOH was removed under
reduced pressure from each of the eluants and each residue was combined with the appropriate ethyl acetate extract. The extracts were dried with magnesium sulfate and the solvent was removed under reduced pressure. Pool (A) with an average retention time of 22-24 min contained 21.5 mg of mainly agelasine A contaminated with agelasine B,C and D by $^1$H NMR; pool (B) with an average retention time of 24-27 min contained 79.2 mg of mainly agelasine B contaminated with agelasine C and D by $^1$H NMR; pool (C) with an average retention time of 27-30 min contained 48.5 mg of a mixture of agelasine B,C,D and E by $^1$H NMR; and pool (D) with an average retention time longer than 30 min gave 18.5 mg of almost pure agelasine E by $^1$H NMR.

The pool (B) (~50 mg dissolved in the minimum amount of MeOH:water 1:1) was purified using the same preparative HPLC column and system, eluting with an isochratic mixture of acetonitrile:0.2 M aqueous sodium chloride (1:1, 5 mL/min). Four separate runs were done. Three pools were obtained using the same extraction protocol as in the preceding preparative HPLC purification: pool (1) with an average retention time of 52-57 min contained 4.9 mg of agelasine B by $^1$H NMR; pool (2) with an average retention time of 57-61 min contained 10.7 mg of a mixture of agelasine B and C by $^1$H NMR; pool (3) with an average retention time of more than 61 min contained 4.4 mg of agelasine C by $^1$H NMR.

The pool (1) was purified further by TLC grade silica chromatography (0.8 g H type silica, 85:15, 10 mL, 8:2, 10 mL, dichloromethane:MeOH) to give 3.9 mg of pure natural (-)-agelasine B (31) mp 170–175 °C (lit.$^{31,192b}$ 167–170 °C). The product exhibited IR (1% KBr): 3350, 3160, 2962, 1646, 1612, 1592, 1462, 1390, 1302, 1223, 1195, 1086, 735 cm$^{-1}$ [lit.$^{192b}$ IR (chloroform): 3370, 3160, 2960, 1640, 1610, 1590, 1460, 1385, 1300, 1240, 1195, 1090 cm$^{-1}$]; $^1$H NMR (400 MHz) δ: 0.69 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.75 (d, 3H, $J$ = 6 Hz, Me-17), 0.98 (s, 3H, Me-19), 1.12 (m, 1H), 1.20-1.62 (m, 11H, including δ 1.55 [m, 3H, Me-18]), 1.69 (dm, 1H, $J$ = 12 Hz), 1.84 (s, 3H, Me-16), 1.77-2.10 (m, 4H, H's-12,?), 4.08 (s, 3H, N-Me), 5.16 (br s, 1H, H-3), 5.40 (br t, 1H, $J$ = 6.5 Hz, H-14), 5.72 (d, 2H, $J$ = 6.5 Hz, H's-15), 6.69 (br
s, 2H, NH₂ [exchanged with D₂O]), 8.50 (s, 1H), 11.10 (s, 1H [slowly exchanged with D₂O]), [lit.\textsuperscript{192b} \textsuperscript{1}H NMR (CDCl₃) δ: 0.70 (s, 3H), 0.76 (d, 3H, J = 5.2 Hz), 0.97 (s, 3H), 1.57 (s, 3H), 1.86 (br s, 3H), 0.7-2.2 (m, 14H), 4.10 (s, 3H), 5.17 (br s, 1H), 5.41 (br t, 1H, J = 6.5 Hz), 5.71 (br d, 2H, J = 6.5 Hz), 6.84 (br s, 2H, [exchanged with D₂O]), 8.50 (s, 1H), 10.89 (s, 1H)]; \textsuperscript{13}C NMR (125.8 MHz) δ: 16.00 (Me-17), 17.57 (Me-16), 17.94 (Me-20), 18.31 (Me-18), 19.89 (Me-19), 18.28, 26.85, 27.39 (C-1, C-2, C-7), 31.96 (NMe), 33.09, 36.26, 36.28, 36.76, 38.15, 38.68 (C-5, C-6, C-8, C-9, C-11, C-12), 46.40 (C-10), 48.72 (C-15), 109.9 (C-5'), 116.0 (C-14), 120.3 (C-3), 142.3 (C-8'), 144.5 (C-4), 147.6 (C-13), 149.6 (C-4'), 152.3 (C-6'), 156.3 (C-2') [lit.\textsuperscript{192b} \textsuperscript{13}C NMR (22.5 MHz) δ: 16.0 (q, Me-17), 17.5 (q, Me-16), 17.9 (q, Me-20), 18.3 (t, C-1), 18.3 (q, Me-18), 19.9 (q, Me-19), 26.9 (t, C-5), 27.5 (t, C-2), 32.0 (q, N-Me), 33.1 (t, C-11), 36.3 (d, C-8), 36.3 (t, C-6), 36.8 (t, C-12), 38.2 (s, C-9), 38.7 (s, C-5), 46.4 (d, C-10), 48.7 (t, C-15), 109.7 (d, C-5'), 115.7 (d, C-14), 120.3 (d, C-3), 141.7 (d, C-8'), 144.3 (s, C-4), 147.5 (s, C-13), 149.5 (s, C-4'), 152.5 (s, C-6'), 156.0 (d, C-2'); LRMS: M⁺-Cl(422) 0.5%; HRMS calcd for C₂₆H₃₉N₅(M⁺-HCl): 421.3205, found: 421.3204; UV (1.66 x 10⁻⁴ M in MeOH): 272.5 nm, ε 8420 [lit.\textsuperscript{192b} 272 nm, ε 8240].

