STUDIES ON THE STEREOCONTROLLED
SYNTHESIS OF MEDIUM RING COMPOUNDS

ALISON E. THOMAS

UNIVERSITY OF LEICESTER
The accompanying thesis submitted for the degree of PhD entitled 'Studies on the Stereocontrolled Synthesis of Medium Ring Compounds' is based on work by the author in the Department of Chemistry of the University of Leicester mainly during the period between October 1986 and September 1989.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by reference. None of the work has been submitted for another degree in this or any other university.

Signed: A.E. Thomas. Date: 5.9.92
ACKNOWLEDGEMENT

I am deeply indebted to all concerned for their support and encouragement during my studies.

Special thanks are accorded to my supervisor Dr. P. R. Jenkins for his advice and able assistance during the period of my research, Dr. R. Bowie and Dr. G. Robinson of I.C.I. Pharmaceuticals, Macclesfield for their welcome and assistance, and Dr. P. Kenney for the molecular modelling studies. Additionally, I am most grateful to Sue Booth for printing the diagrams, and my father for his assistance with the production of this manuscript.

I was fortunate to have undertaken my studies in a convivial environment fostered by my fellow students and staff in the Chemistry Department at Leicester University. The period on site at I.C.I. was no less enjoyable as I was made most welcome and availed of all the support needed. I thank all persons concerned.

Finally, I am indebted to my family for their wholehearted support and commitment throughout my studies.
ABSTRACT

Several approaches towards the synthesis of an acyclic molecule possessing one chiral centre along with suitable functionality to enable cyclisation to a medium ring were investigated. The intramolecular cyclisation reaction would create a second chiral centre so that two diastereoisomeric products would be possible. Potential cyclisation reactions appeared to include allylsilane - aldehyde and allyl tin - aldehyde cyclisations.

The first route attempted involved the coupling of an oxygen protected ω-hydroxy-aldehyde with 3,3-diethoxy-2-bromopropene via a Grignard reaction or an alkyl lithium reaction, to generate the first chiral centre.

A slight variation was also investigated. In this second case the key reaction to form the first chiral centre was the reaction of an oxygen protected ω-hydroxy-α-bromoalkane with 2-(trimethylsilyl)methyl-2-propenal via a Grignard reaction.

A third approach to the key reaction to introduce the first chiral centre involved the reaction of 2-bromo-3-(trimethylsilyl)propene with an oxygen protected ω-hydroxy-aldehyde via Grignard reaction. The products of this reaction then underwent further reactions to generate acyclic molecules containing both allylsilane and aldehyde functionality mediated intramolecular allylsilane - aldehyde cyclisations were then performed. The reaction did not appear to be very stereoselective for the simple molecules which were investigated, as in all cases the diastereoisomer ratios were approximately 1:1.

In an attempt to synthesise heterocyclic medium rings an intramolecular acetal initiated allylsilane cyclisation in the presence of Lewis Acid was investigated. It appeared that with the tetrahydropyranyl ethers which were investigated, deprotection of the alcohol group occurred with loss of Thp in preference to breaking of the alternative C-O bond which would have led to cyclisation and the formation of medium ring ethers.
# LIST OF CONTENTS

## CHAPTER 1: INTRODUCTION

1.1 Strain in Medium Rings and Cyclisation ........................................... 1  
1.2 Conformations of Medium Rings .................................................. 5  
1.3 Cyclisation Reactions
   1.3.1 Intramolecular Diels-Alder Reaction .................................. 10  
   1.3.2 An Intramolecular Allyltin-Aldehyde Cyclisation ............... 10  
   1.3.3 An Intramolecular Allylsilane-Aldehyde Cyclisation .......... 11  
1.4 Literature Medium Ring Syntheses ............................................. 14  
   1.4.1 Ring Expansions and Contractions .................................. 14  
   1.4.2 Cycloaddition Reactions .................................................. 22  
   1.4.3 Medium Ring Ethers ..................................................... 25  
   1.4.4 Cyclisations Involving Allylsilanes ................................ 27  
   1.4.5 Other Medium Ring Syntheses ......................................... 32  

## CHAPTER 2: ATTEMPTED ALDEHYDE-BROMOALKENE COUPLING

2.1 Introduction .................................................................................. 39  
2.2 Results and Discussion ............................................................... 41  

## CHAPTER 3: ATTEMPTED GRIGNARD SYNTHESIS OF AN ACYCLIC PRECURSOR

3.1 Introduction .................................................................................. 48  
3.2 Results and Discussion ................................................................ 51  

LIST OF CONTENTS (Continued)

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 4:</td>
<td>INTRAMOLECULAR ALLYLSILANE-ALDEHYDE CYCLISATION</td>
<td></td>
</tr>
<tr>
<td>4.1</td>
<td>Introduction</td>
<td>56</td>
</tr>
<tr>
<td>4.2</td>
<td>Results and Discussion</td>
<td>58</td>
</tr>
<tr>
<td>CHAPTER 5:</td>
<td>ATTEMPTED ACETAL-INITIATED ALLYLSILANE CYCLISATION</td>
<td></td>
</tr>
<tr>
<td>5.1</td>
<td>Introduction</td>
<td>85</td>
</tr>
<tr>
<td>5.2</td>
<td>Results and Discussion</td>
<td>86</td>
</tr>
<tr>
<td>EXPERIMENTAL</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>REFERENCES</td>
<td></td>
<td>147</td>
</tr>
</tbody>
</table>
ABBREVIATIONS

D.M.A.P.  4-dimethylaminopyridine
DME     1,2-dimethoxyethane
TMS     trimethylsilyl
THF     tetrahydrofuran
Thp     tetrahydropyranyl
P.P.T.S. pyridinium p-toluenesulphonate
p.c.c.  pyridinium chlorochromate
DMF     dimethyl formamide
HMPA    hexamethylphosphoramide
TMSOTf  trimethylsilyltriflate
DBU     1,8-diazabicyclo [5.4.0] undec-7-ene
TBDMS   tertiary butyldimethylsilyl
COD     cyclooctadiene
Red Al  3.4M solution of bis(2-methoxyethoxy)aluminium hydride in toluene
MEM     methoxyethoxymethyl
CHAPTER 1

INTRODUCTION
CHAPTER 1

INTRODUCTION

Medium size rings (those containing between 8 and 12 atoms in the ring) are found in many important natural products. Compounds containing an 8-membered carbocyclic ring include the taxane series\(^1\), ophiobolin\(^2\) and fusicoccin\(^3\).

\[
\text{OAcAcO}
\begin{array}{c}
\text{Ph} \\
\end{array}
\text{OAc}
\]

\text{Taxinine}

\[
\text{HO RO}
\begin{array}{c}
\text{Me} \\
\end{array}
\text{O}
\]

\text{Fusicoccin}

\[
\text{HO Me}
\begin{array}{c}
\text{Me} \\
\end{array}
\text{O}
\]

\text{Ophiobolin}

Few total syntheses of these compounds have been achieved, which may be due to a lack of methods for the stereocontrolled synthesis of the medium rings that they contain. Therefore, it is the aim of this work to develop such methods, which could then ultimately be applied to the synthesis of these target structures.

1.1 Strain in Medium Rings and Cyclisation\(^4\)

A comparison of the stability of a cycloalkane relative to that of cyclohexane may be derived from their heats of combustion. For any cycloalkane \((\text{CH}_2)_n\) the enthalpy excess relative to that for a ring composed of \(n\) \(\text{CH}_2\) units of cyclohexane is given by:
Enthalpy excess = -(\(\Delta H(n) - \Delta H(C_6H_{12})\)) / 6

where \(\Delta H(n)\) is the heat of combustion of the cycloalkane \((CH_2)_n\) and \(\Delta H(C_6H_{12})\) that for cyclohexane. These results are tabulated as follows:

\[
\begin{array}{ccccccccccc}
 n & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 & 11 & 12 \\
 enthalpy excess & 27.6 & 26.0 & 6.5 & 0 & 6.3 & 9.6 & 12.6 & 12.0 & 11.0 & 3.6 \\
 Kcal/mol & \\
\end{array}
\]

This shows that cyclohexane is the most stable of the cycloalkanes, and that the medium ring hydrocarbons are significantly less stable. How does this strain arise? Looking at the values for the small rings \((n=3,4)\) it can be seen that these are highly strained and this can be explained by "Baeyer Strain Theory" which was proposed by the German chemist in 1885. He suggested that the normal angles between the four valences of a tetrahedral carbon atom are 109° 28' whereas the internal angles of regular polygons containing 3, 4, 5 and 6 members are 60°, 90°, 108°, and 120° respectively. Thus, cyclopropane and cyclobutane molecules would be strained because of the distortion of the C-C-C angle from the tetrahedral value. Later, quantum mechanical calculations showed that orbitals of 1st. row elements could not have angles of less than 90°, and so it was proposed that the bonding orbitals in cyclopropane were not pointed directly at each other but at angles of 22° outside the equilateral triangle, giving an angle between the orbitals of 104°, thus reducing overlap and making them more strained.

Clearly in medium rings the opposite situation would arise, i.e. widened bond angles, however this strain is less severe in medium rings, which can lose planarity to accommodate the tetrahedral angle. Another possible source of increased strain (reduced stability) is torsional or Pitzer strain, caused by partial butane interactions of a syn-periplanar or anticalinal type. This is most clearly illustrated for the case of n-butane.
Clearly conformation 4 will be of highest energy since non-bonded repulsion between the two methyl groups is at a maximum.

A final possible source of strain arises through non-bonded interactions between hydrogen atoms across the ring (transannular interactions). This arises when two atoms across a ring are closer together than the sum of their van der Waal's radii (2.4Å for two H's). This can be seen in the boat-chair-boat conformation of cyclodecane.

A consequence of this structural feature of medium ring compounds is the occurrence of transannular 1,5- and 1,6- hydride shifts. This can be illustrated by the following reaction of cis-cyclo-octene epoxide (1) with heated formic acid.

As well as the 'expected' product (2), the formation of products (3), (4) and (5) can be explained by either a 1,5- or 1,3- hydride shift which would in either case lead to the
same ion, from which products (3), (4) and (5) could be formed. However, this alone cannot explain the fact that (3) is formed solely as the cis diol. To explain this, the involvement of bridged 'non-classical' ions is suggested.

Deuterium labelling experiments have shown that 61% of the cis-1,4-cyclo-octane-diol is produced via 1,5-hydride shift and 39% via 1,3-hydride shift.

As well as the strain of a medium, or any, sized ring there is another problem to overcome in the successful formation of a ring via a ring closure reaction. This is the chance of near approach of the groups which must react together to form the ring. As early as 1926 Ruzicka suggested that these two factors could be summated to give results which closely correspond to experimental observations.
However, he assumed that strain for all rings larger than 5-membered is constant, which is not the case.

A comparison of three cyclisation reactions in terms of yield vs ring size is shown on the following graph.

This illustrates the difficulty of forming medium size rings.

1.2 Conformations of Medium Rings

Macrocyclic compounds are capable of existing in a number of stable conformations, but only a few of these are low enough in energy to be appreciably populated at normal temperatures. The lowest energy conformations of the 7-10 membered cycloalkanes are shown below\textsuperscript{5}.
Although cyclooctane exists predominantly in the boat chair conformation, it has been shown\(^6\) that at room temperature, 6% exists in a crown family conformation. There are three conformations in the crown family.

Still and Galynker\(^7\) have shown that the conformational preference of medium rings has a profound effect on the stereochemistry of their reactions. In their work they use an alternative to absolute stereochemical control, i.e. the use of enantiomerically pure starting material, resolution of an intermediate, or asymmetric induction by an enantiomerically pure reagent. Instead, the stereoselectivity of the reaction is directed by pre-existing substrate chirality which may be quite distant from the reaction site. Control arises from a conformational bias, such as is found in cyclohexane-derived systems where there are axial-equatorial preferences. Conformational biasing is a general property of macrocyclic
compounds and arises because of their tendency to minimise transannular non-bonded repulsions.

In medium-ring compounds, substituents usually prefer the pseudoequatorial environments. Calculations on the energy cost of moving a methyl group into a pseudoaxial position show that this is effectively forbidden as the energy differences are too large. This is except at C4 and C6 where there is no energy difference between the two positions, and this arises because of the gauche butane interaction in both the axial and equatorial sites:

![Diagram of a medium-ring compound with labels 4, 5, and 6]

In this paper, several reactions of medium rings were studied and molecular mechanics calculations were used to rationalise the observed stereoselectivities. In all cases the calculations of the diastereoisomer ratios agreed with the experimentally observed ratios. One of the reactions that they studied was the kinetic alkylation of the mono-methyl substituted 8-membered ring ketones. Alkylation of 2-methylcyclooctanone gave >95% 2,8-trans dimethylcyclooctanone, whereas alkylation of 3-methylcyclooctanone gave 98% cis 3,8-dimethylcyclooctanone.

1. i-Pr₂NLi / THF
2. MeI, -60°C

>95% trans

98% cis

These results were explained by consideration of the possible conformations of the intermediate enolates involved and their relative energies. These are shown as follows:
It can be seen that the relatively low energies of enolates (6) and (7) can explain the observed preference for the trans product in the 2,8-dimethylcyclooctanone. In the 3,8-dimethylcyclooctanone case there is little difference in the energies of the possible enolates, however, alkylation of (8) and (9) gives a large increase in the transannular strain, and so consideration of (10) and (11) alone or by considering the energies of all the products then a Boltzmann distribution at the reaction temperature gives the observed ratio.

The formation of these ratios of diastereoisomers appears to be related to the preferred conformation of the macrocyclic ring since in the reactions which were studied there was only a single methyl substituent on the ring to provide the conformational bias.

In this paper, experiments are being performed on a medium ring, whereas it is the aim of this project to synthesise the ring and it is hoped that the conformational preferences of the medium ring will also influence the energy of the transition state leading to ring formation. There is a precedent for this in the formation of the 8-membered ring of the taxane group of natural products where the following cyclisation was observed:

\[
\text{Me} \quad \text{Et}_2\text{AlCl} \quad \text{Me} \\
\text{O} \quad \text{H} \quad \text{O} \quad \text{H}
\]

In this cyclisation reaction the 8-membered ring is formed in its preferred boat-chair conformation to give the tricyclic product as a single diastereoisomer.

1.3 Cyclisation Reactions

To investigate whether or not the ring closure reaction is influenced by the preferred conformation of the medium ring produced, it is hoped to synthesise an acyclic precursor containing one chiral centre. Using a cyclisation which generates a second chiral centre there is the possibility of forming diastereoisomers of the product. For the reasons outlined earlier, it is hoped that the cyclised structure will be formed as a single diastereoisomer whose stereochemistry is predictable from the boat-chair conformation of the medium ring. A number of suitable reactions have been reported in the literature.
1.3.1 Intramolecular Diels-Alder Reaction

Modification of the taxane model route would enable the following cyclisation to be studied. However, this leads to the formation of a bicyclic structure:

\[
\begin{align*}
&\text{Me} \quad \text{Me} \\
&\text{O} \quad \text{O} \\
&\text{H} \quad \text{H} \\
&\text{Et}_2\text{AlCl} \\
\end{align*}
\]

1.3.2 An Intramolecular Allyltin-Aldehyde Cyclisation

Mukaiyama found that allyl iodide reacted with stannous halide under mild conditions to form allyltin dihaloiodide, which will react with carbonyl compounds in an aprotic solvent to give good yields of the corresponding homoallylic alcohol derivatives.

\[
\begin{align*}
\text{SnF}_2 & \quad \text{Aprotic solvent} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{R}_2 \\
\text{OH} \\
\text{SnF}_2 & \quad \text{Aprotic solvent} \\
\text{R}_1 & \quad \text{R}_2 \\
\text{R}_1 & \quad \text{R}_2 \\
\text{OH} \\
\end{align*}
\]

Subsequently the use of metallic tin enabled this reaction to be extended to include the reaction of allyl bromide as well as allyl iodide with carbonyl compounds.

\[
\begin{align*}
\text{Sn} & \quad \text{THF} \\
\text{H}_2\text{O} \\
\text{OH} \\
\text{Sn} & \quad \text{THF} \\
\text{H}_2\text{O} \\
\text{OH} \\
\end{align*}
\]

(X=Br, I)

Both of these reactions gave good yields of the alcohol, especially when an aldehyde rather than ketone was used, >70% in the first case, >75% in the second one. It would appear that these reactions could be used intramolecularly.
1.3.3 An Intramolecular Allylsilane-Aldehyde Cyclisation

Allylsilanes were reacted with carbonyl compounds in the presence of titanium tetrachloride\textsuperscript{11} to yield $\gamma$, $\delta$-unsaturated alcohols:

\[
\text{Me}_3\text{SiCH}_2\text{CH} = \text{CH}_2 + R^1\text{Si} - \text{CH}_2=\text{CHCH}_2\text{COHR}^1\text{R}^2 \xrightarrow{\text{TiCl}_4, \text{CH}_2\text{Cl}_2, \text{H}_2\text{O}} \text{CH}_2=\text{CHCH}_2\text{COHR}^1\text{R}^2
\]

Carbon-carbon bond formation was shown to have occurred exclusively at the $\gamma$-carbon of the allylsilane.

\[
\text{Me}_3\text{SiCHRCH} = \text{CH}_2 + R^1\text{Si} - \text{CH}_2=\text{CHCH}_2\text{COHR}^1\text{R}^2 \xrightarrow{\text{TiCl}_4, \text{CH}_2\text{Cl}_2, \text{H}_2\text{O}} \text{RCH} = \text{CHCH}_2\text{COHR}^1\text{R}^2
\]

Subsequently a similar reaction was performed in the presence of fluoride ion\textsuperscript{12}.

\[
\text{Me}_3\text{SiCH}_2\text{CH} = \text{CHR} + R^1\text{Si} - \text{CH}_2=\text{CHCH}_2\text{COHR}^1\text{R}^2 \xrightarrow{\text{TiCl}_4, \text{CH}_2\text{Cl}_2, \text{H}_2\text{O}} \text{CH}_2=\text{CHCH} = \text{CHRCOHR}^1\text{R}^2
\]

These reactions have been used in an intramolecular sense to produce 6-membered\textsuperscript{13,13a} and 5-membered\textsuperscript{14} rings.

The first example of an intramolecular allylsilane carbonyl cyclisation was reported by Sarker and Anderson\textsuperscript{13a}, when they synthesised six-membered rings.
The cyclisation occurred in the presence of Lewis acids (SnCl\textsubscript{4}, BF\textsubscript{3}.Et\textsubscript{2}O) and fluoride ion. With BF\textsubscript{3}.Et\textsubscript{2}O the ratio of the two diastereoisomers produced is 85:15 (12:13); with SnCl\textsubscript{4} the ratio is at best 60:40 (12:13) and with fluoride ion the opposite selectivity is observed, i.e. 18:82 (12:13). This difference in selectivity arises because of the different mechanisms involved.

With Lewis acid conditions, the mechanism is concerted as shown, which leads to formation of (12) as the major product. The oxygen atom of the aldehyde coordinates to the Lewis acid encouraging attack by the double bond onto this group and simultaneous transfer of the SiMe\textsubscript{3} group onto the oxygen atom. On work up the SiMe\textsubscript{3} group is replaced by a proton.

The mechanism of the fluoride ion catalysed cyclisation is likely to be a "push-pull" process, which leads to an anionic intermediate.
The fluoride ion attacks the silicon atom, so that the SiMe₃ group is removed from the molecule and the initial allylic anion formed attacks the electropositive carbon atom of the carbonyl group, creating an oxygen anion which is quenched on work up to give the alcohol (13) as the major product.

The other cyclisations reported¹³,¹⁴ were as follows:

When this second reaction was performed in the presence of Lewis Acid or fluoride ion, a mixture of diastereoisomers was produced, whereas with CF₃COOH/CH₂Cl₂ or CF₃CH₂OH (14) gave only (15), and (17) only (16). They explain this stereospecificity in terms of the likely transition states for (14), i.e. (18) and (19):

\[
\text{(18)} \\
\text{(19)}
\]

\[X = \text{SiMe}_3, Y = \text{SPh} \text{ or } X = \text{SPh}, Y = \text{SiMe}_3\]

If (18) is favoured over (19) this explains formation of the cis product.
1.4 Literature Medium Ring Syntheses

Recently, several syntheses of medium ring compounds have been reported in the literature. Many different approaches have been used to overcome the problem of forming the medium ring itself.

1.4.1 Ring Expansions and Contractions

One method which has been utilized for ring expansions is the use of radicals. Baldwin et al.\(^\text{15}\) have used a free radical mediated ring expansion of cis- and trans-α-substituted -β-stannylcyclohexanones (20) and (21) to provide efficient syntheses of cis- and trans-cyclononenones and cyclodecenones. For example, (20) when treated with catalytic AIBN and Bu$_3$SnH (10 mol %) underwent a radical chain reaction to give (22), and under identical conditions (21) reacted to give (23).

They found that the relative stereochemistry of the substituents at Cα and Cβ gave control of the alkene geometry, i.e. trans-substrates gave trans-alkenes and cis-substrates gave...
cis-alkenes. The trialkyl stannyl radical is lost via a concerted coplanar anti-elimination mechanism.

Dowd\textsuperscript{16} has developed a 1-C ring expansion of haloalkyl $\beta$-keto esters, by which method 5, 6 and 7 membered rings have been expanded to 6, 7 and 8 membered rings respectively.

They also extended this work to include expansions by three and four carbons. For example:
From their results they conclude that the mechanism involved is radical attack on the carbonyl carbon.

![Chemical reaction diagram](image)

Trost\textsuperscript{13} has developed a three carbon expansion which involves a silyl-mediated fragmentation of β-keto sulphones. Thus, a 5-membered ketone could be transformed into an 8-membered ketone via the following method:

![Chemical reaction diagram](image)

Boeckman\textsuperscript{17} recently published a synthesis of ceroplastol I, which contains a cyclooctane ring. The approach to this compound involved fragmentation of the appropriately functionalised bicyclo [3.3.1] nonanone system.
Another approach to the 5-8 fused ring system has been reported by Mehta\textsuperscript{18} in his synthesis of the marine natural product (+)-precapnelladiene. The crucial formation of the 8-membered ring was achieved via catalytic ruthenium dioxide oxidation of the tricyclic system as follows:

Several methods of synthesising medium ring lactones have been reported. The first of these is a general synthesis of medium ring lactones which is achieved via a regioselective $\beta$-scission of alkoxy radicals\textsuperscript{19}. These radicals are generated by photolysis from the hypotolides of catacondensed lactols of general structure A.

$$A$$

9-Membered lactones are synthesised from 6/5 fused lactols, 10-membered lactones from 6/6 or 7/5 fused lactols, and 11-membered lactones from 7/6 or 8/5 fused lactols.
Schore\(^{20}\) has utilised metal-promoted alkyne bending to prepare medium ring acetylenic lactones. Prior to this paper the smallest odd-numbered acetylenic lactone was 15-membered.

Complexation of the alkyne with Co\(_2\)(CO)\(_6\) removes the linearity of the alkyne bond 'bending' it to an angle of \(~140^0\). Treatment of this cobalt complexed lactone with sodium hydride in D.M.E. overnight afforded the cobalt complexed lactone in 71% yield.
The free acetylenic lactone can be isolated after oxidative removal of the cobalt.

A specific synthesis of 8-membered lactones containing a 5,6-double bond has been reported by Holmes\textsuperscript{21}. Starting from their corresponding selenoxides, vinyl ketene acetals are generated in situ in refluxing xylene and these undergo Claisen rearrangement to give the 8-membered lactone.

$$\text{SePh} \quad \text{DBU} \quad \text{MgSO}_4 \quad \text{xylene} \quad \text{reflux}$$

Both the cis and trans isomers undergo the rearrangement, the trans via an all chair transition state (24), and the cis via a boat chair (25) due to 1,3-diallal interactions that occur in the all chair, between the R group and the proton on the ring junction.

The Claisen rearrangement was also utilised by Paquette\textsuperscript{22} to synthesise annulated 4-cyclooctenones and also in the stereospecific synthesis of precapnelladiene.

[Chemical structures and reaction schemes are depicted in the text.]
Paquette$^{23}$ has used an oxy-Cope rearrangement to produce the 5-8-5 carbocyclic framework found in many natural products such as the ophiobolins.

Silicon has been used to direct a one-carbon ring enlargement reaction$^{24}$. The silyl group influences the rearrangement step so that the β-silicon stabilised cationic species is formed.
The TMS group is not lost and 1,2-hydride shift occurs to give the product.

For the three ring sizes used (6,8,12) the yields from (26), (27) and (28) were respectively 100%, 97% and 85% when X=OPh.

One method reported in the literature has made use of a ketone enolate reacting with an ester carbonyl in an intramolecular cyclisation.

The alternative transition state which would have given the alternative 3(2H)-furanone, involves the conformationally restricted aldolate which has non-bonded interactions between the protons on C3 and C4:
1.4.2 Cycloaddition Reactions

As mentioned previously, the intramolecular Diels-Alder reaction can be used to generate the 6-8 fused ring system. An extension to this work has recently been reported. The precursor for the Diels-Alder reaction now possesses three methyl groups present in the natural product taxinine.

\[
\begin{align*}
\text{As previously, the 8-membered ring is formed in the boat-chair conformation.}
\end{align*}
\]

Shea has also used an intramolecular Diels-Alder cyclisation to synthesise the 6-8-6 fused system found in the taxane series of compounds.

\[
\begin{align*}
\text{Under thermal conditions (200°C/24hrs), the cyclisation reaction did not proceed, and even under Lewis acid conditions, the best yield obtained was 30% using Et}_2\text{AlCl.}
\end{align*}
\]

The intramolecular Diels-Alder reaction has also been used to synthesise the 6-11 fused ring system of cytochalasin. In the first of these papers an 11-membered cyclic ketone is produced via the following cycloaddition:
However, these products were produced in only ~ 30% yield, but further studies showed that use of a conjugated triene instead of the diene gave increased yields of the products (up to 50%).

The other papers\(^{28b,c}\) consist of modified syntheses to include certain substituents which are found in the naturally occurring compounds.

An alternative cycloaddition reaction, which has also been used in an approach to the taxane skeleton, uses a nickel catalysed cycloaddition of bis-dienes\(^{29}\). This can be performed in one of two ways so that either of the 6–8 fused systems of the taxane skeleton is formed.

\[
\begin{align*}
\text{O} & \quad \text{NCOPh} & \quad \text{Ph} \\
\text{Ph} & \quad \text{NCOPh} & \quad \text{Ph} \\
\text{Ph} & \quad \text{NCOPh} & \quad \text{Ph} \\
\text{Ph} & \quad \text{NCOPh} & \quad \text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{PhP, Ni(COD)}_2 & \quad \text{toluene, 0.1M, } 60^\circ\text{C} \\
& \quad \text{CO}_2\text{Me} \\
\end{align*}
\]

(29) : (30) 1.3 : 1

(29) R=H, R^1=\text{OTBDMS}  \\
(30) R=\text{OTBDMS}, R^1=\text{H}
Subsequently, this methodology has been applied to the synthesis of a natural product, (+)-asteriscanolide. In this enantioselective synthesis, the key nickel-catalysed intramolecular cycloaddition proceeded in 67% yield with good stereoselectivity.

Wender has also reported a photo induced intramolecular diene-diene cycloaddition, to give 8-membered rings. The initial products of the benzophenone sensitised photo induced [2+2] cycloaddition are the cyclobutanes (31) and (32). (31) and (32) undergo thermal Cope rearrangement to give the cyclooctane product (33). (31) gave (33) in 100% yield whereas (32) gave 50% of (33) and 50% of cyclohexane (34) which was formed as a mixture of isomers.

