Synthesis of Iboga Alkaloids Using
Cascade Cyclisation, Nitrone
Cycloaddition

Submitted by
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Abstract

This thesis details the study of nitrone cycloadditions to synthesize some novel isoxazolidines. Condensation of aldehydes A and B, with N-methylhydroxylamine led to the formation of nitrones. Cycloaddition of these nitrones gave a range of bicyclic isoxazolidine products.

The cascade chemistry, involving condensation, cyclisation, and nitrone cycloaddition was utilised in the synthesis of the core structure found in iboga alkaloid natural products. Aldehydes C were synthesised and condensed with hydroxylamine to obtain a variety of isoquinuclidine cycloadducts.

This cascade chemistry was used for the formal synthesis of 19-hydroxy-ibogamine. Starting with aldehyde C, X = Cl, R,R = S(CH₂)₃S, R' = CH₃ gave the cycloadduct D. This was converted to the amide E that represents the completion of the formal synthesis of this alkaloid.

In addition, some studies were carried out towards an aldehyde needed for the cascade chemistry to investigate a proposed biosynthesis of the alkaloids daphlongeranines A and B.
DEDICATED

My Father

For being my first teacher
For earning an honest living for us and for supporting and
encouraging me to believe in myself

My Mother

A strong and gentle soul who taught me to trust in Allah, believe
in hard work and that so much could be done with little

I would never get this without you!
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### Abbreviations

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<tr>
<td>Ac</td>
<td>acyl</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>Cl</td>
<td>chemical ionisation</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CPME</td>
<td>cyclopentyl methyl ether</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>DCC</td>
<td>dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
</tr>
<tr>
<td>DIAD</td>
<td>diisopropyl azodicarboxylate</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-N,N-dimethylaminopyridine</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMP</td>
<td>2,2-dimethoxypropane</td>
</tr>
<tr>
<td>DMPU</td>
<td>1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone</td>
</tr>
<tr>
<td>DMS</td>
<td>dimethylsulfide</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dr</td>
<td>diastereoisomer ratio</td>
</tr>
<tr>
<td>EDCI</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomer excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron ionisation (or electron impact)</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalent</td>
</tr>
<tr>
<td>ES</td>
<td>electrospray ionisation</td>
</tr>
<tr>
<td>EWG</td>
<td>electron withdrawing group</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier Molecular Orbital</td>
</tr>
</tbody>
</table>
GC  gas chromatography
HMPA  hexamethyl phosphoramide
HOMO  Highest Occupied Molecular Orbital
HPLC  high performance liquid chromatography
HRMS  high resolution mass spectrometry
HSQC  heteronuclear single quantum correlation
IR  infra red
KHMDIS  potassium bis(trimethylsilyl)amide
LDA  lithium diisopropylamide
LRMS  low resolution mass spectrometry
LUMO  Lowest Unoccupied Molecular Orbital
m/z  mass number
m.p.  melting point
m-CPBA  meta-chloroperoxybenzoic acid
Ms  methanesulfonyl or mesyl
MW  microwave
NaHMDS  sodium bis(trimethylsilyl)amide
NBS  N-bromosuccinimide
NCS  N-chlorosuccinimide
NMR  nuclear magnetic resonance
NOESY  nuclear Overhauser effect spectroscopy
Ph  phenyl
PIFA  (bis(trifluoroacetoxy)iodo)benzene
PMB  para-methoxybenzyl
Py  pyridine
Red-Al  sodium bis(2-methoxyethoxy)aluminium hydride
Rf  retention factor
rt  room temperature
TBAI  tetrabutylammonium iodide
TBS  tert-butyldimethylsilyl
‘Bu  tert-butyl
TES  triethylsilyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl or triflate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TIB</td>
<td>2,4,6-triisopropylbenzoyl</td>
</tr>
<tr>
<td>TIPB</td>
<td>1,3,5-triisopropylbenzene</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>$N,N',N',N'$-tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Ts</td>
<td>para-toluenesulfonyl or tosyl</td>
</tr>
</tbody>
</table>
Chapter 1

1.1 Introduction to cascade reactions

A big challenge for the synthetic organic chemist is the synthesis of complex molecules which contain polycyclic structures. Their synthesis typically requires multiple steps, and so the generation of three or more bonds in one step is very useful methodology and is generally known as "cascade" or "tandem" reactions. Cascade reactions have been widely studied, and have seen huge progress in recent years. The benefits of cascade chemistry are apparent and include the generation of polycyclic ring systems in one step, reduction in time and waste, and the high levels of stereocontrol. Therefore, cascade chemistry accords with the principle of “green chemistry”. In the Coldham group, extensive research has been carried out on the cascade processes of condensation, cyclisation, and dipolar cycloaddition reactions towards the synthesis of core structures involving fused ring and bridged ring systems. This report will discuss this type of chemistry, and how the methodology which has been developed in the group will be used towards the synthesis of iboga alkaloids, and the formation of a two-carbon bridged system in a single step from an acyclic aldehyde.

1.2 Cascade cycloadditions with nitroalkenes

Aliphatic compounds having nitro groups are important intermediates in organic synthesis as they are easy to convert into other functional groups, such as amides, hydroxylamines, nitronates, nitrile oxides, amines, nitrones and the remarkable transformation into carbonyl compounds using the Nef reaction. In 1986, Denmark and co-workers reported that nitroalkenes undergo Diels–Alder [4 + 2] cycloaddition when treated with a dienophile to yield nitronates. For unactivated dienophiles, such as simple alkenes, a Lewis acid is required to effect the reaction, by lowering the energy of the diene LUMO and reduce the gap between the HOMO of the alkene and the LUMO of the diene (nitroalkene). For example, reacting nitroalkene 1 and cyclopentene 2, with SnCl₄, gave two diastereoisomeric cycloadducts 3 and 4 in a 12:1 ratio (Scheme 1.1).
The major cycloadduct 3 comes from the *exo* approach of the alkene towards the nitroalkene, while cycloadduct 4 arises from an *endo* approach. Moreover, the cycloaddition of nitroalkenes can take place in an intramolecular reaction. For example, when treating nitro compound 5 with SnCl$_4$ at −78 °C in toluene, after a short period of time the nitronate 6 was formed as a single diastereoisomer. Similarly, to demonstrate the effect of the Lewis acid, the same reaction was heated at reflux in cymene for 1 h in the absence of a Lewis acid to give the same nitronate 6 (Scheme 1.2).

A 1964 study by Tartakovskii and co-workers showed that nitronates can serve as dipoles and can easily undergo a [3 + 2] dipolar cycloaddition to produce 5-membered cycloadducts. For example, the reaction between nitronate 7 and acrylonitrile yielded nitrile 8 in 46% yield (the stereoselectivity was not reported) (Scheme 1.3).
Denmark and co-workers reported that the use of an inverse electron demand [4 + 2] cycloaddition of a nitroalkene bearing an electron-donating dienophile, followed by a normal electron demand [3 + 2] dipolar cycloaddition of an electron-withdrawing dipolarophile, is very useful as a cascade process. This could allow the generation of four rings and six stereogenic centres in one pot, as shown in Figure 1.1.4

The cascade reaction can be classified into four classes, these are inter– and intramolecular versions of both cycloaddition reactions (Figure 1.2). Some of these will be discussed in detail in this section.
1.2.1 Intermolecular [4 + 2]/intramolecular [3 + 2] cycloadditions

The intermolecular [4 + 2] cycloaddition of a nitroalkene followed by intramolecular [3 + 2] cycloaddition has been widely studied, due to the fact that it can lead to different types of cycloadducts. These are fused and two different types of bridged compounds.

1.2.1.1 Fused ring systems

For formation of a fused ring system, the dipolarophile needs to be connected to the α-carbon of the nitrone, which undergoes the cycloaddition. In 1990, Denmark and co-workers studied the effect of the length of the tether between the dipole and the dipolarophile, nitronate substitution as well as the dipolarophile configuration. The [3 + 2] cycloaddition of the substrates with two or three methylene units between the dipole and dipolarophile formed five or six membered nitroso acetal cycloadducts rapidly in good yield. Following the [4 + 2] cycloaddition, substrates with two methylene units mostly underwent [3 + 2] cycloaddition, while heating is required for the substrates bearing three methylene units to form the desired cycloadduct. On the other hand, substrates with four methylene units failed to form seven membered cycloadducts, and only intermediate nitronates were obtained, even on heating.

An example of a [4 + 2] then [3 + 2] cycloaddition is shown in Scheme 1.4. Treating the nitroalkene 9 with tetramethylethylene 10 in the presence of SnCl₄ in PhMe at –78 °C gave the [4 + 2] cycloaddition product. This was followed by heating at 80 °C in PhMe, which afforded the [3 + 2] cycloadduct 11 in 78% yield and with high diastereoselectivity (20:1).

![Scheme 1.4](image-url)
To enhance the complexity of the cascade, 2-substituted vinyl ethers, which are oxygen-containing dienophiles were used in the [4 + 2] cycloaddition, allowing generation of up to six stereocentres in one step. Compound 12 was treated with ether 13, in the presence of Lewis acid Ti(O\(\text{OPr})_2\text{Cl}_2\), to give anomers 14a and 14b, in 5.7:4.3 ratio (Scheme 1.5). In the [4 + 2] cycloaddition, the time of reaction affects the anomer ratio; in short time 14a was the major isomer, which is derived from the endo orientation of the ethoxy group, whereas using longer times the proportion of isomer 14b was increased. The effect of electron deficient dipolarophiles on the [3 + 2] cycloaddition was studied and in many cases the reaction was found to take place in good yield and moderate diastereoselectivity, but occurred more slowly.\(^\text{11}\)

![Scheme 1.5](image)

The nitrosoacetals 14a and 14b underwent hydrogenolysis leading to the formation of tricyclic lactam 18. Initially, breaking of the N–O bonds occurs, followed by hemiacetal removal to form the aldehyde 16 which then cyclises and is reduced to give the amine 17. This then cyclises to form the lactam.\(^\text{9,10}\)

This type of chemistry has been used in the synthesis of many natural products, including \((-\)-rosmarinecine,\(^\text{12}\) \((-\)-mesembrine,\(^\text{13}\) \((-\)-detoxinine,\(^\text{14}\) and castanospermine.\(^\text{15}\)
1.2.1.2 Bridged ring systems

Bridged systems are different from fused systems, as the dipolarophile connects to the dienophile (either α- or β-) carbon instead of the nitroalkene, to give bridged cyclic compounds. The products after the reduction reaction are either cyclohexanols or cyclopentanols. For example, treating nitroalkene 19 with 1,4-pentadiene in the presence of SnCl$_4$ at −15 °C in CH$_2$Cl$_2$ gave the nitronate 20 in 91% yield as a single diastereoisomer, in exo oriented conformation. The product was heated at reflux in PhMe to facilitate the [3 + 2] cycloaddition leading to the formation of the bridged cycloadduct 21 (Scheme 1.6).

![Scheme 1.6](image)

1.2.2 Intramolecular [4 + 2]/intramolecular [3 + 2] cycloadditions

The intramolecular [4 + 2] cycloaddition of a nitroalkene followed by intramolecular [3 + 2] cycloaddition requires the dienophile and the dipolarophile to be attached to the nitroalkene. In terms of tethering there are many ways in which they can be attached together. Denmark has done extensive research on the fused/bridged systems where the dipolarophile is attached at C(6) or C(5) of the nitronate (Figure 1.3).
An example related to the C(6) position stated that heating the nitroalkene 22 with SnCl₄ at −78 °C in PhMe afforded a mixture of nitronates 23 and the nitrosoacetal 24. Warming the crude mixture yielded a single diastereoisomer of nitrosoacetal 24 in good yield (Scheme 1.7).¹⁸

In order to rationalize the stereochemistry of the [4 + 2] cycloaddition step there are two possible transition states, *exo* and *endo* (Figure 1.4).²⁰ The *endo*-shape is the less preferred, due to the steric interaction between the Lewis acid and the R group. In addition, in the *endo* transition state there is an interaction of the methyl group with the allylic proton and a methylene proton within the chain. However, in the favorable *exo*-shape, the steric interaction is less, where the methyl group and Lewis acid interact with alkene protons.
To examine the reactivity of the C(5) position, compound 25 was chosen, in which a vinyl ether has been introduced. This allows investigating the effect of tether length. Thus, compound 25 and SnCl₄ in toluene were stirred for 20 min at −78 °C, and a mixture of nitronates 26 and the desired product 27 was formed in 3:2 ratio. To effect the intermolecular cycloaddition, the reaction mixture was stirred for 1 h at room temperature to afford cycloadduct 27 as a single diastereoisomer in 87% yield (Scheme 1.8).¹⁸

1.3 Cascade cycloadditions with nitrones

Nitrones, azomethine ylides, azomethine imines, and nitronates are all classified as dipoles and are valuable intermediates in organic chemistry. A 1,3-dipole is basically a three atom π-electron system, with four π-electrons distributed over the three atoms. The allyl type is bent, involving four electrons in three parallel pz orbitals perpendicular to the plane of the dipole (Figure 1.5).²¹
This study will be focused on nitrones as 1,3-dipoles, which have been shown to be crucial intermediates in organic chemistry. These were named by Pfeiffer from an abbreviation of “nitrogen-ketone”, for compounds have the structure 28, compared to the similarity with ketones (Figure 1.6).

1.3.1 Nitrones

A nitrone is a system of three atoms C–N–O over which are delocalised four \( \pi \) electrons. The combination of a nitrone and an unsaturated dipolarophile is a cycloaddition reaction, which is thermally allowed, and involves a total of six electrons \([\pi 4_s + \pi 2_s]\) in a suprafacial process according to the Woodward–Hoffmann rules (Figure 1.7).

The product from the 1,3-dipolar cycloaddition reaction of a nitrone with an alkene is called an isoxazolidine. This concerted reaction leads to the formation of O–C and C–C \( \sigma \) bonds and up to three new stereocentres in the product (Figure 1.8).
In support of frontier molecular orbital (FMO) theory, it is possible to examine the 1,3-dipolar cycloaddition between the nitrone and alkene. The dominant orbital interaction is thought to involve the HOMO (highest occupied molecular orbital) of the electron rich nitrone and the LUMO (lowest unoccupied molecular orbital) of the dipolarophile (Figure 1.9).\(^{26}\)

Theoretical calculations could help to estimate the relative energies of the HOMO and LUMO of the nitrone and dipolarophiles (Figure 1.10).\(^{27}\)

The main interaction will be between the orbitals having closer energy and coefficient size. Thus, prediction of regioselectivity of the cycloaddition reaction can be made, based on the known energy and size (Figure 1.11). In addition, the effects of steric factors must be considered.\(^{28}\) In an intramolecular cycloaddition the
conformational restraints can play a role to enhance the selectivity and might lead to form only one regioisomer.\textsuperscript{27}

\begin{center}
\includegraphics[width=0.8\textwidth]{figure1.11.png}
\end{center}

\textbf{Figure 1.11}

The \([3 + 2]\) cycloaddition reaction is a concerted step and the regioselectivity is often controlled by the substituent group that is attached to the dipolarophile. However, easy reactions can occur with dipole LUMO control for electron rich nitrones \textsuperscript{29}, and dipole HOMO control with electron deficient alkenes \textsuperscript{30}. Introducing a substituent group on the dipole can generate a steric effect, leading to the preferential formation of isoxazolidines \textsuperscript{31} in which the substituent from the dipolarophile is located at C-5 (Scheme 1.9).\textsuperscript{27}

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme1.9.png}
\end{center}

\textbf{Scheme 1.9}

\subsection*{1.3.2 The formation of nitrones}

Nitrones can be generated either by oxidation methods such as oxidation of amines, imines, or hydroxylamines, or non-oxidation methods: from oximes, or \textit{via} the condensation of carbonyl compounds with hydroxylamines (Figure 1.12). Examples of non-oxidation methods are discussed in brief below.
1.3.2.1 From oximes

A 1991 study by Grigg and co-workers explored the formation of nitrones from oximes and made a significant development. The preparation of nitrones from oximes can involve a 1,2-prototropy reaction. Heating the oxime results in a small equilibrium concentration of its nitrone (Figure 1.13). He showed that unstable nitrones could be incorporated into the subsequent 1,3-dipolar cycloaddition reaction (for an example of this see Scheme 1.22). The nitrone can undergo either intra- or intermolecular 1,3-dipolar cycloaddition reaction.

Grigg and co-workers reported that the N-alkylation of oximes with electron-poor substituted alkenes generated nitrones; this was presumed to proceed through a Michael addition reaction. The group suggested a 1,3-azaprotic cyclotransfer mechanism (Figure 1.14).

![Figure 1.12](image)

![Figure 1.13](image)

![Figure 1.14](image)
For example, the reaction of oxime 33 with diene 34 in acetonitrile at 80 °C formed the nitrone 35. Subsequently, the nitrone underwent cycloaddition reaction to give cycloadduct 36 in excellent yield (Scheme 1.10).  

![Scheme 1.10](image)

Chakrabarty and co-workers have extended the 1,3-azaprotic cyclotransfer methodology into the synthesis of indol-nitrones from the corresponding oximes. Oxime 37 and acrylonitrile (38) were heated at reflux in benzene to afford the nitrone 39 in 85% yield (Scheme 1.11).

![Scheme 1.11](image)

In 2007, Imada and Naota reported a catalytic process to form nitrones 41 and 43 from hydroxylamine 40 and secondary amine 42 respectively.  

The flavin 44 was used as a catalyst and molecular O₂ effected the oxidation reaction. This reaction allows high selectivities and good yield to be obtained (Scheme 1.12).
1.3.2.2 Hydroxylamine and carbonyl condensation

A useful and common method for forming nitrones is by treating carbonyl compounds with hydroxylamines. Condensation of aldehydes with hydroxylamine hydrochloride gives nitrones and this method can also be successful with ketones.\(^\text{23}\)

Philip and co-workers reported that treatment of aldehyde 45 with \(N\)-benzylhydroxylamine hydrochloride at room temperature gave nitrone 46 in excellent yield (Scheme 1.13).\(^\text{34}\)

In 2003, formation of a nitrone possessing an \(\alpha\) stereocentre was reported by Bøgevig and co-workers.\(^\text{35}\) Proline was employed as the catalyst to activate the aldehyde 47 and reaction with ketone 48 gave the aldol product. Finally, the addition of \(N\)-benzylhydroxylamine \textit{in-situ} formed nitrone 49 (96% ee) in 83% yield (Scheme 1.14).\(^\text{35}\)
A 2009 study by Pfeiffer and Beauchemin reported a simple method for the synthesis of nitrones from ketones. The $N$-substituted hydroxylamine $50$ and acyclic ketone $51$ in $t$BuOH were heated in a sealed tube to give ketonitrone $52$. Treating the $N$-substituted hydroxylamine $53$ and cyclic ketone $54$ gave oxime $55$. This method allowed the formation of acyclic and exocyclic ketonitrones (Scheme 1.15).

(i) $t$BuOH, $110 \degree C$ (sealed vial), 18 h

Scheme 1.15

### 1.4 1,3-Dipolar cycloadditions of nitrones

Out of a wide range of nitrone reactions, the 1,3-dipolar cycloaddition with a dipolarophile is the most useful reaction in which the nitrone behaves as a 1,3-dipole. Nitrones are among the most synthetically useful 1,3-dipolar species, as their cycloaddition reactions with alkenes or alkynes yield isoxazolidines or isoxazolines, respectively, which are suitable intermediates for the synthesis of bioactive compounds, mainly alkaloids. The reductive cleavage of the N–O bond leads to the
formation of 1,3-amino-alcohols that are present in many natural products and biologically active compounds.

1.4.1 [3+2] Intermolecular cycloadditions involving nitrones

Huisgen and co-workers were the first to report that nitrones could be involved in intermolecular [3 + 2] cycloadditions with alkene dipolarophiles.\(^{38}\) Nitrone 56 and alkene 57 were heated at 90 °C to afford cycloadduct 58 in quantitative yield (Scheme 1.16, stereochemistry of 58 was not indicated).

![Scheme 1.16](image)

An example of an intermolecular cycloaddition reaction involving Michael addition is shown in Scheme 1.17. Grigg and co-workers showed that reaction between the oxime 59 and benzyl acrylate 60 (which acts as an alkylating agent and a dipolarophile) in acetonitrile for 20 h gave nitrone 61 (Scheme 1.17).\(^{39}\) The nitrone 61 then underwent intermolecular 1,3-dipolar cycloaddition to afford isoxazolidine 62 in 73% yield.

![Scheme 1.17](image)

A similar reaction can be set up in which the alkylating reagent and the dipolarophile are different. An example is shown in Scheme 1.18 to give the isoxazolidine product 63.\(^{39}\)
A study\textsuperscript{40} by Heaney and co-workers investigated the intermolecular 1,3-dipolar cycloaddition reaction of the nitrone derived from oxime 64. The oxime 64 underwent cyclization to generate the nitrone 65. This was heated with methyl acrylate in toluene for 18 h to afford regioisomeric adducts 66 in quantitative yield in a 2:1 ratio (Scheme 1.19).

A cyclisation of oxime 67 with an alkene gave the nitrone 68. Subsequently, the alkene moiety of another molecule of oxime 67 participates in intermolecular 1,3-dipolar cycloaddition reaction to give the cycloadduct 69 (Scheme 1.20).\textsuperscript{30} Based on this, the proposed mechanism is that the reaction proceeds \textit{via} an oxime ene-like reaction.
In 2009, Coldham and co-workers reported an intermolecular reaction between the aldehyde 70 and dipolarophile 71 in toluene to form cycloadducts 72a and 72b in 77% yield (Scheme 1.21).\(^\text{41}\) The condensation reaction took place then the oxime underwent cyclisation to give a nitrone followed by intermolecular 1,3-dipolar cycloaddition to afford the cycloadducts in 1.6:1 ratio.

\[
\begin{align*}
\text{CHO} & \quad \text{CO}_2\text{Me} \\
\text{Cl} & \quad \text{CO}_2\text{Me} \\
70 & \quad 71 \\
\text{NH}_2\text{OH}+\text{HCl} & \quad \text{iPr}_2\text{NEt}, \text{PhMe} \\
\text{110 °C} & \quad 72a \\
& \quad 72a
\end{align*}
\]

Scheme 1.21

Recent work demonstrated successful reaction even with enolisable aldehydes lacking the \textit{gem}-dimethyl group.\(^\text{42}\)

### 1.4.2 [3+2] Intramolecular cycloadditions involving nitrone

The intramolecular cycloaddition of 1,3-dipoles provides a versatile method to form the heterocyclic rings in bicyclic \textit{O}-polycyclic systems. Oppolzer reported the first example of the 1,2-prototropy and subsequent cycloaddition reaction. Oxime 73 was heated under reflux in toluene to give isoxazolidine product 75 in moderate yield (Scheme 1.22).\(^\text{43}\) It is believed that the reaction proceeded \textit{via} nitrone 74.

\[
\begin{align*}
\text{PhMe, 110 °C} & \quad \begin{array}{c}
\text{H, } \text{N} \\
\text{O} \\
\end{array} \\
73 & \quad 74 \\
\text{74} & \quad 75 \\
& \quad 75
\end{align*}
\]

Scheme 1.22

An intramolecular reaction is demonstrated in Scheme 1.23, where the substrate oxime bears both the alkylating agent and the dipolarophile. On heating oxime 76 at reflux in toluene, cyclisation then 1,3-dipolar cycloaddition reaction took place to result in tricyclic product 78 \textit{via} the intermediate nitrone 77.\(^\text{44}\)
Scheme 1.23

Scheme 1.24 provides an example where the dipole is derived from oxime 79, which undergoes conjugate addition with phenyl vinyl sulfone followed by a 1,3-dipolar cycloaddition reaction via the nitrone 80, to give isoxazolidine 81 in good yield.\(^45\)

Scheme 1.24

A 2011 study by Coldham and co-workers demonstrated an intramolecular dipolar cycloaddition of aldehyde 82. A mixture of aldehyde 82 with \(N\)-methylhydroxylamine and sodium bicarbonate in ethanol was heated in a sealed tube to give cycloadduct 83 in 73% yield (Scheme 1.25).\(^46\)

Scheme 1.25
1.5 Cascade processes including cycloaddition of a nitrone

Cascade chemistry using cycloaddition reactions can lead to a variety of ring systems such as bridged and fused modes. Tietze defined cascade reactions as “reactions where two or more bond-forming transformations occur under the same reaction conditions, without the addition of further reagents or catalysts”.47 Grigg and co-workers have shown that a cascade process involving the intramolecular conjugate addition of an oxime, followed by intramolecular cycloaddition, leads to compounds containing three new rings. Thus, treating ketone 84 with hydroxylamine yielded oxime 85, which underwent conjugate addition to give nitrone 86, then, 6-5-5 spiro cycloadduct 87 was obtained by cycloaddition with the terminal olefin in 70% yield (Scheme 1.26).44

![Scheme 1.26](image)

Based on this, a range of ketones of varying chain length and position of the dipolarophile were synthesized. For example, increasing the chain length between the oxime and dipolarophile would produce a 6-5-6 spiro system. Additionally, increasing the length of the tether between the nitrone and the dipolarophile resulted in less regioselective cycloaddition reactions, as other transition states can now be accessed. The strategy of oxime formation followed by Michael addition and [3 + 2] cycloaddition has been used by several researchers to synthesise the azaspirocyclic core of (±)-histrionicotoxin.48-50 A 2004 study by Stockman and co-workers showed that condensing ketone 88 and hydroxylamine leads to nitrone 89. This was then
heated at reflux in toluene in a sealed tube to yield the thermodynamically favoured cycloadduct 90 (Scheme 1.27).^{49}

\[
\begin{align*}
88 \quad \text{i.} \quad & \text{NH}_2\text{OH} \cdot \text{HCl}, \text{NaOAc} \quad \text{MeOH} \\
& \text{ii.} \quad \text{PhMe,} \ 190 \degree \text{C,} \ 3.5 \text{ h}
\end{align*}
\]

Scheme 1.27

Coldham and co-workers investigated the condensation, cyclisation, cycloaddition cascade reaction for the synthesis of tricyclic compounds. Aldehyde 91 was treated with hydroxylamine hydrochloride and diisopropylethylamine in toluene, to give cycloadduct 92 in 64% yield as a single isomer (Scheme 1.28).^{51}

\[
\text{91} \quad \text{NH}_2\text{OH} \cdot \text{HCl}, \text{Pr}_2\text{NEt} \quad \text{110} \degree \text{C,} \ 4.5 \text{ h}
\]

Scheme 1.28

In 2009, Coldham and co-workers reported the synthesis of myrioxazine A by treating aldehyde 93 with hydroxylamine in PhMe at 110 °C. This gave the cycloadduct 94 as a single isomer in 77% yield (with some oxime 95, which could be converted to 94 on further heating) (Scheme 1.29).^{52} This fused cycloadduct was converted to the natural product myrioxazine A 96 in two steps. The oxime 95 presumably cyclised to displace chloride to give the intermediate nitrone which undergoes dipolar cycloaddition.
Later, Coldham and co-workers used cascade chemistry for the formation of one-carbon bridged systems. Tethering the dipolarophile to the \( \beta \)- rather than \( \alpha \)-carbon of the aldehyde can lead to a bridged ring system. For example, the aldehyde 97 was treated with hydroxylamine in PhMe to yield the cycloadduct 99 as a single stereoisomer in 90% yield, and likely occurred via the intermediate nitrone 98 (Scheme 1.30).

This introduction has presented examples of cycloaddition and cascade reactions and relevant methods of the synthesis of nitrones and their uses in cascade reactions. We were interested in utilizing this chemistry for the synthesis of some novel isoxazolidines and towards the synthesis of compounds within the iboga alkaloid family. The next chapters will describe this application.
Chapter 2  Cycloaddition of Nitrones Derived from Quaternary Aldehydes

2.1 Introduction

As discussed in the previous chapter, the intramolecular dipolar cycloaddition reactions of nitrones were discovered over 50 years ago. The intramolecular nitrone-alkene cycloaddition reaction can give bridged or fused isoxazolidines (Figure 2.1). Extensive research has been done into the use of nitrones in the intramolecular 1,3-dipolar cycloaddition with a dipolarophile. When the nitrone and dipolarophile are located on the same molecule, a cycloaddition can take place to form a bicyclic molecule. These bicyclic intermediates are very important in the synthesis of natural products. Generally, this type of reaction is synthetically useful, due to its high regio- and stereo-selectivity.

Considerable research into intramolecular nitrone cycloaddition has been reported. LeBel was the first person who reported the intramolecular cycloaddition reaction of a simple alkene with a nitrone to form a fused bicyclic ring, isoxazolidine (Scheme 2.1). Our research group is interested in this chemistry and extensive work has been done towards natural product synthesis using nitrones.
A lot of initial work has been reported which is related to the intramolecular cycloadditions of nitrones bearing an aromatic substituent attached \( \beta \) to the nitrogen atoms.\textsuperscript{37,63-65} To our knowledge, there has been only one use of a quaternary \( \alpha \)-aromatic aldehyde 102 in an intramolecular cycloaddition, which was reported by Vinick and co-workers, where a nitrone bearing a neighbouring aromatic substituent and a methyl group was used to give one isomer (Scheme 2.2). The stereochemistry arises from the fact that the less bulky methyl group prefers to locate in the \textit{endo} position, forming the cycloadduct 103.\textsuperscript{66}

![Scheme 2.2](image)

### 2.2 Synthesis of isoxazolidine 5-5 ring system

#### 2.2.1 Synthesis of requisite aldehyde

Polycyclic amines are found in many alkaloids, especially those that not only contain an amino group but an aromatic ring as well, often derived from \( \beta \)-aryllethylamine precursors. The plan was to investigate the cycloaddition of nitrones that would lead to \( \beta \)-aryllethylamines. The ultimate aim was to make compounds of the iboga family, which has this \( \beta \)-aryllethylamine core (see chapter 3), and could derive from a quaternary aldehyde (Figure 2.2). However, the initial plan was to study this approach without the \( \text{CH}_2\text{X} \) branch.

![Figure 2.2](image)
To synthesize the key aldehyde 110, ester 104 was treated with methyl formate 105 in the presence of titanium tetrachloride and triethylamine. This gave the aldehyde 106 in 65% yield (Scheme 2.3).  

\[
\begin{align*}
\text{Ph} \quad \text{CO}_2\text{Me} & \quad + \quad \text{O} \quad \text{O} \quad \text{Me} \\
104 & \quad 105 \\
\text{TiCl}_4, \text{Et}_3\text{N}, \text{CH}_2\text{Cl}_2 & \quad \text{1 h at 0 °C, then 2 h at rt} \\
\text{Ph} \quad \text{CHO} \quad \text{CO}_2\text{Me} & \quad 106 \\
& \quad 65\%
\end{align*}
\]

**Scheme 2.3**

The alkylation step involved the reaction of aldehyde 106 with an electrophile and potassium carbonate in dry acetone (Scheme 2.4). Unfortunately all the efforts to optimise the conditions failed to afford the desired product 107 (Table 2.1). $^1$H NMR spectroscopy for the crude products showed no aldehyde peak and we proposed that O-alkylation took place instead of C-alkylation. Treatment of aldehyde 106 with allyl bromide in the presence of potassium carbonate in acetone gave two compounds in 60% yield and 30% yield (entry 1). Mass spectrometry showed that both compounds had the same mass. $^1$H NMR spectra for both compounds showed no aldehyde peak, and instead a singlet peak at 7.64 ppm was observed for the major product. A singlet peak at 6.75 ppm was also noticed for the minor compound. As a result, we suggest that O-alkylation took place and these peaks belong to CH protons for $E$ and $Z$ isomers 108. For the other reactions (entries 2–6) the $^1$H NMR of crude products showed no aldehyde peak.  

\[
\begin{align*}
\text{CHO} \quad \text{CO}_2\text{Me} & \quad \text{E'}, \text{K}_2\text{CO}_3, \text{acetone} \\
106 & \quad \text{time, temp.} \\
\text{MeO}_2\text{C} \quad \text{CHO} \quad \text{MeO}_2\text{C} & \quad \text{O} \quad \text{E} \\
\text{Ph} & \quad \text{E} & \quad \text{Ph} \\
107 & \quad 108
\end{align*}
\]

**Scheme 2.4**
Table 2.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>E*</th>
<th>Time</th>
<th>Temp. °C</th>
<th>Yield% 107</th>
<th>Yield% 108</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allyl bromide</td>
<td>45 min</td>
<td>50</td>
<td>0</td>
<td>60/30\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>Allyl bromide</td>
<td>2h</td>
<td>rt</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Benzyl bromide</td>
<td>45 min</td>
<td>50</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Benzyl bromide</td>
<td>2h</td>
<td>rt</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Methyl iodide</td>
<td>2h</td>
<td>rt</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4-bromo-1-butene</td>
<td>2h</td>
<td>rt</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a} these are separated by column chromatography

Table 2.1

In a slightly different approach, we started with ester 104, which on treatment with LDA and 4-bromo-1-butene gave alkylated compound 109 (Scheme 2.5). Due to the low yield some optimisation was made to increase the yield. DMPU was used for this purpose, and gave the product 109 in 67% yield (Table 2.2, entry 4).

![Scheme 2.5](image)

Table 2.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Additive</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18 h</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>2</td>
<td>2 h</td>
<td>DMPU</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>6 h</td>
<td>DMPU</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>18 h</td>
<td>DMPU</td>
<td>67</td>
</tr>
</tbody>
</table>

Treating compound 109 with methyl formate 105 in the presence of titanium tetrachloride and triethylamine produced an inseparable mixture (Scheme 2.6). No
identifiable desired product was observed, either by mass spectrometry or by $^1$H NMR spectroscopy.

![Scheme 2.6](image)

As an alternative, the alkylation of compound 109 using LDA and paraformaldehyde afforded alcohol 111 (Scheme 2.7). Firstly, to a suspension of compound 109 and LDA at $-78$ °C, paraformaldehyde (1.1 equiv.) was added to give a low yield of alcohol 111 (Table 2.3). Slightly higher yields were obtained at $-20$ °C, particularly on increasing to two equivalents of paraformaldehyde. A yield of 70% was obtained when 1.0 equivalent of electrophile was added followed by a further 1.0 equivalent after 1 h (Table 2.3, entry 4).

![Scheme 2.7](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>(CH$_2$O)$_n$ equiv.</th>
<th>Temp °C</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1</td>
<td>$-78$</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
<td>$-20$</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>$-20$</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>$-20$ to rt</td>
<td>70</td>
</tr>
</tbody>
</table>

Table 2.3

Subsequently, alcohol 111 was oxidised with Swern oxidation$^{69}$ to give the aldehyde 110 in 77% yield (Scheme 2.8).
2.2.2 Cyclisation-cycloaddition reaction

From the outcome of the previous results in the group the best result was obtained from the reaction of $N$-alkylhydroxylamines, therefore we decided to start with the same conditions. Aldehyde 110 was heated under reflux with $N$-methylhydroxylamine hydrochloride (1.5 equiv.) and diisopropylethylamine (2.5 equiv.) in toluene. After 2 h TLC analysis showed that all the starting material was consumed, so the mixture was allowed to cool to room temperature. After purification two cycloadducts were isolated, 112a in 54% yield and 112b in 32% yield (Scheme 2.9). The *cis* ring junction of both cycloadducts was revealed by single crystal X-ray structure analyses (Figure 2.3).

![Scheme 2.9](image)

**Figure 2.3** X-ray structure of compounds 112a and 112b
2.2.3 Stereochemistry of 112a and 112b

The stereochemistry of the major cycloaddition product 112a must arise from a preference for one transition state (Figure 2.4c) of the nitrone in the cycloaddition. A study by LeBel$^{54,55}$ suggested that both syn- and anti-configurations of the intermediates lead to a cis ring junction.

This reaction is a direct comparison with the formation of the cycloadduct 103 (Scheme 2.2, page 24), where a single stereoisomer was reported.$^{66}$ In the study by Vinick and co-workers, the phenyl group has a stronger preference for the exo position than the methyl group. However, in our work there is a preference for the methyl ester, rather than the phenyl group, to be in the exo position. A possible reason to explain why the major cycloadduct came with the exo position of the methyl ester is evident in the X-ray crystal structure of 112a (Figure 2.4a). The ester carbonyl oxygen atom and the proton at the ring junction α to the nitrogen atom are only 2.346 Å apart and the carbonyl is almost directly in line with the C–H bond. A 2015 report by Sartillo-Piscil and co-workers discusses the stabilisation of molecular conformation via intramolecular (N)C–H$^\alpha$···O(C) hydrogen interaction in a cyclic amide.$^{70}$ In collaboration with Dr. Anthony Meijer in the Department of Chemistry, University of Sheffield, DFT calculations show that this interaction (calculated C=O···H−CN distance = 2.26 Å) could be present in the transition state for the cycloaddition (Figure 2.4b) and in the nitrone. This would lead to the preferred transition state 113, which gives the isomer 112a.
2.3 Synthesis of isoxazolidine 6-5 and 5-7 ring systems

2.3.1 Synthesis of aldehyde 116

To investigate the effect of the distance between the aldehyde and the alkene on the ring formation, we predicted that alkylation of ester 104 with 5-bromo-1-pentene would provide a longer tether to attempt cycloaddition to give a cyclohexane ring system. In order to prepare the key aldehyde precursor, following the same chemistry as before, the ester 104 was alkylated using 5-bromo-1-pentene to give the ester 114 in 69% yield (Scheme 2.10).

\[
\begin{align*}
\text{Ph} & \quad \text{CO}_2\text{Me} \\
\text{LDA (1.1 equiv.), DMPU} & \quad 5\text{-bromo-1-pentene} \quad \text{THF, \text{78 °C}} \\
\text{104} & \quad \text{114} \quad 69\%
\end{align*}
\]

Scheme 2.10

The ester 114 underwent a second alkylation with paraformaldehyde, using the previous conditions to give alcohol 115 in good yield (Scheme 2.11).
The alcohol **115** was oxidised by Swern oxidation\(^6^9\) to afford the desired aldehyde **116** in 79% yield (Scheme 2.12).

