Chiral imidazoline nitrones for cycloaddition reactions

Thesis

How to cite:


For guidance on citations see FAQs.

© 2000 The Author

Version: Version of Record

Copyright and Moral Rights for the articles on this site are retained by the individual authors and/or other copyright owners. For more information on Open Research Online’s data policy on reuse of materials please consult the policies page.
Chiral Imidazoline Nitrones for Cycloaddition Reactions

by

Jason Neil Martin

Author's No: M7206243

Date of Submission: 20 December 1999
Date of Award: 21 March 2000

Thesis submitted to the Open University for the Degree of Doctor of Philosophy

December 1999
For my brother and my parents
Declaration

I declare that the work presented in this thesis is the result of my own investigations, and where the work of others is cited, it is fully acknowledged. The material embodied in the thesis has not been submitted, nor is currently being submitted for any other degree.

........................................

Jason N. Martin

........................................

Prof. R. C. F. Jones
Supervisor
Acknowledgements

I extend my thanks in the first instance to Ray for his supervision and guidance, but especially for his happy-go-lucky approach with the RCFJ-group chequebook when it came to conferences, glassware and chemicals. Secondly, I thank my industrial supervisor Paul Smith and his group at SmithKline Beecham, Harlow. I turned a corner with this work during my time with his group and I thank them all for their help and their tolerance. Grateful thanks go to EPSRC and SB for their generous financial support.

None of this work would have been possible without the able assistance of the OU technical staff, in particular Pravin "chuck-it-in" Patel, Alan "gone-fishing" Leslie and Jim "Nerrrrr, bruvver" Gibbs; and cheers to Jenny "niffer" Burrage for comic relief. I humbly acknowledge the stunning data generated through very little effort on my part, using the skills of many other talented people. Thanks then go to Gordon Howell of the OU and the NMR group at SB for nOe's, to the OU's Brandon Cook for MS, and to Graham Jeffs for his HPLC-magic. Thanks, too, to the EPSRC MS Service (University of Wales, Swansea) and Crystallographic Service (University of Southampton).

Big thanks go to the all RCFJ crew past and present, especially John Snaith (whose songs play on in my mind), Steve "southern twart" Hollis and Pasc "Agent Orange" Dimopoulos (who always knew when it was time for a game of keck-clip footie). I am extremely grateful to Mike "give-us-a-jump" Bullivant, who foolishly agreed to proof read this thesis and to Jim Iley for helpful discussions. Finally, the biggest thanks of all to my marvellous Karine and Gonzales, I couldn't have done it without you.
Abstract

Previous work in this group has demonstrated that azomethine ylide 1,3-dipoles based on the 2-imidazoline chiral template show high regio- and enantioselectivity in their 1,3-dipolar cycloaddition reactions with a range of dipolarophiles. We proposed to synthesise nitrone 1,3-dipoles based on this 2-imidazoline template in order to investigate their utility in 1,3-dipolar cycloaddition chemistry.

We have developed the synthesis of chiral 4-phenyl-2-imidazoline nitrones 126a-c via a key hydroxylamino amine dihydrochloride intermediate 140a, available in four steps (61% overall yield) from commercial 2-chloroacetophenone. Nitrones 126a & 126b are generated rapidly and quantitatively from 140a by treatment with the appropriate triethyl orthoester. 2-Methyl nitrone 126b does not undergo a 1,3-dipolar cycloaddition reaction with common dipolarophiles, suggesting C-2 substitution is not tolerated in the transition state. On the other hand, we have shown 2-H nitrone 126a to react with many mono- and disubstituted alkynes and alkenes. The relative stereochemistry of the cycloadducts formed with 126a has been assigned by NOESY and X-ray crystallography. In each case, the dipole shows total diastereofacial selectivity in which the incoming dipolarophile is directed to the less hindered face of 126a by the bulky 4-phenyl group. The isolated cycloadducts are, almost without exception, formed via the exo transition state.

The cycloadduct of 126a with dimethyl maleate has been the focus of our efforts towards cleavage of the 2-imidazoline template. It is unreactive towards the conditions developed for template removal in the analogous azomethine ylides, despite many modifications. Cleavage of the isoxazolidine N-O bond followed by spontaneous lactamisation afforded the lactam 271. Reduction of the lactam carbonyl would afford the
pyrroloimidazole ring system, for which a template removal strategy is in place, but 271 has not to date afforded the desired material under a number of reaction conditions. For example, borane-complexed reagents gave a partially aromatised system in which three chiral centres are lost.

Thus, we have illustrated that these reagents, available from cheap commercial materials, are viable 1,3-dipoles capable of generating multiple chiral centres in a single step with total facial selectivity and have made progress towards the synthesis of chiral pyrrolidines.
Abbreviations

The following symbols and abbreviations are used in this text:

\[\alpha\]_D^{20} \quad \text{specific rotation (measured with sodium D line, sample at 20°C), in degrees}

Å \quad \text{angstroms}

Ac \quad \text{acetyl}

APCI+ MS \quad \text{atmospheric pressure chemical ionisation mass spectrometry (positive ion mode)}

aq. \quad \text{aqueous}

atmos. \quad \text{atmosphere (pressure)}

Bn \quad \text{benzyl}

Boc \quad \text{tert-butoxycarbonyl}

Boc_2O \quad \text{di-tert-butyl dicarbonate}

bp \quad \text{boiling point}

c. or conc. \quad \text{concentrated}

cat. \quad \text{catalyst}

Cbz \quad \text{benzyloxycarbonyl}

DBU \quad 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC \quad \text{see DCCI}

DCCI \quad \text{dicyclohexylcarbodiimide}

DCM \quad \text{dichloromethane}

de \quad \text{diastereomeric excess}

DEAD \quad \text{diethyl azodicarboxylate}
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEM</td>
<td>diethyl maleate</td>
</tr>
<tr>
<td>DIBAL</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAD</td>
<td>dimethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DMM</td>
<td>dimethyl maleate</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>equivs.</td>
<td>molar equivalents</td>
</tr>
<tr>
<td>FMO</td>
<td>Frontier Molecular Orbital</td>
</tr>
<tr>
<td>gl.</td>
<td>glacial</td>
</tr>
<tr>
<td>h</td>
<td>hours</td>
</tr>
<tr>
<td>HOBT</td>
<td>1-hydroxybenzotriazole</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HOSu</td>
<td>N-hydroxysuccinimide</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>inj.</td>
<td>injection</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M+</td>
<td>molecular ion</td>
</tr>
<tr>
<td>m-CBA</td>
<td>m-chlorobenzoic acid</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-chloroperbenzoic acid</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mmol</td>
<td>millimoles</td>
</tr>
</tbody>
</table>
mol%  percentage by moles
mp    melting point
MS    mass spectrometry
m/z   mass to charge ratio
NMO   N-methylmorpholine-N-oxide
NMR   nuclear magnetic resonance
nOe   nuclear Overhauser enhancement
NOESY nuclear Overhauser enhancement spectroscopy (2-dimensional)
PCC   pyridinium chlorochromate
5% Pd-C palladium adsorbed on carbon (5% w/w)
Ph-Gly phenylglycine
PNB   \( p \)-nitrobenzyl
psi   pounds per square inch
\( p \)-Ts \( p \)-toluenesulfonyl
py    pyridine
Ra-Ni Raney Nickel catalyst
redn. reduction
SiO\(_2\) silica gel
soln. solution
TBAF tetrabutylammonium fluoride
TBDMS \textit{tert}-butyldimethylsilyl
TBDMS\(\text{Cl}\) \textit{tert}-butyldimethylsilylchloride
TBDPS \textit{tert}-butyldiphenylsilyl
\textit{`Bu} \textit{tert}-butyl
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>temp.</td>
<td>temperature</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin-layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>tetramethysilane or trimethylsilyl</td>
</tr>
<tr>
<td>TPAP</td>
<td>tetrapropylammonium perruthenate</td>
</tr>
<tr>
<td>Ts</td>
<td>see p-Ts</td>
</tr>
<tr>
<td>TsOH</td>
<td>p-toluenesulfonic acid</td>
</tr>
<tr>
<td>TSP-d₄</td>
<td>3-(trimethylsilyl)-2,2,3,3-tetradueuteropropionic acid sodium salt</td>
</tr>
<tr>
<td>v/v</td>
<td>proportions of two components expressed as a ratio of their volumes</td>
</tr>
<tr>
<td>w/w</td>
<td>proportions of two components expressed as a ratio of their masses</td>
</tr>
</tbody>
</table>
# Contents

1.0 Introduction  

1.1 The 1,3-dipolar cycloaddition reaction 2  
  1.1.1 The 1,3-dipole 3  
  1.1.2 The dipolarophile 6  
  1.1.3 The cycloaddition mechanism 7  
  1.1.4 Frontier Molecular Orbital (FMO) theory 11  

1.2 Nitrone 1,3-dipoles 16  
  1.2.1 Physicochemical properties 16  
  1.2.2 Preparation of nitrones 18  
  1.2.3 Reactions of nitrones 22  

1.3 Asymmetric 1,3-dipolar cycloaddition reactions of nitrones 28  
  1.3.1 Chiral nitrones in 1,3-dipolar cycloaddition reactions 30  
  1.3.2 Chiral alkene dipolarophiles in 1,3-dipolar cycloadditions 45  
  1.3.3 Chiral catalysts 53  

2.0 Results and Discussion  

2.1 Strategy 57  
  2.1.1 Homochiral 2-imidazoline azomethine ylides 58  
  2.1.2 Homochiral 2-imidazoline nitrones 62
2.2 Synthesis of 2-imidazoline nitrones

2.2.1 Approaches from 2-phenylglycine

2.2.2 Approaches from benzoylformic acid

2.2.3 From 2-haloacetophenones

2.3 1,3-Dipolar cycloaddition reactions

2.4 Progress towards a template removal strategy

2.5 Attempted achiral imidazoline nitrone syntheses

2.5.1 Towards nitrones via 2-imidazolines

2.5.2 Towards nitrones from β-aminoalcohols

2.5.3 Towards nitrones from N-benzylglycine ethyl ester

2.6 Future work

3.0 Experimental

References

Appendix I: X-ray crystallographic data

Appendix II: HPLC conditions
Chapter 1

Introduction
1.1 The 1,3-dipolar cycloaddition reaction

![Diagram of 1,3-Dipolar cycloaddition.](image)

**Figure 1**: 1,3-Dipolar cycloaddition.

Our knowledge of 1,3-dipolar cycloaddition reactions goes back to the discovery of diazoacetic ester by Curtius in 1883\(^1,2\) and the elucidation by Ley of the structure of fulminic acid in 1899 - the first 1,3-dipoles. In 1893 Buchner, a colleague of Curtius, reacted diazoacetic ester with methyl acrylate to produce pyrazolines in the first example of a 1,3-dipolar cycloaddition reaction.\(^3\) However, it was not until Huisgen proposed the concept of 1,3-dipolar cycloadditions in 1960 that the full scope of these reactions began to be realised.\(^4\) The product of the bimolecular reaction between the 1,3-dipole (+a-b-c-) and a multiply-bonded system (d=e or d≡e), the “dipolarophile”, is a 5-membered ring (Figure 1); judicious choice of 1,3-dipole and dipolarophile allows access to a plethora of possible carbocyclic and heterocyclic ring systems. The large volume of recent literature in this field is testament to the fact that these reactions are not only versatile, but also highly robust.\(^5-10\) They represent a powerful tool in modern synthetic chemistry, whose limits are still being explored more than a century after their discovery.
1.1.1 The 1,3-dipole

The term 1,3-dipole describes a range of 3-atom systems which can only be represented by ground state zwitterionic resonance structures, one of which has the charges at the terminal atoms (atoms 1 and 3). It was deduced from experimental models\(^6\) that the allyl-anion type orbitals (four \(\pi\) electrons in three parallel atomic orbitals) are responsible for the cycloaddition reaction. However, in contrast with the nucleophilic termini of the allyl anion, the termini of the 1,3-dipole (a "heteroallyl anion") are both electrophilic and nucleophilic (Figure 2a).

![Resonance structures of allyl-anion type 1,3-dipoles.](image)

**Figure 2a**: Resonance structures of allyl-anion type 1,3-dipoles.

A second, smaller class of 1,3-dipoles, the "propargyl-allenyl" type, is provided by incorporating an additional \(\pi\)-bond such that one resonance form contains a triple bond (Figure 2b). These 1,3-dipoles are therefore linear, in contrast to the bent allyl-anion type 1,3-dipoles. Occasionally, the two classes are shown as hypervalent resonance forms (Figure 2c).
Restricting the three atoms of the 1,3-dipole to C, N and O (with a central heteroatom), Huisgen has classified the eighteen possibilities; six propargyl-allenyl and twelve allyl-anion type (Table 1).\textsuperscript{11} Representatives of almost all classes have been shown to take part in 1,3-dipolar cycloaddition reactions, although those most commonly used are the nitrones, nitrile oxides and azomethine ylides, followed by the azomethine imines, azides and diazoalkanes. Many of these 1,3-dipoles have been isolated and characterised, but it has often been found to be advantageous to generate the dipole \textit{in situ} for subsequent reaction.
A: Allyl-anion type 1,3-dipoles

\[ \begin{array}{c}
\text{Azomethine ylides} \\
\text{Azomethine imines} \\
\text{Nitrones} \\
\text{Azimines} \\
\text{Azoxy compounds} \\
\text{Nitro compounds} \\
\text{Carbonyl ylides} \\
\text{Carbonyl imines} \\
\text{Carbonyl oxides} \\
\text{Nitrosimines} \\
\text{Nitrosoxides} \\
\text{Ozone} \\
\end{array} \]

Table 1: Heteroatom-based 1,3-dipoles.11
B : Propargyl-allenyl type 1,3-dipoles

\[
\begin{array}{cccc}
\ce{C≡N—C} & \longrightarrow & \ce{C≡N=C} & \text{Nitrile ylides} \\
\ce{C≡N—N} & \longrightarrow & \ce{C≡N=N} & \text{Nitrile imines} \\
\ce{C≡N—O} & \longrightarrow & \ce{C≡N=O} & \text{Nitrile oxides} \\
\ce{N≡N—C} & \longrightarrow & \ce{N≡N=C} & \text{Diazooalkanes} \\
\ce{N≡N—N} & \longrightarrow & \ce{N≡N=N} & \text{Azides} \\
\ce{N≡N—O} & \longrightarrow & \ce{N≡N=O} & \text{Nitrous oxide}
\end{array}
\]

Table 1 (continued) : Heteroatom-based 1,3-dipoles.\textsuperscript{11}

1.1.2 The dipolarophile

A vast number of multiply-bonded structures has been used as dipolarophiles in 1,3-dipolar cycloaddition reactions, though the most common and ultimately most useful are alkenes. Other contenders in terms of popularity include alkynes, isocyanates, imines, carbonyls, thiocarbonyls and azo-compounds. The nature of the dipolarophile has a profound effect on the cycloaddition reaction, not only in terms of its reactivity but also its shape, size and propensity towards non-covalent interactions with the 1,3-dipole.
1.1.3 The cycloaddition mechanism

In 1960, Huisgen proposed the concerted electrocyclic process of 1,3-dipolar cycloaddition which has now won universal acceptance with little need for refinement. A year later, Doering and Roth described these reactions as "no mechanism" processes - highlighting the fact that the theory explained much but accepted many odd results. By 1968, the weight of experimental evidence allowed Huisgen to say that their view showed "pessimism...which seems no longer justified".

In 1968, an alternative to the concerted, single-step cycloaddition mechanism was proposed by Firestone involving a two-step reaction which proceeds via a di-radical intermediate (Figure 3). Huisgen championed the concerted mechanism, citing the abundant examples of stereospecific addition in the literature as the essential supporting proof of this mechanism. He argued that for the general rule of high stereospecificity of these reactions to be upheld by the di-radical mechanism, the energy barrier to rotation around the

Figure 3: Concerted and di-radical mechanism of 1,3-dipolar cycloaddition.
single bond d–e of the di-radical, once formed, must be less than the barrier to the cyclisation that would yield the cycloadduct. He calculated that the energy of rotation of the potential diradical intermediates for a number of known 1,3-dipolar cycloaddition reactions would need to be zero, and so demonstrated that the energy profile cannot contain the di-radical as an intermediate.\(^{11}\) The debate between Huisgen and Firestone (later chronicled by Houk et al.)\(^ {17}\) was long and intense, and included back-to-back papers in the *Journal of Organic Chemistry*.\(^ {13,14}\) The contest looked to have been decided when Houk and Firestone were able to show that a nitrile oxide 1,3-dipole reacts with cis- or trans- deuteroethylenes in a cycloaddition reaction that was more than 98% stereospecific.\(^ {18}\) They concluded that the reactions were concerted processes with no intermediates, in accordance with the predicted products from Huisgen's proposed mechanism. Somewhat ironically, Huisgen then reported the first well-documented stepwise 1,3-dipolar cycloaddition involving an intermediate, but stressed that this only served to further support the concerted mechanism for the majority of cycloaddition reactions since they lack the stereochemical scrambling characteristic of the stepwise process.\(^ {19,20}\)

The high regio- and stereoselectivity of these reactions is widely interpreted as an indication that the addition takes place *via* a highly ordered aromatic transition state, a feature shared with the Diels-Alder reaction. This interpretation is supported by a number of experimentally-determined parameters for 1,3-dipolar cycloaddition reactions:\(^6\)

- the reaction rate is largely independent of solvent polarity,

- the entropy of activation tends to be large and negative,

- the enthalpy of activation tends to be modest.

This high degree of order during the bond-forming process means that chiral information in the dipole or dipolarophile may be used to enforce a particular orientation of
the two components in the transition state. Thus, the desired chirality in the cycloadduct may be produced by judicious selection of the chiral component of the cycloaddition. First, however, we must consider the source and nature of the possible transition state geometries.

![Diagram](image)

**Figure 4**: Possible orientations of the dipole and dipolarophile in a 1,3-dipolar cycloaddition reaction.

It is generally accepted that in the 1,3-dipolar cycloaddition reaction the 1,3-dipole and the dipolarophile will prefer to approach one another as 'stacked planes'. A reaction in which the new bonds form on the *same* surface of a particular reactant is described as *suprafacial* in that component. Figure 4a shows the orientation of an allyl-anion type 1,3-dipole and an alkene dipolarophile in a cycloaddition which is suprafacial in both components. As the reactants approach one another along the axis of bond formation (shown by dotted lines), it is clear that this transition state facilitates overlap of the relevant molecular
orbitals. We would expect the same high degree of orbital overlap were the dipolarophile to approach the top face of the 1,3-dipole rather than from underneath as shown.

Alternatively, if one bond is formed on one surface of a reactant and one bond is formed on the other surface, then the reaction is described as *antarafacial* in that component (Figure 4b). This diagram shows that we can consider the two planar components of the cycloaddition now approaching at right angles to each other. Figure 4b demonstrates that reactions involving one antarafacial component have much more exacting spatial requirements, and effective orbital overlap is much more difficult to achieve. Such reactions are rare and it is clear that optimum overlap of the molecular orbitals of the two components in a 1,3-dipolar cycloaddition reaction, and so formation of the major product, most often occurs *via* the suprafacial orientation.

Even with this much decided, there are still a number of different ways in which the orientation of approach of the 1,3-dipole to the dipolarophile will determine the eventual regio- and stereochemistry of the cycloadduct. Firstly, the planar 1,3-dipole may be approached from above or below, each face giving rise to different stereochemistry in the adduct. This fact has not gone unnoticed - many reagents have been developed that are facially differentiated in order to direct incoming dipolarophiles.

When substituents are added to the dipolarophile it becomes apparent that further possibilities present themselves whilst maintaining the suprafacial arrangement of the two reactants. Firstly, the dipolarophile may approach with the substituent directly beneath the 1,3-dipole during bond formation - this is the *endo* transition state (Figure 5). Such a transition state may become the energetically more favourable pathway by finding some extra stabilisation from a non-covalent interaction between the dipole and the substituent $Z$. An example is the stacking of $\pi$-systems on dipole and dipolarophile. Alternatively, where, for
instance, Z is a bulky group, steric factors may force the dipolarophile to approach with the substituent pointing away from the dipole; in this case bonding will occur via the exo transition state.

![Diagram showing endo- and exo- transition states for 1,3-Dipolar cycloaddition](image)

**Figure 5**: 1,3-Dipolar cycloaddition transition states.

1.1.4 Frontier Molecular Orbital (FMO) theory

Whilst the concerted nature of the 1,3-dipolar cycloaddition reaction was being debated, the factors that governed the regiochemistry still remained a mystery. In 1972, Fukui demonstrated that the regiochemistry can be explained most reliably by Frontier Molecular Orbital (FMO) theory, for which he shared the 1981 Nobel Prize for Chemistry with Hoffmann. He proposed that the cycloadditions take place in the direction of maximum overlap of the frontier molecular orbitals of the 1,3-dipole and dipolarophile, in other words, the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of each component. By the Woodward-Hoffmann theory of
conservation of orbital symmetry, it can be seen that the interaction of the HOMO of one component with the LUMO of the other is symmetry allowed and would represent the strongest bond-making interaction. Fukui reasoned that the optimum orbital overlap occurs between orbitals that are separated by the smallest energy gap, and that the smaller the gap, the faster the rate of reaction. If the relative energies of these FMOs are known it should therefore be possible to predict the dominant FMO interaction - with this information we can often then directly predict the preferred regiochemistry of the reaction.

Sustmann classified the possible modes of interaction of frontier molecular orbitals in dipolar cycloadditions according to their relative energies, recognising three different situations (Figure 6). When the HOMO of the 1,3-dipole and the LUMO of the dipolarophile have the smallest energy gap, then the cycloaddition is classed as the Type I case by Sustmann notation. We shall henceforth conform to the recognised convention and refer to such a reaction as HOMO-controlled. Conversely, should the LUMO of the dipole
and the HOMO of the dipolarophile have the smaller energy gap, then this is the Type III case, a reaction exhibiting LUMO-control. Obviously, these two extremes will be bisected by a third situation, in which neither interaction is favoured in frontier orbital terms. This is referred to as the Type II case.

Figure 7: FMO theory and the regiochemistry of 1,3-dipolar cycloaddition reactions.

In the case of concerted cycloadditions, the preferred regiochemistry depends upon the relative sizes of the orbital coefficients at the reacting termini of the dipole and dipolarophile. Figure 7 shows the orbital coefficients for a cycloaddition in which the
dominant interaction is the dipole HOMO - dipolarophile LUMO, in other words HOMO-
control. Here, the lobes have been drawn to represent the sign of the wave function by their
shading and the magnitude of the coefficient on that atom by their size. There are two
regiochemically different products that arise as a result of the different orientations of the
alkene during bond formation. The largest orbital coefficient of the 1,3-dipole is at atom 3
and the smallest coefficient at atom 1, with the dipolarophile orbital coefficient being largest
adjacent to the substituent X. Case A in Figure 7 represents the maximum overlap of the
molecular orbitals, as in this case the orbital coefficients are matched - large with large, and
small with small. We would expect the 4-substituted cycloadduct to be the major product
from this reaction. In case B, the orbital coefficients are not matched, and we would predict
that the 5-substituted cycloadduct will, as a result, be a minor product.

Both the energy of the frontier molecular orbitals of alkenes and the orbital
coefficients at each end of the double bond are affected by the nature of their substituents.
Electron-withdrawing groups decrease both HOMO and LUMO energies, especially the
LUMO, and in both FMOs the largest coefficient is at the unsubstituted end of the alkene.
Conversely, the energy of both FMOs is increased by electron-donating groups, with the
largest effect on the HOMO. In this case, the largest orbital coefficient is at the unsubstituted
end of the HOMO but at the substituted end of the LUMO. In alkenes containing a
conjugating group, the energy of the HOMO is raised but the LUMO is lowered, and the
orbital coefficient is largest at the unsubstituted end for both MOs.\textsuperscript{25}

Typical relative energies of the frontier orbitals for the three classes of alkene
dipolarophile are shown in Figure 8. Electron-donating groups are represented by the
substituent $X$, and include alkenes such as vinyl ethers. Conjugating groups are represented
by C, and electron-withdrawing groups by Z: such alkenes include styrenes and acrylate
esters respectively. Thus, as the rate of the cycloaddition depends on the size of the HOMO-LUMO energy gap, we can imagine that for a chosen dipole, the rate of reaction will be different in its cycloadditions with electron-deficient and electron-rich dipolarophiles. Taken to the extreme, we might even expect to observe a change in the regiochemical preference of a dipole in its reaction with these two classes of dipolarophile. This theoretical prediction has been borne out by experimental observation by a number of researchers. 26-34 Most significantly, Houk et al. have shown that for a range of nitrone 1,3-dipoles, the regiochemistry in the cycloadduct depends on the ionisation potential of both the dipole and the dipolarophile. 35 The lower the ionisation potential of the nitrone (that is the more electron-rich), the more likely it is to show this reversal of regiochemistry. The same is true as the ionisation potential of the dipolarophile increases (that is the more electron-deficient), and this phenomenon is exaggerated if both effects are combined.

Figure 8: Relative energies of dipolarophile frontier orbitals.
1.2 Nitrone 1,3-dipoles

Nitrones (or azomethine oxides), Figure 9, were first prepared by Beckmann in 189036,37 and named from a shortening of "nitrogen-ketones" by Pfeiffer in 1916 to emphasise their similarity to ketones.38 Aromatic N-oxides contain the nitrone moiety, but retain the name of the N-oxides whose reactivity they more closely resemble. The general terms aldo- and keto-nitrones are used on occasion, to distinguish between those with and without a proton on the α-carbon respectively. Their chemistry is hugely varied, enough so to be frequently reviewed,39-48 but as we shall see it is ultimately dominated by their use as 1,3-dipoles for cycloaddition reactions.

1.2.1 Physicochemical properties

Many nitrones are stable at room temperature in air, but rearrangements may occur on prolonged exposure to light. The treatment of nitrones with acid or base leads to cleavage of the double bond to produce a carbonyl compound and an N-substituted hydroxylamine.
Nitrones are slightly basic in character, the pKa of their conjugate acids most often lying in the range 7-9. N-Methyl-C-phenylnitroline, for example, has a pKa of 8.26.

![E-isomer and Z-isomer](image)

**Figure 10**: Geometric isomerism of nitrones.

Because of their double bond, nitrones exhibit geometric isomers, Figure 10, the first example of which was confirmed by dipole moment measurements. The E- form is energetically unfavourable, being converted to the Z- form by heating. It has been established that aldonitrone exist in the stable Z- form; an E- aldonitrone, formed from the oxaziridine, was completely isomerised after 24 hours in benzene solution. Often this isomerisation can be followed by the change in the NMR spectrum. The activation energy for the isomerisation of E-α-phenyl-α-p-tolyl-N-benzyl nitroline to the Z- form is 33.6 kcal mol\(^{-1}\) (Scheme 1).

![Scheme 1](image)
The infrared spectra of aromatic ketonitrones commonly exhibit an N–O stretch between 1200-1280 cm\(^{-1}\) (1100 cm\(^{-1}\) in aldonitrones), with a C=N stretching frequency in the range 1560-1620 cm\(^{-1}\). The UV spectrum of a nitrone most often shows a strong absorption in the range 230-290 nm, with the intensity increasing with increasing conjugation to the C=N double bond.\(^{25}\) The \(^1\)H and \(^{13}\)C NMR chemical shifts of the two geometric isomers of a nitrone are often sufficiently different to allow discrimination between them, although the assignment of the configuration is most commonly based on dipole-moment measurements. Several groups have studied the mass spectra of variously substituted and deuterated nitrones,\(^{44}\) and all exhibit the loss of oxygen (M-16) which is characteristic of N-oxides. The fragmentation patterns are, on the whole, much simpler for negative rather than positive ionisation.

1.2.2 Preparation of nitrones

There are a number of synthetic methods by which nitrones can be prepared. This topic has been reviewed thoroughly,\(^{25,39-41}\) so we shall merely consider a few important examples in each of the following groups:

a. from hydroxylamines and carbonyl compounds
b. from N,N-disubstituted hydroxylamines
c. from oximes
d. from imines
e. from nitroso compounds
a. from hydroxylamines and carbonyl compounds

\[
\text{RCHO} + \text{R}^1\text{NHOH} \rightarrow \text{R}^+\text{N}^\cdot\text{O}^-\text{R}^1
\]

Scheme 2

The most common method of preparing nitrones is the condensation of a carbonyl compound and an N-monosubstituted hydroxylamine (Scheme 2). This reaction proceeds in high yield when the N-substituent is alkyl or aryl, and when the carbonyl compound carries non-bulky groups. The nature of the single substituent (R\(^1\)) on the hydroxylamine nitrogen has a limited effect on the condensation, but it can affect the isomer ratio of a subsequent 1,3-dipolar cycloaddition reaction. The substituent on the carbonyl carbon (R) will be placed \(\alpha\)-to the nitrone nitrogen, adding greatly to the range of products available by cycloaddition reactions of these compounds. The carbonyl compounds may also be masked, for example, the synthesis of oxazoline nitrones from orthoesters or amide acetals.

b. from N,N-disubstituted hydroxylamines

\[
\text{R}^\cdot\text{N}^\cdot\text{O}^-\text{R}^1 \rightarrow \text{R}^+\text{N}^\cdot\text{O}^-\text{R}^1 \rightarrow \text{R}^+\text{N}^\cdot\text{O}^-\text{R}^1
\]

Scheme 3

The preparation of cyclic and acyclic nitrones by dehydrogenation of N,N-disubstituted hydroxylamines has been achieved with any of a number of common oxidants.
including yellow mercuric oxide, lead oxide, potassium ferricyanide, potassium permanganate, potassium dichromate, palladium, peroxides, sodium periodate and salts of copper (II), iron (III) and silver. Oxidation of the hydroxylamine anion to the radical is the first step in the reaction, followed by abstraction of hydrogen (Scheme 3).

c. from oximes

The ambident nucleophilicity of oximes means that the alkylation of oximes can lead to a mixture of the nitrone and O-alkyl oxime, the products of N- and O-alkylation respectively (Scheme 4). The alkylation agent (for example, alkyl halides or dialkyl sulphates) and counter ion (for example, Li⁺, Na⁺, Me₄N⁺) have a relatively small effect on the product ratio. This problem has been overcome in certain cases by initial conversion to the O-silylated oximes and subsequent reaction with trialkyloxonium tetrafluoroborate.

d. from imines

The imine function can be oxidised to a nitrone, even when the imine is part of a heterocyclic system. The most common reagents for this oxidation are peroxycarboxylic acids (for example, peracetic acid, m-chloroperbenzoic acid), although other reagents, most notably hydrogen peroxide, are known in the literature. Imines generally give the oxaziridine on oxidation, which is then isomerised to the nitrone (Scheme 5), but the conversion may be
direct in some instances. Attempts to thermally isomerise some oxaziridines has led not to the desired nitrones, but to a variety of rearrangement products, predominantly amides.\textsuperscript{39}

![Scheme 5](image)

\textbf{Scheme 5}

e. from nitroso compounds

![Scheme 6](image)

\textbf{Scheme 6}

The reaction of an aromatic nitroso compound with a compound containing an activated methylene group, in the presence of catalytic base, leads to a mixture of nitrones and imines. Yields can be high without contamination using the Krönke reaction (Scheme 6), in which the methylene group is attached to the nitrogen of a pyridinium salt. In principle, the methylene requires an activating group (for example, aryl, cyanide or isocyanate) and a good leaving group (for example, pyridinium, sulphonium or halogen).\textsuperscript{25,39}
An example is the reaction of 9-dimethylsulfoniumfluorenylide with nitroso benzene to afford the corresponding N-phenyl nitrone in quantitative yield (Scheme 7).

\[
\text{[Diagram of Scheme 7 showing reaction between \(9\text{-dimethylsulfoniumfluorenylide} + PhN=O\).]}
\]

Scheme 7

1.2.3 Reactions of nitrones

a. Dimerisation

\[
\text{[Diagram of Scheme 8 showing dimerisation of \(N\text{-hydroxypiperidine} \rightarrow \text{dimer} \rightarrow \text{trimer}\).]}
\]

Scheme 8

It has been observed that oxidative routes to certain nitrones lead to the isolation of the nitrone dimer or trimer. For example, the mercuric oxide oxidation of \(N\)-hydroxypiperidine gives the dimer (Scheme 8) or even the trimer, whereas the oxidation of \(N\)-hydroxypyrrolidine affords the monomeric nitrone only. It seems that certain of the more reactive nitrones are susceptible to these association reactions, although this can be controlled.
by preparing the nitrone in solution. Alternatively, the dimer or trimer may be thermally cracked, to give the desired monomeric nitrone.

b. Rearrangements

i) Photolysis

Nitrones undergo photochemical isomerisation into oxaziridines via a disrotatory cyclisation (Scheme 9). The oxaziridines may undergo further photochemical or thermal reaction to produce the amide by migration of one substituent from the "nitrone" carbon atom to the nitrogen atom. The reverse reaction - isomerisation of oxaziridines to the nitrone with, for example, silica gel or heating, is a popular nitrone synthetic route. The presence of substituents on the nitrone will affect the feasibility of these reactions. It has been shown that 2-unsubstituted pyrroline-N-oxides and the 2,5,5-trimethyl analogue formed the oxaziridine, whereas the 2-substituted isomers did not. A radical mechanism has been postulated as being the most likely for oxaziridine formation.

\[
\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{H} & \quad \text{N} \\
\text{R}^2 & \quad \text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{hv} & \Rightarrow \quad \begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\end{align*} \\
\text{hv or } \Delta & \Rightarrow \quad \begin{align*}
\text{R}^1 & \quad \text{CONHR}^2 \\
\text{H} & \quad \text{CONR}^1 \\
\end{align*}
\]

Scheme 9

ii) Amide formation

As well as photolytic rearrangements, nitrones may also be rearranged to amides by a number of chemical means. The list of reagents includes phosphorus pentachloride, acetyl chloride, sulphur dioxide and bases in ethanolic solution; yields are often high. However, the most effective reagents are phosphorus trichloride (though this may deoxygenate the
nitron), phosphorus oxychloride and acetic anhydride. Kröhnke has put forward two mechanisms to explain those reactions in which rearrangement occurs with and without migration of substituents. The proposed migration-free mechanism of amide formation with acetic anhydride is shown in Scheme 10.

![Scheme 10](image)

**Scheme 10**

iii) Isomerisation to oxime O-ethers.

![Scheme 11](image)

**Scheme 11**

Certain nitrones are converted into oxime O-ethers by heating, but the reaction is not general. Thermolysis of N-(diphenyl)methyl nitrones proceeds via isomerisation of the iminoxy radicals (Scheme 11). The radical intermediacy has been proven by chemically induced dynamic nuclear polarisation (CIDNP), as well as the generation of crossover
products. Geometric isomerisation of the iminoxy radicals leads to formation of the $E$- and $Z$- isomers of the oxime ether.

iv) Behrends rearrangement

![Scheme 12]

The rearrangement of nitrones may be effected by catalytic base, in which the double bond is moved to favour the isomer with the lowest energy. Thus, it has been shown that many ketonitrones rearrange into the more stable corresponding aldonitrone isomer (Scheme 12).

c. Addition of Nucleophiles.

![Scheme 13]

A number of nucleophiles add to the carbon terminus of nitrones to form $\alpha$-substituted hydroxylamines, as for example, in acid or base-catalysed hydrolysis. The
isolated products depend on the nucleophile in question, as many adducts undergo secondary reactions. Hydrogen cyanide adds to aldonitrones to yield α-cyano-hydroxylamines, which can then eliminate water, producing α-cyanoimines (Scheme 13). These imines may react with a second molecule and cyclise to the imidazoles, a process promoted by the addition of a thiol. Carbanions, active methylene compounds, ylides and organometallic compounds have been added to nitrones. Ketonitrones may be less reactive to nucleophilic addition than aldonitrones, for example, they often resist the addition of Grignard reagents, being reduced to imines, but most addition reactions are general.

d. 1,3-Dipolar cycloadditions.

![Scheme 14]

The chemistry of nitrones is dominated by their use as 1,3-dipoles in cycloaddition reactions. Cyclic and acyclic nitrones have been reacted with a range of dipolarophiles including alkenes to afford the isoxazolidine cycloadducts (Scheme 14) as well as alkynes and isocyanates (Section 1.1.2). It has been demonstrated that the cycloaddition reaction can exhibit high stereo- and regioselectivity (Section 1.1.3). In the cycloaddition reactions of simple alkyl and aryl nitrones the 5-substituted isoxazolidine cycloadducts are commonly the predominant regioisomers. However, as we shall see in the following section, there is much potential for predicting and controlling the stereochemical outcome of these reactions and this
has led to the widespread use of nitrone cycloadditions in the synthesis of a number of biologically important molecules.
1.3 Asymmetric 1,3-dipolar cycloaddition reactions of nitrones

1,3-Dipolar cycloaddition reactions have long been recognised as possessing the potential for high stereo- and regio-control, and the number of natural product total syntheses utilising the 1,3-dipolar cycloaddition reactions of nitrones as a key step testifies to their usefulness. In the reaction of a nitrone 1 with a disubstituted alkene 2, three new contiguous chiral centres are generated in the isoxazolidine cycloadducts (Scheme 15).

![Scheme 15](image)

It is clear from Scheme 15 that there are two regiochemical senses of addition as well as either exo or endo approach of the two components, leading to two pairs of regioisomeric and diastereomeric products. Thus, whilst 3 and 4 have the same regiochemistry, they are formed via the endo and exo transition states, respectively, and this is reflected in the differing stereochemistry at C-4 and C-5. Similarly, whilst 5 and 6 arise from cycloaddition in the same regiochemical sense, they, too, are formed from the endo and exo transition states, respectively. However, the nitrone 1 also has two faces, each of which may be
involved in the cycloaddition and so we must also consider the formation of the enantiomers of all four products. These structures can be realised by inversion of the stereochemistry at C-3 in each of the cycloadducts 3-6. The likelihood of obtaining a single product from so many possibilities may seem remote, but a wealth of experimental evidence has allowed certain rules-of-thumb to be drawn up. For example, the relative stereochemistry at C-4 and C-5 in the isoxazolidine is controlled by the choice of the alkene dipolarophile. The geometry of the alkene substituents determines, without exception, the relative stereochemistry at the corresponding positions in the isoxazolidine. For example, we can predict that, as $R^4$ and $R^5$ are cis- in the alkene, they will be cis- in the products.

In the absence of over-riding steric factors, the Frontier Molecular Orbital theory provides a reliable guide to the regiochemical outcome of the reaction of an alkene with a nitrone (Section 1.1.4). The endo or exo preference is harder to predict, as it depends on the steric bulk of the nitrone and alkene, as well as on any secondary orbital interactions that may be present in the transition state. The facial nature of the nitrone, as with other 1,3-dipoles, provides the potential to restrict reactivity to just one of the two possible faces. Thus, a chiral substituent on the nitrone may sterically hinder the approach of the alkene to one face, favouring the formation of one particular enantiomer of the product.

As we shall see, asymmetric induction in 1,3-dipolar cycloaddition reactions with chiral nitrones can be an effective strategy (Section 1.3.1) and many experimenters have also found success using alkenes that carry the chiral information (Section 1.3.2). It is clear from the recent literature that interest in the application of chiral catalysis to cycloaddition reactions has blossomed in the past few years (Section 1.3.3). We shall examine a selection of examples in each case, as all three of these induction strategies have been recently thoroughly reviewed. Firstly, we shall examine the literature on 1,3-dipolar
1.3.1 Chiral nitrones in 1,3-dipolar cycloaddition reactions

The availability of chiral nitrones by various short synthetic routes, often from abundant enantiopure natural materials, has allowed their application to the total synthesis of diverse chemical targets. One of the most impressive syntheses utilising nitrones bearing the chirality on the carbon atom is the preparation of analogues of cholecalciferol (Vitamin D₃) and ergocalciferol (Vitamin D₂) by Baggiolini et al. (Scheme 16). The chiral nitrone 10 was prepared from the corresponding aldehyde, which ultimately derived from a known chiral keto-acid intermediate. The 1,3-dipolar cycloaddition reaction of 10 with methyl 3,3-dimethylacrylate afforded the desired (3S, 4S)-isoxazolidine product 11, which was separated from a 1:1 mixture with the (3R, 4R)-isomer. The unwanted isomer was thermally isomerised in xylene at 140°C to give the desired cycloadduct 11 in yields of up to 71%. Reduction of the ester and quaternisation of the nitrogen atom of isoxazolidine 11, cleavage of the N-O bond with Hoffmann elimination and oxidation gave the desired non-nitrogenous
ketone 12. The phosphine oxide 13 underwent a Wittig-Horner reaction with 12 and, after desilylation with TBAF, the Vitamin D₂ analogue 14 was isolated.\textsuperscript{54}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{reaction_diagram}
\caption{Scheme 16}
\end{figure}

\textit{Reagents:} i, xylene, Me₂C=CHCO₂Me, 140°C; ii, LiAlH₄, THF; iii, p-TsCl, pyridine; iv, LiAIH₄, THF, Δ; v, MeI, toluene, 60°C then Zn, AcOH; vi, MeI, toluene, 70°C then ¹BuOH, ¹BuOK, Δ; vii, PCC, DCM; viii, N-TMS-imidazole, THF; ix, n-BuLi, THF, -78°C; x, TBAF, THF.

Brandi has also studied the 1,3-dipolar cycloaddition of facially differentiated α,β-dialkoxynitrones with vinylphosphine oxides (Scheme 17).\textsuperscript{55-60} The homochiral nitrone 15 shows high diastereofacial selectivity in its cycloaddition with vinylphosphine oxides 16 and 17. In the reaction of 16 with 15, the \textit{endo} diphenylphosphinyl isoxazolidine isomer 18 is the major product, but it is formed along with the \textit{exo} isomer and the 4-regioisomer in a ratio

\textbf{Scheme 16}

\textbf{Scheme 17}
of 63:12:21 after 10 hours reflux in chloroform. Exchange of one of the phenyl groups on phosphorus in 16 for methyl enforces a double asymmetric induction strategy, and leads to the isolation of the isoxazolidine 19 (75%) after 7 days at room temperature. The endo:exo ratio is now 95:5, with no observed formation of the 4-regioisomer and a small increase in the diastereomeric excess of the endo product to an impressive 96%.55 A racemate of nitrone 15 has been reacted with vinyl ester and ether dipolarophiles by De Shong.61,62 Reaction proceeds with high endo-selectivity, as well as high diastereofacial selectivity, to generate an intermediate in the synthesis of the amino-sugar daunosamine. Similar nitrones have been used by Thomas to give essentially one isoxazolidine isomer in a 1,3-dipolar cycloaddition with methyl crotonate.63

Scheme 17

Scheme 18
Saito et al. have developed homochiral nitrones, such as 20, derived from threitol (Scheme 18). Nitron e 20 was found to give predominantly the endo isoxazolidine 21 (endo:exo 10:1) in a 1,3-dipolar cycloaddition reaction with methyl crotonate, with high diastereofacial selectivity.

Amongst other nitrones with the chiral centre attached to the nitrone carbon atom are the N-benzyl nitrones developed by Kametani and Ito et al. (Figure 12). However, these two nitrones both give rise to a mixture of diastereoisomers in their 1,3-dipolar cycloaddition reactions with benzyl crotonate.

