1999

Asymmetric synthesis of glycosidase inhibitors

Gareth William O'Meara

University of Wollongong

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ASYMMETRIC SYNTHESIS

of

GLYCOSIDASE INHIBITORS

A Thesis Submitted for the Degree of

Doctor of Philosophy

of

The University of Wollongong

Department of Chemistry

Gareth William O'Meara
B. Sc. (Hons.)

January 1999
DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University or other tertiary institution and, to the best of my knowledge or belief, contains no material previously published or written by another person, except where due reference is made in the text.

Gareth W. O'Meara

January 1999
Sections of the work described in this thesis have been reported in the following publications.


ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge Professor Stephen G. Pyne for not only providing me with a challenging and interesting project, but also for his expert supervision and invaluable advice over the past four years.

I would like to thank both past and present members of the Pyne research group, especially Dr Alison Ung, Dr Matthew Cliff and Dr Zemin Dong, for their help and assistance, as well as their tolerance in putting up with me during the thesis write up. Thanks also to the many people who have drifted through the Chemistry Department and made it a great place to work.

Many thanks must go to the technical staff, especially Ellen Manning (NMR and computers), Sandra Chapman (NMR), Larry Hick (HRMS) and Roger Kanitz (MS and BBQs), for everything they've done for me.

Finally, I would like to thank anyone else who has helped me at some stage over the past four years and whose name I've forgotten during thesis writing burnout.
This thesis presents the results of studies aimed at the development of general strategies for the synthesis of azasugars, which act as glycosidase inhibitors. In the first Chapter a review is made of the role of carbohydrates and glycosidases in biological systems. The strategies developed for the synthesis of azasugars are discussed, as well as the aims of this project and the literature relevant to the synthetic aspects of this project.

The successful synthesis of $\gamma$-amino-$\alpha,\beta$-unsaturated ketones from allylic sulfoximines utilising a palladium(0) catalysed rearrangement is presented in Chapter 2. The regioselectivities and diastereoselectivities of these transformations are also discussed.

In Chapter 3, the palladium(0) catalysed amination of allylic sulfoximines utilising external nucleophiles is described. The regioselectivities of these reactions with various allylic sulfoximines is reported, as are the results of competition reactions between the external nucleophile and the sulfinamide anion. The results of attempts to induce asymmetry into the reaction via the use of enantiomerically pure sulfoximines, chiral ligands and chiral external nucleophiles are also discussed.

The attempted synthesis of azasugars from allylic sulfoximines is presented in Chapter 4. Results from investigations into the use of both the intramolecular rearrangement examined in Chapter 2 and the allylic amination reaction described in Chapter 3 towards the synthesis of azasugars are detailed.

In Chapter 5, the attempted synthesis of azasugars from a carbohydrate source is reported. The key steps in the synthetic path are elongation via Grignard addition, palladium(0) catalysed allylic amination, oxidation of a double bond and cyclisation.
A brief summary of the work carried out in this thesis is provided in Chapter 6, as well as current and future work in this area.
# ABBREVIATIONS

The following abbreviations have been used throughout this thesis.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
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<tbody>
<tr>
<td>$[\alpha]$</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>AD</td>
<td>asymmetric dihydroxylation</td>
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<td>aryl</td>
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<td>Asn</td>
<td>asparagine</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Boc</td>
<td>tertiary-butyloxy carbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>br</td>
<td>broad</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bucast</td>
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<td>Bz</td>
<td>benzoyl</td>
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<td>c</td>
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<tr>
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<td>degrees Celsius</td>
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<td>calc'd</td>
<td>calculated</td>
</tr>
<tr>
<td>Cbz</td>
<td>benzyloxy carbonyl</td>
</tr>
<tr>
<td>C=O</td>
<td>carbonyl group</td>
</tr>
<tr>
<td>COSY</td>
<td>correlation spectroscopy</td>
</tr>
<tr>
<td>CSA</td>
<td>camphor sulfonic acid</td>
</tr>
<tr>
<td>$\delta$</td>
<td>chemical shift in parts per million</td>
</tr>
<tr>
<td>d</td>
<td>deuterated</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylidene acetone</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
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<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>DEPT</td>
<td>distortionless enhancement by polarisation transfer</td>
</tr>
<tr>
<td>DHQ</td>
<td>dihydroquinine</td>
</tr>
<tr>
<td>DHQD</td>
<td>dihydroquinidine</td>
</tr>
<tr>
<td>DIBAL</td>
<td>di-iso-butylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMDP</td>
<td>2R,5R-dihydroxymethyl-3R,4R-dihydroxypyrrolidine</td>
</tr>
<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
</tr>
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<td>DMF</td>
<td>N,N-dimethylformamide</td>
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<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
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<tr>
<td>e.e.</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>equiv.</td>
<td>(molar) equivalents</td>
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<tr>
<td>ES</td>
<td>electrospray</td>
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<tr>
<td>Et</td>
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<td>ether</td>
<td>diethyl ether</td>
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<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration (US)</td>
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<tr>
<td>g</td>
<td>grams</td>
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<td>Gal</td>
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<td>glucose</td>
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<td>GlcCer</td>
<td>glucosylceramide</td>
</tr>
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<td>GlcNAc</td>
<td>N-acetylglucosamine</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMPA</td>
<td>hexamethylphosphoramide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>hr</td>
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<td>HRMS</td>
<td>high resolution mass spectroscopy</td>
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<tr>
<td>Hz</td>
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<tr>
<td>Symbol</td>
<td>Definition</td>
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<td>------------</td>
</tr>
<tr>
<td>i</td>
<td>iso</td>
</tr>
<tr>
<td>i-Pr</td>
<td>iso-propyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium di-iso-propylamid e</td>
</tr>
<tr>
<td>Ln</td>
<td>unspecified number of ligands</td>
</tr>
<tr>
<td>m</td>
<td>multiplet</td>
</tr>
<tr>
<td>M</td>
<td>moles per litre</td>
</tr>
<tr>
<td>M</td>
<td>molecular ion</td>
</tr>
<tr>
<td>Man</td>
<td>mannose</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeOH</td>
<td>methanol</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mL</td>
<td>millilitre</td>
</tr>
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<td>millimole</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>Ms</td>
<td>methanesulfonyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>MSH</td>
<td>O-mesitylsulfonylhydroxylamine</td>
</tr>
<tr>
<td>m/z</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>NB-DGJ</td>
<td>N-butyl-1-deoxygalactononojirimycin</td>
</tr>
<tr>
<td>NB-DNJ</td>
<td>N-butyl-1-deoxynojirimycin</td>
</tr>
<tr>
<td>n</td>
<td>neo</td>
</tr>
<tr>
<td>NeuAc</td>
<td>sialic acid</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>nOESY</td>
<td>nuclear overhauser effect spectroscopy</td>
</tr>
</tbody>
</table>
Nuc  nucleophile
O/N  overnight
Pent  pentyl
Ph  phenyl
PHAL  phthalazine
ppm  parts per million
p-Tol  para-toluene
q  quartet
R  unspecified substituent
Rf  retention factor
RT  room temperature
s  singlet
Ser  serine
t  triplet
t  temperature
t  tertiary
TBDMS  tertiary-butyldimethylsilyl
t-Bu  tertiary-butyl
Tf  trifluoromethanesulfonyl
THF  tetrahydrofuran
Thr  threonine
TLC  thin layer chromatography
TMS  trimethysilyl
tosyl  para-toluenesulfonyl
Ts  para-toluenesulfonyl
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7.3 Experimental for Chapter 3

7.4 Experimental for Chapter 4

7.5 Experimental for Chapter 5

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INTRODUCTION
Chapter 1

1.1 Glycobiology

Glycobiology is the study of carbohydrates and their role in biological events. For many years carbohydrates were not as well studied as proteins and DNA for two main reasons. Firstly, many researchers did not believe that carbohydrates had a significant role aside from providing structural support and energy storage, for example, cellulose and starch, respectively. Secondly, the small amounts of carbohydrates present in many cases were too minute and too complex to be studied with the technology available at the time. Changes in attitudes and technology have led to the field of glycobiology rapidly expanding.\textsuperscript{1,2,3}

1.2 Carbohydrates

Carbohydrates differ from other biopolymers such as proteins and DNA in their potential for variation. Carbohydrate chains can be branched, can link at several different points with other sugars, can exist as both $\alpha$ and $\beta$ anomers, and can undergo modifications such as sulfation, phosphorylation, acetylation and lactonisation.\textsuperscript{4} This means an extraordinary number of isomers can be formed from a short oligosaccharide chain. Two identical amino acids or nucleotides can only produce one dipeptide or dinucleotide. Whereas two identical pyranose monosaccharides can give 11 different disaccharides, considering only those without any modifications.\textsuperscript{5}
Carbohydrates have been found to be implicated in both normal and abnormal cell behaviour. The fundamental cellular processes of recognition, adhesion, growth, and regulation are dependent upon sugars, although as yet no single general function has been ascribed.

1.3 Glycoconjugates

Glycoconjugates are proteins and lipids with a carbohydrate chain attached. These glycoproteins and glycolipids are common components of cell membranes, cell walls, and organelle membranes. The exposed carbohydrate chains act as receptors for proteins, enzymes, and other cells, as well as bacteria and viruses. Even mammalian egg-sperm recognition is believed to be mediated by recognition of a glycoprotein.

Figure 1.1: Cell Interactions Mediated by Carbohydrates
Most glycoconjugates have a limited lifespan before being degraded in order to provide the raw materials for the biosynthesis of other glycoconjugates. In this manner cells are able to regulate the amount and types of glycoconjugates present.

1.3.1 Glycoprotein Biosynthesis

There are two main classes of glycoprotein: \( N \)-linked and \( O \)-linked. The \( N \)-linked glycoproteins are the more common of the two. As shown in Scheme 1.1, the carbohydrate chain is attached to the nitrogen of the asparagine residue in the sequence Asn-X-Ser/Thr. The initial oligosaccharide chain (Glc\(_3\)Man\(_9\)GlcNAc\(_2\)) is assembled on a phospholipid carrier called dolichol. The oligosaccharide is then transferred \textit{en bloc} to the growing polypeptide chain. Trimming enzymes (see Section 1.5) remove the outer three glucoses, followed by the removal of four of the mannoses by the corresponding enzymes to give a common core of sugars called the trimannosyl core. After trimming, mannose and other sugars such as \( N \)-acetyl-glucosamin\(\dot{\text{e}}\), galactose, sialic acid, and fucose may be added by the appropriate enzymes.\(^9\)

The reason why the cell builds the oligosaccharide structure, then deconstructs it, only to reconstruct it once again is unknown. Possibly it acts as a marker for the cell's machinery to keep track of the maturation status of the newly formed protein.\(^{10}\) Another suggestion is that the process allows an oligosaccharide chain to be attached to widely differing proteins without having to code the information into the DNA segment for each protein.\(^1\)
Scheme 1.1: Biosynthesis of N-linked Glycoproteins
There are three main classifications within the \( N \)-linked glycoproteins: high mannose, complex, and hybrid. High mannose types, as could be expected from their name, contain only \( \alpha \)-mannosyl residues attached to the core. Complex types contain no mannose apart from the core, but have branches consisting of GlcNAc, Gal, and NeuAc (sialic acid). They can also have a fucose and a GlcNAc branching off the trimannosyl core. Hybrids have characteristics of both high mannose and complex type glycans.

\[
\begin{align*}
\text{Man} & \quad \text{Man} & \quad \text{Man} \\
\text{Man} & \quad \text{Man} & \quad \text{Man} \\
\text{Man} & \quad \text{Man} & \quad \text{Man} \\
\text{GlcNAc} & \quad \text{GlcNAc} & \quad \text{Asn-X-Ser(Thr)} \\
\end{align*}
\]

\[
\begin{align*}
\text{NeuNAc} & \quad \text{NeuNAc} & \quad \text{NeuNAc} \\
\text{Gal} & \quad \text{Gal} & \quad \text{Gal} \\
\text{GlcNAc} & \quad \text{GlcNAc} & \quad \text{GlcNAc} \\
\text{Man} & \quad \text{Man} & \quad \text{GlcNAc} \\
\text{GlcNAc} & \quad \text{GlcNAc} & \quad \text{Fuc} \\
\text{Asn-X-Ser(Thr)} & \quad & \\
\end{align*}
\]

\( \text{Figure 1.2: Types of } N \text{-linked Glycoproteins: (a) High Mannose, (b) Complex} \)

\( O \)-Linked glycoproteins are linked via serine, threonine, or hydroxy-lysine. They do not share a common core structure in contrast to the \( N \)-linked glycoproteins. The sugars are added sequentially to the parent protein.

The attachment of oligosaccharides to nascent polypeptide chains makes intermediates in the folding process more soluble. They can also act as recognition markers for
molecular chaperones that participate in the folding process, so that the newly
synthesised protein reaches its proper functional form.\textsuperscript{10,11}

The carbohydrate portion of glycoproteins also confer conformational stability,
quaternary structure, resistance against proteolytic degradation, charge, and water
binding capacity.\textsuperscript{2}

1.3.2 Glycolipid Biosynthesis

There are many types of glycolipids, which are defined by the type of lipid. The
glycolipids are synthesised by sequential addition of carbohydrates to the parent lipid.
An example of glycolipid biosynthesis is given below in the synthesis of gangliosides
found in the cells of the nervous system.\textsuperscript{12}
1.4 Roles of Sugars and Glycoconjugates

It is difficult to fully encompass the wide range of biological roles in which carbohydrates and glycoconjugates have been implicated. Currently most of the knowledge about the roles of carbohydrates in biological events is empirical. There is at present no set of rules that carbohydrates seem to follow. A carbohydrate that performs one function on a certain protein may perform a completely different...
function on another. The following sections serve merely to highlight the wide and diverse roles of carbohydrates in biological events.

1.4.1 Blood Group Antigens

Among the first oligosaccharides whose importance was recognised was the blood group antigens. Immunochemical experiments to investigate the antigens recognised by serum antibodies began in the 1940s and began to yield results in the 1960s. These antigens were eventually shown to be glycoconjugates. Many tumour associated antigens are chemically modified forms of the blood group antigens.

1.4.2 Cell Recognition, Adhesion, and Regulation

The cell recognition process is the initial step in virtually all biological events. The Sections 1.4.3, 1.4.4, 1.4.5 all contain examples where the recognition process is mediated by carbohydrates.

Cell-cell and cell-matrix adhesions are essential for the structural organisation and behaviour of cells in tissues. Many of the cell adhesion receptors are transmembrane glycoproteins such as the integrins and proteoglycans. Defects in adhesion between cells and their underlying basement membrane can lead to diseases such as muscular dystrophy.
The survival of many cell types require adhesion to extracellular matrix proteins. In the absence of specific signals from these proteins the cells enter into a programmed cell death pathway called apoptosis.\textsuperscript{19}

Many hormones are glycoproteins for which the attached carbohydrates are essential for full expression of their regulatory activity. The initial binding to a cell surface receptor stimulates a chain of events involving chemical messengers along a specific response pathway to generate the hormonal action.\textsuperscript{20}

Cell surface glycoproteins have been shown to modulate the activity of growth factors. Many growth factors need to exist as oligomers before they can interact with their specific signaling receptors. Formation of a complex with low binding affinity glycoproteins allows the oligomerisation of the growth factors to proceed.\textsuperscript{21}

1.4.3 Immune System

Recognition of a carbohydrate antigen on a foreign body can elicit an immune system response. A glycolipid in the outer membrane of the bacterial cell wall of the pathogen \textit{Salmonella} contains a tetrasaccharide repeating unit that is recognised by the human body’s immune system as being non-self, and the immune system is then activated to destroy the invader.\textsuperscript{22}
Selectins are a class of lectins (carbohydrate binding proteins) that reside on both the endothelial cell surface and the leukocyte (white blood cell) surface. They mediate the initial recognition in immunological important events such as leukocyte recruitment to an injury site. The lectins bind to a tetrasaccharide named sialyl Lewis^X (1) on the leukocytes. After this initial recognition the leukocytes are able to pass through the endothelium to the site of injury or infection.

When too many leukocytes are recruited to the injury site, normal cells can be damaged causing inflammation. Control of this process by inhibiting the adhesion step has been considered as a new anti-inflammatory strategy. Sialyl Lewis^X in solution has been shown to directly compete with sialyl Lewis^X on the surface of white blood cells for binding to the selectins, and as such gives a useful lead as an anti-inflammatory drug.

The two trisaccharide structures below (2) and (3) have been shown to play a fundamental role in the rejection of organs in xenotransplantation from pigs to man.
Both trisaccharides are on the endothelial cells of the graft and act as antigens for xeno-reactive antibodies.\textsuperscript{27}

\[ R = \text{Et or Bu or Ph} \]

\[ (2) \]

\[ (3) \]

1.4.4 Cancer

Transformation of a normal cell into a tumour cell is accompanied by changes in the chemical composition, metabolism, and organisation of cell surface glycoconjugates. Glycoconjugates in many human cancers contain novel glycosylation patterns.\textsuperscript{28,29,30} The accumulation of specific glycoconjugates within tumour cells opens up the possibility of using the recognition of these unique features as a diagnostic tool for the early detection of cancer.

Metastasis is the process of the spreading of cancer throughout the body.\textsuperscript{31} The increase in activity of glycosyltransferases in some tumour cells and resultant novel glycosylation patterns have been shown to be associated with the metastatic potential of
the cancer.\textsuperscript{32} It is not certain at this time whether the increased activity of the glycosyltransferases is a cause or effect of metastasis.

It has been shown that tumour cells may be recognised by endo-thelial cell surface molecules that are normally involved in the adhesion of blood leukocytes (see Section 1.4.3). The tumour cells are able to utilise the same mechanisms as the leukocytes to pass through the endothelium into the tissue where a new tumour can begin to grow.\textsuperscript{33}

1.4.5 Infections

The initial step of any infectious cycle is the recognition between the host cell and the pathogen. Many of these recognition processes are mediated by carbohydrates whether they are on the host cell or the pathogen.\textsuperscript{14,34,35} The envelope proteins of the HIV virus are heavily glycosylated, and approximately half the apparent weight of many of the glycoproteins are carbohydrate in nature. The HIV infectious cycle requires an interaction between the viral glycoprotein gp120 and a specific receptor on the surface of CD4 T-cells.\textsuperscript{36,37}

Some viruses do not have the enzymes to produce N-linked oligosaccharides, and thus they rely upon the host cell's glycosylation machinery. Due to this, the characteristics of the viral oligosaccharides are very similar to that of the host and cannot be recognised by the immune system as non-self. The oligosaccharide chains may further
assist the virus to escape detection by masking the polypeptide chain which could be recognised as non-self by the immune system.\textsuperscript{2}

1.5 Glycosidases

Glycosidases are enzymes that cleave carbohydrates. They are involved in several important biological processes such as digestion of dietary carbohydrates, and the biosynthesis (see Section 1.3.1) and catabolism of glycoconjugates.

Absence of glycosidases can lead to serious illness. In Tay-Sachs disease the enzyme $\beta$-hexosaminidase A is deficient. This enzyme is involved in the degradation of several glycosphingolipids. Its absence causes accumulation of the ganglioside GM2 in neuronal cells, which then swell and eventually die. Sufferers have a life expectancy of 3-4 years.\textsuperscript{38}

1.5.1 Glycosidase Mechanism

There are two basic types of glycosidase, one where the anomic configuration of the sugar is retained, and the second where it is inverted. The retaining glycosidases work via a double displacement mechanism involving an enzyme nucleophile as shown in the diagram below.\textsuperscript{39,40}
Scheme 1.3: Mechanism of a Retaining Glycosidase
Inverting glycosidases act via the single displacement by a nucleophilic water molecule via a process that is enhanced by a general enzymatic base.  

![Diagram of the mechanism of an inverting glycosidase](image)

**Scheme 1.4: Mechanism of an Inverting Glycosidase**

**1.6 Glycosidase Inhibitors**

Glycosidase inhibitors have the potential to be investigative and therapeutic agents in cancer, viral infection, genetic disorders, diabetes, and obesity. They work by interfering with the biosynthesis and degradation of glycoconjugates. The effects of
these changes can then be studied. They also serve to investigate the mechanism of action, binding specificity, and the topography of the active site of the glycosidase.

1.6.1 Types of Glycosidase Inhibitors

The most common types of glycosidase inhibitors are carbohydrate analogues. The two main categories of these carbohydrate analogues are where the ring oxygen is replaced by another atom or where the anomeric hydroxyl group is replaced.\(^{41}\)

However most work in the literature, especially in recent years, has been directed towards azasugars.\(^{41,42,43}\)

1.6.2 Azasugars

Azasugars are analogues of sugars in which nitrogen replaces the oxygen of the sugar ring. There are several naturally occurring azasugars, including nojirimycin (4),\(^{44}\) dihydroxymethyldihydroxypyrrolidine (DMDP) (5),\(^{45}\) swainsonine (6),\(^{46}\) and castanospermine (7).\(^{47}\)
The biosynthesis of azasugars is not exactly clear. The most obvious biosynthetic route occurs from natural sugars, which undergo oxidation and reductive amination, followed by cyclization (Scheme 1.5). However, it has also been shown that swainsonine (6) can be synthesised from pipecolic acid in fungi and plants (Scheme 1.6).
Azasugars are believed to be metabolically inert in mammalian tissue and generally inhibit in a reversible and competitive manner. They mimic the positive charge on the sugar ring of the high energy glycosyl cation intermediate (see intermediate C in Scheme 1.3) since the heterocyclic nitrogen is protonated at physiological pH. Furthermore, the heterocyclic ring adopts a flattened half-chair conformation similar to that of the glycosyl cation.

The furanose type azasugars tend to be more general in inhibiting different glycosidases than the pyranose type. It is assumed that the envelope shape and positive charge of protonated furanose azasugars resemble the flattened chair shape of the intermediate glycosyl cation much better.

The reversible nature of the binding has already led to the use of suitably linked azasugars as affinity chromatography ligands for the purification of glycosidases.
Affinity chromatography is one of the best methods for the separation of enzymes. It takes advantage of the biologically specific binding interactions that occur on protein surfaces. Correct selection of the ligand makes it possible to separate different enzymes that perform the same function e.g. glucosidase I can be separated from glucosidase II using 1-deoxynojirimycin (8).

![Deoxynojirimycin](image)

deoxynojirimycin (8)

A more recent application has been the use of the N-aryl azasugar (9) to generate antibodies in vitro that are capable of cleaving glycosidic bonds. The rate of hydrolysis of (10) by the generated antibodies is $10^4$ faster than by acetic acid. These antibody glycosidases could be used to chemically manipulate oligosaccharides when the natural glycosidase either does not exist or cannot be isolated from natural sources.

![Aryl Azasugar](image)

(9)

![Aryl Glycosidase](image)

(10)
1.6.3 Biological Activity

Several azasugars have been shown to be effective agents against various diseases such as diabetes, HIV infection, and cancer. The following sections are meant only to give an overview of the medical research into the use of azasugars as therapeutic agents, and as such this section is by no means comprehensive or detailed. It only serves to highlight the diverse nature of the roles in which carbohydrates are used in biological processes. As more becomes known about the functions of carbohydrates it more than likely that carbohydrate analogues will play a larger role in the field of therapeutic and preventative medicine.

1.6.3.1 Diabetes

Diabetics absorb glucose much more slowly due to the lack of insulin. Type II non-insulin dependent diabetes mellitus is a disease that usually develops in adulthood and is due to a relative insufficiency of insulin and impaired sensitivity to its actions. The subsequent slow absorption of glucose can be offset by slowing down the release of glucose from sources such as starch and sucrose. This can be acheived by the inhibition of intestinal glucosidases. Miglitol (11) is an intestinal α-glucosidase inhibitor that has been approved for market, under the name Glyset, by the FDA in the United States. It has been developed by Bayer (BAY m1099) and is only for the treatment of Type II non-insulin dependent diabetes.
Other intestinal α-glucosidase inhibitors have been tested as possible anti-diabetic therapies. The diglucose analogue (12) has also been shown to be a useful adjunctive therapy for the treatment of diabetes mellitus, but thus far has not made it onto the market.\(^{54,55}\)

### 1.6.3.2 Viral Infections

A range of sugar analogues have been screened for anti-HIV activity.\(^ {36,56}\) α-Glucosidase inhibitors have been found to be most effective in inhibiting viral infectivity. 6-O-Butanoyl-castanospermine (Bucast) (13) and N-butyl-1-deoxynojirimycin (NB-DNJ) (14) were found to be good inhibitors of HIV replication at concentrations well below cytotoxic levels. Both NB-DNJ and Bucast have undergone
Phase I and II clinical trials. The use of a hydrophobic substituent, in this case a butyl group, is most likely to help the drug to penetrate the cell wall before enzymatic cleavage releases the active form of the drug. It is believed that the aberrant glycosylation patterns induced by the drugs cause an alteration of local conformation in the glycoprotein gp120 which leaves it unable to interact with cells.\(^{57}\) (see Section 1.4.5)

\[
\begin{align*}
\text{BuCOO}^- & \quad \text{Bu} \\
\text{OH} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{OH} & \\
\end{align*}
\]

Bucast (13)

\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
\text{N} & \quad \text{CH}_2\text{OH} \\
\text{Bu} & \\
\end{align*}
\]

NB-DNJ (14)

The secretion of Hepatitis B virus can be prevented by treating cells with the \(\alpha\)-glucosidase inhibitor NB-DNJ (14). It was found that if the Hepatitis B viral M glycoprotein is improperly glycosylated then the viral DNA, accompanied by the envelope and core proteins, accumulate within the lysosomal compartment of the infected cell. This suggests that correct glycosylation is necessary for the processes involved in the transport of the virus out of the cell.\(^{58,59}\)

1.6.3.3 Cancer

Several azasugars have shown anti-cancer potential. Swainsonine (4) has undergone Phase I clinical trials and was shown to have minimal toxicity when administered
intravenously to patients with advanced malignancies. It is believed that swainsonine works by enhancing the sensitivity of tumour cells to natural killer cells. The natural killer cells discriminate between targets on the basis of the carbohydrates present on the cell surface. Those with high mannose oligosaccharide chains are much more likely to be targeted. Swainsonine inhibits the removal of the mannose from the oligosaccharide core thus leaving the cells with terminal mannose residues.

1.6.3.4 Gaucher's Disease

Gaucher's disease is an autosomal recessive disorder characterised by the impaired ability to degrade glucosyl ceramide (GlcCer) due to defects in the gene encoding the enzyme needed. By partially inhibiting the biosynthesis of the glycolipid, the impaired catabolism of GlcCer can be offset, thus balancing the levels of GlcCer. N-Butyldeoxygalactononojirimycin (NB-DGJ) (15) has been shown to inhibit GlcCer biosynthesis by inhibition of the glucosyl-transferase specific to ceramide. It does this without inhibiting the lysosomal β-glucocerebrosidase which degrades GlcCer in the normal catabolic pathway.

\[
\text{NB-DGJ (15)}
\]
1.6.3.5 Antifeedant Properties

Trace amounts of DMDP (5) have been shown to deter locusts from feeding on plants, while castanospermine (7) has a similar effect on aphids. Natural biodegradable pesticides like this, which do not kill the insects, but simply deter them from feeding would make an ideal agent for crop protection.\textsuperscript{63,64}

1.7 Synthesis of Azasugars

Due to the great potential of azasugars as therapeutics, there have have enumerable strategies devised for their synthesis and have utilised a wide range of starting materials. These include carbohydrates, chiral natural products, and other non-natural starting materials.\textsuperscript{41,65,66,67} It would be impossible to cover all the synthetic methods that have appeared in the literature. Hence only a few representative syntheses will be shown to highlight the work being carried out by laboratories all over the world towards the synthesis of azasugars.

1.7.1 Synthesis using Carbohydrate Starting Materials

Due to the high number of stereocentres in many of the azasugars, numerous researchers utilise naturally occurring sugars as their starting materials. The advantages of using sugars is two-fold: firstly, many sugars are relatively inexpensive
and are widely available, and secondly, the stereogenic centres already exist in the correct form. Many other factors increase their attractiveness to chemists including availability in both cyclic and acyclic forms, presence of functional groups, varying chain lengths, and different oxidation and reduction states.41,66,68,69

A common approach to azasugar synthesis is the conversion of a hydroxyl group of a sugar derivative to an azide followed by a reductive cyclisation. In the example below the azide (16) is reduced by tin(II) chloride and the resultant amine reacts with the carbonyl group to form the lactam (17).70

![Reaction scheme](image)

In another example, the lactol below (18) undergoes Wittig elongation when treated with the appropriate phosphorane. Diastereoselective conjugate addition of ammonia to the double bond followed by cyclisation of the resultant amine with the mesylate gives the protected azasugar (19).71
Reductive amination of dicarbonyl compounds (20) with a protected amine followed by deprotection provides a very convenient and simple route to azasugars (21).\(^7\)

1.7.2 Synthesis from Non-Carbohydrate Starting Materials

Chemoenzymatic methods have been extensively utilised by Wong to synthesise a broad range of azasugars with excellent enantioselectivity. One of the many syntheses published by Wong is shown here. The condensation of the azido aldehyde (22) with
dihydroxyacetonephosphate (23) is catalysed by the enzyme Fuc-1-P aldolase. The phosphate group is then removed from the terminal hydroxyl by the enzyme acid phosphatase. Reductive cyclisation then gives the final product (24).\(^7\)

\[
\begin{align*}
\text{CHO} & + \text{HO-\text{C}O^{-}} \text{PO}_3^- \xrightarrow{1. \text{Fuc-1-P aldolase}} \text{HO-OH} \xrightarrow{2. \text{Acid phosphatase}} \text{H}_2, \text{Pd-C} \xrightarrow{H_2, \text{Pd-C}} \text{N}_3 \text{O} \\
(22) & \quad (23) & \quad (24)
\end{align*}
\]

The protected cyclohexadiene derivative (25) can be dihydroxylated and then converted into the azide (26) via a triflate. Ozonolysis of the double bond followed by reductive cyclisation gives the protected azasugar (27).\(^7\)
The methyl ester of L-serine (28) is firstly protected as an oxazoline. Reduction of the ester followed by Wittig elongation provides the vinyl oxazoline (29) which can then be dihydroxylated with OsO4. Hydrolysis of the oxazoline with aqueous acid and then cyclisation gives the lactam (30), which can then be converted to the azasugar (31).
1.8 Aims of the Project

The proven potential of azasugars as pharmaceutical agents and as probes in the investigation of the mechanisms of glycosidases make them an attractive target for synthesis. The main challenge in the synthesis of carbohydrates and their analogues is the high number of stereocentres. This can be overcome by either utilising the existing stereocentres in natural sugars or employing highly enantioselective and diastereoselective synthetic methods to procure the required stereochemistry.
The aim of this thesis is the development of general strategies that are flexible enough to be applicable to the synthesis of a wide range of azasugars and their analogues. Two synthetic paths were devised: one using non-carbohydrate starting materials and the other from a carbohydrate source.