### Scheme 2.12

#### 2.3.2 Cycloaddition of the nitrone derived from aldehyde 116

The aldehyde **116** was heated at reflux with N-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene to give cycloadducts **117a** and **117b** as a mixture of regioisomers (ratio 2:1) in good yield (assigned based on \(^1\)H NMR and \(^{13}\)C NMR spectroscopy) (Scheme 2.13). The two isomers were difficult to separate by flash column chromatography. Successful efforts were carried out to separate the major regioisomer **117a** by recrystallisation. The cycloadduct **117a** was revealed by single crystal X-ray structure analysis (Figure 2.5).

### Scheme 2.13
2.3.3 Stereochemistry

The stereochemistry of the major cycloadduct 117a was established by single crystal X-ray analysis. Increasing the tether length allows easier access to the transition state to form the bridged cycloadduct. This will be discussed later in this chapter (see section 2.4.2).

The ¹H NMR spectra showed that the ring junction proton at 4.66 ppm appeared as a doublet of doublets with $J$ values of 9.0 and 4.0 Hz, and the proton at 3.88 ppm as a doublet of doublets with $J$ values of 8.0 and 1.5 Hz. The COSY spectrum shows no interaction between these protons. The HSQC spectrum showed that protons at 4.66 ppm and 3.88 ppm are attached to carbons 77.3 ppm and 72.7 ppm respectively. The bridge carbon CH₂ at 32.1 ppm is correlated to proton at 2.74 ppm that appeared as a doublet of triplets $J$ values of 13.5 and 9.0 Hz, and proton at 2.30–2.27 ppm appeared as a multiplet (see Appendix 7). The stereochemistry of the ester group was confirmed by the single crystal X-ray analysis (Figure 2.5, and Appendix 3).

The elucidation of the structure of the second isomer 117b was based on ¹H NMR and HSQC spectroscopy. The two CH signals of the OCH₂ appear as a doublet of doublets at $\delta$ 4.06 ppm and a doublet at $\delta$ 3.52 ppm. The interaction between the two H of the ring junction was confirmed by ¹H COSY spectra, and the coupling of these protons is 6.0 Hz, corresponding to cis orientation. The HSQC spectrum shows that the ring junction protons at 3.43 ppm and 2.93–2.87 ppm are attached to carbons at 73.2 ppm and 43.4 ppm respectively (see Appendix 8). The stereochemistry of the ester group was proposed based on the previous result with major isomer 112a and
in which the ester group preferred the exo position. The mixture of regioisomers was thought to arise from a kinetically controlled reaction with a lower transition state energy for forming isomer 117a, rather than by a reversible thermodynamically controlled process.

A 2006 study by Weinreb and co-workers reported the retrocycloaddition reaction on a bridged cycloadduct to form fused cycloadduct. So, to test the possibility of the retro 1,3-dipolar cycloaddition reaction, the bridged cycloadduct 117a was heated in xylene. After 18 h, only the starting material was recovered (Scheme 2.14). If the cycloaddition were under thermodynamic control then a 2:1 mixture of adducts would be expected.

![Scheme 2.14](image)

### 2.4 Cross-metathesis of the aldehyde

We wanted to investigate the effect of an activated alkene on the regioselectivity of the cycloaddition reaction. Therefore, an electron-withdrawing group such as a methyl ester was introduced to the terminal alkene via a cross metathesis reaction of alkene 116 using Grubbs’ 2nd generation catalyst 118 and methyl acrylate to give the new aldehyde 119 in a good yield (Scheme 2.15).

![Scheme 2.15](image)
2.4.1 Cycloaddition reaction of aldehyde 119

We were pleased to find that heating aldehyde 119 at reflux with \( N \)-methylhydroxylamine hydrochloride and diisopropylethylamine in toluene yielded a single regioisomer and was highly stereoselective in favour of the isomer 120a (Scheme 2.16). Clearly, there is a preference to form a fused ring and not a bridged ring, compared to the corresponding reaction with unsubstituted alkene 116. Figure 2.6 shows the single crystal X-ray structure of the cycloadduct.

![Scheme 2.16](image)

**Figure 2.6** X-ray structure of compound 120a

The single crystal X-ray analysis confirmed the stereochemistry of the major isomer 120a, and shows similarity to all previous cycloadducts, in which the methyl ester group favours the \( \text{exo} \) position. Moreover, the regioselectivity of the cycloaddition reaction was significantly affected by the terminal ester group of the alkene as only a fused ring was observed.

2.4.2 The regioselectivity of the cycloaddition reaction

It is instructive to discuss the regioselectivity of this reaction in comparison to aldehyde 116 in which the bridged cycloadduct is the major product. A 2011 study by Shing and So reported that the \( \alpha,\beta \)-unsaturated ester has no effect on the
regioselectivity of the intramolecular 1,3-dipolar cycloaddition reaction with their nitrone to form the bridged cycloadduct rather than the fused cycloadduct. They proposed that the steric effect of the substituted adjacent carbon to the nitrone controls the orientation to give the endo-mode. However, Grigg and co-workers showed that the rate and regioselectivity could be affected in the presence of a withdrawing group. In their example the nitrone intramolecular cycloaddition reaction favoured the fused 6/6 rather than the bridged 5/7 ring adduct. Clearly our result shows that the substituent ester group led to a significant change in the selectivity from bridged to fused cycloadducts. The reason behind the stereochemical outcome must be due to the enhancing of the transition state by the terminal ester substituent on the dipolarophile. Molecular models show that the formation of compound 117a required arranging the pendent alkenes to be oriented to inside the molecule (structure 122, Figure 2.7). Therefore, introducing a substituent group such as methyl ester could restrict such arrangement sterically and work against this disposition. In intermolecular reactions, generally the nitrone oxygen prefers to add to the more hindered site. Based on this, the fused cycloadduct is formed as a major product and no bridged one is observed.

\[ \text{Figure 2.7} \]

2.4.3 Cleavage the N–O bond

The mixture of cycloadducts 120 was treated with zinc in acetic acid to break the N–O bond. Subsequent cyclisation of the amine onto the ester yielded the lactam 123 (Scheme 2.17). Unfortunately, the cyclisation proceeded incompletely, and stirring with sodium methoxide in methanol was required to complete the process. The lactam was isolated together with a small amount of the other stereoisomer in good yield (Scheme 2.17). The major isomer 123a was recrystallized and the relative stereochemistry was verified by single-crystal X-ray diffraction (Figure 2.8).
major isomer was confirmed by the $^1$H NMR spectroscopy of the mixture and of the recrystallized isomer.

Figure 2.8  X-ray structure of compound 123a
4.5 Conclusion
We have synthesized some aldehydes with quaternary α carbon stereocentres bearing a phenyl, an alkenyl, and a methyl ester group. We subsequently demonstrated the amenability of these aldehydes to intramolecular nitrone cycloadditions to produce a range of isoxazolidine 5-5, 6-5 and 5-7 ring systems. In all cases the methyl ester group preferred the exo position over the phenyl group. The regio- and stereochemical outcomes are affected by the length of the tether to the alkene dipolarophile and by the nature of the dipolarophile (terminal alkene or with attached electron-withdrawing group). For example, introducing a methyl ester on the alkene moiety then cycloaddition resulted in a preference to form the fused ring over the bridged ring systems. We investigated the cleavage of the N–O bond then cyclisation to afford the lactam. The chemistry allows the synthesis of bicyclic isoxazolidines containing an α-phenylethylamine moiety. This results from this chapter have published.
Chapter 3

3.1 Biosynthesis of iboga alkaloids

Several publications surrounding the biosynthesis of the iboga alkaloids have been published, mostly concentrating on the existence of the tryptamine fragment present in these compounds. Initial work into this area by Wenkert\textsuperscript{78} suggested that the synthesis started from the \textit{sec-o}-prephenate-formaldehyde (SPF) unit \textbf{124} which is present in some plants. It was postulated that the SPF unit could be trapped by tryptamine (\textbf{125}) in the cell giving iminium ion \textbf{126}. At this point, it was thought that a synthesis pathway could diverge with access to both the iboga and aspidosperma alkaloids possible. Proceeding \textit{via} cyclic iminium species \textbf{126}, \textbf{127} and \textbf{128} access to structures similar to the iboga alkaloid catharanthine \textbf{130} was thought to be possible (Scheme 3.1).
3.2 Iboga alkaloids

Iboga alkaloids are found in African shrubs of the Tabernanthe genus. They are indole containing alkaloids which are pharmacologically active. They all contain a seven membered, fused ring system with a rigid isoquinuclidine ring (Figure 3.1).

![Figure 3.1 The General Structure of iboga alkaloids, isoquinuclidine shown in red](image)

R1 = H or OMe, R2 = H or CO2Me
R3 = H or OH, R4 = H or OH

To date several iboga alkaloids have been characterised as having pharmacological properties. The indoloazepine ring is a key structural component of the iboga alkaloids. Several routes have been published towards the synthesis of the indoloazepine ring system. Examples of members of the iboga alkaloids include ibogamine 131, ibogaine 132, heyneanine 133, 18-methoxycoronaridine 134, isovoacristine 135, 19(R)-hydroxyibogamine 136, cononuridine 137, and catharanthine 130 (Figure 3.2).
3.3 Pharmacological properties of iboga alkaloids

The pharmacological properties of iboga alkaloids have been widely studied.\textsuperscript{89-93} Iboga alkaloids have attracted attention of many researchers due to their reported ability to treat the human addition to several drugs, alcohol and cocaine.\textsuperscript{93} Ibogaine \textsuperscript{132} showed a psychoactive effect based on the anecdotal observations.\textsuperscript{94} It was reported that using ibogaine reduced the self-administration of morphine and cocaine.\textsuperscript{95} Due to their hallucination side effect at high doses, this has not been used as a medication.\textsuperscript{96} Additionally, it shows some degeneration of cerebellar Purkinje cells.\textsuperscript{97} Glick and Kuehne reported that 18-methoxycoronaridine \textsuperscript{134} is a selective inhibitor of the $\alpha 3\beta 4$ nicotinic receptor.\textsuperscript{98} This possess anti-addiction, anti-fungal, anti-lipase, anti-HIV, anti-leishmanic and anti-cholinesterasic properties.\textsuperscript{99,100} Another example, 19($R$)-hydroxyibogamine \textsuperscript{136} shows marked antibiotic activity.\textsuperscript{88}
3.4 Retrosynthetic strategies of iboga alkaloids

Some retrosynthetic strategies of iboga alkaloids are summarized in Figure 3.3. The major routes of the syntheses that have been reported are through the strategy of forming \( \beta \)-(indolylacetyl or indolyethyl) isoquinuclidines or indolyl isoquinuclidines. Some of these will be discussed in this chapter.

![Synthesis of some iboga alkaloids](image)

**Figure 3.3**

3.5 Synthesis of some iboga alkaloids

3.5.1 Büchi’s synthesis of ibogamine

Büchi and co-workers were the first to report a synthesis of an iboga alkaloid in 1965 (Scheme 3.1). They started with a simple pyridine derivative 138 which was reduced using aqueous potassium carbonate and sodium borohydride to give a complex mixture of three dihydropyridine derivatives. From this mixture, only one dihydropyridine 139 could undergo a Diels-Alder reaction with methyl vinyl ketone, to give isoquinuclidine 140 in 13% yield over two steps. Further reduction using
sodium borohydride in methanol afforded a mixture of alcohols. Sodium hypochlorite was used to promote the rearrangement of the amide to give the tricyclic urethane 141 in 42% yield over two steps. Hydrolysis using aqueous sulfuric acid and acetylation using acetic anhydride in pyridine gave acetoxyketone 142 in 94% yield. To introduce the indole ring, 142 was hydrogenated and treated with β-indolyl acetyl chloride, followed by p-toluenesulfonic acid to form the 7-membered ring product. Treating with zinc in acetic acid partially reduced the lactam and then reduction with lithium aluminium hydride gave carbinolamine 144 in 74% yield (Scheme 3.2).

![Scheme 3.2]

The imine 145 was obtained in 50% yield by the successful oxidation of alcohol 144 using dicyclohexylcarbodiimide and dimethyl sulfoxide, followed by treatment with sodium methoxide. Reduction using zinc in acetic acid followed by Wolff-Kishner reduction gave both epimers ibogamine 131 and epiibogamine 131a in 0.01% yield overall (Scheme 3.3).
The limitation of Buchi's synthesis is shown by the low yield of the Diels-Alder cycloaddition (due to the mixture of hydropyridines), and that the final reduction step afforded both epimers of the natural product 131 and 131a.

3.5.2 Nagata’s synthesis of ibogamine

Nagata and co-workers\textsuperscript{102} reported that treatment of the amine 146 with Pb(OAc)$_4$, gave the aziridine 147 in 55–60% yield. The reaction of aziridine 147 with $\beta$-indolylacetic anhydride gave isoquinuclidine 148, which then underwent alkaline hydrolysis to form alcohol 149 in 33% and 20% yield for exo and endo ethyl epimers respectively, related to a hydroxyl group. Oxidation using the Oppenauer method was followed by cyclisation with tosic acid and treatment with sodium methoxide to afford methoxylactam 150 in 34% yield (over three steps). The product was then reduced with lithium aluminium hydride to give enamine 151.\textsuperscript{103} Catalytic hydrogenation of enamine on palladium afforded compound 152 in 55% for exo and 67% for endo. Nagata completed the synthesis by removing the methoxy group on the exo isomer with LiAlH$_4$ to yield ibogamine 131 (Scheme 3.4).
Scheme 3.4

The limitation of this route is that the separation of diastereoisomers for both the endo and exo ethyl group proved difficult, and that low yields were obtained in several steps of the synthesis.

3.5.3 Trost’s synthesis of ibogamine

In 1978 Trost and co-workers reported a racemic and asymmetric route towards ibogamine.\(^{104}\) The reaction of diene 153 with acrolein by a Diels-Alder reaction gave cyclohexene 154 in 90% yield as a single diastereoisomer and regioisomer. This underwent a reductive amination with tryptamine and sodium borohydride resulting in 155 in 93% yield. Using palladium (tetrakis)triphenylphosphine Trost showed the possibility of forming the palladium π-allyl species which in turn gave the cyclised product 156 in 45% yield. This was treated with silver tetrafluoroborate and
bis(acetonitrile)palladium(II) chloride and then NaBH$_4$ to give ibogamine 131 in 40-45% yield over both steps (Scheme 3.5).

![Scheme 3.5](image)

An asymmetric version of this route has been reported by Trost using a chiral auxiliary for the Diels-Alder reaction step in 80:20 dr (Scheme 3.6).\textsuperscript{104}

![Scheme 3.6](image)

3.5.4 Hanaoka’s synthesis of ibogamine

Hanaoka and co-workers began their synthesis towards ibogamine 131 by using 5-(2-oxoethyl)-3-piperidinone to reach the ketone 157 in 70% yield in three steps (Scheme 3.7).\textsuperscript{105} Cyclisation occurred via a Michael addition done using ethanolic
potassium carbonate under reflux to afford a good yield of the **endo** ester 158a, while use of sodium hydride favoured formation of **exo** ester 158b.

The mixture of diastereoisomers was treated with trimethylorthoformate to protect the ketone group, followed by ester reduction using lithium aluminium hydride to give the alcohol 159 in 89% yield over both steps. Mesylation of the alcohol and treatment with zinc and sodium iodide gave 160 in 82% yield.

Then compound 160 was refluxed with aqueous HCl (1%) in acetone, followed by hydrogenation on palladium in methanol, and then condensation with β-indolylacetyl chloride to give ketone 161 in 93% yield. Compound 161 was treated with trimethylorthoformate in methanol, and then cyclisation was carried out in the presence of TsOH in benzene. The synthesis was completed by the reduction with a complex of LiAlH₄ and AlCl₃ and a 1:1 ratio of (+)-ibogamine 131 and (+)-epi–ibogamine 131a was obtained in 86% yield (Scheme 3.8).
The 6-*exo*-trig conjugate addition of the enolate of 157 onto the unsaturated ester was the novel approach of this synthesis. This key step could be controlled by the nature of the base, with the *endo* product being more favored, but under more strongly basic conditions, the *exo* product was slightly increased. The synthesis used a high number of protection group manipulations in order to obtain a good yield of the natural product.

3.5.5 Huffman’s formal synthesis of ibogamine

The lactone 162 was the starting material by which Huffman and co-workers began their synthesis towards ibogamine (Scheme 3.9). Treatment with ethyl magnesium bromide in the presence of copper iodide and dimethyl sulfide afforded *trans*-diastereoisomer 163. For the final product the *cis* isomer was required, and so ester 163 was epimerised using sodium methoxide to obtain ester 163a. Epoxidation with *m*-CPBA gave epoxide 164 in 5:1 dr, and this was followed by ring opening and amidation using tryptamine, which afforded lactam 165 in poor yield. At this stage the work was stopped because, at the same time, Kuehne and co-workers published the total synthesis of ibogamine, using very similar chemistry from the alkene 163a.
3.5.6 Kuehne’s synthesis of ibogamine

The acid 166 underwent esterification using boron trifluoride in methanol to afford ester 163a in 86% yield as a 1:1 ratio of inseparable diastereoisomers by $^1$H NMR spectroscopy (Scheme 3.10). Then ester 163a was treated with m-CPBA to give the epoxide product 164 as a mixture of diastereoisomers (1:1:1 dr). This was then treated with tryptamine to give the alcohol 165 (1:1 dr) in 48% yield. After recrystallization, tosylated product 167 3:1 dr was obtained in 85% yield. The final step was the cyclisation, which was done using aluminium chloride to give an intermediate lactam followed by reduction using lithium aluminium hydride to give (±)-ibogamine 131 in 30% yield. Kuehne’s method showed the route of the synthesis of isoquinuclidine ring system by epoxide opening followed by cyclisation using aluminium chloride but with low yield of the desired product. The reason for the low yield can be explained by the formation of the inseparable mixture of 164. The tosylation of alcohol 165 gave an inseparable mixture even after recrystallization (ratio 3:1), with 25% of the minor isomer (endo-ethyl), which was confirmed by $^1$H NMR spectroscopy.
In the last few years, much research has been done towards the synthesis of iboga alkaloids. Some of them were a new synthesis of iboga alkaloids and modification of some methods.

3.5.7 Borschberg’s synthesis of (–)-(19R)-ibogamin-19-ol

In 2004 Borschberg and co-workers reported a synthesis of the core isoquinuclidine structure of the iboga alkaloids. The ester (single diastereoisomer and enantiomer) was made over 3 steps and underwent an Ireland-Claisen rearrangement followed by reduction with lithium aluminium hydride to give an alcohol. Conversion to the aldehyde by Swern oxidation, followed by formation of the oxime, and reduction using NaBH₃CN gave hydroxylamine in 76% yield over three steps. The key step was a cascade process involving hydrolysis of the acetal, cyclisation, and dipolar cycloaddition resulting in the cycloadduct in 67% yield as a single diastereoisomer. Finally, reduction using zinc and acetic acid gave alcohol in good yield (Scheme 3.11).
An important step in this synthesis by Borschberg was controlling the stereochemistry at C-4 in the compound 169. The chirality transfer from the asymmetric centre was done via Ireland-Claisen rearrangement. The preference for the E silyl ketene acetal and the chair shaped transition state 173 lead to a high stereoselectivity (Scheme 3.12).

Later in 2006 Borschberg used compound 172 towards the first total synthesis of (19R)-ibogamin-19-ol 136. Amino-alcohol 172 was treated with protected indole acetic acid 175 using DCC as coupling reagent. This was followed by O-acetylation to give compound 176. Hydrogenolysis to remove the benzyl group and oxidation via Swern oxidation, followed by ketone protection using trimethyl orthoformate in methanol, and indole deprotection gave amide 177 in good yield (Scheme 3.13).
The synthesis was completed in three further steps. Cyclisation was carried out using acetyl chloride and acetic acid with methanol (cat.) in dry conditions. The amide and the acetyl groups were reduced with LiAlH₄ and BF₃ to give compound 178. Finally, another reduction using LiAlH₄ and AlCl₃ was carried out to obtain the desired product 136 in good yield (Scheme 3.14).

Scheme 3.13

Scheme 3.14
Chapter 4  Synthesis of bridged ring compounds by cascade chemistry

Cascade chemistry within the group has allowed access to fused and one-carbon bridged compounds, including the synthesis of the natural product myrioxazine A and the core of daphnilactone B (Figure 4.1). This was achieved by using a cascade of condensation, cyclisation and cycloaddition reactions. We then decided to explore the possibility of using the cascade chemistry to access the two-carbon bridged ring system, as found in the iboga alkaloids. It was believed that utilising the condensation, cyclisation, cycloaddition sequence would provide an efficient route to access the isoquinuclidine ring system of the iboga alkaloids.

![myrioxazine A and daphnilactone B core](image)

**Figure 4.1**

The key aldehyde 180 contains a branch point from which the alkyl halide and alkenyl tethers originate γ- to the aldehyde functional group (Figure 4.2). It has been shown in the Coldham group that for access to the fused tricyclic products, the best equivalent precursor for an aldehyde is a nitrile, which can easily undergo an alkylation\(^\text{117}\) reaction in the presence of a base. The product generated can then be reduced to give the corresponding aldehyde. The ease by which the nitrile can be alkylated is due to their high-polar inductive effect and their small size.\(^\text{118}\) Coldham and co-workers have used the nitrile often as a source of the corresponding aldehyde.\(^\text{62,119-122}\) It has been reported that nitrone can undergo intramolecular cycloaddition with terminal alkene dipolarophiles. Herein, we wanted to test the use of nitrone in the cascade reaction and so aldehyde 179 was predicted to give a positive result in the cascade chemistry.
4.1 Allyl type compounds

4.1.1 Enolisable aldehyde

Preliminary work that had been tested in the Coldham group showed that aldehyde 180 was unable to undergo the cascade reaction (Scheme 4.1). Therefore we chose to lower the LUMO of the dipolarophile by introducing an electron withdrawing group, and test the effect on the cascade process for aldehyde 188. To achieve this, a cross-metathesis reaction was used to install a methyl ester group to the alkene moiety.

![Scheme 4.1](image)

4.1.1.1 Substrate synthesis

The key aldehyde 180, was originally synthesized in the Coldham group by Guerrand. This chemistry was repeated as described below. Beginning with commercially available diethylallyl malonate 182, it was possible to reduce both esters using lithium aluminium hydride to give the diol 183 in 71% yield. To provide a good leaving group for alkylation in the next step, the iodination reaction was carried out by adding iodine (1.1 equiv.) portionwise over 30 minutes to a mixture of triphenylphosphine (1.0 equiv.) and diol 183 (1.0 equiv.) in THF. This afforded mono-iodo compound 184 in 76% yield, with 3% yield of the di-iodide 185 (Scheme 4.1).
In order to obtain a good yield of mono-iodide 184, the reaction was diluted and the iodine was added portionwise.

\[
\begin{align*}
\text{MeO}_2\text{C}-\text{CO}_2\text{Me} & \quad \xrightarrow{\text{LiAlH}_4, \text{Et}_2\text{O}} \quad \xrightarrow{0 \degree \text{C} \text{ to rt, 16 h}} \quad \xrightarrow{\text{imidazole, I}_2, \text{PPh}_3, \text{THF}} \quad \xrightarrow{\text{rt, 3 h}} \quad \text{HO-CH}_2\text{I} +
\end{align*}
\]

\[
\begin{array}{c|c|c|c}
\text{182} & \text{183} & \text{184} & \text{185} \\
\hline
\text{71\%} & \text{76\%} & \text{3\%} \\
\end{array}
\]

**Scheme 4.2**

Acetonitrile (4.0 equiv.) was deprotonated using LDA (2.0 equiv.) in THF at −78 °C. The iodo-alcohol 184 was then added to give nitrile 186 in 87% yield. Based on the efforts that have been made in the group in terms of minimizing the by-product, the dialkylated nitrile, 4.0 equivalents of the nitrile were used. To provide a good leaving group for later cyclisation, bromination was carried out using carbon tetrabromide (1.1 equiv.) and triphenylphosphine in dichloromethane, which gave bromo-nitrile compound 187 in 85% yield (Scheme 4.3).

\[
\begin{align*}
\text{HO-CH}_2\text{I} & \quad \xrightarrow{\text{i. LDA (2.0 equiv.)}} \quad \xrightarrow{\text{THF, −78 \degree C}} \quad \xrightarrow{\text{ii. MeCN (4.0 equiv.), 30 min}} \quad \xrightarrow{\text{iii. 184 (1.0 equiv.)}} \quad \xrightarrow{\text{iv. 1 h at −78 \degree C then 1 h, rt}} \quad \text{CN} \\
184 & \quad \text{186} & \quad \text{187} \\
\hline
\text{87\%} & \text{85\%} \\
\end{align*}
\]

**Scheme 4.3**

Reduction using DIBAL-H followed by work up with aqueous hydrochloric acid gave the precursor aldehyde 180 in 75% yield (Scheme 4.4). Initially the yield was about 55% due to instability of the aldehyde on purification using dry loading on silica gel. Therefore, purification was performed quickly using column chromatography on silica gel without dry loading, which afforded a better yield of the aldehyde 180.
Then, a cross-metathesis reaction was used to convert the alkene to the unsaturated ester. For this, aldehyde 180 and Grubbs’ 2nd generation catalyst\textsuperscript{73} were heated at reflux in dichloromethane with methyl acrylate as the metathesis partner, to give aldehyde 188 in 45% yield (\textit{E} isomer was determined by \textsuperscript{1}H NMR spectroscopy) (Scheme 4.5). For better yield (67\%), the catalyst was added portionwise during the reaction.

**Scheme 4.5**

### 4.1.1.2 Cyclisation–cycloaddition cascade

With the key aldehyde 188 in hand, the cascade reaction was attempted to investigate the activated dipolarophile. The aldehyde 188 was heated at reflux in toluene with hydroxylamine hydrochloride and \textit{N},\textit{N}-diisopropylethylamine (Scheme 4.6).

**Scheme 4.6**
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>Additive</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>4 h</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>30 min at 60 °C then 4 h reflux</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>30 min at 60 °C then 3 h reflux</td>
<td>MgSO₄</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>2.5 h</td>
<td>MgSO₄</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>1.5 h</td>
<td>MgSO₄</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>2.5 h</td>
<td>MgSO₄/TBAI</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Xylene</td>
<td>1 h at 60 °C then 1.5 h reflux</td>
<td>MgSO₄</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.1**

Initially, aldehyde 188 was heated with hydroxylamine (1.0 equiv.) and base in toluene. No desired cycloadduct 189 was observed. This could be due to the susceptibility for enolisation of the aldehyde 188 when condensed with hydroxylamine. Table 4.1 shows the optimisation of conditions to obtain better yields. Heating the mixture of aldehyde 188 with hydroxylamine hydrochloride and N,N-diisopropylethylamine in toluene at 60 °C for 30 min, followed by TLC analysis indicated that most of the starting material was consumed and was probably converted to the oxime. The reaction mixture was then heated at 110 °C, but subsequent TLC analysis showed many spots on the TLC plate (entry 2). As a result, the reaction was repeated using MgSO₄, after 3 h the reaction was cooled to room temperature and a low yield of the cycloadduct was obtained (entry 3). Direct heating gave a similar yield (entry 4), and adding MgSO₄ as a dehydrating agent helped to obtain the desired product. We thought that heating for a long time caused decomposition of the product resulting in a low yield, and so the reaction was heated for 1.5 h, but only 10% yield was isolated with 20% yield of recovered starting material (entry 5). We thought that the bromide might not be a suitable leaving group for this type of reaction, and so to initiate the cyclisation, the more reactive iodide could facilitate the step. Indeed, further optimisation would be required in order to increase the yield. Cyclisation promoter TBAI was used, but no desired cycloadduct was observed and the starting material decomposed very quickly (entry 6). It was
suggested that the cyclisation might be slow and xylene was used instead of toluene (entry 7). This proceeded un成功fully as the reaction mixture started to quickly decompose after 1.5 h.

4.1.1.3 The stereochemistry of cycloadduct 189

The stereochemistry of the product 189 was proposed initially on the basis of the $^1$H NMR spectrum in CDCl$_3$ (Figure 4.3). The $^G$H peak at 4.24 ppm appeared as a singlet rather than a doublet and $^E$H peak at 2.43 ppm showed as a doublet of doublets with $J$ values of 9.5 and 3.0 Hz. This indicated that there is no coupling between the vicinal protons. Based on the Karplus equation, the $J$ value is zero when the dihedral angle is 90°. Models of the two diastereomers indicate that the dihedral angles should be a 90° for 189 and 0° for its diastereomer. This suggested that the product is indeed compound 189 as expected based on a concerted cycloaddition of E isomer of unsaturated ester.

![Schematic diagram of cycloadduct 189](image)

**Figure 4.3**
Additionally, COSY spectra showed that there is no interaction between the protons $H^G$ and $H^E$. This is similar to the analogue compound 212 (Appendix 6), which was confirmed by X-ray crystallography as described later in this chapter. The correlation of protons and carbons was assigned via 2D HSQC experiments. $H^G$ is connected to the carbon at 86.8 ppm and protons $H^D$, $H^E$ and $H^F$ are connected to the carbons located at 55.6 ppm, 42.3 ppm and 16.3 ppm respectively (Figure 4.4). The 2D NOESY spectrum indicates that there is no nuclear Overhauser effect between $H^G$ and $H^E$, but irradiation of proton $H^E$ enhanced $H^D$ and one proton of $H^F$.

![Figure 4.4](image)

4.1.2 Non-enolisable aldehyde
The Coldham group has shown the value of generating cycloadducts from non–enolisable aldehydes. In 2007, Coldham and co-workers reported rapid access to a complex tricyclic amine from an acyclic precursor, which was used for the synthesis of aspidospermidine. Treatment of aldehyde 190 with glycine in toluene gave cycloadduct 191 in 79% yield. Acetal hydrolysis using aqueous HCl (5%) in THF, gave ketone 192 in 89% yield. Aspidospermidine 193 was obtained in 42% yield over three steps (Scheme 4.7).

![Scheme 4.7](image)
The chemistry shown in Scheme 4.7 involves an azomethine ylide as the dipole. Coldham and co-workers have extended this to nitrones to give fused and one-carbon bridged compounds (Scheme 1.29 and 1.30).

Further investigation into whether promotion of the cycloaddition reaction would allow any cycloadduct to be obtained in better yield compared to cycloadduct 189 would be of interest in this series. We believed that introducing a gem-dimethyl group at the α-carbon to the carbonyl group would prevent enolisation and this could help the cascade reaction. The cascade process on the aldehyde 194 with a terminal alkene was tested in the group previously and gave the cycloadduct 195 in 56% yield (Scheme 4.8).*  

![Scheme 4.8](image)

### 4.1.2.1 Synthesis of aldehyde 199

We decided to investigate the cascade reaction for the α,β-unsaturated ester 199. Therefore, we began with iodo-alcohol 184, which on alkylation with isobutyronitrile using the same conditions as before, led to compound 196 in 92% yield. Compound 197 was formed by replacing the hydroxyl group with bromide by treating compound 196 with carbon tetrabromide and triphenylphosphine in dichloromethane which gave 198 in excellent yield (Scheme 4.9).

![Scheme 4.9](image)
The nitrile 197 was then converted to aldehyde 198 in 90% yield through DIBAL-H reduction (Scheme 4.10). We thought that lowering the LUMO of the alkene could give a good yield of cycloadduct. To do so, cross-metathesis was carried out using Grubbs’ 2nd generation catalyst in degassed dichloromethane with methyl acrylate under reflux conditions which gave the key aldehyde 199 (E isomer was determined by 1H NMR spectroscopy) in good yield.

\[
\begin{align*}
\text{Br} & \quad \text{CN} \quad \text{i. DIBAL-H, CH}_2\text{Cl}_2 \quad 3 \text{~h, rt} \\
\text{CHO} & \quad \text{Br} \quad \text{ii. HCl(aq)} \\
\text{197} & \quad \text{198} \quad 90\% \\
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \quad \text{CH}_2\text{Cl}_2, \text{heat, 2.5 h} \\
\text{CHO} & \quad \text{MeO}_2\text{C} & \quad \text{118 (5 mol%)}
\end{align*}
\]

Scheme 4.10

4.1.2.2 Cyclisation–cycloaddition cascade

The aldehyde 199 was heated with hydroxylamine hydrochloride and N,N-diisopropylethylamine in toluene (Scheme 4.11). After some optimisation was carried out, the desired cycloadduct 200 was obtained in moderate yield (Table 4.2). Heating for 3 h in toluene or xylene using (1.5 equiv.) hydroxylamine hydrochloride did not afford the desired product (entries 1 and 2) and inseparable mixture was obtained. A low yield of the desired product was obtained by first aiming to form the oxime at 60 °C followed by heating at reflux (entry 3). Decreasing the equivalents of hydroxylamine hydrochloride, which possibly led to a reduction in the conjugation addition reaction, and adding MgSO₄, gave better yields (entries 4 and 5).

\[
\begin{align*}
\text{Br} & \quad \text{CHO} \quad \text{NHOH-HCl,} \text{Pr}_2\text{NEt, solvent} \\
\text{MeO}_2\text{C} & \quad \text{CHO} \quad \text{solvent, additive} \\
\text{199} & \quad \text{200}
\end{align*}
\]

Scheme 4.11
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>NH$_2$OH (equiv.)</th>
<th>Time</th>
<th>Additive</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>1.5</td>
<td>3 h, 110 °C</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Xylene</td>
<td>1.5</td>
<td>3 h, 140 °C</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>1.5</td>
<td>1 h at 60 °C then 3 h reflux</td>
<td>None</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>1.0</td>
<td>1 h at 60 °C then 3 h reflux</td>
<td>MgSO$_4$</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>1.0</td>
<td>30 min at 60 °C then 2 h reflux</td>
<td>MgSO$_4$</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 4.2

4.1.1.3 The stereochemistry of cycloadduct 200

The stereochemistry was tentatively assigned, as based on comparison to cycloadduct 212 that was confirmed by X-ray crystallography (Appendix 6). The $^1$H NMR spectrum (Figure 4.5) showed the H$^G$ singlet at 4.19 ppm and H$^E$ doublet of doublets with J values of 9.5 and 3.0 Hz at 2.56 ppm, which almost match the outcome from cycloadduct 212. The higher yield as compared to cycloadduct 189 could be explained by the inability to form an enolate or enamine and the Thorpe–Ingold effect. The moderate yields of the cycloadduct compound could be because of competing conjugate addition to the ester group. The COSY spectrum showed that there is no coupling between protons H$^G$ and H$^E$, but H$^E$ coupled to one proton of H$^F$ and proton H$^D$. Importantly, the 2D HSQC spectrum showed that protons H$^G$ is connected to a carbon at 86.7 ppm, and proton H$^E$ is connected to carbon located at 40.3 ppm.
4.2 Crotyl type compounds

Based on the target molecule 136 which contains a methyl group at C(19) and postulating that conjugate addition was preventing the cyclisation step with activated dipolarophile 199 to give the cycloadduct in good yield, we believed that it would be beneficial to use a methyl-substituted alkene as the dipolarophile.

4.2.1 Synthesis of the aldehyde precursor

We started our work with the aim to prepare the aldehyde 208. Crotylation of commercially available diethyl malonate 201 gave the diester 202. The commercial crotyl bromide is a 5.6:1 E:Z mixture. The crude mixture 202 was reduced using LiAlH₄ in Et₂O to give diol 203 in 80% yield as an inseparable mixture of E:Z isomers (5.6:1) that was confirmed by NMR spectroscopy and GC/mass spectrometry. A small amount of di-crotylated product (~2%) was formed and could be partially separated by careful column chromatography (Scheme 4.12). The addition sequence of the reactants plays an important role in obtaining a high yield of product and reducing the yield of by-product. The best yield was obtained by adding...
the diethyl malonate 201 to a stirred solution of sodium hydride in THF, and then this was added dropwise to crotyl bromide in THF. It was not necessary to purify the crotylated diester and the crude mixture was subjected to LiAlH₄ reduction, however purification of 202 by column chromatography resulted in a similar yield of the diol 203.

![Scheme 4.12](image)

It was necessary to prepare the electrophile 204 that would be used to alkylate isobutyronitrile. Therefore, diol 203 was iodinated using the same conditions as in the allyl series, and the product 204 was obtained in 72% yield (Scheme 4.13).

![Scheme 4.13](image)

The iodo-alcohol compound 204 was then subjected to the same alkylation conditions as in the allyl series in the previous section, using LDA (2.0 equiv.) and isobutyronitrile (4.0 equiv.). This gave the nitrile 205 in 92% yield (Scheme 4.14).