4.2.5.5. Cyclo-voltammetric Studies of 7-Geranyl-N⁶-methoxy-9-methyl Adeninium Bromide Derivative 313, (-)-7-Kolavenyl-N⁶-methoxy-9-methyl Adeninium Bromide Derivative 302 and (-)-Agelasine B (31)

The cyclic voltammetry measurements were done using an EG&G PARC (Princeton Applied Research Co.) model 303 Hanging Drop Mercury Electrode (HMDE) as the work electrode, a platinum wire as the counter electrode and a silver/silver chloride reference electrode (Ag wire in saturated AgCl in 4 M aqueous KCl with a Vicor\textsuperscript{®} glass porous bridge). The electrodes were controlled by an EG&G PARC model 264A Polarographic Analyser/Stripping Voltammeter. The voltammograms were recorded on an EG&G model RE 0089 X-Y Recorder. The solvent used for all samples was a 0.1 M sodium acetate buffer, pH 4.5.\textsuperscript{262} The samples were dissolved in the buffer (10 mL) and were put into the cell compartment. The solution
was purged of oxygen for 4 min with nitrogen, a fresh drop of mercury was delivered at
the tip of the capillary work electrode and the system was equilibrated, without stirring,
for 15 s before the measurements were done. The voltages were scanned at a rate of
100 mV/s.

A) Cyclic Voltammogram of 7-Geranyl-N$_6$-methoxy-9-methyl Adeninium Bromide
Derivative 313

7-Geranyl-N$_6$-methoxy-9-methyl adeninium bromide derivative 313 (1.0 mg,
2.5 x 10$^{-3}$ M) in the sodium acetate buffer was scanned between 0 and -1.2 V. An
irreversible wave was observed at a potential of -1.06 V and at a current of 2.4 $\mu$A
($E_{1/2} = -0.99$ V). The current reached a minima at a potential of -1.12 V ($i = 2.0$ $\mu$A) and
then the current became very high at -1.15 V (catalytic hydrogen reduction of the
solvent).$^{217}$

B) Cyclic Voltammogram of (-)-7-Kolavenyl-N$_6$-methoxy-9-methyl Adeninium Bromide
Derivative 302

(-)-7-Kolavenyl-N$_6$-methoxy-9-methyl adeninium bromide derivative 302
(0.7 mg, 1.3 x 10$^{-3}$ M) in the sodium acetate buffer was scanned between 0 and
-1.3 V. An irreversible wave was observed at a potential of -1.01 V and at a current of
1.5 $\mu$A ($E_{1/2} = -0.95$ V). A second irreversible wave was observed at a potential of
-1.18 V ($i = 0.7$ $\mu$A) and then become very high at -1.29 V (catalytic hydrogen reduction
of the solvent). No maxima, except the solvent reduction limit is observed during the
second and third cycle. If the wave is “clipped” at -1.23 V still no maxima are observed
in the second cycle. If the wave is clipped at -1.08 V, a maxima at -1.01 V (the current
is 80% of the first maxima) is observed.

C) Cyclic Voltammogram of Natural (-)-Agelasine B (31)

Natural (-)-agelasine B (31, 1.1 mg, 2.4 x 10$^{-3}$ M) in the sodium acetate buffer
was scanned between 0.15 and -1.2 V. A small maxima was observed at -1.02 V
($i = 0.08$ $\mu$A) and the solvent limit was reached at -1.2 V.
4.2.5.6. Electrochemical Reduction of 7-Geranyl-N°-methoxy-9-methyl Adeninium Bromide Derivative 313 and (-)-7-Kolavenyl-N°-methoxy-9-methyl Adeninium Bromide Derivative 302

The electrochemical reductions were done using a EG&G PARC model 173 Potentiostat/Galvanostat equipped with a model 176 Current Follower, a model 176 Electrometer and an "in house" (UBC Electronic Shop) Voltage-Time Integrator EDC-371. The mercury cell used (see Figure 2.29) was made by the UBC glass shop and the UBC mechanical shop. The work electrode was composed of a pool of mercury (BDH, triply distilled, 6 mL) connected to the potentiostat by a platinum wire.

