STUDIES TOWARDS THE TOTAL SYNTHESIS OF LINTENONE

by

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Date 25th October 2000
Abstract

A 32 step synthesis of the racemic compound \( (1R^*,3S^*,4R^*,7R^*,8R^*,10R^*,11S^*)-10\text{-}\text{tert}-\text{butyldimethylsiloxy}-4,7,8,11\text{-}\text{tetramethyl}-3\text{-}\text{triethylsilyloxytricyclo}[5.3.1.0^{3,11}]\text{undecane (224)} \) is described. This is a highly advanced intermediate in the attempted total synthesis of racemic lintenone (1). The novel trifunctional reagent 76 was developed and was used to synthesis the series of substituted cyclohex-2-en-ones 104-106 and 78. The substituted cyclohex-2-en-1-ones 104-106 and 78 underwent copper(I) cyanide mediated intramolecular conjugate addition reactions to give the ketones 112-114 and 71. Ketone 71 was subsequently utilized in the attempted total synthesis of lintenone (1). Ketone 71 was converted into the enone 73. Addition of \( \text{Me}_2\text{CuLi} \) to enone 73 occurred stereoselectively to give the ketone 74. Ketone 74 was subsequently converted into the nitrile 166, which was alkylated stereoselectively with benzyl chloromethyl ether to give the alkylated nitrile 173. Alkylated nitrile 173 was converted into the diazoketone 177. Treatment of diazoketone 177 with dimeric rhodium acetate gave exclusively the tricyclic keto nitrile 178 with complete stereoselectivity. Reduction of the tricyclic keto nitrile 178 with \( \text{LiAlH}_4 \) followed by immediate protection as the TES ether and then treatment with carbon disulfide and DCC in methylene chloride gave the isothiocyanate 222. Reduction of isothiocyanate 222 with \( \text{Bu}_3\text{SnH} \) and AIBN led to the formation of the tricyclic disilyl ether 224.
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List of Abbreviations

AcOH       acetic acid
AIBN       azobisisobutyrylnitrile
Bn         benzyl, CH₂Ph
Benz       benzene
br         broad
n-BuLi      n-butyllithium
t-BuOH     tert-butyl alcohol (2-methyl-2-propanol)
n-Bu₃SnH   tributylstannane
n-Bu₃SnCN  tributylstannylcyanide
cat.       catalytic amount
CH₃CN      acetonitrile
m-CPBA     3-chloroperoxybenzoic acid
conc.       concentrated
COSY       ¹H-¹H homonuclear correlation spectroscopy
CuCl       copper(I) chloride
CuCN       copper(I) cyanide
d          doublet
DCC        dicyclohexylcarbodiimide
DCI        direct chemical ionization
DIBAL      diisobutylaluminium hydride (i-Bu₂AlH)
DMAP       4-dimethylaminopyridine
DMF  \( N,N\)-dimethylformamide
DMSO  dimethyl sulfoxide
e.g.  \textit{exempli gratia}, for example
EI  electron impact
equiv.  equivalents
eq  equation
Et\(_3\)N  triethylamine
Et\(_2\)O  diethyl ether
EtOAc  ethyl acetate
GLC  gas liquid chromatography
Hz  Hertz
HMOC  \(^1\)H detected Heteronuclear Multiple Quantum Coherence
HMBC  \(^1\)H detected Heteronuclear Multiple Bond Coherence
HSQC  \(^1\)H detected Heteronuclear Single Quantum Coherence
HRMS  high resolution mass spectroscopy
Imid  imidazole
LDA  lithium diisopropylamide
LiNEt\(_2\)  lithium diethylamide
LRMS  low resolution mass spectroscopy
m  multiplet
MeLi  methyl lithium
MHz  megahertz
Mp.  melting point
NMR  nuclear magnetic resonance
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<th>Abbreviation</th>
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<tr>
<td>ppm</td>
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<tr>
<td>p</td>
<td>pentet</td>
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<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>pyr</td>
<td>pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>refl.</td>
<td>reflux</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl, t-BuMe₂Si</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyldiphenylsilyl, t-BuPhe₂Si</td>
</tr>
<tr>
<td>TES</td>
<td>triethylsilyl, Et₃Si</td>
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<td>trifluoroethyl trifluoroacetate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TMSCI</td>
<td>trimethylsilyl chloride</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>p-TsOH</td>
<td>para-toluene sulfonic acid</td>
</tr>
<tr>
<td>+ve</td>
<td>positive</td>
</tr>
<tr>
<td>-ve</td>
<td>negative</td>
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Introduction
General Introduction

“As the flagship of organic synthesis, total synthesis often guides and demands new synthetic methods and strategies. It also becomes the testing ground where new technologies are tested and judged for their applicability, efficiency and practicality. In a way, total synthesis provides the tough and real challenges to new synthetic methods, often before they are passed over to those who use them extensively in their daily research and/or for their manufacturing needs. Indeed, the total synthesis of complex natural products is frequently given as the reason for the need to develop a new synthetic method to achieve a goal unattainable by existing methods. Furthermore, newly appearing synthetic methods often become convincingly useful once they have been successfully applied to total synthesis. Examples here include the Diels-Alder reaction, the Wittig reaction, the hydroboration reaction, the Corey dithiane reaction, the Sharpless asymmetric epoxidation reaction, the various palladium-catalyzed coupling reactions, the olefin metathesis reaction and last but by no means least, the multitude of protecting groups available to the synthetic chemist today.”

Taken from a recent review by K.C. Nicolaou,¹ this passage highlights the usefulness of total synthesis and how natural products chemistry continues to test the methods available to the synthetic chemist. Significant advances in the field of organic chemistry have provided the answers to many of our scientific questions. The challenges facing the organic chemist however, continue to multiply because these same advances continue to provide ever more intractable problems. Elaborate natural and unnatural products of biological interest are continuously being discovered, providing ever more challenging targets for synthesis. When a natural product of medicinal importance is isolated it is not certain that this will be the most
effective compound from a medicinal point of view. Closely related compounds are often found to have a higher potency, lower toxicity or an improved solubility profile. A method developed to synthesize a particular natural product often also allows for the synthesis of closely related structural analogues. The additional information provided by compounds with these structural modifications is then of use in the discovery of a final compound with the most desirable properties.

In recent years there have been great advances in the field of asymmetric synthesis. Significant impetus for this was provided by the discovery that the severe birth defects associated with the drug Thalidomide were the result of only one of its enantiomers. The enantiomer that had the desired biological activity was found to not cause birth defects, whereas the enantiomer that caused birth defects was found to not have the desired biologically activity. Legislation was enacted almost worldwide to ensure that there should be no repeat of this tragedy. All new therapeutic agents developed by pharmaceutical companies for the treatment of medical conditions now have to be isolated in an enantiomerically pure form. If a compound cannot be synthesized as a single enantiomer, each isomer present must be obtained pure and subjected to individual toxicity testing. The formation of stereogenic carbon centres is one of the major challenges facing the synthetic organic chemist today. Research in the Piers laboratories is focussed on the development of new reagents and methods for stereogenic carbon centre formation and the application of this methodology to the synthesis of structurally novel natural products of biological interest. The subject of this thesis is the development of methodology for the synthesis of novel trifunctional reagents and their application to the attempted total synthesis of (-)-lintenone (1).
A recent report from our laboratories\textsuperscript{2} detailed the efficient stereospecific intramolecular cross couplings of vinyltrimethylstannane functions and alkenyl halides by treatment of the requisite substrates with copper(I) chloride (eq 1).

\[
\begin{align*}
\text{SnMe}_3 & \quad \text{I} & \quad \text{CuCl}\ (2.2\ \text{eq}) \\
\text{DMF, 62 °C, 3 min} & \quad 80\% \\
\rightarrow & \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

(1)

It has been shown that this coupling process is initiated by interaction of the copper(I) salt with the vinyltrimethylstannane functionality. This generates trimethylstannyl chloride and presumably an intermediate vinylcopper species \textit{2} (eq 2).

\[
\begin{align*}
\text{SnMe}_3 & \quad \text{CuCl} \\
\leftrightarrow & \\
\text{Me}_3\text{SnCl} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

(2)

Consequently, intramolecular conjugate additions of alkenyl functions to \(\alpha,\beta\)-unsaturated ketones via a protocol outlined in general terms in (eq 3) were investigated\textsuperscript{3} and found to give exclusively the cis-addition products. It was hoped to extend this methodology to synthesize compounds with structures similar to that of compound \textit{4}, with functionality at \(R^3\) suitable for future elaboration to give the (-)-lintenone (1) ring system.
Background

(-)-Lintenone (1) came to our attention because it contains a highly complicated tricyclic carbon skeleton, which encompasses fused cyclohexane, cyclopentane and cyclobutane rings. Its unusual cis-fused tricyclo[4.3.0.0^3,10]decane ring system possesses six contiguous stereogenic centres, three of which are quaternary. This ring system includes a highly strained four-membered ring and has four methyl groups, three of which are situated at the ring junctions. These will consequently have to be introduced in a stereoselective manner. (-)-Lintenone appealed to us as a synthetic target due to its highly complicated structure, which makes it a demanding yet attractive target for a total synthesis. Lintenone (1) possesses a degree of structural similarity to the ketone 5, which has been previously synthesized in our laboratories.  

It can be seen that both compounds possess cis-fused bicyclo[4.3.0]nonane structural elements with methyl groups at the ring junctions. The bicyclic ketone 5 was synthesized as follows (Scheme 1).  

The vinylogous ester 6 was alkylated with the allylic bromide 7 and the product
was then alkylated a second time with MeI. Addition of methylmagnesium bromide to the alkylated product, followed by acid promoted hydrolysis of the resultant product, gave the enone 8. An intramolecular copper(I) mediated conjugate addition of the vinyltrimethylstannane functionality to the α,β-unsaturated ketone function gave the bicyclic ketone 5.

It was hoped that this methodology could be extended to provide a means to synthesize the ketone 10 (eq 4). Ketone 10 was envisioned as a key intermediate in the total synthesis of lintenone (1). It possesses functionality that provides a number of options for both the formation of the four-membered ring and the introduction of the methyl group at the 9-position (bicyclo[4.3.0]nonane numbering system). It was anticipated that the methyl group at the 5-position of the enantiomerically pure α,β-unsaturated ketone 11 could be used to control the stereochemistry at the adjacent centre by sequential alkylation (Scheme 2).
Previous attempts at alkylation of ketone lithium enolates with the alkylating agent 12 have proceeded with elimination rather than alkylation, to give the starting ketone and the diene elimination product of 12. The higher nucleophilicity of the anion derived from the dimethylhydrazone derivative of 11 should prevent this elimination. Both alkylating agents should approach the anions of the dimethylhydrazones from the face of the anions opposite to the methyl group at the 5-position, to give the alkylated enone 13. Addition of methylmagnesium bromide to the alkylated product 13, followed by PCC oxidation of the resultant product, should give the enone 9. Enone 9 should undergo the aforementioned intramolecular copper(I) mediated conjugate addition reaction to give the desired ketone 10.

Isolation, Structure Elucidation and Biological Activity of (-)-Lintenone (1)

In 1992 Fattorusso and co-workers at the Dipartimento di Chimica delle sostanze Naturali, Naples, Italy, reported the isolation of the natural product lintenone (1) from the Caribbean sponge Cacospongia cf. linteiformis. (-)-Lintenone (1) is a novel bioactive sesterterpene based on a structurally unprecedented substituted tricyclo[4.3.1.0^3.10]decane skeleton. The animals were extracted with MeOH/Toluene (3:1) and the EtOAc soluble material was subjected to medium-pressure liquid chromatography on silica gel. Successive silica gel HPLC separations of the non-polar fractions gave pure lintenone (1) as an oily product (0.0025% of dry weight...
after extraction. The structure of lintenone (1) was assigned by use of IR, \(^1\)H NMR, \(^{13}\)C NMR, mass spectra and a variety of 1D and 2D NMR experiments.\(^5\)

Lintenone (1) was found to be very toxic to the mosquito fish *Gambusia affinis* at 10 ppm. Antifeedant assays conducted with the fish *Carassius auratus* showed high feeding deterrence for 1 at 30 \(\mu\)g per cm\(^3\) of food pellets. Lintenone (1) was also found to possess moderate toxicity (LD\(_{50} = 109\) ppm) in the brine shrimp (*Artemia salina*) assay.\(^5\)

A sesterterpene, lintenone (1) could derive from the folding and formal cyclization of a five-isoprene unit 25-carbon precursor and a single methyl migration. The possible arrangement of the isoprene units is shown in Figure 1.

![Figure 1: Possible arrangement of isoprene units leading to the lintenone carbon skeleton](image)
Formation of Four-Membered Carbocycles

There is significant interest in the construction of four-membered carbocycles. This is because of their inherent reactivity and the consequent possibility of further synthetic manipulations that this reactivity provides. At present the two major methods for the construction of four-membered carbocycles are photochemical [2+2] cycloadditions and ring contraction of cyclic α-diazocyclopentanones by the Wolff rearrangement. A recent report from our laboratories has detailed the synthesis of functionalized cyclobutane derivatives via intramolecular conjugate addition of alkenyltrimethylstannane functions to α,β-alkynic esters mediated by copper(I) chloride. This report represents preliminary work in this area. Its applicability to complicated fused ring systems has yet to be studied.

Syntheses Relevant to the Total Synthesis of (-)-Lintenone (1)

Of particular relevance to the synthesis of lintenone is work published on the synthesis of compounds in the series of [4.4.5.5]fenestranes (14) and [4.4.4.5]fenestranes (15). These substances experience severe strain and distortion at the central quaternary carbon atoms and their syntheses provide precedence for the construction of four-membered carbocyclic rings in such strained systems. The synthesis of the four-membered rings in these compounds utilized both [2+2] photocycloaddition and ring contraction of a cyclopentanone by a Wolff rearrangement.

![Diagram of compounds 14 and 15]
The synthesis of the [4.4.4.5]fenestrane 15 is a representative example from this series.\textsuperscript{11} Enone 18 served as an advanced intermediate in the synthesis of a variety of the fenestranes. Condensation of the \(\beta\)-keto ester 16 with methyl 4-bromoacetoacetate gave 17 in high yield. Selective removal of the carbomethoxy group by treatment of 17 with sodium iodide and acetic acid in hot diglyme (Scheme 3) gave the enone 18.

```
\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {16};
\node (b) at (1.5,0) {17};
\node (c) at (3,0) {18};
\draw[->] (a) -- node[above] {1. NaH} (b);
\draw[->] (b) -- node[below] {2. Br\textsuperscript{2}O\textsuperscript{2}OMe} (c);
\end{tikzpicture}
\end{center}
```

\textbf{Scheme 3}

Photochemical [2+2] cyclization of the enone 18 (\(\lambda > 340\) nm, hexane solvent) furnished a 2:1 mixture of the ester 19 and the minor product, which was isomeric with 19 at the carbon \(\alpha\) to the ester function. Ester 19 was the thermodynamically more stable product. This was shown by treatment of the minor isomer with base, which led to a 2:1 mixture of isomers with 19 as the major product.

```
\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {19};
\node (b) at (1.5,0) {20a};
\node (c) at (3,0) {20b};
\node (d) at (4.5,0) {20c};
\node (e) at (6,0) {21};
\draw[->] (a) -- node[above] {\textit{a}, X = OH} (b);
\draw[->] (b) -- node[below] {\textit{b}, X = Cl} (c);
\draw[->] (c) -- node[above] {\textit{c}, X = CHN\textsubscript{2}} (d);
\draw[->] (d) -- node[below] {\textsuperscript{10}} (e);
\end{tikzpicture}
\end{center}
```

Ketalization of 19 and saponification of the ester function led to the acid 20\textsubscript{a}, which was converted into the acyl chloride 20\textsubscript{b} by treatment with oxalyl chloride. The \(\alpha\)-diazo ketone 20\textsubscript{c} was obtained by addition of diazomethane to 20\textsubscript{b}. Rhodium(II) acetate mediated carbene insertion gave the tetracyclic [4.4.5.5]fenestrane 21 as the only isolated product (64\% from 20\textsubscript{a}). It was then intended to access the [4.4.4.5]fenestranes via a Wolff rearrangement, which would effect a ring contraction of the cyclopentanone ring. Conversion of 21 into the
diazoketone 22b, the required precursor for the Wolff rearrangement, proved to be problematic. Both deformylative diazo transfer involving intermediate 22a, as well as a direct procedure for converting 21 into 22b using trisyl azide under phase transfer conditions, gave poor yields.

The [4.4.4.5]fenestranes were finally accessed by formation of the α-diazo ketone at the alternate site. Ketone 23 was the desired precursor for the synthesis of the diazo ketone 24b. Hydride reduction, tosylation and further hydride reduction served to convert 21 into the tricyclic ketal 28. Deketalization then gave the desired ketone 23 (Scheme 4).

Formylation of ketone 23 with ethyl formate provided 24a and subsequent diazo transfer using tosyl azide gave the desired α-diazo ketone 24b. Photolysis of 24b in methanol gave a 3:1 mixture of the corresponding [4.4.4.5]fenestranes, with 25 as the major product; presumably methanol addition to the intermediate ketene occurred from the less hindered rear face.
Conversion of the fenestrane 25 to its p-bromoanilide, followed by slow recrystallization of this derivative, yielded a sample suitable for X-ray crystallographic studies. The X-ray crystal structure confirmed the stereochemistry and proved that the Wolff rearrangement could be used to provide such exceedingly strained four-membered rings.

Work by Shultz on the intramolecular [2+2] photocycloadditions of 4-(3'-alkenyl)- and 4-(3'-pentynyl)-2,5-cyclohexadien-1-ones is also of particular relevance to a possible synthesis of lintenone. Shultz reported the synthesis of the tricyclic ketone 31, which has a carbocyclic core similar to that of lintenone (Scheme 5). A series of photochemical [2+2] cyclizations gave a 9:1 mixture of the diastereomers 31 and 32, favouring the product 31, from both 29 and 30. This result is suggestive of an intermediate 1,4-biradical, since rotation around a C-C bond obviously occurs within the mechanism.

![Scheme 5]

Previous Attempts at the Total Synthesis of (-)-Lntenone

To date, no total synthesis of lintenone (1) has been published. Meyers has published an as yet unsuccessful approach towards lintenone (1) involving an intramolecular photochemical [2+2] cycloaddition of an enantiomerically pure 4,4-disubstituted cyclohexenone which builds upon
Shultz's work. Meyers has also published work on the synthesis of 4,4- and 6,6-disubstituted cyclohexenones in enantiomerically pure form from chiral bicyclic lactams\(^\text{15}\) and on the use of chiral bicyclic lactams in the synthesis of compounds containing stereogenic quaternary carbon centres.\(^\text{16}\) In an extension to this work, 4,4-dialkyl cyclohexenones have been synthesized in which one alkyl substituent has an appropriately positioned alkene to take part in an intramolecular [2+2] photocycloaddition.

![Scheme 6: Synthesis of the 4,4-disubstituted cyclohexenones 43-45.](image)

The syntheses of the cyclohexenones are outlined in Scheme 6. This work was the basis of Meyers' approach towards the total synthesis of lintenone (1). Lactam 33 was alkylated with a series of homoallylic iodides 34-36 and the products 37-39 were subsequently alkylated with MeI to give the lactams 40-42 as single diastereomers (the approach of the MeI being entirely axial). Addition of MeLi to the lactams, followed by hydrolysis of the resultant products, gave the 4,4-disubstituted cyclohexenones 43-45 with no sign of the 1,5-dicarbonyl compounds.
Photocycloaddition of 43 gave the expected tricyclic product 46 in high yield, proving that the cyclization to form the required [4.3.1.0410]dec-7-one ring system was viable in a model system. However photocycloaddition of 44 (R = CH₃) and 45 (R functionalised for future elaboration of the lintenone skeleton) proceeded to give the decanes 47 and 48 in high yield, but with poor stereoselectivity (Scheme 7).

Scheme 7: [2+2] Photochemical cyclizations of the 4,4-disubstituted cyclohexenones 43-45.

This loss of stereochemical integrity in the [2+2] photocycloadditions of enones has been reported previously¹³ and as stated earlier (page 12) is thought to occur via a diradical mechanism. The lower than anticipated stereoselectivity, observed when R was larger than a hydrogen, would appear to be the result of an unforeseen steric repulsion in the transition state. This steric repulsion presumably occurs between the R group and the methyl substituent in the 9-position of the cyclohexenones 44 and 45.
Proposal

Lintenone (1) is a very attractive target for total synthesis. It has a highly complicated structure making it a challenging synthetic target. It also possesses a degree of structural similarity to the ketone 5, which has been previously synthesized in our laboratories.\textsuperscript{3}

It was therefore decided to attempt a synthesis of lintenone via a route employing a copper(I) mediated intramolecular conjugate addition reaction previously developed in our laboratories.\textsuperscript{3} This is the basis of the research project discussed herein. The proposed synthetic route towards the total synthesis of lintenone (1) is discussed in detail in the Results and Discussion section of this thesis.
Results and Discussion
Proposed Routes Towards the Total Synthesis of (-)-Lintenone

It was expected that compounds of general structure 4, formed by the copper(I) mediated conjugate addition of the vinyltrimethylstannane 3, would provide suitable precursors for elaboration towards the synthesis of lintenone (1). An appropriate choice of substituent at R₃ (eq 5) should provide both a means to form the four-membered ring and to introduce the methyl group at the 9-position (bicyclo[4.3.0]nonane numbering system).

\[ \text{Ketone 10 was chosen as a suitable initial target as it possesses the desired cis-fused ring system and the correct methyl substitution at the ring junctions. Ketone 10 is structurally very similar to the general structure 4 except that it has an exocyclic rather than an endocyclic double bond. Theoretically, the exocyclic alkene function could be used in a variety of routes, which would allow the required functional group manipulations necessary to both introduce the final methyl group and form the four-membered ring. In an extension of the methodology discussed above, ketone 10 should be accessible from the enone 9 via a copper(I) mediated intramolecular conjugate addition (eq 6).} \]
In another method previously developed in our laboratories, a Pd(0) catalyzed ring closure had been shown to be applicable to the formation of fused five, six and seven-membered carbocyclic rings. It was expected that this methodology could be extended to provide the desired four-membered ring. Thus, iodo ketone 49 should undergo a Pd(0) catalyzed ring closure in the presence of a base to give the tricyclic compound 50 (eq 7). A variety of methods can be envisioned that would provide the iodo ketone 49 from the bicyclic ketone 10.

A model study was conducted simultaneously to this project to show whether or not this annulation strategy would be successful at forming four-membered rings. In this work, the bifunctional reagent 3-iodo-2-trimethylgermylprop-1-ene (51) was envisaged to serve as a synthetic equivalent of the 1-propene a, d synthon 52.

The iodide 51 was converted into the lower order cuprate 54, which upon reaction with cyclohexenone 53, gave the vinylgermane adduct 55a (Scheme 8). The vinylgermane adduct
55a was subsequently converted to the vinyl iodide 55b. Unfortunately the envisaged Pd(0) catalyzed cyclization reaction proved to be unsuccessful at forming four-membered rings. Treatment of the vinyl iodide 55b with Pd(PPh$_3$)$_3$ in the presence of base yielded none of the desired keto alkene 56.

In light of this development, it was decided to attempt the synthesis of the tricyclic ester 57, as this substance could also, in theory, serve as an advanced intermediate in the synthesis of lintenone (1) (Scheme 9). Reduction of the ester 57 followed by a one-carbon chain extension and further reduction would be expected to lead to the alcohol 58. Presumably 58 would be a suitable intermediate for the synthesis of lintenone (1).

It was expected that 57 would be accessible from the diazoketone 59 (Scheme 10), with the highly strained four-membered ring being formed in a sequence similar to that used in the synthesis of [4.4.4.5] fenestrane 15.$^{11}$ This strategy would involve forming a five-membered ring by the use of C-H insertion methodology developed by Doyle.$^{18,19}$ Treatment of diazoketone 59 with a rhodium catalyst was anticipated to give the tricyclic ketone 60, the
product of C-H insertion into the unactivated C-H σ-bond α to the protected hydroxyl function in diazoketone 59. Subsequent ring contraction of the cyclopentanone using a Wolff rearrangement\textsuperscript{8,9} should give the desired four-membered ring ester 57.

Scheme 10

The substrate required for the Wolff rearrangement is diazoketone 61. The formation of diazoketone 61 was anticipated to be problematic. Synthesis would involve either diazo transfer to the extremely hindered five-membered ring\textsuperscript{19} (only limited success has been achieved in this transformation) or use of one of the older methods for diazoketone formation which are discussed in more detail later in this thesis (page 96). The Wolff rearrangement would generate a ketene intermediate, which upon quenching with the reaction solvent, an alcohol, should give the ester 57 or its epimer at the carbon α- to the ester functionality. The ester 57 which possesses the required stereochemistry, would be expected to be the thermodynamically most stable product. Thus if ester 57 is not formed as the major product conversion of the product mixture into ester 57 should be possible via epimerization at the carbon α- to the ester functionality.
It was anticipated that the diazoketone 59 would be accessible from the bicyclic ketone 10 (Scheme 11). A variety of strategies can be envisioned for the introduction of the methyl group at the 9-position (bicyclo[4.3.0]nonane numbering system). For example reduction of the ketone, suitable protection of the acquired alcohol group and subsequent hydroboration of the alkene function should serve to convert 10 into the alcohol 62. Conversion of the alcohol 62 into a derivative suitable for alkylation (e.g. 63, X = CHO, COOR, COOH, CN, or CNNMe₂) would allow the methyl group to be introduced using alkylation chemistry.

\[ \text{Scheme 11} \]

The stereochemical outcome of alkylation of an anion derived from 63 is not easy to predict. Initial impressions lead to the assumption that 64 would be the major product. Approach of MeI from the convex face of the anion (same face as the cis-methyl groups) would appear to be the least hindered route. If alkylation of 63 with MeI were to give the alkylated derivative 64, the latter compound could subsequently be converted into the diazoketone 59. Diazoketones can be synthesized from carboxylic acids by conversion to the acid chloride followed by addition of diazomethane. If however, alkylation of 63 were to occur from the opposite face of the anion, it would be necessary to use an alkylating agent such as benzyl chloromethyl ether.
This would then give the alkylated product 65, which could subsequently be converted into the desired diazoketone 59 (Scheme 12). A variety of methods exist which could be used to effect the reduction of the X function into a methyl group. Removal of the benzyl protecting group would set the stage for conversion of the resultant alcohol into the diazoketone 59.

\[ X = \text{CHO, COOR, COOH, CN, CNNMe}_2 \]

Scheme 12

Ketone 10 should be accessible from enone 9 as a single enantiomer via an extension of ring annulation methodology developed in our laboratories (Scheme 13). It was hoped that alkylation of the enantiomerically pure enone 11 with the iodide 66, followed by alkylation of the resultant product 67 with MeI would effect the synthesis of the enone 13 as a single enantiomer. Each alkylation would be expected to occur from the face of the respective enolate.
opposite to the methyl group in the 5-position. Synthesis of the enantiomerically pure enone 11 has been reported previously. Enone 9 would be formed by addition of methylmagnesium bromide to enone 13, followed by a PCC oxidative rearrangement of the resultant product.

Two alternative plans for synthesis of racemic lintenone (1) are also available should our initial non-racemic strategy prove unsuccessful. The first plan involves the projected synthesis of racemic enone 9 using methodology developed previously in these laboratories. Addition of the bifunctional organocopper reagent 69 to the racemic enone 68 in the presence of TMSBr, followed by alkylation of the resultant product with MeI should set up the required relative stereochemistry in the vinylogous ester 70. Addition of methylmagnesium bromide to 70 and subsequent hydrolysis of the acquired product should give the desired racemic enone 9 (Scheme 14).

The second alternative plan involves the possible synthesis of ketone 74 as a racemic mixture (Scheme 15). Enone 73 should be obtainable from ketone 71 via syn elimination from either a selenoxide or a sulfoxide derivative 72. Steroelectronic and steric factors are known to be important in determining the stereochemical outcome of cuprate addition reactions. Consideration of these factors, leads to the assumption that approach of a methylcuprate

Scheme 14

Two alternative plans for synthesis of racemic lintenone (1) are also available should our initial non-racemic strategy prove unsuccessful. The first plan involves the projected synthesis of racemic enone 9 using methodology developed previously in these laboratories. Addition of the bifunctional organocopper reagent 69 to the racemic enone 68 in the presence of TMSBr, followed by alkylation of the resultant product with MeI should set up the required relative stereochemistry in the vinylogous ester 70. Addition of methylmagnesium bromide to 70 and subsequent hydrolysis of the acquired product should give the desired racemic enone 9 (Scheme 14).

The second alternative plan involves the possible synthesis of ketone 74 as a racemic mixture (Scheme 15). Enone 73 should be obtainable from ketone 71 via syn elimination from either a selenoxide or a sulfoxide derivative 72. Steroelectronic and steric factors are known to be important in determining the stereochemical outcome of cuprate addition reactions. Consideration of these factors, leads to the assumption that approach of a methylcuprate
reagent to enone 73 would be anticipated to occur from the face of the molecule opposite to the cis-methyl groups, to give the ketone 74.

Scheme 15

The cis-fused ketone 71 should be accessible from enone 78 using the previously mentioned annulation methodology developed in our laboratories. Alkylation of the vinylogous ester 6 with allylic bromide 76 should give the alkylated product 77 (Scheme 16). Further alkylation of 77 with MeI followed by addition of methylmagnesium bromide and hydrolysis of the resultant product should give the racemic enone 78. Copper(I) mediated cyclization of 78 would be expected to give exclusively the cis-fused product 71, based upon previous studies. Allylic bromide 76 was anticipated to be readily accessible from the ester 75 which has been previously synthesized.
Ketone 74 should serve as a precursor to the diazoketone 59, with the methyl group at the 5-position being introduced either via the previously outlined alkylation method or alternatively via cyclopropanation chemistry. Simmons-Smith cyclopropanation of 74 would be expected to give the cyclopropane 79. Cleavage of the least substituted cyclopropane bond by hydrogenation\(^{25}\) followed by removal of the silyl ether function and oxidation of the resultant alcohol to the carboxylic acid, should provide a precursor for the synthesis of the diazoketone 59.
Formation of the cis-fused bicyclo[4.3.0]nonane ring system

Preparation of Substituted Cyclohex-2-en-1-ones

Initial work was directed towards the synthesis of the enantiomerically pure α,β-unsaturated ketone 11. It had been shown previously by work performed in our laboratories as well as work reported in the chemical literature that the α,β-unsaturated ketone 11 is readily accessible in an enantiomerically pure form from (+)-pulegone. The synthesis of ketone 11 was carried out according to the synthetic sequence outlined in Scheme 18. This sequence has undergone extensive development in our laboratories. A solution of (+)-pulegone in MeOH was treated with 30% H₂O₂(aq) in 25% KOH(aq) to provide a mixture of the cis- and trans-pulegone epoxides 80. Careful control of the reaction temperature by slow addition of base gave an 85% yield of the mixture of diastereomers. Thiophenoxide opening of the epoxides 80 with concomitant retro-aldol expulsion of acetone gave the regioisomerically pure phenyl sulfides 81. Oxidation of the phenyl sulfides with peracetic acid gave the desired phenyl

Scheme 18: Synthesis of the enantiomerically pure enone 11 from (+)-pulegone
sulfoxides 82 cleanly and in excellent yield. Heating a mixture of the sulfoxide, CaCO₃ and butanone to reflux, followed by careful fractional distillation of the product from the reaction mixture, gave the enantiomerically pure α,β-unsaturated ketone 11, which exhibited spectra in accordance with those already reported.²⁰

With the enantiomerically pure α,β-unsaturated ketone 11 in hand, work was directed towards the synthesis of the substituted cyclohexen-2-en-1-one 9 which was expected to undergo the aforementioned intramolecular copper(I) mediated conjugate addition reaction³ to give the desired ketone 10 (Scheme 29). The enone 9 was expected to be accessible from compound 13 by addition of methylmagnesium bromide, followed by PCC oxidation of the resultant product.

Previous attempts at alkylation of ketone lithium enolates with the alkylating agent 12 have been shown to proceed with elimination rather than alkylation, to give the starting ketone and the elimination product from 12.⁴ It was therefore decided to synthesize the dimethylhydrazone derivative of the ketone 11, since the lower basicity of the dimethylhydrazone anion was expected to prevent such elimination. It was anticipated that the methyl group at the 5-position of the dimethylhydrazone derivatives 83 and 84 could be used to control the stereochemistry at the adjacent centre (Scheme 20). Both alkylation agents would be expected to approach the
Anions derived from the dimethylhydrazone derivatives 83 and 84 from the face opposite to that which is blocked by the methyl group at the 5-position. Thus, the second alkylation should give as the major product the dimethylhydrazone derivative 85, which has the required stereochemistry. Subsequent hydrolysis of the dimethylhydrazone function should give the alkylated enone 13.