![Scheme 4.14](image)
A number of optimisations have been done in the Coldham group to find suitable conditions for halogenation of a similar nitrile.\textsuperscript{127} The Appel reaction\textsuperscript{128} using trichloroacetonitrile or using carbon tetrabromide provided the best results. Bromination of alcohol 205 with carbon tetrabromide and triphenylphosphine gave bromo-nitrile 206 in 90% yield, while chlorination using trichloroacetonitrile and triphenylphosphine in dichloromethane gave chloro-nitrile 207 in 93% yield (Scheme 4.15).

![Diagram showing the reaction between HO-205, CBr₄, PPh₃ in CH₂Cl₂, 4 h, rt to give X-C≡N-206, E:Z 5:6:1, X = Br, 90%, and Cl-C≡N-207, E:Z 5:6:1, X = Cl, 93%.]

Scheme 4.15

An alternative route to prepare chloro-nitrile 207 was carried out by treating isobutyronitrile (1.2 equiv.) with LDA (1.1 equiv.) in THF, then the chloro-iodo compound 215 (1.0 equiv.) was added to afford the chloro-nitrile 207 in 78% yield (Scheme 4.16). Pleasingly, the reaction was found to be highly selective towards the $\alpha$–carbon of the iodide over the $\alpha$–position of the chloride.

![Diagram showing the reaction between Cl-215, LDA (1.1 equiv.) in THF, −78 °C, iPrCN (1.2 equiv.), 30 min, 215 (1.0 equiv.), 1 h at −78 °C then 1 h, rt to give Cl-C≡N-207, E:Z 5:6:1, 78%.]

Scheme 4.16

The reduction of nitriles 206 and 207 using DIBAL–H and acidic work up to hydrolyse the imine intermediate gave aldehyde 208 in 85% yield and 209 in 91%
yield (Scheme 4.17) respectively. The E/Z ratio for all compounds maintained the same 5.6:1 ratio, and this was confirmed by using GC/mass spectrometry.

![Scheme 4.17]

4.2.2 1,3-Dipolar cycloaddition of aldehydes 208 and 209
After the successful synthesis of the key aldehydes 208 and 209, the final step involved attempting the tandem cyclisation–cycloaddition. Using the same conditions from the previous work on the bridged ring system in the Coldham group, the aldehyde 208 was treated with hydroxylamine hydrochloride (1.5 equiv.) and N,N-diisopropylethylamine (2.5 equiv.) in toluene at 110 °C overnight which gave the desired cycloadduct 210. This reaction gave a single stereoisomer of 210 in 60% yield. Carrying out the same reaction in xylene for 3 h provided the same stereoisomer in 70% yield (Scheme 4.18). Heating chloro-aldehyde 209 using the same conditions afforded almost the same yield (Table 4.3). Interestingly, the cycloaddition reaction of the aldehyde 199 with the electron deficient ester group required less time than aldehydes 208 and 209 with a moderate electron donating methyl group. Presumably, this is due to activation of the alkene by the ester group which is not present in the case of compound 208.

![Scheme 4.18]
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>X</th>
<th>Time h</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>Br</td>
<td>16</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>Xylene</td>
<td>Br</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Xylene</td>
<td>Cl</td>
<td>3</td>
<td>67</td>
</tr>
</tbody>
</table>

Table 4.3

4.2.3 Assignment of stereochemistry of 210

The prediction of the stereochemistry of the methyl group was based on the starting material E/Z 5.6:1. Therefore, the concerted cycloaddition across an E alkene would give predominantly stereoisomer 210 (Figure 4.5). Only one isomer was isolated after column chromatography. The $^1$H NMR spectrum showed that the proton H$^G$ appeared as a quartet with a $J$ value of 6.0 Hz at 4.09 ppm probably because it is interacting with the methyl group but not H$^E$ which was observed at 2.17 ppm as a doublet of doublets with $J$ values of 9.5 and 3.0 Hz. This exactly matches the observation from cycloadduct 212 that was confirmed by X-ray crystallography (Appendix 6). A molecular model showed that the dihedral angle ($\phi$) between these vicinal protons is nearly 90° and based on the Karplus correlation was found, the $J$ value is 0 Hz.$^{124,129}$ Furthermore, a 2D NOESY correlation was found between H$^G$ and the methyl group and H$^F$ but not H$^E$. The correlation of protons and carbons was assigned using the 2D HSQC spectrum, this showed that H$^G$ is connected to the carbon located at 86.0 ppm, and protons H$^E$ and H$^F$ are attached to carbons 41.0 ppm and 33.5 ppm respectively.
The cleavage of the N–O bond was carried out using zinc and acetic acid in H₂O with heating at 70 °C to give amino-alcohol 211 in quantitative yield (Scheme 4.19). The structure of the product was confirmed by ¹H NMR spectroscopy, as proton H^G showed at 3.89 ppm as a quartet of doublets with J values of 6.5 and 3.0 Hz, which is in contrast to cycloadduct 210.

**Figure 4.6**

**Scheme 4.19**
4.3 Towards iboga alkaloids

19-Hydroxy-ibogamine is an alkaloid compound which can be isolated from the iboga tree. The compound shows biological activity as an antibiotic agent.\textsuperscript{88} With the successful result we had obtained towards the isoquinuclidine core structures, it was initially proposed that a cascade reaction of aldehyde 213 would yield, after acetal hydrolysis, cycloadduct 212 that would require only a few more steps in order to be able to access 19-hydroxy-ibogamine 136 (Figure 4.7).

4.3.1 Retrosynthesis analysis

The retrosynthesis of 19-hydroxy-ibogamine 136 has been proposed by Coldham (Figure 4.7). The disconnection of the indole can give the cycloadduct 212, which can be prepared from commercially available diethyl malonate. It was thought that crotylation followed by reduction using LiAlH\textsubscript{4}, halogenation and nucleophilic substitution could generate the key precursor aldehyde 213. Cascade reaction of 213 with hydroxylamine should give the tricyclic product 212. This could potentially be transformed into the final product.

![Figure 4.7 Coldham's suggested total synthesis of 19-hydroxy-ibogamine](image)

4.3.2 Synthesis of the key aldehyde

Towards the synthesis of an iboga alkaloid, we decided to investigate this chemistry using a dialkoxyacetal in place of the gem-dimethyl group compound 209. This
would allow installation of a carbonyl group for further functionalisation. We hoped that treating diethoxyacetonitrile 216 with the iodo-compound 215 could allow access to the desired aldehyde and the corresponding cycloadduct should then be able to be converted to the desired natural product using routine chemistry.

To a mixture of diol 203 and triphenylphosphine (1.2 equiv.) in dichloromethane, trichloroacetonitrile (1.0 equiv.) was added dropwise at 0 °C, to give mono chloride 214 in 85% yield. In contrast, carbon tetrachloride gave a low yield. This was followed by iodination using triphenylphosphine (1.2 equiv.), imidazole (1.2 equiv.) and iodine (1.1 equiv.) in THF, which afforded iodo-chloro compound 215 in 83% yield (Scheme 4.20).

![Scheme 4.20](image)

We thought that using diethoxyacetonitrile 216 would be a good source of a masked carbonyl, which on acetal removal, should give the required functional group for the following steps. A very small number of publications report the use of this nitrile as a nucleophile and in all cases, the reported yield was low. Attempts were made for a reaction of iodide 215 with diethoxyacetonitrile 216. Unfortunately, all attempts failed to form alkylated compound 217 (Scheme 4.21, Table 4.4). For entries 1 and 2, LC/mass analysis of the crude mixture showed that there were trace amounts of the alkylated product in the mixture. Thus, to understand the reason for the failure of the reaction, two possibilities were considered: either the nitrile anion has a very short lifetime (insufficient nucleophile), or the iodo-chloro compound 215 was not electrophilic enough to be attacked by the anion.

![Scheme 4.21](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>E*</th>
<th>Base</th>
<th>Time</th>
<th>Temp (°C)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl</td>
<td>LDA</td>
<td>16 h</td>
<td>–78 to rt</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>NaH</td>
<td>16 h</td>
<td>rt</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>NaH</td>
<td>16 h</td>
<td>rt</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂CCN</td>
<td>&quot;BuLi</td>
<td>10 min</td>
<td>–78</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>MeO₂CCN</td>
<td>&quot;BuLi</td>
<td>30 min</td>
<td>–78</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>MeO₂CCN</td>
<td>&quot;BuLi</td>
<td>1 h</td>
<td>–78</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.4**

Table 4.4 shows that changing either the base, electrophile or the time did not affect the yield. Using methyl cyanoformate (1.1 equiv.) as the electrophile and a variety of different conditions for the above reaction, no product was detected either by TLC analysis or by crude ¹H NMR spectroscopy. Therefore, we decided to proceed with a different anion and an alternative method was employed for the alkylation.

We envisaged that alkylation of ethyl 1,3-dithiane-2-carboxylate would allow access to the desired aldehyde. Reaction of ethyl 1,3-dithiane-2-carboxylate 218 with NaH and iodo compound 215 in THF at room temperature gave a mixture of the desired product 219 in 32% yield (after purification), together with recovered starting material dithiane (similar polarity), and iodide 215 as well (Scheme 4.22). As expected, this reaction shows selective alkylation at the carbon α to the iodide over the chloride. Efforts to optimise the alkylation were carried out (Table 4.5). To ethyl 1,3-dithiane-2-carboxylate 218, "BuLi was added followed by iodo-compound 215 in THF. Using 1.1 equivalent of "BuLi gave low–moderate yield of the desired ester 219 (entries 3–5).
Scheme 4.22

<table>
<thead>
<tr>
<th>Entry</th>
<th>$E^+$</th>
<th>$N$-</th>
<th>Base (equiv.)</th>
<th>Base (equiv.)</th>
<th>Temp ($^\circ$C)</th>
<th>Time</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>1.1</td>
<td>NaH</td>
<td>1.1</td>
<td>rt</td>
<td>16 h</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.2</td>
<td>$^a$BuLi</td>
<td>1.3</td>
<td>$-78$ to $-rt$</td>
<td>16 h</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>$^a$BuLi</td>
<td>1.1</td>
<td>$-78$ to $-rt$</td>
<td>16 h</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1.1</td>
<td>$^a$BuLi</td>
<td>1.1</td>
<td>$-78$ to $-rt$</td>
<td>2 d</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>1.1</td>
<td>1</td>
<td>$^a$BuLi</td>
<td>1.1</td>
<td>$-78$ to $-rt$</td>
<td>16 h</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>1</td>
<td>$^a$BuLi</td>
<td>1.2</td>
<td>$-78$ to $-40$ to $rt$</td>
<td>16 h</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>1</td>
<td>$^a$BuLi</td>
<td>1.2</td>
<td>$-78$ to $-40$ to $rt$</td>
<td>16 h</td>
<td>75$^a$</td>
</tr>
</tbody>
</table>

$^a$ The molarity of Entry 6 is (0.16 M) and (0.33 M) for Entry 7

Table 4.5

After further optimisation, $^a$BuLi (1.2 equiv.) was added to ethyl 1,3-dithiane-2-carboxylate 218 (1.0 equiv.) at $-78$ $^\circ$C in THF. After 10 min, chloroiodo compound 215 (1.2 equiv.) was added at $-40$ $^\circ$C. The mixture was then warmed and stirred for 16 h at room temperature, after which the ester 219 was obtained in 65% yield (entry 6). Pleasingly, increasing the reaction concentration led to the ester 219 in 75% yield (entry 7). With the ester in hand, the next step was to prepare the aldehyde. However, efforts to obtain the aldehyde 220 in one step, using Red–Al with morpholine in toluene, were not successful and only starting material was recovered (Scheme 4.23).$^{131}$
Likewise, using DIBAL-H (1.1 equiv.) was unsatisfactory and a mixture of compounds was formed with many spots observed by TLC analysis. Only a trace of aldehyde was observed by $^1$H NMR spectroscopy. Adding more equivalents of DIBAL-H and warming the mixture to room temperature for full reduction gave none of the desired alcohol (Scheme 4.24).

As an alternative, ester 219 was reduced using LiAlH$_4$ in Et$_2$O to give alcohol 221 in 80% yield, which was followed by a Swern oxidation$^{69}$ to afford the desired aldehyde 220 in 85% yield with a 1,3-dithiane group α to the aldehyde (Scheme 4.25).
4.3.3 Tandem cyclisation–cycloaddition reaction

With aldehyde 220 in hand, it was now possible to attempt the tandem cyclisation–cycloaddition reaction. Using the same conditions from previous work on the bridged ring system, the aldehyde 220 was treated with hydroxylamine hydrochloride and N,N-diisopropylethylamine in toluene (Scheme 4.26). Different conditions were tried, but in all cases the cycloadduct 222 was formed in low yield (Table 4.6). We suspected that the reaction required higher temperatures than heating in toluene, though with xylene no enhancement was seen. In all cases a mixture was obtained as judged by many spots on TLC analysis.

![Scheme 4.26]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (°C)</th>
<th>Additive</th>
<th>222 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>3.5</td>
<td>110</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>18</td>
<td>110</td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>2 h at 60 °C then 18 h</td>
<td>110</td>
<td>TBAI 0.1 eq.</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>2 h at 60 °C then 18 h</td>
<td>110</td>
<td>MgSO₄</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>2 h at 60 °C then 18 h</td>
<td>110</td>
<td>Molecular sieves</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>48</td>
<td>110</td>
<td>MgSO₄</td>
<td>decomposed</td>
</tr>
<tr>
<td>7</td>
<td>PhMe</td>
<td>18</td>
<td>60</td>
<td>MgSO₄</td>
<td>Oxime trace &amp; starting material</td>
</tr>
<tr>
<td>8</td>
<td>Xylene</td>
<td>3.5</td>
<td>110</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Xylene</td>
<td>18</td>
<td>110</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Xylene</td>
<td>18</td>
<td>110</td>
<td>TBAI</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 4.6
4.3.4 Reaction optimisation

Table 4.6 shows that the best yield of the cycloadduct was obtained by using MgSO₄ as an additive (entry 4). The condensation step is probably reversible, which can explain why using a dehydrating agent is helpful. To explain the low yields in forming the cycloadduct, there are many possibilities, some of which are that:

1. The condensation step is difficult to carry out in this case, probably because it is a reversible reaction.

2. The propensity of the dithiane moiety to act as a nucleophile (cyclization with chloride displacement).

3. The chloride is not a sufficiently good leaving group to enable the cyclisation step.

To circumvent this problem, a strategy was devised that would increase the yield. First, the hydroxylamine hydrochloride and N,N-diisopropylethylamine in toluene were heated at 60 °C over a variety of times in order to form the oxime; unfortunately the yield was too low and mostly the starting aldehyde 220 was recovered (entry 7). Using molecular sieves did not enhance the cycloadduct yield (entry 5). Heating the reaction mixture for a long time (such as 48 h) led to decomposition. As a result, this indicated that the formation of the oxime is a difficult step under these conditions.

Coldham and co-workers reported that having a dimethyl acetal α to the aldehyde is better than a dithiane for the cycloaddition to give the ABC ring system of the manzamine alkaloids.⁹²,⁹³ Postulating that steric hindrance or nucleophilicity of the dithiane was causing problems, we decided that it would be better to explore the dimethyl acetal for our synthesis. To do so, the dithiane alcohol 221 was treated with silver nitrate, 2,4,6-collidine and trichloroacetonitrile in methanol but this gave no product and only starting material was recovered. However, using N-chlorosuccinimide under the same conditions afforded the diacetal 223 in 65% yield (Scheme 4.28).⁹³ Attempts were made to purify the desired compound which was difficult because of the 2,4,6-collidine.
The next step in our synthesis was the oxidation of the alcohol 223 using a Swern oxidation\textsuperscript{69} to generate aldehyde 224. Surprisingly, no desired aldehyde was isolated and the dimethyl acetal had decomposed. We thought that this might be due to the acidic work up of the Swern oxidation, but doing the work up without HCl did not help to obtain the desired product (Scheme 4.29).

To circumvent this, the scope of the search was expanded to find suitable conditions, and we found that the dithiane aldehyde 220 was converted to the diacetal 224 in 65\% yield, using [bis(trifluoroacetoxyl)iodo]benzene (PIFA) in methanol (Scheme 4.30).\textsuperscript{134} We were now at the step to attempt the cascade reaction with our new precursor aldehyde. As such, heating aldehyde 224 at 60 °C in toluene showed the formation of the oxime, then the solution was heated under reflux overnight to give a low yield of 225 (Table 4.7, entry 4). Decomposition products were also obtained.
Although MgSO₄ seemed to help the reaction to some extent (entry 4), using a promoter like TBAI gave no effect and the starting material decomposed quickly.

![Scheme 4.30](image)

**Scheme 4.30**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>Additive</th>
<th>225 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>16 h</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>16 h</td>
<td>MgSO₄</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>2 h at 60 °C then reflux 16 h</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>PhMe</td>
<td>30 min at 60 °C then reflux</td>
<td>MgSO₄</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>PhMe</td>
<td>30 min at 60 °C then reflux</td>
<td>TBAI 0.1 equiv.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>30 min at 60 °C then reflux</td>
<td>MgSO₄/TBAI 0.1 equiv.</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>Xylene</td>
<td>16 h</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Xylene</td>
<td>16 h</td>
<td>MgSO₄</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4.7**

The stereochemistry was assigned tentatively based on the $^1$H NMR spectrum (Figure 4.8). This showed the $^1$H peak at 4.10 ppm as a quartet with a $J$ value of 6.0 Hz, and $^3$H as a doublet of doublets with $J$ values of 9.0 and 3.5 Hz at 2.97 ppm. This is similar to the previous result in the formation of cycloadducts 210 and 222.
We thought that HCl might be generated *in situ* to hydrolyse the diacetal, and so the oxime 226 was isolated and purified by column chromatography on silica gel, in excellent yield. The oxime 226 was then heated under reflux in toluene with diisopropylethylamine to afford the cycloadduct in low yield (Scheme 4.31).

One possibility for the poor formation of the cycloadduct 225 is that the chloride may not be a sufficiently good leaving group for this reaction. Previous work in the Coldham group by Burrell, showed that conversion of a chloride to an iodide via a Finkelstein reaction, could improve a related cycloaddition. Aldehyde 220 was treated with sodium iodide in acetone under reflux for 18 h (Scheme 4.32), but unfortunately only aldehyde 220 was recovered.
Due to these issues, an alternative route was explored in which we began with crotylated dibromide 228 instead of the iodo-chloro 215 compound. Treatment of the diol 203 with carbon tetrabromide (2.2 equiv.) and triphenylphosphine (2.2 equiv.) in dichloromethane gave dibromide 228 in 95% yield (Scheme 4.33). Using the previously optimised reaction conditions, the dibromide was treated with the ethyldithiane carboxylate using nBuLi as a base. This gave a complex mixture of products with many spots observable by TLC analyses.

Based on this result, we thought that the iodo-bromo compound 230 would be better to use instead. Therefore, treatment of iodo-alcohol 204 with carbon tetrabromide (1.1 equiv.) and triphenylphosphine (1.1 equiv.) in dichloromethane gave iodo-bromide 230 in 88% yield. Alkylation with the ethyldithiane carboxylate using nBuLi as the base, gave ester 229 in 60% yield (Scheme 4.34).
Unfortunately, attempts to reduce the ester 229 using 1.0 equivalent LiAlH$_4$ in THF or DIBAL–H in dichloromethane failed to yield the desired aldehyde and an inseparable mixture was formed (Scheme 4.35). The outcome of this reaction was clearly disappointing. It was thought that the bromide was probably not stable enough to tolerate the reduction.

Scheme 4.35

With substrate 220 in hand, it was necessary to optimise the conditions that allowed for successful condensation, cyclisation, then cycloaddition. Therefore, we envisaged that making the oxime (which was partially successful using hydroxylamine hydrochloride and Hünig’s base) would be the key to access the cycloadduct. So, aldehyde 220 was treated with hydroxylamine hydrochloride and sodium acetate in anhydrous methanol at room temperature to give the oxime 232 in a quantitative yield using the method reported by Stockman and co-workers (Scheme 4.36).
The oxime 232 was then heated under reflux in toluene for 18 h but surprisingly, no cycloadduct was detected either by TLC or \textsuperscript{1}H NMR spectroscopy and only aldehyde and oxime were observed. Switching the solvent to xylene did not give the desired cycloadduct either. When MgSO\textsubscript{4} was added to the mixture, only 20\% yield of the cycloadduct 222 together with degradation products were obtained (Table 4.8, Scheme 4.37). Furthermore, when the reaction was conducted with or without TBAI in acetonitrile for 18 h, only mixtures that were difficult to purify were obtained (Table 4.8, entries 4 and 5). As hydrochloric acid is formed the addition of \textit{N},\textit{N}-diisopropylethylamine (Hünig’s base) could affect the nitrene formation from oxime 232 but heating the oxime with Hünig’s base in toluene gave a low yield of the desired cycloadduct.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Additive</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>110</td>
<td>18</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>PhMe</td>
<td>110</td>
<td>18</td>
<td>MgSO₄</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>PhMe</td>
<td>110</td>
<td>18</td>
<td>TBAI</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>83</td>
<td>18</td>
<td></td>
<td>0</td>
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<tr>
<td>5</td>
<td>MeCN</td>
<td>83</td>
<td>18</td>
<td>TBAI</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>PhMe</td>
<td>110</td>
<td>18</td>
<td>iPr₂NEt</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 4.8

We attempted to form the desired product using both Hünig’s base and a dehydrating agent. Interestingly, upon refluxing the oxime with magnesium sulphate and Hünig’s base in toluene for 18 h afforded the desired cycloadduct in up to 57% yield (Scheme 4.38). Addition of magnesium sulphate is due to the need to avoid water to hydrolyse the oxime, and Hünig’s base was added to remove the generated hydrochloric acid that might promote hydrolysis of the oxime. The reason for the poor cycloadduct formation straight from the aldehyde 220 might be due to the difficulty of the condensation to give the oxime.

Scheme 4.38

4.3.5 Stereochemistry assignment of cycloadduct 222

The stereochemistry of the product 222 was predicted tentatively as compared to other cycloadducts that were mentioned in this chapter. The proton H⁺ was observed at 4.19 ppm as a quartet with a J value of 6.0 Hz, and proton H⁵ at 2.42 ppm as a doublet of doublets with J values of 9.5 and 3.5 Hz (see ¹H NMR spectrum, Figure...
4.9). The lack of any coupling between protons $H^G$ and $H^E$ indicates the stereochemistry as shown (Scheme 4.38) as this is also observed in the cycloadducts 210 and 212 (page 65 and 84).

![Figure 4.9](image)

Having demonstrated the suitability of the cyclisation–cycloaddition cascade in the synthesis of the bridged system of the iboga alkaloid core structure, we believed that it would be possible now, with the cycloadduct in hand, to complete the synthesis of 19-hydroxy-ibogamine 136.

### 4.4 Formal synthesis of the 19-hydroxy-ibogamine

According to the synthetic plan, the next step was to break the N–O bond, using the same method as before. The cycloadduct 222 was heated with zinc and acetic acid in water. After 4 h this method only returned starting material. Leaving the reaction for a longer time led to decomposition (Scheme 4.39). This failure was attributed to the coordination of sulphur to zinc which might have prevented the reaction at the N–O bond.
It was therefore thought that removing the dithiane, and then cleaving the N–O bond could provide the amino-alcohol compound. A decision was made to transform the dithiane to the dimethylacetal. The transketalisation reaction was performed using the same conditions as used for compound 224. Cycloadduct 222 was treated with PIFA in methanol (Scheme 4.40) but only 35% yield of the diacetal cycloadduct 225 was obtained and mostly the starting material was recovered. All efforts to optimise the yield, such as adding more equivalents of catalyst and leaving the reaction for a longer time, failed to improve the conversion.

An alternative method involved deprotecting the dithiane to generate the ketone, using the same method as before, but with MeCN/H$_2$O (9:1) instead of methanol. As the $R_f$ of starting material and the product were almost the same, the reaction was stopped after 4 h, dichloromethane was added and the mixture was neutralised with sodium bicarbonate. Unfortunately, the $^1$H NMR spectrum showed that the starting material remained with some product. Therefore, further attempts were tried to optimise the conditions. Using MeCN/H$_2$O (1:1) and increasing the reaction time did enhance the yield slightly. In response to this observation, the reaction was repeated with increasing the amount of PIFA up to 5.0 equivalents. The equivalents were
added in three portions; initially 1.0 equivalent was added, followed by 1.5 equivalents after 30 minutes and then an additional 2.5 equiv. were added to afford the desired ketone 212 in good yield (Scheme 4.41).

Scheme 4.41

The stereochemistry of the product 212 was confirmed by single crystal X-ray crystallography, which showed the orientation of the methyl group. Based on the $^1$H NMR spectroscopy (Figure 4.10), proton H$^G$ was a quartet at 4.26 ppm and the $J$ value was 6.0 Hz, while proton H$^E$ was observed as a doublet of doublets at 2.45 ppm with $J$ values of 9.5 and 3.5 Hz. As before, no coupling between these vicinal protons was observed and this supports the predictions that were made for all of the other cycloadducts that have been discussed previously in this chapter.

Figure 4.10
The following step was to cleave the N−O bond, using zinc in acetic acid and water. No reaction occurred while heating the reaction at 70 °C for 6 h and only starting material was recovered. Repeating the reaction with heating overnight led to decomposition of the starting material. Alternatively, zinc in acetic acid and methanol was used. After 4 h at room temperature, the $^1$H NMR spectrum of the crude product showed a mixture of product and starting material. Similarly, the reaction was repeated using activated zinc (stirring in 1.0 M HCl freshly prepared, washed with ethanol, ether and dried under vacuum) in acetic acid and methanol for 4 h at room temperature and this gave the desired amino alcohol 234 in quantitative yield (Scheme 4.42).\(^{136}\)

![Scheme 4.42](image)

With the amino-alcohol in hand, we were in a position to target the desired molecule 136. Treating indole-3-acetic acid 235 with oxalyl chloride in DMF and dichloromethane afforded compound 236 in a quantitative yield. The crude product was used with no further purification in a reaction with amine 234. Using a solution of potassium carbonate in dichloromethane compound 237 was obtained in a moderate yield (Scheme 4.43).
To optimise the yield, the reaction was carried out using pyridine in dichloromethane, but the product was obtained in almost similar yield. Alternatively, a direct condensation by treating secondary amine 234 and indole-3-acetic acid 235 (1.1 equiv.), using EDCI as coupling reagent in dichloromethane, gave amide 237 in quantitative yield (Scheme 4.44).

In order to form the 7-membered ring product 238, Hanaoka and co-workers reported that treating the dimethyl acetal formed from ketone 161 (Scheme 3.8) in boiling benzene with p-toluenesulfonic acid gave the cyclised product. We wondered whether the same type of chemistry would be successful with the ketone 237. However, attempts to form the 7-membered ring compound 238 using toluene and p-toluenesulfonic acid gave a mixture that was difficult to purify (Scheme 4.45).
Related chemistry by Höck and Borschberg reported that a similar ketone was inactive towards the cyclisation reaction. However, the acetal 177 (Scheme 3.14) was reported to undergo successful cyclisation. Therefore, we treated ketone 237 with trimethylorthoformate and p-toluenesulfonic acid in methanol to give compound 239 in good yield (Scheme 4.46).

Towards the cyclisation, acetal 239 was treated with acetyl chloride and acetic acid in methanol (cat.) using the same conditions described by Höck and Borschberg, but no cyclised product was observed and a mixture of inseparable products was formed (Scheme 4.47).
It has been reported that reversibility of the cyclisation reaction due to traces of water produces the corresponding ketone which can resist the cyclisation. So we carried out the reaction with dry glacial acetic acid and distilled acetyl chloride in dry methanol but inseparable mixture was formed. Finally, we decided to go through the formal synthesis. Pleasingly, treatment of alcohol 239 with acetyl chloride and pyridine in dichloromethane gave the ester 177 in 87% yield (Scheme 4.48). Ester 177 has been reported by Höck and Borschberg in their synthesis of 19-hydroxy-ibogamine.

![Scheme 4.48](image)

### 4.4.1 The NMR data analysis of ester 177

We compared the NMR data of ester 177 in CDCl₃ with that reported by Höck and Borschberg (they report their ¹H NMR spectrum in CDCl₃). Our NMR spectra and the one reported by Borschberg are clearly the same. It is possible to see that in the data reported by Borschberg, there are only a few differences in the ¹H NMR data in comparison with our data (Table 4.9, main differences highlighted in red). One aromatic proton appeared as a doublet at 7.57 ppm with J value of 7.5 Hz; Borschberg, instead, reported this as ddd at 7.55 ppm with J values of 7.8, 1.2 and 0.6 Hz. Protons at 3.77–3.76 ppm and 3.75–3.74 ppm appeared as a multiplet, while they were reported as dd at 3.72 ppm and 3.68 ppm respectively. The proton at 2.22 ppm was reported as a ddd, whilst, in our sample this appeared as a multiplet at 2.29–2.20 ppm. The multiplet protons in the Borschberg data were not reported as a range. Unfortunately, the Borschberg NMR spectra were not available in the supplementary information to be compared to our spectra (see appendix 9).
<table>
<thead>
<tr>
<th>Borschberg data</th>
<th>Our sample data*</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.26 (1H, br. s, NH)</td>
<td>8.30 (1H, br. s, NH)</td>
</tr>
<tr>
<td>7.55 (1H, ddd, J 7.8, 1.2, 0.6 Hz, ArH)</td>
<td>7.57 (1H, d, J 7.5, ArH)</td>
</tr>
<tr>
<td>7.34 (1H, dt, J 8.0, 0.9 Hz, ArH)</td>
<td>7.36 (1H, dt, J 8.0, 1.0 Hz, ArH)</td>
</tr>
<tr>
<td>7.21 (1H, m, ArH)</td>
<td>7.23–7.22 (1H, m, ArH)</td>
</tr>
<tr>
<td>7.17 (1H, ddd, J 8.2, 7.1, 1.2 Hz, ArH)</td>
<td>7.19 (1H, ddd, J 8.0, 7.0, 1.0 Hz, ArH)</td>
</tr>
<tr>
<td>7.12 (1H, ddd, J 7.9, 7.1, 1.1 Hz, ArH)</td>
<td>7.13 (1H, ddd, J 8.0, 7.5, 1.0 Hz, ArH)</td>
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<tr>
<td>4.89 (1H, d, J 1.5 Hz, CH)</td>
<td>4.91 (1H, d, J 1.5 Hz, CH)</td>
</tr>
<tr>
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<td>3.72 (1H, dd, J 15.2, 1.0 Hz, CH)</td>
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</tr>
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<td>3.68 (1H, dd, J 15.2, 1.2 Hz, CH)</td>
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<tr>
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<td>3.29 (1H, dt, J 10.0, 2.5 Hz, CH)</td>
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<tr>
<td>3.24 (3H, s, CH₃)</td>
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</tr>
<tr>
<td>3.18 (3H, s, CH₃)</td>
<td>3.20 (3H, s, CH₃)</td>
</tr>
<tr>
<td>2.22 (1H, ddd, J 10.6, 6.1, 1.6 Hz, CH)</td>
<td>2.29–2.20 (1H, m, CH)</td>
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<tr>
<td>2.11 (3H, s, CH₃)</td>
<td>2.13 (3H, s, CH₃)</td>
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<tr>
<td>2.02 (1H, m, CH)</td>
<td>2.05–2.02 (1H, m, CH)</td>
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<td>1.22 (3H, d, J 6.0 Hz, CH₃)</td>
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<tr>
<td>0.93 (1H, ddt, J 10.9, ca. 5.5, 2.5 Hz, CH)</td>
<td>0.92(1H, ddt, 13.0, 5.5, 2.5 Hz, CH)</td>
</tr>
</tbody>
</table>

*all our J values reported to nearest 0.5 Hz

Table 4.9

For the $^{13}$C NMR spectra, the molecule contains 23 carbons. The $^{13}$C NMR data are a good match between Borschberg’s and ours (Table 4.10). Our conclusion is that our ester had the same NMR spectra as that reported. Finally, this chemistry therefore completes a formal synthesis of 19-hydroxy-ibogamine.
<table>
<thead>
<tr>
<th>Borschberg</th>
<th>Our sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>171.3 (s)</td>
<td>171.3 (C=O)</td>
</tr>
<tr>
<td>171.1 (s)</td>
<td>171.1 (C=O)</td>
</tr>
<tr>
<td>136.1 (s)</td>
<td>136.1 (C)</td>
</tr>
<tr>
<td>127.4 (s)</td>
<td>127.4 (C)</td>
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<tr>
<td>122.9 (d)</td>
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<td>121.9 (CH)</td>
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<tr>
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<tr>
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<td>48.9 (CH₂)</td>
</tr>
<tr>
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<td>48.1 (CH₃)</td>
</tr>
<tr>
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<td>45.7 (CH)</td>
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<tr>
<td>38.1 (d)</td>
<td>38.1 (CH)</td>
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<td>36.9 (CH₂)</td>
</tr>
<tr>
<td>30.6 (t)</td>
<td>30.6 (CH₂)</td>
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<tr>
<td>28.2 (t)</td>
<td>28.2 (CH₂)</td>
</tr>
<tr>
<td>27.5 (d)</td>
<td>27.5 (CH)</td>
</tr>
<tr>
<td>21.5 (q)</td>
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</tr>
<tr>
<td>17.8 (q)</td>
<td>17.8 (CH₃)</td>
</tr>
</tbody>
</table>

Table 4.10
4.5 Conclusion

In this chapter, we have demonstrated that the cyclisation–cycloaddition methodology developed in the group can be used for the synthesis of two-carbon bridged tricyclic cycloadducts, and this was applied towards the synthesis of the core of the iboga alkaloids. We have synthesized a range of precursor aldehydes and identified optimum conditions for carrying out novel cyclisation, nitrone cycloaddition, cascade chemistry between aldehydes and hydroxylamine to produce a range of two-carbon bridged systems.

An aldehyde bearing enolisable hydrogens was tested in the cascade chemistry, but in this case, the cyclisation-cycloaddition cascade gave a low yield of the desired cycloadduct. Non-enolisable aldehyde substrates were found to give better yield and worked well in the cascade chemistry. We successfully achieved the formal synthesis of one iboga alkaloid called 19-hydroxy-ibogamine. A summary of the complete formal synthesis is shown in Scheme 4.49.
Scheme 4.49
Chapter 5 Towards the test of a proposed biosynthetic route of daphlongeranines

5.1 The Daphniphyllum alkaloids

_Daphniphyllum_ alkaloids are a structurally diverse type of natural products isolated from the Yuzuriha tree, found in central and southern Japan.¹³⁻⁸ _Daphnimacrine_ was first isolated in 1909 by Yagi.¹³⁻⁹ It is one of the C30 type of _Daphniphyllum_ alkaloids, but the structure was difficult to elucidate using the technology at the time. Extensive research has been done by Hirata into the _Daphniphyllum_ alkaloids and to date more than 200 _Daphniphyllum_ alkaloids have been discovered and characterised.¹⁴⁻⁰ They are all complex and polycyclic molecules, and have been classified into 6 groups based on their structures: daphnilactone A ²⁴⁻⁰, daphnilactone B ²⁴⁻¹, yuzurimine ²⁴⁻², yuzurine ²⁴⁻³, daphniphylline ²⁴⁻⁴ and secodaphniphylline ²⁴⁻⁵ (Figure 5.1).¹³⁻⁸

![Diagram of alkaloid structures](image)

Figure 5.1

As one can imagine, from such a structurally diverse family of natural products, there is a great deal of research interest in the _Daphniphyllum_ alkaloids, and as such, several reviews and books have been written on the subject.¹⁴⁻¹ This large subject area
is too vast to be fully described in this introduction. The *Daphniphyllum* alkaloids possess complex ring systems, which are a real challenge to synthetic chemists looking to synthesize them in the lab. Yamamura and Suzuki and co-workers reported that these alkaloids were derived from squalene, a triterpene that is also important in humans as a biochemical precursor for the synthesis of all steroids. In 1996, Heathcock suggested a laboratory synthesis route and postulated that squalene could be a suitable starting material to give the core ring structure of secodaphniphylline skeleton 246. The daphniphylline skeleton 248 could potentially be obtained through compound 247 (Figure 5.2).

![Secodaphniphylline Skeleton](image)

**Figure 5.2**

To test this, Heathcock and co-workers designed a plan to achieve the total synthesis of methyl homosecodaphniphylline 255. The amide 249, ester 250 and iodide 252 were subjected to a cascade 1,4-addition-alkylation to afford compound 252. This was transformed to aldehyde 253 in several steps, followed by a condensation reaction with methylamine to give cycloadduct 254. Reduction and oxidation reactions, followed by an esterification reaction afforded methyl homosecodaphniphylline 255 (Scheme 5.1).
The dialdehyde 253 was converted to 254 through condensation with methylamine to form iminium ion 256 which underwent an intramolecular Diels-Alder reaction to generate 257. A cyclisation reaction took place followed by hydrolysis to give 254 (Scheme 5.2). Heathcock and co-workers suggested that the tetracyclisation step is a possible biomimetic step and pyridoxamine or the amine group of the amino acid could be used to help the cyclisation process.\textsuperscript{145}
Later, Heathcock and Stafford successfully synthesized the secodaphniphylline 262 from methyl homosecodaphniphylline 255 in two steps. Thus, treatment of ester 255 with LDA, then adding acid chloride 260 formed ketone 261, which underwent a Krapcho decarboxylation to afford secodaphniphylline 262 (Scheme 5.3).