A) Preparation of 7-Geranyl-9-methyl Adeninium Chloride Derivative 315

The acetate buffer (0.1 M, pH 4.5, 10 mL each) was put into the counter and work electrode compartments. The voltage between the work electrode and the reference electrode (\(E_R \text{ vs. } W\)) was measured at +0.25 V. The potentiostat was set at -1.8 V and 10 Coulomb (C) were passed between the counter and the work electrodes. \(E_R \text{ vs. } W\) was now -0.8 V. The buffers were removed from both compartments and were replaced by fresh ones \(E_R \text{ vs. } W = +0.05 V\). The potentiostat was set at +0.6 V and 3.5 C were passed between the electrodes (a white precipitate was formed, \(E_R \text{ vs. } W = +0.36 V\)). The buffers were removed again and were replaced by fresh ones \(E_R \text{ vs. } W = +0.35 V\) and the potentiostat was set at -1.6 V and 4 C were passed between the electrodes \(E_R \text{ vs. } W = +0.3 V\). The buffers were removed again and were replaced by fresh ones \(E_R \text{ vs. } W = +0.3 V\) and 7-geranyl-N°-methoxy-9-methyl adnininium bromide derivative 313 (powdered, 13.9 mg, 0.035 mmol) was
added ($E_R$ vs. $w = +0.1$ V). The potentiostat was set at -1.0 V producing an initial current of ~0.9 mA through the cloudy solution. After 15 min, the current was ~0.6 mA, 0.6 C had passed between the electrodes and $E_R$ vs. $w$ was 0.0 V. After 2.1 h, the solution was getting clear and the current was ~0.4 mA, 3.6 C had passed through the solution, and $E_R$ vs. $w$ was -0.07 V. After 4.1 h, the current passing through the clear solution was ~0.15 mA, 5.5 C had passed between the electrodes and $E_R$ vs. $w$ was -0.2 V. After 5.1 h, the current passing through the clear solution was ~0.08 mA, 6.1 C (1.9 equiv of electrons) had passed through the solution and $E_R$ vs. $w$ was -0.25 V.

At this stage the power was shut off and the electrolytes (from the counter and the work electrodes compartment) were transferred into a 100 mL round bottom flask. The electrodes and the cell were washed with methanol and the washings were added to the 100 mL round bottom flask. Powdered sodium chloride (5 g) was added and the mixture was concentrated to 20 mL under reduced pressure (bath ~25 °C). The residue was extracted with chloroform (4 x 30 mL), the aqueous fraction was put aside and the combined organic extracts were washed with brine (5 mL). The two aqueous fractions were put together and were extracted with chloroform (30 mL) and ethyl acetate (2 x 30 mL). All the organic extracts were combined and were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 15.4 mg of a white solid. The solid was purified by TLC grade silica chromatography (1.5 g H type silica, 9:1, 20 mL, 8:2, 20 mL, 7:3, 10 mL dichloromethane:MeOH) to give 3.4 mg (28%) of 7-geranyl-$N^6$-methoxy-9-methyl adeninium chloride derivative 321 and 4.6 mg (41%, 57% based on the recovered 321) of the 7-geranyl-9-methyl adeninium chloride derivative 315 mp 154-157 °C [lit.\textsuperscript{31} 145-150 °C]. The product exhibited IR (1% KBr): 3322, 3131, 2950, 1651, 1613, 1590, 1477, 1373, 1296, 1231, 1180 cm\textsuperscript{-1}; $^1$H NMR (400 MHz) $\delta$: 1.52 (s, 3H, Me-10), 1.61 (s, 3H, Me-8), 1.81 (s, 3H, Me-9), 2.08 (m, 4H, H's-4 and H's-5), 4.07 (s, 3H, N-Me), 4.98 (br s, 1H, H-6), 5.42 (br t, 1H, $J = 6.5$ Hz, H-2), 5.70 (d, 2H, $J = 6.5$ Hz, H's-1), 6.78 (br s, 2H, NH$_2$ [exchanged with D$_2$O]), 8.49 (s, 1H, H-2'), 10.95 (s, 1H, H-8' [exchanged with D$_2$O]); HMQC and
HMBC: see Table 4.2; $^{13}$C NMR (125.8 MHz)$^{263}$: 17.26 (q, -ve, Me-9), 17.72 (q, -ve, Me-10), 25.61 (q, -ve, Me-8), 25.98 (t, C-5), 32.07 (q, -ve, N-Me), 39.43 (t, C-4), 48.68 (t, C-1), 109.86 (s, C-5'), 116.1 (d, -ve, C-2), 123.2 (d, -ve, C-6), 132.3 (s, C-7), 141.7 (d, -ve, C-8'), 146.4 (s, C-3), 149.6 (s, C-4'), 152.4 (s, C-6'), 156.0 (d, -ve, C-2'); LRMS: M$^+$-HCl(285) 0.2%; HRMS calcd for C$_{16}$H$_{23}$N$_5$ (M$^+$-HCl): 285.1953, found: 285.1950; UV (2.78 x 10$^{-4}$ M in MeOH): 272.5 nm, ε 6777.

