Investigation of Metal Mediated Reactions for Natural Product Synthesis

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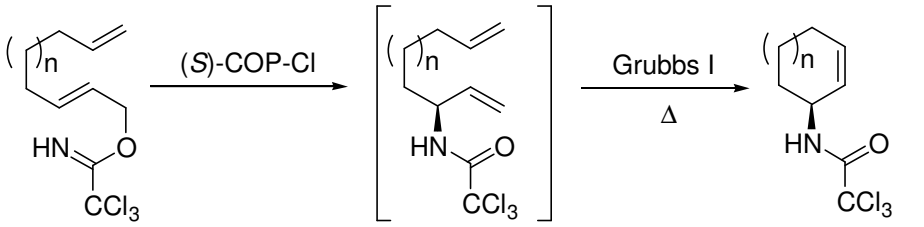
Abstract

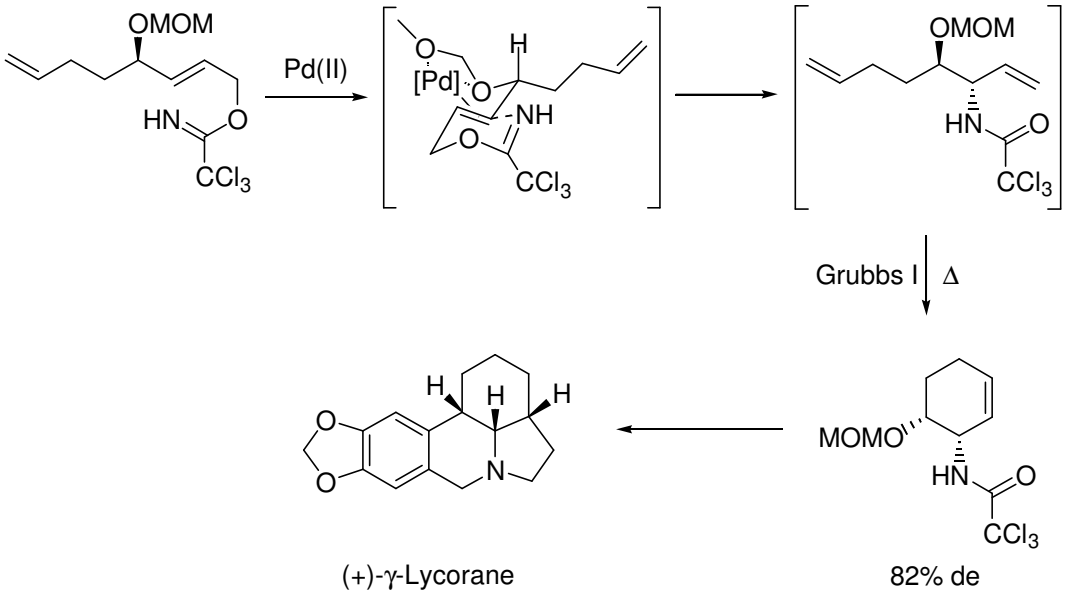
During the course of the studies outlined in this thesis, an ether-directed Pd(II)-catalysed aza-Claisen rearrangement reaction that had previously been developed by the Sutherland group was expanded to include more functionalised rearrangement substrates. This methodology has been applied for the synthesis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



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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.

M. D. Swift and A. Sutherland, *Org. Biomol. Chem.*, 2006, **4**, 3889.

M. D. Swift and A. Sutherland, *Tetrahedron. Lett*., 2007, **48**, 3771.

M. D. Swift and A. Sutherland, *Org. Lett*., 2007, **9**, 5239.

M. D. Swift and A. Sutherland, *Tetrahedron.*, 2008, **64**, 9521.

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	cobaltocenyloxazoline palladacycle
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
^oC	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

MeOH	methanol
M	Molar
MOM	Methoxymethyl
Me	Methyl
mg	milligram(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
Ms	methanesulfonyl
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
Pd/C	Palladium on carbon
PMB	*para*-methoxybenzoic acid
PrOH	propanol
P	protecting group
ppm	parts per million
PS	Proton Sponge
Py	pyridine
^{1}H	proton
q	quartet
quin	quintet
RCM	Ring Closing Metathesis
RT	Room Temperature
sept	septet
sex	sextet
s	singlet
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBAF	*tetra*-*n*-butylammonium fluoride
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
t	triplet
Ts	tosyl

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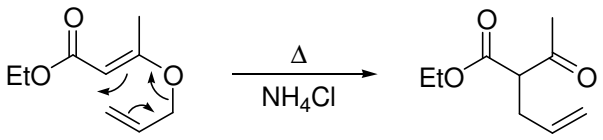
1.0 Introduction

1.1 Aza-Claisen Rearrangements

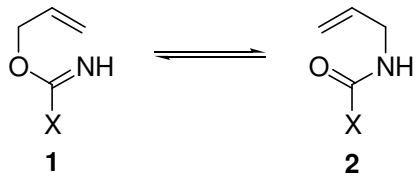
Synthetic organic chemists in the 21st century have a hugely diverse range of reaction methodologies and synthetic approaches at their disposal. In recent years, chemists have turned their attention to reactions that have greater atom efficiency, enhanced stereoselectivity and those that require less 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]



Scheme 1 - The first aliphatic Claisen rearrangement

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.



1 **2**

X= H, Ar, CCl_3, CF_3

Scheme 2 - Aza-Claisen rearrangement

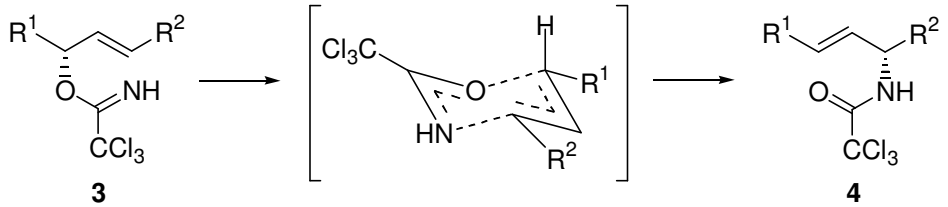
The aza-Claisen rearrangement was first reported by Mumm and Möller in 1937 who reported the rearrangement of an allylic benzimidate to the corresponding benzamide.[4]

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).[5] 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.[6]

1.1.1 Thermal Overman Rearrangement

Overman reported both the thermal and metal catalysed aza-Claisen rearrangement of allylic trichloroacetimidates.[5,7] The thermal reaction typically occurs at elevated temperatures of approximately 140 ^{o}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 $(4q+2)_s$ and $(4r)_a$ components must be odd.[8] The thermal aza-Claisen rearrangement has 3 components (one σ-bond and two π-bonds), although only the alkene $_{\pi}2_s$ component is counted. As such the rearrangement has one $(4q+2)_s$ component and no $(4r)_a$ 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.[9] 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 σ-bond breaks, thus making the reaction extremely useful in organic synthesis (Scheme 3).



Scheme 3 - Thermal rearrangement of allylic trichloroacetimidates

The thermal process has been shown to obey first order kinetics,[7] whilst the rate of reaction is also affected by both steric and electronic effects of the substrate, thus leading to large

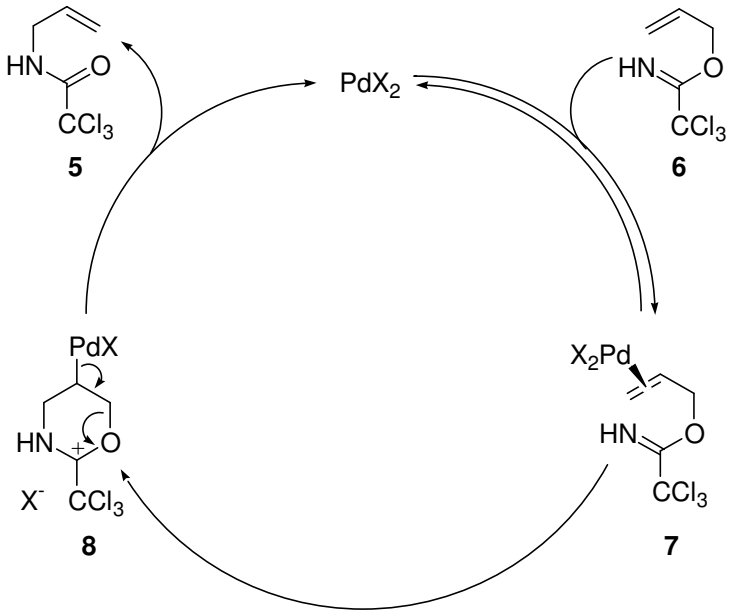
variations in reactivity between different substrates.[6] In particular, *E*-imidates usually react more rapidly than *Z*-imidates due to the fact that they are less stable.

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}.[10,11] As such, this process is effectively irreversible.

1.1.2 Metal catalysed aza-Claisen rearrangement

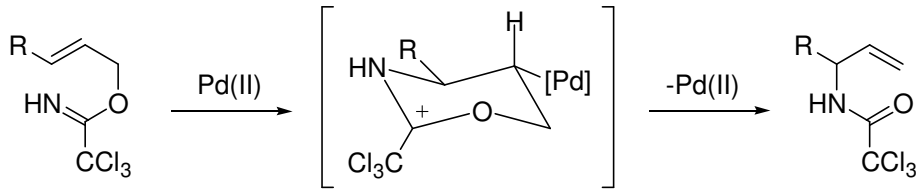
Initially Overman reported the metal catalysed aza-Claisen rearrangement, using mercury(II) salts,[5,7] however it has subsequently been shown that a variety of transition metals (including Pd, Au and Pt) can catalyse the rearrangement process.[3,12-14] The metal catalysed aza-Claisen rearrangement has been shown to increase the reaction rate very significantly (by approximately the order of 10^{12}).[5] 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.[15,16] 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).[9,16-18] This mechanism proceeds *via* a stepwise pathway where the alkene of the imidate substrate **6** is subjected to carbo-palladation **7**, thus activating the olefin to antarafacial nucleophilic attack from the imidate nitrogen. This leads to the formation of the cyclic carbocation intermediate **8**, which then rapidly undergoes Grob-like fragmentation to give the amide product **5**,[6,16,19] 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.



Scheme 4 - Mechanism of Pd(II)-catalysed Overman rearrangement

The above mechanism is similar to that previously proposed by Henry for the rearrangement of allylic esters.[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).[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.

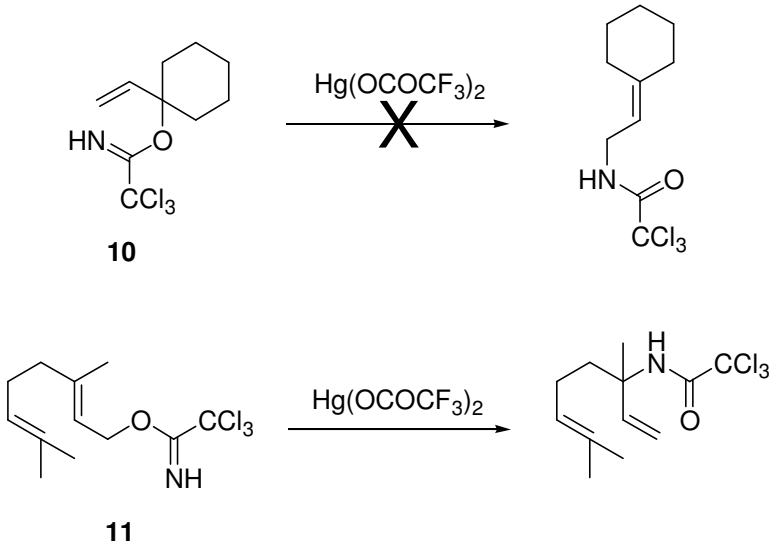


9

Scheme 5 - Proposed chair-like transition state

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).[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.[22]



Scheme 6 - Scope of metal catalysed rearrangement

1.2 Enantioselective aza-Claisen Rearrangement

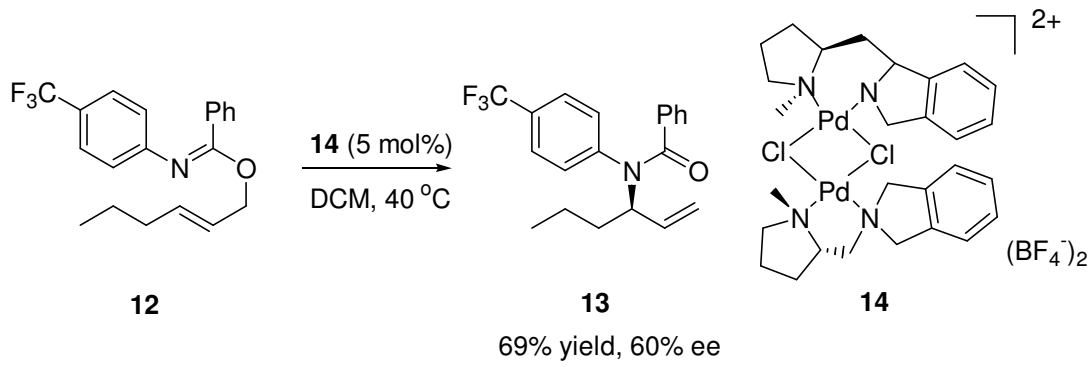
Following the development of a metal catalysed rearrangement process, recent efforts have turned to developing an enantioselective variant of the aza-Claisen rearrangement for use in asymmetric synthesis. Early applications of the aza-Claisen rearrangement as a key synthetic step were either non-enantioselective,[23] or made use of a chiral secondary imidate to introduce stereoselectivity *via* chirality transfer.[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.

1.2.1 Diamine catalysts

Overman developed the first chiral catalyst for the aza-Claisen rearrangement in 1997.[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).

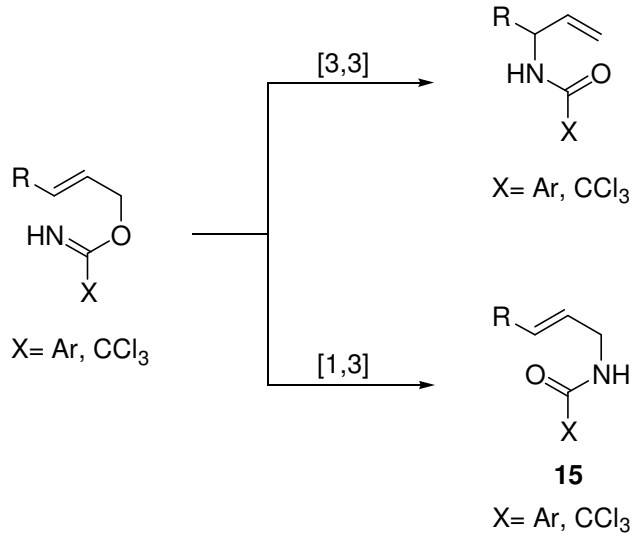


12 **13** **14**

69% yield, 60% ee

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= CCl_3, CF_3) 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]

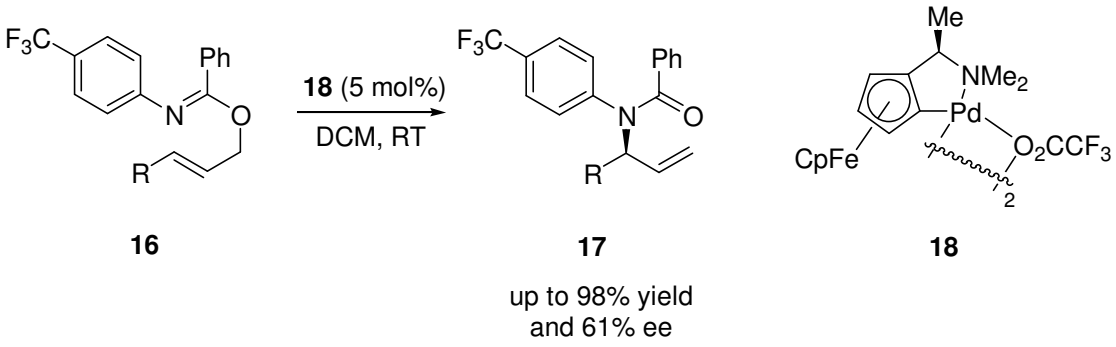


Scheme 8 - [3,3]- and [1,3]- rearrangement pathways

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.



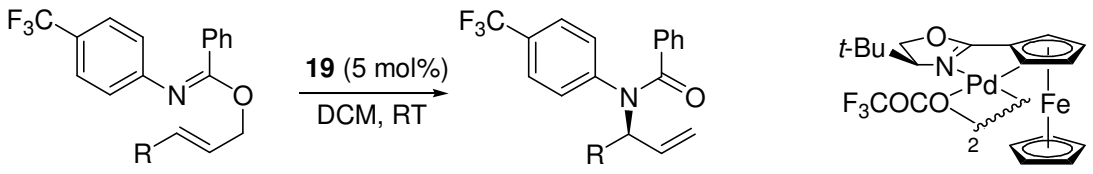
16 **17** **18**

up to 98% yield
and 61% ee

Scheme 9 - Neutral chiral ferrocenyl palladacycle catalysts

1.2.3 Ferrocenyl oxazoline (FOP) catalysts

Significant enhancements of the enantioselectivity of the aza-Claisen rearrangement were reported by Donde and Overman,[29] 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.

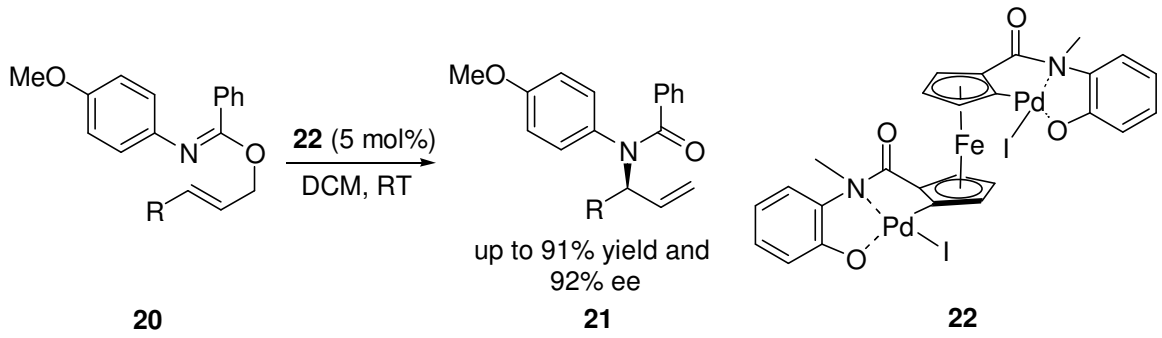


16 **17** **19**

E-imidates: up to 79% ee
Z-imidates: up to 92% ee

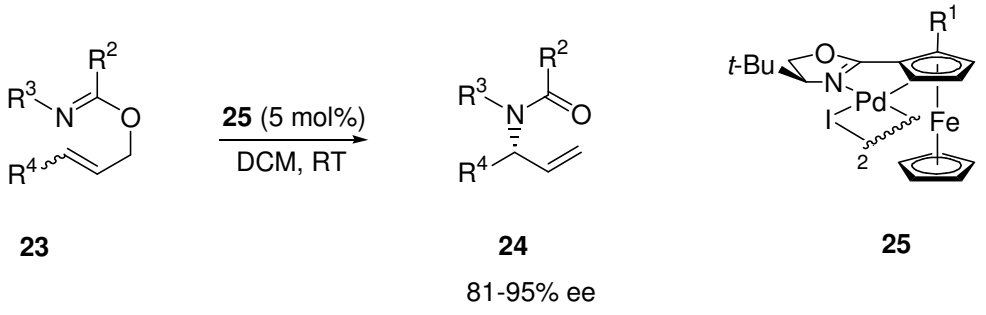
Scheme 10 - Rearrangement using ferrocenyl oxazoline catalysts

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).[30] Once again the catalyst was limited in scope to benzimidate substrates **20**.



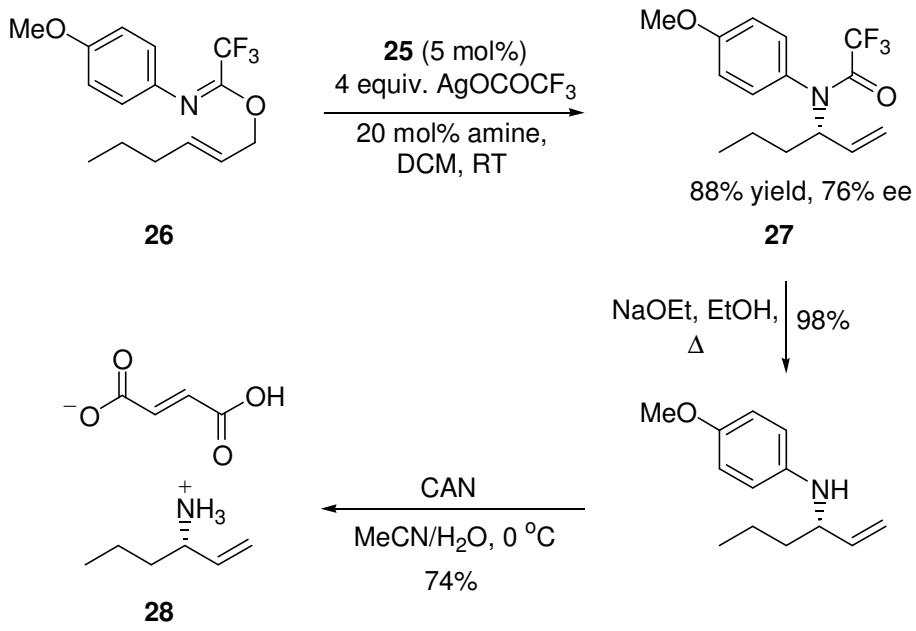
Scheme 11 - Neutral ferrocenyl catalysts for the rearrangement developed by Kang

In 2005, Overman and co-workers reported a comprehensive evaluation of the FOP catalyst scaffold.[31] 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

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** (CF_3 at position R^2), with a variety of aryl protecting groups at R^3. 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).



Scheme 13 - Conversion of amide to allylic amine

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 $AgOCOCF_3$ 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. CF_3). 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 CF_3 and CCl_3 amides), whilst retaining excellent enantioselectivity.

1.2.4 Cobalt Oxazoline Palladcycle (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,[32] but the first use of this complex as a catalyst for the aza-Claisen rearrangement was reported by Kang and co-workers,[33] who reported the rearrangement of allylic benzimidates using a $AgOCOCF_3$ 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.

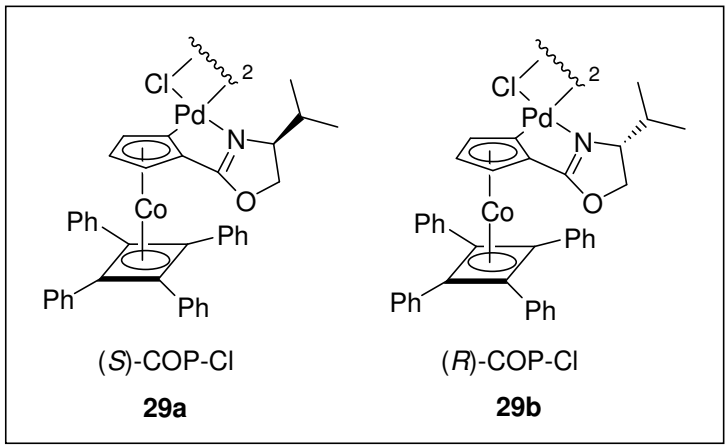
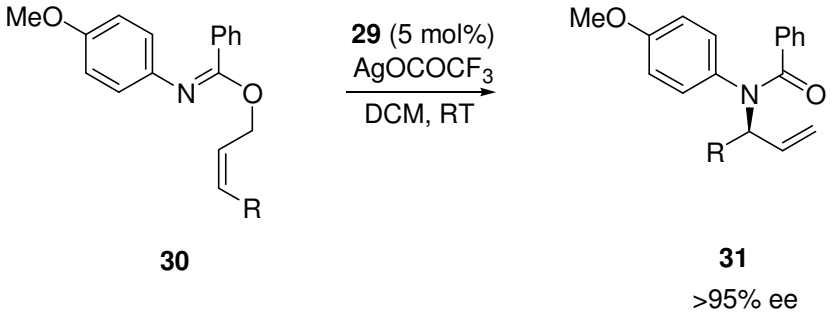
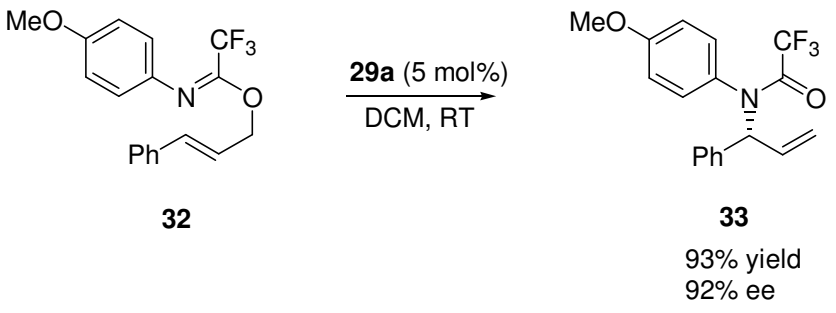


Figure 1 - COP-Cl catalyst complexes



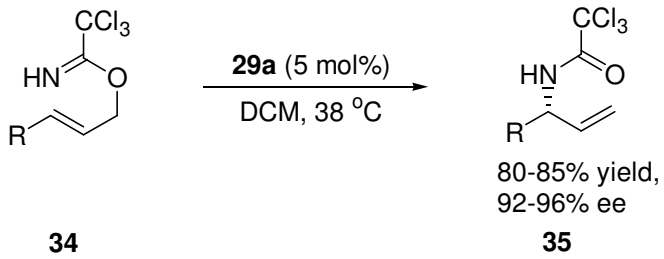
Scheme 14 - Rearrangement of *Z*-benzimidates with an activated COP catalyst

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).[34] 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,[33] 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.



Scheme 15 - Rearrangement of *E*-imidates with COP catalyst

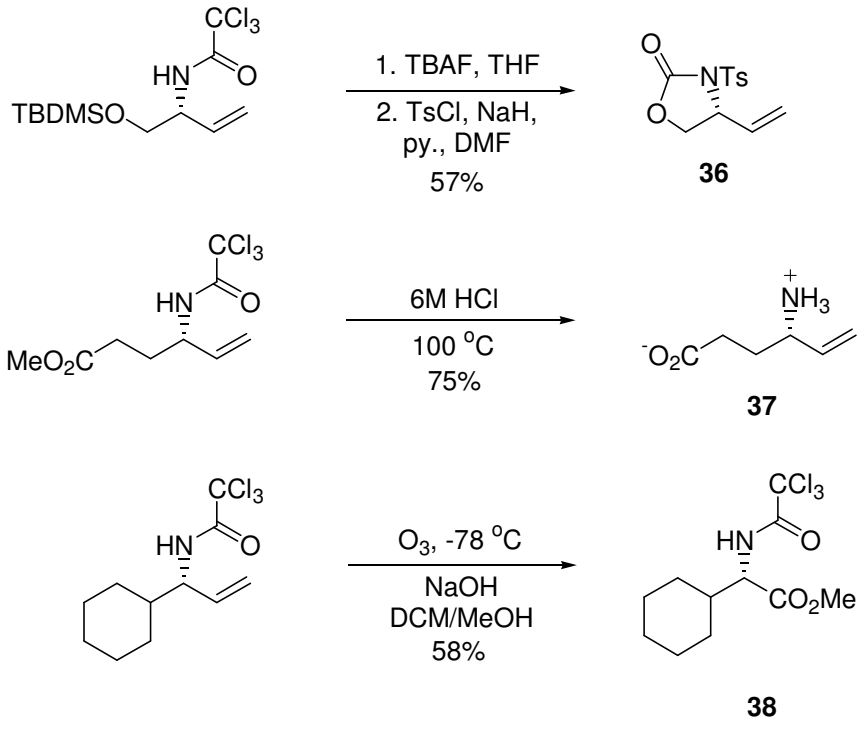
Further improvements to this approach were reported by Anderson and Overman,[35] who demonstrated that COP-Cl could also catalyse the rearrangement of *E*-allylic trichloroacetimidates **34**, to the trichloroacetamides **35**, in excellent yield and enantioselectivity (Scheme 16). These allylic trichloroacetimidates **34** are the preferred substrates for the aza-Claisen rearrangement because they are readily synthesised from the corresponding allylic alcohols in high yields.



34 **35**

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 α-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.

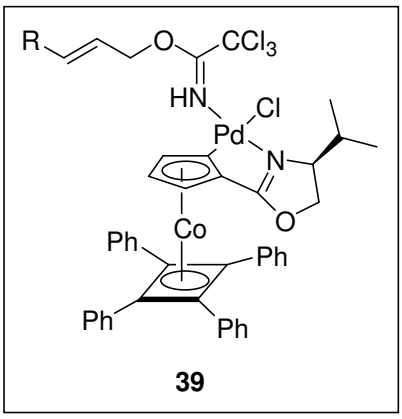


Figure 2 - COP-Cl-imidate complex as observed by Overman

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).[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 **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.

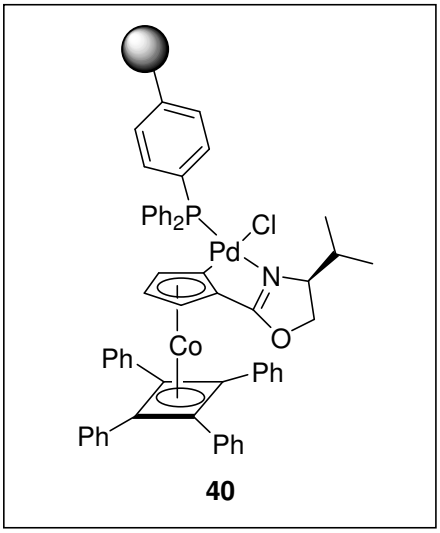


Figure 3 - Polymer supported COP-Cl catalyst

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) **41** (Figure 4) are excellent chiral catalysts for the aza-Claisen rearrangement of *N-para*-methoxyphenyl trifluoroacetimidates such as **42**.[40]

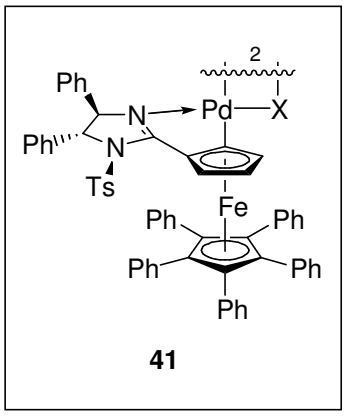
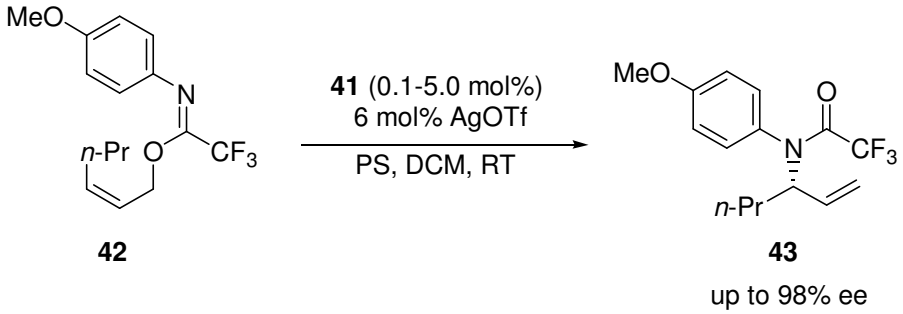


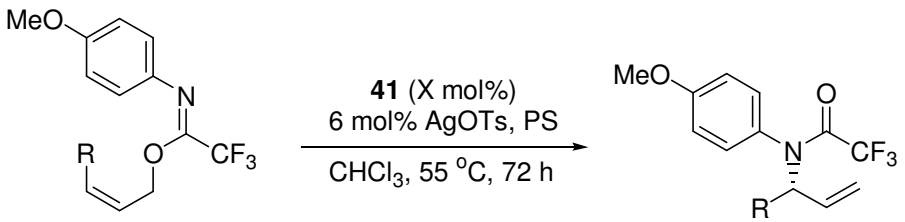
Figure 4 - Peters' FIP catalyst

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.[34] 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 **43**, 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.



Scheme 18 - Rearrangement using activated FIP catalyst

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 **44**.[41] As a result, the catalyst could be used to prepare several highly enantiopure allylic amines **45**, which are useful building blocks for organic synthesis (Table 1).



44 **45**

R	Catalyst Loading (mol%)	yield	ee
$(CH_2)_2CO_2Me$	0.5	98%	98%
$(CH_2)_2C(=O)Me$	0.5	97%	97%
$(CH_2)_3OBn$	0.2	100%	97%
$(CH_2)_3N(Bn)Boc$	0.2	99%	98%
CH_2OTBS	0.05	94%	97%
CH_2OTHP	0.2	94%	98%
CH_2OBn	0.2	99%	96%

Table 1 - Asymmetric synthesis of functionalised allylic amines

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.

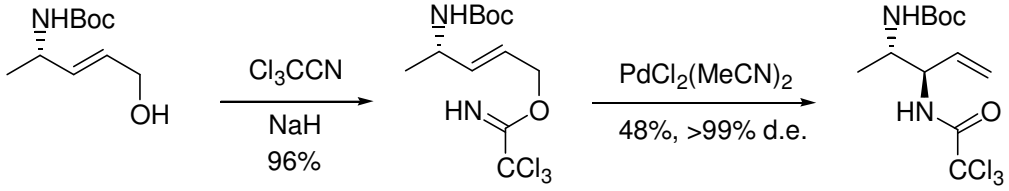
1.2.6 Conclusions to chiral catalysts

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.

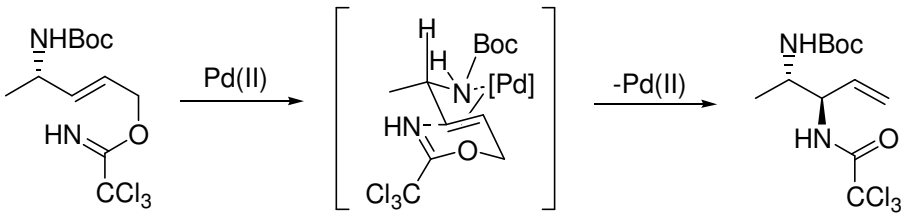
The first example of a substrate directed aza-Claisen rearrangement was reported by Bellûs, for the synthesis of diamines.[42] Bellûs synthesised allylic alcohol **46** containing a chiral Boc protected nitrogen. This nitrogen directing group was then used successfully for the palladium(II)-catalysed rearrangement of **47** to give the *anti*-diastereomer **48** with excellent diastereoselectivity, although yields were fairly modest (Scheme 19).



