Studies Towards a Biomimetic Synthesis of Agelastatin A

By

Nicola Jane White

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Christopher Ingold Laboratories
Department of Chemistry
University College London
London WC1H 0AJ
UMI Number: U602799

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This thesis is dedicated to my family
for their endless support and encouragement
"The search for truth is more precious than its possession."

Albert Einstein
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Abstract

Agelastatin A is a tetracyclic alkaloid isolated from the marine sponge Agelas dendromorpha. It exhibits cytotoxicity towards KB and lymphocytic leukaemia cells, arthropod toxicity and insecticidal activity and selectively inhibition of glycogen synthase kinase-3β. Agelastatin A is one of a structurally related group of pyrrole-imidazole alkaloids derived from the “linear” skeleton of oroidin and it is postulated that it is biologically derived from oroidin via the generation of an N-acyliminium ion, which undergoes two cyclisations, via a second N-acyliminium ion, followed by hydration to afford the natural product.

This thesis describes the work undertaken towards the biomimetic synthesis of Agelastatin A and efforts towards the synthesis of an oroidin-like precursor from which the N-acyliminium ion could be generated. Disconnection of the precursor gave a 3-pyrroline A-ring, which was prepared using a Birch reduction, but efforts to synthesise the D-ring imidazolone fragment were hampered by low solubility, necessitating the use of protecting groups. Selective introduction of the Z-alkene was made difficult by conjugation to the imidazolone and efforts to maintain the Z-alkene geometry failed.

Parikh-Doering oxidation of a propargylic alcohol intermediate afforded a novel β-thioaldehyde that underwent an acid-catalysed cyclisation via an N-acyliminium ion analogous to the second N-acyliminium ion in the proposed biomimetic synthesis. The β-thioaldehyde forced the required alkene conformation and was therefore applied in the synthetic route to the imidazolone fragment. The introduction of a leaving group was ultimately unsuccessful, but a precursor for generation of the ion by oxidation was prepared by reductive amination of the corresponding aldehyde.

The precursor was treated with trityl tetrafluoroborate but the expected oxidation did not occur, instead an acid–catalysed cyclisation was observed. This cyclisation again proceeded via an N-acyliminium ion analogous to that predicted to be generated in the biomimetic synthesis, to afford a novel bicycle.

Therefore although the double cyclisation required for the biomimetic synthesis was not mimicked, the two novel cyclisations provide good evidence that both cyclisations are plausible.
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### Abbreviations

<table>
<thead>
<tr>
<th>Ac</th>
<th>acetyl</th>
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<tbody>
<tr>
<td>Acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>AIBN</td>
<td>2,2'-azobisobutyronitrile</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BMEA</td>
<td>bis-2-methoxyethylamine</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butoxycarbonyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>tBu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>CDK</td>
<td>cyclin dependent kinase</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
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<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
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<td>dicyclohexylcarbodiimide</td>
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<td>dichloromethane</td>
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<tr>
<td>DBMP</td>
<td>2,6-di-tert-butyl-4-methylpyridine</td>
</tr>
<tr>
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<td>dichlorodicyanoquinone</td>
</tr>
<tr>
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<td>DIPEA</td>
<td>diisopropylethylamine</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
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<td>DMP</td>
<td>Dess Martin periodinane</td>
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<tr>
<td>DME</td>
<td>1,2-dimethoxyethane</td>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
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<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>d.r.</td>
<td>diastereomeric ratio</td>
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<tr>
<td>EDCI</td>
<td>1-ethyl-3-(3-dimethylaminopropyl)carbodiimide</td>
</tr>
<tr>
<td>Et</td>
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<tr>
<td>GSK</td>
<td>glycogen synthase kinase</td>
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<td>HBTU</td>
<td>O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate</td>
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<tr>
<td>HMPT</td>
<td>hexamethyolphosphorous triamide</td>
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<td>hv</td>
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<tr>
<td>IBX</td>
<td>1-hydroxy-1,2-benziodoxolin-3(1H)-one</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>mCPBA</td>
<td>meta-chloroperbenzoic acid</td>
</tr>
<tr>
<td>MSA</td>
<td>methane sulfonic acid</td>
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<td>Me</td>
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<td>nucleophile</td>
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<td>PDC</td>
<td>pyridinium dichromate</td>
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</tr>
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<td>PMB</td>
<td>para-methoxybenzyl</td>
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<td>parts per million</td>
</tr>
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<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>py</td>
<td>pyridine</td>
</tr>
<tr>
<td>pyBOP</td>
<td>benzotriazol-1-yl-oxytritypyrrolidinophosphonium hexafluorophosphate</td>
</tr>
<tr>
<td>SES</td>
<td>2-[(trimethylsilyl)ethyl]sulfonyl</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutyl ammonium fluoride</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butylhydroperoxide</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Tf</td>
<td>triflate</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>Tol</td>
<td>p-tolyl</td>
</tr>
<tr>
<td>Ts</td>
<td>tosyl</td>
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CHAPTER I

INTRODUCTION

1.1 Pyrrole-Imidazole Alkaloids

The pyrrole-imidazole alkaloids are a structurally related group of natural products. They contain both a pyrrole-2-carboxamide moiety, which can be brominated, and an imidazole derived moiety, which can vary in its oxidation and hydrolysis state. Many pyrrole-imidazole alkaloids have been isolated from marine organisms and they are of interest due to their structural diversity and biological activity. These alkaloids are exclusively elaborated by the secondary metabolism of marine sponges of the geni *Agelas*, *Axinella* and *Halichondria*, and more than 90 pyrrole-imidazole alkaloids have now been isolated.¹,²

The structures of the various pyrrole-imidazole alkaloids can be conceived to be derivatives of oroidin 1, an alkaloid first isolated in 1971 from the marine sponge *Agelas oroides* in the Bay of Naples³, and more recently from other sponges.⁴⁻⁸

![Oroidin](image)

This basic “building block” deters predation by the reef fish *Thalassoma bifasciatum*.⁹ As the biosynthesis of the more complex pyrrole-imidazole alkaloids consumes vital amino acids, this must have some evolutionary advantage and the secondary metabolites must therefore have important biological properties. The precise roles of many of the more complex pyrrole-imidazole alkaloids have yet to be determined, although some are known to exhibit chemical defence properties. These include a range of interesting biological activities, such as protection of sponges from bacteria,⁹ viruses,¹¹ and inhibition of barnacle larvae metamorphosis.⁸
1.2 Structural Variations

Many alkaloids exhibiting variations on the oroidin structure have been isolated from marine sponges. These include variations on the carbon chain link between the pyrrole amide and imidazole moieties, dimerisation of the oroidin structure, and a series of interesting cyclised structures. The 2-amino-4(5)vinylimidazole unit can vary with respect to its oxidation or hydrolysis state. Bromination is frequently observed in marine alkaloids as bromide anions from seawater can be catalytically oxidised by haloperoxidases, and subsequent alkaloid bromination effected by a series of specific halogenases. The pyrrole-2-carboxamide moiety in the pyrrole-imidazole alkaloids can be non-, mono- or dibrominated at the 4 or 5 positions, but no bromination at the 3-position has been observed.

1.2.1 Non Cyclised Structures

![Chemical structures](image)

1 Oroidin R=Br  
2 Clathrodin R=H  
3 Keramidine  
4 Midpacamide  
5 Mukanadin A  
6 Dispacamide A: R=Br  
7 Dispacamide B: R=H  
8 Dispacamide C: R=Br  
9 Dispacamide D: R=H  
10 Clathramide A  
11 Tauroacidin A: R=OH  
12 Taurodispacamide: R=H
There are many examples of pyrrole-imidazole alkaloids with structures linearly related to oroidin, but with no further cyclisations. These include clathrodi\textsuperscript{13} 2, which is simply the debrominated analogue of oroidin. Other variations on the oroidin structure include keramidine\textsuperscript{14} 3, which contains a (Z)-olefin, and midpacamide\textsuperscript{15} 4 where pyrrole nitrogen methylation is observed along with oxidation of the imidazole ring. Mukananin A\textsuperscript{16} 5 and the dispamacides\textsuperscript{4, 17} 6, 7, 8 and 9 also exhibit variations on the imidazole ring and a shift in position of the olefin in the carbon chain linking the pyrrole and imidazole moieties.

Oxidation along the linking chain is found in dispamacides C\textsuperscript{8} and D\textsuperscript{9} 4 and clathramide A\textsuperscript{18} 10 contains a carboxylate group attached to this chain. Interestingly, the chain linking the pyrrole and imidazole units is one carbon shorter in clathramide A than in the other linear structures. It appears that the "missing" carbon has migrated onto the imidazole ring and formed a quaternary centre. Finally, tauroacidin A\textsuperscript{19} 11 and taurodispacamide\textsuperscript{20, 21} 12 have a taurine residue attached to the imidazole ring.

"Linear" oroidin derivatives are often isolated in high amounts from marine sponges, for example dispamacides A\textsuperscript{6} and B\textsuperscript{7} were found in 1-5% of the butanolic extracts from four Caribbean Agelas species: A. dispar, A. clathrodes, A. longissima, and A. conifera.\textsuperscript{17} This suggests a pivotal role for the linear alkaloids, possibly as progenitors for biosynthesis of other, more complex structures.

1.2.2 Dimerised Structures

Six different modes of dimerisation of the uncyclised oroidin skeleton have been observed. The natural products sceptrin\textsuperscript{22} 13 and ageliferin\textsuperscript{23} 14 exhibit dimerisation through bond formation between of the carbon chains linking the pyrrole and imidazole moieties, formally the products of $[2\pi+2\pi]$ and $[4\pi+2\pi]$ cycloaditions respectively. The structure of mauritiamine\textsuperscript{8} 15 dimerises through a link between the imidazole moieties of two oroidin-like fragments. The axinellamine\textsuperscript{24} 16 structure exhibits three separate links between the two subunits forming a highly functionalised tetracyclic core. Massadine\textsuperscript{25} 17 also exhibits three links between the two subunits, but an oxidation has occurred to introduce a tetrahydroxyran ring in the tetracyclic core.
The alkaloid archerine\textsuperscript{26} \textbf{18} exhibits dimerisation of the 2-amino-4(5)-(3-aminopropenyl)-portion of the oroidin, but lacks the pyrrole part. These dimerised alkaloids display a broad range of biological activities including antifouling activity,\textsuperscript{8} blocking of \(\alpha\)-adrenoceptors,\textsuperscript{27} activation of ATPase\textsuperscript{23} and antihistaminic activity.\textsuperscript{26} No pyrrole-imidazole alkaloids assembled from three or more subunits have yet been discovered.

\subsection*{1.2.3 Cyclised Structures}

This particularly interesting group of alkaloids occurs as a result of one or more cyclisations of the oroidin skeleton, to form tricyclic or tetracyclic structures. Six cyclisation modes\textsuperscript{20} have so far been observed through the isolation of natural products and these can be classified based on the oroidin atoms involved in the linkage formation. Many of the cyclisation modes exhibit structural variations based on a common cyclised skeleton, including variations of the imidazole moiety and bromination of the pyrrole ring.

\subsubsection*{1.2.3.1 Tricyclic Structures}

\begin{itemize}
\item \textbf{19} Cycloooroidin
\item \textbf{20} Hymenialdisine
\item \textbf{21} (\(E\))-3-bromohymenialdisine
\item \textbf{22} Stevensine
\item \textbf{23} Hymenin
\item \textbf{24} Slagenin A
\end{itemize}

Three cyclisation modes of the oroidin skeleton result in tricyclic pyrrole-imidazole alkaloid structures. Cycloooroidin\textsuperscript{20} \textbf{19} is so far the only pyrrole-imidazole alkaloid
isolated with the N1/C9 cyclisation mode, although related structural fragments which exhibit this cyclisation mode but which do not contain the pyrrole moiety have been isolated, including longamide\textsuperscript{28} and hanishin\textsuperscript{7}, which are discussed later. The C4/C10 cyclisation mode results in a 7-membered cyclic lactam fused to the pyrrole ring. The basic C4/C10 cyclisation skeleton exhibits a number of structural variations, including the inclusion of a double bond, which can be located in either the 7-membered lactam, as in the structure of stevensine\textsuperscript{29} \textsuperscript{22}, or in the carbon-carbon bridge between this ring and the imidazole moiety, exhibited in the structure of hymenialdisine\textsuperscript{5} \textsuperscript{20}. The pyrrole ring can be either mono- or di brominated.

The tricyclic structure of slagenin A\textsuperscript{30} \textsuperscript{24}, exhibits a simple oxidation/cyclisation mode of the oroidin skeleton, where a tetrahydrofuran ring has been introduced between C12 and C9 of the imidazolone and the carbon chain linking the pyrrole and imidazole moieties. This structure is proposed to result from oxidation of oroidin via an intermediate related to the linear alkaloid mukanadin\textsuperscript{31} \textsuperscript{5}.

\textbf{1.2.3.2 Tetracyclic Structures}

![Diagram of tetracyclic structures](image-url)
The oroidin skeleton can also undergo two cyclisations to form tetracyclic pyrrole-imidazole alkaloids. Four different tetracyclic structures are known, again classified by the linkages formed between the oroidin atoms. The pyrrole nitrogen can be linked either through nitrogen, as seen in dibromoagelasponge 25, or through the C3 carbon atom, as in the structure of dibromisophakellin 27. Both mono-and dibromination of the pyrrole ring have been observed.

The N1/C9 and C8/C12 cyclisation mode is of particular interest as this forms the tetracyclic structure of the agelastatins.

1.2.3.3 Hexacyclic Structures

The most complex pyrrole-imidazole alkaloids isolated are represented by the hexacyclic palau’amine 29 and styloguanidine 30. These are based on the tetracyclic cyclisation modes exhibited by dibromophakellin 26 and dibromoisophakellin 27 respectively with the addition of a further imidazole unit via intermolecular cyclisation to form the E-ring.

![Palau’amine and Styloguanidine structures](image)

Palau’amine and styloguanidine are current targets for total synthesis owing to their unprecedented hexacyclic bisguanidine structure, and although the core structure has been prepared, a total synthesis of either of these structures has yet to be published.

The cyclised pyrrole-imidazole alkaloids also have a broad range of biological activities, including inhibition of nuclear transcription factors, inhibition of cyclin-dependent kinases, and immunomodulatory activity.
1.2.4 Oroidin Fragments

In addition to alkaloids containing the complete building block of oroidin, several metabolites that are possible fragments of the oroidin structure have been isolated. These include brominated pyrrole ring fragments 31-36,\textsuperscript{3, 7, 39-41} the brominated maleimides 37 and 38,\textsuperscript{21} imidazole derived 3-amino-1-(2aminoimidazolyl)-prop-1-ene 39,\textsuperscript{39} and girolline 40.\textsuperscript{21} Cyclised structures containing only the bromopyrrole moiety (the longamides 41 and 45,\textsuperscript{18, 28, 40, 42} mukanadin 42,\textsuperscript{16} the hanishin esters 43 and 44,\textsuperscript{7, 41} and agelongine 48\textsuperscript{4} and N-methylmazacidin C 47\textsuperscript{21} have also been isolated.

\begin{align*}
31: R &= \text{CO}_2\text{H}, 32: R = \text{CO}_2\text{CH}_3, \\
33: R &= \text{CN} \\
34: R &= \text{Br}, 35: R = \text{H} \\
36: R &= \text{OCH}_3 \\
37: R &= \text{Br}, 38: R = \text{H} \\
39: R &= \text{NH}_2 \\
40: \text{Girolline} \\
41: \text{Longamide R} &= \text{Br} \\
42: \text{Mukanadin C} R &= \text{H} \\
43: \text{Hanishin} R &= \text{Et} \\
44: R &= \text{Me} \\
45: \text{Longamide B} R &= \text{OH} \\
46: \text{Ugibohlin} \\
47: \text{N-methylmazacidin C} \\
48: \text{Aelongine}
\end{align*}

Ugibohlin 46 was isolated from the marine sponge \textit{Axinella carteri} along with dibromoisophakellin 27.\textsuperscript{43} Elimination of dibromoisophakellin could potentially be affected by treatment with acid, and as trifluoroacetic acid was utilised in the extraction,
ugibohlin 46 could be an artefact of the extraction process rather than a true natural product. However it could potentially be a biosynthetic precursor of dibromoisophakellin. Other fragments that could also be artefacts of the extraction process rather than true natural products include the hanishin esters 43 and 44, especially as alcoholic solvents were utilised in the extraction process.
1.3 The Agelastatins

Agelastatin A 28 is a tetracyclic marine alkaloid first isolated in 1993 from the deep water marine sponge *Agelas dendromorpha* of the Coral Sea near New Caledonia.\(^{44}\) Agelastatin A has been assigned the absolute configuration shown by a combination of molecular mechanics calculations and exciton splitting techniques.\(^{45}\) In *Agelas dendromorpha* it is accompanied by a small amount of the 2,3-dibrominated analogue agelastatin B 49 and the two analogues are inseparable when extracted from the sponge.

Agelastatins C 50 and D 51 have also been isolated, along with agelastatin A, from the Western Australian marine sponge *Cymbastela sp.*\(^{46}\) Agelastatin C differs from A in that it bears an additional hydroxyl group at C-5b, and agelastatin D is simply the N-demethylated analogue of agelastatin A.

Agelastatin A exhibits marked cytotoxicity towards KB cells (EC\(_{50} = 0.5\mu g\) mL\(^{-1}\)) and L1210 cells (IC\(_{50} = 33\) ng mL\(^{-1}\)). It also exhibited arthropod toxicity: it was found to be highly toxic in a brine shrimp bioassay (LC\(_{50} = 1.7\) ppm)\(^{46}\), it exhibited insecticidal activity against the larvae of the beet army worm *Spodoptera exigua* (IC\(_{50} = 26\) \(\mu g\) mL\(^{-1}\) after 4 days) and the corn root worm *Diabrotica undecimpunctata* (IC\(_{50} = 37\) \(\mu g\) mL\(^{-1}\) after 4 days).

Agelastatin A selectively inhibits the glycogen synthase kinase-3β (GSK-3β)\(^{38}\), an enzyme identified as having a role in the development of Alzheimer's disease, with IC\(_{50} = 12\) μM. The dementia characteristic of Alzheimer's disease results from the death of neurons in the brain associated with several anatomo-pathological hallmarks including neurofibrillary tangles. These tangles consist mainly of hyperphosphorylated tau proteins, and this hyperphosphorylation is carried out by the enzymes GSK-3β and cyclin-dependent kinase 5 (CDK5/p35). GSK-3β also plays an important role in the
Wnt/β-catenin/TCF cell-signalling pathway. Wnts are glycoproteins that bind to the surface of cells to activate the protein Dishevelled (Dv1), which inhibits GSK-3β. Wnt signalling causes the up-regulation and accumulation of β-catenin in the cytosol, which subsequently translocates to the nucleus where it complexes with members of the T-cell factor family of transcription factors, to activate the expression of genes involved in cell growth and proliferation. Functionally inactivating mutations to GSK-3β and inhibition of GSK-3β cause an accumulation of β-catenin and this can then activate certain tumorigenic promoters involved in melanoma and colon cancer such as TCF4. Therefore as agelastatin A can selectively inhibit GSK-3β and also act as an antitumor agent, it is of significant biological interest.

Structure activity studies of agelastatin A have shown that the C-8a hydroxyl group and both NH moieties are required for optimal activity, and acylation of these and removal of the C-1 pyrrole bromine results in a significant loss of potency in *in vitro* assays.⁴⁷
1.4 Previous Work on the Synthesis of Agelastatin A

Weinreb and co-workers completed the first total synthesis of racemic Agelastatin A in 1999.\textsuperscript{48} They utilised cyclopentadiene as the source of the carbocyclic C ring and their strategy was to use the double bonds as handles to incorporate the four nitrogens and stereogenic centres of the natural product. Their synthesis utilises \textit{N}-sulfinyl dienophile Diels-Alder methodology previously described by the Weinreb group.

![Scheme 1](image)

Cycloaddition of cyclopentadiene 52 and \textit{N}-sulfinyl methyl carbamate 53 in benzene at 0 °C gave the cycloadduct 54. Treatment with phenylmagnesium bromide gave the allylic sulfoxide 55 which, upon heating with HMPT in ethanol, underwent a [2,3] sigmatropic rearrangement via the sulfenate ester 56 to give a 1:1 mixture of the desired olefinic oxazolidinone 58 and hydroxyethyl carbamate 57, which could be simply converted to oxazolidinone 58 by treatment with potassium \textit{t}-butoxide in THF. The oxazolidinone was converted to the \textit{N}-Boc derivative 59 in order to give more reproducible results in the subsequent steps of the synthesis.
The next stage was to add a handle for the attachment of the pyrrole A ring of the target (scheme 2). Sulfodiimide 60 was prepared from β-trimethylsilylthanesulfonamide (SES-NH₂) and coupled to oxazolidinone 59 in a Sharpless/Kresze allylic amination procedure. The reaction proceeds via an ene reaction to generate the intermediate 61 which then undergoes a [2,3] sigmatropic rearrangement to give the carbamate product 62. The bis sulfodiimide reaction occurs from the convex face of the oxazolidinone. Treatment with sodium borohydride yielded the cyclic carbamate 63.

The A-ring was prepared from N-Boc-2,5-dibromopyrrole 64 (scheme 3), which was treated with "BuLi and TMSCl to give the TMS bromopyrrole 65. Further treatment with "BuLi and carbon dioxide gave the lithio carboxylate 66 which could easily be deprotected by heating the neat salt to 150 °C. Conversion to the acid chloride was carried out by reaction with oxalyl chloride to give silyl pyrrole 68, which was then
utilised in the acylation of cyclic carbamate 63 (scheme 4). It was found that if the corresponding brominated pyrrole carbonyl chloride was used in the acylation step the yields were poor, and so the bromine was introduced at a later stage in the synthesis.

Acylation of the cyclic carbamate 63 with silyl pyrrole 68 gave the N-acyl sulfonamide 69 (scheme 4). Treatment with TBAF removed the SES group to afford 70 and lithium hydroxide hydrolysis gave a 1:4 inseparable mixture of the N-deprotected oxazolidinone 71 and the alcohol 72. Oxidation of the mixture with PDC gave the separable enone 72 and the recovered oxazolidinone 71, which could be selectively reprotected and hence could be recycled.

Treatment of enone 73 with caesium carbonate in methanol (scheme 5) gave the ABC tricycle 74 and the TMS group was cleanly exchanged for the bromide with N-bromosuccinimide to afford 75. Removal of the Boc group was facilitated with excess TMS iodide in DCM at room temperature and subsequent addition of methyl isocyanate and NaOH yielded Agelastatin A 28. The D ring annulation is believed to involve initial formation of silyl carbamate 76, which upon addition of aqueous sodium hydroxide is converted to the free amine 77, which is trapped by methyl isocyanate to give the tetracyclic product.
In 2002, Hale and co-workers published a formal enantiospecific total synthesis of agelastatin A. They achieved this by preparing one of Weinreb's advanced synthetic intermediates (69) in optically pure form. The Weinreb intermediate was prepared from aziridine 78.

The aziridine precursor 78 was prepared in 5 steps from D-glucosamine hydrochloride 79 using the method published by Hough and Richardson. The aziridine was converted to the N-methylcarbamate 80 and subsequent reaction with sodium azide in hot DMF gave trans-diaxial ring opening to give solely azide 81 in 88% yield. Hydrogenolysis of the azide afforded 82 and subsequent amine protection with trimethylsilylethanesulfonyl chloride (SESCI) gave 83.
The O-benzylidene acetal was removed by treatment of 83 with anhydrous HCl in MeOH (scheme 7) and the primary alcohol 84 selectively tosylated to afford 85. The secondary alcohol was then O-silylated with TES, and then 86 was subsequently converted to the iodide 87 by refluxing with NaI in acetone in a Finkelstein reaction. A Vasella reductive ring opening with zinc dust in THF/H₂O was utilised to introduce the alkene and aldehyde functionalities of 88.

Several efforts to effect a Wittig methylenation on the aldehyde of 88 failed but Kocienski’s modification of the Julia olefination was successful in forming 89. The subsequent intermediates could not be completely purified but a metathesis reaction using a recently developed Hoveyda-Grubbs catalyst 90 and subsequent heating of the
cyclic alkene 91 with potassium carbonate in MeOH gave the desired oxazolidinone 92 in 36% over three steps (scheme 8).

The oxazolidinone was next chemoselectively \( N \)-acylated with Boc anhydride to afford 91 and then the A-ring introduced by acylation with acid chloride 68 (scheme 9).

With the optically pure form of Weinreb's advanced synthetic intermediate 69 now prepared, the formal enantiospecific total synthesis was completed. However the optically pure intermediate was prepared in 19 steps compared with just 8 for Weinreb's intermediate.
In a subsequent publication in 2004, Hale and co-workers reported an alternative endgame to the Weinreb route.\textsuperscript{51}

Weinreb's route had utilised the methyl isocyanate for the introduction of the cyclic hemiaminal subunit, but this was undesirable due to its high toxicity and difficulties in handling. They sought an alternative route where the chiral oxazolidinone 92 is converted into a cyclopentenone 95 (scheme 10) and an intramolecular Michael addition used to form the B-ring in 96. Closure of the D ring would complete the synthesis of agelastatin A 28.

\[ \text{Scheme 10} \]
The new route was commenced from chiral oxazolidinone 90 with selective carbamoylation with acid chloride 94, 4BuLi and DABCO to give N-carbamoyloxazolidinone 97. A second N-acylation was then carried out with pyrrole acid chloride 68 required for the A ring of the natural product. Having formed pyrrolocarboxamide 98, the SES group was selectively removed with tributyltinhydride and AIBN in toluene to give free pyrroloamide 99.

The hydrolysis of oxazolidinone 99 to allylic alcohol 100 was carried out with LiOH in THF at ambient temperature without hydrolysis of the urea unit, but a long reaction time (128 h) was required to obtain a 40% yield of the alcohol. However, the unreacted oxazolidinone could be recycled back into the reaction. The alcohol was subsequently oxidised to the cyclopentenone 95 with pyridinium dichromate (scheme 12).

Unfortunately, all efforts to effect the ring closing Michael addition of 95 under various basic conditions failed. Hale rationalised this lack of reactivity was as a consequence of the high pKa of the pyrrole nitrogen. It was therefore planned to react 94 with N-bromosuccinamide, expecting to obtain the 2,3 dibromopyrrole derivative which would have a lower pKa. (scheme 13). However the pKa cannot be the only factor affecting this reaction as similar ring-closures have been easily carried out with an N-substituted amide, such as in Weinreb's synthesis, with caesium carbonate utilised as the base.
Bromination of 95 did not afford a single product, however, instead a complex mixture containing di- and tribrominated products 101 and 102 and other mono- and dibrominated products was obtained. So instead of attempting to purify the individual products, the mixture was treated with Hünigs base to affect the Michael addition. The crude mixture of products was then treated with H₂ and 10% wet Pd on C in MeOH to dehalogenate the products and the desired ketone 103 could then be isolated in 24-35% in two steps from cyclopentenone 95. The N-debenzylation of 103 was effected using H₂ and Pearlman’s catalyst (20% Pd(OH)₂ on C) in THF (scheme 14), with concomitant closure of the D ring to afford 104, and finally the bromine was reintroduced into the pyrrole ring using the NBS/THF/MeOH method described by Feldman and Saunders to give (-)-agelastatin A 28.
In 2002, Feldman and Saunders published an enantiospecific total synthesis of Agelastatin A. The key step in their method utilised an alkynylidonium salt 108 as a precursor to an alkylidene carbene 109 that then underwent a 1,5 CH insertion into the otherwise unreactive secondary CH of the oxazolidinone ring.

Their synthesis commenced with the chiral epoxyalkyne 105 (Scheme 15), which was prepared readily from BH$_3$.THF-mediated addition of LiC≡CTMS to chiral epichlorohydrin. The epoxide was opened with azide at the less hindered carbon and then Vilarrasa’s oxazolidinone synthesis$^{52}$ gave 106 in 67% yield. Conversion to stannane 107 gave the precursor for the alkynylidonium salt preparation. 107 was treated with Stang’s reagent (PhI(CN)OTf) at $-42$ °C and addition of the crude alkynylidonium salt 108 into a refluxing suspension of TolSO$_2$Na in DME gave a mixture of two products. The first was the desired 1,5 insertion product 110 but sulfonylalkyne 111 was also isolated, which arises from a 1,2-shift with the carbene.
Conjugate addition of o-nitrobenzylamine to the unsaturated sulfone moiety in 110 gave the secondary amine 112 in the desired stereochemistry as a single isomer, and consequently all 4 of the required chiral centres around the C ring were introduced. The amine was acylated with pyrrole-2-carbonyl chloride 113 to afford amide 114 and oxazolidinone hydrolysis led to alcohol 115. Treatment of the alcohol under Swern oxidation conditions gave cleanly the tricycle 116, presumably via an unobserved cyclopentenone intermediate. Deprotection of the tricycle using long wavelength light under neutral conditions gave cleanly debromoagelastatin A 104. Selective monobromination of the pyrrole moiety completed the total synthesis (Scheme 17). Use of excess electrophilic bromine gave the dibrominated product agelastatin B, but careful titration of 104 with NBS in a polar solvent mixture gave (-)-agelastatin A 28 free from other brominated products in a good yield of 73%.
In 2004 Davis and co-workers published an enantiospecific total synthesis of agelastatin A\textsuperscript{53} utilising a combination of two methodologies developed by their group: the synthesis of asymmetric α,β-diamino acids via the addition of glycine enolates to enantiopure sulfinimines\textsuperscript{54} and the synthesis of (±)-4-aminocyclopentenone via ring closing metathesis of a sulfinimine derived N-sulfinyl amino β-ketodiene.\textsuperscript{55}

The key intermediate in this synthesis is the 4,5-diaminocyclopent-2-enone 117, which contains the C-ring of the natural product.

The α,β-diamino ester was prepared by addition of sulfinimine 119 to 5 equivalents of the lithium enolate of ethyl(dibenzylamino)acetate 118 (scheme 18). Three of the four possible diastereoisomers were detected an 18:1:5 ratio, with the major syn diastereoisomer 120 isolated in 73% yield.

Scheme 18

120 Was then treated with lithium N,O-dimethylhydroxylamine to afford the corresponding Weinreb amide 121 in 89% yield. Deprotection of the N-sulfinylamino
group with TFA in MeOH gave amine 122, which was not isolated before coupling with pyrrole-2-carboxylic acid 123, HBTU and Hünig’s base to give amide 124 in 88% over the two steps.

Amide 124 was subsequently treated with allylmagnesium bromide 125 and the intermediate isomerised by treatment with Et$_3$N in EtOH to afford diamino ketadiene 123 (scheme 19). 123 was then refluxed in DCM with 20 mol % of Grubbs second generation catalyst 124 to afford the desired C-ring intermediate 116 in 87% yield.

Having prepared the C-ring intermediate 117, the B-ring was constructed using an intramolecular Michael addition similar to that utilised in the Weinreb route (scheme 20). Treatment of 117 with caesium carbonate in MeOH afforded the desired ABC tricyclic intermediate 128.
Removal of the benzyl protecting groups could not be affected using hydrogenation conditions until the reaction was attempted in the presence of methylisocyanate to affect the deprotection and D-ring closure in a one-pot process. Debromoagelastatin 104 was isolated in 47% yield, along with N-benzyl debromoagelastatin 129 in 37% yield. The N-benzyl debromoagelastatin 129 could not be deprotected which suggests that 129 is not an intermediate in the formation of 104. Finally 104 was treated with NBS in THF using the method described by Feldman and Saunders\textsuperscript{52} to give (-)-agelastatin A 28 in 11 steps in 9% overall yield.

In 2002 O’Brien and co-workers published synthetic studies towards the C-ring core of agelastatin A.\textsuperscript{56} They also employed cyclopentadiene in their synthetic route (scheme 21). Aziridine 130 was prepared from cyclopentadiene 52 using the monoaziridination procedure described by Knight and Muldowney\textsuperscript{57} using [N-(p-toluenesulfonyl) imino]iodane (PhI=NTs) and Cu(acac)\textsubscript{2}. Ring opening with ammonia followed by Boc protection gave diamino cyclopentene 131.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme21.png}
\caption{Scheme 21: Synthesis of the C-ring core of agelastatin A.}
\end{figure}

The cyclopentene was epoxidised \textit{cis} to the NHBoc group with \textit{m}-CPBA to give a single diastereoisomer 132 and subsequently treated with diamine-derived base 133 to give the corresponding allylic alcohol 134. Alcohol 134 was acetylated to 135 to allow separation from unreacted epoxide, and subsequent deprotection with potassium carbonate followed by oxidation with PDC gave the enone 136. This new method gave the enone 136 in five steps from cyclopentadiene, and it has comparable functionality to the intermediate 63 of the Weinreb synthetic route. The O’Brien group is currently
carrying out further work on the rearrangement of epoxide 132 under kinetic resolution conditions in order to generate enantiomerically enriched intermediates.
1.5 Biomimetic Synthesis

1.5.1 Previously Reported Biomimetic Syntheses of Oroidin Alkaloids

The concept of biomimetic synthesis involves the synthetic preparation of a natural product structure in a way that mimics its biosynthesis. As has been discussed previously, many polycyclic pyrrole-imidazole alkaloids are structurally related to oroidin or its linear derivatives, and are therefore assumed to be biosynthesised from similar structures.

Foley and Büchi carried out the first biomimetic synthesis of a pyrrole-imidazole alkaloid in 1982.\textsuperscript{58} They synthesised racemic dibromophakellin 26, an alkaloid isolated from the marine sponge \textit{Phakellia flabellata}, by oxidative cyclisation of non-natural dihydroooroidin 137 (\textbf{scheme 22}). The hydrochloride salt of dihydroooroidin was treated with bromine in acetic acid, upon which an insoluble, highly unstable salt precipitated. Treatment of this salt with potassium tert-butoxide in butanol led to the quantitative formation of racemic dibromophakellin. Foley and Büchi predicted that this biomimetic synthesis proceeded through a spirocyclic transition state 138, although the intermediate could not be fully characterised. They also demonstrated that bromination of the dihydroooroidin precursor 137 was essential to the success of the cyclisation step.

\begin{center}
\textbf{Scheme 22}
\end{center}

![Scheme 22](image)

The group of Horne and co-workers carried out biomimetic syntheses of oroidin 1, clathrodin 2 and the dispacamides A and B (6, 7) by the preparation and rearrangement
of 2-amino-4,5-dialkoxy-4,5-dihydroimidazoles.\textsuperscript{59} The precedent for the 4,5-oxidative addition to the double bond of 2-aminoimidazole was seen previously in Büchi’s synthesis.