Bukittinggine alkaloid 266 was extracted from the leaves of *Sapium baccatum*. Due to its unique structure, which shows similarity to secodaphniphylline and the
yuzurimine alkaloids, this compound became a focus of research. Heathcock and co-workers were the first to report the total synthesis of (±)-Bukittinggine 266. They synthesized the diol 265 using the same Michael addition-alkylation step as before, followed by oxidation and tetracyclisation in the presence of ammonia to give tetracycle 264. This then underwent cyclisation using palladium di(trifluoroacetate) as a catalyst to afford the exo alkene 265. The cyclisation step using Pd(II) proceeded through reaction where the nucleophilic nitrogen atom attacks the Pd π-allyl complex. The final product 266 was obtained in four steps from compound 265 (Scheme 5.4). The total yield was 3% over the whole 18 step synthesis.

![Scheme 5.4](image)

Other research groups have reported the synthesis of part structures of the *daphniphyllum* alkaloids.¹⁴⁹-⁵³
5.2 Preliminary work in the group

Due to the complex structure of the *Daphniphyllum* alkaloids, they have become an interest to many synthetic organic chemists. A paper in 2004\textsuperscript{153} reported the isolation of daphcalycic acid \textbf{267} from the seeds of *Daphniphyllum calycinum*.

![Figure 5.3](image)

Coldham and co-workers had explored the use of cascade cyclisation-cycloaddition chemistry of a nitrone towards the synthesis of core structure \textbf{268} (Figure 5.3)\textsuperscript{154}. To do this, the nitrile \textbf{269} (prepared from Roche ester) was alkylated using LDA and iodide \textbf{270} to afford nitrile \textbf{271} in 98% yield in a 2:1 ratio of diastereoisomers. The hydroxyl group was deprotected to give alcohol \textbf{272} in good yield; this was treated with \textsuperscript{t}PrMgCl, then sulfonylation with PhSSPh formed nitrile \textbf{273} as a 2:1 mixture of diastereoisomers in 92% yield. Chlorination was carried out using carbon tetrachloride in dichloromethane, then nitrile \textbf{274} was converted to key aldehyde \textbf{275} using a DIBAL-H reduction [ratio of diastereoisomers (dr 7:3)]. Aldehyde \textbf{275}, hydroxylamine hydrochloride and diisopropylethylamine were then refluxed in toluene to give the cycloadducts \textbf{276a} and \textbf{276b}. These were separable isomers obtained in 80% yield in the ratio of 7:3 (Scheme 5.5).
The minor cycloadduct 276b was treated with zinc in acetic acid to give amino alcohol 277. The synthesis of the core structure was completed by treating compound 277 with paraformaldehyde in the presence of p-toluenesulfonic acid to afford compound 278 in 61% yield (Scheme 5.6).

Additionally, Coldham and co-workers reported an efficient route to synthesize the core structure 279 found in daphnilactone B 280 (Figure 5.4).
The unsaturated aldehyde 281 was treated with silyl ketene acetal 282 and a bulky Lewis acid to give aldehyde 283 in 93% yield. The aldehyde group was reduced using NaBH₄ and the alcohol was converted to bromo-compound 284. The ester was reduced using DIBAL-H, followed by Swern oxidation, and then cross metathesis using Grubbs 2nd generation catalyst and ethyl acrylate to give aldehyde 285 in 82% yield. Condensation, cyclization cycloaddition cascade reaction was then attempted. The aldehyde 285 with hydroxylamine hydrochloride and diisopropylethylamine was heated under reflux in toluene to give the tricyclic product 286 as a single isomer in excellent yield (Scheme 5.7).

Compound 286 was subjected to Raney nickel and sodium methoxide to give lactam 287 in 75% yield. On oxidation compound 288 was formed in very good yield. This
underwent Wittig reaction to generate an alkene, then reduction was carried out to give the desired core structure 279 in 90% yield as a single isomer (Scheme 5.8).\textsuperscript{121}

![Scheme 5.8](Image)

### 5.3 Biosynthetic route to daphlongeranines

In a 2007 study\textsuperscript{155} Hao and co-workers reported two new compounds called daphlongeranines A and B (Figure 5.5). Isolated from *Daphniphyllum longeracemosum*, their structures were elucidated with an unprecedented ring system.

![Figure 5.5](Image)

Furthermore, to understand the formation of these two compounds they proposed a biosynthetic route (Scheme 5.9), which involved a pinacol rearrangement step (from 289 to 290).
The proposed biosynthesis was of interest to the Coldham group as we thought that we could access the core ring system 291 by utilising the condensation, cyclisation, cycloaddition chemistry of a nitrone that had been developed in the group. Therefore, we believed that this would allow us to probe the pinacol rearrangement step, and would provide evidence whether it was possible for it to take place or not. This could then support the proposed biosynthesis. To test this hypothesis, Coldham proposed a strategy to study the key pinacol rearrangement step. The aim was to synthesise the
cyclic structure 291, which is similar in structure to the daphlongeranine precursor 289 (Figure 5.6).

![Figure 5.6](image)

### 5.5 Towards the synthesis of the core structure 291

#### 5.5.1 First strategy

Rychnovsky and co-workers\textsuperscript{156,157} reported the synthesis of a cyclic nitrile and scoped the alkylation with a variety of electrophiles. Using similar chemistry, we planned a strategy to access the core structure 297. Scheme 5.10 outlines the general route that could lead to the cycloadduct 291. We proposed that the Roche ester 292 would be a suitable starting material. Protection and reduction followed by a cyanation reaction and acetonide protection should give 293. Alkylation with an electrophile followed by removal of the acetonide and subsequent chlorination, and reduction would form 296. We believed that this could then undergo a nitrene 1,3-dipolar cycloaddition reaction to create cycloadduct 291 (Scheme 5.10). The final step would be to test the pinacol rearrangement in the lab.

![Scheme 5.10](image)
To prepare the nitrile \textbf{293}, the Roche ester \textbf{292} was treated with TESCl (1.3 equiv.) and imidazole (1.3 equiv.) in CH$_2$Cl$_2$ to give compound \textbf{298} in 80\% yield (Scheme 5.11). Using 1.5 equivalents of both TESCl and imidazole gave 93\% yield. A quantitative yield was obtained when the purification used alumina instead of silica gel. This was followed by reduction of the ester group to an aldehyde using DIBAL-H (1.05 equiv.) in CH$_2$Cl$_2$ at \(-78^\circ\text{C}\), and after 2 h, the aldehyde \textbf{299} was obtained in 92\% yield (Scheme 5.11).

![Scheme 5.11](image)

The next step was the synthesis of the cyclic nitrile compound \textbf{293} following a method similar to that reported.\textsuperscript{156} The cyanation reaction was achieved by treating aldehyde \textbf{299} with TMSCN and KCN/[18-crown-6] complex at \(0^\circ\text{C}\). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The acetonide protection step was carried out \textit{in situ} by adding dry acetone, 2,2-dimethoxypropane and CSA. The reaction mixture was then left for 16 h before adding triethylamine, and the desired product was obtained in 52\% yield. A better yield of 64\% was obtained when both the cyanation step and the protection step were left for 16 h (Scheme 5.12).

![Scheme 5.12](image)
Two diastereoisomers showed up on the $^1$H and $^{13}$C NMR spectra in (1.1:1) ratio. The $^{13}$C NMR spectra in CDCl$_3$ showed four peaks at 28.7 ppm, 25.0 ppm, 24.3 ppm and 19.0 ppm, this correspond to the geminal methyl groups of syn-isomer and anti-isomer (Figure 5.7, 293a and 293b). Based on the studies that have been reported on substituted 2,2-dimethyl 1,3-dioxanes,$^{159-161}$ The studies on compounds A and B showed that the geminal methyl groups of the of syn-isomer is about 30.0 ppm and 19.0 ppm and for anti-isomer is about 25.0 ppm (Figure 5.7, A and B).

![Figure 5.7](image.png)

**Figure 5.7**

### 5.5.1.1 Alkylation with 5-bromo-1-pentene

Using LDA (1.1 equiv.) in THF at $-78$ °C for the deprotonation of nitrile 293, followed by addition of 5-bromo-1-pentene gave a single isomer 300 in 55% yield (Table 5.1, entry 1). Therefore, to obtain a better yield, some optimisation took place. Increasing the equivalents of LDA did not give a better yield, but reducing the deprotonation time with 1.2 equivalents afforded a slightly better yield (entries 4-6). The best yield was obtained when 1.2 equivalents of LDA was used, with a deprotonation time of 30 minutes, followed by electrophile addition, stirring for 2 h at $-78$ °C and then for 1 h at $-20$ °C (entry 7). Adding DMPU under the same conditions, to initiate the lithiation step, reduced the yield (entries 8 and 9).

![Scheme 5.13](image.png)

**Scheme 5.13**
Table 5.1

The stereochemistry of 1,3-dioxanes has been widely investigated by many research groups.\textsuperscript{118,162} Alkylations of sterically hindered cyano-1,3-dioxanes are extremely stereoselective. Cyano-1,3-dioxanes selectively alkylate a broad range of electrophiles from the equatorial direction which could arise from steric interactions between the incoming electrophile and the axial methyl group in the acetal or by stereoelectronic control (Figure 5.8).\textsuperscript{118} Based on that the stereochemistry of the product 300 was proposed. Additionally, the methyl group controls the orientation of

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time</th>
<th>Yield (%)</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>1 h at −78 °C then E(^+), 2 h</td>
<td>55</td>
<td>one isomer</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>1 h at −78 °C then E(^+), 2 h and 2 h at rt</td>
<td>56</td>
<td>one isomer</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>1 h at −78 °C then E(^+), 2 h and 2 h at −20 °C</td>
<td>50</td>
<td>one isomer</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>45 min at −78 °C then E(^+), 2 h and 2 h at −20 °C</td>
<td>60</td>
<td>one isomer</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>45 min at −78 °C then E(^+), 2 h and 2 h at rt</td>
<td>60</td>
<td>one isomer</td>
</tr>
<tr>
<td>6</td>
<td>LDA</td>
<td>45 min at −78 °C then E(^+), 2 h</td>
<td>63</td>
<td>one isomer</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>30 min at −78 °C then E(^+), 2 h and 1 h at −20 °C</td>
<td>65</td>
<td>one isomer</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>30 min at −78 °C then DMPU and E(^+), 2 h and 1 h at −20 °C</td>
<td>35</td>
<td>one isomer</td>
</tr>
<tr>
<td>9</td>
<td>LDA</td>
<td>30 min at −78 °C then DMPU and E(^+), 2 h and rt 18 h</td>
<td>40</td>
<td>one isomer</td>
</tr>
</tbody>
</table>
the electrophile. As a result, the product resulting from an equatorial approach of the electrophile would be preferentially observed.

![Figure 5.8](image)

The next step was to remove the acetonide and generate the diol‒nitrile 301 (Scheme 5.14). The cyclisation reaction can then be tested after chlorination followed by nitrile reduction.

![Scheme 5.14](image)

Treatment of compound 300 (50 mg) with aqueous HCl (37%) in hexane for 4 h afforded diol 301 in 50% yield (Table 5.2, entry 1). Unfortunately, all attempts for acetonide deprotection on a bigger scale failed to give one isomer, and for all reactions epimerisation took place to end up with inseparable isomers (Table 5.2). Using acetic acid and water, after 9 days, only 3% yield was obtained in 20:1 ratio, observed by $^1$H NMR spectroscopy.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Time</th>
<th>Yield%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hexane</td>
<td>HCl 37%</td>
<td>4 h</td>
<td>50</td>
<td>one isomer</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>TFA/H$_2$O 1.2:0.2</td>
<td>4 h</td>
<td>20</td>
<td>two isomers$^a$ (1:1)</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>AcOH/H$_2$O 1:3</td>
<td>9 days</td>
<td>3%</td>
<td>20:1$^a$</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>HCl in Et$_2$O 1 M</td>
<td>4 h</td>
<td>20</td>
<td>two isomers$^a$ (1:1)</td>
</tr>
</tbody>
</table>

$^a$ Based on the $^1$H NMR spectrum

Table 5.2
Attempts were made at the chlorination reaction of the mixture of diastereoisomers, but these did not work and many spots were seen by TLC analysis (Scheme 5.15).

Scheme 5.15

### 5.5.1.2 Alkylation with 4-pentenal

With the positive result of the nitrile alkylation reaction of compound 293, we believed that using 4-pentenal 304 could provide the key nitrile 294. Therefore, 5-penten-1-ol 303 was oxidised to the aldehyde 304 using a Swern oxidation. The resulting aldehyde was highly volatile, and was difficult to purify (Scheme 5.16).

Scheme 5.16

Alternatively, we started with commercially available allyl vinyl ether 305, which was heated at 150 °C in the microwave to give the aldehyde 304 in quantitative yield via a Claisen rearrangement (Scheme 5.17).

Scheme 5.17

Compared with the previous method, this provides a clean product 304, observed by ¹H NMR spectroscopy of the crude product, and so it was used without further purification. Following the reaction by ¹H NMR spectroscopy showed us that the reaction required 7 h to proceed to full conversion on 2 g scale.
A 1997 study by Rychnovsky and Swenson investigated the alkylation of a cyclic 1,3-dioxane nitrile. Many parameters were scoped such as base, time, temperature and electrophile. The only aldehyde they tested was benzaldehyde, and the yield was only 28%. In our chemistry aldehyde 304 gave varying yields of the desired product 306 (Scheme 5.18). Treatment of cyclic nitrile 293 with n-BuLi (1.2 equiv.) in THF at –78 °C, followed by addition of aldehyde 304 gave four diastereoisomers (Table 5.3, entry 1), observed by ¹H NMR spectroscopy of the crude product. Furthermore, using NaHMDS (1.5 equiv.) for deprotonation of the nitrile followed by addition of aldehyde 304 afforded 14% yield of the product as a single isomer (entry 2). Deprotonation with KHMDS gave no product and most of the starting material was recovered (Table 5.3).

![Scheme 5.18](image.png)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base equiv.</th>
<th>Time</th>
<th>Yield%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi 1.2</td>
<td>1 h at –78 °C then E⁺, 1 h and 1 h at –20 °C then 30 min rt</td>
<td>–</td>
<td>4 isomers</td>
</tr>
<tr>
<td>2</td>
<td>NaHMDS 1.5</td>
<td>2 h at –78 °C then E⁺, 2 h and 1 h at 0 °C</td>
<td>14</td>
<td>one isomer</td>
</tr>
<tr>
<td>3</td>
<td>KHMDS 1.5</td>
<td>2 h at –78 °C then E⁺, 2 h and 1 h at 0 °C</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3

However, the use of LDA showed better results than the other bases (Table 5.4, entry 1). Efforts to optimise the conditions were made to obtain better yields. It was very difficult to find suitable conditions for better yields, which is why each reaction was
repeated many times. Adding a catalyst such as MgBr$_2$·Et$_2$O failed to give a better yield (entry 4–6). Increasing the equivalents of the LDA dropped the yield to 41% only (entry 8). Finally, the nitrile 293 was deprotonated over 30 minutes, the aldehyde 304 was added and the reaction was left for 1 h at −78 °C. The reaction mixture was warmed to −20 ºC, and then room temperature to afford the desired product in good yield (Table 5.4, entry 9).

<table>
<thead>
<tr>
<th>Entry</th>
<th>LDA equiv.</th>
<th>Time</th>
<th>Yield%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>30 min at −78 ºC then E$^+$, 2 h and 1 h at −20 ºC</td>
<td>65</td>
<td>1.1:1</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>2 h at −78 ºC then E$^+$, 2 h and 2 h at −20 ºC</td>
<td>50</td>
<td>1.1:1</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>2 h at −78 ºC then E$^+$, 2 h and 1 h at 0 ºC</td>
<td>50</td>
<td>1.1:1</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>2 h at −78 ºC then 0.2 eq MgBr$_2$·Et$_2$O and E$^+$, 2 h and 2 h at −20 ºC</td>
<td>50</td>
<td>1.1:1</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>2 h at −78 ºC then 0.2 eq MgBr$_2$·Et$_2$O and E$^+$, 2 h and 1 h at 0 ºC</td>
<td>30</td>
<td>1.1:1</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>2 h at −78 ºC then 0.1 eq MgBr$_2$·Et$_2$O and E$^+$, 2 h and 1 h at 0 ºC</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.2</td>
<td>2 h at −78 ºC then E$^+$, 2 h</td>
<td>55</td>
<td>1.1:1</td>
</tr>
<tr>
<td>8</td>
<td>1.3</td>
<td>2 h at −78 ºC then E$^+$, 2 h and 2 h at −20 ºC</td>
<td>41</td>
<td>1.1:1</td>
</tr>
<tr>
<td>9</td>
<td>1.2</td>
<td>30 min h at −78 ºC then E$^+$ stir 1 h and 1 h at −20 ºC then 30 min rt</td>
<td>75</td>
<td>1.1:1</td>
</tr>
</tbody>
</table>

Table 5.4
In most cases, the ratio of the cyanohydrin compound was 1.1:1 by $^1$H NMR spectroscopy, and it was difficult to know which isomer was the major and which was the minor. The possible stereochemistry of the two diastereoisomers is shown in Figure 5.9.

![Figure 5.9](image)

Alternatively, we thought that treating nitrile 293 with acid chloride 308 instead of aldehyde 304, could generate ketone 309, which could then be reduced to give either one isomer or give a better ratio. To do this, oxalyl chloride was added to 4-pentenoic acid 307 at room temperature, to give 4-pentenoyl chloride 308 in quantitative yield (Scheme 5.19).

![Scheme 5.19](image)

With compound 308 in hand, it was possible to test the alkylation reaction. Acetonide 293 was treated with base and 4-pentenoyl chloride 308 in THF was added (Scheme 5.20). Unfortunately, using different bases and different conditions afforded no product and many spots were observed by TLC analysis (Table 5.5). $^1$H NMR spectroscopy and LC/mass detected no identifiable product.
Using another alternative method, oxidation of alcohol 306 via a Swern oxidation gave ketone 309 in good yield. Work up with HCl gave a low yield, while a better yield was obtained without the work up (Scheme 5.21).
This compound 309 was then subjected to reduction to give compound 306 in good yield and good selectivity (Scheme 5.22).

Using K-Selectride in THF as a reducing agent gave only a 3:1 ratio, which was the same ratio that was obtained with sodium borohydride in methanol at room temperature (Table 5.6). Fortunately, the reaction with sodium borohydride in methanol at $-78 \degree C$ was successful and gave compound 306 in a 11:1 ratio in good yield (entry 3), and this was easily purified by silica gel chromatography.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>equiv.</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield%</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K-selectride</td>
<td>1.5</td>
<td>THF</td>
<td>1 h at $-78 \degree C$ then 4 h</td>
<td>65</td>
<td>3:1</td>
</tr>
<tr>
<td>2</td>
<td>NaBH$_4$</td>
<td>1.2</td>
<td>MeOH</td>
<td>2 h at rt</td>
<td>65</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>NaBH$_4$</td>
<td>1.2</td>
<td>MeOH</td>
<td>2 h at $-78 \degree C$</td>
<td>75$^a$</td>
<td>11:1</td>
</tr>
</tbody>
</table>

Table 5.6 $^a$ the percentage is for pure isomer
We do not know which is the major isomer at this stage. To investigate the acetonide removal of compound 306, we carried out a screen of literature procedures that related to five and six membered acetonides.\textsuperscript{164-166} Ideally we wanted to convert acetonide 306 to the new acetonide 310 (Scheme 5.23). Unfortunately, by using \textit{p}-toluenesulfonylic acid many spots were observed by TLC analysis.

\begin{align*}
\text{CN} & \quad \text{OH} \\
\text{O} & \quad \text{O} & \quad \text{CN} & \quad \text{OH} \\
\text{306} & \quad \text{p-TsOH, acetone} & \quad \text{310}
\end{align*}

\textbf{Scheme 5.23}

Alternatively, deprotection of one diastereoisomer of the acetonide was attempted (Scheme 5.24). Acetonide 306 (50 mg) was treated with aqueous HCl (37\%) in hexane. After 4 h, triol 311 was afforded in 40\% yield (Table 5.7, entry 1). Unfortunately, all the attempts to remove the acetonide on a bigger scale failed to give one isomer, using different conditions (Table 5.7, entries 2 and 3).\textsuperscript{167} The one isomer of acetonide 306 gave two inseparable isomers of the triol 311 in varied yield (entries 2 and 3). This epimerisation could be due to the reversibility of the formation of the cyanohydrin compound in an acidic medium. The reaction was repeated using THF with aqueous HCl (1 M) but gave two diastereoisomers (entry 4),\textsuperscript{168} based on the \textit{^1H} NMR spectra of the crude product. Other attempts were made using TFA/water in acetonitrile (entries 5-7).\textsuperscript{164} Disappointingly, two diastereoisomers were obtained as observed by \textit{^1H} NMR spectroscopy of the crude product.

\begin{align*}
\text{CN} & \quad \text{OH} \\
\text{O} & \quad \text{O} & \quad \text{CN} & \quad \text{OH} \\
\text{306} & \quad \text{311}
\end{align*}

\textbf{Scheme 5.24}
<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Acid</th>
<th>Time</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hexane</td>
<td>HCl 37%</td>
<td>4 h</td>
<td>40\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>Hexane</td>
<td>HCl 37%</td>
<td>2 h</td>
<td>30\textsuperscript{b}</td>
</tr>
<tr>
<td>3</td>
<td>Hexane</td>
<td>HCl/H\textsubscript{2}O 1:1</td>
<td>6 h</td>
<td>55\textsuperscript{b}</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>HCl 1 M</td>
<td>4 h</td>
<td>-\textsuperscript{c}</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>TFA/H\textsubscript{2}O 5:1</td>
<td>1.5 h at 0 °C</td>
<td>-\textsuperscript{c}</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>TFA/H\textsubscript{2}O 5:1</td>
<td>3 h at rt</td>
<td>-\textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>MeCN</td>
<td>TFA/H\textsubscript{2}O 1:2</td>
<td>4 h at rt</td>
<td>-\textsuperscript{c}</td>
</tr>
</tbody>
</table>

\textsuperscript{a} one isomer after purification, \textsuperscript{b} two isomers dr 1:1 after purification, \textsuperscript{c} dr 1:1 crude product

Table 5.7

Next, the inseparable mixture of the triol-nitrile was to be subjected to a chlorination reaction to give chloro-compound 312. Using the earlier conditions trichloroacetonitrile (1.0 equivalent) was added to a mixture of triol 311 and triphenylphosphine (1.0 equivalent) in CH\textsubscript{2}Cl\textsubscript{2} (Scheme 5.25). The TLC analysis showed that the starting material was consumed but many new spots appeared. No identifiable product was detected by \textsuperscript{1}H NMR spectroscopy or LC/mass spectrometry.

![Scheme 5.25](image)

We hypothesised that changing to a different protecting group, which would require non-acidic conditions to be removed later, would be a good idea to control the epimerisation. Therefore, using the same conditions as used for compound 293, aldehyde 299 was treated with TMSCN and catalytic KCN/[18-crown-6] complex at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for 16 h. Dichloromethane was then added followed by anisaldehyde dimethyl acetal 313 with CSA. The mixture reaction was then left for 16 h before adding
triethylamine (Scheme 5.26). Unfortunately, no products were detected and the reaction generated an inseparable mixture of products which was difficult to purify.

\[
\begin{align*}
\text{CHO} & \quad \text{TMSCN (1.2 equiv.), KCN (0.02 equiv.), 18-crown-6 (0.02 equiv.), 4 h at rt then CSA, CH}_2\text{Cl}_2, 16 \text{ h then Et}_2\text{N} \\
299 & \quad \text{314}
\end{align*}
\]

Scheme 5.26

Alternatively, to avoid the epimerisation issue, we planned to reduce the nitrile group to an aldehyde group and then protect with a dithiane to give 315 (Scheme 5.27). Removal of the acetonide would then give diol 316, which could undergo a chlorination reaction. Subsequent dithiane removal would then form the aldehyde 317. The free hydroxyl group in alcohol 306 could be protected with a benzyl ether, which was assumed to be stable during the acetonide removal in acidic conditions.

\[
\begin{align*}
\text{306} & \quad \rightarrow \quad \text{294} \\
& \quad \rightarrow \quad \text{315} \\
& \quad \downarrow \\
\text{318} & \quad \rightarrow \quad \text{317} \\
& \quad \rightarrow \quad \text{316}
\end{align*}
\]

Scheme 5.27

To begin with, a mixture of PMBCl and alcohol 306 in THF was added to a solution of sodium hydride in DMF at −78 °C. The reaction mixture was allowed to warm to
room temperature overnight. The desired compound was obtained in good yield (Scheme 5.28).

![Scheme 5.28](image)

The next step was the conversion of the nitrile 319 to the corresponding aldehyde 320. As mentioned previously in chapter 4, this type of reaction proceeded smoothly via DIBAL-H reduction. Therefore, DIBAL-H (1.5 equiv.) was added to nitrile 319 in CH$_2$Cl$_2$ at $-78 \ ^\circ$C, but unfortunately only starting material was recovered (Scheme 5.29). The reaction was repeated many times using different equivalents of DIBAL-H and temperatures, but only starting material was detected.

![Scheme 5.29](image)

The result of this was clearly disappointing. A study by Kim$^{169}$ reported that a cyclic nitrile showed resistance towards reduction and gave a low yield of the corresponding aldehyde. Carreira and co-workers suggested modified conditions through the use of an ate complex formed from DIBAL-H and $n$-BuLi to reduce the acetonide 321 (Scheme 5.30).$^{170}$
Therefore, this complex was reacted with nitrile 319 at 0 °C and room temperature (Scheme 5.31). We were disappointed that only the starting material was recovered.

The nitrile is probably too sterically hindered to react. Though we had difficulty in the synthesis of aldehyde 320, we still thought that it was worth trying to prepare the key aldehyde to accomplish the aim. So an alternative strategy was devised.

5.5.2 Second strategy
In conjunction with a Masters student (Mr James Lyons), we investigated the steps given in Scheme 5.32. In a slightly different strategy, we designed a new route towards the synthesis of the key aldehyde 328. The chemistry starts with Roche ester and its conversion to the aldehyde 323. Hoppe reported the formation of lithiated carbamates that can be subsequently alkylated. So, we considered using similar chemistry in which the aldehyde 323 can react with lithiated carbamate 332 to create alcohol 324. Oxidation followed by a cyanation reaction would form nitrile 326.
The next step is to remove the $O$-protecting silyl (R) group, then chlorination to form 327. Reduction of nitrile 327 would produce the key aldehyde 328. At this point, we would be able to test the cycloaddition reaction.

To predict the stereoselectivity after the cyanation reaction of the carbonyl group with an adjacent sterogenic centre, the Felkin-Ahn model was used. Thus, the Newman projection of 323 shows that the model deduces the orientation of attack from either side of the alkene group gives the same stereoisomer (Figure 5.10).
To start this sequence, Roche ester was treated with TBSCl to give the protected ester 330 in quantitative yield, following the earlier method. This underwent a DIBAL-H (1.05 equiv.) reduction to afford aldehyde 331 in good yield (Scheme 5.33).

The next step was to treat the aldehyde 331 with the carbamate 332. In order to do this, compound 332 was prepared via reaction of 4-penten-1-ol 303 with CbCl and Et3N in dichloromethane. The mixture was heated at reflux for 24 h to afford compound 332 in 95% yield (Scheme 5.34). Alternatively, this was prepared by microwave irradiation over 1 h at 150 °C to give the desired product in 63% yield. The second method was quicker but only allowed reaction on a small scale and so the first method was used.

Hoppe and co-workers were the first to report high enantioselectivities using s-BuLi and (-)-sparteine in a lithiation of alkyl carbamates. Aggarwal and co-workers have done extensive research on the lithiation of carbamates. Therefore, lithiation of the alkyl carbamate 332 was carried out in-situ using s-BuLi and a diamine in diethyl ether, to afford intermediate 333. Organolithium chemistry can be affected very much by chiral ligands due to the ligand’s ability to transfer chirality to the substrate. Using a chiral diamine, such as sparteine, the lithiation could proceed with high stereoselectivity, leading to a stereoselective reaction of aldehyde 332 to
form intermediate 335. However, to prove the concept, we decided to use achiral, inexpensive TMEDA instead, to find suitable conditions (Scheme 5.35).

![Scheme 5.35](image)

Thus, carbamate 332 was lithiated with s-BuLi (1.5 equiv.) and TMEDA (1.5 equiv.) at $-78 \, ^\circ\text{C}$ over 6 h (Scheme 5.36). Subsequently compound 331 (1.2 equiv.) was added and the mixture was allowed to warm to room temperature. Unfortunately, this reaction was unsuccessful producing a mixture of unidentifiable products while no desired product was detected.

![Scheme 5.36](image)

The reaction was repeated again, and the lithiation time was reduced to 1 h instead of 6 h. We were disappointed that after purification, the $^1\text{H}$ NMR spectra showed the product was present but in very low yield and there was not enough for any meaningful analysis.

To understand the failure of the reaction two things were explored; the lithiation step and the coupling step choosing a different electrophile. Firstly, monitoring the lithiation by *in-situ* ReactIR spectroscopy would provide information about the time that the reaction takes to occur, depending on the carbonyl stretch in the carbamate group. The lithiation will change the frequency of the C=O bond, due to the coordination between the oxygen and lithium (Scheme 5.37). Thus, s-BuLi (1.2 equiv.) was added to the carbamate compound 332 at $-78 \, ^\circ\text{C}$, while monitoring by ReactIR spectroscopy (Figure 5.11). The ReactIR trace shows that the deprotonation
was completed within a few minutes, and only 60% of the carbamate was being deprotonated. After that the lithiated carbamate 335 was not stable enough and started slowly decomposing.

\[
\begin{align*}
\text{N} & \text{O} \quad \text{O} \quad \text{O} \\
332 & \quad \text{s-BuLi} & \quad 335
\end{align*}
\]

**Scheme 5.37**

![Figure 5.11](image)

Based on the ReactIR study, we thought that increasing the number of equivalents of s-BuLi and shortening the lithiation time would form the product. So, we started by premixing the s-BuLi (1.5 equiv.) and the TMEDA (1.5 equiv.), then after 10 min the aldehyde 331 was added. This gave the product 334 in 8% yield as a mixture of isomers (Scheme 5.38). The reaction was repeated using s-BuLi (2.0 equiv.) with a 5 min deprotonation time. This resulted in a 7% yield of product. In both cases the \(^1\)H NMR spectrum showed two diastereoisomers. As a result, increasing the number of equivalents showed no affect on the yield.
We wondered whether a different electrophile such as ester \( 330 \) would give the ketone \( 335 \), as this could save two steps, the reduction of ester \( 330 \) and oxidation of alcohol \( 334 \). Despite the lack of literature precedent, the reaction was attempted. The ester \( 330 \) was added to a premixed solution of \( s\text{-BuLi} \) (1.5 equiv.) and TMEDA (1.5 equiv.), however, no product was observed (Scheme 5.39).

This outcome was disappointing and we postulate that after lithiation, the lithiated carbamate \( 333 \), may not be sufficiently reactive. To explore this, a study using deuterium oxide as the quench was set up in order to test the lithiation. Two reactions were tested with different lithiation times, using 1.5 equivalents of \( s\text{-BuLi} \) and TMEDA. After 10 minutes, the first reaction was quenched with D\(_2\)O, and the second one was quenched after 30 minutes (Scheme 5.40).
The products were then analysed by comparing the integration of the \(^1\)H NMR spectra to the integration of the starting material. Thus, in the complete deuteration, the integration of the CHD in compound 336 should be half compared to the CH\(_2\) in compound 332. The \(^1\)H NMR spectra showed that after 10 minutes lithiation time the carbamate integration is about 60\%, whilst after 30 minutes lithiation time, it was less than 10\%.

O’Brien and co-workers have investigated the use of a variety of diamines and solvents, and they have explored the effect of these on the yield of the reaction.\(^{177}\) The study showed that the diamine can affect both yield and enantioselectivity for the chiral amine and proposed that careful consideration be placed into reaction conditions. Based on this, the reaction of carbamate 332 and aldehyde 331 was tried again, and (+)-sparteine was used instead of TMEDA. The chiral amine (–)-sparteine is the ligand that is expected to afford the correct isomer for our product,\(^{178}\) but for availability reasons (+)-sparteine was used instead. Therefore, to a mixture of carbamate 332 and (+)-sparteine (1.5 equiv.) was added s-BuLi (1.5 equiv.). After 10 min, aldehyde 331 was added, and upon purification the alcohol 334 was obtained in 13\% yield as a single isomer (Scheme 5.41). The stereochemistry was predicted based on the Felkin-Ahn model (Figure 2.5).

\[ \text{Scheme 5.41}^{171} \]

Aggarwal and co-workers investigated the lithiation of secondary alkyl carbamates, using a different protecting/activating group and the solvent cyclopentenyl methyl ether (CPME).\(^{179}\) It was envisioned that the reported conditions could be used with our carbamate 332. Therefore, to a mixture of carbamate 332 and TMEDA (6.0 equiv.) in CPME, s-BuLi (1.6 equiv.) was added at –60 °C. After 1 h, aldehyde 331 was added dropwise (Scheme 5.42). Unfortunately, only a complex mixture of
products was obtained based on TLC analysis and $^1$H NMR spectroscopy of the crude product.

![Scheme 5.42]

In the same paper it was reported that using 2,4,6-triisopropylbenzoic acid (TIB) as a protecting/activating group could lead to a positive result. Alcohol 303 was treated with triphenylphosphine, triisopropylbenzoic acid and DIAD in THF to give the protected alcohol 337 in 95% yield (Scheme 5.43).

![Scheme 5.43]

Compound 337 and TMEDA (6.0 equiv.) were treated with $s$-BuLi (1.6 equiv.) at $-60 \, ^\circ\text{C}$ in CPME. After 1 h, aldehyde 331 was added dropwise and the mixture was left for 5 h (Scheme 5.44). Disappointingly no desired product was obtained.

![Scheme 5.44]
5.6 Conclusion

This project has concluded with the successful synthesis of nitrile 319 in good yield. The aims of this project were not fully met, but some problems have been solved, such as acetonide alkylation. Although solutions to some problems have not been solved, most notably verifying the stereochemistry of alcohol 319, and acetonide removal without epimerisation.

The reduction of nitrile 319 to the correspond aldehyde failed to proceed using DIBAL-H with and without the addition of n-BuLi.

An alternative strategy using Hoppe-like lithiation and electrophilic addition gave a low yield with both TMEDA and (+)-sparteine.

This project has a very wide scope for future work; it is obvious that the synthesis of 318 should be completed, ideally by using the cascade precursor 317. Once the cascade reaction has been completed, full crystal analysis needs to be undertaken to verify that 317 or 318 has been synthesised with the correct stereochemistry upon which the proposed biosynthetic pinacol rearrangement can be tested.
Chapter 6  Experimental

6.1 General
All reagents were obtained from commercial suppliers and were used without further purification unless otherwise specified. CH$_2$Cl$_2$, DMF, Et$_2$O and THF were obtained from Grubbs dry solvent system (model: SPS-200-6). Petrol refers to the fractions that boil between 40 to 60 °C and oxalyl chloride was freshly distilled before use. Acetone was dried over CaH$_2$ and degassed. Thin layer chromatography was performed on Macherey-nagel-Alugram Sil G/UV 254 silica plates and visualized by U.V. irradiation at 254 nm, by staining with alkaline KMnO$_4$ or Brady’s Reagent. $^1$H NMR spectra were recorded on either a Bruker AC400 (400 MHz), Bruker AV3HD400 (400 MHz) or Bruker AC500 (500 MHz) instrument. Chemical Shifts (δ) are reported in ppm and coupling constants (J values) are quoted to one decimal place with values in Hertz (Hz) and were corrected. NMR peak multiplicities are given the abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sex = sextet, m = multiplet, br = broad. $^{13}$C NMR spectra were recorded on the above Bruker instrument at 101 MHz. Low and high resolution (accurate mass) mass spectra were recorded on a Micromass Autospec for Electron Impact (EI) and on a Walters LCT instrument for Electro-Spray (ES/ESI). Infra-red spectra were recorded on a Perkin Elmer Spectrum RX Fourier Transform-IR system. Only selected peaks are reported and absorption maxima are given in cm$^{-1}$. Crystals were obtained by recrystallising the compound in hexane/CH$_2$Cl$_2$ and X-ray data was measured on a Bruker Smart CCD area detector with Oxford Cryosystems low temperature system. Melting points were recorded on a Gallenkamp hot stage and were uncorrected.
6.2 Experimental procedures

**Methyl 2-phenyl-3-hydroxyprop-2-enoate 106**

To a mixture of ester 104 (2.0 g, 13.3 mmol) and methylformate 105 (2.4 g, 40 mmol) in CH₂Cl₂ (27 mL) was added TiCl₄ (5.0 g, 26.6 mmol) dropwise, followed by addition of Et₃N (4.4 mL, 32 mmol) dropwise at 0 °C. After 1 h, the mixture allowed to warm to room temperature. After 2 h, water (15 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL), the organic layers were combined and washed with brine (20 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the ester 106 (1.5 g, 8.6 mmol, 65%) as an oil; Rₕ 0.45 [petrol–EtOAc (9:1)]; ¹H NMR (400 MHz, CDCl₃) δ = 12.05 (1H, d, J 1.5 Hz, CH), 7.38–7.26 (6H, m, ArH and CH), 3.83 (3H, s, CH₃O). Data consistent with the literature.⁶⁷

**Methyl 3-(allyloxy)-2-phenylacrylate 108**

To a stirred solution of aldehyde 106 (500 mg, 2.8 mmol) in dry acetone (9 mL) was added potassium carbonate (0.77 g, 5.6 mmol) followed by allyl bromide (1.7 g, 14 mmol) at room temperature. After 45 min at 50 °C, the mixture was cooled to room temperature, was diluted with CH₂Cl₂ (20 mL) and was filtered. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave two separable isomers 108;

Data for isomer 108a (367 mg, 1.8 mmol, 60%) as an oil; Rₕ 0.48 [petrol–EtOAc (9:1)]; ¹H NMR (400 MHz, CDCl₃) δ = 7.64 (1H, s, CH), 7.38–7.37 (4H, m, ArH), 7.30–7.28 (1H, m, ArH), 5.98–5.90 (1H, m, CH=CH₂), 5.38–5.31 (2H, m, CH₂=CH), 4.55–4.52 (2H, m, CH₂), 3.76 (3H, s, CH₃O); ¹³C NMR (101 MHz, CDCl₃) δ = 168.2
(C=O), 157.9 (CH), 132.6 (C), 132.4 (CH), 130.2 (CH), 127.8 (CH), 127.1 (CH), 118.9 (CH₂), 111.8 (C), 75.0 (CH₂), 51.6 (CH₃); HRMS m/z (ES) Found: MH⁺, 219.1017, C₁₃H₁₅O₃ requires MH⁺, 219.1021; LRMS m/z (ES) 219 (MH⁺, 100%).

