Studies Towards a Biomimetic Synthesis of Agelastatin A

By

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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

Ac	acetyl
Acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
ATP	adenosine triphosphate
BMEA	bis-2-methoxyethylamine
Boc	*t*-butoxycarbonyl
Bn	benzyl
Bu	butyl
^{t}Bu	*tert*-butyl
CDK	cyclin dependent kinase
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	dicyclohexylcarbodiimide
DCM	dichloromethane
DBMP	2,6-di-*tert*-butyl-4-methylpyridine
DDQ	dichlorodicyanoquinone
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMP	Dess Martin periodinane
DME	1,2-dimethoxyethane
DMSO	dimethylsulfoxide
DMF	dimethylformamide
d.r.	diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
GSK	glycogen synthase kinase
HBTU	*O*-benzotriazole-*N*,*N*,*N*,*N*'-tetramethyl-uronium-hexafluoro-phosphate
HMPT	hexamethylphosphorous triamide
hν	ultra violet light
IBX	1-hydroxy-1,2-benziodoxolin-3(1*H*)-one

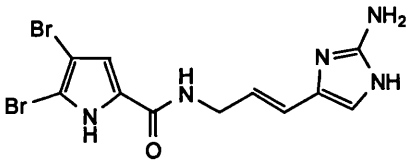
LDA	lithium diisopropylamide
mCPBA	*meta*-chloroperbenzoic acid
MSA	methane sulfonic acid
Me	methyl
Mes	mesyl
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nuc	nucleophile
*o*NB	*ortho*-nitrobenzyl
PDC	pyridinium dichromate
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
Pr	propyl
py	pyridine
pyBOP	benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
SES	2-[(trimethylsilyl)ethyl]sulfonyl
TBAF	tetrabutyl ammonium fluoride
TBHP	*tert*-butylhydroperoxide
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
Tf	triflate
TFA	trifluoroacetic acid
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	tosyl

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 Naples[3], and more recently from other sponges.[4-8]



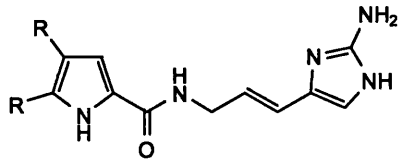
1 Oroidin

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,[10] viruses,[11] and inhibition of barnacle larvae metamorphosis.[8]

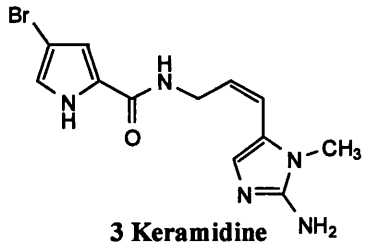
1.2 Structural Variations

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.[12] 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.

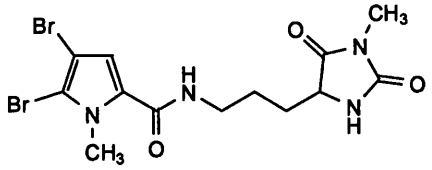
1.2.1 Non Cyclised Structures



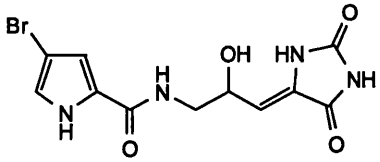
1 Oroidin R=Br
2 Clathrodin R=H



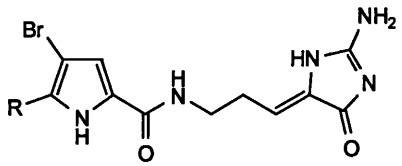
3 Keramidine



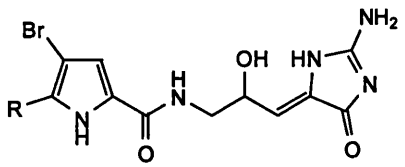
4 Midpacamide



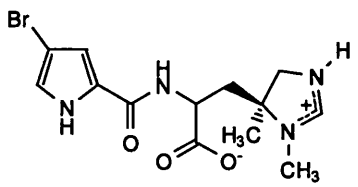
5 Mukanadin A



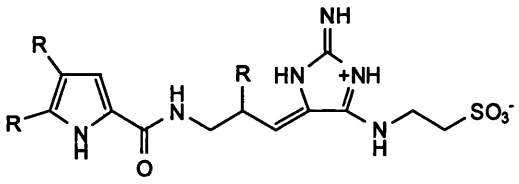
6 Dispacamide A: R=Br
7 Dispacamide B: R=H



8 Dispacamide C: R=Br
9 Dispacamide D: R=H



10 Clathramide A



11 Tauroacidin A: R=OH
12 Taurodispacamide: R=H

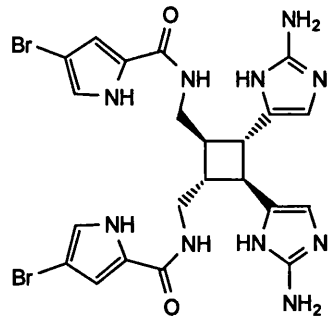
There are many examples of pyrrole-imidazole alkaloids with structures linearly related to oroidin, but with no further cyclisations. These include clathrodin[13] **2**, which is simply the debrominated analogue of oroidin. Other variations on the oroidin structure include keramidine[14] **3**, which contains a (*Z*)-olefin, and midpacamide[15] **4** where pyrrole nitrogen methylation is observed along with oxidation of the imidazole ring. Mukanadin A[16] **5** and the dispacamides[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 dispacamides C **8** and D **9**[4] and clathramide A[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[19] **11** and taurodispacamide[20, 21] **12** have a taurine residue attached to the imidazole ring.

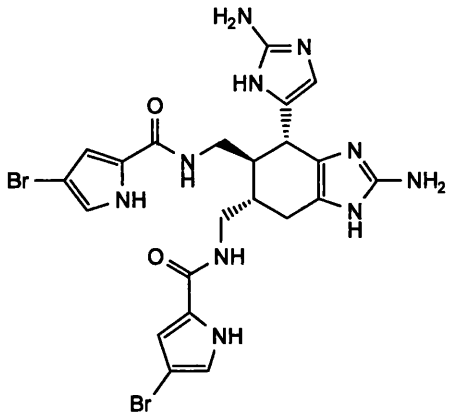
"Linear" oroidin derivatives are often isolated in high amounts from marine sponges, for example dispacamides A **6** and B **7** were found in 1-5% of the butanolic extracts from four Caribbean *Agelas* species: *A. dispar*, *A. clathrodes*, *A. longissima*, and *A. conifera*.[17] This suggests a pivotal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

1.2.2 Dimerised Structures

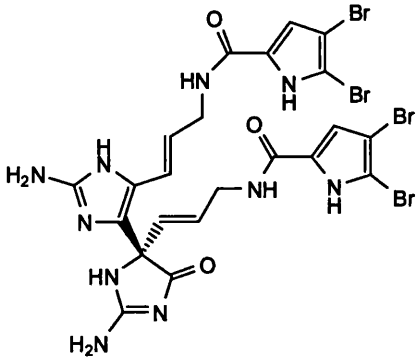
Six different modes of dimerisation of the uncyclised oroidin skeleton have been observed. The natural products sceptrin[22] **13** and ageliferin[23] **14** exhibit dimerisation through bond formation between of the carbon chains linking the pyrrole and imidazole moieties, formally the products of [2π+2π] and [4π+2π] cycloadditions respectively. The structure of mauritiamine[8] **15** dimerises through a link between the imidazole moieties of two oroidin-like fragments. The axinellamine[24] **16** structure exhibits three separate links between the two subunits forming a highly functionalised tetracyclic core. Massadine[25] **17** also exhibits three links between the two subunits, but an oxidation has occurred to introduce a tetrahydropyran ring in the tetracyclic core.



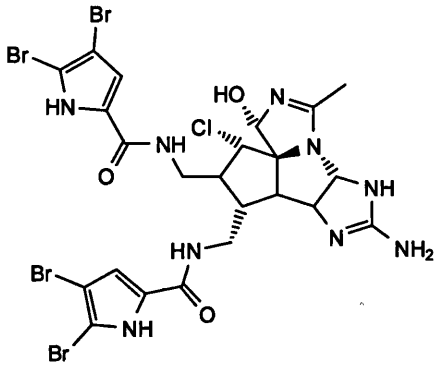
13 Sceptrin



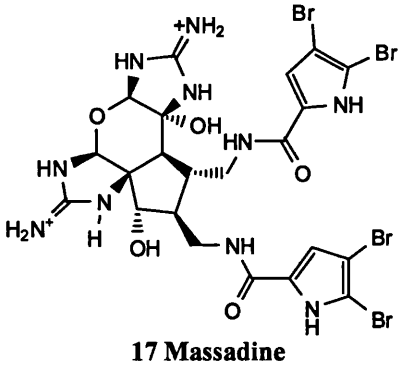
14 Ageliferin



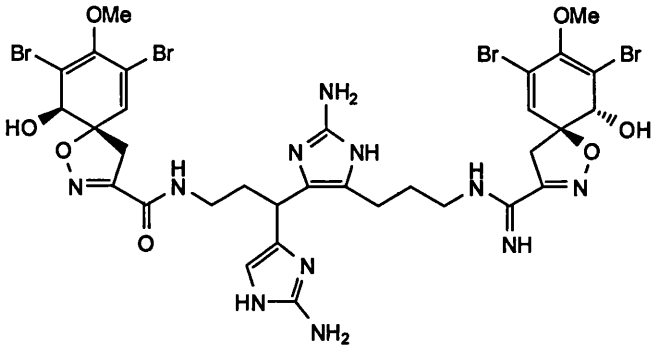
15 Mauritiamine



16 Axinellamine A



17 Massadine



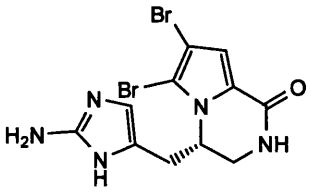
18 Archerine

The alkaloid archerine[26] **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,[8] blocking of α-adrenoceptors,[27] activation of ATPase[23] and antihistamic activity.[26] No pyrrole-imidazole alkaloids assembled from three or more subunits have yet been discovered.

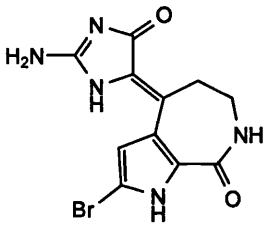
1.2.3 Cyclised Structures

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[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.

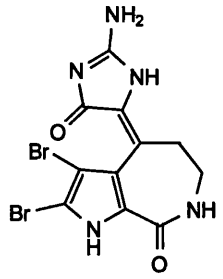
1.2.3.1 Tricyclic Structures



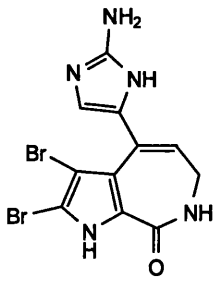
19 Cyclooroidin



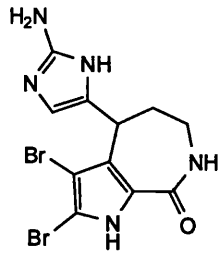
20 Hymenialdisine



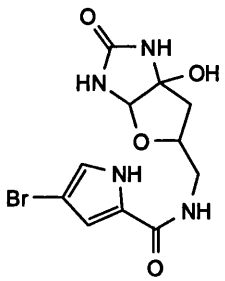
21 (*E*)-3-bromohymenialdisine



22 Stevensine



23 Hymenin



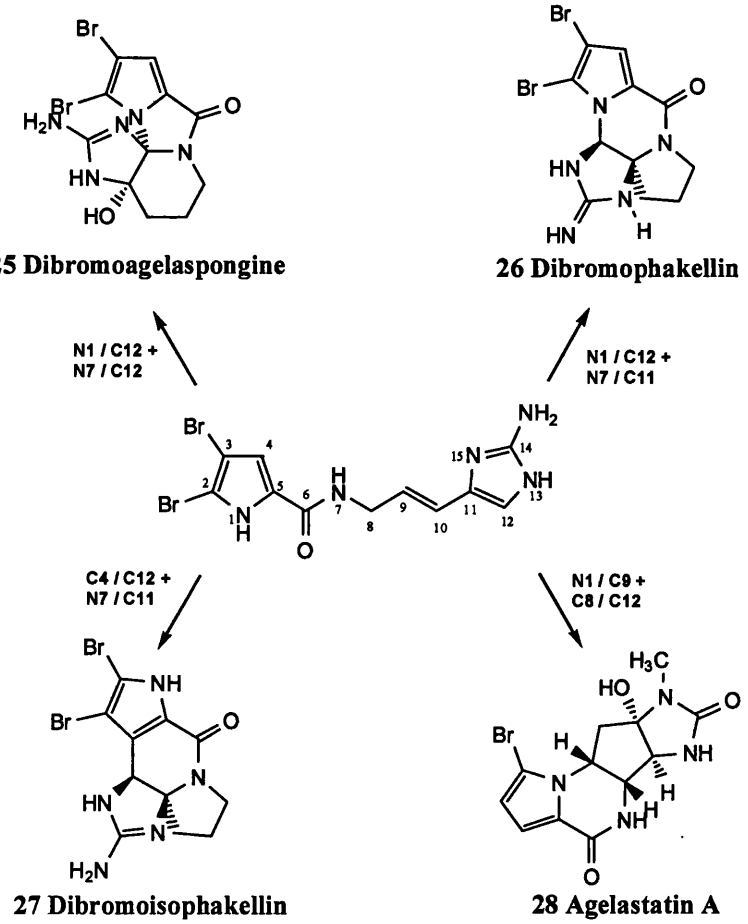
24 Slagenin A

Three cyclisation modes of the oroidin skeleton result in tricyclic pyrrole-imidazole alkaloid structures. Cyclooroidin[20] **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[28] and hanishin[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[29] **22**, or in the carbon-carbon bridge between this ring and the imidazole moiety, exhibited in the structure of hymenialdisine[5] **20**. The pyrrole ring can be either mono- or di brominated.

The tricyclic structure of slagenin A[30] **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[31] **5**.

1.2.3.2 Tetracyclic Structures

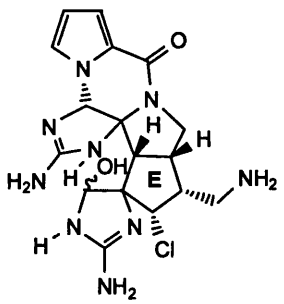


The oroidin skeleton can also undergo two cyclisations to form tetracyclic pyrrole-imidazole alkaloids. Four different tetracyclic structures are known, again classified by the linkages formed between the oroidin atoms. The pyrrole nitrogen can be linked either through nitrogen, as seen in dibromoagelaspongine **25**, or through the C3 carbon atom, as in the structure of dibromisophakellin **27**.[21] Both mono-and dibromination of the pyrrole ring have been observed.

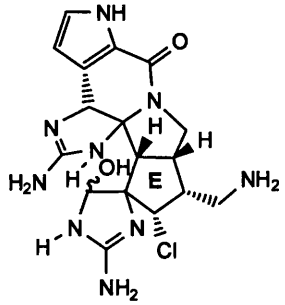
The N1/C9 and C8/C12 cyclisation mode is of particular interest as this forms the tetracyclic structure of the agelastatins.

1.2.3.3 Hexacyclic Structures

The most complex pyrrole-imidazole alkaloids isolated are represented by the hexacyclic palau'amine[32] **29** and styloguanidine[33] **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.



29 Palau'amine



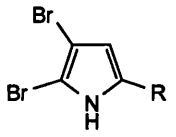
30 Styloguanidine

Palau'amine and styloguanidine are current targets for total synthesis owing to their unprecedented hexacyclic bisguanidine structure,[34, 35] and although the core structure has been prepared, a total synthesis of either of these structures has yet to be published.

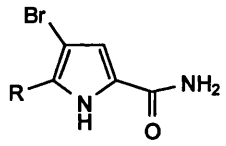
The cyclised pyrrole-imidazole alkaloids also have a broad range of biological activities, including inhibition of nuclear transcription factors,[36, 37] inhibition of cyclin-dependent kinases,[38] and immunomodulatory activity.[32]

1.2.4 Oroidin Fragments

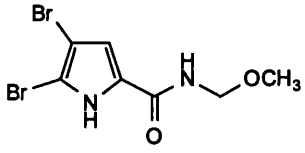
In addition to alkaloids containing the complete building block of oroidin, several metabolites that are possible fragments of the oroidin structure have been isolated. These include brominated pyrrole ring fragments **31-36**,[3, 7, 39-41] the brominated maleimides **37** and **38**,[21] imidazole derived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



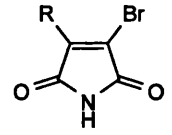
31: R=CO_2H, 32: R=CO_2CH_3, 33 :R=CN



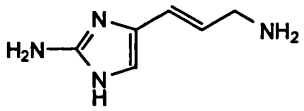
34: R=Br, 35: R=H



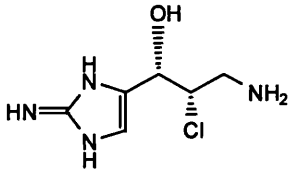
36



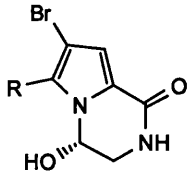
37: R=Br, 38: R=H



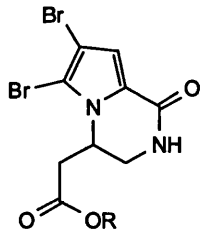
39



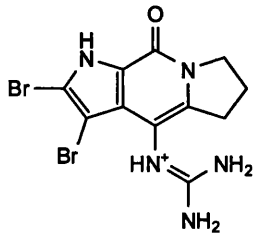
40 Girolline



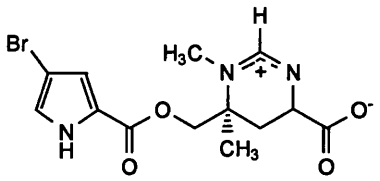
41: Longamide R=Br
42: Mukanadin C R=H



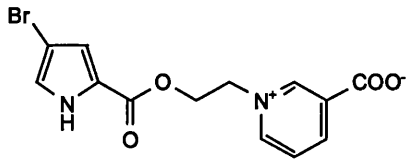
43: Hanishin R=Et
44: R=Me
45: Longamide B R=OH



46: Ugibohlin



47: *N*-methylmazacidin C

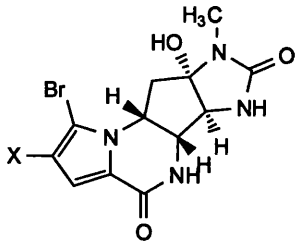


48: Agelongine

Ugibohlin **46** was isolated from the marine sponge *Axinella carteri* along with dibromoisophakellin **27**.[43] Elimination of dibromoisophakellin could potentially be affected by treatment with acid, and as trifluroacetic acid was utilised in the extraction,

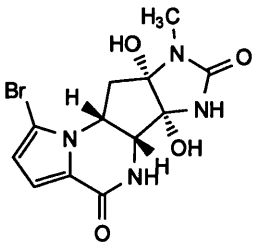
ugibohlin **46** could be an artefact of the extraction process rather than a true natural product. However it could potentially be a biosynthetic precursor of dibromoisophakellin. Other fragments that could also be artefacts of the extraction process rather than true natural products include the hanishin esters **43** and **44**, especially as alcoholic solvents were utilised in the extraction process.

1.3 The Agelastatins

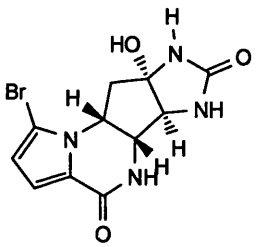


28 Agelastatin A, X=H

49 Agelastatin B, X=Br



50 Agelastatin C



51 Agelastatin D

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} = 0.5μg mL^{-1}) and L1210 cells (IC_{50} 33 $ngmL^{-1}$). 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 μgmL^{-1} after 4 days) and the corn root worm *Diabrotica undecimpunctata* (IC_{50} = 37 μgmL^{-1} after 4 days).

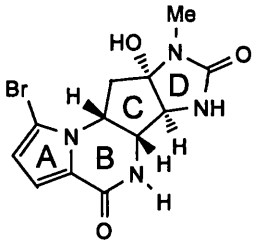
Agelastatin A selectively inhibits the glycogen synthase kinase-3β (GSK-3β)[38], an enzyme identified as having a role in the development of Alzheimer's disease, with IC_{50} = 12 μM. The dementia characteristic of Alzheimer's disease results from the death of neurons in the brain associated with several 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 (Dvl), 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]

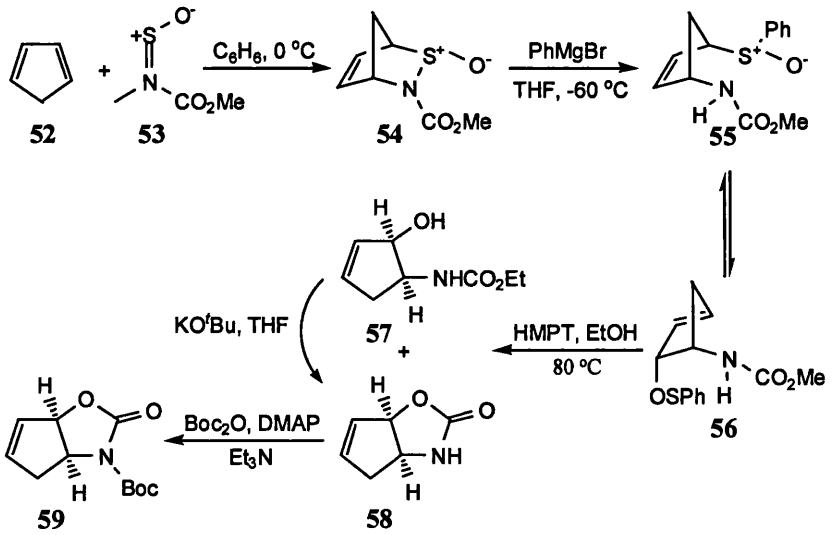
1.4 Previous Work on the Synthesis of Agelastatin A

Weinreb and co-workers completed the first total synthesis of racemic Agelastatin A in 1999.[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 *N*-sulfinyl dienophile Diels-Alder methodology previously described by the Weinreb group.



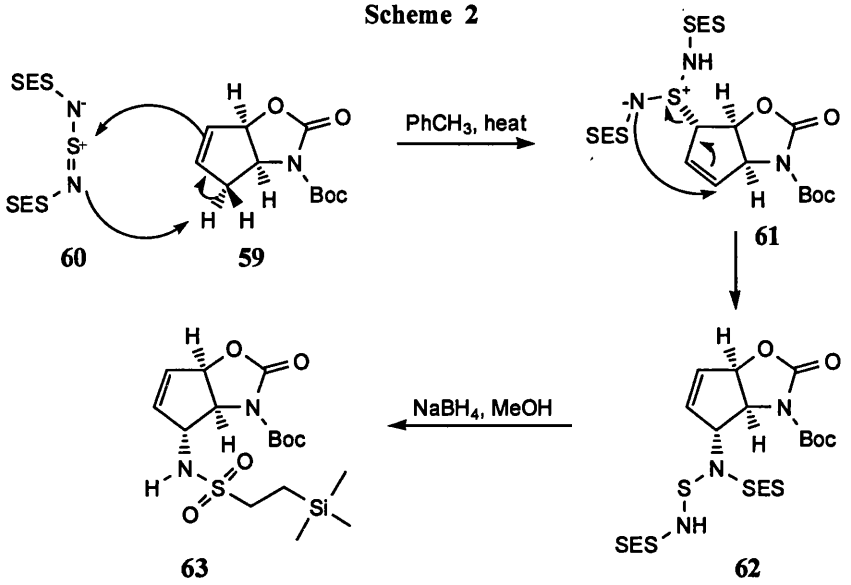
28 Agelastatin A

Scheme 1



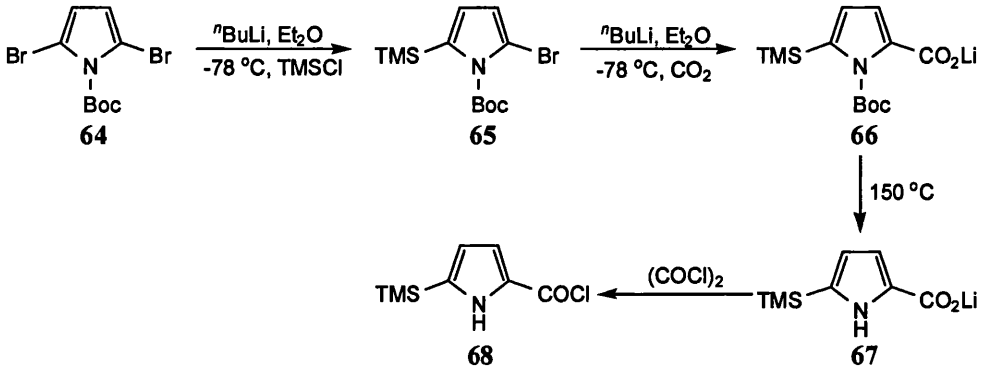
Cycloaddition of cyclopentadiene **52** and *N*-sulfinyl methyl carbamate **53** in benzene at 0 °C gave the cycloadduct **54**. Treatment with phenylmagnesium bromide gave the allylic sulfoxide **55** which, upon heating with HMPT in ethanol, underwent a [2,3] sigmatropic rearrangement via the sulfenate 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 *t*-butoxide in THF. The oxazolidinone was converted to the *N*-Boc derivative **59** in order to give more reproducible results in the subsequent steps of the synthesis.

Scheme 2



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-trimethylsilylethanesulfonamide (SES-NH_2) 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**.

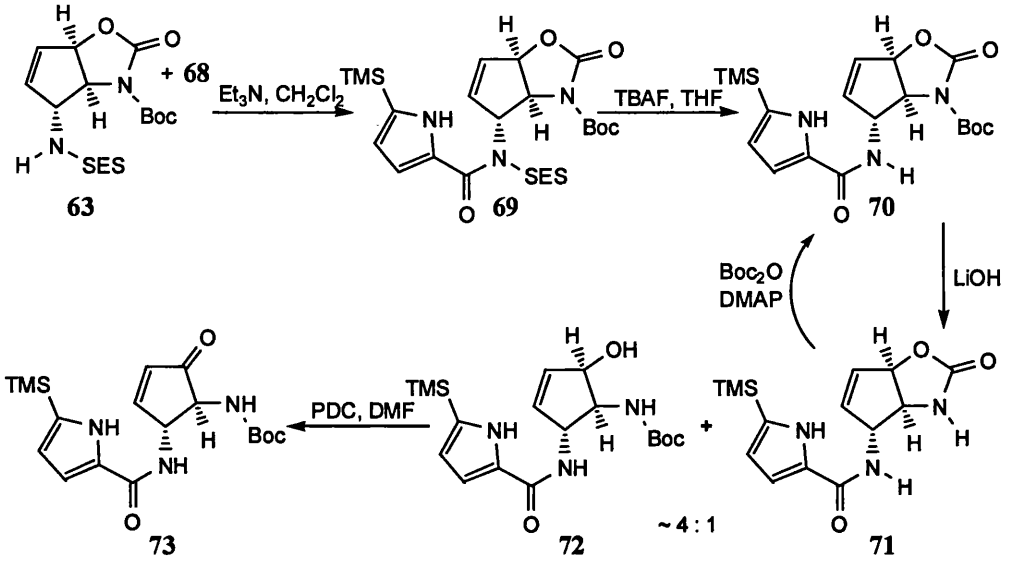
Scheme 3



The A-ring was prepared from *N*-Boc-2,5-dibromopyrrole **64** (**scheme 3**), which was treated with ^{n}BuLi and TMSCl to give the TMS bromopyrrole **65**. Further treatment with ^{n}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.

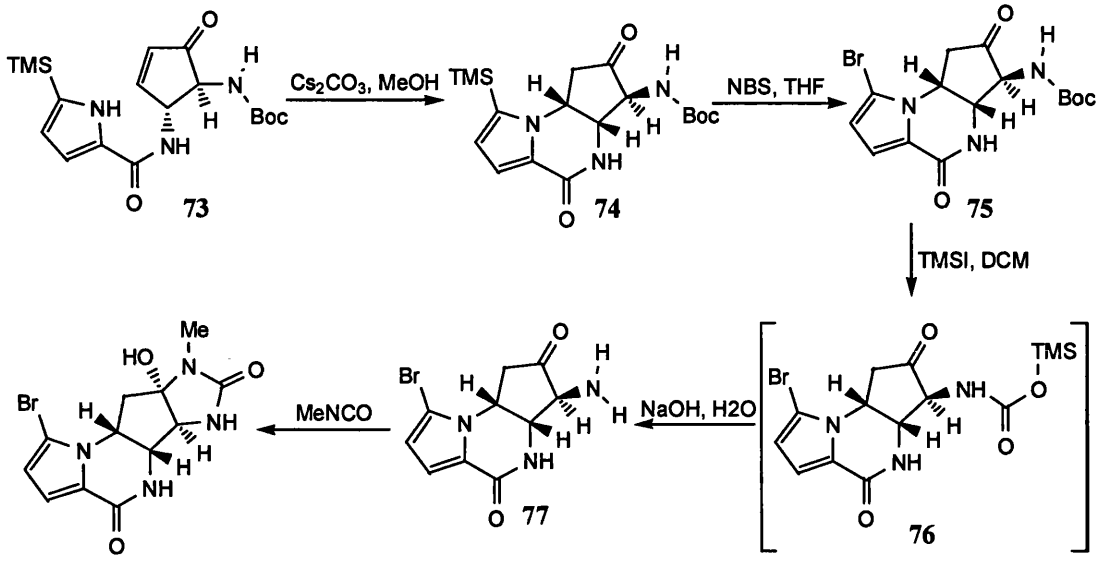
Scheme 4



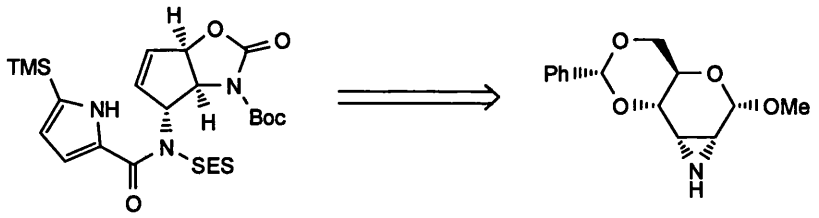
Acylation of the cyclic carbamate **63** with silyl pyrrole **68** gave the *N*-acyl sulfonamide **69** (**scheme 4**). Treatment with TBAF removed the SES group to afford **70** and lithium hydroxide hydrolysis gave a 1:4 inseparable mixture of the *N*-deprotected oxazolidinone **71** and the alcohol **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.

Scheme 5



In 2002, Hale and co-workers published a formal enantiospecific total synthesis of agelastatin A.[49] 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**.

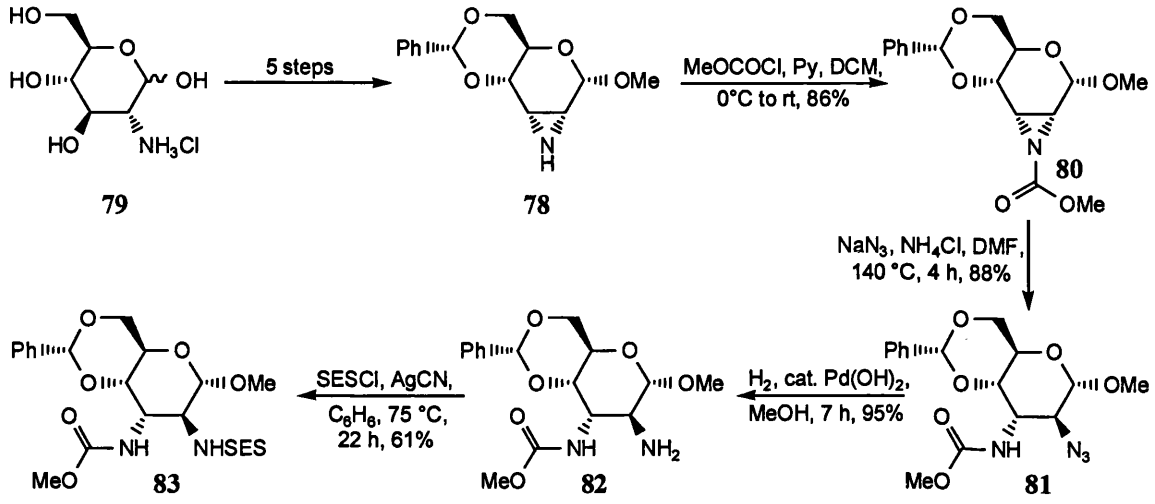


69 Optically pure Weinrebs Intermediate

78 Hough-Richardson Aziridine

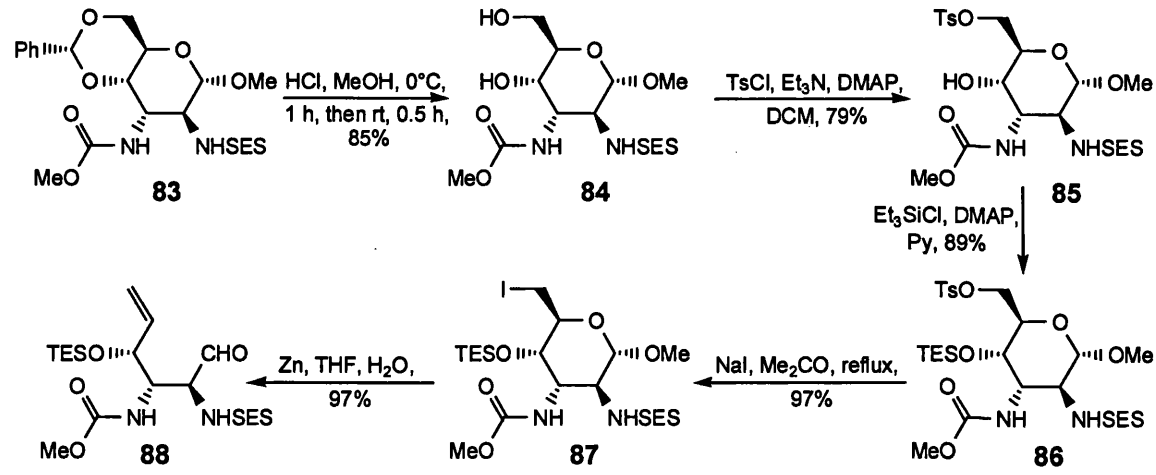
The aziridine precursor **78** was prepared in 5 steps from D-glucosamine hydrochloride **79** using the method published by Hough and Richardson.[50] The aziridine was converted to the *N*-methylcarbamate **80** and subsequent reaction with sodium azide in hot DMF gave trans-diaxial ring opening to give solely azide **81** in 88% yield. Hydrogenolysis of the azide afforded **82** and subsequent amine protection with trimethylsilylethanesulfonyl chloride (SESCl) gave **83**.

Scheme 6



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/H_2O was utilised to introduce the alkene and aldehyde functionalities of **88**.

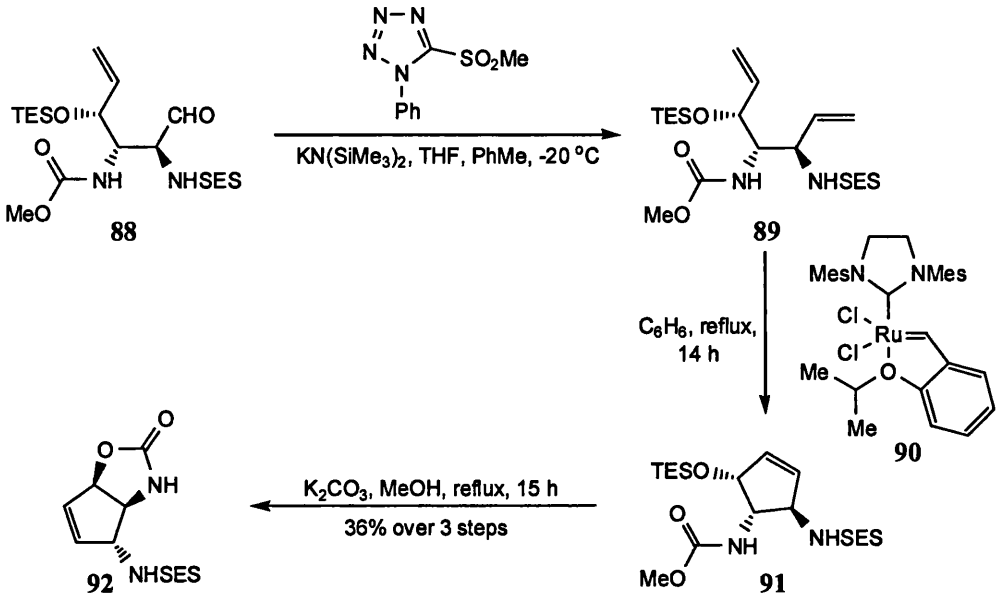
Scheme 7



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

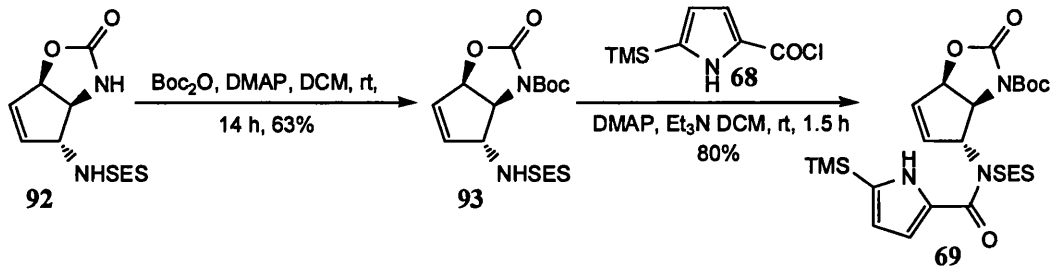
cyclic alkene **91** with potassium carbonate in MeOH gave the desired oxazolidinone **92** in 36% over three steps (**scheme 8**).

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**).

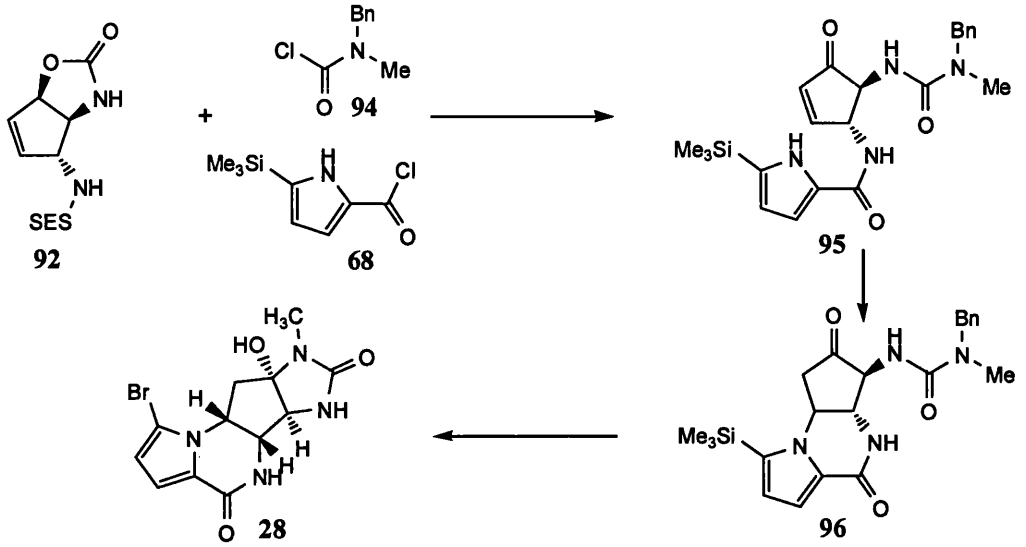
Scheme 9



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.

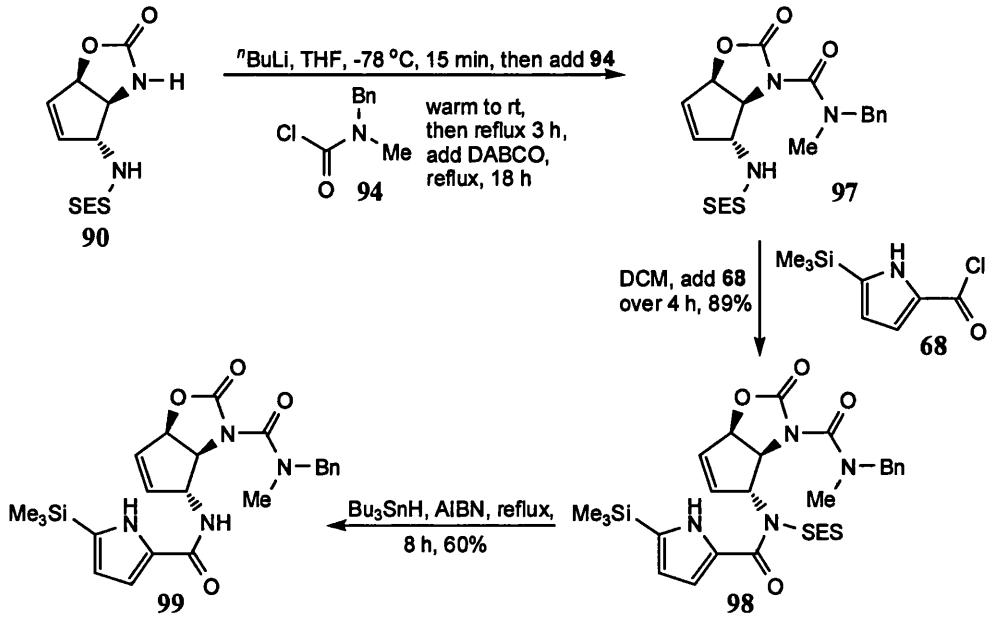
In a subsequent publication in 2004, Hale and co-workers reported an alternative endgame to the Weinreb route.[51]

Scheme 10



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**.

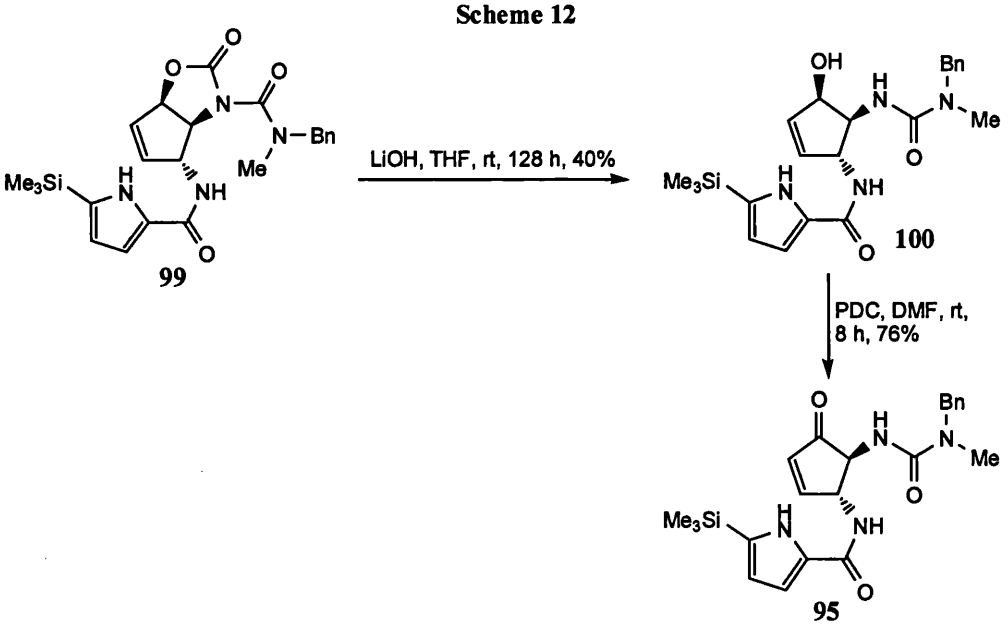
Scheme 11



The new route was commenced from chiral oxazolidinone **90** with selective carbamoylation with acid chloride **94**, ^{n}BuLi 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**.