46 **47** **48**

Scheme 19 - The first substrate directed rearrangement

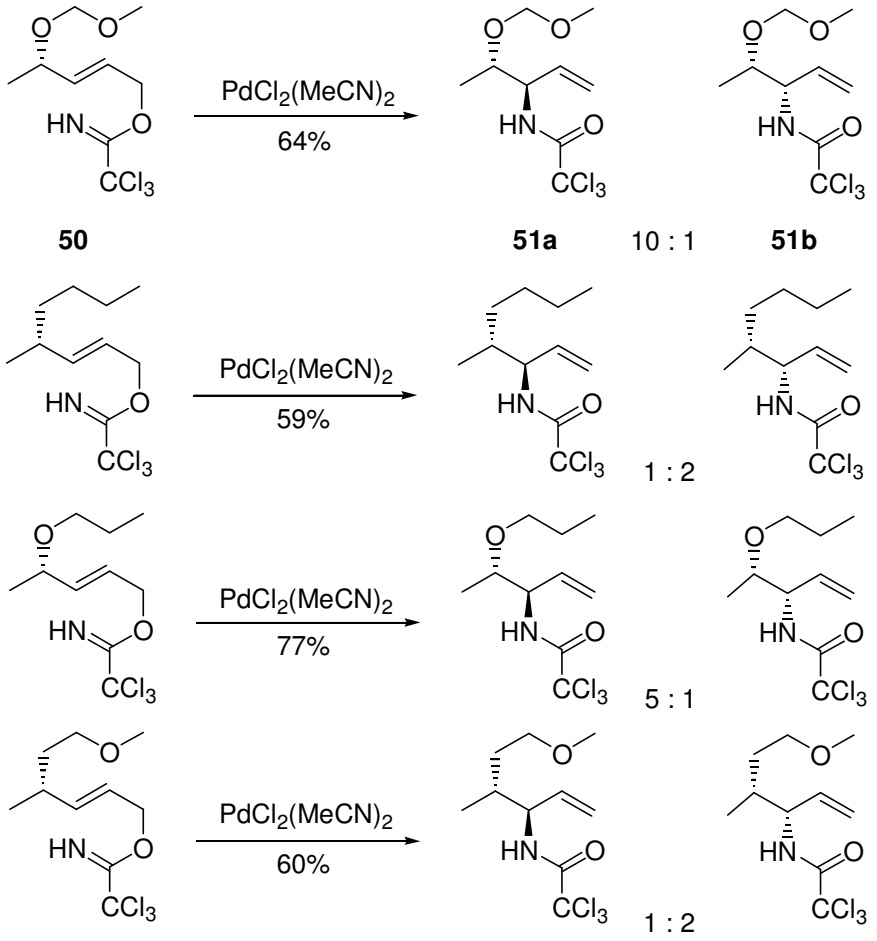
It was postulated that the significant anti-diastereoselectivity of this process was the result of rearrangement *via* a chair-like transition state **49**, with coordination of the palladium catalyst to both the amine nitrogen atom and double bond forcing the nitrogen of the trichloroacetimidate to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



47 **49** **48**

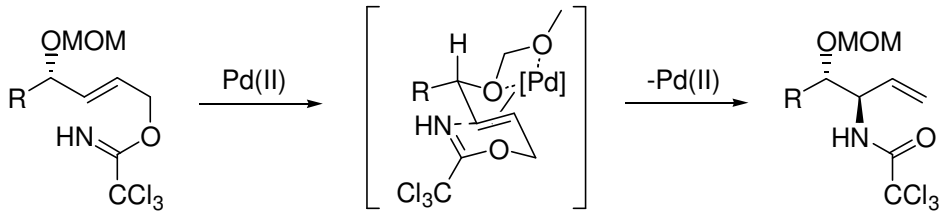
Scheme 20 - Coordination of nitrogen to Pd(II) directs the rearrangement

Work by Jamieson and Sutherland has demonstrated that ether directing groups can be employed in the substrate directed aza-Claisen rearrangement of allylic trichloroacetimidates.[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.[43,44]



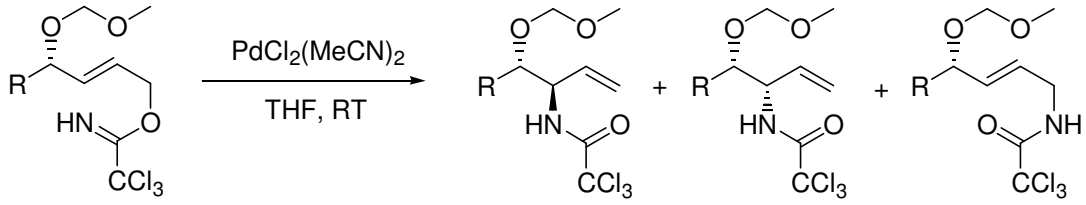
Scheme 21 - MOM ether-directed rearrangement

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).



Scheme 22 - Coordination of oxygen atoms to palladium

Sutherland and co-workers then expanded upon this work with the synthesis of several MOM protected trichloroacetimidates **52**, with a variety of side-chains.[45] 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.[9] 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).



52 **53a** **53b** **53c**

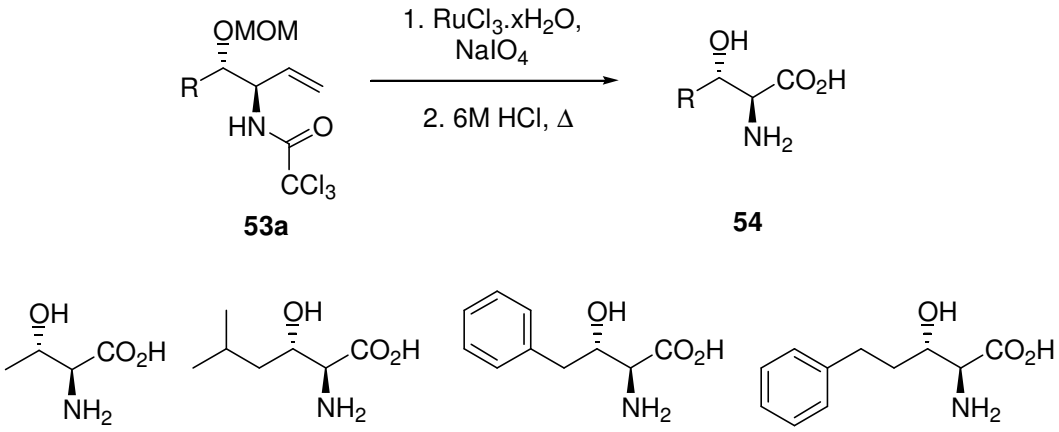
Entry	R	Additive	Yield[a] (%)	Ratio (**a** : **b** : **c**)
1	^{i}Bu	---	60	14 : 1 : 1
2	$PhCH_2$	---	54	12 : 1 : 0
3	$PhCH_2CH_2$	---	65	9 : 1 : 4
4	^{i}Bu	*p*-benzoquinone	73	14 : 1 : 0
5	$PhCH_2$	*p*-benzoquinone	70	12 : 1 : 0
6	$PhCH_2CH_2$	*p*-benzoquinone	69	9 : 1 : 0

[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

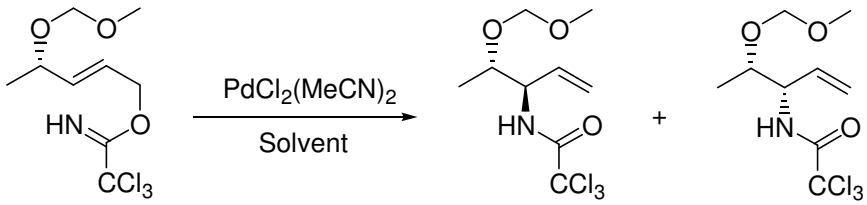
first reported by Sharpless;[46] hydrolysis of the protecting groups under acidic conditions then gave the target amino acid products (Scheme 23).



53a **54**

Scheme 23 - β-Hydroxy-α-amino acids

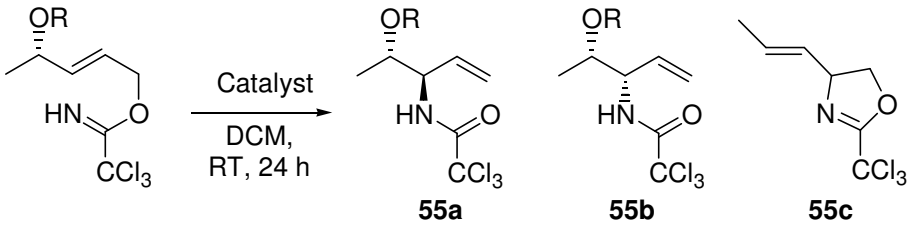
Further work by the Sutherland group using a catalyst screen to study the rearrangement, showed that a variety of transition metal complexes including: Pd(II), Pt(II) and Au(III) could be successfully employed with high diastereoselectivity as catalysts for the ether-directed aza-Claisen rearrangement. Although no catalyst was seen to exceed the capabilities that had previously been observed with $PdCl_2(MeCN)_2$, 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).[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.



Solvent	Reaction time/h	yield	Ratio (**a** : **b**)
THF	24	64%	10 : 1
Et_2O	24	47%	12 : 1
MeCN	24	32%	9 : 1
CH_2Cl_2	24	49%	12 : 1
Toluene	24	56%	15 : 1
$(BMI)BF_4$	148	37%	5 : 1

Table 3 - The effect of solvent upon MOM ether directing effect

More recently, Jaunzeme and Jirgensons have reported a comparative study of metal catalysts for the ether-directed aza-Claisen rearrangement (Table 3).[48] 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.



55a **55b** **55c**

Catalyst	R	yield (**a**+**b**)	Ratio (**a** : **b**)	Ratio (**a**+**b** : **c**)
$PtCl_2$	Me	65%	11 : 1	3 : 1
$PtCl_4$		35%	10 : 1	2 : 1
AuCl		48%	5 : 1	1 : 1
$AuCl_3$		41%	5 : 1	1 : 1
$PdCl_2$		50%	8 : 1	2 : 1
$PtCl_2$	TBDMS	85%	6 : 1	8 : 1
$PtCl_4$		50%	6 : 1	10 : 1
AuCl		70%	2 : 1	5 : 1
$AuCl_3$		40%	2 : 1	5 : 1
$PdCl_2$		62%	2 : 1	n.d.

Table 4 - Ether-directed rearrangement by Jaunzeme and Jirgensons

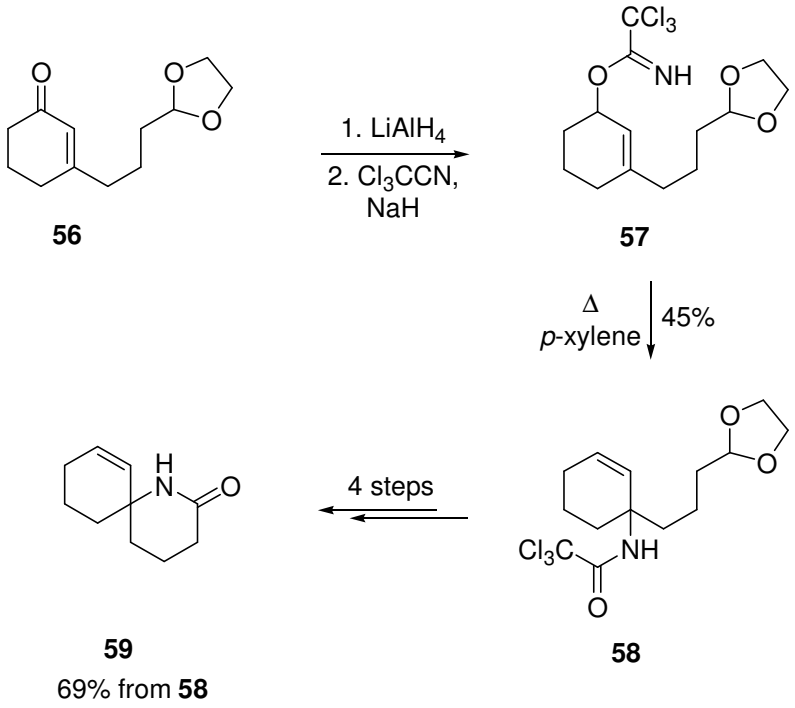
1.3.1 Conclusions to substrate directed rearrangement

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

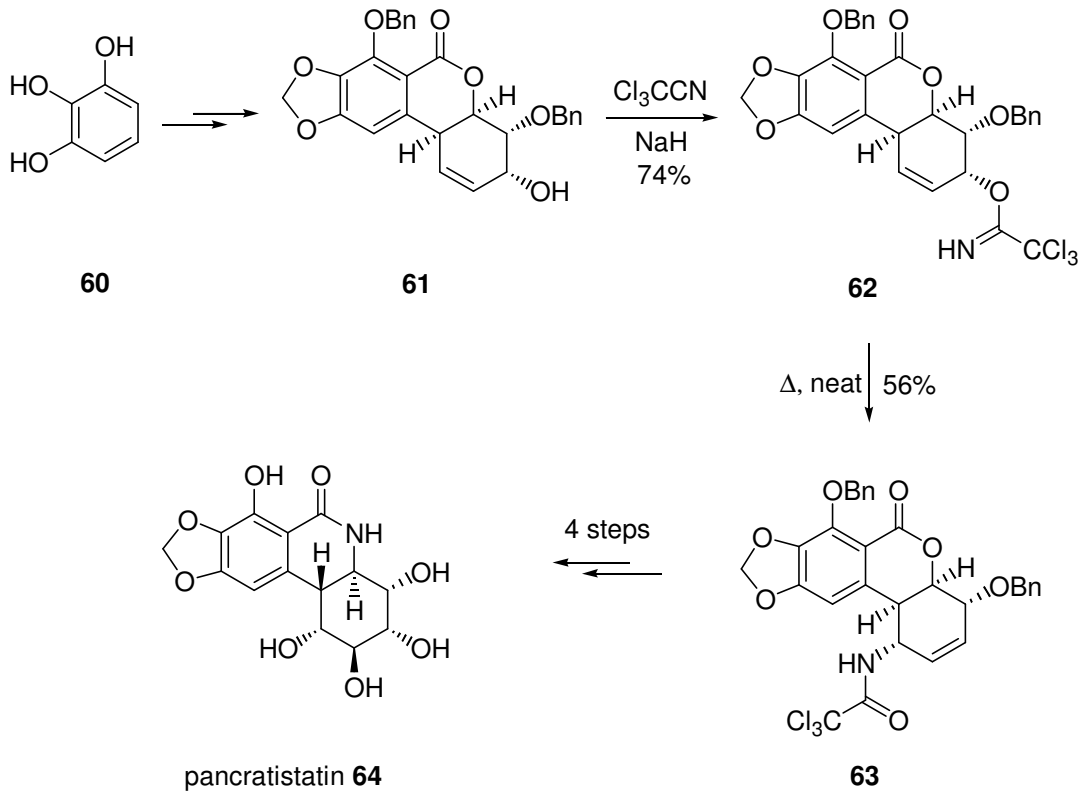
Aza-Claisen rearrangements have found widespread application in the synthesis of natural products since Overman first reported the rearrangement of allylic trichloroacetimidates to the corresponding amides in 1974.[5] As highlighted previously, the reason why this reaction is so widely employed in organic 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.



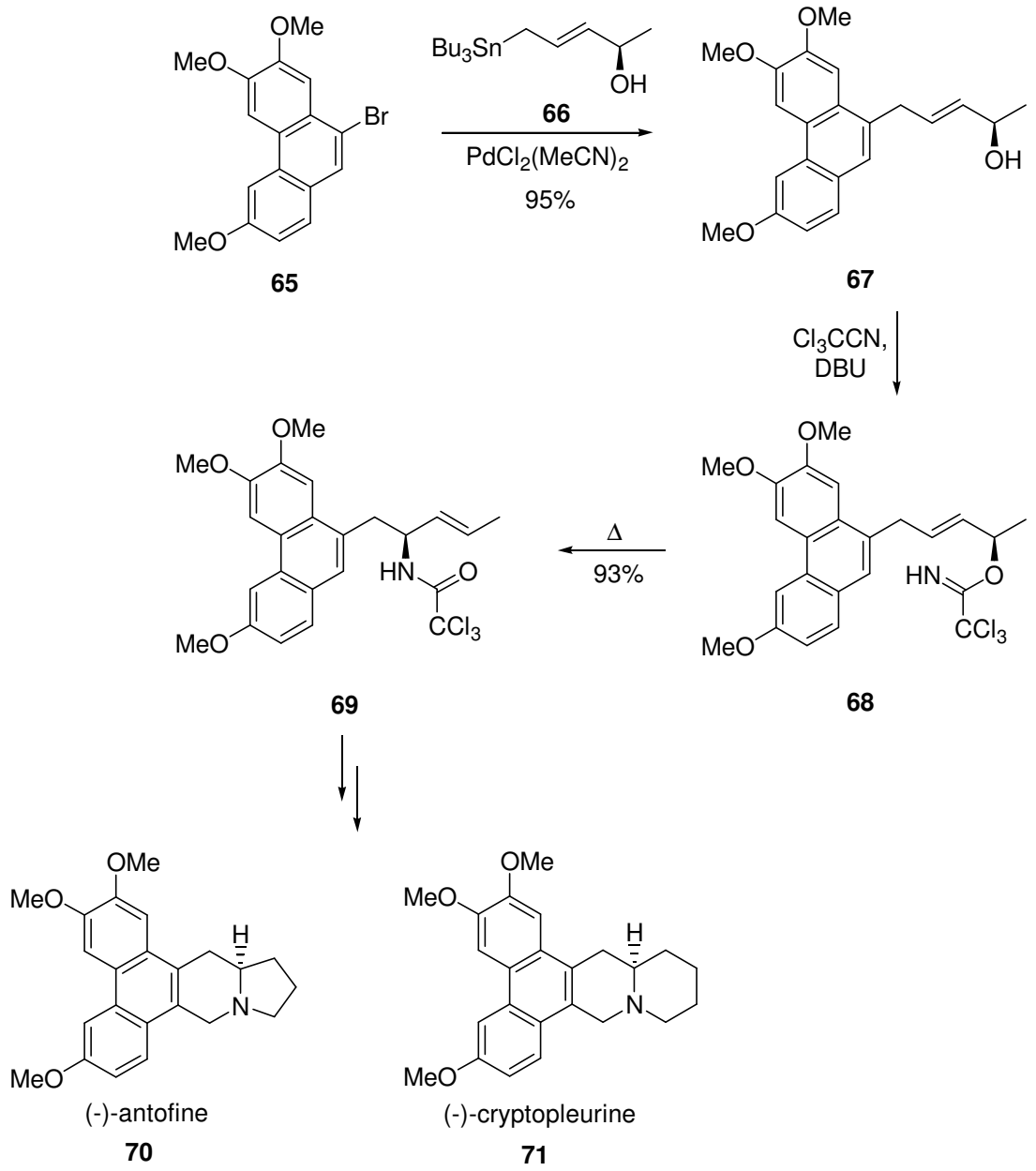
Scheme 24 - Overman synthesis of 1-azaspiro[5.5]undec-7-en-2-one

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.



Scheme 25 - Danishefsky's synthesis of (±)-pancratistatin

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).[52] These alkaloids are known for their potent cytoxicity 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**.



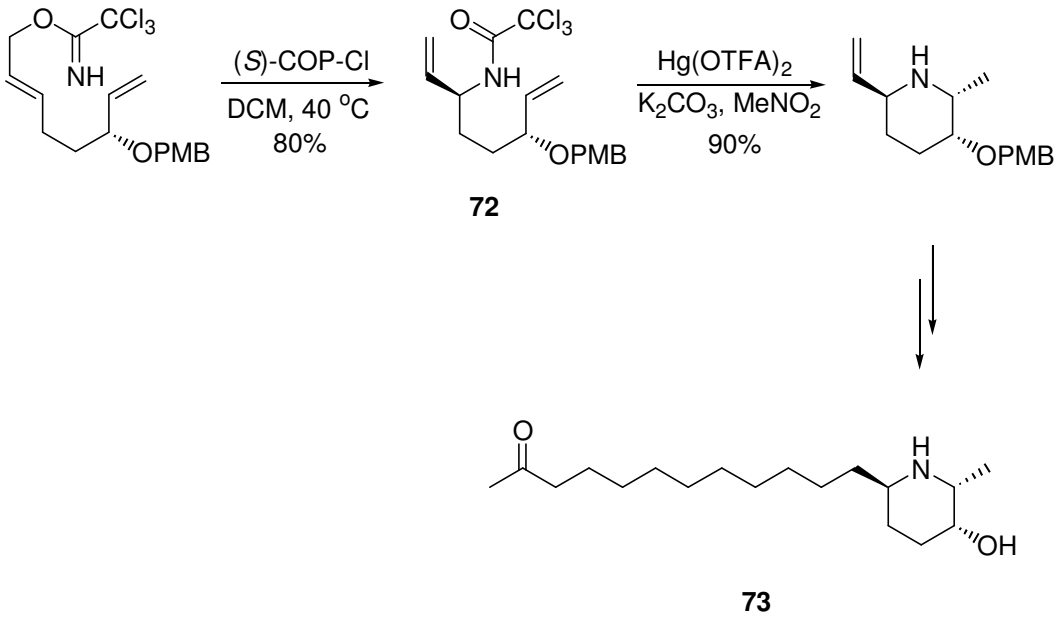
Scheme 26 - Synthesis of (-)-antofine and (-)-cryptopleurine *via* Overman rearrangement

The above examples make use of chirality transfer to introduce the correct relative stereochemistry in the new C-N σ-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).[31] 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.

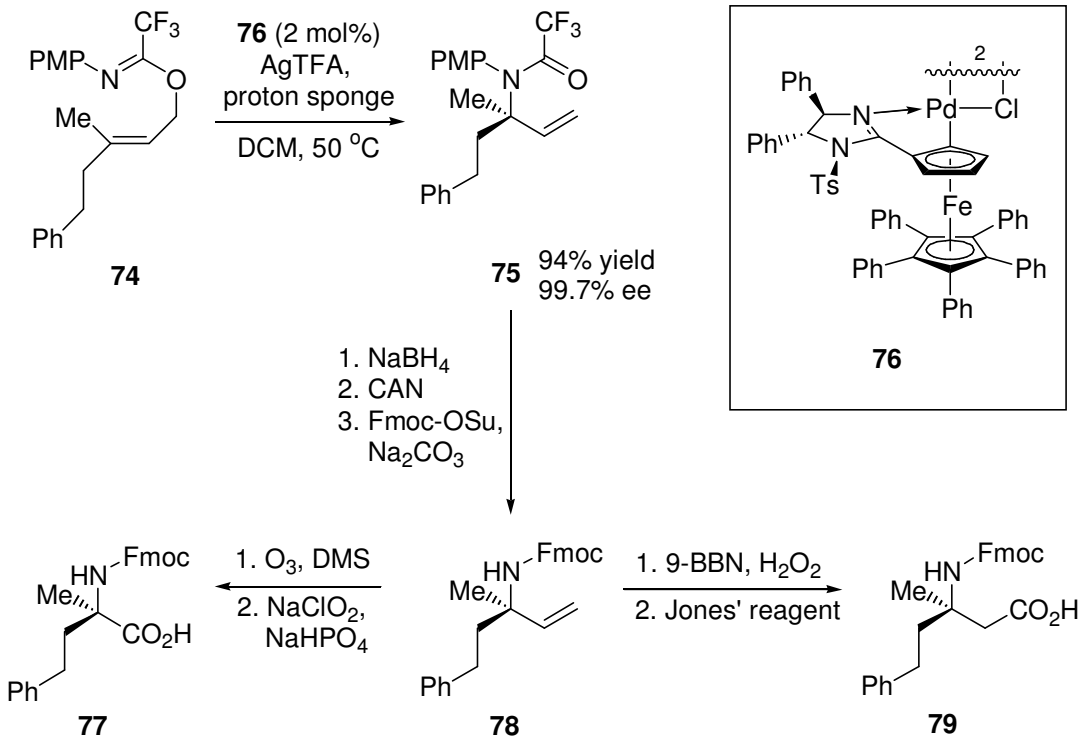
One example of the application of chiral catalysts to natural products has been recently reported by Han and co-workers in their synthesis of (+)-*iso*-6-cassine **73**.[53] The target compound has three stereocentres and the first was introduced *via* enzymatic resolution. An (*S*)-COP-Cl catalysed asymmetric aza-Claisen rearrangement was then used to establish the second stereocentre. The trichloroacetamide product **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 **73** (Scheme 27).



Scheme 27 - Synthesis of (+)-*iso*-6-cassine by Han and co-workers

Peters and co-workers have demonstrated the application of their highly enantioselective FIP catalysts **76** to the synthesis of several interesting organic compounds (Scheme 28).[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 **75** synthesised from imidate **74**, were converted to a number of secondary allylic amines **78**, which could then

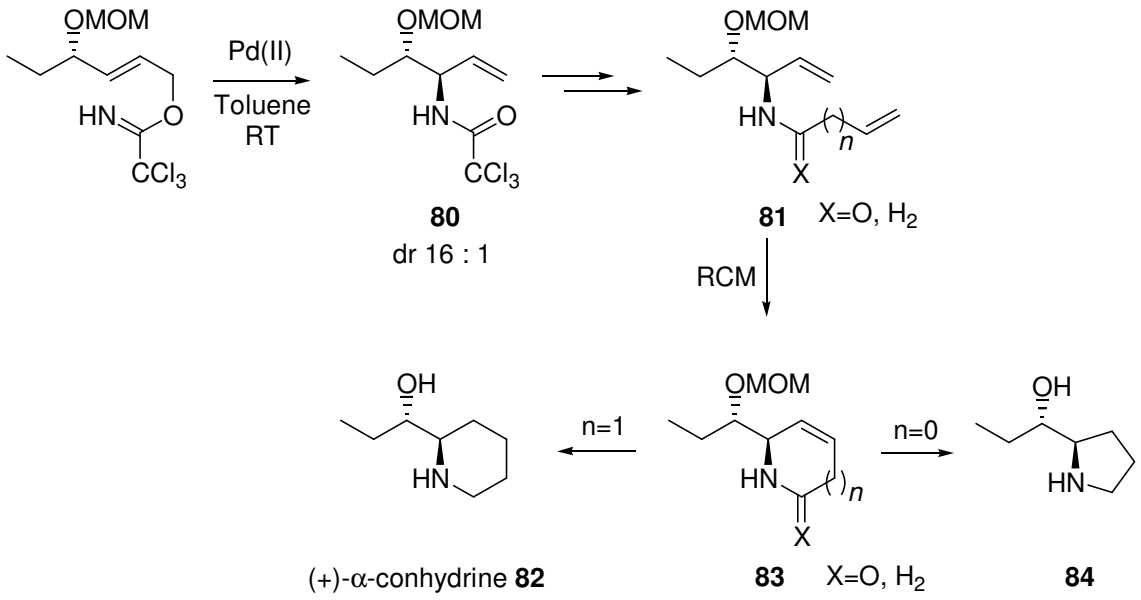
undergo further manipulation to synthesise α,α-disubstituted α-amino acids **77** and β,β-disubstituted β-amino acids **79**.



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]

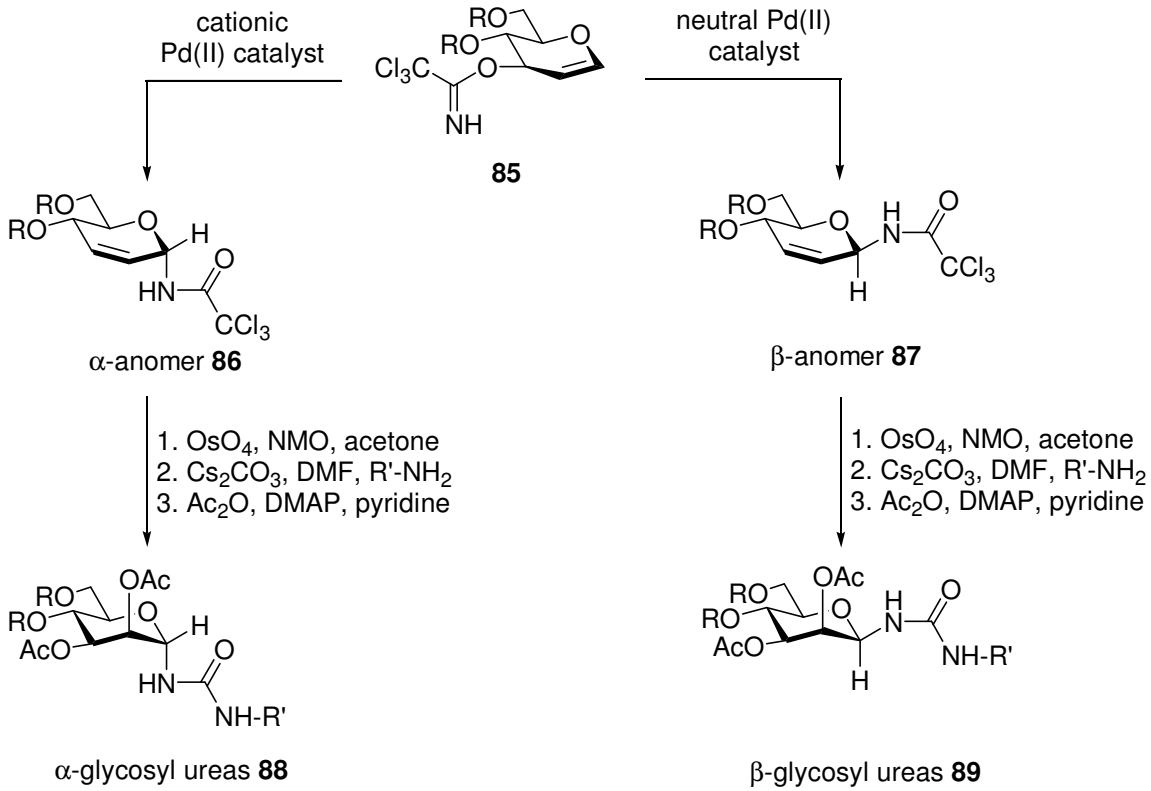
Jamieson and Sutherland have recently employed a substrate directed aza-Claisen rearrangement for the synthesis of the alkaloid natural product (+)-α-conhydrine **82**.[57] In this approach, the trichloroacetamide product **80** of the highly diastereoselective rearrangement was converted to the *N*-heterocycle **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 (+)-α-conhydrine **82** and a pyrrolidine analogue **84** that is also known to have biological activity.



Scheme 29 - Synthesis of (+)-α-conhydrine using a substrate directed rearrangement

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).[58] 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 α- and β-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 α-*N*-glycosyl trichloroacetamide **86**, whilst neutral palladium(II) catalysts were shown to favour the β-*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 α-glycosyl **88** or β-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,[26] thus promoting a non-concerted ionization pathway, which leads to formation of α-*N*-glycosyl trichloroacetamide **86**. Neutral palladium(II) complexes coordinate instead to the olefin, promoting a concerted cyclisation mechanism,[19,35] thus leading to formation of β-*N*-glycosyl trichloroacetamide **87**.



Scheme 30 - Stereoselective synthesis of glycosyl ureas

1.4.1 Conclusions

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

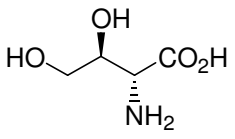
2.1 Studies on the aza-Claisen rearrangement of dihydroxylated allylic trichloroacetimidates: synthesis of 2-amino-3,4-dihydroxybutyric acids.

2.1.1 Hydroxylated amino acids

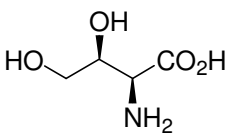
Hydroxylated natural products are widely prevalent in nature, many of which also possess biological activity.[59] As such there is great interest in new methodologies for their stereoselective synthesis to enable full evaluation of these compounds for the treatment of disease.

(2*R*,3*S*)-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*.[60] 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 (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **90** and its unnatural (2*S*,3*S*)-diastereomer **91** (Figure 5), with the key C-N stereocentre at C2, introduced *via* a diastereoselective aza-Claisen rearrangement.



90



91

Figure 5 - (2*R*,3*S*)-2-Amino-3,4-dihydroxybutyric acid and its (2*S*,3*S*)-diastereomer

2.1.2 Synthesis of (2*S*,3*S*)-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.[43] It has also been shown that the oxygen adjacent to the olefin is critical for diastereoselectivity.[44] It was proposed that the acetonide protected allylic trichloroacetimidate **97** might undergo a diastereoselective rearrangement in a similar manner.

The synthesis of an acetonide protected allylic alcohol **96** was achieved in 3 steps from commercially available chiral pool starting material, D-mannitol **92** (Scheme 31). Firstly **92** was protected as the acetonide at the 1,2- and 5,6- positions, using 2,2-dimethoxypropane **93**. A one-pot oxidation with sodium periodate (oxidative cleavage of **94**, 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,[61] gave exclusively the *E*-α,β-unsaturated ester **95**. The geometry of the resulting alkene could be easily determined from the ^{1}H 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.