Scheme 19
Mukai et al. have investigated the use of chromium tricarbonyl-derived nitrones with a number of alkene dipolarophiles (Scheme 19). The nitrene 24 reacts with styrene at 90°C to give the isoxazolidine 25 as a mixture of endo and exo diastereoisomers in the ratio 82:18 respectively. The related chromium tricarbonyl-substituted nitrone 26 by contrast, gives the exo isomer of isoxazolidine 27 as the only observed product. The authors explain their observations by the ability of the chromium tricarbonyl moiety to shield one face of the nitrone, which then leads to very high diastereofacial induction (deexo of 96-98%).

The most common chiral substituent on the nitrogen atom of the nitrone is the 1-phenylethyl group, the corresponding nitrones 28 being formed from 1-phenylethylamine 29 (both enantiomers are available optically pure) via the hydroxylamine 30. In 1,3-dipolar cycloadditions with styrene, 28a gave predominantly the exo isoxazolidine isomers 31a & 31b with fair to excellent diastereofacial selectivity (Scheme 20).<ref>

![Scheme 20](image)

Reagents: i, (PhCO)_2O; ii, PhCHO, C_6H_6; iii, CH_2=CHPh, C_6H_6, Δ, 15h.

Scheme 20
Tice and Ganem used a similar nitrone 32 in the synthesis of the polyamine bovine brain extract (+)-hypusine 33 by cycloaddition with allyl alcohol, which gave a 1:1 mixture of two diastereomers 34a and 34b (Scheme 21).\textsuperscript{72} Swern oxidation of 34a to afford the aldehyde 35 was followed by reductive amination with a derivative of lysine and exhaustive hydrogenation to yield the natural product 33. In a similar fashion, the enantiomer of nitrone 32 was used to furnish the enantiomer of 35 and so afforded non-natural 9-epihypusine [(9S)-33].

\begin{center}
\includegraphics[width=\textwidth]{Scheme21.png}
\end{center}

\textit{Reagents:} \textsuperscript{i}, CH\textsubscript{2}=CHCH\textsubscript{2}OH, C\textsubscript{6}H\textsubscript{6}, Δ, 3h; \textsuperscript{ii}, (COCl)\textsubscript{2}, DMSO, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, -70°C; \textsuperscript{iii}, 3Å mol. sieves, C\textsubscript{6}H\textsubscript{6}; \textsuperscript{iv}, NaBH\textsubscript{4}, H\textsubscript{2}N(CH\textsubscript{2})\textsubscript{2}CH(CO\textsubscript{2}Bn)NHCbz, MeOH, 5°C; \textsuperscript{v}, H\textsubscript{2}, Pd-C, HCl, EtOH.

\textbf{Scheme 21}

Overton has applied the 1,3-dipolar cycloaddition of N-(1-phenylethyl)nitrones to the synthesis of a number of amino-acids, including (R)- and (S)-lysine,\textsuperscript{73,74} as well as aspartame and its (R)-aspartyl isomer.\textsuperscript{75} Kametani used related nitrones in the synthesis of precursors to (+)-thienamycin 36 and its (-)-isomer, as well as to penems and carbapenems.\textsuperscript{66,76,77} The reaction of nitrone 37 with benzyl crotonate gave a 1:1 mixture of the desired (3S)-isoxazolidine 38 and its (3R)-isomer (Scheme 22). Hydrogenolysis of
38 was followed by DCC coupling to generate the azetidinone moiety. After TBDMS-protection of both the hydroxy and lactam functionalities, the ethyl ester was hydrolysed for conversion to the \( p \)-nitrobenzyl ester to afford the known (+)-thienamycin intermediate 39. In this fashion, the (3R)-isomer of 38 was used to prepare the analogous intermediate to (-)-thienamycin.

![Scheme 22](image)

Reagents: i, MeCH=CHCO_2Bn , C_6H_6, \( \Delta \), 16h; ii, H_2, 10% Pd-C, AcOH, 38h; iii, DCC, MeCN, 60°C, 3h; iv, TBDMSCl, Et_3N, DMF; v, 0.25M aq. NaOH, H_2O, THF; vi, \( p \)-NO_2-BnBr, DMF, 2h; vii, c. HCl, MeOH.

Although cheap and readily available, in general, these N-(1-phenyl)ethylnitrones are, as reported by Belzecki, of limited use in asymmetric 1,3-dipolar cycloaddition reactions.\(^{70,71}\) This is due to poor discrimination resulting from the free rotation about the N-to-auxiliary bond, leading to a mixture of diastereoisomers.

The use of glycosides as the chiral group on the nitrone nitrogen atom was pioneered by Vasella and has been used in the asymmetric synthesis of a number of biologically
important molecules or their analogues including proline,\textsuperscript{78,79} nucleosides\textsuperscript{80} and (+)-
ojirimycin and its 1-deoxy-analogue.\textsuperscript{81} For example, the captopril anaologue 40 was
prepared, in which the proline of the natural material has been replaced by the 5-oxaproline
moiety (Scheme 23).\textsuperscript{79} The optically active N-glycosynitrone 41a underwent a 1,3-dipolar
cycloaddition with ethene at 65 atmos. in 90\% yield to give predominantly the desired
isoxazolidine isomer 42. Cleavage of the glycoside was followed by treatment with
methacryloyl chloride to afford the amide 43. Conjugate addition of thioacetic acid gave a
1:1 mixture of the diastereoisomers, which could be separated by chromatography.
Hydrolysis of the tert-butyl ester with TFA and aminolysis of the thioester with concentrated
ammonia, afforded the target compound 40. One distinct advantage of the glycoside
auxiliaries developed by Vasella and co-workers is their recovery after acid hydrolysis from
the isoxazolidine cycloadduct.

\begin{center}
\begin{tikzpicture}
  \node [draw, align=left] (a) at (0,0) {\textbf{Reagents:} i, CH\textsubscript{2}=CH\textsubscript{2}, 65 atmos., 80\degree C; ii, aq. HCl, 6h; iii, methacryloyl chloride, pyridine, -10\degree C, 2h; iv, CH\textsubscript{3}COSH, 0\degree C, 15min; v, TFA, 1-chlorobutane, 25\degree C, 2h; vi, c. aq. NH\textsubscript{3}, 25\degree C, 24h.}
\end{tikzpicture}
\end{center}

\textbf{Scheme 23}
Brandi has applied a similar glycosyl nitrone (±)-41b to the synthesis of the unusual amino-acid (2S)-4-oxopipecolic acid 44 (Scheme 24). The tetrahydropyridin-4-one 45 was obtained, along with the open chain by-product 46, via thermal rearrangement of the spirocyclic isoxazolidine cycloadduct 47. The chiral auxiliary (R*) was recovered after its removal from 45 with TFA, and hydrolysis of the amino ester with 6M aqueous HCl afforded the amino-acid 44.

\[
\begin{align*}
(±)-41b & \xrightarrow{\text{I}} 47 \\
R = \text{Et} & \quad \text{ii} \\
\text{R}^* & = \text{Et}
\end{align*}
\]

\[
\begin{align*}
45 & + 46 \\
\text{iii - iv} & \quad 44
\end{align*}
\]

*Reagents:* i, methylenecyclopropane, toluene, 60°C, 5 days; ii, xylenes, 140°C; iii, TFA, EtOH; iv, 6M aq. HCl.

**Scheme 24**

A number of carbohydrate-derived nitrones have been prepared by Kibayashi. The gulofuranose nitrone 48 exists as a mixture of E- and Z- isomers, and led to a mixture of two diastereomeric isoxazolidines in the 1,3-dipolar cycloaddition to Cbz-protected allylamine (Scheme 25). The diastereomers were separated, and the auxiliary removed, to yield the optically pure isoxazolidines 49a and 49b. Adduct 49a was converted into the nitrile and thence to the acid 50 in order to facilitate formation of the hydrazide moiety. The
Cbz-group was removed by catalytic hydrogenolysis, and simultaneous N-O cleavage afforded (+)-negamycin 51. Similarly, the isoxazolidine 49b was manipulated to afford the (3S)-epimer of this natural product, (-)-epinegamycin 51.

\[
\begin{align*}
\text{Reagents:} & \quad \text{i, CH}_2\text{=CHCH}_2\text{NHCbz; ii, 10% aq. HCl; iii, BnBr iv, LiAlH}_4; \quad \text{v, TsCl, iPrNEt, Et}_3\text{N;} \quad \\
& \quad \text{vi, NaCN, DMSO; vii, HCl/EtOH; viii, 4% aq. NaOH, MeOH; ix, CICO}_2\text{Et, Et}_3\text{N, toluene;} \\
& \quad \text{x, benzyl (1-methylhydrazino)acetate; xi, H}_2, 3 \text{ atm., Pd-C, 10% aq. AcOH, MeOH.}
\end{align*}
\]

Scheme 25

One problem that has regularly reduced the potential for asymmetric induction of many of the nitrones discussed thus far is the free rotation of the C- or N-to-auxiliary bond. Many researchers have found that the auxiliary is of little use if it is free to rotate in the transition state of the 1,3-dipolar cycloaddition reaction. The use of chiral cyclic nitrones confers a much more rigid conformation on the nitrone and allows highly effective shielding of the chosen face of the nitrone by the chiral substituent in the ring. In addition, cyclic
nitrones are unable to interconvert between the $E$- and $Z$-isomers of the nitrone, so this extra stereochemical complication is absent. Vasella was one of the first to take advantage of the improved facial selectivity in 1,3-dipolar cycloaddition reactions offered by cyclic nitrones. His sugar-derived spirocyclic nitrone 53 was followed by many others including the range of tartaric-acid-derived nitrones such as 54a and 54b or 55 derived from erythritol,1,90,91 56 from malic acid,92,93 or 57 from prolinol (Figure 13).94

Figure 13

Reagents : i, methylenecyclopropane, $C_6H_6$, 7 days, 25°C; ii, xylene, 140°C, 1.5h; iii, TsNNH$_2$, MeOH, 7h; iv, NaBH$_4$, 65°C, 20h; v, 40% aq. HF, CH$_3$CN, 25°C, 2 days.

Scheme 26
Brandi has used these reagents in the synthesis of a number of indolizidines, also utilising the 5-aza-4-oxaspiro[2,4]heptane to piperidin-4-one rearrangement seen in his route to (2S)-4-oxopipeolic acid 44 (Scheme 24). For example, the L-tartrate-derived nitrone 54a gave the desired regioisomer of the spiro-isoaxazolidine cycloadduct 58 as a 10:1 mixture of the separable diastereoisomers (Scheme 26). The desired isomer was thermally rearranged to the intermediate ketone 59. The target indolizidine alkaloid lentiginosine 60 was then obtained by decarbonylation and removal of the silyl protecting groups. The bicyclic ketone 59 was also used to prepare both of the C-7 hydroxylated epimers of this target molecule. Brandi has employed a similar strategy with the malic acid-derived nitrone 56, to synthesise further indolizidines.

Wightman et al. have developed nitrone 55 derived from erythritol for cycloaddition with a silyl-protected allyl alcohol to prepare homochiral polyhydroxylated pyrrolizidines and indolizidines. The L-(+)-prolinol-derived nitrone of de March et al. 57 gave complete diastereofacial selectivity in its cycloaddition reactions with a number of different dipolarophiles, but endo:exo selectivities were variable. The homochiral nitrone 61 (Scheme 27) developed by Saito et al. combines features from nitrones 54 and 57 and its cycloadditions with fumaric and maleic acid derivatives proceed with complete regio- and diastereoselectivity. Oppolzer et al. have used a nitrone carrying their well-known (2S)-bornane-10,2-sultam chiral auxiliary 62 in the total synthesis of (-)-allosedamine 63. The homochiral nitrone 64, produced from an acyclic starting material 65, underwent a 1,3-dipolar cycloaddition with styrene to produce only the exo isomer of isoxazolidine 66 with a de = 93%. The sultam auxiliary was removed with lithium hydroxide, and recovered in almost quantitative yield, whilst the resultant carboxylate side-chain was
converted to the nitrile. N-Methylation with methyl triflate was followed by N-O bond cleavage and decyanation with zinc in acetic acid to afford the natural product 63.

**Scheme 27**

**Reagents:** i, NaN(SiMe$_3$)$_2$, THF, -78°C, 1h; ii, 1-chloro-1-nitrosocyclohexane, -78°C, 1h; iii, 2M aq. HCl, -78°C, 12h; iv, styrene, CH$_2$Cl$_2$, Δ, 2h; v, LiOH, THF, 55°C, 30h; vi, iBuOCOCl, N-methylmorpholine, -15°C then gaseous NH$_3$, 25°C; vii, (CF$_3$CO)$_2$O, 1,4-dioxane, pyridine, 25°C, 1h; viii, MeOSO$_2$CF$_3$, CH$_2$Cl$_2$, -10°C, 20min, → 25°C, 30min.; ix, Zn dust, H$_2$O, THF, 2M aq. HCl, AcOH, 25°C, 20h.

**Scheme 28**

**Reagents:** i, RC(OEt)$_3$, CH$_2$Cl$_2$, 25°C, 1h; ii, Et$_3$N.
The synthesis of oxazoline nitrones 67 from the β-hydroxylaminoalcohols 68, originally devised by Coates and Ashburn (Scheme 28), has been extended by Langlois et al. to produce the camphor-derived nitrone 69 for the total synthesis of (-)-frontalin 70 (Scheme 29). The 1,3-dipolar cycloaddition of the nitrone 69 with methyl methacrylate produces the endo isomer of the 5-isoxazolidine 71 as the major product (endo:exo >95:5, 5-substituted:4-substituted >95:5). The methyl ester of this cycloadduct is reduced to the alcohol and protected as the benzyl ether before isoxazolidine N-O cleavage, and removal and recovery of the camphor auxiliary 72 to give the aldehyde 73. This compound is a known intermediate in the synthesis of (-)-frontalin 70, and is converted to the natural pheromone in two steps.

Reagents: i, methyl methacrylate, toluene, 80°C, 2h; ii, LiAlH₄, Et₂O, 0.5h; iii, BnBr, cat. n-Bu₄I, THF/DMF, 0 → 25°C, 4h; iv, mCPBA, Et₂O, 25°C, 1h; v, 2M aq. HCl, THF, 25°C, 5mins.; vi, Ph₃P=CHCOCH₃, MeCN, Δ, 4h; vii H₂, Pd-C, MeOH, 18h.

Scheme 29
The Langlois group has also used this methodology in the synthesis of β-lactones and the potential AIDS treatment (+)-carbovir. In this latter example, the 1,3-dipolar cycloaddition of nitrone 69 with cyclopentadiene proceeds at 40°C with high regio- and stereoselectivity and, as in the frontalin synthesis, the camphor skeleton 72 is recovered.

![Figure 14](image)

**Figure 14**

The L-menthone-derived nitrone 74 was produced by Katagiri et al., and gave a single isoxazolidine product in 90% yield in its 1,3-dipolar cycloaddition reaction with allyltrimethylsilane at 40°C and 800MPa (Figure 14). This cycloadduct was manipulated to yield enantiomerically pure amino-acids via methodology that allowed regeneration of the L-menthone auxiliary. The morpholinone nitrone 75 was prepared by Tamura et al. for reaction with a number of alkene dipolarophiles: the reaction with 2-methylpropene gives an 87% yield of a single isomer of the isoxazolidine cycloadduct.
1.3.2 Chiral alkene dipolarophiles in 1,3-dipolar cycloadditions

The first chiral alkenes to be employed in nitrone 1,3-dipolar cycloaddition reactions were unsaturated natural products and related compounds, including lumisantonin, the steroid skeleton and elaiophylin. Subsequent work has focussed mainly on the utility of chiral α,β-unsaturated carbonyl compounds (especially lactones, esters, esters, and amides), vinylic and allylic ethers, allylic amines, as well as vinylic sulphoxides and phosphine oxides.

```
Reagents : i, NaOMe, MeOH, 20°C, 15min; ii, NaIO₄, MeOH, H₂O, 20°C, 24h; iii, NaCNBH₃, 2M aq. HCl, MeOH, 20°C, 1h; iv, TBDMSCl, imidazole, DMF, 20°C; v, H₂, 10% Pd-C, MeOH, 20°C.
```

Scheme 30
The use of chiral \( \alpha,\beta \)-unsaturated lactone dipolarophiles derived from sugars has been studied vigorously by a number of groups, and Chmielewski et al. were able to apply this cycloaddition approach to the synthesis of chiral \( \beta \)-lactams.\(^{110,112}\) The chiral dehydrolactone 76 reacted regio-, stereo- and facioselectively with C-(4-methoxyphenyl)-N-phenylnitrone 77, to give the bicyclic isoxazolidine 78 in 56% yield (Scheme 30). The acetate protecting groups and the lactone were methanolysed to afford a monocyclic triol, from which a two-carbon segment was excised by vicinal diol cleavage with sodium periodate. This afforded the aldehyde 79, which was reduced with sodium cyanoborohydride, and the resultant alcohol protected as its TBDMS ether. Hydrogenolysis of the isoxazolidine N-O bond allowed spontaneous ring-closure to afford the \( \beta \)-lactam 80 in 60% overall yield. In a related report, Paton et al. have shown that the 1,3-dipolar cycloaddition reaction between the cellulose-derived bicyclic lactone levoglucosenone and C,N-diphenylnitrone, give a single diastereomer of the cycloadduct (68%) although reaction is slow (two days at 110°C).\(^{113,114}\)

Feringa et al. have carried out a number of nitrone cycloadditions with chiral furanone dipolarophiles.\(^{116,117}\) They prepared the chiral 4-substituted furanone 81 from the racemic 4-hydroxyfuranone and menthol, by epimerisation of the unwanted diastereomer.
and simultaneous crystallisation of 81 from the reaction mixture. Subsequent reaction with C,N-diphenylnitrone 82 affords the exo isoxazolidine 83 along with the endo isomer (80% yield, exo:endo = 65:35) (Scheme 31). The diastereofacial selectivity of the cycloaddition is due to the highly effective shielding of one face of the alkene by the menthol moiety (R*). A similar strategy has been used in the synthesis of bicyclo[3.3.0]isoxazolidinyl nucleosides in the discovery of novel anti-HIV agents.115

An example of the use of chiral, acyclic α,β-unsaturated ester dipolarophiles is provided by Saito et al., who have employed a range of tartaric acid derivatives in nitrone cycloadditions.140 Reaction between 84 and 2,3,4,5-tetrahydropyridine-N-oxide 85 gives almost exclusively endo-86, with excellent diastereofacial selectivity (>98%) (Scheme 32). Other nitrones, both cyclic and acyclic, were used in 1,3-dipolar cycloaddition reactions with this alkene and they showed moderate to excellent endo:exo selectivities and excellent diastereofacial selectivity. 1,3-Dipolar cycloaddition reactions with γ-hydroxy-α,β-unsaturated carbonyl compounds have been investigated by other research groups119,141,142 but all show lower selectivities than those of Saito et al.

![Scheme 32](image)

There has been a small number of investigations which have used vinyl ester dipolarophiles carrying the chiral auxiliary on the carboxylate. The esters 87 developed by
Tejero\textsuperscript{143} and 88 by Carriere\textsuperscript{144} showed very poor selectivities, in contrast to the camphor-derived vinyl ester 89 of Olssen,\textsuperscript{145} which demonstrated excellent diastereofacial selectivity but no \textit{endo:exo} selectivity (Figure 15).

![Figure 15](image)

**Scheme 33**

N. Langlois \textit{et al.} have applied chiral $\alpha,\beta$-unsaturated $\gamma$-lactams such as 90 derived from (S)-pyroglutaminol in reactions with N-benzylnitrone 91 (Scheme 33).\textsuperscript{146} They observed a 75% yield of tricyclic isoxazolidine 92 and only 3% and 5% of two other isomers as well as 4% of the product of 1,4-addition of N-benzylhydroxylamine. Murahashi \textit{et al.} have utilised chiral $\alpha,\beta$-unsaturated amides to prepare isoxazolidine precursors to enantiopure natural products (Scheme 34).\textsuperscript{122} The cyclic nitrones 93 and 85 were reacted with crotonamide dipolarophiles 94 containing either the (2R)-enantiomer of Oppolzer’s
sultam moiety (2R)-62 or (R)-4-benzyl-2-oxazolidinone 95 as the chiral auxiliary, to afford excellent yields of the endo cycloadducts 96/97 and 98/99. The sultam of isoxazolidine 98 was further manipulated to afford (+)-sedridine 100 after hydrolysis, Barton decarboxylation and hydrogenolysis. The related natural product (+)-hygroline 101 was prepared from the sultam of isoxazolidine 97 by a similar procedure, which included N-methylation prior to N–O bond hydrogenolysis.

Reagents: (X= (2R)-62 : 98→100) i, aq. LiOH ii BuOCOCI, N-methyl-morpholine; iii, 2-mercaptopyridine-N-oxide, Et3N; iv, BuSH, hv; v, H2, Pd-C; (X=95 : 97→101) i to iv, above; v, CH3I; vi, H2, Pd-C.

Scheme 34

Chiral vinyl ethers have generated little research interest in the field of asymmetric nitrone cycloadditions, although most notably these dipolarophiles have been used by Carruthers et al. to prepare enantiopure piperidine alkaloids,123 and by De Shong et al. in the synthesis of the amino-sugar daunosamine.62 By contrast, the use of chiral allylic ethers and alcohols is extensive and well illustrated in the work of Kibayashi et al. who
championed this approach and demonstrated its worth by the total synthesis of a number of natural products including (-)-coniine 102,126 (+)-monomorine 1 103,124,125 and (-)-oncinotine 104 (Scheme 35).127 The O-benzylallylic ether 105a was reacted with 2,3,4,5-tetrahydropyridine-N-oxide 85 to afford a 4:1 mixture of isoxazolidine cycloadducts from which the major isomer 106 was isolated to provide (-)-coniine 102 in a further five steps. The cycloadduct of 85 and a silylated allylic ether 105b was manipulated to afford the macrocyclic spermidine alkaloid (-)-oncinotine 104. The indolizidine (+)-monomorine 1103 was also prepared from allylic ether 105a by cycloaddition to a glyoxalate-derived nitrone, followed by a lengthy elaboration. A number of other workers have carried out related investigations with chiral allylic ether dipolarophiles.147,148

\[
\begin{align*}
\text{Norseoxide} & \quad \text{PhMe, } \Delta \quad 66\% \\
85 & \quad 105a \quad R^1 = \text{Bn}, R^2 = \text{Bu} \\
& \quad 105b \quad R^1 = \text{TBDPS}, R^2 = \text{Bu} \\
\end{align*}
\]

\[
\begin{align*}
85 & + \quad 105a \quad \text{PhMe, } \Delta \quad 66\% \\
& \quad 105b \\
& \quad 106 \\
& \quad \text{Reagents : i, H}_2, 5 \text{ atm}, \text{PdCl}_2, \text{MeOH}; \\
& \quad \text{ii, BnOCOCl, Na}_2\text{CO}_3, \text{CH}_2\text{Cl}_2; \\
& \quad \text{iii, HI}_4, \text{THF, H}_2\text{O}; \\
& \quad \text{iv, Ph}_3\text{PMeBr, BuLi, THF}; \\
& \quad \text{v, H}_2, \text{Pd-C, MeOH}. \\
\end{align*}
\]

Scheme 35

Those chiral allylic amines used in 1,3-dipolar cycloaddition reactions have invariably been derived from L-α-amino-acids.129-134 The N-protected allylic amine 107,
prepared from phenylalanine, was used in the synthesis of the polyamide 108 - a novel renin inhibitor and potential anti-hypertensive agent (Scheme 36).\textsuperscript{133} The cycloaddition of 107 with N-benzyl-C-methylnitrone 109 gave isoxazolidine 110 after chromatography, before hydrogenolysis of the N-O bond, debenzylation and conversion of the free amine to the pentanamide. The synthesis of 108 was completed by removal of the Boc group and DCC-mediated coupling of this moiety with (S)-cyclopentylglycine and then morpholinocarbonylphenylalanine.

Other research groups have demonstrated the utility of chiral vinyl glycine derivatives; for example, in the preparation of (3R)- and (3S)-hydroxyornithines and arginines.\textsuperscript{130-132} Reported yields are high but with little diastereoselectivity (3:2), although the cycloadducts are separable by chromatography. Whitney \textit{et al.} have used a similar strategy in the synthesis of the naturally occurring antitumour antibiotic acivicin.\textsuperscript{149,150}

![Scheme 36](image)

\textit{Reagent} : i, HCO\textsubscript{2}NH\textsubscript{4}, 10% Pd-C, MeOH, 64°C; ii, (n-BuCO)\textsubscript{2}O, Et\textsubscript{3}N, MeOH; iii, 4M aq. HCl, dioxane; iv, (S)-cyclopentylglycine, DCC, HOBT, iPr\textsubscript{2}NEt; v, 4M aq. HCl, dioxane; vi, morpholinocarbonylphenyl-alanine, DCC, HOBT, iPr\textsubscript{2}NEt.

\textbf{Scheme 36}
Japanese workers have developed a large-scale synthesis of the alkaloid (2R, 4R, 5S)-tetrahydropseudodistimin 111 from a chiral vinylglycinol derivative 112 (Scheme 37). A tetradecanal-derived nitrone 113 reacts with allylamine 112 to give a mixture of four isoxazolidines from which the desired isomer 114 is readily separable. Conversion to the desired alkaloid 111 is accomplished in three steps, which compares very favourably with the previously reported 24-step synthesis.

Reagents: \( i, \text{MsCl, C}_5\text{H}_5\text{N, 0°C}; ii, 10\% \text{Pd(OH)}_2-\text{C, MeOH, 20°C}; iii, \text{TFA, CH}_2\text{Cl}_2, 20°C. \)

Scheme 37

Reactions involving chiral vinyl sulphoxide dipolarophiles are a less well studied area of nitrone cycloaddition chemistry. Rare examples include the synthesis of iso-ephedrines which has been achieved by Japanese researchers using \((R)-(+)\)-p-tolylvinyl

Scheme 38
sulphoxide whilst Bravo et al. have synthesised fluorinated isoxazolidines.\textsuperscript{137} Reaction of 2,3,4,5-tetrahydropyridine-N-oxide 85 with sulphoxide 115 gave a 95\% yield of 116 and another isomer (91:9) after a 7-day reaction. Isoxazolidine 116 was converted to (+)-sedridine 100 in a single N-O cleavage and desulphurisation step with Raney Nickel (Scheme 38).\textsuperscript{138}

Amongst the more unusual dipolarophiles are the chiral exo-cyclic alkenes of Diazortiz et al. and Pyne et al. (Scheme 39).\textsuperscript{152,153} For example, reaction of 117 with C,N-diphenylnitrone 83 affords isoxazolidine 118 as a mixture of endo:exo isomers in a ratio of 70:30. Both products arise from attack of the nitrone at the face of the alkene which is anti to the phenyl substituent.\textsuperscript{153}

![Scheme 39](image)

**1.3.3 Chiral catalysts**

The use of sub-stoichiometric amounts of optically active materials to induce chirality has found broad application in carbo- and hetero-Diels-Alder reactions.\textsuperscript{154} However, chiral catalysis of nitrone 1,3-dipolar cycloaddition reactions was until recently a relatively
unexplored area. Important pioneering work\textsuperscript{155,156} was carried out by Kanemasa et al. who in 1992 published their investigations of the effect of zinc- and titanium-based catalysts on the reaction of N-methyl-C-phenyl nitrone 119 with the enone 120 (Scheme 40).\textsuperscript{155} The uncatalysed reaction proceeded in 8 hours at 80°C to afford a 40:60 mixture of the endo and exo 4-keto-isoxazolidines 121a and 121b in 78% yield. In their best result, the use of a stoichiometric amount of Ti(OiPr)\textsubscript{2}Cl\textsubscript{2} afforded only a 50% yield of the two isoxazolidines after 32 hours at 0°C, but with an impressive endo:exo ratio of 99:1.

Scheme 40

Scheme 41
In a more recent example, Jørgensen showed that C,N-diphenylnitrone 83 reacts with N-crotonyl-2-oxazolidinone 122 in the presence of Ti-TADDOL catalyst 123 to give predominantly the exo-cycloadduct 124b in high yield (94%) and fair diastereomeric excess (58%) (Scheme 41). The same group later applied Mg(II) and Cu(II)-derived bis-oxazoline catalysts to similar transformations to achieve an enantiomeric purity of the isoxazolidine cycloadduct of up to 82%.158
Chapter 2

Results and Discussion
2.1 Strategy

From the foregoing examples from the recent literature (Section 1.3), it can be seen that nitrone reagents 8 carrying a chiral auxiliary on nitrogen have the potential for highly effective asymmetric induction in 1,3-dipolar cycloaddition reactions (Figure 16). As we have shown, their usefulness is often limited by the conformational mobility about the C- or N-to-auxiliary bond. The use of chiral cyclic nitrones 9 introduces a means of rotational restraint and enforces the diastereofacial influence of the auxiliary.

![Figure 16: The diastereofacial nature of 1,3-dipoles based on chiral 2-imidazolines.](image)

Previous workers in the Jones group have prepared azomethine ylide 1,3-dipoles based on the 2-imidazoline (or 4,5-dihydroimidazole) moiety 125a as a template. These reagents undergo 1,3-dipolar cycloaddition reactions with a number of dipolarophiles, offering access to functionalised pyrrolidines, pyrroles and pyrroloimidazoles.159-161 These workers were able to demonstrate that the optically active ylide 125b and its enantiomer show complete facial discrimination in their 1,3-dipolar cycloaddition reactions.162,163 A simple two-step template removal strategy was subsequently developed to complete this elegant synthetic route to optically active substituted pyrrolidines.164 In
order to capitalise on the properties of this 2-imidazoline moiety as a chiral template, we proposed to prepare the novel chiral nitrone 1,3-dipoles 126 and their enantiomers in order to investigate their 1,3-dipolar cycloaddition chemistry.

2.1.1 Homochiral 2-imidazoline azomethine ylides

![Scheme 42](image)

Reagents: i, PhCH$_2$OCOCl, aq. NaOH; ii, N-methylmorpholine, EtOCOCl, BnNH$_2$; iii, H$_2$, Pd-C; iv, BH$_3$.THF; v, HC(OEt)$_3$, p-TsOH.

Scheme 42

The synthesis of these 1,3-dipoles uses (R)- and (S)-phenylglycine 127 as the chiral source and proceeds via the 2-imidazolines 128 (Scheme 42) from which the azomethine ylides are generated for use in situ. The cheap, commercially available enantiopure amino-acids were first protected on nitrogen as the benzyloxycarbonyl (Cbz) derivatives in
high yield using benzyl chloroformate. These carbamates could then be used without purification to prepare the N-benzyl amides 129 via the mixed anhydrides formed with ethyl chloroformate. Quantitative hydrogenolysis of the Cbz-protection over palladium on carbon to give the amino amides 130 was followed by reduction of the carbonyl groups with borane-tetrahydrofuran complex (BH₃·THF) to afford the diamines 131. The synthesis was completed by heating the diamines 131 with triethyl orthoformate in the presence of catalytic p-toluenesulfonic acid to generate the homochiral 2-imidazolines (R)- or (S)-128 in 46% or 52% overall yield from (R)- or (S)-127, respectively.

![Scheme 43](image)

The azomethine ylides (R)- and (S)-125b were generated by a one-pot process which begins by alkylation of the 2-imidazolines (R)- and (S)-128 in refluxing THF with an activated haloalkane such as methyl or tert-butyl bromoacetate under anhydrous conditions (Scheme 43). In the presence of 3 equivalents of the dipolarophile, 1 equivalent of DBU is added over 4 hours to allow immediate cycloaddition of the ylide as soon as it is formed. For example, the azomethine ylide (S)-132 was prepared from (S)-128 and tert-butyl bromoacetate, and 1,3-dipolar cycloaddition with methyl methacrylate afforded the hexahydropyrroloimidazole 133 (61%).
The major product in the 1,3-dipolar cycloaddition reactions to the chiral azomethine ylide dipoles (R)- or (S)-125b was found to be the isomer arising from attack at the less hindered face of the ylide and via the endo transition state (Figure 17). This was determined using nuclear Overhauser enhancement (nOe) spectroscopy. This NMR technique, which will be discussed in more detail in Section 2.3, allows us to determine which protons in the $^1$H spectrum are adjacent through space.

![Figure 17: Assignment of stereochemistry of 133 by nOe and the endo transition state from which it arises.](image)

In this way, it was found that for adduct 133, through-space interaction existed between the protons connected by arrows in Figure 17; that is, between H$^a$, H$^b$ and H$^c$, and between H$^d$, the C-7 methyl group and H$^e$. Thus, with the C-3 stereochemistry known, we can see that H$^a$, H$^b$ and H$^c$ lie on the lower face of 133, with H$^d$, the C-7 methyl group and H$^e$ on the top face. The configuration of the bridgehead proton at C-7a (H$^f$) shows that the dipolarophile is directed to the lower face of the ylide (S)-132; reaction at the upper face is made unfavourable by the bulk of the phenyl group at C-3. The stereochemistry at C-7
would arise from the *endo* transition state, suggesting a secondary orbital interaction between the 1,3-dipole and the ester functionality stabilising this transition state geometry prior to bond formation. From the stereochemistry at C-5, we can see that the X-substituent is *anti* to the C-3 to N-4 bond as drawn for the *endo* transition state in Figure 17.

![Chemical Structures and Reagents](image)

*Reagents*: i, NaCNBH₃, pH3; ii, H₂, Pd-C; iii, PhCH₂OCOCl, Et₃N, DCM; iv, TFA; v DCCI, HOSu, THF then NaBH₄, THF; vi, TPAP, NMO, DCM; vii, (EtO)₂PCH₂CO₂Et, NaH, THF; viii, H₂, 60psi, 10% Pd-C, MeOH; ix, Xylene, Δ.

**Scheme 44**

Removal of the imidazoline chiral template was achieved in two steps (Scheme 44). Firstly, reduction of the aminal moiety of 133 with sodium cyanoborohydride at pH3 afforded a near quantitative yield of the pyrrolidine 134. This was followed by hydrogenolysis of the pyrrolidine N-benzyl moiety over Pearlman’s catalyst (palladium hydroxide on carbon) to afford the proline derivative 135. The differentiated ester protection at C-2 and C-4 should allow manipulation to take place at either position. As an illustration,
pyrrolizidinone 136 was prepared by conversion of the C-2 ester to the aldehyde and chain extension by the Wadsworth-Emmons reaction, followed by thermal cyclisation to the lactam.

In conclusion, it is clear that this 2-imidazoline chiral template offers complete diastereofacial selectivity in azomethine ylide cycloaddition reactions, making this a powerful strategy for rapid access to enantiopure natural products.

2.1.2 Homochiral 2-imidazoline nitrones

![Diagram of the synthesis of 136 through 139 and their derivatives]

Reagents proposed: Ⅰ, NaNO₂, HBr; Ⅱ, EtOCl, N-Methylmorpholine, BnNH₂; Ⅲ, NH₂OR.HCl, base; Ⅳ, BH₃·THF; Ⅴ, R = Bn, H₂, Pd-C; Ⅵ, R'C(OEt)₃, H⁺.

Scheme 45
With this azomethine ylide methodology in hand, we initially proposed to prepare the related homochiral nitrone dipoles \((R)\)- and \((S)\)-126 using a revised and novel route (Scheme 45), again using phenylglycine as the chiral source. The plan was to first brominate via diazotisation in the presence of aqueous HBr to afford the \(\alpha\)-bromoacid 137. This centre is now set up for nucleophilic substitution by an O-alkylhydroxylamine (for example, \(R=\text{Bn}\)). The bromo amide 138 would be provided by reaction of the acid chloride from 137 with benzylamine before amide reduction with \(\text{BH}_3\cdot\text{THF}\) followed by catalytic hydrogenolysis of the N-benzyl protecting group to afford the amino hydroxylamine 140. Ring closure of this key intermediate would be effected with triethyl orthoesters to access nitrones 126 with defined C-2 substitution. We proposed to prove our methodology on racemic material before applying it to the synthesis of the enantiopure nitrones.

![Scheme 46](image)

Once we had developed a robust synthesis of our novel 2-imidazoline nitrone reagents, we would examine the scope of their 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles. Our first priority would then be to determine whether the cycloaddition proceeds with facial selectivity and regioselectivity. We hoped to be able to chart the electronic requirements of the dipolarophile by reaction with doubly- and triply-bonded species carrying electron-withdrawing, conjugating or electron-donating substituents.
and we will discuss our findings in terms of Frontier Molecular Orbital theory. We proposed that a 1,2-disubstituted alkene would add to the less hindered face of these nitrones. Therefore, we suggest that the reaction of (S)-126a (R=H) with such an alkene would afford the isoxazolidine 141 in which the stereochemistry at C-7a is defined by the C-5 stereochemistry of the dipole 126a (Scheme 46). We planned to investigate the cycloaddition reactions of C-2 functionalised 2-imidazoline nitrones, for example 126b (R=Me) and 126c (R=Ph). We will ascertain the preferred transition state geometry from the stereochemistry of the isolated isoxazolidine products. Analogy to the corresponding azomethine ylides would predict endo approach to be dominant here, that is to say the isoxazolidine endo-141 would be the major product of the reaction of a trans- disubstituted alkene with nitrone (S)-126a.

![Scheme 47](image)

We planned to remove the chiral template by a two-step protocol of aminal reduction to 142 then hydrogenolysis (Scheme 47). We will take advantage of the synthetic track record of isoxazolidines based on N–O bond cleavage and will seek to fulfil the potential of
our cycloadducts for recyclisation, for example via lactamisation to afford homochiral substituted pyrrolidinones 143. Alternatively, one can envisage cleavage of the N–O bond with acid hydrolysis of the cycloadducts to unmask carbonyl functionality and access enantiopure substituted β-hydroxyaldehydes and ketones 144.

\[
\begin{align*}
\text{Scheme 48}
\end{align*}
\]

To the best of our knowledge, 1,3-dipolar cycloaddition reactions of 2-imidazoline nitrones are unknown in the literature although, as we shall see, closely related reagents have been prepared. In contrast, the 1,3-dipolar cycloaddition reactions of 3-imidazoline nitrones have been investigated by three separate research groups.\textsuperscript{165-173} Most recently, Coskun \textit{et al.} have prepared a series of 3-imidazoline nitrones from the corresponding imines (Scheme 48).\textsuperscript{174,175} The imine 145 is alkylated with syn-2-bromoacetophenone oxime 146 to generate the brominated species 147 which cyclises on addition of triethylamine to
afford the 3-imidazoline nitrones 148 in poor yields (22-31%). The 5,6-dihydro-4H-1,2,5-oxadiazines 149 were also isolated in small, as yet unreported, yields. A selection of these 3-imidazoline nitrones has been utilised in 1,3-dipolar cycloaddition reactions with styrene or with aryl isocyanate dipolarophiles to afford the adducts 150. These reactions afford fair (49-50%) and excellent yields (90-100%) of each type of cycloadduct after 72 hours in refluxing toluene or 2.5 hours in refluxing acetonitrile respectively.165-167

Hungarian, French and Russian researchers have reported the preparation of 2- and 3-imidazoline nitrones as intermediates in the synthesis of imidazoline-derived nitroxyl radicals.168,176-185 These highly stable radicals have been used as spin labels and probes for the study of other radical species (for example, NO⁻), and as paramagnetic ligands in the chemistry of coordination compounds. The 3-imidazoline nitrones of Volodarsky et al. have been shown to undergo a 1,3-dipolar cycloaddition reaction with isocyanates168,169 and alkenes,168,170,171. For example, the 2,2,5,5-tetramethyl-3-imidazoline-3-oxide-1-oxyl radical 151 reacted with isocyanates to afford the oxadiazolinone cycloadducts 152 (Scheme 49).169 Sharma et al. have prepared substituted 3-imidazoline nitrones from diazabutadienes and nitrosostyrenes.172 These workers have also used these reagents to synthesise

![Scheme 49](image-url)
functionalised N-oxides of imidazole which react with DMAD to afford dihydroimidazoisoaxazole cycloadducts.173

Scheme 50

Chmielewski et al. prepared a range of 2-imidazolinone nitrones based on the work of Toda et al.186 who had reported their synthesis of these reagents as intermediates in the preparation of nitroxide radicals. The Polish group described the reaction of their nitrones with a number of dipolarophiles including acrylate esters, styrene and phenyl isocyanate, from which they isolated the desired cycloadduct in each case.187 For example, the 2,5,6-diphenyl-5-methyl-2-oxo-imidazolin-1-oxide 153 was reacted with excess methyl crotonate in refluxing toluene for 10 hours to produce imidazoisoaxazol-2-one 154 in 95% yield (Scheme 50). The assignment of their stereochemistry was based on earlier observations where similar nitrones added via the exo transition state.

Scheme 51
The chemistry of nitrones based on piperidine and pyrrolidine rings is well-documented in the literature. A number of research groups have now reported the synthesis of the unusual 4-membered heterocyclic nitrones.\textsuperscript{188-192} Black \textit{et al.} have prepared these azetidine nitrones by the intramolecular cyclisation of \( \gamma \)-tosyloxy oximes.\textsuperscript{189} Elsewhere, Reinhoudt has demonstrated that oxidation of N-hydroxyazetidines such as 155 with lead(IV) oxide affords the azetine-1-oxides 156 (Scheme 51).\textsuperscript{188,190,191} They went on to prove their utility in a 1,3-dipolar cycloaddition reaction of 156 with DMAD at 0°C to afford the isoxazoline cycloadduct 157 in a yield of 42%.

Having established the novelty and feasibility of our proposed 2-imidazoline nitrone reagents from this reference to the literature, the following section will detail the results of our investigations.
2.2 Synthesis of 2-imidazoline nitrones

In this section, we will show how our synthetic route to 2-imidazoline nitrones was developed and how these reagents were applied in 1,3-dipolar cycloaddition reactions. A common strategy of nitrone synthesis is direct oxidation of the corresponding imine and our attempts in this area will be presented at the end of this section along with other attempted syntheses.

2.2.1 Approaches from 2-phenylglycine

As we have shown (Section 2.1), our initial starting point for the synthesis of nitrones containing the 2-imidazoline moiety was 2-phenylglycine 127. We proposed to introduce the hydroxylamino functionality at the α-position of this amino acid via 2-bromo-2-phenylacetic acid 137 (Scheme 52). Our initial strategy was to take advantage of the well-studied α-deaminative halogenation reactions of amino acids to form intermediate 137 with control of configuration and then perform nucleophilic substitution with inversion using a hydroxylamine. Bromination of racemic 2-phenylglycine as a model was thus performed by diazotisation with aqueous sodium nitrite at 0°C in the presence of conc.
HBr such that the diazonium species 158 was immediately quenched with bromide. However, the aqueous reaction conditions meant that we were often unable to prevent formation of the α-hydroxy acid (mandelic acid) 159 by attack of water on the diazonium intermediate. Fortunately, this impurity was easily separated from the desired product 137 by column chromatography on silica gel.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ph-Gly (grams)</th>
<th>NaNO₂ (equivs.)</th>
<th>H₂O:c. HBr (v/v)</th>
<th>137:159 (moles)</th>
<th>Yield of 137 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>1.1</td>
<td>1:3.33</td>
<td>18:1</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>1.1</td>
<td>1:2</td>
<td>12:1</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>2.0</td>
<td>1.1</td>
<td>1:2</td>
<td>8:1</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>1.1</td>
<td>1:1</td>
<td>3.7:1</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>1.1</td>
<td>1:1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>1.1</td>
<td>1.6:1</td>
<td>2.4:1</td>
<td>32</td>
</tr>
<tr>
<td>7</td>
<td>5.0</td>
<td>1.1</td>
<td>2:1</td>
<td>1.7:1</td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td>5.0</td>
<td>1.1</td>
<td>5:1</td>
<td>2:1</td>
<td>67</td>
</tr>
</tbody>
</table>

Table 2: Effect of solvent mixture on yield and purity of 137.