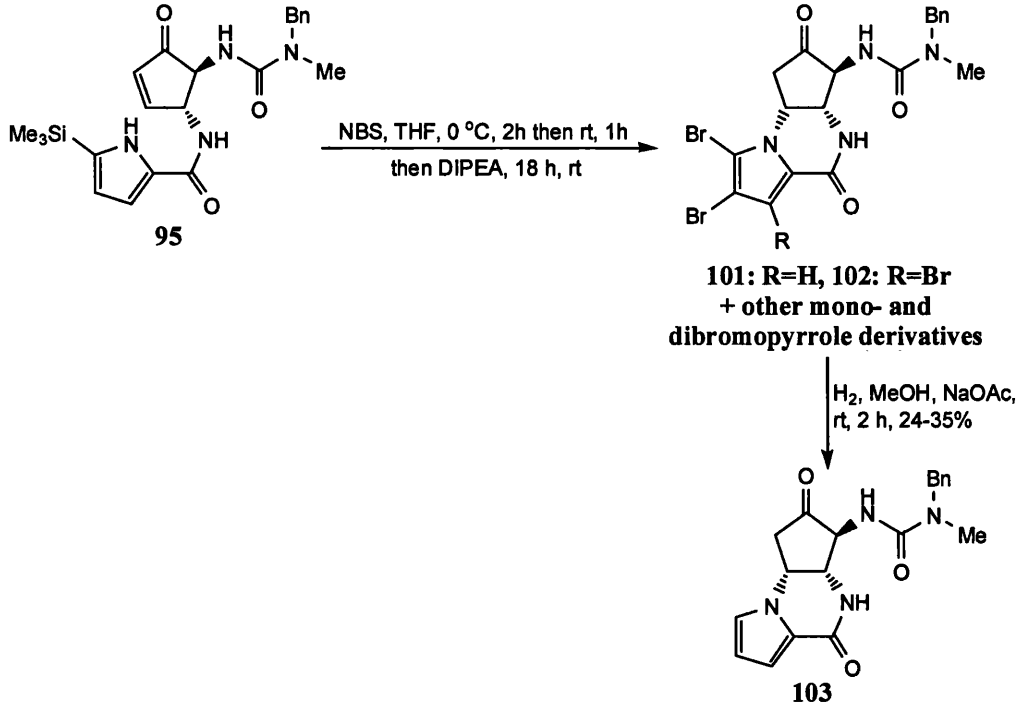
The hydrolysis of oxazolidinone **99** to allylic alcohol **100** was carried out with LiOH in THF at ambient temperature without hydrolysis of the urea unit, but a long reaction time (128 h) was required to obtain a 40% yield of the alcohol. However, the unreacted oxazolidinone could be recycled back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

Scheme 12



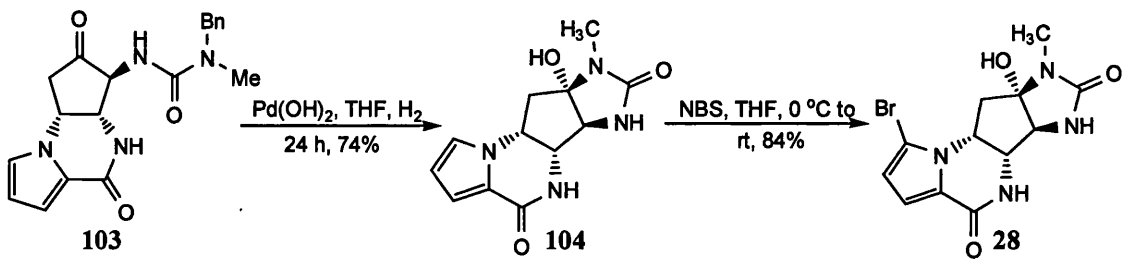
Unfortunately, all efforts to effect the ring closing Michael addition of **95** under various basic conditions failed. Hale rationalised this lack of reactivity was as a consequence of the high pKa of the pyrrole nitrogen. It was therefore planned to react **94** with *N*-bromosuccinamide, expecting 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.

Scheme 13



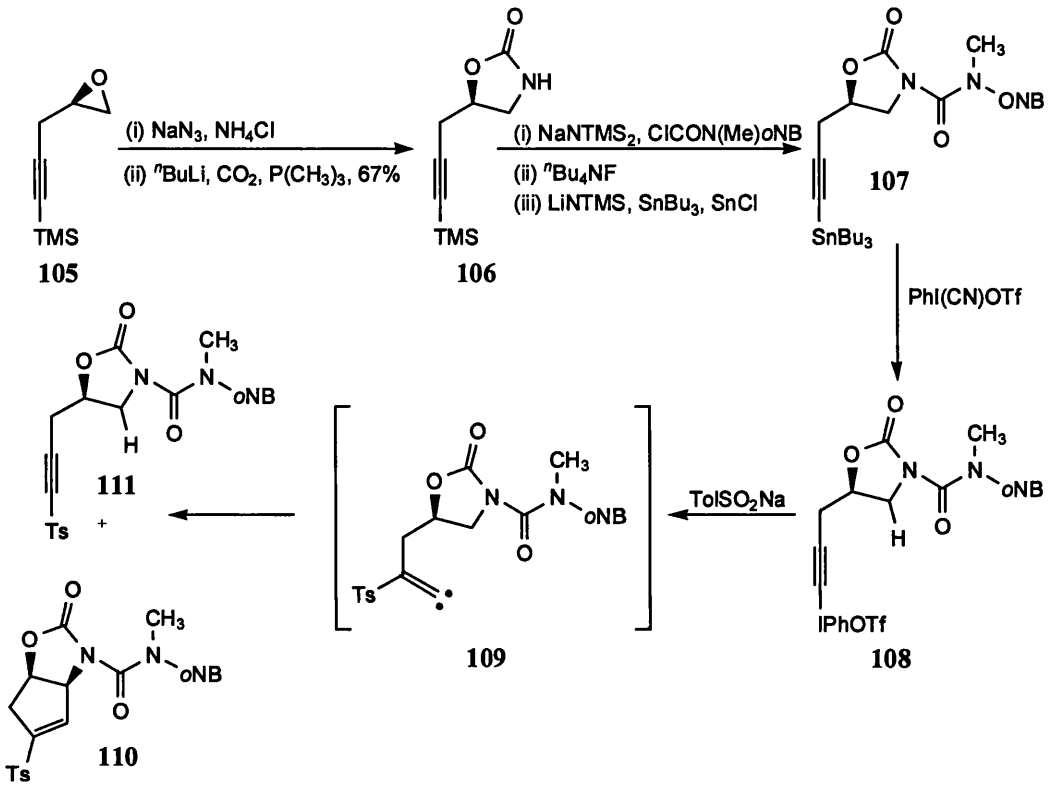
Bromination of **95** did not afford a single product, however, instead a complex mixture containing di- and tribrominated products **101** and **102** and other mono- and dibrominated products was obtained. So instead of attempting to purify the individual products, the mixture was treated with Hünigs base to affect the Michael addition. The crude mixture of products was then treated with H_2 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 H_2 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**.

Scheme 14



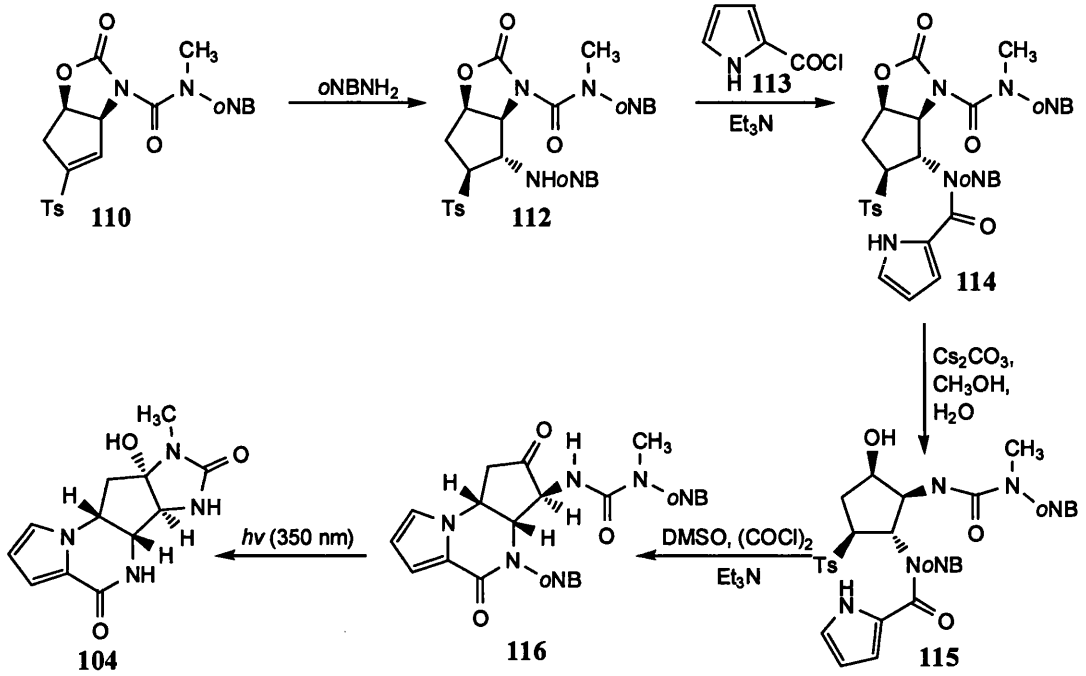
In 2002, Feldman and Saunders published an enantiospecific total synthesis of Agelastatin A.[52] The key step in their method utilised an alkynyliodonium salt **108** as a precursor to an alkylidenecarbene **109** that then underwent a 1,5 CH insertion into the otherwise unreactive secondary CH of the oxazolidinone ring.

Scheme 15



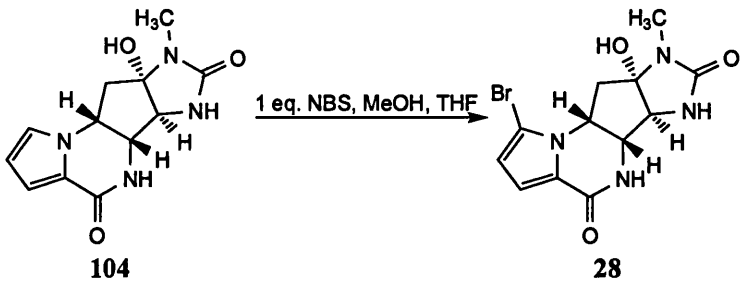
Their synthesis commenced with the chiral epoxyalkyne **105** (**scheme 15**), which was prepared readily from BH_3.THF-mediated addition of LiC≡CTMS to chiral epichlorohydrin. The epoxide was opened with azide at the less hindered carbon and then Vilarrasa's oxazolidinone synthesis[52] gave **106** in 67% yield. Conversion to stannane **107** gave the precursor for the alkynyliodonium salt preparation. **107** was treated with Stang's reagent (PhI(CN)OTf) at –42 °C and addition of the crude alkynyliodonium salt **108** into a refluxing suspension of $TolSO_2Na$ 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.

Scheme 16



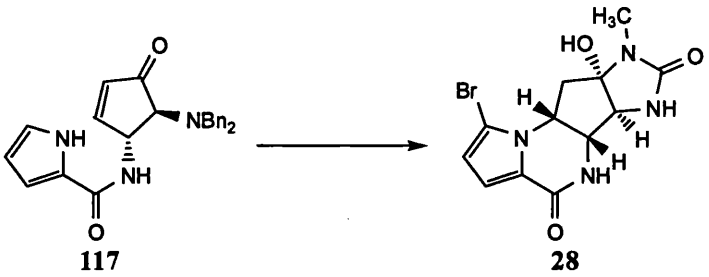
Conjugate addition of *o*-nitrobenzylamine to the unsaturated sulfone moiety in **110** gave the secondary amine **112** in the desired stereochemistry as a single isomer, and consequently all 4 of the required chiral centres around the C ring were introduced. The amine was acylated with pyrrole-2-carbonyl 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%.

Scheme 17



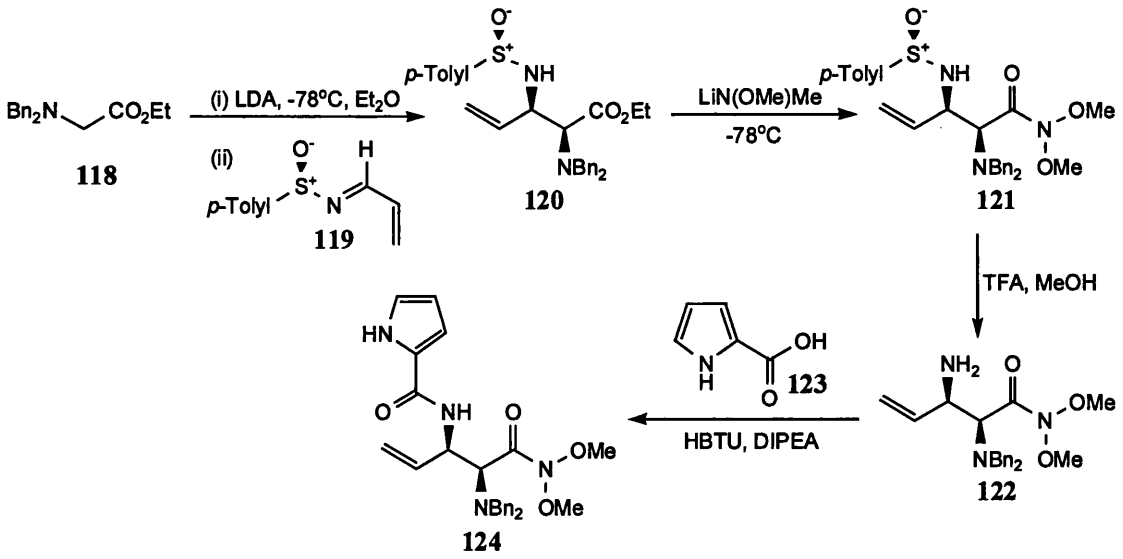
In 2004 Davis and co-workers published an enantiospecific total synthesis of agelastatin A[53] utilising a combination of two methodologies developed by their group: the synthesis of asymmetric α,β-diamino acids via the addition of glycine enolates to enantiopure sulfinimines[54] and the synthesis of (+)-4-aminocyclopentenone via ring closing metathesis of a sulfinimine derived *N*-sulfinyl amino β-ketodiene.[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(dibenzylamimo)acetate **118** (**scheme 18**). Three of the four possible diastereoisomers were detected in an 18:1:5 ratio, with the major *syn* diastereoisomer **120** isolated in 73% yield.

Scheme 18

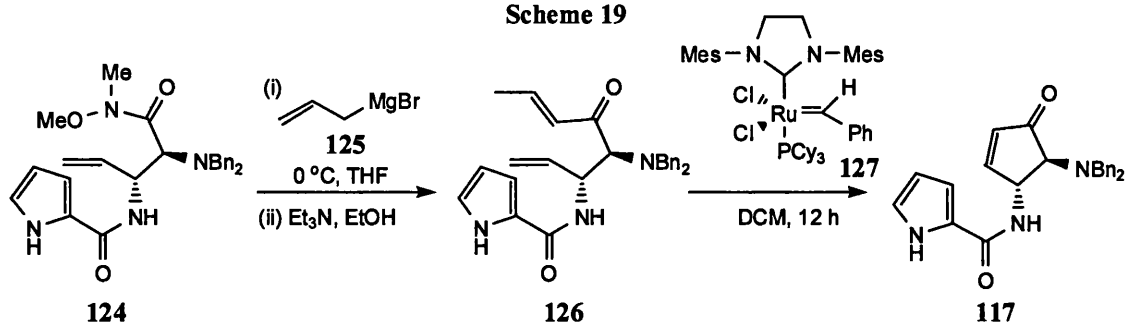


120 Was then treated with lithium *N,O*-dimethylhydroxylamine to afford the corresponding Weinreb amide **121** in 89% yield. Deprotection of the *N*-sulfinylamino

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_3N 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.

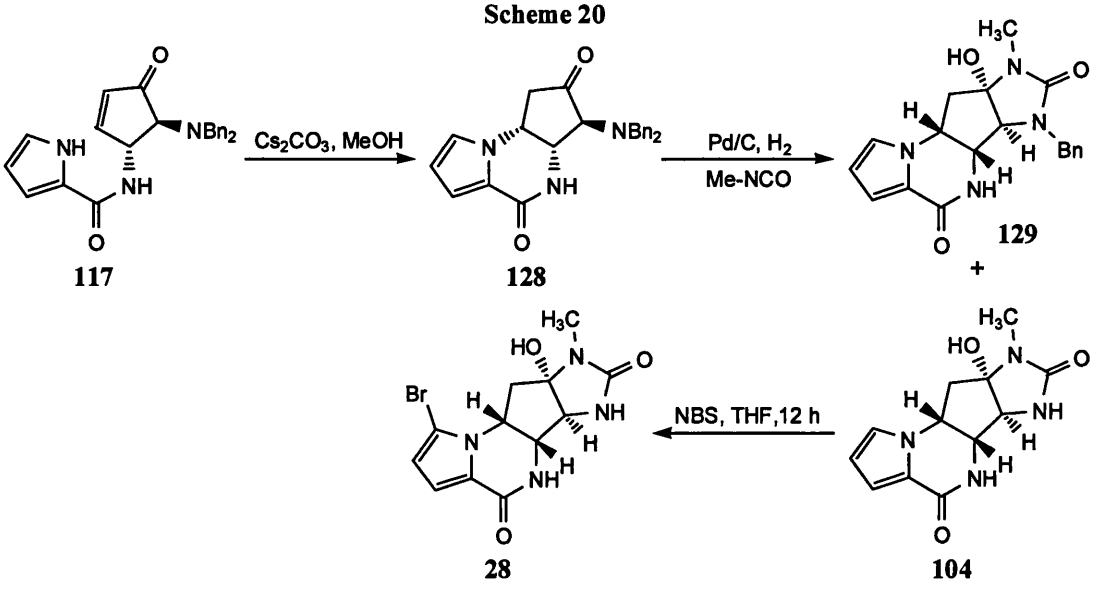
Scheme 19



124 **126** **117**

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**.

Scheme 20

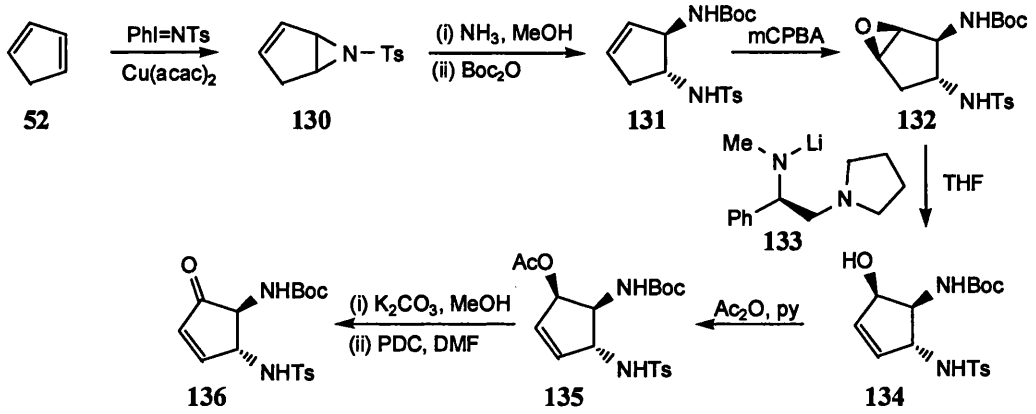


117 **128**

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[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.[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[57] using [*N*-(p-toluenesulfonyl) imino]iodinane (PhI=NTs) and $Cu(acac)_2$. Ring opening with ammonia followed by Boc protection gave diamino cyclopentene **131**.

Scheme 21



52 130 131 132 133 134 135 136

The cyclopentene was epoxidised *cis* to the NHBoc group with *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.

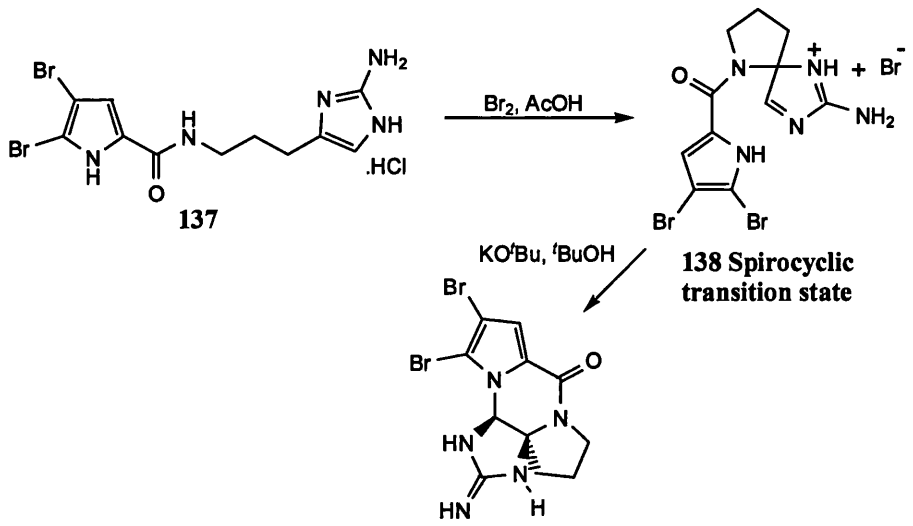
1.5 Biomimetic Synthesis

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.[58] They synthesised racemic dibromophakellin **26**, an alkaloid isolated from the marine sponge *Phakellia flabellata*, by oxidative cyclisation of non-natural dihydrooroidin **137** (**scheme 22**). The hydrochloride salt of dihyrooroidin 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 dibromphakellin. 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 dihydrooroidin precursor **137** was essential to the success of the cyclisation step.

Scheme 22



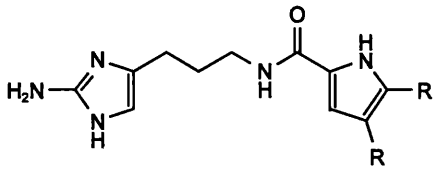
137

138 Spirocyclic transition state

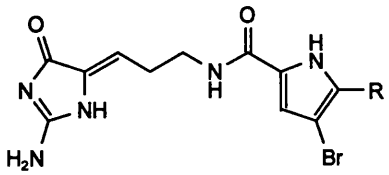
26 (±) dibromophakellin

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.[59] The precedent for the 4,5-oxidative addition to the double bond of 2-aminoimidazole was seen previously in Büchi's synthesis.



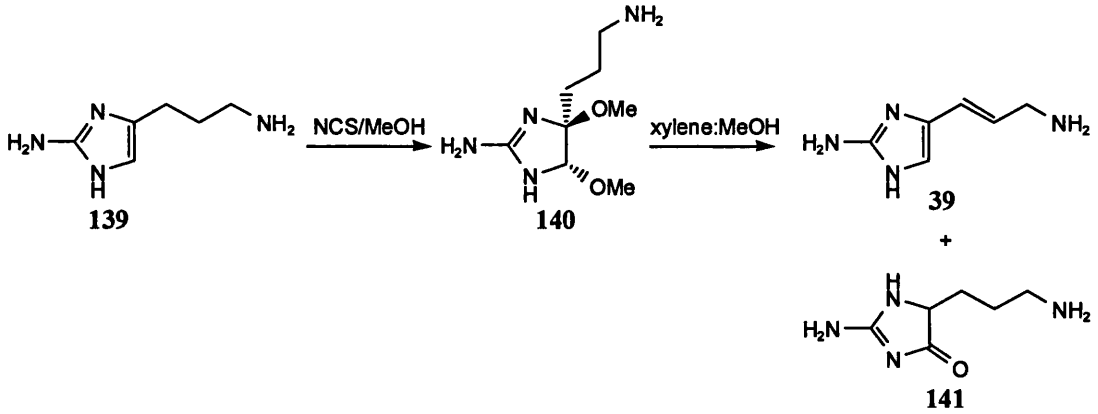
1 Oroidin, R = Br
2 Clathrodin, R = H



6 Dispacamide A, R = Br
7 Dispacamide B, R = H

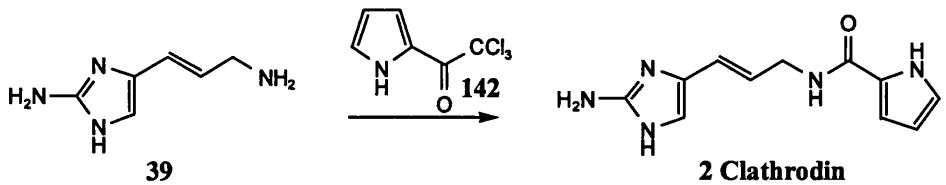
The 2-aminoimidazole precursor **139** can be considered as a hypothetical precursor to the $C_{11}N_5$ natural products.

Scheme 23



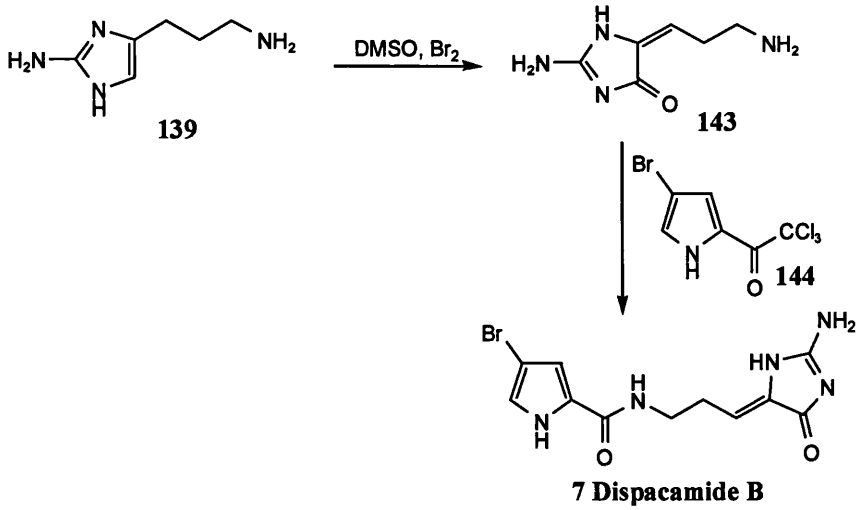
Oxidation of **139** with NCS followed by heating with xylene:methanol gave two rearrangement products **39** and **141** (**scheme 23**). 3-Amino-1-(2-aminoimidazolyl)-prop-1-ene **39**, also a natural product isolated from the Axinellidae sponges *T. Morchella* and *P. walpersi*, was acylated with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

Scheme 24



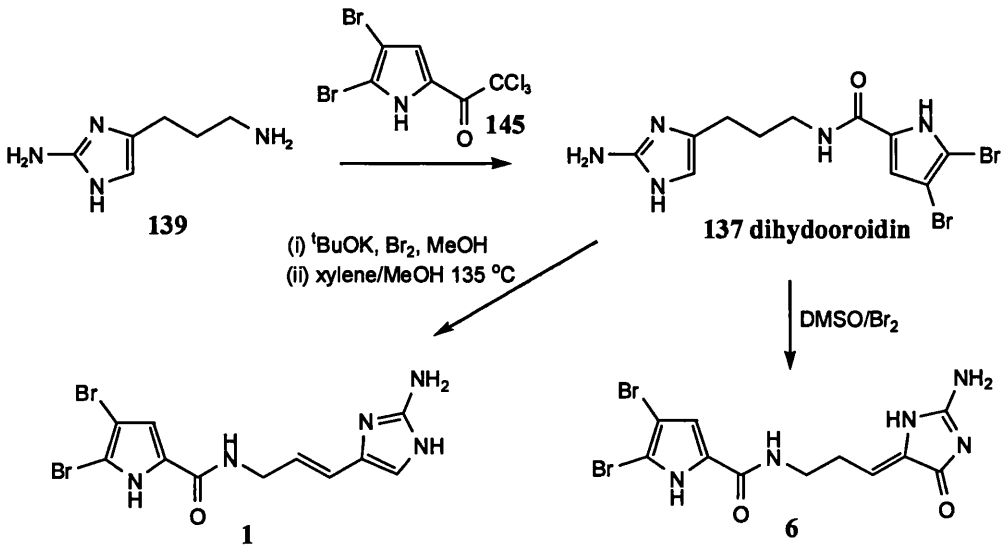
Oxidation of 2-aminoimidazole precursor **139** with bromine in DMSO with concomitant elimination of dimethyl sulfide leads to the unsaturated imidazoline ring system **143** found in the dispacamides, and acylation with bromopyrrole **144** gave dispacamide B **7**.

Scheme 25



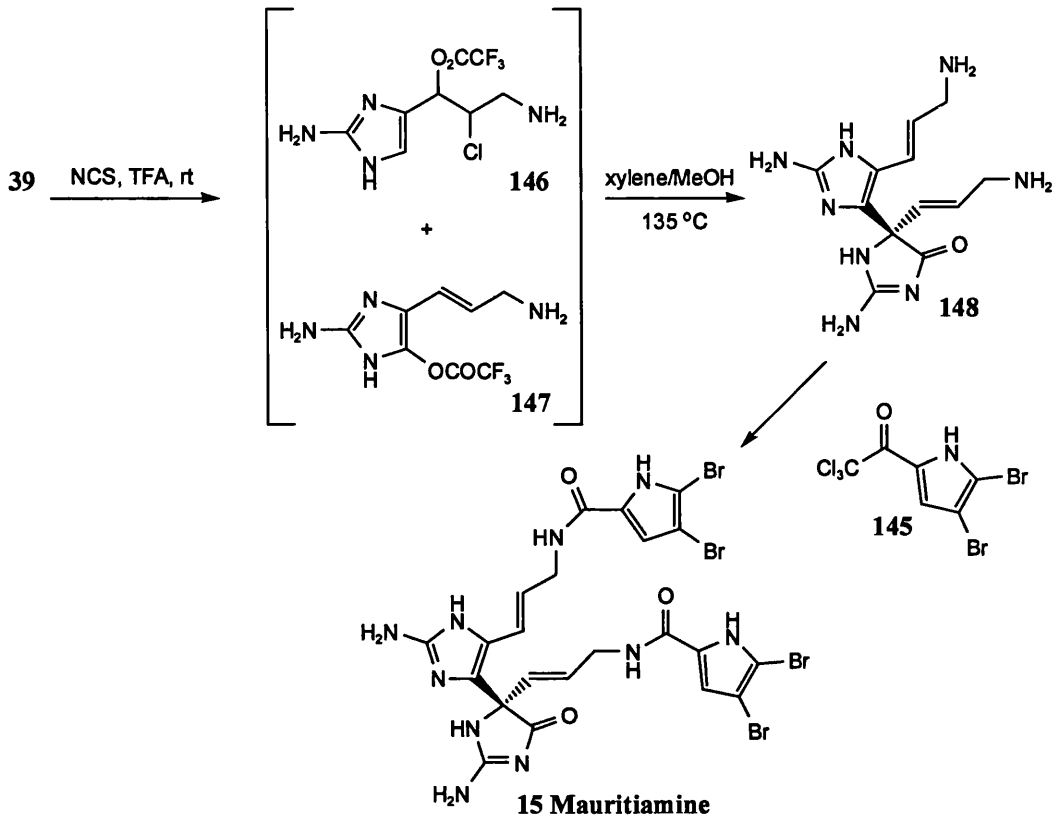
Acylation of **139** with dibromopyrrole **145** gave dihydrooroidin **137** and then treatment with bromine and potassium ^{t}butoxide followed by rearrangement by heating with xylene:methanol gave oroidin **1**. Oxidation of **137** with bromine/DMSO gave dispacamide A **6**.

Scheme 26



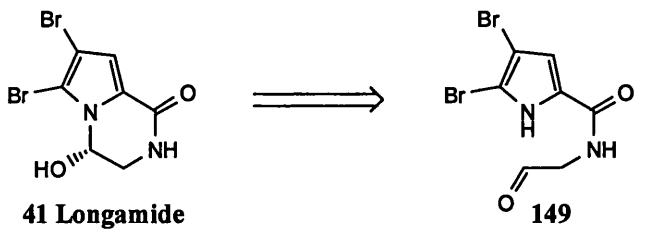
The Horne group used 2-aminoimidazole intermediate **39** to synthesise the dimeric alkaloid mauritiamine.[60]

Scheme 27



Oxidation of **39** in NCS/TFA gave two intermediates **146** and **147**, formally the products of 1,2 addition of Cl^+ and CF_3COO^- and 1,4 addition followed by elimination of HCl (**scheme 27**). Heating in xylene:methanol afforded the dimerised product **148** which was acylated with dibromopyrrole **145** to give mauritiamine **15**.

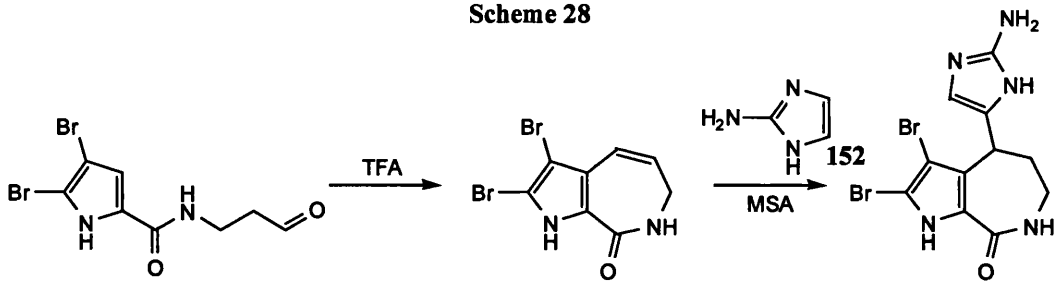
The biomimetic synthesis of cyclic analogues has also been completed, one of the simplest being that of (±)-longamide **41**.[42]



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 synthesises of cyclised oroidin alkaloids. They completed the synthesis of (±)-hymenin **23**[61] isolated from the Okinawan sponge, *Hymeniacidon sp.*

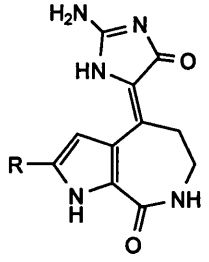
Scheme 28



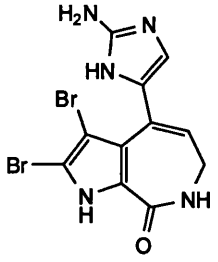
150 **151** **23 Hymenin**

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-aminoimidazole 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**.[62] All of these natural products share the same common fused bicyclic olefin system.



20 Hymenialdisine, R=Br
153 Debromohymenialdisine, R=H



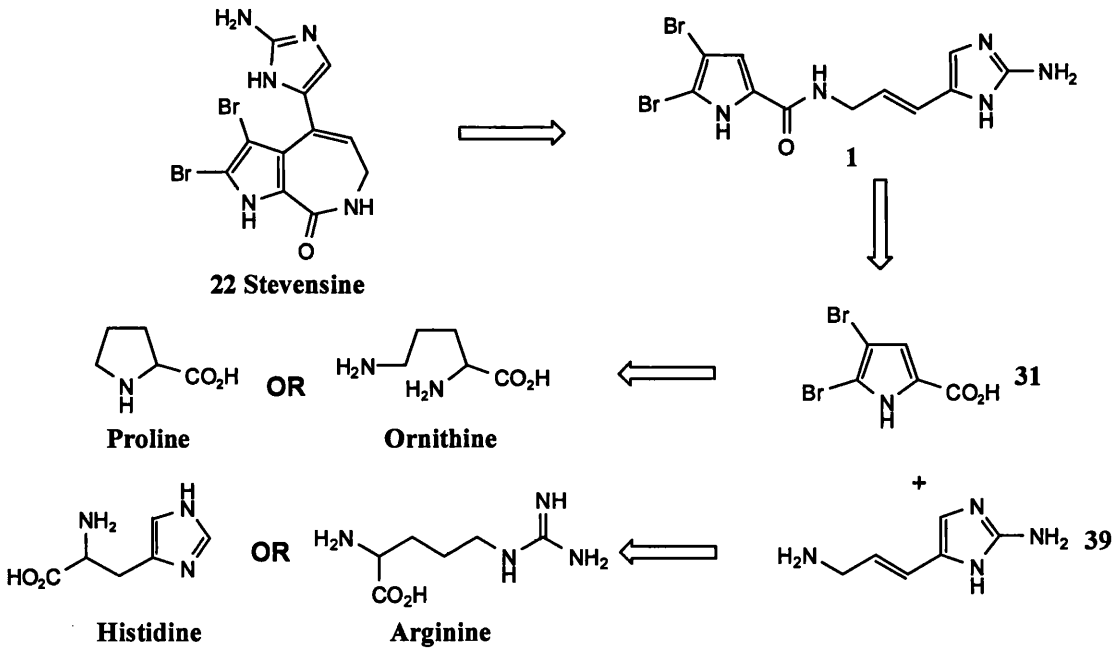
22 Stevensine

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-amimoimidazoyl)-prop-1-ene **39** (an intermediate in the biomimetic syntheses of both clathrodin and mauritiamine described earlier), and 4,5-dibromopyrrole-2-carboxylic acid **31** (**scheme 29**).[63] 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.

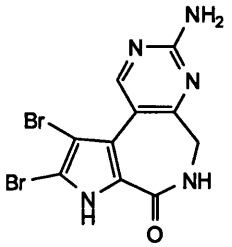
Scheme 29



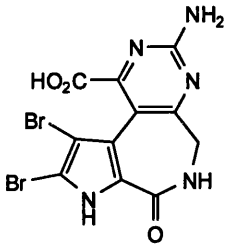
Kerr and co-workers, using feeding studies with a cell culture from the Axinellidae sponge *Teichaxinella morchella*, demonstrated that radiolabelled proline, histidine and ornithine were incorporated into stevensine, whereas arginine was not. Their theory on the biosynthetic route to stevensine was 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, Linington and co-workers reported the isolation of latonduines A **154** and B **155** from the marine sponge *Stylissa carteri*.[64]



154 Latonduine A



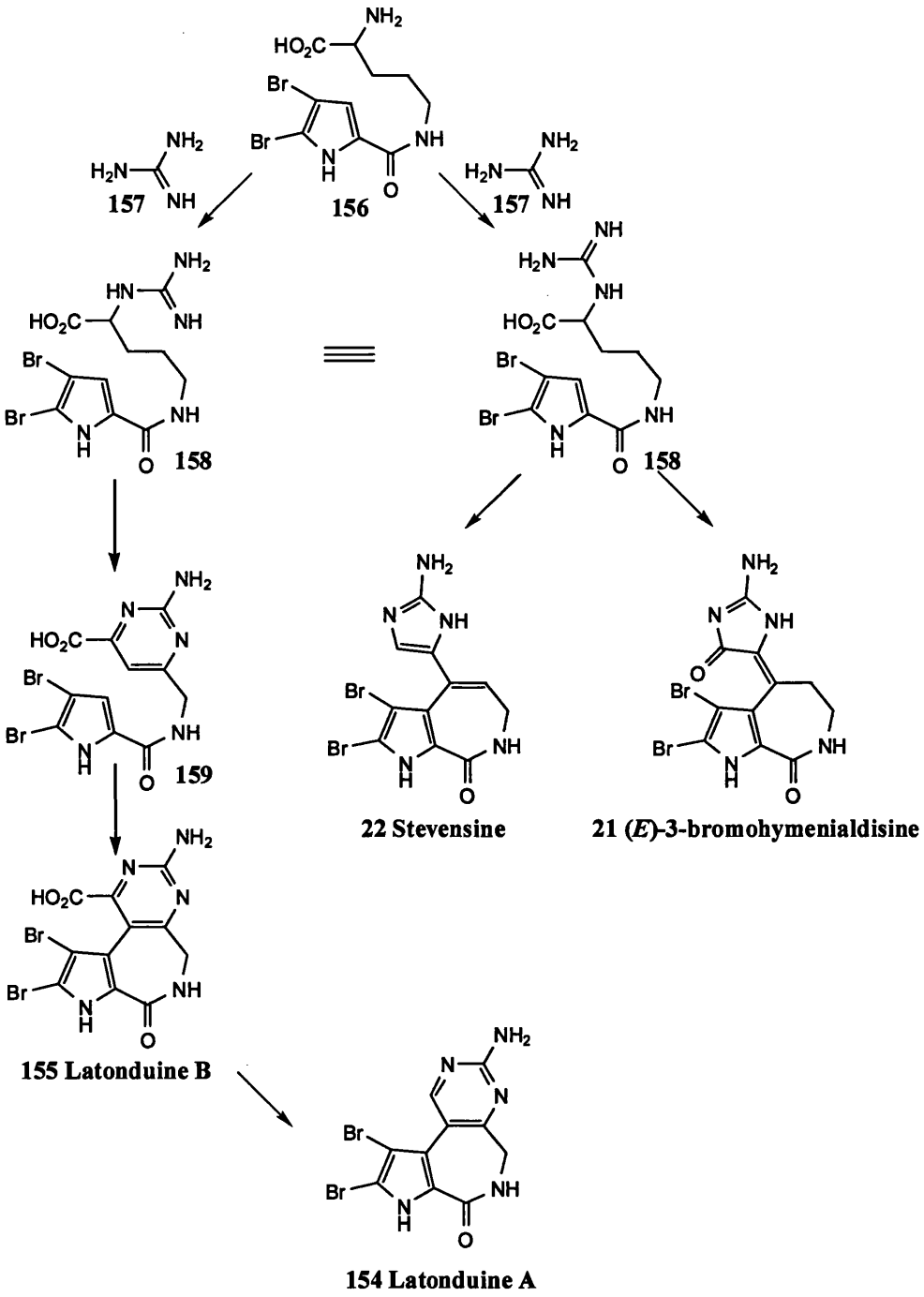
155 Latonduine B

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.

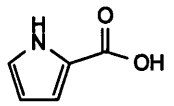
Linington and co-workers proposed that the building blocks for latonduine B are instead 4,5-dibromopyrrole-2-carboxylic acid **145**, ornithine and guanidine, which form the precursor **158** and then two cyclisations form latonduine B **155** (**scheme 30**). Latonduine A **154** would result from the decarboxylation of latonduine B. Linington'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 aminoimidazole moiety.

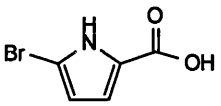
Scheme 30


156
157
157
158
158
159
22 Stevensine
21 (E)-3-bromohymenialdisine
155 Latonduine B
154 Latonduine A

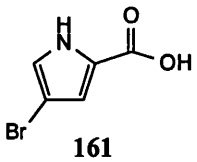
A recent communication by Al Mourabit and co-workers has proposed a logical biogenetic pathway to all the groups of the pyrrole-imidazole alkaloids.[65] He proposed that the pyrrole-imidazole alkaloids are biosynthetically derived from four pyrrole-2-carboxylic acid building blocks **123, 160, 161** and **31** and the vinyl-aminoimidazole building block **39**.



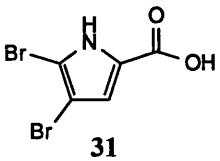
123



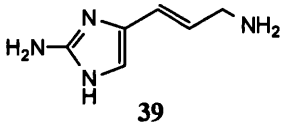
160



161

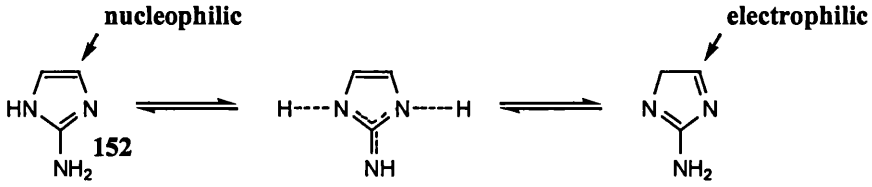


31

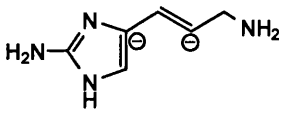


39

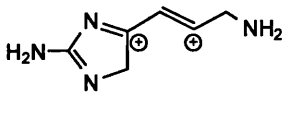
The two nucleophilic positions at N1 and C3 of the four pyrrole building blocks allow for eight different modes of incorporation into the family of pyrrole-imidazole alkaloids. The 3-amino-1-(2-aminoimidazolyl)-prop-1-ene unit **39** can be incorporated in several ways via the ambivalent reactivity of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

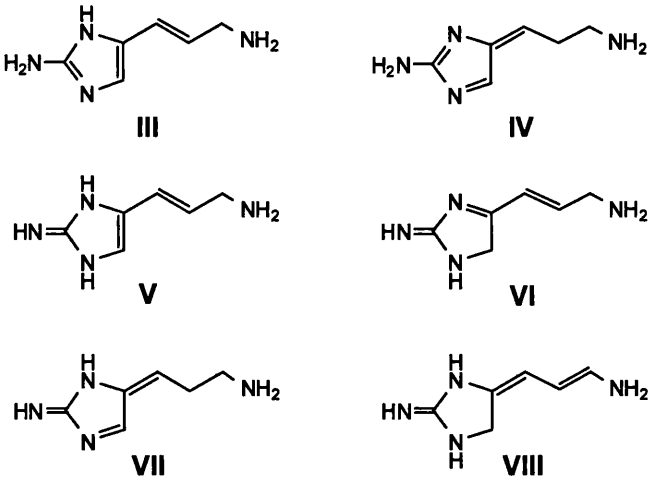


Tautomer I



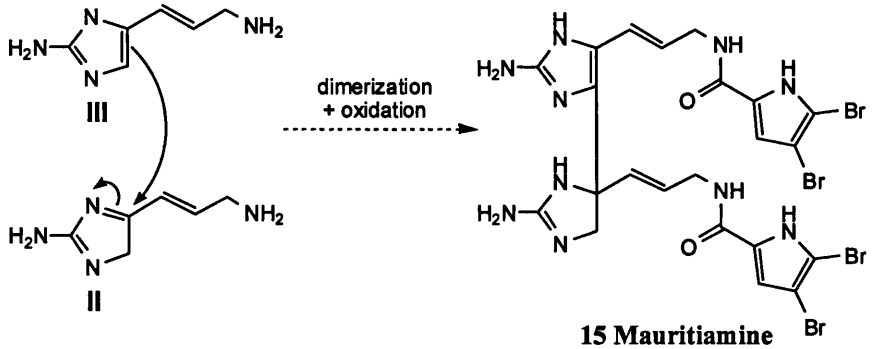
Tautomer II

A total of eight possible tautomeric forms can be drawn for the aminoimidazole-containing fragment **39**.