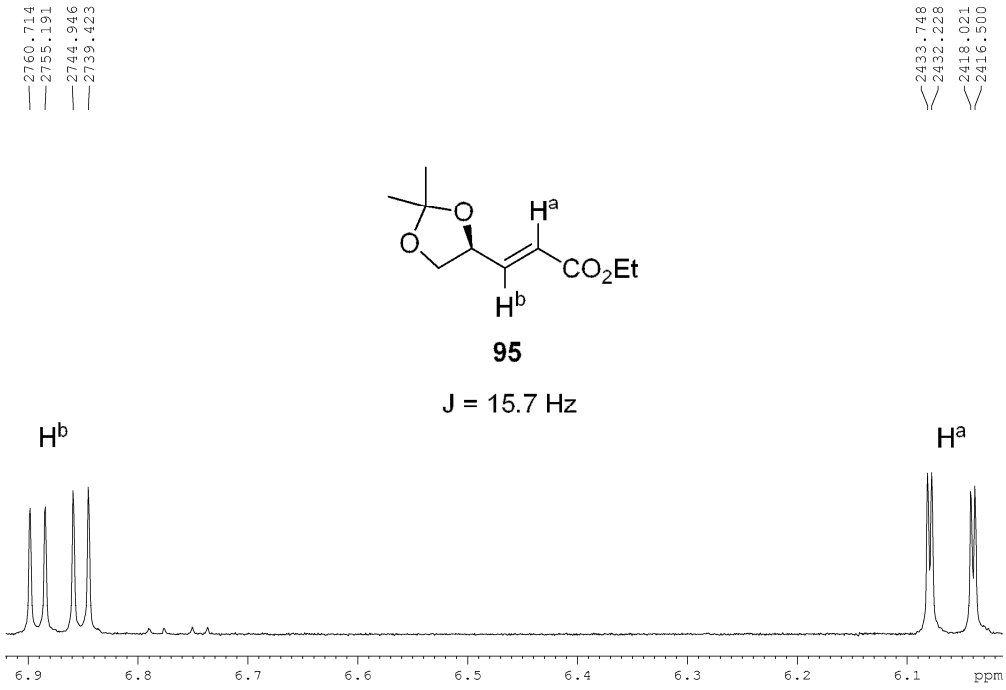
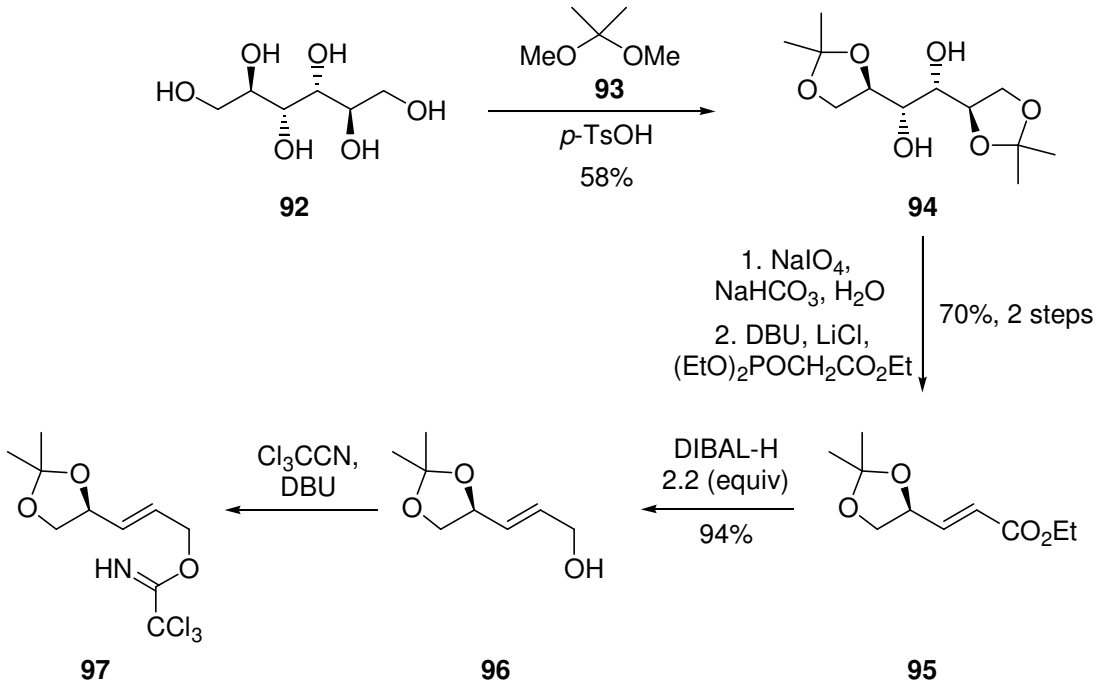


Figure 6 - Alkene signals in ^{1}H NMR spectrum of compound 95

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

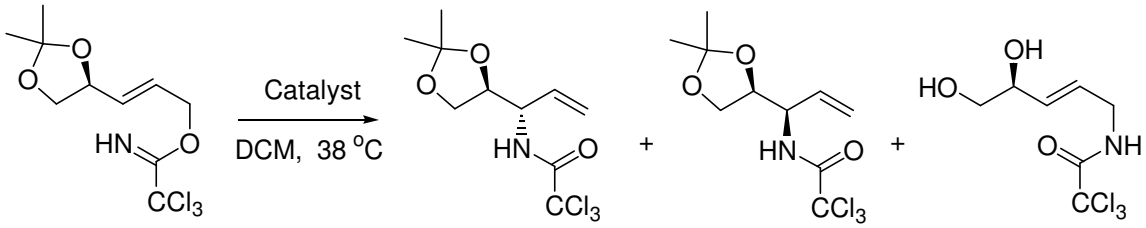
Allylic trichloroacetimidate **97** was then subjected to a Pd(II)-catalysed aza-Claisen rearrangement using standard conditions (Table 5, entry 1). Surprisingly, no [3,3]-product was formed, with only the deprotected [1,3]-product **98c** isolated. This compound likely forms *via* Pd(II)-catalysed hydrolysis of the acetonide followed by 1,3-rearrangement through a known competing ionisation pathway.[9,45] Previously Schmeck and Hegedus have reported the hydrolysis of acetonides by palladium in aqueous acetonitrile,[62] 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 ^{o}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 $PdCl_2(MeCN)_2$. 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).[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 (3*R*,4*S*) 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 (4*S*) 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**.



97 **98a** **98b** **98c**

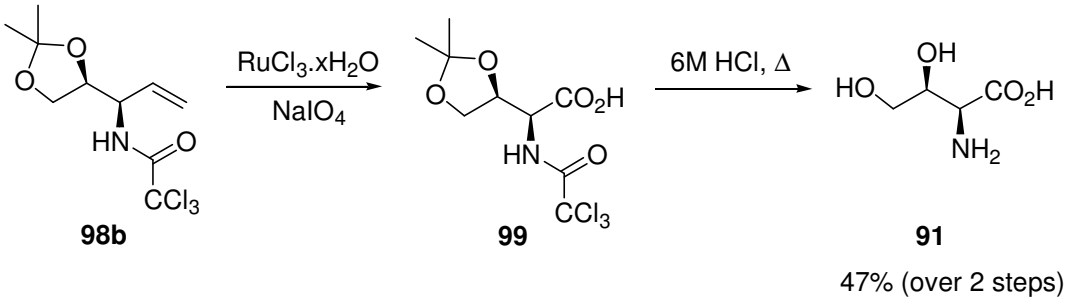
Entry	Catalyst	Catalyst Loading (mol %)	Reaction time	Yield[a] (%)	Ratio (**a** : **b** : **c**)
1	$PdCl_2(MeCN)_2$[b]	10	24 h	---	0 : 0 : 1
2	$PdCl_2(MeCN)_2$	10	24 h	32	7 : 1 : 7
3	$PtCl_2$	10	5 days	31	4 : 1 : 9
4	$HAuCl_4.3H_2O$	10	5 days	25	2 : 1 : 3
5	AuCl	10	4 days	31	2 : 1 : 4
6	(*S*)-COP-Cl	3	7 days	81	1 : 52 : 0
7	(*R*)-COP-Cl	3	14 days	23	6 : 1 : 1

[a] Isolated combined yields of [3,3]-products (**a** + **b**) from allylic alcohol **96**

[b] Reaction carried out in THF at room temperature

Table 5 - Rearrangement of acetonide protected trichloroacetimidate 97

The highly successful rearrangement using (*S*)-COP-Cl provided significant quantities of the (3*R*,4*S*)-diastereomer **98b** and allowed the synthesis of (2*S*,3*S*)-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).[46] 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.



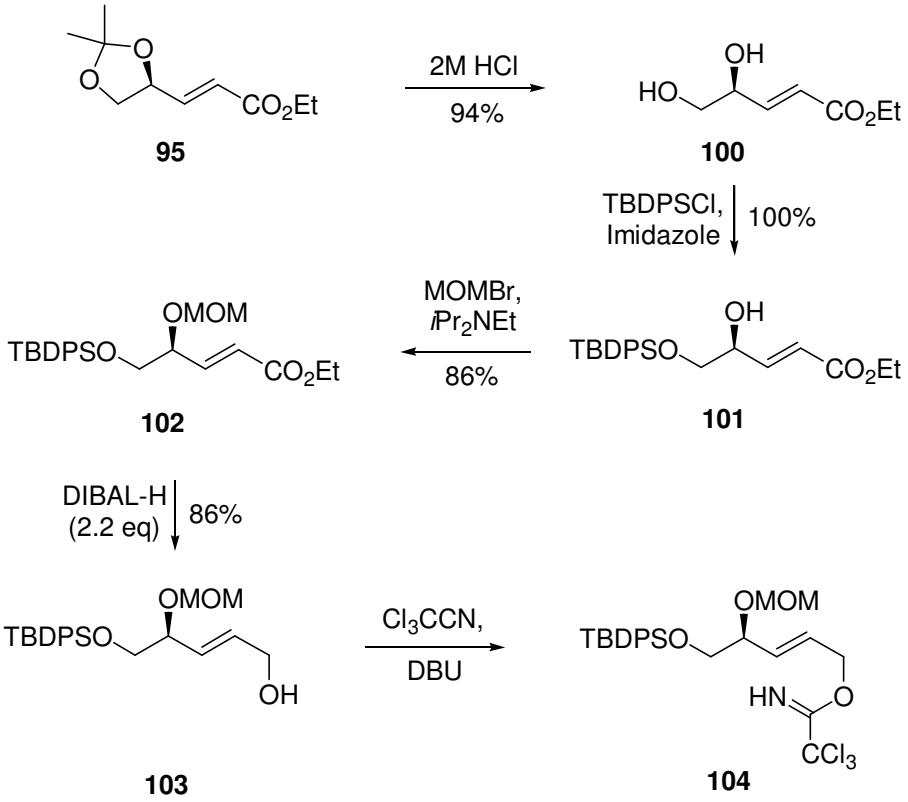
Scheme 32 - Synthesis of (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid

The synthesis of (2*S*,3*S*)-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 2*R*-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 (2*R*,3*S*)-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.[43,44] 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.[43,56]

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).



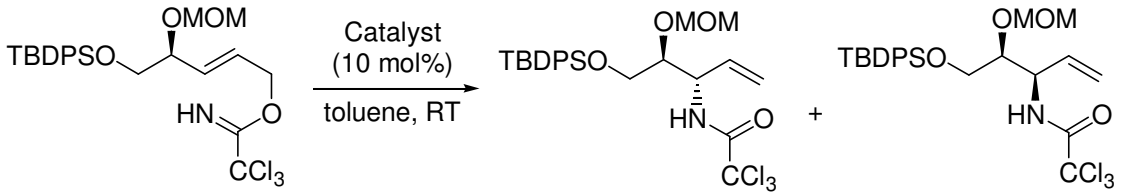
Scheme 33 - Synthesis of the second trichloroacetimidate

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).[47]

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).



104 **105a** **105b**

Entry	Catalyst	Reaction Time	Yield[a] (%)	Ratio (**a** : **b**)
1	$PdCl_2(MeCN)_2$[b]	24 h	32	3 : 1
2	$PdCl_2(MeCN)_2$	12 h	68	4 : 1
3	$PtCl_2$	7 days	25	4 : 1
4	$HAuCl_4.3H_2O$	2 days	49	2 : 1
5	AuCl	7 days	40	3 : 1
6	$AuCl_3$	7 days	26	2 : 1
7	(*R*)-COP-Cl[c]	14 days	68	16 : 1

[a] Isolated combined yields of **a** and **b** from allylic alcohol **103**

[b] Reaction carried out in THF at room temperature

[c] Reaction carried out in DCM at 38 ^{o}C

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).

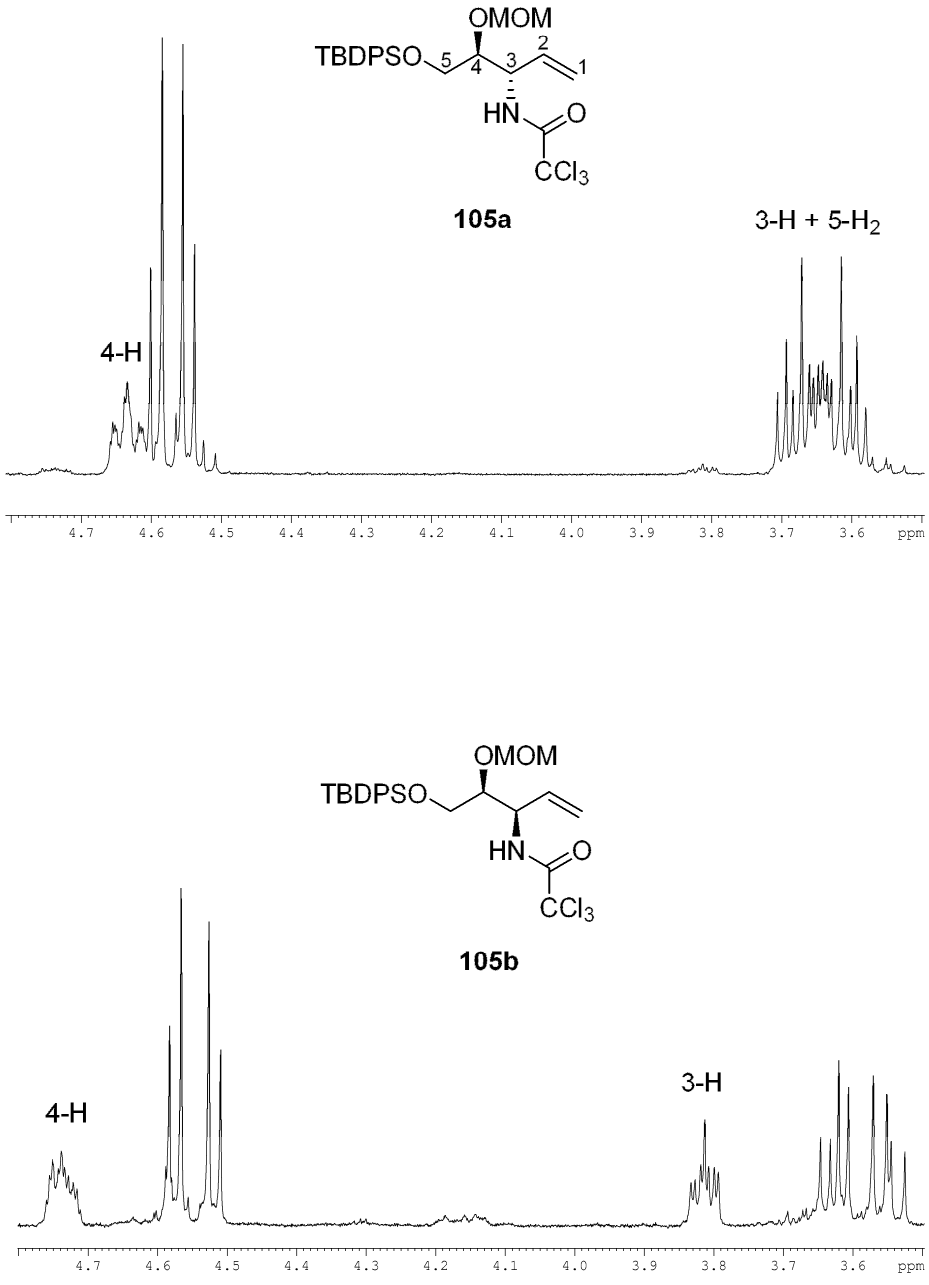
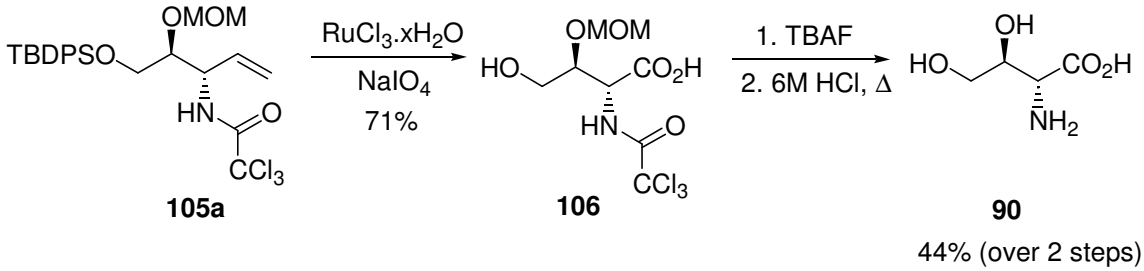


Figure 7 - NMR spectrum of *anti*-(top) and *syn*-(bottom) diastereomers

With significant quantities of the *anti*-(3*S*,4*S*)-diastereomer available, using either $PdCl_2(MeCN)_2$ or (*R*)-COP-Cl as catalyst for the rearrangement, the synthesis of (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **90** was completed successfully.

This was achieved in a similar manner as for (2*S*,3*S*)-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).[46] 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, (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **90**,[64] in 44% yield over 2 steps from **106** (Scheme 34).



Scheme 34 - Synthesis of (2*R*,3*S*)-2-amino-3,4-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 (3*R*,4*S*)-*syn*-diastereomer in an excellent yield and diastereoselectivity. Efforts to stereoselectively synthesise the (3*S*,4*S*)-*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.

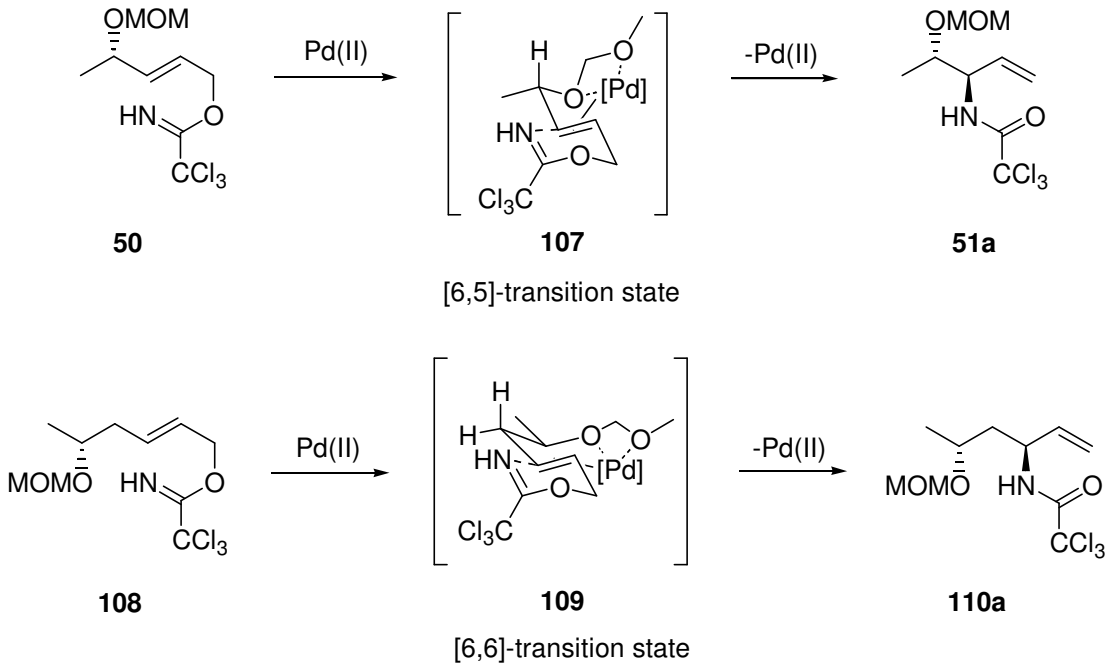
These rearranged products are more complex than have previously been synthesised using this approach and their subsequent conversion to the dihydroxylated α-amino acids (2*R*,3*S*)-2-amino-3,4-dihydroxybutyric acid **90** and its unnatural diastereomer (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **91** 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 γ-hydroxy-α-amino acids.

2.2.1 γ-Hydroxy-α-amino acids

Previously, the Sutherland group has shown that chiral MOM-ether groups (at the δ-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]

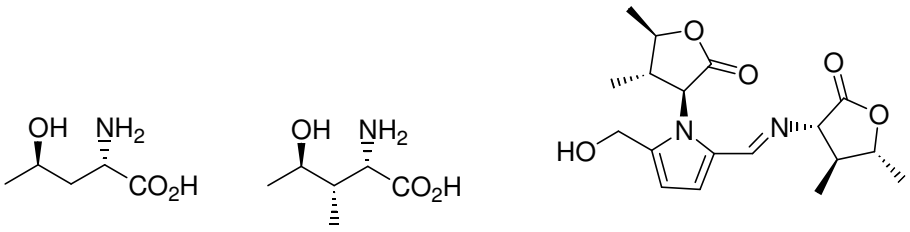
It was proposed that an allylic trichloroacetimidate **108** with a MOM ether situated at the ε-position (one carbon further from the olefin) might rearrange to give the corresponding amide **110a** in higher stereoselectivity due to the fact that the rearrangement should proceed *via* a 6,6-chair like 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 γ-hydroxy-α-amino acids such as γ-hydroxynorvaline **111** (Figure 8).



Scheme 35 - Proposed transition states of ether-directed rearrangement

γ-Hydroxy-α-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 (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **112**, which is the amino acid component of, the potent cytotoxic alkaloid, funebrine **113** and was isolated in 1984 from *Quararibea funebris*.[65]



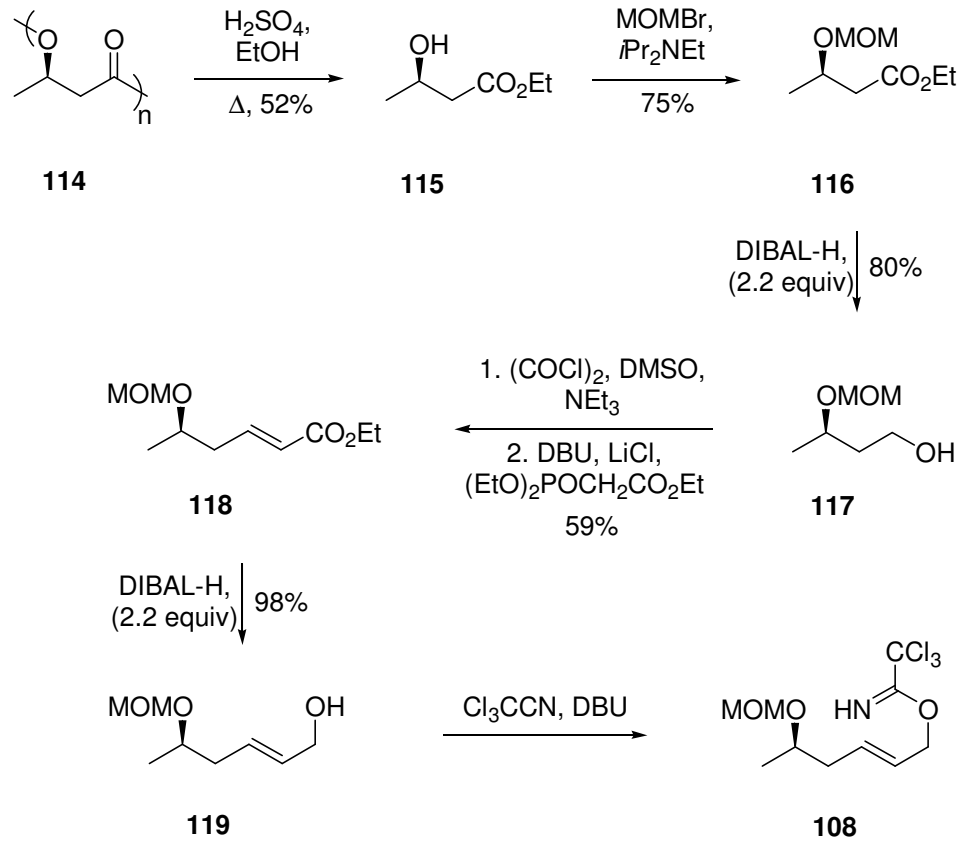
111 **112** **113**

Figure 8 - Hydroxylated natural products

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-directed aza-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

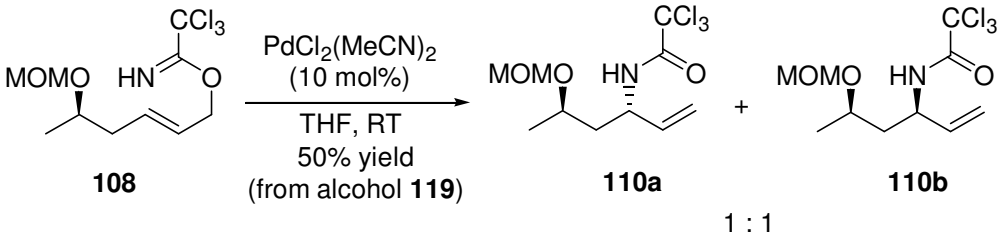
To investigate this proposal, a synthetic route to ε-substituted allylic trichloroacetimidate **108** was developed. Initially, poly (3*R*)-3-hydroxybutyrate **114** was hydrolysed under acidic conditions to give the hydroxy ester **115** (Scheme 36). MOM protection of **115** under standard conditions 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,[61] then gave exclusively the *E*-α,β-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 ε-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.

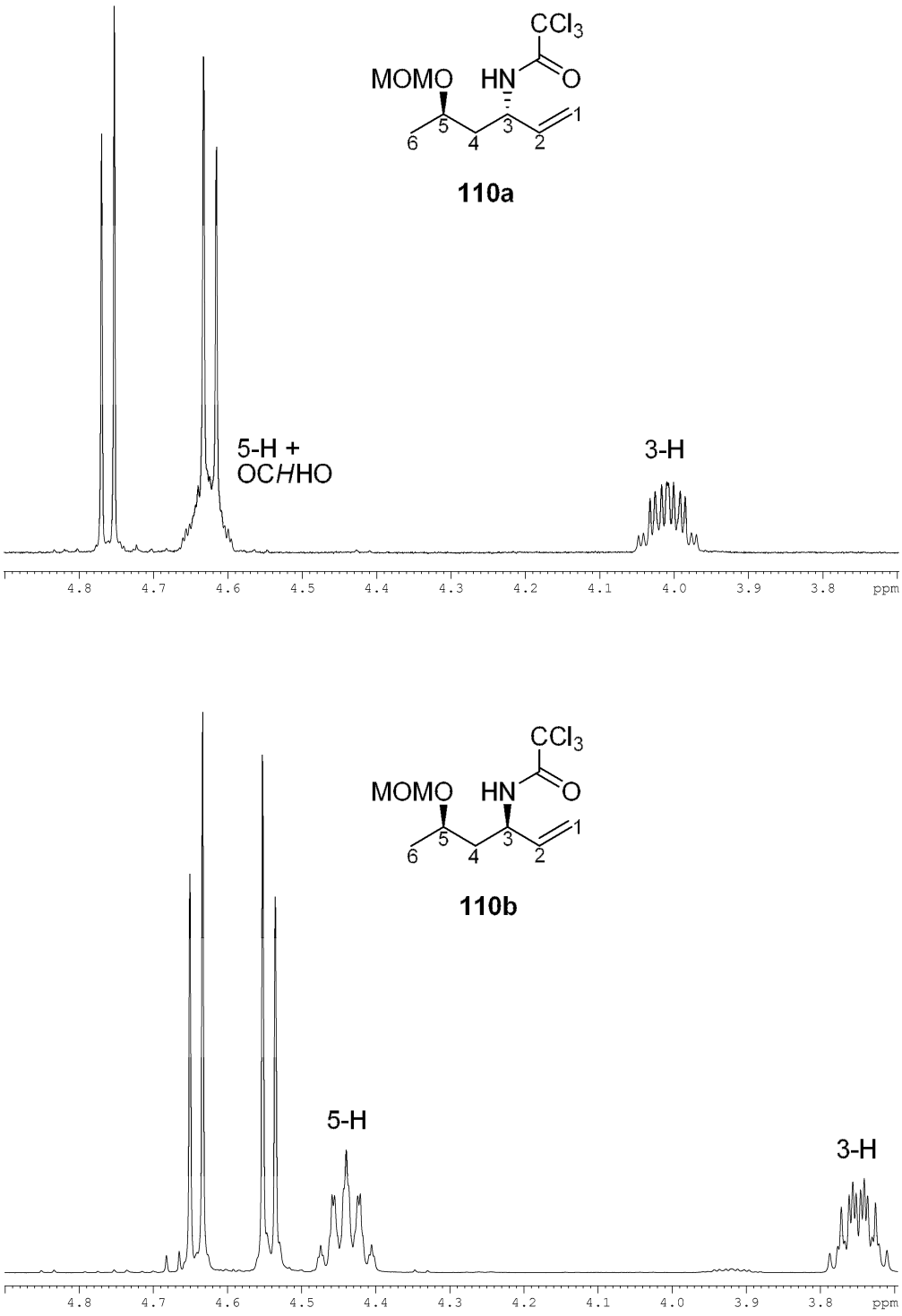
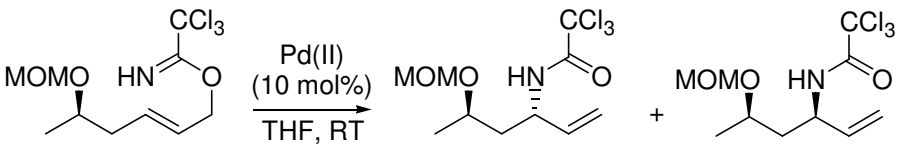


Figure 9 - ^{1}H NMR spectrum of diastereomers

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).



108 **110a** **110b**

Entry	Catalyst	Additive	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	$PdCl_2(MeCN)_2$	---	50	1 : 1
2	$PdCl_2(MeCN)_2$	DBU	45	1 : 1
3	$PdCl_2(MeCN)_2$	*p*-benzoquinone	38	1 : 1
4[c]	---	K_2CO_3	85	1 : 1

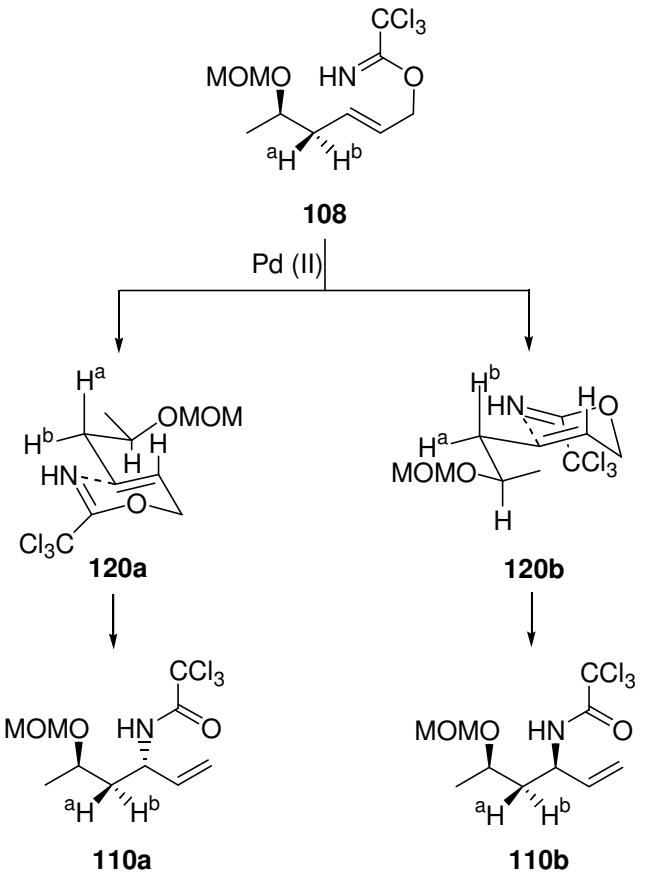
[a] Isolated combined yields of **a** and **b** from allylic alcohols.
[b] Ratio in crude reaction mixture.
[c] Reaction performed in *p*-xylene at 130 °C.

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.[66] 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.

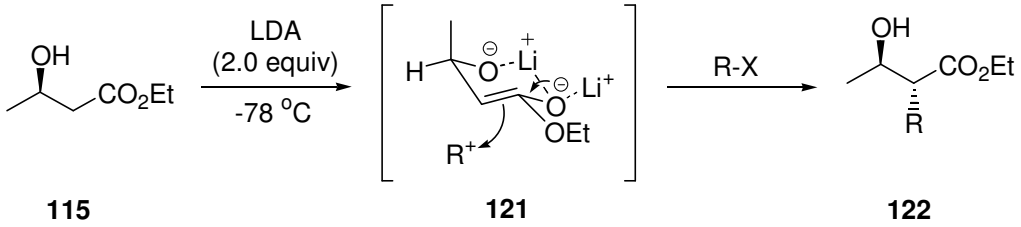


Scheme 38 - Transition states for rearrangement

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

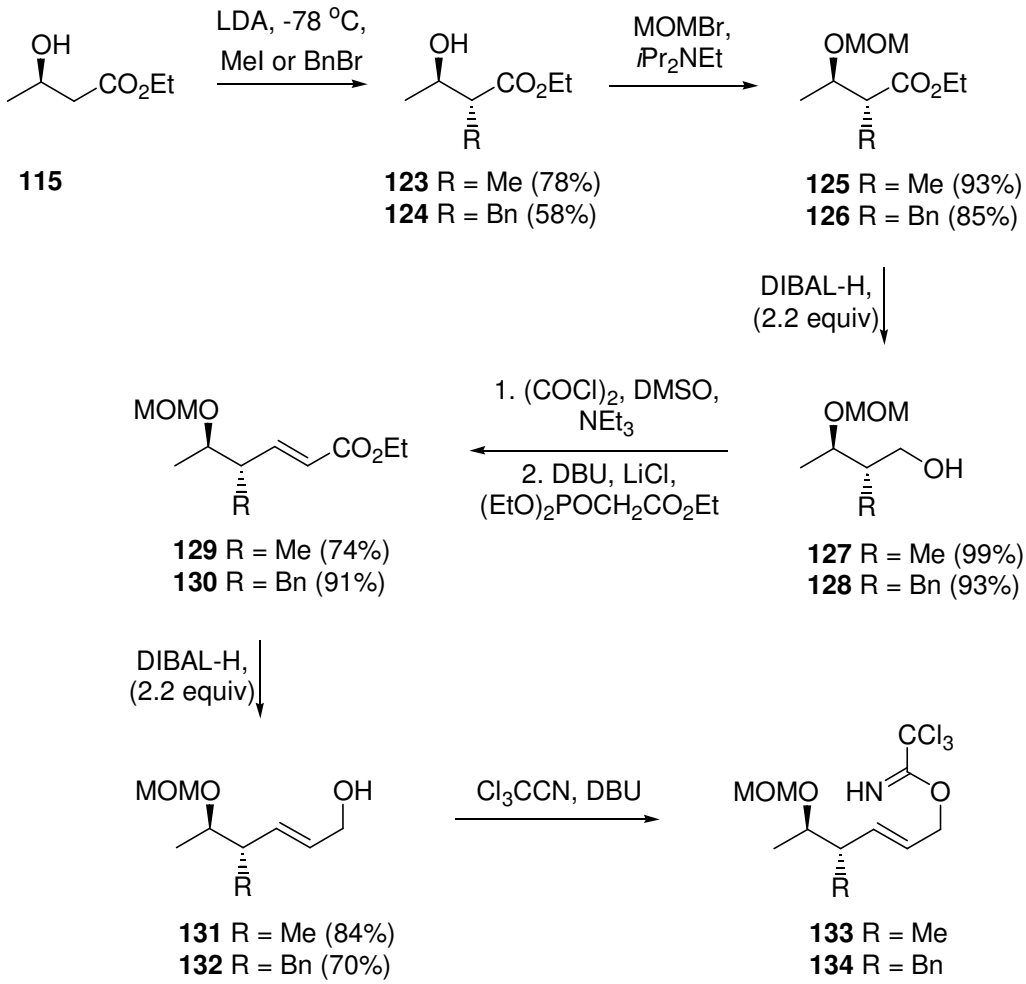
Two new δ-,ε-substituted allylic trichloroacetimidates **133** and **134**, were synthesised by a similar synthetic route to that used previously for the synthesis of substrate **108** (Scheme 40). Methyl and benzyl substituents were introduced in place of hydrogen by a stereoselective alkylation. This 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).[67,68]



115 **121** **122**

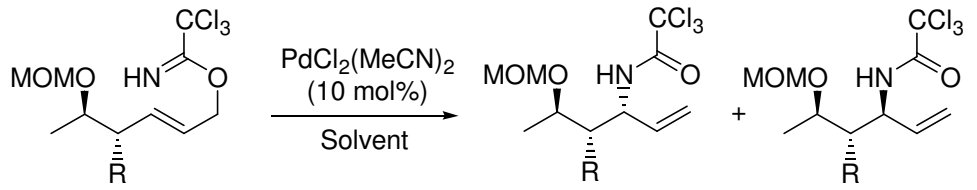
Scheme 39 - Stereoselective alkylation *via* di-lithiated enolate

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.