1.9 Asymmetric Synthesis of Azasugars from Non-Carbohydrate Starting Materials

The first proposed synthetic route is outlined in the retrosynthetic analysis below. The key steps are: (a) the palladium(0) catalysed rearrangement of an allylic sulfoximine to an allylic amine, (b) asymmetric dihydroxylation, and (c) deprotection and reductive amination.

Scheme 1.7: Synthesis of Azasugars from Allylic Sulfoximines
1.9.1 Allylic Sulfoximines

The synthetic route proposed above begins with an allylic sulfoximine. Sulfoximines are readily accessible and have a rich and diverse chemistry.\textsuperscript{76,77,78} The sulfonimidoyl group imparts both chirality and carbanion stabilising properties to the molecule. Allylic sulfoximines can act both as nucleophiles in a basic medium and as electrophiles in the presence of a Lewis acid.\textsuperscript{79}

1.9.1.1 Preparation of Allylic Sulfoximines

There have been several published syntheses for the assembly of allylic sulfoximines. Harmata and Claisen reacted sulfimidoyl halogens (32) and (33) with metallated allyl groups to provide allylic sulfoximines (34).\textsuperscript{80}

\[
\begin{align*}
\text{Li} & \quad \text{p-Tol-S—F} + \quad \text{allyl-Li} \\
& \quad \text{NPh} \\
& \quad \text{(32)} \\
\text{SnBu3} & \quad \text{p-Tol-S—Cl} + \quad \text{allyl-SnBu3} \\
& \quad \text{NPh} \\
& \quad \text{(33)}
\end{align*}
\]

Reggelin and Weinberger synthesised cyclic sulfonimidates (36) from protected amino acid derivatives such as \textit{O}-trimethylsilylvalinol (35). Allyl magnesium
bromide underwent addition to (36) to afford the $N$-valinol allyl sulfoximines (37).$^8$^1

Pyne and Boche iminated the known allyl phenyl sulfoxide (38) with $O$-mesitylsulfonylhydroxylamine (MSH) to give the corresponding allyl phenyl sulfoximine (39).$^8$^2
Lithiated S-methyl sulfoximines (40) undergo 1,2-addition with aldehydes and ketones to afford β-hydroxy sulfoximines (41) which are then dehydrated to the allyl sulfoximines (42).\(^8\)

1.9.1.2 Reactions of Allylic Sulfoximines

Lithiated allylic sulfoximines (43) can undergo Michael type conjugate additions with high diastereoselectivities. The products (44) can be isolated via low temperature protonation, however warming to room temperature sees the electrophilic nature of the sulfoximine realised and it can act as a leaving group to provide highly functionalised cyclopropanes (45).\(^7\)
Allylic sulfoximines (46) have been shown by Gais et al. to undergo $S_N2$ and $S_N2'$ like displacement reactions with organocuprates selectively in the $\gamma$-position in the presence of boron trifluoride and lithium iodide to give terminal alkenes (47). \(^{83}\)

Pyne and Boche reacted the protected allylic sulfoximine (48) with benzaldehyde to give exclusively the $\alpha$-1,2 product (49) when the reaction was carried out in THF. However the use of THF/HMPA gave both the $\alpha$-1,2 (49) and $\gamma$-1,2 products (50) in the ratio of 2.3:1. \(^{82}\)
Gais et al. have shown it is possible to direct the regioselectivity of the reaction between lithiated allylic sulfoximines (51) and aldehydes by judicious utilisation of transmetallation with titanium compounds. When CITi(O/Pr)_3 is used γ-1,2 addition is favoured and gives (52), while CITi(NEt)_3 is selective for α-1,2 addition product (53).
1.9.1.3 Rearrangement of Allylic Sulfoximines to Allylic Sulfonamides

The first palladium(0) catalysed rearrangement of an allylic sulfoximine to an allylic sulfonamide was reported by Pyne and Dong.\textsuperscript{86} Previous attempts to rearrange allylic sulfoximines via thermal methods had generally failed.\textsuperscript{80,82} The only success coming from Gais \textit{et al.}, who were able to rearrange some $\gamma$-phenyl allylic sulfoximines (54), albeit in generally low yields and with modest regioselectivity.\textsuperscript{87}
With this resistance to rearrangement, allylic sulfoximines are very different to allylic sulfilimines that readily undergo thermal [2,3] sigmatropic rearrangements to the corresponding sulfenamides. The allylic sulfilimines are so reactive that it is often impossible to isolate them at room temperature before the rearrangement occurs.\(^8\)

\[
\text{Semi-empirical calculations by both Pyne and Harmata have indicated that the allylic sulfinamides are thermodynamically more stable than their isomeric allylic sulfoximines. Harmata found the heat of formation for the sulfoximine (57) was 118 kcal/mol compared to 32 kcal/mol for the isomeric sulfinamide (58).}^{80}
\]
For the sulfoximine (59) Pyne calculated the heat of formation was 145 kcal/mol while the sulfinamide (60) was 57 kcal/mol. Both calculations indicated that a large kinetic barrier must exist for the thermal rearrangement to proceed.\(^8^2\)

Later \textit{ab initio} calculations by Harmata found the conversion of (57) to (58) was exothermic by 24.1 kcal/mol and the activation energy was estimated at 28 kcal/mol.\(^8^9\)

The palladium(0) catalysed rearrangement neatly overcomes this kinetic barrier to provide allylic sulfinamides under mild conditions as shown by the facile conversion of (61) to (62) by Pyne and Dong.\(^8^6\)
The sulfinamides can be subjected to mild base hydrolysis to provide protected allylic amines. These types of amines are extremely useful for organic synthesis\textsuperscript{90} as key structural components for peptide isosteres\textsuperscript{91} and as antimycotic agents\textsuperscript{92}.

The mechanism of palladium(0) catalysed allylic alkylations and aminations is well documented\textsuperscript{93,94,95,96}. The rearrangement of the allylic sulfoximines is likely to go through a similar mechanism as shown in Scheme 1.8. (For more details on the mechanism of palladium catalysed allylic aminations see Section 1.10.2)

\begin{equation}
\begin{align*}
\text{(A)} & \xrightarrow{\text{Pd(0)}} \text{(B)} \\
\text{(B)} & \xrightarrow{\text{RNSR'}} \text{(C)}
\end{align*}
\end{equation}

\textbf{Scheme 1.8: Likely Mechanism of the Palladium(0) Catalysed Rearrangement of Allylic Sulfoximines}
Chapter 1

The palladium attacks anti to the sulfoximine leaving group via an oxidative addition process to form a cationic (η^3-allyl)Pd(II) complex (B). Next the sulfinamide anion acts as a nucleophile and adds anti to the palladium to form the allylic product (C). Overall this results in a retention of configuration at the substituted carbon.

An asymmetric version of this rearrangement can in theory be realised by either using optically active sulfoximines or by the use of chiral ligands on the palladium.

Pyne and Dong found the palladium catalysed reactions of primary and secondary sulfoximines were completely regioselective with the formation of only primary allylic amines. The reaction rates of the palladium(0) catalysed rearrangement correlated closely with the electron withdrawing ability of the nitrogen substituent on the sulfoximine. As the electron withdrawing ability increases, the reaction time decreases and the yield after conversion to the final amine increases as shown in Table 1.2.97,98
Chapter 1

M

Pd(PPh₃)₄

THF

SOPh

NaOH

MeOH/H₂O

(64)

(65)

(66)

<table>
<thead>
<tr>
<th>R</th>
<th>t(min)*</th>
<th>Yield(%)#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ts</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>COOMe</td>
<td>30</td>
<td>66</td>
</tr>
<tr>
<td>Me</td>
<td>60</td>
<td>21</td>
</tr>
</tbody>
</table>

* Reaction time for Pd(0) catalysed rearrangement
# Yield of (66) after cleavage of the sulfinamide group

Table 1.2: Reaction Rate Dependence Upon Electron Withdrawing Ability of the Nitrogen Substituent

1.9.1.4 γ-Amino-α,β-Unsaturated Esters and Ketones

In their papers Pyne and Dong examined the rearrangements of primary and secondary allylic azoiminines to the corresponding allylic sulfinamides. However, work was performed upon substrates that would provide γ-amino-α,β-unsaturated esters and ketones such as would be required for this proposed synthesis of aza sugars (Scheme 1.1).
Previous work by Jackson and Strauss showed that the allyl palladium complexes of $\alpha,\beta$-unsaturated esters and ketones are regioselectively functionalised with stabilised carbanions at the $\gamma$ position to give (67). This indicates that a similar regiochemistry could be expected from the allylic sulfoximine rearrangement with the incoming sulfinamide anion attacking the allyl substrate at the $\gamma$-position.

\[
\text{\begin{align*}
\text{NaCCH(COOEt)R} & \xrightarrow{\text{Pd}} \text{R=CN, SO}_2\text{Me, PO(OEt)}_2 \\
\end{align*}}
\]

These $\gamma$-amino-$\alpha,\beta$-unsaturated esters and ketones are useful as "vinyllogous amino acids" in the preparation of novel polypeptides to study the effects on the secondary and tertiary structures. The $\gamma$-amino-$\alpha,\beta$-unsaturated carbonyl compounds also appear as intermediates in the synthesis of natural products as structurally diverse as cytotoxic marine sponge metabolites, macrocyclic serine protease inhibitors, pyrrolidine antibiotics, and transition state mimics for renin inhibition.

These compounds are usually prepared from $\alpha$-amino aldehydes (68) via a Wittig-Horner reaction. The $\alpha$-amino aldehydes (68) are derived from naturally occurring $\alpha$-amino acids in a few short steps. Consequently, it is not possible to prepare $\gamma$-amino-$\alpha,\beta$-unsaturated esters and ketones that do not come from "the pool" of naturally occurring $\alpha$-amino acids.
A reaction analogous to the palladium(0) catalysed amination has also been used for the synthesis of \( \gamma \)-amino-\( \alpha,\beta \)-unsaturated esters. The (\( \pi \)-allyl)tetracarbonyliron complex (72) was formed in an stoichiometric reaction between Fe\(_2\)(CO)\(_9\) and the \( \gamma \)-benzyloxy unsaturated ester (71) and then reacted with amines to provide the \( \gamma \)-amino-\( \alpha,\beta \)-unsaturated esters (73). \(^{106}\)

1.9.2 Asymmetric Dihydroxylation of Allylic Amines

The osmium catalysed vicinal dihydroxylation of olefins has found wide applicability in organic synthesis. The usefulness of the reaction increased when Sharpless introduced cinchona based chiral ligands to provide diols in high enantioselectivity. \(^{107}\) Two
preformed admixtures containing potassium osmate, chiral ligand, co-oxidant, and base are now available commercially from Aldrich as AD-mix α® and AD-mix β®.

As mentioned before the main challenge in the synthesis of carbohydrate analogues is the high number of stereocenters and the need to be able to procure the required stereochemistry. Much of the asymmetry of this reaction pathway will be generated by the dihydroxylation of the allylic amine. The γ-amino-α,β-unsaturated ketones will provide an essentially flat environment around the double bond and as such will provide an excellent substrate for the dihydroxylation.

1.10 Asymmetric Synthesis of Azasugars from Carbohydrate Starting Materials

The second synthetic pathway to be explored in this thesis uses a carbohydrate starting material as outlined in the retrosynthetic analysis below. Analogues that vary in the stereochemistry of the hydroxyl groups can be prepared by changing the carbohydrate starting material. The key steps are: (a) chain extension, (b) palladium(0) catalysed allylic amination, (c) oxidation of the alkene, either by dihydroxylation or epoxidation, followed by conversion of the primary hydroxyl group into an amine, and (d) cyclisation and then deprotection.
Scheme 1.9: Synthesis of Azasugars from Carbohydrates

The final product shown in Scheme 1.9 can, in principle, also be further cyclised to produce analogues of bicyclic azasugars such as swainsonine (6) and castanospermine (7).
1.10.1 Addition to the Lactol

The first step in the second synthesis is the addition of a Grignard reagent to the lactol (73). The lactol is in equilibrium with the hydroxy aldehyde (74).

The two faces of this masked aldehyde functionality are diastereotopic due to the adjacent chiral centre. The reaction of similar carbonyl groups with organometallic compounds is known to proceed with good selectivity and is a frequently employed strategy for the diastereoselective chain extension of carbohydrates. The basis for the selectivity can be explained by the Felkin-Anh transition state model for the addition to carbonyl groups.

The largest group, in this case the acetonide, is at an angle of 90° to the plane of the carbonyl and the incoming nucleophile has a preferred trajectory which is at an angle
of −109° to the carbonyl. This gives predominantly the anti product where the newly formed hydroxyl group is anti to the existing acetonide.

1.10.2 Palladium(0) Catalysed Allylic Amination

Palladium(0) complexes catalyse a wide variety of reactions. Like the first synthetic route this pathway also employs a palladium(0) catalysed allylic amination, in this case to convert a secondary hydroxyl group into a primary amine. Other nucleophiles such as alkoxides, thiols, and stabilised carbanions, could be utilised to introduce any number of functionalities at the primary position. This introduces a large degree of flexibility in order to produce analogues.

Palladium(0) catalysed allylic amination is a versatile process that has been known for over 30 years and encompasses a wide range of allyl systems and nucleophiles. Both primary and secondary amines, but not ammonia, efficiently aminate allylic substrates.

Central to this reaction is the facile redox nature of palladium and the ease with which it can change between a zero oxidation state and a +2 oxidation state via oxidative addition and reductive elimination reactions. As with a number of transition metal catalysed reactions, allylic amination is a stepwise process as shown in Scheme 1.10.
The first step is the coordination of the palladium(0) with the alkene on the face opposite to the leaving group (A). The electron density around the palladium then initiates the expelling of the leaving group to produce a (π-allyl) intermediate with inversion of configuration (B) via oxidative addition. The final step is the reductive displacement of the palladium species by a nucleophile to give the product (E) and regeneration of the palladium(0) catalyst.

Scheme 1.10: Mechanism of Palladium(0) Catalysed Allylic Alkylation and Amination
"Soft" nucleophiles, such as amines, attack the allyl group directly (C) with inversion of configuration and overall retention of configuration. "Soft" nucleophiles are defined as those whose conjugate acids have a pKa > 25, although this definition is not rigid. "Hard" nucleophiles attack the metal centre first (D) and then migrate to the allyl ligand to give overall inversion of configuration.

A number of variables influence the regioselectivity including the steric environment of the complex, electronic factors, and the relative stability of the terminii in the intermediate (π-allyl) complex.

1.10.3 Completion of the Second Proposed Synthetic Pathway

In the final few steps the double bond of the allylic amine is oxidised either by dihydroxylation or epoxidation. The diastereoselectivity of this reaction should be enhanced by the chiral acetonide group adjacent to the double bond. The free primary hydroxyl group will then be converted via a sulfonate into an amine. This step can be varied with other nucleophiles such as thiols or phosphines or even stabilised carbanions used to produce other carbohydrate analogues. The final two steps are cyclisation and deprotection to give the pyrrolidine azasugar, which can undergo further cyclisation to give a bicyclic azasugar (see Section 1.10).
CHAPTER 2

SYNTHESIS OF γ-AMINO-α,β-UNSATURATED KETONES
2.1 Introduction

The first synthetic pathway outlined in Scheme 1.7 (see Chapter 1) has as its crucial step the palladium(0) catalysed rearrangement of an allylic sulfoximine. No previous work\textsuperscript{86,97,98} had been carried out on allylic sulfoximine substrates that would provide γ-amino-α,β-unsaturated ketones as would be required for the synthesis of azasugars. Thus it was necessary to investigate the rearrangement of these substrates.

2.2 Preparation of Allylic Sulfoximines

As a model system it was decided to use the allylic sulfoximines (75) shown below. The chosen protecting group for the nitrogen was the methyl carbamate as it was anticipated that a carbamate would be an useful protecting group in the actual synthesis of azasugars. Pyne and Dong had previously shown in simpler systems that the best yields and shortest reaction times were obtained with the strongly electron withdrawing tosyl substituent on the sulfoximine nitrogen.\textsuperscript{98} Consideration was therefore given to the tosyl group as the protecting group. However N-tosyl groups are normally deprotected under relatively harsh conditions\textsuperscript{111} and for this reason were not considered suitable for a general synthetic path that has to be tolerant of other functionalities. This caveat does not apply to the electron withdrawing carbamates which can be deprotected under a variety of mild conditions depending upon the specific carbamate used.\textsuperscript{111}
2.2.1 Synthesis of 2-(N-Methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-ethan-1-one (80)

The starting material was the readily available racemic S-methyl-S-phenylsulfoximine (77).\textsuperscript{112} This was protected as the methyl carbamate by treatment with sodium hydride and methyl chloroformate in dimethoxyethane at 45°C overnight.\textsuperscript{113} After purification by column chromatography the yield of the protected sulfoximine (78) was 77%.

\[
\begin{align*}
\text{Ph} & \quad \text{S} \quad \text{Me} \qquad \text{Ph} \quad \text{S} \quad \text{Me} \\
\text{NH} & \quad \text{77\%} \\
\text{(77)} & \quad \text{(78)}
\end{align*}
\]

The protected S-methyl-S-phenylsulfoximine (78) was deprotonated with LDA in THF at \(-78^\circ\text{C}\). The resulting lithiated sulfoximine underwent 1,2-addition with benzaldehyde at \(-78^\circ\text{C}\) for 30 minutes to furnish the \(\beta\)-hydroxy sulfoximine (79) as a 82:18 mixture of diastereomers.
The alcohol moiety was then oxidised with Jones reagent in acetone at RT to give the β-ketosulfoximine (80) in an overall yield of 35% from the protected S-methyl-S-phenylsulfoximine (78). None of the isomeric enol form of (80) could be detected in the \( ^1 \)H NMR spectrum of the compound. The \( ^1 \)H NMR spectrum of (80) showed doublets at 5.5.5 and 5.1 (\( J = 13.8 \text{Hz} \)) as shown in Figure 2.1 for the diastereotopic methylene protons \( \alpha \) to the carbonyl group.
2.2.2 Knoevenagel Condensations of (80)

The next step was the base catalysed Knoevenagel type condensation between an aldehyde and β-ketosulfoximine to produce the allylic sulfoximines (81).

\[
\text{RCHO} + \text{R'}\text{CO} \rightarrow \text{R\text{\textsuperscript{\,\alpha,\beta}}CO} \\
R = \text{alkyl or aryl}, \quad R' = \text{alkyl or aryl} \quad (81)
\]

EWG = COOMe, Ts, etc
Knoevenagel condensations are reactions between carbonyl compounds and methylene groups activated by the presence of two electron withdrawing substituents. There are two known mechanisms for the condensation\textsuperscript{114,115} as shown in Scheme 2.1 (which omits the many proton transfer reactions for reason of brevity). The first is known as the Knoevenagel mechanism and involves the activation of the carbonyl compound via formation of an iminium compound with a nitrogen base. This is followed by addition to the active methylene compound and subsequent elimination of the amine to give the vinyl product (82). The Hann-Lapworth mechanism involves deprotonation of the active methylene compound followed by 1,2-addition to the carbonyl group to give an intermediate hydroxyl compound. This hydroxyl compound undergoes dehydration to furnish the vinyl product (82). The actual path taken depends upon the catalyst used. Many catalysts are available for the reaction including primary, secondary and tertiary amines and their salts, basic metal salts, Lewis acids, silica gel,\textsuperscript{116} alumina,\textsuperscript{117} microwave irradiation\textsuperscript{118} and many others. Both mechanisms give the same vinylic product (82) which can then, in the presence of base, isomerise to the allylic compound (83).
Scheme 2.1: Known Mechanisms of the Knoevenagel Condensation with Knoevenagel Mechanism (top) and Hann-Lapworth Mechanism (bottom)

In this study on the Knoevenagel condensation of (80) with aldehydes, catalytic amounts of piperidine and acetic acid in acetonitrile was used. It is believed that the piperidium acetate catalysed Knoevenagel condensation follows the Hann-Lapworth mechanism. The 4Å molecular sieves were added to absorb the water released during the dehydration step.
Table 2.1: Synthesis of Allylic Sulfoximines (84) Utilising a Knoevenagel Type Condensation

The results of the Knoevenagel condensation between the $\beta$-ketosulfoximine (80) and various aldehydes are presented in Table 2.1. In all cases only the allylic sulfoximines were observed and there was no evidence of the isomeric vinyl sulfoximines. The chemical yields were directly related to the length of the alkyl chain of the aldehyde. The condensation with heptanal ($R=$Pent) gave an acceptable yield, while propanal ($R=$Me) gave a very poor yield.

The low yields are most likely due to competing base catalysed self-condensation of the aldehyde to give $\beta$-hydroxy aldehydes. This reaction occurs quite easily for low molecular weight aldehydes such as acetaldehyde and propanal, while higher homologues such as heptanal require heating for the self-condensation to occur. In the example below the self-condensation of propanal occurs at RT under the catalysis of a basic ion-exchange resin. The corresponding reaction involving heptanal has to be
heated to 120°C for the reaction to occur. The high temperature for the heptanal self-condensation leads to dehydration of the intermediate alcohol to give the enal.\textsuperscript{120}

\[
\begin{align*}
2 \times & \text{CHO} \xrightarrow{\text{basic ion-exchange resin, 25°C}} \text{CHO} \\
2 \times & \text{C}_5\text{H}_11\text{CHO} \xrightarrow{\text{basic ion-exchange resin, 120°C}} \text{C}_5\text{H}_11\text{CHO}
\end{align*}
\]

In light of these findings, since the Knoevenagel reactions of the β-ketosulfoximines (80) were carried out at RT it would then be expected that the low molecular weight aldehydes would give low yields of the Knoevenagel products due to the competing self-condensation while higher homologues would give better yields of Knoevenagel products. Indeed this is what is observed as shown in Table 2.1.

The two diastereomers of (84) that formed in these Knoevenagel reactions could not be separated by column chromatography. However the diastereomeric ratios could be determined from their \textsuperscript{1}H NMR spectra as shown for (84a, R=Me) in Figure 2.2. The proton α to the sulfoximine group in the \textsuperscript{1}H NMR spectra for the four derivatives of (84) appeared as a doublet at ~δ7.1 (J=9.3Hz) for the major diastereomer and at ~δ6.5 (J=9.0Hz) for the minor diastereomer. Apart from (84c, R=Bu) all the allylic sulfoximines were formed in very similar diastereomeric ratios of approximately 2:1.
Chapter 2

Figure 2.2: Partial $^1$H NMR Spectrum (CDCl$_3$) of the Two Diastereomers of (84a) Showing the Resonances for the Proton $\alpha$ to the Sulfoximine

The relative stereochemistry of the diastereomeric allylic sulfoximines (84) could not be determined by NMR experiments as there were no significant nOes and furthermore all the products were oils and therefore not suitable for X-ray crystallographic analysis.

The allylic sulfoximines (84) formed exclusively the (E) stereochemistry around the double bond. This was determined from their $^1$H NMR spectra which showed coupling constants of $J=$15-16 Hz between the olefinic protons. In comparison, a coupling constant of $J=$10 Hz would be expected for the (Z) stereochemistry.\textsuperscript{121}
2.3 Palladium(O) Catalysed Rearrangements Of Allylic Sulfoximines

As mentioned in Chapter 1, the palladium(O) catalysed rearrangement of allylic sulfoximines to allylic sulfinamides proceeds in good to high yields under very mild reaction conditions. The allylic sulfinamides can then be cleaved under basic conditions to provide allylic amines.

2.3.1 Mechanism of the Sulfinamide Cleavage

The method chosen for the cleavage of the sulfinamide group was treatment with catalytic amounts of triethylamine in methanol to furnish the desired amine. The mechanism of the cleavage of the sulfinamide group is likely to involve attack of a methoxide anion on the sulfur, followed by cleavage of the sulfur nitrogen bond as shown below.

Scheme 2.2: Mechanism of the Cleavage of the Sulfinamide Group
The nitrogen anion then abstracts a proton from methanol to regenerate the methoxide ion. Thus only catalytic amounts of triethylamine are required for the cleavage of the sulfinamide group.

2.3.2 The Palladium(0) Catalysed Rearrangement and Sulfinamide Cleavage of the Allylic Sulfoximines (84)

Treatment of the prepared allylic sulfoximines (84) with freshly prepared tetrakis(triphenylphosphine)palladium(0) (5 mol%) in dry THF for approximately one hour at RT gave, after evaporation of the THF in vacuo, the allylic sulfinamides (85) which were not isolated due to extensive decomposition when subjected to column chromatography. Mild base cleavage of the sulfur-nitrogen bond with triethylamine in methanol for 30 minutes at RT gave the monoproTECTED γ-amino-α,β-unsaturated ketones (86).
Table 2.2: Palladium(0) Catalysed Rearrangement of Allylic Sulfoximines Followed by Cleavage of the Sulfinamide Group

The yields shown in Table 2.2 are modest to acceptable and are the overall yields for the final amines (86) after cleavage of the sulfinamide moiety and then purification via column chromatography on silica gel. The slightly lower yield for (86b, R=E) is due to the reaction initially being worked up too early after the TLC appeared to indicate that the reaction was complete. The mixture of product plus starting material was then retreated with identical amounts of catalyst. The time indicated in Table 2.2 is the combined time for the two reactions.
There was no observable (E)-(Z) isomerisation during these reactions. The coupling constants in the $^1$H NMR spectra between the olefinic protons are approximately $J=15-16$ Hz indicating (E) stereochemistry. If isomerisation were to occur it would involve the formation of a less stable anti complex, which has severe steric interactions with the coordination sphere of the palladium.

![Scheme 2.3: Interconversion of Syn and Anti Complexes](image)

2.3.3 Diastereoselectivity of the Palladium(0) Catalysed Rearrangements

The diastereomeric ratios of the allylic sulfinamides (85) were determined from analysis of the $^1$H NMR spectra of the crude reaction mixtures prior to treatment with triethylamine in methanol. In the case of (85b) this ratio was determined by integration of the terminal methyl resonances for the two diastereomers as shown in Figure 2.3.
There were some slight differences between the diastereomeric ratios of the starting sulfoximines (84) and the intermediate sulfinamides (85). This is possibly due to either configurational instability of the sulfinamide anion or the interconversion of the enantiomeric intermediate palladium complexes (C and D) as shown below in Scheme 2.4.

Figure 2.3: Partial $^1$H NMR Spectrum (CDCl$_3$) Showing the Terminal Methyl Resonances of (85b)
Scheme 2.4: Interconversion of Intermediate Palladium Complexes

The most likely mechanism for the interconversion of the (π-allyl)palladium complexes (C and D) is nucleophilic attack by free palladium(0) upon the complex. In 1992, Backvall and Granberg were able to isolate both the cis and trans complexes of (87) which were then treated with Pd(PPh₃)₄. Since the complexes were diastereomeric, utilisation of both ^1H and ^31P NMR spectroscopy could detect isomerisation between the two forms even at -14°C.¹²²
2.3.4 Regioselectivity of the Palladium(0) Catalysed Rearrangement

The allylic rearrangements of the sulfoximines (84) were completely regioselective with only γ-amino-α,β-unsaturated ketones being observed. The $^1$H NMR spectra of (84) showed the presence of two vinyl protons, one as a doublet and the other as a doublet of doublets as seen in the Figure 2.4 below which is from the spectrum of (86b).
As noted in Chapter 1, previous work by Jackson and Strauss found that the palladium complexes of α,β-unsaturated esters also undergo nucleophilic addition exclusively at the γ position. The basis of the selectivity is most likely to be the electronic effects of the ketone functionality. The intermediate π-allyl palladium complex can be portrayed as an interconversion of two isomeric complexes with the positive charge on either allylic terminus. When the charge is on the terminus next to the ketone the partial positive charge on the ketone carbon gives an unfavourable electronic interaction with the positive charge. Thus the complex where the positive
charge is $\gamma$ to the ketone is more stable and more likely to react with the incoming nucleophile which agrees with the observed regioselectivity.

Furthermore the product formed from nucleophilic attack at the $\gamma$-carbon would be expected to be thermodynamically more stable due to the conjugation of the double bond with the carbonyl group.

2.4 $^1$H NMR Studies of Changes in the Diastereomeric Ratio with Time

A $^1$H NMR experiment was set up to investigate how the diastereomeric ratio of the intermediate allylic sulfinamides would change in solution over time. The $N$-tosyl allylic sulfoximine (88) was prepared in an analogous method to (84d, $R=$Pent). The sulfoximine (88) and Pd(PPh$_3$)$_4$ were dissolved in d$^8$-THF and placed in a NMR tube. The $^1$H NMR spectrum was taken at regular intervals over the period of one month and the integrals of the protons $\alpha$ to the sulfinamide group of the two diastereomers measured.
The two diastereomers of (89) that were formed were termed D₁ and D₂ and the ratio of the two diastereomers was observed over time. After 10 minutes no more starting material could be seen and D₁ was the predominant isomer by a ratio of 3:1. An hour later the amount of D₁ had decreased and the ratio was now 3:2. By the next morning D₂ was now the more prevalent isomer and the ratio had become 3:4. When one month had passed and it could be assumed that some kind of thermodynamic equilibrium had been reached, D₂ was now clearly the dominant isomer and the ratio was 1:2.2.

<table>
<thead>
<tr>
<th>Time</th>
<th>D₂:D₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mins</td>
<td>0.30</td>
</tr>
<tr>
<td>20 mins</td>
<td>0.42</td>
</tr>
<tr>
<td>30 mins</td>
<td>0.52</td>
</tr>
<tr>
<td>70 mins</td>
<td>0.61</td>
</tr>
<tr>
<td>21 hours</td>
<td>1.33</td>
</tr>
<tr>
<td>28 days</td>
<td>2.21</td>
</tr>
</tbody>
</table>

Table 2.3: Change in the Diastereomeric Ratio of (89) over Time
As there was no starting material present in the $^1$H NMR spectrum after 10 minutes, the change of the diastereomeric ratio over time seems to indicate the possibility that the formation of the allylic sulfinamide is reversible. That is, if the formation of the allylic sulfinamide was irreversible then once it was formed the only way the diastereomeric ratio could change would be via epimerisation of the hydrogen $\alpha$ to the sulfinamide nitrogen by a base. However, the identity of a potential base is not readily surmisable.

