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Investigation of Metal Mediated Reactions for Natural Product Synthesis

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A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy.

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Abstract

During the course of the studies outlined in this thesis, an ether-directed Pd(II)-catalysed aza-Claisen rearrangement reaction that had previously been developed by the Sutherland group was expanded to include more functionalised rearrangement substrates. This methodology has been applied for the synthesis of several natural products including dihydroxylated-α-amino acids.

Further investigation of substrates for the rearrangement led to the synthesis of δ,ε-substituted trichloroacetimidates. Rearrangement of these compounds demonstrated the role of 1,3-allylic strain on the stereocontrol of the rearrangement and also highlighted the role that solvent can have upon the diastereoselectivity of ether-directed rearrangements.

In addition to this, a novel tandem aza-Claisen rearrangement and ring closing metathesis reaction has been developed. This reaction allows the synthesis of cyclic allylic trichloroacetamides in excellent yields from simple allylic alcohols. The use of commercially available chiral rearrangement catalysts allowed a highly enantioselective tandem process to be developed.

Further development of this process has provided an ether-directed tandem aza-Claisen rearrangement and RCM reaction which occurs with high yield and diastereoselectivity to provide functionalised cyclic products. The use of these compounds for the total synthesis of the amaryllidaceae alkaloid (+)-γ-lycorane was also investigated.
Acknowledgements

The financial support of the Engineering and Physical Sciences Research Council (EPSRC) is gratefully acknowledged.

I would like to express my sincere appreciation to my supervisor, Dr Andrew Sutherland, for accepting me as a PhD student in his research group. I have learnt a great deal during the last 3 years and would like to convey my gratitude to him, for all of his help and support throughout the course of my PhD. In addition, my thanks also go to my second supervisor, Dr Richard C. Hartley, for his advice.

I would also like to thank all of the technical and support staff at the University of Glasgow for their kind assistance throughout the course of my studies. The assistance of Dr Andrei Malkov and Mikhail Kabeshov with chiral HPLC is also gratefully acknowledged.

Thank you also to the past and present members of the Sutherland group who have assisted me throughout my PhD. I particularly want to acknowledge Dr Andrew Jamieson whose initial studies in this area prompted much of the research which makes up this thesis and who also provided significant practical assistance in the early months of my PhD.

Finally, I would like to thank all of those who have supported me throughout my academic studies, in particular: my wife Tori and other friends and family for their encouragement and support throughout my time in Glasgow.
Author’s Declaration

This thesis represents the original work of Michael David Swift unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow in the Loudon and Henderson laboratories, under the supervision of Dr Andrew Sutherland, during the period, October 2005 to September 2008. Certain aspects of this work have been published elsewhere and are listed below.

List of Abbreviations

Ac  acetyl
Ar  aromatic
9-BBN  9-borabicyclo[3.3.1]nonane
Bn  benzyl
Boc  tert-butoxycarbonyl
(BMI)BF$_4$  1-butyl-3-methylimidazolium tetrafluoroborate
br  broad
Cat.  catalyst
CAN  Ceric Ammonium Nitrate
CI  Chemical Ionisation
COP  cobaltocenylimidazoline palladacycle
DBU  1,8-diazabicyclo[5,4,0]undec-7-ene
°C  degrees centigrade
de  diastereomeric excess
DCM  dichloromethane
DDQ  dichlorodicyanoquinone
DCC  $N,N'$-dicyclohexylcarbodiimide
DMAP  4-dimethylaminopyridine
DMF  $N,N'$-dimethylformamide
DMSO  dimethyl sulfoxide
DIBAL-H  diisobutylaluminium hydride
d  doublet
EI  Electron Impact
ee  enantiomeric excess
ΔH  enthalpy change
EtOAc  ethyl acetate
FIP  ferrocenylimidazoline palladacycle
FOP  ferrocenyloxazoline palladacycle
FTIR  Fourier Transform Infrared
g  gram(s)
H  Hour(s)
HPLC  High Performance Liquid Chromatography
kcal  kilocalorie(s)
LDA  lithium diisopropylamide
LHMDS  lithium hexamethyldisilazide
<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>MeOH</td>
<td>methanol</td>
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<tr>
<td>M</td>
<td>Molar</td>
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<tr>
<td>MOM</td>
<td>Methoxymethyl</td>
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<td>Me</td>
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<td>mg</td>
<td>milligram(s)</td>
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<td>mol</td>
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<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>NMO</td>
<td>N-Methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>Pd/C</td>
<td>Palladium on carbon</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzoic acid</td>
</tr>
<tr>
<td>PrOH</td>
<td>propanol</td>
</tr>
<tr>
<td>P</td>
<td>protecting group</td>
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<tr>
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<td>parts per million</td>
</tr>
<tr>
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<td>Proton Sponge</td>
</tr>
<tr>
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<td>pyridine</td>
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<td>1H</td>
<td>proton</td>
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<td>quartet</td>
</tr>
<tr>
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<td>quintet</td>
</tr>
<tr>
<td>RCM</td>
<td>Ring Closing Metathesis</td>
</tr>
<tr>
<td>RT</td>
<td>Room Temperature</td>
</tr>
<tr>
<td>sept</td>
<td>septet</td>
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<td>TBDPS</td>
<td>tert-Butyldiphenylsilyl</td>
</tr>
<tr>
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<td>tetra-n-butylammonium fluoride</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>Trifluoromethanesulfonic acid</td>
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<tr>
<td>t</td>
<td>triplet</td>
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<td>Ts</td>
<td>tosyl</td>
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1.0 Introduction

1.1 Aza-Claisen Rearrangements

Synthetic organic chemists in the 21st century have a hugely diverse range of reaction methodologies and synthetic approaches at their disposal. In recent years, chemists have turned their attention to reactions that have greater atom efficiency, enhanced stereoselectivity and those that require less purification, whilst using less toxic reagents. All of these approaches are designed to reduce the environmental impact of the chemistry that is undertaken and increase the efficiency of synthetic applications.¹

[3,3]-Sigmatropic rearrangements are a class of organic reaction that is highly atom efficient. The reaction involves the migration of a σ-bond to form a new bond with a [3,3] relationship to the original bond, as such every atom from the starting reagent is retained in the product. The Claisen rearrangement is one of the most well known types of [3,3]-sigmatropic rearrangement and was originally discovered by Ludwig Claisen in 1912 (Scheme 1).² There are several different variants of the Claisen rearrangement, many of which have found widespread use in synthetic chemistry.³

One such variant, widely used in synthetic chemistry is the aza-Claisen rearrangement reaction (Scheme 2). This is the [3,3]-sigmatropic rearrangement of an allylic imidate 1 to the amide 2, containing both an oxygen and nitrogen atom.

The aza-Claisen rearrangement was first reported by Mumm and Möller in 1937 who reported the rearrangement of an allylic benzimidate to the corresponding benzamide.⁴
However, this reaction did not see widespread application until 1974 when Overman developed the rearrangement of allylic trichloroacetimidates 3 to the corresponding allylic trichloroacetamides 4 (Scheme 3). This reaction (often referred to as the Overman rearrangement) has been widely used in synthetic chemistry over the last 30 years due to the relative ease with which a wide variety of allylic trichloro- and trifluoroacetimidates can be prepared from the corresponding allylic alcohol.

### 1.1.1 Thermal Overman Rearrangement

Overman reported both the thermal and metal catalysed aza-Claisen rearrangement of allylic trichloroacetimidates. The thermal reaction typically occurs at elevated temperatures of approximately 140 °C, usually in aromatic solvents such as p-xylene, whilst the metal catalysed process is normally conducted at room temperature.

The thermal process proceeds via a highly ordered chair-like transition state and obeys Woodward Hoffmann rules which state that in a thermal pericyclic reaction, the total number of \((4q+2)\) and \((4r)\) components must be odd. The thermal aza-Claisen rearrangement has 3 components (one \(\sigma\)-bond and two \(\pi\)-bonds), although only the alkene \(\pi\) component is counted. As such the rearrangement has one \((4q+2)\) component and no \((4r)\) components (an odd number) so this suprafacial process is thermally allowed. The mechanism for this thermal reaction has been shown to occur via a concerted pathway, although a competing non-concerted ionisation pathway leading to the [1,3]-rearranged product has been observed. A concerted mechanism means that the reaction proceeds with excellent transfer of chirality from the starting material to the amide product. This is because the new C-N bond forms on the same face as to where the C-O \(\sigma\)-bond breaks, thus making the reaction extremely useful in organic synthesis (Scheme 3).

![Scheme 3 - Thermal rearrangement of allylic trichloroacetimidates](image)

The thermal process has been shown to obey first order kinetics, whilst the rate of reaction is also affected by both steric and electronic effects of the substrate, thus leading to large
variations in reactivity between different substrates. In particular, E-imidates usually react more rapidly than Z-imidates due to the fact that they are less stable.

The reaction is driven to completion by a negative change in enthalpy associated with the conversion of the imidate to the corresponding amide, with a negative enthalpy change of approximately 15 kcal mol\(^{-1}\). As such, this process is effectively irreversible.

### 1.1.2 Metal catalysed aza-Claisen rearrangement

Initially Overman reported the metal catalysed aza-Claisen rearrangement, using mercury(II) salts, however it has subsequently been shown that a variety of transition metals (including Pd, Au and Pt) can catalyse the rearrangement process. The metal catalysed aza-Claisen rearrangement has been shown to increase the reaction rate very significantly (by approximately the order of 10\(^{12}\)). This rate enhancement often allows the reaction to proceed at room temperature and under much milder conditions than for the thermal process, often giving the rearrangement products in improved yields.

Palladium(II) has emerged as the most effective catalyst for the aza-Claisen rearrangement, this is because it equilibrates with the substrate more quickly than other transition metal catalysts and as such in most cases, the reaction proceeds more rapidly and in higher yield. As a result it is also usually possible to use lower catalyst loadings if palladium(II) is used as catalyst. Extensive studies by Overman and others have shown that the palladium (II)-catalysed process is likely to proceed by a cyclisation induced mechanism (Scheme 4). This mechanism proceeds via a stepwise pathway where the alkene of the imidate substrate is subjected to carbo-palladation, thus activating the olefin to antarafacial nucleophilic attack from the imidate nitrogen. This leads to the formation of the cyclic carbocation intermediate, which then rapidly undergoes Grob-like fragmentation to give the amide product, thus regenerating the catalyst to react with a second imidate molecule. In a similar way to the thermal process, amide formation is irreversible and is the driving force for the reaction.
The above mechanism is similar to that previously proposed by Henry for the rearrangement of allylic esters.\textsuperscript{20} Schenck and Bosnich have also suggested that the cyclic carbocation intermediate 9 formed during the reaction adopts a chair-like conformation, with the bulky metal complex at C2, in the equatorial position (Scheme 5).\textsuperscript{18} This chair-like transition state would be the most stable and as such explains why the process occurs with complete suprafacial transfer of chirality, as the new C-N bond forms on the same face as the breaking C-O bond.

The metal catalysed aza-Claisen rearrangement has broad scope and can be applied to a wide variety of primary and secondary imidates. Early work by Overman demonstrated that the imidates must have a substituent at C-3 that favours nucleophilic attack from the imidate nitrogen (Scheme 6).\textsuperscript{21} Imidates that favour C-2 attack such as 10 do not rearrange, whereas imidate 11 (which favours C-3 attack) rearranges successfully. In addition, substitution at the C-2 position is not favoured as this is where the metal catalyst is thought to coordinate (see Scheme 5 above). Only C-2 substituted imidate substrates with an
electron donating group (which stabilises the transition state) at C-3 will undergo rearrangement.\textsuperscript{22}

\[ \text{HNOCl}_3 \overset{\text{Hg(OCOCF}_3)_2}{\longrightarrow} \text{HNOCl}_3 \]

\[ \text{OCLOH} \overset{\text{Hg(OCOCF}_3)_2}{\longrightarrow} \text{OCLOH} \]

\textbf{Scheme 6 - Scope of metal catalysed rearrangement}

\subsection*{1.2 Enantioselective aza-Claisen Rearrangement}

Following the development of a metal catalysed rearrangement process, recent efforts have turned to developing an enantioselective variant of the aza-Claisen rearrangement for use in asymmetric synthesis. Early applications of the aza-Claisen rearrangement as a key synthetic step were either non-enantioselective,\textsuperscript{23} or made use of a chiral secondary imidate to introduce stereoselectivity \textit{via} chirality transfer.\textsuperscript{24,25} This clearly placed limits on the application of this reaction in modern organic synthesis where stereoselective synthetic methods are of great importance. Different approaches to develop a stereoselective aza-Claisen rearrangement to address this problem have been developed.

A variety of chiral metal catalysts have been developed to introduce enantioselectivity to the rearrangement process.

\subsection*{1.2.1 Diamine catalysts}

Overman developed the first chiral catalyst for the aza-Claisen rearrangement in 1997.\textsuperscript{26} Initially bis(oxazoline) palladium(II) catalysts were synthesised, however these were largely unsuccessful. Cationic diamine palladium complexes 14, proved to be more successful. The catalysts were constructed from two diamine ligands, synthesised from (S)-
proline and could catalyse the rearrangement of various benzimidate substrates including 12, to the amides such as 13, in good yield and modest enantioselectivity (Scheme 7).

Scheme 7 - Overman's first chiral catalyst for the aza-Claisen rearrangement

Unfortunately these cationic catalysts were incompatible with other imidate substrates (e.g. X= CCl₃, CF₃) and caused the formation of significant quantities of an undesired 1,3-rearranged product, similar to 15, which is formed via a competing ionisation pathway (Scheme 8). Various elimination products were also formed using these catalysts.⁹

Scheme 8 - [3,3]- and [1,3]- rearrangement pathways

1.2.2 Ferrocenyl palladacycles

Leung and co-workers reported similar cationic complexes to that reported by Overman and these suffered from the same problems of ionisation and elimination.²⁷ As such, new catalysts that were less prone to providing products associated with a non-concerted ionisation pathway were required. Overman and co-workers were the first to develop such catalysts.²⁸ The first neutral chiral complexes for the rearrangement of benzimidate substrates 16, were ferrocenyl palladacycles 18, consisting of a dimeric complex that gave
much greater yields for the aza-Claisen rearrangement, whilst also eliminating formation of the undesired by-products (Scheme 9). Although the yield of the rearranged products 17 was greatly enhanced with these catalysts (up to 98%), enantioselectivity remained moderate at 61% ee.

![Scheme 9 - Neutral chiral ferrocenyl palladacycle catalysts](image)

1.2.3 Ferrocenyl oxazoline (FOP) catalysts

Significant enhancements of the enantioselectivity of the aza-Claisen rearrangement were reported by Donde and Overman, who synthesised several ferrocenyl oxazoline complexes with structures similar to 19. These complexes catalysed the rearrangement of various benzimidate substrates 16 to the corresponding benzamides 17, in poor to excellent yields and in up to 92% ee (Scheme 10). Unfortunately, whilst these FOP catalysts gave much improved enantioselectivities, initially they were rather limited in scope being successful for benzimidate substrates only, which are not easily converted to synthetically useful products (e.g. the corresponding chiral allylic amines). Higher enantioselectivities were achieved using Z- rather than E-imidates, although enantioselectivities with E-imidates were still very reasonable for some substrates.

![Scheme 10 - Rearrangement using ferrocenyl oxazoline catalysts](image)
Later Kang and co-workers expanded upon this work to synthesise a variety of palladacycles based upon complex 22 which gave improved yields of the rearranged products 21 whilst also providing excellent enantioselectivity (Scheme 11). Once again the catalyst was limited in scope to benzimidate substrates 20.

![Scheme 11 - Neutral ferroceny catalysts for the rearrangement developed by Kang](image)

In 2005, Overman and co-workers reported a comprehensive evaluation of the FOP catalyst scaffold. In this study they synthesised a variety of FOP catalysts 25 and substrates 23 giving differing functionality of rearranged products 24 (Scheme 12). Results from this study led to an increase in the reported enantioselectivity achievable with these catalysts, due to an optimisation of both the catalyst structure and its substrate, thus providing a greater understanding of the scope and activity of these FOP complexes.

![Scheme 12 - Evaluation of FOP catalyst for the aza-Claisen rearrangement reaction](image)

Perhaps more importantly, this paper also showed that the FOP catalyst 25 could rearrange substrates containing removable protecting groups on the nitrogen atom. Best results were attained with E-trifluoroacetimidates 26 (CF₃ at position R²), with a variety of aryl protecting groups at R³. These substrates could readily undergo rearrangement to the amide 27, in good yield and ee (although somewhat lower than with the corresponding benzimidates) but could then be readily cleaved to the synthetically useful allylic amines 28 using sodium ethoxide to hydrolyse the trifluoroacetyl group, followed by treatment with CAN to remove the aryl group (Scheme 13).
Although FOP complexes 25 catalyse the rearrangement of several allylic imidates in excellent yield and enantioselectivity, they suffer from a number of drawbacks. Firstly, the air stable pre-catalysts must be activated with stoichiometric quantities of AgOOCOCF₃ to generate the active catalyst which is unstable to air and moisture. Secondly, although the substrate scope is broader for these catalysts than for previous examples it remains limited by the requirement for an aromatic substituent on the imidate and only limited tolerance of cleavable protecting groups (e.g. CF₃). As such, attention turned to the development of a catalyst that would not require pre-activation, successfully tolerate a wider variety of imidates (particularly the readily cleavable CF₃ and CCl₃ amides), whilst retaining excellent enantioselectivity.

### 1.2.4 Cobalt Oxazoline Palladacycle (COP) Catalysts

Cobalt oxazoline palladacycles (COP) 29 (Figure 1), have recently emerged as highly successful chiral catalysts for the aza-Claisen rearrangement. The COP scaffold was first reported by Richards, but the first use of this complex as a catalyst for the aza-Claisen rearrangement was reported by Kang and co-workers, who reported the rearrangement of allylic benzimidates using a AgOOCOCF₃ activated COP complex (Scheme 14). Excellent yields and enantioselectivities of rearranged products 31 were achieved using Z-benzimidates 30, although results for the corresponding E-imidates were disappointing.
At the same time, the groups of Overman and Richards reported the use of COP complexes 29 for the aza-Claisen rearrangement of allylic trifluoroacetimidates (Scheme 15). Optimal results of the rearranged products 33, were achieved using $E$-trifluoroacetimidates 32 (80-85% yield, 92-96% ee) in direct contrast to the results by Kang, who saw very poor yields and enantioselectivities with $E$-benzimidates. An additional advantage to this work by Overman was that COP-Cl complexes 29 did not require any pre-activation to achieve excellent yields and stereoselectivities, thus making this a more practical catalytic method.
Further improvements to this approach were reported by Anderson and Overman, who demonstrated that COP-Cl could also catalyse the rearrangement of $E$-allylic trichloroacetimidates 34, to the trichloroacetamides 35, in excellent yield and enantioselectivity (Scheme 16). These allylic trichloroacetimidates 34 are the preferred substrates for the aza-Claisen rearrangement because they are readily synthesised from the corresponding allylic alcohols in high yields.

Scheme 16 - Highly enantioselective rearrangement of allylic trichloroacetimidates

This paper also demonstrated the synthetic potential for these chiral trichloroacetamide products by their straightforward conversion to the oxazolidinones 36, bioactive natural products ((S)-vigabatrin 37) and $\alpha$-amino esters 38 (precursors for unnatural amino acids) (Scheme 17).

Scheme 17 - Synthetic utility of chiral allylic trichloroacetamides
It has subsequently been demonstrated by Overman and co-workers that the loading of COP catalysts \(29\) can be lowered to 2 mol\% for some substrates whilst maintaining excellent yield and enantioselectivity.\(^{36}\) \((S)\)-COP-Cl \(29a\) and \((R)\)-COP-Cl \(29b\) are now commercially available aza-Claisen rearrangement catalysts.\(^{36,37}\)

Recently, Overman and co-workers have reported a comprehensive kinetic and computational study of COP-Cl catalysed aza-Claisen rearrangements.\(^{19}\) The purpose of this study was to probe in more detail the reaction mechanism and provide insights into the further development of these chiral catalysts. Data from this study further supported the cyclisation-induced reaction mechanism that had previously been proposed (discussed in section 1.1). In addition to this, the study identified a previously undiscovered palladium-imidate complex \(39\) (Figure 2), which appears to be the resting state of the catalyst. It is unclear what role (if any) this complex plays in the rearrangement reaction mechanism as both kinetic and computational calculations conducted during this study, supported the formation of a palladium-olefin intermediate, which activates the C=C double bond to nucleophilic attack from the imidate nitrogen. Further data also supported the hypothesis that C-N bond formation is indeed both the rate- and enantio-determining step, leading to formation of a six-membered cyclic alkyl palladium intermediate, which rapidly fragments to give the trichloroamide product.

![Figure 2 - COP-Cl-imidate complex as observed by Overman](image)

In addition, these results also supported previous work by the Overman and Richards groups that suggested enantioselectivity of COP-Cl catalysed rearrangements was the result of planar chirality of the tetraarylcyclobutadiene ligand and not the chirality on the oxazoline substituent.\(^{38}\) It was proposed that increasing the steric bulk of the tetraarylcyclobutadiene ligand should further enhance enantioselectivity. This is because the transition state leading to formation of the undesired enantiomer would be further disfavoured due to steric hindrance. The synthesis of COP-Cl is achieved by a modular
synthesis so the authors suggested that bulkier ligands should be easily introduced to provide more selective COP catalysts.

At a similar time, Richards and Nomura reported a study showing that COP with a Cl ligand is the favoured catalyst of this type, due to the fact that chlorine is a better leaving group than other similar ligands (e.g. Br, I, OAc).\textsuperscript{39} They also showed that if the reaction was performed at elevated temperatures then the catalyst loading could be lowered to only 0.25 mol%, whilst still maintaining good yields and excellent enantioselectivities. Problems with purification of a large scale reaction led to the synthesis of a polymer supported rearrangement catalyst \textsuperscript{40} (Figure 3) which retained excellent yields and enantioselectivities whilst reducing problems with purification. Recycling of the catalyst led to disappointing yields in further reactions but excellent enantioselectivities were retained. This could be a promising area for future study if a truly recyclable polymer supported chiral catalyst could be developed.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Polymer supported COP-Cl catalyst}
\end{figure}

1.2.5 Ferrocenylimidazoline Palladacycle (FIP) Catalysts

Peters and co-workers have recently reported an alternative rearrangement catalyst to the COP complexes. These ferrocenylimidazoline palladacycles (FIP) \textsuperscript{41} (Figure 4) are excellent chiral catalysts for the aza-Claisen rearrangement of \textit{N}-\textit{para}-methoxyphenyl trifluoroacetimidates such as \textsuperscript{42}.\textsuperscript{40}
The catalyst is most effective with Z-imidates as these (in direct contrast to the COP catalysts) react more quickly and in much higher yield than with E-imidates (Scheme 18). Interestingly, FIP catalysts also give the opposite enantiomer to that reported for the COP catalysts by Overman. It is also possible to use much lower catalyst loadings using this FIP catalyst (as low as 0.1 mol%) than has been reported typically for the COP complexes. Yields and enantioselectivities of the rearranged products, are generally superior than those achieved using other chiral complexes but the FIP complex must be pre-activated by stoichiometric quantities of a silver salt prior to use and a proton sponge is also added to the reaction as an acid scavenger to suppress formation of by-products via an ionisation pathway. The COP-Cl catalysts prepared by Overman do not require this.

In a later paper, Peters and co-workers reported that the FIP catalysts can tolerate a wide variety of different alkyl groups attached to the (Z)-N-para-methoxyphenyl trifluoroacetimidate rearrangement substrates. As a result, the catalyst could be used to prepare several highly enantiopure allylic amines, which are useful building blocks for organic synthesis (Table 1).
The above results clearly demonstrate that these FIP catalysts could find significant applications in the asymmetric synthesis of a variety of nitrogen containing natural products. The FIP catalysts are readily synthesised in only 4 steps from ferrocene and although they require pre-activation, the high yields and enantioselectivities achieved coupled with excellent functional group tolerance makes them good alternatives (especially for Z-imidates) to the COP-Cl catalysts.

### 1.2.6 Conclusions to chiral catalysts

Significant attention has turned to the development of chiral catalysts for use in a stereoselective aza-Claisen rearrangement. Efforts in this area have led to several highly effective catalysts for use in this reaction and have been the subject of several comprehensive reviews.\(^6,13,14\) One drawback of this approach is that the most enantioselective catalysts often suffer from substrate specificity issues due to their highly complex and bulky nature. As has already been highlighted in this short overview, extensive efforts to tailor the activity of catalysts to suit different substrates can take considerable time and require the synthesis and screening of many different catalyst complexes.
1.3 Substrate directed aza-Claisen rearrangement

Another approach to introduce stereoselectivity in the aza-Claisen rearrangement reactions involves the use of a chiral substrate to direct the stereochemical outcome of the rearrangement. This is achieved by coordination of the directing group to the achiral metal catalyst and as such this type of approach is more flexible than for the use of chiral catalysts and in theory can be applied to a much broader number of substrates. It does however, require an asymmetric centre on the molecule close enough to coordinate to the catalyst to exert a directing effect upon the rearrangement process. Diastereoselectivities can also be somewhat variable as this is controlled by the effectiveness of the directing group.

The first example of a substrate directed aza-Claisen rearrangement was reported by Bellûs, for the synthesis of diamines. Bellûs synthesised allylic alcohol 46 containing a chiral Boc protected nitrogen. This nitrogen directing group was then used successfully for the palladium(II)-catalysed rearrangement of 47 to give the anti-diastereomer 48 with excellent diastereoselectivity, although yields were fairly modest (Scheme 19).

![Scheme 19 - The first substrate directed rearrangement](image)

It was postulated that the significant anti-diastereoselectivity of this process was the result of rearrangement via a chair-like transition state 49, with coordination of the palladium catalyst to both the amine nitrogen atom and double bond forcing the nitrogen of the trichloroacetimidate to attack from the opposite face when forming the new stereocentre.

![Scheme 20 - Coordination of nitrogen to Pd(II) directs the rearrangement](image)
Work by Jamieson and Sutherland has demonstrated that ether directing groups can be employed in the substrate directed aza-Claisen rearrangement of allylic trichloroacetimidates.\textsuperscript{43} The directing effect is believed to occur in a similar fashion to that described by Bellûs, in that the oxygen atom coordinates to the metal catalyst, once again giving the anti-diastereomer as the major product of the rearrangement. A number of different ether groups were tested and it was discovered that the methoxymethyl (MOM) ether 50 was the most selective, giving the rearranged products 51 in 64\% yield and in a 10 : 1 ratio of diastereomers (Scheme 21). The importance of the oxygen atoms of this directing group was subsequently demonstrated by the comprehensive synthesis and rearrangement of several analogues of the MOM group.\textsuperscript{43,44}

These results clearly demonstrated that an oxygen atom adjacent to the alkene is crucial for diastereoselectivity, whilst the presence of a second oxygen atom on the MOM ether leads to an enhancement in this diastereoselectivity due to the coordination of both oxygen atoms to the palladium catalyst (Scheme 22).
Sutherland and co-workers then expanded upon this work with the synthesis of several MOM protected trichloroacetimidates 52, with a variety of side-chains. These all underwent diastereoselective rearrangement to the corresponding trichloroacetamides 53 and demonstrated the flexibility of a substrate directed rearrangement approach to a variety of different substrates. In some cases however, formation of the [1,3]-rearranged product was observed. This was most apparent with bulkier substrates which rearrange fairly slowly. These slower rearrangements allowed Pd(0) to eliminate from the cyclisation induced pathway and this then catalysed formation of the [1,3]-product via the ionisation pathway that had previously been reported by Ikariya. This problem was overcome by addition of the in situ oxidant p-benzoquinone, to re-oxidise the Pd(0) to Pd(II), thus inhibiting formation of the [1,3]-products and increasing the yield of the desired [3,3]-products (Table 2).

![Scheme 22 - Coordination of oxygen atoms to palladium](image)

**Scheme 22 - Coordination of oxygen atoms to palladium**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Additive</th>
<th>Yielda (%)</th>
<th>Ratio (a : b : c )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-C₃H₇</td>
<td>---</td>
<td>60</td>
<td>14 : 1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>PhCH₂</td>
<td>---</td>
<td>54</td>
<td>12 : 1 : 0</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂CH₂</td>
<td>---</td>
<td>65</td>
<td>9 : 1 : 4</td>
</tr>
<tr>
<td>4</td>
<td>i-C₃H₇</td>
<td>p-benzoquinone</td>
<td>73</td>
<td>14 : 1 : 0</td>
</tr>
<tr>
<td>5</td>
<td>PhCH₂</td>
<td>p-benzoquinone</td>
<td>70</td>
<td>12 : 1 : 0</td>
</tr>
<tr>
<td>6</td>
<td>PhCH₂CH₂</td>
<td>p-benzoquinone</td>
<td>69</td>
<td>9 : 1 : 0</td>
</tr>
</tbody>
</table>

a Isolated combined yields of a, b and c from allylic alcohol

**Table 2 - Suppression of 1,3-products using an in situ oxidant**

The trichloroacetamides 53a, formed as major products from these rearrangements, were converted to the corresponding β-hydroxy-α-amino acids 54 using an oxidation procedure
first reported by Sharpless;\textsuperscript{46} hydrolysis of the protecting groups under acidic conditions then gave the target amino acid products (Scheme 23).

\begin{equation*}
\begin{array}{c}
\text{OMOM} \\
\text{HN} \\
\text{CCl}_3 \\
\text{R} \text{R CO} \\
\text{OH} \\
\text{NH}_2 \\
\text{CO}_2 \\
\text{H} \\
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{OH} \\
\text{CO}_2 \\
\text{H} \\
\text{NH}_2 \\
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{OH} \\
\text{CO}_2 \\
\text{H} \\
\text{NH}_2 \\
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{OH} \\
\text{CO}_2 \\
\text{H} \\
\text{NH}_2 \\
\end{array}
\end{equation*}

\begin{equation*}
\begin{array}{c}
\text{OH} \\
\text{CO}_2 \\
\text{H} \\
\text{NH}_2 \\
\end{array}
\end{equation*}

Scheme 23 - β-Hydroxy-α-amino acids

Further work by the Sutherland group using a catalyst screen to study the rearrangement, showed that a variety of transition metal complexes including: Pd(II), Pt(II) and Au(III) could be successfully employed with high diastereoselectivity as catalysts for the ether-directed aza-Claisen rearrangement. Although no catalyst was seen to exceed the capabilities that had previously been observed with PdCl\textsubscript{2}(MeCN)\textsubscript{2}, which is the most commonly employed metal catalyst for this reaction. A solvent screen was also employed and this showed that switching from THF, a known coordinating solvent, to toluene which is a non-coordinating solvent, leads to a great enhancement in diastereoselectivity (from 10 : 1 to 15 : 1) (Table 3).\textsuperscript{47} This enhancement of selectivity was explained by the fact that coordinating solvents (such as THF) compete with the chiral ether directing group to coordinate to the palladium catalyst, reducing its effectiveness in controlling the diastereomeric outcome of the rearrangement. Non-coordinating solvents (such as toluene) do not compete with the directing group to coordinate with the catalyst, thus giving enhanced diastereoselectivities from the rearrangement reaction. Further evidence to confirm this was provided when the rearrangement was performed in a highly coordinating ionic liquid solvent. As expected, the diastereoselectivity was significantly reduced at 5 : 1.
More recently, Jaunzeme and Jirgensons have reported a comparative study of metal catalysts for the ether-directed aza-Claisen rearrangement (Table 3). Their results showed that for δ-methoxy and δ-TBDMSO ethers, diastereoselectivity for the trichloroacetamide products 55a and 55b was enhanced if PtCl\(_2\) was used as catalyst. They also reported the formation of oxazoline 55c as a significant by-product in the δ-methoxy rearrangement reaction.
1.3.1 Conclusions to substrate directed rearrangement

Substrate directed aza-Claisen rearrangements have emerged as an excellent alternative to chiral catalysts for a stereoselective rearrangement. Typically a chiral directing group capable of coordination to the achiral metal catalyst is required. MOM ether groups have been extensively studied as directing groups for the rearrangement and have been shown to have broad scope for a variety of substrates. The rearrangement is often more stereoselective if a non-coordinating solvent is employed for the reaction. Substrate-directed rearrangement is a flexible methodology that has broad scope; as such it has seen a variety of applications in natural product synthesis making it an excellent alternative to chiral catalysis.