The cyclooctadiene was produced solely as the cis-fused isomer, due to the initial formation of the cis-fused products in the photolysis step, rather than the more strained trans-fused 5-4 fused system. When the method is used to synthesise bicyclo [6.4.0] systems, some of the trans-fused product is formed.
This is thought to arise because of the relatively lower strain involved in forming the initial [4.2.0] cycloadducts than the [3.2.0] ones.

1.4.3 Medium Ring Ethers

One approach to the synthesis of medium ring ethers has made use of the more readily available lactones. The lactone is converted into its corresponding thionolactone. Nucleophilic addition to the thionolactone gives the thiolate anion (the thiolate anion is more stable than the corresponding oxygen anion hence the use of thionolactones) and quenching with methyl iodide allows isolation of the corresponding addition product. Reduction with the tin hydride/catalytic AIBN reagents removes the methylthio group to give the alkylated cyclic ether. The synthesis of a variety of the 7-, 8-, and 9-membered cyclic ethers is reported in the paper. The reaction sequence is also highly diastereospecific. For example, underwent nucleophilic addition by n-butyl lithium followed by quenching with excess methyl iodide to give in 56% yield as a single addition product (stereochemistry unassigned). Reduction of with tin hydride/AIBN gave in 85% yield solely as the cis diastereoisomer shown.
Seven- and eight-membered cyclic ethers have been synthesised by Moody\(^3\)\(^4\) using a rhodium carbenoid mediated cyclisation of diazo alcohols. Seven-membered ethers were formed in good yields >70%, but eight-membered in only 24%.

The attempted formation of a ten-membered compound proved to be unsuccessful.

Overman has developed methods of synthesising cyclic ethers\(^3\)\(^5\). 5-, 6- and 7-Membered allylically unsaturated ethers were synthesised via acetal-initiated cyclisations of vinyl silanes\(^3\)\(^5\)\(^a\).

Interestingly, 8- and 9-membered rings are formed by a related cyclisation reaction of a vinyl silane with a terminal CH\(_2\) group in which the trimethylsilyl group is not lost from the molecule\(^3\)\(^5\)\(^b\).
The 8-membered ring containing natural product (-)-Laurennyne was synthesised using this approach\textsuperscript{35e}. The key cyclisation step of the sequence is shown as follows:

$$\text{TMS} \quad \text{t-BuPhSiO} \quad \text{Cl}$$

1. 2eq. SnCl\textsubscript{4}, 0°C,

2. CH\textsubscript{2}Cl\textsubscript{2}, 1.5hr

\[ \text{1.5hr} \]

2. n-Bu\textsubscript{4}NF

This step went in 37% yield, and (41) was shown to be the sole cyclic ether product which had been produced as the single diastereoisomer shown.

1.4.4 Cyclisations Involving Allylsilanes

As mentioned earlier in the introduction, allylsilanes have been used in intramolecular allylsilane/aldehyde cyclisations to form 5- and 6-membered rings\textsuperscript{13,13a,14}.

The allylsilane/carbonyl cyclisation of Trost\textsuperscript{13} mentioned earlier was used indirectly to synthesise medium ring compounds. The allylsilane-carbonyl reaction initially generates a fused five-membered ring; treatment of these compounds with potassium hydride and 18-crown-6 leads to fragmentation and concurrent elimination of the elements of benzene sulphinic acid. The result of this is the formation of the three-carbon ring expanded product. Eight- and eleven-membered rings were synthesised via this method:

In the 11-membered case, treatment of (42) with fluoride led directly to the ring expanded product. The reaction mechanism is as follows:
Different reactions involving allylsilanes have been applied to the synthesis of medium ring compounds. One such reaction has been developed by Grieco and Fobare. This reaction is an intramolecular aminomethano desilylation reaction.

\[
\begin{align*}
\text{PhCH}_2\text{NH} \quad & \quad \underset{\text{CF}_3\text{CO}_2\text{H}, \text{HCHO}}{\text{CF}_3\text{CO}_2\text{H}, \text{HCHO}} \quad \underset{\text{H}_2\text{O}-\text{THF (3:1)}}{\text{H}_2\text{O}-\text{THF (3:1)}} \\
(\text{CH}_2)_n \quad & \quad \underset{\text{TMS}}{\text{TMS}} \quad \underset{\text{PhCH}_2\text{N}}{\text{PhCH}_2\text{N}} \\
& \quad \underset{\text{n= 1-3}}{\text{n= 1-3}} \\
\end{align*}
\]

The yields for the three products where \(n=1, 2, 3\) were 73%, 96%, 64% respectively. However, the formation of this yield of the eight-membered ring compound required a reaction time of five days at 50°C.

Majetich has synthesised fused cyclooctane rings via fluoride induced addition of unsymmetrical allylsilanes to conjugated dienones.
However, the highest yield of the fused cyclooctane product was 65% for the following product:

![Diagram of the fused cyclooctane product](image)

but in some cases the yield was as low as 12%. The formation of the fused cyclooctane using fluoride ion catalyst is in contrast to the formation of the fused cyclo-hexane via an intramolecular Sakurai reaction under Lewis acid conditions. In their studies of both fluoride ion and Lewis acid catalysed cyclisations of several compounds, in no case was a mixture of these two products obtained. Later studies enabled the elucidation of the mechanism of the formation of the 8-membered ring. After initial ambiguous results, the proof was finally achieved by synthesising a precursor lacking the 2,3-double bond with respect to the carbonyl group. In the example shown previously it appears that the allylsilane is undergoing 1,6 addition to the conjugated dienone system which requires conversion of the trans olefin in the starting material to the cis olefin in the product. This is presumably via isomerisation of an intermediate allylic anion.

![Mechanism diagram](image)

When the 2,3-double bond is lacking then clearly if the 8-membered product can still be obtained, this mechanism cannot be operating, the allylsilane must simply be adding across the olefin to give the 8-membered ring.

Treatment of (43) with sodium phenyl selenide gave (44) which when treated with fluoride ion gave the fused 4-5 ring (45) in 40% yield as well as 45% of (46). Treatment of (45) with fluoride gave quantitative conversion to (46).
They concluded that this Michael addition/Cope rearrangement mechanism must be operating.

The intramolecular allylsilane/conjugated dienone reaction has been applied to natural product synthesis. (±)-Epi-Widdrol has been synthesised via two methods\(^{39}\). The key cyclisation steps are as follows:

\[
\text{EtAlCl}_2 (78\%) \quad \text{TiCl}_4 (77\%)
\]

\[
(47) : (48) \\
3 : 1
\]

(47) \(R = \text{CH}_3, R' = \text{vinyl}\)  
(48) \(R = \text{vinyl}, R' = \text{CH}_3\)

several steps

Epi-Widdrol
Majetich has also used this methodology to synthesise three perforanes. These compounds along with the common cyclisation reaction are as follows:

\[
\begin{align*}
\text{TMS} & \quad \text{EtAlCl}_2 \\
& \quad >90\% \\
\text{H}^+ / \text{THF} & \\
2:1 \text{ mixture of epimers} \\
\downarrow & \\
\text{Perforenone} & \\
\downarrow & \\
\text{Epiguadalupol} & \quad \text{Guadalupol}
\end{align*}
\]

Similar work has been reported by Schinzer. He reports the formation of a 6-7 fused system as well as a 6-8 fused system. A single diastereoisomer was formed but the authors have not proved the stereochemistry of the product.
1.4.5 Other Medium Ring Syntheses

1,2-Cycloalkane diols have been synthesised by intramolecular titanium-induced pinacol coupling\(^\text{42}\). The ring sizes varied from 6-14 and so the whole range of medium ring compounds can be synthesised by this method.

They observed that in the smaller rings the cis isomer predominated (in the cyclohexane-1,2-diol these were exclusively cis product), and as the ring size increases, there is an increasing preference for the trans product. Similar methodology has been used to form the 8-membered ring in the synthesis of ceroplastol II\(^\text{43}\).
A different coupling reaction was used by Kishi\textsuperscript{44} in the total synthesis of (+)-ophiobolin C. This involves an intramolecular Ni(II)/Cr(II)-mediated coupling of an aldehyde and a vinyl iodide. A single diastereoisomer was produced but it is not known which one.

Kocienski has used intramolecular directed Aldol reactions to synthesise a variety of medium ring compounds\textsuperscript{45,46}. Initially\textsuperscript{45}, the method was applied to tetrahydropyran-4-ones, oxepan-4-ones, and oxocan-4-ones.
When the Lewis acid used was TiCl$_4$(1-2 eq.), cis-dioxolane gave exclusively cis-tetrahydropyran-4-one (49) in 65% yield, whereas trans dioxolane gave a 1:1 mixture of (49) and (50) in 72% yield. Of the other Lewis acids used, SiCl$_4$, ZnCl$_4$, EtAlCl$_2$ gave none of the cyclised products under a variety of conditions, but (PriO)$_2$TiCl$_2$ / CH$_2$Cl$_2$ / -40°C and trimethylsilyl trifluoromethane sulphonate / CH$_2$Cl$_2$ / -78°C gave exclusively the cis product (49) from both the cis- and trans-dioxolane precursors. Treatment of the dioxepane (51) (a 1:1 mixture of diastereoisomers) with TiCl$_4$ / CH$_2$Cl$_2$ / -78°C gave a mixture of the two oxepanes and an oxocanone in combined 88% yield as a 7:6:4 mixture (52):(53):(54) respectively.

According to the nomenclature of this type of reaction the above examples are 6-endo$_e$endo$_n$ in the formation of (49) and (50) and 7-endo$_e$endo$_n$ in the formation of (52) and (53). The terms exo and endo are used to define the relation of the electrophilic (e) oxonium ion and nucleophilic (n) enol silane in relation to the ring being formed. They also examined the 8-endo$_e$endo$_n$ cyclisation: Use of the Lewis acid TiCl$_4$ on compounds (55) and (56) gave only the product (57) in 34% and 9% yield respectively from (58) and (59).

Another two examples of the 8-endo$_e$endo$_n$ cyclisation were also given. Reaction of (60) and (61) with TiCl$_4$ at -78°C gave the oxocanones (62) and (63) in 43% and 25% yield respectively.
The second study concerns the 8-exo endo cyclisation, which was used to synthesise β-alkoxy cyclo-octanones, for example:

The reaction was studied for a variety of substituents and an attempt was made to assess the scope of the gem-dimethyl effect in promoting these 8-exo endo annulations. There was a marked improvement in cyclisation yield in some cases compared to the demethyl analogues. For example, the reaction of (64) with TiCl₄ gives (65) in 13% yield, whereas (66) gives (67) in 43% yield under identical conditions. These results can be interpreted by assuming a ring-like transition state geometry where (66) would adopt a chair-boat conformation with the methyl groups in the site shown (i.e. the position where the gauche butane interaction removes axial/equatorial preferences).
In this conformation the methyl groups will not have any unfavourable transannular interactions to counteract the benefit of their presence.

Snider used a manganese (III) oxidative free radical cyclisation to form seven- and eight-membered rings. The yield varied according to the substituent on the α-position of the starting β-keto esters.

(68) n=1
(69) n=2

(68) gave a 13% yield of (71a), and (69) gave a 17% yield of (71b). The poor yield is thought to arise, at least in part, because of over oxidation of the products (71a) and (71b). None of
(72) was produced which was thought to be due to over oxidation as the compound has an allylic enolisable hydrogen. Replacement of this hydrogen with a methyl group (73) or chlorine (74) gives greater yields of the cyclised products (75) and (76) respectively.

\[ \text{(73)} \quad \text{CO}_2\text{Et} \quad 2\text{eq. Mn(OAc)}_3 \quad \text{leq. Cu(OAc)}_2 \quad \text{(75) 38%} \]

\[ \text{(74)} \quad \text{Cl} \quad \text{CO}_2\text{Et} \quad 2\text{eq. Mn(OAc)}_3 \quad \text{leq. Cu(OAc)}_2 \quad \text{(76) 47%} \]

Trost has reported a cyclisation utilising vinyl cyclopropanol as the cyclisation terminator and acetals as the initiators. Eight-membered rings were formed readily via this reaction.

\[ \text{OTMS} \quad \text{OMe} \quad 0.7\text{eq. pyridine.} \quad \text{OMe} \quad \text{CH}_2\text{Cl}_2 \quad \text{(77) 96%} \]

The product was a 9:1 mixture of diastereoisomers, the one shown is thought to be the major one. 5-8 Fused rings could also be synthesised via this method.

\[ \text{OTMS} \quad \text{OMe} \quad \text{Me} \quad \text{Me} \quad \text{OMe} \quad \text{H} \quad \text{H} \quad \text{OMe} \quad \text{OMe} \quad \text{(77) 96%} \]

(77) Was produced as an 11.5:1:1 mixture of three isomers. The major one (shown) was isolated pure in 85% yield. The mechanism of the reaction is thought to be as follows:
The orientation will be of the "extended" type shown below where there is a crown conformation and the oxonium ion is in the equatorial position.

This accounts for the formation of (77) as the major product. The alternative conformation which is referred to as the "crossed" would lead to the opposite stereochemistry to (77).
CHAPTER 2

ATTEMPTED ALDEHYDE-BROMOALKENE COUPLING
CHAPTER 2

ATTEMPTED ALDEHYDE-BROMOALKENE COUPLING

2.1 Introduction

The object of this work, as outlined in the introduction (Chapter 1), was to study an intramolecular cyclisation reaction which creates a new chiral centre. As the chain would be set up to already possess one chiral centre prior to cyclisation, then two diastereoisomeric products are possible.

The aim was to see whether the conformational preferences of the chain would affect the transition state leading to cyclisation, so that unequal amounts of the possible isomers would be formed.

The initial idea was to follow the route outlined below. The route can be adapted to use either an allyl tin - aldehyde reaction\textsuperscript{9,10}, or an allylsilane - aldehyde cyclisation, as mentioned in Chapter 1\textsuperscript{12}:

![Chemical structure diagram]
cyclisation
2.2 Results and Discussion

1,6-Hexanediol was converted into 6-t-butyldimethylsilyloxy-hexanol (78) in 25% yield. Less than 1% of the 1,6-di-t-butyldimethylsilyloxy-hexane (79) was also obtained. The two products were easily separated by flash chromatography and they were identified by $^1$H n.m.r. spectroscopy. Monoprotected alcohol (78) possessed the characteristic Me-Si & t-Bu singlets at 0.86 and 0.88 respectively along with two multiplets at 1.2-1.65 and 3.4-3.65 which integrated to the expected thirteen protons for this compound. The diprotected compound (79) had an n.m.r. spectrum which showed clearly the aforementioned Me-Si & t-Bu signals along with two multiplets which integrated to the expected twelve protons.

Monoprotected alcohol (78) was oxidised using buffered pyridinium chlorochromate to give the aldehyde, 6-t-butyldimethylsilyloxy-hexanal (80) in 60% yield. This aldehyde was separated from unreacted alcohol by flash chromatography and the product was identified by $^1$H n.m.r. The key signal was the broad singlet at 9.75 which corresponds to the aldehyde proton. Other signals included the methyl and t-Bu at 0.86 and 0.88 respectively. There was also a six proton multiplet between 1.35 and 1.75. The 2-CH$_2$ is seen as a triplet at 2.355 and the 6-CH$_2$ is seen as a triplet at 3.65.

The aldehyde proton adjacent to a CH$_2$ group appears as a broad singlet rather than a triplet because of the very small coupling constant. Several similar aldehydes were prepared during later studies and all appeared as singlets or triplets with a coupling constant of less than 1Hz. These are listed as follows:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Page No.</th>
<th>Aldehyde Proton n.m.r. Signal</th>
</tr>
</thead>
<tbody>
<tr>
<td>(83)</td>
<td>103</td>
<td>Broad singlet, 9.86</td>
</tr>
<tr>
<td>(109)</td>
<td>119</td>
<td>Triplet J &lt;1Hz, 9.86</td>
</tr>
<tr>
<td>(112)</td>
<td>120</td>
<td>Triplet J &lt;1Hz, 9.755</td>
</tr>
<tr>
<td>(128)</td>
<td>121</td>
<td>Triplet J &lt;1Hz, 9.75</td>
</tr>
<tr>
<td>(120)</td>
<td>122</td>
<td>Triplet J &lt;1Hz, 9.75</td>
</tr>
<tr>
<td>(116)</td>
<td>138</td>
<td>Triplet J 1Hz, 9.765</td>
</tr>
<tr>
<td>(124)</td>
<td>139</td>
<td>Triplet J 1Hz, 9.745</td>
</tr>
</tbody>
</table>

\[ \text{HO}-(\text{CH}_2)_6-\text{OH} \xrightarrow{\text{TBDMSCl}} \text{TBDMSO}-(\text{CH}_2)_6-\text{OH} \]

\[ \text{TBDMSO}-(\text{CH}_2)_5-\text{CHO} \]
The 1,6-hexanediol was also converted into 6-tetrahydropyranoxy-1-hexanol (81) using dihydropyran in the presence of pyridinium p-toluenesulphonic acid\(^{49,52}\). The yield of this monoprotected alcohol was 25%, and there was also a 23% yield of the diprotected alcohol, 1,6-di-tetrahydropyranoxy-hexane (82). The two products were easily separable by flash chromatography, and the two compounds were identified by a combination of \(^1\)H n.m.r. and I.R. spectroscopy. The monoprotected alcohol (81) had a strong broad absorption centred at 3400 cm\(^{-1}\) in its I.R. spectrum, along with a singlet, which exchanges with D\(_2\)O, at 2.18 in the proton n.m.r. spectrum. Both of these clearly show the presence of an alcohol group. Another key signal, which clearly shows the presence of the tetrahydropyranoxy group is a triplet at 4.68 in the proton n.m.r. spectrum. This corresponds to the O-CH-O proton. Other signals in the proton n.m.r. included a fourteen proton multiplet between 1.38 and 1.958 corresponding to the seven C-CH\(_2\)-C units. The 1-CH\(_2\) is seen as a triplet at 3.625. The other protons adjacent to oxygen are seen as two one-proton doublets of triplets at 3.408 and 3.758 and two one proton multiplets at 3.47-3.568 and 3.878. The di-protected alcohol (82) lacked the signals expected for an alcohol group but clearly contained two tetrahydropyranoxy groups per molecule, as measured by the integration of the proton n.m.r. spectrum.

As before, monoprotected alcohol (81) was oxidised using buffered pyridinium chlorochromate\(^{51}\), to give 6-tetrahydropyranoxy-hexanal (83) in 55% yield. This product was separated from unreacted alcohol (81) by flash chromatography and was identified by \(^1\)H n.m.r. and I.R. spectroscopy. In the I.R. spectrum there was a strong absorption at 1730 cm\(^{-1}\) corresponding to the aldehyde group and no longer absorption at 3400 cm\(^{-1}\) corresponding to an alcohol group. There was also a signal (broad singlet) at 9.88 in the proton n.m.r. spectrum confirming the presence of the aldehyde group. Again, the aldehyde -CHO proton appears as a broad singlet due to the small coupling constant with the two adjacent protons. These appear as a doublet of triplets at 2.458. The twelve C-CH\(_2\)-C protons appear as a multiplet between 1.28 and 1.88. The four protons adjacent to oxygen appear as two doublet of triplets at 3.388 and 3.758, and two multiplets at 3.45-3.558 and 3.82-3.958. The proton adjacent to two oxygens appears as a broad singlet at 4.508.
3,3-Diethoxy-2-bromopropene (84) was prepared from 3,3-diethoxy-propene in two stages as follows. The 3,3-diethoxy-propene was reacted with bromine in chloroform at -60°C to produce 3,3-diethoxy-1,2-dibromopropane (85) which was reacted with potassium hydroxide in ethanol, at room temperature, to give (84) in overall 30% yield. The proton n.m.r. spectrum showed a triplet at 1.15δ corresponding to the methyl groups. The two O-CH₂ groups were seen as a multiplet between 3.2δ and 3.6δ. A singlet at 4.7δ corresponds to the 3-H. The two olefinic protons were seen as singlets at 5.6δ and 6.0δ.

\[ \text{OEt} \quad \text{OEt} \quad \xrightarrow{\text{Br}_2} \quad \text{OEt} \quad \text{OEt} \quad \text{Br} \quad \xrightarrow{\text{KOH}} \quad \text{OEt} \quad \text{OEt} \]

The orientation of the elimination is the same as that expected from the corresponding aldehyde where the α-hydrogen is removed by the base.

\[ \text{O} \quad \text{O} \quad \xrightarrow{\text{base}} \quad \text{O} \quad \text{O} \]

This can be compared with another case where ketone and acetal give the same product.
One possible explanation for the preferred orientation is destabilisation of the carbon-hydrogen bond by the carbon-oxygen bond of the acetal group, making the hydrogen α to the acetal more acidic.

This is analogous to the α-effect which is seen in molecules such as H-O-O-H\textsuperscript{56}. A further possible explanation may be that potassium cation coordinates to the lone pairs on the
acetal oxygen atom leading to a preference for the -OH to remove the α proton. This type of effect is known as directed metallation\textsuperscript{57} and although it is normally observed in lithiation reactions it may be playing a role here. It is difficult to be sure of the explanation of the highly selective deprotonation of (85) and both these factors may be playing a role.

Bromoalkene (84) reacted with butyl lithium to generate the corresponding anion which was then reacted with aldehyde (83) in THF\textsuperscript{58,59}. However, the reaction was not very clean, and t.l.c. showed the presence of a large number of products which proved impossible to separate or conclusively identify. The Grignard reaction of aldehyde (83) with 2-bromopropene (89) was attempted\textsuperscript{60}. Poli and co-workers performed this exact reaction i.e. the Grignard reagent of 2-bromopropene (89) with 6-tetrahydropyranoloxy-hexanal (83), and isolated 2-methyl-8-tetrahydropyranoloxy-oct-1-en-3-ol (90) in 84% yield.

\[
\begin{align*}
\text{ThpO} & \text{H} + \text{Br} \xrightarrow{\text{Mg}} \text{ThpO} \text{OH} \\
(83) & \quad (89) & \quad (90)
\end{align*}
\]

After a couple of attempts at the reaction using ether as the solvent, in which the formation of the complex between (89) and the magnesium was not achieved, the reaction was repeated using THF as the solvent. Monitoring of the reaction by t.l.c. again suggested that several products had been formed, approximately eight. The products were separated by preparative t.l.c. and identification by \textsuperscript{1}H n.m.r. was inconclusive. However the key signals i.e. the acetal proton (O-CH-O) at \(-4.66\) and the olefinic signals at \(5.5-6.06\) were not both present in any of the molecules, suggesting that the desired product had not been formed.

As it appeared that the Grignard species had not been formed, a similar reaction was performed using bromoalkene (84). In this case the reaction between the magnesium and (84) could not be initiated with either iodine, heat, or 1,2-dibromomethane.

As these reactions were proving to be difficult, it was decided to react the lithium anion of bromoalkene (84) and the Grignard reagent of (89) with 3-phenylpropanal (91). Both of these reactions occurred readily and both gave the expected products; 2-diethoxymethyl-5-phenyl-1-penten-3-ol (92), and 2-methyl-5-phenyl-1-penten-3-ol (93) respectively, in greater than 50% yield. In both cases, identification was by proton n.m.r. (92) Possessed the
ethoxymethyl triplets at 1.2\(\delta\), the acetal proton (O-CH-O) as a broad singlet at 4.8\(\delta\), the olefinic protons as a singlet at 5.2\(\delta\), and the phenyl group at 7.2\(\delta\), as well as a broad singlet corresponding to the alcohol proton at 4.2\(\delta\). (93) Possessed the methyl group part of a five proton multiplet at 1.6-1.9\(\delta\), the broad alcohol singlet at 3.7\(\delta\), the olefinic signals at 4.8\(\delta\) and 4.9\(\delta\) (both broad singlets), and the phenyl group seen as a broad singlet at 7.1\(\delta\). The proton adjacent to the oxygen appeared as a triplet at 4.0\(\delta\).

This suggests that there is no problem in forming the anion or the Grignard reagent respectively. Therefore the reactions of the lithium anion of (84) and the Grignard reagent of (89) with aldehyde (83) were repeated. In the reaction of (84) and (83), a large number of products were formed and after isolation by flash chromatography there wasn't a sufficient amount of any of the products to identify them. In the case of (89) and (83) again there were several products which were not isolated in sufficient quantities to assign their structures.

As clean reactions were not being obtained with this aldehyde (83), it was decided to attempt the previous reactions using the silicon protected aldehyde (80). As in the case of aldehyde (83), the reaction of (80) with the anion of (84) gave a large number of products. Three of these were isolated, however only in poor yields, so that conclusive identification was impossible. Promisingly, one of them showed olefinic signals as well as signals corresponding to the t-butyldimethylsilyl group in the proton n.m.r. spectrum.
In the reaction of (80) with the Grignard reagent of (89) there was a clean reaction to give just two products, one of which appeared to be the expected one; 8-t-butyldimethylsilyloxy-2-methyl-1-octen-3-ol (94) as the proton n.m.r. spectrum shows the presence of olefinic signals at 4.85 and 4.95 and t-butyldimethylsilyl signals at 0.85 and 0.86.

\[
\text{TBDMSO} \quad \text{H} \quad \text{Br} \quad \text{Mg} \quad \text{TBDMSO} \quad \text{OH}
\]

(80) (89) (94)

The yield of the product was only 20%, however, and also the product isn't really suitable for use in the proposed scheme, because of the need to convert the methyl group into some useful functionality, for example the bromoethyl group shown in the scheme. These later experiments using aldehyde (80) appear more promising since (80) seems to react more cleanly than aldehyde (83).

Throughout these reactions there were problems with identification of the products due to the large number of products formed, and consequently the small amounts of each product produced. Repetition of these four reactions on a much larger scale would possibly have enabled this identification to have been made.
CHAPTER 3

ATTEMPTED GRIGNARD SYNTHESIS OF AN ACYCLIC PRECURSOR
CHAPTER 3

ATTEMPTED GRIGNARD SYNTHESIS OF AN ACYCLIC PRECURSOR

3.1 Introduction

As the initial approach of Chapter 2 appeared to be quite difficult, it was decided to try to find an alternative solution to the problem. It was felt that the reaction of an oxygen-protected ω-hydroxy-α-bromoalkane with 2-(trimethylsilyl)methyl-2-propenal (95) via a Grignard reaction would lead to a suitable acyclic precursor to a medium ring.

The allylsilane moiety would already be present, enabling an allylsilane-aldehyde cyclisation\textsuperscript{15} to be attempted.

\[
\text{RO} \rightarrow (\text{CH}_2)_n - \text{Br} \xrightarrow{\text{Mg}} \text{RO} \rightarrow (\text{CH}_2)_n - \text{MgBr}
\]

\( R = \text{protecting group} \quad n = 5, 6 \)

From (96) it should be possible to protect the secondary alcohol, deprotect the primary alcohol and oxidise to the aldehyde, as in the initial scheme. The acyclic precursor would then be set up to attempt the cyclisation reaction.
HO\text{SiMe}_3O
HO\text{SiMe}_3Br
RO\text{SiMe}_3Br

\begin{align*}
\text{cyclisation}
\end{align*}
As the allylsilane moiety is introduced early on in the sequence, the route is specific for the allylsilane-aldehyde cyclisation, unlike the scheme of Chapter 2 which could be adapted to use a variety of cyclisation reactions, including this. However, this second route is three steps shorter than the initial route and so if successful would be synthetically more useful.