Therefore it might be possible that the palladium can oxidatively add to the allylic sulfinamide with the sulfinamide acting as the leaving group to reform the palladium $\pi$-allyl complex as shown in Scheme 2.5 below. This would be facilitated by the two strongly electron withdrawing substituents on the nitrogen enabling it to accept the

Figure 2.5: Graph Showing the Changes in Diastereomeric Ratio of (89) over Time
two electrons associated with the oxidative addition process. The palladium complex can then undergo isomerisation via nucleophilic attack by free palladium(0) as discussed earlier. The sulfinamide anion can then act as a nucleophile to again form the allylic sulfinamide in a different diastereomeric ratio.

\[ \text{PhS(O)} \quad \text{N} \quad \text{Ts} \quad \text{Pd(0)} \]

\[ \text{PhS(O)} \quad \text{N} \quad \text{Ts} \quad \text{Pd(0)} \]

Scheme 2.5: Possible Mechanism for the Interconversion of Allylic Sulfinamides

2.5 Thermal Rearrangement of Allylic Sulfoximines

An attempt was made to thermally induce an allylic rearrangement of (84d). The sulfoximine was refluxed in THF overnight and after cooling to RT, the solvent removed in vacuo. The crude mixture was then treated with triethylamine in methanol for 30 minutes at RT. The \(^1\)H NMR spectrum showed mainly starting material plus some new peaks. However after purification via column chromatography, no compound that could be unequivocally assigned as structures (86d) or (90) from \(^1\)H NMR analysis could be isolated.
As mentioned in Chapter 1, very few allylic sulfoximines undergo thermally induced rearrangement. The failure of (84d) to undergo rearrangement when heated, reinforces the view that the thermal allylic rearrangement is not a generally favoured reaction for allylic sulfoximines, especially when compared to the facile palladium(0) catalysed reaction.

2.6 Conclusion

This chapter has shown that the palladium(0) catalysed rearrangement of allylic sulfoximines to allylic sulfinamides, followed by base catalysed cleavage of the sulfinamide group, is a general and mild method for the synthesis of monoprotected γ-amino-α,β-unsaturated ketones. These compounds would be useful as intermediates for the synthesis of azasugars and other compounds.

It was noted that the diastereomeric ratio of the starting allylic sulfoximines and product allylic sulfinamides are different, possibly due to nucleophilic attack of free
palladium(0) upon the intermediate (π-allyl)palladium complex. A $^1$H NMR study raised the possibility that the formation of the allylic sulfinamides is reversible from the observation that over the period of one month the diastereomeric ratio continued to change.

It was also shown that the allylic sulfoximine (84d) does not undergo a thermally induced rearrangement in stark contrast to its palladium(0) catalysed reaction.
CHAPTER 3

AMINATION OF ALLYLIC SULFOXIMINES USING EXTERNAL NUCLEOPHILES
3.1 Introduction

Previous work on the palladium(0) catalysed rearrangement of allylic sulfoximines had concentrated solely upon the use of the sulfinamide anion as the incoming nucleophile during the reductive elimination. No work on the use of an external nucleophile had been carried out.

It was shown by Pyne and Dong that use of a $N$-methyl protected sulfoximine leads to a very poor yield of rearranged product.\textsuperscript{98} Hence it is not feasible to produce usefully protected allylic amines bearing an electron donating substituent on the nitrogen using the intramolecular palladium(0) catalysed rearrangement of allylic sulfoximines. This could in principle be overcome by use of an external nucleophile with electron donating substituents.

Furthermore, it was of interest to see if the external nucleophile and sulfinamide anion competed for allylation by the palladium complex. For instance, it could be possible that sulfinamide anion blocks the attack of an external nucleophile by forming a close ionic pair with the cationic palladium complex.
3.2 Preparation of Allylic Sulfoximines

As no prior work had been carried out using external nucleophiles it was decided to expand the range of substrates used so that the regioselectivity and the enantioselectivity of the reaction could be investigated.

The N-tosyl-S-phenyl-S-(2-propenyl)sulfoximine (91) was prepared by reaction of the known allyl sulfoximine (39) with tosyl chloride, pyridine and 4-dimethylaminopyridine in anhydrous DCM to give (91) by a known literature procedure.  

\[
\text{O} \quad \text{S-Ph} \quad \text{O} \\
\text{NH} \quad \text{NTs} \quad \text{NTs}
\]

The second substrate, 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-ol (92), was prepared also by a literature procedure. Treatment of N-tosyl-S-phenyl-S-(2-propenyl)-sulfoximine (91) with n-BuLi gave a lithiated salt which underwent $\alpha$-1,2 addition with benzaldehyde to give the desired product (92) as a mixture of diastereomers in a yield of 87%.
2-(N-Tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-one (93) was prepared by oxidation of 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-ol (92) with Jones reagent in acetone with a yield of 97% after purification. The product was formed as a 71:29 mixture of diastereomers as determined from the $^1$H NMR spectra as outlined in Section 2.2.2.

The next substrate, 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88), was also prepared via a literature procedure. In this case a Knoevenagel condensation (see Chapter 2) between the protected $\beta$-ketosulfoximine (94) and
heptanal gave (88) in a yield of 69% and as a inseparable 72:28 mixture of diastereomers.

\[
\begin{align*}
\text{Ph} & \quad \overset{\text{heptanal, piperidine, AcOH}}{\longrightarrow} & \quad \text{Ph} \\
\overset{\text{O=S=NTs}}{\text{C=O}} & \quad \overset{\text{CH₃CN, RT, 5 hours}}{\longrightarrow} & \quad \overset{\text{C₅H₁₁}}{\text{C=O}} \\
(94) & \quad \longrightarrow & \quad (88)
\end{align*}
\]

The exocyclic sulfoximine, N-tosyl-S-phenyl-S-(1-cyclohex-1-enylmethyl)-sulfoximine (95), was prepared using the method of Pyne and Dong. The protected S-methyl-S-phenylsulfoximine (96) was deprotonated with n-BuLi to give the lithiated salt. This was allowed to undergo 1,2-addition with cyclohexanone to give the hydroxy intermediate (97). Dehydration of this hydroxy compound gave the allylic sulfoximine (95).
The final substrate was prepared by methylation of $N$-tosyl-$S$-phenyl-$S$-($1$-cyclohex-1-enylmethyl)sulfoximine (95) with lithium diisopropylamide and methyl iodide. According to Pyne and Dong this methylation proceeds in a diastereoselective manner to give the product (98) with the (S) stereochemistry at the newly formed chiral centre.
3.3 Palladium(0) Catalysed Amination of Allylic Sulfoximines in the Presence of an External Nucleophile

The allylic sulfoximines listed in Table 3.1 were treated with Pd(PPh₃)₄ (5-10 mol%) and the external nucleophile (1.2 mole equivalent) indicated in anhydrous THF for the time denoted. The progress of these reactions were monitored by TLC analysis. The solvent was removed in vacuo and the products were purified via column chromatography.

3.3.1 Palladium(0) Catalysed Amination of Allylic Sulfoximines Using Dibenzylamine as an External Nucleophile

The allylic sulfoximines (91), (92), (93), (88), (95) and (98) all reacted very smoothly and regioselectively with Pd(PPh₃)₄ and dibenzylamine to provide the corresponding N,N-dibenzyl protected allylic amines (99), (101), (102), (103), (104) and (105) respectively, in 10 minutes at RT in poor to good yields.
<table>
<thead>
<tr>
<th>substrate</th>
<th>nucleophile</th>
<th>time (mins)</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{Ph} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{NBN}_{2} )</td>
<td>67</td>
</tr>
<tr>
<td>( \text{(9)1} )</td>
<td>( \text{Boc}<em>2\text{N}</em>\ominus \text{Li} )</td>
<td>O/N</td>
<td>( \text{NBoc}_2 )</td>
<td>54</td>
</tr>
<tr>
<td>( \text{O} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{NBN}_{2} )</td>
<td>66</td>
</tr>
<tr>
<td>( \text{(9)2} )</td>
<td>( \text{Boc}<em>2\text{N}</em>\ominus \text{Li} )</td>
<td>O/N</td>
<td>( \text{NBoc}_2 )</td>
<td>26</td>
</tr>
<tr>
<td>( \text{O} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{NBN}_{2} )</td>
<td>43</td>
</tr>
<tr>
<td>( \text{(9)3} )</td>
<td>( \text{Boc}<em>2\text{N}</em>\ominus \text{Li} )</td>
<td>O/N</td>
<td>( \text{NBoc}_2 )</td>
<td>18</td>
</tr>
<tr>
<td>( \text{C}<em>6\text{H}</em>{11} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{C}<em>6\text{H}</em>{11} \text{NBn}_2 )</td>
<td>62</td>
</tr>
<tr>
<td>( \text{(8)8} )</td>
<td>( \text{C}<em>6\text{H}</em>{11} \text{NBn}_2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{O} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{BN}_{2} )</td>
<td>73</td>
</tr>
<tr>
<td>( \text{(9)5} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{Me} = \text{S} = \text{NTs} )</td>
<td>( \text{Bn}_2\text{NH} )</td>
<td>10</td>
<td>( \text{MeNBn}_2 )</td>
<td>13</td>
</tr>
<tr>
<td>( \text{(9)8} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3.1: Allylic Amination Reactions of Allylic Sulfoximines with Palladium(0) and External Nucleophiles
The mild reaction conditions required for the allylic amination of allylic sulfoximines compare very favourably with similar reactions utilising an acetate as the leaving group. Those reactions involving allylic acetates often require heating to reflux to proceed.\textsuperscript{124}

2-(N-Tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-ol (92) and 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-one (93) both reacted regioselectively to give the corresponding primary allylic amines (101) and (102) respectively. None of the isomeric secondary amine could be detected in either the $^1$H NMR spectra of the crude reaction mixture nor in any of the fractions isolated by column chromatography.

In accordance with the results obtained in \textbf{Chapter 2}, only the $\gamma$-amino enone (103) was formed in the reaction of 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88) with dibenzylamine. As pointed out in \textbf{Section 2.3.4} for the intramolecular allylic rearrangement of (86), this is likely to be due to both the electronic effects of the ketone functionality and the formation of the thermodynamically more stable conjugated $\pi$ system.

In the reaction between dibenzylamine and N-tosyl-S-phenyl-S-(1-cyclohex-1-enylmethyl)sulfoximine (95) again only the primary amine was observed as product. No isomeric secondary amine could be detected in either the $^1$H NMR spectra of the crude reaction mixture nor in any of the fractions isolated by column chromatography.
The amination of \( N\)-tosyl-\( S\)-phenyl-\( S\)-(1-cyclohex-1-enylethyl)-sulfoximine (98) with dibenzylamine was also very regioselective with amination only occurring \( \alpha \) to the methyl group. The \(^1\)H NMR spectrum showed the proton \( \alpha \) to the methyl group as a quartet \((J=6.6\text{Hz})\) at \( \delta 3.100\). If the double bond was in the exocyclic position that proton would be expected to come at \( \sim \delta 5.6 \).

![Figure 3.1: Partial \(^1\)H NMR Spectrum (CDCl\(_3\)) of (104) and (105)](image)

Even though both allylic terminii of the intermediate palladium complex shown below are secondary carbons, the greater steric bulk of the cyclohexene ring compared to the methyl group is the likely driving force behind the observed regioselectivity in the reaction of (98) and \( \text{Bn}_2\text{NH} \).
Furthermore, attack at the exocyclic position generates the product with the double bond in the thermodynamically more stable endocyclic position.

The yield indicated for the reaction of $N$-tosyl-$S$-phenyl-$S$-(1-cyclohex-1-enylethyl)sulfoximine (98) with palladium(0) and dibenzylamine is only an approximation. The initial starting material was a mixture of methylated (98) and non-methylated (95) sulfoximines in a ratio of 66:33. The methylated sulfoximine (98) is very unstable and decomposes when subjected to column chromatography and as such cannot be separated from the non-methylated sulfoximine (95). The product is also a mixture of methylated and non-methylated, however the ratio had changed to 44:56 (see Figure 3.1 for the $^1$H NMR spectrum of (104) and (105)). This implies that the methylated product (105) is also susceptible to decomposition on a column of silica gel. The instability of both the starting material and product is the possible reason for the very poor yield of 13%.
3.3.2 Palladium(0) Catalysed Amination of Allylic Sulfoximines Using Lithiated Boc₂NH as an External Nucleophile

The first report concerning the use of lithiated Boc₂NH (106) in allylic amination was an article by Connell et al.¹²⁵ in which allylic acetates were converted into the corresponding N,N-diprotected allylic amines. It was found that the lithium salt of Boc₂NH (106) was much more soluble in THF and DMF than the corresponding potassium and sodium salts. It was also disclosed that 1,2-bis(diphenylphosphino)ethane was a much more effective ligand than triphenylphosphine. The active palladium(0) catalyst was generated \textit{in situ} by the reaction of tris(dibenzylideneacetone)dipalladium(0) and 1,2-bis(diphenylphosphino)ethane.

The reactions involving the lithium salt of Boc₂NH (106) and allylic sulfoximines proceeded much slower than the equivalent reactions with dibenzylamine (Table 3.1). According to the TLC taken during the course of these reactions, starting material remained long after the equivalent reaction with dibenzylamine would have been completed. This seems to indicate that the intermediate palladium complex is forming much more slowly. Since the only difference is the nucleophile used, this implies that there might be an interaction between the lithiated Boc₂NH and the palladium(0). It must also be noted that there was no evidence of any allylic sulfinamides resulting from the intramolecular rearrangement of the starting sulfoximines in both the ¹H NMR spectra of the crude reaction mixture and the fractions isolated via column chromatography. This absence of allylic sulfinamides
further indicates that it is the formation of the palladium-allyl complex that is rate
determining step in the reactions with lithiated Boc₂NH.

A point of interest here is the reactions between the lithium salt of Boc₂NH (106) and
the sulfoximines (92) and (93). In both reactions the extended reaction time allowed
the metallated amine to cleave the benzoyl moiety of the molecule. This led to the
subsequent formation of the allylic amine (100) via a palladium(0) catalysed
amination. The allylic amine (100) was the only product from both reactions that
could identified definitively. A possible mechanism for the cleavage of the benzoyl
group of 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-one (93) is
shown in Scheme 3.1 below.

Scheme 3.1: Mechanism for the Cleavage of the Benzoyl Moiety from (93)
The cleavage of the benzyl alcohol moiety from the alcohol (92) is likely to follow a retro-aldol pathway as shown in Scheme 3.2 below. The alcohol is deprotonated by the lithiated Boc₂NH (106) to form the anion which then undergoes a retro-aldol reaction to form the lithiated allylic sulfoximine (43). This species is protonated then undergoes the palladium(0) catalysed allylic amination to form the diprotected allylic amine (100).

![Scheme 3.2: Possible Mechanism of Cleavage of the Benzyl Alcohol Moiety from (92)](image)

The low yield of the product allylic amine (100) from substrates (92) and (93) is probably due to other side reactions involving the anionic allylic sulfoximine (43) intermediate.
3.4 Competition Between the Sulfinamide Nucleophile and an External Nucleophile

As noted in Section 2.4, it was possible that the formation of the allylic sulfinamide from the intermediate palladium complex is reversible. If this was the case then it should be possible to firstly form the allylic sulfinamide, then react this with an external nucleophile in a two step reaction. This would help give a further indication as to whether the formation of the allylic sulfinamide was reversible.

The allylic sulfoximine \(N\)-tosyl-\(S\)-phenyl-\(S\)-(2-propenyl)sulfoximine (91), was treated with \(\text{Pd(PPh}_3\text{)}_4\) (5 mol\%) in anhydrous THF for 15 minutes to give a bright red solution. After removal of the solvent the allylic sulfinamide was put on a very short column of silica gel to remove the palladium. After checking the \(^1\text{H NMR}\) spectrum to ensure that no starting material remained the allylic sulfinamide (107) was retreated with \(\text{Pd(PPh}_3\text{)}_4\) in anhydrous THF, only this time dibenzylamine (1.1 equivalents) was added and stirring continued for 10 minutes. After the standard workup only the diprotected allylic amine (99) was observed in the \(^1\text{H NMR}\) spectrum.
The sole formation of the allylic amine (99) plus observation that the diastereomeric ratio of allylic sulfinamides changes over time would seem to indicate the formation of the allylic sulfinamide from the intermediate palladium complex is reversible. The electron withdrawing ability of the two substituents on the sulfinamide nitrogen make it a good leaving group willing to accept the electrons associated with the bond cleavage during the oxidative addition process.

The mechanism for the palladium(0) catalysed allylic amination of allylic sulfoximines originally shown in Scheme 1.8, therefore needs to be adjusted accordingly to indicate this reversibility.
The reaction of (B) with the incoming external nucleophile could be expected to be irreversible, provided the nucleophile does not have strong electron withdrawing substituents. The irreversibility of the nucleophilic addition drives the reaction towards the formation of the allylated product (D).

3.5 Palladium(0) Catalysed Allylic Amination of Enantiomerically Pure Sulfoximines

Optically active sulfoximines can be prepared by fractional crystallisation of the diastereomeric salts of S-methyl-S-phenyl-sulfoximine (77) with (1S)-(+) camphor sulfonic acid, followed by neutralisation with base, to provide the (S)-(+) S-methyl-S-phenyl sulfoximine (77) in e.e. > 99\%.
The (S)-(+) \(N\)-tosyl-\(S\)-phenyl-\(S\)-(1-cyclohex-1-enymethyl)sulfoximine \((95)\) was prepared. This compound was then diastereoselectively methylated with LDA and methyl iodide to furnish optically active \((S,S)\)-\(N\)-tosyl-\(S\)-phenyl-\(S\)-(1-cyclohex-1-enylethyl)sulfoximine \((98)\).\(^{98}\)

As mentioned in Section 3.3.1 the methylated sulfoximine \((98)\) is very unstable and cannot be purified. This means any reaction has to be performed in the presence of unmethylated sulfoximine which accordingly complicates the purification process and the calculation of the yield.

Treatment of \((S,S)\)-\(N\)-tosyl-\(S\)-phenyl-\(S\)-(1-cyclohex-1-enylethyl)sulfoximine \((98)\) with dibenzylamine in the presence of palladium(0), regioselectively gave \(N,N\)-dibenzyl-\(N\)-(1-cyclohex-1-enylethyl)amine \((105)\) in a yield of approximately 59% after purification via column chromatography. The product had a specific rotation of \([\alpha]_{D}^{27} = +4.0\) (c=0.9,CHCl\(_3\)).
Based upon the mechanism for palladium(0) catalysed allylic amination outlined in Scheme 1.10 the reaction, between the allylic sulfoximine (98) and the “soft” nucleophile dibenzylamine, would be expected to occur with overall retention of configuration. Thus the exocyclic amine (105) should have the (S) stereochemistry at the chiral centre.

The optically active amine was subjected to $^1$H NMR chiral shift studies. A conventional chiral shift reagent tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium (Resolve-AI™) gave absolutely no indication of any enantiomeric purity. However use of (S)-mandelic acid was much more successful. The $^1$H NMR spectra of (105) (Figure 3.2) prepared from both racemic and optically active sulfoximines was taken in the presence of (S)-mandelic acid. The doublet for the methyl group, \( \alpha \) to the dibenzylamine functionality, appears as two well defined signals for (105) prepared from the racemic sulfoximine. Only one doublet appears in the spectrum for (105) prepared from the optically active sulfoximine. This indicates that the product from the reaction using the optically active sulfoximine is enantiomerically pure.
Figure 3.2: Partial $^1$H NMR Spectra (CDCl$_3$) of Racemic (left) and Optically Active (right) (105) Showing Methyl Doublets in the Presence of (S)-Mandelic Acid

3.6 Palladium(0) Catalysed Allylic Amination Utilising a Chiral Ligand

In principle it should be possible to control the enantioselectivity of the allylic amination reaction by use of a chiral ligand. The use of achiral ligands leads to two intermediate enantiomeric palladium complexes which can interconvert. These two enantiomeric complexes will react with an incoming nucleophile at the same rate to give racemic products.
However the presence of a chiral ligand coordinated to the palladium creates two
diastereomeric intermediate complexes which can react with the incoming nucleophile
at differing rates. If both $k_2$ and $k_3$ are slower than the interconversion ($k_1$ and $k_{-1}$)
then there will be a preference for the formation of one enantiomeric product over the
other provided $k_2$ is different to $k_3$.

There are many chiral ligands available for use in all types of transition metal
catalysed reactions. These ligands include ferrocene derivatives (108),\textsuperscript{127} binaphyls
(109),\textsuperscript{128} and even sulfoximine derivatives (110).\textsuperscript{129}
It was decided to utilise the phosphino-oxazoline chiral ligand (111) based upon the excellent results that have been obtained with ligands of this type in palladium(0) catalysed allylic aminations.\textsuperscript{130}

The active palladium complex is formed by reacting the oxazoline ligand (111) and the dimer [Pd(\(\pi\)-allyl)CI\(_2\)]. Since the palladium is in the (+2) oxidation state it needs to be reduced down to the zero oxidation state. If the palladium is not in the zero oxidation state it will not be able to undergo oxidative addition which is the first step in the allylic amination process (see Scheme 1.10). This reduction is performed \textit{in situ} using a reductive elimination process. The incoming nucleophile, which in this case is
dibenzylamine, attacks the allyl ligand which then undergoes reductive elimination to provide the allylic amine (99) and the palladium in the zero oxidation state.

\[
\begin{align*}
\text{Pd(II)} & \rightarrow \text{Pd(0)} + \text{NBn}_2 \text{N} \\
\text{Pd(II)} & \rightarrow \text{Pd(0)} + \text{NBn}_2 \text{N}
\end{align*}
\]

The reaction of the allylic sulfoximine (88) with dibenzylamine in the presence of the chiral ligand (111) and palladium(0) proceeded much more slowly when compared to the rate of reaction for when triphenylphosphine was used as the ligand. After being stirred at RT overnight only a small amount of product (103) had been formed according to the TLC of the reaction mixture.

\[
\begin{align*}
\text{Ph} & \text{O=S=NTs} \rightarrow [\text{Pd(\pi\text{-allyl})Cl}]_2, (111) \\
\text{Bn}_2\text{NH}, \text{RT, THF} & \rightarrow \text{NBn}_2 \text{N}
\end{align*}
\]

The slowness of the reaction is probably due to the nature of the ligand. In an investigation into the influence of ligands on the rates and regiochemistry, Åkermark et al. found that ligands with greater \( \pi \) electron accepting abilities such as triphenylphosphine increase the rate of the reaction when compared to sulfur and nitrogen containing ligands. This is due to the ligands drawing electron density away from the metal and hence increasing the overall positive character of the allyl ligand. The chiral oxazoline contains one phosphine but it also contains a nitrogen
which participates as a ligand. Thus the reaction with the oxazoline ligand is slower than the corresponding reaction with triphenylphosphine.

Despite being incomplete the reaction was worked up in order to investigate the enantioselectivity of the product produced. The $^1H$ NMR spectrum of the crude reaction mixture confirmed that only a small amount of product had formed and the majority of the reaction mixture was still starting material. It also showed the presence of the allylic amine (99) formed during the reduction of the palladium(II) to palladium(0).

The purified product (103) had a specific rotation of $[\alpha]_D^{22} = +12.2$ (c=0.475, CHCl$_3$) which indicated that it was not racemic. $^1H$ NMR studies of the product (103) with chiral shift reagents including tris(2,2,6,6-tetramethyl-3,5-heptanedionato)europium (Resolve-AI™) and tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octane-dionato)europium (Resolve-Al EuFOD™) were inconclusive as to the enantiomeric purity of the compound. The only effect of the shift reagents was to move the signals of the double bond downfield so that they were hidden under the signals belonging to the aromatic rings.

It was then attempted to resolve the product via a chiral HPLC column. The column used was a Regis Pirkle column using D-N-(2-naphthyl)alanine covalently bound to 11-undecyl silica. The column is manufactured specifically to separate amines, amino acids and alcohols. Chromatographic separations were attempted with the product (103) prepared not only with the chiral oxazoline ligand (111), but also with
triphenylphosphine as the ligand. All attempts at resolving the racemic compound were unsuccessful, even in solvents of low polarity (0.5% ethyl acetate/petroleum spirit) the product (103) came off the column very quickly as one peak.

Later attempts to resolve these compounds on a range of Chirasil HPLC columns by collaborators in Prof. H. Pfaltz's group at Muelheim were also unsuccessful.

Possibly the reason for the failure of the chiral HPLC column to separate any enantiomers is due to the sheltered nature of the single chiral centre in the molecule. The chiral centre is surrounded by a phenyl ketone on one side, a pentyl chain on the other and an amine protected with two bulky protecting groups. The steric bulk of the molecule also shelters the nitrogen making it difficult to interact with the D-\(N\)-(2-naphthyl)alanine of the column. Thus the enantiomeric excess of the amine could not be determined and hence the selectivity induced by the chiral oxazoline ligand is at present unknown.

3.7 Palladium(0) Catalysed Amination Utilising Chiral Amines

Another method to theoretically induce asymmetry into the allylic amination reaction is the use of chiral nucleophiles. As shown in Scheme 3.4 the oxidative addition of palladium to the allylic substrate produces two enantiomeric complexes when the ligands are achiral. The incoming chiral nucleophile will have a preference for one of the enantiomeric complexes thus leading to an excess of one diastereomeric product.
The initial reaction tried was with \( N\text{-benzyl-}N\text{-}\alpha\text{-methylbenzylamine (112)} \) as the nucleophile and 2-(\( N\text{-tosyl-}S\text{-phenylsulfoximidoyl})\text{-1-phenyl-non-3-en-1-one (88)} \) as the substrate.

\[
\begin{align*}
\text{(88)} & \quad \text{(112)} \\
\text{Ph} & \quad \text{CH}_3 \\
\text{O} & \quad \text{N} & \text{S} & \text{NTs} \\
\text{C}_5\text{H}_1 & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{Pd(PPh}_3\text{)}_4 & \quad \text{No reaction}
\end{align*}
\]

Despite its apparent similarity to dibenzylamine, the \( N\text{-benzyl-}N\text{-}\alpha\text{-methylbenzylamine (112)} \) did not react with the substrate (88) even after being left to stir overnight with palladium(0). Both the amine and the allylic sulfoximine were recovered intact. Rather than spend time tracking down the reason for the failure of the reaction it was decided to try a different chiral amine. It was decided to proceed using the less sterically hindered \( \alpha\text{-methylbenzylamine (113)} \).

\[
\begin{align*}
\text{(88)} & \quad \text{(113)} & \quad \text{(114)} \\
\text{Ph} & \quad \text{CH}_3 & \quad \text{Ph} \\
\text{O} & \quad \text{N} & \quad \text{S} & \text{NTs} \\
\text{C}_5\text{H}_1 & \quad \text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{Pd(PPh}_3\text{)}_4 & \text{THF, RT}
\end{align*}
\]

An interesting result was obtained for the reaction between (S)-\( \alpha\text{-methylbenzylamine (113)} \) and the allylic sulfoximine (88). The allylic amine (114) cyclised to produce the substituted pyrrole (115) in a yield of 67%.
The structure of (115) was assigned from its $^1$H NMR spectrum, as shown below in Figure 3.3, which showed two doublets ($J=3.6$Hz) at 66.2 and 6.0 corresponding to the two pyrrole protons. The proton at the chiral centre adjacent to the nitrogen appears as a quartet at 65.6 when it would be expected to be 63-4 for the allylic amine (114). There was also no doublet and doublet of doublet at approximately 67-7.1, where the two olefinic protons of the allylic amine (114) would be expected to appear.

Figure 3.3: Partial $^1$H NMR Spectrum (CDCl$_3$) of the Pyrrole (115)
Only one previous case where a similar reaction occurred has been reported. In 1980, Trost et al. reported that the allylic acetate (116) spontaneously cyclised to the pyrrole after undergoing a palladium(0) catalysed allylic amination.\textsuperscript{132}

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

\text{Pd(PPh}_3\text{)}_4, \text{BnNH}_2, \text{toluene, } \Delta \rightarrow \text{(47\%)}

\[
(116) \quad \rightarrow \quad (117)
\]

It must be mentioned that the conditions employed by Trost et al., of refluxing in toluene, are much more harsh than those used with allylic sulfoximines. This is due to the use of an acetate as the leaving group for the allylic amination step.

### 3.8 Comparision of Reaction Conditions with Allylic Sulfones

The reaction conditions required for the intramolecular and intermolecular rearrangements of allylic sulfoximines are much milder than those for common leaving groups such as allylic acetates. It was decided that it would be preferable to be able to compare the reactivity of the allylic sulfoximines in the allylic amination reaction to similar compounds. Therefore the known allyl phenyl sulfone (118) was thus prepared by oxidation of allyl phenyl sulfide (119) with Oxone®.
The sulfone (118) was treated with Pd(PPh₃)₄ and dibenzylamine in refluxing anhydrous THF overnight. After removal of the solvent in vacuo, the ¹H NMR spectrum showed only starting material.

Thus when compared to the reaction conditions of 10 minutes at RT for the equivalent sulfoximine, this experiment showed that the reaction conditions required for the amination of allylic sulfoximines are very mild.

3.9 Conclusion

This chapter showed that it is possible to use an external amine instead of the sulfinamide anion as the incoming nucleophile in the palladium(0) catalysed amination of allylic sulfoximines. The reactions proceed under mild conditions to provide the allylic amines in acceptable to good yields.
Further evidence was obtained to show that the formation of allylic sulfinamides from allylic sulfoximines is reversible. It was also shown that the use of optically active sulfoximines can lead to optically active allylic amines. The use of a chiral ligand in the palladium(0) catalysed intermolecular rearrangement produced an allylic amine that was not racemic, however the enantiomeric excess was not able to be determined.

Extended treatment of the allylic sulfoximine (88) with palladium(0) and (S)-α-methylbenzylamine allowed the allylic amine product to undergo spontaneous cyclisation to furnish the substituted pyrrole (115).