Scheme 40 - Synthesis of δ,ε-disubstituted allylic trichloroacetimidates

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).



133-135 **136a** **136b**

Entry	R	Solvent	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	H	THF	50%	1 : 1
2	Me	THF	49%	3 : 1
3	Bn	THF	72%	6 : 1

[a] Isolated combined yields of **a** and **b** from allylic alcohols.

[b] Ratio in crude reaction mixture.

Table 8 - Rearrangement of δ,ε-disubstituted substrates in THF

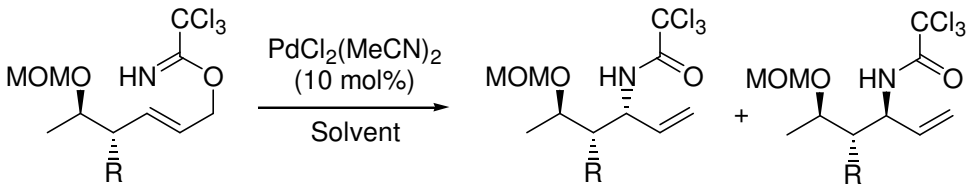
Although diastereoselectivity can be achieved by the introduction of methyl or benzyl groups at the δ-position, the selectivity was still lower than what had previously been reported for other substrates.[43,45] Previously, it has been shown that non-coordinating solvents such as toluene can enhance the diastereoselectivity of ether-directed rearrangements.[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.



133-135 **136a** **136b**

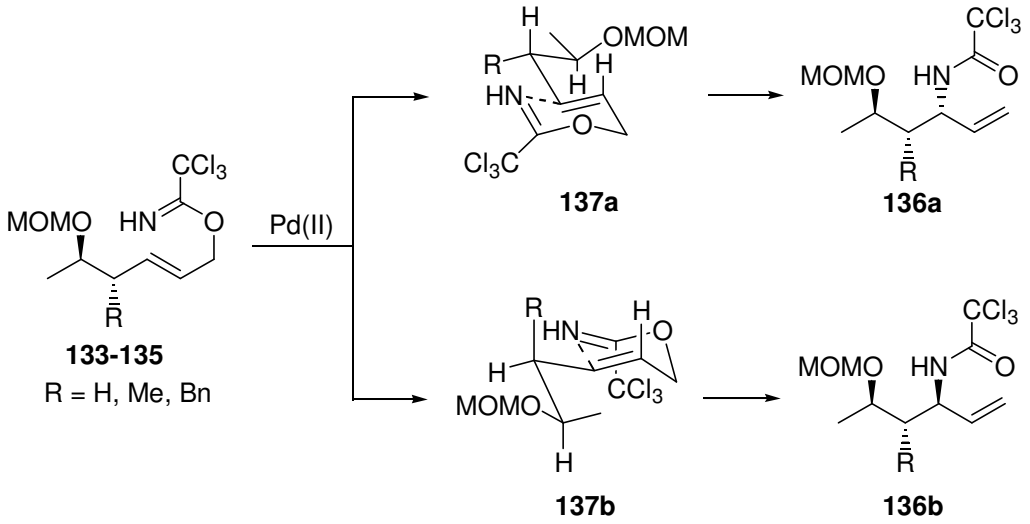
Entry	R	Solvent	Yield[a] (%)	Ratio[b] (**a** : **b**)
1	H	toluene	71%	3 : 1
2	Me	toluene	66%	13 : 1
3	Bn	toluene	82%	11 : 1

[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

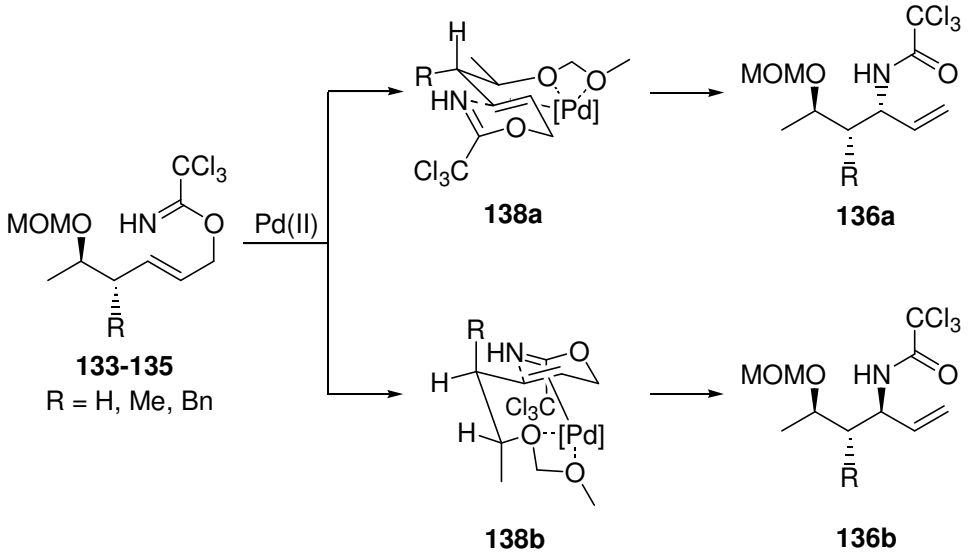
A number of conclusions can be drawn from these results. Firstly, the rearrangement of δ,ε-disubstituted substrates in THF occurs with only moderate selectivity because selectivity is governed by a number of steric factors and there is no directing effect from the MOM group (Scheme 41). Any stereoselectivity occurs due to a destabilisation of transition state **137b** by more bulky groups at the δ-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**).



Scheme 41 - Rearrangement in THF

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.

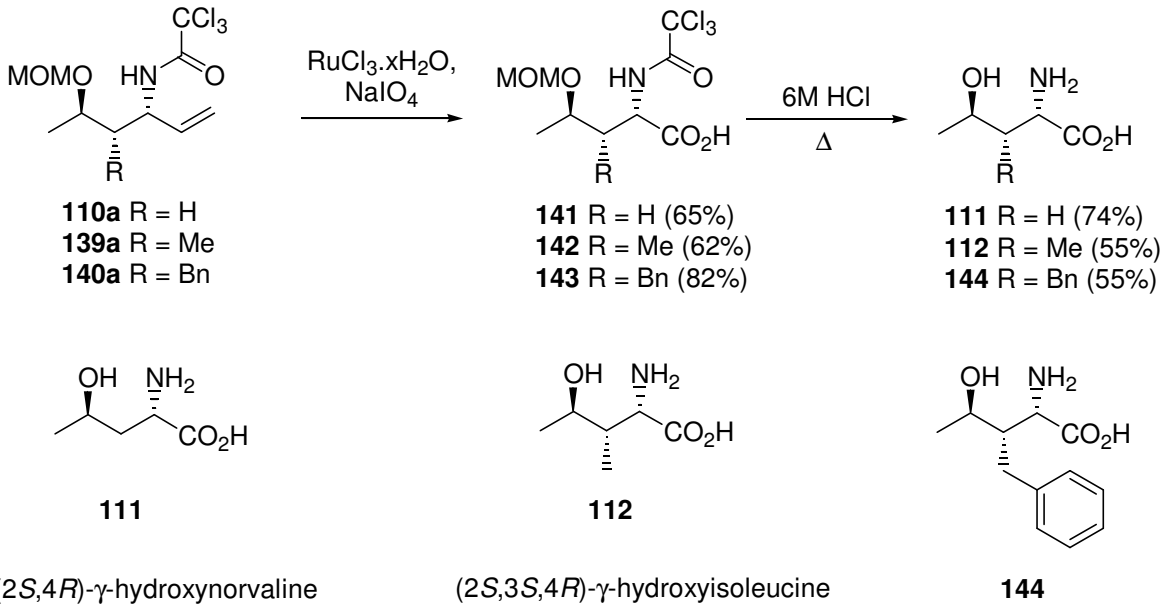


Scheme 42 - Rearrangement in toluene

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: (2*S*,4*R*)-γ-hydroxynorvaline **111**,[69] (2*S*,3*S*,4*R*)-γ-hydroxyisoleucine **112**,[65] and a novel benzyl substituted γ-hydroxy-α-amino acid **144**.



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

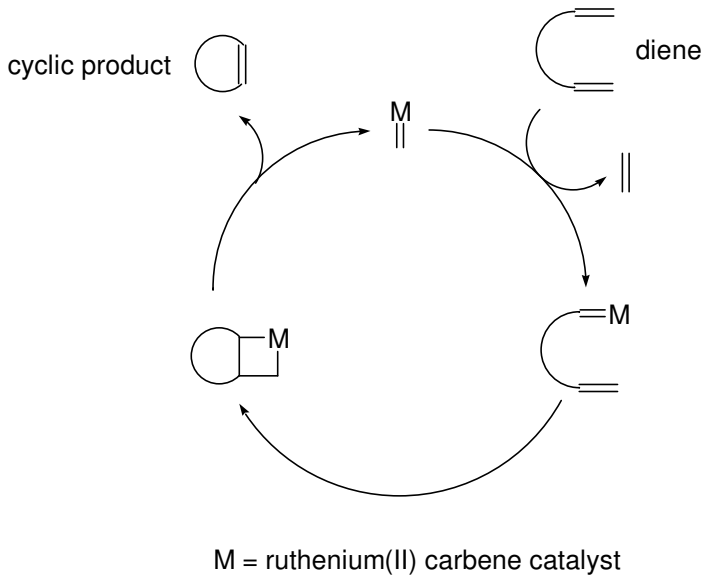
In summary, the role of steric strain on the MOM ether-directed aza-Claisen rearrangement has been investigated in two solvents; THF and toluene. In THF which is a coordinating solvent, stereocontrol is exerted by a stereo-relay effect and there is no directing effect as the solvent prevents coordination 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 γ-hydroxy-α-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.[70-73] 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.[1] 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.

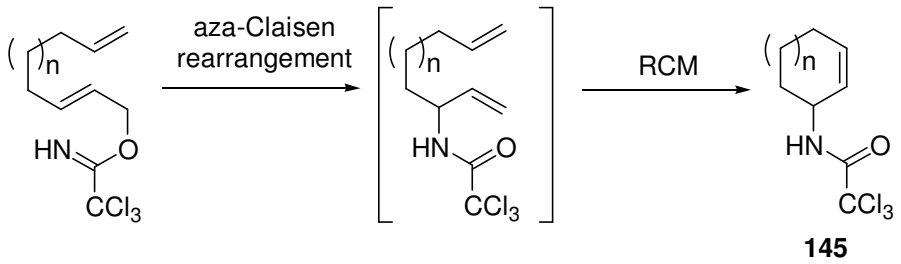
Ring closing metathesis has emerged in recent years as an excellent reaction for use in organic synthesis. It is a highly versatile and mild reaction process that enables the formation of a variety of different ring sizes often in excellent yields. The reaction proceeds *via* a well studied reaction 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.[74] In addition to RCM there are two other commonly used metathesis processes. Cross metathesis (CM)[74] which is the intermolecular metathesis reaction (whereas RCM is an intramolecular process) and Ring Opening Metathesis (ROM),[74] which is commonly employed in polymerisations.



Scheme 44 - Mechanism of ring closing metathesis

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,[75] aza-Michael reactions,[76] Diels-Alder reactions,[77] isomerizations,[78] Claisen rearrangements,[79] Kharasch cyclisations,[80] and dihydroxylations.[81]

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,[57] and previously it had been shown that ruthenium catalysts do not catalyse the aza-Claisen rearrangement.[47] 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 **145** (Scheme 45).



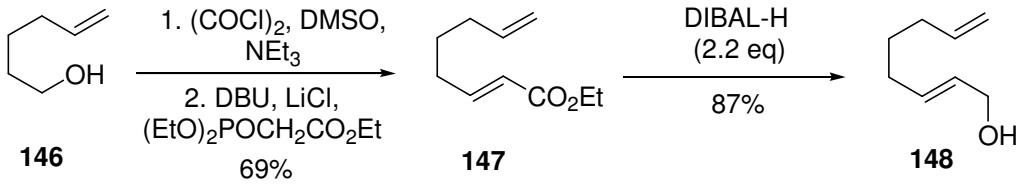
Scheme 45 - Proposed tandem aza-Claisen rearrangement and RCM reaction

Cyclic allylic trichloroacetamides **145** are useful synthetic intermediates, having found widespread applications e.g. in dihydroxylations,[82] epoxidations[83] and Kharasch

cyclisations.[80] 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

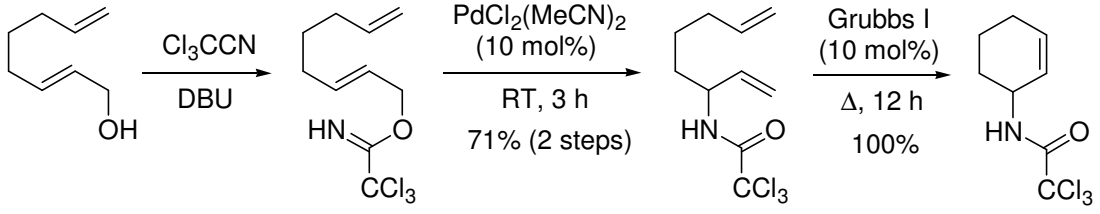
It was decided to attempt to develop this tandem process for the synthesis of 6-membered cyclic allylic trichloroacetamide **151**. To achieve this, a concise synthetic route to allylic alcohol **148** was required. This was rapidly achieved from commercially available 5-hexen-1-ol **146**, using a one-pot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



146 **147** **148**

Scheme 46 - Concise synthesis of terminal alkene containing allylic alcohol

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.

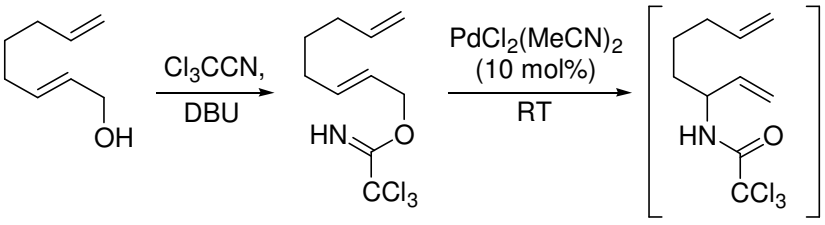


148 **149** **150** **151**

Scheme 47 - Development of reaction conditions for tandem process

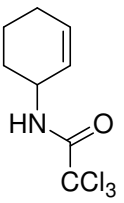
Following this, a tandem reaction was then attempted (Scheme 48). Initially, a one-pot procedure involving addition of both rearrangement and metathesis catalysts together then heating under reflux was attempted. Somewhat surprisingly, analysis of the crude reaction product by ^{1}H NMR showed that the 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).



RCM catalyst, Δ

RCM catalyst	Yield (%) of **151** from **148**
Grubbs I	89
Grubbs II	95
Hoveyda/ Grubbs II	95



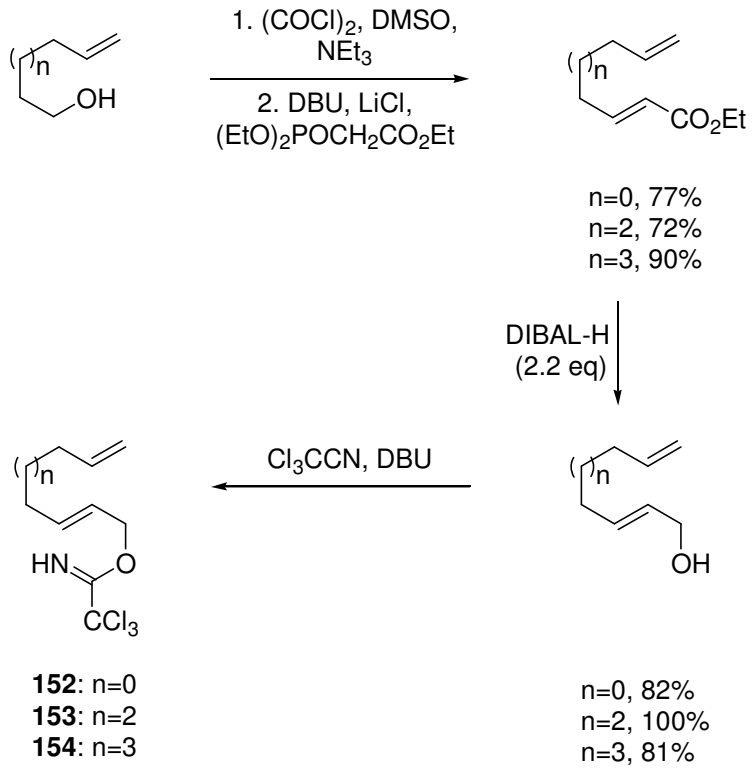
151

Scheme 48 - Tandem aza-Claisen rearrangement and RCM reaction

2.3.3 Scope of tandem process

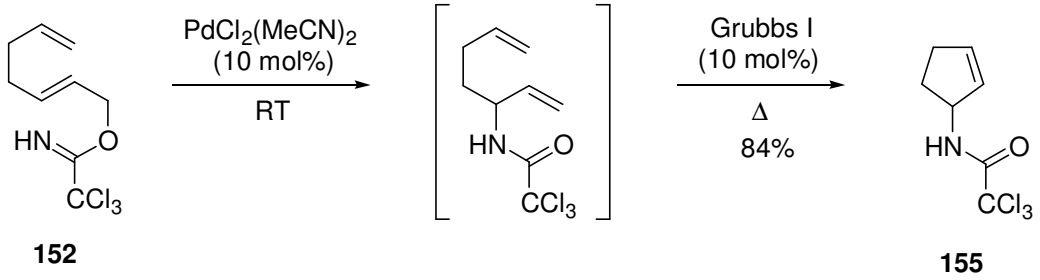
With optimized reactions conditions developed, synthesis of additional ring sizes was then investigated. It was decided to continue using Grubbs I as RCM catalyst, even though it showed a slightly lower yield for the reaction than the other catalysts. This was due to its lower cost and greater availability 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).



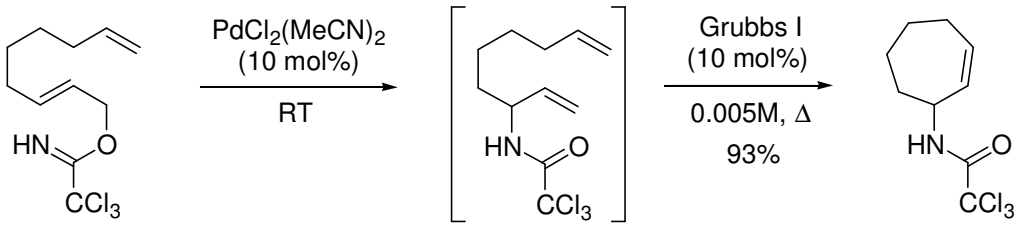
Scheme 49 - Synthesis of additional tandem reaction substrates

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).



Scheme 50 - Synthesis of 5-membered allylic trichloroacetamide

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.[84] 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).

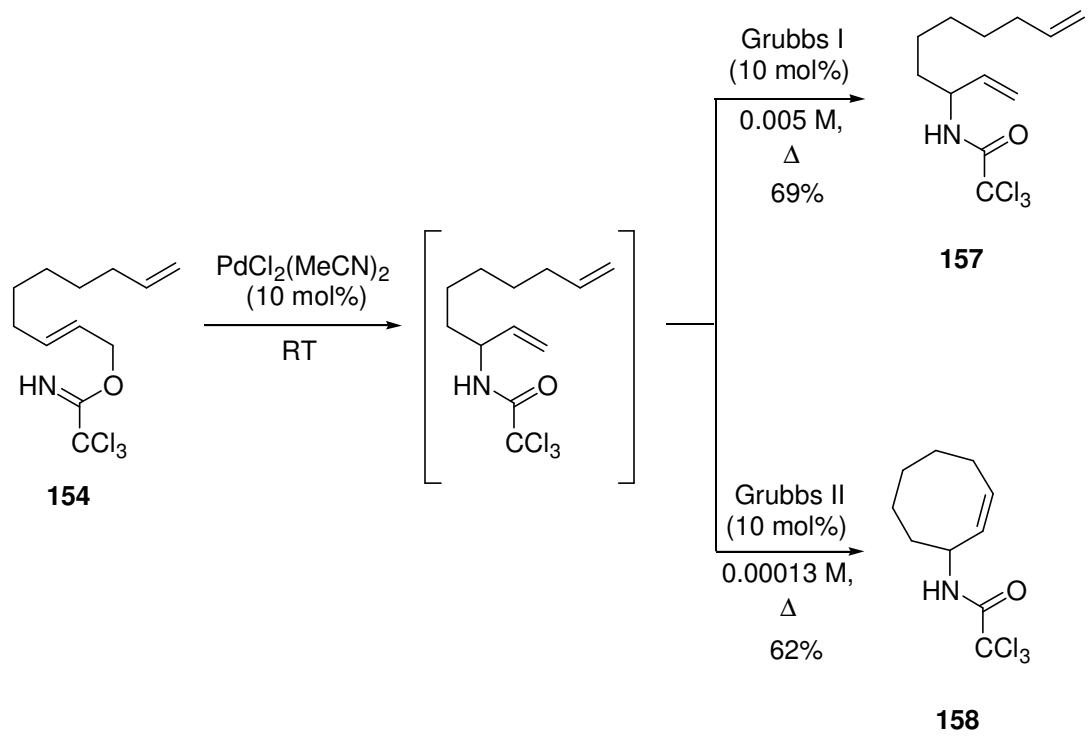


153 **156**

Scheme 51 - 7-Membered cyclic allylic trichloroacetamide

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.[85] 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).

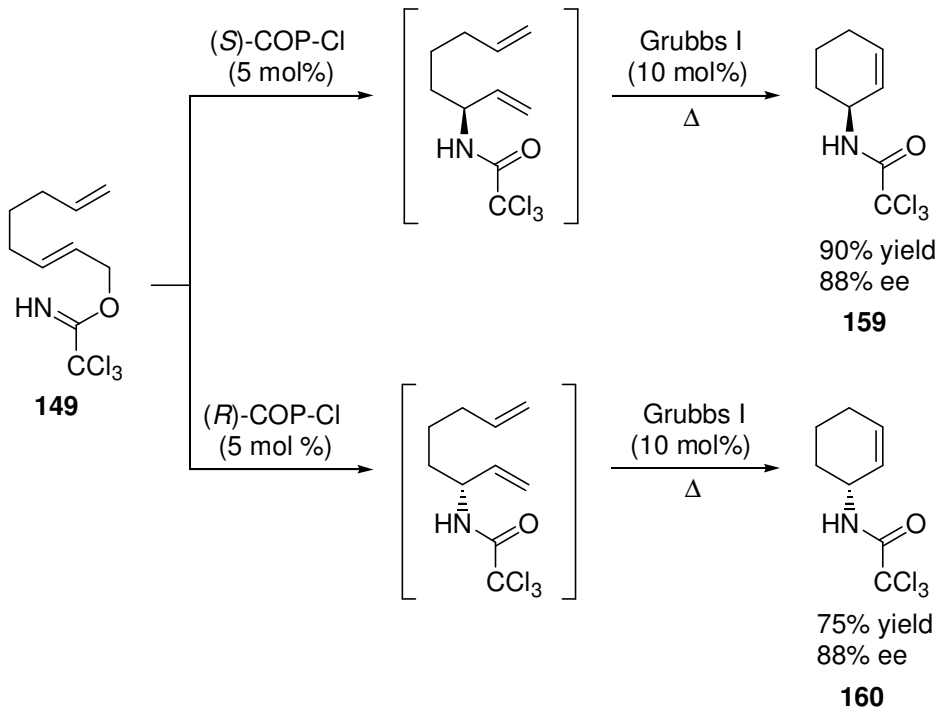


Scheme 52 - Synthesis of 8-membered allylic amide using Grubbs II

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.[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).

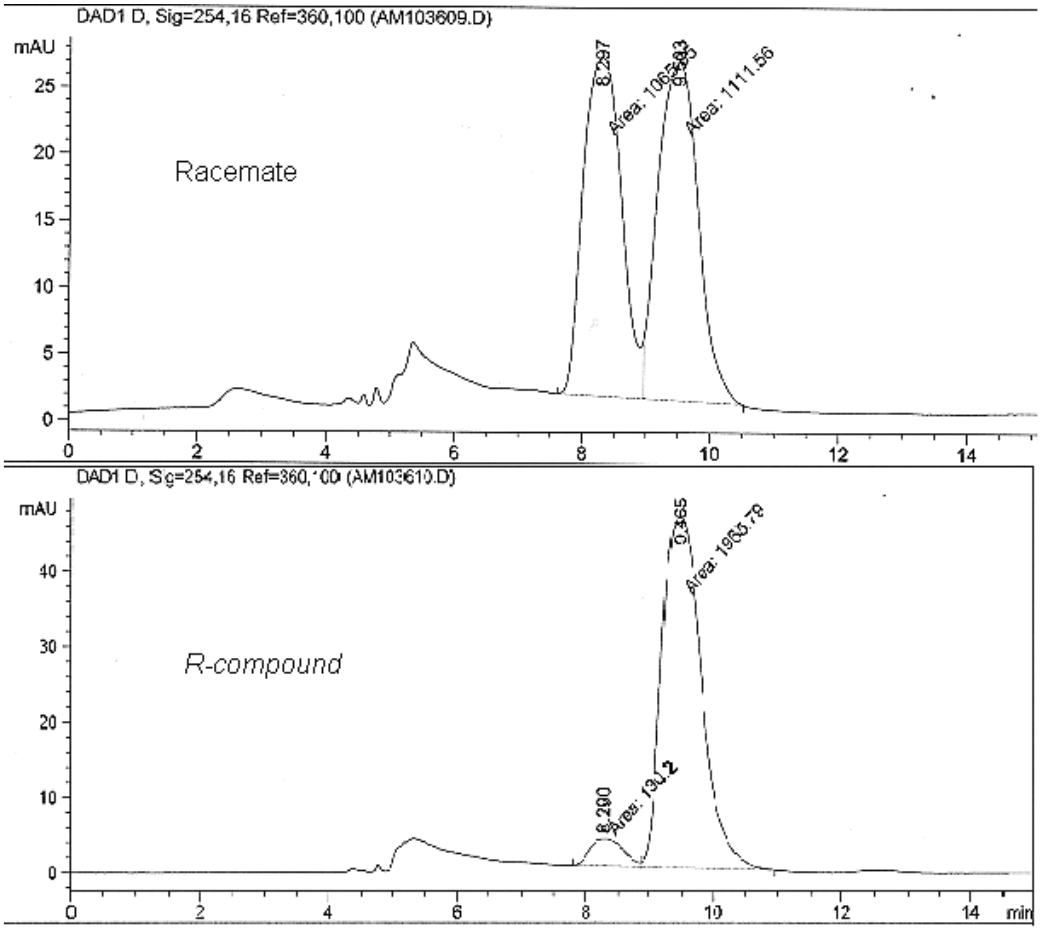
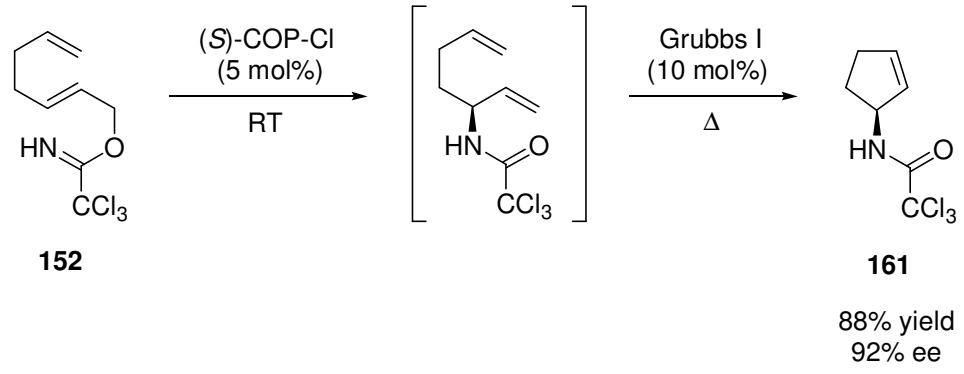


Figure 10 - Chiral HPLC trace of racemate (top) and *R*-compound 160 (bottom)

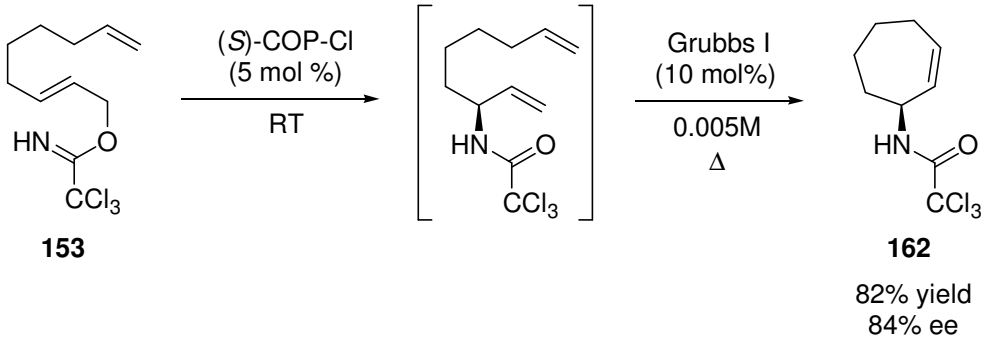
To confirm that this asymmetric tandem reaction could be employed widely for other ring sizes, substrates **152** and **153** precursors of the 5- and 7-membered amides respectively, were employed with the (*S*)-COP-Cl catalyst.

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).



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

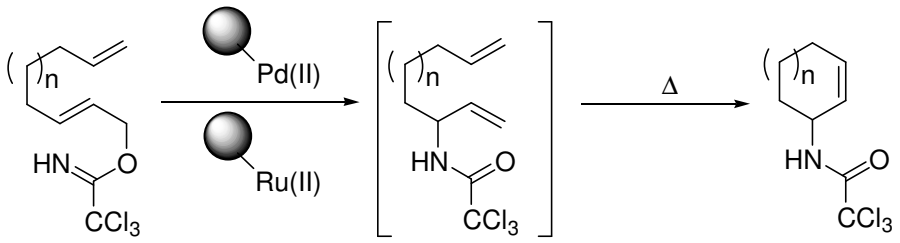
2.3.5 Conclusions

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

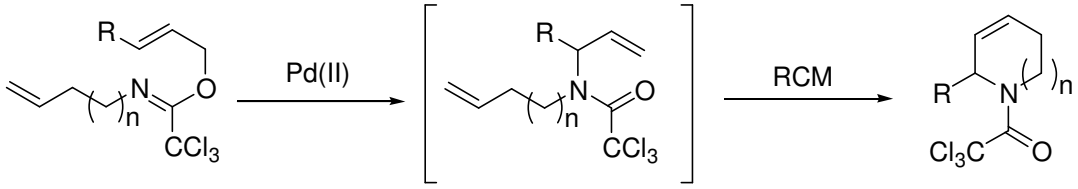
Future work in this area involves several different aspects.

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).



Scheme 56 - Possible development of a cascade process

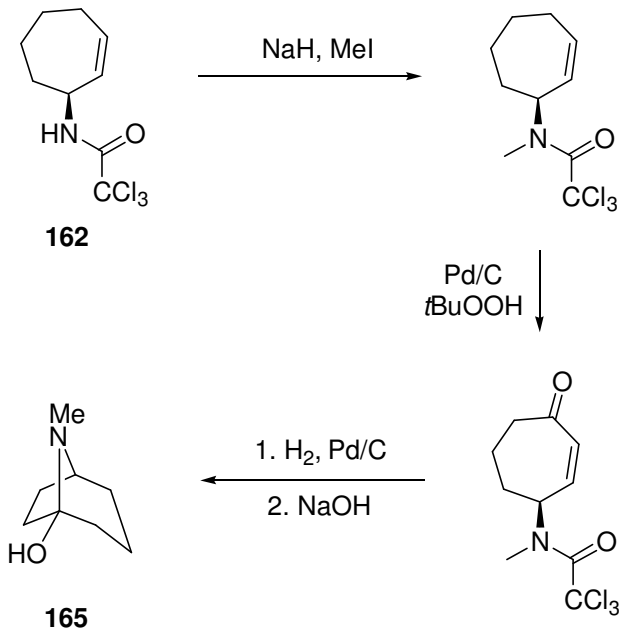
Secondly, this methodology could be expanded for the synthesis of *N*-heterocycles **164**. At present these compounds cannot be directly synthesised by this tandem approach, but the synthesis of *N*-substituted allylic trichloroacetimidates **163** would possibly allow the tandem synthesis of these 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.



163 **164**

Scheme 57 - Synthesis of *N*-heterocycles using a tandem rearrangement and RCM reaction

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*.[86] This could be synthesised from the 7-membered trichloroacetamide **162**, prepared previously, in only 4 steps (Scheme 58).



162 **165**

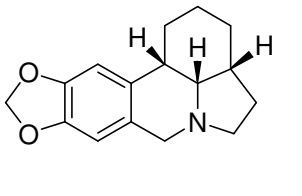
Scheme 58 - Proposed synthesis of physoperuvine

2.4 Development of an ether-directed tandem aza-Claisen rearrangement and RCM reaction for natural product synthesis

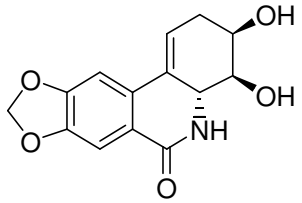
2.4.1 Introduction

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.