The most useful \( \omega \)-bromoalkanols as far as this project is concerned would be 5-bromopentanol and 6-bromohexanol as these would lead to the possibility of producing 8- and 9-membered rings respectively. However, neither of these compounds is available commercially, only the shorter chain 3-bromopropanol and 2-bromooctanol are. In the literature there are methods of synthesising \( \omega \)-bromoalkanols from their corresponding \( \alpha \)-, \( \omega \)-diols. 5-Bromopentanol was obtained in 68% yield and 6-bromohexanol in 60% yield via this method\(^6\).

\[
\text{HO} \to (\text{CH}_2)_n \to \text{OH} \xrightarrow{\text{HBr} / C_6H_6, \text{reflux, 18-30 hr}} \text{HO} \to (\text{CH}_2)_n \to \text{Br}
\]

Mori\(^6\) synthesised 1-tetrahydropyranloxy-7-bromohexane and 1-tetrahydropyranloxy-6-bromohexane and formed their corresponding Grignard reagents in THF. These were then reacted successfully with an allyl halide as shown.

\[
\begin{align*}
\text{Br} & \quad \text{OThp} \quad \text{1. Mg, THF} \\
\text{\quad} & \quad \text{THF/HMPA,} \\
\text{\quad} & \quad \text{Br}
\end{align*}
\]

As there appeared to be literature precedent for the crucial Grignard reaction that our scheme required, but the \( \omega \)-bromoalkanols would have to be synthesised, it was decided to
initially attempt the scheme using 3-bromopropanol (97) which would hopefully lead to the synthesis of a 6-membered ring.

\[
\begin{align*}
\text{HO} & \quad \text{Br} \quad \text{P.P.T.S.} \quad \text{TMS} \quad \text{Br} \quad \text{Mg, THF} \\
\text{(97)} & \quad \text{ThpO} & \quad \text{H} \quad \text{TMS} \quad \text{H} \\
\text{1. Mg, THF} & \quad \text{2.} & \quad \text{H} \\
\text{ThpO} & \quad \text{OH} \quad \text{TMS} \quad \text{NaH} \quad \text{TMS} \quad \text{OMe} \\
\text{(98)} & \quad \text{1. NaH} & \quad \text{2. MeI} \\
\text{MeO} & \quad \text{TMS} \quad \text{H} \quad \text{MeO} \quad \text{H} \\
\text{1. H^+, H_2O} & \quad \text{2. CrO_3.2pyr} & \quad \text{F^-} \\
\end{align*}
\]

3.2 Results and Discussion

Bromoalcohol (97) was protected with dihydropyran in the presence of pyridinium p-toluene sulphonic acid to yield 1-tetrahydropyranyloxy-3-bromopropane (98) in 70% yield. I.R. clearly showed that there was no longer an alcohol group as there was no absorption at ≈3400 cm\(^{-1}\), and proton n.m.r. showed the characteristic broad singlet at 4.5δ corresponding to the acetal proton (O-CH-O). Other signals in the proton n.m.r. were a six proton multiplet between 1.4δ and 1.8δ (three C-CH\(_2\)-C), a two proton multiplet between 3.4δ and 3.6δ corresponding to the two CH\(_2\)-O structures within the molecule and a multiplet corresponding to CH\(_2\)-Br between 3.7δ and 4.0δ. Aldehyde (95) was synthesised from its corresponding alcohol 2-(trimethylsilyl)methyl-2-propen-1-ol using a manganese dioxide oxidation\(^{51}\). The active manganese dioxide used in the oxidation was prepared according to the method described in this paper. Aldehyde (95) was obtained in 93% yield. (95) Was identified by I.R. and \(^1\)H n.m.r. spectroscopy. The TMS singlet was observed at 0δ in the \(^1\)H n.m.r. spectrum. Two singlets at 5.8δ and 6.1δ showed that the alkene functionality had not been affected by the oxidation, and the singlet at 9.58 showed that the alcohol had been
successfully oxidised to the aldehyde. The -CH$_2$- was seen as a singlet at 1.8$\delta$. Absorptions at 1700cm$^{-1}$ and 1615cm$^{-1}$ in the I.R. spectrum confirm the presence of the aldehyde and alkene functionality respectively. When the Grignard reagent of (98) was prepared using magnesium in THF and aldehyde (95) was added, it was discovered that very little, if any, of the Grignard reagent had been formed as only starting materials were visible on t.l.c.

Aldehyde (95) was reacted with phenyl magnesium bromide and two products were isolated in poor yield (<10%). $^1$H N.m.r. spectra were run on these products, and the first, which was isolated in <5% yield, appears not to be pure, although signals corresponding to the phenyl, trimethylsilyl, and olefinic groups are present, as well as a multiplet signal at 3.7$\delta$ which could correspond to the proton adjacent to the alcohol, phenyl, and double bonds. Due to the poor yield it was not possible to further purify and hence conclusively identify this compound, and even if it is the desired one, the yield suggests that the reaction has not been very successful. The second isolated compound is clearly lacking the T.M.S. singlet at -0.8$\delta$ and so cannot possibly be the desired product.

The Grignard reaction of (98) with two commercially available aldehydes, 3-phenyl propanal (91) and benzaldehyde (99) was then attempted on a slightly larger scale.

\[
\begin{align*}
\text{ThpO} & \quad \text{MgBr} \\
\text{(98)} & \quad + \quad \text{Ph} \quad \text{H} \\
\text{O} & \quad \rightarrow \quad \text{ThpO} \quad \text{Ph} \\
\text{(91)} & \quad \text{OH} \\
\text{(100)} & \\
\text{ThpO} & \quad \text{MgBr} \\
\text{(98)} & \quad + \quad \text{Ph} \quad \text{H} \\
\text{O} & \quad \rightarrow \quad \text{ThpO} \quad \text{Ph} \\
\end{align*}
\]

In the reaction of (91) and (98), several product spots were visible on t.l.c., and after isolation by flash chromatography, one of the products did appear to be the expected one, 6-phenyl-1-tetrahydropyranoxyl-hexan-4-ol (100), however the yield was only ~8%.

Identification of this compound was made by $^1$H n.m.r. and I.R. spectroscopy. The proton n.m.r. spectrum showed the presence of the phenyl group (singlet, 7.18), the Thp group (broad singlet, 4.5$\delta$, O-CH-O, and the characteristic broad hump at 1.3-1.6$\delta$), as well as
other signals which integrated to the remaining protons in the expected compound. The I.R. spectrum showed the presence of the alcohol group with a broad absorption at 3400cm\(^{-1}\). In the reaction of (98) with (99), again there were several products. The major compound isolated was benzyl alcohol (~30%), from reduction of the benzaldehyde. The other major compound lacks the phenyl signal and appears to be unreacted halide (98). Small amounts of two products were isolated but neither appeared to be completely pure and although they possessed signals which could correspond to the expected phenyl, and Thp groups, the poor yields made it impossible to further purify and hence conclusively identify them.

A further attempt was made at the reaction of (98) with aldehyde (95), as the Grignard reagent of (98) did appear to have been formed in the previous two reactions; if only in a small amount. The reaction scale was further increased to compensate for this (~800mg of halide was used). Successful formation of the Grignard species was achieved, and after addition of the aldehyde, t.l.c. showed the presence of two products, along with some unreacted starting material. After isolation by flash chromatography, the two compounds were identified as being 1-tetrahydropyranloxy-propane (101), formed by quenching of unreacted Grignard reagent in 4% yield, and 1,6-di-tetrahydropyranloxy-hexane (82) formed in 54% yield by coupling of the Grignard reagent. Mass spectroscopy showed a small molecular ion at m/z 286, along with signals corresponding to loss of Thp m/z 201(M-Thp) and 85 Thp, and the presence of a \((\text{CH}_2)_6\) chain. This evidence for the structure of (82) was supported by the \(^1\text{H}\) n.m.r. and I.R. spectra. The proton n.m.r. contained a twenty proton multiplet at 1.3-1.75 from the ten C-\(\text{CH}_2\) and an eight proton multiplet between 3.35 and 3.95 from the four \(\text{CH}_2\)-O. The acetal protons were seen as a broad singlet at 4.55.

Grignard coupling is known, for example, where Grignard reagents undergo an oxidative coupling reaction in the presence of transition metal halides\(^6\). It is thought that these dimers are produced via organo transition metal intermediates:

\[
2\text{PhMgBr} + \text{CrCl}_2 \rightarrow \text{Ph-Cr-Ph} + 2\text{MgClBr}
\]

\[
\text{Ph-Cr-Ph} \rightarrow \text{Ph-Ph} + \text{Cr}
\]

It is possible that if there were chromium residues remaining from the oxidation reaction they could assist in this type of reaction. However, Mori\(^3\) reacted 1-tetrahydropyranloxy-6-bromohexane with an allyl bromide. If addition of the alkyl bromide (98) to the magnesium and solvent is too rapid so that it is not all immediately converted to the Grignard reagent then any Grignard reagent can react with it and so the coupled product will be formed. To minimise this undesirable reaction, the reaction could have been
repeated with slower addition of the alkyl bromide (98) to the magnesium, and also performing the reaction at a greater dilution may have helped.

1-Tetrahydropyranloxy-propane (101) was made by the reaction of propan-1-ol with dihydropyran in the presence of pyridinium p-toluenesulphonic acid, and was shown to have identical spectral properties ($^1$H n.m.r., I.R., mass spectrum) to that produced in the previous reaction.

In another experiment, the Grignard reagent of (98) was formed and then, at the stage of the procedure where the aldehyde would be added, the reaction was quenched with water. T.l.c. showed products with identical r.f.'s to previous reactions, and indeed, after purification, (101) and (82) were isolated.

Formation of the lithium anion of (98) was thought to be a possible solution to the problem of the Grignard coupling, however an attempt at this reaction showed that very little reaction had occurred, even after several hours.

At this point it was decided to use an alternative protecting group to dihydropyran to see whether this would affect the amount of coupling that was being observed. Hence, the t-butyldimethylsilyl protecting group was used, and 1-t-butyldimethylsilyloxy-3-bromo-propane (102) was produced in 75% yield from (97) in the presence of imidazole.

Identification of (102) was made from the following spectral data. The proton n.m.r. showed a signal for the two methyl groups as a singlet at 0.85. The t-Bu group was seen as a singlet at 0.88. A two proton multiplet at 1.95 represented the C-CH$_2$-C and the other four protons were seen as a multiplet between 3.38 and 3.76. The I.R. spectrum showed no absorption at $\sim$3400 cm$^{-1}$, confirming that the -OH group is no longer present.
When an attempt was made to form the Grignard reagent of (102) and react it with aldehyde (95), there appeared to be very little formation of the Grignard reagent, as t.l.c. showed mainly starting materials to be present.

In summary, this route proved problematical because of the coupling of the Grignard reagent of the 1-tetrahydropyranloxy-3-bromo-propane (98), in preference to reacting with an aldehyde. However, Mori has shown that the analogous compounds that would be needed to form medium rings (9- and 10-membered) i.e. 1-tetrahydropyranloxy-6-bromo-hexane, and 1-tetrahydropyranloxy-7-bromo-heptane, will form Grignard reagents which will react with an allyl halide. This suggests that it may have been worthwhile moving on to the medium ring syntheses, despite the problems with the smaller ring syntheses, to investigate whether coupling would still be preferred to reaction with an aldehyde.
CHAPTER 4

INTRAMOLECULAR ALLYLSILANE-ALDEHYDE CYCLISATION
CHAPTER 4

INTRAMOLECULAR ALLYLSILANE-ALDEHYDE CYCLISATION

4.1 Introduction

A further route has been investigated which has, like that of the previous chapter, involved synthesising a molecule containing both allylsilane and aldehyde functionality, and then attempting an intramolecular cyclisation to give a carbocyclic medium ring. As the allylsilane functionality is introduced early in the synthesis, the route is specific for the allylsilane-aldehyde cyclisation, unlike the route explored in Chapter 2. An outline of the route is shown below.

As in the previous attempted synthesis, this route would lead to a cyclised product possessing two chiral centres so that potentially a mixture of diastereoisomers could be produced. The molecule is once again fairly simple so that any selectivity will be influenced by conformational preferences.
cyclisation
4.2 Results and Discussion

Initially the route was investigated with the aim of synthesising an 8-membered ring, as follows:

1,6-Hexanediol was mono-protected by dihydropyran in the presence of P.P.T.S., as previously\textsuperscript{49,52}, to give 6-tetrahydropyranoloxy-hexan-1-ol (81). This was oxidised by buffered p.c.e.\textsuperscript{51} to give 6-tetrahydropyranoloxy-hexanal (83). 2,3-Dibromopropene was reacted with trichlorosilane in the presence of triethylamine and copper (I) chloride according to the method of Furuya and Sukawa\textsuperscript{65} to give 2-bromo-3-(trichlorosilyl)propene (103). Distillation of this crude product did not improve its purity and so it was used crude in its reaction with methyl magnesium bromide\textsuperscript{60}. Distillation afforded pure 2-bromo-3-(trimethylsilyl)propene (104) in overall 25% yield. This was identified by its proton n.m.r. spectrum and I.R. spectrum. The trimethylsilyl methyl groups appear as a singlet at 0.13\delta. There is a singlet at 2.13\delta representing the C-CH\textsubscript{2}-Si, and the olefinic protons are seen as two singlets at 5.1\delta and 5.2\delta.

![Diagram](image)

Halide (104) has previously been reacted with aldehydes\textsuperscript{66} either via a Grignard reaction or halogen metal exchange with t-butyl lithium.

Initially, the Grignard reagent of halide (104) was generated and reacted with benzaldehyde. Interestingly, the products isolated were 2-(trimethylsilyl)methyl-1-phenyl-2-propen-1-one (105) in 22% yield and benzyl alcohol in 32% yield. This compound was completely characterised by \textsuperscript{1}H and \textsuperscript{13}C n.m.r., I.R. and mass spectroscopy. The key peaks in the I.R. spectrum were at 1655cm\textsuperscript{-1}, which is characteristic of an \alpha,\beta-unsaturated ketone, 1610cm\textsuperscript{-1} characteristic of an alkene bond which is part of an \alpha,\beta-unsaturated carbonyl compound, and the phenyl absorptions at 1600cm\textsuperscript{-1} and 1580cm\textsuperscript{-1}. The mass spectrum showed a strong molecular ion peak at m/z 218 along with a peak representing loss of a methyl group (m/z 203), a peak of PhC = 0 at m/z 105, and the trimethyl silyl group at m/z 73.
In the proton n.m.r., the aromatic signals are:

7.43, 2H, tt, 8Hz, 1Hz \( \text{H}^1 \text{ and H}^5 \) deshielded as near to carbonyl group coupled to \( \text{H}^4 \) and \( \text{H}^2 \) 8Hz, \( \text{H}^3 \) 1Hz.

7.53, 1H, tt, 8Hz, 1Hz \( \text{H}^3 \) coupled to \( \text{H}^2 \text{ and H}^4 \) 8Hz, \( \text{H}^1 \text{ and H}^5 \) 1Hz.

7.74, 2H, dt, 8Hz, 1Hz \( \text{H}^2 \) and \( \text{H}^4 \) coupled to \( \text{H}^1 \) and \( \text{H}^5 \) and \( \text{H}^3 \).

The methyl groups are seen as a singlet at 0.075, and the -CH\(_2\)- is seen as a doublet at 2.058. The coupling constant is 1Hz and this group is coupled to the olefinic proton which is trans to it. This proton is seen as a doublet of doublets at 5.738. The other olefinic proton is seen as a doublet at 5.518. The coupling constant between the two olefinic protons is 1Hz which is in the expected range.

These unexpected products are thought to have arisen via hydride transfer:

\[ \text{TMSCH}_2\text{CH}_2\text{Br} \xrightarrow{\text{MgBr}} \text{TMSCH}_2\text{CH}_2\text{MgBr} \xrightarrow{\text{O}^\cdot} \text{TMSCH}_2\text{CH} = \text{CHPh} \xrightarrow{\text{H}^+} \text{PhOH} \]

\[ \text{Ph} \ x \text{H}^+ \rightarrow \text{Ph} + \text{TMSCH}_2\text{CHPh} \]

\[ \text{TMSCH}_2\text{CHPh} \xrightarrow{\text{O}^\cdot} \text{TMSCH}_2\text{CH} = \text{CHPh} \]

\[ \text{TMSCH}_2\text{CHPh} \xrightarrow{\text{O}^\cdot} \text{TMSCH}_2\text{CH} = \text{CHPh} \]

\[ \text{TMSCH}_2\text{CHPh} \xrightarrow{\text{O}^\cdot} \text{TMSCH}_2\text{CHPh} \]
2-(Trimethylsilyl)methyl-1-phenyl-2-propen-1-one (105)
This type of intermolecular hydride transfer is seen in the Cannizzaro reaction\(^\text{67}\) which involves hydride transfer from an aldehyde molecule lacking an \(\alpha\)-H atom to another aldehyde molecule.

![Chemical structure of the Cannizzaro reaction](image)

Preliminary attempts at the Grignard reaction of halide (104) with aldehyde (83) proved problematical, not because of generating the Grignard species itself, but because of difficulty in isolating the products. It appears that the 8-tetrahydroxy-2-(trimethylsilyl)methyl-1-octen-3-ol (106) is unstable because if the reaction is left for longer than is necessary, the relative amount of this product decreases whilst that of other products increases. Attempts to isolate pure (106) by flash chromatography were unsuccessful as this appeared to assist the decomposition. Identification of this compound was achieved by g.c. mass spectrometric analysis of the crude reaction mixture. The conditions used were 25m CPSil 19 CB capillary g.c. column with a temperature ramp of 100\(^\circ\)C to 250\(^\circ\)C at an increase of 10\(^\circ\)C/minute and the injector temperature was 220\(^\circ\)C. This showed that the compound corresponding to the major product by t.l.c. was (106). The mass spectrum was run under chemical ionisation conditions. A gas such as methane, ammonia, or isobutane is present at higher pressures than the substance to be examined. Electron impact causes mainly ionisation of this other gas which then undergoes the following series of reactions (shown here for methane):

\[
\begin{align*}
\text{CH}_4^+ \text{•} + \text{CH}_4 & \rightarrow \text{CH}_5^+ + \text{CH}_3^+ \\
\text{CH}_5^+ + \text{A} & \rightarrow \text{CH}_4 + \text{AH}^+ \\
\text{A} & \text{= substrate}
\end{align*}
\]
These substrate ions $\text{AH}^+$ have enough energy to fragment and consequently produce a chemical ionisation mass spectrum. The mass spectrum showed a peak at 315 mass units representing $(\text{M+H})^+$. Other compounds were identified as being unreacted aldehyde (83) with a signal at 218 mass units representing $(\text{M+NH}_4)^+$, and 6-tetrahydropyranyloxy-hexan-1-ol (81), with a signal at 220 mass units representing $(\text{M+NH}_4)^+$, formed by reduction of the aldehyde. Three other compounds which were not identified had the following characteristics: 225 molecular ion, 295 molecular ion, and 418 molecular ion.

Subsequently, this reaction was monitored by t.l.c. and once reaction appeared complete and only decomposition was occurring, the reaction was worked up and g.c. was used to measure the yield. The crude product mixture was used immediately in the following reaction. The alcohol (106) was acetylated using acetic anhydride and triethylamine in the presence of D.M.A.P. This gave 3-acetoxy-8-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-5-ene (107) in overall 28% yield. This compound was completely characterised and key spectral data includes the presence of $\text{C}=0$ from the absorption at 1740 cm$^{-1}$ in the I.R. spectrum, and the signal at 170.28 in the $^{13}$C n.m.r. spectrum. In total there were 17 carbon atom signals; two methyl from the TMS and acetoxy groups; eleven $\text{CH}_2$'s, two $\text{CH}$'s, and two carbons without a proton bonded to them. The absorption at 1640 cm$^{-1}$ in the I.R. spectrum, and the singlets at 4.63δ and 4.72δ in the $^1$H n.m.r. spectrum confirm the presence of the double bond. A nine proton singlet at 0.05δ shows the presence of the trimethylsilyl group, and the triplet at 4.53δ the Thp group. The other signals in the proton n.m.r. included a sixteen proton multiplet between 1.2δ and 1.85δ corresponding to the $\text{CH}_2$-Si, and seven C-$\text{CH}_2$-C. The $\text{CH}_2$-O protons were seen as two doublets of triplets at 3.33δ and 3.68δ (8-H$_2$) and two multiplets at 3.4-3.5δ and 3.78-3.90δ (5′-H$_2$). The olefinic protons were seen as two singlets at 4.63δ and 4.72δ. A triplet at 5.08δ represents the proton adjacent to the acetoxy group.

There were several peaks in the mass spectrum (chemical ionisation); $(\text{M+NH}_4)^+$ at m/z 374, $(\text{M+H})^+$ at m/z 357, and peaks corresponding to loss of the various molecular components: $(\text{M+H-AcOH})^+$ at m/z 297, $(\text{M+H-Thp})^+$ at m/z 273, $(\text{M+H-AcOH-TMS})^+$ at m/z 225, and $(\text{M+H-Thp-AcOH})^+$ at m/z 213. The accurate mass measurement of the $(\text{M+NH}_4)^+$ signal confirms the molecular structure.

Treatment of (107) with p-toluenesulphonic acid removed the Thp group to yield 6-acetoxy-7-(trimethylsilyl)methyl-7-octen-1-ol (108) in quantitative yield. The presence of the hydroxyl group was seen clearly by the absorption centred at 3400 cm$^{-1}$ in the I.R. spectrum. Other key signals, for the ester carbonyl group at 1740 cm$^{-1}$ and the alkene group at 1643 cm$^{-1}$ showed that the remainder of the molecule had not been affected by the reaction.
The proton n.m.r. showed a nine proton singlet at 0δ corresponding to the TMS group. There was also a ten proton multiplet between 1.2δ and 1.7δ corresponding to the 2-, 3-, 4-, 5- and 1'-CH₂'s. The acetate methyl group was observed as a three proton singlet at 2.05δ and the hydroxyl proton was seen as a singlet at 2.25δ. The 1-CH₂ protons were seen as a triplet at 3.6δ, the olefinic protons appeared as two singlets at 4.65δ and 4.85δ, and the methine proton on C6 appeared as a triplet at 5.15. The ¹³C n.m.r. spectrum showed the expected twelve signals including characteristic ones at 62.9δ for C1 (bonded to -OH), 77.1δ for C6 (bonded to acetoxy), 109.2 for C8, 145.3 for C7, and 170.5 for the ester carbonyl carbon atom. The mass spectrum (chemical ionisation) showed several peaks, including one at m/z 290 representing (M+NH₄)⁺, one at m/z 273 representing (M+H)⁺, and a significant peak caused by loss of acetic acid from this (M+H)⁺ ion at m/z 213.

The alcohol (108) was oxidised by buffered p.c.c.⁵¹ to give 6-acetoxy-7-(trimethylsilyl)methyl-7-octenal (109) in 62% yield. The presence of the aldehyde group was most easily seen by the triplet at 9.80δ (coupling constant <1Hz) in the proton n.m.r. spectrum. As well as an eight proton multiplet between 1.3δ and 1.8δ, corresponding to protons on C3, C4, C5 and C1', the ester methyl group appeared as a singlet at 2.10δ. The signal corresponding to the protons on C2 was a doublet of triplets with coupling constants of 6.8 and <1Hz. The olefinic protons appeared as two singlets at 4.7δ and 4.9δ, and the proton on C6 appeared as a triplet at 5.15δ with a coupling constant of 6.1Hz. In the I.R. spectrum there was no absorption above 3095cm⁻¹ confirming that the hydroxyl group was no longer present, but there were signals at 1740cm⁻¹ and 1640cm⁻¹ corresponding to the carbonyls and alkene groups respectively. The mass spectrum (electron impact) showed no molecular ion although one of the signals (at m/z 211) corresponds to (M+H-AcOH)⁺. The synthesis of the acyclic precursor containing allylsilane and aldehyde functionality and one chiral centre had now been successfully achieved.

Sarker and Andersen⁵², in the first example of an intramolecular addition of an allylsilane to a carbonyl group showed that this reaction can be performed either in the presence of a Lewis acid or fluoride ion. Identical conditions to those of Sarkar and Andersen, i.e. 3 equivalents of fluoride at 55°C in THF at a concentration of 30mMolar were employed initially. The reaction was monitored by t.l.c. which showed the formation of one major product (along with several minor products and baseline material), which after isolation by flash chromatography and complete characterisation, was identified as 4-acetoxy-3-methylene cyclooctanol (110). The isolated yield was 27%, and g.c. analysis of the crude reaction mixture showed that the product had been formed as a 1:1:1 mixture of diastereoisomers. Using g.c. to analyse the diastereoisomer ratio could give misleading results since the use of temperatures in the region of 200°C could assist in decomposition...
of the molecule. For example, (110) could lose the acetoxy group by a syn-elimination (E1) mechanism. If this occurred at a different rate in the two diastereoisomers then the apparent ratio would not be the true one. However, the 1H n.m.r. of the crude product also suggests that the ratio is 1:1:1 and so if decomposition is occurring then it must be happening at the same rate for both diastereoisomers. Key data, along with the accurate mass measurement is the I.R. absorptions at 3600cm⁻¹ and 3450cm⁻¹ showing the presence of the hydroxyl group, and at 1640cm⁻¹ from the double bond. A carbonyl group (the ester) is still present as seen by the absorption at 1720cm⁻¹. The lack of signals in the 1H n.m.r. spectrum for the trimethylsilyl (−06) and aldehyde groups (−9.88) show that the desired reaction has occurred. The other signals in the proton n.m.r. spectrum were as follows: between 1.25 and 2.08 there is an eighteen proton multiplet corresponding to the hydroxyl proton, 5-H2, 6-H2, 7-H2, and 8-H2 of both diastereoisomers. The ester methyl group is seen at 2.03δ and 2.06δ. The protons on the 2-position are seen as four doublet of doublets; at 2.23δ with coupling constants of 13.5Hz and 8.1Hz, at 2.33δ with coupling constants of 13.5Hz and 9.5Hz, at 2.57δ with coupling constants of 13.5Hz and 5.4Hz, and at 2.64δ with coupling constants of 13.5Hz and 5.4Hz. The proton on the 1-position (carbon also bonded to the hydroxyl group) appears as a multiplet at 3.75-3.85δ and 3.85-3.96δ. The olefinic protons appear as four singlets at 5.06δ, 5.08δ, 5.15δ, and 5.23δ. The proton on the 4-position is seen as two doublet of doublets at 5.24δ and 5.33δ with coupling constants of 4.3Hz and 9Hz, and 4.3Hz and 8.1Hz respectively.

The 13C n.m.r. spectrum showed the required number of pairs of signals (eleven) representing the eleven carbon atoms of each diastereoisomer. The off resonance decoupled spectrum showed that the molecule contained one CH3 group, six CH2 group, two CH groups, and two quaternary carbon atoms.