A comparison of the reaction conditions required for allylic amination, showed that allylic sulfoximines react under much milder conditions compared to the structurally similar allylic sulfones.
CHAPTER 4

SYNTHESIS OF AZASUGARS
FROM ALLYLIC SULFOXIMINES
4.1 Introduction

The first proposed pathway for the synthesis of azasugars was outlined in Scheme 1.7 (see Chapter 1). This chapter documents the attempts to bring that scheme to fruition. The actual target chosen as a model system was the aryl azasugar (120). This is structurally similar to the natural products codonopsine (121), codonopsinine (122) and anisomycin (123).

![Chemical structures](image)

(120) (121) R=OMe (122) R=H (123)

4.2 Choice of Protecting Group for the Nitrogen

Since the final cyclisation involves the reduction of a cyclic imine formed in situ from a γ-amino-α,β-dihydroxy ketone, it was decided that the protecting group for the nitrogen in the γ-amino-α,β-dihydroxy ketone should be cleavable under reductive conditions.
The two main contenders for the role of protecting group were the benzyl (Bn) and the carbonylbenzyloxy (Cbz) groups. As the benzyl protecting group was an electron donating group, it could only be introduced as an external nucleophile (see Chapter 3). While the Cbz group as an electron withdrawing carbamate would be easier to introduce as the protecting group of the sulfoximine nitrogen in an intramolecular allylic sulfoximine rearrangement.

Since work had already be done on the amination of allylic sulfoximines with dibenzylamine to provide γ-amino-α,β-unsaturated ketones (see Chapter 3) it was decided to follow this route.
4.3 Synthesis of Azasugars Utilising a Palladium(0) Catalysed Allylic Amination of an Allylic Sulfoximine

2-\(N\text{-Tosyl-S-phenylsulfoximidoyl}\)-1-phenyl-but-3-en-1-one \(93\) was prepared and subjected to an intermolecular palladium(0) catalysed allylic amination with dibenzylamine as outlined in Chapter 3 to give the \(\gamma\)-amino-\(\alpha,\beta\)-unsaturated ketone \(102\).

\[
\begin{align*}
\text{Ph} & \quad \text{O} \quad \text{N} \quad \text{Ts} \\
\text{\(93\)} & \quad \text{Ph} \quad \text{Ph} \\
\to & \\
\text{Ph} & \quad \text{O} \quad \text{N} \quad \text{Bn}_2 \\
\text{\(102\)} & \quad \text{Ph} \quad \text{Ph} \\
\end{align*}
\]

\(\text{Pd(PPh}_3\text{)}_4, \text{Bn}_2\text{NH} \quad \text{THF, RT, 10 mins}\)

The ketone \(102\) could also be produced by the oxidation of the \(N,N\text{-dibenzyl-4-amino-1-phenyl-but-2-en-1-ol}\) \(101\), which can be prepared by the allylic amination of the corresponding \(\beta\)-hydroxy sulfoximine \(92\). Oxidation with pyridinium dichromate in DCM at RT overnight gave the ketone \(102\) in 53% yield. A much better yield was obtained with Jones reagent in acetone which gave the ketone \(102\) in a yield of 98%.

\[
\begin{align*}
\text{NBn}_2 & \quad \text{Ph} \\
\text{\(101\)} & \quad \text{Ph} \quad \text{OH} \\
\to & \\
\text{NBn}_2 & \quad \text{Ph} \\
\text{\(102\)} & \quad \text{Ph} \\
\end{align*}
\]

\(\text{PDC, DCM (53%)} \quad \text{or} \quad \text{Jones reagent, acetone (98%)}\)
With the \( \gamma \)-amino-\( \alpha,\beta \)-unsaturated ketone \((102)\) in hand there were two final steps in the synthetic pathway to azasugars. These two steps were dihydroxylation and cyclisation.

The \( \gamma \)-amino-\( \alpha,\beta \)-unsaturated ketone \((102)\) was subjected to standard Sharpless asymmetric dihydroxylation conditions of either AD-mix \( \alpha \) or AD-mix \( \beta \) in tert-butanol/water in the presence of methanesulfonamide.\(^{135}\) After stirring at \( 0^\circ C \) for 11 days the TLC of the reaction mixture indicated complete consumption of the starting material, which was verified by the \( ^1H \) NMR spectrum of the crude reaction mixture after work-up.

![Chemical Reaction](image)

The \( ^1H \) NMR spectrum of the crude reaction mixture showed what appeared to be possible product \((124)\). However when subjected to column chromatography this could not be isolated in a pure form. The \( ^1H \) NMR spectra of the isolated fractions indicated that there were more impurities in the “purified” sample than there were in the crude reaction mixture. Successive attempts to purify the compound further on another column and on a TLC plate also failed to furnish pure product.
In an attempt to procure a possibly more stable derivative the crude diol (124) was treated with acetic anhydride and pyridine in anhydrous DCM to form the diacetate (125).

\[
\begin{align*}
\text{NBn}_2\text{OH} & \quad \text{Ac}_2\text{O}, \text{pyridine} \\
\text{Ph} & \rightarrow \text{NBn}_2\text{OAc}
\end{align*}
\]

\[
\text{DCM, RT, O/N}
\]

However the $^1$H NMR spectrum of the crude reaction mixture was inconclusive as to whether the diacetate (125) had been formed, nor did any fraction isolated by column chromatography appear to be the desired product. It is possible that due to the basic $N,N$-dibenzyl amino group that the desired product (125) underwent elimination to the alkene (126) which could then undergo further reactions to an unknown final product.
Attempts to deprotect the amine functional group of the crude diol (124) with H₂ and palladium on carbon in methanol gave a complex mixture of compounds whose ¹H NMR spectra when isolated, did not resemble any imaginable products.

A likely explanation for these difficulties is the oxidation of the tertiary nitrogen by either the OsO₄ or K₃Fe(CN)₆ in the reaction mixture to form a highly unstable compound. If this is the case then there are several options for what the unstable and unisolatable product might be. If oxidation of the nitrogen occurs at a similar reaction rate to the dihydroxylation of the alkene then the product would most likely be the amine N-oxide (128).

This compound could then undergo a Cope elimination¹³⁶ to give the N,N-dibenzylhydroxylamine (129) and the alkene (130) which could undergo further reactions.
However if the nitrogen oxidation is faster than the dihydroxylation then there are several different possible products. The allylic amine $N$-oxide (131) produced can undergo a Meisenheimer rearrangement\textsuperscript{137} via either allylic or benzylic rearrangement to the corresponding hydroxylamine derivatives (132) and (133). The hydroxylamine derivatives (132) and (133) could then be dihydroxylated or undergo further decomposition to unknown products.

![Scheme 4.1: Possible Meisenheimer Rearrangements of Allylic Amine $N$-Oxides](image-url)
It was decided at this point not to investigate whatever product was being formed in the dihydroxylation of the allylic amine (102) and instead to pursue the strategy of using Cbz as the protecting group for the nitrogen. This entailed the synthesis of an allylic sulfoximine with a Cbz protecting group and utilisation of the palladium(0) catalysed intramolecular rearrangement of the allylic sulfoximine.

### 4.4 Synthesis of Azasugars Utilising an Intramolecular Rearrangement of an Allylic Sulfoximine

The unprotected S-phenyl-S-(2-propenyl)sulfoximine (39) was synthesised according to a literature procedure. The allylic sulfoximine (39) was then treated with benzyl chloroformate, pyridine and a catalytic amount of 4-dimethylaminopyridine in anhydrous DCM to give \(N\)-(benzyloxycarbonyl)-S-phenyl-S-(2-propenyl)sulfoximine (134) in 70% yield.

\[
\begin{align*}
\text{(39)} & \xrightarrow{\text{Cbz-Cl, pyridine, DMAP}} \text{(134)} \\
\text{DCM, 0°C->RT,70%} & \end{align*}
\]

The protected allylic sulfoximine (134) was deprotonated with \(n\)-BuLi and allowed to undergo \(\alpha\)-1,2 addition to benzaldehyde to give the \(\beta\)-hydroxy allylic sulfoximine (135). In accordance with the observations of Pyne and Boche there was no \(\gamma\)-1,2 addition, which would have been easy to detect in the \(^1\)H NMR spectrum by the presence of an alkyl CH\(_2\) as well as a doublet for one of the vinyl protons. The alcohol
(135) was then oxidised with Jones reagent in acetone to give the β-keto allylic sulfoximine (136) in 62% yield. The product was isolated as an inseparable 71:29 mixture of diastereomers as determined from the integration of the proton α to the sulfoximine in the $^1$H NMR spectrum.

The β-keto allylic sulfoximine (136) was then subjected to an intramolecular palladium(0) catalysed rearrangement followed by cleavage of the sulfinamide group with triethylamine in methanol as outlined in Chapter 2.
As expected only the primary allylic amine (137), in a yield of 62%, was observed in accordance with previous results. This was confirmed by the $^1$H NMR spectrum which showed the allylic CH$_2$ next to the double bond as a doublet of doublets ($J$=1.5,4.2Hz) at 84.077.

The asymmetric dihydroxylation of the allylic amine (137) proceeded very smoothly under standard Sharpless conditions$^{135}$ using either AD-mix $\alpha$ or AD-mix $\beta$ with methanesulfonamide at 0°C overnight to afford the $\gamma$-amino-$\alpha,\beta$-dihydroxy ketones (138) in reasonable yields and excellent enantioselectivity. The specific rotations of the two products (138a and 138b) had opposite signs but did not have equal magnitude. This suggested that (138a) and (138b) were enantiomers but had different enantiomeric purities.

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>e.e.</th>
<th>Specific rotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-mix $\alpha$ 138a</td>
<td>66</td>
<td>&gt;95%</td>
<td>+17.3° (c=1.3,CHCl$_3$)</td>
</tr>
<tr>
<td>AD-mix $\beta$ 138b</td>
<td>73</td>
<td>&gt;99%</td>
<td>-11.3° (c=3,CHCl$_3$)</td>
</tr>
</tbody>
</table>

Table 4.1: Asymmetric Dihydroxylation of the Allylic Amine (137)
The enantiomeric excesses of (138a) and (138b) were determined from $^1$H NMR studies using the chiral shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)-europium (Resolve Al EuFOD™) as well as (-)-camphor sulfonic acid. The $^1$H NMR spectra taken using Resolve Al EuFOD™ were inconclusive with regards to the enantiomeric excess. However use of the (1R)-camphor sulfonic acid was much more successful. The two spectra shown in Figure 4.1 display the two methyl groups of (1R)-camphor sulfonic acid. The left hand spectrum is for the AD-mix α product and shows a possible second enantiomer between the peaks for the major enantiomer. The enantiomeric excess was thus characterised as being greater than 95%. The right hand spectrum is for the AD-mix β product and shows only one set of peaks, thus the enantiomeric excess was characterised as being greater than 99%. The enantiomeric purities are not consistent with the magnitudes of the specific rotations found for these compounds, which suggests the presence of an optically active impurity in either one or both of the compounds.
The isolated diols (138a and 138b) were oils and therefore unsuitable for X-ray crystal structure analysis. There were also no significant nOes in the 2D nOesy spectrum that gave a clue to the stereochemistry. Therefore this has been assigned by analogy to the work by Reetz et al. on mono-Boc protected \(\gamma\)-amino-\(\alpha,\beta\)-unsaturated esters (139).^{138}
Table 4.2: Asymmetric Dihydroxylation of Mono-Boc Protected γ-

Amino-α,β- Unsaturated Esters

The final steps in the synthetic pathway were the deprotection of the nitrogen, followed by cyclisation to the imine and subsequent reduction to give the pyrrolidine ring.
Initially the \((2R,3S)-N\text{-benzyloxycarbonyl}-4\text{-amino}-2,3\text{-dihydroxy-1-phenyl-}
butan-1\text{-one (138b)}\) was treated with 10\% palladium on carbon in methanol under a
balloon of \(\text{H}_2(g)\). After stirring for 24 hours, 10\% \(\text{HCl(aq)}\) was added and stirring
continued for 1 hour. After working up the reaction mixture, the \(^1\text{H NMR spectrum}
showed no starting material. However there were no signals in the spectrum that
corresponded to what would be expected for the product (141). Nevertheless in the
hope that some product might be in the mixture it was placed on an ion-exchange
column. However no product could be detected in the \(^1\text{H NMR spectrum of the fractions
obtained from the column.}

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

(138b)

Next it was decided to try transfer hydrogenation which is reputedly a faster and more
efficient method than traditional hydrogenation methods.\(^{139}\) The diol (138a) was
treated with 10\% palladium on carbon and formic acid in methanol.\(^{140}\) After 24 hours
no reaction could be detected by TLC so the reaction was worked up. The \(^1\text{H NMR spectrum of the crude reaction mixture confirmed that there was only starting
material present.}
The next method tried was the use of ammonium formate in methanol in the presence of 10% palladium on carbon\(^1\). Again after 24 hours no reaction had occurred and only starting material was present.

The third transfer hydrogenation method used was 1,4-cyclohexadiene in methanol, again in the presence of 10% palladium on carbon\(^2\). This method produced a complex mixture of compounds after stirring at RT for 24 hours. None of the fractions isolated via column chromatography resembled the desired product in their \(^1\)H NMR spectra.
Next the palladium catalyst was changed from 10% palladium on carbon to palladium black. This was prepared by reduction of palladium(II) chloride to elemental palladium(0) following a literature procedure. Treatment of the diol (138a) with palladium black in methanol under a balloon of H$_2$(g) again only produced a mixture of compounds that did not include either the product or starting material. The same result was also obtained with (138b) using palladium black with 1,4-cyclohexadiene in methanol.

Regrettably at this point the synthetic path had to be abandoned due to the pressing need to begin the thesis write-up and the need to synthesise more of the starting material (39) in order to procure more of the diol (138). However, it should purely be a matter of determining the correct reaction conditions in order to deprotect and cyclise the diol (138) to form the azasugar (141).
4.5 Conclusion

Initial attempts to synthesise azasugars utilising the palladium(0) catalysed allylic amination of (93) with dibenzylamine, faltered when the asymmetric dihydroxylation of the allylic amine (102) provided an unisolatable product.

A switch to the use of the intramolecular allylic rearrangement of the allylic sulfoximine (136) provided the allylic amine (137). The asymmetric dihydroxylation of (137) gave the diols (138a and 138b) with excellent enantioselectivity. However all attempts to deprotect the amine functionality failed and disappointingly the synthetic pathway had to be abandoned at a point when it seemed so close to coming to fruition.
CHAPTER 5

SYNTHESIS OF AZASUGARS
FROM CARBOHYDRATES
5.1 Introduction

The second proposed synthetic pathway for the synthesis of azasugars was outlined in Scheme 1.9 and has a carbohydrate as starting material. As mentioned in Chapter 1, carbohydrates are very popular starting materials due to their cheapness and availability, the already present stereogenic centres, availability of cyclic and acyclic forms, different chain lengths, and different oxidation states. This chapter documents the attempts to bring the synthetic pathway to fruition.

5.2 Chain Extension of a Lactol

The lactol (142) was formed by the reduction of the commercially available (-)-2,3-isopropylidene-D-erythronolactone (143) with DIBAL in DCM at -78°C following a literature procedure. The lactol (142) was not purified, but inspection of the $^1$H NMR spectrum of the crude reaction mixture indicated the diastereomeric ratio of the products was approximately 95:5.

The crude lactol (142), which is in equilibrium with the hydroxyaldehyde (144), was then subjected to a Grignard addition. As pointed out in Chapter 1 this is a highly
diastereoselective reaction with the products having anti stereochemistry between the carbinol carbon and its adjacent stereogenic carbon. In this case vinyl magnesium bromide was added to the crude lactol (145) in THF at 0°C to give the vinyl diol. Inspection of the \(^1\)H NMR spectrum indicated that only one diastereomer was formed in the reaction.

Again this compound was not purified, but instead was protected as the dibenzoate (146) using benzoyl chloride, pyridine, and a catalytic amount of 4-dimethylaminopyridine in anhydrous DCM. The overall yield for the 3 steps was 51% after purification by column chromatography of the dibenzoate (146).
5.3 Palladium(0) Catalysed Allylic Amination

The next step of the proposed synthesis involved converting the secondary benzoate (146) into a primary amine (147). This was achieved by utilising the palladium(0) catalysed allylic amination reaction, the mechanism of which was outlined in Scheme 1.10.

\[
\text{Pd}_2(\text{dba})_3, \text{Ph}_2\text{P} \rightarrow \text{PPh}_2
\]

In this instance the nucleophile used was the lithium salt of Boc₂NH. The dibenzoate (146), the palladium(0) catalyst and the lithiated carbamate in THF were heated to 50°C and stirred overnight. The reaction was worked up to give the \(N,N\)-diprotected primary amine (148) in 69% yield after purification by column chromatography.

Only the protected primary allylic amine (148) was observed in the reaction. There was no isomeric protected secondary amine visible in either the \(^1\)H NMR spectra of the
crude reaction mixture or in any of the fractions isolated via column chromatography. This was as expected as any secondary amine would come from attack of the nucleophile at the more sterically hindered terminus of the palladium-allyl complex.

The alkene exclusively formed the (E) stereochemistry around the double bond as evidenced by a coupling constant of $J=15.3\text{Hz}$ between the olefinic protons in the $^1\text{H}$ NMR spectrum. There was no evidence indicating the existence of the (Z) isomer.

Although it was not explored in this work, it should be possible to utilise other nucleophiles in this reaction. In such a manner other analogues could be produced with atoms like sulfur or phosphorus or even carbon at the primary position.

5.4 Dihydroxylation of the Allylic Amine (148)

The allylic amine (148) was dihydroxylated smoothly under both standard Sharpless conditions, with either AD-mix α or AD-mix β and methanesulfonamide at 0°C overnight, or by treatment with potassium osmate and $N$-methyl-morpholine-$N$-oxide at 0°C overnight. These reactions gave a separable mixture of the diastereomeric oxazolidones (149a) and (149b).
In accordance with previous work by Sharpless et al.\textsuperscript{135} when there is a nitrogen protected with two Boc groups in the allylic position, one of the Bocs will cyclise under the reaction conditions to give the oxazolidone product. The mechanism of this is likely to involve attack of the alkoxide anion upon the carbonyl group of the Boc and subsequent ejection of the tert-butyl oxy anion. The cyclisation provides a method for selectively differentiating the two newly formed hydroxyl groups.
The oxazolidone structure was determined via NMR spectroscopy. The integrals of the signals in the \(^1\)H NMR spectrum indicated that the singlet for the Boc methyl group had only 9 protons instead of the 18 required for two Boc groups. There was also a slight upfield shift for the carbonyl carbon in the \(^{13}\)C NMR spectrum. The oxazolidone carbonyl appears at \(\delta 149.3\) compared to the Boc carbonyl at \(\delta 152.1\). The low resolution mass spectrum also indicated the loss of the tert-butyl portion of the Boc group with the [M+Na]\(^+\) peak occurring at \(m/z 474.0\) instead of \(m/z 548\).

This type of cyclisation is not seen when the nitrogen is only monoprotected with one Boc group. Reetz \textit{et al.} dihydroxylated the mono-Boc protected allylic amine (139) as shown below and did not report any cyclisation.\(^{138}\) The second Boc group is clearly needed to make the cyclisation a facile process.
The stereochemistry of the products have been assigned by 2D nOesy NMR spectroscopy. For the compound (149a) there exists a nOe between the free hydroxyl proton and the proton next to the acetonide group as shown in the spectra below.

Figure 5.1: Partial Negative 2D nOesy Spectrum (CDCl₃) of (149a)
This nOe interaction was not seen in the corresponding 2D nOesy spectra for (149b). Furthermore there is a coupling constant of $J=7.5\text{Hz}$ between $H1'$ and $H2'$ in (149a), compared to $J=3.1\text{Hz}$ for (149b), indicating that $H1'$ and $H2'$ are trans to each other in (149a).

![Diagram](image)

Molecular modelling using Insight II (Biosym/MSI) generated the lowest energy conformations of the possible products arising from the dihydroxylation of (148), portions of which are shown below in Figure 5.2. The top model shows the product (149a) arising from attack of the osmium at the bottom face of the alkene while the second model shows the product (149b) arising from attack from the top face. The numbers associated with the dotted lines indicate the calculated distances in angstroms between the free hydroxyl group and some of the nearby protons.

Although the models are purely theoretical in nature, they do support what is observed in the 2D nOesy experiments. For (149a) the free hydroxyl group is approximately 2.52Å from H2', while for (149b) the separation is 3.40Å. It is generally believed that the limit for nOe interactions is approximately 3Å, therefore given the calculated
Figure 5.2: Molecular Models Generated by Insight II Showing the
Product (149) Arising from Attack from Below (top) and Attack from
Above (bottom)
distances, a nOe would be expected between the free hydroxyl group and H2' only for the product arising from attack at the bottom face of the double bond.

This is indeed what is observed - the 2D nOesy NMR spectrum for (149a) shows this interaction, while the spectrum of (149b) does not. Furthermore, the dihedral angle between H1' and H2' in (149a) was approximately 175°, while that of (149b) was approximately 75°, which is also consistent with their respective $J_{1',2'}$ values. Thus the products (149a) and (149b) would seem to have the stereochemistry as shown below.

The facial selectivity of the reaction was much better for AD-mix α compared to AD-mix β, although neither was particularly good. The predominance of (149a) over (149b) in the reaction with AD-mix α is consistent with the Sharpless mnemonic\textsuperscript{107} which is designed to act as tool to help prediction of stereoselectivity.
It is not obvious which of the two possible orientations of the substrate is predominant, but in both of them the acetonide group is pointing above the plane of the double bond. The stereochemical outcome of the dihydroxylation of (148) in the case of AD-mix α is consistent with the mnemonic, however in the case of AD-mix β the acetonide would be expected to hinder attack from the β-face leading to a very poor diastereoselectivity.
Unlike the reactions with AD-mix α and AD-mix β, the dihydroxylation of the allylic amine (148) with potassium osmate and \(N\)-methylmorpholine-\(N\)-oxide was completely stereospecific with only (149b) observed. It would have been expected in this case that the bulky osmium tetroxide would approach from the sterically less hindered side to furnish (149a).

In the literature little work has been done on the stereoselectivity of the dihydroxylation of allylic amines. However, work has been carried out on allylic alcohols and several theoretical models have been developed. To explain the seemingly anomalous result obtained from the dihydroxylation of (148) with potassium osmate and \(N\)-methylmorpholine-\(N\)-oxide, it was attempted to fit the allylic amine (148) to one of these models.

Attempts were made to fit (148) to the Vedejs model\(^ {145} \) (Figure 5.4) using the acetonide oxygen as the allylic alcohol as shown in Figure 5.5. In this model, the osmium attacks the alkene from the same side as the hydrogen α to the alcohol. For (148) this leads to attack from the bottom face to give (149a).
This result with the theoretical model indicates that the dihydroxylation of (148) with potassium osmate and N-methyl-morpholine-N-oxide is likely to be a highly anomalous reaction. The basis of the selectivity it displays by giving (148b) as the sole product is difficult to explain using the Vedejs model. Perhaps chelation of the osmium to one or more of the various heteroatoms in (148) is responsible for the unexpected stereochemical outcome.

Although the general synthetic pathway was going well it was decided to take a step back and remove the benzoyl protecting group for the primary hydroxyl group before the asymmetric dihydroxylation. The rationale behind this was that the base catalysed removal of the benzoyl group in (149) would also cleave the oxazoline ring, thereby removing the selective differentiation of the two secondary hydroxyl groups.
The alcohol (150) was readily accessible via base mediated debenzoylation of (148), with 1%(w/v) NaOH in methanol, in a yield of 83%.

\[ \text{BzO} \quad \text{BzO} \]
\[ \rightarrow \quad \text{BzO} \]
\[ \text{NBoc}_2 \quad \text{NBoc}_2 \]
\[ \begin{array}{c}
\text{RT, 1 hour}
\end{array} \]

Treatment of the alcohol (150) with either AD-mix $\alpha$ or AD-mix $\beta$ and methanesulfonamide under standard Sharpless reaction conditions proceeded very smoothly to afford the product (151) in good yields.

\[ \begin{array}{c}
\text{HO} \\
\text{HO} \\
\end{array} \]
\[ \begin{array}{c}
\text{Boc} \\
\text{Boc} \\
\end{array} \]
\[ \begin{array}{c}
\text{HO} \\
\text{HO} \\
\end{array} \]
\[ \begin{array}{c}
\text{Boc} \\
\text{Boc} \\
\end{array} \]

\[ \begin{array}{c}
\text{Os} \\
\text{Os} \\
\end{array} \]
\[ \begin{array}{c}
\text{f-BuOH/H}_2\text{O, 0°C}
\end{array} \]

<table>
<thead>
<tr>
<th>“Os”</th>
<th>Yield(%)</th>
<th>151a:151b</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD-mix $\alpha$, CH$_3$SO$_2$NH$_2$</td>
<td>72</td>
<td>100:0</td>
</tr>
<tr>
<td>AD-mix $\beta$, CH$_3$SO$_2$NH$_2$</td>
<td>85</td>
<td>100:0</td>
</tr>
</tbody>
</table>

Table 5.2: Asymmetric Dihydroxylation of (150)
Surprisingly both AD-mix α and AD-mix β seemed to give the same isomer in a diastereomeric ratio of 100:0. The experiment was repeated and this time before purification on a column of silica gel, a small aliquot was taken from the crude reaction mixtures of both reactions. These aliquots were treated with benzoyl chloride, pyridine and 4-dimethylaminopyridine in anhydrous DCM to form the monobenzoate (149).

![Chemical Structures](image)

The $^1$H NMR spectra of the monobenzoates thus prepared were identical to that of (149a) and there was no evidence of (149b) in the crude benzylation reaction mixture. This indicated that the dihydroxylation of (150) was highly diastereoselective and the stereochemistry of the product (151) was the same as for (149a).

Since both of the AD-mix reagents were the same as had been used for the dihydroxylation of the benzoate (148), it was obvious there must be some form of stereochemical control being exerted by the substrate (150). The only difference between the two substrates is the presence of the free hydroxyl, which might be directing the attack of the osmium complex by coordinating with the osmium.
Molecular modelling with Insight II showed that the bottom face of the double bond of (150) is slightly tilted towards the alcohol. This side of the double bond is also much more open than the top face which has the bulky Boc groups hindering attack from osmium on that side.

Figure 5.6: Molecular Model of (150) Showing the Tilt of the Double Bond Towards the Hydroxyl Group

Although it is certainly unusual for both AD-mix reagents to give the same result, it is not unprecedented. In 1995 Iwashima et al. reported that the dihydroxylation of the terminal alkene (152) with AD-mix α and AD-mix β gave identical ratios of the two possible diastereomeric products (153a and 153b).
5.5 Attempted Cyclisation of the Diol (151)

The next step in the synthesis of azasugars was the cyclisation of the diol (151) to the corresponding pyrrolidine.
The diol was initially converted into the bis(mesylate) (154) with methanesulfonylchloride and triethylamine in DCM. Attempted purification of the bis(mesylate) (154) on a column of silica gel led to extensive decomposition, therefore the crude reaction mixture was used for the next step. Treatment of the bis(mesylate) (154) with BnNH2 at both RT and at 110°C in toluene gave a complex mixture of compounds. The $^1$H NMR spectra of both the crude reaction mixture and the fractions isolated from a column of silica gel did not contain anything that could be unequivocably assigned as product.
Next the crude bis(mesylate) (154) was treated with the sodium salt of BocNH₂ in DMF at RT overnight. Again this gave a complex mixture of compounds that did not appear to contain either the pyrrolidine (156) or starting material in the ¹H NMR spectrum of the crude reaction mixture.
This failure of the bis(mesylate) (154) to give the pyrrolidine products was a little bit odd considering that similar bis(mesylates) had reacted with primary amines to give the desired cyclisation products. Kim et al. were able to cyclise the bis(mesylate) (157) with BnNH₂ by refluxing in toluene for 24 hours.¹⁴⁸

The most obvious reason for the failure to get the desired product was that the bis(mesylate) system (154) was not stable to the reaction conditions. A possibility is that the amine is displacing the primary mesylate to give (159), but the cyclisation is hindered by the bulky acetonide group which forms a steric barrier. Thus it is not possible to form the desired pyrrolidine and the highly reactive secondary mesylate undergoes decomposition to an unknown product.
To procure a more stable system the diol (151) was treated with toluenesulfonyl chloride with pyridine and catalytic amounts of 4-dimethylaminopyridine in DCM to form the bis(tosylate). However only the monotosylate (160) was formed, most probably due to the steric hindrance of the primary tosylate preventing the formation of the secondary tosylate.

The monotosylate (160) was then treated with methanesulfonyl chloride and triethylamine in DCM to form the secondary mesylate (161).

This was treated with BnNH₂ in toluene at RT for two days until TLC analysis showed complete consumption of the starting material. However, once again the reaction
product was a complex mixture of compounds. None of the fractions isolated via column chromatography could be definitively assigned as the desired pyrrolidine (155) on the basis of their $^1$H NMR spectra.

![Chemical structures](image)

The conversion of the diol (151) to sulfonate derivatives appeared to provide highly unstable compounds that were undergoing decomposition when exposed to the cyclisation reaction conditions. Possibly the decomposition was occurring initially via nucleophilic attack of the amine upon the oxazolidine ring and subsequent reactions following on from this were leading to the complex mixture of products observed.

It was decided at this point to take another tack and convert the primary hydroxyl of (151) into an azide (162). The secondary alcohol could then be mesylated and the azide reduced to the corresponding amine and allowed to cyclise onto the secondary mesylate.

The diol (151) was treated with lithium azide, triphenylphosphine and carbon tetrabromide in DMF. This method works by converting the hydroxyl group to a
bromide *in situ* followed by nucleophilic displacement of the bromide by the azide anion.\(^1\) However after treatment at RT overnight, only starting material was present in the \(^1\)H NMR spectrum of the crude reaction mixture.

![Chemical Structure](image)

\((151)\)

### 5.6 Conversion of the Primary Hydroxyl Group of (150) to an Amine Derivative

Bearing in mind the results obtained in the attempted cyclisation of (151) it was obvious that a rethink of the general strategy was in order. To this end it was decided to convert the primary hydroxyl of (150) into an amine derivative before the oxidation of the double bond which would help prevent exposing the compound to amination conditions it was obviously not stable under.