1.4 Applications in Natural Product Synthesis

Aza-Claisen rearrangements have found widespread application in the synthesis of natural products since Overman first reported the rearrangement of allylic trichloroacetimidates to the corresponding amides in 1974.\(^5\) As highlighted previously, the reason why this reaction is so widely employed in organic synthesis is the relative ease in which the rearrangement substrates can be prepared from the corresponding allylic alcohols. In addition to this, both the thermal and metal-catalysed processes are well understood and generally proceed in high yield via a highly concerted reaction mechanism that occurs with excellent transfer of chirality.

An early application of this reaction was reported by Overman in 1975 for the synthesis of 1-azaspiro[5.5]undec-7-en-2-one \(^59\) (Scheme 24), which is a precursor for a number of spirocyclic natural products.\(^49\) In this paper, a thermal aza-Claisen rearrangement was employed as a key step in the synthesis. Enone \(^56\) was converted to the trichloroacetimidate rearrangement substrate \(^57\) via reduction of the ketone to the alcohol, followed by treatment with trichloroacetonitrile and base. Overman rearrangement was carried out in refluxing \(p\)-xylene to give the trichloroacetamide product \(^58\) in a modest yield. After successful synthesis of \(^58\), the acetal protecting group was hydrolysed to the aldehyde and the aldehyde was oxidised to give the carboxylic acid. After hydrolysis of the trichloroacetyl group with base, spontaneous cyclisation gave the desired spirocyclic product \(^59\). This synthesis by Overman highlighted at an early stage, the great synthetic potential of this reaction in the synthesis of complex organic compounds.
Danishefsky and co-workers reported the use of a thermal Overman rearrangement as a key step in their 1989 synthesis of (±)-pancratistatin \(64\).\(^{50}\) Pancratistatin \(64\) is an alkaloid natural product that has potent biological activity against many cancers and also possesses antiviral activity.\(^{51}\) As such, there has been much interest in the development of total syntheses towards this potential drug target. This first total synthesis of (±)-pancratistatin \(64\) was achieved from the simple aromatic starting material pyrogallol \(60\) (Scheme 25), which was converted in several steps to allylic alcohol \(61\). Compound \(61\) was readily converted under standard conditions to the corresponding allylic trichloroacetimidate \(62\), which upon heating under vacuum in the absence of any solvent underwent Overman rearrangement to the trichloroacetamide \(63\) in 56% yield. The rearranged product \(63\) was then subjected to dihydroxylation and following treatment with base to unmask the amine and carboxylic acid, cyclisation with DCC gave, after cleavage of the benzyl protecting groups, the target compound (±)-pancratistatin \(64\), in only four steps from \(63\). This very elegant synthetic approach by Danishesky made use of the concerted nature of aza-Claisen rearrangements to transfer chirality from the allylic alcohol to the new C-N bond.
Another example of the utilization of the suprafacial nature of the Overman rearrangement to give the desired chirality on the trichloroacetamide product was reported by Kim and co-workers who used the Overman rearrangement in their synthesis of the phenanthroindolizidine and phenanthroquinolizidine alkaloids (-)-antofine 70 and (-)-cryptopleurine 71 (Scheme 26). These alkaloids are known for their potent cytotoxicity hence the interest in their asymmetric synthesis. The synthesis was achieved by a Stille coupling of aromatic compound 65 using the chiral stannyl alcohol 66, to give the allylic alcohol 67 in excellent yield. Synthesis of the allylic trichloroacetimidate 68 was then achieved under standard conditions. Overman rearrangement of 68 gave 69 as a single enantiomer, in an excellent 93% yield. Rearranged product 68 was then further functionalised to complete the asymmetric syntheses of (-)-antofine 70 and (-)-cryptopleurine 71.
Scheme 26 - Synthesis of (-)-antofine and (-)-cryptopleurine via Overman rearrangement

The above examples make use of chirality transfer to introduce the correct relative stereochemistry in the new C-N \( \sigma \)-bond formed during the aza-Claisen rearrangement. However, recent developments of an asymmetric aza-Claisen rearrangement reaction using either chiral catalysis or a substrate directed rearrangement have opened many new opportunities for the reaction to be employed in asymmetric synthesis.

As mentioned previously, Overman and co-workers have demonstrated the application of their COP-Cl chiral catalyst 29 to the synthesis of the natural product (S)-vigabatrin 37 and precursors of unnatural amino acids (Scheme 17). Despite this, there are still relatively few examples of these COP complexes being applied to natural product synthesis. This is perhaps due to the relatively recent advances in the development of these chiral catalysts,
such as COP-Cl, which have only been commercially available for a short time. It is also possible that further development of these catalysts is required to make them more practical catalysts for the complex substrates that are often required for the synthesis of natural products.

One example of the application of chiral catalysts to natural products has been recently reported by Han and co-workers in their synthesis of (+)-iso-6-cassine \textsuperscript{73}.\textsuperscript{53} The target compound has three stereocentres and the first was introduced \textit{via} enzymatic resolution. An (S)-COP-Cl catalysed asymmetric aza-Claisen rearrangement was then used to establish the second stereocentre. The trichloroacetamide product \textsuperscript{72} of this rearrangement was then used to direct the introduction of the third stereogenic centre through a diastereoselective intramolecular amido mercuration. Cross metathesis was then employed to introduce the side-chain of the target compound \textsuperscript{73} (Scheme 27).

\begin{center}
\textbf{Scheme 27 - Synthesis of (+)-iso-6-cassine by Han and co-workers}
\end{center}

Peters and co-workers have demonstrated the application of their highly enantioselective FIP catalysts \textsuperscript{76} to the synthesis of several interesting organic compounds (Scheme 28).\textsuperscript{54,55} In particular, the catalyst can be used for the enantioselective synthesis of quaternary centres, which is something that still remains a significant challenge in organic synthesis. This process is even more remarkable in that excellent yields and enantioselectivities could be achieved with very low catalyst loadings (0.5-4.0 mol\%) making this process highly efficient. The rearranged products such as \textsuperscript{75} synthesised from imidate \textsuperscript{74}, were converted to a number of secondary allylic amines \textsuperscript{78}, which could then
undergo further manipulation to synthesise $\alpha,\alpha$-disubstituted $\alpha$-amino acids 77 and $\beta,\beta$-disubstituted $\beta$-amino acids 79.

**Scheme 28 - Stereoselective synthesis of amino acids with quaternary centres**

A common application of aza-Claisen rearrangements in natural product synthesis is the synthesis of chiral secondary amines which themselves are precursors for the synthesis of various unusual amino acids. As mentioned previously, the Bellûs and Sutherland groups have both made use of a substrate-directed rearrangement to synthesise several of these compounds.42,45,56

Jamieson and Sutherland have recently employed a substrate directed aza-Claisen rearrangement for the synthesis of the alkaloid natural product (+)-$\alpha$-conhydrine 82.57 In this approach, the trichloroacetamide product 80 of the highly diastereoselective rearrangement was converted to the N-heterocycle 83 of the target compound using ring closing metathesis of the diene 81 (Scheme 29). This approach demonstrated that the trichloroacetyl protecting group could be removed and the amine undergo further functionalisation to give (+)-$\alpha$-conhydrine 82 and a pyrrolidine analogue 84 that is also known to have biological activity.
Aza-Claisen rearrangements have also found application for the synthesis of complex carbohydrates. A recent example of this has been reported by Nguyen and co-workers for the stereoselective synthesis of glycosyl ureas (Scheme 30). In this paper, the authors synthesised a number of $N$-glycosyl trichloroacetamides 86 and 87 from the corresponding $N$-glycosyl imidates 85. Interestingly, it was possible to exert control over the $\alpha$- and $\beta$-stereoselectivity of the rearranged compound at the anomeric position. This was achieved through the choice of the palladium(II) catalyst that was employed for the aza-Claisen rearrangement. Cationic palladium(II) complexes gave predominantly the $\alpha$-$N$-glycosyl trichloroacetamide 86, whilst neutral palladium(II) catalysts were shown to favour the $\beta$-$N$-glycosyl trichloroacetamide 87. Hydrolysis of the trichloroacetyl group then allowed the easy introduction of a variety of amine substituents, giving rise to several different $\alpha$-glycosyl 88 or $\beta$-glycosyl ureas 89 for biological evaluation of their anti-bacterial activity.

The selectivity of this process was explained by the fact that cationic palladium(II) catalysts have been shown to coordinate to the imidate nitrogen, thus promoting a non-concerted ionization pathway, which leads to formation of $\alpha$-$N$-glycosyl trichloroacetamide 86. Neutral palladium(II) complexes coordinate instead to the olefin, promoting a concerted cyclisation mechanism, thus leading to formation of $\beta$-$N$-glycosyl trichloroacetamide 87.
Aza-Claisen rearrangement has been employed as a key step in the synthesis of many natural products. Recent advances in highly enantioselective chiral catalysts potentially broaden its synthetic applicability and examples of the use of commercially available COP-Cl catalysts in natural product synthesis have recently been reported. In addition to this, the development of highly diastereoselective substrate-directed rearrangement methodologies has also provided an excellent approach for the synthesis of a variety of natural products. Both of these approaches provide significant scope for further development, to enable even more elaborate methodologies and applications in asymmetric organic synthesis.
2.0 Results and Discussion

2.1 Studies on the aza-Claisen rearrangement of dihydroxylated allylic trichloroacetimidates: synthesis of 2-amino-3,4-dihydroxybutyric acids.

2.1.1 Hydroxylated amino acids

Hydroxylated natural products are widely prevalent in nature, many of which also possess biological activity. As such there is great interest in new methodologies for their stereoselective synthesis to enable full evaluation of these compounds for the treatment of disease.

(2R,3S)-2-Amino-3,4-dihydroxybutyric acid 90 is one such hydroxylated natural product (Figure 5). It was first isolated by Sasaoka and co-workers from the edible mushroom Lyophyllum ulmarium. Although this compound does not possess any known biological activity, it represents an interesting initial target to investigate the effect of more complex and functionalised substrates upon the ether-directed aza-Claisen rearrangement reaction, whilst also demonstrating the use of this methodology for the stereoselective synthesis of functionalised natural products.

As such, it was proposed to undertake the synthesis of both (2R,3S)-2-amino-3,4-dihydroxybutyric acid 90 and its unnatural (2S,3S)-diastereomer 91 (Figure 5), with the key C-N stereocentre at C2, introduced *via* a diastereoselective aza-Claisen rearrangement.

![Figure 5 - (2R,3S)-2-Amino-3,4-dihydroxybutyric acid and its (2S,3S)-diastereomer](image)

2.1.2 Synthesis of (2S,3S)-2-amino-3,4-dihydroxybutyric acid

The strategy to prepare the above amino acids was to synthesise a 4,5-dihydroxylated allylic alcohol which upon conversion to the corresponding allylic trichloroacetimidate and subsequent aza-Claisen rearrangement should provide the two diastereomers that were
required. Conversion of these compounds to the desired amino acids should then be easily achieved. Previously the Sutherland group have shown that chiral ether groups can direct the aza-Claisen rearrangement of allylic trichloroacetimidates in a highly diastereoselective fashion. It has also been shown that the oxygen adjacent to the olefin is critical for diastereoselectivity. It was proposed that the acetonide protected allylic trichloroacetimidate might undergo a diastereoselective rearrangement in a similar manner.

The synthesis of an acetonide protected allylic alcohol was achieved in 3 steps from commercially available chiral pool starting material, D-mannitol (Scheme 31). Firstly was protected as the acetonide at the 1,2- and 5,6- positions, using 2,2-dimethoxypropane. A one-pot oxidation with sodium periodate (oxidative cleavage of , gave two equivalents of the aldehyde) followed by Horner-Wadsworth-Emmons (HWE) reaction under conditions reported by Masamune and Roush, which uses triethylphosphonoacetate, LiCl and DBU, gave exclusively the E-α,β-unsaturated ester. The geometry of the resulting alkene could be easily determined from the 1H NMR spectrum of the product (Figure 6). In this example, the alkene protons show a 15.7 Hz coupling constant proving that the geometry is trans. All unsaturated esters synthesised by this method, showed this coupling pattern and a coupling constant greater than 15.0 Hz, thus demonstrating that in all reactions the synthesised product was the E-alkene.

**Figure 6 - Alkene signals in 1H NMR spectrum of compound 95**
Following this, reduction of the ester 95 using DIBAL-H then gave the desired allylic alcohol 96 in excellent yield. Compound 96 could then be readily converted to the corresponding allylic trichloroacetimidate 97, which was used without further purification.

![Scheme 31 - Synthesis of allylic trichloroacetimidate 97](image)

Allylic trichloroacetimidate 97 was then subjected to a Pd(II)-catalysed aza-Claisen rearrangement using standard conditions (Table 5, entry 1). Surprisingly, no [3,3]-product was formed, with only the deprotected [1,3]-product 98c isolated. This compound likely forms via Pd(II)-catalysed hydrolysis of the acetonide followed by 1,3-rearrangement through a known competing ionisation pathway. Previously Schmeck and Hegedus have reported the hydrolysis of acetonides by palladium in aqueous acetonitrile, but it is surprising to observe the hydrolysis also occurring in anhydrous solvents.

In an effort to overcome this problem, a variety of metal catalysts were screened in DCM in an attempt to find reaction conditions that would provide the desired [3,3]-products 98a and 98b, whilst eliminating formation of the undesired [1,3]-product 98c (Table 5). Switching solvent (whilst also performing the reaction at 38 °C) meant that the Pd(II)-catalysed rearrangement (Table 5, entry 2) gave the two [3,3]-products 98a and 98b in a modest 32% yield (7 : 1 ratio, 98a : 98b). Unfortunately, significant quantities of the [1,3]-product 98c were still formed. Other metal catalysts [Pt(II), Au(III) and Au(I)] were then employed for the rearrangement (Table 5, entries 3 - 5) without any improvement over that achieved using PdCl₂(MeCN)₂. With all of these catalysts, the 1,3-ionisation pathway...
remained a problem, preventing the formation of the desired products in synthetically useful yields.

The rearrangement was also performed using the commercially available chiral COP-Cl catalysts (Table 5, entries 6 and 7).\textsuperscript{36,63} These catalysts are very sterically hindered (see Chapter 1.2.4, Figure 1) and it was hoped that this would prevent hydrolysis of the acetonide group, whilst also giving an enhancement in diastereoselectivity. Rearrangement using (S)-COP-Cl catalyst proceeded in an excellent 81% yield (over 2 steps) and an outstanding 52 : 1 ratio of the expected (3R,4S) diastereomer 98b, with no [1,3]-product 98c isolated. This is an example of a matched pairing as the chirality of both the substrate and chiral catalyst complement one another; the bulky catalyst coordinates to the opposite face to the existing (4S) stereocentre (so blocking the back side from attack) thus ensuring that the new C-N bond forms on the same side as the stereocentre and giving a significant enhancement in diastereoselectivity.

Rearrangement using the mismatched (R)-COP-Cl proceeded much more slowly (14 days). This is because the bulky catalyst was required to coordinate to the same side of the compound as the existing stereocentre. As expected, this resulted in lower diastereoselectivity of the [3,3]-products 98a and 98b, lower yields and some formation of the [1,3]-product 98c.

- | Entry | Catalyst | Catalyst Loading (mol %) | Reaction time | Yield\textsuperscript{a} (%) | Ratio (a : b : c) |
- | 1 | PdCl\(_2\)(MeCN)\(_2\)\textsuperscript{b} | 10 | 24 h | --- | 0 : 0 : 1 |
- | 2 | PdCl\(_2\)(MeCN)\(_2\) | 10 | 24 h | 32 | 7 : 1 : 7 |
- | 3 | PtCl\(_2\) | 10 | 5 days | 31 | 4 : 1 : 9 |
- | 4 | HAuCl\(_4\)-3H\(_2\)O | 10 | 5 days | 25 | 2 : 1 : 3 |
- | 5 | AuCl | 10 | 4 days | 31 | 2 : 1 : 4 |
- | 6 | (S)-COP-Cl | 3 | 7 days | 81 | 1 : 52 : 0 |
- | 7 | (R)-COP-Cl | 3 | 14 days | 23 | 6 : 1 : 1 |

\textsuperscript{a} Isolated combined yields of [3,3]-products (a + b) from allylic alcohol 96
\textsuperscript{b} Reaction carried out in THF at room temperature

Table 5 - Rearrangement of acetonide protected trichloroacetimdate 97
The highly successful rearrangement using (S)-COP-Cl provided significant quantities of the (3R,4S)-diastereomer 98b and allowed the synthesis of (2S,3S)-2-amino-3,4-dihydroxybutyric acid 91 to be completed. This was achieved by a ruthenium(III)-catalysed oxidation of allylic trichloroacetamide 98b, to the carboxylic acid 99, using a procedure reported by Sharpless (Scheme 32). Deprotection of the amine and hydroxyl groups was then achieved using 6M hydrochloric acid, to give the target amino acid 91 in 47% yield over 2 steps.

Scheme 32 - Synthesis of (2S,3S)-2-amino-3,4-dihydroxybutyric acid

The synthesis of (2S,3S)-2-amino-3,4-dihydroxybutyric acid 91 was successfully completed in just 7 steps from D-mannitol 92. The use of the commercially available (S)-COP-Cl gave excellent stereoselectivity for the S-stereocentre. Unfortunately the acetonide protecting group was readily cleaved under standard rearrangement conditions, meaning that it was impossible to synthesise the opposite 2R-stereocentre selectively, which was required to synthesise the natural butyric acid isomer, in practical yields. Consequently, a second synthetic route was employed, making use of more stable protecting groups.

2.1.3 Synthesis of (2R,3S)-2-amino-3,4-dihydroxybutyric acid

A second synthetic approach was designed to begin from acetonide protected compound 95. This was hydrolysed under acidic conditions to give the diol 100 in excellent yield (Scheme 33). Protecting groups known to be stable to metal catalysed aza-Claisen rearrangements yet easily removed in subsequent steps were required. As such it was decided to introduce a MOM ether at the secondary alcohol as this group has previously proved to both withstand rearrangement conditions and also to provide an enhanced directing effect for the desired anti-diastereomer. A silyl ether was chosen to protect the primary alcohol as these are also known to survive the rearrangement yet are readily cleaved under very mild conditions.
Protection of the primary alcohol using the TBDPS ether proceeded smoothly to give 101 in quantitative yield. Initially, the less bulky TBDMS ether was employed, but when introducing the MOM ether protecting group, the TBDMS was lost. This problem was successfully overcome by the use of the less labile TBDPS group. The MOM ether was then successfully introduced in excellent yield to give orthogonally protected diol 102. Reduction of the ester was once again successfully achieved in high yield using DIBAL-H, to give allylic alcohol 103 (Scheme 33).

![Diagram](image)

Scheme 33 - Synthesis of the second trichloroacetimidate

 Allylic alcohol 103 was then converted to the allylic trichloroacetimidate 104 and subjected to Pd(II)-catalysed aza-Claisen rearrangement in THF (Table 6, entry 1). This substrate successfully gave the [3,3]-products 105, with no [1,3]-product isolated. Unfortunately, the yield of the reaction was disappointing at 32% (over 2 steps) and in a rather modest 3 : 1 ratio for the desired anti-diastereomer 105a. In an attempt to improve both the yield and stereoselectivity, a catalyst screen was employed, whilst the solvent was also changed to toluene (which is a non-coordinating solvent and has recently been shown to improve the stereoselectivity of ether-directed aza-Claisen rearrangements) (Table 6).
Rearrangement using PdCl$_2$(MeCN)$_2$ as catalyst in toluene gave a much improved 68% yield of the [3,3]-products 105 and the reaction was complete in 12 hours. Diastereoselectivity of the reaction was only slightly improved (4 : 1 in favour of anti diastereomer 105a) and this was somewhat surprising as previous results within the group had shown that switching to toluene as a solvent, gave a significant enhancement of diastereoselectivity for MOM ether-directed rearrangements.$^{47}$ A likely explanation for this is that the bulky TBDPS group attached at the primary alcohol interferes with the directed rearrangement, meaning that the MOM ether coordinates less effectively to the catalyst, leading to a reduction in diastereoselectivity. It is likely that if a less bulky group could be introduced at the primary position then diastereoselectivity of the rearrangement would be improved.

Once again Pt(II), Au(I) and Au(III) complexes were also tested with this substrate (Table 6, entries 3 - 6) in an attempt to find a more selective catalyst. All of these metal complexes could successfully catalyse the rearrangement; however, yields were poor to modest (25-49%, over 2 steps). The diastereoselectivity was also quite variable (2 : 1 - 4 : 1, 105a : 105b) and no catalyst was seen to give an improved diastereoselectivity when compared to PdCl$_2$(MeCN)$_2$. These results, coupled with the results from table 5, clearly demonstrate that for these dihydroxylated substrates Pd(II) is the most efficient catalyst for the rearrangement. As was discussed previously, palladium is an excellent metal catalyst for the Overman rearrangement and often provides the rearranged products in high yields and short reaction times. PdCl$_2$(MeCN)$_2$ is often used to catalyse the rearrangement as it possesses organic acetonitrile ligands which help to make the catalyst soluble in a wide variety of organic solvents. The excellent catalytic activity and solubility makes this the optimal catalyst for ether-directed aza-Claisen rearrangements, which rely on a rapid rearrangement process to allow the desired anti-diastereomer to be synthesised selectively in high yields and in preference to other competing reaction pathways.

In an attempt to improve the diastereoselectivity of the rearrangement process, allylic trichloroacetimidate 104 was subjected to rearrangement using (R)-COP-Cl. Although, this is a mismatched catalyst-substrate pairing, (R)-COP-Cl did successfully catalyse the rearrangement in a 68% yield and an excellent 16 : 1 ratio (105a : 105b). The yield also compares favourably with PdCl$_2$(MeCN)$_2$ (also 68% in toluene).
Table 6 - Metal catalysed rearrangement of trichloroacetimidate 104

For all rearrangements studied during the course of this PhD, the diastereomeric ratio was determined by examining the $^1$H NMR spectra of the products. This is possible because the syn-and anti-diastereomers have different NMR spectra, which show dissimilar chemical shifts between the two protons at the chiral centres on each molecule. In the example below (Figure 7), the protons of the anti-diastereomer 105a are observed at 3.65 ppm (3-H) and 4.64 ppm (4-H) respectively, whereas for the syn-diastereomer 105b these protons appear at 3.82 ppm (3-H) and 4.75 ppm (4-H).
With significant quantities of the anti-(3S,4S)-diastereomer available, using either PdCl$_2$(MeCN)$_2$ or (R)-COP-Cl as catalyst for the rearrangement, the synthesis of (2R,3S)-2-amino-3,4-dihydroxybutyric acid 90 was completed successfully.

This was achieved in a similar manner as for (2S,3S)-2-amino-3,4-dihydroxybutyric acid 91, using a ruthenium catalysed oxidation of allylic trichloroacetamide 105a, to the carboxylic acid 106, once again using the Sharpless procedure (71% yield). Initially hydrolysis of all protecting groups was attempted using 6M hydrochloric acid as before,
but this reaction was low yielding and gave a complex mixture of products. It proved more efficient to cleave the TBDPS group using TBAF and then subject the resulting compound to 6M hydrochloric acid to hydrolyse the trichloroacetamide and MOM groups. This gave the natural product, \((2R,3S)-2\text{-amino}-3,4\text{-dihydroxybutyric acid}\) \(^{90}\), in 44% yield over 2 steps from \(106\) (Scheme 34).

**Scheme 34 - Synthesis of \((2R,3S)-2\text{-amino}-3,4\text{-dihydroxybutyric acid}\)**

2.1.4 Conclusions

In summary, two dihydroxylated allylic trichloroacetimidates have been successfully synthesised and subjected to aza-Claisen rearrangement using a variety of transition metal catalysts. Initial problems with loss of the acetonide protecting group were overcome by a catalyst screen which demonstrated that a variety of transition metals (including Pd(II), Pt(II), Au(III) and Au(I)) could be used as catalysts for this rearrangement. Secondly, it was discovered that the chiral catalyst (S)-COP-Cl could be successfully employed for this rearrangement in a matched pairing to give the \((3R,4S)\)-syn-diastereomer in an excellent yield and diastereoselectivity. Efforts to stereoselectively synthesise the \((3S,4S)\)-anti-diastereomer required for the synthesis of the natural amino acid led to the synthesis of a second orthogonally protected allylic trichloroacetimidate. This successfully underwent ether-directed aza-Claisen rearrangement in good yield but with moderate diastereoselectivity. This was enhanced by the use of \((R)\)-COP-Cl, which in a mismatched catalyst-substrate pairing gave the desired products in an excellent 16 : 1 ratio and a good 68% yield, despite long reaction times.

These rearranged products are more complex than have previously been synthesised using this approach and their subsequent conversion to the dihydroxylated \(\alpha\)-amino acids \((2R,3S)-2\text{-amino}-3,4\text{-dihydroxybutyric acid}\) \(^{90}\) and its unnatural diastereomer \((2S,3S)-2\text{-amino}-3,4\text{-dihydroxybutyric acid}\) \(^{91}\) highlights the potential of this methodology for the synthesis of more complex natural products.
2.2 Investigation of stereocontrol using a stereo-relay effect and a solvent mediated directing effect, the synthesis of \(\gamma\)-hydroxy-\(\alpha\)-amino acids.

2.2.1 \(\gamma\)-Hydroxy-\(\alpha\)-amino acids

Previously, the Sutherland group has shown that chiral MOM-ether groups (at the \(\delta\)-position) adjacent to the olefin of an allylic trichloroacetimidate 50 can direct the Pd(II) catalysed aza-Claisen rearrangement reaction, giving the corresponding amide 51a, with a high degree of diastereoselectivity.\(^{43-45}\)

It was proposed that an allylic trichloroacetimidate 108 with a MOM ether situated at the \(\varepsilon\)-position (one carbon further from the olefin) might rearrange to give the corresponding amide 110a in higher stereoselectivity due to the fact that the rearrangement should proceed via a 6,6-chair like transition state 109 as opposed to the 6,5-transition state 107 observed with the previous rearrangement substrates (Scheme 35). In addition, should this reaction prove to be successful then it would provide a highly efficient synthetic route to \(\gamma\)-hydroxy-\(\alpha\)-amino acids such as \(\gamma\)-hydroxynorvaline 111 (Figure 8).

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
50 & \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
51a & \quad \text{[6,6]-transition state} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
107 & \quad \text{[6,5]-transition state} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
110a & \quad \text{[6,6]-transition state} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
108 & \quad \text{[6,5]-transition state} \\
\end{align*}
\]

\[
\begin{align*}
\text{OMOM} & \quad \text{Pd(II)} & \text{OMOM} \\
\text{HN} & \quad \text{O} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{O} & \quad \text{CCl}_3 \\
51a & \quad \text{[6,6]-transition state} \\
\end{align*}
\]

Scheme 35 - Proposed transition states of ether-directed rearrangement

\(\gamma\)-Hydroxy-\(\alpha\)-amino acids are unnatural amino acids that have been isolated from several different sources and are components of a number of natural products, including cyclic...
peptides. A well known example is \((2S,3S,4R)-\gamma\text{-hydroxyisoleucine} 112\), which is the amino acid component of, the potent cytotoxic alkaloid, funebrine 113 and was isolated in 1984 from *Quararibea funebris*.\(^6\)

![Figure 8 - Hydroxylated natural products](image)

New methods for the synthesis of these and similar amino acids would be of significant benefit to synthetic chemistry. It would also broaden the scope of the ether-directedaza-Claisen rearrangement methodology previously developed by the group, allowing it to be employed for the synthesis of a wider variety of natural products.

### 2.2.2 Synthetic route to allylic trichloroacetimidates

To investigate this proposal, a synthetic route to \(\varepsilon\)-substituted allylic trichloroacetimidate 108 was developed. Initially, poly \((3R)-3\text{-hydroxybutyrate} 114\) was hydrolysed under acidic conditions to give the hydroxy ester 115 (Scheme 36). MOM protection of 115 under standard conditions then gave 116 in good yield (75%). The ester 116 was then reduced to the alcohol 117 using two equivalents of DIBAL-H, once again in high yield. A one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions,\(^6\) then gave exclusively the \(E-\alpha,\beta\)-unsaturated ester 118 in 59% yield from the alcohol. Reduction of ester 118 with DIBAL-H provided the allylic alcohol 119 (in 98% yield), which was then converted to the desired \(\varepsilon\)-substituted allylic trichloroacetimidate 108. This synthetic route provided the desired rearrangement substrate 108 in only 6 steps using highly robust and scaleable chemistry, allowing the desired substrate to be obtained in multi-gram quantities.
Scheme 36 - Synthetic route to a ε-substituted allylic trichloroacetimidate

2.2.3 Pd(II)-catalysed rearrangement in THF

Trichloroacetimidate 108 was then subjected to an aza-Claisen rearrangement using PdCl$_2$(MeCN)$_2$ in THF. These are the reaction conditions that had successfully been used previously within the group for other MOM ether rearrangement substrates and as such would allow a direct comparison of this new substrate with earlier work. Rearrangement gave the resulting allylic trichloroacetamide products 110a and 110b in 50% yield (over 2 steps from 119) and in a 1 : 1 ratio (Scheme 37).

Scheme 37 - Rearrangement in THF
Once again, the diastereomeric ratio between syn- and anti- compounds could be determined by analysis of their $^1$H NMR spectra (Figure 9). The protons of the anti-diastereomer 110a are observed at 4.00 ppm (3-H) and 4.62 ppm (5-H, underneath CH from MOM ether) and the protons of the syn-diastereomer 110b are observed at 3.75 ppm (3-H) and 4.45 ppm (5-H) respectively.

Figure 9 - $^1$H NMR spectrum of diastereomers
The completely unselective rearrangement observed with this substrate was initially very puzzling. To gain a better understanding of this process, the reaction was repeated with addition of a base (DBU) and an oxidant (p-benzoquinone), whilst a thermal un-catalysed rearrangement was also performed in an attempt to eliminate any competing pathways that might contribute to an unselective rearrangement (Table 7).

![Scheme 38: Aza-Claisen rearrangement](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Yield$^a$ (%)</th>
<th>Ratio$^b$ (a : b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>---</td>
<td>50</td>
<td>1 : 1</td>
</tr>
<tr>
<td>2</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>DBU</td>
<td>45</td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$(MeCN)$_2$</td>
<td>p-benzoquinone</td>
<td>38</td>
<td>1 : 1</td>
</tr>
<tr>
<td>4$^c$</td>
<td>---</td>
<td>K$_2$CO$_3$</td>
<td>85</td>
<td>1 : 1</td>
</tr>
</tbody>
</table>

$^a$ Isolated combined yields of a and b from allylic alcohols.
$^b$ Ratio in crude reaction mixture.
$^c$ Reaction performed in p-xylene at 130 °C.

**Table 7 - Attempts to identify the cause of unselective rearrangement**

As all of the above reactions were completely unselective it was initially thought that the MOM group was too far away from the olefin to exert a directing effect on the process. However, an examination of the two transition states for the rearrangement show that both reaction pathways to diastereomers **110a** and **110b** are equally likely (Scheme 38).

It is known that metal catalysed aza-Claisen rearrangements adopt a chair-like transition state that minimizes steric strain. Typically the transition state that most minimizes any steric strain will have any bulky groups in equatorial positions, with small groups (e.g. hydrogen) in the axial positions. Such a transition state will be the lowest energy conformer and so is favoured, resulting in the major product of the rearrangement. As any energy difference between the transition states increases, then the ratio between the two products should also increase.
For substrate 108 both conformations 120a and 120b are equally favoured (hence the 1:1 ratio). This is because by moving the directing group from the δ- to the ε-position, there are now two hydrogens at the δ-position (previous substrates for the rearrangement had one hydrogen and one methyl substituent, see schemes 22 and 35). As both groups (H^a and H^b) are the same equally small substituent, they both minimize any steric strain to the same extent, meaning it makes no difference which hydrogen is in the axial position. Thus, equal quantities of each product are formed.

