Novel Hydroxylamine Chemistry and Advances in Product Purification

A thesis submitted to Cardiff University

by

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For Lesley, Nigel

and Felicity

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Finally, I would like to thank all of my friends and, last but not least, Clare, for her love and support. I am forever grateful.

Declaration

We, the undersigned, declare that the work presented in this thesis is the result of the candidate's own investigation.

Anthony James Proctor
(Candidate)

Date: 1/12/'07

Prof. David W. Knight
(Director of Studies)

Date: 3/12/07

I declare that the work in this thesis has not previously been accepted in the substance for any degree and is not being concurrently submitted in candidature for any degree.

Anthony James Proctor

Date: 1/12/'07

I hereby give my concent for this thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Anthony James Proctor

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Abstract

The Knight group has been working for some time on the formation of polysubstituted heterocycles through 5-*endo* cyclisations, employing both oxygen and nitrogen nucleophiles. It seemed a logical progression to investigate the use of suitably functionalised hydroxylamines in the same manner, as a route to the synthesis of polysubstituted isoxazole derivatives.

The *N*-tosyl *O*-allylic hydroxylamine **100** was shown to participate in a 5-*endo*-trig iodocyclisation to yield the iodoisoxazolidine **101**. The iodo-substituent was then displaced with an azide nucleophile and the isoxazolidine **132** subsequently reduced to yield the aminoisoxazolidene **134**.

Problems encountered with the use of the Mitsunobu reaction in the synthesis of the required starting materials had previously led the group to develop the use of the oxaziridine **107** as an aminating agent. In this project, however, the structural assignment of the products generated by this procedure was shown to be incorrect.

A range of *O*-propargyl hydroxylamines were shown to participate in silver nitrate-catalysed 5-*endo*-dig ring closures, affording a diverse set of 2,5-dihydroisoxazoles, 4,5-dihydroisoxazoles and, through *in situ* oxidation, isoxazoles; all where received in excellent yield and with no requirement for additional purification.

N-tosyl *O*-alkyl hydroxylamines were shown to participate in acid-catalysed cyclisations, generating 5-membered and 6-membered rings with exceptionally high levels of purity. These substrates allowed for the synthesis of *spiro*-cycles and fused ring systems through cascade reactions. Minor products obtained in several cases were identified as regioisomers. Careful repositioning of the alkene bond prevented this isomerisation. Cleavage of the nitrogen-oxygen bond allowed for the synthesis of an amino alcohol **360**, demonstrating that such cyclisations are effectively 'transfer hydroaminations'.

In order to limit the laborious processing required for purification of products resulting from the Mitsunobu reaction, a procedure was developed that allowed for removal of contaminants by selective oxidation. This represents the first 'chromatography-free' work up procedure for the Mitsunobu reaction.

The conditions utilised in the purification of products resulting from the Mitsunobu reaction were also applied to the removal of ruthenium contaminants from metathesis products. This approach yielded splendid results.

Contents

Abbreviations

Abbreviations used in this text:

APCI	Atmospheric Pressure Chemical Ionisation
Aq.	Aqueous
^{i}Bu	*iso*-Butyl
^{t}Bu	*tert*-Butyl
Boc	Butoxycarbonyl
Boc-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
bp	Boiling point
15-c-5	15-crown-5
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIAD	Diisopropylazodicarboxylate
DMF	Dimethylformamide
ee	Enantiomeric excess
Eq.	Equivalents
FTIR	Fourier Transform Infra-Red
h	Hours
HRMS	High Resolution Mass Spectrometry
HPLC	High Pressure Liquid Chromatography
M	Molar (moles L^{-1})
MeCN	Acetonitrile
Mesyl/Ms	Methanesulphonyl
mins	Minutes
Moc	Methoxycarbonyl
mp	Melting Point
ms	Mass Spectrometry
NaH	Sodium Hydride
NMR	Nuclear Magnetic Resonance
Nosyl/Ns	*para*-Nitrobenzenesulphonyl
o/n	Over Night
Ppb	Parts per billion
Ppm	Parts per million
^{i}Pr	*iso*-Propyl

Rf	Relative front
rt	Room Temperature
Sat.	Saturated
SiO_2	Silica gel
TBAF	Tetrabutyl ammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFAA	Trifluoroacetic anhydride
TFA	Trifluoroacetic acid
pTSA	*para*-Toluenesulphonic acid
Tosyl/Ts	*para*-Toluenesulphonyl

CHAPTER 1

Chapter One

Introduction

Background

For some time the Knight group has held an interest in the means by which heteroatomic nucleophiles can be induced to perform intramolecular additions to carbon-carbon π bonds; generally with high levels of regioselectivity and, where relevant, stereoselectivity.[1] After enjoying success in the synthesis of furans, pyrroles and their respective saturated analogues, it seemed a logical progression to extend these efforts towards the synthesis of heterocycles containing multiple heteroatoms. Of particular interest were those heterocycles that contain a nitrogen-oxygen (N-O) bond, given the frequent occurrence of such structures in Nature and in several synthetic compounds exhibiting high levels of biological activity. The comparative weakness of the N-O bond (200 kJ/mol for N-O σ bond *c.f.* C-N 308 kJ/mol and C-O 360 kJ/mol) also makes such compounds ideal synthetic precursors to amino-alcohols and a range of functional groups that may result there from.[2]

We began this project by examining how such a methodology might be applied to the synthesis of poly-substituted derivatives of the isoxazole **1**, 4,5-dihydroisoxazole **2**, 2,5-dihydroisoxazole **3**, 2,3-dihydroisoxazole **4** and isoxazolidine **5** systems (Diagram 1).

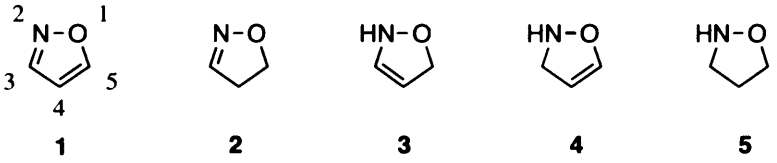
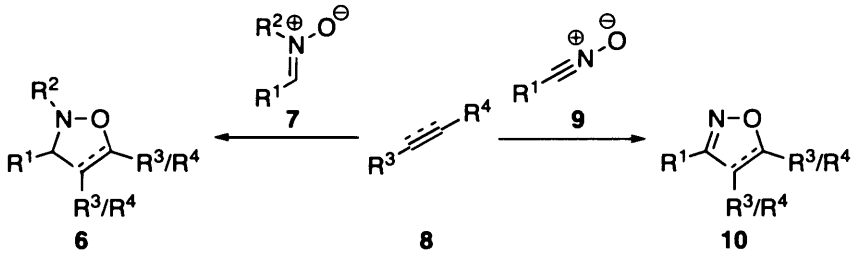


Diagram 1

Classical synthesis

The isoxazoles and their various reduced derivatives are typically synthesised by a concerted [3+2] cycloaddition of a nitrone or nitrile oxide to an alkene or alkyne (Scheme 1).

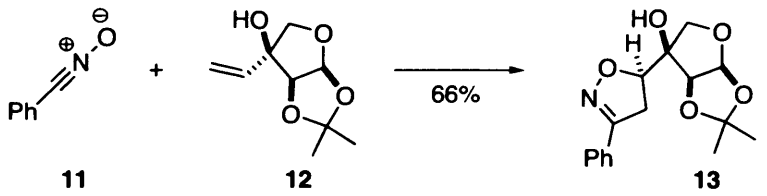


Scheme 1

These reactions, commonly known as [1,3]-dipolar cycloadditions, were first reported by Buchner in 1888 and have been the subject of extensive investigation.[3] This robust process allows for a broad range of functionality to be incorporated in the reacting species, thus

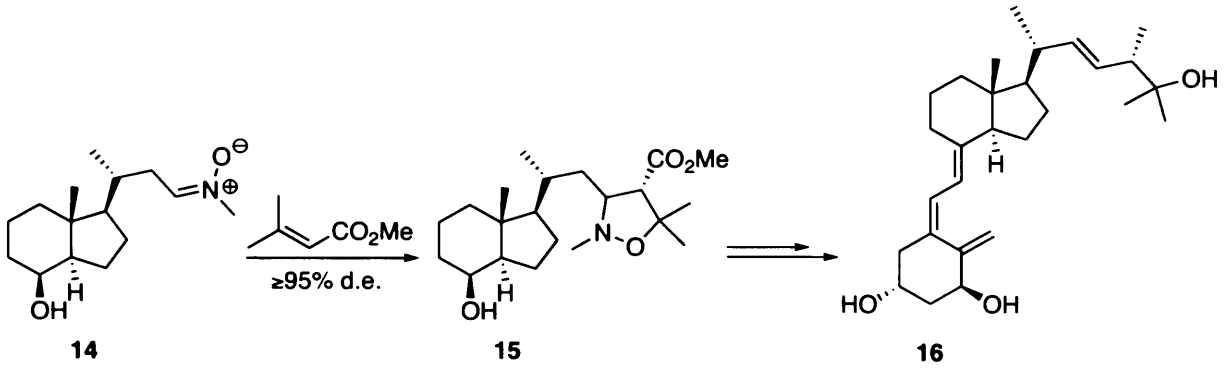
affording considerable flexibility regarding substituents that may be required in a given product. The synthesis of the required substrates is typically readily achieved given the abundance of synthetic approaches to alkenes, alkynes and nitrones. The synthesis of nitrile oxides is also simple to achieve, although these substrates are rarely isolable and must be handled with care.

Nevertheless, the principle drawback associated with such transformations is the regio- and stereo-chemical outcome of the ring-forming step. Determined by variations in the efficiency of orbital overlap between the dipole and the alkene or alkyne, as a general rule the observed regioselectivity most often arises from attack by the oxygen nucleophile at the more substituted position of the carbon-carbon π bond. Instances of such selectivity are numerous, for example, the complete regioselectivity observed in the cycloaddition of nitrile oxide **11** to the sugar-derivative **12**, reported by Tronchet (Scheme 2).[4]



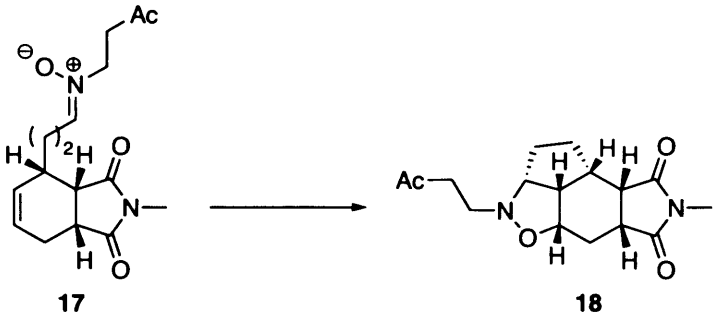
Scheme 2

Similar frontier orbital considerations can also be used to rationalise the stereo-chemical outcome of the reaction, although such analyses are considerably more capricious.[5] With the potential for the creation of up to three contiguous stereo-centres in the cyclic product, the interest in controlling the stereoselectivity of the reaction has been considerable. Tactics employed to this end have included the use of alkenes, alkynes, nitrones and nitrile oxides bearing stereogenic centres close to the reaction site and the use of tethered reagents in intramolecular cycloadditions.[6] There has also been considerable interest in the use of Lewis acid catalysts that induce intermolecular complexation, often in conjunction with a chiral ligand, as a means of favouring the desired approach path prior to cyclisation.[7] The efficiency of one such approach was aptly demonstrated by Baggiolini and co-workers, who used the chiral nitrone **14** to control the stereochemistry of a cycloaddition to methyl 3,3-dimethylacrylate, en route to the synthesis of 1α, 25-dihydroxy-ergocalciferol **16**, a product of the degradation of vitamin D_3 in human liver and kidneys (Scheme 3).



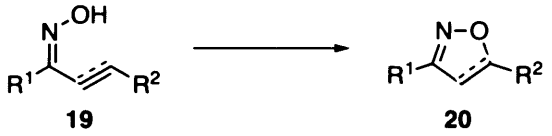
Scheme 3

Alternatively, the use of tethered reaction components was demonstrated by Grigg and co-workers in the synthesis of the tetra-cyclic isoxazolidine **18**, *via* the *in situ* generation and cyclisation of nitrone **17** (Scheme 4).[8]



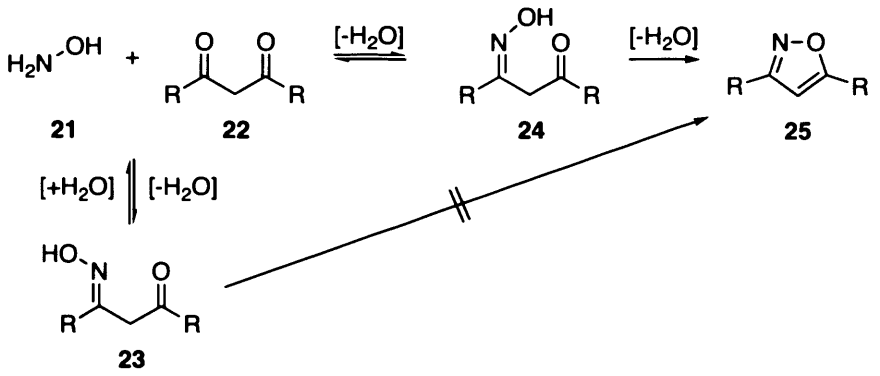
Scheme 4

A significant, albeit limited alternative to such cycloadditions is the intramolecular cyclisation of alkenyl or alkynyl oximes **19**, resulting in the formation of isoxazoles or 4,5-dihydroisoxazoles respectively (Scheme 5).[9]



Scheme 5

The required substrates are typically formed by condensation of hydroxylamine with a suitable carbonyl, however, oximes are predominantly obtained as a mixture of *cis* and *trans* isomers (with respect to the alkene-alkyne), with only the *cis* isomer capable of cyclisation. Alternatively, isoxazoles may be synthesised through a double condensation of hydroxylamine **21** with a 1,3-dicarbonyl **22** (Scheme 6).[2]

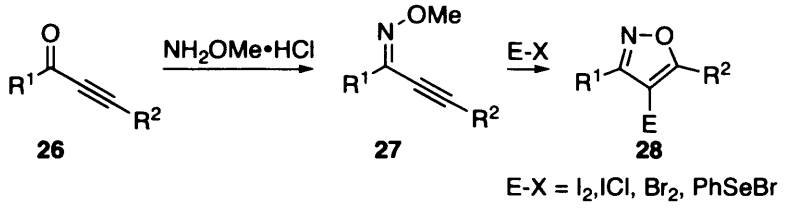


Scheme 6

Unsymmetrical dicarbonyls generally yield a mixture of regioisomers, thus severally limiting this approach.

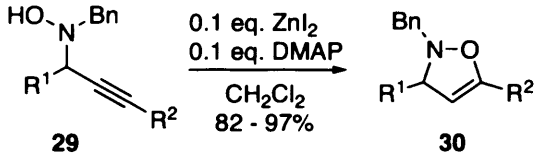
Recent advances

In a recent variation on the aforementioned cyclisation of oximes (Schemes 5 and 6), Larock has reported that 2-alkyn-1-one *O*-methyl oximes **27**, formed *in situ* by condensation, can undergo electrophile-induced cyclisation, yielding a range of electrophile-functionalised isoxazoles **28**, under mild reaction conditions (Scheme 7).[10]



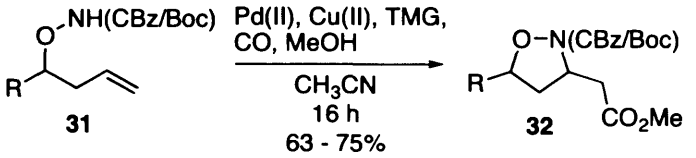
Scheme 7

Once again, only one of the possible oxime stereoisomers is capable of cyclisation and thus oxime formation must be reversible if good yields are to be achieved. The potential application of hydroxylamines in dihydroisoxazole synthesis has been highlighted by Carreira and co-workers, who have reported a metal catalysed, intramolecular 5-*endo*-dig cyclisation of a nitrone-derived *N*-benzyl-*N*-propargyl hydroxylamine **29**, as a means for generating a range of *N*-benzyl-2,3-dihydroisoxazoles **30**, in high yield (Scheme 8).[11]



Scheme 8

An intriguing variation was subsequently reported by Bates and Sa-Ei who demonstrated that a combination of palladium, copper, methanol, tetramethyl guanidine (TMG) and carbon monoxide could induce the 5-*exo*-trig cyclisation of *O*-alkenyl hydroxylamines **31**, with the nitrogen portion of the hydroxylamine acting as a nucleophile, whilst at the same time homologating the terminal alkene by carbonylation (Scheme 9).[12]

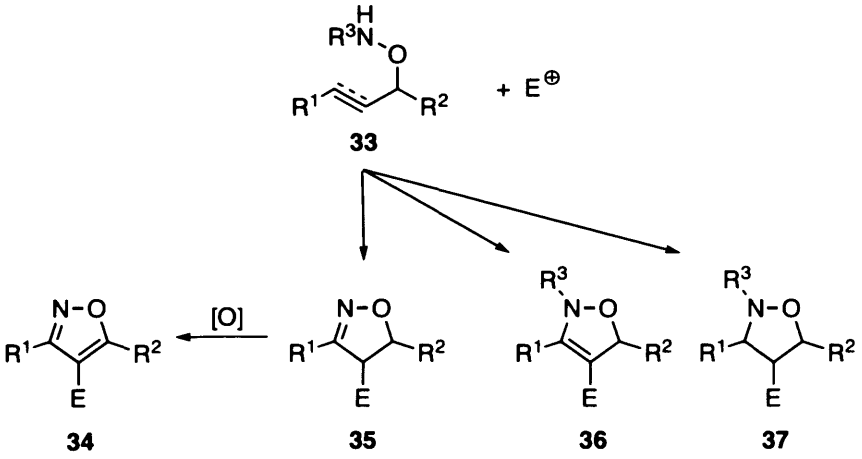


Scheme 9

Although the examples reported in both cases are undoubtedly limited, they serve as an important illustration of the potential of such ring-closures in the synthesis of heterocycles of this kind.

An alternative synthesis

The inherent regiospecificity and potential for significant advances in stereocontrol makes the intramolecular cyclisation of functionalised hydroxylamines an attractive prospect as an alternative method for the synthesis of the isoxazoles, complementary to the aforementioned [1,3]-dipolar cycloadditions. Thus it seems highly likely that, should a suitable electrophile be found, both alkenes and alkynes could be sufficiently activated to allow for attack by a range of suitably functionalised hydroxylamine-derived nucleophiles. The nitrogen portion of such a hydroxylamine seemed to be the obvious candidate for a ring-closure nucleophile, as its inherent nucleophilicity should be greater than that of the oxygen atom and substitution at this point lends itself to the synthesis of four out of the five possible isoxazole analogues described previously (*i.e.* electrophile-substituted isoxazoles **34**, 4,5-dihydroisoxazoles **35**, 2,5-dihydroisoxazoles **36** and isoxazolidines **37**) (Scheme 10).