The mass spectrum, which was run under chemical ionisation conditions, showed a large peak at m/z 216 representing (M+NH4)⁺. Other signals observed were at m/z 199 (M+H)⁺, at m/z 181 (M+H-H2O)⁺, at m/z 170 (M-C2H4)⁺, at m/z 156 (M+H-Ac)⁺, and at m/z 139 (M+H-AcOH)⁺. Accurate mass measurement of (M+NH4)⁺ gave a result of 216.1604 as against the expected 216.1600.
4-Acetoxy-3-methylene cyclooctanol (110)
In an attempt to alter the ratio of diastereoisomers, the reaction was repeated under several different conditions. Firstly, the concentration was altered by dilution by a factor of 10, with the temperature still 55°C. Secondly, the reaction was performed at 0°C at the initial concentration. G.C. analysis of these reactions showed that there was no effect on the diastereoselectivity, as in both cases it remained at 1.1:1. The reaction was also attempted under Lewis acid catalysis conditions using BF₃.OEt, initially at 0.1 equivalent then 1 equivalent. Reaction was at -78°C, but was later warmed to room temperature as no reaction appeared to be occurring, and still there was no reaction when analysed by t.l.c. and g.c. The reaction was also attempted using TiCl₄ as Lewis acid catalyst, using 1 equivalent at -78°C. Again, there did not appear to be any reaction.
Some molecular modelling calculations were performed on this system to see whether this would explain the apparent lack of stereoselectivity in the cyclisation reaction. The modelling strategy used was to fix the reacting centres at a fixed distance apart, and molecular mechanics (MMPI) was used to compare the energies of the two diastereomeric transition state models. MMPI is a conjugated version of the MM2 extended Hückel calculation. The relative stereochemistry of the reacting centres and tightness of the geometrical constraints are shown as follows. This calculates the approach of the olefin to the carbonyl in an early transition state, where \( \alpha \) is the angle of approach between the olefin and the carbonyl oxygen, and \( r \) is the distance apart. With the C-C bond length of 1.54\( \AA \), \( r \) is taken at 4.0\( \AA \) as an estimate of the distance between the olefin and carbonyl groups just as the bond is about to form in the early transition state. Allyl silanes react under two conditions with a ketone. One involves treatment with acid by the following mechanism where the transition state is late as the initial step is attack of the allyl silane on the protonated aldehyde. In the reaction with fluoride ion the initial attack is on the silicon which then reacts with the carbonyl group, it is therefore assumed that the transition state for this reaction is more like the starting material than the product, i.e. an early transition state:

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

<table>
<thead>
<tr>
<th>Diastereoisomer (see note a)</th>
<th>( r/\AA )</th>
<th>( \alpha/\degree )</th>
<th>Constraints (see note b)</th>
<th>E/Kcal mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4.0</td>
<td>100</td>
<td>tight</td>
<td>13.29</td>
</tr>
<tr>
<td>A</td>
<td>4.0</td>
<td>100</td>
<td>loose</td>
<td>12.27</td>
</tr>
<tr>
<td>B</td>
<td>4.0</td>
<td>100</td>
<td>tight</td>
<td>13.44</td>
</tr>
<tr>
<td>B</td>
<td>4.0</td>
<td>100</td>
<td>loose</td>
<td>12.38</td>
</tr>
</tbody>
</table>

The lowest energy found in the absence of geometrical constraints = 10.62 Kcal mol\(^{-1}\).
Notes:

(a) The stereochemistries 'A' and 'B' are represented in the following stereo diagrams (for 3-D effect, view the diagrams through the special glasses provided), as in the lowest energy conformation.

(b) Under the tight constraint, the aldehyde group and olefinic methylene lie in parallel planes, whereas under loose this constraint is absent.

(c) A tert-butyl group has replaced the trimethylsilyl group in this work as the software had not been adequately parameterised for silicon.
TRANSITION STATE MODEL; DIASTEREOMER A; TIGHT CONSTRAINTS
TRANSITION STATE MODEL; DIASTEROMER A; TIGHT CONSTRAINTS
TRANSITION STATE MODEL; DIASTEREOMER B; TIGHT CONSTRAINTS
TRANSITION STATE MODEL; DIASTEREOMER B; TIGHT CONSTRAINTS
8 RING PRECURSOR: LOWEST ENERGY CONFORMER FOUND
8 RING PRECURSOR: LOWEST ENERGY CONFORMER FOUND
The conclusion drawn from this work was that the costs in enthalpy of adopting a transition state are such that the cyclisations should proceed, although little stereoselectivity would be expected. These predictions seem to agree with the observed experimental results.

The rate of a reaction can be represented by:

\[
\text{Rate constant (k)} = Ae^{-E/RT}
\]

Under the tight constraint:

\[
\text{Rate constant for A} = Ae^{-13.29/RT} \\
\text{Rate constant for B} = Ae^{-13.44/RT}
\]

Since the difference in energy is so small, the cyclisation is reversible and therefore it must be under kinetic control.

Since there appeared to be no selectivity in the formation of an 8-membered ring via this intramolecular allylsilane-aldehyde reaction, it was decided to repeat the route, starting from 1,4-butane-diol which would lead to the synthesis of a 6-membered ring. Hopefully, with the smaller ring there would be a greater chance of getting selectivity, and also the usefulness of the reaction in terms of yield could be compared with alternative methods.

The 1,4-butane-diol was monoprotected with dihydropyran as previously to give 4-tetrahydropyranyloxy-butan-1-ol (111) in 50% yield. The I.R. spectrum showed that there was still a hydroxyl group in the molecule as there was an absorption at 3400cm\(^{-1}\). The proton n.m.r. spectrum had a ten proton multiplet between 1.35 and 1.95, a one proton broad singlet at 2.16 representing the hydroxyl group, a further six proton multiplet between 3.35 and 4.05 representing the three CH\(_2\)-O groups, and a one proton broad singlet at 4.56 representing the acetal proton. Alcohol (111) was oxidised using p.c.c. to give 4-tetrahydropyranyloxy-butanal (112) in 83% yield. As before, identification was confirmed by the presence of an absorption at 1720cm\(^{-1}\) in the I.R. spectrum, and a triplet at 9.75 in the proton n.m.r. spectrum caused by the aldehyde moiety. Aldehyde (112) was reacted with 2-bromo-3-[(trimethylsilyl)propene (104) in a Grignard reaction. Unlike 8-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-1-octen-3-ol (106) which appeared to be unstable, the 6-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-1-hexen-3-ol (113) was isolated as a pure compound in 27% yield. The accurate mass measurement confirmed the molecular formula, and the expected signals corresponding to the trimethylsilyl (0.055, \(^1\)H n.m.r. spectrum), double bond (1630cm\(^{-1}\), I.R. spectrum; 4.67\(\delta\) and 4.93\(\delta\), \(^1\)H n.m.r. spectrum), alcohol (3460cm\(^{-1}\), I.R. spectrum, singlet 2.43\(\delta\) \(^1\)H n.m.r spectrum), and tetrahydropyranyloxy (4.60\(\delta\), \(^1\)H n.m.r. spectrum [O-CH-O], 85 mass units in the mass spectrum) groups.
Alcohol (113) was acetylated as previously\(^6\) to give 3-acetoxy-6-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-hex-1-ene (114) in 53% yield as a 1:1 mixture of diastereoisomers. The I.R. spectrum had no absorption above 3000 cm\(^{-1}\) showing that the hydroxyl group was no longer present. There were absorptions at 1735 cm\(^{-1}\) caused by the ester carbonyl group, and at 1640 cm\(^{-1}\) caused by the double bond. The proton n.m.r. showed the TMS group as an eighteen proton singlet at 0.04\(\delta\). A twenty-four proton multiplet between 1.48 and 1.98 was caused by the 4-H\(_2\), 5-H\(_2\), 2'-H\(_2\), 3'-H\(_2\), 4'-H\(_2\), and 1''-H\(_2\) of both diastereoisomers. The methyl groups were seen as a six proton singlet at 2.05\(\delta\). The four CH\(_2\)-O groups were seen as multiplets at 3.35-3.43\(\delta\), 3.43-3.53\(\delta\), 3.67-3.78\(\delta\), and 3.78-3.90\(\delta\) and the olefinic protons were seen as two two-proton singlets at 4.68\(\delta\) and 4.85\(\delta\). The 3-H was seen as a triplet at 5.12\(\delta\). The correct number of carbon atoms (15) were observed in the \(^{13}\)C n.m.r. spectrum. Peaks corresponding to (M+NH\(_4^+\)) at m/z 346, (M+H\(^+\)) at m/z 329, as well as peaks caused by fragmentation of the ion and loss of Thp, TMS, and AcOH were seen in the mass spectrum (chemical ionisation).

Removal of the Thp group was achieved using p-toluene sulphonic acid to give 4-acetoxy-5-(trimethylsilyl)methyl-5-hexenal (115). The I.R. spectrum showed absorption at 3400 cm\(^{-1}\), confirming that the Thp group had been removed, and absorptions at 1735 cm\(^{-1}\) and 1640 cm\(^{-1}\) showing that the ester and double bond functionality was unaffected. The proton n.m.r. showed signals for TMS, a nine proton singlet at 0.05\(\delta\), the ester methyl group, a three proton singlet at 2.08\(\delta\), the 6-H\(_2\), a triplet at 3.65\(\delta\), the olefinic protons as two doublets at 4.70\(\delta\) and 4.87\(\delta\) (showing coupling of \(<1\) Hz to each other), and the 3-H as a triplet at 5.14\(\delta\). The \(^{13}\)C n.m.r. showed ten signals as expected. The mass spectrum (chemical ionisation) showed peaks at m/z 262 corresponding to (M+NH\(_4^+\))\(^+\), and m/z 245 corresponding to (M+H\(^+\))\(^+\) as well as peaks corresponding to fragmentation of these ions.

Collins oxidation\(^7\) afforded 4-acetoxy-5-(trimethylsilyl)methyl-5-hexenal (116) in 46% yield. The I.R. spectrum showed that the hydroxyl group was no longer present since there was no absorption above 3100 cm\(^{-1}\). As before, there is absorption at 1735 cm\(^{-1}\) which is caused by both the ester and aldehyde carbonyl groups. The proton n.m.r. spectrum shows a triplet with a coupling constant of 1 Hz at 9.76\(\delta\) caused by the aldehyde group, as well as confirming the presence of the TMS (nine proton singlet at 0.05\(\delta\)), double bond (two doublets with coupling constants of \(1\) Hz at 4.71\(\delta\) and 4.86\(\delta\)), and ester (part of a five proton multiplet along with the 3-H\(_2\) between 1.91\(\delta\) and 2.15\(\delta\)) groups. The \(^{13}\)C n.m.r. spectrum confirms that (116) contains ten carbon atoms.

Fluoride ion catalysed cyclisation was achieved in 38% yield, however the diastereoisomer ratio, measured by proton n.m.r. on the crude reaction mixture, of 4-acetoxy-3-methylene
cyclohexanol (117) was only 1.3:1, which is essentially the same as that for the 8-membered ring case. Complete characterisation confirmed the structure of (117); signals caused by alcohol (3600, 3440 cm⁻¹, I.R. spectrum), double bond (1650 cm⁻¹, I.R. spectrum; 4.875, 4.918, 4.938, and 5.018, ¹H n.m.r. spectrum), and acetoxy (1720 cm⁻¹, I.R. spectrum; 1708, ¹³C spectrum) groups were present, and the accurate mass measurement confirmed the molecular composition. The diastereoisomer ratio suggests that, as before, there must be little energy difference between the conformations of the transition states leading to cyclisation. However, it can be seen from the proton n.m.r. spectrum that although the cyclisation appears to have worked (117) is not completely pure, since small unaccounted for peaks are also present.
4-Acetoxy-3-methylene cyclohexanol (117)
Between 1.52δ and 2.50δ there is a multiplet which integrates to twenty-four protons rather than the expected nineteen: the CH₃, 5-H₂, 6-H₂, 2-H (three of the total of four), and OH of both diastereoisomers. The remaining 2-H is observed as a doublet of doublets with couplings of 3Hz and 5Hz at 2.67δ. The 1-H is seen as a multiplet between 3.76δ and 3.90δ. The olefinic protons are seen as four singlets at 4.87δ, 4.91δ, 4.93δ and 5.01δ, and the 4-H is seen as a two proton multiplet at 5.21δ.

The ¹³C n.m.r. spectrum shows that there are four CH₂'s, two CH's, one CH₃, and two quaternary carbon atoms in the molecule. The mass spectrum was run under chemical ionisation conditions and showed the following peaks: at m/z 188 (M+NH₄)⁺, at m/z 171 (M+H)⁺, at m/z 170 M⁺, at m/z 153 (M+H-H₂O)⁺, at m/z 128 (M+H+Ac)⁺, at m/z 111 (M+HAcoH)⁺, and at m/z 93 (M+H-Aco-H₂O)⁺. An accurate mass measurement was made on the (M+NH₄)⁺ ion and this gave a result of 188.1289 as against the expected 188.1287.

The route was also repeated to synthesise 4-acetoxy-3-methylene-cycloheptanol (118). 5-Tetrahydropyranloxy-pentan-1-ol (119) was synthesised from 1,5-pentane-diol in 46% yield. Absorption at 3620cm⁻¹ and 3460cm⁻¹ in the I.R. spectrum confirm that an OH group is still present, and the singlet at 4.58 in the ¹H n.m.r. spectrum shows that Thp is now present, along with the total integration of the peaks in this spectrum. (119) was then oxidised using p.c.c. to give 5-tetrahydropyranloxy-pentanal (120) in 64% yield. The I.R. spectrum showed no absorption due to OH above 3000cm⁻¹, but had an absorption at 1720cm⁻¹ showing the presence of an aldehyde group. The proton n.m.r. spectrum had the characteristic broad singlet of the acetal proton, and also had a triplet with a coupling constant of <1Hz at 9.75 showing the presence of the aldehyde functionality.

Aldehyde (120) was reacted with 2-bromo-3-(trimethylsilyl)propene (104) in a Grignard reaction and the product (121) was used crude in the acetylation reaction to give 3-acetoxy-7-tetrahydropyranloxy-2-(trimethylsilyl)methyl-hept-1-ene (122) in overall 15% yield after the two reactions. This compound was completely characterised. The presence of ester and double bond can be seen in the I.R. spectrum by absorptions at 1740cm⁻¹ and 1640cm⁻¹ respectively. The proton n.m.r. had a nine proton singlet at 0.05δ corresponding to TMS. Between 1.27δ and 1.94δ there was a fourteen proton multiplet corresponding to 4-H₂, 5-H₂, 6-H₂, 2'-H₂, 3'-H₂, 4'-H₂, and 1"-H₂. The ester methyl group was seen as a singlet at 2.07δ. The 7-H's were seen as two doublet of triplets at 3.40δ with coupling constants of 6.4Hz and 9Hz, and at 3.75δ with the same coupling constants. The 5'-H's were seen as multiplets at 3.47-3.57δ and 3.83-3.93δ. The olefinic protons were seen as two singlets at 4.70δ and 4.88δ, whilst the 3-H was seen as a triplet at 5.13δ. The ¹³C n.m.r. showed the expected sixteen signals. The mass spectrum was run under chemical
ionisation conditions and showed a (M+NH₄⁺) peak at m/z 360 and (M+H)⁺ at m/z 343 as well as other peaks caused by ions formed by fragmentation of these ions by loss of Thp, TMS, AcOH and combinations of these. Accurate mass measurement of (M+NH₄⁺) gave a value of 360.2570 which is identical to the expected value.

Deprotection of (122) gave 5-acetoxy-6-(trimethylsilyl)methyl-6-hepten-1-ol (123) in 75% yield. Key data for this compound shows the presence of the OH group (3620cm⁻¹ and 3480cm⁻¹ I.R. spectrum, 2.67δ broad singlet n.m.r. spectrum, and peaks involving loss of water in the mass spectrum) as well as confirming that the TMS (nine proton singlet at 0.05δ in ¹H n.m.r. spectrum, and peaks involving loss of TMS in the mass spectrum), ester (absorption at 1730cm⁻¹ in the I.R. spectrum, methyl singlet at 2.05δ in the ¹H n.m.r. spectrum, signal at 170.2δ in the ¹³C n.m.r. spectrum, and peaks involving loss of Ac and AcO in the mass spectrum), and double bond (absorption at 1635cm⁻¹ in the I.R. spectrum, and doublets both with coupling constants <1Hz at 4.67δ and 4.84δ in the n.m.r. spectrum) groups are still present.

(123) Was oxidised using a Collins oxidation⁷⁰ to give 5-acetoxy-6-(trimethylsilyl)methyl-6-heptenal (124) in 60% yield. The spectral data confirms the presence of TMS, ester, and double bond functionalities as the key peaks and signals are still present as in compound (123) with slight differences in the values. The OH peak is no longer present as confirmed by the I.R. spectrum which no longer has absorption above 3000cm⁻¹. The presence of the aldehyde group is seen by the absorption at 1725cm⁻¹ in the I.R. spectrum (the ester carbonyl also absorbs in this region), the triplet with a coupling constant of 1Hz at 9.74δ in the ¹H n.m.r. spectrum, and the signal at 201.7δ in the ¹³C n.m.r. spectrum.

Cycloheptanol (118) was produced in 46% yield as a 1.3:1 mixture of diastereoisomers (¹H n.m.r.) from (124) under fluoride ion catalysis. Accurate mass measurement confirmed the molecular formula and other spectral data confirmed the molecular structure: alcohol (3410cm⁻¹, I.R. spectrum), double bond (1640cm⁻¹, I.R. spectrum; 5.05δ, 5.07δ, 5.17δ, and 5.18δ, ¹H n.m.r. spectrum), and acetoxy (1730cm⁻¹, I.R. spectrum, 1708 ¹³C n.m.r. spectrum) groups are clearly present. The proton n.m.r. spectrum has a twenty-three proton multiplet between 1.22δ and 2.55δ and this is caused by the 5-H₂, 6-H₂, 7-H₂, OH, and CH₃ of both diastereoisomers along with three of the four protons on C2. The fourth of these is seen as a doublet of doublets, coupling constants 3Hz and 5.8Hz, at 2.66δ. The proton on C1 is seen as two multiplets at 3.7-3.85δ and 3.88-3.98δ respectively. The four olefinic protons are seen as two doublets with coupling constants of <1Hz at 5.05δ and 5.07δ and two triplets with coupling constants of 1Hz at 5.17δ and 5.18δ. For them to appear as triplets there must be long range coupling to one of the protons on C2 (which are
In the large multiplet between 1.225 and 2.555). The $^{13}$C n.m.r. spectrum confirms that there are four CH$_2$'s, three CH's, one CH$_3$, and two quaternary carbon atoms in the molecule. The mass spectrum was run under chemical ionisation conditions and had peaks for (M+NH$_4$)$^+$ at m/z 202, and (M+H)$^+$ at m/z 185. Other peaks were for (M+H$_2$O)$^+$ at m/z 167, (M+H-Ac)$^+$ at m/z 142, (M+H-AcOH)$^+$ at m/z 125, and (M+H-AcOH-H$_2$O)$^+$ at m/z 107. Accurate mass measurement of (M+NH$_4$)$^+$ gave a value of 202.1443 which was identical with the expected value.
4-Acetoxy-3-methylene cycloheptanol (118)
A summary of the results of these intramolecular allylsilane-aldehyde cyclisations is shown as follows:

<table>
<thead>
<tr>
<th>Cyclisation</th>
<th>Yield</th>
<th>Diastereoisomer Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Cyclisation" /></td>
<td>38%</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td><img src="image2" alt="Cyclisation" /></td>
<td>46%</td>
<td>1.3 : 1</td>
</tr>
<tr>
<td><img src="image3" alt="Cyclisation" /></td>
<td>27%</td>
<td>1.1 : 1</td>
</tr>
</tbody>
</table>

In conclusion, it seems that the intramolecular allylsilane-aldehyde cyclisation will occur in these simple molecules to give reasonable yields of the cyclised product. There appears, however, to be insufficient enthalpy difference between conformations adopted in the transition states which lead to cyclisation, to confer any stereoselectivity upon the reaction. This is in contrast to Still's work where reactions were performed on medium ring compounds, and then selectivity was clearly observed in a variety of reactions. In Still's work, however, the two substituents were both methyl groups. These will have different steric and conformational preferences to the hydroxyl and acetoxy substituents used in this work and so a direct comparison between the two pieces of work is not necessarily valid. Clearly in the Diels-Alder cyclisation mentioned in the introduction where the 8-membered
ring was produced as a single diastereoisomer, the greater substitution of the acyclic precursor leading to the 8-membered ring assists greatly the selectivity of the reaction.
CHAPTER 5

ATTEMPTED ACETAL-INITIATED
ALLYLSILANE CYCLISATION
CHAPTER 5

ATTEMPTED ACETAL-INITIATED ALLYLSILANE CYCLISATION

5.1 Introduction

The initial aim of the project was to synthesise not only carbocyclic but also heterocyclic medium rings, and so it was decided to attempt an acetal initiated cyclisation of an allylsilane. There is precedent for this type of reaction, both intermolecularly and also intramolecularly.

Fleming and co-workers⁷¹ formed a 6-membered ring via this reaction to give the single olefin shown:

In contrast, when the trimethylsilyl group is replaced by hydrogen, a mixture of five products is obtained: three olefins and two diastereoisomeric ethers. This illustrates the controlling influence of the trimethylsilyl group on the outcome of the reaction.

Overman and co-workers⁷² used an intramolecular vinyl silane acetal cyclisation reaction to generate 8- and 9-membered cyclic ethers.
The reaction was performed at -20°C with two equivalents of SnCl₄ for 1 hour to give a 30:1 mixture of cis- and trans-2,8-dimethyl oxocene products in 34% yield.

Subsequently, this method was used in the total synthesis of (-)-laurenyne, a marine natural product, where the key step is the cyclisation of a mixed acetal to yield the oxocene (125).

1. 2eq. SnCl₄, CH₂Cl₂, 0°C, 1.5hr
2. n-Bu₄NF

(125) Was produced in 37% yield as the sole cyclic ether product, and there was no evidence for an isomer of (125) in the crude cyclisation product mixture when analysed by ¹H n.m.r.

5.2 Results and Discussion

It was, therefore, decided to attempt an acetal initiated allylsilane reaction on compounds (107) and (114) which had previously been synthesised as part of the scheme to study the allylsilane aldehyde cyclisation reaction (Chapter 4), and also 3-acetoxy-5-tetrahydropyran-3-yloxy-2-(trimethylsilyl)methyl-pent-1-ene (126).

The key question in the attempted cyclisation is which of the carbon-oxygen bonds of the acetal would break in preference, or whether there would be a mixture of products. For a ring to be produced it is necessary for the bond shown to break.
The alternative bond breaking process leads to deprotection of the primary hydroxyl group, i.e. release of dihydropyran. The standard method of achieving this deprotection is acidic conditions and these molecules have been deprotected using 0.08 equivalents of p-toluene sulphonylic acid (see previous chapter), and this suggests that this will in fact be the preferred route of reaction. In the Introduction, all the examples that were found in the literature on the reaction of acetals with allyl silanes under Lewis acid catalysis conditions were discussed. None has the choice of an endo or exo cyclic bond to undergo cleavage.

The conditions employed for this attempted cyclisation were identical to Overman^{72}, i.e. 2 equivalents of tin (IV) chloride in CH$_2$Cl$_2$ at -20°C. Reaction time was dependent upon reaction progress as monitored by t.l.c. The first reaction attempted was with 3-acetoxy-5-tetrahydropyranloxy-2-(trimethylsilyl)methyl-pent-l-ene (126) which was synthesised as follows: Propane-1,3-diol was monoprotected with dihydropyran in the presence of P.P.T.S. to give 3-tetrahydropyranloxy-1-propanol (127). This showed an absorption at 3410cm$^{-1}$ in the I.R. spectrum, as well as a broad singlet at 2.68 in the proton n.m.r. spectrum corresponding to the hydroxyl group. The proton n.m.r. also had an eight proton multiplet at 1.3-1.98 from the four CH$_2$'s, a six proton multiplet at 3.4-4.18 from the three CH$_2$-O's, and the characteristic broad singlet at 4.58 from the acetal proton. Oxidation of (127) by p.c.c. gave aldehyde (128) which was shown to possess an aldehyde group by the presence of a one proton triplet with a coupling constant of <1Hz at 9.78 in the proton n.m.r. spectrum. (128) was reacted with (104) to give 5-tetrahydropyranloxy-2-(trimethylsilyl)methyl-1-penten-3-ol (129) as 1:1 mixture of diastereoisomers. This compound was seen to contain a hydroxyl (absorption at 3450cm$^{-1}$ I.R. spectrum and singlet at 2.978 in the $^1$H n.m.r. spectrum), TMS (singlet at 08 in the $^1$H n.m.r. spectrum, peak at m/z 73 in the mass spectrum), double bond (absorption at 1630cm$^{-1}$ in the I.R. spectrum, singlet at 4.708 and doublet at 5.028 in the $^1$H n.m.r. spectrum), and Thp (triplet at 4.638 in the $^1$H n.m.r. from the O-CH-O proton, peak at m/z 85 in the mass spectrum) groups. Compound (129) was acetylated to give 3-acetoxy-5-tetrahydropyranloxy-2-(trimethylsilyl)methyl-pent-l-ene (126). The presence of
the acetoxy group can be seen from the absorption at 1740 cm\(^{-1}\) in the I.R. spectrum, the three-proton singlets at 2.078 and 2.088 in the \(^1\)H n.m.r spectrum, the quartet at 21.28 in the \(^{13}\)C off-resonance decoupled spectrum, and peaks in the mass spectrum corresponding to loss of this group.

Under the Overman conditions, t.l.c. showed one major reaction product which appeared to be one of the expected ones. The yield was 36% and the product was a 2.4:1 mixture of diastereoisomers.
It can be seen that it is difficult to assign which of these two compounds has been produced by $^1$H or $^{13}$C n.m.r. or I.R. spectroscopy as both compounds would have similar spectral characteristics. Both have identical molecular weight, and the most conclusive evidence seemed to be the fragmentation pattern of the mass spectrum. There was a strong signal at m/z 85, corresponding to Thp$^+$. It is difficult to envisage an ion of molecular weight 85 arising from the alternative product (130). This suggests that the undesired reaction has occurred to give (131), 3-acetoxy-2-(tetrahydropyranyl)methyl-1-penten-5-ol. The I.R. spectrum had absorptions at 3515 cm$^{-1}$ and 3480 cm$^{-1}$ from the hydroxyl group, 1730 cm$^{-1}$ from the ester carbonyl group, and 1645 cm$^{-1}$ from the double bond. The $^1$H n.m.r. showed an eighteen proton multiplet at 1.20-2.08 from the 4-H$_2$, 5'-H$_2$, 3'-H$_2$, 4'-H$_2$, and -OH of both diastereoisomers. The methyl singlets were seen at 2.086 and 2.096. The 1'-H$_2$'s were seen as two proton multiplets at 2.01-2.22 and 2.25-2.37. The protons adjacent to oxygen (6'-H$_2$, 5-H$_2$) were seen as four proton multiplets at 3.35-3.52 and 3.55-3.84 respectively. The 2'-H's were seen as a multiplet 3.92-4.04. The olefinic protons were seen as two two-proton singlets at 5.015 and 5.155, and the proton adjacent to the acetoxy group was seen as two proton triplets at 5.395 and 5.415. The $^{13}$C n.m.r. showed that (131) contained eight CH$_2$'s, two CH's, one CH$_3$, and two quaternary carbon atoms. The mass spectrum, which was run under chemical ionisation conditions, showed a peak at m/z 243 from (M+H)$^+$ as well as further peaks at m/z 219 (M+NH$_4$-C$_3$H$_5$)$^+$, m/z 183 (M+H-AcOH)$^+$, m/z 165 (M+H-AcOH-H$_2$O)$^+$, m/z 153 (M+H-AcO-CH$_2$OH)$^+$, and m/z 85 Thp$^+$. The accurate mass measurement of (M+H)$^+$ gave a value of 243.1596 which is identical to the expected value.

The reaction was also performed upon 3-acetoxy-6-tetrahydropyranoxyloxy-2-(trimethylsilyl)methyl-hex-1-ene (114).
Unlike the previous example, two products were isolated one of which appeared to be the analogue of (131), i.e. 3-acetoxy-2-(tetrahydropyranyl)methyl-1-hexen-6-ol (132) in 28% yield as a 5:1 ratio of diastereoisomers. (132) showed similar properties, including the characteristic signals in the mass spectrum corresponding to the presence of Thp in the molecule. The I.R. spectrum showed absorptions at 3615cm⁻¹ and 3450cm⁻¹ from hydroxyl, 1725cm⁻¹ from the carbonyl group, and 1645cm⁻¹ from the double bond. The ¹H n.m.r. had a twenty proton multiplet at 1.20-1.88δ corresponding to the 4-H₂, 5-H₂, 5'-H₂, 3'-H₂, 4'-H₂ of both diastereoisomers. The methyl groups were seen as two singlets at 2.05δ and 2.06δ. There was a doublet of doublets at 2.10δ and 2.32δ from the 1'-H's. The hydroxyl proton was seen as a broad singlet at 2.45δ. The protons adjacent to oxygen were seen as a four proton multiplet and a four proton triplet at 3.36-3.53δ and 3.64δ. The 2'-H's were seen as a doublet of triplets at 3.96δ and the olefinic protons were seen as two one proton doublets at 4.96δ and 4.98δ, and two one proton singlets at 5.06δ and 5.09δ. The 3-H was seen as a triplet at 5.25δ. The ¹³C n.m.r. confirmed that the molecule contained nine CH₂'s, two CH's, one CH₃, and two quaternary carbon atoms. The mass spectrum, run under chemical ionisation conditions, had a peak from (M+H)⁺ at m/z 257 in addition to peaks at m/z 239 (M+H-H₂O)⁺, m/z 197 (M+H-AcOH)⁺, m/z 179 (M+H-AcOH-H₂O)⁺, m/z 102 ThpOH⁺, and m/z 85 Thp⁺. The accurate mass measurement gave a value for (M+H)⁺ of 257.1753 which was identical to the expected value. Recently, a synthesis of (+)-octahydroacetyldebronomouscin (133) has been reported in the literature.