Our efforts towards optimisation of this reaction centred on the relative proportions of water and conc. HBr (Table 2). In a general procedure, 2-phenylglycine 127 was dissolved in 75% of the total water used and treated with all of the conc. HBr. The solution was cooled to 0°C and treated with a solution of sodium nitrite (1.1 equivalents) in the remaining 25% of the water. After 30 minutes at 0°C, the solution was warmed to room
temperature and stirred for a further hour. The resultant mixture was diluted with DCM and water before extraction with further DCM. It was found that a large excess of water in the reaction solvent gave the highest yield of 137 (67%) but also gave the least favourable product mixture (2:1 mixture of 137 & 159 respectively) (entry 8). Experiments performed in excess conc. HBr (entries 1, 2 & 3) gave relatively little mandelic acid 159 but yields of the bromide 137 were disappointingly low (20-44%). Experiments which used 1:1 mixtures (entries 4 & 5) performed worst of all (0-6%) with a marked improvement in yield as the ratio moved to either side.

We were encouraged by these results to attempt α-bromination of non-racemic 2-phenylglycine (entry 7). However, the α-bromo acid we isolated after reaction of (S)-127 showed essentially no optical activity; $[\alpha]_D^{20} = 0.73^\circ$ (c=0.15, DCM) [lit. $[\alpha]_D^{20} = -104.6^\circ$ (c=3, ether), $[\alpha]_D^{13.5} = -147.0^\circ$ (c=2, benzene)]. It is clear that nucleophilic attack of bromide on the diazonium species (S)-158 with concomitant loss of the leaving group (N₂ gas) via Walden inversion would afford (R)-137 (Scheme 53). The deaminative bromination reaction of α-amino-acids usually proceeds with inversion of configuration at the α-carbon stereocentre, but where retention of configuration is observed, it is thought to occur via neighbouring group participation of the carboxylic acid. Here, the first nucleophilic attack at the α-carbon of (S)-127 is by the adjacent carboxylate which is said to be lending anchimeric assistance. Ring-opening of the severely strained 3-membered α-lactone intermediate 160 should be extremely facile, and as this mechanism involves a second inversion of the stereocentre, the isolated product is now (S)-137. If either of these two potential mechanisms predominates, our homochiral synthesis would be intact. This racemisation suggests either that both mechanisms operate to a near identical extent, or more
likely in this case, that the phenyl substituent promotes an $S_N1$ pathway via a planar benzylic carbocation 161.

Since the completion of our study, Coric et al. have reported the synthesis of a number of $\alpha$-bromo carboxylic acids, with retention of configuration, from the corresponding amino-acids$^{194}$ by the Fischer procedure.$^{208}$ Their report includes the preparation of (R)-137 by treatment of a solution of (R)-phenylglycine in 8 equivalents of 48% HBr and water ($2/3 \, v/v$) at 0°C with an aqueous solution containing 3.2 equivalents of NaNO$_2$. After 2 hours at 0°C this solution afforded the oily bromo acid, which slowly crystallised on standing, in a yield of 96%.
2-Bromo-2-phenylacetic acid 137 is not available commercially as a single enantiomer but can be resolved by fractional crystallisation of the diastereomeric salts formed with the commercial chiral amine brucine 162 (Figure 18). Therefore, we were content to proceed with the further development of this route on racemic material, with the intention to employ optically active bromo acid at a later stage.

![Figure 18](image)

![Scheme 54](image)

The racemic α-bromo acid 137 was converted to the acid chloride 163 by treatment with thionyl chloride in DCM at reflux for 18 hours, with purification by vacuum distillation.
The N-benzyl amide 138 was formed instantaneously on addition of an ether solution of the acid chloride 163 to an ether solution of benzylamine at 0°C. The crude off-white product was isolated by filtration and washed with 1M aqueous HCl and then with ether to give the pure material (81%). We hoped to prepare the hydroxylamino amide 164 by treating the α-bromo amide 138 with hydroxylamine hydrochloride and triethylamine at reflux in anhydrous ethanol. Reaction proceeded to completion but the identity of the isolated product was not immediately apparent. Purification by column chromatography gave a yellow solid that appeared to be a single product but analysis by reverse-phase HPLC (Appendix II) showed this was not the case. The product was in fact the α-oximino amide 165, present as a mixture of the (E)- and (Z)-oxime isomers which we were only able to separate and characterise in small quantities using preparative HPLC under carefully developed conditions (Appendix II).

There is a precedent for the spontaneous conversion of α-hydroxylamino acids to oximino acids with the corresponding α-nitroso compounds as the proposed intermediate.
It has been suggested that in solution, the $\alpha$-nitroso acid 166 is formed from the hydroxylamino acid 167 by a pH-dependent oxidative process in which one equivalent of water is eliminated. Whereas $\alpha$-nitroso acid 166 can then undergo either decarboxylation to the aldoxime 168 or tautomerisation to the oximino acid 169, the analogous nitroso amide 170 can only tautomerise to the isolated $\alpha$-oximino amide 165 (Scheme 56).

The hydroxylamino acids may also undergo a disproportionation in which two molecules rearrange to the $\alpha$-nitroso acid and the $\alpha$-amino acid, although this proposal has been questioned. By analogy, disproportionation of our $\alpha$-hydroxylamino amide 164 should yield not only the $\alpha$-oximino amide 165 (in a maximum yield of 50%) but also the $\alpha$-amino amide 130. It is perhaps significant that we never observed the amino amide - suggesting a predisposition for formation of the nitroso amide 170 by an oxidative process.

Scheme 56
mechanism rather than disproportionation, and thence to the oxime 165. Attempts to perform the reaction under oxygen-free conditions still produced the oximino amide 165, suggesting that the excess of hydroxylamine used may be acting as the oxidant, possibly via the cyclic mechanism.

![Scheme 57](image)

In order to prevent the formation of the oxime, we decided to prepare the O-benzylhydroxylamino amide 171 (Scheme 57). Whilst many O-alkyl substituents could have prevented the rearrangement, we were mindful that this group would need to be easily removed using as mild conditions as possible to preserve 164 once formed. Thus, O-benzyl protection seemed reasonable, being derived from a commercial hydroxylamine and allowing potential deprotection by hydrogenolysis at ambient temperature and pressure. A solution of the α-bromo amide 138 in DCM was treated with triethylamine and O-benzylhydroxylamine hydrochloride and heated at reflux for 4 hours. After column chromatography, the O-benzylhydroxylamino amide 171 was isolated as a white solid (33%) along with starting material 138 (55%). This reaction proved to be highly capricious, resisting all our attempts to optimise and scale-up beyond this early success into useful quantities of this key intermediate.
The success of the hydroxylamination reactions of α-bromo carboxylic acid esters has been shown to depend to some extent on the choice of ester. In order to find the carboxylic acid derivative most effective for our intended hydroxylamination, we prepared the methyl α-bromo ester 172 (Scheme 58). Heating a solution of the acid chloride 163 at reflux in methanol gave the desired product (83%) with the α-methoxy ester 173 as a trace impurity. We also made a single attempt to prepare ester 172 by the deaminative bromination of the α-amino ester hydrochloride 174 (Scheme 59). Ester 174 was prepared in a 97% yield after treatment of 2-phenylglycine with thionyl chloride in methanol, but the subsequent reaction of 174 with sodium nitrite and HBr at 0°C gave only 4% of the desired α-bromo ester 172. Attempts to prepare the α-hydroxylamino ester 175 by heating a solution of the α-bromo ester 172 in methanol at reflux with hydroxylamine hydrochloride and triethylamine gave an intractable mixture of products (Scheme 58).

Scheme 58

Scheme 59
With the α-bromo acid 137 in hand, we were in a position to further investigate the effect of the acid derivative on the substitution reaction with hydroxylamines (Scheme 60). A mixture of hydroxylamine hydrochloride, sodium methoxide and acid 137 was heated in methanol at reflux for 18 hours but instead of the desired acid 167, the α-methoxy acid 176 was isolated (21%) after column chromatography. Mindful of the reported instability of the α-hydroxylamino acids towards oxidation, we attempted to synthesise the O-benzylhydroxylamino acid 177. The α-bromo acid 137 was dissolved in aqueous sodium carbonate and treated with O-benzylhydroxylamine hydrochloride but no reaction was observed after 7 days at reflux. This substitution was also unsuccessful in DCM solution in the presence of triethylamine, despite consumption of the starting material after 18 hours at reflux.

Scheme 60

```
\[
\begin{array}{c}
\text{CO}_2\text{H} & \text{CO}_2\text{H} \\
\text{Ph} & \text{Ph} \\
\text{OMe} & \text{NH}_2\text{OH.HCl}
\end{array}
\xrightleftharpoons{\text{NaOMe, } \Delta} \begin{array}{c}
\text{CO}_2\text{H} & \text{CO}_2\text{H} \\
\text{Ph} & \text{Ph} \\
\text{Br} & \text{Br}
\end{array}
\xrightarrow{\text{NH}_2\text{Obn.HCl, } \Delta} \begin{array}{c}
\text{CO}_2\text{H} \\
\text{Ph} \\
\text{NMObn}
\end{array}
\]
\]

176 167 137 177
```