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)**.

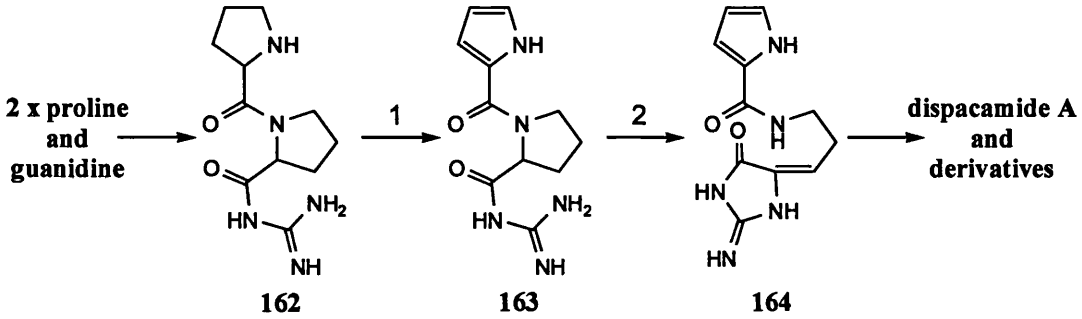
Scheme 31



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.[66] 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.

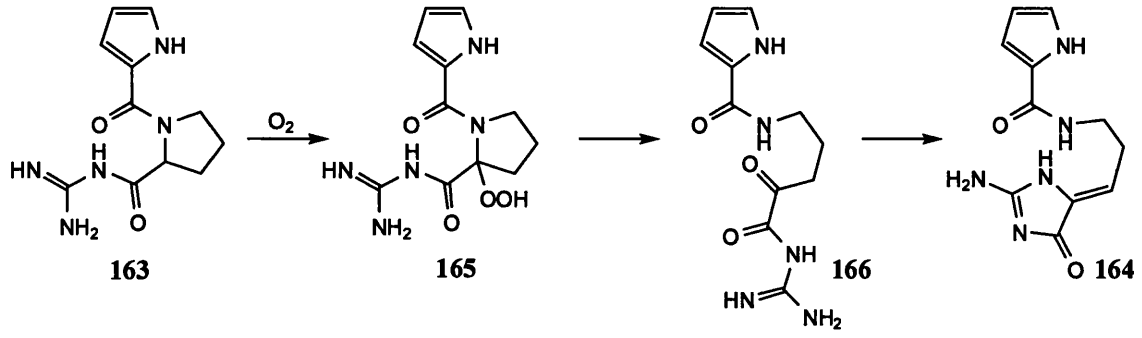
Al Mourabit proposed that the biosynthesis of the linear alkaloids, such as dispacamide A **6**, proceeds via a pseudo-dipeptide pyrrole-proline-guanidine **163** (**scheme 32**).

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**.

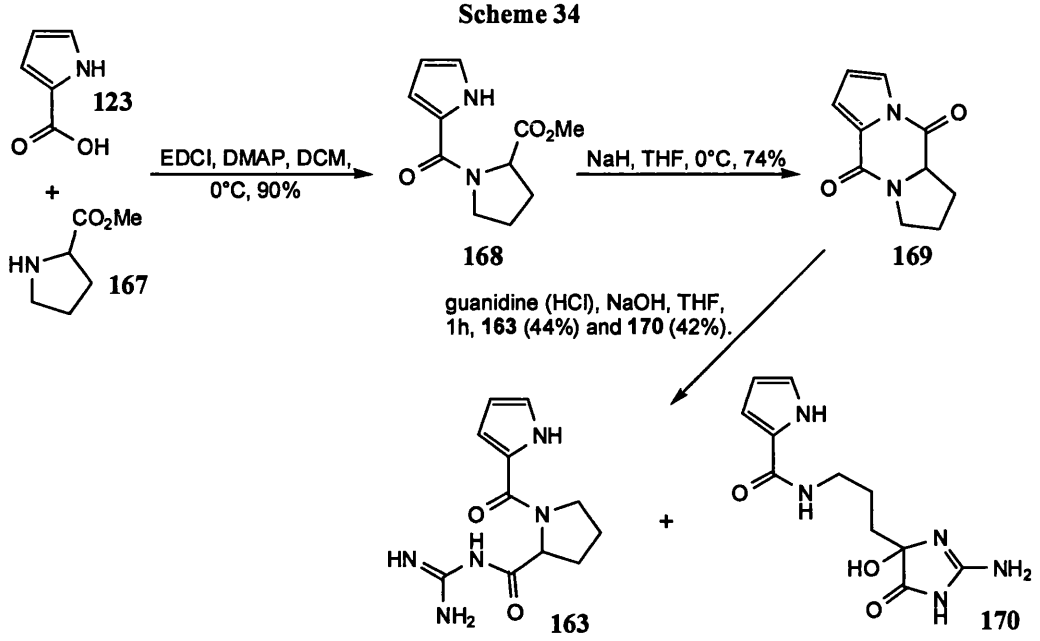
Scheme 33



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

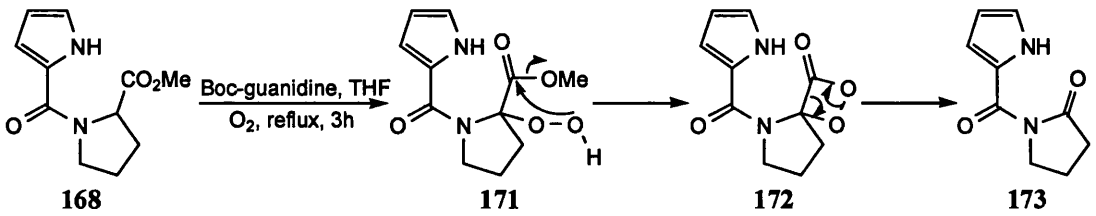
methyl ester **167**, coupled together using standard conditions to afford amide **168** and subsequently treated with sodium hydride in THF to afford asymmetric tricycle **169**.

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**.

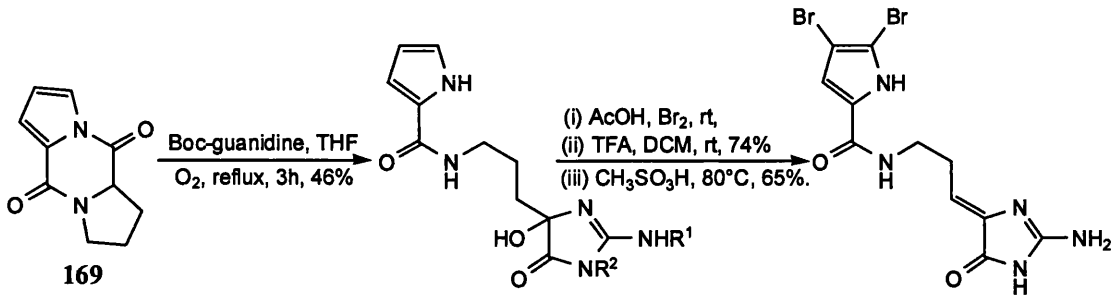
Scheme 35



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.

Scheme 36



169

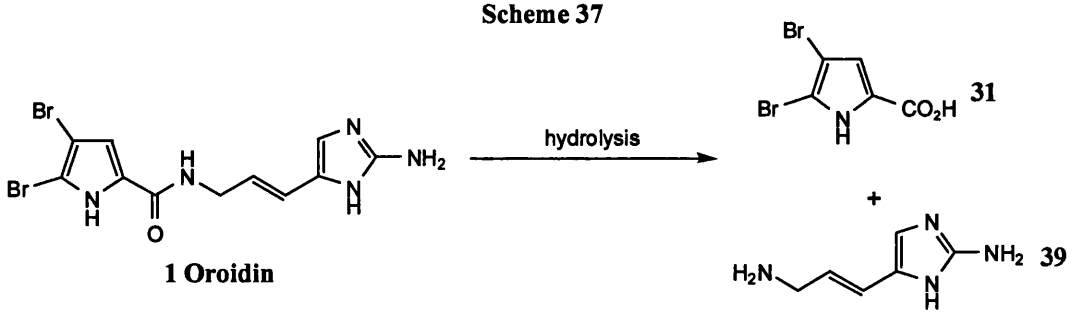
174: R^1=H, R^2=Boc
175: R^1=Boc, R^2=H

6 Dispacamide A

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-amimoimidazoyl)-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**).

Scheme 37



1 Oroidin

31

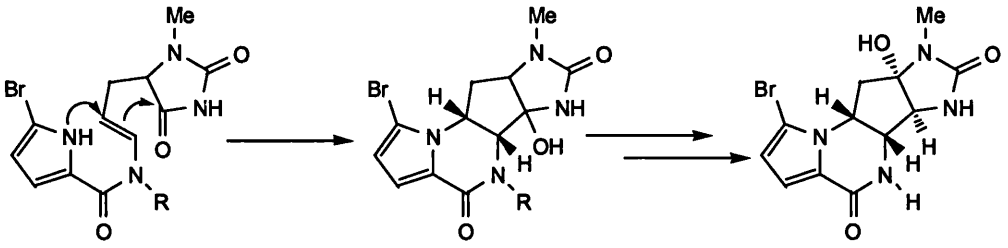
39

Currently there is not enough evidence from *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 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 refunctionalisation at C(4) and C(5) of **177** to give agelastatin A **28**.[44]

Scheme 38

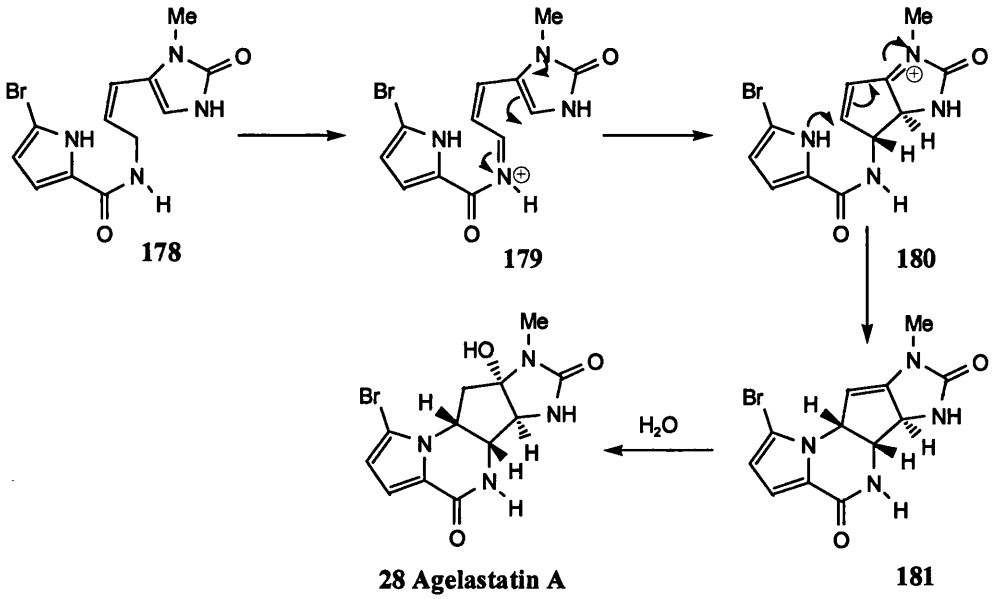


176 **177** **28**

But this proposed mechanism requires an emamide 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.

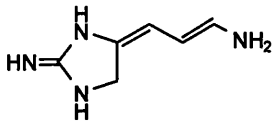
Scheme 39



178 **179** **180** **28 Agelastatin A** **181**

The aim of this project is to investigate the viability of such a route for the biomimetic synthesis of agelastatin A.

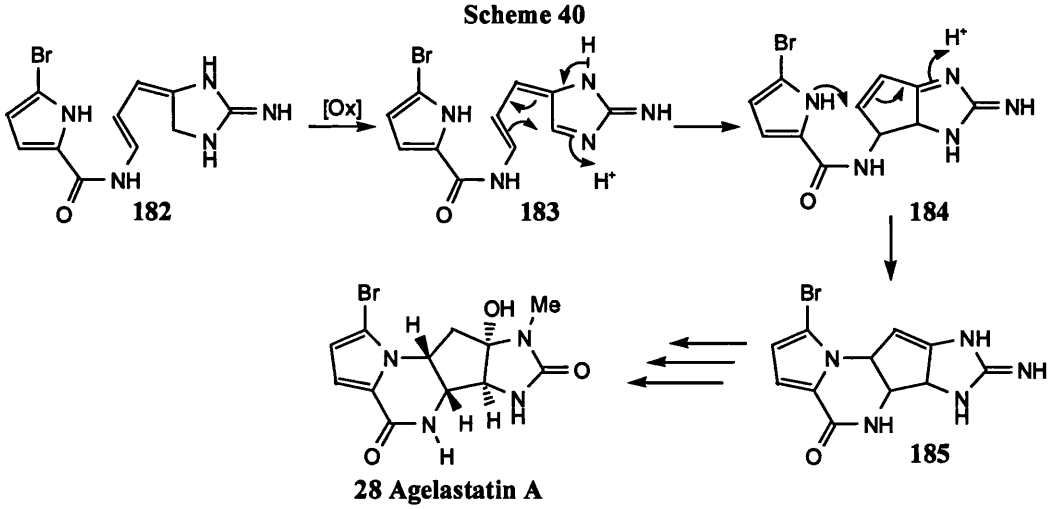
Al Mourabit has also proposed a similar biomimetic synthesis via the oxidation of tautomer VIII of aminoimidazole-containing fragment **39**.[65]



39 Tautomer VIII

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

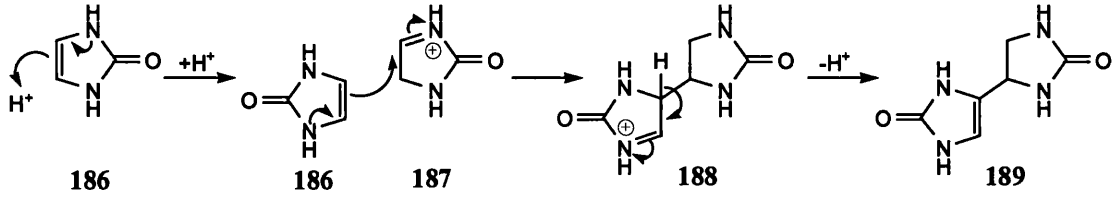


28 Agelastatin A

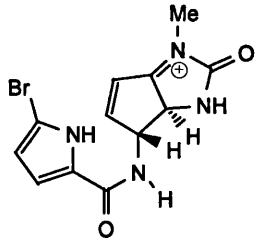
1.6.1 Evidence for an *N*-acyliminium Ion Intermediate

In 1965, Zigeuner and Rauter observed that when imidazolone **186** was heated with hydrochloric acid dimerisation to **189** occurred.[67] 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**.

Scheme 41



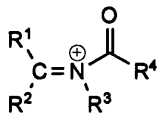
This mechanism is important evidence for our proposed biomimetic synthesis of Agelastatin A, as we will generate a similar *N*-acyliminium ion to **187** after the first cyclisation step.



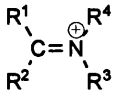
180 Second *N*-acyliminium ion in biomimetic synthesis

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



191 Mannich reagent

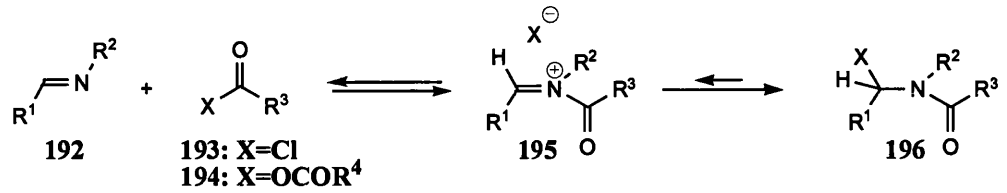
N-Acyliminium ions **190** are powerful electrophiles, which have a large number of synthetic applications. The presence of a strongly electron withdrawing group on the nitrogen leads to a highly electron deficient imino-carbon atom. This group enhances the reactivity of *N*-acyliminium ions compared 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.

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.

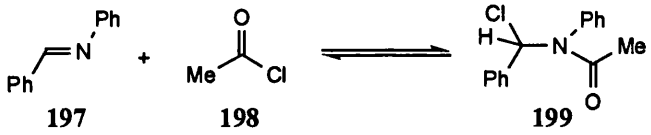
Scheme 42



192 **193: X=Cl** **194: X=OCOR[4]** **195** **196**

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.

Scheme 43



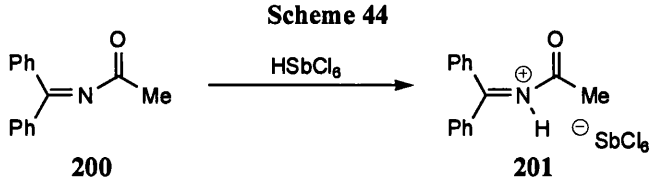
197 **198** **199**

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.[70]

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, β-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**[71] (**scheme 44**).

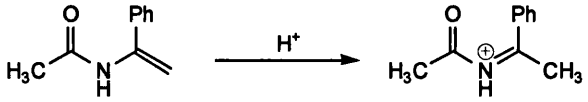
Scheme 44



200 **201**

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**.

Scheme 45

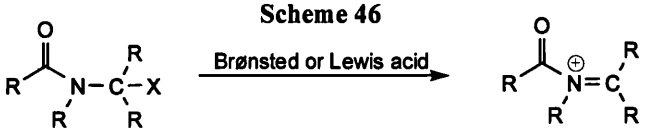


202 **203**

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]

Scheme 46



204 **205**

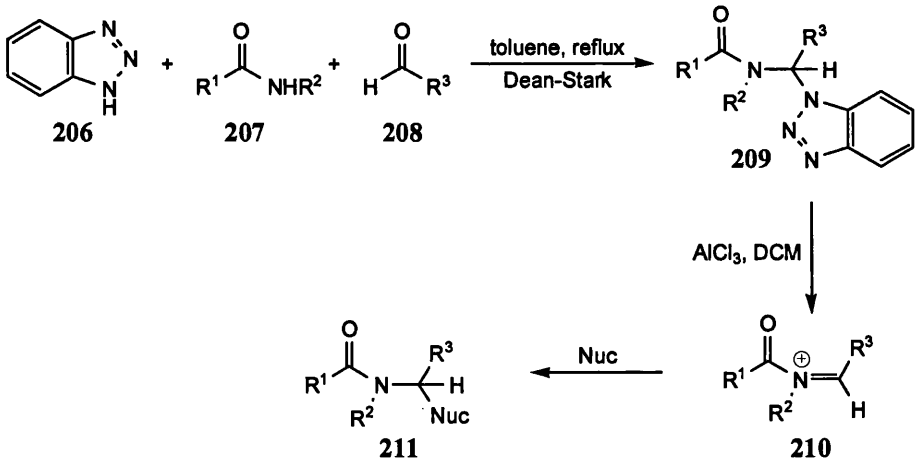
When an alkoxy substituent is used, then subsequent treatment with a Lewis or Brønsted acid effects the formation of the *N*-acyliminium ion **205**. If an acetoxy[72] or methanesulfonyloxy[73] group is used, no acidic catalyst is required.

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.[74] 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

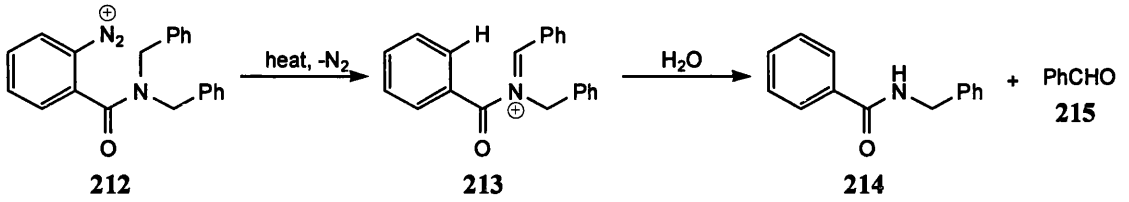


The benzotriazole leaving group was removed by treatment with aluminium chloride in DCM, and the intermediate *N*-acyliminium ion **210** generated was subsequently trapped by a variety of nucleophiles, including activated malonate esters and other active methylene compounds.

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**.[75] Nitrogen is lost and a hydride shift to the phenyl ring generates the acyliminium ion **213**.

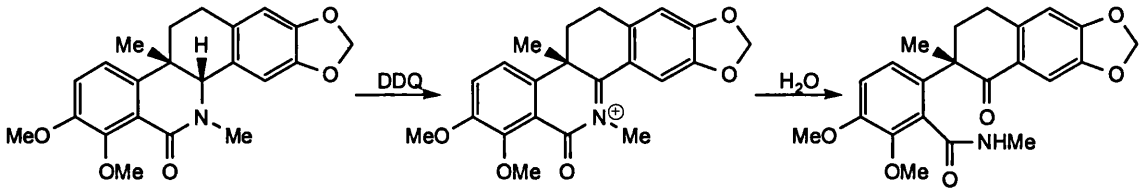
Scheme 48



212 **213** **214**

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**.

Scheme 49

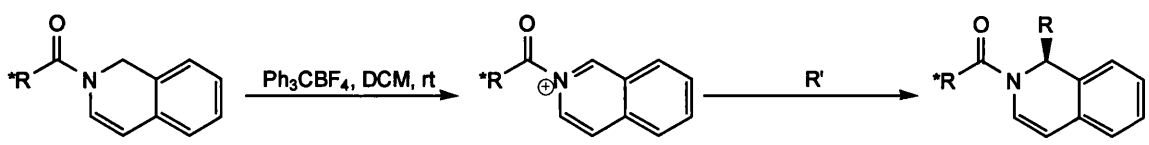


216 **217** **218**

Other oxidising agents that have been utilised in the literature for the generation of *N*-acyliminium ions include $FeCl_3/H_2SO_4$,[76] $RuCl_2(PPh_3)_3$/TBHP,[77] 1-*tert*-butylperoxy-1,2-benziodoxol-3(1*H*)-one[78] and cerium(IV) diammonium nitrate.[79]

Trityl 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.[80] Hydride abstraction from chiral amide **229** generated *N*-acyliminium ion **220** (**scheme 50**).

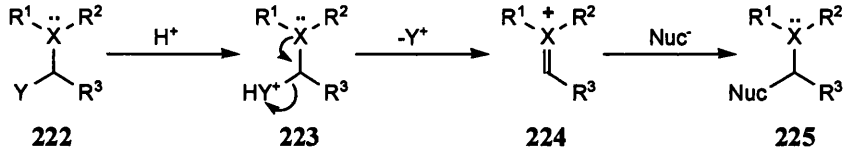
Scheme 50



219 **220** **221**

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^-.

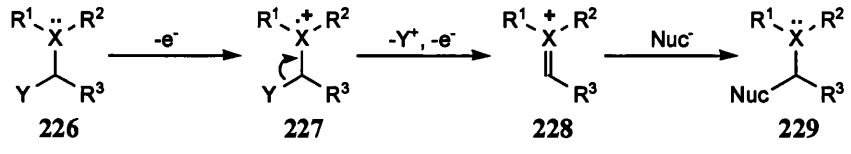
Scheme 51



222 **223** **224** **225**

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^+. 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**.

Scheme 52

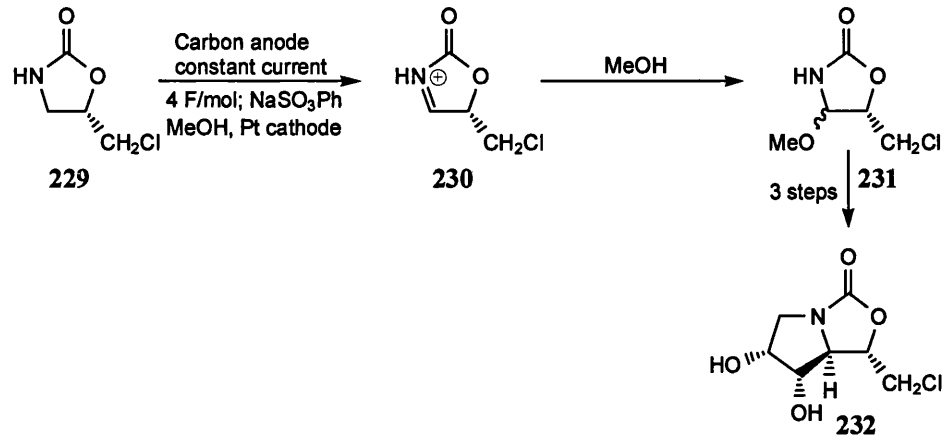


226 **227** **228** **229**

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[81] (**scheme 53**).

Scheme 53

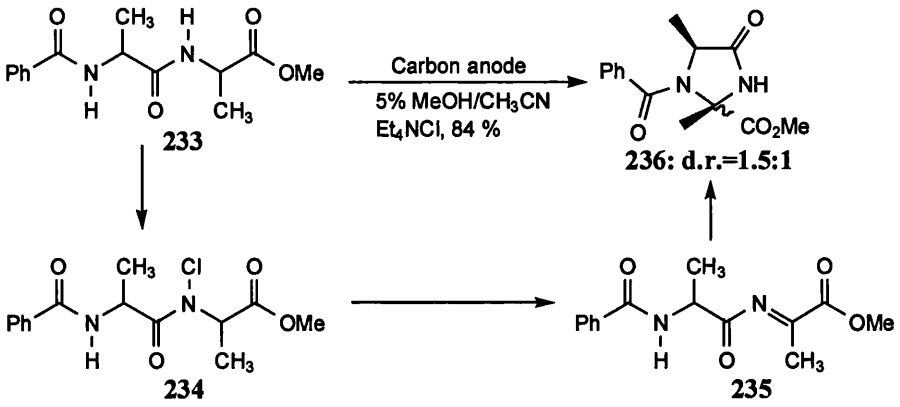


Oxidation at a carbon anode generated an *N*-acyliminium ion **230** that was subsequently quenched by the methanol solvent. The resulting α-methoxy amide **231** was then subjected to further transformations to give the chiral product **232**. 4 F/mol indicates that four moles of electrons were utilized 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.[82] 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**).

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

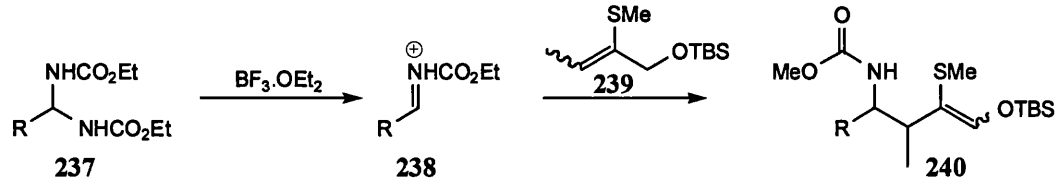
N-Acyliminium ions are highly useful intermediates in organic synthesis. The *N*-acyliminium ions can be either cyclic or linear and can undergo reactions with nucleophiles in an inter- or intramolecular fashion. A wide range of nucleophiles have been utilised to trap the *N*-acyliminium ion intermediates, 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.

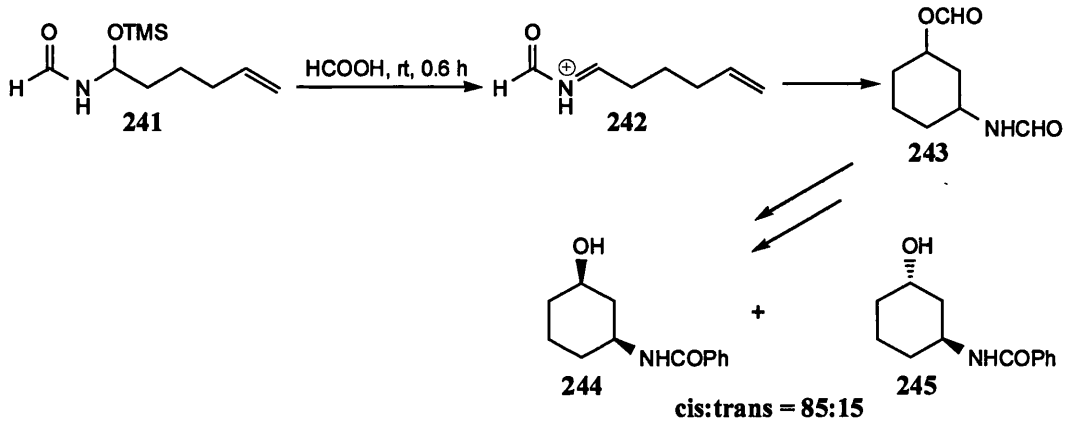
Bis-carbamates **237** have been used as precursors for the generation of *N*-acyliminium ions by treatment with $BF_3.OEt_2$ complex[84] (**scheme 55**). The resulting *N*-acyliminium ion intermediate **238** was trapped with an 2-(alkylthio)allyl silyl ether nucleophile **239**.

Scheme 55



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.[85] 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**.

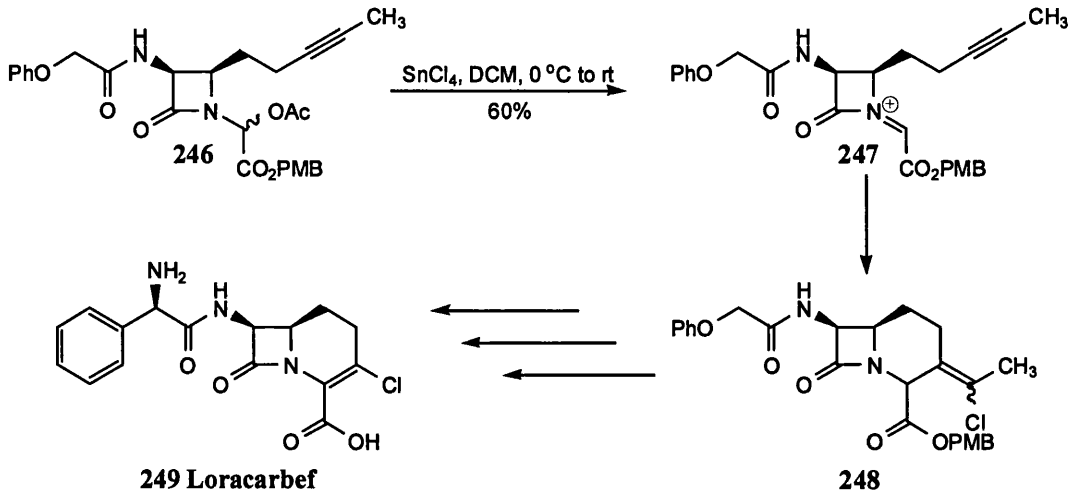
Scheme 56



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 C=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**.[86] 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**).

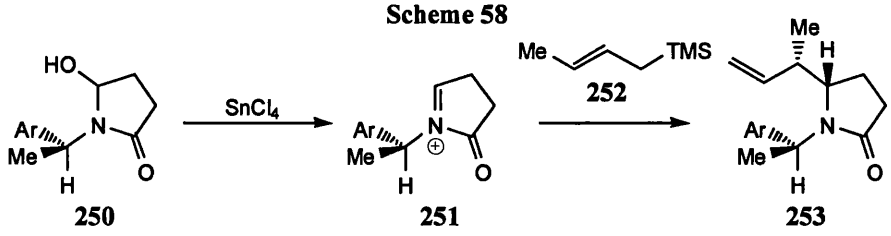
Scheme 57



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.[87]

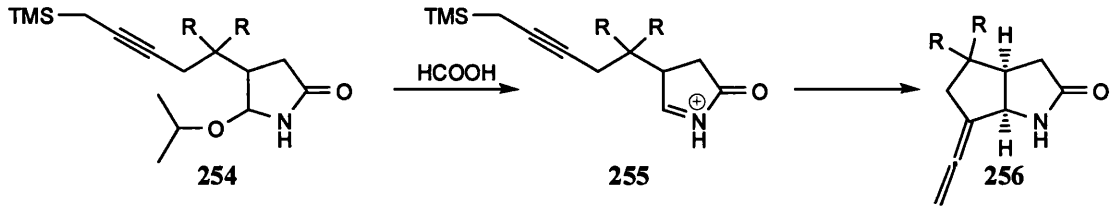
Scheme 58



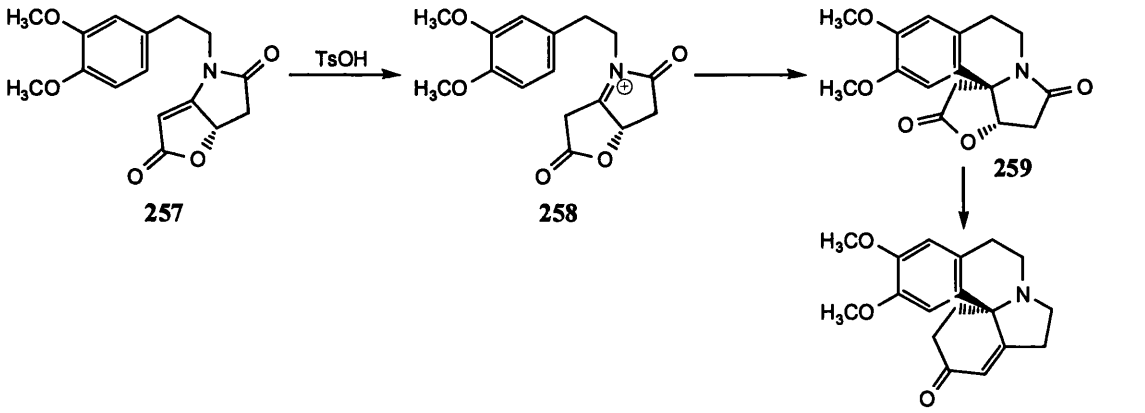
The ratio of diastereoisomers was dependent on the nature of the aryl group, with chlorination on the phenyl ring in **250** reversing the observed facial selectivity. The best diastereomeric ratio was obtained when a phenyl group was used.

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**[88] (**scheme 59**), and 5,6-fused ring systems, such as the synthesis of the core of the *Erythrina* alkaloids including (-)-3-demethoxyerythratidinone[89] (**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.

Scheme 59



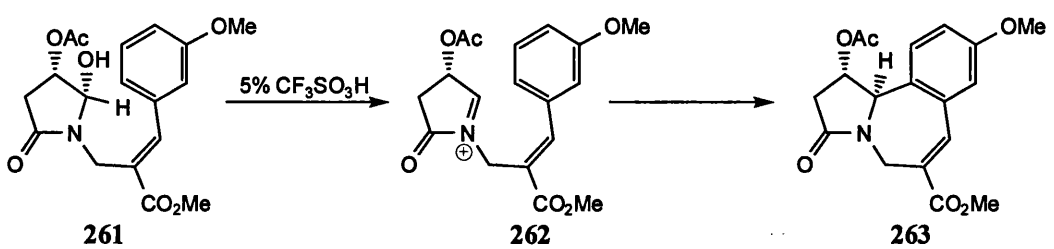
Scheme 60



260: (-)-3-Demethoxyerythratidinone

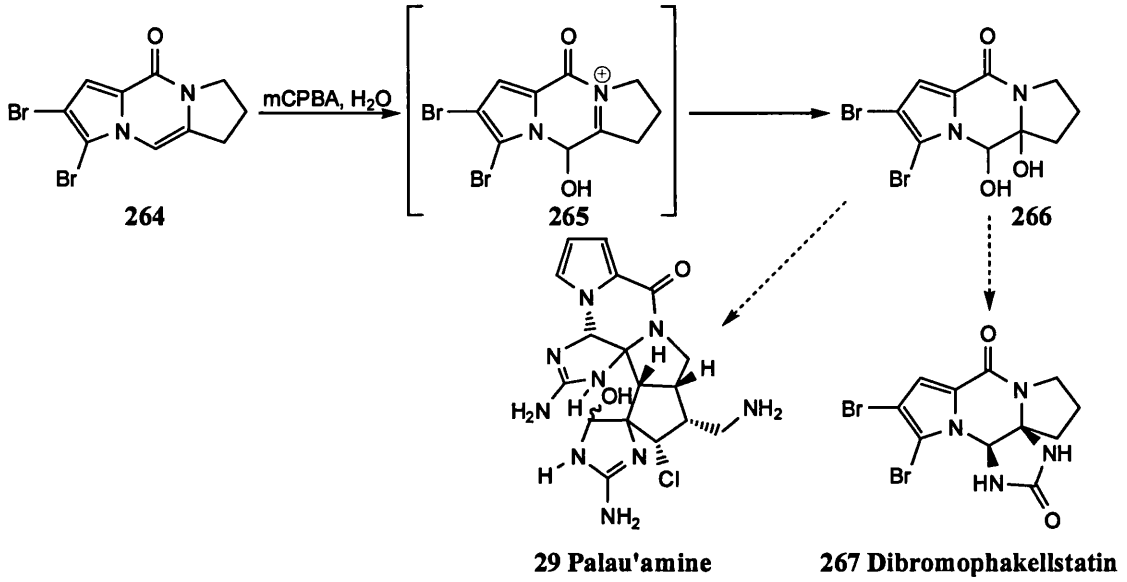
A 5,7-fused ring system was prepared by Marson and co-workers using *N*-acyliminium ion intermediate **262**[90]; the 5,7,6 system in **263** generated by this is a key motif in several natural products, including the aconitine alkaloids (**scheme 61**).

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**[91] (**scheme 62**).

Scheme 62

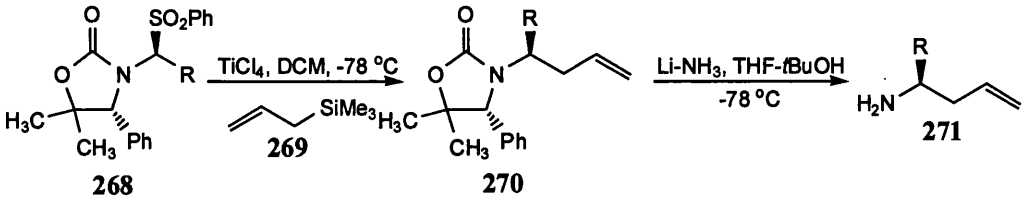


1.7.3 Asymmetric Synthesis

The mechanistic pathway for the generation of *N*-acyliminium ions does not allow direct stereocontrol. An S_N1-type intermediate has been detected by NMR studies, and a mechanistic study demonstrated that an optically pure *N*-acyliminium ion precursor, when treated with $BF_3.Et_2O$ and a nucleophile, led to completely racemised products.[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.

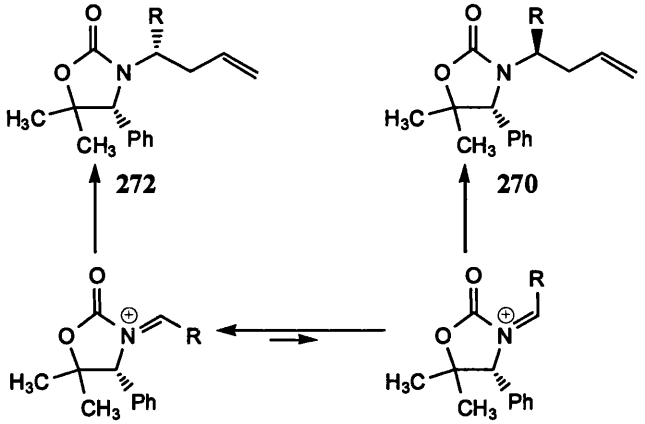
A phenylsulfonyl leaving group was utilised by Marcantoni and co-workers[93] for the generation of chiral exocyclic *N*-acyliminium ions using a chiral auxiliary (**scheme 63**). The phenylsulfonyl group was removed by treatment with titanium tetrachloride and then alkylation effected with allyltrimethylsilane **269**.

Scheme 63



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.

Scheme 64

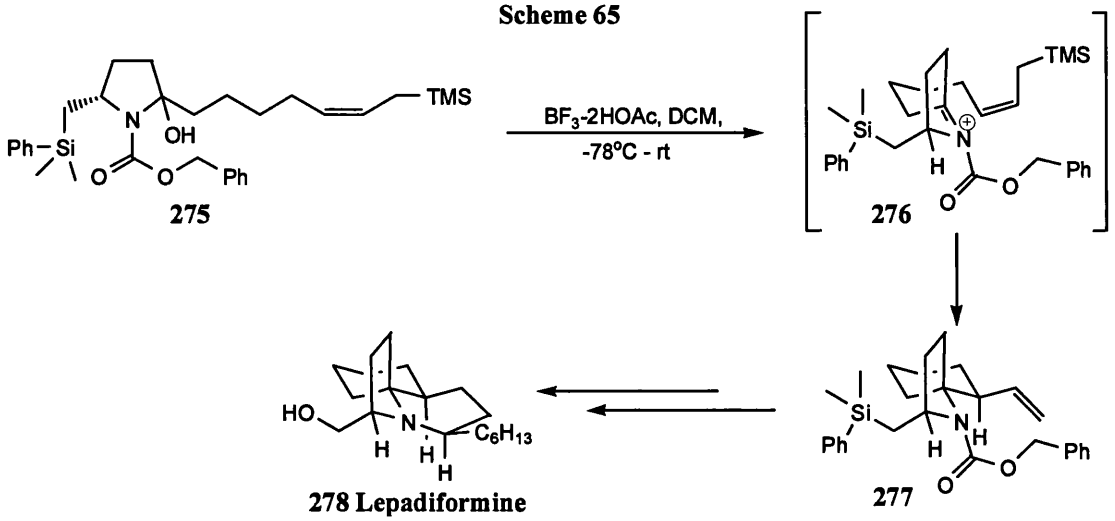


Marcantoni *et al* also observed the opposite selectivity for the alkylation of the intermediate *N*-acyliminium ions than that expected by energy calculations for the intermediates. The *Z*-acyliminium ion **274** was predicted to be more unstable than the *E*-isomer **272** by 0.7 to 1.4 kcal/mol based 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**[94] (**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.

Scheme 65



The chiral amide precursor **275** was treated with borontrifluoride-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**.

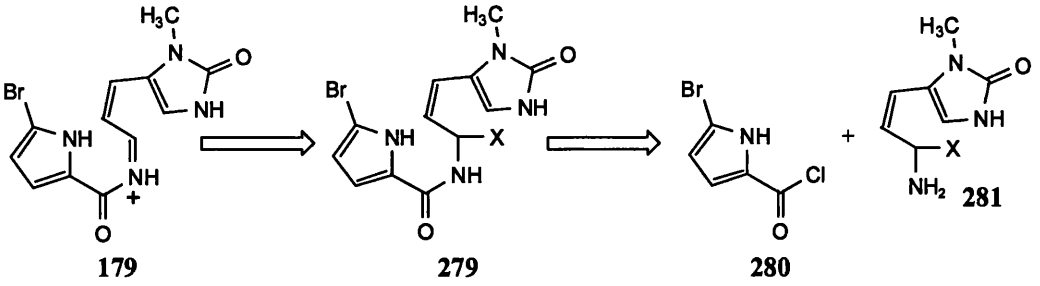
As the literature contains many examples of applications of *N*-acyliminium ions, it was hoped that it would be possible to find a set of conditions suitable for the generation of the *N*-acyliminium ion required in our proposed biomimetic synthesis of agelastatin A.