Data for isomer 108b (184 mg, 0.85 mmol, 30%) as an oil; Rf 0.34 [petrol–EtOAc (9:1)]; ¹H NMR (400 MHz, CDCl₃) δ = 7.34–7.33 (2H, m, ArH), 7.30–7.27 (3H, m, ArH), 6.75 (1H, s, CH), 6.06–5.97 (1H, m, CH=CH₂), 5.47–5.33 (2H, m, CH₂=CH), 4.58–4.54 (2H, m, CH₂), 3.79 (1H, s, CH₃O); ¹³C NMR (101 MHz, CDCl₃) δ = 166.4 (C=O), 156.1 (CH), 135.6 (C), 132.6 (CH), 129.0 (CH), 128.2 (CH), 127.0 (CH), 119.2 (CH₂), 112.5 (C), 75.3 (CH₂), 51.6 (CH₃); HRMS m/z (ES) Found: MH⁺, 219.1005, C₁₃H₁₅O₃ requires MH⁺, 219.1021; LRMS m/z (ES) 219 (MH⁺, 100%).

Methyl 2-phenylhex-5-enoate 109

⁴Butyllithium (9.15 mL, 22 mmol, 2.4 M solution in hexanes) was added to freshly distilled diisopropylamine (3.0 mL, 22 mmol) in THF (40 mL) at −78 °C. After 30 min, methyl phenylacetate 104 (3.0 g, 20 mmol) was added dropwise over 10 min. After 1 h, DMPU (5 mL) was added. After 10 min, 3-bromo-1-butene (2.98 g, 24 mmol) was added. The mixture was allowed to warm to room temperature over 16 h, then saturated aqueous NH₄Cl (15 mL) and brine (15 mL) were added. The mixture was extracted with Et₂O (3 × 15 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:8:0.2), gave the ester 109 (2.75 g, 13.5 mmol, 67%) as an oil; Rf 0.3 [petrol–EtOAc (9.8:0.2)]; IR ʋmax(film)/cm⁻¹ 2950 (C–H), 1730 (C=O), 1430 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 7.37–7.26 (5H, m, ArH), 5.80 (1H, ddt, J 17.0, 10.0, 6.5 Hz, CH=CH₂), 5.05–4.99 (2H, m, CH₂=CH), 3.67 (3H, s, CH₃O), 3.56 (1H, t, J 7.5 Hz, CH), 2.24–2.10 (1H, m, CH), 2.07–2.00 (2H, m, 2 × CH), 1.93–1.85 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 174.4 (C=O), 138.9 (C), 137.5 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 115.4 (CH₂), 51.9 (CH), 50.7 (CH₃), 32.5 (CH₂), 31.5
(CH₂); HRMS m/z (ES) Found: MH⁺, 205.1217, C₁₃H₁₇O₂ requires MH⁺, 205.1223; LRMS m/z (ES) 205 (MH⁺, 100%).

**Methyl 2-(hydroxymethyl)-2-phenylhex-5-enoate 111**

![Methyl 2-(hydroxymethyl)-2-phenylhex-5-enoate 111](image)

To freshly distilled diisopropylamine (1.13 mL, 8.04 mmol) in THF (20 mL) was added n-butyllithium (3.22 mL, 8.04 mmol, 2.5 M solution in hexanes) at −78 °C. After 30 min, ester 109 (1.5 g, 7.3 mmol) was added dropwise over 10 min. After 30 min, the mixture was warmed to −20 °C and paraformaldehyde (220 mg, 7.3 mmol) in THF (2 mL) was added and the mixture was stirred for 1 h. Additional paraformaldehyde (220 mg, 7.3 mmol) was added and the mixture was allowed to warm to room temperature over 1 h, then saturated aqueous NH₄Cl (15 mL) and brine (15 mL) were added. The mixture was extracted with Et₂O (3 × 15 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the alcohol 111 (1.1 g, 4.70 mmol, 65%) as an oil; Rf 0.27 [petrol–EtOAc (4:1)]; IR ν_max(film)/cm⁻¹ 3460 (br. OH), 2950 (C‒H), 1720 (C=O), 1430 (C‒H); ¹H NMR (400 MHz, CDCl₃) δ = 7.36–7.34 (2H, m, ArH), 7.32–7.30 (1H, m, ArH), 7.29–7.26 (2H, m, ArH), 5.84 (1H, ddt, J 17.0, 10.5, 6.5 Hz, CH=CH₂), 5.08–4.98 (2H, m, CH₂=CH), 4.10 (1H, dd, J 11.5, 7.5 Hz, CH), 3.99 (1H, dd, J 11.5, 6.0 Hz, CH), 3.76 (3H, s, CH₃O), 2.28–2.07 (3H, m, 3 × CH and OH), 2.05–1.95 (1H, m, CH); ¹³C NMR (400 MHz, CDCl₃) δ = 175.7 (C=O), 139.7 (C), 138.0 (CH), 128.6 (CH), 127.3 (CH), 126.4 (CH), 114.8 (CH₂), 66.7 (CH₂), 55.9 (C), 52.2 (CH₃), 32.9 (CH₂), 28.9 (CH₂); HRMS m/z (ES) Found: MH⁺, 235.1331, C₁₄H₁₈O₃ requires MH⁺, 235.1329; LRMS m/z (ES) 235 (MH⁺, 100%).
Methyl 2-formyl-2-phenylhex-5-enolate 110

\[\text{MeO}_2C\text{CHO} \quad \text{Ph} \]

DMSO (0.65 mL, 9.2 mmol) was added to a solution of freshly distilled oxalyl chloride (0.40 mL, 4.6 mmol) in CH₂Cl₂ (15 mL) at −60 °C. After 5 min, the alcohol 111 (980 mg, 4.19 mmol) was added dropwise over 10 min. After 30 min, Et₃N (2.93 mL, 20.9 mmol) was added. After 10 min, the mixture was allowed to warm to room temperature. Water (10 mL), aqueous HCl (10 mL, 1 M), and aqueous saturated Na₂CO₃ (10 mL) were added, the mixture was extracted with CH₂Cl₂ (3 × 20 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the aldehyde 110 (750 mg, 3.25 mmol, 77%) as an oil; Rf 0.43 [petrol–EtOAc (9.2:0.8)]; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2955 (C–H), 1720 (C=O), 1430 (C–H); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta = 9.95\) (1H, s, CHO), 7.44–7.33 (3H, m, ArH), 7.24–7.21 (2H, m, ArH), 5.82 (1H, ddt, J 17.0, 10.5, 6.5 Hz, \(\text{CH=CH}_2\)), 5.08–4.97 (2H, m, \(\text{CH}_2=\text{CH}\)), 3.85 (3H, s, CH₃O), 2.47–2.39 (1H, m, CH), 2.26–2.18 (1H, m, CH), 2.17–2.07 (1H, m, CH), 1.97–1.87 (1H, m, CH); \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta = 196.5\) (C=O), 171.6 (C=O), 137.6 (CH), 135.3 (C), 129.2 (CH), 128.2 (CH), 127.3 (CH), 115.2 (CH₂), 65.7 (C), 52.6 (CH₃), 31.6 (CH₂), 29.3 (CH₂); HRMS \(m/z\) (ES) Found: MH⁺, 233.1164, C₁₄H₁₇O₃ requires MH⁺, 233.1172; LRMS \(m/z\) (ES) 233 (MH⁺, 100%).

\((\pm)-(3\text{a}R,6\text{R},6\text{a}R)\)-Methyl 1-methyl-6-phenylhexahydro-1H-cyclopenta[c]isoazazole-6-carboxylate 112a and \((\pm)-(3\text{a}S,6\text{R},6\text{a}R)\)-Methyl 1-methyl-6-phenylhexahydro-1H-cyclopenta[c]isoazazole-6-carboxylate 112b

\[\begin{align*}
\text{MeO}_2C \quad \text{Ph} \quad \text{H} \quad \text{Me} \\
\text{H} \quad \text{N} \quad \text{O} \\
112a \\
\end{align*}\]

\[\begin{align*}
\text{MeO}_2C \quad \text{Ph} \quad \text{H} \quad \text{Me} \\
\text{H} \quad \text{N} \quad \text{O} \\
112b \\
\end{align*}\]

The aldehyde 110 (100 mg, 0.43 mmol), N-methylhydroxylamine hydrochloride (45 mg, 0.52 mmol) and diisopropylethylamine (0.18 mL, 1.03 mmol) in toluene (4 mL)
was heated at 110 °C. After 2 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:3), gave the cycloadduct 112a (35.5 mg, 0.14 mmol, 32%) as a solid and the cycloadduct 112b (60 mg, 0.23 mmol, 54%) as a solid. These were each recrystallized from CH₂Cl₂/hexane (1:1) to give needles.

Data for cycloadduct 112a: m.p. 90–92.5 °C; Rf 0.43 [petrol–EtOAc (7:3)]; IR νmax(film)/cm⁻¹ 2955 (C–H), 1720 (C=O), 1445 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 7.35–7.27 (5H, m, ArH), 4.17 (1H, dd, J 8.5, 7.5 Hz, CH), 3.91 (1H, dd, J 7.0, 1.0 Hz, CH), 3.66 (3H, s, CH₃O), 3.51 (1H, dd, J 8.5, 4.5 Hz, CH), 3.31–3.23 (1H, m, CH), 2.57–2.48 (1H, m, CH), 2.42–2.36 (1H, m, CH), 2.23 (3H, s, CH₃), 1.71–1.65 (2H, m, 2 × CH); ¹³C NMR (101 MHz, CDCl₃) δ = 175.5 (C=O), 138.2 (C), 128.4 (CH), 127.4 (CH), 127.2 (CH), 78.1 (CH), 72.4 (CH₂), 62.7 (C), 52.5 (CH₃), 48.0 (CH₃), 45.5 (CH), 31.1 (CH₂), 29.0 (CH₂); HRMS m/z (ES) Found: MH⁺, 262.1434, C₁₅H₂₀NO₃ requires MH⁺, 262.1438; LRMS m/z (ES) 262 (MH⁺, 100%).

Data for cycloadduct 112b: m.p. 96–98.5 °C; Rf 0.39 [petrol–EtOAc (7:3)]; IR νmax(film)/cm⁻¹ 2955 (C–H), 1735 (C=O), 1445 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 7.38–7.26 (5H, m, ArH), 4.20 (1H, dd, J 9.0, 6.0 Hz, CH), 3.91 (1H, d, J 8.0 Hz, CH), 3.73 (1H, dd, J 9.0, 2.0 Hz, CH), 3.68 (3H, s, CH₃O), 3.21–3.15 (1H, m, CH), 2.76 (3H, s, CH₃), 2.59 (1H, dt, J 13.0, 10.0 Hz, CH), 2.07 (1H, dd, J 13.0, 6.0 Hz, CH), 1.67–1.32 (2H, m, 2 × CH); ¹³C NMR (101 MHz, CDCl₃) δ = 173.8 (C=O), 140.8 (C), 128.6 (CH), 127.1 (CH), 126.2 (CH), 78.4 (CH), 72.4 (CH₂), 63.6 (C), 51.9 (CH₃), 47.8 (CH), 45.6 (CH₃), 34.5 (CH₂), 29.3 (CH₂); HRMS m/z (ES) Found: MH⁺, 262.1432, C₁₅H₂₀NO₃ requires MH⁺, 262.1438; LRMS m/z (ES) 262 (MH⁺, 100%).
Methyl 2-phenylhept-6-enoate 114

In the same way as the ester 109, n-butyllithium (9.15 mL, 22 mmol, 2.4 M solution in hexanes), diisopropylamine (3.0 mL, 22 mmol), methyl phenylacetate 104 (3.0 g, 20 mmol), DMPU (5 mL), and 4-bromo-1-pentene (3.57 g, 24 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the ester 114 (3.0 g, 13.8 mmol, 69%) as an oil; R_f 0.25 [petrol–EtOAc (9.8:0.2)]; IR ν_max(film)/cm⁻¹ 2945 (C–H), 1735 (C=O), 1430 (C–H); ^1H NMR (400 MHz, CDCl₃) δ = 7.36–7.26 (5H, m, ArH), 5.78 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.03–4.94 (2H, m, CH₂=CH), 3.67 (3H, s, CH₃O), 3.56 (1H, t, J 8.0 Hz, CH), 2.15–2.05 (3H, m, 3 × CH), 1.86–1.76 (1H, m, CH), 1.46–1.28 (2H, m, 2 × CH); ^13C NMR (101 MHz, CDCl₃) δ = 174.5 (C=O), 139.2 (C), 138.3 (CH), 128.6 (CH), 127.9 (CH), 127.2 (CH), 114.8 (CH₂), 51.9 (CH), 51.5 (CH₃), 33.5 (CH₂), 33.0 (CH₂), 26.8 (CH₂); HRMS m/z (ES) Found: M⁺, 219.1367, C₁₄H₁₈O₂ requires M⁺, 219.1380; LRMS m/z (ES) 159 (45%), 219 (M⁺, 100%).

Methyl 2-(hydroxymethyl)-2-phenylhept-6-enoate 115

In the same way as the ester 111, n-butyllithium (12.6 mL, 5.04 mmol, 2.5 M solution in hexanes), diisopropylamine (0.70 mL, 5.04 mmol), ester 114 (1.0 g, 4.6 mmol), and paraformaldehyde (270 mg, 9.2 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the ester 115 (750 mg, 3.02 mmol, 66%) as an oil; R_f 0.27 [petrol–EtOAc (4:1)]; IR ν_max(film)/cm⁻¹ 3455 (br. OH), 2955 (C–H), 1720 (C=O), 1435 (C–H); ^1H NMR (400 MHz, CDCl₃) δ = 7.39–7.35 (2H, m, ArH), 7.31–7.25 (3H, m, ArH), 5.80 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.06–4.96 (2H, m, CH₂=CH), 4.07 (1H, dd, J 11.5, 8.0 Hz, CH), 3.98 (1H, dd, J 11.5, 6.0 Hz, CH), 3.75 (3H, s, CH₃O), 2.19–2.00 (4H, m, 4 × CH and OH), 1.53–1.41 (1H, m, CH), 1.37–1.26 (1H, m, CH); ^13C NMR (101 MHz, CDCl₃)
\( \delta = 175.0 \) (C=O), 140.0 (C), 138.2 (CH), 128.6 (CH), 127.2 (CH), 126.7 (CH), 115.0 (CH\(_2\)), 66.7 (CH\(_2\)), 56.1 (C), 52.2 (CH\(_3\)), 34.1 (CH\(_2\)), 33.2 (CH\(_2\)), 23.9 (CH\(_2\)); HRMS \textit{m/z} (ES) Found: MH\(^+\), 249.1487, C\(_{15}\)H\(_{20}\)O\(_3\) requires MH\(^+\), 249.1485; LRMS \textit{m/z} (ES) 249 (MH\(^+\), 80%), 231 (100%).

**Methyl 2-formyl-2-phenyleth-6-enoate 116**

In the same way as the aldehyde 110, oxalyl chloride (0.28 mL, 3.23 mmol), DMSO (0.46 mL, 6.46 mmol), alcohol 115 (730 mg, 2.94 mmol) and Et\(_3\)N (2.05 mL, 14.7 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), the aldehyde 116 (570 mg, 2.31 mmol, 79%) as an oil; R\(_f\) 0.5 [petrol–EtOAc (9:1)]; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2950 (C–H), 1715 (C=O), 1435 (C–H); \(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta = 9.93\) (1H, s, CHO), 7.43–7.32 (3H, m, ArH), 7.23–7.20 (2H, m, ArH), 5.79 (1H, ddt, \(J = 17.0, 10.0, 7.0\) Hz, \(CH=CH\_2\)), 5.06–4.96 (2H, m, \(CH\_2=CH\)), 3.84 (3H, s, CH\(_3\)O), 2.37–2.29 (1H, m, CH), 2.16–2.07 (3H, m, 3 \times CH), 1.52–1.40 (1H, m, CH), 1.30–1.19 (1H, m, CH); \(^{13}\)C NMR (101 MHz, CDCl\(_3\) \(\delta = 196.6\) (C=O), 171.8 (C=O), 138.0 (CH), 135.5 (C), 129.1 (CH), 128.1 (CH), 127.3 (CH), 115.0 (CH\(_2\)), 65.9 (C), 52.5 (CH\(_3\)), 34.0 (CH\(_2\)), 31.8 (CH\(_2\)), 24.9 (CH\(_2\)); HRMS \textit{m/z} (ES) Found: MH\(^+\), 247.1344, C\(_{15}\)H\(_{19}\)O\(_3\) requires MH\(^+\), 247.1334; LRMS \textit{m/z} (ES) 247 (MH\(^+\), 100%).
(±)-(1RS,2RS,6RS)-Methyl 8-methyl-2-phenyl-7-oxa-8-azabicyclo[4.2.1]nonane-2-carboxylate 117a and (±)-(3aRS,7RS,7aRS)-Methyl 1-methyl-7-phenyloctahydrobenzo[c]isoxazole-7-carboxylate 117b

In the same way as the cycloadducts 112, the aldehyde 116 (100 mg, 0.40 mmol), N-methylhydroxylamine hydrochloride (40 mg, 0.48 mmol) and diisopropylethylamine (0.17 mL, 0.96 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), the cycloadducts 117a and 117b (84 mg, 0.3 mmol, 75%) as a mixture (ratio 1:2 determined by 1H NMR spectroscopy) as an oil. Cycloadduct 117a could be partially separated by crystallization using CH₂Cl₂/hexane (1:1). The remaining mixture of 117a and 117b was analysed by NMR spectroscopy and the peaks for isomer 117b could be identified as follows:

Data for cycloadduct 117a: m.p. 105–108 °C; Rf 0.15 [petrol–EtOAc (9:1)]; IR νmax(film)/cm⁻¹ 2950 (C–H), 1715 (C=O), 1445 (C–H); 1H NMR (400 MHz, CDCl₃) δ = 7.41–7.38 (2H, m, ArH), 7.35–7.30 (2H, m, ArH), 7.26–7.21 (1H, m, ArH), 4.66 (1H, dd, J 9.0, 4.0 Hz, CH), 3.88 (1H, dd, J 8.0, 1.5 Hz, CH), 3.68 (3H, s, CH₃O), 2.74 (1H, dt, J 13.5, 9.0 Hz, CH), 2.54–2.47 (1H, m, CH), 2.40 (3H, s, CH₃N), 2.30–2.27 (1H, m, CH), 1.95–1.85 (1H, m, CH), 1.82–1.73 (1H, m, CH), 1.63–1.56 (2H, m, 2 × CH), 1.53–1.41 (1H, m, CH); 13C NMR (101 MHz, CDCl₃, assignments by DEPT NMR) δ = 175.7 (C=O), 142.4 (C), 128.3 (CH), 126.7 (CH), 126.5 (CH), 77.3 (CH), 72.7 (CH), 58.0 (C), 52.1 (CH₃), 47.6 (CH₃), 33.3 (CH₂), 32.1 (CH₂), 29.0 (CH₂), 20.5 (CH₂); HRMS m/z (ES) Found: MH⁺, 276.1598, C₁₆H₂₂NO₃ requires MH⁺, 276.1600; LRMS m/z (ES) 276 (MH⁺, 100%).

Data for cycloadduct 117b: 1H NMR (400 MHz, CDCl₃) δ = 7.41–7.24 (5H, m, ArH), 4.06 (1H, dd, J 8.0, 3.5 Hz, CH), 3.69 (3H, s, CH₃O), 3.52 (1H, d, J 8.0 Hz, CH), 3.43 (1H, d, J 5.0 Hz, CH), 2.93–2.87 (1H, m, CH), 2.37–2.33 (1H, m, CH), 2.27–2.22 (1H, m, CH), 1.93–1.86 (1H, m, CH), 1.83 (3H, s, CH₃N), 1.77–1.72 (2H,
m, 2 × CH), 1.33–1.20 (1H, m, CH); 13C NMR (101 MHz, CDCl3, assignments by DEPT NMR) δ = 175.7 (C=O), 141.3 (C), 128.6 (CH), 127.4 (CH), 126.4 (CH), 73.2 (CH), 70.2 (CH2), 53.9 (C), 52.3 (CH3), 47.4 (CH3), 43.4 (CH), 26.7 (CH2), 25.6 (CH2), 22.0 (CH2); HRMS m/z (ES) Found: MH+, 276.1598, C16H22NO3 requires MH+, 276.1600; LRMS m/z (ES) 276 (MH+, 100%).

(E)-Dimethyl 7-formyl-7-phenyloct-2-enedioate 119

The alkene 116 (136 mg, 0.55 mmol) and methyl acrylate (0.10 mL, 1.2 mmol) in degassed CH2Cl2 (5 mL) was heated at 40 °C before adding Grubbs’ 2nd generation catalyst (23 mg, 0.03 mmol) in CH2Cl2 (3 mL) dropwise over 1 h. After 2.5 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the diester 119 (133 mg, 0.44 mmol, 80%) as an oil; Rf 0.26 [petrol–EtOAc (9:1)]; IR νmax(film)/cm−1 2950 (C–H), 1725 (C=O), 1715 (C=O), 1655 (C–H), 1435; 1H NMR (400 MHz, CDCl3) δ = 9.91 (1H, s, CHO), 7.41–7.33 (3H, m, ArH), 7.20–7.18 (2H, m, ArH), 6.94 (1H, dt, J 15.5, 7.0 Hz, CH=CH), 5.84 (1H, dt, J 15.5, 1.5 Hz, CH=CH), 3.85 (3H, s, CH3O), 3.74 (3H, s, CH3O), 2.37–2.22 (3H, m, 3 × CH), 2.15–2.08 (1H, m, CH), 1.59–1.48 (1H, m, CH), 1.36–1.25 (1H, m, CH); 13C NMR (101 MHz, CDCl3) δ = 196.3 (CHO), 171.5 (C=O), 167.0 (C=O), 148.4 (CH), 135.3 (C), 129.3 (CH), 128.2 (CH), 127.2 (CH), 121.4 (CH), 65.9 (C), 52.6 (CH3), 51.4 (CH3), 32.4 (CH2), 31.8 (CH2), 23.5 (CH2); HRMS m/z (ES) Found: MH+, 305.1380, C17H21O3 requires MH+, 305.1384; LRMS m/z (ES) 305 (MH+, 100%).
In the same way as the cycloadducts 112, the aldehyde 119 (100 mg, 0.33 mmol), N-methylhydroxylamine hydrochloride (30 mg, 0.36 mmol) and diisopropylethylamine (0.12 mL, 0.66 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:2), the cycloadducts 120a and 120b (67 mg, 0.2 mmol, 61%) as a mixture (ratio 5:1 by $^1$H NMR spectroscopy) from which isomer 120a was isolated by crystallization from CH$_2$Cl$_2$/hexane (1:1) as amorphous solid; m.p. 98–100 °C; R$_f$ 0.28 [petrol–EtOAc (7:2)]; IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 2950 (C‒H), 1750 (C=O), 1435 (C‒H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.38–7.34 (2H, m, ArH), 7.31–7.26 (3H, m, ArH), 4.13 (1H, s, CH), 3.79 (3H, s, CH$_3$O), 3.67 (3H, s, CH$_3$O), 3.57 (1H, d, $J$ 4.0 Hz, CH), 3.23–3.19 (1H, m, CH), 2.46–2.38 (1H, m, CH), 2.35–2.26 (1H, m, CH), 1.97–1.87 (5H, m, 2 × CH and CH$_3$N), 1.74–1.59 (1H, m, CH), 1.37–1.26 (1H, m, CH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 175.1 (C=O), 172.9 (C=O), 140.7 (C), 128.8 (CH), 127.7 (CH), 126.3 (CH), 80.4 (CH), 70.5 (CH), 53.2 (C), 52.4 (CH$_3$), 52.2 (CH), 48.1 (CH$_3$), 47.8 (CH$_3$), 26.9 (CH$_2$), 26.5 (CH$_2$), 22.2 (CH$_2$); HRMS m/z (ES) Found: MH$^+$, 334.1646, C$_{18}$H$_{24}$NO$_5$ requires MH$^+$, 334.1649; LRMS m/z (ES) 334 (MH$^+$, 100%).

To the cycloadducts 120a and 120b (64 mg, 0.19 mmol) (ratio 5:1) in AcOH/H$_2$O (0.6:0.8 mL) was added Zn powder (50 mg, 0.77 mmol) and the mixture was heated...
at 70 °C. After 4 h, the mixture was allowed to cool to room temperature. The zinc salts were filtered, washed with CH$_2$Cl$_2$ and the solvent was evaporated. Aqueous ammonia solution (2 mL) and CH$_2$Cl$_2$ (2 mL) were added to the residue. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 5 mL) and the organic layers were dried (MgSO$_4$) and evaporated. The residue was dissolved in methanol (5.0 mL) and sodium methoxide (31 mg, 0.58 mmol, 25 wt% MeOH) was added at room temperature. After 2.5 h, NH$_4$Cl (30 mg) was added, and the mixture was stirred for 5 min until complete dissolution was achieved. The solvent was evaporated and the mixture was purified by column chromatography on silica gel, eluting with CH$_2$Cl$_2$–MeOH–NH$_3$ (98:2:0.1), to give the lactam 123 (34 mg, 0.11 mmol, 59%) as needles after recrystallization from CH$_2$Cl$_2$–hexane (1:1); m.p. 177–180 °C; R$_f$ 0.18

[CH$_2$Cl$_2$–MeOH–NH$_3$ (98:2:0.1)]; IR $v_{\text{max}}$(film)/cm$^{-1}$ 3295 (OH), 2955 (C–H), 1725 (C=O), 1680 (C=O), 1430 (C–H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50–7.31 (5H, m, ArH), 4.48 (1H, dd, J 3.5, 1.5 Hz, CH), 4.34 (1H, d, J 6.5 Hz, CH), 3.63 (3H, s, CH$_3$O), 2.99–2.92 (1H, m, CH), 2.89 (1H, d, J 1.5 Hz, OH), 2.72–2.66 (1H, m, CH), 2.02 (3H, s, CH$_3$N), 1.96–1.90 (1H, m, CH), 1.79–1.67 (2H, m, 2 × CH), 1.32–1.27 (1H, m, CH), 1.19–1.14 (1H, m, CH); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 177.0 (C=O), 173.6 (C=O), 140.6 (C), 128.9 (CH), 127.9 (CH), 126.2 (CH), 73.0 (CH), 60.1 (CH), 52.6 (CH$_3$), 52.2 (C), 38.9 (CH), 29.9 (CH$_3$), 26.5 (CH$_2$), 21.2 (CH$_2$), 20.4 (CH$_2$); HRMS $m/z$ (ES) Found: MH$^+$, 304.1542, C$_{17}$H$_{22}$NO$_4$ requires MH$^+$, 304.1543; LRMS $m/z$ (ES) 304 (MH$^+$, 100%).

2-Allylpropane-1,3-diol 183

![2-Allylpropane-1,3-diol](image)

To a solution of LiAlH$_4$ (7.5 g, 200 mmol) in Et$_2$O (150 mL) was added a solution of diethyl allylmalonate 182 (19.7 mL, 100 mmol) in Et$_2$O (50 mL) at 0 °C. The mixture was allowed to warm to room temperature. After 16 h, aqueous sodium hydroxide (30 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite, washed with CH$_2$Cl$_2$–MeOH (9:1) (200 mL) and
the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:6), gave the diol 183 (8.2 g, 70.6 mmol, 71%) as an oil; R_f 0.16 [petrol–EtOAc (4:6)]; ¹H NMR (400 MHz, CDCl₃) δ = 5.81 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.12–5.05 (2H, m, CH₂=CH), 3.83 (2H, dd, J 10.5, 4.5 Hz, 2 × CHHO), 3.69 (2H, dd, J 10.5, 7.5 Hz, 2 × CHHO), 2.42 (2H, s, 2 × OH), 2.10–2.07 (2H, m, CH₂), 1.94–1.85 (1H, m, CH). Data consistent with the literature.¹²³

2-(Iodomethyl)pent-4-en-1-ol 184 and 185

To alcohol 183 (4.0 g, 34.5 mmol) in THF (125 mL) were added imidazole (2.35 g, 34.5 mmol) and PPh₃ (9.0 g, 34.5 mmol). After 15 min, ground iodine (9.62 g, 37.9 mmol) was added portionwise at room temperature. After 3 h, CH₂Cl₂ (75 mL) was added and the suspension was filtered through Celite, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (8:2) gave the iodide 184 (5.9 g, 26.11 mmol, 76%) as an oil; R_f 0.33 [petrol–EtOAc (8:2)]; ¹H NMR (400 MHz, CDCl₃) δ = 5.74 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.20–5.07 (2H, m, CH₂=CH), 3.74–3.53 (1H, m, CHHO), 3.56–3.51 (1H, m, CHHO), 3.39 (1H, dd, J 10.0, 5.0 Hz, CHHI), 3.29 (1H, dd, J 10.0, 6.0 Hz, CHHI), 2.19–2.04 (3H, m, 2 × CH and OH), 1.59–1.50 (1H, m, CH). Data consistent with the literature.¹²³

Data for diiodide 185: R_f 0.75 [petrol–Et₂O (8:2)]; ¹H NMR (400 MHz, CDCl₃) δ = 5.70 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.24–5.11 (2H, m, CH₂=CH), 3.40 (2H, dd, J 9.5, 4.5 Hz, 2 × CHHI), 3.25 (2H, dd, J 9.5, 6.0 Hz, 2 × CHHI), 2.23–2.17 (2H, m, CH₂), 1.55–1.40 (1H, m, CH). Data consistent with the literature.¹²³
4-(Hydroxymethyl)hept-6-enenitrile 186

![Image of 4-(Hydroxymethyl)hept-6-enenitrile 186]

To diisopropylamine (3.75 mL, 26.5 mmol) in THF (25 mL) at −78 °C was added n-BuLi (10.60 mL, 26.5 mmol, 2.5 M solution in hexanes). The mixture was stirred for 30 min, and then acetonitrile (2.77 mL, 53.1 mmol) was added dropwise. After 30 min, 184 (3.00 g, 13.3 mmol) was added. After 1 h, the mixture was allowed to warm to room temperature over 1 h, and saturated aqueous ammonium chloride (20 mL) was added. The mixture was extracted with Et₂O (3 × 25 mL). The organic layers were combined, dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (6:4), gave the nitrile 186 (1.6 g, 11.5 mmol, 87%) as an oil; Rf 0.3 [petrol–EtOAc (7:3)]; ¹H NMR (400 MHz, CDCl₃) δ = 5.76 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.11−5.04 (2H, m, CH₂=CH), 3.64−3.59 (1H, m, CHHO), 3.55−3.50 (1H, m, CHHO), 2.46−2.42 (2H, m, 2 × CH), 2.14−2.06 (3H, m, 2 × CH and OH), 1.78−1.69 (3H, m, 3 × CH). Data consistent with the literature.¹²³

4-(Bromomethyl)hept-6-enenitrile 187

![Image of 4-(Bromomethyl)hept-6-enenitrile 187]

To triphenylphosphine (1.58 g, 8.70 mmol) in CH₂Cl₂ (30 mL) was added carbon tetrabromide (2.0 g, 8.7 mmol) at room temperature. After 5 min, 186 (1.1 g, 7.9 mmol) was added. After 3 h, the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic layer was washed with H₂O (15 mL) and brine (15 mL), dried (MgSO₄), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (6:4), gave the bromide 187 (1.35 g, 6.72 mmol, 85%) as an oil; Rf 0.4 [petrol–EtOAc (8:2)]; ¹H NMR (400 MHz, CDCl₃) δ = 5.74 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.20−5.13 (2H, m, CH₂=CH), 3.64−3.59 (1H, m, CHHO), 3.48−3.47 (2H, m, CH₂Br), 2.47−2.42 (2H, m, CH₂CH=CH₂), 2.22−2.18 (2H, m, 2 ×
CH, 1.98–1.89 (1H, m, CH), 1.87–1.75 (2H, m, 2 × CH). Data consistent with the literature.\(^{123}\)

**4-(Bromomethyl)hept-6-enal 180**

![](image)

To the nitrile 187 (1.0 g, 5.0 mmol) in CH\(_2\)Cl\(_2\) (16 mL) at –78 °C was added DIBAL-H (7.5 mL, 7.5 mmol, 1.0 M solution in hexanes) dropwise. After 1.5 h, aqueous HCl (2.5 mL, 2 M) was added. After 30 min, the mixture was allowed to warm to room temperature. After 30 min, the mixture was extracted with Et\(_2\)O (20 mL). The organic layer was washed with aqueous HCl (2.5 mL, 2 M) and the aqueous portions were extracted with Et\(_2\)O (3 × 20 mL). The organic layers were dried (MgSO\(_4\)) and evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the aldehyde 180 (700 mg, 3.43 mmol, 69%) as an oil; \(R_f\) 0.28 [petrol–EtOAc (9:1)]; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 9.80\) (1H, t, \(J = 1.5\) Hz, CHO), 5.73 (1H, ddt, \(J = 17.0, 10.0, 7.0\) Hz, \(CH=CH_2\)), 5.17–5.09 (2H, m, \(CH_2=CH\)), 3.45 (2H, d, \(J = 4.5\) Hz, \(CH_2\)), 2.54–2.48 (2H, m, 2 × CH), 2.20–2.17 (2H, m, 2 × CH), 1.80–1.74 (3H, m, 3 × CH). Data consistent with the literature.\(^{123}\)

**(E)-Methyl 5-(bromomethyl)-8-oxooct-2-enoate 188**

![](image)

To alkene 180 (500 mg, 2.45 mmol) in degassed CH\(_2\)Cl\(_2\) (16 mL), was added methyl acrylate (0.5 mL, 5.4 mmol). This was heated to reflux before Grubbs’ 2nd generation catalyst (100 mg, 0.12 mmol) in CH\(_2\)Cl\(_2\) (7mL) was added dropwise. After 2.5 h, the mixture was opened up to air and was allowed to cool to room
temperature and the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8:2), gave the aldehyde 188 (430 mg, 1.64 mmol, 67%) as an oil; Rf 0.18 [petrol–EtOAc (8:2)]; IR ν\text{max}(film)/cm⁻¹ 2952 (C–H), 2862 (C–H), 1717 (C=O), 1660 (C=O); ¹H NMR (400 MHz, CDCl₃) δ = 9.80 (1H, t, J 1.4 Hz, CHO), 6.92–6.83 (1H, m, CH=CH), 5.95 (1H, dt, J 15.5, 1.4 Hz, CH=CH₂), 3.75 (3H, s, CH₃O), 3.42–3.41 (2H, m, CH₂Br), 2.60–2.45 (2H, m, 2 × CH), 2.41–2.30 (2H, m, 2 × CH), 1.93–1.86 (1H, m, CH), 1.77 (2H, q, J 7.5 Hz, CH₂); ¹³C NMR (101 MHz, CDCl₃) δ = 201.2 (C=O), 166.6 (C=O), 145.3 (CH), 123.7 (CH), 51.6 (CH₃), 40.9 (CH₂), 37.2 (CH₂), 35.2 (CH₂), 24.6 (CH₂); HRMS m/z (ES) Found: MH⁺, 263.0279, C₁₀H₁₆O₃Br requires MH⁺, 263.0283; LRMS m/z (ES) 263 (MH⁺ for ⁷⁹Br, 100%), 265 (MH⁺ for ⁸¹Br, 100%).