![Chemical structures of Oroidin and Clathrodin](image)

The 2-aminoimidazole precursor 139 can be considered as a hypothetical precursor to the C\textsubscript{11}N\textsubscript{5} natural products.

![Chemical reactions](image)

Oxidation of 139 with NCS followed by heating with xylene:methanol gave two rearrangement products 39 and 141 (scheme 23). 3-Amino-1-(2-aminoimidazolyl)-prop-1-ene 39, also a natural product isolated from the Axinellidae sponges \textit{T. Morchella} and \textit{P. walpersi}, was acylated with trichloroacetylpyrrrole 142 to give clathrodin 2 (scheme 24).

![Chemical reaction](image)

Oxidation of 2-aminoimidazole precursor 139 with bromine in DMSO with concomitant elimination of dimethyl sulfide leads to the unsaturated imidazoline ring system 143 found in the dispacamides, and acylation with bromopyrrole 144 gave dispacamide B 7.
Acylation of 139 with dibromopyrrole 145 gave dihydroooroidin 137 and then treatment with bromine and potassium butoxide followed by rearrangement by heating with xylene:methanol gave oroidin 1. Oxidation of 137 with bromine/DMSO gave dispacamide A 6.
The Horne group used 2-aminomidazole intermediate \(39\) to synthesise the dimeric alkaloid mauritiamine.\(^{60}\)

Scheme 27

Oxidation of \(39\) in NCS/TFA gave two intermediates \(146\) and \(147\), formally the products of 1,2 addition of \(\text{Cl}^+\) and \(\text{CF}_3\text{COO}^-\) and 1,4 addition followed by elimination of HCl (scheme 27). Heating in xylene:meanol afforded the dimerised product \(148\) which was acylated with dibromopyrrole \(145\) to give mauritiamine \(15\).

The biomimetic synthesis of cyclic analogues has also been completed, one of the simplest being that of \((\pm)\)-longamide \(41\).\(^{42}\)
Al Mourabit and co-workers demonstrated that the cyclisation of bromopyrrole containing compounds such as 149 could be regioselectively controlled by altering the reaction conditions. N-1 cyclisation required treatment with methanol at ambient temperature to afford longamide 41, and C-3 cyclisation could be selected by treatment with methane sulfonic acid. This regioselectivity is predicted to be useful for the biomimetic synthesis of other polycyclic natural products containing the bromopyrrole moiety.

Horne and co-workers have also conducted biomimetic syntheses of cyclised oroidin alkaloids. They completed the synthesis of (±)-hymenin 23\textsuperscript{61} isolated from the Okinawan sponge, Hymeniacidon sp.

The key cyclisation step to afford 151 was effected by treatment of aldehyde 150 with trifluoroacetic acid for several days (scheme 128). Coupling of the 2-aminomidazole fragment 151 onto the bicyclic core to afford 23 was carried out by treatment with methanesulfonic acid.

In a further study, Horne also uses the same cyclisation strategy to synthesise hymenialdisine 20, debromohymenialdisine 153 and stevensine 22.\textsuperscript{62} All of these natural products share the same common fused bicyclic olefin system.
1.5.2 In Vivo Biosynthetic Studies

The investigation of metabolic pathways in marine sponges is difficult as only a few organisms are amenable to culture. Hence stevensine 22 is one of only a few marine sponge secondary metabolites whose biosynthesis has been investigated in an in vivo study, and the only pyrrole-imidazole alkaloid biosynthesis investigated to date. Kerr and co-workers postulated that the biosynthesis of stevensine proceeds via 3-amino-1-(2-aminoimidazoyl)-prop-1-ene 39 (an intermediate in the biomimetic syntheses of both clathrodis and mauritiamine described earlier), and 4,5-dibromopyrrole-2-carboxylic acid 31 (Scheme 29). It was proposed that these two fragments are linked to form oroidin or an oroidin-like structure, which then undergoes an intramolecular cyclisation to give the seven-membered ring of stevensine. Kerr predicted that intermediate 31 could be biosynthetically derived from either proline or ornithine, and that 39 could be derived from either histidine or arginine.

Scheme 29

Kerr and co-workers, using feeding studies with a cell culture from the Axinellidae sponge Teichaxinella morchella, demonstrated that radiolabelled proline, histidine and ornithine were incorporated into stevensine, whereas arginine was not. Their theory on the biosynthetic route to stevensine was also supported by the isolation of both intermediates 31 and 39 from Teichaxinella morchella along with stevensine.
1.5.3 Other Predicted Biosynthetic Pathways

In 2003, Lington and co-workers reported the isolation of latonduines A 154 and B 155 from the marine sponge *Stylissa carteri.*

![Diagram of Latonduine A and B](image)

These alkaloids contain the pyrrole moiety present in oroidin but instead of an imidazole ring they contain a previously unprecedented six-membered aminopyrimidine substructure. The isolation of these alkaloids indicates a divergence of biosynthetic pathways before the formation of the imidazole and they cannot be derived from intramolecular cyclisation of the oroidin skeleton.

Lington and co-workers proposed that the building blocks for latonduine B are instead 4,5-dibromopyrrole-2-carboxylic acid 145, ornithine and guanidine, which form the precursor 158 and then two cyclisations form latonduine B 155 (scheme 30). Latonduine A 154 would result from the decarboxylation of latonduine B. Lington’s biogenetic scheme also indicates however that the hymenialdisines could be derived from the intermediate 158, where the ornithine carboxyl functionality and guanidine nitrogen combine to form the oxoaminoimidazole ring found in (E)-3-bromohymenialdisine 21.

Although Kerr and co-workers demonstrated via a biosynthetic study that radiolabelled ornithine was incorporated into stevensine 22, they did not degrade the radiolabelled product to determine where in the natural product ornithine was incorporated. Instead or indeed in addition to being the precursor to proline for the biosynthesis of the pyrrole moiety, ornithine could be incorporated into the aminooimidazole moiety.
A recent communication by Al Mourabit and co-workers has proposed a logical biogenetic pathway to all the groups of the pyrrole-imidazole alkaloids. He proposed that the pyrrole-imidazole alkaloids are biosynthetically derived from four pyrrole-2-carboxylic acid building blocks 123, 160, 161 and 31 and the vinyl-aminoimidazole building block 39.

The two nucleophilic positions at N1 and C3 of the four pyrrole building blocks allow for eight different modes of incorporation into the family of pyrrole-imidazole alkaloids. The 3-amino-1-(2-aminoimidazolyl)-prop-1-ene unit 39 can be incorporated in several ways via the ambivalent reactivity of its key structural feature, the 2-aminoimidazole moiety 152.

The same carbon position in the aminoimidazole-containing moiety can therefore be either electrophilic or nucleophilic on a specific carbon atom, depending on the tautomeric form of the fragment. For example, tautomer I of 39 has 2 nucleophilic positions at C-4 and C-7, whereas form II has two electrophilic sites at the same positions.
A total of eight possible tautomeric forms can be drawn for the aminomidazole-containing fragment 39.

\[
\begin{align*}
&\text{III} & & \text{IV} \\
&\text{V} & & \text{VI} \\
&\text{VII} & & \text{VIII}
\end{align*}
\]

Al Mourabit proposed that the formation of the different tautomeric forms and their relative behaviour in vivo is enzymatically controlled by proton exchange with an enzyme. The simple coupling of nucleophilic C5 of tautomer III and electrophilic C4 of tautomer II is predicted to give the basic skeleton of mauritiamine 15 (Scheme 31).

Scheme 31

\[
\begin{align*}
\text{III} & \xrightarrow{\text{dimerization + oxidation}} \text{15 Mauritiamine} \\
\text{II} & \xrightarrow{} \text{15 Mauritiamine}
\end{align*}
\]
Al Mourabit and co-workers have more recently proposed that the 3-carbon chain linking the pyrrole and imidazole moieties in the linear pyrrole-imidazole alkaloids including oroidin 1 and the dispacamides 6 and 7 could be biosynthetically derived from proline. They predicted that as the metabolism of proline in some plants is known to be stress dependent, it might be possible that the same theory applies to proline metabolism in sponges as many of the pyrrole-imidazole alkaloids have roles in chemical defence.

Al Mourabit proposed that the biosynthesis of the linear alkaloids, such as dispacamide A 6, proceeds via a pseudo-dipeptide pyrrole-proline-guanidine 163 (scheme 32).

They proposed that step 2 of the biosynthesis involves a self-catalysed intramolecular transamination reaction of 163 under oxidative conditions via a peroxide intermediate (scheme 33). Dismutation of the peroxide followed by cleavage of the C-N bond to afford 166 and then cyclisation followed by dehydration would give the dispacamide A skeleton 164.

Al-Mourabit investigated this hypothesis using a synthetic study (scheme 34). The pseudo-dipeptide 163 was prepared from pyrrole-2-carboxylic acid 123 and L-proline.
methyl ester 167, coupled together using standard conditions to afford amide 168 and subsequently treated with sodium hydride in THF to afford asymmetric tricycle 169.

Scheme 34

169 was treated with guanidine to afford a mixture of the dipeptide 163 and 2-aminoimidazolinone 170. Al Mourabit proposed that the formation of 170 was effected by air oxidation of dipeptide 163 via a peroxide intermediate. This mechanism was confirmed by treatment of amide 168 with Boc-guanidine and oxygen (scheme 35), where the decarboxylated product 173 was formed in 7% yield. This decarboxylation proceeds via peroxide intermediate 171, which subsequently eliminates carbon dioxide to afford 173.

Scheme 35

The formation of 170 does not occur if the reaction is carried out under argon using degassed solvent.
A mixture of two Boc-protected analogues (174 and 175) of aminoimidazolinone 170 was subsequently utilised by Al Mourabit and co-workers in a total synthesis of dispacamide A (scheme 36). These analogues of 170 were prepared by treatment of tricycle 169 with Boc-protected guanidine, to afford two products differing in the position of the Boc group.

Subsequent bromination of the mixture of 174 and 175 using bromine and acetic acid, TFA promoted Boc deprotection and finally dehydration with methanesulfonic acid afforded dispacamide A 6.

This synthetic study raises two interesting points with respect to the biosynthesis of the linear pyrrole-imidazole alkaloids. Al Mourabit proposes, as a result of this study, that dispacamide A 6 is a precursor to oroidin 1. Also, although it has been predicted that natural products 3-amino-1-(2-aminoimidazoyl)-prop-1-ene 39 and 4,5-dibromopyrrole-2-carboxylic acid 31 are precursors to oroidin and the oroidin related cyclic structures, if the 3-carbon chain of oroidin and the dispacamides is derived from proline then Al Mourabit proposes that 31 and 39 probably result from the hydrolysis of oroidin rather than being biosynthetic precursors to it (Scheme 37).
Currently there is not enough evidence from \textit{in vivo} studies to prove that either of these routes is correct and some degree of speculation is present in all of the studies on oroidin alkaloid biosynthesis.
1.6 Biomimetic Synthesis of Agelastatin A

D’Ambrosio proposed a biomimetic route for the synthesis of agelastatin A 28 (scheme 38) which involved enzyme driven attack at C(4) in a hymenidin-like precursor 176, followed by pyrrole-N attack at the developing positive site at C(7), followed by refuctionalisation at C(4) and C(5) of 177 to give agelastatin A 28. 

But this proposed mechanism requires an enamide to react as a nucleophile at the α-position, which is a reversal of the predicted reaction at the β-position.

A more plausible mechanism involves an oroidin-like precursor 178, which, when converted into an acyl-iminium ion 179, would undergo nucleophilic attack by the imidazolone forming the cyclopentane C-ring and a new acyl-iminium ion 180. Attack by the pyrrole nitrogen gives the strained enamine 181, which should be readily hydrated to give agelastatin A.
The aim of this project is to investigate the viability of such a route for the biomimetic synthesis of agelastatin A.

Al Mourabit has also proposed a similar biomimetic synthesis via the oxidation of tautomer VIII of aminoimidazole-containing fragment 39.\textsuperscript{65}

![Tautomer VIII](image)

Al Mourabit proposed that this tautomer is first coupled to a pyrrole-2-carboxamide fragment, then subsequently oxidised. Two intramolecular cyclisations then take place followed by further refunctionalisation to give agelastatin A 28. Intermediate 184 in Al Mourabit’s route is similar to 180 in our proposed biomimetic synthesis of agelastatin A.

![Scheme 40](image)
1.6.1 Evidence for an \(N\)-acyliminium Ion Intermediate

In 1965, Zigeuner and Rauter observed that when imidazolone 186 was heated with hydrochloric acid dimerisation to 189 occurred.\(^7\) The mechanism involves generation of an \(N\)-acyliminium ion 187 by protonation of the enamide double bond, and then nucleophilic attack of a second molecule of imidazolone occurs generating a second \(N\)-acyliminium ion 188. The second \(N\)-acyliminium ion then loses a proton to generate dimer 189.

\[ \text{Scheme 41} \]

This mechanism is important evidence for our proposed biomimetic synthesis of Agelastatin A, as we will generate a similar \(N\)-acyliminium ion to 187 after the first cyclisation step.

\[ \text{180 Second } N\text{-acyliminium ion in biomimetic synthesis} \]
1.7 *N*-Acyliminium Ions

Our proposed biomimetic synthesis of agelastatin A involves two *N*-acyliminium ions, the first of which must be generated from a precursor. We predicted that the biomimetic cyclisation steps would occur spontaneously after generation of the first *N*-acyliminium ion. There are many methods employed in the literature for the generation of *N*-acyliminium ions from a variety of precursor structures and some of the commonly used methods are discussed here.

![190 N-acyliminium ion](image)

190 *N*-acyliminium ion  191 Mannich reagent

*N*-Acyliminium ions 190 are powerful electrophiles, which have a large number of synthetic applications. The presence of a strongly electron withdrawing group on the nitrogen leads to a highly electron deficient imino-carbon atom. This group enhances the reactivity of *N*-acyliminium ions compared to the corresponding iminium ions (Mannich reagents, 191), which allows them to react even with weak nucleophiles at low temperatures. Typically *N*-acyliminium ions are generated and then immediately trapped by a nucleophile, and the rate-determining step appears to be the generation of the *N*-acyliminium ion in mechanistic studies. The generation of *N*-acyliminium ions can be effected in several different ways, and both their generation and preparation of their precursors has been extensively reviewed.68,69

1.7.1 Generation of *N*-Acyliminium Ions and Preparation of Precursors

A variety of different methods can be employed for the generation of *N*-acyliminium ions from both stable and unstable precursors. These include acylation of an imine, protonation of an *N*-acylimine, electrophilic addition to an enamide, heterolysis of an amide with an α-leaving group, and oxidation by removal of a hydride using an oxidising agent or electrochemical oxidation.
$\text{N-Acyliminion ions can be generated by acylation of an imine (Schiff base), the product of a condensation between an aldehyde or ketone and a primary amine.}$

\begin{align*}
\text{Scheme 42} \\
\text{192} + \text{193: } X=\text{Cl} \\
\text{195} \quad \text{196: } X=\text{OCOR}^4
\end{align*}

Acylation with a carboxylic acid derivative such as an anhydride 194 or carbonyl chloride 193 (scheme 42) gives an adduct 196 containing a labile C-X (carbon-chlorine or carbon-acyloxy group) bond and the lability of this bond is important for N-acyliminium 195 ion generation. The stability of the adduct is dependent on the nature of the imine and the reactivity of the carboxylic acid derivative.

\begin{align*}
\text{Scheme 43} \\
\text{197} + \text{198} \quad \text{199}
\end{align*}

The imine acylation is an equilibrium, which proceeds via the N-acyliminium ion. The position of the equilibrium shifts to the side of the adduct at lower temperatures. The acylation of benzylidenephenylamine 197 with acetyl chloride 198 (scheme 43) gave 95% of adduct 199 at 40 °C, but only 90% at 65 °C.\(^7\)

In this method the precursor to the N-acyliminium ion is unstable but it can be easily prepared and the N-acyliminium ion subsequently generated in a one-pot process. N-acyliminium ions generated by this method can be converted into enamides, $\beta$-lactams and can be trapped with carbon and heteroatom nucleophiles.

Protonation of $N$-acylimines leads to $N$-acyliminium ions. But as the $N$-acylimine precursors are themselves unstable, this method is more of mechanistic than synthetic interest. A study by Würthwein and co-workers demonstrated by NMR studies than protonation of $N$-acylimine 200 gave the $N$-acyliminium ion 201\(^7\) (scheme 44).
Electrophilic addition to enamides such as 202 leads to the generation of N-acyliminium ions (scheme 45). With Brønsted acids protonation on carbon occurs, which is the rate-determining step. This generates an N-acyliminium ion 203.

Other electrophilic additions to enamides resulting in the formation of N-acyliminium ions include Friedel-Crafts and Vilsmeier-type reactions. The enamide precursors are readily prepared via acylation of an imine with an anhydride or acid chloride followed by elimination.

The most commonly employed method of N-acyliminium ion generation is heterolysis of amides with an α-leaving group (scheme 46). This leaving group is often an alkoxy or hydroxyl substituent but other examples utilise a halogen, nitrogen, cyanide, sulfur or phosphorus leaving group.68,69

When an alkoxy substituent is used, then subsequent treatment with a Lewis or Brønsted acid effects the formation of the N-acyliminium ion 205. If an acetoxy72 or methanesulfonyloxy73 group is used, no acidic catalyst is required.

Many of the oxygen-based leaving groups require harsh conditions for the generation of N-acyliminium ions. α-Hydroxy-alkyl amines are the most commonly used for
alkylation reactions, but the necessary treatment with concentrated acid often leads to low yields and unwanted by-products. When the leaving group is a halogen, the reagents are very reactive and therefore often difficult to prepare, handle and store. They are often prepared in situ from the α-hydroxy precursors and subsequently used without purification or isolation. The α-alkoxy substrates are often prepared using electrochemical methods, covered in a subsequent section of this introduction, and are mostly limited to cyclic amides.

In a publication in 1991, Katritzky and co-workers described the use of a benzotriazole leaving group for the generation of N-acyliminium ions for subsequent α-amidoalkylation. The benzotriazole derivatives were easily prepared using a one-pot condensation reaction of aldehyde 208, amide 207 and benzotriazole 206, with azeotropic removal of water (scheme 47). The α-benzotriazole derivatives 209 were found to be significantly more stable than the corresponding α-halogeno derivatives.

![Scheme 47]

The benzotriazole leaving group was removed by treatment with aluminium chloride in DCM, and the intermediate N-acyliminium ion 210 generated was subsequently trapped by a variety of nucleophiles, including activated malonate esters and other active methylene compounds.

Oxidation by the formal removal of a hydride from the amide α-carbon generates an N-acyliminium ion. Examples in the literature include intramolecular hydride abstraction
(scheme 48) by the thermal decomposition of diazonium salt 212. Nitrogen is lost and a hydride shift to the phenyl ring generates the acyliminium ion 213.

Oxidising agents such as DDQ, have also been utilised (scheme 49). Oxidation of the cyclic amide 216 and quenching with water gave ketone 218, presumably via a cyclic N-acyliminium ion intermediate 217.

Other oxidising agents that have been utilised in the literature for the generation of N-acyliminium ions include FeCl₃/H₂SO₄, RuCl₂(PPh₃)₃/TBHP, 1-tert-butylperoxy-1,2-benziadoxol-3(1H)-one and cerium(IV) diammonium nitrate.

Tryptyl tetrafluoroborate has also been utilised as an oxidizing agent for the generation of N-acyliminium ions. Wanner and co-workers used this method for the generation of substituted tetrahydroquinolines. Hydride abstraction from chiral amide 229 generated N-acyliminium ion 220 (scheme 50).
Anodic electrochemistry offers a unique oxidative route into reactive intermediates. The anodic one-electron oxidation of a neutral substrate leads to a reactive radical cation that can then undergo an elimination followed by a further one-electron oxidation to give a reactive cationic intermediate. These reactive species can subsequently trap nucleophiles and the transformations are notable because in the generation of the cationic intermediate a reversal of the normal flow of electrons in the substrate occurs. In a generic non-electrochemical oxidation (scheme 51), a cationic intermediate 224 is generated by protonation of the leaving group in 222 with acid. The lone pair of electrons on 223 then assists in the departure of the leaving group as $Y^\cdot$.

In a generic anodic oxidation process (scheme 52) a single electron is removed from heteroatom $X$ in 226, generating a radical cation 227. The C-$Y$ bond donates electron density to this radical cation, followed by loss of $Y^+$ and then a further 1 electron oxidation occurs to give the ion 228. Hence $Y$ is this case is not a leaving group, rather a hydrogen, silyl group etc. and is lost as $Y^\cdot$. The electrochemical oxidation is conducted in the presence of a nucleophile, such as methanol, which traps the $N$-acyliminium ion as soon as it is formed to afford 229.

The most widely utilised application of this anodic electrochemistry is in the oxidative generation of $N$-acyliminium ions from amides and carbamates. This reaction has been effectively utilized for the synthesis of complex organic molecules, including the constructions of building blocks for asymmetric synthesis, the synthesis of natural products and synthesis of peptidomimetics.
Steckan and co-workers have used electrochemical carbamate oxidation to synthesise chiral building blocks\(^1\) (scheme 53).

Oxidation at a carbon anode generated an N-acyliminium ion 230 that was subsequently quenched by the methanol solvent. The resulting \(\alpha\)-methoxy amide 231 was then subjected to further transformations to give the chiral product 232. 4 F/mol indicates that four moles of electrons were utilized for each mole of substrate, so theoretically twice the required charge was utilised. Constant current conditions were used and up to twelve grams of product were prepared in a single reaction.

Recently Yoshida and co-workers used an electrochemical oxidation in combinatorial chemistry.\(^2\) A pool of N-acyliminium ions was generated from cyclic amides and this was subsequently split and each mixed with separate nucleophiles. Two features of this method are interesting. The use of dichloromethane as a solvent and low temperatures meant that the chiral pool was stable, so it was not necessary for the nucleophile to be present during the oxidation, hence oxidation sensitive nucleophiles could be utilised.

In addition to direct oxidation to the acyliminium ion, a halogen electrolyte has been employed in electrochemical oxidation (scheme 54).
This is itself oxidised which at the anode surface to afford a reactive ‘X+’ species. The X+ then reacts with the amide 233 nitrogen and a subsequent elimination step generates the N-acylimine 235. This method has been used to functionalise amino acids.83

1.7.2 Reactions and Applications of N-Acyliminium Ions

N-Acyliminium ions are highly useful intermediates in organic synthesis. The N-acyliminium ions can be either cyclic or linear and can undergo reactions with nucleophiles in an inter- or intramolecular fashion. A wide range of nucleophiles have been utilised to trap the N-acyliminium ion intermediates, carbon nucleophiles being the most commonly used and include alkynes, alkenes and enol ethers. Heteroatom nucleophiles have also been utilised.

1.7.2.1 Linear N-Acyliminium Ion Intermediates

New bond formation via linear N-acyliminium ion intermediates has applications in synthesis, although acyclic species have not received as much attention as cyclic species owing to a lack of suitable stable precursors.

Bis-carbamates 237 have been used as precursors for the generation of N-acyliminium ions by treatment with BF₃.OEt₂ complex84 (scheme 55). The resulting N-acyliminium ion intermediate 238 was trapped with an 2-(alkylthio)allyl silyl ether nucleophile 239.
Linear $N$-acyliminium ions can also undergo intramolecular reaction to form rings (scheme 56). Johnson and co-workers showed that $N$-acyliminium ion 242, generated by treatment of precursor 241 with formic acid, underwent cyclisation by nucleophilic attack of the olefin on the intermediate ion. The stereochemistry of the initial product 243 could not be determined but further transformations into the benzamido alcohols indicated a 85:15 ratio of 244:245.

1.7.2.2 Cyclic N-Acyliminium Ions

Exocyclic $N$-acyliminium ions are the least commonly utilised of the cyclic intermediates, as no stability is gained relative to linear $N$-acyliminium ions by having the $\text{C}=\text{N}$ bond external to the ring. One example of the use of an exocyclic $N$-acyliminium ion is in the synthesis of the carbacephem antibiotic Loracarbef 249. An exocyclic four-membered $N$-acyliminium ion 247 is generated by treatment of 246 with tin chloride and the intermediate is subsequently attacked by the alkyne in an intramolecular fashion to form the 4,6 fused-ring structure 248 in a $6$-endo process (scheme 57).
Endocyclic N-acyliminium ions are much more widely utilised in synthetic applications as their precursors are often more stable than their linear variants. Endocyclic N-acyliminium ions are also more stable than the exocyclic intermediates. Examples of reactions of endocyclic N-acyliminium ions with nucleophiles in the literature include intermolecular variants and also intramolecular reactions, which are important in the generation of fused-ring systems. Fused rings of various sizes are common features of natural products.

Intermolecular reactions of endocyclic N-acyliminium ion have received significant attention, particularly with respect to the reactions of chiral and prochiral substrates. Polniaszek and co-workers developed a intermolecular diastereoselective reaction (scheme 58) between a chiral endocyclic N-acyliminium ion 251 and a prochiral crotyl reagent 252 for application in the synthesis of indolizidine alkaloids.\textsuperscript{87}

The ratio of diastereoisomers was dependent on the nature of the aryl group, with chlorination on the phenyl ring in 250 reversing the observed facial selectivity. The best diastereomeric ratio was obtained when a phenyl group was used.
Other ring sizes can also be generated using endocyclic $N$-acyliminium ions. These include 5,5-fused systems, illustrated in the formation of allene azabicycle 256\(^8^8\) (scheme 59), and 5,6-fused ring systems, such as the synthesis of the core of the *Erythrina* alkaloids including (-)-3-demethoxyerythratidinone\(^8^9\) (scheme 60). In this case an enamide precursor 257, when treated with tosic acid, forms an intermediate $N$-acyliminium ion 255 which then undergoes nucleophilic attack by the phenyl ring to form 259 containing the key quaternary centre found in these alkaloids.

A 5,7-fused ring system was prepared by Marson and co-workers using $N$-acyliminium ion intermediate 262\(^9^0\); the 5,7,6 system in 263 generated by this is a key motif in several natural products, including the aconitine alkaloids (scheme 61).
N-Acyliminium ions have been extensively utilised in the synthesis of polycyclic marine natural products with both simple and complex structures. Examples include an mCPBA/water oxidation utilised for the introduction of diol 266 in the synthesis of the ABC ring system found in the pyrrole-imidazole alkaloids dibromophakellstatin 267 and palau'amine 29\textsuperscript{91} (scheme 62).

\begin{center}
\textbf{Scheme 62}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{scheme62.png}
\end{center}

\textbf{29 Palau'amine} \hspace{1cm} \textbf{267 Dibromophakellstatin}

1.7.3 Asymmetric Synthesis

The mechanistic pathway for the generation of N-acyliminium ions does not allow direct stereocontrol. An S\textsubscript{N}1-type intermediate has been detected by NMR studies, and a mechanistic study demonstrated that an optically pure N-acyliminium ion precursor, when treated with BF\textsubscript{3}.Et\textsubscript{2}O and a nucleophile, led to completely racemised products\textsuperscript{92}. Therefore stereocontrol must be brought about via indirect methods such as utilising substrates with a chiral centre additional to the N-acyliminium ion generation site, or the use of chiral auxiliaries. The choice of Lewis acid can also control the stereochemistry.

A phenylsulfonyl leaving group was utilised by Marcantoni and co-workers\textsuperscript{93} for the generation of chiral exocyclic N-acyliminium ions using a chiral auxiliary (scheme 63). The phenylsulfonyl group was removed by treatment with titanium tetrachloride and then alkylation effected with allyltrimethylsilane 269.
Some interesting observations were made; firstly the stereochemistry of the phenylsulfonyl precursor 268 had no effect on the stereochemistry of the alkylation product 270, probably meaning the selectivity of the reaction was entirely dependent on the N-acyliminium ion intermediate and the nucleophile being added.

Marcantoni *et al* also observed the opposite selectivity for the alkylation of the intermediate N-acyliminium ions than that expected by energy calculations for the intermediates. The Z-acyliminium ion 274 was predicted to be more unstable than the E-isomer 272 by 0.7 to 1.4 kcal/mol based on semi-empirical calculations (scheme 64). It was therefore predicted that the product of the alkylation of the intermediate N-acyliminium ion would have R-stereochemistry 272. However, they observed the formation of predominantly the opposite S-stereochemistry 270 at the newly formed centre. They utilised a range of alkyl groups as R, and obtained the amine products 271 in 65-95% yield with favourable diastereomeric ratios of 90:10 to 75:25.

An application of a chiral N-acyliminium ion precursor is found in the synthesis of the marine alkaloid lepadiformine 278 (scheme 65). A novel N-acyliminium ion/allylsilane spirocyclisation strategy was utilised in this synthesis, completed by
Weinreb and co-workers, as the key step for introduction of the A and C rings in the synthesis of the natural enantiomer.

The chiral amide precursor 275 was treated with boron trifluoride-acetic acid complex in DCM, which generated the cyclic $N$-acyliminium ion 276. The olefin then underwent an attack on the ion, forming the spirocyclic A-C ring junction as a single stereoisomer 277. This bicycle was then carried through several more steps to the natural enantiomer of lepadiformine 278.

As the literature contains many examples of applications of $N$-acyliminium ions, it was hoped that it would be possible to find a set of conditions suitable for the generation of the $N$-acyliminium ion required in our proposed biomimetic synthesis of agelastatin A.
2.1 Disconnection of the Biomimetic Precursor and Synthetic Modifications

Our proposed biomimetic synthesis of agelastatin A requires the generation of an \( \text{N-acyliminium ion 179.} \) The initially planned synthetic route was to generate this \( \text{N-acyliminium ion by removal of a leaving group X from amide precursor 279.} \) As discussed previously amides with \( \alpha \)-leaving groups are commonly utilised as precursors for the generation of \( \text{N-acyliminium ions.} \) Substituted amide 279 can be disconnected through the amide bond to give a pyrrole “left hand” fragment 280 and an imidazolone “right hand” fragment 281.

Our investigation into the biomimetic synthesis of agelastatin A initially required a simplified model precursor 283 (scheme 67). The modifications would allow the viability of our route to be investigated. The planned modifications included omission of the pyrrole bromination; this could be reintroduced at a later stage if initial investigation into the biomimetic synthesis were successful. We planned to substitute the amide nitrogen with an alkyl group (R) as this was predicted to be required to bias
the amide conformation towards that required for the second cyclisation step in the biomimetic synthesis.

The pyrrole nitrogen may not be sufficiently nucleophilic to affect the second cyclisation step in the biomimetic synthesis owing to delocalisation of the nitrogen lone pair into the pyrrole ring. Therefore it may be necessary, if the application of a pyrrole ring 284 is unsuccessful, to employ a 3-pyrroline ring 285 in the biomimetic synthesis and oxidise it to the pyrrole at a later stage.
2.2 Synthesis of the 3-Pyrroline "Left Hand" Fragment

Our first aim was the synthesis of a suitable 3-pyrroline for use as the left hand fragment 284 if the pyrrole fragment 123 is not sufficiently nucleophilic to affect the second cyclisation step in the biomimetic synthesis. The 3-pyrroline could be oxidised to the required pyrrole after the biomimetic step.

123 pyrrole fragment
284 3-pyrroline fragment

Therefore, initial efforts focused on the synthesis of N-Boc-3-pyrroline-2-carboxylic acid 284 using the method described by Donohoe et al.\textsuperscript{95} Scheme 68 illustrates the synthesis of the Birch reduction substrate.

Scheme 68

Pyrrrole-2-carboxylic acid 123 was converted to its carboxylate salt 285 with aqueous potassium hydroxide in quantitative yield (scheme 68). Reaction with oxalyl chloride afforded the crude acid chloride, which was immediately esterified by refluxing with propan-2-ol. The resulting isopropyl ester 286 was used in the next step without purification. Boc protection of the pyrrole nitrogen was achieved by deprotonation with sodium hydride (without prior removal of the mineral oil)\textsuperscript{95} and addition of Boc-anhydride with gentle heating. Purification by flash chromatography gave the N-Boc protected pyrrole ester 287 in 60% yield over three steps from pyrrole-2-carboxylic acid.
The reduction of the pyrrole ester 287 to the corresponding 3-pyrroline 289 was achieved using a Birch reduction (Scheme 69). Initial attempts to use sodium in liquid ammonia failed to give the desired product. The reaction was then attempted with lithium in ammonia but again, none of the desired 3-pyrroline product was isolated. Instead, a ring cleaved product, 288, was isolated. This open-chain product is formed when the lithium in the reaction mixture is not completely quenched on addition of ammonium chloride solution.

Instead, it is proposed that the lithium adds another electron to the ester carbonyl group of the initial pyrroline product 289 and the resulting radical anion 291 then eliminates the N-Boc group (Scheme 70). A second electron is added to 292 to give dianion 293, which is protonated on work-up with ammonium chloride to afford the ring-cleaved product 288.
A further paper from the Donohoe group\textsuperscript{96} reported that a significant number of products from various Birch reductions of $N$-protected pyrrole derivatives were the deprotected analogues. They demonstrated that the addition of an excess of bis(2-methoxyethyl)amine (BMEA) to the Birch reduction significantly improved the yields of the reactions, with substrates similar to the one being employed here, by preventing $N$-deprotection from occurring. The exact role of the BMEA is unclear, but it was designed to be deprotonated in preference to ammonia. When ammonia is deprotonated in the Birch reduction a nucleophilic NH$_2^-$ anion is formed which can remove the Boc group. The anion 294 formed from BMEA is less nucleophilic than NH$_2^-$ due to coordination of the oxygen lone pairs to sodium, and so this deprotection does not occur.

![Image of 294]

Utilising 10 equivalents of BMEA, added to the reaction with pyrrole 287, enabled the reaction to proceed in 62\% yield after flash chromatography.\textsuperscript{97} Subsequent hydrolysis of the ester 289 was effected by reaction with saturated potassium hydroxide solution (scheme 71), which following acidification, afforded the free carboxylic acid 295 in 98\% yield.

![Scheme 71]

The carboxylic acid 295 can then coupled at a later stage to the “right hand” imidazolone fragment with a coupling agent or via conversion to the corresponding acid chloride.

Both the pyrrole isopropyl ester 289 and the free carboxylic acid 295 exhibited broad signals in their room temperature $^1$H NMR spectra and two sets of signals in their $^{13}$C NMR spectra. Thus the $^1$H NMR of the pyrrole carboxylic acid 295 was recorded in DMSO at 40 °C, 80 °C and 110 °C. The temperature increase effected a sharpening of
the signals, noticeably the signal for the tert-butyl group, which changes from a broad doublet at 40 °C, due to the presence of rotamers, to a sharp singlet at 110 °C.
2.3 Synthesis of the Imidazole “Right Hand” Fragment

We envisioned that the required imidazolone fragment 286 could be retrosynthetically derived from imidazole 300 via a Sonogashira coupling step and oxidation to introduce the imidazolone carbonyl group (Scheme 72).