Table 4.2: Assignment of the NMR Data for the Geranyl Methyl Adeninium Derivative

<table>
<thead>
<tr>
<th>Assignment (C-X)</th>
<th>$^{13}$C Spectrum δ (APT)</th>
<th>HMQC 1H NMR Correlations δ (mult., # of H, J (Hz), Assignment)</th>
<th>Long Range H-1$^{13}$C HMBC Correlations H-X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me-9</td>
<td>17.26, -ve, q$^a$</td>
<td>1.52 (s, 3H, Me-10)</td>
<td>H's-4, H-2</td>
</tr>
<tr>
<td>Me-10</td>
<td>17.72, -ve, q</td>
<td>1.61 (s, 3H, Me-8)</td>
<td>Me-8</td>
</tr>
<tr>
<td>Me-8</td>
<td>25.61, -ve, q</td>
<td>1.81 (s, 3H, Me-9)</td>
<td>Me-10, H-6</td>
</tr>
<tr>
<td>C-5</td>
<td>25.98, t</td>
<td>2.08 (m, 4H, H's-4 and H's-5)</td>
<td>H's-4, H-6</td>
</tr>
<tr>
<td>N-Me</td>
<td>32.07, -ve, q</td>
<td>4.07 (s, 3H, N-Me)</td>
<td>---$^b$</td>
</tr>
<tr>
<td>C-4</td>
<td>39.43, t</td>
<td>2.08 (m, 4H, H's-4 and H's-5)</td>
<td>Me-9, H-2, H's-5</td>
</tr>
<tr>
<td>C-1</td>
<td>48.68, t</td>
<td>5.70 (d, 2H, J = 6.5 Hz, H's-1)</td>
<td>H-2</td>
</tr>
<tr>
<td>C-5'</td>
<td>109.86, s</td>
<td>---$^b$</td>
<td>H's-1, H-8'</td>
</tr>
<tr>
<td>C-2</td>
<td>116.1, -ve, d</td>
<td>5.42 (br t, 1H, J = 6.5 Hz, H-2)</td>
<td>Me-9, H's-1, H's-4</td>
</tr>
<tr>
<td>C-6</td>
<td>123.2, -ve, d</td>
<td>4.98 (br s, 1H, H-6)</td>
<td>Me-8, Me-10</td>
</tr>
<tr>
<td>C-7</td>
<td>132.3, s</td>
<td>---$^b$</td>
<td>Me-8, Me-10</td>
</tr>
<tr>
<td>C-8'</td>
<td>141.7, -ve, d</td>
<td>10.95 (s, 1H, H-8')$^c$</td>
<td>N-Me, H's-1</td>
</tr>
<tr>
<td>C-3</td>
<td>146.4, s</td>
<td>---$^b$</td>
<td>Me-9, H's-1, H's-4</td>
</tr>
<tr>
<td>C-4'</td>
<td>149.6, s</td>
<td>---$^b$</td>
<td>N-Me, H-2', H-8'</td>
</tr>
<tr>
<td>C-6'</td>
<td>152.4, s</td>
<td>---$^b$</td>
<td>H-2'</td>
</tr>
<tr>
<td>C-2'</td>
<td>156.0, -ve, d</td>
<td>8.49 (s, 1H, H-2')</td>
<td>---</td>
</tr>
</tbody>
</table>

* See Table 2.24 for instruction on how to read this table.

a Off resonance hydrogen decoupled $^{13}$C multiplicity, -ve is reported when a negative peak is observed in the APT experiment.

b No correlation.

c Exchanged with D$_2$O.
B) Preparation of Synthetic (-)-Agelasine B (31)