Scheme 38 - Transition states for rearrangement

As a consequence of this, it was proposed that the introduction of a bulkier group in place of one of these hydrogens, would lead to the re-introduction of stereocontrol as the lowest energy transition state would be the one with the bulky group in the equatorial position (the bulky group in the axial position would be higher energy so less favoured due to an increase in steric strain) (see Scheme 41).
2.2.4 Stereocontrol using a Stereoselective Relay

Two new δ-,ε-substituted allylic trichloroacetimidates 133 and 134, were synthesised by a similar synthetic route to that used previously for the synthesis of substrate 108 (Scheme 40). Methyl and benzyl substituents were introduced in place of hydrogen by a stereoselective alkylation. This was achieved by treatment of 115 with two equivalents of LDA, this forms a di-lithiated chair-like enolate 121 which undergoes alkylation from the least hindered face to give the desired erythro products 122 (Scheme 39).\textsuperscript{67,68}

\begin{equation}
\text{Scheme 39 - Stereoselective alkylation via di-lithiated enolate}
\end{equation}

MOM protection of both hydroxy esters 123 and 124 proceeded in excellent yield to give 125 and 126. DIBAL-H reduction then gave the primary alcohols 127 and 128, once again in excellent yield. A one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction gave E-α,β-unsaturated esters 129 and 130, which were reduced to the allylic alcohols 131 and 132 with DIBAL-H and converted to the desired allylic trichloroacetimidates 133 and 134 in the usual manner.
With the desired trichloroacetimidates 133 and 134 in hand, they were subjected to Pd(II)-catalysed aza-Claisen rearrangement in THF (Table 8). As expected, the introduction of these more bulky δ-substituents does induce diastereoselectivity. A 3 : 1 ratio was observed for methyl substituted substrate 133, and a 6 : 1 ratio for the benzyl substrate 134. The fact that diastereoselectivity is greatest for the bulkiest group (where R = benzyl) demonstrates that this selectivity results from the minimization of any steric strain. Steric strain is greater in the transition state where the benzyl is in the axial position; meaning that the opposite transition state (benzyl in equatorial position), which is lower in energy, is favoured (see Scheme 41).
Although diastereoselectivity can be achieved by the introduction of methyl or benzyl groups at the $\delta$-position, the selectivity was still lower than what had previously been reported for other substrates.\textsuperscript{43,45} Previously, it has been shown that non-coordinating solvents such as toluene can enhance the diastereoselectivity of ether-directed rearrangements.\textsuperscript{47} This is because coordinating solvents such as THF compete with the ether group for coordination to the metal catalyst. It was proposed that due to the greater distance between the directing group and the olefin, then THF might completely prevent stereoselective coordination of the MOM group to the metal catalyst, thus leading to such modest diastereoselectivities.

### 2.2.5 Rearrangement in Toluene

The Pd(II)-catalysed rearrangement reactions of allylic trichloroacetimidates $108$, $133$ and $134$ were repeated in toluene (Table 9). By switching solvent to toluene there was a significant increase in diastereoselectivity when compared to the results for THF.

Firstly, allylic trichloroacetimidate $108$ now rearranges in a 3 : 1 ratio (previously 1 : 1 in THF), this selectivity can solely be due to the directing effect of the MOM group as previously it was shown that there was little difference in steric strain for this substrate. Secondly, the results for allylic trichloroacetimidates $133$ and $134$ are even more impressive with a 13 : 1 ratio for methyl substituted substrate $133$ and an 11 : 1 ratio for benzyl substrate $134$. Yields are also greatly improved.
As can be clearly seen from the table, toluene does indeed enhance selectivity when it is used in place of THF as solvent. The use of toluene as solvent appears to “switch on” the MOM substrate directing effect and allows excellent diastereoselectivities of up to 13:1 to be achieved for these substrates.

![Chemical reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Solvent</th>
<th>Yield(^{a}) (%)</th>
<th>Ratio(^{b}) (a : b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>toluene</td>
<td>71%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>toluene</td>
<td>66%</td>
<td>13 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Bn</td>
<td>toluene</td>
<td>82%</td>
<td>11 : 1</td>
</tr>
</tbody>
</table>

\(^{a}\) Isolated combined yields of a and b from allylic alcohols.

\(^{b}\) Ratio in crude reaction mixture.

**Table 9 - Rearrangement in Toluene**

### 2.2.6 Summary of results

A number of conclusions can be drawn from these results. Firstly, the rearrangement of \(\delta,\varepsilon\)-disubstituted substrates in THF occurs with only moderate selectivity because selectivity is governed by a number of steric factors and there is no directing effect from the MOM group (Scheme 41). Any stereoselectivity occurs due to a destabilisation of transition state 137b by more bulky groups at the \(\delta\)-position adopting an axial conformation. This is unfavoured so transition state 137a, which minimizes steric hindrance, leads to formation of the major diastereomer 136a. If both transition states minimize steric strain equally well then no selectivity is observed, giving an equal ratio of the two diastereomers 136a and 136b (as was observed with substrate 108).
Rearrangement of the substrates in toluene occurs in much higher diastereoselectivity than in THF. This is because there is no competition from the toluene solvent so the MOM directing group can coordinate to the palladium catalyst. This introduces a substrate-directing effect leading to much higher diastereoselectivities (Scheme 42).

Also coordination of the directing group to the metal catalyst causes the adjacent methyl group in transition state 138b to adopt an unfavourable axial position. This explains the diastereoselectivity of 3 : 1 that was observed for substrate 108 in toluene. For substrates 133 and 134 (where the presence of bulky methyl and benzyl groups already resulted in diastereoselectivity) the axial methyl group causes transition state 138b to be further destabilised. This causes a significant enhancement in diastereoselectivity when the rearrangement is performed in toluene.
The proposed transition states above provide a possible explanation for the results observed with these substrates. However, it has not been possible to obtain any proof of their existence either by kinetic studies or computational analysis. As such, whilst these proposed structures correlate well to the available experimental data and provide rationalization for the observed differences in diastereoselectivity between the two solvents, alternative transition states cannot be ruled out.

2.2.7  Synthesis of γ-Hydroxy-α-amino acids

The major trichloroacetamide products from the rearrangement (110a, 139a and 140a) were then converted to the corresponding γ-hydroxy-α-amino acids via the same two step approach used previously (Section 2.1). Firstly, the trichloroacetamides were subjected to a ruthenium catalysed oxidation of the alkene to the carboxylic acids. These carboxylic acids (141, 142 and 143) were then heated under acidic conditions to hydrolyse the MOM and trichloroacetamido protecting groups (Scheme 43). Thus, three γ-hydroxy-α-amino acids were successfully synthesised by this method, natural products: (2S,4R)-γ-hydroxynorvaline 111,69 (2S,3S,4R)-γ-hydroxyisoleucine 112,65 and a novel benzyl substituted γ-hydroxy-α-amino acid 144.

\[
\begin{align*}
\text{MOMO} & \quad \text{HN} \quad \text{CCl}_3 \\
\text{RuCl}_3 \cdot x\text{H}_2\text{O}, \quad \text{NaIO}_4 \\
\text{110a} & \quad \text{R} = \text{H} \\
\text{139a} & \quad \text{R} = \text{Me} \\
\text{140a} & \quad \text{R} = \text{Bn} \\
\text{MOMO} & \quad \text{HN} \quad \text{CO}_2\text{H} \\
\text{6M HCl} \quad \Delta \\
\text{141} & \quad \text{R} = \text{H} (65\%) \\
\text{142} & \quad \text{R} = \text{Me} (62\%) \\
\text{143} & \quad \text{R} = \text{Bn} (82\%) \\
\text{OH} & \quad \text{NH}_2 \quad \text{CO}_2\text{H} \\
\text{111} & \quad \text{R} = \text{H} (74\%) \\
\text{112} & \quad \text{R} = \text{Me} (55\%) \\
\text{144} & \quad \text{R} = \text{Bn} (55\%) \\
\end{align*}
\]

\[
\begin{align*}
(2S,4R) & \quad \gamma\text{-hydroxynorvaline} \\
(2S,3S,4R) & \quad \gamma\text{-hydroxyisoleucine} \\
\end{align*}
\]

Scheme 43 - Synthesis of γ-hydroxy-α-amino acids
This efficient methodology for the synthesis of these three nonproteinogenic amino acids further expands the scope of a MOM-ether-directed aza-Claisen rearrangement and also allowed the absolute stereochemistry of the major diastereomers from the rearrangements to be confirmed by comparison of the synthesised amino acids to the known natural products.\(^{65,69}\)

### 2.2.8 Conclusions

In summary, the role of steric strain on the MOM ether-directed aza-Claisen rearrangement has been investigated in two solvents; THF and toluene. In THF which is a coordinating solvent, stereocontrol is exerted by a stereo-relay effect and there is no directing effect as the solvent prevents coordination of the MOM group to the catalyst, and so, diastereoselectivity is very modest. However, when toluene (a non-coordinating solvent) was used, the MOM ether group was able to successfully coordinate to the catalyst, switching on a directing effect, which when combined with minimisation of steric strain gave a significant increase in the diastereoselectivity. The products from these rearrangements could then be easily converted to three \(\gamma\)-hydroxy-\(\alpha\)-amino acids, providing a highly efficient and stereoselective route to these amino acids.
2.3 Development of a tandem aza-Claisen rearrangement and ring closing metathesis reaction.

2.3.1 Introduction to tandem reactions

A rapidly growing area of chemistry in the 21st century is the development of tandem, domino and cascade reactions. The reason for this is that these processes allow several synthetic transformations to be undertaken in one-pot and this has several advantages over traditional one step-one-pot procedures. Firstly, there is no requirement to isolate or handle reaction intermediates, saving time in purification of what can often be unstable compounds. Secondly, there are substantial reductions in the waste generated (particularly in solvent waste), which significantly reduces the environmental impact of these classes of reaction when compared to traditional methodologies. In particular, as the cost of petrochemical feedstocks and their subsequent disposal has risen in recent years, this is an area of chemistry that has become increasingly important to the chemical and pharmaceutical industries.

Ring closing metathesis has emerged in recent years as an excellent reaction for use in organic synthesis. It is a highly versatile and mild reaction process that enables the formation of a variety of different ring sizes often in excellent yields. The reaction proceeds via a well studied reaction mechanism (Scheme 44) using stable ruthenium catalysts that are also commercially available. The importance of this reaction to synthetic organic chemistry was highlighted by the award of the Nobel Prize for Chemistry in 2005 to Robert Grubbs, Richard Schrock and Yves Chauvin who developed the metathesis process for synthetic chemistry. In addition to RCM there are two other commonly used metathesis processes. Cross metathesis (CM) which is the intermolecular metathesis reaction (whereas RCM is an intramolecular process) and Ring Opening Metathesis (ROM), which is commonly employed in polymerisations.
The reaction is thermodynamically driven to completion often by the release of a gas (usually ethene) and does not lead to the racemisation of stereogenic centres. As a result of all of this, metathesis has also seen extensive use in tandem reactions, for example in conjunction with dehydrogenation-hydrogenation reactions, aza-Michael reactions, Diels-Alder reactions, isomerizations, Claisen rearrangements, Kharasch cyclisations, and dihydroxylations.

Recent work by Jamieson and Sutherland demonstrated the use of both aza-Claisen rearrangement and RCM as key steps in the synthesis of heterocyclic natural products, and previously it had been shown that ruthenium catalysts do not catalyse the aza-Claisen rearrangement. With this in mind, it was decided to attempt to develop a novel tandem Pd(II)-catalysed aza-Claisen rearrangement and ruthenium catalysed RCM reaction for the one-pot synthesis of cyclic allylic trichloroacetamides (Scheme 45).

Cyclic allylic trichloroacetamides are useful synthetic intermediates, having found widespread applications e.g. in dihydroxylations, epoxidations and Kharasch
cyclisations. It was hoped that this new methodology would provide a rapid synthesis to a variety of these compounds which could then undergo further functionalisation for use in the synthesis of natural products.

### 2.3.2 Development of a tandem process

It was decided to attempt to develop this tandem process for the synthesis of 6-membered cyclic allylic trichloroacetamide 151. To achieve this, a concise synthetic route to allylic alcohol 148 was required. This was rapidly achieved from commercially available 5-hexen-1-ol 146, using a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction (once again using Masamune-Roush conditions) to give the $E$-$\alpha,\beta$-unsaturated ester 147 (Scheme 46). DIBAL-H reduction of ester 147 gave allylic alcohol 148 in excellent yield.

![Scheme 46 - Concise synthesis of terminal alkene containing allylic alcohol](image)

 Allylic alcohol 148 was then converted to the desired trichloroacetimidate rearrangement substrate 149 (Scheme 47). To determine the optimal reaction conditions for development of a tandem process, the rearrangement was carried out (3 hours at room temperature) and purified, giving the rearranged product 150 in 71% yield. Rearranged product 150 was then subjected to RCM using Grubbs I catalyst (12 h under reflux), to provide the desired cyclic allylic trichloroacetamide 151 in quantitative yield. Not only did these reactions help in the development of the reaction conditions for the tandem process, isolating the two compounds 150 and 151 provided reference $^1$H NMR spectra for comparison when performing the tandem process.

![Scheme 47 - Development of reaction conditions for tandem process](image)
Following this, a tandem reaction was then attempted (Scheme 48). Initially, a one-pot procedure involving addition of both rearrangement and metathesis catalysts together then heating under reflux was attempted. Somewhat surprisingly, analysis of the crude reaction product by $^1$H NMR showed that the major compound present was rearranged product 150, whilst ring-closed product 151 could not be identified. Since the rearrangement is known to proceed at room temperature, a second attempt where the reaction was performed at room temperature for 3 hours and then heated to reflux was carried out, with the same result. As such, it would appear that during the aza-Claisen rearrangement process the Grubbs metathesis catalyst is inactivated (perhaps via ligand exchange with PdCl$_2$(MeCN)$_2$) meaning that it is no longer able to catalyse the metathesis reaction. It was discovered that if the catalysts were added in stepwise fashion then this problem could be overcome. This was achieved by initially adding the rearrangement catalyst, leaving the reaction for 3 hours to allow the rearrangement to proceed to completion and then adding the metathesis catalyst and heating the reaction under reflux. This approach allowed cyclic allylic trichloroacetamide 151 to be readily synthesised in excellent yields.

Three commercially available and frequently used metathesis catalysts were employed for the tandem aza-Claisen rearrangement and RCM reaction using these optimised conditions (Scheme 48). All three catalysts gave the desired 6-membered cyclic allylic trichloroacetamide 151 in excellent yields (89-95% over 3 steps).
2.3.3 Scope of tandem process

With optimized reactions conditions developed, synthesis of additional ring sizes was then investigated. It was decided to continue using Grubbs I as RCM catalyst, even though it showed a slightly lower yield for the reaction than the other catalysts. This was due to its lower cost and greater availability and since we hoped to develop a robust synthetic methodology for natural product synthesis, it was important to use a catalyst that could be employed on a large scale, at reasonable cost.

Rearrangement substrates 152-154, were synthesized from commercially available alcohols using a similar route as for the preparation of substrate 149 (Scheme 49).
Substrate 152 was then subjected to the optimized tandem aza-Claisen rearrangement and ring closing metathesis conditions to give the expected 5-membered cyclic allylic trichloroacetamide 155, in excellent yield (84%, over 3 steps) (Scheme 50).

Tandem aza-Claisen rearrangement and RCM of substrate 153, using the above conditions provided a mixture of the desired product and a dimeric product (the result of an intermolecular metathesis reaction) which could not be separated by column chromatography. Larger ring sizes can often form dimeric products as the rate of intermolecular metathesis can become competitive with the rate of intramolecular metathesis. A common solution to this problem is to perform the reaction at lower concentrations, thus eliminating formation of the dimer. The reaction was then repeated under diluted conditions (0.005 M) and successfully yielded the desired 7-membered allylic trichloroacetamide 156 in an excellent 93% yield over 3 steps (Scheme 51).
With synthesis of the 5-, 6- and 7-membered cyclic allylic trichloroacetamides completed so successfully and in high yields, attention turned to the 8-membered allylic trichloroacetamide 158. The formation of 8-membered rings is not kinetically favoured, so the discovery of new methods to successfully synthesise 8-membered rings in high yields is particularly important.

Initially, substrate 154 was treated according to the diluted reaction conditions previously employed for the synthesis of 7-membered product 156. However, instead of the desired product 158, only the aza-Claisen product 157 was isolated. The reaction was repeated using longer reaction times to attempt to drive the reaction to completion, but without success. Grubbs metathesis catalysts are known to have differing substrate specificities and it became clear that Grubbs I was unable to catalyse the RCM reaction of this substrate.

Careful experimentation using Grubbs II and Hoveyda/Grubbs II catalysts was then undertaken, in an attempt to discover reaction conditions that would allow the synthesis of the 8-membered cyclic trichloroacetamide 158. Eventually it was shown that the Grubbs II catalyst could be successfully employed for the synthesis of the 8-membered product 158. Optimal reaction conditions required the use of higher catalyst loadings (20 mol%) and also a lower substrate concentration (0.00013M) than for substrate 153. Under these reaction conditions, the 8-membered product 158, was successfully synthesized in a 62% yield over 3 steps (Scheme 52).
Scheme 52 - Synthesis of 8-membered allylic amide using Grubbs II

2.3.4 Development of an asymmetric tandem reaction

Having demonstrated the scope of this methodology for different ring sizes, an asymmetric process for application in natural product synthesis was required. As was discussed in previous chapters, Overman has developed chiral Pd(II)-COP-Cl catalysts for the aza-Claisen rearrangement and these catalysts are commercially available.\textsuperscript{31,34,35} Having previously shown that these catalysts could be successfully employed for diastereoselective rearrangements during natural product synthesis, attention then turned to their use for the development of an asymmetric tandem aza-Claisen rearrangement and RCM reaction.

Both (R)- and (S)-COP-Cl catalyst were tested in the tandem process for the synthesis of the six membered cyclic allylic amides (Scheme 53). This proved to be very successful as the tandem process proceeded with excellent yield and enantioselectivity (88% ee) thus, allowing either the R or S enantiomer (159 or 160) of the desired cyclic allylic trichloroacetamide to be accessed by this approach. The slightly lower yield afforded by the (R)-COP-Cl catalysed tandem reaction can be explained by the significantly longer reaction times when using this catalyst compared to the (S)-COP-Cl catalyst. The two catalysts are pseudo-enantiomers of one another so it is possible that minor differences in the catalyst structure could explain the slower rearrangement using (R)-COP-Cl.
Scheme 53 - Asymmetric tandem process

The enantioselectivities of these chiral catalysed reactions were calculated using chiral High Performance Liquid Chromatography (HPLC). This was achieved by comparison of the reaction products with their corresponding racemic mixtures (Figure 10).
To confirm that this asymmetric tandem reaction could be employed widely for other ring sizes, substrates 152 and 153 precursors of the 5- and 7-membered amides respectively, were employed with the (S)-COP-Cl catalyst.

The chiral catalyst performed well for both substrates, giving the 5-membered cyclic allylic trichloroacetamide 161 in 88% yield over 3 steps and in 92% ee (Scheme 54).

![Figure 10 - Chiral HPLC trace of racemate (top) and R-compound 160 (bottom)](image)

**Figure 10 - Chiral HPLC trace of racemate (top) and R-compound 160 (bottom)**

Scheme 54 - 5-Membered cyclic allylic trichloroacetamide
The 7-membered cyclic allylic trichloroacetamide 162 was also synthesised in 81% yield over 3 steps and 84% ee (Scheme 55).

Scheme 55 - Asymmetric synthesis of 7-membered trichloroacetamide

2.3.5 Conclusions

In conclusion, a one-pot tandem aza-Claisen rearrangement and ring closing metathesis reaction has been successfully developed, which allows cyclic allylic trichloroacetamides to be synthesised in a highly efficient manner and in excellent yield. The process uses a palladium(II)-catalysed rearrangement which occurs rapidly at room temperature. A variety of commercially available metathesis catalysts can be employed for the RCM step, although the RCM catalyst must be added after rearrangement is complete; otherwise it is inactivated via a side reaction. The scope of this methodology has been demonstrated with the successful synthesis of 5-, 6-, 7- and 8-membered rings, whilst an asymmetric tandem reaction has also been developed using commercially available COP-Cl catalysts. These catalysts work extremely well for this tandem reaction giving the resultant chiral amide in both excellent yield and enantioselectivity.

2.3.6 Future Work

Future work in this area involves several different aspects.

Firstly, whilst the tandem process is highly efficient, it would be very desirable to develop a true cascade process where both catalysts can be added together, to provide the cyclic amide products without subsequent addition of other catalysts. This could possibly be achieved by the use of polymer supported catalysts which would hopefully prevent the RCM catalyst from being inactivated. Should this be achieved, the tandem process could also be expanded to include other reactions (Scheme 56).
Secondly, this methodology could be expanded for the synthesis of N-heterocycles 164. At present these compounds cannot be directly synthesised by this tandem approach, but the synthesis of N-substituted allylic trichloroacetimidates 163 would possibly allow the tandem synthesis of these compounds to be developed (Scheme 57). The use of different terminal alkene substituents attached to the nitrogen, would allow the synthesis of various ring sizes and as before, the use of chiral rearrangement catalysts should allow an asymmetric process to be developed for use in natural product synthesis.

Finally the existing asymmetric tandem reaction could be employed in natural product synthesis. One target currently under investigation is the bicyclic alkaloid, physoperuvine 165, which was first isolated in 1976 from *Physalis peruviana*. This could be synthesised from the 7-membered trichloroacetamide 162, prepared previously, in only 4 steps (Scheme 58).
Scheme 58 - Proposed synthesis of physoperuvine
2.4 Development of an ether-directed tandem aza-Claisen rearrangement and RCM reaction for natural product synthesis

2.4.1 Introduction

Having successfully developed a tandem aza-Claisen rearrangement and RCM reaction, attention then turned to further development of the process. It was decided to undertake the synthesis of some complex natural products using this methodology to demonstrate its application for synthetic chemistry. It was also desirable to combine the tandem process with previous work within the group on ether-directed aza-Claisen rearrangements. Not only would this provide an excellent extension of the existing asymmetric tandem process using chiral catalysts, but the presence of a second stereogenic centre on the resulting cyclic allylic trichloroacetamide products of the reaction would provide an additional handle for further functionalisation, enabling the synthesis of more complex natural products.

A search of the literature was undertaken to identify suitable synthetic targets. Several alkaloids from the amaryllidaceae plant family quickly came to our attention. Alkaloids from this plant family include: (+)-γ-lycorane 166, 2-deoxylycoricidine 167, pancratistatin 64 and narciclasin 168 (Figure 11). All of these compounds possess the galanthane ring system, which is widely known to confer various biological activities including antiviral, antineoplastic and antimitotic activity.87

![Figure 11 - Lycorane type alkaloids](image-url)
It was decided to attempt the synthesis of (+)-γ-lycorane 166, using a novel ether-directed tandem aza-Claisen rearrangement and RCM reaction. Although compound 166 is not known to possess any significant biological activity, this is the core structure of a number of alkaloids that do possess potent bioactivity. As such its synthesis might open up possible synthetic routes to other alkaloids of the lycorane class and their analogues with more potent activities.

2.4.2 Previous syntheses of (+)-γ-lycorane

γ-Lycorane 166 has been the target of several racemic total syntheses. Many fewer enantioselective approaches have been reported. The first asymmetric approach to (+)-γ-lycorane 166 was reported by Mori and co-workers in 1995. This used an asymmetric Pd(0)-catalysed allylic alkylation reaction as the key enantioselective step to give 171. The synthesis was then completed by a Pd(0)-catalysed allylic amination reaction to introduce the 5-membered ring followed by a Pd(0)-catalysed intramolecular Heck reaction to form the final ring of 172 (these two steps could be performed in one-pot), and allowed the synthesis of 166 in 23% yield (5 steps) and a modest 46% ee. Recently Ojima and co-workers have revisited and improved the Mori synthesis (Scheme 59). Using the same synthetic approach as reported by Mori, they focused upon improving the yield and enantioselectivity of the key Pd(0)-catalysed allylic alkylation. This was achieved by the use of chiral monodentate phosphoramidite ligands which could undergo modification to provide improved yields and enantioselectivities compared to those in Mori’s synthesis. Using these new ligands, the synthesis of (+)-γ-lycorane 166 was achieved in 6 steps (41% overall yield and >99% ee) from compounds 169 and 170 (Scheme 59).
Both of these syntheses provided the target compound in very few steps and in reasonable yield, whilst the Ojima synthesis also provides the target compound in excellent enantioselectivity (>99% ee).

In addition to the above syntheses, Gong and co-workers have also reported an enantioselective synthesis of 166. This was achieved by an asymmetric rhodium(II)-catalysed nitroallylation reaction using an aryl boronic acid 173 and a nitroallyl acetate 174 (Scheme 60), thus giving 175. The synthesis of (+)-γ-lycorane 166 was then completed in four further steps in a 38% overall yield (5 steps) and 98% ee. Once again, this is a very concise synthesis providing the target compound with excellent enantioselectivity.
All of these previous asymmetric syntheses of (+)-γ-lycorane 166, make use of chiral catalysis to perform the key enantioselective steps. We proposed to use the tandem aza-Claisen rearrangement and RCM reaction in combination with the previously developed ether-directed aza-Claisen rearrangement methodology to develop a novel synthesis of (+)-γ-lycorane 166, which would also allow the synthesis of other amaryllidaceae alkaloids in the lycorane family.

2.4.3 Proposed synthesis of (+)-γ-lycorane

With these previous syntheses of (+)-γ-lycorane 166 in mind, our new synthetic approach is outlined below (Scheme 61). The key step of the proposed synthesis is an ether-directed tandem aza-Claisen rearrangement and ring closing metathesis reaction of allylic trichloroacetimidate 176, to give the corresponding cyclic allylic trichloroacetamide 177a. A Kharasch cyclisation should introduce the required 5-membered ring 178.80,94 Dechlorination followed by cleavage of the MOM ether under acidic conditions would allow the introduction of a sulfonate leaving group to give 179. This compound should readily undergo elimination upon treatment with base to give the resulting alkene 180. An acylation reaction would then introduce the known left hand aromatic fragment 181 to give compound 182.95 A Heck-type cyclisation, similar to that employed by the groups of Mori and Ojima should perform the final ring closure to give 183.89,90 Finally hydrogenation of the alkene and reduction of the imide should give (+)-γ-lycorane 166.
Scheme 61 - Proposed synthesis of (+)-γ-lycorane

2.4.4 Development of an ether-directed tandem reaction

The first stage of this synthesis required the synthesis of allylic trichloroacetimidate 176 which is readily available from the corresponding allylic alcohol 190. This was achieved in 7 steps from (S)-glycidol 184. Initially, silyl protection of 184 gave the silyl ether 185. A regioselective copper(I)-catalysed epoxide opening using allyl magnesium bromide then gave 186. MOM protection of the resulting secondary alcohol under standard conditions gave 187, which was then treated with TBAF to provide the primary alcohol 188. Primary alcohol 188 was subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction to give the E-α,β-unsaturated ester 189. Finally DIBAL-H reduction gave allylic alcohol 190, in an excellent 80% yield over 7 steps (Scheme 62).
Compound 190 was converted to the corresponding allylic trichloroacetimidate 176 and subjected to tandem aza-Claisen rearrangement followed by RCM, to successfully give trichloroacetamides 177a and 177b, as a 5 : 1 ratio of diastereomers and in a reasonable 45% yield over 3 steps from allylic alcohol 190 (Scheme 63).

In a similar manner to previous reactions, the diastereomeric ratio of the cyclic products could be determined from the $^1$H NMR spectrum (Figure 12). The desired cyclic product 177a, where both stereocentres are syn has protons at 4.05 ppm (1-H) and 4.63 ppm (2-H) respectively. The protons for the undesired anti-product 177b are observed at 3.75 ppm (1-H) and 4.42 ppm (2-H).
The rather modest yields achieved for this directed rearrangement can perhaps be explained by the much greater complexity of substrate 176 when compared to the previous rearrangement substrate 149 (Section 2.3.2), this leads to a slower aza-Claisen rearrangement thus allowing competing side reactions to take place.
Given the intention was to use this methodology for natural product synthesis, an improved yield and stereoselectivity was needed to make the tandem process more efficient so that it could provide the desired cyclic amide 177a in multi-gram quantities. Previously, the Sutherland group have shown that toluene (which is a non-coordinating solvent) can enhance the yield and diastereoselectivity of MOM ether-directed aza-Claisen rearrangements.\textsuperscript{47} When the tandem reaction was carried out in toluene (starting the rearrangement at 0 °C) the yield was much improved and the diastereoselectivity increased to 10 : 1 (Scheme 63).

\begin{center}
\begin{tabular}{c|c|c}
Reaction conditions & yield from 190 (%) & ratio (a : b) \\
\hline
DCM, RT & 45 & 5 : 1 \\
Toluene, 0 °C to RT & 60 & 10 : 1 \\
\end{tabular}
\end{center}

\textbf{Scheme 63 - Ether-directed tandem aza-Claisen rearrangement and RCM reaction}

\subsection*{2.4.5 Application towards the synthesis of (+)-\textit{γ}-lycorane}

After successful synthesis of cyclic allylic trichloroacetamide 177a in multi-gram quantities, attention then turned to the Kharasch cyclisation which is the second key step in the synthesis of (+)-\textit{γ}-lycorane 166.

A Kharasch cyclisation is a Ru(II)-catalysed reaction that proceeds via a radical mechanism (Scheme 64), where ruthenium(II) attacks the trichloroacetyl group 191 forming a radical 192 and Ru(III)-Cl. The radical 192 then attacks the alkene and forms the
new C-C bond of the 5-membered ring 193. The reaction is terminated by reintroduction of Ru(III)-Cl which introduces a chloride to the face opposite the new 5-membered ring (the top face as shown in the diagram), thus providing the Kharasch product 194 and recycling of the Ru(II)-catalyst. The groups of Snapper and Itoh have previously reported Kharasch cyclisations upon similar substrates to 177a, with the resulting products isolated in high yields. In addition, both groups showed that the reaction proceeds to produce exclusively the cis-ring junction between the 5- and 6-membered rings, which is the required stereochemistry for the synthesis of (+)-γ-lycorane 166.

Originally, it was planned to follow the experimental procedure described by Snapper, which uses Grubbs I catalyst as the ruthenium catalyst. This would have potentially introduced an extra step to the tandem process as the Kharasch cyclisation occurs at much higher temperatures than the preceding RCM reaction. So it is possible that simply heating the reaction mixture of the tandem process to approximately 150 °C would provide the desired Kharasch product 178, without the requirement for purification. When the allylic trichloroacetamide 177a was treated with Grubbs I catalyst in toluene at 155 °C, the desired Kharasch product 178 was not isolated; instead a tricyclic product 195 was formed in a rather disappointing 24% yield (Scheme 65).
With Grubbs catalyst failing to provide the desired product, it was decided instead to continue our efforts using the simpler RuCl$_2$(PPh$_3$)$_3$ catalyst and reaction conditions previously reported by Itoh. By switching catalyst, a mixture of the desired Kharasch product 178 and tricyclic product 195 were synthesized, both in rather modest yields. Careful experimentation to optimize the yield of 178 showed that concentrated reaction conditions (0.1 M) and elevated temperatures (>150 °C) were required to ensure the reaction proceeded to completion as rapidly as possible. If the reaction was performed at lower concentrations or temperatures and over lengthy reaction times, only the tricyclic product 195 and other decomposition products were isolated. Eventually, using the reaction conditions shown in scheme 66, synthesis of Kharasch product 178, was successfully achieved in a reasonable 42% yield (10% of product 195 was also isolated). Scale-up was then attempted to generate sufficient quantities of 178 to complete the synthesis of (+)-γ-lycorane 166. Unfortunately this yielded only a very small quantity of 178, instead mostly 195 was isolated.

Investigation into the causes of these problems with the Kharasch cyclisation was then undertaken. Radical processes typically occur quickly so it is likely that the Kharasch cyclisation occurs first to introduce the desired 5-membered ring 178. Unfortunately this product can then undergo attack of the MOM-ether from the nitrogen of the amide, thus leading to the formation of the tricyclic product 195 observed. This unwanted side reaction is likely mediated by acid (HCl), which could form at these elevated reaction temperatures through decomposition of the metal catalyst or the reaction of Cl radicals with the solvent.

The previous examples reported by Snapper and Itoh were less complex than substrate 177a and lacked acid sensitive groups such as the MOM ether, and so, they would be less sensitive to the formation of these by-products. It was proposed that if a method could be found for trapping any acid produced during the reaction, then the side reaction leading to the tricyclic product 195 would be prevented. Hopefully, compound 178 could then be isolated in good yields.
An acid scavenger was required that would trap any acid produced during the reaction and yet not interfere with the ruthenium-catalysed radical process. After a search, three possible additives were identified: DBU, K$_2$CO$_3$ and molecular sieves (4Å). All three reagents were then separately examined as additives to the Kharasch cyclisation. The addition of DBU yielded only the starting material 177a, whilst K$_2$CO$_3$ appeared to have little effect as it yielded a mixture of the two products (178 and 195). However, the reaction using molecular sieves gave the desired product 178 in an encouraging 56% yield. Further optimisation of this reaction was undertaken and after switching to powdered molecular sieves (4Å), which presents a greater surface area to trap any acid; the yield of reaction was increased to 75% and could be reliably performed on a reasonable scale (0.5 g) (Scheme 67).