![Scheme 20](image)

Formation of the dimethylhydrazone derivative 83 was accomplished by refluxing the ketone 11 in neat dimethylhydrazine with removal of the resultant water using a Dean-Stark trap. The first alkylation proceeded successfully to give the corresponding vinyltrimethylstannane 84. Unfortunately alkylation of compound 84 with MeI proved to be unsuccessful and none of the alkylated product 85 was obtained. To circumvent this problem it was decided to attempt hydrolysis of the dimethylhydrazone function and then alkylate the resultant ketone 86. Unfortunately this too proved unsuccessful. Conditions could not be found that would cleave the hydrazone moiety without causing destannylation (Scheme 21).
As a result of these difficulties it was decided to attempt the synthesis of the enone 88. This enone was also expected to undergo an intramolecular copper(I) mediated conjugate addition reaction to give the ketone 89, which possesses an endocyclic rather than an exocyclic double bond (Scheme 22). The enone 88 was expected to be accessible from compound 87 by addition of methylmagnesium bromide, followed by PCC oxidation of the resultant product.
The alkylating agent 7 would not undergo elimination, therefore the enone 87 could be synthesized from the \( \alpha,\beta \)-unsaturated ketone 11 without formation of the dimethylhydrazone, thus avoiding potential hydrazone hydrolysis problems.

Scheme 23

Enone 11 was deprotonated by addition to an excess of LDA and the enolate formed was alkylated with the allylic bromide 7 at -78 °C to give enone 90 and its diastereomer 91 as a 6:1 mixture (Scheme 23). It was presumed that the bulky allylic bromide had approached enone 11 from the face opposite to the methyl group as predicted and it was hoped that this stereoselectivity would also be observed in the second alkylation with MeI.

Unfortunately, deprotonation of this mixture of diastereomers by addition to an excess of LDA and alkylation of the enolate formed with MeI gave a 1:1 mixture of the desired enone 87 and its diastereomer 92. Presumably the enolate anion derived from the mixture of 90 and 91
adopts a conformation that minimizes steric interactions between the C-4 substituent and the methyl group in the 5-position (Figure 2). Unfortunately, this postulated conformation appears to place the C-4 group in a position where it hinders approach to the top face of the molecule. This, combined with the methyl group hindering approach to the bottom face, probably results in the observed lack of stereoselectivity.

![Proposed conformation of the enolate derived from compounds 90 and 91](image)

**Figure 2: Proposed conformation of the enolate derived from compounds 90 and 91**

This undesired lack of stereoselectivity in the alkylation of enones 90 and 91 made it necessary to proceed with an alternate synthesis of enone 9. This racemic synthesis also used methodology developed in these laboratories (Scheme 24). Addition of the bifunctional organocopper reagent 69 in the presence of TMSBr to the racemic enone 68 should give compound 93. Alkylation of compound 93 with MeI should then give the vinylogous ester 70. It was hoped that differences in the conformations of the anion of the α,β-unsaturated ketone and the anion of the α,β-unsaturated vinylogous ester might allow this alkylation with MeI to proceed with a greater degree of stereoselectivity than that previously observed. Hopefully this would set up the required relative stereochemistry in the vinylogous ester 70. Addition of
methylmagnesium bromide to the vinylogous ester 70, followed by hydrolysis of the resultant product, should give the desired racemic enone 9 (eq 8).

\[
\text{O} \quad 1. \text{MeMgBr} \\
\text{MeSn} \quad 2. \text{H}^+ \\
\text{O} \quad 70 \quad 9 \quad (8)
\]

The \(\alpha,\beta\)-unsaturated vinylogous ester 68 was synthesized from 5-methyl-1,3-cyclohexanedione (94)\(^2\) as shown (Scheme 25). Treatment of dione 94 with \(p\)-TsOH and iso-butyl alcohol gave the vinylogous ester 95. The anion derived from compound 95 was treated with Eschenmoser’s salt to give the amine 96. Treatment of this amine with MeI gave quaternary ammonium salt 97, which underwent a base promoted elimination to give the desired \(\alpha,\beta\)-unsaturated vinylogous ester 68.

\[94 \xrightarrow{p\text{-TsOH}, \text{HO}} 95 \xrightarrow{1. \text{LDA, THF, } 0\, ^\circ\text{C, } 1\, \text{hr}} 96 \xrightarrow{2. [\text{Me}_2\text{N=CH}_2]I} 68 \]
With the desired \( \alpha,\beta \)-unsaturated vinylogous ester 68 synthesized, the crucial addition of the organocopper reagent 69 to the exocyclic double bond of 68 was investigated. Unfortunately, despite numerous attempts, this unprecedented addition proved to be unsuccessful, with none of the desired vinylogous ester 93 being observed (eq 9).

Following this setback, attention was directed towards the synthesis of enone 78, which was also expected to cyclize via a copper(I) mediated intramolecular conjugate addition reaction\(^3\) (eq 10) to give the racemic ketone 71. Ketone 71 was chosen as an advanced intermediate because it possessed functionality that would allow the introduction of the two remaining methyl groups. Additionally, the 9-oxymethyl side chain would hopefully provide a means to form the third ring using rhodium catalyzed C-H insertion methodology. Any protecting group introduced this early in the synthesis would have to be resilient to the variety of different reaction conditions that would be encountered prior to its cleavage. The TBS protecting group was chosen because it is known to be tolerant of a wide variety of reaction conditions and also its cleavage is usually facile when desired.\(^{29}\)
To assess the feasibility of the proposed copper(I) mediated intramolecular conjugate addition reaction a series of substituted cyclohex-2-en-1-ones of general structure 98 were prepared, using methodology developed by Stork.\textsuperscript{30,31}

\[
\text{O} \quad \text{SnMe}_3 \quad \text{TBSO} \\
\begin{array}{c}
\text{R}^1 = \text{Me or H} \\
\text{R}^2 = \text{Me or H}
\end{array}
\]

Alkylating agent 76 was synthesized as shown in Scheme 26. Commercially available propargyl alcohol was converted to the corresponding TBS ether 99 in 99% yield by treatment with tert-butyldimethylsilyl chloride and imidazole in CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{32} Silyl ether 99 was converted into the ester 100 by deprotonation with MeLi at -20 °C for 30 minutes and trapping of the resultant alkyne stabilized carbanion with ethyl chloroformate.\textsuperscript{33}

\[
\text{MeLi, -20 °C, THF} \quad \text{EtOCOC\textsubscript{2}Et, -20 °C} \quad 78\%
\]

\[
\begin{array}{c}
\text{TBSO} \quad \text{CO}_2\text{Et} \\
\text{99} \quad \text{100}
\end{array}
\]

\[
\text{1. [Me}_3\text{SnCu(CN)]Li, THF, -48 °C, 15 min, rt, 2 hr} \\
\text{2. NH}_4\text{Cl(aq)}-\text{NH}_4\text{OH(aq) (pH ~ 8)} \quad 90\%
\]

\[
\begin{array}{c}
\text{Me}_3\text{Sn} \quad \text{CO}_2\text{Et} \\
\text{TBSO} \\
\text{75}
\end{array}
\]

\[
\text{DIBAL, THF, 0 °C, 2 hr} \quad 76\%
\]

\[
\begin{array}{c}
\text{TBSO} \quad \text{Me}_3\text{Sn} \quad \text{Br} \\
\text{76} \quad \text{83%} \\
\end{array}
\]

\[
\begin{array}{c}
\text{TBSO} \quad \text{Me}_3\text{Sn} \quad \text{OH} \\
\text{102} \quad \text{76%}
\end{array}
\]

Scheme 26
Treatment of ester 100 with lithium (trimethylstannyl)(cyano)cuprate (101)\textsuperscript{24,34,35} in THF at -48 °C for 2 hours and at rt for 2 hours, followed by treatment with aqueous NH\textsubscript{4}Cl-NH\textsubscript{4}OH (pH ~8), provided the ester 75. Ester 75 was then reduced with DIBAL\textsuperscript{36,37} to give the allylic alcohol 102. Allylic alcohol 102 was converted into the corresponding allylic bromide 76 by treatment with Ph\textsubscript{3}P-Br\textsubscript{2} in the presence of imidazole.\textsuperscript{38-40} The allylic bromide 76 was found to be volatile and unstable to purification by column chromatography on silica gel and so was isolated using the method developed by Friesen\textsuperscript{41} and used immediately.

Vinylogous ester 6\textsuperscript{42} was alkylated\textsuperscript{30,31} by treatment with LDA, followed by addition of the allylic bromide 76, to give the vinylogous ester 77 in 71% yield (Scheme 27). The second alkylation was accomplished by deprotonation with LiNEt\textsubscript{2}, followed by addition of MeI, to give the vinylogous ester 103 in 77% yield.

\begin{center}
\textbf{Scheme 27}
\end{center}

Reaction of the vinylogous ester 77\textsuperscript{30,31} with DIBAL or MeMgBr, followed by acid-promoted hydrolysis and dehydration of the resultant alcohols, gave the enones 104 and 105 in excellent yields (Scheme 28).
The hydrolysis and dehydration steps were performed using a catalytic amount of p-TsOH in a two-phase system of 100:1 diethyl ether-H$_2$O at room temperature. These mildly acidic conditions resulted in no measurable protiodestannylation of the alkenyltin moiety.
To prepare similar substrates but with a methyl group at the 4-position of the cyclohex-2-en-1-one functionality, the vinylogous ester 103 was treated with either DIBAL or MeMgBr. The resultant alcohols were subjected to acid-promoted hydrolysis, followed by dehydration, to give the enones 106 and 78 in excellent yields (Scheme 29).

Structural assignments for the enones 104-106 and 78 were based upon IR, $^1$H NMR, $^{13}$C NMR and mass spectra. The IR spectra of these materials show carbonyl absorption frequencies in the range of 1686-1657 cm$^{-1}$ which is characteristic for the enone functionality.$^{43}$

The $^1$H NMR spectra of enones 104-106 and 78 displayed signals in the range $\delta$ 6.05-6.16 with $^3J_{Sn-H}$ values in the range 134-136 Hz for the vinylic protons trans to the Me$_3$Sn groups. These relatively large three bond tin-proton coupling constants are characteristic of compounds containing a trialkylstannane function on a double bond with a Z geometry.$^{44}$ The vinylic protons at the $\alpha$-position to the enone function in compounds 104-106 and 78 display signals at $\delta$ 5.81-5.95, while the alkenyl protons $\beta$ to the carbonyl in compounds 104 and 106 display signals at $\delta$ 6.83 and 6.66. The coupling constants between the vinylic protons $\alpha$ and $\beta$ to the carbonyl are 10 Hz in both 104 and 106. The resonance for the methylene group geminal to the Me$_3$Sn function in each of the enones 104-106 and 78 appears as a singlet at $\delta$ 4.19-4.22 with $^3J_{Sn-H}$ coupling constants in the range 35.7-36.6 Hz.

The $^{13}$C NMR spectra for enones 104-106 and 78 show signals for the carbonyl groups in the region $\delta$ 199.2-199.6. Each of the enones displays signals for four more sp$^2$ carbons in the range $\delta$ 127.2-167.7. Characteristic resonances for the Me$_3$Sn group are visible at $\delta$ -8.0.
In the high-resolution mass spectra of enones 104-106 and 78 compounds 104, 105 and 78 show a peak corresponding to M*-Me, whilst compound 106 shows a peak corresponding to M'H.

Each new compound discussed in this section, except for the allylic bromide 76, which was volatile and unstable, provided satisfactory elemental (C, H) analyses.

Copper(I) Cyanide Mediated Conjugate Additions of the Substituted Cyclohex-2-en-1-ones

Previous work in these laboratories\(^3\) has shown that cyclizations of substituted cyclohex-2-en-1-ones 3 proceed to give exclusively cis-fused ring annulation products 4 (eq 11) and this was anticipated to be true for substituted cyclohex-2-en-1-ones 104-106 and 78. The stereochemical outcome of these reactions will be determined kinetically.\(^3\) Initial transmetallation of the alkenylstannane function in 107 leads to formation of the alkenylcopper(I) intermediates 108a and 108b (Scheme 30). The alkenylcopper(I) moiety of 108a and 108b then approaches the enone from the face opposite to R\(^1\) to generate the cis-fused product 109. The transition state (resulting from conformer 110) leading to the trans-fused product 111 is predicted to be significantly more strained than the transition states resulting from conformers 108a and 108b, which lead to the cis-fused product 109. Considerable angle
strain is introduced in conformer 110 by placing the alkenylcopper(I) moiety in a position to attack the top face of the enone. A steric interaction can also be anticipated between the CH$_2$OP group and R$^1$.

Scheme 30

Initial attempts at cyclization of cyclohex-2-en-1-ones 104 and 106 using 2.0 equiv. of CuCl in DMF at room temperature proved unsuccessful, giving none of the desired product. Only starting material and the product of protiodestannylation were recovered. However, treatment of 104 and 106 with 2.5 equiv. of CuCN in DMSO at 60 °C for 2 hours gave good yields of the exclusively cis-fused products 112 and 114 (Table 1, entries 1 and 3). Cyclohex-2-en-1-ones 105 and 78 also cyclized under these conditions to give exclusively the cis-fused products 113 and 71, but the reactions were significantly more sluggish, requiring 18 hours to proceed to completion (Table 1, entries 2 and 4).

Structural assignments for the ketones 112-114 and 71 were based upon IR, $^1$H NMR, $^{13}$C NMR and mass spectra. The stereochemistry of the products 112-114 and 71 was assigned on the
basis of the known configurational outcome of these types of copper(I) mediated conjugate addition reactions (see Scheme 30).³

![Chemical structure](image)

\[
\begin{align*}
104 & : R^1 = H, R^2 = H & 112 \\
105 & : R^1 = H, R^2 = Me & 113 \\
106 & : R^1 = Me, R^2 = H & 114 \\
78 & : R^1 = Me, R^2 = Me & 71
\end{align*}
\]

Table 1: Copper(I) cyanide mediated conjugate additions of substituted cyclohex-2-en-1-ones 104-106 and 78

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R(^1)</th>
<th>R(^2)</th>
<th>Time(h)</th>
<th>Product(^a)</th>
<th>Yield(^b)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>104</td>
<td>H</td>
<td>H</td>
<td>2</td>
<td>112</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>H</td>
<td>Me</td>
<td>18</td>
<td>113</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>106</td>
<td>Me</td>
<td>H</td>
<td>2</td>
<td>114</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>78</td>
<td>Me</td>
<td>Me</td>
<td>18</td>
<td>71</td>
<td>76</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of purified product.  \(^b\) The major side products from these reactions were unyclized compounds in which the Me,Sn function in 104-106 and 78 had been replaced by hydrogen.

The IR spectra of the products shown in Table 1 exhibit carbonyl absorption frequencies in the range 1718-1719 cm\(^{-1}\) which is characteristic for cyclohexanones.⁴³

The \(^1\)H NMR spectra of ketones 112-114 and 71 display signals in the range δ 5.51-5.56, which corresponds to their vinylic protons. The allylic O-methylene protons display signals in the range δ 4.09-4.10.
The $^{13}$C NMR spectra of ketones 112-114 and 71 show signals for the carbonyl carbons in the range $\delta$ 213.0-213.8. Each of these products displays signals for two more sp$^2$ carbons in the range $\delta$ 123.4-149.1.

In the high-resolution mass spectra of ketones 112-114 and 71 each compound shows a peak corresponding to $M^+$. Each ketone provided a satisfactory result from elemental (C, H) analyses.

**Attempted Introduction of the Methyl group at the 9-Position via Cyclopropanation**

With the success of the ring closures and the preparation of compounds 112-114 and 71, the next challenge was introduction of the methyl groups at the 5- and 9-positions (bicyclo[4.3.0]nonane numbering system). Introduction of the methyl group at the 9-position was attempted first. It was anticipated that this could be achieved in the fewest possible steps from ketone 71 by utilizing Simmons-Smith cyclopropanation methodology$^{45,46}$ to give the cyclopropane 115. Subsequent cleavage of the least substituted cylopropane bond by hydrogenation$^{25}$ should give compound 116 (Scheme 31).

First reported in 1958, the Simmons-Smith reaction$^{45,46}$ remains to this day one of the premier methods for cyclopropanation. Initially the procedure employed a zinc-copper couple and a
geminal diiodide to form the carbenoid species, which then reacted with an olefin to form the cyclopropane. Over the years many interesting developments of the Simmons-Smith reaction have been reported: these include the Furukawa modification\textsuperscript{47} in which the zinc-copper couple is replaced with diethylzinc and the strong directing effect of allylic alcohols reported by Winstein.\textsuperscript{48} Recently chloroiodomethane\textsuperscript{49} has proven to be significantly more reactive in this reaction than diiodomethane.

\[
\text{hv, CH}_2\text{I}_2, \text{CH}_2\text{Cl}_2 \rightarrow \text{55%}
\]

Treatment of the ketone 71 with diethylzinc and chloroiodomethane under a variety of conditions resulted in no formation of the desired cyclopropane, only recovery of the starting material. This lack of reactivity experienced with ketone 71 is not entirely unexpected. Steric hinderance presumably prevents the reaction from occurring. Careful consideration of the structural backbone of ketone 71 shows that it contains the skeleton of compound 117. There is no literature precedence for successful Simmons-Smith reactions of hindered vinylic substrates similar to compound 117.

\[
\begin{align*}
\text{hv, CH}_2\text{I}_2, \\
\text{CH}_2\text{Cl}_2 & \rightarrow \text{55%}
\end{align*}
\]

The extremely hindered alkene 118 has been converted to cyclopropane 119 by irradiation of a solution of the alkene and diiodomethane in dichloromethane (eq 10).\textsuperscript{50} This method was attempted with ketone 71 but it too was found to be unsuccessful. No further attempts were made to effect cyclopropanation.
Introduction of the Methyl Group at the 5-position

With the lack of success encountered in trying to introduce a methyl group at the 9-position of ketone 71 (bicyclo[4.3.0]nonane numbering system) via cyclopropanation, it was decided to switch focus and try to introduce the methyl group at the 5-position. It was thought that this would be possible via addition of a methylcuprate reagent to the enone 73 to give the ketone 74 (eq 11). A later return to the problem of methyl introduction at the 9-position was planned.

Formation of Enone 73 from Ketone 71

Enone 73 was anticipated to be accessible from ketone 71 either via Saegusa’s Pd(OAc)₂ methodology (Scheme 32, route (a)) or via a syn elimination involving a selenoxide or a sulfoxide derivative 72 (Scheme 32, route (b)).
Initially work was directed towards the formation of the TMS enol ether \( \text{120} \), which requires conversion of the ketone \( \text{71} \) exclusively to the desired enolate \( \text{122} \). Solutions of isomeric enolates are known to rapidly interconvert when in the presence of a proton donating source such as a protic solvent or non-ionized ketone.\(^{52,53}\) Interconversion is slow in the absence of a proton source.\(^{53}\) Consequently, deprotonation of ketone \( \text{71} \) would have to be performed under non-equilibrating conditions, by addition of the ketone to an excess of a strong hindered base. Such a protocol should give enolate \( \text{122} \) (Scheme 33). Enolate \( \text{122} \) is the product of removal of the least hindered proton. Subsequent reaction of \( \text{122} \) with TMSCl\(^{54,55}\) should give the desired TMS enol ether \( \text{120} \) as the major product.

![Scheme 33](image)

Thus, ketone \( \text{71} \) was deprotonated by addition of this material to 2 equiv. of LDA in THF at -78 °C. The solution was stirred for 30 minutes at -78 °C and was then treated with TMSCl. This provided an 87:13 mixture of TMS enol ethers \( \text{120} \) and \( \text{123} \) (Scheme 34). The ratio was determined from the \(^1\)H NMR spectrum of the crude material.
Treatment of the mixture of TMS enol ethers 120 and 123 with Pd(OAc)$_2$ according to Saegusa's methodology$^{51}$ resulted in a mixture of the desired enone 73 and the ketone 71. Enone 73 and the ketone 71 were found to be inseparable by chromatography on silica gel and it was assumed that the cuprate addition product 74 would be of very similar polarity. It was therefore considered probable that compounds 71 and 74 would also be inseparable by chromatography on silica gel. Ketone 71 would consequently have to be separated from enone 73 prior to the cuprate addition reaction. A method for formation of enone 73 was thus required that either proceeded to completion or that would allow synthesis of the enone product 73 without contamination with ketone 71. Reich’s methodology$^{56-59}$ involving elimination from selenoxide derivatives was chosen because formation of phenylselenides from ketones usually proceed in high yield. Additionally the phenylselenide 124 was expected to exhibit
considerably different polarity to ketone 71 and so if required, separation of 71 and 124 using column chromatography on silica gel should be possible.

The original method for preparing phenylselenenides involved the reaction of ketone enolates with phenylselenenyl halides or diphenyldiselenide. This reaction has drawbacks with respect to generality and regiospecificity in the case of unsymmetrical ketones and so an improved method involving the reaction of phenylselenenyl halides with enol silyl ethers has been developed. This improved method allows the use of a wide variety of established methods for the synthesis of enol silyl ethers and results in the phenylseleno group being introduced regiospecifically under mild reaction conditions.

![Scheme 35](attachment:image.png)

The mixture of the TMS enol ethers 120 and 123, prepared as previously described (Scheme 35), was dissolved in diethyl ether and the solution was treated with 1 equiv. of phenylselenenyl chloride in diethyl ether to cleanly provide phenylselenenides 124 and 125 (Scheme 35). One step oxidation and elimination of phenylselenenides 124 and 125 with H$_2$O$_2$.
gave an unexpectedly poor yield (50%) of the desired enone 73. A number of unidentifiable side products were also obtained. Problems are known to arise in similar reactions\(^5^9\) when the selenoxide or the product \(\alpha,\beta\)-unsaturated carbonyl compound is sensitive to oxidation, or when the reaction conditions (e.g. pH, solvent polarity) for oxidation promote decomposition of the selenoxide.\(^5^9\) In such cases, a two-step low temperature oxidation, elimination process is recommended.\(^5^9\) 3-Chloroperoxybenzoic acid (with triethylamine to control the pH) or ozone are both known to work well as oxidants at low temperatures.\(^5^9\) Treatment of phenylselenides 124 and 125 with 3-chloroperoxybenzoic acid in methylene chloride at \(-78 \, ^\circ\text{C}\), followed by addition of triethylamine and heating of the resultant mixture to reflux for 3 hours, provided enone 73 in good yield (80%) from ketone 71 after purification (Scheme 35).

The structural assignment of enone 73 was based upon IR, \(^1\text{H} \, \text{NMR}, \, ^{13}\text{C} \, \text{NMR} \) and mass spectra. The IR spectrum of this material shows a carbonyl absorption frequency at 1682 cm\(^{-1}\) which is characteristic of the enone functionality.\(^4^3\)

The \(^1\text{H} \, \text{NMR} \) spectrum of enone 73 displays a signal at \(\delta \, 5.86\) for the vinylic proton \(\alpha\) to the carbonyl, while the alkenyl proton \(\beta\) to the carbonyl displays a signal at \(\delta \, 6.42\). The coupling constant between these protons is 10.1 Hz. The spectrum also displays a singlet at \(\delta \, 5.46\) for the remaining vinylic proton.

The \(^{13}\text{C} \, \text{NMR} \) spectrum for enone 73 shows a signal for the carbonyl group at \(\delta \, 199.2\) and displayed signals for four more \(\text{sp}^2\) carbons in the range \(\delta \, 121.6-157.8\).
The high-resolution mass spectrum of enone 73 shows a peak corresponding to \( \text{M}^+ - (\text{CH}_3)_3\text{C} \).
Satisfactory results were also obtained from elemental (C, H) analysis.

TMS enol ethers 120 and 123 and phenyl selenides 124 and 125 were not fully characterized as the crude materials were used immediately without further purification.

**Methylcuprate Addition to Enone 73**

 Addition of cuprates to enones is thought to occur with \( d,\pi^* \)-complexation, involving copper as a \( d^{10} \)-base and the \( \alpha,\beta \)-and carbonyl carbons (\( \pi 3^* \)) as a \( \pi \)-acid.\(^{22,23} \) This \( d,\pi^* \)-mechanistic proposal is summarized in Scheme 36 for cyclohexenone as substrate and lithium dimethylcuprate as the cuprate reagent. The mechanism is thought to be similar for [Me\(_2\)Cu(CN)]Li\(_2\).\(^{22,23} \)
Scheme 37 illustrates Corey's d,π*-mechanism applied to enone 73. Equilibrium would be expected to exist between the two lowest energy conformers 126 and 127 of enone 73 and their corresponding d,π*-complexes 128 and 129 formed by interaction with a methylcuprate reagent. Clearly, 129 should be considerably lower in energy than 128 because of the repulsion between the copper and the axial methyl substituent in the latter complex. Thus, the cuprate reagent would be expected to approach the enone 73 from the face opposite to the cis-methyl substituent.

Scheme 37: Application of Corey’s d,π*-mechanism to enone 112
groups, proceeding through 129 (the lowest energy d,π*-complex), to give the lithium complex 131. Upon work up this should give ketone 74 as the major product.

Higher order organocuprate reagents are today generally considered to be the organocuprate reagents of choice in preference to lower order organocuprate reagents. The former species are usually found to be more reactive especially with sterically hindered substrates. Thus, enone 73 was treated with 5 equiv. of [Me₂Cu(CN)]Li₂ in diethyl ether at -10 °C. This gave a mixture of two products in 80% yield and no starting material was recovered (Scheme 38). These two products were separated using column chromatography on silica gel.

![Scheme 38](image)

The minor product was identified to be a single diastereomer of the 1,2-addition product 132. The stereochemistry of this product was not determined. The structural assignment of the 1,2-addition product 132 was based upon IR, ¹H NMR and mass spectra. The IR spectrum of this material shows a broad absorption between 3600 and 3100 cm⁻¹ which is characteristic of an alcohol.

The ¹H NMR spectrum of the 1,2-addition product 132 displays a broad singlet at δ 5.55 for the vinylic proton in the cyclopentene ring. Two additional signals from vinylic protons are present, a doublet of doublets at δ 5.56, with J = 9.9 and 1.5 Hz, and a doublet at δ 5.30, with J
The allylic O-methylene protons are present as two doublets at $\delta$ 4.40 and 4.22, with $J = 13.5$ Hz. Three singlets at $\delta$ 0.92, 0.99 and 1.11 correspond to the three methyl groups.

The high-resolution mass spectrum of the 1,2-addition product 132 shows a peak corresponding to $M^+$. The major product was assumed to be the desired 1,4-addition product 74, which is the product of addition from the predicted face of the enone 73. However, with the spectral data obtained it was not possible to determine from which face of the molecule addition had occurred. The structural assignment of ketone 74 was based upon IR, $^1$H NMR, $^{13}$C NMR and mass spectra. The IR spectrum of this material shows a carbonyl absorption frequency at 1718 cm$^{-1}$ which is characteristic for cyclohexanones.\(^{43}\)

The $^1$H NMR spectrum of ketone 74 displays a signal at $\delta$ 5.58 for the vinylic proton. The allylic O-methylene protons display a signal at $\delta$ 4.09. A quartet of doublets of doublets at $\delta$ 2.00 with $J = 6.6, 6.7$ and 4.9 Hz corresponds to the proton at the 5-position. The observed quartet of doublets of doublets is the result of the proton at the 5-position coupling to the methyl group and the two diastereotopic protons at the 4-position. Two singlets at $\delta$ 0.99 and 1.01 correspond to the two tertiary methyl groups. A doublet at $\delta$ 0.97 with $J = 6.6$ Hz corresponds to the secondary methyl group. This is coupled to the signal at $\delta$ 2.00 corresponding to the proton at the 5-position.

The $^{13}$C NMR spectrum for ketone 74 shows signals for the carbonyl group at $\delta$ 212.0 and signals for two more sp$^2$ carbons at $\delta$ 123.3 and 149.6.
The high-resolution mass spectrum of ketone 74 shows a peak corresponding to M⁺. Satisfactory results were also obtained from elemental (C, H) analysis.

The three methyl groups in compound 74 resonate between δ 0.97 and 1.01 in the ¹H NMR spectrum. COSY and nOe experiments with 74 were anticipated to be ineffective at showing the stereochemistry of addition due to insufficient baseline separation to differentiate between the methyl signals. It would therefore not be possible to selectively irradiate the signals from the methyl groups for a successful nOe experiment, or differentiate between their signals in a COSY experiment. The purified product was a clear colourless oil, which also rendered X-ray crystal structure analysis unavailable as a means of proving the stereochemistry. Alcohols have greater intramolecular attractions than the corresponding silyl ethers and so are more likely to form the ordered arrangement of molecules necessary for a crystalline solid. To try and solve the structure of the 1,4-addition product 74 the TBS ether function was removed using TBAF in THF (eq 12). The alcohol 133 was thus obtained as a crystalline solid.

\[
\begin{align*}
\text{74} & \xrightarrow{TBAF, THF, \text{rt, 18 hr}} \text{133} \\
\text{74} & \xrightarrow{TBAF, THF, \text{rt, 18 hr}} \text{133} \\
\end{align*}
\]

Slow recrystallization of 133 from diethyl ether/hexane gave a quantitative yield of clear colourless crystals, which were found to be of a size and shape suitable for X-ray crystal structure analysis. The relative configuration of alcohol 133 was confirmed, as seen in the ORTEP diagram displayed in Figure 3. The data for the X-ray crystal structure analysis of this substance is collated in X-Ray Crystallographic Data (page 182). It was thus apparent that the
cuprate reagent had approached enone 73 from the desired face, opposite to the *cis*-methyl groups to give the desired alcohol 74.

![Figure 3: ORTEP diagram of alcohol 133 (note that the numbering system used in this diagram is different to that used for this substance (133) elsewhere in the thesis)](image)

The structural assignment of alcohol 133 was also based upon IR, $^1H$ NMR, $^{13}C$ NMR and mass spectra. The IR spectrum of this material shows a broad absorption between 3600 and 3100
cm$^{-1}$ which is characteristic of an alcohol. The carbonyl absorption frequency of 1693 cm$^{-1}$ is characteristic of cyclohexanones.$^{43}$

The $^1$H NMR spectrum of alcohol 133 displays a signal at $\delta$ 5.63 for the vinylic proton. The allylic $O$-methylene protons display a signal at $\delta$ 4.02-4.14. A broad singlet at $\delta$ 1.63 exchanges with D$_2$O, which provides supporting evidence that compound 133 is an alcohol. A quartet of doublets of doublets at $\delta$ 2.04 with $J = 6.6, 6.7$ and 6.4 Hz corresponds to the proton at the 5-position. Two singlets at $\delta$ 1.01 and 1.04 correspond to the two tertiary methyl groups. A doublet at $\delta$ 0.97 with $J = 6.6$ Hz corresponds to the secondary methyl group. This doublet is coupled to the signal at $\delta$ 2.04, which corresponds to the proton at the 5-position.

The $^{13}$C NMR spectrum for alcohol 133 shows signals for the carbonyl group at $\delta$ 212.6 and signals for two more sp$^2$ carbons at $\delta$ 124.5 and 149.3.

The high-resolution mass spectrum of alcohol 133 shows a peak corresponding to M$^+$. Satisfactory results were also obtained from elemental (C, H) analysis.

With the facial selectivity of the conjugate addition reaction determined, attention was turned to eliminating the formation of the unwanted 1,2-addition product 132. Conducting the reaction at $-78 \, ^\circ$C and using exactly 1 equiv. of the cuprate also resulted in the formation of significant amounts of the undesired 1,2-addition product 132. Ashby has proposed that higher order
organocuprates exist in solution as an equilibrium mixture with MeLi. The presence of MeLi in the reaction mixture could account for the formation of the 1,2-addition product 132. It is believed that Me₂CuLi (Gilman’s Reagent) does not exist in solution as an equilibrium mixture with MeLi. Gratifyingly, treatment of enone 73 with 2 equiv. of Me₂CuLi in diethyl ether at -10 °C for 2 hours, resulted in an 85% yield of the 1,4-addition product 74 (eq 13). The stereochemistry of addition was the same as was observed with [Me₂Cu(CN)]Li₂. None of the 1,2-addition product 132 was detected.

\[
\begin{align*}
\text{73} & \quad \text{2eq Me₂CuLi, Et₂O,} \\
\text{-10 °C, 2 hr} & \quad \rightarrow \\
\text{85%} & \quad \text{74}
\end{align*}
\]

(eq 13)

Introduction of the Methyl Group at the 9-Position

Following the successful introduction of the methyl group at the 5-position via the addition of a methylcuprate reagent to enone 73 to give the ketone 74, attention was once again directed towards the introduction of the methyl group at the 9-position. Two methods were envisioned that could feasibly lead to successful introduction of the required carbon atom.
The first method would involve an extension of work developed by Stille and Mitra. Treatment of the allyl stannylmethyl ether 135 with n-BuLi should lead to a [2,3]-sigmatropic rearrangement to give the homoallylic alcohol 136 (Scheme 39). The allyl stannylmethyl ether 135 should be accessible by deprotonation of the allylic alcohol 134 and subsequent alkylation with iodomethyltributyltin. The 9-hydroxymethyl and the 9-ethene substituents could both theoretically be converted into the required methyl group. However, it is not easy to predict which diastereomer of 136 would be formed preferentially in the rearrangement of 135 into 136.