CHAPTER II

RESULTS AND DISCUSSION

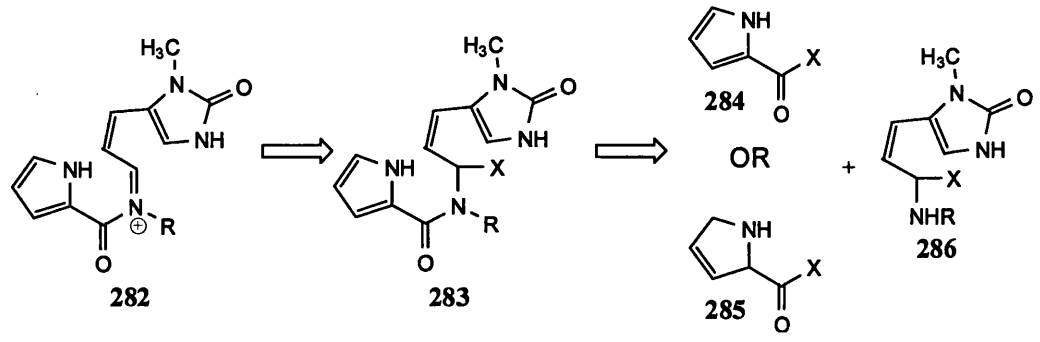
2.1 Disconnection of the Biomimetic Precursor and Synthetic Modifications

Scheme 66



Our proposed biomimetic synthesis of agelastatin A requires the generation of an *N*-acyliminium ion **179**. The initially planned synthetic route was to generate this *N*-acyliminium ion by removal of a leaving group X from amide precursor **279**. As discussed previously amides with α-leaving groups are commonly utilised as precursors for the generation of *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**.

Scheme 67



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.

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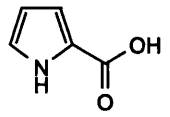
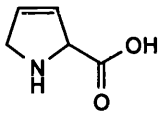
The pyrrole nitrogen may not be sufficiently nucleophilic to affect the second cyclisation step in the biomimetic synthesis owing to delocalisation of the nitrogen lone pair into the pyrrole ring. Therefore it may be necessary, if the application of a pyrrole ring **284** is unsuccessful, to employ a 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.



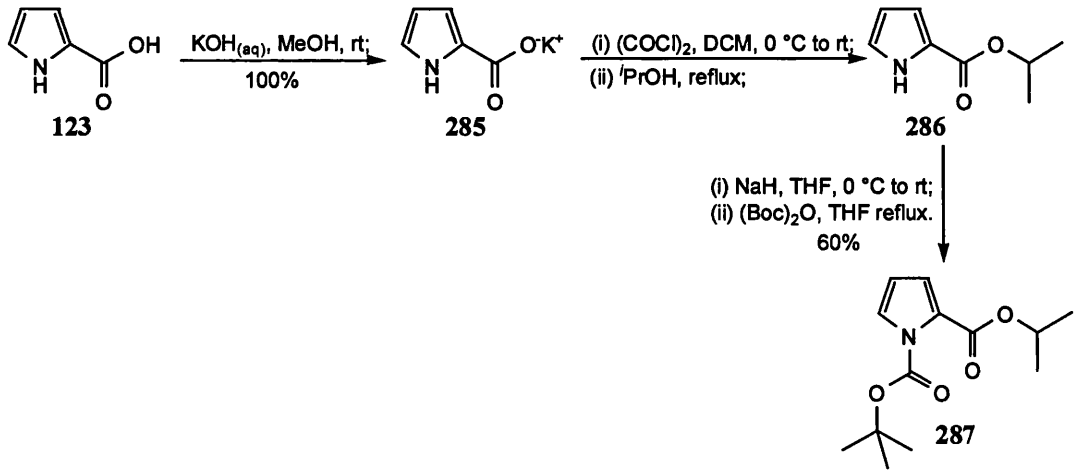
123 pyrrole fragment



284 3-pyrroline fragment

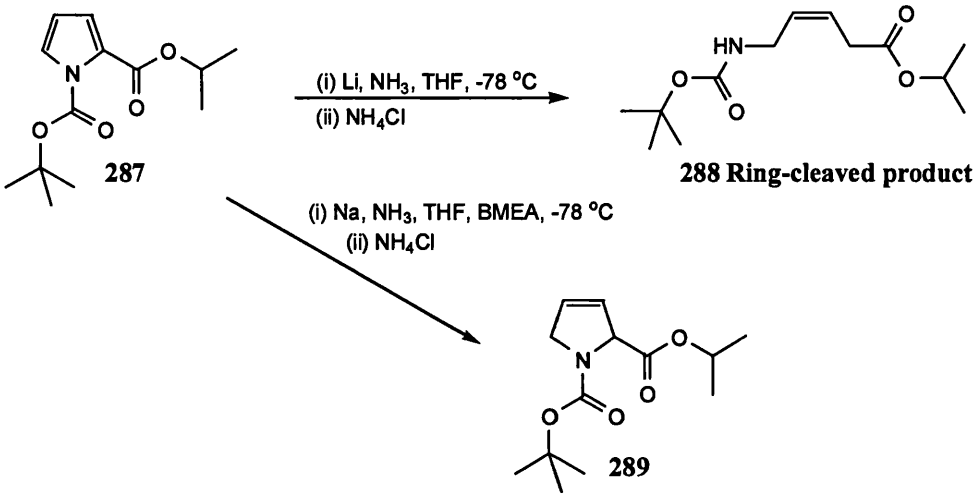
Therefore, initial efforts focused on the synthesis of *N*-Boc-3-pyrroline-2-carboxylic acid **284** using the method decribed by Donohoe et al.[95] **Scheme 68** illustrates the synthesis of the Birch reduction substrate.

Scheme 68



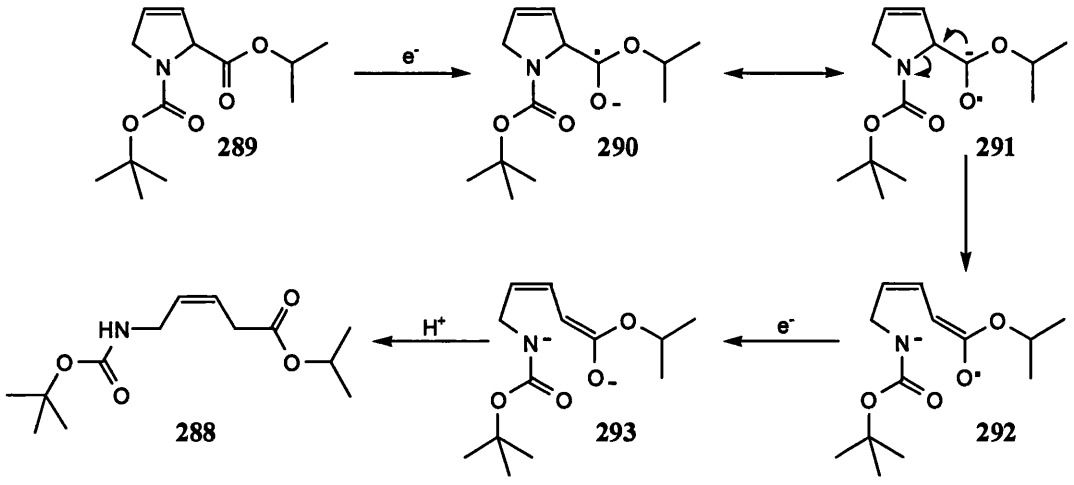
Pyrrole-2-carboxylic acid **123** was converted to its carboxylate salt **285** with aqueous potassium hydroxide in quantitative yield (**scheme 68**). Reaction with oxalyl chloride afforded the crude acid chloride, which was immediately esterified by refluxing with propan-2-ol. The resulting isopropyl 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)[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.

Scheme 69



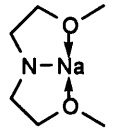
The reduction of the pyrrole ester **287** to the corresponding 3-pyrroline **289** was achieved using a Birch reduction (**Scheme 69**). Initial attempts to use sodium in liquid ammonia failed to give the desired product. The reaction was then attempted with lithium in ammonia but again, none of the 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.

Scheme 70



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**.

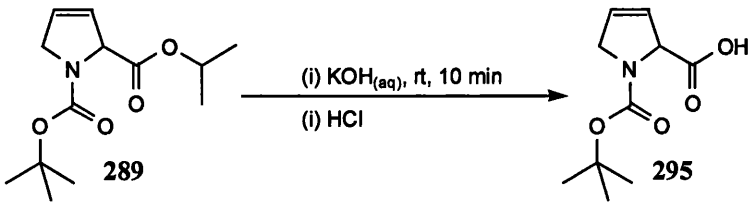
A further paper from the Donohoe group[96] reported that a significant number of products from various Birch reductions of *N*-protected pyrrole derivatives were the deprotected analogues. They demonstrated that the addition of an excess of bis(2-methoxyethyl)amine (BMEA) to the Birch reduction significantly 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.



294

Utilising 10 equivalents of BMEA, added to the reaction with pyrrole **287**, enabled the reaction to proceed in 62% yield after flash chromatography.[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



289 **295**

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.

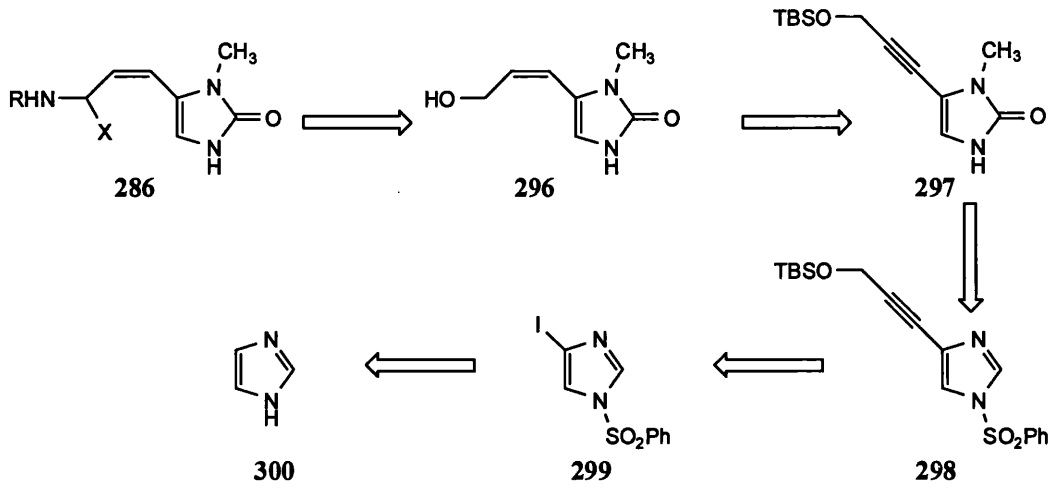
Both the pyrroline isopropyl ester **289** and the free carboxylic acid **295** exhibited broad signals in their room temperature ^{1}H NMR spectra and two sets of signals in their ^{13}C NMR spectra. Thus the ^{1}H NMR of the pyrroline carboxylic acid **295** was recorded in DMSO at 40 °C, 80 °C and 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**).

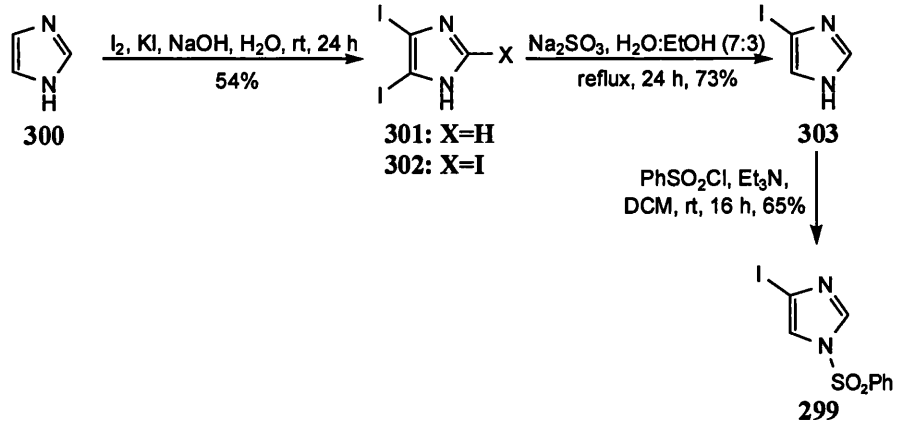
Scheme 72



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,[98] hexane,[99] or light petroleum[100] 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[101] 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-[98, 102] **302** or the 4,5-diodoimidazole[103, 104] **301** is the major product, but either product would be acceptable as both can be converted into the same product, 4(5)-iodoimidazole **303**, by treatment with Na_2SO_3.[98, 102, 105]

Use of a biphasic system with chloroform as the organic solvent was initially attempted for the synthesis of 2,4,5-triiodoimidazole.[98] 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 **301**. The

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[106] and 190-192°C[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,[106] is tedious,[108] and hazardous[109] to synthesise, whereas that for triiodination, bis(trifluoroacetoxyl)iodobenzene[107] is very expensive. These procedures were therefore not investigated.

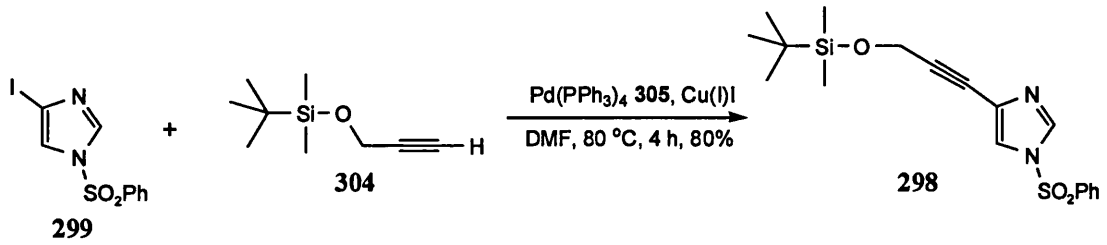
In order to convert 4,5-diiodoimidazole **301** into the monoiodinated product **303** it was refluxed with 8 equivalents of sodium sulfite in a 7:3 mixture of H_2O:EtOH for 24 h, concentrated *in vacuo* to almost dryness and 4(5)-iodoimidazole **303** isolated by filtration in 73% yield. The literature 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 ^{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 ^{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[110] reported that an acetylenic hydrogen can easily be substituted by halogenoarenes with a palladium catalyst, copper(I)iodide and triethylamine under mild conditions.[110] The reaction between 1-benzenesulfonyl-4-iodoimidazole **299** and TBS-protected propargyl alcohol **304** (scheme below) was carried out by Cliff and Pyne[98] as part of a larger investigation into the palladium catalysed coupling of imidazoles to various alkynyl substrates.

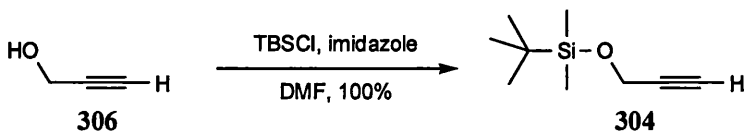
Scheme 74



299 304 298

Initially propargyl alcohol **306** was protected by reaction with triethylamine and *tert*-butyldimethylchlorosilane 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*-butyldimethyl chlorosilane and imidazole, removal of the DMF solvent by extraction with water and purification of the product by distillation under reduced pressure.[98] This method provided the protected alcohol **304** in quantitative yield.

Scheme 75



306 304

The tetrakis(triphenylphosphine)palladium catalyst **305** was prepared from palladium dichloride, triphenylphosphine and hydrazine in 90% yield using a reported procedure,[111] and stored under nitrogen in the absence of light. Total discolouration

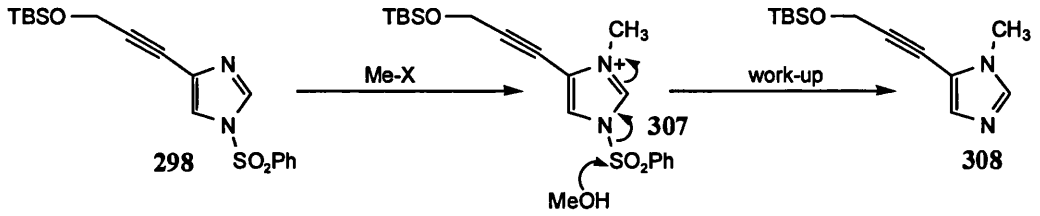
from bright yellow to an orange colour was observed after storage for approximately six weeks, and so the catalyst was used within 1 week of preparation.

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

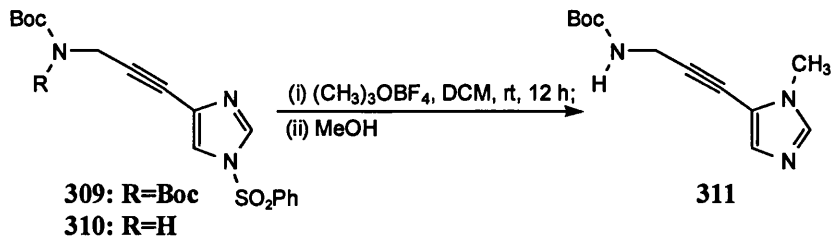
The next stage in the synthesis of the "right hand" fragment was methylation of the imidazole nitrogen. This could be carried out with concomitant removal of the benzenesulfonyl protecting group, via cationic intermediate **307**.

Scheme 76



Literature precedent for this reaction was found in two publications by Lindel and Hochgürtel,[112, 113] where the methylation reaction was carried out using trimethyloxonium 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 $MeOSO_2Ph$ is then removed by methanolysis during work-up.

Scheme 77



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 trifluoro-methanesulfonate) 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 1

Me_3OBF_4 (equiv)	Proton Sponge (equiv)	Solvent	Temp	t (h)	% conversion
1	1	DCM	rt	4	12
1	1	DCM	rt	22	21
1.2	1.2	DCM	reflux	16	42
2	2	DCM	reflux	16	50
1	1	$CHCl_3$	reflux	16	8.3
1.2	1.2	DCM	reflux	24 36 48	27 27 27[a]
1.3	1.3	$CHCl_3$	reflux	4	27
5	5	DCM	reflux	16	63
10	10	DCM	reflux	16	50

[a]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 trimethyloxonium 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 ^1H 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 ^1H 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 ^1H NMR.

Table 2

MeOTf (equiv)	Proton Sponge (equiv)	Solvent	Time (h)	% conversion
2	2	THF	1	74
3	3	THF	2	~100[a]
3.5	3.5	THF	2	100

[a]Trace of substrate observed by ^1H 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_3OD) 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® and the methylation product. However, although the Proton Sponge® 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.

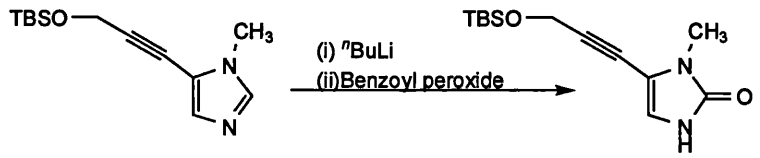
Table 3

MeOTf (equiv)	Base	Base equiv	Solvent	Reaction Time (h)	Results
3.5	DBMP	3.5	THF	2	100 % Conversion No column separation
3.5	methyl imidazole	3.5	THF	2	No reaction
3.5	sodium carbonate	3.5	THF	2.5	Some removal of TBS group
2	Proton Sponge	2	DCM	3	40% conversion
4	Proton Sponge	4	DCM	3	~100% conversion
5	Proton Sponge	5	DCM	3	100% conversion No separation
5	Hünigs base	5	DCM	2	No conversion Substrate recovered

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 Hünig'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



308 **297**

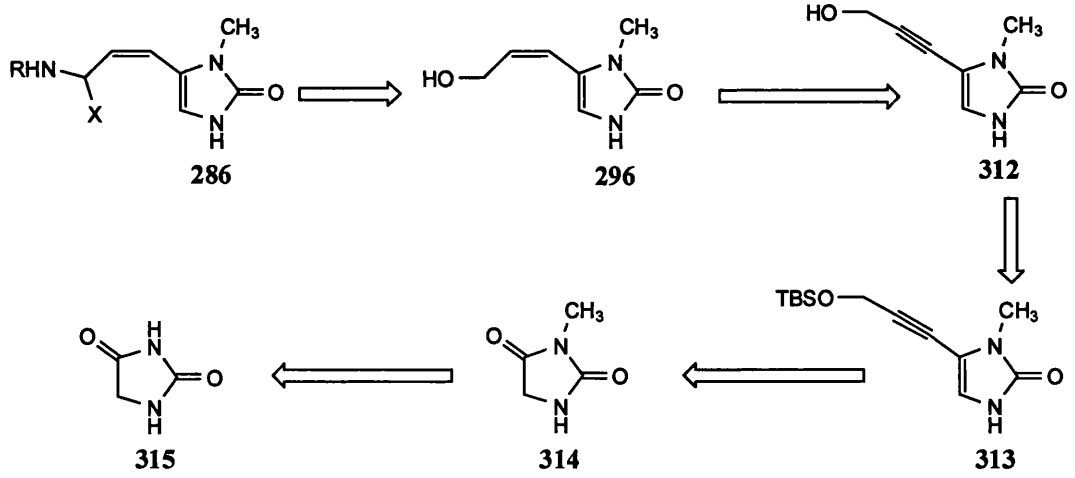
As there was little literature precedent for the reaction a clean substrate would be paramount for its investigation. As it was not possible to completely purify the methylated product **308**, an alternative strategy had to be considered for a route into the "right hand" fragment.

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.

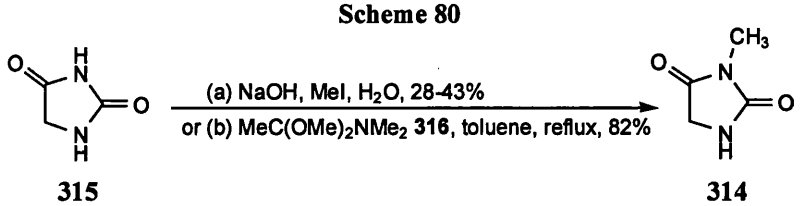
Scheme 79 outlines the alternative retrosynthetic analysis for the "right hand" imidazolone fragment **286**. Initial 3-methylation of **315** to afford **314** followed by a Grignard addition to introduce the side chain, and then side chain manipulation with introduction of the leaving group X will 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



2.4.1 Preparation of 3-Methylhydantoin

Scheme 80



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 1h, 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.

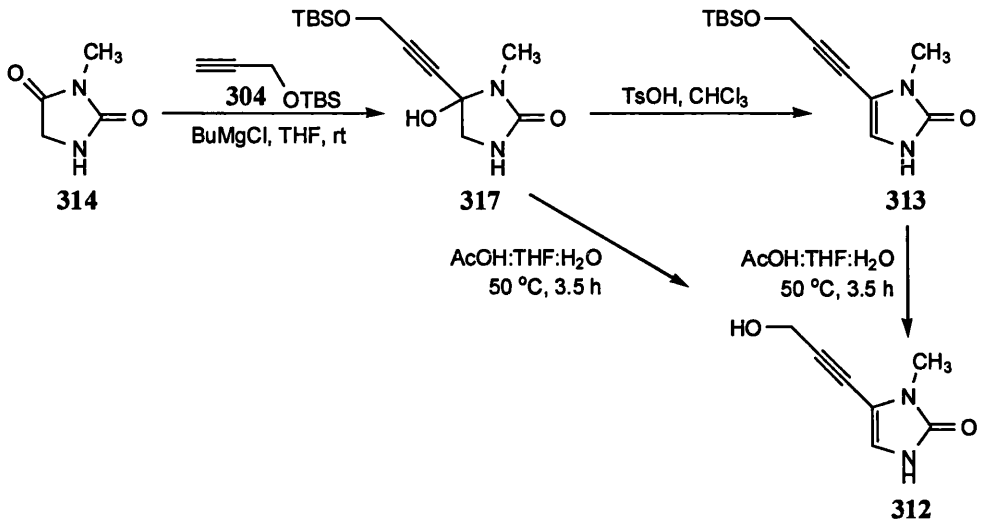
The second literature method (which was reported for the 3-benzylation of hydantoin) was next investigated; this involved deprotonation and alkylation with 1 equivalent of benzyl chloride in refluxing H_2O.[114] However methyl iodide has a significantly lower boiling point than benzyl chloride and the 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 H_2O, 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 H_2O as for the 3-benzyl product, so an extractive workup was employed. Extraction with $CHCl_3$ 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 NaCl and repeated extraction with $CHCl_3$. 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 $CHCl_3$. 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 a 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.

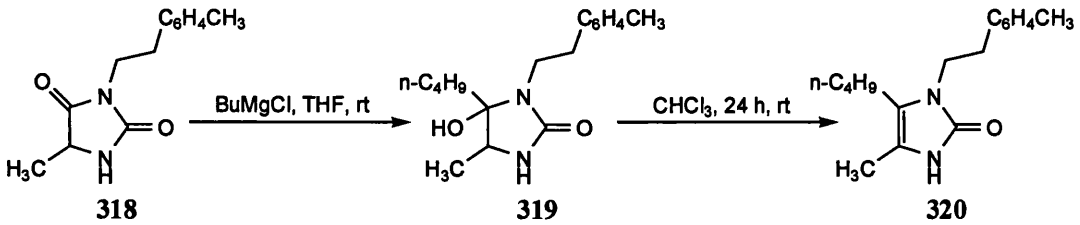
2.5 Addition of the Alkyne Side Chain

Scheme 81



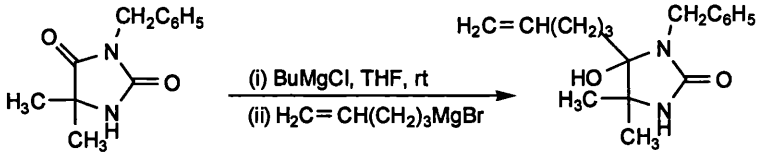
It was planned to use a Grignard reaction to introduce the alkyne side chain to initially give tertiary alcohol **317**, which we hoped could be dehydrated to give the conjugated alkene in the imidazolone ring in **313** (**scheme 81**). Kohn and co-workers[116] demonstrated that a Grignard reagent could 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**).

Scheme 82



With 5-disubstituted hydantoins, including hydantoin **321**, they were able to successfully deprotonate at N-1 with one equivalent of *n*-butylmagnesium chloride before addition of a different side chain as a Grignard reagent, to afford tertiary alcohol **322** (**scheme 83**).

Scheme 83



321 **322**

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_4Cl and extracted with Et_2O. 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 4

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

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

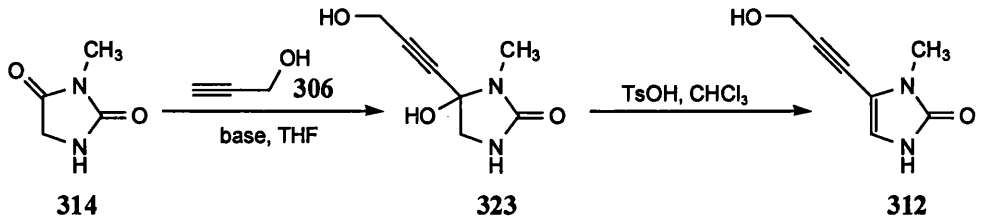
Removal of the TBS group was possible with TBAF but the high water solubility of the unprotected alcohol **312** meant that recovery after aqueous workup was low. However the use of acetic acid:THF:H_2O 3:1:1 allowed the by-products to be removed *in vacuo* and no workup was required. Silyl ether **313** was heated to 50 °C in a 3:1:1 mixture of AcOH:THF:H_2O 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_2O at 50 °C to effect the elimination and deprotection in a one-pot process to afford alcohol **312**. After the solvent was removed *in vacuo*, a suspension of the crude alcohol in Et_2O 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

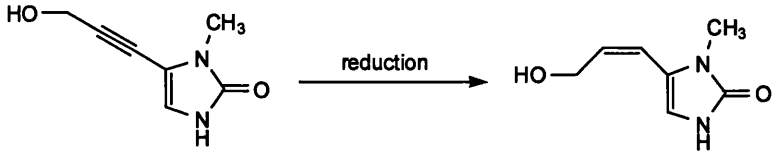


314 **323** **312**

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 ^{1}H 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 ^{1}H 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.

2.7 Reduction of the Propargylic Alcohol to the *cis*-Allylic Alcohol

Scheme 85

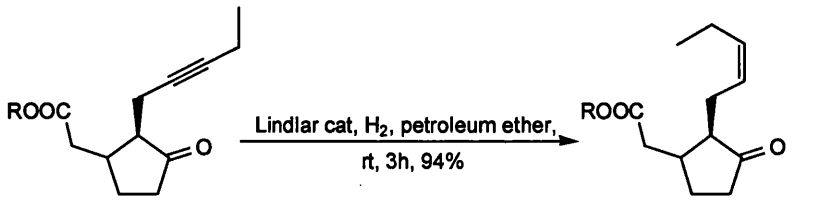


312 **296**

2.7.1 Lindlar Reduction

Several methods in the literature are reported for the reduction of alkynes selectively to *Z*-alkenes. Lindlar reduction[122] has been widely used in the literature for the reduction alkynes to *cis*-alkenes.[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**[124] **(scheme 86)**.

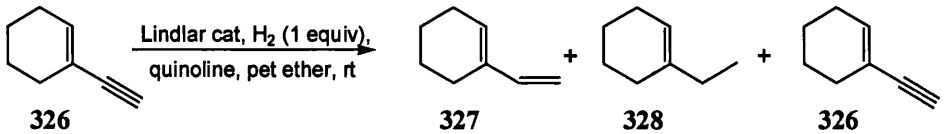
Scheme 86



324 **325 methyl jasmonate**

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[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**[126] **(scheme 87)**.

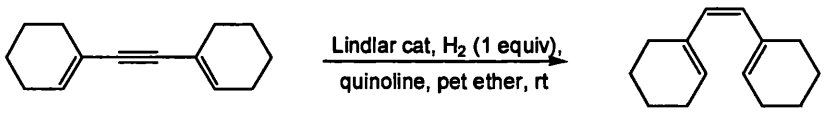
Scheme 87



326 → **327** 86% + **328** 8% + **326** 6%

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-dicyclohexenylacetylene **329** with one equivalent of hydrogen gave less than 50% of *cis*-1,2-dicyclohexenylethylene **330**[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.

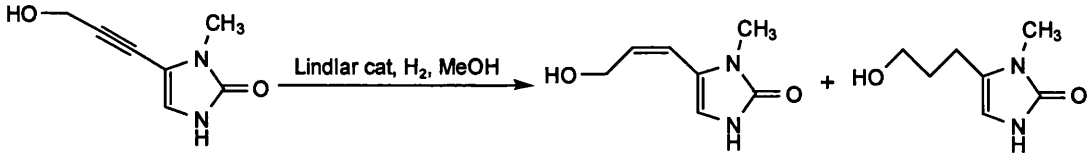
Scheme 88



329 → **330** <50%

There is some evidence to suggest that non-polar solvents can give a higher selectivity in the Lindlar reduction,[127] and additives such as quinoline[128] and potassium hydroxide[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.[130] Therefore it may not be possible to control the reaction by changing the reaction temperature.

Scheme 89



312 **296** **331: over-reduced product**

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 $CaCO_3$ with 3.5% lead poisoning in MeOH under a H_2 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 5

Entry	Scale (mg 212)	Mol % catalyst	Temperature	Time (min)	Ratio 312:296:331
1	60	10	25	60	0:0:1
2	80	10	0	15	28% **296**
3	40	5	0	10	3:6:2
4	30	5	0	120[a]	0:4:1
5	100	5	0	120	0:0:1
6	50	5	0	60[b]	0:1:1
7	40	5	0	45	0:2:1
8	30	5	-20	80[c]	2:1:0
9	40	5	-20	120	1:3:1
10	40	5	-78	300	1:0:0
11	40	5	-20	120	0:7:3[d]
12	200	5	-20	120	0:0:1

[a]TLC at 10, 20, 30, 40, 60, 90 and 120 min; [b]TLC at 30 and 60 min; [c]TLC at 60 and 80 min; [d]trace of **312** observed

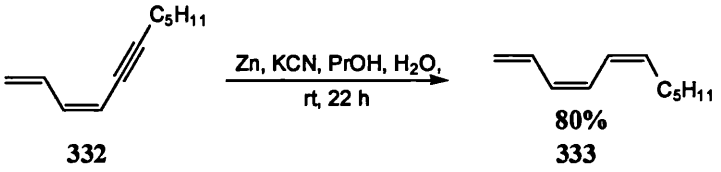
One factor that became apparent during the investigation was the effect of TLC monitoring. The H_2 atmosphere was replaced by air for removal of TLC samples, but it appeared that after reintroduction of hydrogen there was an induction period before the reaction recommenced. Hence entry 4, monitored by 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[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**[134] **(scheme 90)**.

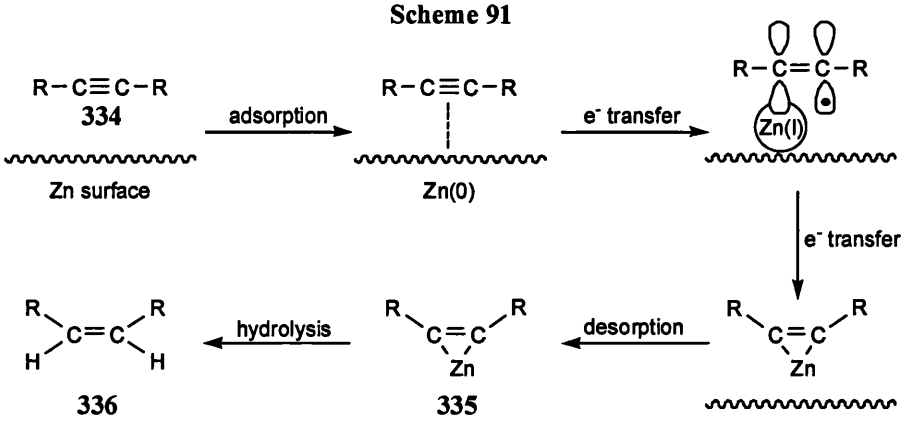
Scheme 90



332 **333**

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 π*-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**.

Scheme 91



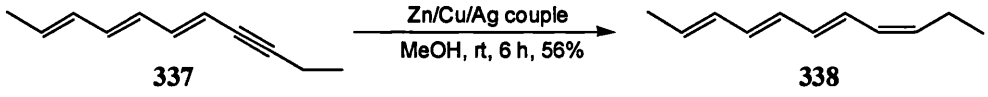
336 **335**

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[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,[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 *ca.* 50 °C. The resulting brick red coloured solid was isolated by filtration and dried *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[136], especially where other methods such as catalytic hydrogenation were unsuccessful.

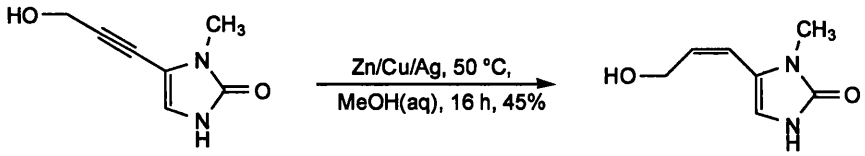
Scheme 92



337 **338**

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.

Scheme 93

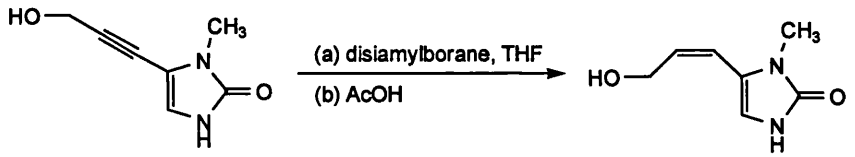


312 **296**

The zinc/copper/silver couple was prepared by the method of Avignon-Tropis,[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

Scheme 94



312 **296**

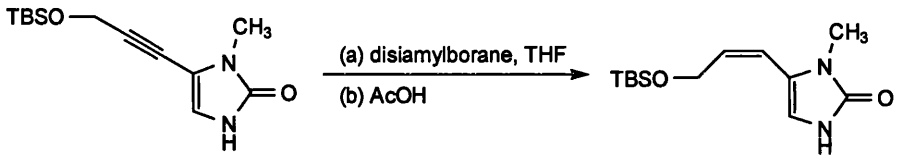
Hydroboration has been widely for the conversion of alkynes to alkenes,[137] via a vinylborane intermediate that is subsequently converted to the alkene. In the case of internal alkynes the result is a net *syn*-hydrogenation to give the *Z*-alkene. Therefore the reaction is stereoselective. Disiamylborane 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_3.THF at 0 °C[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**).

Scheme 95



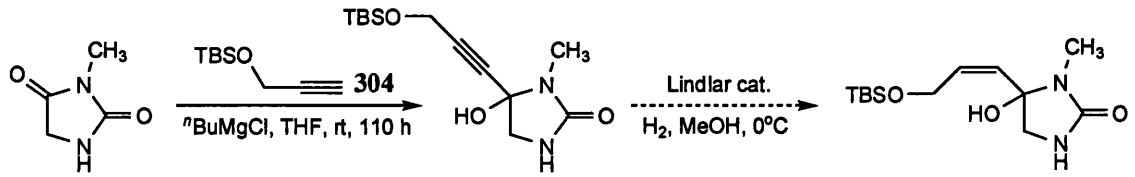
313 **339**

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**).

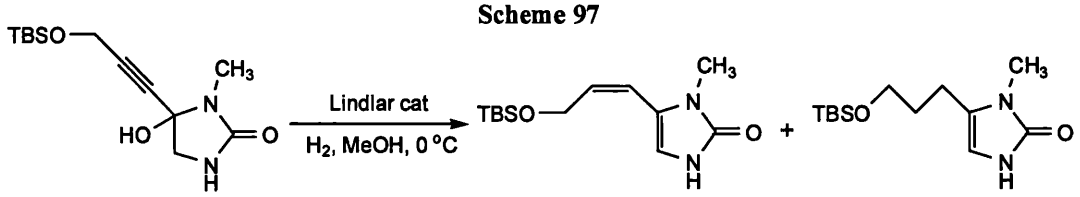
Scheme 96



314 **317** **340**

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**).

Scheme 97

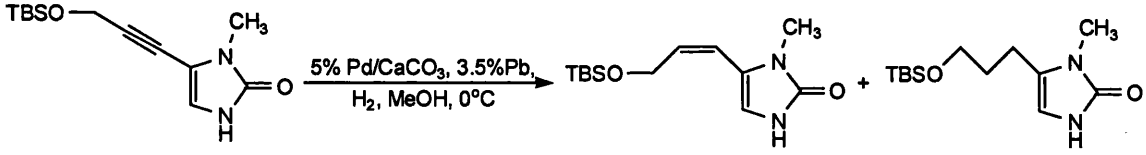


317 **339** **341**

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**.

Scheme 98



313 **339** **341**

Table 6

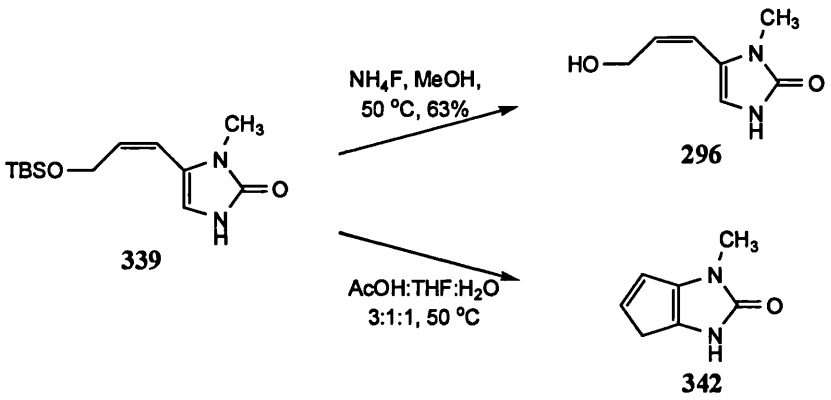
Entry	313 (mg)	H_2 (mL)	Time (min)	Yield of 339 (%)
1	95	–[a]	120[b]	62
2	203	–[a]	100[c]	78
3	503	–[a]	90	100 (**341**)
4	300	–[a]	50	38[f]
5	333	30[d]	–	56
6	277	30[e]	–	53[g]

[a]H_2 balloon utilised and volume not measured; [b]TLC at 60 and 120 min; [c]TLC at 80 and 100 min; [d]1 equiv. H_2; [e]1.2 equiv. H_2; [f]**339**:**341** ratio 1:1 by ^{1}H NMR; [g]**339**:**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 H_2 a reproducible yield of 53% of **339** could be obtained (entry 6). The extra 0.2 equivalents of H_2 added to remove all of the substrate to facilitate isolation of alkene **339** by flash chromatography on a larger scale.

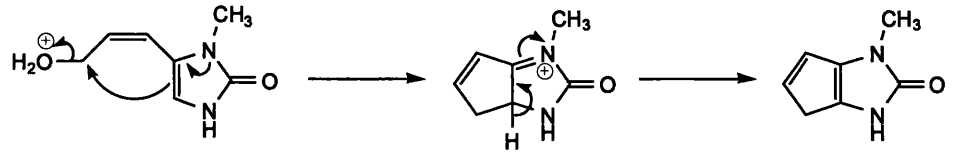
2.8 Deprotection of the Allylic Silyl Ether

Scheme 99



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:H_2O 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 H_2O 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**.

Scheme 100

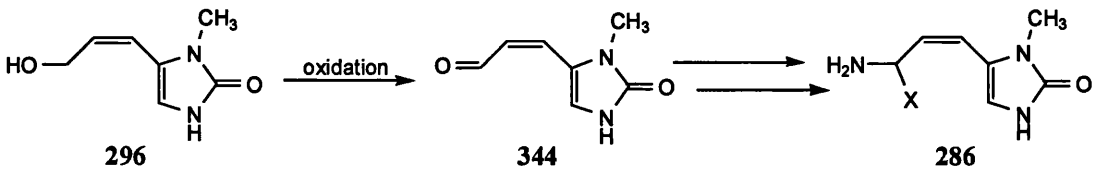


296 343 342

When NH_4F 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

Scheme 101



296 344 286

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.[139] It is a non stoichiometric material MnO_x where $1.93<x<2$, but usually stated as MnO_2. The activity of manganese dioxide depends on the method of preparation. It is commonly used in chlorinated solvents such as DCM[140] or $CHCl_3$,[141] petroleum ether[142] or benzene[143] and typically between 5 and 20 equivalents of the oxidant are required. MnO_2 can be used in polar solvents such as alcohols[144] and acetone[145] but these can deactivate the oxidant as the solvent molecules compete with the substrate for binding on the MnO_2 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 MnO_2 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 MnO_2 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 MnO_2 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 permanganate[139, 146, 147], would allow the oxidation to proceed with a smaller mass of oxidant and in turn facilitate product recovery.

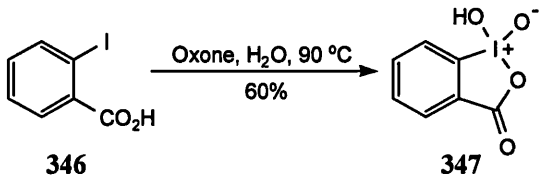
Manganese dioxide **345** was prepared in quantitative yield from manganese chloride tetrahydrate and potassium permanganate according to the method of Fatiadi.[146] However, when 10 equivalents of this active oxidant in refluxing MeOH were employed for the oxidation of **296**, again only a trace of the aldehyde was observed by ^1H NMR. It was therefore concluded that the combination of polar solvent and highly polar substrate was deactivating the MnO_2 surface and binding was occurring. Hence an alternative oxidant was sought.