Previously Snapper and Itoh have shown that the Kharasch cyclisation occurs to give exclusively the cis ring junction.$^{80,94}$ This was confirmed for compound 178 by nOe studies, which showed a positive nOe between protons 3a and 7a (1.8%), thus proving that this compound also had the cis ring junction (Figure 13). In addition, an enhancement of proton 7 (1.0% nOe) was observed upon irradiation of proton 7a, confirming the all cis geometry between protons 3a, 7a and 7. Finally the stereochemistry at C-4 was confirmed by irradiation of proton 3a, as expected there was no enhancement of proton 4 proving that the chlorine was on the top face of the molecule.

![Scheme 67 - Optimised reaction conditions for Kharasch cyclisation](image)

![Figure 13 - nOe studies confirming cis ring junction](image)
With the problem encountered with the Kharasch cyclisation successfully overcome, the reductive dechlorination of both Kharasch products 178 and 195 was successfully completed. This was performed using Raney-Nickel and a procedure described by Barrero and co-workers, resulting in formation of the desired dechlorinated products 196 and 197 in good yields (Scheme 68).

![Scheme 68 - Dechlorination using Raney-Nickel](image)

The next stage was to prepare methanesulfonate 179. This was achieved by hydrolysis of the MOM group of 197 under acidic conditions, followed by introduction of the mesylate under standard conditions, giving 179 in an excellent 88% yield over 2 steps (Scheme 69).

![Scheme 69 - Synthesis of mesylate](image)

Elimination of mesylate 179 was then attempted. Initially, the strong base potassium tert-butoxide (tBuOK) was used. However, this reagent led to decomposition of the starting material and no product was formed. Consequently, it was decided to use a milder base in an attempt to overcome this decomposition. DBU was chosen as base due to the fact that this hindered base is milder than tBuOK so should hopefully lead to elimination of the mesylate without causing decomposition. The reaction was heated to 60 °C for 24 h, but only starting material was present. Elevation of temperature to 120 °C for a further 24 h showed that the starting material had begun to decompose (Scheme 70). Elimination
reactions require the leaving group and the hydrogen atom, which is to be removed by base, to have an anti-periplanar conformation. It is possible that the rigid 6,5-ring system of 179, prevents it from adopting such a conformation, hence the lack of reactivity. It was decided in the light of this to pursue an alternative synthetic strategy.

Scheme 70 - Attempts to eliminate mesylate

Fujioka and co-workers have recently reported the synthesis of (-)-γ-lycorane 202 (the unnatural enantiomer of 166) which uses a Friedel-Crafts alkylation to close the final ring to give compound 201. The substrate for this reaction 200, was synthesised by an acylation reaction of known aromatic chloride 199 and bromo compound 198 (Scheme 71).97

Scheme 71 - Synthesis of (-)-γ-lycorane

It was hoped that a simple nucleophilic S$_{N}$2 reaction of mesylate 179 or an activated intermediate of alcohol 204 would provide 203 (the enantiomer of 198), thus allowing the use of similar chemistry to complete the synthesis of (+)-γ-lycorane 166. The mesylate 179 or alcohol 204 was therefore treated under a variety of bromination conditions to attempt to synthesise 203 (Scheme 72).
Unfortunately, none of these procedures was successful. It was hypothesised that the hydrogen of the amide might interfere with the substitution reaction, so it was decided instead to perform the acylation reaction prior to bromination, as the introduction of the aromatic substituent should block this position and hopefully then allow the substitution to proceed.

Initial attempts to perform the acylation using mesylate 179 were unsuccessful. The $^1\text{H}$ NMR showed a complex mixture of compounds and none of the desired product was observed. In addition, the signals associated with the mesylate were no longer present, and so, it appeared that the strong base (NaH) employed to de-protonate the amide was not compatible with the mesylate. Instead, it was decided to re-order the synthetic steps and perform the acylation prior to introduction of the mesylate. The MOM protected compound 197 was subjected to the acylation reaction, under the reaction conditions as reported previously by Fujioka and co-workers,$^{97}$ using bromide 205.$^{98}$ With a more stable protecting group in place, the reaction proceeded smoothly to give the desired product in an excellent 90% yield (Scheme 73). Cleavage of the MOM protecting group gave the alcohol 207 in quantitative yield, which was then subjected to conditions in an attempt to introduce the bromide, unfortunately without success (Scheme 73).
Scheme 73 - Acylation to introduce aromatic substituent

The exact reasons why various attempts to synthesise the bromide have been unsuccessful are unclear and could involve a combination of factors.

In a final attempt to complete the synthesis, the alcohol 207 was converted to the mesylate 209 (Scheme 74). It was hoped that the mesylate might act as a better leaving group and so undergo conversion to the desired bromide 208. Unfortunately, when this reaction was attempted no product was formed, despite the elevated temperatures and extended reaction times (Scheme 74).
Mesylates have previously been shown to undergo Friedel-Crafts reactions.\textsuperscript{99,100} It was decided to attempt the Friedel-Crafts reaction on the mesylate 209 in the hope that it might indeed yield the ring closed product 210. The reaction was attempted twice under different reaction conditions (Scheme 75), without formation of the desired product.

Due to time and material constraints, work was halted at this stage and although there are a number of alternatives that could still be attempted, it appears that conversion of the hydroxyl group to the bromide either directly or via the mesylate, will not be successful. It is not clear why this is the case as in theory the reaction is fairly straightforward; however, in practice this transformation has proved incredibly challenging and an alternative strategy might yield more encouraging results.
2.4.6 Conclusions

In conclusion, the tandem aza-Claisen rearrangement and RCM reaction that was developed in section 2.3 has been successfully combined with the previously developed ether-directed methodology, to give a MOM ether-directed tandem aza-Claisen rearrangement and RCM reaction. This reaction provides chiral cyclic allylic trichloroacetamides in good yield and in high diastereoselectivity. The synthesis of (+)-γ-lycorane 166 has been attempted using this methodology to introduce the required six-membered ring. A ruthenium(II)-catalysed Kharasch cyclisation was then employed to introduce the fused 5-membered ring. The nitrogen of the amide was successfully acylated with the known aromatic component 205, but efforts to perform the final ring closure via a Friedel-Crafts reaction were unsuccessful. Significant progress towards the synthesis of (+)-γ-lycorane 166 has been made, although problems encountered with the final steps of the route prevented the successful synthesis of the target within the timeframe of this PhD project. Modifications to the final synthetic steps should then allow the synthesis of (+)-γ-lycorane 166 and other amaryllidaceae alkaloids, to be completed.

2.4.7 Future Work

An alternative synthetic strategy is outlined below (Scheme 76). Given the success of the acylation of MOM compound 197, acylation using the aromatic component 189 as originally proposed, should provide 211 in good yield. With this in hand, conversion of the protected hydroxyl group to the mesylate 212 should be straightforward. Elimination of the mesylate under basic conditions could then be successful as with the amide protected by the aromatic group it should no longer interfere with the elimination process, although questions remain as to whether the compound is able to adopt the syn- or anti-periplanar conformation required for it to react successfully. Assuming that alkene 182 can be successfully synthesised then a Heck type cyclisation should provide the ring closed product 183, in a similar way to that originally proposed and demonstrated previously by Mori and Ojima. Thus, the synthesis of (+)-γ-lycorane 166, should still be achievable using this highly successful ether-directed tandem aza-Claisen rearrangement and RCM methodology.
Upon successful synthesis of (+)-γ-lycorane 166, the ether-directed tandem reaction could then be applied for the synthesis of other alkaloids in the *amaryllidaceae* family. One such compound is (+)-2-deoxylycoricidine 167, which has only previously been synthesised in racemic form. This compound is a more challenging synthetic target, but its asymmetric synthesis could also be achieved from allylic trichloroacetamide 177a (Scheme 77). Conversion of 177a to the oxazolidinone 213, followed by dihydroxylation would introduce the syn-diol require for the target compound. After protection of the diol, the oxazolidinone would be hydrolysed to provide the amino alcohol 214. The final steps would be similar to the synthesis of (+)-γ-lycorane (166, above): acylation to introduce the aromatic component would give 215, which would be converted to 216. This would undergo a Heck-type cyclisation which would provide, after deprotection, the first asymmetric synthesis of (+)-2-deoxylycoricidine 167.
Scheme 77 - Proposed synthesis of (+)-2-deoxycoricididine
3.0 Experimental Section

General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. Dry solvents were purified using a PureSolv 500 MD solvent purification system or THF and diethyl ether were distilled from sodium and benzophenone, whilst dichloromethane (DCM) was distilled from calcium hydride. All reactions were performed under an atmosphere of argon or nitrogen unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV$_{254}$) were used for thin layer chromatography and were visualised by staining with KMnO$_4$. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS ($\delta$H 0.00 and $\delta$C 0.0) or residual chloroform ($\delta$H 7.28 and $\delta$C 77.2) as standard. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained using a JASCO FTIR 410 using a Golden Gate apparatus. Optical rotations were determined as solutions irradiating with the sodium D line ($\lambda$ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10$^{-1}$ deg cm$^2$ g$^{-1}$. Chiral HPLC was performed on a Agilent 1100 series instrument and were calibrated with the appropriate racemic mixture.

General Procedure 1: One pot Swern oxidation-Horner/Wadsworth/Emmons reaction.

Dimethyl sulfoxide (2.5 equiv.) was added to a stirred solution of oxalyl chloride (1.4 equiv.) in DCM (100 mL) at -78 °C. The reaction mixture was stirred for 0.3 h before the alcohol (1.0 equiv.) in DCM (50 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (5 equiv.) was added. This reaction mixture was stirred for 0.5 h at -78 °C and then allowed to warm to room temperature and stirred for a further 2 h. Meanwhile, a solution of lithium chloride (1.8 equiv.), triethylphosphonoacetate (1.8 equiv.) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.8 equiv.) in acetonitrile (100 mL) was prepared and stirred for 1.0 h. The Swern solution was concentrated in vacuo, then the Wadsworth Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 x 75 mL). The organic layers were combined, dried
(MgSO₄) and concentrated to give an orange oil. Purification by flash column chromatography using diethyl ether : petroleum ether as eluent gave the pure product.

**General Procedure 2: DIBAL-H reduction to allylic alcohol.**

The ester (1.0 equiv.) was dissolved in diethyl ether (100 mL) and cooled to -78 °C. DIBAL-H (1 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was stirred at -78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (400 mL). The filtrate was then dried (MgSO₄) and concentrated *in vacuo*. Purification was carried out by flash column chromatography eluting with diethyl ether : petroleum ether.

**General procedure 3: MOM protection of secondary alcohol.**

\(N,N\)-Diisopropylethylamine (1.5 equiv.) and bromomethyl methyl ether (1.5 equiv.) were added to a solution of the alcohol (5.0 mmol) in DCM (20 mL). The reaction mixture was then heated under reflux for 12 h before being diluted with DCM (50 mL) and washed with 2 M hydrochloric acid solution (25 mL). The organic layer was dried (MgSO₄) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether : petroleum ether to give the desired compounds as colourless oils.

**General procedure 4: Synthesis of allylic trichloroacetimidate and subsequent metal catalysed aza-Claisen rearrangement.**

Allylic alcohol (1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.25 equiv.) was then added to the solution followed by trichloroacetonitrile (1.5 equiv.). The reaction mixture was warmed to room temperature and stirred for 2 h under an argon atmosphere. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification in the rearrangements that followed. The allylic trichloroacetimidate was then dissolved in THF, toluene or DCM (10 mL) under an argon atmosphere. The metal catalyst (0.1 equivalent, 10 mol%) was then added to the solution...
and the mixture was stirred at room temperature until the reaction was observed to reach completion by $^1$H NMR spectroscopy. The mixture was then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate and purification by flash column chromatography (elution with petroleum ether : diethyl ether) gave the pure trichloroamide products as brown oils.

**General procedure 5: Synthesis of allylic trichloroacetimidate and subsequent thermal rearrangement.**

Allylic alcohol (1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.25 equiv.) was then added to the solution followed by trichloroacetonitrile (1.5 equiv.). The reaction mixture was warmed to room temperature and stirred for 2 h under an argon atmosphere. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 ml). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification in the rearrangements that followed. The crude trichloroacetimidate was dissolved in $p$-xylene (20 mL) and heated to 140 °C until reaction was complete as observed by $^1$H NMR spectroscopy. The reaction mixture was concentrated in vacuo to give a brown oil. Purification by chromatography (elution with petroleum ether : diethyl ether) gave the trichloroamide products as brown oils.

**General Procedure 6: Synthesis of allylic trichloroacetimidate and subsequent tandem aza-Claisen rearrangement - Ring Closing Metathesis.**

Allylic alcohol (1.0 equiv.) was dissolved in DCM (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.25 equiv.) was added to the solution followed by trichloroacetonitrile (1.5 equiv.). The solution was then warmed to room temperature and stirred for 2 h. The reaction mixture was filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification. Allylic trichloroacetimidate (1 equiv.) was then dissolved in DCM (10 mL) under an argon atmosphere. The rearrangement catalyst (0.1 equivalent, 10 mol%) was added to the solution and the reaction mixture was stirred at room temperature for 3 h. Grubbs catalyst (1st Generation) (0.1 equivalent, 10 mol%) was then added and the reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL).
Concentration of the filtrate followed by flash column chromatography gave the pure cyclic allylic amides as white solids.

**General procedure 7: Ruthenium trichloride catalysed oxidation to carboxylic acid.**

The trichloroacetamide (1 mmol) was dissolved in carbon tetrachloride (14 mL) and acetonitrile (14 mL). Sodium metaperiodate (4.1 equiv.) in water (21 mL) was then added followed by ruthenium trichloride hydrate (5 mol%). The reaction mixture was stirred vigorously for 6 h before a further portion of sodium metaperiodate (1 equiv.) was added. The reaction mixture was stirred vigorously for 12 h and then extracted with DCM (3 x 40 mL). The organic layers were combined, dried (MgSO4) and concentrated to give the carboxylic acid as a viscous oil.

**General procedure 8: Acidic hydrolysis of protecting groups to provide target amino acid.**

The carboxylic acid (1 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated under reflux for 12 h. The reaction mixture was then cooled before being extracted with diethyl ether (10 mL). The aqueous layer was concentrated to give a brown liquid. Purification by ion-exchange chromatography on Dowex® 50WX8-100 (elution with 0.5 M ammonium hydroxide solution) gave the amino acid products as white solids.

**1,2,5,6-Di-O-isopropyldene-D-mannitol (94).**

![Structural formula of D-Mannitol 92](image)

D-Mannitol 92 (15.0 g, 82.3 mmol) was dissolved in dimethyl sulfoxide (30 mL). 2,2-Dimethoxypropane 93 (25.3 mL, 206.0 mmol) and p-toluenesulfonic acid (0.75 g, 0.9 mmol) were then added and the reaction mixture was stirred at room temperature overnight. The mixture was washed with a 5% solution of sodium hydrogen carbonate (30 mL) and then extracted with ethyl acetate (3 x 20 mL). The organic layer was washed again with (5%) sodium hydrogen carbonate solution (25 mL), then dried (MgSO4) and concentrated *in vacuo* to give the crude product as a white solid. Re-crystallisation from petroleum ether and ethyl acetate, yielded the title product 94 as a crystalline white solid.
(12.55 g, 58%). mp 114-118 °C, lit. 102 115-119 °C; $\delta_H$ (400 MHz, CDCl$_3$) 1.29 (6H, s, CH$_3$), 1.35 (6H, s, CH$_3$), 2.51 (2H, br s, 2 x OH), 3.67 (2H, d, $J$ 6.7 Hz, 3-H and 4-H), 3.92 (2H, dd, $J$ 8.4, 5.3 Hz, 1'-HH and 6'-HH), 4.00-4.14 (4H, m, 1'-HH, 2'-H, 5'-H and 6'-HH); $\delta_C$ (100 MHz, CDCl$_3$) 25.2 (CH$_3$), 26.7 (CH$_3$), 66.8 (CH$_2$), 71.2 (CH), 76.3 (CH), 109.4 (C); m/z (CI) 263 (MH$^+$), 205 (28%).

**Ethyl (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxypentan-2-enoate (95).**

![Ethyl (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxypentan-2-enoate](image)

1,2,5,6-Di-O-isopropylidene-D-mannitol 94 (7.0 g, 26.7 mmol) was suspended in 5% sodium hydrogen carbonate solution (75.0 mL) and cooled to 0 °C. Sodium periodate (6.9 g, 32.2 mmol) in water (15.0 mL) was added dropwise to the suspension and the reaction mixture was stirred at room temperature for 1 h before cooling to 0 °C. Triethyl phosphonoacetate (11.7 mL, 58.8 mmol) and a potassium carbonate solution (6 M) (80.0 mL) were then added to the mixture, which was stirred overnight at room temperature. The reaction was extracted with DCM (4 x 40 mL), washed with saturated sodium chloride solution (50 mL) and dried (MgSO$_4$). Concentration under vacuum gave a clear oil. Purification by flash column chromatography (elution with petroleum ether : ethyl acetate, 10 : 1) gave the title compound 95, as a clear oil (7.5 g, 70%). Spectroscopic data in accordance with literature. 103 [$\alpha$]$_{D}^{25}$ +43.1 (c 1.0, CHCl$_3$), lit. 103 [$\alpha$]$_{D}^{25}$ +43.3 (c 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.22 (3H, t, $J$ 7.2 Hz, OCH$_2$CH$_3$), 1.34 (3H, s, CH$_3$), 1.38 (3H, s, CH$_3$), 3.61 (1H, dd, $J$ 7.9, 7.5 Hz, 5'-HH), 4.09-4.17 (3H, m, OCH$_2$ and 5'-HH), 4.57-4.62 (1H, m, 4-H), 6.03 (1H, dd, $J$ 15.6, 1.2 Hz, 2-H), 6.80 (1H, dd, $J$ 15.6, 5.6 Hz, 3-H); $\delta_C$ (100 MHz, CDCl$_3$) 14.2 (CH$_3$), 25.4 (CH$_3$) 26.4 (CH$_3$), 60.6 (CH$_2$), 68.8 (CH$_2$), 74.9 (CH), 110.2 (C), 122.4 (CH), 144.6 (CH), 166.0 (C); m/z (CI) 201 (MH$^+$, 100%), 183 (37%), 143 (19), 81 (6).
(2E,4S)-4,5-(O-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (96).\textsuperscript{104}

![Chemical structure](image)

Reaction was carried out according to general procedure 2 using ethyl (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxypentan-2-enoate 95 (0.50 g, 2.5 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 5:1), gave the title compound as a colourless oil (0.37 g, 94%). $[\alpha]_D^{25} +31.0$ (c 1.6, CHCl$\textsubscript{3}$), lit.$^{104}$ $[\alpha]_D^{24} +33.9$ (c 1.0, CHCl$\textsubscript{3}$); $\delta_H$ (400 MHz, CDCl$\textsubscript{3}$) 1.40 (3H, s, CH$\textsubscript{3}$), 1.43 (3H, s, CH$\textsubscript{3}$), 3.61 (1H, dd, $J$ 8.1, 7.6 Hz, 5-HH), 4.10 (1H, dd, $J$ 8.1, 6.1 Hz, 5-HH), 4.16 (2H, d, $J$ 5.0 Hz, 1-H$\textsubscript{2}$), 4.51-4.58 (1H, m, 4-H), 5.72 (1H, dd, $J$ 15.5, 7.5 Hz, 3-H), 5.95 (1H, dt, $J$ 15.5, 5.0 Hz, 2-H); $\delta_C$ (100 MHz, CDCl$\textsubscript{3}$) 25.9 (CH$\textsubscript{3}$), 26.7 (CH$\textsubscript{3}$), 62.5 (CH$\textsubscript{2}$), 69.4 (CH$\textsubscript{2}$), 76.5 (CH), 109.4 (C), 128.3 (CH), 133.2 (CH); $m/z$ (Cl) 159 (MH$^+$, 100%), 141 (27), 83 (49).

Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using PdCl$\textsubscript{2}$(MeCN)$\textsubscript{2}$ as catalyst.

![Chemical structures](image)

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (0.20 g, 1.3 mmol) and bis(acetonitrile)palladium(II) chloride (0.03 g, 3 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 3 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9:1) yielded 98b followed by 98a as brown oils (0.14 g, 36% combined yield) and in a ratio of 7:1 (98a : 98b). Further elution (petroleum ether : diethyl ether, 1:9) gave 98c also as a brown oil (0.11 g, 32% yield). Data for 98a and 98b: $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3418 (NH), 2988 (CH), 1719 (CO), 1506 (C=C), 1373, 1217, 1068; (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-
isopropylidene)-4,5-dihydroxypenta-1-ene 98b: $[\alpha]_D^{25} +34.4$ (c 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.30 (3H, s, CH$_3$), 1.41 (3H, s, CH$_3$), 3.64 (1H, dd, $J$ 8.6, 6.5 Hz, 5-HH), 4.04 (1H, dd, $J$ 8.6, 6.5 Hz, 5-HH), 4.28 (1H, td, $J$ 6.5, 2.4 Hz, 4-H), 4.41-4.46 (1H, m, 3-H), 5.22-5.31 (2H, m, 1-H$_2$), 5.81 (1H, ddd, $J$ 17.1, 10.5, 5.7 Hz, 2-H), 6.98 (1H, br s, NH); $\delta_C$ (100 MHz, CDCl$_3$) 24.7 (CH$_3$), 26.4 (CH$_3$), 53.9 (CH), 66.4 (CH$_2$), 76.6 (CH), 92.6 (C), 110.0 (C), 117.7 (CH$_2$), 133.9 (CH), 162.0 (C); $m/z$ (CI) 306.0055 (MH$^+$, C$_{10}$H$_{15}$O$_3$N$_3$Cl$_2$ requires 306.0062), 293 (40%), 244 (75), 210 (80), 176 (100), 71 (60). Data for (2S,3R)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene 98a: $\delta_H$ (400 MHz, CDCl$_3$) 1.30 (3H, s, CH$_3$), 1.41 (3H, s, CH$_3$), 3.78 (1H, dd, $J$ 9.1, 5.1 Hz, 5-HH), 4.02 (1H, dd, $J$ 9.1, 5.1 Hz, 5-HH), 4.22-4.27 (1H, m, 4-H), 4.40-4.46 (1H, m, 3-H), 5.25-5.32 (2H, m, 1-H$_2$), 5.78 (1H, ddd, $J$ 15.8, 10.3, 6.2 Hz, 2-H), 7.00 (1H, br s, NH); $\delta_C$ (100 MHz, CDCl$_3$) 24.7 (CH$_3$), 26.1 (CH$_3$), 55.8 (CH), 65.5 (CH$_2$), 76.1 (CH), 92.5 (C), 110.2 (C), 119.3 (CH$_2$), 131.6 (CH), 161.5 (C). Data for (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene 98c: $\upsilon_{\text{max}}$/cm$^{-1}$ (neat) 3510 (OH), 3417 (NH), 2985 (CH), 1720 (CO), 1512 (C=C), 1311, 1068; $[\alpha]_D^{25} +1.5$ (c 1.0, CHCl$_3$), $\delta_H$ (400 MHz, CDCl$_3$) 1.89 (2H, br s, 2 x OH), 4.20 (2H, dd, $J$ 5.0, 1.2 Hz, 1-H$_2$), 4.36 (1H, dd, $J$ 8.5, 8.3 Hz, 5-HH), 4.78 (1H, dd, $J$ 9.8, 8.3 Hz, 5-HH), 4.88-4.95 (1H, m, 4-H), 5.77 (1H, ddt, $J$ 15.5, 7.3, 1.2 Hz, 3-H), 5.95 (1H, dt, $J$ 15.5, 5.0 Hz, 2-H); $\delta_C$ (100 MHz, CDCl$_3$) 62.5 (CH$_2$), 67.9 (CH$_2$), 76.1 (CH), 88.1 (C), 128.2 (CH), 133.3 (CH), 163.3 (C); $m/z$ (CI) 261.9729 (MH$^+$, C$_7$H$_{11}$NO$_3$Cl$_3$ requires 261.9729), 244 (100%), 228 (41), 210 (38), 192 (15), 118 (95).

Synthesis of (3S,4S,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene 98a, (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using PtCl$_2$ as catalyst.

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (0.10 g, 0.6 mmol) and platinum(II) chloride (0.017 g, 10 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 5 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded 98b followed by 98a as brown oils (0.06 g, 31% combined yield) and in a 4 : 1 ratio (98a : 98b). Further elution (petroleum ether : diethyl ether, 1 : 9) gave 98c also as a brown oil (0.13 g, 66%). Spectroscopic data as reported above.
Synthesis of (3S,4S,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using HAuCl₄.3H₂O as catalyst.

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (0.10 g, 0.6 mmol) and hydrogen tetrachloroaurate(III) hydrate (0.025 g, 10 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 5 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded 98b followed by 98a as brown oils (0.05 g, 25% combined yield) and in a 2 : 1 ratio (98a : 98b). Further elution (petroleum ether: diethyl ether, 1 : 9) gave 98c also as a brown oil (0.07 g, 36%). Spectroscopic data as reported above.

Synthesis of (3S,4S,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using AuCl as catalyst.

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (0.10 g, 0.6 mmol) and gold(I) chloride (0.015 g, 10 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 4 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded 98b followed by 98a as brown oils (0.06 g, 31% combined yield) and in a 2 : 1 ratio (98a : 98b). Further elution (petroleum ether: diethyl ether, 1 : 9) gave 98c also as a brown oil (0.13 g, 68%). Spectroscopic data as reported above.

Synthesis of (3S,4S,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b), using (S)-COP-Cl as catalyst.

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (1.00 g, 6.3 mmol) and di-µ-chlorobis[η⁵-
(S)-(pR)-2-(2'-4'-isopropyl)oxazolinylcycloentadienyl,1-C,3'-N)-(η^4-tetraphenylcyclobutadiene)cobalt[dipalladium [(S)-COP-Cl] (0.20 g, 3 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 7 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded 98b followed by 98a, as brown oils (1.55 g, 81% combined yield) and in a 52 : 1 ratio (98b : 98a). Spectroscopic data as reported above.

Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2E,4S)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using (R)-COP-Cl as catalyst.

The reaction was carried out according to general procedure 4 using (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol 96 (0.10 g, 0.6 mmol) and [bis[μ-chloro]dipalladium]bis[(η^4,1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]]bis[μ-[(1-η:1,2,3,4,5-η)-2-[(4R)-4,5-dihydro-4-(1-methylethyl)-2-oxazoyl]-2,4-cyclopentadienylidene]]dicobalt [(R)-COP-Cl] (0.023 g, 3 mol%) was used as catalyst. The reaction mixture was stirred at 38 °C for 14 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded 98b followed by 98a as brown oils (0.044 g, 23% combined yield) and in a 6 : 1 ratio (98a : 98b). Further elution (petroleum ether: diethyl ether, 1 : 9) gave 98c also as a brown oil (0.027 g, 16%). Spectroscopic data as reported above.

(2S,3S)-2-(2',2',2'-Trichloromethylcarbonylamino)-3,4-(O-isopropylidene)-4,5-dihydroxybutanoic acid (99).

The reaction was carried out according to general procedure 7 using (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(O-isopropylidene)-4,5-dihydroxypenta-1-ene 98b (0.50 g, 1.7 mmol). Purification through a plug of silica gel (elution with diethyl ether : petroleum ether, 9 : 1) gave the title compound 99 (0.25 g, 47% yield) as a brown oil.
\[ \nu_{\text{max}}/\text{cm}^{-1} \text{ (neat)} 3423 (\text{NH and OH}), 2990 (\text{CH}), 1694 (\text{CO}); [\alpha]_D^{21} -58.0 \text{ (c 0.25, MeOH)}; \]
\[ \delta_{\text{H}} (400 \text{ MHz, CD}_3\text{OD}) 1.49 (3\text{H}, \text{s}, \text{CH}_3), 1.46 (3\text{H}, \text{s}, \text{CH}_3), 1.38 (1\text{H}, \text{dd}, J 8.9, 5.7 \text{ Hz}, 4-\text{H}); \]
\[ \delta_{\text{C}} (100 \text{ MHz, CD}_3\text{OD}) 26.8 (\text{CH}_3), 26.8 (\text{CH}_3), 56.8 (\text{CH}), 67.8 (\text{CH}_2), 76.2 (\text{CH}), 93.6 (\text{C}), 111.0 (\text{C}), 164.0 (\text{C}), 171.4 (\text{C}); m/z (\text{Cl}) 321.9835 (\text{MH}^+ \text{ C}_9\text{H}_{13}\text{O}_3\text{N}^{35}\text{Cl}_2^{37}\text{Cl} \text{ requires } 321.9831), 264 (100\%), 228 (50). \]

**{(2S,3S)-2-Amino-3,4-dihydroxybutyric acid (91)}**

![Chemical structure of (2S,3S)-2-Amino-3,4-dihydroxybutyric acid](attachment:image)

The reaction was carried out according to general procedure 8 using (2S,3S)-2-(2',2',2'-trichloromethylcarbonylamino)-3,4-(O-isopropylidene)-4,5-dihydroxybutanoic acid (0.16 g, 0.5 mmol). Purification by ion exchange chromatography (elution with 0.5 M NH₄OH solution) yielded (2S,3S)-2-amino-3,4-dihydroxybutyric acid (91) as a white solid (0.07 g, 100% yield). Spectroscopic data in agreement with literature.\(^\text{105}\) [\(\alpha\)] \(_D\) \(^{18} -9.6 \text{ (c 1.0, H}_2\text{O);} \text{lit.}\(^\text{105}\) [\(\alpha\)] \(_D\) \(^{26} -10.0 \text{ (c 1.0, H}_2\text{O);} \delta_{\text{H}} (400 \text{ MHz, D}_2\text{O}) 3.59-3.68 (3\text{H}, \text{m, 3-H and 4-H}); \delta_{\text{C}} (100 \text{ MHz, D}_2\text{O}) \text{56.7 (CH), 63.3 (CH}_2\text{), 69.3 (CH), 172.7 (C); m/z (Cl) 136 (MH}^+, 6\%); 123 (13), 91 (30), 83 (100), 69 (76), 67 (48). **Ethyl (2E,4S)-4,5-dihydroxypent-2-enoate (100)**

![Chemical structure of Ethyl (2E,4S)-4,5-dihydroxypent-2-enoate](attachment:image)

Ethyl (2E,4S)-4,5-(O-isopropylidene)-4,5-dihydroxypentan-2-enoate (95) (2.00 g, 10.0 mmol) was dissolved in ethanol (20 mL). 2 M Hydrochloric acid (10 mL) was then added and the solution was stirred at room temperature for 3 h. The reaction was quenched by addition of sodium hydrogen carbonate (6.0 g). Following filtration, the reaction mixture was concentrated \textit{in vacuo}. After a second filtration the solution was dried (MgSO\(_4\)) and purified through a short pad of silica gel to give the title compound (100) as a clear oil (1.51 g, 94%). [\(\alpha\)] \(_D\) \(^{24} -5.0 \text{ (c 0.5, CHCl}_3); \text{lit.}\(^\text{106}\) [\(\alpha\)] \(_D\) \(^{25} -5.8 \text{ (c 1.6, CHCl}_3); \delta_{\text{H}} (400 \text{ MHz, CDCl}_3) 1.29 (3\text{H}, \text{t, J 7.1 Hz, OCH}_2\text{CH}_3), 2.60 (2\text{H}, \text{br s, 2 x OH}), 3.53 (1\text{H}, \text{dd, J 11.5, 7.1 Hz, 5-HH}), 3.74 (1\text{H}, \text{dd, J 11.5, 3.4 Hz, 5-HH}), 4.19 (2\text{H}, \text{q, J 7.1 Hz, OCH}_2\text{CH}_3), 4.39-4.45
(1H, m, 4-H), 6.12 (1H, dd, J 15.7, 1.8 Hz, 2-H), 6.90 (1H, dd, J 15.7, 4.4 Hz, 3-H); δC (100 MHz, CDCl3), 14.2 (CH3), 60.8 (CH2), 65.6 (CH2), 71.7 (CH), 121.9 (CH), 146.3 (CH), 166.7 (C); m/z (CI) 161 (MH+, 100%), 99 (57), 75 (30).