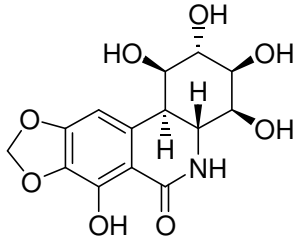
A search of the literature was undertaken to identify suitable synthetic targets. Several alkaloids from the *amaryllidaceae* plant family quickly came to our attention. Alkaloids from this plant family include: (+)-γ-lycorane **166**, 2-deoxylycoricidine **167**, pancratistatin **64** and narciclasin **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]



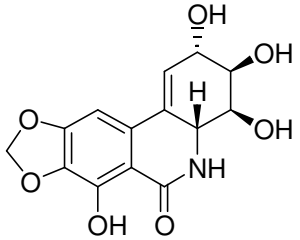
(+)-γ-Lycorane **166**



(+)-2-deoxylycoricidine **167**



(+)-pancratistatin **64**



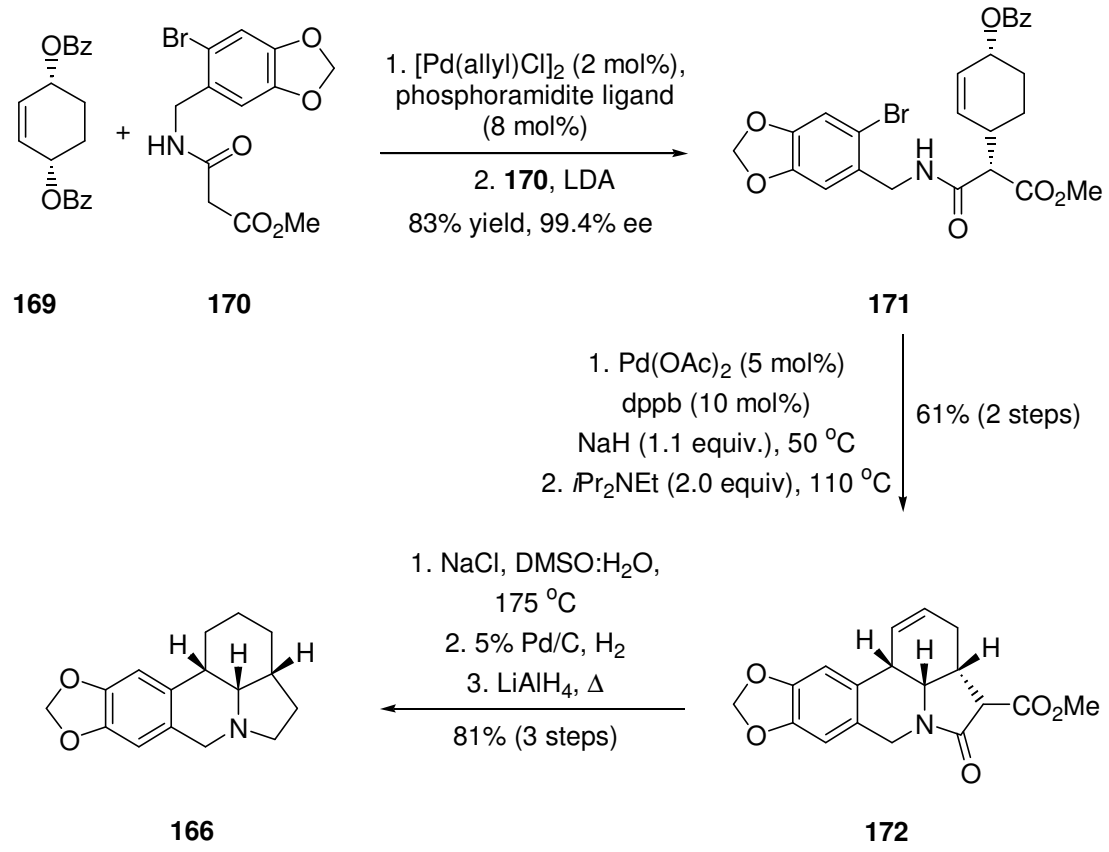
(+)-narciclasin **168**

Figure 11 - Lycorane type alkaloids

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

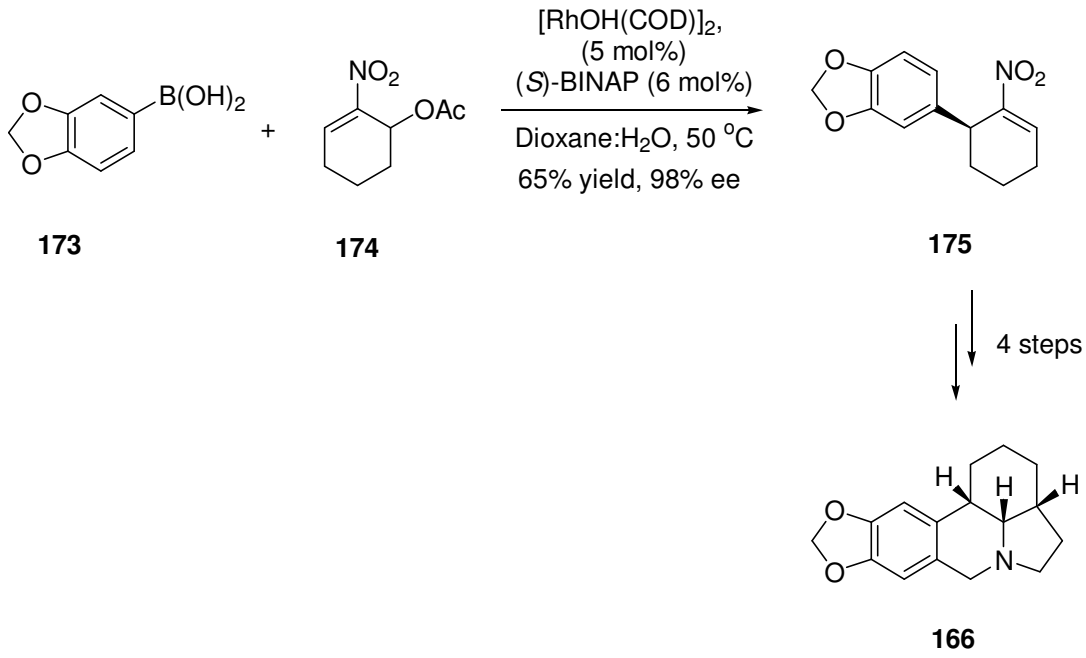
γ-Lycorane **166** has been the target of several racemic total syntheses.[88] Many fewer enantioselective approaches have been reported.[89-93] The first asymmetric approach to (+)-γ-lycorane **166** was reported by Mori and co-workers in 1995.[90] This used an asymmetric Pd(0)-catalysed allylic alkylation 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).[89] 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).



Scheme 59 - Ojima synthesis of (+)-γ-lycorane

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**.[93] 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.

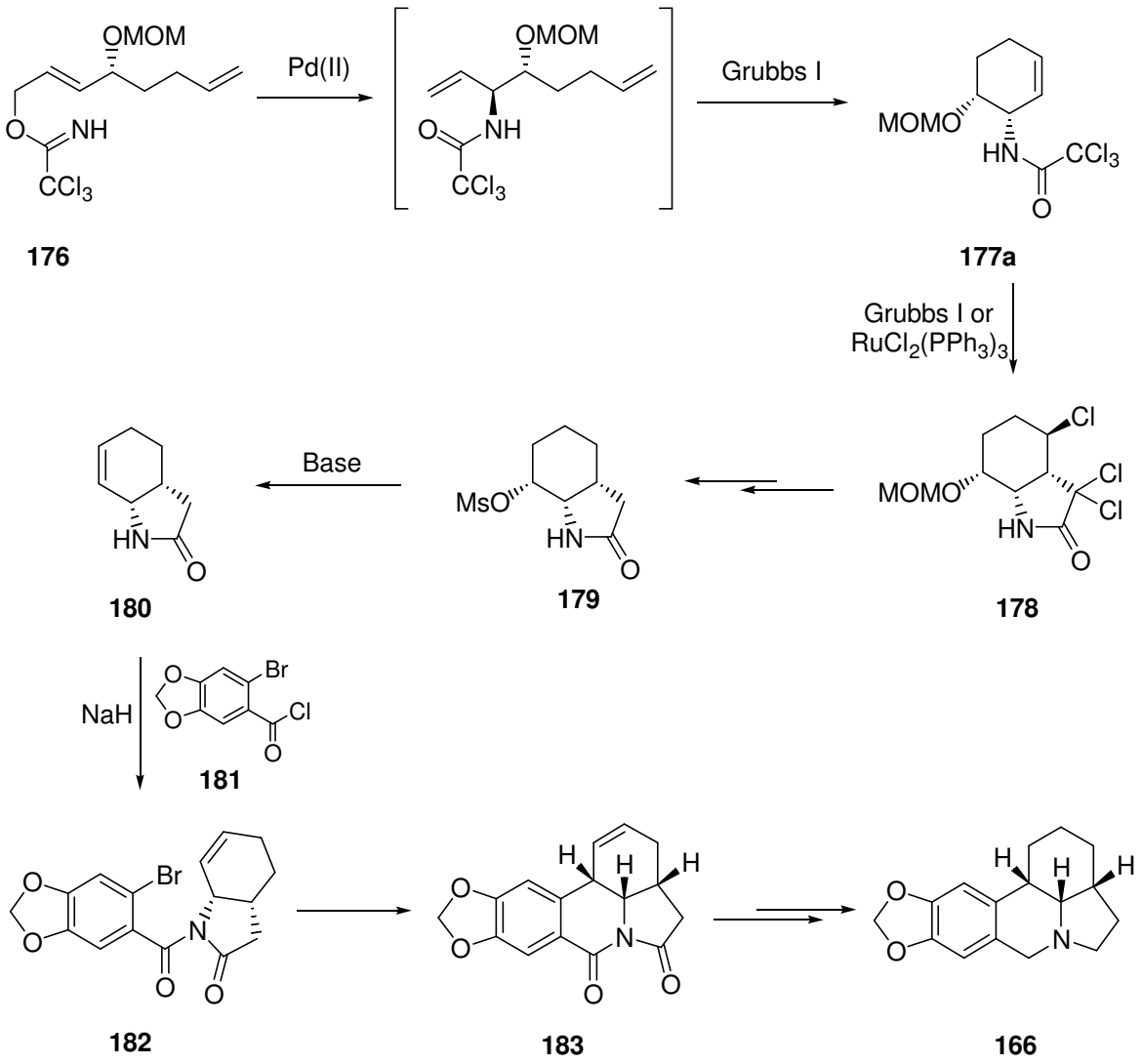


Scheme 60 - Gong synthesis of (+)-γ-lycorane

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

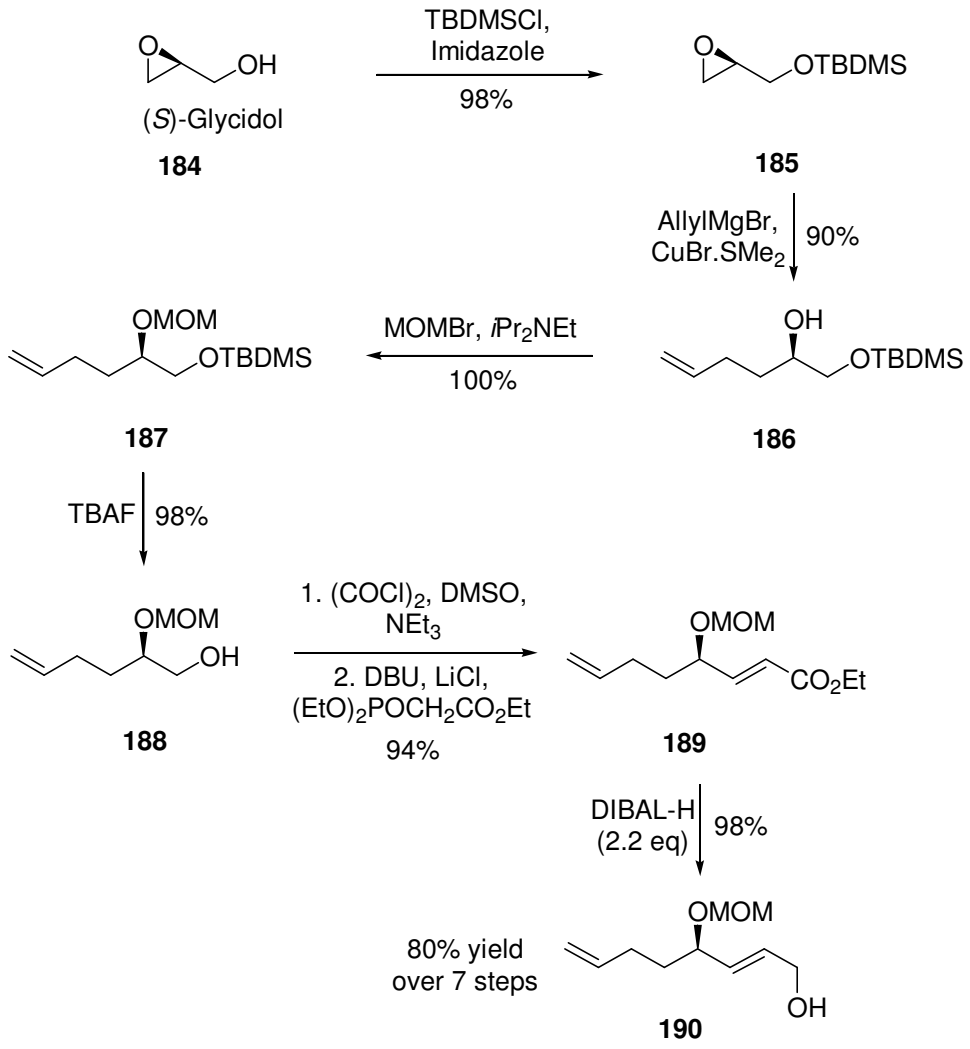
With these previous syntheses of (+)-γ-lycorane **166** in mind, our new synthetic approach is outlined below (Scheme 61). The key step of the proposed synthesis is an ether-directed tandem aza-Claisen rearrangement and ring closing metathesis reaction of allylic trichloroacetimidate **176**, to give 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).



Scheme 62 - Synthesis of allylic alcohol for directed rearrangement

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).

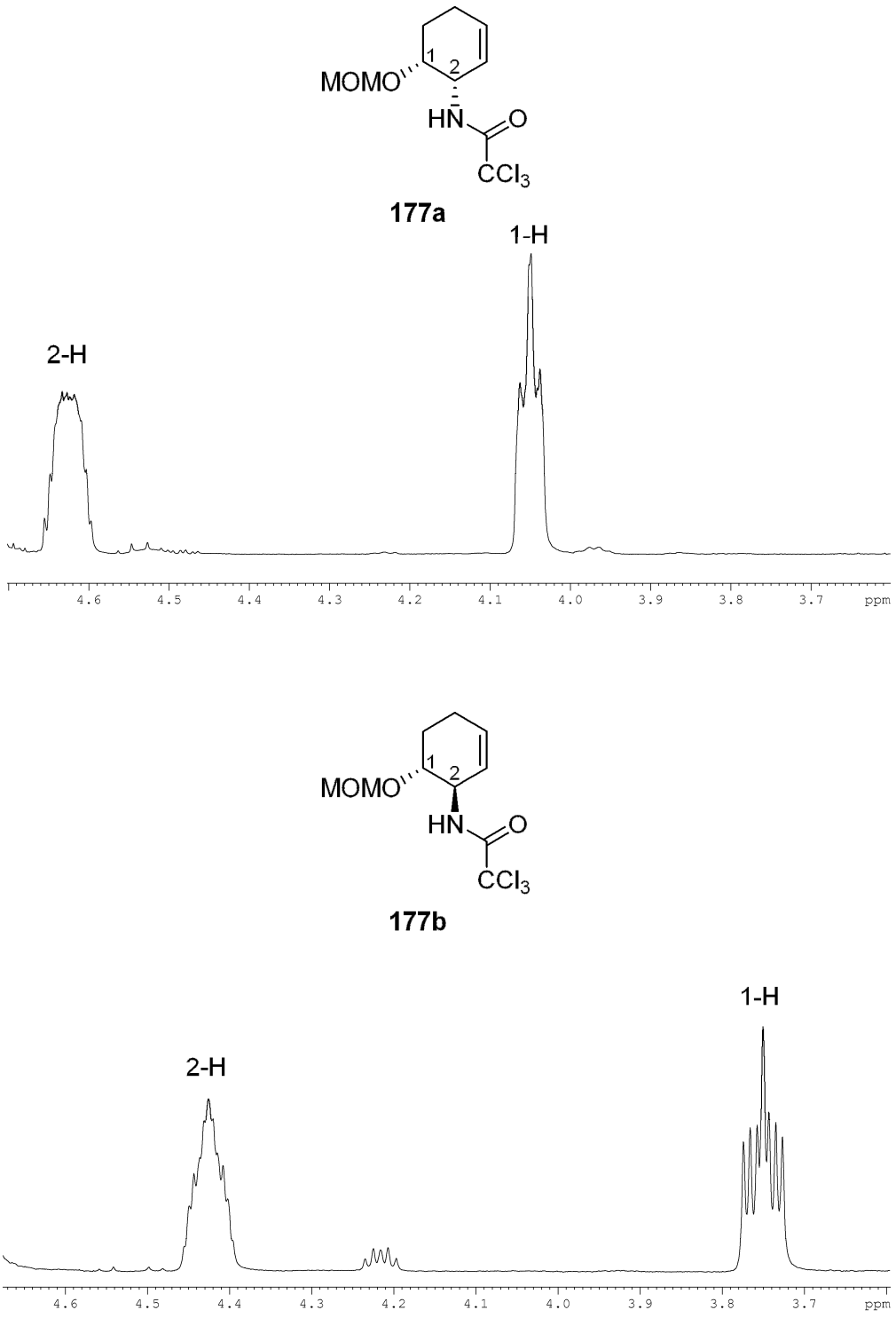
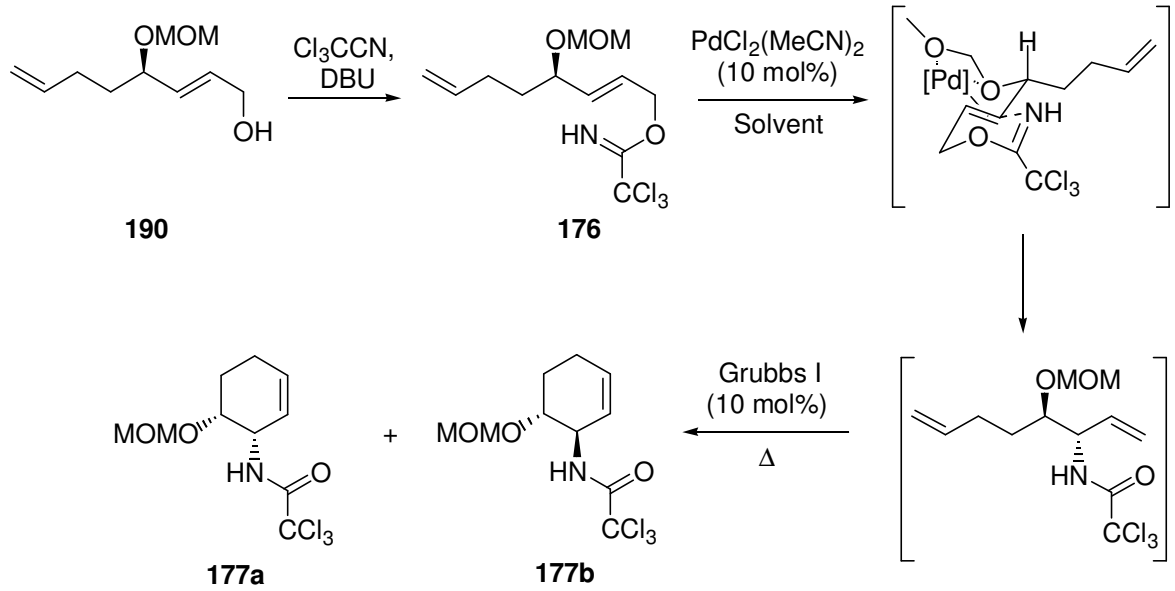


Figure 12 - ^{1}H NMR spectrum of cyclic products 177a and 177b

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.[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).



Reaction conditions	yield from **190** (%)	ratio (**a** : **b**)
DCM, RT	45	5 : 1
Toluene, 0 °C to RT	60	10 : 1

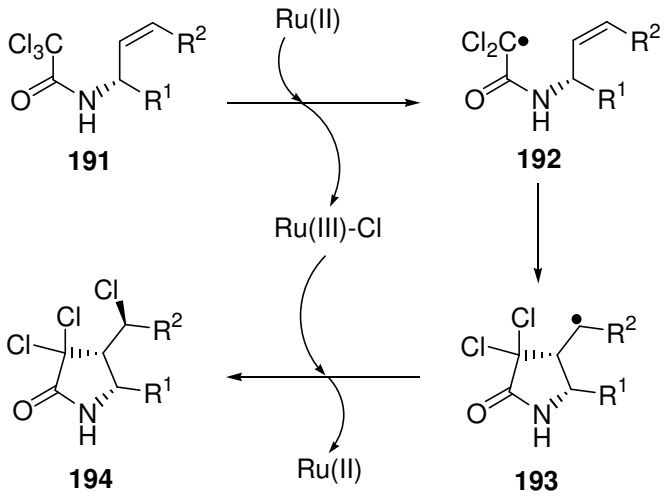
Scheme 63 - Ether-directed tandem aza-Claisen rearrangement and RCM reaction

2.4.5 Application towards the synthesis of (+)-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 (+)-γ-lycorane **166**.

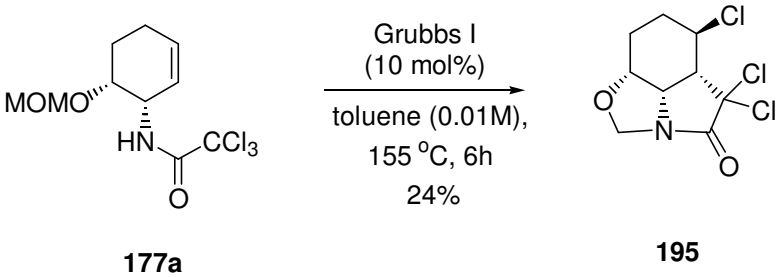
A Kharasch cyclisation is a Ru(II)-catalysed reaction that proceeds *via* a radical mechanism (Scheme 64), where ruthenium(II) attacks the trichloroacetyl group **191** forming a radical **192** and Ru(III)-Cl. The radical **192** then attacks the alkene and forms the

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.[94] The groups of Snapper and Itoh have previously reported Kharasch cyclisations upon similar substrates to **177a**, with the resulting products isolated in high yields.[80,94] 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**.



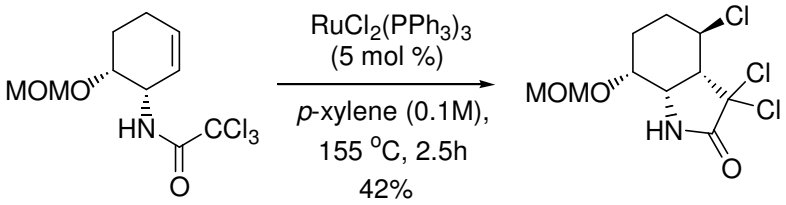
Scheme 64 - Radical mechanism of Kharasch cyclisation

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 ^{o}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 ^{o}C, the desired Kharasch product **178** was not isolated; instead a tricyclic product **195** was formed in a rather disappointing 24% yield (Scheme 65).



Scheme 65 - Kharasch cyclisation using Grubbs catalyst

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.[94] 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 ^oC) 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.



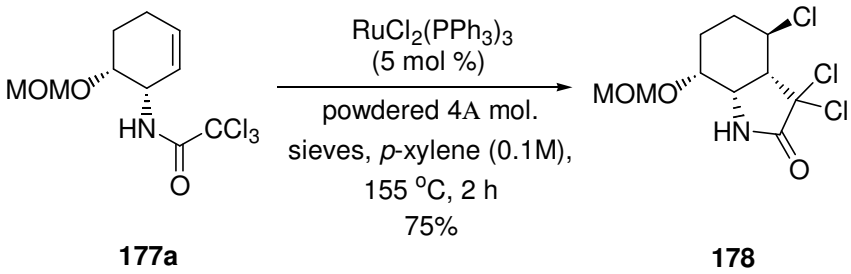
177a **178**

Scheme 66 - Kharasch cyclisation using $RuCl_2(PPh_3)_3$

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.

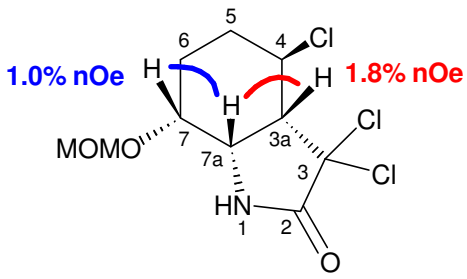
An acid scavenger was required that would trap any acid produced during the reaction and yet not interfere with the ruthenium-catalysed radical process. After a search, three possible additives were identified: DBU, K_2CO_3 and molecular sieves (4Å). All three reagents were then separately examined as additives to the Kharasch cyclisation. The addition of DBU yielded only the starting material **177a**, whilst K_2CO_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).



177a **178**

Scheme 67 - Optimised reaction conditions for Kharasch cyclisation

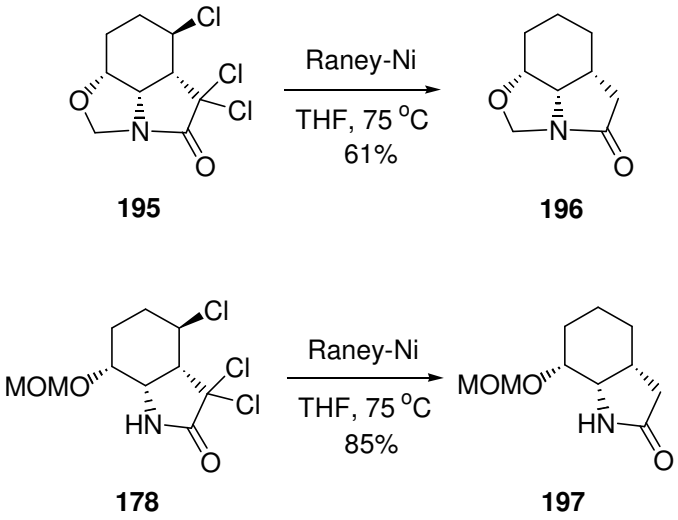
Previously Snapper and Itoh have shown that the Kharasch cyclisation occurs to give exclusively the *cis* ring junction.[80,94] This was confirmed for compound **178** by nOe studies, which showed a positive nOe between protons 3a and 7a (1.8%), thus proving that this compound also had the *cis* ring 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.



178

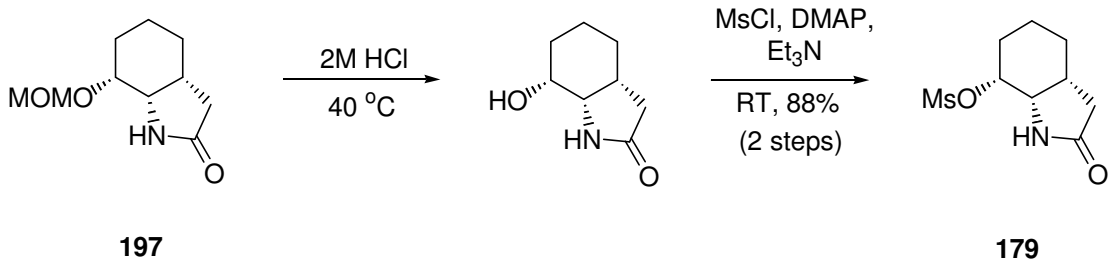
Figure 13 - nOe studies confirming *cis* ring junction

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,[96] resulting in formation of the desired dechlorinated products **196** and **197** in good yields (Scheme 68).



Scheme 68 - Dechlorination using Raney-Nickel

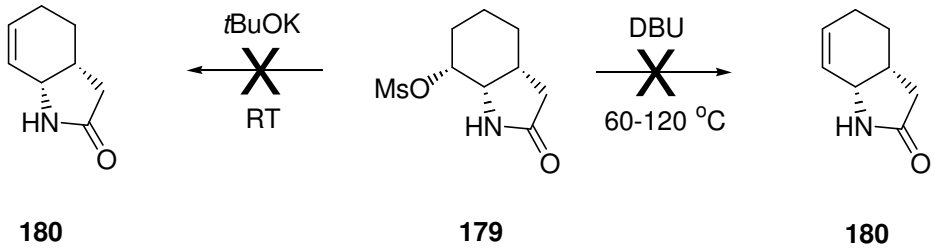
The next stage was to prepare methanesulfonate **179**. This was achieved by hydrolysis of the MOM group of **197** under acidic conditions, followed by introduction of the mesylate under standard conditions, giving **179** in an excellent 88% yield over 2 steps (Scheme 69).



Scheme 69 - Synthesis of mesylate

Elimination of mesylate **179** was then attempted. Initially, the strong base potassium *tert*-butoxide (*t*BuOK) 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 *t*BuOK 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

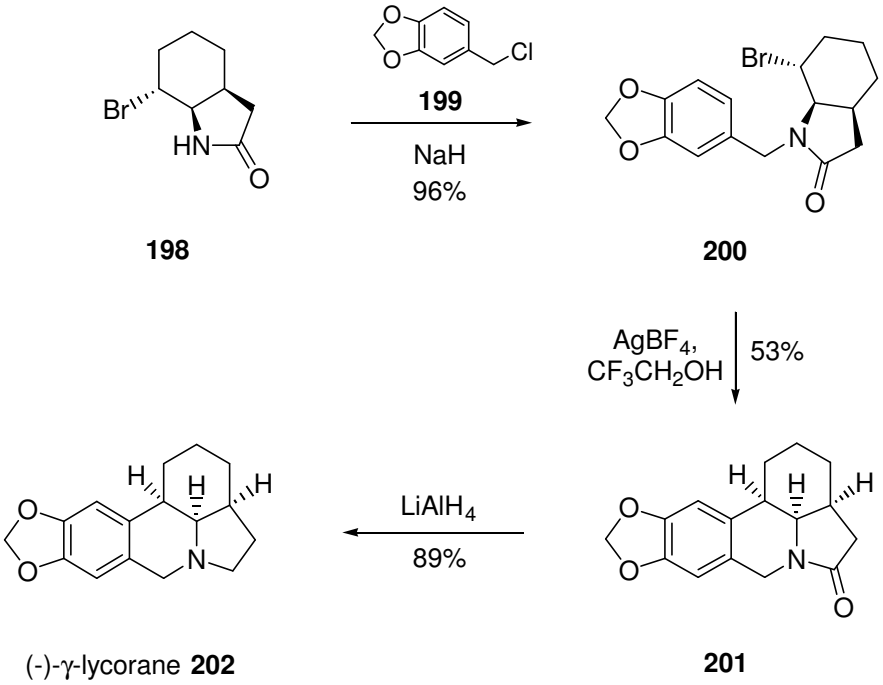
reactions require the leaving group and the hydrogen atom, which is to be removed by base, to have an *anti*-periplanar conformation. It is possible that the rigid 6,5-ring system of **179**, prevents it from adopting such a conformation, hence the lack of reactivity. It was decided in the light of this to pursue an alternative synthetic strategy.



180 **179** **180**

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]

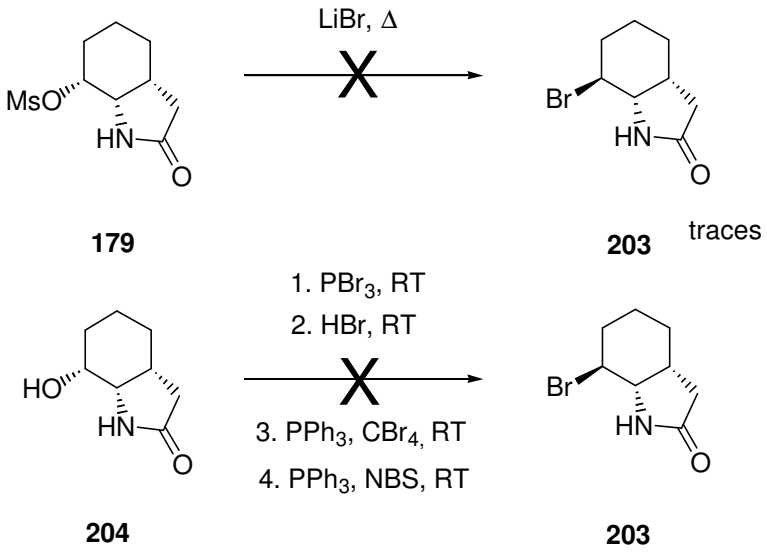


198 **200**

(-)-γ-lycorane **202** **201**

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

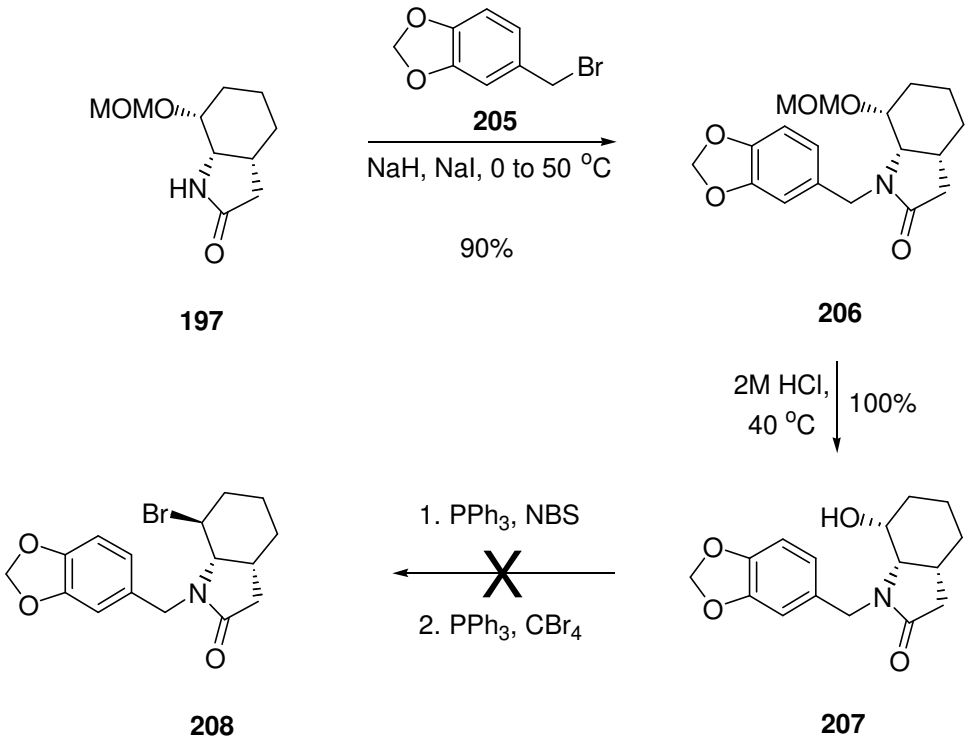
It was hoped that a simple nucleophilic S_N2 reaction of mesylate **179** or an activated intermediate of alcohol **204** would provide **203** (the enantiomer of **198**), thus allowing the use of similar chemistry to complete the synthesis of (+)-γ-lycorane **166**. The mesylate **179** or alcohol **204** was therefore treated under a variety of bromination conditions to attempt to synthesise **203** (Scheme 72).