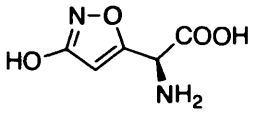


Scheme 10

Isoxazoles

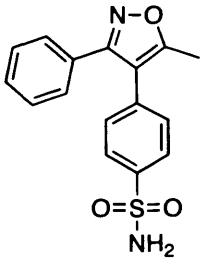
First identified by Claisen in 1888, 'monazole', as it was originally christened was later re-named 'isoxazole' by Hantszch, indicating its structural relationship to oxazole. During subsequent years, partially saturated analogues of these compounds were isolated but it was not until 1942 that the fully saturated analogue, isoxazolidine, was first synthesised.[3]

A variety of isoxazole analogues are found in Nature and are often core structural components of compounds with significant biological activity. For example, the toxin Ibotenic acid **38** can be isolated from the mushrooms *Amanita muscarina* and *Amanita panterina* and can cause hallucinations and muscle spasms if ingested.[13]



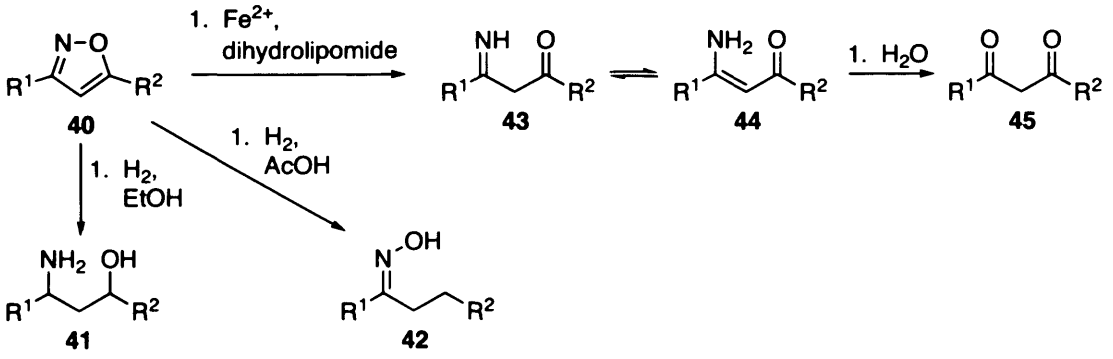
38

Several synthetic isoxazoles have shown significant biological activity. For example, isoxazoles have found continued application as antifungal agents[14] and in the treatment of pulmonary aspergillosis.[15] Until 2005, the potent COX-2 inhibitor Valdecoxib **39** was marketed by G. D. Searle & Co, under the trade name Bextra®, and used clinically for the treatment of arthritis and menstrual pain, although it was very recently withdrawn from sale after concerns were raised regarding a reported increase in the risk of heart attack, brought about by its regular consumption.[16]



39

Isoxazoles themselves can be readily reduced to yield 1,3-amino-alcohols **41**, oximes **42** or imines **43** / enamines **44** (which can subsequently be hydrolysed to yield 1,3-dicarbonyls **45**) depending upon the conditions used (Scheme 11).[17]



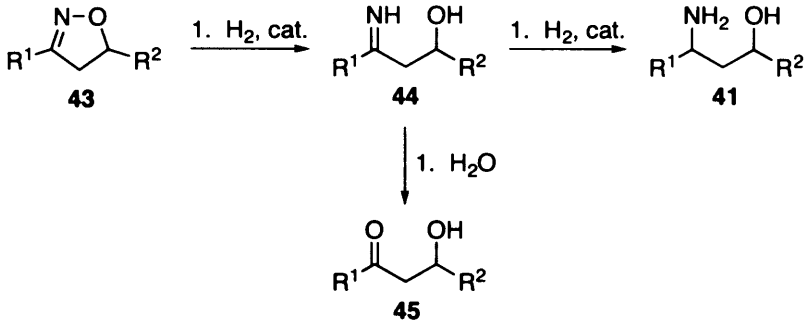
Scheme 11

As a consequence, isoxazoles are often used as protected forms of these functional groups.[18]

Dihydroisoxazoles

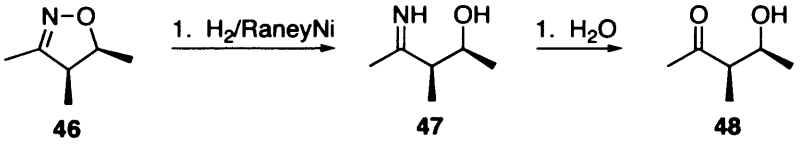
4,5-Dihydroisoxazoles display an impressive degree of biological activity, possessing antibacterial, antifungal and herbicidal properties.[19] As is the case with isoxazoles, these

isomers are also readily reduced, with catalytic hydrogenation affording β-hydroxyimines **44**, which can either be further reduced to 1,3-amino-alcohols **41** or hydrolysed to generate β-hydroxyketones **45** (Scheme 12).[3]



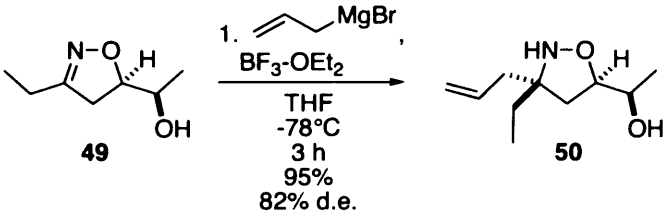
Scheme 12

Such processes often proceed with retention of stereochemistry, for example, yielding a single diastereoisomer of the hydroxyketone **48**, as demonstrated by Curran (Scheme 13).[20]



Scheme 13

4,5-Dihydroisoxazoles are also susceptible to nucleophilic attack at the *N*-substituted carbon. Recently, Mapp and co-workers have reported that a variety of Grignard reagents can, in the presence of a Lewis acid, undergo addition at this point and that the subsequent stereochemistry can be controlled by stereochemical features in the substrate (*e.g.* Scheme 14).[21]

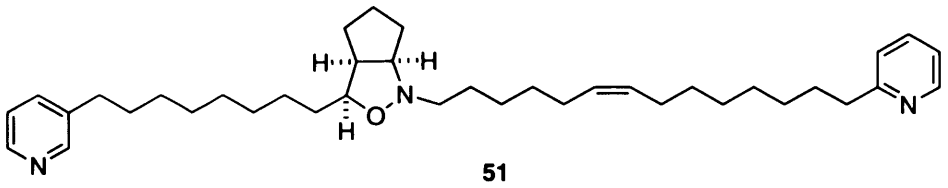


Scheme 14

Considerably less attention has been directed towards the chemistry of 2,5-dihydroisoxazoles, highlighting a clear need for further investigation.

Isoxazolidines

Several isoxazolidines are found in Nature, for example, the alkaloid Pyrinodemin A **51**, which was isolated from the Okinawan marine sponge *Amphimedon sp.* by Kobayashi and co-workers.[22]



51

The stereochemistry of the core isoxazolidine ring was subsequently confirmed by Baldwin, by means of an elegant total synthesis.[23]

Intriguingly, isoxazolidines have, along with isoxazoles and dihydroisoxazoles, also been reported to possess significant antifungal properties.[24] Isoxazolidines once again find synthetic utility as precursors to 1,3-amino-alcohols, with lithium aluminium hydride and catalytic hydrogenation among the most popular reagents for nitrogen-oxygen bond cleavage.[21]

CHAPTER 2

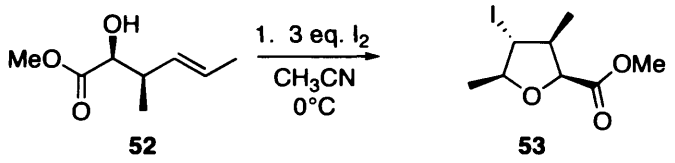
Chapter Two

5-*Endo* Iodocyclisations of Functionalised Hydroxylamines and the Chemistry of the Products

Background

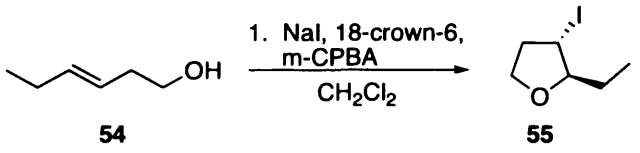
The application of the iodocyclisation procedure in the synthesis of heterocycles has been a heavily exploited tool. The electrophilic activation of unsaturated carbon-carbon bonds by an iodonium electrophile increases their susceptibility towards attack by a heteroatomic nucleophile, thus allowing for the synthesis of a wide range of polysubstituted heterocycles through ring closures, many of which apparently contravene Baldwin's rules.[25]

Such reactions were first documented as a versatile method for iodolactonisation. As this application gained popularity however, many working in the field documented the presence of significant amounts of iodo-tetrahydrofurans in the crude reaction products. Such observations were further investigated by Bartlett and Myerson who, in 1978, reported that the β,γ-unsaturated alcohol **52** produced large amounts of the iodo-tetrahydrofuran **53** as a single diastereoisomer, under standard iodolactonisation conditions (Scheme 15).[26]



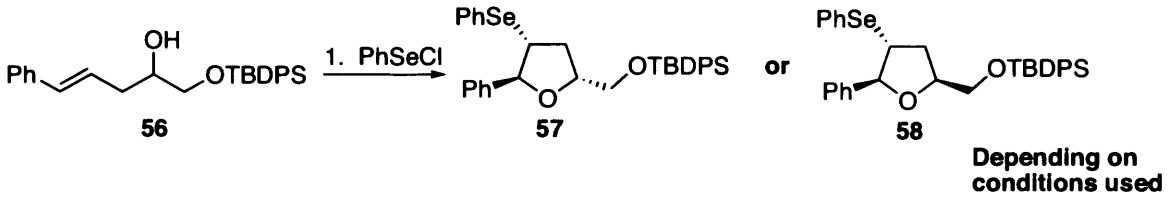
Scheme 15

In 1984, Srebnik and Mechoulam further refined the methodology by demonstrating that an iodine cation, generated *in situ*, could induce 5-*endo*-trig cyclisation of a primary alcohol **54**, yielding the iodo-tetrahydrofuran **55** (Scheme 16).[27]

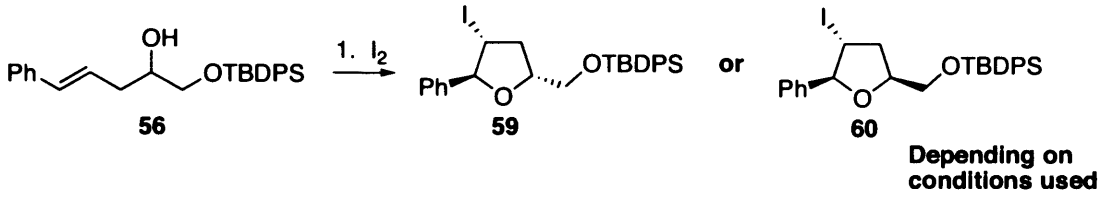


Scheme 16

Over several years, further investigation yielded significant improvements in the procedure and, along with iodine, various bromine cations and organo-selenium reagents were successfully applied to the synthesis of both furan and pyrrole derivatives. For example, Kang reported that both selenonium (*e.g.* Scheme 17)[28] and iodonium ions (*e.g.* Scheme 18)[29] could be used in the synthesis of polysubstituted tetrahydrofurans.

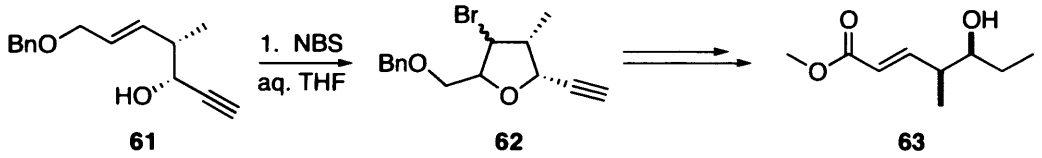


Scheme 17



Scheme 18

Takano has also applied NBS (*N*-bromosuccinimide) to a related bromocyclisation, generating the bromo-tetrahydrofuran **62**, en route to the synthesis of ester **63**, believed to be an intermediate in the biosynthesis of protomycinolide IV (Scheme 19).[30]

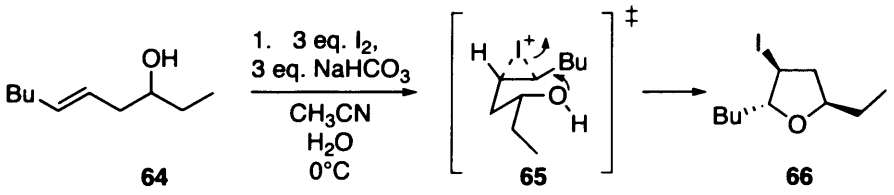


Scheme 19

Previous work within the Knight group

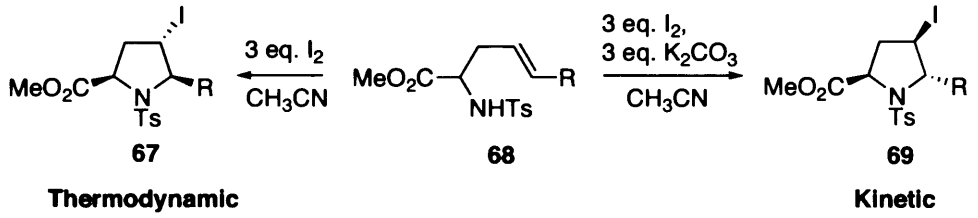
Iodocyclisations

The Knight group was among the first to show interest in the potential application of this novel methodology. Having spent much time investigating iodolactonisation reactions, they had also observed the presence of iodo-tetrahydrofurans in some crude reaction mixtures and resolved to develop the procedure further. Knight set about exploiting this intriguing reaction as a means for the synthesis of a variety of iodine-substituted heterocycles. Further investigation revealed that the cyclisation probably proceeds *via* a highly ordered late transition state, thus conferring very high levels of stereoselectivity. Such an effect was exemplified by the synthesis of the iodo-tetrahydrofuran **66** (Scheme 20).[31]



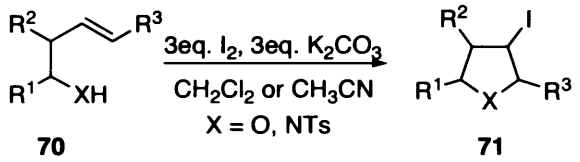
Scheme 20

Such observations were sustained when Knight extended the approach further and investigated the suitability of nitrogen as a nucleophile. Through cyclisation of the amino-ester **68**, two alternative products were obtained, depending on the conditions applied (Scheme 21).[32]

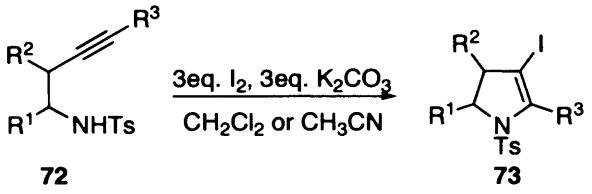


Scheme 21

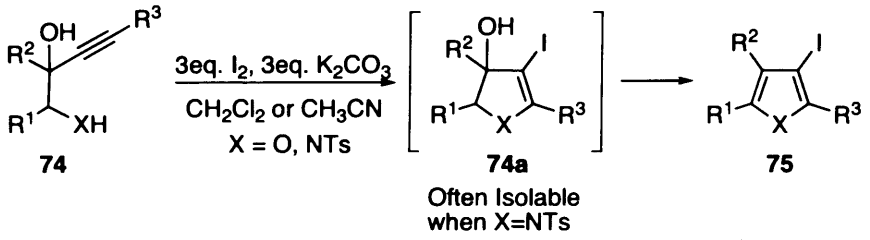
Building upon these successes, Knight was able to develop a broad and versatile set of methods for the synthesis of fully saturated (Scheme 22), partially saturated (Scheme 23) and fully unsaturated (Scheme 24) furan and pyrrole derivatives.



Scheme 22

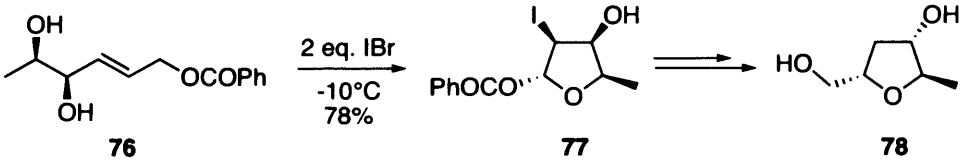


Scheme 23

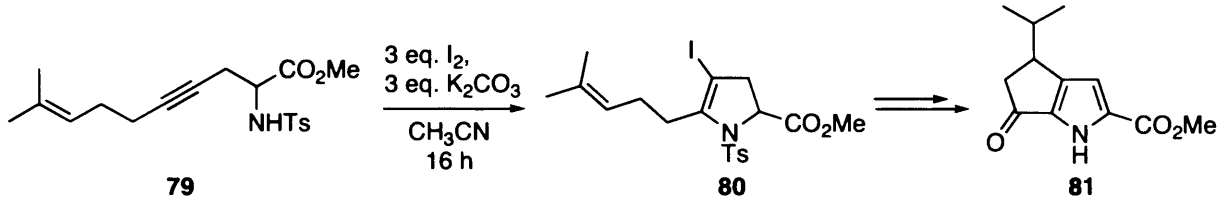


Scheme 24

The synthetic utility of the methodology has been aptly demonstrated by its application to target synthesis, for example, allowing for a practical and efficient construction of the core structural components of aplasmomycin **78** (Scheme 25)[33] and roseophilin **81** (Scheme 26).[34]



Scheme 25

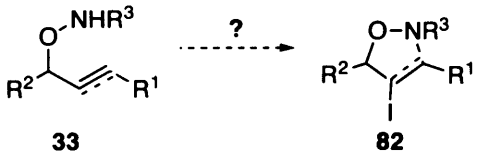


Scheme 26

The versatility of 5-*endo* iodocyclisations in the synthesis of polysubstituted furans and pyrroles led the Knight group to consider the possibility of applying this powerful methodology to the synthesis of more complicated heterocycles. Of particular interest were the isoxazoles.

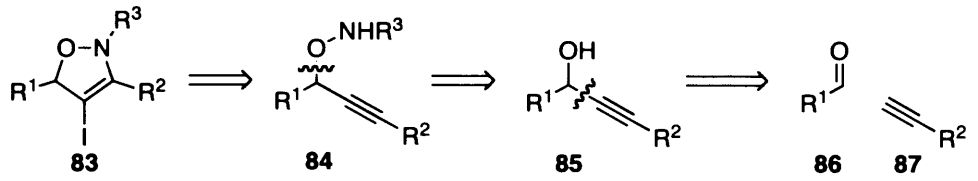
Synthesis of 4-iodo-2, 5-dihydroisoxazoles

As discussed in the introduction to this thesis, isoxazoles hold a uniquely important position in heterocyclic chemistry not only for their frequent occurrence in compounds displaying high levels of biological activity but also for the ease with which they can be manipulated as precursors to a wide range of derivatives. Cleavage of the relatively weak nitrogen-oxygen bond, for example, generates an amino-alcohol with absolute regioselectivity. As both nitrogen and oxygen had shown themselves to be excellent participants in iodocyclisation reactions there was a strong possibility that a suitably constructed hydroxylamine could undergo cyclisation through either potential nucleophile. Given that the nitrogen portion of the molecule is likely to be the more nucleophilic, it was decided that constructing a suitable *N*-protected, *O*-alkyl hydroxylamine was an excellent starting point for such investigations (Scheme 27).



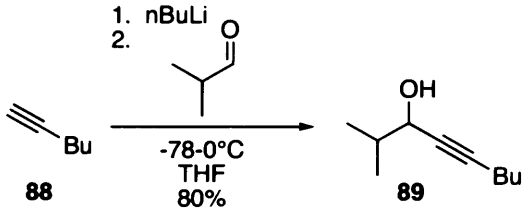
Scheme 27

Foot, a member of the Knight group, took up the challenge and set about constructing a suitable substrate for a 5-*endo*-dig dihydroisoxazole synthesis. A retrosynthetic analysis of the required cyclisation substrate **84** suggested constructing a propargyl alcohol **85** by alkyne addition to an aldehyde. Rather than attempt to then form the nitrogen-oxygen bond directly, a highly challenging undertaking as will be discussed later in this Chapter, it was instead decided to install the nitrogen-oxygen bond by displacing the alcohol with a pre-formed hydroxylamine. Protecting group manipulation would then yield a hydroxylamine **84** which, when subjected to iodocyclisation conditions, could undergo ring-closure to form the desired dihydroisoxazole **83** (Scheme 28).



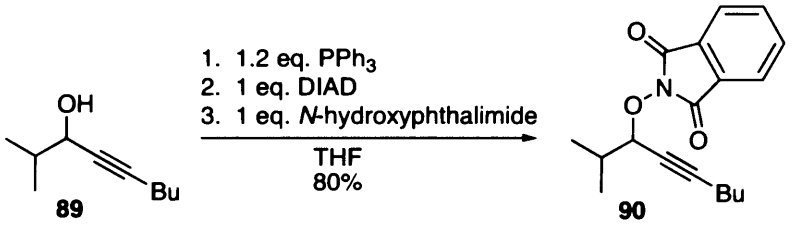
Scheme 28

A typical synthetic approach involved deprotonation of hexyne **88** with a single equivalent of n-butyl lithium and transfer to a solution of *iso*-butanal, furnishing the desired propargyl alcohol **89** in excellent yield (Scheme 29).



Scheme 29

The nitrogen-oxygen bond was then installed by Mitsunobu displacement of the propargyl hydroxyl group by *N*-hydroxyphthalimide, with careful chromatography of the crude reaction mixture returning the phthalimide-protected hydroxylamine **90**, in good yield (Scheme 30).

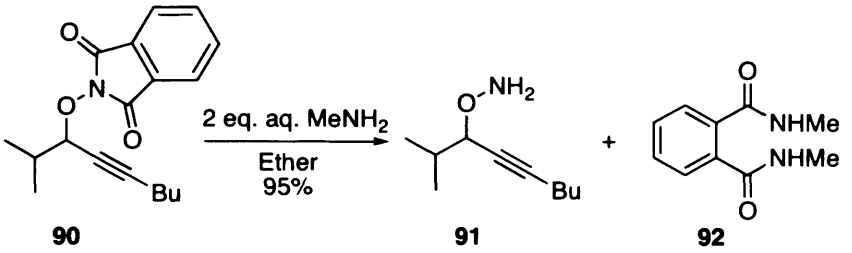


Scheme 30

The Mitsunobu reaction involves sequential activation and displacement of the alcohol, generating a phosphine oxide and a new carbon-nucleophile bond. Although in this case the desired product **90** was returned in excellent yield, other examples proved far less successful, often due to the cumbersome and capricious nature of the chromatography required to obtain pure product. This will be discussed in greater detail in Chapter Five of this thesis.

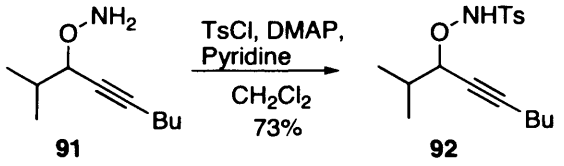
With the phthalimide-protected hydroxylamine **90** in hand, Foot found that the protecting group could be efficiently removed *via* a double displacement of the hydroxylamine using two equivalents of aqueous methylamine, by the method reported by Wolfe and Hasan.[35] When performed in ether, the phthalimide-derived diamide **92** was found to precipitate out of solution

and could be removed by filtration to leave the free hydroxylamine **91**, again in good yield and without need for further purification (Scheme 31).



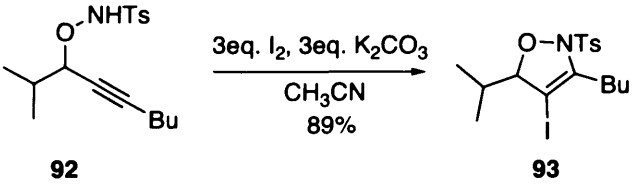
Scheme 31

Knight and co-workers had previously found that nitrogen nucleophiles employed in iodocyclisations could be effectively protected using the *p*-toluenesulphonyl (tosyl) group.[36] Employing this strategy once again, Foot reacted the free hydroxylamine under standard tosylation conditions to give a mixture of products, from which the desired tosylate **92** was obtained by chromatography (Scheme 32).