2.9.2 IBX Oxidation

1-hydroxy-1,2-benziodoxolin-3(1*H*)-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-workers[149] (**scheme 102**) involving the oxidation of 2-iodobenzoic acid **346** by

Oxone® ($2KHSO_5$-$KHSO_4$-K_2SO_4) in water at 70 °C. This method for IBX preparation by oxidation with Oxone is superior to that of Greenbaum[150] where carcinogenic potassium bromate is utilised in hot aqueous sulphuric acid.

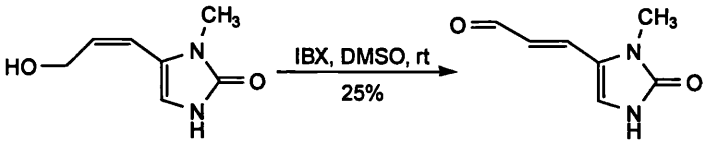
Scheme 102



346 **347**

The oxone oxidation method afforded IBX in high purity in but some adaptation of the literature procedure[149] 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-d_6 with ^{1}H NMR monitoring. A solution of IBX in DMSO-d_6 was added to allylic alcohol **296** at ambient temperature. After 3h, all of the alcohol had been consumed. However, ^{1}H 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**).

Scheme 103

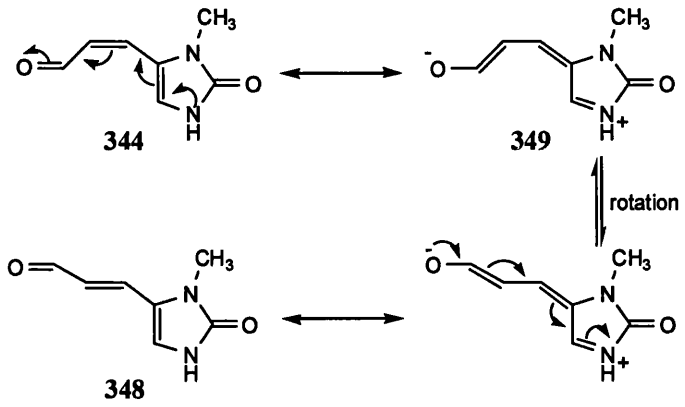


296 **348**

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

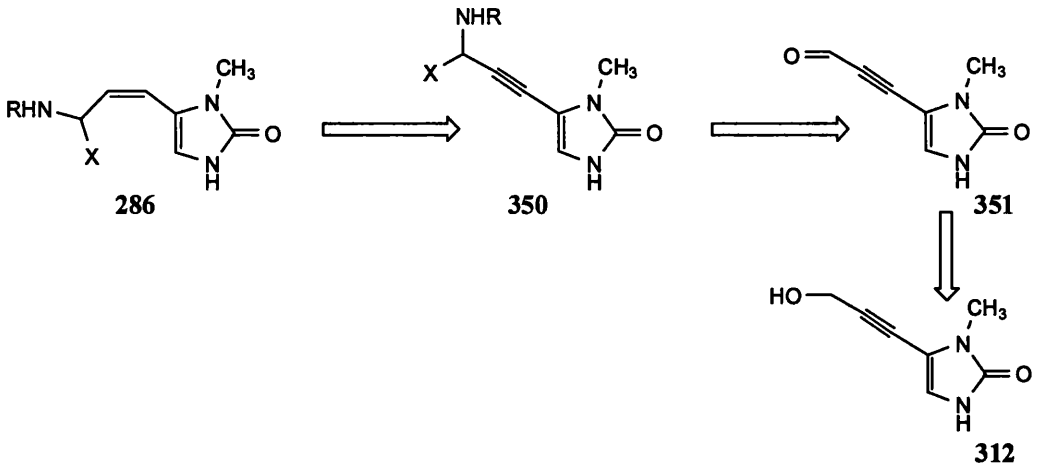


A 0.31 mmol scale reaction was carried out in DMSO in order to determine the reaction yield and after extraction from water, the *E*-allylic aldehyde **348** was isolated in 25% yield after flash chromatography. Isolation was again hampered by the high water solubility of the product.

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**).

Scheme 105



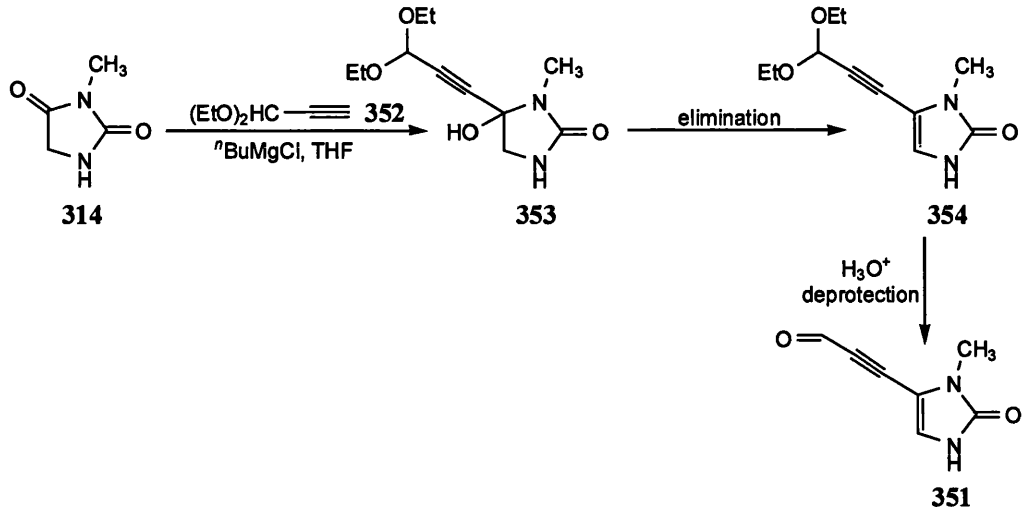
Propargylic alcohol **312** was insoluble in most of the solvents commonly used for oxidations, such as DCM and $CHCl_3$, but it was soluble to a degree in more polar solvents. Alcoholic solvents were unsuitable do to their ease of oxidation with most common oxidising agents. The alcohol was however soluble in DMSO and therefore oxidation with IBX could be attempted. A test reaction was then carried out in DMSO-d_6 and ^{1}H 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 CF_3 group. Test reactions using IBX in trifluoroethanol showed aldehyde product by ^{1}H NMR. However on a larger scale the results were not reproducible.

2.11 Application of the Diethylacetal as a Route to the Ynal

Scheme 106



As the methods of oxidation had not been successful, an alternative route to ynal **351** was investigated. Introduction of the side chain using an alkynyl Grignard reagent derived from 3,3-diethoxylpropyne **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 7

	314 (mmol)	352 (equiv)	Base	Time (h)	T	% conversion	% yield 354
1	4.4	2	^{n}BuMgCl [a]	42	rt	0	-
2	4.4	3	^{n}BuMgCl	24	rt	50 [b]	-
3	2.2	3	^{n}BuLi	23	rt	12 [b]	-
4	1.8	3	^{n}BuMgCl	48	rt	60 [b]	4 [c]
5	1.8	3	^{n}BuMgCl	66	rt	47 [b]	-
6	4.3	10	^{n}BuMgCl	24	rt	85 [b]	-
7	8.8	3	^{n}BuMgCl	26	rt	-	14 [d,e]
8	8.9	3	^{n}BuMgCl	65	rt	-	21 [d,e]
9	1.7	3	^{n}BuMgCl	19	40	-	32 [d,e]

[a]Grignard reagent added to a solution of **314** in THF; [b]estimated from ^{1}H NMR integrals; [c]4% obtained after recrystallisation; [d]Crude eliminated by stirring with silica/$CHCl_3$ overnight; [e]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

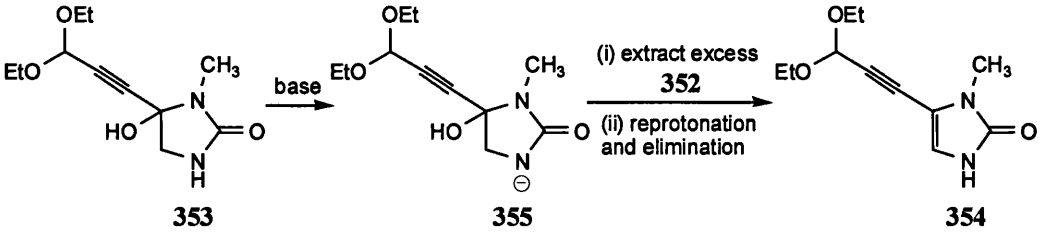
previously with the addition of silyl ether **304**, the reaction did not go to completion. After work up the excess alkyne could not be removed in vacuo to give the tertiary alcohol product **353** as a solid. Instead the crude tertiary alcohol product was a tarry material, containing a solid, which 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 H_2O 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**).

Scheme 107



353 **355** **354**

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 Et_2O. ^1H NMR of these Et_2O 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.

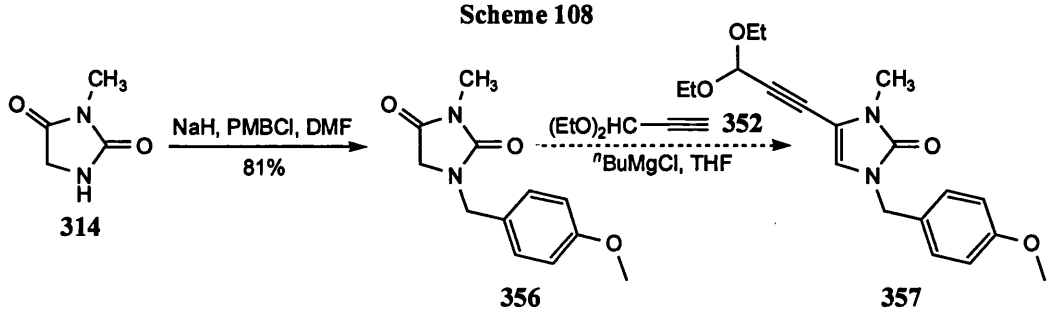
2.12 A New Approach - Protecting Group Strategy

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**).

Scheme 108

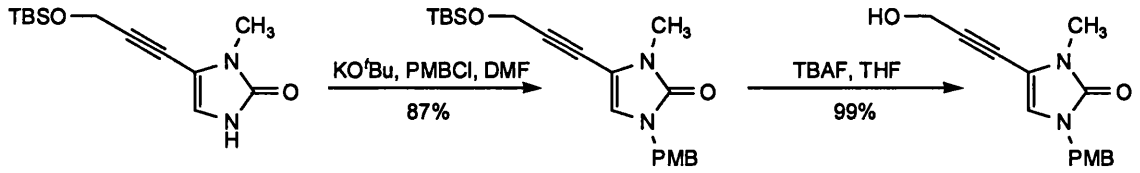


Attempts to add the diethyl acetal Grignard reagent derived from **352** however failed to give any product by ^{1}H NMR when using the same conditions as for the addition to the unprotected hydantoin.

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.

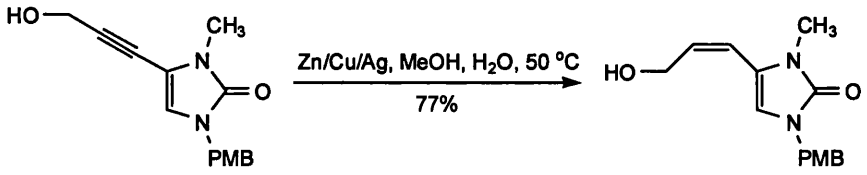
Scheme 109



313 **358** **359**

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**).

Scheme 110

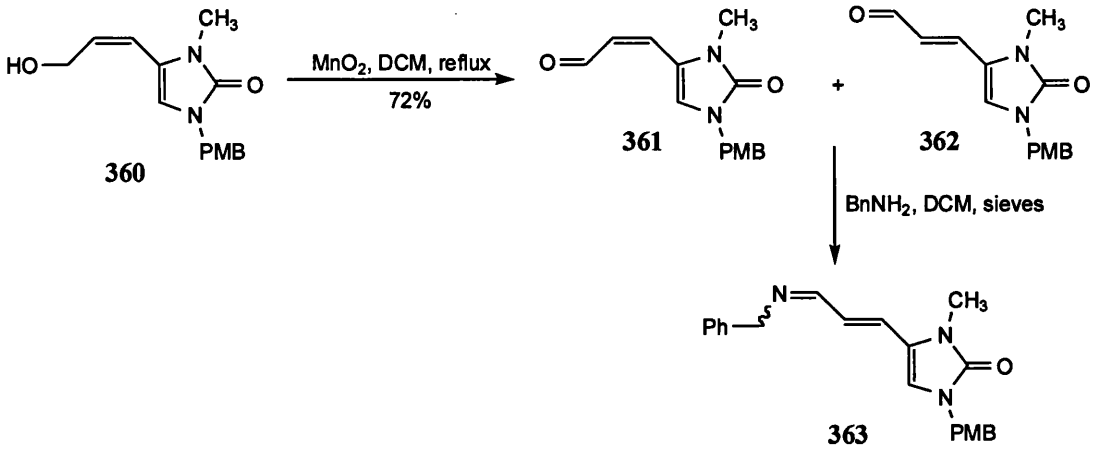


559 **360**

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.

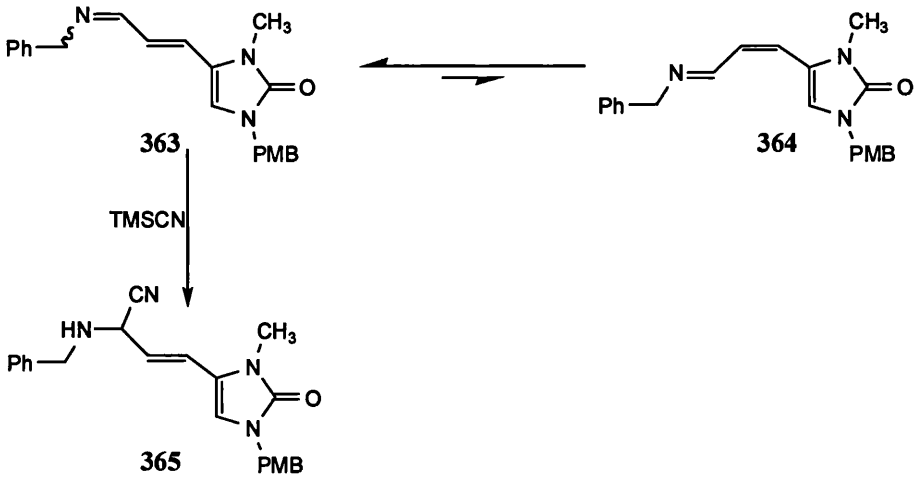
Scheme 111



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 trimethylsilylcyanide (TMSCN) (**scheme 112**).

Scheme 112



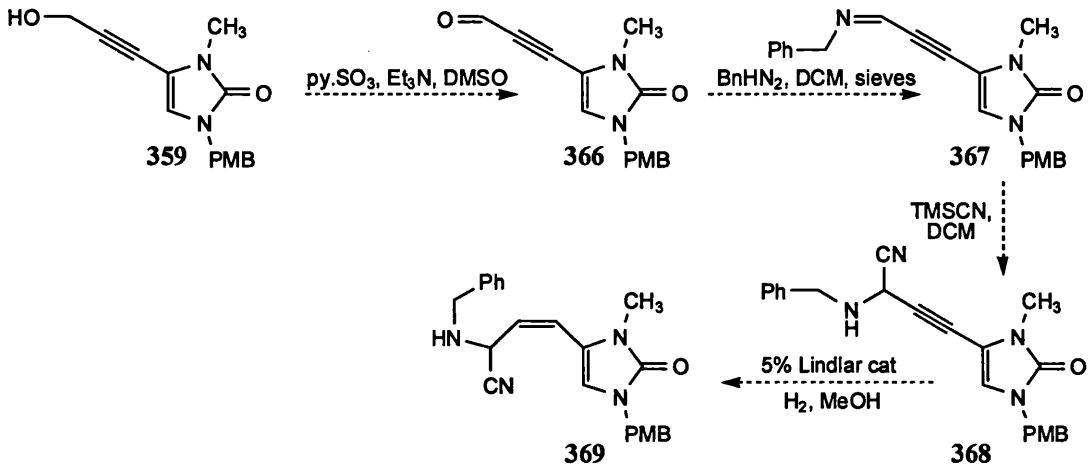
However reaction of imine **363** with TMSCN and formation of the α-aminonitrile functionality in **365** would "trap" the undesired (*E*)-isomer of the product as the imine

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



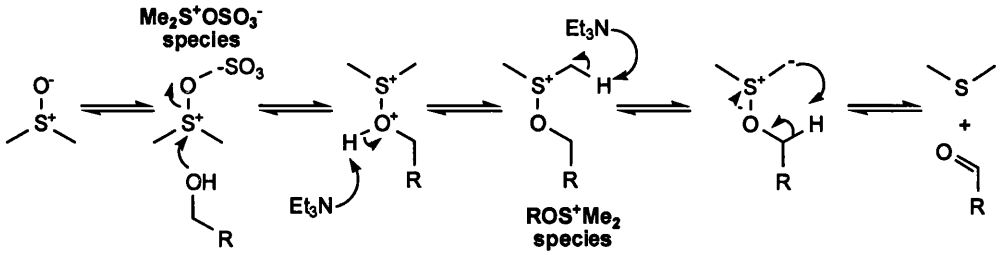
Oxidation of propargylic alcohol **359** and imine formation from the resulting aldehyde **366** and benzylamine will allow a cyanide leaving group to be introduced before the alkyne reduction to afford the "right hand" imidazolone fragment **369**.

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_3N. The Parikh-Doering oxidation[152] involves initial formation of an $Me_2S^+OSO_3^-$ complex from sulfur trioxide and DMSO,[153] which upon addition of an alcohol and Et_3N forms the ROS^+Me_2 species. This intermediate is then deprotonated

by Et_3N 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.

Scheme 114

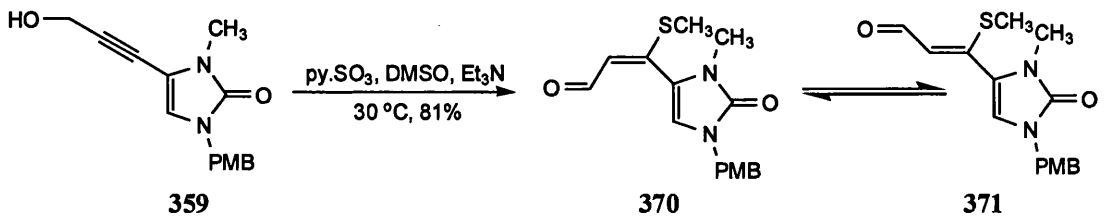


The advantage of the Parikh-Doering oxidation over other methods is that only near-ambient temperatures are required. Sulfur trioxide is commercially available as its complex with pyridine, which is an easy to handle solid. The formation of by-products is also decreased and the reaction yields are comparable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

Scheme 115

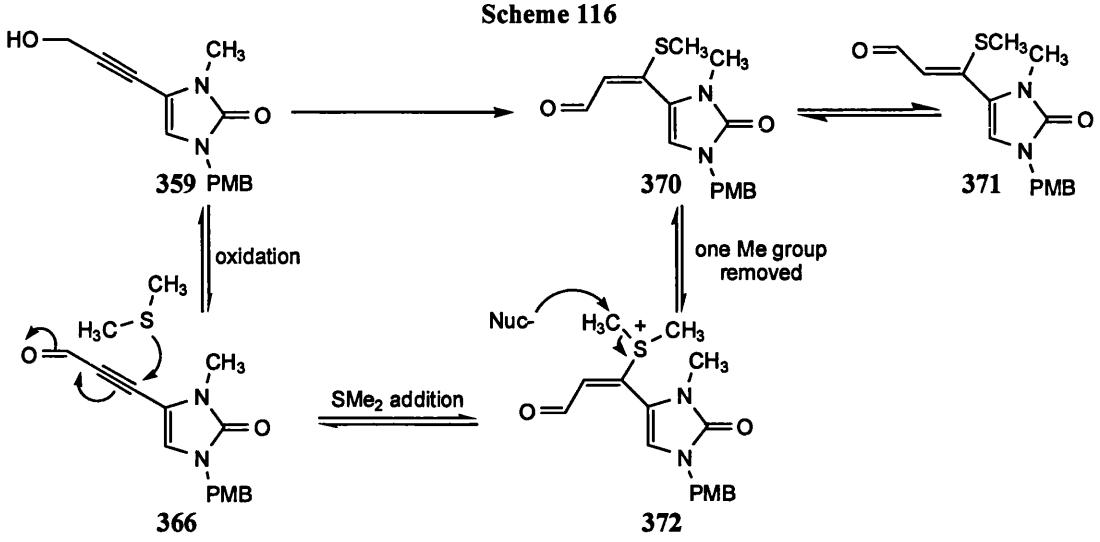


359 **370** **371**

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**

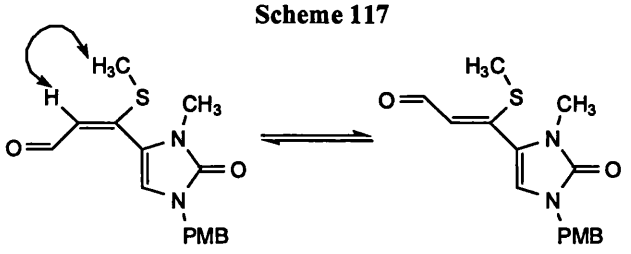
(**Scheme 116**). A nucleophile, such as pyridine or triethylamine, then removes one of the methyl groups to give the observed aldehyde products **370** and **371**.

Scheme 116



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)**.

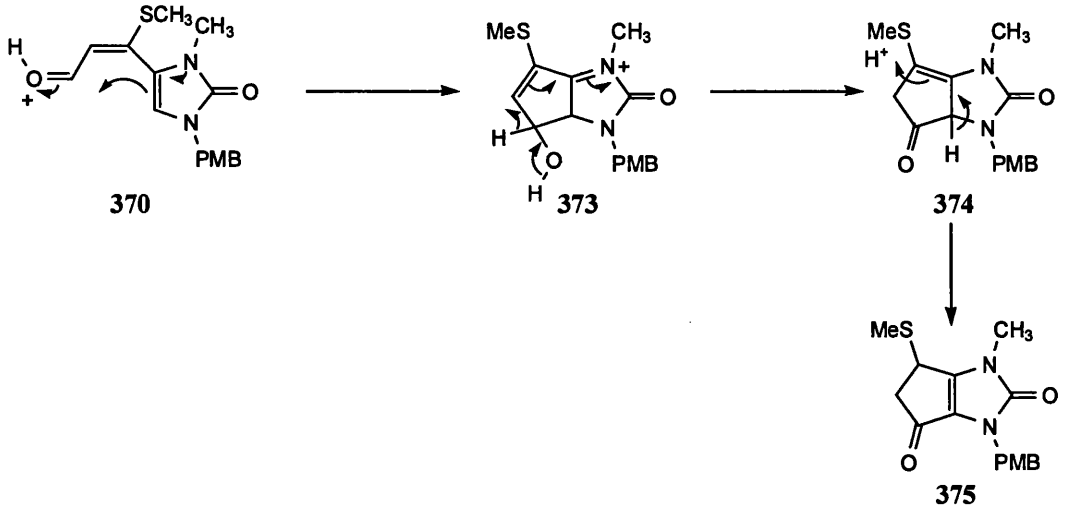
Scheme 117



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_6D_6 solution. At ambient temperature, the ratio of *E*:*Z* was 9:1, and upon heating of the ^1H 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)**.

Scheme 118

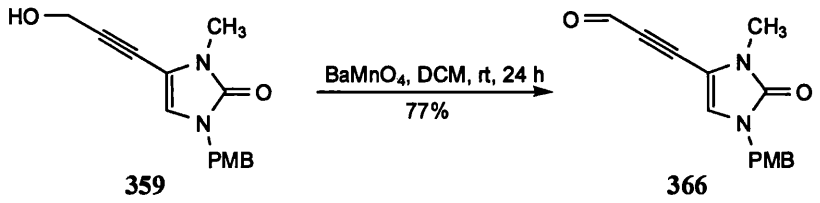


Although not expected, this result was interesting. In the cyclisation mechanism a cation is formed on the aldehyde oxygen in the same position as we planned to generate an *N*-acyliminium ion in the biomimetic synthesis. The initial attack on the aldehyde by the imidazolone lone pair is analogous to 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[155] is an alternative stable Mn^{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**).

Scheme 119

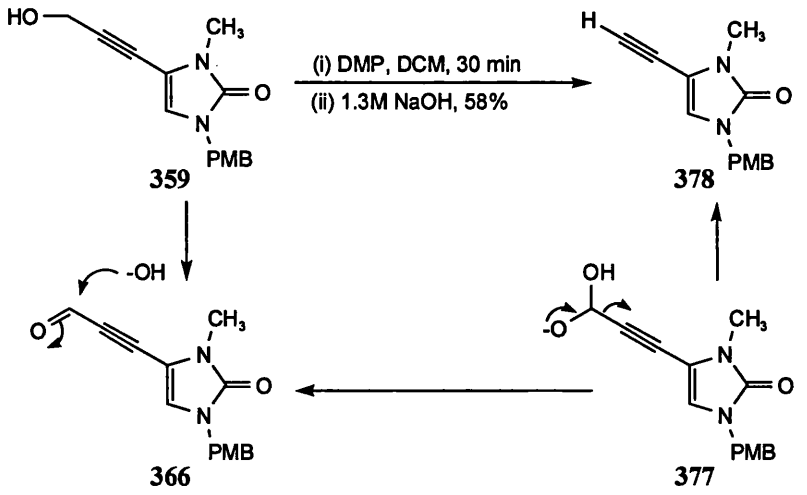


359 366

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.[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 Et_2O. 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^-, followed by loss of formic acid to afford the terminal acetylene (**scheme 120**).

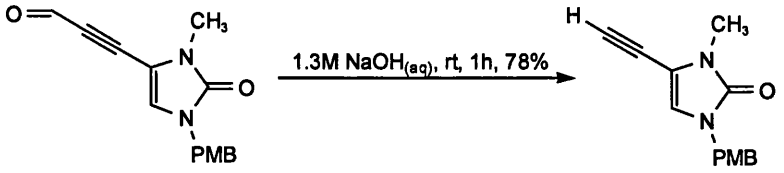
Scheme 120



359 378 366 377

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**).

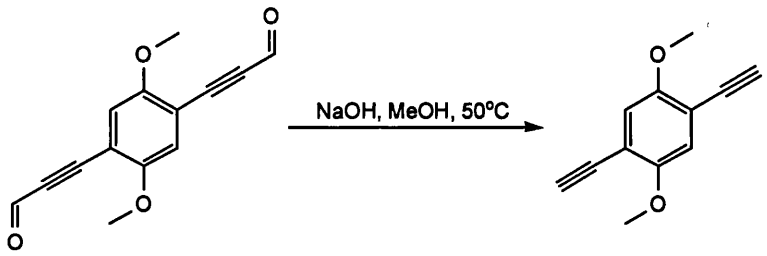
Scheme 121



366 **378**

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)**.

Scheme 122

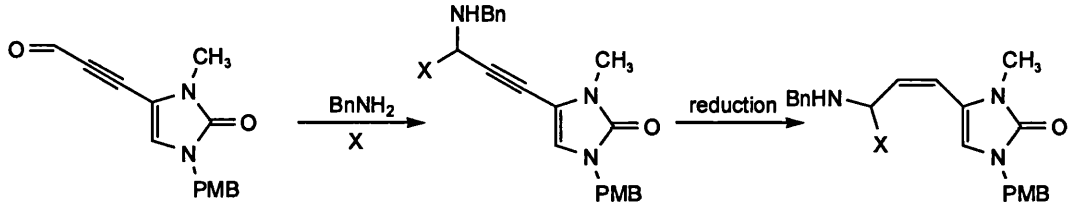


379 **380**

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)**.

Scheme 123



366

368 X=CN
381 X=benzotriazole

369 X=CN
382 X=benzotriazole

Propargylic aldehyde **366** was treated with benzylamine and trimethylsilylcyanide at 0 °C according to a literature procedure.[158] 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.

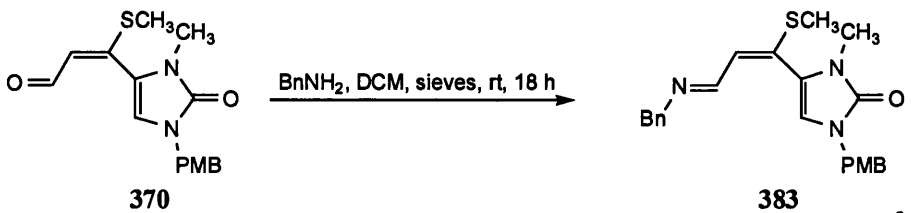
Benzotriazole can also be used as a leaving group for the generation of acyliminium ions[74]. However a one-pot reaction between the aldehyde **366,** benzylamine and benzotriazole in toluene under Dean Stark conditions also gave none of the desired product **381.**

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).**

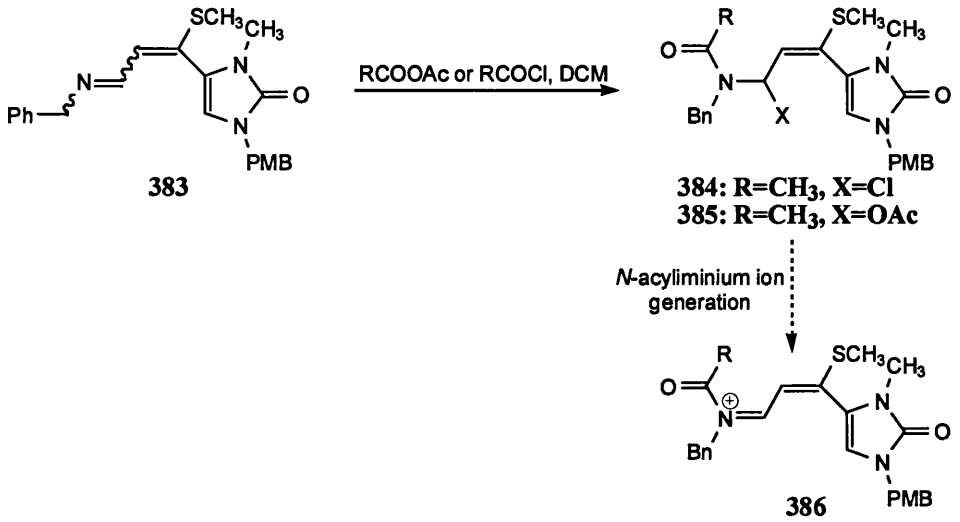
Scheme 124



370 **383**

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



383

384: R=CH3, X=Cl
385: R=CH3, X=OAc

386

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 α-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**.

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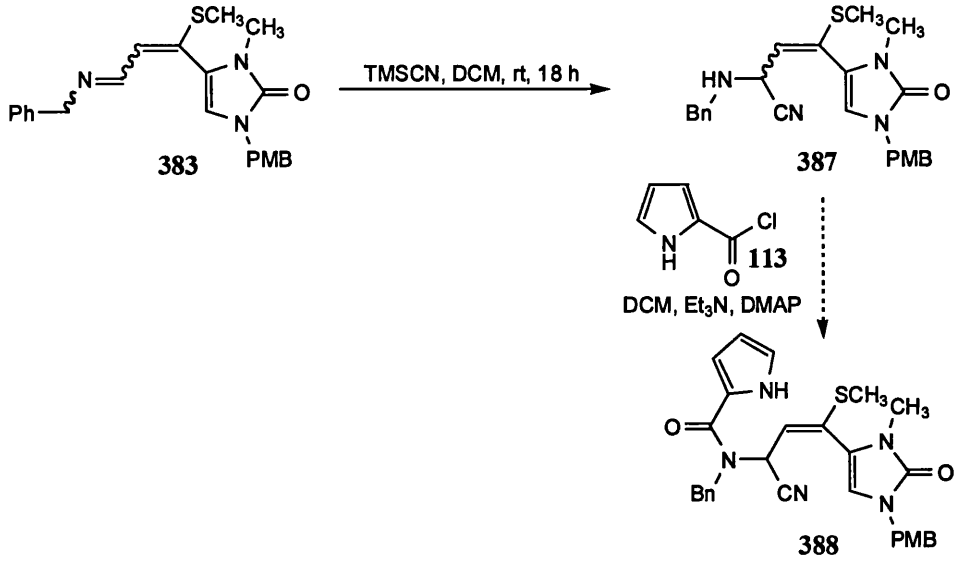
Scheme 126



Imine **383** was treated with 6 equivalents of trimethylsilylcyanide 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.

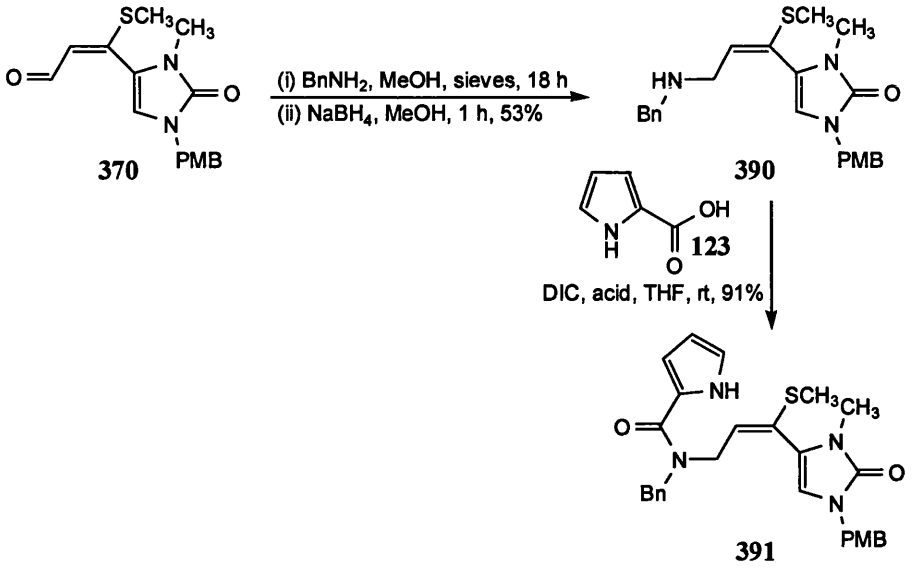
Unfortunately the α-aminonitrile **387** was not stable to flash chromatography and decomposed to a mixture of imine **383** and aldehyde **370**. Therefore crude α-aminonitrile **387** was treated with pyrrole-2-carbonyl chloride **113** and triethylamine, but none of the coupling product **388** was 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 **123** acid would afford the desired tertiary amide **391** (**scheme 127**).

Scheme 127



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.

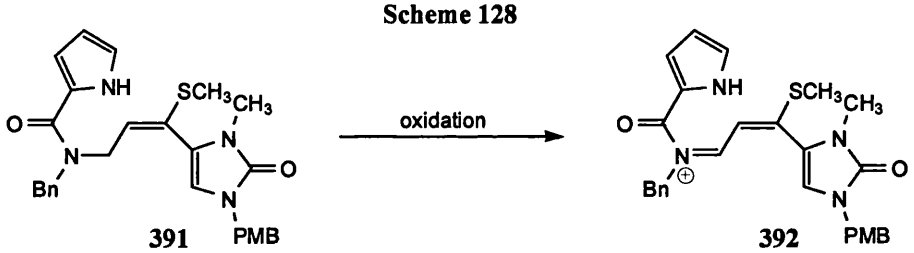
Pyrrole-2-carboxylic acid **123** was converted to the corresponding acid chloride **113** by treatment with oxalyl chloride. Amine **390** was then treated with the acid chloride and triethylamine, but no amide was observed. The addition of DMAP resulted in the formation of some of amide as broad signals 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.[95]

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 diisoproyl 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.

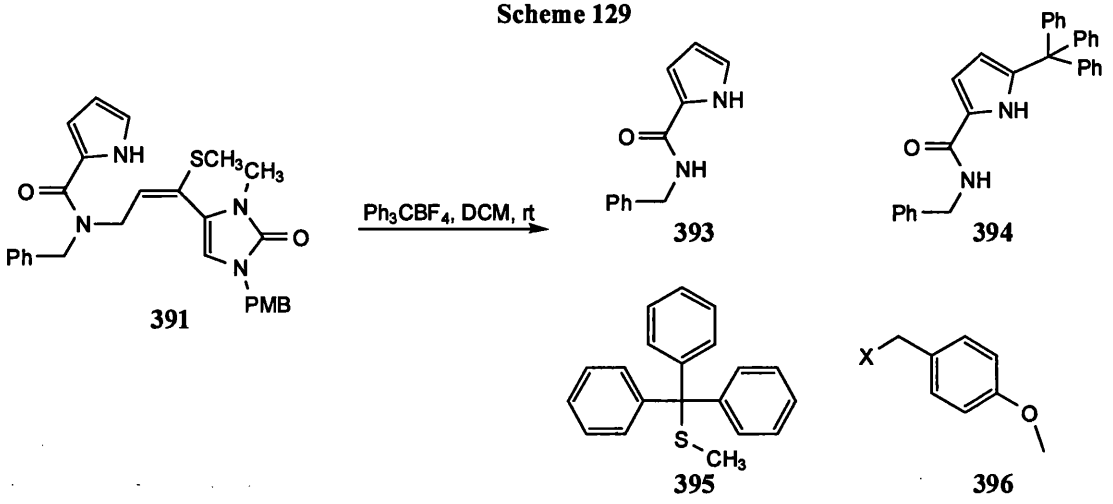
Having prepared amide **391**, we planned to carry out its oxidation to *N*-acyliminium ion **392** (**scheme 128**) and to observe subsequent reactions.

Scheme 128



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.[80] However the expected reaction was not observed. Instead several fragments of amide **391** were isolated (**scheme 129**).

Scheme 129

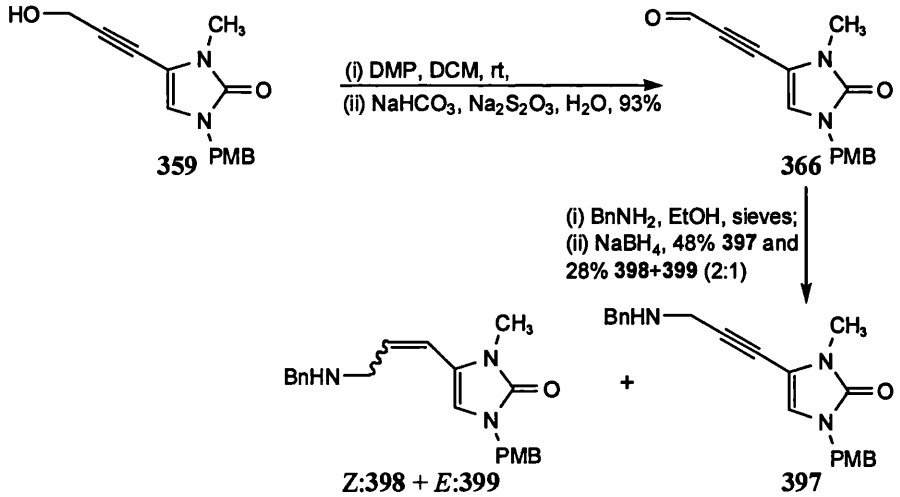


Isolation of fragment **395** indicates that the trityl group has attacked and removed the methylsulfanyl group. The trityl group has also added to the pyrrole ring fragment to afford fragment **394**. Removal of the PMB protecting group also occurred, evident by the isolation of fragment **396**, although 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 methylsulfanyl 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.[159]

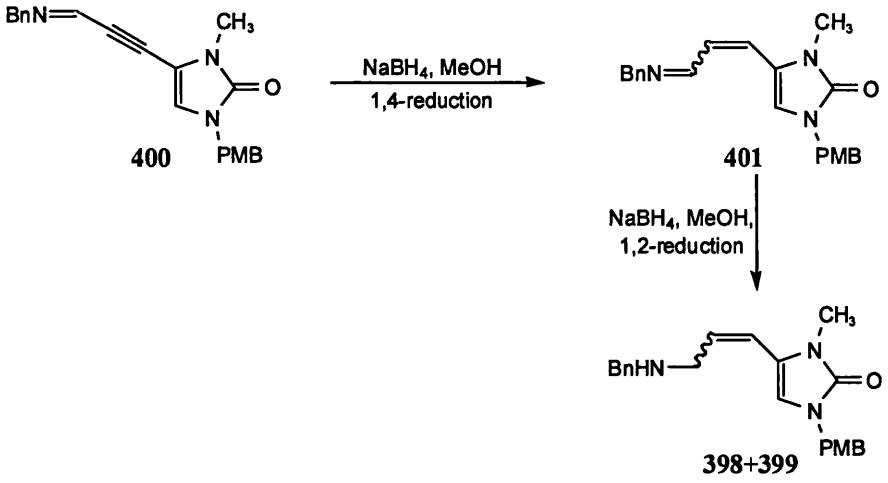
Scheme 130



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).**

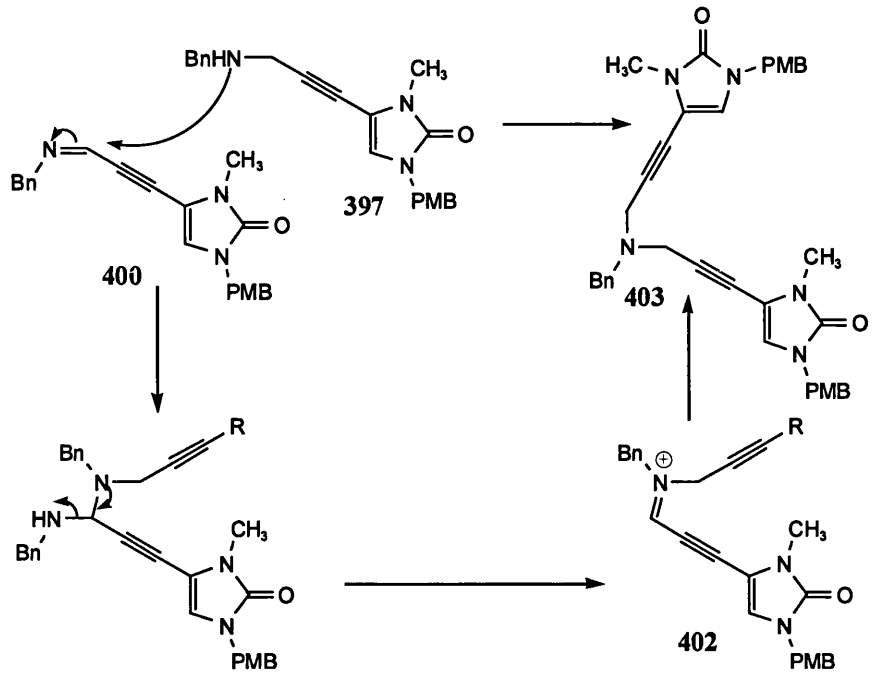
Scheme 131



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[160] but when utilised here the reaction did not proceed cleanly and the yields were low. A far superior reagent was sodium triacetoxyborohydride,[161] which has the advantage of being compatible with chlorinated solvents and therefore has a longer lifetime.

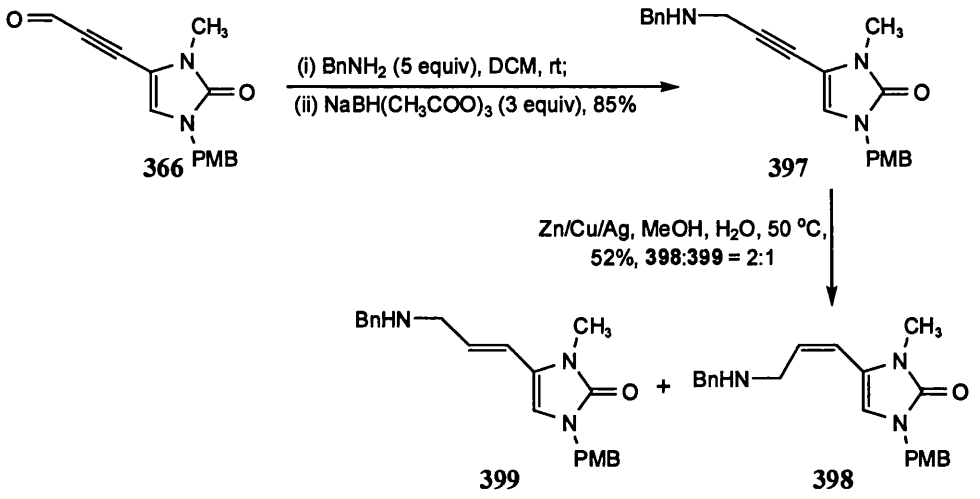
However when one equivalent of sodium triacetoxyborohydride was utilised the yield of the desired propargylic amine was low. This was due to the occurrence of a side reaction and formation of a tertiary amine **403** (**scheme 132**). This resulted from the addition of the secondary amine **397** (from the reductive amination) to the unreduced imine **400** affording iminium ion **402,** which was subsequently reduced to give the undesired tertiary amine **403.**

Scheme 132



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.