Scheme 61

```
\[
\begin{array}{c}
\text{CO}_2\text{H}
\end{array}
\xrightleftharpoons{\text{TsCl}} \begin{array}{c}
\text{Ph} \\
\text{OTs}
\end{array}
\]
\[
\begin{array}{c}
\text{CO}_2\text{H}
\end{array}
\xrightarrow{\text{SOCl}_2} \begin{array}{c}
\text{Ph} \\
\text{OH}
\end{array}
\xrightarrow{\text{MeOH, } \Delta} \begin{array}{c}
\text{O} \\
\text{OMe}
\end{array}
\xrightarrow{\text{TsCl}} \begin{array}{c}
\text{Ph} \\
\text{OTs}
\end{array}
\]
\]

179 158 178 180

The use of sulfonate esters as leaving groups is a common strategy to perform a functional group interconversion of the hydroxyl moiety. Such a strategy has been
employed by Ottenheijm et al. in the preparation of \( \alpha-(O\text{-alkyl}) \)hydroxylamino esters via the corresponding \( \alpha \)-trifluoromethanesulfonate (triflate) esters,\(^{219}\) and by Kolasa in the synthesis of \( \alpha-(O\text{-benzyl}) \)hydroxylaminoaspartate esters via a \( p \)-toluenesulfonate (tosylate) intermediate.\(^{220}\) To investigate the effectiveness of a more easily displaced nucleofuge, we proposed to prepare the tosylates of mandelic acid \( 158 \) and its methyl ester \( 178 \) (Scheme 61). The esterification of \( 158 \) was achieved by refluxing with thionyl chloride in methanol solution for 18 hours (81%). However, neither \( 158 \) or \( 178 \) afforded the desired tosylates \( 179 \) and \( 180 \) respectively.

### 2.2.2 Approaches from benzoylformic acid

\[
\begin{align*}
\text{CO}_2\text{H} & \xrightarrow{\text{I}} \text{COCl} & \text{COCl} & \xrightarrow{\text{II}} \text{NH} & \xrightarrow{\text{III}} \text{NOBn} \\
\text{Ph} & \xrightarrow{85\%} \text{Ph} & \text{Ph} & \xrightarrow{84\%} \text{Ph} & \text{Ph} \\
181 & 182 & 183 & 184
\end{align*}
\]

*Reagents:* I, \((\text{COCl})_2, \text{DCM}, \text{cat. DMF}, 20^\circ\text{C}, 72\text{h}; \) II, \( \text{BnNH}_2, \text{DCM}, 0^\circ\text{C}; \) III, \( \text{NH}_2\text{OBn.HCl, Et}_3\text{N, EtOH, } \Delta, 18\text{h}.\)

**Scheme 62**

The synthesis of \( O\text{-benzylhydroxylamino amide 171 from the bromo amide 163 \) remained our most promising route thus far, although the problems of scale-up we had encountered rendered this approach unattractive. It was apparent to us that we could circumvent these difficulties by revision of our synthesis to obtain useful quantities of this
key intermediate via reduction of the corresponding oxime, and a synthetic strategy from benzoyl formic acid 181 was thus devised (Scheme 62).

Benzoylformyl chloride 182 was formed from acid 181 after stirring in DCM solution with oxalyl chloride and catalytic DMF for 72 hours. The solvent was removed under vacuum before distillation to yield the product as a yellow oil (85%).221 The N-benzyl ketoamide 183 was formed on dropwise addition of benzoylformyl chloride to a solution of benzylamine and triethylamine (1 equivalent each) in DCM at 0°C. The amide was isolated as an off-white solid (84%) after washing the solution with 2M aqueous HCl followed by drying and evaporating the solvent. The ensuing oximation reaction required heating for 18 hours at reflux of a mixture of 183 with O-benzylhydroxylamine hydrochloride and triethylamine in ethanol. Column chromatography on silica gel afforded the oximino amide 184 as a mixture of E- and Z- isomers (80%).

Scheme 63

Ottenheijm et al. have developed a methodology for the reduction of α-oximino amides and esters to the α-hydroxylamino analogues using borane-amine complexes.222,223 As others have found,224 the use of borane reagents and mild
conditions avoids the over-reduction of the oxime function to the amine that is observed with stronger reducing agents such as lithium aluminium hydride and sodium borohydride. However, there are exceptions; both the o-phenyl oximino ester 185a and the corresponding N-methyl amide decompose under the acidic conditions required for reduction with either borane-trimethylamine complex (BH₃.NMe₃) or borane-pyridine complex (BH₃.py) (Scheme 63).

In order to verify the reduction of oximino acid derivatives, the oximes 185a and 185b were prepared from commercial ethyl benzoylformate 186 by heating in ethanol solution with the corresponding hydroxylamine hydrochloride and pyridine at reflux for 1 hour (32% and 54% respectively after chromatography). We confirmed the instability of the OH oxime 185a under the acidic conditions of BH₃.NMe₃ reduction, but we successfully reduced the O-benzyl oxime 185b to the hydroxylamine 187b in a modest yield of 25% as a mixture with 185b. A pure sample of 187b was isolated by preparative HPLC (Appendix II). Encouraged by the reported yield of 95% for BH₃.NMe₃ reduction of the N-methyl amide analogous to 187b, this reagent was applied to the reduction of 2-phenyl-2-benzylximino-N-benzylacetamide 184 (Scheme 64). The amide was taken up in 7M anhydrous ethanolic HCl and treated with 11 equivalents of BH₃.NMe₃ complex. The solution was stirred at 20°C until all of the amide was consumed, before partitioning between DCM and 1M aqueous NaOH and separation, drying and evaporation of the organic phase to afford the O-benzylhydroxylamino amide 171 as an off-white solid (60%).

We now invoked the methodology that had been developed in our group in connection with the preparation of the 2-imidazoline azomethine ylides 125b, in which the diamine 131 is prepared by reduction of the amino amide 130 with BH₃.THF complex. Thus, a solution of 0.50g of the amide 171 in anhydrous THF was treated dropwise with 7
equivalents of BH₃·THF complex (as a 1M solution in THF), before heating at reflux to complete consumption of the starting material. Slow addition of 6M aqueous HCl at 25°C was used to cleave the borane-product complex and to decompose excess reagent before extraction into DCM. However, the isolated product was not the desired hydroxylamino amine 188 but 0.45g of a mixture containing the product of amide reduction and concomitant hydroxylamine N-O cleavage 131 and the amino amide 130 (4:1), along with benzyl alcohol. A repeat of this experiment with 4 equivalents of BH₃·THF and amide 171 gave no reduction at 20°C, and after a short period at reflux afforded the diamine 131 and the amino amide 130 (2:1), along with benzyl alcohol. Reaction did not proceed at ambient temperature with 1 equivalent of BH₃·THF, and after 18 hours at reflux, the crude product bore no trace of the diamine 131. The isolated material proved to contain an approximately equimolar mixture of the hydroxylamino amide 171 and the amino amide 130, indicating, to our cost, that the N-O reduction occurs before the amide carbonyl is reduced.

**Scheme 64**

Reagents: i, BH₃·NMe₃, 7M HCl/EtOH, 20°C; ii, BH₃·THF, THF, A. 18h then 6M aq. HCl; iii, H₂, Pd-C, 20°C, 1 atmos. in gl. AcOH or TFA.
The O-debenzylation of amino hydroxylamine 188 was to have been carried out by catalytic hydrogenolysis. It was decided to test the feasibility of this deprotection on the amide 171. We initially studied the reaction of 171 and H₂ at 1 atmos. in the presence of 30mol% of 10% Pd-C at 20°C, a published procedure for O-benzylhydroxamate hydrogenolysis. Unfortunately, this only afforded the N-O cleavage product 130 and benzyl alcohol; this was also the case when the proportion of catalyst was reduced to a more familiar 5mol%. Replacement of the organic solvent with glacial acetic acid or TFA did lead to the desired hydroxylamino amide 164, but the yields were extremely low (2% and 4%, respectively). As an alternative debenzylation strategy, the amide 171 was refluxed in a solution of conc. HBr/glacial acetic acid but the starting material was recovered unchanged.

Our choice of hydroxylamine protecting group was then reconsidered, on the premise that changing the nature of this group might affect the N-O cleavage under carbonyl reduction conditions. The O-tert-butyloximino amide 189 and the unprotected oximino amide 165 were prepared from a common keto amide starting material 183 (Scheme 65). Ottenheijm has demonstrated the instability of the analogous unprotected oximino ester 185a under the strongly acidic conditions required for reduction with the borane-amine complexes, and we found that oximino amide 165 was unreactive to BH₃·THF complex or sodium.
cyanoborohydride in THF, or aqueous methanol at pH 3-4.227-229 Our studies on these compounds were concluded when we discovered to our surprise that the O-tert-butyl oxime 189 was unreactive to either BH₃.NMe₃ or sodium cyanoborohydride reduction methodologies, and did not afford the desired hydroxylamine.

2.2.3 Approaches from haloacetophenones

We reviewed our synthetic strategy and concluded that the N-benzylamino-functionality we needed could be introduced without recourse to amide reduction. Thus, we resolved to prepare the key nitrene precursor hydroxylmino amine 140 via the O-benzyl
analogue 188 (Scheme 66). We reacted 2-bromoacetophenone 190 and O-
benzylhydroxylamine hydrochloride in ethanol in the presence of triethylamine to afford the 
α-bromo oxime 191 which could not be purified further. A chloroform solution of this 
crude oxime and 2 equivalents of benzylamine was heated at reflux for 18 hours to give the 
oximino amine 192 after chromatography (50% from 190). However, we observed no 
reduction of the oxime 192 with either sodium cyanoborohydride at pH 3 or BH$_3$NMe$_3$ in 
ethanolic HCl solution. We then considered alkylation at the oxime carbon by nucleophilic 
attack of an organometallic reagent,$^{230,231}$ as demonstrated with asymmetric induction by 
both Moody$^{232,233}$ and Marco.$^{234}$ Addition of a methyl group to the oxime carbon of 192 
would, after O-debenzylation, afford the hydroxylamino amine 193. This material is the 
potential precursor of a nitrone with groups of very different steric demand at the nitrone α-
carbon and so would preserve our synthesis of a facially differentiated 1,3-dipole. Thus, a 
solution of 192 at -78°C in dry ether under nitrogen was treated with methyllithium (1.6M 
solution in ether). After 1 hour, the solution was quenched with water and the organic layer 
separated. However, purification of the crude product mixture by column chromatography 
afforded none of the desired compound 193. We reasoned that addition of a Lewis acid may 
increase the reactivity of the carbon reaction centre of the oxime towards nucleophiles by 
complexing to the oxime nitrogen via its lone pair. However, treatment of the solution of 
192 with boron trifluoride etherate (BF$_3$Et$_2$O) at -78°C for 15 minutes before adding the 
methyllithium, and treatment as previously described, still afforded none of the desired 
material.
Figure 19: Collapse of adjacent benzylic CH₂ signals of 194 in variable temperature ¹H NMR spectroscopy.
After these results, the benzylamino moiety of 192 was protected, to avoid any potential interference of the N-benzylamide anion. Stirring a solution of 192 with di-tert-butyl dicarbonate (Boc$_2$O) and Et$_3$N in DCM solution for 18 hours afforded the carbamate 194 as a white solid (74%) after chromatography. The purified material was found to exist as a pair of E- and Z-carbamate rotamers at 21°C by $^1$H NMR spectroscopy. By variable temperature $^1$H NMR spectroscopy in d$_6$-DMSO, we were able to observe collapse of the doubling of the N-benzyl CH$_2$ signals above 35°C to give two sharp singlets by 95°C (Figure 19) and so prove the presence of a single compound. A solution of 194 in anhydrous ether at -78°C was treated with 3 equivalents of a 1.6M solution of MeLi in ether but no reaction was observed after 1.5 hours. The solution was warmed to 0°C without change after a further 1.5 hours and, although no starting material remained after warming to 20°C overnight, none of the desired N-Boc-α-methyl hydroxylamine was isolated. A repeat experiment with addition of excess BF$_3$.Et$_2$O to the oxime 194 prior to addition of the MeLi solution was also unsuccessful.

![Scheme 67](image)
We were able to successfully reduce the oxime 192 under anhydrous conditions with BH₃·THF in dry THF (Scheme 67). Inside a few hours, the disappearance of the oxime starting material and the formation of the product-borane complex was easily determined by TLC. This solution was then carefully treated with 2M aqueous HCl and warmed to 60°C until this complexed material disappeared. Neutralisation with 2M aqueous NaOH and extraction into ether gave the desired hydroxylamino amine 188 (79%).

The removal of O-benzyl protecting groups by catalytic hydrogenolysis is often rapid and high-yielding, making it a commonplace strategy in the synthetic literature. Of those reactions of N–O compounds in which O-debenzylation takes place, the palladium-catalysed reactions of O-benzyl hydroxamates are the most numerous, but also included is the debenzylation of benzyloxyimidazole. When a solution of the hydroxylamino amine 188 in methanol was stirred with 10% Pd-C under 1atm. of H₂, the isolated product was not the desired deprotected hydroxylamine 140 but the diamine 131 and benzyl alcohol. Reinhoudt et al. have reported high yielding hydrogenolysis reactions of O-benzyl azetidines and azetidinones with palladium catalyst in glacial acetic acid. This result, plus our limited success in the O-debenzylation by hydrogenolysis of the amino amide 171 under acidic conditions, led us to repeat our experiment with glacial acetic acid in place of the organic solvent. However, the isolated products were once again the diamine 131 and benzyl alcohol. The hydrogenolysis of benzyl ethers with Raney Nickel catalyst at ambient temperature and pressure has been reported but, after 72 hours under such conditions, the hydroxylamine 188 was recovered unchanged.

Following precedent for cleavage of benzylic alcohols and amines by catalytic transfer hydrogenolysis, hydroxylamino amine 188 was heated at reflux in methanol with 10% Pd-C and ammonium formate. After 18 hours, the reaction was halted...
but the isolated material was an intractable mixture of products. Brown et al. have generated N-hydroxypurine derivatives from the corresponding benzyloxypurines by heating in a solution of conc. HBr in glacial acetic acid. We found that the hydroxylamino amine 188 was retrieved unreacted after 18 hours at reflux in 30% HBr in glacial acetic acid. In a more exotic example, the O-benzylhydroxylamino phosphonic and phosphinic acids of Elhaddadi et al. are deprotected without N–O cleavage using boron tris(trifluoroacetate), B(TFA)₃. This reagent was prepared by treatment of a solution of distilled TFA in anhydrous DCM with boron tribromide under an atmosphere of nitrogen. A white precipitate of B(TFA)₃ formed instantaneously and was isolated by removal of the solvents in vacuo, before it was added to a solution of 188 in TFA and the mixture stirred under nitrogen for 18 hours. The solution was diluted with MeOH before basifying with aqueous NaOH (2M) but only the unchanged starting material 188 was recovered. We were somewhat consoled by the fact that many other researchers have found O-benzylhydroxylamines to be susceptible to N–O cleavage under catalytic hydrogenolysis conditions. Interestingly, Corey et al. have reported oxime O-debenzylation by Pd-catalysed hydrogenolysis but, using this method, the oxime 192 afforded a 1:1 mixture of the diamine 131 and benzyl alcohol rather than the desired oxime 196. On balance, we decided that the search for an alternative hydroxylamine protection strategy was our most judicious option.

To this end, the α-bromo-O-tert-butyl oxime 197 became our next target, offering, after elaboration, a potentially facile non-hydrogenolytic dealkylation to afford the hydroxylamine 140 (Scheme 68). Unfortunately, we were unable to prepare this oxime from 2-bromoacetophenone 190 by conditions developed during the preparation of 192 with O-tert-butylhydroxylamine hydrochloride and either triethylamine in refluxing ethanol
or in aqueous sodium acetate at 20°C or 50°C. Similarly, we were unable to prepare the analogous unprotected oxime 198 under these conditions.

![Scheme 68](image)

**Reagents**: i, NH$_2$O$'$/Bu. HCl, Et$_3$N, EtOH, $\Delta$, 18h; ii, NH$_2$O$'$/Bu. HCl, NaOAc, H$_2$O, 50°C or 25°C, 18h; iii, NH$_2$OH. HCl, Et$_3$N, EtOH, $\Delta$, 48h.

![Scheme 69](image)

**Reagents**: i, NH$_2$OH. HCl, NaOAc, MeOH, 18h, 20°C; ii, BnNH$_2$, CHCl$_3$, $\Delta$; iii BH$_3$. THF, THF then 6M aq. HCl, 24h at 20°C (or 4h at 50°C); iv, NH$_2$OTMS, 4Å sieves, dry CHCl$_3$, 20°C, 36h; v, NaOAc, EtOH, $\Delta$, 18h; vi, as i with NH$_2$O$'$/Bu. HCl.

**Scheme 69**
Our difficulties with α-bromo oximes led us to investigate their α-chloro analogues. Much work has been done on the preparation of α-chloro oximes as precursors to nitrosoalkenes. By the method of Denmark and Dappen, a methanol solution of 2-chloroacetophenone was treated with 1.5 equivalents each of hydroxylamine hydrochloride and potassium acetate but returned none of the desired oxime. In contrast, an alternative procedure from these researchers using 1.5 equivalents of both hydroxylamine hydrochloride and sodium acetate furnished the desired chloro oxime in a near quantitative yield (98%). Subsequent amination of oxime proceeded in a moderate yield (38%) by the method developed for the synthesis of the O-benzyl oxime, with benzylamine in chloroform. However, the oximino amine was not reduced by the BH₃·THF complex after 24 hours at 20°C nor after 4 hours at 50°C.

Similarly, reaction of 199 with O-tert-butylhydroxylamine hydrochloride and sodium acetate gave the desired chloro oxime in excellent yield (93%). Optimisation studies showed that scale did not seem to adversely affect the isolated yield of 201, an experiment using 0.56g of 199 proceeding with a yield of 79%, with 82% from 1.12g and 87% from 2.80g. The alternative reaction conditions using potassium acetate in glacial acetic acid were successful, but the yields were significantly lower (49% and 68% in two attempts). We made a single attempt to prepare the O-trimethylsilyl chloro oxime as an alternative protecting-group strategy by a third method from Denmark's work using O-trimethylsilylhydroxylamine, but observed no reaction after 36 hours. During our optimisation, we investigated the effect of prolonged exposure of 2-chloroacetophenone to the oximation conditions. Thus, after 18 hours at reflux of a solution of 2-chloroacetophenone in ethanol with sodium acetate, we isolated the acetate adduct 203, but only in 13% yield. Our findings here support our contention that this side product will not
significantly affect our isolated yield of oxime 201 in the room temperature oximation reaction.

**Scheme 70**

The prohibitive cost of O-tert-butylhydroxylamine hydrochloride 204 (£21.40/g) encouraged us to prepare our own supplies using a literature synthesis from N-hydroxyphthalimide 205 (Scheme 70). This method is reported to afford a 99% yield of the O-alkylated product 206 with 10 equivalents of tert-butyl acetate and catalytic perchloric acid in 1,4-dioxane. We found that this could be reduced to 4 equivalents with no loss of yield of a product that required only to be washed with hexane for analytical purity. The tert-butyl acetate was prepared by esterification of acetyl chloride with tert-butanol in the presence of N,N-dimethylaniline (60% in our hands after distillation). Whilst this synthesis was suited to a large scale, we found the commercial ester to be of sufficient purity and without deterrent cost once we had developed a route to the phthalimide intermediate 206 with more modest demands of this ester.

Cleavage of the O-tert-butylphthalimide 206 with hydrazine monohydrate was performed according to the method of Chimiak and Kolasa. Reaction had proceeded to completion after 3 hours at reflux, and so the solution was cooled and treated with 5%
aqueous Na₂CO₃ solution. After 30 minutes at 20°C, this solution was extracted with ether and the dried organic phase was treated with dry gaseous HCl. Initial experiments in ethanol or tert-butanol gave identical, modest yields of O-tert-butylhydroxylamine hydrochloride 204 (52%) along with copious amounts of phthalhydrazide which precipitated from the aqueous phase on standing. Ethanol later proved to be our best solvent with a yield of 77%, although we have not matched the literature reports of 85%. Previous attempts to prepare the phthalimide 206 in a Mitsunobu-type reaction by the treatment of 205 with tert-butanol, triphenyl phosphine and diethyl azodicarboxylate afforded none of the desired product. Alkylation of 205 with tert-butyl iodide in DMF and triethylamine was also unsuccessful.

The subsequent substitution of the chloride of O-tert-butyl oxime 201 proceeded most efficiently with 2 equivalents of benzylamine in DMF at 20°C (Scheme 71). Whilst removal of the high-boiling solvent is tedious, the compensation is a high yield of the oximino amine 207 (94%). Less effective experiments included heating at reflux in chloroform (for a 17% yield of 207 with 60% recovered 201), THF (63%), toluene (73% of 207 with 12% 201) and an experiment with no solvent and 30 equivalents of benzylamine (71%). The reduction procedure used 4 equivalents of BH₃·THF complex, added to a dry THF solution of the oximino amine 207 as a 1M solution at 0°C under nitrogen. Even on a multi-gram scale, the oximino amine was consumed in only a few hours at 20°C, and careful addition of 6M aqueous HCl at 0°C freed the desired hydroxylamino amine 208 from its complex with borane. The solution was basified and extracted with ether, before drying and evaporation of the solvent and purification of the residue by column chromatography.
The susceptibility of the BH$_3$.THF complex to hydrolysis meant that moisture had to be excluded from these experiments, but we also found that older samples of this complex contained THF-related contaminants. Kollonitsch discovered that THF is subject to ring-opening by borane, such that tributyl borate had formed in the borane-THF sample over time, and we also observed this during the reduction of oxime 207. Consequently, one of the contaminants we had observed was butan-1-ol formed in the acid hydrolysis step of the reduction and derived from tributyl borate. Similarly, we isolated a second impurity which we identified as 4-chlorobutan-1-ol, clearly formed by chloride-induced ring-opening of THF during the hydrolysis step with HCl. Both impurities were avoided by the use of a fresh solution of the complex with storage in the cold between uses, and minimal hydrolysis times with immediate work-up on completion. In early experiments where excessive amounts of these ring-cleavage products had formed, silica column chromatography proved
to be ineffective, co-eluting these impurities with the product. It was, therefore, necessary in these cases to distill the crude reaction mixture to remove the alcohols, before performing a final chromatographic purification leading to a seriously diminished yield of hydroxylamino amine 208.

Our initial protocol to deprotect the O-tert-butylhydroxylamino amine 208 was treatment with TFA, but this only led to isolation of the TFA salt of our starting material. Literature precedent for O-tert-butyl ether cleavage led us to try hydrolysis with TFA and anisole, but no desired material was returned. This was followed by attempts with trimethylsilyl iodide (TMSI) - a reagent that is reported to afford instantaneous cleavage of benzyl and tert-butyl ethers but which was unfruitful here. Our first successful deprotection of 208 was observed after prolonged heating at reflux in a solution of equal volumes of conc. HCl and methanol. On completion, the mixture was cooled then basified with 2M aqueous NaOH and extracted with ether. From this solution was obtained a yellow-green gum, consistent with the desired hydroxylamino amine by NMR spectroscopy, but showing signs of decomposition in less than 7 days in CDCl₃ solution. Attempts to purify this oily amine by distillation or column chromatography also seemed to induce decomposition. We were eventually able to effect purification and isolation after treatment of the free base in DCM solution with ethereal HCl to afford the pure dihydrochloride salt 140a.

Optimisation studies led us us to deprotection with conc. H₂SO₄. Dropwise addition of this acid to a methanol solution of 208 gave an immediate and significant exotherm. The deep brown solution so produced was internally and externally cooled with ice during basification with 6M aqueous NaOH at first and later solid NaOH, before extraction with DCM and drying of the extracts over anhydrous MgSO₄. The solution was filtered and then
treated with dry HCl gas for 1 hour. The dihydrochloride salt 140a slowly precipitated from the solution on standing and was removed by filtration before drying under vacuum.

Occasionally, we have encountered difficulties in the purification of the salt, especially if the O-tert-butyl amine 208 was not pure or if the DCM solution of the free base was not dried thoroughly over anhydrous MgSO₄. Usually, however, the material isolated in this way was a white amorphous solid, with high purity by NMR spectoscopy, in yields of up to 76%. Purity was also assessed by a reverse-phase HPLC method (Appendix II), using an aqueous acetonitrile eluent. A gradient elution system was employed (i.e. of decreasing solvent polarity with time), which initially eluted with a 10% solution of acetonitrile in water with 0.1% TFA (solution A) and a flow rate of eluent of 1cm³/min. A 90% solution of acetonitrile in water with 0.1% TFA (solution B) was introduced such that after 15 minutes of run time, the ratio of A:B was 1:9 by volume which eluted for a further 10 minutes (Figure 20).

![Figure 20: HPLC eluent gradient as used for analysis of 140a.](image)

This system eluted the hydroxylamino amine salt 140a with a retention time of approximately 10 minutes, and in this way we were able to show that the purity of the
isolated material was increased significantly by trituration with a little cold DCM (Figure 21). This system used a UV detector at a wavelength of 258nm, where most organic compounds absorb strongly. However, we were mindful of the fact that the relative absorption of a mixture of organic compounds does not always relate to the relative concentrations on account of their different UV absorption coefficients. We did not seek to make our analysis quantitative, but found it to be a useful guide in our development of subsequent cycloaddition reactions.

![Figure 21: HPLC analysis of dihydrochloride salt 140a before and after DCM trituration.](image)

**Figure 21**: HPLC analysis of dihydrochloride salt 140a before and after DCM trituration.

We had initially attempted unsuccessfully to reduce the O-tert-butyl oxime 207 with sodium cyanoborohydride, and this prompted us to consider attack on this oxime with an organometallic reagent. Thus, we hoped to prepare hydroxylamine 209 using methyllithium
at -75°C, but we were to enjoy no success, even when the oxime was treated with a Lewis acid (BF₃·Et₂O) prior to addition of the alkyllithium (Scheme 72). Protection of the benzylamino function as the tert-butoxycarbamate in a hope to discourage unwanted side reactions, proceeded in high yield to afford 210 as a mixture of carbamate rotamers and oxime geometric isomers. ¹H NMR analysis of 210 in a mixture of CDCl₃ and d₆-DMSO showed collapse of the rotamer signals at 50°C, to become sharp singlets by 110°C and allow characterisation of both oxime isomers. Attempted alkylation of 210 with methyllithium at -75°C afforded none of the desired hydroxylamine 211 after warming to 20°C overnight. When the experiment was repeated with initial treatment with BF₃·Et₂O, only 6% of 210 was returned, along with 47% of the deprotected oxime 207. Fortunately, our successful reduction of 207 with BH₃·THF made our problems here academic.

Reagents : i, Boc₂O, Et₃N, DCM, 20°C, 1.5h; ii, MeLi, Et₂O, -75°C, 18h; iii, BF₃·Et₂O, Et₂O, -75°C, then ii; iv, Proposed reagents : 2M aq. HCl.

Scheme 72
The free hydroxylamino amine 140 was unsuccessfully subjected to the cyclisation conditions developed for the synthesis of the 1-benzyl-4-phenyl-2-imidazolines 128, under reflux with triethyl orthoformate and a catalytic amount of p-toluenesulfonic acid. Similarly, these conditions did not convert the O-tert-butylhydroxylamino amine 208 into the desired nitrone 126a; we had speculated that the acidic conditions might promote deprotection as well as heterocycle formation. When a slurry of the dihydrochloride salt 140a in DCM was treated with triethyl orthoformate and warmed to reflux we were able to observe consumption of the solid within 1 hour, and removal of the solvent afforded the 3-benzyl-5-phenyl-2-imidazoline-1-oxide 126a or '2-H nitrone' in quantitative yield (Scheme 73). Similarly, the '2-methyl nitrone' 126b was prepared using triethyl orthoacetate in a quantitative yield and the '2-phenyl nitrone' 126c was detected by mass spectrometry in a mixture prepared in this way from triethyl orthobenzoate.

![Scheme 73](image)

**Reagents**: I, RC(OEt)₃, DCM, Δ, 1h.

**Scheme 73**

In work beyond the scope of this report, it is clear that the potential exists in our synthesis to prepare these nitrone reagents in enantiopure form. Firstly, we might introduce enantiopurity by reduction of the O-tert-butyl oxime 207 with asymmetric induction, to afford the homochiral hydroxylamine (R)- or (S)-208. Asymmetric oxime reduction has
been achieved using a number of systems\textsuperscript{260,261} including chiral oxazaborolidine complexes prepared from homochiral aminoalcohols and borane-complexes.\textsuperscript{262-267} The stereochemistry of the isolated hydroxylamine is known to depend on the stereochemistry of the complex as well as the geometry of the oxime (that is to say $E$- and $Z$-oxime isomers give rise to different stereochemistry in the isolated hydroxylamine). Secondly, the O-\textit{tert}-butylhydroxylamino amine \textit{208} or the dealkylated hydroxylamine \textit{140} might be resolved by fractional crystallisation\textsuperscript{268,269} of the diastereomeric salts formed by treatment with a homochiral carboxylic acid. It might then be possible to assign the absolute stereochemistry of our reagents by X-ray crystallographic analysis of the salts formed with a homochiral carboxylic acid.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure22.png}
\caption{Reverse-phase HPLC traces of 2-imidazoline nitrones \textit{126a} and \textit{126b}.}
\end{figure}
Our synthesis of these 2-imidazoline nitrones was carried out in the presence of 2 equivalents of HCl liberated from the dihydrochloride salt 140a, and so the nitrones we isolated will presumably be present as the hydrochloride. Therefore, it was not feasible to monitor the reaction using conventional silica TLC, and so they were analysed by the reverse-phase HPLC method developed earlier to observe the formation of 140a from 208 (Appendix II). This system allowed us to follow the reaction using one drop of the crude reaction mixture, which was diluted to 4ml with solution A and up to 20μl loaded into the injection loop of the HPLC instrument. Thus, we distinguished the salt 140a, eluted at approximately 10.0 minutes, from the salt of the 2-H nitrone 126a with a retention time of approximately 14.2 minutes or the salt of the 2-methyl nitrone 126b eluted at 14.1 minutes (Figure 22). We, therefore, were easily able to determine whether the hydroxylamino amine had been consumed and in this way we found the nitrone 126a to be the only product after warming to 60°C for 1 hour with triethyl orthoformate.

Coates and Ashburn have reported the synthesis of 2-substituted oxazoline nitrones using amide acetals. Using their method we detected the presence of the 2-H nitrone 126a by atmospheric pressure chemical ionisation mass spectrometry (positive ion mode), or APCI+, after stirring a slurry of 140a with dimethylformamide diethylacetal in dry DCM for 18 hours. Here we observed m/z 253 (MH+) with intensity of 8% as well as 237 (MH+-O) at 100% intensity. Subsequent HPLC analysis showed this solution to be a mixture of the nitrone 126a and the salt 140a (4.7:1), thus proving this method less effective than our orthoester methodology.

These nitrones were sufficiently stable to be characterised by NMR in CDCl₃ and by APCI+ mass spectrometry (from methanol solution). The APCI+ mass spectrum of the 2-H nitrone 126a showed the protonated molecular ion (MH+) at m/z 253 (15% intensity) as well
as the deoxygenation fragment 238 (MH⁺-O), characteristic of nitrones and N-oxides, as the base peak. We observed a peak at 505 (4%) equivalent in mass to 2 molecules of 126a, and tentatively concluded that under these conditions this nitrone forms a dimer such as 212 (m/z 504) (Scheme 74).

Our proposal is supported by many well-documented cases of nitrone dimer- and trimerisation from the literature. Certain acyclic nitrones have been shown to form self-condensation products. For example, C-dimethyl-N-phenyl nitrone 213 reacts with the α,β-unsaturated hydroxylamine 214 with which it is in equilibrium, to afford the 4-hydroxylaminoisoxazolidine cycloadduct 215 (Scheme 75). However, the nitrone 126a cannot tautomerise in this way, and so we discount this type of product. By contrast, some cyclic nitrones can give rise to the 'head-to-tail' dimer. Here, the 'head-to-tail' description is used to indicate that the atoms of the new ring are arranged in the order N-O-C-N-O-C in the dimeric species, rather than the 'head-to-head' dimer where they are arranged N-O-C-C-O-N. An example is the oxidation of N-hydroxypiperidine 216 which affords the tricyclic dimer 217 on attempted isolation, rather than the desired 1,2-dehydropiperidine-N-oxide 85. The monomeric nitrone 85 can be made available for
1,3-dipolar cycloaddition chemistry by thermal cracking of the dimer 217. Preferably, oxidation to the nitrone 85 is carried out in solution with an alkene dipolarophile for in situ trapping of the nitrone once formed.

Other evidence to support a proposed dimer structure such as 212 (m/z 504) is provided by the peaks at m/z 489 (7%) and 473 (10%) corresponding to partial and complete deoxygenation of the dimer with loss of one and two O atoms respectively, via rearrangement to an unknown structure. In the APCI+ mass spectra of the 2-methyl and 2-phenyl nitrones, the protonated molecular ion (MH+) is observed and the base peak corresponds to nitrone deoxygenation, but with no suggestion of dimerisation. We propose that this may be due to the steric hindrance offered by a carbon substituent at the 2-position of the nitrone blocking one of the reacting centres in dimer formation.

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{Ph} \quad \text{H} & \quad \text{N} \\
\text{213} & + & \text{214} & \nonumber \\
\text{215} & \nonumber \\
\text{216} & \quad \text{OH} & \nonumber \\
\text{217} & \quad \text{ON} & \quad \text{N+} & \nonumber \\
\end{align*}
\]

Scheme 75
2.3 1,3-Dipolar cycloaddition reactions.

Our choice of nitrone to take forward into dipolar cycloadditions was affected by the experience of previous workers in our group who had found that no 1,3-dipolar cycloaddition took place with the C-2 substituted 2-imidazoline azomethine ylides 218 (R≠H) (Scheme 76).

We therefore chose the least substituted 2-H nitrone 126a, and took dimethyl acetylenedicarboxylate (DMAD) as our initial dipolarophile on the basis of its normally high cycloaddition reactivity. Our studies thus far had shown that whilst these nitrones could be prepared in essentially quantitative yield, the isolated material may suffer decomposition. It was therefore decided that a one-pot procedure combining \textit{in situ} generation of the nitrone dipole followed by immediate addition of the dipolarophile would be most prudent. Our nitrone was prepared as described in Section 2.2.3, before addition of 2 equivalents of the hindered base N,N-diisopropylethylamine (Hünig’s base) at 40°C, to neutralise the HCl generated from the dihydrochloride salt 140a, followed by 1.25 equivalents of DMAD. This mixture was stirred at 40°C for 18 hours then treated with saturated aqueous NaHCO₃ and extracted into DCM. Drying and removal of the solvent gave an oily residue which was purified by column chromatography to afford the keto lactam 219 (37%) rather than the desired cycloadduct 220 (Scheme 77).
We propose that 219 is produced from a rearrangement reaction of the cycloadduct 220, initiated by a 1,5-shift (C-to-N) of the bridgehead proton and N–O bond lysis, to afford the α,β-unsaturated ketodiester 221. Spontaneous ring-closure by lactamisation onto the free benzylamino function affords the isolated keto lactam 219. The product of this reaction was unaffected by changing the base to Et₃N, although the yield was improved to 58%; diethyl acetylenedicarboxylate gave the analogous cycloadduct 222 (20%) along with the formal product of dehydration of nitrone 126a, the imidazole 223. We resolved to probe the generality of this reaction using mono-carboxylates of acetylene. Thus, we treated the nitrone 126a separately with methyl and tert-butyl propiolate to afford the α,β-unsaturated keto aldehydes 224 (37%) and 225 (45%), respectively. Their formation can be easily rationalised via our proposed 1,5-H shift mechanism from the primary cycloadducts 226 (Scheme 78). Nitrone 126a was then reacted with phenyl isocyanate (PhNCO), another highly reactive dipolarophile, but no cycloadduct could be isolated from a complex mixture of products.
Encouraged by our first cycloadditions with these nitrones we sought to discourage the rearrangement reaction by the use of the 2-methyl nitrone 126b which would give cycloadducts having no bridgehead proton to participate in the 1,5-shift. Thus, the nitrone was prepared by treatment of a solution of salt 140a in dry DCM with 1.25 equivalents of triethyl orthoacetate and heating for 1 hour at reflux under a nitrogen atmosphere, before addition of 1.25 equivalents of triethylamine and the dipolarophile. Reaction of 126b with DMAD did not afford the desired cycloadduct 227 (Scheme 79) nor any product from rearrangement of 227. Similarly, no cycloadducts or rearrangement products were isolated from the reaction of this nitrone with PhNCO, methyl propiolate, dimethyl maleate, methyl acrylate or maleic anhydride. As we had seen in the reactions of 126a, we were often able to isolate the formal 'dehydration product' 1-benzyl-2-methyl-4-phenyl-1H-imidazole 228. We propose that the first step in the formation of 228 is the protonation of the N-oxide 126b to set up loss of water across the N-1 to C-5 bond. The loss of the C-4 proton is then driven by aromatisation of the ring and makes this process catalytic in H⁺. We tried to recreate this reaction by prolonged reflux of this nitrone in toluene with the drying agent P₂O₅, but without
success. We propose that the analogous imidazoline 223 is also formed by this mechanism. In the case of DMAD as the dipolarophile, the diester 229 was identified which is a known condensation product of this acetylene reagent with triethylamine via the elimination of ethene (Scheme 79). 279-281

![Scheme 79](image)

We concluded that C-2 functionalisation was not tolerated in these nitrones, even with the most reactive dipolarophiles. We, therefore, refocussed our attention on the 2-H
nitrone 126a and resolved to conduct a series of cycloaddition reactions with alkene
dipolarophiles which (if our mechanistic proposal is valid) should disfavour the
rearrangement described above for alkyne dipolarophiles. Our study commenced with
symmetrical alkenes in order to restrict the potential product mixture by eliminating the
possibility of generating mixtures of regioisomers. The 2-H nitrone 126a was prepared in
toluene solution before addition of 1.25 equivalents of Et₃N and 1.25 equivalents of trans
alkene dipolarophile (Scheme 80) and heating overnight at 60°C.

Huisgen has shown that the geometry of substituents in the alkene dipolarophile is
always retained in the cycloadduct of a 1,3-dipolar cycloaddition reaction. Therefore, the
relative stereochemistry of the cycloaddition products from the E- and Z-isomers of a chosen
alkene with a given nitrone should differ only in the geometry at the former alkene
stereocentres. This is reflected in Scheme 80, where the stereochemistry at C-6 and C-7 of
the imidazaoisoxazole cycloadducts has been arbitrarily assigned to distinguish between the
expected cycloadduct from reaction of a cis alkene 230 from that of a trans alkene 231.
However, no reaction was observed with the trans alkenes dimethyl fumarate 232,
fumaronitrile 233 or methyl crotonate 234. This suggests that the dipole 126a does not
tolerate any endo component to the transition state, which must exist for the reaction of these
trans alkenes. We proceeded to react the 2-H nitrone 126a with cis alkenes under the same
conditions, starting with dimethyl maleate 235. After stirring a toluene solution of 126a
with 1.25 equivalents of DMM at 60°C for 18 hours we were delighted to isolate the
cycloadduct 230 as a colourless oil after chromatography (64%).

The partial stereochemistry in Scheme 80 is assumed; in order to determine the
relative stereochemistry of this material, it was examined by difference nuclear Overhauser
enhancement spectroscopy (nOe) (Figure 23). This NMR technique exploits the ability of
protons to interact not only through bonds but also through space with other proximal protons. In the nOe experiment, the normal $^1$H spectrum is acquired but with simultaneous irradiation at a frequency corresponding to a chosen proton signal in the spectrum. An increase in the intensity of any other proton resonance in the spectrum indicates that the irradiated and enhanced protons are sufficiently close to interact through space. The difference nOe spectra are obtained by subtraction of the normal $^1$H spectrum from the enhanced spectra. It is important to note that the lack of enhancement between chosen protons does not prove that they are non-adjacent, but may merely indicate the presence of other relaxation mechanisms.

![Diagram of molecule 230 with annotated protons]

<table>
<thead>
<tr>
<th>Irradiated</th>
<th>Enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H^a$</td>
<td>$H^b$ (8%), $H^f$ (3%)</td>
</tr>
<tr>
<td>$H^b$</td>
<td>$H^a$ (9%), $H^c$ (7%)</td>
</tr>
<tr>
<td>$H^c$</td>
<td>$H^b$ (10%), $H^d$ (8%)</td>
</tr>
<tr>
<td>$H^d$</td>
<td>$H^c$ (9%), $H^e$ (24%)</td>
</tr>
<tr>
<td>$H^e$</td>
<td>$H^d$ (24%), $H^f$ (5%)</td>
</tr>
<tr>
<td>$H^f$</td>
<td>$H^a$ (3%), $H^c$ (3%)</td>
</tr>
</tbody>
</table>