Scheme 32

In the case of the example illustrated, the tosylate **92** was recovered in good yield; however, in many of the examples subsequently pursued, the yield from this transformation was far less encouraging. A common problem reported by Foot was *bis*-tosylation of a significant amount of the hydroxylamine, at the expense of the mono-tosylation of an equal proportion. This problem would continue to affect such procedures and will be further explored in later Chapters of this thesis. Finally, upon subjecting the tosylate **92** to a standard set of iodocyclisation conditions, Foot was able to obtain the iodo-dihydroisoxazole **93**, in excellent yield (Scheme 33).[37]

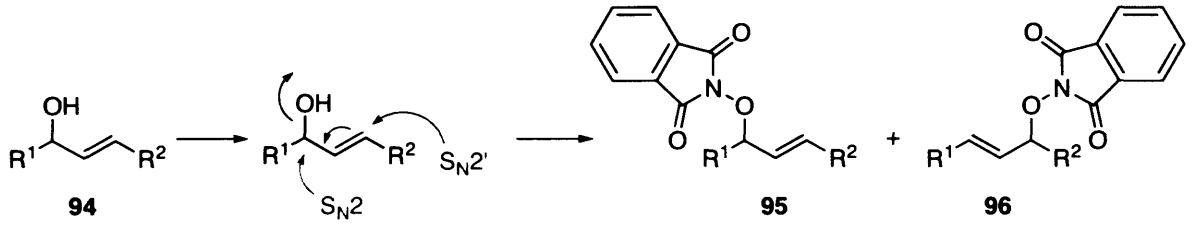


Scheme 33

Utilising this synthetic sequence, Foot was able to synthesise a broad range of iodo-dihydroisoxazoles incorporating a diverse set of functional groups. He also explored the possibility of extending the substitution of these compounds by palladium-catalysed couplings and radical cyclisations, albeit with variable success.[37]

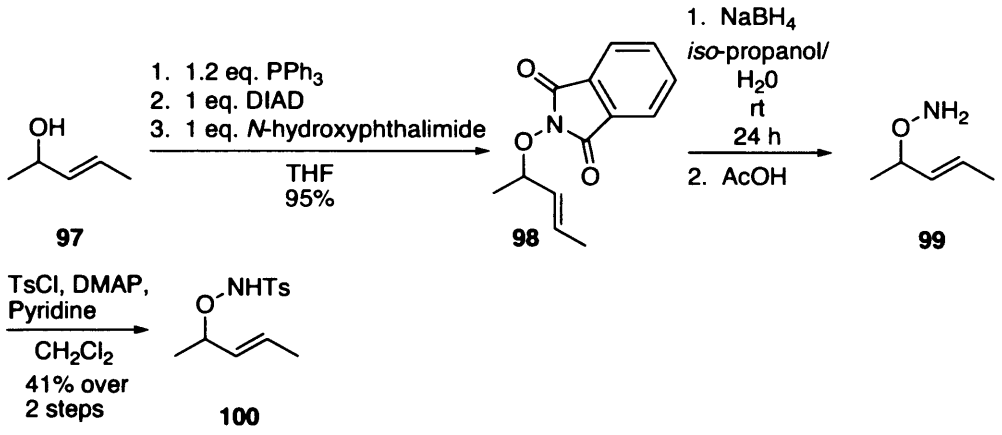
Synthesis of 4-Iodo-isoxazolidines

Having successfully applied the iodocyclisation procedure to 5-*endo*-dig cyclisations of alkynyl hydroxylamine derivatives, Foot embarked upon the logical extension of this methodology, a 5-*endo*-trig synthesis of iodo-isoxazolidines. With a range of allylic alcohols commercially available, the obvious starting point for this synthesis was again the Mitsunobu reaction. This approach, however, suffered from a severe limitation. Such displacements, when applied to allylic alcohols, are known to undergo competing S_N2 and S_N2' pathways to give the isomeric products **95** and **96** (Scheme 34).



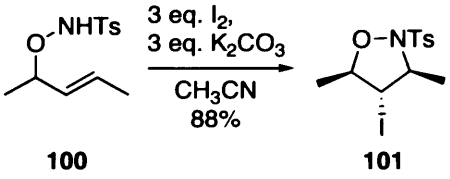
Scheme 34

A preliminary investigation showed this to indeed be the case when using *N*-hydroxyphthalimide, with attempts at separating the regioisomeric products yielding little success. In order to investigate the feasibility of the novel iodocyclisation reaction, Foot decided to proceed by employing the Mitsunobu reaction of (*E*)-pent-3-en-2-ol **97** – a substrate expected to yield a single product **98** irrespective of the reaction pathway. Further elaboration, in this case utilising the phthalimide-deprotection method reported by Ganem[38] followed by tosylation, generated a suitable cyclisation precursor **100** (Scheme 35).



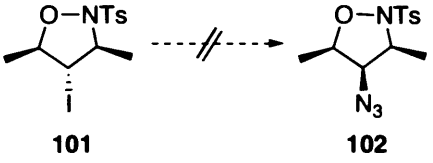
Scheme 35

Through careful control of the iodocyclisation conditions (performed in acetonitrile and in the presence of base), Foot was able to generate the cyclic product **101** in good yield and as a single diastereoisomer, the structure of which was confirmed by nOe experiments and X-ray crystallographic analysis (Scheme 36).



Scheme 36

Keen to examine the possibility of elaborating such compounds further, Foot sought to utilise the iodo substituent as a leaving group in a substitution reaction, and began by attempting displacement of the substituent with azide; however, under a range of conditions this proved unsuccessful (Scheme 37).

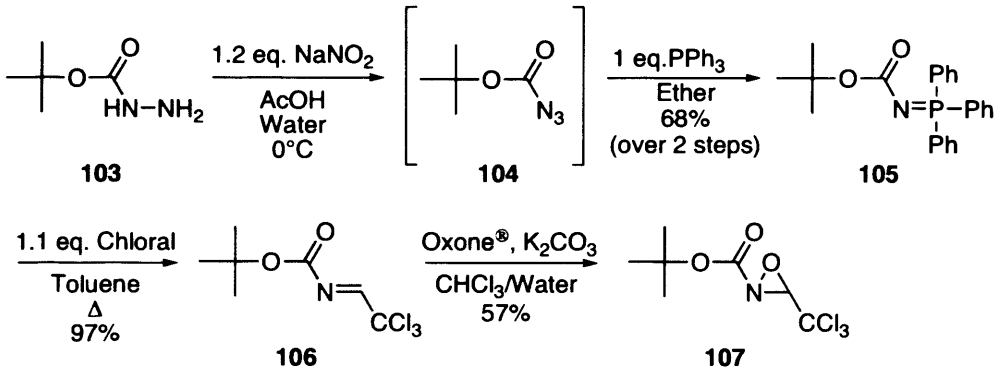


Scheme 37

Given its linear structure, azide is known to be an excellent nucleophile and is largely unaffected by a reasonable degree of steric hindrance. With the use of azide yielding no sign of substitution, it was thought that other displacements would also be equally unsuccessful and so Foot abandoned this line of investigation.

Amination reactions

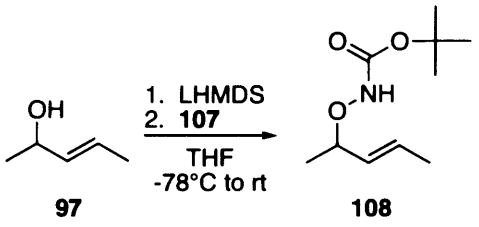
With the evident requirement for a method for the synthesis of a wider range of *O*-allylic hydroxylamines, Foot investigated alternative means of generating the nitrogen-oxygen bond. An obvious alternative to the installation of a pre-formed nitrogen-oxygen bond was to investigate the amination of an alcohol or alkoxide. In a series of highly influential publications, Vidal and Collet, reported investigations into the synthesis of novel oxaziridines and their application in amination reactions. One of the most successful of these reagents was the novel *N*-Boc-oxaziridine **107** (Scheme 38).[39]



Scheme 38

Utilising this reagent as a source of highly electron-deficient nitrogen, they were able to perform aminations by transfer of an N-Boc group to amine, enolate, sulphur and phosphorous nucleophiles. Conspicuous by its absence was the amination of an oxygen nucleophile.

Attempting to employ such a reaction in the synthesis of *O*-allylic hydroxylamines, Foot found that addition of the oxaziridine **107** to a solution of (*E*)-pent-3-en-2-ol **97** afforded only the return of unreacted alcohol. Attributing this to insufficient nucleophilicity, he instead carried out the reaction on a pre-formed alkoxide, generated by addition of LHMDS to a solution of the alcohol, followed by a slow addition of a solution of the oxaziridine **107** (Scheme 39).[40]



Scheme 39

Analysis of the reaction mixture by tlc showed rapid consumption of the starting materials and extraction of the reaction mixture followed by distillation of the crude product appeared to give

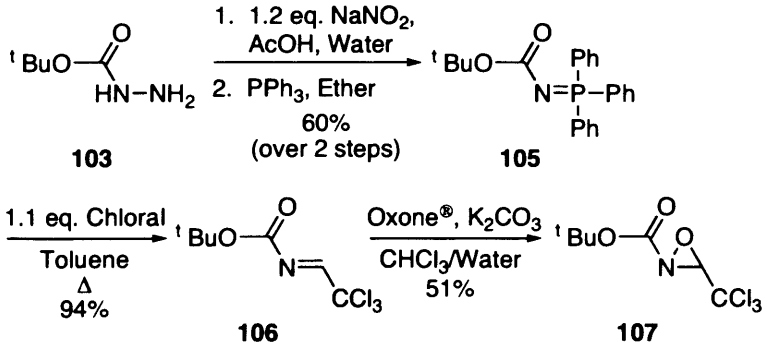
hydroxylamine **108**, in virtually quantitative yield. Analysis of this product by mass spectrometry proved inconclusive as only degradation products were observed. Nevertheless, analysis of the product by NMR and IR appeared to corroborate the evaluation that the product was indeed the result of overall amination of the alcohol **97**.

With this representative substrate thought to be in hand, Foot set about investigating its participation in iodocyclisation reactions. Disappointingly, subjecting the compound **108** to the iodocyclisation conditions described previously resulted only in its quantitative return. Attributing this to a difference in nucleophilicity between the Boc- and tosyl- protected amino groups, the logical solution seemed to be to attempt protecting group exchange. Upon trying to remove the Boc protecting group (using trifluoroacetic acid), however, Foot observed only degradation of the starting material. An investigation of these conundra represented one of the starting points of the present project.

Results and discussion

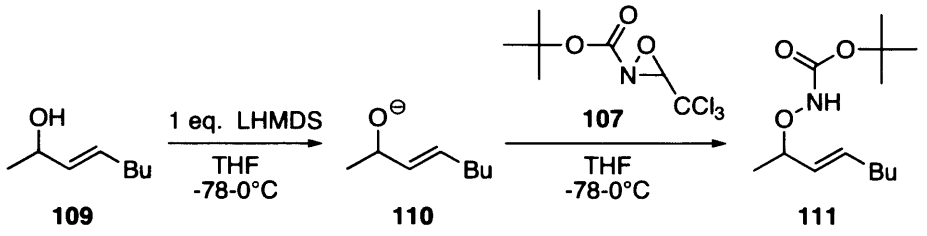
Oxaziridine chemistry

With further investigation into the oxaziridine amination process clearly warranted, we reasoned that an ideal starting point would be to investigate the amination of commercially available (*E*)-oct-3-en-2-ol **109**, given that Foot had found the competing Mitsunobu products generated from this substrate to be largely inseparable.[41] A sample of the oxaziridine **107** was synthesised in a comparable yield to that reported by Foot (Scheme 40).



Scheme 40

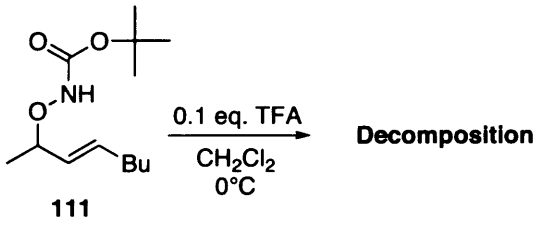
This was then reacted with an LHMDS-generated alkoxide **110** formed from the allylic alcohol **109**, yielding a single product thought to be hydroxylamine **111** (Scheme 41).



Scheme 41

As Foot had observed previously, analysis of the product by mass spectrometry revealed only a complex fragmentation pattern. Comparison of the NMR spectrum of the product **111** with that of the starting material clearly showed that chemical modification of the alkoxide (indicated by a change in chemical shift of the protons in close vicinity to the allylic alcohol) had indeed occurred and also confirmed the presence of a *tert*-butyl group, suggesting incorporation of the Boc protecting group. Given this, it seemed logical to conclude that the oxaziridine **107** had reacted in the manner reported by Foot and delivered the required *N*-Boc hydroxylamine **111**.

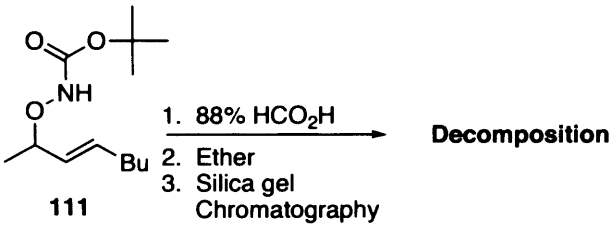
With a suitable substrate in hand, we first attempted ring-closure under both basic and non-basic iodocyclisation conditions; however, as Foot had reported, this returned only unreacted starting material. The need for exchange of protecting group was clear and, given our previous experience, the tosyl group seemed the obvious candidate. Attempts to introduce the tosyl group directly into the Boc-protected compound **111** delivered only unreacted starting material, perhaps unsurprisingly given the considerable steric hindrance generated by the Boc group. Faced with the obvious need to liberate the unprotected hydroxylamine, removal of the Boc group using trifluoroacetic acid (TFA) was attempted. Unfortunately, repeated attempts yielded only small amounts of unidentified, decomposition products (Scheme 42).



Scheme 42

Believing that the decomposition of the "hydroxylamine" may have been caused by the instability of the relatively weak nitrogen-oxygen bond towards TFA, alternative means for the removal of the protecting group were sought. Removal of an *N*-Boc group is commonly achieved under acidic conditions, with protonation leading to decarboxylation and the generation of *iso*-butene, along with regeneration of a proton.[42] Although TFA is by far the most commonly used reagent, a number of alternatives exist. Woster and co-workers reported

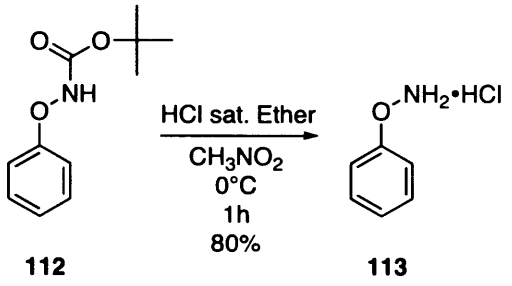
the need for a set of mild conditions for Boc removal whilst investigating the synthesis of novel enzyme inhibitors.[43] Encouragingly, in these cases the Boc-protected nitrogen also formed part of a hydroxylamine and a variety of acid-sensitive functionality was also present in the substrate. They found that prolonged exposure to an excess of 88% aqueous formic acid, followed by extraction into an organic solvent and silica gel chromatography furnished the unprotected hydroxylamine in good yield and with little sign of substrate decomposition. However, applying these conditions to the hydroxylamine **111** once again led to decomposition (Scheme 43).



Scheme 43

An extremely mild approach to Boc removal was reported by Apelqvist and Wensbo, who found that adsorption of a variety of Boc-protected amines onto a large excess of silica gel, followed by prolonged heating (to 180°C) under reduced pressure and finally silica gel chromatography, gave the corresponding deprotected amines in high yield (80-93%).[44] Attempting this procedure on the substrate **111** resulted only in a reduced yield of returned starting material.

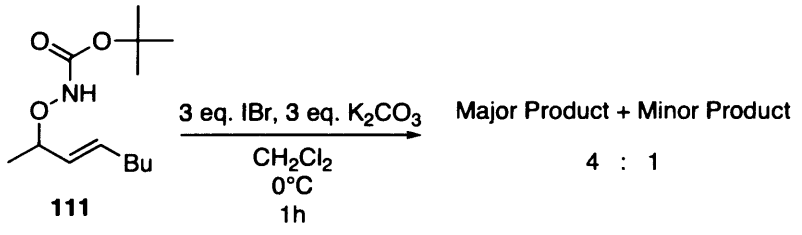
Finally, suspecting that decomposition may be due to the affect of the acidic conditions on the expected unprotected hydroxylamine product, rather than the Boc-protected substrate, we investigated the use of an inorganic acid, in the hope that an excess of such a reagent would immediately generate the acid salt of the free hydroxylamine and that this would prove to have greater stability. Maiorana and co-workers reported that addition of saturated ethereal HCl to a solution of *N*-Boc-*O*-aryl hydroxylamine **112** in nitromethane resulted in precipitation of the HCl salt of the deprotected hydroxylamine **113** (Scheme 44).[45]



Scheme 44

Unfortunately, attempts to apply this procedure to the substrate **111** once again returned only small amounts of unidentified degradation products. Frustrated by our apparent inability to liberate the free hydroxylamine from our Boc-protected oxaziridine product, we decided to re-visit our attempts to utilise the protected hydroxylamine in an iodocyclisation.

Given the initial lack of success encountered when applying the standard set of iodocyclisation conditions, we were drawn to investigate alternative conditions for the iodocyclisation reaction. It had been known to the group for some time that iodine monobromide (IBr) can facilitate iodocyclisation reactions and demonstrates an increased level of reactivity compared to molecular iodine. Thus, it was decided to subject the substrate **111** to a modified set of iodocyclisation conditions, replacing the excess of molecular iodine with an excess of IBr. To our delight, analysis of the crude reaction product showed complete conversion of the starting material to a mixture of two products, in a 4 : 1 ratio, whose identities were initially unclear (Scheme 45).

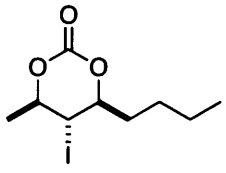


Scheme 45

The two products were easily separated by silica gel chromatography and both were obtained as pale yellow solids. Analysis of the major product by proton NMR spectroscopy revealed, surprisingly, that the resonance corresponding to the *tert*-butyl component of the Boc protecting group (appearing as a sharp singlet at 1.41 ppm in the spectrum of the starting hydroxylamine **111**) was no longer present. The resonances corresponding to the olefinic protons present in the starting material were also no longer apparent. An apparent triplet, possibly resulting from an overlapping double doublet, showing the minimum unit of integration and appearing at 3.72

ppm, was consistent with a proton attached to a carbon bearing the iodine substituent. Two further resonances, both showing the minimum unit of integration, appearing as a double double doublet at 4.47 ppm and a doubled quartet at 4.57 ppm both suggested protons attached to carbons bonded to electron-withdrawing groups and both showed coupling to the proton at 3.72 ppm. A relatively large coupling constant associated with these resonances (10.6 Hz) suggested a *trans* relationship between vicinal substituents on what appeared to be a 6-membered ring. The IR spectrum of the product showed a sharp absorbance at 1715 cm^{-1}, which was indicative of a carbonyl bond in the vicinity of at least one electron-withdrawing group, and intriguingly showed no absorbance corresponding to a proton-heteroatom bond (NH or OH).

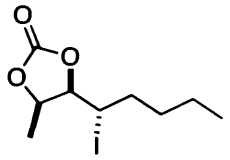
When considered in its entirety, the analysis of the product suggested that iodocyclisation had indeed occurred, with the carbon-carbon double bond being attacked by a heteroatomic nucleophile to result in a new carbon-heteroatom bond. The data obtained were also indicative of a new carbon-iodine bond, flanked by two carbons each bonded to electron-withdrawing heteroatoms. Also, as a result of this process, the *tert*-butyl portion of the Boc group appeared have been lost, although some form of carbonyl had been retained. The final piece of the puzzle fell into place when we were able to obtain a low resolution mass spectrum of the compound, showing what appeared to be the parent ion, a peak with 100% intensity and a relative mass of 299, presumably corresponding to $M^+ + H$, indicating the relative mass of the product to be 298. This strongly suggested the absence of nitrogen in the product, as the valency of nitrogen would give rise to an odd relative mass. With all the information in place (and admittedly after an extending period of confusion), it was tentatively postulated that the major product was the 6-membered cyclic carbonate **114**, resulting from a 6-*endo*-trig iodocyclisation. In particular, this was consistent with the resonances at 4.47 and 4.57 ppm – these protons are very similar in all respects.



114

Upon comparison with the major product, analysis of the minor product revealed largely similar features and an identical relative molecular mass. In this case, however, it was clear from the coupling pattern shown in the proton NMR spectrum that the iodo-substituent was no longer positioned on the ring. An apparent carbonyl absorbance was again present in the IR spectrum, although at a higher wavenumber than in the major product, 1816 cm^{-1}. This strongly

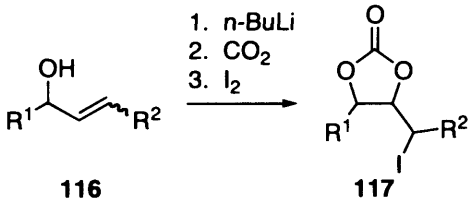
suggested that the minor compound was the product formed by iodocyclisation *via* the alternative 5-*exo*-trig pathway, *i.e.* the 5-membered cyclic carbonate **115**, presumably a less favoured transformation. The relative stereochemistry was tentatively proposed based on analysis of the relevant couplings observed in the proton NMR, although it is worth noting such assignments are often less reliable in 5-membered ring systems.



115

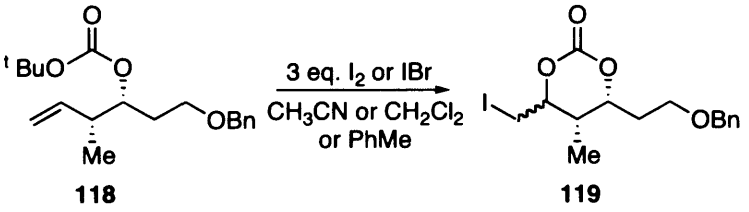
Overall the reaction had proceeded in good yield (91% combined) and both products appeared to be obtained as single diastereoisomers. With no obvious route for the synthesis of these products from the Boc protected hydroxylamine **111**, we were forced to consider the possibility that the structural assignment for the product resulting from the reaction between the oxaziridine **107** and oct-3-en-2-ol **109** was incorrect.

