New Methodology for the Stereoselective Synthesis of Unnatural α-Amino Acids

Lorna J. Drummond (M. Sci)

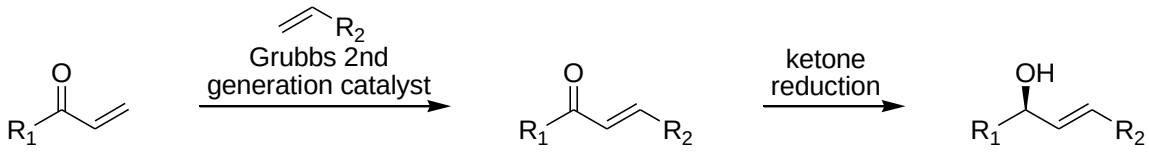
A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

School of Chemistry
College of Science & Engineering
University of Glasgow

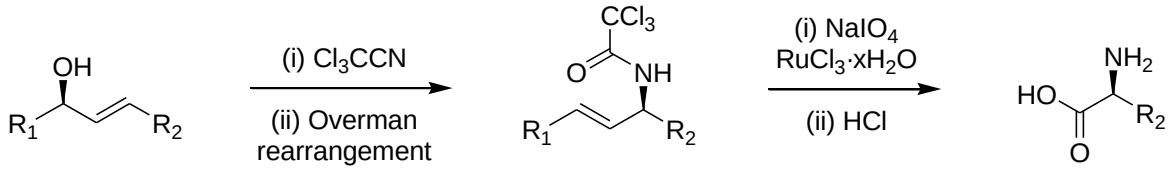
July 2011

Abstract

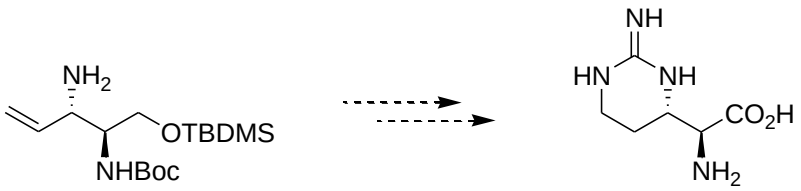
New general methodology for the stereoselective synthesis of unnatural α-amino acids has been developed. Early work focussed on investigating methods for the generation of chiral allylic alcohols using cross-metathesis of a simple enone with various terminal alkenes, followed by an asymmetric ketone reduction.



The allylic alcohols were then converted to protected allylic amines *via* Overman rearrangement chemistry. Oxidative alkene cleavage and hydrolysis of these intermediates generated a range of α-amino acid targets. Attempts were also made to apply the developed methodology to the synthesis of a simple α,α-disubstituted α-amino acid target.



The Overman rearrangement was also applied to the generation of a late-stage intermediate which could be used in the synthesis of (2*S*,3*S*)-capreomycidine, a component of a number of peptides which exhibit antibacterial activity.



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

Contents

Acknowledgements

I would like to express my thanks to Dr. Andrew Sutherland for excellent supervision throughout the course of my PhD research. I am very grateful for the opportunity to work in his group and for all the support and encouragement he has provided during the last four years.

Thanks to my second supervisor Dr. Richard Hartley for helpful discussions and to all other staff in the chemistry department, both academic and technical.

Thanks to Nicola, Mike, Louise, Lindsay, Ahmed, Sajjad, Mark D, Adele, Mark G and Alastair for sharing the Sutherland group experience with me, and also to Stephen and Andrew for making me laugh in the Loudon Lab.

Special mention goes to three amazing people: Jennifer, Fiona and Mhairi. Without their unwavering support in the chemistry department and provision of many *many* fun times outwith, I genuinely could not have got through the tricky times.

Credit also goes to some wonderful friends I am extremely lucky to have: FiFi, Julie, Tracey, Gill, Francesca, Clare, Laura and Hayley for the best nights out and nights in, away from the chemistry department.

Thanks to some great people I have met along the way: Thomas, Saleem, Liam, Jennifer, Stevie, Bryan, Anna, Lucia, Alasdair and Alan to name just a few.

I am grateful to all my family, particularly my Gran, my Grandma, my sister Mhairi and brother-in-law David for encouragement.

Most importantly, I would like to thank my amazing Mum and Dad, who have always done everything possible to support me through all that I have achieved.

Financial support from the Carnegie Trust for the Universities of Scotland and the University of Glasgow is gratefully acknowledged.

Author's Declaration

This thesis represents the original work of Lorna Jane Drummond unless otherwise explicitly stated in the text. The research was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr. Andrew Sutherland during the period of October 2007 to February 2011. Portions of the work described herein have been published elsewhere, as below:

L. J. Drummond and A. Sutherland, *Tetrahedron*, 2010, **66**, 5349–5356.

Abbreviations

Ac	acetyl
Ar	aryl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
^{t}BuOH	*tert*-butanol
^{t}BuOOH	*tert*-butylhydroperoxide
°C	degrees centigrade
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
COD	cyclooctadiene
COP	cobaltocenyloxazoline palladacycle
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EI	electron impact
eq	equivalents
Et	ethyl
Et_2O	diethyl ether
EtOAc	ethyl acetate
FAB	fast atom bombardment
FOP	ferrocenyloxazoline palladacycle
FTIR	Fourier transform infrared
g	gram(s)
h	hours

^{1}H	proton
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons
Hz	hertz
IR	infrared
J	NMR spectra coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
L	litre
lit.	literature
M	molar
m	multiplet
*m*CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
Mes	mesityl
mg	milligram(s)
MHz	megahertz
mL	millilitre(s)
mmol	millimole(s)
Me	methyl
MOM	methoxymethyl
Mp	melting point
Ms	methanesulfonyl
NaHMDS	sodium bis(trimethylsilyl)amide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
Ph	phenyl
ppm	parts per million
^{i}Pr	isopropyl
q	quartet
quin	quintet
s	singlet
r.t.	room temperature
t	triplet

TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethysilyl

1.0 Introduction

1.1 α-Amino acids

1.1.1 Properties of α-amino acids

α-Amino acids are very important natural products, which constitute the subunits of proteins. Their prevalence in nature means that they have a vast range of potential applications across many fields including biology, medicine, and chemistry.[1]

α-Amino acids exist in either the D or L form, as shown in Figure 1 and all of the natural proteinogenic examples are of the L form with the exception of glycine (R = H), which does not bear a stereogenic centre.

L-amino acid **D-amino acid**

Figure 1. α-Amino acid structures

α,α-Disubstituted α-amino acids bear an additional group on the α-carbon atom relative to their natural counterparts (Figure 2), and this gives these compounds a number of interesting properties.

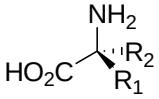
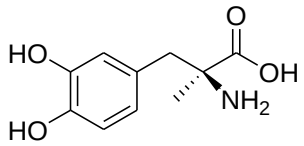


Figure 2. α,α-Disubstituted α-amino acids

The incorporation of these units into peptides gives rise to a number of unusual secondary structures as a result of the additional steric bulk.[2,3] α,α-Disubstituted α-amino acids can therefore be used to design and synthesise peptides with relatively rigid, well-defined secondary structures which may give rise to improved substrate specificity and biological activity. The lack of an α-hydrogen atom also

means that these structures have the potential to act as enzyme inhibitors which have the ability to bind to an active site, but not to undergo a number of standard enzymatic reactions. The α,α-disubstituted α-amino acid motif is found in a number of pharmaceutical compounds, such as methyldopa **1** (Figure 3), a known anti-hypertensive drug.[4]



1

Figure 3. Methyldopa

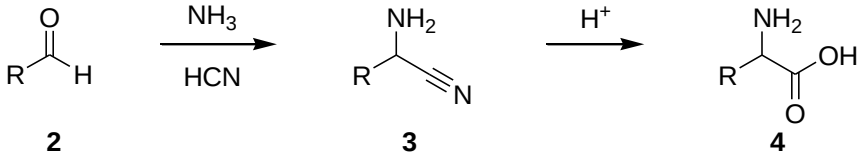
While many methods for the synthesis of α-amino acids have been published in the literature, with the addition in recent years of methodology for generating α,α-disubstituted examples, there remains the need for fast and efficient syntheses of both classes of compounds which are flexible for the generation of a wide range of these targets with varying side chains. In particular, routes which lead to the formation of these compounds in a highly enantioselective manner are desirable.

1.1.2 Previous syntheses of α-amino acids

The development of methods for the enantioselective synthesis of α-amino acids is commonplace in the literature and often makes use of the chiral pool, or approaches using chiral auxiliaries[5] or chiral catalysis.[6,7] While a detailed review of these methods is outwith the scope of this thesis, selected examples of approaches to their synthesis are summarised below:

- **Asymmetric addition of cyanide to aldehydes (Strecker synthesis)**

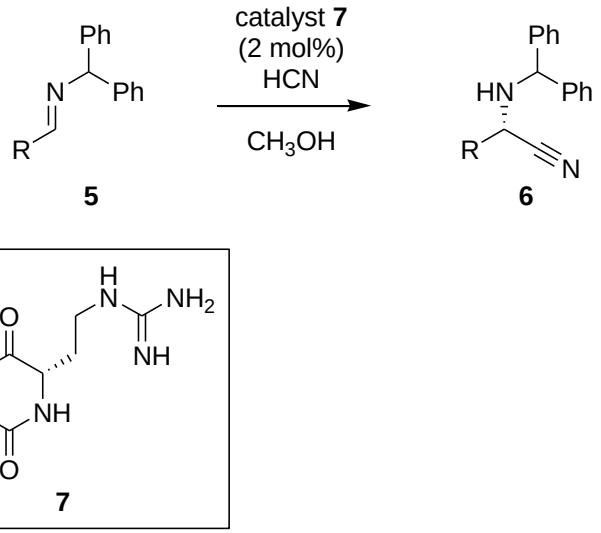
In 1850, Strecker first published a method for the synthesis of α-amino acids which involves the condensation of an aldehyde **2** with ammonia to give a Schiff base, to which cyanide can be added, yielding an α-amino nitrile intermediate **3**. Subsequent hydrolysis then yields the racemic α-amino acid product **4**, as summarised in Scheme 1.1.[8]



2 **3** **4**

Scheme 1.1. Strecker synthesis of α-amino acids

More recently, asymmetric variants of the Strecker synthesis have been reported in the literature, which make use of both organocatalysts and metal catalysts,[9] and the first of these was reported in 1996 by Lipton and co-workers.[10] This method makes use of a diketopiperazine organocatalyst **7** in the generation of the α-amino nitrile intermediates **6** from pre-formed imines **5**, as shown in Scheme 1.2. Formation of the α-amino nitriles proved successful in high yield, and with high enantiomeric excess values observed in the products with a range of substituted aryl groups. For example, when R = Ph, a 97% product yield with >99% e.e. was reported. This approach was not applicable, however, to examples with heteroaromatic or aliphatic R groups, where e.e. values were as low as <10%.



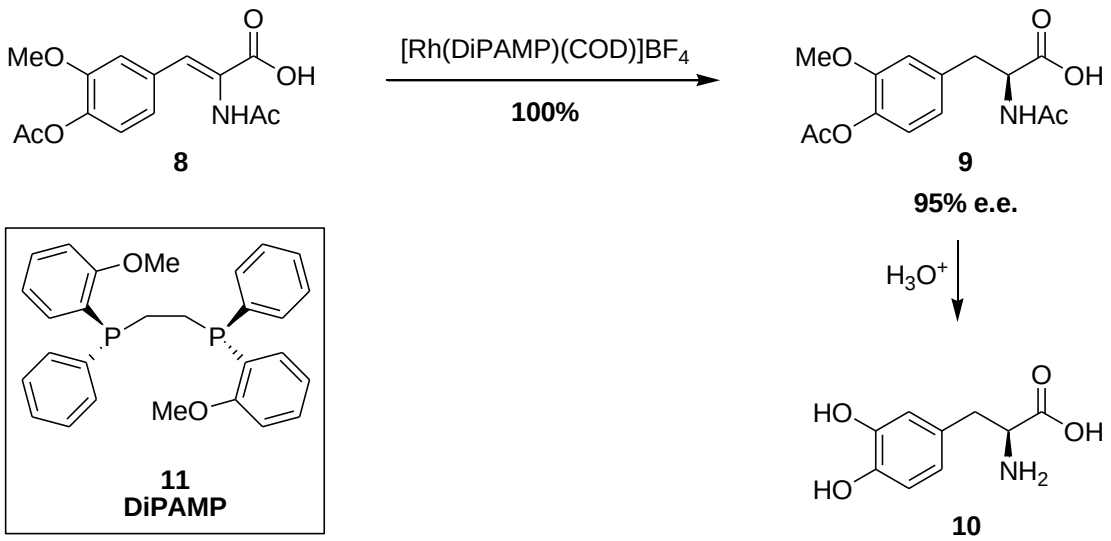
5 **6** **7**

Scheme 1.2. Diketopiperazine-catalysed Strecker synthesis

- **Catalytic asymmetric hydrogenation of dehydroamino acids**

A particularly efficient method for the stereoselective synthesis of α-amino acids is the asymmetric hydrogenation of dehydroamino acids using metal catalysts, typically rhodium(I) or ruthenium(II), complexed with a chiral ligand which can be capable of achieving addition of hydrogen across a carbon-carbon double bond in a

highly enantioselective manner. An early, well-known example of a chiral phosphane ligand used for this reaction is DiPAMP **11**, a dimeric form of methylphenyl-o-anisylphosphane (PAMP) which was developed by Knowles and co-workers.[11] The utility of this ligand, complexed to rhodium, is highlighted in its application to a key step in an industrial synthesis of L-3,4-dihydroxyphenylalanine (L-DOPA) **10**, a drug used in the treatment of Parkinson's disease. The dehydroamino acid intermediate **8** can be hydrogenated enantioselectively in the presence of [Rh(DiPAMP)(COD)]BF_4, giving the protected L-DOPA derivative **9** in quantitative yield, and with an enantiomeric excess value of 95%. Completion of the L-DOPA target was then achieved by removal of the protecting groups under acidic conditions, as shown in Scheme 1.3.[12]

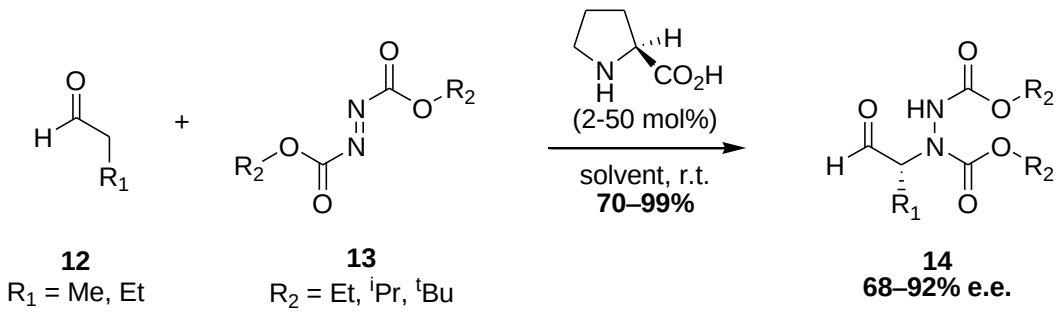


Scheme 1.3. Synthesis of L-DOPA *via* asymmetric hydrogenation

- **Asymmetric carbon-nitrogen bond formation**

It is possible to incorporate the α-amino group of α-amino acids using either nucleophilic or electrophilic nitrogen sources. One such use of an electrophilic reagent was discussed in 2002 by Jørgensen and co-workers, who reported the α-amination of aldehydes **12** with azodicarboxylates **13**, allowing eventual access to a range of α-amino acid products.[13] The presence of L-proline as an organocatalyst allowed these amination reactions to be carried out with moderate levels of enantioselectivity by forming an enamine intermediate with the aldehyde substrate

and then directing the incoming nitrogen atom of the azodicarboxylate **13** selectively to one face. The approach is summarised in Scheme 1.4.



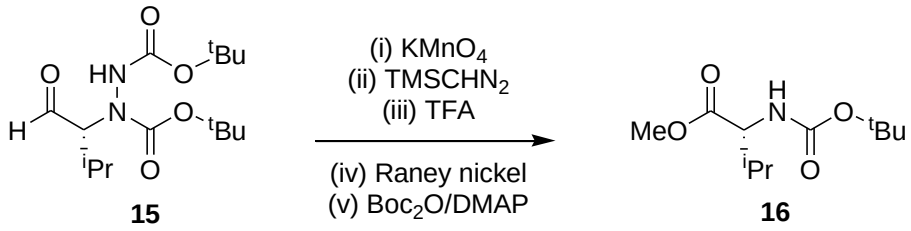
12
R_1 = Me, Et

13
R_2 = Et, ^{i}Pr, ^{t}Bu

14
68–92% e.e.

Scheme 1.4. L-Proline-catalysed electrophilic amination of aldehydes

Conversion of the α-aminated products **14** to protected α-amino acids was possible using a series of relatively straightforward transformations. One particular example **15** discussed in the paper is shown below in Scheme 1.5, and involved the conversion of the aldehyde to the corresponding methyl ester by permanganate oxidation followed by treatment with (trimethylsilyl)diazomethane. Trifluoroacetic acid was then employed to remove the Boc groups, and reduction and finally Boc reprotection gave protected α-amino acid **16** with no loss of enantiomeric excess established in the amination step (>90% e.e.).

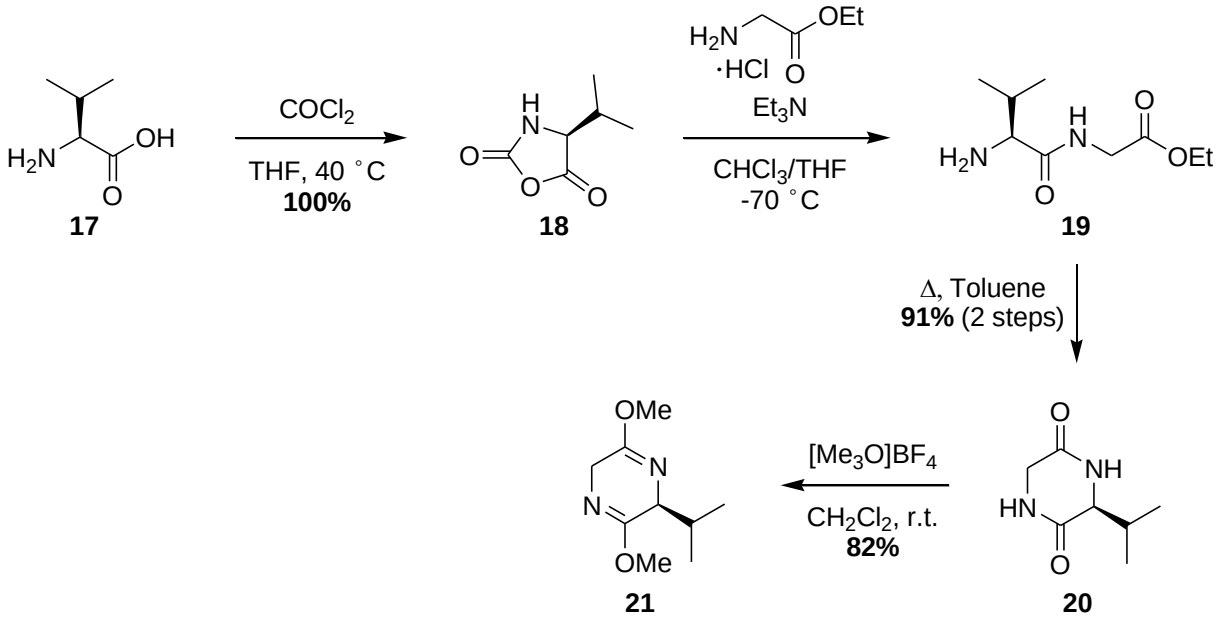


15 **16**

Scheme 1.5. Completion of protected α-amino acid 16

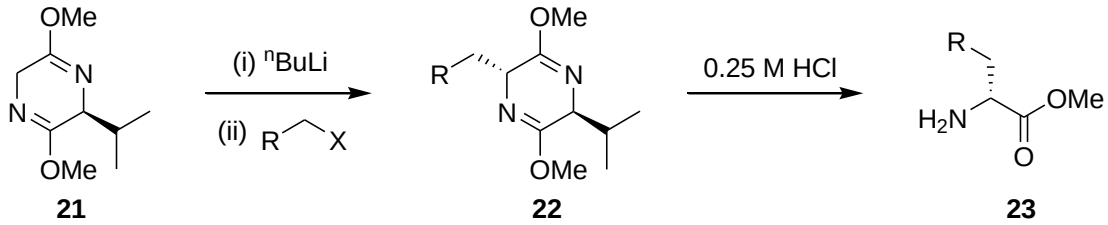
- **Asymmetric alkylation of glycine derivatives**

In 1981, Schöllkopf and co-workers published details of a method for the enantioselective synthesis of (*R*)-amino acids using L-valine **17** as a chiral auxiliary. L-Valine was attached to the ethyl ester of glycine, and this was followed by a cyclisation to generate diketopiperazine **20**, and finally *O*-methylation to give bis-lactim ether **21**, as shown in Scheme 1.6.[5]



Scheme 1.6. Synthesis of Schöllkopf bis-lactim ether 21

The bis-lactim ether **21** could then be subjected to diastereoselective alkylation with a range of alkyl halides, with the presence of the relatively large isopropyl group leading to alkylation taking place preferentially from the opposite face of the anion of **21**, generated by deprotonation with *n*-butyllithium (Scheme 1.7). Completion of the α-amino acid targets was then achieved by hydrolysis of ether **22** with dilute acid, which gives initially the methyl ester derivative of the α-amino acids **23**, which could then be converted to the α-amino acids by hydrolysis with either acid or base.



Scheme 1.7. Diastereoselective alkylation of Schöllkopf bis-lactim ether 21

Selected results for the alkylation and hydrolysis steps are highlighted below in Table 1, with enantiomeric excess values determined for methyl esters **23**.

Alkylating agent	Yield of 22 (%)	Yield of 23 (%)	e.e. of ester 23 (%)
$BrCH_2C_6H_5$	81	73	91-95
$Br(CH_2)_6CH_3$	62	75	75-80
$BrCH_2$-3,4-$(OCH_3)_2C_6H_3$	91	78	85
$BrCH_2$-CH=CH-C_6H_5	90	89	>95

Table 1. Results of alkylation of bis-lactim ether 21

While relatively high yields and levels of enantioselectivity were encountered using this approach, the requirement for additional steps to both incorporate and remove the chiral auxiliary lead to a less efficient synthetic route than catalytic procedures.

1.1.3 Previous syntheses of α,α-disubstituted α-amino acids

In recent years, much literature has been published which discusses methods for the synthesis of α,α-disubstituted α-amino acids using a number of approaches for the functionalisation of α-amino acid derivatives.[14] These include the diastereoselective alkylation of oxazinones derived from asymmetric Strecker reaction products,[15] and the asymmetric alkylation of α-amino acid enolates.[16]

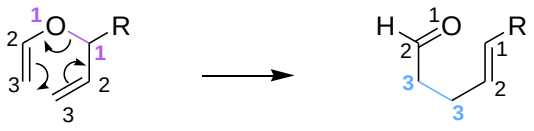
Another approach which has proven to be applicable to the synthesis of both α-amino acids and α,α-disubstituted α-amino acids is the use of Overman rearrangement chemistry to generate protected allylic amines, which can be readily converted to α-amino acid targets. The Overman rearrangement is a well-established reaction which has been shown to have wide scope for the generation of a large variety of allylic amines and importantly, the stereochemical outcome of these reactions can be controlled.

1.2 The Overman rearrangement

1.2.1 [3,3]-Sigmatropic rearrangements

[3,3]-Sigmatropic rearrangements, such as the Claisen rearrangement shown in Scheme 1.8, are a class of pericyclic reaction in which a sigma bond moves from the

1 position to the relative 3 position at each of its ends. Rearrangements of this type proceed in a concerted manner, *via* a highly ordered 6-membered transition state.[17]



24 **25**

Scheme 1.8. [3,3]-Sigmatropic rearrangement

As with all pericyclic reactions, [3,3]-sigmatropic rearrangement reactions obey the Woodward-Hoffmann rules,[18] which state that:

- A ground-state (thermal) pericyclic reaction is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is odd
- A pericyclic reaction in the first electronically excited state (photochemical) is symmetry-allowed when the total number of $(4q+2)_s$ and $(4r)_a$ components is even

Here, 'component' refers to a bond or orbital which takes part in a pericyclic reaction. The letters q and r here are simply integers. The letter s stands for suprafacial, with a suprafacial component forming new bonds on the same face at both ends. The letter a represents antarafacial, and an antarafacial component forms new bonds on opposite faces at both ends.

In the case of [3,3]-sigmatropic rearrangements, three components are involved in the reaction: two nonconjugated π bonds, and one σ bond which joins these. Each of these components contributes two electons, and is assigned according to Figure 4.[19,20]

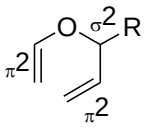


Figure 4. Assignment of components in [3,3]-sigmatropic rearrangement

By drawing a three-dimensional representation of the orbitals involved in the reaction, it can be determined if each of these components is a suprafacial or antarafacial component, as shown in Figure 5.

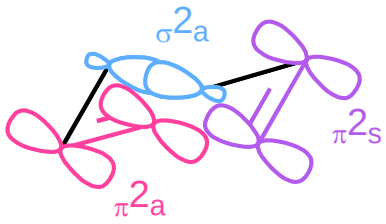
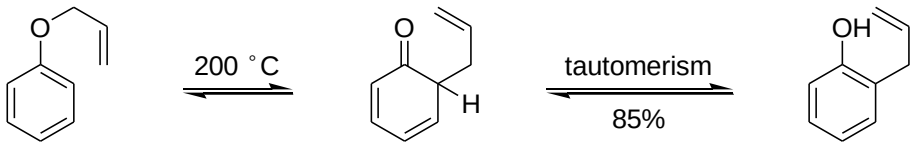


Figure 5. Orbitals involved in [3,3]-sigmatropic rearrangement

Therefore in the case of [3,3]-sigmatropic rearrangement reactions, there is one component which satisfies the $(4q+2)_s$ formula ($\pi 2_s$), and no components which satisfy $(4r)_a$. This gives a total of 1, which is odd, and hence [3,3]-sigmatropic rearrangements in the ground state are symmetry-allowed according to the Woodward-Hoffmann rules.

1.2.2 The Claisen rearrangement

The Claisen rearrangement was the first example of a [3,3]-sigmatropic rearrangement, originally reported in the literature in 1912.[21] Claisen found that aromatic allylic ethers **26** were able to rearrange to substituted phenol derivatives **28** when heated to 200 °C, as shown in Scheme 1.9.

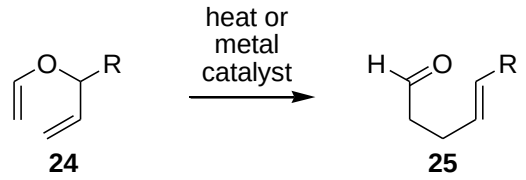


26 **27** **28**

Scheme 1.9. Aromatic Claisen rearrangement

Following this result, efforts were focussed on developing an aliphatic variant of the Claisen rearrangement, involving the [3,3]-sigmatropic rearrangement of allylic vinyl ethers **24** to α,γ-unsaturated carbonyl compounds **25** (Scheme 1.10).[22] The

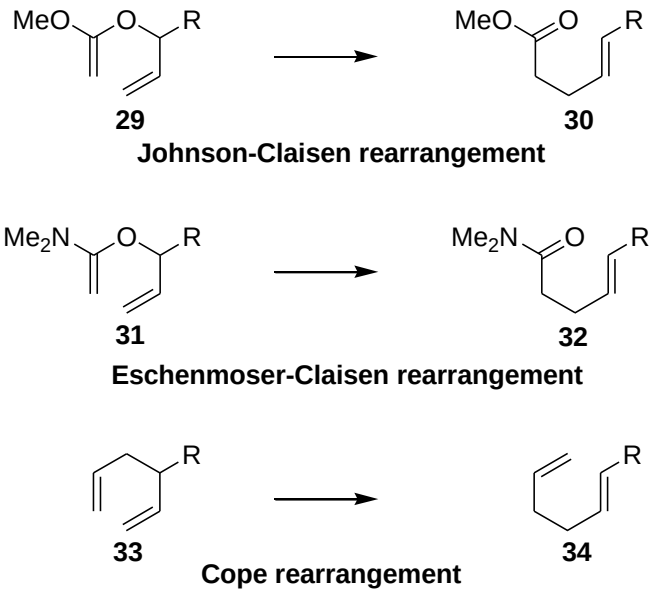
driving force of this reaction is the formation of a new carbon-oxygen double bond at the expense of a weaker carbon-carbon double bond.



24 **25**

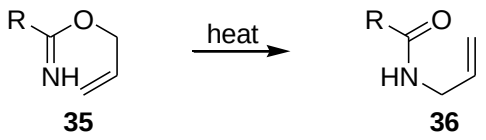
Scheme 1.10. Aliphatic Claisen rearrangement

Further variations of the Claisen rearrangement were subsequently developed to allow the formation of functional groups other than aldehydes. These include the Johnson-Claisen rearrangement for the generation of esters **30**,[23] the Eschenmoser-Claisen rearrangement of *N,O*-ketene acetals **31** to amides **32**,[24] and the all-carbon version of the Claisen rearrangement, known as the Cope rearrangement[25] as summarised in Scheme 1.11.



Scheme 1.11. Variations of the Claisen rearrangement

A further analogous reaction to the Claisen rearrangement was reported in the literature by Mumm and Möller, who first discussed the rearrangement of allylic imidates **35**, shown in Scheme 1.12.[26]



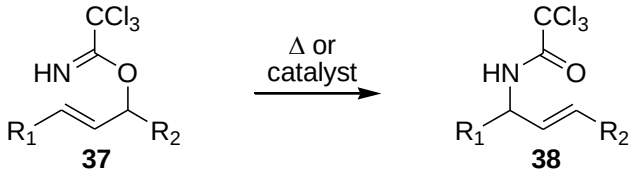
35 **36**

Scheme 1.12. Rearrangement of allylic imidates

While this rearrangement provides a potentially useful method for accessing protected allylic amines from derivatives of more readily available allylic alcohols, the generation of the allylic imidate intermediates and their subsequent rearrangement are often slow and tend to require high temperatures to proceed. As a result of these elevated temperatures, decomposition of the imidates prior to rearrangement is a potential issue.

1.2.3 History of the Overman rearrangement

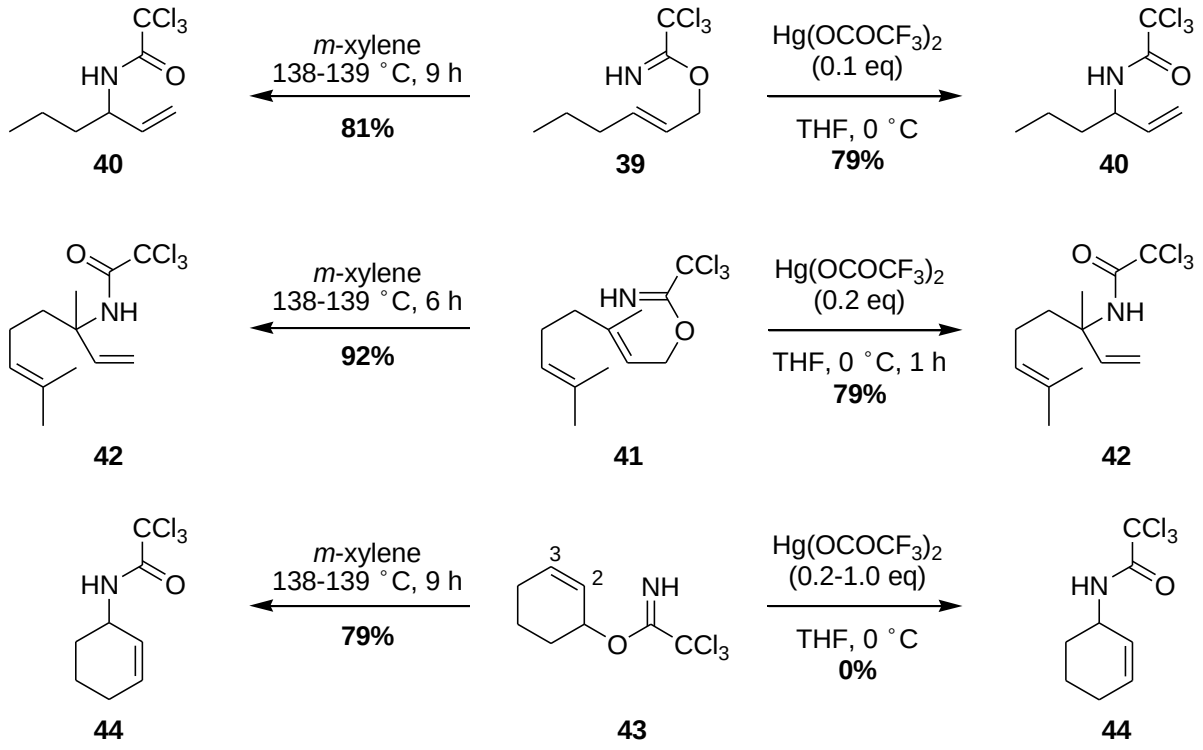
In 1974, Professor Larry Overman first reported a subtype of the imidate rearrangement which involved the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates **37** to allylic trichloroacetamides **38**, as outlined in Scheme 1.13.[27]



37 **38**

Scheme 1.13. [3,3]-Sigmatropic rearrangement of allylic trichloroacetimidates

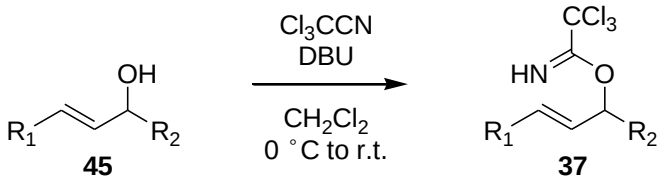
Now referred to as the Overman rearrangement, these reactions were shown to proceed in high yield under either thermal reaction conditions, or using mercury(II) catalysis. Selected results from Overman's original paper are shown in Scheme 1.14. Note that the failure of the mercury(II)-catalysed rearrangement of the 2-cyclohexen-1-yl acetimidate **43** can be attributed to the preference for nucleophilic attack by nitrogen at the C-2 position as opposed to the required C-3 attack.



Scheme 1.14. First reported examples of Overman rearrangement

Following the publication of these results, the Overman rearrangement has proved popular as it provides an effective method for the 1,3-transposition of alcohol and amine functionality which does not require particularly harsh conditions. Hydrolysis of the trichloroacetamides to corresponding free amines can also be easily achieved, and hence the Overman rearrangement has found utility in the synthesis of many important classes of molecules, such as amino sugars, nucleotides, *N*-heterocycles and amino acids.[28]

Importantly, generation of the allylic trichloroacetimidate substrates **37** for the Overman rearrangement is very straightforward from the corresponding allylic alcohols **45**, which are treated with trichloroacetonitrile in the presence of a catalytic quantity of base[29,30] such as sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene, as shown in Scheme 1.15.[31] Generally, the allylic trichloroacetimidates are used immediately after formation, with simple purification by filtration through a short plug of silica capable of providing the pure allylic trichloroacetimidates required.



Scheme 1.15. Synthesis of allylic trichloroacetimidates

The use of allylic trifluoroacetimidates in Overman rearrangements has also been reported and in some cases, an increased reaction rate has been observed for the rearrangement of these substrates. However, formation of the required allylic trifluoroacetimidate substrates is significantly more challenging than allylic trichloroacetimidates, often requiring the use of the highly toxic gas, trifluoroacetonitrile. Therefore, allylic trifluoroacetimidates have not found comparably widespread utility as rearrangement substrates.[32,33]

1.2.4 Thermal Overman rearrangements

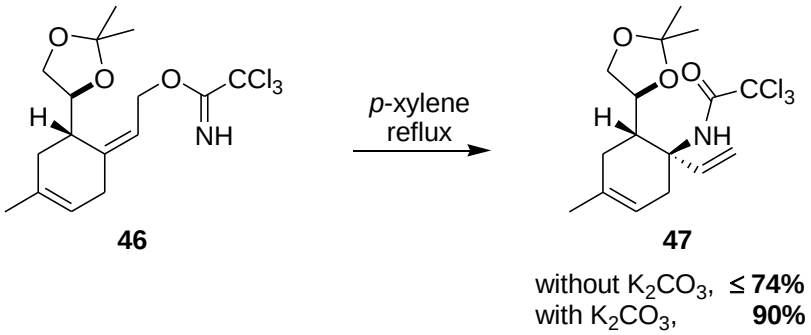
The reaction conditions required for a thermal Overman rearrangement initially involved simply dissolving the trichloroacetimidate substrate in an aprotic, high-boiling point solvent such as toluene or xylene, and heating under reflux until completion.

Allylic trichloroacetimidates derived from primary, secondary and tertiary-substituted allylic alcohols have all been shown to be applicable to the Overman rearrangement, and an increase in reaction rate is observed with increasing substitution. Primary substituted systems tend to require temperatures of 140 °C and 4–24 hours, while the tertiary variants can rearrange at 80 °C in a few hours.[34]

In 1998, an important modification was made to standard thermal Overman rearrangement conditions when Isobe and co-workers reported that the addition of a small quantity of potassium carbonate to the reaction mixture generally improves product yields.[35] The higher yields can be attributed to the neutralisation of acid that may be generated at the high temperatures encountered during thermal

rearrangement conditions, which in turn can lead to decomposition of the acid-sensitive trichloroacetimidate.

One particular example which highlights this improvement involved the thermal Overman rearrangement of allylic trichloroacetimidate **46**, shown in Scheme 1.16. With no potassium carbonate present, this reaction initially proceeded in 74% yield over 2 steps from the allylic alcohol, although this drastically lowered by around 50% upon scale-up. Addition of potassium carbonate (2 mg/ mL of solvent) led to the generation of the trichloroacetamide product **47** in a yield of 90%, which was reproducible on scaling the reaction up to using 10 g of the allylic alcohol starting material.



46 **47**

without K_2CO_3, ≤ **74%**
with K_2CO_3, **90%**

Scheme 1.16. Isobe modification of thermal rearrangement conditions

As previously mentioned, the involvement of a 6-membered transition state dictates the stereochemical outcome of Overman rearrangement reactions. Selectivity exists for the formation of allylic trichloroacetamides with *E* geometry across the allylic double bond, as a result of the large trichloromethyl group occupying an axial position in the chair-like transition state. 1,3-Diaxial interactions are minimised when the hydrogen atom is placed in an axial position, with the larger R group equatorial, as shown in Figure 6.[34] Thus, allylic trichloroacetimidates derived from both *E*- and *Z*-allylic alcohols show a high level of preference for the formation of *E*-products in the vast majority of cases, with the main exception being tertiary substituted alcohols with two similarly-sized substitutents on the α-carbon. It is worth noting that the substrates derived from allylic alcohols with *Z*-geometry require longer reaction times and / or higher reaction temperatures in comparison to the *E* allylic alcohols.

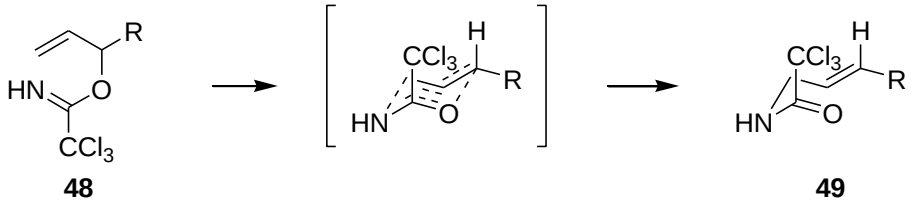
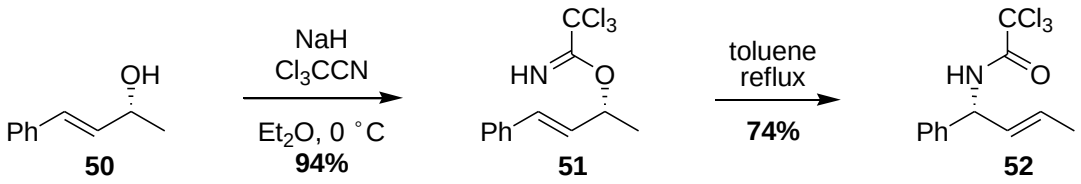


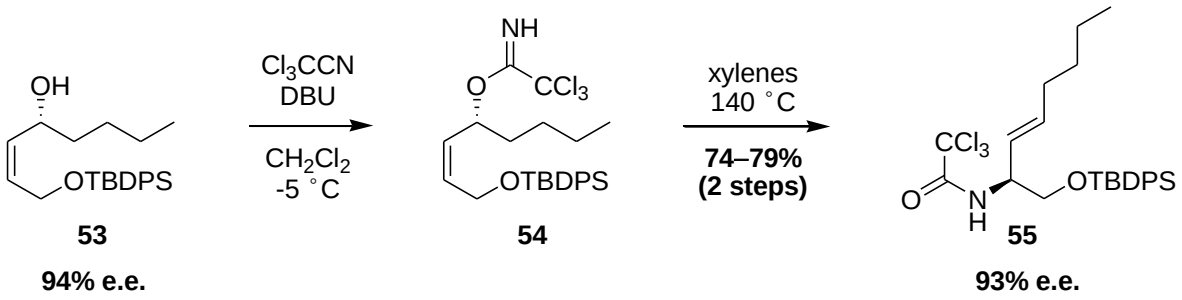
Figure 6. Preferred Overman rearrangement transition state leading to *E*-product

One of the most attractive features of using a [3,3]-sigmatropic rearrangement to access protected allylic amines is that complete transfer of chirality between stereocentres is observed as a direct result of the well-ordered transition state. Therefore, in the case of an enantiomerically enriched sample of a secondary or tertiary allylic alcohol, the level of enantiomeric excess will be carried through to the trichloroacetamide product. This was first discussed in the literature by Yamamoto *et al.*, who converted allylic alcohol **50** to the corresponding allylic trichloroacetimidate **51** which was subjected to a thermal Overman rearrangement, as shown in Scheme 1.17. Comparison of optical rotation values of rearrangement product derivatives and ^{1}H NMR spectroscopic analysis using chiral shift reagents allowed the group to confirm that the allylic alcohol starting material **50** had an optical purity of 45±2%, while the rearrangement product **52** was 45.6% optically pure. This result served to show that a complete transfer of chirality is achieved in rearrangements of this type, and additionally provided evidence for progress of the rearrangement *via* a chair-like transition state.[36]



Scheme 1.17. Chirality transfer in secondary allylic trichloroacetimidates

The complete transfer of chirality is not limited to only *E*-allylic trichloroacetimidates, but is also observed in the thermal rearrangement of the equivalent compounds with *Z*-geometry such as **54** as discussed by Bloch and co-workers in 1999, highlighted in Scheme 1.18.[37]



Scheme 1.18. Chirality transfer in rearrangement of *Z*-allylic trichloroacetimidates

In examples where an additional stereogenic centre is present in the rearrangement substrate, diastereoselectivity in formation of the new C-N bond is possible, although this greatly depends on the substituents present. However, the use of metal catalysis in Overman rearrangements can allow much greater control of the stereochemical outcome of such reactions.

1.2.5 Metal-catalysed Overman rearrangements

As previously discussed, Overman published details of the first metal-catalysed [3,3]-sigmatropic rearrangements of allylic trichloroacetimidates in 1974.[27] Here, he showed that the presence of catalytic mercuric trifluoroacetate ($Hg(O_2CCF_3)_2$) allowed these reactions to successfully proceed at room temperature or below, often within minutes owing to a proposed enhancement in rate calculated to be over 1×10^{12} in comparison to the corresponding thermal reactions.[34]

Following this observation, the use of alternative metal catalysts was studied, and it was subsequently discovered that palladium(II) catalysis was also applicable.[38] The most commonly used palladium(II) catalysts in Overman rearrangement chemistry now are $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$, which are typically present in loadings of approximately 4 to 8 mol%. These catalysts are soluble in aprotic solvents such as tetrahydrofuran and toluene, which are often used during these rearrangements.

In the presence of a metal catalyst, the Overman rearrangement is thought to proceed *via* a cyclisation-induced mechanism, as shown in Figure 7. Here, the

metal centre coordinates to the alkene and promotes cyclisation *via* nucleophilic attack by nitrogen. Collapse of the 6-membered ring then generates the carbonyl, and movement of the allylic system gives the desired allylic trichloroacetamide product.[39]

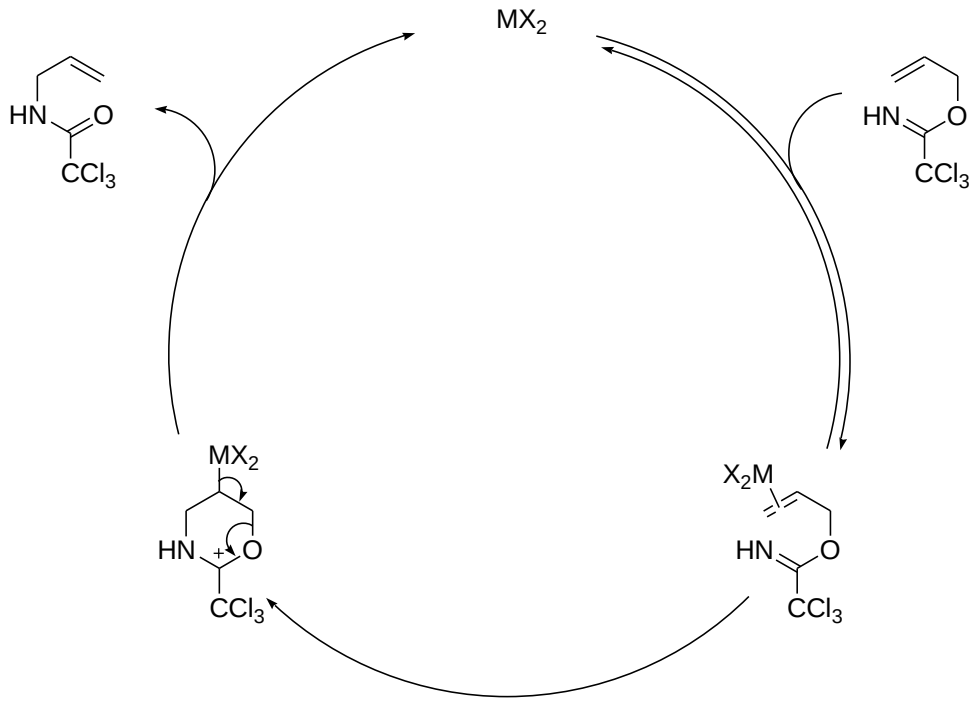
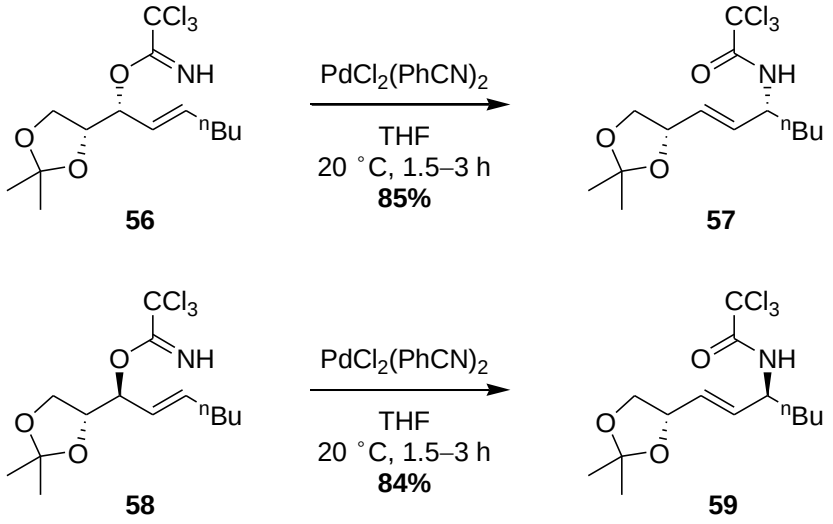


Figure 7. Mechanism of metal-catalysed Overman rearrangement

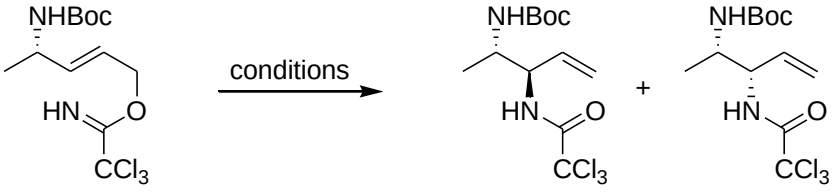
As with the thermal Overman rearrangement, the progression of the metal-catalysed variant through a 6-membered intermediate means that the stereochemical outcome of the reaction is once again controlled.

In 1992, Metz and co-workers discussed the palladium(II)-catalysed Overman rearrangement of a range of secondary allylic trichloroacetimidates, and found that as in the case of thermal rearrangements of these compounds, the products were formed with complete selectivity for *E* geometry across the double bond, and with complete transfer of chirality between the stereogenic centres (Scheme 1.19).[40] It is worth noting that the rearrangement of **56** was also attempted under thermal conditions, and the desired product was isolated in a yield of 61%, although a reaction time of 8 hours in toluene heating under reflux was required.



Scheme 1.19. Palladium(II)-catalysed rearrangement of secondary allylic trichloroacetimidates

As in the case of thermal rearrangements, metal-catalysed Overman rearrangments can proceed with some degree of diastereoselectivity depending on the substitutents present as a result of steric control. However, one of the most attractive features associated with the use of metal catalysts in Overman rearrangements is their potential to coordinate to not only the alkene, but also certain groups present in the vicinal position, such as protected amines. This can have a marked effect on the diastereoselectivity observed in these reactions. For example, Gonda *et al*. reported the results of both the thermal and palladium(II)-catalysed rearrangement of allylic trichloroacetimidate **60**, as shown in Scheme 1.20.[41]



conditions			
1) 140 °C, *o*-xylene, 24 h	**62**	:	**38**
2) $PdCl_2(CH_3CN)_2$, THF, r.t., 3 h	**>99**	:	**1**

Scheme 1.20. Diastereoselective Overman rearrangement

These results showed that the presence of a metal catalyst greatly enhanced the diastereoselectivity of this rearrangement reaction, and it was believed that

coordination of the palladium centre was occurring to both the alkene and the protected nitrogen, thus directing the rearrangement *via* the transition state shown in Figure 8, resulting in the observed preference for formation of the diastereoisomer ***anti*-61**.

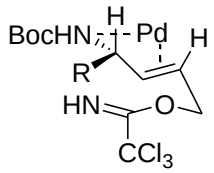
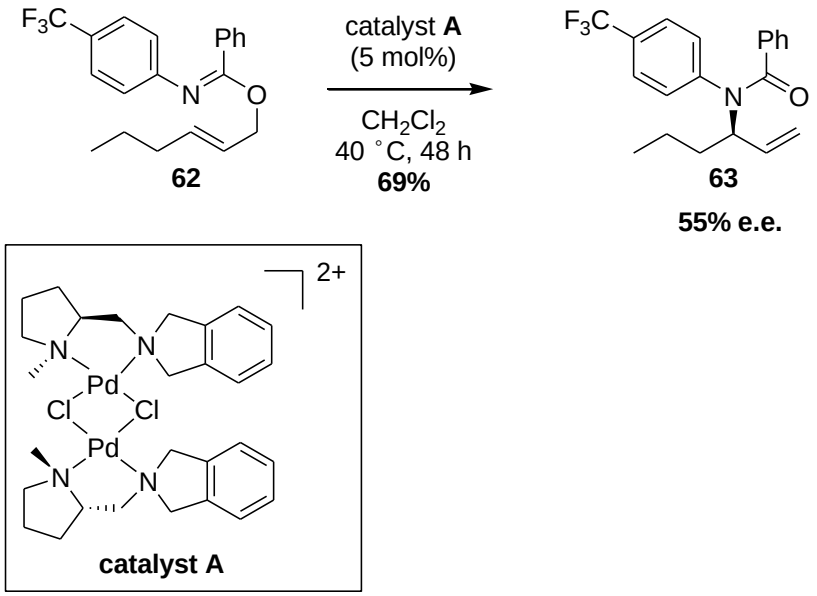


Figure 8. Source of diastereoselectivity in palladium(II)-catalysed rearrangement

1.2.6 Enantioselective metal-catalysed Overman rearrangements

One of the greatest advancements in metal-catalysed Overman rearrangements has been the development of chiral palladium(II) catalysts capable of conducting the Overman rearrangement of allylic trichloroacetimidates derived from primary allylic alcohols in an enantioselective manner. This is possible because direct coordination of the palladium centre to the rearrangement substrate occurs during the reaction.

In 1997, Overman and co-workers discussed the first application of palladium(II) diamine catalysts such as **A** to the enantioselective rearrangement of allylic imidates, shown in Scheme 1.21.[42] While the rearrangement of *N*-arylbenzimidate **62** proceeded in moderate yield and with an encouraging level of enantioselectivity, catalyst **A** failed to promote rearrangement of the corresponding allylic trichloroacetimidate in the same manner. It was believed that this was due to a strong coordination between the trichloroacetimidate's nitrogen atom and the cationic palladium complex which led to a competing elimination of trichloroacetamide.



Scheme 1.21. First enantioselective Overman rearrangement catalyst

Following this result, Donde and Overman studied the rearrangement of similar allylic *N*-arylbenzimidates using a selection of ferrocenyloxazoline palladacyclic (FOP) catalysts.[43] These rearrangements proved successful, proceeding with much improved enantiomeric excess values of up to 96% in the products. One drawback to this work is that the *N*-arylbenzamide products are not particularly useful synthetic intermediates, as their conversion to the corresponding desired allylic amines is not easily achieved.

A key paper published by Overman and co-workers in 2003 discussed the results of a screen of chiral palladium(II) catalysts **B**–**I** (Figure 9), including the FOP catalysts **B** and **C** for the enantioselective rearrangement of allylic *N*-aryltrifluoroacetimidates.[44]

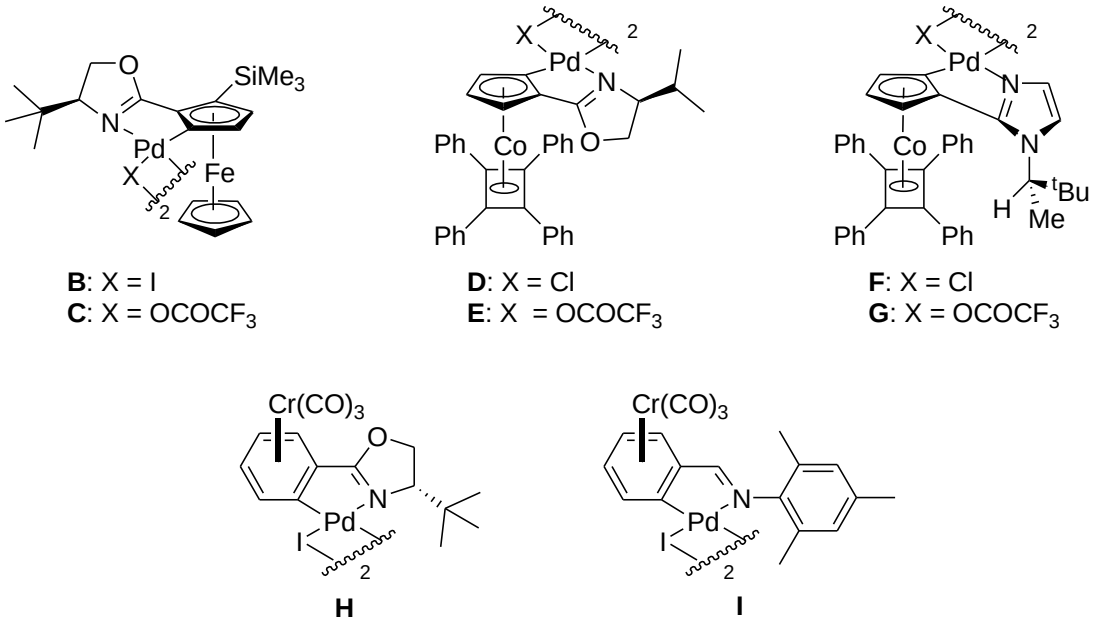
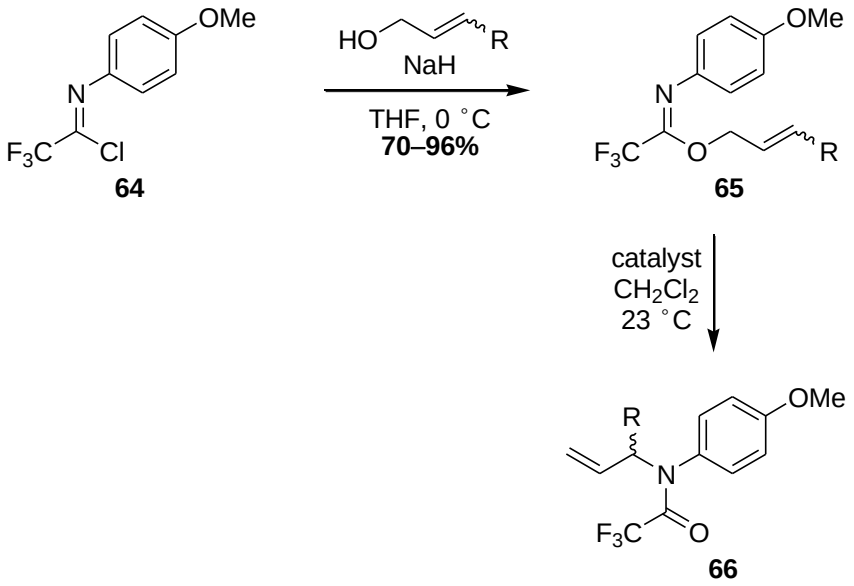


Figure 9. Asymmetric rearrangement catalysts

These catalysts were applied to rearrangement reactions involving a selection of substrates with both *E* and *Z* geometry in the double bond. The catalysts were used in a loading of 5 mol%, and the trifluoroacetate-bridged examples **C**, **E** and **G** were generated by treatment of the corresponding halides (**B**,**D** and **F**) with 4 equivalents (relative to the halide-bridged precursors) of $AgOCOCF_3$. Catalysts **H** and **I** were activated by TlOTf (4 equivalents) prior to use. The formation and rearrangement of the *N*-aryltrifluoroacetimidates **65** is outlined in Scheme 1.22.