![Scheme 72]

2.3.1 Iodination of Imidazole

The synthesis of the right hand imidazole derived fragment, from which the required N-acyliminium ion will be prepared in the biomimetic cyclisation step, was carried out using imidazole 300 as the initial substrate.

![Scheme 73]
Literature procedures for the synthesis of poly-iodinated imidazoles fall into two methods. The first utilises a biphasic system, where imidazole is dissolved in aqueous sodium hydroxide solution and a solution of iodine in chloroform, hexane, or light petroleum added. Vigorous stirring of the bi-phasic mixture followed by isolation and neutralisation of the aqueous phase yields the iodinated product as a precipitate. The second method involves a homogeneous aqueous system where iodine in a 20% potassium iodide solution is added to a solution of imidazole in sodium hydroxide solution. Again, neutralisation and filtration yields the product. There appears to be some confusion in the literature as to whether the 2,4,5-triiodo- or the 4,5-diodoimidazole is the major product, but either product would be acceptable as both can be converted into the same product, 4(5)-iodoimidazole, by treatment with Na$_2$SO$_3$.

Use of a biphasic system with chloroform as the organic solvent was initially attempted for the synthesis of 2,4,5-triiodoimidazole. A solution of iodine in chloroform was added to a solution of imidazole in 2M sodium hydroxide solution and stirred until the organic phase became colourless. The literature procedure utilised sodium thiosulfate solution to remove the residual colour, due to excess iodine, from the aqueous phase; but despite several attempts using different concentrations of thiosulfate solution, and solid sodium thiosulfate, the residual colour could not be removed. Neutralisation with acetic acid gave the product as a purple precipitate and the colour remained even after recrystallisation from acetonitrile.

The second procedure, utilising a totally aqueous system, was therefore tried. A solution of iodine in 20% potassium iodide solution was added dropwise to a stirred solution of imidazole in 2M sodium hydroxide solution. The solution was stirred for 24 h, neutralised as before and the product isolated by filtration. Recrystallisation from EtOH gave the product in moderate yield of 40 – 54 % as a white solid.

Characterisation of the product from the iodination reaction proved to be difficult as the C-I signals in the $^{13}$C NMR spectrum were very weak. However, overnight acquisition allowed observation of two peaks at 143.0 and 86.0 ppm corresponding to a C-H and C-I shift respectively. A C-H singlet was also observed in the $^1$H NMR spectrum. These observations indicated the formation of only the 4,5-diiodinated product.
recorded melting point of the product from this reaction was 188°C, but as the ranges reported for the di- and tri-iodinated products were 189-191°C\textsuperscript{106} and 190-192°C\textsuperscript{107} respectively, melting point is not a good method for determination of the isolated product. Mass spectrometric analysis determined the formation of the di-iodinated product, and no molecular ion for the tri-iodinated product was detected. Elemental analysis was also consistent with the formation of solely the 4,5-diiodinated imidazole product.

More recently, procedures have been published which claim to produce only the 4,5-diiodo- or 2,4,5-triiodoimidazole products. However, the reagent for diiodination, potassium dichloroiodinate,\textsuperscript{106} is tedious,\textsuperscript{108} and hazardous\textsuperscript{109} to synthesise, whereas that for triiodination, bis(trifluoroacetoxy)iodobenzene\textsuperscript{107} is very expensive. These procedures were therefore not investigated.

In order to convert 4,5-diiodoimidazole 301 into the monoiodinated product 303 it was refluxed with 8 equivalents of sodium sulfite in a 7:3 mixture of H\textsubscript{2}O:EtOH for 24 h, concentrated \textit{in vacuo} to almost dryness and 4(5)-iodoimidazole 303 isolated by filtration in 73% yield. The literature procedure suggested that the 4(5)-iodoimidazole product could be used without recrystallisation as the purity was sufficiently high, but a sample was recrystallised for analytical purposes. Again, in the \textsuperscript{13}C NMR, the C-I signal at 79.0 ppm was only observed as a very weak signal, even at a saturating concentration with overnight acquisition. The melting point was recorded as 133°C, which is comparable to the range of 136-137°C recorded in the literature.

Protection of the NH moiety of the imidazole ring was affected using a literature procedure by reaction of 4(5)-iodoimidazole 303 with benzenesulfonyl chloride and triethylamine in THF. Recrystallisation from EtOH gave 1-benzenesulfonyl-4-iodoimidazole 299 in an acceptable 65% yield. It is interesting to note that in the \textsuperscript{13}C NMR spectrum of the protected product, a saturated solution was not required to see the C-I signal at 85.5 ppm as it was easily observed at a normal concentration.
2.3.2 Introduction of the Alkyne Side Chain

With the N-protected iodoimidazole prepared, attention was turned to the introduction of the alkyne side-chain. This could be effected by the reaction of an O-protected propargyl alcohol with the iodoimidazole, via a palladium catalysed coupling reaction. In 1975, Sonogashira\textsuperscript{110} reported that an acetylenic hydrogen can easily be substituted by halogenoarenes with a palladium catalyst, copper(II)iodide and triethylamine under mild conditions.\textsuperscript{110} The reaction between 1-benzenesulfonyl-4-iodoimidazole 299 and TBS-protected propargyl alcohol 304 (scheme below) was carried out by Cliff and Pyne\textsuperscript{98} as part of a larger investigation into the palladium catalysed coupling of imidazoles to various alkynyl substrates.

\textbf{Scheme 74}

\[
\begin{align*}
\text{N} & \quad \text{SO}_2\text{Ph} \\
299 & \quad + \\
\begin{array}{c}
\text{H} \\
\text{Si-O} \\
\text{304}
\end{array} & \quad \text{Pd(PPh}_3\text{)}_4, \text{Cu(I)} \quad \text{DMF, 80 °C, 4 h, 80%}
\end{align*}
\]

Initially propargyl alcohol 306 was protected by reaction with triethylamine and tert-butylidimethylchlorosilane in DCM and the product purified by flash chromatography. However, it was found that the yield of the protected alcohol was inconsistent, possibly due to its volatility. These problems were overcome by carrying out the reaction in DMF with tert-butylidimethyl chlorosilane and imidazole, removal of the DMF solvent by extraction with water and purification of the product by distillation under reduced pressure.\textsuperscript{98} This method provided the protected alcohol 304 in quantitative yield.

\textbf{Scheme 75}

\[
\begin{align*}
\text{H} & \quad \text{HO} \\
306 & \quad \text{TBSCI, imidazole} \\
\text{DMF, 100%} & \quad \text{H} \\
\end{align*}
\]

The tetrakis(triphenylphosphine)palladium catalyst 305 was prepared from palladium dichloride, triphenylphosphine and hydrazine in 90% yield using a reported procedure,\textsuperscript{111} and stored under nitrogen in the absence of light. Total discoloration
from bright yellow to an orange colour was observed after storage for approximately six weeks, and so the catalyst was used within 1 week of preparation.

The Sonogashira coupling step was carried out using the distilled alkyne and with freshly prepared catalyst, and the coupling product 298 was obtained in 80% yield after purification.

2.3.3 Methylation of Imidazole Nitrogen

The next stage in the synthesis of the “right hand” fragment was methylation of the imidazole nitrogen. This could be carried out with concomitant removal of the benzenesulfonyl protecting group, via cationic intermediate 307.

![Scheme 76](image)

Literature precedent for this reaction was found in two publications by Lindel and Hochgürtel, where the methylation reaction was carried out using trimethylxonium tetrafluoroborate (Meerwein’s Salt) on a substrate containing a protected nitrogen on the alkyne chain instead of oxygen. Their reaction was applied to both the mono- and di- Boc-protected substrates 309 and 310, with either 1 or 1.5 equivalents of Meerwein’s salt being utilised. In both cases the mono Boc-protected product 311 was obtained. The reaction mechanism proceeds with methylation occurring first to give a salt from which MeOSO₂Ph is then removed by methanolysis during work-up.

![Scheme 77](image)
As our substrate for the methylation reaction was similar to the literature substrates, the procedure was first attempted using the same reaction conditions. Therefore 298 was treated with 1.5 equivalents of trimethyloxonium tetrafluoroborate. After methanol work-up, the crude $^1$H NMR of the product showed loss of the tert-butyldimethylsilyl protecting group peaks. The procedure was repeated with just 1 equivalent of the methylating agent, to confirm whether the excess reagent was responsible for the TBS removal, but the same effect was observed. For both of these reactions the crude $^1$H NMR showed no change in the aromatic region, suggesting that the benzenesulfonyl group had not been removed.

The reaction was next attempted using methyl triflate (methyl trifluoromethanesulfonate) as the methylating agent. Therefore 1 equivalent of methyl triflate was used in THF but again, upon methanol work-up, the TBS group was absent. It was then considered triflic acid might be generated during the methanol work-up and may be responsible for the removal of the TBS group. Therefore the methyl triflate reaction was repeated using sodium methoxide in methanol for the work-up. However, the $^1$H NMR spectrum of the crude product showed that the relative intensity of the TBS peaks was greatly decreased, suggesting that the acidic conditions occur in the initial reaction.

<table>
<thead>
<tr>
<th>Me$_3$OBF$_4$ (equiv)</th>
<th>Proton Sponge (equiv)</th>
<th>Solvent</th>
<th>Temp</th>
<th>t (h)</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>DCM</td>
<td>rt</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>DCM</td>
<td>rt</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>1.2</td>
<td>1.2</td>
<td>DCM</td>
<td>reflux</td>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>DCM</td>
<td>reflux</td>
<td>16</td>
<td>50</td>
</tr>
<tr>
<td>1.2</td>
<td>1.2</td>
<td>CHCl$_3$</td>
<td>reflux</td>
<td>16</td>
<td>8.3</td>
</tr>
<tr>
<td>1.3</td>
<td>1.3</td>
<td>CHCl$_3$</td>
<td>reflux</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>48</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>DCM</td>
<td>reflux</td>
<td>16</td>
<td>63</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>DCM</td>
<td>reflux</td>
<td>16</td>
<td>50</td>
</tr>
</tbody>
</table>

*No further conversion observed after 24 h.

In order to prevent the removal of the TBS group by acid forming in the reaction it was necessary to add a base to “mop up” the protons from the solution. 1,8-bis-(dimethylamino)naphthalene (Proton Sponge®) was utilised for this purpose. Various
numbers of equivalents of trimethylxonium tetrafluoroborate were utilised in the methylation reaction and one equivalent of the proton sponge was added for each equivalent of methylating agent. **Table 1** summarises the reaction conditions used in this approach. The percentage conversion from the substrate **298** to the product **308** was determined by measuring the ratio of the integrals for the propargylic CH$_2$ peaks of the substrate **298** and the product in the $^1$H NMR spectrum of the crude product. A shift downfield from 4.44 to 4.51 ppm was observed for this signal on conversion from substrate to product.

These results indicated that no further conversion occurs after refluxing for 24 h and that changing the solvent from DCM to the higher boiling point CHCl$_3$ did not increase the percentage conversion. Also, when using 10 equivalents of Meerwein’s salt the percentage conversion decreased compared to when 5 equivalents were used.

As 100% conversion to **308** could not be achieved with Meerwein’s salt, attention was turned to the more potent methylating agent, methyl triflate. The results of the investigation are summarised in **Table 2**. Again, 1 equivalent of Proton Sponge® was used for each equivalent of methyl triflate. When 3 equivalents of methyl triflate were used, a trace of the substrate was observed in the $^1$H NMR, so an extra half equivalent was added to complete the conversion to the product. Hence 3.5 equivalents each of methyl triflate and Proton Sponge gave 100 % conversion to **308** as determined by the crude $^1$H NMR.

<table>
<thead>
<tr>
<th>MeOTf (equiv)</th>
<th>Proton Sponge (equiv)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>% conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>THF</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>THF</td>
<td>2</td>
<td>~100$^a$</td>
</tr>
<tr>
<td>3.5</td>
<td>3.5</td>
<td>THF</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$Trace of substrate observed by $^1$H NMR

With 100% conversion achieved, attention was turned to the purification of the methylated product. Unfortunately the product was very difficult to visualise on TLC. The proton sponge also streaked on the column and it tended to co-run with the
methylated product. However it was possible to assign shifts in the $^1$H NMR (CD$_3$OD) spectrum of one of the column fractions for the $N$-methyl group (3.92 ppm, 2H, d, $J$=2.1 Hz) and the propargylic CH$_2$ group (4.66 ppm, 3H, d, $J$=2.1 Hz). It was not possible to assign both C-H shifts for the protons on the imidazole ring as the aromatic signals of the proton sponge are strong in this area. A singlet at 7.89 ppm was observed, with an integral value of 1H relative to the CH$_2$ peak, which may correspond to one of these protons.

The fractions from the first column were analysed by TLC and it was found that by using an eluent containing approximately 0.5 % aqueous ammonia, the proton sponge could be prevented from streaking on the TLC plate and a good separation was achieved between the Proton Sponge$^\circledR$ and the methylation product. However, although the Proton Sponge$^\circledR$ came off relatively cleanly, the methylation product 308 was impossible to visualise by TLC. Therefore this method was therefore not suitable for purification of the methylated product.

Different bases were investigated in the methylation reaction as an alternative to Proton Sponge in order to facilitate the separation of the methylated product 308 from the base (Table 3). It was also discovered that methyl triflate can polymerise THF solvent, and so a switch to DCM solvent was also investigated for this reaction.

<table>
<thead>
<tr>
<th>MeOTf (equiv)</th>
<th>Base</th>
<th>Base equiv</th>
<th>Solvent</th>
<th>Reaction Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>DBMP</td>
<td>3.5</td>
<td>THF</td>
<td>2</td>
<td>100% Conversion No column separation</td>
</tr>
<tr>
<td>3.5</td>
<td>methyl imidazole</td>
<td>3.5</td>
<td>THF</td>
<td>2</td>
<td>No reaction</td>
</tr>
<tr>
<td>3.5</td>
<td>sodium carbonate</td>
<td>3.5</td>
<td>THF</td>
<td>2.5</td>
<td>Some removal of TBS group</td>
</tr>
<tr>
<td>2</td>
<td>Proton Sponge</td>
<td>2</td>
<td>DCM</td>
<td>3</td>
<td>40% conversion</td>
</tr>
<tr>
<td>4</td>
<td>Proton Sponge</td>
<td>4</td>
<td>DCM</td>
<td>3</td>
<td>~100% conversion</td>
</tr>
<tr>
<td>5</td>
<td>Proton Sponge</td>
<td>5</td>
<td>DCM</td>
<td>3</td>
<td>100% conversion No separation</td>
</tr>
<tr>
<td>5</td>
<td>Hünig's base</td>
<td>5</td>
<td>DCM</td>
<td>2</td>
<td>No conversion Substrate recovered</td>
</tr>
</tbody>
</table>
2,6-di-tert-butyl-4-methylpyridine (DBMP) was investigated, however, although 100% conversion to 308 was observed, we were unable to separate the product from the excess DBMP by column chromatography. 1-methylimidazole gave no product from the methylation reaction, only recovered substrate was observed. This can be explained by the fact that the base may have reacted directly with the methyl triflate before the desired methylation reaction could occur. Sodium carbonate was also investigated, but some TBS deprotection of the product was observed, so this was an unsuitable base. As methyl triflate was causing polymerisation of the THF in the reaction, a switch to DCM was applied, but the reaction with Proton Sponge® as a base still required an excess of MeOTf and base, and the product could not be separated by flash chromatography. The use of Hüning’s base gave no product, again presumably due to the direct reaction of the base with methyl triflate.

The next planned step in this route was to introduce the required carbonyl group into the imidazole ring of 308 by oxidation of the 2-lithio derivative with benzoyl peroxide (scheme 78).

![Scheme 78](image)

As there was little literature precedent for the reaction a clean substrate would be paramount for its investigation. As it was not possible to completely purify the methylated product 308, an alternative strategy had to be considered for a route into the “right hand” fragment.
2.4 Hydantoin Route

Preparation of the imidazolone fragment from hydantoin would remove the previously encountered problem of the nitrogen methylation at the 3-position, as methylation can be carried out as the first step in the synthesis. The problem of oxidation to introduce the carbonyl group in the 2-position is also removed as hydantoin already contains this functionality.

Scheme 79 outlines the alternative retrosynthetic analysis for the “right hand” imidazolone fragment 286. Initial 3-methylation of 315 to afford 314 followed by a Grignard addition to introduce the side chain, and then side chain manipulation with introduction of the leaving group X will afford 286. X will be required for generation of the N-acyliminium ion after the coupling with the “left hand” nitrogen heterocycle fragment, this could be halogen, OR, CN, or various other leaving groups.

![Scheme 79](image)

2.4.1 Preparation of 3-Methylhydantoin

Scheme 80

![Scheme 80](image)
Surprisingly, 3-methylhydantoin 314 is not commercially available, so methylation at the 3-position of hydantoin 315 was attempted. Two methods for the alkylation of hydantoin were found in the literature. The first method involved the preparation and isolation of the potassium salt of hydantoin, followed by alkylation with the alkyl halide in DMF\(^{114}\). The second involved heating an aqueous solution of hydantoin, sodium hydroxide and the alkyl halide at reflux.

The former procedure was attempted first. The potassium salt was prepared by addition of an ethanolic solution of potassium hydroxide to a solution of hydantoin in ethanol at 60 °C. The potassium salt was isolated as a white precipitate in 75 % yield and dried in vacuo. The salt was then suspended in DMF and methyl iodide added, the suspension stirred at ambient temperature for 22 h and finally heated to 80 °C for 1 h, cooled and concentrated in vacuo. \(^1\)H NMR indicated that the reaction had gone to completion and had given the desired 3-methylhydantoin product, but the product was obtained as a yellow oil, rather than a white solid, due to the presence of residual DMF. Removal of this residual solvent by extraction was impossible due to the high water-solubility of the 3-methylhydantoin product.

The second literature method (which was reported for the 3-benzylation of hydantoin) was next investigated; this involved deprotonation and alkylation with 1 equivalent of benzyl chloride in refluxing \(\text{H}_2\text{O}\).\(^{114}\) However methyl iodide has a significantly lower boiling point than benzyl chloride and the reaction did not go to completion at reflux due to loss of methyl iodide from the condenser. At lower temperatures the reaction did not go to completion, even after several hours of reaction time. Therefore a large excess of methyl iodide was used at reflux temperature. Hydantoin and 1 equivalent of sodium hydroxide were heated to reflux in \(\text{H}_2\text{O}\), and 5 equivalents of methyl iodide were added slowly through reflux condenser. The reaction was then heated at reflux for 20 h. After cooling the 3-methylhydantoin could not be isolated by precipitation from cold \(\text{H}_2\text{O}\) as for the 3-benzyl product, so an extractive workup was employed. Extraction with \(\text{CHCl}_3\) gave 3-methylhydantoin in only 13 % yield but \(^1\)H NMR analysis of the aqueous phase after this extraction indicated that that some 3-methyl hydantoin product was still present, due to the high solubility of the product in water. This yield could be increased to 23% by saturation of the aqueous solution with \(\text{NaCl}\) and repeated extraction with \(\text{CHCl}_3\). Problems with the aqueous solubility of the product could be avoided by
concentration of the reaction mixture and trituration of the resulting solid with hot CHCl₃. Subsequent extraction from the residual solid with DCM, using a Soxhlet apparatus, led to a combined yield of 43%. Further experiments used only the Soxhlet extraction procedure, but the results were not entirely reproducible as the efficiency of the extraction appeared to depend on scale, and possibly on the dryness and particle size of the material being extracted. Thus on a 10 g scale, a 38% yield of 314 could be obtained after Soxhlet extraction for 20 h, but on an 80 g scale only 28% of 314 was obtained after a 7 day extraction. The 3-methylhydantoin was further purified for analysis by recrystallisation from hot MeOH with a recovery of 77%.

Due to poor yields and reproducibility with the methyl iodide an alternative method was sought for the methylation of hydantoin. Janin et al have described the use of N,N-dimethylacetamide dimethyl acetal 316, for methylation of a variety of heterocycles, including hydantoin.¹¹⁵ This reagent was utilised in the literature in refluxing toluene, with the product crystallising out of solution upon cooling to ambient temperature. The literature procedure utilises 5 equivalents of the N,N-dimethylacetamide dimethyl acetal reagent, but in our hands this produced a low yield of a tarry material which was difficult to purify by recrystallisation. After extensive optimisation, we found that the reaction of hydantoin with 1.5 equivalents of 316 at reflux in toluene gave 314 in 82% yield as a pale brown solid, which crystallised from the reaction mixture on cooling. The optimum yield was obtained at a high dilution of 50 mL toluene per gram of hydantoin, presumably due to the reaction medium being less polar which increased the recovery of 314 on cooling. The rate of cooling of the reaction also had a significant effect on the reaction yield; a reaction cooled quickly to 0°C gave 22% less yield of 314 compared to a reaction allowed to cool slowly. The crude material was sufficiently pure for use in subsequent reactions, but a highly pure sample (99.9%) could be obtained by decolourisation with NORIT SX charcoal followed by recrystallisation from methanol.
2.5 Addition of the Alkyne Side Chain

It was planned to use a Grignard reaction to introduce the alkyne side chain to initially give tertiary alcohol 317, which we hoped could be dehydrated to give the conjugated alkene in the imidazolone ring in 313 (scheme 81). Kohn and co-workers\textsuperscript{116} demonstrated that a Grignard reagent could be added to the 4-position of various hydantoins, and when a 5-monosubstituted hydantoin 318 was utilised, the tertiary alcohol 319 initially formed underwent elimination in chloroform solution to afford the corresponding imidazolone 320 (scheme 82).

With 5-disubstituted hydantoins, including hydantoin 321, they were able to successfully deprotonate at N-1 with one equivalent of \textit{n}-butylmagnesium chloride before addition of a different side chain as a Grignard reagent, to afford tertiary alcohol 322 (scheme 83).
However, attempts to deprotonate N-1 of 3-methylhydantoin 314 with 1 equivalent of n-butyl magnesium chloride followed by addition of the required Grignard reagent resulted in addition of an n-butyl group at the 4-position. We therefore concluded that the addition of an extra equivalent of the desired Grignard reagent would be required to deprotonate the hydantoin at N-1 before the side-chain addition. On a larger scale we envisioned that the excess alkyne 304 could be recovered by distillation after workup.

A solution of the required alkyne Grignard reagent was prepared by addition of n-butylmagnesium chloride in THF to a solution of silyl ether 304 in THF,\(^{117}\) and this was then added to hydantoin 314 in THF. An excess of n-butylmagnesium chloride resulted in the addition of an n-butyl group to hydantoin, so exactly 1 equivalent, relative to the alkyne, was used in subsequent experiments. The initially formed product from the reaction was the tertiary alcohol 317, which underwent slow elimination in CDCl\(_3\) on a small scale. The tertiary alcohol was treated with 1 mol % p-toluenesulfonic acid in CHCl\(_3\) to completely effect the elimination in less than 1 h for larger scale reactions. Table 4 summarises the optimisation of the Grignard addition reaction.

The reaction was quenched with sat. NH\(_4\)Cl and extracted with Et\(_2\)O. Unreacted 3-methylhydantoin was removed from the reaction mixture by aqueous extraction. Although some of the desired product was lost in this extraction, it was more efficient than flash chromatography. Initial reactions were carried out by addition of the Grignard reagent to a solution of 314 (entries 1-4) giving yields of 15-25%; however the low solubility of 314 meant that the reactions were very dilute. Increasing the concentration by addition of the Grignard reagent to a suspension of 314 led to an increase in the yield of 313 to 62-69%. The literature suggested that 6 equivalents of the Grignard reagent were required\(^{118}\) (entries 2-6), however the same yield of 313 could be obtained with only 3 equivalents (entries 7-11). On a large scale 313 was
purified by recrystallisation from hot EtOAc (entries 9-11), as the low solubility of the product made flash chromatography difficult.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mass of 314/g</th>
<th>304 (equiv.)</th>
<th>BuMgCl (equiv.)</th>
<th>Solution or Suspension</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.11</td>
<td>6</td>
<td>7.2</td>
<td>Solution</td>
<td>18</td>
<td>-\textsuperscript{a}</td>
</tr>
<tr>
<td>2</td>
<td>0.11</td>
<td>6</td>
<td>6</td>
<td>Solution</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>0.25</td>
<td>5</td>
<td>5</td>
<td>Solution</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>0.85</td>
<td>6</td>
<td>6</td>
<td>Solution</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>0.23</td>
<td>5</td>
<td>6</td>
<td>Suspension</td>
<td>40</td>
<td>48\textsuperscript{b}</td>
</tr>
<tr>
<td>6</td>
<td>0.32</td>
<td>6</td>
<td>6</td>
<td>Suspension</td>
<td>44</td>
<td>47\textsuperscript{c}</td>
</tr>
<tr>
<td>7</td>
<td>0.32</td>
<td>3</td>
<td>3</td>
<td>Suspension</td>
<td>44</td>
<td>47\textsuperscript{c}</td>
</tr>
<tr>
<td>8</td>
<td>1.0</td>
<td>3</td>
<td>3</td>
<td>Suspension</td>
<td>110</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>1.5</td>
<td>3</td>
<td>3</td>
<td>Suspension</td>
<td>44</td>
<td>69\textsuperscript{d}</td>
</tr>
<tr>
<td>10</td>
<td>7.9</td>
<td>3</td>
<td>3</td>
<td>Suspension</td>
<td>100</td>
<td>54\textsuperscript{d}</td>
</tr>
<tr>
<td>11</td>
<td>17.0</td>
<td>2.7</td>
<td>2.7</td>
<td>Suspension</td>
<td>130</td>
<td>59\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Addition of \textsuperscript{b}Bu group to hydantoin observed; \textsuperscript{b}Grignard solution added to a suspension of 3-methylhydantoin in THF; \textsuperscript{c}Two reactions carried out in parallel; \textsuperscript{d}Recrystallised yield.

Removal of the TBS group was possible with TBAF but the high water solubility of the unprotected alcohol 312 meant that recovery after aqueous workup was low. However the use of acetic acid:THF:H\textsubscript{2}O 3:1:1 allowed the by-products to be removed \textit{in vacuo} and no workup was required. Silyl ether 313 was heated to 50 °C in a 3:1:1 mixture of AcOH:THF:H\textsubscript{2}O for 3.5 h giving the alcohol 312 in 81% yield after flash chromatography. On a larger scale flash chromatography was again not practical due to the very high polarity and low solubility of the alcohol. Therefore larger quantities of the alcohol were prepared by treatment of tertiary alcohol product 317 from the Grignard reaction with AcOH:THF:H\textsubscript{2}O at 50 °C to effect the elimination and deprotection in a one-pot process to afford alcohol 312. After the solvent was removed \textit{in vacuo}, a suspension of the crude alcohol in Et\textsubscript{2}O was stirred overnight. This allowed the low polarity impurities to be removed, and after filtration the crude alcohol was obtained in 65% yield over two steps. Recrystallisation from hot MeOH gave the clean alcohol 312 in 33 % yield over the two steps.

2.6 Addition of Propargyl Alcohol to 3-Methylhydantoin

Examination of the literature showed that it is possible to add propargyl alcohol 306 as a carbon nucleophile to aldehydes and ketones in the presence of a base such as potassium
**tert-butoxide**[^119][^120] or **butyllithium**[^121]. If propargyl alcohol could be added directly to the C-4 carbonyl group of 3-methylhydantoin it would eliminate the need for the protection-deprotection strategy utilised in the first instance (**scheme 84**).

![Scheme 84](image)

Initially the double deprotonation of propargyl alcohol 306 was attempted with **n**-butyllithium. **n**-Butyllithium was added to a stirred solution of propargyl alcohol in THF at −20 °C. The viscous solution was stirred at −20 °C for 30 min and then cooled to −78 °C. A solution of 3-methylhydantoin 314 in THF was then added to the deprotonated propargyl alcohol solution and the reaction was allowed to warm to ambient temperature. However the viscosity of the resulting mixture was very high which prevented magnetic stirring, therefore the mixture was heated to 40 °C, at which temperature stirring was possible. After 40 h at 40 °C the same work-up as for the Grignard addition reaction was carried out, but without the tosic acid elimination step. The ^1H NMR of the crude reaction mixture showed a very small peak at ca. 6.9 ppm, which could possibly be due to the imidazolone proton of 312, but no AB system was observed to indicate the formation of the expected initial tertiary alcohol product 323 from the addition. The reaction was also attempted using **n**-butylmagnesium chloride as the base. In this case ^1H NMR of the crude reaction showed again a small peak at 6.9 ppm but no evidence of an AB system, and recovered starting material. As there was no obvious promise with this method, the original protection-deprotection strategy was used.

[^119]: 119[^120]: 120[^121]: 121
2.7 Reduction of the Propargylic Alcohol to the cis-Allylic Alcohol

Scheme 85

2.7.1 Lindlar Reduction

Several methods in the literature are reported for the reduction of alkynes selectively to Z-alkenes. Lindlar reduction\textsuperscript{122} has been widely used in the literature for the reduction alkynes to cis-alkenes.\textsuperscript{123} It requires hydrogen and a lead-poisoned palladium catalyst on an inert support such as calcium carbonate, charcoal, barium carbonate or barium sulfate. Typically between 5-10 mol\% of the catalyst is used. The Lindlar reaction is most successful for isolated triple bonds, for example it was successfully employed by Büchi and Egger as the key step in their synthesis of methyl jasmonate 325\textsuperscript{124} (scheme 86).

Scheme 86

However the Lindlar reduction is not as successful for the partial reduction of triple bonds in conjugated systems, with the exception of alkynes conjugated to benzene or aromatic rings (for example phenyl propiolic acid\textsuperscript{125}) which behave as isolated triple bonds. Generally with conjugated enynes a selectivity of between 85-90\% is observed. For example Marvell and Tashino reported that the reduction of ethynylcyclohexene 326 gave 86\% of the diene 327 along with 8\% of ethylcyclohexene 338 and 6\% of the starting material 326\textsuperscript{126} (scheme 87).
In these cases, it is not generally possible to observe a notable break in the uptake of hydrogen after completion of the alkyne reduction to the alkene; therefore the reaction must be arbitrarily interrupted. In the case of the reduction of ethynylcyclohexene, after 1 equivalent of hydrogen was taken up. However some conjugated alkynes do not give such synthetically useful selectivities under Lindlar reduction conditions. Marvell and Tashino also reported that Lindlar reduction of 1,2-dicyclohexylacetylene 329 with one equivalent of hydrogen gave less than 50% of cis-1,2-dicyclohexylethylene 330\textsuperscript{126} (scheme 88). The reduction products could not be completely separated but compounds where the alkyne had been completely reduced as well as cyclohexane-containing reduction products were also detected.

There is some evidence to suggest that non-polar solvents can give a higher selectivity in the Lindlar reduction,\textsuperscript{127} and additives such as quinoline\textsuperscript{128} and potassium hydroxide\textsuperscript{129} can also increase the selectivity. Some studies into the catalytic reduction of alkynes indicate that the selectivity for reduction of the alkyne over the alkene is not due a large difference in alkyne and alkene reduction rates, rather selective adsorption of the alkyne over the alkene onto the catalyst surface.\textsuperscript{130} Therefore it may not be possible to control the reaction by changing the reaction temperature.
The very low solubility of propargylic alcohol 312 meant that the only suitable solvent for our Lindlar reduction was methanol. A test reaction using 10% palladium on CaCO₃ with 3.5% lead poisoning in MeOH under a H₂ balloon showed no substrate remaining by TLC after 1h at ambient temperature. However, ¹H NMR analysis of the crude reaction product showed only the over reduced saturated side chain product 331. We therefore reduced the catalyst loading to 5% for subsequent reactions. Table 5 summarises the subsequent optimisation of the Lindlar reduction of alkyne 312.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Scale (mg 212)</th>
<th>Mol % catalyst</th>
<th>Temperature</th>
<th>Time (min)</th>
<th>Ratio 312:296:331</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>10</td>
<td>25</td>
<td>60</td>
<td>0:0:1</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
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<td>0</td>
<td>15</td>
<td>28% 296</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>5</td>
<td>0</td>
<td>10</td>
<td>3:6:2</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
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<td>0</td>
<td>120&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>100</td>
<td>5</td>
<td>0</td>
<td>120</td>
<td>0:0:1</td>
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<tr>
<td>6</td>
<td>50</td>
<td>5</td>
<td>0</td>
<td>60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0:1:1</td>
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<td>8</td>
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<td>5</td>
<td>-20</td>
<td>80&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2:1:0</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>5</td>
<td>-20</td>
<td>120</td>
<td>1:3:1</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>5</td>
<td>-78</td>
<td>300</td>
<td>1:0:0</td>
</tr>
<tr>
<td>11</td>
<td>40</td>
<td>5</td>
<td>-20</td>
<td>120</td>
<td>0:7:3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>200</td>
<td>5</td>
<td>-20</td>
<td>120</td>
<td>0:0:1</td>
</tr>
</tbody>
</table>

<sup>a</sup>TLC at 10, 20, 30, 40, 60, 90 and 120 min; <sup>b</sup>TLC at 30 and 60 min; <sup>c</sup>TLC at 60 and 80 min; <sup>d</sup>trace of 312 observed

One factor that became apparent during the investigation was the effect of TLC monitoring. The H₂ atmosphere was replaced by air for removal of TLC samples, but it appeared that after reintroduction of hydrogen there was an induction period before the reaction recommenced. Hence entry 4, monitored by TLC, gave a satisfactory ratio of 312:296:331 of 0:4:1 with a total reaction time of 120 min, but a similar reaction (entry 5), left without monitoring for the same reaction time, afforded only 100% of the over-reduced side product 331. It was therefore necessary to carry out several reactions to
determine the optimum the reaction time (entries 6-11). However, on a larger scale (entry 12) under otherwise identical conditions to entry 11, only the over-reduced product 331 was obtained. Therefore due to the capricious and unpredictable nature of this reaction, the Lindlar reduction approach was abandoned and an alternative strategy sought.

2.7.2 Zinc Reduction

Zinc has been used as a reagent for the reduction of alkynes to (Z)-alkenes\textsuperscript{131-133}. Frequently the metal is utilised as a couple with copper and/or silver, and activated with 1,2-dibromoethane. Zinc has also been utilised in the reduction of conjugated alkynes to (Z)-alkenes where Lindlar reduction has failed owing to lack of selectivity, such as in the reduction of dienyne 332 to undecatriene 333\textsuperscript{134} (scheme 90).