The alcohol (150) was treated with lithium azide, triphenylphosphine and carbon tetrabromide in DMF at RT overnight. However after working up the crude reaction mixture, only starting material was present in the \(^1\)H NMR spectrum.
The alcohol (150) was then converted into the triflate (163) with trifluoromethanesulfonic anhydride and pyridine in DCM. Due to its sensitive nature the triflate (163) was not purified, but instead was treated with NaN₃ in DMF at 50°C overnight. The ¹H NMR spectrum of the crude reaction mixture showed a complex mixture of compounds. None of the fractions isolated via column chromatography could be definitively assigned the structure of the desired product.
The less reactive mesylate (165) was formed by treating the alcohol (150) with methanesulfonylchloride and triethylamine in DCM for 30 minutes. This was treated with sodium azide in DMF at 50°C overnight to once again yield a complex mixture of compounds that did not appear to contain either the desired product nor starting material.

\[
\begin{align*}
\text{HO} &\quad \xrightarrow{\text{MsCl, Et}_3\text{N, DCM}} \quad \text{MsO} \\
150 &\quad \xrightarrow{\text{NaN}_3, \text{DMF}} \quad \text{N}_3
\end{align*}
\]

The primary tosylate (166) was prepared from toluenesulfonylchloride and pyridine in DCM in a yield of 55%. Due to its less reactive nature the tosylate was treated with lithium azide, which is more reactive than sodium azide. However after treating the tosylate (166) with lithium azide in DMF at 50°C overnight, only starting material was present in the $^1$H NMR spectrum.
To get away from the attempted formation of an azide, the tosylate (166) was treated with the sodium salt of BocNH₂ in DMF. Initially at 50°C no reaction occurred, however, increasing the temperature to 100°C led to the formation of the amine (167) in 56% yield after purification by column chromatography.

An interesting facet of this reaction is the loss of a Boc group from the other nitrogen. A possible explanation for this side reaction is that the sodium salt of BocNH₂ attacks the carbonyl group of one of the Bocs. Subsequent ejection of the former protecting group leads to the formation of Boc₂NH (168) and the nitrogen anion (169). Protonation of the nitrogen occurs possibly by hydrogen abstraction from BocNH₂ or during the aqueous work up.
5.7 Epoxidation of the Allylic Amine (167)

With the diamine (167) in hand the choice now was whether to dihydroxylate or epoxidise the double bond. Since there had been so many problems associated with the attempted cyclisation of the diol (151) (Section 5.5) it was decided to form the epoxide.

Treatment of the alkene (167) with meta-chloroperbenzoic acid in DCM at RT gave the epoxide (170) in 23% yield in a diastereomeric ratio of approximately 2:1.
The diastereomeric ratio was determined from the $^1$H NMR spectrum as shown below in Figure 5.7. The partial spectrum shows the H4 proton, $\alpha$ to the acetonide group, as an apparent triplet for both diastereomers of (170). Two dimensional NMR nOesy experiments failed to shed any light upon the stereochemistry of these epoxides.

Figure 5.7: Partial $^1$H NMR Spectrum (CDCl$_3$) of Epoxide (170)

5.8 Attempted Cyclisation of the Epoxide (170)

The final step in the synthetic path was the cyclisation of the amine onto the epoxide. It was believed that the pyrrolidine ring formation would be favoured over the aziridine.
The epoxide (170) was treated with sodium hydride in DMF at 50°C overnight. However, after workup the \textsuperscript{1}H NMR spectrum of the crude reaction mixture showed nothing that could be assigned as product (171).

Regrettably at this point the synthetic path had to be abandoned due to the pressing need to begin the thesis write-up and the need to return to the starting material (143) in order to procure more of the epoxide (170). However, it should purely be a matter of determining the correct reaction conditions in order to cyclise the epoxide (170) and form the protected azasugar (171).
5.9 Conclusion

This chapter detailed the attempts to synthesise azasugars starting from a carbohydrate source. The lactol (143) was converted into the dibenzoate (146) in three steps. This was followed by a palladium(0) catalysed allylic amination to provide the allylic amine (148). The allylic amine (148) smoothly underwent dihydroxylation in good yields, but very poor stereoselectivity.

To avoid possible complications during deprotection the benzoyl moiety in (148) was removed to furnish the alcohol (150). The alcohol (150) underwent dihydroxylation with both AD-mix α and AD-mix β to selectively give the same diastereomer (151). Despite many attempts the diol (151) could not be cyclised via sulfonate derivatives to the pyrrolidines (155 and 156) nor could the primary hydroxyl group be converted into an azide.

The hydroxyl group of (150) also could not be converted into an azide, but conversion of the hydroxyl into a tosyl derivative (166) followed by nucleophilic displacement with the lithium salt of BocNH₂ gave the diamine (167). The double bond of the diamine (167) was treated with m-CPBA to furnish the epoxide (170). Disappointingly the cyclisation of the amine onto the epoxide could not be realised with the amount of sample left and frustratingly the synthetic pathway had to be abandoned at that point.
CHAPTER 6

CONCLUSION AND FUTURE WORK
This thesis has documented investigations into the palladium(0) catalysed rearrangement of allylic sulfoximines to provide $\gamma$-amino-$\alpha,\beta$-unsaturated ketones, the palladium(0) catalysed amination of allylic sulfoximines, applications of both these reactions towards the synthesis of azasugars and the utilisation of carbohydrates as starting material for the synthesis of azasugars.

The rearrangement of allylic sulfoximines to $\gamma$-amino-$\alpha,\beta$-unsaturated ketones proceeded in moderate to good yields and proved to be very regioselective. The regioselectivity of the reaction was believed to be driven by the relative stability of the intermediate allylic cations and the thermodynamic stability of the conjugated systems formed by nucleophilic attack at the $\gamma$ position.

The palladium(0) catalysed amination of allylic sulfoximines also proved to be highly regioselective. The use of an optically active sulfoximine led to the formation of an optically active amine, while treatment of an allylic sulfoximine with a primary chiral amine furnished a pyrrole derivative. Evidence was gathered that indicated that the formation of allylic sulfinamides from allylic sulfoximines was reversible.

Initial attempts to synthesise azasugars from allylic sulfoximines proved unsuccessful when the $N,N$-dibenzy1 protected allylic amine gave an unisolatable product when subjected to dihydroxylation conditions. Later attempts using an intramolecular rearrangement were more successful, but failed attempts to remove an Cbz protecting group led to the synthetic path being abandoned.

The initial steps of the synthesis of azasugars from carbohydrates - reduction, chain extension, protection and palladium(0) catalysed allylic amination - proceeded very smoothly. The allylic amine underwent dihydroxylation in good yields, but with poor diastereoselectivity. The benzoyl protecting of the allylic amine was removed to give an alcohol, which underwent dihydroxylation in good yields and excellent diastereo-
selectivity. However the diols produced could not be cyclised to the protected azasugars. The hydroxyl group of the allylic amine was then converted into an amine and the double bond epoxidised, but this too could not be cyclised. This meant a extremely frustrating and ultimately disappointing end to the project with neither synthetic pathway coming to fruition.

Future work would obviously include investigating other methods of deprotecting nitrogens with a Cbz group and investigations into suitable cyclisation conditions for the epoxide in order to furnish azasugars.
CHAPTER 7

EXPERIMENTAL
7.1 General Notes

1. All NMR spectra were run either on a Varian Unity 400 spectrometer (400MHz for $^1$H, 100MHz for $^{13}$C) or a Varian Unity 300 spectrometer (300MHz for $^1$H, 75 MHz for $^{13}$C). All spectra were run in deuterated chloroform unless noted otherwise. Each signal is described in terms of its chemical shift (δ) in parts per million from tetramethylsilane (internal standard). The $^1$H spectra are then described in terms of multiplicity, coupling constants, integration and assignment. Abbreviations used to denote the multiplicity of the signals are: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. The $^{13}$C NMR signals are assigned and an indication given of the number of protons attached to the carbon wherever possible, as determined from DEPT NMR experiments.

2. Low resolution mass spectra were recorded on a VG Quattro triple quadrupole mass spectrometer. Spectra are described in terms of its mode of ionisation (ES = electrospray), polarity of ionisation (+ve or -ve) then charge to mass ratio (m/z) of the major peaks. Next in parentheses is the assignment followed by the percentage of the base peak. High resolution mass spectra were recorded on a Fisons/VG Autospec-oa-TOF mass spectrometer. Spectra are described as, firstly, the calculated mass of the sample followed by, secondly, the found mass of the sample.

3. Melting points were determined on a Gallenkamp MF 370 melting point apparatus and are uncorrected.
4. Optical rotations were recorded with a JASCO DIP-370 Digital Polarimeter in analytical reagent grade solvents. Specific rotations \( ([\alpha]_D^1) \) are recorded in degrees per decimetre, with the concentration \( (c) \) given in grams per 100mL in the specified solvent.

5. Column chromatography was performed with silica gel, 0.063-0.2 mm (Merck). Thin layer chromatography (TLC) was carried out on plastic backed silica gel plates F254 (Merck). The developed plates were visualised either under shortwave (254nm) ultraviolet light or by immersion in an aqueous solution containing 5% (w/v) \((\text{NH}_4\text{)}\text{Mo}_7\text{O}_{24}\), 0.2% (w/v) \(\text{Ce(SO}_4\text{)}_2\) and 5% (v/v) \(\text{H}_2\text{SO}_4\), followed by heat activation. High performance liquid chromatography was carried out using a Waters pump model 510 and a Regis Pirkle Covalent D-Naphthylalanine column (particle size 5 micron, pore size 100Å, dimensions 4.6mm x 250mm). The U.V. detector was a Waters series 450 variable wavelength detector operating at 254 nm.

6. Molecular modelling was performed using the CVFF force field parameters of Insight II, Version 2.3.0, Biosym Technologies, San Diego, CA.

7. Dichloromethane and dimethylformamide were dried by distillation from calcium hydride and stored over molecular sieves under a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium/benzophenone under a nitrogen atmosphere and used immediately.
8. All reactions requiring anhydrous reaction conditions were performed in glassware that had been oven-dried and cooled in a dessicator containing self-indicating silica gel.

9. The term "dried", unless specified otherwise, refers to an organic extract being dried over anhydrous MgSO₄. The terms "evaporation" and "in vacuo" are used synonymously and imply removal of solvents on a Buchi rotoevaporator (water aspiration pressure) followed by removal of the last traces of solvent on a high vacuum oil pump.

10. Allyl phenyl sulfide, Jones reagent, lithium azide and palladium black were prepared via literature procedures. All other reagents were obtained from commercial sources unless noted otherwise.

**7.2 Experimental for Chapter 2**

**7.2.1 Synthesis of the Sulfoximines (77), (78) and (80)**

**S-Methyl-S-phenyl sulfoximine (77)**

\[
\begin{align*}
\text{O} & \quad \text{Ph} & \quad \text{S} & \quad \text{Me} \\
\text{NH} & & & & \\
\end{align*}
\]

The title compound (77) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.
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N-Methoxycarbonyl-S-methyl-S-phenyl sulfoximine (78)

\[
\begin{align*}
\text{Ph} & \quad \text{S-Me} \\
\quad & \quad \text{NCOOMe}
\end{align*}
\]

The title compound (78) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.\textsuperscript{113}

2-[(N-Methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-ethan-1-one (80)

\[
\begin{align*}
\text{Ph} \\
\quad & \quad \text{O=S=NCOCOCH}_3
\end{align*}
\]

To a stirred solution of diisopropylamine (1.4mL, 9.9mmol) in anhydrous THF (5mL) at 0°C was added dropwise n-BuLi (1.6M in hexanes, 6.6mL, 10.6mmol) to give a pale yellow solution. This solution was stirred at 0°C for 20 minutes then transferred via syringe to a stirred solution of N-methoxycarbonyl-S-methyl-S-phenylsulfoximine (78) (1.502g, 7.0mmol) in anhydrous THF (20mL) at -78°C. The resulting yellow/orange solution was stirred at -78°C for 20 minutes. Benzaldehyde (1.2mL, 11.8mmol) was added to the solution and stirring was continued for a further 40 minutes at -78°C. The reaction was quenched by addition of saturated NH\textsubscript{4}Cl\textsubscript{(aq)} (4mL) and then the solution was warmed to RT. The solution was diluted with H\textsubscript{2}O.
(40mL) then extracted with ethyl acetate (2 x 100mL). The combined organic layers were dried, filtered and evaporated to a yellow/orange semi-solid.

Jones reagent (12mL) was added dropwise to the crude alcohol (79) in acetone (100mL) to give a brown solution which was left to stir for 15 minutes. The reaction was quenched by slow addition of iso-propanol (10mL) to give a green solution. The solution was diluted with H2O (30mL) and extracted with ethyl acetate (2 x 100mL). The combined organic layers were washed with H2O (30mL) then dried, filtered and evaporated to a yellow residue. The crude product was purified on a short column of silica gel using initially 5% ethyl acetate/hexane, followed by 10% ethyl acetate/hexane and finally 30% ethyl acetate/hexane as eluent to give the title compound (80) (0.783g, 35%) as a thick yellow oil.

H NMR: δ7.4-8.0 (m,5H,Ar-H); 5.537 (d,J=13.8Hz,1H,one of methylene CH2); 5.069 (d,J=13.8Hz,1H,one of methylene CH2); 3.702 (s,3H,carbamate CH3).

C NMR: δ187.6 (ketone C=O); 159.6 (carbamate C=O); 135.9 (Ar-C); 135.7 (Ar-C); 134.4 (Ar-CH); 134.4 (Ar-CH); 129.3 (Ar-CH); 129.2 (Ar-CH); 128.8 (Ar-CH); 128.7 (Ar-CH); 60.7 (S-CH2); 53.3 (carbamate CH3).

MS: ES (+ve) m/z 317.7 ([M+H]+,43); 286.3 ([M-OCH3]+,100).

HRMS: Calc'd. for C16H15NO4S, 317.072180; found, 317.071791.
7.2.2 Synthesis of Allylic Sulfoximines Via Knoevenagel Condensations

*(E)-2-(N-Methoxycarbonyl-S-phenylsulfoximidyoyl)-1-phenyl-pent-3-en-1-one*(

(84a)

A general procedure for the Knoevenagel type condensation between a β-ketosulfoximine and an aldehyde.

To a stirred mixture of 2-(N-methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-ethan-1-one (80) (0.194g, 0.611mmol), propanal (0.6mL, 8mmol) and 3Å molecular sieves (~1g) in anhydrous acetonitrile (10mL) was added a solution of piperidine (18μL, 0.182mmol) and acetic acid (21μL, 0.367mmol) in acetonitrile (3mL). The mixture was stirred at RT for 24 hours under an atmosphere of nitrogen. The cloudy yellow solution was then filtered through a bed of Celite® and the solvent removed in vacuo. Purification of the crude product on a short column of silica gel using initially 5% ethyl acetate/hexane and finally 10% ethyl acetate/hexane as eluent gave the title compound (84a) as a yellow oil (0.040g, 18%) and as a 67:33 mixture of diastereomers.
Major diastereomer:

$^1$H NMR: $\delta$ 7.4-8.1 (m, 10H, Ar-H); 7.077 (d, J=9.3Hz, 1H, S-CH); 6.0-5.9 (m, 1H, vinyl H); 5.45-5.35 (m, 1H, vinyl H); 3.816 (s, 3H, carbamate CH$_3$); 1.728 (d, J=6.6Hz, 3H, alkyl CH$_3$).

$^{13}$C NMR: $\delta$ 191.0 (ketone C=O); 160.1 (carbamate C=O); 137.8 (vinyl CH); 136.4 (Ar-C); 134.4 (Ar-CH); 134.2 (Ar-CH); 134.0 (Ar-C); 130.4 (Ar-CH); 129.5 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 119.9 (vinyl CH); 68.6 (S-CH); 53.4 (carbamate CH$_3$); 18.3 (alkyl CH$_3$).

Minor diastereomer:

$^1$H NMR: $\delta$ 7.4-8.1 (m, 10H, Ar-H); 6.402 (d, J=9.0Hz, 1H, S-CH); 6.1-6.0 (m, 1H, vinyl H); 5.45-5.35 (m, vinyl H); 3.518 (s, 3H, carbamate CH$_3$); 1.728 (d, J=6.6Hz, 3H, alkyl CH$_3$).

$^{13}$C NMR: $\delta$ 191.0 (ketone C=O); 159.3 (carbamate C=O); 139.5 (vinyl CH); 128-136 (8 aryl carbons-not all visible under major diastereomer); 118.5 (vinyl CH); 73.0 (S-CH); 53.1 (carbamate CH$_3$); 18.4 (alkyl CH$_3$).

MS: ES (+ve) m/z 358.0 ([M+H]$^+$, 45); 199.5 ([PhS(O)NCOOCH$_3$+H]$^+$, 26); 158.7 ([M-(PhS(O)NCOOCH$_3$+H)]$^+$, 100).

HRMS: Calc'd. for C$_{19}$H$_{19}$NO$_4$S, 357.103480; found, 357.105085.
(E)-2-(N-Methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-hex-3-en-1-one

(84b)

The title compound (84b) was prepared from 2-(N-methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-ethan-1-one (80) (0.400g, 1.26mmol), butanal (0.3mL, 3.32mmol), piperidine (29µL, 0.297mmol) and acetic acid (36µL, 0.599mmol) as described previously for (84a), as a yellow oil (0.195g, 42%) and as a 66:34 mixture of diastereomers.

Major diastereomer:

$^1$H NMR: δ 7.2-8.2 (m, 10H, Ar-H); 7.055 (d, J=9.3Hz, S-CH); 5.997 (dt, J=6.3, 15.3Hz, 1H, vinyl H); 5.3-5.4 (m, 1H, vinyl H); 3.809 (s, 3H, carbamate CH$_3$); 2.024 (m, 2H, alkyl CH$_2$); 0.793 (t, J=7.5Hz, 3H, alkyl CH$_3$).

$^{13}$C NMR: δ 190.9 (ketone C=O); 160.1 (carbamate C=O); 142.1 (vinyl CH); 136.3 (Ar-C); 134.3 (Ar-CH); 134.0 (Ar-CH); 133.9 (Ar-C); 130.3 (Ar-CH); 129.4 (Ar-CH); 128.6 (Ar-CH); 128.4 (Ar-CH); 118.3 (vinyl CH); 68.6 (S-CH$_2$); 53.3 (carbamate CH$_3$); 20.7 (alkyl CH$_2$); 14.0 (alkyl CH$_3$).
Minor diastereomer:

\(^1\)H NMR: \(\delta 7.2-8.2\) (m,10H,Ar-H); \(6.392\) (d,\(J=8.7\)Hz,1H,S-CH); \(6.082\) (dt,\(J=6.3,15.3\)Hz,1H,viny H); \(5.4\) (m,1H,viny H); \(3.510\) (s,3H, carbamate CH\(_3\)); \(2.1-1.9\) (m,2H,alkyl CH\(_2\)); \(0.940\) (t,\(J=7.5\)Hz,3H,alkyl CH\(_3\)).

\(^{13}\)C NMR: \(\delta 190.9\) (ketone C=O); \(159.2\) (carbamate C=O); \(144.6\) (vinyl CH); \(128-136\) (8 aryl carbons-not all visible under major diastereomer); \(117.1\) (vinyl CH); \(73.1\) (S-CH); \(53.0\) (carbamate CH\(_3\)); \(20.5\) (alkyl CH\(_2\)); \(13.9\) (alkyl CH\(_3\)).

MS: ES (+ve) \(m/z\) 372.0 ([M+H]\(^+\),53); 213.5 ([PhS(O)NCOOCH\(_3\)+H]\(^+\), 23); 172.7 ([M-(PhS(O)NCOOCH\(_3\)+H)]\(^+\),100).

HRMS: Calc'd. for C\(_{20}\)H\(_{21}\)NO\(_4\)S, 371.120810; found, 371.120564.

\((E)\)-2-(\(N\)-Methoxycarbonyl-S-phenylsulfoxtmidoyl)-1-phenyl-oct-3-en-1-one

\((84c)\)

\[\text{Ph} \quad \text{O=S=NCOMe} \]
\[\text{C}_4\text{H}_9 \quad \text{Ph} \quad \text{O} \quad \text{C} \]

The title compound \((84c)\) was prepared from 2-(\(N\)-methoxycarbonyl-S-phenylsulfoxtmidoyl)-1-phenyl-ethan-1-one \((80)\) (0.269g, 0.848mmol), hexanal (0.2mL, 1.66mmol), piperidine (18\(\mu\)L, 0.182mmol) and acetic acid (21\(\mu\)L,
0.367 mmol) as described previously for (84a), as a yellow oil (0.155 g, 46%) and as a 76:24 mixture of diastereomers. \( R_f = 0.41 \) (30% ethyl acetate/hexane).

Major diastereomer:

\(^1\)H NMR: \( \delta \) 7.2-8.2 (m, 10H, Ar-H); 7.067 (d, \( J = 9.3 \) Hz, 1H, S-CH); 5.9-6.0 (m, 1H, vinyl H); 5.3-5.4 (m, 1H, vinyl H); 3.804 (s, 3H, carbamate CH\(_3\)); 2.0-2.1 (m, 2H, alkyl CH\(_2\)); 1.2-1.4 (m, 4H, alkyl CH\(_2\)); 0.869 (t, \( J = 7.8 \) Hz, 3H, alkyl CH\(_3\)).

\(^{13}\)C NMR: \( \delta \) 190.9 (ketone C=O); 160.0 (carbamate C=O); 143.1 (vinyl CH); 136.3 (Ar-C); 134.3 (Ar-CH); 134.1 (Ar-CH); 133.9 (Ar-C); 130.3 (Ar-CH); 129.4 (Ar-CH); 128.7 (Ar-CH); 128.5 (Ar-CH); 118.4 (vinyl CH); 68.6 (S-CH\(_3\)); 53.3 (carbamate CH\(_3\)); 32.2 (alkyl CH\(_2\)); 30.4 (alkyl CH\(_2\)); 21.9 (alkyl CH\(_2\)); 13.6 (alkyl CH\(_3\)).

Minor diastereomer:

\(^1\)H NMR: \( \delta \) 7.2-8.2 (m, 10H, Ar-H); 6.404 (d, \( J = 9.3 \) Hz, 1H, S-CH); 6.0-6.1 (m, 1H, vinyl H); 5.3-5.4 (m, 1H, vinyl H); 3.509 (s, 3H, carbamate CH\(_3\)); 2.0-2.1 (m, 2H, alkyl CH\(_2\)); 1.2-1.4 (m, 4H, alkyl CH\(_2\)); 0.869 (t, \( J = 7.8 \) Hz, 3H, alkyl CH\(_3\)).

\(^{13}\)C NMR: \( \delta \) 191.0 (ketone C=O); 159.2 (carbamate C=O); 144.7 (vinyl CH); 128-136 (8 aryl carbons-not all visible under major diastereomer); 117.0 (vinyl CH); 73.0 (S-CH); 53.0 (carbamate CH\(_3\)); 32.3 (alkyl CH\(_2\)); 30.3 (alkyl CH\(_2\)); 21.9 (alkyl CH\(_2\)); 13.6 (alkyl CH\(_3\)).
MS: ES (+ve) m/z 400.1 ([M+H]^+, 69); 241.6 ([PhS(O)NCOOCH3+H]^+, 18); 200.8 ([M-(PhS(O)NCOOCH3+H)]^+, 100).

HRMS: Calc'd. for C22H25NO4S, 399.152109; found, 399.152498.

(E)-2-(N-Methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (84d)

The title compound (84d) was prepared from 2-(N-methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-ethan-1-one (80) (0.302g, 0.952mmol), heptanal (0.3mL, 2.14mmol), piperidine (22μL, 0.22mmol) and acetic acid (25μL, 0.44mmol) as described previously for (84a), as a yellow oil (0.269g, 65%) and as a 69:31 mixture of diastereomers.

Major diastereomer:

$^1$H NMR: δ7.4-8.2 (m,10H,Ar-H); 7.075 (d,J=9.0Hz,1H,S-CH); 6.0-6.1 (m,1H,vinyl H); 5.3-5.4 (m,1H,vinyl H); 3.801 (s,3H,carbamate CH3); 2.0-2.1 (m,2H,alkyl CH2); 1.25-1.4 (m,6H,alkyl CH2); 0.879 (t,J=7.6 Hz,3H,alkyl CH3).

$^{13}$C NMR: δ190.9 (ketone C=O); 160.0 (carbamate C=O); 143.1 (vinyl CH); 136.3 (Ar-C); 134.3 (Ar-CH); 134.0 (Ar-CH); 133.8 (Ar-C); 130.3 (Ar-CH); 129.4
(Ar-CH); 128.7 (Ar-CH); 128.4 (Ar-CH); 118.4 (vinyl CH); 68.6 (S-CH\textsubscript{2}); 53.2 (carbamate CH\textsubscript{3}); 32.4 (alkyl CH\textsubscript{2}); 31.4 (alkyl CH\textsubscript{2}); 27.9 (alkyl CH\textsubscript{2}); 22.4 (alkyl CH\textsubscript{2}); 13.7 (alkyl CH\textsubscript{3}).

Minor diastereomer:

\textsuperscript{1}H NMR: 8 7.4-8.2 (m, 10H, Ar-H); 6.413 (d, J=9.3 Hz, 1H, S-CH\textsubscript{2}); 6.0-6.1 (m, 1H, vinyl H); 5.3-5.4 (m, 1H, vinyl H); 3.509 (s, 3H, carbamate CH\textsubscript{3}); 2.0-2.1 (m, 2H, alkyl CH\textsubscript{2}); 1.25-1.4 (m, 6H, alkyl CH\textsubscript{2}); 0.879 (t, J=7.6 Hz, 3H, alkyl CH\textsubscript{3}).

\textsuperscript{13}C NMR: 8 191.0 (ketone C=O); 159.2 (carbamate C=O); 144.7 (vinyl CH); 128-136 (8 aryl carbons-not all visible under major diastereomer); 117.1 (vinyl CH); 73.1 (S-CH\textsubscript{2}); 53.0 (carbamate CH\textsubscript{3}); 32.6 (alkyl CH\textsubscript{2}); 31.0 (alkyl CH\textsubscript{2}); 27.8 (alkyl CH\textsubscript{2}); 22.2 (alkyl CH\textsubscript{2}); 14.0 (alkyl CH\textsubscript{3}).

MS: ES (+ve) m/z 414.1 ([M+H]+, 72); 255.6 ([PhS(O)NCOOCH\textsubscript{3}+H]+, 12); 214.8 ([M-(PhS(O)NCOOCH\textsubscript{3}+H)]+, 100).

HRMS: Calc'd. for C\textsubscript{23}H\textsubscript{27}NO\textsubscript{4}S, 413.167758; found, 413.168015.
7.2.3 Palladium(0) Catalysed Rearrangement of Allylic Sulfoximines

\((E)-N\text{-}N\text{-methoxycarbonyl}\text{-}4\text{-}amino\text{-}1\text{-}phenyl\text{-}pent\text{-}2\text{-}en\text{-}1\text{-}one\) (86a)

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

A general procedure for the intramolecular rearrangement of allylic sulfoximines.

To a stirred solution of \((E)\text{-}2\text{-}(N\text{-}N\text{-}\text{methoxycarbonyl}\text{-}S\text{-}phenylsulfoximidoyl)}\text{-}1\text{-}phenyl\text{-}pent\text{-}3\text{-}en\text{-}1\text{-}one\) (84a) (0.084g, 0.235mmol) in anhydrous THF (10mL) at RT was added tetrakis(triphenylphosphine)palladium(0) (0.028g, 0.024mmol). The yellow/orange solution was stirred at RT for 60 minutes. The solvent was removed \textit{in vacuo} and the resulting red residue dissolved in methanol (20mL). To this solution was added triethylamine (5 drops) and stirring continued for 30 minutes. Evaporation of the solvent gave a red residue. Purification of the crude product on a short column of silica gel using initially 5% ethyl acetate/hexane and finally 10% ethyl acetate/hexane as eluent gave the title compound (86a) as a yellow oil (0.027g, 50%).

\(^1\text{H NMR:} \delta 7.4\text{-}8.0 \text{ (m,5H,Ar-H);} \ 6.986 \text{ (d,} J=12.0\text{Hz,vinyl H);} \ 6.819 \text{ (dd,} J=3.3,12.0\text{Hz,vinyl H);} \ 4.859 \text{ (br s,1H,NH);} \ 4.561 \text{ (br s,1H,N-CH);} \ 3.700 \text{ (s,3H,carbamate CH}_3\text{);} \ 1.356 \text{ (t,} J=5.1\text{Hz,alkyl CH}_3\text{).} \)
\textsuperscript{13}C NMR: 8191.0 (ketone C=O); 159.3 (carbamate C=O); 149.2 (vinyl CH); 137.8 (Ar-C); 134.2 (Ar-CH); 128.8 (Ar-CH); 128.6 (Ar-CH); 119.9 (vinyl CH); 68.6 (N-CH); 53.4 (carbamate CH\textsubscript{3}); 18.3 (alkyl CH\textsubscript{3}).

MS: ES (+ve) \textit{m/z} 234.1 ([M+H]\textsuperscript{+}, 21); 202.0 ([M-OCH\textsubscript{3}]\textsuperscript{+}, 24); 159.0 ([M-HNCOOCH\textsubscript{3}]\textsuperscript{+}, 100); 105.0 (PhC(O)\textsuperscript{+}, 33).

HRMS of M+H: Calc'd for C\textsubscript{13}H\textsubscript{16}NO\textsubscript{3}, 234.113009; found, 234.112775.

(E)-\textit{N}-Methoxycarbonyl-4-amino-1-phenyl-hex-2-en-1-one (86b)

The title compound was prepared from (E)-2-(\textit{N}-methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-hex-3-en-1-one (84b) (0.120g, 0.323mmol) and tetrakis(triphenylphosphine)palladium(0) (0.038g, 0.033mmol) for 85 minutes followed by treatment with triethylamine in methanol as described above for (86a), as an oil (0.025g, 31%).