**Figure 23**: Nuclear Overhauser enhancements for cycloadduct 230.

Using this technique, not only can adjacent protons be identified, but the strength of the interaction can be quantified by the increase of the integrated peak area of the affected protons. For $^1$H spectra, an enhancement of +1% is considered significant, but values may be far greater. It has been shown that the enhancements decrease by a factor of $r^6$ where $r$ is
the distance between the interacting nuclei and are generally observed between protons separated by up to 4 Å. The chiral racemic hydroxylamino amine we had prepared would ultimately lead us to chiral racemic nitrones. Therefore, we would isolate chiral racemic cycloadducts but the nOe technique would still allow us to characterise the relative sterochemistry via these enhancements of our products (arrowed in Figure 23) and so map the profile of the 2-H nitro in its 1,3-dipolar cycloaddition chemistry.

Irradiation of the α-proton of the C-7 ester, Hα, of cycloadduct produced an enhancement of the signal of the α-proton of the adjacent C-6 ester, Hβ, by 8%. A reciprocal enhancement of Hα by 9% was observed by irradiation of Hβ; irradiation of Hβ also augments the signal of Hε at C-3 by 7% with a return enhancement of 10%. This suggests that Hα, Hβ and Hε occupy the same face of the adduct, the lower face as drawn. The mutual enhancements between the geminal C-2 protons Hδ and Hε are, as might be expected, relatively large (24% in both directions) due to their close proximity. The increase of Hδ seen on irradiation of Hε (8%, with a return enhancement of 9%) allows its assignment to the lower face with Hα, Hβ and Hε. The other proton of this CH2 (Hγ), which must lie on the opposite face, is enhanced on irradiation of bridgehead proton Hγ by 5% with a reciprocal increase of 3%, and thus both Hδ and Hγ are assigned to the top face of the cycloadduct.

To our surprise, a reciprocal enhancement was observed between Hγ and the adjacent proton Hα (with zero scalar coupling in the 1H NMR spectrum), which we had thus far assigned to opposite faces of the cycloadduct. A simple molecular model of cycloadduct shows that Hγ and Hα can adopt a dihedral angle of approximately 90° through ring-flip of the bicyclic skeleton but only if these protons have a trans arrangement. Therefore, from the theoretical dependence of the 1H NMR coupling constant on dihedral angle given by the Karplus relation, a 90° dihedral angle should give rise to near-zero scalar coupling between
these adjacent protons.\textsuperscript{283} A similar bicyclic isoxazolidine system \textbf{236} has been synthesised by Ali \textit{et al.} (Figure 24). The H' proton appears as a doublet in the \textsuperscript{1}H spectrum, which the authors claim is indicative of coupling between H' and H' only. Thus, there is zero scalar coupling between H' and H' suggesting a dihedral angle of H'–C–C–H' of approximately 90°.\textsuperscript{284}

![Figure 24](image)

We were then able to crystallise the cycloadduct \textbf{230} from methanol and obtained an X-ray crystal structure which confirmed our nOe assignments (Figure 25). In the crystalline state, the dihedral angle between H' and H' was measured at 92.1°, corroborating our findings. Our quantitative difference nOe experiment was later repeated using the more sophisticated, qualitative, 2-dimensional "NOESY" technique, which was found to agree with our interpretation.

The assignment of relative stereochemistry allows us to make several conclusions about the transition state of the 1,3-dipolar cycloaddition reaction of the nitrone \textbf{126a} with DMM. The \textit{cis} relationship between the two ester \alpha-protons (H' and H') is maintained as was expected - the alkene geometry is always maintained during the concerted bond-forming process of the cycloaddition.\textsuperscript{32} The stereochemistry at the C-6 and C-7 stereocentres is
evidence of the preference for the exo transition state. It is clear that only exo approach would lead to the observed adduct 230, with the endo transition state producing the diastereomer 237 (Scheme 81). Most importantly, the trans relationship between H° and H° indicates the complete diastereofacial selectivity of this 2-imidazoline nitrene reagent. It is the steric bulk of the phenyl group adjacent to the nitrene nitrogen atom that directs incoming dipolarophiles to the less hindered face. The bridgehead C-7a proton (H°) and the C-3 phenyl group will thus share the same face of the nitrene in the favoured transition state, and so the isolated product 230 reflects this geometry.

Figure 25: X-ray crystal structure of cycloadduct 230.
Our next task was to optimise the yield of the DMM cycloadduct 230. We were aware that the hydrochloride of the analogous oxazoline nitrone 67 (Scheme 28) was neutralised prior to addition of the dipolarophile,\textsuperscript{99,100} and we isolated no cycloadduct from reaction of the 2-H nitrone 126a with DMM with no base present (Table 3, entry 1). The nitrone precursor 140a is a dihydrochloride salt which should therefore require 2 equivalents of base to neutralise the acid. Our experiments showed that the yield of cycloadduct 230 is maximised with 2.1 equivalents of triethylamine (64%) (entry 3). We found that a further equivalent of base (i.e. 3.1 equivalents overall, entry 4) gave a very poor yield (16%) compared to incomplete neutralisation with 1.1 equivalents (42%) (entry 2). We decided to probe the influence of the nature of the base on the cycloaddition. No cycloaddition was observed when the triethylamine was replaced by 2.1 equivalents of DBU (entry 5), and a yield of only 10% was observed with potassium carbonate (entry 6).
Replacement of triethylamine with the more hindered analogue diisopropylethylamine afforded a yield of 44% with 1.25 equivalents of DMM (entry 7). This yield was increased to 52% by the use of 5 equivalents of DMM (entry 8).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base / equivs.</th>
<th>Equivs. of DMM</th>
<th>Yield of 230 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N / 0</td>
<td>1.25</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Et₃N / 1.1</td>
<td>1.25</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>Et₃N / 2.1</td>
<td>1.25</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Et₃N / 3.1</td>
<td>1.25</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>DBU / 2.1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>K₂CO₃ / 2.1</td>
<td>1.25</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>iPr₂NEt / 2.1</td>
<td>1.25</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>iPr₂NEt / 2.1</td>
<td>5</td>
<td>52</td>
</tr>
</tbody>
</table>

a: All of these cycloaddition reactions were carried out at 60°C in toluene over 18 hours.

Table 3: Effect of base on yield of cycloadduct 230.

Having decided upon 2.1 equivalents of triethylamine as the optimum, we resolved to use these conditions with various proportions of the dipolarophile (Table 4). We found significant differences between our best yield for 1.25 equivalents of DMM (64%) (Tables 3 and 4, entry 3) with those for 3 and 5 equivalents of DMM (40% and 57%) (Table 4, entries 9 and 10, respectively). We performed side-by-side reactions under strictly anhydrous conditions on 1.25 and 5 equivalents of DMM with rigorously purified reagents and solvents, to afford 46% and 49% yields, respectively (Table 4, entries 11 and 12). Thus, we
were able to conclude that the purity and dryness of the reagents were not key factors in determining the yield of our cycloaddition. We also ruled out the effect of adventitious moisture after experiments with 4Å and 5Å molecular sieves afforded poor yields of impure material (18% and 6%; entries 13 and 14 respectively).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivs. DMM</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield of 230 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.25</td>
<td>60</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>60</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>60</td>
<td>18</td>
<td>57</td>
</tr>
<tr>
<td>11b</td>
<td>1.25</td>
<td>60</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>12b</td>
<td>5</td>
<td>60</td>
<td>18</td>
<td>49</td>
</tr>
<tr>
<td>13c</td>
<td>1.25</td>
<td>60</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>14d</td>
<td>1.25</td>
<td>60</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>1.25</td>
<td>60</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>1.25</td>
<td>60</td>
<td>8</td>
<td>38</td>
</tr>
<tr>
<td>17</td>
<td>1.25</td>
<td>60</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>18</td>
<td>1.25</td>
<td>60</td>
<td>40</td>
<td>27</td>
</tr>
<tr>
<td>19</td>
<td>3</td>
<td>90</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>90</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

*a*: All of these cycloaddition reactions were carried out in toluene with 2.1 equivalents of Et₃N over 18 h.  
*b*: Rigorously purified and dried reagents.  
*c*: with 4Å molecular sieves.  
*d*: with 5Å molecular sieves.

Table 4: Optimisation of cycloaddition reaction of 126a with DMM.
Increasing the cycloaddition reaction time was not revealing; 4, 24 and 40 hours at 60°C gave nearly identical yields (25%, 25% and 27%) (entries 15, 17 and 18, respectively). An 8 hour reaction time afforded 38% of 230 (entry 16), but did not challenge our optimum of 18 hours (entry 3). We found that no cycloadduct was formed when our best reaction conditions so far at 60°C (1.25 equivalents of triethyl orthoformate, 2.1 equivalents of Et₃N, 1.25 equivalents of DMM; Table 4, entry 3) were used at 90°C with 3 or 5 equivalents of DMM (entries 19 and 20) and so resolved to use 60°C or less in further optimisations.

Our modifications to the cycloaddition having been effective, we prepared to optimise the nitrone formation step using our best cycloaddition conditions (2.1 equivalents Et₃N, 1.25 equivalents DMM, 60°C, 18 hours; Table 5, entry 3). We resolved to use 60°C in the nitrone formation step, having observed reaction to completion inside 1 hour to isolate 126a as the hydrochloride in quantitative yield and in high purity by HPLC analysis (Figure 22). The isolated yield of cycloadduct 230 after stirring 140a and triethyl orthoformate for 3 hours at 60°C before effecting the cycloaddition was only 55% (Table 5, entry 21). A 6 hour reaction time reduced this yield to 46% (entry 22), and after 8 hours to 40% (entry 23).

Having decided upon 1 hour as the optimum reaction time for formation of the nitrone, we proposed to investigate the effect of the proportion of triethyl orthoformate. We approached our best yield to date (64%) (Table 5, entry 3) by the use of 3 equivalents of triethyl orthoformate (55%) (entry 24), and matched it by increasing the proportion to 5 equivalents (63%) (entry 25) or 10 equivalents (64%) (entry 26). We decided upon a final series of experiments with extended cycloaddition reaction times at 60°C and 20°C. A 1 hour nitrone formation step with 10 equivalents of triethyl orthoformate at 60°C was thus followed by a 40 hour cycloaddition step with 1.25 and 5 equivalents of DMM to afford 39% and 59% of cycloadduct 230, respectively (entries 27 and 28). Our optimisation was
completed by a similar experiment with a 24 hour cycloaddition at 20°C with 1.25 equivalents of DMM to afford the bicycle 230 in our best ever yield of 72% (entry 29). Thus, we found the optimum conditions for the nitrone formation to be treatment of a slurry of dihydrochloride 140a in anhydrous toluene with 10 equivalents of triethyl orthoformate at 60°C under nitrogen for 1 hour. The resultant solution then gives the highest yield of cycloadduct 230 (72%) when treated with 2.1 equivalents of Et₃N then 1.25 equivalents of DMM at 20°C and stirred for 24 hours.

<table>
<thead>
<tr>
<th>Entry</th>
<th>HC(OEt)₃ (equivs.)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield of 230 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.25</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>21</td>
<td>1.25</td>
<td>60</td>
<td>3</td>
<td>60</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>22</td>
<td>1.25</td>
<td>60</td>
<td>6</td>
<td>60</td>
<td>18</td>
<td>46</td>
</tr>
<tr>
<td>23</td>
<td>1.25</td>
<td>60</td>
<td>8</td>
<td>60</td>
<td>18</td>
<td>40</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>18</td>
<td>63</td>
</tr>
<tr>
<td>26</td>
<td>10</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>40</td>
<td>39</td>
</tr>
<tr>
<td>28a</td>
<td>10</td>
<td>60</td>
<td>1</td>
<td>60</td>
<td>40</td>
<td>59</td>
</tr>
<tr>
<td>29</td>
<td>10</td>
<td>60</td>
<td>1</td>
<td>20</td>
<td>24</td>
<td>72</td>
</tr>
</tbody>
</table>

a: 5 equivalents of DMM; otherwise 1.25 equivalents. All reactions performed in dry toluene.

Table 5: Nitrone formation optimisation and final conditions.
We followed up our success with DMM by reaction of the 2-H nitrone 126a with other symmetrical dipolarophiles containing a cis double bond (Scheme 82). These reactions and those that follow later in this section were performed by treatment of the hydroxylamino amine 140a with 1.25 equivalents of triethyl orthoformate in toluene at 60°C for 1-2 hours before addition of 2.1 equivalents of triethylamine and 1.25 equivalents of DMM and stirring for 18-24 hours. They do not, therefore, reflect the optimised yield in each case. By this methodology, we were able to isolate the cycloadducts 238 of diethyl maleate (36%), 239 of N-methyl maleimide (58%) and 240 of N-phenyl maleimide (38%). Despite the decomposition of N-methyl maleimide cycloadduct 239 after extended periods in solution, its relative stereochemistry was assigned as for the previous cycloadduct by NOESY. Firstly, we confirmed the cis-relationship between the former maleimide protons H^a and H^b by observing their mutual enhancements (arrowed in Figure 26). Enhancements were observed between H^b and H^c and between H^f and H^h, allowing us to assign all three to one face of the cycloadduct. As expected, geminal protons H^d and H^e showed reciprocating enhancements, whilst H^e also enhanced H^f. Therefore, we were able to conclude that if H^a, H^b, H^c and H^d occupy the lower face of 239, then H^e and H^f must occupy the upper face. In this case, we observed small enhancements between the bridgehead proton H^f and the
adjacent proton H² which indicates their close proximity and might call into question our *trans* assignment. As for adduct 230, there is no observable scalar coupling between H⁵ and H⁶ in the ¹H NMR spectrum, suggesting a dihedral angle of approximately 90° which can only be achieved if H⁵ and H⁶ have a *trans* arrangement. Our assignment of the relative stereochemistry of 239 is thus consistent with the observations made for the dimethyl maleate cycloadduct 230 (Figure 23). The stereochemistry of cycloadducts 238 and 240 was thus assigned by comparison of their NMR data to that of 239.

![Diagram of compound 239](image)

**Figure 26**: Relative stereochemistry of 239 by 2-D nOe spectroscopy.

The next step for our studies was to investigate the regiochemical preference of 126a by reaction with unsymmetrical alkene dipolarophiles. Thus, we reacted the nitrone 126a with methyl acrylate to afford the cycloadduct 241 (31%) (Scheme 83). Similarly, this reagent was reacted with other monosubstituted alkene dipolarophiles to prepare the cycloadduct 242 from acrylonitrile which was identified as the major component of an inseparable mixture on the basis of its similarity of its ¹H NMR spectrum with other 7-substituted cycloadducts. In this way, we also prepared 243 from ethyl acrylate (44%) and
244 from tert-butyl acrylate (8%). It seems reasonable to speculate that the low yield of 244 reflects the effect on reactivity of accommodating the bulk of the tert-butyl moiety in the transition state. The regiochemical outcome was consistent in all of our reactions with mono-substituted alkenes, from which we only isolated the 7-substituted isoxazolidine cycloadducts. The reaction of 2(5H)-furanone with nitrone 126a also followed this pattern in that the electron-withdrawing ester substituent is found at the 10-position in the isoxazolidine ring of the isolated tricyclic cycloadduct 245 (36%).

Scheme 83

The relative stereochemistry of ethyl acrylate cycloadduct 243 was determined by NOESY (Figure 27). In this way, we were able to determine that H₄, H₅, H₆ and H₇ occupy one face of the cycloadduct whilst H₈ and H₉ occupy the other face. Again, whilst there is an observed enhancement between H₈ and H₉, the zero coupling constant in the ¹H NMR again suggests a 90° dihedral angle and so a trans relationship. Comparison with the NMR data of adduct 243 has allowed the assignment of this same relative stereochemistry to the other cycloadducts in this series 241, 242, 244 and 245.
Figure 27: Relative stereochemistry of 243 by 2-D nOe spectroscopy.

Common alkyl nitrones generally give the 5-substituted isoxazolidines in their cycloaddition reactions with monosubstituted alkenes, and only form the 4-substituted isoxazolidine cycloadducts with very electron-deficient dipolarophiles, such as vinyl sulphoxides, vinyl sulphones and vinyl sulphonates. Thus, we might expect to isolate the 6-rather than 7-substituted imidazoisoxazole cycloadducts from reaction of 126a with all but the most electron-deficient dipolarophiles. However, 126a has shown total regioselectivity with moderately electron-deficient dipolarophiles and those dipolarophiles with exaggerated electron-deficiency should only serve to enhance the demonstrated proclivity of our nitrone 126a to form 7-substituted imidazoisoxazole cycloadducts.

We isolated cycloadduct 246 from the reaction of 126a with methyl vinyl sulfone (46%), 247 from ethyl vinyl sulfone (32%), and 248 from phenyl vinyl sulfone (49%) (Scheme 84). Again, the regioselectivity is complete; the 7-substituted imidazoisoxazoles are the only isolated products. The assignment of the relative stereochemistry of the methyl vinyl sulfone adduct 246 was made by NOESY. As before, the bridgehead proton Hf enhances the adjacent proton Ha (α-to the sulfone) but with a zero coupling constant. The other
enhancements are also as for adduct 243 and, by comparison of these NMR data with those for 247 and 248, the relative stereochemistry of these adducts was assigned as previously. In addition, the phenyl vinyl sulfone cycloadduct 248 was crystallised from methanol and X-ray crystallographic analysis confirmed our earlier nOe assignments (Figure 28). Again, we observed total facial selectivity in the cycloadditions of 126a and total selectivity for the exo product.

Figure 28: X-ray crystal structure of 248.
The propensity of a given 1,3-dipole / dipolarophile combination to form a particular regioisomer has often been explained in terms of their Frontier Molecular Orbitals (FMOs) (Section 1.1.4). In order to analyse the preference of our 2-imidazoline nitrone 126a, we must first consider the frontier orbitals of the generalised unsubstituted nitrone 1,3-dipole 249 (Figure 29). It has been shown that for any 1,3-dipolar cycloaddition, the smallest energy gap between the corresponding FMOs of the dipole and dipolarophile represents the optimum orbital overlap and therefore the fastest reaction (Section 1.1.4). The relative energies of the HOMO and LUMO of many classes of 1,3-dipole, including the
unsubstituted nitrone 249, have been calculated. Comparison of the relative energy of these FMOs with those calculated for an alkene dipolarophile 250 bearing an electron-withdrawing substituent Z, clearly shows that the dipole HOMO-dipolarophile LUMO interaction has the smallest energy gap. As this is the strongest bonding interaction, the reaction should be dipole HOMO controlled and constitutes a Type I interaction in the notation proposed by Sustmann (Section 1.1.4) (Figure 29). 24

Figure 30: Nitrone HOMO control affords mixed isoxazolidine cycloadducts.

The orbital interaction is greatest between orbitals with similar orbital coefficients at the interacting atoms, in other words, small with small and large with large. The terminal orbital coefficients for the HOMO of nitrone 249 are nearly identical (C = 1.11 and O = 1.06), and so neither regioisomer is preferred on this basis (Figure 30). Thus, dipole HOMO control will lead to a mixture of 4- and 5-substituted isoxazolidine cycloadducts. In this case, the regiochemistry of addition is decided by the weaker interaction of the dipole LUMO and dipolarophile HOMO. Here, the nitrone LUMO coefficients differ significantly (C =
0.98 and O = 0.32), and so a much stronger bonding interaction can occur in the orientation for which the orbital coefficients are matched. Thus, the cycloaddition reactions of unsubstituted nitrones 249 most often proceed via apparent dipole LUMO control to give the 5-substituted isoxazolidine product 251 rather than the 4-substituted cycloadduct 252 for which the coefficients are mis-matched (Figure 31).

![Figure 31: Nitrone LUMO control affords 5-substituted isoxazolines.](image)

If we substitute at the nitrone carbon with a conjugating donor nitrogen atom, we would expect to increase the energy of both the dipole HOMO and LUMO (Figure 29). Thus, we might predict that the energy gap between the HOMO of the dipole 126a and the LUMO of an electron-deficient dipolarophile 250 would be sharply reduced and the cycloaddition reactions of these dipoles should be strongly HOMO controlled. Whereas the unsubstituted nitrone 249 offers little difference in the terminal orbital coefficients, the presence of the nitrogen atom at the nitrone α-carbon of 126a will strongly enhance the dipole HOMO orbital coefficient on oxygen. This new polarisation should now allow the dipole HOMO to determine the regiochemistry of the product and so the 4-substituted isoxazolidine should predominate. Thus, by FMO theory we expect to isolate the 7-
substituted imidazoisoxazole cycloadducts with our 2-H nitrone 126a rather than the 6-substituted regioisomers. Our hypothesis is supported by the regiochemical preference shown by the related oxazoline nitrone 67a developed by Coates and Ashburn. They observed total selectivity for the 6-substituted isoxazolopyrrole* in the cycloaddition of the pyrrolidine nitrone 253 with acrylonitrile, as predicted by FMO theory (Scheme 85). This selectivity was reversed (7:6-substitution* = 3:1) after the introduction of an oxygen atom at the nitrone α-carbon to give the oxazoline nitrone 67a.

* Both the isoxazolopyrrole and oxazoloisoxazole rings are numbered according to the latter for clarity.

Study of the cycloadditions of our 2-imidazoline nitrone 126a with 1,1-disubstituted alkenes began with methyl methacrylate, which afforded the 6,6-disubstituted imidazoisoxazole 254 (16%) as the only observed cycloadduct, (Scheme 86). Similarly, we reacted 126a with ethyl methacrylate to afford cycloadduct 255 (13%) and with methacrylonitrile to afford 256 (<5%) which was assigned from a mixture by comparison of its ¹H NMR data with 254 and 255. Here, the regiochemical preference of nitrone 126a for 7-substituted adducts is overturned and it is clear that the frontier orbitals are no longer enforcing regiocontrol. This reversal of regiochemistry and associated poor yields are probably the result of the increased steric bulk of these 1,1-disubstituted dipolarophiles. No
longer able to approach the imidazoline ring without unfavourable steric clash, it seems that the 1,1-disubstitution pattern is better accommodated by the exocyclic position of the nitrone oxygen and so the 6,6-disubstituted products predominate. The relative stereochemistry of 254 was assigned by NOESY and it is clear that this cycloadduct is formed via the transition state in which the ester functionality is endo, and we have assigned 255 and 256 in this way.

![Diagram](image)

**Scheme 86**

The reaction of the 2-H nitrone 126a with ethyl vinyl ether 257 failed to produce any 1,3-dipolar cycloadduct (Figure 32). Similarly, no cycloaddition was observed with vinyl trimethylsilane 258 or vinyl acetate 259, suggesting that this nitrone is not reactive towards electron-rich dipolarophiles. Styrene 260 likewise produced no sign of an isoxazolidine with 126a, allowing us to reason that alkenes substituted with conjugating groups are also ineffective dipolarophiles here. The failure to observe any cycloadduct with maleic anhydride 261 may be tentatively attributed to the instability of the cycloadduct to hydrolysis, producing highly polar zwitterionic material which would be difficult to isolate. We might expect the cycloaddition reactions of more reactive dipolarophiles to compete with unwanted side-reactions, but no cycloadducts were observed in the reaction of 126a with
dimethyl azodicarboxylate or phenyl isocyanate. Other electron-deficient dipolarophiles for which no cycloaddition was observed included 5,6-dihydro-2H-pyran-2-one 262, 2,2-dimethyl-3(2H)-furanone 263, vinyl acrylate 264, acrylamide 265, methyl vinyl ketone 266, phenyl methacrylate 267 and Tuppy's maleimide 268.

![Chemical Structures](image)

Figure 32
2.4 Progress towards a template removal strategy

The planned template removal strategy began with a sodium cyanoborohydride reduction of the aminal functionality. It was hoped that it would then be possible to perform simultaneous catalytic hydrogenolysis of the N-O bond of the isoxazolidine and the N-benzyl moiety of the template to afford functionalised amino alcohols 269 (Scheme 87) or cyclisation products derived from them.

![Scheme 87](image)

It was decided that the dimethyl maleate cycloadduct 230 should be taken forward into the template removal phase as it offered the highest cycloaddition yields and the greatest potential for later functionalisation. However, this cycloadduct was unreactive to NaCNBH$_3$ at pH 4 in ethanolic solution, or glacial acetic acid at 20°C, returning unchanged starting material after lengthy reaction times. A similar experiment in which the solution was heated to 60°C for 1.5 hours, showed some consumption of the cycloadduct but none of the desired isoxazolidine 270 was isolated from the resultant mixture. We were also unsuccessful in attempts to reduce cycloadduct 230 with NaBH$_4$ or LiAlH$_4$ at 20°C, or with BH$_3$·THF at 20°C or at reflux.
As the aminal reduction presumably depends upon the availability of the lone pair on
the isoxazolidine nitrogen (to generate an amino-iminium salt), we decided to cleave the N–O
bond and thus facilitate the participation of these electrons. The hydrogenolysis of the N–O
bond of isoxazolidines with common, commercial catalysts is well documented in the
literature.285-287 The cycloadduct 230 was therefore subjected to atmospheric pressure
hydrogenolysis with 5mol% of 5% Pd-C at 30°C for 18 hours to afford the lactam 271
(13%) (Scheme 88). This product is consistent with the expected N–O cleavage followed by
spontaneous lactamisation of the secondary amino function. However, this lactam was not
isolated from such reaction at room temperature even in the presence of a drop of conc. HCl,
nor in acid-free solution with 5mol% of 10% Pd-C. Atmospheric pressure hydrogenolysis at
50°C, and hydrogenolysis at 50psi of H₂ at 20°C, were also unsuccessful.

A reagent we had intended to use for simultaneous N–O cleavage and debenzylation
was Pearlman’s catalyst (palladium(II) hydroxide). Hydrogenolysis at ambient temperature
and pressure with this catalyst, however, gave our best yield of the lactam 271 to date,
albeit a modest 27%. At the same time we were exploring other catalysts and conditions of
which 10% Pd-BaSO₄ was the first, but this returned the starting material unchanged after 18
hours, as did 5% Pt-C, PtO₂, 5% Rh-C or 5% Ru-C, either at ambient or elevated pressure.
We extended our search to the less usual reagents and methods, looking to Birch reduction with sodium metal in liquid ammonia, and catalytic transfer hydrogenation with 10% Pd-C and ammonium formate as well as extended reflux with zinc and acetic acid but all were unsuccessful. Langlois et al. have developed a method for isoxazolidine cleavage using m-CPBA in which a nitrone is regenerated and hydrolysed with dilute acid to yield the corresponding aldehyde. However, we found no evidence for the formation of the desired aldehyde from bicycle. We were similarly unsuccessful in our attempts to apply the chemistry of van Boggelen et al., in which N-O lysis is achieved via N-methylation with Mel in THF. Literature precedent exists for the cleavage of N-O bonds in isoxazoles, isoxazolines and isoxazolidines with metal-carbonyl complexes. Isoxazolidine was heated at reflux in moist acetonitrile for 30 minutes with molybdenum hexacarbonyl, to give a dark brown gum possibly consistent with the complex of cycloadduct and Mo(CO)₆, but not the desired ring-cleaved product or the lactam.

We were encouraged by literature precedent to try high-pressure hydrogenation with commercial Raney nickel (analogous to W-2 or Raney 28), but found the amount of catalyst used to vary greatly between experimenters. After 18 hours at 60psi of H₂ with 0.5 equivalents w/w of catalyst, the starting material was unchanged, and so an additional 4 equivalents were added before agitating at 60psi for a further 18 hours. Chromatographic purification of the resulting mixture afforded the desired lactam as a white crystalline solid (19%) and encouraged further optimisation. As hydrogenation apparatus that would tolerate significantly increased pressures was not readily available, we looked to varying the solvent as well as the proportion and activity of the catalyst. At 2 equivalents of Raney nickel w/w we isolated the lactam in a yield of 32-42% after chromatography. All experiments thus far had been conducted in methanol, but we observed no improvement in yield by
hydrogenation in ethanol or ethyl acetate (25% and 0%, respectively). Reaction with 3 equivalents of catalyst gave the lactam in a yield of 59%, but this was slightly bettered by reaction with 12 equivalents to afford 66% of 271. We prepared a sample of nickel catalyst by the Raney method from nickel-aluminium amalgam, washing out the aluminium with aqueous sodium hydroxide. Whilst this material seemed highly active, to the point of spontaneous ignition in air, the 39% yield of the lactam 271 did not challenge that of the commercial catalyst.

<table>
<thead>
<tr>
<th>Irradiated</th>
<th>Enhanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&lt;sup&gt;a&lt;/sup&gt;</td>
<td>H&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>H&lt;sup&gt;b&lt;/sup&gt;</td>
<td>H&lt;sup&gt;f&lt;/sup&gt;, H&lt;sup&gt;a&lt;/sup&gt;, OH</td>
</tr>
<tr>
<td>H&lt;sup&gt;c&lt;/sup&gt;</td>
<td>H&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>H&lt;sup&gt;d&lt;/sup&gt;</td>
<td>H&lt;sup&gt;c&lt;/sup&gt;, H&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>H&lt;sup&gt;e&lt;/sup&gt;</td>
<td>H&lt;sup&gt;d&lt;/sup&gt;, H&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>H&lt;sup&gt;f&lt;/sup&gt;</td>
<td>H&lt;sup&gt;c&lt;/sup&gt;, H&lt;sup&gt;a&lt;/sup&gt;, H&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>OH</td>
<td>H&lt;sup&gt;a&lt;/sup&gt;, H&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Figure 33**: Nuclear Overhauser enhancements for lactam 271

Qualitative difference nOe experiments allowed reliable assignment of the relative stereochemistry of the imidazoline ring of the lactam 271; enhancements were observed in both directions between H<sup>e</sup> and H<sup>d</sup>, H<sup>d</sup> and H<sup>e</sup> as well as H<sup>f</sup> and H<sup>f</sup> (Figure 33). Thus we were able to conclude that if H<sup>e</sup> and H<sup>d</sup> shared the lower face then H<sup>1</sup> and H<sup>f</sup> shared the upper face.
However, assignment was not so straightforward for the relative stereochemistry of the lactam ring. We found by NOESY that the bridgehead proton $H^f$, and that adjacent to it, $H^g$ showed reciprocal enhancements, suggesting that they both occupied the upper face. This suggested a total inversion of the C-7 stereochemistry of 271, which seemed much less likely than partial epimerisation of this relatively acidic centre. We were not alarmed by this finding in the light that we had found in previous cycloadducts that this NOe was indicative of a trans- relationship between these two protons. We also found that irradiation of $H^f$ enhanced $H^b$ but not the C-6 OH whilst irradiation of the C-6 OH enhanced not only the geminal proton ($H^b$), but also $H^a$. Here, we had evidence which could assign $H^f$ and $H^b$ with
confidence to the upper face and H\textsuperscript{a} to either. Fortunately, we were able to recrystallise the lactam 271 from methanol and the resulting X-ray crystal structure (Figure 34) confirmed that the C-7 relative stereochemistry of 271 was unchanged from that of the parent cycloadduct 230 and agreed with our earlier observations that the enhancements between H\textsuperscript{f} and H\textsuperscript{a} come about through their trans relationship. These data support our proposed reaction pathway in which the N–O cleavage product 272 cyclises through nitrogen onto the pendant ester function (Scheme 89) to form the 5-membered lactam, rather than the strained 4-membered alternative via reaction with the adjacent ester function. Rotation about the carbon-carbon bond which becomes C-6 to C-7 in the pyrroloimidazolone 271 is required to bring this ester favourably close for lactamisation and so the observed stereochemistry at C-6 of this lactam will have the hydroxyl moiety below the plane of the ring as drawn whereas the ester of the parent molecule 230 was above.

![Scheme 89](image)
When the Raney nickel reduction of cycloadduct 230 was performed on a large scale, it was possible to isolate a small amount of a second product which has been identified by NMR as the 2-functionalised 3-imidazoline 273 (Scheme 89), which is formally the result of dehydrogenation across C-3 and N-4 of 230 as well as the desired N-O hydrogenolysis, but could equally arise from a proton shift from C-3 to O.

The initial N-O bond cleavage step of our template removal strategy was also applied to the cycloadducts 241 of methyl acrylate and 238 of diethyl maleate. We found that the former adduct 241 was unreactive to H₂ with 5mol% of 10% Pd-C even after 48 hours at 20°C. Atmospheric pressure hydrogenolysis with 5mol% of Pd(OH)₂, or treatment with Raney nickel at 60psi of H₂, were also unsuccessful. Similarly, the diethyl maleate cycloadduct 238 did not yield any identifiable material after elevated pressure hydrogenolysis at 20°C with Raney nickel.

![Scheme 90](image-url)
Having cleaved the N–O bond, we hoped that the lactam 271 would undergo aminal reduction with NaCNBH₃ to afford 274 (Scheme 90). Thus, 271 was stirred in ethanolic solution at pH4 with NaCNBH₃ for 48 hours but without change. Reaction at room temperature with NaCNBH₃ in glacial acetic acid was unsuccessful, and heating this mixture to reflux returned an intractable mixture of products. Thus, we sought to cleave the aminal with NaBH₄, but after 72 hours at room temperature the mixture was purified by column chromatography to isolate the diol 275 (19%). This experiment was repeated in order to determine the fate of the missing material but after 18 hours at room temperature again we only isolated a 19% yield of 275. We resolved to carry out simultaneous cleavage of the aminal moiety and reduction of both the lactam and ester functionalities using LiAlH₄, but room temperature reaction only produced complex mixtures. In situ trapping of the desired amino diol 276 with acetone²⁹⁴ was attempted in order to facilitate isolation of this highly polar product, if present, as the cyclic acetal 277, but this afforded no desired material. We presume that the lone pair of the amide nitrogen of the lactam 271 is unable to participate in the aminal reduction by assisting amino-iminium ion formation.

We decided to reduce the lactam carbonyl, to afford a pyrroloimidazole ring system similar to 133 (Scheme 43) for which we have a template removal strategy in hand. There is a plethora of amide reduction strategies to choose from in the literature²⁹⁵-²⁹⁷ including complexed borane reagents²⁹⁸-³⁰⁷ Thus, a solution of the lactam 271 in dry THF was heated at reflux with BH₃·THF complex for 18 hours but the isolated material was not the desired pyrroloimidazole 278 but the partially aromatic product 279 (Scheme 91). From these results, we propose that pyrrole 279 forms via the aminol intermediate 280 in the reduction of the lactam carbonyl. This eliminates a water molecule across the C-6 to C-7 bond taking advantage of the acidity of the C-7 proton to afford the α,β-unsaturated ester
intermediate 281. The C-7a bridgehead proton is then lost along with the aminol C-5 hydroxyl group of 281 in a 1,4-elimination driven by aromatisation of the pyrrole ring of 279.

![Scheme 91](image)

Of the other known lactam reduction protocols, we attempted the trichlorosilane methodology of Nagata et al. who reported facile reduction of N,N-disubstituted lactams by this procedure. Thus, the lactam 271 was heated to reflux in toluene with 4 equivalents of HSiCl₃ but only the lactam starting material was isolated after 24 hours. A number of lactam reductions by catalytic hydrogenation are known, but agitation of a solution of the lactam in methanol with 5mol% of 10% Pd-C at a pressure of 60psi of H₂ did not afford the desired product, even after 72 hours.
2.5 Attempted achiral imidazoline nitrone syntheses.

As we have described in the previous section, the development of our final synthesis of the 2-imidazoline nitrones led us a long way from the initial strategy that we proposed. We were at the same time investigating other routes to our target reagents from a diverse range of starting materials, and our findings will be reported in this section.

2.5.1 Towards nitrones via 2-imidazolines.

It is clear from the literature that one of the mainstays of nitrone preparative methods is direct oxidation of the corresponding imine. Imidazole and its derivatives are unreactive toward mild oxidation, and under more vigorous conditions yield a range of ring-cleavage products rather than the N-oxides. Similarly, there is no track record of 2-imidazoline N-oxidation, although the closely analogous oxazoline nitrones have been formed in this way. Keana and Lee used m-CPBA to oxidise the oxazolines 282 to the oxaziridines 284, which spontaneously isomerised over silica gel to the moisture-sensitive nitrones 67 (Scheme 92).
We proposed that we might prepare the achiral 2-imidazoline nitrone 284 by this methodology from the 2-imidazoline 285 (Scheme 93). This compound is familiar to us as the intermediate in the synthesis of the achiral 2-imidazoline azomethine ylides 125a (Section 2.1). Therefore N-benzylethlenediamine 286 was prepared by dropwise treatment of a solution of ethlenediamine 287 with benzyl chloride at 0°C followed by 72 hours at reflux, to afford the alkylated product as a colourless oil (51%) after vacuum distillation. Cyclisation of the diamine 286 was performed with triethyl orthoformate and catalytic p-TsOH by heating to 130°C for 36 hours. The crude product mixture was purified by vacuum distillation to afford the 3-benzyl-4,5-dihydroimidazole 285 as a highly hygroscopic white solid (71%). Our first attempts at oxidation of 285 were performed in glacial acetic acid by heating to reflux with aqueous hydrogen peroxide. The solution was basified and extracted with chloroform to afford a mixture containing the starting material but with no indication of the nitrone 284 or the corresponding oxaziridine 288. In an alternative oxidation procedure,
a solution of the 2-imidazoline 285 in dry ether was treated with m-CPBA at 0°C before warming to 20°C and stirring for 24 hours. The reaction was treated with EtOAc and 10% Na₂CO₃ before addition of solid NaCl to force the organic material from the aqueous phase. The EtOAc was dried and evaporated to afford a mixture from which only m-CPBA and m-CBA were identified. This experiment was repeated with addition at -10°C, but without success. An experiment kept at 4°C for 48 hours gave a complex mixture of products from which no nitrone was could be isolated.

2.5.2 Towards nitrones from β-aminoalcohols

\[ \begin{align*}
\text{Ph} & \quad \text{Ph} & \quad \text{Ph} \\
\text{NH} & \quad \text{Br} & \quad \text{NH} \\
\text{OH} & \quad \text{N} & \quad \text{O}\text{-Boc} \\
290 & \quad 291 & \quad 292 \\
\text{Ph} & \quad \text{Ph} & \quad \text{NH} \\
\text{NH} & \quad \text{Br} & \quad \text{NH} \\
\text{N-Boc} & \quad \text{N-Boc} & \quad \text{N-Boc} \\
294 & \quad 295 & \quad 296 & \quad 297
\end{align*} \]

Reagents: i, 48% aq. HBr, 130°C, 4h; ii, NH₂OR·HCl, Et₃N, EtOH, Δ, 72h or DMF, Δ, 18h; iii, HN(Boc)OBoc (293), K₂CO₃, DMF, 30°C, 18h; iv, Boc₂O, Na₂CO₃, H₂O, 20°C, 18h.

Scheme 94
The achiral nitrone precursor 289 is only removed from the commercial β-amino alcohol 290 by a single functional group interconversion. However, the poor leaving group ability of the hydroxide moiety in 290 forced us to find a way to enhance its reactivity towards substitution. To this end, we proposed to prepare N-benzyl-2-bromoethylamine as its hydrobromide salt 291 by the method of Martin and Campbell, and subsequently to perform substitution of the bromide by hydroxylamine.

After the reaction of N-benzylethanolamine 290 and 48% aqueous HBr at 130°C for 4 hours, the brown residue was cooled and washed with ether then DCM to afford an off-white solid. This proved to contain a mixture of the desired product 291 and the starting material 290 each as their hydrobromide salt in the ratio 4:1, which corresponded to a 19% yield of the desired compound. Repeats of the procedure showed no improvement in yield or purity, which led us to attempt the substitution reaction with hydroxylamines on this mixture. Reaction with 1.1 equivalents of hydroxylamine hydrochloride or O-benzylhydroxylamine hydrochloride and 3.1 equivalents of triethylamine in ethanol yielded none of the desired substitution products 289 or 292. Nor was success achieved with hydroxylamine after changing the solvent to THF, or with 5 equivalents of the nucleophile in ethanol. We prepared N,O-bis-tert-butoxycarbonylhydroxylamine 293 to use as an alternative nucleophile, from hydroxylamine hydrochloride and di-tert-butyl dicarbonate (Boc₂O) in aqueous sodium carbonate by the method of Whiting and Baillie as a white crystalline solid (54%). Despite using this reagent in DMF with potassium carbonate to promote the SN₂ reaction, we isolated none of the desired product 294 after 18 hours at room temperature. A large proportion of the N,O-bis-tert-butoxycarbonylhydroxylamine was recovered (67%), along with the product of intramolecular nucleophilic substitution, N-