**Ethyl (2E,4S)-4-hydroxy-5-(tert-butyldiphenylsilyloxy)pent-2-enoate (101).**

![Ethyl (2E,4S)-4-hydroxy-5-(tert-butyldiphenylsilyloxy)pent-2-enoate](image)

Ethyl (2E,4S)-4,5-dihydroxypent-2-enoate 100 (1.00 g, 6.3 mmol) was dissolved in THF (40 mL). tert-Butyldiphenylchlorosilane (2.40 g, 8.7 mmol) and imidazole (0.90 g, 13.0 mmol) were then added and the solution was stirred at room temperature overnight. The solution was then diluted with ethyl acetate (50 mL) and washed with water (50 mL). The organic extracts were dried (MgSO4) and concentrated in vacuo. Flash column chromatography (petroleum ether : diethyl ether, 10 : 1) yielded ethyl (2E,4S)-4-hydroxy-5-(tert-butyldiphenylsilyloxy)pent-2-enoate 101, as a clear oil (2.48 g, 100%). [α]D25 17.8 (c 1.6, CHCl3), lit.107 [α]D25 16.4 (c 0.17, CHCl3); δH (400 MHz, CDCl3) 1.08 (9H, s, C(CH3)3), 1.27 (3H, t, J 7.2 Hz, OCH2CH3), 2.74 (1H, br d, J 4.2 Hz, 4-OH), 3.55 (1H, dd, J 10.2, 4.0 Hz, 5-HH), 3.76 (1H, dd, J 10.2, 2.1 Hz, 5-HH), 4.19 (2H, q, J 7.2 Hz, OCH2CH3), 4.38-4.42 (1H, m, 4-H), 6.14 (1H, dd, J 15.7, 2.2 Hz, 2-H), 6.80 (1H, dd, J 15.7, 4.3 Hz, 3-H), 7.37-7.47 (6H, m, Ph), 7.62-7.68 (4H, m, Ph); δC (100 MHz, CDCl3), 14.3 (CH3), 19.3 (C), 26.9 (CH3), 60.5 (CH2), 67.0 (CH2), 71.5 (CH), 122.0 (CH), 127.9 (CH), 130.0 (CH), 132.8 (C), 135.6 (CH), 145.8 (CH), 166.3 (C); m/z (CI) 381 (MH+-OH, 14%), 321 (100), 257 (5), 217 (4), 143 (8).

**Ethyl (2E,4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-enoate (102).**

![Ethyl (2E,4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-enoate](image)

The reaction was carried out according to general procedure 3 using ethyl (2E,4S)-4-hydroxy-5-(tert-butyldiphenylsilyloxy)pent-2-enoate 101 (0.10 g, 0.3 mmol) and N,N-diisopropylethylamine (5.0 equiv.) and bromomethyl methyl ether (5.0 equiv.). Flash column chromatography (petroleum ether : diethyl ether, 5 : 1) yielded the title compound 102 as a brown oil (0.13 g, 86%). [α]D25 +11.7 (c 2.9, CHCl3), lit.107 [α]D21 +12.3 (c 1.7, CHCl3); δH (400 MHz, CDCl3) 1.06 (9H, s, C(CH3)3), 1.30 (3H, t, J 7.2 Hz, OCH2CH3), 3.38 (3H, s, OCH3), 3.69 (1H, dd, J 11.1, 5.0 Hz, 5-HH), 3.77 (1H, dd, J 11.1, 6.2 Hz, 5-
H/H), 4.22 (2H, q, J 7.2 Hz, OCH₂CH₃), 4.35-4.40 (1H, m, 4-H), 4.67 (1H, d, J 7.1 Hz, OCH₂HO), 4.72 (1H, d, J 7.1 Hz, OCH₂HO), 5.68 (1H, dd, J 16.3, 2.0 Hz, 2-H), 6.90 (1H, dd, J 16.3, 6.4 Hz, 3-H), 7.34-7.48 (6H, m, Ph), 7.56-7.72 (4H, m, Ph); δc (100 MHz, CDCl₃), 14.3 (CH₃), 19.3 (C), 26.8 (CH₃), 55.6 (CH₃), 60.5 (CH₂), 66.1 (CH₂), 75.9 (CH), 95.2 (CH₂), 122.8 (CH), 127.9 (CH), 129.8 (CH), 133.1 (CH), 145.1 (CH), 166.1 (C); m/z (CI) 443 (MH⁺, 2%), 381 (100), 321 (7), 257 (16), 243 (15), 143 (10).

(2E,4S)-4-(Methoxymethoxy)-5-(tert-butylidiphenylsilyloxy)pent-2-en-1-ol (103).

The reaction was carried out according to general procedure 2 using ethyl (2E,4S)-4-(methoxymethoxy)-5-(tert-butylidiphenylsilyloxy)pent-2-enoate 102 (2.80 g, 6.0 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 1 : 1) yielded (2E,4S)-4-(methoxymethoxy)-5-(tert-butylidiphenylsilyloxy)pent-2-en-1-ol 103, as a yellow oil (2.19 g, 86%). υmax/cm⁻¹ (neat) 3422 (OH), 3071 (CH), 2931 (CH), 1589 (C=C), 1428, 1112 (C-O), 704; [α]D₂₈ +31.2 (c 1.0, CHCl₃); δH (400 MHz, CDCl₃) 1.05 (9H, s, C(CH₃)₃), 1.29 (1H, br s, OH), 3.37 (3H, s, OCH₃), 3.63 (1H, dd, J 11.1, 6.0 Hz, 5-HH), 3.74 (1H, dd, J 11.1, 7.6 Hz, 5-HH), 4.12 (2H, br d, J 5.0 Hz, 1-H₂), 4.18-4.24 (1H, m, 4-H), 4.64 (1H, d, J 7.1 Hz, OCH₂HO), 4.70 (1H, d, J 7.1 Hz, OCH₂HO), 5.58 (1H, ddd, J 16.3, 8.0, 2.1 Hz, 3-H), 5.89 (1H, ddd, J 16.3, 5.0, 1.0 Hz, 2-H), 7.37-7.45 (6H, m, Ph), 7.67-7.71 (4H, m, Ph); δc (100 MHz, CDCl₃), 19.3 (C), 26.8 (CH₃), 55.4 (CH₃), 63.0 (CH₂), 66.8 (CH₂), 76.8 (CH), 94.4 (CH₂), 127.7 (CH), 128.5 (CH), 129.7 (CH), 132.9 (CH), 133.5 (C), 135.7 (CH); m/z (CI) 401 (MH⁺, 3%), 339 (100), 261 (24), 209 (25), 167 (21), 143 (19), 117 (29).
Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105a) and (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105b) using bis-acetonitrile-dichloropalladium(II) catalysed aza-Claisen rearrangement in THF.

The reaction was carried out according to general procedure 4 using (2E,4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-en-1-ol 103 (0.15 g, 0.4 mmol) and the aza-Claisen rearrangement was performed in THF using bis-acetonitrile dichloropalladium(II) (0.01 g, 0.04 mmol) as catalyst. Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) gave (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b followed by (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a as brown oils (0.063 g, 32% combined yield over 2 steps) and in a 3 : 1 ratio (105a : 105b). υ_{max}/cm^{-1} (neat) 3393 (NH), 3072 (CH), 2931 (CH), 1717 (CO), 1645 (C=C), 1509, 1113, 1032, 822. (3R,4S)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b: [α]_D^{25} +5.7 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.09 (9H, s, C(CH₃)₃), 3.30 (3H, s, OCH₃), 3.65 (1H, dd, J 11.1, 8.0 Hz, 5-HH), 3.74 (1H, dd, J 11.1, 7.3 Hz, 5-HH), 3.88-3.92 (1H, m, 5-H), 4.63 (1H, d, J 7.1 Hz, OCHHO), 4.67 (1H, d, J 7.1 Hz, OCHHO), 4.81-4.84 (1H, m, 3-H), 5.29-5.36 (2H, m, 1-H₂), 5.91 (1H, ddd, J 17.1, 10.6, 5.1 Hz, 2-H), 7.16 (1H, br d, J 8.2 Hz, NH), 7.47-7.55 (6H, m, Ph); 7.77-7.81 (4H, m, Ph); δ_C (100 MHz, CDCl₃) 19.2 (C), 26.8 (CH₃), 53.5 (CH), 55.9 (CH₃), 63.0 (CH₂), 78.0 (CH), 93.0 (C), 96.6 (CH₂), 116.8 (CH₂), 127.8 (CH), 129.9 (CH), 132.9 (C), 134.6 (CH), 135.6 (CH), 161.5 (C), (3S,4S)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a: [α]_D^{25} -28.1 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.10 (9H, s, C(CH₃)₃), 3.40 (3H, s, OCH₃), 3.65-3.82 (3H, m, 5-H₂ and 4-H), 4.60-4.76 (3H, m, OCH₂O and 3-H), 5.28-5.35 (2H, m, 1-H₂), 5.79 (1H, ddd, J 17.1, 10.3, 6.6 Hz, 2-H), 7.39-7.48 (6H, m, Ph), 7.67-7.70 (4H, m, Ph), 8.04 (1H, br d, J 7.9 Hz, NH); δ_C (100 MHz, CDCl₃) 19.2 (C), 26.9 (CH₃), 54.4 (CH), 55.9 (CH₃), 63.8 (CH₂), 81.7 (CH), 93.1 (C), 97.7 (CH₂), 118.8 (CH₂), 127.8 (CH), 129.9 (CH), 131.6 (C),
132.9 (CH), 135.6 (CH), 161.4 (C). \( m/z \) (CI) 544.1249 (MH\(^+\) C\(_{12}\)H\(_{33}\)O\(_4\)N\(^{35}\)Cl\(_3\)Si requires 544.1244), 512 (100%), 478, (35), 448 (20), 344 (16), 257 (10).

**Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105a) and (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105b) using bis-acetonitrile-dichloropalladium(II) catalysed aza-Claisen rearrangement in toluene.**

The reaction was carried out according to general procedure 4 using (2\(E\),4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-en-1-ol 103 (0.14 g, 0.3 mmol) and bis-acetonitrile-dichloropalladium(II) (10 mol%) as catalyst in toluene (10 mL). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) gave (3\(R\),4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b followed by (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a as brown oils (0.09 g, 68% combined yield over two steps) and in a 4 : 1 ratio (105a : 105b). Spectroscopic data as reported above.

**Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105a) and (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105b) by PtCl\(_2\) catalysed aza-Claisen rearrangement.**

The reaction was carried out according to general procedure 4, using (2\(E\),4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-en-1-ol 103 (0.18 g, 0.5 mmol) and platinum(II) chloride (10 mol%) as catalyst. Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave (3\(R\),4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b followed by (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a as brown oils (0.04 g, 25% yield over two steps) and in a 4 : 1 ratio (105a : 105b). Spectroscopic data as reported above.
Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105a) and (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105b) using hydrogen tetrachloroaurate(III) hydrate catalysed aza-Claisen rearrangement.

The reaction was carried out according to general procedure 4 using (2E,4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-en-1-ol 103 (0.05 g, 0.1 mmol) and hydrogen tetrachloroaurate(III) hydrate (10 mol%) was used as catalyst in toluene (10 mL). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) gave (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b followed by (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a as brown oils (0.03 g, 49% combined yield over two steps) and in a 2 : 1 ratio (105a : 105b). Spectroscopic data as reported above.

Synthesis of (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105a) and (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene (105b) using gold(I) chloride catalysed aza-Claisen rearrangement.

The reaction was carried out according to general procedure 4, using (2E,4S)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-2-en-1-ol 103 (0.10 g, 0.5 mmol) and gold(I) chloride (10 mol%) as catalyst in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105b followed by (3S,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a as brown oils (0.06 g, 40% combined yield over two steps) and in a 3 : 1 ratio (105a : 105b). Spectroscopic data as reported above.
Synthesis of \((3S,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{ tert-butyldiphenylsilyloxy})\)pent-1-ene \((105a)\) and \((3R,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \((105b)\) using gold(III) chloride catalysed aza-Claisen rearrangement.

The reaction was carried out according to general procedure 4, using \((2E,4S)-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-2-en-1-ol \(103\) (0.10 g, 0.5 mmol) and gold(III) chloride (10 mol\%) as catalyst in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave \((3R,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \(105b\) followed by \((3S,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \(105a\) as brown oils (0.04 g, 26\% combined yield over two steps) and in a 2 : 1 ratio \((105a : 105b)\). Spectroscopic data as reported above.

Synthesis of \((3S,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \((105a)\) and \((3R,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \((105b)\) using \((R)\)-COP-Cl catalysed aza-Claisen rearrangement.

The reaction was carried out according to general procedure 4, using \((2E,4S)-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-2-en-1-ol \(103\) (0.10 g, 0.5 mmol) and \([\text{bis}[\mu-\text{chloro}]\text{dipalladium}][\text{bis}[(\eta^4-1,3\text{-cyclobutadiene}-1,2,3,4\text{-tetracyl})\text{tetrakis}[\text{benzene}]]\text{bis}[\mu-\{(1-\eta;1,2,3,4,5-\eta)-2-[(4R)-4,5\text{-dihydro}-4-(1\text{-methylthyl})-2\text{-oxazolyl}]-2,4\text{-cyclopentadien-1-ylidene}]\text{dicobalt} [(R)-\text{COP-Cl}]\) (10 mol\%) was used as catalyst, in DCM (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave \((3R,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \(105b\) followed by \((3S,4S)-3-(2',2',2'-\text{trichloromethylcarbonylamino})-4-(\text{methoxymethoxy})-5-(\text{tert-butyldiphenylsilyloxy})\)pent-1-ene \(105a\) as brown oils (0.13 g, 68\% combined yield over two steps) and in a 16 : 1 ratio \((105a : 105b)\). Spectroscopic data as reported above.
The reaction was carried out according to general procedure 7 using (3R,4S)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(tert-butyldiphenylsilyloxy)pent-1-ene 105a (0.20 g, 0.4 mmol). The crude product was dissolved in an aqueous solution of sodium hydrogen carbonate (10 mL), extracted with ethyl acetate (2 x 10 mL) and re-acidified by addition of 2 M hydrochloric acid (15 mL). The aqueous phase was extracted with ethyl acetate (5 x 10 mL), dried (MgSO₄) and concentrated in vacuo to give (2R,3S)-2-(2',2',2'-trichloromethylcarbonylamino)-3-methoxymethoxy-4-(tert-butyldiphenylsilyloxy)butanoic acid 106 (0.15 g, 71% yield) as a brown oil. $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3334 (NH and OH), 2958 (CH), 1774 (CO); $[^{\alpha}]_{D}^{24} -12.5$ (c 1.5, MeOH); $\delta_H$ (400 MHz, CD$_3$OD) 0.98 (9H, s, C(CH$_3$)$_3$), 3.24 (3H, s, OCH$_3$), 3.85 (1H, dd, $J$ 10.8, 6.3 Hz, 4-HH), 3.92 (1H, dd, $J$ 10.8, 4.6 Hz, 4-HH), 3.98-4.02 (1H, m, 3-H), 4.50 (1H, d, $J$ 3.0 Hz, 2-H), 4.56 (1H, d, $J$ 6.8 Hz, OCHHO), 4.58 (1H, d, $J$ 6.8 Hz, OCHHO), 7.22-7.35 (6H, m, Ph), 7.59-7.63 (4H, m, Ph); $\delta_C$ (100 MHz, CD$_3$OD) 20.1 (C), 27.2 (CH$_3$), 56.4 (CH$_3$), 57.8 (CH), 65.8 (CH$_2$), 80.5 (CH), 93.8 (C), 98.2 (CH$_2$), 128.6 (CH), 130.9 (CH), 134.5 (C), 136.8 (CH), 163.0 (C), 173.3 (C); m/z (CI) 547 (MH$^+$-CH$_4$, 3%), 376 (5), 325, (10), 274 (100), 196 (30).

(2R,3S)-2-Amino-3,4-dihydroxybutyric acid (90).$^{64}$

(2R,3S)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-methoxymethoxy-4-(tert-butyldiphenylsilyloxy)butanoic acid 106 (0.12 g, 0.2 mmol) was dissolved in THF (10 mL). Tetrabutylammonium fluoride (1.0 M solution in THF) (0.73 mL, 0.7 mmol) was then added and the solution was stirred at room temperature overnight. The reaction mixture was concentrated and the residue re-dissolved in ethyl acetate (15 mL) then washed with water (15 mL). The organic layer was dried (MgSO$_4$) and concentrated to
give a brown oil (0.1 g), which was then dissolved in 6 M hydrochloric acid solution (10 mL) and heated under reflux overnight. After cooling to room temperature the reaction mixture was extracted with diethyl ether (10 mL). The aqueous phase was then concentrated in vacuo to give the crude product. Purification by ion exchange chromatography (eluting with 0.5 M NH₄OH solution), yielded (2R,3S)-2-amino-3,4-dihydroxybutyric acid 90 as a white solid (11 mg, 44% over two steps). Spectroscopic data in agreement with literature. [64] \( [\alpha]_D^{24} +10.6 \) (c 0.5, H₂O), lit. [64] \( [\alpha]_D^{24} +11.3 \) (c 7.0, H₂O); \( \delta \) (400 MHz, D₂O) 3.66-3.71 (2H, m, 4-H), 3.84-3.88 (1H, m, 3-H), 4.07-4.11 (1H, m, 2-H); \( m/z \) (CI) 136 (MH⁺, 5%), 130 (100), 114 (32), 69 (30).

**Ethyl (3R)-3-hydroxybutanoate (115).**

\[
\begin{align*}
&\text{OH} \\
&\text{CO}_2\text{Et}
\end{align*}
\]

Poly-(3R)-3-hydroxybutanoate 114 (9.0 g, 0.1 mol), ethanol (100 mL), 1,2-dichloroethane (75 mL) and concentrated sulphuric acid (10 mL) were heated under reflux for 7 days. Further sulphuric acid (8 mL) was then added and the reaction mixture was heated for an additional 5 days. The solution was then filtered through Celite® and the filtrate was washed with a saturated sodium chloride solution (75 mL), dried (MgSO₄) and concentrated to give the crude product. Distillation under vacuum gave the title compound 115 as a colourless oil (6.9 g, 52%). [\( \alpha \) D]$_{21}^{21}$ -39.6 (c 1.0, CHCl₃), lit. [108] [\( \alpha \) D]$_{25}^{25}$ -42.0 (c 1.0, CHCl₃); \( \delta \) (400 MHz, CDCl₃) 1.23 (3H, d, J 6.1 Hz, 4-H₃), 1.28 (3H, t, J 7.0 Hz, OCH₂CH₃), 2.42 (1H, dd, J 9.7, 6.1 Hz, 2-HH), 2.50 (1H, dd, J 9.7, 2.5 Hz, 2-HH), 3.10 (1H, br s, OH), 4.15-4.21 (3H, m, OCH₂CH₃ and 3-H); \( m/z \) (CI) 133 (MH⁺, 100%), 115 (9), 87 (8).

**Ethyl (3R)-3-methoxymethoxybutanoate (116).**

\[
\begin{align*}
&MOMO \\
&\text{CO}_2\text{Et}
\end{align*}
\]

Reaction was carried out according to general procedure 3 using ethyl (3R)-3-hydroxybutanoate 115 (5.00 g, 0.04 mol). Purification by flash column chromatography (elution with petroleum ether : ethyl acetate, 9 : 1) yielded ethyl (3R)-3-methoxymethoxybutanoate 116, as a clear oil (5.27 g, 75%). [\( \alpha \) D]$_{22}^{22}$ -10.4 (c 1.5, CHCl₃),
lit.\textsuperscript{109} [\alpha]_D^{25} -11.7 (c 0.7, CHCl\textsubscript{3}); \delta_H (400 MHz, CDCl\textsubscript{3}) 1.25 (3H, d, J 6.1 Hz, 4-H\textsubscript{3}), 1.27 (3H, t, J 7.0 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 2.41 (1H, dd, J 15.2, 5.5 Hz, 2-HH), 2.59 (1H, dd, J 15.2, 7.0 Hz, 2-HH), 3.36 (3H, s, OCH\textsubscript{3}), 4.12-4.19 (3H, m, OCH\textsubscript{2}CH\textsubscript{3} and 3-H), 4.65 (1H, d, J 6.9 Hz, OCHHO), 4.68 (1H, d, J 6.9 Hz, OCHHO); \delta_C (100 MHz, CDCl\textsubscript{3}) 14.2 (CH\textsubscript{3}), 20.6 (CH\textsubscript{3}), 42.4 (CH\textsubscript{2}), 55.4 (CH\textsubscript{3}), 60.4 (CH\textsubscript{2}), 70.4 (CH), 95.4 (CH\textsubscript{2}), 171.3 (C); m/z (CI) 177 (MH\textsuperscript{+}, 8%), 145 (100), 115 (5).

(3R)-3-Methoxymethoxybutan-1-ol (117).\textsuperscript{110}

\[
\text{OMOM} \quad \text{OH}
\]

The reaction was carried out according to general procedure 2 using ethyl (3R)-3-methoxymethoxybutanoate 116 (5.00 g, 30.0 mmol). Flash column chromatography (elution with petroleum ether : diethyl ether, 3 : 2) gave (3R)-3-methoxymethoxybutan-1-ol 117 as a light yellow oil (3.0 g, 80%). Spectroscopic data in agreement with literature.\textsuperscript{110} [\alpha]_D^{21} -91.3 (c 1.0, CHCl\textsubscript{3}); \delta_H (400 MHz, CDCl\textsubscript{3}) 1.22 (3H, d, J 6.3 Hz, 4-H\textsubscript{3}), 1.71-1.79 (2H, m, 2-H\textsubscript{2}), 2.39 (1H, br s, OH), 3.40 (3H, s, OCH\textsubscript{3}), 3.70-3.85 (2H, m, 1-H\textsubscript{2}), 3.90-3.98 (1H, m, 3-H), 4.64 (1H, d, J 6.8 Hz, OCHHO), 4.72 (1H, d, J 6.8 Hz, OCHHO); \delta_C (100 MHz, CDCl\textsubscript{3}) 20.2 (CH\textsubscript{3}), 39.2 (CH\textsubscript{2}), 55.5 (CH\textsubscript{3}), 60.2 (CH\textsubscript{2}), 72.2 (CH), 95.0 (CH\textsubscript{2}); m/z (CI) 135 (MH\textsuperscript{+}, 30%), 103 (100), 73 (8).

Ethyl (2E,5R)-5-methoxymethoxyhex-2-enoate (118).

\[
\text{OMOM} \quad \text{CO}_2\text{Et}
\]

Reaction carried out according to general procedure 1 using (3R)-3-methoxymethoxybutan-1-ol 117 (1.00 g, 7.5 mmol). Purification of the crude material by flash column chromatography (eluting with petroleum ether : diethyl ether, 1 : 1) gave the title compound 118 as a yellow oil (0.9 g, 59% yield). \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 2974 (CH), 1716 (CO), 1655 (C=C), 1454, 1373; [\alpha]_D^{22} +3.3 (c 1.7, CHCl\textsubscript{3}); \delta_H (400 MHz, CDCl\textsubscript{3}) 1.20 (3H, d, J 6.3 Hz, 6-H\textsubscript{3}), 1.28 (3H, t, J 7.0 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 2.32-2.49 (2H, m, 4-H\textsubscript{2}), 3.36 (3H, s, OCH\textsubscript{3}), 3.81-3.89 (1H, m, 5-H), 4.19 (2H, q, J 7.0 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 4.62 (1H, d, J 7.0 Hz, OCHHO), 4.69 (1H, d, J 7.0 Hz, OCHHO), 5.88 (1H, dt, J 15.7, 1.4 Hz, 2-H), 6.96 (1H, dt, J 15.7, 7.4 Hz, 3-H); \delta_C (100 MHz, CDCl\textsubscript{3}) 14.3 (CH\textsubscript{3}), 20.3 (CH\textsubscript{3}), 39.6 (CH\textsubscript{2}),
55.4 (CH₃), 60.2 (CH₂), 71.8 (CH), 94.9 (CH₂), 123.6 (CH), 145.1 (CH), 166.3 (C); m/z (CI) 203.1285 (MH⁺. C₁₀H₁₉O₄ requires 203.1283), 171 (100%), 141 (10).

(2E,5R)-5-Methoxymethoxyhex-2-en-1-ol (119).

The reaction was done according to general procedure 2 using ethyl (2E,5R)-5-methoxymethoxyhex-2-enoate 118 (1.20 g, 6.0 mmol). Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 3 : 1) gave (2E,5R)-5-methoxymethoxyhex-2-en-1-ol 119 as a light yellow oil (0.9 g, 98%). v_max/cm⁻¹ (neat) 3410 (OH), 2931 (CH), 1662 (C=C), 1450, 1381; [α]D22 +6.3 (c 1.5, CHCl₃); δ_H (400 MHz, CDCl₃) 1.18 (3H, d, J 6.2 Hz, 6-H₃), 1.60 (1H, br s, OH), 2.19-2.36 (2H, m, 4-H₂), 3.36 (3H, s, OCH₃), 3.76 (1H, sextet, J 6.2 Hz, 5-H), 4.10-4.22 (2H, m, 1-H₂), 4.64 (1H, d, J 6.9 Hz, OCH₂), 4.68 (1H, d, J 6.9 Hz, OCH₂), 5.70-5.73 (2H, m, 2-H and 3-H); δ_C (100 MHz, CDCl₃) 20.0 (CH₃), 39.7 (CH₂), 55.3 (CH₃), 63.6 (CH₂), 72.7 (CH), 94.9 (CH₂), 128.8 (CH), 131.7 (CH); m/z (CI) 161.1179 (MH⁺. C₈H₁₇O₃ requires 161.1178), 143 (12%), 129 (100), 99 (30), 89 (40), 81 (22).

(3S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and (3R,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b).

The reaction was carried out according to general procedure 4 using (5R)-5-methoxymethoxyhex-2-en-1-ol 119 (0.09 g, 0.6 mmol) in THF (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 17 : 3) yielded the title compounds as brown oils (0.08 g, 50% combined yield over 2 steps), in a 1 : 1 ratio (110a : 110b). (3S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110a: v_max/cm⁻¹ (neat) 3336 (NH), 2931 (CH), 1709 (CO), 1647 (C=C), 1516; [α]D22 +9.9 (c 1.0, CHCl₃); δ_H (400 MHz, CDCl₃) 1.26 (3H, d, J 6.1 Hz, 6-H₃), 1.81 (1H, ddd, J 15.0, 6.2, 3.0 Hz, 4-HH), 1.95 (1H, ddd, J 15.0, 10.1, 4.0 Hz, 4-HH), 3.39 (3H, s, OCH₃), 3.96-
4.05 (1H, m, 5-H), 4.60-4.66 (2H, m, OCHHO and 3-H), 4.76 (1H, d, J 6.8 Hz, OCHHO), 5.23-5.29 (2H, m, 1-H2), 5.85 (1H, ddd, J 17.3, 10.1, 5.0 Hz, 2-H), 8.12 (1H, br s, NH); δC (100 MHz, CDCl3) 20.3 (CH3), 40.2 (CH2), 51.5 (CH), 56.0 (CH3), 71.0 (CH), 93.0 (C), 95.1 (CH2), 115.8 (CH2), 135.7 (CH), 161.2 (C); m/z (Cl) 304.0270 (MH+, C10H17NO335Cl3 requires 304.0274), 272 (100%), 201 (20), 114 (26), 45 (80).

Synthesis of (3S,5R)-3-(2’,2’,2’-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110a and (3R,5R)-3-(2’,2’,2’-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b) using palladium catalysed rearrangement with addition of DBU.

The reaction was carried out according to general procedure 4 using (5R)-5-methoxymethoxyhex-2-en-1-ol 119 (0.18 g, 1.1 mmol) in THF (10 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (1 equiv.) was also added to the reaction mixture. Flash column chromatography (elution with petroleum ether : diethyl ether, 17 : 3) yielded the title compounds as brown oils (0.13 g, 41% combined yield over 2 steps) and in a 2 : 1 ratio (110a : 110b). Spectroscopic data as reported above.

Synthesis of (3S,5R)-3-(2’,2’,2’-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110a and (3R,5R)-3-(2’,2’,2’-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b) using palladium catalysed rearrangement with addition of ρ-benzoquinone.

The reaction was carried out according to general procedure 4 using (5R)-5-methoxymethoxyhex-2-en-1-ol 119 (0.18 g, 1.1 mmol) in THF (10 mL). ρ-Benzoquinone (2 equiv.) was also added to the reaction mixture. Flash column chromatography (elution with petroleum ether : diethyl ether, 17 : 3) yielded the title compounds as brown oils (0.13
g, 41% combined yield over 2 steps) and in a 2 : 1 ratio (110a : 110b). Spectroscopic data as reported above.

**Synthesis of** $(3S,5R)$-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and $(3R,5R)$-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b) using thermal rearrangement.

The reaction was carried out according to general procedure 5 using (5R)-5-methoxymethoxyhex-2-en-1-ol 119 (0.09 g, 0.6 mmol). Flash column chromatography (elution with petroleum ether : diethyl ether, 10 : 1) yielded (3S,5R)-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110a and (3R,5R)-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110b as brown oils (0.11 g, 66% combined yield over 2 steps) in a 1 : 1 ratio (110a : 110b). Spectroscopic data as reported above.

**Synthesis of** $(3S,5R)$-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and $(3R,5R)$-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b) using palladium catalysed rearrangement in toluene.

The reaction was carried out according to general procedure 4 using (5R)-5-methoxymethoxyhex-2-en-1-ol 119 (0.05 g, 0.3 mmol) in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 17 : 3) yielded the title compounds as brown oils (0.06 g, 71% combined yield over 2 steps) and in a 3 : 1 ratio (110a : 110b). Spectroscopic data as reported above.
(2S,4R)-2-(2′,2′,2′-Trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid (141).

\[
\begin{align*}
\text{MOMO} & \quad \text{HN} \\
\text{CCl}_3 & \quad \text{CO}_2\text{H}
\end{align*}
\]

The reaction was carried out according to general procedure 7 using (3S,5R)-3-(2′,2′,2′-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene 110a (0.15 g, 0.5 mmol) to give (2S,4R)-2-(2′,2′,2′-trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid 141, as a brown oil (0.11 g, 65% yield). \( \nu_{\text{max}}/\text{cm}^{-1} \) (neat) 3335 (NH and OH), 2931 (CH), 1774 (CO), 1706 (CO), 1523; \([\alpha]_D^{25} +4.6 \) (c 1.1, CHCl\(_3\)); \( \delta_H \) (400 MHz, CDCl\(_3\)) 1.21 (3H, \text{d}, \text{J} 6.1 \text{ Hz}, 5-\text{H}), 2.02 (1H, \text{ddd}, \text{J} 15.0, 9.8, 4.2 \text{ Hz}, 3-\text{HH}), 2.11 (1H, \text{ddd}, \text{J} 15.0, 6.2, 3.0 \text{ Hz}, 3-\text{HH}), 3.34 (3H, s, OCH\(_3\)), 3.90-3.95 (1H, \text{m}, 4-\text{H}), 4.56-4.63 (2H, m, OCH\(_2\)OH and 2-H), 4.71 (1H, \text{d}, \text{J} 7.0 \text{ Hz}, \text{OCH}H\(_2\)), 8.29 (1H, \text{br d}, \text{J} 7.0 \text{ Hz}, \text{NH}), 9.70 (1H, \text{br s}, \text{OH}); \( \delta_C \) (100 MHz, CDCl\(_3\)) 20.1 (CH\(_2\)), 37.2 (CH\(_3\)), 52.4 (CH), 56.1 (CH\(_3\)), 71.6 (CH), 92.2 (C), 95.0 (CH\(_2\)), 162.0 (C), 174.9 (C); \( m/z \) (CI) 323.9975 (MH\(^+\). \( \text{C}_9\text{H}_{15}\text{NO}_5^{35}\text{Cl}_2^{37}\text{Cl} \)) requires 323.9982), 290 (65%), 260 (100), 226 (24).