![Structure of (133)](image)

However, as expected the spectroscopic data for this compound are difficult to interpret because of the number of CH₂'s it contains and this exemplifies the problem of conclusive identification of the product (132) or (134) of the Lewis acid cyclisation attempted.

The other product appeared to be the doubly acetylated product 3,6-di-acetoxy-2-(tetrahydropyranyl)methyl-hex-1-ene (135) in 26% yield, as a 3:1 ratio of diastereoisomers where the reaction product has picked up acetate from the reaction mixture prior to quenching. (None of the corresponding di-alcohol product was isolated, however this would have run very low on the t.l.c. plate, hence amongst the other baseline material?) The I.R. spectrum had no absorption above 3040cm⁻¹ showing that there is no alcohol group in the molecule. The ¹H n.m.r. showed twelve protons which are part of the ester methyl group -
two methyl groups per diastereoisomers. The $^{13}$C n.m.r. confirmed the presence of two carbonyl groups as there were signals at 170.05 and 170.95, both from quaternary carbon atoms. The mass spectrum, run under chemical ionisation conditions, showed a peak at m/z 179 corresponding to the (M+2H-2AcOH)$^+$ ion indicating the presence of two acetate groups. The accurate mass measurement of the (M+H)$^+$ ion gave a value 299.1858 which exactly agrees with the value expected for (135).

When 3-acetoxy-8-tetrahydropyranoxy-2-(trimethylsilyl)methyl-oct-1-ene (107) was treated with tin (IV) chloride under these conditions a single major product was isolated in 52% yield as a 2.3:1 mixture of diastereoisomers and as previously was the product formed via initial loss of Thp; 3-acetoxy-2-(tetrahydropyranyl)methyl-1-octen-8-ol (136). The I.R. spectrum had absorptions at 3615 cm$^{-1}$ and 3450 cm$^{-1}$ from the -OH, 1725 cm$^{-1}$ from the carbonyl, and 1640 cm$^{-1}$ from the double bond. The $^1$H n.m.r. had a twenty-six proton multiplet at 1.20-1.70 δ from the 6-H$_2$, 7-H$_2$, 5-H$_2$, 5'-H$_2$, and 3'-H$_2$ of both diastereoisomers and one of the 4-H$_2$'s. The other 4-H$_2$ is seen as a multiplet at 1.78-1.87 δ. The methyl groups were seen as two singlets at 2.04δ and 2.05δ. The 1'H's were seen as four doublet of doublets, two at 2.00-2.15δ (masked by CH$_3$), 2.26δ, and 2.31δ. The hydroxyl proton was seen as a two proton singlet at 2.50δ, and the CH$_2$'s adjacent to oxygen were seen as a multiplet at 3.35-3.52δ and a triplet at 3.59δ. The 2'-H's were seen as a doublet of triplets at 3.96δ, and the olefinic protons were seen as two doublets at 4.94δ and 4.96δ and two singlets at 5.04δ and 5.06δ, whilst the 3-H's were seen as a triplet at 5.18δ. The $^{13}$C n.m.r. confirmed that the molecule contains eleven CH$_2$'s, two CH's, one CH$_3$, and two quaternary carbon atoms. The mass spectrum was run under chemical ionisation conditions and had peaks at m/z 302 from (M+NH$_4$)$^+$ and m/z 285 from (M+H)$^+$, as well as at m/z 225 from (M+H-AcOH)$^+$, m/z 207 from (M+H-AcOH-H$_2$O)$^+$, m/z 123 from (M+H-AcO-H$_2$O-Thp)$^+$, m/z 102 from ThpOH$^+$, and m/z 85 from Thp$^+$. The accurate mass measurement of the (M+H)$^+$ ion gave a value of 285.2065 and the expected value is 285.2066.
In all the foregoing reactions isolated products arise via Lewis acid initiated breaking of the C-O bond leading to loss of Thp, followed by an intermolecular reaction of the allylsilane with this electrophile.

An attempt was made to gain further evidence for the suggested mode of reaction, as follows:

Alcohol (132) was acetylated to give the doubly acetylated product (135), this also proves the initial identification of (135) as the other product of the Lewis acid catalysed reaction, given the identical spectral properties of the compounds produced via the two methods. Acetal/allylsilane (114) was deprotected using p-toluene sulphonic acid\(^{62}\) to give alcohol (115) (see Chapter 4). The free primary hydroxyl group was acetylated by the previous method\(^{69}\) to give 3,6-di-acetoxyl-2-(trimethylsilyl)methyl-hex-1-ene (137). The I.R. spectrum had no absorption above 3060cm\(^{-1}\) showing that there is no hydroxyl group. There is absorption at 1735cm\(^{-1}\) showing the presence of at least one acetoxyl group. The presence of two groups is seen from the two methyl singlets at 2.046 and 2.075 in the \(^1\)H n.m.r., and two quartets at 20.88 and 21.18 in the \(^{13}\)C n.m.r. spectrum. In the mass spectrum there are peaks corresponding to loss of two acetoxyl groups: m/z 185 (\(\text{M}+2\text{H}-\text{AcOH-Ac}^+\)), m/z 167 (\(\text{M}+\text{H}-2\text{AcOH})^+\), and m/z 112 from (\(\text{M}+2\text{H}-\text{TMS-Ac-AcOH})^+\). This compound was reacted with dihydropyran in the presence of two equivalents of tin (IV) chloride under identical conditions to previously.

Unfortunately, this reaction was not successful, and no product could be conclusively identified. A couple of products were isolated in small quantities, however they did not appear to be pure. Also, there was a large quantity of baseline material.
In retrospect, the scheme outlined is not necessarily very good, and it may have been better to have used, for example, an ethoxy- or methoxy-tetrahydropyranoyloxy protecting group as then it may have been possible to conclusively identify the products of the Lewis acid catalysed reactions. This may have been possible through use of n.m.r. techniques such as the Nuclear Overhauser Effect where irradiation of a nucleus in the molecule will affect the intensity of signals caused by nuclei which lie close to this irradiated nucleus.

Alternatively, a completely different approach could have been used. For example, consider the products (132) and (134). Firstly, the hydroxyl group is oxidised to the carboxylic acid and secondly, the acetoxy group is hydrolysed to the hydroxyl group. Under esterification conditions, the derivative of (132) gives the $\gamma$-lactone whereas the derivative of (134) gives either an intermolecular ester or a 9-membered lactone. As before, the $^1$H and $^{13}$C n.m.r. spectra would not conclusively identify which of the two products had been formed, however the I.R. spectrum would show a characteristic absorption for the carbonyl group. The $\gamma$-lactone would have an absorption between 1780cm$^{-1}$ and 1760cm$^{-1}$, whereas the intermolecular ester/9-membered lactone would have an absorption between 1750cm$^{-1}$ and 1735cm$^{-1}$.
In summary, it appears that the desired cyclisation is not occurring, instead Thp is being lost in preference and this is reacting with the allylsilane to give the observed products. The evidence for this alternative mode of reaction stems mainly from the mass spectral data which is far from conclusive. As in the Overman work, it may be better to have an acyclic acetal protecting group instead of Thp. For example:
EXPERIMENTAL
EXPERIMENTAL

All 90 MHz $^1$H n.m.r. spectra were recorded on a Varian EM-390 spectrometer. High-field $^1$H n.m.r. (300 MHz) and $^{13}$C n.m.r. (75 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. High-field $^1$H n.m.r. (270 MHz) and $^{13}$C n.m.r. (67.8 MHz) spectra were recorded on a Jeol JNM-GX270 spectrometer at I.C.I. Pharmaceuticals, Macclesfield. Accurate mass measurements were made at the SERC Mass Spectrometry Centre, University College of Swansea and standard mass spectra were recorded on a micromass 16B spectrometer. Infra-red spectra were recorded on a Perkin-Elmer 298 spectrometer.

Flash chromatography was carried out according to the method of Still et al$^{75}$ using silica gel manufactured by Merck and Co., Kiesel 60, 230-400 mesh (ASTM). T.l.c. was conducted on precoated aluminium sheets (60-254) with a 0.2 mm layer thickness, manufactured by Merck and Co.

The concentration of the n-butyllithium was determined by back titration with 0.1 M hydrochloric acid from solutions in dibromoethane and water using phenolphthalein as an indicator.

Petroleum ether refers to the 40-60°C fraction and all petroleum ether and ethyl acetate was distilled prior to use. THF and toluene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether and was distilled from LiAlH$_4$.

Dichloromethane, triethylamine and pyridine were distilled from powdered calcium hydride and trimethylsilyl chloride was distilled immediately prior to use from tributylamine. Methanol was distilled from magnesium and iodine.

In the t-butyldimethylsilyloxy-protected compounds and trimethylsilyl containing compounds, the signal corresponding to the methyl groups is assumed to appear at 08 in the $^1$H n.m.r. spectrum and this signal was used as an internal standard. In all other compounds, tetramethyl silane was used as a standard.
General Procedure A. Protection of alcohols as their tetrahydropyranloxy ethers.

The alcohol (42mmol), dihydropyran (42mmol), and pyridinium p-toluenesulphonic acid (5mmol) were stirred together in dichloromethane (40ml) at room temperature. Once reaction was complete, the solvent was evaporated under reduced pressure. The crude product was taken up in saturated brine solution (20ml) and then extracted with ether (3x20ml). The combined extracts were dried (MgSO₄), and after removal of the solvent, flash chromatography allowed isolation of pure tetrahydropyranloxy ethers.

General Procedure B. Pyridinium chlorochromate oxidation of alcohols.

A solution of the alcohol (5mmol) in dichloromethane (2ml) was added to a stirred suspension of pyridinium chlorochromate (12.5mmol) and sodium acetate (12.5mmol) in dichloromethane (20ml) under nitrogen. Once reaction was complete, the reaction mixture was passed through a column of silica to remove chromium residues and washed through with ether (20ml). The solvent was evaporated under reduced pressure and purification by flash chromatography allowed isolation of the pure aldehyde.

General Procedure C. Generation of Grignard reagents of alkyl and vinyl bromides and their reaction with aldehydes.

The halide (1.5mmol) was added dropwise to magnesium (1.65mmol) and a crystal of iodine in THF (0.5ml). Sometimes, to initiate reaction it was necessary to use a heat gun, an ultrasonic bath, or 10μl of 1,2-dibromoethane after all of the halide had been added. The mixture was refluxed for approximately 1hr., when most of the magnesium had dissolved. A further 4ml THF was added to dissolve the Grignard salt at this point. A solution of the aldehyde (1.4mmol) in THF (0.5ml) was added and the mixture refluxed for a further 1hr. The reaction was quenched with saturated aqueous ammonium chloride solution (5ml). The product was extracted with ether (3x5ml), dried (MgSO₄), and the solvent evaporated under reduced pressure. Flash chromatography allowed isolation of the pure products.
**General Procedure D. Acetylation of Alcohols.**

A solution of the alcohol (6mmol) in dichloromethane (2ml) was added to a stirred solution of acetic anhydride (11mmol), triethylamine (11mmol) and D.M.A.P. (0.5mmol) in dichloromethane (25ml) at room temperature under nitrogen. Once reaction was complete, the solution was diluted with further dichloromethane (20ml) and washed successively with 2M hydrochloric acid (40ml) and saturated aqueous sodium bicarbonate (40ml). The organic layer was dried (MgSO\(_4\)) and the solvent evaporated under reduced pressure. Purification by flash chromatography allowed isolation of the pure acetate ester.

**General Procedure E. Removal of Thp protecting groups to give alcohols**

The tetrahydroxyran-2-yl protected alcohol (0.29mmol) was reacted with p-toluenesulphonic acid (5.7\(\mu\)mol) in methanol (5ml) at room temperature under nitrogen. Once reaction was complete, the reaction mixture was made alkaline with pyridine. The methanol was evaporated off under reduced pressure. The crude product was taken up in water (10ml) and extracted with ether (3x10ml). The combined extracts were washed with saturated brine (10ml) dried (MgSO\(_4\)), and the solvent evaporated under reduced pressure. Purification by flash chromatography allowed isolation of the pure alcohol.

**General Procedure F. Oxidation of alcohols to their corresponding aldehydes using chromium trioxide/pyridine.**

Chromium trioxide (2.4mmol; dried at 60°C in vacuo overnight) was added to a stirred solution of pyridine (4.9mmol) in dichloromethane (10ml) under nitrogen. Rapid stirring was continued at room temperature for 0.5hr to produce a deep red solution. The alcohol (0.4mmol) in dichloromethane (1ml) was added & the solution immediately turned brown. Once the reaction was complete (ca 0.5hr) the mixture was filtered through a short silica column & the chromium residues were washed with ether (2x20ml). The solvent was evaporated under reduced pressure and flash chromatography allowed isolation of the aldehyde.
General Procedure G. Allylsilane-Aldehyde cyclisation reaction

A solution of the aldehyde (0.6mmol) in tetrahydrofuran (5ml) was added to a stirred solution of tetrabutylammonium fluoride (1.8mmol) in tetrahydrofuran (15ml) under nitrogen. The mixture was heated at 55°C for 3.5 hours and then cooled to room temperature for a further 16 hours. The reaction was quenched with water and the aqueous phase was extracted with ether (3x20ml). The combined ether extracts were dried (MgSO₄) and the solvent removed in vacuo. After flash chromatography, the cyclised product was isolated.

General Procedure H. Attempted Lewis acid catalysed intramolecular Allylsilane-acetal reaction.

Tin(IV) chloride (0.64 mmol) was added to a solution of the allylsilane/acetal (0.32mmol) in dichloromethane (5ml) at -20°C under nitrogen. This temperature was maintained throughout the reaction. Once reaction was complete it was quenched with aqueous saturated ammonium chloride solution (10ml) and the aqueous layer extracted with ether (3x10ml). The combined extracts were dried (MgSO₄) and the solvent evaporated under reduced pressure. Flash chromatography allowed isolation of the pure products.
1,6-hexane-diol (3.49g, 29.6 mmol), imidazole (3.01g, 44.3 mmol), and t-butyldimethylsilyl chloride (3.02g, 20.0 mmol) were stirred together in D.M.F. (8 ml) under nitrogen for 7 hours at 40°C. After standing at room temperature overnight, the upper colourless layer was separated from the pale green lower layer and dissolved in ether (20 ml) and saturated aqueous brine (25 ml). The lower layer was then extracted with ether (4x25 ml) and the extracts were washed each time as before. The organic extracts were dried (MgSO₄) and the solvent removed under reduced pressure. After purification by flash chromatography (petroleum ether-ether, 1:1), 6-t-butyldimethylsilyloxy-1-hexanol (78) was obtained as a yellow oil (1.16g, 25%), Rf 0.41 (petroleum ether-ether, 1:1);

δH (90 MHz, CDCl₃) 0 (6H, s, 2xCH₃), 0.8 (9H, s, t-Bu), 1.2-1.6 (9H, m, 4xCH₂, OH), 3.4-3.6 (4H, m, 2xCH₂O)
6-t-Butyldimethylsilyloxy-hexanal (80)

A solution of 6-t-butyldimethylsilyloxy-1-hexanol (78) (1.1g, 5mmol) in dichloromethane (2ml) was added to a stirred suspension of pyridinium chlorochromate (2.68g, 12.4mmol) and sodium acetate (1.02g, 12.5mmol) according to general procedure B. After purification by flash chromatography (petroleum ether-ether, 1:1) 6-t-butyldimethylsilyloxy-hexanal (80) was obtained as a yellow oil (0.69g, 60%), Rf 0.81 (petroleum ether-ether, 1:1);

δH (90MHz, CDCl3) 0 (6H, s, 2xCH3), 0.8 (9H, s, tBu), 1.3-1.7 (6H, m, 3xCH2), 2.35 (2H, brt, J 7.5Hz, CH2-CO), 3.6 (2H, t, J 6Hz, CH2O), 9.7 (1H, brs, CHO).
6-Tetrahydropyanyloxy-1-hexanol (81)

1,6-hexanediol (5.0g, 42mmol), and dihydropyran (3.5g, 42mmol), were reacted together according to general procedure A. After purification by flash chromatography (petroleum ether-ether, 7:3) 6-tetrahydropyanyloxy-1-hexanol (81) was obtained as a yellow oil (4.07g, 48%). Rf 0.45 (petroleum ether-ether, 7:3);

\( \nu_{\text{max}} \text{(film)} \) 3400 brs (OH), 2950 s, 2870 s, 1450 m, 1440 m, 1390 m, 1350 m, 1260 m, 1200 m, 1120 m, 1070 s, 905 m, 870 m, 820 m, 730 m;

\( \delta_{\text{H}} \) (270MHz, CDCl\textsubscript{3}) 1.30-1.95 (14H, m, 7xCH\textsubscript{2}), 2.10 (1H, s, OH) exchanges D\textsubscript{2}O, 3.40 (1H, dt, J 8.1Hz, 6.7Hz, CH-O), 3.47-3.56 (1H, m, CH-O), 3.62 (2H, t, J 6.1Hz, 1'-H), 3.75 (1H, dt, J 8.1Hz, 6.7Hz, CH-O), 3.87 (1H, m, CH-O), 4.60 (1H, t, J 3.4Hz, 1'-H).
6-Tetrahydropyran-1-yl-hexanal (83)\textsuperscript{78}

6-Tetrahydropyran-1-yl-hexan-1-ol (81) (0.52g, 2.5mmol) was oxidised by pyridinium chlorochromate (1.36g, 6.2mmol) and sodium acetate (0.51g, 6.2mmol) according to general procedure B. After purification by flash chromatography (petroleum ether-ether, 1:1), 6-tetrahydropyran-1-yl-hexanal (83) was obtained as a colourless oil (0.30g, 58%), R\text{f} 0.51 (petroleum ether-ether, 1:1);

$\nu_{\text{max}}$ (film) 3020m, 2950s, 2880s, 2720m, 1730s (C=O), 1455m, 1445m, 1390m, 1355s, 1200s, 1140s, 1125s, 1080s, 1030s, 980m, 910m, 870m, 815m, 760s, 670m;

$\delta_H$ (270MHz, CDCl\textsubscript{3}) 1.2-1.8 (12H, m, 6xCH\textsubscript{2}), 2.45 (2H, brt, J 6.8Hz, CH\textsubscript{2}CO), 3.38 (1H, dt, J 9.2Hz, 6Hz, CH-O), 3.45-3.55 (1H, m, CH-O), 3.75 (1H, dt, J 9.2Hz, 6Hz, CH-O), 3.82-3.95 (1H, m, CH-O) 4.50 (1H, brs, 1'-H), 9.80 (1H, brs, 1-H).
3,3-Diethoxy-1,2-dibromopropane (85)\textsuperscript{53}

![Chemical Structure]

A solution of bromine (5.1 ml, 0.1 mol) in chloroform (26 ml) was added dropwise over 2.5 hours to a stirred solution of 3,3-diethoxypropene (12.9 g, 0.1 mol) in chloroform (32 ml) at -78°C under nitrogen. After a further hour at this temperature it was warmed to room temperature and left overnight (in the dark as the product is light sensitive). The solvent was evaporated at reduced pressure and the remaining orange liquid distilled at reduced pressure to give 3,3-diethoxy-1,2-dibromopropane (85) as a colourless oil (23.1 g, 81%), b.p. 86-88°C/3 mm Hg (Literature b. p. 79 - 84°C/1.1 torr\textsuperscript{53});

\(\delta_H (90\text{MHz}, \text{CCl}_4) 1.2-1.4 (6\text{H, m, }2\text{xCH}_3), 3.5-4.2 (7\text{H, m, }1\text{-H}, 2\text{-H}, 5\text{-H}, 2\text{-H}), 4.6 (1\text{H, d, }J 4.5\text{Hz, }3\text{-H})\)
3,3-Diethoxy-2-bromopropene (84)$^{53}$

![Chemical Structure](image)

The 3,3-diethoxy-1,2-dibromopropane (85) (23.1g, 80mmol) was added dropwise over 10 minutes to a stirred solution of potassium hydroxide (5.61g, 99mmol) in ethanol (50ml) under nitrogen. A white precipitate of potassium bromide was produced almost immediately and after stirring overnight, the reaction mixture was diluted with ether (50ml) and filtered through celite. The celite was washed with ether (2x25ml) and the filtrate was washed with saturated brine (3x30ml), dried ($K_2CO_3$), and evaporated under reduced pressure to leave an orange oil. Distillation gave 3,3-diethoxy-2-bromopropene (84) as a colourless oil (6.13g, 30%), b.p. 50-54°C/2mmHg (Literature b. p. 40-45°C/1.5 torr.$^{53}$);

$\delta^H$ (90MHz, $CCl_4$) 1.15 (6H, t, $J$ 6Hz, 2xCH$_2$), 3.2-3.6 (4H, m, 2'-H$_2$, 5-H$_2$), 4.7 (1H, s, 3-H), 5.6 (1H, s, 1-H), 6.0 (1H, s, 1-H).
2-Diethoxymethyl-5-phenyl-1-penten-3-ol (92)

Butyl lithium (0.39ml, 0.94mmol) was added to a stirred solution of 3,3-diethoxy-2-bromopropene (84) (197mg, 0.94mmol) in THF (2ml) at -78°C under nitrogen. Stirring was continued at this temperature for 1 hour and then a solution of 3-phenylpropanal (91) (113mg, 0.84mmol) in THF (2ml) was added. After 1 hour at this temperature, the reaction mixture was allowed to warm to room temperature for 1 hour before being quenched with saturated aqueous ammonium chloride solution (10ml). The mixture was extracted with ether (3x5ml), dried (Na$_2$SO$_4$), and evaporated under reduced pressure to leave an orange oil. After purification by flash chromatography (petroleum ether-ether, 1:1), 2-diethoxymethyl-5-phenyl-1-penten-3-ol (92) was obtained as a pale yellow oil (113mg, 51%), R$_f$ 0.48 (petroleum ether-ether, 1:1);

$\delta$$_H$ (90MHz, CDCl$_3$) 1.2 (6H, t, J >1Hz, 2xCH$_3$), 2.5-2.7 (4H, m, 5-H$_2$, 4-H$_2$), 3.4-3.7 (5H, m, 3'-H$_2$, 2''-H$_2$, 3-H), 4.2 (1H, brs, OH), 4.8 (1H, s, 1'-H), 5.2 (2H, s, 1-H$_2$), 7.2 (5H, s, Ph).
The Grignard reagent of 2-bromopropene (89) (0.13ml, 1.5 mmol) was formed and reacted with 3-phenyl-propanal (91) (188mg, 1.4mmol) according to general procedure C. No further purification was necessary and 2-methyl-5-phenyl-pent-1-en-3-ol (93) was obtained as a yellow oil (130mg, 52%), Rf 0.51 (petroleum ether-ether, 1:1);

δ_H (90MHz, CDCl_3) 1.6-1.9 (5H, m, 2-CH_3, 4-H_2), 2.6 (2H, t, J 6Hz, 5-H_2), 3.6-3.8 (1H, brs, OH), 4.0 (1H, t, J 6Hz, 3-H), 4.8 (1H, s, 1-H), 4.9 (1H, s, 1-H), 7.1 (5H, brs, Ph).
8-t-Butyldimethylsiloxo-2-methyl-1-octen-3-ol (94)

The Grignard reagent of 2-bromopropene (89) (0.06 ml, 0.68 mmol) was formed and reacted with 6-t-butyldimethylsilylox-hexanal (80) (148 mg, 0.64 mmol) according to general procedure C. After purification by flash chromatography (petroleum ether-ether, 1:1), 8-t-butyldimethylsilylox-2-methyl-1-octen-3-ol (94) was obtained as a yellow oil (41 mg, 23%), Rf 0.56 (petroleum ether-ether, 1:1);

δH (90 MHz, CDCl3) 0 (6H, s, 2xCH3), 0.8 (9H, s, tBu), 1.2-1.8 (12H, m, 2-CH3, OH, 4xCH2), 3.5 (2H, t, J 6 Hz, CH2-O), 4.0 (1H, t, J 6 Hz, 3-H), 4.7 (1H, s, 1-H), 4.9 (1H, s, 1-H).
1-Tetrahydropyranyloxy-3-bromopropane (98)

3-Bromopropanol (97) (1.03g, 7.4mmol), and dihydropyran (0.7ml, 7.7mmol) were reacted together according to general procedure A. After purification by flash chromatography (petroleum ether-ether, 4:1), 1-tetrahydropyranyloxy-3-bromopropane (98) was obtained as a colourless oil (1.15g, 70%), Rf 0.59 (petroleum ether-ether, 4:1);

$\delta_H$ (90MHz,CDCl$_3$) 1.4-1.8 (6H, m, 3xCH$_2$), 2.0-2.3 (2H, m, CH$_2$), 3.4-3.6 (4H, m, 2xCH$_2$-O), 3.7-4.0 (2H, m, CH$_2$-Br), 4.5 (1H, brs, OCHO).
2-(Trimethylsilyl)methyl-2-propenal (95)

\[
\begin{array}{c}
\text{Me}_3\text{Si} \quad \text{OH} \\
\downarrow \\
\text{Me}_3\text{Si} \quad \text{CHO}
\end{array}
\]

(95)

2-(Trimethylsilyl)methyl-2-propen-1-ol (0.60g, 4.1mmol) and manganese dioxide (5.92g, 4.2mmol) were stirred together in petroleum ether (60ml) for 24 hours when t.l.c. showed that starting material was no longer present. The manganese dioxide was filtered off and the solvent was evaporated under reduced pressure to leave 2-(trimethylsilyl)methyl-2-propenal (95) as a colourless oil (0.55g, 93%), Rf 0.89 (petroleum ether-ether, 7:3):

\[\nu_{\text{max}}\text{ (film) } 3080\text{w}, 2950\text{s}, 2800\text{s}, 2700\text{m}, 1700\text{s} (C=0), 1615\text{m}, 1460\text{w}, 1420\text{m}, 1315\text{s}, 1250\text{s}, 1160\text{s}, 970\text{m}, 920\text{m}, 850\text{s}, 770\text{m}, 720\text{m}, 695\text{m}, 660\text{m};\]

\[\delta_H\text{ (90MHz, CDCl}_3\text{) } 0.9 (9\text{H, s, TMS}), 1.8 (2\text{H, s, 1'-H}_2), 5.8 (1\text{H, s, 3-H}), 6.1 (1\text{H, s, 3-H}), 9.5 (1\text{H, s, 1-H}).\]
The Grignard reagent of 1-tetrahydropyranyloxy-3-bromopropane (98) (861mg, 3.8mmol) was prepared according to general procedure C and reacted with 3-phenyl-propanal (91) (0.52g, 3.8mmol). Addition took place at 0°C and subsequently the mixture was allowed to warm to room temperature. After purification by flash chromatography (petroleum ether-ether, 1:1), 6-phenyl-1-tetrahydropyranyloxy-hexan-4-ol (100) was obtained as a yellow oil (90mg, 8%), Rf 0.76 (petroleum ether-ether, 1:1);

$\nu_{\text{max}}$ (film) 3400brm(OH), 3040w, 3020m, 2930s, 2860s, 1730m, 1600m, 1490m, 1450m, 1350m, 1260m, 1200s, 1120s, 1075s, 1030s, 985m, 905m, 870m, 700s;

$\delta_{\text{H}}$ (90MHz, CDCl$_3$) 1.3-1.8 (9H, m, 2-H$_2$, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$, OH), 2.4-2.8 (4H, m, 3-H$_2$, 5-H$_2$), 3.2-4.0 (7H, m, 1-H$_2$, 6-H$_2$, 5'-H$_2$, 4-H), 4.4 (1H, brs, 1'-H), 7.1 (5H, brs, Ph).
The Grignard reagent of 1-tetrahydropyran-3-bromopropane (98) (784mg, 3.5mmol) was prepared according to general procedure C and reacted with 2-(trimethylsilyl) methyl-2-propenal (95) (483mg, 3.4mmol). Addition and reaction took place at 0°C. After purification by flash chromatography (petroleum ether-ether, 17:2) two products were isolated.