(±)-Methyl (1RS,5SR,6SR,7RS)-4-oxa-3-azatricyclo[4.3.1.⁰³,⁷]decane-5-carboxylate 189

To aldehyde 188 (200 mg, 0.76 mmol) in toluene (4 mL), was added hydroxylamine hydrochloride (80 mg, 1.14 mmol) and N,N–dipropylethylamine (0.34 mL, 1.9 mmol) and MgSO₄ (200 mg). The mixture was heated at 60 °C for 30 min, then heated under reflux. After 1.5 h, the mixture was cooled to room temperature, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (97:3), gave the cycloadduct 189 (26 mg, 0.12 mmol, 17%) as an oil; Rf 0.14 [CH₂Cl₂–MeOH (97:3)]; IR ν\text{max}(film)/cm⁻¹ 2945 (C–H), 1735 (C=O); ¹H NMR (400 MHz, C₆D₆) δ = 4.25 (1H, s, CH(C)), 3.49–3.46 (1H, m, CH(C)), 3.40 (3H, s, CH₃O), 3.25 (1H, dd, J 15.0, 3.0 Hz, CHA(H)), 3.00 (1H, dt, J 15.0, 3.0 Hz, CHA(H)), 2.43 (1H, dd, J 10.0, 3.0 Hz, CH(C)), 1.89–1.79 (1H, m, CH(C)), 1.49–1.42 (2H, m, 2 × CHF⁺⁺K⁺), 1.15–1.03 (3H, m, 3 × CH₂⁺⁺C⁺⁺K⁺), 0.99–0.92 (1H, m, CH(C)); ¹³C NMR (101 MHz, C₆D₆) δ = 171.0 (C), 86.5 (CH), 61.7 (CH₂), 55.6 (CH), 51.3 (CH₃), 42.3 (CH), 34.0 (CH₂), 25.5 (CH₂), 21.4 (CH), 16.3 (CH₂); HRMS m/z (ES) Found: MH⁺, 198.1122, C₁₀H₁₆NO₃ requires MH⁺, 198.1130; LRMS m/z (ES) 198 (100%).

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142
4-(Hydroxymethyl)-2,2-dimethylhept-6-enenitrile 205

Using the same method as the nitrile 186, diisopropylamine (6.20 mL, 44.25 mmol), n-butyllithium (17.70 mL, 44.25 mmol, 2.5 M solution in hexanes), isobutyronitrile (7.94 g, 88.5 mmol), and alcohol 184 (5.0 g, 22.1 mmol) gave, after purification by column chromatography, eluting with petrol–Et₂O (6:4), the nitrile 196 (3.4 g, 20.35 mmol, 92%) as an oil; R_f 0.15 [petrol–Et₂O (6:4)]; ^1H NMR (400 MHz, CDCl₃) δ = 5.81 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.14–5.08 (2H, m, CH₂=CH), 3.71 (1H, dd, J 11.0, 5.5 Hz, CH₂OH), 3.65 (1H, dd, J 11.0, 5.5 Hz, CHHO), 2.32–2.18 (2H, m, 2 × CH), 1.87–1.78 (1H, m, CH), 1.69 (1H, dd, J 14.0, 6.0 Hz, CHH), 1.58 (1H, t, J 5.5 Hz, OH), 1.47 (1H, dd, J 14.0, 5.0 Hz, CHH), 1.39 (3H, s, CH₃), 1.38 (3H, s, CH₃). Data consistent with the literature.¹²³

4-(Bromomethyl)-2,2-dimethylhept-6-enenitrile 197

To triphenylphosphine (5.64 g, 21.5 mmol) in CH₂Cl₂ (75 mL) was added carbon tetrabromide (7.10 g, 21.5 mmol) at room temperature. After 5 min, 196 (3.40 g, 19.6 mmol) was added. After 4 h, the mixture was extracted with CH₂Cl₂ (3 × 30 mL). The organic layers were washed with H₂O (20 mL) and brine (20 mL), dried (MgSO₄), filtered, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (8:2), gave the bromide 197 (4.15 g, 18.12 mmol, 93%) as an oil; R_f 0.3 [petrol–EtOAc (9:1)]; IR νmax(film)/cm⁻¹ 2970 (C−H), 2940 (C−H), 2230 (C≡N), 1725 (C=O); ^1H NMR (400 MHz, CDCl₃) δ = 5.75 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.20–5.13 (2H, m, CH₂=CH), 3.59 (1H, dd, J 10.5, 5.0 Hz, CHHBr), 3.54 (1H, dd, J 10.5, 5.0 Hz, CHH/Br), 2.37–2.25 (2H, m, 2 × CH), 2.04–1.95 (1H, m, CH), 1.75 (1H, dd, J 14.5, 6.0 Hz, CHH), 1.55 (1H, dd, J 14.5, 5.0 Hz, CHH), 1.41 (3H, s, CH₃), 1.40 (3H, s, CH₃); ^13C NMR (101
MHz, CDCl$_3$) \( \delta = 134.7 \) (CH), 125.0 (C), 118.0 (CH$_2$), 42.8 (CH$_2$), 39.0 (CH$_2$), 38.1 (CH$_2$), 36.6 (CH), 31.3 (C), 27.6 (CH$_3$), 27.4 (CH$_3$); HRMS $m/z$ (ES) Found: MH$^+$, 230.0539, C$_{10}$H$_{17}$O$^{79}$BrN requires MH$^+$, 230.0539; LRMS $m/z$ (ES), 230 (MH$^+$ for $^{79}$Br, 100%), 232 (MH$^+$ for $^{81}$Br, 98%).

4-(Bromomethyl)-2,2-dimethylhept-6-enal 198

![Chemical structure of 4-(Bromomethyl)-2,2-dimethylhept-6-enal](image)

Using the same method as the aldehyde 180, the nitrile 197 (2.00 g, 8.69 mmol) and DIBAL-H (13.04 mL, 13.04 mmol, 1 M solution in hexanes) gave, after purification by column chromatography, eluting with petrol–EtOAc (9.4:0.6), the aldehyde 198 (1.81 g, 7.82 mmol, 90%) as an oil; R$_f$ 0.4 [petrol–EtOAc (9:1)]; IR $\nu_{max}$(film)/cm$^{-1}$ 2965 (C−H), 2925 (C−H), 1727 (C=O); $^1$H NMR (400 MHz, CDCl$_3$) $\delta = 9.52$ (1H, s, CHO), 5.69 (1H, ddt, $J = 17.0$, 10.0, 7.0 Hz, CH=CH$_2$), 5.16–5.09 (2H, m, CH$_2$=CH), 3.43 (1H, dd, $J = 10.5$, 4.0 Hz, CH/Br), 3.35 (1H, dd, $J = 10.5$, 4.5 Hz, CHBr), 2.17–2.12 (2H, m, $2 \times$ CH), 1.81–1.74 (1H, m, CH), 1.74–1.70 (1H, m, CH), 1.57–1.51 (1H, m, CH), 1.11 (3H, s, CH$_3$), 1.10 (3H, s, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$, one quaternary carbon could not be observed) $\delta = 206.0$ (C=O), 135.0 (CH), 118.0 (CH$_2$), 39.7 (CH$_2$), 39.4 (CH$_2$), 38.2 (CH$_2$), 35.7 (CH), 22.2 (CH$_3$), 21.7 (CH$_3$); HRMS $m/z$ (ES) Found: M$^+$, 232.0454, C$_{10}$H$_{17}$O$^{79}$Br requires M$^+$, 232.0547; LRMS $m/z$ (ES), 232 (M$^+$ for $^{79}$Br, 100%), 234 (M$^+$ for $^{81}$Br, 95%).

(E)-Methyl 5-(bromomethyl)-7,7-dimethyl-8-oxooct-2-enoate 199

![Chemical structure of (E)-Methyl 5-(bromomethyl)-7,7-dimethyl-8-oxooct-2-enoate](image)

Using the same method as ester 188, to the aldehyde 198 (300 mg, 1.29 mmol) in degassed CH$_2$Cl$_2$ (15 mL), was added methyl acrylate (0.26 mL, 2.85 mmol). This was heated to reflux before Grubbs’ 2nd generation catalyst 118 (55 mg, 0.06 mmol) in CH$_2$Cl$_2$ (5 mL) was added dropwise. Purification by column chromatography,
eluting with petrol–Et₂O (8:2), gave the aldehyde 199 (273 mg, 0.94 mmol, 73%) as an oil; R_f 0.18 [petrol–Et₂O (8:2)]; IR ν_{max}(film)/cm⁻¹ 2960 (C–H), 2850 (C–H), 1720 (C=O), 1660 (C=C); ¹H NMR (400 MHz, CDCl₃) δ = 9.51 (1H, s, CHO), 6.88–6.80 (1H, m, CH=CH), 5.94 (1H, dt, J 15.5, 1.5 Hz, CH=CH), 3.76 (3H, s, CH₃O), 3.39 (1H, dd, J 10.5, 4.0 Hz, CHHBr), 3.32 (1H, dd, J 10.5, 5.0 Hz, CHHBr), 2.39–2.24 (2H, m, 2 × CH), 1.93–1.85 (1H, m, CH), 1.77 (1H, dd, J 15.0, 6.5 Hz, CHH), 1.53 (1H, dd, J 15.0, 5.5 Hz, CHH), 1.12 (3H, s, CH₃), 1.11 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 205.0 (C=O), 166.0 (C=O), 145.3 (CH), 123.9 (CH), 51.6 (CH₃), 45.9 (C), 39.7 (CH₂), 38.8 (CH₂), 36.5 (CH₂), 35.4 (CH), 22.4 (CH₃), 21.5 (CH₃); HRMS m/z (ES) Found: MH⁺, 291.0591, C₁₂H₂₆O₃⁷⁹Br requires MH⁺, 291.0596; LRMS m/z (ES) 291 (MH⁺ for ⁷⁹Br, 100%), 293 (MH⁺ for ⁸¹Br, 100%).

(±)-Methyl (1SR,5SR,6SR,7SR)-8,8-dimethyl-4-oxa-3-azatricyclo[4.3.1.0³,⁷]decane-5-carboxylate 200

Using the same method as cycloadduct 189, to aldehyde 199 (100 mg, 0.35 mmol) in toluene (4.0 mL), was added hydroxylamine hydrochloride (23.0 mg, 0.35 mmol) and N,N–diisopropylethylamine (0.12 mL, 0.69 mmol) and MgSO₄ (200 mg), the mixture was heated at 60 °C for 1 h, then the mixture was heated at reflux. After 3 h, the mixture was cooled to room temperature, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (97:3), gave the cycloadduct 200 (41.9 mg, 0.18 mmol, 53%) as an oil; R_f 0.20 [CH₂Cl₂–MeOH (97:3)]; IR ν_{max}(film)/cm⁻¹ 2955 (C–H), 1450 (C–H); ¹H NMR (400 MHz, C₆D₆) δ = 4.19 (1H, s, CH²), 3.42 (3H, s, CH₃O), 3.16 (1H, d, J 3.0 Hz, CH²), 3.10 (1H, ddd, J 15.0, 3.0, 1.5 Hz, CH³H), 2.81 (1H, dt, J 15.0, 3.0 Hz, CH³H), 2.56 (1H, dd, J 9.5, 3.0 Hz, CH²), 1.47–1.39 (1H, m, CH²), 1.11–1.07 (1H, m, CH²), 1.03 (3H, s, CH₃), 1.00–0.94 (1H, m, CH²), 0.93–0.91 (1H, m, CH³), 0.88–0.86 (1H, m, CH³), 0.75 (3H, s, CH₃); ¹³C NMR (101 MHz, C₆D₆) δ = 171.0 (C=O), 86.7 (CH), 66.6 (CH), 59.7 (CH₂), 51.2 (CH₃), 40.8 (CH₂), 40.3 (CH), 32.4 (CH₂), 31.1 (CH₃), 30.8 (CH₃), 25.0 (CH₂).
30.7 (CH₃), 28.5 (C), 23.1 (CH); HRMS m/z (ES) Found: MH⁺, 226.1444, C₁₂H₂₀NO₃ requires MH⁺, 226.1443; LRMS m/z (ES) 226 (100%).

‘The NMR spectra for 200 were also recorded in CDCl₃.’ ¹H NMR (400 MHz, CDCl₃) δ = 4.37 (1H, s, CH⁶), 3.75 (3H, s, CH₃O), 3.33 (1H, dd, J 15.0, 2.0 Hz, CH⁴H), 3.03 (1H, dt, J 15.0, 3.0 Hz, CH⁴H), 2.98 (1H, d, J 3.0 Hz, CH⁵D), 2.79 (1H, dd, J 10.0, 3.0 Hz, CH⁵D), 2.02–1.95 (1H, m, CH), 1.72–1.68 (1H, m, CH⁵D), 1.57–1.51 (1H, m, CH⁵D), 1.32–1.29 (2H, m, 2 × CH), 1.16 (3H, s, CH₃), 1.09 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 171.2 (C=O), 86.7 (CH), 66.5 (CH), 59.9 (CH₂), 52.2 (CH₃), 41.0 (CH₂), 40.6 (CH), 32.7 (CH₂), 31.3 (CH₃), 31.2 (CH₃), 28.8 (C), 23.2 (CH).

2-[But-2-en-1-yl]propane-1,3-diol 203

![Structure of 2-[But-2-en-1-yl]propane-1,3-diol 203](image)

To sodium hydride (1.44 g, 60 mmol) in THF (40 mL) was added diethyl malonate 201 (24.0 g, 100 mmol) at room temperature. After 15 min, the suspension was added dropwise to crotyl bromide (6.69 g, 50 mmol, E:Z 5.6:1) in THF (100 mL). After 3 h, saturated aqueous ammonium chloride (100 mL) and H₂O (100 mL) were added. The aqueous layer was extracted with Et₂O (3 × 75 mL) and the combined organic extracts were dried (MgSO₄) and the solvent was evaporated. The crude product was added dropwise to a suspension of Et₂O (50 mL) and LiAlH₄ (3.7 g, 100 mmol) at 0 °C. After 10 min, the mixture was warmed to room temperature. After 3 h, aqueous sodium hydroxide (ca. 25 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through Celite®, washed with CH₂Cl₂–MeOH (9:1) (200 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (6:4), gave the diol 203 (5.2 g, 40 mmol, 80%) as an oil as a 5.6:1 E:Z mixture; Rf 0.2 [petrol–EtOAc (1:1)]; IR νmax(film)/cm⁻¹ 3315 (O–H), 2915 (C–H), 2885 (C–H); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.57–5.37 (2H, m, 2 × CH=CH), 3.80 (2H, dd, J 10.5, 4.0 Hz, 2 × CHHOH), 3.66 (2H, dd, J 10.5, 7.5 Hz, 2 × CHHOH), 2.55 (2H, s, OH), 1.98 (2H, t, J 7.0 Hz, CH₂), 1.87–1.79 (1H, m, CH),
1.67 (3H, dd, J 6.0, 1.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 128.5 (CH), 127.2 (CH), 65.8 (CH₂), 42.2 (CH), 31.3 (CH₂), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 131.1072, C₇H₁₅O₂ requires MH⁺, 131.1070; LRMS m/z (ES) 131 (MH⁺, 60%).

2-(Iodomethyl)hex-4-en-1-ol 204

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\text{HO} \quad 1
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To diol 203 (2.00 g, 15.4 mmol) in THF (75 mL) was added imidazole (1.04 g, 15.4 mmol) and PPh₃ (4.00 g, 15.4 mmol) at room temperature. After 15 min, ground iodine (4.29 g, 16.9 mmol) was added portionwise. After 3 h, CH₂Cl₂ (50 mL) was added and the suspension was filtered through Celite®, and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et₂O (4:1), gave iodide 204 (2.76 g, 11.50 mmol, 72%) as an oil as a 5.6:1 E:Z mixture; Rf 0.4 [petrol–Et₂O (3:2)]; IR νmax(film)/cm⁻¹ 3328 (OH), 2961 (C–H), 1434 (C–H); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.57−5.50 (1H, m, CH=CH), 5.38−5.30 (1H, m, CH=CH), 3.62 (1H, dd, J 11.0, 5.0 Hz, CHH), 3.50 (1H, dd, J 11.0, 7.0 Hz, CHH), 3.36 (1H, dd, J 10.0, 5.0 Hz, CHH), 3.27 (1H, dd, J 10.0, 5.5 Hz, CHH), 2.36 (1H, br. s, OH), 2.11−1.97 (2H, m, 2 × CH), 1.66 (3H, dd, J 6.5, 1.5 Hz, CH₃), 1.53−1.48 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 128.0 (CH), 127.5 (CH), 65.1 (CH₂), 41.7 (CH), 34.2 (CH₂), 18.0 (CH₃), 11.7 (CH₂); HRMS m/z (ES) Found: M⁺, 240.0003, C₇H₁₅IO requires M⁺, 240.0011; LRMS m/z (ES) 240 (M⁺, 17%), 95 (100%) .
3-(Hydroxymethyl)-2,2-dimethylhept-5-enenitrile 205

To diisopropylamine (1.4 mL, 7.5 mmol) in THF (6.5 mL) at –78 °C was added n-BuLi (3.0 mL, 7.5 mmol, 2.5 M solution in hexanes). The mixture was stirred for 30 min, and then isobutyronitrile (1.10 g, 15.0 mmol) was added dropwise. After 30 min, iodide 204 (0.9 g, 3.8 mmol) was added. After 1 h, the mixture was allowed to warm to room temperature over 1 h, and saturated aqueous ammonium chloride (2.7 mL) was added. The mixture was extracted with Et₂O (3 × 10 mL). The organic layers were combined, dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et₂O (3:2), gave the nitrile 205 (0.63 g, 3.5 mmol, 92%) as an oil as a 5.6:1 E:Z mixture; Rf 0.2 [petrol–Et₂O (3:2)]; IR νmax(film)/cm⁻¹ 3435 (OH), 2975 (C−H), 2935 (C−H), 2880 (C−H), 2235 (C≡N); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.56−5.49 (1H, m, C=CH), 5.46−5.38 (1H, m, CH=CH), 3.69 (1H, dd, J 11.0, 5.5 Hz, CH_HOH), 3.63 (1H, dd, J 11.0, 5.0 Hz, CH_HOH), 2.19−2.15 (2H, m, 2 × CH), 1.81−1.73 (1H, m, CH), 1.69 (3H, dd, J 6.0, 1.0 Hz, CH₃CH=CH), 1.66−1.63 (1H, m, CH), 1.59−1.54 (1H, br. s, OH), 1.46 (1H, dd, J 14.0, 5.0 Hz, CH), 1.39 (3H, s, CH₃), 1.37 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 128.4 (CH), 127.7 (CH), 125.6 (CN), 65.0 (CH₂), 41.0 (CH₂), 37.9 (CH), 35.6 (C), 31.6 (CH₂), 27.6 (CH₃), 27.0 (CH₃), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 182.1551, C₁₁H₂₀NO requires MH⁺, 182.1545; LRMS m/z (ES) 182 (MH⁺, 100%).

3-(Bromomethyl)-2,2-dimethylhept-5-enenitrile 206

To triphenylphosphine (0.96 g, 3.6 mmol) in CH₂Cl₂ (17 mL) was added carbon tetrabromide (1.21 g, 3.64 mmol) at room temperature. After 5 min, alcohol 205 (0.6
g, 3.30 mmol) was added. After 4 h, the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic layer was washed with H₂O (20 mL) and brine (20 mL), dried (MgSO₄), filtered and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et₂O (7:3), gave the bromide 206 (0.71 g, 2.95 mmol, 90%) as an oil as a 5.6:1 E:Z mixture; R_f 0.4 [petrol–Et₂O (9:1)]; IR νmax(film)/cm⁻¹ 2977 (C–H), 2935 (C–H), 2880 (C–H), 2235 (C≡N); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.66–5.54 (1H, m, CH=CH), 5.40–5.33 (1H, m, CH=CH), 3.58 (1H, dd, J 10.0, 4.5 Hz, CHBr), 3.52 (1H, dd, J 10.0, 4.5 Hz, CHBr), 2.26–2.16 (2H, m, CH₂CH=CH), 1.99–1.89 (1H, m, CH), 1.77–1.67 (4H, m, CH and CH₃CH=CH), 1.52 (1H, dd, J 14.5, 5.0 Hz, CH) 1.40 (3H, s, CH₃), 1.39 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 128.0 (CH), 127.1 (CH), 125.0 (CN), 42.9 (CH₂), 39.3 (CH₂), 37.0 (CH), 36.8 (CH₂), 31.3 (C), 27.6 (CH₃), 27.3 (CH₃), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 244.0713, C₁₁H₁₉N⁷⁹Br requires MH⁺, 244.0701; LRMS m/z (ES) 244 (MH⁺ for ⁷⁹Br, 100%), 246 (MH⁺ for ⁸¹Br, 87%).

3-(Chloromethyl)-2,2-dimethylhept-5-enenitrile 207

Method 1

Using the same method as the nitrile 205, diisopropylamine (1.8 mL, 12.8 mmol) in THF (25 mL) at −78 °C was added nBuLi (5.32 mL, 12.8 mmol, 2.4 M solution in hexanes). The mixture was stirred for 30 min, and then isobutyronitrile (0.96 g, 13.95 mmol) was added dropwise. After 30 min, iodide 215 (3.0 g, 11.62 mmol) was added. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile 207 (1.80 g, 9.0 mmol, 78%) as an oil as a 5.6:1 E:Z mixture; R_f 0.37 [petrol–EtOAc (9:1)].
Method 2

To a solution of alcohol 205 (700 mg, 3.86 mmol) in CH₂Cl₂ (50 mL) was added triphenylphosphine (1.33 g, 5.10 mmol) at 0 °C. After 10 min, trichloroacetonitrile (0.43 mL, 4.25 mmol) was added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile 207 (720 mg, 3.60 mmol, 93%) as an oil as a 5.6:1 E:Z mixture.

IR \( \nu_{\text{max}}\) (film)/\( \text{cm}^{-1} \): 2977 (C–H), 2935 (C–H), 2880 (C–H), 2235 (C≡N); \(^1\)H NMR (400 MHz, CDCl₃, peaks for the major \(E\) isomer) \( \delta = 5.67−5.52 \) (1H, m, CH=CH), 5.42–5.34 (1H, m, CH=CH), 3.67 (1H, dd, \(J = 11.0, 5.0\) Hz, CHHCl), 3.61 (1H, dd, \(J = 11.0, 5.0\) Hz, CHHCl), 2.26–2.20 (2H, m, CH₂CH=CH), 2.00–1.94 (1H, m, CH), 1.75 (1H, dd, \(J = 14.5, 5.5\) Hz, CH), 1.70 (3H, dd, \(J = 6.5, 1.0\) Hz, CH₃CH=CH), 1.52 (1H, dd, \(J = 14.5, 5.0\) Hz, CH), 1.40 (3H, s, CH₃), 1.39 (3H, s, CH₃); \(^{13}\)C NMR (101 MHz, CDCl₃) \( \delta = 128.8 \) (CH), 127.2 (CH), 125.0 (CN), 48.6 (CH₂), 41.8 (CH₂), 37.5 (CH), 35.9 (CH₂), 30.2 (C), 27.6 (CH₃), 27.3 (CH₃), 18.0 (CH₃); HRMS \( m/z \) (ES) Found: MH⁺, 200.1198, \( \text{C}_{11}\text{H}_{19}\text{N}^{35}\text{Cl} \) requires MH⁺, 200.1206; LRMS \( m/z \) (ES) 200 (MH⁺ for \(^{35}\text{Cl}, 100\%\)), 202 (MH⁺ for \(^{37}\text{Cl}, 35\%\)).

3-(Bromomethyl)-2,2-dimethylhept-5-enal 208

![Structure of 3-(Bromomethyl)-2,2-dimethylhept-5-enal 208](image)

To nitrile 206 (0.6 g, 2.5 mmol) in CH₂Cl₂ (8 mL) at −78 °C was added DIBAL–H (3.5 mL, 3.5 mmol, 1.0 M solution in cyclohexane) dropwise. After 3 h, aqueous hydrochloric acid (3.5 mL, 1 M) was added and the solution was allowed to warm slowly to room temperature over 30 min. The mixture was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed with H₂O (20 mL), brine (20 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et₂O (9:1), gave the aldehyde 208 (0.50 g, 2.05 mmol, 82%) as an oil as a 5.6:1 E:Z mixture; \( R_f \) 0.4 [petrol–Et₂O (9:1)];
IR ν_{max}(film)/cm\(^{-1}\) 2960 (C–H), 2930 (C–H), 1725 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), peaks for the major E isomer) δ = 9.51 (1H, s, CHO), 5.57–5.48 (1H, m, CH=CH), 5.34–5.25 (1H, m, CH=CH), 3.41 (1H, dd, J 10.0, 4.0 Hz, CHHBr), 3.30 (1H, dd, J 10.0, 4.0 Hz, CHHBr), 2.07–2.02 (2H, m, CH\(_2\)CH=CH), 1.79–1.62 (5H, m, CH\(_3\)CH=CH and 2 × CH), 1.57–1.47 (1H, m, CH), 1.10 (3H, s, CH\(_3\)), 1.09 (3H, s, CH\(_3\)); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) δ = 206.0 (C=O), 128.5 (CH), 127.4 (CH), 46.0 (C), 39.8 (CH\(_2\)), 39.6 (CH\(_2\)), 36.9 (CH\(_2\)), 36.1 (CH), 22.1 (CH\(_3\)), 21.7 (CH\(_3\)), 18.0 (CH\(_3\)); HRMS m/z (ES) Found: M\(^+\), 246.0614, C\(_{11}\)H\(_{19}\)O\(_7\)Br requires M\(^+\), 246.0619; LRMS m/z (ES), 246 (M\(^+\) for \(^79\)Br, 20%), 248 (M\(^+\) for \(^81\)Br, 18%), 228 (99%), 230 (100%).

3-(Chloromethyl)-2,2-dimethylhept-5-enal 209

![3-(Chloromethyl)-2,2-dimethylhept-5-enal 209](image)

To nitirle 207 (1.7 g, 8.5 mmol) in CH\(_2\)Cl\(_2\) (30 mL) at –78 °C was added DIBAL–H (12.75 mL, 12.75 mmol, 1.0 M solution in cyclohexane) dropwise. After 3 h, aqueous hydrochloric acid (10 mL, 1 M) was added and the solution was allowed to warm slowly to room temperature over 30 min. The mixture was extracted with CH\(_2\)Cl\(_2\) (3 × 25 mL). The combined organic layers were washed with H\(_2\)O (20 mL), brine (20 mL), dried (MgSO\(_4\)), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the aldehyde 209 (1.57 g, 7.73 mmol, 91%) as an oil as a 5.6:1 E:Z mixture; R\(_f\) 0.5 [petrol–Et\(_2\)O (9:1)]; IR ν_{max}(film)/cm\(^{-1}\) 2960 (C–H), 2930 (C–H), 1725 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\), peaks for the major E isomer) δ = 9.50 (1H, s, CHO), 5.55–5.47 (1H, m, CH=CH), 5.35–5.27 (1H, m, CH=CH), 3.50 (1H, dd, J 11.0, 4.0 Hz, CHHCl), 3.45 (1H, dd, J 11.0, 4.5 Hz, CHHCl), 2.12–2.00 (2H, m, 2 × CH), 1.80–1.70 (2H, m, 2 × CH), 1.68 (3H, dd, J 6.5, 1.0 Hz, CH\(_3\)), 1.54–1.47 (1H, m, CH), 1.10 (3H, s, CH\(_3\)), 1.09 (3H, s, CH\(_3\)); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) δ = 206.1 (C=O), 128.5 (CH), 127.5 (CH), 48.8 (CH\(_2\)), 46.0 (C), 38.7 (CH\(_2\)), 36.6 (CH\(_2\)), 36.3 (CH), 22.1 (CH\(_3\)), 21.7 (CH\(_3\)), 18.0 (CH\(_3\)); HRMS m/z (ES) Found: M\(^+\), 203.1211,
C<sub>11</sub>H<sub>20</sub>O<sup>35</sup>Cl requires MH<sup>+</sup>, 203.1203; LRMS m/z (ES), 203 (MH<sup>+</sup> for <sup>35</sup>Cl, 100%), 205 (MH<sup>+</sup> for <sup>37</sup>Cl, 25%).

(±)-(1SR,5RS,6SR,7SR)-5,8,8-Trimethyl-4-oxa-3-azatricyclo[4.3.1.0<sup>3,7</sup>]decane

To aldehyde 208 (E:Z 5.6:1) (100 mg, 0.40 mmol) in xylene (4 mL), was added hydroxylamine hydrochloride (40 mg, 0.60 mmol) and N,N-diisopropylethylamine (0.18 mL, 1.0 mmol) and the mixture was heated under reflux. After 3 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>–MeOH (97:3), gave the cycloadduct 210 (50 mg, 0.28 mmol, 70%) as an oil as a single stereoisomer; R<sub>f</sub> 0.3 [CH<sub>2</sub>Cl<sub>2</sub>–MeOH (97:3)]; IR ν<sub>max</sub>(film)/cm<sup>–1</sup> 2955 (C–H), 1450 (C–H); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ = 4.08 (1H, q, J<sub>6.5 Hz</sub>, CH<sup>G</sup>), 3.30 (1H, dd, J<sub>14.5, 1.5 Hz</sub>, CH<sup>D</sup>H), 2.95 (1H, dd, J<sub>14.5, 3.0 Hz</sub>, CH<sup>A</sup>H), 2.88 (1H, d, J<sub>3.0 Hz</sub>, CH<sup>B</sup>H), 2.17 (1H, dd, J<sub>9.5, 3.0 Hz</sub>, CH<sup>E</sup>), 1.92–1.85 (1H, m, CH<sup>F</sup>), 1.68–1.64 (1H, m, CH<sup>E</sup>), 1.48 (1H, dd, J<sub>13.5, 4.5 Hz</sub>, CH<sup>F</sup>), 1.31–1.28 (2H, m, CH<sub>2</sub>), 1.19 (3H, d, J<sub>6.5 Hz</sub>, CH<sub>3</sub>), 1.18 (3H, s, CH<sub>3</sub>), 1.09 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ = 86.0 (CH), 66.6 (CH), 59.9 (CH<sub>2</sub>), 41.4 (CH<sub>2</sub>), 41.0 (CH), 33.5 (CH<sub>2</sub>), 31.5 (CH<sub>3</sub>), 31.2 (CH<sub>3</sub>), 28.8 (C), 23.4 (CH), 21.0 (CH<sub>3</sub>); HRMS m/z (ES) Found: MH<sup>+</sup>, 182.1552, C<sub>11</sub>H<sub>20</sub>NO requires MH<sup>+</sup>, 182.1545; LRMS m/z (ES) 182 (100%).

(±)-(1RS)-1-[(1SR,4SR,6SR)-7,7-Dimethyl-2-azabicyclo[2.2.2]octan-6-yl]ethanol

To the cycloadducts 210 (130 mg, 0.71 mmol) in AcOH/H<sub>2</sub>O (2.2:2.8 mL) was added zinc powder and the mixture was stirred at 70 °C. After 2 h the zinc salts were
filtered through celite®, and the solvent was evaporated. The residue was dissolved in MeOH (3.0 mL) and poured onto aqueous sodium hydroxide (2.5 mL, 2.0 M). The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL) and the organic layers were dried (MgSO₄) and evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH–NH₃ (98:2:0.2), gave the cycloadduct 211 (125 mg, 0.69 mmol, 98%) as an oil; Rf 0.3 [CH₂Cl₂–MeOH–NH₃ (98:2:0.2)]; IR νmax (film)/cm⁻¹ 3311 (OH), 2960 (N–H), 2860 (C–H), 1450 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 3.89 (1H, qd, J 6.5, 3.0 Hz, CH), 2.97–2.93 (1H, dt, J 10.0, 3.0 Hz, CH), 2.90–2.86 (1H, dt, J 10.0, 2.5 Hz, CH), 2.59–2.53 (1H, d, J 2.0 Hz, CH), 1.90–1.85 (1H, m, CH), 1.79–1.69 (3H, m, 3 × CH), 1.48–1.42 (1H, m, CH), 1.34 (1H, dt, J 13.0, 2.5 Hz, CH), 1.25 (3H, d, J 6.5 Hz, CH₃), 1.00 (3H, s, CH₃), 0.97 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 71.5 (CH), 53.9 (CH), 45.3 (CH₂), 40.7 (CH₂), 36.7 (CH), 33.0 (C), 29.3 (CH₃), 29.1 (CH₂), 29.0 (CH₃), 27.1 (CH₃), 22.6 (CH); HRMS m/z (ES) Found: MH⁺, 184.1702, C₁₁H₂₂NO requires MH⁺, 184.1701; LRMS m/z (ES) 184 (100%).

2-(Chloromethyl)hex-4-en-1-ol 214

To a solution of diol 203 (3.0 g, 23 mmol) in CH₂Cl₂ (230 mL) was added triphenylphosphine (7.25 g, 27.6 mmol) at 0 °C. After 10 min, trichloroacetonitrile (2.31 mL, 23.05 mmol) was added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:1), gave the chloride 214 (2.89 g, 19.6 mmol, 85%) as an oil as a 5.6:1 E:Z mixture; Rf 0.27 [petrol–EtOAc (4:1)]; IR νmax (film)/cm⁻¹ 3330 (OH), 2935 (C–H), 2915 (CH), 1435 (C–H), 725 (C–Cl); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.57–5.50 (1H, m, CH=CH), 5.43–5.35 (1H, m, CH=CH), 3.72–3.68 (2H, m, CH₂O), 3.67–3.60 (2H, m, CH₂Cl), 2.13–2.08 (2H, m, CH₂CH=CH), 1.97–1.90 (1H, m, CH), 1.68 (3H, dd, J 6.0, 1.0 Hz, CH₃), 1.64 (1H, br. s, OH); ¹³C NMR (101 MHz, CDCl₃) δ = 128.0 (CH), 127.7 (CH), 62.8 (CH₂), 45.6 (CH₂), 42.8 (CH), 31.8 (CH₂), 18.0 (CH₃);
HRMS \( m/z \) (ES) Found: MH\(^+\), 148.0655; \( \text{C}_7\text{H}_{14}^{35}\text{ClO} \) requires MH\(^+\), 148.0655; LRMS \( m/z \) (ES) 148 (MH\(^+\) for \( ^{35}\text{Cl} \), 100%), 150 (MH\(^+\) for \( ^{37}\text{Cl} \), 60%).

6-Chloro-5-(iodomethyl)hex-2-ene 215

![Structural diagram](image)

To alcohol 214 (3.2 g, 21.6 mmol) in THF (75 mL) were added imidazole (1.64 g, 25.9 mmol) and PPh\(_3\) (6.80 g, 25.9 mmol). After 15 min, ground iodine (6.00 g, 23.8 mmol) was added portionwise at room temperature. After 3 h, CH\(_2\)Cl\(_2\) (50 mL) was added and the suspension was filtered through Celite\(^{\text{®}}\) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the iodide 215 (4.62 g, 17.9 mmol, 83%) as an oil as a 5.6:1 \( E:Z \) mixture; \( R_f \) 0.5 (petrol); IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 2960 (C−H), 1435 (C−H); \(^1\)H NMR (400 MHz, CDCl\(_3\)) peaks for the major \( E \) isomer \( \delta = 5.62−5.54 \) (1H, m, C\(=\)H), 5.38−5.29 (1H, m, CH=C\(=\)H), 3.66 (1H, dd, \( J = 11.0, 4.5 \) Hz, CHH), 3.52 (1H, dd, \( J = 11.0, 6.5 \) Hz, CHH), 3.40 (1H, dd, \( J = 10.0, 4.5 \) Hz, CHH), 3.30 (1H, dd, \( J = 10.0, 6.0 \) Hz, CHH), 2.16−2.06 (2H, m, 2 \( \times \) CH), 1.80−1.72 (1H, m, CH), 1.69 (3H, dd, \( J = 6.5, 1.5 \) Hz, CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta = 128.9 \) (CH), 126.7 (CH), 47.9 (CH\(_2\)), 41.8 (CH), 35.1 (CH\(_2\)), 18.0 (CH\(_3\)), 10.5 (CH\(_2\)); HRMS \( m/z \) (ES) Found: M\(^+\), 257.9669, \( \text{C}_7\text{H}_{12}^{35}\text{ClI} \) requires M\(^+\), 257.9672; LRMS \( m/z \) (EI) 258 (M\(^+\) for \( ^{35}\text{Cl} \), 6%), 260 (M\(^+\) for \( ^{37}\text{Cl} \), 2%), 55 (100%).