The synthesis of cyclic carbonates *via* iodocyclisation had indeed been previously reported, notably by Barlett, as an extension of the aforementioned iodolactonisation studies.[46] Such observations were also reported by Cardillo, who demonstrated the synthesis of iodo-carbonates *via* a one-pot carboxylation of alkoxides followed by either 5-*exo*-trig or 6-*exo*-trig cyclisation of the resulting allylic carbonates (*e.g.* Scheme 46).[47]



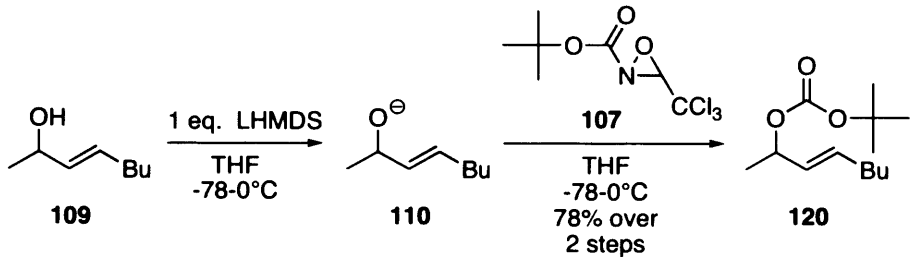
Scheme 46

More recently, Amos B. Smith III reported that the unsymmetrical carbonate **118**, bearing a *tert*-butyl moiety, could be cyclised with an excess of IBr to give the iodo-carbonate **119** as a mixture of diastereoisomers depending upon the conditions used (Scheme 47).[48]



Scheme 47

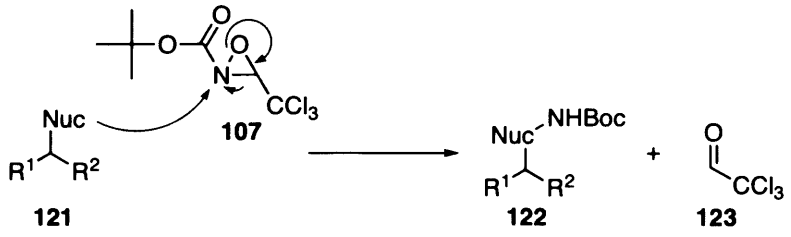
The iodo-carbonates generated were further elaborated as a highly stereoselective route to the synthesis of highly functionalised 1,3 diols and β-hydroxy epoxides.[49] Based on these findings, it seemed reasonable to suggest that, rather than a Boc-protected hydroxylamine, the product of the reaction between the alkoxide **110** and oxaziridine **107** was the carbonate **120** (Scheme 48).



Scheme 48

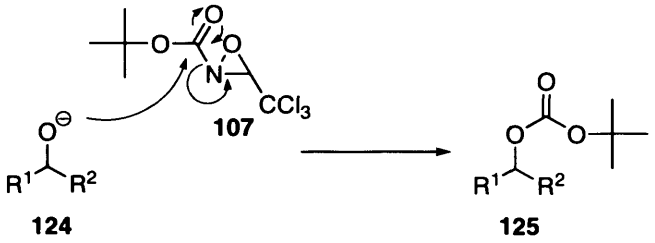
With analysis by mass spectrometry yielding little information and NMR evidence proving inconclusive, we decided to investigate the composition of the product through elemental analysis. Although the elemental ratios obtained were outside of the acceptable margin of error required to prove the empirical composition conclusively (perhaps due to the persistent presence of moisture in the sample) these did provide a stark vindication of our revised structural assignment. The analysis showed the product contained only a negligible amount of nitrogen (0.36%, *c.f.* 5.76% required for hydroxylamine **111** and 0% required for carbonate **120**).

For this to indeed be the case, the reaction of an alkoxide with the oxaziridine **107** would clearly have to follow an alternative mechanism to that which occurs in the reactions with amines and other nucleophiles, as detailed by Vidal and Collet (simplified in Scheme 49).[39]



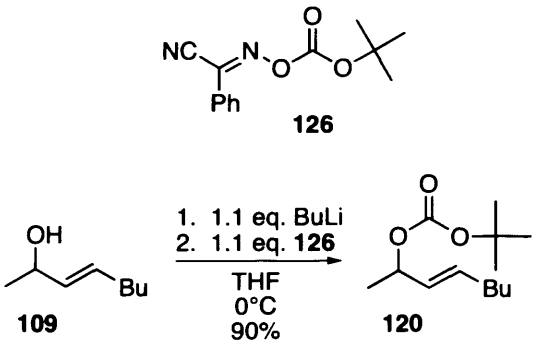
Scheme 49

The alkoxide, however, must be following an alternative pathway, for example, preferentially attacking the carbonyl, transferring the Boc group and causing the oxaziridine to be displaced and subsequently to decompose (Scheme 50).



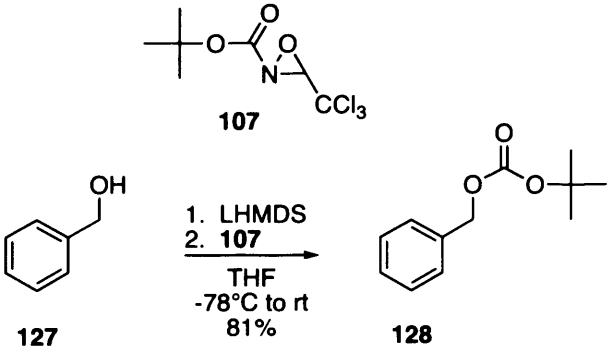
Scheme 50

In order to verify these suspicions, we required an alternative route to mono-*tert*-butyl carbonates **125**. This was found in the reports on iodocyclisation of such carbonates by Amos B. Smith III, mentioned previously. Smith had reported that these carbonates could be obtained by reaction of a lithio-alkoxide with a slight excess of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON) **126**, followed by silica gel chromatography.[48, 49] Applying this procedure to oct-3-en-2-ol **109** we were able to obtain the desired carbonate **120** (Scheme 51).

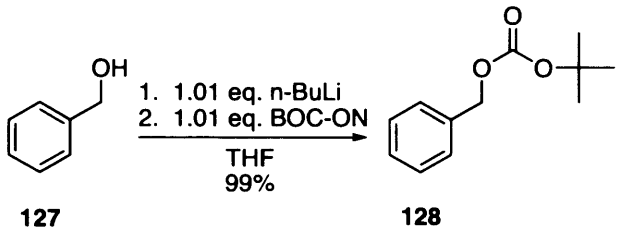


Scheme 51

The product displayed identical NMR spectra to those obtained for the reaction of the same alcohol with the oxaziridine **107** (Scheme 48, pp 26). As a final confirmation, we reacted a sample of commercially available (Sigma Aldrich) benzyl alcohol **127** with oxaziridine **107** (Scheme 52) and separately with BOC-ON **126** (Scheme 53) and in each case delivered what appeared to be identical products, the carbonate **128**.

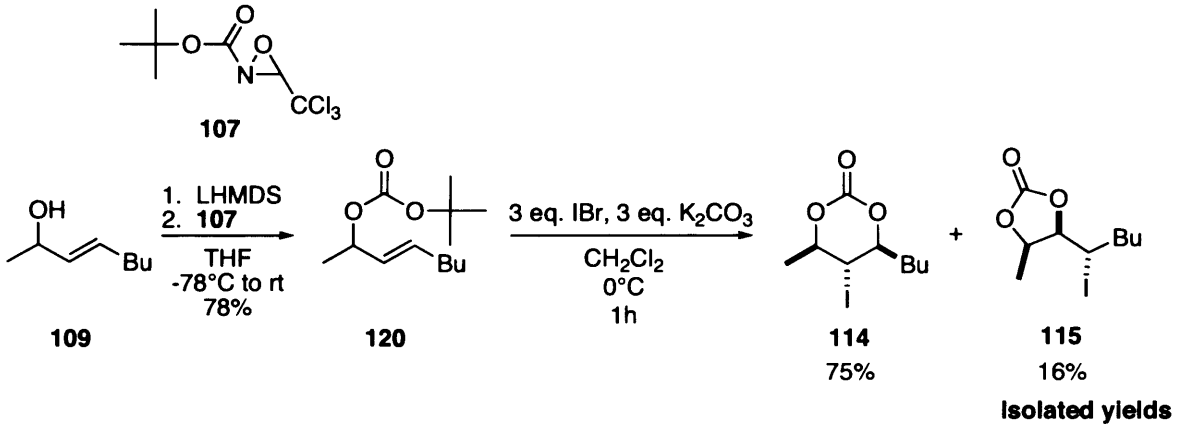


Scheme 52



Scheme 53

The spectroscopic data obtained also matched those reported by Foot for the amination of the same alcohol.[40, 41] As a consequence, we were confident that the reaction of alcohol **109** with oxaziridine **107** had delivered a *tert*-butyl carbonate **120**, rather than the desired hydroxylamine and that this carbonate had cyclised upon reaction with iodine monobromide to yield a mixture of the cyclic 6-membered iodocarbonate **114** and the 5-membered analogue **115**, resulting from competing 6-*endo*-trig and 5-*exo*-trig pathways respectively (Scheme 54).



Scheme 54

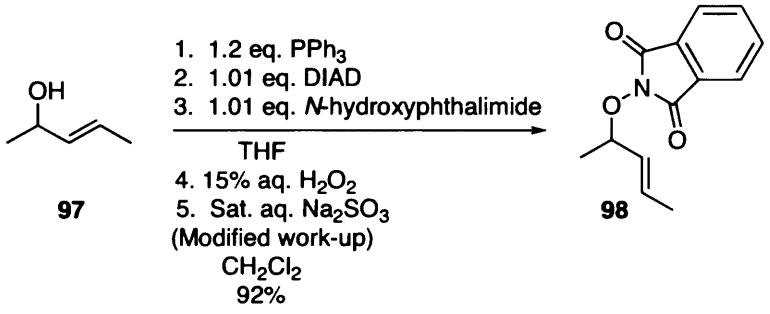
Whilst the iodocyclisation of such carbonates is indeed interesting, especially given that this is the first example of a 6-*endo*-trig cyclisation of this kind, further investigation was beyond the remit of the current project. With the oxaziridine **107** failing to deliver the required hydroxylamines and the task of developing an alternative likely to be a laborious one, we decided to further investigate the chemistry of iodo-dihydroisoxazoles, by returning to the substrate we were able to obtain from the synthetic sequence utilising the Mitsunobu reaction.

The synthesis and chemistry of 4-iodoisoxazolidines

As is common with allylic alcohols, the Mitsunobu reaction between (*E*)-3-penten-2-ol **97** and *N*-hydroxyphthalimide has the potential to yield a mixture of products *via* competing S_N2 and S_N2' reaction pathways; however, in this case the products obtained are identical. This example, whilst limited, allowed for a brief examination of the reactivity of 4-iodoisoxazolidines. As described previously, Foot found that displacement of this alcohol with

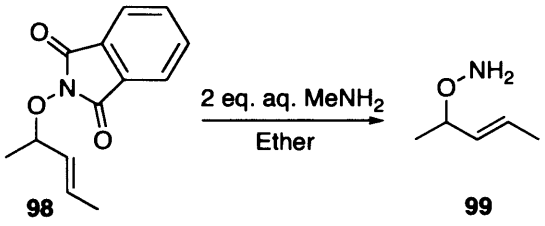
N-hydroxyphthalimide gave the expected product **98** in good yield (Scheme 35, pp 18). A significant drawback to this approach was, however, the need for cumbersome and time-consuming chromatography of the crude reaction mixture in order to separate the reaction product from the multitude of unreacted and spent reagents present.

In order to eliminate this requirement, we developed a chromatography-free work-up procedure that was shown to yield analytically pure Mitsunobu products in high yield.[50] The process involves selective oxidation of the reaction contaminants prior to silica gel filtration and will be discussed, in detail in Chapter Five of this thesis. The modified reaction procedure was applied to the Mitsunobu reaction between *N*-hydroxyphthalimide and 3-penten-2-ol **97** and gave the phthalimide product **98** in good yield and with no further need for purification (Scheme 55).



Scheme 55

With the phthalimide-protected hydroxylamine **98** in hand we were then able to remove the phthalimide protecting group using aqueous methylamine (Scheme 56).[35]

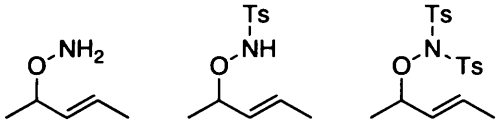


Scheme 56

Foot had noted that the 'free' hydroxylamines generated by such deprotections were unstable to purification and thus it was decided to use them as crude products in subsequent transformations. In our hands, we noted that these 'free' hydroxylamines were also unstable at room temperature, with decomposition often occurring prior to the acquisition of NMR data. This property of unprotected, *O*-alkyl hydroxylamines is indeed reported in the literature, with such compounds often being isolated as the hydrochloride salt in order to enhance stability.[51] Rather than subject our syntheses to this rather cumbersome additional step, we instead

routinely decided to subject these compounds to the next step in the synthesis, in this case tosylation, immediately following isolation and without making attempts to either purify or characterize these intermediates.

A further problem encountered by Foot in the synthesis of the *N*-tosyl cyclisation precursors occurred in the tosylation of such unprotected hydroxylamines. The donation of electron density to a heteroatom nucleophile from an adjacent heteroatom is commonly referred to as the alpha-effect and, in this case, results in both heteroatoms in the hydroxylamine group possessing increased nucleophilicity.[52] Foot found that exposing the unprotected hydroxylamines to a single equivalent of *p*-toluenesulphonyl chloride, under standard tosylation conditions, returned crude reaction mixtures containing several products, from which the mono-tosylated hydroxylamines could be separated by silica gel chromatography. When applying these conditions to the hydroxylamine **99**, it was found that the predominant impurity in the crude reaction mixture was the bis-tosylated derivative **129** of the desired product, presumably formed at the expense of a further equivalent of *p*-toluenesulphonyl chloride and leaving unreacted an equal mount of the hydroxylamine **99**, which had been found to be unstable to chromatography.

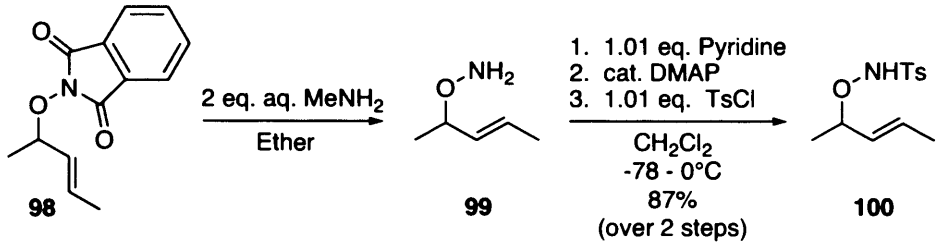


99 **100** **129**

It was reasoned that, in order for *bis*-tosylation to occur in the presence of only a single equivalent of the tosyl chloride, the reactivity of a mono-tosylate towards the tosyl chloride must be at least comparable to that of an unprotected hydroxylamine. Nonetheless, the increased steric hindrance of the mono-tosylated hydroxylamine along with the decreased nucleophilicity caused by the presence of an electron-withdrawing tosyl group, could reasonably be expected to result in the second tosylation reaction being marginally slower than the first.

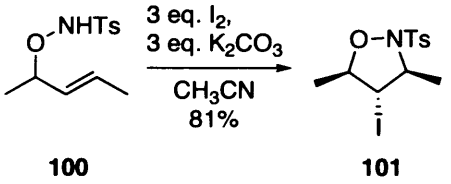
It was found that by cooling the reaction to -78°C prior to the addition of a slight excess of tosyl chloride and then allowing it to immediately warm to room temperature, the proportion of mono-tosylate in the reaction mixture could be greatly increased. Maintaining the reaction at -78°C for an extended period resulted in significant amounts of starting material remaining, even after 24 hours. As a compromise, it was found that by performing the addition of reagents to a reaction cooled to -78°C in an acetone-dry ice bath and then allowing the bath to warm slowly over a period of around 4 h (by omitting to replenish the dry ice), the reaction could be both

controlled and allowed to reach completion. Application of this set of conditions to the hydroxylamine **99** afforded predominantly a single product, the *N*-tosyl hydroxylamine **100**, with the crude reaction mixture containing only trace amounts of *p*-toluenesulphonic acid as an impurity (Scheme 57).



Scheme 57

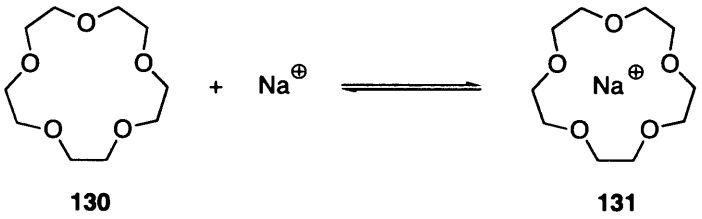
Using the conditions described by Foot (Scheme 36, pp 18), the iodocyclisation product was obtained in comparative yield (Scheme 58).



Scheme 58

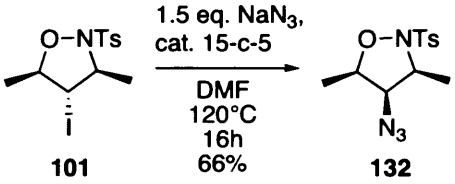
With the iodo-isoxazolidine in hand, we set about investigating the potential for further elaboration of such compounds. Of prime interest was the potential for nucleophilic displacement of the iodine substituent. The azide nucleophile is a superb candidate for such a displacement. In previous work, Foot treated the iodo-isoxazolidine **101** with an excess of sodium azide under a range of conditions: refluxing DMF, ethanol, toluene and acetonitrile (with the addition of tetrabutylammonium chloride in the latter two cases), but had observed no sign of displacement.

A frequently overlooked limitation to the use of sodium azide as a nucleophile is that although the azide anion is itself a relatively small, linear nucleophile, able to overcome considerable steric hindrance, in non-aqueous media the sodium counter-ion is not fully dissociated, thus hindering the efficacy of the nucleophile. A common method for the removal of metal counter-ions from nucleophilic processes is to selectively and reversibly complex these ions. In the case of alkali metal ions, crown ethers have often been used for this purpose, to good effect.[53] It is well know that sodium ions can be complexed in this manner by the cyclic ether 15-crown-5 (15-c-5) **130** (Scheme 59).



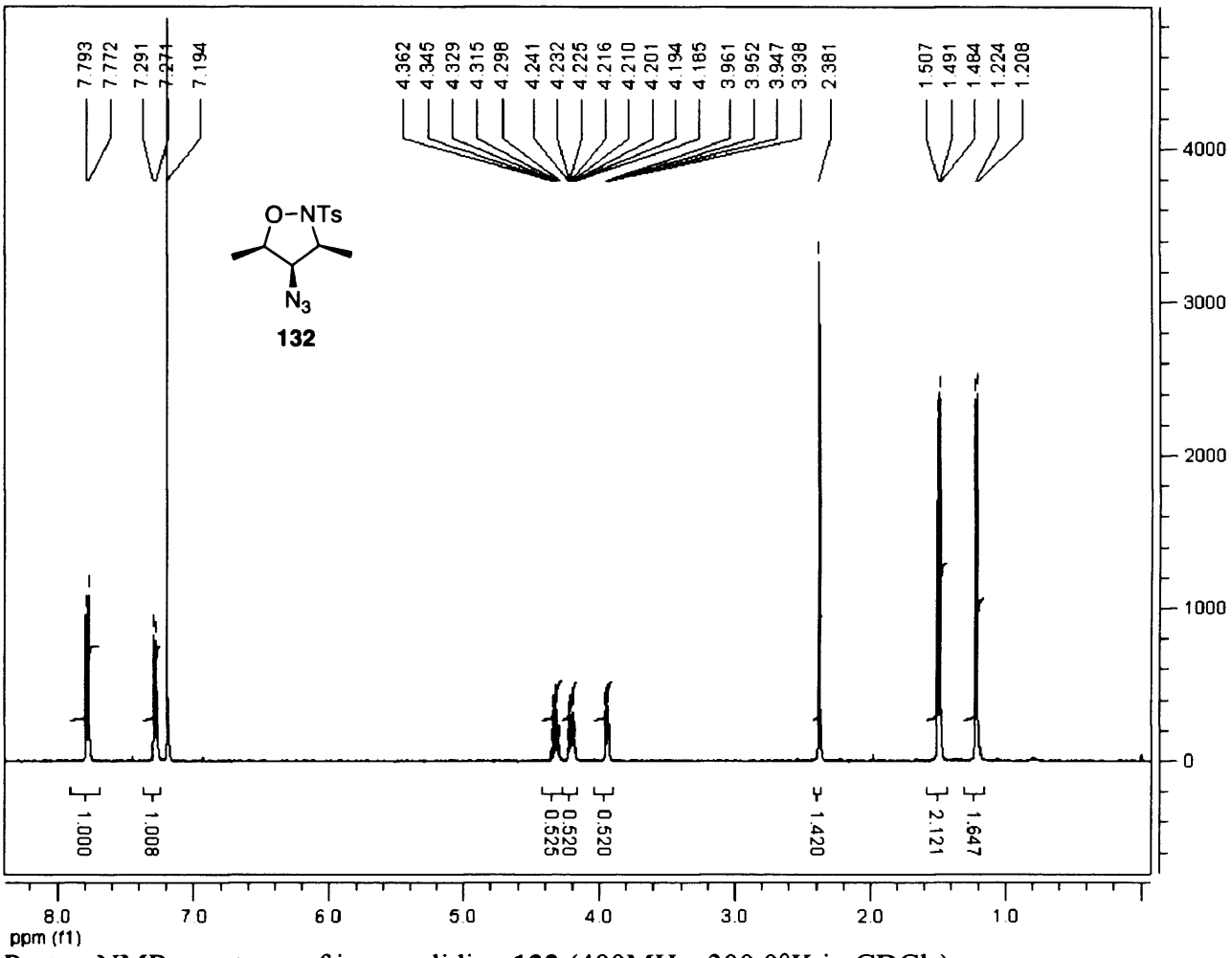
Scheme 59

Heating the substrate **101** to 120°C in DMF in the presence of an excess of sodium azide (1.5 equivalents) and a catalytic amount of 15-crown-5, we found that complete conversion into the azide **132** occurred in 16 h, with silica gel chromatography affording the azide **132** in 66% yield (Scheme 60).



Scheme 60

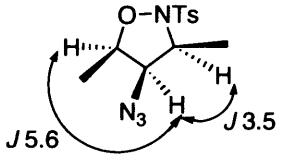
The proton NMR of the purified product **132** indicated that it had been obtained as a single diastereoisomer (Diagram 2), indicative of an S_N2 reaction pathway.



Proton NMR spectrum of isoxazolidine **132** (400MHz, 300.0°K in $CDCl_3$).

Diagram 2

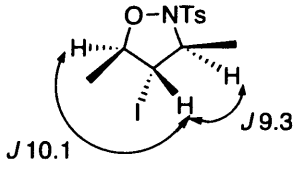
Analysis of the coupling pattern produced by the product strongly supported the belief that the reaction had proceeded *via* an S_N2 mechanism (Diagram 3).