1,6-Di-tetrahydropyran-3-xy-hexane (82) was obtained as a colourless oil (275mg, 54%), RF 0.09 (petroleum ether-ether, 17:2):

\[
\text{max} \quad \text{v} = \begin{align*}
2940s, & \quad 2860s, & \quad 1450m, & \quad 1440m, & \quad 1380m, & \quad 1350m, & \quad 1320m, & \quad 1260m, & \quad 1200s, & \quad 1180m, \\
& \quad 1160m, & \quad 1135s, & \quad 1120s, & \quad 1075s, & \quad 1035s, & \quad 980m, & \quad 905m, & \quad 870m, & \quad 815m;
\end{align*}
\]

\[
\delta H \quad (90MHz, CDCl3) \quad 1.3-1.7 (20H, m, 10\times CH2), \quad 3.3-3.9 (8H, m, 4\times CH2-O), \quad 4.5 (2H, brs, 2\times OCHO);
\]

\[
m/z \quad (E.I.) \quad 286(M^+,1%), \quad 201(M+H-Thp), \quad 117(M+H-2Thp), \quad 101(100, \text{C}_6\text{H}_{12}\text{OH}), \quad 85(100, \text{Thp}), \quad 84(100, \text{C}_6\text{H}_{11});
\]

1-Tetrahydropyran-3-xy-propane (101) was obtained as a colourless oil (21mg, 4%), RF 0.42 (petroleum ether-ether, 17:2):

\[
\text{max} \quad \text{v} = \begin{align*}
3000m, & \quad 2940s, & \quad 2870s, & \quad 1450m, & \quad 1430m, & \quad 1380m, & \quad 1350m, & \quad 1320m, & \quad 1260m, & \quad 1200s, \\
& \quad 1180m, & \quad 1120s, & \quad 1075s, & \quad 1030s, & \quad 1010s, & \quad 960m, & \quad 910s, & \quad 865m, & \quad 810m, \\
& \quad 750s, & \quad 735s, & \quad 665m, & \quad 645m;
\end{align*}
\]

\[
\delta H \quad (90MHz, CDCl3) \quad 0.85(3H, t, J7Hz, 3-Me), \quad 1.3-1.9(8H, m, 2-H, 2'-H, 3'-H, 4'-H), \quad 3.2-3.8(4H, m, 1-H, 5'-H, 2'), \quad 4.5(1H, brs, 1'-H);
\]

\[
m/z \quad (E.I.) \quad 144(M^+,8%), \quad 143(10, M-H), \quad 115(9, \text{M-C}_2\text{H}_5), \quad 101(7, \text{M-C}_3\text{H}_7), \quad 85(100, \text{Thp}), \quad 56(100, \text{C}_4\text{H}_9), \quad 43(100, \text{C}_3\text{H}_7).
\]
1-Tetrahydropyranyloxy-propane (101)\(^8\)

![Chemical Structure](image)

Propan-1-ol (1.04g, 17.3mmol), was reacted with dihydropyran (1.46g, 17.3mmol), according to general procedure A. After purification by flash chromatography (petroleum ether-ether, 7:3) 1-Tetrahydropyranyloxy propane (101) was obtained as a colourless oil (1.43g, 60%), Rf 0.82 (petroleum ether-ether, 7:3);

\(\nu_{\text{max}}\) (film) 2940s, 2880s, 1465m, 1450m, 1430m, 1380s, 1350m, 1285m, 1260m, 1200s, 1185s, 1125s, 1085s, 1030s, 1000s, 980s, 970s, 905s, 870s, 820m, 770w;

\(\delta_H\) (90MHz, CDCl\(_3\)) 0.8 [3H, t, J 6Hz, CH\(_3\)], 1.3-1.7 [8H, m, 4xCH\(_2\)], 3.2-3.9 [4H, m, 2xCH\(_2\)O], 4.5 [1H, brs, OCHO];

m/z (E.I.) 144 (M\(^+\), 5%), 143 (5), 115 (5), 101 (5, ThpO), 85 (100, Thp), 57 (60).
1,6-Di-tetrahydropyran-3-yloxy-hexane (82)

A solution of 1-tetrahydropyran-3-yloxy-3-bromopropane (98) (896mg, 4.0mmol) in THF (2ml)
was added to magnesium (111mg, 4.6mmol) and a crystal of iodine in THF (2ml) under
nitrogen, and the mixture refluxed for 1.5hr. After cooling to 0°C, water (2ml) was added
and after 1hr, when t.l.c showed that starting material was no longer present, the reaction
was quenched with saturated aqueous ammonium chloride solution (10ml). The product
was extracted with ether (3x20ml), dried (MgSO\(_4\)), and the solvent evaporated under
reduced pressure. After purification by flash chromatography (petroleum ether-ether, 7:3)
two products were isolated;

1,6-di-tetrahydropyran-3-yloxy-hexane (82) was obtained as a pale yellow oil (119mg, 21%), R\(_f\)
0.59 (petroleum ether-ether, 7:3);

\(\nu_{\text{max}}\) (film) 2940s, 2880s, 1465m, 1380m, 1350m, 1320m, 1285w, 1260m, 1200s,
1180m, 1160m, 1135s, 1120s, 1080s, 1030s, 985m, 905m, 870m, 815m, 760m;

\(\delta_H\) (300MHz, CDCl\(_3\)) 1.35-1.9 (20H, m), 3.4 (2H, ddd, J 10Hz, 6Hz, 6Hz, 1-H, 6-H), 3.5 (2H,
m, 1-H, 6-H), 3.75 (2H, ddd, J 10Hz, 6Hz, 6Hz, 5'-Hx2), 3.85 (2H, m, 5'-Hx2), 4.5 (2H, t, J
3Hz, 1'-Hx2);

m/z (E.I.) 286 (M\(^+\), 1%), 201 (5, M-Thp), 101 (24, ThpO), 85 (100, Thp).

1-Tetrahydropyran-3-yloxy-propane (101) was obtained as a colourless oil (52mg, 9%), R\(_f\) 0.89
(petroleum ether-ether, 7:3);

\(\nu_{\text{max}}\) (film) 2930s, 2870s, 1465m, 1450m, 1430m, 1380m, 1350s, 1320m, 1280m, 1260m,
1200s, 1180s, 1120s, 1075s, 1030s, 1000s, 970m, 960m, 905m, 865s, 815s, 755m;

\(\delta_H\) (90MHz, CDCl\(_3\)) 0.8 (3H, t, J 6Hz, CH\(_3\)), 1.3-1.7 (8H, m, 4xCH\(_2\)), 3.2-3.9 (4H, m,
2xCH\(_2\)O), 4.5 (1H, brs, OCHO);

m/z (E.I.) 144 (M\(^+\), 5%), 143 (5), 115 (5), 101 (5, ThpO), 85 (100, Thp), 57(50).
1-t-Butyldimethylsilyloxy-3-bromopropane (102)

3-bromopropan-1-ol (97) (3g, 22.1mmol), t-butyldimethylsilyl chloride (2.65g, 17.6mmol), and imidazole (3.04g, 44.7mmol) were stirred together at room temperature under nitrogen in D.M.F. (10ml). After 24 hours t.l.c showed that starting material was no longer present and so the product was extracted with ether (4x25ml). These extracts were washed with 1M hydrochloric acid (30ml) and saturated aqueous ammonium chloride solution (30ml), dried (MgSO₄), and the solvent evaporated under reduced pressure. After purification by flash chromatography (petroleum ether-ether, 3:2) 1-t-butyldimethylsilyloxy-3-bromopropane (102) was obtained as a colourless oil (3.28g, 74%), Rf 0.72 (petroleum ether-ether, 3:2):

$\delta_H (\text{90MHz, CDCl}_3) \ 0 \ (6H, s, 2\times\text{CH}_3), \ 0.8 \ (9H, s, \text{^3Bu}), \ 1.9 \ (2H, m, 2\text{-H}_2), \ 3.3-3.7 \ (4H, m, 1\text{-H}_2, 3\text{-H}_2).$
4-Tetrahydropyranoxy-1-butanol (111)

1,4-Butanediol (10.23g, 0.11mol) and dihydropyran (9.68g, 0.11mol) were reacted together according to general procedure A. After purification by flash chromatography (petroleum ether-ether-methanol, 10:9:1) 4-tetrahydropyranoxy-1-butanol (111) was obtained as a colourless oil (9.96g, 50%), Rf 0.45 (petroleum ether-ether-methanol, 10:9:1);

$\nu_{\text{max}}$ (film) 3400brs (OH), 2960s, 2875s, 1440m, 1380s, 1350s, 1320m, 1275m, 1260m, 1200s, 1185m, 1160m, 1140s, 1125s, 1075s, 1060s, 1020s, 990s, 970s, 910m, 870m, 815m;

$\delta_H$ (90MHz, CDCl$_3$) 1.3-1.9 (10H, m, 5xCH$_2$), 2.1 (1H, brs, OH), 3.3-4.0 (6H, m, 3xCH$_2$-O), 4.5 (1H, brs, O-CH-O).
3-Tetrahydropyranolxy-1-propanol (127)

1,3-Propanediol (9.72g, 0.13mol) and dihydropyran (11.06g, 0.13mol) were reacted together according to general procedure A. After purification by flash chromatography (petroleum ether-ethyl acetate, 1:1), 3-tetrahydropyranolxy-1-propanol (127) was obtained as a colourless oil (11.05g, 54%), Rf 0.17 (petroleum ether-ethyl acetate, 1:1);

υmax (film) 3410brs (OH), 2940s, 2870s, 1440s, 1380s, 1320m, 1280m, 1260m, 1200s, 1180s, 1160s, 1140s, 1120s, 1070s, 1030s, 905s, 885m, 870s, 810s;

δH (90MHz, CDCl3) 1.3-1.9 (8H, m, 4xCH2), 2.6 (1H, brs, OH), 3.4-4.1 (6H, m, 3xCH2-O), 4.5 (1H, brs, O-CH-O).
5-Tetrahydropyranoxy-1-pentanol (119)

\[
\text{HO} \quad \text{ThpO} \quad \text{OH}
\]

(119)

1,5-Pentanediol (30.0g, 0.29mol) and dihydropyran (24.0g, 0.29mol) were reacted together according to general procedure A. After purification by flash chromatography (petroleum ether-ethyl acetate, 7:1), 5-tetrahydropyranoxy-1-pentanol (119) was obtained as a colourless oil (25.08g, 46%), \( R_f 0.14 \) (petroleum ether-ethyl acetate, 7:1);

\[
\nu_{\text{max}} (\text{CH}_2\text{Cl}_2) 3620 \text{m} (\text{OH}), 3460 \text{brw} (\text{OH}), 2940 \text{s}, 2875 \text{s}, 1450 \text{m}, 1440 \text{m}, 1370 \text{m}, 1350 \text{m}, 1320 \text{w}, 1275 \text{m}, 1240 \text{m}, 1200 \text{m}, 1135 \text{s}, 1120 \text{s}, 1075 \text{s}, 1060 \text{s}, 1035 \text{s}, 1020 \text{s}, 990 \text{m}, 975 \text{m}, 905 \text{m}, 870 \text{m}, 810 \text{m};
\]

\[
\delta_{\text{H}} (90\text{MHz}, \text{CDCl}_3) 1.2-1.9 (12\text{H, m, 6xCH}_2), 2.0 (1\text{H, s, OH}), 3.3-3.9 (6\text{H, m, 3xCH}_2\text{-O}), 4.5 (1\text{H, brs, O-CH-O}).
\]
6-Acetoxy-7-(trimethylsilylmethyl)-7-octen-1-ol (108), (290mg, 1.18mmol) was oxidised by p.c.c. (636mg, 3.0mmol) in the presence of sodium acetate (242mg, 3.0mmol) according to general procedure B. After purification by flash chromatography (hexane-ethyl acetate, 3:1), 3-Acetoxy-7-(trimethylsilylmethyl)-7-octenal (109) was obtained as a colourless oil (182mg, 62%), Rf 0.64 (hexane-ethyl acetate, 3:1);

$\nu_{\text{max}}$ (film) 3095w, 2950s, 2820m, 2720w, 1740s (C=Ox2), 1640m, 1460m, 1420m, 1370s, 1245s, 1165m, 1020m, 940m, 850s, 770w, 700m;

$\delta_{\text{H}}$ (270MHz, CDCl$_3$) 0 (9H, s, TMS), 1.3-1.8 (8H, m, 4xCH$_2$) including 1.45 (1H, d, J 13Hz, CH-Si) & 1.60 (1H, d, J 13Hz, CH-Si), 2.10 (3H, s, CH$_3$), 2.48 (2H, dt, J 6.8Hz, <1Hz, CH$_2$-CO), 4.70 (1H, s, C=CH), 4.90 (1H, s, C=CH), 5.15 (1H, t, J 6.1Hz, HC-OC=O), 9.80 (1H, t, J <1Hz, HC=O);

$\delta_{\text{C}}$ (67.8MHz, CDCl$_3$) 0 (q), 22.0 (t), 22.5 (t), 23.5 (t), 26.0 (t), 33.5 (q), 44.5 (t), 77.5 (d), 110.0 (s), 146.0 (s), 171.0 (s), 203.0 (s);

m/z (E.I.) 211 (M+H-AcOH, 2%), 154 (2), 133 (25), 117 (62, C$_6$H$_{12}$O$_2$), 109 (7), 95 (17), 79 (20), 73 (97, TMS), 67 (10), 59 (7), 55 (17), 43 (100, AcO).
4-Tetrahydropyranoyloxy-butanal (112)\textsuperscript{84}

\[
\begin{align*}
\text{ThpO} & \quad \text{OH} \quad \rightarrow \quad \text{ThpO} \quad \text{CHO} \\
(111) & \quad & (112)
\end{align*}
\]

4-Tetrahydropyranoyloxy-1-butanol (111) (3.56g, 20mmol) was oxidised by p.c.c. (51mmol) in the presence of sodium acetate (51mmol) according to general procedure B. After purification by flash chromatography (petroleum ether-ether, 1:1), 4-tetrahydropyranoyloxy-butanal (112) was obtained as a colourless oil (2.87g, 83%), R\text{f} 0.42 (petroleum ether-ether, 1:1);

\textcolor{blue}{$\nu$}_{\text{max}} \text{ (film)} 2960s, 2880s, 2710m, 1720s, 1440m, 1380m, 1350m, 1320w, 1200m, 1135s, 1120s, 1075s, 1030s, 905m, 870m, 810m;

\textcolor{blue}{$\delta$}_{\text{H}} \text{ (90MHz, CDCl}_3) 1.3-2.0 \text{ (8H, m, 4xCH}_2), 2.5 \text{ (2H, dt, J 7Hz, 2-H}_2), 3.3-3.9 \text{ (4H, m, 4-H}_2, 5'-H}_2), 4.5 \text{ (1H, brs, 1'-H)}, 9.75 \text{ (1H, t, J <1Hz, 1-H)}.
3-Tetrahydropyran-1-ol (127) (8.36g, 52mmol) was oxidised by p.c.c. (136mmol) in the presence of sodium acetate (136mmol). After purification by flash chromatography (petroleum ether-ether-methanol, 13:6:1), 3-tetrahydropyran-1-ol-propanal (128) was obtained as a colourless oil (4.92g, 60%), Rf 0.27 (petroleum ether-ether-methanol, 13:6:1);

$\delta_H$ (90MHz, CDCl$_3$) 1.3-1.9 (6H, m, 2'-H$_2$, 3'-H$_2$, 4'-H$_2$), 2.6 (2H, dt, J 6Hz, <1Hz, 2-H$_2$), 3.3-4.1 (4H, m, 3-H$_2$, 5'-H$_2$), 4.6 (1H, brs, 1'-H), 9.7 (1H, t, J <1Hz, 1-H).
5-Tetrahydropyran-1-ol (119) (25.08 g, 133 mmol) was oxidised by p.c.c. (330 mmol) in the presence of sodium acetate (330 mmol) according to general procedure B. After purification by flash chromatography (petroleum ether-ethyl acetate, 4:1), 5-tetrahydropyran-1-ol (119) was obtained as a colourless oil (15.87 g, 64%), Rf 0.37 (petroleum ether-ethyl acetate, 4:1);

$\nu_{\text{max}} \text{ (film)}$ 2940 s, 2870 s, 2720 m, 1720 s (C=O), 1450 m, 1440 m, 1385 m, 1355 s, 1320 m, 1260 m, 1200 s, 1140 s, 1120 s, 1080 s, 1030 s, 1020 s, 990 s, 905 m, 870 s, 815 m;

$\delta_H$ (90 MHz, CDCl$_3$) 1.3-2.1 (10 H, m, 5xCH$_2$), 2.5 (2 H, dt, J 7 Hz, 9-H$_2$), 3.2-4.1 (4 H, m, 5-H$_2$, 5'-H$_2$), 4.5 (1 H, brs, 1'-H), 9.7 (1 H, t, J <1 Hz, 1-H).

5-Tetrahydropyran-1-ol (119) (25.08 g, 133 mmol) was oxidised by p.c.c. (330 mmol) in the presence of sodium acetate (330 mmol) according to general procedure B. After purification by flash chromatography (petroleum ether-ethyl acetate, 4:1), 5-tetrahydropyran-1-ol (119) was obtained as a colourless oil (15.87 g, 64%), Rf 0.37 (petroleum ether-ethyl acetate, 4:1);

$\nu_{\text{max}} \text{ (film)}$ 2940 s, 2870 s, 2720 m, 1720 s (C=O), 1450 m, 1440 m, 1385 m, 1355 s, 1320 m, 1260 m, 1200 s, 1140 s, 1120 s, 1080 s, 1030 s, 1020 s, 990 s, 905 m, 870 s, 815 m;

$\delta_H$ (90 MHz, CDCl$_3$) 1.3-2.1 (10 H, m, 5xCH$_2$), 2.5 (2 H, dt, J 7 Hz, 9-H$_2$), 3.2-4.1 (4 H, m, 5-H$_2$, 5'-H$_2$), 4.5 (1 H, brs, 1'-H), 9.7 (1 H, t, J <1 Hz, 1-H).
A mixture of 2,3-dibromopropene (10.64g, 53.2mmol) and trichlorosilane (7.92g, 58.6mmol) was added dropwise with stirring, at 0°C over 0.5hr., to copper (1) chloride (0.24g, 2.4mmol) and a solution of triethylamine (5.35g, 53.0mmol) in ether (25ml). Once addition was complete the reaction mixture was allowed to warm to room temperature. After 21hrs., the white solid, triethylammonium bromide, was filtered off, and the ether was evaporated under reduced pressure. The crude 2-bromo-3-(trichlorosilyl)propene (103) was used directly in the next step.

A solution of crude 2-bromo-3-(trichlorosilyl)propene (103) in ether (30ml) was added to a stirred solution of methyl magnesium bromide (3M, 44.7ml) in ether (60ml), at 0°C under nitrogen. Once addition was complete, the reaction mixture was allowed to warm to room temperature. After 21hrs., the reaction was quenched with saturated aqueous ammonium chloride solution (100ml). The aqueous layer was extracted with ether (3x50ml), the combined extracts dried (MgSO₄), and the solvent evaporated under reduced pressure. After Kugelrohr distillation, 2-bromo-3-(trimethylsilyl)propene (104) was obtained as a colourless oil (1.97g, 25%), b.p. 64-67°C at 39mmHg (lit., b.p. 64-65°C at 38-39mmHg);

ν<sub>max</sub> (film) 2960s, 2900s, 1620s, 1380m, 1250s, 1190s, 1160s, 1075s, 940s, 910m, 850brs, 770s, 740s, 710s, 655s;

δ<sub>H</sub> (90MHz, CDCl₃) 0.13 (9H, s, TMS), 2.13 (2H, s, 3-H₂), 5.1 (1H, s, 1-H), 5.2 (1H, s, 1-H).
3-Phenyl-2-((trimethylsilyl)methyl)-1-propen-3-one (105)

The Grignard reagent of 2-bromo-3-((trimethylsilyl)propene (104) (524mg, 2.7mmol) was prepared according to general procedure C, and reacted with benzaldehyde (99) (289mg, 2.7mmol) at room temperature. After purification by flash chromatography (petroleum ether-ether, 19:1), 3-phenyl-2-((trimethylsilyl)methyl)-1-propen-3-one (105) was obtained as a colourless oil (126mg, 22%), Rf 0.55 (petroleum ether-ether, 19:1);

$\nu_{\text{max}}$ (film) 3085w, 3060w, 3025w, 2960w, 2900m, 1720w, 1655s (C=O), 1610m, (C=C), 1600m (Ph), 1580w (Ph), 1445m, 1415m, 1325m, 1250s, 1210s, 1175m, 1160m, 1005w, 985m, 935m, 920s, 860s, 775w, 755w, 720s, 695s, 655m;

$\delta_{\text{H}}$ (300MHz, CDCl$_3$) 0.07 (9H, s, TMS), 2.05 (2H, d, J 1Hz, 1'-H$_2$), 5.51 (1H, d, J 1Hz, 3-H), 5.73 (1H, dd, J 1Hz, 1Hz, 3-H), 7.43 (2H, tt, J 8Hz, 1Hz, 3''-H, 5''-H), 7.53 (1H, tt, J8Hz, 1Hz, 4''-H), 7.74 (2H, dt, J8Hz, 1Hz, 2''-H, 6''-H);

$\delta_{\text{C}}$ (75MHz, CDCl$_3$) 0 (q), 21.15 (t), 122.64 (t, =CH$_2$), 126.48 (d), 127.83 (d), 130.20 (d), 136.31 (s), 144.61 (s), 196.37 (s, C=O);

m/z (E.I.) 218 (M*, 31%), 217 (42), 203 (27, M-CH$_3$), 129 (30), 105 (12, PhC=O), 77 (20, Ph), 75 (22), 73 (100, TMS) [Found: M*, 218.1109. C$_{13}$H$_{18}$OSi requires M*, 218.1127].
8-Tetrahydropyranoxy-2-(trimethylsilyl)methyl-1-octen-3-ol (106)

The Grignard reagent of 2-bromo-3-(trimethylsilyl)propene (104) (1.88g, 9.8mmol) was prepared according to general procedure C, and added to 6-tetrahydropyranoxy-hexanal (83) (1.55g, 7.8mmol) at 0°C. This temperature was maintained throughout the reaction. 8-Tetrahydropyranoxy-2-(trimethylsilyl)methyl-1-octen-3-ol (106) was unstable to flash chromatography, and so was shown to have been formed in 53% yield by g.c./mass spectrometry. The conditions used were a CPSil 19CB capillary g.c. column initially at a temperature of 100°C rising to 200°C over 10 minutes.

m/z (Isobutane C.I.) 315 ([M+H]⁺, 10%), 297 (48, M+H₂O), 231 (45, M+2H-Thp), 213 (100, M+H₂O-Thp), 207 (30), 189 (12), 141 (18), 123 (60), 102 (58, ThpOH);

Rₜ (CPSil 19CB, temp. 100-200°C in 10min.) 8.15min.
6-Tetrahydropyranloxy-2-(trimethylsilyl)methyl-1-hexen-3-ol (113)

The Grignard reagent of 2-bromo-3-(trimethylsilyl)propene (104) (9.12g, 48mmol) was prepared according to general procedure C, and added to 4-tetrahydropyranloxy-butanal (112) (8.26g, 48mmol) at 0°C. After purification by flash chromatography, (petroleum ether-ethyl acetate, 4:1), 6-tetrahydropyranloxy-2-(trimethylsilyl)methyl-1-hexen-3-ol (113) was obtained as a 1:1 mixture of diastereoisomers, as a colourless oil (3.70g, 27%), Rf 0.49 (petroleum ether-ethyl acetate, 4:1);

$\nu_{\text{max}}$ (film) 3460brm (OH), 2945s, 2885s, 1740m (EtOAc), 1630w (C=C), 1440m, 1370m, 1350m, 1320w, 1245s, 1200m, 1160m, 1140s, 1120s, 1075s, 1030s, 990m, 850s, 690m;

$\delta_{H}$ (300MHz, CDCl$_3$) 0.05 (18H, s, 2xTMS), 1.40 (2H, dd, J13.5Hz, 1H, 1'-Hx2), 1.45-1.90 (22H, m, 1'-Hx2, 4-H$_2$x2, 5-H$_2$x2, 2'-H$_2$x2, 3'-H$_2$x2, 4'-H$_2$x2), 2.43 (2H, brs, OHx2), 3.35-3.55 (4H, m, CH$_2$Ox2), 3.72-3.90 (4H, m, CH$_2$Ox2), 3.95 (1H, brs, 3-H), 3.98 (1H, brs, 3-H), 4.60 (2H, t, J 3Hz, 1'-Hx2), 4.67 (2H, s, 1-Hx2), 4.93 (2H, d, J <1Hz, 1-Hx2);

$\delta_{C}$ (75MHz, CDCl$_3$) 0 (q, TMS), 19.4 (t) & 19.4 (t), 22.5 (t), 25.4 (t), 25.8 (t) & 26.0 (t), 30.5 (t), 32.7 (t), 62.0 (t) & 62.1 (t), 67.4 (t) & 67.5 (t), 75.0 (d) & 75.1 (d), 98.6 (d), 107.0 (t), 149.7 (s);

m/z (NH$_3$ C.I.) 590 ([2M+NH$_4$]*, 2%), 388 (12), 304 (30, M+NH$_4$), 287 (5, M+H), 269 (100, M+H-H$_2$O), 197 (78, M+2H-H$_2$O-TMS), 185 (39, M+H-ThpO), 169 (11), 113 (11, C$_3$H$_5$TMS), 102 (10, ThpOH), 85 (33, Thp) [Found: (M+NH$_4$)*, 304.2313. C$_{15}$H$_{30}$O$_3$Si requires (M+NH$_4$)*, 304.2308].