The use of zinc as a reducing agent affords the (Z)-alkene via the following proposed mechanism. Adsorption of the alkyne 334 onto the metal surface, followed by two successive one-electron transfers from the zinc 4s orbital to the alkyne $\pi$*-orbital gives organozinc intermediate 335 with its R substituents in the Z-configuration. Desorption of 335 from the metal surface followed by hydrolysis affords the (Z)-alkene 336.
Activation of zinc with potassium cyanide is not ideal for use owing the high toxicity of the latter. However Brandsma and co-workers have also developed an activated couple reduction using a zinc/copper/dibromoethane\textsuperscript{133} couple for the reduction of alkynes to (Z)-alkenes. This couple has also been utilised in the reduction of alkynes where Lindlar reduction failed,\textsuperscript{135} and was safer to use in the laboratory.

The zinc/copper/dibromoethane activated couple was prepared by heating zinc in ethanol at reflux with 1,2-dibromoethane, followed by the addition of lithium bromide and copper(I) bromide at \textit{ca.} 50 °C. The resulting brick red coloured solid was isolated by filtration and dried \textit{in vacuo}. A solution of alkyne 312 in EtOH was heated to reflux with the prepared couple, and subsequently filtered. When a small mass of the couple was utilised, incomplete reaction was observed and only a very small amount of the desired alkene was observed by $^1$H NMR. However, when the mass of couple was increased this had a detrimental effect on the reaction. With large masses of the couple no alkene was observed by $^1$H NMR and the recovered product mass was significantly decreased. This indicated a possible retention of the substrate and/or products by the zinc couple. Hence this method was unsuitable and an alternative was sought.

Another activated zinc couple, prepared with copper and silver has also been utilised in the literature for the reduction of alkynes to (Z)-alkenes\textsuperscript{136}, especially where other methods such as catalytic hydrogenation were unsuccessful.

\begin{center}
\textbf{Scheme 92}
\end{center}

\[
\begin{array}{c}
\text{MeOH, r.t, 6 h, 56%} \\
337 \quad \xrightarrow{\text{Zn/Cu/Ag couple}} \quad 338
\end{array}
\]

Many of the literature substrates using this Zn/Cu/Ag couple contained highly conjugated alkynes, for example the reduction of enyne 337 to 338 (scheme 92). This reduction was unsuccessful under Lindlar conditions, and the Zn/Cu/dibromoethane method caused isomerisation owing to the elevated temperature required with this couple. The Zn/Cu/Ag couple has an advantage over the Zn/Cu/dibromoethane method, as it can be utilised at ambient temperature.
The zinc/copper/silver couple was prepared by the method of Avignon-Tropis,\textsuperscript{136} and was freshly prepared for each reaction. The reduction of alkyne 312 was carried out in aqueous methanol (scheme 93). However only a trace of alkene 296 was observed when the reaction was carried out at ambient temperature, but by heating to 50 °C, the reduction of alkyne 312 was effected in 45% yield. The low yield was attributed to retention of the product and/or substrate by the couple, but no reaction was observed if the quantity of zinc was halved.

2.7.3 Hydroboration

Hydroboration has been widely for the conversion of alkynes to alkenes,\textsuperscript{137} via a vinylborane intermediate that is subsequently converted to the alkene. In the case of internal alkynes the result is a net syn-hydrogenation to give the Z-alkene. Therefore the reaction is stereoselective. Disiamylborane is often utilised for the hydroboration of alkynes and it is more selective than dicyclohexylborane.

The main challenges faced when approaching the hydroboration of alkyne 312 was solubility in a compatible solvent. Polar solvents such as alcohols, which completely dissolve the propargyl alcohol substrate, cannot be used due to their reactivity with disiamylborane. The substrate had a very low solubility in THF and, as low temperature was required, the disiamylborane solution (prepared by treatment of 2-methylbut-2-ene with BH\textsubscript{3}.THF at 0 °C\textsuperscript{138}) was added to a suspension of the alcohol in THF at −20 °C. However, even after stirring the suspension for 18 h only the starting material 312 was obtained.
The failure of the hydroboration of alkyne 312 could be explained by the presence of the free alcohol, which would be expected to react with the borane, and its low solubility in THF. Thus the hydroboration was attempted on silyl ether 313. We hoped that the TBS group would give increased solubility to the substrate (scheme 95).

However with either one or two equivalents of disiamylborane, again only unreacted starting material was recovered. The lack of reactivity may be due to the presence of the free NH group in the molecule, although extra equivalents of disiamylborane were added to the reaction to allow for this. Therefore an alternative strategy was sought.

2.7.4 An Alternative Lindlar Reduction Strategy

After the addition of the Grignard reagent derived from silyl ether 304 to 3-methylhydantoin 314, the product is the tertiary alcohol 317, in which the alkyne is not conjugated. Therefore we hoped that the reduction of this tertiary alcohol product would proceed more selectively and afford tertiary alcohol 340 (scheme 96).

However attempted Lindlar reduction of 317 led to elimination of the tertiary alcohol, and alkene 339 and the over-reduced product 341 were obtained in a 3:1 ratio (scheme 97).
The acidic nature of the catalyst may be effecting the elimination step. Therefore sodium carbonate was added to the reaction. However, this failed to improve the reaction yield or ratio of products.

The low solubility of propargylic alcohol 312 may have been contributing to the problems encountered with the Lindlar reduction to the allylic alcohol, as the concentration of alcohol in solution at 0 °C was quite low. Therefore we decided to reverse the deprotection and reduction steps and carry out the Lindlar reduction of silyl ether 313 (scheme 98) prior to TBS deprotection to afford the allylic alcohol 296.

Table 6

<table>
<thead>
<tr>
<th>Entry</th>
<th>313 (mg)</th>
<th>H₂ (mL)</th>
<th>Time (min)</th>
<th>Yield of 339 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>a</td>
<td>120⁵</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>203</td>
<td>a</td>
<td>100⁶</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>503</td>
<td>a</td>
<td>90</td>
<td>100 (341)</td>
</tr>
<tr>
<td>4</td>
<td>300</td>
<td>a</td>
<td>50</td>
<td>38⁷</td>
</tr>
<tr>
<td>5</td>
<td>333</td>
<td>30⁸</td>
<td></td>
<td>56</td>
</tr>
<tr>
<td>6</td>
<td>277</td>
<td>30⁹</td>
<td></td>
<td>53⁹</td>
</tr>
</tbody>
</table>

⁴H₂ balloon utilised and volume not measured; ⁵TLC at 60 and 120 min; ⁶TLC at 80 and 100 min; ⁷1 equiv. H₂; ⁸1.2 equiv. H₂; ⁹339:341 ratio 1:1 by ¹H NMR; ¹⁰339:341 ratio 4:1.
5 Mol % of the Lindlar catalyst was used for the reaction as this gave the optimum results for the propargyl alcohol substrate 312 and the temperature was kept at 0 °C throughout. Table 6 summarises details the optimisation of the reaction. The initial attempts at Lindlar reduction of 313 using a hydrogen balloon looked promising, with yields of up to 78% of the desired alkene 339 being obtained (entry 2). This result, however, was not reproducible on a larger scale (entries 3 and 4). By monitoring the uptake of H₂ a reproducible yield of 53% of 339 could be obtained (entry 6). The extra 0.2 equivalents of H₂ added to remove all of the substrate to facilitate isolation of alkene 339 by flash chromatography on a larger scale.

2.8 Deprotection of the Allylic Silyl Ether

![Scheme 99](image)

The conditions used for deprotection of silyl ether 313 were also attempted for the allylic substrate 339, but upon heating in a 3:1:1 mixture of AcOH:THF:H₂O at 50 °C clean deprotection did not occur, and a side product 342 was observed. Attempts to purify this side product were unsuccessful, but it was tentatively assigned the structure 342. We proposed that this cyclisation occurs by protonation of the allylic alcohol 296 and subsequent attack of the imidazolone lone pair with loss of the H₂O leaving group (scheme 100). This attack generates N-acyliminium ion 343, which is analogous to the second N-acyliminium ion required in our proposed biomimetic synthesis of Agelastatin A and is therefore worthy of note. The N-acyliminium ion subsequently underwent loss of H⁺ to afford 342.
When NH₄F in MeOH at 50 °C was used as an alternative deprotection strategy, the reaction was clean with no side reactions, and allylic alcohol 297 was obtained in 63% yield.

2.9 Oxidation of the Allylic Alcohol

After obtaining a route to the allylic alcohol, the next step was to carry out oxidation to aldehyde 344 in order to carry out further functionalisation for introduction of the leaving group X in 286 (scheme 101). The leaving group will be required for N-acyliminium ion generation after coupling to the A-ring. Several mild methods exist for the oxidation of Z-allylic alcohols to Z-enals.

2.9.1 Manganese Dioxide Oxidation

Manganese dioxide is a synthetically useful oxidising agent for the selective oxidation of allylic alcohols to aldehydes. It is a non stoichiometric material MnOₓ where 1.93<ₓ<2, but usually stated as MnO₂. The activity of manganese dioxide depends on the method of preparation. It is commonly used in chlorinated solvents such as DCM or CHCl₃, petroleum ether or benzene and typically between 5 and 20 equivalents of the oxidant are required. MnO₂ can be used in polar solvents such as alcohols and acetone but these can deactivate the oxidant as the solvent molecules compete with the substrate for binding on the MnO₂ surface. Hence even larger excesses are required in these cases. Manganese dioxide is commercially available but more highly active forms can be easily prepared synthetically.
The oxidation of allylic alcohol 296 with commercial MnO₂ was investigated in MeOH and acetone as solutions of 296 could be obtained in these solvents at reflux. In both cases, the crude ¹H NMR indicated a trace of an aldehyde product by the presence of a very small peak at 9.7 ppm, but the spectrum mainly indicated recovered starting material. Addition of a second portion of MnO₂ after heating with an initial portion for 16 h gave no further conversion to the aldehyde by ¹H NMR. The addition of large excesses of MnO₂ also resulted in a decrease in the mass of crude material recovered. It was therefore concluded that the alcohol and/or the aldehyde product was adhering to the surface of the couple, and despite washing the spent couple with copious amounts of solvent, the recovered mass could not be increased.

Manganese dioxide can be prepared in more active forms than the commercially available material.¹³⁹ We hoped that a highly active form of manganese dioxide, prepared by a conproportionation reaction of manganese chloride and potassium permanganate¹³⁹,¹⁴⁶,¹⁴⁷, would allow the oxidation to proceed with a smaller mass of oxidant and in turn facilitate product recovery.

Manganese dioxide 345 was prepared in quantitative yield from manganese chloride tetrahydrate and potassium permanganate according to the method of Fatiadi.¹⁴⁶ However, when 10 equivalents of this active oxidant in refluxing MeOH were employed for the oxidation of 296, again only a trace of the aldehyde was observed by ¹H NMR. It was therefore concluded that the combination of polar solvent and highly polar substrate was deactivating the MnO₂ surface and binding was occurring. Hence an alternative oxidant was sought.

2.9.2 IBX Oxidation

1-hydroxy-1,2-benziodoxolin-3(1H)-one (IBX) 347 is a hypervalent iodine oxidising agent prepared by oxidation of 2-iodobenzoic acid 346. It is of limited synthetic use owing to its low solubility in most organic solvents, however it is a valuable oxidant when used in DMSO.¹⁴⁸ It can also be used as a suspension in other solvents. IBX is utilised for the oxidation of secondary alcohols to ketones and primary alcohols to aldehydes. The most practical method for the preparation of IBX is that of Santogostino and co-workers¹⁴⁹ (scheme 102) involving the oxidation of 2-iodobenzoic acid 346 by
Oxone® (2KHSO₃-KHSO₄-K₂SO₄) in water at 70°C. This method for IBX preparation by oxidation with Oxone is superior to that of Greenbaum¹⁵⁰ where carcinogenic potassium bromate is utilised in hot aqueous sulphuric acid.

The oxone oxidation method afforded IBX in high purity in but some adaptation of the literature procedure¹⁴⁹ was required. The reagents were not soluble at the stated temperature of 70°C; therefore the temperature was cautiously increased until, at 90°C, complete dissolution occurred. After cooling, the precipitate of IBX 347 was isolated in 60% yield and was stored in the absence of light at 0°C. Initially a test reaction was carried out in DMSO-d₆ with ¹H NMR monitoring. A solution of IBX in DMSO-d₆ was added to allylic alcohol 296 at ambient temperature. After 3h, all of the alcohol had been consumed. However, ¹H NMR analysis indicated an alkene J coupling constant value of 16 Hz, which was not consistent with a Z-alkene. It was therefore concluded that the oxidation afforded only the undesired E-enal 348 (scheme 103).

This observation can be rationalised by considering the conjugated nature of the allylic aldehyde (scheme 104). The (Z)-enal 344 is initially formed but a resonance form 349 can be envisaged with a positive charge on nitrogen and negative charge on oxygen. This form now has a single bond in what was originally the ene position. This resonance form indicates that the alkene bond has a high degree of single bond character. Therefore, after initial formation of the (Z)-enal, rotation can occur around the alkene bond. Although the two isomers are in equilibrium, the (E)-isomer 348 is
more thermodynamically stable and hence is the only product observed by $^1$H NMR
analysis.

![Scheme 104](image)

A 0.31 mmol scale reaction was carried out in DMSO in order to determine the reaction
yield and after extraction from water, the $E$-allylic aldehyde 348 was isolated in 25% yield after flash chromatography. Isolation was again hampered by the high water
solubility of the product.

2.10 Oxidation of the Propargylic Alcohol

Our attempts to oxidise the allylic alcohol 296 demonstrated that conjugation to the
aldehyde would prevent the (Z)-alkene being introduced and retained throughout the
synthetic route if it were introduced before the oxidation step. Therefore the strategy to
prepare the “right hand” imidazolone fragment was altered so as to carry out the other
necessary manipulations for introduction of the required leaving group to give 350
before alkyne reduction to the (Z)-alkene 286 (Scheme 105).
Propargylic alcohol 312 was insoluble in most of the solvents commonly used for oxidations, such as DCM and CHCl₃, but it was soluble to a degree in more polar solvents. Alcoholic solvents were unsuitable do to their ease of oxidation with most common oxidising agents. The alcohol was however soluble in DMSO and therefore oxidation with IBX could be attempted. A test reaction was then carried out in DMSO-d₆ and ¹H NMR detected the product aldehyde.

However on a larger scale the isolation of aldehyde 351 was not possible, due to its high polarity and water solubility. Attempts to remove the DMSO by heating in vacuo resulted in the decomposition of the aldehyde.

It was postulated that trifluoroethanol would be less easily oxidised than other alcoholic solvents due to the electron withdrawing effect of the CF₃ group. Test reactions using IBX in trifluoroethanol showed aldehyde product by ¹H NMR. However on a larger scale the results were not reproducible.
2.11 Application of the Diethylacetal as a Route to the Ynal

As the methods of oxidation had not been successful, an alternative route to ynal 351 was investigated. Introduction of the side chain using an alkyne Grignard reagent derived from 3,3-diyethoxypropyne 352 to 3-methylhydantoin 314 and subsequent elimination would allow the required ynal 351 to be obtained by acid catalysed removal of the acetal from 354 (scheme 106). Table 7 summarises the investigation into this Grignard addition.

<table>
<thead>
<tr>
<th></th>
<th>314 (mmol)</th>
<th>352 (equiv)</th>
<th>Base</th>
<th>Time (h)</th>
<th>T</th>
<th>% conversion</th>
<th>% yield 354</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.4</td>
<td>2</td>
<td>BuMgCl</td>
<td>42</td>
<td>rt</td>
<td>0</td>
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</tr>
<tr>
<td>2</td>
<td>4.4</td>
<td>3</td>
<td>BuMgCl</td>
<td>24</td>
<td>rt</td>
<td>50&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2.2</td>
<td>3</td>
<td>BuLi</td>
<td>23</td>
<td>rt</td>
<td>12&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>1.8</td>
<td>3</td>
<td>BuMgCl</td>
<td>48</td>
<td>rt</td>
<td>60&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>1.8</td>
<td>3</td>
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</tr>
<tr>
<td>6</td>
<td>4.3</td>
<td>10</td>
<td>BuMgCl</td>
<td>24</td>
<td>rt</td>
<td>85&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>8.8</td>
<td>3</td>
<td>BuMgCl</td>
<td>26</td>
<td>rt</td>
<td>-</td>
<td>14&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>8.9</td>
<td>3</td>
<td>BuMgCl</td>
<td>65</td>
<td>rt</td>
<td>-</td>
<td>21&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
<tr>
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<td>1.7</td>
<td>3</td>
<td>BuMgCl</td>
<td>19</td>
<td>40</td>
<td>-</td>
<td>32&lt;sup&gt;d,e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Grignard reagent added to a solution of 314 in THF; <sup>b</sup>estimated from H NMR integrals; <sup>c</sup>4% obtained after recrystallisation; <sup>d</sup>Crude eliminated by stirring with silica/CHCl<sub>3</sub> overnight; <sup>e</sup>yield from flash chromatography.

Unlike the addition of silyl ether 304 to 3-methylhydantoin 314, the addition of the diethyl acetal 352 as a Grignard reagent did not give a clean reaction and as observed
previously with the addition of silyl ether 304, the reaction did not go to completion. After work up the excess alkyne could not be removed in vacuo to give the tertiary alcohol product 353 as a solid. Instead the crude tertiary alcohol product was a tarry material, containing a solid, which could not be easily or consistently recrystallised in more than a few percent yield (entry 4). In an attempt to facilitate purification, the tosic acid elimination step used previously for the silyl ether addition was attempted, but this effected some deprotection of the acetal as well as the desired elimination step. Treatment of the crude product containing excess acetal with acid was therefore undesirable as the free propargylic aldehyde is known to be explosive. Flash chromatography of the tertiary alcohol 353 was not possible as incomplete elimination to the imidazolone was observed on silica. Stirring a solution of the crude product with silica overnight was sufficient to effect the elimination on a small scale (entries 7-9), but this was not suitable for scale-up. Therefore two aspects of this reaction were investigated: Increasing the % conversion to 353 and the subsequent isolation of the eliminated imidazolone product 354.

The reaction was carried out using the same method as for the addition of silyl ether 304, but the H₂O wash step was omitted from the workup. This allowed the % conversion of 314 to tertiary alcohol 353 to be estimated by ¹H NMR. Changing the base to n-butyl lithium had a detrimental effect on the conversion (entries 2 and 3). An increase to 10 equivalents of the Grignard reagent gave 85% conversion in 24 h (entry 6), but recrystallisation of the product failed.

2.11.1 Work Up Investigation

The work up procedure was next investigated in order to facilitate the isolation of the product. If the crude tertiary alcohol 353 could be deprotonated, the excess free acetal could be extracted from a basic aqueous solution of the crude material (scheme 107).
The crude reaction product was dissolved in aqueous 1M NaOH to deprotonate the product. The excess diethyl acetal and tarry material was then extracted with Et₂O. ¹H NMR of these Et₂O extracts indicated the presence of the unreacted acetal 352, but also some of the Grignard product 354. Extraction of the product from the aqueous solution was then investigated using two methods.

Firstly the solution was neutralised with 1M HCl to pH 7-8 and extracted with EtOAc. ¹H NMR of these extracts indicated the presence of the desired product, but the product could not be recrystallised. Column chromatography gave a low yield of product (entry 8). In the second method the aqueous solution was acidified to pH 1 with 1M HCl and stirred for 4 h at ambient temperature to effect the elimination and removal of the acetal in a one-pot procedure to afford aldehyde 351. However after six successive extractions the extraction was not complete. This can be attributed to the high polarity and hence water solubility of the aldehyde product and is typical of the intermediates in this synthetic strategy. Due to the incomplete extraction this workup method was unsuitable.

The small-scale acetal addition reactions gave, at best, a 32% yield of the Grignard addition product 354, which was significantly lower than that for the silyl ether Grignard addition and the results were not reproducible. Difficulties were encountered in the recrystallisation of the product, and as column chromatography on a large scale would be difficult the reaction was unsuitable for preparation of multi-gram quantities.
2.12 A New Approach - Protecting Group Strategy

By this point in the project it became clear that the high polarity and low organic solvent solubility were preventing many reaction conditions and reagents from being utilised. Isolation of products was also being hindered by this problem. Therefore it was concluded that in order to achieve some progress in the synthesis a protecting group would need to be added to the free NH in the imidazolone ring. Although this was not present in the natural product, if the biomimetic synthesis could be carried out on a N-protected substrate, it would give some indication as to its feasibility. Initially a p-methoxybenzyl (PMB) group was utilised as this can be easily removed under a variety of different conditions.

2.12.1 Introduction of a PMB Group

It was predicted that the addition of the PMB group after hydantoin methylation would facilitate the Grignard addition of the side chain by solubilising the hydantoin substrate. The protecting group would also remove the need for an extra equivalent of the Grignard reagent for NH deprotonation before the addition. Treatment of 3-methylhydantoin 314 with sodium hydride and p-methoxybenzyl chloride afforded the protected 3-methylhydantoin 356 in 81% yield (Scheme 108).

Attempts to add the diethyl acetal Grignard reagent derived from 352 however failed to give any product by $^1$H NMR when using the same conditions as for the addition to the unprotected hydantoin.
The Grignard reagent formed from silyl ether 304 was also added to the PMB protected hydantoin 356, and although this gave some product the yields were decreased compared with the same addition to the free NH substrate.

As the addition of the PMB group before the Grignard addition appeared to be detrimental to the Grignard addition yield, the protecting group was added to 313 after the Grignard reaction (scheme 109). The use of potassium tert-butoxide as a base gave higher yields of 358 than sodium hydride. The subsequent TBS deprotection with TBAF/THF was facile, and afforded propargylic alcohol 359 in 99% yield.

Having prepared propargylic alcohol 359, the alkyne was subsequently reduced using the previously discussed zinc/copper/silver couple in 77% yield. No over-reduction was observed and the reaction afforded the (Z)-alkene 360 exclusively (scheme 110).

2.13 Oxidation of the Allylic Alcohol and Imine Formation

With the (Z)-allylic alcohol 360 in hand, the oxidation to enal 361 could be investigated. We hoped that the presence of the PMB protecting group would allow milder conditions for the oxidation to be utilised, thus retaining the (Z)-geometry of the enal.
Oxidation of alcohol 360 with manganese dioxide gave a 9:1 ratio of the (Z)- and (E)-enals 361 and 362, but upon reaction with benzylamine in the presence of activated molecular sieves, the imine formed was exclusively the undesired (E)-isomer 363 (scheme 111). This result can be rationalised by considering the resonance forms of the imine in the same way as for the enal 348 in the unprotected hydantoin strategy. The two isomers of the imine are in equilibrium but the equilibrium lies in favour of the undesired E-isomer 363 as this is the more thermodynamically stable.

We had hoped to introduce a cyanide leaving-group to the imine 363 at this stage by reaction of the imine with trimethylsilylcyanoide (TMSCN) (scheme 112).

However reaction of imine 363 with TMSCN and formation of the α-aminonitrile functionality in 365 would “trap” the undesired (E)-isomer of the product as the imine
C=N bond, through which delocalisation occurs, is removed. Therefore this route was not pursued.

2.14 Introduction of the Leaving Group Before Alkyne Reduction

Despite the increased solubility gained from introduction of the PMB protecting group allowing milder chemistry to be attempted, the enal bond still could not be retained as its (Z)-isomer. Therefore the alternative strategy of introduction of the (Z)-alkene after refunctionalisation of the propargylic aldehyde was revisited (Scheme 113).

Scheme 113

Oxidation of propargylic alcohol 359 and imine formation from the resulting aldehyde 366 and benzylamine will allow a cyanide leaving group to be introduced before the alkyne reduction to afford the "right hand" imidazolone fragment 369.

2.14.1 Parikh-Doering Oxidation

Several methods exist in the literature for the oxidation of primary alcohols to aldehydes and secondary alcohols to ketones by "activated" DMSO via the formation of a ROS$^+$Me$_2$ species. The most widely used is the Swern oxidation$^{151}$ involving oxalyl chloride and Et$_3$N. The Parikh-Doering oxidation$^{152}$ involves initial formation of an Me$_2$S$^+$OSO$_3^-$ complex from sulfur trioxide and DMSO,$^{153}$ which upon addition of an alcohol and Et$_3$N forms the ROS$^+$Me$_2$ species. This intermediate is then deprotonated
by Et$_3$N and rearranges to give the aldehyde or ketone and dimethyl sulfide. Scheme 114 illustrates the mechanism for oxidation of a generic primary alcohol to an aldehyde.

The advantage of the Parikh-Doering oxidation over other methods is that only near-ambient temperatures are required. Sulfur trioxide is commercially available as its complex with pyridine, which is an easy to handle solid. The formation of by-products is also decreased and the reaction yields are comparable with those from the Swern oxidation.

When carrying out the oxidation in DMSO the low ambient temperature in the laboratory made it necessary to maintain the reaction temperature at 30 °C in order to prevent freezing of DMSO during the reaction. Literature procedures typically use a three-fold excess of the pyridine-sulfur trioxide complex and a 10-fold excess of triethylamine so these conditions were utilised.

However, the reaction of propargylic alcohol 359 yielded an unexpected aldehyde, where an SMe group had added to the alkyne (Scheme 115). This resulted in a mixture of the (E)- and (Z)-isomers, 370 and 371, of the allylic aldehyde.$^{154}$

This result can be explained by considering that an initial oxidation to aldehyde 366 occurs followed by 1,4-addition of S(CH$_3$)$_2$ to form a cationic intermediate 372.
(Scheme 116). A nucleophile, such as pyridine or triethylamine, then removes one of the methyl groups to give the observed aldehyde products 370 and 371.

NOE experiments showed an enhancement of the alkene proton on irradiation of the SCH$_3$ group of the major product, indicating that the major product was the $E$-isomer 370 (scheme 117).

Furthermore, irradiation of the ($Z$)-isomer aldehyde proton signal at 9.42 ppm gave a NOE enhancement of the ($E$)-isomer signal at 10.26 of 1.05 %, indicating that the two isomers were interconverting in C$_6$D$_6$ solution. At ambient temperature, the ratio of $E$:Z was 9:1, and upon heating of the $^1$H NMR sample to 50 °C the ratio decreased to 5:1.

When the mixture of aldehydes was left in CDCl$_3$ for several hours, an unexpected transformation to a new product was observed. Protonation of aldehyde 370 by the mild acid in CDCl$_3$ and a subsequent cyclisation occurred to give a bicyclic ketone 375 (scheme 118).
Although not expected, this result was interesting. In the cyclisation mechanism a cation is formed on the aldehyde oxygen in the same position as we planned to generate an N-acyliminium ion in the biomimetic synthesis. The initial attack on the aldehyde by the imidazolone lone pair is analogous to the first cyclisation of the proposed biosynthesis and the cyclisation forms N-acyliminium ion 373 in the same position as that required for the second cyclisation of the biomimetic synthesis.

2.14.2 Barium Manganate Oxidation

The oxidation of the propargylic alcohol 359 to the desired propargylic aldehyde 366 was effected using 20 equivalents of manganese dioxide, but only in a moderate yield of 53%. Barium manganate\textsuperscript{155} is an alternative stable Mn\textsuperscript{VI} salt, which selectively oxidises allylic and benzylic alcohols to aldehydes, and is often used as a substitute for manganese dioxide. The yields are equal to or better than for manganese dioxide and the reactions are often more rapid. It is also a more attractive reagent for medium to large-scale reactions as less oxidant is required, typically 1 to 10 equivalents (compared with 5 to 50 equivalents for manganese dioxide). The oxidation of propargylic alcohol 359 was affected in a good 77% yield using only 8 equivalents barium manganate (scheme 119).
2.14.3 Dess-Martin Periodinane Oxidation

The oxidation was also attempted with Dess Martin periodinane 376 in order to further increase the yield. The oxidant was prepared in 73% yield by heating IBX 347 in acetic anhydride with tosic acid according to the method of Ireland and Liu.\textsuperscript{156} The oxidation was effected by the addition of Dess-Martin periodinane to a solution of alcohol 359 in wet DCM. After 1 h the reaction was complete, NaOH solution was added to remove the periodinane by-products and then the product was extracted with Et₂O. However an unexpected result was observed. The product no longer contained the aldehyde and instead terminal acetylene 378 was observed in 58% yield. This result can be rationalised by considering that aldehyde 366 is initially formed but then undergoes nucleophilic attack by OH\textsuperscript{-}, followed by loss of formic acid to afford the terminal acetylene (scheme 120).

This mechanism was confirmed by treatment of the ynal 366 with sodium hydroxide at ambient temperature. The terminal alkyne 378 was obtained in 78% yield (scheme 121).
Although reactions of this type are known in the literature, normally high temperatures are required, for example diynal 379 requires heating to 50 °C in 5M NaOH for formylation to occur to afford 380\(^{157}\) (scheme 122).

The desired propargylic aldehyde can be obtained from the Dess-Martin periodinane oxidation if an alternative workup using a combination of sodium hydrogen carbonate and sodium thiosulfate is utilised. Using these conditions aldehyde 366 was obtained in an excellent 93% yield.

Having prepared ynal 366, we planned to introduce a leaving group to remove the 1,2 unsaturation. We hoped that the introduction of an α-aminonitrile or a related functionality would allow the subsequent reduction of alkyne 368 or 381 to (Z)-alkene 369 or 382 to proceed without any interconversion to the undesired (E)-alkene (scheme 123).
Propargylic aldehyde 366 was treated with benzylamine and trimethylsilylcyanide at 0 °C according to a literature procedure. Some imine formation was observed by $^1$H NMR but no α-aminonitrile was detected. A two-step procedure was then attempted. Pre-formation of imine 367 was effected by treatment of aldehyde 366 with benzylamine and activated molecular sieves in DCM. A sample was removed to confirm imine formation by $^1$H NMR analysis. However subsequent addition of TMSCN at ambient temperature gave no reaction and only unreacted imine was observed. Heating the reaction led to product decomposition.

Benzotriazole can also be used as a leaving group for the generation of acyliminium ions. However a one-pot reaction between the aldehyde 366, benzylamine and benzotriazole in toluene under Dean Stark conditions also gave none of the desired product 381.

2.15 Application of the β-Thio Aldehyde

As the leaving group could not be introduced via ynal 366, attention was turned to the β-thioaldehydes 370 and 371 obtained from Parikh-Doering oxidation of propargylic alcohol 359. This mixture predominantly adopts the required alkene geometry 370 and as the alkene is introduced during the oxidation step alkyne reduction is avoided. Although agelastatin A does not contain the methylsulfanyl group, if a model biomimetic synthesis could be effected from a precursor containing this group, some indication as to the feasibility of our target biomimetic synthesis could be obtained. The methylsulfanyl group could be reductively removed after cyclisation.

We planned to introduce a leaving group to aldehyde 370, via the formation of an imine 383 (scheme 124).
Two methods for introduction of the leaving group were investigated. Acylation of imine 383 would give a precursor for $N$-acyliminium ion generation. We hoped that reaction of imine 383 with acetic anhydride or acetyl chloride (scheme 125) would give a model $N$-acyliminium ion precursor 384 or 385, and if this were successful the pyrrole amide could be introduced in same way.

![Scheme 125](image)

Treatment of the mixture of aldehydes 370 and 371 with benzylamine and activated 4 Å molecular sieves in DCM gave a mixture of 4 structural isomers of imine 383. Upon treatment with acetyl chloride the imine disappeared by NMR, however no products could be isolated or characterised. Upon treatment of the imine with acetic anhydride, imine and aldehyde were the only products detected by $^1$H NMR.

As imine acylation was unsuccessful, we hoped that imine 383 could be converted into the corresponding $\alpha$-aminonitrile 387 and hence afford an alternative $N$-acyliminium ion precursor. This method would introduce the leaving group and the amine functionality required for attachment of the A-ring to afford 388.
Imine 383 was treated with 6 equivalents of trimethylsilyl cyanide and a mixture of two α-aminonitrile products 387 in a (E):(Z) ratio of 1.6:1 was observed by $^1$H NMR. These compounds were identified by an alkene CH doublet at 5.30 (E-isomer) and 5.42 (Z-isomer), and a corresponding doublet for the CHCN proton at 3.97/4.59 ppm. Unfortunately the α-aminonitrile 387 was not stable to flash chromatography and decomposed to a mixture of imine 383 and aldehyde 370. Therefore crude α-aminonitrile 387 was treated with pyrrole-2-carbonyl chloride 113 and triethylamine, but none of the coupling product 388 was detected. Broad peaks would be expected in the $^1$H NMR spectrum owing the presence of rotamers in the product. The addition of DMAP had no effect on the reaction and the use of trichloroacetylpyrrole 389, prepared using a literature procedure from pyrrole and trichloroacetyl chloride in 92% yield, in the place of the acid chloride also gave no coupling products. Instead only a mixture of the α-aminonitrile 387, imine 383 and aldehyde 370 was observed.

2.16 N-Acyliminium Ion Generation By Oxidation

Our efforts thus far indicated that the introduction of a leaving group in the “right hand” imidazole fragment would be unlikely to afford a stable amine for introduction of the A-ring. Therefore an alternative method for the generation of the N-acyliminium ion was sought. If a hydrogen atom was present in the place of the leaving group then the N-acyliminium ion could be introduced by oxidation, of which several methods are available (ref). The β-thio aldehyde 370 could be converted into an allylic amine 390
by reductive amination, and subsequent coupling with pyrrole-2-carboxylic acid 123 would afford the desired tertiary amide 391 (scheme 127).

![Scheme 127](image)

The reductive amination was effected as a two-step process. Treatment of aldehyde 370 with benzylamine in MeOH and activated molecular sieves gave imine 383 and this was subsequently reduced by sodium borohydride to give the secondary amine 390 in 51% yield. At this stage it was possible to separate some of the (E)-isomer but on a larger scale a mixture of isomers was carried through.

Pyrrole-2-carboxylic acid 123 was converted to the corresponding acid chloride 113 by treatment with oxalyl chloride. Amine 390 was then treated with the acid chloride and triethylamine, but no amide was observed. The addition of DMAP resulted in the formation of some of amide as broad signals were detected by $^1$H NMR, corresponding to rotamers of the amide product 391. However the reaction did not go to completion, even with a large excess of the acid chloride. This could be explained by the low reactivity and/or stability of pyrrole-2-carbonyl chloride, as where it has been previously utilised a large excess of the nucleophile is often required to allow reactions to proceed.\(^9\)

Amides are often prepared by the reaction of an amide and a carboxylic acid in the presence of a $N,N'$-alkylcarbodiimide coupling reagent, a method commonly used for
the synthesis of peptides. \( N,N' \)-diisopropylcarbodiimide (DIC) is often used in preference to \( N,N' \)-dicyclohexylcarbodiimide (DCC) as the diisopropyl reagent is a liquid, making it easier to handle than the solid DCC, which is highly sensitising. Chlorinated solvents are most commonly used for this type of coupling reactions, however they were unsuccessful here owing to the low solubility of pyrrole-2-carboxylic acid. Amine 390 was therefore treated with a two-fold excess of pyrrole-2-carboxylic acid 123 and DIC in THF at ambient temperature and the desired amide 391 isolated in 91% yield.