132

Diagram 3

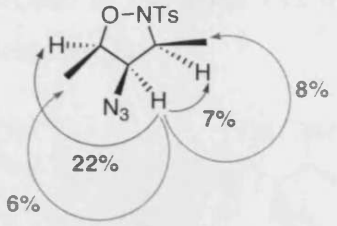
These couplings were distinctly different from those observed for the corresponding protons in the starting material **101** (Diagram 4)



101

Diagram 4

Further analysis of the product by nOe experimentation revealed that irradition of the proton in the 4-position (4.04 ppm) caused enhancements in the intensities of the resonances due to both the protons and the methyl groups in the 3- and 5-positions of the ring (Diagram 5).



132

Diagram 5

As expected, these data suggested the absence of either a clear *trans* or *cis* diaxial relationship between the ring-bound protons. This becomes clearer when considering the likely conformation of the product **132**. The X-ray crystal structure of the iodoisoxazolidine **101**, obtained by Foot, revealed a mildly twisted pseudo-chair conformation, thus it can reasonably be expected that a similar, twisted conformation exists for the azide product. A simple energy minimisation experiment performed using ChemDraw 3D indeed suggested that the compound adopts a twisted conformation, with the azide substituent occupying a space closer to the nitrogen atom in the ring than to the oxygen, in turn bringing the proton in the 4-position closer to the methyl group and proton in the 5-position, although the distortion was only mild and perhaps less than would be expected given the results of the aforementioned nOe experiments. The result of this energy minimisation experiment is depicted below, with the distortion mildly exaggerated for clarity (Diagram 6).

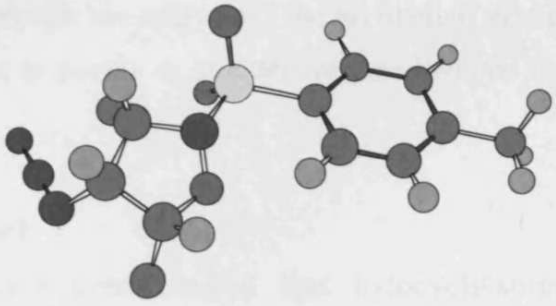
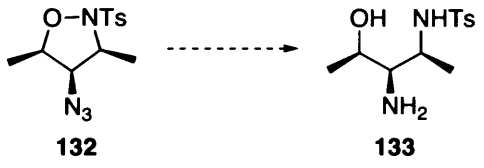


Diagram 6

Unfortunately, the oily nature of the product ruled out obtaining confirmation of the structure through X-ray analysis. The proposed conformation does, however, tally with the observed NMR data (*i.e.* a greater nOe enhancement and ^{1}H ^{1}H ^{3}J coupling between the protons in the 4- and 5-positions than those observed between the protons in the 3- and 4-positions indicating increased proximity and more acute dihedral angle). Although we were pleased to obtain a good yield of the desired product, we were conscious of the fact that the reagents and conditions used are clearly not safely reproducible on a larger scale. Also, given that

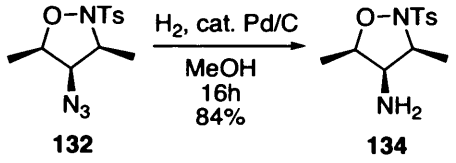
displacement with an azide nucleophile required such harsh conditions, this did not bode well for the potential utility of other, less reactive nucleophiles.

Finally, we attempted a double reduction of the azide **132** to the amino-alcohol **133**, under catalytic hydrogenation conditions (Scheme 62).



Scheme 62

Frustratingly, NMR spectroscopy and mass spectrometry confirmed that only reduction of the azide had occurred, affording the 4-amino-3,5-dimethylisoxazolidine **134** as an amorphous solid, in good yield (Scheme 62).



Scheme 62

Subjecting the product to further attempts at hydrogenation failed to display any sign of nitrogen-oxygen bond cleavage and, with other areas of the project commanding greater interest, we decided to abandon our attempts. The problem of nitrogen-oxygen bond cleavage would, nonetheless, return to trouble us in latter work and will be further discussed in Chapter Four of this thesis.

Summary and future work

These investigations have demonstrated that iodocyclisation of *O*-allylic *N*-tosyl hydroxylamines is an effective method for the synthesis of iodoisoxazolidines. Overall, the as yet unresolved problem of precursor formation means that progress, beyond very inefficient procedures, was always going to be very limited in this direction. Given this, more seemingly productive ideas were therefore pursued at this point, however, the development of a more productive means for the synthesis of the required substrates, perhaps involving novel oxaziridines, would clearly open the door to a wide-range of possible synthesises.

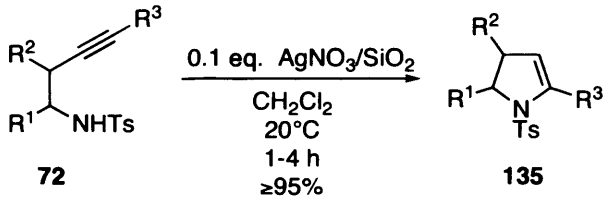
CHAPTER 3

Chapter Three

A Silver Nitrate-Catalysed Dihydroisoxazole Synthesis

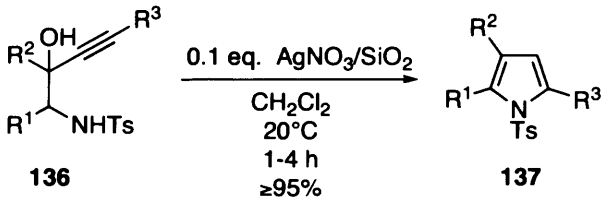
Background

As discussed in previous Chapters of this thesis, the Knight group has, for some time, held an interest in the synthesis of a broad range of heterocycles. A logical progression of the group's investigations was to explore the possibility of using a catalyst to effect such transformations; a metal catalyst seemed an attractive possibility. After assaying a range of metals, Sharland found silver nitrate to be extremely effective in this respect. In particular, the commercially available and easily handled dispersion of silver nitrate, 10% w/w silver nitrate on silica gel, proved an ideal reagent for such reactions.[54] Using a catalytic amount of this reagent, he was able to demonstrate its use in the synthesis of a wide range of dihydropyrroles **135** *via* 5-*endo*-dig cyclisation of suitably constructed sulphonamides **72**. In each case the products were delivered in virtually quantitative yield and with exceptional purity (Scheme 63).



Scheme 63

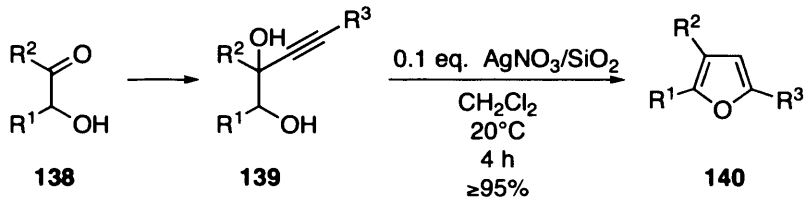
By combining the cyclisation with a concomitant dehydration, the group was also able to directly access a range of trisubstituted pyrroles **137** – again in exceptionally high yield (Scheme 64).



Scheme 64

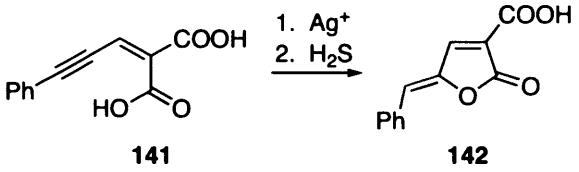
Again a key feature of the reaction was the absence of any impurities in the crude reaction product, thus obviating the need for further purification.

Expanding the methodology further still, the group explored the application of oxygen nucleophiles in 5-*endo*-dig cyclisations, delivering high yields of exceptionally pure trisubstituted furans **140** (Scheme 65).[55]



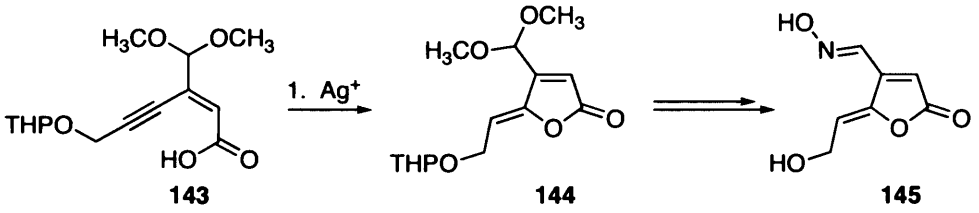
Scheme 65

The ability of various silver(I) salts to induce heteroatoms to undergo intramolecular cyclisation has been known for some time. As early as 1958, Castener and Pascual reported the use of silver salts in 5-*exo*-dig lactonisations, as a means for the synthesis of the butenolide **142** (Scheme 66).[56]



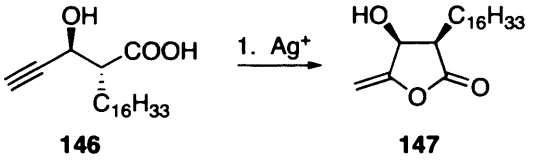
Scheme 66

Similar observations were later reported by Serratosa, who performed a silver-catalysed lactonisation as part of an approach to Patulin oxime **145** (Scheme 67).[57]



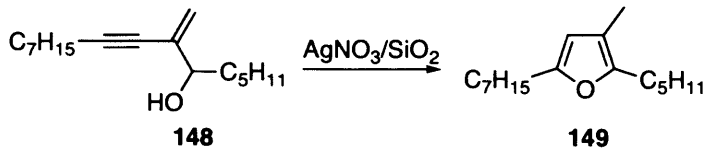
Scheme 67

A more recent application was reported by Pale, who demonstrated that various silver(I) salts could effect 5-*exo*-dig cyclisations of 3-hydroxy-4-pentynoic acid **146**, with complete retention of stereochemical features in the lactone product **147** (Scheme 68).[58]



Scheme 68

Of particular inspiration was the pioneering work of Marshall and Sehon who, in a series of influential publications, reported using silver(I) nitrate on silica gel to induce an oxygen nucleophile to attack a range of carbon electrophiles. They applied these findings to an efficient and highly versatile furan synthesis, involving a 5-*endo*-dig cyclisation of a β-hydroxy alkyne **148**, followed by concurrent isomerisation of an exocyclic alkene bond to generate the furan **149** (Scheme 69).[59]



Scheme 69

The use of late transition metals in heterocyclic synthesis is by no means limited to silver - Muller, for example, reports Rh, Ir, Ni, Pd, Pt, Cu and Au as being able to perform similar transformations, albeit with varying success.[60] The high yields and exceptionally clean products generated by the use of a silver nitrate catalyst, however, made it a highly attractive candidate for further exploitation.

Mechanistic explanation

Despite the considerable attention that has been paid to the use of transition metals in this manner, there has been relatively little investigation of a mechanistic explanation for the transformation. The reagent, silver nitrate on silica, used in the aforementioned studies is commercially available from a variety of sources as a reagent for chromatography, with significant utility in the separation of alkene stereoisomers and alkynes, due to the ability of silver(I) to interact with these structural features to varying extents.[61] The interaction of transition metals with carbon-carbon π-bonds is typically described using the Dewar-Chatt-Duncanson model, whereby a complex is formed through donation of electrons from the π-bond of the alkene/alkyne to a vacant d-orbital of the metal coupled with back-donation of electrons from a filled metal d-orbital into the carbon-carbon π^*-orbital (Diagram 7).

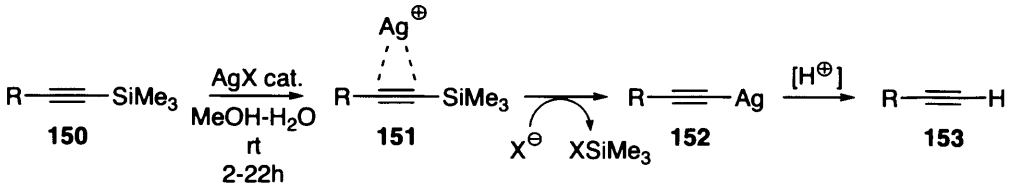
σ donation from π-bond to vacant d-orbital

π donation from filled d -orbital to π^*-orbital

Diagram 7

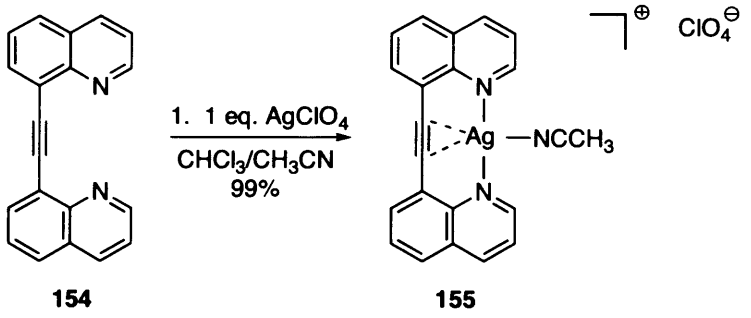
The overall effect of such an interaction is a lengthening and weakening of the π-bond; a possible explanation for the increased susceptibility towards nucleophilic attack.

Pale and co-workers have reported the use of silver nitrate in the desilylation of acetylenes **150** and have postulated a mechanism involving formation of a alkyne-metal complex **151**, followed by generation of a silver acetylide **152** and finally silver-proton exchange to yield a terminal acetylene **153** (Scheme 70).[62]



Scheme 70

This rationale was based on the group's earlier observations that the application of various silver(I) salts to a range of terminal alkynes resulted in two consecutive shifts in the resonance observed in the ^{109}Ag NMR spectra over time.[63] Along with weakening the carbon-carbon π-bond, it is also possible that the metal promotes attack by a heteroatom nucleophile by bonding with a lone pair of electrons and thus bringing it into direct proximity to the π-bond. Such a postulate is supported by the existence of stable complexes formed by the interaction of transition metals with alkynes and heteroatoms. Such a complex **155**, formed by the interaction of silver(I) with an alkyne and three sets of nitrogen lone-pair electrons, was recently reported by Tor and co-workers (Scheme 71).[64]



Scheme 71

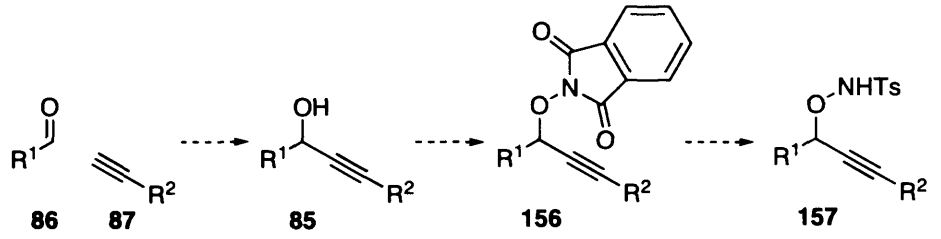
Despite the lack of a clear mechanistic explanation for the process, the success observed in the synthesis of furans and pyrroles sets a clear challenge for the expansion of the methodology into the synthesis of more complicated heterocyclic systems. It was with this in mind that we set about investigating the synthesis of polysubstituted isoxazolines.

Results and discussion

Initial findings

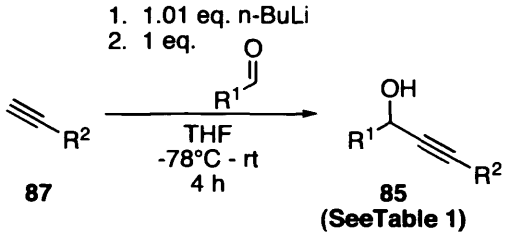
It seemed a logical starting point for this investigation to begin by examining the effect the silver nitrate catalyst had upon the starting materials utilised in the group's previous iodocyclisation studies. Although the *p*-toluenesulphonyl (tosyl) group is considered by many to be a poor choice of amine protecting group, due to the difficulties often encountered when attempting regeneration of the free-amine, its utility in iodocyclisation reactions and the stability of the various sulphonamide precursors, made us reluctant to investigate alternatives at this point. Retrosynthetic analysis suggested that the required *N*-tosyl hydroxylamines could be rapidly obtained using the synthetic sequence employed in our previous studies (*i.e.* Mitsunobu

displacement of a propargylic hydroxyl group followed by functional group interconversion). We were also keen to examine the effect the catalyst would have on unprotected hydroxylamines, shown to be easily synthesised by the same synthetic sequence (Scheme 72).



Scheme 72

The required propargylic alcohols were synthesised by the addition of a range of lithiated alkynes to a selection of suitable aldehydes (Scheme 73).



Scheme 73

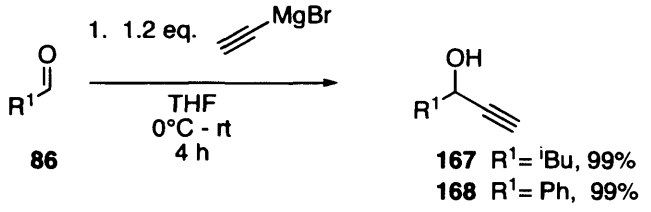
By varying the steric and electronic properties of the substituents a diverse set of substrates was synthesised (Table 1).

Table 1: *Synthesised propargyl alcohols.*

Product	R^1	R^2	Yield (%)
158	*iso*-Butyl	Butyl	99
159	*iso*-Butyl	Phenyl	98
160	*iso*-Butyl	CH_2OBn	90
161	*iso*-Butyl	$CH_2CH_2OTBDPS$	99
162	*iso*-Butyl	$CH_2CH_2OTBDMS$	98
163	*iso*-Butyl	*p*-(MeO)Ph	96
164	*iso*-Butyl	*p*-(NO_2)Ph	-
165	*iso*-Butyl	*tert*-Butyl	98
166	Phenyl	Phenyl	99

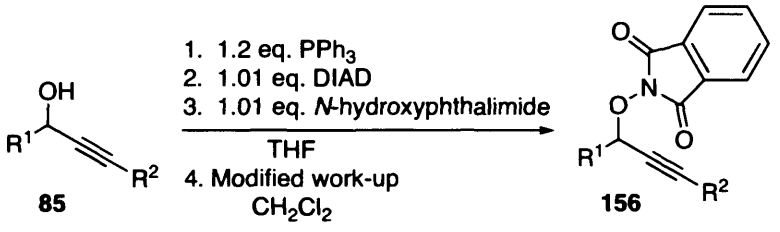
All but one of the additions furnished propargyl alcohols in good yield and with no requirement for additional purification. The notable exception was the attempted addition of *p*-nitrophenylacetylene to isovaleraldehyde (in an attempted synthesis of propargyl alcohol **164**), which delivered only a small amount of an unidentified mixture of products that could not be separated by silica gel chromatography – we would return to this example later in our studies.

We were also keen to examine whether or not we could perform our desired cyclisation with a terminal alkyne, *i.e.* one having a proton in the 'R^2' position. Such 'terminal' alkynes were synthesised by the addition of the commercially available ethynylmagnesium bromide to representative aldehydes (Scheme 74).



Scheme 74

With a range of propargyl alcohols in hand, we set about installing the hydroxylamine functionality by displacing the propargyl hydroxyl group with *N*-hydroxyphthalimide, under Mitsunobu conditions. Using the modified Mitsunobu conditions discussed previously (Scheme 55, pp 29) and discussed in detail in Chapter Five of this thesis, we were able to obtain a range of phthalimide-protected hydroxylamines (Scheme 75, Table 2).



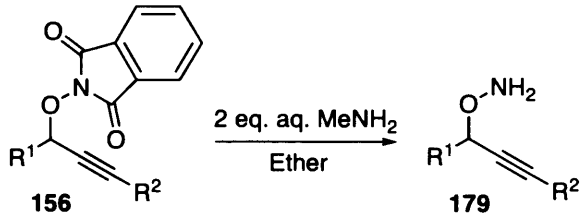
Scheme 75

Table 2: *Synthesised phthalimide-protected hydroxylamines.*

Product	R^1	R^2	Yield (%)
169	*iso*-Butyl	Butyl	89
170	*iso*-Butyl	Phenyl	87
171	*iso*-Butyl	CH_2OBn	79
172	*iso*-Butyl	$CH_2CH_2OTBDPS$	74
173	*iso*-Butyl	$CH_2CH_2OTBDMS$	73
174	*iso*-Butyl	*p*-(MeO)Ph	81
175	*iso*-Butyl	*tert*-Butyl	89
176 [a]	Phenyl	Phenyl	41
177	*iso*-Butyl	H	85
178 [a]	Phenyl	H	69

[a] – After initially poor yields, it was feared the intermediates formed from benzylic alcohols (*i.e.* when R^1 = Ph) might be unstable, leading to compound degradation. In these cases, it was found yields could be improved by omitting the interval between the addition of reagents.

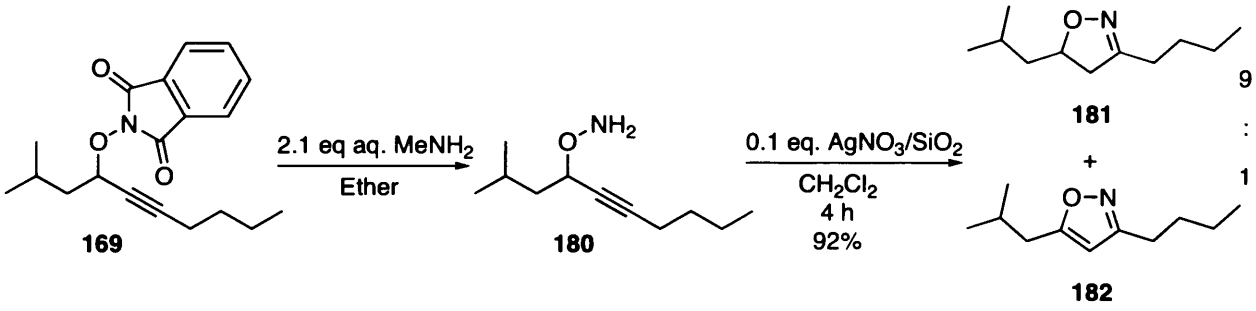
The phthalimide group was then removed using aqueous methylamine (Scheme 78).