125
The Grignard reagent of 2-bromo-3-(trimethylsilyl)propene (104) (5.98g, 31mmol) was prepared according to general procedure C, and reacted with 3-tetrahydropyranyloxypropanal (128) (4.92g, 31mmol) at 0°C. After purification by flash chromatography (petroleum ether-ethyl acetate, 7:3), 5-tetrahydropyranloyloxy-2-(trimethylsilyl)methyl-1-penten-3-ol (129) was obtained as a 1:1 mixture of diastereoisomers, as a colourless oil (1.18g, 14%), Rf 0.56 (petroleum ether-ethyl acetate, 7:3);

$\nu_{\text{max}}$ (film) 3450m (OH), 2950s, 2880m (C=C), 1630w (C=C), 1415m, 1355m, 1320w, 1250s, 1200m, 1160m, 1140s, 1120s, 1075s, 1060s, 1035s, 990m, 975m, 850s, 760m; 

$\delta_{\text{H}}$ (300MHz, CDCl$_3$) 0 (18H, s, TMSx2), 1.38 (1H, dd, J 3Hz, 1''-H), 1.44 (1H, dd, J3 Hz, <1Hz, 1''-H), 1.47-2.03 (18H, m, 2'-H$_2$x2, 3'-H$_2$x2, 4'-H$_2$x2, 1'-Hx2, 4-H$_2$x2), 2.97 (2H, brs, OHx2), 3.49-3.65 (4H, m, CH$_2$Ox2), 3.83-4.03 (4H, m, CH$_2$Ox2), 4.15 (1H, s, 3-H), 4.18 (1H, s, 3-H), 4.63 (2H, t, J 3Hz, 1'-Hx2), 4.70 (2H, s, 1-Hx2), 5.02 (2H, d, J <1Hz, 1-Hx2);

$\delta_{\text{C}}$ (75MHz, CDCl$_3$) 0 (q), 19.3 (t) & 19.5 (t), 22.7 (t) & 22.7 (t), 25.3 (t), 30.5 (t) & 30.6 (t), 
35.1 (t) & 35.2 (t), 62.1 (t) & 62.3 (t), 65.6 (t) & 65.9 (t), 73.8 (d) & 74.3 (d), 98.9 (d) & 98.9 (d), 107.0 (t) & 107.0 (t), 149.1 (s) & 149.2 (s);

m/z (NH$_3$ C.I.) 562 ([2M+NH$_4^+*$, 3%], 544 (1, 2M), 374 (32, 2M-2Thp), 290 (59, M+NH$_4^+$), 273 (55, M+H), 255 (30, M+H-H$_2$O), 183 (100, M+H-H$_2$O-TMS), 102 (28, ThpOH), 85 (54, Thp), 73 (4, TMS) [Found: (M+H)$^+$, 273.1884. C$_{14}$H$_{29}$O$_3$Si requires (M+H), 273.1886].
The Grignard reagent of 2-bromo-3-(trimethylsilyl)propene (104) (496mg, 2.58mmol) was prepared according to general procedure C, and reacted with 5-tetrahydropyranyloxy-pentanal (120) (489mg, 2.63mmol) at 0°C. Monitoring of the reaction by t.l.c. (petroleum ether-ethyl acetate, 4:1) showed that the product was not very stable, and so it was used crude in the subsequent acetylation reaction. (See preparation of 3-Acetoxy-7(tetrahydropyran-2-yl)oxy-2-(trimethylsilyl)methyl-1-hept-1-ene (122).)
3-Acetoxy-8-tetrahydropyranloxy-2-(trimethylsilyl)methyl-oct-1-ene (107)

\[
\begin{align*}
\text{ThpO} & \quad \text{OH} & \quad \text{SiMe}_3 \\
(106) & \rightarrow & \quad \text{ThpO} & \quad \text{AcO} & \quad \text{SiMe}_3 \\
(107)
\end{align*}
\]

A solution of crude 8-tetrahydropyranloxy-2-(trimethylsilyl)methyl-1-octen-3-ol (106) (max. 6 mmol) was reacted with acetic anhydride (11 mmol) in the presence of triethylamine (11 mmol) and D.M.A.P. (0.5 mmol) according to general procedure D. After purification by flash chromatography (hexane-ethyl acetate, 3:1), 3-Acetoxy-8-tetrahydropyranloxy-2-(trimethylsilyl)methyl-oct-1-ene (107) was obtained as a colourless oil (769 mg, 28% 2 steps from 6-tetrahydropyranloxy-hexanal (83)), Rf 0.89 (hexane-ethyl acetate, 3:1);

\(\nu_{\text{max}}\) (film) 2940 s, 2870 m, 1740 s (C=O), 1640 m, 1440 m, 1420 m, 1370 m, 1320 w, 1250 s, 1200 m, 1160 m, 1140 m, 1120 m, 1080 m, 1035 s, 995 m, 850 s, 695 m;

\(\delta_H\) (270 MHz, CDCl\(_3\)) 0.05 (9H, s, TMS), 1.2-1.85 (16H, m, 4-H\(_2\), 5-H\(_2\), 6-H\(_2\), 7-H\(_2\), 2'-H\(_2\), 3'-H\(_2\), 4'-H\(_2\), 1''-H\(_2\)), 2.05 (3H, s, CH\(_3\)), 3.33 (1H, dt, J 6.7 Hz, 5.3 Hz, 8-H), 3.40-3.50 (1H, m, 5'-H), 3.68 (1H, dt, J 6.7 Hz, 5.3 Hz, 8-H), 3.78-3.90 (1H, m, 5'-H), 4.53 (1H, t, J <1 Hz, 1'-H), 4.63 (1H, s, 1'-H), 4.72 (1H, s, 1'-H), 5.08 (1H, t, J 6.1 Hz, 3-H);

\(\delta_C\) (67.8 MHz, CDCl\(_3\)) -1.2 (q), 19.6 (t), 21.2 (q), 22.5 (t), 25.3 (t), 25.4 (t), 26.0 (t), 29.6 (t), 30.7 (t), 32.9 (t), 62.3 (t), 67.4 (t), 77.0 (d), 98.8 (d), 108.9 (t), 145.2 (s), 170.2 (s, C=O);

\(m/z\) (NH\(_3\) C.I.) 374 ([M+NH\(_4\)]\(^+\), 100%), 357 (15, M+H), 297 (60, M+H-AcOH), 273 (14, M+H-Thp), 225 (27, M+H-AcOH-TMS), 213 (47, M+H-Thp-AcOH), 189 (6), 123 (14), 102 (72, ThpOH), 85 (61, Thp), 73 (4, TMS) (Found: [M+NH\(_4\)]\(^+\), 374.2733. \(C_{19}H_{36}O_4Si\) requires \(M+NH_4\), 374.2726).
5-Tetrahydropyran-2-yloxy-2-(trimethylsilyl)methyl-1-pentene (129) (1.18g, 4.3mmol) was reacted with acetic anhydride (0.61ml, 6.5mmol) in the presence of triethylamine (6.5mmol) and D.M.A.P. (0.35mmol) according to general procedure D. After purification by flash chromatography (petroleum ether-ethyl acetate, 9:1), 3-Acetoxy-5-tetrahydropyran-2-yloxy-2-(trimethylsilyl)methyl-1-pentene (126) was obtained as a colourless oil, as a 1:1 mixture of diastereoisomers, (1.08g, 79%), Rf 0.42 (petroleum ether-ethyl acetate, 9:1);

\[
\begin{align*}
\delta_H (300MHz, CDCl_3) & 0.07 (9H, s, TMS), 0.08 (9H, s, TMS), 1.43-2.05 (20H, m, 4-H_2x2, 2'-H_2x2, 3'-H_2x2, 4'-H_2x2, 1''-H_2x2), 2.07 (3H, s, CH_3), 2.08 (3H, s, CH_3), 3.34-3.55 (4H, m, CH_2Ox2), 3.66-3.90 (4H, m, CH_2Ox2), 4.55 (1H, t, J 3.4Hz, 1-H), 4.59 (1H, t, J 3.4Hz, 1-H), 4.69 (1H, s, 1-H), 4.69 (1H, s, 1-H), 4.88 (1H, t, J <1Hz, 1-H), 4.89 (1H, t, J <1Hz, 1-H), 5.26 (1H, t, J 4.1Hz, 3-H), 5.28 (1H, t, J 4.1Hz, 3-H); \\
\delta_C (75MHz, CDCl_3) & -1.3 (q), 19.2 (t) & 19.5 (t), 21.2 (q), 22.8 (t) & 22.8 (t), 25.4 (t), 30.6 (t), 33.4 (t) & 33.5 (t), 61.8 (t) & 62.2 (t), 63.6 (t) & 64.0 (t), 74.0 (d) & 74.3 (d), 98.4 (d) & 99.2 (d), 108.5 (t), 145.3 (s), 169.9 (s); \\
m/z (NH_3 C.I.) & 332 ([M+NH_4]^+, 3%), 315 (2, M+H), 255 (10, M+H-AcOH), 231 (8, M+H-Thp), 183 (12, M+H-AcOH-TMS), 170 (10, M-Thp-AcOH), 102 (100, ThpOH), 90 (62), 85 (57, Thp) (Found:[M+NH_4]^+, 332.2257. C_{16}H_{30}O_4Si requires (M+NH_4), 332.2257). 
\end{align*}
\]
3-Acetoxy-6-tetrahydropyran-2-yl)oxy-2-(trimethylsilyl)methyl-hex-1-ene (114)

![Diagram](image)

6-Tetrahydropyran-2-yl)oxy-2-(trimethylsilyl)methyl-1-hexen-3-ol (113) (841mg, 2.9mmol) was reacted with acetic anhydride (450mg, 4.4mmol) in the presence of triethylamine (4.4mmol) and D.M.A.P. (0.23mmol) according to general procedure D. After purification by flash chromatography (petroleum ether-ethyl acetate, 4:1), 3-Acetoxy-6-tetrahydropyran-2-yl)oxy-2-(trimethylsilyl)methyl-hex-1-ene (114) was obtained as a colourless oil, as a 1:1 mixture of diastereoisomers, (516mg, 53%), Rf 0.50 (petroleum ether-ethyl acetate, 4:1)

$\nu_{\text{max}}$ (film) 2950s, 2875m, 1735s (C=O), 1640m (C=C), 1440m, 1370m, 1320s, 1200m, 1160m, 1140s, 1120s, 1080s, 1035s, 1020s, 990m, 850s, 770w, 735m, 695m;

$\delta_H$ (300MHz, CDCl$_3$) 0.04 (18H, s, TMSx2), 1.40-1.90 (24H, m, 4-H$_2$x2, 5-H$_2$x2, 2'-H$_2$x2, 3'-H$_2$x2, 4'-H$_2$x2, 1''-H$_2$x2), 2.05 (6H, s, CH$_3$x2), 3.35-3.43 (2H, m, CH$_2$O), 3.43-3.53 (2H, m, CH$_2$O), 3.67-3.78 (2H, m, CH$_2$O), 3.78-3.90 (2H, m, CH$_2$O), 4.56 (2H, t, J 3Hz, 1'-'Hx2), 4.68 (2H, s, 1'-Hx2), 4.85 (2H, s, 1-Hx2), 5.12 (2H, t, J 6Hz, 3-Hx2);

$\delta_C$ (75MHz, CDCl$_3$) -1.2 (q), 19.6 (t), 21.2 (q), 22.5 (t), 25.4 (t), 25.6 (t) & 25.7 (t), 29.7 (t), 30.7 (t), 62.2 (t), 67.0 (t), 76.7 (d) & 77.2 (d), 98.7 (d), 109.0 (t), 145.0 (s), 170.0 (s, C=O);

m/z (NH$_3$ C.I.) 346 ([M+NH$_4$]$^+$, 10%), 329 (2, M+H), 269 (25, M+H-AcOH), 245 (7, M+H-Thp), 197 (15, M+H-AcOH-TMS), 185 (20, M+H-AcOH-Thp), 169 (4, M+H-Thp-TMS), 102 (100, ThpOH), 85 (45, Thp) (Found: (M+NH$_4$)$^+$, 346.2420. C$_{17}$H$_{32}$O$_4$Si requires (M+NH$_4$), 346.2413).
3-Acetoxv-7-tetrahvdroroxy-2-(trimethylsilyl)methyl-hept-1-ene (122)

A solution of crude 7-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-1-hepten-3-ol (121) (max. 25mmol) was reacted with acetic anhydride (37.5mmol), in the presence of triethylamine (37.5mmol) and D.M.A.P. (2mmol), according to general procedure D. After purification by flash chromatography (petroleum ether-ethyl acetate, 9:1), 3-Acetoxv-7-tetrahvdroroxy-2-(trimethylsilyl)methyl-hept-1-ene (122) was obtained as a colourless oil (1.23g, 15% 2 steps from 5-tetrahydropyranyloxy-pentanal (120)), Rf 0.70 (petroleum ether-ethyl acetate, 9:1);

νmax (film) 2950s, 2875s, 1740s (C=O), 1640m, 1455m, 1440m, 1370m, 1325w, 1245s, 1200m, 1160m, 1140s, 1125s, 1080s, 1035s, 1020s, 990m, 975m, 850s, 775w, 695m;

δH (300MHz, CDCl3) 0.05 (9H, s, TMS), 1.27-1.94 (14H, m, 4-H2, 5-H2, 6-H2, 2'-H2, 3'-H2, 4'-H2, 1''-H2), 2.07 (3H, s, CH3), 3.40 (1H, dt, J 6.4Hz, 9Hz, 7-H), 3.47-3.57 (1H, m, 5'-H), 3.75 (1H, dt, J 6.4Hz, 9Hz, 7-H), 3.83-3.93 (1H, m, 5'-H), 4.59 (1H, t, J 3.2Hz, 1'-H), 4.70 (1H, s, 1-H), 4.88 (1H, s, 1-H), 5.13 (1H, t, J 6Hz, 3-H);

δC (75MHz, CDCl3) -1.2 (q), 19.6 (t), 21.2 (q), 22.2 (t), 22.5 (t), 25.5 (t), 29.4 (t), 30.7 (t), 32.8 (t), 62.2 (t), 67.2 (t), 77.0 (d), 98.7 (d), 109.0 (t), 145.1 (s), 170.1 (s);

m/z (NH3 C.I.) 360 [(M+NH4)+, 35%), 343 (4, M+H), 283 (35, M+H-AcOH), 259 (12, M+2H-Thp), 211 (28, M+2H-AcOH-TMS), 199 (34, M+2H-Thp-AcOH), 183 (10, M-H-TMS-Thp), 126 (3, M+2H-Thp-TMS-AcOH), 102 (100, ThpOH), 85 (40, Thp) (Found: (M+NH4)+, 360.2570. C18H34O4Si requires (M+NH4), 360.2570).
3.6-Diacetox-2-(trimethylsilyl)methyl-hex-1-ene (137)

3-Acetoxy-2-(trimethylsilyl)methyl-1-hexen-6-ol (115) (164mg, 0.67mmol) was reacted with acetic anhydride (102mg, 1.0mmol) in the presence of triethylamine (1.0mmol) and D.M.A.P. (0.054mmol) according to general procedure D. After purification by flash chromatography (petroleum ether-ethyl acetate, 9:1), 3,6-diacetox-2-(trimethylsilyl)methyl-hex-1-ene (137) was obtained as a colourless oil (145mg, 76%), Rf 0.50 (petroleum ether-ethyl acetate, 9:1);

$\nu_{\text{max}}$ (CH$_2$Cl$_2$) 3060w, 2960m, 2900w, 1735s (C=O), 1640m (C=C), 1420w, 1370m, 1280m, 1235s, 1165w, 1040m, 1020m, 975w, 940w, 890m, 850s;

$\delta_H$ (300MHz, CDCl$_3$) 0.06 (9H, s, TMS), 1.42 (1H, dd, J 13.5Hz, <1Hz, 1'-H), 1.57 (1H, dd, J 13.5Hz, <1Hz, 1'-H), 1.60-1.77 (4H, m, 4-H$_2$, 5-H$_2$), 2.04 (3H, s, CH$_3$), 2.07 (3H, s, CH$_3$), 4.07 (2H, t, J 6Hz, 6-H$_2$), 4.70 (1H, d, J <1Hz, 1-H), 4.87 (1H, t, J <1Hz, 1-H), 5.13 (1H, dt, J 5.3Hz, <1Hz, 3-H$_2$);

$\delta_C$ (75MHz, CDCl$_3$) -1.3 (q), 20.8 (q), 21.1 (q), 22.5 (t), 24.6 (t), 29.3 (t), 64.0 (t), 76.3 (d), 109.2 (t), 144.7 (s), 170.0 (s), 170.9 (s);

m/z (NH$_3$ C.I.) 304 ([M+NH$_4$]$^+$, 74%), 287 (7, M+H), 267 (3, M-H$_2$O), 244 (5, M+H-Ac), 227 (15, M+H-AcOH), 209 (1, M+H-AcOH-H$_2$O), 195 (2, M-H$_2$O-TMS), 185 (3, M+2H-AcOH-Ac), 167 (33, M+H-2AcOH), 155 (10, M+2H-TMS-AcOH), 135 (7, M-H$_2$O-TMS-AcOH), 112 (33, M+2H-TMS-Ac-AcOH), 90 (100) [Found: (M+NH$_4$)$^+$, 304.1944. C$_{14}$H$_{26}$O$_4$Si requires (M+NH$_4$), 304.1944].
3.6-Diacetoxy-2-(tetrahydropyranyl)methyl-hex-1-ene (135)

3-Acetoxy-2-(tetrahydropyranyl)methyl-1-hexen-6-ol (132) (114mg, 0.45mmol) was reacted with acetic anhydride (68mg, 0.67mmol) in the presence of triethylamine (0.67mmol) and D.M.A.P. (0.036mmol) according to general procedure D. After purification by flash chromatography (petroleum ether-ethyl acetate, 4:1), 3.6-diacetoxy-2-(tetrahydropyranyl)methyl-hex-1-ene (135) was isolated as a colourless oil, as a 6:1 mixture of diastereoisomers, (79mg, 60%), Rf 0.43 (petroleum ether-ethyl acetate, 4:1), 0.75 (petroleum ether-ethyl acetate, 6:4);

νₘₐₓ (CH₂Cl₂) 3050w, 2940s, 2850m, 1730s (C=O), 1645w (C=C), 1440m, 1370s, 1275m, 1235s, 1175w, 1085s, 1045s, 975m, 910m, 800m;

δₓ (300MHz, CDCl₃) 1.20-1.88 (20H, m, 3'-H₂x₂, 4'-H₂x₂, 5'-H₂x₂, 5-H₂x₂, 4-H₂x₂), 2.04 (3H, s, CH₃major), 2.04 (3H, s, CH₃minor), 2.06 (3H, s, CH₃major), 2.07 (3H, s, CH₃minor), 1.95-2.08 (2H, m, masked by CH₃'s, 1'-Hx₂), 2.29 (2H, dd, J 6.7Hz, 14.3Hz, 1'-Hx₂), 3.34-3.50 (4H, m, 6'-H₂x₂), 3.95 (2H, dt, J 10Hz, 3Hz, 2'-Hx₂), 4.06 (4H, t, J 6Hz, 6-H₂x₂), 4.98 (1H, s, 1-Hminor), 5.0 (1H, d, J <1Hz, 1-Hmajor), 5.06 (1H, s, 1-Hminor), 5.09 (1H, s, 1-Hmajor), 5.22 (2H, t, J 5.6Hz, 3-Hx₂);

δₓ (75MHz, CDCI₃) 20.9 (q, CH₃), 21.2 (q, CH₃), 23.6 (t), 24.7 (t), 26.0 (t), 29.5 (t), 31.7 (t) & 31.8 (t), 39.6 (t) & 39.8 (t), 64.0 (t), 68.5 (t), 75.7 (d) & 76.1 (d), 76.3 (d), 113.4 (t) & 113.6 (t) (=<H), 144.0 (s, C=), 170.1 (s, C=), 170.9 (s, C=);

m/z (NH₃ C.I) 316 ([M+NH₄]+, 22%), 299 (25, M+H), 257 (3, M+2H-Ac), 239 (100, M+H-AcOH), 196 (3, M+H-Ac-AcOH), 179 (30, M+2H-2AcOH), 102 (2, THpOH), 95 (1), 85 (37, THp) (Found: (M+H)+, 299.1858. C₁₆H₂₆O₅ requires (M+H), 299.1858).
3-Acetoxy-8-tetrahydropyranloxy-2-(trimethylsilyl)methyl-oct-1-ene (107) (102mg, 0.3mmol) was reacted with p-toluenesulphonic acid (1.2mg, 5.7μmol) according to general procedure E. No further purification proved necessary and 6-Acetoxy-7-(trimethylsilyl)methyl-7-octen-1-ol (108) was isolated as a colourless oil (77mg, 98%). Rf 0.63 (hexane-ethyl acetate, 1:1);

$\text{v}_{\text{max}}$ (film) 3400brm (OH), 3100w, 2940s, 2860m, 1740m (C=O), 1640m (C=C), 1465w, 1420m, 1370m, 1250s, 1165m, 1055m, 1025s, 945w, 850s, 695m;

$\delta_H$ (270MHz, CDCl$_3$) 0 (9H, s, TMS), 1.20-1.70 (10H, m, 2-H$_2$, 3-H$_2$, 4-H$_2$, 5-H$_2$, 1'-H$_2$), 2.05 (3H, s, CH$_3$), 2.25 (1H, s, OH), 3.60 (2H, t, J 6.8Hz, 1-H$_2$), 4.65 (1H, s, 8-H), 4.85 (1H, s, 8-H), 5.1 (1H, t, J 5.4Hz, 6-H);

$\delta_C$ (67.8MHz, CDCl$_3$) -1.0 (TMS), 21.3, 22.5, 25.2, 25.6, 32.8, 33.0, 62.9 (C[1]), 77.1 (C[6]), 109.2 (C[8]), 145.3 (C[7]), 170.5 (C=O);

m/z (NH$_3$ C.I.) 562 ([2M+NH$_4$]$^+$, 2%), 502 (1, 2M+NH$_4$-AcOH), 290 (53, M+NH$_4$), 273 (M+H), 253 (5, M+H-H$_2$O), 230 (6, M+H-Ac), 213 (100, M+H-AcOH), 123 (43), 90 (48), 73 (7, TMS) (Found: (M+H)$^+$, 273.1881. C$_{14}$H$_{28}$O$_3$Si requires (M+H), 273.1886).
3-Acetoxy-6-tetrahydropyranyloxy-2-(trimethylsilyl)methyl-hex-1-ene (114) (1.57g, 4.8mmol) was reacted with p-toluenesulphonic acid (16mg, 95μmol) according to general procedure E. After purification by flash chromatography (petroleum ether-ethylacetate, 3:1) 4-Acetoxy-5-(trimethylsilyl)methyl-5-hexen-1-ol (115) was isolated as colourless oil (969mg, 83%), Rf 0.22 (petroleum ether-ethylacetate, 3:1);

$\nu_{\text{max}}$ (film) 3440 brs (OH), 2960s, 1735s, 1640m, 1420m, 1370s, 1245s, 1165m, 1040s, 980m, 950m, 840s, 770m, 695s;

$\delta_{\text{H}}$ (300MHz, CDCl$_3$) 0.05 (9H, s, TMS), 1.40-1.85 (6H, m, 2-H$_2$, 3-H$_2$, 1'-H$_2$), 2.08 (3H, s, CH$_3$), 3.65 (2H, t, J 6.3Hz, 1-H$_2$), 4.70 (1H, d, J <1Hz, 6-H$_{\text{trans}}$), 4.87 (1H, t, J <1Hz, 6-H$_{\text{cis}}$), 5.14 (1H, t, J 6-H$_{\text{cis}}$, 4-H);

$\delta_{\text{C}}$ (75MHz, CDCl$_3$) -1.3 (q), 21.2 (q), 22.5 (t), 28.5 (t), 29.2 (t), 62.2 (t), 76.8 (d), 109.2 (t), 144.9 (s), 170.2 (s);

m/z (NH$_3$ C.I) 262 ([M+NH$_4$]$^+$, 5%), 245 (10, M+H), 205 (8, M+NH$_4$-C$_3$H$_7$O), 185 (47, M+H-AcOH), 169 (35, M+2H-AcO-H$_2$O), 155 (10), 133 (6, C$_6$H$_{13}$O$_3$), 112 (62, TMS-C$_3$H$_9$), 95 (100, C$_6$H$_7$O), 71 (1, C$_4$H$_7$O), 56 (3, C$_3$H$_6$O) [Found: (M+H)$^+$, 245.1576. C$_{12}$H$_{24}$O$_3$Si requires (M+H), 245.1573].
5-Acetoxy-6-(trimethylsilyl)methyl-6-hept-1-ol (123)

3-Acetoxy-7-tetrahydropyran-2-ylmethyl-hept-1-ene (122) (128mg, 0.47mmol) was reacted with p-toluenesulphonic acid (1.8mg, 9.3μmol) according to general procedure E. After purification by flash chromatography (petroleum ether-ethyl acetate, 7:3), 5-Acetoxy-6-(trimethylsilyl)methyl-6-hept-1-ol (123) was isolated as a colourless oil (77mg, 75%), Rf 0.38 (petroleum ether-ethyl acetate, 7:3);

$\nu_{\text{max}}$ (CH$_2$Cl$_2$) 3620m (OH), 3480brw (OH), 3060w, 2950s, 1730s (C=O), 1635m (C=C), 1420m, 1370s, 1275m, 1240s, 1165m, 1050m, 1025s, 980m, 940m, 885m, 850s;

$\delta_H$ (300MHz, CDCl$_3$) 0.05 (9H, s, TMS), 1.25-1.85 (8H, m, 2-H$_2$, 3-H$_2$, 4-H$_2$, 1'-H$_2$), 2.05 (3H, s, CH$_3$), 2.67 (1H, brs, -OH), 3.60 (2H, t, J 6.4Hz, 1-H$_2$), 4.67 (1H, d, J <1Hz, 7-H), 4.84 (1H, t, J <1Hz, 7-H), 5.10 (1H, t, J 6Hz, 5-H);

$\delta_C$ (75MHz, CDCl$_3$) -1.3 (q, TMS), 21.2 (q), 21.7 (t), 22.4 (t), 32.3 (t), 32.7 (t), 62.4 (t), 76.9 (d), 109.0 (t), 145.0 (s), 170.2 (s);

m/z (NH$_3$ C.I) 276 ([M+NH$_4$]+, 14%), 259 (20, M+H), 239 (5, M-H-H$_2$O), 216 (4, M+H-Ac), 199 (53, M+H-AcOH), 183 (47, M+2H-AcO-H$_2$O), 144 (6, M+NH$_4$-AcO-TMS), 127 (20, M+H-AcO-TMS), 109 (100, M+H-AcO-TMS-H$_2$O), 90 (68), 71 (2) (Found: (M+H)$^+$, 259.1729. C$_{13}$H$_{26}$O$_3$Si requires (M+H), 259.1729).
3-Acetoxy-2-(trimethylsilyl)methyl-1-hexen-6-ol (115) (985mg, 4mmol) was oxidised by chromium trioxide (2.42g, 24mmol) and pyridine (3.8g, 48mmol) according to general procedure F. After purification by flash chromatography (petroleum ether-ethyl acetate, 6:1), 4-Acetoxy-5-(trimethylsilyl)methyl-5-hexenal (116) was isolated as a colourless oil (447mg, 46%), Rf 0.54 (petroleum ether-ethyl acetate, 6:1);

\[ \text{3-Acetoxy-2-(trimethylsilyl)methyl-1-hexen-6-ol (115)} \]

\[ \text{4-Acetoxy-5-(trimethylsilyl)methyl-5-hexenal (116)} \]

\[ \text{HO} \quad \text{SiMe}_3 \]

(115) \quad \rightarrow \quad \text{OHC} \quad \text{SiMe}_3

(116)

\[ \text{\( \delta_H \)} \text{ (300MHz, CDC}\_3) \text{ } 0.05 \text{ (9H, s, TMS)}, \text{ } 1.42 \text{ (1H, dd, J 13.5Hz, <1Hz, 1'-H)}, \text{ } 1.57 \text{ (1H, dd, J 13.5Hz, <1Hz, 1'-H)}, \text{ } 1.91-2.15 \text{ (5H, m, CH}_3 \text{ & 3-H}_2 \text{)}, \text{ } 2.47 \text{ (2H, dt, J 7.1Hz, 1Hz, 2-H}_2 \text{)}, \text{ } 4.71 \text{ (1H, d, J <1Hz, 6-H}_\text{trans}) \text{, } 4.86 \text{ (1H, t, J <1Hz, 1-H}_\text{cis}) \text{, } 5.13 \text{ (1H, t, J 5.7Hz, 4-H)}, \text{ } 9.76 \text{ (1H, t, J 1Hz, 1-H)}; \]

\[ \text{\( \delta_C \)} \text{ (75MHz, CDC}\_3) \text{ } -1.3 \text{ (q) (TMS)}, \text{ } 21.0 \text{ (q), } 22.6 \text{ (t), } 25.1 \text{ (t), } 39.6 \text{ (t), } 75.6 \text{ (d), } 109.2 \text{ (t), } 144.3 \text{ (s), } 169.7 \text{ (s), } 201.0 \text{ (d) (CH=0)}; \]

\[ \text{m/z (E.I.) } 117 \text{ (20%), } 110 \text{ (13), } 105 \text{ (18), } 75 \text{ (40), } 73 \text{ (62, TMS), } 44 \text{ (17, C}_2\text{H}_4\text{O), } 43 \text{ (44, CH}_3\text{CO}_2\text{).} \]
5-Acetoxy-6-(trimethylsilyl)methyl-6-heptenal (124)