Having prepared amide 391, we planned to carry out its oxidation to \( N \)-acyliminium ion 392 (scheme 128) and to observe subsequent reactions.

![Scheme 128](image)

Amide 391 was treated with trityl tetrafluoroborate, which has also been utilised as an oxidizing agent for the generation of \( N \)-acyliminium ions. Wanner and co-workers used this method for the generation of substituted tetrahydroquinolines. However the expected reaction was not observed. Instead several fragments of amide 391 were isolated (scheme 129).

![Scheme 129](image)
Isolation of fragment 395 indicates that the trityl group has attacked and removed the methylsulfonyl group. The trityl group has also added to the pyrrole ring fragment to afford fragment 394. Removal of the PMB protecting group also occurred, evident by the isolation of fragment 396, although we were unable to determine the nature of group X. But the apparent hydrolysis of the amide suggests that the desired oxidation may have taken place to some extent. Having evidence that the methylsulfonyl group was interfering with the oxidation step, we chose to prepare a precursor lacking this functionality.

2.17 Preparation of the Target \( N \)-Acyliminium Ion Precursor

Alcohol 359 was treated with benzenesulfonyl chloride and \( n \)-butyllithium in THF. This afforded the benzenesulfonate adduct, but upon treatment with benzylamine in acetonitrile none of propargylic amine 397 was isolated. Instead a complex mixture of unidentified products was obtained. The same result was obtained if the tosylate was utilised in place of the benzenesulfonate adduct. This result was unexpected as but-2-yn-1-yl tosylate is readily converted into \( N \)-but-2-ynyl-\( N \)-benzylamine in 71% yield under the same conditions.\textsuperscript{159}

![Scheme 130](image)

The propargylic amine could alternatively be introduced by reductive amination of the corresponding imine (scheme 130). Aldehyde 366, prepared by oxidation of alcohol 359 with Dess-Martin periodinane 376, was stirred with benzylamine and activated.
molecular sieves in EtOH to afford the corresponding imine. However upon treatment of this imine 400 with sodium borohydride, only 48% of the desired propargylic amine 397 was obtained. This was explained by the isolation of 28% of the allylic amine as a 2:1 mixture of Z- and E-isomers 398 and 399 arising from the 1,4 reduction of imine 401 prior to 1,2 reduction of imine 400 (Scheme 131).

Scheme 131

The reducing agent sodium borohydride has only a short life in alcoholic solvents and the addition of subsequent aliquots was often required after the initial addition in order for the reduction to go to completion by TLC analysis. Sodium cyanoborohydride is reported to give high yields in reductive aminations\textsuperscript{160} but when utilised here the reaction did not proceed cleanly and the yields were low. A far superior reagent was sodium triacetoxyborohydride,\textsuperscript{161} which has the advantage of being compatible with chlorinated solvents and therefore has a longer lifetime.

However when one equivalent of sodium triacetoxyborohydride was utilised the yield of the desired propargylic amine was low. This was due to the occurrence of a side reaction and formation of a tertiary amine 403 (scheme 132). This resulted from the addition of the secondary amine 397 (from the reductive amination) to the unreduced imine 400 affording iminium ion 402, which was subsequently reduced to give the undesired tertiary amine 403.
This side reaction occurs because the rate of addition of secondary amine 397 to imine 400 is faster than the reduction of imine 400. Increasing the excess of benzylamine used in the initial imine formation significantly reduced the amount of 403 formed. Addition of benzylamine to imine 400 competes with addition of the secondary amine 397, and with benzylamine addition the initial imine 400 is regenerated. An increase in the amount of reducing agent also decreased the yield of 403 formed as the rate of imine reduction is increased relative to the addition of 397 to the imine 400. Therefore upon treatment of aldehyde 366 with 5 equivalents of benzylamine in DCM and subsequent reduction of imine 400 with 3 equivalents of sodium triacetoxyborohydride, the yield of the secondary amine 397 was increased to 85% and the unwanted side reaction reduced to trace levels by $^1$H NMR (scheme 133). On a large scale the excess benzylamine was removed azeotropically with $p$-xylene.
Treatment of alkyne 397 with the zinc/copper/silver couple however gave a mixture of (Z)- and (E)-alkenes 398 and 399 in a 2:1 ratio in 52% yield. This result was unexpected as reduction of propargylic alcohol 359 gave only the (Z)-alkene 360 using the same method. If the free amine binds more tightly to the surface of the couple, this could allow double bond isomerisation to occur and would be evidence for the moderate yield for this reduction. It was difficult to completely separate isomers, especially on a larger scale. As the combined yield was low an alternative route was sought.

We hoped that if pyrrole-2-carboxylic acid 123 could be coupled to propargylic amine 397, subsequent reduction of alkyne 404 would selectively introduce the desired (Z)-alkene (Scheme 134). Propargylic amine 397 was treated with pyrrole-2-carboxylic acid and DIC in THF and pyrrole amide 404 was obtained in 65% yield on a 0.2 mmol scale. However this yield was not reproducible particularly on a larger scale. Despite the addition of excess DIC and pyrrole-2-carboxylic acid, only 30% of amide 404 was consistently obtained.
The phosphorous coupling reagent pyBOP 405 has been extensively used in the synthesis of complex peptides, especially where the yields have been low with other methods.

The mechanism of the pyBOP coupling involves the initial preparation of an activated ester 406 by the reaction of pyBOP 405, carboxylic acid and a base. This activated ester species is subsequently attacked by the nucleophilic amine 397. The complete preparation of the activated ester 406 before the addition of the nucleophile prevents side reactions from occurring and increases the yield of the amide product.

Diisopropylethylamine was added to a suspension of pyrrole-2-carboxylic acid 123 and PyBOP 405 in DCM, and dissolution occurred to give a yellow solution, which indicated the formation of the activated ester. Subsequent addition of amine 397 afforded amide 404 in 78% after 24 h. This yield was reproducible on a large scale, unlike the carbodiimide coupling reaction.

Amide 404 was subsequently treated with the zinc/copper/silver couple reducing agent, using the conditions previously described (scheme 136). (Z)-Alkene 407 was obtained exclusively, with none of the (E)-isomer detected by NMR. The yield was also markedly increased to 85%.
This reduction yield was significantly higher than that obtained previously for the reduction of other substrates with the zinc/copper/silver couple. It may be possible that this substrate does not bind as tightly to the surface of the reducing agent. This would explain why no isomerisation to the (E)-isomer occurs as well as the high yield. Alkyne 404 lacks the amine NH moiety, which may contribute to the stronger binding with amine substrate 397.
2.18 Oxidation of the N-Acyliminium Ion Precursor

Having prepared amide 407, a suitable oxidative method for the generation of the N-acyliminium ion was sought. Treatment of the precursor with trityl tetrafluoroborate resulted in a new cyclised product 408 in 27% yield (scheme 137).

However the expected oxidation did not occur. Instead, as trityl tetrafluoroborate is acidic due to the presence of fluoroboric acid, protonation of the imidazolone ring occurred, forming a different N-acyliminium ion 409 (scheme 138). The pyrrole C3 carbon then attacks this N-acyliminium ion, through the (Z)-alkene, forming a new six-membered ring. A subsequent isomerisation of 410 then occurs to regenerate the imidazolone.

Although this reaction does not generate the predicted N-acyliminium ion, two observations are interesting.
Firstly $N$-acyliminium ion 409 generated by protonation is in the same position as the second $N$-acyliminium ion 180 that we predicted would be formed in the biomimetic synthesis of agelastatin A. Secondly, the action of pyrrole C3 as a nucleophile confirms our prediction that the pyrrole nitrogen may not be sufficiently nucleophilic for the biomimetic synthesis to occur, although if the pyrrole moiety were brominated then attack via the pyrrole nitrogen could still occur, as bromination will significantly affect the nitrogen pKa. Other oxidising agents including DDQ, $^{162}$ RuCl$_2$(PPh$_3$)$_3$, $^{77}$ and $t$-butylperbenzoate/copper(II) ethylhexanoate $^{163}$ were also attempted, but although changes to the $^1$H NMR occurred, no products could be characterised.
2.19 Electrochemical Oxidation

Electrochemical methods have been widely used for the generation of $N$-acyliminium ions.\textsuperscript{164} A 10mM solution of alkene 407 was prepared in acetonitrile containing 0.1M tetrabutylammonium chloride background electrolyte. A glassy carbon working electrode of 0.07 cm$^2$ geometric surface was utilised. Figure 1 shows a cyclic voltammogram measured with a scan rate of 0.05 V s$^{-1}$, at room temperature.

Figure 1

![Cyclic Voltammogram](image)

Trace B is a background scan containing only the electrolyte. Trace A consists of two traces, the top trace indicates the change in the current as the voltage was increased and the lower trace corresponds to the current change as the voltage was decreased. The two peaks in the top trace indicate that two oxidations occurred at 0.85 and 1.30 V and the absence of these peaks in the lower trace indicated that the oxidations were irreversible. We hoped that one of these oxidation steps is the generation of the required $N$-acyliminium ion, with the ion undergoing a subsequent reaction before the oxidation could be reversed.
Unfortunately on a reasonable timescale it was not possible to pass enough charge through the solution to detect any change to the substrate by \textsuperscript{1}H NMR. At a higher current significant passivation of the electrode was observed, where an unknown substance was deposited onto the electrode surface, therefore reducing its effectiveness.
2.20 An Alternative Protecting Group Strategy

Scheme 139

As the \( p \)-methoxybenzyl group can be removed using oxidative methods\(^{79,165} \), it may not be the best choice of protecting group if oxidative methods are to be utilised for the generation of the necessary \( N \)-acyliminium ion in the biomimetic synthesis. Therefore the \( o \)-nitrobenzyl (onNB) group was introduced in place on the PMB group. The onNB group was introduced at the same stage in the synthesis as the PMB group was in the
previous route. The solubility of the oNB-protected molecules was significantly less than the corresponding PMB-protected moieties. This only affected the oxidation of alcohol 412 to ynal 413, where 380 mL/g of DCM was required for complete dissolution of the alcohol at ambient temperature, however a satisfactory 87% yield of aldehyde 413 was obtained. As with the PMB-protected route, the reductive amination of aldehyde 413 required an excess of benzylamine and sodium triacetoxyborohydride to afford the amine 425 in good yield, use of one equivalent afforded the tertiary amine 414.

The final step of the synthesis proved to be the most challenging, as we should have anticipated that reduction of alkyne 416 with the zinc/copper/silver couple would also reduce the nitro group of the oNB group to afford 417 (Scheme 140).

![Scheme 140](image)

As there appeared to be no appreciable difference in the rate of alkyne reduction versus the rate of nitro group reduction using the zinc couple an alternative method for the reduction of alkyne 416 was sought. Hydroboration of alkyne 416 was attempted with disiamylborane and borane.THF complex, but only unreacted substrate was recovered.

Cis-Diimide 418 has been widely utilised for the reduction of alkene\(^{166}\) and alkyne\(^{167}\) multiple bonds. This reduction occurs via a concerted transfer of hydrogen from diimide to the C-C multiple bond. However, diimide also undergoes a disproportionation reaction to afford nitrogen and hydrazine, which is in competition with the multiple bond reduction. Therefore large excesses of diimide are usually required. One important feature in the reduction of C-C \(\pi\) systems with diimide is that reactive functional groups containing N-N, N-O and O-O bonds, which often suffer
reductive cleavage using other reductive conditions, survive during diimide reductions. Generally alkynes are more reactive than alkenes to diimide reduction and the relative reactivity of the alkene decreases as the level of substitution increases.

There are several procedures for the synthesis of diimide but in practice only two are widely utilised: the oxidation of hydrazine 419 by oxygen or hydrogen peroxide with copper(I) and a catalytic amount of carboxylic acid (Scheme 141) or the reaction of potassium azodicarboxylate 421 with a carboxylic acid (Scheme 142). Potassium azodicarboxylate is formed by the reaction of commercially available azodicarboxamidine 420 and potassium hydroxide.

![Scheme 141](image)

The most successful application of the partial reduction of alkynes with diimide is in the reduction of 1-iodoalkynes, which are reduced to cis-1-iodoalkenes in good yields using the azodicarboxylate method. One example is the reduction of alkyne 422 to the corresponding alkene 423 in 82% yield.

![Scheme 143](image)

The reduction of alkyne 416 with potassium azodicarboxylate and acetic acid was therefore investigated and is summarised in Table 8. Potassium azodicarboxylate 421 was prepared on a large scale in 78% yield according to a literature procedure.
At low temperature no reaction was observed even with an excess of potassium azodicarboxylate (entries 1 and 2). At higher temperatures, the rate of disproportionation of diimide increased, evident by the rapid evolution of gas upon addition of acetic acid to the alkyne 421 and potassium azodicarboxylate. To obtain the highest possible yield it was important to add acetic acid to a suspension of alkyne 421 and potassium azodicarboxylate at 50 °C. However, upon increasing the amount of potassium azodicarboxylate from 30 to 100 equivalents, a decrease in the yield of alkene 429 was observed. This was attributed to loss of product during workup and extraction rather than over-reduction, as no evidence of over-reduction was observed by TLC or ¹H NMR analysis.

As even with a large excess of diimide only a low yield of alkene 429 could be obtained this route was abandoned.
2.21 Future work

If a higher yielding method for the reduction of alkyne 416 to alkene 424 can be developed then the oxidation of 424 to form \(N\)-acyliminium ion 425 by chemical or electrochemical methods can be investigated and subsequent reactions of the \(N\)-acyliminium ion observed.

An alternative method for the generation of the required \(N\)-acyliminium ion 428 is via protonation and subsequent C-N bond cleavage in dehydroprolinamide adduct 426 (scheme 146).

![Scheme 146](image-url)
A preliminary study using methylsulfanyl aldehyde 370 and prolinamide 429 afforded a model prolinamide adduct 431, via iminium ion 430, as a mixture of the (E)- and (Z)-alkene isomers (scheme 147). However a mixture of diastereoisomers was obtained and separation using flash chromatography was not possible.

An alternative strategy for the generation of prolinamide derivative N-acyliminium ion precursor 426 would be to condense ynal 432 with prolinamide and subsequently reduce alkyne 433 to the required (Z)-alkene 434 (scheme 148).

Preliminary studies on the prolinamide condensation indicated some potential problems: Derivative 433 is formed as a mixture of diastereoisomers by $^1$H NMR but solubility problems prevented isolation and complete characterisation. Attempts to carry out the alkyne reduction on crude 433 failed with the previously applied zinc/copper/silver reduction method, and again this was attributed to high polarity and low solubility of
433. It may therefore be necessary to protect the secondary amide nitrogen in order to overcome these problems and allow reduction to alkene 434.
CHAPTER III

EXPERIMENTAL

3.1 General Experimental Procedures

Chemicals were purchased from Sigma-Aldrich Co. Ltd, Lancaster, Fluka, Acros, Apollo, Avocado and NovaBiochem. Unless stated they were used without further purification, and where indicated reagents were purified in accordance with the methods described in D. D. Perrin and W. L. F. Armarego, “Purification of laboratory chemicals”, Pergamon Press, Third edition, 1988.

All solvents were distilled under nitrogen atmosphere before use. Anhydrous diethyl ether and THF were obtained by distillation using a sodium/benzophenone still. Anhydrous dichloromethane was obtained by distillation using a calcium hydride still. Diisopropylethylamine and triethylamine were distilled from calcium hydride onto anhydrous potassium hydroxide pellets. Anhydrous dimethyl sulfoxide was obtained by stirring over calcium hydride followed by distillation under reduced pressure onto activated 4Å molecular sieves.

Non aqueous reactions were carried out under an inert atmosphere of nitrogen or argon using anhydrous solvents, unless otherwise stated.

TLC was carried out on pre-coated, aluminium backed normal phase Merck 60 F254 silica plates and visualised using UV (λmax 254 nm) and by staining with vanillin, anisaldehyde, phosphomolybdic acid, potassium permanganate, ammonium molybdate or 2,4-dinitrophenylhydrazine, followed by heat. Flash chromatography was carried out on BDH silica 40-60 μm unless specified. Where petroleum ether was utilised for flash chromatography the fraction boiling between 40-60°C was used unless otherwise stated. Solvents were evaporated at 30°C or below on a Büchi RE111 rotavapor

Melting points was obtained using a Reichert-Jung thermovar hot stage apparatus and are uncorrected.

Microanalyses were recorded on a Perkin Elmer 2400 CHN elemental analyser and were carried out by Jill Maxwell, University College London.

Infrared spectra were recorded as thin films, CDCl₃ casts, KBR discs or nujol mulls on a SHIMADZU FT-IR 8700 transform spectrometer and wavenumbers of the major peaks are reported.
Proton NMR spectra were recorded at 300MHz on a Bruker AMX300 spectrometer, at 400MHz on a Bruker AMX400 spectrometer or at 500MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet; and br, broad.

Carbon-13 NMR spectra were recorded at 75MHz on Bruker AMX300 spectrometer, at 100MHz on Bruker AMX400 spectrometer or 125MHz on Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak.

Low- and high-resolution mass spectra were recorded on a ZAB-SE4F spectrometer at the University College London School of Pharmacy or using the University College London chemistry departmental mass spectrometry service. Only molecular ions and major peaks are reported.
3.2 Experimental Procedures

Potassium pyrrole-2-carboxylate (285)\(^{95}\)

![Chemical Structure](image)

Pyrrole-2-carboxylic acid 123 (2.01 g, 18.0 mmol) was dissolved in EtOH (40 mL) at ambient temperature. A solution of KOH (1.02 g, 18.0 mmol) in water (2 mL) was added dropwise with stirring and the solution stirred for 5 min. The solvent was removed \textit{in vacuo} to give potassium pyrrole-2-carboxylate 285 (2.63 g, 17.6 mmol, 98%) as a white amorphous solid, mp 154 °C, \(\nu_{\text{max}}\) (nujol) 4000 (NH stretch), 1556 (C=O stretch), 1105 (CO stretch), 1076 (CO stretch), 798 (CH bending), 771 (CO stretch) cm\(^{-1}\); \(\delta_H\) (400 MHz, D\(_2\)O) 6.83 (1H, t, \(J=2.0, 1.6\) Hz, NHCH), 6.61 (1H, dd, \(J=3.5, 1.3\) Hz, CHCCO\(_2\)K), 6.10 (1H, t, \(J=3.1, 3.0\) Hz, NHCHCH) ppm; \(\delta_C\) (75 MHz, D\(_2\)O) 169.1 (CCO\(_2\)K), 127.9 (CCO\(_2\)K), 122.6 (NHCH), 133.6 (CHCCO\(_2\)K), 109.6 (NHCHCH) ppm; m/z (FAB) 124 (84), 104 (37), 95 (40).

Isopropyl (1H)-pyrrole-2-carboxylate (286)\(^{95}\)

![Chemical Structure](image)

A suspension of potassium pyrrole-2-carboxylate 285 (2.43 g, 16.3 mmol) in dry DCM (20 mL) was cooled to 0 °C. Oxalyl chloride (2.3 mL, 26 mmol) was added dropwise with stirring and the reaction was allowed to warm to ambient temperature. After 4 h the solvent was removed \textit{in vacuo} to give pyrrole-2-carbonyl chloride. The crude acid chloride was placed under nitrogen, propan-2-ol (25 mL, 0.33 mol) added and the solution was heated at reflux for 15 h. After cooling, the solution was concentrated \textit{in vacuo} and then diluted with water (8 mL). The product was extracted with EtOAc (3×150 mL), dried over MgSO\(_4\) and concentrated \textit{in vacuo} to give crude pyrrole-ester 286 (2.56 g) as a brown oil. \(\nu_{\text{max}}\) cm\(^{-1}\) (thin film) 3317 (NH stretch), 2982 (CH stretch), 745 (CH bending); \(\delta_H\) (300 Mz, CDCl\(_3\)) 9.19 (1H, broad s, NH), 6.93-6.92
(1H, m, aromatic CH), 6.90-6.89 (1H, m, aromatic CH), 6.24 (1H, dd, \( J = 6.1 \), 2.7 Hz, aromatic CH), 5.24 (1H, sep, \( J = 6.2 \) Hz, CH(CH\(_3\))\(_2\)), 1.32 (6H, d, \( J = 6.2 \) Hz, CH(CH\(_3\))\(_2\)) ppm; \( m/z \) (FAB) 153 (39%), 136 (45), 133 (58), 94 (100), 91 (58).

**Pyrrole-1,2-dicarboxylic acid 1-tert-butyl ester 2-isopropyl ester (287)**

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\text{O} \quad \text{O}
\]

Crude pyrrole-2-carboxylic acid isopropyl ester 286 (2.56 g) was diluted in dry THF (80 mL). The solution was cooled to 0 °C, sodium hydride (60% in mineral oil, 1.35 g, 33.4 mmol) was added portionwise with stirring and the solution allowed to warm to ambient temperature. After 3 h, di-tert-butyl dicarbonate (7.37 g, 33.8 mmol) in dry THF (60 mL) was added dropwise with gentle heating and vigorous stirring. The solution was heated to reflux for 4 h, cooled and cautiously diluted with H\(_2\)O (50 mL). The product was extracted with EtOAc (4×100 mL), the organics dried over MgSO\(_4\) and concentrated in vacuo. Flash chromatography (petrol 40-60°C:EtOAc, 98:2) gave pyrrole 287 (2.49 g, 9.8 mmol, 60% over 3 steps) as a pale yellow oil. \( \nu_{\text{max/cm}^{-1}} \) (thin film) 2982 (CH stretch), 1724 (broad, 2×C=O stretch), , 775 (aromatic CH bending), 746 (aromatic CH bending); \( \delta_\text{H} \) (300 MHz, CDCl\(_3\)) 7.26 (1H, dd, \( J = 3.1 \), 1.7 Hz, NCH\(_3\)), 6.77 (1H, dd, \( J = 3.5 \), 1.7 Hz, NCHCHCH\(_3\)), 6.12 (1H, m, NCHCHCH\(_3\)), 5.14 (1H, sept, \( J = 6.2 \) Hz, CH(CH\(_3\))\(_2\)), 1.56 (9H, s, C(CH\(_3\))\(_3\)), 1.31 (6H, d, \( J = 6.3 \), CH(CH\(_3\))\(_2\)) ppm; \( \delta_\text{C} \) (75 MHz, CDCl\(_3\)) 160.3 (NCO\(_2\)C(CH\(_3\))\(_3\)), 148.4 (CO\(_2\)CH(CH\(_3\))\(_2\)), 126.4 (NCH\(_3\)), 126.1 (NCCO\(_2\)C(CH\(_3\))\(_3\)), 120.3 (NCHCHCH\(_3\)), 109.9 (NCH\(_3\)), 84.6 (CO\(_2\)C(CH\(_3\))\(_3\)), 68.2 (CH(CH\(_3\))\(_2\)), 27.7 (C(CH\(_3\))\(_3\)), 21.8 (CH(CH\(_3\))\(_2\)) ppm; \( m/z \) (FAB) 254 (MH\(^+\), 15%), 253 (15), 198 (100), 156 (38), 153 (53), 138 (41), 111 (25); HRMS calcd. for C\(_{13}\)H\(_9\)NO\(_4\) (MH\(^+\)) 254.1392, found 254.1400.
5-tert-Butoxycarbonylamino-pent-3-enoic acid isopropyl ester (288)

A solution of ammonia (75 mL), THF (10 mL) and lithium (46 mg, 6.6 mmol) was stirred at −78 °C under nitrogen until the solution had turned deep blue in colour. Pyrrole 287 (253 mg, 0.99 mmol) in THF (5 mL) was added rapidly and the solution stirred for a further 2 h. Saturated NH₄Cl solution (1 mL) was then added and the solution was left at ambient temperature for 16 h to allow evaporation of the ammonia. The reaction was then diluted with brine (50 mL) and extracted with DCM (4×100 mL), then the combined organic extracts were dried over MgSO₄ and concentrated in vacuo. Flash chromatography (petrol 40-60:EtOAc, 93:7) gave 288 (22.1 mg, 0.086 mmol, 9%) as a colourless oil; νₐₘₙ⁵¹ (thin film) 1670 (C=O stretch), 1640 (C=C stretch), 1627 (C=O stretch); δH (300 MHz, CDCl₃) 5.71-5.54 (2H, m, CH=CH and CH=CH₂), 4.97 (1H, sept, J=6.3 Hz, CH(CH₃)₂), 4.58 (1H, broad s, NH), 3.71 (2H, broad t, J=5.9 Hz, NHCH₂CH=CH), 3.05 (2H, d, J=6.8 Hz, CH=CHCH₂), 1.39 (9H, s, C(CH₃)₃), 1.18 (6H, d, J=6.3 Hz, CH(CH₃)₂) ppm; δC (75 MHz, CDCl₃) 170.8 (ester C=O), 155.7 (C=O), 129.5 and 124.2 (CH=CH and CH=CH), 79.4 (C(CH₃)₃), 68.2 (CH(CH₃)₂), 37.6 (CH₂NH), 33.3 (CH₂CO), 28.4 (C(CH₃)₃), 21.7 (CH(CH₃)₂) ppm; m/z (+ve CI-methane) 258 (MH⁺, 37%), 216 (42), 201 (100); HRMS calcd. for C₁₃H₂₄NO₄ (MH⁺): 258.1705, found 258.1689.

3-Pyrroline-1,2-dicarboxylic acid 1-tert-butyl ester 2-isopropyl ester (289)⁹⁷

A solution of ammonia (50 mL), THF (10 mL), bis(2-methoxyethyl)amine (1.8 mL, 12 mmol) and sodium (220 mg, 9.5 mmol) was stirred at −78 °C under nitrogen until the solution had turned deep blue in colour. Pyrrole 287 (564 mg, 2.23 mmol) in THF (10
mL) was added rapidly and the solution stirred for a further 45 min. Saturated NH4Cl solution (5 mL) was added and the solution was left at ambient temperature for 16 h to allow evaporation of the ammonia. Water (40 mL) was then added, the mixture was extracted with DCM (4×40 mL), then the combined organic extracts were dried over MgSO4 and concentrated in vacuo. Flash chromatography (hexane:acetone, 98:2) gave 3-pyrroline 289 (351 mg, 1.37 mmol, 62%) as a colourless oil; v(m)/cm⁻¹ (thin film) 2982 (CH stretch), 2936 (CH stretch), 1698 (broad, C=O stretch), 1622 (C=O stretch); δH (300 MHz, CDCl3) 5.95-5.94 (1H, m, CH=CH), 5.68-5.67 (1H, m, CH=CH), 5.00 (1H, sep, J=6.3 Hz, CH(CH3)2), 4.88-4.87 (1H, m, CH=CHCH), 4.27-4.14 (2H, m, CH2CH=CH), 1.44 (9H, s, C(CH3)3), 1.23 (6H, d, J=6.3 Hz, CH(CH3)2) ppm; δC (75 MHz, CDCl3) 170.5 and 170.1 (CO2CH(CH3)2), 153.9 (CO2C(CH3)3), 129.6 and 129.5 (CH=CH), 125.4 and 125.3 (CH=CH), 80.5 and 80.3 (CO2C(CH3)3), 69.1 (CO2CH(CH3)2), 67.2 and 66.9 (CH=CHCH), 53.9 and 53.7 (CH2CH=CH), 28.8 and 28.7 (CO2C(CH3)3), 22.2 and 22.1 (CO2CH(CH3)2); m/z (FAB) 254 (MH⁺, 31%), 200 (79), 154 (97), 112 (100); HRMS calcd. for C13H21NO4 (MH⁺) 256.1549, found 256.1560.

2,5-Dihydropyrrole-1,2-dicarboxylic acid 1-tert-butyl ester (295)⁹⁵

3-Pyrroline 289 (98.3 mg, 0.39 mmol) was dissolved in MeOH (2.5 mL). Saturated potassium hydroxide solution (0.5 mL) was added dropwise with stirring and the solution stirred at ambient temperature for 3 h. 2M HCl (10 mL) was added, the mixture extracted with EtOAc (3×25 mL), then the combined extracts were dried over MgSO4 and concentrated in vacuo to give carboxylic acid 295 (80.5 mg, 0.38 mmol, 98%) as a white amorphous solid, mp 112 °C; v(m)/cm⁻¹ (thin film) 3445 (OH stretch), 2978 (CH stretch), 2928 (CH stretch), 2872 (CH stretch), 1682 (broad, C=O stretch), 1620 (C=O stretch); δH (300 MHz, CDCl3) 9.04 (1H, broad s, OH), 6.02 (1H, broad d, CHCO2H), 5.86 (1H, broad d, CH=CHCH), 5.08 (1H, broad d, CH=CHCH), 4.28 (2H, broad d, CH2CH=CH), 1.52 (9H, broad d, CO2C(CH3)3) ppm; δH (400 MHz, DMSO-d6, 133
383 K) 6.01 (1H, dq, J=6.3, 2.2 Hz, CHCO₂H), 5.78 (1H, dq, J=6.3, 2.3 Hz, CH=CHCH), 4.82 (1H, tt, J=4.3, 2.2 Hz, CH=CHCH), 4.10 (2H, dt, J=4.2, 2.2 Hz, CH₂CH=CH), 1.42 (9H, s, C(CH₃)₃ ppm; δC (75 MHz, CDCl₃) 175.7 and 173.7 (CO₂H), 155.4 and 153.6 (CO₂C(C(CH₃)₃), 129.8 and 128.7 (CH=CH), 124.7 and 124.4 (CH=CH), 81.5 and 80.8 (CO₂C(C(CH₃)₃), 66.4 and 66.3 (CH=CHCH), 53.8 and 53.4 (CH₂CH=CH), 29.7 and 28.4 (CO₂C(C(CH₃)₃)) ppm; m/z (FAB) 252 (30%), 158 (36), 147 (50), 136 (36), 112 (50), 97 (66), 95 (66), 83 (100).

4,5-Diiodo-(1H)-imidazole (301)

![Diagram of 4,5-Diiodo-(1H)-imidazole (301)]

A solution of iodine (6.67 g, 260 mmol) in 20% aqueous potassium iodide (450 mL) was added dropwise to a stirred solution of imidazole 300 (10.0 g, 147 mmol) in 2M aqueous sodium hydroxide solution (900 mL) and stirred for 16 h at ambient temperature. Acetic acid was then added until the solution was neutral and the resulting precipitate isolated by filtration and washed with water (100 mL). Recrystallisation from EtOH gave 4,5-diiodoimidazole 301 (19.8 g, 61.9 mmol, 42%) as a white solid, mp 188 ºC (lit 189-191 ºC); νmax/cm⁻¹ (nujol) 1283, 1151, 955, 721; δH (300 MHz, CD₃OD) 7.64 (1H, s, CH) ppm; δC (375 MHz, CD₃OD) 143.0 (CH), 86.3 (CD) ppm; m/z (FAB) 321 (MH⁺, 100%), 195 (57); HRMS calcd. for C₃H₃N₂I₂ (MH⁺): 320.8386, found 320.8398.

4(5)-Iodo-(1H)-imidazole (303)

![Diagram of 4(5)-Iodo-(1H)-imidazole (303)]

4,5-Diiodoimidazole 301 (15.1 g, 47.0 mmol) and sodium sulfite (4.7 g, 380 mmol) were heated at reflux in H₂O:EtOH, 7:3 (1 L) for 24 h. After cooling the solution was concentrated in vacuo almost to dryness, filtered and the resulting solid washed with water (100 mL), to afford 4(5)-iodoimidazole 303 (6.64 g, 34.2 mmol, 73%) as an
amorphous white solid, mp 133 °C (lit 136-137 °C\textsuperscript{101}); \( \nu_{\text{max/cm}^{-1}} \) (nujol) 1290, 1069, 955, 822, 760, 721, 619; \( \delta_H \) (300 MHz, CD\textsubscript{3}OD) 7.52 (1H, s, CH), 7.09 (1H, s, CH) ppm; \( \delta_C \) (75 MHz, CD\textsubscript{3}OD) 139.3 (CH), 125.4 (CH), 79.0 (Cl) ppm; \( m/z \) (FAB) 195 (MH\textsuperscript{+}, 100%); HRMS calcd for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}I (MH\textsuperscript{+}) 194.9419, found 194.9425.

**1-Benzanesulfonyl-4-iodo-(1H)-imidazole (299)\textsuperscript{98}**

![Diagram of 1-Benzanesulfonyl-4-iodo-(1H)-imidazole](image)

To a solution of 4(5)-iodoimidazole 303 (5.87 g, 30.3 mmol) and benzenesulfonyl chloride (4.3 mL, 33 mmol) in THF (90 mL) was added triethylamine (4.3 mL, 30 mmol) with stirring. The solution was stirred for 16 h, filtered and the filtrate concentrated in vacuo to give a yellow solid. Recrystallisation from EtOH gave imidazole 299 (6.58 g, 19.7 mmol, 65%) as a white solid, mp 130 °C (lit 124-126 °C\textsuperscript{98}). \( \nu_{\text{max/cm}^{-1}} \) (nujol) 1305 (S=O stretch), 1153 (S=O stretch), 721 (CH bending); \( \delta_H \) (300 MHz, CD\textsubscript{3}OD) 8.07-8.06 (1H, m, CH), 8.00-7.96 (2H, m, 2×CH), 7.71-7.64 (2H, m, 2×CH), 7.59-7.53 (2H, m, 2×CH) ppm; \( \delta_C \) (75 MHz, CD\textsubscript{3}OD) 140.0 (CH), 138.7 (SO\textsubscript{2}C), 136.6 (CH), 131.2 (CH), 128.8 (CH), 124.5 (CH), 85.5 (Cl) ppm; \( m/z \) (FAB) 335 (MH\textsuperscript{+}, 74%), 321 (100), 195 (91), 141 (43), 93 (48), 77 (48); HRMS calcd. for C\textsubscript{9}H\textsubscript{8}N\textsubscript{2}SO\textsubscript{2}I (MH\textsuperscript{+}) 334.9351, found 334.9357.