Similarly harsh conditions were applied in a synthesis of 295 with conc. sulfuric acid but only the starting material was recovered. At this point, we became aware of the aziridine preparations of Pfister using Mitsunobu chemistry. He reports good yields of aziridines with substitution at one or both of the ring carbons but a poor yield of N-benzylaziridine (18%) and no reaction when the nitrogen is unsubstituted. We chose (1R,2S)-(−)-ephedrine 299 as a convenient chiral source, and treated it, in solution, with triphenylphosphine then diethyl azodicarboxylate (DEAD) before stirring at 20°C for 18 hours in an attempt to prepare the aziridine 300. However, the only identifiable material from this reaction was the expected by-product diethoxycarbonylhydrazine. We applied these conditions to the synthesis of N-benzylaziridine 295 and N-methylaziridine 301 from the corresponding β-amino alcohols but without success. A small, impure sample of N-methylaziridine 301 was later prepared by reaction with chlorosulphonic acid and the previously described vigorous conditions. This material was reacted with hydroxylamine or benzylhydroxylamine (generated from the hydrochlorides in situ by addition of 1 equivalent of triethylamine) in the presence of catalytic ammonium chloride in methanol at room temperature for 48 hours in an attempt to prepare hydroxylamines 302a and 302b, but no ring-opening was observed.

At this point, we decided to re-examine the synthesis of N-benzylaziridine, this time using the mild sulfonating agent sulfur trioxide-trimethylamine complex. A mixture of N-benzylethanolamine and 1.2 equivalents of the complex were heated to reflux for 2 hours. After cooling to 60°C, the mixture was treated with excess 10M aqueous NaOH and heated at reflux for a further 2 hours. The whole mixture was cooled to room temperature and extracted with toluene, before drying and evaporation in vacuo to yield pure N-benzylaziridine 295 as a colourless oil (30%). This material was taken forward for ring opening with hydroxylamine but gave a highly complex mixture of products from which
none of the desired material could be isolated. As an alternative ring-opening reagent, we applied the N,O-bis-tert-butoxycarbonylhydroxylamine 293 which, in contrast to hydroxylamine itself, was unreactive under the attempted ring-opening conditions, returning unchanged starting material.

2.5.3 Towards nitrones from N-benzylglycine ethyl ester

![Scheme 97]

Reagents: i, Boc₂O, Et₃N, DCM, 20°C, 18h; ii, DIBAL, PhMe, -78°C, 1.5h then aq. Rochelle salt, 20°C, 1.5h; iii, NH₂OH.HCl, NaOAc, H₂O, EtOH, 60°C, 2h; iv, BH₃.THF, THF, N₂, 20°C, 60h then 6M aq. HCl; v, AcCl, pyridine, 20°C, 18h vi, NH₂OBn.HCl, NaOAc, EtOH.

Scheme 97

Having been unsuccessful in the introduction of hydroxylamino functionality into our achiral synthetic targets by substitution, we were encouraged by much literature precedent for hydroxylamine preparation via oximes. This scheme required formation of the oxime
benzylaziridine 295 (42%), and the less obvious product, 3-benzyloxazolidin-2-one 296 (28%).

We attempted to deter the participation of the benzylamino moiety in the intramolecular aziridination reaction during substitution with hydroxylamines, by protection of this nucleophilic nitrogen as the carbamate. Thus, we treated a solution of the bromo amine hydrobromide 291 in aqueous sodium carbonate with Boc$_2$O and stirred the resulting mixture at 20°C for 48 hours. The residue yielded no desired material after column chromatography although Boc$_2$O (20%) was recovered, once again, along with the 3-benzyloxazolidin-2-one 296 (27%). The generation of 296 from two quite different reactions suggests a common pathway and therefore we propose that in both instances, this product is derived from the desired N-Boc bromo amine 297 (Scheme 95). In the reaction of bromo amine 291 with the bis-Boc-hydroxylamine 293, we propose that the Boc-protected bromo amine 297 arises via transfer of the O-tert-butoxycarbonyl group from the bis-Boc reagent onto the benzylamine nitrogen. In both cases, this is then followed by attack at the $\alpha$-position through donation of the benzylamino nitrogen lone pair into the N-C bond, leading to ring-closure through oxygen with the loss of bromide. Loss of the tert-butyl carbonium ion from intermediate 298 will regenerate the carbonyl moiety and so afford the isolated oxazolidin-2-one 296.

![Scheme 95](image_url)
An alternative synthesis of achiral 2-imidazoline nitrones was devised which might afford the target compound in as little as 3 steps (Scheme 96). Firstly, we needed to prepare N-benzylaziridine 295, available via any of the well-known methods for conversion of the hydroxyl moiety to a more effective nucleofuge, such as the sulfate. This would facilitate an intramolecular $S_N2$ reaction through the amino-nitrogen of 290 to afford the aziridine 295. Being highly-strained ring systems, aziridines are commonly ring-opened by nucleophiles including the hydroxylamine we require to afford the desired intermediate 289, the potential nitrone precursor.

Reagents : i, SO$_3$,NMe$_3$, $\Delta$, 2h then 10M aq. NaOH, $\Delta$, 2h; ii, NH$_2$OH, NH$_4$Cl, MeOH, 30°C, 18h; iii, Ph$_3$P, DEAD, Et$_2$O, 20°C, 18h or ClSO$_3$H, 130°C, 20mmHg, 2h then 16M aq. KOH; iv, NH$_2$OR, NH$_4$Cl, MeOH, 20°C, 48h.

Scheme 96

We attempted to prepare the sulfate of N-benzylethanolamine 290 by the method of Wenker and Leighton et al., heating to 130°C under vacuum with chlorosulfonic acid. However, after base treatment, we observed none of the desired aziridine 295.
from the aldehyde, followed by controlled reduction to the hydroxylamine avoiding over-reduction to the amine. Our synthetic efforts were greatly assisted by methodology developed within this research group to prepare protected amino aldehydes similar to \( \text{303} \).

Thus, a DCM solution of commercial N-benzylglycine ethyl ester \( \text{304} \) was treated with Boc\(_2\)O and triethylamine and stirred at 20°C for 18 hours (Scheme 97). Thorough washing with 1M aqueous citric acid to remove excess Boc\(_2\)O, and column chromatography afforded a white solid (76%), shown to be a mixture of carbamate rotamers of protected amino ester \( \text{305} \) by \(^1\text{H} \) NMR spectroscopy.

Reduction of the N-Boc-amino ester \( \text{305} \) was performed in dry toluene by slow addition of diisobutylaluminium hydride (DIBAL) at -78°C followed by quenching with methanol and addition of a solution of potassium sodium tartrate (Rochelle salt) to remove aluminium residues. After 1.5 hours of vigorous stirring, two phases formed from which the organic phase was separated to afford the N-Boc-amino aldehyde \( \text{303} \) as a colourless oil (82%). Once again, the product was shown to exist as a mixture of carbamate rotamers by \(^1\text{H} \) NMR spectroscopy. This aldehyde was treated with a solution of sodium acetate and hydroxylamine hydrochloride to form 2 immiscible phases which were not combined by addition of a little ethanol. Despite this, the mixture was heated to 60°C for 2 hours before cooling to 20°C and, after column chromatography, afforded the β-oximino amine \( \text{306} \) as a white solid (48%).

\( \text{BH}_3 \cdot \text{THF} \) complex is one of the few reducing agents capable of performing the controlled reduction of an oxime to a hydroxylamine without over-reduction to the amine. Therefore, a solution of the oxime in dry THF was treated with \( \text{BH}_3 \cdot \text{THF} \) at 20°C dropwise under an atmosphere of nitrogen. After 60 hours at 20°C, the solution was treated with 6M aqueous HCl and stirred for 1 hour, before basifying with KOH and extraction into DCM.
However, the desired hydroxylamine 289 was not isolated from the intractable mixture so formed. It is reported in the literature that O-acetylation enhances the reactivity of an oxime towards reduction. 224 To this end, a solution the oximino amine 306 in pyridine was treated with acetyl chloride at 0°C before stirring at 20°C for 18 hours. 319 The solution was then partitioned between ether and aqueous citric acid, but none of the desired O-acetyloxime 307 was isolated after column chromatography. The aldehyde 303 was also used in an experiment to prepare the O-benzyloximino amine 308 but, again, none of the desired oxime was observed.
2.6 Future work

We have demonstrated that the 2-imidazoline nitrone 126a shows complete diastereofacial selectivity in its 1,3-dipolar cycloaddition reactions. Thus, in future work, this methodology will be applied to homochiral nitrones (R)- and (S)-126a, potentially available via one of the strategies outlined in Section 2.2.3. Once a method for reduction of the lactam 271 is found, it will be possible to apply the developed template removal methodology. Here, aminal cleavage of 278 by sodium cyanoborohydride would afford the N-substituted pyrrolidine 309. Debenzylation of 309 by catalytic hydrogenolysis would then furnish 310 and complete the route to homochiral functionalised pyrrolidines via nitrone cycloadditions (Scheme 97).
Chapter 3

Experimental
Instrumentation

Proton (^1H) and carbon (^13C) NMR spectra were recorded on a JEOL JNM-EX400 (400MHz and 100MHz respectively) or a JNM-LA300 (300Mz and 75MHz respectively) Fourier Transform NMR spectrometer. Chemical shift values are reported in parts per million (ppm) from tetramethylsilane (TMS) or 3-(trimethylsilyl)-2,2,3,3-tetradecuteropropionic acid sodium salt (TSP-d4) as the internal standard for ^1H spectra, and from the solvent peaks for ^13C spectra. Multiplicities are given as s-singlet, d-doublet, q-quartet, m-multiplet and br-broad signal. Coupling constants (J) are expressed in Hz to one decimal place. Infrared spectra were recorded using a Perkin-Elmer 1710 Fourier Transform Infrared spectrometer. Optical rotation measurements were made using a JASCO DIP-1000 digital polarimeter. Low resolution mass spectra were recorded on a VG Micromass VG-250 mass spectrometer by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) in a thioglycerol matrix in both positive and negative ion modes. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (Univerity of Wales, Swansea). Elemental analyses were performed by MEDAC Ltd. and X-ray crystallography by the EPSRC X-Ray Crystallographic Service (University of Southampton). Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. APCI was performed on a Fisons VG Platform instrument from samples in methanol or acetonitrile solution.

All column chromatography was carried out using Fluka Silica Gel 60 (220-440mesh) (Brockmann 2-3). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV254 plates on a plastic backing (with fluorescent indicator) and visualised by ultraviolet light or aqueous potassium permanganate spray (KMnO4:K2CO3:water, 6:1:100,
w/w/v). All chemicals were purified by distillation or recrystallisation where appropriate. THF, toluene and ether were dried over sodium or potassium and distilled. DCM was dried over sodium hydride and distilled. Dry reactions were carried out using oven-dried glassware with all transfers performed using oven-dried syringes and syringe needles.
2-Bromo-2-phenylacetic acid (137)

A solution of 2-phenylglycine 127 (0.500g, 3.31mmol) in aqueous HBr (48% w/v; 4cm³) was treated with a solution of sodium nitrite (0.250g, 3.64mmol) in water (2cm³) at 0°C. After stirring for 30 min, the mixture was warmed to 20°C and stirred for a further hour. The mixture was diluted with water (10cm³) and extracted with DCM (3 x 50cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 137 as a cream-coloured solid (0.340g, 48%), mp 79-80°C (lit., 81-84°C); ν_max (KBr) /cm⁻¹ 3400-2500, 1715, 1457, 1418, 1291, 1233, 1167, 1148, 917, 719, 701 ; δ_H (CDCl₃; 400MHz) 5.35 (s, 1H, PhCHBr), 7.36 & 7.55 (m, 5H, Ar-H), 10.08 (br s, 1H, CO₂H); δ_C (CDCl₃; 100MHz) 46.1 (PhCHBr), 128.7, 128.9 & 129.6 (Ar-CH), 134.9 (Ar-C), 174.0 (CO₂H); m/z 214 (M⁺-H, 7%), 171 (11%), 169 (11%), 136 (12%), 135 (100%), 118 (5%), 107 (34%), 90 (32%).
Attempted preparation of 2-benzyloxyamino-2-phenylacetic acid (177)

![Chemical structure](image)

To a solution of 2-bromo-2-phenylacetic acid 137 (0.100g, 0.465mmol) in DCM (5cm³) was added dropwise a solution of triethylamine (0.280cm³, 2.01mmol) and O-benzylhydroxylamine hydrochloride (80.0mg, 0.501mmol) in DCM (5cm³). The solution was heated to reflux for 18 h and, after cooling to 20°C, acidified with aqueous HCl (2M; 30cm³) and extracted with DCM (3 x 50cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated but the residue yielded none of the desired material after column chromatography (SiO₂, hexane:EtOAc 1:1 v/v).

Attempted preparation of 2-hydroxyamino-2-phenylacetic acid (167)

![Chemical structure](image)

To a solution of sodium (0.920g, 40.0mmol) in anhydrous methanol (15cm³) was added hydroxylamine hydrochloride (1.16g, 16.7mmol). To this solution was added 137 (2.00g, 9.30mmol) before heating to reflux for 18 h. The solution was acidified with aqueous HCl (2M) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated and the residue purified by column
chromatography (SiO₂, DCM:MeOH 19:1 v/v) to afford 2-methoxy-2-phenylacetic acid 176 (0.21g, 21%) as a brown oil; δₜ (CDCl₃; 400MHz) 3.40 (s, 3H, OCH₃), 4.79 (s, 1H, PhCH), 7.26-7.49 (m, 5H, Ar-H), 9.01 (br s, 1H, CO₂H); δₒ (CDCl₃; 100MHz) 57.3 (OCH₃), 82.0 (PhCH), 127.2, 128.6 & 129.0 (Ar-CH), 135.3 (Ar-C), 175.4 (C=O).

Attempted preparation of (R)-2-bromo-2-phenylacetic acid ((R)-137)

A solution of (S)-(+)2-phenylglycine (S)-127 (5.00g, 33.1mmol) in water (15cm³) and aqueous HBr (48% w/v; 10cm³) was treated with a solution of sodium nitrite (2.50g, 36.4mmol) in water (5cm³) dropwise at 0°C over 30 min. After warming to 20°C overnight, the solution was extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered then evaporated under reduced pressure and purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford a cream-coloured solid whose data was consistent with 137 (1.71g, 24%) prepared earlier in racemic form. Optical rotation measurement showed almost total racemisation: [α]D²⁰ = 0.73°, DCM; c = 0.15 (lit., 200 - 178°, benzene, c = 2 for R-enantiomer).
2-Bromo-2-phenylacetyl chloride (163)

A solution of 2-bromo-2-phenylacetic acid 127 (10.0g, 64.5mmol) in DCM (30cm³) was treated dropwise with thionyl chloride (3.73cm³, 51.2mmol) and heated to reflux for 24 h, protected from the atmosphere by a calcium chloride guard tube. Evaporation of the solvent under reduced pressure gave a brown oil which was distilled under reduced pressure to afford the title compound 163 as a yellow oil (9.90g, 91%), bp 142-148°C at 20mmHg, (lit., 321 135-137°C at 20mmHg); ν_max (film) /cm⁻¹ 3066, 3034, 1801, 1494, 1456, 1005, 981, 916, 697; δ_H (CDCl₃; 400MHz) 5.67 (s, 1H, PhCHBr), 7.40-7.49 (m, 5H, Ar-H); δ_C (CDCl₃; 100MHz) 54.8 (PhCHBr), 128.9, 129.4 & 130.2 (Ar-CH), 133.4 (Ar-C), 167.9 (C=O); m/z 234 (MH⁺, 16%), 199 (2%), 172 (8%), 171 (94%), 169 (95%), 163 (12%), 153 (31%), 127 (28%), 125 (100%), 91 (17%), 90 (94%).
2-Bromo-2-phenyl-N-benzylacetamide (138)

![Chemical Structure](image)

To a stirred solution of benzylamine (8.83 cm³, 80.9 mmol) in ether (250 cm³) at 0°C was added 2-bromo-2-phenylacetyl chloride 163 (9.00 g, 38.5 mmol) in ether (50 cm³). A thick, white precipitate formed instantly on addition, which was collected by filtration under reduced pressure and washed with ether (50 cm³) and aqueous HCl (2M; 50 cm³) before drying under reduced pressure to give the title compound 138 as an off-white solid (9.45 g, 31.1 mmol, 81%), mp 94-95°C (lit., 96-97°C); ν max (nujol) /cm⁻¹ 3289, 2923, 2854, 1660, 1480; δ H (CDCl₃; 400 MHz) 4.46 (m, 2H, NHCH₂Ph), 5.45 (s, 1H, PhCHBr), 7.03 (br s, 1H, NH), 7.24-7.45 (m, 10H, Ar-H); δ C (CDCl₃; 100 MHz) 44.3 (NHCH₂Ph), 51.3 (PhCHBr), 127.7, 128.3, 128.8, 128.9 & 129.1 (Ar-CH), 137.3 & 137.4 (Ar-C), 167.1 (C=O); m/z 304 (M⁺, <1%), 224 (95%), 196 (9%), 181 (48%), 169 (35%), 118 (40%), 106 (53%), 91 (100%).
Methyl 2-bromo-2-phenylacetate (172)

A solution of 2-bromo-2-phenylacetyl chloride 163 (1.80g, 7.71mmol) in methanol (50cm³) was heated to reflux for 18 h, protected from the atmosphere by a calcium chloride guard-tube. Evaporation of the solvent gave a pale brown, mobile oil which, after column chromatography (SiO₂, hexane:EtOAc 4:1 v/v), gave the title compound 172 material as a colourless oil (0.620g, 35%); δₜ (CDCl₃; 400MHz) 3.77 (s, 3H, OCH₃), 5.36 (s, 1H, PhCHBr), 7.36 & 7.52 (m, 5H, Ar-H); δₓ (CDCl₃; 100MHz) 46.5 (OCH₃), 53.4 (PhCHBr), 128.6, 128.8 & 129.3 (Ar-CH), 135.7 (Ar-C), 168.7 (C=O); m/z 228 (M-H⁺, 2%), 184 (29%), 169 (13%), 149 (66%), 125 (100%), 121 (39%), 105 (24%), 89 (44%).

Also isolated by chromatography was a trace of methyl 2-methoxy-2-phenylacetate 173; δₜ (CDCl₃; 400MHz) 3.40 (s, 3H, PhCHOCH₃), 3.71, (s, 3H, CO₂CH₃), 4.78 (s, 1H, PhCH), 7.33-7.45 (m, 5H, Ar-H).
Phenylglycine methyl ester hydrochloride (174)

![Chemical structure]

A solution of phenylglycine 127 (1.00g, 6.62mmol) in methanol (30cm³) was treated with thionyl chloride (0.530cm³, 7.28mmol) at 0°C. The solution was heated to reflux for 3 h before evaporation of the solvent under reduced pressure to afford 174 as a white solid (1.29g, 97%), mp 196-197°C (lit.,24 205-207°C); δH (d6-DMSO; 400MHz) 3.72 (s, 3H, CO2CH), 5.24 (s, 1H, PhCHNH3⁺), 7.43-7.58 (m, 5H, Ar-H), 9.28 (br s, 3H, NH3⁺); δc (CDCl3; 100MHz) 53.0 & 55.2 (CO2CH3 & PhCHNH3⁺), 128.2, 128.8 & 129.4 (Ar-CH), 132.5 (Ar-C), 168.7 (C=O).

Methyl 2-bromo-2-phenylacetate (172)

![Chemical structure]

A solution of phenylglycine methyl ester hydrochloride 174 (1.00g, 6.62mmol) in water (3cm³) and aqueous HBr (48% w/v; 4cm³) was treated with a solution of sodium nitrite (0.500g, 7.25mmol) in water (1cm³) at 0°C with stirring in one portion. After 30 min at 0°C, the reaction was allowed to warm to 20°C overnight. The reaction was diluted with
water (10cm³) and extracted with DCM (3 x 30cm³). The combined organic extracts were
dried (MgSO₄), filtered and evaporated under reduced pressure and the residue purified by
column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford 172 as a brown oil
(40.0mg, 4%), having data identical to a sample described above.

Methyl mandelate (178)

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

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

A solution of l-mandelic acid 158 (5.00g, 32.9mmol) in methanol (150cm³) at 0°C
was treated dropwise with thionyl chloride (2.64cm³, 36.1mmol). The solution was heated
under reflux for 18 h before evaporation of the solvent under reduced pressure. The brown,
crystalline residue was taken up in CHCl₃ (150cm³) and the solution washed with aqueous
NaOH (2M; 3 x 150cm³), before drying (MgSO₄), filtering and evaporation to dryness to
afford the title compound 178 as an off-white crystalline solid (4.40g, 81%); δₜ (d₆-DMSO;
400MHz) 3.58 (br s, 1H, OH), 3.71 (s, 3H, OCH₃), 5.16 (s, 1H, PhCHOH), 7.30-7.41
(m, 5H, Ar-H); δₖ (d₆-DMSO; 100MHz) 51.6 (OCH₃), 55.2 (PhCHOH), 126.4, 127.7 &
128.0 (Ar-CH), 139.3 (Ar-C), 172.8 (C=O).
Attempted preparation of 2-(p-toluenesulfonyl)mandelic acid (179)

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \text{X} \quad \text{CO}_2\text{H} \\
\text{Ph} & \quad \text{Ph} \\
158 & \quad 179
\end{align*}
\]

A stirred solution of l-mandelic acid 158 (1.00g, 6.57mmol) in acetonitrile (30cm\(^3\)) at 20°C was treated with triethylamine (1.97cm\(^3\), 14.1mmol). The solution was cooled to 0°C and treated with a solution of p-toluenesulfonyl chloride (2.63g, 13.8mmol) in acetonitrile (30cm\(^3\)) dropwise and stirred at 0°C for 30 min. TLC analysis showed no sign of reaction, and so the solution was warmed to 20°C for 1 h but without observable change. After heating the solution at reflux (80°C) for 18 h, the solvent was removed under reduced pressure but the residue did not contain any of the desired material 179.

Attempted preparation of methyl 2-(p-toluenesulfonfonyl)mandelate (180)

\[
\begin{align*}
\text{O} & \quad \text{OMe} & \quad \text{O} & \quad \text{OMe} \\
\text{Ph} & \quad \text{OH} & \quad \text{Ph} & \quad \text{OTs} \\
178 & \quad 180
\end{align*}
\]

Using the procedure described for the attempted preparation of 2-(p-toluenesulfonato)mandelic acid 179, a solution of methyl mandelate 178 (0.100g, 0.602mmol) in chloroform (5cm\(^3\)) was treated with triethylamine (0.170cm\(^3\), 1.20mmol) then p-tosyl chloride (0.130g, 0.661mmol). An identical procedure used pyridine (97.0µl,
1.20mmol) and acetonitrile (5cm³). In both cases the crude reaction mixture was purified by column chromatography (SiO₂, EtOAc:hexane 1:1 v/v), but afforded only starting material 178 and an intractable mixture of products.

**Ethyl 2-phenyl-2-hydroxyiminoacetate (185a)**

![Chemical structure](image)

A solution of ethyl benzoylformate 186 (2.00g, 11.2mmol), hydroxylamine hydrochloride (0.86g, 12.3mmol) and pyridine (0.996cm³, 12.3mmol) in absolute ethanol (20cm³) was heated under reflux for 1 h. The solvent was evaporated and the residue purified by column chromatography (SiO₂, hexane: EtOAc 4:1 v/v) to yield the title compound 185a as a clear oil which slowly crystallised on standing to a white crystalline solid (0.690g, 32%); ν₁ (film) /cm⁻¹ 3409, 1737, 1499, 1448, 1372, 1308, 1219, 1042, 1025, 1001, 944, 770, 691, 666, 655; δₜ (CDCl₃; 400MHz) 1.42 (t, 3H, OCH₂CH₃, J 7.2Hz), 4.47 (q, 2H, OCH₂CH₃, J 7.2Hz), 7.38 & 7.58 (m, 5H, Ar-H), 8.83 (br s, 1H, NOH); δₓ (CDCl₃; 100MHz) 14.1 (OCH₂CH₃), 62.1 (OCH₂CH₃), 126.4, 128.8, 130.2 & 130.5 (Ar-C & Ar-CH), 151.9 (PhC=NOH), 163.6 (CO₂Et); m/z 193 (M⁺, 52%), 164 (5%), 147 (29%), 120 (60%), 119 (69%), 104 (38%), 103 (42%), 77 (100%).
Ethyl 2-phenyl-2-benzyloxyiminoacetate (185b)

A solution of ethyl benzoylformate 186 (4.46cm³, 28.1mmol), pyridine (2.50cm³, 30.9mmol) and O-benzylhydroxylamine hydrochloride (3.37g, 21.1mmol) in absolute ethanol (50cm³) was heated under reflux for 1 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford the title compound 185b as a clear oil containing a mixture of E and Z oxime geometric isomers (4.32g, 54%) (11:1 major:minor) from which a sufficient quantity of the major isomer was separated for characterisation. Major isomer: νmax (film) /cm⁻¹ 2983, 1738, 1447, 1369, 1332, 1220, 1019, 737, 693; δH (CDCl₃; 400MHz) 1.37 (t, 3H, OCH₂CH₃, J 7.2Hz), 4.34 (q, 2H, OCH₂CH₃, J 7.2Hz), 5.33 (s, 2H, OCH₂Ph), 7.29-7.44 & 7.60 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 14.2 (OCH₂CH₃), 61.8 (OCH₂CH₃), 76.9 (OCH₂Ph), 126.3, 127.8, 128.0, 128.3, 128.7, 130.3 & 137.3 (Ar-C), 151.2 (PhC=NOBn), 163.7 (CO₂Et); m/z 283 (M⁺, 6%), 266 (14%), 180 (6%), 135 (12%), 91 (100%), 77 (52%).

Minor isomer: δH (CDCl₃; 400MHz) 1.37 (t, 3H, J 7.2Hz, OCH₂CH₃), 4.44 (q, 2H, J 7.2Hz, OCH₂CH₃), 5.29 (s, 2H, OCH₂Ph), 7.29-7.44 & 7.59 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 14.2 (OCH₂CH₃), 62.1 (OCH₂CH₃), 77.9 (OCH₂Ph), 126.3, 127.8, 128.3, 128.7, 130.2, 130.3 & 137.3 (Ar-CH & Ar-C), 151.2 (PhC=NOBn), 163.7 (CO₂Et).
Ethyl 2-phenyl-2-benzyloxyaminoacetate (187b)

A solution of ethanolic HCl (7M) was prepared by the dropwise addition of acetyl chloride (29.9 cm$^3$) to absolute ethanol (50 cm$^3$) at 0°C. Using the procedure of Ottenheijm et al., ethyl 2-phenyl-2-benzyloxyiminoacetate 185b (1.00 g, 3.53 mmol) was dissolved in this solution (27 cm$^3$) which was treated with borane-trimethylamine complex (1.03 g, 14.1 mmol) in one portion and stirred under an atmosphere of nitrogen for 48 h. To this solution was added sodium carbonate (2.00 g, 18.9 mmol) before stirring for 5 h, filtering and evaporating the solvent under reduced pressure. The residue was purified by column chromatography (SiO$_2$, hexane:EtOAc 9:1 v/v) to give the title compound 187b contaminated with the oxime starting material 185b as a clear film (3:2 respectively, 0.250 g 187b, 25%). A pure sample of the desired product was eventually obtained by preparative reverse phase HPLC (40.0 mg); $\delta$$_H$(CDCl$_3$, 400 MHz) 1.28 (t, 3H, J 7.2 Hz, OCH$_2$CH$_3$), 4.23 & 4.30 (each dq, 1H, J 7.2, 15.0 Hz, OCH$_2$CH$_3$), 4.72 (s, 1H, PhCHNHOBn), 4.79 & 4.82 (each d, 1H, J 11.6 Hz, OCH$_2$Ph), 7.32-7.41 (m, 10H, Ar-H); $\delta$$_C$(CDCl$_3$, 100 MHz) 14.0 (OCH$_2$CH$_3$), 61.2 (OCH$_2$CH$_3$), 67.8 (PhCHNHOBn) 76.3 (OCH$_2$Ph), 127.8, 127.9, 128.1, 128.5, 128.6 & 128.7 (Ar-CH), 134.0 & 137.6 (Ar-C), 171.9 (CO$_2$Et); m/z 286 (MH$^+$, 8%), 212 (34%), 104 (12%), 91 (100%).
Benzoylformyl Chloride (182)

A solution of benzoylformic acid 181 (5.00g, 33.3mmol) in DCM (50cm³) was treated with oxalyl chloride (3.20cm³, 36.7mmol) and 5 drops of DMF. After stirring the solution at room temperature for 72 h, the solvent was evaporated under reduced pressure and the residue distilled to yield benzoylformyl chloride 182 as a yellow oil (4.75g, 85%), bp 90-92°C, 3mmHg (lit., 221°C, 80°C, 3mmHg); ν_max (film) /cm⁻¹ 1775, 1697, 1596, 1581, 1493, 1452, 1257, 1044, 829, 781; δ_ν (CDCl₃; 400MHz) 7.57 (m, 2H, Ar-H), 7.75 (m, 1H, Ar-H) & 8.01 (m, 2H, Ar-H); δ_C (CDCl₃; 100MHz) 129.4, 129.5 & 130.6 (Ar-CH), 136.0 (Ar-C), 166.8 (COCl), 181.2 (PhC=O).

N-Benzylbenzoylformamide (183)

A solution of benzylamine (17.1cm³, 163mmol) and triethylamine (22.7cm³, 163mmol) in DCM (500cm³) was cooled to 0°C before dropwise addition of benzoylformyl chloride 182 (25.0g, 148mmol). The solution was warmed to 20°C and stirred for 18 h then
washed with aqueous HCl (2M; 3 x 250cm³) to yield the title compound 183 as a pale yellow solid (29.1g, 82%), mp 93-96°C (lit., 326 92°C) (Found : C, 75.22; H, 5.43; N, 5.86%; M+ 239.0947. C₁₅H₁₃NO₂ requires C, 75.30; H, 5.48; N, 5.85%, M+ 239.0946); νmax (KBr) /cm⁻¹ 3263, 3103, 3067, 1685, 1646, 1595, 1572, 1497, 1452, 1431, 1230, 1180, 1033, 945, 689, 675; δH (CDCl₃; 400MHz) 4.58 (d, 2H, J 5.9Hz, NCH₂Ph), 7.26-7.65 (m, 8H, Ar-H), 8.36 (m, 2H, Ar-H); δC (CDCl₃; 100MHz) 127.9, 128.5, 128.9, 131.2 & 133.3 (Ar-CH), 134.5 & 137.1 (Ar-C), 161.5 (NC=O), 187.5 (PhC=O); m/z 240 (MH⁺, 24%), 181 (27%), 107 (28%), 105 (100%), 91 (100%), 77 (57%).

2-Phenyl-2-benzyloxyimino-N-benzylacetamide (184)

\[
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{NH} \\
\text{O} \\
\text{NH} \\
\text{Ph} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\xrightarrow{\text{EtOAc}}
\begin{array}{c}
\text{Ph} \\
\text{O} \\
\text{NH} \\
\text{O} \\
\text{NH} \\
\text{Ph} \\
\text{NOBn} \\
\text{Ph} \\
\text{O} \\
\end{array}
\]

A solution of N-benzylbenzoylformamide 183 (0.500g, 2.08mmol), O-benzylhydroxylamine hydrochloride (0.330g, 2.08mmol) and triethylamine (0.290cm³, 2.08mmol) in absolute ethanol (20cm³) was heated under reflux for 18 h. The solution was evaporated under reduced pressure before purification by column chromatography (SiO₂, heaxane:EtOAc 9:1 v/v) to yield the title compound 184 as white solid containing a mixture of oxime geometric isomers (4.7:1) (0.560g, 80%), mp 148-149°C (Found: C, 76.06; H, 5.84 ; N, 7.95%; M⁺ 344.1506. C₂₂H₂₀N₂O₂ + 0.2H₂O requires C, 75.93; H, 5.85; N, 8.05%; M⁺ 344.1506); (major + minor isomers) m/z 345 (MH⁺) (3%), 327 (5%), 237 (5%),
91 (100%). Further careful chromatography allowed separation of a small amount of the major isomer from this mixture for characterisation; $\nu_{\text{max}}$ (KBr) /cm$^{-1}$ (major isomer) 3271, 3089, 3064, 3033, 2925, 2877, 1646, 1557, 1455, 1026, 965, 749, 730, 692; $\delta_h$ (CDCl$_3$; 400MHz) (minor isomer) 4.55 (d, 2H, J 6.0Hz, NHCH$_2$Ph), 5.20 (s, 2H, OCH$_2$Ph), 7.10 (br s, 1H, NH), 7.25-7.38, 7.40 (m, 15H, Ar-H); (major isomer) 4.62 (d, 2H, J 5.9Hz, NHCH$_2$Ph), 5.24 (s, 2H, OCH$_2$Ph), 6.16 (br s, 1H, NH), 7.25-7.38 & 7.68 (m, 15H, Ar-H); $\delta_c$ (CDCl$_3$; 100MHz) (minor isomer) 43.4 (NHCH$_2$Ph), 77.4 (OCH$_2$Ph), 153.1 (PhC=N), 162.9 (NC=O), 127.5, 128.0, 128.7, 129.5 & 129.6 (Ar-CH), 136.8 & 137.3 (Ar-C); (major isomer) 43.4 (NHCH$_2$Ph), 77.3 (OCH$_2$Ph), 126.8, 127.6, 128.1, 128.5, 128.6, 128.7 & 130.1 (Ar-CH), 131.1, 136.8 & 137.3 (Ar-C), 153.1 (PhC=N), 162.9 (NC=O).

2-Phenyl-2-benzyloxyamino-N-benzylacetamide (171)

Acetyl chloride (50cm$^3$) was added to dry ethanol (100cm$^3$) over 30 min at 0°C under an atmosphere of nitrogen. This solution was then added dropwise to 2-phenyl-2-benzyloxyimino-N-benzylacetamide 184 (4.00g, 11.6mmol) and borane-trimethylamine complex (9.00g, 123mmol) under a nitrogen atmosphere. After stirring at room temperature for 18 h, the solvent was evaporated under reduced pressure and the residue taken up in

166
DCM (100cm³), before washing with aqueous NaOH (1M; 3 x 100cm³) and drying over MgSO₄. The solution was filtered, evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, DCM:MeOH 99:1 v/v) to yield the *desired product* 171 as an off-white solid (1.40g, 60%), mp 107-108°C (Found: C, 76.05; H, 6.26; N, 8.02%; MH⁺ 347.1759. C₂₂H₂₂N₂O₂ requires C, 76.28; H, 6.44; N, 8.13%; MH⁺ 347.1759); ν_max (KBr) /cm⁻¹ 3251, 3069, 2921, 1657, 1558, 1497, 1453, 1422, 1365, 1358, 1268, 1249, 1030, 1004, 754, 733, 698; δ_H (CDCl₃; 400MHz) 4.41 (2 x dd, 2H, J 5.9, 15.1Hz, NHCH₂Ph), 4.61 (s, 1H, PhCHNO), 4.65 (m, 2H, OCH₂Ph), 5.94, (s, 1H, NHOCH₂Ph), 6.81 (m, 1H, HNC=O), 7.20-7.31 (m, 15H, Ar-H); δ_C (CDCl₃; 100MHz) 43.7 (NHCH₂Ph), 69.9 (PhCHNO), 76.7 (OCH₂Ph), 128.0, 128.4, 128.5, 128.9, 129.0, 129.1 & 129.3 (Ar-CH), 135.9, 137.5 & 138.6 (Ar-C), 171.0 (C=O); m/z 347 (MH⁺, 9%), 331 (11%), 279 (5%), 238 (2%), 223 (18%), 212 (44%), 135 (22%), 120 (88%), 104 (95%), 91 (100%).

**Attempted preparation of N-benzyl-2-benzoyloxyamino-2-phenylethylamine (188)**

![Chemical structure]

A solution of 2-phenyl-2-benzoyloxyamino-N-benzylacetamide 171 (0.500g, 1.44mmol) in dry distilled THF (5cm³) was treated dropwise with borane-THF complex
(1M solution in THF, 10.1cm³, 10.1mmol) under an atmosphere of nitrogen. After heating at reflux for 2 h, no starting material was detected by TLC analysis, and so the solution was cautiously treated dropwise with aqueous HCl (6M; 25cm³) and stirred for 2 h at 20°C. The solution was then basified with aqueous NaOH (2M) and extracted with DCM (3 x 50cm³) and the organics dried over MgSO₄ before filtering and evaporation to yield pale brown oil consistent with a mixture of the diamine 131 and benzyl alcohol; N-Benzyl-2-phenyl-1,2-diaminoethane 131; δ_H (CDCl₃; 400MHz) 1.95 (br s, 3H, NH₂ & NH), 2.77 (dd, 1H, J 8.4, 11.8Hz, PhCHCH₂N), 2.86 (dd, 1H, J 4.8, 11.8Hz, PhCHCH₂N), 3.82 (s, 2H, NHCH₂Ph), 4.07 (dd, 1H, J 4.8, 8.4Hz, PhCHCH₂N), 7.23-7.43 (m, 5H, Ar-H); δ_C (CDCl₃; 100MHz) 53.7 & 55.4 (NCH₂Ph & PhCHCH₂N), 56.7 (PhCHCH₂N), 126.4, 126.9, 127.2, 128.0, 128.4 & 128.5 (Ar-CH), 140.2 & 144.4 (Ar-C), identical with an independently prepared sample.

An experiment with 4 equivalents of borane-THF complex (based on hydroxylamine 171) under identical conditions afforded a mixture of the diamine 131, amino amide 130 and benzyl alcohol. Reducing the amount of borane-THF complex to 1 equivalent returned a mixture of hydroxylamine 171 and amino amide 130 under these conditions. N-Benzyl-2-phenyl-2-aminoacetamide 130; δ_H (CDCl₃; 400MHz) 4.47 (s, 2H, NHCH₂Ph), 4.60 (m, 1H, PhCHNH₂), 7.23-7.43 (m, 5H, Ar-H); δ_C (CDCl₃; 100MHz) 43.2 (NHCH₂Ph), 59.8 (PhCHNH₂), 126.3, 127.8, 127.9, 128.6, 128.8 (Ar-CH), 138.3 & 141.0 (Ar-C), 172.9 (C=O), identical with an independently prepared sample.
2-Phenyl-2-hydroxyamino-N-benzylacetamide (164)

A solution of 2-phenyl-2-benzyloxyamino-N-benzylacetamide 171 (0.500g, 1.44mmol) in glacial acetic acid (7cm³) was treated with 10% Pd-C (72.0mg, 5mol%) and stirred at 20°C under hydrogen (1 atmos.) for 18 h. The solvent was evaporated under reduced pressure and the residue basified with saturated aqueous NaHCO₃ and extracted with DCM (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered then evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the title compound 164 as a white crystalline solid (9.0mg, 2%); δH (CDCl₃; 400MHz) 1.63 (br s, 1H, NHOH), 3.68 (br s, 1H, NHOH), 4.43 (2 x dd, 2H J 5.0, 14.0Hz, NCH₂Ph), 5.07 (s, 1H, PhCNHOH), 6.53 (br s, 1H, HNC=O), 7.17-7.43 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 43.4 (NCH₂Ph), 74.2 (PhCNHOH), 126.9, 127.6, 128.7 & 128.9 (Ar-CH), 137.7 & 139.3 (Ar-C), 172.1 (C=O); m/z 257 (MH⁺, <1%), 242 (60%), 224 (23%), 196 (17%), 167 (12%), 135 (33%), 108 (59%), 107 (100%), 106 (55%), 91 (82%).

A 48 h reaction time under these conditions again afforded the title compound 164 after chromatography but in a poor yield (4mg, 1%). Changing the solvent to TFA produced, after 2 h under identical conditions, the title compound in a slightly increased yield (14.0mg, 4%).
The procedure described above for the preparation of 2-phenyl-2-benzyloxyimino-N-benzylacetamide 184, was applied to the synthesis of 189 using N-benzylbenzoylformamide 183 (0.950g, 3.98mmol), O-tert-butylhydroxylamine hydrochloride (0.500g, 3.98mmol) and triethylamine (0.55cm³, 3.98mmol) in ethanol (50cm³) to afford the E- and Z- isomers of the title compound 189 as a white crystalline solid (0.990g, 81%) after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v), mp 78-80°C (Found: C, 73.54; H, 7.14 ; N, 8.87%; M⁺ 310.1681. C₁₉H₂₂N₂O₂ requires C, 73.52; H, 7.14; N, 9.03%; M⁺ 310.1681); νmax (KBr) /cm⁻¹ 3257, 3063, 2975, 2936, 1645, 1540, 1365, 1247, 1189, 977, 958, 700, 694; δH (CDCl₃; 400MHz) major isomer: 1.29 (s, 9H, OC(CH₃)₃), 4.60 (d, 2H, J 7.3Hz, NHCH₂Ph), 7.20-7.32 (m, 10H, Ar-H), 7.62 (m, 1H, NH); minor isomer : 1.23 (s, 9H, OC(CH₃)₃), 4.52 (d, 2H, J 7.3Hz, NHCH₂Ph), 7.20-7.32 (m, 10H, Ar-H), 7.46 (m, 1H, NH); δc (CDCl₃; 100MHz) major isomer: 27.5 (OC(CH₃)₃), 43.3 (NHCH₂Ph), 81.0 (OC(CH₃)₃), 126.5-130.0 (Ar-CH), 132.3 & 137.7 (Ar-C), 150.9 (PhC=N), 163.4 (NC=O); m/z 311 (MH⁺, 2%), 310 (1%), 254 (23%), 237 (21%), 106 (26%), 104 (30%), 91 (100%).
Attempted preparation of 2-phenyl-2-tert-butoxyamino-N-benzylacetamide

The method described for the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide 184 was applied to 2-phenyl-2-tert-butoxyimino-N-benzylacetamide 189 (0.500g, 1.61mmol) with ethanolic HCl (11M; 8cm³) and borane-trimethylamine complex (0.940g, 12.9mmol). Purification of the resulting mixture afforded unchanged starting material as the only identifiable product.

In a separate experiment, a solution of 2-phenyl-2-tert-butoxyimino-N-benzylacetamide 189 (0.200g, 0.644mmol) in methanol (10cm³) was treated with NaCNBH₃ (61.0mg, 0.966mmol) in one portion. One drop of bromocresol green indicator was added and the solution brought to a yellow colour (approximately pH3) with methanolic HCl (2M). No reaction was observed by TLC after 2, 24 and 48 h at 20°C or after 48 h at reflux. The mixture as cooled to 20°C and quenched with water (10cm³) before partitioning between DCM and water (100cm³ each). The organic extract was separated, dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was found to contain the starting material 189 only by subsequent NMR spectroscopic analysis.
2-Phenyl-2-hydroxyimino-N-benzylacetamide (165)

Prepared as described above for the preparation of 2-phenyl-2-benzylxoyimino-N-benzylacetamide 184, using N-benzylbenzoylformamide 183 (2.00g, 8.36mmol), hydroxylamine hydrochloride (1.74g, 25.1mmol) and triethylamine (3.50cm³, 25.1mmol) to afford the title compound 165 as a white solid containing a mixture of oxime geometric isomers (major:minor isomer = 1.5:1) (1.20g, 4.72mmol, 56%) after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v), mp 135-137°C (Found: C, 70.99; H, 5.53; N, 10.89%; M⁺ 254.1055. C₁₃H₁₄N₂O₂ requires C, 70.85; H, 5.55; N, 11.02%; M⁺ 254.1055); ν_max (KBr) /cm⁻¹ 3274, 1639, 1608, 1560, 1496, 1455, 1433, 1368, 1255, 996, 943, 689; δ_H (d₆-DMSO; 400MHz) (minor isomer) 4.38 (d, 2H, J 6.4Hz, NHCH₂Ph), 7.24-7.53 (m, 10H, Ar-H), 8.80 (m, 1H, NHCH₂Ph), 11.87 (s, 1H, NOH); (major isomer) 4.46 (d, 2H, J 5.6Hz, NHCH₂Ph), 7.24-7.53 (m, 10H, Ar-H), 9.06 (t, 1H, J 6.2Hz, NHCH₂Ph), 11.58 (s, 1H, NOH); δ_C (d₆-DMSO; 100MHz) (mixed isomers) 41.8 & 42.2 (NHCH₂Ph), 125.7, 126.7, 126.8, 127.1, 127.2, 127.7, 128.2, 128.3, 128.7, 128.9, 129.3 & 129.4 (Ar-CH), 130.1, 132.3, 139.0 & 139.5 (Ar-C), 150.7 & 152.7 (C=NOH), 163.6 & 164.1 (C=O); m/z 254 (3%), 237 (22%), 236 (12%), 106 (27%), 104 (35%), 91 (100%), 77 (22%).
Attempted preparation of 2-phenyl-2-hydroxyamino-N-benzylacetamide (164)

![Chemical structure](image)

The method described for the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide 184 was applied to 2-phenyl-2-hydroxyimino-N-benzylacetamide 165 (0.500g, 1.97mmol), methanol (25cm³) and NaCNBH₃ (0.190g, 2.95mmol). Overnight reaction at 20°C returned the starting material unchanged. In a similar experiment, a solution of 165 (0.270g, 1.06mmol) in THF (10cm³) was treated with NaCNBH₃ (1M solution in THF, 1.17cm³, 1.17mmol) and acidified with 2 drops of methanolic HCl (2M). No reaction was observed after 5h at 20°C, nor was reaction evident after addition of further NaCNBH₃ solution (2.50cm³, 2.50mmol), re-acidification and stirring for 18 h.

Similarly, a solution of 165 (0.130g, 0.51mmol) in dry distilled THF (10cm³) at 0°C under an atmosphere of nitrogen was treated with borane-THF complex complex (1M solution in THF, 2.04cm³, 2.04mmol) and stirred at 20°C overnight. The solution was cooled to 0°C and cautiously treated with aqueous HCl (6M; 5cm³) before warming to 60°C for 1 h. The solution was basified with aqueous NaOH (2M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure but the residue contained none of the desired product 164.
2-Bromoacetophenone O-benzyloxime (191)

A solution of 2-bromoacetophenone 190 (5.00g, 25.1mmol) in ethanol (250cm³) was treated with O-benzylhydroxylamine hydrochloride (4.41g, 27.6mmol) and triethylamine (3.84cm³, 27.6mmol). After heating under reflux for 2 h, the solvent was evaporated under reduced pressure and the crude product 191 obtained as a mixture of geometric isomers (major:minor = 5.25:1) by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) and used directly; δ_H (CDCl₃; 400MHz) major isomer: 4.57 (s, 2H, BrCH₂C=N), 5.31 (s, 2H, OCH₂Ph), 7.30-7.46 (m, 8H) & 7.70 (m, 2H, Ar-H); minor isomer: 4.39 (s, 2H, BrCH₂C=N), 5.32 (s, 2H, OCH₂Ph), 7.30-7.46 (m, 8H) & 7.70 (m, 2H, Ar-H); δ_C (CDCl₃; 100MHz) major isomer: 32.7 (BrCH₂C=N), 76.9 (OCH₂Ph), 126.2, 128.0, 128.1, 128.2, 128.4 & 129.7 (Ar-CH), 133.4 & 137.4 (Ar-C), 152.9 (C=N).
A solution of the crude 2-bromoacetophenone O-benzyloxime 191 (7.64g, \( \approx 25.1 \text{mmol} \)) in chloroform (200cm\(^3\)) was treated with benzylamine (8.23cm\(^3\), 75.3mmol) and heated under reflux for 18 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO\(_2\), hexane:EtOAc 4:1 v/v) to yield the separated oxime isomers of 192 as pale yellow oils (4.68g, 56% from 2-bromoacetophenone 190) (major:minor isomer = 8:1) (Found: M\(^+\) 331.1810. C\(_{22}\)H\(_{22}\)N\(_2\)O requires M\(^+\) 331.1810); \( \nu \text{max (film) } /\text{cm}^{-1} \) 3062, 3029, 2925, 2874, 1496, 1454, 1364, 923, 737, 696; \( \delta \) (CDCl\(_3\); 400MHz) major isomer: 1.69 (br s, 1H, NH), 3.74 (s, 2H, NHCH\(_2\)Ph), 3.90 (s, 2H, PhCCH\(_2\)N), 5.25 (s, 2H, OCH\(_2\)Ph), 7.21-7.41 (m, 12H, Ar-H), 7.63 (m, 3H, Ar-H); minor isomer: 1.69 (br s, 1H, NH), 3.56 & 3.68 (each s, 2H, NHCH\(_2\)Ph & PhCCH\(_2\)N), 5.15 (s, 2H, OCH\(_2\)Ph), 7.21-7.42 (m, 15H, Ar-H), 7.63 (m, 3H, Ar-H); \( \delta \) (CDCl\(_3\); 100MHz) major isomer: 44.2 (PhCCH\(_2\)N), 53.3 (NHCH\(_2\)Ph), 76.7 (OCH\(_2\)Ph), 126.5, 126.9, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6 & 129.2 (Ar-CH), 135.1, 137.6 & 139.8 (Ar-C), 157.4 (PhC=N); minor isomer: 52.1 & 52.7 (PhCCH\(_2\)N & NHCH\(_2\)Ph), 76.0 (OCH\(_2\)Ph), 127.0, 127.6, 127.9, 128.0, 128.2, 128.3, 128.3 & 129.0 (Ar-CH), 132.7, 138.2 & 139.7 (Ar-C), 155.3 (C=N); \( m/z \) 331 (MH\(^+\), 45%), 223 (41%), 210 (12%), 120 (52%), 91 (100%).
Attempted preparation of N-benzyl-2-benzyloxyamino-2-phenylethylamine (188)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NH} & \quad \text{NH} \\
\text{Ph} & \quad \text{Ph} \\
\text{NOBn} & \quad \text{NHOBn}
\end{align*}
\]

192 \quad 188

The method used in the reduction of 2-phenyl-2-benzyloxyimino-N-benzylacetamide 184 was applied to 2-(N-benzylamino)acetophenone O-benzyloxime 192 (0.670g, 2.03mmol), using ethanolic HCl (11M; 10cm³) and borane-trimethylamine complex (0.590g, 8.12mmol). However, the isolated residue contained only unchanged starting material.

In a separate experiment, this reduction was undertaken using the method applied to the attempted reduction of 2-phenyl-2-(hydroxyimino)-N-benzylacetamide 165, using 192 (1.00g, 3.03mmol), methanol (50cm³), bromocresol green (10 drops) and NaCNBH₃ (0.290g, 4.55mmol), keeping the solution acidic with dropwise addition of methanolic HCl (2M). The solution was unchanged by TLC analysis after 18 h at 20°C and, after work-up, afforded the starting material 184 only.
Attempted preparation of N-benzyl-2-benzyloxyamino-2-phenylpropylamine (195)

A solution of 2-(N-benzylamino)acetophenone O-benzyloxime 192 (0.200g, 0.610mmol) in anhydrous ether (10cm³) was treated with methyl lithium (1.6M solution in ether, 1.82cm³, 2.92mmol) at 0°C dropwise. After stirring at 0°C for 1 h, the reaction was quenched with water (2cm³) and the solution warmed to 20°C. The organic layer was washed with water (2 x 20cm³), dried over MgSO₄, filtered and evaporated under reduced pressure. However, the residue yielded none of the desired material 195 after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

In a separate experiment, a solution of 2-(N-benzylamino)acetophenone O-benzyloxime 192 (0.50g, 1.51mmol) in anhydrous ether (10cm³) was cooled to -75°C before dropwise treatment with boron trifluoride etherate (2.80cm³, 22.1mmol) keeping the temperature below -70°C. This turbid mixture was stirred for 15 min at -75°C before slow dropwise addition of methyl lithium (1.6M solution in ether, 2.80cm³, 4.5mmol) over 10 min. After stirring at -75°C for 5 h, the solution was quenched with water (1cm³) and warmed to 20°C for 18 h. The residue was partitioned between DCM and water (20cm³ each) and the aqueous phase separated and further extracted with DCM (3 x 20cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced
Column chromatography of the residue (SiO₂, hexane:EtOAc 2:1 v/v) afforded none of the desired product 195.

2-(N-Benzyl-N-tert-butoxycarbonyl)aminoacetophenone O-benzylxoxide  

(194)