3-Acetoxy-2-(trimethylsilyl)methyl-1-hepten-7-ol (123) (1.12g, 4.3 mmol) was oxidised by chromium trioxide (2.6g, 26 mmol) and pyridine (4.1g, 52 mmol) according to general procedure F. After purification by flash chromatography (petroleum ether - ethyl acetate, 6:1), 5-Acetoxy-6-(trimethylsilyl)methyl-6-heptenal (124) was isolated as a colourless oil (676mg, 60%), Rf 0.85 (petroleum ether-ethyl acetate, 6:1);

ν\text{max} (CH\text{Cl}_2) 2960m, 2900m, 2830w, 2730w, 1725s, 1635m, 1370s, 1280w, 1240s, 1160m, 1080w, 1025m, 980w, 950w, 850s;

δ\text{H} (300MHz, CDCl\text{3}) 0.04 (9H, s, TMS), 1.41 (1H, dd, J 13.5Hz, <1Hz, 1'-H), 1.55 (1H, dd, J 13.5Hz, <1Hz, 1'-H), 1.57-1.73 (4H, m, 3-H\text{2}, 4-H\text{2}), 2.06 (3H, s, CH\text{3}), 2.42-2.47 (2H, m, 2-H\text{2}), 4.68 (1H, d, J <1Hz, 7-H), 4.85 (1H, t, J <1Hz, 7-H), 5.10 (1H, t, J 4.9Hz, 5-H), 9.74 (1H, t, J 1Hz);

δ\text{C} (75MHz, CDCl\text{3}) -1.3 (q, TMS), 17.9 (t), 21.1 (q, CH\text{3}), 22.5 (t), 32.1 (t), 43.3 (t), 76.3 (d, C-5), 109.1 (t, C-7), 144.6 (s, C-6), 169.9 (s, O-C=O), 201.7 (d, C-1);

m/z (NH\text{3} C.l) 274 ([M+NH\text{4}]+, 30%), 257 (10, M+H), 214 (8, M+H-Ac), 197 (32, M+H-AcOH), 142 (7, M+2H-TMS-Ac), 125 (100, M+2H-TMS-AcOH), 107 (100, M+2H-TMS-AcOH-H\text{2}O), 90 (93), 73 (3, TMS) (Found: (M+NH\text{4})+, 274.1838. C\text{13}H\text{24}O\text{3}Si requires (M+NH\text{4}), 274.1838).
4-Acetoxy-3-methylene-cyclooctanol (110)

\[
\begin{align*}
\text{OHC} & \quad \text{SiMe}_3 \\
\text{AcO} & \quad \text{OH}
\end{align*}
\]

(109) \quad (110)

6-Acetoxy-7-(trimethylsilyl)methyl-7-octenal (109) (162mg, 0.6mmol) was reacted with tetrabutyl ammonium fluoride (569mg, 1.8mmol) according to general procedure G. After flash chromatography 4-Acetoxy-3-methylene-cyclooctanol (110), a colourless oil was obtained, as a mixture of diastereoisomers in a ratio of 1:1:1 (by gas chromatography) (32mg, 27%), Rf 0.47 (ethyl acetate-toluene, 2:3). The g.c. conditions used were a 25m CPSil 19CB capillary column at a temperature of 200°C. Retention times were 4.663 minutes for the minor isomer and 4.772 minutes for the major isomer.

\[
\begin{align*}
\text{v}_{\text{max}} & (\text{CH}_2\text{Cl}_2) 3600\text{m} (\text{OH}), 3450\text{brw} (\text{OH}), 3050\text{w}, 2940\text{s}, 2860\text{m}, \\
& 1720\text{s} (\text{C} = \text{O}), 1640\text{w} (\text{C} = \text{C}), 1440\text{w}, 1370\text{m}, 1040\text{s}, 1020\text{s}, 945\text{m}, 910\text{m};
\end{align*}
\]

\[
\begin{align*}
\text{δ}_{\text{H}} (270\text{MHz, CDCl}_3) & 1.2-2.0 (18\text{H, m, OHx2, 5-H}_2\text{x2, 6-H}_2\text{x2, 7-H}_2\text{x2, 8-H}_2\text{x2}), 2.03 (3\text{H, s, CH}_3), 2.06 (3\text{H, s, CH}_3), 2.23 (1\text{H, dd, J 13.5Hz, 8.1Hz, 2-H}), 2.33 (1\text{H, dd, J 13.5Hz, 9.5Hz, 2-H}), 2.57 (1\text{H, dd, J 13.5Hz, 5.4Hz, 2-H}), 2.64 (1\text{H, dd, J 13.5Hz, 5.4Hz, 2-H}), 3.75-3.85 (1\text{H, m, 1-H}), 3.86-3.96 (1\text{H, m, 1-H}), 5.06 (1\text{H, s, 1'-H}), 5.08 (1\text{H, s, 1'-H}), 5.15 (1\text{H, s, 1'-H}), 5.23 (1\text{H, s, 1'-H}), 5.24 (1\text{H, dd, J 4.3Hz, 9Hz,4-H}), 5.33 (1\text{H, dd, J 4.3Hz, 8.1Hz, 4-H});
\end{align*}
\]

\[
\begin{align*}
\text{δ}_{\text{C}} (67.8\text{MHz, CDCl}_3) & 20.5 (\text{t} & 21.0 (\text{t}), 21.3 (\text{q} & 21.4 (\text{q}), 22.7 (\text{t} & 22.9 (\text{t}), 29.1 (\text{t} & 29.5 (\text{t}), 33.9 (\text{t} & 34.2 (\text{t}), 38.9 (\text{t} & 39.4 (\text{t}), 71.6 (\text{d} & 73.2 (\text{d}), 76.5 (\text{d} & 76.9 (\text{d}), 116.2 (\text{t} & 117.8 (\text{t}), 143.6 (\text{s} & 144.1 (\text{s}), 170.1 (\text{s} & 170.1 (\text{s});
\end{align*}
\]

\[
\begin{align*}
m/z (\text{NH}_3 \text{Cl.}) & 216 ([\text{M+NH}_4]^+, 100\%), 199 (5, \text{M+H}), 181 (5, \text{M+H-H}_2\text{O}), 170 (2, \text{M-C}_2\text{H}_4), \\
& 156 (50, \text{M+H-Ac}), 139 (12, \text{M+H-AcOH}), 121 (4), 109 (3), 94 (3) \text{(Found: [M+NH}_4]^+,} \\
& 216.1604. \text{C}_{11}\text{H}_{18}\text{O}_3 \text{requires [M+NH}_4], 216.1600).}
\]
4-Acetoxy-3-methylene-cyclohexanol (117)

4-Acetoxy-5-(trimethylsilylmethyl)-5-hexenal (116) (102mg, 0.4mmol) was reacted with tetrabutylammonium fluoride (530mg, 1.68mmol) according to general procedure G. After flash chromatography (petroleum ether-ethyl acetate, 1:1), 4-Acetoxy-3-methylene-cyclohexanol (117) was isolated as a colourless oil (27mg, 38%) as a 1.3:1 mixture of diastereoisomers (by \(^1\)H nmr), Rf 0.42 (petroleum ether-ethyl acetate, 1:1);

\[\text{m/z (NH}_3\text{ C.I.) } 188 (\text{[M+NH}_4^+]^+, 89\%), 171 (15, \text{M+H}), 170 (39, \text{M+NH}_4^+\text{-H}_2\text{O}), 153 (100, \text{M+H}-\text{H}_2\text{O}), 128 (63, \text{M+H-Ac}), 111 (16, \text{M+H-AcOH}), 93 (3, \text{M+H-AcO-H}_2\text{O}), 81 (1) (\text{Found: (M+NH}_4^+)^+, 188.1289. C}_9\text{H}_14\text{O}_3\text{ requires (M+NH}_4^+)^+, 188.1287).\]
4-Acetoxy-3-methylene-cycloheptanol (118)

\[
\begin{array}{c}
\text{OHC} \\
\text{AcO} \\
\text{SiMe}^3
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{AcO} \\
\text{OH}
\end{array}
\]

(124) (118)

5-Acetoxy-6-(trimethylsilyl)methyl-6-heptenal (124) (578mg, 2.3mmol) was reacted with tetrabutylammonium fluoride (2.14g, 6.8mmol) according to general procedure G. After flash chromatography (petroleum ether-ethyl acetate, 7:3), 4-Acetoxy-3-methylene-cycloheptanol (118) was isolated as a colourless oil, as a 1.3:1 mixture of diastereoisomers (\(^{1}H\) nmr) (191mg, 46%), \(R_f\) 0.27 (petroleum ether-ethyl acetate, 7:3);

\(u_{\text{max}}\) (film) 3410 brs (OH), 2930s, 2860m, 1730s (C=O), 1670m, 1370s, 1240s, 1020s, 985m, 955m, 910m;

\(\delta_H\) (300MHz, CDC\(_3\)) 1.22-2.55 (23H, m, 5-H\(_2\)x2, 6-H\(_2\)x2, 7-H\(_2\)x2, OHx2, CH\(_3\)x2, 2-Hx3), 2.66 (1H, dd, J 5.8Hz, 2-H), 3.73-3.85 (1H, m, 1-H\(_{\text{major}}\)), 3.88-3.98 (1H, m, 1-H\(_{\text{minor}}\)), 5.05 (1H, d, J <1Hz, 1'-H\(_{\text{minor}}\)), 5.07 (1H, d, J <1Hz, 1'-H\(_{\text{major}}\)), 5.17 (1H, t, J 1Hz, 1'-H\(_{\text{major}}\)), 5.18 (1H, t, J 1Hz, 1'-H\(_{\text{minor}}\)), 5.34 (1H, t, J 6.8Hz, 4-H\(_{\text{major}}\)), 5.40 (1H, t, J 6Hz, 4-H\(_{\text{minor}}\));

\(\delta_C\) (75MHz, CDC\(_3\)) major diastereoisomer: 18.6 (t), 33.2 (t), 38.3 (t), 40.7 (t), 71.5 (d), 76.0 (d), 117.6 (l), 142.8 (s),

minor diastereoisomer: 18.1 (t), 33.4 (t), 37.8 (t), 40.2 (t), 69.4 (d), 76.0 (d), 117.2 (t), 142.6 (s),

both diastereoisomers: 21.4 (q), 170.2 (s, C=O);

m/z (NH\(_3\) CI) 202 ([M+NH\(_4\)]\(^{+}\), 30%), 185 (18, M+H), 167 (16, M+H-H\(_2\)O), 142 (80, M+H-Ac), 125 (58, M+H-AcOH), 107 (100, M+H-AcOH-H\(_2\)O), 95 (12), 91 (7), 78 (9), 68 (5), 58 (2)
(Found: (M+NH\(_4\))\(^{+}\), 202.1443. \(C_{10}H_{16}O_3\) requires (M+NH\(_4\)), 202.1443).
3-Acetoxy-5-tetrahydropyranyl methyl-1-penten-5-ol (131)

3-Acetoxy-5-tetrahydropyranyl-2-(trimethylsilyl)methyl-pent-1-ene (126) (100mg, 0.32mmol) was reacted with Tin (IV) chloride (0.64mmol) according to general procedure H. After purification by flash chromatography (petroleum ether-ether, 3:2), 3-Acetoxy-2-tetrahydropyranyl methyl-1-penten-5-ol (131) was isolated as a colourless oil as a 2.4:1 mixture of diastereoisomers (27.4mg, 36%), Rf 0.20 (petroleum ether-ether, 3:2);

\[ \text{max} \ (\text{CH}_2\text{Cl}_2) \ 3515 \text{w} \ (\text{OH}), \ 3480 \text{brw} \ (\text{OH}), \ 3040 \text{w}, \ 2940 \text{s}, \ 2850 \text{m}, \ 1730 \text{s} \ (\text{O}=\text{O}), \ 1645 \text{w} \ (\text{O}=\text{O}), \ 1420 \text{w}, \ 1370 \text{m}, \ 1275 \text{w}, \ 1235 \text{s}, \ 1085 \text{s}, \ 1040 \text{s}, \ 900 \text{m}; \]

\[ \delta_\text{H} \ (300\text{MHz}, \text{CDCl}_3) \ 1.20-2.0 \ (18\text{H}, \text{m}, \text{H}_2\text{x}2), \ 5'-\text{H}_2\text{x}2, \ 3'-\text{H}_2\text{x}2, \ 4'-\text{H}_2\text{x}2, \ \text{OH}x2), \ 2.08 \ (3\text{H}, \text{s}, \text{CH}_3\text{minor}), \ 2.09 \ (3\text{H}, \text{s}, \text{CH}_3\text{major}), \ 2.10-2.22 \ (2\text{H}, \text{m}, \text{H}_2\text{x}2), \ 2.25-2.37 \ (2\text{H}, \text{m}, \text{H}_2\text{major}), \ 3.35-3.52 \ (4\text{H}, \text{m}, \text{H}_2\text{x}2), \ 3.55-3.84 \ (4\text{H}, \text{m}, \text{H}_2\text{x}2), \ 3.92-4.04 \ (2\text{H}, \text{m}, \text{H}_2\text{minor}), \ 5.01 \ (2\text{H}, \text{s}, \text{H}_2\text{x}2), \ 5.15 \ (2\text{H}, \text{s}, \text{H}_2\text{x}2), \ 5.39 \ (1\text{H}, \text{t}, \text{J} \ 3.8\text{Hz}, \text{3-H}), \ 5.41 \ (1\text{H}, \text{t}, \text{J} \ 3.8\text{Hz}); \]

\[ \delta_\text{C} \ (75\text{MHz}, \text{CDCl}_3) \ \text{major \ diastereoisomer:} \ 31.7 \ (\text{t}), \ 36.3 \ (\text{t}), \ 58.8 \ (\text{t}), \ 76.3 \ (\text{d}), \ 113.4 \ (\text{t}), \ 144.3 \ (\text{s}), \]

\text{minor \ diastereoisomer:} \ 31.9 \ (\text{t}), \ 36.3 \ (\text{t}), \ 58.9 \ (\text{t}), \ 76.1 \ (\text{d}), \ 113.5 \ (\text{t}), \ 144.4 \ (\text{s}), \]

\text{both \ diastereoisomers:} \ 21.2 \ (\text{q}), \ 23.5 \ (\text{t}), \ 25.9 \ (\text{t}), \ 39.9 \ (\text{t}), \ 68.5 \ (\text{t}), \ 73.7 \ (\text{d}), \ 170.8 \ (\text{s}); \]

\[ \text{m} / \text{z} \ (\text{NH}_3 \ \text{C.l.)} \ 243 \ [(\text{M}+\text{H})^+], \ 15\%, \ 219 \ (6, \text{M}+\text{NH}_4\cdot\text{C}_3\text{H}_5), \ 183 \ (100, \text{M}+\text{H}-\text{AcOH}), \ 165 \ (1, \text{M}+\text{H}-\text{AcOH}-\text{H}_2\text{O}), \ 153 \ (3, \text{M}+\text{H}-\text{AcO-CH}_2\text{OH}), \ 85 \ (17, \text{Thp}) \ \text{[Found:} \ (\text{M}+\text{H})^+, \ 243.1596. \]

\text{C}_{13}\text{H}_{22}\text{O}_4 \ \text{requires} \ (\text{M}+\text{H}), \ 243.1596. \]
3-Acetoxy-2-(tetrahydropyranyloxy)methyl-1-hex-6-en-1-ol (132)

\[
\begin{align*}
\text{ThpO} & \quad \text{AcO} & \quad \text{SiMe3} \\
& \quad \text{HO} \\
(114) & \quad \text{AcO} & \quad \text{AcO} & \quad \text{O} \\
& \quad \text{AcO} \\
(132) & \quad \text{AcO} & \quad \text{AcO} & \quad \text{O} \\
(135)
\end{align*}
\]

3-Acetoxy-6-tetrahydropyranyloxy-2-(trimethylsilylmethyl-hex-1-ene (114) (108mg, 0.29mmol) was reacted with tin (IV) chloride (0.58mmol) according to general procedure H. After flash chromatography (petroleum ether-ethyl acetate, 6:4), two products were isolated:

3-Acetoxy-2-(tetrahydropyranloxy)methyl-1-hexen-6-ol (132) was isolated as a colourless oil, as a 5:1 ratio of diastereoisomers (21mg, 28%), Rf 0.21 (petroleum ether-ethyl acetate, 6:4);

\[ \nu_{\text{max}} (\text{CH}_2\text{Cl}_2) \quad 3615 \text{m} \quad (\text{OH}), \quad 3450 \text{brw} \quad (\text{OH}), \quad 3040 \text{w}, \quad 2940 \text{s}, \quad 2850 \text{s}, \quad 1725 \text{s} \quad (\text{C=O}), \quad 1645 \text{w} \quad (\text{C=C}), \quad 1525 \text{W}, \quad 1435 \text{m}, \quad 1370 \text{s}, \quad 1275 \text{m}, \quad 1235 \text{s}, \quad 1175 \text{m}, \quad 1085 \text{s}, \quad 1045 \text{s}, \quad 980 \text{m}, \quad 910 \text{m}; \]

\[ \delta_{\text{H}} (300\text{MHz, CDCl}_3) \quad 1.20-1.88 \quad (20\text{H, M, 4-H}_2\text{X2, 5-H}_2\text{X2, 5'-H}_2\text{X2, 3'-H}_2\text{X2, 4'-H}_2\text{X2}), \quad 2.05 \quad (3\text{H, s, CH}_3\text{minor}), \quad 2.06 \quad (3\text{H, s, CH}_3\text{major}), \quad 2.10 \quad (2\text{H, dd, J 4.5Hz, 15Hz, 1'-H}_2\text{X2}), \quad 2.32 \quad (2\text{H, dd, J 6.7Hz, 15Hz, 1'-H}_2\text{X2}), \quad 2.45 \quad (2\text{H, brs, OH}_2\text{X2}), \quad 3.36-3.53 \quad (4\text{H, m, 6'-H}_2\text{X2}), \quad 3.64 \quad (4\text{H, t, J 6.4Hz, 6'-H}_2\text{X2}), \quad 3.96 \quad (2\text{H, dt, J 1.9Hz, 10.5Hz, 2'-H}_2\text{X2}), \quad 4.96 \quad (1\text{H, d, J <1Hz, 1-H}_\text{cis} \text{ to C6 minor}), \quad 4.98 \quad (1\text{H, d, J <1Hz, 1-H}_\text{cis} \text{ to C6 major}), \quad 5.06 \quad (1\text{H, s, 1-H}_\text{trans} \text{ to C6 minor}), \quad 5.09 \quad (1\text{H, s, 1-H}_\text{trans} \text{ to C6 major}), \quad 5.25 \quad (2\text{H, t, J 6Hz, 3-HX2}); \]

\[ \delta_{\text{C}} (75\text{MHz, CDCl}_3) \quad \text{major diastereoisomer} : \quad 29.1 \quad (\text{t}), \quad 31.5 \quad (\text{t}), \quad 39.4 \quad (\text{t}), \quad 76.2 \quad (\text{d}), \quad 113.3 \quad (\text{t}), \quad 143.9 \quad (\text{s}), \quad \text{minor diastereoisomer} : \quad 29.1 \quad (\text{t}), \quad 31.7 \quad (\text{t}), \quad 39.6 \quad (\text{t}), \quad 75.9 \quad (\text{d}), \quad 113.1 \quad (\text{t}), \quad 144.2 \quad (\text{s}), \quad \text{both diastereoisomers} : \quad 21.1 \quad (\text{q}), \quad 23.4 \quad (\text{t}), \quad 25.8 \quad (\text{t}), \quad 28.3 \quad (\text{t}), \quad 62.0 \quad (\text{t}), \quad 68.4 \quad (\text{t}), \quad 76.3 \quad (\text{d}), \quad 170.2 \quad (\text{s}); \]

\[ \text{m/z (NH}_3 \text{ Cl)} \quad 257 \quad ([\text{M+H}]^+ \quad 15\%), \quad 239 \quad (28, \text{ M+H-H}_2\text{O}), \quad 197 \quad (100, \text{ M+H-AcOH}), \quad 179 \quad (10, \text{ M+H-AcOH-H}_2\text{O}), \quad 155 \quad (1), \quad 111 \quad (1), \quad 102 \quad [2, \text{ ThpOH}], \quad 95 \quad (3), \quad 85 \quad (57, \text{ Thp}) \quad \text{(Found: [M+H]^+}, \quad 257.1753. \quad \text{C}_{14}\text{H}_{24}\text{O}_4 \quad \text{requires (M+H), 257.1753).} \]
3.6-Diacetoxy-2-(tetrahydropyran-2-yl)methyl-hex-1-ene (135) was isolated as a colourless oil, as a 3:1 ratio of diastereoisomers (23mg, 26%), Rf 0.75 (petroleum ether-ethyl acetate, 6:4);

\( \nu_{\text{max}}(\text{CH}_2\text{Cl}_2) \) 3040w, 2940s, 2845m, 1725s (C=O), 1640w, 1525w, 1440m, 1315m, 1275m, 1230s, 1085s, 1045s, 975w, 915m;

\( \delta_H (300\text{MHz, CDCl}_3) \) 1.20-1.37 (2H, m) & 1.40-1.90 (18H, m, 4-H_2x2, 5-H_2x2, 5'-H_2x2, 3'-H_2x2, 4'-H_2x2), 2.04 (6H, s, CH_3x2), 2.06 (6H, s, CH_3x2), 2.00-2.18 (2H, ddx2, 6-H_2x2) (masked by CH3's), 2.25 (1H, dd, J 6.7MHz, 13Hz, 1'-H_{\text{minor}}), 2.29 (1H, dd, J 6.7MHz, 13Hz, 1'-H_{\text{major}}), 3.34-3.52 (4H, m, 6'-H_2x2), 3.95 (2H, dt, J 1Hz, 10.5Hz, 2'-Hx2), 4.07 (4H, t, J 6Hz, 6-H_2x2), 4.98 (1H, d, J <1Hz, 1-H_{cix to C6 minor}), 4.99 (1H, d, J <1Hz, 1-H_{cix to C6 major}), 5.07 (1H, s, 1-H_{trans to C6 minor}), 5.09 (1H, s, 1-H_{trans to C6 major}), 5.23 (2H, t, J 6Hz, 3-Hx2);

\( \delta_C (75\text{MHz, CDCl}_3) \) **major diastereoisomer:** 23.6 (t), 31.7 (t), 39.6 (t), 76.1 (d), 76.4 (d), 113.6 (t), 144.0 (s),
**minor diastereoisomer:** 23.5 (t), 31.8 (t), 39.8 (t), 75.6 (d), 76.2 (d), 113.3 (t), 144.2 (s),
**both diastereoisomers:** 20.9 (q), 21.2 (q), 24.7 (t), 26.0 (t), 29.5 (t), 64.0 (t), 68.5 (t), 170.0 (s), 170.9 (s);

m/z (NH_3 C.I.) 316 ([M+NH_4]^+, 12%), 299 (27, M+H), 239 (100, M+H-AcOH), 225 (3), 196 (9), 179 (92, M+2H-2AcOH), 162 (2), 111 (l), 102 (14, ThpOH), 95 (12), 85 (100, Thp) (Found: (M+H)^+, 299.1858. C_{16}H_{26}O_{5} requires (M+H), 299.1858).
3-Acetoxy-2-[(tetrahydropyranyl)methyl]-1-octen-8-ol (136)

3-Acetoxy-8-tetrahydropyranyloxy-2-[(trimethylsilyl)methyl]-oct-1-ene (107) (770mg, 2.16mmol) was reacted with tin(IV) chloride according to general procedure H. After purification by flash chromatography (petroleum ether-ethyl acetate, 3:2), 3-Acetoxy-2-[(tetrahydropyranyl)methyl]-1-octen-8-ol (136) was isolated as a 2.3:1 mixture of diastereomers, as a colourless oil (322mg, 52%), Rf 0.25 (petroleum ether-ethyl acetate, 3:2);

νmax (CH2Cl2) 3615m (OH), 3450brw (OH), 2940s, 2860s, 1725s (0=0), 1640w (0=0), 1435m, 1370s, 1275m, 1235s, 1175w, 1085s, 1040s, 1020s, 910m;

δH (300MHz, CDCl3) 1.20-1.70 (26H, m, 6-H2x2, 7-H2x2, 5-H2x2, 5'-H2x2, 3'-H2x2, 4'-H2x2, 4-H2), 1.78-1.87 (2H, m, 4-H2), 2.04 (3H, s, CH3minor), 2.05 (3H, s, CH3major), 2.00-2.15 (masked by CH3's) (2H, 2xddd, J 5.4Hz, 15Hz, 1'-Hx2), 2.26 (1H, dd, J 6.7Hz, 15Hz, 1'-Hmajor), 2.31 (1H, dd, J 6.7Hz, 15Hz, 1'-Hminor), 2.50 (2H, s, OxHx2), 3.35-3.52 (4H, m, 6'-H2x2), 3.59 (4H, t, J 6.2Hz, 8-H2x2), 3.96 (2H, dt, J 11.2Hz, 1.5Hz, 2'-Hx2), 4.94 (1H, d, J <1Hz, 1-Hcis to C8 minor), 4.96 (1H, d, J <1Hz, 1-Hcis to C8 major), 5.04 (1H, s, 1-Htrans to C8 minor), 5.06 (1H, s, 1-Htrans to C8 major), 5.18 (2H, t, J 6.5Hz, 3-Hx2);

δC (75MHz, CDCl3) major diastereisomer: 23.3 (t), 31.5 (t), 39.3 (t), 76.1 (d), 113.3 (t), 143.9 (s),
minor diastereisomer: 23.3 (t), 31.6 (t), 39.5 (t), 76.0 (d), 113.0 (t), 144.2 (s),
both diastereomers: 21.0 (q), 25.0 (t), 25.3 (t), 25.8 (t), 32.8 (t), 33.0 (t), 62.2 (t), 68.3 (t), 76.5 (d), 170.1 (s);

3.6-Diacetoxy-2-(trimethylsilyl)methyl-hex-1-ene (135)

\[ \text{AcO} \quad \text{AcO} \quad \text{SiMe}_3 \quad \rightarrow \quad \text{AcO} \quad \text{AcO} \quad \text{O} \]

(137) \hspace{1cm} (135)

3,6-Diacetoxy-2-(trimethylsilyl)methyl-hex-1-ene (137) (138mg, 0.48mmol) was reacted with tin(IV) chloride (0.96mmol) and dihydropyran (41mg, 0.48mmol) in dichloromethane (5ml) at -20°C under nitrogen. Once reaction was complete, it was quenched with saturated aqueous ammonium chloride solution (10ml), and the aqueous layer was extracted with ether (3x10ml). The combined extracts were dried (MgSO\(_4\)), and the solvent evaporated under reduced pressure. Purification was attempted by flash chromatography (petroleum ether-ethyl acetate, 6:1).

None of the products was conclusively identified.
REFERENCES