Scheme 1.22. Formation and rearrangement of allylic *N*-aryltrifluoroacetimidates

Preliminary results in this study showed that the coboltocenyl oxazolidine palladacycle (COP) complex **E** successfully catalysed the rearrangement of substrates with either *E*- or *Z*-geometry in high yield and with the best levels of enantioselectivity in this catalyst screen. The FOP catalyst **C** also achieved promising results with the substrate (when R = ^{n}propyl), as summarised in Table 2.

Catalyst	Substrate Geometry	Yield (%)	e.e. (%) / configuration
C	*E*	88	76/*S*
C	*Z*	21	87/*R*
E	*E*	84	84/*S*
E	*Z*	71	94/*R*
G	*E*	43	86/*S*
G	*Z*	19	88/*R*
H	*E*	49	82/*S*
H	*Z*	15	67/*R*
I	*E*	66	48/*S*
I	*Z*	13	42/*R*

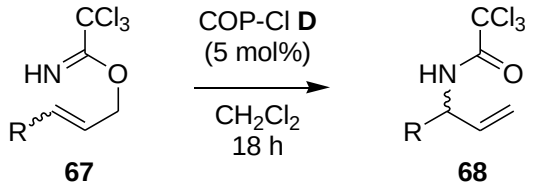
Table 2. Results of catalyst screen

A further study also showed that the chloride-bridged COP catalyst (COP-Cl) **D** was capable of achieving comparable product yields and high enantioselectivity even when not activated with $AgOCOCF_3$, as had been used previously with catalysts **B**, **D**, and **F**. This was a particularly positive result, as it improves the efficiency of these rearrangement reactions, allowing the direct use of a stable catalyst.

A final investigation in this paper compared the use of the unactivated COP-Cl catalyst **D** and its activated trifluoroacetate derivative **E** with a number of rearrangement substrates. It was found that while product yields and enantiomeric excess values were high in each instance with both catalysts, there was a slight advantage in applying COP **E** to the rearrangement of substrates with *Z*-geometry across the double bond and COP-Cl **D** to examples with *E*-geometry.

Following these encouraging results, Anderson and Overman showed that the COP-Cl catalyst **D** could also be successfully applied to the enantioselective Overman

rearrangement of allylic trichloroacetimidates **67** to the synthetically useful allylic trichloroacetamides **68**, as shown in Scheme 1.23.[45]



Scheme 1.23. COP-Cl catalysed rearrangement of allylic trichloroacetimidates

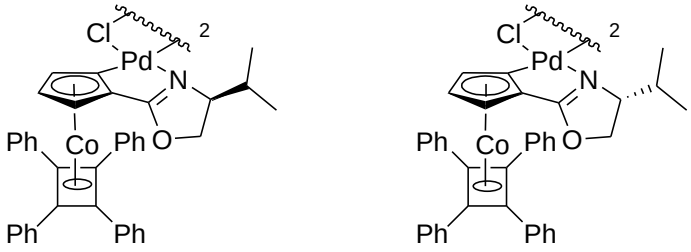
A range of allylic trichloroacetimidate substrates **67** with varying R groups present were subjected to Overman rearrangement in the presence of 5 mol% of COP-Cl **D**. Excellent product yields and enantioselectivity levels were achieved in the rearrangement of allylic trichloroacetimidates with *E*-geometry, while the rearrangement of *Z*-allylic trichloroacetimidates was not favoured. It was also found that the optimum reaction temperature for the use of this catalyst was 38 °C, which resulted in the highest product yields. These results are summarised in Table 3.

R	Geometry	Temperature	Yield (%)	e.e. (%) / configuration
^{n}propyl	*E*	r.t.	80	94/*S*
^{n}propyl	*E*	38 °C	99	95/*S*
^{n}propyl	*Z*	38 °C	17	71/*R*
cyclohexyl	*E*	38 °C	82	96/*S*
CH_2CH_2Ph	*E*	38 °C	93	93/*S*
^{t}butyl	*E*	38 °C	7	unknown
$(CH_2)_2COMe$	*E*	38 °C	98	95/*S*
$(CH_2)_2COMe$	*E*	r.t.	80	94/*S*
$(CH_2)_3NBn(Boc)$	*E*	38 °C	96	95/*S*
$(CH_2)_3NBn(Boc)$	*E*	r.t.	87	95/*S*

Table 3. COP-Cl catalysed Overman rearrangement results

These results exemplify the excellent utility of the COP-Cl catalyst **D** in the enantioselective generation of allylic trichloroacetamides, which are extremely useful synthetic intermediates as they are readily deprotected to form the corresponding allylic amines.

Following on from the publication of the results discussed above, the COP-Cl catalysts **D** and **J**, commonly referred to as (*S*)-(+)-COP-Cl and (*R*)-(-)COP-Cl respectively (Figure 10) have become popular, and hence are now available commercially, in addition to some similar derivatives capable of promoting Overman rearrangement reactions enantioselectively.



D **J**

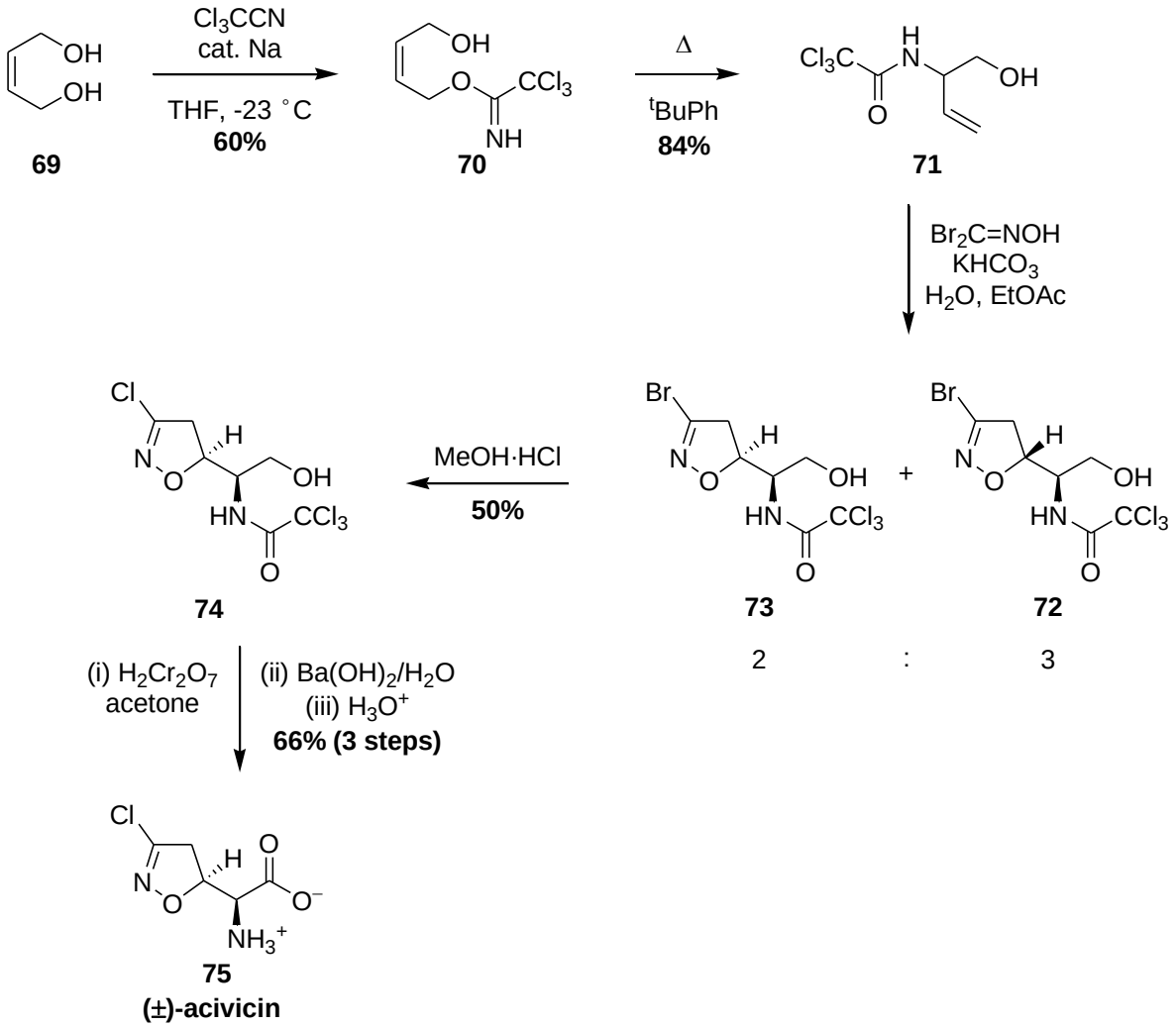
(*S*)-(+)-COP-Cl **(*R*)-(-)-COP-Cl**

Figure 10. Commercially available asymmetric Overman rearrangement catalysts

1.2.7 The Overman rearrangement applied to α-amino acid synthesis

As the Overman rearrangement has proved to be a reliable method of introducing amine functionality in a stereoselective manner, it has found utility in the synthesis of a range of natural products including α-amino acids in literature examples.

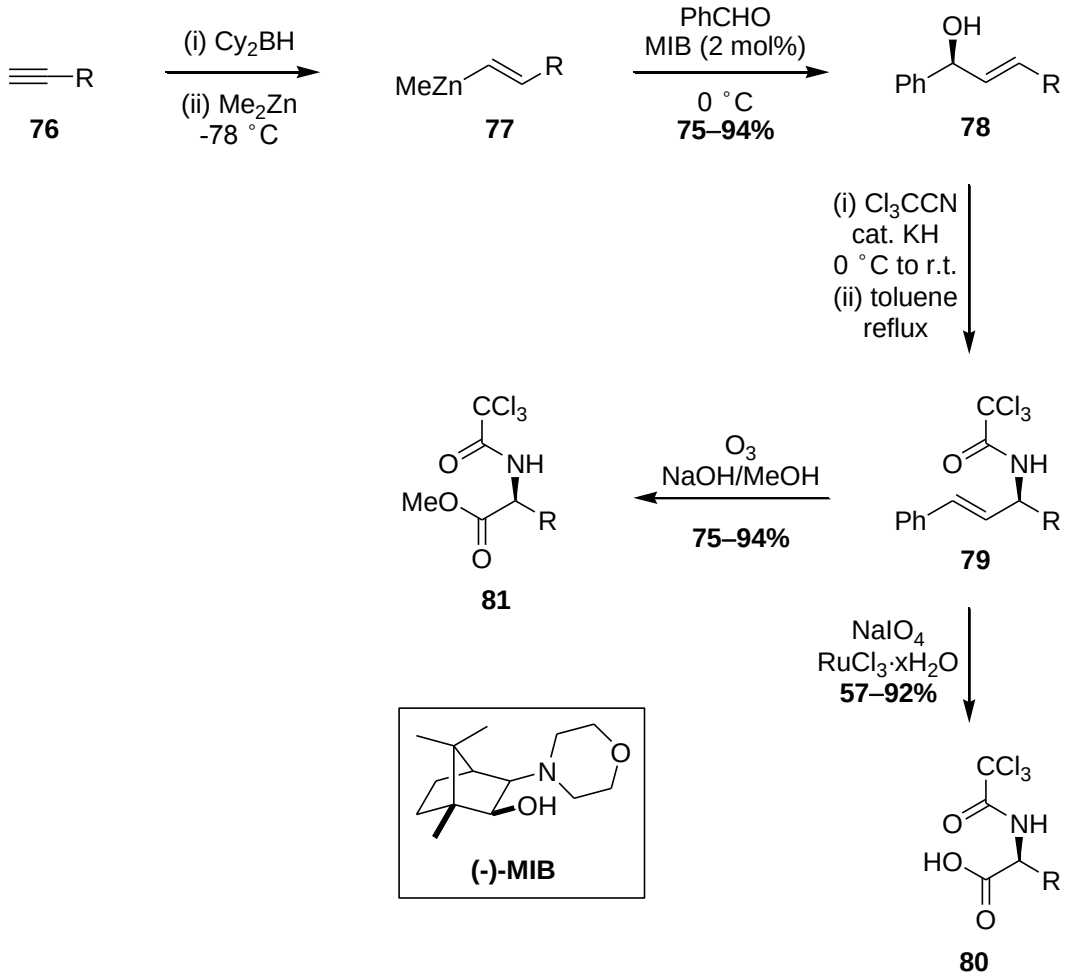
Vyas and co-workers reported in 1984 the introduction of the key amine group of (±)-acivicin **75** by way of a thermal Overman rearrangement, carried out on the trichloroacetimidate derivative of the diol **69**. The presence of the second hydroxyl group allows eventual completion of the α-amino acid functionality by oxidation to a carboxylic acid (Scheme 1.24).[46]



Scheme 1.24. Vyas synthesis of (±)-acivicin

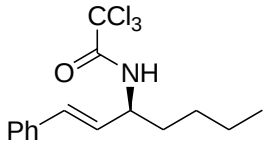
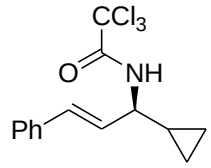
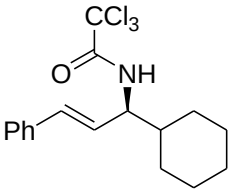
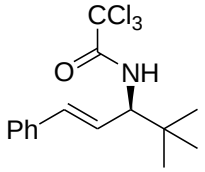
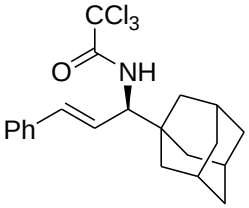
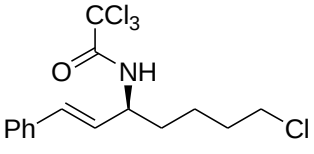
In 2002, Walsh and co-workers applied the thermal Overman rearrangement reaction to the formation of a range of allylic amines, which were then converted to protected α-amino acid targets by means of an oxidative cleavage of the alkene, followed by trichloroacetamide hydrolysis (Scheme 1.25).[47] The allylic alcohol substrates for the rearrangement were synthesised *via* the asymmetric vinylation of aldehydes. The vinylzinc reagents **77** were formed from a range of commercially available terminal alkynes **76** and their subsequent addition to benzaldehyde was conducted in the presence of an enantiomerically pure isoborneol-based amino alcohol ligand known as (-)-MIB, which generated the allylic alcohols **78** with enantiomeric excess values ranging from 93% to 97%. These allylic alcohols were then subjected to a standard thermal Overman rearrangement, generating the corresponding protected allylic amides **79**, which proceeded with conservation of

the high enantiomeric excess values in all cases except when R = cyclopropyl, which saw a decrease from 95% in the alcohol to 89% in the trichloroacetamide. Finally, oxidative cleavage of the double bond led to the completion of protected α-amino acids **80** or the corresponding methyl esters **81**, as shown in Scheme 1.25.



Scheme 1.25. Walsh approach to α-amino acids

The rearrangement step applied in this route allowed the generation of a range of relatively sterically hindered allylic trichloroacetamides in good to excellent yield, generally requiring heating under reflux for just 1–2 hours. Selected yields are summarised in Table 4.

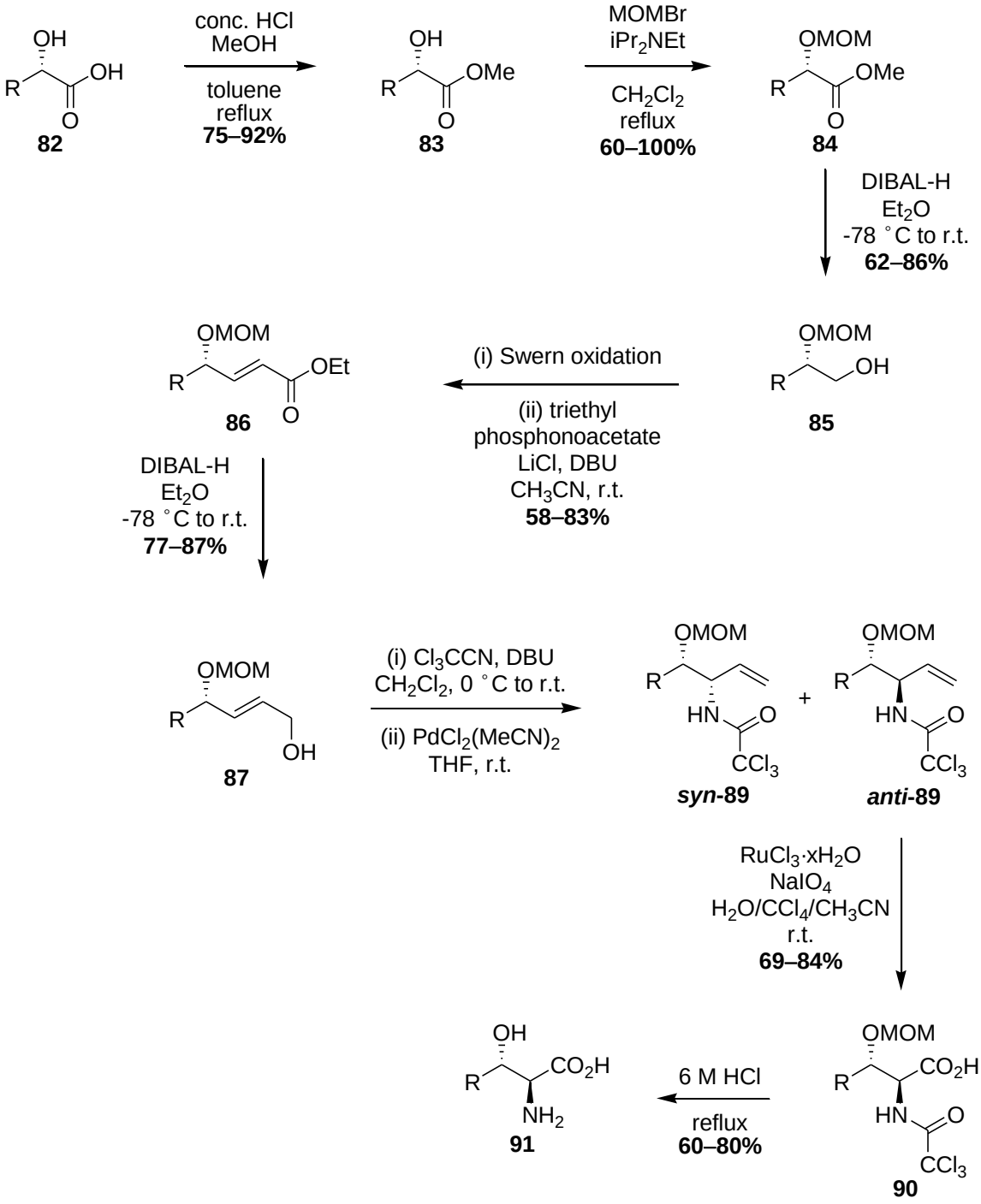
Trichloroacetamide	Yield (%)	e.e. (%)
	64	95 (99[a])
	93	89
	96	95 (99[a])
	90	96 (99[a])
	83	97 (99[a])
	66	93[a]

[a] e.e. value after recrystallisation

Table 4. Overman rearrangement results

Within the Sutherland research group, previous projects have investigated the application of metal-catalysed Overman rearrangements to the synthesis of β-hydroxy-α-amino acids.[48] The methodology, outlined in Scheme 1.26, involved the generation of allylic alcohols by a chiral pool approach, with a Horner-Wadsworth-Emmons reaction utilised to introduce the required double bond. The presence of the methoxymethyl (MOM)-protected hydroxyl not only provides the required hydroxyl group in the β-position of the final amino acid products, but is also

capable of directing the Overman rearrangement step to proceed in a highly diastereoselective manner.



Scheme 1.26. Synthesis of β-hydroxy α-amino acids

During the Overman rearrangement stage, it was essential to achieve a high level of selectivity for the required diastereoisomer ***anti*-89**. The presence of the MOM

protected hydroxyl group on allylic trichloroacetimidate **88** allowed a substrate-directed rearrangement to take place, where palladium co-ordinates to the alkene and also two oxygen atoms, which directs co-ordination to one face, as shown in the transition state in Figure 11, leading to selective formation of the *anti*-product diastereoisomer.

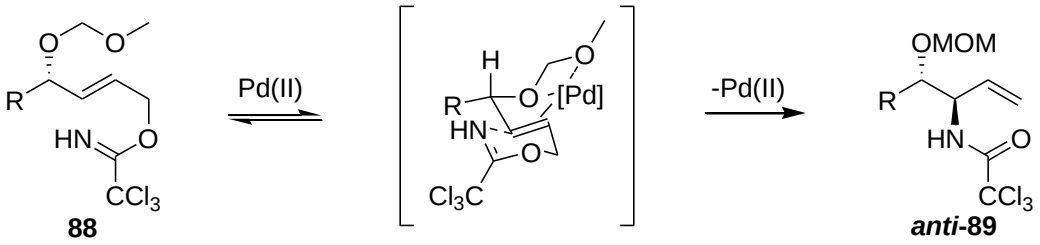


Figure 11. Directing effect of MOM group in Overman rearrangement

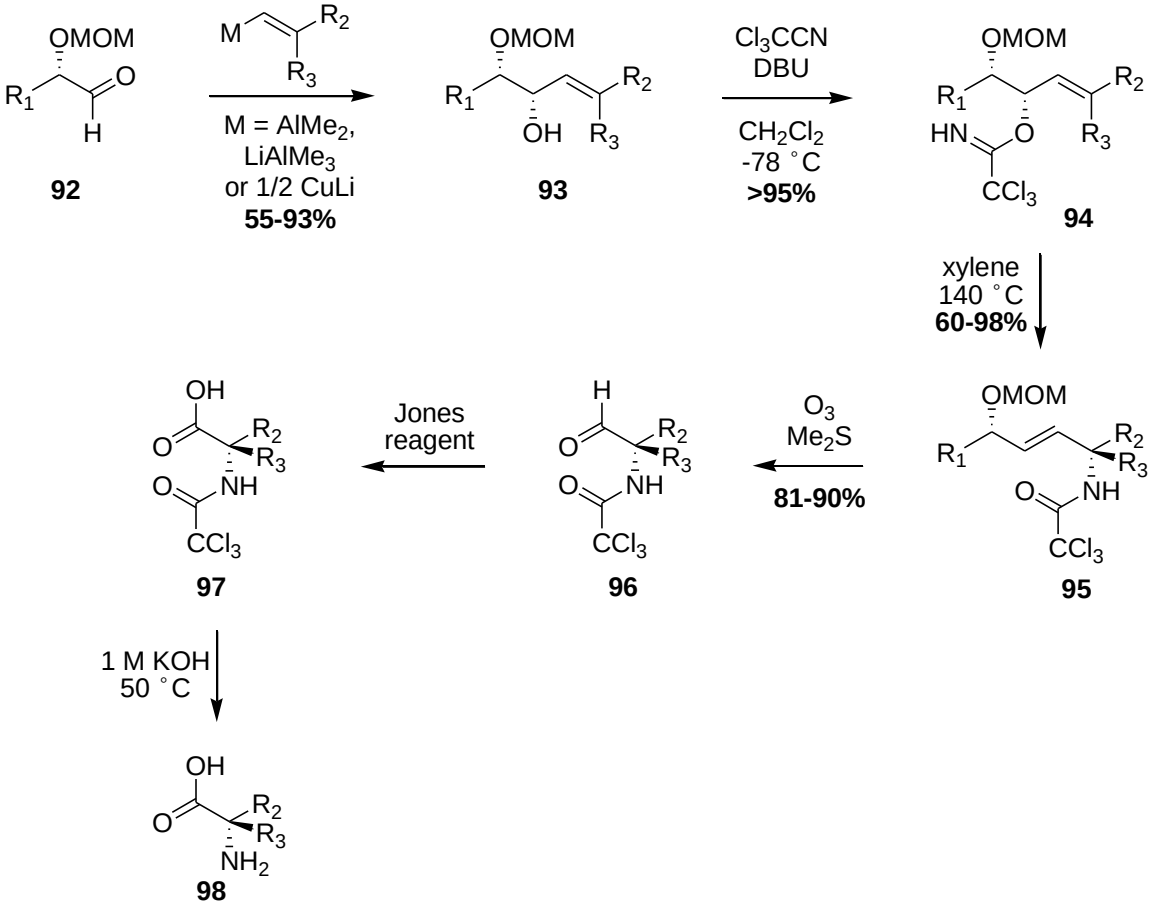
In the cases where R = CH_3, the rearrangement proceeded in 64% yield and with an *anti* : *syn* ratio of 10 : 1. However, in examples where steric bulk was greater in this position, the slower rate of rearrangement allowed a competing reaction to proceed, where palladium(0) catalysed an undesired allylic substitution reaction. Helpfully, the addition of *p*-benzoquinone, a mild oxidant which converts palladium(0) to palladium(II) prevented formation of this by-product. The results of the rearrangement step, which then proceeded in good yield and with high diastereoselectivity, are summarised in Table 5.

R	Additive	Yield (%)	*anti* : *syn*
CH_3	none	64	10 : 1
^tBu	*p*-benzoquinone	73	14 : 1
$PhCH_2$	*p*-benzoquinone	70	12 : 1
$PhCH_2CH_2$	*p*-benzoquinone	69	9 : 1

Table 5. Overman rearrangement results

Following the successful rearrangement chemistry, completion of the desired amino acid targets was achieved in high yield by oxidation of the alkene and removal of the protecting groups (Scheme 1.26).

In 1996, Larchevêque and co-workers reported the application of the Overman rearrangement to the generation of α,α-disubstituted α-amino acids and α-amino aldehydes, synthesised *via* trisubstituted monoprotected allylic diols **93**.[49] Here, the required allylic diols are synthesised by treatment of an α-hydroxy aldehyde **92** with a vinylic organometallic reagent. In order to generate the required amino acid enantiomers, control of the stereochemistry of the hydroxyl group of the allylic alcohol was essential. Helpfully, the addition of the organometallic reagents proceeded not only in good yield, but also with high *syn* : *anti* ratios greater than 92:8 in all but one instance. Conversion of these intermediates to the corresponding allylic trichloroacetimidates **94** and subsequent Overman rearrangement installed the required quaternary substituted carbon centre of the allylic amines. Ozonolysis of the alkene, oxidation of the aldehyde intermediate to the required carboxylic acid and then trichloroacetamide hydrolysis completed formation of the amino acid targets **98**, as shown in Scheme 1.27.



Scheme 1.27. Larchevêque approach to α,α-disubstituted α-amino acids

In the development of this methodology, the thermal Overman rearrangement step was conducted with a variety of R groups present. The yields achieved for a selection of the allylic trichloroacetamides **95** are summarised in Table 6 below. In each case, only a single product diastereoisomer was detected by ^{1}H NMR spectroscopic analysis.

R_1	R_2	R_3	Yield (%)
Ph	^{n}Bu	Me	98
^{i}Pr	Me	^{n}Bu	62
^{i}Pr	Me	Et	60
^{i}Pr	Ph	Me	70

Table 6. Results of thermal Overman rearrangement step

It is worth noting that attempts were made to conduct the rearrangement step in the presence of mercury(II) and palladium(II) catalysts, although the desired products were not isolated and instead, elimination of the trichloroacetamides was occurring to generate dienes.

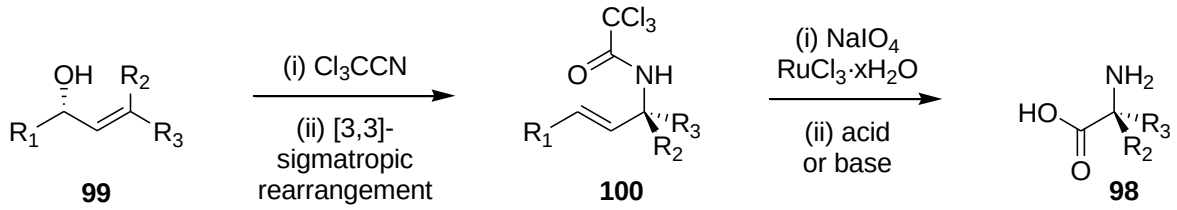
This route represents a highly stereoselective method for accessing α,α-disubstituted α-amino acids which relies on the Overman rearrangement proceeding with complete chirality transfer to give enantiomerically pure α-amino acid products.

The Overman rearrangement represents an excellent reaction which provides access to a large array of protected allylic amines which have widespread utility in organic synthesis. Importantly, the stereochemical outcome of these reactions is highly controlled and predictable. Additionally, the substrates required are easily generated from allylic alcohols, which are common synthetic intermediates. The conversion of protected allylic amines to α-amino acids has proven successful in a number of literature examples, as outlined above and hence the investigation of methodology for the enantioselective synthesis of allylic alcohols could provide an efficient method for the generation of a variety of α-amino acid targets.

1.3 Proposed Research

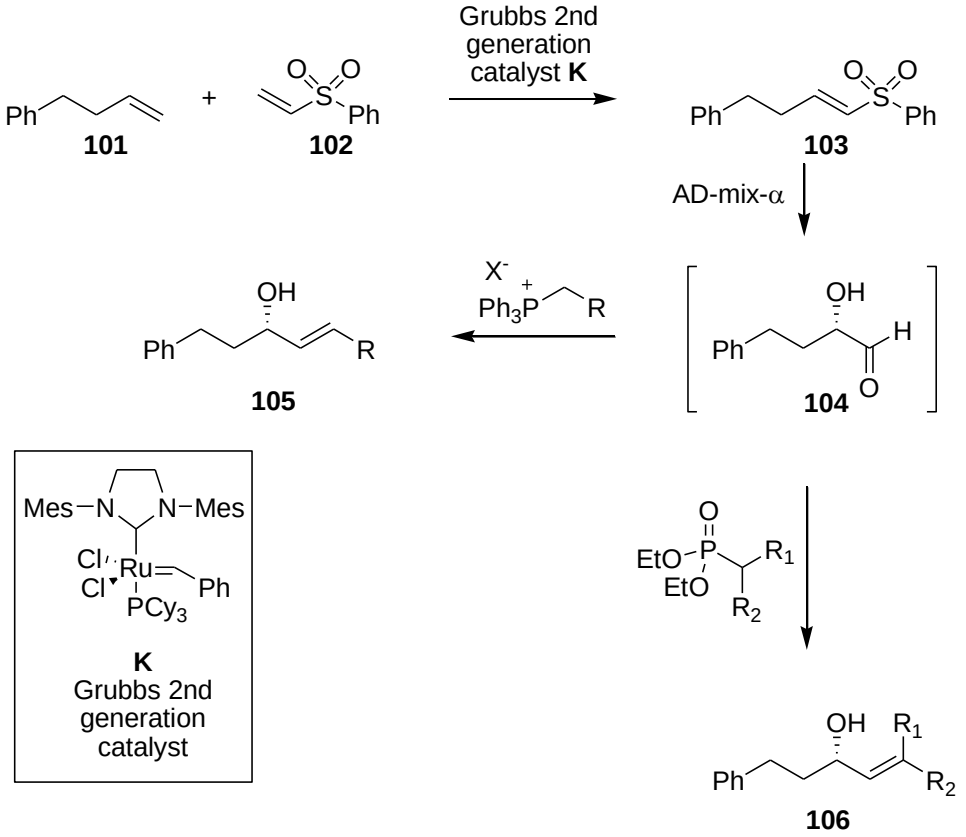
The aim of this research project was to develop new methodology for the stereoselective synthesis of a range of α-amino acids. The route studied should be flexible enough to allow the eventual generation of both α-amino acid and α,α-disubstituted α-amino acid targets with a variety of side chains which can be accessed in a fast, efficient manner.

The strategy under investigation here can be considered in three distinct stages, summarised in Scheme 1.28. Firstly, a range of di- and tri-substituted chiral allylic alcohols **99** would be generated enantioselectively. These would then be subjected to Overman rearrangement chemistry to convert them to allylic trichloroacetamides **100**. Finally, oxidative cleavage of the allylic double bond and amide hydrolysis would complete the formation of the desired α-amino acid targets **98**.



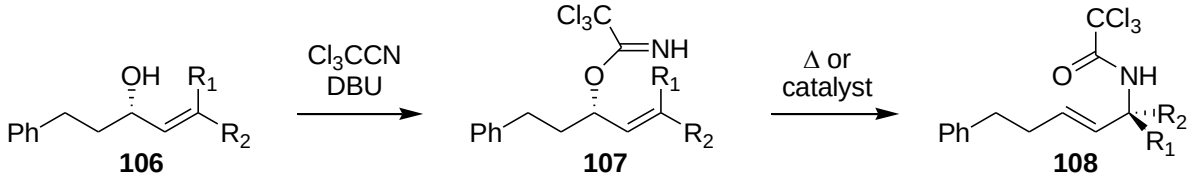
Scheme 1.28. Proposed synthetic strategy

The proposed method for the generation of chiral allylic alcohols is outlined in Scheme 1.29, and relies on chemistry published by Evans and Leffray whereby a vinyl sulfone derivative such as **103** is subjected to an asymmetric dihydroxylation. This installs the desired configuration at the alcohol's stereogenic centre and the presence of the α-hydroxyl group promotes a spontaneous 1,2-elimination to generate the corresponding aldehyde **104** *in situ*. This could then be trapped with a range of phosphonium salts or phosphonate esters under Wittig or Horner-Wadsworth-Emmons (HWE) olefination conditions respectively to complete the formation of di- or tri-substituted allylic alcohols.[50]



Scheme 1.29. Proposed synthesis of substituted chiral allylic alcohols

In order to transform these allylic alcohols to the corresponding protected allylic amines, Overman rearrangement chemistry would be employed. The alcohols **106** could be easily converted to allylic trichloroacetimidates **107**, which are the necessary substrates for the [3,3]-sigmatropic rearrangement, as shown in Scheme 1.30.



Scheme 1.30. Conversion of allylic alcohols to allylic trichloroacetamides

From these allylic trichloroacetamides **108**, the desired α-amino acid targets can be generated by carrying out a ruthenium-catalysed oxidation of the allylic double bond to introduce the required carboxylic acid functionality, followed by hydrolysis

of the trichloroacetamide group under acidic or basic conditions as highlighted in Scheme 1.28.

In order to develop the methodology proposed, initial studies would focus on the generation of α-amino acids before being applied to the more challenging α,α-disubstituted examples.

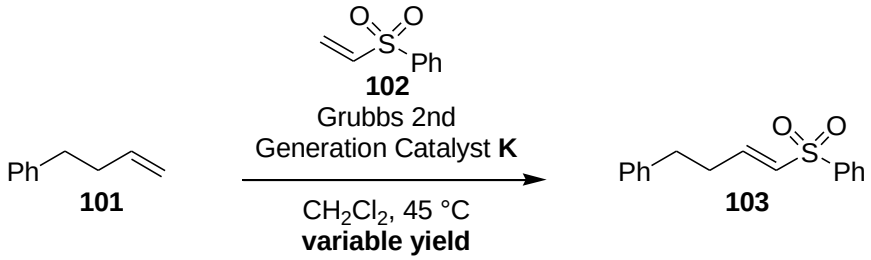
2.0 Results and Discussion

2.1 Synthesis of α-amino acids *via* organophosphorus olefinations

2.1.1 Synthesis of chiral allylic alcohols *via* dihydroxylation and olefination

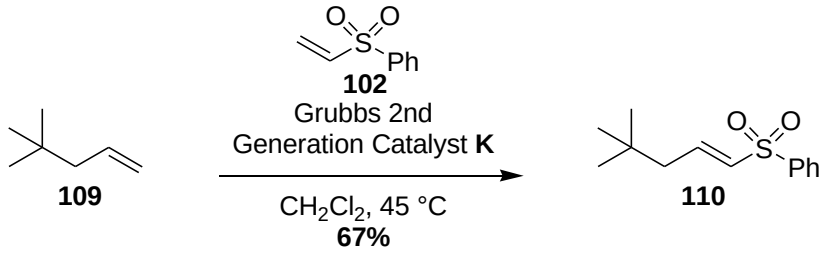
The first step in the proposed synthesis of substituted chiral allylic alcohols involved generation of the vinyl sulfone derivative **103** *via* a cross-metathesis reaction between the terminal alkene 4-phenyl-1-butene **101** and phenyl vinyl sulfone **102** in the presence of Grubbs 2nd generation catalyst **K** as outlined in Scheme 2.1.

This reaction was carried out according to a literature procedure published by Grela and Bieniek, using a 2:1 ratio of phenyl vinyl sulfone **102** : 4-phenyl-1-butene **101** in the presence of 5 mol% of catalyst **K**.[51] Under these conditions, the reaction reached completion in 6 hours. However, repeated purification of the crude reaction product by silica column chromatography failed to adequately separate the desired product **103** from excess phenyl vinyl sulfone **102**. In an attempt to prevent the requirement for separation of these two components, the reaction was repeated with 4-phenyl-1-butene in excess (1.5 equivalents). However, this did not reach completion and unreacted phenyl vinyl sulfone remained after 46 h. Finally, the cross-metathesis reaction was run using a 1:1 ratio of the terminal alkene partners and a total catalyst loading of 6 mol%, which on a small scale (0.1 g of phenyl vinyl sulfone) led to the successful formation and isolation of the clean product **103** in 77% yield. However, when the same conditions were applied on a larger scale (1.4 g of phenyl vinyl sulfone), the reaction required repeated additions of both 4-phenyl-1-butene and Grubbs 2nd generation catalyst **K**, despite which traces of phenyl vinyl sulfone still remained after an extended reaction time which again could not be removed by column chromatography.



Scheme 2.1. Cross-metathesis of 4-phenyl-1-butene and phenyl vinyl sulfone

Due to the significant problems associated with the isolation of vinyl sulfone derivative **103**, it was decided to substitute 4-phenyl-1-pentene with an alternative alkene bearing an inert side chain which would give a product with polarity that differs enough from that of phenyl vinyl sulfone, thus allowing separation of the two by chromatography. As the side chain introduced here will be cleaved later in the route, a variety of groups could be present in this position with no effect on the eventual targets. Therefore, 4,4-dimethyl-1-pentene **109** was subjected to cross-metathesis with phenyl vinyl sulfone using the original Grela and Bieniek conditions (Scheme 2.2). As expected, the reaction successfully reached completion and this time the polarity of cross-metathesis product **110** differed enough from that of phenyl vinyl sulfone **112** to allow successful separation of the two components by silica column chromatography, leading to isolation of the desired product **110** in 67% yield. As the *tert*-butyl substituted vinyl sulfone **110** was easily synthesised, this was used for a study of the next stage of the proposed route.



Scheme 2.2. Cross-metathesis of 4,4-dimethyl-1-pentene and phenyl vinyl sulfone

Introduction of the required hydroxyl group and allylic double bond was attempted using a combined Sharpless asymmetric dihydroxylation and Horner-Wadsworth-Emmons olefination approach previously described by Evans and Leffray.[50]

The Sharpless asymmetric dihydroxylation was first reported in 1988, and fully developed reaction conditions were outlined by Sharpless and co-workers in 1992.[52,53] The reaction achieves the *cis*-vicinal dihydroxylation of alkenes, capable of proceeding with enantiomeric excess values greater than 90% in the product diols. Two pre-mixed, commercially available reagent powders known as AD-mix-α and AD-mix-β are most commonly used. They both contain a chiral ligand and give opposing stereochemical outcomes, which are based on the size of the alkene substitutents as summarised in Figure 12.

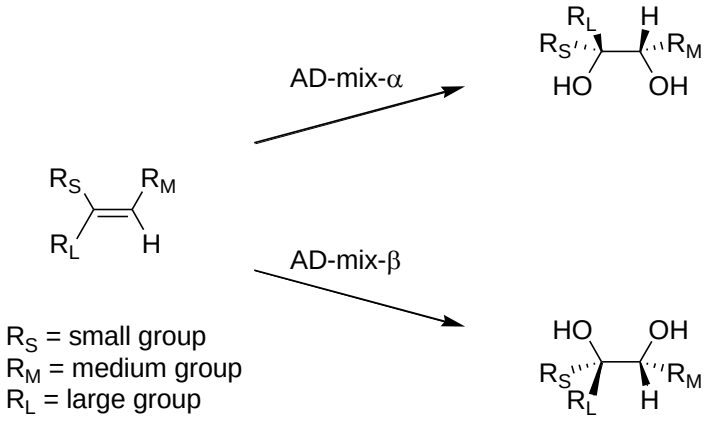


Figure 12. Stereochemical outcome of Sharpless asymmetric dihydroxylation

The AD-mixes contain the following components:

- catalytic potassium osmate ($K[OsO_2(OH)_4]$), a non-volatile source of osmium tetroxide, the required oxidant
- stoichiometric potassium ferricyanide ($K_3Fe(CN)_6$), used to oxidise the H_2OsO_4 by-product back to reactive osmium tetroxide, making the reaction catalytic with respect to the expensive, toxic osmium reagent
- potassium carbonate (K_2CO_3) which maintains the reaction pH
- $(DHQ)_2PHAL$ (in AD-mix-α) or $(DHQD)_2$-PHAL (in AD-mix-β), enantiomerically-pure cinchona alkaloid ligands which provide the chiral environment necessary for an enantioselective reduction (Figure 13)

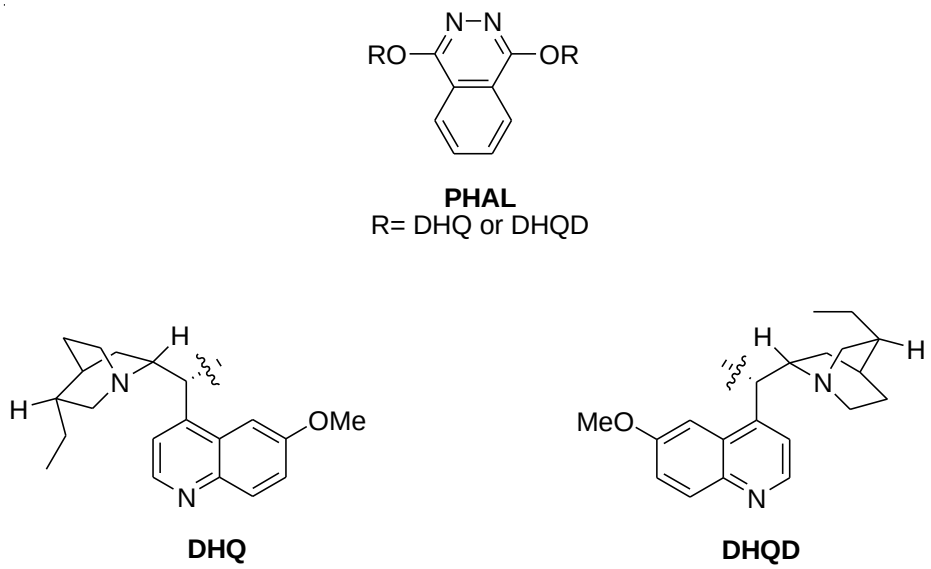


Figure 13. Sharpless asymmetric dihydroxylation ligands

In addition to the required AD-mix, the reactions are generally carried out in the presence of methanesulfonamide, which increases the rate of hydrolysis of the osmate ester intermediates.

The large cinchona alkaloid ligands such as $(DHQ)_2$-PHAL and $(DHQD)_2$-PHAL provide a chiral environment in which the dihydroxylation takes place in U-shaped binding pocket.[54] From the results of applying the Sharpless asymmetric dihydroxylation to a wide range of substrates, a mnemonic has been developed which provides a model of the catalyst active site and can be used to predict the stereochemical outcome of a Sharpless dihydroxylation (Figure 14).[53]

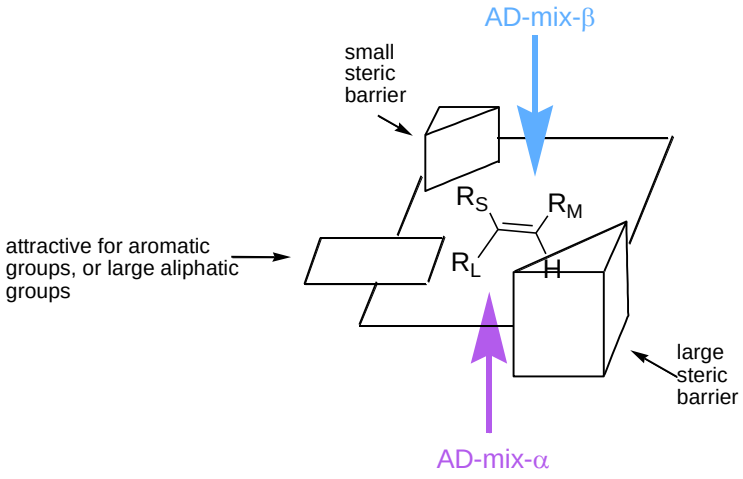
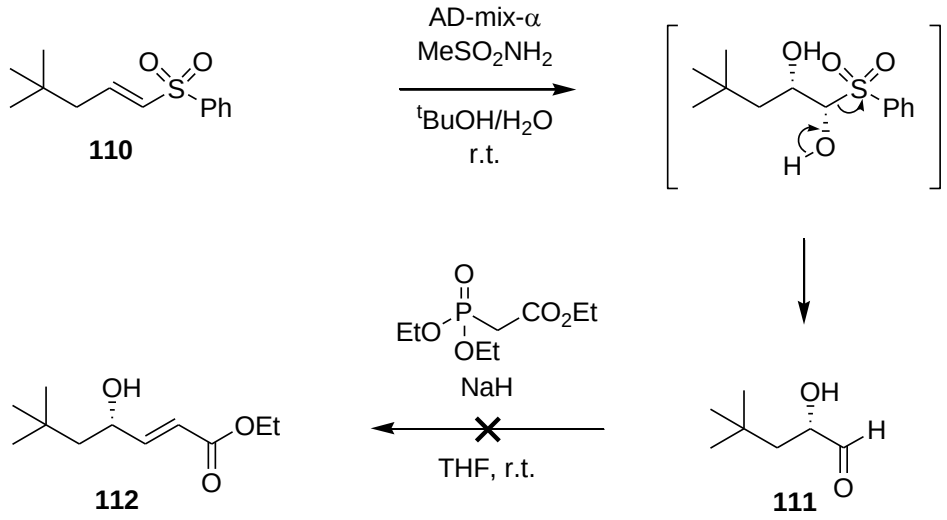


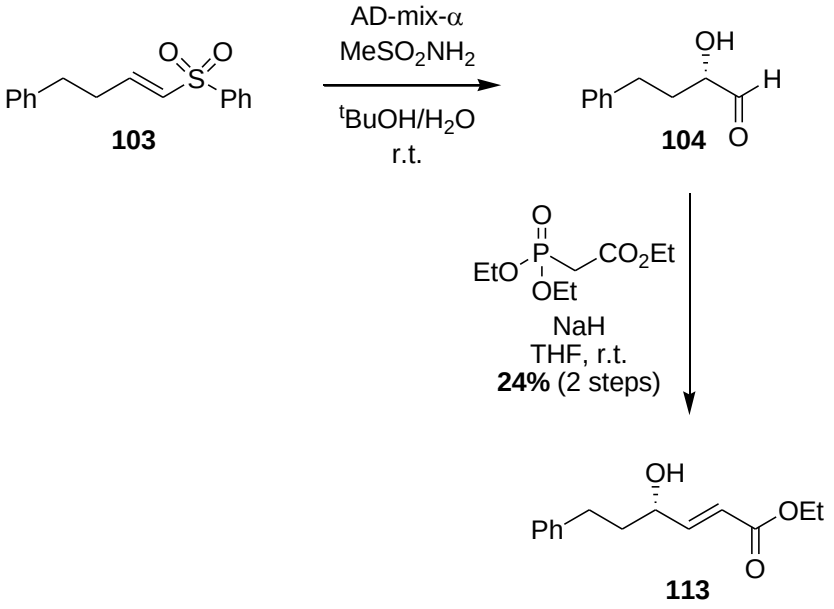
Figure 14. Mnemonic for prediction of enantioselectivity

The vinyl sulfone **110**, with R_L = sulfone, was treated with AD-mix-α to achieve the desired enantioselectivity and dihydroxylation of the alkene should lead to a spontaneous 1,2-elimination, generating the α-hydroxy aldehyde **110** *in situ*. Addition of a solution of deprotonated triethyl phosphonoacetate under Horner-Wadsworth-Emmons conditions should then give the desired allylic alcohol **112** in a single step, as shown in Scheme 2.3. Unfortunately when this reaction was attempted under the Evans and Leffray conditions, none of the desired allylic alcohol product **112** was detected after the olefination step. In fact, only the vinyl sulfone starting material **110** was found to be present in the crude reaction product, indicating that the reaction had failed at the dihydroxylation stage.



Scheme 2.3. Dihydroxylation/ Horner-Wadsworth-Emmons olefination

It was thought that the failure of this reaction could be attributed to the presence of the bulky *tert*-butyl group preventing access of the substrate to the catalyst active site. To assess this hypothesis, the same reaction was carried out on phenyl-substituted vinyl sulfone **103**, as shown in Scheme 2.4. Using the phenyl-substituted substrate **103**, the reaction proved successful and the desired allylic alcohol product **113** was isolated in 24% yield.

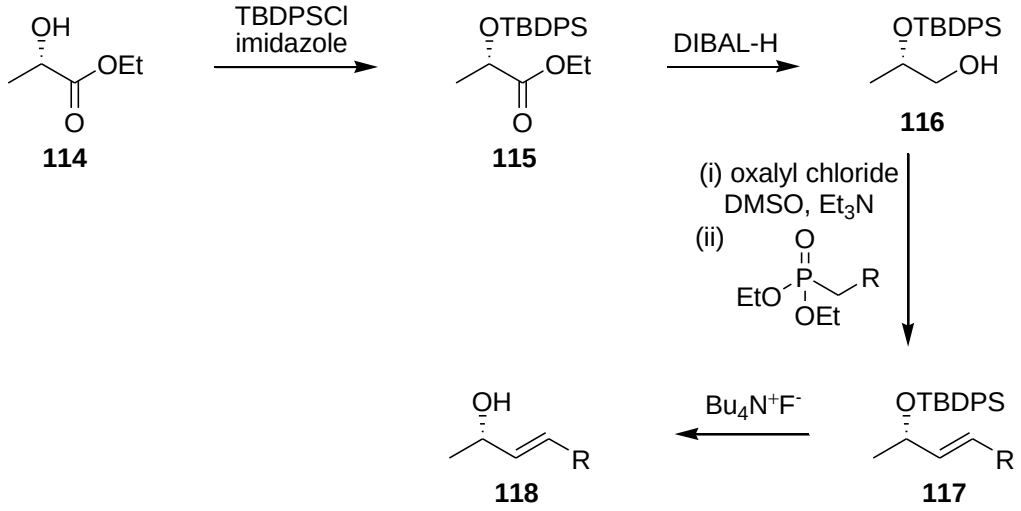


Scheme 2.4. Dihydroxylation/ Horner-Wadsworth-Emmons olefination

Due to the problems associated with the purification of the vinyl sulfone intermediate **103** and the low yield of the subsequent dihydroxylation/olefination reaction, it was decided that an alternative synthesis of allylic alcohols should be investigated.

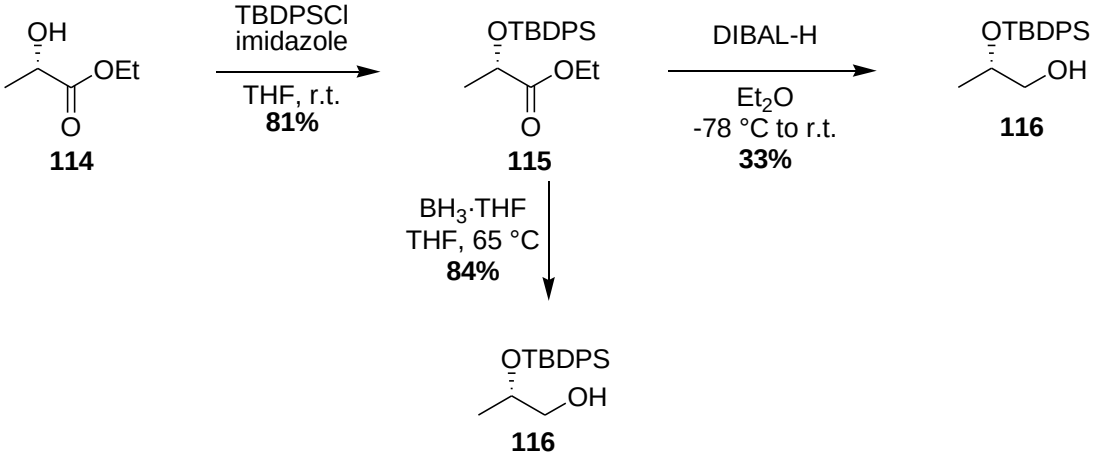
2.1.2 Synthesis of chiral allylic alcohols *via* chiral pool approach

The alternative approach to allylic alcohols adopted is shown in Scheme 2.5, and relies on a combined Swern oxidation and Horner-Wadsworth-Emmons olefination to install the allylic double bond. This time, the required hydroxyl group is in place in the starting material (*S*)-ethyl lactate **114**, which is cheap and readily available.



Scheme 2.5. Proposed alternative synthesis of allylic alcohols

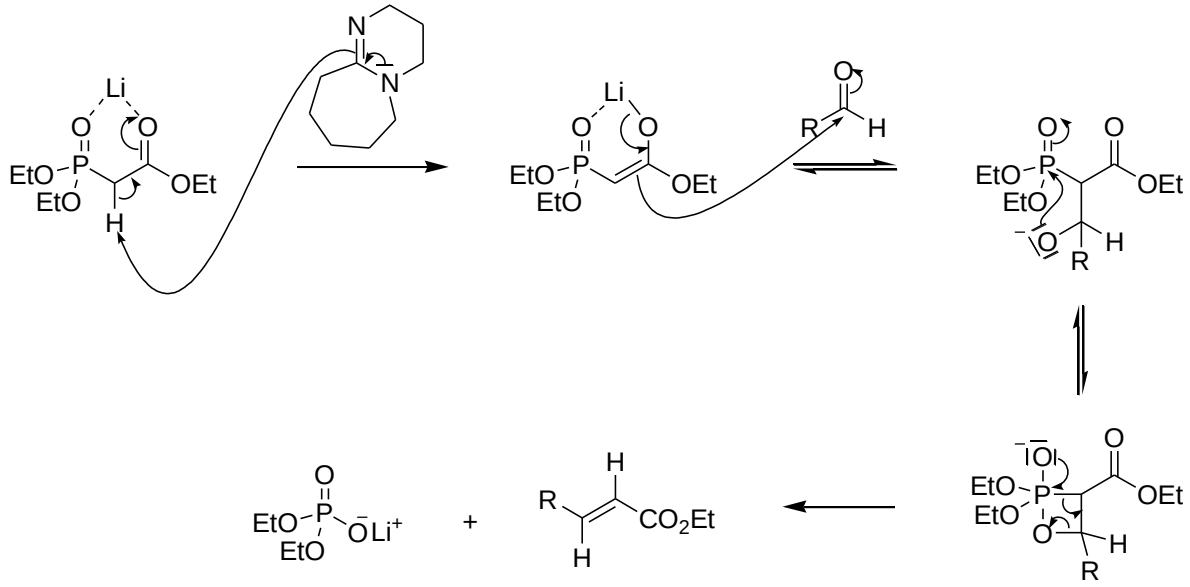
The first step in this route involved a simple hydroxyl protection using *tert*-butyldiphenylchlorosilane in the presence of imidazole according to a literature procedure, as shown in Scheme 2.6.[55] This reaction proceeded successfully, giving ether **115** in 81% yield. This was followed by reduction of the ethyl ester to the corresponding primary alcohol **116**. Initially, this was attempted using 2.2 equivalents of diisobutylaluminium hydride solution however the product yield was a relatively low 33% and it appeared that loss of the silyl group was occurring during the reaction. A literature procedure published by Duffield and Pettit which describes the reduction of ester **115** to alcohol **116** was then trialled using borane-tetrahydrofuran complex solution, and this successfully generated the desired product in 84% yield.[56]



Scheme 2.6. Synthesis of monoprotected diol 116

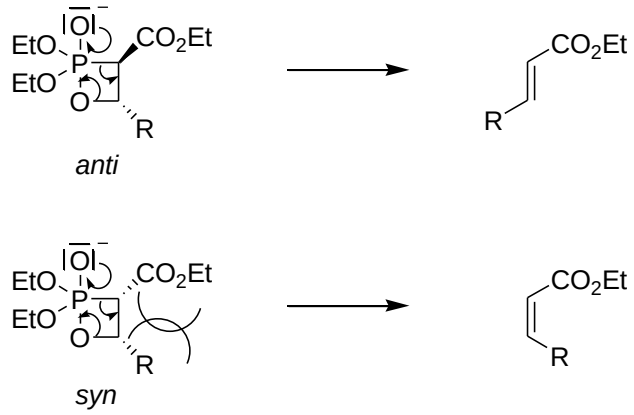
In order to introduce the allylic double bond and a potentially wide variety of side chains, the primary alcohol **116** was subjected to a Swern oxidation to the corresponding aldehyde,[57] which could then be trapped with a range of phosphonate esters, forming a new carbon-carbon double bond. This type of strategy has been successfully utilised within the research group many times previously, and the conditions are well-established.[58,59] The Swern oxidation product simply requires concentration *in vacuo* before being treated with a solution of the deprotonated phosphonate ester, providing the protected allylic alcohol in a fast, efficient manner.

The first phosphonate ester used for the investigation of the olefination step was triethyl phosphonoacetate. In order to promote the selective formation of the *E*-alkene product, the Masamune Roush variation of the Horner-Wadsworth-Emmons olefination was employed.[60] The proposed mechanism for the Horner-Wadsworth-Emmons olefination is shown in Scheme 2.7. The lithium cation present in the reaction mixture coordinates between the two oxygen atoms of the phosphonate ester, and acts as a Lewis acid to facilitate its deprotonation. The deprotonated ester is stabilised both by this coordination, and by resonance and so the acidic proton can be removed by 1,8-diazabicyclo[5.4.0]undec-7-ene. These conditions are particularly mild and can be applied to the olefination of a wide range of substrates, including those where sensitivity to strong bases such as butyllithium is an issue.