Scheme 133

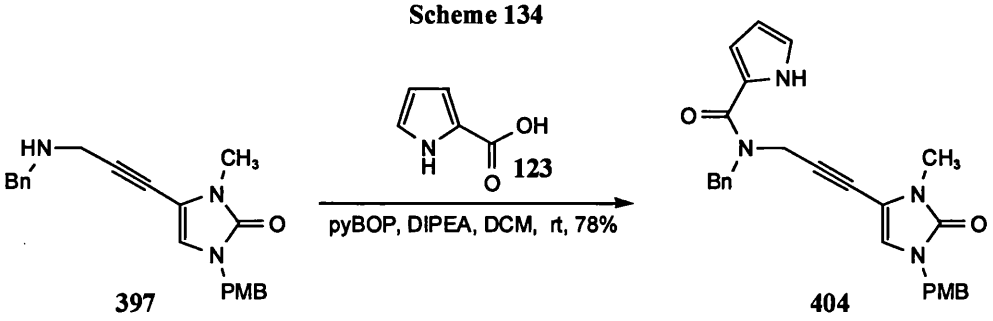


366 397 399 398

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.

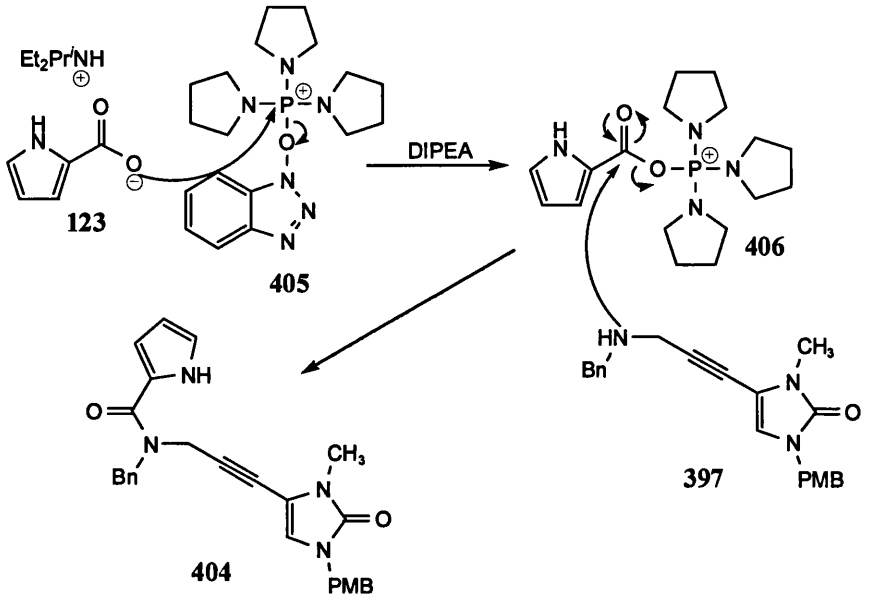
Scheme 134



397 123 404

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.

Scheme 135

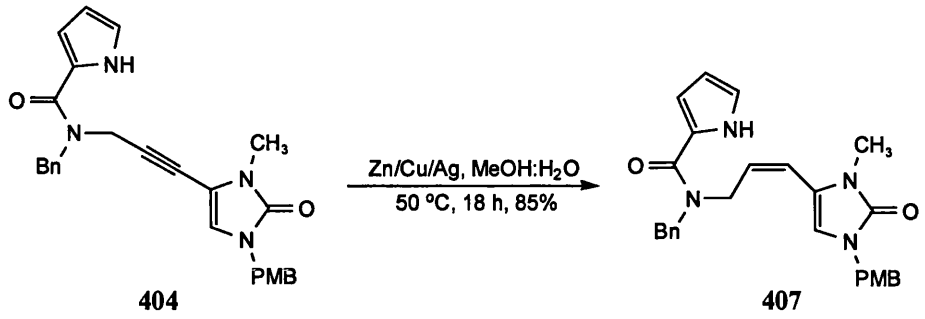


The mechanism of the pyBOP coupling involves the initial preparation of an activated ester **406** by the reaction of pyBOP **405**, carboxylic acid and a base. This activated ester species is subsequently attacked by the nucleophilic amine **397**. The complete preparation of the activated ester **406** 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%.

Scheme 136



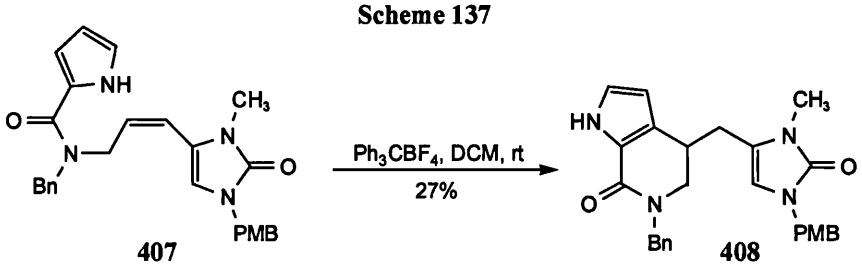
404 **407**

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 tetrafluroborate resulted in a new cyclised product **408** in 27% yield (**scheme 137**).

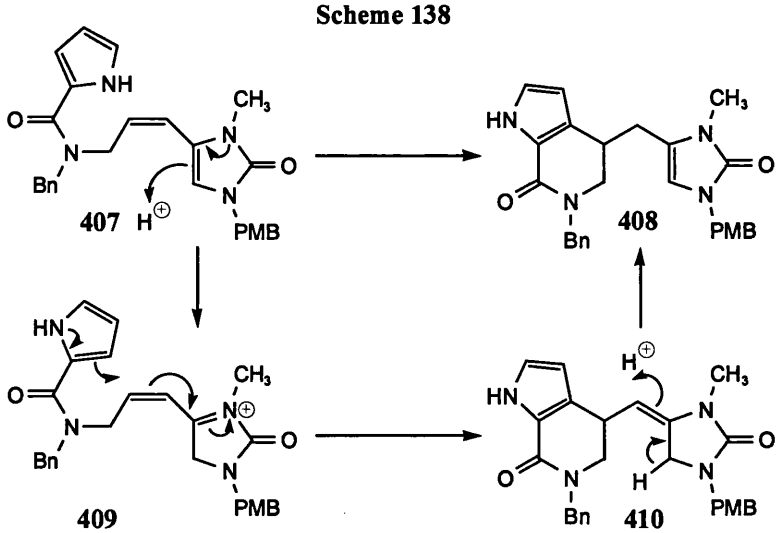
Scheme 137



407 **408**

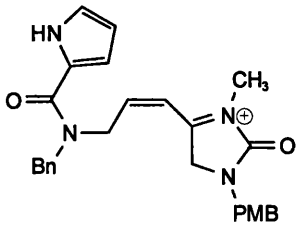
However the expected oxidation did not occur. Instead, as trityl tetrafluroborate is acidic due to the presence of fluoroboric acid, protonation of the imidazolone ring occurred, forming a different *N*-acyliminium ion **409** (**scheme 138**). The pyrrole C3 carbon then attacks this *N*-acyliminium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

Scheme 138

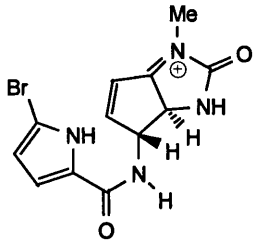


407 **408** **409** **410**

Although this reaction does not generate the predicted *N*-acyliminium ion, two observations are interesting.



409



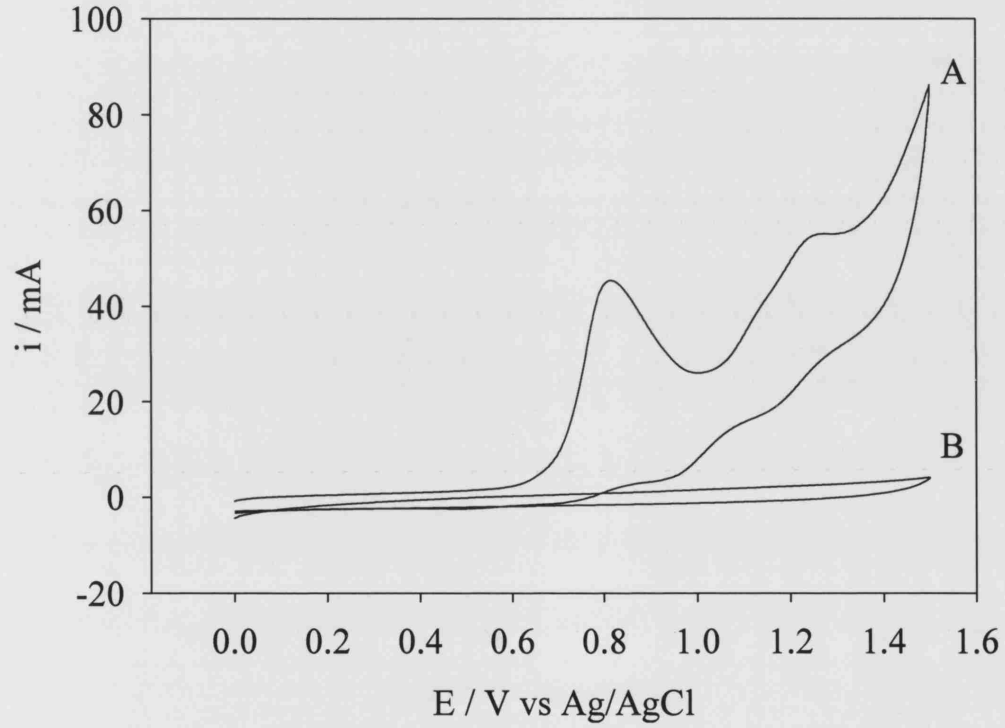
180

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 ^1H NMR occurred, no products could be characterised.

2.19 Electrochemical Oxidation

Electrochemical methods have been widely used for the generation of *N*-acyliminium ions.[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

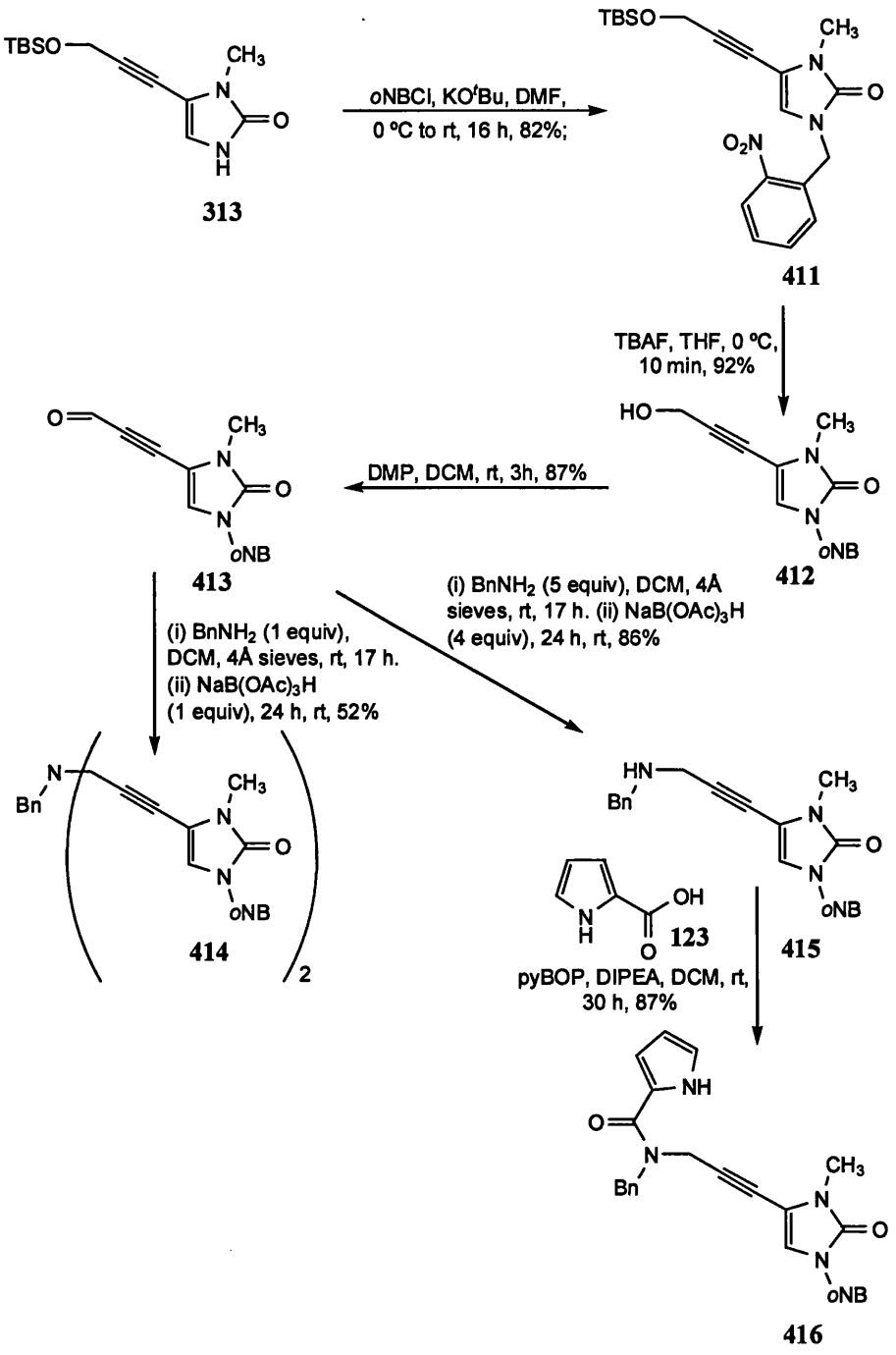


Trace B is a background scan containing only the electrolyte. Trace A consists of two traces, the top trace indicates the change in the current as the voltage was increased and the lower trace corresponds to the current change as the voltage was decreased. The two peaks in the top trace indicate that 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 ^{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

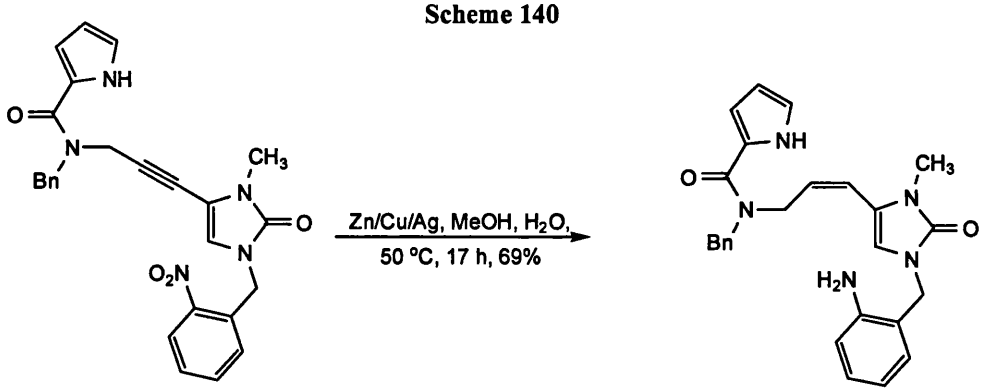


As the *p*-methoxybenzyl group can be removed using oxidative methods,[79, 165] it may not be the best choice of protecting group if oxidative methods are to be utilised for the generation of the necessary *N*-acyliminium ion in the biomimetic synthesis. Therefore the *o*-nitrobenzyl (*o*NB) group was introduced in place on the PMB group. The *o*NB group was introduced at the same stage in the synthesis as the PMB group was in the

previous route. The solubility of the *o*NB-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 *o*NB group to afford **417** (**scheme 140**).

Scheme 140



416 **417**

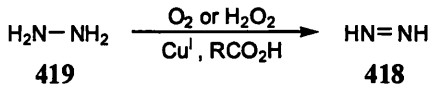
As there appeared to be no appreciable difference in the rate of alkyne reduction versus the rate of nitro group reduction using the zinc couple an alternative method for the reduction of alkyne **416** was sought. Hydroboration of alkyne **416** was attempted with disiamylborane and borane.THF complex, 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 diproportionation 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 π 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.[168-170] Generally alkynes are more reactive than alkenes to diimide reduction and the relative reactivity of the alkene decreases as the level of substitution increases.

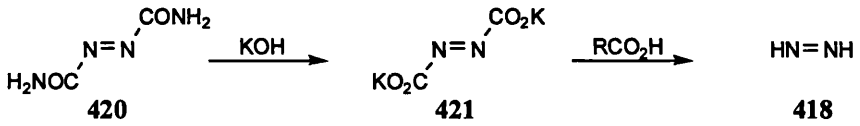
There are several procedures for the synthesis of diimide but in practise only two are widely utilised: the oxidation of hydrazine **419** by oxygen or hydrogen peroxide with copper(I) and a catalytic amount of carboxylic acid (**scheme 141**) or the reaction of potassium azodicarboxylate **421** with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

Scheme 141



419 **418**

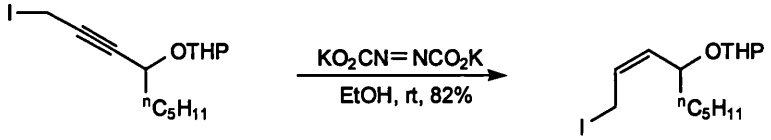
Scheme 142



420 **421** **418**

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.[171]

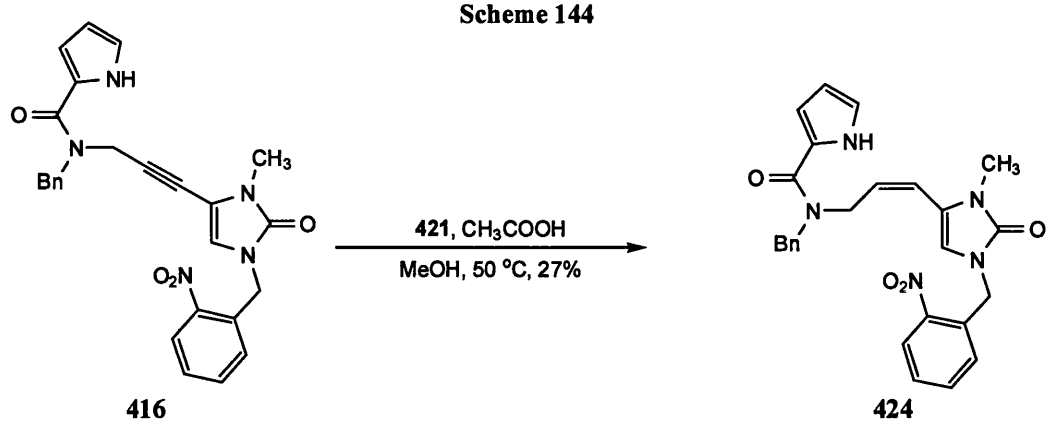
Scheme 143



422 **423**

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.[172]

Scheme 144



416 **424**

Table 8

	416 (mmol)	Solvent	421 (equiv)	T (°C)	Time (h)	% yield 429
1	0.06	MeOH	2	0	0.1	0
2	0.10	MeOH	10	20	20	0[a]
3	0.08	MeOH	10	50	40	10[b]
4	0.13	MeOH	30	50	18	27
5	0.20	MeOH	100	50	17	19

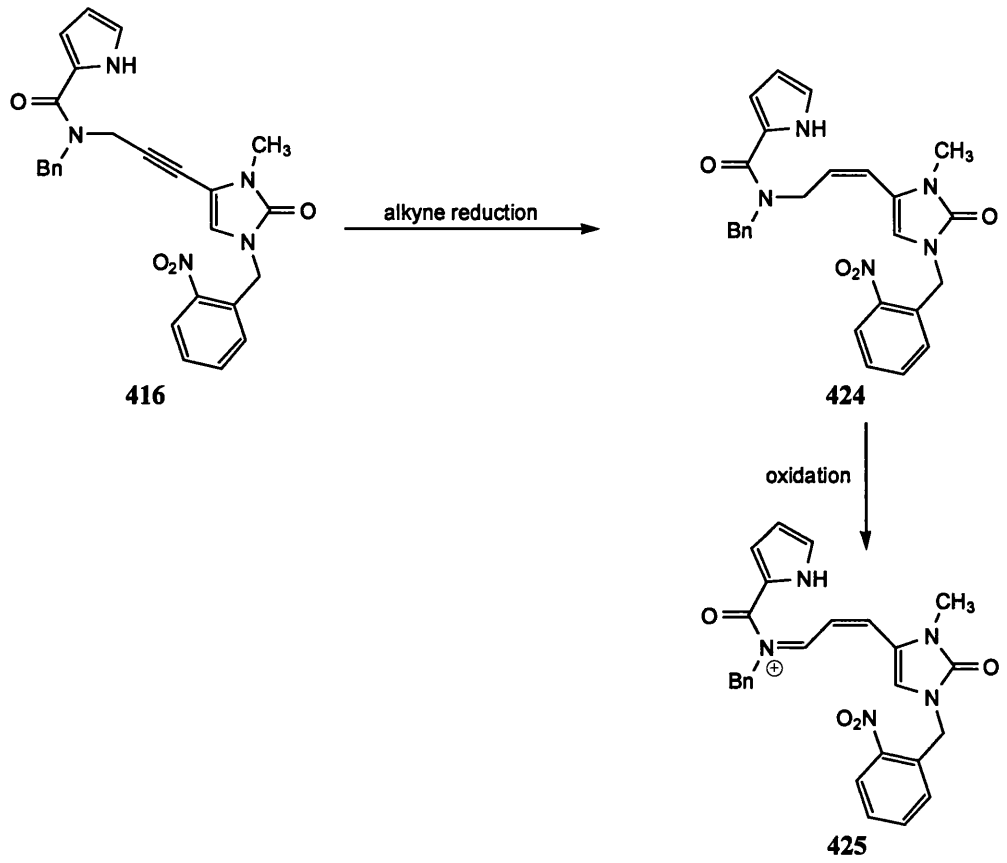
[a]Trace of product observed by ^{1}H NMR; [b]% yield estimated from ^{1}H NMR.

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 ^{1}H 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

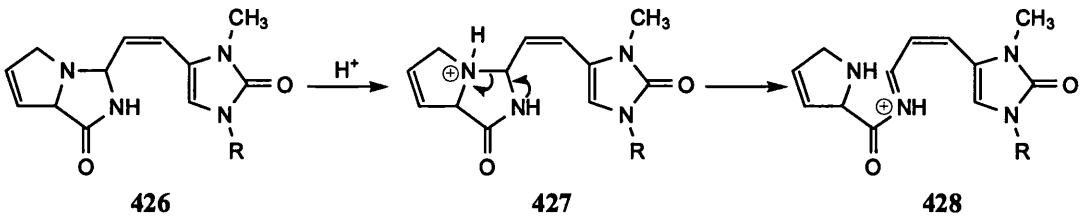
If a higher yielding method for the reduction of alkyne **416** to alkene **424** can be developed then the oxidation of **424** to form *N*-acyliminium ion **425** by chemical or electrochemical methods can be investigated and subsequent reactions of the *N*-acyliminium ion observed.



416 **424** **425**

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)**.

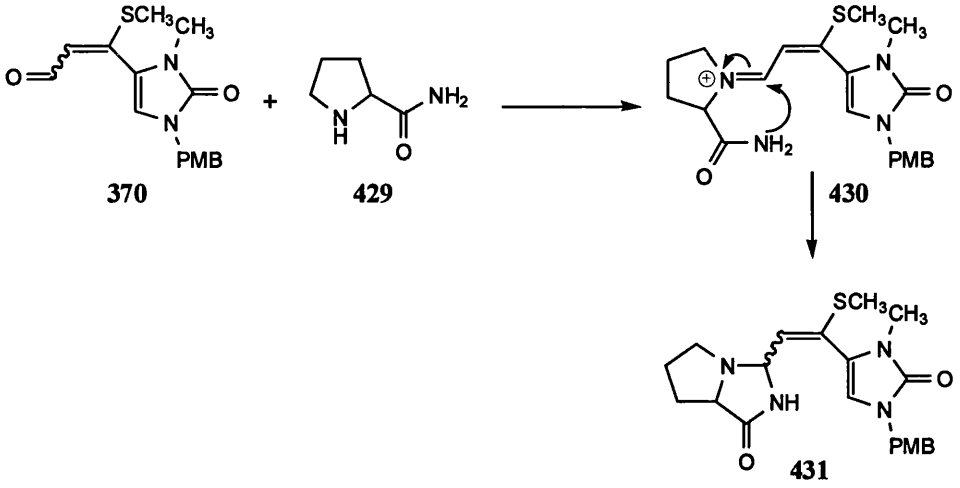
Scheme 146



426 **427** **428**

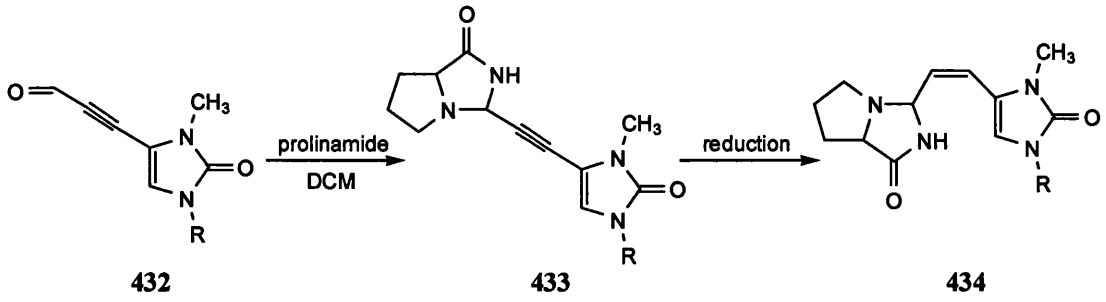
A preliminary study using methylsulfanyl aldehyde **370** and prolinamide **429** afforded a model prolinamide adduct **431**, via iminium ion **430**, as a mixture of the (*E*)- and (*Z*)-alkene isomers (**scheme 147**). However a mixture of diastereoisomers was obtained and separation using flash chromatography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

Scheme 147



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**).

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 F_{254} silica plates and visualised using UV (λ_{max} 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, $CDCl_3$ casts, KBR discs or nujol mulls on a SHIMADZU FT-IR 8700 transform spectrometer and wavenumbers of the major peaks are reported.

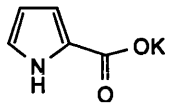
Proton NMR spectra were recorded at 300MHz on a Bruker AMX300 spectrometer, at 400MHz on a Bruker AMX400 spectrometer or at 500MHz on a Bruker AVANCE500 spectrometer. Chemical shifts are quoted in parts per million (ppm) and are referenced to the residual solvent peak. The following abbreviations are 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.

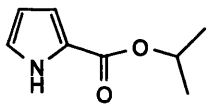
3.2 Experimental Procedures

Potassium pyrrole-2-carboxylate (285)[95]



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 *in vacuo* to give potassium pyrrole-2-carboxylate **285** (2.63 g, 17.6 mmol, 98%) as a white amorphous solid, mp 154 °C, ν_{max} **(nujol)** 4000 (NH stretch), 1556 (C=O stretch), 1105 (CO stretch), 1076 (CO stretch), 798 (CH bending), 771 (CO stretch) cm^{-1}; δ_H **(400 MHz, D_2O)** 6.83 (1H, t, *J*=2.0, 1.6 Hz, NHC<u>H</u>), 6.61 (1H, dd, *J*=3.5, 1.3 Hz, C<u>H</u>CCO$_2$K), 6.10 (1H, t, *J*=3.1, 3.0 Hz, NHCHC<u>H</u>) ppm; δ_C **(75 MHz, D_2O)** 169.1 (C<u>C</u>O$_2$K), 127.9 (<u>C</u>CO$_2$K), 122.6 (NH<u>C</u>H), 133.6 (<u>C</u>HCCO$_2$K), 109.6 (NHCH<u>C</u>H) ppm; **m/z (FAB)** 124 (84), 104 (37), 95 (40).

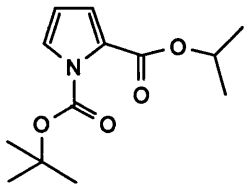
Isopropyl (1*H*)-pyrrole-2-carboxylate (286)[95]



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 *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 *in vacuo* and then diluted with water (8 mL). The product was extracted with EtOAc (3×150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give crude pyrrole-ester **286** (2.56 g) as a brown oil. ν_{max}/cm^{-1} **(thin film)** 3317 (NH stretch), 2982 (CH stretch), 745 (CH bending); δ_H **(300 Mz, $CDCl_3$)** 9.19 (1H, broad s, N<u>H</u>), 6.93-6.92

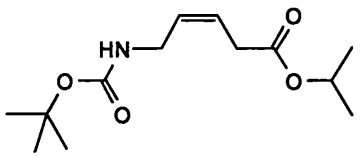
(1H, m, aromatic C<u>H</u>), 6.90-6.89 (1H, m, aromatic C<u>H</u>), 6.24 (1H, dd, *J*=6.1, 2.7 Hz, aromatic C<u>H</u>), 5.24 (1H, sep, *J*=6.2 Hz, C<u>H</u>$(CH_3)_2$), 1.32 (6H, d, *J*=6.2 Hz, CH(C<u>H</u>$_3)_2$) ppm; ***m/z* (FAB)** 153 (39%), 136 (45), 133 (58), 94 (100), 91 (58).

Pyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-isopropyl ester (287)[95]



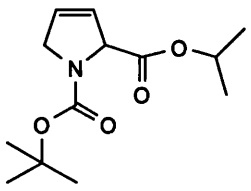
Crude pyrrole-2-carboxylic acid isopropyl ester **286** (2.56 g) was diluted in dry THF (80 mL). The solution was cooled to 0 °C, sodium hydride (60% in mineral oil, 1.35 g, 33.4 mmol) was added portionwise with stirring and the solution allowed to warm to ambient temperature. After 3 h, di-*tert*-butyl 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_2O (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. **ν_{max}/cm^{-1} (thin film)** 2982 (CH stretch), 1724 (broad, 2×C=O stretch), , 775 (aromatic CH bending), 746 (aromatic CH bending); **δ_H (300 MHz, $CDCl_3$)** 7.26 (1H, dd, *J*=3.1, 1.7 Hz, NC<u>H</u>CH), 6.77 (1H, dd, *J*=3.5, 1.7 Hz, NCHCHC<u>H</u>), 6.12 (1H, m, NCHC<u>H</u>CH), 5.14 (1H, sept, *J*=6.2 Hz, C<u>H</u>$(CH_3)_2$), 1.56 (9H, s, C(C<u>H</u>$_3)_3$), 1.31 (6H, d, *J*=6.3, CH(C<u>H</u>$_3)_2$) ppm; **δ_C (75 MHz, $CDCl_3$)** 160.3 (N<u>C</u>$O_2C(CH_3)_3$), 148.4 (<u>C</u>$O_2CH(CH_3)_2$), 126.4 (N<u>C</u>HCH), 126.1 (N<u>C</u>$CO_2CCH(CH_3)_3$), 120.3 (NCHCH<u>C</u>H), 109.9 (NCH<u>C</u>H), 84.6 (CO_2<u>C</u>$(CH_3)_3$), 68.2 (<u>C</u>H$(CH_3)_2$), 27.7 (C(<u>C</u>H$_3)_3$), 21.8 (CH(<u>C</u>H$_3)_2$) ppm; ***m/z* (FAB)** 254 (MH^+, 15%), 253 (15), 198 (100), 156 (38), 153 (53), 138 (41), 111 (25); **HRMS** calcd. for $C_{13}H_{19}NO_4$ (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 NH_4Cl 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 $MgSO_4$ 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; ν_{max}**/cm^{-1} (thin film)** 1670 (C=O stretch), 1640 (C=C stretch), 1627 (C=O stretch); δ_H **(300 MHz, $CDCl_3$)** 5.71-5.54 (2H, m, C<u>H</u>=CH and CH=C<u>H</u>), 4.97 (1H, sept, *J*=6.3 Hz, C<u>H</u>$(CH_3)_2$), 4.58 (1H, broad s, N<u>H</u>), 3.71 (2H, broad t, *J*=5.9 Hz, NHC<u>H</u>$_2$CH=CH), 3.05 (2H, d, *J*=6.8 Hz, CH=CHC<u>H</u>$_2$), 1.39 (9H, s, C(C<u>H</u>$_3)_3$), 1.18 (6H, d, *J*=6.3 Hz, CH(C<u>H</u>$_3)_2$) ppm; δ_C **(75 MHz, $CDCl_3$)** 170.8 (ester <u>C</u>=O), 155.7 (<u>C</u>=O), 129.5 and 124.2 (<u>C</u>H=CH and CH=<u>C</u>H), 79.4 (<u>C</u>$(CH_3)_3$), 68.2 (<u>C</u>H$(CH_3)_2$), 37.6 (CH_2NH), 33.3 (<u>C</u>H_2CO), 28.4 (C(<u>C</u>$H_3)_3$), 21.7 (CH(<u>C</u>$H_3)_2$) ppm; ***m/z* (+ve CI-methane)** 258 (MH^+, 37%), 216 (42), 201 (100); **HRMS** calcd. for $C_{13}H_{24}NO_4$ (MH^+): 258.1705 , found 258.1689.

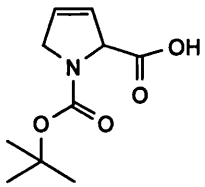
3-Pyrroline-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-isopropyl ester (289)[97]



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 NH_4Cl 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 $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (hexane:acetone, 98:2) gave 3-pyrroline **289** (351 mg, 1.37 mmol, 62%) as a colourless oil; **ν_{max}/cm^{-1} (thin film)** 2982 (CH stretch), 2936 (CH stretch), 1698 (broad, C=O stretch), 1622 (C=O stretch); **δ_H (300 MHz, $CDCl_3$)** 5.95-5.94 (1H, m, C<u>H</u>=CH), 5.68-5.67 (1H, m, CH=C<u>H</u>), 5.00 (1H, sep, *J*=6.3 Hz, C<u>H</u>$(CH_3)_2$), 4.88-4.87 (1H, m, CH=CHC<u>H</u>), 4.27-4.14 (2H, m, C<u>H</u>$_2$CH=CH), 1.44 (9H, s, C(C<u>H</u>$_3)_3$), 1.23 (6H, d, *J*=6.3 Hz, CH(C<u>H</u>$_3)_2$) ppm; **δ_C (75 MHz, $CDCl_3$)** 170.5 and 170.1 ($\underline{C}O_2CH(CH_3)_2$), 153.9 ($\underline{C}O_2C(CH_3)_3$), 129.6 and 129.5 (<u>C</u>H=CH), 125.4 and 125.3 (<u>C</u>H=CH), 80.5 and 80.3 ($CO_2\underline{C}(CH_3)_3$), 69.1 ($CO_2\underline{C}H(CH_3)_2$), 67.2 and 66.9 (CH=CH<u>C</u>H), 53.9 and 53.7 (<u>C</u>H$_2$CH=CH), 28.8 and 28.7 ($CO_2C(\underline{C}H_3)_3$), 22.2 and 22.1 ($CO_2CH(\underline{C}H_3)_2$; ***m/z* (FAB)** 254 ($MH^+$, 31%), 200 (79), 154 (97), 112 (100); **HRMS** calcd. for $C_{13}H_{21}NO_4$ (MH^+) 256.1549, found 256.1560.

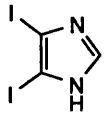
2,5-Dihydropyrrole-1,2-dicarboxylic acid 1-*tert*-butyl ester (295)[95]



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 $MgSO_4$ and concentrated *in vacuo* to give carboxylic acid **295** (80.5 mg, 0.38 mmol, 98%) as a white amorphous solid, mp 112 °C; **ν_{max}/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); **δ_H (300 MHz, $CDCl_3$)** 9.04 (1H, broad s, O<u>H</u>), 6.02 (1H, broad d, C<u>H</u>CO_2H), 5.86 (1H, broad d, CH=C<u>H</u>CH), 5.08 (1H, broad d, C<u>H</u>=CHCH), 4.28 (2H, broad d, C<u>H</u>$_2$CH=CH), 1.52 (9H, broad d, $CO_2C(C\underline{H}_3)_3$ ppm; **δ_H (400 MHz, DMSO-d_6,**

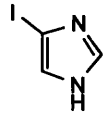
383 K) 6.01 (1H, dq, *J*=6.3, 2.2 Hz, C<u>H</u>CO_2H), 5.78 (1H, dq, *J*=6.3, 2.3 Hz, CH=C<u>H</u>CH), 4.82 (1H, tt, *J*=4.3, 2.2 Hz, C<u>H</u>=CHCH), 4.10 (2H, dt, *J*=4.2, 2.2 Hz, $C\underline{H}_2$CH=CH), 1.42 (9H, s, $C(C\underline{H}_3)_3$) ppm; δ_C **(75 MHz, $CDCl_3$)** 175.7 and 173.7 ($\underline{C}O_2H$), 155.4 and 153.6 ($\underline{C}O_2C(CH_3)_3$), 129.8 and 128.7 (<u>C</u>H=CH), 124.7 and 124.4 (CH=<u>C</u>H), 81.5 and 80.8 ($CO_2\underline{C}(CH_3)_3$), 66.4 and 66.3 (CH=CH<u>C</u>H), 53.8 and 53.4 ($\underline{C}H_2$CH=CH), 29.7 and 28.4 ($CO_2C(\underline{C}H_3)_3$) ppm; ***m/z*** **(FAB)** 252 (30%), 158 (36), 147 (50), 136 (36), 112 (50), 97 (66), 95 (66), 83 (100).

4,5-Diiodo-(1*H*)-imidazole (301)[101]



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 °C (lit 189-191 °C[101]); ν_{max}**/cm^{-1} (nujol)** 1283, 1151, 955, 721; δ_H **(300 MHz, CD_3OD)** 7.64 (1H, s, C<u>H</u>) ppm; δ_C **(375 MHz, CD_3OD)** 143.0 (<u>C</u>H), 86.3 (<u>C</u>I) ppm; ***m/z*** **(FAB)** 321 (MH^+, 100%), 195 (57); **HRMS** calcd. for $C_3H_3N_2I_2$ (MH^+): 320.8386, found 320.8398.

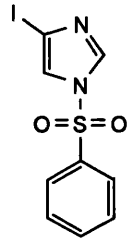
4(5)-Iodo-(1*H*)-imidazole (303)[101]



4,5-Diiodoimidazole **301** (15.1 g, 47.0 mmol) and sodium sulfite (4.7 g, 380 mmol) were heated at reflux in H_2O: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

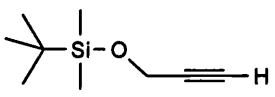
amorphous white solid, mp 133 °C (lit 136-137 °C[101]); ν_{max}/cm^{-1} **(nujol)** 1290, 1069, 955, 822, 760, 721, 619; δ_H **(300 MHz, CD_3OD)** 7.52 (1H, s, C<u>H</u>), 7.09 (1H, s, C<u>H</u>) ppm; δ_C **(75 MHz, CD_3OD)** 139.3 (<u>C</u>H), 125.4 (<u>C</u>H), 79.0 (<u>C</u>I) ppm; ***m/z*** **(FAB)** 195 (MH^+, 100%); **HRMS** calcd for $C_3H_4N_2I$ (MH^+) 194.9419, found 194.9425.

1-Benzenesulfonyl-4-iodo-(1*H*)-imidazole (299)[98]



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[98]). ν_{max}/cm^{-1} **(nujol)** 1305 (S=O stretch), 1153 (S=O stretch), 721 (CH bending); δ_H **(300 MHz, CD_3OD)** 8.07-8.06 (1H, m, C<u>H</u>), 8.00-7.96 (2H, m, 2×C<u>H</u>), 7.71-7.64 (2H, m, 2×C<u>H</u>), 7.59-7.53 (2H, m, 2×C<u>H</u>) ppm; δ_C **(75 MHz, CD_3OD)** 140.0 (<u>C</u>H), 138.7 ($SO_2\underline{C}$), 136.6 (<u>C</u>H), 131.2 (<u>C</u>H), 128.8 (<u>C</u>H), 124.5 (<u>C</u>H), 85.5 (<u>C</u>I) ppm; ***m/z*** **(FAB)** 335 (MH^+, 74%), 321 (100), 195 (91), 141 (43), 93 (48), 77 (48); **HRMS** calcd. for $C_9H_8N_2SO_2I$ (MH^+) 334.9351, found 334.9357.

***tert*-Butyldimethylprop-2-ynyloxysilane (304)[98]**



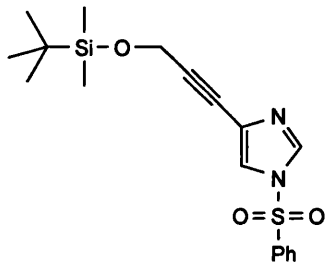
Imidazole (14.1 g, 0.2 mol) and *t*-butyldimethylchlorosilane (15.5 g, 0.1 mol) were dissolved in anhydrous DMF (50 mL) and cooled to 0 °C. Propargyl alcohol **306** (5.6 mL, 0.1 mmol) was added dropwise with stirring and the solution allowed to warm to ambient temperature. After stirring for 16 h the solution was diluted with Et_2O (250

mL), washed with H_2O (3×40 mL), dried over $MgSO_4$ 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, $CDCl_3$)** 4.19 (2H, d, *J*=2.4 Hz, CH_2), 2.25 (1H, t, *J*=2.4 Hz, HC≡C), 0.79 (9H, s, $SiC(CH_3)_3$, 0.01 (6H, s, $Si(CH_3)_2$) ppm; δ_C **(300 MHz, $CDCl_3$)** 82.8 (C≡CH), 73.2 (C≡CH), 51.9 (CH_2), 26.2 ($SiC(CH_3)_3$), 18.7 ($SiC(CH_3)_3$), -4.8 ($Si(CH_3)_2$ ppm; ***m/z*** **(FAB)** 192 (100%), 154 (37), 136 (40), 124 (22), 89 (27).

Tetrakis(triphenylphosphine)palladium(0) (305)[111]

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 Et_2O (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.

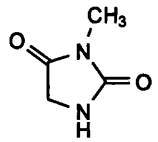
1-Benzenesulfonyl-4-[3-(*tert*-butyldimethylsilanyloxy)-prop-1-ynyl]-(1*H*)-imidazole (298)[98]



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

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 Et_2O (550 mL), washed with H_2O (3×120 mL), dried over $MgSO_4$ 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. ν_{max}/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); δ_H **(300MHz, $CDCl_3$)** 7.98-7.91 (3H, m, 3×aromatic C<u>H</u>), 7.71-7.65 (1H, m, aromatic C<u>H</u>), 7.59-7.52 (2H, m, 2×aromatic C<u>H</u>), 7.37 (1H, s, aromatic C<u>H</u>), 4.62 (2H, s, $C\underline{H}_2C{\equiv}C$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 0.11 (6H, s, $Si(C\underline{H}_3)_2$) ppm; δ_C **(75 MHz, $CDCl_3$)** 137.6 (aromatic $\underline{C}SO_2N$), 136.4 (N<u>C</u>HN), 135.1 (aromatic *para*-<u>C</u>H), 129.2 (aromatic *meta*-<u>C</u>H), 127.4 (aromatic *ortho*-<u>C</u>H), 126.9 ($CH_2C{\equiv}C\text{-}\underline{C}$), 120.3 (imidazole $\underline{C}HCC{\equiv}C$), 90.1 ($CH_2\underline{C}{\equiv}C$), 76.3 ($CH_2C{\equiv}\underline{C}$), 52.0 ($\underline{C}H_2C{\equiv}C$), 25.8 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.2 ($Si(\underline{C}H_3)_2$) ppm; ***m/z* (FAB)** 377 (MH^+, 67%), 319 (28), 289 (23), 245 (64), 179 (39), 141 (46), 105 (100), 89 (76); HRMS calcd. for $C_{18}H_{25}N_2O_3SSi$ (MH^+) 377.1355, found 377.1370.