Scheme 72 - Attempts at bromination

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.

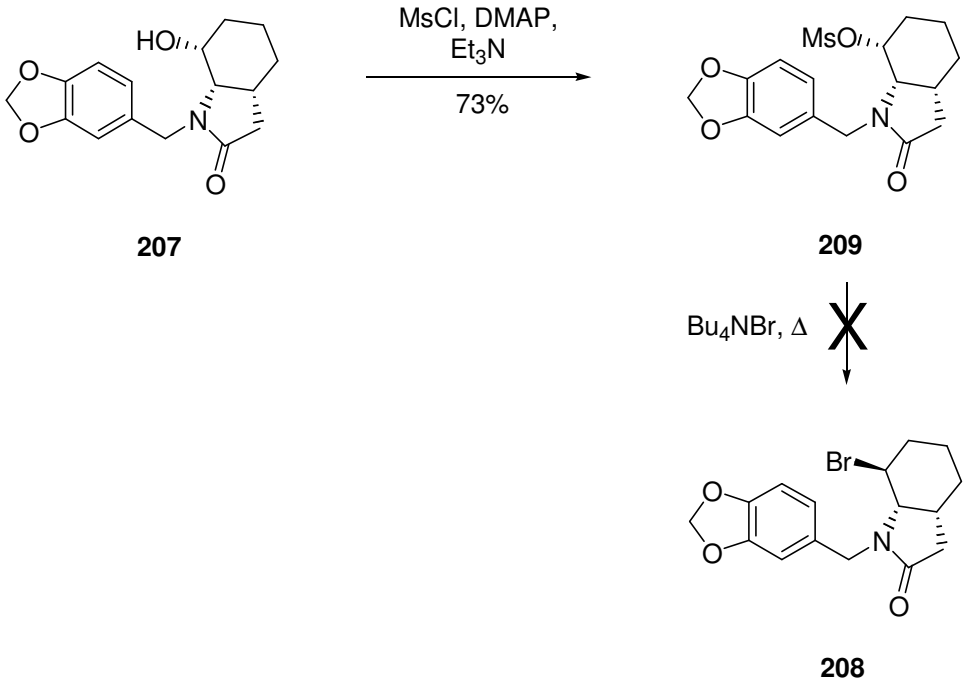
Initial attempts to perform the acylation using mesylate **179** were unsuccessful. The ^{1}H NMR showed a complex mixture of compounds and none of the desired product was observed. In addition, the signals associated with the mesylate were no longer present, and so, it appeared that the strong base (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

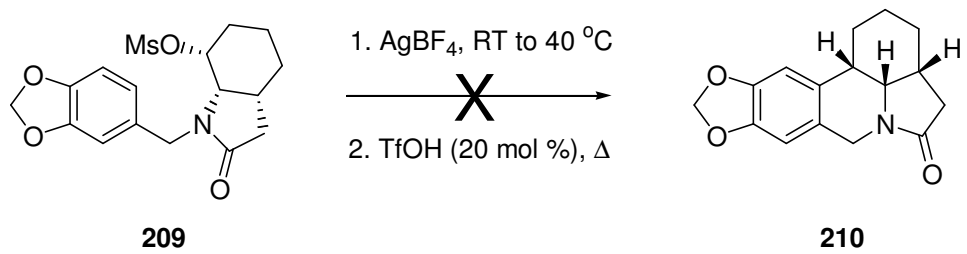
The exact reasons why various attempts to synthesise the bromide have been unsuccessful are unclear and could involve a combination of factors.

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).



Scheme 74 - A further attempt to introduce the bromide

Mesylates have previously been shown to undergo Friedel-Crafts reactions.[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.



Scheme 75 - Attempts at Friedel-Crafts reaction

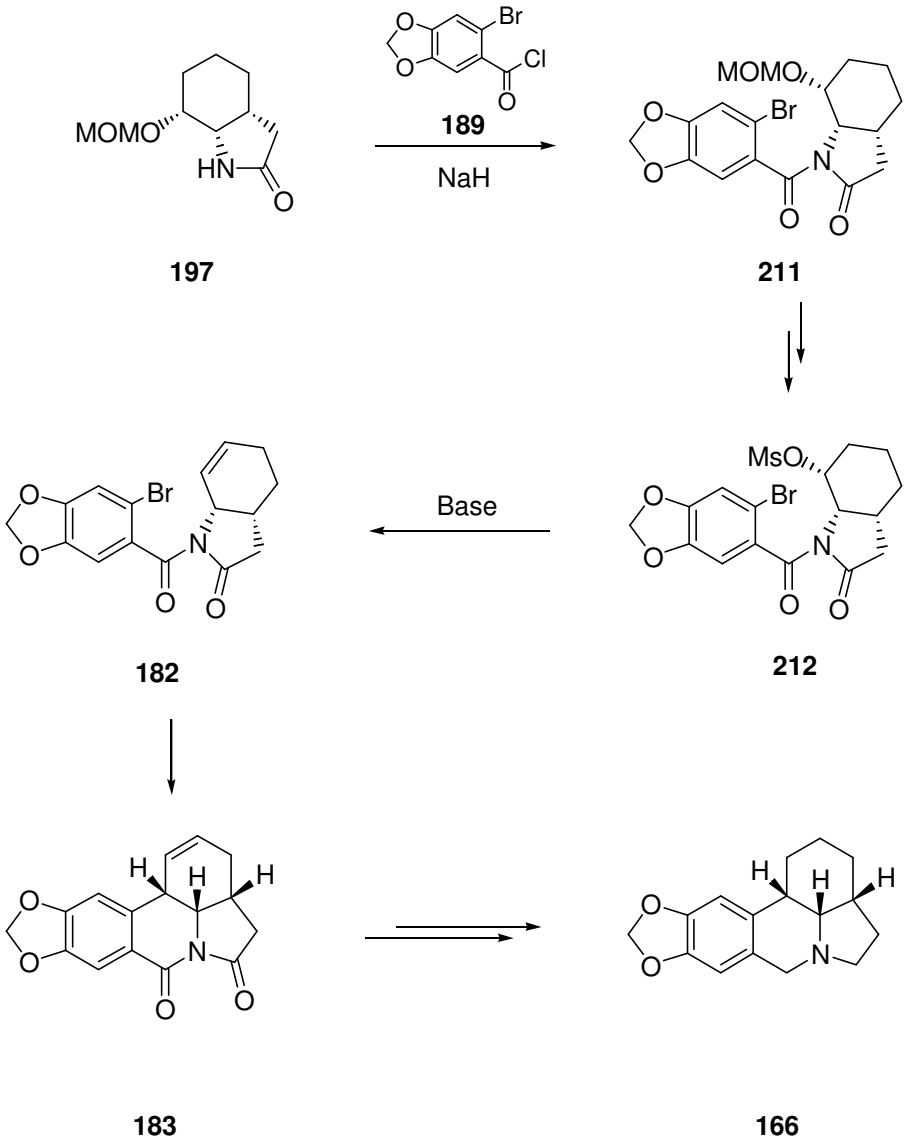
Due to time and material constraints, work was halted at this stage and although there are a number of alternatives that could still be attempted, it appears that conversion of the hydroxyl group to the bromide either directly or *via* the mesylate, will not be successful. It is not clear why this is 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.

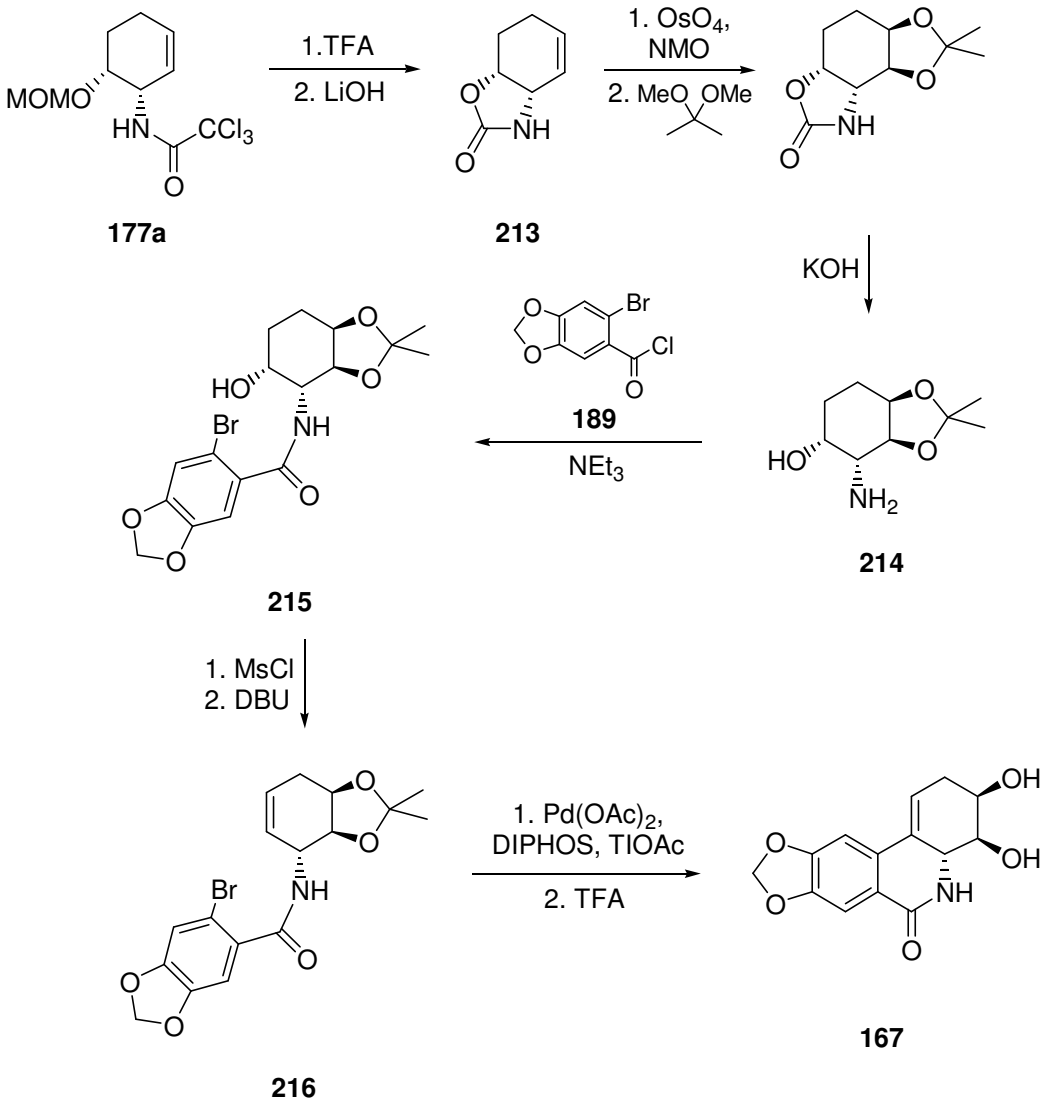
2.4.7 Future Work

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.[89,90] Thus, the synthesis of (+)-γ-lycorane **166**, should still be achievable using this highly successful ether-directed tandem aza-Claisen rearrangement and RCM methodology.



Scheme 76 - Proposed final steps for the total synthesis of (+)-γ-lycorane

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.[101] 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-deoxylycoricidine

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 $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_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 (λ = 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 ^oC. 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 ^oC 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

($MgSO_4$) 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 ^{o}C. DIBAL-H (1 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was stirred at -78 ^{o}C for 3 h, before warming to room temperature. The solution was cooled to 0 ^{o}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 ($MgSO_4$) 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 ($MgSO_4$) 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 ^{o}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 ^{o}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 ^{o}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 equiv.) was dissolved in DCM (20 mL) and cooled to 0 ^{o}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.

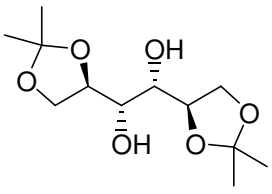
General procedure 7: Ruthenium trichloride catalysed oxidation to carboxylic acid.

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.

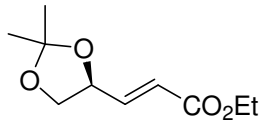
1,2,5,6-Di-*O*-isopropylidene-D-mannitol (94).[102]



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 ($MgSO_4$) 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

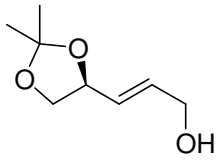
(12.55 g, 58%). mp 114-118 °C, lit.[102] 115-119 °C; δ_H (400 MHz, $CDCl_3$) 1.29 (6H, s, CH_3), 1.35 (6H, s, CH_3), 2.51 (2H, br s, 2 x OH), 3.67 (2H, d, *J* 6.7 Hz, 3-H and 4-H), 3.92 (2H, dd, *J* 8.4, 5.3 Hz, 1-*H*H and 6-*H*H), 4.00-4.14 (4H, m, 1-H*H*, 2-H, 5-H and 6-H*H*); δ_C (100 MHz, $CDCl_3$) 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 (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxypentan-2-enoate (95).[103]



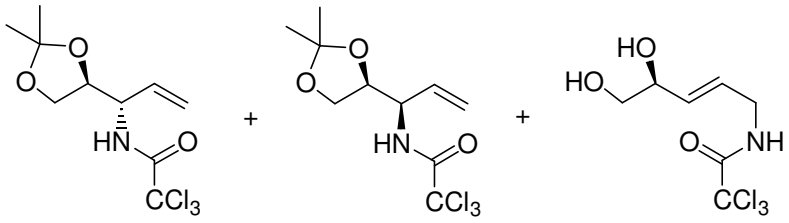
1,2,5,6-Di-*O*-isopropylidene-D-mannitol **94** (7.0 g, 26.7 mmol) was suspended in 5% sodium hydrogen carbonate solution (75.0 mL) and cooled to 0 °C. Sodium periodate (6.9 g, 32.2 mmol) in water (15.0 mL) was added dropwise to the suspension and the reaction mixture was stirred at room temperature 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, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.34 (3H, s, CH_3), 1.38 (3H, s, CH_3), 3.61 (1H, dd, *J* 7.9, 7.5 Hz, 5-*H*H), 4.09-4.17 (3H, m, OCH_2 and 5-H*H*), 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); δ_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).

(2*E*,4*S*)-4,5-(*O*-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (96).[104]



Reaction was carried out according to general procedure 2 using ethyl (2*E*,4*S*)-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, $CHCl_3$), lit.[104] $[\alpha]_D^{24}$ +33.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, CH_3), 1.43 (3H, s, CH_3), 3.61 (1H, dd, *J* 8.1, 7.6 Hz, 5-*H*H), 4.10 (1H, dd, *J* 8.1, 6.1 Hz, 5-H*H*), 4.16 (2H, d, *J* 5.0 Hz, 1-H_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); δ_C (100 MHz, $CDCl_3$) 25.9 (CH_3), 26.7 (CH_3), 62.5 (CH_2), 69.4 (CH_2), 76.5 (CH), 109.4 (C), 128.3 (CH), 133.2 (CH); *m/z* (CI) 159 (MH^+, 100%), 141 (27), 83 (49).

Synthesis of (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2*E*,4*S*)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using $PdCl_2(MeCN)_2$ as catalyst.



The reaction was carried out according to general procedure 4 using (2*E*,4*S*)-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 ^oC 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**: υ_{max}/cm^{-1} (neat) 3418 (NH), 2988 (CH), 1719 (CO), 1506 (C=C), 1373, 1217, 1068; (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-

isopropylidene)-4,5-dihydroxypenta-1-ene **98b**: $[\alpha]_D^{25}$ +34.4 (*c* 1.0, $CHCl_3$); δ_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, 6-*H*H), 4.04 (1H, dd, *J* 8.6, 6.5 Hz, 5-H*H*), 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); δ_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^+. $C_{10}H_{15}O_3N^{35}Cl^{37}Cl_2$ requires 306.0062), 293 (40%), 244 (75), 210 (80), 176 (100) 71 (60). Data for (2*S*,3*R*)-(3*S,*4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene **98a**: δ_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-*H*H), 4.02 (1H, dd, *J* 9.1, 5.1 Hz, 5-H*H*), 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); δ_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 (2*E*,4*S*)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene **98c**: υ_{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, $CHCl_3$), δ_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-*H*H), 4.78 (1H, dd, *J* 9.8, 8.3 Hz, 5-H*H*), 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); δ_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) 261.9726 (MH^+, $C_7H_{11}NO_3{}^{35}Cl_3$ requires 261.9729), 244 (100%), 228 (41), 210 (38), 192 (15), 118 (95).

Synthesis of (3*S,*4*S*,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R,*4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2*E*,4*S*)-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 (2*E*,4*S*)-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 ^oC 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 (3*S*,4*S*,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2*E*,4*S*)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (98c) using $HAuCl_4.3H_2O$ as catalyst.

The reaction was carried out according to general procedure 4 using (2*E*,4*S*)-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 ^oC 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 (3*S*,4*S*,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2*E*,4*S*)-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 (2*E*,4*S*)-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 ^oC 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 (3*S*,4*S*,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b), using (*S*)-COP-Cl as catalyst.

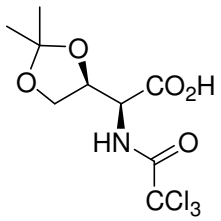
The reaction was carried out according to general procedure 4 using (2*E*,4*S*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol **96** (1.00 g, 6.3 mmol) and di-μ-chlorobis[η^5-

(*S*)-(p*R*)-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 ^oC for 7 days. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 9 : 1) yielded **98b** followed by **98b**, as brown oils (1.55 g, 81% combined yield) and in a 52 : 1 ratio (**98b** : **98a**). Spectroscopic data as reported above.

Synthesis of (3*S,*4*S*,)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98a), (3*R,*4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (98b) and (2*E*,4*S*)-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 (2*E*,4*S*)-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-[(4*R*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-2,4-cyclopentadien-1-ylidene]]dicobalt [(*R*)-COP-Cl] (0.023 g, 3 mol%) was used as catalyst. The reaction mixture was stirred at 38 ^oC 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.

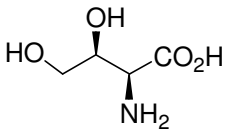
(2*S*,3*S*)-2-(2',2',2'-Trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)-4,5-dihydroxybutanoic acid (99).



The reaction was carried out according to general procedure 7 using (3*R,*4*S*)-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.

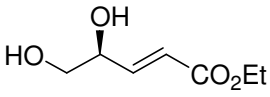
υ_{max}/cm^{-1} (neat) 3423 (NH and OH), 2990 (CH), 1694 (CO); $[\alpha]_D^{21}$ -58.0 (*c* 0.25, MeOH); δ_H (400 MHz, CD_3OD) 1.35 (3H, s, CH_3), 1.44 (3H, s, CH_3), 3.84 (1H, dd, *J* 8.9, 5.7 Hz, 4-*H*H), 4.19 (1H, dd, *J* 8.9, 6.6 Hz, 4-H*H*), 4.59 (1H, d, *J* 4.3 Hz, 2-H) 4.68-4.73 (1H, m, 3-H); δ_C (100 MHz, CD_3OD) 25.1 (CH_3), 26.8 (CH_3), 56.8 (CH), 67.8 (CH_2), 76.2 (CH), 93.6 (C), 111.0 (C), 164.0 (C), 171.4 (C); *m/z* (CI) 321.9835 (MH^+. $C_9H_{13}O_5N^{35}Cl_2{}^{37}Cl$ requires 321.9831), 264 (100%), 228 (50).

(2*S*,3*S*)-2-Amino-3,4-dihydroxybutyric acid (91).[105]



The reaction was carried out according to general procedure 8 using (2*S*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3,4-(*O*-isopropylidene)-4,5-dihydroxybutanoic acid **99** (0.16 g, 0.5 mmol). Purification by ion exchange chromatography (elution with 0.5 M NH_4OH solution) yielded (2*S*,3*S*)-2-amino-3,4-dihydroxybutyric acid **91** as a white solid (0.07 g, 100% yield). Spectroscopic data in agreement with literature.[105] $[\alpha]_D^{18}$ -9.6 (*c* 1.0, H_2O); lit.[105] $[\alpha]_D^{26}$ -10.0 (*c* 1.0, H_2O); δ_H (400 MHz, D_2O) 3.59-3.68 (3H, m, 3-H and 4-H_2), 4.03-4.08 (1H, m, 2-H); δ_C (100 MHz, D_2O) 56.7 (CH), 63.3 (CH_2), 69.3 (CH), 172.7 (C); *m/z* (CI) 136 (MH^+, 6%), 123 (13), 91 (30), 83 (100), 69 (76), 67 (48).

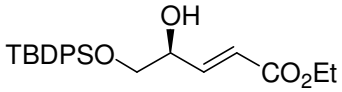
Ethyl (2*E*,4*S*)-4,5-dihydroxypent-2-enoate (100).[106]



Ethyl (2*E*,4*S*)-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 *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 (*c* 0.5, $CHCl_3$), lit.[106] $[\alpha]_D^{25}$ -5.8 (*c* 1.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.60 (2H, br s, 2 x OH), 3.53 (1H, dd, *J* 11.5, 7.1 Hz, 5-*H*H), 3.74 (1H, dd, *J* 11.5, 3.4 Hz, 5-H*H*), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.39-4.45

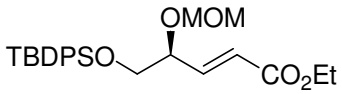
(1H, m, 4-H), 6.12 (1H, dd, *J* 15.7, 1.8 Hz, 2-H), 6.90 (1H, dd, *J* 15.7, 4.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$), 14.2 (CH_3), 60.8 (CH_2), 65.6 (CH_2), 71.7 (CH), 121.9 (CH), 146.3 (CH), 166.7 (C); *m/z* (CI) 161 (MH^+, 100%), 99 (57), 75 (30).

Ethyl (2*E*,4*S*)-4-hydroxy-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate (101). [107]



Ethyl (2*E*,4*S*)-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 ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether : diethyl ether, 10 : 1) yielded ethyl (2*E*,4*S*)-4-hydroxy-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate **101**, as a clear oil (2.48 g, 100%). $[\alpha]_D^{25}$ -17.8 (*c* 1.6, $CHCl_3$), lit.[107] $[\alpha]_D^{22}$ -16.4 (*c* 0.17, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, $C(CH_3)_3$), 1.27 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.74 (1H, br d, *J* 4.2 Hz, 4-OH), 3.55 (1H, dd, *J* 10.2, 4.0 Hz, 5-*H*H), 3.76 (1H, dd, *J* 10.2, 2.1 Hz, 5-H*H*), 4.19 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 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); δ_C (100 MHz, $CDCl_3$), 14.3 (CH_3), 19.3 (C), 26.9 (CH_3), 60.5 (CH_2), 67.0 (CH_2), 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).

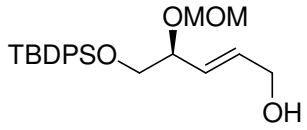
Ethyl (2*E*,4*S*)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate (102).[107]



The reaction was carried out according to general procedure 3 using ethyl (2*E*,4*S*)-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%). $[\alpha]_D^{25}$ +11.7 (*c* 2.9, $CHCl_3$), lit.[107] $[\alpha]_D^{21}$ +12.3 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, $C(CH_3)_3$), 1.30 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 3.38 (3H, s, OCH_3), 3.69 (1H, dd, *J* 11.1, 5.0 Hz, 5-*H*H), 3.77 (1H, dd, *J* 11.1, 6.2 Hz, 5-

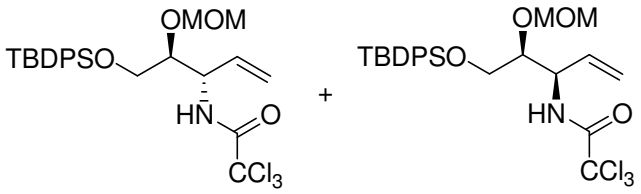
H*H*), 4.22 (2H, q, *J* 7.2 Hz, OC*H*$_2$CH$_3$), 4.35-4.40 (1H, m, 4-H), 4.67 (1H, d, *J* 7.1 Hz, OC*H*HO), 4.72 (1H, d, *J* 7.1 Hz, OCH*H*O), 5.68 (1H, dd, *J* 16.3, 2.0 Hz, 2-H), 6.90 (1H, dd, *J* 16.3, 6.4 Hz, 3-H), 7.34-7.48 (6H, m, Ph), 7.56-7.72 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$), 14.3 (CH_3), 19.3 (C), 26.8 (CH_3), 55.6 (CH_3), 60.5 (CH_2), 66.1 (CH_2), 75.9 (CH), 95.2 (CH_2), 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).

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



The reaction was carried out according to general procedure 2 using ethyl (2*E*,4*S*)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-2-enoate **102** (2.80 g, 6.0 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 1 : 1) yielded (2*E*,4*S*)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol **103**, as a yellow oil (2.19 g, 86%). υ_{max}/cm^{-1} (neat) 3422 (OH), 3071 (CH), 2931 (CH), 1589 (C=C), 1428, 1112 (C-O), 704; $[\alpha]_D^{28}$ +31.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, $C(CH_3)_3$), 1.29 (1H, br s, OH), 3.37 (3H, s, OCH_3), 3.63 (1H, dd, *J* 11.1, 6.0 Hz, 5-*H*H), 3.74 (1H, dd, *J* 11.1, 7.6 Hz, 5-H*H*), 4.12 (2H, br d, *J* 5.0 Hz, 1-H_2), 4.18-4.24 (1H, m, 4-H), 4.64 (1H, d, *J* 7.1 Hz, OC*H*HO), 4.70 (1H, d, *J* 7.1 Hz, OCH*H*O), 5.58 (1H, ddt, *J* 16.3, 8.0, 2.1 Hz, 3-H), 5.89 (1H, dtd, *J* 16.3, 5.0, 1.0 Hz, 2-H), 7.37-7.45 (6H, m, Ph), 7.67-7.71 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$), 19.3 (C), 26.8 (CH_3), 55.4 (CH_3), 63.0 (CH_2), 66.8 (CH_2), 76.8 (CH), 94.4 (CH_2), 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 (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-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 (2*E*,4*S*)-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 (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-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. (3*R*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b**: $[\alpha]_D^{25}$ +5.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 3.30 (3H, s, OCH_3), 3.65 (1H, dd, *J* 11.1, 8.0 Hz, 5-*H*H), 3.74 (1H, dd, *J* 11.1, 7.3 Hz, 5-H*H*), 3.88-3.92 (1H, m, 4-H), 4.61 (1H, d, *J* 7.1 Hz, OC*H*HO), 4.67 (1H, d, *J* 7.1 Hz, OCH*H*O), 4.81-4.84 (1H, m, 3-H), 5.29-5.36 (2H, m, 1-H_2), 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, $CDCl_3$) 19.2 (C), 26.8 (CH_3), 53.5 (CH), 55.9 (CH_3), 63.0 (CH_2), 78.0 (CH), 93.0 (C), 96.6 (CH_2), 116.8 (CH_2), 127.8 (CH), 129.9 (CH), 132.9 (C), 134.6 (CH), 135.6 (CH), 161.5 (C). (3*S*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (**105a**): $[\alpha]_D^{25}$ -28.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 3.40 (3H, s, OCH_3), 3.65-3.82 (3H, m, 5-H_2 and 4-H), 4.60-4.76 (3H, m, O*C*H_2O and 3-H), 5.28-5.35 (2H, m, 1-H_2), 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, $CDCl_3$) 19.2 (C), 26.9 (CH_3), 54.4 (CH), 55.9 (CH_3), 63.8 (CH_2), 81.7 (CH), 93.1 (C), 97.7 (CH_2), 118.8 (CH_2), 127.8 (CH), 129.9 (CH), 131.6 (C),

132.9 (CH), 135.6 (CH), 161.4 (C). *m/z* (CI) 544.1249 (MH^+ $C_{12}H_{33}O_4N^{35}Cl_3Si$ requires 544.1244), 512 (100%), 478, (35), 448 (20), 344 (16), 257 (10).

Synthesis of (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-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*,4*S*)-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*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-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 (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-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*,4*S*)-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*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-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 (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-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 (2*E*,4*S*)-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 (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-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 (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-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 (2*E*,4*S*)-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 (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-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.

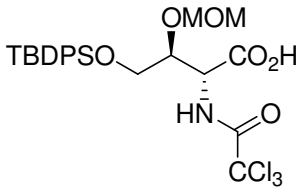
Synthesis of (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105b) using gold(III) chloride catalysed aza-Claisen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

The reaction was carried out according to general procedure 4, using (2*E*,4*S*)-4-(methoxymethoxy)-5-(*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 (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*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 (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105a) and (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene (105b) using (*R*)-COP-Cl catalysed aza-Claisen rearrangement.

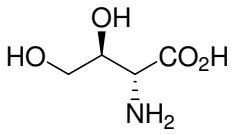
The reaction was carried out according to general procedure 4, using (2*E*,4*S*)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol **103** (0.10 g, 0.5 mmol) and [bis[μ-chloro]dipalladium]bis[(η^4-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]]bis[μ-[(1-η:1,2,3,4,5-η)-2-[(4*R*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-2,4-cyclopentadien-1-ylidene]]dicobalt [(*R*)-COP-Cl] (10 mol%) was used as catalyst, in DCM (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*tert*-butyldiphenylsilyloxy)pent-1-ene **105b** followed by (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)-5-(*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.

(2*R*,3*S*)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-methoxymethoxy-4-(*tert*-butyldiphenylsilyloxy)butanoic acid (106).



The reaction was carried out according to general procedure 7 using (3*R*,4*S*)-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 ($MgSO_4$) and concentrated *in vacuo* to give (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-methoxymethoxy-4-(*tert*-butyldiphenylsilyloxy)butanoic acid **106** (0.15 g, 71% yield) as a brown oil. υ_{max}/cm^{-1} (neat) 3334 (NH and OH), 2958 (CH), 1774 (CO); $[\alpha]_D^{24}$ -12.5 (*c* 1.5, MeOH); δ_H (400 MHz, CD_3OD) 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-*H*H), 3.92 (1H, dd, *J* 10.8, 4.6 Hz, 4-H*H*), 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, OC*H*HO), 4.58 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.22-7.35 (6H, m, Ph), 7.59-7.63 (4H, m, Ph); δ_C (100 MHz, CD_3OD) 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).

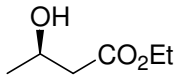
(2*R*,3*S*)-2-Amino-3,4-dihydroxybutyric acid (90).[64]



(2*R*,3*S*)-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

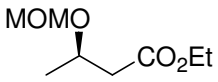
give a brown oil (0.1g), which was then dissolved in 6 M hydrochloric acid solution (10 mL) and heated under reflux overnight. After cooling to room temperature the reaction mixture was extracted with diethyl ether (10 mL). The aqueous phase was then concentrated *in vacuo* to give the crude product. Purification by ion exchange chromatography (eluting with 0.5 M NH_4OH solution), yielded (2*R*,3*S*)-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, H_2O), lit.[64] $[\alpha]_D^{24}$ +11.3 (*c* 7.0, H_2O); δ_H (400 MHz, D_2O) 3.66-3.71 (2H, m, 4-H_2), 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 (3*R*)-3-hydroxybutanoate (115).[108]



Poly-(3*R*)-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 ($MgSO_4$) and concentrated to give the crude product. Distillation under vacuum gave the title compound **115** as a colourless oil (6.9 g, 52%). $[\alpha]_D^{21}$ -39.6 (*c* 1.0, $CHCl_3$), lit.[108] $[\alpha]_D^{25}$ -42.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.1 Hz, 4-H_3), 1.28 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.42 (1H, dd, *J* 9.7, 6.1 Hz, 2-*H*H), 2.50 (1H, dd, *J* 9.7, 2.5 Hz, 2-H*H*), 3.10 (1H, br s, OH), 4.15-4.21 (3H, m, OCH_2CH_3 and 3-H); *m/z* (CI) 133 (MH^+, 100%), 115 (9), 87 (8).

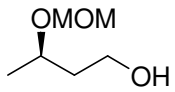
Ethyl (3*R*)-3-methoxymethoxybutanoate (116).[109]



Reaction was carried out according to general procedure 3 using ethyl (3*R*)-3-hydroxybutanoate **115** (5.00 g, 0.04 mol). Purification by flash column chromatography (elution with petroleum ether : ethyl acetate, 9 : 1) yielded ethyl (3*R*)-3-methoxymethoxybutanoate **116**, as a clear oil (5.27 g, 75%). $[\alpha]_D^{22}$ -10.4 (*c* 1.5, $CHCl_3$),

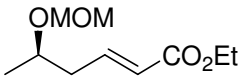
lit.[109] $[\alpha]_D^{25}$ -11.7 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.1 Hz, 4-H_3), 1.27 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.41 (1H, dd, *J* 15.2, 5.5 Hz, 2-*H*H), 2.59 (1H, dd, *J* 15.2, 7.0 Hz, 2-H*H*), 3.36 (3H, s, OCH_3), 4.12-4.19 (3H, m, OCH_2CH_3 and 3-H), 4.65 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.68 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 20.6 (CH_3), 42.4 (CH_2), 55.4 (CH_3), 60.4 (CH_2), 70.4 (CH), 95.4 (CH_2), 171.3 (C); *m/z* (CI) 177 (MH^+, 8%), 145 (100), 115 (5).

(3*R*)-3-Methoxymethoxybutan-1-ol (117).[110]



The reaction was carried out according to general procedure 2 using ethyl (3*R*)-3-methoxymethoxybutanoate **116** (5.00 g, 30.0 mmol). Flash column chromatography (elution with petroleum ether : diethyl ether, 3 : 2) gave (3*R*)-3-methoxymethoxybutan-1-ol **117** as a light yellow oil (3.0 g, 80%). Spectroscopic data in agreement with literature.[110] $[\alpha]_D^{21}$ -91.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, *J* 6.3 Hz, 4-H_3), 1.71-1.79 (2H, m, 2-H_2), 2.39 (1H, br s, OH), 3.40 (3H, s, OCH_3), 3.70-3.85 (2H, m, 1-H_2), 3.90-3.98 (1H, m, 3-H), 4.64 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_3), 39.2 (CH_2), 55.5 (CH_3), 60.2 (CH_2), 72.2 (CH), 95.0 (CH_2); *m/z* (CI) 135 (MH^+, 30%), 103 (100), 73 (8).