\textsuperscript{1}H NMR: 87.4-8.0 (m,5H,Ar-H); 7.005 (d, J=14.7Hz, vinyl H); 6.893 (dd, J=5.1,14.7Hz, vinyl H); 4.877 (br s,1H,NH); 4.380 (br s,1H,N-CH); 3.705 (s,3H, carbamate CH\textsubscript{3}); 1.663 (m,2H, alkyl CH\textsubscript{2}); 0.992 (t, J=7.3 Hz, alkyl CH\textsubscript{3}).
$^{13}$C NMR: $\delta$190.4 (ketone C=O); 156.5 (carbamate C=O); 147.7 (vinyl CH); 137.6 (Ar-C); 132.9 (Ar-CH); 128.6 (Ar-CH); 128.5 (Ar-CH); 125.2 (vinyl CH); 53.9 (N-CH); 52.2 (carbamate CH$_3$); 29.6 (alkyl CH$_2$); 14.1 (alkyl CH$_3$).

MS: ES (+ve) m/z 248.1 ([M+H]$^+$, 28); 216.1 ([M-OCH$_3$]$^+$, 33); 173.1 ([M-HNCOOCH$_3$]$^+$, 100); 105.0 (PhC(O)$^+$, 30).

HRMS of M+H: Calc'd for C$_{14}$H$_{18}$N0$_3$, 248.128669; found, 248.129166.

(E)-N-Methoxycarbonyl-4-amino-1-phenyl-oct-2-en-1-one (86c)

\[
\begin{align*}
\text{H} & \quad \text{COOMe} \\
\text{C}_4\text{H}_9 & \quad \text{Ph}
\end{align*}
\]

The title compound was prepared from (E)-2-([N-methoxycarbonyl]-S-phenylsulfoximidoyl)-1-phenyl-oct-3-en-1-one (84c) (0.124g, 0.310mmol) and tetrakis(triphenylphosphine)palladium(0) (0.039g, 0.033mmol) for 65 minutes followed by treatment with triethylamine in methanol as described above for (86a), as an oil (0.055g, 64%).

$^1$H NMR: $\delta$8.0-7.4 (m,5H,Ar-H); 6.998 (d, J=15.6,1H,vinyl H); 6.892 (dd, J=5.1,15.6Hz,1H,vinyl H); 4.927 (br s,1H,NH); 4.403 (br s,1H,N-CH); 3.702 (s,3H,carbamate CH$_3$); 2.0-1.2 (m,6H,alkyl CH$_2$); 0.895 (t, J=7.5Hz,3H,alkyl CH$_3$).
$^{13}$C NMR: 8190.4 (ketone C=O); 156.4 (carbamate C=O); 148.1 (vinyl CH); 137.6 (Ar-C); 132.8 (Ar-CH); 128.5 (Ar-CH); 128.5 (Ar-CH); 125.1 (vinyl CH); 54.0 (N-CH); 52.5 (carbamate CH$_3$); 34.4 (alkyl CH$_2$); 27.7 (alkyl CH$_2$); 22.3 (alkyl CH$_2$); 13.8 (alkyl CH$_3$).

MS: ES (+ve) $m/z$ 276.2 ([M+H]$^+$, 40); 256.3 (100); 244.1 ([M-OCH$_3$]$^+$, 42); 201.1 ([M-NHCOOCH$_3$]$^+$, 79); 105.0 (PhC(O)$^+$, 24).

HRMS of M+H: Calc'd for C$_{16}$H$_{22}$NO$_3$, 276.159969; found, 276.160961.

(E)-N-Methoxycarbonyl-4-amino-1-phenyl-non-2-en-1-one (86d)

The title compound was prepared from (E)-2-(N-methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (84d) (0.240g, 0.58mmol) and tetrakis(triphenylphosphine)palladium(0) (0.063g, 0.055mmol) for 60 minutes followed by treatment with triethylamine in methanol as described above for (86a), as a yellow oil (0.082g, 49%).

$^1$H NMR: 87.4-8.0 (m,5H,Ar-H); 7.001 (d,$J$=16.2Hz,1H,vinyl H); 6.893 (dd,$J$=5.4,16.2Hz,1H,vinyl H); 4.977 (br d,$J$=7.8Hz,1H,NH); 4.426 (br s,1H,N-
CH); 3.696 (s,3H,carbamate CH₃); 1.2-1.7 (m,8H,alkyl CH₂); 0.883 (t,J=7.6Hz,3H,alkyl CH₃).

¹³C NMR: δ190.5 (ketone C=O); 156.4 (carbamate C=O); 148.1 (vinyl CH); 137.6 (Ar-C); 132.8 (Ar-CH); 128.5 (Ar-CH); 128.5 (Ar-CH); 124.9 (vinyl CH); 52.5 (N-CH); 52.2 (carbamate CH₃); 34.6 (alkyl CH₂); 31.4 (alkyl CH₂); 25.3 (alkyl CH₂); 22.3 (alkyl CH₂); 13.8 (alkyl CH₃).

MS: ES (+ve) m/z 290.2 ([M+H]⁺, 62); 258.1 ([M-OCH₃]⁺, 57); 215.1 ([M-HNCOOCH₃]⁺, 100); 105.0 (PhC(O)⁺, 23).

HRMS of M+H: Calc'd for C₁₇H₂₄NO₃, 290.175619; found, 290.172888.

7.2.4 ¹H NMR Study of Changes in Diastereomeric Ratio with Time

Tetrakis(triphenylphosphine)palladium(0) (0.011g, 9.52µmol) was added to a NMR tube containing 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88) (0.048g, 0.094mmol) in d⁸-THF (0.7mL). The ¹H NMR spectrum was taken after 10, 20, 30, 70 minutes, 21 hours and 28 days.

7.2.5 Attempted Thermal Rearrangement of (84d)

2-(N-Methoxycarbonyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (84d) (0.101g, 0.244mmol) was dissolved in anhydrous THF (20mL) and heated at
reflux overnight. The solution was allowed to cool to RT, then the solvent was removed
in vacuo. The residue was dissolved in methanol (20mL) and triethylamine (5 drops),
then stirred for 45 minutes. The solvent was then removed in vacuo. The residue was
placed on a column of silica gel using initially 5% ethyl acetate/hexane, then 10%
ethyl acetate/hexane and finally 15% ethyl acetate/hexane as eluent. None of the
compounds isolated could have their structures assigned as rearrangement products
from their $^1$H NMR spectrum.

7.3 Experimental for Chapter 3

7.3.1 Synthesis of Allylic Sulfoximines

S-Phenyl-S-(2-propenyl)sulfoximine (39)

The title compound (39) was synthesised according to the literature procedure and
was found to have identical spectral properties to those reported.

N-Tosyl-S-phenyl-S-(2-propenyl)sulfoximine (91)
The title compound (91) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.

2-(N-Tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-ol \( (92) \)

\[
\text{Ph} \\
\text{O=S=NTs} \\
\text{Ph} \\
\text{OH}
\]

The title compound (92) was synthesised according to a literature procedure and was found to have identical spectral properties to those reported.

2-(N-Tosyl-S-phenylsulfoximidoyl)-1-phenyl-but-3-en-1-one \( (93) \)

\[
\text{Ph} \\
\text{O=S=NTs} \\
\text{Ph} \\
\text{Ph} \\
\text{O}
\]

To a stirred solution of 2-(N-tosyl-S-phenylsulfoximidoyl)-phenyl-but-3-en-1-ol (92) (0.725g, 1.64mmol) in acetone (100mL) at 0°C was added Jones reagent (3.3mL) in a dropwise fashion. After stirring for 5 minutes, iso-propanol (5mL) was added dropwise to give a green solution. This solution was diluted with H\(_2\)O (100mL) and then extracted with CHCl\(_3\) (2 x 100mL). The organic layers were combined then dried, filtered and evaporated to a yellow oil. Purification of the crude product on a
column of silica gel using 30% ethyl acetate/hexane gave the title compound (93) as a yellow oil (0.698g, 97%) and as a 69:31 mixture of diastereomers.

Major diastereomer:

\[ ^1H \text{ NMR: } \delta 7.4-8.2 (m,14H.\text{Ar-H}); \quad 7.179 \ (d,J=9.0 \text{Hz},1\text{H},\text{S-CH}); \quad 5.5-5.9 \ (m,3\text{H,vinyl H}); \quad 2.371 \ (s,3\text{H},\text{tosyl CH}_3). \]

\[ ^{13}C \text{ NMR: } \delta 188.9 \ (\text{ketone C}=O); \quad 143.0 \ (\text{Ar-C}); \quad 140.7 \ (\text{Ar-C}); \quad 136.6 \ (\text{Ar-C}); \]
\[ 135.3 \ (\text{vinyl CH}); \quad 134.7 \ (\text{Ar-CH}); \quad 134.2 \ (\text{Ar-C}); \quad 133.5 \ (\text{Ar-CH}); \quad 130.4 \ (\text{Ar-CH}); \]
\[ 129.7 \ (\text{Ar-CH}); \quad 129.3 \ (\text{Ar-CH}); \quad 129.3 \ (\text{Ar-CH}); \quad 128.7 \ (\text{Ar-CH}); \quad 128.5 \ (\text{Ar-CH}); \]
\[ 126.7 \ (\text{vinyl CH}_2); \quad 69.2 \ (\text{S-CH}); \quad 21.5 \ (\text{tosyl CH}_3). \]

Minor diastereomer:

\[ ^1H \text{ NMR: } \delta 7.4-8.2 (m,14H.\text{Ar-H}); \quad 6.331 \ (d,J=8.7 \text{Hz},1\text{H},\text{S-CH}); \quad 5.5-5.9 \ (m,3\text{H,vinyl H}); \quad 2.421 \ (s,3\text{H},\text{tosyl CH}_3). \]

\[ ^{13}C \text{ NMR: } \delta 192.1 \ (\text{ketone C}=O); \quad 128-143 \ (12 \text{ aryl carbons}); \quad 135.6 \ (\text{vinyl CH}); \]
\[ 127.4 \ (\text{vinyl CH}_2); \quad 68.6 \ (\text{S-CH}); \quad 22.9 \ (\text{tosyl CH}_3). \]

\text{MS: ES (+ve) } m/z 440.2 \ ([M+H]^+,95); \quad 296.0 \ ([\text{PhS(O)NTs}+2\text{H}]^+,30); \quad 278.2 \ ([\text{PhS(O)NTs-H}_2\text{O}]^+,49); \quad 145.0 \ ([\text{M-PhS(O)NTs}]^+,100). \]
HRMS: Calc'd. for $\text{C}_{23}\text{H}_{21}\text{NO}_4\text{S}_2$, 439.091202; found, 439.091691.

$(E)$-$2$-($N$-Tosyl-$S$-phenylsulfoximoyl)-1-phenyl-non-3-en-1-one (88)

The title compound (88) was synthesised according to a literature procedure and was found to have identical spectral properties to those reported.$^{123}$

$N$-Tosyl-$S$-phenyl-$S$-(cyclohex-1-enylmethyl)sulfoximine (95)

The title compound (95) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.$^{98}$
(S)-N-Tosyl-S-phenyl-S-(α-methyl-cyclohex-1'-enylmethyl)-sulfoximine (98)

The title compound (98) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.98

(S,S)-N-Tosyl-S-phenyl-S-(α-methyl-cyclohex-1'-enylmethyl)-sulfoximine (98)

The title compound (98) was synthesised according to the literature procedure and was found to have identical spectral properties to those reported.98

7.3.2 Synthesis of the Allylic Sulfone (118)

S-Phenyl-S-(2-propenyl)sulfone (118)
S-Phenyl-S-(2-propenyl)sulfide (119) (16.320g, 0.109mol) was dissolved in CH$_3$CN (100mL) and added to a suspension of Oxone® (180g, 0.293mol). The suspension was allowed to stir O/N and was then filtered. The solution was extracted with DCM (3 x 200mL) and the combined organic layers were dried, filtered and evaporated to a yellow liquid. The liquid was distilled at 150°C/10mmHg to give the title compound (119) (19.400g, 98%). The title compound (119) was found to have identical spectral properties to those reported.$^{153}$

7.3.3 Palladium(0) Catalysed Amination of Allylic Sulfoximines

$N,N$-Dibenzyl-$N$-(2-propenyl)amine (99)

\[
\text{N}^\text{NBn}_2
\]

A general procedure for the intermolecular rearrangement of allylic sulfoximines using dibenzylamine.

Tris(dibenzyliideneacetone)dipalladium(0) (0.016g, 0.017mmol) and triphenylphosphine (0.034g, 0.13mmol) were dissolved in anhydrous THF (10 mL) and stirred at RT for 10 minutes to give a yellow solution of tetrakis(triphenylphosphine)-palladium(0). To this solution was added $N$-tosyl-$S$-phenyl-$S$-(2-propenyl)-sulfoximine (91) (0.099g, 0.31mmol) and dibenzylamine (0.08mL, 0.42mmol). After stirring for 10 minutes the red solution was evaporated to a dark red residue.
Purification of the crude product on a short column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound (99) as a yellow oil (0.049 g, 67%).

\[ ^1H \text{NMR: } \delta 7.1-7.4 \text{ (m,10H,Ar-H); } 5.90(dddd, J = 6.0, 6.0, 10.2, 14.1 Hz, 1H, vinyl H); 5.202 (dd, J = 2.1, 14.1 Hz, 1H, vinyl H); 5.139 (d, J = 2.1, 10.2 Hz, 1H, vinyl H); 3.566 (s, 4H, Bn CH\textsubscript{2}); 3.055 (dt, J = 1.2, 6.3 Hz, 2H, N-CH\textsubscript{2}). \]

\[ ^13C \text{NMR: } \delta 139.7 \text{ (Ar-C); } 136.0 \text{ (vinyl CH); } 128.7 \text{ (Ar-CH); } 128.2 \text{ (Ar-CH); 126.8 (Ar-CH); 117.3 (vinyl CH\textsubscript{2}); 57.8 (Bn CH\textsubscript{2}); 56.3 (N-CH\textsubscript{2}).} \]

MS: ES (+ve) \text{m/z 238.2 ([M+H]+,100).}

HRMS: Calc'd. for C\textsubscript{17}H\textsubscript{19}N, 237.151750; found, 237.150950.

The title compound (99) was also prepared by reacting \textit{N}-tosyl-\textit{S}-phenyl-\textit{S}-(2-propenyl)sulfoximine (91) (0.061g, 0.182mmol) and tetrakis(triphenylphosphine)palladium(0) (0.011g, 9.5umol) in anhydrous THF (10mL) for 15 minutes. The solvent was removed in vacuo and the crude reaction mixture put onto a column of silica gel using ethyl acetate as eluent. The isolated sulfinamide was dissolved in anhydrous THF (10mL). To this was added tetrakis(triphenylphosphine)palladium(0) (0.012g, 10.4\mu mmol) and dibenzylamine (0.1mL, 0.520mmol). The solution was stirred at RT for 10 minutes and the solvent removed in vacuo. The title
compound (99) was not purified, however analysis of the $^1$H NMR spectrum of the crude reaction mixture indicated that it was the sole product.

An attempt was made to prepare the title compound (99) by refluxing S-phenyl-S-(2-propenyl)sulfone (118) (0.198g, 1.09 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.061g, 52.8 µmol) and dibenzylamine (0.3mL, 1.56mmol) in anhydrous THF overnight. The solution was cooled to RT then the solvent was removed in vacuo. Analysis of the $^1$H NMR spectrum of the crude reaction mixture only showed starting material.

$N,N$-Bis(tert-butylxocarbonyl)-$N$-(2-propenyl)amine (100)

\[
\text{\begin{tikzpicture}
\draw (-0.5,0) -- (0.5,0);
\draw (-0.5,0) -- (-0.5,0.5);
\filldraw[fill=white] (-0.5,0) -- (0.5,0) -- (0.5,0.5) -- (-0.5,0.5) -- cycle;
\end{tikzpicture}}_{\text{NBoc}_2}
\]

A general procedure for the palladium(0) catalysed intermolecular rearrangement of allylic sulfoximines using lithiated Boc$_2$NH.

Boc$_2$NH (0.148g, 0.681mmol) was dissolved in anhydrous THF (5mL) and cooled to 0°C. n-BuLi (1.3M in hexanes, 0.79mL, 0.615mmol) was added dropwise and stirring continued for 15 minutes at 0°C followed by stirring at RT until a white precipitate formed. Tris(dibenzylideneacetone)dipalladium(0) (0.014g, 0.015mmol) and triphenylphosphine (0.034g, 0.130mmol) were stirred in anhydrous THF (5mL) to prepare the tetrakis(triphenylphosphine)palladium(0) solution which was then added
to the lithiated Boc₂NH suspension, followed by \( N\)-tosyl-\( S\)-phenyl-\( S\)-(2-propenyl)sulfoximine (91) (0.202g, 0.602mmol). The yellow suspension was stirred at RT for 24 hours before the solvent was removed \textit{in vacuo}. Purification of the crude product on a short column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound (100) as a yellow oil (0.084 g, 54%).

\(^1\)H NMR: \( \delta \)5.847 (dddd, \( J=5.4,5.4,10.2,17.1 \) Hz, 2H, vinyl H); 5.161 (dd, \( J=1.5,17.1 \) Hz, 1H, vinyl H); 5.121 (dd, \( J=1.5,10.2 \) Hz, 1H, vinyl H); 4.175 (dt, \( J=1.5,5.4 \) Hz, 2H, N-CH\(_2\)); 1.501 (s, 18H, carbamate CH\(_3\)).

\(^1^3\)C NMR: \( \delta \)152.1 (carbamate C=O); 133.6 (vinyl CH); 116.0 (vinyl CH\(_2\)); 82.1 (carbamate C); 48.3 (N-CH\(_2\)); 27.9 (carbamate CH\(_3\)).

MS: ES (+ve) \( m/z \) 258.1 ([M+H]\(^+\),18); 202.0 ([((M-t-Bu)+H]\(^+\),24); 145.9 (100).

HRMS of M+H: Calc'd. for C\(_{13}\)H\(_{24}\)NO\(_4\), 258.170534; found, 258.170255.

The title compound (100) was also prepared from 2-(\( N\)-tosyl-\( S\)-phenylsulfoximidoyl)-1-phenylbut-3-en-ol (92) (0.211g, 0.478 mmol), Boc₂NH (0.121g, 0.557mmol), \( n\)-BuLi (1.6M in hexanes, 0.35 mL, 0.560mmol), tris(dibenzylideneacetone)dipalladium(0) (0.011g, 0.012mmol), triphenylphosphine (0.026g, 0.101mmol) as described previously for (100) as a yellow oil (0.032g, 26%) as the major component of a complex mixture of products.
The title compound (100) was also prepared from 2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenylbut-3-en-one (93) (0.198g, 0.450 mmol), Boc₂NH (0.117g, 0.541mmol), n-BuLi (1.6M in hexanes, 0.34 mL, 0.544mmol), tris(dibenzylideneacetone)dipalladium(0) (0.011 g, 0.012mmol), triphenylphosphine (0.025g, 0.095mmol) as described previously for (100) as a yellow oil (0.021g, 18%) as the major component of a complex mixture of products.

(E)-N,N-Dibenzyl-4-amino-1-phenyl-but-2-en-1-ol (101)

The title compound (101) was prepared from (E)-2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenylbut-3-en-ol (92) (0.199g, 0.451 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.012g, 0.013 mmol), triphenylphosphine (0.024g, 0.092mmol) and dibenzylamine (0.1 mL, 0.559mmol) as described previously for (99), as an oil (0.103g, 66%).

¹H NMR: δ7.16-7.36 (m,15H,Ar-H); 5.873 (m,2H,viny l H); 5.110 (d, J=3.9Hz,1H,CH-O); 3.548 (s,4H,Bn CH₂); 3.047 (d, J=4.5Hz,2H,N-CH₂); 2.270 (br s,1H,OH).
\(^{13}\)C NMR: \(\delta 143.0\) (Ar-C); 139.5 (Ar-C); 135.2 (vinyl CH); 129.0 (Ar-CH); 128.4 (Ar-CH); 128.1 (Ar-CH); 127.5 (vinyl CH); 126.8 (Ar-CH); 126.1 (Ar-CH); 74.5 (CH-O); 58.0 (Bn CH\(_2\)); 55.1 (N-CH\(_2\)).

MS: ES (+ve) m/z 344.2 ([M+H]\(^+\),100).

HRMS: Calc'd. for C\(_{24}\)H\(_{25}\)NO, 343.193615; found, 343.192285.

\((E)-N,N\)-Dibenzy1-4-amino-1-phenyl-but-2-en-1-one \((102)\)

The title compound \((102)\) was prepared from \((E)-2-(N\text{-}tosyl-S\text{-phenylsulfoximido}y1)-1\text{-}phenyl\text{-}but\text{-}3\text{-}en\text{-}1\text{-}one \((93)\) (0.195g, 0.444 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.011g, 0.012 mmol), triphenylphosphine (0.023g, 0.088mmol) and dibenzylamine (0.1mL, 0.559mmol) as described previously for \((99)\), as an oil (0.065g, 43%).

\(^1\)H NMR: \(\delta 7.2-7.9\) (m,10H,Ar-H); 7.0-7.1 (m,2H,vinyl H); 3.644 (s,4H,Bn CH\(_2\)); 3.309 (d,\(J=3.6\)Hz,2H,N-CH\(_2\)).
The title compound (102) was also prepared by stirring a solution of (E)-N,N-dibenzyl-4-amino-1-phenyl-but-2-en-1-ol (101) (0.100g, 0.291mmol) and pyridium dichromate (0.146g, 0.388mmol) in anhydrous DCM (10mL) O/N. The solvent was removed in vacuo and the resulting residue taken up in ether. The solution was filtered and the ether removed by evaporation to give a yellow oil. The crude oil was purified on a column of silica gel using 20% ethyl acetate as eluent to give the title compound (102) (0.052g, 53%) as a yellow oil.

The title compound (102) was also prepared by slowly adding Jones reagent (2mL) to a stirred solution of (E)-N,N-dibenzyl-4-amino-1-phenyl-but-2-en-1-ol (101) (0.090g, 0.262mmol) in acetone (50mL). After stirring for 10 minutes, isopropanol was added dropwise to give a green solution, which was then diluted with H₂O (100mL). The solution was extracted with DCM (3 x 100mL) and the combined organic layers were dried, filtered and evaporated to a yellow oil. The crude oil was purified on a column of silica gel using 20% ethyl acetate as eluent to give the title compound (102) (0.088g, 98%) as a yellow oil.
The title compound (103) was prepared from (E)-2-(N-tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88) (0.108g, 0.212mmol), tris(dibenzylideneacetone)dipalladium(0) (0.005g, 5.5 μmol), triphenylphosphine (0.013g, 0.049mmol) and dibenzylamine (0.05mL, 0.26mmol) as described previously for (99), as an oil (0.054g, 62%).

$^1$H NMR: δ7.2-8.0 (m, 15H, Ar-H); 7.090 (dd, $J=6.3, 11.7$ Hz, 1H, vinyl H); 6.879 (d, $J=11.7$ Hz, 1H, vinyl H); 3.674 (dd, $J=10.5, 122.1$ Hz, 4H, Bn CH$_2$); 1.1-1.9 (m, 11H, alkyl H).

$^{13}$C NMR: δ190.3 (ketone C=O); 147.8 (vinyl CH); 139.9 (Ar-C); 137.9 (Ar-C); 132.8 (Ar-CH); 128.6 (Ar-CH); 128.6 (Ar-CH); 128.5 (Ar-CH); 128.3 (Ar-CH); 127.5 (Ar-CH); 126.9 (vinyl CH); 59.5 (N-CH); 53.8 (Bn CH$_2$); 31.7 (alkyl CH$_2$); 31.2 (alkyl CH$_2$); 26.0 (alkyl CH$_2$); 22.6 (alkyl CH$_2$); 14.0 (alkyl CH$_3$).

MS: ES (+ve) m/z 412.4 ([M+H]$^+$, 100).

HRMS of M+H: Calc'd. for C$_{29}$H$_{33}$NO, 412.264040; found, 412.260241.
**N,N-Dibenzyl-N-(cyclohex-1-enyl)methylamine (104)**

The title compound (104) was prepared from N-tosyl-S-phenyl-S-(1-cyclohex-1'-enylmethyl)sulfoximine (95) (0.106g, 0.271mmol), tris(dibenzylideneacetone)dipalladium(0) (0.015g, 0.016mmol), triphenylphosphine (0.032g, 0.122mmol) and dibenzylamine (0.07 mL, 0.364mmol) as described previously for (99), as an oil (0.058g, 73%).

**1H NMR:** δ7.16-7.39 (m,10H,Ar-H); 5.620 (br s,1H,vinyl H); 3.472 (s,4H,Bn CH2); 2.846 (s,2H,N-CH2); 1.9-2.1 (m,4H,cyclic CH2); 1.45-1.65 (m,4H,cyclic CH2).

**13C NMR:** δ140.2 (Ar-C); 136.1 (vinyl C); 128.7 (Ar-CH); 128.1 (Ar-CH); 126.6 (Ar-CH); 124.6 (vinyl CH); 61.5 (N-CH2); 58.0 (Bn CH2); 27.1 (cyclic CH2); 25.3 (cyclic CH2); 22.9 (cyclic CH2); 22.7 (cyclic CH2).

**MS:** ES (+ve) m/z 291.8 ([M+H]+).

**HRMS:** Calc’d. for C_{21}H_{25}N, 291.198688; found, 291.198178.
**N,N-Dibenzyl-N-(α-methyl-cyclohex-1-enyl)methylamine (105)**

![Chemical Structure](image)

The title compound (105) was prepared from N-tosyl-S-phenyl-S-(α-methyl-cyclohex-1-enylethyl)sulfoximine (98) (66:33 mixture of methylated and unmethylated sulfoximine, 0.195g, 0.490mmol), tris(dibenzylideneacetone)-dipalladium(0) (0.026g, 0.028mmol), triphenylphosphine (0.066g, 0.251mmol) and dibenzylamine (0.3mL, 1.56mmol) as described previously for (99), as an oil (44:56 mixture of methylated and unmethylated amine, 0.043g, 19%). The percentage yield of 19% was calculated for the methylated amine (105) by taking into account the amount of unmethylated compound in both the starting material and the product material.

^1H NMR: δ7.15-7.39 (m,10H,Ar-H); 5.552 (br s,1H,viny1 H); 3.543 (dd,J=13.8,107.4Hz,4H,Bn CH2); 3.100 (q,J=6.6Hz,1H,N-CH); 2.446 (m,1H,cyclic H); 1.992 (m,2H,cyclic CH2); 1.751 (m,1H,cyclic H); 1.541 (m,4H,cyclic CH2); 1.076 (d,J=6.6Hz,alkyl CH3).

^13C NMR: δ140.9 (Ar-C); 139.8 (viny1 C); 128.8 (Ar-CH); 128.1 (Ar-CH); 126.5 (Ar-CH); 122.4 (viny1 CH); 57.7 (N-CH); 53.6 (Bn CH2); 27.4 (cyclic CH2); 25.4 (cyclic CH2); 23.1 (cyclic CH2); 22.8 (cyclic CH2); 9.7 (alkyl CH3).
MS: ES (+ve) m/z 306.7 ([M+H]^+,58); 197.8 (Bn₂NH₂^+,100); 109.0 ([M-
Bn₂N]^+,21).

HRMS: Calc’d. for C₂₂H₂₇N, 305.214350; found, 305.212768.

(S)-N,N-Dibenzyl-N-(α-methyl-cyclohex-1-enyl)ethylamine  (S)-(105)

The title compound (S)-(105) was prepared from (S,S)-N-tosyl-S-phenyl-S-(α-
methyl-cyclohex-1-enylethyl)sulfoximine (98) (85:15 mixture of methylated and
unmethylated sulfoximine, 0.278g, 0.687mmol), tris(dibenzylideneacetone)-
dipalladium(0) (0.017g, 0.019mmol), triphenylphosphine (0.043g, 0.164mmol)
and dibenzylamine (0.2mL, 1.04mmol) as described previously for (99), as an oil
(74:26 mixture of methylated and unmethylated amine, 0.124g, 52%) and as one
enantiomer with (S) stereochemistry. The percentage yield of 52% was calculated for
the methylated amine (105) by taking into account the amount of unmethylated
compound in both the starting material and the product material.

[α]²⁷°D = +4.0 (c = 0.9, CHCl₃).

The spectral data was identical to that reported above.
7.3.4 Palladium(0) Catalysed Amination of Allylic Sulfoximines Utilising a Chiral Ligand

*(E)-N,N-Dibenzyl-4-amino-1-phenyl-non-2-en-1-one (103)*

\[
\text{[Pd(\pi-C_3H_5)Cl]_2 (0.0048g, 13\mu mol) and (S)-2-[2-(diphenyl phosphino)phenyl]-4-iso-propyl-3,4-dihydrooxazole (111) (0.025g, 68\mu mol) were dissolved in anhydrous THF (5mL) and allowed to stir at RT for 10 minutes to afford a yellow solution. To this solution was added (E)-2-(A/-tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88) (0.158g, 0.310mmol) in anhydrous THF (10mL) and dibenzylamine (0.07mL, 0.364mmol). The solution was allowed to stir at RT overnight. The solvent was removed *in vacuo* to give a yellow oil. Purification of the crude product on a short column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound as a yellow oil (0.024g, 19%) and recovered starting material (0.123g, 78%).}

\[
[a]^{22}_D = +12.2^\circ \text{ (c = 0.475, CHCl}_3\text{).}
\]
7.3.5 Synthesis of Pyrroles from Allylic Sulfoximines.

\[ \text{N-((S)-\alpha-Methylbenzyl)-5-pentyl-2-phenylpyrrole (115)} \]

\[(E)-2-(N-Tosyl-S-phenylsulfoximidoyl)-1-phenyl-non-3-en-1-one (88)\]

0.180g, 0.353mmol), tetrakis(triphenylphosphine)palladium(0) (0.041g, 0.0355 mmol) and (S)-\alpha-methylbenzylamine (113) (0.07mL, 0.543mmol) were dissolved in anhydrous THF (10mL) and allowed to stir at RT for 120 minutes. Removal of the solvent \textit{in vacuo} gave a yellow oil. Purification of the crude product on a short column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound (115) as a yellow oil (0.074 g, 66%).

\[^1H\text{ NMR: } \delta 7.0-7.35 \text{ (m,10H,Ar-H); } 6.172 \text{ (d,J=3.6Hz,1H,pyrrole H); } 6.031 \text{ (d,J=3.6Hz,1H,pyrrole H); } 5.607 \text{ (q,J=7.2Hz,1H,N-CH); } 2.377 \text{ (ddd,J=6.0,9.3,15.3Hz,1H,one of alkyl CH}_2\text{ next to the pyrrole); } 2.087 \text{ (ddd,J=6.0,9.3,15.3Hz,1H,one of alkyl CH}_2\text{ next to the pyrrole); } 1.839 \text{ (d,J=6.9Hz,3H,Ph-C(-N)-CH}_3\text{); } 1.35-1.6 \text{ (m,2H,alkyl CH}_2\text{); } 1.1-1.2 \text{ (m,4H,alkyl CH}_2\text{); } 0.807 \text{ (t,J=6.9Hz,3H,alkyl CH}_3\text{).} \]
\(^{13}\)C NMR: \(\delta 142.9 \text{ (Ar-C); 135.1 (Ar-C); 134.9 (Ar-C); 134.6 (Ar-C); 129.5 (Ar-CH); 128.4 (Ar-CH); 128.2 (Ar-CH); 126.7 (Ar-CH); 126.7 (Ar-CH); 125.8 (Ar-CH); 108.0 \text{ (pyrrole CH); 106.6 (pyrrole CH); 52.9 (Ph-CH(-N)-C); 31.6 (alkyl CH}_2\text{); 28.4 (alkyl CH}_2\text{); 27.7 (alkyl CH}_2\text{); 22.4 (alkyl CH}_2\text{); 19.7 (Ph-C(-N)-CH}_3\text{); 13.9 (alkyl CH}_3\text{).}\\

MS: ES (+ve) \(m/z\) 318.2 \([\text{M+H}^+],100\); 214.1 \([\text{[(M-PhCHCH}_3\text{)+H}^+],80\); 105.0 \((\text{PhCHCH}_3^+],57\).