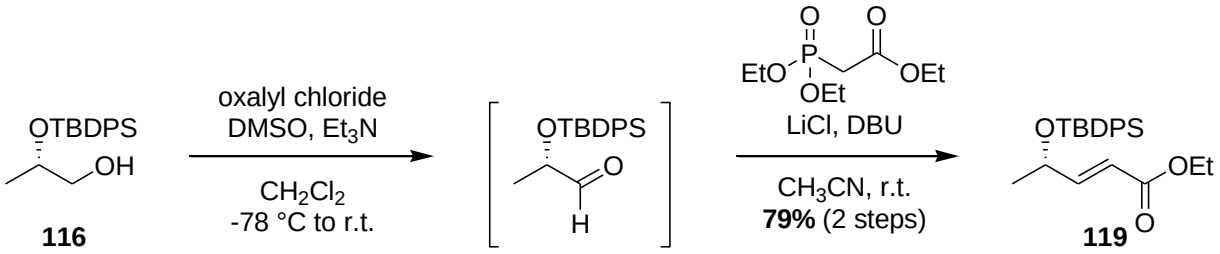
Scheme 2.7. Mechanism of Horner-Wadsworth-Emmons olefination

The stereochemical outcome of this olefination is determined by the stereochemistry achieved in the 4-membered oxaphosphetane ring intermediate. Here, there are two options possible, where the ester group and the R group can be in either a *syn* or *anti* relationship with one another. As the formation of the oxaphosphetane ring is a reversible process, the thermodynamic product is favoured which here is the *anti* stereoisomer with minimal steric clash between the relatively bulky ester and R groups. Subsequent decomposition of the *anti* oxaphosphetane ring leads to the *E* alkene product, as shown in Scheme 2.8.[61]



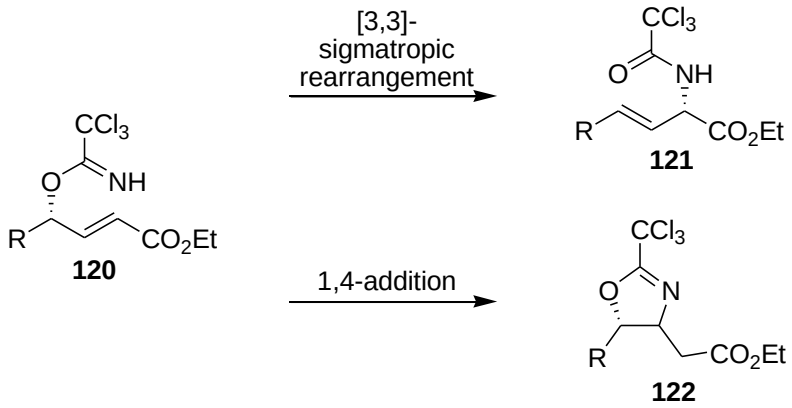
Scheme 2.8. Origin of stereoselectivity in Horner-Wadsworth-Emmons reaction

This approach proved successful and gave the desired product **119** in a yield of 79% over the two steps from alcohol **116** (Scheme 2.9). Only the desired *E*-alkene was observed by ^{1}H NMR spectroscopic analysis of the product, indicated by a coupling constant of 15.5 Hz in the signals arising from the alkene protons.



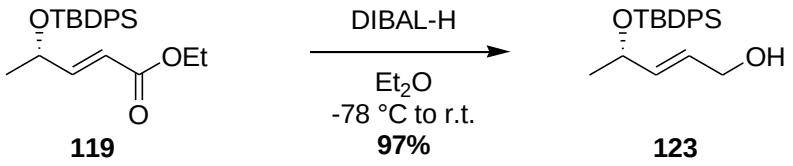
Scheme 2.9. Swern oxidation and Horner-Wadsworth-Emmons olefination

As previously reported in the literature, compounds bearing electron-withdrawing sidechains such as esters in conjugation with the alkene tend to be unsuccessful substrates for Overman rearrangement chemistry, although the allylic trichloroacetimidate formation step is known to proceed as normal.[62] It has been shown that the presence of an electron-withdrawing group in conjugation with the alkene such as in **120** leads to the possibility of a conjugate addition taking place from the trichloroacetimidate nitrogen atom to form the corresponding oxazoline **122**, as shown in Scheme 2.10. This process competes with the desired [3,3]-sigmatropic rearrangement, and in general, very little of the rearrangement product **121** is observed.[63]



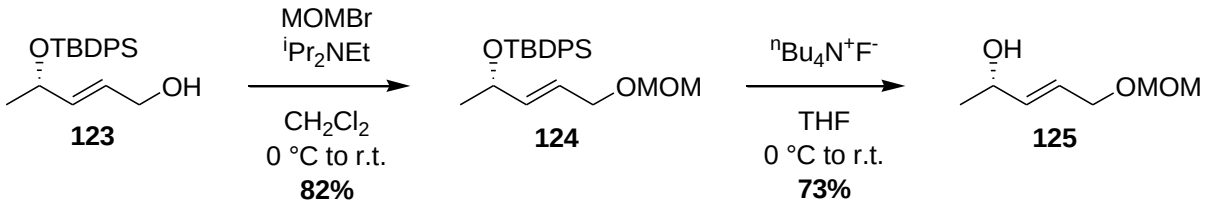
Scheme 2.10. Competing reaction pathways with conjugated ester

In order to overcome this potential problem, manipulation of the ester side chain was required. Conversion of the ester to a protected hydroxyl group would lead to generation of a substrate suitable for investigation of the Overman rearrangement chemistry. First, ester **119** was reduced to the corresponding alcohol **123** using 2.2 equivalents of diisobutylaluminium hydride, a reaction which proceeded in 97% without the need for purification (Scheme 2.11).



Scheme 2.11. Diisobutylaluminium hydride reduction

Protection of the free hydroxyl group was then required, and the methoxymethyl (MOM) protecting group was selected as orthogonal deprotection conditions are required for this and the already-installed silyl group which required removal in the next synthetic step, as shown in Scheme 2.12. Alcohol **123** was treated with bromomethyl methyl ether in the presence of Hünig's base to give ether **124** in 82% yield, while the removal of the silyl protecting group was achieved in 73% yield using tetra-*n*-butylammonium fluoride.

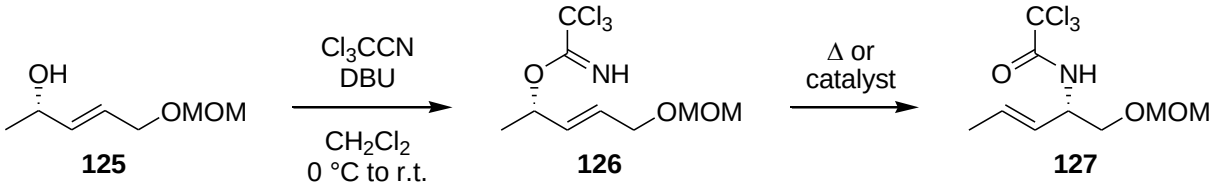


Scheme 2.12. Generation of allylic alcohol 125

2.1.3 Conversion of allylic alcohol to allylic trichloroacetamide

With the first allylic alcohol **125** in hand, it was then possible to conduct an investigation of the formation of allylic trichloroacetimidate **126** and its subsequent Overman rearrangement to allylic trichloroacetamide **127**, as shown in Scheme 2.13. Synthesis of the allylic trichloroacetimidate was carried out successfully using

trichloroacetonitrile in the presence of base. As these compounds are relatively unstable, the reaction product was immediately subjected to rearrangement.



Scheme 2.13. Synthesis and rearrangement of allylic trichloroacetimidate 126

In order to determine the optimum method for carrying out the Overman rearrangement, four sets of reaction conditions including both thermal and metal-catalysed variants were tested. In addition to the standard palladium(II) rearrangement catalyst bis(acetonitrile)palladium(II) chloride, platinum(II) chloride and gold(III) chloride were also screened, as both literature precedent and studies within our group have indicated that these could be successfully applied to Overman rearrangement reactions.[64,65] The results are summarised below in Table 7. Note that the product yields quoted are over two steps from the allylic alcohol **125**.

Reaction conditions	Product Yield (%)
K_2CO_3, *p*-xylene, 140 °C, 15 h	66
$PdCl_2(CH_3CN)_2$ (10 mol%), toluene, r.t., 15 h	51
$PtCl_2$ (15 mol%), THF, r.t., 135 h	34
$AuCl_3$ (15 mol%), THF, r.t.	No reaction

Table 7. Results of Overman rearrangement study

The results of this study showed that the reaction was successfully achieved under both thermal reaction conditions and palladium(II) catalysis, with both approaches generating the allylic trichloroacetamide in good yield. When platinum(II) catalysis was trialled, a relatively high loading and longer reaction time were required, to attain only a moderate product yield. The gold(III) catalyst failed to promote the rearrangement, and no product was detected after 192 h. The use of thermal rearrangement conditions led to a significantly cleaner reaction profile than utilising palladium(II) catalysis, explaining the lower product yield observed.

2.1.4 Completion of α-amino acid target

With the protected amine functionality in place, it was then possible to introduce the required carboxylic acid group by use of an oxidative cleavage of the allylic double bond. This was to be achieved under conditions originally published by Sharpless and co-workers where sodium periodate is used in the presence of a ruthenium(III) catalyst to install a carboxylic acid group on each carbon originating from the alkene.[66] The catalytic cycle involved in this reaction is outlined below in Figure 15.[67] Here, periodate oxidises ruthenium(III) chloride to ruthenium tetroxide, which enters the catalytic cycle and dihydroxylates the alkene. This diol is then cleaved by periodate to form two aldehyde intermediates, which are then converted to carboxylic acids by ruthenium tetroxide, which itself is reformed by oxidation.

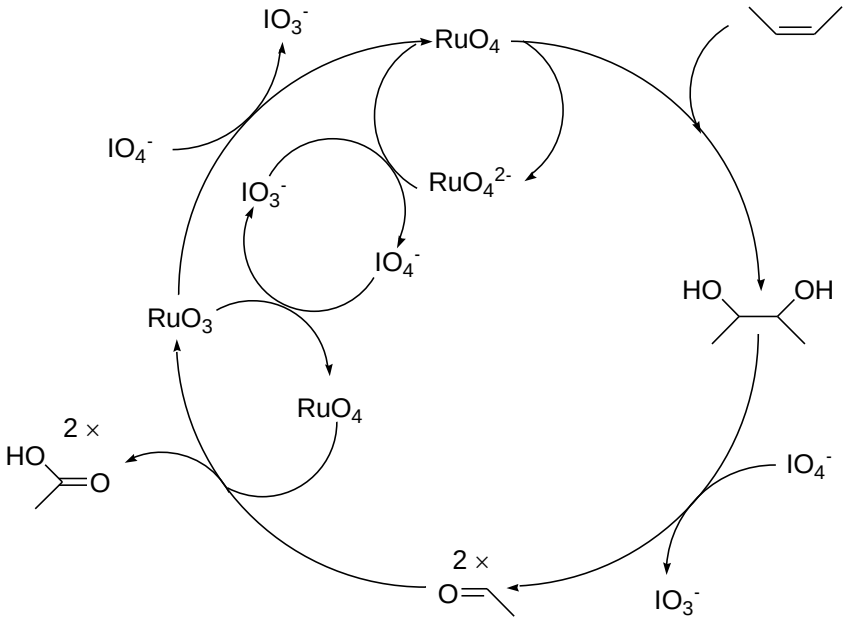
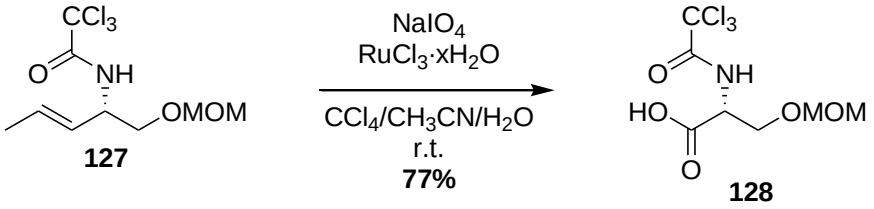


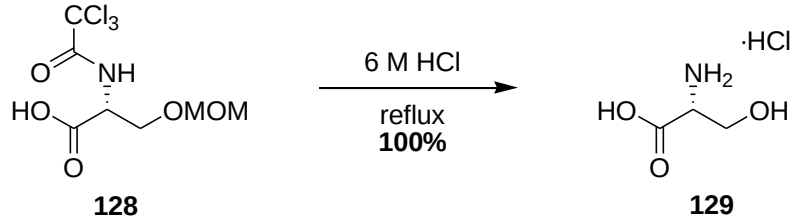
Figure 15. Proposed catalytic cycle of Sharpless oxidative cleavage

When these conditions were applied to the oxidation of trichloroacetamide **127**, the desired carboxylic acid product **128** was successfully generated with a crude yield of 77% (Scheme 2.14). In this instance, the carboxylic acid by-product formed is acetic acid, which was removed upon work-up.



Scheme 2.14. Oxidative cleavage of alkene

Following this, removal of both the trichloroacetamide and methoxymethyl protecting groups was required in order to complete the synthesis of the first α-amino acid target. Helpfully, it was possible to achieve this simultaneously by heating the carboxylic acid **128** in 6 M hydrochloric acid under reflux, as shown in Scheme 2.15. Using this approach, the amino acid target, D-serine **129** was formed in quantitative yield, and isolated as the hydrochloride salt.



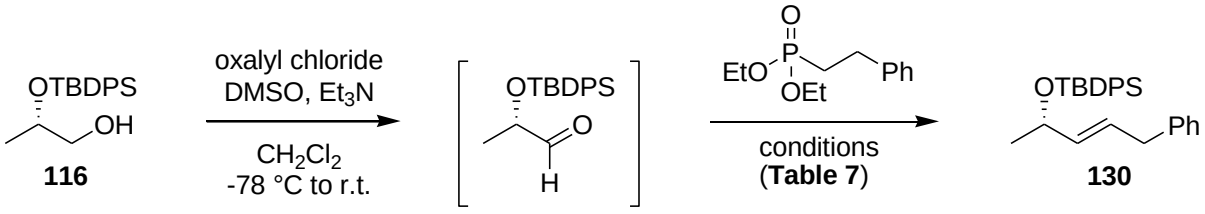
Scheme 2.15. Completion of α-amino acid target

2.1.5 Attempted synthesis of further allylic alcohol intermediates

As the chemistry required to synthesise the first amino acid target had been developed, attempts were made to apply the methodology to the synthesis of a number of other α-amino acids with a variety of side chains. These groups would be introduced during the Horner-Wadsworth-Emmons step by treating the aldehyde with different phosphonate esters. If inert alkyl side chains were added at this stage, no further manipulation would be required before the Overman rearrangement step and hence the final α-amino acid targets could be generated rapidly.

The next phosphonate ester to be applied to the olefination step was diethyl phenylethyl phosphonate, shown in Scheme 2.16. Alcohol **116** was again oxidised

to the corresponding aldehyde as previously discussed and this was to be treated with a solution of the deprotonated phosphonate ester.



Scheme 2.16. Swern oxidation and Horner-Wadsworth-Emmons olefination

As there is no electron-withdrawing group in the phosphonate ester side chain, co-ordination to a metal cation would be possible only to the P=O bond, and would not be expected to significantly aid deprotonation in this instance, and so it was likely that a stronger base than DBU would be required. Therefore, a search of the literature was conducted to find conditions which would be suitable for the deprotonation of alkyl-substituted phosphonate esters. The success of this search was limited, and the closest matching procedures were those which involved the use of phosphonate esters bearing unsaturated alkyl groups.

The olefination was initially attempted using lithium bis(trimethylsilyl)amide according to a procedure described by Trost and Gunzner,[68] although none of the desired alkene **130** was isolated upon purification. Next, the reaction was repeated using lithium diisopropylamide as the base, which was generated *in situ* from diisoproylamine and butyllithium.[69] Again, the reaction failed and so an attempt was made to carry out the olefination under the Masamune Roush conditions previously discussed although as expected, none of the desired product was observed.[60] It was then considered that perhaps using the aldehyde as a crude product of the Swern oxidation step was impeding the progress of the reaction, and so an attempt was made to remove the residual triethylamine by carrying out washes with water and 2 M hydrochloric acid before addition of the phosphonate ester, the deprotonation of which had again been attempted using lithium diisopropylamide. Unfortunately, this reaction failed to yield the desired product. These results are summarised in Table 8.

Conditions	Outcome
LiHMDS, THF, -78 °C to r.t.	No product isolated
^{n}BuLi, $^{i}Pr_2NH$, THF, -78 °C to r.t.	No product isolated
LiCl, DBU, CH_3CN, r.t.	No product isolated
^{n}BuLi, iPr_2NH, THF, -78 °C; aldehyde worked up	No product isolated

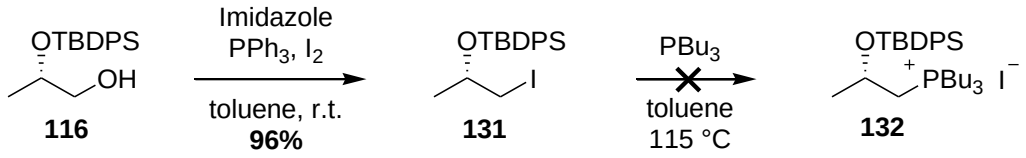
Table 8. Attempted Horner-Wadsworth-Emmons olefination

The failure of these attempted olefinations was considered to be a result of the lack of an electron-witdrawing sidechain on the phosphonate ester, and indeed in 1966, Corey and Kwiatkowski showed that while the deprotonation of these phosphonates and their subsequent attack of aldehydes is possible, it is the elimination of phosphate *via* the oxaphosphetane ring which fails (see mechanism in Scheme 2.7). It is thought that an electon-withdrawing group is required to dissipate a negative charge which builds up on the carbon α- to phosphorus in the 4-membered transition state, therefore allowing rapid elimination to proceed.[70]

These results showed that the methodology developed within this project would not prove flexible enough for the synthesis of the wide range of α-mono- and α,α-di-substituted α-amino acids required bearing alkyl functionality and therefore, an alternative approach was investigated in which the reactivity of the components involved in the olefination step was reversed.

The new method involved an attempt to convert the alcohol intermediate **116** to the corresponding tributylphosphonium salt **132** *via* the iodide **131**, as shown in Scheme 2.17. The phosphonium salt **132** could then be used in *E*-selective Wittig olefination reactions with a range of aldehydes, which are readily available commercially. This would introduce the allylic double bond and desired side chain. The iodination was carried out according to a literature procedure described by Garegg and Samuelsson, and the desired product **131** was isolated in 96% yield.[71] However, when this was treated with tributylphosphine, none of the desired phosphonium salt was detected by ^{1}H NMR spectroscopic analysis of the reaction mixture after 4 days. It was believed that the approach of tributylphosphine to the substrate may have been sterically hindered by the presence of the large silyl protecting group. ^{1}H NMR spectroscopic analysis also indicated that oxidation of

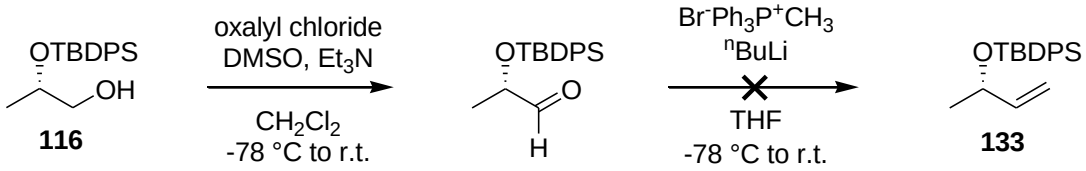
tributylphosphine to tributylphosphine oxide was occurring during the course of the reaction, and degassing the reaction mixture did not help the reaction to proceed successfully.



Scheme 2.17. Attempted synthesis of phosphonium salt 132

A final attempt was then made to introduce the required alkene and various side chains to the alcohol intermediate **116**. If the alcohol could be converted to a terminal alkene, this could be subjected to cross-metathesis chemistry with some simple terminal alkene partners to generate the desired protected allylic alcohol substrates.

Scheme 2.18 shows the method attempted for the generation of the desired terminal alkene **133** *via* Swern oxidation and Wittig methylenation, which was carried out according to a literature procedure described by Schmidt and Sattelkau.[72] Unfortunately, this methylenation proved unsuccessful and none of the desired product **133** was isolated. It was believed that the presence of the strong butyllithium base was perhaps causing decomposition of the aldehyde intermediate by loss of the silyl protecting group.



Scheme 2.18. Attempted generation of terminal alkene 133

As several approaches based on organophosphorus olefinations had failed to incorporate the required alkene and side chains to the alcohol intermediate **116**, the decision was made to focus efforts on an alternative strategy for the synthesis

of the desired range of allylic alcohols which would prove flexible enough to introduce many side chains without the need for harsh reaction conditions.

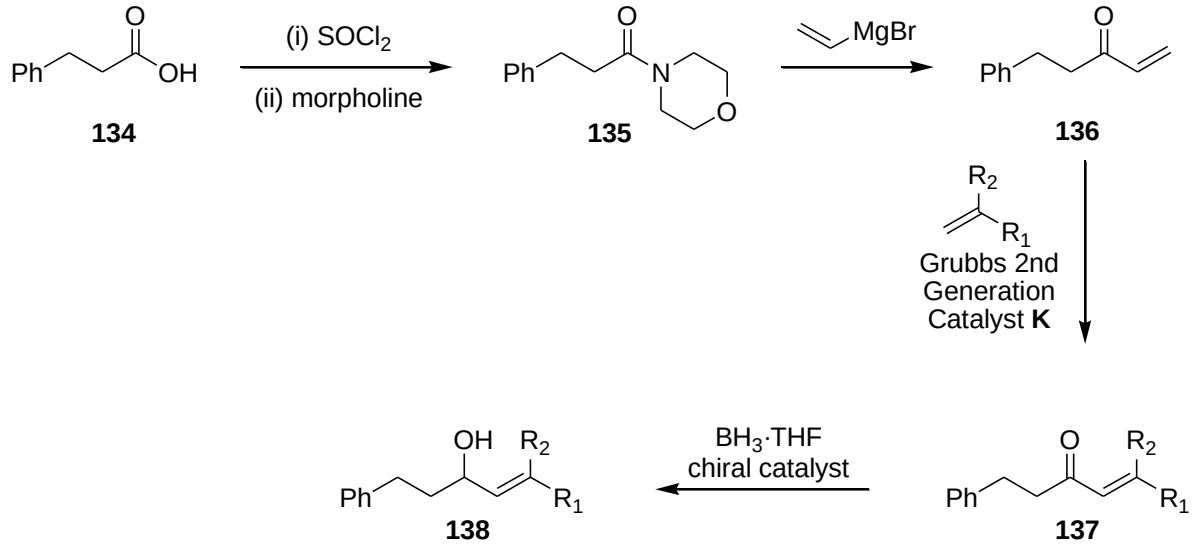
2.2 Synthesis of α-amino acids *via* cross-metathesis

2.2.1 Proposed route to allylic alcohols

The new approach proposed for the synthesis of allylic alcohols, outlined in Scheme 2.19, focuses on the use of cross-metathesis chemistry with a common enone intermediate to incorporate the required side chain substitution on the eventual allylic double bond. Due to the large number of both mono- and di-substituted terminal alkenes available commercially, this strategy would potentially allow the eventual generation of a wide variety of di- and tri-substituted allylic alcohol intermediates.

In order to install the hydroxyl group, a 1,2-reduction of the carbonyl could be carried out and crucially, the stereochemistry at this centre can be controlled if the reaction is carried out in an appropriate chiral environment.

As before, the proposed methodology would be developed initially for the synthesis of α-amino acids before later application to the generation of targets bearing α,α-disubstitution.

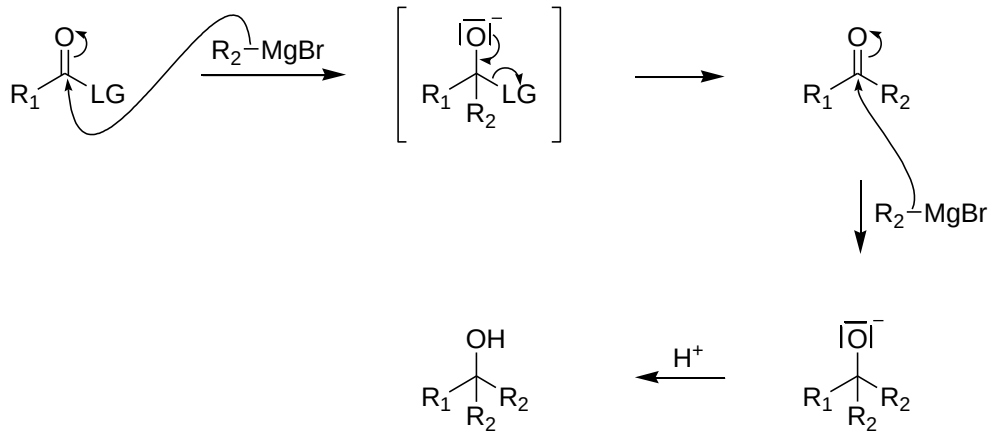


Scheme 2.19. Proposed synthesis of allylic alcohols

2.2.2 Synthesis of enone intermediates *via* cross-metathesis

The first aim of this route was to synthesise a simple enone to be used as a substrate for cross-metathesis with the various terminal alkene partners. As the oxidative cleavage reaction later in the synthesis removes the alkyl portion of this enone, the use of almost any inert group should be appropriate. Here, a phenylethyl group was selected as it should not be capable of reacting under any of the conditions it will be subjected to, and provides a simple ^{1}H NMR pattern, making analysis of subsequent intermediates straightforward. The starting material required, hydrocinnamic acid, is also relatively cheap and readily available.

Crucial to the generation of the required enone intermediate **136** is the introduction of a vinyl group to hydrocinnamic acid. A problem commonly encountered in the alkylation of carboxylic acid derivatives with organometallic reagents to form ketones is the propensity of the reaction products to undergo a second alkylation, generating the corresponding tertiary alcohol, as shown in Scheme 2.20. Often, complex mixtures of starting material, ketone, and tertiary alcohol are detected after reaction.



Scheme 2.20. Nucleophilic alkylation of carboxylic acid derivatives

In 1981, Weinreb showed that formation of the undesired tertiary alcohol can be minimised if the alkylation is carried out on an *N*-methoxy-*N*-methyl amide, which are easily generated from the corresponding carboxylic acid derivative and amine. The methoxy oxygen atom here coordinates to the organometallic reagent (Figure 16), stabilising the tetrahedral intermediate formed upon the first addition. This intermediate does not collapse to the ketone product until quenched by acid during the work-up, thus preventing attack by a second equivalent of the organometallic reagent.[73]

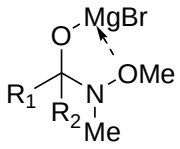
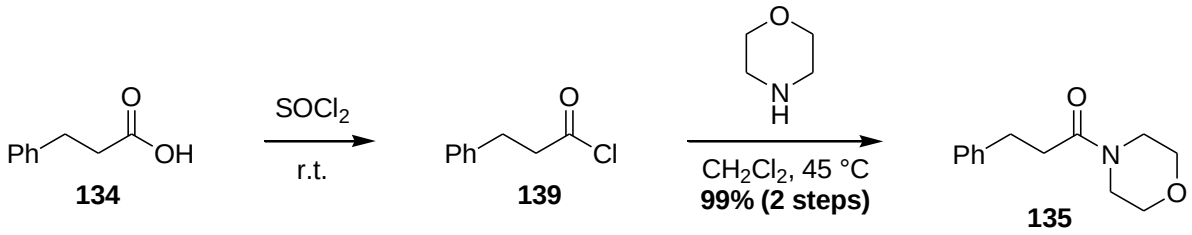


Figure 16. Weinreb amide coordination

While the use of Weinreb amides has proven successful in circumventing the issue of tertiary alcohol formation, the cost of starting materials required for amide formation is relatively high. In 1997, Martín *et al*. reported the use of morpholine amides as substrates for alkylation by organometallic reagents to generate ketones.[74] Morpholine itself is a very cheap amine and can be used to easily form amides. The oxygen atom present in the morpholine ring is able to stabilise the tetrahedral intermediate formed during alkylation in a similar way to the Weinreb amides, and studies have shown that the alkylation reactions proceed in relatively high yield with minimal tertiary alcohol formation. Indeed, Martín's paper reported

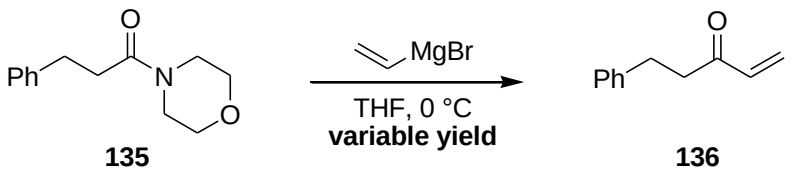
the synthesis of the enone **136** required for this project, and hence this approach was adopted here.

As shown in Scheme 2.21, the desired morpholine amide **135** was generated easily *via* the corresponding acid chloride **139** which was formed by simply stirring hydrocinnamic acid **134** in neat thionyl chloride. As the acid chloride is likely to be very reactive and sensitive to hydrolysis, no purification was carried out at this stage, and the crude product was immediately treated with morpholine to give the amide **135** in an excellent yield of 99% over the two steps.



Scheme 2.21. Synthesis of morpholine amide 135

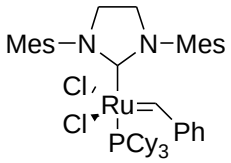
Conversion of the morpholine amide **135** to the key enone intermediate **136** was carried out according to the conditions outlined in the Martín paper, using vinylmagnesium bromide, as shown in Scheme 2.22. Helpfully, this Grignard reagent is commercially available as a solution in tetrahydrofuran. The alkylation was carried out with a highest yield of 74%, although on a number of repeats of this experiment, this high yield proved somewhat inconsistent. It was found that low product yields obtainedin some instances could be attributed to the formation of the double-alkylated tertiary alcohol. In order to limit the formation of this undesired by-product and achieve consistently high yields of enone **136**, the reaction time was kept to 1 hour or less to limit the possibility of the second alkylation taking place.



Scheme 2.22. Formation of key enone intermediate 136

With the key enone intermediate **136** successfully synthesised, introduction of the eventual α-amino acid side chains was achieved *via* cross-metathesis chemistry, which is very well established in the literature.[75,76] Cross-metathesis has proved very popular in recent years, as it represents a simple method for the generation of new carbon-carbon double bonds which does not require harsh conditions, and is relatively atom-economical as only small loadings of the catalyst are required. The cross-metathesis of two monosubstituted alkene partners also proceeds with selectivity for the *E*-alkene product, which is desired in this project.

A number of catalysts have been developed which can promote alkene metathesis reactions including ring-closing metathesis, cross-metathesis and ring-opening metathesis. The most commonly-encountered catalyst applied to cross-metathesis is Grubbs second generation catalyst **K** (Figure 17), first discussed in the literature in 1999.[77]



Grubbs 2nd generation catalyst **K**

Figure 17. Grubbs 2nd generation catalyst for cross-metathesis

This catalyst acts as a source of a metal-carbene complex, and this undergoes a [2+2]-cycloaddition with the first alkene partner to form a 4-membered metallocyclobutane. Collapse of this generates an alkene by-product (ethane in the methathesis of two terminal alkenes) and a new metal-carbene which is able to react with the second alkene partner, forming another metallocyclobutane from which the desired metathesis product is generated. Note that in the first cycle, the phenyl group will be present on the metal-carbene complex, and this will be lost in the first alkene by-product in place of ethene. This widely-accepted mechanism for the cross-metathesis of two alkenes was first proposed in 1970 by Hérisson and Chauvin and is shown in Figure 18.[78]

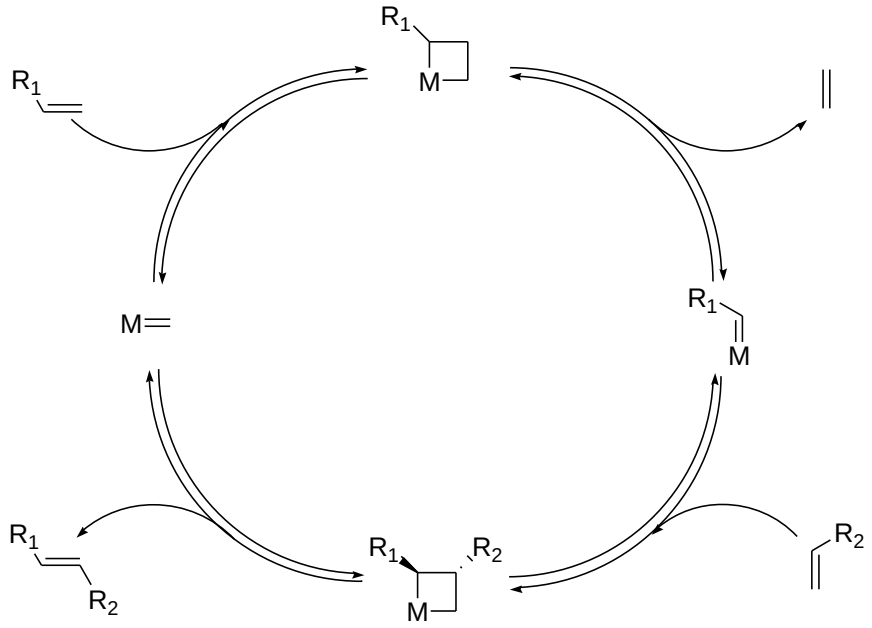


Figure 18. Mechanism of alkene cross-metathesis

A paper published by Grubbs and co-workers in 2003 categorised the various types of olefins which can undergo cross-metathesis according to their ability to homodimerise in the presence of a particular metathesis catalyst.[79] Four 'types' of olefins were discussed, ranging from type I, which undergo homodimerisation rapidly, type II which homodimerise slowly, to type III which do not homodimerise, and finally type IV which fail to undergo cross-metathesis themselves but do not interfere with the metathesis catalyst's activity. The categories essentially relate to the order of reactivity of the olefin partners, with type I being the most reactive to cross-metathesis.

According to this classification, the enone intermediate **136** is a type II olefin in reactions catalysed by Grubbs 2nd generation catalyst **K**, while simple terminal alkenes such as the metathesis partners used in this project are of type I. Grubbs' paper states that cross-metathesis reactions between an olefin of type I and one of type II should successfully lead to a selective heterodimerisation of the two alkene partners. This is due to the fact that although homodimerisation of the type I alkene is possible, the homodimer itself can undergo a second metathesis reaction with the type II olefin to generate the desired product (Figure 19).

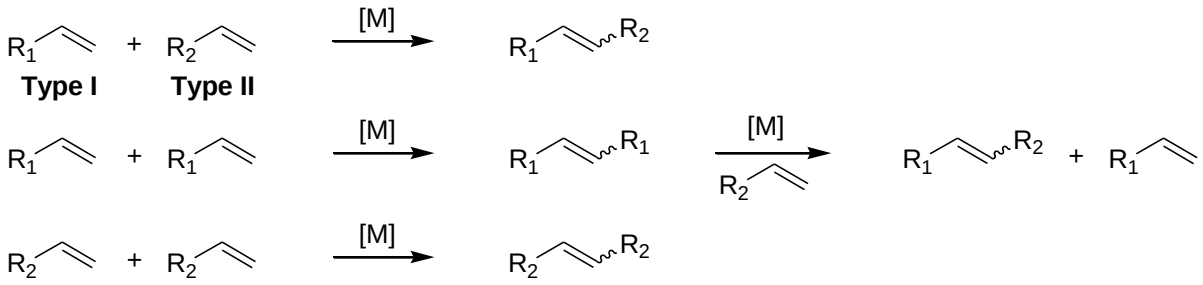
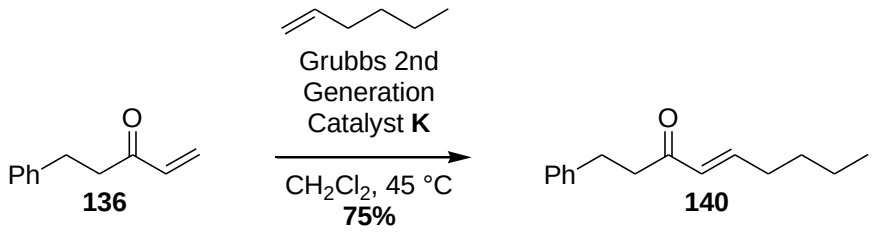


Figure 19. Selectivity in cross-metathesis between type I and type II olefins

The first terminal alkene partner selected for metathesis with enone **136** was 1-hexene, which provided a simple alkyl chain for initial development of the methodology. The first of these cross-metathesis reactions was carried out according to standard conditions.[80] In the presence of Grubbs 2nd generation catalyst **K** (4 mol%), the substituted enone **140** was successfully generated in 75% yield, as shown in Scheme 2.23.



Scheme 2.23. Cross-metathesis of enone 136 with 1-hexene

Importantly, this reaction proceeded with complete selectivity for the desired *E*-alkene product, and none of the alkene with *Z*-geometry was detected by ^{1}H NMR spectroscopic analysis of the crude reaction product, as indicated by an observed coupling constant value of J = 15.8 Hz in the two signals derived from the alkene protons, which are shown in Figure 20.

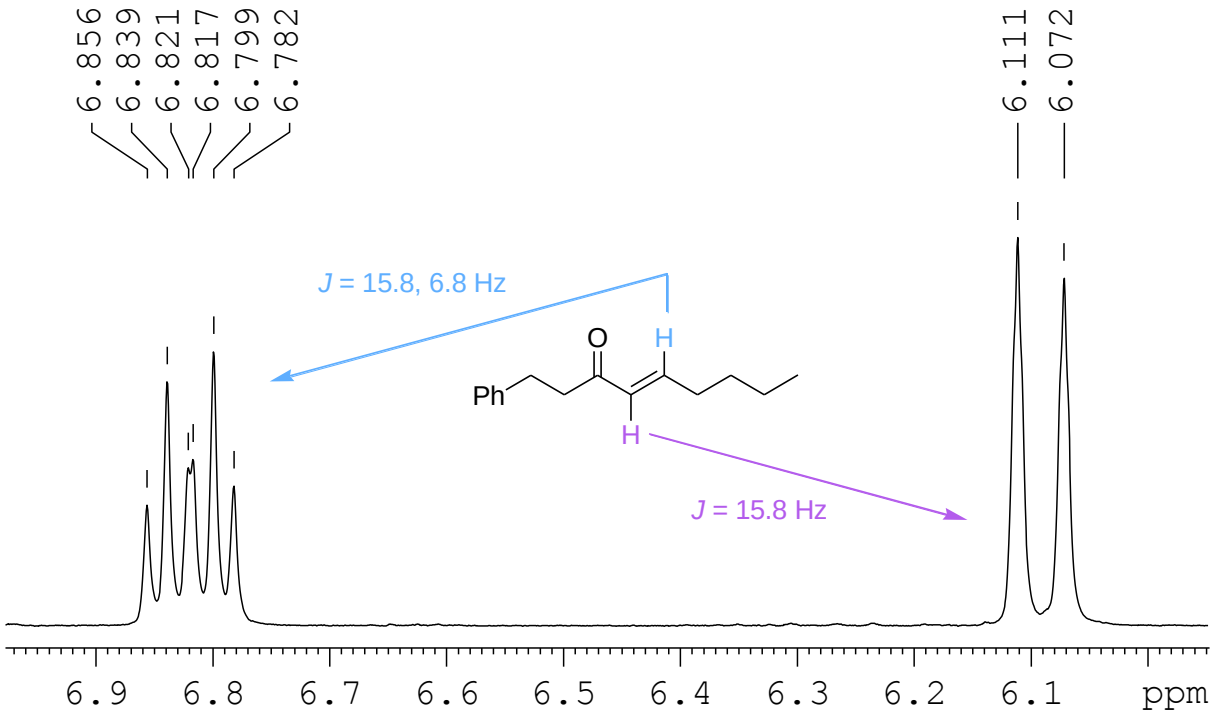
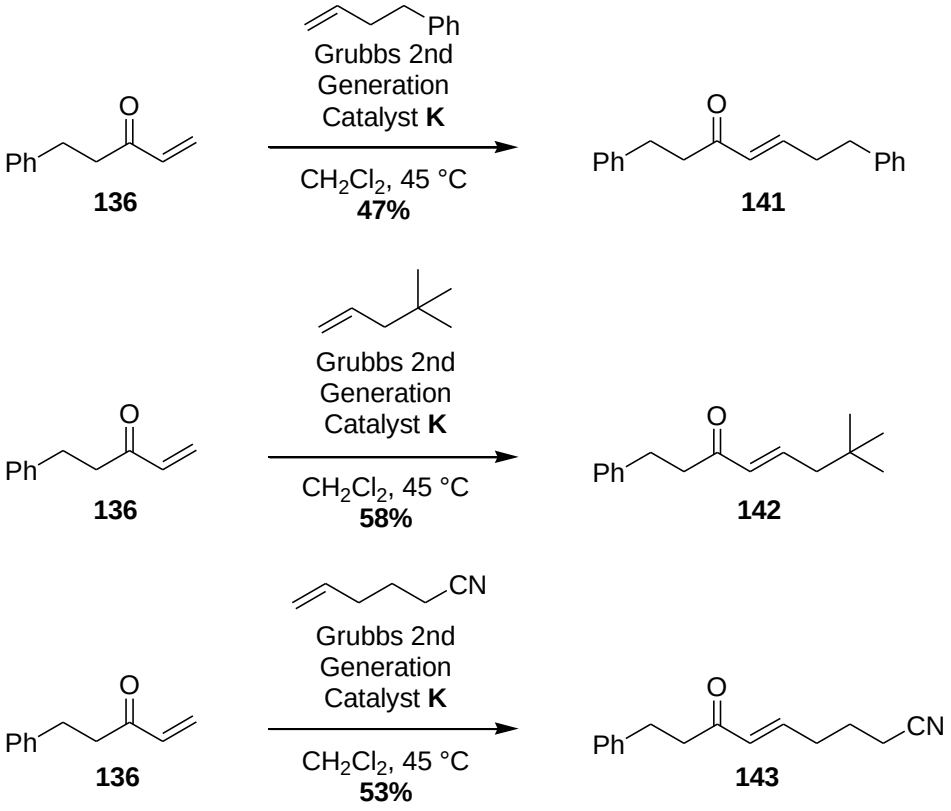


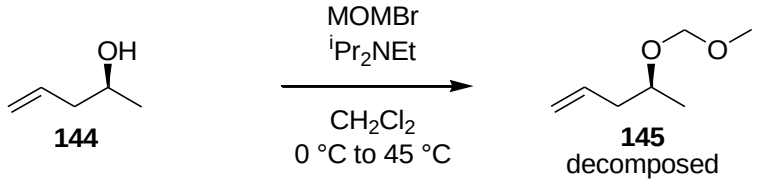
Figure 20. ^{1}**H NMR spectroscopy signals derived from alkene protons of 140**

As this cross-metathesis reaction proceeded in a straightforward manner with a high product yield, the same key enone intermediate was subjected to these reaction conditions with three other terminal alkene partners, as shown in Scheme 2.24. These reactions achieved product yields ranging from a moderate 47% to 58%, observed for the *tert*-butyl substituted example **142**. The reaction involving the synthesis of nitrile-substituted trichloroacetamide **143** proved sluggish, and required repeated additions of catalyst (total catalyst loading = 9 mol%) to achieve complete consumption of the enone starting material **136**.



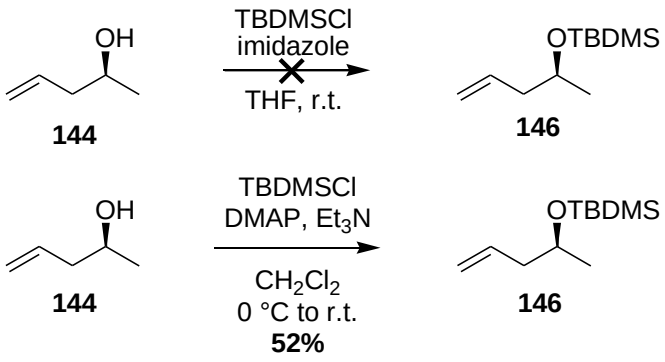
Scheme 2.24. Cross-metathesis reaction with additional alkene partners

An additional α-amino acid target, which bears a stereogenic centre in the γ-position was also selected for synthesis and in order to introduce the required side chain, a cross metathesis reaction between enone **136** and a protected derivative of (*S*)-(+)-4-penten-2-ol **144** was necessary. Protection of the hydroxyl group was first needed and the methoxymethyl group was selected as a suitable choice. (*S*)-(+)-4-penten-2-ol **144** was therefore subjected to standard MOM protection conditions using bromomethyl methyl ether in the presence of base, as shown in Scheme 2.25. ^{1}H NMR spectroscopic analysis of the crude product showed that the required alkene **145** had been successfully generated in 89% crude yield, with only minor impurities present. However when purification by silica column chromatography was attempted, decomposition of the product occurred, and none of the required product was isolated in a pure form.



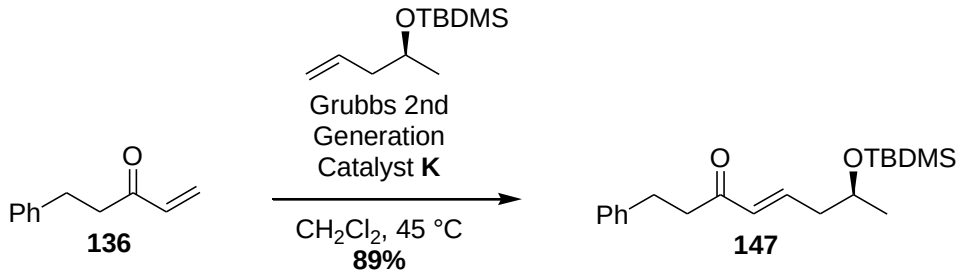
Scheme 2.25. Attempted MOM protection of (*S*)-(+)-4-penten-2-ol

An alternative protection strategy was then selected for (*S*)-(+)-4-penten-2-ol **144**, and silyl protection was deemed appropriate, as it would be capable of resisting the reaction conditions involved with the route under development. Therefore, the alcohol was treated with *tert*-butyldimethylsilyl chloride in the presence of imidazole according to a literature procedure by Overman and Rishton, as shown in Scheme 2.26.[81] However, neither the desired protected product **146** or starting material alcohol were identified upon work-up. The protection was then attempted using triethylamine and 4-di(methylamino)pyridine, as described in the literature by Kalivretenos *et al.*, and this time the desired protected alcohol was generated in 52% yield.[82]



Scheme 2.26. Silyl protection of (*S*)-(+)-4-penten-2-ol

The silyloxy-substituted terminal alkene **146** was then subjected to cross-metathesis with enone **136** using the standard reaction conditions, as shown in Scheme 2.27. Although a slightly increased loading of Grubbs catalyst **K** (5 mol%) was required, the reaction proceeded successfully with an excellent yield of 89%.



Scheme 2.27. Cross metathesis of enone 136 with silyloxy-substituted terminal alkene 146

2.2.3 Enantioselective ketone reductions to generate allylic alcohols

In order to complete the generation of the desired allylic alcohol intermediates, reduction of the enone carbonyl groups was required. This could be achieved enantioselectively by employing CBS protocol. The CBS reduction, named after its developers Corey, Bakshi and Shibata, was developed in the late 1980s and involves a 1,2-reduction of ketones to alcohols in the presence of an enantiomerically pure oxazaborolidine catalyst of the type shown in Figure 21 and a borane reducing agent.[83,84] These oxazaborolidine catalysts are capable of achieving the reduction of simple ketones in excellent yield attaining enantiomeric excess values greater than 90% in the alcohol products.

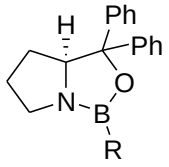


Figure 21. Typical CBS oxazaborolidine catalyst

Both enantiomers of these oxazaborolidine catalysts are available commercially and as expected, opposite enantiomers of oxazaborolidine lead to generation of opposite allylic alcohol product enantiomers. The product enantiomer formed preferentially can be predicted (Figure 22). It can be seen that a highly enantioselective reduction is possible when there is a significant difference in size between the groups on either side of the carbonyl. With the enone substrates **140**–**143** and **147** used in this project, there is not a particularly significant difference in

the size between these groups although it has been shown that in general, a vinylic double bond will generally behave as the large group in these reductions.[85]

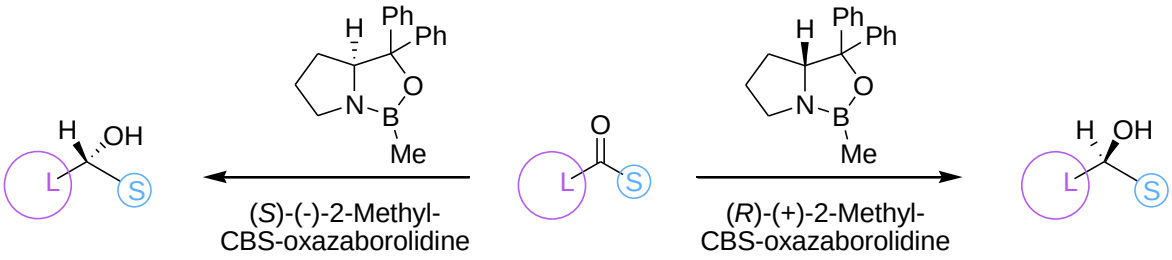


Figure 22. Prediction of enantiomeric outcome of CBS reduction

The source of enantioselectivity observed in the CBS reduction can be understood by consideration of the reaction mechanism, a simplified version of which is shown in Figure 23.[86] The active reducing agent here is formed when borane coordinates to the oxazaborolidine nitrogen. The ketone substrate then coordinates to the boron atom within the oxazaborolidine bicycle, the Lewis acidity of which is increased by the initial coordination of borane to nitrogen. The ketone binds in a manner which minimises steric interaction between the large substituent and the oxazaborolidine, with the large substituent placed in a pseudoequatorial position in the 6-membered transition state. This coordination then allows the hydride from borane to be delivered preferentially to one face of the ketone.

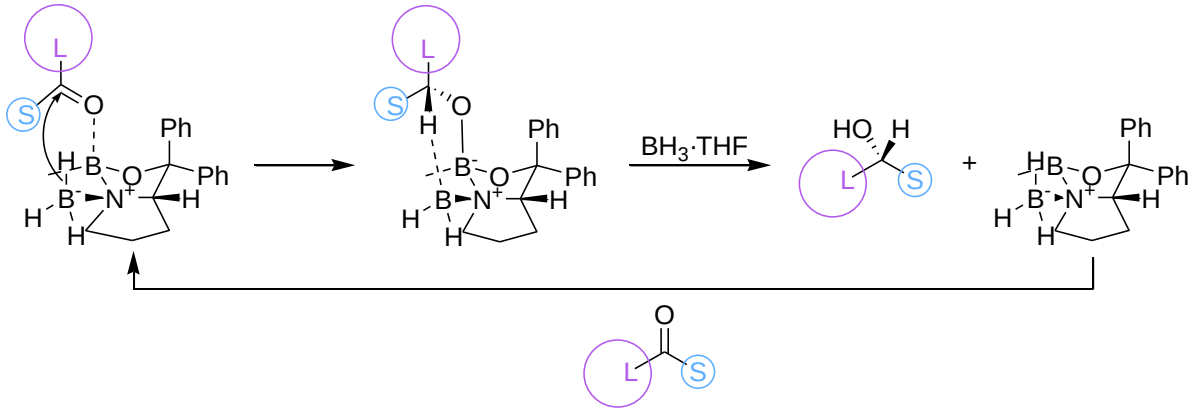
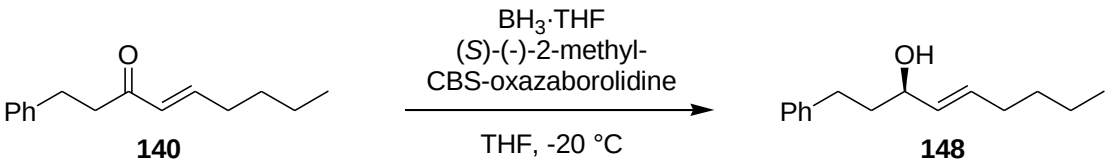


Figure 23. Source of enantioselectivity with (*S*)-(-)-2-methyl-CBS-oxazaborolidine

In order to find the optimal conditions for this CBS reduction, a study was carried out to determine the effect of altering the loading of the CBS catalyst on both the

yield and enantiomeric excess of the product. The butyl-substituted enone **140** was selected as a standard substrate for the reduction reactions with (*S*)-(-)-2-methyl-CBS-oxazaborolidine, selected as the catalyst to favour formation of the desired (*R*)-enantiomer of the allylic alcohol **148**, as shown in Scheme 2.28.



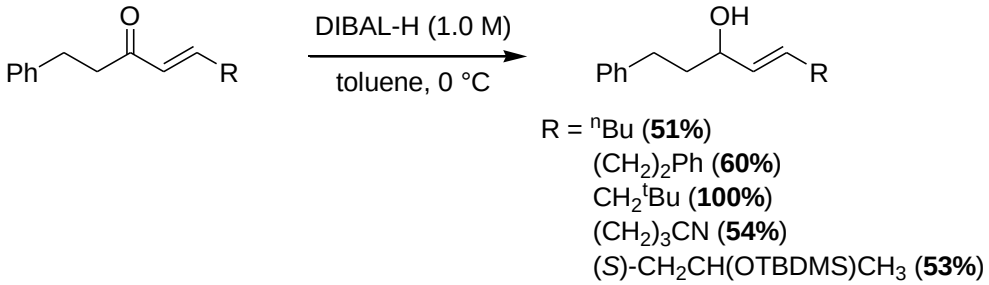
Scheme 2.28. CBS reduction of enone 140

This reduction reaction was attempted under standard conditions discussed by Evans and Morken in the literature, and initially carried out in the presence of 0.2 equivalents of the CBS oxazaborolidine catalyst.[87] This was subsequently increased to 0.5 equivalents in a repeat of the reduction, and finally to a stoichiometric quantity of the oxazaborolidine. The product yields were high in each instance, although the enantiomeric excess values were shown to improve significantly with increasing equivalents of oxazaborolidine, as shown in Table 9. Comparison of $[\alpha]_D$ values to literature data confirmed the formation of the required (*R*)-enantiomer of the allylic alcohol.

Equivalents of oxazaborolidine	Yield (%)	e.e (%)
0.2	57	31
0.5	100	71
1.0	99	84

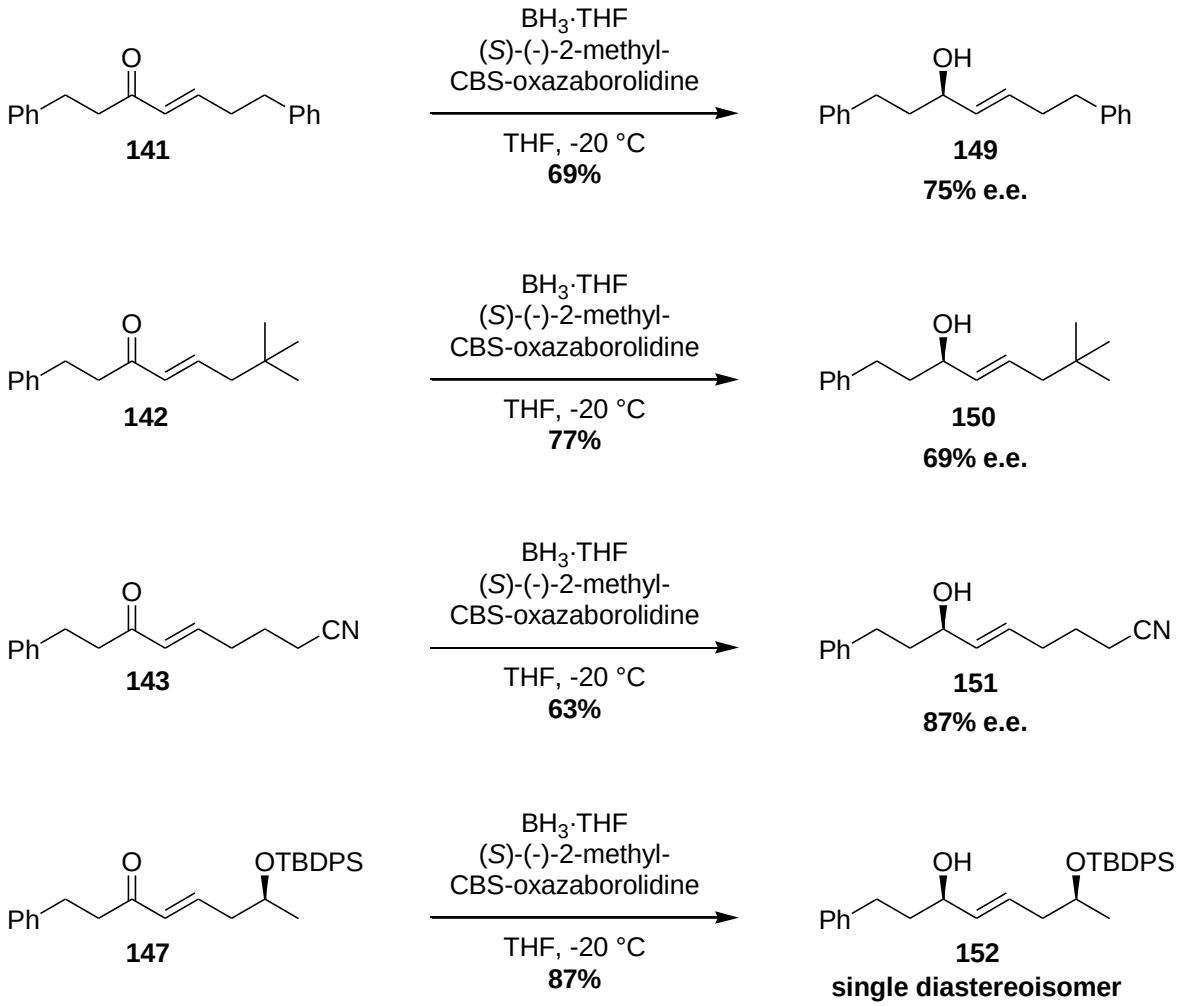
Table 9. Results of CBS reduction study

The enantiomeric excess values quoted here were determined by chiral HPLC analysis, using a Chiralcel IB column. In order to determine HPLC conditions for the separation of enantiomers of the enol products, a racemic sample of each of these was required. These enol racemates were generated by carrying out a straightforward reduction using diisobutylaluminium hydride, as shown in Scheme 2.29.