**tert-Butyldimethylprop-2-nyloxy silane (304)\textsuperscript{98}**

![Diagram of tert-Butyldimethylprop-2-nyloxy silane](image)

Imidazole (14.1 g, 0.2 mol) and tert-butyldimethylchlorosilane (15.5 g, 0.1 mol) were dissolved in anhydrous DMF (50 mL) and cooled to 0 °C. Propargyl alcohol 306 (5.6 mL, 0.1 mmol) was added dropwise with stirring and the solution allowed to warm to ambient temperature. After stirring for 16 h the solution was diluted with Et\textsubscript{2}O (250
mL), washed with H₂O (3×40 mL), dried over MgSO₄ and concentrated in vacuo. The resulting oil was distilled under reduced pressure to give silyl ether 304 (16.4 g, 0.1 mol, 100%) as a colourless oil, bp 40 °C/6 mmHg (lit 40 °C/8 mmHg). ν_{max}/cm⁻¹ 3331 (C≡CH stretch) 2192 (C≡C stretch); δ_H (300 MHz, CDCl₃) 4.19 (2H, d, J=2.4 Hz, CH₂), 2.25 (1H, t, J=2.4 Hz, HCC≡C), 0.79 (9H, s, SiC(CH₃)₃), 0.01 (6H, s, Si(CH₃)₂) ppm; δ_C (300 MHz, CDCl₃) 82.8 (C≡CH), 73.2 (C≡CCH), 51.9 (CH₂), 26.2 (SiC(CH₃)₃), 18.7 (SiC(CH₃)₃), -4.8 (Si(CH₃)₂) ppm; m/z (FAB) 192 (100%), 154 (37), 136 (40), 124 (22), 89 (27).

**Tetrakis(triphenylphosphine)palladium(0) (305)**

Palladium dichloride (150 mg, 0.85 mmol) and triphenylphosphine (1.11 g, 4.23 mmol) were placed under a nitrogen atmosphere and freshly distilled DMSO (11 mL) was added. The solution was heated with stirring until complete dissolution occurred (ca 150 °C) and stirred at this temperature for 20 min. Hydrazine monohydrate (170 μL, 3.40 mmol) was added rapidly with evolution of nitrogen and the solution immediately cooled in a hot water bath until crystallisation started. The solution was then left without external cooling until crystallisation was complete. The yellow crystals were isolated by filtration under nitrogen, washed with EtOH (2×1 mL) and Et₂O (2×1 mL), and dried under a stream of nitrogen for 4 h. Tetrakis(triphenylphosphine)palladium(0) 305 (886 mg, 0.77 mmol, 90%) was obtained as a bright yellow solid.

**1-Benzencesulfonyl-4-[3-(tert-butylidimethylsilyloxy)-prop-1-ynyl]-(1H)-imidazole (298)**

![Chemical structure](image)

Iodoimidazole 299 (4.45 g, 13.3 mmol), tetrakis(triphenylphosphine)palladium(0) 305 (812 mg, 0.70 mmol, 5 mol%) and copper(I) iodide (269 mg, 1.4 mmol, 10 mol%) were
CHAPTER III

stirred with dry DMF (120 mL) under a nitrogen atmosphere. Silyl ether 304 (3.54 g, 20.8 mmol) and triethylamine (18.6 mL, 133 mmol) were added and the solution heated to ca. 80 °C for 4 h. After cooling, the solution was diluted with Et₂O (550 mL), washed with H₂O (3×120 mL), dried over MgSO₄ and concentrated in vacuo to give a brown oil. Flash chromatography (EtOAc:petrol, 1:4) yielded imidazole 298 (4.01 g, 10.7 mmol, 80%) as a light brown solid. νmax/cm⁻¹ 2956 (CH stretch), 2930 (CH stretch), 2856 (CH stretch), 1474 (CH deformation), 1327 (S=O stretch), 1258, 1188, 1177 (S=O stretch), 837 (SiO stretch), 779, 727 (aromatic CH bending); δH (300MHz, CDCl₃) 7.98-7.91 (3H, m, 3×aromatic CH), 7.71-7.65 (1H, m, aromatic CH), 7.59-7.52 (2H, m, 2×aromatic CH), 7.37 (1H, s, aromatic CH), 4.62 (2H, s, CH₂-C≡C), 0.89 (9H, s, SiC(CH₃)₃), 0.11 (6H, s, Si(CH₃)₂) ppm; δC (75 MHz, CDCl₃) 137.6 (aromatic CSO₂N), 136.4 (NCHN), 135.1 (aromatic para-CH), 129.2 (aromatic meta-CH), 127.4 (aromatic ortho-CH), 126.9 (CH₂=C≡C), 120.3 (imidazole C=HCC=C), 90.1 (CH₂=C≡C), 76.3 (CH₂=C≡C), 52.0 (CH₂=C≡C), 25.8 (Si(C(CH₃)₃), 18.3 (Si(C(CH₃)₃), -5.2 (Si(CH₃)₂) ppm; m/z (FAB) 377 (MH⁺, 67%), 319 (28), 289 (23), 245 (64), 179 (39), 141 (46), 105 (100), 89 (76); HRMS calcd. for C₁₈H₂₅N₂O₃SSi (MH⁺) 377.1355, found 377.1370.

3-Methylhydantoin (314)

![3-Methylhydantoin (314)](image)

**Method A**¹⁴: Hydantoin 315 (40.0 g, 0.40 mol), sodium hydroxide (16.1 g, 0.40 mmol) and H₂O (200 mL) were heated to reflux and methyl iodide (50 mL, 0.80 mol) added dropwise. The solution was then heated at reflux for a further 24 h, cooled and the solvent removed in vacuo. The product was triturated with hot DCM (12×100 mL) and the remaining crude solid extracted with DCM using a Soxhlet extraction apparatus for 48 h. The combined extracts were concentrated in vacuo to give 3-methylhydantoin 314 (19.8 g, 0.17 mol, 43%) as a white solid.

**Method B**¹⁵: Hydantoin 315 (30.0 g, 0.30 mol), N,N-dimethylacetamide dimethylacetal (66 mL, 0.45 mol) and toluene (1.5 L) were heated to reflux for 3.5 h. The solution was left to cool to ambient temperature without external cooling and then
cooled in an ice bath. The resulting precipitate was isolated by filtration and dried in a vacuum oven to give 3-methylhydantoin 314 (28.0 g, 0.25 mol, 82%) as a pale brown solid. The solid was recrystallised from refluxing MeOH to give a pale brown solid (23.3 g, 83% recovery). A 5.00 g sample of pale brown 3-methylhydantoin was dissolved in 400 mL cold MeOH and stirred with Norit-SX activated carbon (260 mg, ca 5% by weight) for 2 h. The carbon was removed by filtration over Celite and the solvent removed in vacuo. The resulting solid was recrystallised from MeOH to give 3.48 g of 3-methylhydantoin 314 as a white solid. Strength by $^1$H NMR was 99.9%, mp 185 °C. $\nu_{\text{max}}$/cm$^{-1}$ (KBr disc) 3287 (NH stretch), 1751 (C=O stretch), 1695 (C=O stretch), 1472 (CH deformation), 1450, 1329, 1267, 1109, 1067, 957, 768, 714, 610; $\delta_H$ (400 MHz, DMSO-d$_6$) 7.95 (1H, broad s, NH), 3.34 (2H, s, CH$_2$), 2.80 (3H, s, NCH$_3$) ppm; $\delta_C$ (100 MHz, DMSO-d$_6$) 172.2 (C=O), 157.9 (C=O), 46.0 (CH$_2$), 23.9 (NCH$_3$) ppm; $m/z$ (+ve Cl-methane) 115 (MH$^+$, 100%), 72 (10); HRMS calcd. for C$_4$H$_7$N$_2$O$_2$ (MH$^+$): 115.0508; found 115.0505; Analysis calculated for C$_4$H$_6$N$_2$O$_2$ (115.0508): C, 42.1, H, 5.3, N, 24.6; found C, 42.1; H, 5.3, N, 24.5%.

5-[3-(tert-Butyldimethylsilyloxy)prop-1-ynyl]-1-methyl-1,3-dihydroimidazol-2-one (313)

Silyl ether 304 (4.5 g, 26 mmol) in THF (30 mL) was cooled to 0 °C and n-butyllmagnesium chloride (2M in THF, 13 mL, 26 mmol) added. The solution was allowed to warm to ambient temperature and stirred for a further 5.5 h. The solution was then added via cannula to a suspension of 3-methylhydantoin 314 (1.0 g, 8.8 mmol) in THF (30 mL) at 0 °C. The resulting suspension was allowed to warm to ambient temperature and stirred for a further 110 h. The solution was then poured onto saturated NH$_4$Cl (100 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were washed with water (2 x 10 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo to afford tertiary alcohol 317 as an orange solid.
\[ \delta_H \ (400 \text{ MHz, CD}_3\text{OD}) \ 4.41 \ (2\text{H}, \text{s}, \text{CH}_2\text{OSi}), \ 3.67 \ (1\text{H}, \text{d}, J=10.1 \text{ Hz, CH}_2\text{COH}), \ 3.45 \ (1\text{H}, \text{d}, J=10.1 \text{ Hz, CH}_2\text{COH}), \ 2.79 \ (3\text{H}, \text{s, NCH}_3), \ 0.91 \ (9\text{H}, \text{s, SiC(CH}_3)_3), \ 0.13 \ (6\text{H}, \text{s, Si(CH}_3)_2), \ 85.5, \ 83.7 \text{ and } 83.4 \ (2\times \text{C=C} \text{ and COH}), \ 55.3 \text{ and } 52.7 \ (\text{CH}_2\text{NH and CH}_2\text{OSi}), \ 26.6 \ (\text{SiC(CH}_3)_3), \ 25.6 \ (\text{NCH}_3) \ 19.4 \ (\text{SiC(CH}_3)_3), \ -4.7 \ (\text{Si(CH}_3)_2) \text{ ppm.}

Alcohol 317 was dissolved in CHCl\text{\textsubscript{3}} (200 mL), \textit{p}-toluenesulfonic acid (84 mg, 0.4 mmol, 5 mol %) added, the solution stirred for 1 h and the solvent removed \textit{in vacuo}. Flash chromatography (EtOAc:iso-hexane, gradient elution, 55:45, 60:40, 70:30, 80:20, 100% EtOAc) gave silyl ether 313 (1.5 g, 5.4 mmol, 62%) as a pale yellow solid, mp 165 °C. \( \nu_{\text{max/cm}} \) (KBr disc) 3113 (NH stretch), 2930, 2856 (CH stretch), 2226 (C=C stretch), 1670 (C=O stretch), 1448, 1367, 1254, 1082, 835, 791, 781; \( \delta_H \ (400 \text{ MHz, CD}_3\text{OD}) \ 6.70 \ (1\text{H}, \text{s, C=C}), \ 4.56 \ (2\text{H}, \text{s, CH}_2), \ 3.21 \ (3\text{H}, \text{s, NCH}_3), \ 0.92 \ (9\text{H}, \text{s, C(CH}_3)_3), \ 0.14 \ (6\text{H}, \text{s, Si(CH}_3)_2) \text{ ppm; } \delta_C \ (100 \text{ MHz, CDCl}_3) \ 154.0 \ (\text{C=O}), \ 134.0 \ (\text{CH=C}), \ 108.1 \ (\text{CH=C=C}), \ 93.6 \ (\text{C=C}), \ 73.2 \ (\text{C=C}), \ 52.1 \ (\text{CH}_2), \ 27.9 \ (\text{NCH}_3), \ 25.7 \ (\text{SiC(CH}_3)_3), \ 18.3 \ (\text{SiC(CH}_3)_3), \ -5.1 \ (\text{Si(CH}_3)_2) \text{ ppm; m/z (+ve CI-methane) 267 (MH}^+\text{, 100%), 209 (42); HRMS calcd. for C}_{13}\text{H}_{22}\text{N}_2\text{O}_2\text{Si (MH}^+)\ 267.1529, \text{ found } 267.1534; \textbf{Analysis} \text{ calculated for } C_{13}H_{22}N_2O_2Si: \text{ C, 58.6, H, 8.3, N, 10.5%; found C, 58.6, H, 8.4, N, 10.5%}.

5-(3-Hydroxyprop-1-ynyl)-1-methyl-1,3-dihydroimidazol-2-one (312)

Silyl ether 313 (0.67 g, 2.5 mmol) was dissolved in AcOH:THF:H\text{\textsubscript{2}}O (3:1:1, 50 mL), heated to 50 °C for 3.5 h, cooled and solvent removed \textit{in vacuo}. Flash chromatography (gradient elution, EtOAc:MeOH, 96:4, 94:6, 92:8) afforded alcohol 312 (0.31 mg, 2.0
mmol, 82%) as a yellow solid, mp 210 °C. \( \nu_{\text{max/cm}^{-1}}(\text{KBr disc}) \) 3339 (OH stretch), 3134 (NH stretch), 2230 (C=O stretch), 1663 (C=O stretch), 1354; \( \delta_H (400 \text{ MHz, } \text{DMSO-d}_6) \) 10.39 (1H, s, NH), 6.83 (1H, s, C=CH), 5.34 (1H, broad t, COH), 4.29 (2H, d, \( J=4.5 \text{ Hz, CH}_2\text{OH} \)), 3.05 (3H, s, NCH_3) ppm; \( \delta_C (100 \text{ MHz, } \text{DMSO-d}_6) \) 152.6 (C=O), 114.0 (C=CH), 106.6 (C=CH), 94.7 (C=C), 73.0 (C=C), 49.5 (CH_2OH), 27.4 (NCH_3) ppm; \text{m/z (}^{+}\text{ve FAB} \) 153 (MH\(^+\), 100%); HRMS calcd. for C\(_7\)H\(_8\)N\(_2\)O\(_2\) (MH\(^+\)) 153.0664, found 153.0661.

(Z)-5-(3-Hydroxypropenyl)-1-methyl-1,3-dihydroimidazol-2-one (296)

\[
\text{HO=CH=CH-N}=\text{C}<\text{N}>
\]

Method A: Zinc dust (700 mg, 10.7 mmol) was suspended in H\(_2\)O (4 mL), copper acetate monohydrate (70 mg, 0.4 mmol) added and the suspension stirred at ambient temperature for 15 min. Silver nitrate (70 mg, 0.4 mmol) was then added and the suspension stirred for a further 15 min. The precipitate was isolated by filtration, washed successively with 8 mL portions of H\(_2\)O, MeOH, acetone and Et\(_2\)O and dried under vacuum. Propargylic alcohol 312 (55 mg, 0.36 mmol) was dissolved in MeOH:H\(_2\)O, 1:1 (8 mL) and the activated zinc added. The suspension was heated to 50 °C for 16 h cooled then filtered over Celite\({}\textsuperscript{®}\) and the solvent removed \textit{in vacuo}. Purification by flash chromatography (gradient elution EtOAc:MeOH, 100:0, 100:1, 100:2, 100:4: 9:1, 8:2) gave allylic alcohol 296 (25 mg, 0.16 mmol, 45%) as a yellow solid.

Method B: Silyl ether 339 (492 mg, 1.83 mmol) was dissolved in MeOH (40 mL) and ammonium fluoride (1.0 g, 28 mmol) added. The solution was heated to 60 °C for 17 h and solvent removed \textit{in vacuo}. Flash chromatography (gradient elution 100% EtOAc, 99:1, 98:2, 95:5, 90:10 to 85:15 EtOAc:MeOH) gave the allylic alcohol 296 (178 mg, 1.15 mmol, 63% as a yellow solid, mp 145 °C. \( \nu_{\text{max/cm}^{-1}}(\text{KBr disc}) \) 3354 (OH stretch), 3165 (NH stretch), 1666 (C=O stretch), 1580 (C=C stretch); \( \delta_H (400 \text{ MHz, } \text{CD}_3\text{OD}) \) 6.33 (1H, s, NHCH=CH), 6.15 (1H, d, \( J=11.7 \text{ Hz, CH}_2\text{CH}=\text{CH} \)), 5.89 (1H, dt, \( J=11.9, 6.0 \text{ Hz, CH}_2\text{CH}=\text{CH} \)), 4.24 (2H, dd, \( J=6.0, 1.7 \text{ Hz, CH}_2\text{CH}=\text{CH} \)), 3.20 (3H, s, NCH_3)
ppm; δc (75 MHz, CD3OD) 155.3 (C=O), 133.9 (CH2CH=CH), 122.6 (C=CH), 116.1 (CH2CH=CH), 109.2 (C=CH), 60.2 (CH2OH), 27.5 (NCH3) ppm; m/z (+ve CI-methane) 155 (MH+, 100%), 137 (64); HRMS calcd. for C7H11N2O2 (MH+) 155.0821, found 155.0820.

5-(3-Hydroxypropyl)-1-methyl-1,3-dihydroimidazol-2-one (331)

To a solution of alcohol 312 (56 mg, 0.37 mol) in MeOH (10 mL) was added Lindlar catalyst (5% Pd on CaCO3, 3.5 % Pb; 78 mg, 0.04 mmol Pd). The suspension was placed under an atmosphere of H2 by three pump-fill cycles and stirred at ambient temperature for 1 h. The suspension was filtered, solvent removed in vacuo, and purified by flash chromatography to afford alcohol 331 (47 mg, 0.30 mmol, 82%) as a yellow oil. v max/cm⁻¹ (KBr disc) 3349 (OH stretch), 3161 (NH stretch), 1661 (C=O stretch); δH (300 MHz, CD3OD) 6.11 (1H, s, C=CH), 3.61 (2H, t, J=6.2 Hz, CH2OH), 3.18 (3H, s, NCH3), 2.49 (2H, t, J=6.7 Hz, CH2C=CH), 1.77 (2H, tt, J=6.7, 6.2 Hz, CH2CH2OH) ppm; δc (75 MHz, CD3OD) 156.0 (C=O), 126.1 (C=CH), 104.8 (C=CH), 61.8 (CH2OH), 31.3 (CH2C=CH), 27.4 (NCH3), 21.9 (CH2CH2OH) ppm; m/z (+ve CI-methane) 157 (MH+, 100%), 137 (58); HRMS calcd. for C7H13N2O2 (MH+) 157.0977; found 157.0980.

5-(3-(tert-Butyldimethylsilyloxy)-propenyl)-1-methyl-1,3-dihydro-imidazol-2-one (339)

Silyl ether 313 (277 mg, 1.04 mmol) was dissolved in MeOH (28 mL) and Lindlar catalyst (5% Pd on CaCO3, 3.5 % Pb; 111 mg, 0.05 mmol, 5 mol % Pd) added. The suspension was cooled to 0 °C and placed under an atmosphere of H2 until 30 mL (1.25 mmol) had been taken up. The solution was filtered and the solvent removed in vacuo.
Purification by flash chromatography (EtOAc:petrol 40-60, 7:3) gave alkene 339 (147 mg, 0.55 mmol, 53%) as a pale yellow solid, mp 126 °C and 341 (63 mg, 0.23 mmol, 22%) as a yellow oil; \( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr disc) 3398 (NH stretch), 1684 (C=O stretch), 1670 (C=C stretch), 1636 (C=C stretch), 1086, 837; \( \delta_H \) (300 MHz, CD\(_3\)OD) 6.33 (1H, s, NHCH=C), 6.14 (1H, d, J=11.6 Hz, CH\(_2\)CH=CH\(_2\)), 5.86 (1H, dt, J=11.7, 5.9 Hz, CH\(_2\)CH=CH), 4.34 (2H, dd, J=5.9, 1.6 Hz CH\(_2\)CH=CH), 3.19 (3H, s, NCH\(_3\)), 0.90 (9H, s, Si(CH\(_3\))\(_3\)), 0.07 (6H, s, Si(CH\(_3\))\(_2\)) ppm; \( \delta_C \) (75 MHz, CD\(_3\)OD) 154.5 (C=O), 133.2 (CH\(_2\)CH=CH\(_2\)), 121.0 (CH=CH), 114.3 (CH\(_2\)CH=CH\(_2\)), 108.1 (CH=CH), 60.7 (CH\(_2\)OSi), 27.1 (NCH\(_3\)), 25.9 (Si(CH\(_3\))\(_3\)), 18.3 (Si(CH\(_3\))\(_3\)), -3.61 (Si(CH\(_3\))\(_2\)) ppm; \( m/z \) (+ve FAB) 269 (MH\(^+\), 44%), 216 (13), 153 (35); HRMS calcd. for C\(_{13}H_{28}N_2O_2Si\) (MH\(^+\)) 269.1685, found 269.1675.

5-[3-(tert-Butyldimethylsilyloxy)propyl]-1-methyl-1,3-dihydroimidazol-2-one (341)

\[ \begin{align*}
\text{Si-O} & \quad \text{N} \quad \text{CON} \\
\text{CH}_3 & \quad \text{H} \\
\end{align*} \]

\( \nu_{\text{max}}/\text{cm}^{-1} \) (KBr disc) 3156 (NH stretch), 1658 (C=O stretch); \( \delta_H \) (400 MHz, CD\(_3\)OD) 6.10 (1H, t, J=1.2 Hz, C=CH), 3.70 (2H, t, J=6.0 Hz, CH\(_2\)OSi), 3.18 (3H, s, NCH\(_3\)), 2.49 (2H, td, J=7.6, 1.1 Hz, CH\(_2\)C=CH), 1.76 (2H, tt, J=7.6, 6.0 Hz, CH\(_2\)CH\(_2\)OSi), 0.91 (9H, s, Si(CH\(_3\))\(_3\)), 0.06 (6H, s, Si(CH\(_3\))\(_2\)) ppm; \( \delta_C \) (100 MHz, CD\(_3\)OD) 156.1 (C=O), 126.4 (C=CH), 104.2 (C=CH), 61.8 (CH\(_2\)OSi), 31.7 (CH\(_2\)C=CH), 27.9 (NCH\(_3\)), 25.7 (Si(CH\(_3\))\(_3\)), 24.2 (CH\(_2\)CH\(_2\)OSi), 18.3 (Si(CH\(_3\))\(_3\)), -5.1 (Si(CH\(_3\))\(_2\)) ppm; \( m/z \) (+ve CI-methane) 271 (MH\(^+\), 100%), 137 (62); HRMS calcd. for C\(_{13}H_{27}N_2O_2Si\) (MH\(^+\)) 271.1842; found 271.1845.
1-Hydroxy-1,2-benziodoxol-3(1H)-one (IBX) (347)\(^{149}\)

![Chemical Structure](image)

2-Iodobenzoic acid 346 (5.00 g, 20.2 mmol) was added to a stirred solution of Oxone\(^{®}\) (37.2 g, 60.5 mmol) in H\(_2\)O (200 mL). The solution was heated to 70 °C for 1 h and then to 90 °C until complete dissolution occurred. The solution was allowed to cool to ambient temperature without external cooling and then cooled in an ice-water bath for 3 h. The resulting precipitate was isolated by filtration, washed with H\(_2\)O (6×20 mL) and acetone (2×10 mL) and dried \textit{in vacuo} to give IBX 347 (3.42 g, 12.2 mmol, 60%) as a white solid.

\[(E)-3-(3-Methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)propenal (348)\]

![Chemical Structure](image)

A solution of IBX 347 (106 mg, 0.38 mmol) in DMSO (0.9 mL) was added to a solution of alcohol 296 in DMSO (0.5 mL) at ambient temperature. After stirring for 1 h, H\(_2\)O (5 mL) was added and the mixture was extracted with EtOAc (4×25 mL). The extracts were washed with H\(_2\)O (5 mL) and brine (5 mL), dried over Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. Flash chromatography (EtOAc:MeOH, 95:5) gave aldehyde 348 (12 mg, 0.08 mmol, 25%) as a yellow oil. \(v_{\text{max}}/\text{cm}^{-1}\) (KBr disc) 3398 (NH stretch), 1684 (C=O stretch), 1670 (C=C stretch), 1636 (C=C stretch); \(\delta_H\) (400 MHz, DMSO-\(d_6\)) 9.48 (1H, d, \(J=7.7\) Hz, CHO), 7.40 (1H, s, C=CH), 7.35 (1H, d, \(J=15.9\) Hz, CHOCH=CH), 6.47 (1H, dd, \(J=15.9, 7.7\) Hz, CHOCH=CH), 3.28 (3H, s, NCH\(_3\)) ppm; \(\delta_C\) (100 MHz, DMSO-\(d_6\)) 174.7 (CHO), 153.1 (C=O), 132.9 (CH=CH), 125.6 (C=CH), 116.1 (CH=CH), 110.3 (C=CH), 27.8 (NCH\(_3\)) ppm; \(m/z\) (+ve CI) 153 (MH\(^+\), 100%), 137 (43); HRMS calcd. for C\(_7\)H\(_9\)N\(_2\)O\(_2\) (MH\(^+\)) 153.0064, found 153.0073.
Propiolaldehyde diethyl acetal (0.76 mL, 5.3 mmol) in THF (6 mL) was cooled to 0 °C and n-butylmagnesium chloride (2.0 M in THF, 2.6 mL, 5.2 mmol) added dropwise with stirring. The resulting solution was allowed to warm to ambient temperature and stirred for a further 4 h. The Grignard solution was then added via cannula to a suspension of 3-methylhydantoin 314 (199 mg, 1.74 mmol) in THF (8 mL) at 0 °C. The resulting suspension was then warmed to 40 °C, stirred for 19 h, cooled and poured into saturated NH₄Cl (10 mL). Et₂O (5 mL) was added and the organics separated, and the aqueous layer was extracted with Et₂O (3×10 mL). The combined organics were washed with brine (10 mL), dried over MgSO₄ and concentrated in vacuo. The crude product was dissolved in CHCl₃ (30 mL), silica (0.25 g) added and the suspension stirred at ambient temperature for 18 h. The solvent was removed in vacuo and flash chromatography (EtOAc:iso-hexane, 8:2) gave alkyne 354 (123 mg, 0.55 mmol, 32%) as a yellow solid, mp 128 °C. \( \nu_{\text{max/cm}^{-1}} \) (KBr disc) 3431 (NH stretch), 2976 (CH stretch), 2235 (C=O stretch), 1670 (C=O stretch); \( \delta_H \) (400 MHz, CDCl₃) 10.33 (1H, broad s, NH), 6.60 (1H, s, C=CH), 5.45 (1H, s, C=CH), 3.79-3.69 (2H, m, OCH₂CH₃), 3.67-3.58 (2H, m, OCH₂CH₃), 3.25 (3H, s, NCH₃), 1.24 (6H, t, J=7.1 Hz, 2×OCH₂CH₃) ppm; \( \delta_C \) (100 MHz, CD₃OD) 154.8 (C=O), 115.9 (C=CH), 108.7 (C=CH), 93.0 (C=CH), 91.4 (C=C), 74.2 (C=O), 62.3 (OCH₂CH₃), 28.3 (NCH₃), 15.4 (OCH₂CH₃) ppm; \( m/z \) (+ve CI methane) 225 (MH⁺, 100%), 179 (57), 103 (15); HRMS calcd. for C₁₁H₁₇N₂O₃ (MH⁺): 225.1239, found 225.1245.
1-(4-Methoxybenzyl)-3-methylhydantoin (356)

3-Methylhydantoin 314 (3.00 g, 26.3 mmol) was dissolved in DMF (75 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 1.27 g, 31.8 mmol) was added in one aliquot and evolution of gas was observed. The suspension was stirred for 30 min then 4-methoxybenzyl chloride (4.3 mL, 32 mmol) was added and the mixture was stirred for a further 6 h. The reaction was then poured into sat. NaHCO₃ (100 mL) and extracted with EtOAc (4×100 mL) and brine (100 mL), dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (EtOAc:isoctane, 35:65) gave hydantoin 356 (5.00 g, 21.3 mmol, 81%) as a white solid, mp 144 °C. νₐ₅v/cm⁻¹ (KBr disc) 2951 (CH stretch), 2932 (CH stretch), 1759 (C=O stretch), 1693 (C=O stretch), 1514, 1477, 1250, 1032, 845, 816; δH (400 MHz, CDCl₃) 7.18 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.89 (2H, d, J=8.6 Hz, 2×aromatic CH), 4.50 (2H, s, CH₂C₆H₄OCH₃), 3.80 (3H, s, OCH₃), 3.70 (2H, s, CH₂C=O), 3.04 (3H, s, NCH₃) ppm; δC (100 MHz, CDCl₃) 170.0 (C=O), 159.5 (aromatic COCH₃), 156.8 (C=O), 129.5 (2×aromatic CH), 127.4 (aromatic CCH₂N), 114.3 (2×aromatic CH), 55.3 (OCH₃), 48.9 (CH₂C₆H₄OCH₃), 46.1 (CH₂C=O), 24.9 (NCH₃) ppm; m/z (+ve Cl-methane) 235 (MH⁺, 100%), 127 (73), 121 (85); HRMS calcd. for. C₁₂H₁₅N₂O₃ (MH⁺): 235.1083, found 235.1073. Analysis calculated for C₁₂H₁₄N₂O₃: C, 61.5, H, 6.0, N, 11.9; found C, 61.9, H, 6.3, N, 11.9 %.
4-(3-(tert-Butyldimethylsilanyloxy)-prop-1-ynyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (358)

Silyl ether 313 (200 mg, 0.75 mmol) was dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 38 mg, 0.95 mmol) was added in one aliquot, the solution was allowed to warm to ambient temperature and then stirred for a further 30 min. p-Methoxybenzyl chloride (120 µL, 0.9 mmol) was added and the solution stirred for a further 4 h. The solution was then poured onto sat. NaHCO₃ (30 mL), extracted with EtOAc (4×30 mL), the extracts washed successively with 30 mL each of H₂O, sat NaHCO₃ and brine, dried over MgSO₄ and concentrated *in vacuo*. Flash chromatography (petrol 40-60:EtOAc, 7:3) gave silyl ether 358 (252 mg, 0.65 mmol, 87%) as a yellow oil. $\nu_{\text{max/cm}}$ (thin film) 2856 (CH stretch), 1717 (C=O stretch), 1109, 837; $\delta$H (400 MHz, CDCl₃) 7.16 (2H, d, J=8.8 Hz, 2×aromatic CH), 6.83 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.33 (1H, s, CH=C), 4.68 (2H, s, CH₂C₆H₄OCH₃), 4.46 (2H, s, CH₂OSi), 3.75 (3H, s, OCH₃), 3.23 (3H, s, NCH₃), 0.88 (9H, s, SiC(CH₃)₃), 0.09 (6H, s, Si(CH₃)₂) ppm; $\delta$C (100 MHz, CDCl₃) 159.3 (aromatic COCH₃), 152.2 (C=O), 129.4 (2×aromatic CH), 128.4 (aromatic CCH₂N), 115.3 (C=CH), 114.2 (2×aromatic CH), 106.8 (C=CH), 93.7 (C=C), 73.1 (C=C), 55.2 (OCH₃), 52.1 (CH₂OSi), 46.7 (CH₂C₆H₄OCH₃), 28.3 (NCH₃), 25.7 (SiC(CH₃)₃), 18.2 (SiC(CH₃)₃), -5.2 (Si(CH₃)₂); m/z (EI) 386 (M⁺, 15%), 121 (100); HRMS calcd. for C₂₁H₃₀N₂O₃Si (M⁺): 386.2020, found 386.2020.
4-(3-Hydroxyprop-1-ynyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (359)

Silyl ether 358 (423 mg, 1.09 mmol) was dissolved in THF (4 mL), cooled to 0 °C and TBAF (1.0 M in THF, 1.20 mL, 1.20 mmol) added dropwise. The solution was warmed to ambient temperature, stirred for 2 h, poured into H2O (10 mL) and extracted with EtOAc (3×20 mL). The organic extracts were washed with brine (20 mL), dried over MgSO4 and concentrated in vacuo. Flash chromatography (EtOAc:iso-hexane, 9:1) gave propargylic alcohol 359 as a pale yellow solid, mp 156 °C; νmax/cm-1 (KBr disc) 3096 (OH stretch), 1663 (C=O), 1612 (C=C); δH (400 MHz, CDCl3) 7.16 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.83 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.12 (1H, s, C=CH), 4.65 (2H, s, NCH2Ar), 4.41 (2H, d, J=6.2Hz, CH2OH), 3.77 (3H, s, OCH3), 3.21 (3H, s, NCH3), 2.98 (1H, t, J=6.2Hz, CH2OH) ppm; δC (100 MHz, CDCl3) 159.5 (aromatic COCH3), 152.2 (C=O), 129.6 (2×aromatic CH), 128.3 (aromatic CCH2N), 115.6 (C=CH), 114.2 (2×aromatic CH), 106.7 (C=CH), 93.8 (C=C), 73.4 (C=C), 55.3 (OCH3), 52.1 (CH2OH), 46.8 (CH2Ar), 28.4 (NCH3) ppm; m/z (+ve FAB) 273 (MH+, 11%), 272 (9), 217 (12); HRMS calcd. for C15H16N2O3 (M+) 272.1161, found 272.1162; Analysis calcd. for C15H16N2O3: C, 66.2, H, 5.9, H 10.3; found C, 66.2, H, 5.9, N, 10.3%. 