(2S,4R)-2-Amino-4-hydroxypentanoic acid (111).\(^{69}\)

\[
\begin{align*}
\text{OH} & \quad \text{NH}_2 \\
\text{CO}_2\text{H}
\end{align*}
\]

(2S,4R)-2-(2′,2′,2′-trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid 141 (0.09 g, 0.3 mmol) was deprotected according to general procedure 8. Purification gave (2S,4R)-2-amino-4-hydroxypentanoic acid 111, as a white solid (0.026 g, 74%). \([\alpha]_D^{25} -32.6 \) (c 1.5, H\(_2\)O), lit.\(^{69}\) \([\alpha]_D^{25} -30.5 \) (c 0.75, H\(_2\)O); \( \delta_H \) (400 MHz, D\(_2\)O) 1.10 (3H, \text{d}, \text{J} 7.1, \text{Hz}, 5-\text{H}), 1.78-1.92 (2H, m, 3-\text{H}), 3.77 (1H, \text{dd}, \text{J} 6.0, 4.3 \text{ Hz}, 2-\text{H}), 3.82-3.87 (1H, \text{m}, 4-\text{H}); \( m/z \) (CI) 134 (MH\(^+\), 22%), 116 (100).
Ethyl (2R,3R)-2-methyl-3-hydroxybutanoate (123).\textsuperscript{111}

\[
\text{\textbullet} \text{OH} \\
\text{\textbullet} \text{CO}_{2}\text{Et}
\]

Diisopropylamine (11.0 mL, 0.08 mol) was dissolved in THF (70 mL) and cooled to 0 \degree C. Butyllithium (2.5 M, 31.0 mL, 0.08 mol) was then added dropwise to the solution and stirred for 1 h. The solution was cooled to -78 \degree C and ethyl (3R)-3-hydroxybutanoate \textsuperscript{115} (4.00 g, 0.03 mol) in THF (10 mL) was added slowly. After stirring for a further 2 h, methyl iodide (4.8 mL, 0.08 mol) was added. The reaction mixture was stirred at -78 \degree C for 1 h before warming to room temperature and stirring for a further 1 h. A saturated solution of ammonium chloride (40 mL) was then added and the solution was acidified to pH 2 by addition of 2 M hydrochloric acid (40 mL). The solution was extracted with ethyl acetate (4 x 75 mL), dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo}. Flash column chromatography (elution with petroleum ether : ethyl acetate, 4 : 1) gave ethyl (2R,3R)-2-methyl-3-hydroxybutanoate \textsuperscript{123} as a colourless oil (3.54 g, 78\%). \([\alpha]_D^{22} -28.8 \text{ (c 0.5, CHCl}_3\text{)}, \text{lit.}\textsuperscript{111} \[\alpha]_D^{22} -30.3 \text{ (c 1.0, CHCl}_3\text{)}; \delta_H (400 MHz, CDCl}_3\text{) 1.21 (3H, d, J 7.0 Hz, 2-CH}_3\text{), 1.24 (3H, d, J 6.2 Hz, 4-H}_3\text{), 1.30 (3H, t, J 7.3 Hz, OCH}_2\text{CH}_3\text{), 2.42-2.51 (1H, m, 2-H), 2.75 (1H, br s, OH), 3.90 (1H, quin, J 6.2 Hz, 3-H), 4.20 (2H, q, J 7.3 Hz, OCH}_2\text{CH}_3\text{); m/z (CI) 147 (MH}^+, 100\%)\text{, 129 (10), 101 (12).}

Ethyl (2R,3R)-2-methyl-3-methoxymethoxybutanoate (125).\textsuperscript{112}

\[
\text{OMOM} \\
\text{\textbullet} \text{CO}_{2}\text{Et}
\]

The reaction was carried out according to general procedure 3 using ethyl (2R,3R)-2-methyl-3-hydroxybutanoate \textsuperscript{123} (3.50 g, 0.024 mol). Flash column chromatography (elution with petroleum ether : ethyl acetate, 5 : 1) yielded ethyl (2R,3R)-2-methyl-3-methoxymethoxybutanoate \textsuperscript{125} as a clear oil (4.26 g, 93\%). \([\alpha]_D^{22} -28.8 \text{ (c 1.0, CHCl}_3\text{)}, \text{lit.}\textsuperscript{112} -28.0 \text{ (c 1.0, CHCl}_3\text{)}; \delta_H (400 MHz, CDCl}_3\text{) 1.15 (3H, d, J 7.2 Hz, 2-CH}_3\text{), 1.21 (3H, d, J 6.3 Hz, 4-H}_3\text{), 1.28 (3H, t, J 7.1 Hz, OCH}_2\text{CH}_3\text{), 2.62 (1H, quin, J 7.2 Hz, 2-H), 3.38 (3H, s, OCH}_3\text{), 3.90-3.98 (1H, m, 3-H), 4.17 (2H, dq, J 7.1, 1.2 Hz, OCH}_2\text{CH}_3\text{), 4.65 (1H, d, J 6.9 Hz, OCHHO), 4.69 (1H, d, J 6.9 Hz, OCHHO); m/z (CI) 191 (MH}^+, 6\%)\text{, 159 (100), 101 (8), 73 (43).}
(2S,3R)-2-Methyl-3-methoxymethoxybutan-1-ol (127).\[113]

![O томе OMOM OH](image)

The reaction was carried out according to general procedure 2 using ethyl (2S,3R)-2-methyl-3-methoxymethoxybutanoate 125 (4.20 g, 0.020 mol). Flash column chromatography (elution with petroleum ether : diethyl ether, 1 : 1) yielded (2S,3R)-2-methyl-3-methoxymethoxybutan-1-ol 127 as a clear oil (3.2 g, 99%). Spectroscopic data in agreement with literature.\[113] \([\alpha]_D^{22} -73.8 \text{ (c 1.0, CHCl}_3\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 0.96 (3H, d, \(J 7.0 \text{ Hz, 2-CH}_3\)), 1.22 (3H, d, \(J 6.3 \text{ Hz, 4-H}_3\)), 1.72-1.80 (1H, m, 2-H), 2.70 (1H, br s, OH), 3.41 (3H, s, OCH\(_3\)), 3.59 (1H, ddd, \(J 11.3, 6.1, 1.0 \text{ Hz, 1-H}_3\)), 3.64-3.76 (2H, m, 1-H/ and 3-H), 4.63 (1H, d, \(J 6.9 \text{ Hz, OCH}_2\)), 4.75 (1H, d, \(J 6.9 \text{ Hz, OCH}_2\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 13.9 (CH\(_3\)), 17.9 (CH\(_3\)), 41.1 (CH), 55.7 (CH\(_3\)), 66.1 (CH\(_2\)), 75.8 (CH), 95.1 (CH\(_2\)); \(m/z\) (Cl) 149 (MH\(^+\), 9%), 117 (100), 105 (13), 87 (12).

Ethyl (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-enoate (129).

![Ethyl (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-enoate](image)

Reaction carried out according to general procedure 1 using (2S,3R)-2-methyl-3-methoxymethoxybutan-1-ol 127 (0.50 g, 3.4 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 5 : 1) gave the title compound as a light yellow oil (0.73 g, 74%). \(\nu_{max}/\text{cm}^{-1}\) (neat) 2982 (CH), 1738 (CO), 1653 (C=C), 1446, 1392; \([\alpha]_D^{22} -26.1 \text{ (c 1.0, CHCl}_3\); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.15 (3H, d, \(J 6.9 \text{ Hz, 4-CH}_3\)), 1.15 (3H, d, \(J 6.3 \text{ Hz, 6-H}_3\)), 1.30 (3H, t, \(J 7.1 \text{ Hz, OCH}_2\CH_3\)), 2.44-2.53 (1H, m, 4-H), 3.39 (3H, s, OCH\(_3\)), 3.69 (1H, quin, \(J 6.3 \text{ Hz, 5-H}\)), 4.20 (2H, q, \(J 7.1 \text{ Hz, OCH}_2\CH_3\)), 4.60 (1H, d, \(J 6.9 \text{ Hz, OCH}_2\)), 4.71 (1H, d, \(J 6.9 \text{ Hz, OCH}_2\)); \(\delta_C\) (100 MHz, CDCl\(_3\)) 14.3 (CH\(_3\)), 15.0 (CH\(_3\)), 17.4 (CH\(_3\)), 42.2 (CH), 55.5 (CH\(_3\)), 60.2 (CH\(_2\)), 75.8 (CH), 95.1 (CH\(_2\)), 121.5 (CH), 150.9 (CH), 166.6 (CO); \(m/z\) (Cl) 217.1431 (MH\(^+\). 
\(\text{C}_{11}\text{H}_{21}\text{O}_4\) requires 217.1440), 185 (100%), 141 (28), 73 (27).
(2E,4S,5R)-4-Methyl-5-methoxymethoxyhex-2-en-1-ol (131).

The reaction was done according to general procedure 2 using ethyl (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-en-1-ol 129 (1.70 g, 8.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 3 : 2) gave (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-en-1-ol 131 as a light yellow oil (1.15 g, 84%). $\nu_{\text{max}}$ cm$^{-1}$ (neat) 3409 (OH), 2971 (CH), 1663 (C=C), 1453, 1377; $[\alpha]_{D}^{22}$ -25.5 (c 1.0, CHCl$_3$); $\delta$H (400 MHz, CDCl$_3$) 1.06 (3H, d, $J$ 7.0 Hz, 4-CH$_3$), 1.13 (3H, d, $J$ 6.1 Hz, 6-H$_3$), 1.45 (1H, br s, OH), 2.30-2.41 (1H, m, 4-H), 3.39 (3H, s, OCH$_3$), 3.60-3.68 (1H, m, 5-H), 4.12-4.17 (2H, m, 1-H$_2$), 4.64 (1H, d, $J$ 6.9 Hz, OCHHO), 4.71 (1H, d, $J$ 6.9 Hz, OCHHO), 5.67-5.71 (2H, m, 2-H and 3-H); $\delta$C (100 MHz, CDCl$_3$) 15.7 (CH$_3$), 17.4 (CH$_3$), 41.9 (CH), 55.4 (CH$_3$), 63.8 (CH$_2$), 76.5 (CH), 95.2 (CH$_2$), 129.5 (CH), 134.8 (CH); m/z (Cl) 157.1236 (MH$^+$ -H$_2$O. C$_{19}$H$_{17}$O$_2$ requires 157.1229), 175 (20%), 157 (80), 143 (96), 113 (90), 99 (100), 69 (63).

(3S,4S,5R)-3-(2’,2’,2’-Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139a) and (3R,4S,5R)-3-(2’,2’,2’-trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139b).

The reaction was carried out according to general procedure 4 using (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-en-1-ol 131 (0.15 g, 0.9 mmol) in THF (10 mL) was used for the rearrangement. Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) yielded the title compounds as brown oils (0.13 g, 49% combined yield over 2 steps) and in a 3 : 1 ratio (139a : 139b). (3S,4S,5R)-3-(2’,2’,2’-Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139a): $\nu_{\text{max}}$ cm$^{-1}$ (neat) 3342 (NH), 2932 (CH), 1715 (CO), 1644 (C=C), 1509, 1459, 1379; $[\alpha]_{D}^{22}$ +18.1 (c 1.0, CHCl$_3$); $\delta$H (400 MHz, CDCl$_3$) 0.91 (3H, d, $J$ 7.0 Hz, 4-CH$_3$), 1.17 (3H, d, $J$ 6.1 Hz, 6-H$_3$), 1.82-1.88 (1H, m, 4-H), 3.31 (3H, s, OCH$_3$), 3.57 (1H, dq, $J$ 9.3, 6.1 Hz, 5-H), 4.36-4.42 (1H, m, 3-H), 4.55 (1H, d, $J$ 6.9 Hz, OCHHO), 4.69 (1H, d, $J$ 6.9 Hz, OCHHO), 5.16-
5.23 (2H, m, 1-H), 5.71-5.80 (1H, m, 2-H), 8.22 (1H, br d, J 6.0 Hz, NH); δC (100 MHz, CDCl₃) 14.4 (CH₃), 18.3 (CH₃), 42.4 (CH), 55.8 (CH), 56.4 (CH), 76.2 (CH₃), 93.1 (C), 95.3 (CH₂), 115.9 (CH₂), 136.1 (CH), 161.4 (C); m/z (Cl) 318.0423 (MH⁺. C₁₁H₁₉NO₃³⁵Cl₃ requires 318.0431), 286 (100%), 256 (38), 238 (80), 204 (39). (3R,4S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139b): [α]D²² - 16.3 (c 0.8, CHCl₃); δH (400 MHz, CDCl₃) 0.95 (3H, d, J 7.0 Hz, 4-CH₃), 1.18 (3H, d, J 6.2 Hz, 6-H₃), 1.89-1.95 (1H, m, 4-H), 3.30 (3H, s, OCH₃), 3.64 (1H, quin, J 6.2 Hz, 5-H), 4.47-4.56 (2H, m, 3-H and OCHHO), 4.64 (1H, d, J 6.9 Hz, OCHHO), 5.10-5.19 (2H, m, 1-H), 5.86 (1H, ddd, J 17.2, 10.5, 5.6 Hz, 2-H), 7.46 (1H, br d, J 6.0 Hz, NH); δC (100 MHz, CDCl₃) 14.5 (CH₃), 18.3 (CH₃), 42.5 (CH), 55.8 (CH), 56.4 (CH), 76.3 (CH₃), 93.1 (C), 95.3 (CH₂), 115.9 (CH₂), 136.1 (CH) 161.5 (C); m/z (Cl) 318.0426 (MH⁺. C₁₁H₁₉NO₃³⁵Cl₃ requires 318.0428), 288 (90%), 286 (95), 258 (77), 238 (84), 188 (100).

**Synthesis of (3S,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139a) and (3R,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139b) using palladium catalysed rearrangement in toluene.**

The reaction was carried out according to general procedure 4 using (2E,4S,5R)-4-methyl-5-methoxymethoxyhex-2-en-1-ol 131 (0.05 g, 0.3 mmol) in toluene (10 mL). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) yielded the title compounds as brown oils (0.066 g, 66% combined yield over 2 steps) and in a 13 : 1 ratio (139a : 139b). Spectroscopic data as reported above.

(2S,3S,4R)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid (142).

The reaction was carried out according to general procedure 7 using (3S,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene 139a (0.20 g, 0.6 mmol). The crude product was then dissolved in a saturated solution of sodium hydrogen carbonate (10 mL), extracted with ethyl acetate (2 x 10 mL), then re-acidified by addition of 2 M hydrochloric acid (15 mL). Extraction with ethyl acetate (4 x 10 mL) followed by
concentration *in vacuo* gave (2S,3S,4R)-2-(2',2',2'-trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid 142 (0.143 g, 62%) as a brown oil. $\nu_{\text{max}}$ (neat) 3334 (NH and OH), 2981 (CH), 1774 (CO), 1523; $[\alpha]_D^{25} +13.0$ (c 0.6, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.02 (3H, d, $J$ 7.2 Hz, 3-CH$_3$), 1.21 (3H, d, $J$ 6.6 Hz, 5-H$_3$), 2.12-2.20 (1H, m, 3-H), 3.31 (3H, s, OCH$_3$), 3.57 (1H, qd, $J$ 6.2, 2.8 Hz, 4-H), 4.59 (1H, d, $J$ 6.9 Hz, OCH$_2$O), 4.66-4.72 (2H, m, OCH/H and 2-H), 7.80 (1H, br d, $J$ 6.4 Hz, NH), 9.10 (br s, OH); $\delta_C$ (100 MHz, CDCl$_3$) 13.3 (CH$_3$), 18.6 (CH$_3$), 41.3 (CH), 55.8 (CH), 56.0 (CH), 76.9 (CH$_3$), 93.5 (C) 96.1 (CH$_2$), 162.0 (C), 174.8 (C); $m/z$ (Cl) 336.0175 (MH$^+$, C$_{10}$H$_{17}$NO$_3$Cl$_3$ requires 336.0173), 319 (100%), 238 (40) and 188 (19).

$(2S,3S,4R)$-2-Amino-3-methyl-4-hydroxypentanoic acid (112).$^{65}$

The reaction was carried out according to general procedure 8 using (2S,3S,4R)-2-(2',2',2'-trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid 142 (0.10 g, 0.3 mmol). Purification by ion exchange chromatography (elution with 0.5 M NH$_4$OH solution) yielded (2S,3S,4R)-2-amino-3-methyl-4-hydroxypentanoic acid 112 as a white solid (0.023 g, 55%). $[\alpha]_D^{27} +2.6$ (c 1.0, H$_2$O), lit.$^{65}$ $[\alpha]_D^{27} +2.9$ (c 1.0, H$_2$O); $\delta_H$ (400 MHz, D$_2$O) 0.89 (3H, d, $J$ 7.2 Hz, 3-CH$_3$), 1.19 (3H, d, $J$ 6.3 Hz, 5-H$_3$), 2.04 (1H, quin d, $J$ 6.8, 2.7 Hz, 3-H), 3.72 (1H, quin, $J$ 6.8 Hz, 4-H), 3.93 (1H, d, $J$ 2.7 Hz, 2-H); $m/z$ (Cl) 148 (MH$^+$, 24%), 130 (100), 85 (15), 74 (12).

Ethyl (2R,3R)-2-benzyl-3-hydroxybutanoate (124).

Diisopropylamine (0.91 mL, 6.4 mmol) was dissolved in THF (10 mL) and cooled to 0 °C. Butyllithium (2.5 M in hexane) (2.50 mL, 6.4 mmol) was then added dropwise to the solution and stirred for 1 h. The solution was then cooled to -78 °C and ethyl (3R)-3-hydroxybutanoate 115 (0.30 g, 2.8 mmol) in THF (10 mL) was added slowly. After stirring for a further 2 h at -78 °C, benzyl bromide (0.75 mL, 6.4 mmol) was added. The reaction
mixture was stirred at -78 °C for 1 h before warming to room temperature and stirring overnight. A saturated solution of ammonium chloride (10 mL) was then added and the solution was acidified to pH 2 by addition of 2 M hydrochloric acid (10 mL). The solution was extracted with ethyl acetate (4 x 30 mL), dried (MgSO₄) and concentrated \textit{in vacuo} to yield the crude product (a viscous oil). Kugelrohr distillation removed unreacted starting material, then flash column chromatography (elution with petroleum ether : ethyl acetate, 5 : 1) gave ethyl (2R,3R)-2-benzyl-3-hydroxybutanoate \textbf{124}, as a colourless oil (0.29 g, 58%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3448 (OH), 3029 (CH), 1729 (CO), 1496, 1377; [\(\alpha\)]\textsubscript{D}\textsuperscript{25} +39.4 (c 3.7, CHCl₃); \(\delta\textsubscript{H} (400 \text{ MHz, CDCl}_3) 1.12 (3\text{H, t, } J 7.1 \text{ Hz, OCH}_2\text{CH}_3), 1.25 (3\text{H, d, } J 6.4 \text{ Hz, 4-H}), 2.63-2.79 (2\text{H, m, 2-H and OH}), 2.98 (2\text{H, d, } J 7.8 \text{ Hz, 2-CH}_2\text{Ph}), 3.92 (1\text{H, qd, } J 6.4, 4.9 \text{ Hz, 3-H}), 4.07 (2\text{H, q, } J 7.1 \text{ Hz, OCH}_2\text{CH}_3), 7.18-7.31 (5\text{H, m, Ph}); \(\delta\textsubscript{C} (100 \text{ MHz, CDCl}_3) 14.1 (\text{CH}_3), 21.8 (\text{CH}_3), 35.6 (\text{CH}_2), 54.2 (\text{CH}), 60.6 (\text{CH}_2), 67.7 (\text{CH}), 126.5 (\text{CH}), 128.4 (\text{CH}), 129.0 (\text{CH}), 138.8 (\text{C}), 174.8 (\text{C}); m/z (Cl) 223.1343 (MH\textsuperscript{+}. C\textsubscript{12}H\textsubscript{19}O\textsubscript{3} requires 223.1334), 204 (15%), 177 (17), 131 (10), 69 (20).

\textbf{Ethyl (2R,3R)-2-benzyl-3-methoxymethoxybutanoate (126).}

\begin{center}
\includegraphics[width=0.3\textwidth]{OMOM.png}
\end{center}

The reaction was done according to general procedure 3 using ethyl (2R,3R)-2-benzyl-3-hydroxybutanoate \textbf{124} (3.20 g, 14.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 5 : 1) yielded ethyl (2R,3R)-2-benzyl-3-methoxymethoxybutanoate \textbf{126}, as a clear oil (3.26 g, 85%). \(\nu_{\text{max}}/\text{cm}^{-1}\) (neat) 3029 (CH), 1731 (CO), 1495, 1379; [\(\alpha\)]\textsubscript{D}\textsuperscript{25} +47.7 (c 1.8, CHCl₃); \(\delta\textsubscript{H} (400 \text{ MHz, CDCl}_3) 1.06 (3\text{H, t, } J 7.1 \text{ Hz, OCH}_2\text{CH}_3), 1.29 (3\text{H, d, } J 6.3 \text{ Hz, 4-H}), 2.79-2.90 (3\text{H, m, 2-CH}_2\text{Ph and 2-H}), 3.38 (3\text{H, s, OCH}_3), 3.98 (1\text{H, qd, } J 6.3, 1.2 \text{ Hz, 3-H}), 4.00 (2\text{H, q, } J 7.1 \text{ Hz OCH}_2\text{CH}_3), 4.64 (1\text{H, d, } J 6.9 \text{ Hz, OCH}_2\text{HO}), 4.70 (1\text{H, d, } J 6.9 \text{ Hz, OCH}_2\text{HO}), 7.16-7.29 (5\text{H, m, Ph}); \(\delta\textsubscript{C} (100 \text{ MHz, CDCl}_3) 14.2 (\text{CH}_3), 18.0 (\text{CH}_3), 34.1 (\text{CH}_2), 54.4 (\text{CH}), 55.6 (\text{CH}_3), 60.3 (\text{CH}_2), 74.3 (\text{CH}), 95.5 (\text{CH}_2), 126.3 (\text{CH}), 128.4 (\text{CH}), 128.9 (\text{CH}), 139.2 (\text{C}), 173.3 (\text{C}); m/z (Cl) 267.1593 (MH\textsuperscript{+}. C\textsubscript{13}H\textsubscript{22}O\textsubscript{4} requires 267.1596), 235 (100%), 223 (28), 177 (7), 85 (37), 69 (52).
(2S,3R)-2-Benzyl-3-methoxymethoxybutan-1-ol (128).

The reaction was carried out according to general procedure 2 using ethyl (2R,3R)-2-benzyl-3-methoxymethoxybutanoate 126 (2.00 g, 7.5 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 1 : 1) gave (2S,3R)-2-benzyl-3-methoxymethoxybutan-1-ol 128, as a clear yellow oil (1.56 g, 93%).

$$\text{υ}_{\text{max}}/\text{cm}^{-1} \text{ (neat)}$$ 3453 (OH), 3026 (CH), 1496, 1454, 1370; $[\alpha]_D^{25}$ -21.4 (c 2.7, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.29 (3H, d, $J$ 6.3 Hz, 4-H$_3$), 1.74-1.81 (1H, m, 2-H), 2.62 (1H, br s, OH), 2.76 (2H, dd, $J$ 6.2, 2.5 Hz, 2-CH$_2$Ph), 3.42 (3H, s, OCH$_3$), 3.50 (1H, dd, $J$ 11.4, 4.8 Hz, 1-HH), 3.83-3.90 (2H, m, 1-HH and 3-H), 4.63 (1H, d, $J$ 6.8 Hz, OCHHO), 4.74 (1H, d, $J$ 6.8 Hz, OCHHO), 7.17-7.31 (5H, m, Ph); $\delta_C$ (100 MHz, CDCl$_3$) 18.6 (CH$_3$), 34.8 (CH$_2$), 48.0 (CH), 55.8 (CH$_3$), 60.3 (CH$_2$), 76.4 (CH), 95.5 (CH$_2$), 126.1 (CH), 128.4 (CH), 129.2 (CH), 140.5 (C); m/z (CI) 225.1489 (MH$^+$). C$_{13}$H$_{21}$O$_3$ requires 225.1491, 193 (100%), 175 (35), 145 (34).

Ethyl (2E,4S,5R)-4-benzyl-5-methoxymethoxyhex-2-enoate (130).

The reaction was carried out according to general procedure 1 using (2S,3R)-2-benzyl-3-methoxymethoxybutan-1-ol 128 (1.00 g, 4.5 mmol). Column chromatography (petroleum ether : diethyl ether, 5 : 1) gave the title compound 130, as a light yellow oil (1.19 g, 91% yield from the alcohol). $\text{υ}_{\text{max}}/\text{cm}^{-1} \text{ (neat)}$ 3027 (CH), 1715 (CO), 1654 (C=C), 1495, 1370; $[\alpha]_D^{25}$ +93.7 (c 2.6, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.22 (3H, d, $J$ 6.4 Hz, 6-H$_3$), 1.26 (3H, t, $J$ 7.1 Hz, OCH$_2$CH$_3$), 2.50-2.58 (1H, m, 4-H), 2.72 (1H, dd, $J$ 13.7, 8.7 Hz, 4-CHHPh), 2.96 (1H, dd, $J$ 13.7, 5.7 Hz, 4-CHHPh), 3.40 (3H, s, OCH$_3$), 3.77 (1H, qd, $J$ 6.4, 2.8 Hz, 5-H), 4.16 (2H, q, $J$ 7.1 Hz, OCH$_2$CH$_3$), 4.62 (1H, d, $J$ 6.9 Hz, OCHHO), 4.73 (1H, d, $J$ 6.9 Hz, OCHHO), 5.67 (1H, dd, $J$ 15.8, 1.2 Hz, 2-H), 6.93 (1H, dd, $J$ 15.8, 9.4 Hz, 3-H), 7.11-
7.29 (5H, m, Ph); δ_C (100 MHz, CDCl₃) 14.3 (CH₃), 18.5 (CH₂), 37.0 (CH₂), 50.7 (CH), 55.7 (CH₃), 60.2 (CH₂), 74.6 (CH), 95.5 (CH₂), 123.5 (CH), 126.2 (CH), 128.4 (CH), 129.1 (CH), 139.7 (C), 148.2 (CH), 166.2 (C); m/z (CI) 293.1752 (MH⁺. C₁₇H₂₅O₄ requires 293.1753), 261 (100%), 248 (15), 217 (53), 191 (12).

(2E,4S,5R)-4-Benzyl-5-methoxymethoxyhex-2-en-1-ol (132).

The reaction was done according to general procedure 2 using ethyl (2E,4S,5R)-4-benzyl-5-methoxymethoxyhex-2-enoate 130 (1.15 g, 3.9 mmol). Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 2 : 3) gave (2E,4S,5R)-4-benzyl-5-methoxymethoxyhex-2-en-1-ol 132, as a yellow oil (0.69 g, 70%). υ_max/cm⁻¹ (neat) 3408 (OH), 2930 (CH), 1603 (C=C), 1495, 1375; [α]_D²⁵ +50.5 (c 0.6, CHCl₃); δ_H (400 MHz, CDCl₃) 1.16 (3H, d, J 6.3 Hz, 6-H₃), 1.23 (1H, br s, OH), 2.40 (1H, tdd, J 9.0, 5.6, 3.3 Hz, 4-H), 2.65 (1H, dd, J 13.5, 9.0 Hz, 4-C₆H₅PH), 2.91 (1H, dd, J 13.5, 5.6 Hz, 4-C₆H₅PH), 3.41 (3H, s, OCH₃), 3.73 (1H, qd, J 6.3, 3.3 Hz, 5-H), 4.03 (2H, dd, J 5.7, 1.0 Hz, 1-H₂), 4.62 (1H, d, J 6.8 Hz, OCH₃), 4.72 (1H, d, J 6.8 Hz, OCH₃), 5.46 (1H, dt, J 15.5, 5.7 Hz, 2-H), 5.62 (1H, ddt, J 15.5, 9.0, 1.0 Hz, 3-H), 7.10-7.28 (5H, m, Ph); δ_C (100 MHz, CDCl₃) 18.3 (CH₃), 37.5 (CH₂), 50.5 (CH), 55.6 (CH₃), 63.6 (CH₂), 75.3 (CH), 95.6 (CH₂), 119.1 (CH), 125.9 (CH), 128.2 (CH), 129.3 (CH), 131.9 (CH), 140.6 (C); m/z (CI) 233.1537 (MH⁺-OH. C₁₅H₂₁O₂ requires 233.1542), 219 (83%), 201 (50), 189 (40), 171 (75), 157 (100).
(3R,4S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140a) and (3S,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140b).

The reaction was carried out according to general procedure 4 using (2E,4S,5R)-4-benzyl-5-methoxymethoxyhex-2-en-1-ol 132 (0.20 g, 0.8 mmol) in THF (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave the title compounds as light brown oils (0.36 g, 72% combined yield over two steps) and in a 6 : 1 ratio (140a : 140b). $\nu_{\text{max}}$/cm$^{-1}$ (neat) 3368 (NH), 2925 (CH), 1718 (CO), 1497, 1455; (3S,4S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 140a: $\left[\alpha\right]_{D}^{25}$ +52.5 (c 1.0, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.35 (3H, d, $J$ 6.1 Hz, 6-H$_3$), 2.09-2.17 (1H, m, 4-H), 2.54 (1H, dd, $J$ 14.2, 8.9 Hz, 4-CH$_3$HPh), 2.79 (1H, dd, $J$ 14.2, 5.6 Hz, 4-CH$_3$HPh), 3.41 (3H, s, OCH$_3$), 3.80 (1H, dq, $J$ 8.3, 6.1 Hz, 5-H), 4.41-4.50 (1H, m, 1-H$_2$), 5.89 (1H, ddd, $J$ 16.9, 10.5, 6.3 Hz, 2-H), 7.16-7.34 (5H, m, Ph), 8.21 (1H, br d, $J$ 6.8 Hz, NH); $\delta_C$ (100 MHz, CDCl$_3$) 19.0 (CH$_3$), 34.1 (CH$_2$), 49.5 (CH), 54.4 (CH), 56.4 (CH$_3$), 60.3 (CH), 93.2 (C), 96.0 (CH$_2$), 118.2 (CH$_2$), 126.7 (CH), 128.8 (CH), 128.9 (CH), 133.2 (CH), 139.1 (C), 160.7 (C). (3R,4S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 140b: $\left[\alpha\right]_{D}^{25}$ -19.4 (c 0.5, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.28 (3H, d, $J$ 6.0 Hz, 6-H$_3$), 2.02-2.07 (1H, m, 4-H), 2.67 (1H, dd, $J$ 13.9, 8.7 Hz, 4-CH$_3$HPh), 2.74 (1H, dd, $J$ 13.9, 6.1 Hz, 4-CH$_3$HPh), 3.38 (3H, s, OCH$_3$), 3.83-3.90 (1H, m, 5-H), 4.50 (1H, d, $J$ 6.8 Hz, OCH$_2$HO), 4.61-4.65 (1H, m, 3-H), 4.71 (1H, d, $J$ 6.8 Hz, OCH$_2$HO), 5.03-5.11 (2H, m, 1-H$_2$), 5.89 (1H, ddd, $J$ 17.2, 10.6, 4.4 Hz, 2-H), 7.10-7.34 (5H, m, Ph), 7.92 (1H, br d, $J$ 8.1 Hz, NH); $\delta_C$ (100 MHz, CDCl$_3$) 20.1 (CH$_3$), 37.1 (CH$_2$), 50.0 (CH), 54.6 (CH), 56.0 (CH$_3$), 76.5 (CH), 93.1 (C), 95.5 (CH$_2$), 114.6 (CH$_2$), 126.6 (CH), 128.9 (CH), 129.2 (CH), 137.1 (CH), 139.6 (C), 161.6 (C); $m/z$ (CI) 394.0747 (MH$^+$). C$_{17}$H$_{23}$NO$_3^{35}$Cl$_3$ requires 394.0744, 362 (100%), 314 (24), 280 (10), 171 (21).
(3S,4S,5R)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140a) and (3R,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140b) using toluene.

The reaction was carried out according to general procedure 4 using (2E,4S,5R)-4-benzyl-5-methoxymethoxyhex-2-en-1-ol 132 (0.067 g, 0.27 mmol) in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave the title compounds as light brown oils (0.09 g, 82% combined yield over 2 steps) and in a 11 : 1 ratio (140a : 140b). Spectroscopic data as described above.

(2S,3S,4R)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid (143).