Scheme 2.29. Racemic reduction of enone intermediates

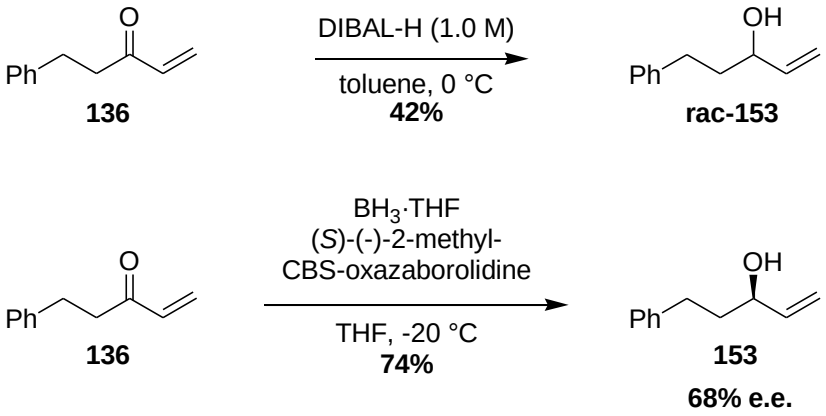
The results of the catalyst screen showed that the highest enantiomeric excess values in the product are observed when a stoichiometric quantity of the CBS oxazaborolidine is used. As the enantioselectivity established in the CBS reduction is carried through to the eventual amino acid target, it is crucial that high enantiomeric excess values are attained at this stage. Therefore, it was decided that a stoichiometric quantity of CBS oxazaborolidine should be utilised in the reduction of the remaining enone intermediates, as shown in Scheme 2.30. High yields were achieved for each of these reduction reactions, with moderate to high levels of enantioselectivity observed. ^{1}H and ^{13}C NMR spectroscopic analysis of alcohol **152**, with comparison to the diisobutylaluminium hydride-reduced sample, indicated that only a single diastereoisomer of the product was detectable.



Scheme 2.30. CBS reduction of remaining enone intermediates

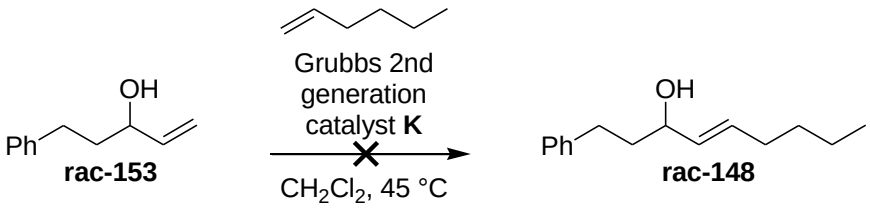
While the CBS reduction was successfully achieved to synthesise all of the desired allylic alcohols, this strategy is slightly lacking in efficiency, as it requires the CBS enantioselective reduction and also racemic diisobutylaluminium hydride reduction of each individual enone synthesised in addition to subsequent chiral HPLC analysis of all these reaction products. An alternative approach was therefore considered, where the 1,2-reduction of the enone functionality was carried out on key enone intermediate **136** prior to cross-metathesis with the various terminal alkene partners. This would mean that chiral HPLC analysis would only be required once, as the stereogenic centre would not be affected by the cross-metathesis chemistry. Using the reduction conditions employed previously, both the racemic and enantioselective reductions were carried out on enone **136**, proceeding in yields comparable to previous examples as shown in Scheme 2.31. It is worth mentioning that an initial attempt to carry out the reduction of enone **136** to racemic alcohol

rac-153 using sodium borohydride had resulted in a 1:1 ratio of the desired product and the product with a fully reduced alcohol with further reduction of the carbon-carbon double bond, the result of a 1,4-addition of hydride to enone **136**.



Scheme 2.31. Reduction of enone 136

With the reduction of enone **136** successfully achieved, the racemic sample was utilised in a test cross-metathesis reaction with 1-hexene, as shown in Scheme 2.32. According to literature precedent, the cross-metathesis of enol partners should be possible to achieve, with enols falling into the Type II category according to Grubbs' classification.[79] However, when this reaction was attempted, none of the desired product **rac-153** was detected by ^{1}H NMR spectroscopic analysis upon purification.



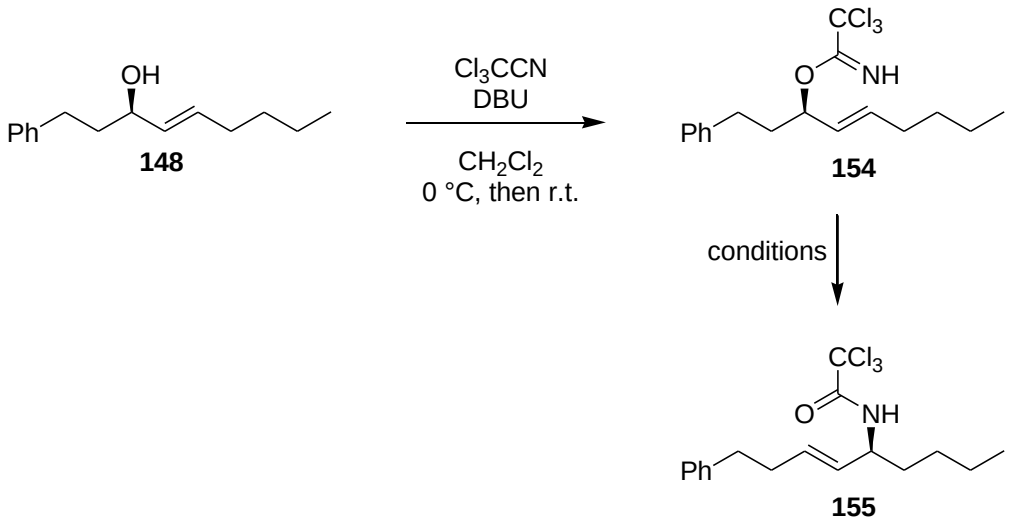
Scheme 2.32. Cross metathesis of alcohol rac-153 with 1-hexene

As this cross-metathesis failed, it was decided to continue with the original strategy of carrying out the cross-metathesis prior to the reduction step.

2.2.4 Conversion of allylic alcohols to allylic trichloroacetimidates

With the desired allylic alcohols successfully synthesised, a study of the Overman rearrangement chemistry was then carried out. As discussed previously, the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates derived from secondary alcohols is possible under both thermal conditions and metal catalysis, although thermal rearrangements tend to give a cleaner reaction profile and hence higher yields.

The butyl-substituted enol **148** was initially used as the substrate for trichloroacetimidate formation and subsequent Overman rearrangement, as shown in Scheme 2.33.



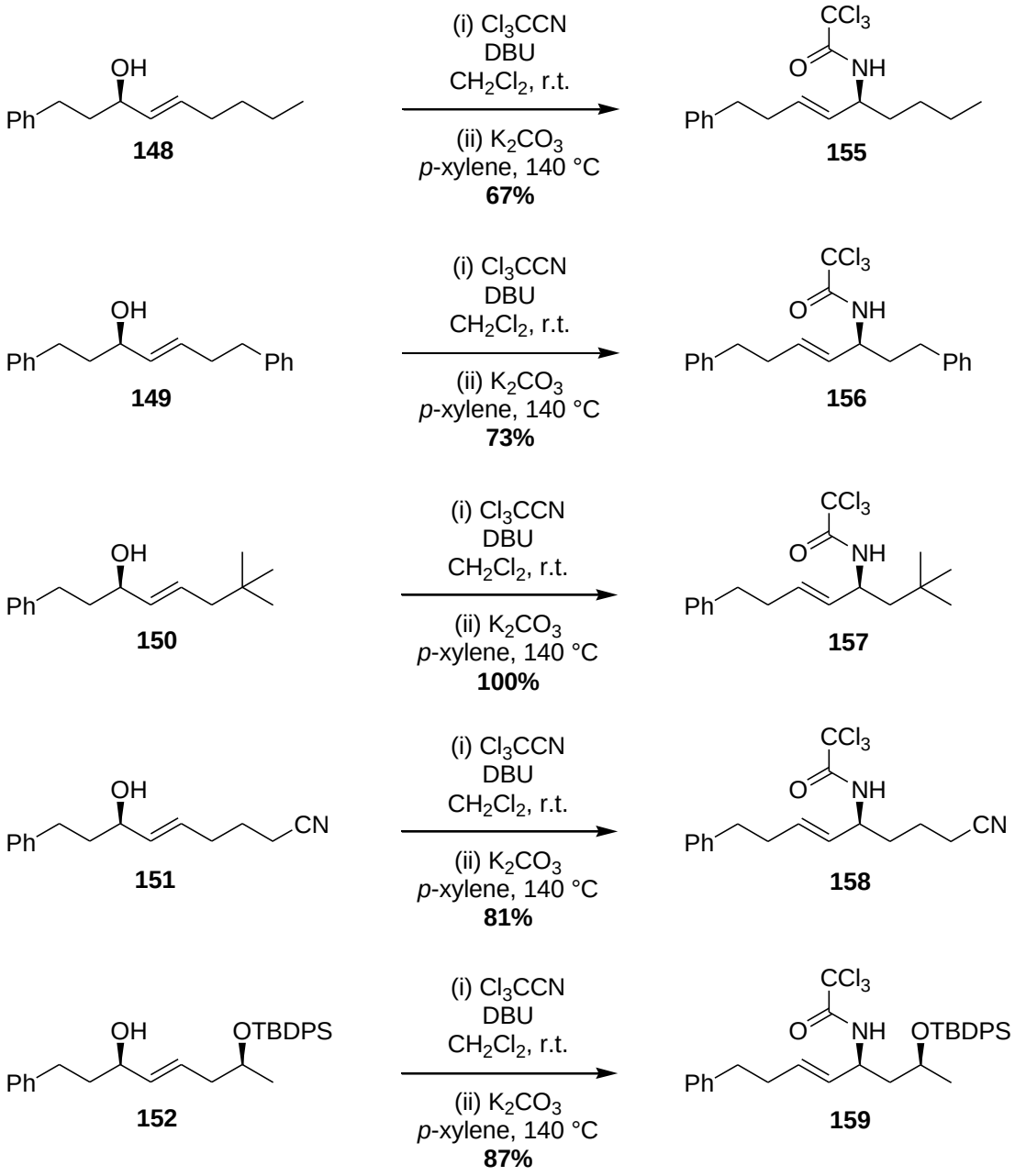
Scheme 2.33. Conversion of enol 148 to trichloroacetimidate and Overman rearrangement

Initially, the trichloroacetimidate formation was carried out using the reaction conditions discussed in chapter 2.1. On the first attempt of this reaction, the acetimidate formation was stirred at room temperature for 9 h, and this was followed by a $PdCl_2(CH_3CN)_2$-catalysed rearrangement. The yield of trichloroacetamide **155** was a relatively disappointing 37% in this instance, and the presence of some remaining unreacted allylic alcohol starting material cited as the reason for this. Therefore, the trichloroacetimidate formation step for alcohol **148** and the remaining examples was allowed to stir at room temperature for 24 h before subjecting to the rearrangement conditions. When this rearrangement

chemistry was repeated in combination with the longer acetimidate formation reaction, a slightly increased product yield of 41% was attained, although repeated purification by silica column chromatography failed to separate the desired product from minor impurities present.

The rearrangement reaction was then carried out under thermal reaction conditions. Again, the acetimidate formation was allowed to stir at room temperature for 24 h. Using this approach, a much cleaner reaction product was observed, and upon purification, a 67% product yield was achieved (Scheme 2.34).

The conditions employed for the synthesis of allylic trichloroacetamide **155** were then applied to conversion of the remaining allylic alcohols, as shown below in Scheme 2.34. All of these reactions were carried out in high yield. Note that the product yields quoted below are over two steps from the corresponding allylic alcohols.

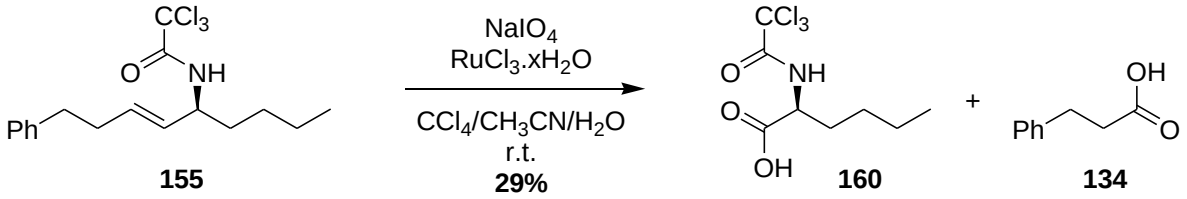


Scheme 2.34. Synthesis of allylic trichloroacetamides 155-159

2.2.5 Completion of α-amino acid targets

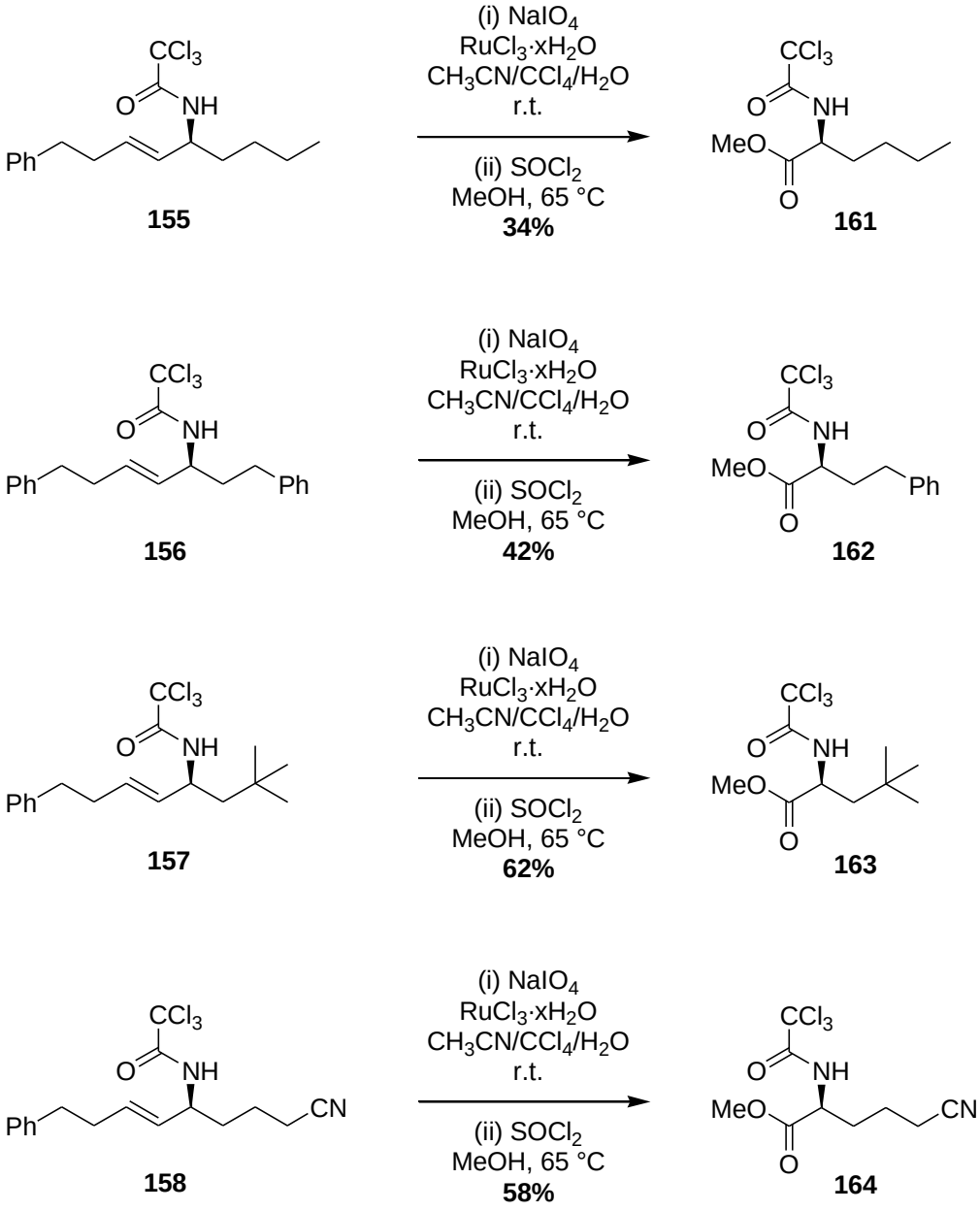
With the desired protected amine functionality in place, it was then possible to introduce the carboxylic acid group required in the final amino acid targets. In order to achieve this, Sharpless oxidation conditions were employed to cleave the alkene using ruthenium(III) catalysis.[66] The reaction was initially carried out on allylic trichloroacetamide **155**, as shown in Scheme 2.35, generating the desired

product **160** and hydrocinnamic acid **134** as a by-product. Attempts to separate these two reaction components by silica column chromatography proved difficult due to their ability to form hydrogen bonds with the stationary phase, and resulted in a relatively low product yield of 29%.



Scheme 2.35. Oxidative cleavage of allylic trichloroacetamide 155

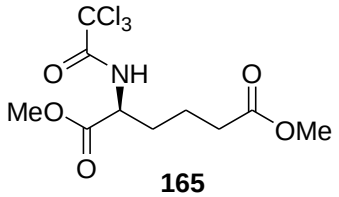
As separation of the two acid products was problematic, it was decided to subject the crude reaction product to a simple esterification to generate the corresponding methyl esters, which would be significantly easier to purify by column chromatography. This method was successfully applied to the generation of esters **155**-**158**, as shown in Scheme 2.36. Again, the product yields quoted are over 2 steps from the allylic trichloroacetamides.



Scheme 2.36. Oxidative cleavage and esterification

During one instance of carrying out this oxidation and esterification on the nitrile-substituted trichloroacetamide **158**, additional ruthenium trichloride hydrate (2.5 mol%) and sodium periodate (1 equivalent) were added after a reaction time of 18 h, as TLC analysis at this stage appeared to show the presence of residual starting material. Upon purification after the esterification step, a significant by-product was isolated. Analysis indicated that the nitrile group had undergone hydrolysis to the corresponding carboxylic acid during the oxidative cleavage reaction, and subsequent esterification led to the formation of the diester **165**, which was

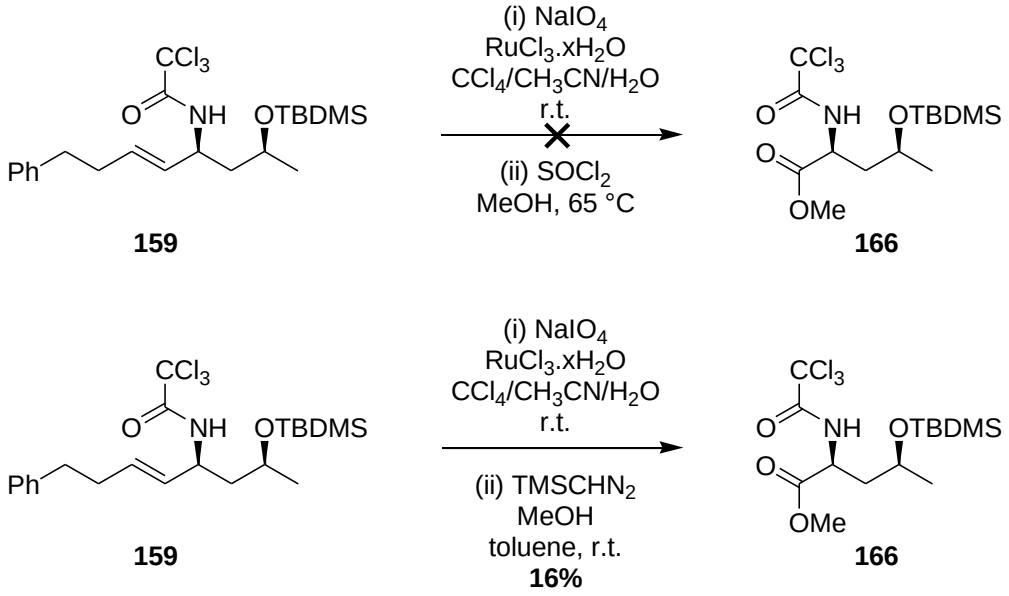
isolated in 35% yield (Figure 24). The presence of this diester resulted in a significantly lower yield of 17% of the desired ester **164**.



165

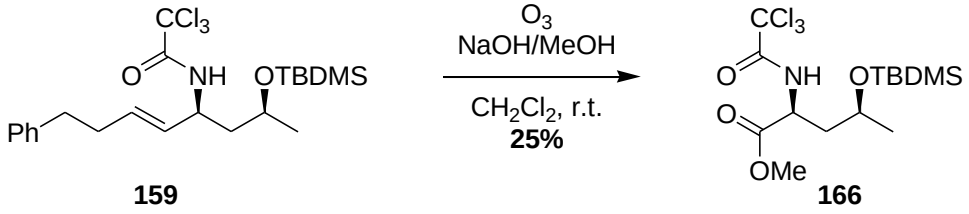
Figure 24. Diester by-product

Problems were encountered in the oxidative cleavage of silyloxy-substituted trichloroacetamide **159**. When subjected to the Sharpless oxidation and esterification, none of the desired ester **166** was formed, and a complex product mixture was observed by ^{1}H NMR spectroscopic analysis. At this stage, it was believed that this was perhaps due to loss of the silyl protecting group occurring during the esterification step where relatively harsh reaction conditions are encountered and HCl is generated. Therefore, the oxidation was repeated according to the Sharpless protocol, although this was followed by a milder esterfication procedure utilising (trimethylsilyl)diazomethane as shown in Scheme 2.37. The desired ester product **166** was isolated upon purification, although in a disappointing yield of just 16% over the 2 steps. This result suggested that the oxidative cleavage step was problematic with the silyloxy-substituted substrate. This was confirmed when attempts to purify the cleaved carboxylic acid directly from the Sharpless oxidation step without esterification failed.



Scheme 2.37. Attempted generation of ester 166

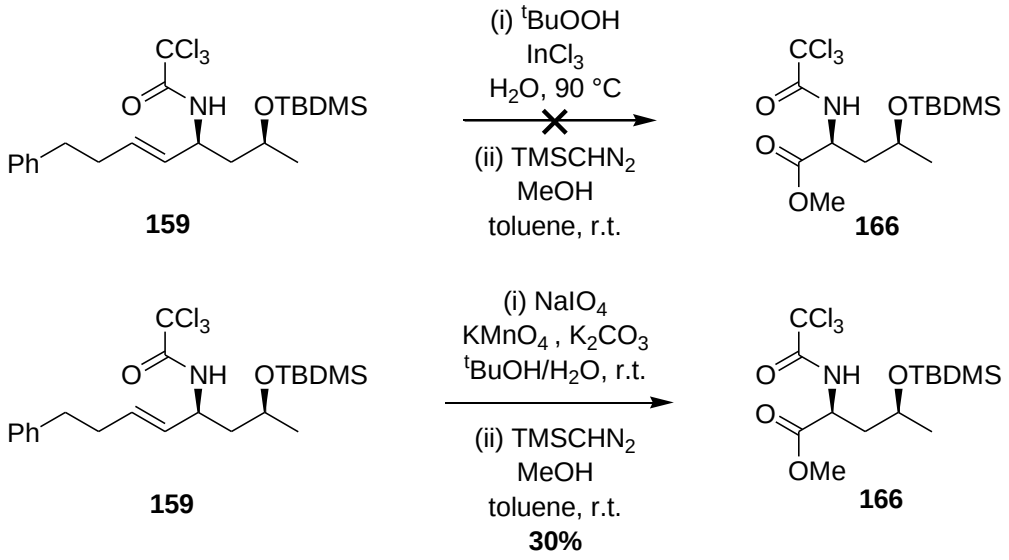
Alternative methods for the oxidative cleavage of the alkene **159** were then investigated, the first of which was ozonolysis in the presence of a methanolic solution of sodium hydroxide in an attempt to carry out the oxidation and esterification in a single reaction. The conditions applied were described in the literature by Marshall and Garofalo (Scheme 2.38), and resulted in the successful isolation of the desired ester **166** in a modest 25% yield upon purification.[88]



Scheme 2.38. Ozonolysis of trichloroacetamide 159

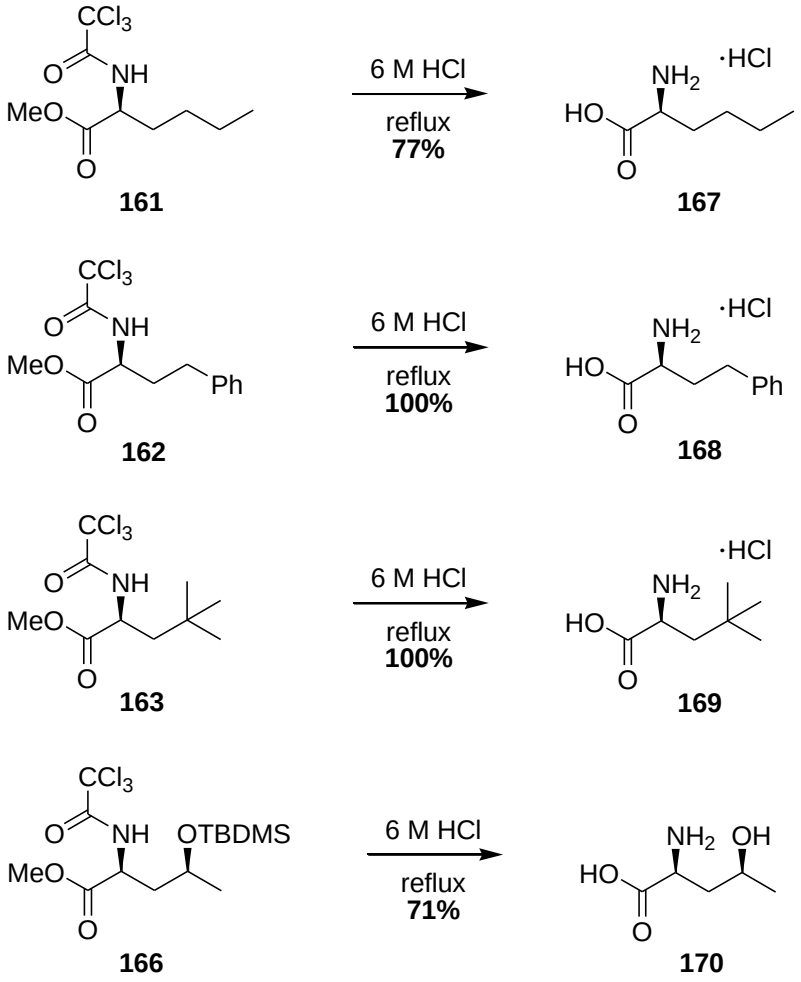
A literature procedure published by Ranu *et al.*[89] which uses *tert*-butylhydroperoxide in the presence of a Lewis acid catalyst was then trialled as this uses relatively mild conditions, and was followed by the mild TMS-diazomethane esterification as shown in Scheme 2.39. However, none of the desired ester **166** was isolated and a proportion of the unreacted starting material **159** remained in the crude product. Finally, conditions published by Figueiredo *et al.* were employed, and the oxidation was carried out using potassium permanganate and

sodium periodate.[90] When followed by the same TMS-diazomethane esterification, ester **166** was isolated in a satisfactory yield of 30% over the two steps.



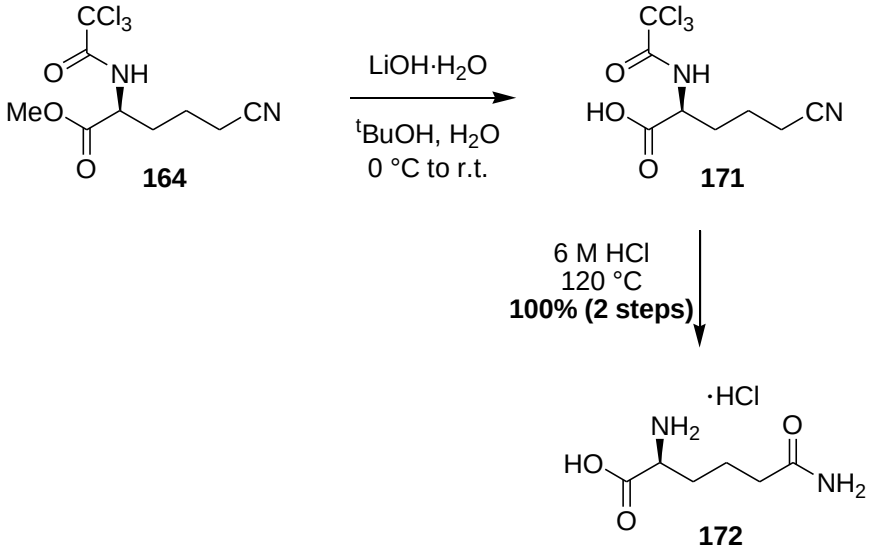
Scheme 2.39. Alternative oxidations of trichloroacetamide 159

In order to complete the synthesis of the α-amino acid targets, removal of both the trichloroacetamide group and the methyl ester was required for each example. This was achieved by heating the ester intermediates under reflux in 6 M hydrochloric acid, as shown in Scheme 2.40. In the case of the silyloxy substituted compound **166**, it was found that the silyl protecting group was also removed as desired under these reaction conditions. Upon workup however, it was found that lactonisation had occurred also and so in order to reopen the lactone ring, purification was carried out using an ion exchange column. This gave the α-amino acid target **170** in a yield of 71%.



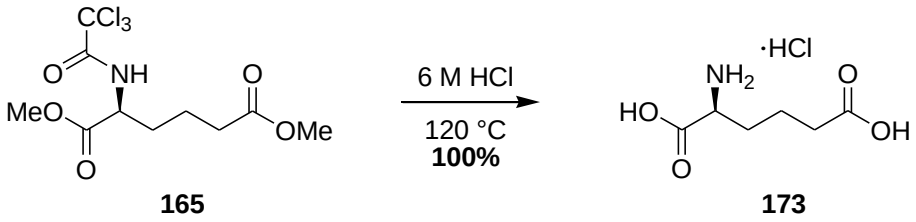
Scheme 2.40. Completion of α-amino acid targets

As the nitrile functionality on ester **164** is sensitive to hydrolysis in the presence of 6 M hydrochloric acid, an alternative strategy was utilised for its deprotection. An attempt was made to hydrolyse the methyl ester and trichloroacetamide groups simultaneously in the presence of base, which would hopefully leave the nitrile group intact. Lithium hydroxide was employed, as shown in Scheme 2.41, although it was found that while ester hydrolysis was successful, the trichloroacetamide groups remained unreacted. Therefore the acid intermediate **171** was reacted with 6 M HCl under reflux and as expected, hydrolysis of the trichloroacetamide group occurred. The harsh reaction conditions led to conversion of the nitrile group to the corresponding amide **172**, which was formed in quantitative yield over the two steps.



Scheme 2.41. Deprotection of trichloroacetamide 164

It was also possible to complete the synthesis of an additional α-amino acid target **173** from the diester **165**, isolated as a by-product during the oxidative cleavage/esterification step as previously described. This was achieved as above by treating the diester with acid under reflux, as shown in Scheme 2.42, and the target L-aminoadipic acid **173** was generated in quantitative yield.



Scheme 2.42. Completion of diacid 173

At this stage, the new methodology for the generation of α-amino acids had been successfully developed. Importantly, the introduction of a variety of side chains was possible during the mild cross-metathesis conditions, and the use of an asymmetric ketone reduction to form the required chiral allylic alcohols meant that access to either product enantiomer would be possible by application of both enantiomers of the commercially-available CBS oxazaborolidine reagent. A study of conditions required for the Overman rearrangement conditions and subsequent conversion to α-amino acids led to the completed synthesis of the target

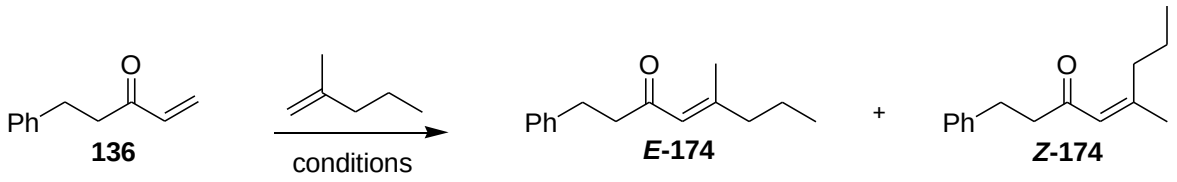
compounds **167**–**170** and **172** in an efficient, stereoselective manner from simple starting materials.

2.2.6 Synthesis of trisubstituted enone *via* cross-metathesis

With α-amino acid targets **167**–**170** and **172** successfully completed, the developed methodology was applied to the attempted synthesis of α,α-disubstituted examples. This could be achieved by using disubstituted terminal alkenes in the cross-metathesis reaction with the enone intermediate **136**. For this approach to be successful, this cross-metathesis has to proceed in good yield and with a high degree of *E*/*Z*-selectivity. In 1999, Chatterjee and Grubbs published details of the synthesis of trisubstituted alkenes *via* cross-metathesis and showed that Grubbs 2nd generation catalyst **K** succeeded in promoting these reactions with a number of examples where one of the substituents on the disubstituted alkene partner is a methyl group.[80] The reactions discussed proceeded in good yield and with moderate levels of *E*:*Z* selectivity, the highest being a 4:1 product ratio.

Under Grubbs' classification of olefin cross-metathesis partners, simple 2,2-disubstituted olefins belong to the type III category when Grubbs 2nd generation catalyst **K** is used.[79] Type III olefins are less reactive than type II partners, and are not susceptible to homodimerisation. This reduced reactivity, attributed to steric hindrance, means that often a relatively high excess of the terminal alkene partner is required to attain a high yield of the desired heterocoupled product. This excess can help to prevent the formation of the type II homodimer, which would be unable to undergo a second metathesis with the type III olefin.

Enone intermediate **136** was subjected to cross-metathesis with 2,2-dimethyl pentene, as shown in Scheme 2.43 and both the product yield and *E*/*Z* selectivity were noted using a range of conditions.

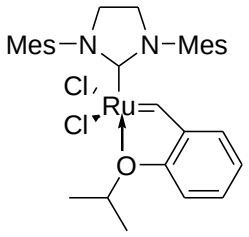


Scheme 2.43. Cross-metathesis to form trisubstituted alkenes

Initially, the standard reaction conditions applied to the synthesis of enone **140** were employed, using 5 mol% of Grubbs 2nd generation catalyst. However, the reaction was slow and required additional 2-methyl-1-pentene and Grubbs 2nd generation catalyst **K**, although a very poor yield product yield of 6% was achieved (Table 10, entry 1). Repeats of this reaction using higher catalyst loadings and increased reaction temperatures were also attempted, with limited improvement in product yield. Use of a copper(I) chloride co-catalyst was also trialled, as literature precedent indicated that this can improve reaction turnover. However, this failed to yield any of the desired alkene product (entry 4).[91] The most significant improvement came in changing the cross-metathesis catalyst to Hoveyda-Grubbs 2nd generation catalyst **L** (Figure 25), with reaction time significantly decreased and improvement in both yield and *E*/*Z*-selectivity observed (entry 5). Further investigation showed that this catalyst provides the highest yield of trisubstituted alkene **174** when the reaction is carried out at 45 °C, allowing lower catalyst loadings to be used.

Entry	Catalyst (initial/ total loading, mol%)	Solvent	Temperature (°C)	Time (h)	Yield (%)	*E* : *Z*
1	**K** (5/15)	CH_2Cl_2	45	190	6	1.7 : 1
2	**K** (20/25)	CH_2Cl_2	45	72	25	3 : 2
3	**K** (20/25)	toluene	80	88	31	1.2 : 1
4	**K** (5/10) + CuI (10)	CH_2Cl_2	45	71	0	_
5	**L** (20)	toluene	80	24	41	2 : 1
6	**L** (5/10)	toluene	80	354	18	1.2 : 1
7	**L** (10/22.5)	toluene	80	162	23	2.2 : 1
8	**L** (5/6)	CH_2Cl_2	45	72	53	1.7 : 1

Table 10. Results of cross-metathesis study



L
Hoveyda-Grubbs
2nd generation
catalyst

Figure 25. Hoveyda-Grubbs 2nd generation catalyst L for cross-metathesis

Confirmation of the geometry of the alkene products was achieved using ^{1}H NMR spectroscopic analysis by the nuclear Overhauser effect. Selective irradiation of the ^{1}H NMR signal arising from the alkene proton at 5.97 ppm provided the ability to distinguish between the *E* and *Z* product isomers. In the *E*-isomer, the alkene proton should interact through space with the CH_2 group of carbon-3, while the *Z*-isomer's alkene proton should interact with the methyl group substituent of the double bond, as indicated in Figure 26.

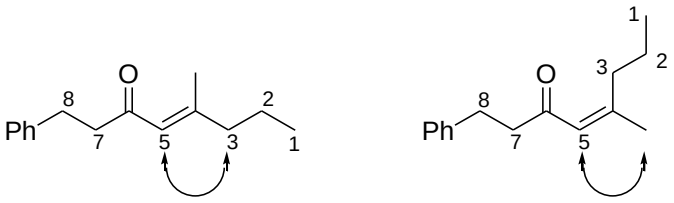


Figure 26. Anticipated through-space interaction with alkene protons

These experiments confirmed that the major isomer formed in each attempt of the reaction was, as expected, the *E*-isomer, and the spectra from this study are shown below in Figure 27 (*E*-isomer) and Figure 28 (*Z*-isomer).

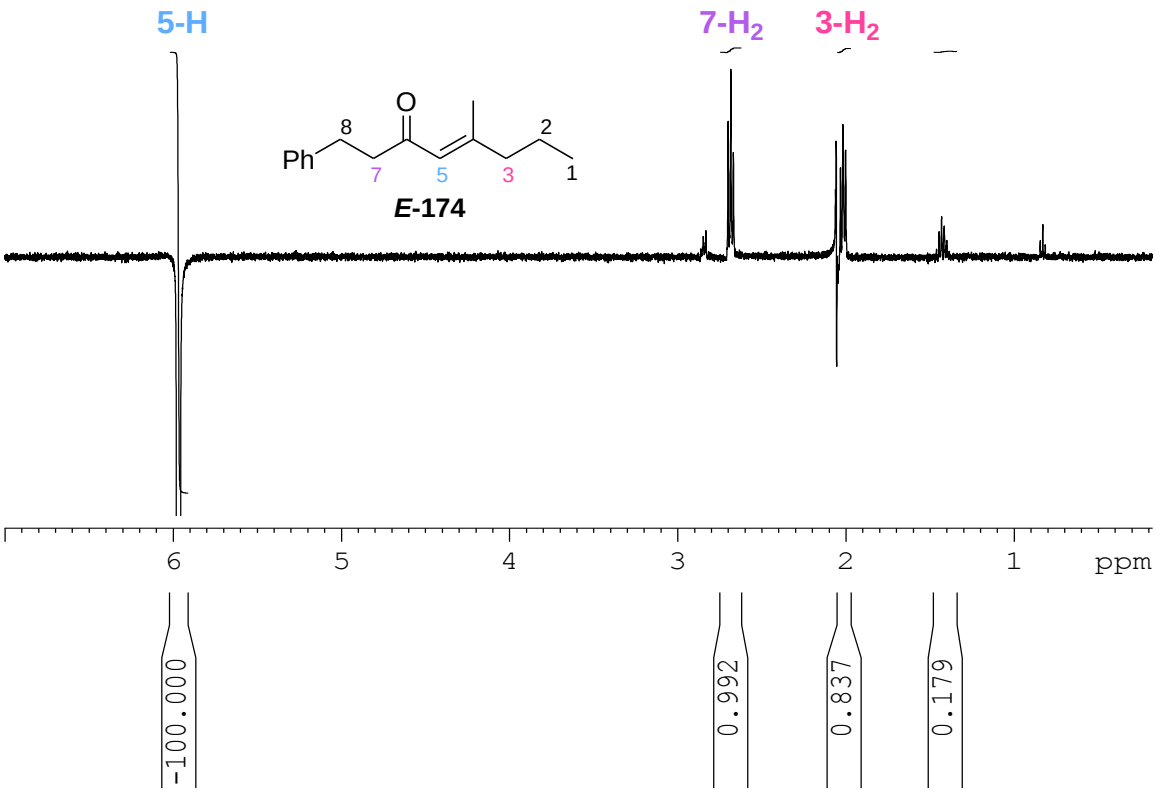


Figure 27. nOe spectrum for *E*-174

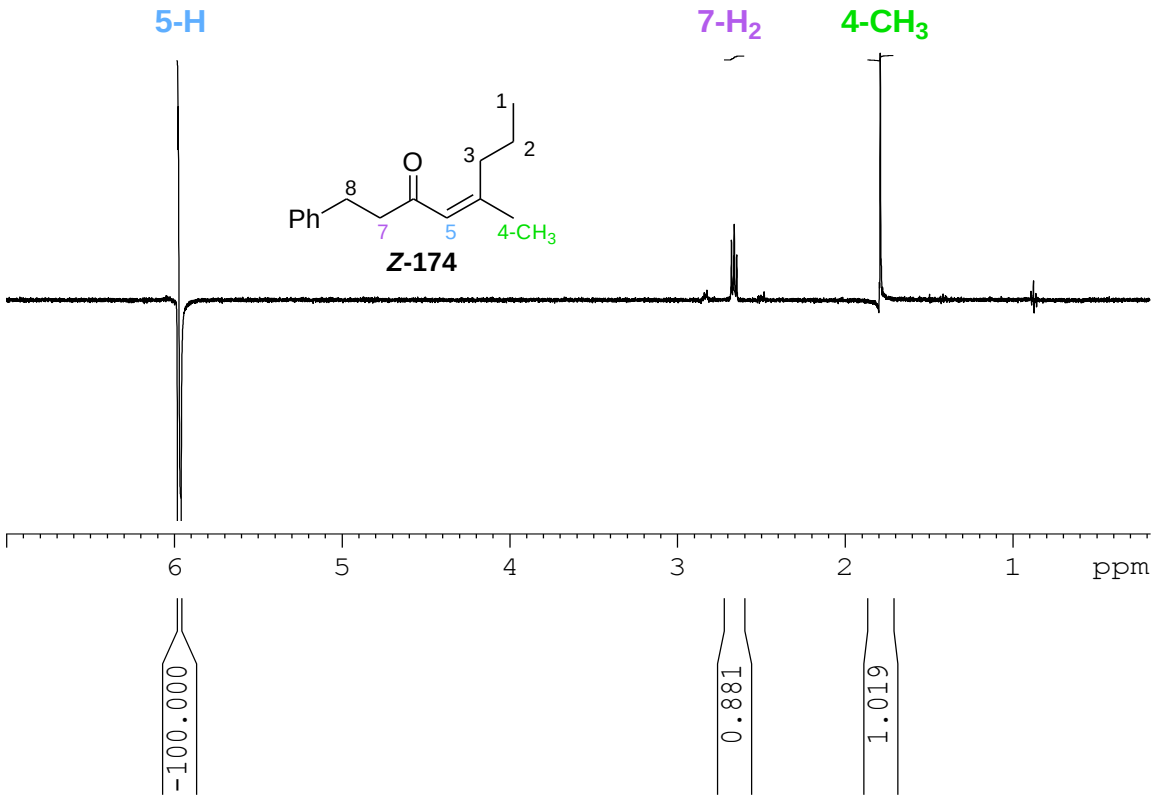
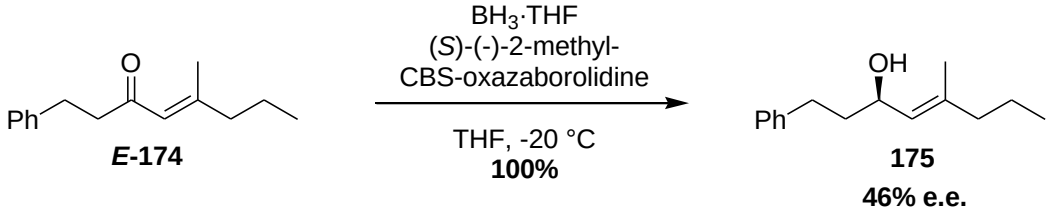


Figure 28. nOe spectrum for *Z*-174

2.2.7 Installation of quaternary centre *via* Overman rearrangement

With the limited quantities of trisubstituted alkene ***E*-174** synthesised, its reduction to allylic alcohol **175** was carried out. As before, this was attempted using the CBS asymmetric reduction protocol and proceeded in quantitative yield, as shown in Scheme 2.44. Again, chiral HPLC analysis was carried out with comparison to a racemic sample of the allylic alcohol (synthesised in 54% *via* DIBAL-H reduction), and this indicated an enantiomeric excess value of 46% in the CBS reduction product.

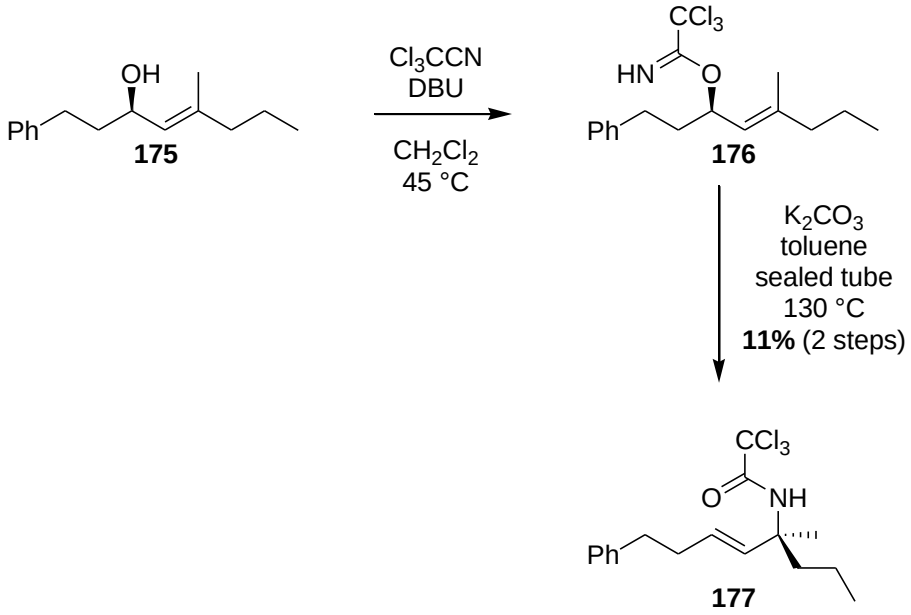


***E*-174** **175** **46% e.e.**

Scheme 2.44. Asymmetric reduction of trisubstituted enone *E*-174

Conversion of allylic alcohol **175** to the corresponding allylic trichloroacetimidate **176** was then attempted using the standard conditions previously discussed. However, the additional methyl group introduced additional steric bulk across the alkene relative to the disubstituted examples and significantly lowered the reaction rates. Therefore, acetimidate formation required additional reaction time and eventually heating under reflux to promote consumption of the starting material **175**.

The rearrangement step was also initially attempted under thermal conditions although again, the presence of the additional methyl group meant that longer reaction times were applied. However, none of the desired product was isolated in the first attempts at this reaction. The use of palladium catalysis also failed to promote the rearrangement. Finally, the reaction was attempted by heating the allylic trichloroacetimidate **175** at 130 °C in toluene in a sealed reaction tube. In this instance, it appeared that a small quantity of the desired rearrangement product **177** had formed, although only in a disappointing yield of 11% over the 2 steps (Scheme 2.45).



Scheme 2.45. Overman rearrangement to form quaternary centre

Although the attempted synthesis of an α,α-disubstituted α-amino acid target was met with limited success, it was hoped that the methodology developed could be applied to the synthesis of more complex α-amino acid targets.

2.2.8 Attempted synthesis of orthogonally-protected *meso*-diaminopimelic acid

An investigation was undertaken to use the chemistry developed for the generation of an orthogonally protected derivative **178** of diaminopimelic acid **179**, a non-proteinogenic diamino diacid (Figure 29).

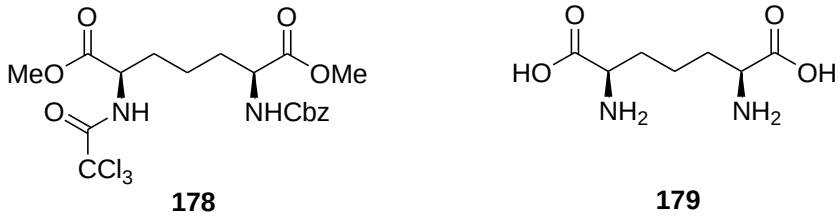
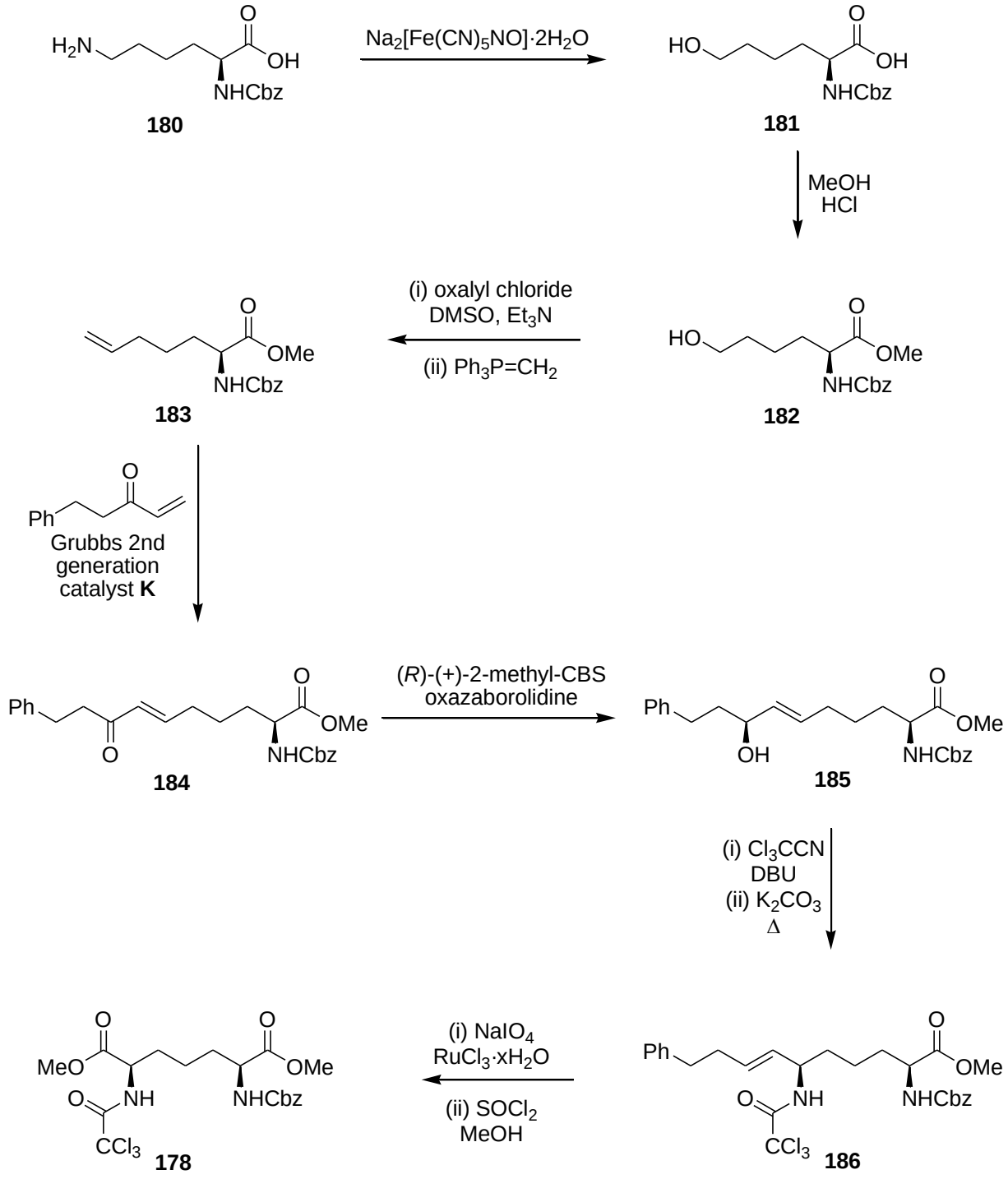


Figure 29. Protected *meso*-diaminopimelic acid derivative and *meso*-diaminopimelic acid

meso-Diaminopimelic acid (*meso*-DAP) **179** is found as a component of bacterial cell walls, and is a precursor in the biosynthesis of L-lysine.[92] Therefore, compounds similar in structure to *meso*-DAP have the potential for exhibiting antibiotic activity

by inhibiting this biosynthetic pathway and preventing bacterial cell wall formation. Rapid generation of *meso*-DAP analogues could be aided with the generation of a synthetically useful orthogonally-protected derivative such as **178**, as this would allow the individual manipulation of the functional groups.

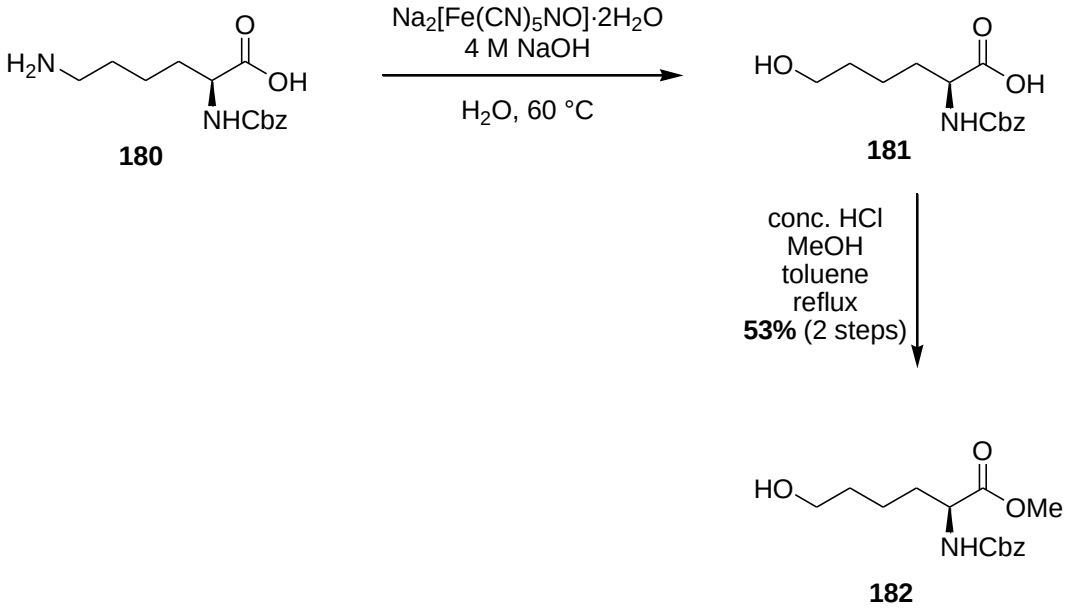
The planned synthesis of **178** involved the generation of a chiral allylic alcohol **185** *via* cross-metathesis and CBS reduction, which could again be subjected to Overman rearrangement to introduce one of the required protected amine groups. Sharpless oxidation followed by esterification would complete the synthesis of **178** by installing the second ester group. The steps proposed to complete the synthesis of the target compound are outlined below in Scheme 2.46. The starting material is Cbz-protected lysine, which is commercially available as a single enantiomer and provides one of the required protected amines and an ester found in the eventual target compound.



Scheme 2.46. Cross-metathesis approach to target 178

The first reaction required for this route was a conversion of Cbz-L-lysine to the corresponding primary alcohol, and this was carried out according to a literature procedure by Bence and Crooks using sodium nitroferricyanide, as shown in Scheme 2.47.[93] The crude product of this reaction was then subjected to esterification

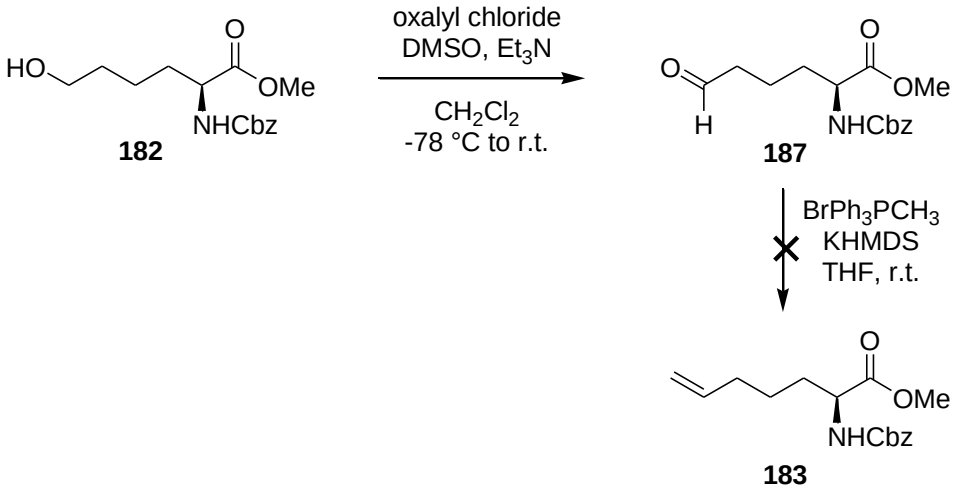
under standard conditions, and the desired methyl ester **182** was isolated in a yield of 53% over the 2 steps.