The acetate buffer (0.1 M, pH 4.5, 10 mL each) was put into the counter and work electrode compartments. The voltage between the work electrode and the reference electrode \( (E_R \text{ vs. } W) \) was +0.22 V. The potentiostat was set at -1.8 V and 10 Coulomb (C) were passed between the counter and work electrodes. \( E_R \text{ vs. } W \) was now -0.28 V. The buffers were removed from both compartments and were replaced by fresh ones \( (E_R \text{ vs. } W = +0.05 \text{ V}) \). The potentiostat was set at +0.6 V and 3.5 C were passed between the electrodes (a white precipitate was formed, \( E_R \text{ vs. } W = +0.37 \text{ V} \)). The buffers were removed again and were replaced by fresh ones \( (E_R \text{ vs. } W = +0.35 \text{ V}) \). The potentiostat was set at -1.6 V and 4 C were passed through the solution \( (E_R \text{ vs. } W = +0.3 \text{ V}) \). The buffers were removed again and fresh buffer (10 mL) was added into the counter electrode cell. A mixture of the (-)-7-kolavenyl-\( N^6 \)-methoxy-9-methyl adeninium bromide derivative 302 (8.7 mg, 0.016 mmol) and the buffer (8 mL) were sonicated (Branson sonic bath) until the mixture was an almost homogeneous milky suspension. The suspension was added into the work electrode compartment and the remainings of the suspension were washed with some buffer (2 mL) and the washings were put into the cell \( (E_R \text{ vs. } W = +0.05 \text{ V}) \). The potentiostat was set at -1.0 V producing an initial current of ~0.8 mA through the milky solution. After 40 min, the current was ~0.25 mA, 0.6 C had passed between the electrodes and \( E_R \text{ vs. } W \) was -0.18 V. After 1.3 h, the solution was getting clearer and the current was ~0.2 mA, 1.1 C had passed through the solution and \( E_R \text{ vs. } W \) was -0.18 V. After 2 h, the current passing through
the almost clear solution was ~0.18 mA, 1.6 C had passed between the electrodes and $E_R$ vs. $w$ was -0.18 V. After 2.5 h, the current passing through the clear solution was ~0.15 mA, 2.1 C had passed through the solution and $E_R$ vs. $w$ was -0.18 V. Additional buffer (2 mL) was added into the counter cell. After 4.4 h, the current passing through the clear solution was ~0.1 mA, 3 C had passed through and $E_R$ vs. $w$ was -0.18 V. After 5.7 h, the current passing through the clear solution was ~0.04 mA, 3.2 C (2.0 equiv of electrons) had passed between the electrodes and $E_R$ vs. $w$ was -0.26 V. At this stage the power was turned off and the electrolytes (from the counter and the work electrode compartments) were transferred to a 100 mL round bottom flask. The electrodes and the cell were washed with methanol and the washings were added into the 100 mL round bottom flask. Powdered sodium chloride (5 g) was added and the solvents were concentrated to 15 mL under reduced pressure (bath ~25 °C). The residue was extracted with chloroform (4 x 30 mL), the aqueous fraction was put aside and the combined organic extracts were washed with brine (5 mL). The two aqueous fractions were put together and were extracted with chloroform (30 mL) and ethyl acetate (2 x 30 mL). All the organic extracts were combined and were dried with magnesium sulfate. The solvents were removed under reduced pressure to give 6.4 mg of a white solid. The solid was purified by TLC grade silica chromatography (1.5 g H type silica, 85:15, 20 mL, 8:2, 10 mL, 7:3, 5 mL, 6:4, 5 mL dichloromethane:MeOH) to give 0.6 mg (8%) of (-)-7-kolavenyl-$N^6$-methoxy-9-methyl adeninium chloride derivative 320 mp 179-181 °C and 4.0 mg (53%, 57% based on the recovered starting material) of the synthetic (-)-agelasine B (31) as an amorphous white solid mp 165-170 °C. The product exhibited IR (1% KBr): 3329, 3146, 2959, 1646, 1605, 1592, 1473, 1383, 1301, 1231, 1189, 1096, 789 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$: 0.69 (s, 3H, Me-20 [NOTE: Clerodane numbering system]), 0.75 (d, 3H, $J = 6$ Hz, Me-17), 0.98 (s, 3H, Me-19), 1.12 (m, 1H), 1.20-1.62 (m, 11H, including $\delta$ 1.55 [m, 3H, Me-18]), 1.69 (dm, 1H, $J = 12$ Hz), 1.84 (s, 3H, Me-16), 1.77-2.10 (m, 4H, H's-12,?), 4.08 (s, 3H, N-Me), 5.16 (br s, 1H, H-3), 5.40 (br t, 1H, $J = 6.5$ Hz, H-14), 5.72 (d, 2H, $J = 6.5$ Hz, H's-15),
6.51 (br s, 2H, NH₂ [exchanged with D₂O]), 8.50 (s, 1H), 11.19 (s, 1H [exchanged with D₂O]), \(^{13}\)C NMR (125.8 MHz) \(\delta\): 16.10, 17.65 (Me), 17.99 (Me), 18.36 (Me), 19.96 (Me), 18.39, 26.93, 27.47, 33.14, 32.02 (NMe), 36.30, 36.32, 36.81, 38.20, 38.72, 46.43 (C-10), 48.78 (C-15), 109.95, 115.86, 120.38, 142.00, 144.50, 147.66, 149.63, 152.31, 156.22; LRMS: \(\text{M}^+\text{-Cl}(422)\) 0.1%; HRMS calcd for \(\text{C}_{26}\text{H}_{39}\text{N}_5\) (\(\text{M}^+\text{-HCl}\)): 421.3205, found: 421.3201 (peak matched); Anal. calcd for \(\text{C}_{26}\text{H}_{40}\text{N}_5\cdot\text{H}_2\text{O}\): C 65.59, H 8.89, N 14.71, found: C 65.28, H 9.00, N 13.01.; \([\alpha]_D^{25}\) -27.2°, c = 1.00 in MeOH [lit.\(^{31,192b}\) \([\alpha]_D\) -21.5°, c = 1.00 in MeOH and \([\alpha]_D^{21}\) -38.4°, c = 1.00 in MeOH]; UV (1.96 x 10⁻⁴ M in MeOH): 272.5 nm, \(\varepsilon\) 10429.
REFERENCES


15. The high demand of the anticancer drug taxol and the low yield of its extraction from the Pacific yew trees are causing a very rapid harvest of the slow-growing plant. An efficient synthesis of taxol should help preserve the species. Junod, T. Life 1992, 15, 71.