The second method would involve introduction of the methyl group using alkylation chemistry. Alkylation of either of the derivatives 63 or 137 (X = CHO, COOR, COOH, CN, or CNNMe₂) with Mel should lead to introduction of the methyl group at the desired 9-position (Scheme 40). As discussed earlier (page 21) it is not trivial to predict from which face of the anions derived
from 63 or 137 alkylation would occur. Initial impressions lead to the assumption that 64 and 138 would be the major products. However, if alkylation of 63 or 137 were to occur from the undesired face of their respective anions, use of an alkylating agent such as benzyl chloromethyl ether would be necessary. This would give the alkylated products 65 or 139 (Scheme 41). A variety of methods exist to effect the reduction of the X function into a methyl group. Removal of the benzyl protecting group would set the stage for future functional group manipulation of the resultant alcohol.

Compound 134 and a variety of derivatives of 63 and 137 should all be accessible from the common starting material, compound 140. Compound 140 should be readily accessible from ketone 74 via reduction of the ketone function, followed by suitable protection of the resultant alcohol and subsequent selective deprotection of the primary alcohol function.
Stereoselective Reduction of Ketone 74

Reduction of ketone 74 with 1.4 equiv. of L-Selectride\textsuperscript{\textregistered} in THF at -78 °C for 2 hours gave the alcohol 141 as one diastereomer (eq 14). The stereochemistry of reduction was assigned on the basis of the \textsuperscript{1}H NMR data, which includes a broad singlet at $\delta$ 4.00. This singlet corresponds to an equatorial cyclohexane carbinol proton,\textsuperscript{43} which indicates that H$_3$ is equatorial as shown in Figure 4. The stereoselectivity of the reduction agrees with the known preference of the bulky Selectride\textsuperscript{\textregistered} reagents for equatorial hydride addition to cyclohexanones.\textsuperscript{74,75} The preferred conformation of ketone 74 in solution was assumed to be similar to that of compound 133 whose solid state conformation was determined by X-ray crystal structure analysis (see ORTEP diagram displayed in Figure 3, page 53).

The structural assignment of alcohol 141 was based upon IR, \textsuperscript{1}H NMR, \textsuperscript{13}C NMR, mass spectra and the results of a COSY experiment. The IR spectrum of this material shows a very broad absorption at 3100-3600 cm\textsuperscript{-1}, which indicates the presence of a hydroxyl group.
The $^1$H NMR spectrum of alcohol 141 displays a signal at $\delta$ 5.44 for the vinylic proton and a broad singlet at $\delta$ 4.00 corresponding to the carbinol proton. A quartet of doublets at $\delta$ 1.93 with $J = 7.1$ and 6.9 Hz corresponds to $H_5$. Interestingly, proton $H_5$ couples to only one of the $H_4$ protons and the methyl group at the 5-position. A singlet observed at $\delta$ 1.15 exchanges with $D_2O$ providing supporting evidence for the presence of an alcohol group. Two singlets at $\delta$ 0.92 and 1.08 and a doublet at $\delta$ 0.87 with $J = 6.9$ Hz correspond to the three methyl groups.

The $^{13}$C NMR spectrum for alcohol 141 shows signals for two $sp^2$ carbons at $\delta$ 121.1 and 150.9 and no signal corresponding to a carbonyl group.

The high-resolution mass spectrum of alcohol 141 shows a peak corresponding to $M^+$. Satisfactory results were also obtained from elemental (C, H) analysis.

![Scheme 42](image)

Following the successful reduction of 74 to give 141, it was necessary to protect the secondary alcohol and selectively remove the protection from the primary alcohol. Initially a TBDPS group was chosen to protect the secondary alcohol. It is known that primary TBS ethers can be
selectively removed in the presence of secondary TBDPS or TBS ethers by addition of 1.0 equiv. of TBAF. Treatment of the secondary alcohol 141 with TBDPS-Cl and imidazole gave the disilyl ether 142 in good yield. Subsequent treatment of 142 with 1.0 equiv. of TBAF in THF selectively removed the primary TBS ether to give alcohol 143. The reaction of 141 with TBDPS-Cl and imidazole proceeded very slowly (~ 1 week), whereas the reaction of TBS-Cl and imidazole proceeded to completion in 1 hr. Thus, it was found that this protection-deprotection sequence could be achieved with a greater degree of success by the use of just TBS groups (Scheme 42).

Investigation of Methyl Group Introduction Using the Stille-Mitra Rearrangement

Stille and Mitra have investigated the synthesis of Z-trisubstituted olefins via [2,3]-sigmatropic rearrangements. Deprotonation of the allylic alcohol 146 with KH and alkylation of the resultant alkoxide with iodomethyltributyltin, gave the allylic stannylmethyl ether 147 in quantitative yield. Direct treatment of this material with excess n-BuLi resulted in tin/lithium exchange followed by a smooth [2,3]-sigmatropic rearrangement to give the homoallylic alcohol 148.
This sequence has previously been used in our laboratories in the synthesis of (±)-sarcodonin G. Alkylation of the allylic alcohol 149 with iodomethyltributyltin gave the required allyl stannylmethyl ether 150 (Scheme 44). Direct treatment of this with an excess of n-BuLi gave exclusively the homoallylic alcohol 151 via a stereospecific [2,3]-sigmatropic rearrangement. It was expected that reaction of the allylic alcohol 152 in a similar sequence would also result in a [2,3]-sigmatropic rearrangement to give the homoallylic alcohol 154 (Scheme 45).

The requisite allylic alcohol 152 was synthesized from alcohol 143 (Scheme 46). Alcohol 143 was oxidized to the α,β-unsaturated aldehyde 155 using TPAP. Reaction of the α,β-unsaturated aldehyde 155 with methoxymethylenetriphenylphosphorane gave the enol ether 156. The latter compound was cleanly converted to the α,β-unsaturated aldehyde 157, by hydrolysis with p-TsOH. Reduction of 157 by LiAlH₄ gave the allylic alcohol 152.
Initial alkylation of the allylic alcohol 152 with iodomethyltributyltin, followed by direct treatment of the resultant solution with n-BuLi proved unsuccessful and gave a complicated mixture of unidentifiable products. The allylic stannylmethyl ether 153 was subsequently isolated and purified by column chromatography on silica gel. The purified stannylmethyl ether 153 was then treated with n-BuLi and the rearrangement appeared to proceed more cleanly. The major product 158 resulted from reaction of the anion with a proton source (Scheme 47). Presumably, this reaction with a proton source occurred during the work-up procedure, indicating that the reaction had not proceeded to completion. It was expected that longer reaction times could reduce the amount of this product. The minor product was the desired [2,3]-sigmatropic rearrangement product 154. Unfortunately 154 was obtained as a 1:1 mixture of diastereomers at the quaternary centre. This lack of stereoselectivity was unexpected. Presumably, both faces of the double bond experience similar steric hinderance, which would also accounts for the slow rate of reaction. Consequently, this strategy was
abandoned and other methods for introduction of the methyl substituent at the 9-position were investigated.

\[
\begin{align*}
\text{TBDPSO} & \quad \overset{\text{1. KH}}{\rightarrow} \quad \text{TBDPSO} \\
152 & \quad \overset{\text{2. 18-crown-6}}{\rightarrow} \quad \text{153} \\
& \quad \overset{\text{3. ICH}_2\text{SnBu}_3}{\rightarrow} \quad \text{SnBu}_3
\end{align*}
\]

\[\text{n-BuLi, THF, -78 °C, 2hr}\]

\[
\begin{align*}
\text{TBDPSO} & \quad \overset{\text{1:1 mixture of diastereomers}}{\rightarrow} \quad \text{TBDPSO} \\
158 & \quad 57\% \\
154 & \quad 33\%
\end{align*}
\]

Scheme 47

Investigation of Methyl Group Introduction Using Alkylation Chemistry

Simmons-Smith cyclopropanation methodology (page 41) and the Stille-Mitra rearrangement were both unsuccessful at stereoselective introduction of a methyl substituent at the 9-position (bicyclo[4.3.0]nonane numbering system). It was thus decided to investigate the use of alkylation chemistry to effect the stereoselective introduction of a methyl substituent at the 9-position.

Alkylation of compounds 155 and 159-163 was attempted with only limited success. A large range of conditions was investigated to effect the deprotonation of compounds 155 and 159-
and their subsequent alkylation. Unfortunately no evidence was obtained which proved that deprotonation had been achieved. Addition of a single diastereomer of the aldehyde 162 to a THF solution of KDA at -78 °C for 30 min, followed by addition of MeI gave compound 164 and the opposite diastereomer of the starting aldehyde 162 (eq 15). The $^1$H NMR spectrum of compound 164 displays a 1H multiplet at $\delta$ 5.58-5.62 corresponding to the vinyl proton and a 3H singlet at $\delta$ 3.50 corresponding to the O-methyl function. Clearly, deprotonation of aldehyde 162 had been achieved, although none of the desired C-alkylation had occurred. Alkylation of the dimethylhydrazone 163 was therefore investigated in an attempt to effect the desired C-alkylation. Addition of a single diastereomer of the dimethylhydrazone 163 to a THF solution of KDA at -78 °C for 30 min, followed by addition of MeI (eq 16) gave a mixture of unidentifiable products and recovered starting material. It was not possible to separate this mixture of compounds from the starting material using column chromatography on silica gel.
Thus, it was not possible to determine if any of the desired alkylation product 165 had been formed.

These results led to the decision to consider alkylation of the nitrile 166. Nitrile stabilized anions are known to exhibit a preference for C-alkylation and precedence exists for the alkylation of highly hindered nitriles.79

**Formation of Nitrile 166**

Nitrile 166 was synthesized from compound 141. The use of Adams’ catalyst is known to effect hydrogenation of allylic alcohols without production of the hydrogenolysis product.80 Hydrogenation of compound 141, using Adams’ catalyst in EtOAc (eq 17), gave a single diastereomer of the hydrogenation product 167.

The structural assignment of alcohol 167 was based upon IR, $^1$H NMR, $^{13}$C NMR and mass spectra. The stereochemistry of the hydrogenation product 167 at the 9-position was not
determined because the chirality at this centre would be destroyed when the desired anion derived from nitrile 166 was formed. The IR spectrum of this material shows a very broad absorption at 3100-3700 cm⁻¹, which indicates the presence of a hydroxyl function.

The ¹H NMR spectrum of alcohol 167 displays no signals corresponding to vinylic protons. The signal from the carbinol proton is visible at δ 4.02. The integration value of a broad multiplet between δ 1.10 and 1.70 decreased from 9H to 8H when the ¹H NMR sample was shaken with D₂O, confirming the presence of the alcohol function. A singlet at δ 0.99 and a singlet and a doublet within a 15H multiplet at δ 0.86-0.88 correspond to the three methyl groups.

The secondary alcohol 167 was treated with TBSCI and imidazole in methylene chloride to give the disilyl ether 168. The primary silyl ether was then selectively removed with 1.0 equiv. of TBAF in THF to give exclusively the primary alcohol 169 in good yield (81%) from alcohol 167 (Scheme 48).

The structural assignment of both the disilyl ether 168 and the alcohol 169 was based upon IR, ¹H NMR, ¹³C NMR and mass spectra. The IR spectrum of alcohol 169 shows a very broad absorption at 3100-3700 cm⁻¹.
The $^1$H NMR spectrum of alcohol 169 displays a pentet at $\delta$ 3.92 with $J = 3.5$ Hz corresponding to the proton at the 3-position. A 1H multiplet at $\delta$ 1.10-1.20 disappeared when the $^1$H NMR sample was shaken with D$_2$O, confirming the presence of the alcohol function. A 6H singlet at $\delta$ 0.00 and a 15H multiplet at $\delta$ 0.83-0.87, incorporating a methyl singlet, a methyl doublet and a tert-butyl singlet confirm the presence of only one TBS group.

The preparation and isolation of aldehyde 170 presented some unexpected difficulties. The aldehyde 170 was obtained by oxidation of the primary alcohol 169. TPAP/NMO$^{77,78}$, PCC on alumina$^{81,82}$ and the Dess-Martin reagent$^{83,84}$ all gave the aldehyde 170. However, all of these reaction conditions required chromatography of the crude product on silica gel to obtain the pure aldehyde 170. Unfortunately the aldehyde 170 was found to be unstable to purification on silica gel. Reaction of the impure aldehyde resulted in a poor yield in the subsequent formation of aldoxime 171. Thus, reaction conditions for oxidation that gave pure product with no requirement for chromatographic purification on silica gel were needed. Swern oxidation$^{85,86}$ (DMSO, oxalyl chloride, Et$_3$N, CH$_2$Cl$_2$ –60 °C) provided the aldehyde 170 in a 98% yield. The purity of the isolated aldehyde 170 was sufficiently high for subsequent use without prior chromatographic purification on silica gel (eq 18).
The structural assignment of aldehyde 170 was based upon IR, $^1$H NMR, $^{13}$C NMR and mass spectra. The stereochemistry at the 9-position of aldehyde 170 was not determined because the chirality of this centre would be destroyed when the desired anion derived from nitrile 166 was formed. The IR spectra of aldehyde 170 shows a strong absorption at 1699 cm$^{-1}$ which is characteristic for the aldehyde function.$^{43}$

The $^1$H NMR spectrum of aldehyde 170 shows a singlet at δ 9.77 corresponding to the aldehyde proton. The signal from the proton at the 3-position is visible at δ 3.97. Singlets at δ 0.87 and δ 0.80 and a doublet at δ 0.84 with $J = 7.1$ Hz correspond to the three methyl groups.

The $^{13}$C NMR spectrum for aldehyde 170 shows a signal corresponding to an aldehyde carbonyl at δ 206.0.

The high-resolution mass spectra of aldehyde 170 shows a peak corresponding to M$^+$. Satisfactory results were also obtained from elemental (C, H) analysis.

By analysis of the $^1$H NMR spectrum, the unpurified aldehyde 170 was determined to be a single diastereomer. Treatment of the aldehyde 170 with hydroxylamine hydrochloride$^{87}$ and pyridine in DMF at 70 °C for 2 hours provided the aldoximes 171 in 92% yield after chromatography of the crude material on silica gel (Scheme 49). The product of the reaction was obtained as a mixture of four compounds. The four compounds were assumed to be a mixture of diastereomers α to the aldoxime function, with the aldoxime present as both $E$ and $Z$ geometric isomers. The $^1$H NMR spectrum of the mixture provided supporting evidence for this assumption. Four doublets were present in the range δ 7.5–6.6, which were assumed to be
the signals corresponding to the four different aldoxime protons. Presumably the aldehyde is epimerized prior to aldoxime formation. Separation of the four isomers was not pursued.

Dehydration of the mixture of aldoximes 171 with 1-chlorosulfinyl-4-dimethylaminopyridinium chloride in methylene chloride at -10 °C gave a 91% yield of the nitriles 166, as an inseparable 3:2 mixture of diastereomers α to the nitrile function. This ratio was determined by analysis of the ¹H NMR spectrum of the mixture.

The mixture of aldoximes 171 and the nitriles 166 were not fully characterized, as both materials were mixtures of diastereomers. Both mixtures were judged to be free from other impurities by analysis of their ¹H NMR spectra.

Alkylation of Nitrile 166

Deprotonation of nitrile 166 was achieved by treatment of this material with 5 equiv. of lithium diethylamide in THF for 2 hours at 0 °C. Alkylation of the resultant carbanion with MeI, gave a single product in 71% yield. Analysis of the ¹H NMR spectrum revealed that this compound was a single diastereomer (eq 19). Three 3H singlets at δ 1.23, 1.29 and 1.33 and a 3H doublet at δ 0.83 with J = 6.9 Hz confirmed that alkylation of nitrile 166 had been achieved. However, it was not possible to assign the stereochemistry of the product from the available data.
Given the lack of separation of the singlet methyl signals, further NMR experiments to assign the stereochemistry of the alkylated nitrile were deemed futile. Slow recrystallization of the alkylated product from acetone/hexane gave a quantitative yield of fine white crystals. X-ray crystal structure analysis of the crystals revealed the product to be alkylated nitrile 172, as shown in the ORTEP diagram of this material (Figure 5). Alkylation of the carbanion derived from nitrile 166 had thus occurred from the face opposite to the angular methyl groups. The data for the X-ray crystal structure analysis of the alkylated nitrile 172 is collated in the appendix X-Ray Crystallographic Data (page 182). Unfortunately, although the methyl group had been introduced stereoselectively, the orientation was opposite to that required for the synthesis of lintenone (1).

The stereoselectivity of alkylation can be rationalized as follows. In the $^1$H NMR spectrum of the mixture of nitriles 166 two pentets are visible at $\delta$ 4.05 and 3.95 (both with $J = 3.0$ Hz). These signals correspond to the protons in the 3-position from each of the diastereomers. Thus, it can be assumed that both diastereomers of 166 exist as conformers in solution with the protons at the 3-position in an equatorial orientation.
Figure 5: ORTEP diagram of the alkylated nitrile 172

It is therefore not unreasonable to assume that the carbanion derived from the mixture of nitriles 166 would also exist in solution as the conformer shown in Figure 6, in which the
Figure 6: Predicted lowest energy conformer of the nitrile stabilized carbanion derived from nitrile 166

proton at the 3-position is also equatorial. The methyl group at the 1-position and the methylene at the 2-position would both appear to offer a similar degree of steric hindrance to the approach of an electrophile. Thus, the methyl group at the 6-position would appear to be the substituent that has the greatest effect upon the direction of approach of MeI to the carbanion derived from 166. This methyl substituent at the 6-position appears to effectively block the approach of MeI from that face of the anion. Therefore, the alkylation occurs from the face of the anion opposite to the angular methyl groups, resulting in compound 172 being formed exclusively.

The structural assignment of nitrile 172 was based upon IR, $^1$H NMR, $^{13}$C NMR, mass spectra and the results of X-ray crystal structure analysis. The IR spectrum of this material shows a weak but sharp absorption at 2222 cm$^{-1}$ which is characteristic of the nitrile function.$^{43}$

The $^1$H NMR spectrum of nitrile 172 displays a $^1$H pentet at $\delta$ 4.03 with $J = 2.9$ Hz corresponding to the proton at the 3-position. The 2.9 Hz coupling constant for the proton in the 3-position indicates that this proton it is orientated equatorially. This provides confirmation that the conformation of 172 in solution is the same as in the solid state (X-ray). Singlets at $\delta$
1.23, 1.29 and 1.33 and a doublet at δ 0.83 with J = 6.9 Hz correspond to the four methyl groups.

The $^{13}$C NMR spectrum of nitrile 172 shows a signal at δ 127.5 corresponding to a nitrile group.

The high-resolution mass spectrum of nitrile 172 shows a peak corresponding to M$^+$. Satisfactory results were also obtained from elemental (C, H) analysis.

The complete stereoselectivity of the alkylation reaction illustrates the high preference for approach of MeI from the face of the anion opposite to the angular methyl groups. Thus, an alkylation agent was needed that would introduce a group, which could be converted to the desired alcohol function required for subsequent synthetic steps. Benzyl chloromethyl ether was selected as the alkylation agent because following alkylation, the benzyl group could be removed to give the required primary alcohol. Conversion of the nitrile function to a methyl group would be attempted later in the synthesis. It was assumed that alkylation of 166 with benzyl chloromethyl ether would occur from the same face of the anion, opposite to the angular methyl groups, as was observed in the alkylation of 166 with MeI.

Unfortunately, the conditions developed for alkylation of the nitrile with MeI (1. KDA, -78 °C, 30 min, THF, 2. MeI) did not prove suitable for alkylation with benzyl chloromethyl ether. Only a 15% yield of product 173 was obtained and many unidentifiable side products were also produced. Presumably, undesired side reactions effectively compete with alkylation by benzyl chloromethyl ether of the anion derived from 166.
Generation of the nitrile-stabilized carbanion from 166 by treatment with lithium bromide and lithium diethylamine in THF for 2 hours at 0 °C, followed by addition of HMPA and then the electrophile led to a significantly increased yield (73%) of compound 173 (eq 20). Both HMPA and LiBr are known to increase the reactivity of carbanions. Their presence is believed to lead to a decrease in aggregation of the anion complexes. Presumably the additives HMPA and LiBr complex to carbanions, which excludes solvent molecules. This complexation results in the formation of more reactive carbanions. LiBr could also cause an in situ displacement of the chloride of the benzyl chloromethyl ether to form the more reactive alkylating agent benzyl bromomethyl ether.

The structural assignment of nitrile 173 was based upon IR, $^1$H NMR, $^{13}$C NMR, and mass spectra. It was not possible to unequivocally determine the stereochemistry of alkylation from this data. The benzyl chloromethyl ether was assumed to have approached the carbanion derived from nitrile 166 from the same face of the anion as was observed in the alkylation of 166 with MeI. This conclusion was confirmed by an unexpected result. Whilst trying to find conditions for the reduction of nitrile 173, reduction with Super-Hydride® at -78 °C in THF was investigated. Rather than the expected imine, the previously observed nitrile 172 was obtained (eq 21). This result proved that the assumed direction of approach of the alkylating agent was correct and that the alkylation product obtained was indeed the desired diastereomer 173.
The IR spectrum of nitrile 173 shows a weak but sharp absorption at 2227 cm\(^{-1}\) which is characteristic for the nitrile function.\(^{43}\)

The \(^1\)H NMR spectrum of nitrile 173 displays an unresolved multiplet at \(\delta\) 3.96-4.00 corresponding to the proton at the 3-position. Two pairs of doublets from the R-CH\(_2\)OCH\(_2\)Ph functionality are visible at \(\delta\) 4.61 and 4.55 with \(J = 12.1\) Hz (R-CH\(_2\)OCH\(_2\)Ph) and at \(\delta\) 3.55 and 3.47 with \(J = 9.2\) Hz (R-CH\(_2\)OCH\(_2\)Ph). Singlets at \(\delta\) 1.22 and 1.46 and a doublet at \(\delta\) 0.81 correspond to the three methyl groups.

The \(^{13}\)C NMR spectrum for nitrile 173 shows five signals between \(\delta\) 125.8 and 137.7 corresponding to a nitrile group and four non-equivalent aromatic carbons. Three signals between \(\delta\) 67.1 and 73.5 correspond to the three carbons attached to an oxygen.

The high-resolution mass spectrum of nitrile 173 shows a peak corresponding to \(M^+\). Satisfactory results were also obtained from elemental (C, H) analysis.
Formation of the Third Ring and Conversion of the Nitrile Function into a Methyl Group

With the successful completion of a stereoselective synthesis of nitrile 173, attention was directed towards the formation of the third carbocyclic ring of lintenone (1). This was to be attempted using a sequence similar to that successfully employed in the synthesis of [4.4.4.5] fenestrane 15.\(^\text{11}\)

Scheme 50
The intention was to form a five-membered ring by treatment of the diazoketone 175 or 177 with a rhodium catalyst\textsuperscript{18,19} to give the tricyclic ketone 176 (Scheme 50, route (a)) or 178 (Scheme 50, routes (b) and (c)). A subsequent Wolff rearrangement\textsuperscript{8,9} should result in ring contraction of the five-membered ring to give the desired four-membered ring.

\[ \text{Reduction of the nitrile function and subsequent conversion to a methyl was anticipated to be feasible at three points in the synthesis. The three points were reduction of the nitrile function in compounds 173, 178 and 179. Of the three options reduction of compound 178 appeared to be the least favourable. Reduction of compound 178 would require protection and later deprotection of the ketone function. This protocol would potentially require two additional two steps in the synthesis. Both of the remaining two options appeared to be equally favourable; however, it was deemed prudent to attempt this conversion as early in the synthesis as possible. Thus, it was decided to initially attempt reduction of the nitrile 173} \]

![Diagram](image)

Two methods for conversion of the nitrile function to a methyl group were considered. The first method used Wolff-Kishner methodology\textsuperscript{87} and called for reduction of the nitrile 173 to the imine 181 (Scheme 51). Reaction of this imine with hydrazine in diethylene glycol
followed by direct treatment of the resultant hydrazone 182 with KOH at elevated temperature should give the desired compound 174.

If it proved possible only to reduce the nitrile 173 directly to the primary amine 183, without being able to halt the reduction at the intermediate imine 181, a second method involving Barton's methodology for radical deamination with Bu$_3$SnH could be used.\textsuperscript{90-96} This would involve conversion of the amine 183 to the isonitrile 184. Direct treatment of the isonitrile 184 with Bu$_3$SnH and a radical initiator (usually AIBN) at elevated temperatures should then give compound 174 (Scheme 52).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {173};
\node at (2,0) {183};
\node at (4,0) {184};
\node at (6,0) {174};

\node at (0,-1) {OTBS};
\node at (2,-1) {OTBS};
\node at (4,-1) {OTBS};
\node at (6,-1) {OTBS};

\node at (0,0) {$\text{CN}$};
\node at (2,0) {$\text{NH}_2$};
\node at (4,0) {$\overset{\text{N=C}}{\text{=}}$};
\node at (6,0) {$\text{OBn}$};

\draw[-] (0.5,0) -- (1.5,0);
\draw[-] (2.5,0) -- (3.5,0);
\draw[-] (4.5,0) -- (5.5,0);

caption{Scheme 52}
\end{tikzpicture}
\end{center}

The nitrile 173 proved to be remarkably resistant to a wide variety of reducing reagents. Attempted reduction with 2 equiv. of DIBAL (THF, refl., 18 hr), 2 equiv. of DIBAL (DME, 60° C, 20 hr), 1.2 equiv. of LiAl( OEt)$_3$ (Et$_2$O, rt, 18 hr), 10 equiv. of Li( t-Bu)$_2$ BuAlH (THF, rt, 1 hr), 5 equiv. of LiAlH$_4$ (Et$_2$O, 0 °C, 2 hr), 10 equiv. of LiAlH$_4$ (toluene, refl., 2 hr) and 10 equiv. of LiAlH$_4$, AlCl$_3$ (Et$_2$O, rt, 3 hr), all resulted only in recovery of starting material. Reduction with 10 equiv. Super-Hydride\textsuperscript{®} (THF, -78 °C, 5 min, rt, 1 hr), unexpectedly gave compound 172 (eq 22).

\begin{center}
\begin{tikzpicture}

\node at (0,0) {173};
\node at (2,0) {172};

\node at (0,-1) {OTBS};
\node at (2,-1) {OTBS};
\node at (2,0) {$\text{CN}$};
\node at (2,-1) {$\text{CN}$};

\draw[-] (0.5,0) -- (1.5,0);
\draw[-] (1.5,-1) -- (2.5,-1);
\draw[-] (2.5,0) -- (3.5,0);
\draw[-] (2.5,-1) -- (3.5,-1);

\node at (2,0) {\textbf{84\%}};
\node at (2,-1) {\textbf{84\%}};

caption{eq 22}
\end{tikzpicture}
\end{center}
Reduction was eventually achieved by treatment of the nitrile 173 with 15 equiv. of LiAlH₄ in refluxing THF for 5 hr. This protocol gave exclusively the amine 183 in quantitative yield (eq 23), necessitating the use of Barton's deamination methodology. It did not prove possible to isolate any of the intermediate imine 181.

\[
\text{173} \quad \xrightarrow{15 \text{ equiv. LiAlH}_4, \text{THF, refl.}} \quad 100\% \quad \text{183}
\]

The radical reaction of Bu₃SnH with an alkyl isocyanide to give Bu₃SnCN and a hydrocarbon (eq 24) was first reported by Saegusa. However, it was Barton who developed this reaction into an effective method for deamination.

\[
\text{R}_3\text{SnH} + \text{R}^-\text{N}^+\text{C}^- \rightarrow \text{R}_3\text{SnCN} + \text{R}^-\text{H} \quad (24)
\]

Isocyanides are formed by formylation of amines followed by dehydration. The former substances are then treated with Bu₃SnH and a radical initiator (usually AIBN) at elevated temperatures to give the hydrocarbon. Formation of the isonitrile 184 from amine 183 proved to be difficult. The product was unstable to column chromatography on silica gel and the unpurified product gave a poor yield of compound 174 in the subsequent radical reduction (Scheme 53).

\[
\text{183} \quad \xrightarrow{1. \text{NaH, ethyl formate}} \quad \text{184} \quad \xrightarrow{2. \text{SOCl}_2, \text{DMF, Na}_2\text{CO}_3} \quad \text{174}
\]

Scheme 53
Although isocyanide containing natural products are known\(^9\) it has been proposed that isocyanides may be unstable, especially to acids.\(^9\) Barton found that isothiocyanates could also be used in this deamination reaction. They are reported to proceed through isonitrile intermediates and give comparable yields to reactions involving isonitriles.\(^9\) Isothiocyanates would appear to offer two advantages over isonitriles in this reaction; they can be formed in one step from amines and they are significantly more stable than isonitriles.

The isothiocyanate 185 was formed in good yield from the crude amine 183 by treatment with carbon disulfide and DCC in CH\(_2\)Cl\(_2\) at 0 °C. The isothiocyanate 185 was purified by column chromatography on silica gel and reduced by treatment with Bu\(_3\)SnH and AIBN in refluxing benzene to give the deaminated product 174 in a 48% yield (Scheme 54).

With compound 174 in hand, attention was directed towards the synthesis of diazoketone 175, the required precursor for the rhodium catalyzed C-H insertion. Treatment of diazoketone 175 with dimeric rhodium acetate was expected to give the desired tricyclic ketone 176 (Scheme 55).
Treatment of the carboxylic acid **186** with oxalyl chloride in CH$_2$Cl$_2$ and catalytic DMF gave compound **187** (Scheme 56). Compound **187** was sufficiently stable to enable its $^1$H NMR spectrum to be obtained. This $^1$H NMR spectrum was only obtainable if compound **187** was isolated under strict anhydrous conditions and dissolved in CDCl$_3$, which had been previously dried by passing through a column of oven-dried basic alumina.

The $^1$H NMR spectrum of compound **187** showed it to be a single pure compound, which was not the starting material of the reaction, carboxylic acid **186**. The $^1$H NMR spectra of compounds **186** and **187** were very similar. Each spectra displayed three 3H singlets and one 3H doublet corresponding to the four methyl groups and a pentet at $\delta$ 4.0 with $J = 3.0$ Hz corresponding to the proton at the 3-position.

It was not possible to obtain an IR spectrum of compound **187** as a thin film or as a solution in CHCl$_3$, without it undergoing hydrolysis to the carboxylic acid **186**. The IR spectrum of the carboxylic acid **186** displays a broad absorption between 3400-2400 cm$^{-1}$ and a strong absorption at 1693 cm$^{-1}$. The GC-MS of compound **187** shows a peak corresponding to M$^+$-Cl and M$^+$-C(CH$_3$)$_3$. The GC-MS of the carboxylic acid **186** shows a peak corresponding to M$^+$-C(CH$_3$)$_3$. 