180 **181** **182**

Scheme 2.47. Synthesis of primary alcohol 182

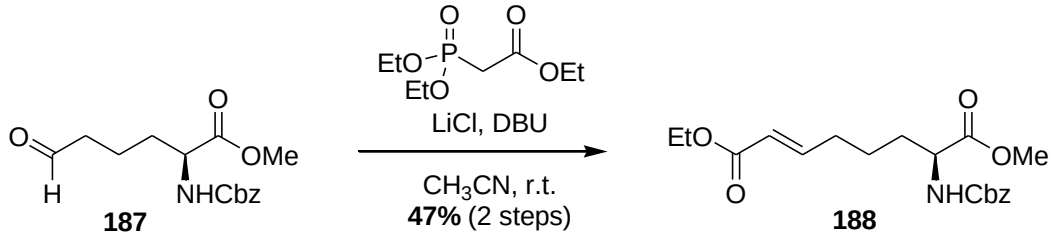
Primary alcohol **182** was treated under standard Swern oxidation conditions, and the crude aldehyde **187** was reacted with a solution of deprotonated methyltriphenylphosphonium bromide (1.5 equivalents), which had been treated with potassium bis(trimethylsilyl)amide (1.3 equivalents).[94] Unfortunately after the olefination reaction mixture had been stirred overnight, none of the desired terminal alkene **183** was isolated (Scheme 2.48).



182 **187** **183**

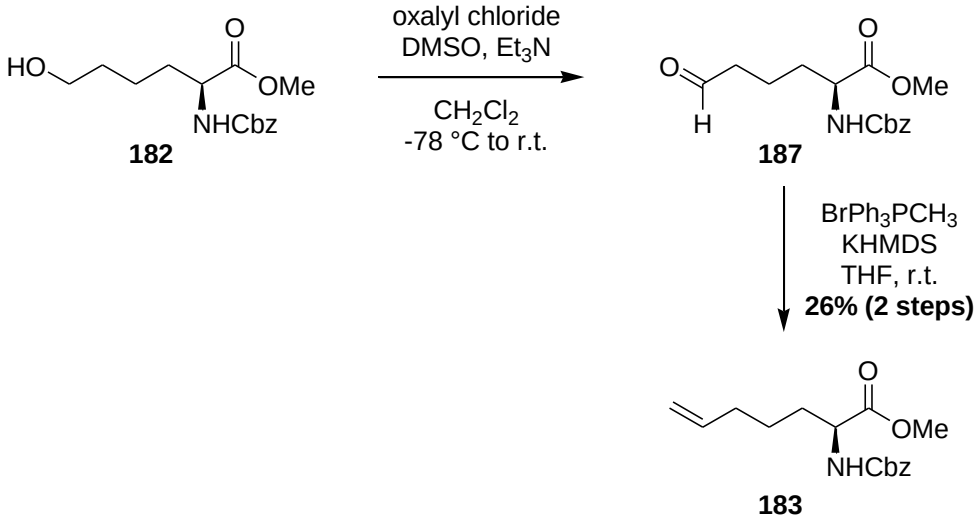
Scheme 2.48. Swern oxidation and methylenation

In order to establish whether this reaction had failed at the Swern oxidation step, or during methylenation, the oxidation was carried out a second time, although this attempt was followed by olefination with triethyl phosphonoacetate under Masamune Roush conditions which had previously been shown to successfully react with crude aldehydes synthesised in the same manner.[58] The test reaction carried out is shown in Scheme 2.49, and successfully generated α,β-unsaturated ester **188** in a yield of 47% over the 2 steps.



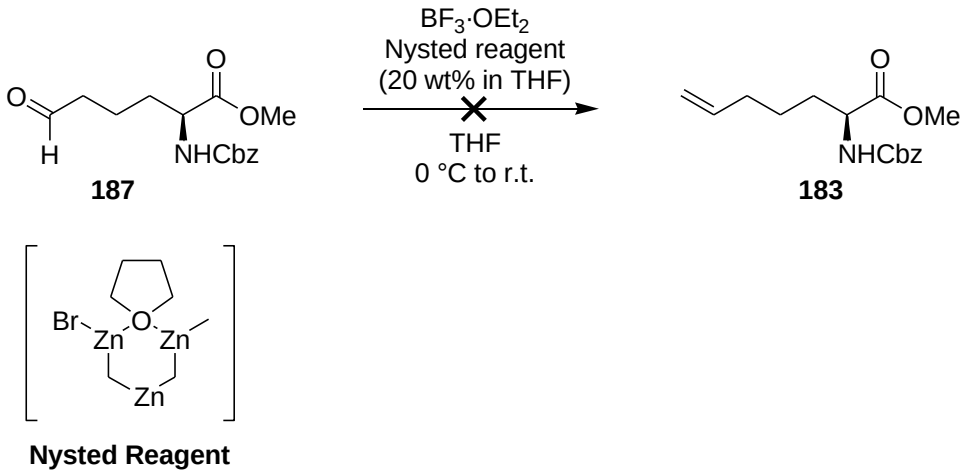
Scheme 2.49. Test Horner-Wadsworth-Emmons olefination

The successful outcome of this HWE olefination confirms that it is possible to generate aldehyde **187** using a Swern oxidation, and it was the methylenation of this intermediate that was proving problematic. The Swern oxidation and methylenation procedure was therefore repeated, increasing the equivalents of phosphonium salt from 1.5 to 5.0 and equivalents of the KHMDS base from 1.3 to 5.0. A fresh bottle of KHMDS was also purchased, although the highest yield of terminal alkene **183** isolated using this was just 26% (Scheme 2.50). Changing the base used to potassium *tert*-butoxide failed to lead to the formation of any of the product.



Scheme 2.50. Improved methylenation of aldehyde 187

An alternative method was then investigated for the desired methylenation reaction. Nysted reagent[95], a zinc-based reagent used for the methylenation of carbonyl compounds, was used to treat aldehyde **187**, which was again generated *via* the Swern oxidation of alcohol **182**. The methylenation was carried out using Nysted reagent in the presence of boron trifluoride diethyl etherate according to a literature procedure by Matsubara *et al.*, as shown in Scheme 2.51.[96] Unfortunately, despite attempting this reaction several times, none of the desired alkene **183** was isolated.



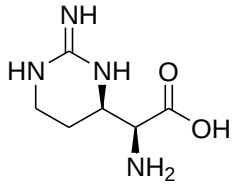
Scheme 2.51. Attempted Nysted methylenation of aldehyde 187

As none of the attempts described above were successful in generating alkene **183** in the high yield required for the eventual synthesis of orthogonally-protected *meso*-diaminopimelic acid **178**, work in this area was discontinued.

2.3 Towards the stereoselective synthesis of capreomycidine

2.3.1 Properties of capreomycidine-containing compounds

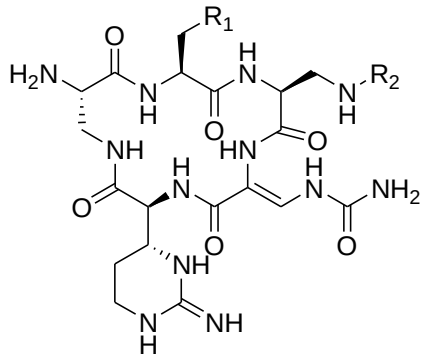
(2*S*,3*R*)-Capreomycidine **189** is a non-proteinogenic α-amino acid with a cyclic structure incorporating a guanidine group (Figure 30).



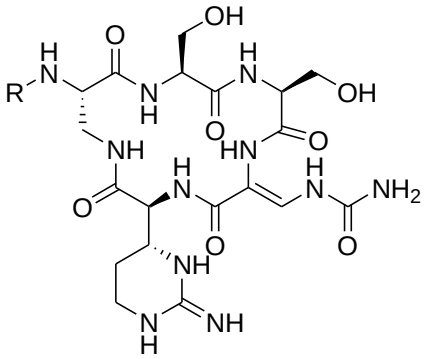
189

Figure 30. (2*S*,3*R*)-Capreomycidine 189

(2*S*,3*R*)-Capreomycidine **189** is a component of the families of capreomycins and the related tuberactinomycins, both of which are cyclic pentapeptides (Figure 31). Capreomycins have been shown to exhibit biological activity against strains of *Mycobacterium tuberculosis* which have proved resistant to other antibiotics.[97] It has been shown that the capreomycidine unit within these structures is necessary for the biological activity exhibited.[98]



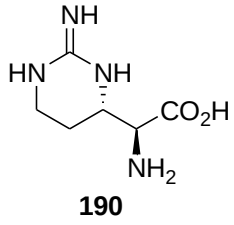
capreomycin IA: R_1=OH, R_2=β-lysine
capreomycin IB: R_1=H, R_2=β-lysine
capreomycin IIA: R_1=OH, R_2=H
capreomycin IIB: R_1=H, R_2=H



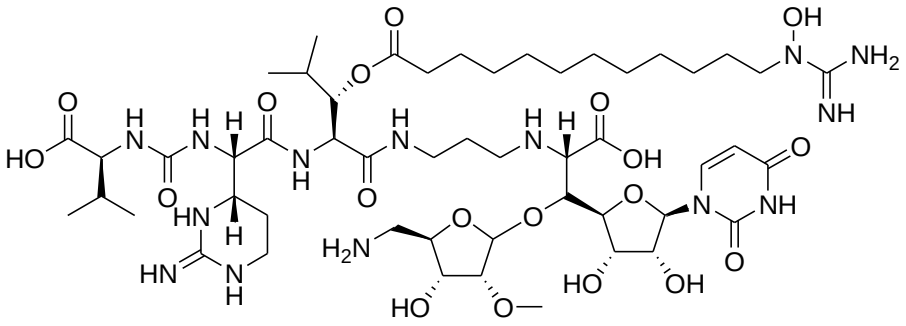
tuberactinomycin N: R=γ-hydroxy-β-lysine
tuberactinomycin O: R=β-lysine

Figure 31. Structures of capreomycins and tuberactinomycins

In addition to the significant biological activity of (2*S*,3*R*)-capreomycidine-containing compounds, its diastereoisomer (2*S*,3*S*)-capreomycidine **190** (also referred to as *epi*-capreomycidine) is also found incorporated into complex structures such as muraymycin A1 (Figure 32) which inhibits a key enzyme involved in peptidoglycan biosynthesis in bacteria.[99]



190



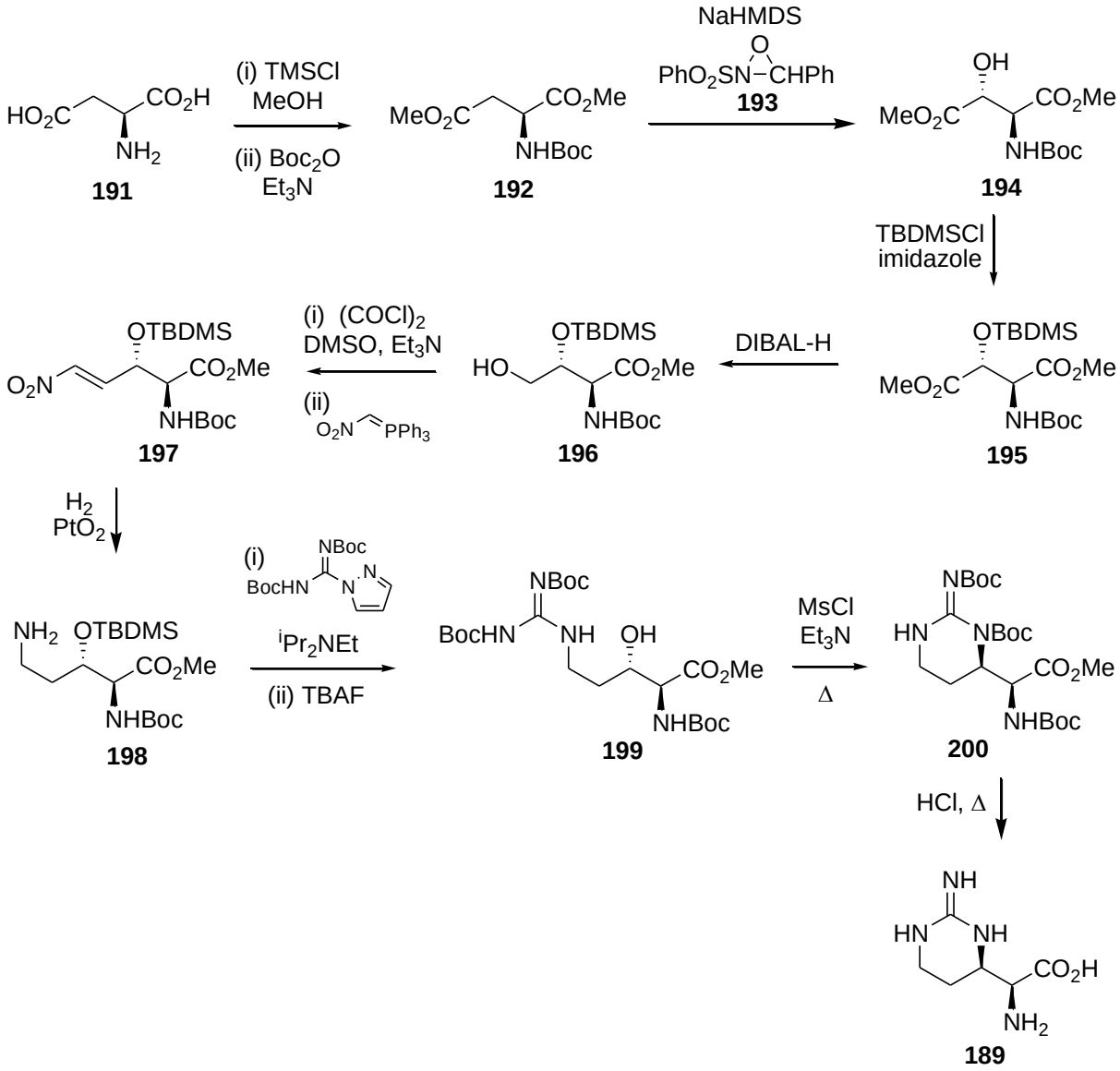
Muraymycin A1

Figure 32. Muraymycin A1, inhibitor of peptidoglycan biosynthesis

Previous approaches to the synthesis of (2*S*,3*R*)-capreomycidine **189** and (2*S*,3*S*)-capreomycidine **190** include the use of kinetic resolution[100] and chiral auxiliaries.[97] The development of a stereoselective, efficient route suitable for the generation of large quantities of these amino acids could aid the generation of a range of compounds with attractive biological activity.

2.3.2 Proposed synthetic route to (2*S*,3*R*)-capreomycidine

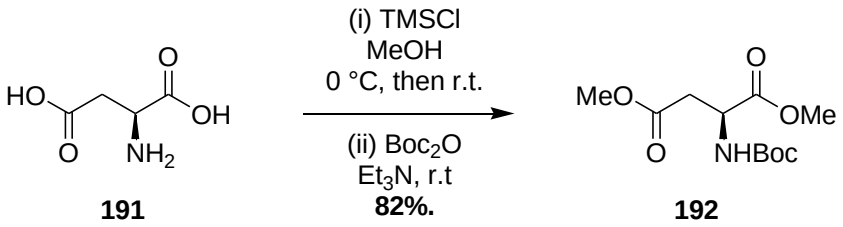
Initial efforts would focus on the synthesis of (2*S*,3*R*)-capreomycidine **189**, using the steps outlined in Scheme 2.52. A key step involved in this route is the stereoselective introduction of a hydroxyl group to an enolate derived from protected L-aspartic acid **192**, which is achieved using Davis' oxaziridine **193**. Protection of this group is followed by reduction of the methyl ester to primary alcohol **196**, which is then subjected to a Swern oxidation/olefination reaction to introduce the required nitro group, which could be converted to amine **198** by hydrogenation. Introduction of a protected guanidine unit, followed by a key ring closure step and deprotection would then generate the desired target compound.



Scheme 2.52. Proposed synthesis of (2*S*,3*R*)-capreomycidine 189

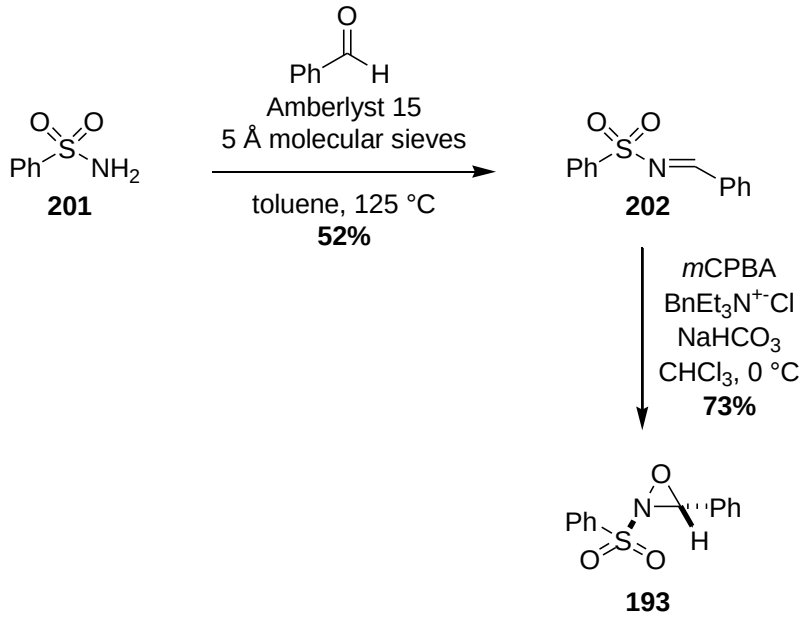
2.3.3 Generation of alcohol *via* stereoselective hydroxylation

The first steps of this proposed route involved the protection of L-aspartic acid **191**. As shown in Scheme 2.53, a single reaction can be used to protect both carboxylic acid groups as methyl esters and the amine with a Boc group. This was carried out according to a procedure previously used within the Sutherland research group and gave the protected product **192** in 82% yield.[101]



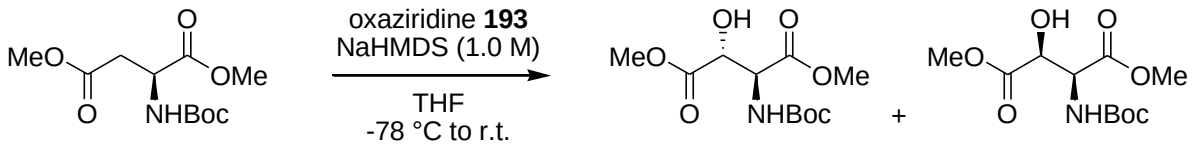
Scheme 2.53. Protection of L-aspartic acid

The next step in the route involved the stereoselective introduction of a hydroxyl group onto the methylene group of diester **192**. This was to be achieved using Davis' oxaziridine **193**, an electrophilic source of oxygen which was first applied to the synthesis of α-hydroxy carbonyl compounds in 1984.[102] The oxaziridine reagent itself was synthesised in 2 steps from commercially available starting materials, as outlined in Scheme 2.54.[103]



Scheme 2.54. Synthesis of Davis' oxaziridine 193

Attempts were then made to carry out the hydroxylation reaction using oxaziridine **193**, as shown in Scheme 2.55. The procedure was carried out according to a literature procedure published by O'Brien and co-workers whereby the enolate derivative of diester **192** was formed by treatment with base before addition of the oxaziridine reagent. The presence of the large Boc group on nitrogen should prevent access of the oxaziridine from the top face, and hence the hydroxyl group should be added in an *anti* relationship with this protected amine.[104] Unfortunately, the first attempts at this reaction failed to yield any of the desired alcohol product ***anti*-194**. Increasing the reaction time from 1 hour to 2 hours led to the isolation of the alcohol product in a low yield of just 9%. However, analysis of the reaction product indicated that the hydroxyl group had the undesired *syn* relationship with the protected amine. The reaction time was then increased further to 6 hours at -78 °C, followed by stirring overnight at room temperature. While this led to the generation of the *anti* product ***anti*-194**, which was isolated in 20% yield, there was still significant formation of the *syn* product, this time formed in 19% yield. Further repeats of this reaction failed to lead to the generation of significant quantities of the desired product, and the ratio of *syn*:*anti* products was inconsistent, varying from 1:1 to approximately 3:1. Therefore, this approach did not allow the generation of significant quantities of the *anti* alcohol product to continue with the investigation of this route.



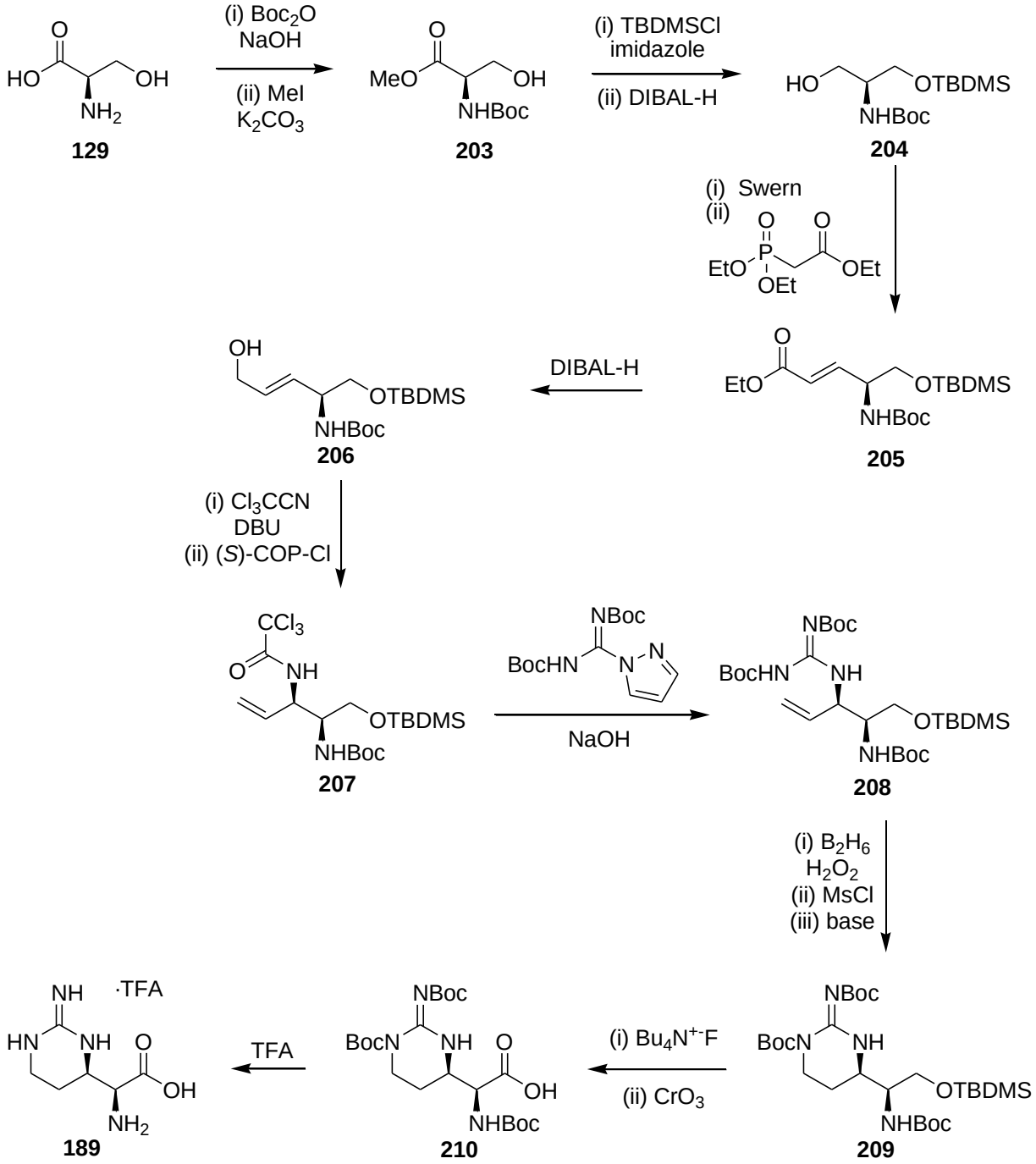
192 ***anti*-194** ***syn*-194**

Scheme 2.55. Stereoselective hydroxylation of 192

The failure of this hydroxylation reaction on a number of attempts led to the proposal of an alternative approach to the synthesis of (2*S*,3*R*)-capreomycidine **189**.

2.3.4 Alternative proposed synthesis of (2*S*,3*R*)-capreomycidine

The alternative route, shown in Scheme 2.56 makes use of the Overman rearrangement of an allylic trichloroacetimidate as a key step. This time, the allylic trichloroacetimidate is derived from a primary allylic alcohol and therefore control of the stereochemical outcome of the rearrangement reaction is necessary. This can be achieved using a chiral Pd catalyst, which will allow the reaction to proceed in an enantioselective manner. A particularly attractive feature of this approach is the use of either (*S*)-(+)-COP-Cl **D** or (*R*)-(-)-COP-Cl **J** as the rearrangement catalyst, which should allow the installation of opposing stereochemistry at C-3 centre, thus meaning that this route has the potential to lead to the eventual synthesis of (2*S*,3*R*)-capreomycidine **189** or (2*S*,3*S*)-capreomycidine **190**. Introduction of the protected guanidine unit, followed by hydroboration and oxidation of the terminal alkene would give a primary alcohol which could undergo mesylation to give the substrate required for a ring closure reaction to form the cyclic amino acid core. Finally, removal of the protecting groups would give the desired capreomycidine target. The starting material required for this route is D-serine **129**, which is again cheap and readily-available and has the required stereochemistry for one of the stereocentres already established.

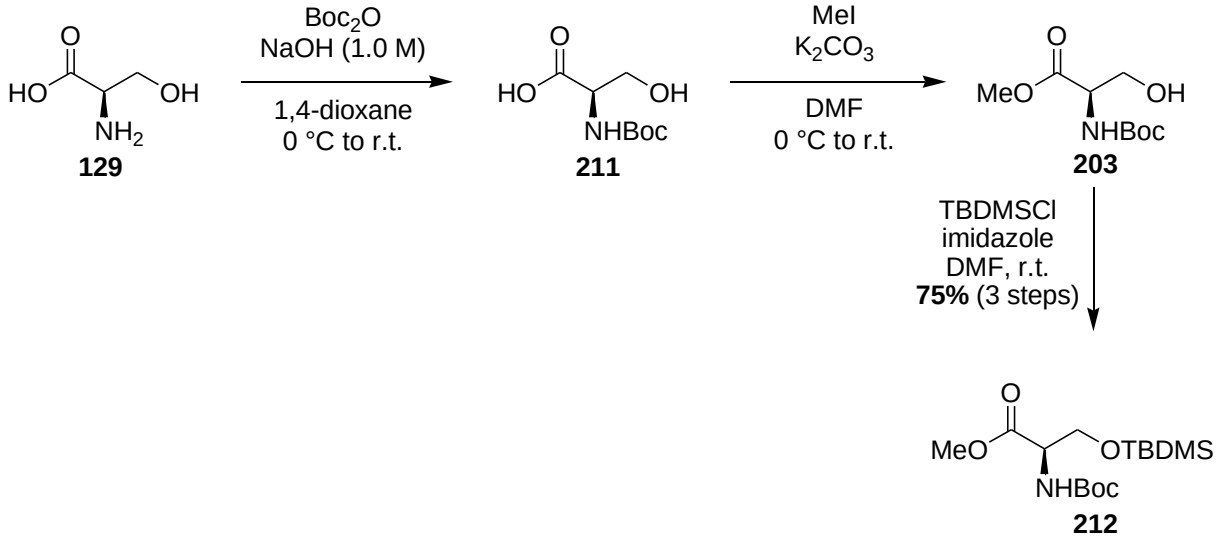


Scheme 2.56. Proposed alternative synthesis of (2*S*,3*R*)-capreomycidine 189

2.3.5 Protection of D-serine

The initial steps of this route are concerned with the complete protection of D-serine **129**. The amine is protected with a Boc group, while the carboxylic acid can be protected as the methyl ester. Finally, the free hydroxyl can be protected as a silyl ether. These protection reactions were carried out in a straightforward

manner using conditions published by Nicolaou and co-workers, as shown below in Scheme 2.57.[105] The required ester **212** was synthesised in a total yield of 75% over the 3 steps. Helpfully, purification was not required until after the silyl protection step, and so this chemistry was able to provide the desired protected derivative of D-serine in a fast, efficient manner.



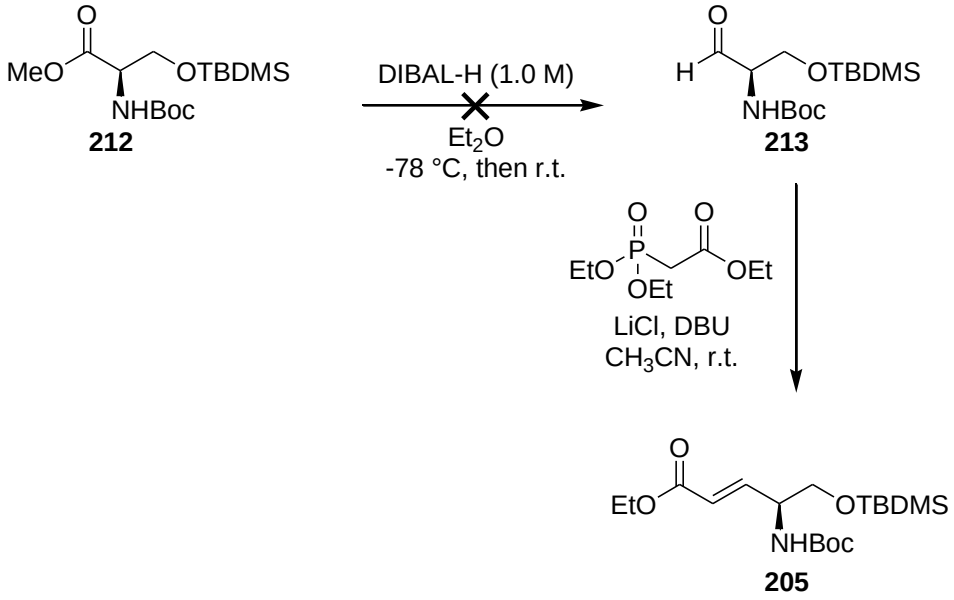
Scheme 2.57. Protection of D-serine

2.3.6 Generation of allylic alcohol intermediate

In order to generate the desired allylic alcohol **206**, an olefination reaction with triethyl phosphonoacetate would be used to install the necessary C=C double bond. To achieve this, conversion of the methyl ester **212** to the corresponding aldehyde was required, and attempts were made to achieve this using diisobutylaluminium hydride. In theory, the use of one equivalent of diisubutylaluminium hydride should cause a single reduction of the methyl ester **212** to the aldehyde **213**.

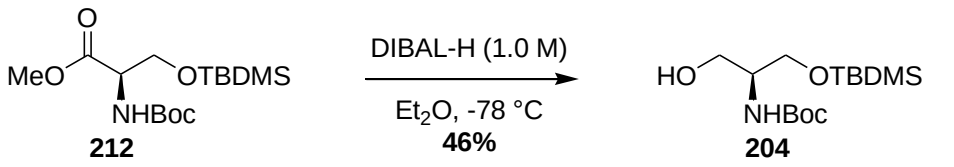
The reduction was attempted using one equivalent of diisobutylaluminium hydride, and the crude product of the reaction was immediately treated with a solution of deprotonated triethyl phosphonoacetate in an attempt to generate the α,β-unsaturated ester **205**, as shown in Scheme 2.58. However upon work-up, none of the desired product was found to have formed, and mostly the methyl ester starting material **212** from the reduction step remained. Several further attempts using this

approach, with the reaction time increased from 1.5 hours to 18 hours, failed to complete the conversion of ester **212** to aldehyde **213** cleanly.



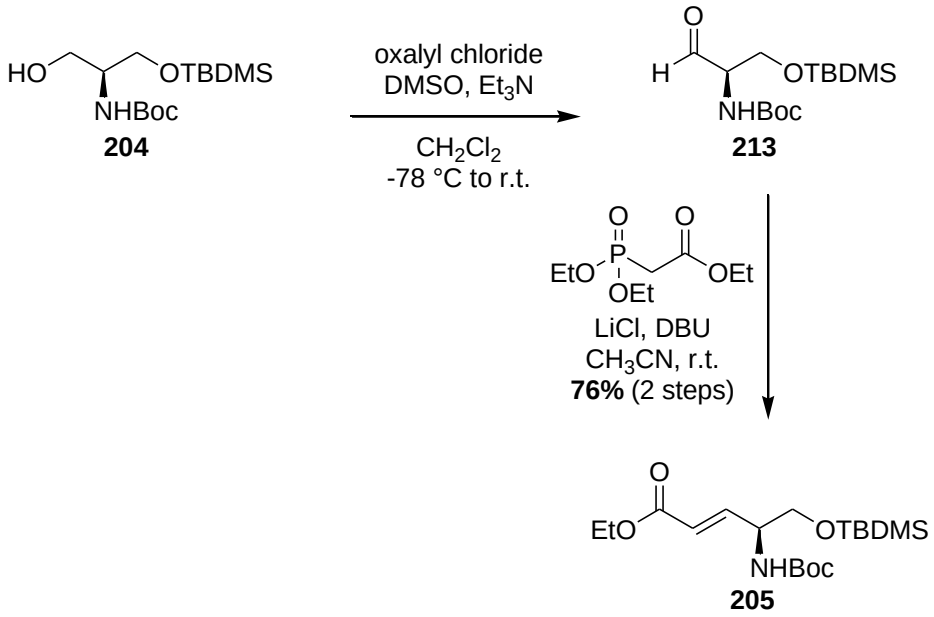
Scheme 2.58. Attempted DIBAL-H reduction and Horner-Wadsworth-Emmons olefination

As the reduction step was failing to generate the desired aldehyde intermediate, it was decided to alter this approach to one which involved chemistry which was well-established within the group for the formation of similar compounds. As shown in Scheme 2.59 below, this required first of all the generation of the primary alcohol **204**, which could then be subjected to a combined Swern oxidation and Horner-Wadsworth-Emmons olefination reaction, as discussed previously within this thesis. Again, the reduction could be achieved using diisobutylaluminium hydride, although this time 2.2 equivalents of this reducing agent was employed to fully reduce the methyl ester **212** to primary alcohol **204**. As expected, this reaction successfully generated the required alcohol **204** in 46% yield.



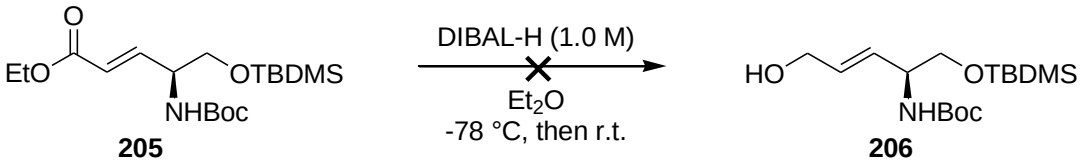
Scheme 2.59. Reduction of methyl ester to primary alcohol

The primary alcohol **204** was then subjected to a Swern oxidation reaction, and the crude product of this was immediately treated with a solution of deprotonated triethyl phosphonoacetate to complete the olefination. This took place under Masamune-Roush conditions, as outlined in Scheme 2.60.[60] The reaction outlined here proved successful, and the desired α,β-unsaturated ester product **205** was formed in 76% yield, with a high *E*/*Z* ratio of 13:1. Helpfully, separation of the two geometric isomers was straightforward *via* silica column chromatography.



Scheme 2.60. Swern oxidation and HWE olefination

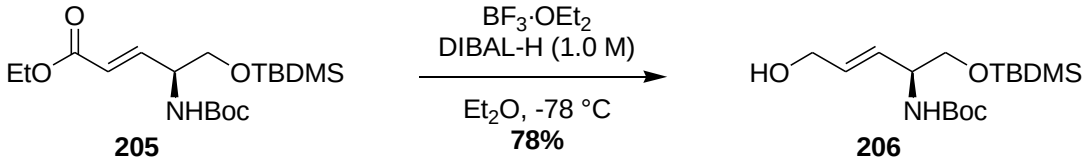
In order to complete the formation of the desired allylic alcohol substrate, a reduction of the ethyl ester **205** was carried out. As diisobutylaluminum hydride had proven to successfully achieve the reduction of esters to primary alcohols within this and previous projects, this was initially selected as the reducing agent, as shown in Scheme 2.61. Unfortunately, none of the desired allylic alcohol product was isolated. It was thought that a 1,4-reduction of the allylic double bond may have been occurring under these conditions.



Scheme 2.61. Attempted reduction to allylic alcohol

This particular issue encountered with the 1,2-reduction of γ-amino-α,β-unsaturated esters of this type has previously been discussed in the literature, and is thought to be attributed to the coordination of diisobutylaluminium to the Boc protecting group and the alkene, increases the susceptibility of the ester to 1,4-reduction. Moriwake *et al*. showed that this undesired reduction can be prevented if the unsaturated ester is treated with a Lewis acid such as boron trifluoride diethyl etherate before addition of diisobutylaluminium hydride. The Boc group's oxygen atom coordinates to the Lewis acid, while diisobutylaluminium hydride can coordinate only to the ester carbonyl group, promoting the desired 1,2-reduction.

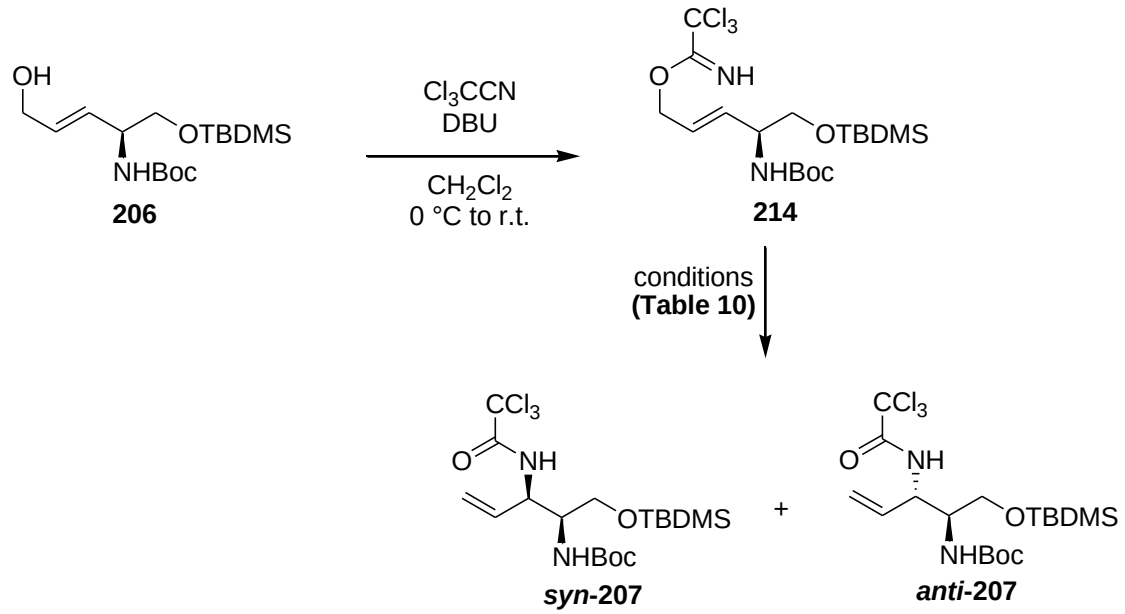
These alternative reaction conditions were therefore applied to the formation of allylic alcohol **206**, as shown below in Scheme 2.62, and this time successfully generated the desired product in 78% yield.[106]



Scheme 2.62. Improved reduction to allylic alcohol

2.3.7 Investigation of Overman rearrangement conditions

With the allylic alcohol in hand, it was then possible to investigate the stereoselective Overman rearrangement step. As shown in Scheme 2.63, the allylic trichloroacetimidate formation step was carried out as previously described, although as a primary alcohol was involved this time, the reaction time required was just 5 hours.



Scheme 2.63. Synthesis and Overman rearrangement of allylic trichloroacetimidate 214

From the allylic trichloroacetimidate **214**, a range of reaction conditions were used to promote the Overman rearrangement and both product yield and ratio of *syn*:*anti*-product diastereoisomers were noted (Table 11).

Initially, (*S*)-(+)-COP-Cl was used as, according to literature precedent, this was expected to furnish the desired product diastereoisomer ***syn*-207**. For a thorough investigation of this reaction, the same rearrangement was carried out this time in the presence of (*R*)-(-)-COP-Cl in an attempt to install the opposite stereochemistry, henceforth generating the *anti*-product diastereomer ***anti*-207**. However, upon comparison of the ^{1}H NMR spectra of the major products of both of these reactions, it was discovered that the same product diastereomer had preferentially formed in the presence of both of these catalysts, which was an unexpected observation.

The rearrangement was also carried out using the achiral Pd(II) catalyst, $PdCl_2(CH_3CN)_2$ and again, the same product diastereoisomer was formed in preference. The rearrangement was also carried out under thermal conditions, heating at 140 °C in *p*-xylene with a small amount of potassium carbonate present. Little to no stereoselectivity for the rearrangement reaction under these conditions should be observed, and indeed a 1:1 ratio of both diastereomers was detected by ^{1}H NMR spectroscopic analysis. Separation of these diastereoisomers was possible

by silica column chromatography, and gave individual samples of both products. Further analysis and comparison to literature data confirmed that the diastereoisomer formed preferentially in each of the metal-catalysed reactions was in fact the *anti*-diastereoisomer.[41]

Conditions	Catalyst loading	Time (h)	Yield (%)	*anti* : *syn*
(*S*)-(+)-COP-Cl, CH_2Cl_2, 38 °C	8 mol%	161	76	4.7 : 1
(*R*)-(-)-COP-Cl, CH_2Cl_2, 38 °C	9 mol%	162	58	6 : 1
K_2CO_3, *p*-xylene, 140 °C	N/A	140	67	1 : 1
$PdCl_2(CH_3CN)_2$, CH_2Cl_2, 38 °C	10 mol%	24	53	11 : 1

Table 11. Results of Overman rearrangement study

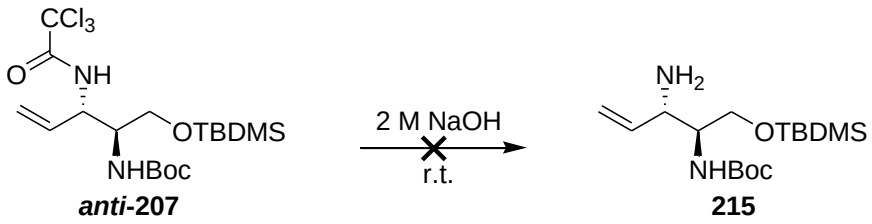
These unexpected results suggest that some factor is interfering with the expected progression of these rearrangement reactions, as it had been predicted that the (*S*)-(+)-COP-Cl catalyst **D** and (*R*)-(-)-COP-Cl catalyst **J** should be selective for the formation of opposite product diastereoisomers, which is not the observed outcome. The levels of diastereoselectivity are not as high as may have been anticipated, and also very long reaction times were required in the presence of these catalysts. It was thought that the presence of the two bulky protecting groups on the rearrangement substrate **214** may have hindered the approach of these large catalysts in the expected manner, thus leading to the observed stereochemical outcome in the rearrangement step.

At this stage, it was decided to take forward the ***anti*-207** and continue with the proposed route in an attempt to develop the methodology for the synthesis of (2*S*,3*S*)-capreomycidine **190**, which itself is found in as a component of many compounds which exhibit antibacterial activity. From the results of this reaction study shown in Table 10, it can be seen that while the (*S*)-(+)-COP-Cl **D** catalysed reaction gives the overall highest product yield, the highest diastereomeric ratio product is achieved when the simple $PdCl_2(CH_3CN)_2$ catalyst is utilised. The reaction time is also significantly lower here compared to when the larger chiral catalysts are used, and so when this rearrangement reaction was carried out on a larger scale, this catalyst was selected to achieve the desired product efficiently.

Formation of compounds such as **207** *via* Overman rearrangement chemistry has previously been discussed in the literature by Gonda *et al*.[41] Selectivity for the formation of the *anti* product diastereoisomer in the presence of $PdCl_2(CH_3CN)_2$ can be explained by co-ordination of palladium(II) to the amine nitrogen atom which promotes the progress of the rearrangement *via* the transition state shown in Figure 8 in chapter 1.2.

2.3.8 Removal of trichloroacetyl group

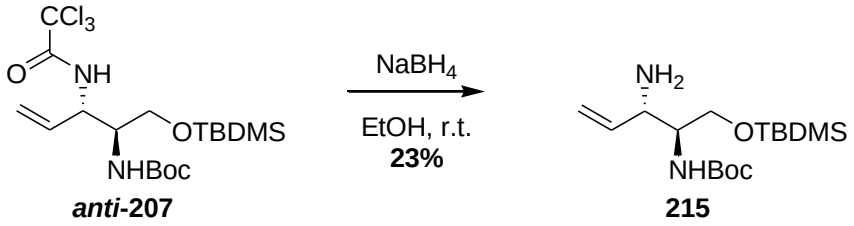
In order to introduce the required protected guanidine unit, hydrolysis of the trichloroacetyl while leaving the two other protecting groups intact was necessary. This was initially attempted using sodium hydroxide, as shown in Scheme 2.64. Unfortunately, the hydrolysis of the trichloroacetamide failed to proceed at room temperature after 4 days, and the unreacted starting material was recovered. The reaction was repeated, this time with heating to 65 °C although again no reaction occurred.



***anti*-207** **215**

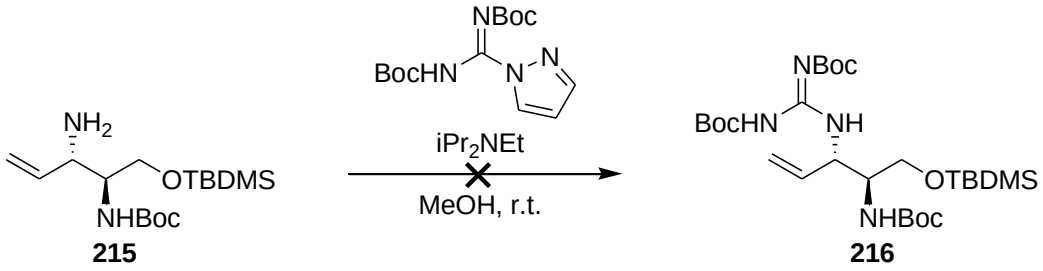
Scheme 2.64. Attempted hydrolysis of trichloroacetyl group

An alternative approach was then adopted for the removal of the trichloroacetamide group, this time by reduction. Sodium borohydride was employed, as shown in Scheme 2.65. These conditions were expected to readily generate amine **215**, although the reduction proved to be slow, and required stirring for 5 days. Despite the long reaction time, the product yield was relatively low at 23%.



Scheme 2.65. Removal of trichloroacetyl group by reduction

As small quantities of the amine **215** were generated *via* this method, only a preliminary investigation into the introduction of the protected guanidine unit was conducted, implementing reaction conditions used within the group previously as outlined in Scheme 2.66.[107,108,109] Unfortunately, none of the desired product was detected.

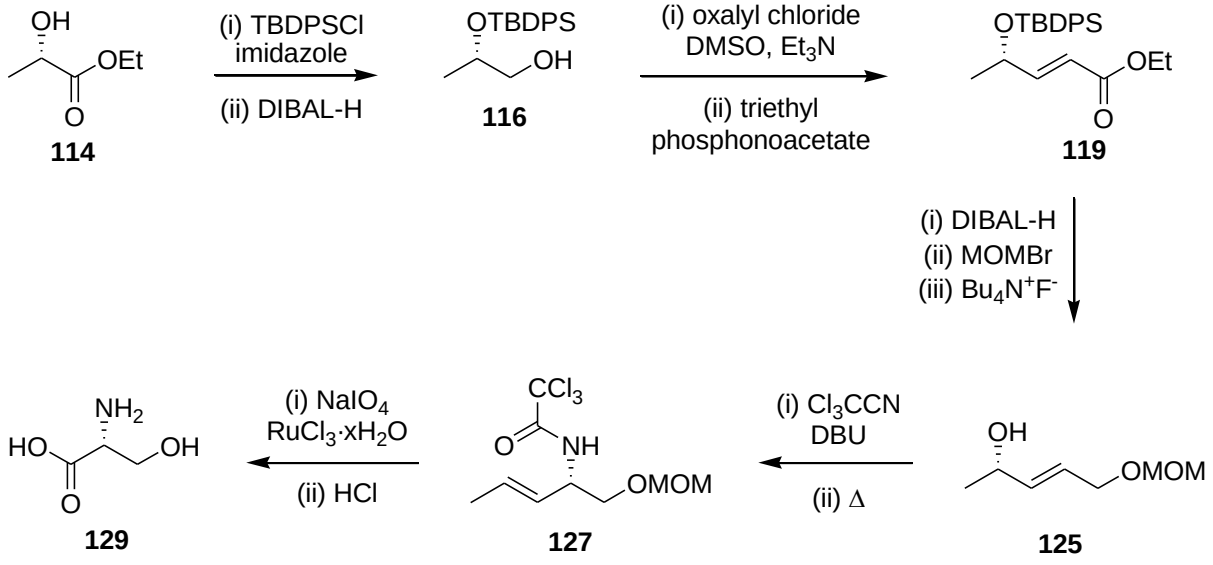


Scheme 2.66. Attempted introduction of guanidine unit

At this stage, time restrictions unfortunately dictated that further development of this synthetic route is not currently possible. However, successful generation of the late-stage amine intermediate **215** was achieved and therefore, further investigation of this route would be desirable. The use of a stronger reducing agent could improve the formation of the required amine **215** and as the chemistry required for introduction of the Boc-protected guanidine unit is known within the literature, so would be expected to successfully generate the intermediate required for the ring-closing step. Following this, relatively straightforward chemistry can be applied to complete the formation of the desired (2*S*,3*S*)-capreomycidine target **190** as described in Scheme 2.56.

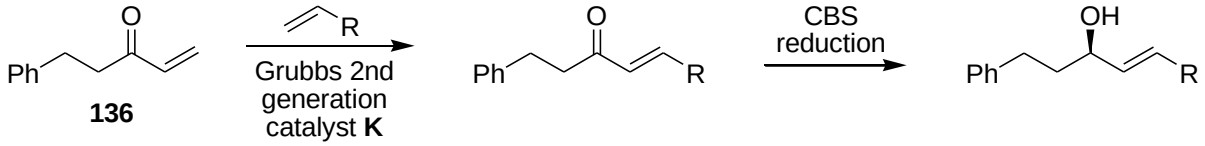
2.4 Conclusions

During the course of this research project, new methodology has been developed for the synthesis of chiral allylic alcohols which could be utilised in the generation of α-amino acid targets. Initial studies investigated the use of organophosphorus olefination reagents for allylic alcohol generation and while the scope of this methodology was limited, an investigation of Overman rearrangement conditions was conducted to determine the optimum method for the conversion of secondary allylic alcohol **125** to allylic trichloroacetamide **127**. α-Amino acid target D-serine **129** was then formed by oxidative cleavage of the double bond, followed by hydrolysis of the trichloroacetamide under acidic conditions (Scheme 2.67).



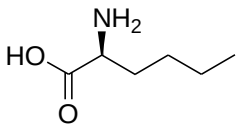
Scheme 2.67. Synthesis of D-serine *via* organophosphorus olefination chemistry

An alternative approach was then investigated for the synthesis of chiral allylic alcohols which has improved flexibility for the generation of a range of alcohols with various side chains in place. This involved the cross-metathesis of enone **136** with terminal alkene partners, followed by asymmetric CBS-catalysed ketone reduction (Scheme 2.68).

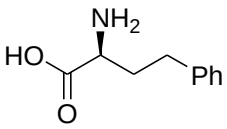


Scheme 2.68. Alternative methodology developed for chiral allylic alcohol generation

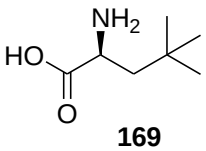
Again, the Overman rearrangement was employed to generate allylic trichloroacetamides which was followed by oxidative cleavage and hydrolysis as shown in Scheme 2.67 to furnished α-amino acid targets **167**–**170** and **172** in a highly efficient manner, with good product yields encountered during the key steps of the route. Importantly, the use of Overman rearrangement chemistry allows the levels of enantiomeric excess established during CBS reduction to be transferred directly to the allylic trichloroacetamides, and hence to the eventual α-amino acid targets.



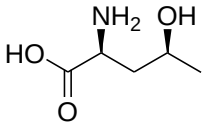
167



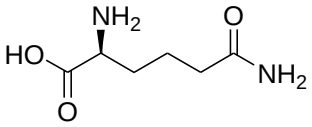
168



169

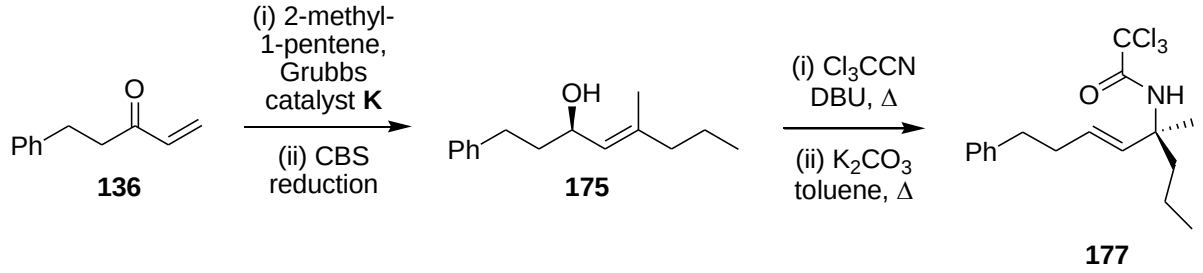


170



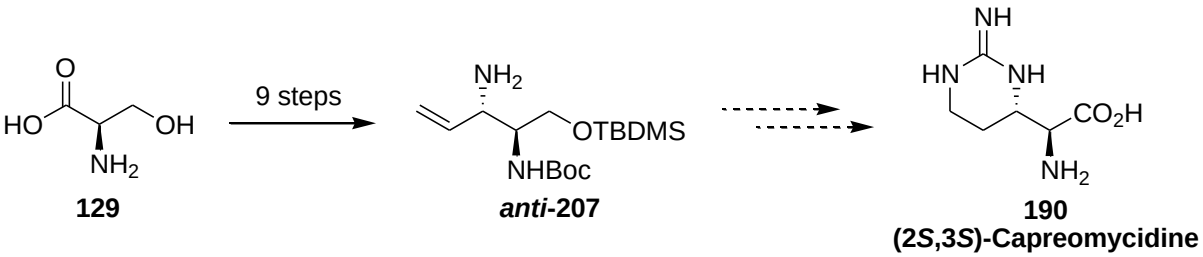
172

Attempts were then made to apply the successfully developed methodology to the generation of some more complex α-amino acid targets, including a target bearing quaternary-substitution on the α-carbon atom, formed *via* a trisubstituted allylic alcohol **175** which was again generated from a cross-metathesis reaction with enone **136**, followed by CBS reduction. Initial results indicated that installation of the required quaternary centre is possible using a thermal Overman rearrangement reaction (Scheme 2.69).



Scheme 2.69. Introduction of quaternary centre *via* Overman rearrangment

Finally, a late-stage intermediate ***anti*-207** which can be applied to the eventual synthesis of (2*S*,3*S*)-capreomycidine **190** was generated using Horner-Wadsworth-Emmons olefination chemistry to form the double bond, and a metal-catalysed Overman rearrangement to introduce the trichloroacetamide functionality in a diastereoselective manner. The intermediate was successfully formed in 9 steps from D-serine, again encountering high yields in many of the reactions required (Scheme 2.10). Future work conducted in this area should allow the generation of the desired (2*S*,3*S*)-capreomycidine target **190** following the steps outlined in Scheme 2.56.



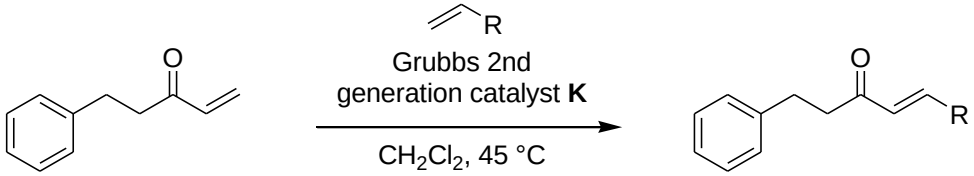
Scheme 2.70. Generation of intermediate *anti*-207

3.0 Experimental

General Experimental Information

Reactions were carried out in oven- or flame-dried glassware under an argon atmosphere unless otherwise stated. Starting materials and reagents were obtained from commercial sources and used as received. Lithium chloride was oven-dried for at least 12 hours prior to use. Dry solvents were purified using a PureSolv 500 MD solvent purification system. 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 potassium permanganate. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in parts per million relative to tetramethylsilane (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer or using sodium chloride plates on a JASCO FTIR 410 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an AA series Automatic polarimeter. $[\alpha]_D$ values are given in units 10^{-1} $degcm^2g^{-1}$. Chiral HPLC was performed on a Hewlett Packard Agilent 1100 Series instrument and was calibrated with the appropriate racemic sample mixture.

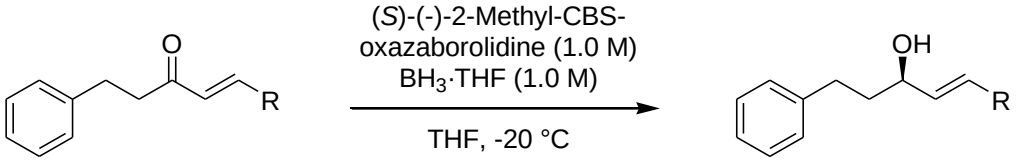
General Procedure 1: Cross-metathesis of 5-phenylpent-1-en-3-one 114 with terminal alkene partners



The terminal alkene partner was added to a stirred solution of 5-phenylpent-1-en-3-one **114** in dichloromethane, followed by a solution of Grubbs 2nd generation catalyst (4 mol%) in dichloromethane. The resulting reaction mixture was heated to 45 °C and allowed to stir under reflux until complete consumption of 5-phenylpent-

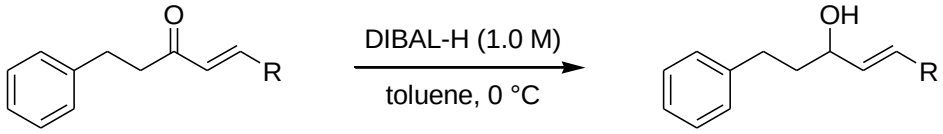
1-en-3-one **114** was detected by TLC analysis. The reaction mixture was then allowed to cool to room temperature and concentrated *in vacuo*. Purification was carried out by silica column chromatography to give the desired enone product.