3-Methylhydantoin (314)

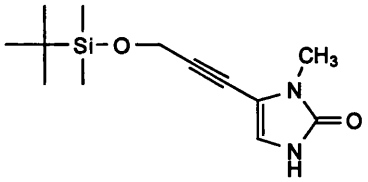


Method A[114]**:** Hydantoin **315** (40.0 g, 0.40 mol), sodium hydroxide (16.1 g, 0.40 mmol) and H_2O (200 mL) were heated to reflux and methyl iodide (50 mL, 0.80 mol) added dropwise. The solution was then heated at reflux for a further 24 h, cooled and the solvent removed *in vacuo*. The product was 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.

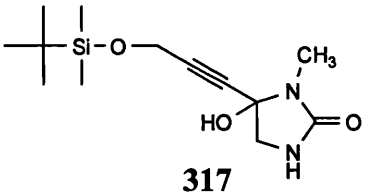
Method B[115]**:** Hydantoin **315** (30.0 g, 0.30 mol), *N*,*N*-dimethylacetamide dimethylacetal (66 mL, 0.45 mol) and toluene (1.5 L) were heated to reflux for 3.5 h. The solution was left to cool to ambient temperature without external cooling and then

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. **ν_{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; **δ_H (400 MHz, DMSO-d$_6$)** 7.95 (1H, broad s, N<u>H</u>), 3.34 (2H, s, C<u>H</u>$_2$), 2.80 (3H, s, NC<u>H</u>$_3$) ppm; **δ_C (100 MHz, DMSO-d$_6$)** 172.2 (<u>C</u>=O), 157.9 (<u>C</u>=O), 46.0 (<u>C</u>H$_2$), 23.9 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve CI-methane)** 115 (MH$^+$, 100%), 72 (10); **HRMS** calcd. for $C_4H_7N_2O_2$ (MH$^+$): 115.0508; found 115.0505; **Analysis** calculated for $C_4H_6N_2O_2$ (115.0508): C, 42.1, H, 5.3, N, 24.6; found C, 42.1; H, 5.3, N, 24.5%.

5-[3-(*tert*-Butyldimethylsilanyloxy)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-butylmagnesium 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_4Cl (100 mL) and extracted with EtOAc (4 × 50 mL). The combined organic extracts were washed with water (2 × 10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to afford tertiary alcohol **317** as an orange solid.

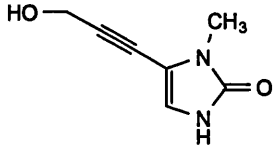


317

δ_H **(400 MHz, CD_3OD)** 4.41 (2H, s, $C\underline{H}_2OSi$), 3.67 (1H, d, *J*=10.1 Hz, $C\underline{H}_2COH$), 3.45 (1H, d, *J*=10.1 Hz, $C\underline{H}_2COH$), 2.79 (3H, s, $NC\underline{H}_3$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 0.13 (6H, s, $Si(C\underline{H}_3)_2$) ppm; δ_C **(75 MHz, CD_3OD)** 162.7 ($\underline{C}$=O), 85.5, 83.7 and 83.4 (2×$\underline{C}$≡C and $\underline{C}$OH), 55.3 and 52.7 ($C\underline{H}_2NH$ and $C\underline{H}_2OSi$), 26.6 ($SiC(\underline{C}H_3)_3$), 25.6 ($N\underline{C}H_3$) 19.4 ($Si\underline{C}(CH_3)_3$), -4.7 ($Si(\underline{C}H_3)_2$) ppm.

Alcohol **317** was dissolved in $CHCl_3$ (200 mL), *p*-toluenesulfonic acid (84 mg, 0.4 mmol, 5 mol %) added, the solution stirred for 1 h and the solvent removed *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. ν_{max}**/cm^{-1} (KBr disc)** 3113 (NH stretch), 2930, 2856 (CH stretch), 2226 (C≡C stretch), 1670 (C=O stretch), 1448, 1367, 1254, 1082, 835, 791, 781; δ_H **(400 MHz, CD_3OD)** 6.70 (1H, s, C=C$\underline{H}$), 4.56 (2H, s, $C\underline{H}_2$), 3.21 (3H, s, $NC\underline{H}_3$), 0.92 (9H, s, $C(C\underline{H}_3)_3$), 0.14 (6H, s, $Si(C\underline{H}_3)_2$) ppm; δ_C **(100 MHz, $CDCl_3$)** 154.0 ($\underline{C}$=O), 134.0 ($\underline{C}$H=C), 108.1 (CH=$\underline{C}$C≡C), 93.6 ($\underline{C}$≡C), 73.2 (C≡$\underline{C}$), 52.1 ($\underline{C}H_2$), 27.9 ($N\underline{C}H_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 18.3 ($Si\underline{C}(CH_3)_3$), -5.1 ($Si(\underline{C}H_3)_2$) ppm; ***m/z*** **(+ve CI-methane)** 267 (MH^+, 100%), 209 (42); **HRMS** calcd. for $C_{13}H_{23}N_2O_2Si$ (MH^+) 267.1529, found 267.1534; **Analysis** calculated for $C_{13}H_{22}N_2O_2Si$: C, 58.6, H, 8.3, N, 10.5; found C, 58.6, H, 8.4, N, 10.5%.

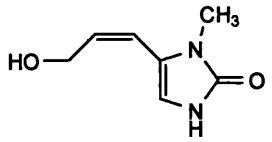
5-(3-Hydroxyprop-1-ynyl)-1-methyl-1,3-dihydroimidazol-2-one (312)



Silyl ether **313** (0.67 g, 2.5 mmol) was dissolved in AcOH:THF:H_2O (3:1:1, 50 mL), heated to 50 °C for 3.5 h, cooled and solvent removed *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. ν_{max}/cm^{-1} **(KBr disc)** 3339 (OH stretch), 3134 (NH stretch), 2230 (C≡C stretch), 1663 (C=O stretch), 1354; δ_H **(400 MHz, 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 Hz, CH_2OH), 3.05 (3H, s, NCH_3) ppm; δ_C **(100 MHz, 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; ***m/z*** **(+ve FAB)** 153 (MH^+, 100%); **HRMS** calcd. for $C_7H_9N_2O_2$ (MH^+) 153.0664, found 153.0661.

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

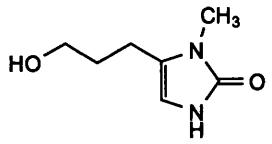


Method A: Zinc dust (700 mg, 10.7 mmol) was suspended in H_2O (4 mL), copper acetate monohydrate (70 mg, 0.4 mmol) added and the suspension stirred at ambient temperature for 15 min. Silver nitrate (70 mg, 0.4 mmol) was then added and the suspension stirred for a further 15 min. The precipitate was isolated by filtration, washed successively with 8 mL portions of H_2O, MeOH, acetone and Et_2O and dried under vacuum. Propargylic alcohol **312** (55 mg, 0.36 mmol) was dissolved in MeOH:H_2O, 1:1 (8 mL) and the activated zinc added. The suspension was heated to 50 °C for 16 h cooled then filtered over Celite® and the solvent removed *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 *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. ν_{max}/cm^{-1} **(KBr disc)** 3354 (OH stretch), 3165 (NH stretch), 1666 (C=O stretch), 1580 (C=C stretch); δ_H **(400 MHz, CD_3OD)** 6.33 (1H, s, NHCH=CH), 6.15 (1H, d, *J*=11.7 Hz, CH_2CH=CH), 5.89 (1H, dt, *J*=11.9, 6.0 Hz, CH_2CH=CH), 4.24 (2H, dd, *J*=6.0, 1.7 Hz, CH_2CH=CH), 3.20 (3H, s, NCH_3)

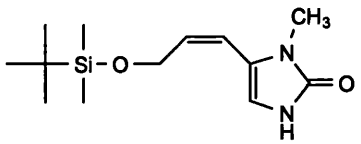
ppm; δ_C **(75 MHz, CD_3OD)** 155.3 (C=O), 133.9 (CH_2CH=CH), 122.6 (C=CH), 116.1 (CH2CH=CH), 109.2 (C=CH), 60.2 (CH_2OH), 27.5 (NCH_3) ppm; ***m/z*** **(+ve CI-methane)** 155 (MH^+, 100 %), 137 (64); **HRMS** calcd. for $C_7H_{11}N_2O_2$ (MH^+) 155.0821, found 155.0820.

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 $CaCO_3$, 3.5 % Pb; 78 mg, 0.04 mmol Pd). The suspension was placed under an atmosphere of H_2 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. ν_{max}**/cm^{-1} (KBr disc)** 3349 (OH stretch), 3161 (NH stretch), 1661 (C=O stretch); δ_H **(300 MHz, CD_3OD)** 6.11 (1H, s, C=CH), 3.61 (2H, t, *J*=6.2 Hz, CH_2OH), 3.18 (3H, s, NCH_3), 2.49 (2H, t, *J*=6.7 Hz, CH_2C=CH), 1.77 (2H, tt, J=6.7, 6.2 Hz, CH_2CH_2OH) ppm; δ_C **(75 MHz, CD_3OD)** 156.0 (C=O), 126.1 (C=CH), 104.8 (C=CH), 61.8 (CH_2OH), 31.3 (CH_2C=CH), 27.4 (NCH_3), 21.9 (CH_2CH_2OH) ppm; ***m/z*** **(+ve CI-methane)** 157 (MH^+, 100 %), 137 (58); **HRMS** calcd. for $C_7H_{13}N_2O_2$ (MH^+) 157.0977; found 157.0980.

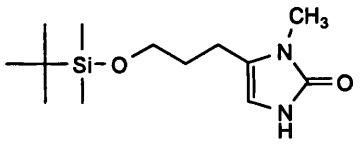
5-(3-(*tert*-Butyldimethylsilanyloxy)-propenyl)-1-methyl-1,3-dihydro-imidazol-2-one (339)



Silyl ether **313** (277 mg, 1.04 mmol) was dissolved in MeOH (28 mL) and Lindlar catalyst (5% Pd on $CaCO_3$, 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 H_2 until 30 mL (1.25 mmol) had been taken up. The solution was filtered and the solvent removed *in vacuo*.

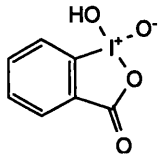
Purification by flash chromatography (EtOAc:petrol 40-60, 7:3) gave alkene **339** (147 mg, 0.55 mmol, 53%) as a pale yellow solid, mp 126 °C and **341** (63 mg, 0.23 mmol, 22%) as a yellow oil; ν_{max}/cm^{-1} **(KBr disc)** 3398 (NH stretch), 1684 (C=O stretch), 1670 (C=C stretch), 1636 (C=C stretch), 1086, 837; δ_H **(300 MHz, CD_3OD)** 6.33 (1H, s, NHC<u>H</u>=C), 6.14 (1H, d, *J*=11.6 Hz, CH_2CH=C<u>H</u>), 5.86 (1H, dt, *J*=11.7, 5.9 Hz, CH_2C<u>H</u>=CH), 4.34 (2H, dd, *J*=5.9, 1.6 Hz C<u>H_2</u>CH=CH), 3.19 (3H, s, NC<u>H_3</u>), 0.90 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.07 (6H, s, Si(C<u>H_3</u>)$_2$) ppm; δ_C **(75 MHz, CD_3OD)** 154.5 (<u>C</u>=O), 133.2 (CH_2<u>C</u>H=CH), 121.0 (CH=<u>C</u>), 114.3 (CH_2CH=<u>C</u>H), 108.1 (<u>C</u>H=C), 60.7 (<u>C</u>H_2OSi), 27.1 (N<u>C</u>H_3), 25.9 (SiC(<u>C</u>H_3)$_3$), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -3.61 (Si(<u>C</u>H_3)$_2$) ppm; ***m/z*** **(+ve FAB)** 269 (MH^+, 44%), 216 (13), 153 (35); **HRMS** calcd. for $C_{13}H_{25}N_2O_2Si$ (MH^+) 269.1685, found 269.1675.

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



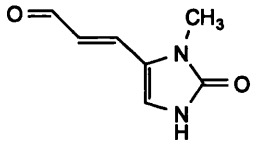
ν_{max}/cm^{-1} **(KBr disc)** 3156 (NH stretch), 1658 (C=O stretch); δ_H **(400 MHz, CD_3OD)** 6.10 (1H, t, *J*=1.2 Hz, C=CH), 3.70 (2H, t, *J*=6.0 Hz, C<u>H_2</u>OSi), 3.18 (3H, s, NC<u>H_3</u>), 2.49 (2H, td, *J*=7.6, 1.1 Hz, C<u>H_2</u>C=CH), 1.76 (2H, tt, *J*=7.6, 6.0 Hz, C<u>H_2</u>CH_2OSi), 0.91 (9H, s, SiC(C<u>H_3</u>)$_3$), 0.06 (6H, s, Si(C<u>H_3</u>)$_2$ ppm; δ_C **(100 MHz, CD_3OD)** 156.1 (<u>C</u>=O), 126.4 (<u>C</u>=CH), 104.2 (C=<u>C</u>H), 61.8 (<u>C</u>H_2OSi), 31.7 (<u>C</u>H_2C=CH), 27.9 (N<u>C</u>H_3), 25.7 (SiC(<u>C</u>H_3)$_3$), 24.2 (<u>C</u>H_2CH_2OSi), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -5.1 (Si(<u>C</u>H_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-benziodoxolin-3(1*H*)-one (IBX) (347)[149]



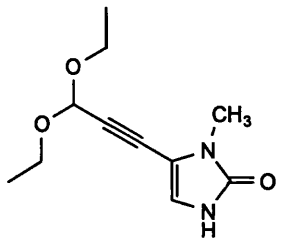
2-Iodobenzoic acid **346** (5.00 g, 20.2 mmol) was added to a stirred solution of Oxone® (37.2 g, 60.5 mmol) in H_2O (200 mL). The solution was heated to 70 °C for 1 h and then to 90 °C until complete dissolution occurred. The solution was allowed to cool to ambient temperature without external cooling and then cooled in an ice-water bath for 3 h. The resulting precipitate was isolated by filtration, washed with H_2O (6×20 mL) and acetone (2×10 mL) and dried *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-1*H*-imidazol-4-yl)propenal (348)



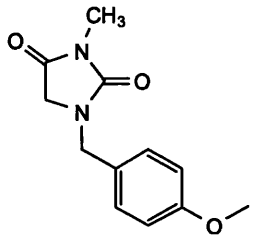
A solution of IBX **347** (106 mg, 0.38 mmol) in DMSO (0.9 mL) was added to a solution of alcohol **296** in DMSO (0.5 mL) at ambient temperature. After stirring for 1 h, H_2O (5 mL) was added and the mixture was extracted with EtOAc (4×25 mL). The extracts were washed with H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (EtOAc:MeOH, 95:5) gave aldehyde **348** (12 mg, 0.08 mmol, 25%) as a yellow oil. ν_{max}**/cm^{-1} (KBr disc)** 3398 (NH stretch), 1684 (C=O stretch), 1670 (C=C stretch), 1636 (C=C stretch); δ_H **(400 MHz, DMSO-d_6)** 9.48 (1H, d, *J*=7.7 Hz, C<u>H</u>O), 7.40 (1H, s, C=C<u>H</u>), 7.35 (1H, d, *J*=15.9 Hz, CHOCH=C<u>H</u>), 6.47 (1H, dd, *J*=15.9, 7.7 Hz, CHOC<u>H</u>=CH), 3.28 (3H, s, NCH_3) ppm; δ_C **(100 MHz, DMSO-d_6)** 174.7 (<u>C</u>HO), 153.1 (<u>C</u>=O), 132.9 (<u>C</u>H=CH), 125.6 (<u>C</u>=CH), 116.1 (CH=<u>C</u>H), 110.3 (C=<u>C</u>H), 27.8 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve CI)** 153 (MH^+, 100%), 137 (43); **HRMS** calcd. for $C_7H_9N_2O_2$ (MH^+) 153.0064, found 153.0073.

5-(3,3-Diethoxyprop-1-ynyl)-1-methyl-1,3-dihydroimidazol-2-one (354)



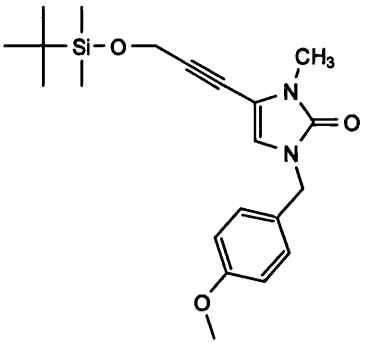
Propiolaldehyde diethyl acetal (0.76 mL, 5.3 mmol) in THF (6 mL) was cooled to 0 °C and *n*-butylmagnesium chloride (2.0 M in THF, 2.6 mL, 5.2 mmol) added dropwise with stirring. The resulting solution was allowed to warm to ambient temperature and stirred for a further 4 h. The Grignard solution was 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 NH_4Cl (10 mL). Et_2O (5 mL) was added and the organics separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was dissolved in $CHCl_3$ (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. ν_{max}**/cm^{-1} (KBr disc)** 3431 (NH stretch), 2976 (CH stretch), 2235 (C≡C stretch), 1670 (C=O stretch); δ_H **(400 MHz, $CDCl_3$)** 10.33 (1H, broad s, NH), 6.60 (1H, s, C=CH), 5.45 (1H, s, C≡CCH), 3.79-3.69 (2H, m, OCH_2CH_3), 3.67-3.58 (2H, m, OCH_2CH_3), 3.25 (3H, s, NCH_3), 1.24 (6H, t, *J*=7.1 Hz, 2×OCH_2CH_3) ppm; δ_C **(100 MHz, CD_3OD)** 154.8 (C=O), 115.9 (C=CH), 108.7 (C=CH), 93.0 (C≡CCH), 91.4 (C≡C), 74.2 (C≡C), 62.3 (OCH_2CH_3), 28.3 (NCH_3), 15.4 (OCH_2CH_3) ppm; ***m/z* (+ve CI methane)** 225 (MH^+, 100%), 179 (57), 103 (15); **HRMS** calcd. for $C_{11}H_{17}N_2O_3$ (MH^+): 225.1239, found 225.1245.

1-(4-Methoxybenzyl)-3-methylhydantoin (356)



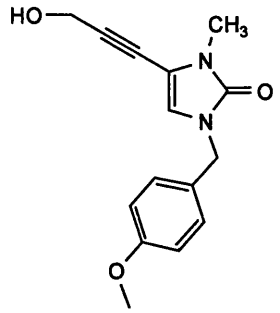
3-Methylhydantoin **314** (3.00 g, 26.3 mmol) was dissolved in DMF (75 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 1.27 g, 31.8 mmol) wad added in one aliquot and evolution of gas was observed. The suspension was stirred for 30 min then 4-methoxybenzyl chloride (4.3 mL, 32 mmol) was added and the mixture was stirred for a further 6 h. The reaction was then poured into sat. $NaHCO_3$ (100 mL) and extracted with EtOAc (4×100 mL). The combined extracts were washed with H_2O (2×100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc:*iso*hexane, 35:65) gave hydantoin **356** (5.00 g, 21.3 mmol, 81%) as a white solid, mp 144 °C. ν_{max}**/cm^{-1} (KBr disc)** 2951 (CH stretch), 2932 (CH stretch), 1759 (C=O stretch), 1693 (C=O stretch), 1514, 1477, 1250, 1032, 845, 816; δ_H **(400 MHz, $CDCl_3$)** 7.18 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.89 (2H, d, *J*=8.6 Hz, 2×aromatic C<u>H</u>), 4.50 (2H, s, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.80 (3H, s, OC<u>H</u>$_3$), 3.70 (2H, s, C<u>H</u>$_2$C=O), 3.04 (3H, s, NC<u>H</u>$_3$) ppm; δ_C **(100 MHz, $CDCl_3$)** 170.0 (<u>C</u>=O), 159.5 (aromatic <u>C</u>OCH$_3$), 156.8 (<u>C</u>=O), 129.5 (2×aromatic <u>C</u>H), 127.4 (aromatic <u>C</u>CH$_2$N), 114.3 (2×aromatic <u>C</u>H), 55.3 (O<u>C</u>H$_3$), 48.9 (<u>C</u>H$_2$C$_6$H$_4$OCH$_3$), 46.1 (<u>C</u>H$_2$C=O), 24.9 (N<u>C</u>H$_3$) ppm; ***m/z*** **(+ve CI-methane)** 235 (MH^+, 100%), 127 (73), 121 (85); **HRMS** calcd. for. $C_{12}H_{15}N_2O_3$ (MH^+): 235.1083, found 235.1073. **Analysis** calculated for $C_{12}H_{14}N_2O_3$: 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)



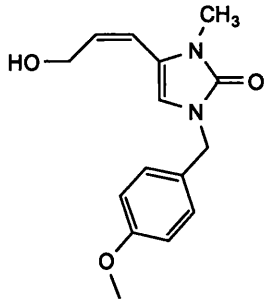
Silyl ether **313** (200 mg, 0.75 mmol) was dissolved in anhydrous DMF (10 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 38 mg, 0.95 mmol) was added in one aliquot, the solution was allowed to warm to ambient temperature and then stirred for a further 30 min. *p*-Methoxybenzyl chloride (120 μL, 0.9 mmol) was added and the solution stirred for a further 4 h. The solution was then poured onto sat. $NaHCO_3$ (30 mL), extracted with EtOAc (4×30 mL), the extracts washed successively with 30 mL each of H_2O, sat $NaHCO_3$ and brine, dried over $MgSO_4$ 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. ν_{max}**/cm^{-1} (thin film)** 2856 (CH stretch), 1717 (C=O stretch), 1109, 837; δ_H **(400 MHz, $CDCl_3$)** 7.16 (2H, d, *J*=8.8 Hz, 2×aromatic C<u>H</u>), 6.83 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.33 (1H, s, C<u>H</u>=C), 4.68 (2H, s, $C\underline{H}_2C_6H_4OCH_3$), 4.46 (2H, s, $C\underline{H}_2OSi$), 3.75 (3H, s, $OC\underline{H}_3$), 3.23 (3H, s, $NC\underline{H}_3$), 0.88 (9H, s, $SiC(C\underline{H}_3)_3$), 0.09 (6H, s, $Si(C\underline{H}_3)_2$) ppm; δ_C **(100 MHz, $CDCl_3$)** 159.3 (aromatic $\underline{C}OCH_3$), 152.2 (<u>C</u>=O), 129.4 (2×aromatic C<u>H</u>), 128.4 (aromatic $\underline{C}CH_2N$), 115.3 (C=<u>C</u>H), 114.2 (2×aromatic C<u>H</u>), 106.8 (<u>C</u>=CH), 93.7 (<u>C</u>≡C), 73.1 (<u>C</u>≡C), 55.2 ($O\underline{C}H_3$), 52.1 ($\underline{C}H_2OSi$), 46.7 ($\underline{C}H_2C_6H_4OCH_3$), 28.3 ($N\underline{C}H_3$), 25.7 ($SiC(\underline{C}H_3)_3$), 18.2 ($Si\underline{C}(CH_3)_3$), -5.2 ($Si(\underline{C}H_3)_2$); ***m/z*** **(EI)** 386 (M^+, 15%), 121 (100); **HRMS** calcd. for $C_{21}H_{30}N_2O_3Si$ (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 H_2O (10 mL) and extracted with EtOAc (3×20 mL). The organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography (EtOAc:*iso*-hexane, 9:1) gave propargylic alcohol **359** as a pale yellow solid, mp 156 °C; **ν_{max}/cm^{-1} (KBr disc)** 3096 (OH stretch), 1663 (C=O), 1612 (C=C); **δ_H (400 MHz, $CDCl_3$)** 7.16 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.83 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.12 (1H, s, C=C<u>H</u>), 4.65 (2H, s, NC<u>H</u>$_2$Ar), 4.41 (2H, d, *J*=6.2Hz, C<u>H</u>$_2$OH), 3.77 (3H, s, OC<u>H</u>$_3$), 3.21 (3H, s, NC<u>H</u>$_3$), 2.98 (1H, t, *J*=6.2Hz, CH$_2$O<u>H</u>) ppm; **δ_C (100 MHz, $CDCl_3$)** 159.5 (aromatic <u>C</u>OCH$_3$), 152.2 (<u>C</u>=O), 129.6 (2×aromatic <u>C</u>H), 128.3 (aromatic <u>C</u>CH$_2$N), 115.6 (C=<u>C</u>H), 114.2 (2×aromatic <u>C</u>H), 106.7 (<u>C</u>=CH), 93.8 (<u>C</u>≡C), 73.4 (<u>C</u>≡C), 55.3 (O<u>C</u>H$_3$), 52.1 (<u>C</u>H$_2$OH), 46.8 (<u>C</u>H$_2$Ar), 28.4 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve FAB)** 273 (MH$^+$, 11%), 272 (9), 217 (12); **HRMS** calcd. for $C_{15}H_{16}N_2O_3$ (M$^+$) 272.1161, found 272.1162; **Analysis** calcd. for $C_{15}H_{16}N_2O_3$: C, 66.2, H, 5.9, H 10.3; found C, 66.2, H, 5.9, N, 10.3%.

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

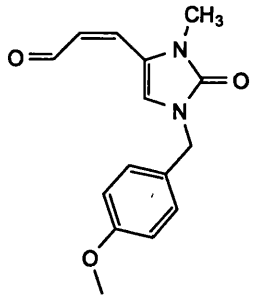


Zinc dust (4.38 g, 67.0 mmol) was suspended in water at ambient temperature, copper acetate monohydrate (880 mg, 4.4 mmol) was added and the suspension stirred for 15 min. Silver nitrate (878 mg, 5.2 mmol) was then added and the suspension stirred for a further 15 min. The activated couple was isolated by filtration and washed successively with 50 mL portions of H_2O, MeOH, acetone and Et_2O and dried under suction for 5 min. Propargylic alcohol **359** (502 mg, 1.84 mmol) was dissolved in H_2O: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. **ν_{max}/cm^{-1} (KBr disc)** 3381 (OH stretch), 1666 (C=O stretch), 1612 (C=C stretch), 1585, 1514, 818; **δ_H (400 MHz, $CDCl_3$)** 7.21 (2H, d, *J*=8.3 Hz, 2×aromatic C<u>H</u>), 6.88 (2H, d, *J*=8.6 Hz, 2×aromatic C<u>H</u>), 6.36 (1H, s, C=C<u>H</u>), 6.14 (1H, d, *J*=11.8 Hz, CH_2CH=C<u>H</u>), 5.87 (1H, dt, *J*=11.7, 6.0 Hz, CH_2C<u>H</u>=CH), 4.75 (2H, s, C<u>H</u>$_2C_6H_4OCH_3$), 4.17 (2H, d, *J*=6.0 Hz, C<u>H</u>$_2$CH=CH), 3.76 (3H, s, OC<u>H</u>$_3$), 3.23 (3H, s, NC<u>H</u>$_3$) ppm; **δ_C (100 MHz, $CDCl_3$)** 160.9 (aromatic <u>C</u>OCH$_3$), 154.3 (<u>C</u>=O), 134.2 (CH_2<u>C</u>H=CH), 130.4 (aromatic <u>C</u>H$_2$N), 130.2 (aromatic <u>C</u>H), 121.6 (<u>C</u>=CH), 115.7 (CH_2CH=<u>C</u>H), 115.1 (aromatic <u>C</u>H), 111.8 (N-C=<u>C</u>H), 60.2 (<u>C</u>H$_2$CH=CH), 55.7 (O<u>C</u>H$_3$), 47.6 (<u>C</u>H$_2C_6H_4OCH_3$), 27.9 (N<u>C</u>H$_3$) 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 $C_{15}H_{19}N_2O_3$ (MH^+) 275.1396, found 275.1390.

Manganese dioxide (345)

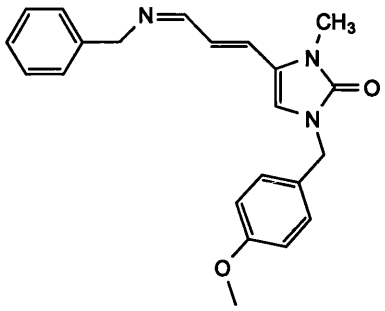
A solution of manganese dichloride tetrahydrate (20 g, 0.1 mol) in water (200 mL) at 70 °C was added over 10 min to a stirred solution of potassium permanganate (16 g, 0.1 mmol) in water (200 mL) at 60 °C. The resulting suspension was stirred at 60 °C for 2 h then overnight at ambient temperature. The 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-1*H*-imidazol-4-yl)-propenal (361)



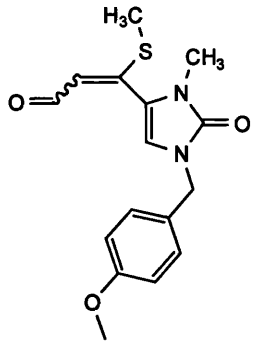
Alcohol **360** (271 mg, 1.0 mmol) was dissolved in DCM (20 mL) and MnO_2 **345** (1.72 g, 20 mmol) added. The suspension was heated to 30 °C for 24 h, filtered and the solvent removed *in vacuo* to afford a mixture of two isomers in *Z*:*E* ratio of 9:1 by ^1H NMR. Flash chromatography (gradient elution: EtOAc:petrol 2:8, 6:4) afforded aldehyde **361** (193 mg, 0.71 mmol, 72%) as a yellow oil. **ν_{max}/cm^{-1} (KBr disc)** 1690 (C=O aldehyde stretch), 1651 (C=O stretch), 1642 (C=C stretch), 823; **δ_H (400 MHz, $CDCl_3$)** (*Z*-isomer): 9.60 (1H, d, *J*=5.2 Hz, C<u>H</u>O), 7.11-7.08 (2H, m, 2×aromatic C<u>H</u>), 6.69-6.66 (2H, m, 2×aromatic C<u>H</u>), 5.87 (1H, d, *J*=11.9 Hz, CHOCH=C<u>H</u>), 5.65 (1H, dd, *J*=11.8, 5.3 Hz, CHOC<u>H</u>=CH), 4.42 (1H, s, C<u>H</u>$_2$), 3.24 (3H, s, OC<u>H</u>$_3$), 2.65 (3H, s, NC<u>H</u>$_3$) ppm; **δ_C (100 MHz, $CDCl_3$)** (*Z*-isomer) 189.5 (<u>C</u>HO), 160.5 (aromatic <u>C</u>OCH$_3$), 155.0 (<u>C</u>=O), 132.6 (CHO<u>C</u>H=CH), 130.8 (aromatic <u>C</u>H$_2$N), 131.0 (aromatic <u>C</u>H), 121.9 (<u>C</u>=CH), 115.1 (CHOCH=<u>C</u>H), 114.5 (aromatic <u>C</u>H), 112.2 (C=<u>C</u>H), 55.5 (O<u>C</u>H$_3$), 47.1 (<u>C</u>H$_2$C$_6$H$_4$OCH$_3$), 27.8 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve CI-methane)** 273 (MH^+, 75%), 272 (62), 167 (43), 122 (35); **HRMS** calcd. for $C_{15}H_{17}N_2O_3$ (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, C_6D_6)** 7.67 (1H, d, *J*=8.6 Hz, N=C<u>H</u>), 7.36-7.11 (5H, m, C_6H_5), 7.08-7.05 (2H, m, 2×aromatic C<u>H</u>), 6.72-6.69 (2H, m, 2×aromatic C<u>H</u>), 6.60 (1H, dd, *J*=16.2, 8.6 Hz, N=CHC<u>H</u>=CH), 6.01 (2H, d, *J*=16.3 Hz, N=CHCH=C<u>H</u>), 5.90 (1H, s, C=C<u>H</u>), 4.60 (2H, s, C<u>H</u>$_2$), 4.49 (2H, s, C<u>H</u>$_2$), 3.26 (3H, s, OC<u>H</u>$_3$), 2.91 (3H, s, NC<u>H</u>$_3$) ppm.

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

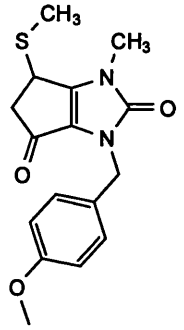


Alcohol **359** (1.00 g, 3.67 mmol) and triethylamine (5.2 mL, 37 mmol) were dissolved in anhydrous DMSO (13 mL) and the solution warmed to 30 °C. A solution of sulfur trioxide-pyridine complex (2.34 g, 14.7 mmol) in DMSO (13 mL) was added via cannula and the resulting solution stirred at 30 °C for 3.5 h. After cooling, the solution was poured into H_2O (130 mL) and extracted with EtOAc (3×130 mL), the extracts

washed with water (2×70 mL), dried over Na_2SO_4 and concentrated *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. **ν_{max}/cm^{-1} (thin film)** 3107, 2997, 2935, 2835, 2165, 1690 (CHO stretch), 1655 (C=O stretch), 1611 (C=C stretch), 1585 (C=C stretch), 820; **δ_H (400 MHz, C_6D_6)** (*E*-isomer **370**) 9.42 (1H, d, *J*=7.4 Hz, C<u>H</u>O), 7.02 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.66 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 5.92 (1H, s, NC=C<u>H</u>), 5.85 (1H, d, *J*=7.4 Hz, C=C<u>H</u>CHO), 4.45 (2H, s, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.23 (3H, s, OC<u>H</u>$_3$), 2.96 (3H, s, NC<u>H</u>$_3$), 1.44 (3H, s, SC<u>H</u>$_3$) ppm; (*Z*-isomer **371**) 10.26 (1H, d, *J*=7.0 Hz, C<u>H</u>O), 7.05 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.70 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.09 (1H, s, NC=C<u>H</u>), 5.98 (1H, d, *J*=7.0 Hz, C=C<u>H</u>CHO), 4.46 (2H, s, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.24 (3H, s, OC<u>H</u>$_3$), 2.89 (3H, s, OC<u>H</u>$_3$), 1.46 (3H, s, SC<u>H</u>$_3$) ppm; **δ_C (75 MHz, C_6D_6)** (*E*-isomer **370**) 187.1 (<u>C</u>HO), 159.9 (aromatic <u>C</u>), 153.7 (<u>C</u>=O), 152.4 (aromatic <u>C</u>), 129.6 (2×aromatic <u>C</u>H), 125.4 (<u>C</u>=CH), 117.4 (<u>C</u>=CH), 114.5 (2×aromatic <u>C</u>H), 114.4 (C=<u>C</u>H), 88.4 (C=<u>C</u>H), 54.7 (O<u>C</u>H$_3$), 46.9 (<u>C</u>H$_2$), 28.8 (N<u>C</u>H$_3$), 14.8 (S<u>C</u>H$_3$); ***m/z* (+ve CI-methane)** 319 (MH$^+$, 94%), 271 (13), 121 (100); **HRMS** calcd. for $C_{16}H_{19}N_2O_3S$ (MH$^+$) 319.1116, found 319.1119.

Irradiation of the ^{1}H NMR (*Z*)-isomer signal at 9.42 ppm gave a NOE enhancement of the (*E*)-isomer signal at 10.26 of 1.05%, indicating that **370** and **371** are interconverting in C_6D_6 solution. Upon heating to 70 °C in C_6D_6 the (*E*):(*Z*)-isomer ratio decreased to 5:1.

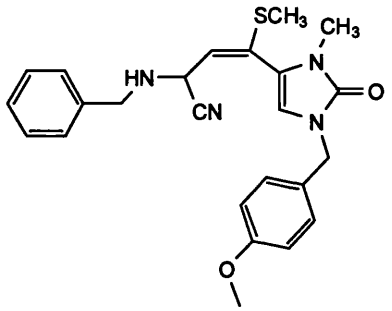
3-(4-Methoxybenzyl)-1-methyl-6-methylsulfanyl-1,3,5,6-tetrahydrocyclo pentaimidazole-2,4-dione (375)



A solution of aldehydes **370** and **371** was left to stand in $CDCl_3$ for 18 h, affording ketone **375**. **ν_{max}/cm^{-1} (thin film)** 3200, 1712 (C=O ketone), 1682 (C=O amide), 1612 (C=C), 1514, 1485, 1245, 1178, 1033 cm^{-1}; **δ_H (400 MHz, $CDCl_3$)** 7.38 (2H, d, *J*=8.6

Hz, 2×aromatic C<u>H</u>), 6.79 (2H, d, *J*=8.6 Hz 2×aromatic C<u>H</u>), 4.89 (1H, d, *J*=14.5 Hz, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 4.82 (1H, d, *J*=14.5 Hz, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 4.12 (1H, dd, *J*=6.1, 1.3 Hz, C<u>H</u>SCH$_3$), 3.73 (3H, s, OC<u>H</u>$_3$), 3.37 (3H, s, NC<u>H</u>$_3$), 3.19 (1H, dd, *J*=18.1, 6.2 Hz, COC<u>H</u>$_2$), 2.68 (1H, dd, *J*=18.1, 1.0 Hz, COC<u>H</u>$_2$), 1.68 (3H, s, SC<u>H</u>$_3$) ppm; **δ_C (100 MHz, CDCl$_3$)** 184.3 (CH$_2$<u>C</u>=O), 159.2 (aromatic <u>C</u>), 156.0 (<u>C</u>=O), 150.7 (aromatic <u>C</u>), 130.1 (2×aromatic <u>C</u>H), 128.9 (<u>C</u>=C), 123.4 (C=<u>C</u>), 113.9 (2×aromatic <u>C</u>H), 55.1 (O<u>C</u>H$_3$), 47.0 (CO<u>C</u>H$_2$), 45.3 (<u>C</u>H$_2$C$_6$H$_4$OCH$_3$), 35.3 (<u>C</u>HSCH$_3$), 28.6 (N<u>C</u>H$_3$), 10.8 (S<u>C</u>H$_3$) ppm; ***m/z* (+ve CI-methane)** 319 (MH$^+$, 98%), 271 (49), 211 (31), 197 (12), 165 (17), 149 (20), 121 (100); **HRMS** calcd. for C$_{16}$H$_{19}$N$_2$O$_3$S (MH$^+$): 319.1116, found 319.1113.

(*E*)-2-Benzylamino-4-(1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl)-4-methylsulfanylbut-3-enenitrile (387)

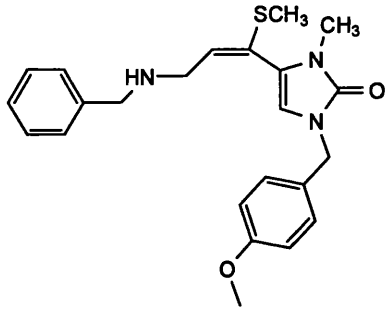


Aldehyde **370** (71 mg, 0.22 mmol), benzylamine (30 μL, 0.27 mmol), 4Å activated molecular sieves (50 mg) and DCM (3 mL) were stirred at ambient temperature for 21 h to form the imine as a mixture of isomers. **δ_H (300 MHz, C$_6$D$_6$)** Major isomer: 8.68 (1H, d, *J*=8.8 Hz, N=C<u>H</u>), 7.45-7.09 (5H, m, C$_6$<u>H</u>$_5$), 7.09-7.03 (2H, m, 2×aromatic C<u>H</u>), 6.69-6.66 (2H, m, 2×aromatic C<u>H</u>), 6.60 (1H, d, *J*=8.8 Hz, C<u>H</u>=C), 5.97 (1H, s, C=C<u>H</u>), 4.59 (2H, s, C<u>H</u>$_2$), 4.34 (2H, s, C<u>H</u>$_2$), 3.23 (3H, s, NC<u>H</u>$_3$), 1.56 (3H, s, SC<u>H</u>$_3$); Minor isomer: 7.91 (1H, d, *J*=8.8 Hz, N=C<u>H</u>), 7.45-7.09 (5H, m, C$_6$<u>H</u>$_5$), 7.09-7.03 (2H, m, 2×aromatic C<u>H</u>), 6.69-6.66 (2H, m, 2×aromatic C<u>H</u>), 6.37 (1H, d, *J*=8.8 Hz, C<u>H</u>=C), 5.92 (1H, s, C=C<u>H</u>), 4.51 (2H, s, C<u>H</u>$_2$), 4.40 (2H, s, C<u>H</u>$_2$), 3.06 (3H, s, NC<u>H</u>$_3$), 1.63 (3H, s, SC<u>H</u>$_3$) 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. **δ_H (300**

MHz, C_6D_6) (*E*)-isomer: 7.15 (5H, m, 5×aromatic C<u>H</u>), 7.00 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 6.66 (2H, d, *J*=8.7 Hz, 2×aromatic C<u>H</u>), 5.87 (1H, s, C=C<u>H</u>), 5.30 (1H, d, *J*=8.9 Hz, CHC<u>H</u>=CSCH$_3$), 3.97 (1H, dd, *J*=10.2, 9.0 Hz, (C<u>H</u>(CN)CHCSH$_3$), 3.75 (1H, dd, *J*=13.0, 5.3 Hz, NHC<u>H</u>$_2$), 3.40 (1H, dd, *J*=13.0, 6.7 Hz, NHC<u>H</u>$_2$), 3.22 (3H, s, OC<u>H</u>$_3$) 3.11 (3H, s, NC<u>H</u>$_3$), 1.55 (3H, s, SC<u>H</u>$_3$), 1.19 (1H, dt, *J*=10.0, 5.3 Hz, N<u>H</u>) ppm

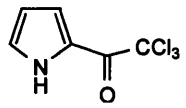
4-(3-Benzylamino-1-methylsulfanylprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (390)



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 μL, 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®, 100% EtOAc) gave amine **390** (234 mg, 0.57 mmol, 69 %) as a yellow oil. **ν_{max}/cm^{-1} (thin film)** 3304 (NH stretch), 1674 (C=O stretch), 1612 (C=C stretch), 820; **δ_H (400 MHz, CD_3OD)** (*E*-isomer) 7.32-7.20 (5H, m, C$_6$<u>H</u>$_5$), 7.18-7.16 (2H, m, 2×aromatic C<u>H</u>), 6.90-6.86 (2H, m, 2×aromatic C<u>H</u>), 6.36 (1H, s, C=C<u>H</u>), 5.87 (1H, t, *J*=7.1 Hz, C<u>H</u>=CSCH$_3$), 4.71 (2H, s, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.63 (2H, s, C<u>H</u>$_2$C$_6$H$_5$), 3.18 (3H, s, NC<u>H</u>$_3$), 3.17 (2H, d, *J*=7.1 Hz, C<u>H</u>$_2$NH), 2.15 (3H, s, SC<u>H</u>$_3$) ppm; (*Z*-isomer) 7.32-7.20 (5H, m, C$_6$<u>H</u>$_5$), 7.18-7.16 (2H, m, 2×aromatic C<u>H</u>), 6.90-6.86 (2H, m, 2×aromatic C<u>H</u>), 6.42 (1H, s, C=C<u>H</u>), 5.91 (1H, t, *J*=6.6 Hz, C<u>H</u>=CSCH$_3$), 4.73 (2H, s, C<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.77 (2H, s, C<u>H</u>$_2$C$_6$H$_5$), 3.75 (3H, s, OC<u>H</u>$_3$), 3.50 (2H, d, *J*=6.4 Hz, C<u>H</u>$_2$NH), 3.29 (3H, s, NC<u>H</u>$_3$), 1.96 (3H, s, SC<u>H</u>$_3$) ppm; **δ_C (75 MHz, $CDCl_3$)** (*E*-isomer) 159.3 (<u>C</u>=O), 153.5

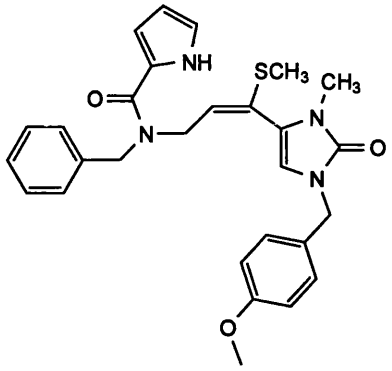
(aromatic C), 139.3 (aromatic C), 129.3 (2×aromatic CH), 128.5 (2×aromatic CH), 128.2 (2×aromatic CH), 127.9 (aromatic CH), 127.2 (aromatic C), 122.2 (C=CH), 118.3 (C=CH), 114.2 (2×aromatic C), 109.9 (C=CH), 109.9 (C=CH), 55.3 ($C_6H_4OCH_3$), 53.1 ($CH_2C_6H_4OCH_3$), 47.9 ($CH_2C_6H_5$), 46.7 (CH_2NH), 28.3 (NCH_3), 15.4 (SCH_3) ppm; ***m/z* (+ve CI-methane)** 410 (MH^+, 46%), 303 (91), 121 (100), 91 (74); **HRMS** calcd. for $C_{23}H_{28}N_3O_2S$ (MH^+) 410.1902, found 410.1905.