---

**Scheme 56**

![Scheme 56](image)
From the data obtained it was assumed that the acid chloride 187 had been obtained by treatment of the carboxylic acid 186 with oxalyl chloride in CH$_2$Cl$_2$ and catalytic DMF, although it was not possible to prove this definitively. Unfortunately treatment of the acid chloride 187 with an ethereal solution of diazomethane formed none of the required diazoketone 175 (Scheme 56). The only compound isolated was carboxylic acid 186 the product of hydrolysis of the acid chloride 187. None of the methyl ester 188 was isolated, which indicated that hydrolysis of the acid chloride 187 had occurred only during its isolation. The use of a solution of diazomethane which had been dried with KOH pellets produced none of the required diazoketone 175. Again only the carboxylic acid 186 was isolated. Presumably the increase in steric bulk of a methyl group relative to a nitrile group blocks the approach of the diazomethane. This inability to form the diazoketone 175 rendered the rhodium catalyzed C-H insertion reaction impossible at this point. Instead, reduction of the nitrile function and subsequent deamination would have to be performed after the ring closure. Thus, the treatment of diazoketone 177 with a rhodium catalyst to give the tricyclic keto nitrile 178 was investigated (eq 25).
Conversion of Nitrile 173 into Diazoketone 177

Removal of the benzyl protecting group from nitrile 173 was expected to be accomplished by the use of 10% by weight palladium on charcoal and atmospheric pressure hydrogenation conditions. However, this deprotection reaction proceeded exceedingly slowly (~1 week) when either EtOH or a 2% by volume solution of AcOH in EtOH were used as solvents. It was therefore decided to use transfer hydrogenation conditions as these often provide significant rate enhancements in the removal of benzyl groups from hindered substrates. Breakdown of the ammonium formate is believed to result in an in situ delivery of the hydrogen, which is thought to cause the observed rate enhancement. A solution of nitrile 173, ammonium formate (0.3 g/mmol of substrate) and 10% by weight palladium on charcoal (1 g/mmol of substrate) in MeOH was heated to reflux for 2 hours (eq 26) at which time the debenzylation reaction was found to be complete.

Synthesis of the carboxylic acid 191 was accomplished by a particularly mild two step procedure from the alcohol 189 (Scheme 57). Earlier in the synthesis, the Swern conditions had been found to be the most successful for the oxidation of alcohol 169 to give the aldehyde 170 (see page 67). Oxidation of alcohol 189 was therefore performed using these conditions.
and this procedure gave the aldehyde 190 in excellent yield. Subsequent oxidation of the aldehyde 190 to the carboxylic acid 191, accomplished with sodium chlorite, also proceeded in excellent yield. This sodium chlorite oxidation has been found to be particularly useful in cases in which steric hindrance and/or sensitive functionality are present.99

Carboxylic acid 191 was transformed into the acid chloride 192 by treatment of the former substance with oxalyl chloride and DMF in methylene chloride. Formation of the diazoketone 177 was then accomplished by reaction of the acyl chloride 192 with an ethereal solution of excess diazomethane19 (Scheme 58). The formation of an acid chloride and its conversion to the corresponding diazoketone usually proceed cleanly to give products which require only minimal purification. This was indeed found to be true in this case. The acid chloride 192 was not purified and was immediately converted into the diazoketone 177.

![Scheme 58](image)

The structural assignments of compounds 189-191 and 177 were based upon IR, 'H NMR, 13C NMR and mass spectra. The IR spectrum of alcohol 189 shows a strong and broad absorption at 3300-3150 cm\(^{-1}\) characteristic of a hydroxyl function. The aldehyde 190 shows a strong absorption at 1735 cm\(^{-1}\), whilst the carboxylic acid 191 exhibits a strong carbonyl absorption at 1734 cm\(^{-1}\) and a broad OH stretch at 3700-2400 cm\(^{-1}\). Diazoketone 177 displays strong absorptions at 2114 and 1745 cm\(^{-1}\) characteristic of the diazo functionality.43 Weak but sharp
signals from the nitrile stretch appear between 2247 and 2228 cm\(^{-1}\) in the IR spectra of compounds 189-191 and 177.

The \(^1\)H NMR spectrum of alcohol 189 shows a multiplet at \(\delta 1.83\) which exchanges with D\(_2\)O, indicating the presence of a hydroxyl function. The spectrum for aldehyde 190 displays a characteristic sharp singlet at \(\delta 9.48\). Substance 177 displays a sharp singlet at \(\delta 5.74\), which is indicative of the presence of an \(\alpha\)-diazoketone function.\(^{43}\)

The \(^{13}\)C NMR spectrum for alcohol 189 shows a signal at \(\delta 125.8\) corresponding to a nitrile carbon. Signals from carbonyl carbons are present in the spectra of aldehyde 190 at \(\delta 193.4\) and carboxylic acid 191 at \(\delta 173.3\).

**Rhodium Catalyzed C-H Insertion to Form the Tricyclic Keto Nitrile 178**

Catalytic metal carbene reactions utilizing rhodium(II) mediated carbenoids, generated from \(\alpha\)-diazo carbonyl compounds, have been extensively reviewed in the recent literature.\(^{19,100-103}\) The first mechanistic pathway for a rhodium(II)-mediated decomposition of an \(\alpha\)-diazo ketone was proposed by Teyssié et al\(^{104-106}\) (Scheme 59). Initial formation of a metal-substrate complex was postulated; this complex is thought to dissociate during the formation of the metallocarbenoid. The substrate and the carbene then react from outside the coordination sphere of the metal. This mechanism has been described as the carbenoid mechanism. Rhodium carbenoids are believed to react in this manner. A coordination mechanism has also been proposed\(^{104-106}\) in which the metal-substrate complex remains intact during the metallocarbenoid formation and the substrate and carbene react within the coordination sphere
of the metal. This second mechanism is now thought to be unimportant for rhodium carbenoids; however palladium carbenoids are believed to react in this manner.

a) \[ M + S \rightleftharpoons M-S \]
\[ M-S + \text{HCOOR} \rightarrow \text{HCOOR} + S \rightarrow \text{OOR} \]

b) \[ M + S \rightleftharpoons M-S \]
\[ M-S + \text{HCOOR} \rightarrow \text{HCOOR} \rightarrow M + \text{OOR} \]

Scheme 59: Mechanism of the transition metal catalyzed reaction of \( \alpha \)-diazo carbonyl compounds according to Teyssie et al. a) Carbenoid mechanism. b) Coordination mechanism.

More recently Doyle has proposed a catalytic cycle (Scheme 60) to explain the course of the reaction between an \( \alpha \)-diazo carbonyl compound and a transition metal such as rhodium.\(^{19}\) Decomplexation of the metal from the Lewis base (usually solvent) is followed by attack of the

\[ \text{SCR}_2 \]

\[ S: \]

\[ L_nM \rightleftharpoons \text{B} \]

\[ L_nM \rightleftharpoons \text{CR}_2 \]

\[ R_2C=N_2 \]

\[ L_nM \rightleftharpoons \text{CR}_2 \]

\[ L_nM \rightleftharpoons \text{CR}_2 \]

\[ N_2 \]

Scheme 60: Mechanism of the transition metal catalyzed reaction of \( \alpha \)-diazo carbonyl compounds according to Doyle et al. S = substrate; M = metal; R = alkyl, aryl; B = Lewis base
diazo moiety at the metal to form a zwitterionic intermediate. Extrusion of nitrogen (this is postulated to occur through \( \pi \)-backbonding) results in formation of the metal carbenoid. Reaction of the carbenoid with a variety of substrates (alkene, C-H bond, etc.) leads to product and regenerates the catalyst to complete the catalytic cycle.

**Figure 7: Proposed structure of the rhodium(II) carbenoid**

The rhodium(II) carbenoid has been described to exist as a combination of resonance structures 193a and 193b\(^{105} \) (Figure 7). However, no rhodium(II) carbenoid has ever been observed or isolated. The resonance structures 193a and 193b suggest that the carbenoid can behave as a metal stabilized carbocation.

This representation of the rhodium(II) carbenoid has been used by Taber et al. in a detailed mechanism (Scheme 61) which describes the role of the metal in C-H insertion reactions.\(^{107} \) Initial attack of the \( \alpha \)-diazo carbonyl 195 at the axial position of the rhodium dimer 194 gives intermediate 196. Cleavage of the Rh-Rh bond and concurrent loss of nitrogen gives complex 197. The rhodium atom must be sufficiently electrophilic to coordinate with a C-H sigma bond in a three-centred arrangement 198. The three-centred arrangement 198 then undergoes an electronic rearrangement resulting in C-C bond formation to give 199. Cleavage of the
rhodium-carbon bond and concomitant hydride migration produces the C-H insertion product and the recovered catalyst.

Scheme 61: Mechanism of C-H insertion according to Taber et al. $E = CO_2R'$; $R' = \text{alkyl, aryl.}$
Doyle proposes a mechanism very similar to that of Taber (Scheme 62), whereby reaction is initiated by overlap of the p-orbital of the metal carbene with the σ-orbital of the reacting C-H bond. However, Doyle proposes that formation of the C-C and C-H bonds occurs concurrently with rhodium dissociation. As the hydrogen migrates, the substituents on the carbon where insertion occurs rotate to their conformationally preferred positions (these conform to their placement in the product). The two mechanisms differ primarily over whether or not the hydrogen attaches to rhodium before regeneration of the catalyst.

Rhodium(II) mediated C-H insertions are known to have a preference to form five-membered rings and have a reactivity of insertion that follows the order tertiary > secondary >> primary. Consideration of this information and both Doyle’s and Taber’s mechanisms led to the expectation that diazoketone 177 would undergo a rhodium(II) mediated intramolecular C-H insertion reaction to give predominantly the tricyclic keto nitrile 178 (eq 27).

It can be seen from application of Doyle’s mechanism to diazoketone 177 (Scheme 63) and consideration of steric matters, that only one C-H σ-bond is available to coordinate with the
Scheme 63: Modified version of Doyle’s mechanism applied to diazoketone 177

rhodium(II) carbenoid. Although insertion into equatorial C-H bonds is most common, conformational effects can and do override this preference.\textsuperscript{19} The axial C-H $\sigma$-bond at the 2-position in the rhodium(II) complex is clearly the most favoured C-H $\sigma$-bond, being most available to interact with the p-orbital of the metal carbene to form a three-centred arrangement. This would lead to tricyclic keto nitrile 178, which has entirely cis-fused ring junctions. The formation of the alternate product, compound 201 was thought unlikely. Compound 201 would be expected to be considerably more strained than 178 due to its cis-trans-6,5,5 ring system and its formation would involve insertion into the equatorial C-H $\sigma$-bond. The equatorial C-H $\sigma$-bond would be expected to be less available to interact with the p-orbital of the metal carbene to form the required three-centred arrangement. This prediction was indeed found to be correct. Slow addition of a dilute solution of diazoketone 177 to a solution of dimeric rhodium acetate (to minimize the intermolecular reaction) gave the predicted tricyclic keto nitrile 178 in good yield with exclusively the desired stereochemistry (eq 28).
The structural assignment of tricyclic keto nitrile 178 was based upon the results from IR, $^1$H NMR, $^{13}$C NMR, HMBC, HMQC spectra, a series of $^1$H NMR decoupling experiments and mass spectra. The IR spectrum of this material shows a weak but sharp absorption at 2220 cm$^{-1}$ which is characteristic for the nitrile functionality and a characteristic cyclopentanone carbonyl absorption at 1751 cm$^{-1}$.

The $^1$H NMR spectrum of 178 displays a multiplet at $\delta$ 3.43-3.47 corresponding to the proton at the 10-position. This signal only displays one COSY correlation to a 2H multiplet at $\delta$ 0.98-1.13. The relevant data from the COSY experiments is collated in Table 2 (page 93). The 2H multiplet at $\delta$ 0.98-1.13 displays COSY correlations to the proton at the 10-position and the proton at the 8-position. The proton at the 8-position can be identified by its COSY correlation to the 3H doublet with $J = 7.0$ Hz corresponding to the methyl group at the 8-position. Thus, the 2H multiplet at $\delta$ 0.98-1.13 was determined to correspond to the two protons at the 9-position. Decoupling of this multiplet caused a coupling of 1.0 Hz within another 2H multiplet at $\delta$ 1.67-1.75 to collapse. This coupling had not been revealed by the COSY experiment. The data from the decoupling experiment is collated in Table 3 (page 94).
The signals corresponding to the protons in the 5- and 6-positions could be readily identified from the data supplied by the COSY experiment (see Table 2). These protons form an isolated spin system and so only exhibit coupling to each other. Thus it is possible to determine that one of the signals within the 2H multiplet at δ 1.67-1.75, corresponds to the signal from one of the two protons at the 5-position. The second signal within this multiplet could also be assigned from the data supplied by the COSY experiment (see Table 2) because the only COSY correlations which, remained unaccounted for from this multiplet were to the protons at the 2-position. Thus, the second signal within the multiplet at δ 1.67-1.75 was determined to correspond to the signal from H₁. The 1.0 Hz coupling that is observed in the decoupling experiment could not be between H₀ and the proton at the 5-position because these two protons are too distant from each other for coupling between them to be observed. Therefore, the coupling must be between H₁ and one of the protons at the 9-position. This four-bond coupling shows the presence of a W-coupling between the ring-fusion methine proton (H₁) and the equatorial proton α to the oxygen (H₉). For this observed W-coupling between H₁ and H₉ to be present the molecule must have the predicted cis-fused ring junction and must adopt the conformation shown in Figure 8. Singlets at δ 0.65 and 1.36 and a doublet at δ 0.62 with J = 7.0 Hz, correspond to the three methyl groups.

Figure 8: Conformation of tricyclic nitrile 178 required for the observed W-coupling to occur
Table 2: Selected results of COSY experiment on compound 178

<table>
<thead>
<tr>
<th>δ (mult, number of protons, J)</th>
<th>Assignment</th>
<th>COSY correlation to H₉ (400 MHz)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.43-3.47 (m, 1H)</td>
<td>H₁₀</td>
<td>H₉ H₉'</td>
</tr>
<tr>
<td>2.00 (td, 1H, J = 15.7, 7.4 Hz)</td>
<td>H₅</td>
<td>H₅ H₆ H₆'</td>
</tr>
<tr>
<td>1.81-1.91 (m, 2H)</td>
<td>H₂ H₈</td>
<td>H₁ H₂ Me₄ H₉ H₉'</td>
</tr>
<tr>
<td>1.67-1.75 (m, 2H)</td>
<td>H₁ H₅</td>
<td>H₂ H₂' H₆ H₆' H₅</td>
</tr>
<tr>
<td>1.53 (dd, 1H, J = 16.5, 14.8 Hz)</td>
<td>H₂</td>
<td>H₁ H₂'</td>
</tr>
<tr>
<td>0.98-1.13 (m, 2H)</td>
<td>H₉ H₉'</td>
<td>H₉ H₁₀</td>
</tr>
<tr>
<td>0.91 (s, 10H)</td>
<td>H₆ (Me)₃CSi</td>
<td>H₃ H₅ H₆'</td>
</tr>
<tr>
<td>0.69-0.74 (m, 2H)</td>
<td>H₆'</td>
<td>H₅ H₅' H₆'</td>
</tr>
<tr>
<td>0.62 (d, 3H, J = 7.0 Hz)</td>
<td>Me₉</td>
<td>H₈</td>
</tr>
</tbody>
</table>

* Entries in this column refer to two, three and four bond H-H₉ correlations as determined by the COSY experiment.

The ¹³C NMR spectrum for compound 178 shows a signal at δ 207.5 corresponding to a carbonyl carbon and a signal at δ 121.5 corresponding to a nitrile group.

The high-resolution mass spectrum of tricyclic keto nitrile 178 shows a peak corresponding to M⁺. Satisfactory results were also obtained from elemental (C, H, N) analysis.
Table 3: Selected results of decoupling experiment on compound 178

<table>
<thead>
<tr>
<th>Decoupling value $\delta$ (ppm)</th>
<th>Assignment $\text{H}_n$</th>
<th>Decoupling correlation in signal $\text{H}_n$ (400 MHz)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.45</td>
<td>$\text{H}_{10}$</td>
<td>$\text{H}_1 \text{H}_9 \text{H}_9'$</td>
</tr>
<tr>
<td>2.00</td>
<td>$\text{H}_5$</td>
<td>$\text{H}_5' \text{H}_6 \text{H}_6'$</td>
</tr>
<tr>
<td>1.84</td>
<td>$\text{H}_2', \text{H}_8$</td>
<td>$\text{H}_1 \text{H}_2 \text{H}_9 \text{H}_9' \text{Me}_8$</td>
</tr>
<tr>
<td>1.70</td>
<td>$\text{H}_1 \text{H}_5'$</td>
<td>$\text{H}_2 \text{H}_2' \text{H}_3 \text{H}_6 \text{H}_6' \text{H}_9 \text{H}<em>9' \text{H}</em>{10}$</td>
</tr>
<tr>
<td>1.53</td>
<td>$\text{H}_2$</td>
<td>$\text{H}_1 \text{H}_2'$</td>
</tr>
<tr>
<td>1.09</td>
<td>$\text{H}_9 \text{H}_9'$</td>
<td>$\text{H}_1 \text{H}<em>3 \text{H}</em>{10}$</td>
</tr>
<tr>
<td>0.72</td>
<td>$\text{H}_6'$</td>
<td>$\text{H}_5 \text{H}_5' \text{H}_6$</td>
</tr>
<tr>
<td>0.62</td>
<td>$\text{Me}_8$</td>
<td>$\text{H}_8$</td>
</tr>
</tbody>
</table>

$^a$ Entries in this column refer to two, three and four bond H-H$_n$ correlations as determined by the $^1$H decoupling experiment

Attempted Ring Contraction via a Wolff Rearrangement

With the successful stereoselective formation of the third ring to give compound 178, attention was directed towards the ring contraction of the cyclopentanone ring in compound 178 to give the desired four-membered ring ester 179 (Scheme 64). A variety of procedures are available for performing one-carbon ring contractions. The method that has proved the most successful for the contraction of strained ring systems is the Wolff rearrangement of cyclic $\alpha$-diazo
ketones.\textsuperscript{8,9,109} It was therefore anticipated that the synthesis of 179 could best be achieved via a Wolff rearrangement of the cyclic diazoketone 202.

The rearrangement can be performed thermally, photochemically or with silver-based catalysts.\textsuperscript{9} The photochemical rearrangement is thought to occur through a concerted mechanism, although arguments have been put forward for the intermediacy of both \(\alpha\)-ketocarbenes and oxirenes.\textsuperscript{9} A singlet carbene is believed to be formed via a first order rate process\textsuperscript{8} and the \(\text{R}^2\) group then migrates with its electron pair to give a ketene\textsuperscript{9} (Scheme 65). The ketene then reacts with a nucleophile such as water, an alcoholic solvent, or ammonia to give the corresponding acid, ester or amide. Addition of the nucleophile to the ketene function is kinetically controlled and occurs from the most accessible face of the ketene. The rearrangement occurs via an intramolecular transfer of the migrating group and occurs with complete conservation of the stereochemical information of the migrating group, irrespective of the method of initiation.\textsuperscript{9} Studies with optically active \(\alpha\)-diazoketones have shown complete retention of the stereochemistry of the migrating group.\textsuperscript{9}
Exceedingly strained ring systems have been constructed using the Wolff rearrangement, with ring strain appearing to impose few restrictions on the rearrangement. This was illustrated by the synthesis of the fenestranes 14 and 15, which both possess highly strained carbon frameworks.

(a) \[
\begin{align*}
\text{NH}_2 
\end{align*}
\xrightarrow{\text{HNO}_2} 
\begin{align*}
\text{N}_2
\end{align*}
\]

(b) \[
\begin{align*}
\text{NOH} 
\xrightarrow{\text{NH}_2\text{Cl}} 
\text{N}_2
\end{align*}
\]

(c) \[
\begin{align*}
\text{N-NH}_2 
\xrightarrow{-\text{H}_2} 
\text{N}_2
\end{align*}
\]

(d) \[
\begin{align*}
\text{N-SO}_2\text{Ar} 
\xrightarrow{\text{OH}} 
\text{N}_2
\end{align*}
\]

(e) \[
\begin{align*}
\text{N-NO} 
\xrightarrow{-\text{H}_2\text{O}, -\text{RCOO}^-} 
\text{N}_2
\end{align*}
\]

Scheme 66

The Arndt-Eistert procedure\(^{19}\) is the most widely used method for the formation of \(\alpha\)-diazoketones. In this procedure acid chlorides are converted into \(\alpha\)-diazoketones by the addition of an excess of diazomethane. This method is not of use for the addition of chains longer than one carbon because the reactions of the higher analogues of diazomethane are problematic. The Arndt-Eistert procedure cannot be used in the synthesis of cyclic \(\alpha\)-diazoketones. Consequently, the following methods have been developed\(^{109}\) (Scheme 66): (a)
amine diazotization, (b) the Forster reaction, (c) dehydrogenation of hydrazones, (d) the Bamford-Stevens reaction and (e) the deacylation of $N$-nitrosocarboxamides.

\[
\begin{align*}
&Z &\xrightarrow{\text{Base, } RN_3} &Z=N_2 \\
&203 & &204
\end{align*}
\]

$Z = \text{COR, CO}_2R, \text{NO}_2, \text{SO}_2R$

$R = T_s, M_s$

Scheme 67

Diazo transfer has largely superceded all of these methods.$^{19}$ Organic azides are treated with the anions derived from activated methylene compounds $203$ to give the required $\alpha$-diazo compounds $204$ (Scheme 67). Originally, tosyl azide$^{110,111}$ was used as the diazo transfer reagent but recently mesyl azide has been the preferred reagent because it provides for easier product purification.$^{112,113}$ The choice of base is dictated by the pK$_a$ of the active methylene group in the substrate. The presence of two anion-stabilizing $Z$-groups ($i.e.$ COR, CO$_2R$, CN, NO$_2$, SO$_2R$) is essential to ensure that a weak enough base can be used to avoid product decomposition. The synthesis of diazo monoketones (which possess only one anion-stabilizing group) therefore requires a procedure in which the presence of only one activating group is circumvented by the temporary introduction of a second activating group.

\[
\begin{align*}
&\text{HCOOR, RO}^- &\xrightarrow{\text{HCOOR, RO}^-} &\text{CHO} \\
&\text{TsN}_3, \text{Et}_3\text{N} &\xrightarrow{\text{TsN}_3, \text{Et}_3\text{N}} &\text{N}_2
\end{align*}
\]

Scheme 68

Initially a formyl group was used as the additional activating group.$^{114}$ The activated adduct is then treated with the diazo transfer reagent and the additional activating group is eliminated in the course of the transfer reaction (Scheme 68).
This approach was previously used in these laboratories in the total synthesis of (±)-β-panasinsene. A variety of attempts were made to perform the formylation of the ketone 205, including the use of NaH/ethyl formate which had proved successful in the synthesis of [4.4.4.5]fenestrane. These attempts resulted in either formation of the product in low yields, or ketone recovery. Eventually, treatment of a benzene solution of the ketone 205 with sodium t-amyl oxide at rt, followed by the addition of methyl formate, was found to lead to a quantitative yield of the keto aldehydes 206a and 206b and their enol tautomer 207 (eq 29).

Unfortunately application of these conditions to the tricyclic ketone 178 gave none of the desired keto aldehydes 208a and 208b or their enol tautomer 209 (eq 30). Only unreacted starting material was recovered.

Recently, the trifluoroacetyl group has been used as an activating group in preference to the formyl group. The former activating group provides efficient access to a wide variety of α-diazo ketones, which had previously been inaccessible. A solution of the ketone in THF is
deprotonated with LiHMDS at -78 °C and the cooled solution is treated with 2,2,2-trifluoroethyl trifluoroacetate to give the trifluoroacetyl substituted product. The latter material, in turn, is treated with mesyl azide and Et₃N in CH₃CN to give the desired diazoketone (Scheme 69).

![Scheme 69: General procedure for diazo transfer using the trifluoroacetyl group as an activating agent.](image)

The ketone 178 was subjected to these conditions. Unfortunately, this reaction also proved unsuccessful and again only unreacted starting material was recovered (Scheme 70).

![Scheme 70](image)

In his syntheses of the gibberellins (±)-GA₁₀₃ (211) and (±)-GA₇₃ (212)¹¹⁷ Mander reported the use of trisyl azide (213)¹² as a diazo transfer reagent. The hindered cyclohexanone 214, a common intermediate in the syntheses of both 211 and 212, was treated with trisyl azide (213) under phase transfer conditions. These conditions performed diazo transfer in a successful one-
step procedure to give the diazoketone 215 (Scheme 71). The diazoketone 215 then underwent a photochemical Wolff rearrangement to effect ring contraction to form compound 216 with the desired cyclopentane ring.

![Scheme 71](image)

Trisyl azide (213) has been found to be particularly useful in the reaction of sterically hindered substrates. Its utility is thought to stem from the steric hindrance afforded by the isopropyl groups ortho- to the sulfonyl azide function. Simpler arylsulfonyl azides are believed to be degraded too rapidly under the required reaction conditions to be useful. Unfortunately this method appears to be less effective with hindered cyclopentanones and several failures have been reported. In the reported cases where the one-step diazo transfer to hindered cyclopentanones with trisyl azide proved unsuccessful, α-diazoketone formation was eventually achieved either by resorting to one of the original methods for diazoketone synthesis (Scheme 66, page 96), or by condensation with ethyl or methyl formate followed by diazo transfer.

Clearly it is not trivial to predict which of these methods would prove successful for the synthesis of compound 202. It was therefore deemed prudent to halt investigation of the Wolff rearrangement at this time. Instead it was decided to first concentrate on the conversion of the nitrile function in compound 178 into a methyl group, to give compound 176. Reduction with LiAlH₄, followed by conversion to the isothiocyanate and subsequent treatment with Bu₃SnH...
and AIBN had been shown to be successful in the conversion of compound 173 into compound 174. It was therefore considered probable that this method would also be applicable to the synthesis of 176 from 178. A return to the problem of ring contraction was envisaged after the successful completion of this conversion.

**Conversion of the Nitrile Function in Compound 178 into a Methyl Group**

The conditions which had been required to effect the reduction of nitrile 173 were such that when applied to the tricyclic keto nitrile 178 they would undoubtedly also result in reduction of the ketone function to give compound 217 (Scheme 72). Treatment of compound 217 with carbon disulfide in DCC was expected to form the desired isothiocyanate 218. However, it was thought possible that the alcohol function in compound 218 could react intramolecularly with
the isothiocyanate function to form the undesirable isothiourea 219 (Scheme 73). Compound 219 would be expected to be unreactive in the subsequent radical reduction.

<table>
<thead>
<tr>
<th>217</th>
<th>218</th>
<th>219</th>
</tr>
</thead>
</table>

Scheme 73

To prevent formation of 219 it would be necessary either to protect the ketone function in keto nitrile 178 or to protect the alcohol function in compound 217. It was decided to protect the alcohol 217 in preference to the keto nitrile 178, even though this would lead to an additional oxidation step later in the synthesis. This decision was taken because it was anticipated that the $^1$H NMR spectrum of compound 221 would be considerably less complicated than that of the ketal derivative 220. The $^1$H NMR spectrum of compound 178 displays a multiplet at $\delta$ 3.43-3.47 corresponding to the proton at the 10-position. In comparison to the $^1$H NMR spectrum of compound 178, the silyl ether protected product 221 would only have additional $^1$H NMR signals from the proton at the 3-position and the protons from the silyl ether substituent. These signals should be readily identifiable in the $^1$H NMR spectrum of compound 221. Only the signal from the proton at the 3-position would be in the same region of the $^1$H NMR spectrum as the proton at the 10-position. If keto nitrile 178 were to be protected as a ketal derivative 220, this would have four additional signals from the diastereotopic protons $\alpha$ to the oxygen in

<table>
<thead>
<tr>
<th>178</th>
<th>220</th>
<th>221</th>
</tr>
</thead>
</table>

102
the region of the $^1$H NMR spectrum where the signal from the proton at the 10-position would also be expected to occur. A protecting group was required that could be removed selectively from a secondary hydroxyl group in the presence of a secondary TBSO group and that would be stable to the deamination conditions. Jones’ synthesis of (-)-FK-506 $^{121}$ had demonstrated that a secondary TESO group could be selectively cleaved in the presence of a secondary TBSO group. It was thus thought that a TES group would be a suitable protecting group in this case. The TES group was anticipated to be sufficiently stable to withstand the conditions necessary for the deamination reaction and also has only two easily identifiable signals in its $^1$H NMR spectrum. The reduction of the ketone and nitrile functions, TES protection of the resultant hydroxyl group and subsequent isothiocyanate formation were all anticipated to proceed sufficiently cleanly that purification would not be necessary until after formation of the isothiocyanate $^{222}$.

These predictions were found to be correct. The reduction, protection, isothiocyanate formation sequence proceeded cleanly and stereoselectively to give only one diastereomer in 72% yield from the tricyclic keto nitrile $^{178}$ (Scheme 74). At this point, the stereochemistry of the 5-triethylsiloxy group was not determined. However, reductions with LiAlH$_4$ are known to proceed stereoselectivity with a preference for axial hydride addition in conformationally biased systems.$^{74,75}$ From the previously analyzed $^1$H NMR data (page 92), compound $^{178}$ can be assumed to exist in solution as the conformer shown (Figure 9). It was therefore anticipated that LiAlH$_4$ had stereoselectively reduced the ketone function in keto nitrile $^{178}$ to give alcohol.
the result of a pseudoaxial hydride approach to the ketone function in compound 178. Thus, the final product was assumed to be compound 222, resulting from TES protection of the hydroxyl group in compound 217, followed by subsequent isothiocyanate formation. It was intended to first test the feasibility of deamination before determining the stereochemistry at this centre.

AIBN was added over a period of 3 days, via a syringe pump, to a refluxing solution of isothiocyanate 222 and Bu₃SnH in benzene to give the desired disilyl ether 224 in 63% yield. Also formed in 14% yield was the isonitrile 223 (Scheme 75). Isonitriles are believed to be intermediates in the conversion of isothiocyanate functions into methyl groups. Isonitrile 223 was subsequently treated with AIBN and Bu₃SnH in refluxing benzene, to give the disilyl ether 224 in 72% yield.
The structural assignment of disilyl ether 224 was based upon IR, mass spectra, $^1$H NMR, $^{13}$C NMR, nOe, COSY, HMBC and HSQC experiments. The IR spectrum of this material shows no characteristic bands for alcohol, nitrile, amine or isocyanide function.\textsuperscript{43}

The $^1$H NMR spectrum of disilyl ether 224 displays a broad singlet at $\delta$ 3.83 corresponding to $H_{10}$ and a doublet of doublets at $\delta$ 3.51 with $J = 11.0$ and 5.9 Hz corresponding to $H_3$. Singlets at $\delta$ 0.99 and 0.95 and a doublet at $\delta$ 0.79 with $J = 6.9$ Hz correspond to three of the four methyl groups. The signal from the fourth methyl group was assumed to be contained with a 12H singlet at $\delta$ 0.87. Confirmation of this assumption is provided by the HSQC experiment (data from this experiment is collated in Table 9, page 179). This shows that the 12H singlet at $\delta$ 0.87 has correlations to two $^{13}$C NMR signals at $\delta$ 25.3 and 25.8. These two $^{13}$C NMR signals at $\delta$ 25.3 and 25.8 correspond to the signals from the three methyl carbons from the $t$-butyl substituent of the TBS group and one additional methyl carbon. Two 3H singlets at $\delta$ 0.00 and $\delta$ 0.01 correspond to the two methyl substituents of the TBS group. A 9H triplet at $\delta$ 0.94 and a 6H quartet at $\delta$ 0.56 confirm the presence of the TES group.

![Figure 10: nOe Difference experiment on disilyl ether 224](image)

In a nOe experiment on disilyl ether 224 (Figure 10), irradiation of $H_3$ ($\delta$ 3.51, doublet of doublets, $J = 11.0$ and 5.9 Hz) resulted in a strong enhancement in the signals for $H_1$ ($\delta$ 1.58-
1.64, multiplet) and H₂ (δ 1.52-1.57, multiplet). Data from the nOe experiment is collated in Table 4, page 106. This result proves that H₁ and H₃ must be on the same side of the molecule. Thus, the hydride from LiAlH₄ must have approached the ketone function in compound 178 in the predicted pseudoaxial fashion as illustrated in Figure 9 (page 104). Confirmation of the assignment of the signals from H₁, H₂ and H₃ is provided by the COSY experiment (the data from this experiment is collated in Table 4, page 106). The signal from H₃ only has COSY correlations to two signals, a 1H multiplet at δ 1.52-1.57 and a 2H multiplet at δ 1.20-1.28.