General Procedure 2: Enantioselective CBS oxazaborolidine-catalysed reduction of enones to allylic alcohols



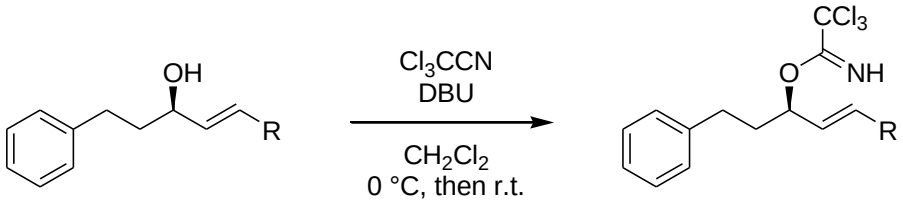
A stirred solution of the enone intermediate in tetrahydrofuran was cooled to -20 °C before (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene) was added, followed by borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran). The resulting reaction mixture was then stirred at -20 °C for 2.5 h before being quenched by the slow addition of methanol (15 mL). Once gas evolution ceased, the mixture was concentrated *in vacuo* and then purified by silica column chromatography to give the desired allylic alcohol product.

General Procedure 3: Reduction of enones to allylic alcohols using diisobutylaluminium hydride



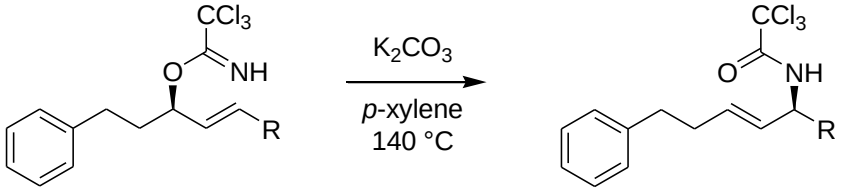
A stirred solution of the enone (1.0 eq) in toluene was cooled to 0 °C before diisobutylaluminium hydride solution (1.0 M in hexanes, 1.5 eq) was added dropwise. The resulting reaction mixture was allowed to stir at 0 °C for 3 h before being quenched by the addition of methanol (20 mL) and filtered through a pad of Celite®, which was washed with warm methanol (50 mL). The combined filtrates were concentrated *in vacuo*, and purification was carried out by silica column chromatography to give the desired allylic alcohol product.

General Procedure 4: Conversion of allylic alcohol to allylic trichloroacetimidate



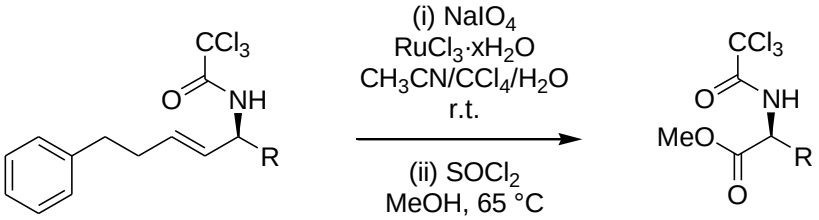
A stirred solution of the allylic alcohol (1.0 eq) in dichloromethane was cooled to 0 °C before 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 eq) was added, followed by trichloroacetonitrile (1.5 eq). The reaction mixture was allowed to stir at 0 °C for 0.2 h, and then at room temperature for 24 h before being filtered through a short plug of silica, which was washed with diethyl ether (50 mL). The combined filtrates were concentrated *in vacuo* to give the desired crude allylic trichloroacetimidate, which was used without further purification.

General Procedure 5: Overman rearrangement of allylic trichloroacetimidate to allylic trichloroacetamide (thermal conditions)



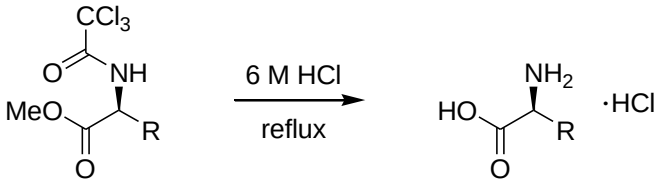
The crude allylic trichloroacetimidate (1.0 eq) was dissolved in *p*-xylene, and potassium carbonate (0.003 g per mL of solvent) was added. The reaction mixture was heated to 140 °C and stirred under reflux overnight before being allowed to cool to room temperature and then concentrated *in vacuo*. Purification was carried out by silica column chromatography to give the desired allylic trichloroacetamide product.

General Procedure 6: Oxidative cleavage of allylic double bond and esterification



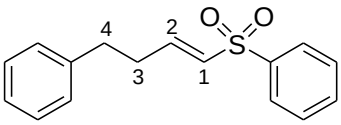
The allylic trichloroacetamide (1.0 eq) was dissolved in acetonitrile and carbon tetrachloride and to this stirred solution, sodium periodate (4.1 eq, dissolved in water) was added. Ruthenium(III) chloride hydrate (0.1 eq) was then added, and the reaction mixture was stirred at room temperature for 22 h before being partitioned between water (100 mL) and dichloromethane (100 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was then dissolved in methanol, and the solution cooled to 0 °C before thionyl chloride (5.0 eq) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 0.1 h and then heated to 65 °C and stirred under reflux for 22 h before being allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned between a saturated aqueous solution of sodium hydrogen carbonate (30 mL) and ethyl acetate (30 mL) and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography to give the desired methyl ester.

General Procedure 7: Deprotection to generate α-amino acid targets



The methyl ester (1.0 eq) was dissolved in 6 M hydrochloric acid, and the resulting reaction mixture was heated under reflux overnight before being allowed to cool to room temperature. Water (20 mL) and diethyl ether (30 mL) were added, the layers were separated, and the aqueous phase was concentrated *in vacuo* to give the desired α-amino acid product as the hydrochloride salt.

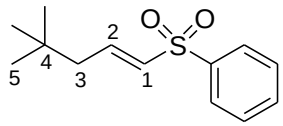
(*E*)-4-Phenyl-1-(phenylsulfonyl)-1-butene[110]



103

Grubbs 2nd generation catalyst **K** (0.025 g, 0.03 mmol, dissolved in 5 mL of dichloromethane) was added to a stirred solution of 4-phenyl-1-butene **101** (0.089 mL, 0.59 mmol) and phenyl vinyl sulfone **102** (0.100 g, 0.59 mmol) in dichloromethane (15 mL). The reaction mixture was heated to 45 °C and stirred under reflux for 20 h before further 4-phenyl-1-butene (0.018 mL, 0.12 mmol) and Grubbs 2nd generation catalyst **K** (0.005 g, 0.006 mmol, dissolved in 2 mL of dichloromethane) were added. The reaction mixture was stirred under reflux for a further 2.5 h before being allowed to cool to room temperature and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 7:43 diethyl ether/petroleum ether gave (*E*)-4-phenyl-1-(phenylsulfonyl)-1-butene **103** as a pale yellow oil (0.124 g, 77%). ν_{max}/cm^{-1} (NaCl) 3060 (CH), 3027 (CH), 2926 (CH), 1626 (C=C), 1496, 1446, 1317, 1146, 1087, 822, 750; δ_H (400 MHz, $CDCl_3$) 2.52–2.60 (2H, m, 3-H_2), 2.77 (2H, t, *J* 7.6 Hz, 4-H_2), 6.29 (1H, dt, *J* 15.0, 1.5 Hz, 1-H), 7.01 (1H, dt, *J* 15.0, 6.9 Hz, 2-H), 7.09–7.14 (2H, m, 2 × ArH), 7.15–7.21 (1H, m, ArH), 7.22–7.28 (2H, m, 2 × ArH), 7.49–7.56 (2H, m, 2 × ArH), 7.58–7.64 (1H, m, ArH), 7.79–7.84 (2H, m, 2 × ArH); δ_C (100 MHz, $CDCl_3$) 33.3 (CH_2), 34.0 (CH_2), 126.5 (CH), 127.7 (2 × CH), 128.5 (2 × CH), 128.7 (2 × CH), 129.3 (2 × CH), 131.2 (CH), 133.4 (CH), 140.1 (C), 140.7 (C), 146.1 (CH); *m/z* (CI) 273.0952 (MH^+. $C_{16}H_{17}O_2S$ requires 273.0949), 259 (11%), 245 (5), 183 (10), 130 (13), 91 (10), 69 (9).

(*E*)-4,4-Dimethyl-1-(phenylsulfonyl)-1-pentene

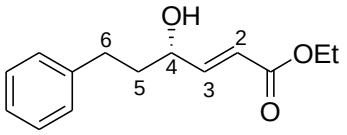


110

Grubbs 2nd generation catalyst **K** (0.200 g, 0.24 mmol, dissolved in 20 mL of dichloromethane) was added to a stirred solution of 4,4-dimethyl-1-pentene **109** (1.17 mL, 8.15 mmol) and phenyl vinyl sulfone **102** (2.74 g, 16.3 mmol) in

dichloromethane (100 mL). The reaction mixture was heated to 45 °C and allowed to stir under reflux for 23 h. Further Grubbs 2nd generation catalyst **K** (0.143 g, 0.17 mmol, dissolved in 10 mL of dichloromethane) was then added and the reaction was again stirred under reflux for 27 h before being concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:7 diethyl ether/petroleum ether gave (*E*)-4,4-dimethyl-1-(phenylsulfonyl)-1-pentene **110** as a colourless oil (1.31 g, 67%). ν_{max}/cm^{-1} (NaCl) 3062 (CH), 2958 (CH), 1631 (C=C), 1475, 1446, 1367, 1317, 1146, 1087, 976, 822, 753 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 2.11 (2H, dd, *J* 7.9, 1.2 Hz, 3-H_2), 6.30 (1H, dt, *J* 15.0, 1.2 Hz, 1-H), 7.01 (1H, dt, *J* 15.0, 7.9 Hz, 2-H), 7.50–7.57 (2H, m, 2 × ArH), 7.58–7.64 (1H, m, ArH), 7.85–7.91 (2H, m, 2 × ArH); δ_C (100 MHz, $CDCl_3$) 29.3 (3 × CH_3), 31.6 (C), 45.7 (CH_2), 127.5 (2 × CH), 129.2 (2 × CH), 132.0 (CH), 133.2 (CH), 140.7 (C), 144.9 (CH); *m/z* (CI) 239.1104 (MH^+. $C_{13}H_{19}O_2S$ requires 239.1106), 69 (6%).

Ethyl (2*E*,4*S*)-4-hydroxy-6-phenylhex-2-enoate

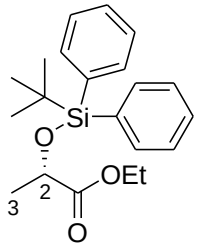


113

(*E*)-4-Phenyl-1-(phenylsulfonyl)-1-butene **103** (0.100 g, 0.37 mmol) was dissolved in *tert*-butanol (2 mL) and water (2 mL) and to the stirred solution, AD-mix-α (1.47 g) was added, followed by methanesulfonamide (0.044 g, 0.46 mmol). The reaction mixture was stirred at room temperature, in air, for 50 h and then water (25 mL) and dichloromethane (25 mL) were added to the flask. The resulting biphasic mixture was stirred at room temperature for 0.5 h and then the layers were separated. The organic layers were further extracted using dichloromethane (4 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the desired aldehyde intermediate. Meanwhile, in a separate flask, sodium hydride (60% dispersion in mineral oil, 0.015 g, 0.37 mmol) was added to a stirred solution of triethyl phosphonoacetate (0.080 mL, 0.40 mmol) in tetrahydrofuran (5 mL). The mixture was stirred at room temperature for 0.5 h and then the crude aldehyde (dissolved in 2 mL of tetrahydrofuran) was added. The

resulting reaction mixture was then allowed to stir at room temperature for 67 h before being partitioned between water (20 mL) and diethyl ether (20 mL). The layers were separated and the organic layers were further extracted using diethyl ether (3 × 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 3:17 ethyl acetate/petroleum ether gave ethyl (2*E*,4*S*)-4-hydroxy-6-phenylhex-2-enoate **113** as a colourless oil (0.021 g, 24%). ν_{max}/cm^{-1} (NaCl) 3448 (OH), 2928 (CH), 1717 (CO), 1656 (C=C), 1454, 1369, 1306, 1179, 1034, 981, 750; $[\alpha]_D^{21}$ + 23.8 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.72–1.81 (1H, br s, OH), 1.83–1.99 (2H, m, 5-H_2), 2.68–2.83 (2H, m, 6-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.28–4.37 (1H, m, 4-H), 6.05 (1H, dd, *J* 15.7, 1.6 Hz, 2-H), 6.96 (1H, dd, *J* 15.7, 4.9 Hz, 3-H), 7.17–7.33 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 31.4 (CH_2), 38.0 (CH_2), 60.5 (CH_2), 70.3 (CH), 120.4 (CH), 126.1 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 141.2 (C), 149.8 (CH), 166.5 (C); *m/z* (CI) 235.1337 (MH^+. $C_{14}H_{19}O_3$ requires 235.1334), 235 (MH^+, 100%), 217 (55), 189 (64), 171 (8), 143 (25), 131 (15), 105 (15), 91 (39), 73 (5).

Ethyl (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propanoate[111]

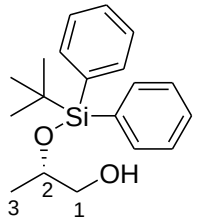


115

To a stirred solution of ethyl L-lactate **114** (4.83 mL, 42.3 mmol) in tetrahydrofuran (50 mL), imidazole (4.32 g, 63.5 mmol) was added, followed by *tert*-butyldiphenylchlorosilane (13.0 mL, 50.7 mmol), upon which a white precipitate formed. The reaction mixture was allowed to stir at room temperature for 22 h before being filtered, and the solid washed with ethyl acetate (20 mL). The combined filtrates were concentrated *in vacuo* and the resulting residue was partitioned between water (200 mL) and ethyl acetate (200 mL). The layers were separated and the organic phase was washed further with water (2 × 150 mL)

before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave ethyl (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propanoate **115** as a colourless oil (12.28 g, 81%). ν_{max}/cm^{-1} (NaCl) 2933 (CH), 2858 (CH), 1753 (CO), 1428, 1137, 703; $[\alpha]_D^{25}$ -42.6 (*c* 1.0, $CHCl_3$) (lit.[111] $[\alpha]_D$ -41.1 (*c* 2.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.09 (9H, s, $SiC(CH_3)_3$), 1.15 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.37 (3H, d, *J* 6.7 Hz, 3-H_3), 4.02 (2H, qd, *J* 7.1, 1.0 Hz, OCH_2CH_3), 4.26 (1H, q, *J* 6.7 Hz, 2-H), 7.32–7.47 (6H, m, 6 × ArH), 7.62–7.71 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 19.2 (C), 21.3 (CH_3), 26.8 (3 × CH_3), 60.6 (CH_2), 68.9 (CH), 127.5 (2 × CH), 127.6 (2 × CH), 129.7 (2 × CH), 133.2 (C), 133.6 (C), 135.7 (2 × CH), 135.9 (2 × CH), 173.8 (C); *m*/*z* (CI) 299 (MH^+-$C(CH_3)_3$, 24%), 279 (100), 251 (15), 69 (7).

(2*S*)-2-(*tert*-butyldiphenylsilyloxy)propan-1-ol[56]

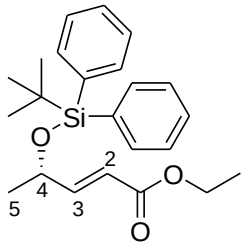


116

Borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 24.0 mL, 24.0 mmol) was slowly added to a stirred solution of ethyl (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propanoate **115** (3.80 g, 10.7 mmol) in tetrahydrofuran (15 mL). The reaction mixture was heated to 65 °C and stirred under reflux for 22 h before being allowed to cool to room temperature. Further borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 3.20 mL, 3.20 mmol) was added, and the reaction was heated to 65 °C and stirred under reflux for 5 h before being allowed to cool to room temperature and quenched by the addition of water (30 mL). The tetrahydrofuran was removed *in vacuo*, and the organic layers were extracted using dichloromethane (3 × 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propan-1-ol **116** as a pale yellow oil (2.82 g, 84%). ν_{max}/cm^{-1} (NaCl) 3386 (OH), 2931 (CH), 2858 (CH), 1427, 1111, 1047, 702; $[\alpha]_D^{25}$ +26.7 (*c* 1.0,

$CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.3 Hz, 3-H_3), 1.07 (9H, s, $SiC(CH_3)_3$), 1.92 (1H, t, *J* 6.4 Hz, OH), 3.39–3.46 (1H, m, 1-*H*H), 3.48–3.55 (1H, m, 1-H*H*), 3.91–4.00 (1H, m, 2-H), 7.35–7.47 (6H, m, 6 × ArH), 7.65–7.71 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 19.6 (CH_3), 27.0 (3 × CH_3), 68.2 (CH_2), 70.2 (CH), 127.6 (2 × CH), 127.8 (2 × CH), 129.7 (CH), 129.8 (CH), 133.8 (C), 134.0 (C), 135.7 (2 × CH), 135.8 (2 × CH); *m*/*z* (CI) 257 (MH^+-$C(CH_3)_3$, 18%), 237 (100), 71 (7).

Ethyl (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)pent-2-enoate[112]

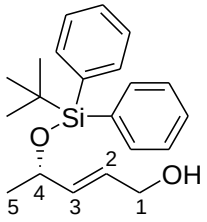


119

A stirred solution of oxalyl chloride (0.65 mL, 7.63 mmol) in dichloromethane (55 mL) was cooled to -78 °C before dimethylsulfoxide (1.10 mL, 15.5 mmol) was added dropwise. The mixture was stirred at -78 °C for 0.25 h and then (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propan-1-ol **116** (2.00 g, 6.36 mmol, dissolved in 5 mL of dichloromethane) was added. The reaction was stirred again at -78 °C for 0.25 h before triethylamine (4.50 mL, 32.3 mmol) was added. The resulting reaction mixture was stirred at -78 °C for 1.25 h, and then at room temperature for 4 h before being concentrated *in vacuo* to give the desired crude aldehyde, which was used without further purification. Meanwhile, in a separate flask, lithium chloride (0.674 g, 15.9 mmol) was suspended in acetonitrile (60 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.40 mL, 16.0 mmol) was added, followed by triethyl phosphonoacetate (3.20 mL, 16.1 mmol). The mixture was stirred at room temperature for 1 h before being added to the crude aldehyde, and the resulting reaction mixture was allowed to stir at room temperature for 22 h before being quenched by the addition of a saturated aqueous solution of ammonium chloride (100 mL). The organic solvent was removed *in vacuo*, and the residue was partitioned between ethyl acetate (150 mL) and water (50 mL). The layers were separated, and the organic layers were further extracted using ethyl acetate (3 ×

150 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 2:23 ethyl acetate/petroleum ether gave ethyl (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)pent-2-enoate **119** as a colourless oil (1.91 g, 79%). ν_{max}/cm^{-1} (NaCl) 3071 (CH), 2932 (CH), 2858 (CH), 1720 (CO), 1660 (C=C), 1428, 1273, 1157, 1112, 979, 703; $[\alpha]_D^{25}$ -42.2 (*c* 1.0, $CHCl_3$) (lit.[112] $[\alpha]_D^{20}$ -40.0 (*c* 2.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, $SiC(CH_3)_3$), 1.12 (3H, d, *J* 6.5 Hz, 5-H_3), 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.13–4.26 (2H, m, OCH_2CH_3), 4.41–4.50 (1H, m, 4-H), 6.01 (1H, dd, *J* 15.5, 1.6 Hz, 2-H), 6.90 (1H, dd, *J* 15.5, 4.4 Hz, 3-H), 7.33–7.47 (6H, m, 6 × ArH), 7.60–7.71 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 19.3 (C), 23.3 (CH_3), 27.0 (3 × CH_3), 60.3 (CH_2), 68.6 (CH), 119.1 (CH), 127.6 (4 × CH), 129.8 (2 × CH), 133.4 (C), 134.0 (C), 135.7 (2 × CH), 135.8 (2 × CH), 151.5 (CH), 166.9 (C); *m*/*z* (EI) 382.1963 (M^+. $C_{23}H_{30}O_3Si$ requires 382.1964), 325 (100%), 227 (47), 199 (77), 175 (33), 135 (13), 123 (10), 77 (14).

(2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol[113]

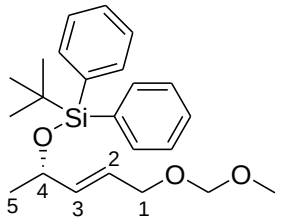


123

A stirred solution of ethyl (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)pent-2-enoate **119** (1.80 g, 4.71 mmol) in diethyl ether (20 mL) was cooled to -78 °C before diisobutylaluminium hydride solution (1.0 M in hexanes, 10.5 mL, 10.5 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 5 h before being cooled to 0 °C and quenched by the addition of a saturated aqueous solution of ammonium chloride (40 mL). Further diethyl ether (40 mL) was added, and the biphasic mixture was warmed to room temperature and stirred for 1.5 h before being filtered through a pad of Celite®. The collected solids were washed with diethyl ether (400 mL) and the combined filtrates were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (2*E*,4*S*)-4-(*tert*-

butyldiphenylsilyloxy)pent-2-en-1-ol **123** as a colourless oil (1.56 g, 97%). ν_{max}/cm^{-1} (NaCl) 3340 (OH), 2929 (CH), 2857 (CH), 1427, 1111, 1075, 997, 701; $[\alpha]_D^{21}$ -20.8 (*c* 0.5, $CHCl_3$) (lit.[113] $[\alpha]_D^{21}$ -21.2 (*c* 2.1, CH_2Cl_2)); δ_H (400 MHz, $CDCl_3$) 0.99 (1H, t, *J* 5.7 Hz, OH), 1.06 (9H, s, $SiC(CH_3)_3$), 1.17 (3H, d, *J* 6.3 Hz, 5-H_3), 3.99 (2H, t, *J* 5.7 Hz, 1-H_2), 4.29–4.38 (1H, m, 4-H), 5.55 (1H, dt, *J* 15.5, 5.7 Hz, 2-H), 5.65 (1H, dd, *J* 15.5, 5.6 Hz, 3-H), 7.32–7.46 (6H, m, 6 × ArH), 7.63–7.71 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 24.2 (CH_3), 27.0 (3 × CH_3), 63.2 (CH_2), 70.0 (CH), 127.4 (2 × CH), 127.5 (2 × CH), 127.7 (CH), 129.5 (CH), 129.6 (CH), 134.3 (C), 134.4 (C), 135.9 (2 × CH), 136.0 (2 × CH), 136.1 (CH); *m*/*z* (CI) 323 (100%), 283 (33), 257 (19), 239 (18), 199 (40), 179 (15), 69 (10).

(2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)-1-(methoxymethoxy)pent-2-ene

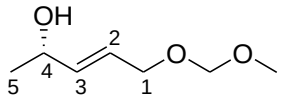


124

A stirred solution of (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)pent-2-en-1-ol **123** (1.24 g, 3.64 mmol) in dichloromethane (40 mL) was cooled to 0 °C before diisopropylethylamine (1.00 mL, 5.74 mmol) was added, followed by bromomethyl methyl ether (0.357 mL, 4.37 mmol). The reaction mixture was allowed to stir at 0 °C for 0.75 h and then heated to 45 °C and stirred under reflux for 26 h before being cooled to room temperature and quenched by the addition of 2 M hydrochloric acid (100 mL). Dichloromethane (100 mL) was added, and the layers were separated. The organic layers were extracted further with dichloromethane (50 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)-1-(methoxymethoxy)pent-2-ene **124** as a colourless oil (1.16 g, 82%). ν_{max}/cm^{-1} (NaCl) 2931 (CH), 2858 (CH), 1472, 1428, 1368, 1149, 1110, 1048, 703; $[\alpha]_D^{21}$ -31.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s,

$SiC(CH_3)_3$), 1.14 (3H, d, *J* 6.0 Hz, 5-H_3), 3.35 (3H, s, OCH_2OCH_3), 3.98 (2H, d, *J* 5.6 Hz, 1-H_2), 4.32 (1H, quin, *J* 6.0 Hz, 4-H), 4.59 (2H, s, OCH_2OCH_3), 5.58 (1H, dt, *J* 15.4, 5.6, 2-H), 5.73 (1H, dd, *J* 15.4, 6.0 Hz, 3-H), 7.33–7.44 (6H, m, 6 × ArH), 7.65–7.69 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 24.2 (CH_3), 27.0 (3 × CH_3), 55.2 (CH_3), 67.2 (CH_2), 69.5 (CH), 95.4 (CH_2), 124.6 (CH), 127.4 (2 × CH), 127.5 (2 × CH), 129.5 (CH), 129.6 (CH), 134.1 (C), 134.5 (C), 135.8 (2 × CH), 135.9 (2 × CH), 137.5 (CH); *m*/*z* (CI) 365 (8%), 323 (91), 297 (100), 277 (22), 253 (19), 213 (77), 199 (20), 183 (10), 153 (8), 129 (29), 91 (20), 69 (17).

(2*E*,4*S*)-1-Methoxymethoxypent-2-en-4-ol

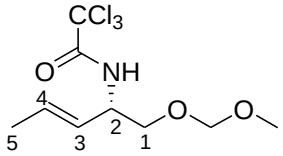


125

A stirred solution of (2*E*,4*S*)-4-(*tert*-butyldiphenylsilyloxy)-1-(methoxymethoxy)pent-2-ene **124** (2.60 g, 6.76 mmol) in tetrahydrofuran (60 mL) was cooled to 0 °C before tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 8.10 mL, 8.10 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.2 h and then at room temperature for 18 h before being cooled again to 0 °C and further tetra-*n*-butylammonium fluoride solution (1.0 M in tetrahydrofuran, 1.50 mL, 1.50 mmol) was added. The reaction mixture was allowed to stir at 0 °C for 0.1 h and then at room temperature for a further 5 h before being concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ethyl acetate (100 mL) and the organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 2:3 ethyl acetate/petroleum ether gave (2*E*,4*S*)-1-methoxymethoxypent-2-en-4-ol **125** as a colourless oil (0.718 g, 73%). ν_{max}/cm^{-1} (NaCl) 3421 (OH), 2931 (CH), 1655 (C=C), 1451, 1371, 1041; $[\alpha]_D^{26}$ +6.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, d, *J* 6.2 Hz, 5-H_3), 1.60 (1H, br s, OH), 3.38 (3H, s, OCH_2OCH_3), 4.06 (2H, d, *J* 5.2 Hz, 1-H_2), 4.35 (1H, quin, *J* 6.2 Hz, 4-H), 4.65 (2H, s, OCH_2OCH_3), 5.72–5.87 (2H, m, 2-H and 3-H); δ_C (100 MHz, $CDCl_3$) 23.2 (CH_3),

55.3 (CH_3), 67.2 (CH_2), 68.2 (CH), 95.7 (CH_2), 125.8 (CH), 137.3 (CH); *m*/*z* (EI) 127 (38%), 97 (33), 83 (100), 57 (70), 45 (87).

(2*S*,3*E*)-1-(Methoxymethoxy)-2-(trichloromethylcarbonylamino)pent-3-ene (*via* thermal rearrangement)

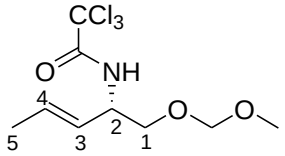


127

A stirred solution of (2*E*,4*S*)-1-methoxymethoxypent-2-en-4-ol **125** (0.200 g, 1.37 mmol) in dichloromethane (10 mL) was cooled to 0 °C before 1,8-diazabicyclo[5.4.0]undec-7-ene (0.051 mL, 0.34 mmol) was added, followed by trichloroacetonitrile (0.210 mL, 2.09 mmol). The reaction mixture was allowed to stir at room temperature for 6.5 h before being filtered through a short plug of silica, which was washed with diethyl ether (200 mL). The combined filtrates were concentrated *in vacuo* to give the desired allylic trichloroacetimidate **126** as a yellow oil (0.335 g), which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.3 Hz, 5-H_3), 3.37 (3H, s, OCH_2OCH_3), 4.09 (2H, d, *J* 4.9 Hz, 1-H_2), 4.64 (2H, s, OCH_2OCH_3), 5.52 (1H, quin, *J* 6.3 Hz, 4-H), 5.76–5.95 (2H, m, 2-H and 3-H), 8.30 (1H, s, NH). A portion of this allylic trichloroacetimidate intermediate **126** (0.142 g, 0.49 mmol) was dissolved in *p*-xylene (10 mL) and potassium carbonate (0.030 g, 0.22 mmol) was added. The reaction mixture was heated to 140 °C and stirred under reflux for 15 h before being allowed to cool to room temperature and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (2*S*,3*E*)-1-(methoxymethoxy)-2-(trichloromethylcarbonylamino)pent-3-ene **127** as a colourless oil (0.112 g, 66% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3331 (NH), 2933 (CH), 1703 (CO), 1517, 1114, 1039, 821; $[\alpha]_D^{25}$ -2.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.74 (3H, d, *J* 6.5 Hz, 5-H_3), 3.38 (3H, s, OCH_2OCH_3), 3.66–3.76 (2H, m, 1-H_2), 4.50-4.58 (1H, m, 2-H), 4.63–4.69 (2H, m, OCH_2OCH_3), 5.52 (1H, dd, *J* 15.4, 6.2 Hz, 3-H), 5.78 (1H, dqd, *J* 15.4, 6.5, 1.3 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) 17.9 (CH_3), 52.8 (CH), 55.6 (CH_3), 70.0 (CH_2), 92.8 (C), 97.0 (CH_2), 126.6 (CH), 129.2 (CH), 161.2 (C); *m*/*z*

(CI) 290.0116 (MH^+. $C_9H_{15}{}^{35}Cl_3NO_3$ requires 290.0118), 260 (100%), 258 (100), 214 (22), 176 (19), 174 (17), 129 (13), 97 (85), 85 (14).

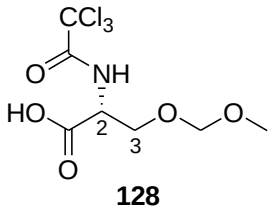
(2*S*,3*E*)-1-(Methoxymethoxy)-2-(trichloromethylcarbonylamino)pent-3-ene (*via* metal-catalysed rearrangement)



127

The allylic trichloroacetimidate starting material **126** (0.193 g, 0.66 mmol) was dissolved in toluene (10 mL) and bis(acetonitrile)palladium(II) chloride (0.017 g, 0.07 mmol) was added. The reaction mixture was allowed to stir at room temperature for 15 h before being concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (2*S*,3*E*)-1-(methoxymethoxy)-2-(trichloromethylcarbonylamino)pent-3-ene **127** as a colourless oil (0.118 g, 51% over 2 steps). For analytical data, see above.

(2*R*)-2-(Trichloromethylcarbonylamino)-3-(methoxymethoxy)propanoic acid

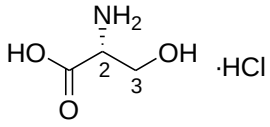


128

(2*S*,3*E*)-1-(Methoxymethoxy)-2-(trichloromethylcarbonylamino)pent-3-ene **127** (0.116 g, 0.40 mmol) was dissolved in acetonitrile (6 mL) and carbon tetrachloride (6 mL) and to the stirred solution, sodium periodate (0.350 g, 1.64 mmol, dissolved in 9 mL of water) was added, followed by ruthenium(III) chloride hydrate (0.004 g, 0.02 mmol). The reaction mixture was stirred at room temperature for 5.5 h, and then the organic layers were extracted using dichloromethane (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (2*R*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)propanoic acid

128 as a blue/black oil (0.091 g), which was used without further purification. δ_H(400 MHz, $CDCl_3$) 3.38 (3H, s, OCH_2OCH_3), 3.86 (1H, dd, *J* 10.8, 2.6 Hz, 3-*H*H), 4.24 (1H, dd, *J* 10.8, 2.6 Hz, 3-H*H*), 4.66 (2H, s, OCH_2OCH_3), 4.73 (1H, d, *J* 7.8 Hz, 2-H), 7.81 (1H, d, *J* 7.8 Hz, NH).

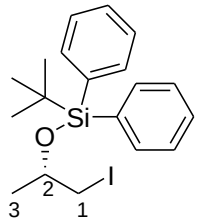
D-Serine hydrochloride[114]



129

(2*R*)-2-(Trichloromethylcarbonylamino)-3-(methoxymethoxy)propanoic acid **128** (0.086 g) was dissolved in 6 M hydrochloric acid (6 mL) and the reaction mixture was heated under reflux for 20 h before being allowed to cool to room temperature. The mixture was washed with diethyl ether (2 × 20 mL) and the aqueous phase was concentrated *in vacuo* to give D-serine hydrochloride **129** as a yellow residue (0.035 g, 100% over 2 steps). ν_{max}/cm^{-1} (neat) 3129 (NH_2/OH), 1613 (CO), 1397, 1215, 1076, 914, 779; $[\alpha]_D^{21}$ -13.4 (*c* 1.0, 1 M HCl) (lit.[114] $[\alpha]_D^{23}$ -14.0 (*c* 0.74, 1 M HCl)); δ_H (400 MHz, D_2O) 3.83–3.95 (3H, m, 2-H and 3-H_2); *m*/*z* (CI) 113 (12%), 85 (100), 69 (54).

(2*S*)-2-(*tert*-Butyldiphenylsilyloxy)-1-iodopropane[115]

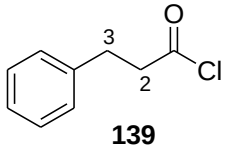


131

To a stirred solution of (2*S*)-2-(*tert*-butyldiphenylsilyloxy)propan-1-ol **116** (1.00 g, 3.2 mmol) in toluene (15 mL), triphenylphosphine (0.95 g, 3.6 mmol) was added, followed by imidazole (0.49 g, 7.3 mmol) and iodine (0.91 g, 3.6 mmol). The reaction mixture was stirred at room temperature, in the absence of light, for 15 h and the solvent was then poured off. The remaining beige-coloured residue was washed with diethyl ether (3 × 20 mL), and the washings were combined with the

reaction solvent and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave (2*S*)-(*tert*-butyldiphenylsilyloxy)-1-iodopropane **131** as a colourless oil (1.29 g, 96%). ν_{max}/cm^{-1} (NaCl) 3019 (CH), 2932 (CH), 2859 (CH), 1473, 1428, 1112, 1062; $[\alpha]_D^{25}$ -22.5 (*c* 1.0, $CHCl_3$) (lit.[115] $[\alpha]_D^{25}$ -26.7 (*c* 1.05, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.0 Hz, 3-H_2), 3.13 (2H, d, *J* 4.4 Hz, 1-H_2), 3.65–3.73 (1H, m, 2-H), 7.36–7.47 (6H, m, 6 × ArH), 7.66–7.71 (4H, m, 4 × ArH); δ_C (100 MHz, $CDCl_3$) 15.9 (CH_2), 19.3 (C), 23.5 (CH_3), 26.9 (3 × CH_3), 68.2 (CH), 127.6 (2 × CH), 127.7 (2 × CH), 129.7 (CH), 129.8 (CH), 133.7 (C), 133.9 (C), 135.7 (2 × CH), 135.8 (2 × CH); *m/z* (CI) 425.0799 (MH^+. $C_{19}H_{26}IOSi$ requires 425.0798), 384 (100%), 75 (54).

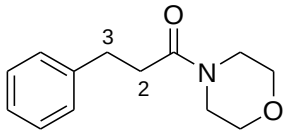
3-Phenylpropionyl chloride[116]



139

Thionyl chloride (12.2 mL, 167 mmol) was slowly added to hydrocinnamic acid **134** (5.00 g, 33.3 mmol) with cooling to 0 °C. The reaction mixture was stirred at 0 °C for 0.2 h, and then at room temperature for 4 h before being concentrated *in vacuo*. Residual thionyl chloride was removed using a toluene azeotrope, giving 3-phenylpropionyl chloride **139** as a yellow oil (5.99 g), which was used without further purification. δ_H (400 MHz, $CDCl_3$) 3.02 (2H, t, *J* 7.4 Hz, 3-H_2), 3.21 (2H, t, *J* 7.4 Hz, 2-H_2), 7.17–7.34 (5H, m, 5 × ArH).

1-Morpholin-4-yl-3-phenylpropan-1-one[117]

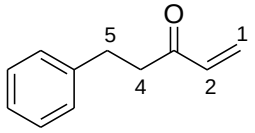


135

Morpholine (15.5 mL, 177 mmol) was added slowly to a stirred solution of 3-phenylpropionyl chloride **139** (5.99 g) in dichloromethane at 0 °C, upon which a white precipitate formed. The resulting suspension was heated to 45 °C and stirred

under reflux for 18 h. The mixture was then allowed to cool to room temperature and further dichloromethane (50 mL) was added. The organic phase was washed with water (2 × 100 mL) before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography and elution with 7:3 ethyl acetate/petroleum ether gave 1-morpholin-4-yl-3-phenylpropan-1-one **135** as a colourless oil (7.24 g, 99% over 2 steps). R_f (1:1 ethyl acetate/petroleum ether) 0.17; δ_H (400 MHz, $CDCl_3$) 2.62 (2H, t, *J* 7.6 Hz, 3-H_2), 2.98 (2H, t, *J* 7.6 Hz, 2-H_2), 3.36 (2H, t, *J* 4.4 Hz, CH_2), 3.51 (2H, t, *J* 4.4 Hz, CH_2), 3.60–3.65 (4H, m, 2 x CH_2), 7.21–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 31.5 (CH_2), 34.9 (CH_2), 42.0 (CH_2), 46.0 (CH_2), 66.5 (CH_2), 66.9 (CH_2), 126.3 (CH), 128.5 (2 × CH), 128.6 (2 × CH), 141.1 (C), 171.0 (C); *m/z* (CI) 220.1343 (MH^+. $C_{13}H_{18}NO_2$ requires 220.1338), 219 (7%), 172 (2), 81 (3).

5-Phenylpent-1-en-3-one[118]

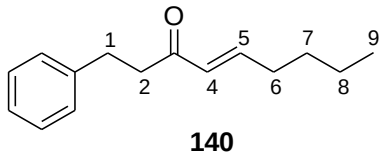


136

A stirred solution of 1-morpholin-4-yl-3-phenylpropan-1-one **135** (0.550 g, 2.51 mmol) in tetrahydrofuran (20 mL) was cooled to 0 °C before vinylmagnesium bromide solution (1.0 M in tetrahydrofuran, 10.0 mL, 10.0 mmol) was added dropwise. The resulting reaction mixture was stirred at 0 °C for 1.75 h before being poured into glacial acetic acid (10 mL) and then concentrated *in vacuo*. The residue was partitioned between dichloromethane (50 mL) and a saturated aqueous solution of ammonium chloride (50 mL) and the organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave 5-phenylpent-1-en-3-one **136** as a colourless oil (0.299 g, 74%). R_f (1:4 ethyl acetate/petroleum ether) 0.69; δ_H (400 MHz, $CDCl_3$) 2.89–2.98 (4H, m, 4-H_2 and 5-H_2), 5.83 (1H, d, *J* 10.8 Hz, 1-*H*H), 6.22 (1H, d, *J* 17.6 Hz, 1-H*H*), 6.36 (1H, dd, *J* 17.6, 10.8 Hz, 2-H), 7.20–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 29.8 (CH_2), 41.2 (CH_2), 126.1 (CH), 128.3 (CH_2), 128.4 (2 × CH), 128.5 (2 × CH), 136.5 (CH),

141.1 (C), 199.8 (C); *m/z* (CI) 161.0965 (MH^+. $C_{11}H_{13}O$ requires 161.0966), 160 (5%), 91 (3).

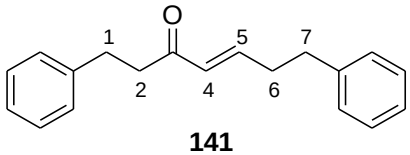
(4*E*)-1-Phenylnon-4-en-3-one[119]



140

The reaction was carried out according to general procedure 1 using 5-phenylpent-1-en-3-one **136** (0.675 g, 4.21 mmol), 1-hexene (1.05 mL, 8.46 mmol) and Grubbs 2nd generation catalyst **K** (0.143 g, 0.17 mmol) in dichloromethane (15 mL). The reaction mixture was stirred under reflux for 20 h. Purification by silica column chromatography, eluting with 1:19 ethyl acetate/petroleum ether, gave (4*E*)-1-phenylnon-4-en-3-one **140** as a colourless oil (0.687 g, 75%). R_f (1:4 ethyl acetate/petroleum ether) 0.68; ν_{max}/cm^{-1} (NaCl) 2931 (CH), 1711 (CO), 1454, 1180, 699; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 7.2 Hz, 1-H_3), 1.30–1.49 (4H, m, 2-H_2 and 3-H_2), 2.17–2.23 (2H, m, 4-H_2), 2.84–2.96 (4H, m, 8-H_2 and 9-H_2), 6.09 (1H, d, *J* 15.8, 6-H), 6.82 (1H, dt, *J* 15.8, 6.8 Hz, 5-H), 7.17–7.30 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.3 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 32.2 (CH_2), 41.6 (CH_2), 126.1 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 130.3 (CH), 141.3 (C), 147.9 (CH), 199.7 (C); *m/z* (CI) 217.1596 (MH^+. $C_{15}H_{21}O$ requires 217.1592), 203 (15%), 159 (9), 97 (5), 85 (32), 69 (29).

(4*E*)-1,7-Diphenylhept-4-en-3-one[120]

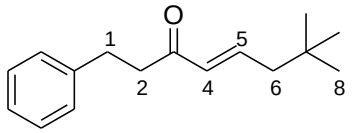


141

The reaction was carried out according to general procedure 1 using 5-phenylpent-1-en-3-one **136** (0.502 g, 3.13 mmol), 4-phenyl-1-butene (0.94 mL, 6.27 mmol) and Grubbs 2nd generation catalyst **K** (0.106 g, 0.12 mmol) in dichloromethane (15 mL). The reaction mixture was stirred under reflux for 18 h before additional Grubbs 2nd

generation catalyst (0.026 g, 0.03 mmol) was added and the reaction was stirred under reflux for a further 6 h. Purification by silica column chromatography, eluting with 3:17 diethyl ether/petroleum ether gave (4*E*)-1,7-diphenylhept-4-en-3-one **141** as a colourless oil (0.386 g, 47%). R_f (1:4 ethyl acetate/petroleum ether) 0.53; δ_H (400 MHz, $CDCl_3$) 2.47–2.53 (2H, m, 2-H_2), 2.77 (2H, t, *J* 7.2 Hz, 1-H_2), 2.81–2.95 (4H, m, 6-H_2 and 7-H_2), 6.11 (1H, d, *J* 15.8 Hz, 4-H), 6.84 (1H, dt, *J* 15.8, 7.2 Hz, 3-H), 7.14–7.32 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 30.1 (CH_2), 34.1 (CH_2), 34.4 (CH_2), 41.7 (CH_2), 126.1 (CH), 126.2 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (4 × CH), 130.7 (CH), 140.7 (C), 141.2 (C), 146.3 (CH), 199.5 (C); *m*/*z* (EI) 264.1516 (M^+. $C_{19}H_{20}O$ requires 264.1514), 159 (54%), 131 (8), 105 (15), 91 (100), 65 (12), 44 (49).

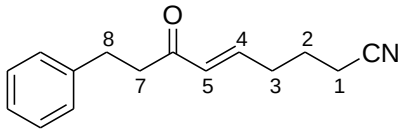
(4*E*)-7,7-Dimethyl-1-phenyloct-4-en-3-one



142

The reaction was carried out according to general procedure 1 using 5-phenylpent-1-en-3-one **136** (0.769 g, 4.80 mmol), 4,4-dimethyl-1-pentene (1.40 mL, 9.74 mmol) and Grubbs 2nd generation catalyst (0.163 g, 0.19 mmol) in dichloromethane (20 mL). The reaction mixture was stirred under reflux for 24 h and purification by silica column chromatography, eluting with 1:9 ethyl acetate/petroleum ether, gave (4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-one **142** as a pale yellow oil (0.646 g, 58%). R_f (1:4 ethyl acetate/petroleum ether) 0.65; ν_{max}/cm^{-1} (NaCl) 2960 (CH), 1670 (CO), 1474, 1367, 1095, 908, 734; δ_H (400 MHz, $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 2.08 (2H, d, *J* 8.0 Hz, 3-H_2), 2.85–2.96 (4H, m, 7-H_2 and 8-H_2), 6.08 (1H, d, *J* 15.6 Hz, 5-H), 6.84 (1H, dt, *J* 15.6, 8.0 Hz, 4-H), 7.17–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 29.4 (3 × CH_3), 30.2 (CH_2), 31.5 (C), 41.7 (CH_2), 47.0 (CH_2), 126.1 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 132.3 (CH), 141.3 (C), 145.2 (CH), 199.4 (C); *m*/*z* (EI) 230.1674 (M^+. $C_{16}H_{22}O$ requires 230.1671), 215 (11%), 174 (6), 159 (100), 133 (5), 105 (18), 91 (46), 84 (42), 57 (56), 47 (6).

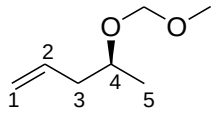
(4*E*)-1-Cyano-8-phenyloct-4-en-6-one



143

The reaction was set up according to general procedure 1 using 5-phenylpent-1-en-3-one **136** (0.972 g, 6.07 mmol), 5-hexenenitrile (1.20 mL, 10.6 mmol) and Grubbs 2nd generation catalyst **K** (0.206 g, 0.24 mmol) in dichloromethane (25 mL). The reaction mixture was stirred under reflux for 22 h before further Grubbs 2nd generation catalyst **K** (0.103 g, 0.12 mmol) was added and the reaction stirred under reflux again for 50 h. Grubbs 2nd generation catalyst **K** (0.103 g, 0.12 mmol) was then added and the reaction mixture was stirred under reflux for a further 72 h before a final addition of Grubbs 2nd generation catalyst **K** (0.052 g, 0.06 mmol) and stirring under reflux for 24 h. Purification by silica column chromatography, eluting with 1:3 ethyl acetate/petroleum ether gave (4*E*)-1-cyano-8-phenyloct-4-en-6-one **143** as a pale brown oil (0.73 g, 53%). R_f (1:4 ethyl acetate/petroleum ether) 0.15; ν_{max}/cm^{-1} (NaCl) 3028 (CH), 2934 (CH), 2246 (CN), 1669 (CO), 1453, 978, 701; δ_H (400 MHz, $CDCl_3$) 1.78–1.87 (2H, m, 1-H_2), 2.32–2.42 (4H, m, 2-H_2 and 3-H_2), 2.84–2.98 (4H, m, 7-H_2 and 8-H_2), 6.13 (1H, d, *J* 15.8 Hz, 5-H), 6.73 (1H, dt, *J* 15.8, 6.8 Hz, 4-H), 7.16–7.33 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 16.7 (CH_2), 23.8 (CH_2), 30.0 (CH_2), 31.0 (CH_2), 42.2 (CH_2), 119.0 (C), 126.2 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 131.6 (CH), 141.1 (C), 143.9 (CH), 199.1 (C); *m*/*z* (EI) 227.1308 (M^+. $C_{15}H_{17}NO$ requires 227.1310), 159 (20%), 122 (9), 105 (16), 91 (16), 77 (18), 44 (100).

(4*S*)-4-(Methoxymethoxy)-1-pentene

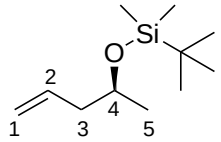


145

A stirred solution of (4*S*)-(+)-1-penten-4-ol **144** (0.12 mL, 1.17 mmol) in dichloromethane (10 mL) was cooled to 0 °C before diisopropylethylamine (0.30 mL, 1.72 mmol) was added, followed by bromomethyl methyl ether (0.11 mL, 1.35 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and then heated to 45 °C

and stirred under reflux for 45 h. The reaction mixture was then allowed to cool to room temperature before further diisopropylethylamine (0.15 mL, 0.86 mmol) and bromomethyl methyl ether (0.06 mL, 0.74 mmol) were added. The reaction mixture was again heated to 45 °C and stirred under reflux for 20 h before being cooled to room temperature, quenched by the addition of 2 M hydrochloric acid (10 mL) and diluted with dichloromethane (20 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give the desired crude product **145** as a yellow oil (0.134 g, 89% crude yield), which decomposed upon attempted purification by silica column chromatography. δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.2 Hz, 5-H_3), 2.17–2.26 (1H, m, 3-*H*H), 2.29–2.37 (1H, m, 3-H*H*), 3.37 (3H, s, OCH_2OCH_3), 3.76 (1H, sex, *J* 6.2 Hz, 4-H), 4.64 (1H, d, *J* 6.8 Hz, $OCHHOCH_3$), 4.69 (1H, d, *J* 6.8 Hz, $OCHHOCH_3$), 5.04–5.12 (2H, m, 1-H_2), 5.75–5.87 (1H, m, 2-H).

(4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-pentene[82]

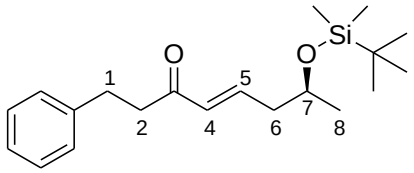


146

A stirred solution of (4*S*)-(+)-1-penten-4-ol **144** (0.623 g, 7.23 mmol), triethylamine (2.00 mL, 14.5 mmol) and 4-dimethylaminopyridine (0.088 g, 0.72 mmol) in dichloromethane (30 mL) was cooled to 0 °C before *tert*-butyldimethylsilyl chloride (1.42 g, 9.40 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 0.2 h, and then at room temperature for 21 h before water (50 mL) and dichloromethane (20 mL) were added. The layers were separated, and the organic layers were further extracted using dichloromethane (30 mL). The combined organic phases were then washed with a saturated aqueous solution of copper sulfate (2 × 40 mL) and then water (40 mL) before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 diethyl ether/petroleum ether gave (4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-pentene **146** as a colourless oil (0.754 g, 52%). R_f (1:4 ethyl acetate/petroleum ether) 0.62; ν_{max}/cm^{-1} (NaCl) 2959 (CH), 2092 (CH), 1643 (C=C), 1472, 1376, 1255, 1093, 1004, 774; $[\alpha]_D^{24}$ +18.1 (*c* 1.0, $CHCl_3$); δ_H (400

MHz, $CDCl_3$) 0.05 (6H, s, 2 × $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.13 (3H, d, *J* 6.0 Hz, 5-H_3), 2.11–2.25 (2H, m, 3-H_2), 3.84 (1H, q, *J* 6.0 Hz, 4-H), 4.99–5.06 (2H, m, 1-H_2), 5.75–5.86 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) -5.7 (CH_3), -5.6 (CH_3), 17.2 (C), 22.4 (CH_3), 24.9 (3 × CH_3), 43.3 (CH_2), 67.4 (CH), 115.5 (CH_2), 134.6 (CH); *m*/*z* (CI) 201 (MH^+, 4%), 193 (9), 167 (8), 151 (7), 113 (29), 95 (22), 69 (100).

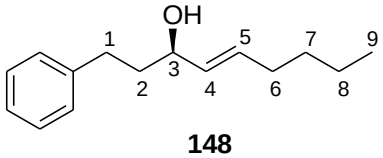
(4*E*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-one



147

The experiment was set up according to general procedure 1 using 5-phenylpent-1-en-3-one **136** (0.800 g, 5.02 mmol), (4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-pentene **K** (1.08 g, 5.39 mmol) and Grubbs 2nd generation catalyst **K** (0.170 g, 0.20 mmol) in dichloromethane (35 mL). The reaction mixture was stirred under reflux for 19 h before further Grubbs 2nd generation catalyst **K** (0.043 g, 0.05 mmol) was added and the reaction mixture was stirred under reflux again for 23 h. Purification by silica column chromatography, and elution with 1:19 diethyl ether/petroleum ether gave (4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-one **147** as a colourless oil (1.48 g, 89%). R_f (1:4 ethyl acetate/petroleum ether) 0.59; ν_{max}/cm^{-1} (NaCl) 2929 (CH), 1674 (CO), 1632 (C=C), 1454, 1375, 1256, 1128, 1003, 836; $[\alpha]_D^{22}$ +14.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.14 (3H, d, *J* 6.5 Hz, 1-H_3), 2.32 (2H, t, *J* 6.5 Hz, 3-H_2), 2.84–2.96 (4H, m, 7-H_2 and 8-H_2), 3.92 (1H, sex, *J* 6.5 Hz, 2-H), 6.10 (1H, d, *J* 16.0 Hz, 5-H), 6.83 (1H, dt, *J* 16.0, 6.5 Hz, 4-H), 7.18–7.30 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) -4.7 (CH_3), -4.4 (CH_3), 18.1 (C), 23.9 (CH_3), 25.9 (3 × CH_3), 30.1 (CH_2), 41.5 (CH_2), 42.8 (CH_2), 67.7 (CH), 126.1 (CH), 128.4 (2 × CH), 128.6 (2 × CH), 132.3 (CH), 141.3 (C), 144.5 (CH), 199.4 (C); *m*/*z* (CI) 333.2253 (MH^+. $C_{20}H_{33}O_2Si$ requires 333.2250), 275 (11%), 237 (9), 201 (9), 181 (9), 159 (43), 137 (12), 97 (53), 71 (100).

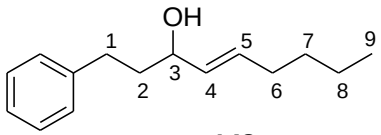
(3*R*,4*E*)-1-Phenylnon-4-en-3-ol[121]



148

The reaction was carried out according to general procedure 2, using (4*E*)-1-phenylnon-4-en-3-one **140** (0.300 g, 1.39 mmol), (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 1.40 mL, 1.40 mmol), and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 7.00 mL, 7.00 mmol) in tetrahydrofuran (10 mL). Purification by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (3*R*,4*E*)-1-phenylnon-4-en-3-ol **148** as a colourless oil (0.299 g, 99%). Chiral HPLC (Chiralcel IB column) analysis using 2% isopropanol in hexane indicated 84% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.39; $[\alpha]_D^{22}$ +17.5 (*c* 1.0, $CHCl_3$) (lit.[121] $[\alpha]_D$ +6.1 (*c* 0.952, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, 1-H_3), 1.26–1.40 (4H, m, 2-H_2 and 3-H_2), 1.45 (1H, br s, OH), 1.75–1.93 (2H, m, 8-H_2), 1.99–2.07 (2H, m, 4-H_2), 2.62–2.79 (2H, m, 9-H_2), 4.03–4.12 (1H, m, 7-H), 5.49 (1H, ddt, *J* 15.2, 6.8, 1.2 Hz, 6-H), 5.66 (1H, dt, *J* 15.2, 6.8 Hz, 5-H), 7.16–7.30 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.2 (CH_2), 31.4 (CH_2), 31.8 (CH_2), 31.9 (CH_2), 38.9 (CH_2), 72.5 (CH), 125.8 (CH), 128.4 (3 × CH), 128.5 (2 × CH), 132.7 (CH), 142.0 (C); *m*/*z* (CI) 201.1646 (MH^+. $C_{15}H_{23}O$-OH requires 201.1643), 187 (11%), 133 (6), 117 (7), 91 (13), 69 (7).

(4*E*)-1-Phenylnon-4-en-3-ol[122]

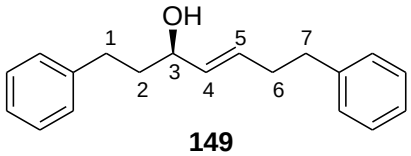


rac-148

A stirred solution of (4*E*)-1-phenylnon-4-en-3-one **140** (0.200 g, 0.93 mmol) in toluene (5 mL) was cooled to 0 °C before diisobutylaluminium hydride solution (1.0 M in hexanes, 1.40 mL, 1.40 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 3 h, and then at room temperature for 15 h before being cooled again to 0 °C and quenched by the slow addition of methanol (50 mL). The resulting cloudy suspension was stirred at 0 °C for 1 h, then at room temperature

for 0.5 h before being filtered through a pad of Celite®. The white gum was washed through with warm methanol (100 mL), and the combined filtrates were concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (4*E*)-1-phenylnon-4-en-3-ol **rac-148** as a colourless oil (0.103 g, 51%). For analytical data, see above compound **148**.

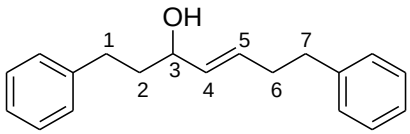
(3*R*,4*E*)-1,7-Diphenylhept-4-en-3-ol



149

The reaction was carried out according to general procedure 2 using (4*E*)-1,7-diphenylhept-4-en-3-one **141** (0.190 g, 0.72 mmol), (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 0.72 mL, 0.72 mmol) and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 2.20 mL, 2.20 mmol) in tetrahydrofuran (10 mL). Purification by silica column chromatography and elution with 3:7 ethyl acetate/petroleum ether gave (3*R*,4*E*)-1,7-diphenylhept-4-en-3-ol **149** as a colourless oil (0.133 g, 69%). Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane indicated 75% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.32; ν_{max}/cm^{-1} (NaCl) 3356 (OH), 2925 (CH), 1602 (C=C), 1454, 970, 698; $[\alpha]_D^{22}$ +9.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.40 (1H, d, *J* 3.2 Hz, OH), 1.70–1.90 (2H, m, 6-H_2), 2.37 (2H, dt, *J* 7.6, 6.8 Hz, 2-H_2), 2.57–2.73 (4H, m, 1-H_2 and 7-H_2), 4.02–4.10 (1H, m, 5-H), 5.50 (1H, ddt, *J* 15.6, 7.0, 1.3 Hz, 4-H), 5.69 (1H, dtd, *J* 15.6, 6.8, 0.7 Hz, 3-H), 7.15–7.30 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 31.7 (CH_2), 33.9 (CH_2), 35.6 (CH_2), 38.7 (CH_2), 72.3 (CH), 125.8 (CH), 125.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 128.5 (4 × CH), 131.4 (CH), 133.5 (CH), 141.6 (C), 142.0 (C); *m*/*z* (EI) 266.1674 (M^+. $C_{19}H_{22}O$ requires 266.1671), 248 (10%), 161 (21), 144 (28), 105 (42), 91 (100), 83 (18), 65 (11), 57 (11).