HRMS: Calc'd. for \(C_{23}H_{27}N\), 317.214337; found, 317.215007.

7.4 Experimental for Chapter 4

7.4.1 Synthesis of Allylic Sulfoximines (134) and (136)

\(N\)-Benzzyloxycarbonyl-\(S\)-phenyl-\(S\)-(2-propenyl)sulfoximine (134)

\[
\begin{array}{c}
\text{NCbz} \\
\text{Ph}
\end{array}
\]

To a stirred solution of \(S\)-phenyl-\(S\)-(2-propenyl)sulfoximine (39) (2.346g, 12.94mmol) in anhydrous DCM (6mL) was added pyridine (1.3mL, 16.07mmol) and 4-dimethylaminopyridine (0.023g, 0.188mmol). This solution was cooled to 0°C then benzzyloxycarbonyl chloride (2.8mL, 19.6mmol) was added dropwise. The yellow
solution was stirred at RT for 1 hour before being diluted with DCM (20mL). The solution was washed with 10% HCl(aq) (10mL) and saturated NaCl(aq) (10mL). The organic layer was dried, filtered and evaporated to a yellow oil. Purification of the crude product on a column of silica gel using 30% ethyl acetate/hexane as eluent gave the title compound (134) as an oil (2.857g, 70%) which slowly crystallised over time to give a white semi-solid.

$^1$H NMR: $\delta$7.2-8.0 (m,10H,Ar-H); 5.695 (dddd,$J=7.6,7.6,10.0,13.2$Hz, 1H,internal vinyl H); 5.331 (dd,$J=0.8,10.0$Hz,1H,vinyl H); 5.106 (dd,$J=0.8$, 13.2Hz,1H,vinyl H); 5.074 (s,2H,Cbz CH$_2$); 4.159 (2xdd, $J=4.4,7.6$Hz,2H,C=C-CH$_2$).

$^{13}$C NMR: $\delta$158.6 (carbamate C=O); 138.6 (Ar-C); 133.9 (Ar-CH); 128.2 (Ar-CH); 128.1 (Ar-CH); 126.0 (vinyl CH$_2$); 123.5 (vinyl CH); 67.7 (carbamate CH$_2$); 60.2 (C=C-CH$_2$).

MS: ES (+ve) m/z 315.9 ([M+H]$^+$,100); 91.3 (PhCH$_2^+$,8).

HRMS: Calc'd. for C$_{17}$H$_{17}$NO$_3$S, 315.094598; found, 315.094977.
To a stirred solution of \( N\)-benzyloxycarbonyl-\( S\)-phenyl-\( S\)-(2-propenyl)sulfoximine (134) (1.998g, 6.33mmol) in anhydrous THF (20mL) at \(-78^\circ\)C was added \( n\)-BuLi (1.6M in hexanes, 4.7mL, 7.52 mmol) dropwise. The orange solution was stirred for 15 minutes then benzaldehyde (0.7mL, 6.89mmol) was added dropwise to give a slightly paler orange solution. This solution was stirred for 10 minutes before glacial acetic acid (0.4mL, 6.99mmol) was added, followed by saturated NH\(_4\)Cl(aq) (1mL) then H\(_2\)O (10mL). After warming to RT the solution was extracted with DCM (2 x 30mL). The combined organic layers were dried, filtered and evaporated to give a thick yellow oil.

The crude alcohol (135) was dissolved in acetone (100mL) and cooled to 0\(^\circ\)C. Jones reagent (10mL) was slowly added dropwise and the resultant brown solution stirred for 10 minutes. The reaction was quenched by the slow addition of iso-propanol (5mL) to give a green solution. This solution was diluted with H\(_2\)O (50mL) and then extracted with DCM (3 x 100mL). The combined organic layers were dried, filtered and evaporated to a yellow oil. The crude product was purified on a column of silica gel
using 30% ethyl acetate/hexane as eluent to give the title compound (136) as a yellow oil (1.533g, 58%) and as an 71:29 mixture of diastereomers.

Major diastereomer:

\(^1\)H NMR: \(\delta 8.2-7.1\) (m,15H,Ar-H); 7.103 (d,\(J=9.3\)Hz,1H,S-CH); 5.9-5.4 (m,3H,vinyl H); 5.253 (s,2H,carbamate CH\(_2\)).

\(^{13}\)C NMR: \(\delta 190.4\) (ketone C=O); 159.1 (carbamate C=O); 136.2 (vinyl CH); 136-125 (12 aryl carbons); 125.7 (vinyl CH\(_2\)); 69.1 (S-CH); 68.0 (carbamate CH\(_2\)).

Minor diastereomer:

\(^1\)H NMR: \(\delta 8.2-7.1\) (m,15H,Ar-H); 6.507 (d,\(J=8.4\)Hz,1H,S-CH); 5.85-5.5 (m,3H,vinyl H); 5.234 (s,2H,carbamate CH\(_2\)).

\(^{13}\)C NMR: \(\delta 190.5\) (ketone C=O); 158.5 (carbamate C=O); 136.1 (vinyl CH); 136-125 (12 aryl carbons); 125.8 (vinyl CH\(_2\)); 73.3 (S-CH); 67.8 (carbamate CH\(_2\)).

MS: ES (+ve) \(m/z\) 420.1 ([M+H]\(^+\),100); 311.4 ([M-PhCH\(_2\)O]\(^+\),19); 144.1 ([M-PhS(O)COOCH\(_2\)Ph]\(^+\),29).

HRMS: Calc'd. for C\(_{24}\)H\(_{21}\)NO\(_4\)S, 419.120810; found, 419.120126.
7.4.2 Palladium(0) Catalysed Rearrangement of Allylic Sulfoximine

\[ \text{(136)} \]

\((E)-N\text{-Benzyloxycarbonyl-4-amino-1-phenyl-but-2-en-1-one \ (137)}\)

\[
\begin{array}{c}
\text{Cbz} \quad \text{N} \\
\text{Ph} \\
\text{O} \\
\end{array}
\]

The title compound was prepared from 2-(\(N\text{-benzyloxycarbonyl-S-phenylsulfoximidoyl}\))-1-phenyl-but-3-en-1-one \((136)\) (1.533g, 3.65mmol) and tetrakis(triphenylphosphine)palladium(0) (0.193g, 0.167mmol) for 20 minutes, followed by treatment with triethylamine in methanol as described previously for \((86a)\), as a yellow oil (0.667g, 62%).

\(^1\text{H NMR: } \delta 7.3-8.0 \ (m, 10H, Ar-H); 6.7-6.9 \ (m, 2H, vinyl H); 5.131 \ (s, 2H, carbamate CH}_2) \); 4.077 \ (dd, J=1.5, 4.2Hz, 2H, N-CH}_2).\]

\(^{13}\text{C NMR: } \delta 190.1 \ (ketone C=O); 156.2 \ (carbamate C=O); 144.1 \ (vinyl CH); 137.5 \ (Ar-C); 134.9 \ (Ar-C); 132.9 \ (Ar-CH); 131.9 \ (Ar-CH); 128.6 \ (Ar-CH); 128.5 \ (Ar-CH); 128.5 \ (Ar-CH); 124.7 \ (vinyl CH); 68.6 \ (carbamate CH}_2); 42.2 \ (N-CH}_2).\]

MS: ES (+ve) \(m/z\) 296.1 ([M+H]^+, 10); 260.1 (8); 91.0 (PhCH}_2^+, 100).
7.4.3 Attempted Asymmetric Dihydroxylation of (102)

\[ \text{HRMS of M+H: Calc'd for C}_{15}\text{H}_{18}\text{NO}_3, 296.128669; \text{found, 296.127228.} \]

\[ \text{N,N-Dibenzyln-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (124)} \]

\[ \text{N,N-Dibenzyln-4-amino-1-phenyl-but-2-en-1-one (102) (0.120g, 0.406mmol), AD-mix } \alpha \text{ (0.464g), MeSO}_2\text{NH}_2 \text{ (0.043g, 0.452mmol), (DHQD)}_2\text{PHAL (0.012g, 15.4}\mu\text{mol) and K}_2\text{O}_2\text{SO}_4.2\text{H}_2\text{O (0.007g, 18.9}\mu\text{mol) were dissolved in tert-butanol/H}_2\text{O (1:1, 15mL). After stirring at 0°C for 11 days, Na}_2\text{SO}_3 \text{ (0.7g, 5.55mmol) was added and the solution allowed to warm to RT. The solution was extracted with ethyl acetate (3 x 50mL). The combined organic layers were dried, filtered and evaporated to a yellow oil. The crude oil was put on a column of silica gel using ethyl acetate as eluent. None of the products isolated from the column were pure nor could their structures be unequivocably assigned as the title compound (124) from their } ^1\text{H NMR spectra.} \]
7.4.3.1 Attempted Formation of the Diacetate (125)

\[ N,N\text{-Dibenzyl-2,3-acetyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one} \quad (125) \]

A sample of what appeared to be crude \( N,N\text{-dibenzyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one} \) (124) (0.031 g, 0.083 mmol) was dissolved in anhydrous DCM (10 mL). To the solution was added pyridine (0.2 mL, 2.47 mmol) and acetic anhydride (0.1 mL, 1.06 mmol). The solution was left to stir at RT overnight then was diluted with DCM (20 mL) and washed with 10% HCl(aq) (20 mL), H₂O (20 mL) and saturated NaCl(aq) (20 mL). The organic layer was dried, filtered and evaporated to a brown residue. The residue was put on a column of silica gel using initially 5% ethyl acetate/hexane and then 25% ethyl acetate/hexane as eluent. None of the compounds isolated from the column could be unequivocally assigned as the title compound (125) from their \(^1\)H NMR spectra.
7.4.4 Asymmetric Dihydroxylation of Allylic Amine (137)

\[(2R,3S)-N\text{-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one} (138a)\]

\[
\begin{align*}
\text{Cbz} & \quad \text{N} \\
\text{H} & \quad \text{OH} \\
\text{OH} & \quad \text{O} \\
\text{Ph} &
\end{align*}
\]

\[N\text{-Benzyloxycarbonyl-4-amino-1-phenyl-but-2-en-1-one} (137) (0.053g, 0.179mmol), \text{AD-mix } \alpha (0.271g), \text{MeSO}_2\text{NH}_2 (0.036g, 0.378mmol), (\text{DHQ})_2\text{PHAL} (0.007g, 9\mu\text{mol}) \text{ and } K_2\text{OsO}_4.2\text{H}_2\text{O} (0.004g, 0.011mmol) \text{ were dissolved in } \text{tert-butanol/H}_2\text{O (1:1, 12mL). After stirring at } 0^\circ\text{C for 24 hours, } \text{Na}_2\text{SO}_3 (0.4g, 3.18mmol) \text{ was added and the solution allowed to warm to RT. The solution was extracted with ethyl acetate (3 x 50mL). The combined organic layers were dried, filtered and evaporated to a yellow oil. Purification of the crude product on a short column of silica gel using ethyl acetate as eluent gave the title compound (138a) as a yellow oil (0.040g, 67%).}
\]

\[\left[a\right]^{25}_D = +17.3^\circ \text{ (c = 1.3, CHCl}_3).\]

\[^1\text{H NMR: } \delta 7.2-8.1 \text{ (m,10H,Ar-H); 5.410 (br s,1H,NH); 5.114 (s,2H, Cbz CH}_2); 5.063 (d,J=12.9Hz,1H,H2); 4.039 (m,1H,H3); 3.484 (dd,J=6.0, 12.9Hz,1H,one of CH}_2); 3.331 (dd,J=5.1,12.9Hz,1H,one of CH}_2).\]
$^{13}$C NMR: δ199.4 (ketone C=O); 157.1 (carbamate C=O); 136.2 (Ar-C); 134.1 (Ar-CH); 133.3 (Ar-CH); 133.0 (Ar-CH); 128.9 (Ar-CH); 128.5 (Ar-CH); 128.1 (Ar-CH); 74.2 (C(2)H-OH); 71.5 (C(3)H-OH); 66.9 (carbamate CH$_2$); 44.6 (N-CH$_2$).

MS: ES (+ve) m/z 329.8 ([M+H]$^+$,100); 91.2 (PhCH$_2$$^+$,87).

HRMS of M+H: Calc'd for C$_{18}$H$_{20}$NO$_5$, 330.134148; found, 330.133326.

(2S,3R)-N-Benzylloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (138b)

N-Benzylloxycarbonyl-4-amino-1-phenyl-but-2-en-1-one (137) (0.051g, 0.173mmol), AD-mix β (0.276g), MeSO$_2$NH$_2$ (0.037g, 0.389mmol), (DHQD)$_2$PHAL (0.008g, 10μmol) and K$_2$OsO$_4$.2H$_2$O (0.004g, 11μmol) were dissolved in tert-butanol/H$_2$O (1:1, 12mL). After stirring at 0°C for 24 hours, Na$_2$SO$_3$ (0.4g, 3.18mmol) was added and the solution allowed to warm to RT. The solution was extracted with ethyl acetate (3 x 50mL). The combined organic layers were dried, filtered and evaporated to a yellow oil. Purification of the crude product on a short column of silica gel using ethyl acetate as eluent gave the title compound (138b) as a yellow oil (0.042g, 72%).
[α]$^D_{25}$ = -11.3° (c = 3, CHCl₃).

The spectral data was the same as for its enantiomer (138a).

7.4.5 Attempted Cyclisation to Azasugars

7.4.5.1 Attempted Cyclisation of $N,N$-Dibenzyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (124)

1-Phenyl-2,3-dihydroxypyrrolidine (127)

A sample of what appeared to be crude $N,N$-dibenzyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (124) (0.117g, 0.312mmol) was dissolved in methanol (10mL). To this solution was added 10% palladium on carbon (0.126g) and the black suspension was stirred under $H_2(g)$ for 2 days. The suspension was filtered and the solvent removed in vacuo to furnish a brown residue. The $^1$H NMR spectrum of the crude residue did not contain anything that could be unequivocally assigned as the title compound (127).
7.4.5.2 Cyclisation of \( N\)-Benzylxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (138)

1-Phenyl-2,3-dihydroxypyrrolidine (141)

![Chemical Structure](image)

**Method One**

\((2S,3R)\)-\(N\)-Benzylxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (138b) (0.030g, 0.091mmol) was dissolved in methanol (5mL). To this was added 10\% palladium on carbon (0.055g) and the black suspension was stirred under an atmosphere of \( H_2(g) \) overnight. The suspension was filtered and acidified with 3M \( HCl(aq) \) (0.5mL) then stirred for a further hour. The solvent was removed in vacuo and the residue placed on an ion-exchange column (Amberlite IR-120, \( H^+ \)) using firstly 5\% \( HCl(aq) \), then \( H_2O \) (until neutral) and finally 2M \( NH_3(aq) \) as eluent. None of the isolated compounds could unequivocally be assigned as the title compound (141) from their \( ^1H \) NMR spectra.
Method Two

\((2R,3S)-N\text{-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one}\) (138a) (0.042g, 0.128mmol) was dissolved in 4.4%(v/v) formic acid in methanol (5mL). To this was added 10% palladium on carbon (0.040g) and the suspension was stirred for 3 days. The suspension was filtered and the solvent removed \textit{in vacuo}. The \(^1\)H NMR spectrum showed only starting material (138a).

Method Three

\((2S,3R)-N\text{-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one}\) (138a) (0.042g, 0.128mmol) was dissolved in methanol (5mL). To this was added 10% palladium on carbon (0.049g) and ammonium formate (0.081g, 1.28mmol). The mixture was stirred for 24 hours and then filtered and the solvent removed \textit{in vacuo}. The \(^1\)H NMR spectrum showed only starting material (138a).

Method Four

\((2S,3R)-N\text{-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one}\) (138b) (0.038g, 0.115mmol) was dissolved in methanol (5mL). To this was added 10% palladium on carbon (0.040g) and 1,4-cyclohexadiene (0.11mL, 1.16mmol). The suspension was stirred for 24 hours and then filtered and the solvent removed \textit{in vacuo} to give a yellow residue. The residue was put on a column of silica gel using
firstly 30% ethyl acetate/hexane and finally ethyl acetate as eluent. None of the isolated compounds could be unequivocably assigned as the title compound (141) from their $^1$H NMR spectra.

*Method Five*

$(2R,3S)$-N-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (138a) (0.036g, 0.109mmol) was dissolved in methanol (5mL). To this was added palladium black (0.040g) and the suspension was stirred under an atmosphere of H$_2$(g) for 24 hours. The suspension was then filtered and the solvent removed *in vacuo* to give a yellow residue. The residue was put on a column of silica gel using firstly 30% ethyl acetate/hexane and finally ethyl acetate as eluent. None of the isolated compounds could unequivocably be assigned as the title compound (141) from their $^1$H NMR spectra.

*Method Six*

$(2S,3R)$-N-Benzyloxycarbonyl-4-amino-2,3-dihydroxy-1-phenyl-butan-1-one (138b) (0.056g, 0.170mmol) was dissolved in methanol (5mL). To this was added palladium black (0.062g) and 1,4-cyclohexadiene (0.16mL, 1.70mmol). The suspension was stirred for 24 hours and then filtered and the solvent removed *in vacuo* to give a yellow residue. The residue was put on a column of silica gel using firstly 30% ethyl acetate/hexane and finally ethyl acetate as eluent. None of the isolated
compounds could unequivocally be assigned as the title compound (141) from their $^1$H NMR spectra.

7.5 Experimental for Chapter 5

7.5.1 Synthesis of Alkene (146)

$$(2R,3R,4S)$-1,4-$O$-Dibenzoyl-2,3-$O$-isopropylidene-5-hexen-1,2,3,4-tetrol (146)

$(-)$-$2,3-O$-Isopropylidene-$D$-erythronolactone (143) (1.997g, 12.6 mmol) was dissolved in anhydrous DCM (40mL) and cooled to -78°C. To this solution was added DIBAL (1M in DCM, 15.2mL, 15.2mmol) in a dropwise fashion. The solution was allowed to stir for 2 hours before quenching with methanol (4mL) and saturated NaCl(aq) (2mL). The solution was allowed to warm to RT then just enough 2M H$_2$SO$_4$ was added to make the solution acidic. The organic layer was separated then dried, filtered and evaporated to a light yellow oil.

The crude lactol (142) was dissolved in anhydrous THF (40mL) and cooled to 0°C. Vinyl magnesium bromide (1M in THF, 32mL, 32mmol) was added dropwise and the
solution allowed to stir at 0°C for 5 hours. Saturated NH₄Cl(aq) (10mL) was added followed by H₂O (20mL). The solution was extracted with ethyl acetate (2 x 100mL) and the organic layers combined, dried, filtered and evaporated to a yellow oil.

The crude reaction mixture was dissolved in anhydrous DCM (10mL) and cooled to 0°C. To the solution were added 4-dimethylaminopyridine (0.010g, 0.082mmol), pyridine (2.5mL, 30.9mmol) and benzoyl chloride (2.5mL, 21.5mmol). The solution was left to stir at RT for 4 hours and then diluted with DCM (100mL). The solution was washed with H₂O (20mL), 10% HCl(aq) (20mL) and saturated NaCl(aq) (20mL). The organic layer was dried, filtered and evaporated to a yellow oil. Purification of the crude product on a column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound (146) as a yellow oil (2.574 g, 51%).

[α]²⁴_D = -7.5° (c = 0.63, CHCl₃).

¹H NMR: δ 7.3-8.1 (m, 10H, Ar-H); 6.044 (ddd, J=6.0, 10.5, 17.1Hz, 1H, H₂); 5.733 (dd, J=6.0, 7.2Hz, 1H, H₃); 5.439 (dt, J=1.2, 17.1Hz, 1H, H₁); 5.367 (dt, J=1.2, 10.5Hz, 1H, H₁); 4.57-4.67 (m, 2H, one of H₆ plus H₅); 4.488 (dd, J=5.7, 7.2Hz, 1H, H₄); 4.402 (dd, J=8.1, 13.2Hz, 1H, one of H₆); 1.503 (s, 3H, isopropylidene CH₃); 1.418 (s, 3H, isopropylidene CH₃).

¹³C NMR: δ 166.2 (ester C=O); 165.0 (ester C=O); 133.2 (Ar-CH); 133.2 (Ar-CH); 133.0 (vinyl CH); 130.5 (Ar-C); 130.1 (Ar-C); 129.7 (Ar-CH); 129.6 (Ar-CH);
128.4 (Ar-CH); 128.2 (Ar-CH); 119.0 (vinyl CH2); 109.4 (isopropylidene C);
77.6 (C4-H); 75.4 (C5-H); 72.6 (C3-H); 63.1 (C6-H2); 27.6 (isopropylidene CH3); 25.4 (isopropylidene CH3).

MS: ES (+ve) m/z 396.8 ([M+H]+, 19); 338.9 ([M-C3H5O]+, 98); 275.0 ([M-PhC(=O)]+, 86); 217.0 (86); 152.7 (87); 105.0 ([PhC(=O)]+, 100).
HRMS of M+H: Calc'd for C23H25O6, 397.165114; found, 397.165286.

7.5.2 Synthesis of Allylic Amines (148) and (150)

(4E)-(2R,3S)-6,N,N-Bis(tert-butyloxycarbonyl)-1-O-benzoyl-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (148)

Boc₂NH (1.321g, 6.08mmol) was dissolved in anhydrous THF (20mL) and cooled to 0°C. n-BuLi (1.5M in hexanes, 3.7mL, 5.55mmol) was added dropwise and the solution was stirred at 0°C for 30 minutes then warmed to RT and allowed to stir until a white precipitate appeared.
Tris(dibenzylideneacetone)dipalladium(0) (0.116 g, 0.127 mmol) and 1,2-bis(diphenylphosphino)ethane (0.150 g, 0.376 mmol) were dissolved in anhydrous THF (10 mL) and stirred for 30 minutes at RT. This solution was then added to the lithiated Boc₂NH solution, followed by (2R,3R,4S)-1,4-O-dibenzoyl-2,3-O-isopropylidene-5-hexen-1,2,3,4-tetrol (146) (2.001 g, 5.05 mmol) in anhydrous THF (10 mL). The yellow suspension was warmed to 50°C and left to stir for 24 hours.

The solution was cooled to RT then diluted with ether (100 mL). The ethereal solution was washed with H₂O (20 mL), saturated NaHSO₃(aq) (20 mL) and saturated NaCl(aq) (20 mL). The organic layer was then dried, filtered and evaporated to a yellow oil. Purification of the crude product on a column of silica gel using 5% ethyl acetate/hexane as eluent gave the title compound (148) as a yellow oil (1.716 g, 69%).

\[ \alpha \]₂⁵° = +13.3 (c = 2.1, CHCl₃).

¹H NMR: 8 7.4-8.1 (m, 5H, Ar-H); 5.908 (dt, J=6,15.3 Hz, 1H, H2); 5.716 (dd, J=7.2, 15.3 Hz, 1H, H3); 4.735 (t, J=6.9 Hz, 1H, H4); 4.474 (ddd, J=4.2, 6.9, 6.9 Hz, 1H, H5); 4.387 (dd, J=4.2, 11.4 Hz, 1H, one of H6); 4.231 (dd, J=6.9, 11.4 Hz, 1H, one of H6); 4.177 (d, J=6 Hz, 2H, H1); 1.506 (s, 3H, isopropylidene CH₃); 1.484 (s, 18H, carbamate CH₃); 1.422 (s, 3H, isopropylidene CH₃).
$^{13}$C NMR: δ 166.2 (ester C=O); 152.2 (carbamate C=O); 133.0 (Ar-CH); 132.0 (Ar-C); 130.4 (vinyl CH); 129.7 (Ar-CH); 128.3 (Ar-CH); 127.4 (vinyl CH); 109.2 (isopropylidene C); 82.5 (C4-H); 81.9 (carbamate C); 75.9 (C5-H); 63.8 (C6-H$_2$); 47.2 (C1-H$_2$); 28.0 (carbamate CH$_3$); 27.7 (isopropylidene CH$_3$); 25.4 (isopropylidene CH$_3$).

MS: ES (+ve) m/z 514.2 ([M+Na]$^+$, 68); 457.2 (45); 414.1 (17); 278.0 (21); 240.0 (100); 183.9 (35); 127.8 (20); 105.8 (22).

HRMS of M+H: Calc'd for C$_{26}$H$_{38}$N$_2$O$_8$, 492.259743; found, 492.259024.

(4E)-(2R,3S)-6-$\gamma$-/V,./Bis(tert-butyloxy carbonyl)-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (150)

(4E)-(2R,3S)-6-$\gamma$-/V,./Bis(tert-butyloxy carbonyl)-1-O-benzoyl-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (148) (1.883g, 3.83mmol) was dissolved in 1%(w/v) NaOH in methanol (15.4mL, 3.85mmol) and allowed to stir at RT for 60 minutes. The solvent was removed in vacuo and the residue was taken up in H$_2$O (20mL) and DCM (50mL). The organic layer was separated then dried, filtered and evaporated to a yellow oil. Purification of the crude product on a column of silica
gel using initially 5% ethyl acetate/hexane and finally ethyl acetate as eluent gave the title compound (150) as a yellow oil (1.232 g, 83%).

\[ \alpha \]_{D}^{19} = +3.13^\circ \ (c = 8.8, \ \text{methanol})..

$^1$H NMR: \( \delta 5.852 \ \text{(dt,} J=6.0,15.3,1\text{H, vinyl H)}; \ 5.672 \ \text{(dd,} J=6.9,15.3\text{Hz, 1H, vinyl H)}; \ 4.680 \ \text{(dd,} J=6.9,6.9\text{Hz, 1H, H4)}; \ 4.240 \ \text{(dd,} J=6.9,12.3\text{Hz, 1H, H5)}; \ 4.194 \ \text{(d,} J=6.0\text{Hz, 2H, H1)}; \ 3.584 \ \text{(dd,} J=6.3,11.7\text{Hz, 1H, one of H6)}; \ 3.524 \ \text{(dd,} J=5.7,11.7\text{Hz, 1H, one of H6)}; \ 1.483 \ \text{(s, 18H, carbamate CH}_3\text{); 1.442 \ \text{(s, 3H, isopropylidene CH}_3\text{); 1.375 \ \text{(s, 3H, isopropylidene CH}_3\text{).}

$^{13}$C NMR: \( \delta 152.3 \ \text{(carbamate C=O)}; \ 129.1 \ \text{(vinyl CH)}; \ 127.1 \ \text{(vinyl CH)}; \ 108.5 \ \text{(isopropylidene C)}; \ 82.6 \ \text{(C4-H)}; \ 81.7 \ \text{(C5-H)}; \ 76.8 \ \text{(carbamate C)}; \ 61.4 \ \text{(C6-H}_2\text{)}; \ 47.3 \ \text{(C1-H}_2\text{)}; \ 28.1 \ \text{(carbamate CH}_3\text{); 27.8 \ \text{(isopropylidene CH}_3\text{); 25.2 \ \text{(isopropylidene CH}_3\text{).}

MS: ES (+ve) \( m/z \ 388.1 \ \text{([M+H]}^+\text{, 49)}; \ 332.2 \ \text{([M-t-Bu]}^+\text{, 77)}; \ 217.9 \ \text{(Boc}_2\text{N}^+,100).

HRMS: Calc'd for C$_{19}$H$_{33}$NO$_7$, 387.225684; found, 387.225987.
7.5.3 Asymmetric Dihydroxylation of (148) and (150)

3-N-(tert-Butyloxy carbonyl)-5-[4'-O-benzoyl-2',3'-O-isopropylidene-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (149)

(4E)-(2R,3S)-6-N,N-Bis(tert-butyloxy carbonyl)-1-O-benzoyl-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (148) (0.262 g, 0.533 mmol).