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(Z)-4-(3-Hydroxypropenyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (360)

\[
\begin{align*}
\text{HO} & \text{N} \text{N} \\
\text{CH}_3 & \text{O} \\
\text{CH} & \text{O}
\end{align*}
\]

Zinc dust (4.38 g, 67.0 mmol) was suspended in water at ambient temperature, copper acetate monohydrate (880 mg, 4.4 mmol) was added and the suspension stirred for 15 min. Silver nitrate (878 mg, 5.2 mmol) was then added and the suspension stirred for a further 15 min. The activated couple was isolated by filtration and washed successively with 50 mL portions of H₂O, MeOH, acetone and Et₂O and dried under suction for 5 min. Propargylic alcohol 359 (502 mg, 1.84 mmol) was dissolved in H₂O:MeOH (1:3, 40 mL), the activated zinc couple added and the suspension stirred at 50 °C for 20 h. After cooling the reaction was filtered and the solvent removed in vacuo. Flash chromatography (100% EtOAc) gave allylic alcohol 360 (390 mg, 1.42 mmol, 77%) as a yellow solid, mp 121 °C. \(\nu_{\text{max/cm}^{-1}}\) (KBr disc) 3381 (OH stretch), 1666 (C=O stretch), 1612 (C=C stretch), 1585, 1514, 818; \(\delta_H\) (400 MHz, CDCl₃) 7.21 (2H, d, J=8.3 Hz, 2×aromatic CH), 6.88 (2H, d, J=8.6 Hz, 2×aromatic CH), 6.36 (1H, s, C=CH), 6.14 (1H, d, J=11.8 Hz, CH₂CH=CH), 5.87 (1H, dt, J=11.7, 6.0 Hz, CH₂CH=CH), 4.75 (2H, s, CH₂C₆H₄OCH₃), 4.17 (2H, d, J=6.0 Hz, CH₂CH=CH), 3.76 (3H, s, OCH₃), 3.23 (3H, s, NCH₃) ppm; \(\delta_C\) (100 MHz, CDCl₃) 160.9 (aromatic COCH₃), 154.3 (C=O), 134.2 (CH₂CH=CH), 130.4 (aromatic CH₂N), 130.2 (aromatic CH), 121.6 (C=CH), 115.7 (CH₂CH=CH), 115.1 (aromatic CH), 111.8 (N-C=CH), 60.2 (CH₂CH=CH), 55.7 (OCH₃), 47.6 (CH₂C₆H₄OCH₃), 27.9 (NCH₃) ppm; \(m/z\) (+ve CI-methane) 275 (MH⁺, 91%), 274 (86), 257 (30), 183 (93), 167 (35), 149 (19), 122 (47), 121 (95), 98 (60); HRMS calcd. for C₁₅H₁₉N₂O₃ (MH⁺) 275.1396, found 275.1390.
Manganese dioxide (345)

A solution of manganese dichloride tetrahydrate (20 g, 0.1 mol) in water (200 mL) at 70 °C was added over 10 min to a stirred solution of potassium permanganate (16 g, 0.1 mmol) in water (200 mL) at 60 °C. The resulting suspension was stirred at 60 °C for 2 h then overnight at ambient temperature. The suspension was filtered, washed with water (3 L) and dried in vacuo to give 22 g of manganese dioxide 345 as a red-brown solid.

\[(E)-3-(1-(4-Methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-propenal (361)\]

Alcohol 360 (271 mg, 1.0 mmol) was dissolved in DCM (20 mL) and MnO₂ 345 (1.72 g, 20 mmol) added. The suspension was heated to 30 °C for 24 h, filtered and the solvent removed in vacuo to afford a mixture of two isomers in Z:E ratio of 9:1 by ¹H NMR. Flash chromatography (gradient elution: EtOAc:petrol 2:8, 6:4) afforded aldehyde 361 (193 mg, 0.71 mmol, 72%) as a yellow oil. ν<sub>max/cm⁻¹</sub> (KBr disc) 1690 (C=O aldehyde stretch), 1651 (C=O stretch), 1642 (C=C stretch), 823; δ<sub>H</sub> (400 MHz, CDCl₃) (Z-isomer): 9.60 (1H, d, J=5.2 Hz, CHO), 7.11-7.08 (2H, m, 2×aromatic CH), 6.69-6.66 (2H, m, 2×aromatic CH), 5.87 (1H, d, J=11.9 Hz, CHOCH=CH), 5.65 (1H, dd, J=11.8, 5.3 Hz, CHOCH=CH), 4.42 (1H, s, CH₃), 3.24 (3H, s, OCH₃), 2.65 (3H, s, NCH₃) ppm; δ<sub>C</sub> (100 MHz, CDCl₃) (Z-isomer) 189.5 (CHO), 160.5 (aromatic COCH₃), 155.0 (C=O), 132.6 (CHOCH=CH), 130.8 (aromatic CH₂N), 131.0 (aromatic CH), 121.9 (C=CH), 115.1 (CHOCH=CH), 114.5 (aromatic CH), 112.2 (C=CH), 55.5 (OCH₃), 47.1 (CH₂C₆H₄OCH₃), 27.8 (NCH₃) ppm; m/z (+ve CI-methane) 273 (MH⁺, 75%), 272 (62), 167 (43), 122 (35); HRMS calcd. for C₁₃H₁₇N₂O₃ (MH⁺) 273.1239, found 273.1261.
4-(3-Benzyliminoprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (363)

Aldehyde 361 (45 mg, 0.17 mmol) was dissolved in DCM (3 mL) and activated 4Å molecular sieves (50 mg) added. Benzylamine (18 μL, 0.17 mmol) was then added and the suspension stirred at ambient temperature for 20 h. The reaction was then filtered and concentrated in vacuo to afford crude imine 363. δ_H (300 MHz, C₆D₆) 7.67 (1H, d, J=8.6 Hz, N=CH), 7.36-7.11 (5H, m, C₆H₅), 7.08-7.05 (2H, m, 2×aromatic CH), 6.72-6.69 (2H, m, 2×aromatic CH), 6.60 (1H, dd, J=16.2, 8.6 Hz, N=CHCH=CH), 6.01 (2H, d, J=16.3 Hz, N=CHCH=CH), 5.90 (1H, s, C=CH), 4.60 (2H, s, CH₂), 4.49 (2H, s, CH₂), 3.26 (3H, s, OCH₃), 2.91 (3H, s, NCH₃) ppm.

(E) and (Z)-3-(1-(4-Methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-3-methyl sulfanylpropenal (370 and 371)

Alcohol 359 (1.00 g, 3.67 mmol) and triethylamine (5.2 mL, 37 mmol) were dissolved in anhydrous DMSO (13 mL) and the solution warmed to 30 °C. A solution of sulfur trioxide-pyridine complex (2.34 g, 14.7 mmol) in DMSO (13 mL) was added via cannula and the resulting solution stirred at 30 °C for 3.5 h. After cooling, the solution was poured into H₂O (130 mL) and extracted with EtOAc (3×130 mL), the extracts
washed with water (2×70 mL), dried over Na₂SO₄ and concentrated \textit{in vacuo}. Flash chromatography (Florisil®, EtOAc:hexane; 7:3) gave E-aldehyde 370 and Z-aldehyde 371 in a 10:1 mixture (948 mg, 2.98 mmol, 81%) as a yellow oil. \(\nu_{\text{max}}/\text{cm}^{-1} \text{ (thin film)}\) 3107, 2997, 2935, 2835, 2165, 1690 (CHO stretch), 1655 (C=O stretch), 1611 (C=C stretch), 1585 (C=C stretch), 820; \(\delta_H \text{ (400 MHz, C}_6\text{D}_6\text{)} \text{ (E-isomer 370)} \) 9.42 (1H, d, J=7.4 Hz, CHO), 7.02 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.66 (2H, d, J=8.7 Hz, 2×aromatic CH), 5.92 (1H, s, NC=CH), 5.85 (1H, d, J=7.4 Hz, C=CHCHO), 4.45 (2H, s, CH₂C₆H₄OCH₃), 3.23 (3H, s, OCH₃), 2.96 (3H, s, NCH₃), 1.44 (3H, s, SCH₃) ppm; \(\delta_C \text{ (75 MHz, C}_6\text{D}_6\text{)} \text{ (E-isomer 370)} \) 187.1 (CHO), 159.9 (aromatic C), 153.7 (C=O), 152.4 (aromatic C), 129.6 (2×aromatic CH), 125.4 (C=CH), 117.4 (C=CH), 114.5 (2×aromatic CH), 114.4 (C=CH), 88.4 (C=CH), 54.7 (OCH₃), 46.9 (CH₂), 28.8 (NCH₃), 14.8 (SCH₃); \(\text{m/z (}^{+}\text{ve Cl-methane)}\) 319 (MH⁺, 94%), 271 (13), 121 (100); HRMS calcld. for C₁₄H₁₉N₂O₃S (MH⁺) 319.1116, found 319.1119.

Irradiation of the \(^1\text{H} \text{NMR} \text{ (Z)-isomer signal at 9.42 ppm gave a NOE enhancement of the (E)-isomer signal at 10.26 of 1.05\%}, \text{ indicating that 370 and 371 are interconverting in C}_6\text{D}_6 \text{ solution. Upon heating to 70°C in C}_6\text{D}_6 \text{ the (E):(Z)-isomer ratio decreased to 5:1.}

3-(4-Methoxybenzyl)-1-methyl-6-methylsulfanyl-1,3,5,6-tetrahydrocyclopentimidazole-2,4-dione (375)

![Chemical Structure](image)

A solution of aldehydes 370 and 371 was left to stand in CDCl₃ for 18 h, affording ketone 375. \(\nu_{\text{max}}/\text{cm}^{-1} \text{ (thin film)}\) 3200, 1712 (C=O ketone), 1682 (C=O amide), 1612 (C=C), 1514, 1485, 1245, 1178, 1033 cm⁻¹; \(\delta_H \text{ (400 MHz, CDCl₃)} \) 7.38 (2H, d, J=8.6
Hz, 2×aromatic CH), 6.79 (2H, d, J=8.6 Hz 2×aromatic CH), 4.89 (1H, d, J=14.5 Hz, CH₂C₆H₄OCH₃), 4.82 (1H, d, J=14.5 Hz, CH₂C₆H₄OCH₃), 4.12 (1H, dd, J=6.1, 1.3 Hz, CHSCH₃), 3.73 (3H, s, OCH₃), 3.37 (3H, s, NCH₃), 3.19 (1H, dd, J=18.1, 6.2 Hz, COCH₃), 2.68 (1H, dd, J=18.1, 1.0 Hz, COCH₃), 1.68 (3H, s, SCH₃) ppm; δC (100 MHz, CDCl₃) 184.3 (CH₂C=O), 159.2 (aromatic C), 156.0 (C=O), 150.7 (aromatic C), 130.1 (2×aromatic CH), 128.9 (C=C), 123.4 (C=C), 113.9 (2×aromatic CH), 55.1 (OCH₃), 47.0 (COCH₃), 45.3 (CH₂C₆H₄OCH₃), 35.3 (CHSCH₃), 28.6 (NCH₃), 10.8 (SCH₃) ppm; m/z (+ve Cl-methane) 319 (MH⁺, 98%), 271 (49), 211 (31), 197 (12), 165 (17), 149 (20), 121 (100); HRMS calcd. for C₁₆H₁₉N₂O₃S (MH⁺): 319.1116, found 319.1113.

(E)-2-Benzylamino-4-(1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-4-methylsulfanylbutox-3-enitrile (387)

Aldehyde 370 (71 mg, 0.22 mmol), benzylamine (30 μL, 0.27 mmol), 4Å activated molecular sieves (50 mg) and DCM (3 mL) were stirred at ambient temperature for 21 h to form the imine as a mixture of isomers. δH (300 MHz, C₆D₆) Major isomer: 8.68 (1H, d, J=8.8 Hz, N=CH), 7.45-7.09 (5H, m, C₆H₅), 7.09-7.03 (2H, m, 2×aromatic CH), 6.69-6.66 (2H, m, 2×aromatic CH), 6.60 (1H, d, J=8.8 Hz, CH=C), 5.97 (1H, s, C=CH), 4.59 (2H, s, CH₂), 4.34 (2H, s, CH₂), 3.23 (3H, s, NCH₃), 1.56 (3H, s, SCH₃); Minor isomer: 7.91 (1H, d, J=8.8 Hz, N=CH), 7.45-7.09 (5H, m, C₆H₅), 7.09-7.03 (2H, m, 2×aromatic CH), 6.69-6.66 (2H, m, 2×aromatic CH), 6.37 (1H, d, J=8.8 Hz, CH=C), 5.92 (1H, s, C=CH), 4.51 (2H, s, CH₂), 4.40 (2H, s, CH₂), 3.06 (3H, s, NCH₃), 1.63 (3H, s, SCH₃) ppm.

Trimethylsilyl cyanide (107 μL, 0.8 mmol) was then added and the solution stirred for a further 16 h. Concentration in vacuo gave α-aminonitrile 387 as a brown oil. δH (300...
MHZ, C\(_6\)D\(_6\) (E)-isomer: 7.15 (5H, m, 5\times aromatic CH), 7.00 (2H, d, \(J=8.7\) Hz, 2\times aromatic CH), 6.66 (2H, d, \(J=8.7\) Hz, 2\times aromatic CH), 5.87 (1H, s, C=CH), 5.30 (1H, d, \(J=8.9\) Hz, CHCH=CSCH\(_3\)), 3.97 (1H, dd, \(J=10.2, 9.0\) Hz, (CH(CN)CHSCH\(_3\)), 3.75 (1H, dd, \(J=13.0, 5.3\) Hz, NHCH\(_2\)), 3.40 (1H, dd, \(J=13.0, 6.7\) Hz, NHCH\(_2\)), 3.22 (3H, s, OCH\(_3\)), 3.11 (3H, s, NCH\(_3\)), 1.55 (3H, s, SCH\(_3\)), 1.19 (1H, dt, \(J=10.0, 5.3\) Hz, NH) ppm

4-(3-Benzylamino-1-methylsulfanylprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (390)

\[
\begin{align*}
\text{CH}_2\text{C}_6\text{H}_4\text{OCH}_3 & \quad \text{CH}_3 \\
& \quad \text{SCH}_3
\end{align*}
\]

Aldehyde 370 (265 mg, 0.83 mmol) was dissolved in anhydrous EtOH (7 mL) and activated 4Å molecular sieves (100 mg) were added. Benzylamine (100 \(\mu\)L, 0.92 mmol) was then added and the solution stirred at ambient temperature for 30 h to afford a mixture of imines. Sodium borohydride (31 mg, 0.82 mmol) was added and the solution stirred for a further 12 h. MeOH (2 mL) was added, the solution filtered and the solvent removed in vacuo. Flash chromatography (Florisil\textsuperscript{®}, 100% EtOAc) gave amine 390 (234 mg, 0.57 mmol, 69%) as a yellow oil. \(v_{\text{max/cm}^{-1}}\) (thin film) 3304 (NH stretch), 1674 (C=O stretch), 1612 (C=C stretch), 820; \(\delta_H\) (400 MHZ, CD\(_3\)OD) (E-isomer) 7.32-7.20 (5H, m, C\(_6\)H\(_5\)), 7.18-7.16 (2H, m, 2\times aromatic CH), 6.90-6.86 (2H, m, 2\times aromatic CH), 6.36 (1H, s, C=CH), 5.87 (1H, t, \(J=7.1\) Hz, CH=CSCH\(_3\)), 4.71 (2H, s, CH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.75 (3H, s, OCH\(_3\)), 3.63 (2H, s, CH\(_2\)C\(_6\)H\(_5\)), 3.18 (3H, s, NCH\(_3\)), 3.17 (2H, d, \(J=7.1\) Hz, CH\(_2\)NH), 2.15 (3H, s, SCH\(_3\)) ppm; (Z-isomer) 7.32-7.20 (5H, m, C\(_6\)H\(_5\)), 7.18-7.16 (2H, m, 2\times aromatic CH), 6.90-6.86 (2H, m, 2\times aromatic CH), 6.42 (1H, s, C=CH), 5.91 (1H, t, \(J=6.6\) Hz, CH=CSCH\(_3\)), 4.73 (2H, s, CH\(_2\)C\(_6\)H\(_4\)OCH\(_3\)), 3.77 (2H, s, CH\(_2\)C\(_6\)H\(_5\)), 3.75 (3H, s, OCH\(_3\)), 3.50 (2H, d, \(J=6.4\) Hz, CH\(_2\)NH), 3.29 (3H, s, NCH\(_3\)), 1.96 (3H, s, SCH\(_3\)) ppm; \(\delta_C\) (75 MHZ, CDCl\(_3\)) (E-isomer) 159.3 (C=O), 153.5
(aromatic C), 139.3 (aromatic C), 129.3 (2×aromatic CH), 128.5 (2×aromatic CH), 128.2 (2×aromatic CH), 127.9 (aromatic CH), 127.2 (aromatic C), 122.2 (C=CH), 118.3 (C=CH), 114.2 (2×aromatic C), 109.9 (C=CH), 109.9 (C=CH), 55.3 (C₆H₄OCH₃), 53.1 (CH₂C₆H₄OCH₃), 47.9 (CH₂C₆H₅), 46.7 (CH₂NH), 28.3 (NCH₃), 15.4 (SCH₃) ppm; m/z (+ve CI-methane) 410 (MH⁺, 46%), 303 (91), 121 (100), 91 (74); HRMS calcd. for C₂₃H₂₈N₅O₂S (MH⁺) 410.1902, found 410.1905.

2-Trichloroacetylpyrrole (389)\(^{173}\)

![Structure of 2-Trichloroacetylpyrrole](image)

A solution of pyrrole (2.59 mL, 37.3 mmol) in Et₂O (20 mL) was added dropwise to a solution of trichloroacetyl chloride (4.75 mL, 42.6 mmol) in Et₂O (6.5 mL) over 40 min. The resulting solution was heated to reflux for 1 h, cooled and then a solution of NaHCO₃ (3.25 g) in H₂O (10 mL) was added slowly. The organic layer was separated, washed with H₂O (4×10 mL) and brine (10 mL) and dried over Na₂SO₄. The solution was treated twice with NORIT SX activated charcoal (2×0.50 g), filtering after each addition, and the solvent removed in vacuo to give trichloroacetyl pyrrole 389 (7.26 g, 34.2 mmol, 92%) as a white solid, mp 77 °C; \(ν_{max}/\text{cm}^{-1}\) (KBr disc) 3306 (NH stretch), 1655 (C=O stretch), 1537, 1462, 1423, 1387, 1358, 1136, 1113, 1036 cm\(^{-1}\); \(δ_H\) (300 MHz, CDCl₃) 9.70 (1H, broad s, NH), 7.39-7.38 (1H, m, pyrrole CH), 7.17-7.16 (1H, m, pyrrole CH), 6.38-6.36 (1H, m, pyrrole CH) ppm; \(δ_C\) (100 MHz, CDCl₃) 173.3 (C=O), 127.4 (aromatic CH), 122.9 (aromatic C), 121.3 (aromatic CH), 111.8 (aromatic CH), 94.9 (CCl₃); m/z (+ve CI-methane) 212 (MH⁺ [³⁵Cl₃], 100%), 178 (40); HRMS calcd. for C₆H₅Cl₃NO (MH⁺) 211.9437, found 211.9439.
4-(3-Benzyl-N-pyrrole-2-carbonylamino)-1-methylsulfanylprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (391)

![Chemical structure image]

Amine 390 (100 mg, 0.24 mmol) and pyrrole-2-carboxylic acid (52 mg, 0.49 mmol) were dissolved in THF (2 mL) and diisopropylcarbodiimide (76 µL, 0.49 mmol) added. The solution was stirred at ambient temperature for 30 h, filtered and the solvent removed in vacuo. The crude product was dissolved in DCM (10 mL), washed with NaOH solution (1.3 M, 5 mL), dried over Na₂SO₄ and the solvent removed in vacuo. Flash chromatography (gradient elution: EtOAc:hexane; 70:30, 80:20) afforded amide 391 (110 mg, 0.22 mmol, 91%) as a yellow oil. νₓ max/cm⁻¹ (thin film) 3269 (NH stretch), 1674 (C=O stretch), 1597 (C=C stretch), 727; δH (400 MHz, DMSO-d₆) 11.32 (1H, broad s, NH), 7.30-7.16 (5H, m, C₆H₅), 7.12-7.10 (2H, m, 2×aromatic CH), 6.89-6.88 (1H, m, pyrrole CH), 6.85-6.83 (2H, m, 2×aromatic CH), 6.35-6.34 (1H, m, pyrrole CH), 6.34 (1H, s, C=CH), 5.74 (1H, t, J=6.5 Hz, CH₂CH=C), 4.69 (2H, s, CH₂C₆H₄OCH₃), 4.59 (2H, s, CH₂C₆H₅), 4.13 (2H, d, J=6.5 Hz, CHCH₂), 3.74 (3H, s, OCH₃), 3.04 (3H, s, NCH₃), 2.09 (3H, s, SCH₃) ppm; δC (125 MHz, DMSO-d₆) 162.5 (pyrrole C=O), 158.8 (aromatic C), 152.9 (C=O), 137.7 (aromatic C), 129.6 (aromatic CH), 128.9 (aromatic C), 128.7 (2×aromatic CH), 128.4 (2×aromatic CH), 128.1 (2×aromatic CH), 127.0 (aromatic CH), 126.6 (aromatic CH), 124.2 (aromatic C), 121.5 (aromatic CH), 116.9 (C=CH), 114.1 (2×aromatic CH), 111.5 (C=CH), 111.3 (C=CH), 108.6 (C=CH), 55.2 (OCH₃), 50.3 (CH₂C₆H₄OCH₃), 46.5 (CH₂C₆H₅), 45.8 (CH₂CH=C), 28.0 (NCH₃), 14.8 (SCH₃) ppm; m/z (+ve FAB) 503 (MH⁺, 5%), 307 (28), 154 (100); HRMS calcd. for C₂₈H₃₁N₄O₃S (MH⁺) 503.2117, found 503.2142.
1H-Pyrrole-2-carboxylic acid benzylamide (397) and trityl derivative (398)

Pyrrole amide 391 (42 mg, 0.084 mmol) and trityl tetrafluoroborate (32 mg, 0.097 mmol) were stirred in DCM (1 mL) at ambient temperature for 12 h and concentrated in vacuo. Flash chromatography (EtOAc:hexane, 3:7) afforded amide 393 (0.5 mg, 1 µmol) and amide 394 (0.4 mg, 2 µmol).

\[ \text{structure diagram} \]

\( \delta_H (400 \text{ MHz, } \text{CD}_3\text{OD}) \) 7.31-7.28 (4H, m, C₆H₅), 7.24-7.22 (1H, m, C₆H₅), 6.91-6.90 (1H, m, pyrrole CH), 6.81-6.80 (1H, m, pyrrole CH), 6.16-6.15 (1H, m, pyrrole CH), 6.51 (2H, s, CH₂C₆H₅) ppm; \( \delta_C (100 \text{ MHz, } \text{CD}_3\text{OD}) \) 164.7 (C=O), 140.6 (aromatic C), 129.5 (2×aromatic C), 128.4 (2×aromatic C), 128.1 (aromatic CH), 126.8 (pyrrole C), 122.9 (pyrrole CH), 111.8 (pyrrole CH), 110.2 (pyrrole CH), 43.8 (CH₂C₆H₅) ppm; \( m/z \) (⁺ve CI-methane) 201 (MH⁺, 100%), 158 (9), 41 (12); HRMS calcd. for C₁₂H₁₃N₂O (MH⁺): 201.1028, found 201.1032.

\[ \text{structure diagram} \]

\( \nu_{\max}/\text{cm}^{-1} \) (thin film) 3450 (NH stretch), 1683 (C=O stretch), 747, 716; \( \delta_H (400 \text{ MHz, } \text{CDCl}_3) \) 8.80 (1H, broad s, pyrrole NH), 7.35-7.20 (13H, m, 13×aromatic CH), 7.11-7.07 (7H, m, 7×aromatic CH), 6.45 (1H, dd, \( J=3.8, 2.5 \text{ Hz, pyrrole CH} \)), 6.05 (1H, broad t, \( J=5.6 \text{ Hz, CH}_2\text{NH} \)), 6.01 (1H, dd, \( J=3.7, 2.9 \text{ Hz, pyrrole CH} \)), 4.54 (2H, d, \( J=5.8 \text{ Hz, CH}_2\text{NH} \)); \( \delta_C (125 \text{ MHz, } \text{CDCl}_3) \) 160.8 (C=O), 145.3 (3×aromatic C), 140.9 (aromatic CH), 138.4 (aromatic CH), 130.3 (6×aromatic CH), 128.7 (2×aromatic CH), 127.9 (6×aromatic CH), 127.8 (2×aromatic CH), 127.8 (aromatic CH), 126.8 (3×aromatic CH), 125.0 (aromatic C), 112.1 (pyrrole CH), 108.5 (pyrrole CH), 60.6 (C(C₆H₅)₃), 43.4
(CH₂); m/z (+ve Cl-methane) 443 (MH⁺, 90%), 243 (53), 178 (39), 91 (70), 71 (100); HRMS calcd. for C₃₁H₂₇N₂O (MH⁺): 443.2123, found 443.2130.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (Dess-Martin periodinane) (376)

IBX 347 (3.57 g, 12.8 mmol) was added to acetic anhydride (14 mL) and heated to 80 °C. p-Toluenesulfonic acid (18 mg, 0.1 mmol) was added and the solution stirred for 2 h then cooled to 0 °C. The resulting precipitate was isolated by filtration, washed with anhydrous Et₂O (3×10 mL) and dried in vacuo to give Dess-Martin periodinane 376 (3.95 g, 9.32 mmol, 73%) as a white solid.

4-Ethynyl-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (378)

Method A: Alcohol 359 (100 mg, 0.37 mmol) was dissolved in DCM (6 mL) at ambient temperature and Dess-Martin Periodinane 376 (172 mg, 0.41 mmol) added. The solution was stirred for 50 min, poured into NaOH solution (1.3M, 3 mL) and extracted with Et₂O (2×10 mL). The organic extracts were washed with NaOH solution (20 mL), dried over Na₂SO₄, and concentrated in vacuo. Purification by flash chromatography (Florisil®:EtOAc;iso-hexane, 1:1) afforded alkyne 378 (51.7 mg, 0.21 mmol, 59%) as a pale yellow solid.

Method B: Aldehyde 366 (50 mg, 0.18 mmol) was dissolved in DCM (3 mL) and 1.3M NaOH solution (3 mL) was added. The biphasic mixture was stirred at ambient temperature for 1 h, the organic layer separated and the aqueous layer extracted with
DCM (3×3 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (EtOAc:hexane, 1:1) afforded alkyne 378 (34 mg, 0.14 mmol, 78%) as a pale yellow solid, mp 102 °C. νmax/cm⁻¹ (KBr disc) 3250 (C=H stretch), 3078 (C=C-H stretch), 2936 (CH stretch), 2833 (CH stretch), 2100 (C≡C stretch), 1676 (C=O stretch), 1618 (C=C stretch), 820, 760, 737; δH (400 MHz, CDCl₃) 7.16 (2H, d, J=8.8 Hz, 2×aromatic CH), 6.82 (2H, d, J=8.8 Hz, 2×aromatic CH), 6.40 (1H, s, CH=CH), 4.67 (2H, s, -CH₂-C₆H₄-OCH₃), 3.74 (3H, s, OCH₃), 3.30 (1H, s, C=CH₂), 3.24 (3H, s, NCH₃) ppm; δC (100 MHz, CDCl₃) 159.3 (aromatic COCH₃), 152.1 (C=O), 129.4 (2×aromatic CH), 128.2 (aromatic CCH₂N), 116.1 (C=CH), 114.2 (2×aromatic CH), 106.3 (C=C-C), 83.3 (C=CH), 72.1 (C=C-C), 55.2 (OCH₃), 46.8 (CH₂-C₆H₄-OCH₃), 28.3 (NCH₃) ppm; m/z (EI) 242 (M⁺, 17%), 122 (11), 121 (100), 78 (8); HRMS calcd. for C₁₄H₁₄N₂O₂ (M⁺): 242.1050; found 242.1049.

3-(1-(4-Methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)propynal (366)

Method A: Propargylic alcohol 359 (676 mg, 2.49 mmol) was dissolved in CHCl₃ and manganese dioxide (4.34 g, 50 mmol) added. The suspension was heated to 40 °C for 19 h, cooled, filtered through Celite® and the solvent removed in vacuo. Flash chromatography (Florisil®, EtOAc:iso-hexane, 1:1) gave aldehyde 366 (353 mg, 1.31 mmol, 53%) as a pale orange solid.

Method B: Propargylic alcohol 359 (1.00 g, 3.67 mmol) was dissolved in anhydrous DCM (100 mL) and freshly ground barium manganate (7.6 g, 29 mmol) added. The suspension was stirred at ambient temperature for 24 h, filtered through Celite® and concentrated in vacuo to give aldehyde 366 (0.76 g, 2.81 mmol, 77%) as a pale orange solid.
**Method C:** Propargylic alcohol 359 (1.00 g, 3.67 mmol) was dissolved in DCM (70 mL), Dess-Martin Periodinane 376 (1.72 g, 4.10 mmol) added and the solution stirred at ambient temperature for 1 h. Saturated NaHCO₃ (30 mL) and Na₂S₂O₃ (10 g in 30 mL H₂O) were added, the biphasic mixture stirred vigorously for 1 h and then the organic layer was separated, dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (Florisil®, EtOAc:hexane, 1:1) afforded aldehyde 366 (0.92 g, 3.40 mmol, 93%) as a pale orange solid. mp 121 °C. ν<sub>max/cm⁻¹</sub> (KBr disc) 3076, 2174 (C=O stretch), 1750 (CHO stretch), 1647 (C=O stretch), 820; δ<sub>H</sub> (400 MHz, CDCl₃) 9.30 (1H, s CHO), 7.19 (2H, d, J=8.8 Hz, 2×aromatic CH), 6.86 (2H, d, J=8.7 Hz (2×aromatic CH), 6.80 (1H, s, C=CH), 4.74 (2H, s, NCH₂C₆H₄OCH₃), 3.78 (3H, s, OCH₃), 3.30 (3H, s, NCH₃) ppm; δ<sub>C</sub> (100 MHz, CDCl₃) 174.7 (CHO), 159.7 (aromatic C), 152.1 (C=O), 129.7 (2×aromatic CH), 127.3 (aromatic C=CH₂N), 123.2 (C=CH), 114.4 (2×aromatic CH), 104.4 (C=CH), 97.1 (C=C), 85.0 (C=C), 55.3 (OCH₃), 47.4 (CH₂C₆H₄OCH₃), 28.5 (NCH₃) ppm; m/z (+ve CI-methane) 271 (MH⁺, 10%), 206 (88), 146 (100), 121 (41), 57 (40); HRMS calcd. for C₁₃H₁₅N₂O₃ (MH⁺): 271.1083; found 271.1075; Analysis calcd. for C₁₃H₁₄N₂O₃: C, 66.7, H, 5.2, N, 10.4. found C, 66.6, H, 5.2, N, 10.4%.

4-(3-Benzylaminoprop-1-ynyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydro imidazol-2-one (397)

![Structure](image)

Aldehyde 366 (49.0 mg, 0.18 mmol) was dissolved in DCM (3 mL) and activated 4Å molecular sieves (200 mg) added. Benzyalmine (99 µL, 0.91 mmol) was then added and the reaction stirred at ambient temperature for 17 h. A small sample was removed for ¹H NMR to confirm complete imine formation and two isomers of imine 367 were observed in a 6:4 ratio. δ<sub>H</sub> (400 MHz, CDCl₃) 7.77 (1H, s, CH=N), 7.73 (1H, s, CH=N), 7.34-7.28 (10H, m, CH₂C₆H₅), 7.21-7.17 (4H, m, 4×aromatic CH), 6.87-6.84 (4H, m, 4×aromatic CH), 6.59 (1H, s, C=CH), 6.53 (1H, s, C=CH), 4.81 (2H, s, CH₂C₆H₅), 4.74
(2H, s, CH$_2$C$_6$H$_4$OCH$_3$), 4.72 (2H, s, CH$_2$C$_6$H$_5$), 4.71 (2H, s, CH$_2$C$_6$H$_4$OCH$_3$), 3.29 (3H, s, NCH$_3$), 3.28 (3H, s, NCH$_3$) ppm.

Sodium triacetoxyborohydride (118 mg, 0.56 mmol) was added and the suspension stirred for a further 24 h, filtered through Celite$^\circledR$ and concentrated in vacuo. Flash chromatography (EtOAc:Et$_3$N, 200:1) afforded amine 397 (55.3 mg, 0.15 mmol, 85%) as a yellow oil. v$_{max}$/cm$^{-1}$ (thin film) 3445, 3308 (NH stretch), 2934 (CH stretch), 2835 (CH stretch), 2224 (C=CH stretch), 1693 (C=O stretch), 1651 (C=C stretch), 1612 (C=C stretch), 1514, 820, 735, 700; $^1$H NMR (400 MHz, CDCl$_3$) δ$_{H}$ 7.31-7.22 (5H, m, 5×aromatic CH), 7.18 (2H, d, J=8.7 Hz, 2×aromatic CH); 6.85 (2H, d, J=8.7 Hz, 2×aromatic CH), 6.32 (1H, s, NCH$_3$=C), 4.70 (2H, s, CH$_2$C$_6$H$_4$OCH$_3$), 3.86 (2H, s, CH$_2$C$_6$H$_5$), 3.77 (3H, s, OCH$_3$), 3.61 (2H, s, NCH$_2$C$_6$H$_5$=C), 3.26 (3H, s, NCH$_3$) ppm; δ$_c$ (100 MHz, CDCl$_3$) 159.3 (aromatic C), 152.2 (C=O), 139.1 (aromatic C), 129.4 (2×aromatic CH), 128.4 (2×aromatic CH), 128.4 (aromatic C), 128.3 (2× aromatic CH), 127.2 (aromatic CH), 114.7 (C=CH), 114.1 (2×aromatic CH), 107.0 (C=CH), 93.3 (C=C), 71.8 (C=C), 55.2 (OCH$_3$), 52.4 (NCH$_2$C$_6$H$_5$), 46.7 (CH$_2$C$_6$H$_4$OCH$_3$), 38.1 (CH$_2$C$_6$H$_5$), 28.3 (NCH$_3$) ppm; m/z (+ve CI-methane) 362 (MH$^+$, 100%), 361 (87), 255 (66), 121 (98), 91 (34); HRMS calcd. for C$_{22}$H$_{24}$N$_3$O$_2$ (MH$^+$) 362.1868, found 362.1859.

(E) and (Z)-4-(3-Benzylaminoprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (398 and 399)

Zinc dust (352 mg, 5.4 mmol) was suspended in water (2 mL), copper acetate monohydrate (71 mg, 0.4 mmol) was added and the suspension stirred for 15 min. Silver nitrate (72 mg, 0.4 mmol) was added and the suspension stirred for a further 15 min. After filtration the zinc couple was washed successively with 5 mL portions of H$_2$O, MeOH, acetone and Et$_2$O and then dried for 5 min under suction. Alkyne 397 (32.7 mg, 0.09 mmol) was dissolved in MeOH (2 mL) and H$_2$O (0.5 mL) and the
prepared zinc couple added. The suspension was heated to 50 °C with stirring for 18 h, cooled, filtered through Celite® and concentrated in vacuo. Flash chromatography (gradient elution: EtOAc:MeOH:Et3N; 200:1:2, 200:1:3) gave alkenes 398 and 399 in a 2:1 ratio of (Z):(E)-isomers (17.1 mg, 0.05 mmol, 52%) as a yellow oil. νmax/cm⁻¹ (thin film) 3439 (NH stretch), 2936 (CH stretch), 1676 (C=O stretch), 1612 (C=C stretch), 1514 (NH bend), 820 (CH bend), 741 (CH bend), 700 (CH bend); δH (400 MHz, CD3OD) (Z)-isomer 7.26-7.20 (5H, m, 5×aromatic CH), 7.15 (2H, dd, J=6.7, 2.0 Hz, 2×aromatic CH), 6.86 (2H, dd, J=6.7, 2.1 Hz, 2×aromatic CH), 6.22 (1H, s, NCH=C), 6.17 (1H, dd, J=11.7, 0.8 Hz, CH=CHCH), 5.81 (1H, dt, J=11.6, 6.3 Hz, CH=CHCH2), 4.69 (2H, s, NCH2C6H4OCH3), 3.76 (3H, s, OCH3), 3.70 (2H, s, NHCH2C6H5), 3.30 (2H, d, J=6.3 Hz, CH2CH=CH), 3.21 (3H, s, NCH3) ppm; δC (75 MHz, CDCl3) (Z)-isomer 159.1 (aromatic C), 152.7 (C=O), 139.7 (aromatic C), 130.9 (CH=CHCH2), 129.1 (2×aromatic CH), 128.8 (aromatic CCH2N), 128.3 (2×aromatic CH), 128.1 (2×aromatic CH), 127.0 (aromatic CH), 119.9 (CH=C), 115.8 (CH=CHCH2), 114.0 (2×aromatic CH), 109.4 (NCH=C), 55.1 (OCH3), 53.4 (NCH2C6H4OCH3), 47.4 (CH=CHCH2), 46.5 (NHCH2C6H5), 27.5 (NCH3) ppm; m/z (+ve CI-methane) 364 (MH⁺, 100%), 363 (33), 257 (51), 121 (85), 91 (55); HRMS calcd. for C22H28N3O2 (MH⁺) 364.2020, found 364.2022.