Scheme 78

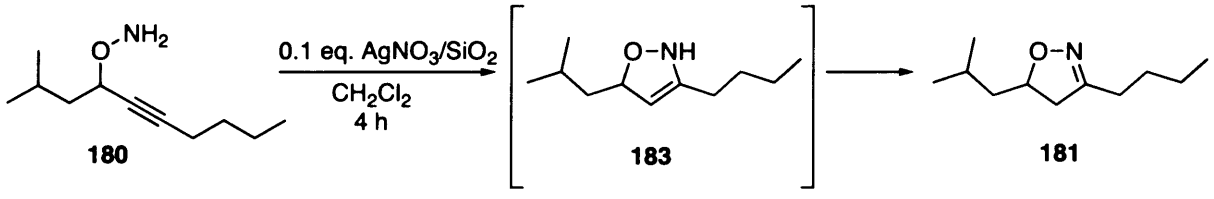
The unprotected hydroxylamines were, as discussed previously, found to be unstable and so were reacted immediately without attempts being made to purify or characterise these compounds. Previous iodocyclisation studies had shown the unprotected hydroxylamines **179** to be incompatible with the reaction conditions and thus the tosyl protecting group had found routine application. When utilising the silver nitrate catalyst, however, we had no reason to believe that the unprotected hydroxylamines would be similarly unsuitable and so it seemed prudent to investigate the effect of the catalyst on these substrates.

Throughout the aforementioned investigations into the synthesis of furans and pyrroles, it had been found that 10 mol% of silver nitrate, utilised as the commercially available 10% w/w dispersion on silica, was adequate to induce full cyclisation in under 4 h. Applying these conditions to the *O*-propargyl hydroxylamine **180**, to our delight, triggered complete conversion of the starting material, yielding a major product and a small amount of a second, minor product, in a > 9 : 1 ratio respectively and in an overall yield of 92% (Scheme 79).



Scheme 79

Analysis of the major product indicated formation of the desired 4,5-dihydroisoxazole **181**, presumably resulting from an initial cyclisation yielding the 2,5-dihydroisoxazole **183**, followed by tautomerisation to yield the observed product (Scheme 80).



Scheme 80

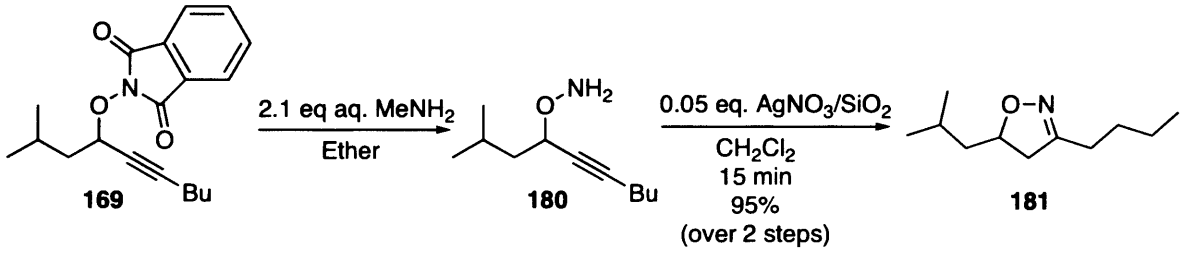
The intermediate "enamine" **183** was not observed in the NMR spectra of the crude product, indicating it to be short-lived and suggesting that, if the tautomeric intermediate **183** in fact

exists in equilibrium with the observed product **181**, this equilibrium strongly favours the observed product. This is typical of both keto-enol and imine-enamine tautomerisation, where in both cases, the former is usually strongly favoured. Upon attempting to purify this product by silica gel chromatography, rapid decomposition occurred to give only highly polar by-products. The sensitivity of these compounds is well documented and this limitation was not unexpected.[65] We were, however, able to obtain the minor product as a stable, highly mobile fraction. Analysis of this compound by high resolution mass spectrometry (HRMS) suggested the compound contained two less protons than the major product. The proton NMR of the compound also contained a distinctive resonance at 5.82 ppm, consistent with a proton in the 4-position of an isoxazole, along with several resonances indicative of the *iso*-butyl and butyl groups, no longer coupling to a proton on the ring. This, when combined with our observations regarding the increased stability and reduced polarity of the minor product compared to that of the major compound, led us to speculate that oxidation of the major product **181** had occurred, producing the isoxazole **182** as the minor product.

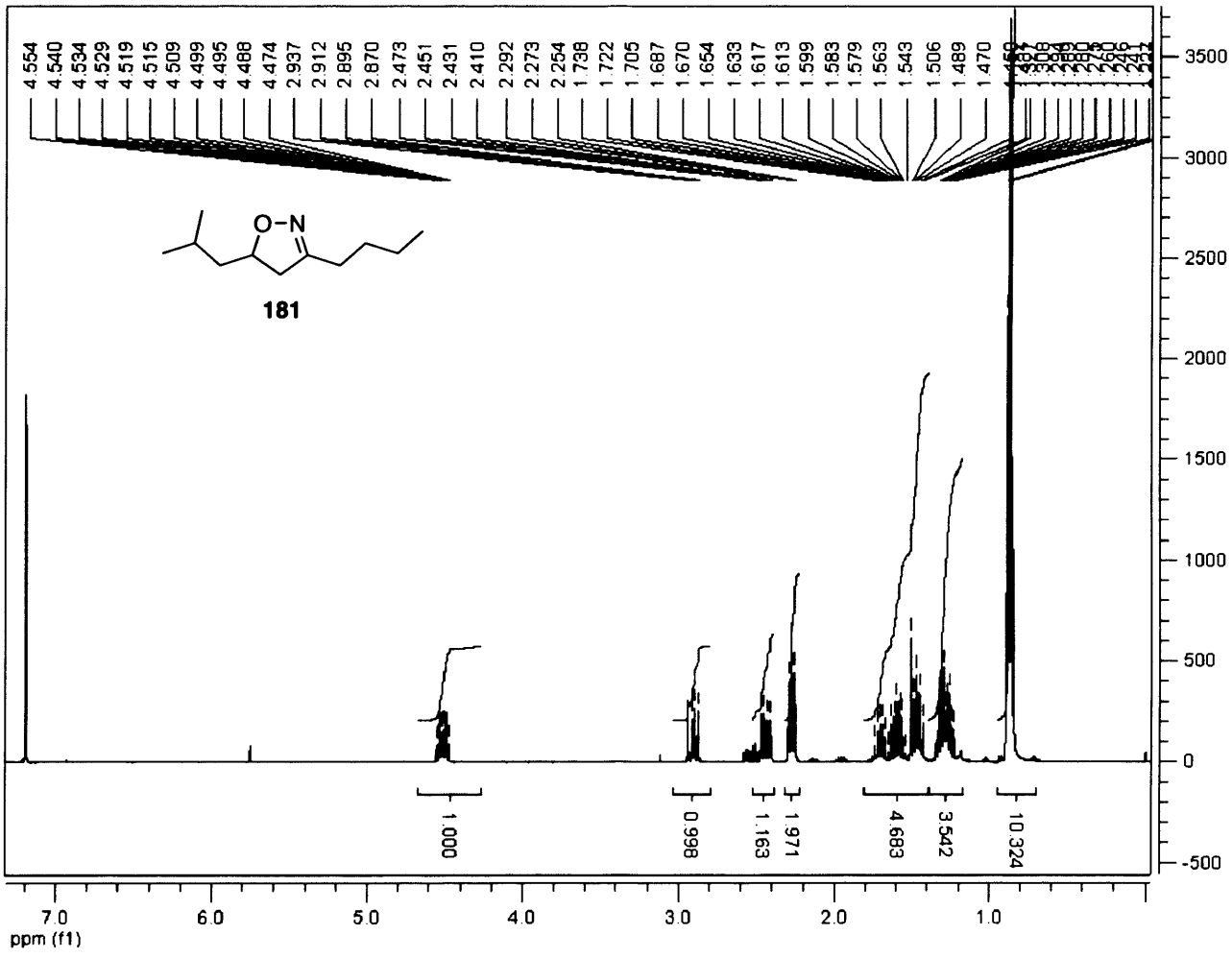
Silver nitrate, as with many silver(I) salts, is a mild oxidant.[66] Given that the level of oxidation so closely mirrored the amount of silver nitrate employed in the cyclisation reaction, we proposed that the substance was not only acting as a catalyst for the ring-closure reaction but also as a stoichiometric oxidant of the initial product **181**. Given our apparent inability to obtain purified dihydroisoxazole from the mixture of the two products, we set about exploring how we might prevent the aforementioned oxidation occurring and thus obtain a single reaction product.

By removing and carefully filtering aliquots of the reaction mixture (in order to remove the catalyst and thus halt the reaction) and then analysing their content by gas chromatography (GC), we were able to follow the progress of the reaction over time. Under the conditions described above, it was found that not only was the consumption of the starting material and its conversion to the cyclic product complete within 15 minutes but also that the slightly sub-stoichiometric amount of oxidation afforded by the catalyst had also reached completion by this point. The same was true when a much larger amount of catalyst was used, with 0.55 equivalents of the catalyst resulting into an approximately equal mixture of major and minor products. With the silver nitrate acting as an oxidant the presumed product is elemental silver(0). This was observed as a blackening of the silica support retrieved upon filtration. Earlier studies within the group have previously shown silver(0) to be an ineffective catalyst of the 5-*endo*-dig cyclisations.[67] Given that no starting material was present at the end of the reaction, it was presumed that the silver(I) must be catalysing the ring closure prior to its reduction. Whilst the speed of both reactions (cyclisation and oxidation) was pleasing it did nonetheless suggest that limiting the amount of oxidation through control of the reaction

conditions would be ineffective. It was therefore decided to limit the level of oxidation by instead altering the amount of catalyst used. By experimenting with varying levels of silver nitrate, it was found that the smallest amount of catalyst that would still effect efficient and rapid cyclisation of unprotected hydroxylamines was 0.05 equivalents, with respect to the hydroxylamine substrate. Using this amount of catalyst, the desired 4,5-dihydroisoxazoline **181** was synthesised in near quantitative yield, in under 15 minutes. Although the isoxazole **182** was still visible in the proton NMR of the crude reaction mixture (Diagram 8), it was only as a set of weak, unintegrated resonances; thus indicating >95% purity of proton-bearing organic content, with respect to the desired product **181** (Scheme 81).



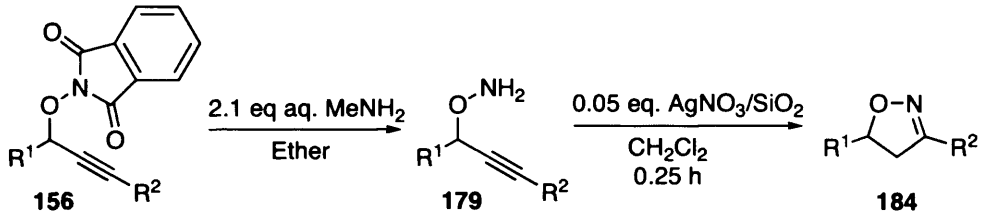
Scheme 81



Proton NMR spectrum of crude isoxazoline **181** (400MHz, 300.0°K in $CDCl_3$).

Diagram 8

This procedure was applied to the synthesis of a range of 4,5-dihydroisoxazoles (Scheme 82, Table 3).



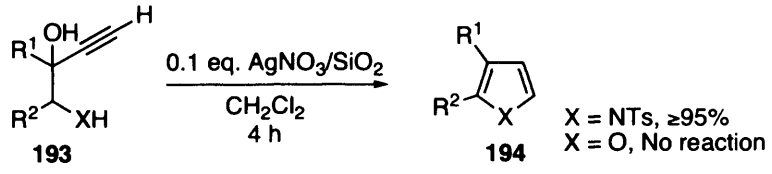
Scheme 82

Table 3: *Synthesised 4,5-dihydroisoxazoles.*

Product	R^1	R^2	Yield (%)
185	*iso*-Butyl	Phenyl	90
186	*iso*-Butyl	CH_2OBn	92
187	*iso*-Butyl	$CH_2CH_2OTBDMS$	91
188	*iso*-Butyl	*p*-(MeO)Ph	91
189	*iso*-Butyl	*tert*-Butyl	96
190	Phenyl	Phenyl	89
191 [a]	*iso*-Butyl	H	96
192 [a]	Phenyl	H	90

[a] – Terminal acetylenes (R^2 = H) required 0.1 equivalents of catalyst and 1h reaction time and once again contained ≤5% of a minor, isoxazole product (based on resonances displayed in the proton NMR of the product).

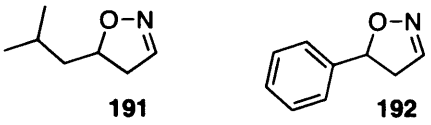
The majority of the yields reported here are unoptimised and it is reasonable to suppose that the differences observed for various substrates may be due to varying losses encountered in the processing of the reaction mixture and that each reaction could, as no degradation products are observed, theoretically be optimised to provide a quantitative yield of product. All but two of these products were obtained from this simple and effective procedure in under 15 minutes – the notable exception being cases where R^2 = H (dihydroisoxazoles **191** and **192**). Previous work within the group had shown that terminal acetylenes are able to participate in the synthesis of 2,3-disubstituted pyrroles; however, such 1-alkynes were incompatible with the synthesis of 2,3-disubstituted furans (Scheme 83).



Scheme 83

This strongly suggested that cyclisations of these terminal acetylenes requires the increased nucleophilicity of a nitrogen nucleophile, as opposed to oxygen, to be successful. It was found

that by increasing the amount of catalyst used to 0.1 equivalents, complete cyclisation of terminal acetylenes occurred within 1 hour. Interestingly, in these cases the increased amount of catalyst still resulted in <5% oxidation of the major product. This indicated that oxidation of the monosubstituted dihydroisoxazoles **191** and **192** was less readily achieved than the corresponding oxidation of their disubstituted analogues. We were also intrigued to find that these compounds possessed pungent, citrus aromas.

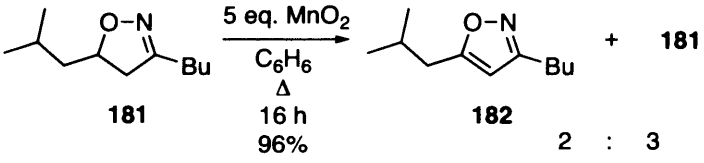


191 **192**

This property was further investigated by Williams, a final year project student working within the Knight group, and was found to extend over a range of similar 5-substituted 4,5-dihydroisoxazoles, *e.g.* the cironellal-derived dihydroisoxazoles **192a** and **192b**, which notably processed markedly different aromas.[68]

192a **192b**

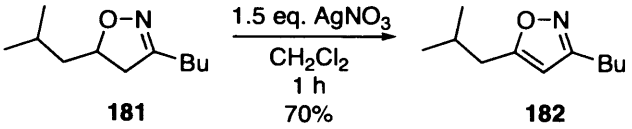
The oxidation of the cyclisation products by the silver nitrate catalyst, whilst an unforeseen complication in the synthesis of the dihydroisoxazoles **185-192**, has valuable synthetic applications as a method for the synthesis of disubstituted isoxazoles. The oxidation of 4,5-dihydroisoxazoles to isoxazoles has been frequently reported, with varying degrees of success. In cases where the substrate bears either one or more aryl substituent, or where the dihydroisoxazole is conjugated with exocyclic alkenes or carbonyl groups (*e.g.* Ac), a plethora of reagents have proven to be effective oxidants, for example: manganese dioxide,[69] *N*-bromosuccinimide (NBS),[70] DDQ,[71] chloranil[72] and lithium perchlorate[73] have all found successful application. The oxidation of substrates bearing simple alkyl (*i.e.* non-conjugated) substituents is much less readily achieved. The reagent of choice for such reactions is most commonly manganese dioxide, with reactions commonly requiring extended periods of heating in order to deliver even moderate yields.[74] Applying this reagent to the dihydroisoxazole **181**, we observed only around 40% conversion into the isoxazole **182**, even when excess of oxidant and an extended period of reflux were applied (Scheme 84).



Scheme 84

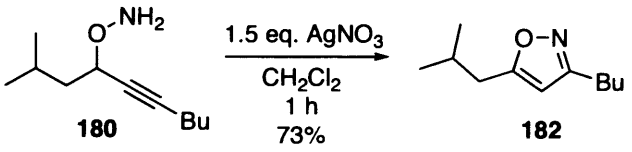
We were immediately struck by the apparent difficulty in oxidising this type of substrate with such a reagent, especially when compared to the ease with which the oxidation was achieved

using the silver nitrate catalyst. By exposing the substrate **181** to an excess of silver nitrate on silica gel for 1 h at room temperature, we were able to obtain a 70% yield of the isoxazole **182**, following silica gel chromatography (Scheme 85).



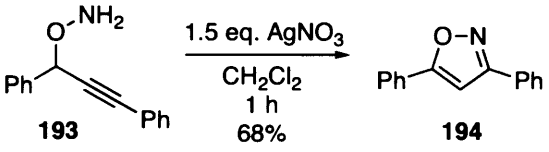
Scheme 85

By performing the ring closure of the *O*-propargyl hydroxylamine **180** with excess of silver nitrate on silica, we were able to obtain the isoxazole **182** in one pot, again in good yield (Scheme 86).



Scheme 86

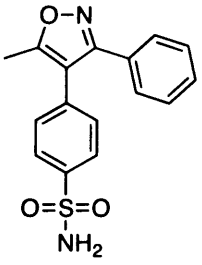
Using this novel procedure, 3,5-diphenylisoxazole **194** was synthesised in high yield and structural confirmation was achieved by comparison with previously reported data (Scheme 87).[75]



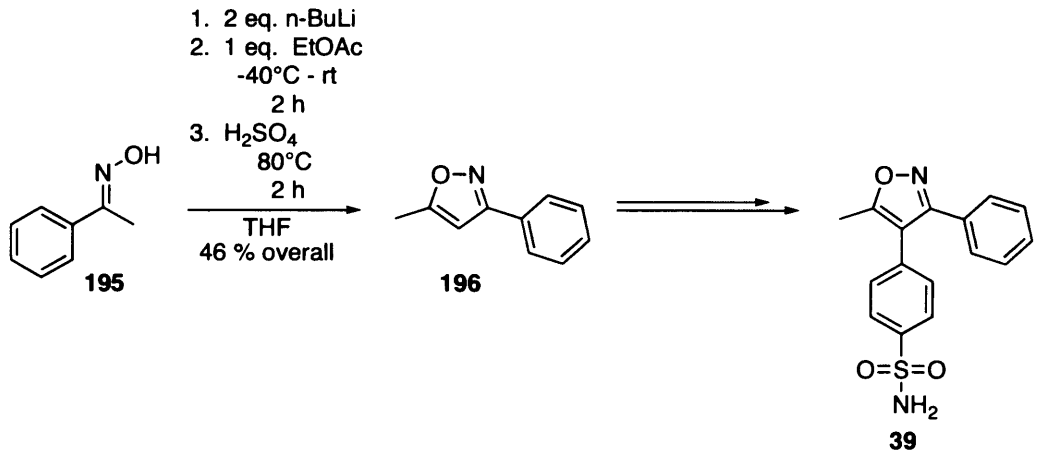
Scheme 87

In each case, silica gel chromatography was required to obtain pure products, with the predominant contaminants being highly polar degradation compounds.

In order to test this novel methodology, a short formal synthesis of the potent COX-2 inhibitor Valdecoxib **39** was attempted.



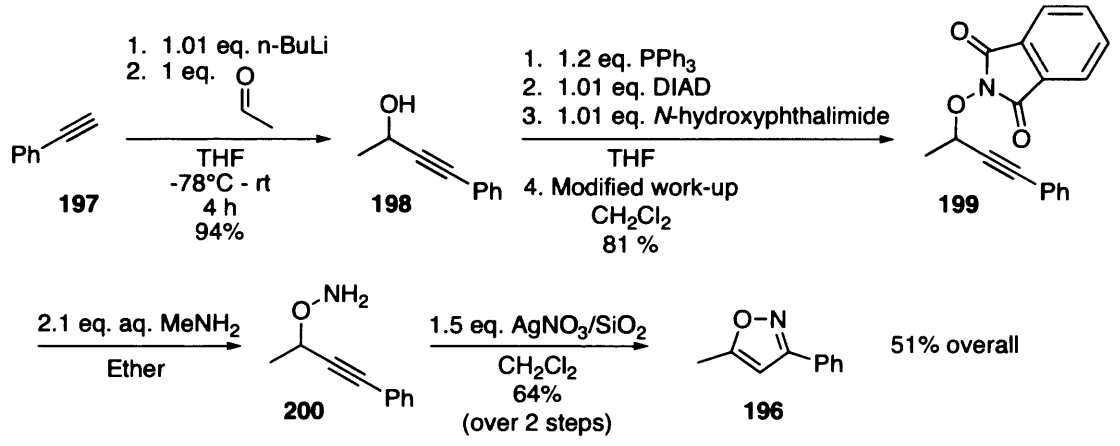
In a facile synthesis of the compound, Toyokuni and co-workers reported obtaining the isoxazole core **196** by condensation of a phenyl acetaldehyde-derived oxime **195** with ethyl acetate, subsequently obtaining the target compound by elaboration to the corresponding 4-boronic acid followed by palladium catalysed coupling with *p*-bromobenzenesulphonamide (Scheme 88).[76]



Scheme 88

Although this synthesis of the isoxazole **196** is expedient and regioselective, we felt the approach was limited in its potential for incorporating varying substituents and by a moderate overall yield.

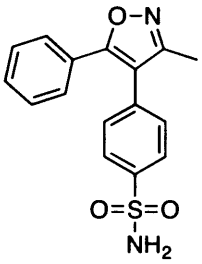
Applying our own synthetic strategy, we first generated the required propargyl alcohol **198** by addition of lithiated phenylacetylene to a freshly distilled sample of acetaldehyde. The resulting alcohol was then displaced by *N*-hydroxyphthalimide under the modified Mitsunobu conditions (detailed in Chapter Five of this thesis). The phthalimide protecting group was removed using aqueous methylamine and the unprotected hydroxylamine **200** then cyclised and oxidised in a one-pot, one-reagent procedure using an excess of 10% w/w silver nitrate on silica gel (Scheme 89).