The reaction was carried out according to general procedure 7 using (3S,4S,5R)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene 140a (0.37 g, 0.9 mmol). The crude product was then dissolved in an aqueous solution of sodium hydrogen carbonate (10 mL), extracted with ethyl acetate (2 x 10 mL) then re-acidified by addition of 2 M hydrochloric acid (15 mL). Extraction with ethyl acetate (4 x 10 mL) followed by concentration in vacuo gave the product, (2S,3S,4R)-2-(2',2',2'-trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid 143 (0.32 g, 82%), as a brown oil. $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3387 (NH and OH), 2937 (CH), 1716 (CO), 1514, 1455; $[\alpha]_D^{25} +40.4$ (c 1.1, CHCl$_3$); $\delta_H$ (400 MHz, CDCl$_3$) 1.29 (3H, d, $J$ 6.3 Hz, 5-H$_3$), 2.34-2.41 (1H, m, 3-H), 2.74 (1H, dd, $J$ 14.1, 8.2 Hz, 3-CH$_2$Ph), 2.85 (1H, dd, $J$ 14.1, 7.2 Hz, 3-CH$_2$Ph), 3.32 (3H, s, OCH$_3$), 3.71 (1H, quin, $J$ 6.3 Hz, 4-H), 4.54 (1H, d, $J$ 6.9 Hz, OCH$_2$O), 4.63-4.68 (2H, m, OCH$_2$O and 2-H), 5.85 (1H, br s, OH), 7.12-7.29 (5H, m, Ph), 7.87 (1H, br d, $J$ 6.3 Hz, NH); $\delta_C$ (100 MHz, CDCl$_3$) 19.3 (CH$_3$), 33.8 (CH$_2$), 48.4 (CH), 53.9 (CH), 56.1 (CH$_3$), 75.6 (CH), 93.3 (C), 96.6 (CH$_2$), 127.0 (CH), 128.9 (CH), 129.1 (CH), 138.2 (C), 161.7 (C), 174.9 (C); m/z (CI) 416.0431 (MH$^+$, C$_{16}$H$_{21}$NO$_5$$^{35}$Cl$^{37}$Cl$_2$ requires 416.0433), 380 (100%), 350 (84), 346 (20), 316 (15).
(2S,3S,4R)-2-Amino-3-benzyl-4-hydroxypentanoic acid (144).

The reaction was carried out according to general procedure 8 using (2S,3S,4R)-2-(2',2',2'-trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid 143 (0.11 g, 0.3 mmol). Purification by ion exchange chromatography (elution with 0.5 M NH₄OH solution) yielded (2S,3S,4R)-2-amino-3-benzyl-4-hydroxypentanoic acid 144, as a white solid (0.033 g, 55%). \(\nu_{\text{max}}\) (KBr) 3400 (NH\_2), 3225 (OH), 2970 (CH), 1652 (CO), 1477; [\(\alpha\)]\text{D}\text{25} +23.0 (c 0.2, H\_2O); \(\delta\)\text{H} (400 MHz, D\_2O) 1.08 (3H, d, \(J\) 6.5, Hz, 5-H), 2.10-2.16 (1H, m, 3-H), 2.56 (1H, dd, \(J\) 13.6, 5.1 Hz, 3-CH\_HPh), 2.62 (1H, dd, \(J\) 13.6, 10.0 Hz, 3-CH\_HPh), 3.78 (1H, qd, \(J\) 6.5, 3.8 Hz, 4-H), 3.92 (1H, d, \(J\) 2.1 Hz, 2-H), 7.14-7.26 (5H, m, Ph); \(\delta\)\text{C} (100 MHz, D\_2O) 14.3 (CH\_3), 27.1 (CH\_2), 31.5 (CH\_2), 60.2 (CH\_2), 115.1 (CH\_2), 121.5 (CH), 138.0 (CH), 149.0 (CH), 166.7 (C); \(m/z\) (EI) 205.1101 (M\^+\text{-H}_2O. C\text{\textsubscript{12}}H\text{\textsubscript{15}}NO\text{\textsubscript{2}} requires 205.1103), 131 (80%), 114 (33), 91 (70), 70 (100).

Ethyl (2E)-2,7-octadienoate (147).\textsuperscript{114}

Reaction was carried out according to general procedure 1, using 5-hexen-1-ol 146 (4.00 g, 0.04 mol). Flash column chromatography (petroleum ether : diethyl ether, 10 : 1) yielded ethyl (2E)-2,7-octadienoate 147 (4.6 g, 69% yield) as a yellow oil. Spectroscopic data entirely consistent with literature.\textsuperscript{114} \(\delta\)\text{H} (400 MHz, CDCl\textsubscript{3}) 1.28 (3H, t, \(J\) 7.1 Hz, OCH\_2CH\_3), 1.52-1.58 (2H, m, 5-H\_2), 2.06-2.12 (2H, m, 6-H\_2), 2.18-2.25 (2H, m, 4-H\_2), 4.17 (2H, q, \(J\) 7.1 Hz, OCH\_2CH\_3), 4.96-5.06 (2H, m, 8-H\_2), 5.73-5.96 (2H, m, 2-H and 7-H), 6.95 (1H, dt, \(J\) 15.5, 6.9 Hz, 3-H); \(\delta\)\text{C} (100 MHz, CDCl\textsubscript{3}) 14.3 (CH\_3), 27.1 (CH\_2), 31.5 (CH\_2), 33.1 (CH\_2), 60.2 (CH\_2), 115.1 (CH\_2), 121.5 (CH), 138.0 (CH), 149.0 (CH), 166.7 (C); \(m/z\) (CI) 169.1232 (M\^+\text{H}^\text{+}). C\text{\textsubscript{10}}H\text{\textsubscript{17}}O\text{\textsubscript{2}} requires 169.1229), 141 (90%), 123 (75), 95 (100), 81 (53), 55 (32).
Ethyl (2E)-2,6-heptadienoate.\textsuperscript{115}

\[
\text{\begin{tikzpicture}
\fill[black!10] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\end{tikzpicture}}
\]

Reaction was carried out according to general procedure 1, using 4-penten-1-ol (0.50 g, 5.8 mmol). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) yielded ethyl (2E)-2,6-heptadienoate (0.69 g, 77% yield) as a yellow oil. Spectroscopic data consistent with literature.\textsuperscript{115} $\delta^H$ (400 MHz, CDCl\textsubscript{3}) 1.29 (3H, t, $J$ 7.1 Hz, OCH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 1.99-2.25 (2H, m, 5-H\textsubscript{2}), 2.27-2.34 (2H, m, 4-H\textsubscript{2}), 4.19 (2H, q, $J$ 7.1 Hz, OCH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 4.99-5.09 (2H, m, 7-H\textsubscript{2}), 5.75-5.80 (1H, m, 6-H), 5.81-5.86 (1H, m, 2-H), 6.96 (1H, dt, $J$ 15.6, 6.8 Hz, 3-H); $\delta^C$ (100 MHz, CDCl\textsubscript{3}) 14.3 (CH\textsubscript{3}), 31.5 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 60.2 (CH\textsubscript{2}), 115.5 (CH\textsubscript{2}), 121.7 (CH), 137.1 (CH), 148.3 (CH), 166.7 (C); $m/z$ (Cl) 155.1075 (MH\textsuperscript{+}. C\textsubscript{9}H\textsubscript{15}O\textsubscript{2} requires 155.1072), 137 (16%), 107 (17), 73 (22).

Ethyl (2E)-2,8-nonadienoate.\textsuperscript{116}

\[
\text{\begin{tikzpicture}
\fill[black!10] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\end{tikzpicture}}
\]

Reaction was carried out according to general procedure 1, using 6-hepten-1-ol (1.00 g, 8.8 mmol). Flash column chromatography (petroleum ether : diethyl ether, 97 : 3) yielded ethyl (2E)-2,8-nonadienoate (1.15 g, 72% yield) as a yellow oil. Spectroscopic data consistent with literature.\textsuperscript{116} $\delta^H$ (400 MHz, CDCl\textsubscript{3}) 1.28 (3H, t, $J$ 7.1 Hz, OCH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 1.38-1.52 (4H, m, 5-H\textsubscript{2} and 6-H\textsubscript{2}), 2.06 (2H, q, $J$ 7.2 Hz, 7-H\textsubscript{2}), 2.21 (2H, qd, $J$ 7.2, 1.5 Hz, 4-H\textsubscript{2}), 4.18 (2H, q, $J$ 7.1 Hz, OCH\textsubscript{2}C\textsubscript{H}\textsubscript{3}), 4.93-4.97 (1H, m, 9-H\textsubscript{H}), 4.97-5.04 (1H, m, 9-H\textsubscript{H}), 5.74-5.78 (1H, m, 8-H), 5.79-5.85 (1H, m, 2-H), 6.96 (1H, dt, $J$ 15.6, 6.9 Hz, 3-H); $\delta^C$ (100 MHz, CDCl\textsubscript{3}) 14.3 (CH\textsubscript{3}), 27.5 (CH\textsubscript{2}), 28.4 (CH\textsubscript{2}), 32.0 (CH\textsubscript{2}), 33.5 (CH\textsubscript{2}), 60.2 (CH\textsubscript{2}), 114.7 (CH\textsubscript{2}), 121.4 (CH), 138.6 (CH), 149.3 (CH), 166.8 (C); $m/z$ (Cl) 183.1382 (MH\textsuperscript{+}. C\textsubscript{11}H\textsubscript{19}O\textsubscript{2} requires 183.1385), 113 (8%), 97 (7), 81 (13), 71 (15).

Ethyl (2E)-2,9-decadienoate.\textsuperscript{117}

\[
\text{\begin{tikzpicture}
\fill[black!10] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
\end{tikzpicture}}
\]

Reaction was carried out according to general procedure 1, using 7-octen-1-ol (1.50 g, 12.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 50 : 1) yielded ethyl (2E)-2,9-decadienoate (2.06 g, 90% yield) as a pale yellow oil. Spectroscopic data
consistent with literature.\textsuperscript{117} δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.29 (3H, t, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 1.31-1.51 (6H, m, 5-H\textsubscript{2}, 6-H\textsubscript{2} and 7-H\textsubscript{2}), 2.05 (2H, q, J 7.1 Hz, 8-H\textsubscript{2}), 2.21 (2H, qd, J 7.1, 1.5 Hz, 4-H\textsubscript{2}), 4.18 (2H, q, J 7.1 Hz, OCH\textsubscript{2}CH\textsubscript{3}), 4.92-4.96 (1H, m, 10-H\textsubscript{H}), 4.97-5.03 (1H, m, 10-H\textsubscript{H}), 5.75-5.86 (2H, m, 2-H and 9-H), 6.96 (1H, dt, J 15.6, 6.9 Hz, 3-H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 14.3 (CH\textsubscript{3}), 27.9 (CH\textsubscript{2}), 28.6 (CH\textsubscript{2}), 28.7 (CH\textsubscript{2}) 32.2 (CH\textsubscript{2}), 33.7 (CH\textsubscript{2}), 60.2 (CH\textsubscript{2}), 114.4 (CH\textsubscript{2}), 121.3 (CH), 138.9 (CH), 149.4 (CH), 166.8 (C); m/z (CI) 197.1540 (MH\textsuperscript{+}. C\textsubscript{13}H\textsubscript{21}O\textsubscript{2} requires 197.1542), 123 (11%), 111 (7).

\textit{(2E)-Octa-2,7-dien-1-ol (148).\textsuperscript{114}}

\begin{center}
\includegraphics[width=0.5\textwidth]{octa-di-en-oil}
\end{center}

The reaction was carried out according to general procedure 2, using ethyl (2E)-2,7-octadienoate \textbf{147} (1.00 g, 6.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 1 : 4) yielded, (2E)-octa-2,7-dien-1-ol \textbf{148} (0.65 g, 87% yield) as a colourless oil. Spectroscopic data consistent with literature.\textsuperscript{114} δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.34 (1H, br s, OH), 1.46-1.51 (2H, m, 5-H\textsubscript{2}), 2.02-2.10 (4H, m, 4-H\textsubscript{2} and 6-H\textsubscript{2}), 4.07 (2H, d, J 4.6 Hz, 1-H\textsubscript{2}), 4.94-4.97 (1H, m, 8-H\textsubscript{H}), 5.01 (1H, dq, J 17.0, 1.7, 8-H\textsubscript{H}), 5.60-5.73 (2H, m, 2-H and 3-H), 5.80 (1H, ddt, J 17.0, 10.2, 6.7 Hz, 7-H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 28.3 (CH\textsubscript{2}), 31.6 (CH\textsubscript{2}), 33.2 (CH\textsubscript{2}), 63.8 (CH\textsubscript{2}), 114.6 (CH\textsubscript{2}), 129.2 (CH), 133.0 (CH), 138.6 (CH); m/z (CI) 109.1009 (M\textsuperscript{+}-OH. C\textsubscript{8}H\textsubscript{13} requires 109.1017), 95 (16%), 81 (12), 67 (47).

\textit{(2E)-Hepta-2,6-dien-1-ol.\textsuperscript{115}}

\begin{center}
\includegraphics[width=0.5\textwidth]{hepta-di-en-oil}
\end{center}

The reaction was carried out according to general procedure 2, using ethyl (2E)-2,6-heptadienoate (1.54 g, 10.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2E)-hepta-2,6-dien-1-ol (0.92 g, 82% yield) as a colourless oil. Spectroscopic data consistent with literature.\textsuperscript{115} δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 1.42 (1H, br s, OH), 2.10-2.15 (4H, m, 4-H\textsubscript{2} and 5-H\textsubscript{2}), 4.08 (2H, d, J 4.8 Hz, 1-H\textsubscript{2}), 4.96-5.03 (2H, m, 7-H\textsubscript{2}), 5.62-5.71 (2H, m, 2-H and 3-H), 5.72-5.89 (1H, m, 6-H); δ\textsubscript{C} (100 MHz, CDCl\textsubscript{3}) 31.5 (CH\textsubscript{2}), 33.3 (CH\textsubscript{2}), 63.7 (CH\textsubscript{2}), 114.9 (CH\textsubscript{2}), 129.4 (CH), 132.4 (CH), 138.1 (CH); m/z (CI) 113.0964 (MH\textsuperscript{+}. C\textsubscript{7}H\textsubscript{13}O requires 113.0966), 95 (100%), 81 (14), 73 (13).
(2E)-Nona-2,8-dien-1-ol.\textsuperscript{116}

\[
\begin{align*}
\text{OH} \\
\text{\includegraphics[width=0.2\textwidth]{nona_dien_1_ol.png}}
\end{align*}
\]

The reaction was carried out according to general procedure 2, using ethyl (2E)-2,8-nonadienoate (1.00 g, 5.5 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2E)-nona-2,8-dien-1-ol (0.77 g, 100% yield) as a colourless oil. Spectroscopic data consistent with literature.\textsuperscript{116} \(\delta\text{H} (400 \text{ MHz, CDCl}_3)\) 1.22 (1H, br s, OH), 1.38–1.42 (4H, m, 5-H\textsubscript{2} and 6-H\textsubscript{2}), 2.02–2.10 (4H, m, 4-H\textsubscript{2} and 7-H\textsubscript{2}), 4.09 (2H, t, \(J\text{ 4.9 Hz, 1-H}\textsubscript{2}\)), 4.92–4.96 (1H, m, 9-H\textsubscript{H}), 5.00 (1H, dq, \(J\text{ 17.0, 1.6 Hz, 9-HH}\)), 5.60–5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, \(J\text{ 17.0, 10.2, 6.7 Hz, 8-H}\)); \(\delta\text{C} \text{(100 MHz, CDCl}_3\)) 26.9 (CH\textsubscript{2}), 27.1 (CH\textsubscript{2}), 30.6 (CH\textsubscript{2}), 32.2 (CH\textsubscript{2}), 62.4 (CH\textsubscript{2}), 112.9 (CH\textsubscript{2}), 127.5 (CH), 131.9 (CH), 137.4 (CH); \(m/z\) (CI) 123.1169 (MH\textsuperscript{+}-H\textsubscript{2}O. C\textsubscript{9}H\textsubscript{15} requires 123.1174), 109 (16%), 95 (12), 81 (63), 67 (17).

(2E)-Deca-2,9-dien-1-ol.\textsuperscript{118}

\[
\begin{align*}
\text{OH} \\
\text{\includegraphics[width=0.2\textwidth]{deca_dien_1_ol.png}}
\end{align*}
\]

The reaction was carried out according to general procedure 2, using ethyl (2E)-2,9-decadinoate (1.50 g, 7.7 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2E)-deca-2,9-dien-1-ol (0.97 g, 81% yield) as a colourless oil. Spectroscopic data consistent with literature.\textsuperscript{118} \(\delta\text{H} (400 \text{ MHz, CDCl}_3)\) 1.25–1.46 (7H, m, 5-H\textsubscript{2}, 6-H\textsubscript{2}, 7-H\textsubscript{2} and OH), 2.01–2.10 (4H, m, 4-H\textsubscript{2} and 8-H\textsubscript{2}), 4.09 (2H, d, \(J\text{ 4.6 Hz, 1-H}\textsubscript{2}\)), 4.92–4.96 (1H, m, 10-H\textsubscript{HH}), 4.97–5.05 (1H, m, 10-H\textsubscript{H}), 5.58–5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, \(J\text{ 17.1, 10.1, 6.7 Hz, 9-H}\)); \(\delta\text{C} \text{(100 MHz, CDCl}_3\)) 28.7 (CH\textsubscript{2}), 28.8 (CH\textsubscript{2}), 29.0 (CH\textsubscript{2}), 32.2 (CH\textsubscript{2}), 33.8 (CH\textsubscript{2}), 63.9 (CH\textsubscript{2}), 114.3 (CH\textsubscript{2}), 128.9 (CH), 133.5 (CH), 139.1 (CH); \(m/z\) (CI) 137.1324 (MH\textsuperscript{+}-H\textsubscript{2}O. C\textsubscript{10}H\textsubscript{17} requires 137.1330), 113 (25%), 95 (49), 81 (100), 69 (88), 67 (59).
The reaction was carried out according to general procedure 4, using (2E)-octa-2,7-dien-1-ol 148 (0.07 g, 0.5 mmol). PdCl₂(MeCN)₂ was used to catalyse the rearrangement, which was carried out in DCM (10 mL) and stirred at room temperature for 3 h. Purification by column chromatography (petroleum ether : diethyl ether, 10 : 1) gave 3-(2’,2’,2’-trichloromethylcarbonylamino)octa-1,7-diene 150 as a brown oil (0.10 g, 71% yield over 2 steps). δ_H (400 MHz, CDCl₃) 1.43-1.52 (2H, m, 5-H), 1.55-1.73 (2H, m, 4-H), 2.06-2.14 (2H, m, 6-H), 4.40-4.50 (1H, m, 3-H), 4.95 (1H, ddt, J 10.2, 2.0, 1.5 Hz, 8-HH), 5.00 (1H, ddt, J 17.1, 3.6, 1.5 Hz, 8-HH), 5.20 (1H, ddd, J 10.5, 1.2, 0.8 Hz, 1-HH), 5.24 (1H, ddd, J 17.2, 1.5, 1.2 Hz, 1-HH), 5.73-5.85 (2H, m, 2-H and 7-H), 6.52 (1H, br s, NH).

3-(2’,2’,2’-Trichloromethylcarbonylamino)octa-1,7-diene 150 (0.10 g, 0.4 mmol) was dissolved in DCM (10 mL). Grubbs I catalyst (10 mol %) (0.03 g, 0.04 mmol) was added and the reaction mixture was heated under reflux for 12 h. The reaction was cooled and filtered through Celite®. Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) yielded 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene 151 as a white solid (0.09 g, 100% yield). mp 85-86 °C, lit.21 85.5-87 °C; δ_H (400 MHz, CDCl₃) 1.62-1.79 (3H, m, 5-H and 6-H), 1.94-2.03 (1H, m, 6-H), 2.03-2.16 (2H, m, 4-H), 4.42-4.54 (1H, m, 1-H), 5.65 (1H, ddt, J 10.0, 4.0, 2.2 Hz, 2-H), 5.98 (1H, ddd, J 10.0, 4.0, 1.9 Hz, 3-H), 6.60 (1H, br s, NH); δ_C (100 MHz, CDCl₃) 19.4 (CH₂), 24.7 (CH₂), 28.6 (CH₂), 46.9 (CH), 92.7 (C), 125.7 (CH), 132.7 (CH), 161.1 (C); m/z (CI) 261.0144 (M+NH₄)⁺. C₈H₁₄N₂O₃Cl₂³⁷Cl requires 261.0143, 259 (100%), 242 (23), 225 (9), 206 (21), 81 (10).
Synthesis of 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene (151),\textsuperscript{21} using Grubbs I catalyst.

The reaction was carried out according general procedure 6 using (2\textit{E})-octa-2,7-dien-1-ol \textbf{148} (0.10 g, 0.8 mmol) and bis(acetonitrile)palladium(II) chloride (0.020 g, 0.08 mmol) was used to catalyze the aza-Claisen rearrangement. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 97 : 3) gave 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene \textbf{151} as a white solid (0.17 g, 89% yield over 3 steps). Spectroscopic data as reported above.

Synthesis of 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene (151),\textsuperscript{21} using Grubbs II catalyst.

The reaction was carried out according general procedure 6 using (2\textit{E})-octa-2,7-dien-1-ol \textbf{148} (0.08 g, 0.6 mmol), bis(acetonitrile)palladium(II) chloride (0.015 g, 0.06 mmol) was used to catalyze the aza-Claisen rearrangement and Grubbs II catalyst (0.05 g, 0.06 mmol) was used to catalyze the RCM. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 97 : 3) gave 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene \textbf{151}, as a white solid (0.14 g, 95% yield over 3 steps). Spectroscopic data as reported above.


The reaction was carried out according general procedure 6 using (2\textit{E})-octa-2,7-dien-1-ol \textbf{148} (0.08 g, 0.6 mmol), bis(acetonitrile)palladium(II) chloride (0.08 g, 0.6 mmol) was used to catalyze the aza-Claisen rearrangement and Grubbs/Hoveyda II catalyst (0.04 g, 0.06 mmol) was used to catalyze the RCM. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 97 : 3) gave 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohexa-2-ene \textbf{151}, as a white solid (0.14 g, 95% yield over 3 steps). Spectroscopic data as reported above.
1-(2',2',2'-Trichloromethylcarbonylamino)cyclopenta-2-ene (155).

![Chemical Structure]

The reaction was carried out according general procedure 6 using (2E)-hepta-2,6-dien-1-ol (0.10 g, 0.9 mmol) and bis(acetonitrile)palladium(II) chloride (0.04 g, 0.2 mmol) was used to catalyze the rearrangement. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 24 : 1) gave 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene 155 as a white solid (0.17 g, 84% yield over 3 steps). mp 81-82 °C; $\nu_{\text{max}}$/cm$^{-1}$ (NaCl) 3291 (NH), 1684 (CO), 1528 (C=C), 823; $\delta_H$ (400 MHz, CDCl$_3$) 1.67-1.75 (1H, m, 4-H), 2.34-2.57 (3H, m, 4-H and 5-H), 4.92-5.01 (1H, m, 1-H), 5.72-5.76 (1H, m, 2-H), 6.05-6.09 (1H, m, 3-H), 6.68 (1H, br s, NH); $\delta_C$ (100 MHz, CDCl$_3$) 28.9 (CH$_2$), 29.4 (CH$_2$), 56.0 (CH), 90.8 (C), 127.5 (CH), 134.2 (CH), 159.3 (C); m/z (CI) 229.9718 (MH$^+$, C$_7$H$_9$NO$_3$Cl$_2$ requires 229.9718), 228 (100%), 194 (22), 162 (5), 67 (13).

1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (156).

![Chemical Structure]

The reaction was carried out according general procedure 6 (at a concentration of 0.005 M) using (2E)-nona-2,8-dien-1-ol (0.10 g, 0.7 mmol) and bis(acetonitrile)palladium(II) chloride (0.02 g, 0.08 mmol) was used to catalyze the aza-Claisen rearrangement. Purification by flash column chromatography (elution with petroleum ether : DCM, 5 : 2) gave 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene 156, as a white solid (0.17 g, 93% yield over 3 steps). mp 104-105 °C, lit.$^{82}$ 105 °C; $\delta_H$ (400 MHz, CDCl$_3$) 1.39-1.49 (1H, m, 6-HH), 1.66-1.79 (3H, m, 6-HH and 7-H), 1.85-1.98 (2H, m, 5-H), 2.10-2.29 (2H, m, 4-H), 4.54-4.62 (1H, m, 1-H), 5.55-5.62 (1H, m, 2-H), 5.88-5.95 (1H, m, 3-H), 6.72 (1H, br s, NH); $\delta_C$ (100 MHz, CDCl$_3$) 24.6 (CH$_2$), 25.2 (CH$_2$), 26.5 (CH$_2$), 31.1 (CH$_2$), 50.5 (CH), 90.8 (C), 130.5 (CH), 131.8 (CH), 158.8 (C); m/z (CI) 256.0060 (MH$^+$, C$_9$H$_{13}$NO$_3$Cl$_2$ requires 256.0063), 258 (97%), 222 (18), 95 (12).
1-(2',2',2''-Trichloromethylcarbonylamino)cycloocta-2-ene (158).

![Chemical Structure](attachment:image.png)

The reaction was carried out according general procedure 6 (at a concentration of 0.0013 M) using (2E)-deca-2,8-dien-1-ol (0.10 g, 0.7 mmol). Bis(acetonitrile)palladium(II) chloride (0.008 g, 0.03 mmol) was used to catalyze the aza-Claisen rearrangement and Grubbs II catalyst (0.05 g, 0.06 mmol, 20 mol %) was used to catalyze the RCM. Purification by flash column chromatography (elution with petroleum ether : DCM, 5 : 2) gave 1-(2',2',2''-trichloromethylcarbonylamino)cycloocta-2-ene 158, as a white solid (0.044 g, 62% yield over 3 steps). mp 126-127 °C; ν\text{max}/cm\(^{-1}\) (NaCl) 3314 (NH), 1684 (CO), 1529 (C=C), 824; δ\text{H} (400 MHz, CDCl\(_3\)) 1.39-1.49 (7H, m, 5-H\(_2\), 6-H\(_2\), 7-H\(_2\) and 8-H\(_2\)), 1.98 (1H, ddt, J 13.1, 8.9, 4.4 Hz, 8-HH), 2.11-2.20 (1H, m, 4-HH), 2.25-2.36 (1H, m, 4-HH), 4.75-4.79 (1H, m, 1-H), 5.31-5.38 (1H, m, 2-H), 5.79 (1H, ddt, J 10.5, 7.5, 1.4 Hz, 3-H), 6.65 (1H, br s, NH); δ\text{C} (100 MHz, CDCl\(_3\)) 22.1 (CH\(_2\)), 23.9 (CH\(_2\)), 24.4 (CH\(_2\)), 26.8 (CH\(_2\)), 33.7 (CH\(_2\)), 47.9 (CH), 90.7 (C), 127.3 (CH), 129.5 (CH), 158.9 (C); m/z (CI) 270.0216 (MH\(^+\). C\(_{10}\)H\(_{15}\)NO\(_3\)Cl\(_3\)) requires 270.0219), 272 (92%), 236 (58), 234 (85), 109 (47), 67 (28).

(1S)-1-(2',2',2''-Trichloromethylcarbonylamino)cyclohexa-2-ene (159).

![Chemical Structure](attachment:image.png)

The reaction was carried out according general procedure 6 using (2E)-octa-2,7-dien-1-ol 148 (0.08 g, 0.6 mmol) and (S)-COP-Cl (0.04 g, 0.03 mmol) as rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 97 : 3) gave (1S)-1-(2',2',2''-trichloromethylcarbonylamino)cyclohexa-2-ene 159 as a white solid (0.15 g, 90% yield over 3 steps). 88% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% iPrOH : hexane at 0.75 mL/min), retention time: t\(_S\)= 8.2 min, and t\(_R\)= 9.2 min; [α]\(_D\)\(^{23}\) -95.3 (c 2.1, CHCl\(_3\)). All other spectroscopic data as
previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene 151 above.

(1R)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclohexa-2-ene (160).

\[
\text{HN} \quad \text{O} \\
\text{N} \quad \text{CCl}_3
\]

The reaction was carried out according general procedure 6 using (2E)-octa-2,7-dien-1-ol 148 (0.08 g, 0.6 mmol) and (R)-COP-Cl (0.04 g, 0.03 mmol) as the catalyst for aza-Claisen rearrangement. Purification by flash column chromatography (elution with petroleum ether : diethyl ether 97 : 3) gave (1R)-1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene 160 as a white solid (0.12 g, 75% yield over 3 steps). 88% ee determined by HPLC analysis using CHIRALPAK-IB column (0.5% iPrOH : hexane at 0.75 mL/min), retention time: \(t_S = 8.3\) min, and \(t_R = 9.4\) min; \([\alpha]_D^{23} +97.4\) (c 1.3, CHCl_3). All other spectroscopic data as previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene 151 above.

(1S)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclopenta-2-ene (161).

\[
\text{HN} \quad \text{O} \\
\text{N} \quad \text{CCl}_3
\]

The reaction was carried out according general procedure 6 using (2E)-hepta-2,6-dien-1-ol 152 (0.08 g, 0.7 mmol) and (S)-COP-Cl (0.05 g, 0.03 mmol) as rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether : DCM, 70 : 30) gave (1S)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene 161 as a white solid (0.13 g, 88% yield over 3 steps). 92% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% iPrOH : hexane at 0.75 mL/min), retention time: \(t_S = 12.7\) min, and \(t_R = 14.5\) min; \([\alpha]_D^{23} -86.6\) (c 1.0, CHCl_3). All other spectroscopic data as previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene 155 above.
**(1S)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohepta-2-ene (162).**

![Chemical structure](image)

The reaction was carried out according general procedure 6 using (2E)-nona-2,8-dien-1-ol 153 (0.08 g, 0.5 mmol) and (S)-COP-Cl (0.04 g, 0.03 mmol) as rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether : DCM, 70 : 30) gave (1S)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohepta-2-ene 162 as a white solid (0.11 g, 81% yield over 3 steps). 84% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% iPrOH : hexane at 0.5 mL/min), retention time: ts= 21.5 min, and tr= 22.1 min; [α]D23 23 -25.0 (c 1.0, CHCl3). All other spectroscopic data as previously reported for 1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohepta-2-ene 156 above.

**(2R)-1-(tert-Butyldimethyldimethylsilyloxy)-2,3-epoxypropane (185).**

![Chemical structure](image)

A mixture of (S)-glycidol 184 (3.10 g, 0.04 mol), tert-butyldimethylsilyl chloride (9.40 g, 0.06 mol) and imidazole (4.20 g, 0.06 mol) in THF (70 mL) were stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated and purified by flash column chromatography (elution with petroleum ether : diethyl ether, 10 : 1) to give (2R)-1-(tert-butyldimethyldimethylsilyloxy)-2,3-epoxypropane 185 (7.7 g, 98%) as a clear oil. [α]D24 +2.7 (c 1.0, CHCl3), lit.119 +2.9 (c 1.0, CHCl3); δH (400 MHz, CDCl3) 0.09 (3H, s, SiCH3), 0.10 (3H, s, SiCH3), 0.92 (9H, s, SiC(CH3)3), 2.66 (1H, dd, J 4.6, 2.4 Hz, 1-HH), 2.79 (1H, dd, J 5.2, 4.6 Hz, 1-HH), 3.10-3.14 (1H, m, 2-H), 3.68 (1H, dd, J 11.8, 4.8 Hz, 3-HH), 3.87 (1H, dd, J 11.8, 3.2 Hz, 3-HH); δC (100 MHz, CDCl3) -5.4 (CH3), -5.3 (CH3), 19.0 (C), 26.0 (CH3), 45.0 (CH2), 52.5 (CH) and 63.9 (CH2); m/z (CI) 189.1309 (MH+). C9H21O2Si requires 189.1311, 145 (35%), 131 (50), 89 (62), 73 (12).
A solution of allyl magnesium bromide (1 M in diethyl ether) (100.0 mL, 100.0 mmol) was added drop-wise to a solution of copper(I) bromide dimethylsulfide complex (0.69 g, 3.4 mmol) in THF (150 mL) at -78 °C and the white suspension was stirred for 0.5 h. (2R)-1-(tert-Butyldimethylsilyloxy)-2,3-epoxypropane 185 (12.70 g, 67.0 mmol) in THF (60 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, dried (MgSO$_4$) and concentrated in vacuo. Purification by flash column chromatography (petroleum ether : diethyl ether, 10 : 1) gave (2R)-1-(tert-butyldimethylsilyloxy)hex-5-en-2-ol 186 (13.9 g, 90%) as a clear oil. Spectroscopic data as reported in literature.$^{120}$ [α]$_D^{24}$ -6.7 ($c$ 1.2, CHCl$_3$); δ$_H$ (400 MHz, CDCl$_3$) 0.01 (6H, s, Si(CH$_3$)$_2$), 0.82 (9H, s, SiC(CH$_3$)$_3$), 1.35-1.55 (2H, m, 3-H$_2$), 2.00-2.22 (2H, m, 4-H$_2$), 2.35 (1H, br d, $J$ 3.3 Hz, OH), 3.33 (1H, dd, $J$ 9.9, 7.1 Hz, 1-HH), 3.53-3.62 (2H, m, 1-HH and 2-H), 4.88-4.92 (1H, m, 6-HH), 4.94-5.00 (1H, m, 6-HH), 5.76 (1H, ddt, $J$ 17.1, 10.3, 6.6 Hz, 5-H); δ$_C$ (100 MHz, CDCl$_3$) -5.4 (CH$_3$), -5.3 (CH$_3$), 18.3 (C), 25.9 (CH$_3$), 29.8 (CH$_2$), 32.0 (CH$_2$), 67.2 (CH$_2$), 71.2 (CH), 114.8 (CH$_2$), 138.4 (CH); m/z (Cl) 231.1776 (MH$^+$. C$_{12}$H$_{27}$O$_2$Si requires 231.1780), 173 (8), 81 (15).