A solution of 2-(N-benzylamino)acetophenone O-benzylxoxide 192 (0.250g, 0.760mmol) in DCM (10cm³) at 0°C was treated with triethylamine (0.210cm³, 1.52mmol) and di-tert-butyl dicarbonate (0.180g, 0.84mmol) under an atmosphere of nitrogen. The solution was warmed to 20°C overnight, before partitioning between DCM (30cm³) and aqueous citric acid (1M; 30cm³). The phases were separated and the organic layer was washed with further citric acid solution (3 x 30cm³) before drying over MgSO₄, filtering and evaporation under reduced pressure to afford the title compound 194 as a colourless oil (150mg, 0.348mmol, 46%). Its existence as a mixture of carbamate rotamers was shown by ¹H NMR spectroscopic analysis. Subsequent variable-temperature ¹H NMR spectroscopic analysis of 194 in d₆-DMSO showed signal-doubling of the two N-CH₂ groups to collapse as the temperature was raised to 50°C, becoming sharp singlets by 80°C, (Found: C, 75.30; H, 7.29; N, 6.49%; MH⁺ 431.2333. C₂₇H₃₀N₂O₃ requires C, 75.32; H, 7.02; N, 6.50%; MH⁺ 431.2334); νmax (KBr) /cm⁻¹ 2968, 1695, 1449, 1416, 1366, 1241, 1158, 1119, 1028,
923, 746, 699; δ<sub>H</sub> (d<sub>6</sub>-DMSO; 400MHz) 1.27 (s, 9H, C(CH<sub>3</sub>)<sub>3</sub>), 4.01 & 4.23, 4.48 & 4.59 (4 x br s, each pair 2H, PhCH<sub>2</sub>N & NHCH<sub>2</sub>Ph), 5.14 (br s, 2H, NOCH<sub>2</sub>Ph), 7.08-7.54 (m, 15H, Ar-H); δ<sub>H</sub> (d<sub>6</sub>-DMSO; 400MHz, 95°C) 4.18 & 4.56 (2 x s, each 2H, PhCH<sub>2</sub>N & NHCH<sub>2</sub>Ph), 5.16 (s, 2H, NOCH<sub>2</sub>Ph), (Ar-H not measured); m/z 374 (M-²Bu+H<sup>+</sup>, 1%), 225 (7%), 223 (6%), 212 (4%), 208 (5%), 184 (5%), 167 (7%), 156 (5%), 120 (9%), 91 (100%), 57 (24%).

Attempted preparation of N-benzyl-N-tert-butoxycarbonyl-2-(benzyloxyamino)-2-phenylpropylamine

A solution of 2-(N-benzyl-N-tert-butoxycarbonyl)aminoacetophenone O-benzylxime 194 (0.100g, 0.232mmol) in anhydrous ether at -78°C under an atmosphere of nitrogen was treated with methyl lithium (1.6M solution in ether, 0.475cm<sup>3</sup>, 0.760mmol) and stirred for 2 h before warming to ambient temperature and quenching with water (2cm<sup>3</sup>). The organic layer was washed with water (3 x 5cm<sup>3</sup>) before drying over MgSO<sub>4</sub>, filtration and evaporation under reduced pressure to yield a brown film from which no desired material was isolated by column chromatography (SiO<sub>2</sub>, hexane:EtOAc 2:1 v/v).

This experiment was repeated with addition of boron trifluoride etherate (1.39cm<sup>3</sup>, 10.9mmol) to a solution of 2-(N-benzyl-N-tert-butoxycarbonyl)aminoacetophenone O-
benzyloxime 194 (0.200g, 0.464mmol) in anhydrous ether (10cm³) at -78°C. The solution was stirred for 30 min before dropwise addition of methyl lithium (1.6M solution in ether, 0.87cm³, 1.39mmol). After 1.5 h, no reaction was observed by TLC analysis and so the mixture warmed to -10°C for a further 1.5 h. Treatment as described above furnished a brown residue was from which none of the title compound was isolated after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

**Attempted preparation of 2-(N-benzylamino)acetophenone oxime (196)**

![Chemical structure](image)

By the method of Corey *et al.*,248 a mixture of 2-(N-benzylamino)acetophenone O-benzyloxime 192 (0.200g, 0.605mmol) and 10% Pd-C (32mg, 5mol%) in methanol (10cm³) was stirred under hydrogen (1 atmos.) at 20°C and atmospheric pressure for 2.5 h by which time no starting material remained by TLC analysis. The mixture was filtered, the catalyst residue washed with methanol (2 x 10cm³) and the filtrate evaporated under reduced pressure. The residue was found to contain not the desired oxime 196, but a mixture of diamine 131 identical with a known sample,327 and benzyl alcohol.
N-Benzyl-2-benzylamino-2-phenylethylamine (188)

A solution of 2-(N-benzylamino)acetophenone O-benzyloxime 192 (2.00g, 6.05mmol) in dry THF (40cm³) was treated with borane-THF complex (1M solution in THF, 12.1cm³, 12.1mmol) at 0°C under a nitrogen atmosphere. The solution was warmed to 20°C for 4 h then slowly treated with aqueous HCl (2M; 20cm³) and heated to 60°C for 2 h. After cooling to room temperature, the reaction was basified with aqueous sodium hydroxide (2M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, before filtration then evaporation under reduced pressure and purification of the residue by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to yield the desired product 188 as a yellow oil (1.59g, 79%) (Found: C, 79.65, H, 7.09, N, 8.41%; MH+ 333.1967. C₂₂H₂₄N₂O requires C, 79.48, H, 7.28, N, 8.43%; MH+ 333.1967); νmax (film) /cm⁻¹ 3062, 3029, 2910, 2853, 1495, 1453, 1362, 1028, 747; δH (CDCl₃; 400MHz) 2.87 (m, 2H, PhCHCH₂N), 3.78 (2 x d, 2H, J 13.2Hz, NHCH₂Ph), 4.18 (dd, 1H, J 5.6, 8.4Hz, PhCHNHOBn), 4.59 (2 x d, 2H, J 11.2Hz, OCH₂Ph), 7.18-7.41 (m, 15H, Ar-H); δC (CDCl₃; 100MHz) 52.2 (PhCHCH₂N), 53.7 (NHCH₂Ph), 65.0 (PhCHNHOBn), 76.7 (OCH₂Ph), 126.9, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4 & 128.6 (Ar-CH), 137.2, 140.1 & 140.7 (Ar-C); m/z 333 (MH+, 3%), 212 (6%), 120 (35%), 106 (53%), 91 (100%).
Attempted preparation of N-benzyl-2-hydroxyamino-2-phenylethylamine (140)

\[
\begin{array}{c}
\text{Ph} \\
\text{NH} \\
\text{Ph} \quad \text{NHOBn} \\
188 \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \ Quad
Nickel (0.260g) in methanol (20cm³) was stirred under hydrogen at 20° (1 atmos.) for 72 h but returned the starting material unchanged.

10% Pd-C / ammonium formate: By the method of Bieg and Szeja, a mixture of N-benzyl-2-benzyloxyamino-2-phenylethylamine 188 (0.100g, 0.300mmol), ammonium formate (0.100g, 1.59mmol) and 10% Pd-C (0.180g, 56mol%) in methanol (20cm³) was heated under reflux under nitrogen (1 atmos.) for 18 h but only returned a complex mixture of unidentifiable products.

Boron tris-trifluoroacetate: The B(TFA)₃ reagent was prepared by the method of Pless and Bauer by treatment of dry DCM (100cm³) with distilled anhydrous TFA (9.20cm³, 120mmol) and boron tribromide (3.80cm³, 39.9mmol) under nitrogen at 0°C to form an instantaneous white precipitate. The solvent was then removed under reduced pressure before addition of this solid (1.50g, 4.97mmol) to a solution of N-benzyl-2-benzyloxyamino-2-phenylethylamine 188 (0.200g, 0.602mmol) in distilled anhydrous TFA (5cm³). The mixture was stirred at ambient temperature for 18 h before evaporation of the solvent under reduced pressure and basifying with aqueous NaOH (2M) and extraction with DCM (3 x 30cm³). The organics were dried over MgSO₄, filtered and evaporated under reduced pressure to return unchanged starting material.

30% HBr / acetic acid: A solution of N-benzyl-2-benzyloxyamino-2-phenylethylamine 188 (0.130g, 0.391mmol) in glacial acetic acid (5cm³) was treated with HBr in acetic acid (30% w/v; 5cm³) and heated under reflux for 18 h. The solution was diluted with water (10cm³) and extracted with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to return the starting material unchanged.
Attempted preparation of 2-bromoacetophenone oxime (198)

\[ \text{Ph} \xrightarrow{\text{Br}} \xrightarrow{\text{X}} \text{Ph} \]

A solution of 2-bromoacetophenone 190 (5.00g, 25.1mmol), hydroxylamine hydrochloride (1.91g, 27.5mmol) and triethylamine (3.85cm³, 27.5mmol) in ethanol (200cm³) was heated to reflux for 48 h before removal of the solvent under reduced pressure. The residue yielded none of the desired material 198 by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).

Attempted preparation of 2-bromoacetophenone O-tert-butyloxime (197)

\[ \text{Ph} \xrightarrow{\text{Br}} \xrightarrow{\text{X}} \text{Ph} \]

A solution of 2-bromoacetophenone 190 (0.810g, 4.06mmol), O-tert-butylhydroxylamine hydrochloride (0.510g, 4.06mmol) and triethylamine (1.13cm³, 8.12mmol) in ethanol (50cm³) was heated to reflux for 18 h. After cooling to 20°C, the solution was evaporated at reduced pressure but column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) failed to afford the title compound 197.
Similarly, a mixture of 190 (0.400g, 2.01mmol), O-tert-butylhydroxylamine hydrochloride (0.250g, 1.99mmol) and sodium acetate (0.330g, 0.402mmol) in water (20cm³) was heated to 50°C. After 18 h, the mixture was cooled to 20°C to afford a complex mixture of products from which the desired material was not isolated. This experiment was then repeated, with methanol as the solvent (10cm³) and stirring for 18 h at 20°C, but this only afforded an intractable mixture of products.

tert-Butyl acetate

According to the published method, dry distilled tert-butanol (294cm³, 3.07moles) and N,N-dimethylaniline (424cm³, 3.34mol) were dissolved in dry ether (400cm³) and heated to gentle reflux. This solution was treated with dry acetyl chloride (226cm³, 3.18moles) at a rate sufficient to maintain reflux (55°C) after removal of the heating. After addition of two-thirds of the acetyl chloride, precipitation of the amine hydrochloride salt began, along with vigorous reflux. The mixture was therefore cooled in an ice bath to halt the reflux, before addition of the remaining acetyl chloride. The resultant cloudy solution was refluxed for 1.5 h at which point two layers had developed. After cooling to 20°C, the solution was treated with water (400cm³) and the upper, organic layer removed. This ether solution was washed with aqueous sulphuric acid (10% w/v; 5 x 100cm³) before drying over MgSO₄ (24 h), filtration and evaporation of the solvent under reduced pressure. Distillation of the crude product gave the title compound as a clear mobile
The title compound 206 was prepared using a method based on that of Chimiak & Kolasa. A solution of N-hydroxyphthalimide 205 (328g, 2.01 moles) in 1,4-dioxane (1300cm³) and 60% perchloric acid (20cm³) was treated with tert-butyl acetate (1085cm³, 8.05mol) and stirred at room temperature for 72 h. The solution was brought to pH9 with saturated aqueous sodium bicarbonate and extracted with chloroform (3 x 500cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was then crushed and triturated with hexane (2 x 50cm³) to yield the title compound 206 as a white crystalline solid (437g, 99%), mp 110-111°C (lit., 110-111°C) (Found: C, 65.80; H, 5.98; N, 6.39%; C₁₂H₁₃N₂O₃ requires C, 65.74; H, 5.98; N, 6.39%); ν_max (KBr) /cm⁻¹ 2976, 2935, 1789, 1734, 1466, 1371, 1352, 1189, 1172, 1111, 1079, 970, 880, 703; δ_H (CDCl₃; 400MHz) 1.42 (s, 9H, C(CH₃)₃), 7.77 & 7.87 (m, 4H, Ar-H); δ_C (CDCl₃; 100MHz) 27.3 (C(CH₃)₃), 86.6 (C(CH₃)₃), 123.4 &
129.3 (Ar-CH), 134.4 (Ar-C), 165.7 (C=O); m/z 219 (M⁺, 3%), 204 (4%), 186 (3%), 164 (37%), 163 (33%), 104 (18%), 90 (13%), 76 (22%), 57 (100%).

O-tert-Butylhydroxylamine hydrochloride (204)

By the method of Chimiak & Kolasa²⁵²,²⁵³ a solution of N-tert-butoxyphthalimide (5.00g, 22.8mmol) in ethanol (50cm³) was treated with hydrazine hydrate (1.10cm³, 22.9mmol) in water (5cm³) to yield the title compound 204 as white amorphous solid (2.20g, 77%), mp 150-152°C (lit.²⁵³, 151-2°C); νmax (KBr) /cm⁻¹ 3100-2800, 2691, 1575, 1529, 1380, 1169, 985, 828, 717; δH (CDCl₃; 400MHz) 1.45 (s, 9H, C(CH₃)₃), 10.56 (br s, 3H, NH₂⁺); δC (CDCl₃; 100MHz) 26.3 (C(CH₃)₃), 83.6 (C(CH₃)₃).
Benzoylmethyl acetate (203)

A solution of 2-chloroacetophenone 199 (1.00g, 6.47mmol) and sodium acetate (1.06g, 12.98mmol) in methanol (50cm³) was heated to reflux for 18 h and stirred at 20°C for 72 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 203 as a colourless oil (150mg, 13%); vₘₐₓ (film)/cm⁻¹ 3065, 2939, 1752, 1704, 1451, 1375, 1282, 1221, 757, 690; δₜ (CDCl₃; 400MHz) 2.23 (s, 3H, CH₃CO₂), 5.35 (s, 2H, PhCOCH₂OAc), 7.47 (m, 2H) & 7.65 (m, 3H) & 7.93 (m, 2H, Ar-H); δₖ (CDCl₃; 100MHz) 20.6 (CH₃CO₂), 66.0 (PhCOCH₂OAc), 127.8, 128.7 & 133.9 (Ar-CH), 134.2 (Ar-C), 170.5 (CH₃CO₂), 192.2 (PhC=O); m/z 179 (MH⁺, 5%), 105 (100%), 91 (12%), 77 (60%), 50 (36%), 43 (52%).
Attempted preparation of 2-chloroacetophenone O-trimethylsilyloxime (202)

By the method of Denmark and Dappen,\textsuperscript{249} a solution of 2-chloroacetophenone 199 (0.15g, 0.951mmol) in dry DCM (2cm$^3$) with 4Å molecular sieves (0.5g) under an atmosphere of nitrogen was treated with O-trimethylsilylhydroxylamine (0.233cm$^3$, 1.90mmol). After stirring at ambient temperature for 36 h, the solution was filtered and the solvent removed under reduced pressure but the residue contained none of the desired material 202.

2-Chloroacetophenone O-\textit{tert}-butyloxime (201)

A solution of 2-chloroacetophenone 199 (3.47g, 22.4mmol) in methanol (45cm$^3$) was treated with O-\textit{tert}-butylhydroxylamine hydrochloride (3.10g, 24.7mmol) and sodium acetate (2.03g, 24.7mmol) at 20°C. After 90 min, the solvent was evaporated under reduced pressure and the residue partitioned between DCM and water (30cm$^3$ each). The aqueous phase was extracted with further DCM (2 x 30cm$^3$) and the combined organic extracts were
dried over Na₂SO₄, filtered and evaporated under reduced pressure to yield the title compound 201 as a clear oil (4.69g, 93%) containing a mixture of geometric isomers (major:minor isomer = 11:1) (Found: M⁺ 225.0920. C₁₂H₁₆NOC₁ requires M⁺ 225.0920); ν max (film) /cm⁻¹ 2979, 1446, 1365, 1262, 1192, 977, 918, 776, 692; δ H (CDCl₃; 400MHz) major isomer: 1.39 (s, 9H, C(CH₃)₃), 4.55 (s, 2H, CH₂Cl), 7.38 (m, 3H) & 7.74 (m, 2H, Ar-H); minor isomer: 1.31 (s, 9H, C(CH₃)₃), 4.48 (s, 2H, CH₂Cl), 7.38 (m, 3H) & 7.72 (m, 2H, Ar-H); δ C (CDCl₃; 100MHz) major isomer: 27.6 (C(CH₃)₃), 32.5 (CH₂Cl), 80.3 (C(CH₃)₃), 125.9, 128.5 & 129.2 (Ar-CH), 134.3 (Ar-C), 150.7 (PhC=N); m/z 227 (¹³Cl M⁺, 2%), 226 (2%), 225 (¹³Cl M⁺, 7%), 172 (3%), 171 (5%), 170 (11%), 169 (13%), 134 (1%), 77 (15%), 57 (100%).

2-(N-Benzylamino)acetophenone O-tert-butyloxime (207)

A solution of 2-chloroacetophenone O-tert-butyloxime 201 (4.69g, 20.8mmol) in DMF (50cm³) was treated with benzylamine (6.81cm³, 62.3mmol) and stirred for 18 h. The solvent was removed under reduced pressure, the residue partitioned between DCM and water (100cm³ each) and the aqueous layer further extracted with DCM (2 x 100cm³). The combined organic extracts were dried over Na₂SO₄, filtered and evaporated under reduced pressure. The residue was prified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).
to yield the *title compound* 207 as a colourless oil containing a mixture of geometric isomers (11.62g, 94%, major:minor isomer = 7.5:1) from which a pure sample of the major isomer was isolated by further careful chromatography (Found: C, 76.88; H, 8.28; N, 9.40%; MH+ 297.1967. C19H24N2O requires C, 76.99; H, 8.16; N, 9.45%; MH+ 297.1967); v_max (film) /cm⁻¹ major isomer: 3062, 3027, 2976, 2929, 1496, 1455, 1364, 1192, 955, 916, 769, 739, 696; 1:1 mixed isomers: 3062, 3028, 2976, 2929, 1495, 1364, 1193, 948, 739, 696; δ_h (CDCl₃; 400MHz) major isomer: 1.36 (s, 9H, C(CH₃)₃), 2.06 (br s, 1H, NH), 3.77 (s, 2H, NHCH₂Ph), 3.85 (s, 2H, PhCCH₂N), 7.26-7.38 (m, 8H, Ar-H), 7.68 (m, 2H, Ar-H); minor isomer: 1.35 (s, 9H, C(CH₃)₃), 1.80 (br s, 1H, NH), 3.70 (s, 2H, NHCH₂Ph), 3.82 (s, 2H, PhCCH₂N), 7.26-7.38 (m, 8H, Ar-H), 7.58 (m, 2H, Ar-H); δ_c (CDCl₃; 100MHz) major isomer: 27.7 (C(CH₃)₃), 43.9 (PhCCH₂N), 53.2 (NHCH₂Ph), 79.4 (C(CH₃)₃), 126.3, 127.1, 128.2, 128.4, 128.5 & 128.8 (Ar-CH), 136.1 & 139.7 (Ar-C), 154.6 (PhC=NOtBu); m/z 297 (MH⁺, 1%), 239 (1%), 223 (23%), 120 (52%), 106 (9%), 91 (100%).
Attempted preparation of N-benzyl-2-tert-butyloxyamino-2-phenylpropylamine (209)

\[
\begin{align*}
\text{Ph} & \quad \text{NH} \\
\text{Ph} & \quad \text{Me} \\
\text{NO}_{\text{tBu}} & \quad \text{NH}\text{O}_{\text{tBu}} \\
\end{align*}
\]

A solution of 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (0.100g, 0.337mmol) in dry distilled THF (2cm³) under nitrogen was cooled to -75°C and treated with methyl lithium (1M solution in THF, 0.760cm³, 0.760mmol) dropwise over 1 min. The solution was stirred at -75°C for 2 h and warmed to 20°C overnight. The solution was quenched with water (10cm³), extracted with ether (3 x 20cm³) and the combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure. The residue did not yield the title compound 209 after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

In a similar experiment, 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (0.100g, 0.337mmol) in dry distilled THF solution (2cm³) was treated with boron trifluoride etherate (93.0µl, 0.734mmol) and, after 10 min, with methyl lithium (1M solution in THF, 0.760cm³, 0.760mmol). Treatment was otherwise as above and did not yield the desired product.

A solution of 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (0.100g, 0.337mmol) in anhydrous ether (2cm³) under nitrogen was cooled to 0°C and treated with methylmagnesium bromide (3M solution in ether, 0.340cm³, 1.02mmol). After 2 h at 0°C,
the solution was allowed to reach 20°C overnight and otherwise treated as above. The residue yielded none of the desired, returning only unreacted starting material.

Similarly, a solution of 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (0.100g, 0.337mmol) in dry ether (2cm³) under nitrogen was cooled to 0°C and treated with boron trifluoride etherate (1.02cm³, 7.97mmol) and, after 20 min, with methylmagnesium bromide (3M solution in ether, 0.340cm³, 1.02mmol). This solution was treated otherwise as described above to afford only unchanged starting material.

2-(N-Benzyl-N-tert-butoxycarbonyl)aminoacetophenone O-tert-butyloxime (210)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NH} & \\
\text{Ph} & \quad \text{N-Boc}
\end{align*}
\]

A solution of 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (1.00g, 3.37mmol) in DCM (5cm³) at 0°C was treated with triethylamine (0.470cm³, 3.37mmol) and then a solution of di-tert-butyl dicarbonate (0.740g, 3.39mmol) in DCM (5cm³). After 1.5 h at 0°C the solution was washed with aqueous citric acid (1M; 5 x 20cm³), dried over MgSO₄, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford the title compound 210 as a white solid (1.10g, 2.77mmol, 82%) containing a mixture of carbamate rotamers (1.96:1) and oxime geometric isomers (5:1). VT ¹H NMR spectroscopy at 110°C in a mixture of CDCl₃.
and d₆-DMSO showed collapse of the doubling of the two benzylic signals of the rotamers to confirm the presence of two compounds (E and Z-oxime isomers) each bearing a pair of tert-butyl signals, mp 107-111°C (Found: C, 71.70; H, 8.08; N, 6.95%; MH⁺ 397.2484. C₂₄H₃₂N₂O₃ + 0.25 H₂O requires C, 71.88; H, 8.11; N, 6.99%; MH⁺ 397.2491; νₘₐₓ (KBr) /cm⁻¹ 2977, 1691, 1417, 1365, 1244, 1191, 1166, 1118, 979, 938, 699; δ_H (CDCl₃; 400MHz, 20°C) 1.29, 1.38-1.45 & 1.52 (m, 18H, NOC(CH₃)₃ & COC(CH₃)₃ of major & minor oxime isomers), 4.11 (s, 1.3H), 4.22 (s, 0.7H), 4.56 (s, 0.3H), 4.73 (s, 1.7H, PhCCH₂N & NHCH₂Ph of major isomer), 4.19, 4.32, 4.34 & 4.47 (each s, 1H, PhCCH₂N & NHCH₂Ph of minor isomer), 7.17-7.78 (m, 10H, Ar-H of major and minor isomers); δ_C (CDCl₃; 100MHz, 20°C) major isomer: 27.4 & 28.3 (NOC(CH₃)₃ & COC(CH₃)₃), 39.2 & 40.6 (PhCCH₂NBoc), 49.1 (N(Boc)CH₂Ph), 79.4 & 80.1 (NOC(CH₃)₃ & COC(CH₃)₃), 126.7, 127.0, 127.6, 127.8, 128.1, 128.4 & 128.8, (Ar-C), 134.8 & 138.0 (Ar-C), 153.2 & 155.6 (PhC=NO & O=COC(CH₃)₃); δ_H (CDCl₃ + d₆-DMSO, 1:1 (v/v); 400MHz, 110°C) major isomer 1.28 & 1.37 (each s, 9H, NOC(CH₃)₃ & COC(CH₃)₃), 4.21 & 4.56 (each s, 2H, PhCCH₂N & NCH₂Ph), 7.13-7.33 & 7.57 (m, 10H, Ar-H); δ_H (CDCl₃ + d₆-DMSO, 1:1 (v/v); 400MHz, 110°C) minor isomer 1.25 & 1.36 (each s, 9H, NOC(CH₃)₃ & COC(CH₃)₃), 4.22 & 4.37 (each s, 2H, PhCCH₂N & NCH₂Ph), 7.13-7.33 & 7.57 (Ar-H); m/z 397 (MH⁺, 0.2%), 341 (1%), 297 (1%), 241 (1%), 185 (5%), 61 (100%), 57 (20%), 43 (85%).
Attempted preparation of N-benzyl-N-tert-butoxycarbonyl-2-tert-butyloxyamino-2-phenylpropylamine (211)

A solution of 2-(N-benzyl-N-tert-butoxycarbonyl)aminoacetophenone O-tert-butyloxime 210 (0.100g, 0.252mmol) in anhydrous toluene (2cm³) under an atmosphere of nitrogen was cooled to -75°C and treated with methyl lithium (1.6M solution in toluene, 473µl, 0.756mmol) over 10 min. No reaction was observed by TLC analysis after 2 h, nor after warming to 20°C over 18 h. The reaction was quenched with water (2cm³) and the solution extracted with toluene (3 x 10cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure to return only unreacted starting material (83%).

This experiment was repeated as above with the slight modification of addition of boron trifluoride etherate (93.0µl, 0.734mmol) at -75°C and stirring for 10 min prior to addition of the methyllithium. After identical treatment thereafter, the residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to afford none of the desired material 211. The isolated products were the starting oxime 210 (6.0mg, 6%) and the deprotected oxime 207 (35.0mg, 47%).
N-Benzyl-2-tert-butyloxyamino-2-phenylethylamine (208)

A solution of 2-(N-benzylamino)acetophenone O-tert-butyloxime 207 (0.500g, 1.69mmol) in dry THF (10cm³) at 0°C was treated with borane-THF complex (1M solution in THF, 6.74cm³, 6.74mmol) under a nitrogen atmosphere. After warming to 20°C for 1 h, the solution was cooled to 0°C and treated dropwise with aqueous HCl (6M; 10cm³), keeping the temperature below 5°C. After 30 min, this solution was warmed to 20°C and stirred for a further 30 min, before basifying with aqueous NaOH (2M) and extraction with ether (3 x 50cm³). The combined organic extracts were dried over MgSO₄, filtered and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v) to yield the title compound 208 as a clear oil (0.500g, 92%). (Found: C, 76.10; H, 8.82; N, 9.09%; M⁺ 299.2123. C₁₉H₂₆N₂O requires C, 76.47; H, 8.78 ; N, 9.38%; MH⁺ 299.2123); νmax (film) /cm⁻¹ 3086, 3063, 3029, 2974, 2929, 2870, 1495, 1455, 1361, 1242, 1196, 755, 700; δH (CDCl₃; 400MHz) 1.11 (C(CH₃)₃), 2.89 (dd, 2H, J 5.4, 12.2Hz, PhCHCH₂N), 3.01 (dd, 1H, J 8.0, 12.2Hz, PhCHCH₂N), 3.81 (s, 2H, NHCH₂Ph), 4.09 (dd, 1H, J 5.4, 8.0Hz, PhCHNO), 7.26-7.36 (Ar-H); δC (CDCl₃; 100MHz) 26.8 (C(CH₃)₃), 52.4 (PhCHCH₂N), 53.7 (NHCH₂Ph), 65.0 (PhCHNO), 76.6 (C(CH₃)₃), 126.8, 127.4, 128.0, 128.2 & 128.3 (Ar-CH), 140.1 & 140.7 (Ar-C); m/z 299 (MH⁺, 94%), 243 (7%), 225 (1%), 210 (24%), 122 (37%), 121 (14%), 120 (100%), 106 (57%), 91 (78%).
N-Benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride (140a)

A solution of N-benzyl-2-tert-butyloxyamino-2-phenylethylamine 208 (33.3g, 112mmol) in methanol (150cm³) was treated dropwise with conc. sulphuric acid (150cm³) with stirring as the temperature rose to approximately 70°C. The resultant solution was cooled to 20°C and basified with ice cold NaOH solution (2M). The solution was extracted with ether (3 x 250cm³) and the combined organic extracts dried over MgSO₄ and filtered. Dry gaseous HCl was bubbled through the resultant solution for 1 h before evaporation of the solvent under reduced pressure. The residue was dried thoroughly under high vacuum before trituration with DCM to yield the title compound 140a as an amorphous white solid (24.1g, 76.4mmol, 68%) (Found: C, 57.10; H, 6.41; N, 8.77%; M⁺ 243.1490. C₁₅H₂₀N₂OCl₂ requires C, 57.15; H, 6.40; N, 8.89%; M⁺ 243.1497); νₛₛₜₜ (KBr) /cm⁻¹ 3400-2200, 1572, 1499, 1458, 1426, 994, 753, 697; δₜₜ (D₂O, internal standard TSP-d₄; 400MHz) 3.68 (dd, 1H, J 7.3, 13.4Hz, PhCHCHHN), 3.89 (dd, 1H, J 6.2, 13.4Hz, PhCHCHHN), 4.33 (s, 2H, NHCH₂Ph), 4.77 (dd, 1H, J 7.3, 6.2Hz, PhCHNHOH), 7.45-7.60 (m, 10H, Ar-H); δᵣᵣ (D₂O; TSP-d₄; 100MHz) 49.1, 54.6 & 64.5 (PhCHCH₂N, NHCH₂Ph & PhCHNHOH) 131.6, 132.3, 132.6, 132.7, 132.9, 133.0 & 134.0 (Ar-C & Ar-CH); m/z FAB⁺ 243 (MH⁺, 19%), 210 (20%), 105 (57%), 91 (56%), 61 (96%), 45 (100%).
In a separate experiment, a solution of N-benzyl-2-tert-butyloxyamino-2-phenylethylamine 208 (0.800g, 2.68mmol) in methanol (10cm³) was treated with conc. hydrochloric acid (10cm³) and heated to reflux for 18 h. The solution was cooled to 20°C then basified with aqueous NaOH (2M) and extracted with EtOAc (3 x 30cm³). The combined organic extracts were separated and dried (Na₂SO₄) before evaporation under reduced pressure. The residue was treated with HCl (1M solution in anhydrous ether, 10cm³) to afford a sticky brown solid (containing 29% of the desired product 140a by reverse phase HPLC analysis). Repeated trituration with cold DCM gave an off-white solid (0.480g, 1.52mmol, 57%) (93% purity by HPLC) consistent with the desired material 140a by ¹H NMR spectroscopy (D₂O).

3-Benzyl-5-phenyl-4,5-dihydroimidazole-1-oxide hydrochloride (126a)

A solution of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.360g, 1.14mmol) in dry toluene (6cm³) was treated with triethyl orthoformate (435µl, 2.62mmol) under a nitrogen atmosphere. After warming to 60°C for 1 h, the solvent was evaporated under reduced pressure and the residue dried thoroughly under high vacuum to yield the title compound 126a as an unstable colourless film (0.329g, 100%); (M⁺-Cl 253.1337. C₁₆H₁₆N₂O requires M⁺-Cl 253.1341); δₙ (CDCl₃; 400MHz) 3.52 & 4.17 (each
t, 1H, J 12.3Hz, PhCHCH₂N), 4.80 (s, 2H, NCH₂Ph), 5.50 (t, 1H, J 12.3Hz, PhCHNO), 7.31-7.42 (m, 10H, Ar-H), 9.67 (s, 1H, N=CH=N) δc (CDCl₃; 100MHz) 52.8, 55.5 (NCH₂Ph & PhCHCH₂N), 67.6 (PhCHNO), 127.4, 128.9, 129.0, 129.3, 129.4 & 129.6 (Ar-CH) 132.0 & 134.4 (Ar-C), 157.3 (N=CH-N) ; m/z 254 (MH⁺, 1%), 85 (60%), 83 (100%), 61 (30%), 47 (44%).

3-Benzyl-2-methyl-5-phenyl-4,5-dihydroimidazole-1-oxide hydrochloride (126b)

Prepared as for the 2-H nitrone 126a, from N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (80.0mg, 0.254mmol) and triethyl orthoacetate (58.0µl, 0.317mmol) in dry DCM (1cm³) to give the title compound 126b as colourless gum (78.0mg, 100%) with 97% purity by HPLC (M⁺-Cl 266.1416. C₁₇H₁₈N₂O requires M⁺-Cl 266.1419); νmax (film) /cm⁻¹ 3450-2400, 1613, 1456, 1261, 1030, 758, 731, 701; δc (CDCl₃; 400MHz) 2.65 (s, 3H, N=C(CH₃)), 3.51 & 4.14 (each t, 1H, J 10.2Hz, PhCHCH₂N), 4.63 (s, 2H, NCH₂Ph), 5.52 (t, 1H, J 10.2Hz, PhCHCH₂N), 7.15-7.45 (Ar-H); δc (CDCl₃; 100MHz) 11.7 (N=C(CH₃)--N), 51.4 & 55.0 (PhCHCH₂N & NCH₂Ph), 66.4 (PhCHCH₂N), 127.1, 127.8, 129.4, 129.5 & 129.7 (Ar-CH), 132.3 & 134.7 (Ar-C), 167.6 (N=C(CH₃)--N); m/z 267 (MH⁺, 13%), 251 (3%), 91 (71%), 61 (100%), 43 (82%).
3-Benzyl-2,5-diphenyl-4,5-dihydroimidazole-1-oxide hydrochloride (126c)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{NH} & \\
\text{Ph} & \quad \text{NHOH} \cdot 2\text{HCl} \\
\text{140a} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N}^+ & \\
\text{O}^- & \\
\text{126b} & \\
\end{align*}
\]

Prepared as for the 2-H nitron 126a from N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.100g, 0.317mmol) and triethyl orthobenzoate (90.0µl, 0.400mmol) in dry DCM (2cm³) to give a mixture containing the title compound 126c by APCI⁺ MS; m/z 329 (MH⁺, 10%), 313 (M⁺-O, 100%).

1-Benzyl-7-methoxycarbonyl-3-phenyl-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole-5,6-dione (219)

\[
\begin{align*}
\text{Ph} & \\
\text{NH} & \\
\text{Ph} & \quad \text{NHOH} \cdot 2\text{HCl} \\
\text{140a} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \\
\text{Ph} & \\
\text{CO}_2\text{Me} & \\
\text{219} & \\
\end{align*}
\]

A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol) in anhydrous DCM (2cm³) at 30°C under an atmosphere of nitrogen was treated with triethyl orthoformate (131µl, 0.793mmol) and stirred for 1.5 h after which time the slurry had become a clear solution. The mixture was then treated with triethylamine
(176 \mu l, 1.26 mmol) and dimethyl acetylenedicarboxylate (97.0 \mu l, 0.793 mmol) and stirred at 30°C for 18 h. The solvent was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the title compound 219 as a brown film (133 mg, 58%) (M⁺ 362.1266. C₂₁H₁₈N₂O₄ requires M⁺ 362.1266); ν_max (KBr) /cm⁻¹ 3030, 2950, 1756, 1677, 1605, 1471, 1347, 1237, 1114, 752, 706; δH (CDCl₃; 300MHz) 3.77 (dd, 1H, J 5.0, 11.6Hz, PhCHCHHN), 3.86 (s, 3H, CO₂CH₃), 4.36 (dd, 1H, J 9.4, 11.6Hz, PhCHCHHN), 5.28 (dd, 1H, J 5.0, 9.4Hz, PhCHCH₂N), 5.55 (s, 2H, NCH₂Ph), 7.12 & 7.26-7.42 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 51.5 (CO₂CH₃), 52.5 (NCH₂Ph), 54.9 (PhCHCH₂N), 62.1 (PhCHCH₂N), 86.8 (CO₂CH₃), 125.9, 128.6, 128.9, 129.2, 129.3 & 129.4 (Ar-CH), 133.8 & 136.4 (Ar-C), 157.7, 163.5, 165.9 & 177.0 (NC=CO₂CH₃, NC=O, CO₂CH₃ & NC(=O)C=O); m/z 362 (M⁺, <1%), 330 (2%), 303 (1%), 157 (2%), 91 (41%), 84 (27%) 44 (58%), 28 (100%).

1-Benzyl-7-ethoxycarbonyl-3-phenyl-2,3,5,6-tetrahydro-1H-pyrrolo[1,2-a]imidazole-5,6-dione (222)

![Chemical structure](image)

Prepared as for dimethyl acetylenedicarboxylate cycloadduct 219 using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.300 g, 0.952 mmol), triethylorthoformate (198 \mu l, 1.19 mmol), triethylamine (264 \mu l, 1.89 mmol) and diethyl
acetylene dicarboxylate (190µl, 1.19mmol) and DCM (3cm³) at 45°C. The crude material
was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford 1-benzyl-4-
phenylimidazole 223 as a white crystalline solid (83.0mg, 37% based on 140a) and the title
compound 222 as a yellow gum (72.0mg, 20%); 222: (Found MH⁺ 377.1498.
C₂₂H₂₉N₂O₄ requires MH⁺ 377.1501); δH (CDCl₃; 400MHz) 1.36 (t, 3H, J 7.0Hz,
OCH₂CH₃), 3.75 (dd, 1H, J 4.8, 11.2Hz, PhCHCHHN), 4.37 (m, 3H, PhCHCHHN &
CO₂CH₂CH₃), 5.28 (dd, 1H, J 4.8, 9.2Hz, PhCHCH₂N), 5.44 & 5.59 (each d, 1H, J
14.8Hz, NCH₂Ph), 7.12 & 7.27-7.41 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 14.5
(OCH₂CH₃), 52.5 (NCH₂Ph), 54.9 (PhCHCH₂N), 60.3 (CO₂CH₂CH₃), 62.1
(PhCHCH₂N), 87.1 (C=CCO₂CH₂CH₃), 125.9, 128.5, 128.9, 129.2, 129.3 & 129.4 (Ar-
CH), 133.9 & 136.4 (Ar-C), 157.7, 163.0, 165.9 & 177.1 (NC=CCO₂CH₂CH₃, NC=O,
CO₂CH₂CH₃ & NC(=O)C=O); m/z 377 (MH⁺, 1%), 331 (11%), 303 (2%), 235 (2%), 105
(55%), 91 (100%); 1-Benzyl-4-phenyl-1H-imidazole 223: (Found: C, 79.15; H,
6.07; N, 11.02%; M⁺ 234.1157. C₁₆H₁₄N₂ + 0.5 H₂O requires C, 78.98; H, 6.20; N,
11.51%; M⁺ 234.1157); δH (CDCl₃; 400MHz) 5.06 (s, 2H, NCH₂Ph), 7.16-7.38 (m, 9H,
Ar-H & PhC=CHN), 7.56 (m, 1H, N=CH=N), 7.76 (m, 2H, Ar-H); δC (CDCl₃; 100MHz)
50.8 (NCH₂Ph), 115.0 (PhC=CHN), 124.6, 126.7, 127.2, 128.2, 128.4 & 128.9 (Ar-
CH), 133.9 & 135.9 (Ar-C), 137.5 (N=CH=N), 142.4 (PhC=CHN); m/z 234 (M⁺, 23%),
91 (100%), 77 (15%).
1-Benzyl-2-(formylmethoxycarbonylmethylene)-4-phenyl-tetrahydroimidazole (224)

Prepared as for the dimethyl acetylenedicarboxylate cycloadduct 220, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132µl, 1.19mmol), triethylamine (177µl, 1.26mmol) and methyl propiolate (71.0µl, 0.793mmol) in toluene (3cm³) at 60°C. The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford 1-benzyl-4-phenyl-1H-imidazole 223 as a white crystalline solid (9mg, 6%) and the title compound 224 as a pale yellow oil (78.0mg, 37%); (Found: C, 69.17; H, 6.02 ; N, 8.16%; M⁺ 336.1474. C₂₀H₂₀N₂O₃ + 0.5 H₂O requires C, 69.55; H, 6.12 ; N, 8.11%; M⁺ 366.1474); υ max (film) /cm⁻¹ 3026, 1678, 1604, 1439, 1352, 1278, 1101; δ n (CDCl₃; 400MHz) 3.32 (dd, 1H, J 7.3, 9.8Hz, PhCHCHHN), 3.69 (s, 3H, CO₂CH₃), 3.88 (t, 1H, J 9.8Hz, PhCHCHHN), 4.58 & 4.67 (each d, 1H, J 16.3Hz, NCH₂Ph), 4.99 (dd, 1H, J 7.3, 9.8Hz, PhCHCH₂N), 7.15-7.37 (m, 10H, Ar-H), 9.69 (s, 1H, CHO), 9.86 (br s, 1H, NH); δ c (CDCl₃; 100MHz) 50.8 (CO₂CH₃), 53.3 (NCH₂Ph), 56.5 (PhCHCH₂N), 58.0 (PhCHCH₂N), 88.0 (C=CCO₂CH₃), 125.9, 128.1, 128.8, 128.9 & 129.1 (Ar-CH), 135.6 & 139.9 (Ar-C), 165.0 & 168.5 (NC=CCO₂CH₃ & CO₂CH₃), 186.7 (CHO); m/z 336 (M⁺, 14%), 276 (12%), 176 (31%), 175 (12%), 149 (12 %), 147 (11%), 111(13%), 105 (17%), 104 (41%), 97 (18%), 91 (100%).
1-Benzyl-2-(formyl-tert-butoxycarbonylmethylene)-4-phenyl-
tetrahydroimidazole (225)

Prepared as for the dimethyl acetylenedicarboxylate cycloadduct 219, using N-
benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol),
triethylorthoformate (132µl, 1.19mmol), triethylamine (186µl, 1.33mmol), tert-butyl
propiolate (109µl, 0.793mmol) and toluene (3cm³) at 60°C. The crude material was purified
by column chromatography (SiO₂, hexane:EtOAc 1:1 v/v) to afford the 1-benzyl-4-phenyl-
IH-imidazole 223 (67.0mg, 45%) and the title compound 225 as a pale yellow oil (108mg, 45%) (Found: MH⁺ 379.2022. C₂₃H₂₆N₂O₃ requires MH⁺ 379.2022); δq (CDCl₃; 400MHz) 1.51 (s, 9H, C(CH₃)₃), 3.32 (dd, 1H, J 8.5, 10.8Hz, PhCHCHHN), 3.82 (t, 1H, J 10.8Hz, PhCHCH₂N); δc (CDCl₃; 100MHz) 28.6 (C(CH₃)₃), 53.0 (NCH₂Ph),
56.1 (PhCHCH₂N), 58.0 (PhCHCH₂N), 79.4 (C(CH₃)₃), 89.6 (CO₂C(CH₃)₃), 126.0, 128.0, 128.3, 128.4, 128.6 & 128.7 (Ar-CH), 135.7 & 139.8 (Ar-C), 164.9 & 167.8
(CO₂C(CH₃)₃ & NC=CCO₂C(CH₃)₃), 186.7 (CHO); m/z 379 (MH⁺, 12%), 323 (22%), 305
(20%), 277 (6%), 215 (6%), 120 (7%), 117 (5%), 105 (15%), 104 (15%), 91 (100%), 57
(14%).
Attempted preparation of 1-benzyl-7α-methyl-6,7-dimethoxycarbonyl-3-phenyl-1,2,3,7α-tetrahydro-1H-imidazo[1,2-b]isoxazole (227)

A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.100g, 0.317mmol) in anhydrous DCM (2cm³) under nitrogen was treated with triethyl orthoacetate (73.0µl, 0.398mmol) and warmed to 20°C for 18 h before addition of triethylamine (88.0µl, 0.632mmol) and then dimethyl acetylenedicarboxylate (49.0µl, 0.399mmol). After 18 h at 20°C, the solution was evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) but none of the desired cycloadduct 227 was isolated. However, from this mixture it was possible to isolate and characterise 1-benzyl-2-methyl-4-phenyl-1H-imidazole 228 (31.0mg, 39% based on 140a) and dimethyl 2-(diethylamino)but-2-endiolate 229 (24.0mg, 28% based on DMAD); 1-Benzyl-2-methyl-4-phenyl-1H-imidazole 228: δ<sub>H</sub> (CDCl₃; 250MHz) 2.39 (s, 3H, CH₃), 5.05 (s, 2H, NCH₂Ph), 7.09-7.37 & 7.75 (m, 11H, Ar-H & PhC=CHN); δ<sub>c</sub> (CDCl₃; 63MHz) 12.8 (CH₃), 49.5 (NCH₂Ph) 115.3 (PhC=CHN), 124.2, 126.1, 126.3, 127.0, 128.0 & 128.7 (Ar-CH), 133.8 & 135.8 (Ar-C), 139.7 & 145.0 (PhC=CHN & N=CCH₃); APCI⁺ m/z 249 (MH⁺, 100%). Dimethyl 2-
(diethylamino)but-2-enedioate 229: $\delta_H$ (CDCl$_3$; 400MHz) 1.18 (t, 6H, $J$ 7.1Hz, N(CH$_2$CH$_3$)$_2$), 3.18 (q, 4H, $J$ 7.1Hz, N(CH$_2$CH$_3$)$_2$), 3.63 & 3.93 (each s, 3H, CO$_2$CH$_3$), 4.61 (s, 1H, HCCO$_2$CH$_3$); $\delta_C$ (CDCl$_3$; 100MHz) 12.4 (N(CH$_2$CH$_3$)$_2$), 44.6 (N(CH$_2$CH$_3$)$_2$), 50.4 & 52.6 (CO$_2$CH$_3$), 82.6 (HC=CCO$_2$CH$_3$), 153.5 (N=C=CO$_2$CH$_3$), 165.9 & 168.0 (CO$_2$CH$_3$); APCI* m/z 216 (MH*, 100%).

1-Benzyl-6,7-dimethoxycarbonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole (230)

A slurry of N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol) in dry toluene (3cm$^3$) under a nitrogen atmosphere was treated with triethylorthoformate (1.06cm$^3$, 6.34mmol) and warmed to 60°C for 1 h. The resultant solution was then treated with triethylamine (186µl, 1.33mmol) and dimethyl maleate (99.0µl, 0.793mmol) and stirred at 60°C for 18 h. The solution was cooled to 20°C and treated with saturated aqueous sodium bicarbonate (10cm$^3$) and extracted with DCM (3 x 30cm$^3$). The combined organic extracts were dried over MgSO$_4$, filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO$_2$, hexane:EtOAc 4:1 v/v) to give the title compound 230 as a colourless oil (182mg, 72%). Recrystallisation from methanol gave white needles for X-ray crystallographic analysis, mp
106-107°C (Found: C, 66.67; H, 6.09; N, 7.06%; M⁺ 396.1685; C₂₂H₂₄N₂O₅ requires C, 66.65; H, 6.10; N, 7.06%; M⁺ 396.1685); νₓₜ (KBr) / cm⁻¹ 3028, 2952, 2894, 2812, 1760, 1446, 1435, 1364, 1270, 1223, 1165, 1049, 757, 737, 699; δH (CDCl₃; 400MHz) 2.40 (dd, 1H, J 9.5, 10.8Hz, PhCHCHHN), 3.38 (dd, 1H, J 6.4, 9.5Hz, PhCHCHHN), 3.47 (d, 1H, J 5.8Hz, NCHCHCO₂Me), 3.58 (d, 1H, J 12.6Hz, NCHPh), 3.70 & 3.77 (each s, 3H, CO₂CH₃), 3.93 (d, 1H, 12.6Hz, NCHPh), 4.42 (dd, 1H, J 6.4, 10.8Hz, PhCHNO), 4.63 (s, 1H, NCHCHCO₂CH₃), 4.98 (d, 1H, J 5.8Hz, NOCHCO₂CH₃), 7.20-7.39 (Ar-H); δC (CDCl₃; 100MHz) 52.4 (2 x CO₂CH₃), 57.4 (NCHCHCO₂CH₃), 57.5 (NCH₂Ph), 58.6 (PhCHCH₂N), 69.2 (PhCHNO), 75.5 (NOCHCO₂CH₃), 87.6 (NCHCHCO₂CH₃), 126.9, 127.4, 127.6, 128.2, 128.5 & 128.9 (Ar-CH), 136.8 & 138.7 (Ar-C), 168.4 & 169.1 (2 x CO₂CH₃); m/z 397 (MH⁺, 4%), 381 (0.2%), 337 (0.3%), 253 (5%), 105 (100%), 91 (37%) 61 (49%), 45 (49%).

1-Benzyl-6,7-diethoxycarbonyl-3-phenylhexahydro-1H-imidazo[1,2-b]isoxazole (238)

Prepared as for the dimethyl maleate cycloadduct 230 using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (2.00g, 6.34mmol), triethylorthofomate (1.32cm³, 7.93mmol), triethylamine (1.86cm³, 13.3mmol) and diethyl
maleate (1.03 cm$^3$, 6.61 mmol). The crude material was purified by column chromatography (SiO$_2$, hexane:EtOAc 4:1 v/v) to afford the title compound 238 as a pale yellow oil (966 mg, 2.28 mmol, 36%) (Found: C, 66.76; H, 6.96; N, 6.84%; MH$^+$ 425.2076. C$_{24}$H$_{28}$N$_2$O$_3$ + 0.5 H$_2$O requires C, 66.49; H, 6.74; N, 6.46%; MH$^+$ 425.2081); v$_{max}$ (film) /cm$^{-1}$ 3062, 3030, 2982, 2934, 1737, 1276, 1206, 1044, 701; $\delta$$_H$ (CDCl$_3$; 400 MHz) 1.26 (t, 3H, J 7.1 Hz, CO$_2$CH$_2$CH$_3$), 1.30 (t, 3H, J 7.1 Hz, CO$_2$CH$_2$CH$_3$), 2.40 (dd, 1H, J 9.5, 10.8 Hz, PhCHCH$_2$N), 3.36 (dd, 1H, J 6.4, 9.5 Hz, PhCHCH$_2$N), 3.45 (dd, 1H, J 1.1, 5.9 Hz, NCHCH$_2$O$_2$CH$_2$CH$_3$), 3.58 & 3.96 (each d, 1H, J 12.8 Hz, NCH$_2$Ph), 4.20 & 4.24 (each m, 2H, 2 x CO$_2$CH$_2$CH$_3$), 4.42 (dd, 1H, J 6.4, 10.8 Hz, PhCHCH$_2$N), 4.63 (s, 1H, NCHCH$_2$O$_2$CH$_2$CH$_3$), 4.95 (d, 1H, J 5.9 Hz, NOCHCO$_2$CH$_2$CH$_3$), 7.22-7.42 (m, 10, Ar-H); $\delta$$_C$ (CDCl$_3$; 100 MHz) 14.1 (2 x CO$_2$CH$_2$CH$_3$), 57.5 (NCHCHCO$_2$CH$_2$CH$_3$ & NCH$_2$Ph), 58.7 (PhCHCH$_2$N), 61.5 (2 x CO$_2$CH$_2$CH$_3$), 69.2 (PhCHCH$_2$N), 75.6 (NOCHCO$_2$CH$_2$CH$_3$), 87.7 (NCHCHCO$_2$CH$_2$CH$_3$), 127.0, 127.4, 127.6, 128.3, 128.5 & 129.0 (Ar-CH), 137.0 & 139.0 (Ar-C), 168.0 & 168.8 (2 x CO$_2$CH$_2$CH$_3$); m/z 425 (MH$^+$, 18%), 237 (17%), 235 (22%), 192 (78%), 190 (29%), 175 (82%), 173 (76%), 122 (23%), 120 (56%), 108 (62%), 106 (100%).
1-Benzyl-8-methyl-3-phenyloctahydro-8H-imidazo[1,2-b]pyrrolo[3,4-d]isoxazole-7,9-dione (239)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.300g, 0.952mmol), triethylorthoformate (198µl, 1.19mmol), triethylamine (166µl, 1.19mmol) and N-methylmaleimide (132mg, 1.19mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 239 as an unstable pale yellow oil (202mg, 58%) (Found: MH⁺ 364.1675. C₂₁H₂₁N₃O₃ requires MH⁺ 364.1661); νmax (CHCl₃ soln.) /cm⁻¹ 3026, 1719, 1665, 1500, 1385, 1228, 1191, 909, 701; δH (CDCl₃; 400MHz) 2.56 (t, 1H, J 9.2Hz, PhCHCHHN), 2.98 (s, 3H, NCH), 3.60 (m, 3H, PhCHCHHN, NCHHPh & NCHCHC=O), 4.01 (d, 1H, J 15.4Hz, NCHHPh), 4.27 (s, 1H, NCHCHC=O), 4.61 (t, 1H, J 7.7Hz, PhCHCH₂N), 4.97 (d, 1H, J 7.7Hz, NOCHC=O), 7.19-7.38 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 25.0 (NCH₃), 53.9 (NCHCHC=O), 56.4 (NCH₂Ph), 59.9 (PhCHCH₂N), 69.1 (PhCHNO), 75.7 (NOCHC=O), 88.2 (NCHCHC=O), 126.5, 127.3, 127.5, 128.1, 128.3 & 128.6 (Ar-CH), 136.8 & 139.3 (Ar-C), 173.8 & 174.3 (2 x C=O) m/z 364 (MH⁺, 2%), 253 (5%), 252 (4%), 237 (5%), 235 (2%), 210 (4%), 208 (4%), 105 (14%), 104 (18%) 91 (100%).
1-Benzyl-3,8-diphenyloctahydro-8H-imidazo[1,2-b]pyrrolo[3,4-d]-
isoazole-7,9-dione (240)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-
hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol),
triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and N-
phenylmaleimide (0.137g, 0.793mmol). The crude material was purified by column
chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 240 as a pale
yellow oil (103mg, 38%) (Found: MH⁺ 426.1818. C₂₆H₂₃N₃O₃ requires MH⁺ 426.1818);
ν max (CHCl₃ soln.) /cm⁻¹ 3026, 1714, 1437, 1384, 1288, 701; δ H (CDCl₃; 300MHz) 2.49 (t,
1H, J 9.2Hz, PhCHCHHN), 3.63 (m, 3H, PhCHCHHN, NCHHPh & NCHCHC=O),
3.98 (d, 1H, J 13.2Hz, NCHHPh), 4.36 (s, 1H, NCHCHC=O), 4.62 (t, 1H, J 8.1Hz,
PhCHNO), 5.05 (d, 1H, J 8.1Hz, NOCHC=O), 7.21-7.42 (m, 10H, Ar-H); δ C (CDCl₃;
100MHz) 54.4 (NCHCHC=O), 56.6 (NCH₂Ph), 59.8 (PhCHCH₂N), 68.8 (PhCHNO),
75.6 (NOCHC=O), 88.5 (NCHCHC=O), 126.3, 126.7, 127.5, 127.7, 129.0 & 129.2 (Ar-
CH), 131.2, 136.6 & 139.1 (Ar-C), 172.9 & 173.0 (2 x C=O); m/z 426 (MH⁺, 36%), 424
(25%), 253 (100%), 252 (63%), 237 (41%), 208 (32%), 174 (12%), 159 (8%), 120
(14%).
1-Benzyl-6-cyano-3-phenylhexahydroimidazo[1,2-b]isoxazole (242)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and acrylonitrile (52.0µl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford a mixture of two related compounds which could not be separated. One was assigned on the basis of comparison to analogous structures as the title compound 242 (44mg, <23%); δ<sub>H</sub> (CDCl₃; 400MHz) 2.52 (t, 1H, J 10.6Hz, PhCHCHHN), 2.88 (d, 1H, 3.8Hz, NCHCHC≡N), 3.42 (dd, 1H, J 7.5, 10.6Hz, PhCHCHHN), 3.77 (2 x d, 2H, J 12.2Hz, NCH₂Ph), 4.02 (m, 2H, NOCH₂), 4.33 (m, 1H, PhCHCH₂N), 4.48 (s, 1H, NCHCHC≡N); δ<sub>C</sub> (CDCl₃; 100MHz) 41.0 (NCHCHC≡N), 58.0 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.3 (NOCH₂), 67.7 (PhCHCH₂N), 88.8 (NCHCHC≡N), 118.6 (C≡N), 126.9, 127.6, 127.7, 128.5, 129.0 & 129.4 (Ar-CH), 136.6 & 138.5 (Ar-C).
1-Benzyl-7-methoxycarbonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole

(241)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (3.62g, 11.5mmol), triethylorthoformate (2.39cm³, 14.4mmol), triethylamine (3.36cm³, 24.2mmol) and methyl acrylate (1.29cm³, 14.4mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 241 as a pale yellow oil (1.30g, 3.84mmol). (Found: C, 67.03; H, 7.02; N, 8.02%; MH⁺ 339.1721. C₂₀H₂₂N₂O₃ + H₂O requires C, 67.40; H, 6.79; N, 7.86%; MH⁺, 339.1709); v max (film) /cm⁻¹ 3029, 2951, 2876, 1738, 1662, 1496, 1454, 1437, 1273, 1197, 1175, 747, 702; δ H (CDCl₃; 300MHz) 2.45 (t, 1H, J 10.4Hz, PhCHCHHN), 3.10 (d, 1H, J 4.0Hz, CHCO₂CH₃), 3.36 (dd, 1H, J 6.1, 10.4Hz, PhCHCHHN), 3.61 (d, 1H, J 12.8Hz, NCHHPH), 3.71 (s, 3H, CO₂CH₃), 3.92 (d, 1H, J 12.8Hz, NCHHPH), 4.21 (m, 2H, NOCH₂), 4.37 (dd, 1H, J 6.1, 10.4Hz, PhCHNO), 5.29 (s, 1H, NCHCHCO₂CH₃), 7.23-7.41 (m, 10H, Ar-H); δ c (CDCl₃; 100MHz) 52.2 (CO₂CH₃), 55.3 (CHCO₂CH₃), 57.7 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.2 (NOCH₂), 68.1 (PhCHNO), 87.6 (NCHCHCO₂CH₃), 126.9, 127.4, 127.5, 128.2 & 129.1 (Ar-CH), 137.3 & 139.3 (Ar-C), 171.2 (C=O); m/z 339 (MH⁺, 2%), 307 (0.3%), 253 (2%), 238 (4%), 208 (5%), 104 (22%), 91 (100%).
1-Benzyl-7-ethoxycarbonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole

\[(243)\]

Prepared as for dimethyl maleate cycloadduct \(230\), using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride \(140a\) (0.200g, 0.634mmol), triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and ethyl acrylate (86µl, 0.793mmol). The crude material was purified by column chromatography (SiO\(_2\), hexane:EtOAc 4:1 v/v) to afford the title compound \(243\) as a colourless oil (99.0mg, 44%) (Found: C, 71.26; H, 6.91; N, 8.02%; MH\(^+\) 353.1842. C\(_{21}\)H\(_{24}\)N\(_2\)O\(_3\) requires C, 71.57; H, 6.86; N, 7.94%; MH\(^+\) 353.1865); \(\nu_{\text{max}}\) (film) \(\text{cm}^{-1}\) 3063, 3030, 2981, 2875, 2811, 1734, 1496, 1454, 1370, 1305, 1273, 1186, 1126, 1059, 1029, 913, 736, 701; \(\delta\) (CDC\(_3\), 400MHz) 1.27 (t, 3H, J 7.1Hz, CO\(_2\)CH\(_2\)CH\(_3\)), 2.45 (dd, 1H, J 9.4, 10.8Hz, PhCHCHHN), 3.08 (m, 1H, CHCO\(_2\)CH\(_2\)CH\(_3\)), 3.36 (dd, 1H, J 6.2, 9.4Hz, PhCHCHHN), 3.62 & 3.92 (each d, 1H, J 12.8Hz, NCH\(_2\)Ph), 4.15 (q, 2H, J 7.1Hz, CO\(_2\)CH\(_2\)CH\(_3\)), 4.20 (m, 1H, NOCH\(_2\)H), 4.26 (dd, 1H, J 2.4, 9.0Hz, NOCH\(_2\)H), 4.38 (dd, 1H, J 6.2, 10.8Hz, PhCHNO), 4.61 (s, 1H, NCHCHCO\(_2\)CH\(_2\)CH\(_3\)), 7.21-7.42 (m, 10H, Ar-H); \(\delta\) (CDC\(_3\), 100MHz) 14.1 (CO\(_2\)CH\(_2\)CH\(_3\)), 55.4 (CHCO\(_2\)CH\(_2\)CH\(_3\)), 57.7 (NCH\(_2\)Ph), 59.0 (PhCHCH\(_2\)N), 61.2 (CO\(_2\)CH\(_2\)CH\(_3\)), 66.3 (NOCH\(_2\)), 68.1 (PhCHNO), 87.5 (NCHCHCO\(_2\)CH\(_2\)CH\(_3\)), 127.1, 127.4, 127.5, 128.4, 128.5 & 129.1 (Ar-CH), 137.3