![Chemical structure](image)

**Table 4: Selected results of COSY and nOe experiments on compound 224**

<table>
<thead>
<tr>
<th>δ(mult, no. of protons, J)</th>
<th>Assignment</th>
<th>COSY correlation to Hₙ(500 MHz)</th>
<th>nOe correlation to Hₙ(400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.83 (br. s, 1H,)</td>
<td>H₁₀</td>
<td>H₁ H₉ H₉</td>
<td></td>
</tr>
<tr>
<td>3.51 (dd, 1H, J = 11.0, 5.9 Hz)</td>
<td>H₃</td>
<td>H₅ H₂</td>
<td>H₁ H₂</td>
</tr>
<tr>
<td>2.33 (dd, 1H, J = 12.3, 8.6 Hz)</td>
<td>H₅</td>
<td>H₅ H₆ H₆.</td>
<td></td>
</tr>
<tr>
<td>1.87-1.97 (m, 1H)</td>
<td>H₈</td>
<td>Me₈ H₉</td>
<td></td>
</tr>
<tr>
<td>1.58-1.64 (m, 1H)</td>
<td>H₁</td>
<td>H₅ H₂</td>
<td>See note c</td>
</tr>
<tr>
<td>1.52-1.57 (m, 1H)</td>
<td>H₂</td>
<td>H₁ H₂ H₃</td>
<td>See note c</td>
</tr>
<tr>
<td>1.45-1.52 (m, 2H)</td>
<td>H₆ H₉</td>
<td>H₅ H₆ H₆. H₆ H₉ H₉ H₁₀</td>
<td>See note c</td>
</tr>
<tr>
<td>1.20-1.28 (m, 2H)</td>
<td>H₂ H₉</td>
<td>H₁ H₂ H₃ H₉ H₁₀</td>
<td></td>
</tr>
<tr>
<td>1.05-1.14 (m, 2H)</td>
<td>H₅ H₆</td>
<td>H₃ H₆</td>
<td></td>
</tr>
<tr>
<td>0.79 (d, 3H, J = 6.9 Hz)</td>
<td>Me₈</td>
<td></td>
<td>H₈</td>
</tr>
</tbody>
</table>

a Entries in this column refer to two and three bond H-H correlations as determined by the COSY experiment.
b Entries in this column refer to proton signals that showed an enhancement on irradiation of Hₙ. c It was not possible to separately irradiate these signals, therefore unambiguous results could not be obtained from these irradiations.
Consequently, these two multiplets were assumed to contain the signals from H₂ and H₂. A 1H multiplet at δ 1.58-1.64 only has COSY correlations to the signals from H₂, H₂, and H₁₀, therefore this multiplet was assumed to correspond to the signal from H₁. From the nOe experiment, irradiation at δ 3.51 resulted in a strong enhancement in the signals at δ 1.58-1.64 and δ 1.52-1.57. This result confirms that the protons corresponding to the signals from these multiplets are all on the same face of the molecule. Thus, the signal at δ 1.52-1.57 must correspond to H₂, rather than H₂. Irradiation at δ 1.62 simultaneously irradiates H₁, H₂, and the multiplet at δ 1.45-1.52 (due to the proximity of these signals; it is not possible to irradiate them separately). Therefore, it was not possible to provide additional confirmation of the spatial proximity of H₃ to those protons neighbouring it from the reverse nOe experiment.

The ¹³C NMR spectrum for disilyl ether 224 shows two signals at δ 80.3 and at 69.9, which correspond to carbons attached to oxygens. Signals at δ 25.9, 25.3, 23.2 and 17.3 correspond to the four methyl groups.

The high-resolution mass spectrum of disilyl ether 224 shows a peak corresponding to M⁺. Elemental (C, H) analysis of the disilyl ether 224 was not performed due the scarcity of the material.

With the successful stereoselective synthesis of compound 224 the desired conversion of the nitrile function in compound 178 into a methyl group had now been completed. Compound
224 possesses all four of the methyl groups present in lintenone (1) with the correct relative stereochemistry and it also possesses functionality, which should allow its future elaboration into the lintenone structure. It was now intended to return to the problem of ring contraction and to attempt the formation of the four-membered ring ester 180. Unfortunately time constraints and lack of material prevented any further advances in this synthesis.
Summary and Conclusions
The work described in the results and discussion section of this thesis constitutes the synthesis of the racemic compound \((1R^*,3S^*,4R^*,7R^*,8R^*,10R^*,11S^*-)\)-10-\text{-}\text{tert-}\text{butylidimethylsiloxy}-4,7,8,11-tetramethyl-3-triethylsilyloxytricyclo[5.3.1.0^{4,11}]undecane (224) this compound is a highly advanced intermediate in the attempted total synthesis of racemic lintenone (1). Compound 224 contains the correct relative stereochemistry at the ring junctions and has all of the desired methyl substituents present with the correct stereochemical relationship. Hopefully a ring contraction via a Wolff rearrangement\(^8,9,10\) will enable the completion of the carbocyclic core of lintenone (1), subsequent addition of the side chain should complete the racemic total synthesis.

Compound 224 was synthesized in 32 steps from commercially available propargyl alcohol with an approximately 1.7% overall yield. The key features of this synthesis were the formation of the second and third rings and the introduction of the methyl substituents with the correct relative stereochemistry.

The second ring was formed by an extension of copper(I) mediated intramolecular conjugate additions of alkenyl(trimethylstannane functions to enones developed in our laboratories.\(^3\) The novel trifunctional reagent 76 was developed and this was used to synthesize the vinylogous esters 77 and 103.
Treatment of the vinylogous esters 77 and 103 with either DIBAL or MeMgBr gave the enones 104-106 and 78, which upon heating at 60 °C with CuCN in DMSO underwent the aforementioned intramolecular conjugate additions to give the ketones 112-114 and 71 (Scheme 77). The conjugate additions were significantly slower when R₂ was a methyl group rather than hydrogen. The reaction required 18 hours to proceed to completion when R₂ was a methyl group compared to 2 hours when R₂ was hydrogen. Only the products from protiodestannylation of enones 98 were observed when CuCl was used as the source of copper(I).

Using this methodology ketone 71 was synthesized stereoselectively. Ketone 71 has the desired cis-fused ring junction and two of the required methyl substituents. Conversion of ketone 71 into enone 73 was then accomplished by an application of Reich’s methodology
involving elimination from selenoxide derivatives. The third methyl group was introduced with the required stereochemistry by addition of enone 73 to a solution of Me₂CuLi in diethyl ether. This gave exclusively the ketone 74, the product of an entirely stereoselective 1,4-addition to enone 73.

Alkylation of nitrile 166, derived from compound 74 with benzyl chloromethyl ether proceeded stereoselectively to give the alkylated nitrile 173. This compound provided a means for introduction of both the third ring and the final methyl substituent.

Conversion of the alkylated nitrile 173 into the diazoketone 177 and subsequent treatment of the diazoketone with dimeric rhodium acetate (eq 31) gave exclusively the tricyclic keto nitrile 178, forming, the third ring with complete stereoselectivity.

The final methyl group was formed by reduction of the nitrile function in compound 178 using Barton’s radical deamination methodology. The tricyclic keto nitrile 178 was reduced with
LiAlH₄, protected as the TES ether and then subsequently treated with carbon disulfide and DCC in methylene chloride to give the isothiocyanate 222 (Scheme 78). Reduction of isothiocyanate 222 with Bu₃SnH and AIBN led to the formation of the tricyclic disilyl ether 224 (Scheme 79). This reaction proceeded through the intermediate isonitrile 223.

Scheme 79

In the only previously published attempt at the total synthesis of lintenone (1), Meyers reported the synthesis of compound 50.¹⁴ This compound possesses the desired carbocyclic core, however it does not have all the methyl substituents present. Meyers was also unable to control the stereochemistry of the [2+2] photochemical cycloaddition used to form the four-membered ring (eq 32). It is thought that this lack of stereoselectivity was due to rotation about the double bond in the substrate 45, which is thought to occur via a diradical.

The complete stereoselectivity so far observed in our synthesis and the incorporation of all the methyl groups with the desired stereochemical relationship clearly provide improvements over
Meyers' attempted synthesis of linnenone (1). Another significant advantage in our synthesis is provided by the ester functionality present in the ring contraction product 180. If the ring contraction proceeds as anticipated, compound 180 will be the major diastereomer. However if the ratio of diastereomers is not as desired the ester group should provide a means to control the stereochemistry at the 9-position. Epimerization of the ester under thermodynamic controlled conditions should lead to formation of compound 180 as the major product. Presumably compound 180 will be the thermodynamically most stable isomer.
Experimental
General

Infrared spectra were recorded using a Perkin-Elmer model 1600 Fourier transform infrared spectrometer with internal calibration. Spectra were recorded either neat between NaCl plates for liquids, or as 1 to 2 weight percent potassium bromide pellets for solids.

Proton nuclear magnetic resonance (\(^{1}\)H NMR) spectra were recorded on Bruker models WH-400 or AVA-500 spectrometers at 400.100 MHz or 500.130 MHz, respectively. Deuteriochloroform (CDCl\(_3\)) was used as the solvent unless noted otherwise. Signal positions (\(\delta\)) are given in parts per million (ppm) from trimethylsilane (TMS) and are referenced relative to chloroform (\(\delta 77.24\)). Coupling constants (\(J\)) are given in Hertz (Hz). The multiplicity, integration value, coupling constants and signal assignment are given in parentheses after the signal position. Tin-hydrogen (\(J_{\text{Sn-H}}\)) and tin carbon (\(J_{\text{Sn-C}}\)) coupling constants quoted are the average for those displayed by \(^{117}\)Sn and \(^{119}\)Sn.

Carbon nuclear magnetic resonance (\(^{13}\)C NMR) spectra were recorded on Bruker model AC-200, Varian model XL-300, Bruker models WH-400 or AVA-500 spectrometers at 50.323 MHz, 75.400 MHz, 100.614 MHz or 125.757 MHz, respectively. Deuteriochloroform (CDCl\(_3\)) was used as the solvent unless noted otherwise. Signal positions (\(\delta\)) are given in parts per million (ppm) from trimethylsilane (TMS) and are referenced relative to chloroform (\(\delta 77\)).

Low and high-resolution electron impact (EI) mass spectra were recorded using Kratos MS50 or MS80 mass spectrometers at 70 eV. Low and high resolution desorption chemical ionization (DCI+) mass spectra were recorded using a Delsi Nermag model R-10-10C mass spectrometer.
using either ammonia, isobutane, methane or mixtures thereof as ionizing gas. The UBC Mass Spectrometry Laboratory performed these analyses.

Melting points were measured on a Fisher-Johns melting point apparatus and are uncorrected. Boiling points refer to wet bulb stillhead temperatures measured with a thermometer and are uncorrected. Distillation temperatures refer to air bath temperatures of Kügelrohr type distillations and are uncorrected. Pressures quoted refer to that of the manifold to which the apparatus was attached.

Elemental analyses were performed either on a Carlo Erba model 1106 CHN elemental analyzer, a Fisons EA model 1108 elemental analyzer or using standard elemental technique. Mr. Peter Borda of the UBC Microanalytical Laboratory performed these analyses.

Gas-liquid chromatographic (GLC) analyses were performed using Hewlett-Packard models 5880A or 5890 capillary gas chromatographs with commercial fused silica columns (20 m x 0.21 mm x 30 μm) coated with cross-linked 5% phenyl 95% methyl silicone.

Thin layer chromatography (TLC) was carried out using commercial aluminium backed silica gel 60 plates (E. Merck, type 5554, 0.2 mm on aluminium). Chromatographs were visualized with ultraviolet light (254 nm), commercial 20% phosphomolybdic acid, basic aqueous potassium permanganate, iodine and or vanillin.

Liquid-solid chromatography was performed using either 230-400 mesh silica gel (E. Merck, silica gel 60) according to the method described by Williams et al.122 with apparatus as
described by Still et al.\textsuperscript{123} or type H 5-25 μm silica gel (Sigma, TLC grade silica) and the method described by Taber.\textsuperscript{124}

All reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame or oven dried, unless stated otherwise. Glass syringes, stainless steel needles, stainless steel and Teflon\textsuperscript{®} canulae were oven dried prior to use and cooled in a dessicator containing Drierite\textsuperscript{®} prior to use. Plastic syringes were flushed with dry argon.

Removal of solvent refers to concentration using a rotary evaporator at 20 torr followed by evacuation under reduced pressure (rotary vacuum pump, 0.1 torr) if appropriate.

Cold temperatures were maintained by use of the following baths: 0 °C, ice/water; -10 °C, NaCl/ice/water; -20 °C, -30 °C, -40 °C, -48 °C, Dry Ice\textsuperscript{®}/aqueous calcium chloride (27, 35, 41 and 47 g of CaCl\textsubscript{2} per 100 mL of H\textsubscript{2}O respectively); -78 °C, Dry Ice\textsuperscript{®}/acetone; -95 °C, methanol/liquid nitrogen; -198 °C, liquid nitrogen.
Solvents and Reagents

Argon gas was purchased from either Matheson Gas Products or Praxair of Canada Incorporated. Dry argon was obtained by passing argon through concentrated sulfuric acid, potassium hydroxide pellets and Drierite® prior to use.

All solvents were dried and distilled using standard procedures. Dry tetrahydrofuran (THF) and diethyl ether were obtained by refluxing over and then distilling from sodium metal under an atmosphere of dry argon. Petroleum ether refers to an alkane hydrocarbon mixture with a boiling point of 35-60 °C. Dry methylene chloride, benzene, hexamethylphosphoric triamide (HMPA), chlorotrimethylsilane, triethylamine, diisopropylamine and diethylamine were obtained by refluxing over and then distilling from calcium hydride under an atmosphere of dry argon. Benzyl chloromethyl ether was distilled from potassium carbonate under reduced pressure (0.1 torr) and then filtered through oven dried basic alumina prior to use. Lithium bromide was dried by heating it to 120 °C under reduced pressure (0.1 torr). Dimethyl sulfoxide (DMSO) and N,N-dimethylformamide (DMF) were dried sequentially over 3 Å molecular sieves. MeI was purified by passing it through oven dried basic alumina prior to use. Aqueous ammonium chloride-ammonium hydroxide (NH₄Cl-NH₄OH (pH ~8)) was prepared by the addition of ~50 mL of aqueous ammonia (28-30%) to ~950 mL of saturated NH₄Cl(aq).

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Procedures

Synthesis of 3-**tert**-butyldimethylsilyloxyprop-1-yne (99)

\[
\text{TBDMSO}_99
\]

Propargyl alcohol (5.80 mL, 0.10 mol) and imidazole (10.2 g, 0.15 mol) were dissolved in 100 mL of methylene chloride and the solution was cooled to 0 °C. **tert**-Butylchlorodimethylsilane (15.1 g, 0.10 mol) was added and the solution was stirred at 0 °C for 1 hour after which time a white suspension had formed. Addition of 250 mL of saturated NaHCO₃(aq) was followed by separation of the phases. The aqueous phase was extracted with 3 x 100 mL of diethyl ether and the combined organic extracts were dried over MgSO₄. Filtration and removal of the solvent in vacuo gave 15.76 g (93%) of the silyl ether 99 as a colourless oil, which exhibited spectra in accordance with those already reported.²²

Synthesis of ethyl 4-**tert**-butyldimethylsiloxybut-2-ynoate (100)

\[
\text{TBDMSO}_{100}\text{CO}_2\text{Et}
\]

The silyl ether 99 (15.6 g, 92.0 mmol) was dissolved in 70 mL of THF and the stirred solution was cooled to -78 °C. A 1.4 N solution of MeLi in diethyl ether (55.5 mL, 92.0 mmol) was added and the resultant solution was warmed to -20 °C and stirred at -20 °C for 30 minutes. The resultant dark brown solution was cooled to -78 °C and ethyl chloroformate (8.80 mL, 92.0 mmol) was added over 5 minutes. The reaction mixture was stirred at -20 °C for 1 hour, treated
with 100 mL of saturated NaHCO₃(aq) and the phases were separated. The aqueous phase was extracted with 3 x 100 mL of diethyl ether and the combined organic extracts were dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 22.4 g of a dark brown oil. Purification of the crude material by column chromatography (70-230 mesh silica gel, 40:1 petroleum ether-diethyl ether eluant, 13.5 cm x 12 cm column, 10 x 500 mL fractions) gave 17.4 g (78%) of a clear colourless oil which exhibited spectra in accordance with those already reported.²⁴

**Synthesis of lithium (trimethylstannyl)(cyano)cuprate (101)²⁶**

\[
[\text{Me}_3\text{SnCuCN}]\text{Li}
\]

101

To a stirred solution of hexamethylditin (1 equiv.) in THF (2 mL/mmol) at -20 °C was added a solution of MeLi (1 equiv.) in diethyl ether. The resultant pale yellow solution of trimethylstannyllithium³⁵ was stirred at -20 °C for 15 minutes and then cooled to -78 °C. Solid CuCN (1 equiv.) was added in one portion and the mixture was stirred at -48 °C for 15 minutes to produce a red solution of lithium (trimethylstannyl)(cyano)cuprate (101).
Synthesis of ethyl (Z)-4-tert-butyldimethylsiloxy-3-trimethylstannylbut-2-enoate (75)$^{34}$

![Formula Image]

To a stirred solution of lithium (trimethylstannylyl)(cyano)cuprate (101) (72.0 mmol) in 140 mL THF at -48 °C was added a solution of the ester 100 (17.4 g, 72.0 mmol) in 70 mL of THF. The resultant solution was stirred at -48 °C for 2 hours and at rt for 2 hours. The mixture was treated with 500 mL of aqueous NH$_4$Cl-NH$_4$OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the aqueous phase was extracted with 3 x 250 mL of diethyl ether. The combined organic extracts were dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 26.2 g (90%) of crude material which exhibited spectra in accordance with those already reported.$^{24}$ This material was used without further purification.

Synthesis of (Z)-4-tert-butyldimethylsiloxy-3-trimethylstannylbut-2-en-1-ol (102)

![Formula Image]

The ester 75 (24.4 g, 60.0 mmol) was dissolved in 250 mL of THF and the solution was cooled to 0 °C. A 1.0 N solution of diisobutylaluminium hydride in hexanes (132 mL, 132 mmol) was added dropwise over 15 minutes and the solution was stirred at 0 °C for 2 hours. The reaction mixture was then warmed to rt, treated with 15 mL of aqueous NH$_4$Cl-NH$_4$OH (pH ~8) and the resultant mixture was stirred vigorously for 30 minutes. Magnesium sulfate (3.00 g) was added
and the resultant suspension was stirred for a further 15 minutes. The suspension was filtered through a 13 cm x 8 cm column of Florisil® and the column was eluted with 2 L of diethyl ether. The combined eluant was concentrated in vacuo to give 20.4 g of crude product, which was purified by Kügelrohr distillation (100-120 °C @ 0.05 torr) to give 16.6 g (76%) of the alcohol 102.

The alcohol 102 displayed:

IR (neat): 3400-3000 (v. br.), 2930, 2858, 1472, 1363, 1254, 1088, 1050, 1004, 837, 775 cm⁻¹.

¹H NMR (400 MHz): δ = 6.34-6.40 (m, 1H, ³J_{Sn-H} = 131.5 Hz, CH=C), 4.24 (br. s, 2H, ³J_{Sn-H} = 33.0 Hz, CH₂OSi), 4.14 (t, 2H, J = 5.3 Hz, CH₂OH), 1.25 (t, 1H, J = 5.3 Hz, OH), 0.88 (s, 9H, (CH₃)₃CSi), 0.17 (s, 9H, ²J_{Sn-H} = 27.3 Hz, (CH₃)₃Sn), 0.03 (s, 6H, (CH₃)₂Si).

¹³C NMR (50 MHz): δ = 147.6, 136.5, 69.5, 63.6, 25.9, 18.3, -5.3, -7.8.

LRMS (EI): m/z = 351 (10%, M⁺-CH₃).

HRMS (EI): calculated for C₁₂H₂₇O₂¹²⁰SnSi (M⁺-CH₃): 351.08023; found: 351.07948.

Anal. calculated for C₁₃H₃₀O₂SnSi: C 42.76, H 8.28; found: C 42.87, H 8.31.
Synthesis of (Z)-4-bromo-1-tert-butyldimethylsiloxy-2-trimethylstannylbut-2-ene (76)

\[
\begin{array}{c}
\text{Me}_3\text{Sn} \quad \text{Br} \\
\text{TBSO} \quad 76
\end{array}
\]

Triphenylphosphine (21.3 g, 68.0 mmol) was dissolved in 300 mL of methylene chloride and the stirred solution was cooled to -10 °C. Bromine (4.19 mL, 81.6 mmol) was added dropwise until a slight yellow colour persisted, one crystal of triphenylphosphine was then added followed by triethylamine (11.3 mL, 81.6 mmol). The solution was stirred at -10 °C for 15 minutes. The alcohol 102 (24.7 g, 68.0 mmol) was added over a period of 15 minutes and the mixture was stirred for a further 2 hours at -10 °C. Most of the solvent was removed by rotary evaporation (approx. 50 mL remaining) and the solution was filtered through a 10 x 8 cm column of Celite\textsuperscript{®}, which had been prewetted with pentane. The Celite\textsuperscript{®} column was eluted with 300 mL of pentane and the combined filtrate was concentrated by rotary evaporation (approx. 50 mL remaining). Filtration through Celite\textsuperscript{®}, followed by concentration was repeated twice more and the remaining solvent was removed carefully by rotary evaporation to give 27.1 g (83%) of the bromide 76 which was used immediately without further purification.

The bromide 76 displayed:

IR (neat): 2956, 2857, 1472, 1363, 1257, 1201, 1094, 1047, 1006, 838, 776 cm\textsuperscript{-1}.
\( \text{\textsuperscript{1}H NMR (400 MHz)}: \delta = 6.4 \text{ (tt, } 1H, J = 8.2, 1.8 \text{ Hz, } \text{\textsuperscript{3}J}_{\text{Sn-H}} = 119.0 \text{ Hz, CH=C}), 4.25 \text{ (d, } 2H, J = 1.8 \text{ Hz, } \text{\textsuperscript{3}J}_{\text{Sn-H}} = 32.4 \text{ Hz, CH}_{2}\text{OSi}), 3.96 \text{ (d, } 2H, J = 8.2 \text{ Hz, CH}_{2}\text{Br}), 0.88 \text{ (s, } 9H, (\text{CH}_{3})_{3}\text{CSi}), 0.24 \text{ (s, } 9H, 2J_{\text{Sn-H}} = 54.5 \text{ Hz, } (\text{CH}_{3})_{3}\text{Sn}), 0.03 \text{ (s, } 6H, (\text{CH}_{3})_{2}\text{Si}). 

\text{\textsuperscript{13}C NMR (50 MHz)}: \delta = 152.3, 133.5, 69.3, 33.7, 25.9, 18.3, -5.2, -8.1.

\text{LRMS (El): } m/z = 413 \text{ (6.4\%, M}^{+}\text{-CH}_{3}).

\text{HRMS (El): calculated for } \text{C}_{12}\text{H}_{28}\text{O}\text{SnSi}_{81}\text{Br (M}^{+}\text{-CH}_{3}): 414.99377; \text{found: } 414.99544.

\text{Synthesis of the 3-isobutoxy-6-((Z)-4-\text{tert}-butyldimethylsilox}-3\text{-trimethylstannylbut-2-en-1-yl)cyclohex-2-en-1-one (77)}

\begin{align*}
\text{Diisopropylamine (21.0 mL, 0.16 mol) was dissolved in 300 mL of THF and the stirred solution was cooled to -78 °C. A 1.6 N solution of } \text{n-butyllithium in hexanes (100 mL, 0.16 mol) was added via cannula, the solution was warmed to 0 °C and stirred at 0 °C for 15 minutes. The solution was cooled again to -78 °C and a solution of 3-isobutoxycyclohex-2-en-1-one (6) (25.2 g, 0.15 mol) in 100 mL of THF was added via cannula. The solution was warmed to 0 °C, stirred at 0 °C for 2 hours and cooled again to -78 °C. A solution of the bromide 76 (48.5 g, 0.10 mmol) in 100 mL of THF was then added via cannula over a period of}
\end{align*}
15 minutes. The reaction mixture was warmed to rt, stirred at rt for 18 hours and then treated with 250 mL of H₂O. The phases were separated and the aqueous phase was extracted with 3 x 250 mL of diethyl ether. The combined organic extracts were washed with 250 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave a yellow oil, which was purified by column chromatography (70-230 mesh silica gel, 6:1 petroleum ether-diethyl ether eluant, 13 cm x 10 cm column, 10 x 500 mL fractions). Removal of the solvent from the appropriate fractions gave 36.8 g (71%) of vinylogous ester 77 as a clear colourless oil.

The vinylogous ester 77 displayed:

IR (neat): 2958, 1657, 1611, 1472, 1404, 1384, 1368, 1252, 1194, 1084, 1041, 1005, 837, 776, 668 cm⁻¹.

¹H NMR (400 MHz): δ = 6.10 (br. t, 1H, J = 7 Hz, ³JSn-H = 134.0 Hz, SnC=CH), 5.30 (s, 1H, OC=CH), 4.20 (s, 2H, ²JSn-H = 39.7 Hz, CH₂OSi), 3.52-3.60 (m, 2H, OCH₂CH(CH₃)₂), 2.64-2.72 (m, 1H), 2.36-2.44 (m, 2H), 2.16-2.24 (m, 1H), 1.94-2.08 (m, 3H), 1.60-1.68 (m, 1H), 0.95 (d, 6H, J = 6.7 Hz, CH(CH₃)₂), 0.86 (s, 9H, (CH₃)₂CSi), 0.16 (9H, ²JSn-H = 54.0 Hz, (CH₃)₃Sn), 0.01 (s, 6H, (CH₃)₂Si).

¹³C NMR (75 MHz): δ = 200.4, 177.2, 145.8, 137.1, 102.3, 74.8, 70.4*, 45.5, 33.6*, 28.4, 27.7, 26.2, 26.0, 19.1, 18.3, -5.1, -8.0.

*¹³C - Sn coupling visible.
LRMS (DCI+): m/z = 517 (24.0%, MH⁺).

HRMS (DCI+): calculated for $C_{23}H_{45}O^{120}\text{SnSi}$ (MH⁺): 517.21597; found: 517.21519.

Anal. calculated for $C_{23}H_{44}OSnSi$: C 53.36, H 8.61; found: C 53.74, H 8.58.

**Synthesis of 3-isobutoxy-6-((Z)-4-tert-butyldimethylsiloxy-3-trimethylstannyl but-2-en-1-yl)-6-methylcyclohex-2-en-1-one (103)**

Diethylamine (4.38 mL, 39.0 mmol) was dissolved in 150 mL of THF and the stirred solution was cooled to -78 °C. A 1.6 N solution of n-butyllithium in hexanes (24.4 mL, 39.0 mmol) was added via cannula, the solution was warmed to 0 °C and stirred at 0 °C for 15 minutes. The solution was cooled again to -78 °C and the vinylogous ester 77 in 100 mL of THF was added via cannula. This solution was warmed to 0 °C, stirred at 0 °C for 2 hours and cooled again to -78 °C. MeI (11.9 mL, 191 mmol) was added via syringe, the reaction mixture was warmed to rt, stirred at rt for 18 hours and then treated with 125 mL of saturated NaHCO₃(aq) and 125 mL of H₂O. The phases were separated and the aqueous phase was extracted with 3 x 200 mL of diethyl ether. The combined organic extracts were washed with 250 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 20.0 g of a
yellow oil, which was purified by column chromatography (230-400 mesh silica gel, 3:1 petroleum ether-diethyl ether eluant, 7.5 cm x 30 cm column, 60 x 50 mL fractions). Removal of the solvent from the appropriate fractions gave 16.0 g (77%) of vinylogous ester 103 as a clear colourless oil.

The vinylogous ester 103 displayed:

IR (neat): 2959, 1657, 1614, 1471, 1405, 1385, 1365, 1317, 1252, 1195, 1092, 1042, 1002, 838, 776, 668 cm$^{-1}$.

$^1$H NMR (400 MHz): $\delta = 5.90-6.25$ (m, 1H, $^3J_{Sn-H} = 137.0$ Hz, CH=CSn), 5.22 (s, 1H, COCH=C), 4.18 (d, 2H, $J = 1.1$ Hz, $^3J_{Sn-H} = 39.8$ Hz, CH$_2$OSi), 3.56 (d, 2H, $J = 6.7$ Hz, OCH$_2$CH(CH$_3$)$_2$), 2.36-2.42 (m, 3H), 2.15-2.20 (m, 1H), 2.00 (nonet, 1H, $J = 6.7$ Hz, OCH$_2$CH(CH$_3$)$_2$), 1.87-1.94 (m, 1H), 1.65-1.71 (m, 1H), 1.07 (s, 3H, CH$_3$), 0.95 (d, 6H, $J = 6.7$ Hz, CH(CH$_3$)$_2$), 0.86 (s, 9H, (CH$_3$)$_2$CSi), 0.15 (s, 9H, $^2J_{Sn-H} = 53.6$ Hz, Sn(CH$_3$)$_3$), 0.01 (s, 6H, (CH$_3$)$_2$Si).

$^{13}$C NMR (75 MHz): 203.4, 176.0, 146.6, 134.7, 101.4, 74.7, 70.4, 43.4, 40.9, 32.0, 27.7, 26.0, 26.0, 22.4, 19.1, 18.3, -5.2, -7.9.

LRMS (DCI+, NH$_3$): m/z = 531 (4.7%, MH$^+$).

HRMS (DCI+, NH$_3$): calculated for C$_2$H$_4$O$_2$Si$^{120}$Sn (MH$^+$): 529.23108; found: 529.23337.
Anal. calculated for C_{24}H_{46}O_{3}SiSn: C 54.32, H 8.74; found: C 54.71, H 8.74

**Synthesis of 4-((Z)-4-tert-butyldimethylsiloxyl-3-trimethylstannylbut-2-en-1-yl)cyclohex-2-en-1-one (104)**

The vinylogous ester 77 (500 mg, 0.97 mmol) was dissolved in 15 mL of THF and the stirred solution was cooled to 0 °C. A 1.0 N solution of diisobutylaluminium hydride in hexanes (2.91 mL, 2.91 mmol) was added via syringe and the solution was stirred at 0 °C for 1 hour. The reaction mixture was then carefully treated with 0.25 mL of aqueous NH\textsubscript{4}Cl-NH\textsubscript{4}OH (pH ~8) at 0 °C and the resultant mixture was stirred vigorously for 30 minutes to give a white slurry. Magnesium sulfate (50 mg) was added, the mixture was stirred at rt for 15 minutes and filtered through a 4 cm x 3 cm column of Florisil\textsuperscript{®}. The Florisil\textsuperscript{®} column was eluted with 300 mL of diethyl ether. The combined eluant was concentrated in vacuo and the product was dissolved in 10 mL of diethyl ether. p-Toluenesulfonic acid (10 mg) and 100 µL of H\textsubscript{2}O were added and the solution was stirred at rt for 1 hour. Addition of 10 mL of H\textsubscript{2}O was followed by separation of the phases. The aqueous phase was extracted with 3 x 15 mL of diethyl ether. The organic extracts were combined, washed with 10 mL of saturated NaCl\textsubscript{(aq)} and dried over MgSO\textsubscript{4}. Filtration, followed by removal of the solvent in vacuo gave 381 mg (87%) of enone 104, which was used without further purification.
The enone 104 displayed:

IR (neat): 2929, 2857, 1685, 1389, 1362, 1252, 1210, 1087, 1040, 1006, 939, 838, 776, 668 cm⁻¹.

¹H NMR (400 MHz): δ = 6.83 (dm, 1H, J = 10.1 Hz, CH=CHCO), 6.15 (t, 1H, J = 7.2 Hz, ³J_{Sn-H} = 134.0 Hz, CH=CSn), 5.95 (dd, 1H, J = 10.1, 2.4 Hz, CH=CHCO), 4.22 (s, 2H, ³J_{Sn-H} = 36.6 Hz, CH₂OSi), 2.44-2.52 (m, 2H), 2.30-2.40 (m, 1H), 2.18-2.24 (m, 2H), 2.04-2.12 (m, 1H), 1.64-1.74 (m, 1H), 0.87 (s, 9H, (CH₃)₃CSi), 0.17 (s, 9H, ²J_{Sn-H} = 54.0 Hz, (CH₃)₂Sn), 0.03 (s, 6H, (CH₃)₂Si).

¹³C NMR (50 MHz): δ = 199.6, 154.1, 147.1, 135.3, 129.3, 70.1, 38.6, 37.0, 36.6, 28.7, 26.0, 18.3, -5.2, -8.0.

LRMS (EI): m/z = 443 (1.2%, M⁺).

HRMS (EI): calculated for C₁₉H₃₆O₂Si¹₂₀Sn (M⁺-CH₃): 429.12720; found: 429.12761.