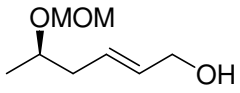
Ethyl (2*E*,5*R*)-5-methoxymethoxyhex-2-enoate (118).



Reaction carried out according to general procedure 1 using (3*R*)-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). υ_{max}/cm^{-1} (neat) 2974 (CH), 1716 (CO), 1655 (C=C), 1454, 1373; $[\alpha]_D^{22}$ +3.3 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.3 Hz, 6-H_3), 1.28 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 2.32-2.49 (2H, m, 4-H_2), 3.36 (3H, s, OCH_3), 3.81-3.89 (1H, m, 5-H), 4.19 (2H, q, *J* 7.0 Hz, OCH_2CH_3), 4.62 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.69 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.88 (1H, dt, *J* 15.7, 1.4 Hz, 2-H), 6.96 (1H, dt, *J* 15.7, 7.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 20.3 (CH_3), 39.6 (CH_2),

55.4 (CH_3), 60.2 (CH_2), 71.8 (CH), 94.9 (CH_2), 123.6 (CH), 145.1 (CH), 166.3 (C); *m/z* (CI) 203.1285 (MH^+. $C_{10}H_{19}O_4$ requires 203.1283), 171 (100%), 141 (10).

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



The reaction was done according to general procedure 2 using ethyl (2*E*,5*R*)-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 (2*E*,5*R*)-5-methoxymethoxyhex-2-en-1-ol **119** as a light yellow oil (0.9 g, 98%). υ_{max}/cm^{-1} (neat) 3410 (OH), 2931 (CH), 1662 (C=C), 1450, 1381; $[\alpha]_D^{22}$ +6.3 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.2 Hz, 6-H_3), 1.60 (1H, br s, OH), 2.19-2.36 (2H, m, 4-H_2), 3.36 (3H, s, OCH_3), 3.76 (1H, sextet, *J* 6.2 Hz, 5-H), 4.10-4.22 (2H, m, 1-H_2), 4.64 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.68 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.70-5.73 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) 20.0 (CH_3), 39.7 (CH_2), 55.3 (CH_3), 63.6 (CH_2), 72.7 (CH), 94.9 (CH_2), 128.8 (CH), 131.7 (CH); *m/z* (CI) 161.1179 (MH^+. $C_8H_{17}O_3$ requires 161.1178), 143 (12%), 129 (100), 99 (30), 89 (40), 81 (22).

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

The reaction was carried out according to general procedure 4 using (5*R*)-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**). (3*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **110a**: υ_{max}/cm^{-1} (neat) 3336 (NH), 2931 (CH), 1709 (CO), 1647 (C=C), 1516; $[\alpha]_D^{22}$ +9.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.1 Hz, 6-H_3), 1.81 (1H, ddd, *J* 15.0, 6.2, 3.0 Hz, 4-*H*H), 1.95 (1H, ddd, *J* 15.0, 10.1, 4.0 Hz, 4-H*H*), 3.39 (3H, s, OCH_3), 3.96-

4.05 (1H, m, 5-H), 4.60-4.66 (2H, m, OC*H*HO and 3-H), 4.76 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.23-5.29 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.3, 10.1, 5.0 Hz, 2-H), 8.12 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_3), 40.2 (CH_2), 51.5 (CH), 56.0 (CH_3), 71.0 (CH), 93.0 (C), 95.1 (CH_2), 115.8 (CH_2), 135.7 (CH), 161.2 (C); *m/z* (CI) 304.0270 (MH^+. $C_{10}H_{17}NO_3{}^{35}Cl_3$ requires 304.0274), 272 (100%), 201 (20), 114 (26), 45 (80). (3*R*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **110b**: $[\alpha]_D^{22}$ -9.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.1 Hz, 6-H_3), 1.80 (1H, ddd, *J* 14.3, 6.0, 4.1 Hz, 4-*H*H), 1.90 (1H, dt, *J* 14.3, 8.1 Hz, 4-H*H*), 3.39 (3H, s, OCH_3), 3.81-3.87 (1H, m, 5-H), 4.40-4.49 (1H, m, 3-H), 4.63 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.73 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.22 (1H, dt, *J* 10.4, 1.1, 1-*H*H), 5.28 (1H, dt, *J* 17.5, 1.1 Hz, 1-H*H*), 5.85 (1H, ddd, *J* 17.5, 10.4, 6.0 Hz, 2-H), 7.15 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.9 (CH_3), 41.5 (CH_2), 52.3 (CH), 55.6 (CH_3), 71.9 (CH), 93.0 (C), 95.4 (CH_2), 116.1 (CH_2), 136.6 (CH), 161.2 (C); *m/z* (CI) 304.0271 (MH^+. $C_{10}H_{17}NO_3{}^{35}Cl_3$ requires 304.0274), 272 (100%), 242 (51), 224 (66), 201 (25), 45 (84).

Synthesis of (3*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and (3*R*,5*R*)-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 (5*R*)-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 (3*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and (3*R*,5*R*)-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 (5*R*)-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.

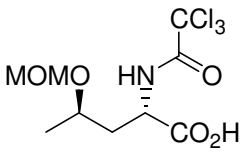
Synthesis of (3*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110a) and (3*R*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene (110b) using thermal rearrangement.

The reaction was carried out according to general procedure 5 using (5*R*)-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 (3*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **110a** and (3*R*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **110b** as brown oils (0.11g, 66% combined yield over 2 steps) in a 1 : 1 ratio (**110a** : **110b**). Spectroscopic data as reported above.

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

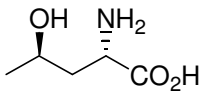
The reaction was carried out according to general procedure 4 using (5*R*)-5-methoxymethoxyhex-2-en-1-ol **119** (0.05 g, 0.3 mmol) in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 17 : 3) yielded the title compounds as brown oils (0.06 g, 71% combined yield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

(2*S*,4*R*)-2-(2',2',2'-Trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid (141).



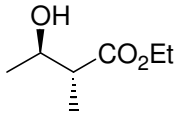
The reaction was carried out according to general procedure 7 using (3*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-methoxymethoxyhex-1-ene **110a** (0.15 g, 0.5 mmol) to give (2*S*,4*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid **141**, as a brown oil (0.11 g, 65% yield). υ_{max}/cm^{-1} (neat) 3335 (NH and OH), 2931 (CH), 1774 (CO), 1706 (CO), 1523; $[\alpha]_D^{25}$ +4.6 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.1 Hz, 5-H_3), 2.02 (1H, ddd, *J* 15.0, 9.8, 4.2 Hz, 3-*H*H), 2.11 (1H, ddd, *J* 15.0, 6.2, 3.0 Hz, 3-H*H*), 3.34 (3H, s, OCH_3), 3.90-3.95 (1H, m, 4-H), 4.56-4.63 (2H, m, OC*H*HO and 2-H), 4.71 (1H, d, *J* 7.0 Hz, OCH*H*O), 8.29 (1H, br d, *J* 7.0 Hz, NH), 9.70 (1H, br s, OH); δ_C (100 MHz, $CDCl_3$) 20.1 (CH_3), 37.2 (CH_2), 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^+. $C_9H_{15}NO_5{}^{35}Cl_2{}^{37}Cl$) requires 323.9982), 290 (65%), 260 (100), 226 (24).

(2*S*,4*R*)-2-Amino-4-hydroxypentanoic acid (111).[69]



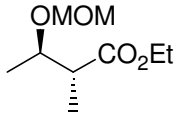
(2*S*,4*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-4-methoxymethoxypentanoic acid **141** (0.09 g, 0.3 mmol) was deprotected according to general procedure 8. Purification gave (2*S*,4*R*)-2-amino-4-hydroxypentanoic acid **111**, as a white solid (0.026 g, 74%). $[\alpha]_D^{25}$ -32.6 (*c* 1.5, H_2O), lit.[69] $[\alpha]_D$ -30.5 (*c* 0.75, H_2O); δ_H (400 MHz, D_2O) 1.10 (3H, d, *J* 7.1, Hz, 5-H_3), 1.78-1.92 (2H, m, 3-H_2), 3.77 (1H, dd, *J* 6.0, 4.3 Hz, 2-H), 3.82-3.87 (1H, m, 4-H); *m/z* (CI) 134 (MH^+, 22%), 116 (100).

Ethyl (2*R*,3*R*)-2-methyl-3-hydroxybutanoate (123).[111]



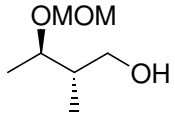
Diisopropylamine (11.0 mL, 0.08 mol) was dissolved in THF (70 mL) and cooled to 0 °C. Butyllithium (2.5 M, 31.0 mL, 0.08 mol) was then added dropwise to the solution and stirred for 1 h. The solution was cooled to -78 °C and ethyl (3*R*)-3-hydroxybutanoate **115** (4.00 g, 0.03 mol) in THF (10 mL) was 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 °C for 1h before warming to room temperature and stirring for a further 1h. 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 ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (elution with petroleum ether : ethyl acetate, 4 : 1) gave ethyl (2*R*,3*R*)-2-methyl-3-hydroxybutanoate **123** as a colourless oil (3.54 g, 78%). $[\alpha]_D^{22}$ -28.8 (*c* 0.5, $CHCl_3$), lit.[111] $[\alpha]_D^{22}$ -30.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 7.0 Hz, 2-CH_3), 1.24 (3H, d, *J* 6.2 Hz, 4-H_3), 1.30 (3H, t, *J* 7.3 Hz, OCH_2CH_3), 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_2CH_3); *m/z* (CI) 147 (MH^+, 100%), 129 (10), 101 (12).

Ethyl (2*R*,3*R*)-2-methyl-3-methoxymethoxybutanoate (125).[112]



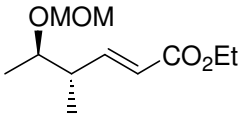
The reaction was carried out according to general procedure 3 using ethyl (2*R*,3*R*)-2-methyl-3-hydroxybutanoate **123** (3.50 g, 0.024 mol). Flash column chromatography (elution with petroleum ether : ethyl acetate, 5 : 1) yielded ethyl (2*R*,3*R*)-2-methyl-3-methoxymethoxybutanoate **125** as a clear oil (4.26 g, 93%). $[\alpha]_D^{22}$ -28.8 (*c* 1.0, $CHCl_3$), lit.[112] -28.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 7.2 Hz, 2-CH_3), 1.21 (3H, d, *J* 6.3 Hz, 4-H_3), 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.62 (1H, quin, *J* 7.2 Hz, 2-H), 3.38 (3H, s, OCH_3), 3.90-3.98 (1H, m, 3-H), 4.17 (2H, dq, *J* 7.1, 1.2 Hz, OCH_2CH_3), 4.65 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.9 Hz, OCH*H*O); *m/z* (CI) 191 (MH^+, 6%), 159 (100), 101 (8), 73 (43).

(2*S*,3*R*)-2-Methyl-3-methoxymethoxybutan-1-ol (127).[113]



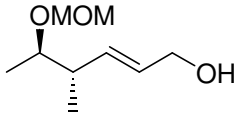
The reaction was carried out according to general procedure 2 using ethyl (2*S*,3*R*)-2-methyl-3-methoxymethoxybutanoate **125** (4.20 g, 0.020 mol). Flash column chromatography (elution with petroleum ether : diethyl ether, 1 : 1) yielded (2*S*,3*R*)-2-methyl-3-methoxymethoxybutan-1-ol **127** as a clear oil (3.2 g, 99%). Spectroscopic data in agreement with literature.[113] $[\alpha]_D^{22}$ -73.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 7.0 Hz, 2-CH_3), 1.22 (3H, d, *J* 6.3 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 Hz, 1-*H*H), 3.64-3.76 (2H, m, 1-H*H* and 3-H), 4.63 (1H, d, *J* 6.9, Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9, Hz, OCH*H*O); δ_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* (CI) 149 (MH^+, 9%), 117 (100), 105 (13), 87 (12).

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



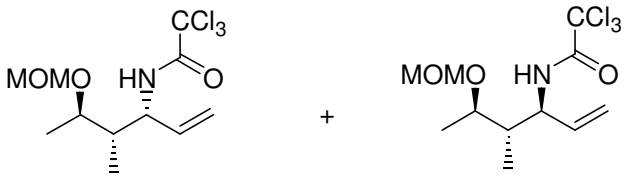
Reaction carried out according to general procedure 1 using (2*S*,3*R*)-2-methyl-3-methoxymethoxybutan-1-ol **127** (0.50 g, 3.4 mmol). Purification by flash column chromatography (eluting with petroleum ether : diethyl ether, 5 : 1) gave the title compound as a light yellow oil (0.73 g, 74%). υ_{max}/cm^{-1} (neat) 2982 (CH), 1738 (CO), 1653 (C=C), 1446, 1392; $[\alpha]_D^{22}$ -26.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.9 Hz, 4-CH_3), 1.15 (3H, d, *J* 6.3 Hz, 6-H_3), 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.44-2.53 (1H, m, 4-H), 3.39 (3H, s, OCH_3), 3.69 (1H, quin, *J* 6.3 Hz, 5-H), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.60 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.71 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.85 (1H, dd, *J* 15.8, 1.0 Hz, 2-H), 6.98 (1H, dd, *J* 15.8, 7.9 Hz, 3-H); δ_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* (CI) 217.1431 (MH^+. $C_{11}H_{21}O_4$ requires 217.1440), 185 (100%), 141 (28), 73 (27).

(2*E*,4*S*,5*R*)-4-Methyl-5-methoxymethoxyhex-2-en-1-ol (131).



The reaction was done according to general procedure 2 using ethyl (2*E*,4*S*,5*R*)-4-methyl-5-methoxymethoxyhex-2-enoate **129** (1.70 g, 8.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 3 : 2) gave (2*E*,4*S*,5*R*)-4-methyl-5-methoxymethoxyhex-2-en-1-ol **131** as a light yellow oil (1.15 g, 84%). υ_{max}/cm^{-1} (neat) 3409 (OH), 2971 (CH), 1663 (C=C), 1453, 1377; $[\alpha]_D^{22}$ -25.5 (*c* 1.0, $CHCl_3$); δ_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, OC*H*HO), 4.71 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.67-5.71 (2H, m, 2-H and 3-H); δ_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* (CI) 157.1236 (MH^+-H_2O. $C_{19}H_{17}O_2$ requires 157.1229), 175 (20%), 157 (80), 143 (96), 113 (90), 99 (100), 69 (63).

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



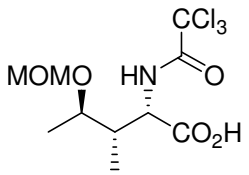
The reaction was carried out according to general procedure 4 using (2*E*,4*S*,5*R*)-4-methyl-5-methoxymethoxyhex-2-en-1-ol **131** (0.15 g, 0.9 mmol) in THF (10 mL) was used for the rearrangement. Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) yielded the title compounds as brown oils (0.13 g, 49% combined yield over 2 steps) and in a 3 : 1 ratio (**139a** : **139b**). (3*S*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (**139a**): υ_{max}/cm^{-1} (neat) 3342 (NH), 2932 (CH), 1715 (CO), 1644 (C=C), 1509, 1459, 1379; $[\alpha]_D^{22}$ +18.1 (*c* 1.0, $CHCl_3$); δ_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, OC*H*HO), 4.69 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.16-

5.23 (2H, m, 1-H_2), 5.71-5.80 (1H, m, 2-H), 8.22 (1H, br d, *J* 6.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 18.3 (CH_3), 42.4 (CH), 55.8 (CH), 56.4 (CH), 76.2 (CH_3), 93.1 (C), 95.3 (CH_2), 115.9 (CH_2), 136.1 (CH), 161.4 (C); *m/z* (CI) 318.0423 (MH^+. $C_{11}H_{19}NO_3{}^{35}Cl_3$ requires 318.0431), 286 (100%), 256 (38), 238 (80), 204 (39). (3*R*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (**139b**): $[\alpha]_D{}^{22}$ -16.3 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 7.0 Hz, 4-CH_3), 1.18 (3H, d, *J* 6.2 Hz, 6-H_3), 1.89-1.95 (1H, m, 4-H), 3.30 (3H, s, OCH_3), 3.64 (1H, quin, *J* 6.2 Hz, 5-H), 4.47-4.56 (2H, m, 3-H and OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.10-5.19 (2H, m, 1-H_2), 5.86 (1H, ddd, *J* 17.2, 10.5, 5.6 Hz, 2-H), 7.46 (1H, br d, *J* 6.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.5 (CH_3), 18.3 (CH_3), 42.5 (CH), 55.8 (CH), 56.4 (CH), 76.3 (CH_3), 93.1 (C), 95.3 (CH_2), 115.9 (CH_2), 136.1 (CH) 161.5 (C); *m/z* (CI) 318.0426 (MH^+. $C_{11}H_{19}NO_3{}^{35}Cl_3$ requires 318.0428), 288 (90%), 286 (95), 258 (77), 238 (84), 188 (100).

Synthesis of (3*S*,4*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-methyl-5-methoxymethoxyhex-1-ene (139a) and (3*R*,4*S*,5*R*)-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 (2*E*,4*S*,5*R*)-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.

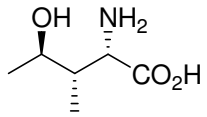
(2*S*,3*S*,4*R*)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid (142).



The reaction was carried out according to general procedure 7 using (3*S*,4*S*,5*R*)-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

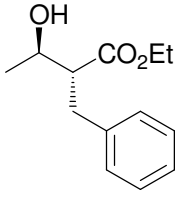
concentration *in vacuo* gave (2*S*,3*S*,4*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-methyl-4-methoxymethoxypentanoic acid **142** (0.143 g, 62%) as a brown oil. υ_{max}/cm^{-1} (neat) 3334 (NH and OH), 2981 (CH), 1774 (CO), 1523; $[\alpha]_D^{25}$ +13.0 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 7.2 Hz, 3-CH_3), 1.21 (3H, d, *J* 6.2 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, OC*H*HO), 4.66-4.72 (2H, m, OCH*H*O and 2-H), 7.80 (1H, br d, *J* 6.4 Hz, NH), 9.10 (br s, OH); δ_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* (CI) 336.0175 (MH^+. $C_{10}H_{17}NO_3{}^{35}Cl_3$ requires 336.0173), 319 (100%), 238 (40) and 188 (19).

(2*S*,3*S*,4*R*)-2-Amino-3-methyl-4-hydroxypentanoic acid (112).[65]



The reaction was carried out according to general procedure 8 using (2*S*,3*S*,4*R*)-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_4OH solution) yielded (2*S*,3*S*,4*R*)-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_2O), lit.[65] $[\alpha]_D^{27}$ +2.9 (*c* 1.0, H_2O); δ_H (400 MHz, D_2O) 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* (CI) 148 (MH^+, 24%), 130 (100), 85 (15), 74 (12).

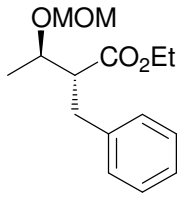
Ethyl (2*R*,3*R*)-2-benzyl-3-hydroxybutanoate (124).



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 (3*R*)-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

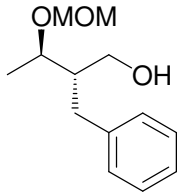
mixture was stirred at -78 ^{o}C for 1 h before warming to room temperature and stirring overnight. A saturated solution of ammonium chloride (10 mL) was then added and the solution was acidified to pH 2 by addition of 2 M hydrochloric acid (10 mL). The solution was extracted with ethyl acetate (4 x 30 mL), dried ($MgSO_4$) and concentrated *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 (2*R*,3*R*)-2-benzyl-3-hydroxybutanoate **124**, as a colourless oil (0.29 g, 58%). υ_{max}/cm^{-1} (neat) 3448 (OH), 3029 (CH), 1729 (CO), 1496, 1377; $[\alpha]_D^{25}$ +39.4 (*c* 3.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.25 (3H, d, *J* 6.4 Hz, 4-H_3), 2.63-2.79 (2H, m, 2-H and OH), 2.98 (2H, d, *J* 7.8 Hz, 2-CH_2Ph), 3.92 (1H, qd, *J* 6.4, 4.9 Hz, 3-H), 4.07 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 7.18-7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 21.8 (CH_3), 35.6 (CH_2), 54.2 (CH), 60.6 (CH_2), 67.7 (CH), 126.5 (CH), 128.4 (CH), 129.0 (CH), 138.8 (C), 174.8 (C); *m/z* (CI) 223.1343 (MH^+. $C_{12}H_{19}O_3$ requires 223.1334), 204 (15%), 177 (17), 131 (10), 69 (20).

Ethyl (2*R*,3*R*)-2-benzyl-3-methoxymethoxybutanoate (126).



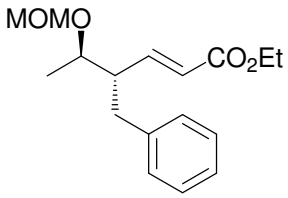
The reaction was done according to general procedure 3 using ethyl (2*R*,3*R*)-2-benzyl-3-hydroxybutanoate **124** (3.20 g, 14.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 5 : 1) yielded ethyl (2*R*,3*R*)-2-benzyl-3-methoxymethoxybutanoate **126**, as a clear oil (3.26 g, 85%). υ_{max}/cm^{-1} (neat) 3029 (CH), 1731 (CO), 1495, 1379; $[\alpha]_D^{25}$ +47.7 (*c* 1.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.06 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.29 (3H, d, *J* 6.3 Hz, 4-H_3), 2.79-2.90 (3H, m, 2-CH_2Ph and 2-H), 3.38 (3H, s, OCH_3), 3.98 (1H, qd, *J* 6.3, 1.2 Hz, 3-H), 4.00 (2H, q, *J* 7.1 Hz OCH_2CH_3), 4.64 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 7.16-7.29 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 18.0 (CH_3), 34.1 (CH_2), 54.4 (CH), 55.6 (CH_3), 60.3 (CH_2), 74.3 (CH), 95.5 (CH_2), 126.3 (CH), 128.4 (CH), 128.9 (CH), 139.2 (C), 173.3 (C); *m/z* (CI) 267.1593 (MH^+. $C_{15}H_{23}O_4$ requires 267.1596), 235 (100%), 223 (28), 177 (7), 85 (37), 69 (52).

(2*S*,3*R*)-2-Benzyl-3-methoxymethoxybutan-1-ol (128).



The reaction was carried out according to general procedure 2 using ethyl (2*R*,3*R*)-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 (2*S*,3*R*)-2-benzyl-3-methoxymethoxybutan-1-ol **128**, as a clear yellow oil (1.56 g, 93%). ν_{max}/cm^{-1} (neat) 3453 (OH), 3026 (CH), 1496, 1454, 1370; $[\alpha]_D^{25}$ -21.4 (*c* 2.7, $CHCl_3$); δ_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_2Ph), 3.42 (3H, s, OCH_3), 3.50 (1H, dd, *J* 11.4, 4.8 Hz, 1-*H*H), 3.83-3.90 (2H, m, 1-H*H* and 3-H), 4.63 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.17-7.31 (5H, m, Ph); δ_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).

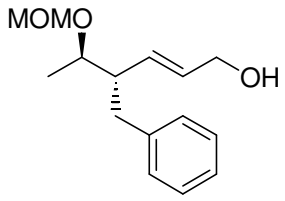
Ethyl (2*E*,4*S*,5*R*)-4-benzyl-5-methoxymethoxyhex-2-enoate (130).



The reaction was carried out according to general procedure 1 using (2*S*,3*R*)-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). υ_{max}/cm^{-1} (neat) 3027 (CH), 1715 (CO), 1654 (C=C), 1495, 1370; $[\alpha]_D^{25}$ +93.7 (*c* 2.6, $CHCl_3$); δ_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_2CH_3), 2.50-2.58 (1H, m, 4-H), 2.72 (1H, dd, *J* 13.7, 8.7 Hz, 4-C*H*HPh), 2.96 (1H, dd, *J* 13.7, 5.7 Hz, 4-CH*H*Ph), 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, OC$H_2$$CH_3$), 4.62 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.9 Hz, OCH*H*O), 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-

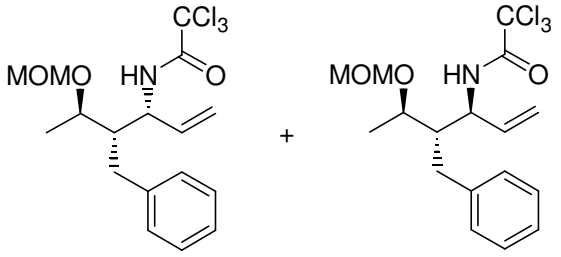
7.29 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 18.5 (CH_3), 37.0 (CH_2), 50.7 (CH), 55.7 (CH_3), 60.2 (CH_2), 74.6 (CH), 95.5 (CH_2), 123.5 (CH), 126.2 (CH), 128.4 (CH), 129.1 (CH), 139.7 (C), 148.2 (CH), 166.2 (C); *m/z* (CI) 293.1752 (MH^+. $C_{17}H_{25}O_4$ requires 293.1753), 261 (100%), 248 (15), 217 (53), 191 (12).

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



The reaction was done according to general procedure 2 using ethyl (2*E*,4*S*,5*R*)-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 (2*E*,4*S*,5*R*)-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; $[\alpha]_D^{25}$ +50.5 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.3 Hz, 6-H_3), 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-C*H*HPh), 2.91 (1H, dd, *J* 13.5, 5.6 Hz, 4-CH*H*Ph), 3.41 (3H, s, OCH_3), 3.73 (1H, qd, *J* 6.3, 3.3 Hz, 5-H), 4.03 (2H, dd, *J* 5.7, 1.0 Hz, 1-H_2), 4.62 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 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, $CDCl_3$) 18.3 (CH_3), 37.5 (CH_2), 50.5 (CH), 55.6 (CH_3), 63.6 (CH_2), 75.3 (CH), 95.6 (CH_2), 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. $C_{15}H_{21}O_2$ requires 233.1542), 219 (83%), 201 (50), 189 (40), 171 (75), 157 (100).

(3*R*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140a) and (3*S*,4*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140b).

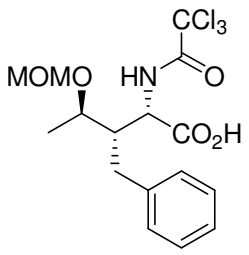


The reaction was carried out according to general procedure 4 using (2*E*,4*S*,5*R*)-4-benzyl-5-methoxymethoxyhex-2-en-1-ol **132** (0.20 g, 0.8 mmol) in THF (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave the title compounds as light brown oils (0.36 g, 72% combined yield over two steps) and in a 6 : 1 ratio (**140a** : **140b**). υ_{max}/cm^{-1} (neat) 3368 (NH), 2925 (CH), 1718 (CO), 1497, 1455; (3*S*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene **140a**: $[\alpha]_D^{25}$ +52.5 (*c* 1.0, $CHCl_3$); δ_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-C*H*HPh), 2.79 (1H, dd, *J* 14.2, 5.6 Hz, 4-CH*H*Ph), 3.41 (3H, s, OCH_3), 3.80 (1H, dq, *J* 8.3, 6.1 Hz, 5-H), 4.41-4.50 (1H, m, 3-H), 4.62 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.77 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.26-5.35 (2H, 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); δ_C (100 MHz, $CDCl_3$) 19.0 (CH_3), 34.1 (CH_2), 49.5 (CH), 54.4 (CH), 56.4 (CH_3), 76.0 (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). (3*R*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene **140b**: $[\alpha]_D^{25}$ -19.4 (*c* 0.5, $CHCl_3$); δ_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-C*H*HPh), 2.74 (1H, dd, *J* 13.9, 6.1 Hz, 4-CH*H*Ph), 3.38 (3H, s, OCH_3), 3.83-3.90 (1H, m, 5-H), 4.50 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.61-4.65 (1H, m, 3-H), 4.71 (1H, d, *J* 6.8 Hz, OCH*H*O), 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); δ_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).

(3*S*,4*S*,5*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140a) and (3*R*,4*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene (140b) using toluene.

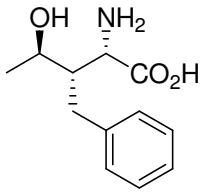
The reaction was carried out according to general procedure 4 using (2*E*,4*S*,5*R*)-4-benzyl-5-methoxymethoxyhex-2-en-1-ol **132** (0.067 g, 0.27 mmol) in toluene (10 mL). Flash column chromatography (elution with petroleum ether : diethyl ether, 20 : 1) gave the title compounds as light brown oils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

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



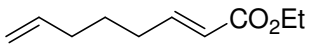
The reaction was carried out according to general procedure 7 using (3*S*,4*S*,5*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-benzyl-5-methoxymethoxyhex-1-ene **140a** (0.37 g, 0.9 mmol). The crude product was then dissolved in an aqueous solution of sodium hydrogen carbonate (10 mL), extracted with 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, (2*S*,3*S*,4*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid **143** (0.32 g, 82%), as a brown oil. υ_{max}/cm^{-1} (neat) 3387 (NH and OH), 2937 (CH), 1716 (CO), 1514, 1455; $[\alpha]_D^{25}$ +40.4 (*c* 1.1, $CHCl_3$); δ_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-C*H*HPh), 2.85 (1H, dd, *J* 14.1, 7.2 Hz, 3-CH*H*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, OC*H*HO), 4.63-4.68 (2H, m, OCH*H*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); δ_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).

(2*S*,3*S*,4*R*)-2-Amino-3-benzyl-4-hydroxypentanoic acid (144).



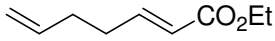
The reaction was carried out according to general procedure 8 using (2*S*,3*S*,4*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-benzyl-4-methoxymethoxypentanoic acid **143** (0.11 g, 0.3 mmol). Purification by ion exchange chromatography (elution with 0.5 M NH_4OH solution) yielded (2*S*,3*S*,4*R*)-2-amino-3-benzyl-4-hydroxypentanoic acid **144**, as a white solid (0.033 g, 55%). υ_{max} (KBr) 3400 (NH_2), 3225 (OH), 2970 (CH), 1652 (CO), 1477; $[\alpha]_D^{25}$ +23.0 (*c* 0.2, H_2O); δ_H (400 MHz, D_2O) 1.08 (3H, d, *J* 6.5, Hz, 5-H_3), 2.10-2.16 (1H, m, 3-H), 2.56 (1H, dd, *J* 13.6, 5.1 Hz, 3-C*H*HPh), 2.62 (1H, dd, *J* 13.6, 10.0 Hz, 3-CH*H*Ph), 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); δ_C (100 MHz, D_2O) 20.8 (CH_3), 32.1 (CH_2), 46.3 (CH), 54.6 (CH), 66.7 (CH), 126.6 (CH), 128.7 (CH), 129.3 (CH), 139.3 (C), 173.9 (C); *m/z* (EI) 205.1101 (M^+-H_2O. $C_{12}H_{15}NO_2$ requires 205.1103), 131 (80%), 114 (33), 91 (70), 70 (100).

Ethyl (2*E*)-2,7-octadienoate (147).[114]



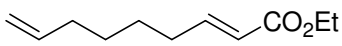
Reaction was carried out according to general procedure 1, using 5-hexen-1-ol **146** (4.00 g, 0.04 mol). Flash column chromatography (petroleum ether : diethyl ether, 10 : 1) yielded ethyl (2*E*)-2,7-octadienoate **147** (4.6 g, 69% yield) as a yellow oil. Spectroscopic data entirely consistent with literature.[114] δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 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 (MH^+. $C_{10}H_{17}O_2$ requires 169.1229), 141 (90%), 123 (75), 95 (100), 81 (53), 55 (32).

Ethyl (2*E*)-2,6-heptadienoate.[115]



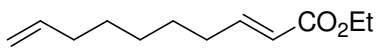
Reaction was carried out according to general procedure 1, using 4-penten-1-ol (0.50 g, 5.8 mmol). Flash column chromatography (petroleum ether : diethyl ether, 20 : 1) yielded ethyl (2*E*)-2,6-heptadienoate (0.69 g, 77% yield) as a yellow oil. Spectroscopic data consistent with literature.[115] δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.99-2.25 (2H, m, 5-H_2), 2.27-2.34 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.99-5.09 (2H, m, 7-H_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); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.5 (CH_2), 32.0 (CH_2), 60.2 (CH_2), 115.5 (CH_2), 121.7 (CH), 137.1 (CH), 148.3 (CH), 166.7 (C); *m/z* (CI) 155.1075 (MH^+. $C_9H_{15}O_2$ requires 155.1072), 137 (16%), 107 (17), 73 (22).

Ethyl (2*E*)-2,8-nonadienoate.[116]



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 (2*E*)-2,8-nonadienoate (1.15 g, 72% yield) as a yellow oil. Spectroscopic data consistent with literature.[116] δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.38-1.52 (4H, m, 5-H_2 and 6-H_2), 2.06 (2H, q, *J* 7.2 Hz, 7-H_2), 2.21 (2H, qd, *J* 7.2, 1.5 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.93-4.97 (1H, m, 9-*H*H), 4.97-5.04 (1H, m, 9-H*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); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.5 (CH_2), 28.4 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 60.2 (CH_2), 114.7 (CH_2), 121.4 (CH), 138.6 (CH), 149.3 (CH), 166.8 (C); *m/z* (CI) 183.1382 (MH^+. $C_{11}H_{19}O_2$ requires 183.1385), 113 (8%), 97 (7), 81 (13), 71 (15).

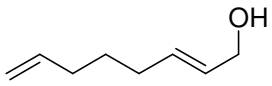
Ethyl (2*E*)-2,9-decadienoate.[117]



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 (2*E*)-2,9-decadienoate (2.06 g, 90% yield) as a pale yellow oil. Spectroscopic data

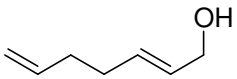
consistent with literature.[117] δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.31-1.51 (6H, m, 5-H_2, 6-H_2 and 7-H_2), 2.05 (2H, q, *J* 7.1 Hz, 8-H_2), 2.21 (2H, qd, *J* 7.1, 1.5 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.92-4.96 (1H, m, 10-*H*H), 4.97-5.03 (1H, m, 10-H*H*), 5.75-5.86 (2H, m, 2-H and 9-H), 6.96 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.9 (CH_2), 28.6 (CH_2), 28.7 (CH_2) 32.2 (CH_2), 33.7 (CH_2), 60.2 (CH_2), 114.4 (CH_2), 121.3 (CH), 138.9 (CH), 149.4 (CH), 166.8 (C); *m/z* (CI) 197.1540 (MH^+. $C_{12}H_{21}O_2$ requires 197.1542), 123 (11%), 111 (7).