2-Trichloroacetylpyrrole (389)[173]



A solution of pyrrole (2.59 mL, 37.3 mmol) in Et_2O (20 mL) was added dropwise to a solution of trichloroacetyl chloride (4.75 mL, 42.6 mmol) in Et_2O (6.5 mL) over 40 min. The resulting solution was heated to reflux for 1 h, cooled and then a solution of $NaHCO_3$ (3.25 g) in H_2O (10 mL) was added slowly. The organic layer was separated, washed with H_2O (4×10 mL) and brine (10 mL) and dried over Na_2SO_4. 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}/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, $CDCl_3$)** 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, $CDCl_3$)** 173.3 (C=O), 127.4 (aromatic CH), 122.9 (aromatic C), 121.3 (aromatic CH), 111.8 (aromatic CH), 94.9 (CCl_3); ***m/z* (+ve CI-methane)** 212 (MH^+ [$^{35}Cl_3$], 100%), 178 (40); **HRMS** calcd. for $C_6H_5Cl_3NO$ (MH^+) 211.9437, found 211.9439.

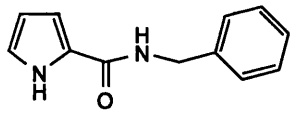
4-(3-Benzyl-N-pyrrole-2-carbonylamino)-1-methylsulfanylprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3-dihydroimidazol-2-one (391)



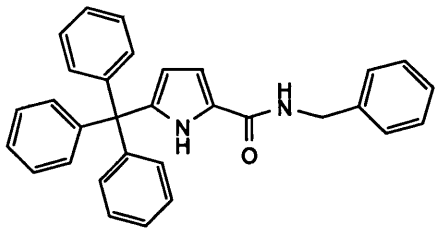
Amine **390** (100 mg, 0.24 mmol) and pyrrole-2-carboxylic acid (52 mg, 0.49 mmol) were dissolved in THF (2 mL) and diisopropylcarbodiimide (76 μL, 0.49 mmol) added. The solution was stirred at ambient temperature for 30 h, filtered and the solvent removed *in vacuo*. The crude product was dissolved in DCM (10 mL), washed with NaOH solution (1.3M, 5 mL), dried over Na_2SO_4 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. **ν_{max}/cm^{-1} (thin film)** 3269 (NH stretch), 1674 (C=O stretch), 1597 (C=C stretch), 727; **δ_H (400 MHz, DMSO-d_6)** 11.32 (1H, broad s, NH), 7.30-7.16 (5H, m, C_6H_5), 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, CH_2CH=C), 4.69 (2H, s, $CH_2C_6H_4OCH_3$), 4.59 (2H, s, $CH_2C_6H_5$), 4.13 (2H, d, *J*=6.5 Hz, $CHCH_2$), 3.74 (3H, s, OCH_3), 3.04 (3H, s, NCH_3), 2.09 (3H, s, SCH_3) ppm; **δ_C (125 MHz, DMSO-d_6)** 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 (OCH_3), 50.3 ($CH_2C_6H_4OCH_3$), 46.5 ($CH_2C_6H_5$), 45.8 (CH_2CH=C), 28.0 (NCH_3), 14.8 (SCH_3) ppm; ***m/z* (+ve FAB)** 503 (MH^+, 5%), 307 (28), 154 (100); **HRMS** calcd. for $C_{28}H_{31}N_4O_3S$ (MH^+) 503.2117, found 503.2142.

1*H*-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).



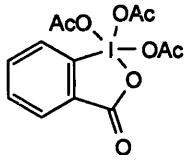
δ_H (400 MHz, CD_3OD) 7.31-7.28 (4H, m, $C_6\underline{H}_5$), 7.24-7.22 (1H, m, $C_6\underline{H}_5$), 6.91-6.90 (1H, m, pyrrole C<u>H</u>), 6.81-6.80 (1H, m, pyrrole C<u>H</u>), 6.16-6.15 (1H, m, pyrrole C<u>H</u>), 6.51 (2H, s, $C\underline{H}_2C_6H_5$) ppm; **δ_C (100 MHz, CD_3OD)** 164.7 (<u>C</u>=O), 140.6 (aromatic <u>C</u>), 129.5 (2×aromatic <u>C</u>H), 128.4 (2×aromatic <u>C</u>H), 128.1 (aromatic <u>C</u>H), 126.8 (pyrrole <u>C</u>), 122.9 (pyrrole <u>C</u>H), 111.8 (pyrrole <u>C</u>H), 110.2 (pyrrole <u>C</u>H), 43.8 ($\underline{C}H_2C_6H_5$) ppm; ***m/z* (+ve CI-methane)** 201 (MH^+, 100%), 158 (9), 41 (12); **HRMS** calcd. for $C_{12}H_{13}N_2O$ (MH^+): 201.1028, found 201.1032.



ν_{max}/cm^{-1} (thin film) 3450 (NH stretch), 1683 (C=O stretch), 747, 716; **δ_H (400 MHz, $CDCl_3$)** 8.80 (1H, broad s, pyrrole N<u>H</u>), 7.35-7.20 (13H, m, 13×aromatic C<u>H</u>), 7.11-7.07 (7H, m, 7×aromatic C<u>H</u>), 6.45 (1H, dd, *J*=3.8, 2.5 Hz, pyrrole C<u>H</u>), 6.05 (1H, broad t, *J*=5.6 Hz, $CH_2N\underline{H}$), 6.01 (1H, dd, *J*=3.7, 2.9 Hz, pyrrole C<u>H</u>), 4.54 (2H, d, *J*=5.8 Hz, $C\underline{H}_2NH$); **δ_C (125 MHz, $CDCl_3$)** 160.8 (<u>C</u>=O), 145.3 (3×aromatic <u>C</u>), 140.9 (aromatic <u>C</u>H), 138.4 (aromatic <u>C</u>H), 130.3 (6×aromatic <u>C</u>H), 128.7 (2×aromatic <u>C</u>H), 127.9 (6×aromatic <u>C</u>H), 127.8 (2×aromatic <u>C</u>H), 127.8 (aromatic <u>C</u>), 126.8 (3×aromatic <u>C</u>H), 125.0 (aromatic <u>C</u>), 112.1 (pyrrole C<u>H</u>), 108.5 (pyrrole C<u>H</u>), 60.6 ($\underline{C}(C_6H_5)_3$), 43.4

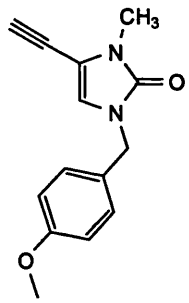
($\underline{C}H_2$); ***m/z*** **(+ve CI-methane)** 443 (MH^+, 90%), 243 (53), 178 (39), 91 (70), 71 (100); **HRMS** calcd. for $C_{31}H_{27}N_2O$ (MH^+): 443.2123, found 443.2130.

1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-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 Et_2O (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)

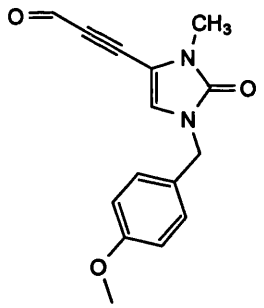


Method A: Alcohol **359** (100 mg, 0.37 mmol) was dissolved in DCM (6 mL) at ambient temperature and Dess-Martin Periodinane **376** (172 mg, 0.41 mmol) added. The solution was stirred for 50 min, poured into NaOH solution (1.3M, 3 mL) and extracted with Et_2O (2×10 mL). The organic extracts were washed with NaOH solution (20 mL), dried over Na_2SO_4, 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 Na_2SO_4 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. ν_{max}**/cm^{-1} (KBr disc)** 3250 (C≡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; δ_H **(400 MHz, $CDCl_3$)** 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, C=CH), 4.67 (2H, s, $CH_2C_6H_4OCH_3$), 3.74 (3H, s, OCH_3), 3.30 (1H, s, C≡CH), 3.24 (3H, s, NCH_3) ppm; δ_C **(100 MHz, $CDCl_3$)** 159.3 (aromatic $COCH_3$), 152.1 (C=O), 129.4 (2×aromatic CH), 128.2 (aromatic CCH_2N), 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 (OCH_3), 46.8 ($CH_2C_6H_4OCH_3$), 28.3 (NCH_3) ppm; ***m/z*** **(EI)** 242 (M^+, 17%), 122 (11), 121 (100), 78 (8); **HRMS** calcd. for $C_{14}H_{14}N_2O_2$ (M^+): 242.1050; found 242.1049.

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

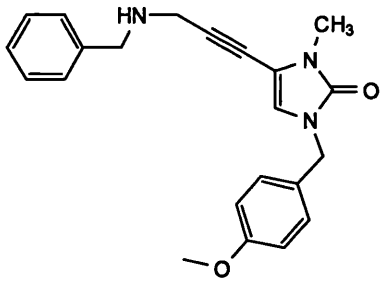


Method A: Propargylic alcohol **359** (676 mg, 2.49 mmol) was dissolved in $CHCl_3$ and manganese dioxide (4.34 g, 50 mmol) added. The suspension was heated to 40 °C for 19 h, cooled, filtered through Celite® and the solvent removed *in vacuo*. Flash chromatography (Florisil®, EtOAc:*iso*-hexane, 1:1) 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 $NaHCO_3$ (30 mL) and $Na_2S_2O_3$ (10 g in 30 mL H_2O) were added, the biphasic mixture stirred vigorously for 1 h and then the organic layer was separated, dried over Na_2SO_4 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_{max}**/cm^{-1} (KBr disc)** 3076, 2174 (C≡C stretch), 1750 (CHO stretch), 1647 (C=O stretch), 820; δ_H **(400 MHz, $CDCl_3$)** 9.30 (1H, s C<u>H</u>O), 7.19 (2H, d, *J*=8.8 Hz, 2×aromatic C<u>H</u>), 6.86 (2H, d, *J*=8.7 Hz (2×aromatic C<u>H</u>), 6.80 (1H, s, C=C<u>H</u>), 4.74 (2H, s, NC<u>H</u>$_2$C$_6$H$_4$OCH$_3$), 3.78 (3H, s, OC<u>H</u>$_3$), 3.30 (3H, s, NC<u>H</u>$_3$) ppm; δ_C **(100 MHz, $CDCl_3$)** 174.7 (<u>C</u>HO), 159.7 (aromatic <u>C</u>), 152.1 (<u>C</u>=O), 129.7 (2×aromatic <u>C</u>H), 127.3 (aromatic <u>C</u>CH$_2$N), 123.2 (C=<u>C</u>H), 114.4 (2×aromatic <u>C</u>H), 104.4 (<u>C</u>=CH), 97.1 (<u>C</u>≡C), 85.0 (<u>C</u>≡C), 55.3 (O<u>C</u>H$_3$), 47.4 (<u>C</u>H$_2$C$_6$H$_4$OCH$_3$), 28.5 (N<u>C</u>H$_3$) ppm; ***m/z*** **(+ve CI-methane)** 271 (MH^+, 10%), 206 (88), 146 (100), 121 (41), 57 (40); **HRMS** calcd. for $C_{15}H_{15}N_2O_3$ (MH^+): 271.1083; found 271.1075; **Analysis** calcd. for $C_{15}H_{14}N_2O_3$: 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)

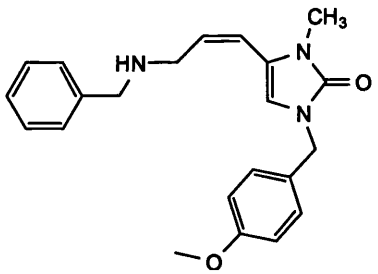


Aldehyde **366** (49.0 mg, 0.18 mmol) was dissolved in DCM (3 mL) and activated 4Å molecular sieves (200 mg) added. Benzylamine (99 μL, 0.91 mmol) was then added and the reaction stirred at ambient temperature for 17 h. A small sample was removed for ^{1}H NMR to confirm complete imine formation and two isomers of imine **367** were observed in a 6:4 ratio. δ_H **(400 MHz, $CDCl_3$)** 7.77 (1H, s, C<u>H</u>=N), 7.73 (1H, s, C<u>H</u>=N), 7.34-7.28 (10H, m, CH$_2$C$_6$<u>H</u>$_5$), 7.21–7.17 (4H, m, 4×aromatic C<u>H</u>), 6.87-6.84 (4H, m, 4×aromatic C<u>H</u>), 6.59 (1H, s, C=C<u>H</u>), 6.53 (1H, s, C=C<u>H</u>), 4.81 (2H, s, C<u>H</u>$_2$C$_6$H$_5$), 4.74

(2H, s, $C\underline{H}_2C_6H_4OCH_3$), 4.72 (2H, s, $C\underline{H}_2C_6H_5$), 4.71 (2H, s, $C\underline{H}_2C_6H_4OCH_3$), 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® and concentrated *in vacuo*. Flash chromatography (EtOAc:Et_3N, 200:1) afforded amine **397** (55.3 mg, 0.15 mmol, 85%) as a yellow oil. **ν_{max}/cm^{-1} (thin film)** 3445, 3308 (NH stretch), 2934 (CH stretch), 2835 (CH stretch), 2224 (C≡C 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 C$\underline{H}$), 7.18 (2H, d, *J*=8.7 Hz, 2×aromatic C$\underline{H}$); 6.85 (2H, d, *J*=8.7 Hz, 2×aromatic C$\underline{H}$), 6.32 (1H, s, NC$\underline{H}$=C), 4.70 (2H, s, $C\underline{H}_2C_6H_4OCH_3$), 3.86 (2H, s, $C\underline{H}_2C_6H_5$), 3.77 (3H, s, OCH_3), 3.61 (2H, s, $NC\underline{H}_2C{\equiv}C$), 3.26 (3H, s, NCH_3) ppm; **δ_C (100 MHz, $CDCl_3$)** 159.3 (aromatic $\underline{C}$), 152.2 ($\underline{C}$=O), 139.1 (aromatic $\underline{C}$), 129.4 (2×aromatic $\underline{C}$H), 128.4 (2×aromatic $\underline{C}$H), 128.4 (aromatic $\underline{C}$), 128.3 (2× aromatic $\underline{C}$H), 127.2 (aromatic $\underline{C}$H), 114.7 (C=$\underline{C}$H), 114.1 (2×aromatic $\underline{C}$H), 107.0 ($\underline{C}$=CH), 93.3 ($\underline{C}{\equiv}C$), 71.8 ($\underline{C}{\equiv}C$), 55.2 ($O\underline{C}H_3$), 52.4 ($N\underline{C}H_2C_6H_5$), 46.7 ($\underline{C}H_2C_6H_4OCH_3$), 38.1 ($C\underline{H}_2C{\equiv}C$), 28.3 ($N\underline{C}H_3$) ppm; ***m/z* (+ve CI-methane)** 362 (MH^+, 100%), 361 (87), 255 (66), 121 (98), 91 (34); **HRMS** calcd. for $C_{22}H_{24}N_3O_2$ (MH^+) 362.1868, found 362.1859.

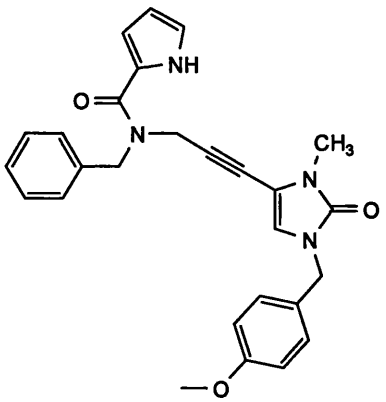
(*E*) and (*Z*)-4-(3-Benzylaminoprop-1-enyl)-1-(4-methoxybenzyl)-3-methyl-1,3 -dihydroimidazol-2-one (398 and 399)



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_2O, MeOH, acetone and Et_2O and then dried for 5 min under suction. Alkyne **397** (32.7 mg, 0.09 mmol) was dissolved in MeOH (2 mL) and H_2O (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:Et_3N; 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. **ν_{max}/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); **δ_H (400 MHz, CD_3OD)** (*Z*)-isomer 7.26-7.20 (5H, m, 5×aromatic C<u>H</u>), 7.15 (2H, dd, *J*=6.7, 2.0 Hz, 2×aromatic C<u>H</u>), 6.86 (2H, dd, *J*=6.7, 2.1 Hz, 2×aromatic C<u>H</u>), 6.22 (1H, s, NC<u>H</u>=C), 6.17 (1H, dd, *J*=11.7, 0.8 Hz, C<u>H</u>=CHCH$_2$), 5.81 (1H, dt, *J*=11.6, 6.3 Hz, CH=C<u>H</u>CH$_2$), 4.69 (2H, s, NC<u>H$_2$</u>C$_6$H$_4$OCH$_3$), 3.76 (3H, s, OC<u>H$_3$</u>), 3.70 (2H, s, NHC<u>H$_2$</u>C$_6$H$_5$), 3.30 (2H, d, *J*=6.3 Hz, C<u>H$_2$</u>CH=CH), 3.21 (3H, s, NC<u>H$_3$</u>) ppm; **δ_C (75 MHz, $CDCl_3$)** (*Z*)-isomer 159.1 (aromatic <u>C</u>), 152.7 (<u>C</u>=O), 139.7 (aromatic <u>C</u>), 130.9 (CH=<u>C</u>HCH$_2$), 129.1 (2×aromatic <u>C</u>H), 128.8 (aromatic <u>C</u>CH$_2$N), 128.3 (2×aromatic <u>C</u>H), 128.1 (2×aromatic <u>C</u>H), 127.0 (aromatic <u>C</u>H), 119.9 (CH=<u>C</u>), 115.8 (<u>C</u>H=CHCH$_2$), 114.0 (2×aromatic <u>C</u>H), 109.4 (N<u>C</u>H=C), 55.1 (O<u>C</u>H$_3$), 53.4 (N<u>C</u>H$_2$C$_6$H$_4$OCH$_3$), 47.4 (CH=CH<u>C</u>H$_2$), 46.5 (NH<u>C</u>H$_2$C$_6$H$_5$), 27.5 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve CI-methane)** 364 (MH$^+$, 100%), 363 (33), 257 (51), 121 (85), 91 (55); **HRMS** calcd. for $C_{22}H_{26}N_3O_2$ (MH$^+$) 364.2020, found 364.2022.

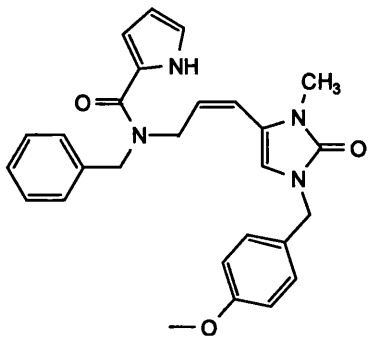
1*H*-Pyrrole-2-carboxylic acid benzyl-(3-[1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl]-prop-2-ynyl)amide (404)



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. **ν_{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; **δ_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^4), 4.85 (2H, s, $CH_2C_6H_5$), 4.64 (2H, s, $CH_2C_6H_4OCH_3$), 4.54 (2H, s, $CH_2C{\equiv}C$), 3.74 (3H, s, OCH_3), 3.03 (3H, s, NCH_3) ppm; **δ_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^{3}H), 108.4 (pyrrole C^{4}H), 105.1 (C=CH), 90.0 (C≡C), 72.1 (C≡C), 54.8 (OCH_3), 50.2 ($C_6H_5CH_2N$), 45.5 ($NCH_2C_6H_4OCH_3$), 37.6 ($CH_2C{\equiv}C$), 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 $C_{27}H_{27}N_4O_3$ (MH$^+$) 455.2083, found 455.2069.

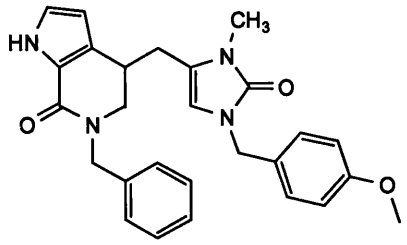
1*H*-Pyrrole-2-carboxylic acid benzyl-(3-[1-(4-methoxy-benzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl]-allyl)-amide (407)



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

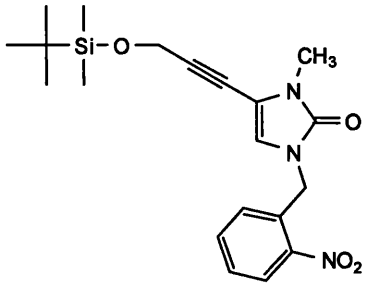
temperature. Silver nitrate (129 mg, 0.8 mmol) was then added and the suspension stirred for a further 15 min. The zinc couple was isolated by filtration, washed successively with 10 mL portions of H_2O, MeOH, acetone and Et_2O, and dried under suction. Alkyne **404** (101 mg, 0.22 mmol) was dissolved in MeOH (6 mL) and H_2O (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_{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_2CH=CH), 6.06-6.05 (1H, m, pyrrole C^{4}H), 5.67 (1H, dt, *J*=11.7, 5.9 Hz, CH_2CH=CH), 4.73 (2H, s, $CH_2C_6H_5$), 4.62 (2H, s, $CH_2C_6H_4OCH_3$), 4.25 (2H, dd, *J*=5.8, 1.7 Hz, CH_2CH=CH), 3.73 (3H, s, $C_6H_4OCH_3$), 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_2CH=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 $C_{27}H_{29}N_4O_3$ (MH^+) 457.2240, found 457.2249.

6-Benzyl-4-[1-(4-methoxybenzyl)-3-methyl-2-oxo-2,3-dihydro-1*H*-imidazol-4-ylmethyl]-1,4,5,6-tetrahydropyrrolo[2,3-*c*]pyridin-7-one (408)



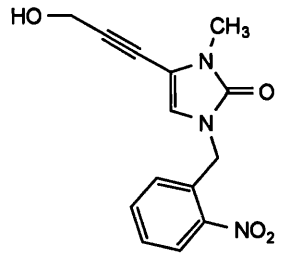
Alkene **407** (30.2 mg, 0.066 mmol) and trityl tetrafluoroborate (21.9 mg, 0.066 mmol) were dissolved in DCM (1 mL). The resulting solution was stirred at ambient temperature for 18 h and then concentrated *in vacuo*. Flash chromatography (gradient elution: DCM:MeOH:100:0, 100:2, 100:4, 100:8, 100:16) gave bicycle **408** (8.2 mg, 0.018 mmol, 27%) as a yellow oil. ν_{max}**/cm^{-1} (CDCl$_3$ film)** 3207 (NH stretch), 1674 (C=O stretch), 1634 (C=O stretch), 733 cm^{-1}; δ_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$_2$); δ_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 CH), 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 CI-methane)** 457 (MH$^+$, 68%), 225 (49), 135 (62), 121 (100), 91 (33); **HRMS** calcd. for $C_{27}H_{29}N_4O_3$ (MH$^+$) 457.2240, found 457.2235.

4-(3-(*tert*-Butyldimethylsilanyloxy)-prop-1-ynyl)-3-methyl-1-(2-nitrobenzyl)-1,3-dihydroimidazol-2-one (411)



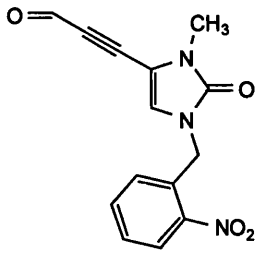
Silyl ether **313** (1.00 g, 3.75 mmol) was dissolved in DMF (80 mL) and cooled to 0 °C. Potassium *tert*-butoxide (463 mg, 4.13 mmol) was added in and the solution stirred at ambient temperature for 30 min. 2-Nitrobenzylbromide (1.60 g, 7.41 mmol) was then added and the solution stirred for a further 16 h. The solution was poured into H_2O (100 mL), extracted with EtOAc (3×100 mL), dried over Na_2SO_4 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. ν_{max}/cm^{-1} (KBr disc) 2230 (C≡C stretch), 1684 (C=O stretch), 1558 (NO_2 stretch); 1335 (NO_2 stretch); 1088; δ_H **(300 MHz, $CDCl_3$)** 8.07 (1H, dd, *J*=8.2, 1.3 Hz, aromatic C<u>H</u>), 7.58 (1H, td, *J*=7.5, 1.4 Hz, aromatic C<u>H</u>), 7.44 (1H, td, *J*=8.2, 1.5 Hz, aromatic C<u>H</u>), 7.32 (1H, dd, *J*=7.8, 1.1 Hz, aromatic C<u>H</u>), 6.56 (1H, s, C=C<u>H</u>), 5.17 (2H, s, C<u>H</u>$_2$C$_6$H$_4$NO$_2$), 4.50 (2H, s, C<u>H</u>$_2$OSi), 3.27 (3H, s, NC<u>H</u>$_3$), 0.90 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 0.12 (6H, s, Si(C<u>H</u>$_3$)$_2$) ppm; δ_C **(75 MHz, $CDCl_3$)** 152.6 (<u>C</u>=O), 147.8 (aromatic <u>C</u>NO$_2$), 134.1 (aromatic <u>C</u>H), 132.3 (aromatic <u>C</u>CH$_2$N), 130.1 (aromatic <u>C</u>H), 128.8 (aromatic <u>C</u>H), 125.2 (aromatic <u>C</u>H), 116.0 (C=<u>C</u>H), 107.6 (<u>C</u>=CH), 94.2 (<u>C</u>≡C), 72.8 (<u>C</u>≡C), 52.1 (<u>C</u>H$_2$OSi), 44.6 (<u>C</u>H$_2$C$_6$H$_4$NO$_2$), 28.5 (N<u>C</u>H$_3$), 25.8 (SiC(<u>C</u>H$_3$)$_3$), 18.3 (Si<u>C</u>(CH$_3$)$_3$), -5.1 (Si(<u>C</u>H$_3$)$_2$) ppm; ***m/z*** **(+ve CI-methane)** 402 (MH^+, 100%), 372 (74), 267 (8), 106 (13); **HRMS** calcd. for $C_{20}H_{28}N_3O_4Si$ (MH^+): 402.1849, found 402.1839; **Analysis** calcd. for $C_{20}H_{27}N_3O_4Si$: 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)



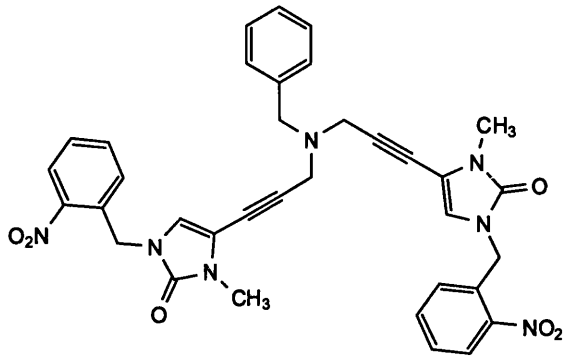
Silyl ether **411** (1.19 g, 2.96 mmol) was dissolved in THF (50 mL) and cooled to 0 °C. TBAF (1M in THF, 3.3 mL, 3.3 mmol) was added dropwise and the solution stirred for 10 min. The solution was then poured into H_2O (50 mL), extracted with EtOAc (3×50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (100% EtOAc) afforded alcohol **411** (0.78 g, 2.71 mmol, 92%) as a pale yellow solid, mp 154 °C. ν_{max}**/cm^{-1} (KBr disc)** 3381 (OH stretch), 2218 (C≡C stretch), 1663 (C=O stretch), 1529 (NO_2 stretch), 1335 (NO_2 stretch); δ_H **(300 MHz, $CDCl_3$)** 8.07 (1H, dd, *J*=8.2, 1.3 Hz, aromatic C<u>H</u>), 7.59 (1H, td, *J*=7.5, 1.4 Hz, aromatic C<u>H</u>), 7.48-7.42 (1H, m, aromatic C<u>H</u>), 7.35-7.32 (1H, m, aromatic C<u>H</u>), 6.59 (1H, s, C=C<u>H</u>), 5.18 (2H, s, C<u>H</u>$_2$Ar), 4.48 (2H, d, *J*=5.4 Hz, C<u>H</u>$_2$OH), 3.28 (3H, s, NC<u>H</u>$_3$), 1.76 (1H, broad t, *J*=6.3 Hz, CH$_2$O<u>H</u>) ppm; δ_C **(75 MHz, CD_3OD)** 153.9 (<u>C</u>=O), 149.4 (aromatic <u>C</u>NO$_2$), 135.1 (aromatic <u>C</u>H), 133.4 (aromatic <u>C</u>CH$_2$N), 130.1 (aromatic <u>C</u>H), 130.0 (aromatic <u>C</u>H), 126.2 (aromatic <u>C</u>H), 117.8 (C=<u>C</u>H), 109.2 (<u>C</u>=CH), 95.9 (<u>C</u>≡C), 73.0 (<u>C</u>≡C), 51.1 (<u>C</u>H$_2$OH), 45.7 (<u>C</u>H$_2$C$_6$H$_4$NO$_2$), 28.8 (N<u>C</u>H$_3$) ppm; ***m/z*** **(+ve CI-methane)** 288 (MH^+, 33%), 183 (16), 153 (29), 121 (100), 106 (22); **HRMS** calcd. for $C_{14}H_{14}N_3O_4$ (MH^+): 288.0984, found 288.0989.

3-Methyl-1-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl-propynal (413)



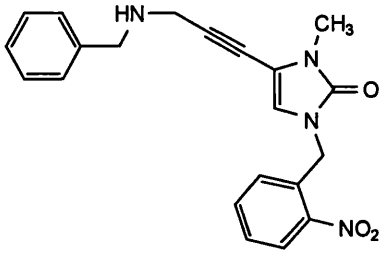
Alcohol **412** (650 mg, 2.26 mmol) was dissolved in DCM (250 mL) at ambient temperature and Dess-Martin Periodinane (1.16 g, 2.73 mmol) added. The solution was stirred for 3 h then sodium thiosulfate (20 g) in H_2O (60 mL) and saturated $NaHCO_3$ solution (60 mL) were added. The biphasic mixture was 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 Na_2SO_4 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. **ν_{max}/cm^{-1} (KBr disc)** 3076 (CH stretch), 2178 (C≡C stretch), 1693 (C=O aldehyde stretch), 1647 (C=O urea stretch), 1533 (NO_2 stretch), 1335 (NO_2 stretch), 731; **δ_H (300 MHz, $CDCl_3$)** 9.34 (1H, s, C<u>H</u>O), 8.08 (1H, dd, *J*=8.1, 1.3 Hz, aromatic C<u>H</u>), 7.62 (1H, td, *J*=7.6, 1.4 Hz, aromatic C<u>H</u>), 7.52-7.42 (2H, m, 2×aromatic C<u>H</u>), 7.10 (1H, s, C=C<u>H</u>), 5.17 (2H, s, C<u>H</u>$_2$Ar), 3.32 (3H, s, NC<u>H</u>$_3$) ppm; **δ_C (75 MHz, $CDCl_3$)** 174.8 (<u>C</u>HO), 152.3 (<u>C</u>=O), 147.9 (aromatic <u>C</u>NO_2), 134.2 (aromatic <u>C</u>), 131.0 (aromatic <u>C</u>), 129.4 (aromatic <u>C</u>), 125.3 (aromatic <u>C</u>), 123.7 (aromatic <u>C</u>), 165.0 (C=<u>C</u>H), 96.9 (<u>C</u>=CH), 84.2 (<u>C</u>≡C), 77.2 (C≡<u>C</u>), 45.0 (<u>C</u>H$_2$C$_6$H$_4$NO$_2$), 28.7 (N<u>C</u>H$_3$) ppm; ***m/z* (+ve CI-methane)** 286 (MH^+, 100%), 256 (30), 151 (67), 138 (33), 106 (18), 71 (18); **HRMS** calcd. for $C_{14}H_{12}N_3O_4$ (MH^+): 286.0828, found 286.0822; **Analysis** calculated for $C_{14}H_{11}N_3O_4$: C, 59.0, H, 3.9, N, 14.7; found C, 58.6, H, 3.8, N, 14.5%.

Benzyldi-(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 triacetoxyborohydride (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:Et_3N, 200:1) gave tertiary amine **414** (42 mg, 0.06 mmol, 52%) as a yellow oil. **ν_{max}/cm^{-1} ($CDCl_3$ film)** 2938 (CH stretch), 2235 (C≡C stretch), 1687 (C=O stretch), 1532 (NO_2 stretch), 1349 (NO_2 stretch), 1173, 730; **δ_H (400 MHz, $CDCl_3$)** 8.06 (2H, dd, *J*=8.2, 1.2 Hz, 2×aromatic C<u>H</u>), 7.59 (2H, td. *J*= 7.6, 1.3 Hz, 2×aromatic C<u>H</u>), 7.44 (2H, td, *J*=7.8, 1.4 Hz, 2×aromatic C<u>H</u>), 7.35 (2H, dd, *J*=7.8, 1.0 Hz, 2×aromatic C<u>H</u>), 7.33-7.24 (5H, m, 5×aromatic C<u>H</u>), 6.58 (2H, s, 2×C=C<u>H</u>), 5.16 (4H, s, 2×C<u>H</u>$_2$), 3.72 (2H, s, C<u>H</u>$_2$$C_6H_5$), 3.63 (4H, s, 2×C<u>H</u>$_2$), 3.28 (6H, s, 2×NC<u>H</u>$_3$) ppm; **δ_C (100 MHz, $CDCl_3$)** 152.4 (2×<u>C</u>=O), 147.8 (2×aromatic <u>C</u>NO_2), 137.3 (2×aromatic <u>C</u>CH_2N), 134.0 (2×aromatic <u>C</u>H), 132.1 (aromatic <u>C</u>), 130.3 (2×aromatic <u>C</u>H), 129.0 (2×aromatic <u>C</u>H), 128.9 (2×aromatic <u>C</u>H), 128.5 (2×aromatic <u>C</u>H), 127.7 (aromatic <u>C</u>H), 125.2 (2×aromatic <u>C</u>H), 115.8 (2×C=<u>C</u>H), 107.5 (2×<u>C</u>=CH), 90.8 (2×<u>C</u>≡C), 73.4 (2×<u>C</u>≡C), 57.5 (N<u>C</u>$H_2C_6H_5$), 44.5 and 43.0 (2×<u>C</u>$H_2C_6H_4NO_2$ and 2×<u>C</u>H_2N), 28.5 (2×N<u>C</u>H_3) ppm; ***m/z* (+ve FAB)** 646 (MH^+, 9%), 340 (9), 270 (20), 177 (15), 154 (100); **HRMS** calcd. for $C_{35}H_{32}N_7O_6$ (MH^+) 646.2414, found 646.2443.

4-(3-Benzylaminoprop-1-ynyl)-3-methyl-1-(2-nitrobenzyl)-1,3-dihydroimidazol-2-one (415)

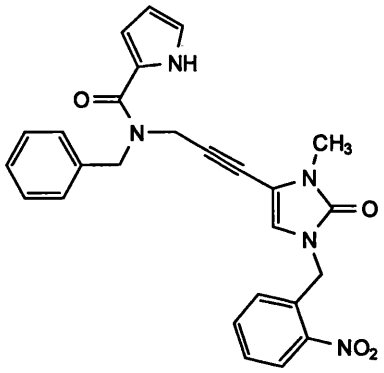


Aldehyde **413** (455 mg, 1.60 mmol) was dissolved in DCM (30 mL) with activated 4Å molecular sieves (1.27 g). Benzylamine (0.90 mL, 8.24 mmol) was added and the solution stirred at ambient temperature for 17 h. A small sample was removed for ^{1}H NMR to confirm complete imine formation and two imine isomers were observed in a 1:1 ratio. δ_H **(300 MHz, $CDCl_3$)** 8.11-8.09 (2H, m, 2×aromatic C<u>H</u>), 7.83 (1H, s, C<u>H</u>=N), 7.78 (1H, s, C<u>H</u>=N), 7.63-7.60 (2H, m, 2×aromatic C<u>H</u>), 7.45-7.37 (2H, m, 2×aromatic C<u>H</u>), 7.37-7.30 (10H, m, $CH_2C_6\underline{H}_5$), 7.29-7.26 (2H, m, 2×aromatic C<u>H</u>), 6.88 (1H, s, C<u>H</u>=C), 6.80 (1H, s, C<u>H</u>=C), 5.23 (2H, s, $C\underline{H}_2C_6H_4NO_2$), 5.22 (2H, s, $C\underline{H}_2C_6H_4NO_2$), 4.86 (2H, s, $C\underline{H}_2C_6H_5$), 4.77 (2H, s, $C\underline{H}_2C_6H_5$), 3.33 (6H, s, $NC\underline{H}_3$) ppm.

Sodium triacetoxyborohydride (1.35 g, 6.38 mmol) was added, the reaction stirred for a further 24 h, filtered through Celite® and concentrated *in vacuo*. Flash chromatography (EtOAc:Et_3N; 200:1) afforded amine **415** (518 mg, 1.38 mmol, 86%) as a yellow oil. ν_{max}**/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; δ_H **(400 MHz, $CDCl_3$)** 7.97 (1H, d, *J*=8.1 Hz, aromatic C<u>H</u>), 7.50 (1H, t, *J*=7.6 Hz, aromatic C<u>H</u>), 7.35 (1H, t, *J*=7.4 Hz, aromatic C<u>H</u>), 7.23-7.21 (5H, m, $CH_2C_6\underline{H}_5$) 7.09-7.08 (1H, m, aromatic C<u>H</u>), 6.46 (C=C<u>H</u>), 5.08 (2H, s, $C\underline{H}_2C_6H_4NO_2$), 3.80 ($NC\underline{H}_2C_6H_5$) 3.55 ($NC\underline{H}_2C{\equiv}C$), 3.20 ($NC\underline{H}_3$) ppm; δ_C **(100 MHz, $CDCl_3$)** 152.3 (<u>C</u>=O), 147.7 (aromatic <u>C</u>), 139.1 (aromatic <u>C</u>), 133.9 (aromatic <u>C</u>H), 132.2 (aromatic <u>C</u>), 129.9 (aromatic <u>C</u>H), 128.7 (aromatic <u>C</u>H), 129.4 (2×aromatic <u>C</u>H), 128.2 (2×aromatic <u>C</u>H), 127.1 (aromatic <u>C</u>H), 125.1 (aromatic <u>C</u>H), 115.3 (C=<u>C</u>H), 107.7 (<u>C</u>=CH), 93.8 (<u>C</u>≡C), 71.4 (<u>C</u>≡C), 52.4 ($N\underline{C}H_2C_6H_5$), 44.4 ($N\underline{C}H_2C_6H_4NO_2$), 38.1.0 ($NH\underline{C}H_2C{\equiv}C$), 28.4 ($N\underline{C}H_3$) ppm; ***m/z*** **(+ve CI-methane)** 377

(MH^+, 100%), 347 (27), 270 (49), 242 (30), 120 (21), 106 (51); **HRMS** calcd. for $C_{21}H_{21}N_4O_3$ (MH^+) 377.1614, found 377.1609

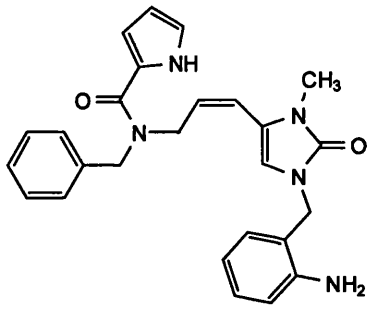
1*H*-Pyrrole-2-carboxylic acid benzyl-(3-(3-methyl-1-(2-nitrobenzyl)-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl)-prop-2-ynyl)-amide (416)



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. $NaHCO_3$ (10 mL) and brine (10 mL), dried over Na_2SO_4 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≡C stretch), 1693 (C=O stretch), 1607 (C=O stretch), 1526 (NO_2 stretch), 1423, 1339 (NO_2 stretch), 739; δ_H **(DMSO-d_6, 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, $CH_2C_6H_4NO_2$), 4.87 (2H, s, $NCH_2C_6H_5$), 4.57 (2H, s, $NCH_2C{\equiv}C$), 3.06 (3H, s, NCH_3) ppm; δ_C **(DMSO-d_6, 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

(aromatic C), 128.9 (aromatic CH), 128.5 (aromatic CH), 128.1 (2×aromatic CH), 126.9 (2×aromatic CH), 126.8 (aromatic CH), 124.3 (aromatic CH), 123.4 (aromatic C or C=CH), 121.6 (pyrrole CH), 116.5 (C=CH), 111.6 (pyrrole CH), 108.4 (pyrrole CH), 105.8 (aromatic C or C=CH), 91.3 (C≡C), 71.9 (C≡C), 50.3 ($CH_2C_6H_5$), 43.3 (CH_2), 37.7 (CH_2), 27.5 (NCH_3) ppm; ***m/z* (+ve FAB)** 470 (MH^+, 6%), 307 (32), 289 (15), 155 (30), 154 (100); **HRMS** calcd. for $C_{26}H_{24}N_5O_4$ (MH^+): 470.1828, found 470.1813.

(*Z*)-1*H*-Pyrrole-2-carboxylic acid benzyl-(3-3-methyl-1-(2-aminobenzyl)-2-oxo-2,3-dihydro-1*H*-imidazol-4-yl)-allyl)amide (417)



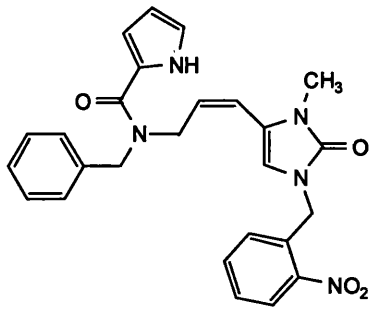
Zinc dust (500 mg, 7.64 mmol) was suspended in H_2O (3 mL), copper acetate monohydrate (66 mg, 0.33 mmol) added and the suspension stirred vigorously for 15 min. Then silver nitrate (65 mg, 0.38 mmol) was added and the suspension stirred for a further 15 min. The zinc couple was isolated by filtration, washed successively with 5 mL portions of H_2O, MeOH, acetone and Et_2O, and dried under suction. Alkyne **416** (48.2 mg, 0.10 mmol) was dissolved in MeOH (3 mL) and H_2O (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. **ν_{max}/cm^{-1} ($CDCl_3$ film)** 3242 (NH stretch), 2928 (CH stretch), 1674 (broad, 2 overlapping C=O stretch), 739; **δ_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_2CH=CH), 6.06-6.04 (1H, m, pyrrole CH), 5.66 (1H, dt, *J*=11.7, 5.9 Hz, CH_2CH=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_2CH=CH), 3.11 (3H, s, NCH_3) ppm;

δ_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 ($CH_2C_6H_5$), 42.6 (CH_2CH=CH), 39.3 ($CH_2C_6H_4NH_2$), 23.2 (NCH_3) ppm; ***m/z*** **(+ve EI)** 442 (MH^+, 100%), 348 (28), 242 (54), 200 (19), 152 (41), 149 (22); **HRMS** calcd. for $C_{26}H_{28}N_5O_2$ (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.

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



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. ν_{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); δ_H **(DMSO-d_6, 500 MHz, 343K)** 11.26 (1H, broad s, NH), 8.03 (1H, dd, *J*=8.1, 1.2 Hz, aromatic CH), 7.61 (1H, td, *J*=7.6, 1.2 Hz, aromatic CH), 7.53 (1H, td, *J*=6.6, 1.2 Hz, aromatic CH), 7.30-7.22 (5H, m, 5×aromatic CH), 7.05 (1H, broad d, *J*=7.3 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 Hz, CH_2CH=CH), 6.06-6.04 (1H, s, pyrrole CH), 5.72 (1H, dt, *J*=11.7, 5.9 Hz, CH_2CH=CH), 5.03 (2H, s, $NCH_2C_6H_4NO_2$), 4.73 (2H, s, $NCH_2C_6H_5$), 4.23 (2H, dd, *J*=6.0, 1.6 Hz, CH_2CH=CH), 3.14 (1H, s, NCH_3); δ_c **(DMSO-d_6, 125 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 ($CH_2C_6H_5$), 46.2 ($CH_2C_6H_4NO_2$), 43.1 (CH_2CH=CH), 27.0 (NCH_3) ppm; ***m/z* (+ve FAB)** 427 (MH^+, 8%), 307 (27), 155 (29), 154 (100), 127 (61); **HRMS** calcd. for $C_{26}H_{26}N_5O_4$ (MH^+) 472.1985, found 472.2010.

CHAPTER IV

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