Ethyl 2-[2-(chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate 219

![Structural diagram](image)

To ethyl 1,3-dithiane-2-carboxylate 218 (2.0 mL, 13.0 mmol) in THF (35 mL) was added "BuLi (6.2 mL, 15.6 mmol, 2.5 M in hexanes) at −78 °C. After 15 min, the
iodide 215 (4.0 g, 15.6 mmol) in THF (5 mL) was added at –40 °C and the mixture was allowed to warm to room temperature. After 16 h, H₂O (40 mL) was added and the aqueous layer was extracted with Et₂O (3 × 50 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (98:2), gave the ester 219 (3.2 g, 9.9 mmol, 75%) as an oil as a 5.6:1 E:Z mixture; Rₚ 0.3 [petrol–EtOAc (98:2)]; IR 𝜈ₘₐₓ(film)/cm⁻¹ 2980 (C−H), 2920 (C−H), 1720 (C=O); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.60−5.51 (1H, m, CH=CH), 5.40−5.32 (1H, m, CH=C), 4.31–4.24 (2H, m, CH₂O), 3.68−3.61 (2H, m, CH₂Cl), 3.33–3.25 (2H, m, CH₂), 2.72 (1H, dd, J 4.5, 3.0 Hz, CHH), 2.68 (1H, dd, J 4.5, 3.0 Hz, CHH), 2.27–2.23 (1H, m, CHH), 2.20–2.15 (3H, m, 3 × CH), 2.14–2.11 (1H, m, CHH), 2.05 (1H, dd, J 14.0, 4.0 Hz, CHH), 1.93–1.82 (1H, m, CHH), 1.68 (3H, dd, J 6.0, 1.0 Hz, CH₃CH=CH), 1.36 (3H, t, J 7.0 Hz, CH₃CH₂O); ¹³C NMR (101 MHz, CDCl₃) δ = 171.0 (C=O), 128.4 (CH), 127.5 (CH), 62.1 (CH₂), 52.9 (C), 49.1 (CH₂), 39.8 (CH₂), 36.8 (CH), 35.9 (CH₂), 27.95 (CH₂), 27.9 (CH₂), 24.4 (CH₂), 18.0 (CH₃), 14.2 (CH₃); HRMS m/z (ES) Found: MH⁺, 323.0909, C₁₄H₂₄O₂S₂35Cl requires MH⁺, 323.0906; LRMS m/z (ES) 323 (MH⁺ for 35Cl, 100%), 325 (MH⁺ for 37Cl, 45%).

2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithian-2-ylmethanol 221

To a suspension of LiAlH₄ (0.56 g, 14.7 mmol) in Et₂O (25 mL) was added ester 219 (3.17 g, 9.8 mmol) in Et₂O (5 mL) at room temperature. After 2.5 h, aqueous NaOH (30 mL, 1 M) was added until a white precipitate was observed. The mixture was filtered through celite and washed with CH₂Cl₂−MeOH (9:1) (100 mL) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (8:2), gave the alcohol 221 (2.2 g, 7.84 mmol, 80%) as an oil as a 5.6:1 E:Z mixture; Rₚ 0.5 [petrol–EtOAc (4:1)]; IR 𝜈ₘₐₓ(film)/cm⁻¹ 3275 (OH), 2935 (C−H), 2910 (C−H); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ =
5.59–5.50 (1H, m, CH=CH), 5.42–5.34 (1H, m, CH=CH), 3.77–3.74 (2H, m, CH₂O), 3.72–3.66 (2H, m, CH₂Cl), 2.99–2.90 (2H, m, 2 × CH), 2.63 (1H, dd, J 4.5, 3.0 Hz, CH), 2.60 (1H, dd, J 4.5, 3.0 Hz, CH), 2.28–2.19 (3H, m, 2 × CH and OH), 2.15–2.06 (2H, m, 2 × CH), 1.93–1.78 (2H, m, 2 × CH), 1.73 (1H, dd, J 15.0, 3.0 Hz, CH), 1.68 (3H, dd, J 6.0, 1.0 Hz, CH₂CH=CH); ¹³C NMR (101 MHz, CDCl₃) δ = 128.3 (CH), 127.7 (CH), 64.0 (CH₂), 54.8 (C), 49.6 (CH₂), 39.0 (CH₂), 36.4 (CH₂), 35.9 (CH), 25.9 (CH₂), 25.8 (CH₂), 24.6 (CH₂), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 281.0796, C₁₂H₂₂OS₂35Cl requires MH⁺, 281.0801; LRMS m/z (ES) 281 (MH⁺ for 35Cl, 8%), 283 (MH⁺ for 37Cl, 3%), 263 (100%), 265 (45%).

2-[2-(Chloromethyl)hex-4-en-1-yl]-1,3-dithiane-2-carbaldehyde 220

DMSO (0.80 mL, 11.0 mmol) in CH₂Cl₂ (1 mL) was added dropwise to oxalyl chloride (0.50 mL, 5.5 mmol) in CH₂Cl₂ (15 mL) at –60 °C. After 5 min, alcohol 221 (1.4 g, 5.0 mmol) in CH₂Cl₂ (1 mL) was added dropwise. After 10 min, N,N-diisopropylethylamine (4.5 mL, 25.0 mmol) was added. After 15 min at –60 °C the mixture was allowed to warm to room temperature, then water (20 mL) was added. The mixture was extracted with CH₂Cl₂ (3 × 30 mL), the combined organic layers were washed successively with aqueous HCl (2 × 15 mL, 1 M), H₂O (15 mL), Na₂CO₃ (15 mL, 5%), and H₂O (20 mL), then dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1) gave the aldehyde 220 (1.15 g, 4.13 mmol, 83%) as an oil as a 5.6:1 E:Z mixture; Rₜ 0.5 [petrol–EtOAc (9:1)]; IR νmax (film)/cm⁻¹ 2930 (C−H), 2855 (C−H), 1705 (C=O); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 9.03 (1H, s, CHO), 5.57–5.50 (1H, m, CH=CH), 5.36–5.28 (1H, m, CH=CH), 3.61 (1H, dd, J 11.5, 4.0 Hz, CHHCl), 3.56 (1H, dd, J 11.5, 4.0 Hz, CHHCl), 3.10–2.98 (1H, m, CHH), 3.01–2.93 (1H, m, CHH), 2.65–2.58 (2H, m, CH₂CH=CH), 2.24–2.17 (1H, m, CHH), 2.13–2.08 (3H, m, 3 × CH), 2.04 (1H, dd, J 15.0, 7.0 Hz, CHH),
1.87–1.75 (2H, m, 2 × CH), 1.68 (3H, dd, J 6.0, 1.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 188.7 (C=O), 128.9 (CH), 127.1 (CH), 57.7 (C), 48.2 (CH₂), 37.0 (CH₂), 35.9 (CH), 30.1 (CH₂), 26.8 (CH₂), 26.7 (CH₂), 24.0 (CH₂), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 279.0646, C₁₂H₂₀O₂S₂Cl requires MH⁺, 279.0644; LRMS m/z (ES) 279 (MH⁺ for ³⁵Cl, 100%), 281 (MH⁺ for ³⁷Cl, 45%)

2-(2-(Chloromethyl)hex-4-en-1-yl)-1,3-dithiane-2-carbaldehyde oxime 232

To aldehyde 220 (500 mg, 1.80 mmol) in dry methanol (25 mL) was added hydroxylamine hydrochloride (135 mg, 2.0 mmol) and sodium acetate (365 mg, 4.5 mmol) at room temperature. After 5 h, the solvent was evaporated. The white residue was washed with CH₂Cl₂, and then concentrated to give the oxime 232 in quantitative yield which was used without further purification. ¹H NMR (400 MHz, CDCl₃ peaks for major isomer) δ = 7.44 (1H, s, CH=N), 5.62–5.50 (1H, m, CH=CH), 5.38–5.30 (1H, m, CH=CH), 3.67–3.60 (2H, m, CH₂Cl), 3.16–3.11 (1H, m, CHH), 3.10–3.04 (1H, m, CHH), 2.73–2.70 (1H, m, CHH), 2.69–2.66 (1H, m, CHH), 2.27–2.07 (5H, m, 5 × CH), 1.94–1.83 (2H, m, 2 × CH), 1.69 (3H, dd, J 6.0, 1.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 153.0 (CH), 128.6 (CH), 127.4 (CH), 51.5 (C), 48.8 (CH₂), 41.0 (CH₂), 36.2 (CH₂), 35.8 (CH), 27.3 (CH₂), 27.2 (CH₂), 24.8 (CH₂), 18.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 294.0746, C₁₂H₂₁NOS₂³⁵Cl requires MH⁺, 294.0753; LRMS m/z (ES) 294 (MH⁺ for ³⁵Cl, 100%), 296 (MH⁺ for ³⁷Cl, 48%).
(±)-(1'SR,5'RS,6'SR,7'SR)-5'-Methyl-4'-oxa-3'-azaspiro[1,3-dithiane-2,8'-tricyclo[4.3.1.0³,⁷]decane] 222

Oxime 232, N,N-diisopropylethylamine (0.32 mL, 1.8 mmol) and MgSO₄ (100 mg) in toluene (15 mL) were heated under reflux. After 16 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (97:3), gave the cycloadduct 222 (263 mg, 1.0 mmol, 57%) as an oil as a single stereoisomer; Rᵥ 0.3 [CH₂Cl₂–MeOH (97:3)]; IR vₘₐₓ(film)/cm⁻¹ 2925 (C–H), 2900 (C–H), 1440 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 4.19 (1H, q, J 6.0 Hz, CH₆), 3.87 (1H, d, J 3.5 Hz, CH₅), 3.46 (1H, dd, J 14.5, 2.0 Hz, CH⁴H), 3.20–3.13 (1H, m, CH⁵H), 2.13–2.00 (3H, m, CHF and 2 × CH), 1.91–1.88 (2H, m, CH₃), 1.79–1.77 (1H, m, CH⁶), 1.55 (1H, dd, J 13.5, 4.5 Hz CH⁷H), 1.26 (3H, d, J 6.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 86.6 (CH), 61.8 (CH), 59.4 (CH₂), 44.7 (C), 44.5 (CH₂), 41.9 (CH), 33.2 (CH₂), 27.5 (CH₂), 27.2 (CH₂), 24.7 (CH₂), 23.0 (CH), 21.1 (CH₃); HRMS m/z (ES) Found: MH⁺, 258.0994, C₁₂H₂₀NOS₂ requires MH⁺, 258.0986; LRMS m/z (ES) 258 (100%).

4-(Chloromethyl)-2,2-dimethoxyoct-6-enal 224

To aldehyde 220 (1.12 g, 4.04 mmol) in anhydrous methanol (5 mL) was added bis(trifluoroacetoxy)iodo benzene (3.00 g, 6.85 mmol) at room temperature. After 15 min, saturated aqueous sodium bicarbonate (5 mL) was added. The mixture was extracted with Et₂O (3 × 10 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–Et₂O (9:1),
gave the aldehyde 224 (580 mg, 2.5 mmol, 62%) as an oil a 5.6:1 E:Z mixture; Rf 0.3 [petrol–Et2O (9:1)]; IR v\textsubscript{max}(film)/cm\textsuperscript{-1} 2945 (C–H), 2840 (C–H), 1750 (C=O), 1440 (C–H); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}, peaks for the major E isomer) δ = 9.46 (1H, s, CHO), 5.56–5.47 (1H, m, CH=CH), 5.34–5.25 (1H, m, CH=CH), 3.60–3.55 (2H, m, CH\textsubscript{2}Cl), 3.31 (3H, s, CH\textsubscript{3}O), 3.30 (3H, s, CH\textsubscript{3}O), 2.17–2.05 (3H, m, 3 × CH), 1.87–1.80 (1H, m, CH), 1.75 (1H, dd, J 15.0, 5.0 Hz, CH), 1.67 (3H, dd, J 6.0, 1.0 Hz, CH\textsubscript{3}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ = 199.5 (C=O), 128.7 (CH), 127.3 (CH), 102.1 (C), 49.1 (CH\textsubscript{3}), 49.7 (CH\textsubscript{3}), 48.4 (CH\textsubscript{2}), 35.6 (CH\textsubscript{2}), 34.3 (CH), 32.6 (CH\textsubscript{2}), 18.0 (CH\textsubscript{3}); HRMS m/z (ES) Found: MH\textsuperscript{+}, 235.1097, C\textsubscript{11}H\textsubscript{20}O\textsubscript{3}3Cl requires MH\textsuperscript{+}, 235.1101; LRMS m/z (ES) 235 (MH\textsuperscript{+} for \textsuperscript{35}Cl, 100%), 237 (MH\textsuperscript{+} for \textsuperscript{37}Cl, 35%).

4-(Chloromethyl)-2,2-dimethoxyoct-6-enal oxime 226

![4-(Chloromethyl)-2,2-dimethoxyoct-6-enal oxime 226](image)

Aldehyde 224 (100 mg, 0.43 mmol), hydroxylamine hydrochloride (0.04 g, 0.64 mmol), N,N-diisopropylethylamine (0.18 mL, 1.06 mmol) and (MgSO\textsubscript{4}) in toluene (4 mL) were heated at 60 °C. After 30 min, the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH\textsubscript{2}Cl\textsubscript{2}–MeOH (96:4), gave the oxime 226 (96 mg, 0.38 mmol, 90%) as an oil as a mixture of E and Z alkene and oxime isomers; Rf 0.3 [CH\textsubscript{2}Cl\textsubscript{2}–MeOH (96:4)]; IR v\textsubscript{max}(film)/cm\textsuperscript{-1} 3340 (OH), 2935 (C–H), 1440 (C–H); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3} peaks for major isomer) δ = 7.45 (1H, s, OH), 7.31 (1H, s, CH=N), 5.62–5.49 (1H, m, CH=CH), 5.37–5.29 (1H, m, CH=CH), 3.63–3.60 (2H, m, CH\textsubscript{2}Cl), 3.28 (3H, s, CH\textsubscript{3}O), 3.26 (3H, s, CH\textsubscript{3}O), 2.19–2.10 (2H, m, 2 × CH), 2.08 (1H, dd, J 15.0, 7.5 Hz CHH), 1.95–1.88 (1H, m, CH), 1.75 (1H, dd, J 15.0, 5.0 Hz, CHH), 1.68 (3H, dd, J 6.0, 1.5 Hz, CH\textsubscript{3}); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ = 151.0 (CH), 128.4 (CH), 127.6 (CH), 100.7 (C), 49.3 (CH\textsubscript{3}), 49.1 (CH\textsubscript{3}), 48.6 (CH\textsubscript{2}), 35.6 (CH\textsubscript{2}), 35.5 (CH\textsubscript{2}), 35.4 (CH), 18.0 (CH\textsubscript{3}). HRMS and LRMS could not be obtained despite attempts with ES.
(±)-(1SR,5RS,6SR,7SR)-8,8-Dimethoxy-5-methyl-4-oxa-3-azatricyclo[4.3.1.0³,⁷]decane 225

Method 1

Using the same method as the cycloadduct, the aldehyde 224 (E:Z 5.6:1) (100 mg, 0.43 mmol), N,N-diisopropylethylamine (0.18 mL, 1.07 mmol), hydroxylamine hydrochloride (40 mg, 0.64 mmol) and MgSO₄ (50 mg) in toluene (4 mL). After 16 h, purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (97:3), gave the cycloadduct 225 (13.8 mg, 0.06 mmol, 15%) as an oil as a single stereoisomer; Rf 0.36 [CH₂Cl₂–MeOH (9.7:0.3)];

IR νmax(film)/cm⁻¹ 2950 (C–H), 2900 (C–H), 1460 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 4.10 (1H, q, J 6.0 Hz, CH₂), 3.49 (1H, d, J 3.5 Hz, CH₃), 3.37–3.01 (4H, m, CH and CH₃), 3.26 (3H, s, CH₃), 2.97 (1H, dt, J 14.5, 3.0 Hz, CH), 2.18 (1H, dd, J 9.5, 3.5 Hz, CH), 1.96–1.89 (1H, m, CH), 1.82–1.80 (1H, m, CH), 1.67 (1H, t, J 3.0 Hz, CH), 1.66 (1H, t, J 3.0 Hz, CH), 1.52 (1H, dd, J 13.0, 4.0 Hz, CH), 1.21 (3H, d, J 6.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 100.0 (C), 85.6 (CH), 60.6 (CH), 60.3 (CH₂), 48.7 (CH₃), 47.8 (CH₃), 40.6 (CH), 39.03 (CH₂), 34.1 (CH₂), 23.0 (CH), 21.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 214.1433, C₁₁H₂₀NO₃ requires MH⁺, 214.1438; LRMS m/z (ES) 182 (50%), 214 (MH⁺, 100%).

Method 2

To dithiane cycloadduct 222 (70 mg, 0.27 mmol) in methanol (7.0 mL) was added bis(trifluoroacetoxy)iodo benzene (0.11 g, 0.27 mmol) at room temperature. Additional bis(trifluoroacetoxy)iodo benzene (0.45 g, 1.1 mmol) was added during 1 h period, and the mixture was stirred for 2.5 h. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (9.7:0.3), gave acetal 225 (8.7 mg, 0.04 mmol, 15%);
6-Bromo-5-(bromomethyl)hex-2-ene 228

\[ \text{Br} \quad \text{Br} \]

Triphenylphosphine (4.45 g, 16.9 mmol) was added over 30 min to diol 203 (1.00 g, 7.68 mmol) and carbon tetrabromide (5.60 g, 16.9 mmol) in CH\(_2\)Cl\(_2\) (40 mL) at 0 °C. After 4 h, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the bromide 228 (1.8 g, 7.0 mmol, 92%) as an oil as a 5.6:1 E:Z mixture; R\(_f\) 0.6 (petrol); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2965 (C−H), 2910 (C−H); \(^1\)H NMR (400 MHz, CDCl\(_3\), peaks for the major E isomer) \(\delta = 5.67−5.55\) (1H, m, CH=CH), 5.39−5.32 (1H, m, CH=CH), 3.59 (2H, dd, \(J = 10.0, 4.5\) Hz, 2 × CHBr), 3.49 (2H, dd, \(J = 10.0, 6.0\) Hz, 2 × CHBr), 2.18 (2H, t, \(J = 7.0\) Hz, CH\(_2\)−CH=CH), 2.06−2.01 (1H, m, CH), 1.70 (3H, dd, \(J = 6.5, 1.0\) Hz, CH\(_3\)); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 128.9\) (CH), 126.7 (CH), 41.9 (CH), 36.0 (CH\(_2\)), 34.6 (CH\(_2\)) 18.0 (CH\(_3\)); HRMS m/z (ES) Found: M\(^+\) 255.9281, C\(_7\)H\(_{13}\)\(^{79}\)Br\(_2\) requires M\(^+\), 255.9280; LRMS m/z (EI) 254 (M\(^+\) for \(^{79}\)Br, 50%), 256 (M\(^+\) for \(^{79}\)Br + \(^{81}\)Br, 100%), 258 (M\(^+\) for \(^{81}\)Br, 47%).

6-Bromo-5-(iodomethyl)hex-2-ene 230

\[ \text{Br} \quad \text{I} \]

To iodo-alcohol 204 (2.0 g, 8.4 mmol) in CH\(_2\)Cl\(_2\) (50 mL) and CBr\(_4\) (3.0 g, 9.2 mmol) was added PPh\(_3\) (2.4 g, 9.2 mmol) over 30 min at 0 °C. The mixture was stirred for 2 h at room temperature then the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol (neat), gave the iodide 230 (2.2 g, 7.28 mmol, 88%) as an oil as a 5.6:1 E:Z mixture; R\(_f\) 0.6 (petrol); IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2960 (C−H), 2915 (C−H); \(^1\)H NMR (400 MHz, CDCl\(_3\), peaks for the major E isomer) \(\delta = 5.66−5.55\) (1H, m, CH=CH), 5.37−5.29 (1H, m, CH=CH), 3.56 (1H, dd, \(J = 10.0, 4.5\) Hz, CH\(_2\)), 3.45−3.40 (2H, m, 2 × CH), 3.30 (1H, dd, \(J = 10.0, 6.0\) Hz, CH\(_3\)).
Hz, CHH), 2.17–2.11 (2H, m, 2 × CH), 1.73–1.67 (4H, m, CH and CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 128.9 (CH), 126.7 (CH), 41.4 (CH), 37.9 (CH₂), 35.9 (CH₂), 18.0 (CH₃), 11.6 (CH₂); HRMS m/z (ES) Found: M⁺, 301.9176, C₇H₁₂⁷⁹BrI requires M⁺, 301.9162; LRMS m/z (EI) 302 (M⁺ for ⁷⁹Br, 6%), 304 (M⁺ for ⁸¹Br, 6%), 95 (100%).

**Ethyl 2-[2-(bromomethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate 229**

![Ethyl 2-[2-(bromomethyl)hex-4-en-1-yl]-1,3-dithiane-2-carboxylate 229](image)

To ethyl 1,3-dithiane-2-carboxylate (1.75 mL, 11.0 mmol) in THF (30 mL) was added nBuLi (5.2 mL, 13.25 mmol, 2.5 M in hexanes) at −78 °C. After 15 min, the iodide 230 (4.00 g, 13.2 mmol) in THF (5 mL) was added at −40 °C and the mixture was allowed to warm to room temperature. After 16 h, H₂O (35 mL) was added and the aqueous layer was extracted with Et₂O (3 × 50 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (96:4), gave the ester 229 (2.4 g, 6.6 mmol, 60%) as an oil as a 5.6:1 E:Z mixture; Rf 0.3 [petrol–EtOAc (96:4)]; IR νmax (film)/cm⁻¹ 2960 (C–H), 2925 (C–H), 1720 (C=O); ¹H NMR (400 MHz, CDCl₃, peaks for the major E isomer) δ = 5.63–5.53 (1H, m, CH=CH), 5.40–5.32 (1H, m, CH=CH), 4.30–4.25 (2H, m, CH₂O), 3.58–3.55 (2H, m, CH₂Br), 3.31–3.25 (2H, m, 2 × CH), 2.73–2.70 (1H, m, CHH), 2.69–2.66 (1H, m, CHH), 2.23–2.10 (5H, m, 5 × CH), 2.07–2.00 (1H, m, CHH), 1.94–1.82 (1H, m, CHH), 1.68 (3H, d, J 6.5, 1.5 Hz, CH₂CH=CH), 1.36 (3H, t, J 7.0 Hz, CH₃CH₂O); ¹³C NMR (101 MHz, CDCl₃) δ = 171.0 (C=O), 128.5 (CH), 127.4 (CH), 62.1 (CH₂), 52.8 (C), 40.8 (CH₂), 40.2 (CH₂), 36.9 (CH₂), 36.3 (CH), 28.0 (CH₂), 27.9 (CH₂), 24.4 (CH₂), 18.0 (CH₃), 14.2 (CH₃); HRMS m/z (ES) Found: MH⁺, 367.0416, C₁₄H₂₄O₂S₂⁷⁹Br requires MH⁺, 367.0401; LRMS m/z (ES) 367 (MH⁺ for ⁷⁹Br, 97%), 369 (MH⁺ for ⁸¹Br, 100%).
(±)-(1SR,5RS,6SR,7SR)-5-Methyl-4-oxa-3-azatricyclo[4.3.1.0³,⁷]decan-8-one 212

To dithiane 222 (300 mg, 1.16 mmol) in acetonitrile/water (1:1) (44 mL) was added bis(trifluoroacetoxy)iodo benzene (0.5 g, 1.16 mmol), and trifluoroacetic acid (10.0 equiv.) at room temperature. Additional bis(trifluoroacetoxy)iodobenzene (1.9 g, 4.4 mmol) was added over a 1 h period, and the mixture was stirred for 2.5 h, before being neutralised with saturated aqueous sodium bicarbonate (30 mL). The mixture was extracted with CH₂Cl₂ (3 × 10 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (9.7:0.3), gave ketone 212 (155 mg, 0.93 mmol, 80%) as a needles, m.p. 62–63.5 °C; Rf 0.32 [CH₂Cl₂–MeOH (9.7:0.3)]; IR νmax(film)/cm⁻¹ 2965 (C–H), 1730 (C=O), 1450 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 4.26 (1H, q, J 6.0 Hz, CH₃), 3.62 (1H, d, J 3.5 Hz, CHD), 3.51 (1H, dd, J 14.5, 2.5 Hz, CH¹H), 3.30–3.20 (1H, m, CH₁H), 2.45 (1H, dd, J 9.0, 3.5 Hz, CH²H), 2.25–2.23 (2H, m, 2 × CH₃F), 2.20–2.18 (1H, m, CH²H), 2.03–1.96 (1H, m, CH³H), 1.79 (1H, dd, J 13.5, 4.5 Hz, CH¹H), 1.21 (3H, d, J 6.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 209 (C=O), 85.6 (CH), 68.9 (CH), 61.5 (CH₂), 44.8 (CH), 44.5 (CH₂), 34.1 (CH₂), 23.3 (CH), 20.5 (CH₃); HRMS m/z (ES) Found: MH⁺, 168.1020, C₉H₁₄NO₂ requires MH⁺, 168.1019; LRMS m/z (ES) 168 (100%).

(±)-(1SR,4SR,7SR)-7-[(1RS)-1-Hydroxyethyl]-2-[2-(1H-indol-3-yl)acetyl]-2-azabicyclo[2.2.2]octan-6-one 237

To the cycloadducts 212 (100 mg, 0.60 mmol) in AcOH/MeOH (0.6:0.8 mL) was added activated Zn powder [washed with freshly prepared aqueous HCl (1.0 M), EtOH, then Et₂O] and the mixture was stirred at room temperature. After 4 h the zinc
salts were filtered through Celite®, and the solvent was evaporated. The residue was dissolved in MeOH (3.0 mL) and poured onto aqueous sodium hydroxide (3.0 mL, 2.0 M). The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL) and the organic layers were dried (MgSO₄) and evaporated. Indole acetic acid (89 mg, 0.51 mmol) and EDCI (97 mg, 0.51 mmol) was added to a solution of crude product of amino alcohol (100 mg, 0.51 mmol) in CH₂Cl₂ (6 mL) at room temperature. The mixture was stirred for 1.5 h, then was extracted with CH₂Cl₂ (3 × 15 mL), washed with aqueous HCl (1.5 mL, 0.01 M), saturated aqueous solution of K₂CO₃ (1.5 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (9:1), gave the amide 237 (195 mg, 0.60 mmol, 100%) as a foam; Rₛ/0.39 [CH₂Cl₂–MeOH (9:1)]; IR νmax(film)/cm⁻¹ 3320 (OH), 2970 (C–H), 1730 (C=O), 1625 (C=O), 1460 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 8.50 (1H, br. s, NH), 7.59 (1H, d, J 7.5 Hz, ArH), 7.38 (1H, d, J 7.5 Hz, ArH), 7.24−7.21 (1H, m, ArH), 7.13−7.11 (2H, m, 2 × ArH), 5.01 (1H, d, J 1.6 Hz, CH), 3.96−3.93 (2H, m, 2 × CH), 3.83–3.81 (2H, m, 2 × CH), 3.59−3.52 (2H, m, 2 × CH), 2.39–2.37 (2H, m, 2 × CH), 1.85–1.83 (1H, m, CH), 1.82–1.81 (1H, m, CH), 1.16 (3H, d, J 6.0 Hz, CH₃), 1.07−1.03 (1H, m, CH); ¹³C NMR (101 MHz, CDCl₃) δ = 206.6 (C=O), 173.3 (C=O), 136.1 (C), 127.0 (C), 122.8 (CH), 122.3 (CH), 119.7 (CH), 118.3 (CH), 111.5 (CH), 107.7 (C), 68.6 (CH), 45.7 (CH), 50.3 (CH₂), 43.7 (CH), 42.5 (CH₂), 30.7 (CH₂), 28.4 (CH), 27.6 (CH₂), 19.5 (CH₃); HRMS m/z (ES) Found: MH⁺, 327.1703, C₁₉H₂₂N₂O₃ requires MH⁺, 327.1703; LRMS m/z (ES) 327 (100%).

(±)-1-[(1SR,4SR,7SR)-7-[(1RS)-1-Hydroxyethyl]-6,6-dimethoxy-2-azabicyclo[2.2.2]octan-2-yl]-2-(1H-indol-3-yl)ethanone 239

p-Toluenesulfonic acid (7.5 mg, 0.04 mmol) was added to a mixture of crude 237 (100 mg, 0.31 mmol), trimethylorthofomate (1.21 mL, 11.0 mmol) and MeOH (1.2 mL) at room temperature. After 7 h, saturated aqueous solution of NaHCO₃ (1.5 mL)
was added and the mixture was extracted with CH₂Cl₂ (3 × 10 mL), dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (9.7:0.3), gave amide 239 (98 mg, 0.26 mmol, 85%) as a foam; Rf 0.35 [CH₂Cl₂–MeOH (9.5:0.5)]; IR νmax (film) cm⁻¹ 3319 (OH), 2970 (C–H), 1623 (C=O), 1460 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 8.33 (1H, br. s, NH), 7.61 (1H, d, J 8.0 Hz, ArH), 7.38 (1H, d, J 8.0 Hz, ArH), 7.23–7.21 (1H, m, ArH), 7.20–7.18 (1H, m, ArH), 7.16–7.15 (1H, m, ArH), 4.78 (1H, d, J 1.0 Hz, CH), 3.81–3.80 (2H, m, 2 × CH), 3.50 (1H, dt, J 10.0, 2.0 Hz, CH), 3.36 (1H, dd, J 10.0, 3.0 Hz, CH), 3.23 (3H, s, CH₃), 3.14 (3H, s, CH₃), 2.09–2.05 (1H, m, CH), 1.96–1.88 (1H, m, CHH), 1.76–1.73 (2H, m, 2 × CH), 1.72–1.96 (2H, m, 2 × CH), 1.15 (3H, d, J 6.0 Hz, CH₃), 0.84–0.79 (1H, m, CHH); ¹³C NMR (101 MHz, CDCl₃) δ = 172.7 (C=O), 136.1 (C), 127.2 (C), 122.7 (CH), 122.2 (CH), 119.6 (CH), 118.5 (CH), 111.3 (CH), 108.6 (C), 101.4 (C), 69.6 (CH), 49.2 (CH₂), 48.6 (CH₃), 48.1 (CH₃), 47.1 (CH), 40.9 (CH), 37.2 (CH₂), 30.4 (CH₂), 28.7 (CH₂), 27.6 (CH), 19.6 (CH₃); HRMS m/z (ES) Found: MH⁺, 373.2122, C₂₁H₂₈N₂O₄ requires MH⁺, 373.2122; LRMS m/z (ES) 373 (100%).

(±)-(1RS)-1-[(1SR,4SR,6SR)-2-[2-(1H-Indol-3-yl)acetyl]-7,7-dimethoxy-2-azabicyclo[2.2.2]octan-6-yl]ethyl acetate 177

To a solution of alcohol 239 (100 mg, 0.28 mmol) in dichloromethane (6 mL) and acetyl chloride (20 µL, 0.3 mmol) was added pyridine (24 µL, 0.3 mmol) at room temperature. After 30 min, the solvent was evaporated. Purification by column chromatography on silica gel, eluting with CH₂Cl₂–MeOH (9.75:0.25), gave ester 177 (98 mg, 0.24 mmol, 87%) as a foam; Rf 0.26 CH₂Cl₂–MeOH (9.75:0.25); IR νmax (film) cm⁻¹ 3280 (OH), 2940 (C–H), 1730 (C=O), 1640 (C=O), 1450 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 8.30 (1H, br. s, NH), 7.57 (1H, d, J 7.5 Hz, ArH), 7.36 (1H, dt, J 8.0, 1.0 Hz, ArH), 7.23–7.22 (1H, m, ArH), 7.19 (1H, ddd, J 8.0, 7.0, 1.0 Hz, ArH), 7.13 (1H, ddd, J 8.0, 7.5, 1.0 Hz, ArH), 4.91 (1H, d, J 1.5 Hz, CH), 4.52
(1H, dq, J 10.5, 6.0 Hz, CH), 3.77–3.76 (1H, m, CH), 3.75–3.74 (1H, m, CH), 3.39 (1H, dt, J 10.5, 2.5 Hz, CHH), 3.29 (1H, dt, J 10.0, 2.5 Hz, CHH), 3.26 (3H, s, CH3), 3.20 (3H, s, CH3), 2.29–2.20 (1H, m, CHH), 2.13 (3H, s, CH3), 2.05–2.02 (1H, m, CH), 1.78 (1H, dt, J 14.0, 2.0 Hz, CH), 1.72–1.96 (1H, m, CHH), 1.66 (1H, dt, J 13.5, 3.0 Hz, CHH), 1.22 (3H, d, J 6.0 Hz, CH3), 0.92 (1H, ddt, J 6.0, 5.5, 2.5 Hz, CH); 13C NMR (101 MHz, CDCl3) δ = 171.3 (C=O), 171.1 (C=O), 136.1 (C), 127.4 (C), 122.9 (CH), 121.9 (CH), 119.3 (CH), 118.4 (CH), 111.2 (CH), 108.8 (C), 101.7 (C), 71.4 (CH), 49.0 (CH3), 48.9 (CH2), 48.1 (CH3), 45.7 (CH), 38.1 (CH), 36.9 (CH2), 30.6 (CH2), 28.2 (CH2), 27.5 (CH), 21.5 (CH3), 17.8 (CH3); HRMS m/z (ES) Found: MH+, 415.2227, C23H31N2O5 requires MH+, 415.2227; LRMS m/z (ES) 415 (100%). Data corresponds with literature.116

(R)-Methyl 2-methyl-3-((triethylsilyl)oxy)propanoate 298

To the alcohol 294 (2.50 g, 21.2 mmol) and imidazole (1.72 g, 31.7 mmol) in CH2Cl2 (45 mL), was added TESCl (4.14 g, 31.7 mmol) dropwise at 0 °C. The mixture was allowed to warm to room temperature. After 16 h, the mixture was diluted with CH2Cl2 and was washed with water (3 × 15 mL) and brine (15 mL). The organic layer was dried (MgSO4) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.5:0.5), gave the ester 298 (4.74 g, 20.4 mmol, 97%) as an oil; Rf 0.34 [petrol–EtOAc (9:1)]; IR νmax(film)/cm–1 2960 (C−H), 2880 (C−H), 1741 (C=O); 1H NMR (400 MHz, CDCl3) δ = 3.81 (1H, dd, J 10.0, 7.0 Hz, CH), 3.70 (3H, s, CH3O), 3.65 (1H, dd, J 10.0, 6.0 Hz, CH), 2.72–2.63 (1H, m, CH), 1.16 (3H, d, J 7.0 Hz, CH3), 0.96 (9H, t, J 8.0 Hz, 3 × CH3), 0.60 (6H, q, J 8.0 Hz, 3 × CH2); 13C NMR (101 MHz, CDCl3) δ = 175.1 (C=O), 65.0 (CH2), 51.6 (CH3), 42.6 (CH), 13.6 (CH3), 6.7 (CH3), 4.3 (CH2); HRMS m/z (ES) Found: MNa+, 255.1397, C11H20O5SiNa requires MNa+, 255.1392; LRMS m/z (ES) 255 (MNa+, 100%); [α]D23 –41.3 (0.80, CHCl3). No data reported in the literature.158
(R)-2-Methyl-3-((triethylsilyl)oxy)propanal 299

To ester 298 (4.00 g, 17.3 mmol) in CH$_2$Cl$_2$ (100 mL) at −78 °C was added DIBAL–H (19.0 mL, 19.0 mmol, 1 M solution in hexane) dropwise. After 2 h, methanol (20 mL) was added and the solution was allowed to warm to room temperature over 30 min. The mixture was filtered through celite® and the solvent was evaporated. Purification by flash column chromatography on silica gel, eluting with petrol–EtOAc (9.5:0.5), gave the aldehyde 299 (3.18 g, 15.8 mmol, 92%) as an oil; R$_f$ 0.5 [petrol–EtOAc (9.5:0.5)]; IR $\nu_{\text{max}}$(film)/cm$^{-1}$ 2952 (C–H), 2935 (C–H), 1734 (C=O); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 9.77 (1H, d, $J$ 1.6 Hz, CHO), 3.86–3.84 (2H, m, CH$_2$), 2.61–2.51 (1H, m, CH), 1.11 (3H, d, $J$ 7.0 Hz, CH$_3$), 0.97 (9H, t, $J$ 8.0 Hz, 3 × CH$_3$), 0.61 (6H, q, $J$ 8.0 Hz, 3 × CH$_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 204.0 (C=O), 63.0 (CH$_2$), 48.9 (CH), 10.3 (CH$_3$), 6.7 (CH$_3$), 4.3 (CH$_2$); HRMS m/z (ES) Found: MNa$^+$, 225.1298, C$_{10}$H$_{22}$O$_x$NaSi requires MNa$^+$, 225.1287; LRMS m/z (ES) 225 (MNa$^+$, 100%); [$\alpha$]$^D_{23}$ −5.0 (0.80, CHCl$_3$). No data reported in the literature.$^{158}$

(5R)-2,2,5-Trimethyl-1,3-dioxane-4-carbonitrile 293

To the aldehyde 299 (3.98 g, 19.7 mmol) and TMSCN (2.51 g, 25.7 mmol), was added potassium cyanide (25 mg, 0.39 mmol) and 18-crown-6 (100 mg, 0.39 mmol) at 0 °C. The mixture was allowed to warm to room temperature. After 16 h, camphorsulfonic acid (640 mg, 2.76 mmol), acetone (50 mL) and 2,2-dimethoxypropane (29.8 g, 286 mmol) was added. After 16 h, the reaction was quenched with triethylamine (20 mL). The mixture was washed with aqueous Na$_2$CO$_3$ (1 M), then was extracted with Et$_2$O (3 × 25 mL). The combined organic layers were dried (MgSO$_4$) and the solvent was evaporated. Purification by column
chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile 293 (1.98 g, 12.7 mmol, 64%) as an oil as a mixture of diastereoisomers (dr 1:1:1); Rf 0.29 [petrol–EtOAc (9:1)]; IR νmax(film)/cm⁻¹ 2970 (C–H), 2879 (C–H); ¹H NMR (400 MHz, CDCl₃) for major isomer δ = 4.36 (1H, d, J 10.5 Hz, CH), 3.86 (1H, dd, J 12.0, 5.0 Hz, CH), 3.56 (1H, dd, J 12.0, 10.0 Hz, CH), 2.26–2.15 (1H, m, CH), 1.59 (3H, s, CH₃), 1.44 (3H, s, CH₃), 1.00 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 117.6 (CN), 99.5 (C), 65.8 (CH), 64.8 (CH₂), 33.3 (CH), 25.0 (CH₃), 24.3 (CH₃), 12.4 (CH₃); minor isomer δ = 4.85 (1H, d, J 4.5 Hz, CH), 3.94 (1H, dd, J 12.0, 4.0 Hz, CH), 3.74 (1H, dd, J 12.0, 7.0 Hz, CH), 2.14–2.06 (1H, m, CH), 1.47 (3H, s, CH₃), 1.46 (3H, s, CH₃), 1.21 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 117.0 (CN), 100.0 (C), 64.3 (CH), 63.4 (CH₂), 30.8 (CH), 28.7 (CH₃), 19.0 (CH₃), 12.5 (CH₃); HRMS m/z (ES) Found: MH⁺, 156.1016 C₈H₁₄NO₂ requires MH⁺, 156.1019; LRMS m/z (ES) 156 (MH⁺, 100%).