1H-Pyrrole-2-carboxylic acid benzyl-(3-[1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl]-prop-2-ynyl)amide (404)

![Diagram of the molecule](image)

Pyrrole-2-carboxylic acid 123 (34.1 mg, 0.31 mmol) and pyBOP (176 mg, 0.34 mmol) were suspended in DCM (1.5 mL) and DIEA (59 µL, 0.34 mmol) added. The mixture
was stirred for 15 min and dissolution occurred. A solution of amine 397 (102 mg, 0.28 mmol) in DCM (1 mL) was added via cannula, the resulting solution stirred at ambient temperature for 40 h and concentrated *in vacuo*. Flash chromatography (gradient elution: DCM:MeOH: 100:0, 200:1, 100:1, 200:3) afforded amide 404 (99.3 mg, 0.22 mmol, 78%) as a pale yellow solid, mp 59 °C. $v_{\text{max/cm}^{-1}}$ (KBr disc) 3416 (NH stretch), 2930 (CH stretch), 2228 (C=C stretch), 1684 (C=O stretch), 1652 (C=O stretch), 1612 (C=C stretch), 734; $\delta_H$ (400 MHz, DMSO-d$_6$, 343K) 11.34 (1H, broad s, NH), 7.35-7.30 (4H, m, 4×aromatic CH), 7.27-7.23 (1H, m, aromatic CH), 7.19 (2H, d, $J$=8.7 Hz, 2×aromatic CH), 6.93-6.91 (1H, m, pyrrole CH$_5$), 6.89 (2H, d, $J$=8.7 Hz, 2×aromatic CH), 6.84 (1H, s, C=CH), 6.56 (1H, broad m, pyrrole CH$_3$), 6.12-6.10 (1H, m, pyrrole CH$_2$), 4.85 (2H, s, CH$_2$C$_6$H$_5$), 4.64 (2H, s, CH$_2$C$_6$H$_4$OCH$_3$), 4.54 (2H, s, CH$_2$C=C), 3.74 (3H, s, OCH$_3$), 3.03 (3H, s, NCH$_3$) ppm; $\delta_C$ (100 MHz, DMSO-d$_6$, 343K) 161.9 (amide C=O), 158.5 (aromatic COCH$_3$), 151.3 (imidazolone C=O), 136.9 (aromatic C), 129.0 (aromatic C), 128.6 (2×aromatic CH), 128.0 (2×aromatic CH), 126.9 (2×aromatic CH), 126.7 (aromatic CH), 123.4 (aromatic C), 121.5 (pyrrole C$_5$H), 116.2 (C=CH), 113.7 (2×aromatic CH), 111.5 (pyrrole C$_4$H), 108.4 (pyrrole C$_3$H), 105.1 (C=CH), 90.0 (C=C), 72.1 (C=C), 54.8 (OCH$_3$), 50.2 (C$_6$H$_2$CH$_2$N), 45.5 (NCH$_2$C$_6$H$_4$OCH$_3$), 37.6 (CH$_2$C=C), 27.4 (NCH$_3$) ppm; $m/z$ (+ve CI-methane) 455 (MH$^+$, 13%); 280 (8); 201 (26); 174 (100); 121 (82); 100 (91); HRMS calcd. for C$_{27}$H$_{27}$N$_4$O$_3$ (MH$^+$) 455.2083, found 455.2069.

**1H-Pyrrole-2-carboxylic acid benzyl-(3-[1-(4-methoxy-benzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl]-allyl)-amide (407)**

![Chemical structure](image)

Zinc dust (1.0 g, 15 mmol) was suspended in water (6 mL), copper acetate monohydrate (122 mg, 0.6 mmol) added and the suspension stirred for 15 min at ambient
temperature. Silver nitrate (129 mg, 0.8 mmol) was then added and the suspension stirred for a further 15 min. The zinc couple was isolated by filtration, washed successively with 10 mL portions of H$_2$O, MeOH, acetone and Et$_2$O, and dried under suction. Alkyne 404 (101 mg, 0.22 mmol) was dissolved in MeOH (6 mL) and H$_2$O (1 mL), the zinc couple added and the suspension stirred at 50 °C for 17 h. After cooling, the mixture was filtered and concentrated in vacuo. Flash chromatography (EtOAc:hexane, 8:2) afforded alkene 407 (86 mg, 0.19 mmol, 85%) as a pale yellow solid, mp 67 °C. ν$_{\text{max}}$/cm$^{-1}$ (KBr disc) 3226 (NH stretch), 3003 (C=CH stretch), 1674 (C=O stretch), 1601 (overlapping C=O and C=C stretch), 741, 700; δ$_H$ (400 MHz, DMSO-d$_6$, 343K) 7.30-7.22 (5H, m, 5×aromatic CH), 7.13 (2H, d, J=8.6 Hz, 2×aromatic CH), 6.90-6.89 (1H, m, pyrrole C$^5$H), 6.83 (2H, d, J=8.6 Hz, 2×aromatic CH), 6.42 (1H, s, C=CH), 6.32-6.31 (1H, m, pyrrole C$^3$H), 6.19 (1H, d, J=11.7 Hz, CH$_2$CH=CH), 6.06-6.05 (1H, m, pyrrole C$^4$H), 5.67 (1H, dt, J=11.7, 5.9 Hz, CH$_2$CH=CH), 4.73 (2H, s, CH$_2$C$_6$H$_5$), 4.62 (2H, s, CH$_2$C$_6$H$_4$OCH$_3$), 4.25 (2H, dd, J=5.8, 1.7 Hz, CH$_2$CH=CH), 3.73 (3H, s, C$_6$H$_4$OCH$_3$), 3.10 (3H, s, NCH$_3$) ppm; δ$_C$ (100 MHz, DMSO-d$_6$, 343K) 161.9 (amide C=O), 158.3 (aromatic C), 151.9 (imidazolone C=O), 137.2 (aromatic C), 129.3 (aromatic C), 128.3 (aromatic CH), 128.0 (aromatic CH), 127.9 (2×aromatic CH), 127.0 (aromatic CH), 126.6 (aromatic CH), 123.9 (aromatic C), 121.0 (pyrrole C), 118.5 (C), 116.3 (CH), 113.6 (2×aromatic CH), 111.1 (pyrrole CH), 110.5 (C=CH), 108.2 (pyrrole CH), 54.7 (OCH$_3$), 49.9 (CH$_2$), 46.1 (CH$_2$CH=CH), 45.3 (CH$_2$), 26.7 (NCH$_3$) ppm; m/z (+ve CI-methane) 457 (MH$^+$, 7%), 259 (23), 201 (72), 121 (100), 91 (40), 68 (32); HRMS calcd. for C$_{27}$H$_{29}$N$_4$O$_3$ (MH$^+$) 457.2240, found 457.2249.
6-Benzyl-4-[1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-ylmethyl]-1,4,5,6-tetrahydropyrrolo[2,3-c]pyridin-7-one (408)

Alkene 407 (30.2 mg, 0.066 mmol) and trityl tetrafluoroborate (21.9 mg, 0.066 mmol) were dissolved in DCM (1 mL). The resulting solution was stirred at ambient temperature for 18 h and then concentrated in vacuo. Flash chromatography (gradient elution: DCM:MeOH:100:0, 100:2, 100:4, 100:8, 100:16) gave bicycle 408 (8.2 mg, 0.018 mmol, 27%) as a yellow oil. $v_{\text{max/cm}^{-1}}$ (CDCl$_3$ film) 3207 (NH stretch), 1674 (C=O stretch), 1634 (C=O stretch), 733 cm$^{-1}$; $\delta_H$ (400 MHz, CDCl$_3$) 9.83 (1H, broad s, NH), 7.24 (5H, m, 5×aromatic CH), 7.13 (2H, dd, $J=6.7$, 2.1 Hz, 2×aromatic CH), 6.87-6.86 (1H, m, pyrrole CH), 6.84 (2H, d, $J=6.7$ Hz, 2×aromatic CH), 5.94 (1H, t, $J=2.4$ Hz, pyrrole CH), 5.09 (1H, s, C=CH), 5.04 (1H, d, $J=14.6$ Hz, CH$_2$), 4.63 (1H, d, $J=14.9$ Hz, CH$_2$), 4.53 (1H, d, $J=14.9$ Hz, CH$_2$), 4.16 (1H, d, $J=14.6$ Hz, CH$_2$), 3.78 (3H, s, OCH$_3$), 3.54 (1H, dd, $J=12.6$, 5.2 Hz, CH$_2$), 3.18 (1H, dd, $J=12.6$, 4.0 Hz, CH$_2$), 3.09 (3H, s, NCH$_3$), 2.85 (1H, sex, $J=5.0$ Hz, CH$_2$CHCH$_2$), 2.42 (1H, dd, $J=15.4$, 4.3 Hz, CH$_2$), 2.26 (1H, dd, $J=15.5$, 9.6 Hz, CH$_2$); $\delta_C$ (125 MHz, CDCl$_3$) 160.2 (amide C=O), 159.2 (aromatic C), 153.5 (imidazolone C=O), 137.8 (aromatic C), 129.4 (aromatic C), 129.2 (2×aromatic CH), 128.9 (aromatic C), 128.6 (2×aromatic CH), 128.5 (2×aromatic CH), 127.6 (aromatic C), 122.9 (pyrrole C$^5$H), 121.8 (C), 120.2 (C), 114.1 (2×aromatic CH), 107.1 (C=CH), 106.4 (pyrrole C$^4$H), 55.3 (OCH$_3$), 50.4 (CH$_2$), 48.9 (CH$_2$), 46.3 (CH$_2$), 31.9 (CH$_2$CHCH$_2$), 28.7 (CH$_2$), 27.4 (NCH$_3$) ppm; $m/z$ (+ve Cl-methane) 457 (MH$^+$, 68%), 225 (49), 135 (62), 121 (100), 91 (33); HRMS calcd. for C$_{27}$H$_{32}$N$_4$O$_3$ (MH$^+$) 457.2240, found 457.2235.
4-(3-(tert-Butyldimethylsilyloxy)-prop-1-ynyl)-3-methyl-1-(2-nitrobenzyl)-1,3-dihydroimidazol-2-one (411)

Silyl ether 313 (1.00 g, 3.75 mmol) was dissolved in DMF (80 mL) and cooled to 0 °C. Potassium tert-butoxide (463 mg, 4.13 mmol) was added in and the solution stirred at ambient temperature for 30 min. 2-Nitrobenzylbromide (1.60 g, 7.41 mmol) was then added and the solution stirred for a further 16 h. The solution was poured into H₂O (100 mL), extracted with EtOAc (3×100 mL), dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (EtOAc: hexane, 3:7) afforded silyl ether 411 (1.23 g, 3.06 mmol, 82%) as pale yellow solid, mp 119 °C. v_max/cm⁻¹ (KBr disc) 2230 (C==C stretch), 1684 (C=O stretch), 1558 (NO₂ stretch); 1335 (NO₂ stretch); 1088; δ_H (300 MHz, CDCl₃) 8.07 (1H, dd, J=8.2, 1.3 Hz, aromatic CH), 7.58 (1H, td, J=7.5, 1.4 Hz, aromatic CH), 7.44 (1H, td, J=8.2, 1.5 Hz, aromatic CH), 7.32 (1H, dd, J=7.8, 1.1 Hz, aromatic CH), 6.56 (1H, s, C=CH), 5.17 (2H, s, CH₂C₆H₄NO₂), 4.50 (2H, s, CH₂OSi), 3.27 (3H, s, NCH₃), 0.90 (9H, s, SiC(CH₃)₃), 0.12 (6H, s, Si(CH₃)₂) ppm; δ_C (75 MHz, CDCl₃) 152.6 (C=O), 147.8 (aromatic CNO₂), 134.1 (aromatic CH), 132.3 (aromatic CCH₂N), 130.1 (aromatic CH), 128.8 (aromatic CH), 125.2 (aromatic CH), 116.0 (C=CH), 107.6 (C=CH), 94.2 (C=C), 72.8 (C=C), 52.1 (CH₂OSi), 44.6 (CH₂C₆H₄NO₂), 28.5 (NCH₃), 25.8 (SiC(CH₃)₃), 18.3 (SiC(CH₃)₃), -5.1 (Si(CH₃)₂) ppm; m/z (+ve CI-methane) 402 (MH⁺, 100%), 372 (74), 267 (8), 106 (13); HRMS calcd. for C₂₀H₂₇N₃O₄Si (MH⁺): 402.1849, found 402.1839; Analysis calcd. for C₂₀H₂₇N₃O₄Si: C, 59.8, H, 6.8, N, 10.5; found C, 59.8, H, 7.0, N, 10.4%.
4-(3-Hydroxyprop-1-ynyl)-3-methyl-1-(2-nitrobenzyl)-1,3-dihydroimidazol-2-one (412)

Silyl ether 411 (1.19 g, 2.96 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. TBAF (1M in THF, 3.3 mL, 3.3 mmol) was added dropwise and the solution stirred for 10 min. The solution was then poured into H2O (50 mL), extracted with EtOAc (3×50 mL), dried over Na2SO4 and concentrated in vacuo. Flash chromatography (100% EtOAc) afforded alcohol 411 (0.78 g, 2.71 mmol, 92%) as a pale yellow solid, mp 154 °C. νmax/cm⁻¹ (KBr disc) 3381 (OH stretch), 2218 (C=O stretch), 1663 (C=O stretch), 1529 (NO₂ stretch), 1335 (NO₂ stretch); δH (300 MHz, CDCl₃) 8.07 (1H, dd, J=8.2, 1.3 Hz, aromatic CH), 7.59 (1H, td, J=7.5, 1.4 Hz, aromatic CH), 7.48-7.42 (1H, m, aromatic CH), 7.35-7.32 (1H, m, aromatic CH), 6.59 (1H, s, C=CH), 5.18 (2H, s, CH₂Ar), 4.48 (2H, d, J=5.4 Hz, CH₂OH), 3.28 (3H, s, NCH₃), 1.76 (1H, broad t, J=6.3 Hz, CH₂OH) ppm; δC (75 MHz, CD₃OD) 153.9 (C=O), 149.4 (aromatic CNO₂), 135.1 (aromatic CH), 133.4 (aromatic CH₂N), 130.1 (aromatic CH), 130.0 (aromatic CH), 126.2 (aromatic CH), 117.8 (C=CH), 109.2 (C=CH), 95.9 (C=C), 73.0 (C=C), 51.1 (CH₂OH), 45.7 (CH₂C₆H₄NO₂), 28.8 (NCH₃) ppm; m/z (+ve CI-methane) 288 (MH⁺, 33%), 183 (16), 153 (29), 121 (100), 106 (22); HRMS calcd. for C₁₄H₁₄N₃O₄ (MH⁺): 288.0984, found 288.0989.
3-Methyl-1-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1H-imidazol-4-yl-propynal (413)

Alcohol 412 (650 mg, 2.26 mmol) was dissolved in DCM (250 mL) at ambient temperature and Dess-Martin Periodinane (1.16 g, 2.73 mmol) added. The solution was stirred for 3 h then sodium thiosulfate (20 g) in H₂O (60 mL) and saturated NaHCO₃ solution (60 mL) were added. The biphasic mixture was stirred vigorously for 3 h, and then the organic layer was separated. The aqueous layer was extracted with DCM (20 mL) and the combined organics dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography (Florisil®, EtOAc:hexane; 1:1) gave aldehyde 413 (559 mg, 1.96 mmol, 87%) as a pale orange solid, mp 145 °C. νmax/cm⁻¹ (KBr disc) 3076 (CH stretch), 2178 (C=C stretch), 1693 (C=O aldehyde stretch), 1647 (C=O urea stretch), 1533 (NO₂ stretch), 1335 (NO₂ stretch), 731; δH (300 MHz, CDCl₃) 9.34 (1H, s, CHO), 8.08 (1H, dd, J=8.1, 1.3 Hz, aromatic CH), 7.62 (1H, td, J=7.6, 1.4 Hz, aromatic CH), 7.52-7.42 (2H, m, 2×aromatic CH), 7.10 (1H, s, C=CH), 5.17 (2H, s, CH₂Ar), 3.32 (3H, s, NCH₃) ppm; δC (75 MHz, CDCl₃) 174.8 (CHO), 152.3 (C=O), 147.9 (aromatic CNO₂), 134.2 (aromatic C), 131.0 (aromatic C), 129.4 (aromatic C), 125.3 (aromatic C), 123.7 (aromatic C), 165.0 (C=CH), 96.9 (C=CH), 84.2 (C=O), 77.2 (C=O), 45.0 (CH₂C₆H₄NO₂), 28.7 (NCH₃) ppm; m/z (+ve CI-methane) 286 (MH⁺, 100%), 256 (30), 151 (67), 138 (33), 106 (18), 71 (18); HRMS calcd. for C₁₄H₁₂N₃O₄ (MH⁺): 286.0828, found 286.0822; Analysis calculated for C₁₄H₁₁N₃O₄: C, 59.0, H, 3.9, N, 14.7; found C, 58.6, H, 3.8, N, 14.5%.
Benzylid-(3-(3-methyl-1-(2-nitrobenzyl)-2-oxo-2,3-dihydroimidazol-4-yl)prop-2-ynyl)amide (414)

Aldehyde 413 (71 mg, 0.25 mmol) was dissolved in DCM (3 mL) with activated 4Å molecular sieves (180 mg). Benzylamine (28 μL, 0.26 mmol) was added and the reaction stirred at ambient temperature for 20 h. Sodium triacetoxycoborohydride (59 mg, 0.28 mmol) was then added and the reaction stirred for a further 3 h, filtered though Celite® and concentrated in vacuo. Flash chromatography (EtOAc:Et2N, 200:1) gave tertiary amine 414 (42 mg, 0.06 mmol, 52%) as a yellow oil. νmax/cm⁻¹ (CDCl₃ film) 2938 (CH stretch), 2235 (C≡C stretch), 1687 (C=O stretch), 1532 (NO₂ stretch), 1349 (NO₂ stretch), 1173, 730; δH (400 MHz, CDCl₃) 8.06 (2H, dd, J=8.2, 1.2 Hz, 2×aromatic CH), 7.59 (2H, td, J= 7.6, 1.3 Hz, 2×aromatic CH), 7.44 (2H, td, J=7.8, 1.4 Hz, 2×aromatic CH), 7.35 (2H, dd, J=7.8, 1.0 Hz, 2×aromatic CH), 7.33-7.24 (5H, m, 5×aromatic CH), 6.58 (2H, s, 2×C=CH), 5.16 (4H, s, 2×CH₂), 3.72 (2H, s, CH₂CH₃), 3.63 (4H, s, 2×CH₂), 3.28 (6H, s, 2×NCH₃) ppm; δC (100 MHz, CDCl₃) 152.4 (2×C=O), 147.8 (2×aromatic CNO₂), 137.3 (2×aromatic C(CH₂)₂N), 134.0 (2×aromatic CH), 132.1 (aromatic C), 130.3 (2×aromatic CH), 129.0 (2×aromatic CH), 128.9 (2×aromatic CH), 128.5 (2×aromatic CH), 127.7 (aromatic CH), 125.2 (2×aromatic CH), 115.8 (2×C=CH), 107.5 (2×C=CH), 90.8 (2×C=C), 73.4 (2×C=C), 57.5 (NCH₂CH₃), 44.5 and 43.0 (2×CH₂CH₃NO₂ and 2×CH₂N), 28.5 (2×NCH₃) ppm; m/z (⁺ve FAB) 646 (MH⁺, 9%), 340 (9), 270 (20), 177 (15), 154 (100); HRMS calcd. for C₃₅H₃₂N₇O₆ (MH⁺) 646.2414, found 646.2443.
4-(3-Benzylaminoprop-1-ynyl)-3-methyl-1-(2-nitrobenzyl)-1,3-dihydroimidazol-2-one (415)

Aldehyde 413 (455 mg, 1.60 mmol) was dissolved in DCM (30 mL) with activated 4Å molecular sieves (1.27 g). Benzylamine (0.90 mL, 8.24 mmol) was added and the solution stirred at ambient temperature for 17 h. A small sample was removed for 1H NMR to confirm complete imine formation and two imine isomers were observed in a 1:1 ratio. \( \delta_H (300 \text{ MHz, } \text{CDCl}_3) \) 8.11-8.09 (2H, m, 2×aromatic CH), 7.83 (1H, s, CH=N), 7.78 (1H, s, CH=N), 7.63-7.60 (2H, m, 2×aromatic CH), 7.45-7.37 (2H, m, 2×aromatic CH), 7.37-7.30 (10H, m, CH\(_2\)C\(_6\)H\(_5\)), 7.29-7.26 (2H, m, 2×aromatic CH), 6.88 (1H, s, CH= C), 6.80 (1H, s, CH= C), 5.23 (2H, s, CH\(_2\)C\(_6\)H\(_4\)NO\(_2\)), 5.22 (2H, s, CH\(_2\)C\(_6\)H\(_4\)NO\(_2\)), 4.86 (2H, s, CH\(_2\)C\(_6\)H\(_5\)), 4.77 (2H, s, CH\(_2\)C\(_6\)H\(_5\)), 3.33 (6H, s, NCH\(_3\)) ppm.

Sodium triacetoxyborohydride (1.35 g, 6.38 mmol) was added, the reaction stirred for a further 24 h, filtered through Celite\(^\circledast\) and concentrated in vacuo. Flash chromatography (EtOAc:Et\(_3\)N; 200:1) afforded amine 415 (518 mg, 1.38 mmol, 86%) as a yellow oil.

\( \nu_{\text{max}}/\text{cm}^{-1} \) (thin film) 3312 (NH stretch), 2226 (C=C stretch), 1684 (C=O stretch), 1526 (NO\(_2\) stretch), 1448, 1339 (NO\(_2\) stretch), 1175, 729; \( \delta_H (400 \text{ MHz, } \text{CDCl}_3) \) 7.97 (1H, d, J=8.1 Hz, aromatic CH), 7.50 (1H, t, J=7.6 Hz, aromatic CH), 7.35 (1H, t, J=7.4 Hz, aromatic CH), 7.23-7.21 (5H, m, CH\(_2\)C\(_6\)H\(_5\)) 7.09-7.08 (1H, m, aromatic CH), 6.46 (C=CH), 5.08 (2H, s, CH\(_2\)C\(_6\)H\(_4\)NO\(_2\)), 3.80 (NCH\(_2\)C\(_6\)H\(_5\)) 3.55 (NCH\(_2\)C= C), 3.20 (NCH\(_3\)) ppm; \( \delta_C (100 \text{ MHz, } \text{CDCl}_3) \) 152.3 (C=O), 147.7 (aromatic C), 139.1 (aromatic C), 133.9 (aromatic CH), 132.2 (aromatic C), 129.9 (aromatic CH), 128.7 (aromatic CH), 129.4 (2×aromatic CH), 128.2 (2×aromatic CH), 127.1 (aromatic CH), 125.1 (aromatic CH), 115.3 (C=CH), 107.7 (C=CH), 93.8 (C=C), 71.4 (C=C), 52.4 (NCH\(_2\)C\(_6\)H\(_5\)), 44.4 (NCH\(_2\)C\(_6\)H\(_4\)NO\(_2\)), 38.1.0 (NHCH\(_2\)C=C), 28.4 (NCH\(_3\)) ppm; \( \text{m/z (+ve Cl-methane)} \) 377
(MH⁺, 100%), 347 (27), 270 (49), 242 (30), 120 (21), 106 (51); HRMS calcd. for C_{21}H_{21}N_{4}O_{3} (MH⁺) 377.1614, found 377.1609

**1H-Pyrrole-2-carboxylic acid benzyl-(3-(3-methyl-1-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-prop-2-ynyl)-amide (416)**

![Chemical Structure](image)

Pyrrole-2-carboxylic acid 123 (22.9 mg, 0.21 mmol) and pyBOP (113 mg, 0.22 mmol) were suspended in DCM (1 mL) and DIEA (38 µL, 0.22 mmol) added. The suspension was stirred for 2 min until dissolution occurred and then a solution of amine 415 (67.4 mg, 0.18 mmol) in DCM (1 mL) was added via cannula, followed by DCM (0.5 mL) to wash flask and cannula. The resulting solution was stirred at ambient temperature for 30 h and then concentrated *in vacuo*. The crude oil was dissolved in EtOAc (10 mL) and washed with 3M HCl solution, (10 mL), sat. NaHCO₃ (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated *in vacuo*. Flash chromatography (gradient elution, DCM:MeOH, 100:0, 200:1, 100:1) gave amide 416 (73.3 mg, 0.16 mmol, 87%) as a yellow solid, mp 71 °C. ν_{max}/cm⁻¹ (KBr disc) 3420 (NH stretch), 2232 (C=O stretch), 1693 (C=O stretch), 1607 (C=O stretch), 1526 (NO₂ stretch), 1423, 1339 (NO₂ stretch), 739; δ_{H} (DMSO-d₆, 400 MHz, 343K) 11.34 (1H, broad s, NH), 8.06 (1H, dd, J=8.1, 1.2 Hz, aromatic CH), 7.71 (1H, t, J= 7.6, 1.3 Hz, aromatic CH), 7.57 (1H, t, J=8.1, 1.3 Hz, aromatic CH), 7.36-7.31 (4H, m, 4×aromatic CH), 7.28-7.23 (1H, m, aromatic CH), 7.19 (1H, d, J=7.8 Hz, aromatic CH), 6.94-6.92 (1H, m, pyrrole CH), 6.87 (1H, s, C=CH), 6.57 (1H, broad m, pyrrole CH), 6.13-6.11 (1H, m, pyrrole CH), 5.07 (2H, s, CH₂C₆H₄NO₂), 4.87 (2H, s, NCH₂C₆H₅), 4.57 (2H, s, NCH₂C≡C), 3.06 (3H, s, NCH₃) ppm; δ_{C} (DMSO-d₆, 100 MHz, 343K) 161.9 (C=O pyrrole amide), 151.5 (C=O imidazolone), 147.6 (aromatic C), 136.9 (aromatic C), 133.6 (aromatic CH), 131.6
(Z)-1H-Pyrrole-2-carboxylic acid benzyl-(3-3-methyl-1-(2-aminobenzyl)-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-allyl amide (417)

Zinc dust (500 mg, 7.64 mmol) was suspended in H$_2$O (3 mL), copper acetate monohydrate (66 mg, 0.33 mmol) added and the suspension stirred vigorously for 15 min. Then silver nitrate (65 mg, 0.38 mmol) was added and the suspension stirred for a further 15 min. The zinc couple was isolated by filtration, washed successively with 5 mL portions of H$_2$O, MeOH, acetone and Et$_2$O, and dried under suction. Alkene 416 (48.2 mg, 0.10 mmol) was dissolved in MeOH (3 mL) and H$_2$O (0.5 mL), the activated couple added and the suspension vigorously stirred at 50 °C for 17 h. After cooling, the mixture was filtered through Celite® and concentrated in vacuo. Flash chromatography (EtOAc:hexane, 8:2) gave alkene 417 (31.5 mg, 0.071 mmol, 69%) as a yellow oil. $\nu_{\text{max}}$/cm$^{-1}$ (CDCl$_3$ film) 3242 (NH stretch), 2928 (CH stretch), 1674 (broad, 2 overlapping C=O stretch), 739; $\delta_H$ (DMSO-d$_6$, 400 MHz, 343K) 11.22 (1H, broad s, NH), 7.30-7.23 (5H, m, 5×aromatic CH), 7.22 (2H, d, $J$=7.4 Hz, 2×aromatic CH), 9.65 (2H, d, $J$=7.4 Hz, 2×aromatic CH), 6.89-6.87 (1H, m, pyrrole CH), 6.63-6.61 (1H, m, aromatic CH), 6.48-6.46 (1H, m, aromatic CH), 6.45 (1H, s, C=CH), 6.33-6.31 (1H, m, pyrrole CH), 6.17 (1H, d, $J$=11.7 Hz, CH$_2$CH=CH), 6.06-6.04 (1H, m, pyrrole CH), 5.66 (1H, dt, $J$=11.7, 5.9 Hz, CH$_2$CH=CH), 5.09 (2H, broad s, NH$_2$), 4.72 (2H, s CH$_2$), 4.54 (2H, s CH$_2$), 4.24 (2H, dd, $J$=5.9, 1.9 Hz, CH$_3$CH=CH), 3.11 (3H, s, NCH$_3$) ppm;
$\delta_C$ (DMSO-$d_6$, 100 MHz, 343K) 158.3 (C=O), 148.5 (C=O), 142.3 (aromatic C), 133.6 (aromatic C), 125.5 (aromatic CH), 124.7 (aromatic CH), 124.5 (aromatic CH), 124.3 (2×aromatic CH), 123.4 (2×aromatic CH), 123.0 (aromatic CH), 120.3 (C=CH), 117.4 (aromatic CH or C=CH), 116.6 (C=CH or aromatic C), 115.1 (C=CH or aromatic C), 112.5 (aromatic CH or C=CH), 112.0 (aromatic CH or C=CH), 111.1 (aromatic CH or C=CH), 107.5 (aromatic CH), 107.0 (aromatic CH), 104.6 (aromatic CH or C=CH), 46.4 (CH$_2$C$_6$H$_5$), 42.6 (CH$_2$CH=CH), 39.3 (CH$_2$C$_6$H$_4$NH$_2$), 23.2 (NCH$_3$) ppm; $m/z$ (tVe EI) 442 (MH$^+$, 100%), 348 (28), 242 (54), 200 (19), 152 (41), 149 (22); HRMS calcd. for C$_{26}$H$_{28}$N$_2$O$_2$ (MH$^+$) 442.2238, found 442.2191.

**Dipotassium azodicarboxylate (421)$^{172}$**

Azodicarboxamide 420 (5.0 g, 43 mmol) was added in small portions with stirring to a 40% KOH solution (31 mL) at 8 °C over 2 h. After the addition, the suspension was stirred for a further 1 h with the temperature maintained at 5-10 °C. The yellow precipitate was isolated by filtration and washed with cold MeOH (20×20 mL) and dried in vacuo to give potassium azodicarboxylate 421 (6.6 g, 34 mmol, 79%) as a yellow solid.

**1H-Pyrrole-2-carboxylic acid (3-(1-(2-nitrobenzyl)-3-methyl-2-oxo-2,3-dihydro-1H-imidazol-4-yl)-allyl)benzylamide (424)**

![Chemical Structure](image)

To alkyne 416 (61.0 mg, 0.130 mmol) and dipotassium azodicarboxylate 421 (764 mg, 3.84 mmol) was added MeOH (3 mL). The suspension was stirred and acetic acid (0.22 mL, 3.84 mmol) was added. The reaction was heated to 50 °C for 18 h, cooled and solvent removed in vacuo. Flash chromatography (gradient elution, EtOAc:hexane, 7:3,
8.2, 10:0) afforded alkene 424 (16.3 mg, 0.035 mmol, 27%) as a yellow solid, mp 82 °C. v\textsubscript{max}/cm\(^{-1}\) (CDCl\(_3\) film) 3242 (NH stretch), 2928 (CH stretch), 1675 (C=O stretch), 1670 (C=O stretch), 1525 (NO\(_2\) stretch), 1330 (NO\(_2\) stretch); \(\delta\textsubscript{H} (\text{DMSO-d}_6, 500\text{ MHz, 343K})\) 11.26 (1H, broad s, NH), 8.03 (1H, dd, \(J=8.1, 1.2\text{ Hz, aromatic CH}\)), 7.61 (1H, td, \(J=7.6, 1.2\text{ Hz, aromatic CH}\)), 7.53 (1H, td, \(J=6.6, 1.2\text{ Hz, aromatic CH}\)), 7.30-7.22 (5H, m, 5×aromatic CH)), 7.05 (1H, broad d, \(J=7.3\text{ Hz, aromatic CH}\)), 6.89-6.88 (1H, m, pyrrole CH), 6.50 (1H, s, C=CH), 6.31-6.30 (1H, m, pyrrole CH), 6.25 (1H, s, \(J=11.4\text{ Hz, CH}_2\text{CH}CH\)), 6.06-6.04 (1H, s, pyrrole CH), 5.72 (1H, dt, \(J=11.7, 5.9\text{ Hz, CH}_2\text{CH}CH\)), 5.03 (2H, s, NCH\(_2\text{C}_6\text{H}_4\text{NO}_2\)), 4.73 (2H, s, NCH\(_2\text{C}_6\text{H}_5\)), 4.23 (2H, dd, \(J=6.0, 1.6\text{ Hz, CH}_2\text{CH}CH\)), 3.14 (1H, s, NCH\(_3\)); \(\delta\textsubscript{e} (\text{DMSO-d}_6, 125\text{ MHz, 343K})\) 162.0 (pyrrole amide C=O), 152.2 (imidazolone C=O), 147.5 (aromatic CNO\(_2\)), 137.2 (aromatic CH), 133.5 (aromatic CH), 132.2 (aromatic C), 128.8 (aromatic CH), 128.4 (aromatic C), 128.3 (aromatic CH), 128.1 (2×aromatic CH), 127.1 (2×aromatic CH), 126.7 (aromatic CH), 124.3 (C=CH or CH=CH) 123.9 (aromatic C), 121.2 (aromatic CH), 119.2 (C=CH), 116.2 (C=CH or CH=CH), 111.2 (aromatic CH), 111.0 (C=CH or CH=CH), 108.3 (pyrrole CH), 50.0 (CH\(_2\text{C}_6\text{H}_3\)), 46.2 (CH\(_2\text{C}_6\text{H}_4\text{NO}_2\)), 43.1 (CH\(_2\text{CH}CH\)), 27.0 (NCH\(_3\)) ppm; \(m/z (+ve \text{ FAB})\) 427 (MH\(^+\), 8%), 307 (27), 155 (29), 154 (100), 127 (61); HRMS calcd. for C\(_{26}\)H\(_{26}\)N\(_5\)O\(_4\)(MH\(^+\)) 472.1985, found 472.2010.
CHAPTER IV

BIBLIOGRAPHY

Reference List