AD-mix α (0.732 g), CH₃SO₂NH₂ (0.095 g, 0.999 mmol), (DHQ)₂PHAL (0.010 g, 0.0128 mmol) and K₂OsO₄.2H₂O (0.005 g, 0.0136 mmol) were dissolved in tert-butanol/H₂O (1:1, 12 mL). This solution was stirred at 0°C for 24 hours then Na₂S₀₃ (0.4 g, 3.18 mmol) was added. The solution was warmed to RT before being extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried, filtered and evaporated to a yellow oil. Purification of the crude compound on a column of silica gel using 30% ethyl acetate/hexane as eluent to give two diastereomers in a 72:28 ratio.
The first diastereomer (149a) was a slowly crystallising white semi-solid (0.106g, 44%) with (1'S,2'R,3'R,5'R) stereochemistry.

\[
\text{BzO} \quad \text{HO} \quad ^2 \quad ^3 \quad ^4 \quad ^1 \quad ^2 \quad ^3 \quad ^4
\]

\[
\begin{align*}
\text{H NMR: } & \delta 7.4-8.1 \text{ (m,5H,Ar-H)}; \quad 4.808 \text{ (td,} J=2.4,6.0\text{Hz,1H,H5)}; \quad 4.712 \\
& (dd, J=3.0,9.0\text{Hz,1H,one of H4')}; \quad 4.615 \text{ (td,} J=3.0,4.8\text{Hz,1H,H3'}); \quad 4.467 \\
& (dd, J=4.8,9.0\text{Hz,1H,one of H4')}; \quad 4.375 \text{ (dd,} J=4.8,7.5\text{Hz,1H,H2')}; \quad 3.981 \\
& (d,J=6Hz,2H,H4); \quad 3.767 \text{ (m,1H,H1')}; \quad (d,J=6.3Hz,1H,OH); \quad 1.512 \text{ (s,9H,carbamate CH}_3); \quad 1.494 \text{ (s,3H,isopropylidene CH}_3); \quad 1.452 \text{ (s,3H, isopropylidene CH}_3). \\
\end{align*}
\]

\[
\begin{align*}
\text{C NMR: } & \delta 166.5 \text{ (ester C=O)}; \quad 152.1 \text{ (carbamate C=O)}; \quad 149.3 \text{ (oxazolidone C=O)}; \\
& 133.1 \text{ (Ar-CH)}; \quad 129.8 \text{ (Ar-C)}; \quad 129.7 \text{ (Ar-CH)}; \quad 128.4 \text{ (Ar-CH)}; \quad 109.5 \\
& (isopropylidene C); \quad 83.9 \text{ (carbamate C)}; \quad 75.4 \text{ (C2'-H)}; \quad 75.3 \text{ (C3'-H)}; \quad 73.0 \text{ (C1'-H)}; \\
& 69.8 \text{ (C5-H)}; \quad 63.6 \text{ (C4'-H2)}; \quad 45.0 \text{ (C4-H2)}; \quad 27.9 \text{ (carbamate CH}_3); \quad 27.6 \\
& (isopropylidene CH}_3); \quad 25.3 \text{ (isopropylidene CH}_3). \\
\end{align*}
\]

MS: ES (+ve) m/z 474.0 ([M+Na]+, 100); 374.0 ([M-Ph]+,88); 352.0 ([M-\text{Boc}+\text{H}]+,59); 294.0 (41).

HRMS: Calc'd for C22H29NO9, 452.192057; found, 452.192400.
The second diastereomer (149b) was a yellow oil (0.041 g, 17%) with 
(1'R,2'R,3'R,5S) stereochemistry.

\[
\begin{aligned}
\text{1H NMR: } & \delta 7.4-8.2 \text{ (m,5H,Ar-H); } 4.794 \text{ (dd,} J=2.4,8.7 \text{Hz,1H,H3'); } 4.570 \\
& \text{ (m,2H,H2'+one of H4'); } 4.398 \text{ (dd,} J=5.4,8.7 \text{Hz,1H,one of H4'); } 4.284 \\
& \text{ (dd,} J=3.1,5.1 \text{Hz,1H,H1'); } 3.623 \text{ (dd,} J=3.1,5.4 \text{Hz,1H,H5); } 3.120 \text{ (dd,} \\
& J=5.4,7.5 \text{Hz,2H,H4); } 1.497 \text{ (s,9H,carbamate CH3); } 1.418 \text{ (s,3H,isopropylidene CH3); } 1.382 \\
& \text{(s,3H, isopropylidene CH3).}
\end{aligned}
\]

\[
\begin{aligned}
\text{13C NMR: } & \delta 166.3 \text{ (ester C=O); } 153.5 \text{ (carbamate C=O); } 132.8 \text{ (aryl CH); } 129.9 \\
& \text{(aryl C); } 129.6 \text{ (aryl CH); } 128.2 \text{ (aryl CH); } 108.9 \text{ (isopropylidene C); } 83.3 \\
& \text{(carbamate C); } 75.5 \text{ (C2'-H); } 75.0 \text{ (C3'-H); } 69.1 \text{ (C1'-H); } 68.8 \text{ (C5-H); } 63.6 \\
& \text{(C4'-H2); } 48.5 \text{ (C4-H2); } 27.8 \text{ (carbamate CH3); } 27.7 \text{ (isopropylidene CH3); } 25.4 \\
& \text{(isopropylidene CH3).}
\end{aligned}
\]

\[
\begin{aligned}
\text{MS: ES (+ve) } m/z & \text{ 474.0 ([M+Na]^+, 100); } 374.0 \text{ ([M-Ph]^+,69); } 352.0 \text{ ([M-} \\
&Boc)+H]^+,74); } 308.0 \text{ (28); } 294.0 \text{ (22); } 104.8 \text{ (19).}
\end{aligned}
\]

HRMS: Calc'd for C_{22}H_{29}NO_{9}, 452.192057; found, 452.192295.
The title compound (149) was also prepared in a diastereomeric ratio of 46:54 from (4E)-(2R,3S)-6-N,N-bis(tert-butyloxycarbonyl)-1-O-benzoyl-2,3-O-isopropylidene-6-aminohex-4-en-1,2,3-triol (148) (0.303g, 0.616mmol), AD-mix β (0.849g), CH₃SO₂NH₂ (0.112g, 1.18mmol), (DHQD)₂PHAL (0.010g, 0.0128mmol) and K₂OsO₄·2H₂O (0.005g, 0.0136mmol) dissolved in tert-butanol/H₂O (1:1, 12mL) and stirred at 0°C for 24 hours. The (VS,2'R,3'R,5R) diastereomer was again a slowly crystallising semi-solid (0.084g, 30%) and the (1'R,2'R,3'R,5S) diastereomer was again a yellow oil (0.099g, 36%).

The spectral data of both isomers were identical to that recorded previously.

The title compound (149) was also prepared in a diastereomeric ratio of 0:100. To a solution of (4E)-(2R,3S)-6-N,N-bis(tert-butyloxycarbonyl)-1-O-benzoyl-2,3-O-isopropylidene-6-aminohex-4-en-1,2,3-triol (148) (0.990g, 2.01mmol) in tert-butanol/H₂O (1:1, 15mL) was added K₂OsO₄·2H₂O (0.036g, 0.0977mmol) and N-methylmorpholine-N-oxide (0.725g, 6.19mmol). The solution was allowed to stir at 0°C for 24 hours. Na₂SO₃ (1.2g, 9.54mmol) was added to the solution which was then allowed to warm to RT. The solution was extracted with DCM (3 x 50mL) and the organic layers were combined then dried, filtered and evaporated. Purification of the crude product on a column of silica gel using 30% ethyl acetate/hexane gave only the (1'R,2'R,3'R,5S) diastereomer (149b) as a yellow oil (0.435g, 48%).

The spectral data was identical to that recorded previously.
The title compound (149) was also prepared in a diastereomeric ratio of 100:0. To a stirred solution of (1'S,2'R,3'R,5R)-3-N-(tert-butyloxy carbonyl)-5-[2',3'-O-isopropylidene-1',2',3',4'-tetra-hydroxybutyl]oxazolid-2-one (151) (0.066g, 0.190mmol) in anhydrous DCM (1mL) was added pyridine (0.035mL, 0.433mmol), 4-dimethylaminopyridine (~0.002g, 16.4umol) and benzoyl chloride (0.035mL, 0.302mmol). The solution was stirred for 30 minutes then diluted with DCM (20mL) and washed with 5% HCl(aq) (5mL). The organic layer was dried, filtered and evaporated to a yellow oil. The crude product was not purified, however inspection of the $^1$H NMR spectrum showed only (1'S,2'R,3'R,5R)-N-(tert-butyloxycarbonyl)-5-[4'-O-benzoyl-2',3'-O-isopropylidene-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (149a).

(1'S,2'R,3'R,5R)-3-N-(tert-Butyloxy carbonyl)-5-[2',3'-O-isopropylidene-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (151)
12mL). This solution was stirred at 0°C for 24 hours then Na₂SO₃ (1.2g, 9.54mmol) was added. The solution was warmed to RT before being extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with saturated NaCl(aq) (20mL) then dried, filtered and evaporated to a yellow oil. Purification of the crude compound on a short column of silica gel using initially 10% ethyl acetate/hexane and finally 10% methanol/ethyl acetate as eluent gave one diastereomer with the (1'S,2'R,3'R,5'R) stereochemistry as a yellow oil (0.689g, 85%).

\[ \alpha^21_D = -15.1^\circ \] (c = 8.5, methanol).

\( ^1H \) NMR: \( \delta 4.796 \ (t,J=7.2Hz,1H,H3'); 4.365 \ (m,2H,H1'+H5); 4.266 \ (dd,J=5.7,9.6Hz,1H,H2'); 3.990 \ (d,J=7.8Hz,2H,H4); 3.803 \ (m,1H,H1'); 1.509 \ (s,9H,carbamate CH₃); 1.478 \ (s,3H,isopropylidene CH₃); 1.352 \ (s,3H, isopropylidene CH₃).

\( ^13C \) NMR: \( \delta 152.5 \) (carbamate C=O); 149.5 (oxazolidone C=O); 108.7 (isopropylidene C); 83.8 (carbamate C); 76.8 (C2'-H); 75.7 (C3'-H); 72.8 (C1'-H); 69.7 (C5'-H); 60.4 (C4'-H); 45.1 (C4-H₂); 27.9 (carbamate CH₃); 27.7 (isopropylidene CH₃); 25.1 (isopropylidene CH₃).

MS: m/z 370.4 ([M+Na]^+,100); 248.4 ([M-Boc]+H]^+,89); 190.2 (55).

HRMS: Calc'd. for C₁₅H₂₅NO₈, 347.158001; found, 347.157684.
The title compound (151) could also be prepared from (4E)-(2R,3S)-6-N,N-bis(tert-butyloxy carbonyl)-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (150) (0.102g, 0.170mmol), AD-mix α (0.396g), CH₃SO₂NH₂ (0.054g, 0.568mmol), (DHQ)₂PHAL (0.009g, 11.6μmol) and K₂OsO₄·2H₂O (0.006g, 16.3μmol) in tert-butanol/H₂O (1:1,6mL) as described previously for (151) as an oil (0.066g, 72%).

The spectral data was identical to that recorded previously.

7.5.4: Conversion of Alcohols into Sulfonates

(1'S,2'R,3'R,5R)-3-N-(tert-Butyloxy carbonyl)-5-[1',4'-bis-(methanesulfonyl)-2',3'-O-isopropylidene-1',2',3',4'-tetra-hydroxybutyl]-oxazolid-2-one (154)
A general procedure for the synthesis of mesylates.

(1'S,2'R,3'R,5'R)-3-N-(tert-Butyloxycarbonyl)-5-[2',3'-O-isopropylidene-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (151) (0.140g, 0.403mmol) was dissolved in anhydrous DCM (2mL) and cooled to 0°C. To this solution was added triethylamine (0.2mL, 1.43mmol) and methanesulfonylchloride (0.1 mL, 1.29mmol) in a dropwise fashion. The cloudy yellow solution was stirred at 0°C for 30 minutes and then diluted with DCM (20mL). The solution was washed with H₂O (10mL), 5% HCl(aq) (10mL), 10% NaHCO₃(aq) (10mL) and saturated NaCl(aq) (10mL). The organic layer was dried, filtered and evaporated to a yellow oil. When purification was attempted on a column of silica gel decomposition occurred and so the title compound (154) was used without purification.

(1'S,2'R,3'R,5'R)-3-N-(tert-Butyloxycarbonyl)-5-[2',3'-O-isopropylidene-1'-O-methanesulfonyl-4'-O-toluenesulfonyl-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (161)
A general procedure for the synthesis of tosylates.

(1'S,2'R,3'R,5'R)-3-N-(tert-Butyloxycarbonyl)-5-[2',3'-O-isopropylidene-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one (151) (0.099g, 0.285mmol) was dissolved in anhydrous DCM (0.5mL). To this solution was added triethylamine (0.2mL, 1.43mmol) and toluenesulfonylchloride (0.145g, 0.761mmol). The solution was stirred at RT overnight and then diluted with DCM (10mL). The solution was washed with H₂O (5mL), 5% HCl(aq) (5mL) and saturated NaCl(aq) (5mL). The organic layer was dried, filtered and evaporated to a yellow oil. Analysis of the ¹H NMR spectrum indicated the compound was monotosylated.

The title compound (161) was prepared from the crude monotosylate prepared above, triethylamine (0.2mL, 1.43mmol) and methanesulfonylchloride (0.1mL, 1.29mmol), as described previously for (154), as a yellow oil. When purification was attempted on a column of silica gel decomposition occurred, and so the title compound (161) was used without purification.

(4E)-(2R,3S)-6-N,N-Bis(tert-butyloxycarbonyl)-1-O-toluenesulfonyl-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (166)
The title compound (166) was prepared from (4E)-(2R,3S)-6-N,N-bis(tert-butyloxy carbonyl)-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (150) (0.506g, 1.31mmol), pyridine (0.3mL, 3.71mmol) and tolenesulfonyl chloride (0.264g, 1.38mmol) as described previously for (161). The crude product was purified on a column of silica gel using 30% ethyl acetate/hexane as eluent to give the title compound (166) as a yellow oil (0.390g, 55%).

$^1$H NMR: 87.800 (d, J=8.4Hz, 2H, tosyl Ar-H); 7.350 (d, J=8.4Hz, 2H, tosyl Ar-H); 5.836 (dt, J=6.0, 15.3Hz, 1H, vinyl H3); 5.506 (dd, J=7.2, 15.6Hz, 1H, vinyl H2); 4.629 (dd, J=7.2, 7.2Hz, 1H, H4); 4.315 (ddd, J=4.5, 7.2, 7.2Hz, 1H, H5); 4.148 (d, J=5.7Hz, 2H, H1); 4.020 (dd, J=4.5, 10.5Hz, 1H, one of H6); 3.894 (dd, J=7.2, 10.5Hz, 1H, one of H6); 2.449 (s, 3H, tosyl CH$_3$); 1.495 (s, 18H, carbamate CH$_3$); 1.366 (s, 3H, isopropylidene CH$_3$); 1.315 (s, 3H, isopropylidene CH$_3$).

$^{13}$C NMR: 8152.2 (carbamate C=O); 144.8 (Ar-C); 133.0 (Ar-C); 130.8 (vinyl CH); 129.8 (Ar-CH); 128.0 (Ar-CH); 109.5 (isopropylidene C); 82.5 (C4-H); 82.0 (carbamate C); 75.5 (C5-H); 68.7 (C6-H$_2$); 47.2 (C1-H$_2$); 28.1 (carbamate CH$_3$); 27.6 (isopropylidene CH$_3$); 25.3 (isopropylidene CH$_3$).

MS: ES (+ve) m/z 541.6 (M$^+$, 77); 391.6 (33); 217.9 (Boc$_2$N$^+$, 100); 159 (29).

HRMS: Calc'd for C$_{26}$H$_{39}$NO$_9$S, 541.236223; found, 541.236970.
7.5.5 Attempted Cyclisation of Bis(sulfonates)

\[(2S,3S,4R,5'R)-1'-N-Benzyl-3'-N'-tert-butyloxycarbonyl-3,4-O-isopropylidene-2-oxazolid-2'-onyl-3,4-dihydroxypyrrolidine \ (155)\]

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{Bn} \\
\text{O} \\
\text{N=O} \\
\end{array}
\]

Method One

The crude \((1'S,2'R,3'R,5R)-3'-N-(\text{tert-butyloxycarbonyl})-3-[1',4'-O-bis-(\text{methanesulfonyl})-2',3'-O-isopropylidene-1',2',3',4'-tetra-hydroxybutyl]-\)

oxazolid-2-one \((154)\) \((0.126g, 0.250\text{mmol})\) was dissolved in dry toluene \((1\text{mL})\). To this was added benzylamine \((0.1\text{mL}, 0.915\text{mmol})\) and the solution was heated to reflux and left to stir for 24 hours. The solution was cooled to RT and the solvent removed \emph{in vacuo}. The brown residue was placed on a column of silica gel using 10% ethyl acetate as eluent. However none of the fractions isolated could have their structures unequivocally assigned as that of the title compound \((155)\) from their \(^1\text{H}\) NMR spectra.
Method 2

The crude \((1'S,2'R,3'R,5'R)-3-N-(\text{tert-butyloxy carbonyl})-5-[2',3'-O-isopropylidene-1'-O-methanesulfonyl-4'-O-toluenesulfonyl-1',2',3',4'-tetrahydroxybutyl]oxazolid-2-one\) (161) (0.112g, 0.193mmol) was dissolved in benzylamine (1mL, 9.15mmol) and left to stir at RT for 2 days. The solvent removed \textit{in vacuo} and the brown residue was placed on a column of silica gel using 10% ethyl acetate as eluent. However none of the fractions isolated could have their structures unequivocally assigned as that of the title compound (155) from their \(^1\text{H}\) NMR spectra.

\((2S,3S,4R,5'R)-1,3'-\text{N,N'-Di(tert-butyloxy carbonyl)}-2,3'-O-isopropylidene-2-(oxazolid-2'-onyl)-2,3-dihydroxypyrrolidine\) (156)

\textit{tert}-Butyl carbamate (0.033g, 0.282mmol) and sodium hydride (60% in oil, 0.020g, 0.522mmol) were added to anhydrous DMF (2mL) and stirred until foaming ceased. To this was added crude \((1'S,2'R,3'R,5'R)-3-N-(\text{tert-butyloxy carbonyl})-5-[1',4'-O-bis-(methanesulfonyl)-2',3'-O-isopropylidene-1',2',3',4'-tetra-}
hydroxybutyl]oxazolid-2-one \((154)\) \((0.105\text{g}, 0.209\text{mmol})\) and the solution allowed to stir at RT for 24 hours. The solution was diluted with \(\text{H}_2\text{O} (10\text{mL})\) then extracted with diethyl ether \((3 \times 10\text{mL})\). The combined ethereal extracts were washed with saturated \(\text{NaCl(aq)} (10\text{mL})\) then dried, filtered and the solvent removed \textit{in vacuo} to give a brown oil. The crude mixture was put on a column of silica gel using 10\% ethyl acetate/hexane as eluent. However none of the fractions isolated could have their structures unequivocably assigned as that of the title compound \((156)\) from their \(^1\text{H}\) NMR spectra.

7.5.6 Attempted Formation of Azides

\((1'S,2'R,3'R,5R)-3-N-(\text{tert-Butyloxycarbonyl})-5-[2',3'-O-isopropylidene-4'-azido-1'2',3'-trihydroxybutyl]oxazolid-2-one\) \((162)\)

\((1'S,2'R,3'R,5R)-3-N-(\text{tert-Butyloxycarbonyl})-5-[2',3'-O-isopropylidene-1'2',3'-trihydroxybutyl]oxazolid-2-one\) \((151)\) \((0.151\text{g}, 0.435\text{mmol})\) was dissolved in anhydrous DMF \((2\text{mL})\). To this solution was added lithium azide \((0.105\text{g}, 2.14\text{mmol})\), triphenylphosphine \((0.118\text{g}, 0.451\text{mmol})\) and carbon tetrabromide
(0.152g, 0.458mmol) and then allowed to stir at RT for 24 hours. The solution was diluted with H₂O (10mL) and then extracted with ether (3 x 20mL). The combined ethereal extracts were washed with saturated NaCl(aq) (10mL) and then dried, filtered and the solvent removed in vacuo to furnish a yellow oil. The ¹H NMR spectrum showed only starting material.

(4E)-(2R,3S)-6-N,N-Bis(tert-butyloxycarbonyl)-2,3-O-isopropylidene-6-amino-1-azido-hex-4-en-2,3-diol (164)

Method One

An attempt to prepare the title compound (164) from (4E)-(2R,3S)-6-N,N-bis(tert-butyloxycarbonyl)-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (150) (0.040g, 0.103mmol), lithium azide (0.026g, 0.531mmol), triphenylphosphine (0.029g, 0.110mmol) and carbon tetrabromide (0.036g, 0.108mmol) as described previously for (162) yielded only starting material.
Method Two

\((4E)-(2R,3S)-6-N,N\text{-Bis(}\text{t}er\text{t-\text{butyloxycarbonyl})\text{-2,3-\text{O-isopropylidene-6-}}\text{amino-hex-4-en-1,2,3-triol}}\text{ (150) (0.036g, 0.093mmol) was dissolved in anhydrous DCM (1mL) and cooled to 0°C. To this solution was added pyridine (0.02mL, 0.247mmol) and trifluoromethanesulfonic anhydride (0.02mL, 0.119mmol). After warming to RT, the solution was stirred for 3 hours. The solution was then diluted with DCM (20mL) and washed with 10% HCl(aq) (5mL), H\text{2O (5mL), 10% NaHCO}_3(aq) (5mL) and saturated NaCl(aq) (5mL). The organic layer was then dried, filtered and evaporated to a yellow oil.}

The crude triflate (163) (0.049g, 0.094mmol) and sodium azide (0.017g, 0.261mmol) were dissolved in anhydrous DMF (1mL). The solution was heated to 50°C and left to stir for 24 hours. The solution was then diluted with H\text{2O (10mL) and extracted with diethyl ether (3 x 20mL). The combined ethereal layers were washed with saturated NaCl(aq) (10mL) then were dried, filtered and evaporated to a yellow oil. The crude mixture was put on a column of silica gel using 30% ethyl acetate/hexane as eluent. However none of the fractions isolated could have their structures unequivocally assigned as that of the title compound (164).
Method Three

(4E)-(2R,3S)-6-N,N-Bis(tert-butyloxy carbonyl)-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (150) (0.090g, 0.232 mmol) was dissolved in anhydrous DCM (1mL) and cooled to 0°C. To this solution was added triethylamine (0.05mL, 0.359mmol) and methanesulfonyl chloride (0.03mL, 0.388mmol). After warming to RT, the solution was stirred for 30 minutes. The solution was then diluted with DCM (20mL) and washed with 10% HCl(aq) (10mL) and saturated NaCl(aq) (10mL). The organic layer was then dried, filtered and evaporated to a yellow oil.

The crude mesylate (165) (0.110g, 0.236mmol) and sodium azide (0.020g, 0.308mmol) were dissolved in anhydrous DMF (1mL). The solution was heated to 50°C and left to stir for 24 hours. TLC of the reaction mixture indicated that there was only starting material, therefore the solution was heated to 100°C. After stirring for 24 hours the solution was diluted with H2O (10mL) and extracted with ether (3 x 20mL). The combined ethereal layers were washed with saturated NaCl(aq) (10mL), then dried, filtered and evaporated to a yellow oil. The crude mixture was put on a column of silica gel using 30% ethyl acetate/hexane as eluent. However, none of the fractions isolated could have their structures unequivocally assigned as that of the title compound (164) from their 1H NMR spectra.
Method Four

(4E)-(2R,3S)-6-N,N-Bis(tert-butyloxy carbonyl)-1-O-toluenesulfonyl-2,3-O-isopropylidene-6-amino-hex-4-en-1,2,3-triol (166) (0.044g, 0.081mmol) and lithium azide (0.026g, 0.531mmol) were dissolved in anhydrous DMF (1mL). The solution was heated to 50°C and left to stir for 24 hours. The solution was then diluted with H₂O (10mL) and extracted with diethyl ether (3 x 20mL). The combined ethereal layers were washed with saturated NaCl(aq) (10mL) then were dried, filtered and evaporated to a yellow oil. The ¹H NMR spectrum showed only starting material.

7.5.7 Displacement of a Tosylate with BocNH₂/Sodium Hydride

(2E)-(4S,5R)-N,N'-Bis(tert-butyloxy carbonyl)-4,5-O-isopropylidene-4,5-dihydroxy-hex-2-en-1,6-diamine (167)

Sodium hydride (60% in mineral oil, 0.036g, 0.939mmol) was suspended in anhydrous DMF (1mL). To this suspension was added tert-butylicarbamate (0.112g, 0.956mmol) and stirring continued until no more gas was evolved. (4E)-(2R,3S)-6-N,N-Bis(tert-butyloxy carbonyl)-1-O-toluenesulfonyl-2,3-O-isopropylidene-6-
amino-hex-4-en-1,2,3-triol (166) (0.354g, 0.653mmol) in anhydrous DMF (3mL) was added to the suspension and then warmed to 100°C. After stirring overnight the suspension was cooled to RT and diluted with H₂O (10mL). The solution was extracted with diethyl ether (3 x 30mL) and the organic layers combined and washed with saturated NaCl(aq) (20mL). The solution was dried, filtered and evaporated to a yellow oil. Purification on a column of silica gel using 10% ethyl acetate/hexane as eluent to give the title compound (167) as a yellow oil (0.141g, 56%).

¹H NMR: δ 5.843 (dt, J=6,15.3Hz,1H, vinyl H); 5.598 (dd, J=7.8, 15.3Hz,1H, vinyl H); 4.604 (t, J=6.3Hz,1H,H4); 4.344 (t, J=7.5Hz,1H, H5); 3.773 (m, 2H, H1); 3.449 (d, J=7.5Hz,2H,H6); 1.510 (s, 3H, isopropylidene CH₃); 1.501 (s, 18H, 2 x carbamate CH₃); 1.431 (s, 3H, isopropylidene CH₃).

¹³C NMR: δ 160.6 (carbamate C=O); 155.6 (carbamate C=O); 127.9 (vinyl CH); 125.5 (vinyl CH); 109.2 (isopropylidene C); 78.1 (CH); 77.7 (CH); 75.7 (carbamate C); 75.4 (carbamate C); 43.0 (CH₂); 41.8 (CH₂); 28.4 (carbamate CH₃); 27.8 (isopropylidene CH₃); 27.7 (isopropylidene CH₃).

MS: ES (+ve) m/z 370.4 (41); 350.3 (68); 200.1 (48); 192.1 (100).

HRMS: Calc'd for C₁₉H₃₄N₂O₆, 386.241667; found, 386.241154.
7.5.8 Epoxidation of the Allylic Amine (167)

(1"S,2"R)-1',3'-\textit{N,N}'-Di(\textit{tert}-butyloxy carbonyl)-2-(1'-aminomethyl)-3-(1",2"-O-isopropylidene-propan-1",2"-diol)oxirane (170)

(2E)-(4S,5R)-\textit{N,N}'-Di(\textit{tert}-butyloxy carbonyl)-4,5-O-isopropylidene-4,5-dihydroxy-hex-2-en-1,6-diamine (167) (0.046g, 0.119mmol) was dissolved in anhydrous DCM (1mL). To this solution was added meta-chloroperoxybenzoic acid (0.052g, 0.301mmol) and the solution stirred at RT overnight. The solution was filtered through a sintered glass funnel and then diluted with DCM (10mL). The solution was then washed with saturated NaHCO$_3$(aq) (2 x 5mL) and saturated NaCl(aq) (5mL) before being dried, filtered and evaporated to a yellow oil. Purification on a column of silica gel using initially 10% ethyl acetate/hexane and finally ethyl acetate to give the title compound (170) as a yellow oil (0.011g, 23%) and as a 2:1 mixture of diastereomers.
Major diastereomer

$^1$H NMR: 84.741 (br s, 1H, NH); 4.452 (dd, J=6.0, 6.0, 6.9 Hz, 1H, H5); 3.974 (dd, J=6.0, 6.0 Hz, 1H, H4); 3.718 (m, 2H, H6); 3.504 (m, 1H, one of H1); 3.312 (dd, J=5.7, 5.7 Hz, 1H, one of H1); 3.123 (m, 1H, H2); 2.983 (dd, J=2.1, 6.3 Hz, 1H, H3); 1.500 (s, 3H, isopropylidene CH$_3$); 1.448 (s, 18H, 2 x carbamate CH$_3$); 1.370 (s, 3H, isopropylidene CH$_3$).

$^{13}$C NMR: 8155.9 (carbamate C=O); 155.8 (carbamate C=O); 109.9 (isopropylidene C); 77.8 (CH); 77.2 (CH); 55.7 (CH); 53.3 (CH); 42.2 (C6-H2); 28.331 (C1-H2); 28.327 (carbamate CH$_3$); 27.6 (isopropylidene CH$_3$); 25.1 (isopropylidene CH$_3$).

Minor diastereomer

$^1$H NMR: 84.7 (br s, 1H, NH); 4.4 (m, 1H, H5); 4.038 (dd, J=6.0, 6.0 Hz, 1H, H4); 3.7 (m, 1H, 2H, H6); 3.5 (m, 1H, one of H1); 3.265 (dd, J=5.7, 5.7 Hz, 1H, one of H1); 3.092 (m, 1H, H2); 2.9 (m, 1H, H3); 1.487 (s, 3H, isopropylidene CH$_3$); 1.448 (s, 18H, 2 x carbamate CH$_3$); 1.358 (s, 3H, isopropylidene CH$_3$).

$^{13}$C NMR: 8156.1 (carbamate C=O); 156.0 (carbamate C=O); 109.9 (isopropylidene C); 77.7 (CH); 77.3 (CH); 55.8 (CH); 53.3 (CH); 42.2 (C6-H2); 28.4 (C1-H2); 28.3 (carbamate CH$_3$); 27.6 (isopropylidene CH$_3$); 25.1 (isopropylidene CH$_3$).
MS: ES (+ve) m/z 344.1 ([M-isopropylidene]^+,100); 266.1 (95); 156.0 (53).

HRMS: Calc'd for C_{19}H_{34}N_{2}O_{7}, 402.236582; found, 402.236086.

7.5.9 Cyclisation of the Epoxide

1,2'-N,N'-Di(tert-Butyloxycarbonyl)-3,4-O-isopropylidene-2-(1'-hydroxy-2'-aminoethyl)-3,4-dihydroxyprrolidine (171)

(1"S,2"R)-1',3"-N,N'-Di(tert-butyloxycarbonyl)-2-(1'-amino-methyl)-3-(1",2"-O-isopropylidene-propan-1",2"-diol)oxirane (170) (0.011g, 0.027 mmol) was dissolved in anhydrous DMF (0.5mL). To this was added sodium hydride (60% in oil, 0.004g, 0.104mmol) and the suspension was then heated to 50°C. After stirring for 24 hours the suspension was cooled to RT then diluted with H_{2}O (10mL). The solution was extracted with ether (3 x 20mL) and the combined ethereal extracts were washed with saturated NaCl(aq) then dried, filtered and evaporated to a yellow oil. The ^1H NMR spectrum of the crude reaction mixture could not be unequivocally assigned as that of the desired product (171).
CHAPTER 8

REFERENCES
plants, John Wiley & Sons, **1990**, 112-125.


137. E. H. White and D. J. Woodcock, In *The Chemistry of the Amino Group*, S. Patai