(2*E*)-Octa-2,7-dien-1-ol (148).[114]



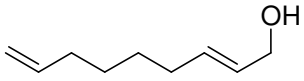
The reaction was carried out according to general procedure 2, using ethyl (2*E*)-2,7-octadienoate **147** (1.00 g, 6.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 1 : 4) yielded, (2*E*)-octa-2,7-dien-1-ol **148** (0.65 g, 87% yield) as a colourless oil. Spectroscopic data consistent with literature.[114] δ_H (400 MHz, $CDCl_3$) 1.34 (1H, br s, OH), 1.46-1.51 (2H, m, 5-H_2), 2.02-2.10 (4H, m, 4-H_2 and 6-H_2), 4.07 (2H, d, *J* 4.6 Hz, 1-H_2), 4.94-4.97 (1H, m, 8-*H*H), 5.01 (1H, dq, *J* 17.0, 1.7, 8-H*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_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 63.8 (CH_2), 114.6 (CH_2), 129.2 (CH), 133.0 (CH), 138.6 (CH); *m/z* (CI) 109.1009 (M^+-OH. C_8H_{13} requires 109.1017), 95 (16%), 81 (12), 67 (47).

(2*E*)-Hepta-2,6-dien-1-ol.[115]



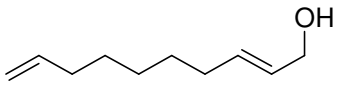
The reaction was carried out according to general procedure 2, using ethyl (2*E*)-2,6-heptadienoate (1.54 g, 10.0 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2*E*)-hepta-2,6-dien-1-ol (0.92 g, 82% yield) as a colourless oil. Spectroscopic data consistent with literature.[115] δ_H (400 MHz, $CDCl_3$) 1.42 (1H, br s, OH), 2.10-2.15 (4H, m, 4-H_2 and 5-H_2), 4.08 (2H, d, *J* 4.8 Hz, 1-H_2), 4.96-5.03 (2H, m, 7-H_2), 5.62-5.71 (2H, m, 2-H and 3-H), 5.72-5.89 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 31.5 (CH_2), 33.3 (CH_2), 63.7 (CH_2), 114.9 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); *m/z* (CI) 113.0964 (MH^+. $C_7H_{13}O$ requires 113.0966), 95 (100%), 81 (14), 73 (13).

(2*E*)-Nona-2,8-dien-1-ol.[116]



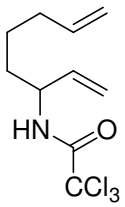
The reaction was carried out according to general procedure 2, using ethyl (2*E*)-2,8-nonadienoate (1.00 g, 5.5 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2*E*)-nona-2,8-dien-1-ol (0.77 g, 100% yield) as a colourless oil. Spectroscopic data consistent with literature.[116] δ_H (400 MHz, $CDCl_3$) 1.22 (1H, br s, OH), 1.38-1.42 (4H, m, 5-H_2 and 6-H_2), 2.02-2.10 (4H, m, 4-H_2 and 7-H_2), 4.09 (2H, t, *J* 4.9 Hz, 1-H_2), 4.92-4.96 (1H, m, 9-*H*H), 5.00 (1H, dq, *J* 17.0, 1.6 Hz, 9-H*H*), 5.60-5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 8-H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 27.1 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 62.4 (CH_2), 112.9 (CH_2), 127.5 (CH), 131.9 (CH), 137.4 (CH); *m/z* (CI) 123.1169 (MH^+-H_2O. C_9H_{15} requires 123.1174), 109 (16%), 95 (12), 81 (63), 67 (17).

(2*E*)-Deca-2,9-dien-1-ol.[118]



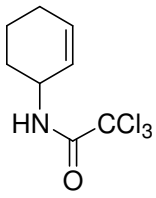
The reaction was carried out according to general procedure 2, using ethyl (2*E*)-2,9-decadienoate (1.50 g, 7.7 mmol). Flash column chromatography (petroleum ether : diethyl ether, 7 : 3) yielded, (2*E*)-deca-2,9-dien-1-ol (0.97 g, 81% yield) as a colourless oil. Spectroscopic data consistent with literature.[118] δ_H (400 MHz, $CDCl_3$) 1.25-1.46 (7H, m, 5-H_2, 6-H_2, 7-H_2 and OH), 2.01-2.10 (4H, m, 4-H_2 and 8-H_2), 4.09 (2H, d, *J* 4.6 Hz, 1-H_2), 4.92-4.96 (1H, m, 10-*H*H), 4.97-5.05 (1H, m, 10-H*H*), 5.58-5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, *J* 17.1, 10.1, 6.7 Hz, 9-H); δ_C (100 MHz, $CDCl_3$) 28.7 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 32.2 (CH_2), 33.8 (CH_2), 63.9 (CH_2), 114.3 (CH_2), 128.9 (CH), 133.5 (CH), 139.1 (CH); *m/z* (CI) 137.1324 (MH^+-H_2O. $C_{10}H_{17}$ requires 137.1330), 113 (25%), 95 (49), 81 (100), 69 (88), 67 (59).

3-(2',2',2'-Trichloromethylcarbonylamino)octa-1,7-diene (150).



The reaction was carried out according to general procedure 4, using (2*E*)-octa-2,7-dien-1-ol **148** (0.07 g, 0.5 mmol). $PdCl_2(MeCN)_2$ 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, $CDCl_3$) 1.43-1.52 (2H, m, 5-H_2), 1.55-1.73 (2H, m, 4-H_2), 2.06-2.14 (2H, m, 6-H_2), 4.40-4.50 (1H, m, 3-H), 4.95 (1H, ddt, *J* 10.2, 2.0, 1.5 Hz, 8-*H*H), 5.00 (1H, ddt, *J* 17.1, 3.6, 1.5 Hz, 8-H*H*), 5.20 (1H, ddd, *J* 10.5, 1.2, 0.8 Hz, 1-*H*H), 5.24 (1H, ddd, *J* 17.2, 1.5, 1.2 Hz, 1-H*H*), 5.73-5.85 (2H, m, 2-H and 7-H), 6.52 (1H, br s, NH).

1-(2',2',2'-Trichloromethylcarbonylamino)cyclohexa-2-ene (151).[21]



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, $CDCl_3$) 1.62-1.79 (3H, m, 5-H_2 and 6-H), 1.94-2.03 (1H, m, 6-H), 2.03-2.16 (2H, m, 4-H_2), 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, dtd, *J* 10.0, 4.0, 1.9 Hz, 3-H), 6.60 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 24.7 (CH_2), 28.6 (CH_2), 46.9 (CH), 92.7 (C), 125.7 (CH), 132.7 (CH), 161.1 (C); *m/z* (CI) 261.0144 $(M+NH_4)^+$. $C_8H_{14}N_2O^{35}Cl_2{}^{37}Cl$ requires 261.0143), 259 (100%), 242 (23), 225 (9), 206 (21), 81 (10).

Synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene (151),[21] using Grubbs I catalyst.

The reaction was carried out according general procedure 6 using (2*E*)-octa-2,7-dien-1-ol **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 **151** as a white solid (0.17 g, 89% yield over 3 steps). Spectroscopic data as reported above.

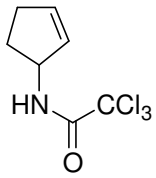
Synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene (151),[21] using Grubbs II catalyst.

The reaction was carried out according general procedure 6 using (2*E*)-octa-2,7-dien-1-ol **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 **151**, as a white solid (0.14 g, 95% yield over 3 steps). Spectroscopic data as reported above.

Synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene (151),[21] using Grubbs/Hoveyda II catalyst.

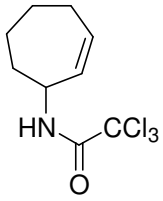
The reaction was carried out according general procedure 6 using (2*E*)-octa-2,7-dien-1-ol **148** (0.08 g, 0.6 mmol), bis(acetonitrile)palladium(II) chloride (0.08 g, 0.6 mmol) was used to catalyze the aza-Claisen rearrangement and Grubbs/Hoveyda II catalyst (0.04 g, 0.06 mmol) was used to catalyze the RCM. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 97 : 3) gave 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene **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).



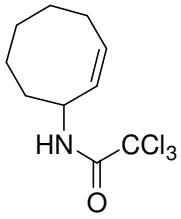
The reaction was carried out according general procedure 6 using (2*E*)-hepta-2,6-dien-1-ol (0.10 g, 0.9 mmol) and bis(acetonitrile)palladium(II) chloride (0.04 g, 0.2 mmol) was used to catalyze the rearrangement. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 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 ^{o}C; ν_{max}/cm^{-1} (NaCl) 3291 (NH), 1684 (CO), 1528 (C=C), 823; δ_H (400 MHz, $CDCl_3$) 1.67-1.75 (1H, m, 4-*H*H) 2.34-2.57 (3H, m, 4-H*H* and 5-H_2), 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); δ_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^+. $C_7H_9NO^{35}Cl_2{}^{37}Cl$ requires 229.9718), 228 (100%), 194 (22), 162 (5), 67 (13).

1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (156).[82]



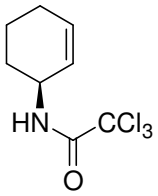
The reaction was carried out according general procedure 6 (at a concentration of 0.005 M) using (2*E*)-nona-2,8-dien-1-ol (0.10 g, 0.7 mmol) and bis(acetonitrile)palladium(II) chloride (0.02 g, 0.08 mmol) was used to catalyze the aza-Claisen rearrangement. Purification by flash column chromatography (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 ^{o}C, lit.[82] 105 ^{o}C; δ_H (400 MHz, $CDCl_3$) 1.39-1.49 (1H, m, 6-*H*H), 1.66-1.79 (3H, m, 6-H*H* and 7-H_2), 1.85-1.98 (2H, m, 5-H_2), 2.10-2.29 (2H, m, 4-H_2), 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); δ_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^+. $C_9H_{13}NO^{35}Cl_3$ requires 256.0063), 258 (97%), 222 (18), 95 (12).

1-(2',2',2'-Trichloromethylcarbonylamino)cycloocta-2-ene (158).



The reaction was carried out according general procedure 6 (at a concentration of 0.0013 M) using (2*E*)-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 ^{o}C; ν_{max}/cm^{-1} (NaCl) 3314 (NH), 1684 (CO), 1529 (C=C), 824; δ_H (400 MHz, $CDCl_3$) 1.39-1.49 (7H, m, 5-H_2, 6-H_2, 7-H_2 and 8-*H*H), 1.98 (1H, ddt, *J* 13.1, 8.9, 4.4 Hz, 8-H*H*), 2.11-2.20 (1H, m, 4-*H*H), 2.25-2.36 (1H, m, 4-H*H*), 4.75-4.79 (1H, m, 1-H), 5.31-5.38 (1H, m, 2-H), 5.79 (1H, dtd, *J* 10.5, 7.5, 1.4 Hz, 3-H), 6.65 (1H, br s, NH); δ_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^+. $C_{10}H_{15}NO^{35}Cl_3$ requires 270.0219), 272 (92%), 236 (58), 234 (85), 109 (47), 67 (28).

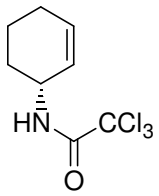
(1*S*)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclohexa-2-ene (159).



The reaction was carried out according general procedure 6 using (2*E*)-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 (1*S*)-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% *i*PrOH : hexane at 0.75 mL/min), retention time: t_S= 8.2 min, and t_R= 9.2 min; $[\alpha]_D^{23}$ -95.3 (*c* 2.1, $CHCl_3$). All other spectroscopic data as

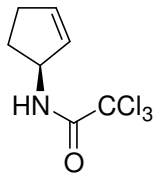
previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-2-ene **151** above.

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



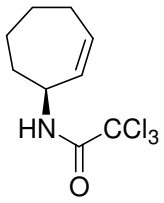
The reaction was carried out according general procedure 6 using (2*E*)-octa-2,7-dien-1-ol **148** (0.08 g, 0.6 mmol) and (*R*)-COP-Cl (0.04 g, 0.03 mmol) as the catalyst for aza-Claisen rearrangement. Purification by flash column chromatography (elution with petroleum ether : diethyl ether 97 : 3) gave (1*R*)-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% *i*PrOH : 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.

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



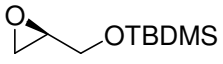
The reaction was carried out according general procedure 6 using (2*E*)-hepta-2,6-dien-1-ol **152** (0.08 g, 0.7 mmol) and (*S*)-COP-Cl (0.05 g, 0.03 mmol) as rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether : DCM, 70 : 30) gave (1*S*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene **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% *i*PrOH : 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.

(1*S*)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (162).



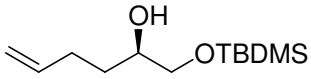
The reaction was carried out according general procedure 6 using (2*E*)-nona-2,8-dien-1-ol **153** (0.08 g, 0.5 mmol) and (*S*)-COP-Cl (0.04 g, 0.03 mmol) as rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether : DCM, 70 : 30) gave (1*S*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene **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% *i*PrOH : hexane at 0.5 mL/min), retention time: t_S= 21.5 min, and t_R= 22.1 min; $[\alpha]_D^{23}$ -25.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene **156** above.

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (185).[119]



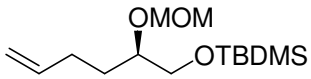
A mixture of (*S*)-glycidol **184** (3.10 g, 0.04 mol), *tert*-butyldimethylsilyl chloride (9.40 g, 0.06 mol) and imidazole (4.20 g, 0.06 mol) in THF (70 mL) were stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated and purified by flash column chromatography (elution with petroleum ether : diethyl ether, 10 : 1) to give (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane **185** (7.7 g, 98%) as a clear oil. $[\alpha]_D^{24}$ +2.7 (*c* 1.0, $CHCl_3$), lit.[119] +2.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 2.66 (1H, dd, *J* 4.6, 2.4 Hz, 1-*H*H), 2.79 (1H, dd, *J* 5.2, 4.6 Hz, 1-H*H*), 3.10-3.14 (1H, m, 2-H), 3.68 (1H, dd, *J* 11.8, 4.8 Hz, 3-*H*H), 3.87 (1H, dd, *J* 11.8, 3.2 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) -5.4 (CH_3), -5.3 (CH_3), 19.0 (C), 26.0 (CH_3), 45.0 (CH_2), 52.5 (CH) and 63.9 (CH_2); *m/z* (CI) 189.1309 (MH^+. $C_9H_{21}O_2Si$ requires 189.1311), 145 (35%), 131 (50), 89 (62), 73 (12).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-ol (186).[120]



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 ^{o}C and the white suspension was stirred for 0.5 h. (2*R*)-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 ^{o}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 (2*R*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol **186** (13.9 g, 90%) as a clear oil. Spectroscopic data as reported in literature.[120] $[\alpha]_D^{24}$ -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-*H*H), 3.53-3.62 (2H, m, 1-H*H* and 2-H), 4.88-4.92 (1H, m, 6-*H*H), 4.94-5.00 (1H, m, 6-H*H*), 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* (CI) 231.1776 (MH^+. $C_{12}H_{27}O_2Si$ requires 231.1780), 173 (8), 81 (15).

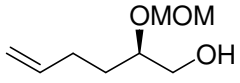
(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene (187).



The reaction was carried out according to general procedure 3 using (2*R*)-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 (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene **187**, as a clear oil (4.7 g, 100%). (Found: C, 61.4; H, 11.0. $C_{14}H_{30}O_3Si$ requires C, 61.3; H, 11.0%); υ_{max}/cm^{-1} (NaCl) 2929 (CH), 1642 (C=C), 1472 (CH), 1255, 1110 (CO), 1040; $[\alpha]_D^{24}$ +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, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.89-4.94 (1H, m, 6-*H*H),

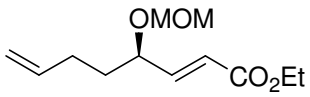
4.95-5.01 (1H, m, 6-H*H*), 5.77 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) -5.4 (CH_3), -5.4 (CH_3), 18.3 (C), 25.9 (CH_3), 29.6 (CH_2), 31.0 (CH_2), 55.5 (CH_3), 65.7 (CH_2), 77.7 (CH), 96.4 (CH_2), 114.6 (CH_2), 138.5 (CH); *m/z* (CI) 243 (M^+-OCH_4, 100%), 231 (8), 133 (11), 81 (18).

(2*R*)-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 (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene **187** (4.30 g, 15.7 mmol) in THF (100 mL) at 0 ^oC. 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 ($MgSO_4$), concentrated and then purified by flash column chromatography (petroleum ether : diethyl ether, 5 : 2) to give (2*R*)-2-(methoxymethoxy)hex-5-en-1-ol **188**, as a clear oil (2.42 g, 98%). (Found: C, 59.9; H, 10.2. $C_8H_{16}O_3$ requires C, 60.0; H, 10.0%); υ_{max}/cm^{-1} (NaCl) 3432 (OH), 2947 (CH), 1641 (C=C), 1450, 1212, 1028; $[\alpha]_D^{24}$ -66.8 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49-1.70 (2H, m, 3-H_2), 2.07-2.24 (2H, m, 4-H_2), 3.14 (1H, br dd, *J* 8.5, 3.4 Hz, OH) 3.44 (3H, s, OCH_3), 3.47-3.64 (3H, m, 1-H_2 and 2-H), 4.69 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.96-5.07 (2H, m, 6-H_2), 5.80 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_2), 30.8 (CH_2), 55.7 (CH_3), 66.7 (CH_2), 81.9 (CH), 97.1 (CH_2), 115.1 (CH_2), 138.0 (CH); *m/z* (CI) 129 (MH^+-OCH_4, 100%), 99 (14), 81 (40), 69 (38).

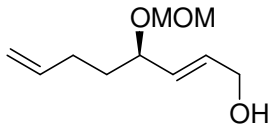
Ethyl (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dienoate (189).



Reaction was carried out according to general procedure 1, using (2*R*)-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 (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-

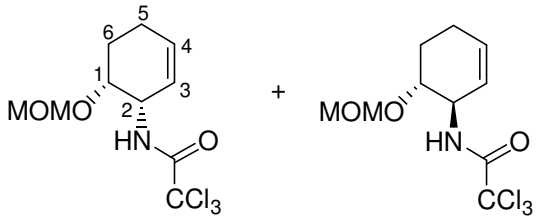
dienoate **189** (1.35 g, 94% yield) as a yellow oil. (Found: C, 63.2; H, 8.9. $C_{12}H_{20}O_4$ requires C, 63.2; H, 8.8%); υ_{max}/cm^{-1} (NaCl) 2941 (CH), 1720 (CO), 1658 (C=C), 1446, 1369, 1269, 1154; $[\alpha]_D^{24}$ +79.2 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.59-1.80 (2H, m, 5-H_2), 2.09-2.21 (2H, m, 6-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, OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 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); δ_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* (CI) 229 (MH^+, 35%), 199 (33), 197 (37), 167 (100), 81 (16), 69 (24).

(2*E*,4*R*)-4-(Methoxymethoxy)octa-2,7-dien-1-ol (190).



The reaction was carried out according to general procedure 2, using ethyl (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dienoate **189** (1.30 g, 5.7 mmol). Flash column chromatography (petroleum ether : diethyl ether, 2 : 3) yielded, (2*E*,4*R*)-4-(methoxymethoxy)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%); υ_{max}/cm^{-1} (NaCl) 3408 (OH), 2937 (CH), 1641 (C=C), 1442, 1373, 1153, 1096, 1036; $[\alpha]_D^{24}$ +126.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.54-1.64 (2H, m, 5-*H*H and OH), 1.68-1.78 (1H, m, 5-H*H*), 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, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 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); δ_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* (CI) 204 (MNH_4^+, 100%), 174 (31), 142 (29), 125 (14), 58 (16).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177a) and (1*R*,2*R*)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177b).

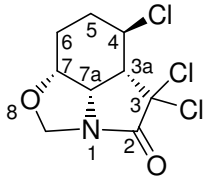


The reaction was carried out according general procedure 6 using (2*E*,4*R*)-4-(methoxymethoxy)octa-2,7-dien-1-ol **190** (1.10 g, 3.4 mmol). Bis(acetonitrile)palladium(II) chloride (0.090 g, 0.3 mmol) was used to catalyze the aza-Claisen rearrangement, which was stirred at room temperature overnight before addition of Grubbs I catalyst. Purification by flash column chromatography (elution with petroleum ether : diethyl ether, 7 : 1) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177a** followed by (1*R*,2*R*)-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**). υ_{max}/cm^{-1} (NaCl) 3421 (NH), 2930 (CH), 1709 (CO), 1654 (C=C), 1500, 1148, 1102, 1036. Data for (1*R*,2*S*)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177a**: $[\alpha]_D^{20}$ +79.1 (*c* 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73-1.82 (1H, m, 6-*H*H), 2.00-2.13 (2H, m, 5-*H*H and 6-H*H*), 2.17-2.28 (1H, m, 5-H*H*), 3.42 (3H, s, OCH_3), 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, OC*H*HO), 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O), 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); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2), 24.2 (CH_2), 48.6 (CH), 55.0 (CH_3), 70.9 (CH), 91.9 (C), 94.5 (CH_2), 123.4 (CH), 129.9 (CH), 160.7 (C). Data for (1*R*,2*R*)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177b**: δ_H (400 MHz, $CDCl_3$) 1.75-1.87 (1H, m, 6-*H*H), 1.90-1.99 (1H, m, 6-H*H*), 2.11-2.29 (2H, m, 5-H_2), 3.39 (3H, s, OCH_3), 3.71-3.79 (1H, m, 1-H), 4.49-4.56 (1H, m, 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.9 Hz, OCH*H*O), 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); δ_C (100 MHz, $CDCl_3$) 23.3 (CH_2), 26.0 (CH_2), 52.5 (CH), 55.7 (CH_3), 74.9 (CH), 92.6 (C), 95.3 (CH_2), 124.1 (CH), 131.4 (CH), 161.6 (C); *m/z* (CI) 306.0056 (MH^+. $C_{10}H_{15}NO_3{}^{35}Cl^{37}Cl_2$ requires 306.0062), 268 (100%), 234 (45), 198 (7).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177a) and (1*R*,2*R*)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene (177b) using toluene as solvent.

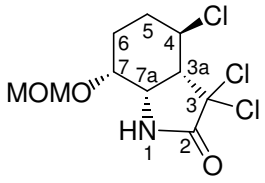
The reaction was carried out according general procedure 6 using (2*E*,4*R*)-4-(methoxymethoxy)-octa-2,7-dien-1-ol **190** (0.10 g, 0.5 mmol). Bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) was used to catalyze the aza-Claisen rearrangement, which was stirred in toluene (10 mL), initially at 0 ^{o}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 (1*R*,2*S*)-1-(methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177a** followed by (1*R*,2*R*)-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**)

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



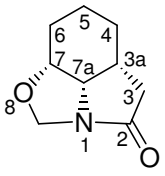
(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177a** (0.085 g, 0.3 mmol) was dissolved in toluene (10 mL) which was then de-gassed for 1h. Grubbs I catalyst (0.012 g, 0.014 mmol) was added and the reaction mixture was heated at 155 ^{o}C for 6 h. The reaction mixture was then concentrated under vacuum and purified by column chromatography (elution with petroleum ether : diethyl ether, 3 : 2) to give (3a*R*,4*R*,7*R*,7a*S*)-3,3,4-trichloro-octahydro[1,8]oxazole-indol-2-one **195**, as a white solid (0.018 g, 24%). υ_{max}/cm^{-1} (NaCl) 2920 (CH), 1745 (CO), 1419, 1223; $[\alpha]_D^{25}$ +39.6 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.28-1.38 (1H, m, 5-*H*H), 1.65-1.75 (1H, m, 6-*H*H), 2.05-2.15 (2H, m, 5-H*H* and 6-H*H*), 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-*H*H), 5.11 (1H, d, *J* 5.3 Hz, 9-H*H*); δ_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* (CI) 271.9825 (MH^+. $C_9H_{11}NO_2{}^{35}Cl_2{}^{37}Cl$ requires 271.9827), 270 (85%), 236 (87), 200 (100), 166 (64).

(3a*R*,4*R*,7*R*,7a*S*)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one (178).



(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2',2',2'-trichloromethylcarbonylamino)cyclohexa-3-ene **177a** (0.45 g, 1.5 mmol) was dissolved in *p*-xylene (10 mL) which was then de-gassed for 1h. 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 ^{o}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 (3a*R*,4*R*,7*R*,7a*S*)-3,3,4-trichloro-7-(methoxymethoxy)octahydroindol-2-one **178**, as a brown oil (0.34 g, 75%). υ_{max}/cm^{-1} (NaCl) 3256 (NH), 2953 (CH), 1741 (CO), 1440, 1036; $[\alpha]_D^{25}$ -60.2 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50-1.66 (1H, m, 6-*H*H), 1.71-1.82 (1H, m, 6-H*H*), 1.89-1.96 (1H, m, 5-*H*H), 2.29-2.36 (1H, m, 5-H*H*), 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, OC*H*HO), 4.72 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.20 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 32.7 (CH_2), 54.0 (CH), 54.7 (CH), 55.0 (CH_3), 59.0 (CH), 73.0 (CH), 84.4 (C), 94.4 (CH_2), 167.7 (C); *m/z* (CI) 302.0115 (MH^+. $C_{10}H_{15}NO_3{}^{35}Cl_3$ requires 302.0118), 268 (30%), 221 (18), 165 (50).

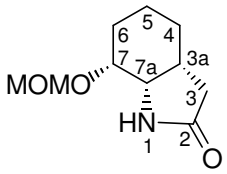
(3a*R*,7*R*,7a*S*)-Octahydro[1,8]oxazole-indol-2-one (196).



(3a*R*,4*R*,7*R*,7a*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

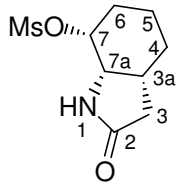
(3a*R*,7*R*,7a*S*)-octahydro[1,8]oxazole-indol-2-one **196**, as a white solid (0.016 g, 61%). υ_{max}/cm^{-1} (NaCl) 2940 (CH), 1708 (CO), 1390, 1223; $[\alpha]_D^{25}$ +71.5 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.17-1.28 (2H, m, 5-H_2), 1.50-1.60 (3H, m, 4-*H*H and 6-H_2), 1.70-1.79 (1H, m, 4-H*H*), 2.00 (1H, dd, *J* 16.3, 1.5 Hz, 3-*H*H), 2.42-2.50 (1H, m, 3a-H), 2.87 (1H, dd, *J* 16.3, 7.7 Hz, 3-H*H*), 3.99-4.09 (2H, m, 7-H and 7a-H), 4.30 (1H, d, *J* 5.4 Hz, 9-*H*H), 5.14 (1H, d, *J* 5.4 Hz, 9-H*H*); δ_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^+. $C_9H_{13}NO_2$ requires 167.0946), 139 (53%), 111 (35), 96 (100), 68 (38).

(3a*R*,7*R*,7a*S*)-7-(Methoxymethoxy)octahydroindol-2-one (197).



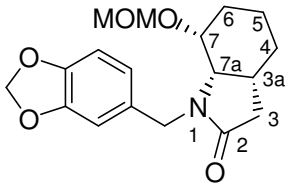
(3a*R*,4*R*,7*R*,7a*S*)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one **178** (0.05 g, 0.2 mmol) was dissolved in THF (10 mL) which was then added to a slurry of activated Raney-Nickel (1.00 g). The reaction was heated under reflux for 24 h and then a further portion of Raney-Nickel was added (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 (3a*R*,7*R*,7a*S*)-7-(methoxymethoxy)octahydroindol-2-one **197**, as a yellow oil (0.03 g, 85%). υ_{max}/cm^{-1} (NaCl) 3423 (NH), 2935 (CH), 1686 (CO), 1448 and 1035; $[\alpha]_D^{25}$ +46.1 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18-1.29 (2H, m, 5-H_2), 1.41-1.52 (1H, m, 6-*H*H), 1.59-1.67 (1H, m, 6-H*H*), 1.69-1.83 (2H, m, 4-H_2), 2.00 (1H, d, *J* 16.0, Hz, 3-*H*H), 2.32-2.41 (1H, m, 3a-H), 2.49 (1H, dd, *J* 16.0, 6.6 Hz, 3-H*H*), 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, OC*H*HO), 4.71 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.70 (1H, br s, NH); δ_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* (CI) 200.1288 (MH^+. $C_{10}H_{18}NO_3$ requires 200.1287), 168 (10%), 73 (10).

(3a*R*,7*R*,7a*S*)-7-(Methanesulfonyloxy)octahydroindol-2-one (179).



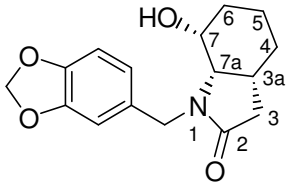
(3a*R*,7*R*,7a*S*)-7-(Methoxymethoxy)octahydroindol-2-one **197** (0.10 g, 0.5 mmol) was dissolved in methanol (2.0 mL) and 2 M hydrochloric acid (6.0 mL). The solution was heated to 40 ^{o}C and stirred vigorously for 14 h. The reaction was cooled and neutralised using a 6 M solution of potassium carbonate (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 (3a*R*,7*R*,7a*S*)-7-(methanesulfonyloxy)octahydroindol-2-one **179**, as a white solid (0.10 g, 88% yield over 2 steps). υ_{max}/cm^{-1} (NaCl) 3397 (NH), 2945 (CH), 1664 (CO), 1424, 1340; $[\alpha]_D^{24}$ +68.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30-1.40 (2H, m, 5-H_2), 1.62-1.71 (1H, m, 4-*H*H), 1.77-1.93 (3H, m, 4-H*H* and 6-H_2), 2.05 (1H, d, *J* 14.0, Hz, 3-*H*H), 2.53-2.42 (2H, m, 3-H*H* 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); δ_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^+. $C_9H_{16}NSO_4$ requires 234.0800), 198 (3%), 138 (6), 85 (2).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one (206).



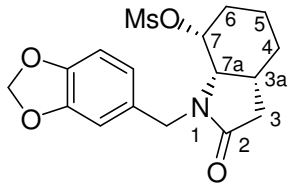
(3a*R*,7*R*,7a*S*)-7-(Methoxymethoxy)octahydroindol-2-one **197** (0.05 g, 0.3 mmol) was dissolved in THF (2.0 mL) and cooled to 0 ^{o}C. Sodium hydride (60% in mineral oil) (0.012 g, 0.3 mmol) was added and the solution was stirred for 5 minutes before piperonyl bromide **205**,[98] (0.097 g, 0.5 mmol) 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 ^{o}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 ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate) gave (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one **206**, as a colourless oil (0.075 g, 90% yield). υ_{max}/cm^{-1} (NaCl) 2937 (CH), 1668 (CO), 1488, 1252; $[\alpha]_D^{25}$ -32.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23-1.38 (2H, m, 5-H_2), 1.51-1.77 (3H, m, 4-H_2 and 6-*H*H), 1.82-1.90 (1H, m, 6-H*H*), 2.25 (1H, dd, *J* 14.6, 7.5 Hz, 3-*H*H), 2.32-2.41 (1H, m, 3a-H), 2.47 (1H, dd, *J* 14.6, 10.4 Hz, 3-H*H*), 3.30 (1H, dd, *J* 6.5, 3.9 Hz, 7-H), 3.35 (3H, s, OCH_3), 3.82 (1H, d, *J* 14.8 Hz, N-C*H*H), 3.89-3.93 (1H, m, 7a-H), 4.48 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.62 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.00 (1H, d, *J* 14.8 Hz, N-CH*H*), 5.94 (2H, s, OCH_2O), 6.71-6.76 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.7 (CH_2), 25.8 (CH_2), 26.9 (CH_2), 32.6 (CH), 36.5 (CH_2), 43.8 (CH_2), 55.6 (CH_3), 56.2 (CH), 72.2 (CH), 95.3 (CH_2), 101.0 (CH_2), 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^+. $C_{18}H_{24}NO_5$ requires 334.1654), 302 (7%), 200 (6), 135 (15), 69 (16).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one (207).



(3a*R*,7*R*,7a*S*)-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 ^{o}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 ($MgSO_4$) and concentrated to give (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one **207** as a white solid (0.173 g, 100%). υ_{max}/cm^{-1} (NaCl) 3370 (OH), 2934 (CH), 1663 (CO), 1489, 1442, 1243; $[\alpha]_D^{25}$ -22.6 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25-1.39 (2H, m, 5-H_2), 1.51-1.61 (1H, m, 4-*H*H), 1.67-1.87 (3H, m, 4-H*H* and 6-H_2), 1.95 (1H, br s, OH), 2.23 (1H, dd, *J* 15.0, 7.8 Hz, 3-*H*H), 2.36-2.45 (1H, m, 3a-H), 2.51 (1H, dd, *J* 15.0, 11.3 Hz, 3-H*H*), 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-C*H*H), 4.71 (1H, d, *J* 14.8 Hz, N-CH*H*), 5.95 (2H, s, OCH_2O), 6.75-6.82 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_2), 25.8 (CH_2), 29.4 (CH_2), 32.4 (CH), 36.4 (CH_2), 44.9 (CH_2), 60.1 (CH), 65.8 (CH), 101.1 (CH_2), 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^+. $C_{16}H_{20}NO_4$ requires 290.1392), 289 (12%), 85 (52), 51 (55), 49 (75).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methanesulfonyloxy)octahydroindol-2-one (209).



(3a*R*,7*R*,7a*S*)-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 ^{o}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 ($MgSO_4$) and concentrated to give the crude product, which was purified by flash column chromatography (eluting with ethyl acetate : petroleum ether, 3 : 2) to give (3a*R*,7*R*,7a*S*)-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; $[\alpha]_D^{25}$ -19.3 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42-1.52 (2H, m, 5-H_2), 1.59-1.66 (2H, m, 4-H_2), 1.70-1.79 (2H, m, 6-H_2), 2.11-2.20 (1H, m, 3-*H*H), 2.32-2.37 (1H, m, 3a-H), 2.43-2.51 (1H, m, 3-H*H*), 3.01 (3H, s, SCH_3), 3.36 (1H, dd, *J* 6.9, 3.9 Hz, 7-H), 3.84 (1H, d, *J* 14.9 Hz, N-C*H*H), 5.06 (1H, d, *J* 14.9 Hz, N-CH*H*), 5.14-5.18 (1H, m, 7a-H), 5.95 (2H, s, OCH_2O), 6.72-6.76 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.9 (CH_2), 25.1 (CH_2), 28.3 (CH_2), 32.0 (CH), 35.8 (CH_2) 39.2 (CH), 43.9 (CH_2), 57.0 (CH), 75.6 (CH_3), 101.1 (CH_2), 108.3 (CH), 108.4 (CH), 121.5 (CH), 130.1 (C), 147.2 (C), 148.1 (C), 175.7 (C); *m/z* (CI) 368.1173 (MH^+. $C_{17}H_{22}NSO_6$ requires 368.1168), 335 (12%), 290 (30), 272 (36), 150 (84), 136 (100).

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