Scheme 89

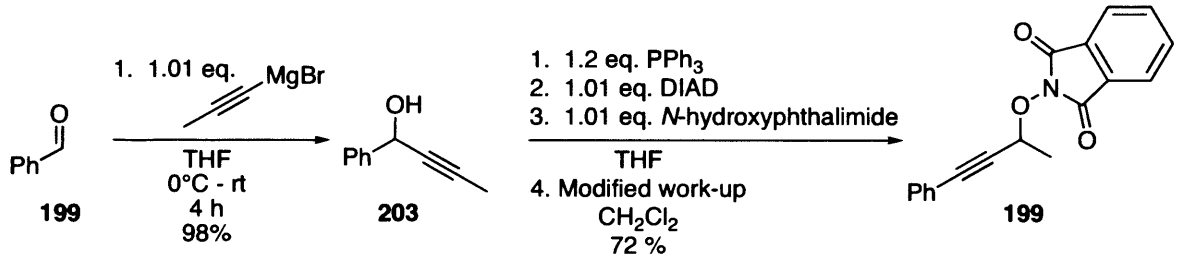
Although the overall yield of the isoxazoline core was only marginally better than that obtained by Toyokuni, it is worth noting that at only the final step was silica gel chromatography required and that the process has the potential to generate analogues bearing a far greater range of substituents than could be accessed *via* Toyokuni's synthetic route.

In order to demonstrate this we attempted a short synthesis of the Valdecoxib regioisomer **201**.



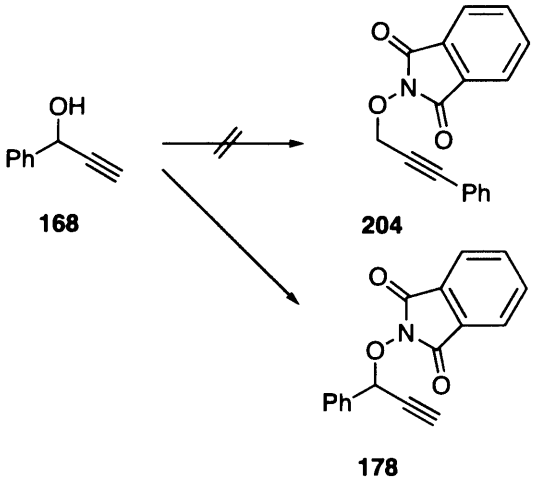
201

Synthesis of the required propargyl alcohol **203** was achieved by addition of the commercially available Grignard reagent propynylmagnesium bromide to benzaldehyde. Surprisingly, however, rather than delivering the required phthalimide-protected hydroxylamine, the subsequent Mitsunobu displacement of the resulting alcohol with *N*-hydroxyphthalimide instead yielded the rearranged product **199**, an identical compound to that which had been obtained previously (Scheme 89) en route to the isoxazole core **196** of Valdecoxib **39** (Scheme 90).



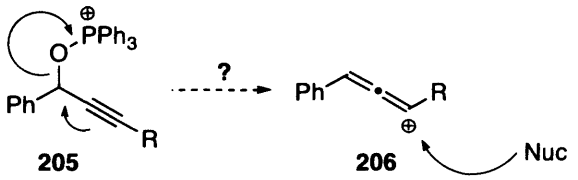
Scheme 90

Such a rearrangement was entirely unanticipated, with no such effect having been observed in any of the previously described Mitsunobu displacements (Table 2, pp 42). Moreover, the obvious driving force for such a rearrangement appeared to be the newly formed conjugation between the alkyne and the phenyl group, yet such a rearrangement had not occurred when 1-phenylprop-2-yn-1-ol **168** had been employed in the Mitsunobu reaction, even though it would have created both increased conjugation and a more substituted alkyne **204** (Scheme 91).



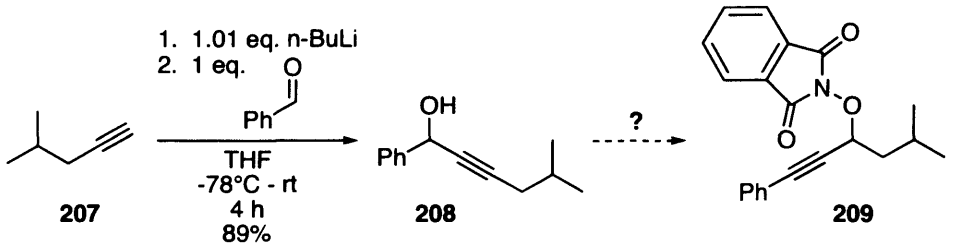
Scheme 91

Thus the rearrangement observed obviously represents a very special case. The sensitivity of benzylic alcohols to Mitsunobu conditions had already been observed in our studies, having led to the necessity for a modified procedure for addition of reagents in order to salvage otherwise poor yields. We began to suspect the possibility that, in cases where the propargyl alcohol was also benzylic, an alternative reaction pathway may exist, which in some cases favours a rearranged product. During the Mitsunobu reaction the alcohol that is to be displaced is activated by a phosphonium species, which may behave differently in cases where it exists in a benzylic position. In such cases the alcohol may undergo elimination to form the allene, with the nucleophile then attacking the carbenium ion so formed (Scheme 92).



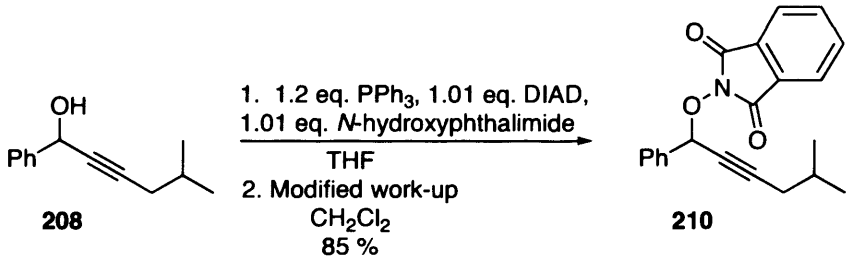
Scheme 92

Nonetheless, rearrangement had thus far only been observed in substrates where the acetylene was substituted with a methyl group. In order to assess whether such a phenomenon extended to more complicated substrates, we synthesised the propargylic alcohol **208**, a substrate that could potentially rearrange *via* our proposed mechanism to give the phthalimide **209**, that had been obtained previously (Scheme 93).



Scheme 93

In fact, when the alcohol **208** was utilised in our Mitsunobu procedure, no such rearrangement occurred. Moreover, the product of nucleophilic substitution of the alcohol by *N*-hydroxyphthalimide was obtained in good yield (Scheme 94).



Scheme 94

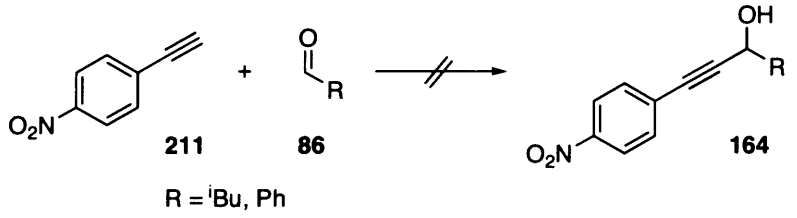
In hindsight, the use of the substrate **208** perhaps did not represent the most balanced assessment of the potential for rearrangement of benzylic alcohols. Regardless of the

mechanism of the rearrangement, it seems highly likely that any alternative reaction pathway would involve some form of conjugate addition of the nucleophile, whether concerted or *via* an intermediate, followed by regeneration of the alkyne. Although the lack of rearrangement in this particular case is in contrast to that observed when a methyl group was present at the terminal end of the alkyne, the distinction may have been more a result of the increased steric hindrance generated by the *iso*-butyl group than the increase in chain length or any difference in associated electronic properties.

Unfortunately, time did not allow us to continue our investigations into such rearrangements and to pursue further the synthesis of analogues of Valdecoxib **39**. The cause and occurrence of the rearrangement observed in the Mitsunobu reaction of the benzylic alcohol **203** remains unclear. With only one example having been observed, it seems likely that, although the effect may not be limited to this particular substrate, it is a rare occurrence and one that does not pose a significant limitation to our methodology.

An alternative phthalimide synthesis

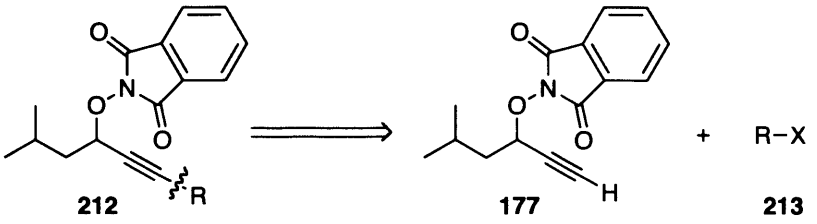
In the approach to the *O*-propargyl hydroxylamines required for the silver nitrate-catalysed 4,5-dihydroisoxazole synthesis, a diverse set of propargyl alcohols had been required and their synthesis had been achieved *via* the addition to various aldehydes of alkynes either as a lithiated species or the corresponding Grignard reagent. A range of substrates was synthesised in high yield, with one notable exception. The attempted addition of lithiated *p*-nitrophenylacetylene to isovaleraldehyde yielded only a complex mixture of products, with repeated attempts at silica gel chromatography failing to yield an identifiable product. Fearing that the altered electron distribution of this substrate, *vs.* phenylacetylene, may favour basisity of the alkyne over nucleophilicity and thus lead to aldol type polymerisation of the aldehyde, an analogous reaction was attempted using benzaldehyde. However, this also resulted in a frustrating lack of the desired product **164** (Scheme 95).



Scheme 95

It became apparent that there might be several cases where the substituents required on our dihydroisoxazoles may be beyond the scope of our alkyne addition strategy, *p*-nitrophenyl being one of these. With this in mind we set about exploring alternative means for the synthesis of our hydroxylamine precursors.

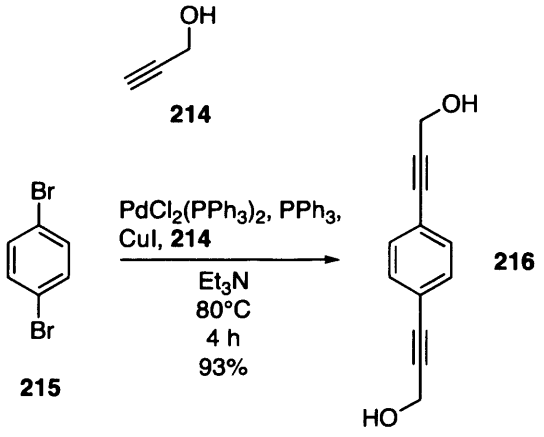
Of particular interest was the phthalimide-protected hydroxylamine containing a terminal alkyne subunit (compound **177**), synthesised previously (Scheme 75, Table 2, pp 42). Retrosynthetic analysis suggested such a substrate might be utilised in a divergent synthesis whereby, after generating the phthalimide protected hydroxylamine **177**, a second substituent could be installed by creating a carbon-carbon bond at the unsubstituted end of the alkyne (Scheme 96).



Scheme 96

Firstly, attempts were made to deprotonate the alkyne in compound **177** and trap it with a suitable electrophile (*e.g.* a primary halide or an aldehyde). In repeated attempts, using a variety of bases (n-BuLi, LDA, sodium hydride), only rapid decomposition of the starting material was observed. A seemingly milder approach involved attempting a palladium-catalysed coupling reaction.

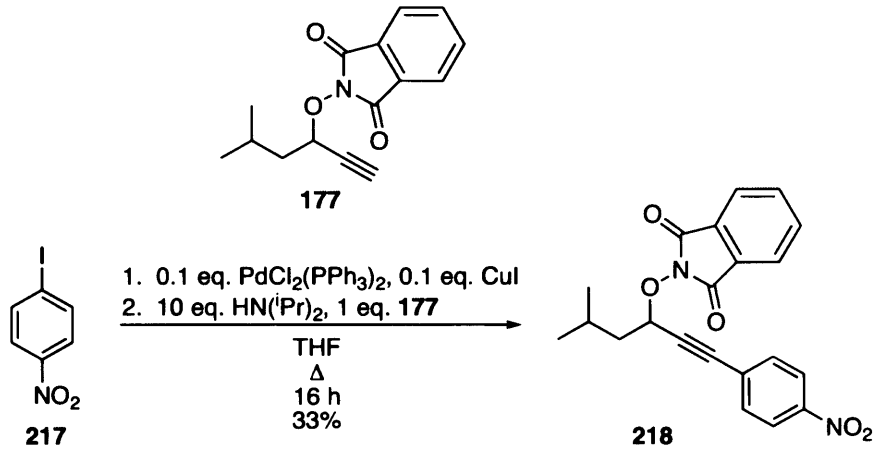
The Sonogashira reaction allows for the coupling of terminal alkynes with vinyl or aryl halides using a palladium catalyst, and in the presence of a copper(I) co-catalyst and an amine base. The reaction has been used extensively in organic synthesis and a broad range of reaction conditions have proved successful.[77] Of these conditions, particular success has been enjoyed with the use of dichloro-*bis*-triphenylphosphinepalladium instead of the more common palladium *tetrakis*-triphenylphosphine catalyst. For example, Braverman and co-workers have successfully performed a doubling coupling of a propargyl alcohol to 1,4-dibromobenzene in exceptionally high yield (Scheme 97).[78]



Scheme 97

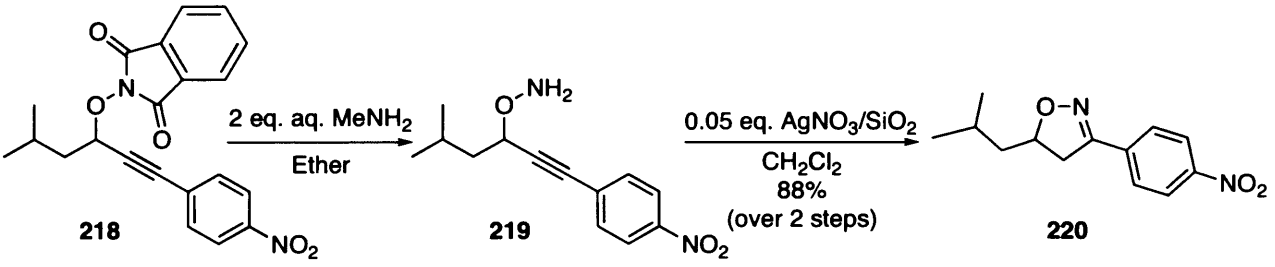
After experimenting unsuccessfully with these conditions and variations thereof, a combination of reagents was found that allowed for our substrate to be coupled to *p*-nitroiodobenzene and

isolated following silica gel chromatography, albeit in a somewhat disappointing yield (Scheme 98).



Scheme 98

This substrate was then deprotected and cyclised to yield the 4,5-dihydroisoxazole **220**, in good yield, thus at least confirming the compatibility of aryl nitro groups with the silver nitrate-catalysed cyclisation (Scheme 99).

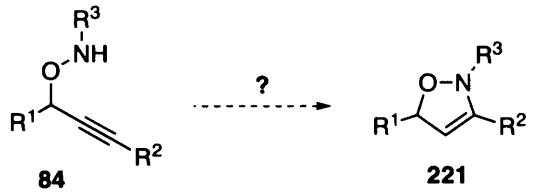


Scheme 99

Although several further couplings, to a range of aryl halides, were attempted, none returned any identifiable product. Moreover, significant amounts of unreacted starting materials or the homo-coupling products commonly generated in such Sonogashira reactions were also not observed. In these cases, only highly polar, unidentifiable by-products were observed, suggesting decomposition of the hydroxylamine **177** was occurring under the reaction conditions. A lack of time precluded further investigation of this means of substrate synthesis and it remains to be seen whether further optimisation of the reaction conditions could lead to greater success in a wider range of couplings. Protecting group exchange, for example, may provide greater compatibility of the substrate **177** towards the reaction conditions; however, it is clear that the simple approach desired was not to be readily available.

A suitable protecting group

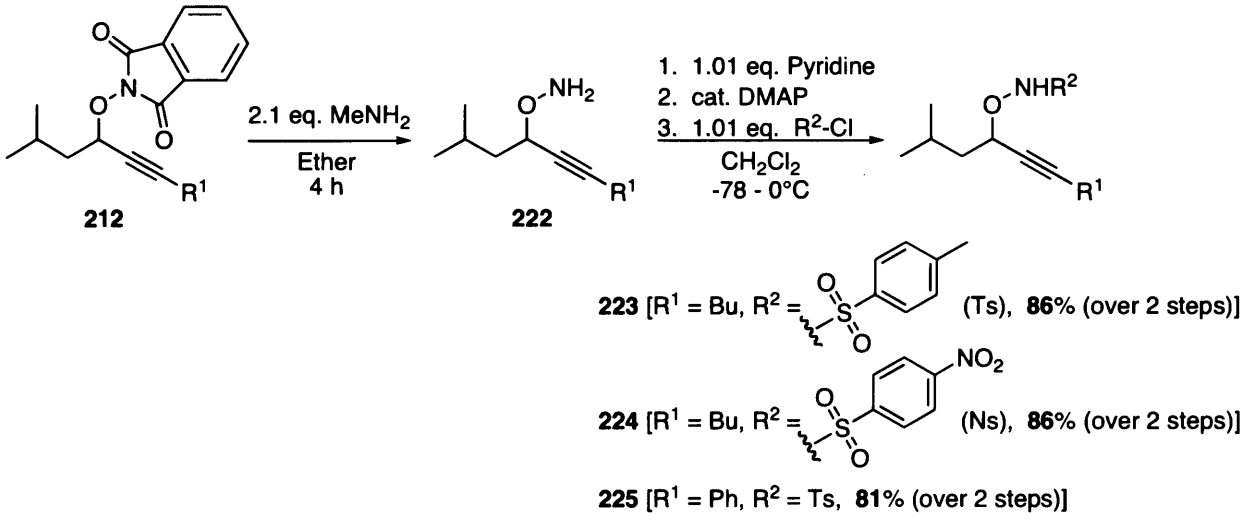
Prior to the observation that unprotected *O*-propargyl hydroxylamines can be cyclised to give direct access to 4,5-dihydroisoxazoles, it had originally been our intention to protect the hydroxylamine before cyclisation. We had hoped such compounds would cyclise under the effect of the silver nitrate catalyst to yield stable 2,5-dihydroisoxazoles **221** (Scheme 100).



Scheme 100

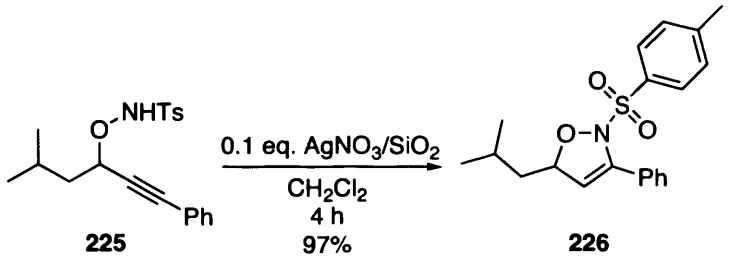
The potential for derivitisation of these products, for example through hydroboration or oxidation of the alkene bond, makes such dihydroisoxazole isomers particularly interesting. As described in the previous Chapter of this thesis, our investigations into the synthesis of dihydroisoxazoles *via* iodocyclisation had shown the tosyl protecting group to be highly suitable for this purpose. Although we regarded this to be an excellent starting point for our investigations we were nonetheless concerned about the difficulties associated with the removal of this group. In order to counter this, we also decided to explore the use of *p*-nitrobenezenesulphonyl (nosyl) as a protecting group. Although sulphonamides of this kind are known to possess similar reactivity to tosyl analogues, their removal can be facilitated in a much milder fashion through their reactions with thio-derived anions (*e.g.* potassium thiophenolate or lithium thioglycolate).[79]

Using the tosylation procedure described in Chapter Two of this thesis (Scheme 57, pp 31), two tosyl protected *O*-propargyl hydroxylamines were synthesised and, using a modification of the same procedure, one substrate bearing a nosyl protecting group (Scheme 101).



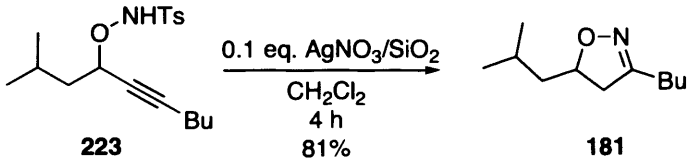
Scheme 101

With no obvious mechanism for the oxidation of the products by silver nitrate, we reverted to using 10 mol% of our catalyst, the conditions that had proven successful in previous furan and pyrrole syntheses and, serendipitously, firstly applied these conditions to sulphonamide **225**. To our delight, the substrate underwent successful cyclisation to generate the 2,5-dihydroisoxazole **226** in quantitative yield, with no need for purification (Scheme 102).



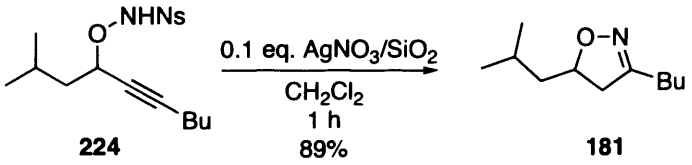
Scheme 102

This success was destined, it seemed, not to last. To our surprise, the tosyl protected butyl-substituted alkyne **223** cyclised to give the 4,5-dihydroisoxazole **181** that had previously been obtained through cyclisation of an analogous, unprotected hydroxylamine (Scheme 103).



Scheme 103

The same effect was observed when cyclisation of the nosyl analogue **224** was attempted (Scheme 104).