& 139.4 (Ar-C), 170.8 (CO₂CH₂CH₃); m/z 353 (M⁺, 100%), 275 (12%), 253 (31%), 252 (71%), 248 (33%), 210 (12%), 208 (15%), 174 (15%).

1-Benzyl-7-tert-butoxycarbonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole (244)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethyl orthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and tert-butyl acrylate (116µl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 244 as a colourless oil (20.0mg, 8%). (Found: MH⁺ Cl 381.2178. C₂₃H₂₈N₂O₃ requires MH⁺ 381.2178); νmax (CHCl₃) /cm⁻¹ 2982, 2932, 1725, 1606, 1455, 1394, 1370, 1156, 1030, 846, 810; δH (CDCl₃; 400MHz) 1.47 (s, 9H, CO₂C(CH₃)₃), 2.46 (dd, 1H, J 9.5, 10.8Hz, PhCHCHHN), 3.02 (m, 1H, CHCO₂C(CH₃)₃), 3.35 (dd, 1H, J 6.2, 9.5Hz, PhCHCHHN), 3.60 & 3.93 (each d, 2H, J 12.8Hz, NCH₂Ph), 4.19 (m, 2H, NOCH₂), 4.37 (m, 1H, PhCHNO), 4.55 (s, 1H, NCHCHCO₂C(CH₃)₃), 7.22-7.39 (m, 10H, Ar-H); δC (CDCl₃; 100MHz) 28.0 (C(CH₃)₃), 56.3 (CHCO₂C(CH₃)₃), 57.7 (NCH₂Ph), 59.0 (PhCHCH₂N), 66.5 (NOCH₂), 68.0 (PhCHNO), 81.6 (C(CH₃)₃), 87.7 (NCHCHCO₂C(CH₃)₃), 127.1, 127.4, 127.5, 128.4,
128.5 & 129.1 (Ar-CH), 137.4 & 139.4 (Ar-C), 170.8 (C=O); m/z 381 (MH+, 3%), 325 (2%), 323 (2%), 307 (1%), 252 (6%), 237 (3%), 210 (6%), 91 (100%).

1-Benzyl-3-phenyloctahydro-1H-imidazo[1,2-b]furo[3,4-d]isoxazol-9-one (245)

Prepared as for dimethyl maleate 230, cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethyl orthoformate (132µl, 0.793mmol), triethylamine (186µ1, 1.33mmol) and 2(5H)-furanone (56.0µl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 245 as an unstable colourless oil (89.0mg, 42%). (Found: MH⁺ 337.1567; C₂₀H₂₀N₂O₃ requires MH⁺ 337.1552); δH (CDCl₃; 400MHz) 2.42 (t, 1H, J 9.5, 10.7Hz, PhCHCHHN), 3.13 (d, 1H, J 5.3Hz, NCHCHC=O), 3.26 (dd, 1H, J 6.0, 9.5Hz, PhCHCHHN), 3.64 and 3.84 (each d, J 12.8Hz, NCH₂Ph), 4.29 (d, 2H, J 1.8Hz, NOCHCH₂O), 4.36 (dd, 1H, J 6.0, 10.7Hz, PhCHNO), 4.54 (s, 1H, NCHHC=O), 4.98 (dt, 1H, J 1.8, 5.3Hz, NOCHCH₂O); δc (CDCl₃; 100MHz) 56.2 (NCHHC=O), 57.7 (NCH₂Ph), 58.6 (PhCHCH₂N), 68.2 (PhCHNO), 69.9 (NOCHCH₂O), 76.2 (NOCHCH₂O), 88.6 (NCHHC=O), 126.8, 134.9 (C=O), 140.8 (Ar-CHO), 159.0 (C=O), 169.8 (C=O), 187.3 (C=O); mlz 381 (MH⁺, 3%), 325 (2%), 323 (2%), 307 (1%), 252 (6%), 237 (3%), 210 (6%), 91 (100%).

215
127.4, 127.5, 128.2, 128.3 & 129.1 (Ar-CH), 136.7 & 138.4 (Ar-C), 174.5 (C=O); m/z 337 (MH+, 21%), 253 (11%), 238 (8%), 210 (6%), 139 (15%), 91 (100%).

1-Benzyl-7-methylsulfonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole (246)

 Prepared as for dimethyl maleate 230, cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and methyl vinyl sulfone (89.0µl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 246 as a colourless oil (95.0mg, 42%) (Found: C, 61.69%; H, 6.09%; N, 7.46%; MH⁺ 359.1420. C₁₉H₂₂N₂O₃S + 0.6H₂O requires C, 61.80%; H, 6.33%; N, 7.59%; MH⁺ 359.1429); νₘₐₓ (film) /cm⁻¹ 3062, 3029, 2929, 2876, 2820, 1655, 1455, 1305, 1130, 971, 751, 702; δₗ (CDCl₃; 400MHz) 2.46 (t, 1H, J 9.8Hz, PhCHCHHN), 2.90 (s, 3H, SO₂CH₃), 3.31 (dd, 1H, J 6.1, 9.8Hz, PhCHCHHN), 3.59 (d, 1H, J 13.2Hz, NCHHPh), 3.65 (br s, 1H, CHSO₂CH₃), 4.04 (d, 1H, J 13.2Hz, NCHHPh), 4.37 (dd, 1H, J 6.1, 9.8Hz, PhCHNO), 4.40 (d, 2H, J 3.1Hz, NOCH₂), 4.62 (s, 1H, NCHCHSO₂CH₃), 7.24-7.41 (m, 1OH, Ar-H); δₗ (CDCl₃; 100MHz) 39.3 (SO₂CH₃), 56.9 (NCH₂Ph), 57.8 (PhCHNO), 64.3 (NOCH₂), 68.1 (PhCHCH₂N), 74.5 (CHSO₂CH₃), 85.6 (NCHCHSO₂CH₃), 126.9,
127.7, 128.5, 128.6 & 129.1 (Ar-CH), 136.2 & 138.4 (Ar-C); m/z 359 (MH⁺, 3%), 279 (2%), 252 (2%), 237 (3%), 210 (5%), 208 (4%), 105 (27%), 104 (47%), 91 (100%), 61 (73%), 45 (90%).

1-Benzyl-7-ethylsulfonyl-3-phenylhexahydroimidazo[1,2-b]isoxazole (247)

Prepared as for dimethyl maleate cycloadduct using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride (0.200g, 0.634mmol), triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and ethyl vinyl sulfone (83.0µl, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 247 as a pale yellow oil (69.0mg, 29%) (Found: C, 64.34%; H, 6.58%; N, 7.37%; MH⁺ 373.1587. C₂₀H₂₂N₂O₃S requires C, 64.49%; H, 6.49%; N, 7.52%); MH⁺ 373.1586; δ (film) /cm⁻¹ 3063, 3030, 2943, 2879, 2818, 1496, 1455, 1357, 1308, 1235, 1120, 1029, 915, 794, 736, 701; δ (CDCl₃, 300MHz) 1.40 (t, 3H, J 7.3Hz, SO₂CH₂CH₃), 2.44 (dd, 1H, J 9.4, 10.8Hz, PhCHCHHN), 3.00 (q, 2H, J 7.3Hz, SO₂CH₂CH₃), 3.31 (dd, 1H, J 6.1, 9.4Hz, PhCHCHHN), 3.59 (d, 1H, J 13.2Hz, NCHHPh), 3.70 (t, 1H, J 3.3Hz, NCHHPhSO₂CH₂CH₃), 4.04 (d, 1H, J 13.2Hz, NCHHPh), 4.34 (m, 1H, PhCHNO), 4.38 (d, 2H, J 3.7Hz, NOCH₂), 4.63 (s, 1H, NCHCHSO₂CH₂CH₃), 7.22-7.38 (Ar-H); δc
(CDCl₃; 100MHz) 5.4 (SO₂CH₂CH₃), 46.2 (SO₂CH₂CH₃), 57.2 (NCH₂Ph), 57.9 (PhCHCH₂N), 64.6 (NOCH₂), 68.2 (PhCHNO), 73.7 (CHSO₂CH₂CH₃), 85.6 (NHCHCHSO₂CH₂CH₃), 127.2, 128.1, 128.9, 129.1 & 129.6 (Ar-CH), 138.4 (Ar-C); 
m/z 373 (MH⁺, 1%), 238 (4%), 237 (2%), 210 (4%), 208 (2%), 132 (2%), 130 (3%), 122 (4%), 105 (13%), 104 (23%), 91 (50%), 61 (62%), 45 (100%).

1-Benzyl-3-phenyl-7-phenylsulfonylhexahydroimidazo[1,2-b]isoxazole (248)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthoformate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and phenyl vinyl sulfone (133mg, 0.793mmol). The crude material was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) to afford the title compound 248 as an off-white white crystalline solid (121mg, 45%). Recrystallisation from methanol afforded white needles crystalline for X-ray crystallographic analysis, mp 105-106°C (Found: C, 68.49%; H, 5.75%; N, 6.66%; MH⁺ 421.1586. C₂₄H₂₄N₂O₃S requires C, 68.55%; H, 5.73%; 6.65%; MH⁺ 421.1586); νmax (KBr) /cm⁻¹ 3062, 3024, 2969, 2884, 2824, 1496, 1448, 1314, 1196, 1166, 1154, 1089, 745, 725, 701, 590, 548; δH (CDCl₃, 300MHz) 2.40 (dd, 1H, J 9.5, 10.6Hz, PhCHCHHN), 3.27 (dd, 1H, J 6.2, 9.5Hz, PhCHCHHN), 3.43 &
3.80 (each d, 1H J 13.2Hz, NCH$_2$Ph), 3.93 (m, 1H, CHSO$_2$Ph), 4.33 (m, 3H, PhCHNO & NOCH$_2$), 4.70 (s, 1H, NCHCHSO$_2$Ph), 7.19-7.35 (m, 10H), 7.59 (m, 2H), 7.66 (m, 1H) & 7.96 (m, 2H, Ar-H); $\delta_c$ (CDCl$_3$; 100MHz) 56.7 (NCH$_2$Ph), 58.3 (PhCHCH$_2$N), 64.9 (NOCH$_2$), 67.3 (PhCHNO), 75.3 (CHSO$_2$Ph), 85.6 (NCHCHSO$_2$Ph), 126.9, 127.6, 127.9, 128.4, 128.5, 128.9 & 129.5 (Ar-CH), 134.3, 137.6 & 138.5 (Ar-C); $m/z$ 421 (MH$^+$, 0.3%), 238 (3%), 210 (3%), 105 (16%), 104 (23%), 91 (57%), 61 (57%), 45 (100%).

1-Benzyl-6-methoxycarbonyl-6-methyl-3-phenylhexahydro-1H-imidazo[1,2-b]isoxazole (254)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.200g, 0.634mmol), triethylorthofomate (132µl, 0.793mmol), triethylamine (186µl, 1.33mmol) and methyl methacrylate (85.0µl, 0.793mmol). The crude material was purified by column chromatography (SiO$_2$, hexane:EtOAc 4:1 v/v) to afford the title compound 254 as a colourless oil (36.0mg, 16%) (Found: MH$^+$ 353.1865. C$_{21}$H$_{24}$N$_2$O$_3$ requires M$^+$ 335.1865); $\delta_h$ (CDCl$_3$; 400MHz) 1.54 (s, 3H, NOCCH$_3$), 2.13 (dd, 1H, J 9.6, 10.2Hz, PhCHCHHN), 2.31 (dd, 1H, J 4.9, 12.8Hz, NCHCHHCCO$_2$CH$_3$), 3.09 (d, 1H, J
12.8Hz, NCHCHHCO2CH3), 3.15 (d, 1H, J 12.5Hz, NCHHPh), 3.32 (dd, 1H, J 7.4, 9.6Hz, PhCHCHHN), 3.78 (s, 3H, CO2CH3), 3.91 (d, 1H, J 12.5Hz, NCHHPh), 4.09 (d, 1H, J 4.9Hz, NCHCH2CO2CH3), 4.96 (dd, 1H, J 7.4, 10.2Hz, PhCHNO), 7.18-7.40 (m, 10H, Ar-CH); δC (CDCl3; 100MHz) 23.3 (NOCCH3), 44.1 (NCHCH2CO2CH3), 52.3 (CO2CH3), 56.7 (NCH2Ph), 60.1 (PhCHCH2N), 71.6 (PhCHNO), 82.2 (NOCCO2CH3), 86.3 (NCHCH2), 126.8, 127.1, 127.3, 128.3, 128.5 & 128.9 (Ar-CH), 137.7 & 140.9 (Ar-C), 175.4 (CO2CH3); m/z 353 (MH+, 16%), 293 (6%), 252 (7%), 237 (6%), 210 (11%), 208 (12%), 174 (25%), 132 (20%), 91 (100%), 77 (13%), 61 (32%).

1-Benzyl-6-ethoxycarbonyl-6-methyl-3-phenylhexahydroimidazo[1,2-β]isoxazole (255)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (2.00g, 6.34mmol), triethylorthoformate (1.32cm3, 7.93mmol), triethylamine (1.86cm3, 13.3mmol) and ethyl methacrylate (0.99cm3, 7.93mmol). The crude material was purified by column chromatography (SiO2, hexane:EtOac 4:1 v/v) to afford the title compound 255 as a colourless oil (312mg, 13%). (Found: MH+ 367.2022. C21H24N2O3 requires MH+ 367.2022); δH (CDCl3; 400MHz) 1.27 (t, 3H, J 6.9Hz, CO2CH2CH3), 1.53 (s, 3H,
NOCC\textsubscript{3}), 2.13 (dd, 1H, J 9.7, 10.2Hz, PhCH\textsubscript{2}HN), 2.29 (dd, 1H, 4.9, 12.9Hz, NCHCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 3.14 (m, 2H, NCH\textsubscript{2}Ph & NCHCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 3.28 (dd, 1H, J 7.4, 9.7Hz, PhCH\textsubscript{2}HN), 3.91 (d, 1H, J 12.6Hz, NCH\textsubscript{2}Ph), 4.09 (d, 1H, J 4.9Hz, NCHCH\textsubscript{2}), 4.18 & 4.35 (each m, 1H, CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 5.01 (dd, 1H, J 7.4, 10.2Hz, PhCHNO), 7.18-7.24 (m, 10H, Ar-H); \(\delta\textsubscript{c} (\text{CDCl}_3; 100MHz)\) 14.1 (CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 23.3 (NOCC\textsubscript{3}), 44.1 (NCHCH\textsubscript{2}), 56.7 (NCH\textsubscript{2}Ph), 59.9 (PhCHCH\textsubscript{2}N), 61.0 (CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 71.5 (PhCHNO), 82.4 (NOCCO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 86.2 (NCHCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 126.7, 126.8, 127.1, 128.1 & 128.8 (Ar-CH), 137.5 & 140.7 (Ar-C), 174.6 (CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}); \(m/z\) 367 (MH\textsuperscript{+}, 5%), 365 (4%), 293 (3%), 252 (5%), 237 (3%), 210 (6%), 208 (8%), 174 (16%), 132 (13%), 91 (100%), 83 (37%).

1-Benzyl-6-cyano-6-methyl-3-phenylhexahydroimidazo[1,2-b]isoxazole (256)

Prepared as for dimethyl maleate cycloadduct 230, using N-benzyl-2-hydroxyamino-2-phenylethylamine dihydrochloride 140a (0.270g, 0.856mmol), triethylorthoformate (178\textmu l, 1.07mmol), triethylamine (149\textmu l, 1.07mmol) and methacrylonitrile (90.0\textmu l, 1.07mmol). The crude material was purified by column chromatography (SiO\textsubscript{2}, hexane:E\textsubscript{2}OAc 4:1 v/v) to afford a mixture from which the title...
compound 256 was tentatively assigned by comparison with similar structures as a colourless oil (14.0mg, <5%); δ_H (CDCl3; 400MHz) 1.70 (s, 3H, NOCCH3), 2.28 (m, 2H, PhCHCHHN & NCHCHHCC≡N), 2.62 (d, 1H, J 13.2Hz, NCHCHHCC≡N), 3.52 (m, 2H, NCHPh & PhCHCHHN), 3.90 (d, 1H, J 13.2Hz, NCHHPh), 4.33 (d, 1H, J 5.6Hz, NCH2CC≡N), 4.99 (m, 1H, PhCHNO).

Attempted preparation of 2-benzylamino-1-phenylethyl-4,5-dimethoxycarbonyltetrahydroisoxazole (270)

A solution of cycloadduct 230 (0.130g, 0.328mmol) in absolute ethanol (5cm³) was treated with sodium cyanoborohydride (25.0mg, 0.361mmol) in one portion and the solution kept acidic to bromocresol green indicator with aqueous HCl (2M), but no change was observed by TLC analysis after 48 h at 20°C. In a similar experiment, an ethanol solution of 230 with sodium cyanoborohydride was heated to reflux for 1.5 h. Upon cooling to 20°C, the solvent was removed under reduced pressure, but only unchanged 230 was identified from the residue.

A glacial acetic acid solution (5cm³) of 230 (0.100g, 0.252mmol) was treated with sodium cyanoborohydride (17.0mg, 0.271mmol) in one portion and stirred at 20°C for 18 h. The solution was basified with aqueous NaOH (2M) before extraction into DCM (3 x
30cm$^3$) which was then dried (MgSO$_4$) and filtered. The solvent was removed under reduced pressure but no desired material was isolated from the residue after column chromatography (SiO$_2$, EtOAc). A similar protocol in which the solution was heated to 100°C for 2 h returned an intractable black tar with these reagents.

1-Benzyl-6-hydroxy-7-methoxycarbonyl-3-phenylhexahydro-5H-
pyrrolo[1,2-$a$]imidazol-5-one (271)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{CO}_2\text{Me} & \quad \text{CO}_2\text{Me} \\
\text{Ph} & \quad \text{Ph} \\
\text{O} & \quad \text{O}
\end{align*}
\]

A solution of dimethyl maleate cycloadduct 230 (0.764g, 1.93mmol) in methanol (30cm$^3$) was treated with W-2 Raney Nickel (from a 50% slurry in water) (approx. 6g of Ni), and agitated under an atmosphere of hydrogen at 65psi (Parr hydrogenator) for 18 h. The mixture was filtered and the filtrate evaporated to dryness. The residue was purified by column chromatography (SiO$_2$, hexane:EtOAc 2:1 v/v) to afford the title compound 271 as an off-white solid (415mg, 59%) along with an impure compound assigned, after further purification by careful chromatography as described above, as 1-benzyl-2-[1-(2-hydroxy-1,2-bis-methoxycarbonyl)ethyl]-4-phenyl-2,4-dihydro-1H-imidazole 273 (16.0mg, 2%); $\delta$ (CDCl$_3$; 400MHz) 3.18 (dd, 1H, $J$ 3.1, 6.7Hz, NCHCHCO$_2$CH$_3$), 3.64 (d, 1H, $J$ 13.4Hz, NCHHPh), 3.74 & 3.77 (each s, 3H, 2x CO$_2$CH$_3$), 3.80 (m, 1H, PhCCHHN), 4.22 (m, 2H, PhCCHHN & NCHHPh), 4.81 (d, 1H, $J$ 3.1Hz, NCHCHCO$_2$CH$_3$), 5.55 (m, 1H, 223
CHOH); δc (CDCl₃; 100MHz) 52.1 & 52.4 (2 x CO₂CH₃), 54.3 (NCHCHCO₂CH₃), 59.6 (NCH₂Ph), 61.0 (PhCCH₂N), 69.9 (NCHCHCO₂CH₃), 92.6 (CHOH), 127.3, 127.8, 128.3, 128.5, 128.6 & 138.9 (Ar-CH), 131.5 & 131.8 (Ar-C), 170.8, 171.0 & 173.2 (2 x CO₂CH₃ & PhC=N).

The relative stereochemistry of lactam 271 was determined by NOESY in CDCl₃ and d₅-DMSO. A sample was later recrystallised from methanol to afford small, white needles which, by X-ray crystallographic analysis, confirmed our assignments, mp 131-132°C (Found: C, 68.80; H, 6.07; N, 7.58%; MH⁺ 367.1652. C₂₁H₂₂N₂O₄ requires C, 68.84; H, 6.05; N, 7.64%; MH⁺ 367.1658); νmax (KBr) cm⁻¹ 3344, 2898, 2827, 1742, 1686, 1438, 1330, 1315, 1287, 1268, 1132, 1120 1017, 750, 703, 697; δH (CDCl₃; 300MHz) 3.17 (dd, 1H, J 5.3, 9.3Hz, CHCO₂CH₃), 3.42 (d, 1H, J 12.9Hz, NCHCH₂Ph), 3.55 (br s, OH), 3.67 (dd, 1H, J 7.8, 9.5Hz, PhCHCHHN), 3.74 (s, 3H, CO₂CH₃), 3.99 (d, 1H, J 12.9Hz, NCHHPh), 4.52 (d, 1H, J 5.3Hz, NCHCHCO₂CH₃), 4.90 (d, 1H, J 9.3Hz, CHOH), 5.02 (dd, 1H, J 7.8, 9.5Hz, PhCHNC=O) 7.17-7.37 (m, 10H, Ar-H); δc (CDCl₃; 100MHz) 52.7 (CO₂CH₃), 55.7 (NCH₂Ph), 55.9 (CHCO₂CH₃), 57.2 (PhCHNC=O), 62.2 (PhCHCH₂N), 74.8 (CHOH), 79.3 (NCHCHCO₂CH₃), 125.8, 127.6, 127.7, 128.5, 128.7 & 128.8 (Ar-CH), 136.9 & 139.4 (Ar-C), 171.6 & 174.0 NC=O & CO₂CH₃; δH (d₅-DMSO; 300MHz) 2.41 (t, 1H, J 9.4Hz, PhCHCHHN), 2.94 (dd, 1H, J 5.4, 9.5Hz, CHCO₂CH₃), 3.44 (d, 1H, J 13.0Hz, NCHHPh), 3.58 (dd, 1H, J 7.6, 9.4Hz, PhCHCHHN), 3.66 (s, 3H, CO₂CH₃), 3.87 (d, 1H, J 13.0Hz, NCHHPh), 4.41 (d, 1H, J 5.4Hz, NCHCHCO₂CH₃), 4.71 (dd, 1H, J 7.4, 9.5Hz, CHOH), 4.85 (dd, 1H, J 7.6, 9.4Hz, PhCHNC=O), 6.13 (d, 1H, J 7.4Hz, OH), 7.23-7.34 (m, 10H, Ar-H); m/z 367 (MH⁺, 30%), 123 (27%), 105 (100%), 91 (80%), 61 (32%), 45 (38%).
In a similar experiment, a slurry of the cycloadduct 230 (100mg, 0.252mmol) and 5% Pd-C (27mg, 5mol%) in methanol (5cm³) was stirred at 30°C under hydrogen (1 atmos.) at 20°C for 18 h. The mixture was filtered and the filtrate evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the title compound 271 as a colourless gum (13.0mg, 14%).

The cycloadduct 230 (0.100g, 0.252mmol) was also dissolved in methanol (5cm³), treated with 10% Pd(OH)₂-C (27.0mg, 5mol%) and stirred under hydrogen (1 atmos.) for 18 h. The solution was filtered, the filtrate evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 2:1 v/v) to afford the lactam 271 (25.0mg, 27%).

**Attempted preparation of 1-benzyl-7-ethoxycarbonyl-6-hydroxy-3-phenylhexahydro-5H-pyrrolo[1,2,-a]imidazol-5-one**

![Chemical structure of 238 and 271](image)

A solution of the diethyl maleate cycloadduct 238 (100mg, 0.236mmol) in methanol (5cm³) was treated with W-2 Raney Nickel (from a 50% slurry in water w/w) (approx. 200mg of Ni), and agitated under an atmosphere of hydrogen (65psi; Parr hydrogenator) for 18 h. The mixture was filtered and the filtrate evaporated to dryness but none of the title
compound was isolated from the mixture of products after column chromatography (SiO₂, hexane:EtOAc 2:1 v/v).

**Attempted preparation of 1-benzyl-2-(1-methoxycarbonyl-2-hydroxyethyl)-4-phenyltetrahydroimidazole**

![Chemical Structure](image)

A solution of methyl acrylate cycloadduct 241 (100mg, 0.295mmol) in MeOH (10cm³) was treated with 10% Pd-C (31mg, 5mol%) and kept under hydrogen (1 atmos.) at 20°C and atmospheric pressure for 48 h. The mixture was filtered and the solvent evaporated under reduced pressure to return the starting material unchanged.

Hydrogenolysis was also attempted using the cycloadduct 241 (100mg, 0.295mmol) in methanol (10cm³) with 20% Pd(OH)₂-C (16mg, 5mol%) under hydrogen (1 atmos.) at 20°C for 18 h. Column chromatography (SiO₂, CHCl₃:PrNH₂ 200:1 v/v) failed to return any identifiable material from the crude product mixture.

A similar experiment used the cycloadduct 241 (100mg, 0.295mmol) and W-2 Raney Nickel (from a 50% slurry in water w/w) (approx. 1g of Ni) in methanol (10cm³). After 18 h at 60psi, the mixture was filtered and the filtrate evaporated. The residue returned no identified products after column chromatography (SiO₂, CHCl₃:PrNH₂ 200:1 v/v).
Attempted preparation of 1-(2-benzylamino-1-phenylethyl)-3-hydroxy-4-methoxycarbonyltetrahydropyrrol-2-one (274)

Using the procedures described for the attempted cleavage of 230 above, 271 was reacted with sodium cyanoborohydride in ethanol at pH3 at 20°C and in glacial acetic acid at reflux. Neither experiment returned any of the title compound.

A solution of lactam 271 (80.0mg, 0.218mmol) in dry distilled THF (5cm³) under nitrogen was treated with sodium borohydride (13.0mg, 0.344mmol) in one portion. The mixture was stirred at 20°C for 72 h before addition of water (5cm³) and extraction with DCM (3 x 30cm³). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure and the residue purified by column chromatography (SiO₂, hexane:EtOAc 1:1) to afford 1-benzyl-6-hydroxy-7-hydroxymethyl-3-phenyl-hexahydropyrrolo[1,2-a]imidazol-5-one 275 as an unstable colourless gum (14.0mg, 19%) δ<sub>H</sub> (CDCl₃; 300MHz) 2.51 (t, 1H, J 9.6Hz, PhCHCHHN), 2.61 (m, 1H, CHCH₂OH), 3.36 (d, 1H, J 13.0Hz, NCHHPh), 3.64 (dd, 1H, J 7.5, 9.6Hz, PhCHCHHN), 3.91 (d, 2H, J 5.3Hz, CHCH₂OH), 4.21 (d, 1H, J 13.0Hz, NCHHPh), 4.27 (d, 1H, J 4.6Hz, NCHCH₂OH), 4.61 (d, 1H, J 9.2Hz, CHOH), 5.04 (dd, 1H, J 7.5, 9.6Hz, PhCHNC=O), 7.19-7.34 (m, 10H, Ar-H); δ<sub>C</sub> (CDCl₃; 75MHz) 53.5 (CH₂OH), 56.1 (CHCH₂OH), 57.1 (PhCHNC=O), 61.5 & 62.2 (PhCHCH₂N & NCH₂Ph), 73.4 (CHOH), 79.9
Attempted preparation of 1-benzyl-6-hydroxy-7-methoxycarbonyl-3-phenyltetrahydropyrrolo[1,2-a]imidazole (278)

A solution of the methyl hydroxy lactam 271 (100mg, 0.273mmol) in distilled anhydrous THF (5cm³) under an atmosphere of nitrogen was treated with borane-THF complex (1M solution in THF, 2.73cm³, 2.73mmol) in one portion and heated under reflux for 18 h. The solution was cooled to 20°C and carefully treated with aqueous HCl (6M; 10cm³) and stirred at 20°C for 1 h. This solution was then basified with aqueous NaOH (10M) and extracted with ether (3 x 30cm³). The combined organic extracts were dried over MgSO₄, filtered and evaporated under reduced pressure before purification of the residue by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v). The isolated product was not the title compound but 1-benzyl-7-methoxycarbonyl-3-phenyl-2,3-dihydro-1H-pyrrolo[1,2-a]imidazole 279 (20.0mg, 23%); δH (CDCl₃; 300MHz) 3.27 (dd, 1H, J 5.6, 12.7Hz, PhCHCHHN), 3.35 (dd, 1H, J 8.8, 12.7Hz, PhCHCHHN), 3.77 (s, 3H, CO₂CH₃), 3.81 (s, 2H, NCH₂Ph), 5.26 (dd, 1H, J 5.6, 8.8Hz, PhCHCH₂N), 6.61 & 6.70 (each m, 1H,
NCH=CH), 7.10 & 7.24-7.58 (m, 10H, Ar-H); δc (CDCl₃; 75MHz) 51.0 (CO₂CH₃), 52.7 (PhCH₂CH₂N), 53.5 (NCH₂Ph), 63.7 (PhCH₂CH₂N), 110.4 (NCH=CH), 121.1 (NCH=CH), 116.2, 125.0, 126.5, 127.3, 128.1, 128.3, 128.5, 128.9, 138.9 & 139.3 (Ar-C, Ar-CH & NC=CCO₂CH₃), 165.2 (CO₂CH₃).

This experiment was then repeated at 20°C for 18 h but afforded only an intractable mixture of products. Similarly, using the methodology of Fleet et al., a solution of the lactam (100mg, 0.273mmol) in distilled anhydrous THF (10cm³) under an atmosphere of nitrogen was treated with borane-dimethyl sulphide complex (2M solution in THF, 0.55cm³, 1.09mmol) in one portion. After stirring at 20°C for 18 h, the solution was evaporated to return a mixture of the starting material 271 and a trace of the pyrroloimidazole 279.

Attempted preparation of 3-benzyl-4,5-dihydroimidazole-1-oxide (284)

1-Benzyl-4,5-dihydroimidazole 285 (0.500g, 3.12mmol), prepared according to the published procedure, was treated with glacial acetic acid (1.85cm³) and aqueous hydrogen peroxide solution (27% w/v; 1.90cm³) and the mixture heated to reflux for 18 h. The cooled solution was concentrated under reduced pressure and made basic with sodium carbonate. The solution was extracted with chloroform (3 x 30cm³) and the combined organic extracts dried (MgSO₄) and evaporated under reduced pressure. The residue was found to contain none of the desired material.
A solution of 285 (1.00g, 61.7mmol) in dry ether (100cm³) under nitrogen was treated with a solution of mCPBA (10.7g, 30.9mmol) in dry ether (100cm³) and stirred at 20°C for 24 h. The mixture was treated with aqueous sodium carbonate (10% w/v, 100cm³) and the ether layer removed. The aqueous layer was saturated with sodium chloride before extraction with ethyl acetate (3 x 100cm³). The combined organic extracts were dried (MgSO₄) and evaporated under reduced pressure but afforded none of the desired material.

N-Benzyl-2-bromoethylamine hydrobromide (291)

\[
\begin{align*}
290 & \quad \text{Ph} \quad \text{NH} \\
\quad \text{OH} & \quad \text{NH.HBr} \quad \text{Br} \\
\quad & \quad \text{Ph}
\end{align*}
\]

A mixture of N-benzylethanolamine 290 (5.00g, 33.1mmol) and aqueous HBr (48% w/v; 12cm³) was heated to 130°C for 4 h, during which time water (7cm³) was allowed to distill off. Upon cooling, a brown solid formed which was washed with ether / ethyl acetate (1:1 v/v; 50cm³) then DCM (50cm³) before drying under reduced pressure. The resultant off-white solid was shown to be a 3.9:1 mixture of the desired product 291 and N-benzylethanolamine 290 by ¹H NMR (2.30g of mixture corresponds to 1.83g of 291, 19%); δ H (CDCl₃; 400MHz) 3.27 (t, 2H, CH₂NH₂⁺, J 7.0Hz), 3.73 (t, 2H, CH₂Br, J 7.0Hz), 4.22 (s, 2H, NH₂CH₂Ph), 7.43 (m, 3H) & 7.53 (m, 2H, Ar-H); δ C (CDCl₃; 100MHz) 26.7 (CH₂Br), 47.6 & 50.0 (CH₂NH₂⁺CH₂Ph).
Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)

\[
\begin{array}{c}
\text{Ph} \\
\text{NH.HBr} \\
\text{Br}
\end{array} \xrightarrow{X} \begin{array}{c}
\text{Ph} \\
\text{NH} \\
\text{NH\textsubscript{OH}}
\end{array}
\]

291 289

A solution of N-benzyl-2-bromoethylamine hydrobromide 291 from the previous preparation (0.500g, 70% pure, ≈1.19mmol) in absolute ethanol (10cm\textsuperscript{3}) was treated with hydroxylamine hydrochloride (0.130g, 1.86mmol) and triethylamine (0.730cm\textsuperscript{3}, 5.24mmol). The solution was heated under reflux for 2 h before the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (SiO\textsubscript{2}, hexane:EtOAc 2:1 v/v) but none of the desired product was isolated. This procedure was repeated with overnight heating at reflux in THF, and in ethanol with 5 equivalents of hydroxylamine hydrochloride and 6 of triethylamine but without success.
Attempted preparation of O-benzyl-N-(2-benzylaminoethyl)hydroxylamine (292)

\[
\begin{align*}
\text{Ph} & \quad \text{NH. HBr} \\
\text{Br} & \quad \xrightarrow{X} \\
291 & \quad \text{NHOBn}
\end{align*}
\]

A solution of 291 from the preparation described above (0.500g, 70% pure, 1.18mmol), triethylamine (0.730cm³, 5.24mmol) and O-benzylhydroxylamine hydrochloride (0.280g, 1.86mmol) was treated as described in the attempted synthesis of 289 above. After 72 h of heating at reflux, none of the desired material was isolated. This procedure was repeated with DMF as the solvent, but without success.

N,O-Bis-tert-Butoxycarbonylhydroxylamine (293)

\[
\begin{align*}
\text{NH}_2\text{OH. HCl} & \quad \xrightarrow{\quad} \\
\text{HN} & \quad \text{Boc} \\
\text{O} & \quad \text{Boc}
\end{align*}
\]

According to the method of Whiting and Baillie,\textsuperscript{313} a mixture of hydroxylamine hydrochloride (2.00g, 28.8mmol) and sodium carbonate (5.17g, 37.4mmol) in water (20cm³) at 30°C was treated portionwise with di-tert-butyl dicarbonate (13.2g, 60.4mmol). After 2 h, the mixture was cooled to 20°C before stirring for 18 h. After extraction with toluene (3 x 30cm³), the organic phase was dried (MgSO₄), filtered and evaporated to yield
the title compound 293 as a white crystalline solid (3.61g, 54%), mp 66-67°C (lit., 67-71°C); δ_H (CDCl_3; 400MHz) 1.50 (s, 9H) & 1.52 (each s, 9H, 2 x C(CH_3)_3), 7.61 (br s, 1H, NH); δ_C (CDCl_3; 100MHz) 27.5 & 28.0 (2 x C(CH_3)_3), 83.1 & 85.4 (2 x C(CH_3)_3), 153.6 & 155.7 (2 x C=O); ν_max (KBr) /cm⁻¹ 3274, 1797, 1740, 1720, 1242, 1156, 1126; m/z 234 (MH⁺, 4%), 231 (12%), 172 (14%), 116 (100%), 72 (15%), 57 (8%).

Attempted preparation of N-(2-benzylaminoethyl)-N,O-bis-tert-butoxycarbonyl-hydroxylamine (294)

![Chemical structure](image)

A stirred solution of N,O-bis-tert-butoxycarbonylhydroxylamine 293 (0.710g, 3.04mmol) in DMF (15cm³) was treated with potassium carbonate (1.00g, 7.23mmol) and N-2-bromo-benzylethylamine hydrobromide 291 (1.00g, 70% pure, 2.36mmol). After 18 h at 20°C, the mixture was diluted with water and toluene (30cm³ each). The organic layer was separated, dried (MgSO_4) and filtered before evaporation under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane:EtOAc 4:1 v/v) but the title compound 294 was not isolated. It was possible to isolate and characterise three compounds from this reaction: recovered N,O-bis-tert-butoxycarbonylhydroxylamine 293 (0.480g, 67% of total quantity used), N-benzylaziridine 295 (0.130g, 42% based on bromide used)
and 3-benzyl-2-oxazolidinone 296 (0.120g, 28% based on bromide); 3-Benzyl-2-oxazolidinone 296: $\delta_H$ (CDCl$_3$; 400MHz) 3.42 (t, 2H, $J$ 8.0Hz, CH$_2$O), 4.31 (t, 2H, $J$ 8.0Hz, CH$_2$NCH$_2$Ph), 4.43 (s, 2H, NCH$_2$Ph), 7.27-7.36 (m, 5H, Ar-H); $\delta_C$ (CDCl$_3$; 100MHz) 43.8 (CH$_2$NCH$_2$Ph), 48.2 (CH$_2$O), 61.6 (NCH$_2$Ph), 127.8, 127.9 & 129.0 (Ar-CH), 135.6 (Ar-C), 158.4 (C=O); $m/z$ 177 (M+, 31%), 176 (30%), 132 (15%), 105 (26%), 104 (100%), 91 (99%); Benzylaziridine 285; the isolated material had data consistent with that for an independently prepared sample described in a following procedure.

The above method was used with THF as the solvent in place of DMF, but without success. This was combined with replacement of the potassium carbonate by sodium hydride, but none of the desired material was observed.

---

**Attempted preparation of N-benzyl-2-bromo-N-tert-butoxycarbonylethylamine (297)**

A stirred solution of N-benzyl-2-bromoethylamine hydrobromide 291 from the earlier preparation (1.00g, 50% pure, 0.560g of 291, 1.90mmol) in water (20cm$^3$) was treated with sodium carbonate (1.72g, 16.2mmol) and di-tert-butyl dicarbonate (2.50g, 7.12mmol) and stirred for 48h at room temperature. The solution was extracted with toluene (3 x 30cm$^3$), dried (MgSO$_4$), filtered and evaporated to dryness under reduced pressure.
before purification of the residue by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).
The only isolated materials were recovered di-tert-butyl dicarbonate (20% of initial quantity) and 3-benzyl-2-oxazolidinone 296 (30% based on bromo amine 291).

N-Benzylaziridine (295)

A solution of N-benzylethanolamine 290 (2.00g, 13.2mmol) in toluene (30cm³) was treated with sulfur trioxide-trimethylamine complex (2.20g, 15.8mmol) and the mixture heated under reflux for 2 h. After cooling to 60°C and addition of aqueous NaOH (10M; 5cm³), the solution was heated under reflux for a further 2 h. The cooled solution was then washed with water (30cm³) and the organic phase dried (MgSO₄), filtered and evaporated under reduced pressure to give the title compound 295 as a clear oil (0.500g, 30%). This material was further purified by distillation, bp 64°C, 6mmHg, lit. 331 80-82°C, 10mmHg; δH (CDCl₃; 400MHz) 1.30 & 1.85 (each m*, 2H, CH₂CH₂), 3.40 (s, 2H, NCH₂Ph), 7.26-7.38 (m, 5H, Ar-H), δC (CDCl₃; 400MHz) 27.5 (CH₂CH₂), 65.3 (NCH₂Ph), 127.0, 128.0, 128.3 (Ar-CH), 139.3 (Ar-C).); [m*: The ring protons are "triplets" with inverted peak ratios, i.e. 2:1:2³³³³-³³³³].
Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)

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

According to the reported procedures\(^{314,315}\) a mixture of hydroxylamine hydrochloride (0.130 g, 1.88 mmol), triethylamine (0.260 cm\(^3\), 1.88 cm\(^3\)) and ammonium chloride (5.0 mg, 93.5 µmol) in methanol (2 cm\(^3\)) was treated with N-benzylaziridine 295 (0.250 g, 1.88 mmol) and stirred vigorously for 18 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.

N-Methylaziridine (301)

\[
\begin{align*}
\text{CH}_3 & \quad \text{N} \\
\text{NH} & \quad \text{CH}_3
\end{align*}
\]

To stirred N-methylethanolamine (5.00 g, 66.6 mmol) was added chlorosulfonic acid (4.43 cm\(^3\), 66.6 mmol) at 0°C with violent evolution of gas. The resultant viscous oil was heated to 150°C under vacuum (20 mmHg) for 2 h. The residue was cooled to 20°C and dissolved in water (10 cm\(^3\)) before addition of aqueous KOH (20 M; 20 cm\(^3\)). The solution was heated to 100°C to distill off a clear oil consisting of a 1:1 mixture of N-
methylethanolamine and the title compound 301, bp 82-86°C (lit., 332 24-25°C); δ\textsubscript{H} (CDCl\textsubscript{3}; 400MHz) 1.03 & 1.70 (each m\textsuperscript{*}, 2H, CH\textsubscript{2}CH\textsubscript{2}NCH\textsubscript{3}), 2.27 (d, 3H, NCH\textsubscript{3}); δ\textsubscript{C} (CDCl\textsubscript{3}; 400MHz) 28.4 (CH\textsubscript{2}CH\textsubscript{2}NCH\textsubscript{3}), 48.3 (NCH\textsubscript{3}); [m\textsuperscript{*} : The ring protons are "triplets" with inverted peak ratios, i.e. 2:1:2\textsuperscript{332-334}].

Attempted preparation of N-(2-methylaminoethyl)hydroxylamine (302a)

![Diagram of 301 and 302a](image)

A mixture of hydroxylamine hydrochloride (0.500g, 7.20mmol), triethylamine (1.01cm\textsuperscript{3}, 7.25mmol) and ammonium chloride (8.0mg, 0.150mmol) in methanol (5cm\textsuperscript{3}) was treated with N-methylaziridine 301 (0.180g, 3.15mmol) and the mixture stirred vigorously for 18 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.
Attempted preparation of O-benzyl-N-(2-methylaminoethyl)hydroxylamine (302b)

\[
\begin{align*}
\text{CH}_3 & \quad \text{CNH} \\
\text{N-CH}_3 & \quad X \\
\text{NHOBn} & \quad \text{302b}
\end{align*}
\]

A mixture of O-benzylhydroxylamine hydrochloride (2.79g, 17.5mmol), triethylamine (2.44cm\(^3\), 17.5mmol) and ammonium chloride (47.0mg, 0.879mmol) in methanol (10cm\(^3\)) was treated with N-methylaziridine 301 (1.00g, 17.5mmol) and the mixture stirred vigorously for 48 h. The solvent was evaporated under reduced pressure to give an intractable mixture of unidentifiable products.

N-Benzyl-N-tert-butoxycarbonylglycine ethyl ester (305)

\[
\begin{align*}
\text{CO}_2\text{Et} & \quad \text{NH} \\
\text{Ph} & \quad \text{304} \\
\text{CO}_2\text{Et} & \quad \text{N-Boc} \\
\text{Ph} & \quad \text{305}
\end{align*}
\]

A stirred solution of N-benzylglycine ethyl ester 304 (5.00g, 25.9mmol) in DCM (100cm\(^3\)) at 0°C under an atmosphere of nitrogen was treated with triethylamine (7.20cm\(^3\), 51.8mmol) and a solution of di-tert-butyl dicarbonate (6.20g, 28.5mmol) in DCM (50cm\(^3\)). After warming to 20°C overnight, the solution was washed with aqueous citric acid (1M; 5 x
20cm\textsuperscript{3}) and the organic phase dried (MgSO\textsubscript{4}), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (SiO\textsubscript{2}, hexane:EtOAc 1:1 v/v) to afford the title compound 305 as a white solid (5.80g, 76%) which was seen to exist as a pair of carbamate rotamers by NMR; $\delta$\textsubscript{H} (CDCl\textsubscript{3}; 400MHz) 1.26 (m, 6H, 2 x OCH\textsubscript{2}CH\textsubscript{3}), 1.48 (2 x br s, 18H, C(CH\textsubscript{3})\textsubscript{3}), 3.78 & 3.92 (each s, 2H, 2 x NCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 4.18 (m, 4H, 2 x OCH\textsubscript{2}CH\textsubscript{3}), 4.52 & 4.55 (each s, 2H, 2 x NCH\textsubscript{2}Ph), 7.22-7.35 (m, 20H, Ar-H); $\delta$\textsubscript{C} (CDCl\textsubscript{3}; 100MHz) 14.1 & 14.2 (OCH\textsubscript{2}CH\textsubscript{3}), 28.2 & 28.3 (C(CH\textsubscript{3})\textsubscript{3}), 47.7 & 48.1, 51.0 & 51.5 (NCH\textsubscript{2}CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3} & NCH\textsubscript{2}Ph), 60.9 & 61.0 (OCH\textsubscript{2}CH\textsubscript{3}), 80.4 & 80.6 (C(CH\textsubscript{3})\textsubscript{3}), 2 x 127.4, 127.5, 128.1, 2 x 128.5 (Ar-CH), 137.6 & 137.3 (Ar-C), 155.6 & 155.8 (NC=O), 169.9 & 170.0 (CO\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}).

N-Benzyl-N-tert-butoxycarbonylglycinal (303)

![N-Benzyl-N-tert-butoxycarbonylglycinal (303)]

A solution of N-benzyl-N-tert-butoxycarbonylglycine ethyl ester 305 (3.29g, 11.2mmol) in anhydrous toluene (80cm\textsuperscript{3}) at -78°C was treated with DIBAL (1M soln. in toluene, 28.0cm\textsuperscript{3}, 28.0mmol) over 25 min. After 1.5 h the reaction was quenched with methanol (10cm\textsuperscript{3}) and poured into a solution of Rochelle's salt (potassium sodium tartrate tetrahydrate) (215g, 0.719mol) in water (500cm\textsuperscript{3}) along with a little toluene present to maintain stirring of the thick emulsion that formed. After vigorous stirring for 1.5 h, two
separate phases had formed. The organic phase was separated and the aqueous further extracted with ether (3 x 150 cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated to dryness under reduced pressure. Column chromatography of the residue gave the title compound 303 as a clear, mobile oil (2.30 g, 82%) containing a mixture of carbamate rotamers; δ_H (CDCl₃; 400 MHz) 1.46 & 1.49 (each s, 9H, 2 x C(CH₃)₃), 3.79 & 3.83 (each s, 2H, 2 x NCH₂CHO), 3.49 & 3.52 (each s, 2H, 2 x NCH₂Ph), 7.18-7.35 (m, 20H, Ar-H), 9.40 & 9.50 (each s, 1H, 2 x CHO); δ_C (CDCl₃; 400 MHz) 28.2 & 28.3 (C(CH₃)₃), 51.5, 52.0, 56.4 x 2 (2 x NCH₂CHO & 2 x NCH₂Ph), 81.1 (2 x C(CH₃)₃), 127.6, 127.7, 127.8, 128.1, 128.6 & 128.8 (Ar-CH), 137.1 & 137.3 (Ar-C), 198.8 & 198.9 (2 x CHO); m/z 250 (MH⁺, 18%), 220 (33%), 194 (100%), 164 (28%), 150 (41%), 120 (49%), 91 (100%), 57 (99%).

N-Benzyl-N-tert-butoxycarbonylglycinaldoxime (306)

A solution of sodium acetate (6.80 g, 82.9 mmol) and hydroxylamine hydrochloride (3.40 g, 48.9 mmol) in a mixture of water (20 cm³) and ethanol (10 cm³) was added to N-benzyl-N-tert-butoxycarbonylglycin 303 (1.70 g, 6.82 mmol) and heated to 60°C for 2 h with vigorous stirring. The solution was cooled to 20°C and extracted with DCM (3 x 150 cm³). The organics were dried (MgSO₄), filtered, evaporated under reduced pressure and
the residue purified by column chromatography (SiO₂, hex:EtOAc 4:1 v/v) to afford the title compound 306 as a white solid (0.885g, 49%) tentatively assigned as a mixture of oxime isomers and carbamate rotamers; δₜ (d₆-DMSO; 400MHz) 1.40 (br s, 9H, C(CH₃)₃), 3.79, 3.86, 3.92 & 3.97 (each br s, 0.5H, NCH₂C=NOH), 4.35 & 4.40 (each s, 1H, NCH₂Ph), 7.20-7.36 (Ar-H); δₑ (CDCl₃; 100MHz) 28.2, 28.4 & 2 x 28.6 (C(CH₃)₃), 42.1, 42.3, 44.9, 45.1, 49.8, 50.1, 51.1 & 51.7 (NCH₂C=NOH & NCH₂Ph), 80.7 (C(CH₃)₃), 127.4, 127.5, 128.8, 128.0, 128.4, 2 x 128.6, 2 x & 128.9 (Ar-CH), 137.6 (Ar-C), 147.5 & 147.8 (CH=NOH), 150.2, 150.5, 150.7, 155.5 & 155.6 (C=O); m/z 265 (MH, 3%), 209 (37%), 191 (16%), 165 (38%), 163 (22%), 150 (60%), 147 (57%), 120 (30%), 106 (64%), 91 (100%).

Attempted preparation of N-(2-benzylaminoethyl)hydroxylamine (289)

A solution of N-benzyl-N-tert-butoxycarbonylglycinaldoxime 306 (0.100g, 0.378mmol) in anhydrous THF (5cm³) was treated with borane-THF complex (1M solution in THF, 0.760cm³, 0.760mmol) at 20°C with stirring under an atmosphere of nitrogen. After 60 h, aqueous HCl (6M; 5cm³) was added dropwise with much evolution of gas and the solution stirred for a further hour before the solution was basified with solid KOH and extracted with DCM (3 x 30cm³). The organics were then dried (MgSO₄), filtered and
evaporated under reduced pressure to give a colourless film (40mg) from which none of the desired product could be identified.

**Attempted preparation of N-benzyl-N-tert-butoxycarbonylglycinal O-acetyloxime (307)**

A solution of N-benzyl-N-tert-butoxycarbonylglycinaldoxime 306 (0.480g, 1.82mmol) in pyridine (2cm³) was treated dropwise with acetyl chloride (0.140cm³, 2.00mmol) at 0°C and warmed to 20°C overnight. The solution was partitioned between ether (20cm³) and aqueous citric acid (1M; 20cm³) and the aqueous extracted with further ether (2 x 30cm³). The combined organic extracts were dried (MgSO₄), filtered and evaporated under reduced pressure to afford a yellow oil which did not yield the title compound after purification by column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).
Attempted preparation of N-benzyl-N-tert-butoxycarbonylglycinal O-benzylhydroxylamine hydrochloride (308)

According to the procedure described for the preparation of 306 above, aldehyde 303 (0.650g, 2.61mmol), O-benzylhydroxylamine hydrochloride (0.460g, 2.87mmol), sodium acetate (1.00g, 12.2mmol) and aqueous ethanol (1:1 v/v, 10cm³) were used in an attempt to synthesise 308. However, after 18 h at 65°C, the crude reaction mixture did not afford the title compound after column chromatography (SiO₂, hexane:EtOAc 9:1 v/v).
References


256


Appendix I

X-ray crystallographic data
Empirical formula | C\textsubscript{17}H\textsubscript{24}N\textsubscript{2}O\textsubscript{4}  
Formula weight | 396.43  
Temperature | 293 (2) K  
Wavelength | 1.54178 Å  
Crystal system | Orthorhombic  
Space group | Pbca  
Unit cell dimensions | 
\begin{align*}
a &= 11.344 (2) \text{ Å} \\
b &= 11.341 (2) \text{ Å} \\
c &= 33.051 (7) \text{ Å}
\end{align*}  
Volume | 4252.1 (14) Å\textsuperscript{3}  
Z | 8  
Density (calculated) | 1.239 Mg/m\textsuperscript{3}  
Absorption coefficient | 0.726 mm\textsuperscript{-1}  
F (000) | 1680  
Crystal size | 0.2 x 0.2 x 0.3 mm  
\( \theta \) range for data collection | 4.73 to 55.00\(^{\circ}\)  
Index ranges | 
\begin{align*}
-14 \leq h \leq 0, & -14 \leq k \leq 0, \quad -41 \leq l \leq 0
\end{align*}  
Reflections collected | 2637  
Independent reflections | 2637 \([R_{int} = 0.0000]\)  
Refinement method | Full-matrix least-squares on \(F^2\)  
Data / restraints / parameters | 2635 / 0 / 264  
Goodness-of-fit on \(F^2\) | 0.984  
Final R indices \([I>2\sigma (I)]\) | \(R1 = 0.494,\ wR2 = 0.1296\)  
R indices (all data) | \(R1 = 0.950,\ wR2 = 0.1532\)  
Largest diff. peak and hole | 0.194 and -0.198 e.Å\textsuperscript{3}  

Crystal data and structure refinement for 227.
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{26}$H$</em>{24}$N$_2$O$_3$S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>420.51</td>
</tr>
<tr>
<td>Temperature</td>
<td>150 (2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>$C2/c$</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 33.5981 (12) Å  $\alpha = 90^\circ$</td>
</tr>
<tr>
<td></td>
<td>b = 14.6601 (5) Å  $\beta = 93.701 (2)^\circ$</td>
</tr>
<tr>
<td></td>
<td>c = 8.5981 (3) Å  $\gamma = 90^\circ$</td>
</tr>
<tr>
<td>Volume</td>
<td>4226.2 (3) Å$^3$</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.322 Mg/m$^3$</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.182 mm$^{-1}$</td>
</tr>
<tr>
<td>F (000)</td>
<td>1776</td>
</tr>
<tr>
<td>Crystal / size</td>
<td>Prism, colourless / 0.6 x 0.075 x 0.075 mm</td>
</tr>
<tr>
<td>$\theta$ range for data collection</td>
<td>2.78 to 25.99$^\circ$</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-41 $\leq$ h $\leq$ 41, -15 $\leq$ k $\leq$ 18, -10 $\leq$ l $\leq$ 10</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>19011 / 4160 [R$_m$ = 0.0779]</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F$^2$</td>
</tr>
<tr>
<td>Completeness to $\theta = 25.99^\circ$</td>
<td>96.5%</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>4160 / 0 / 368</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>0.995</td>
</tr>
<tr>
<td>Final R indices [I&gt;2$\sigma$(I)]</td>
<td>R1 = 0.0427, wR2 = 0.0963</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0861, wR2 = 0.1044</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.0008 (3)</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.253 and -0.368 eÅ$^3$</td>
</tr>
</tbody>
</table>

Crystal data and structure refinement for 241.
<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C₂H₃N₃O₄</td>
</tr>
<tr>
<td>Formula weight</td>
<td>366.41</td>
</tr>
<tr>
<td>Temperature</td>
<td>150 (2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 5.7560 (10) Å α = 85.58 (2)°</td>
</tr>
<tr>
<td></td>
<td>b = 11.341 (2) Å β = 84.21 (2)°</td>
</tr>
<tr>
<td></td>
<td>c = 33.051 (7) Å γ = 81.91 (2)°</td>
</tr>
<tr>
<td>Volume</td>
<td>935.9 (3) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.300 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.091 mm⁻¹</td>
</tr>
<tr>
<td>F (000)</td>
<td>388</td>
</tr>
<tr>
<td>Crystal size</td>
<td>0.6 x 0.075 x 0.075 mm</td>
</tr>
<tr>
<td>θ range for data collection</td>
<td>41.94 to 26.00°</td>
</tr>
<tr>
<td>Limiting indices</td>
<td>-7 ≤ h ≤ 7, -13 ≤ k ≤ 13, -19 ≤ l ≤ 19</td>
</tr>
<tr>
<td>Reflections collected / unique</td>
<td>11704 / 3535 [Rint = 0.0756]</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on F²</td>
</tr>
<tr>
<td>Completeness to θ = 26.00°</td>
<td>96.5%</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>3535 / 0 / 246</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.880</td>
</tr>
<tr>
<td>Final R indices [I&gt;2σ (I)]</td>
<td>R1 = 0.0499, wR2 = 0.1207</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0861, wR2 = 0.1465</td>
</tr>
<tr>
<td>Largest diff. peak and hole</td>
<td>0.223 and -0.306 e.Å³</td>
</tr>
</tbody>
</table>

Crystal data and structure refinement for 265.
Appendix II

HPLC conditions
HPLC Instrumentation and Conditions

Compounds 208, 140a, 126a and 126b were analysed using a Varian Vista Series 5000 Liquid Chromatograph, with a Kratos Spectraflow 757 Absorbance Detector and Chromjet Integrator. The column used was a Waters Symmetry C18 (internal dimensions 25cm x 4.6mm). The injection loop was 20µl and was filled with the sample solution (1 drop of reaction mixture in 4cm³ of eluent A). Eluent A: 9:1 water:acetonitrile + 0.1% TFA (v/v). Eluent B: 1:9 water:acetonitrile + 0.1% TFA (v/v). Gradient elution was employed, with initial eluent 100% A, raising to 90% B after 15 minutes and maintaining this eluent composition for a further 10 minutes. The flow rate throughout was 1cm³ per minute.

Compounds 165 and 187b were isolated by preparative HPLC using a Waters Delta Prep 3000 instrument and Phenomenex Luna 10 C₁₈ (2) column (internal dimensions 25cm x 21mm). The eluent was acetonitrile:water (2:1 v/v), which was removed under reduced pressure to afford the pure compounds.