(2R)-1-(tert-Butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene 187.

The reaction was carried out according to general procedure 3 using (2R)-1-(tert-butyldimethylsilyloxy)hex-5-en-2-ol 186 (4.00 g, 17.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) yielded (2R)-1-(tert-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene 187, as a clear oil (4.7 g, 100%). (Found: C, 61.4; H, 11.0. C$_{14}$H$_{30}$O$_3$Si requires C, 61.3; H, 11.0%); $\nu$$_{max}$/cm$^{-1}$ (NaCl) 2929 (CH), 1642 (C=C), 1472 (CH), 1255, 1110 (CO), 1040; [α]$_D^{24}$ +28.8 ($c$ 1.5, CHCl$_3$); δ$_H$ (400 MHz, CDCl$_3$) 0.01 (6H, s, Si(CH$_3$)$_2$), 0.82 (9H, s, SiC(CH$_3$)$_3$), 1.35-1.54 (2H, m, 3-H$_2$), 2.00-2.21 (2H, m, 4-H$_2$), 3.34 (3H, s, OCH$_3$), 3.50-3.62 (3H, m, 1-H$_2$ and 2-H), 4.60 (1H, d, $J$ 6.8 Hz, OCH$_2$O), 4.72 (1H, d, $J$ 6.8 Hz, OCH$_2$O), 4.89-4.94 (1H, m, 6-HH), 5.76 (1H, ddt, $J$ 17.1, 10.3, 6.6 Hz, 5-H); δ$_C$ (100 MHz, CDCl$_3$) -5.4 (CH$_3$), -5.3 (CH$_3$), 18.3 (C), 25.9 (CH$_3$), 29.8 (CH$_2$), 32.0 (CH$_2$), 67.2 (CH$_2$), 71.2 (CH), 114.8 (CH$_2$), 138.4 (CH); m/z (Cl) 313.1990 (MH$^+$. C$_{16}$H$_{34}$O$_4$Si requires 313.2000), 165 (1), 153 (6), 121 (10).
4.95-5.01 (1H, m, 6-H), 5.77 (1H, ddt, J 17.1, 10.3, 6.6 Hz, 5-H); δC (100 MHz, CDCl₃) -5.4 (CH₃), -5.4 (CH₃), 18.3 (C), 25.9 (CH₃), 29.6 (CH₂), 31.0 (CH₂), 55.5 (CH₃), 65.7 (CH₂), 77.7 (CH), 96.4 (CH₂), 114.6 (CH₂), 138.5 (CH); m/z (Cl) 243 (M⁺-OCH₄, 100%), 231 (8), 133 (11), 81 (18).

(2R)-2-(Methoxymethoxy)hex-5-en-1-ol (188).

A solution of tetrabutylammonium fluoride (1M in THF) (18.8 mL, 18.8 mmol) was added to a solution of (2R)-1-(tert-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene 187 (4.30 g, 15.7 mmol) in THF (100 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (50 mL). The solution was washed with water (50 mL) and the aqueous layer was then extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried (MgSO₄), concentrated and then purified by flash column chromatography (petroleum ether : diethyl ether, 5 : 2) to give (2R)-2-(methoxymethoxy)hex-5-en-1-ol 188, as a clear oil (2.42 g, 98%). (Found: C, 59.9; H, 10.2. C₈H₁₆O₃ requires C, 60.0; H, 10.0%); νmax/cm⁻¹ (NaCl) 3432 (OH), 2947 (CH), 1641 (C=C), 1450, 1212, 1028; [α]D²⁴ -66.8 (c 0.6, CHCl₃); δH (400 MHz, CDCl₃) 1.49-1.70 (2H, m, 3-H), 2.07-2.24 (2H, m, 4-H₂), 3.14 (1H, br dd, J 8.5, 3.4 Hz, OH) 3.44 (3H, s, OCH₃), 3.47-3.64 (3H, m, 1-H₂ and 2-H), 4.69 (1H, d, J 6.9 Hz, OCHHO), 4.75 (1H, d, J 6.9 Hz, OCHH/O), 4.96-5.07 (2H, m, 6-H₂), 5.80 (1H, ddt, J 17.1, 10.3, 6.6 Hz, 5-H); δC (100 MHz, CDCl₃) 29.7 (CH₂), 30.8 (CH₂), 55.7 (CH₃), 66.7 (CH₂), 81.9 (CH), 97.1 (CH₂), 115.1 (CH₂), 138.0 (CH); m/z (Cl) 129 (MH⁺-OCH₄, 100%), 99 (14), 81 (40), 69 (38).

Ethyl (2E,4R)-4-(methoxymethoxy)octa-2,7-dienoate (189).

Reaction was carried out according to general procedure 1, using (2R)-2-(methoxymethoxy)hex-5-en-1-ol 188 (1.00 g, 6.3 mmol). Flash column chromatography (petroleum ether : diethyl ether, 5 : 1) yielded ethyl (2E,4R)-4-(methoxymethoxy)octa-2,7-
dienoate 189 (1.35 g, 94% yield) as a yellow oil. (Found: C, 63.2; H, 8.9. C_{12}H_{20}O_4 requires C, 63.2; H, 8.8%); \nu_{\text{max}}/\text{cm}^{-1} (\text{NaCl}) 2941 (\text{CH}), 1720 (\text{CO}), 1658 (\text{C=C}), 1446, 1369, 1269, 1154; [\alpha]_D^{24} +79.2 (c 1.3, CHCl_3); \delta_H (400 MHz, CDCl_3) 1.30 (3H, t, J 7.1 Hz, OCH_2CH_3), 1.59-1.80 (2H, m, 5-H_2), 3.39 (3H, s, OCH_3), 4.18-4.25 (3H, m, 4-H and OCH_2CH_3), 4.59 (1H, d, J 6.9 Hz, OCHHO), 4.64 (1H, d, J 6.9 Hz, OCHHO), 4.97-5.08 (2H, m, 8-H_2), 5.81 (1H, ddt, J 17.1, 10.3, 6.6 Hz, 7-H), 5.99 (1H, dd, J 15.7, 1.2 Hz, 2-H), 6.82 (1H, dd, J 15.7, 6.5 Hz, 3-H); \delta_C (100 MHz, CDCl_3) 14.2 (CH_3), 29.3 (CH_2), 34.0 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 74.6 (CH), 94.7 (CH_2), 115.2 (CH_2), 122.1 (CH), 137.7 (CH), 147.6 (CH), 166.2 (C); m/z (Cl) 229 (MH^+, 35%), 199 (33), 197 (37), 167 (100), 81 (16), 69 (24).

\[(2E,4R)-4-(\text{Methoxymethoxy})\text{octa-2,7-dien-1-ol (190)}\].

The reaction was carried out according to general procedure 2, using ethyl \((2E,4R)-4-(\text{methoxymethoxy})\text{octa-2,7-dienoate 189}\) (1.30 g, 5.7 mmol). Flash column chromatography (petroleum ether : diethyl ether, 2 : 3) yielded, \((2E,4R)-4-(\text{methoxymethoxy})\text{octa-2,7-dien-1-ol 190}\) (1.00 g, 98% yield) as a colourless oil. (Found: C, 64.5; H, 9.7. C_{10}H_{18}O_3 requires C, 64.5; H, 9.7%); \nu_{\text{max}}/\text{cm}^{-1} (\text{NaCl}) 3408 (OH), 2937 (CH), 1641 (C=C), 1442, 1373, 1153, 1096, 1036; [\alpha]_D^{24} +126.8 (c 1.3, CHCl_3); \delta_H (400 MHz, CDCl_3) 1.54-1.64 (2H, m, 5-HH and OH), 1.68-1.78 (1H, m, 5-HH), 2.06-2.22 (2H, m, 6-H_2), 3.38 (3H, s, OCH_3), 4.02-4.09 (1H, m, 4-H), 4.17 (2H, m, 1-H_2), 4.54 (1H, d, J 6.9 Hz, OCHHO), 4.70 (1H, d, J 6.9 Hz, OCHHO), 4.95-5.06 (2H, m, 8-H_2), 5.58 (1H, ddd, J 15.6, 7.8, 1.4 Hz, 3-H) 5.79-5.87 (2H, m 2-H and 7-H); \delta_C (100 MHz, CDCl_3) 29.6 (CH_2), 34.7 (CH_2), 55.5 (CH_3), 62.9 (CH_2), 75.7 (CH), 93.7 (CH_2), 114.9 (CH_2), 131.2 (CH), 132.3 (CH), 138.2 (CH); m/z (Cl) 204 (MNH_4^+, 100%), 174 (31), 142 (29), 125 (14), 58 (16).
(1R,2S)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177a) and (1R,2R)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177b).

The reaction was carried out according general procedure 6 using (2E,4R)-4-(methoxymethoxy)octa-2,7-dien-1-ol 190 (1.10 g, 3.4 mmol). Bis(acetonitrile)palladium(II) chloride (0.090 g, 0.3 mmol) was used to catalyze the aza-Claisen rearrangement, which was stirred at room temperature overnight before addition of Grubbs I catalyst. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 7 : 1) gave (1R,2S)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene 177a followed by (1R,2R)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene 177b, as a yellow oil (0.46 g, 45% combined yield over 3 steps) and in a 5:1 ratio (177a : 177b). 

Data for (1R,2S)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene 177a: [α]D 20 +79.1 (c 1.9, CHCl3); δH (400 MHz, CDCl3) 1.73-1.82 (1H, m, 6-HH), 2.00-2.13 (2H, m, 5-HH and 6-HH), 2.17-2.28 (1H, m, 5-HH), 3.42 (3H, s, OCH3), 4.05 (1H, td, J 5.6, 1.3 Hz, 1-H), 4.60-4.66 (1H, m, 2-H), 4.72 (1H, d, J 6.9 Hz, OCHHO), 4.76 (1H, d, J 6.9 Hz, OCHHO), 5.51-5.56 (1H, m, 3-H), 5.91-5.97 (1H, m, 4-H), 7.31 (1H, br d, J 7.0 Hz, NH); δC (100 MHz, CDCl3) 20.2 (CH2), 24.2 (CH2), 48.6 (CH), 55.0 (CH3), 70.9 (CH), 91.9 (C), 94.5 (CH2), 123.4 (CH), 129.9 (CH), 160.7 (C). Data for (1R,2R)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene 177b: δH (400 MHz, CDCl3) 1.73-1.82 (1H, m, 6-HH), 1.90-1.99 (1H, m, 6-HH), 2.11-2.29 (2H, m, 5-H2), 3.39 (3H, s, OCH3), 3.71-3.79 (1H, m, 1-H), 4.49-4.56 (1H, m, 2-H), 4.70 (1H, d, J 6.9 Hz, OCHHO), 4.74 (1H, d, J 6.9 Hz, OCHHO), 5.58-5.62 (1H, m, 3-H), 5.91-5.97 (1H, m, 4-H), 6.78 (1H, br d, J 7.1 Hz, NH); δC (100 MHz, CDCl3) 23.3 (CH2), 26.0 (CH2), 52.5 (CH), 55.7 (CH3), 74.9 (CH), 92.6 (C), 95.3 (CH2), 124.1 (CH), 131.4 (CH), 161.6 (C); m/z (CI) 306.0056 (MH+). C10H15NO3Cl35Cl37Cl2 requires 306.0062, 268 (100%), 234 (45), 198 (7).
(1R,2S)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (177a) and (1R,2R)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene (177b) using toluene as solvent.

The reaction was carried out according general procedure 6 using (2E,4R)-4-(methoxymethoxy)-octa-2,7-dien-1-ol 190 (0.10 g, 0.5 mmol). Bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) was used to catalyze the aza-Claisen rearrangement, which was stirred in toluene (10 mL), initially at 0 °C and slowly warmed to room temperature over 24 h before addition of Grubbs I catalyst. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 7 : 1) gave (1R,2S)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene 177a followed by (1R,2R)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene 177b, as a yellow oil (0.11 g, 60% combined yield over 3 steps) and in a 10 : 1 ratio (177a : 177b)

(3aR,4R,7R,7aS)-3,3,4-Trichloro-octahydro[1,8]oxazole-indol-2-one (195).

(1R,2S)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-3-ene 177a (0.085 g, 0.3 mmol) was dissolved in toluene (10 mL) which was then de-gassed for 1h. Grubbs I catalyst (0.012 g, 0.014 mmol) was added and the reaction mixture was heated at 155 °C for 6 h. The reaction mixture was then concentrated under vacuum and purified by column chromatography (elution with petroleum ether : diethyl ether, 3 : 2) to give (3aR,4R,7R,7aS)-3,3,4-trichloro-octahydro[1,8]oxazole-indol-2-one 195, as a white solid (0.018 g, 24%). $\nu_{\text{max}}$/cm$^{-1}$ (NaCl) 2920 (CH), 1745 (CO), 1419, 1223; $[\alpha]_D^{25} +39.6$ (c 0.7, CHCl$_3$); $\delta$H (400 MHz, CDCl$_3$) 1.28-1.38 (1H, m, 5-HH), 1.65-1.75 (1H, m, 6-HH), 2.05-2.15 (2H, m, 5-HH and 6-HH), 3.46 (1H, dd, J 7.6, 6.9 Hz, 3a-H), 3.93 (1H, ddd, J 10.8, 7.6, 3.9 Hz, 4-H), 3.99-4.45 (2H, m, 7-H and 7a-H), 4.78 (1H, d, J 5.3 Hz, 9-HH), 5.11 (1H, d, J 5.3 Hz, 9-HH); $\delta$C (100 MHz, CDCl$_3$) 22.7 (CH$_2$), 29.7 (CH$_2$), 55.2 (CH), 57.2 (CH), 59.2 (CH), 73.0 (CH), 74.3 (CH$_2$), 87.2 (C), 163.7 (C); m/z (Cl) 271.9825 (MH$^+$). C$_9$H$_{11}$NO$_2$ requires 271.9827, 270 (85%), 236 (87), 200 (100), 166 (64).
(3\textit{R},4\textit{R},7\textit{R},7\textit{a}S)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one (178).

\[
\begin{align*}
\text{(1R,2S)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene 177a} & \text{ (0.45 g, 1.5 mmol) was dissolved in } p\text{-xylene (10 mL) which was then de-gassed for 1 h. Powdered molecular sieves (4Å, activated) (0.10 g) and dichlorotris(triphenylphosphine)ruthenium(II) (0.070 g, 0.07 mmol) were then added and the reaction mixture was heated at 155 °C in a sealed tube for 2.0 h. The reaction mixture was then concentrated under vacuum and purified by column chromatography (elution with diethyl ether : petroleum ether, 4 : 1) to give (3\textit{a}R,4\textit{R},7\textit{R},7\textit{a}S)-3,3,4-trichloro-7-(methoxymethoxy)octahydroindol-2-one 178, as a brown oil (0.34 g, 75%). } \\
& \text{\(\nu_{\text{max}}/\text{cm}^{-1}\) (NaCl) 3256 (NH), 2953 (CH), 1741 (CO), 1440, 1036; [\alpha]_D^{25} -60.2 (c 0.5, CHCl}_3; } \\
& \text{\(\delta H\) (400 MHz, CDCl}_3) 1.50-1.66 (1H, m, 6-HH), 1.71-1.82 (1H, m, 6-HH), 1.89-1.96 (1H, m, 5-HH), 2.29-2.36 (1H, m, 5-HH), 3.19 (1H, dd, J 8.6, 5.3 Hz, 3a-H), 3.39 (3H, s, OCH}_3), \ \\
& 3.83-3.93 (2H, m, 4-H and 7-H), 4.23-4.27 (1H, m, 7a-H), 4.67 (1H, d, J 6.9 Hz, OCH}_3), \ \\
& 4.72 (1H, d, J 6.9 Hz, OCH}_3), 6.20 (1H, br s, NH); \text{\(\delta C\) (100 MHz, CDCl}_3) 24.5 (CH}_2), \ \\
& 32.7 (CH}_2), 54.0 (CH), 54.7 (CH), 55.0 (CH}_2), 59.0 (CH), 73.0 (CH), 84.4 (C), 94.4 (CH}_2), \ \\
& 167.7 (C); m/z (CI) 302.0115 (MH\textsuperscript{+}. C\textsubscript{10}H\textsubscript{15}NO\textsubscript{3}Cl\textsubscript{3} requires 302.0118), 268 (30%), 221 (18), 165 (50). }
\end{align*}
\]

(3\textit{a}R,7\textit{R},7\textit{a}S)-Octahydro[1,8]oxazole-indol-2-one (196).

\[
\begin{align*}
(3\textit{a}R,4\textit{R},7\textit{R},7\textit{a}S)-3,3,4-Trichloro-octahydro[1,8]oxazole-indol-2-one 195, (0.04 g, 0.3 mmol) was dissolved in THF (10 mL) which was then added to a slurry of activated Raney-Nickel (1.00 g). The reaction was heated under reflux for 24 h and then cooled, diluted with diethyl ether (10 mL) and filtered through a short silica plug. The plug was washed with diethyl ether (100 mL), then the washings were dried (MgSO}_4) and concentrated. Purification by flash column chromatography (elution with diethyl ether) gave
\end{align*}
\]
(3aR,7R,7aS)-octahydro[1,8]oxazole-indol-2-one 196, as a white solid (0.016 g, 61%).

$\nu_{\text{max}}$/$\text{cm}^{-1}$ (NaCl) 2940 (CH), 1708 (CO), 1390, 1223; [$\alpha$]$_{D}^{25}$ +71.5 (c 1.2, CHCl$_3$); $\delta$$_H$ (400 MHz, CDCl$_3$) 1.17-1.28 (2H, m, 5-H$_2$), 1.50-1.60 (3H, m, 4-HH and 6-H$_2$), 1.70-1.79 (1H, m, 4-HH), 2.00 (1H, dd, $J$ 16.3, 1.5 Hz, 3-HH), 2.42-2.50 (1H, m, 3a-H), 2.87 (1H, dd, $J$ 16.3, 7.7 Hz, 3-HH), 3.99-4.09 (2H, m, 7-H and 7a-H), 4.30 (1H, d, $J$ 5.4 Hz, 9-HH), 5.14 (1H, d, $J$ 5.4 Hz, 9-HH); $\delta$$_C$ (100 MHz, CDCl$_3$) 17.6 (CH$_2$), 24.9 (CH$_2$), 26.4 (CH$_2$), 32.5 (CH), 42.4 (CH$_2$), 60.0 (CH), 73.6 (CH), 75.1 (CH$_2$), 177.7 (C); m/z (EI) 167.0947 (M$^+$, C$_9$H$_{13}$NO$_2$ requires 167.0946), 139 (53%), 111 (35), 96 (100), 68 (38).

(3aR,7R,7aS)-7-(Methoxymethoxy)octahydroindol-2-one (197).

(3aR,4R,7R,7aS)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one 178 (0.05 g, 0.2 mmol) was dissolved in THF (10 mL) which was then added to a slurry of activated Raney-Nickel (1.00 g). The reaction was heated under reflux for 24 h and then a further portion of Raney-Nickel was added (1.00 g). The reaction mixture was heated for a further 24 h then cooled, diluted with diethyl ether (10 mL) and filtered through a short silica plug. The plug was washed with diethyl ether (100 mL), then the washings were dried (MgSO$_4$) and concentrated. Purification by column chromatography (elution with ethyl acetate) gave (3aR,7R,7aS)-7-(methoxymethoxy)octahydroindol-2-one 197, as a yellow oil (0.03 g, 85%).

$\nu_{\text{max}}$/$\text{cm}^{-1}$ (NaCl) 3423 (NH), 2935 (CH), 1686 (CO), 1448 and 1035; [$\alpha$]$_{D}^{25}$ +46.1 (c 0.8, CHCl$_3$); $\delta$$_H$ (400 MHz, CDCl$_3$) 1.18-1.29 (2H, m, 5-H$_2$), 1.41-1.52 (1H, m, 6-HH), 1.59-1.67 (1H, m, 6-HH), 1.69-1.83 (2H, m, 4-H$_2$), 2.00 (1H, d, $J$ 16.0, Hz, 3-HH), 2.32-2.41 (1H, m, 3a-H), 2.49 (1H, dd, $J$ 16.0, 6.6 Hz, 3-HH), 3.38 (3H, s, OCH$_3$), 3.67 (1H, dt, $J$ 11.5, 4.4 Hz, 7-H), 3.95 (1H, t, $J$ 4.4 Hz, 7a-H), 4.65 (1H, d, $J$ 6.9 Hz, OCHHO), 4.71 (1H, d, $J$ 6.9 Hz, OCHHO), 5.70 (1H, br s, NH); $\delta$$_C$ (100 MHz, CDCl$_3$) 21.9 (CH$_2$), 25.8 (CH$_2$), 27.1 (CH$_2$), 35.1 (CH), 39.6 (CH$_2$), 55.6 (CH$_3$), 56.6 (CH), 74.9 (CH), 94.9 (CH$_2$), 177.9 (C); m/z (Cl) 200.1288 (MH$^+$, C$_{10}$H$_{18}$NO$_3$ requires 200.1287), 168 (10%), 73 (10).
(3\(R\),7\(R\),7\(a\)\(S\))-7-(Methanesulfonyloxy)octahydroindol-2-one (179).

(3\(R\),7\(R\),7\(a\)\(S\))-7-(Methoxymethoxy)octahydroindol-2-one 197 (0.10 g, 0.5 mmol) was dissolved in methanol (2.0 mL) and 2 M hydrochloric acid (6.0 mL). The solution was heated to 40 °C and stirred vigorously for 14 h. The reaction was cooled and neutralised using a 6 M solution of potassium carbonate (3.0 mL). The aqueous solution was then extracted with ethyl acetate (6 x 25 mL), the combined organic layer was dried (MgSO\(_4\)) then concentrated in vacuo, to give the hydroxy product 204 as a white solid. This solid was dissolved in DCM (5.0 mL) then methanesulfonyl chloride (0.05 mL, 0.8 mmol), triethylamine (0.25 mL, 1.8 mmol) and 4-dimethylaminopyridine (DMAP, catalytic) were added. The reaction mixture was stirred at room temperature overnight then acidified to pH 2 (using 2 M HCl) and extracted with DCM (3 x 20 mL). The resulting organic layer was dried (MgSO\(_4\)) and concentrated to give the crude product, which was purified by flash column chromatography (eluting with ethyl acetate : methanol, 20 : 1) to give (3\(R\),7\(R\),7\(a\)\(S\))-7-(methanesulfonyloxy)octahydroindol-2-one 179, as a white solid (0.10 g, 88% yield over 2 steps). \(\nu_{\text{max}}/\text{cm}^{-1}\) (NaCl) 3397 (NH), 2945 (CH), 1664 (CO), 1424, 1340; \([\alpha]_D^{24}\) +68.0 (c 0.5, CHCl\(_3\)); \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.30-1.40 (2H, m, 5-H\(_2\)), 1.62-1.71 (1H, m, 4-HH), 1.77-1.93 (3H, m, 4-HH and 6-H\(_2\)), 2.05 (1H, d, \(J\) 14.0, Hz, 3-HH), 2.53-2.42 (2H, m, 3-HH and 3a-H), 3.09 (3H, s, SCH\(_3\)), 4.04 (1H, t, \(J\) 4.6 Hz, 7a-H), 4.84 (1H, dt, \(J\) 10.4, 4.6 Hz, 7-H), 6.20 (1H, br s, NH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 20.9 (CH\(_2\)), 26.3 (CH\(_2\)), 26.5 (CH\(_2\)), 35.0 (CH), 38.8 (CH\(_2\)), 38.9 (CH), 56.0 (CH), 79.4 (CH\(_3\)), 175.7 (C); \(m/z\) (CI) 234.0802 (MH\(^+\). C\(_9\)H\(_{16}\)NSO\(_4\) requires 234.0800), 198 (3%), 138 (6), 85 (2).
(3aR,7R,7aS)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one (206).

(3aR,7R,7aS)-7-(Methoxymethoxy)octahydroindol-2-one 197 (0.05 g, 0.3 mmol) was dissolved in THF (2.0 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil) (0.012 g, 0.3 mmol) was added and the solution was stirred for 5 minutes before piperonyl bromide 205,98 (0.097 g, 0.5 mmol) in THF (1.0 mL) was slowly added. Sodium iodide (0.070 g, 0.5 mmol) was then added and the reaction was heated to 50 °C for 2 h. The reaction mixture was cooled and then a saturated solution of ammonium chloride (2.0 mL) was added. The solution was extracted with ethyl acetate (3 x 20 mL), dried (MgSO₄) and concentrated in vacuo. Purification by flash column chromatography (elution with ethyl acetate) gave (3aR,7R,7aS)-1-(3,4-methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one 206, as a colourless oil (0.075 g, 90% yield). $\nu_{\text{max}}$/cm$^{-1}$ (NaCl) 2937 (CH), 1668 (CO), 1488, 1252; $[\alpha]_D^{25}$ -32.1 (c 1.0, CHCl₃); $\delta_H$(400 MHz, CDCl₃) 1.23-1.38 (2H, m, 5-H₂), 1.51-1.77 (3H, m, 4-H₂ and 6-HH), 1.82-1.90 (1H, m, 6-HH), 2.25 (1H, dd, J 14.6, 7.5 Hz, 3-HH), 2.32-2.41 (1H, m, 3a-H), 2.47 (1H, dd, J 14.6, 10.4 Hz, 3-HH), 3.30 (1H, dd, J 6.5, 3.9 Hz, 7-H), 3.35 (3H, s, OCH₃), 3.82 (1H, d, J 14.8 Hz, N-CH₂), 3.89-3.93 (1H, m, 7a-H), 4.48 (1H, d, J 7.0 Hz, OCHHO), 4.62 (1H, d, J 7.0 Hz, OCHHOO), 5.00 (1H, d, J 14.8 Hz, N-CH₂H), 5.94 (2H, s, OCH₂O), 6.71-6.76 (3H, m, Ph); $\delta_C$ (100 MHz, CDCl₃) 15.7 (CH₂), 25.8 (CH₂), 26.9 (CH₂), 32.6 (CH), 36.5 (CH₂), 43.8 (CH₂), 55.6 (CH₃), 56.2 (CH), 72.2 (CH), 95.3 (CH₂), 101.0 (CH₂), 108.1 (CH), 108.5 (CH), 121.3 (CH), 131.1 (C), 146.9 (C), 147.9 (C), 176.6 (C); m/z (CI) 334.1652 (MH⁺. C₁₈H₂₄NO₅ requires 334.1654), 302 (7%), 200 (6), 135 (15), 69 (16).
(3aR,7R,7aS)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one (207).

(3aR,7R,7aS)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one 206 (0.20 g, 0.6 mmol) was dissolved in methanol (5.0 mL) and 2 M hydrochloric acid solution (5.0 mL). The reaction mixture was heated to 35 °C for 48 h, then cooled and neutralised with a 6 M solution of potassium carbonate (10.0 mL). The solution was extracted with ethyl acetate (4 x 50 mL), the organic layer was then dried (MgSO₄) and concentrated to give (3aR,7R,7aS)-1-(3,4-methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one 207 as a white solid (0.173 g, 100%).

νmax/cm⁻¹ (NaCl) 3370 (OH), 2934 (CH), 1663 (CO), 1489, 1442, 1243; [α]D²⁵ -22.6 (c 1.4, CHCl₃); δH (400 MHz, CDCl₃) 1.25-1.39 (2H, m, 5-H₂), 1.51-1.61 (1H, m, 4-HH), 1.67-1.87 (3H, m, 4-HH and 6-H₂), 1.95 (1H, br s, OH), 2.23 (1H, dd, J 15.0, 7.8 Hz, 3-HH), 2.36-2.45 (1H, m, 3a-H), 2.51 (1H, dd, J 15.0, 11.3 Hz, 3-HH), 3.28 (1H, dd, J 7.0, 3.8 Hz, 7-H), 3.95-4.00 (1H, m, 7a-H), 4.17 (1H, d, J 14.8 Hz, N-CH₂), 4.71 (1H, d, J 14.8 Hz, N-CHH), 5.95 (2H, s, OCH₂O), 6.75-6.82 (3H, m, Ph); δC (100 MHz, CDCl₃) 14.6 (CH₂), 25.8 (CH₂), 29.4 (CH₂), 32.4 (CH), 36.4 (CH₂), 44.9 (CH₂), 60.1 (CH), 65.8 (CH), 101.1 (CH₂), 108.4 (CH), 108.5 (CH), 121.4 (CH), 131.3 (C), 147.1 (C), 148.1 (C), 176.8 (C); m/z (CI) 290.1391 (MH⁺. C₁₆H₂₀NO₄ requires 290.1392), 289 (12%), 85 (52), 51 (55), 49 (75).
(3aR,7R,7aS)-1-(3,4-Methylenedioxybenzyl)-7-((methanesulfonyloxy)octahydroindol-2-one (209).

(3aR,7R,7aS)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one 207 (0.10 g, 0.4 mmol) was dissolved in DCM (3.0 mL). Methanesulfonyl chloride (0.04 mL, 0.5 mmol), triethylamine (0.17 mL, 1.2 mmol) and 4-dimethylaminopyridine (DMAP, catalytic) were added and the solution was heated to 35 °C for 48 h. The reaction mixture was then acidified to pH 2 (using 2 M HCl) and extracted with DCM (3 x 10 mL). The resulting organic layer was dried (MgSO₄) and concentrated to give the crude product, which was purified by flash column chromatography (eluting with ethyl acetate : petroleum ether, 3 : 2) to give (3aR,7R,7aS)-1-(3,4-methylenedioxybenzyl)-7-(methanesulfonyloxy)octahydroindol-2-one 209, as a white solid (0.09 g, 73%). υ_max/cm⁻¹ (NaCl) 2940 (CH), 1687 (CO), 1490, 1443, 1334; [α]_D²⁵ -19.3 (c 1.4, CHCl₃); δ_H (400 MHz, CDCl₃) 1.42-1.52 (2H, m, 5-H₂), 1.59-1.66 (2H, m, 4-H₂), 1.70-1.79 (2H, m, 6-H₂), 2.11-2.20 (1H, m, 3-HH), 2.32-2.37 (1H, m, 3a-H), 2.43-2.51 (1H, m, 3-HH), 3.01 (3H, s, SCH₃), 3.36 (1H, dd, J 6.9, 3.9 Hz, 7-H), 3.84 (1H, d, J 14.9 Hz, N-CHHH), 5.06 (1H, d, J 14.9 Hz, N-CHHH), 5.14-5.18 (1H, m, 7a-H), 5.95 (2H, s, OCH₂O), 6.72-6.76 (3H, m, Ph); δ_C (100 MHz, CDCl₃) 14.9 (CH₂), 25.1 (CH₂), 28.3 (CH₂), 32.0 (CH), 35.8 (CH₂) 39.2 (CH), 43.9 (CH₂), 57.0 (CH), 75.6 (CH₃), 101.1 (CH₂), 108.3 (CH), 108.4 (CH), 121.5 (CH), 130.1 (C), 147.2 (C), 148.1 (C), 175.7 (C); m/z (Cl) 368.1173 (MH⁺. C₁₇H₂₂NSO₆ requires 368.1168), 335 (12%), 290 (30), 272 (36), 150 (84), 136 (100).
4.0 References

37. [www.sigmaaldrich.com](http://www.sigmaaldrich.com).
60. T. Ogawa, Y. Oka and K. Sasaoka, Phytochemistry, 1984, 23, 3749.
64. C. Cativiela, M. D. Día-de-Villegas, J. Gálvez and J. García, Tetrahedron, 1996, 52, 9563.