(4S,5R)-2,2,5-Trimethyl-4-(pent-4-en-1-yl)-1,3-dioxane-4-carbonitrile 300

To diisopropylamine (0.5 mL, 3.5 mmol) in THF (3 mL) at −78 °C was added nBuLi (1.4 mL, 3.5 mmol, 2.5 M solution in hexane). The mixture was stirred for 20 min, and then nitrile 293 (500 mg, 3.20 mmol) in THF (2 mL) was added dropwise. After 30 min, 4-bromo-1-butene (0.76 mL, 6.4 mmol) was added. The mixture was stirred at −78 °C for 2 h. The mixture was stirred for 2 h at −20 °C, then saturated aqueous ammonium chloride was added and the mixture was allowed to warm to room temperature. The mixture was extracted with CH₂Cl₂ (3 × 10 mL). The organic layers were combined, dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the nitrile 300 (466 mg, 2.10 mmol, 65%) as an oil; Rf 0.45 [petrol–EtOAc (9:1)]; IR νmax(film)/cm⁻¹ 2999 (C–H), 2972 (C–H), 2875 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 5.82 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.09–4.99 (2H, m, CH₂=CH), 3.83 (1H, t, J 12.0 Hz, CH), 3.69 (1H, dd, J 12.0, 5.0 Hz, CH), 2.15–2.09 (2H, m, 2 × CH), 2.00–1.87 (2H, m, 2 × CH), 1.78–1.75 (1H, m, CH), 1.69 (3H, s, CH₃), 1.68–
1.62 (2H, m, 2 × CH), 1.40 (3H, s, CH₃), 1.00 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 138.0 (CH), 120.0 (CN), 115.0 (CH₂), 100.5 (C), 75.0 (C), 63.1 (CH₂), 38.9 (CH₂), 35.9 (CH), 33.3 (CH₂), 30.5 (CH₃), 22.3 (CH₂), 21.0 (CH₃), 12.0 (CH₃); HRMS m/z (ES) Found: MH⁺, 224.1643, C₁₃H₂₂N₂O₂ requires MH⁺, 224.1651; LRMS m/z (ES) 224 (MH⁺ for 100%).

2-Hydroxy-2-((2R)-1-hydroxypropan-2-yl)hept-6-enenitrile 301

To a solution of acetal 300 (50 mg, 0.22 mmol) in hexane (1 mL) was added aqueous HCl (0.7 µL, 37%) at room temperature. After 4 h, water (3 mL) was added and the mixture was extracted with Et₂O (3 × 3 mL). The organic layers were combined, dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (7:3), gave the diol 301 (20 mg, 0.11 mmol, 50%) as an oil as a single diastereoisomer; Rf 0.37 [petrol–EtOAc (7:3)]; IR νmax(film)/cm⁻¹ 3300 (OH), 2875 (C−H); ¹H NMR (400 MHz, CDCl₃) δ = 5.82 (1H, ddt, J 17.0, 10.5, 6.5 Hz, CH=CH₂), 5.68–5.59 (1H, br. s, OH), 5.09–4.99 (2H, m, CH₂=CH), 4.01 (1H, t, J 10.5 Hz, CH), 3.90 (1H, dd, J 10.5, 4.0 Hz, CH), 2.17–2.10 (3H, m, 2 × CH and OH), 1.89–1.80 (1H, m, CH), 1.76–1.69 (3H, m, 3 × CH), 1.23–1.09 (1H, m, CH), 0.95 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 138.0 (CH), 120.4 (CN), 115.3 (CH₂), 77.2 (C), 67.1 (CH₂), 41.2 (CH), 38.2 (CH₂), 33.4 (CH₂), 22.2 (CH₂), 12.2 (CH₃). HRMS and LRMS could not be obtained with ES.

4-Pentenal 304

Allyl vinyl ether (2.0 g, 23.8 mmol) was heated to 150 °C at 200 W in a sealed tube for 7 h. The mixture was allowed to cool to room temperature to afford the desired aldehyde 304 (2.0 g, 100%) as an oil, which was used without further purification; ¹H NMR (400 MHz, CDCl₃) δ = 9.79 (1H, t, J 1.5 Hz, CHO), 5.85 (1H, ddt, J 16.5,
10.5, 6.5 Hz, $CH≡CH_2$), 5.09–5.02 (2H, m, $CH_2≡CH$), 2.58–2.54 (2H, m, $CH_2CHO$), 2.43–2.37 (2H, m, $CH_2CH≡CH_2$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 201.9 (C=O), 136.4 (CH), 115.7 (CH$_2$), 42.7 (CH$_2$), 26.1 (CH$_2$). Data consistent with that of the literature.$^{123}$

**(4S,5R)-4-(1-Hydroxypent-4-en-1-yl)-2,2,5-trimethyl-1,3-dioxane-4-carbonitrile 306a and 306b**

\[\begin{align*}
\text{CN} & \text{OH} \\
O & \text{O} \\
\text{CH} & \text{CH} \\
\end{align*}\]

To a solution of diisopropylamine (1.0 mL, 7.68 mmol) in THF (8 mL) at −78 °C was added $^n$BuLi (3.0 mL, 7.68 mmol, 2.5 M solution in hexane), and the mixture was allowed to stir for 20 min. Nitrile 293 (1.00 g, 6.45 mmol) was added and after 30 min, 4-pentenal 304 (1.00 g, 12.8 mmol) in THF (4 mL) was added. After 1 h, the mixture was warmed to −20 °C. After 1 h, the mixture was allowed to warm to room temperature. After 30 min, the reaction was quenched with H$_2$O (4 mL) and was extracted with Et$_2$O (3 × 20 mL). The organic layers were combined and were washed with brine (10 mL), dried (MgSO$_4$) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alcohol 306 (1.26 g, 4.83 mmol, 75%) as a partially separable mixture of two diastereoisomers (ratio 1:1.1) as an oil;

Data for 306a R$_f$ 0.22 [petrol–EtOAc (9:1)]; IR $\nu_{max}$(film)/cm$^{-1}$ 3050 (OH), 2926 (C–H), 1643 (C–H); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 5.85 (1H, ddt, J 17.0, 10.0, 6.5 Hz, $CH≡CH_2$), 5.13–5.03 (2H, m, $CH_2≡CH$), 3.84–3.73 (2H, m, 2 × CH), 3.70 (1H, dd, J 12.0, 5.0 Hz, $CHOH$), 2.50–2.33 (2H, m, 2 × CH), 2.22–2.17 (2H, m, CH and OH), 1.87–1.77 (1H, m, CH), 1.71 (3H, s, CH$_3$), 1.63–1.57 (1H, m, CH), 1.42 (3H, s, CH$_3$), 1.07 (3H, d, J 7.0 Hz, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 137.6 (CH), 119.1 (C), 115.5 (CH$_2$), 100.8 (C), 78.3 (C), 75.6 (CH), 63.1 (CH$_2$), 31.8 (CH$_3$), 30.2 (CH), 30.1 (CH$_2$), 30.0 (CH$_2$), 21.1 (CH$_3$), 12.7 (CH$_3$); HRMS m/z (ES) Found:
MNa⁺, 262.1412, C₁₃H₂₁NO₃Na⁺ requires MNa⁺, 262.1414; LRMS m/z (ES) 262 (MNa⁺ for 100%).

Data for 306b Rf 0.18 [petrol–EtOAc (9:1)]; IR νmax(film)/cm⁻¹ 3050 (OH), 2926 (C–H), 1643 (C=O); ¹H NMR (400 MHz, CDCl₃) δ = 5.87 (1H, ddt, J 17.0, 10.0, 6.5 Hz, CH=CH₂), 5.14‒5.03 (2H, m, CH₂=CH), 3.84 (1H, t, J 12.0 Hz, CH), 3.75 (1H, dd, J 12.0, 5.0 Hz, CH), 3.65 (1H, td, J 11.0, 2.0 Hz, CHOH), 2.55‒2.48 (1H, m, CH), 2.43‒2.34 (1H, m, CH), 2.26‒2.16 (1H, m, CH), 1.98‒1.89 (1H, m, CH), 1.76‒1.73 (2H, m, CH and OH), 1.71 (3H, s, CH₃), 1.42 (3H, s, CH₃), 1.02 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 137.6 (CH), 119.0 (C), 115.5 (CH₂), 100.8 (C), 77.9 (C), 72.3 (CH), 62.8 (CH₂), 31.2 (CH₂), 30.8 (CH₃), 30.2 (CH), 30.1 (CH₂), 21.3 (CH₃), 11.7 (CH₃); HRMS m/z (ES) Found: MNa⁺, 262.1412, C₁₃H₂₁NO₃Na⁺ requires MNa⁺, 262.1414; LRMS m/z (ES) X (MNa⁺ for 100%).

Formation of nitrile 306b by reduction of ketone 309

To a solution of ketone 309 (500 mg, 2.10 mmol) in MeOH (9 mL) at −78 °C was added NaBH₄ (95.7 mg, 2.53 mmol) in MeOH (2 mL) dropwise. After 2 h, the reaction quenched with water (5 mL). The mixture was extracted with Et₂O (3 × 5 mL), the organic layers were combined and were washed with brine (5 mL), dried (MgSO₄) and the solvent was removed under reduced pressure to give the alcohol as a mixture of two diastereoisomers (ratio 11:1 by ¹H NMR spectroscopy) as an oil. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave alcohol 306b (0.35 g, 1.47 mmol, 70%) as an oil ‘Data as above’.

(2R)-Methyl-5,5-dimethyl-4-(pentenyl-1-one)-1,3-dioxane-4-carbonitrile 309

To a solution of freshly distilled oxalyl chloride (0.4 mL, 4.6 mmol) in CH₂Cl₂ (20 mL) at −60 °C was added DMSO (0.65 mL, 9.2 mmol). After 5 min, the alcohol 306
(1.0 g, 4.2 mmol) was added dropwise over 10 min, followed, after 30 min, by addition of Et₃N (2.9 mL, 21 mmol). The reaction mixture was stirred for 10 min then was allowed to warm to room temperature. Water (15 mL) was added, and the mixture was extracted with CH₂Cl₂ (3 x 20 mL) and the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ketone 309 (0.84 g, 3.55 mmol, 85%) as an oil; R_f 0.28 [petrol–EtOAc (9.5:0.5)]; IR ν_max(film)/cm⁻¹ 2926 (C−H), 2859 (C−H), 1674 (C=O), 1643 (C=C); ¹H NMR (400 MHz, CDCl₃) δ = 5.81 (1H, dtt, J 17.0, 10.0, 6.5 Hz, CH=CH₂), 5.12–5.01 (2H, m, CH₂=CH), 5.08 (1H, t, J 12.0 Hz, CH), 5.05 (1H, dd, J 12.0, 5.0 Hz, CH), 2.83 (2H, t, J 7.0 Hz, CH₂), 2.40–2.34 (2H, m, CH₂), 2.21–2.11 (1H, m, CH), 1.73 (3H, s, CH₃), 1.48 (3H, s, CH₃), 0.98 (3H, d, J 7.0 Hz, CH₃); ¹³C NMR (101 MHz, CDCl₃) δ = 200.0 (C), 136.3 (CH), 116.9 (C), 115.9 (CH₂), 101.1 (C), 80.2 (C), 62.5 (CH₂), 35.4 (CH₂), 32.2 (CH₃), 30.2 (CH), 27.2 (CH₂), 21.1 (CH₃), 11.5 (CH₃); HRMS m/z (ES) Found: MH⁺, 260.1260, C₁₃H₁₉NO₃Na⁺ requires MNa⁺, 260.1263; LRMS m/z (ES) 260 (MNa⁺ for 100%).

2,3-Dihydroxy-2-((2R)-1-hydroxypropan-2-yl)hept-6-enenitrile 311

To a solution of acetal 306 (50 mg, 0.20 mmol) in hexane (1 mL) was added aqueous HCl (0.7 µL, 37%) at room temperature. After 4 h, water (3 mL) was added and the mixture was extracted with Et₂O (3 x 3 mL). The organic layers were combined, dried (MgSO₄) and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (4:6), gave the triol 311 (16 mg, 0.08 mmol, 40%) as an oil as a single diastereoisomer; R_f 0.25 [petrol–EtOAc (4:6)]; IR ν_max(film)/cm⁻¹ 3300 (OH), 2875 (C–H); ¹H NMR (400 MHz, CDCl₃) δ = 5.83 (1H, dtt, J 17.0, 10.0, 6.5 Hz, CH=CH₂), 5.14–5.04 (2H, m, CH₂=CH), 4.47 (1H, t, J 9.0 Hz, CHO), 3.86 (1H, dd, J 10.0, 9.0 Hz, CH), 3.77–3.71 (1H, m, CH), 3.65 (1H, s, OH), 2.90–2.81 (1H, m, CH), 2.46–2.36 (1H, m, CH), 2.29–2.21 (1H, m, CH), 2.06–1.99 (1H, m, CH), 1.61 (1H, s, OH), 1.53–1.44 (1H, m, CH), 1.17 (3H, d,
J 7.0 Hz, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$, two quaternary carbons could not be observed) δ = 137.1 (CH), 116.2 (CH$_2$), 71.9 (CH), 71.3 (CH$_2$), 39.4 (CH), 31.4 (CH$_2$), 30.0 (CH$_2$), 10.4 (CH$_3$); HRMS m/z (ES) Found: MH$^+$, 200.1279, C$_{10}$H$_{17}$NO$_3$ requires MH$^+$, 200.1281; LRMS m/z (ES) 200 (MH$^+$ for 100%).

(5R)-4-(1-(4-Methoxyphenoxy)pent-4-en-1-yl)-2,2,5-trimethyl-1,3-dioxane-4-carbonitrile 319

To a solution of NaH (300 mg, 12.6 mmol) in DMF (8 mL) at 0 °C was added, dropwise, a premixed solution of PMBCl (654 mg, 4.18 mmol) and alcohol 306 (500 mg, 2.10 mmol) in THF (2 mL). The solution was left to warm to room temperature overnight. The mixture was then cooled to 0 °C and was quenched with saturated aqueous NH$_4$Cl (3 mL). The products were extracted with Et$_2$O (3 × 15 mL), the organic layers were combined and washed with H$_2$O (3 × 10 mL) and brine (20 mL). The organic solution was dried (MgSO$_4$) and the solvent was removed under reduced pressure. Purification by using column chromatography on silica gel, eluting with petrol–EtOAc (9:1), afforded nitrile 319 (600 mg, 1.68 mmol, 80%) as an oil; R$_f$ 0.28 [petrol–EtOAc (9:1)]; IR ν$_{max}$(film)/cm$^{-1}$ 2928 (C–H), 2855 (C–H); $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.34–7.31 (2H, m, ArH), 6.91–6.89 (2H, m, ArH), 5.85 (1H, ddt, J 17.0, 10.0, 6.5 Hz, C=CH$_2$), 5.12–5.00 (2H, m, C=CH), 4.76 (1H, d, J 10.5 Hz, CH), 4.60 (1H, d, J 10.5 Hz, CH), 3.82–3.80 (4H, m, CH and CH$_3$), 3.71 (1H, dd, J 12.0, 5.0 Hz, CH), 3.68 (1H, dd, J 12.0, 5.0 Hz, CH), 2.38–2.29 (2H, m, 2 × CH), 2.21–2.12 (1H, m, CH), 1.87–1.82 (2H, m, 2 × CH), 1.71 (3H, s, CH$_3$), 1.42 (3H, s, CH$_3$), 1.02 (3H, d, J 7.0 Hz, CH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 159.3 (C), 137.9 (CH), 130.0 (C), 129.7 (CH), 120.2 (CN), 115.4 (CH$_2$), 113.8 (CH), 100.6 (C), 81.4 (CH), 77.5 (C), 73.6 (CH$_2$), 71.5 (CH$_2$), 63.1 (CH$_2$), 55.3 (CH$_3$), 31.1 (CH$_3$), 30.3 (CH), 29.0 (CH$_2$), 21.3 (CH$_3$), 12.3 (CH$_3$); HRMS m/z (ES) Found: MNa$^+$, 382.1979, C$_{21}$H$_{29}$NO$_4$Na$^+$ requires MNa$^+$, 382.1989; LRMS m/z (ES) 382 (MNa$^+$, 100%).
(2R)-Methyl 3-(tert-butyldimethylsilyloxy)-2-methylpropanoate 330\(^{181}\)

To a solution of imidazole (860 mg, 12.6 mmol) in CH\(_2\)Cl\(_2\) (15 mL) was added alcohol 294 (1.0 g, 8.4 mmol). After 10 min, TBSCl (1.69 g, 11 mmol) was added dropwise and the mixture was left to warm for 18 h. The reaction was quenched with H\(_2\)O (10 mL), extracted with CH\(_2\)Cl\(_2\) (3 \times 5 mL), organic layers combined and washed with brine (5 mL), dried (MgSO\(_4\)) and the solvent was removed under reduced pressure. The product was purified by column chromatography on silica gel, eluting with petrol–EtOAc (9.5: 0.5), to give the ester 330 (1.97 g, 8.40 mmol, 100%) as an oil; R\(_f\) 0.35 [petrol–EtOAc (9.5:0.5)]; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2955 (C–H), 2934 (C–H), 1745 (C=O), 1463 (C–H); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 3.79\) (1H, dd, \(J_{10.0, 7.0}\) Hz, CH), 3.69 (3H, s, CH\(_3\)), 3.66 (1H, dd, \(J_{10.0, 6.0}\) Hz, CH), 2.66–2.57 (1H, m, CH), 1.15 (3H, d, \(J 7.0\) Hz, CH\(_3\)), 0.89 (9H, s, 3 \times CH\(_3\)), 0.06 (3H, s, CH\(_3\)), 0.05 (3H, s, CH\(_3\)). Data corresponds with the literature.\(^{181}\)

(2R)-Methyl 3-(tert-butyldimethylsilyloxy)-2-methylpropanal 331\(^{181}\)

To a solution of ester 330 (500 mg, 2.15 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at −78 °C was added DIBAL-H (2.26 mL, 2.26 mmol, 1.0 M solution in hexane) dropwise. After 2 h, the reaction was quenched with MeOH (5 mL) and was filtered through Celite\(^\circledR\). Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.7:0.3), gave the aldehyde 331 (340 mg, 1.72 mmol, 80%) as an oil; R\(_f\) 0.42 [petrol–EtOAc (9.7:0.3)]; IR \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 2955 (C–H), 2907(C–H), 2876 (C–H), 1735 (C=O); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 9.76\) (1H, d, \(J 1.5\) Hz, CHO), 3.88 (1H, dd, \(J 10.0, 5.0\) Hz, CH) 3.82 (1H, dd, \(J 10.0, 6.0\) Hz, CH), 2.59–2.53 (1H, m, CH), 1.11 (3H, d, \(J 7.0\) Hz, CH\(_3\)), 0.89 (9H, s, 3 \times CH\(_3\)), 0.07 (6H, s, 2 \times CH\(_3\)). Data corresponds with the literature.\(^{181}\)
**N,N-Diisopropylcarbamoyl 4-pentene 332**

\[
\text{\includegraphics{image}}
\]

1st method

To a solution of N,N-diisopropylcarbamoyl chloride (1.90 g, 11.6 mmol) and Et\(_3\)N (1.29 g, 12.8 mmol) in CH\(_2\)Cl\(_2\) (15 mL) was added 4-pentenol 303 (1.00 g, 11.6 mmol). The reaction mixture was heated under reflux for 24 h, then with H\(_2\)O (5 mL) was added. The product was extracted with Et\(_2\)O (3 × 5 mL), the organic layers were combined and were washed with brine (5 mL), dried (MgSO\(_4\)) and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9.5:0.5), gave the carbamate 332 (2.34 g, 11.0 mmol, 95%) as an oil.

2nd method

To a solution of N,N-diisopropylcarbamoyl chloride (230 mg, 1.40 mmol) in PhMe (2 mL) was added 4-pentenol 332 (100 mg, 1.16 mmol) and Et\(_3\)N (0.15 g, 1.50 mmol). The reaction mixture was placed in a microwave at 200 W for 1 h at 150 °C. The mixture was cooled to room temperature and was filtered through a silica plug. The solvent was removed under reduced pressure to afford the carbamate 332 (156 mg, 0.73 mmol, 63%) as an oil; R\(_f\) 0.68 [petrol–EtOAc (9:1)]; IR \(\nu_{\text{max}}\) (film) /cm\(^{-1}\) 2970 (C–H), 2940 (C–H), 1687 (C=O), 1434 (C–H); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 5.85\) (1H, ddt, \(J = 17.0, 10.0, 7.0\) Hz, \(CH=CH_2\)), 5.09–4.98 (2H, m, \(CH_2=CH_2\)), \(4.11\) (2H, t, \(J = 6.5\) Hz, \(CH_2O\)), \(3.83–3.62\) (2H, m, \(2 \times \text{CHN}\)), \(2.20–2.14\) (2H, m, \(2 \times \text{CH}\)), \(1.80–1.73\) (2H, m, \(2 \times \text{CH}\)), \(1.22\) (12H, d, \(J = 7.0\) Hz, \(4 \times \text{CH}_3\)). Data corresponds with the literature.\(^{174}\)
(2R,3R,4R)-1-((tert-Butyldimethylsilyl)oxy)-3-hydroxy-2-methyloct-7-en-4-yl diisopropylcarbamate 334

To a solution of (+)-sparteine (160 mg, 0.70 mmol) and sec-BuLi (0.60 mL, 0.84 mmol, 1.4 M solution in hexanes) in Et₂O (5 mL) at −78 °C was added the carbamate 332 (100 mg, 0.47 mmol). After 6 h, the aldehyde 331 (110 mg, 0.56 mmol) was added and the mixture allowed to warm to room temperature over 18 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ (3 mL), and was extracted with Et₂O (3 × 5 mL). The organic layers were combined and were washed with brine (5 mL), dried (MgSO₄), and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alcohol 334 (30 mg, 0.07 mmol, 13%) as an oil; Rₜ 0.16 [petrol–EtOAc (9:1)]; IR ν_max(film)/cm⁻¹ 2970 (C–H), 2930 (C–H), 1685 (C=O); ¹H NMR (400 MHz, CDCl₃) δ = 5.90–5.78 (1H, m, CH≡CH₂), 5.09–4.98 (2H, m, CH₂=CH), 4.18–4.08 (1H, m, CH), 3.77 (1H, dd, J 10.0, 4.0 Hz, CH), 3.69–3.62 (1H, m, CH), 3.60–3.54 (1H, dd, J 10.0, 8.0 Hz, CH), 2.21–2.11 (1H, m, CH), 2.00–1.93 (1H, m, CH), 1.80–1.74 (1H, m, CH), 1.63–1.60 (1H, m, CH), 1.45–1.37 (1H, m, CH), 1.29–0.92 (3H, m, 2 × CH and OH), 1.22 (3H, d, J 7.0 Hz, CH₃), 0.92 (12H, d, J 6.5 Hz, 4 × CH₃), 0.85 (9H, s, 3 × CH₃), 0.12 (3H, s, CH₃), 0.09 (3H, s, CH₃); ¹³C NMR (101 MHz, CDCl₃, one quaternary carbon (C=O) could not be observed) δ = 138.4 (CH), 114.7 (CH₂), 77.7 (CH), 75.2 (CH), 74.2 (CH), 67.3 (CH₂), 64.0 (CH₂), 37.0 (CH), 35.9 (CH₃), 29.9 (CH₂), 25.8 (CH₃), 18.1 (C), 14.3 (CH₃), –5.7 (CH₃); HRMS m/z (ES) Found: MH⁺, 416.3191, C₂₂H₄₆NO₄Si requires MH⁺, 416.3191; LRMS m/z (ES) 416 (MH⁺, 100%).
Pent-4-en-1-yl 2,4,6-triisopropylbenzoate 337

To a mixture of 4-pentenol 303 (2.0 g, 23 mmol), triphenylphosphine (6.7 g, 25 mmol) and 2,4,6-triisopropylbenzoic acid (6.6 g, 27 mmol) in THF (35 mL), was added DIAD (5.2 g, 25 mmol) dropwise at 0 °C. After 18 h at room temperature, the solvent was removed and the residue was dissolved in pentane. After 5 min, the suspension was filtered. Purification by using column chromatography on silica gel, eluting with petrol–EtOAc (9:1), gave the alkene 337 (6.9 g, 22 mmol, 95%) as an oil; Rf 0.33 [petrol–EtOAc (9.5:0.5)]; IR νmax(film)/cm⁻¹ 2960 (C–H), 2930 (C–H), 1720 (C=O); ¹H NMR (400 MHz, CDCl₃) δ = 7.28 (2H, s, ArH), 5.84 (1H, ddt, J 17.0, 10.0, 7.0 Hz, CH=CH₂), 5.10–5.01 (2H, m, CH₂=CH), 4.33 (2H, t, J 6.5 Hz, CH₂O), 2.94–2.83 (3H, m, 3 × CH), 2.23–2.18 (2H, m, 2 × CH), 1.89–1.82 (2H, m, 2 × CH), 1.27 (12H, d, J 7.0 Hz, 4 × CH₃), 1.26 (6H, d, J 7.0 Hz, 2 × CH₃); ¹³C NMR (101 MHz, CDCl₃, two quaternary carbon could not be observed) δ = 150.0 (C=O), 144.7 (C), 137.4 (CH), 120.9 (CH), 115.5 (CH₂), 64.3 (CH₂), 34.4 (CH), 31.5 (CH), 30.2 (CH₂), 27.8 (CH₂), 24.2 (CH₃), 24.0 (CH₃); HRMS m/z (ES) Found: M⁺, 316.2404, C₂₁H₃₂O₂ requires M⁺, 316.2397; LRMS m/z (ES) 316 (M⁺, 100%).
Chapter 7 Appendices

Appendix 1

X-ray crystal structure determination data of 112a

Crystal data and structure refinement for 112a

Empirical formula \( \text{C}_{15}\text{H}_{19}\text{NO}_{3} \)

Formula weight 261.31

Temperature 100(2) K

Wavelength 1.54178 Å

Crystal system Orthorhombic

Space group Pna21

Unit cell dimensions
\[
a = 14.3226(3) \text{ Å} \quad a = 90^\circ.
\]
\[
b = 14.6136(3) \text{ Å} \quad b = 90^\circ.
\]
\[
c = 6.2026(2) \text{ Å} \quad g = 90^\circ.
\]

Volume 1298.23(6) Å³

Z 4

Density (calculated) 1.337 Mg/m³

Absorption coefficient 0.754 mm⁻¹

\( F(000) \) 560

Crystal size 0.340 x 0.340 x 0.280 mm³

Theta range for data collection 4.322 to 65.991°.

Index ranges
-16 ≤ h ≤ 15, -17 ≤ k ≤ 17, -6 ≤ l ≤ 7

Reflections collected 17202

Independent reflections 2091 [R(int) = 0.0273]
Completeness to theta = 66.000° 99.8 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.87 and 0.65
Refinement method Full-matrix least-squares on F2
Data / restraints / parameters 2091 / 1 / 174
Goodness-of-fit on F2 1.060
Final R indices [I>2sigma(I)] R1 = 0.0268, wR2 = 0.0671
R indices (all data) R1 = 0.0279, wR2 = 0.0680
Absolute structure parameter 0.07(6)
Extinction coefficient n/a
Largest diff. peak and hole 0.134 and -0.174 e.Å⁻³

Appendix 2

X-ray crystal structure determination data of 112b

Crystal data and structure refinement for 112b
Empirical formula C₁₅H₁₉NO₃
Formula weight 261.31
Temperature 97(2) K
Wavelength 0.71073 Å
Crystal system Orthonormbic
Space group Pna2₁
Unit cell dimensions

\begin{align*}
a &= 13.3032(15) \ \text{Å} & a &= 90^\circ. \\
b &= 15.4042(17) \ \text{Å} & b &= 90^\circ. \\
c &= 6.8015(7) \ \text{Å} & c &= 90^\circ.
\end{align*}

Volume

1393.8(3) Å³

Z

4

Density (calculated)

1.245 Mg/m³

Absorption coefficient

0.087 mm⁻¹

F(000)

560

Crystal size

0.430 x 0.380 x 0.340 mm³

Theta range for data collection

2.023 to 27.563°.

Index ranges

-17 ≤ h ≤ 16, -18 ≤ k ≤ 20, -8 ≤ l ≤ 8

Reflections collected

15491

Independent reflections

3063 [R(int) = 0.0547]

Completeness to theta = 25.000°

100.0 %

Absorption correction

Semi-empirical from equivalents

Max. and min. transmission

0.87 and 0.77

Refinement method

Full-matrix least-squares on F²

Data / restraints / parameters

3063 / 1 / 174

Goodness-of-fit on F²

1.080

Final R indices [I>2σ(I)]

R₁ = 0.0419, wR₂ = 0.0892

R indices (all data)

R₁ = 0.0551, wR₂ = 0.0972

Absolute structure parameter

?

Extinction coefficient

n/a

Largest diff. peak and hole

0.162 and -0.220 e.Å⁻³
Appendix 3

X-ray crystal structure determination data of 117a

Crystal data and structure refinement for 117a
Empirical formula \( \text{C}_{16}\text{H}_{21}\text{NO}_3 \)
Formula weight 275.34
Temperature 100(2) K
Wavelength 1.54178 Å
Crystal system Monoclinic
Space group \( \text{C2/c} \)
Unit cell dimensions
\[
\begin{array}{c}
a = 23.9178(6) \, \text{Å} \\
b = 7.9721(2) \, \text{Å} \\
c = 16.2844(4) \, \text{Å}
\end{array}
\]
\[
\begin{array}{c}
a = 90°. \\
b = 112.4190(10)°. \\
g = 90°.
\end{array}
\]
Volume 2870.35(13) Å³
Z 8
Density (calculated) 1.274 Mg/m³
Absorption coefficient 0.707 mm⁻¹
\( F(000) \) 1184
Crystal size 0.390 x 0.260 x 0.120 mm³
 Theta range for data collection 3.999 to 66.657°.
Index ranges \(-27 \leq h \leq 28, -8 \leq k \leq 9, -18 \leq l \leq 19\)
Reflections collected 22494
Independent reflections 2537 \([\text{R(int)} = 0.0266]\)
Completeness to theta = 66.657° 99.8 %
Absorption correction None
Refinement method Full-matrix least-squares on F2
Data / restraints / parameters 2537 / 0 / 183
Goodness-of-fit on F2 1.028
Final R indices [I>2sigma(I)] R1 = 0.0353, wR2 = 0.0857
R indices (all data) R1 = 0.0378, wR2 = 0.0875
Extinction coefficient n/a
Largest diff. peak and hole 0.252 and -0.233 e.Å-3

Appendix 4

X-ray crystal structure determination data of 120a

Crystal data and structure refinement for 120a
Empirical formula C_{18}H_{23}NO_{5}
Formula weight 333.37
Temperature 100(2) K
Wavelength 1.54178 Å
Crystal system Triclinic
Space group P-1
Unit cell dimensions
a = 8.0628(3) Å  a = 65.4560(10)°
b = 10.3241(4) Å  b = 71.9819(10)°
c = 11.8540(4) Å  g = 75.4771(11)°
Volume  
844.99(5) Å³

Z  
2

Density (calculated)  
1.310 Mg/m³

Absorption coefficient  
0.787 mm⁻¹

F(000)  
356

Crystal size  
0.500 x 0.400 x 0.400 mm³

Theta range for data collection  
4.216 to 66.492°.

Index ranges  
-8<=h<=9, -12<=k<=12, -14<=l<=14

Reflections collected  
16743

Independent reflections  
2923 [R(int) = 0.0291]

Completeness to theta = 66.500°  
98.2 %

Absorption correction  
Semi-empirical from equivalents

Max. and min. transmission  
0.87 and 0.65

Refinement method  
Full-matrix least-squares on F²

Data / restraints / parameters  
2923 / 0 / 220

Goodness-of-fit on F²  
1.964

Final R indices [I>2sigma(I)]  
R1 = 0.0359, wR2 = 0.1179

R indices (all data)  
R1 = 0.0376, wR2 = 0.1190

Extinction coefficient  
n/a

Largest diff. peak and hole  
0.289 and -0.246 e.Å⁻³

Appendix 5

X-ray crystal structure determination data of 123a
Crystal data and structure refinement 123a

Empirical formula \( \text{C}_{17}\text{H}_{21}\text{NO}_4 \)

Formula weight 303.35

Temperature 97(2) K

Wavelength 0.71073 Å

Crystal system Triclinic

Space group P-1

Unit cell dimensions
\[
\begin{align*}
a &= 8.1998(7) \text{ Å} & a &= 106.900(5)°. \\
b &= 9.9463(8) \text{ Å} & b &= 98.639(4)°. \\
c &= 11.1065(10) \text{ Å} & g &= 113.655(4)°. 
\end{align*}
\]

Volume 756.19(12) Å³

\( Z \) 2

Density (calculated) 1.332 Mg/m³

Absorption coefficient 0.095 mm⁻¹

\( F(000) \) 324

Crystal size 0.320 x 0.210 x 0.180 mm³

Theta range for data collection 2.012 to 27.642°.

Index ranges \(-10\leq h\leq 9, \ -12\leq k\leq 12, \ -14\leq l\leq 14\)

Reflections collected 14880

Independent reflections 3472 \([R(int) = 0.0331]\)

Completeness to theta = 25.000° 99.7 %

Absorption correction Semi-empirical from equivalents

Max. and min. transmission 0.99 and 0.96

Refinement method Full-matrix least-squares on F²

Data / restraints / parameters 3472 / 0 / 202

Goodness-of-fit on F² 1.104

Final R indices [I>2sigma(I)] \( R1 = 0.0409, \ wR2 = 0.1040 \)

R indices (all data) \( R1 = 0.0578, \ wR2 = 0.1258 \)

Extinction coefficient n/a

Largest diff. peak and hole 0.309 and -0.288 e.Å⁻³
Appendix 6

X-ray crystal structure determination data of 212

Crystal data and structure refinement for 212

Empirical formula \( C_7H_{13}NO_2 \)
Formula weight 501.61
Temperature 100(2) K
Wavelength 1.54178 Å
Crystal system Monoclinic
Space group P21
Unit cell dimensions
\[ a = 10.8594(4) \, \text{Å}, \quad a = 90^\circ. \]
\[ b = 7.3763(3) \, \text{Å}, \quad b = 92.469(3)^\circ. \]
\[ c = 15.5152(7) \, \text{Å}, \quad g = 90^\circ. \]
Volume 1241.65(9) Å³
Z 2
Density (calculated) 1.342 Mg/m³
Absorption coefficient 0.772 mm⁻¹
F(000) 540
Crystal size 0.180 x 0.060 x 0.040 mm³
Theta range for data collection 2.851 to 65.991°.
Index ranges -12 <= h <= 12, -8 <= k <= 8, -17 <= l <= 18
Reflections collected 6309
Independent reflections 3609 [R(int) = 0.0537]
Completeness to theta = 65.991° 97.6 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.93 and 0.84
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<th>Value</th>
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<td>Extinction coefficient</td>
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<tr>
<td>Largest diff. peak and hole</td>
<td>0.185 and -0.182 eÅ-3</td>
</tr>
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Appendix 7

$^1$H and $^{13}$C NMR spectra bridged cycloadduct 117a in CDCl$_3$ at 400 MHz and 101 MHz respectively.
Appendix 8

Cosy and HSQC spectra for the mixture of cycloadducts 117a and 117b in CDCl₃

117a

117b

HSQC

Cosy
Appendix 9

$^1$H and $^{13}$C NMR spectra for compound 177 in CDCl$_3$ at 400 MHz and 101 MHz respectively.
Chapter 6  References


(172) Cooksey, J. P.; Ford, R.; Kocieński, P. J.; Pelotier, B.; Pons, J.-M.