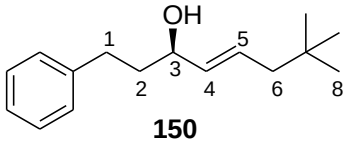
(4*E*)-1,7-Diphenylhept-4-en-3-ol



rac-149

The reaction was carried out according to general procedure 3 using (4*E*)-1,7-diphenylhept-4-en-3-one **141** (0.040 g, 0.15 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 0.23 mL, 0.23 mmol) in toluene (5 mL). Purification by silica column chromatography, eluting with 3:7 ethyl acetate/petroleum ether gave (4*E*)-1,7-diphenylhept-4-en-3-ol **rac-149** as a colourless oil (0.024 g, 60%). For analytical data, see above compound **149**.

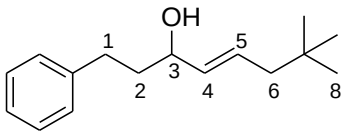
(3*R*,4*E*)-7,7-Dimethyl-1-phenyloct-4-en-3-ol



150

The reaction was carried out according to general procedure 2 using (4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-one **142** (0.200 g, 0.87 mmol), (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 0.90 mL, 0.90 mmol) and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 2.60 mL, 2.60 mmol) in tetrahydrofuran (10 mL). Purification by silica column chromatography, eluting with 1:9 ethyl acetate/petroleum ether gave (3*R*,4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-ol **150** as a colourless oil (0.156 g, 77%). Chiral HPLC (Chiralcel IB column) analysis using 3% isopropanol in hexane indicated 69% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.44; ν_{max}/cm^{-1} (NaCl) 3609 (OH), 3019 (CH), 1475, 1216, 772; $[\alpha]_D^{22}$ +8.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (9H, s, $C(CH_3)_3$), 1.45 (1H, d, *J* 3.6 Hz, OH), 1.76–1.98 (4H, m, 3-H_2 and 7-H_2), 2.63–2.76 (2H, m, 8-H_2), 4.07–4.14 (1H, m, 6-H), 5.49 (1H, dd, *J* 15.2, 7.2 Hz, 5-H), 5.69 (1H, dt, *J* 15.2, 7.6 Hz, 4-H), 7.16–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 29.3 (3 × CH_3), 30.9 (C), 31.8 (CH_2), 38.9 (CH_2), 46.7 (CH_2), 72.5 (CH), 125.8 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 129.5 (CH), 135.1 (CH), 142.0 (C); *m*/*z* (EI) 232.1830 (M^+. $C_{16}H_{24}O$ requires 232.1827), 214 (9%), 161 (26), 143 (24), 127 (46), 91 (100), 83 (51), 57 (98), 44 (15).

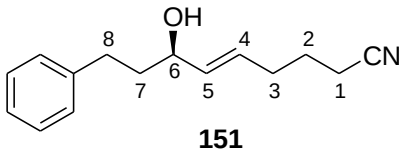
(4*E*)-7,7-Dimethyl-1-phenyloct-4-en-3-ol



rac-150

The reaction was carried out according to general procedure 3 using (4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-one **142** (0.050 g, 0.22 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 0.40 mL, 0.40 mmol) in toluene (5 mL). Purification by silica column chromatography, eluting with 1:9 ethyl acetate/petroleum ether gave (4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-ol **rac-150** as a colourless oil (0.057 g, 100%). For analytical data, see above compound **150**.

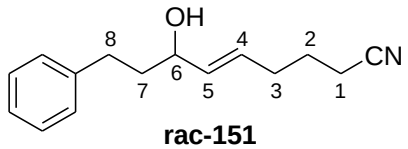
(4*E*,6*R*)-1-Cyano-8-phenyloct-4-en-6-ol



151

The reaction was carried out according to general procedure 2 using (4*E*)-1-cyano-8-phenyloct-4-en-6-one **143** (0.150 g, 0.65 mmol), (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 0.65 mL, 0.65 mmol) and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 1.95 mL, 1.95 mmol) in tetrahydrofuran (3 mL). Purification by silica column chromatography, and elution with 3:7 ethyl acetate/petroleum ether gave (4*E*,6*R*)-1-cyano-8-phenyloct-4-en-6-ol **151** as a colourless oil (0.096 g, 63%). Chiral HPLC (Chiralcel IB column) analysis using 6% isopropanol in hexane indicated 87% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.09; ν_{max}/cm^{-1} (NaCl) 3448 (OH), 2932 (CH), 2251 (CN), 1454, 910, 731; $[\alpha]_D^{23}$ +3.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.47–1.51 (1H, m, OH), 1.71–1.77 (2H, m, 2-H_2), 1.78–1.93 (2H, m, 7-H_2), 2.19-2.25 (2H, m, 3-H_2), 2.35 (2H, t, *J* 7.2 Hz, 1-H_2), 2.62–2.77 (2H, m, 8-H_2), 4.07–4.14 (1H, m, 6-H), 5.59–5.62 (2H, m, 4-H and 5-H), 7.17–7.32 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 16.5 (CH_2), 24.7 (CH_2), 31.0 (CH_2), 31.8 (CH_2), 38.8 (CH_2), 72.1 (CH), 119.6 (C), 125.9 (2 × CH), 128.5 (2 × CH), 129.0 (2 × CH), 135.1 (CH), 141.8 (C); *m/z* (CI) 230.1555 (MH^+. $C_{15}H_{20}NO$ requires 230.1545), 212 (100%), 184 (8), 107 (27), 79 (30).

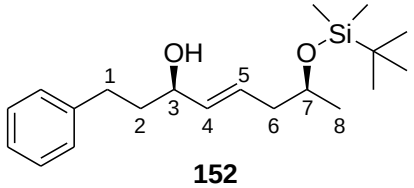
(4*E*)-1-cyano-8-phenyloct-4-en-6-ol



rac-151

The reaction was carried out according to general procedure 3 using (4*E*)-1-cyano-8-phenyloct-4-en-6-one **143** (0.050 g, 0.22 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 0.33 mL, 0.33 mmol) in toluene (5 mL). Purification by silica column chromatography, eluting with 3:7 ethyl acetate/petroleum ether gave (4*E*)-1-cyano-8-phenyloct-4-en-6-ol **rac-151** as a colourless oil (0.027 g, 54%). For analytical data, see above compound **151**.

(3*R*,4*E*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-ol

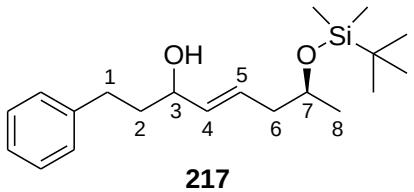


152

The reaction was carried out according to general procedure 2 using (4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-one **147** (0.500 g, 1.50 mmol), (S)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 1.50 mL, 1.50 mmol), and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 7.50 mL, 7.50 mmol) in tetrahydrofuran (15 mL). Purification by silica column chromatography, and elution with 3:17 diethyl ether/petroleum ether gave (3*R*,4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-ol **152** as a colourless oil (0.439 g, 87%). R_f (1:4 ethyl acetate/petroleum ether) 0.43; ν_{max}/cm^{-1} (NaCl) 3395 (OH), 2961 (CH), 1639 (C=C), 1455, 1254, 1084, 835, 774; $[\alpha]_D^{22}$ +17.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, 2 × $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.12 (3H, d, *J* 6.0 Hz, 1-H_3), 1.43 (1H, br s, OH), 1.76–1.93 (2H, m, 7-H_2), 2.10–2.25 (2H, m, 3-H_2), 2.63–2.76 (2H, m, 8-H_2), 3.83 (1H, sex, *J* 6.0 Hz, 2-H), 4.05–4.13 (1H, m, 6-H), 5.53 (1H, dd, *J* 15.4, 6.9 Hz, 5-H), 5.67 (1H, dt, *J* 15.4, 6.9 Hz, 4-H), 7.15–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) -4.7 (CH_3), -4.5 (CH_3), 18.2 (C), 23.5 (CH_3), 25.9 (3 × CH_3), 31.8 (CH_2), 38.8 (CH_2), 42.6 (CH_2), 68.5 (CH), 72.5 (CH), 125.8 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.0 (CH), 135.0 (CH), 142.0 (C); *m*/*z*

(FAB/NOBA/NaI) 357.2221 ([MNa]$^+$. $C_{20}H_{34}O_2Si$ requires 357.2226), 333 (21%), 317 (6), 268 (18), 228 (17), 208 (7), 186 (18), 160 (86), 148 (38), 117 (78), 105 (24), 75 (77).

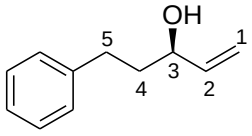
(4*E*,7*S*)-7-[(*tert*-Butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-ol



217

The reaction was carried out according to general procedure 3 using (4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-one **147** (0.060 g, 0.18 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 0.30 mL, 0.30 mmol) in toluene (5 mL). Purification by silica column chromatography, eluting with 1:9 ethyl acetate/petroleum ether gave (4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-ol **217** as a colourless oil (0.032 g, 53%). For analytical data, see above compound **152**.

(3*R*)-5-Phenylpent-1-en-3-ol[123]

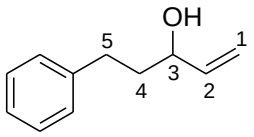


153

The reaction was carried out according to general procedure 2, using 5-phenylpent-1-en-3-one **136** (0.300 g, 1.87 mmol), (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 1.87 mL, 1.87 mmol) and borane tetrahydrofuran complex solution (1.0 M in tetrahydrofuran, 5.62 mL, 5.62 mmol) in tetrahydrofuran (10 mL). Purification was carried out by silica column chromatography, and elution with 1:9 ethyl acetate/petroleum ether gave (3*S*)-5-phenylpent-1-en-3-ol **153** as a colourless oil (0.225 g, 74%). Chiral HPLC (Chiralcel IB column) analysis using 5% isopropanol in hexane indicated 68% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.45; $[\alpha]_D^{25}$ +6.7 (*c* 1.0, $CHCl_3$), (lit.[123] $[\alpha]_D^{20}$ -5.8 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.55 (1H, d, *J* 3.9 Hz, OH), 1.79–1.93 (2H, m, 5-H_2), 2.64–2.80 (2H, m, 4-H_2), 4.09–4.17 (1H, m, 3-

H), 5.14 (1H, d, *J* 10.4 Hz, 1-*H*H), 5.25 (1H, d, *J* 17.2 Hz, 1-H*H*), 5.91 (1H, ddd, *J* 17.2, 10.4, 6.2 Hz, 2-H), 7.16–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 31.6 (CH_2), 38.5 (CH_2), 72.5 (CH), 115.0 (CH_2), 125.8 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 141.0 (CH), 141.8 (C); *m*/*z* (EI) 162.1041 (M^+. $C_{11}H_{14}O$ requires 162.1045), 144 (43%), 129 (76), 105 (91), 91 (100), 5 (66), 51 (24), 44 (12).

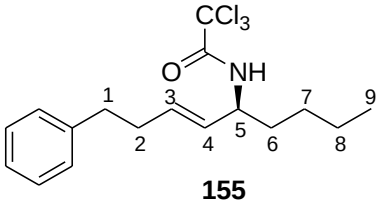
5-Phenylpent-1-en-3-ol[124]



rac-153

The reaction was carried out according to general procedure 3, using 5-phenylpent-1-en-3-one **136** (0.200 g, 1.25 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 1.90 mL, 1.90 mmol) in toluene (5 mL). Purification by silica column chromatography, eluting with 1:4 ethyl acetate/petroleum ether gave 5-phenylpent-1-en-3-ol **rac-153** as a colourless oil (0.085 g, 42%). For analytical data, see above compound **153**.

(3*E*,5*S*)-1-Phenyl-5-(trichloromethylcarbonylamino)non-3-ene

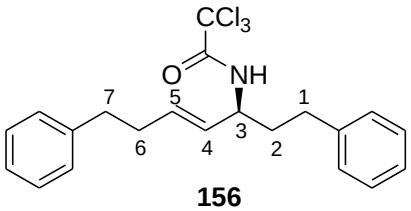


155

The trichloroacetimidate formation reaction was carried out according to general procedure 4, using (3*R*,4*E*)-1-phenylnon-4-en-3-ol **148** (0.253 g, 1.16 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.087 mL, 0.58 mmol), and trichloroacetonitrile (0.175 mL, 1.74 mmol) in dichloromethane (10 mL) to give the desired allylic trichloroacetimidate intermediate **154** (0.484 g). δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0 Hz, 1-H_3), 1.26–1.46 (4H, m, 2-H_2 and 3-H_2), 1.93–2.18 (4H, m, 4-H_2 and 8-H_2), 2.65–2.81 (2H, m, 9-H_2), 5.36 (1H, q, *J* 6.8 Hz, 7-H), 5.49 (1H, dd, *J* 15.4, 6.8 Hz, 6-H), 5.81 (1H, dt, *J* 15.4, 6.7 Hz, 5-H), 7.16–7.31 (5H, m, 5 × ArH), 8.27 (1H, s, NH).

This intermediate was then subjected to an Overman rearrangement reaction, carried out according to general procedure 5 using potassium carbonate (0.060 g, 0.43 mmol) in *p*-xylene (20 mL). Purification by silica column chromatography, eluting with 1:19 diethyl ether/petroleum ether, gave (3*E*,5*S*)-1-phenyl-5-(trichloromethylcarbonylamino)non-3-ene **155** as a colourless oil (0.283 g, 67% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.61; ν_{max}/cm^{-1} (NaCl) 3423 (NH), 2933 (CH), 1712 (CO), 1509, 908, 741; $[\alpha]_D^{17}$ +16.0 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0 Hz, 1-H_3), 1.21–1.36 (4H, m, 2-H_2 and 3-H_2), 1.54–1.59 (2H, m, 4-H_2), 2.37 (2H, q, *J* 7.4 Hz, 8-H_2), 2.70 (2H, t, *J* 7.4 Hz, 9-H_2), 4.29-4.36 (1H, m, 5-H), 5.35 (1H, dd, *J* 15.6, 6.4 Hz, 6-H), 5.69 (1H, dt, *J* 15.6, 7.4 Hz, 7-H), 6.43 (1H, br d, *J* 7.6 Hz, NH), 7.13–7.30 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.4 (CH_2), 27.7 (CH_2), 34.0 (CH_2), 34.5 (CH_2), 35.4 (CH_2), 53.2 (CH), 92.9 (C), 125.9 (CH), 128.3 (2 × CH), 128.5 (2 ×CH), 129.2 (CH), 132.2 (CH), 141.4 (C), 160.9 (C); *m*/*z* (CI) 362.0842 (MH^+. $C_{17}H_{23}{}^{35}Cl_3NO$ requires 362.0845), 329 (46%), 293 (80), 259 (35), 233 (76), 219 (100), 201 (36), 145 (51), 101 (25), 81 (48), 71 (46).

(3*S*,4*E*)-1,7-Diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene

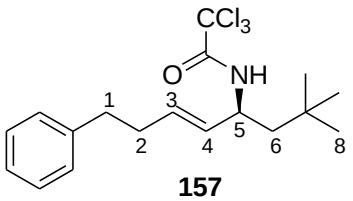


156

The trichloroacetimidate formation reaction was carried out according to general procedure 4 using (3*R*,4*E*)-1,7-diphenylhept-4-en-3-ol **149** (0.098 g, 0.37 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.18 mmol) and trichloroacetonitrile (0.06 mL, 0.55 mmol) in dichloromethane (5 mL) to give the desired allylic trichloroacetimidate intermediate (0.163 g). δ_H (400 MHz, $CDCl_3$) 1.90–2.00 (1H, m, 6-*H*H), 2.04–2.15 (1H, m, 6-H*H*), 2.38 (2H, q, *J* 6.8 Hz, 2-H_2), 2.60–2.76 (4H, m, 1-H_2 and 7-H_2), 5.34 (1H, q, *J* 6.6 Hz, 5-H), 5.50 (1H, ddt, *J* 15.4, 6.6, 1.3 Hz, 4-H), 5.84 (1H, dt, *J* 15.4, 6.8 Hz, 3-H), 7.13–7.21 (5H, m, 5 × ArH), 7.23–7.31 (5H, m, 5 × ArH), 8.26 (1H, s, NH). This was then subjected to an Overman rearrangement reaction, carried out according to general procedure 5 using potassium carbonate (0.015 g,

0.11 mmol) in *p*-xylene (5 mL). Purification by silica column chromatography and elution with 1:9 ethyl acetate/petroleum ether gave (3*S*,4*E*)-1,7-diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene **156** as a colourless oil (0.111 g, 73% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.53; ν_{max}/cm^{-1} (NaCl) 3422 (NH), 3019 (CH), 1713 (CO), 1509, 1216, 756; $[\alpha]_D^{21}$ -12.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.84–1.98 (2H, m, 2-H_2), 2.39–2.47 (2H, m, 6-H_2), 2.61 (2H, t, *J* 7.6 Hz, 1-H_2), 2.70 (2H, t, *J* 7.6 Hz, 7-H_2), 4.33–4.41 (1H, m, 3-H), 5.39 (1H, dd, *J* 15.6, 6.4 Hz, 4-H), 5.71 (1H, dt, *J* 15.6, 6.4 Hz, 5-H), 6.48 (1H, d, *J* 8.0 Hz, NH), 7.12–7.31 (10H, m, 10 × ArH); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_2), 32.0 (CH_2), 35.5 (CH_2), 36.4 (CH_2), 53.1 (CH), 92.9 (C), 126.1 (CH), 126.3 (CH), 128.5 (4 × CH), 128.6 (2 × CH), 128.7 (2 × CH), 128.8 (CH), 132.8 (CH), 141.0 (C), 141.4 (C), 161.1 (C); *m*/*z* (CI) 410.0847 (MH^+. $C_{21}H_{23}{}^{35}Cl_3NO$ requires 410.0845), 376 (18%), 343 (12), 307 (8), 249 (11), 216 (5), 167 (7), 136 (12), 85 (66), 73 (100).

(3*E*,5*S*)-7,7-Dimethyl-5-(trichloromethylcarbonylamino)-1-phenyloct-3-ene

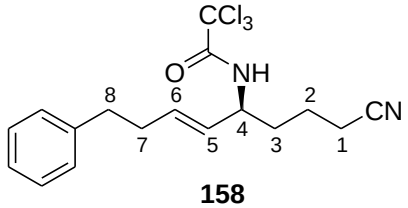


157

The acetimidate formation reaction was carried out according to general procedure 4 using (3*R*,4*E*)-7,7-dimethyl-1-phenyloct-4-en-3-ol **150** (0.123 g, 0.53 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 mL, 0.27 mmol) and trichloroacetonitrile (0.08 mL, 0.79 mmol) in dichloromethane (5 mL) to give the desired allylic trichloroacetimidate (0.284 g). δ_H (400 MHz, $CDCl_3$) 0.87 (9H, s, $C(CH_3)_3$), 1.93 (2H, d, *J* 7.6 Hz, 3-H_2), 1.95–2.05 (1H, m, 7-*H*H), 2.09–2.20 (1H, m, 7-H*H*), 2.66–2.83 (2H, m, 8-H_2), 5.36 (1H, dt, *J* 6.8, 6.2 Hz, 6-H), 5.48 (1H, dd, *J* 15.3, 6.8 Hz, 5-H), 5.86 (1H, dt, *J* 15.3, 7.6 Hz, 4-H), 7.16–7.31 (5H, m, 5 × ArH), 8.28 (1H, s, NH). This was then subjected to an Overman rearrangement reaction, carried out according to general procedure 5 using potassium carbonate (0.018 g, 0.13 mmol) in *p*-xylene (6 mL). Purification by silica column chromatography, eluting with 1:19 ethyl acetate/petroleum ether gave (3*E*,5*S*)-7,7-dimethyl-5-(trichloromethylcarbonylamino)-1-phenyloct-3-ene **157** as a white solid (0.206 g,

100% over 2 steps). Mp 66–69 °C; R_f (1:4 ethyl acetate/petroleum ether) 0.59; ν_{max}/cm^{-1} (NaCl) 3338 (NH), 2955 (CH), 1689 (CO), 1518, 1245, 822; $[\alpha]_D^{22}$ -24.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.95 (9H, s, $C(CH_3)_3$), 1.44 (1H, dd, *J* 14.4, 8.0 Hz, 3-*H*H), 1.53 (1H, dd, *J* 14.4, 4.8 Hz, 3-H*H*), 2.35 (2H, dt, *J* 7.2, 7.0 Hz, 7-H_2), 2.68 (2H, t, *J* 7.2, 8-H_2), 4.40–4.49 (1H, m, 4-H), 5.36 (1H, ddt, *J* 15.4, 6.8, 1.2 Hz, 5-H), 5.68 (1H, dtd, *J* 15.4, 7.0, 1.2 Hz, 6-H), 6.41 (1H, d, *J* 8.0 Hz, NH), 7.14–7.29 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 29.9 (3 × CH_3), 30.5 (C), 34.0 (CH_2), 35.4 (CH_2), 48.9 (CH_2), 50.8 (CH), 92.9 (C), 125.9 (CH), 128.3 (2 × CH), 128.5 (2 × CH), 130.8 (CH), 131.0 (CH), 141.5 (C), 160.2 (C); *m/z* (CI) 376.1005 (MH^+. $C_{18}H_{25}{}^{35}Cl_3NO$ requires 376.1002), 342 (49%), 306 (100), 272 (43), 270 (15), 215 (10), 168 (36), 154 (6), 107 (57), 71 (49).

(4*S*,5*E*)-1-Cyano-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene

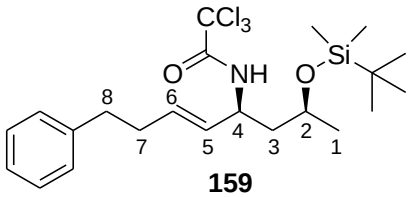


158

The trichloroacetimidate formation reaction was set up according to general procedure 4 using (4*E*,6*R*)-1-cyano-8-phenyloct-4-en-6-ol **151** (0.182 g, 0.79 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.060 mL, 0.40 mmol) and trichloroacetonitrile (0.120 mL, 1.20 mmol) in dichloromethane (6 mL). After stirring for 18 h, further 1,8-diazabicyclo[5.4.0]undec-7-ene (0.030 mL, 0.20 mmol) and trichloroacetonitrile (0.060 mL, 0.60 mmol) were added and the reaction mixture was stirred again at room temperature for 6 h to give the desired allylic trichloroacetimidate intermediate (0.318 g). δ_H (400 MHz, $CDCl_3$) 1.71–1.79 (2H, m, 2-H_2), 1.94–2.04 (1H, m, 7-*H*H), 2.09–2.19 (1H, m, 7-H*H*), 2.23 (2H, q, *J* 6.9 Hz, 3-H_2), 2.32 (2H, t, *J* 7.2 Hz, 1-H_2), 2.66–2.83 (2H, m, 8-H_2), 5.31–5.38 (1H, m, 6-H), 5.59 (1H, dd, *J* 15.4, 6.5 Hz, 5-H), 5.74 (1H, dtd, *J* 15.4, 6.9, 0.9 Hz, 4-H), 7.16–7.32 (5H, m, 5 × ArH), 8.29 (1H, s, NH). This was then subjected to an Overman rearrangement reaction, carried out according to general procedure 5 using potassium carbonate (0.020 g,

0.14 mmol) in *p*-xylene (7 mL). Purification by silica column chromatography, and elution with 1:4 ethyl acetate/petroleum ether gave (4*S*,5*E*)-1-cyano-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **158** as a pale yellow oil (0.241 g, 81% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.24; ν_{max}/cm^{-1} (NaCl) 3330 (NH), 2928 (CH), 2250 (CN), 1702 (CO), 1517, 822, 734; $[\alpha]_D^{23}$ -13.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.55–1.65 (2H, m, 2-H_2), 1.68–1.77 (2H, m, 3-H_2), 2.35–2.43 (4H, m, 1-H_2 and 7-H_2), 2.71 (2H, t, *J* 7.4 Hz, 8-H_2), 4.30–4.38 (1H, m, 4-H), 5.33 (1H, ddt, *J* 15.4, 6.8, 1.3 Hz, 5-H), 5.73 (1H, dtd, *J* 15.4, 6.8, 1.0 Hz, 6-H), 6.46 (1H, d, *J* 8.1 Hz, NH), 7.13–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 16.9 (CH_2), 21.7 (CH_2), 33.7 (CH_2), 33.9 (CH_2), 35.2 (CH_2), 52.5 (CH), 92.8 (C), 119.2 (C), 126.1 (CH), 128.2 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 133.7 (CH), 141.1 (C), 161.3 (C); *m*/*z* (CI) 373.0640 (MH^+. $C_{17}H_{20}{}^{35}Cl_3N_2O$ requires 373.0641), 339 (30%), 305 (13), 288 (12), 269 (8), 212 (11), 186 (17), 162 (23), 132 (13), 128 (8), 107 (37), 85 (23), 79 (100), 69 (28).

(2*S*,4*S*,5*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene

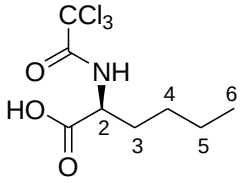


159

The trichloroacetimidate formation reaction was carried out according to general procedure 4, using (3*R*,4*E*,7*S*)-7-[(*tert*-butyldimethylsilyl)oxy]-1-phenyloct-4-en-3-ol **152** (0.100 g, 0.30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.022 mL, 0.15 mmol) and trichloroacetonitrile (0.045 mL, 0.45 mmol) in dichloromethane (5 mL) to give the desired allylic trichloroacetimidate intermediate as a colourless oil (0.130 g). δ_H (400 MHz, $CDCl_3$) 0.03 (6H, s, 2 × $SiCH_3$), 0.87 (9H, s, $SiC(CH_3)_3$), 1.11 (3H, d, *J* 6.1 Hz, 1-H_3), 1.92–2.04 (1H, m, 3-*H*H), 2.07–2.28 (3H, m, 3-H*H* and 7-H_2), 2.64–2.82 (2H, m, 8-H_2), 3.78–3.89 (1H, m, 2-H), 5.33–5.42 (1H, m, 6-H), 5.54 (1H, dd, *J* 15.3, 7.0 Hz, 5-H), 5.82 (1H, dt, *J* 15.3, 7.2 Hz, 4-H), 7.15–7.32 (5H, m, 5 × ArH), 8.27 (1H, s, NH). This was then subjected to an Overman rearrangement reaction, carried out according to general procedure 5, using potassium carbonate

(0.015 g, 0.11 mmol) in *p*-xylene (5 mL). Purification by silica column chromatography, eluting with 1:19 ethyl acetate/petroleum ether gave (2*S*,4*S*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **159** as a colourless oil (0.124 g, 87% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.57; ν_{max}/cm^{-1} (NaCl) 3373 (NH), 2928 (CH), 1702 (CO), 1514, 1254, 1079, 835; $[\alpha]_D^{19}$ -12.0 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.18 (3H, d, *J* 6.0 Hz, 1-H_3), 1.60–1.68 (1H, m, 3-*H*H), 1.71–1.79 (1H, m, 3-H*H*), 2.37 (2H, q, *J* 7.0 Hz, 7-H_2), 2.70 (2H, t, *J* 7.0 Hz, 8-H_2), 3.82 (1H, q, *J* 6.0 Hz, 2-H), 4.46 (1H, quin, *J* 6.8 Hz, 4-H), 5.40 (1H, dd, *J* 15.4, 6.8 Hz, 5-H), 5.72 (1H, dt, *J* 15.4, 7.0 Hz, 6-H), 6.52 (1H, d, *J* 8.0 Hz, NH), 7.14–7.30 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) -4.6 (CH_3), -4.1 (CH_3), 18.1 (C), 24.0 (CH_3), 25.9 (3 × CH_3), 34.0 (CH_2), 35.4 (CH_2), 44.8 (CH_2), 50.7 (CH), 65.8 (CH), 92.9 (C), 126.0 (CH), 128.4 (2 × CH), 128.5 (2 × CH), 129.1 (CH), 132.4 (CH), 141.4 (C), 160.7 (C); *m*/*z* (CI) 480.1490 (MH^+. $C_{22}H_{35}{}^{35}Cl_2{}^{37}ClNO_2Si$ requires 480.1477), 478 (97%), 444 (75), 410 (19), 408 (15), 352 (14), 346 (8), 318 (5), 159 (11), 133 (8), 81 (4).

(2*S*)-2-(Trichloromethylcarbonylamino)hexanoic acid[47]

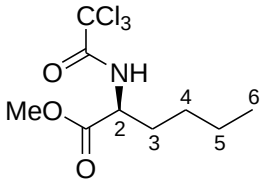


160

(5*S*,6*E*)-9-Phenyl-5-(trichloromethylcarbonylamino)non-6-ene **155** (0.240 g, 0.66 mmol) was dissolved in acetonitrile (9 mL) and carbon tetrachloride (9 mL) and to the stirred solution, sodium periodate (0.580 g, 2.71 mmol, dissolved in 12 mL of water) was added. Ruthenium(III) chloride hydrate (0.007 g, 0.03 mmol) was then added, and the resulting reaction mixture was stirred at room temperature for 26 h before further sodium periodate (0.283 g, 1.32 mmol) and ruthenium(III) chloride hydrate (0.004 g, 0.02 mmol) were added. The reaction mixture was stirred at room temperature for a further 22 h and the organic layers were extracted from the mixture using dichloromethane (100 mL), combined and then concentrated *in*

vacuo. The residue was dissolved in ethyl acetate (100 mL) and washed with a saturated aqueous solution of sodium hydrogen carbonate (100 mL) and then a saturated aqueous solution of ammonium chloride (100 mL). The aqueous phases, found to contain the desired product, were then combined and acidified using 2 M hydrochloric acid before being extracted using ethyl acetate (2 × 125 mL). The organic phases were then combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification was carried out using silica column chromatography, and elution with 1:1 ethyl acetate/petroleum ether gave (2*S*)-2-(trichloromethylcarbonylamino)hexanoic acid **160** as a colourless oil (0.053 g, 29%). R_f (1:4 ethyl acetate/petroleum ether) 0.23; $[\alpha]_D^{22}$ +15.9 (*c* 0.85, $CHCl_3$) (lit.[46] $[\alpha]_D^{29}$ +35.2) (*c* 0.27, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.0 Hz, 6-H_3), 1.32–1.42 (4H, m, 4-H_2 and 5-H_2), 1.79–1.91 (1H, m, 3-*H*H), 1.99–2.10 (1H, m, 3-H*H*), 4.63 (1H, dt, *J* 7.3, 5.5 Hz, 2-H), 7.16 (1H, d, *J* 7.3 Hz, NH); δ_C (100 MHz, $CDCl_3$) 13.8 (CH_3), 22.2 (CH_2), 27.0 (CH_2), 31.5 (CH_2), 53.8 (CH), 92.1 (C), 161.6 (C), 176.1 (C); *m/z* (CI) 275.9953 (MH^+. $C_8H_{13}{}^{35}Cl_3NO_3$ requires 275.9961), 242 (71%), 230 (5), 208 (13), 196 (9), 162 (24), 158 (11), 113 (11), 81 (23), 69 (24).

Methyl (2*S*)-2-(trichloromethylcarbonylamino)hexanoate

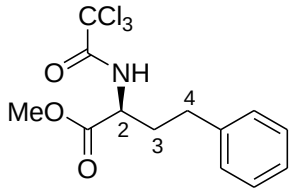


161

The reaction was carried out according to general procedure 6, using (5*S*,6*E*)-9-phenyl-5-(trichloromethylcarbonylamino)non-6-ene **155** (0.142 g, 0.39 mmol), sodium periodate (0.343 g, 1.61 mmol, dissolved in 9 mL of water), and ruthenium(III) chloride hydrate (0.010 g, 0.05 mmol) in acetonitrile (6 mL) and carbon tetrachloride (6 mL) to give a green/blue oil (0.122 g), which was reacted with thionyl chloride (0.20 mL, 2.74 mmol) in methanol (5 mL). Purification by silica column chromatography, eluting with 1:9 diethyl ether/petroleum ether gave methyl (2*S*)-2-(trichloromethylcarbonylamino)hexanoate **161** as a colourless oil (0.039 g, 34% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.58; $[\alpha]_D^{25}$

+19.0 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.87–0.93 (3H, m, 6-H_3), 1.30–1.40 (4H, m, 4-H_2 and 5-H_2), 1.72–1.83 (1H, m, 3-*H*H), 1.92–2.04 (1H, m, 3-H*H*), 3.81 (3H, s, OCH_3), 4.58 (1H, q, *J* 6.2 Hz, 2-H), 7.14 (1H, d, *J* 6.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 13.9 (CH_3), 22.2 (CH_2), 27.0 (CH_2), 31.7 (CH_2), 52.9 (CH_3), 54.0 (CH), 92.2 (C), 161.4 (C), 171.9 (C); *m*/*z* (CI) 290.0130 (MH^+. $C_9H_{15}{}^{35}Cl_3NO_3$ requires 290.0118), 256 (100%), 222 (20), 179 (10), 127 (5), 85 (40), 69 (55).

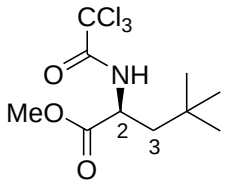
Methyl (2*S*)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate



162

The reaction was carried out according to general procedure 6 using (3*S*,4*E*)-1,7-diphenyl-3-(trichloromethylcarbonylamino)hept-4-ene **156** (0.100 g, 0.24 mmol), sodium periodate (0.213 g, 1.00 mmol, dissolved in 9 mL of water) and ruthenium(III) chloride hydrate (0.003 g, 0.01 mmol) in acetonitrile (6 mL) and carbon tetrachloride (6 mL) to give a blue/black oil (0.094 g), which was reacted with thionyl chloride (0.12 mL, 1.65 mmol) in methanol (5 mL). Purification by silica column chromatography, eluting with 1:9 ethyl acetate/petroleum ether gave methyl (2*S*)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate **162** as a colourless oil (0.035 g, 42%). R_f (1:4 ethyl acetate/petroleum ether) 0.39; ν_{max}/cm^{-1} (NaCl) 3344 (NH), 2925 (CH), 1742 (CO), 1713 (CO), 1513, 1455, 1215, 821; $[\alpha]_D^{21}$ +29.9 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.05–2.14 (1H, m, 3-*H*H), 2.22–2.32 (1H, m, 3-H*H*), 2.55–2.69 (2H, m, 4-H_2), 3.71 (3H, s, OCH_3), 4.56 (1H, q, *J* 5.2 Hz, 2-H), 7.08–7.33 (6H, m, 5 × ArH and NH); δ_C (100 MHz, $CDCl_3$) 31.3 (CH_2), 33.3 (CH_2), 52.9 (CH_3), 53.7 (CH), 93.6 (C), 126.5 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 140.0 (C), 161.5 (C), 171.5 (C); *m*/*z* (CI) 338.0117 (MH^+.$C_{13}H_{15}{}^{35}Cl_3NO_3$ requires 338.0118), 304 (45%), 69 (12).

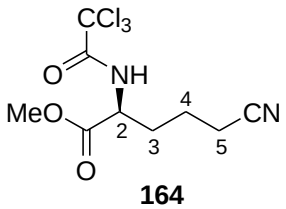
Methyl (2*S*)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate



163

The reaction was carried out according to general procedure 6 using (4*S*,5*E*)-2,2-dimethyl-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **157** (0.150 g, 0.40 mmol), sodium periodate (0.349 g, 1.63 mmol, dissolved in 9 mL of water) and ruthenium(III) chloride (0.008 g, 0.04 mmol) in acetonitrile (6 mL) and carbon tetrachloride (6 mL) to give a blue/black oil (0.160 g), which was then reacted with thionyl chloride (0.2 mL, 2.74 mmol) in methanol (5 mL). Purification by silica column chromatography, eluting with 3:17 diethyl ether/petroleum ether gave methyl (2*S*)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate **163** as a pale yellow solid (0.075 g, 62%). Mp 76-79 °C; R_f (1:4 ethyl acetate/petroleum ether) 0.41; ν_{max}/cm^{-1} (NaCl) 3422 (NH), 2960 (CH), 1743 (CO), 1716 (CO), 1516, 1371, 1215, 908; $[\alpha]_D^{22}$ -3.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.00 (9H, s, $C(CH_3)_3$), 1.58–1.70 (1H, m, 3-*H*H), 1.88 (1H, dd, *J* 14.6, 3.1 Hz, 3-H*H*), 3.78 (3H, s, OCH_3), 4.62 (1H, td, *J* 8.6, 3.1 Hz, 2-H), 6.94 (1H, br m, NH); δ_C (100 MHz, $CDCl_3$) 29.5 (3 × CH_3), 30.7 (C), 45.8 (CH_2), 51.8 (CH_3), 52.8 (CH), 106.9 (C), 161.4 (C), 172.3 (C); *m/z* (CI) 304.0264 (MH^+. $C_{10}H_{17}{}^{35}Cl_3NO_3$ requires 304.0274), 270 (86%), 254 (10), 236 (19), 113 (9), 81 (32), 69 (29).

Methyl (2*S*)-5-cyano-2-(trichloromethylcarbonylamino)pentanoate

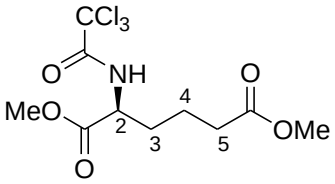


164

The reaction was carried out according to general procedure 6, using (4*S*,5*E*)-1-cyano-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **158** (0.120 g, 0.32 mmol), sodium periodate (0.282 g, 1.37 mmol, dissolved in 6 mL of water) and ruthenium(III) chloride hydrate (0.007 g, 0.03 mmol) in acetonitrile (4 mL) and

carbon tetrachloride (4 mL), stirring for 18 h to give a black oil (0.099 g), which was reacted with thionyl chloride (0.240 mL, 3.29 mmol) in methanol (7 mL). Purification by silica column chromatography, eluting with 3:7 ethyl acetate/petroleum ether gave methyl (2*S*)-5-cyano-2-(trichloromethylcarbonylamino)pentanoate **164** as a colourless oil (0.056g, 58%). R_f (1:4 ethyl acetate/petroleum ether) 0.09; ν_{max}/cm^{-1} (NaCl) 3339 (NH), 2918 (CH), 2253 (CN), 1744 (CO), 1712 (CO), 1521, 1439, 1217, 912, 735; $[\alpha]_D^{21}$ +8.1 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.65–1.85 (2H, m, 4-H_2), 1.88–1.98 (1H, m, 3-*H*H), 2.13–2.23 (1H, m, 3-H*H*), 2.44 (2H, t, *J* 7.0 Hz, 5-H_2), 3.85 (3H, s, OCH_3), 4.61 (1H, td, *J* 7.5, 6.0 Hz, 2-H), 7.33 (1H, d, *J* 6.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 16.8 (CH_2), 21.4 (CH_2), 31.3 (CH_2), 53.1 (CH_3), 53.3 (CH), 92.0 (C), 118.8 (C), 161.9 (C), 171.1 (C); *m/z* (CI) 300.9900 (MH^+. $C_9H_{12}{}^{35}Cl_3N_2O_3$ requires 300.9914), 267 (76%), 251 (10), 233 (48), 199 (9), 183 (9), 155 (12), 142 (8), 113 (25), 107 (85), 71 (100).

(2*S*)-Dimethyl-2-(trichloromethylcarbonylamino)-hexadioate

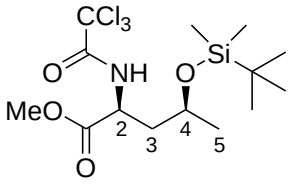


165

The reaction was carried out according to general procedure 6, using (4*S*,5*E*)-1-cyano-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **158** (0.109 g, 0.29 mmol), sodium periodate (0.256 g, 1.20 mmol, dissolved in 6 mL of water) and ruthenium(III) chloride hydrate (0.006 g, 0.03 mmol) in acetonitrile (4 mL) and carbon tetrachloride (4 mL). After stirring for 18 h, further sodium periodate (0.064 g, 0.30 mmol) and ruthenium(III) chloride hydrate (0.002 g, 0.01 mmol) were added, and the reaction was stirred for a futher 6 h to give a blue/black oil (0.102 g), which was reacted with thionyl chloride (0.30 mL, 4.11 mmol) in methanol (7 mL). Purification by silica column chromatography, and elution with 1:4 ethyl acetate/petroleum ether gave (2*S*)-dimethyl-2-(trichloromethylcarbonylamino)-hexadioate **165** as a colourless oil (0.034 g, 35%). ν_{max}/cm^{-1} (neat) 3300 (NH), 2955 (CH), 1738 (CO), 1719 (CO), 1703 (CO), 1520, 1439, 1360, 1263, 1209, 1163, 1121,

821; $[\alpha]_D^{23}$ +19.5 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.59–1.78 (2H, m, 4-H_2), 1.79–1.90 (1H, m, 3-*H*H), 1.96–2.08 (1H, m, 3-H*H*), 2.37 (2H, t, *J* 7.2 Hz, 5-H_2), 3.68 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 4.58 (1H, td, *J* 7.0, 5.2 Hz, 2-H), 7.34 (1H, d, *J* 7.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_2), 31.2 (CH_2), 33.1 (CH_2), 51.7 (CH_3), 53.0 (CH_3), 53.7 (CH), 92.1 (C), 161.6 (C), 171.4 (C), 173.3 (C); *m*/*z* (CI) 334.0002 (MH^+. $C_{10}H_{15}{}^{35}Cl_3NO_5$ requires 334.0016), 300 (24%), 266 (10), 167 (8), 137 (21), 107 (51), 73 (100). Further elution with 1:3 ethyl acetate/petroleum ether also gave methyl (2*S*)-5-nitrile-2-(trichloromethylcarbonylamino)pentanoate **141** as a colourless oil (0.015 g, 17%). (For full analytical data, see above compound **141**).

Methyl (2*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino)pentanoate

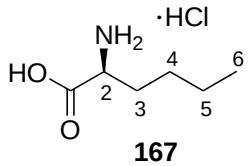


166

(2*S*,4*S*,5*E*)-2-[(*tert*-butyldimethylsilyl)oxy]-4-(trichloromethylcarbonylamino)-8-phenyloct-5-ene **159** (0.107 g, 0.22 mmol) was dissolved in *tert*-butanol (2 mL) and to the stirred solution, potassium carbonate (0.093 g, 0.67 mmol, dissolved in 4 mL of water) was added, followed by sodium periodate (0.143 g, 0.67 mmol) and potassium permanganate (0.032 g, 0.20 mmol). The reaction mixture was stirred at room temperature for 48 h before further potassium carbonate (0.047 g, 0.34 mmol), sodium periodate (0.072 g, 0.34 mmol) and potassium permanganate (0.016 g, 0.10 mmol) were added. The reaction mixture was stirred at room temperature for a further 40 h before potassium carbonate (0.031 g, 0.22 mmol), sodium periodate (0.048 g, 0.22 mmol) and potassium permanganate (0.011 g, 0.07 mmol) were added. The reaction was stirred again at room temperature for 18 h and then filtered through a pad of Celite® and washed with ethyl acetate (50 mL). Water (50 mL) was added to the filtrate, and the layers were separated. The organic layers were further extracted using ethyl acetate (3 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give a yellow oil (0.094 g). This residue was then dissolved in toluene (5 mL) and methanol (5 mL),

and (trimethylsilyl)diazomethane solution (2.0 M in diethyl ether, 2.20 mL, 4.40 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 1.75 h before being concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:9 diethyl ether/petroleum ether gave methyl (2*S*,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino)pentanoate **166** as a colourless oil (0.027 g, 30% over 2 steps). R_f (1:4 ethyl acetate/petroleum ether) 0.46; ν_{max}/cm^{-1} (NaCl) 3420 (NH), 2858 (CH), 1638 (CO), 1254, 1142, 822; $[\alpha]_D^{20}$ +25.6 (*c* 0.75, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, $SiCH_3$), 0.07 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.0 Hz, 5-H_3), 1.98–2.08 (1H, m, 3-*H*H), 2.09–2.18 (1H, m, 3-H*H*), 3.79 (3H, s, OCH_3), 3.95–4.04 (1H, m, 4-H), 4.57 (1H, q, *J* 5.9 Hz, 2-H), 7.51 (1H, d, *J* 5.9 Hz, NH); δ_C (100 MHz, $CDCl_3$) -4.5 (CH_3), -4.3 (CH_3), 18.2 (C), 23.6 (CH_3), 26.0 (3 × CH_3), 40.4 (CH_2), 51.8 (CH_3), 52.8 (CH), 65.7 (CH), 92.2 (C), 161.5 (C), 171.7 (C); *m*/*z* (CI) 408.0746 (MH^+. $C_{14}H_{27}{}^{35}Cl_2{}^{37}ClNO_4Si$ requires 408.0748), 372 (39%), 338 (13), 314 (5), 271 (9), 240 (11), 207 (6), 173 (9), 133 (7), 113 (40), 69 (100).

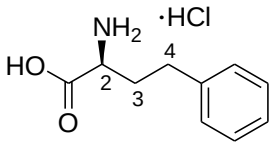
(2*S*)-2-Aminohexanoic acid hydrochloride[125]



167

The reaction was carried out according to general procedure 7, using methyl (2*S*)-2-(trichloromethylcarbonylamino)hexanoate **161** (0.027 g, 0.09 mmol) in 6 M hydrochloric acid (5 mL), stirring under reflux for 18 h to give (2*S*)-2-aminohexanoic acid hydrochloride **167** as a pale yellow solid (0.012 g, 77%). Mp 184–190 °C; $[\alpha]_D^{24}$ +26.7 (*c* 1.0, 6 M HCl) (lit.[125] $[\alpha]_D^{20}$ +10.3 (*c* 1.05, H_2O); δ_H (400 MHz, D_2O) 0.87 (3H, t, *J* 6.7 Hz, 6-H_3), 1.30–1.42 (4H, m, 4-H_2 and 5-H_2), 1.80–2.00 (2H, m, 3-H_2), 4.00 (1H, t, *J* 6.1 Hz, 2-H); δ_C (100 MHz, D_2O) 12.9 (CH_3), 21.5 (CH_2), 26.2 (CH_2), 29.4 (CH_2), 53.2 (CH), 172.7 (C); *m*/*z* (CI) 132.1023 (MH^+. $C_6H_{14}NO_2$ requires 132.1025), 113 (13%), 97 (13), 81 (23), 71 (22).

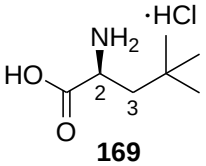
(2*S*)-2-Amino-4-phenylbutanoic acid hydrochloride[126]



168

The reaction was carried out according to general procedure 7 using methyl (2*S*)-4-phenyl-2-(trichloromethylcarbonylamino)butanoate **162** (0.018 g, 0.05 mmol) in 6 M hydrochloric acid, stirring under reflux for 20 h to give (2*S*)-2-amino-4-phenylbutanoic acid hydrochloride **168** as a yellow solid (0.024 g, 100%). Mp 244–247 °C (lit.[126] Mp 250–260 °C); $[\alpha]_D^{23}$ +4.7 (*c* 1.0, 1 M HCl) (lit.[126] $[\alpha]_D^{20}$ +40.0 (*c* 0.6, 3 M HCl); δ_H (400 MHz, D_2O) 2.15–2.36 (2H, m, 3-H_2), 2.70–2.88 (2H, m, 4-H_2), 4.07 (1H, t, *J* 5.8 Hz, 2-H), 7.27–7.43 (5H, m, 5 × ArH); δ_C (100 MHz, D_2O) 30.5 (CH_2), 31.9 (CH_2), 57.4 (CH), 126.6 (CH), 128.5 (2 × CH), 128.9 (2 × CH), 140.3 (C), 173.3 (C); *m*/*z* (CI) 180 (MH^+, 4%), 161 (22), 137 (56), 113 (31), 97 (33), 81 (73), 69 (100).

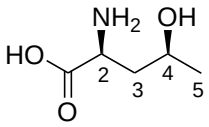
(2*S*)-2-Amino-4,4-dimethylpentanoic acid hydrochloride[127]



169

The reaction was carried out according to general procedure 7 using methyl (2*S*)-4,4-dimethyl-2-(trichloromethylcarbonylamino)pentanoate **163** (0.047 g, 0.15 mmol) in 6 M hydrochloric acid (5 mL), stirring under reflux for 24 h to give (2*S*)-2-amino-4,4-dimethylpentanoic acid hydrochloride **169** as a pale yellow solid (0.040 g, 100%). Mp 198–202 °C; ν_{max}/cm^{-1} (neat) 3395 (NH), 2955 (CH), 1744 (CO), 1636, 1404, 1211, 1072, 1026; $[\alpha]_D^{21}$ -50.0 (c 0.1, AcOH); δ_H (400 MHz, D_2O) 1.00 (9H, s, $C(CH_3)_3$), 1.70 (1H, dd, *J* 15.0, 5.6 Hz, 3-*H*H), 2.04 (1H, dd, *J* 15.0, 5.6 Hz, 3-H*H*), 4.07 (1H, t, *J* 5.6 Hz, 2-H); δ_C (100 MHz, D_2O) 28.3 (3 × CH_3), 29.6 (C), 43.8 (CH_2), 50.5 (CH), 173.2 (C); *m*/*z* (CI) 146.1188 (MH^+. $C_7H_{16}NO_2$ requires 146.1181), 135 (6%), 113 (10), 97 (13), 81 (26), 69 (32).

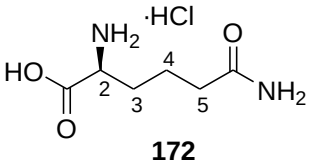
(2*S*,4*S*)-4-Hydroxy-2-aminopentanoic acid[128]



170

The reaction was carried out according to general procedure 7, using methyl (2S,4*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-(trichloromethylcarbonylamino) pentanoate **166** (0.026 g, 0.06 mmol) in 6.0 M hydrochloric acid (4 mL), stirring under reflux for 16 h. Purification was carried out using a DOWEX ion exchange column and elution with 0.5 M ammonium hydroxide solution gave (2*S*,4*S*)-4-hydroxy-2-aminopentanoic acid **170** as a yellow solid (0.006 g, 71%). Mp >250 °C (decomposition) (lit.[128] Mp 228–230 °C); ν_{max}/cm^{-1} 3350 (NH_2, OH), 1601 (CO), 1406, 1117, 1022, 721; $[\alpha]_D^{20}$ +18.6 (*c* 0.2, H_2O) (lit.[128] $[\alpha]_D^{20}$ +21.0 (*c* 1.3, H_2O)); δ_H (400 MHz, D_2O) 1.27 (3H, d, *J* 6.6 Hz, 5-H_3), 1.76–1.84 (1H, m, 3-*H*H), 2.09–2.15 (1H, m, 3-H*H*), 3.82 (1H, dd, *J* 9.4, 4.4 Hz, 2-H), 4.08–4.12 (1H, m, 4-H); δ_C (100 MHz, D_2O) 22.7 (CH_3), 38.6 (CH_2), 54.2 (CH), 66.7 (CH), 174.7 (C); *m*/*z* (CI) 134 (MH^+, 5%), 116 (100), 97 (13), 71 (23).

L-2-aminoadipic acid-6-amide hydrochloride

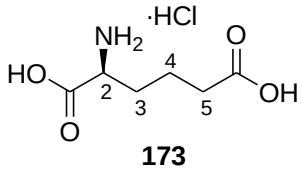


172

A stirred solution of methyl (2*S*)-5-cyano-2-(trichloromethylcarbonylamino)pentanoate **164** (0.025 g, 0.08 mmol) in *tert*-butanol (0.6 mL) and water (0.3 mL) was cooled to 0 °C before lithium hydroxide hydrate (0.008 g, 0.18 mmol) was added. The reaction mixture was stirred at 0 °C for 0.25 h, and then at room temperature for 3 h before being concentrated *in vacuo* to give a pale yellow residue (0.033 g), which was then dissolved in 6 M hydrochloric acid (5 mL). The reaction mixture was allowed to stir under reflux for 24 h before being allowed to cool to room temperature and concentrated *in vacuo*. The residue was partitioned between water (20 mL) and diethyl ether (20 mL), and

the aqueous phase was concentrated *in vacuo* to give L-2-aminoadipic acid-6-amide hydrochloride **172** as a white solid (0.023 g, 100%). Mp 168–172 °C; ν_{max}/cm^{-1} (NaCl) 3329 (NH_2), 2949 (CH), 1697 (CO), 1526, 1437, 1342, 1209, 1026, 821, 779; $[\alpha]_D^{23}$ +10.0 (*c* 2.0, 1 M HCl); δ_H (400 MHz, D_2O) 1.59–1.80 (2H, m, 4-H_2), 1.84–2.02 (2H, m, 3-H_2), 2.46 (2H, t, *J* 7.2 Hz, 5-H_2), 3.88 (1H, t, *J* 6.0 Hz, 2-H); δ_C (100 MHz, D_2O) 22.7 (CH_2), 32.1 (CH_2), 35.9 (CH_2), 56.1 (CH), 175.5 (C), 180.7 (C); *m/z* (CI) 151 (8%), 135 (23), 113 (62), 85 (72), 71 (90).

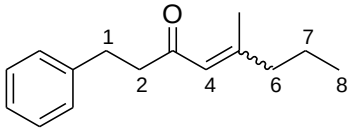
L-2-aminoadipic acid hydrochloride[129]



173

The reaction was carried out according to general procedure 7, using (2*S*)-dimethyl -2-(trichloromethylcarbonylamino)hexadioate **165** (0.027 g, 0.08 mmol) in 6 M hydrochloric acid (5 mL), stirring under reflux for 19 h to give L-2-aminoadipic acid hydrochloride **173** as a pale yellow solid (0.018 g, 100%). Mp 173–175 °C (lit.[129] Mp 170–172 °C); ν_{max}/cm^{-1} 3366 (NH_2), 2936 (CH), 1670 (CO), 1643 (CO), 1587, 1497, 1292, 1217, 1132, 1030, 764; $[\alpha]_D^{25}$ +27.8 (*c* 0.3, 6 M HCl) (lit.[129] $[\alpha]_D^{25}$ +23.5 (*c* 1.0, 5 M HCl)); δ_H (400 MHz, D_2O) 1.63–1.84 (2H, m, 4-H_2), 1.89–2.09 (2H, m, 3-H_2), 2.47 (2H, t, *J* 7.2 Hz, 5-H_2), 4.07 (1H, t, *J* 6.2 Hz, 2-H); δ_C (100 MHz, D_2O) 23.0 (CH_2), 32.4 (CH_2), 36.2 (CH_2), 56.1 (CH), 175.5 (C), 181.0 (C); *m/z* (CI) 144 (100%), 107 (19), 85 (34), 69 (50).

5-Methyl-1-phenyloct-4-en-3-one



174

To a stirred solution of 5-phenylpent-1-en-3-one **136** (0.10 g, 0.6 mmol) in toluene (5 mL), 2-methyl-1-pentene (0.230 mL, 1.86 mmol) was added, followed by

Hoveyda-Grubbs 2nd generation catalyst **L** (0.078 g, 0.12 mmol). The reaction mixture was heated to 80 °C and stirred for 24 h before being allowed to cool to room temperature and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:39 diethyl ether/petroleum ether gave (4*Z*)-5-methyl-1-phenyloct-4-en-3-one ***Z*-174** as a colourless oil (0.026 g, 19%), and (4*E*)-5-methyl-1-phenyloct-4-en-3-one ***E*-174** as a colourless oil (0.030 g, 22%). (NB: ^{1}H NMR spectroscopic analysis of the crude reaction product prior to purification indicated a 1:2 *Z*:*E*-product ratio).

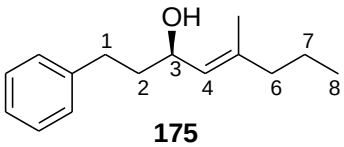
***Z*-isomer:**

R_f (1:4 ethyl acetate/petroleum ether) 0.64; ν_{max}/cm^{-1} (neat) 2960 (CH), 1686 (CO), 1614 (C=C), 1454, 1363, 1115, 1031, 748; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.4 Hz, 1-H_3), 1.35–1.45 (2H, m, 2-H_2), 1.79 (3H, d, *J* 1.4 Hz, 4-CH_3), 2.48–2.53 (2H, m, 3-H_2), 2.64–2.69 (2H, m, 7-H_2), 2.82–2.87 (2H, m, 8-H_2), 5.96–5.98 (1H, m, 5-H), 7.09–7.23 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.5 (CH_2), 25.5 (CH_3), 30.1 (CH_2), 35.7 (CH_2), 45.8 (CH_2), 123.7 (CH), 125.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 141.5 (C), 159.7 (C), 199.5 (C); *m*/*z* (EI) 216.1518 (M^+. $C_{15}H_{20}O$ requires 216.1514), 183 (17%), 173 (100), 145 (5), 133 (16), 111 (94), 91 (73), 84 (72), 49 (55), 47 (10).

***E*-isomer:**

R_f (1:4 ethyl acetate/petroleum ether) 0.57; ν_{max}/cm^{-1} (neat) 3003 (CH), 1710 (CO), 1420, 1358, 1219, 1092, 903, 785; δ_H (400 MHz, $CDCl_3$) 0.83 (3H, t, *J* 7.3 Hz, 1-H_3), 1.37–1.48 (2H, m, 2-H_2), 2.02 (2H, td, *J* 7.6, 1.2 Hz, 3-H_2), 2.06 (3H, d, *J* 1.2 Hz, 4-CH_3), 2.63–2.71 (2H, m, 7-H_2), 2.81–2.88 (2H, m, 8-H_2), 5.97 (1H, sex, *J* 1.2 Hz, 5-H), 7.07–7.24 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.5 (CH_2), 25.5 (CH_3), 30.1 (CH_2), 35.7 (CH_2), 45.9 (CH_2), 123.7 (CH), 125.9 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 141.5 (C), 159.7 (C), 199.5 (C); *m*/*z* (CI) 217.1588 (MH^+. $C_{15}H_{21}O$ requires 217.1592), 215 (13%), 191 (13), 151 (49), 149 (16), 133 (15), 85 (22), 69 (26).