Anal. calculated for C₁₉H₃₆O₂SiSn: C 51.48, H 8.19; found: C 51.52, H 7.99.
Synthesis of 4-((Z)-4-tert-butyldimethylsiloxy-3-trimethylstannybut-2-en-1-yl)-3-methylcyclohex-2-en-1-one (105)

The vinylogous ester 77 (500 mg, 0.97 mmol) was dissolved in 15 mL of THF and the solution was cooled to -78 °C. A 3.0 M solution of methylmagnesium bromide in THF (1.61 mL, 4.85 mmol) was added slowly via syringe, the reaction mixture was warmed to rt and stirred at rt for 18 hours. The reaction mixture was cooled to 0 °C and treated carefully with 10 mL of H₂O. The phases were separated and the aqueous phase was extracted with 3 x 15 mL of diethyl ether. The combined organic phases were concentrated in vacuo to give a brown oil, to which was added 10 mL of diethyl ether. p-Toluenesulfonic acid (10 mg) and 100 μL of H₂O were added and the mixture was stirred at rt for 1 hour. Addition of 10 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 15 mL of diethyl ether. The organic extracts were combined, washed with 10 mL of saturated NaCl(aq) and dried over magnesium sulfate. Filtration, followed by removal of the solvent in vacuo gave 443 mg (91%) of enone 105, which was used without further purification.

The enone 105 displayed:

IR (neat): 2929, 2857, 1657, 1626, 1472, 1379, 1331, 1251, 1088, 1043, 1006, 939, 916, 838, 776, 668 cm⁻¹.
\(^1\)H NMR (400 MHz): \(\delta = 6.08-6.15\) (m, 1H, \(^3\)J\(_{\text{Sn-H}}\) = 136.0 Hz, CH=CSn), 5.83 (s, 1H, C=CHCO), 4.20 (s, 2H, \(^3\)J\(_{\text{Sn-H}}\) = 35.9 Hz, CH\(_2\)OSi), 2.20 - 2.45 (m, 5H), 1.99-2.08 (m, 1H), 1.94 (s, 3H, CH\(_3\)), 1.82-1.90 (m, 1H), 0.87 (s, 9H, (CH\(_3\))\(_3\)Si), 0.17 (s, 9H, \(^2\)J\(_{\text{Sn-H}}\) = 53.7 Hz, (CH\(_3\))\(_3\)Sn), 0.02 (s, 6H, (CH\(_3\))\(_2\)Si).

\(^13\)C NMR (50 MHz): \(\delta = 199.2, 164.9, 146.5, 136.1, 127.2, 70.1, 39.8, 35.3, 34.2, 26.9, 25.9, 23.2, 18.3, -5.2, -8.0.\)

LRMS (EI): \(m/z = 457\) (3.6%, M\(^+\)).

HRMS (EI): calculated for C\(_{19}\)H\(_{35}\)O\(_2\)Si\(_{120}\)Sn (M\(^+\)-CH\(_3\)): 443.14282; found: 443.14343.

Anal. calculated for C\(_{20}\)H\(_{38}\)O\(_2\)SiSn: C 52.53, H 8.38; found: C 52.28, H 8.52.

**Synthesis of 4-((Z)-4-\text{tert\text{-}butyldimethylsiloxy\text{-}3\text{-trimethylstannylbut\text{-}2\text{-en\text{-}1\text{-yl}}}\text{-}4\text{-methylcyclohex\text{-}2\text{-en\text{-}1\text{-one}}} (106)**

The vinylogous ester 103 (200 mg, 0.378 mmol) was dissolved in 15 mL of THF and the stirred solution was cooled to 0 °C. A 1.0 N solution of diisobutylaluminium hydride in hexanes (2.91 mL, 2.91 mmol) was added via syringe and the solution was stirred at 0 °C for 1 hour. The
reaction mixture was then carefully treated with 0.10 mL of aqueous NH₄Cl-NH₄OH (pH ~8) at 0 °C and the resultant mixture was stirred vigorously for 30 minutes to give a white slurry. Magnesium sulfate (50 mg) was added and the mixture was stirred for a further 15 minutes. The suspension was filtered through a 4 cm x 3 cm column of Florisil® and the column was eluted with 200 mL of diethyl ether. The combined eluant was concentrated in vacuo and the product was redissolved in 10 mL of diethyl ether. p-Toluenesulfonic acid (10 mg) and 100 μL of H₂O were added and the solution stirred at rt for 1 hour. Addition of 10 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 15 mL of diethyl ether. The organic extracts were combined, washed with 10 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 185 mg of crude product, which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 4 cm x 10 cm column, 30 x 25 mL fractions). Removal of the solvent from the appropriate fractions gave 150 mg (87%) of enone 106 as a clear colourless oil.

The enone 106 displayed:

IR (neat): 2929, 2858, 1686, 1462, 1389, 1253, 1091, 1044, 838, 776 cm⁻¹.

¹H NMR (400 MHz): δ = 6.66 (d, 1H, J = 10.2 Hz, CH=CHCO), 6.16 (t, 1H, J = 6.6 Hz, ³J_{Sn-H} = 134.3 Hz, CH=CSn), 5.88 (d, 1H, J = 10.2 Hz, CH=CHCO), 4.23 (s, 2H, ³J_{Sn-H} = 36.6 Hz, CH₂OSi), 2.42-2.48 (m, 2H), 2.16-2.26 (m, 2H), 1.94-2.00 (m, 1H), 1.70-1.80 (m, 1H), 1.24 (s, 3H, CH₃), 0.88 (s, 9H, (CH₃)₂CSi), 0.17 (s, 9H, ²J_{Sn-H} = 53.7 Hz, (CH₃)₂Sn), 0.02 (s, 6H, (CH₃)₂Si).
$^{13}$C NMR (75 MHz): $\delta = 199.5, 158.5, 147.7, 133.3, 127.7, 70.1, 44.9, 36.1, 34.1, 33.9, 25.9, 24.9, 18.3, -5.2, -7.9.

LRMS (DCI+, NH$_3$): m/z = 443 (70.2%, MH$^+$-CH$_3$).

HRMS (DCI+, NH$_3$): calculated for C$_{20}$H$_{39}$O$_2$Si$^{125}$Sn (MH$^+$): 459.17411; found: 459.17497.

Anal. calculated for C$_{20}$H$_{38}$O$_2$SiSn: C 52.53, H 8.38; found: C 52.67, H 8.15.

Synthesis of 4-((Z)-4-tert-butyldimethylsiloxo-3-trimethylstannylbut-2-en-1-yl)-3,4-dimethylcyclohex-2-en-1-one (78)

The vinylogous ester 103 (23.6 g, 44.6 mmol) was dissolved in 500 mL of THF and the solution was cooled to -78 °C. A 3.0 M solution of methylmagnesium bromide in THF (45.0 mL, 135 mmol) was added slowly via syringe. The reaction mixture was warmed to rt and stirred at rt for 18 hours. The mixture was cooled to 0 °C and treated carefully with 200 mL of H$_2$O. The phases were separated and the aqueous phase was extracted with 3 x 250 mL of diethyl ether. The combined organic phases were concentrated in vacuo to give a brown oil, to which was added 500 mL of diethyl ether and 5 mL of H$_2$O. $p$-Toluenesulfonic acid (450 mg,
2.23 mmol) and 5 mL of H₂O were added and the solution was stirred at rt for 2 hours. Addition of 300 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 2 x 250 mL of diethyl ether. The organic extracts were combined, washed with 500 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 20.1 g (99%) of enone 78, which was used without further purification.

The enone 78 displayed:

IR (neat): 2930, 2857, 1675, 1619, 1463, 1378, 1332, 1252, 1226, 1188, 1091, 1045, 1007, 939, 838, 775, 665 cm⁻¹.

¹H NMR (400 MHz): δ = 6.00-6.08 (m, 1H, ³J_{Sn-H} = 135.0 Hz, CH=CSn), 5.81 (q, 1H, J = 1.3 Hz, C=CHCO), 4.19 (s, 2H, ³J_{Sn-H} = 35.7 Hz, CH₂Si), 2.35-2.42 (m, 3H), 2.10-2.18 (dd, 1H, J = 14.7, 8.6 Hz), 1.94-2.04 (m, 1H), 1.89 (d, 3H, J = 1.3 Hz, CH₃C=CH), 1.62-1.70 (m, 1H), 1.14 (s, 3H, CH₃), 0.85 (s, 9H, (CH₃)₃CSi), 0.17 (s, 9H, ²J_{Sn-H} = 53.8 Hz, (CH₃)₃Sn), 0.00 (s, 6H, (CH₃)₂Si).

¹³C NMR (50 MHz): δ = 199.6, 167.7, 147.4, 133.7, 127.7, 70.1, 42.6, 38.7, 34.21, 34.16, 25.9, 24.3, 20.3, 18.3, -5.2, -8.0.

LRMS (EI): m/z = 457 (73.7%, M⁺-CH₃).

HRMS (EI): calculated for C₂₀H₃₇O₂Si₁²⁰Sn (M⁺-CH₃): 457.15848; found: 457.15905.

Anal. calculated for C₂₁H₄₉O₂SiSn: C 53.52, H 8.55; found: C 53.41, H 8.58.
Synthesis of (1S',6S')-9-tert-butyldimethylsiloxymethylbicyclo[4.3.0]non-8-en-3-one (112)

The enone 104 (331 mg, 0.747 mmol) was dissolved in 5 mL of DMSO with stirring. CuCN (167 mg, 1.86 mmol) was added in one lot to the stirred solution, the suspension was heated to 60 °C and stirred at 60 °C for 2 hours. The homogeneous solution was treated with 10 mL of aqueous NH₄Cl-NH₄OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic extracts were washed with 50 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 172 mg of a brown oil, which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 2.5 cm x 10 cm column, 20 x 15 mL fractions). Removal of the solvent from the appropriate fractions followed by distillation (135-140 °C @ 0.2 torr) gave 147 mg (70%) of ketone 112 as a clear colourless oil.

The ketone 112 displayed:

IR (neat): 2929, 2856, 1718, 1463, 1406, 1362, 1255, 1160, 1078, 1007, 939, 839, 777, 678 cm⁻¹.
$^1$H NMR (400 MHz): $\delta = 5.54-5.59$ (m, 1H, CH=CH), 4.00-4.20 (m, 2H, CH$_2$OSi), 3.05-3.15 (m, 1H), 2.60-2.72 (m, 2H), 2.53 (dd, 1H, $J = 15.2$, 6.1 Hz), 2.28-2.35 (m, 2H), 2.15-2.23 (m, 1H), 2.07-2.15 (m, 1H), 1.95-2.04 (m, 1H), 1.68-1.78 (m, 1H), 0.87 (s, 9H, (CH$_3$)$_3$CSi), 0.03 (s, 6H, (CH$_3$)$_2$Si).

$^{13}$C NMR (75 MHz): $\delta = 213.8$, 145.1, 124.8, 60.7, 42.8, 41.2, 38.5, 37.5, 34.8, 27.4, 25.9, 18.4, -5.3, -5.4.

LRMS (DCI+, NH$_3$): m/z = 281 (100%, M$^+$H).

HRMS (CI+, NH$_3$/CH$_4$): calculated for C$_{16}$H$_{29}$O$_2$Si (M$^+$H): 281.19367; found: 281.19337.

Anal. calculated for C$_{16}$H$_{28}$O$_2$Si: C 68.52, H 10.06; found: C 68.36, H 10.04.

Synthesis of (15*,6S*)-9-tert-butyldimethylsiloxy methyl-1-methylbicyclo [4.3.0]non-8-en-3-one (113)

The enone 105 (387 mg, 0.846 mmol) was dissolved in 5 mL of DMSO. CuCN (189 mg, 2.11 mmol) was added in one lot to the stirred solution, the suspension was heated to 60 °C and stirred at 60 °C for 18 hours. The homogeneous solution was treated with 5.0 mL of aqueous
NH₄Cl-NH₄OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic extracts were washed with 50 mL of saturated NaCl(aq) and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 250 mg of a brown oil, which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 2.5 cm x 15 cm column, 20 x 15 mL fractions). Removal of the solvent from the appropriate fractions gave 182 mg (73%) of ketone 113 as a clear colourless oil.

The ketone 113 displayed:

IR (neat): 2929, 2857, 1718, 1463, 1406, 1361, 1321, 1256, 1116, 1064, 936, 777, 738, 666 cm⁻¹.

¹H NMR (400 MHz): δ = 5.53 (t, 1H, J = 1.8 Hz, CH=C), 4.05-4.15 (m, 2H, CH₂OSi), 2.62-2.72 (m, 1H), 2.25-2.50 (m, 3H), 2.02-2.19 (m, 3H), 1.90-2.00 (m, 1H), 1.70-1.80 (m, 1H), 1.11 (s, 3H, CH₃), 0.88 (s, 9H, (CH₃)₃CSi), 0.03 (s, 6H, (CH₃)₂Si).

¹³C NMR (75MHz): δ = 213.4, 148.6, 123.8, 59.7, 49.5, 48.7, 44.4, 36.7 (2C), 27.7, 27.4, 25.9, 18.4, -5.4.

LRMS (DCI+, NH₃): m/z = 295 (100%, M⁺H).

HRMS (DCI+, NH₃/CH₄): calculated for C₁₇H₃₁O₂Si (M⁺H): 295.20932; found: 295.20914.
Anal. calculated for C$_{17}$H$_{30}$O$_2$Si: C 69.33, H 10.27; found: C 69.63, H 10.30.

**Synthesis of (1R',6S')-9-tert-butyldimethylsiloxymethyl-6-methylbicyclo [4.3.0]non-8-en-3-one (114)**

The enone 106 (340 mg, 0.743 mmol) was dissolved in 5 mL of DMSO. CuCN (166 mg, 1.85 mmol) was added in one lot to the stirred solution, the suspension was heated to 60 °C and stirred at 60 °C for 2 hours. The homogeneous solution was treated with 10 mL of aqueous NH$_4$Cl-NH$_4$OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the aqueous phase was extracted with 3 x 20 mL of diethyl ether. The combined organic extracts were washed with 20 mL of saturated NaCl$_{aq}$ and dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 181 mg of a brown oil, which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 2 cm x 10 cm column, 30 x 7.5 mL fractions). Removal of the solvent from the appropriate fractions gave 153 mg (70%) of ketone 114 as a clear colourless oil.

The ketone 114 displayed:

IR (neat): 2929, 1719, 1463, 1375, 1255, 1173, 1083, 1006, 838, 777, 662 cm$^{-1}$. 

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$^1$H NMR (400 MHz): $\delta = 5.51$ (s, 1H, CH=C), 4.00-4.12 (m, 2H, CH$_2$OSi), 2.58-2.64 (m, 1H), 2.50-2.56 (dd, 1H, $J = 15.2, 6.1$ Hz), 2.26-2.33 (m, 3H), 2.18-2.24 (m, 2H), 1.77-1.82 (m, 2H), 1.18 (s, 3H, CH$_3$), 0.87 (s, 9H, (CH$_3$)$_3$Si), 0.034 (s, 3H, CH$_3$Si), 0.028 (s, 3H, CH$_3$Si). 

$^{13}$C NMR (75 MHz): $\delta = 213.7, 144.5, 124.1, 60.8, 50.6, 46.6, 40.9, 39.6, 36.1, 34.7, 29.2, 25.9, 18.3, -5.4, -5.3.$

LRMS (EI): m/z = 237 (100%, M$^+$(CH$_3$)$_3$C).

HRMS (EI): calculated for C$_{17}$H$_{30}$O$_2$Si (M$^+$): 294.20151; found: 294.20069.

Anal. calculated for C$_{17}$H$_{30}$O$_2$Si: C 69.33, H 10.27; found: C 69.17, H 10.25.

**Synthesis of (1R*,6S*)-9-tert-butyldimethylsiloxymethyl-1,6-dimethylbicyclo[4.3.0]non-8-en-3-one (71)**

![Image of the compound](OTBS)

The enone 78 (22.3 g, 89 mmol) was dissolved in 250 mL of DMSO. CuCN (10.6 g, 118 mmol) was added in one lot to the stirred solution, the suspension was heated to 60 °C and stirred at 60 °C for 18 hours. After 18 hours the homogeneous solution was treated with 250 mL of aqueous NH$_4$Cl-NH$_4$OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the
aqueous phase was extracted with 3 x 250 mL of diethyl ether, the combined organic extracts were washed with 250 mL of saturated NaCl\textsubscript{(aq)} and dried over MgSO\textsubscript{4}. Filtration, followed by removal of the solvent in vacuo gave 12.0 g of a brown oil which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 5 cm x 15 cm column, 30 x 50 mL fractions). Removal of the solvent from the appropriate fractions gave 10.96 g (76\%) of ketone 71 as a clear colourless oil.

The ketone 71 displayed:

IR (neat): 2930, 2857, 1719, 1463, 1383, 1256, 1137, 1074, 1007, 939, 839, 778, 666 cm\textsuperscript{-1}.

\textsuperscript{1}H NMR (400 MHz): \(\delta = 5.52-5.55\) (m, 1H, CH=C), 4.05-4.15 (m, 2H, CH\textsubscript{2}OSi), 2.20-2.40 (m, 6H), 1.86-1.93 (m, 1H), 1.67-1.74 (m, 1H), 1.10 (s, 3H, CH\textsubscript{3}), 1.02 (s, 3H, CH\textsubscript{3}), 0.88 (s, 9H, (CH\textsubscript{3})\textsubscript{3}Si), 0.031 (s, 3H, CH\textsubscript{3}Si), 0.028 (s, 3H, CH\textsubscript{3}Si).

\textsuperscript{13}C NMR (75 MHz): \(\delta = 213.0, 149.1, 123.4, 60.1, 52.3, 48.5, 44.9, 43.8, 37.2, 36.8, 25.9, 23.1, 22.9, 18.4, -5.39, -5.44\).

LRMS (EI): m/z = 251 (75.3\%, M\textsuperscript{+}-(CH\textsubscript{3})\textsubscript{3}C).

HRMS (EI): calculated for C\textsubscript{18}H\textsubscript{32}O\textsubscript{2}Si (M\textsuperscript{+}): 308.21716; found: 308.21719.

Anal. calculated for C\textsubscript{18}H\textsubscript{32}O\textsubscript{2}Si: C 70.07, H 10.45; found: C 69.68, H 10.28.
Synthesis of \((1R^*,6R^*)\)-9-\(\text{-}\text{tert-}\)butyldimethylsiloxymethyl-1,6-dimethylbicyclo[4.3.0]non-4,8-dien-3-one (73)

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73

Step 1: Synthesis of the TMS enol ethers 120 and 123.

Diisopropylamine (3.50 mL, 26.6 mmol) was dissolved in 80 mL of THF and the stirred solution was cooled to -78 °C. A 1.51 N solution of \(n\)-butyllithium in hexanes (17.7 mL, 26.7 mmol) was added via cannula. The solution was warmed to 0 °C, stirred at 0 °C for 15 minutes and then cooled again to -78 °C. A solution of the ketone 71 (4.06 g, 13.3 mmol) in 60 mL THF was added via cannula. The solution was stirred at -78 °C for 30 minutes and then chlorotrimethylsilane (5.08 mL, 39.9 mmol) was added via syringe. The pale yellow solution was allowed to warm to rt and stirred at rt overnight. The reaction mixture was treated with 50 mL of saturated \(\text{NaHCO}_3\) and 50 mL of \(H_2O\), the phases were separated and the aqueous phase was extracted with 3 x 100 mL pentane. The combined organic extracts were dried over MgSO\(_4\). Filtration, followed by removal of the solvent in vacuo gave 5.02 g (100%) of an 87:13 mixture (determined from the \(^1\text{H}\) NMR spectra of the crude material) of TMS enol ethers 120 and 123, which was used without further purification and characterization.
Step 2: Synthesis of the phenylselenides 124 and 125.

A mixture of TMS enol ethers 120 and 123 (2.51 g, 13.3 mmol) was dissolved in 65 mL of diethyl ether and the solution was cooled to -78 °C. A solution of phenylselenenyl chloride (2.55 g, 13.3 mmol) in 65 mL of diethyl ether at -78 °C was added over 5 minutes via cannula. The pale yellow solution was stirred at -78 °C for 30 minutes and warmed to rt. Removal of the solvent in vacuo gave 6.17 g (100%) of a bright yellow solid, which was an inseparable mixture of the phenylselenides 124 and 125. This mixture was used without further purification and characterization.

Step 3: Synthesis of the enone 73.

The mixture of phenylselenides 124 and 125 (13.3 mmol) was dissolved in 65 mL of methylene chloride and the stirred solution was cooled to -78 °C. A solution of 50-60% by weight of 3-chloroperoxybenzoic acid (4.56 g) in 65 mL of methylene chloride was added to the phenylselenide solution via cannula and the mixture was stirred at -78 °C for 30 minutes. Triethylamine (5.56 mL) was added via syringe and the reaction mixture was refluxed for 3 hours. The reaction mixture was cooled to rt and 100 mL of H₂O was added. The phases were
separated and the aqueous phase was extracted with 3 x 100 mL of diethyl ether. The combined organic extracts were dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 4.1 g of a brown oil, which was purified by column chromatography (230-400 mesh silica gel, 6:1 petroleum ether-diethyl ether eluant, 8 cm x 20 cm column, 50 x 60 mL fractions). Removal of the solvent from the appropriate fractions gave 3.21 g (80% from ketone 71) of enone 73 as a clear colourless oil.

The enone 73 displayed:

IR (neat): 2956, 2857, 1682, 1463, 1390, 1308, 1254, 1172, 1084, 1049, 1007, 965, 839, 778, 739, 669 cm⁻¹.

¹H NMR (400 MHz): δ = 6.42 (d, 1H, J = 10.1 Hz, CH=CHCO), 5.86 (d, 1H, J = 10.1 Hz, CH=CHCO), 5.46 (br. s, 1H, CH=C), 4.04-4.14 (m, 2H, CH₂OSi), 2.39-2.46 (m, 2H), 2.14-2.32 (m, 2H), 1.15 (s, 3H, CH₃), 1.03 (s, 3H, CH₃), 0.87 (s, 9H, (CH₃)₃CSi), 0.02 (s, 3H, CH₃Si), 0.01 (s, 3H, CH₃Si).

¹³C NMR (75 MHz): δ = 199.2, 157.8, 149.5, 127.2, 121.6, 60.1, 49.7, 47.9, 43.8, 43.2, 25.9, 22.2, 19.4, 18.3, -5.4, -5.5.

LRMS (EI): m/z = 249 (100%, M⁺-(CH₃)₃C).

HRMS (EI): calculated for C₁₄H₂₁O₂Si (M⁺-(CH₃)₃C): 249.13109; found: 249.13173.

Anal. calculated for C₁₈H₃₉O₂Si: C 70.53, H 9.87; found: C 70.58, H 9.94.
Synthesis of (1R*,5R*,6R*)-9-tert-butyldimethylsiloxymethyl-1,5,6-trimethyl bicyclo[4.3.0] non-8-en-3-one (74)

Copper-bromide dimethylsulfide complex (CuBr•S(CH₃)₂) (3.67 g, 17.8 mmol) was suspended in 50 mL of diethyl ether and the stirred mixture was cooled to -50 °C. A 1.6 N solution of MeLi in diethyl ether (22 mL, 35.2 mmol) was added via syringe (the solution became yellow during the addition of MeLi, the colour disappeared upon complete addition of MeLi). The mixture was warmed to -10 °C for 15 minutes and then cooled to -30 °C. A solution of enone 73 (2.71 g, 8.84 mmol) in 50 mL of diethyl ether was added via cannula. The mixture was warmed to -10 °C and stirred at -10 °C for 2 hours. The resultant solution was treated with 100 mL of aqueous NH₄Cl-NH₄OH (pH ~8) and the resultant mixture was stirred open to the atmosphere until the aqueous phase turned deep blue. The phases were separated and the aqueous phase was extracted with 3 x 150 mL of diethyl ether. The combined organic extracts were dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 2.50 g of crude product, which was purified by column chromatography (230-400 mesh silica gel, 6:1 petroleum ether-diethyl ether eluant, 8 cm x 25 cm column, 40 x 50 mL fractions). Removal of the solvent from the appropriate fractions gave 2.25 g (85%) of ketone 74 as a clear colourless oil.

The ketone 74 displayed:
IR (neat): 2957, 2857, 1718, 1463, 1378, 1281, 1254, 1118, 1065, 940, 839, 777, 664 cm⁻¹.

¹H NMR (400 MHz): δ = 5.58 (s, 1H, CH=C), 4.09 (m, 2H, CH₂OSi), 2.58 (dq, 1H, J = 16.5, 2.3 Hz), 2.22-2.37 (m, 3H), 2.09-2.17 (m, 1H), 2.00 (qdd, 1H, J = 6.6, 6.7, 4.9 Hz, CHCH₃), 1.88 (dq, 1H, J = 16.5, 2.4 Hz), 1.01 (s, 3H, CH₃), 0.99 (s, 3H, CH₃), 0.97 (d, 3H, J = 6.6 Hz, CHCH₃), 0.88 (s, 9H, (CH₃)₃CSi), 0.03 (s, 6H, (CH₃)₂Si).

¹³C NMR (75 MHz): δ = 212.0, 149.6, 123.3, 60.1, 54.2, 51.6, 48.5, 45.8, 37.4, 37.3, 25.9, 23.6, 19.5, 18.4, 17.4, -5.4.

LRMS (EI): m/z = 265 (64.9%, M⁺-(CH₃)₃C).

HRMS (EI): calculated for C₁₉H₃₄O₂Si (M⁺): 322.23282; found: 322.23246.

Anal. calculated for C₁₉H₃₄O₂Si: C 70.75, H 10.62; found: C 70.60, H 10.45.

Synthesis of (1R',5R',6R')-9-hydroxymethyl-1,5,6-trimethylbicyclo[4.3.0] non-8-en-3-one (133)

A 1.0 N solution of tetrabutylammonium fluoride (0.45 mL, 0.45 mmol) in THF was added to a stirred solution of the ketone 74 (71 mg, 0.22 mmol) dissolved in 2 mL of THF and the
resultant solution was stirred at rt for 18 hours. Addition of 5 mL of saturated NaHCO$_3$(aq) was followed by separation of the phases. The aqueous phase was extracted with 3 x 10 mL of diethyl ether and the combined organic extracts were dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 50 mg of crude material, which was purified by column chromatography (230-400 mesh silica gel, diethyl ether eluant, 1.5 cm x 13 cm column, 30 x 10 mL fractions). Removal of the solvent from the appropriate fractions gave 43 mg (94%) of alcohol 133, which was recrystallized from diethyl ether-hexane to give clear colourless crystals.

The keto alcohol 133 displayed:

IR (KBr disc): 3396, 3042, 2973, 2932, 2877, 1693, 1447, 1423, 1378, 1338, 1290, 1249, 1207, 1149, 1127, 1094, 1021, 998, 946, 889, 852, 820, 788, 698 cm$^{-1}$.

$^1$H NMR (400 MHz): δ = 5.63 (s, 1H CH=C), 4.02-4.14 (m, 2H, CH$_2$OH), 2.48-2.53 (dm, 1H, J = 16.8 Hz), 2.36 (s, 2H, CH$_2$CH=C), 2.14-2.25 (m, 2H), 2.04 (qdd, 1H, J = 6.6, 6.7, 6.4 Hz, CHCH$_3$), 1.85-1.92 (dm, 1H, J = 16.8 Hz), 1.63 (br. s, 1H, exchanged with D$_2$O, OH), 1.04 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 0.97 (d, 3H, J = 6.6 Hz, CHCH$_3$).

$^{13}$C NMR (75 MHz): δ = 212.6, 149.3, 124.5, 59.6, 54.3, 51.3, 48.1, 45.7, 37.7, 36.9, 23.6, 20.0, 17.2.

LRMS (EI): m/z = 208 (22.4%, M$^+$).
HRMS (EI): calculated for C_{13}H_{20}O_{2} (M^+): 208.14633; found: 208.14573.

Anal. calculated for C_{13}H_{20}O_{2}: C 74.96, H 9.68; found: C 75.05, H 9.65.

Mp.: 58-60 °C (recrystallized from diethyl ether-hexane).

The structure the keto alcohol 133 was confirmed by X-ray crystal structure analysis. The data acquired from the X-ray crystal structure analysis is collated in X-Ray Crystallographic Data.

**Synthesis of (1R^*,3R^*,5R^*,6R^*)-9-tert-butyldimethylsiloxymethyl-1,5,6-trimethylbicyclo [4.3.0] non-8-en-3-ol (141)**

![Chemical structure of 141](image)

The ketone 74 (1.71 g, 5.27 mmol) was dissolved in 50 mL of THF and the stirred solution was cooled to -78 °C. A 1.0 N solution of L-Selectride® (7.4 mL, 7.4 mmol) was added over a period of 5 minutes via syringe and the resultant solution was stirred at -78 °C for 2 hours. The pale yellow solution was treated with 20 mL of 10% NaOH(aq), 10 mL of 30% H_{2}O_{2}(aq) and then stirred for 18 hours at rt. The phases were separated and the aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic extracts were dried over MgSO_{4}. Filtration, followed by removal of the solvent in vacuo gave 1.72 g (100%) of crude alcohol 141, which was used without further purification.

The alcohol 141 displayed:
IR (neat): 3100-3600 (v. br.), 2927, 1655 (w.), 1462, 1376, 1255, 1187, 1121, 1067, 957, 938, 916, 838, 775, 736, 696, 664 cm\(^{-1}\).

\(^1\)H NMR (400 MHz): \(\delta = 5.44\) (br. s, 1H, C=CH), 4.07-4.19 (m, 2H, CH\(_2\)OSi), 4.00 (br. s, 1H, H\(_3\)eq), 2.29 (br. d, 1H, \(J = 16.1\) Hz), 1.87-1.97 (qd, 1H, \(J = 6.9, 7.1\) Hz, H\(_{5ax}\)), 1.66-1.74 (m, 2H), 1.47-1.55 (m, 3H), 1.15 (br. s, 1H, exchanged with D\(_2\)O, OH), 1.08 (s, 3H, CH\(_3\)), 0.92 (s, 3H, CH\(_3\)), 0.89 (s, 9H, (CH\(_3\))\(_3\)Si), 0.87 (d, 3H, \(J = 6.9\) Hz, CHCH\(_3\)), 0.05 (s, 6H, (CH\(_3\))\(_2\)Si).

Figure 11: Proposed conformation of alcohol 141

\(^1\)H NMR spectroscopic assignments were assisted by the results from a COSY experiment.

\(^13\)C NMR (75 MHz): \(\delta = 150.9, 121.1, 66.5, 60.6, 48.6, 48.5, 44.0, 38.5, 37.0, 30.0, 25.9, 23.7, 20.5, 18.4, 17.4, -5.4\).

LRMS (EI): m/z = 324 (6.1%, M\(^+\)).

HRMS (EI): calculated for C\(_{19}\)H\(_{36}\)O\(_2\)Si (M\(^+\)): 324.24847; found: 324.24891.

Anal. calculated for C\(_{19}\)H\(_{36}\)O\(_2\)Si: C 70.31, H 11.18; found: C 70.50, H 11.09.
Synthesis of (1R, 3R, 5R, 6S)-9-tert-butyldimethylsiloxymethyl-1, 5, 6-trimethylbicyclo [4.3.0]nonan-3-ol (167) (relative configuration at C-9 not determined)

The crude alcohol 141 (1.72 g, 5.27 mmol) was dissolved in 50 mL of ethyl acetate. Adams’ catalyst (PtO₂, 120 mg) was added and the suspension was stirred under a hydrogen atmosphere for 3 hours using an atmospheric pressure hydrogenator. The reaction mixture was filtered through a 2 cm x 5 cm column of Celite® and the column was eluted with 50 mL of ethyl acetate. Removal of the solvent in vacuo gave 1.71 g (100%) of crude alcohol 167, which was a colourless oil. The crude alcohol 167 was shown by H and C NMR spectroscopy to be a single diastereomer. This material was used in the subsequent reaction without further purification.

The alcohol 167 displayed:

IR (neat): 3100-3700 (v. br.), 2957, 1462, 1387, 1255, 1198, 1093, 953, 939, 837, 775, 670 cm⁻¹.

¹H NMR (400 MHz): 4.00-4.04 (m, 1H, CHOH), 3.62-3.69 (m, 1H, CH₂OSi), 3.41-3.48 (m, 1H, CH₂OSi), 1.76-1.88 (m, 2H), 1.10-1.70 (m, 9H (8H, when shaken with D₂O)), 0.99 (s, 3H, CH₃), 0.86-0.88 (m, 15H, CH₃, CH₃CH, (CH₃)₂CSi), 0.02 (s, 6H, (CH₃)₂Si).
$^{13}$C NMR (75 MHz): $\delta = 67.1, 66.2, 51.7, 47.2, 46.0, 44.7, 37.7, 32.2, 30.8, 26.1, 25.9, 23.5, 20.0, 18.2, 17.6, -5.4.