29. Although avarol is not a clerodane and has a biogenesis different from that of the clerodanes, its bicyclic trans-decalin skeleton has enough similarity with the one present in the trans-clerodanes that its synthesis is included in the list. Sarma, A. S.; Chattopadhyay, P. J. Org. Chem. 1982, 47, 1727.


33. Although palauolide is not a diterpenoid, its bicyclic *trans*-decalin skeleton has enough similarity with the one present in the *trans*-clerodanes that its synthesis is included in the list. See reference 12.


39. This is partly why the FDA (Federal Drug Agency, the United States drug regulating agency) has forced the pharmaceutical industry to move towards the production enantiomerically pure drugs. See reference 3.


41. A chiron is defined as "an enantiomerically pure molecule that contains a good level of stereochemical overlap with a substructure in the target." See Hanessian S. *Aldrichim. Acta* 1989, 22, 3 and references cited therein.


56. Caine and coworkers repeated the procedure reported by Oppolzer and Petrzilka and observed the formation of an 85:15 mixture of enones 55 and 73 after the oxidation and the elimination of the sulfonic acid, thus showing that some of the isomeric sulfides (PhS on the same side of the carbonyl as the Me group) were formed in the sulfinylation step. Caine, D.; Procter, K.; Cassell, R. A. J. Org. Chem. 1984, 49, 2647.


63. Ozone oxidation also gives an equivalent yield of enone 55 after elimination of the selenoxide, but is less convenient to use than hydrogen peroxide.


69. The CD spectra of the compounds obtained in this thesis that display a Cotton effect will be discussed in a separate section.


82. See reference 75, p 299.


85. See reference 74, p 245.


92. The structure of trimethylstannylcyclohexanone 102 was unambiguously established using the spectral data and analyses. The $^1$H NMR and the $^{13}$C NMR spectra can be fully assigned by analogy with the chloro ketone 100.
94. See reference 13f. The chloro butene 110 was generously supplied by Ms. Johanne Renaud from Dr. Piers' research group at UBC.
96. The (E)-trimethylstannyl ester 112 was generously provided by Mr. Timothy Wong from Dr. Piers' research group at UBC.
97. The epimeric chloro ketone 118 was never isolated and its structure is proposed from the $^1$H NMR spectra of the mixture of 117 and 118 and from the similarity with the results from the methylenecyclohexane annulation.
98. M$^+$ is used instead of M$^+$ all through this thesis for convenience.
100. A(1,3) strain stands for the allylic strain between the substituents in a 1,3-relation on a double bond. This was first developed for 6-membered rings and was extrapolated to other systems. See: Johnson, F., *Chem. Rev.* 1968, 68, 9 375.
101. No enhancement for H-5e could be observed when Me-12 was irradiated due to the proximity of its $^1$H NMR signal with the irradiated signal ($\Delta\delta$ 0.08) (see 130a).


111. See reference 109, p 160.


113. The acids and their respective acid chlorides are available from Aldrich Chemical Company, Milwaukee, USA.


116. Dale and Mosher have made it clear that the models 173 and 174 were deduced a posteriori and do not represent the preferred ground state conformations of the MTPA esters. They speculate about the reason for the observed differences in chemical shifts but give no evidence. See reference 114.


121. See reference 109, p 73.

122. Menger gives a good discussion for an explanation of the increase of the rates


124. The combination of a low concentration and a small $[\alpha]_{578}$ of 192 and 195 makes this measurement unreliable proof of both the identity and the enantiomeric purity of the compound 192.


126. See reference 109, p 35.


130. The usual wavelength range of the general-use commercial spectropolarimeter is 175-800 nm, which is the normal ultraviolet-visible (UV-VIS) range.


132. See reference 129a, p.557.

133. See reference 129a, p.559.

134. The Cotton effects in this thesis are reported as the specific ellipticity and the CD. The specific ellipticity is defined as $[\Psi]_{\lambda} = \left(\frac{\Psi}{Ic}\right)$, where $\Psi$ is the measured angle of ellipticity in millidegrees (m°), I is the distance of the light path in centimeters (cm), c is the concentration in grams per 100 milliliters (g/100 cm$^{-3}$), t is the temperature in °C and $\lambda$ is the wavelength of the absorption in nanometers (nm). The units are in $(\text{deg} \cdot \text{cm}^2 / \text{dag})$ where deg = (°) and dag = decagram.

135. The circular dichroism $\Delta\varepsilon$ in L•mol$^{-1}$•cm$^{-1}$ is the difference between the left and the right molar extinction coefficient, and is more adequate for comparison of the CD spectra of compounds of different molecular weight than is the specific ellipticity. The circular dichroism is related to the specific ellipticity by
\[ \Psi = (\frac{3.3 \times 10^5 \Delta \varepsilon}{M}) \] 
where \( M \) is the molecular weight of the compound under comparison.