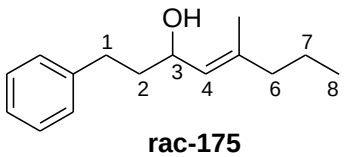
(3*R*,4*E*)-5-methyl-1-phenyloct-4-en-3-ol



175

A stirred solution of (4*E*)-5-methyl-1-phenyloct-4-en-3-one ***E*-174** (0.281 g, 1.30 mmol) and (*S*)-(-)-2-methyl-CBS-oxazaborolidine solution (1.0 M in toluene, 1.30 mL, 1.30 mmol) in tetrahydrofuran (8 mL) was cooled to -20 °C before borane dimethylsulfide complex solution (2.0 M in toluene, 0.98 mL, 1.96 mmol) was slowly added. The reaction mixture was stirred at -20 °C for 7 h before being quenched by the addition of methanol (6 mL) and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 3:37 diethyl ether/petroleum ether gave (3*R*,4*E*)-5-methyl-1-phenyl-4-en-3-ol **175** as a colourless oil (0.289 g, 100%). Chiral HPLC (Chiralcel IB column) analysis using 4% isopropanol in hexane indicated 46% ee; R_f (1:4 ethyl acetate/petroleum ether) 0.54; ν_{max}/cm^{-1} (neat) 2959 (OH), 2924, 2295 (CH) 1460, 1379, 725; $[\alpha]_D^{21}$ +22.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.3 Hz, 1-H_3), 1.38 (1H, br s, OH), 1.39–1.51 (2H, m, 2-H_2), 1.63 (3H, d, *J* 1.2 Hz, 4-CH_3), 1.70–1.81 (1H, m, 7-*H*H), 1.87–1.96 (1H, m, 7-H*H*), 1.98 (2H, t, *J* 7.4 Hz, 3-H_2), 2.59–2.74 (2H, m, 8-H_2), 4.38 (1H, dt, *J* 8.6, 6.6 Hz, 6-H), 5.21 (1H, dq, *J* 8.6, 1.2 Hz, 5-H), 7.14–7.31 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 13.7 (CH_3), 16.5 (CH_3), 20.8 (CH_2), 31.9 (CH_2), 39.3 (CH_2), 41.7 (CH_2), 68.1 (CH), 125.8 (CH), 127.7 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 139.2 (C), 142.1 (C); *m*/*z* (CI) 201.1642 (MH^+. $C_{15}H_{23}O$-H_2O requires 201.1643), 175 (6%), 167 (10), 85 (31), 69 (22).

(4*E*)-5-methyl-1-phenyloct-4-en-3-ol

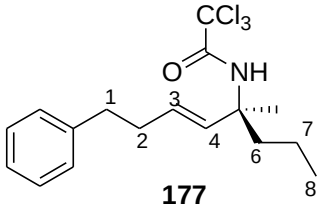


rac-175

The reaction was carried out according to general procedure 3, using (4*E*)-5-methyl-1-phenyloct-4-en-3-one ***E*-174** (0.050 g, 0.23 mmol) and diisobutylaluminium hydride solution (1.0 M in hexanes, 0.35 mL, 0.35 mmol) in toluene (4 mL).

Purification by silica column chromatography, eluting with 1:19 ethyl acetate/petroleum ether gave (4*E*)-5-methyl-1-phenyloct-4-en-3-ol **rac-175** as a colourless oil (0.027 g, 54%). For analytical data, see above compound **175**.

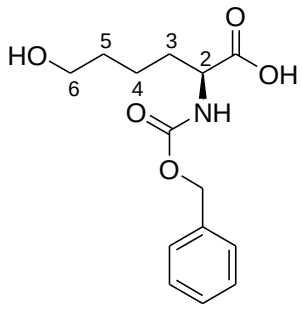
(3*E*,5*S*)-5-methyl-1-phenyl-5-(trichloromethylcarbonylamino)oct-3-ene



177

A stirred solution of (3*R*,4*E*)-5-methyl-1-phenyl-4-en-3-ol **175** (0.040 g, 0.18mmol) in dichloromethane (4 mL) was cooled to 0 °C before 1,8-diazabicyclo[5.4.0]undec-7-ene (0.014 mL, 0.09 mmol) was added, followed by trichloroacetonitrile (0.028 mL, 0.28 mmol). The reaction mixture was heated to 45 °C and allowed to stir under reflux for 72 h before being cooled to room temperature and filtered through a plug of silica, which was washed through with diethyl ether (200 mL). The filtrate was then concentrated *in vacuo* to give the allylic trichloroacetimidate intermediate **176** (0.066 g), which was dissolved in toluene (5 mL). Potassium carbonate (0.015 g) was added, and the reaction mixture was degassed with argon for 5 min before being heated to 130 °C in a sealed Shlenck tube for 72 h. The mixture was then cooled to room temperature and concentrated *in vacuo*. Purification by silica column chromatography gave (3*E*,5*S*)-5-methyl-1-phenyl-5-(trichloromethylcarbonylamino)oct-3-ene **177** as a colourless oil (0.007 g, 11% over 2 steps). δ_H (400 MHz, $CDCl_3$) 0.92 (3H, t, *J* 7.5 Hz, 1-H_3), 1.49 (2H, q, *J* 7.5 Hz, 2-H_2), 1.57 (3H, s, 4-CH_3), 2.12–2.19 (2H, m, 3-H_2), 2.37–2.48 (2H, m, 7-H_2), 2.68–2.76 (2H, m, 8-H_2), 5.74 (1H, dt, *J* 15.8, 6.9 Hz, 6-H), 6.09 (1H, d, *J* 15.8 Hz, 5-H), 7.16–7.32 (5H, m, 5 × ArH).

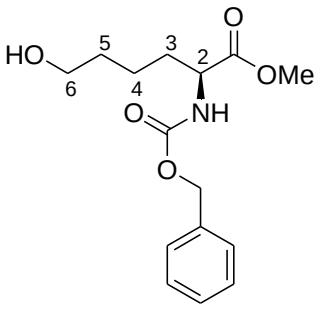
(2*S*)-2-(Benzyloxycarbonylamino)-6-hydroxyhexanoic acid[93]



181

A stirred suspension of N^2-(carbobenxyloxy)-L-lysine **180** (5.00 g, 17.8 mmol) in water (35 mL) was heated to 60 °C and 4 M sodium hydroxide solution was added to adjust the solution to pH 10 before sodium nitroferricyanide(III) dihydrate (6.64 g, 22.3 mmol) was added slowly. The resulting dark brown solution was stirred at 60 °C for 7 h, while maintaining the reaction mixture between pH 8–10 using regular additions of 4 M sodium hydroxide solution. The mixture was then allowed to cool to room temperature and filtered through a pad of Celite® and the filtrate was acidified to pH 1 using 2 M hydrochloric acid. The organic layers were extracted using ethyl acetate (3 × 150 mL), which were then combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (2*S*)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid **181** as a green oil (5.29 g), which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.40–1.90 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 3.65 (2H, t, *J* 5.6 Hz, 6-H_2), 4.38–4.44 (1H, m, 2-H), 5.11 (2H, s, OC$H_2C_6H_5$), 5.44 (1H, d, *J* 8.0 Hz, NH), 7.30–7.37 (5H, m, 5 × ArH).

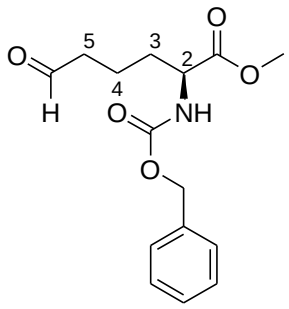
Methyl (2*S*)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoate[130]



182

Concentrated hydrochloric acid (3.8 mL) was added slowly to a stirred solution of (2*S*)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid **181** (5.29 g, 18.8 mmol) in toluene (130 mL) and methanol (95 mL). The reaction mixture was heated to 90 °C and stirred for 18 h before being allowed to cool to room temperature. The mixture was then neutralised by the addition of a saturated aqueous solution of sodium hydrogen carbonate and the organic solvent was removed *in vacuo*. The organic layers were then extracted using ethyl acetate (3 × 150 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with ethyl acetate gave methyl (2*S*)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoate **182** as a yellow oil (2.80 g, 53% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3433 (NH/OH), 3019 (CH), 2953 (CH), 1718 (CO), 1510, 1216, 1058, 755; $[\alpha]_D^{25}$ +12.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.38–1.88 (6H, m, 3-H_2, 4-H_2 and 5-H_2), 3.63 (2H, t, *J* 6.4 Hz, 6-H_2), 3.74 (3H, s, OCH_3), 4.36–4.42 (1H, m, 2-H), 5.11 (2H, s, $OCH_2C_6H_5$), 5.33 (1H, d, *J* 8.0 Hz, NH), 7.29–7.36 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_2), 32.0 (CH_2), 32.5 (CH_2), 52.4 (CH_3), 53.7 (CH), 62.4 (CH_2), 67.0 (CH_2), 128.1 (CH), 128.2 (2 × CH), 128.6 (2 × CH), 136.2 (C), 156.0 (C), 173.0 (C); *m*/*z* (EI) 295.1420 (M^+. $C_{15}H_{21}NO_5$ requires 295.1417), 263 (6%), 236 (66), 192 (89), 143 (19), 91 (100), 85 (32), 65 (17).

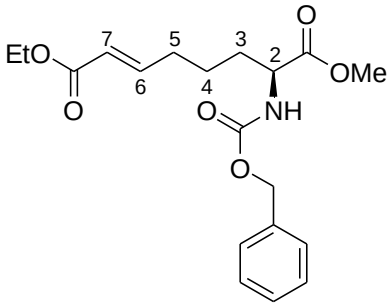
Methyl (2*S*)-2-(benzyloxycarbonylamino)-6-oxohexanoate



187

A stirred solution of oxalyl chloride (0.055 mL, 0.65 mmol) in dichloromethane (2 mL) was cooled to -78 °C, and dimethylsulfoxide (0.090 mL, 1.27 mmol) was added dropwise. The mixture was stirred at -78 °C for 0.25 h and then a solution of (2*S*)-2-(benzyloxycarbonylamino)-6-hydroxyhexanoate **182** (0.150 g, 0.51 mmol) in dichloromethane (3 mL) was added. The mixture was stirred at -78 °C for a further 0.25 h before triethylamine (0.355 mL, 2.55 mmol) was added. The reaction mixture was stirred at -78 °C for 1 h, and then at room temperature for 4 h before being concentrated *in vacuo*. The residue was then dissolved in dichloromethane (50 mL) and washed with 1 M hydrochloric acid (50 mL) and water (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give methyl (2*S*)-2-(benzyloxycarbonylamino)-6-oxohexanoate **187** as a yellow oil (0.129 g), which was used immediately without further purification. δ_H (400 MHz, $CDCl_3$) 1.64–1.73 (3H, m, 3-*H*H and 4-H_2), 1.79–1.92 (1H, m, 3-H*H*), 2.42–2.53 (2H, m, 5-H_2), 3.75 (3H, s, OCH_3), 4.35–4.43 (1H, m, 2-H), 5.11 (2H, s, C*H*$_2C_6H_5$), 5.33 (1H, d, *J* 8.5 Hz, NH), 7.30–7.38 (5H, m, 5 × ArH), 9.75 (1H, s, CHO).

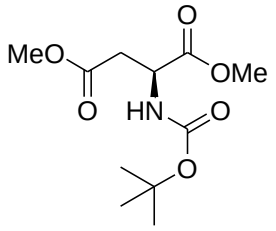
1-Methyl 8-ethyl (2*S*)-2-(benzyloxycarbonylamino)oct-6-enedioate



188

A suspension of oven-dried lithium chloride (0.054 g, 1.27 mmol) in acetonitrile (5 mL) was stirred for 0.2 h before triethyl phosphonoacetate (0.255 mL, 1.29 mmol) was added, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (0.190 mL, 1.27 mmol). The mixture was stirred at room temperature for 0.75 h before being added to methyl (2*S*)-2-(benzyloxycarbonylamino)-6-oxohexanoate **187** (0.129 g). The reaction mixture was then stirred at room temperature for 20 h before being quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL). The organic solvent was removed *in vacuo* and then water (50 mL) and ethyl acetate (100 mL) were added to the flask. The layers were separated and the organic layers were further extracted with ethyl acetate (2 × 50 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:4 ethyl acetate/petroleum ether gave 1-methyl 8-ethyl (2*S*)-2-(benzyloxycarbonylamino)oct-6-ene-dioate **188** as a colourless oil (0.086 g, 47% over 2 steps). ν_{max}/cm^{-1} (neat) 3329 (NH), 2953 (CH), 1713 (CO), 1524, 1456, 1206, 1043, 739; $[\alpha]_D^{25}$ +14.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.36–1.52 (2H, m, 4-H_2), 1.54–1.66 (1H, m, 3-*H*H), 1.73–1.87 (1H, m, 3-H*H*), 2.07–2.23 (2H, m, 5-H_2), 3.68 (3H, s, OCH_3), 4.12 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.27–4.37 (1H, m, 2-H), 5.04 (2H, s, $CH_2C_6H_5$), 5.22 (1H, d, *J* 7.8 Hz, NH), 5.74 (1H, d, *J* 15.6 Hz, 7-H), 6.83 (1H, dt, *J* 15.6, 7.0 Hz, 6-H), 7.22–7.33 (5H, m, 5 × ArH); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 23.7 (CH_2), 31.5 (CH_2), 32.3 (CH_2), 52.5 (CH_3), 53.6 (CH), 60.3 (CH_2), 67.1 (CH_2), 122.0 (CH), 128.2 (CH), 128.3 (2 × CH), 128.6 (2 × CH), 136.2 (C), 147.9 (CH), 155.9 (C), 166.6 (C), 172.8 (C); *m/z* (CI) 364.1758 (MH^+. $C_{19}H_{26}NO_6$ requires 364.1760), 363 (5%), 320 (16), 276 (5), 256 (12), 207 (56), 206 (27), 191 (12), 151 (15), 83 (14).

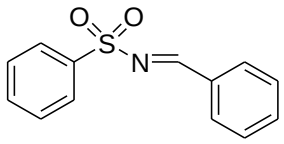
Dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate[101]



192

A stirred suspension of L-aspartic acid **191** (3.00 g, 22.5 mmol) in methanol (60 mL) was cooled to 0 °C before chlorotrimethylsilane (12.6 mL, 99.2 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.1 h and then at room temperature for 24 h before being cooled again to 0 °C. Triethylamine (20.0 mL, 143 mmol) was added slowly, followed by di-*tert*-butyl dicarbonate (5.40 g, 24.8 mmol). The reaction mixture was stirred at room temperature for a further 2 h before being concentrated *in vacuo*. The residue was suspended in diethyl ether (100 mL) and filtered, and the filtrate was concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:3 ethyl acetate/petroleum ether gave dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate **192** as a white solid (4.85 g, 82%). Mp 62–65 °C; ν_{max}/cm^{-1} (neat) 2980 (CH), 1738 (CO), 1701 (CO), 1501, 1346, 1215, 1157, 1032, 997, 783; $[\alpha]_D^{25}$ +39.5 (*c* 1.0, $CHCl_3$) (lit.[101] $[\alpha]_D^{25}$ +35.8 (*c* 1.0, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 2.83 (1H, dd, *J* 16.9, 4.5 Hz, 3-*H*H), 3.01 (1H, dd, *J* 16.9, 4.1 Hz, 3-H*H*), 3.70 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.53–4.64 (1H, m, 2-H), 5.49 (1H, br d, *J* 7.3 Hz, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (3 × CH_3), 36.7 (CH_2), 49.9 (CH), 52.1 (CH_3), 52.8 (CH_3), 80.2 (C), 155.4 (C), 171.5 (C), 171.6 (C); *m*/*z* (CI) 262.1293 (MH^+. $C_{11}H_{20}NO_6$ requires 262.1291), 206 (100%), 162 (29), 113 (7), 97 (6), 85 (14), 69 (16).

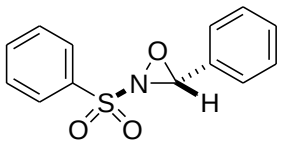
***N*-Benzylidenebenzenesulfonamide**[131]



202

Benzenesulfonamide **201** (15.0 g, 95.4 mmol) was added to a flask containing Amberlyst 15 ion-exchange resin (0.190 g), 5 Å molecular sieves, and toluene (75 mL). Benzaldehyde (9.90 mL, 97.5 mmol) was added, and the reaction mixture was stirred under Dean-Stark condensation conditions for 27 h. The mixture was then allowed to cool to room temperature without stirring, and filtered. The filtrate was concentrated *in vacuo*, and pentane (80 mL) was added to the orange residue. The flask was cooled in the refrigerator overnight, upon which a precipitate formed, which was then separated by filtration and washed with pentane (2 × 20 mL). The solid was then dissolved in ethyl acetate (10 mL) with heating and then pentane (30 mL) was added slowly, upon which the solid product began to precipitate. The suspension was allowed to stand for 2 h before being filtered, and the solid was washed with pentane (30 mL) and air-dried to give *N*-benzylidenebenzenesulfonamide **202** as a pale brown solid (12.1 g, 52%). Mp 70–73 °C (lit.[131] Mp 76–80 °C); ν_{max}/cm^{-1} (neat) 3059 (CH), 1697, 1597, 1570, 1447, 1312, 1155, 1088, 1001, 866, 748; δ_H (400 MHz, $CDCl_3$) 7.45–7.68 (6H, m, 6 × ArH), 7.94 (2H, d, *J* 7.8 Hz, 2 × ArH), 8.02 (2H, d, *J* 7.3 Hz, 2 × ArH), 9.07 (1H, s, C*H*C_6H_5); δ_C (100 MHz, $CDCl_3$) 128.0 (2 × CH), 129.1 (2 × CH), 129.2 (2 × CH), 131.4 (2 × CH), 132.3 (C), 133.6 (CH), 135.1 (CH), 138.2 (C), 170.6 (CH); *m*/*z* (EI) 245.0510 (M^+. $C_{13}H_{12}NO_2S$ requires 245.0511), 214 (8%), 181 (14), 141 (89), 104 (52), 77 (100), 51 (32), 49 (26).

(±)-*trans*-2-(Phenylsulfonyl)-3-phenyloxaziridine[131]

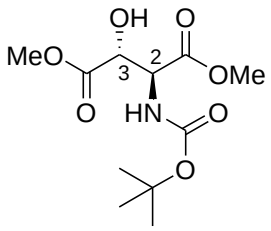


193

N-Benzylidenebenzenesulfonamide **202** (9.84 g, 40.1 mmol) was dissolved in chloroform (30 mL), and a saturated aqueous solution of sodium hydrogen carbonate (40 mL) was added, followed by benzyl triethylammonium chloride (1.01 g, 4.41 mmol). The mixture was cooled to 0 °C, then a solution of *m*-chloroperoxybenzoic acid (7.61 g, 44.1 mmol) in chloroform (80 mL) was added dropwise over 0.3 h and the reaction mixture was stirred at 0 °C for 1.5 h. The mixture was allowed to warm to room temperature and then washed with water (70 mL), 10% aqueous sodium sulfite solution (100 mL), water (2 × 70 mL) and a saturated aqueous solution of sodium chloride (30 mL) before being dried over anhydrous potassium carbonate for 1.5 h, filtered, and concentrated *in vacuo* (rotary evaporator water bath temperature maintained below 40 °C). The white solid residue was then dissolved in minimal ethyl acetate (~80 mL), and the solution was filtered through fluted filter paper. Pentane (40 mL) was added, and the solution was cooled in the refrigerator overnight, upon which a white precipitate formed. The precipitate was collected by filtration, washed with pentane (20 mL) and air-dried for 1 h to give (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine **193** as a white solid (4.15 g). The filtrate was then partially concentrated *in vacuo* and cooled in the refrigerator, upon which a yellow precipitate formed which was collected by filtration. Diethyl ether (6 mL) was added to this solid, followed by pentane (8 mL), and the precipitate formed was collected by filtration and air-dried to give a second batch of (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine **193** as a white solid (3.48 g, 73% total yield). Mp 91–93 °C (lit.[131] Mp 92–94 °C); ν_{max}/cm^{-1} (neat) 3354, 2513 (CH), 1906, 1447, 1348, 1233, 1167, 1086, 829, 760; δ_H (400 MHz, $CDCl_3$) 5.50 (1H, s, C*H*C_6H_5), 7.37–7.51 (5H, m, 5 × ArH), 7.64 (2H, t, *J* 7.9 Hz, 2 × ArH), 7.76 (1H, t, *J* 7.2 Hz, ArH), 8.06 (2H, d, *J* 7.9 Hz, 2 × ArH); δ_C (100 MHz, $CDCl_3$) 76.3 (CH), 128.3 (2 × CH), 128.8 (CH), 129.1 (CH), 129.4 (2 × CH), 129.5 (CH), 129.8 (CH), 130.5 (C), 131.5 (CH), 134.7 (C), 135.1 (CH); *m*/*z* (CI) 262.0534

(MH^+. $C_{13}H_{12}NO_3S$ requires 262.0538), 246 (100%), 183 (5), 158 (39), 143 (21), 106 (66), 85 (12), 71 (15).

Dimethyl (2*S*,3*R*)-*N*-(*tert*-butoxycarbonyl)-2-amino-3-hydroxybutane-1,4-dioate[132]



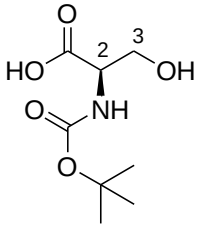
***anti*-194**

A stirred solution of dimethyl (2*S*)-*N*-(*tert*-butoxycarbonyl)-2-aminobutane-1,4-dioate **192** (0.460 g, 1.75 mmol) and (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine **193** (0.690 g, 2.64 mmol) in tetrahydrofuran (7 mL) was cooled to -78 °C before sodium bis(trimethylsilyl)amide solution (1.0 M in tetrahydrofuran, 5.30 mL, 5.30 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 24 h before being quenched by the addition of a saturated aqueous solution of ammonium chloride (20 mL). The organic layers were extracted using diethyl ether (2 × 50 mL) and then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 7:13 ethyl acetate/petroleum ether gave dimethyl (2*S*,3*R*)-*N*-(*tert*-butoxycarbonyl)-2-amino-3-hydroxybutane-1,4-dioate ***anti*-194** as a colourless oil (0.098 g, 20%). ν_{max}/cm^{-1} (neat) 3370 (OH), 2957 (CH), 1708 (CO), 1508, 1364, 1221, 1163, 1059, 1017, 723; $[\alpha]_D^{25}$ -33.9; δ_H (400 MHz, $CDCl_3$) 1.25 (1H, br s, OH), 1.43 (9H, s, $OC(CH_3)_3$), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.70 (1H, d, *J* 4.5 Hz, 3-H), 4.79 (1H, d, *J* 8.8 Hz, 2-H), 5.28 (1H, br d, NH); δ_C (100 MHz, $CDCl_3$) 28.2 (3 × CH_3), 53.0 (CH_3), 53.3 (CH_3), 56.1 (CH), 71.0 (CH), 80.4 (C), 155.3 (C), 169.9 (C), 172.5 (C); *m*/*z* (CI) 278 (MH^+, 8%), 246 (6), 222 (100), 220 (8), 178 (34), 158 (21), 123 (6), 106 (7), 85 (11), 71 (12).

Also isolated from the column was dimethyl (2*S*,3*S*)-*N*-(*tert*-butoxycarbonyl)-2-amino-3-hydroxybutane-1,4-dioate **syn-194** as a colourless oil (0.094 g, 19%). ν_{max}/cm^{-1} (neat) 2957 (CH), 1748 (CO), 1420, 1360, 1221, 1165, 1092, 1019, 723;

$[\alpha]_D^{25}$ +3.7 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25 (1H, br s, OH), 1.46 (9H, s, $OC(CH_3)_3$), 3.75 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.54 (1H, br s, 3-H), 4.86 (1H, d, *J* 7.7 Hz, 2-H), 5.52 (1H, br d, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (3 × CH_3), 52.8 (CH_3), 53.0 (CH_3), 57.1 (CH), 72.2 (CH), 80.7 (C), 155.6 (C), 169.1 (C), 172.0 (C); *m*/*z* (CI) 278 (MH^+, 4%), 262 (15), 222 (100), 204 (10), 178 (65), 158 (46), 122 (30), 71 (29).

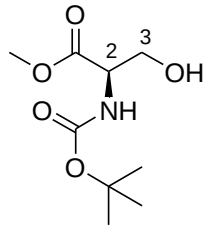
(*R*)-*N*-(*tert*-Butoxycarbonyl)-D-serine[133]



211

A stirred solution of D-serine **129** (4.77 g, 45.4 mmol) in 1,4-dioxane (40 mL) and 1.0 M aqueous sodium hydroxide solution (90 mL, 90.0 mmol) was cooled to 0 °C before di-*tert*-butyl dicarbonate (11.9 g, 54.5 mmol) was added slowly. The reaction mixture was stirred at 0 °C for 0.25 h and then at room temperature for 6 h before the organic solvent was removed *in vacuo* (maintaining water bath temperature at 35 °C). The remaining aqueous phase was acidified to pH 2 using 2.5 M sulfuric acid, and the organic layers were extracted using ethyl acetate (3 × 100 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give (*R*)-*N*-(*tert*-butoxycarbonyl)-D-serine **211** as a colourless oil (11.28 g), which was used without further purification. ν_{max}/cm^{-1} (neat) 3021 (NH), 1707 (CO), 1506, 1420, 1215, 1167, 742; $[\alpha]_D^{23}$ -0.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 3.86 (1H, d, *J* 11.1 Hz, 3-*H*H), 3.96–4.14 (1H, m, 3-H*H*), 4.29–4.44 (1H, m, 2-H), 5.71 (1H, d, *J* 6.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (3 × CH_3), 55.4 (CH), 63.0 (CH_2), 80.9 (C), 156.4 (C), 173.8 (C); *m*/*z* (CI) 206.1029 (MH^+. $C_8H_{16}NO_5$ requires 206.1028), 188 (9%), 150 (100), 132 (6), 106 (20), 104 (6), 71 (8).

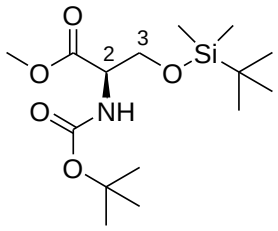
Methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-hydroxypropionate[134]



203

A stirred solution of crude (*R*)-*N*-(*tert*-butoxycarbonyl)-D-serine **211** (11.28 g) in *N*,*N*-dimethylformamide (70 mL) was cooled to 0 °C before potassium carbonate (6.91 g, 50.0 mmol) was added, followed by methyl iodide (5.70 mL, 91.6 mmol). The reaction mixture was stirred at 0 °C for 0.2 h, and then at room temperature for 20 h before being concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ethyl acetate (100 mL) and the layers were separated. The organic layers were extracted further with ethyl acetate (2 × 100 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-hydroxypropionate **203** as a yellow oil (10.73 g), which was used without further purification. δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, $C(CH_3)_3$), 3.79 (3H, s, OCH_3), 3.86–4.03 (2H, m, 3-H_2), 4.34–4.44 (1H, m, 2-H), 5.40–5.58 (1H, m, NH); δ_C (100 MHz, $CDCl_3$) 28.3 (3 × CH_3), 52.7 (CH_3), 55.7 (CH), 63.7 (CH_2), 80.4 (C), 155.8 (C), 171.2 (C); *m*/*z* (CI) 220.1187 (MH^+. $C_9H_{18}NO_5$ requires 220.1185), 164 (100%), 146 (18), 120 (28), 107 (27), 85 (12), 73 (18).

Methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propionate[135]

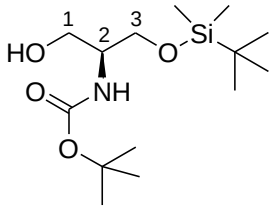


212

To a stirred solution of crude methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-hydroxypropionate **203** (10.73 g) in *N*,*N*-dimethylformamide (70 mL), imidazole

(4.33 g, 63.6 mmol) was added, followed by *tert*-butyldimethylsilyl chloride (8.30 g, 55.1 mmol). The reaction mixture was stirred at room temperature for 20 h before being concentrated *in vacuo*. The residue was partitioned between water (100 mL) and ethyl acetate (150 mL), the layers were separated and the organic layers were further extracted with ethyl acetate (2 × 150 mL). The combined organic phasess were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propionate **212** as a colourless oil (11.29 g, 75% over 3 steps). $[\alpha]_D^{23}$ -16.1 (*c* 1.0, $CHCl_3$) (lit.[135] $[\alpha]_D^{23}$ -19.2 (*c* 1.34, $CHCl_3$)); δ_H (400 MHz, $CDCl_3$) 0.02 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.46 (9H, s, $OC(CH_3)_3$), 3.74 (3H, s, OCH_3), 3.82 (1H, dd, *J* 10.0, 2.8 Hz, 3-*H*H), 4.05 (1H, dd, *J* 10.0, 2.8 Hz, 3-H*H*), 4.36 (1H, dt, *J* 8.8 Hz, 2.8 Hz, 2-H), 5.35 (1H, d, *J* 8.8 Hz, NH); δ_C (100 MHz, $CDCl_3$) -5.6 (CH_3), -5.5 (CH_3), 18.2 (C), 25.7 (3 × CH_3), 28.4 (3 × CH_3), 52.3 (CH_3), 55.6 (CH), 63.8 (CH_2), 79.9 (C), 155.5 (C), 171.3 (C); *m*/*z* (CI) 334.2051 (MH^+. $C_{15}H_{32}NO_5Si$ requires 334.2050), 278 (100%), 220 (17), 85 (6), 69 (7).

(2*S*)-2-*tert*-Butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-ol

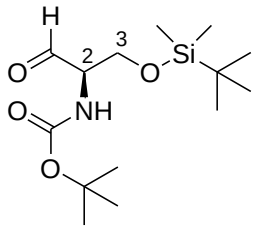


204

A stirred solution of methyl (2*R*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propionate **212** (1.45 g, 4.35 mmol) in diethyl ether (30 mL) was cooled to -78 °C before diisobutylaluminium hydride solution (1.0 M in hexanes, 9.50 mL, 9.50 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h and then at room temperature for 18 h before being quenched by the addition of a saturated aqueous solution of ammonium chloride (5 mL) at 0 °C. The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 0.5 h before being filtered through a pad of Celite® and washed with diethyl ether (200 mL). The filtrate was washed with water (3 × 50 mL) and then dried ($MgSO_4$), filtered,

and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 3:17 ethyl acetate/petroleum ether gave (2*S*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy]-propan-1-ol **204** as a colourless oil (0.615 g, 46%). ν_{max}/cm^{-1} (neat) 3449 (OH), 2930 (CH), 1692 (CO), 1501, 1366, 1252, 1169, 1051, 833, 775; $[\alpha]_D^{23}$ -9.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, 2 × $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 2.58–2.80 (1H, br s, OH), 3.62–3.72 (2H, m, 2-H and 3-*H*H), 3.77–3.90 (3H, m, 3-H*H* and 1-H_2); δ_C (100 MHz, $CDCl_3$) -5.6 (2 × CH_3), 18.2 (C), 25.8 (3 × CH_3), 28.4 (3 × CH_3), 52.5 (CH), 64.2 (2 × CH_2), 79.6 (C), 156.0 (C); *m*/*z* (CI) 306.2097 (MH^+. $C_{14}H_{32}NO_4Si$ requires 306.2101), 301 (11%), 250 (26), 232 (16), 196 (8), 195 (5), 169 (5), 155 (6), 127 (8), 113 (31), 85 (63), 73 (100).

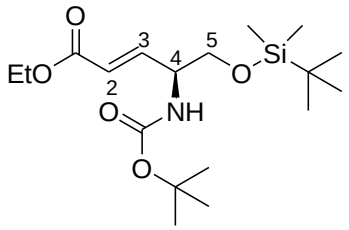
(2*S*)-2-*tert*-Butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-al



213

A stirred solution of oxalyl chloride (0.69 mL, 8.18 mmol) in dichloromethane (50 mL) was cooled to -78 °C before dimethylsulfoxide (1.16 mL, 16.4 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 0.25 h and then a solution of (2*S*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-ol **204** (2.08 g, 6.82 mmol) in dichloromethane (20 mL) was slowly added. The reaction was stirred at -78 °C for 0.5 h and then triethylamine (4.75 mL, 34.1 mmol) was added. The reaction mixture was stirred again at -78 °C for 0.5 h and then at room temperature for 6 h before being concentrated *in vacuo* to give crude (2*S*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-al **213** as a yellow residue, which was used without further purification.

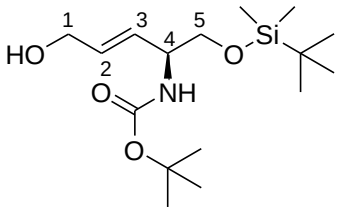
Ethyl (2*E*,4*S*)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-enoate[136]



205

To a stirred suspension of oven-dried lithium chloride (0.723 g, 17.0 mmol) in acetonitrile (70 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (2.55 mL, 17.0 mmol) was added, followed by triethyl phosphonoacetate (3.40 mL, 17.0 mmol). The mixture was stirred at room temperature for 1 h before being added to the crude aldehyde, (2*S*)-2-*tert*-butoxycarbonylamino-3-[(*tert*-butyldimethylsilyl)oxy] propan-1-al **213**. The reaction mixture was then stirred at room temperature for 24 h before being quenched by the addition of a saturated aqueous solution of ammonium chloride (30 mL). The organic solvent was removed *in vacuo*, and the organic layers were extracted using ethyl acetate (3 × 150 mL). The combined organic phases were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:19 ethyl acetate/petroleum ether gave ethyl (2*E*,4*S*)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-enoate **205** as a colourless oil (1.94 g, 76%). $[\alpha]_D^{23}$ +3.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.45 (9H, s, $OC(CH_3)_3$), 3.66–3.76 (2H, m, 5-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.31–4.42 (1H, m, 4-H), 4.92 (1H, d, *J* 6.8 Hz, NH), 5.96 (1H, dd, *J* 15.7, 1.8 Hz, 2-H), 6.91 (1H, dd, *J* 15.7, 5.2 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) -5.4 (2 × CH_3), 14.2 (CH_3), 18.3 (C), 25.8 (3 × CH_3), 28.2 (C), 28.4 (3 × CH_3), 60.4 (CH_2), 64.7 (CH_2), 77.2 (CH), 122.0 (CH), 146.4 (CH), 155.2 (C), 166.2 (C); *m*/*z* (CI) 374.2367 (MH^+. $C_{18}H_{36}NO_5Si$ requires 374.2363), 319 (100%), 257 (12), 118 (7), 85 (8), 69 (10).

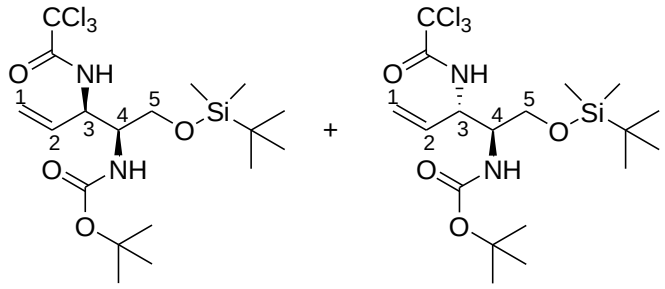
(2*E*,4*S*)-4-*tert*-Butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-en-1-ol



206

A stirred solution of ethyl (2*E*,4*S*)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-enoate **205** (3.19 g, 8.54 mmol) in dichloromethane (100 mL) was cooled to -78 °C before boron trifluoride diethyl etherate (2.00 mL, 11.6 mmol) was added dropwise. The mixture was stirred at -78 °C for 0.5 h before diisobutylaluminium hydride solution (1.0 M in hexanes, 25.5 mL, 25.5 mmol) was added dropwise. The reaction mixture was then stirred at -78 °C for 3 h before being quenched by the addition of 5.0 M acetic acid solution in dichloromethane (30 mL). The mixture was poured into 10% aqueous tartaric acid solution (100 mL), and the organic layers were extracted using dichloromethane (2 × 200 mL). The combined organic phases were washed with a saturated aqueous solution of sodium hydrogen carbonate (150 mL) before being dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification was carried out by silica column chromatography, and elution with 1:3 ethyl acetate/petroleum ether gave (2*E*,4*S*)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-2-en-1-ol **206** as a colourless oil (2.20 g, 78%). ν_{max}/cm^{-1} (neat) 3451 (OH), 2930 (CH), 1701 (CO), 1499, 1368, 1254, 1171, 1111, 909, 837, 733; $[\alpha]_D^{21}$ +2.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 3.61 (1H, dd, *J* 10.0, 4.2 Hz, 5-*H*H), 3.69 (1H, dd, *J* 10.0, 4.4 Hz, 5-H*H*), 4.16 (2H, dt, *J* 5.3, 1.3 Hz, 1-H_2), 4.17–4.24 (1H, m, 4-H), 4.76–4.93 (1H, br, NH), 5.71 (1H, ddt, *J* 15.6, 5.7, 1.3 Hz, 3-H), 5.84 (1H, dtd, *J* 15.6, 5.3, 1.3 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) -5.4 (CH_3), -5.4 (CH_3), 18.3 (C), 25.9 (3 × CH_3), 28.4 (3 × CH_3), 63.1 (CH_2), 65.4 (CH_2), 77.2 (CH), 79.4 (C), 130.0 (CH), 130.5 (CH), 155.4 (C); *m*/*z* (CI) 332.2253 (MH^+. $C_{16}H_{34}NO_4Si$ requires 332.2257), 314 (6%), 277 (100), 259 (23), 225 (16), 213 (24), 159 (7), 133 (10), 113 (21), 81 (52), 69 (77).

(3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-1-ene and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy] pent-1-ene[41]



***syn*-207** ***anti*-207**

The trichloroacetimidate formation reaction was set up according to general procedure 4, using (2*E*,4*S*)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy]-pent-2-en-1-ol **206** (0.100 g, 0.30 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.023 mL, 0.15 mmol) and trichloroacetonitrile (0.045 mL, 0.45 mmol) in dichloromethane (4 mL), stirring at room temperature for 5 h to give the desired allylic trichloroacetimidate intermediate **214** (0.138 g). δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.88 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 3.61–3.73 (2H, m, 5-H_2), 4.12–4.32 (1H, m, 4-H), 4.75–4.93 (3H, m, 1-H_2 and NH), 5.82–5.90 (2H, m, 2-H and 3-H), 8.30 (1H, s, NH). This was then dissolved in dichloromethane (5 mL), and (*S*)-(+)-COP-Cl (0.013 g, 0.01 mmol) was added. The reaction mixture was heated to 38 °C and stirred under reflux for 46 h before further (*S*)-(+)-COP-Cl (0.013 g, 0.01 mmol) was added. The reaction was stirred at 38 °C for 44 h before a final addition of (*S*)-(+)-COP-Cl (0.009 g, 0.006 mmol) was added. The reaction was stirred at 38 °C for a further 71 h before being filtered through a pad of Celite®, which was washed through with diethyl ether (50 mL). The filtrate was concentrated *in vacuo*, and purification was carried out by silica column chromatography. Elution with 3:37 diethyl ether/petroleum ether gave (3*R*,4*S*)-3-(trichloromethylcarbonylamino)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy]-pent-1-ene and (3*S*,4*S*)-3-(trichloromethylcarbonylamino)-4-*tert*-butoxycarbonylamino-5-[(*tert*-butyldimethylsilyl)oxy]-pent-1-ene **207** (0.109 g, 76% total yield over 2 steps). ^{1}H

NMR spectroscopic analysis prior to purification indicated approximately 4.7:1 (3*S*,4*S*):(3*R*,4*S*) ratio of product diastereoisomers.

(3*S*,4*S*)-diastereoisomer (*anti*-207):[41]

Mp 83–87 °C; ν_{max}/cm^{-1} (neat) 3347 (NH), 2930 (CH), 1697 (CO), 1684 (CO), 1514, 1252, 1169, 1096, 1055, 833; $[\alpha]_D^{21}$ +4.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.11 (6H, s, 2 × $SiCH_3$), 0.91 (9H, s, $SiC(CH_3)_3$), 1.45 (9H, s, $OC(CH_3)_3$), 3.74 (1H, dd, *J* 10.1, 3.8 Hz, 5-*H*H), 3.82–3.94 (2H, m, 4-H and 5-H*H*), 4.65–4.74 (1H, m, 3-H), 4.95 (1H, br d, *J* 7.4 Hz, NH), 5.26–5.35 (2H, m, 1-H_2), 5.81 (1H, ddd, *J* 17.2, 10.5, 5.2 Hz, 2-H), 8.24 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) -5.4 (CH_3), -5.3 (CH_3), 18.5 (C), 26.0 (3 × CH_3), 28.3 (3 × CH_3), 53.0 (CH), 56.6 (CH), 63.4 (CH_2), 80.4 (C), 92.9 (C), 117.3 (CH_2), 133.1 (CH), 156.0 (C), 161.8 (C); *m*/*z* (CI) 475.1346 (MH^+. $C_{19}H_{34}{}^{35}Cl_3N_2O_4Si$ requires 475.1353) 421 (100%), 419 (96), 385 (37), 375 (30), 341 (15), 274 (13), 218 (32), 174 (12), 133 (8), 85 (15).

(3*R*,4*S*)-diastereoisomer (*syn*-207):

Mp 97–102 °C; ν_{max}/cm^{-1} (neat) 3325 (NH), 2930 (CH), 1688 (CO), 1530, 1366, 1250, 1165, 1115, 1055, 831, 775; $[\alpha]_D^{25}$ +2.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 1.44 (9H, s, $OC(CH_3)_3$), 3.66–3.75 (2H, m, 4-H and 5-*H*H), 3.80 (1H, dd, *J* 9.9, 2.5 Hz, 5-H*H*), 4.45 (1H, dt, *J* 9.1, 7.6 Hz, 3-H), 5.11 (1H, br d, *J* 7.6 Hz, NH), 5.32 (1H, d, *J* 10.2 Hz, 1-*H*H), 5.41 (1H, d, *J* 17.1 Hz, 1-H*H*), 5.69 (1H, ddd, *J* 17.1, 10.2, 7.5 Hz, 2-H), 7.95 (1H, br d, *J* 6.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) -5.3 (2 × CH_3), 18.4 (C), 26.0 (3 × CH_3), 28.6 (3 × CH_3), 54.2 (CH), 57.1 (CH), 62.2 (CH_2), 80.7 (C), 92.7 (C), 119.8 (CH_2), 133.5 (CH), 157.2 (C), 162.0 (C); *m*/*z* (CI) 475.1370 (MH^+. $C_{18}H_{34}{}^{35}Cl_3N_2O_4Si$ requires 475.1353), 419 (100%), 421 (97), 377 (69), 375 (67), 341 (18), 274 (21), 218 (59), 174 (44), 133 (50), 69 (23).

4.0 References

1) J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, volumes 1–3 Krieger, Malabar, FL, 1984.
2) C. Toniolo, M. Crisma, F. Formaggio and C. Peggion, *Biopolymers*, 2001, **60**, 396–419.
3) M. Tanaka, *Chem. Pharm. Bull.*, 2007, **55**, 349–358.
4) W. S. Saari, W. Halczenko, D. W. Cochran, M. R. Dobrinska, W. C. Vincek, D. C. Titus, S. L. Gaul and C. S. Sweet, *J. Med. Chem.*, 1984, **27**, 713–717.
5) U. Schöllkopf, U. Groth and C. Deng, *Angew. Chem. Int. Ed. Engl.*, 1981, **20**, 798–799.
6) J.-A. Ma, *Angew. Chem. Int. Ed.*, 2003, **42**, 4290–4299.
7) C. Nájera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671.
8) A. Strecker, *Ann. Chem. Pharm.*, 1850, **75**, 27–45.
9) H. Gröger, *Chem. Rev.*, 2003, **103**, 2795–2827.
10) M. S. Iyer, K. M. Gigstad, N. D. Namdev and M. Lipton, *J. Am. Chem. Soc.*, 1996, **118**, 4910–4911.
11) B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, *J. Am. Chem. Soc.*, 1977, **99**, 5946–5952.
12) W. S. Knowles, *Angew. Chem. Int. Ed.*, 2002, **41**, 1998–2007.
13) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2002, **41**, 1790–1793.
14) C. Cativiela and M. D. Díaz-de-Villegas, *Tetrahedron: Asymmetry*, 1998, **9**, 3517–3599.
15) K. Ding and D. Ma, *Tetrahedron*, 2001, **57**, 6361–6366.
16) Y. N. Belokon, D. Bhave, D. D'Addario, E. Groaz, V. Maleev, M. North and A. Pertrosyan, *Tetrahedron Lett.*, 2003, **44**, 2045–2048.
17) W. E. Doering and W. R. Roth, *Tetrahedron*, 1962, **18**, 67–74.
18) R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 1965, **87**, 2511–2513.
19) R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed.*, 1969, **8**, 781–932.
20) J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 2001, p 946–947.
21) L. Claisen, *Chem. Ber.*, 1912, **45**, 3157–3166.

22) F. E. Ziegler, *Chem. Rev.*, 1988, **88**, 1423–1452.
23) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741–742.
24) A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425–2429.
25) A. C. Cope and E. M. Hardy, *J. Am. Chem. Soc.*, 1940, **62**, 441–444.
26) O. Mumm and F. Möller, *Chem. Ber.*, 1937, **37**, 2214–2227.
27) L. E. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 597–599.
28) L. E. Overman and N. E. Carpenter, *Organic Reactions*, 2005, **66**, 1–107.
29) F. Cramer, K. Pawelzik and H. J. Baldauf, *Chem. Ber.*, 1958, **91**, 1049–1054.
30) F. Cramer and H. J. Baldauf, *Chem. Ber.*, 1959, **92**, 370–378.
31) M. Numata, M. Sugimoto, K. Koike and T. Ogawa, *Carbohydr. Res.*, 1987, **163**, 209–225.
32) I. Savage, E. J. Thomas and P. D. Wilson, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3291–3303.
33) I. Savage and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1989, 717–719.
34) L. E. Overman, *J. Am. Chem. Soc.*, 1976, **98**, 2901–2910.
35) T. Nishikawa, M. Asai, N. Ohyabu and M. Isobe, *J. Org. Chem.*, 1998, **63**, 188–192.
36) Y. Yamamoto, H. Shimoda, J. Oda and Y. Inouye, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3247–3249.
37) C. Martin, M. Bortolussi and R. Bloch, *Tetrahedron Lett.*, 1999, **40**, 3735–3736.
38) L. E. Overman, *Angew. Chem. Int. Ed.*, 1984, **23**, 579–586.
39) T. J. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2058–2066.
40) P. Metz, C. Mues and A. Schoop, *Tetrahedron*, 1992, **48**, 1071–1080.
41) J. Gonda, A.-C. Helland, B. Ernst and D. Belluš, *Synthesis*, 1993, 729–734.
42) M. Calter, T. K. Hollis, L. E. Overman, J. Ziller and G. G. Zipp, *J. Org. Chem.*, 1997, **62**, 1449–1456.
43) Y. Donde and L. E. Overman, *J. Am. Chem. Soc.*, 1999, **121**, 2933–2934.
44) L. E. Overman, C. E. Owen, M. M. Pavan and C. J. Richards, *Org. Lett.*, 2003, **5**, 1809–1812.
45) C. E. Anderson and L. E. Overman, *J. Am. Chem. Soc.*, 2003, **125**, 12412–12413.
46) D. M. Vyas, Y. Chiang and T. W. Doyle, *Tetrahedron Lett.*, 1984, **25**, 487–490.

47) Y. K. Chen, A. E. Lurain and P. J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 12225–12231.

48) K. N. Fanning, A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem.*, 2005, **3**, 3749–3756.

49) H. Imogai, Y. Petit and M. Larchevêque, *Tetrahedron Lett.*, 1996, **37**, 2573–2576.

50) P. Evans and M. Leffray, *Tetrahedron*, 2003, **59**, 7973–7981.

51) K. Grela and M. Bieniek, *Tetrahedron Lett.*, 2001, **42**, 6425–6428.

52) E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder and K. B. Sharpless, *J. Am. Chem. Soc.*, 1988, **110**, 1968–1970.

53) K. B. Sharpless, W. Amberg, Y. L. Bennani, G. A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.-M. Wang, D. Xu and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768–2771.

54) E. J. Corey, A. Guzman-Perez and M. C. Noe, *Tetrahedron Lett.*, 1995, **36**, 3481–3484.

55) M. H. Hopkins, L. E. Overman and G. M. Rishton, *J. Am. Chem. Soc.*, 1991, **113**, 5354–5365.

56) J. J. Duffield and G. R. Pettit, *J. Nat. Prod.*, 2001, **64**, 472–479.

57) K. Omura and D. Swern, *Tetrahedron*, 1978, **34**, 1651–1660.

58) R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198–2200.

59) Pfizer Inc., US patent WO/2008/068614, 2006.

60) M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183–2186.

61) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863–927.

62) P. Bey, F. Gerhart and M. Jung, *J. Org. Chem.*, 1986, **51**, 2835–2838.

63) M. Mehmandoust, Y. Petit and M. Larchevêque, *Tetrahedron Lett.*, 1992, **33**, 4313–4316.

64) I. Jaunzeme and A. Jirgersons, *Synlett*, 2005, 2984–2986.

65) A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem.*, 2006, **4**, 2932–2937.

66) P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem.*, 1981, **46**, 3936–3938.

67) U.–St. Bäumer and H. J. Schäfer, *Electrochimica Acta*, 2003, **48**, 489–495.

68) B. M. Trost and J. L. Gunzner, *J. Am. Chem. Soc.*, 2001, **123**, 9449–9450.

69) K. C. Nicolaou, R. E. Zipkin, R. E. Dolle and B. D. Harris,. *J. Am. Chem. Soc.*, 1984, **106**, 3548–3551.
70) E. J. Corey and G. T. Kwiatkowski, *J. Am. Chem. Soc.*, 1966, **88**, 5654–5656.
71) P. J. Garegg and B. Samuelsson, *Chem. Commun.*, 1979, 978–980.
72) B. Schmidt and T. Sattelkau, *Tetrahedron*, 1997, **53**, 12991–13000.
73) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815–3818.
74) R. Martín, P. Romea, C. Tey, F. Urpí and J. Vilarrasa, *Synlett*, 1997, 1414–1416.
75) R. H. Grubbs and S. Chang, *Tetrahedron*, 1998, **54**, 4413–4450.
76) S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.*, 2003, **42**, 1900–1923.
77) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953–956.
78) P. J.-L. Hérisson and Y. Chauvin, *Die Makromolekulare Chemie*, 1970, **141**, 161–176.
79) A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360–11370.
80) A. K. Chatterjee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 1751–1753.
81) L. E. Overman and G. M. Rishton, *Org. Synth.*, 1998, *Coll. Vol. 9*, 139–142.
82) A. Kalivretenos, J. K. Stille and L. S. Hegedus, *J. Org. Chem.*, 1991, **56**, 2883–2894.
83) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551–5553.
84) E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen and V. K. Singh, *J. Am. Chem. Soc.*, 1987, **109**, 7925–7926.
85) E. J. Corey and C. J. Helal, *Tetrahedron Lett.*, 1995, **36**, 9153–9156.
86) J. Clayden, N. Greeves, S. Warren and P. Wothers, *Organic Chemistry*, Oxford University Press, New York, 2001, p1233–1234.
87) M. A. Evans and J. P. Morken, *Org. Lett.*, 2005, **7**, 3371–3373.
88) J. A. Marshall and A. W. Garofalo, *J. Org. Chem.*, 1993, **58**, 3675–3680.
89) B. C. Ranu, S. Bhadra and L. Adak, *Tetrahedron Lett.*, 2008, **49**, 2588–2591.
90) R. M. de Figueiredo, L. Coudray and J. Dubois, *Org. Biomol. Chem.*, 2007, **5**, 3299–3309.
91) M. Rivard and S. Blechert, *Eur. J. Org. Chem.*, 2003, 2225–2228.
92) D. S. Hoare and E. Work, *Biochem. J.*, 1957, **65**, 441–447.
93) A. K. Bence and P. A. Crooks, *Synth. Commun.*, 2002, **32**, 2075–2082.

94) M. Rosillo, E. Arnáiz, D. Abdi, J. Blanco-Urgoiti, G. Domínguez and J. Pérez-Castells, *Eur. J. Org. Chem.*, 2008, 3917–3927.

95) L. N. Nysted, US Patent, 1975, 3 865 848. See: *Chem. Abstr.*, 1975, **83**, 10406q.

96) S. Matsubara, M. Sugihara and K. Utimoto, *Synlett*, 1998, 313–315.

97) D. DeMong and R. M. Williams, *Tetrahedron Lett.*, 2001, **42**, 3529–3532.

98) H. Wank, J. Rogers, J. Davies and R. Schroeder, *J. Mol. Biol.*, 1994, **236**, 1001–1010.

99) A. Yamashita, E. B. Norton and T. S. Mansour, *Synthetic Commun.*, 2004, **34**, 795–803.

100) T. Shiba, T. Ukita, K. Mizuno, T. Teshima and T. Wakamiya, *Tetrahedron Lett.*, 1977, **31**, 2681–2684.

101) K. N. Fanning, PhD thesis, University of Glasgow, 2008, p140–141.

102) F. A. Davis, L. C. Vishwakarma and J. M. Billmers, *J. Org. Chem.*, 1984, **49**, 3241–3243.

103) L. C. Vishwakarma, O. D. Stringer and F. A. Davis, *Org. Syn.*, 1988, **66**, 203–207.

104) S. E. de Sousa, P. O'Brien and C. D. Pilgram, *Tetrahedron*, 2002, **58**, 4643–4654.

105) K. C. Nicolaou, M. E. Bunnage and K. Koide, *J. Am. Chem. Soc.*, 1994, **116**, 8402–8403.

106) T. Moriwake, S. Hamano, D. Miki, S. Saito and S. Torii, *Chem. Lett.*, 1986, 815–818.

107) D. J. Hamilton and A. Sutherland, *Tetrahderon Lett.*, 2004, **45**, 5739–5741.

108) R. Bischoff, N. McDonald and A. Sutherland, *Tetrahedron Lett.*, 2005, **46**, 7147–7149.

109) A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 4394–4399.

110) C. W. G. Au and S. G. Pyne, *J. Org. Chem.*, 2006, **71**, 7097–7099.

111) G. Guanti, L. Banfi, A. Guaragna and E. Narisano, *J. Chem. Soc., Perkin. Trans. 1*, 1988, 2369–2375.

112) J. Mulzer and M. Berger, *J. Org. Chem.*, 2004, **69**, 891–898.

113) M. T. Crimmins and D. L. Jacobs, *Org. Lett.*, 2009, **11**, 2695-2698.

114) P. V. Ramachandran, T. E. Burghardt and M. V. R. Reddy, *J. Org. Chem.*, 2005, **70**, 2329–2331.

115) H. Li, J. Wu, J. Luo and W.-M. Dai, *Chem. Eur. J.*, 2010, **16**, 11530–11534.

116) K. Wakasugi, A. Iida, T. Misaki, Y. Nishii and Y. Tanabe, *Adv. Synth. Catal.*, 2003, **345**, 1209-1214.

117) Y. Yasui, S. Tsuchida, H. Miyabe and Y. Takemoto, *J. Org. Chem.*, 2007, **72**, 5898-5900.

118) Y. Sugawara, W. Yamada, S. Yoshida, T. Ikeno and T. Yamada, *J. Am. Chem. Soc.*, 2007, **129**, 12902-12903.

119) M. Kato and I Kuwajima, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 827-830.

120) M. Tori, A. Hashimoto, K. Hirose and Y. Asakawa, *Phytochemistry*, 1995, **40**, 1263-1264.

121) P. Wipf and S. Ribe, *J. Org. Chem.*, 1998, **63**, 6454-6455.

122) P. Wipf, C. Kendall and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2003, **125**, 761-768.

123) A. Guzman-Martinez and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 10634–10637.

124) A. Mordini, D. Peruzzi, F. Russo, M. Valacchi, G. Reginato and A. Brandi, *Tetrahedron*, 2005, **61**, 3349-3360.

125) W. Oppolzer and R. Moretti, *Tetrahedron*, 1988, **44**, 5541–5552.

126) Q. Xu, G. Wang, X. Wang, T. Wu, X. Pan, A. S. C. Chan and T. Yang, *Tetrahedron: Asymmetry*, 2000, **11**, 2309–2314.

127) S. D. Bull, S. G. Davies, A. C. Garner and M. D. O'Shea, *J. Chem. Soc., Perkin Trans. 1*, 2001, 3281–3287.

128) M. Jacob, M. L. Roumestant, P. Viallefont and J. Martinez, *Synlett*, 1997, 691-692.

129) R. Pellicciari, B. Natalini and M. Marinozzi, *Synth. Commun.*, 1988, **18**, 1707–1713.

130) M. Adamczyk and R. E. Reddy, *Synth. Commun.*, 2001, **31**, 579–586.

131) L. C. Vishwakarma, O. D. Stringer and F. A. Davis, *Organic Syntheses*, 1993, *Coll. Vol. 8*, 546–550.

132) F. Sagui, P. Conti, G. Roda, R. Contestabile and S. Riva, *Tetrahedron*, 2008, **64**, 5079–5084.

133) G. Pavé, S. Usse-Versluys, M.-C. Viaud-Massuard and G. Guillaumet, *Org. Lett.*, 2003, **5**, 4253–4256.

134) T. Iwasaki, K. Agura, Y. Maegawa, Y. Hayashi, T. Ohshima and K. Mashima, *Chem. Eur. J.*, 2010, **16**, 11567–11571.

135) Y. Numajiri, T. Takahashi and T. Doi, *Chemistry – An Asian Journal*, 2009, **4**, 111–125.

136) K. Ishii, H. Ohno, Y. Takemoto, E. Osawa, Y. Yamaoka, N. Fujii and T. Ibuka, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2155–2164.