LRMS (EI): $m/z = 269 (4.5\%, M^+-(CH_3)C)$.

HRMS (DCI+, NH$_3$/CH$_4$): calculated for C$_{19}$H$_{39}$O$_2$Si (M$^+H$): 327.27194; found: 327.27218.

Anal. calculated for C$_{19}$H$_{38}$O$_2$Si: C 69.88, 11.74; found: C 70.12, 11.70.

**Synthesis of (1R*,3R*,5R*,6S*)-3-tert-butyldimethylsiloxy-9-tert-butyl dimethylsiloxymethyl-1,5,6-trimethylbicyclo[4.3.0]nonane (168) (relative configuration at C-9 not determined)**

![Structure of 168](image)

The crude alcohol 167 (1.71 g, 5.27 mmol) and imidazole (1.07 g, 15.7 mmol) were dissolved in 50 mL of methylene chloride and the stirred solution was cooled to 0 °C. Solid tert-butylchlorodimethylsilane (1.58 g, 10.48 mmol) was added and the white suspension that formed was stirred at rt for 18 hours. Addition of 50 mL of H$_2$O was followed by separation of the phases. The aqueous phase was extracted with 3 x 50 mL of methylene chloride. The combined organic extracts were dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 2.31 g (100%) of crude disilyl ether 168, which was shown by $^1$H and $^{13}$C
NMR spectroscopy to be a single diastereomer. This material was used in the subsequent reaction without further purification.

The disilyl ether 168 displayed:

IR (neat): 2926, 1472, 1387, 1255, 1197, 1072, 974, 939, 897, 836, 774, 702, 671 cm⁻¹.

¹H NMR (400 MHz): δ = 3.92 (p, 1H, J = 3.6 Hz, CHOSi), 3.64-3.69 (m, 1H, one of CH₂OSi), 3.41-3.47 (m, 1H, one of CH₂OSi), 1.78-1.88 (m, 2H), 1.65-1.75 (m, 1H), 1.57-1.64 (m, 1H), 1.33-1.46 (m, 5H), 1.15-1.24 (m, 1H), 0.99 (s, 3H, CH₃), 0.82-0.88 (m, 24H, (CH₃)₃CSi, (CH₃)₂CSi, CH₃, CH₃CH), 0.01 (s, 6H, (CH₃)₂Si), -0.01 (s, 6H, (CH₃)₂Si).

¹³C NMR (75 MHz): 67.7, 66.7, 52.4, 47.3, 46.9, 44.8, 38.4, 31.3, 30.4, 26.3, 25.94, 25.87, 23.4, 19.8, 18.3, 18.1, 17.6, -4.9, -5.3.

LRMS (EI): m/z = 383 (24.6%, M⁺-(CH₃)C).

HRMS (DCI+, NH₃/CH₄): calculated for C₂₅H₅₃O₂Si₂ (M⁺H): 441.35840; found: 441.35941.
Synthesis of \((1R^*,3R^*,5R^*,6R^*)\)-3-tert-butyldimethylsiloxyl-9-hydroxymethyl-1,5,6-trimethyl bicyclo[4.3.0]nonane (169) (relative configuration at C-9 not determined)

To a stirred solution of the crude disilyl ether 168 (2.31 g, 5.27 mmol) in 50 mL of THF was added a 1.0 N solution of tetrabutylammonium fluoride in THF (5.27 mL, 5.27 mmol). The resultant solution was stirred for 18 hours at rt. Addition of 50 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 50 mL of diethyl ether. The combined organic extracts were dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 1.62 g of crude product, which was purified by column chromatography (230-400 mesh silica gel, 3:1 petroleum ether-diethyl ether eluant, 5 cm x 20 cm column, 30 x 50 mL fractions). Removal of the solvent from the appropriate fractions gave 1.41 g (81% from alcohol 141) of alcohol 169. This material was shown by \(^1\)H and \(^13\)C NMR spectroscopy to be a single diastereomer.

The alcohol 169 displayed:

IR (neat): 3150-3600 (v. br.), 2931, 1461, 1378, 1253, 1194, 1068, 973, 939, 897, 835, 772, 706, 670, 655 cm⁻¹.

\(^1\)H NMR (400 MHz): \(\delta = 3.93 \text{ (p, } 1\text{H, } J = 3.5 \text{ Hz, CHOSi)}\), 3.74-3.81 (m, 1H, one of CH₂OH), 3.42-3.49 (m, 1H, one of CH₂OH), 1.83-1.97 (m, 2H), 1.62-1.78 (m, 2H), 1.20-1.45 (m, 6H),
1.10-1.20 (m, 1H, exchanged with D₂O, OH), 1.04 (s, 3H, CH₃), 0.83-0.87 (m, 15H, (CH₃)₃Si, CH₃, CH₂CH), 0.00 (s, 6H, (CH₃)₂Si).

¹³C NMR (75 MHz): δ = 67.7, 67.5, 52.8, 47.4, 46.8, 44.9, 38.2, 31.0, 30.3, 26.4, 25.8, 23.3, 19.8, 18.1, 17.5, -5.0.

LRMS (DCI+, NH₃/CH₄): m/z = 327 (1.27%, M⁺).

HRMS (DCI+, NH₃/CH₄): calculated for C₁₉H₃₉O₂Si (M⁺H): 327.27194; found: 327.27160.

Anal. calculated for C₁₉H₃₈O₂Si (M⁺): C 69.88, 11.74; found: C 70.12, H 11.76.

Synthesis of (1R*,3R*,5R*,6R*)-3-tert-butyldimethylsiloxy-9-formyl-1,5,6-trimethyl bicyclo[4.3.0]nonane (170) (relative configuration at C-9 not determined)

A 2.0 N solution of oxalyl chloride in methylene chloride (2.37 mL, 4.75 mmol) was added to 25 mL of methylene chloride and the stirred solution was cooled to -60 °C. DMSO (0.674 mL, 9.5 mmol) was added dropwise and the solution was stirred at -60 °C for 2 minutes. A solution of the alcohol 169 (1.41 g, 4.32 mmol) in 25 mL of methylene chloride was added over a period of 5 minutes via cannula. The reaction mixture was stirred for 15 minutes at -60 °C and then triethylamine (3.46 mL, 21.6 mmol) was added. The reaction mixture was stirred at -60
°C for a further 5 minutes, warmed to rt and stirred at rt for 1 hour. Addition of 50 mL of H$_2$O was followed by separation of the phases. The aqueous phase was extracted with 3 x 50 mL methylene chloride and the combined organic extracts were dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 1.38 g (98%) of aldehyde 170, which was used without further purification.

The aldehyde 170 displayed:

IR (neat): 2955, 2927, 2857, 2737, 1699, 1472, 1462, 1420, 1388, 1378, 1360, 1347, 1327, 1254, 1239, 1154, 1127, 1069, 1006, 974, 939, 897, 872, 836, 804, 773, 707, 654 cm$^{-1}$.

$^1$H NMR (400 MHz): $\delta = 9.77$ (d, 1H, $J = 2.6$ Hz, CHO), 3.97 (p, 1H, $J = 3.0$ Hz, CHOSi), 2.22-2.28 (m, 1H), 2.09-2.19 (m, 1H), 1.85-1.94 (m, 1H), 1.67-1.84 (m, 2H), 1.46-1.64 (m, 2H), 1.37-1.44 (m, 2H), 1.27-1.36 (m, 1H), 1.23 (s, 3H, CH$_3$), 0.87 (s, 9H, (CH$_3$)$_3$Si), 0.84 (d, 3H, $J = 7.1$ Hz, CHCH$_3$), 0.80 (s, 3H, CH$_3$), 0.011 (s, 3H, CH$_3$Si), 0.007 (s, 3H, CH$_3$Si).

$^{13}$C NMR (75 MHz): $\delta = 206.0, 67.9, 62.7, 49.3, 47.5, 46.0, 38.0, 30.1, 30.0, 25.8, 23.2, 20.8, 19.8, 18.0, 17.5, -5.0.$

LRMS (DCI+, NH$_3$/CH$_4$): m/z = 324 (4.1%, M$^+$).

HRMS (DCI+, NH$_3$/CH$_4$): calculated for C$_{19}$H$_{37}$O$_2$Si (M$^+$H): 325.25629; found: 325.25591.

Anal. calculated for C$_{19}$H$_{36}$O$_2$Si: C 70.31, 11.18; found: C 70.31, H 11.10.
Synthesis of $\left(1^R,3^R,5^R,6^R\right)$-3-$\beta$-butyldimethylsiloxy-9-hydroximino formyl-1,5,6-trimethylbicyclo[4.3.0]nonane (171) (diastereomers at C-9, ratio ~ 1:1)

To a stirred solution of the aldehyde 170 (48 mg, 0.15 mmol) in 3 mL of DMF was added hydroxylamine hydrochloride (51 mg, 0.74 mmol) followed by pyridine (66 µL, 0.81 mmol). The resultant solution was heated to 70 °C and stirred at 70 °C for 2 hours. The reaction mixture was then cooled to rt and 5 mL of H$_2$O was added. The phases were separated and the aqueous phase was extracted with 3 x 15 mL of diethyl ether. The combined organic extracts were dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 51 mg of crude product, which was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant, 15 mm x 12 cm column, 20 x 10 mL fractions). Removal of the solvent from the appropriate fractions gave 46 mg (92%) of the aldoxime 171, which was shown by the $^1$H NMR spectrum of the material to be a 1:1 mixture of diastereomers α to the aldoxime function. Both $E$ and $Z$ isomers of each diastereomer were also present and made for an extremely complicated $^1$H NMR spectrum, which was therefore not assigned. This mixture of diastereomers was inseparable by chromatography on silica gel and so was used in the subsequent reaction without separation.

The aldoxime 171 displayed:
IR (neat): 2960, 2950, 2910, 2860, 1656, 1462, 1379, 1360, 1254, 1196, 1159, 1110, 1067, 1006, 974, 896, 836, 806, 773, 655 cm\(^{-1}\).

LRMS (EI): \(m/z = 339\) (1%, \(M^+\))

HRMS (DCI+, \(\text{NH}_3/\text{CH}_4\)): calculated for \(\text{C}_{19}\text{H}_{38}\text{O}_2\text{NSi} (M^+\text{H})\): 340.26718; found: 340.26652.

**Synthesis of \((1R^\ast,3R^\ast,5R^\ast,6R^\ast)-3\text{-}\text{tert\text{-}butyldimethylsiloxy}-9\text{-}\text{cyano}-1,5,6\text{-}\text{trimethylbicycle\text{-}[4.3.0]}\)nonane (166) (diastereomers at C-9, ratio ~ 3:2)**

![Diagram of molecule 166]

To a stirred solution of DMAP (20 mg, 0.16 mmol) in 2 mL of methylene chloride at -10 °C was added \(\text{SOCl}_2\) (12 \(\mu\)L, 0.16 mmol) via syringe. The solution was maintained at -10 °C for 15 minutes and then a solution of the aldoxime 171 (46 mg, 0.14 mmol) in 3 mL of methylene chloride was added, followed by a further addition of DMAP (20 mg, 0.16 mmol). The resultant solution was stirred at rt for 1 hour. Addition of 5 mL of \(\text{H}_2\text{O}\) was followed by separation of the phases. The aqueous phase was extracted with 3 x 10 mL of methylene chloride and the combined organic extracts were dried over \(\text{MgSO}_4\). Filtration, followed by removal of the solvent in vacuo gave 42 mg of crude product. The crude product was purified by column chromatography (230-400 mesh silica gel, 6:1 petroleum ether-diethyl ether eluant, 10 mm x 12 cm column, 25 x 10 mL fractions). Removal of the solvent from the appropriate fractions gave 39.5 mg (91%) of the nitrile 166, a pale yellow oil, which was shown by the \(^1\text{H}\) NMR spectrum to be a 3:2 mixture of diastereomers \(\alpha\) to the nitrile function. This mixture of
diastereomers was inseparable by chromatography on silica gel and so was used in the subsequent reaction without separation.

The nitrile 166 displayed:

IR (neat): 2955, 2928, 2884, 2855, 2223, 1463, 1377, 1360, 1253, 1070, 1050, 1006, 976, 897, 834, 773, 699 cm⁻¹.

LRMS (DCI+, NH₃/CH₄): m/z = 322 (14%, M⁺H)

HRMS (DCI+, NH₃/CH₄): calculated for C₁₉H₃₆ONSi (M⁺H): 322.25662; found: 322.25632.

**Synthesis of (1S*,3R*,5R*,6R*,9S*)-3-tert-butyldimethylsiloxy-9-cyano-1,5,6,9-tetramethylbicyclo[4.3.0]nonane (172)**

![Molecule 172](image)

Diethylamine (0.051 mL, 0.046 mmol) was dissolved in 2 mL of THF and the stirred solution was cooled to -78 °C. A 1.6 N solution of n-butyllithium in hexanes (0.34 mL, 0.055 mmol) was added via syringe, the solution was warmed to 0 °C and stirred at 0 °C for 15 minutes. The solution was cooled to -78 °C and a solution of the nitrile 166 (59 mg, 0.183 mmol) in 3 mL of THF was added via cannula. The reaction mixture was warmed to 0 °C, stirred at 0 °C for 2 hours and then cooled to -78 °C. MeI (0.11 mL, 1.8 mmol) was added via syringe, the reaction
mixture was warmed to rt and stirred at rt for 18 hours. Addition of 5 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 10 mL of diethyl ether and the combined organic extracts were dried with MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 55 mg of crude product, which was purified by column chromatography (230-400 mesh silica gel, 9:1 petroleum ether-diethyl ether eluant, 2 cm x 12 cm column, 20 x 10 mL fractions). Removal of the solvent from the appropriate fractions followed by recrystallization from acetone/hexane gave 44 mg (71%) of the alkylated nitrile 172 as fine colourless crystals.

The alkylated nitrile 172 displayed:

IR (KBr disc): 3436, 2929, 2856, 2222, 1637 (w.), 1542 (w.), 1470, 1384, 1360, 1328, 1254, 1208, 1168, 1105, 1077, 1051, 1006, 980, 938, 901, 836, 807, 774, 696, 653 cm⁻¹.

¹H NMR (400 MHz): δ = 4.03 (p, 1H, J = 2.9 Hz, CHOSi), 2.35-2.45 (m, 1H), 1.86-1.94 (m, 1H), 1.68-1.81 (m, 3H), 1.20-1.45 (m, 13H, includes 3 CH₃ singlets at δ = 1.23, 1.29, 1.33), 0.87 (s, 9H, (CH₃)₃CSi), 0.83 (d, 3H, J = 6.9 Hz, CH₃CH), 0.01 (s, 6H, (CH₃)₂Si).

¹³C NMR (75MHz): δ = 127.5, 67.1, 49.3, 47.8, 46.4, 37.9, 37.9, 35.2, 30.3, 28.9, 25.8, 23.4, 22.6, 19.7, 18.0, 17.3, -5.0.

LRMS (EI): m/z = 335 (1.0%, M⁺).

HRMS (EI): calculated for C₂₀H₃₇ONSi (M⁺): 335.26443; found: 335.26398.
Anal. calculated for C$_{20}$H$_{37}$ONSi: C 71.59, H 11.12, N 4.18; found: C 71.79, H 11.15, N 4.05.

Mp.: 114-115 °C (recrystallized from acetone-hexane).

The structure of the alkylated nitrile 172 was confirmed by X-ray crystal structure analysis. The data acquired from the X-ray crystal structure analysis is collated in X-Ray Crystallographic Data.

Synthesis of (1S*,3R*,5R*,6R*,9R*)-9-benzyloxymethyl-3-tert-butyl dimethylsiloxy-9-cyano-1,5,6-trimethylbicyclo[4.3.0]nonane (173)

![Diagram of 173]

Diethylamine (348 µL, 3.11 mmol) and LiBr (59 mg, 0.68 mmol) were dissolved in 8 mL of THF and the stirred solution was cooled to -78 °C. A 1.6 N solution of n-butyllithium in hexanes (1.95 mL, 3.12 mmol) was added via syringe, the solution was warmed to 0 °C and stirred at 0 °C for 15 minutes. The solution was cooled to -78 °C and a solution of the nitrile 166 (200 mg, 0.62 mmol) in 7 mL of THF was added via cannula. The reaction mixture was warmed to 0 °C, stirred at 0 °C for 2 hours and then cooled to -78 °C. HMPA (119 µL, 0.68 mmol) was added via syringe. The pale yellow solution was warmed to 0 °C, stirred at 0 °C for 30 minutes and then cooled to -78 °C. Benzyl chloromethyl ether (650 µL, 6.2 mmol) was added via syringe, the reaction mixture was warmed to rt and stirred at rt for 18 hours. The
resultant solution was treated with 15 mL of a (10% by weight) solution of CuSO$_4$(aq) and the phases were separated. The aqueous phase was extracted with 3 x 15 mL of diethyl ether and dried over MgSO$_4$. Filtration, followed by removal of the solvent in vacuo gave 242 mg of crude product, which was purified by column chromatography (230-400 mesh silica gel, 10:1 petroleum ether-diethyl ether eluant, 3 cm x 15 cm column, 40 x 5 mL fractions). Removal of the solvent from the appropriate fractions followed by recrystallization from diethyl ether-pentane gave 44 mg (73%) of the alkylated nitrile 173 as fine white crystals.

The alkylated nitrile 173 displayed:

IR (neat): 2928, 2227, 1497, 1454, 1407, 1377, 1359, 1330, 1307, 1278, 1253, 1206, 1163, 1115, 1064, 974, 939, 899, 836, 805, 772, 738, 697 cm$^{-1}$.

$^{1}$H NMR (500 MHz): $\delta = 7.25$-$7.35$ (m, 5H, Ph), 4.61 (d, 1H, $J = 12.1$ Hz, one of OCH$_2$Ph), 4.53 (d, 1H, $J = 12.1$ Hz, one of OCH$_2$Ph), 3.96-4.00 (m, 1H, H$_3$), 3.55 (d, 1H, $J = 9.2$ Hz, one of H$_{10}$ or H$_{10'}$), 3.47 (d, 1H, $J = 9.2$ Hz, one of H$_{10}$ or H$_{10'}$), 2.25-2.38 (m, 1H), 1.86-1.95 (m, 1H), 1.66-1.79 (m, 2H), 1.20-1.55 (m, 5H), 1.46 (s, 3H, Me), 1.22 (s, 3H, Me), 0.87 (s, 9H, (CH$_3$)$_3$Si), 0.81 (d, 3H, $J = 6.9$ Hz, CHCH$_3$), 0.00 (s, 6H, (CH$_3$)$_2$Si).
\[ ^{13}C \text{ NMR} (125 \text{ MHz}): \delta = 137.7, 128.3, 127.6, 127.5, 125.8, 73.5, 73.4, 67.1, 51.8, 49.9, 48.6, 37.8, 36.7, 31.3, 30.0, 28.8, 25.8, 22.9, 21.4, 18.0, 17.3, -5.0, -5.05. \]

Mp.: 82-84 °C (recrystallized from diethyl ether-pentane).

LRMS (DCI+, NH\(_3\)): \( m/z = 384 \) (100%, C-(CH\(_3\))\(_3\)C).

HRMS (DCI+, NH\(_3\)/CH\(_4\)): calculated for \( C_{27}H_{43}O_2NSi (M^+H) \): 442.31411; found: 442.31283.

Anal. calculated for \( C_{27}H_{43}O_2NSi \): C 73.42, H 9.81, N 3.17; found: C 73.22, H 9.78, N 2.97.

**Synthesis of \((1S^*,3R^*,5R^*,6R^*,9R^*)\)-3-tert-butyldimethylsiloxy-9-cyano-9-hydroxymethyl-1,5,6-trimethylbicyclo[4.3.0]nonane (189)**

The nitrile 173 (0.200 g, 0.464 mmol) was dissolved in 15 mL of dry methanol. Ammonium formate (0.140 g) and palladium (0.460 g, 10% by weight, absorbed on to activated charcoal) were added to the stirred solution and the resultant suspension was heated to reflux for 2 hours. The suspension was cooled to room temperature and filtered through Celite® (4 cm x 4 cm cake). The Celite® was eluted with 3 x 50 mL portions of diethyl ether and the combined eluant was concentrated in vacuo. The product was recrystallized from diethyl ether-pentane to give 144 mg (91%) of fine colourless crystals of alcohol 189.
The alcohol 189 displayed:

IR (KBr disc): 3300-3150 (v. br.), 2955, 2884, 2856, 2229, 1633, 1462, 1378, 1361, 1328, 1255, 1201, 1161, 1119, 1071, 1006, 977, 939, 900, 835, 807, 773, 698, 654 cm⁻¹.

¹H NMR (400 MHz): δ = 4.03 (p, 1H, J = 2.95 Hz, CHOSi), 3.78 (dd, 1H, J = 11.2, 6.4 Hz, (upon addition of D₂O, signal simplified to a doublet, J = 11.2 Hz), one of CH₂OH), 3.65 (dd, 1H, J = 11.2, 6.4 Hz, (upon addition of D₂O, signal simplified to a doublet, J = 11.2 Hz), one of CH₂OH), 2.25-2.33 (m, 1H), 1.86-1.95 (m, 1H), 1.81-1.86 (m, 1H, exchanged with D₂O, OH), 1.72-1.81 (m, 2H), 1.47-1.32 (m, 8H, includes CH₃ singlet at δ = 1.39), 1.21 (s, 3H, CH₃), 0.87 (s, 9H, (CH₃)₃Si), 0.83 (d, 3H, J = 6.9 Hz, CHCH₃), 0.01 (s, 6H, (CH₃)₂Si).

¹³C NMR (75 MHz): δ = 125.8, 67.1, 66.3, 54.1, 50.0, 48.5, 37.8, 37.0, 30.9, 29.9, 28.8, 25.8, 23.0, 21.5, 18.0, 17.4, -5.0

Mp.: 184–185 °C

LRMS (DCI+, NH₃): m/z = 294 (30.2%, M⁺-(CH₃)₃C).

HRMS (DCI+, NH₃/CH₄): calculated for C₂₀H₃₈O₂NSi (M⁺H): 352.26717; found: 352.26600.

Synthesis of \((15^*,3R^*,5R^*,6R^*,9R^*)-3\text{-}\text{tert-}\text{butyldimethylsiloxy-}9\text{-}\text{cyano-}9\text{-}\text{formyl-}1,5,6\text{-}\text{trimethylbicyclo[4.3.0]nonane\ (190)}}

A 2.0 N solution of oxalyl chloride in methylene chloride (74 µL, 0.15 mmol) was added to 5 mL of methylene chloride and the stirred solution was cooled to -60 °C. DMSO (21 µL, 0.19 mmol) was added and the resultant colourless solution was stirred at -60 °C for 2 minutes. A solution of the alcohol 189 (47 mg, 0.13 mmol) in 5 mL of methylene chloride was added via cannula over a 5 minute period to the stirring mixture, which was maintained at -60 °C. The solution was stirred at -60 °C for 15 minutes and then triethylamine (107 µL, 0.67 mmol) was added. The resultant solution was stirred for a further 5 minutes at -60 °C, warmed to rt and then stirred for 30 minutes at rt. Addition of 10 mL of H₂O was followed by separation of the layers. The aqueous phase was extracted with 3 x 10 mL of methylene chloride and the combined organic extracts were dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 47 mg (100%) of the desired aldehyde 190, which was used without further purification.

The aldehyde 190 displayed:

IR (neat): 2966, 2937, 2898, 2247, 1735, 1602, 1464, 1381, 1257, 1219, 1214, 1208, 1071, 1054, 975, 896, 839, 700, 655, 650 cm⁻¹.
$^1$H NMR (400 MHz): $\delta = 9.48$ (s, 1H, CHO), 3.97 (p, 1H, $J = 3.0$ Hz, CHO$_2$Si), 2.68 (ddd, 1H, $J = 14.9, 11.1, 2.4$ Hz), 2.04-2.13 (m, 1H), 1.80-1.93 (m, 2H), 1.60 (s, 3H, CH$_3$), 1.48-1.12 (m, 8H, includes CH$_3$ singlet at $\delta = 1.21$), 0.83-0.85 (s + d, 12H, (CH$_3$)$_3$Si, CHCH$_3$), -0.01 (s, 3H, CH$_3$Si), -0.02 (s, 3H, CH$_3$Si).

$^{13}$C NMR (75 MHz): $\delta = 193.4, 120.5, 69.0, 66.7, 53.0, 50.4, 38.7, 37.3, 29.9, 29.4, 25.9, 25.8, 22.8, 21.9, 17.9, 17.4, -5.0, -5.1.$

LRMS (DCI+, NH$_3$): $m/z = 367$ (100%, M$^+$NH$_4$).

HRMS (DCI+, NH$_3$/CH$_4$): calculated for C$_{20}$H$_{36}$O$_2$NSi (M$^+$H): 350.25152; found: 351.25166.

**Synthesis of** (1$S^* , 3R^* , 5R^* , 6R^* , 9R^* $)-3-tert-butyldimethylsiloxy-9-cyano-9-hydroxycarbonyl-1,5,6-trimethylbicyclo[4.3.0]nonane (191)

The aldehyde 190 (47.0 mg, 0.133 mmol) and 2-methyl-2-butene were dissolved in 5 mL of t-BuOH. Sodium chlorite (121 mg, 1.33 mmol) and sodium dihydrogen phosphate (129 mg, 0.931 mmol) were dissolved in 2.5 mL of H$_2$O and the solution was added to the stirred aldehyde solution via syringe. The resultant solution was stirred at rt for 18 hours. Diethyl ether (10 mL) and H$_2$O (5 mL) were added and the phases were separated. The aqueous phase was extracted with 3 x 10 mL of diethyl ether and the combined organic extracts were dried.
over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 48 mg (99%) of the carboxylic acid 191.

The carboxylic acid 191 displayed:

IR (neat): 3700-2400 (v. br.), 2987, 2954, 2926, 2883, 2855, 2241, 1734, 1639, 1473, 1459, 1396, 1382, 1357, 1331, 1302, 1272, 1254, 1236, 1159, 1124, 1072, 1051, 1007, 979, 936, 896, 872, 834, 804, 771, 701, 675 cm⁻¹.

¹H NMR (400 MHz): δ = 4.0 (br. s, 1H, CHOSi), 2.72-2.81 (m, 1H), 2.24-2.35 (m, 1H), 1.83-1.97 (m, 2H), 1.58 (s, 3H, CH₃), 1.37-1.45 (m, 5H), 1.22 (s, 3H, CH₃), 0.84-0.87 (s + d, 12H, (CH₃)₃CSi, CHCH₃), 0.01 (s, 3H, CH₃Si), 0.00 (s, 3H, CH₃Si).

¹³C NMR (75 MHz): δ = 173.0, 121.5, 66.9, 57.7, 52.7, 50.1, 37.9, 37.4, 30.5, 30.3, 29.3, 25.8, 25.7, 22.9, 20.5, 17.3, -5.0.

LRMS (DCI+, NH₃): m/z = 384 (0.81%, M⁺NH₄).

HRMS (DCI+, NH₃/CH₄): calculated for C₂₀H₃₆O₃NSi (M⁺H): 366.24643; found: 366.24571.

Synthesis of (1S*,3R*,5R*,6R*,9R*)-3-tert-butyldimethylsiloxy-9-cyano-9-diazoacetyl-1,5,6-trimethylbicyclo[4.3.0]nonane (177)

A two necked 25 mL round bottomed flask equipped with a magnetic stirrer, a U-tube in one neck and a rubber septum in the other, was charged with a solution of the carboxylic acid 191 (40.5 mg 0.111 mmol) in 3 mL of methylene chloride. The solution was cooled to 0 °C and a 2.0 N solution of oxalyl chloride (166 µL) in methylene chloride was added, followed by DMF (15 µL). The resultant colourless solution was stirred at 0 °C for 1 hour and then the solvent was removed via the U-tube under vacuum. The remaining white solid was dissolved in 3 mL of methylene chloride and the solution was cooled to 0 °C. A freshly prepared solution of diazomethane (~195 mg) in 10 mL of diethyl ether was added via a flame polished Pasteur pipette and the resultant bright yellow solution was stirred for 20 minutes at 0 °C. The reaction mixture was warmed to rt and the solvent and diazomethane were removed by blowing with a steady stream of argon to yield 45 mg of crude product. Purification by column chromatography (230-400 mesh silica gel, 5:1 petroleum ether-diethyl ether eluant, 10 mm x 15 cm column, 20 x 15 mL fractions) yielded 36 mg (67% from alcohol 189) of the diazoketone 177.

The diazoketone 177 displayed:
IR (neat): 3127, 2930, 2857, 2228, 2114, 1745, 1646, 1350, 1254, 1204, 1155, 1071, 1053, 1008, 976, 934, 898, 872, 837, 774, 705 cm\(^{-1}\).

\(^1\)H NMR (400 MHz): \(\delta = 5.74\) (s, 1H, CHN), 3.97 (p, 1H, \(J = 3.0\) Hz, CHOSi), 2.91 (ddd, 1H, \(J = 14.6, 10.9, 2.2\) Hz), 2.10 (dt, 1H, \(J = 14.6, 9.5\) Hz), 1.79-1.91 (m, 2H), 1.53 (s, 3H, CH\(_3\)), 1.32-1.42 (m, 4H), 1.19 (s, 3H, CH\(_3\)), 1.06 (br. d, 1H, \(J = 14.2\) Hz), 0.86 (s, 9H, (CH\(_3\))\(_3\)Si), 0.83 (d, 3H, \(J = 6.9\) Hz, CHCH\(_3\)), 0.00 (s, 3H, CH\(_3\)Si), -0.01 (s, 3H, CH\(_3\)Si).

LRMS (DCI+, NH\(_3\)): \(m/z = 407\) (23.2%, M\(^+\)NH\(_4\)).

HRMS (DCI+, NH\(_3\)/CH\(_4\)): calculated for C\(_{21}\)H\(_{39}\)O\(_2\)N\(_4\)Si (M\(^+\)NH\(_4\)): 407.28424; found: 407.28437.

Synthesis of (1R\(^*\),4R\(^*\),7R\(^*\),8R\(^*\),10R\(^*\),11S\(^*\))-10-tert-butyldimethylsiloxo-4-cyano-7,8,11-trimethyltricyclo[5.3.1.0\(^{4,11}\)]undec-3-one (178)\(^{127}\)

![Chemical Structure](image)

To a stirred solution of dimeric rhodium acetate (0.1 mg) in 5 mL of methylene chloride was added, over a 2 hour period using a syringe pump, a solution of the diazoketone 177 (75 mg, 0.19 mmol) in 5 mL of methylene chloride. The pale green solution was stirred at rt for 72 hours and then the solvent was removed in vacuo. The resultant pale green solid was purified by column chromatography (230-400 mesh silica gel, 4:1 petroleum ether-diethyl ether eluant,
10 mm x 15 cm column, 20 x 10 mL fractions). Removal of the solvent from the appropriate fractions, followed by recrystallization from diethyl ether:pentane, gave 49 mg (72%) of the tricyclic keto nitrile 178 as fine colourless crystals.

The tricyclic keto nitrile 178 displayed:

IR (neat): 3020, 2957, 2930, 2858, 2220, 1751, 1637, 1603, 1559, 1541, 1508, 1460, 1391, 1256, 1219, 1213, 1095, 1060, 973, 887, 839, 786, 781, 776, 770, 765, 760, 754, 747, 741, 737, 731, 678, 670 cm⁻¹.

¹H NMR spectroscopic assignments were assisted by the results from COSY, HMBC, HMQC and a series of ¹H decoupling experiments.

¹H NMR (500 MHz in C₆D₆): δ = 3.43-3.47 (m, 1H), 2.00 (td, 1H, J = 15.7, 7.4 Hz, H₅), 1.81-1.91 (m, 2H, H₂, H₈), 1.67-1.75 (m, 2H, H₅, H₈), 1.53 (dd, 1H, J = 16.5, 14.8 Hz, H₂), 1.36 (s, 3H, Me₁₁), 0.98-1.13 (m, 2H, H₉, H₈), 0.91 (s, 10H, (Me)₃CSi, H₉), 0.69-0.74 (m, 1H, H₂), 0.65 (s, 3H, Me₁₁), 0.62 (d, 3H, J = 7.0 Hz, Me₈), -0.08 (s, 3H, MeSi), -0.10 (s, 3H, MeSi).