137. The polarizability of a moiety on a chiral molecule has been linked to the strength of the measured optical rotation. See Brewster, J. H. *J. Am. Chem. Soc.* 1959, 81, 5475.

138. See reference 129a, p 560.

139. A bisignate CD curve is observed when two non-coincidental Cotton effects of opposite sign overlap. See reference 131.


145. See reference 109, p 165.

146. For a review on \( \text{i-Bu}_2\text{AIH} \) reductions see Winterfeldt, E. *Synthesis*, 1975, 617.

147. See reference 109, p 227.


151. See reference 109, p 231.


153. See reference 109, p 238.


156. See reference 120, p. 190.

157. The HMQC (Heteronuclear Multiple Quantum Coherence) experiment is a reverse detection (detect the insensitive nuclei through the more sensitive $^1$$H$) NMR experiment that gives a correlation between a carbon and the hydrogen(s) directly attached to it (1 bond). See the Experimental section for reference.

158. The HMBC experiment (Heteronuclear Multiple Bond Connectivity) is a reverse detection NMR experiment that gives a correlation between a carbon and the hydrogen(s) attached two and three bonds away from it. See the Experimental section for reference.


164. See reference 109, p 238.

165. The ratio of alcohols 231:232 varied unpredictably between 1:10 to 5:1.

166. Guindon and coworkers have also observed the formation of a formaldehyde dimenthol acetal in the hydrolysis of a menthol-methoxyethoxymethyl ether (menthol-MEM). They have suggested the use of THF and aqueous sodium bicarbonate in the work-up to avoid the formation of the acetal. See reference 152a.

167. See reference 109, pp 232 and 238.


170. A 1:1 mixture of the esters 259 and 260 was also obtained after the initial chromatography (~14% yield). An analytical sample of 260 was obtained after a second tlc grade silica chromatography.


190. We thank Dr. T. Tokoroyama for a sample of (-)-methyl kolavenate and for providing a copy of the spectra (IR, $^1$H and $^{13}$C NMR) of (-)-kolavenol.


201. $\Delta \delta = (\text{Chemical shift of 301})-(\text{chemical shift of 302})$

202. This compound has been prepared previously by Tokoroyama and coworkers (see reference 31) but the physical properties of this compound have not, so far, been reported.

203. Geranyl bromide is available from Aldrich Chemical Co.

204. The partial decomposition of compound 313 on basic alumina resulted in low isolation yield.

205. The UV and $^{13}$C spectra were recorded only for compound 312.


208. A sample of impure agelasine B was also obtained from Dr. D. J. Faulkner. The $^{1}$H NMR and IR spectra of synthetic and natural agelasine B were obtained from Dr. T. Tokoroyama. We thank Drs. Andersen, Faulkner and Tokoroyama for their assistance.

209. The sponge was collected off Motupore Island off Port Moresby southern New Guinea at a depth of 30 to 50 feet by Mr. Mike Leblanc, UBC Oceanography department technician, in November-December 1988. The sponge was identified by Dr. D. J. Faulkner and Ms. Jana Pika.

210. See reference 77, p 1126.


214. The voltammograms shown are for reduction processes but the same arguments apply for oxidation processes.

215. The residual current is the current observed between the work and counter electrodes when the scanning is done with only the solvent and the support electrolyte in the cell.

216. The voltammograms were converted into digital data using an optical scanner (SCANMAN), and the data were processed using the CHEM-DRAW program.


220. See reference 74, p 97.

221. See reference 74, p 245.


224. See reference 72, p 379.

225. Plante, R.; Poupart, M.-A. Bio-Mega Inc. Montréal, personal communication. The technique is a major improvement on Rigby and Hunt’s method (Chem. and Ind. 1967, 1868). The main difference between tlc grade silica and flash chromatography is that the tlc silica is finer and that in the first case the height of silica gel in the column is set to be 2-3 times the diameter of the column. Because the silica is finer higher pressure are necessary (5-15 psi). Caution should be taken to avoid overpressure and a shielded apparatus should be used. This technique is the fastest way to achieved difficult separation. See Taber, D. F. J. Org. Chem. 1982, 47, 1351.


233. See reference 27, p 122.

234. The solution of lithium chloride-copper(I) cyanide complex in THF was prepared using the following procedure [note: the amount of LiCl, CuCN, and THF used are given in the appropriate experimental section]: lithium chloride (2 equiv for each equiv of CuCN) was flame dried under reduced pressure (0.1 torr, vacuum pump), cooled to approximately 80°C, the flask was filled with argon and copper(I) cyanide was added. The mixture was kept under reduced pressure (vacuum pump) for an hour while the flask is cooling and then the flask was filled with argon and the described amount of THF was added before use.