Mp.: 156.5-157.7 °C
### Table 5: Results of decoupling experiment on compound 178

<table>
<thead>
<tr>
<th>Decoupling value $\delta$ (ppm)</th>
<th>Assignment (H$_n$)</th>
<th>Decoupling correlation in signal H$_n$ (400 MHz)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.45</td>
<td>H$_{10}$</td>
<td>H$_1$ H$_9$ H$_9'$</td>
</tr>
<tr>
<td>2.00</td>
<td>H$_5$</td>
<td>H$_5$, H$_6$ H$_6'$</td>
</tr>
<tr>
<td>1.84</td>
<td>H$_2$, H$_6$</td>
<td>H$_1$ H$_2$ H$_9$, H$_9'$; Me$_8$</td>
</tr>
<tr>
<td>1.70</td>
<td>H$_1$, H$_5'$</td>
<td>H$_2$ H$_2'$, H$_5$ H$_6$, H$_6$, H$_9$, H$<em>9'$, H$</em>{10}$</td>
</tr>
<tr>
<td>1.53</td>
<td>H$_2$</td>
<td>H$_1$, H$_2'$</td>
</tr>
<tr>
<td>1.09</td>
<td>H$_6$ H$_9'$</td>
<td>H$_1$ H$<em>8$, H$</em>{10}$</td>
</tr>
<tr>
<td>0.72</td>
<td>H$_6'$</td>
<td>H$_3$, H$<em>9$, H$</em>{6}$</td>
</tr>
<tr>
<td>0.62</td>
<td>Me$_8$</td>
<td>H$_8$</td>
</tr>
</tbody>
</table>

$^a$ Entries in this column refer to two, three and four bond H-H$_n$ correlations as determined by the $^1$H decoupling experiment.

$^{13}$C NMR (125 MHz): $\delta = 207.0$ (C$_3$), 118.8 (C$_{12}$), 68.7 (C$_{10}$), 61.2 (C$_4$), 53.7 (C$_{11}$), 49.8 (C$_1$), 49.2 (C$_7$), 42.6 (C$_2$), 36.5 (C$_3$), 32.7 (C$_9$), 32.4 (C$_6$), 30.6 (C$_8$), 25.9 ((Me)$_3$CSi), 25.5 (Me$_{11}$), 24.8 (Me$_7$), 18.1 ((Me)$_3$CSi), 17.4 (Me$_{10}$), -4.8 (MeSi), -5.0 (MeSi).

LRMS (DCI+, NH$_3$): m/z = 361 (1.14%, M$^+$).

HRMS (DCI+, NH$_3$/CH$_4$): calculated for C$_{21}$H$_{35}$O$_2$NSi (M$^+$): 361.24371; found: 361.24304.

Anal. calculated for C$_{21}$H$_{35}$O$_2$NSi: C 69.75, H 9.76, N 3.87; found: C 70.00, H 9.78, N 4.00.
<table>
<thead>
<tr>
<th>Assignment</th>
<th>COSY correlation to $H_n$ (400 MHz)$^a$</th>
<th>HMQC correlation to $C_n$ ($^{13}$C NMR, 125.8 MHz)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_{10}$</td>
<td>$H_9$ $H_9^\prime$</td>
<td>68.7 (C$_{10}$)</td>
</tr>
<tr>
<td>$H_5$</td>
<td>$H_6$ $H_6^\prime$ $H_5$</td>
<td>36.5 (C$_3$)</td>
</tr>
<tr>
<td>$H_2^\prime$ $H_8$</td>
<td>$H_1$ $H_2$ Me$_3$ $H_9$ $H_9^\prime$</td>
<td>42.6 (C$_2$), 30.6 (C$_8$)</td>
</tr>
<tr>
<td>$H_1$ $H_5$</td>
<td>$H_2$ $H_2^\prime$ $H_6$ $H_6^\prime$ $H_5$</td>
<td>49.8 (C$_1$), 36.5 (C$_3$)</td>
</tr>
<tr>
<td>$H_2$</td>
<td>$H_1$ $H_2^\prime$</td>
<td>42.6 (C$_2$)</td>
</tr>
<tr>
<td>Me$_{11}$</td>
<td></td>
<td>25.5 (Me$_{11}$)</td>
</tr>
<tr>
<td>$H_9$ $H_9^\prime$</td>
<td>$H_8$ $H_{10}$</td>
<td>32.7 (C$_9$)</td>
</tr>
<tr>
<td>$H_6$ (Me)$_3$CSi</td>
<td>$H_5$ $H_9$ $H_6^\prime$</td>
<td>32.4 (C$_6$), 25.9 ((Me)$_3$CSi)</td>
</tr>
<tr>
<td>$H_6$</td>
<td>$H_5$ $H_5^\prime$ $H_6$</td>
<td>32.4 (C$_6$)</td>
</tr>
<tr>
<td>Me$_7$</td>
<td></td>
<td>24.8 (Me$_7$)</td>
</tr>
<tr>
<td>Me$_8$</td>
<td>$H_8$</td>
<td>17.4 (Me$_8$)</td>
</tr>
<tr>
<td>MeSi</td>
<td></td>
<td>-4.8 (MeSi), -5.0 (MeSi).</td>
</tr>
<tr>
<td>MeSi</td>
<td></td>
<td>-4.8 (MeSi), -5.0 (MeSi).</td>
</tr>
</tbody>
</table>

$^a$ Entries in this column refer to two, three and four bond H-H$_n$ correlations as determined by the COSY experiment. $^b$ Entries in this column refer to one bond C-H$_n$ correlations as determined by the HMQC experiment.
<table>
<thead>
<tr>
<th>δ(mult, no. of protons, J)</th>
<th>Assignment</th>
<th>HMBC correlation to Cα</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.43-3.47 (m, 1H)</td>
<td>H10</td>
<td>30.6 (C₈), 53.7 (C₁₁)</td>
</tr>
<tr>
<td>2.00 (td, 1H, J = 15.7, 7.4 Hz)</td>
<td>H₅</td>
<td>207.0 (C₃), 118.8 (C₁₂), 61.2 (C₄) 32.4 (C₆)</td>
</tr>
<tr>
<td>1.81-1.91 (m, 2H)</td>
<td>H₂, H₈</td>
<td>207.0 (C₃), 61.2 (C₄) 53.7 (C₁₁), 49.2 (C₇),</td>
</tr>
<tr>
<td>1.67-1.75 (m, 2H)</td>
<td>H₁, H₅</td>
<td>207.0 (C₃), 68.7 (C₁₀), 61.2 (C₄), 53.7 (C₁₁), 49.2 (C₇), 42.6 (C₂), 32.7 (C₉),</td>
</tr>
<tr>
<td>1.53 (dd, 1H, J = 16.5, 14.8 Hz)</td>
<td>H₂</td>
<td>207.0 (C₃), 68.7 (C₁₀), 49.8 (C₇),</td>
</tr>
<tr>
<td>1.36 (s, 3H)</td>
<td>Me₁₁</td>
<td>61.2 (C₃), 53.7 (C₁₁), 49.8 (C₇), 49.2 (C₉),</td>
</tr>
<tr>
<td>0.98-1.13 (m, 2H)</td>
<td>H₉ H₉</td>
<td>68.7 (C₁₀), 30.6 (C₈),</td>
</tr>
<tr>
<td>0.91 (s, 10H)</td>
<td>H₆ (Me)₃CSi</td>
<td>36.5 (C₃), 25.9 ((Me)₃CSi), 25.5 (Me₁₁), 18.1 ((Me)₃CSi), 17.4 (Me₈),</td>
</tr>
<tr>
<td>0.69-0.74 (m, 2H)</td>
<td>H₆</td>
<td>61.2 (C₄), 53.7 (C₁₁), 49.2 (C₇), 17.4 (Me₈),</td>
</tr>
<tr>
<td>0.65 (s, 3H)</td>
<td>Me₇</td>
<td>53.7 (C₁₁), 49.2 (C₇), 32.4 (C₉), 30.6 (C₈), 17.4 (Me₃),</td>
</tr>
<tr>
<td>0.62 (d, 3H, J = 7.0 Hz)</td>
<td>Me₈</td>
<td>49.2 (C₇), 32.7 (C₉), 30.6 (C₈)</td>
</tr>
<tr>
<td>-0.08 (s, 3H)</td>
<td>MeSi</td>
<td>-4.8 (MeSi), -5.0 (MeSi)</td>
</tr>
<tr>
<td>-0.10 (s, 3H)</td>
<td>MeSi</td>
<td>-4.8 (MeSi), -5.0 (MeSi)</td>
</tr>
</tbody>
</table>

* Entries in this column refer to two, three and four bond C-Hₙ correlations as determined by the HMBC experiment
Synthesis of (1R*,3S*,4R*,7R*,8R*,10R*,11S*)-10-tert-butyldimethylsiloxy-4-isothiocyanomethyl-3-triethylsiloxy-7,8,11-trimethyltricyclo[5.3.1.0^4,11] undecane (222)\(^{95}\)

![Chemical Structure Image]

Step 1: \(\text{LiAlH}_4\) reduction of the tricyclic keto nitrile 178 to give the amino alcohol 217

The tricyclic keto nitrile 178 (44 mg, 0.12 mmol) was dissolved in 5 mL of THF and the solution was added over 15 minutes via cannula to a stirred solution-suspension of \(\text{LiAlH}_4\) (69 mg, 1.8 mmol) in 5 mL of THF at \(-78\) °C. The resultant grey suspension was heated to reflux for 3 hours. Cooling of the reaction mixture to 0 °C was followed by careful sequential addition of \(\text{H}_2\text{O}\) (69 \(\mu\)L), \(\text{NaOH}_{(aq)}\) (69 \(\mu\)L, 15% by weight) and \(\text{H}_2\text{O}\) (207 \(\mu\)L). The cloudy white suspension was stirred vigorously for 2 hours and the resultant grey granular suspension was filtered through a 3 cm x 3 cm column of Celite\(^\circledast\). The Celite\(^\circledast\) column was eluted with 100 mL of diethyl ether. Removal of the solvent in vacuo gave 46 mg of a pale yellow oil which was used immediately without further purification or characterization.
Step 2: TES protection of the amino alcohol 217 to give the amino silyl ether 187.

The pale yellow oil from step 1 and imidazole (62 mg, 0.92 mmol) were dissolved in 10 mL of methylene chloride and the stirred solution was cooled to 0 °C. TESCl was added over 5 minutes via syringe and the resultant white suspension was stirred at rt for 18 hours. Addition of 10 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 10 mL of methylene chloride and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 60 mg of a pale yellow oil which was used immediately without further purification or characterization.

Step 3: Conversion of the amine function to an isothiocyanate to give the tricyclic isothiocyanate 222

The pale yellow oil from step 2 was dissolved in 5 mL of methylene chloride and the solution was added to a cold (-10 °C) solution of carbon disulfide (2 mL) and DCC (25 mg, 0.12 mmol) in 5 mL of methylene chloride at 0 °C via cannula. The resultant solution was stirred at -10 °C for 30 minutes. Addition of 15 mL of H₂O was followed by separation of the phases. The aqueous phase was extracted with 3 x 10 mL of methylene chloride and dried over MgSO₄. Filtration, followed by removal of the solvent in vacuo gave 62 mg of a pale yellow oil, which
was purified by column chromatography (230-400 mesh silica gel, 40:1 petroleum ether-diethyl ether eluant, 20 mm x 15 cm column, 20 x 10 mL fractions). Removal of the solvent from the appropriate fractions gave 46 mg (72% from tricyclic keto nitrile 178) of isothiocyanate 222 as a clear colourless oil.

The isothiocyanate 222 displayed:

IR (neat): 2954, 2929, 2879, 2857, 2189, 2106, 1462, 1437, 1377, 1336, 1281, 1250, 1213, 1129, 1068, 1044, 1010, 976, 958, 882, 835, 773, 735, 663 cm\(^{-1}\).

\(^1\)H NMR (400 MHz): \(\delta = 3.80-3.84 \text{ (m, 2H, 2 x CHOSi), 3.52 (d, 1H, } J = 14.5 \text{ Hz, one of CH}_2\text{N), 3.46 (d, 1H, } J = 14.5 \text{ Hz, one of CH}_2\text{N), 2.25-2.33 (m, 1H), 1.90-2.00 (m, 1H), 1.61-1.72 (m, 3H), 1.52-1.72 (m, 8H (includes 3H singlet at } \delta = 1.53), 0.94 \text{ (t, 9H, } J = 7.9 \text{ Hz, (CH}_3\text{CH}_2)_3\text{Si), 0.90 (s, 3H, CH}_3\text{), 0.87 (s, 9H, (CH}_3\text{)_3CSi), 0.81 (d, 3H, } J = 6.9 \text{ Hz, CHCH}_3\text{), 0.59 (q, 6H, } J = 7.9 \text{ Hz, (CH}_3\text{CH}_2)_3\text{Si), 0.01 (s, 3H, CH}_3\text{Si), 0.00 (s, 3H, CH}_3\text{Si).}

\(^13\)C NMR (75 MHz): \(\delta = 128.8, 75.1, 69.4, 59.7, 51.6, 51.0, 50.7, 49.6, 38.1, 34.1, 32.4, 30.0, 27.2, 25.8, 25.0, 22.7, 18.0, 17.3, 6.9, 5.0, -5.0.

LRMS (DCI+, NH\(_3\)): \(m/z = 524 (18.99\%, \text{ M}'\text{H}).

HRMS (DCI+, NH\(_3\)/CH\(_4\)): calculated for C\(_{28}\)H\(_{54}\)O\(_2\)NSi\(_2\)S (M'\text{H}): 524.34137; found: 524.34105.
Synthesis of (1R',3S',4R',7R',8R',10R',11S')-10-tert-butyldimethylsiloxy-4,7,8,11-tetramethyl-3-triethylsilyloxytricyclo[5.3.1.0^4,11]undecane (224)

The isothiocyanate 222 (32 mg, 0.061 mmol) and Bu₃SnH (118 µL, 0.439 mmol) were dissolved in 10 mL of toluene and the solution was heated to reflux. A solution of AIBN (29 mg, 0.177 mmol) in 5 mL of toluene was added to the refluxing solution over a period of 72 hours using a syringe pump. The solvent was removed under vacuum and the product was purified by column chromatography (230-400 mesh silica gel, pentane eluant, 20 mm x 10 cm column, 20 x 10 mL fractions). Removal of the solvent from the appropriate fractions gave 18 mg (63%) of the tricyclic disilyl ether 224 and 4 mg (14%) of the intermediate isonitrile, which was converted to tricyclic disilyl ether 224 by a repeat of the reduction procedure.

The tricyclic disilyl ether 224 displayed:

IR (neat): 2951, 2877, 1463, 1385, 1252, 1128, 1098, 1005, 965, 886, 865, 835, 773, 726 cm⁻¹.

¹H NMR (500 MHz): δ = 3.83 (br. s, 1H, H₁₀), 3.51 (dd, 1H, J = 11.0, 5.9 Hz, H₃), 2.33 (dd, 1H, J = 12.3, 8.6 Hz, H₂), 1.87-1.97 (m, 1H, H₅), 1.58-1.64 (m, 1H, H₈), 1.45-1.57 (m, 3H, H₆, H₇, H₉), 1.20-1.28 (m, 2H, H₂ H₉), 1.05-1.14 (m, 2H, H₃, H₄), 0.99 (s, 3H, Me₁₁), 0.95 (s, 3H, Me₄), 0.94 (t, 9H, J = 8.0 Hz, (CH₃CH₂)₂Si), 0.87 (s, 12H, Me₇, (Me₃CSi), 0.79 (d, 3H, J = 6.9 Hz, Me₈), 0.56 (q, 6H, J = 8.0 Hz, (CH₃CH₂)₂Si), 0.00 (s, 3H, MeSi), -0.01 (s, 3H, MeSi).
$^{13}$C NMR (125 MHz): $\delta = 80.3, 69.9, 55.5, 51.1, 51.0, 49.5, 38.6, 34.5, 32.7, 31.2, 30.3, 25.9, 25.8, 25.3, 23.2, 18.0, 17.3, 6.9, 5.1.

LRMS (DCI+, NH$_3$): m/z = 465 (0.94%, M$^+$).

HRMS (DCI+, NH$_3$/CH$_4$): calculated for C$_{27}$H$_{54}$O$_2$Si$_2$ (M$^+$): 466.36624; found: 466.36749.

Table 8: Results of COSY and nOe experiments on compound 224

<table>
<thead>
<tr>
<th>$^1$H NMR (500 MHz)</th>
<th>Assignment</th>
<th>COSY correlation to $^1$H (500 MHz)$^a$</th>
<th>nOe correlation to $^1$H (400 MHz)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta$ (mult, no. of protons, J)</td>
<td>($^1$H$_n$)</td>
<td>($^1$H$_n$)</td>
<td>($^1$H$_n$)</td>
</tr>
<tr>
<td>3.83 (br. s, 1H)</td>
<td>H$_{10}$</td>
<td>H$_1$ H$_9$</td>
<td></td>
</tr>
<tr>
<td>3.51 (dd, 1H, J = 11.0, 5.9 Hz)</td>
<td>H$_3$</td>
<td>H$_2$ H$_2^\prime$</td>
<td>H$_1$ H$_3^\prime$</td>
</tr>
<tr>
<td>2.33 (dd, 1H, J = 12.3, 8.6 Hz)</td>
<td>H$_5$</td>
<td>H$_5$ H$_6$ H$_6^\prime$</td>
<td></td>
</tr>
<tr>
<td>1.87-1.97 (m, 1H)</td>
<td>H$_8$</td>
<td>Me$_3$ H$_9$</td>
<td></td>
</tr>
<tr>
<td>1.58-1.64 (m, 1H)</td>
<td>H$_1$</td>
<td>H$_2$ H$_2^\prime$</td>
<td>See note c</td>
</tr>
<tr>
<td>1.52-1.57 (m, 1H)</td>
<td>H$_2^\prime$</td>
<td>H$_1$ H$_2$ H$_3$</td>
<td>See note c</td>
</tr>
<tr>
<td>1.45-1.52 (m, 2H)</td>
<td>H$_6$ H$_9$</td>
<td>H$_5$ H$_5^\prime$ H$_6^\prime$ H$_9^\prime$ H$_9$</td>
<td>See note c</td>
</tr>
<tr>
<td>1.20-1.28 (m, 2H)</td>
<td>H$_2$ H$_9^\prime$</td>
<td>H$_1$ H$_2$ H$_3$ H$_9$ H$_9^\prime$ H$_9$</td>
<td></td>
</tr>
<tr>
<td>1.05-1.14 (m, 2H)</td>
<td>H$_5$ H$_5^\prime$</td>
<td>H$_5$ H$_6$</td>
<td></td>
</tr>
<tr>
<td>0.94 (t, 9H, J = 8.0 Hz)</td>
<td>(CH$_3$CH$_2$)$_3$Si</td>
<td>(CH$_3$CH$_2$)$_3$Si</td>
<td></td>
</tr>
<tr>
<td>0.79 (d, 3H, J = 6.9 Hz)</td>
<td>Me$_8$</td>
<td>H$_8$</td>
<td></td>
</tr>
<tr>
<td>0.56 (q, 6H, J = 8.0 Hz)</td>
<td>(CH$_3$CH$_2$)$_3$Si</td>
<td>(CH$_3$CH$_2$)$_3$Si</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Entries in this column refer to two and three bond H-H correlations as determined by the COSY experiment.

$^b$ Entries in this column refer to proton signals that showed an enhancement on irradiation of H$_n$. It was not possible to separately irradiate these signals, therefore unambiguous results could not be obtained from these irradiations.
<table>
<thead>
<tr>
<th>δ (mult, no. of protons, J )</th>
<th>Assignment</th>
<th>HSQC correlation to C&lt;sub&gt;n&lt;/sub&gt; (1H NMR, 500 MHz)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.83 (br. s, 1H&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>H&lt;sub&gt;10&lt;/sub&gt;</td>
<td>69.8 (C&lt;sub&gt;10&lt;/sub&gt;)</td>
</tr>
<tr>
<td>3.51 (dd, 1H, J = 11.0, 5.9 Hz)</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>80.3 (C&lt;sub&gt;3&lt;/sub&gt;)</td>
</tr>
<tr>
<td>2.33 (dd, 1H, J = 12.3, 8.6 Hz)</td>
<td>H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>31.2 (C&lt;sub&gt;5&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.87-1.97 (m, 1H)</td>
<td>H&lt;sub&gt;8&lt;/sub&gt;</td>
<td>30.3 (C&lt;sub&gt;8&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.58-1.64 (m, 1H)</td>
<td>H&lt;sub&gt;1&lt;/sub&gt;</td>
<td>51.0 (C&lt;sub&gt;1&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.52-1.57 (m, 1H)</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>38.6 (C&lt;sub&gt;2&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.45-1.52 (m, 2H)</td>
<td>H&lt;sub&gt;6&lt;/sub&gt;, H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>32.7 (C&lt;sub&gt;6&lt;/sub&gt;), 34.5 (C&lt;sub&gt;9&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.20-1.28 (m, 2H)</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;9&lt;/sub&gt;</td>
<td>34.5 (C&lt;sub&gt;2&lt;/sub&gt;), 38.6 (C&lt;sub&gt;9&lt;/sub&gt;)</td>
</tr>
<tr>
<td>1.05-1.14 (m, 2H)</td>
<td>H&lt;sub&gt;5&lt;/sub&gt;, H&lt;sub&gt;6&lt;/sub&gt;</td>
<td>31.2 (C&lt;sub&gt;5&lt;/sub&gt;), 32.7 (C&lt;sub&gt;6&lt;/sub&gt;)</td>
</tr>
<tr>
<td>0.99 (s, 3H)</td>
<td>Me&lt;sub&gt;11&lt;/sub&gt;</td>
<td>23.2 (Me&lt;sub&gt;11&lt;/sub&gt;)</td>
</tr>
<tr>
<td>0.95 (s, 3H)</td>
<td>Me&lt;sub&gt;4&lt;/sub&gt;</td>
<td>25.9 (Me&lt;sub&gt;4&lt;/sub&gt;)</td>
</tr>
<tr>
<td>0.94 (t, 9H, J = 8.0 Hz)</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si</td>
<td>6.9 ((CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si)</td>
</tr>
<tr>
<td>0.87 (s, 12H)</td>
<td>Me&lt;sub&gt;7&lt;/sub&gt;, (Me)&lt;sub&gt;3&lt;/sub&gt;CSi</td>
<td>25.3 (Me&lt;sub&gt;7&lt;/sub&gt;), 25.8 ((Me)&lt;sub&gt;3&lt;/sub&gt;CSi)</td>
</tr>
<tr>
<td>0.79 (d, 3H, J = 6.9 Hz)</td>
<td>Me&lt;sub&gt;8&lt;/sub&gt;</td>
<td>17.3 (Me&lt;sub&gt;8&lt;/sub&gt;)</td>
</tr>
<tr>
<td>0.56 (q, 6H, J = 8.0 Hz)</td>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si</td>
<td>5.1 ((CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;Si)</td>
</tr>
<tr>
<td>0.00 (s, 3H), -0.01 (s, 3H)</td>
<td>(Me)&lt;sub&gt;2&lt;/sub&gt;Si</td>
<td>-4.8 (MeSi), -5.0 (MeSi)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Entries in this column refer to one bond C-H<sub>n</sub> correlations as determined by the HSQC experiment.
Table 10: Results of HMBC experiment on compound 224

<table>
<thead>
<tr>
<th>δ(mult, no. of protons, J)</th>
<th>Assignment</th>
<th>HMBC correlation to C₄ (¹H NMR, 500 MHz)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.83 (br. s, 1H)</td>
<td>H₁₀</td>
<td>no correlations</td>
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<tr>
<td>3.51 (dd, 1H, J = 11.0, 5.9 Hz)</td>
<td>H₃</td>
<td>55.5 (C₄), 31.2 (C₃), 25.9 (Me₄)</td>
</tr>
<tr>
<td>2.33 (dd, 1H, J = 12.3, 8.6 Hz)</td>
<td>H₅</td>
<td>80.3 (C₃), 55.5 (C₄), 51.1 (C₁₁), 49.5 (C₇), 32.7 (C₆)</td>
</tr>
<tr>
<td>1.87-1.97 (m, 1H)</td>
<td>H₈</td>
<td></td>
</tr>
<tr>
<td>1.58-1.64 (m, 1H)</td>
<td>H₁</td>
<td>69.3 (C₁₀), 51.1 (C₁₁), 49.5 (C₇), 34.5 (C₉), 38.6 (C₂), 23.2 (Me₁₁)</td>
</tr>
<tr>
<td>1.52-1.57 (m, 1H)</td>
<td>H₂</td>
<td>51.0 (C₁), 80.3 (C₃), 55.5 (C₄)</td>
</tr>
<tr>
<td>1.45-1.52 (m, 2H)</td>
<td>H₆ H₉</td>
<td>55.5 (C₄), 51.1 (C₁₁), 49.5 (C₇), 31.2 (C₅), 30.3 (C₈)</td>
</tr>
<tr>
<td>1.20-1.28 (m, 2H)</td>
<td>H₂ H₉</td>
<td>80.3 (C₃), 69.3 (C₁₀), 51.0 (C₁), 30.3 (C₈)</td>
</tr>
<tr>
<td>1.05-1.14 (m, 2H)</td>
<td>H₅ H₆</td>
<td>80.3 (C₃), 55.5 (C₄), 51.1 (C₁₁), 49.5 (C₇), 25.9 (Me₄)</td>
</tr>
<tr>
<td>0.99 (s, 3H)</td>
<td>Me₁₁</td>
<td>55.5 (C₄), 51.1 (C₁₁), 51.0 (C₁), 49.5 (C₇)</td>
</tr>
<tr>
<td>0.95 (s, 3H)</td>
<td>Me₄</td>
<td>80.3 (C₃), 55.5 (C₄), 51.1 (C₁₁), 31.2 (C₅)</td>
</tr>
<tr>
<td>0.94 (t, 9H, J = 8.0 Hz)</td>
<td>(CH₃CH₂)₃Si</td>
<td>5.1 ((CH₃CH₂)₃Si)</td>
</tr>
<tr>
<td>0.87 (s, 12H)</td>
<td>Me₇, (Me₃)CSi</td>
<td>51.1 (C₁₁), 49.5 (C₇), 32.7 (C₆), 30.3 (C₈), 25.8 ((Me₃)CSi), 18.0 ((Me₃)CSi)</td>
</tr>
<tr>
<td>0.79 (d, 3H, J = 6.9 Hz)</td>
<td>Me₈</td>
<td>49.5 (C₇), 34.5 (C₉), 30.3 (C₈)</td>
</tr>
<tr>
<td>0.56 (q, 6H, J = 8.0 Hz)</td>
<td>(CH₃CH₂)₃Si</td>
<td>6.9 ((CH₃CH₂)₃Si), 5.1 ((CH₃CH₂)₃Si)</td>
</tr>
<tr>
<td>0.00 (s, 3H), -0.01 (s, 3H)</td>
<td>(Me₂)Si</td>
<td>-4.8 (MeSi), -5.0 (MeSi)</td>
</tr>
</tbody>
</table>

*Entries in this column refer to two and three bond C-H correlations as determined by the HMBC experiment.
Appendix
### X-Ray Crystallographic Data.

<table>
<thead>
<tr>
<th>Compound</th>
<th>133</th>
<th>172</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Crystal Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Formula</strong></td>
<td>$C_{13}H_{20}O_2$</td>
<td>$C_{20}H_{37}NOSi$</td>
</tr>
<tr>
<td><strong>Formula Weight</strong></td>
<td>208.30</td>
<td>335.60</td>
</tr>
<tr>
<td><strong>Crystal Colour, Habit</strong></td>
<td>colourless, irregular</td>
<td>colourless, needle</td>
</tr>
<tr>
<td><strong>Crystal System</strong></td>
<td>triclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td><strong>Lattice Type</strong></td>
<td>Primitive</td>
<td>Primitive</td>
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<tr>
<td><strong>Lattice Parameters</strong></td>
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<tr>
<td>$a$ (Å)</td>
<td>7.3532(11)</td>
<td>7.1233(5)</td>
</tr>
<tr>
<td>$b$ (Å)</td>
<td>8.126(2)</td>
<td>10.5269(11)</td>
</tr>
<tr>
<td>$c$ (Å)</td>
<td>10.271(3)</td>
<td>27.9965(7)</td>
</tr>
<tr>
<td>$\alpha$ (°)</td>
<td>100.048(10)</td>
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<tr>
<td>$\beta$ (°)</td>
<td>104.486(2)</td>
<td>93.7694(5)</td>
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<tr>
<td>$\gamma$ (°)</td>
<td>92.179(3)</td>
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<tr>
<td>$V$(Å³)</td>
<td>583.0(2)</td>
<td>2094.8(2)</td>
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<tr>
<td><strong>Space Group</strong></td>
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<td>P2₁/n (#14)</td>
</tr>
<tr>
<td><strong>Z value</strong></td>
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<td>4</td>
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<tr>
<td>$D_{\text{calc}}$ (g/cm³)</td>
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<td>1.064</td>
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<td></td>
<td>( F_{000} )</td>
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<td>------------------</td>
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<tr>
<td>( \mu(\text{MoK}\alpha) ) ( (\text{cm}^{-1}) )</td>
<td>0.78</td>
<td>1.17</td>
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**B. Intensity Measurements**

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<th>Diffractometer</th>
<th>Rigaku/ADSC CCD</th>
<th>Rigaku/ADSC CCD</th>
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</thead>
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<tr>
<td>Radiation</td>
<td>MoK( \alpha \ (\lambda = 0.71069 \ \text{Å}) )</td>
<td>MoK( \alpha \ (\lambda = 0.71069 \ \text{Å}) )</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
<td>graphite monochromated</td>
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<tr>
<td>Detector Aperture</td>
<td>94 mm x 94 mm</td>
<td>94 mm x 94 mm</td>
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<tr>
<td>Data Images</td>
<td>460 exposures at 70.0 seconds</td>
<td>768 exposures at 36.0 seconds</td>
</tr>
<tr>
<td>( \phi ) oscillation range( (\chi = -90) )</td>
<td>0.0 – 190.0°</td>
<td>0.0 – 189.9°</td>
</tr>
<tr>
<td>( \omega ) oscillation range( (\chi = -90) )</td>
<td>-22.0 – 18.0°</td>
<td>-23.0 – 17.8°</td>
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<td>Detector Position (mm)</td>
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<td>Detector Swing Angle</td>
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<td>-10°</td>
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<tr>
<td>( 2\theta_{\text{mu}} )</td>
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</tr>
<tr>
<td></td>
<td>Unique 2513( R_{\text{int}} = 0.032 )</td>
<td>Unique 5544( R_{\text{int}} = 0.075 )</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization Absorption/scaling (trans. factors: 0.463 – 1.0060)</td>
<td>Lorentz-polarization Absorption/decay/scaling (corr. factors: 0.8258 – 1.0000)</td>
</tr>
<tr>
<td></td>
<td>Secondary Extinction (coefficient: 1.15(11) ( \times 10^{-5} )</td>
<td></td>
</tr>
</tbody>
</table>
### C. Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Structure Solution</th>
<th>Direct Methods (SIR92)</th>
<th>Direct Methods (SIR92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refinement</td>
<td>Full-matrix least squares</td>
<td>Full-matrix least squares</td>
</tr>
<tr>
<td>Function minimized</td>
<td>$\sum w \left( \left</td>
<td>F_o^2 \right</td>
</tr>
<tr>
<td>Least Squares Weights</td>
<td>$w = \left( \sigma^2(F_o^2) \right)^{-1}$</td>
<td>$w = \left( \sigma^2(F_o^2) \right)^{-1}$</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations</td>
<td>2513</td>
<td>5544</td>
</tr>
<tr>
<td>No. Variables</td>
<td>217</td>
<td>208</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>11.58</td>
<td>26.65</td>
</tr>
<tr>
<td>Residuals (on $F^2$, all data)</td>
<td>0.081; 0.084</td>
<td>0.120; 0.084</td>
</tr>
<tr>
<td>$R; R^w$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>1.76</td>
<td>1.58</td>
</tr>
<tr>
<td>No. Observations ($I&gt;3\sigma(I)$)</td>
<td>1369</td>
<td>2033</td>
</tr>
<tr>
<td>Residuals (on $F$, $I&gt;3\sigma(I)$)</td>
<td>0.045; 0.040</td>
<td>0.049; 0.038</td>
</tr>
<tr>
<td>$R; R^w$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Maximum Peak in Final Diff. Map</td>
<td>0.29 e$^-$/Å$^3$</td>
<td>0.68 e$^-$/Å$^3$</td>
</tr>
<tr>
<td>Minimum Peak in Final Diff. Map</td>
<td>-0.28 e$^-$/Å$^3$</td>
<td>-0.83 e$^-$/Å$^3$</td>
</tr>
</tbody>
</table>
References


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