236. See reference 117, pp 189-190.

237. Mosher’s acid chloride ((-)-MTPA-CI) was prepared from (+)-MTPA according to Mosher’s procedure: see reference 112.

238. See reference 109, p 161.

239. See reference 109, p 162.

240. See reference 109, p 34.

242. See reference 109, p 165.


244. Impure TosMIC (11 g dissolved in a minimum amount of dichloromethane) was filtered through a column of basic alumina (100 g). The alumina was washed with dichloromethane (200 mL) and the solvent was removed under reduced pressure. The white solid was dissolved in a minimum amount of ether and hex was added until the crystalization started. The mixture was cooled in a refrigerator (4°C) for a few hours. The solid was filtered, washed with cold (0°C) hex and the residual solvents were removed under vacuum (vacuum pump) to give 6-7 g of pure TosMIC. The crystals were kept at -20°C under an argon atmosphere.

245. See reference 109, p 226.

246. 2-Iodo-1-methoxymethoxy ethane (318) was prepared from 2-chloro-1-methoxymethoxy ethane (prepared by J. S. M. Wai) using a procedure identical with that described by Wai: see reference 109, p 225.

247. See reference 109, p 52 and p 231.

248. Anhydrous hydrazine was prepared by refluxing hydrazine hydrate over an equivalent weight of sodium hydroxide for 2 h and then distilling. An explosion shield was used and care was taken that the anhydrous hydrazine is not exposed to oxygen as an explosive reaction could occur. A lot of cold water was added via syringe to the distillation residue before the apparatus was disassembled.


251. The ratio of 232:231 varies from 10:1 to 1:5 (by ¹H NMR) depending on the reaction conditions, the work-up and the source or the purity of the dimethylboron bromide.

252. Guindon and coworkers have also observed the formation of a formaldehyde dimethyl ketal in the hydrolysis of a menthol-methoxyethoxymethyl ether (menthol-MEM). They have suggested the use of THF and aqueous sodium bicarbonate in the work-up to avoid the formation of the ketal. See reference 152a.

253. Pure sample of compounds 213, 283 and 284 were isolated after combining material from a number of reactions and by using repetitive radial chromatography (1 mm, hex).
The zinc dibromide solution was prepared by refluxing freshly distilled 1,2-dibromoethane (35 mL, 0.4 mmol) and a suspension of freshly activated zinc (35 mg, 0.53 mmol, 1.3 equiv) in THF (0.7 mL) for 1 h (the disappearance of the 1,2-dibromoethane was followed by gc analyses). The solution was then cannulated from the residual excess zinc, via Teflon® cannula, to the alkyl lithium.

See reference 227, p 547

Prepared by washing a column of Amberlite® IRA-402-Cl⁻ (30 mL) first with saturated aqueous sodium bicarbonate (300 mL) and then, with deionized water (300 mL).

The latrobeat® silica is a neutral (~pH 7) spherical silica that is useful for purifying unstable compounds. It is available from Latron Laboratories Inc., Tokyo, Japan.

It was found later that the products 313 and 314 are unstable to basic conditions. See reference 198a.

Tokoroyama and coworkers, have demonstrated the concentration dependency of the position of the adenine signals (NH₂, H-2' and H-8') in the ¹H NMR spectrum of (±)-ageline A (285). This discrepancy was probably due to the propensity of the molecule to associate through the polar moiety... This might be the reason why our observed chemical shifts for the adenine signals in our spectrum are different from those reported. See reference 181.

[NOTE: this section is taken from Ms. Jana Pika research notes.] The sponge *Agelas* (probably *nakamurae*) was collected by M. Michel Leblanc in Papua-New Guinea. The orange-red sponge (~4 kg) was soaked in methanol which was decanted, filtered and concentrated under reduced pressure. The sponge was then soaked in a mixture of dichloromethane:methanol (1:1) which was also decanted, filtered and concentrated under reduced pressure. The organic extracts were combined to give ~60 g of crude material.

The crude was dissolved in water and extracted successively with hex (3 x 250 mL), dichloromethane (3 x 250 mL) and ethyl acetate (3 x 250 mL). The organic fractions were dried with sodium sulfate and the solvents were removed under reduced pressure to yield 0.16 g, 11.47 g and 0.67 g, respectively. The residual water fraction was freeze dried to yield 8.7 g.

A portion of the dichloromethane extract (5.0 g) was applied to a gel partition column (Sigma® lipophilic Sephadex® LH-20-100, bead size 25-100 mm, 2.5 x 100 cm, 20:5:2 ethyl acetate:MeOH:water). The agelasines were visualized by tlc (3:1:1 butanol:acetic acid:water, uv), the fractions were pooled and the solvents were removed under reduced pressure to yield 1.3 g of the crude agelasines.

We thank Dr. R. J. Andersen and Ms. Jana Pika for their collaboration.

See reference 72, p 379.
The buffer was prepared by dissolving sodium acetate trihydrate (6.804 g) in doubly deionized water (470 mL) and by adjusting the pH to 4.5 with glacial acetic acid. The pH was measured with glass electrode pH meter calibrated at pH 4.00 and 7.00 using commercial standards. The volume of the buffer solution was made up to 500 mL with doubly deionized water.

The multiplicity of the signals of the off-resonance hydrogen decoupled spectrum are indicated first.