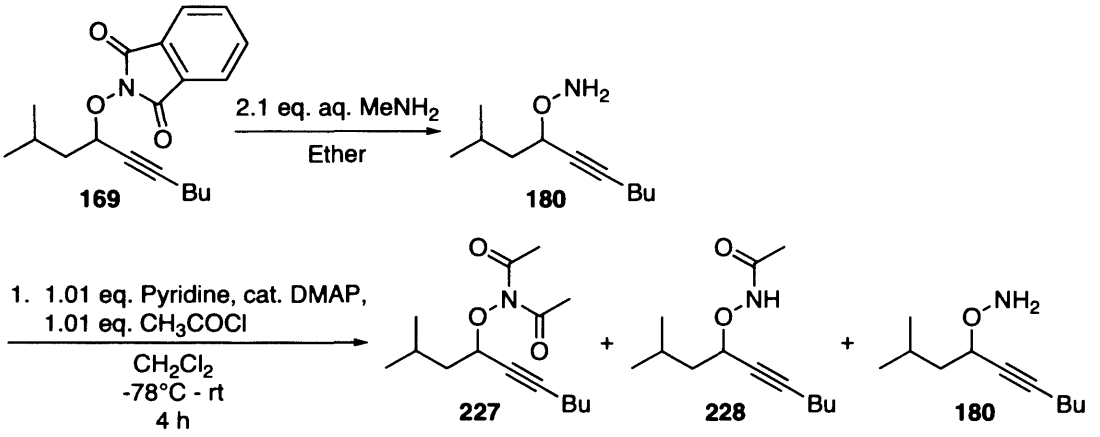
Scheme 104

The outcome of these reactions was met with considerable confusion. Firstly, complete cleavage of the tosyl protecting group had apparently been achieved (using only silver nitrate on silica) and in a form that was completely removed by the work-up procedure. Removal of the tosyl group is often troublesome and requiring of comparatively harsh reaction conditions, thus cleavage under these conditions was highly unexpected. Secondly, the phenyl-substituted alkyne **225** cyclised as intended. Although there are obvious electronic and steric differences at the point of ring closure, it is nonetheless surprising that such a difference would be observed. The removal of sulphur-based protecting groups using silver nitrate is not without precedent. Indeed, in his account of the application of the reagent in organic synthesis,[66] Paquette reports that silver nitrate has proved effective in the conversion of thioacetals,[80] 1,3 dithianes[81] and 1,3 oxathianes[82] to the corresponding ketones, the liberation of *S*-trityl ethers,[83] the hydrolysis of *S*-

tert-butyl esters and thiobenzoates,[84] and the conversion of thioamides[85] and thioureas[86] to amides and ureas respectively. The mechanisms and specificity of the removal of the tosyl and nosyl protecting groups remains unclear and would certainly be worthy of further investigation. Nevertheless, we were keen to continue our studies in the synthesis of 2,5 dihydroisoxazoles and thus, we were clearly in need of an alternative protecting group strategy.

An alternative protecting group

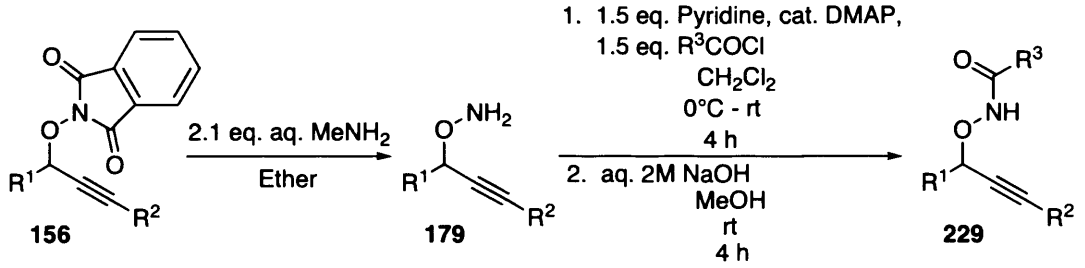
An obvious alternative seemed to be to attempt to protect the hydroxylamine nitrogen as either a 'carbamate' or 'amide' derivative. Fearing *bis*-protection would again be a problem (as had been the case with tosylation) the conditions that had proved successful in the tosylation procedure (Scheme 101, pp 55) were again applied to the acetylation of the hydroxylamine **180** (Scheme 105).



Scheme 105

Once again however, the proton NMR of the crude product revealed, along with the desired acetylated product **228**, the presence of a large amount of the bis-acetylated hydroxylamine **227** along with traces of unreacted hydroxylamine **180**. However, it seemed likely that the additional protecting group on the hydroxylamine would be far less stable than one protecting group alone and considerably more labile towards base-catalysed hydrolysis, *i.e.* *bis*-acylamines are well known to readily lose one of the acyl groups under a variety of conditions. A similar set of observations was made for the reaction of hydroxylamine **180** with various chloroformates.

Given this, it was reasoned that an excess of the protecting reagent could be used to fully acetylate a given hydroxylamine and that this could be followed by *in situ* hydrolysis of any *bis*-protected compounds to give pure, mono-protected hydroxylamines (Scheme 106).



Scheme 106

Using this procedure, a range of hydroxylamine-derived carbamates and amides were synthesised, in good yield and with no trace of the corresponding *bis*-protected compounds (Table 4).

Table 4: *Synthesised protected hydroxylamines.*

Product	R^1=	R^2=	R^3=	Yield (% over 2 steps)
230	*iso*-Butyl	Butyl	OMe	17
231	*iso*-Butyl	Butyl	O^{t}Butyl	81
232	*iso*-Butyl	Butyl	CF_3	85
228[a]	*iso*-Butyl	Butyl	Me	92
233	*iso*-Butyl	Phenyl	Me	90
234	*iso*-Butyl	H	Me	88

a – Discussed previously (Scheme 105).

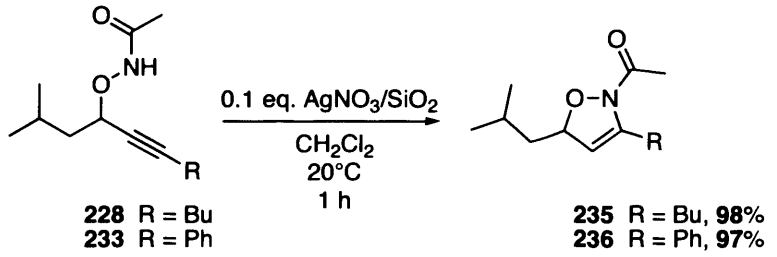
The methoxycarbonyl (Moc)-protected derivative **230** proved highly unstable and rapidly decomposed at room temperature. Given this, characterisation of the compound was severely limited. Attempts were made to cyclise the compound immediately following isolation and again only decomposition was observed, although it was not certain whether this decomposition was due to the effect of the catalyst. The *tert*-butyloxycarbonyl (Boc) protected compound **231** showed much greater stability and could be stored at room temperature, apparently indefinitely. Upon subjecting this compound to the cyclisation conditions for 4 h, only the return of unreacted starting material was observed. This was mildly surprising given that the Boc group possesses roughly similar, but lower electron-withdrawing properties to the tosyl group, although the increased steric hindrance generated by this group may be a factor. Nevertheless, the functionality -O-NH-CO_2R did not appear to be one that would advance the aims of achieving cyclisation.

Analysis of the amide-protected hydroxylamines **228**, **232**, **233** and **234** showed broadening and occasionally doubling of several proton NMR resonances, thus hampering attempts at characterisation. This was attributed to the existence of various rotameric forms. Switching the NMR solvent from deuteriochloroform to deuterated DMSO had a dramatic effect, yielding greatly sharpened resonances. Attempts at heating the NMR samples in a range of deuterated

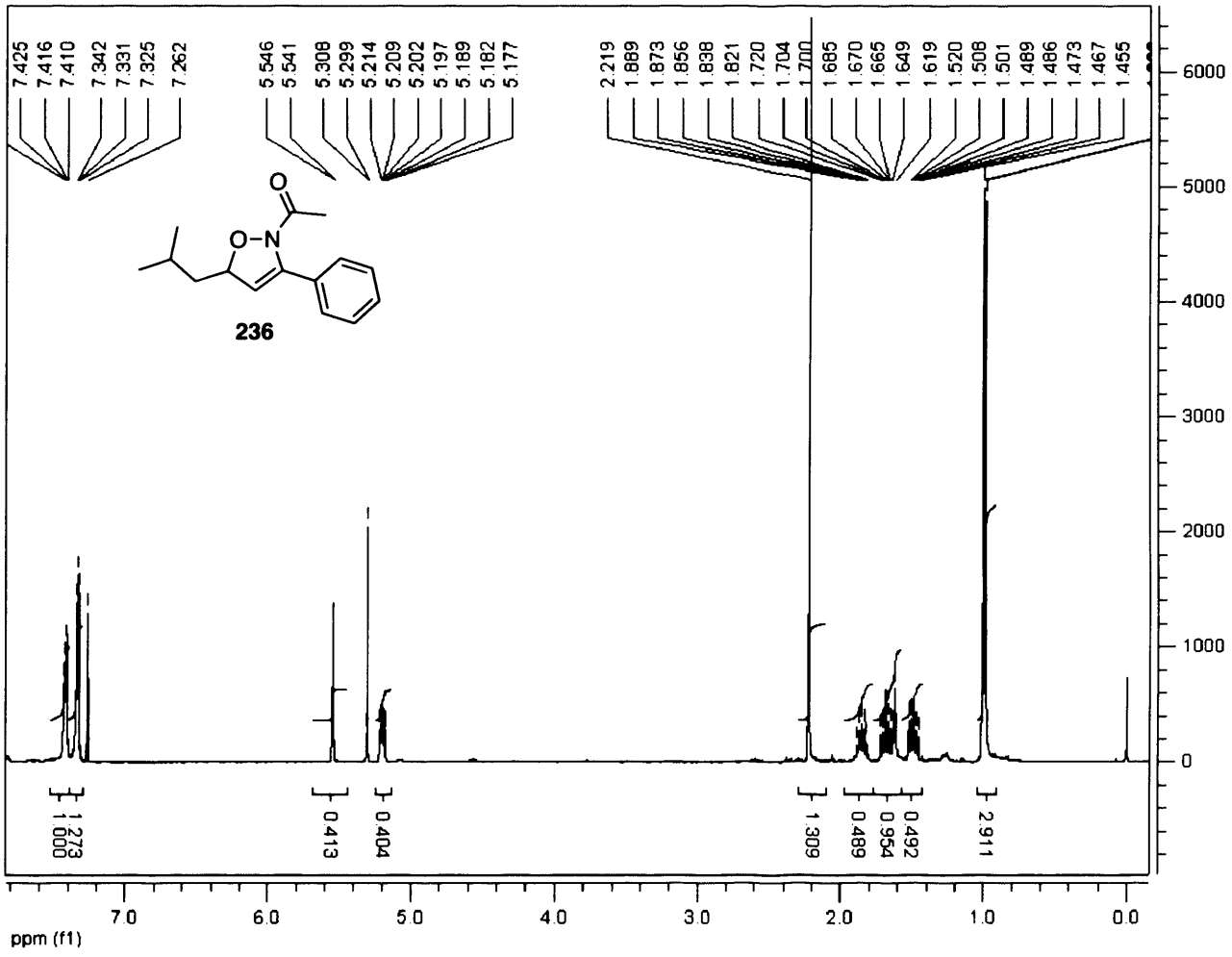
solvents in order to achieve greater clarity resulted in decomposition of the compounds and so were abandoned.

The trifluoroacetyl-protected hydroxylamine **232** was obtained as a stable compound, in good yield. Treating this compound with the silver nitrate/silica catalyst again returned only unreacted starting material. This was attributed to the strong electron-withdrawing properties of the trifluoromethyl group resulting in a reduction of the nucleophilicity of the hydroxylamine nitrogen.

Success was finally achieved with the cyclisation of the acetyl-protected derivatives **228** and **233** (Scheme 107).



Scheme 107

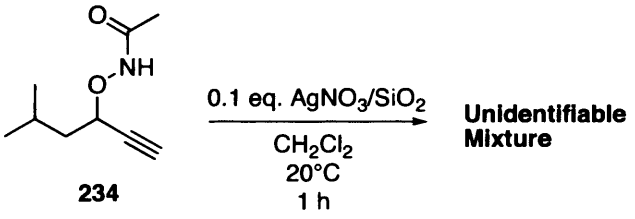


Proton NMR spectrum of dihydroisozazole **236** (400MHz, 300.0°K in $CDCl_3$).

Diagram 8

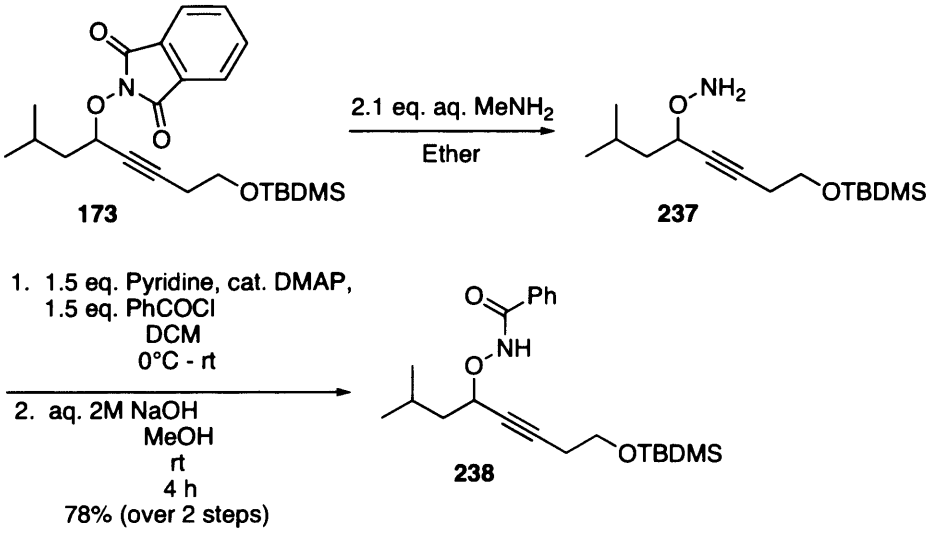
This represented a vital breakthrough, with the acetyl-protected compounds each delivering a single cyclic product, in virtually quantitative yield. The rate of cyclisation was notably slower than that observed for the corresponding unprotected hydroxylamines, with monitoring by tlc showing, in both cases, complete conversion within one hour (*c.f.* 15 minutes in the presence of 0.05 eq. silver nitrate/silica for the corresponding unprotected hydroxylamines). This supported our previous observation that protecting groups with a greater electron-withdrawing effect suppressed the ability of the compound to cyclise.

In the case of the acetyl-protected terminal alkyne **234**, cyclisation was less successful, with the application of the standard conditions yielding only an unidentifiable mixture of products that could not be separated by either distillation or silica gel chromatography (Scheme 108).



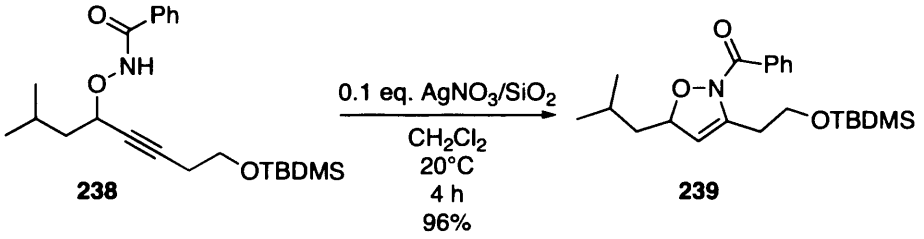
Scheme 108

This was perhaps unsurprising, given that the apparently more reactive unprotected hydroxylamines had been slower to react with terminal alkynes than with disubstituted alkynes. It was also important to investigate how the methodology would respond to more sterically demanding situations; for example the use of a bulky nitrogen-protecting group such as benzoyl in conjunction with a sterically demanding substituent at the point of ring closure. A number of phthalimide-protected hydroxylamines had previously been synthesised, including substrates containing silyl-protected alcohols in their side chains. One such phthalimide **173** contained an alcohol protected with the sterically demanding *tert*-butyldimethylsilyl (TBDMS) group. Using the acetyl-protection methodology, the benzoyl-protected hydroxylamine **238** was synthesised, in excellent overall yield (Scheme 109).



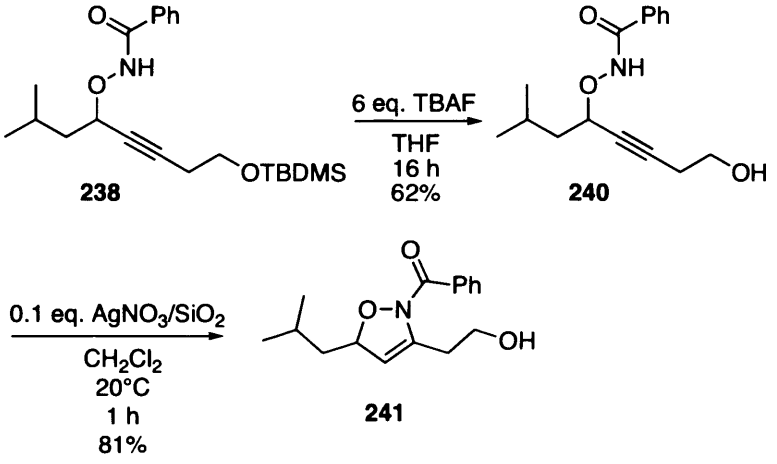
Scheme 109

Upon exposure to the silver nitrate/silica catalyst, this substrate underwent smooth ring-closure to deliver the 2,5-dihydroisoxazole **239**, as a single product and in high yield (Scheme 110).



Scheme 110

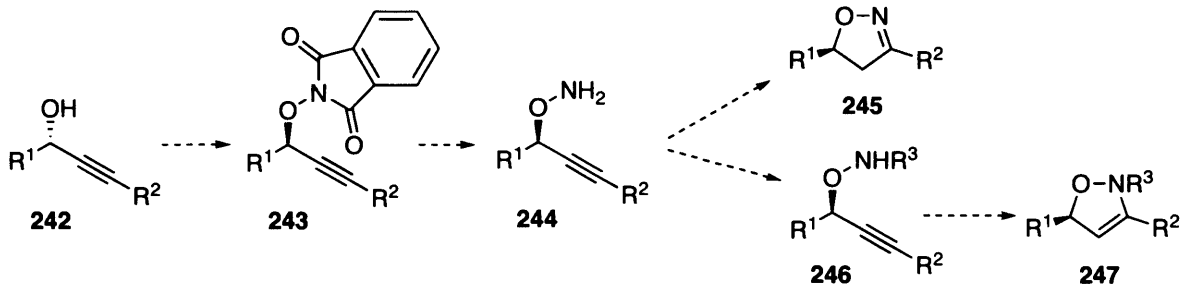
By first removing the silyl-protecting group using a solution of tetrabutylammonium fluoride (TBAF), cyclisation was attempted with the hydroxylamine **240**, bearing an unprotected alcohol. Pleasingly, the compound cyclised to once again give a single product, the dihydroisoxazole **241**, with no sign of any alternative product formed *via* a competitive 5-*endo*-dig cyclisation of the unprotected hydroxyl group (Scheme 111).



Scheme 111

Chiral products

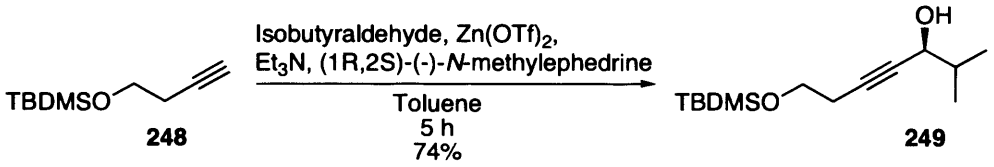
One of potential advantages of the 5-*endo* cyclisation of hydroxylamines over the [1,3]-dipolar cycloaddition procedure, was the complete retention of stereochemistry that can potentially be achieved during ring-formation. For example, in the case of the dihydroisoxazole syntheses, it was hoped that, through synthesis of a chiral, non-racemic propargyl alcohol **242**, subsequent S_N2 displacement of the alcohol by *N*-hydroxyphthalimide and functional group manipulation, an optically pure hydroxylamine (**244** or **246**) could be synthesised that, upon exposure to the cyclisation conditions, would yield a single stereoisomer of the cyclic product (**245** or **247** respectively) (Scheme 112).



Scheme 112

Whether cyclisation was performed with a protecting group or not, we could conceive of no mechanism by which the stereogenic centre present in such a compound would undergo racemisation under the cyclisation conditions; however, this supposition hardly represents a proof of the chemistry.

Whilst conducting investigations into iodocyclisations, Foot had previously reported the synthesis of the propargylic alcohol **249** as a single enantiomer, using the method developed by Carreira (Scheme 113).

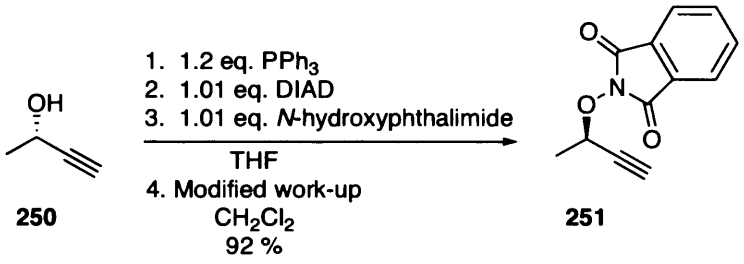


Scheme 113

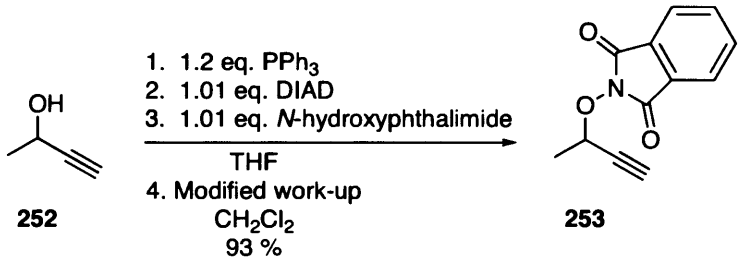
Since (-)-*N*-methylephedrine was used as the chiral ligand Foot had assumed the product to be the (*S*)-enantiomer and had determined >95% ee through the addition of a chiral shift reagent to an NMR sample. He had then gone on to aminate the compound using the, now discredited, oxaziridine amination procedure and abandoned further investigation when difficulties arose whilst attempting cyclisation (Chapter Two of this thesis, pp 10- 65).

In order to investigate to feasibility of preserving such a stereogenic centre in cyclisation reactions, a range of similar, chiral propargyl alcohols were required. Repeated attempts, conducted by several members of the Knight group, to utilise the conditions described by Carreira and latterly by Foot failed to produce any of the required product – either as a single enantiomer or as the racemate. This was a source of great frustration, especially given that Foot appeared to have enjoyed immediate success with the procedure. As reactions of this kind are often highly sensitive to reagent impurities, considerable attention was made to ensure the purity of all the reagents used, but to no avail. Whilst a variety of alternative methods exist for the synthesis of chiral propargyl alcohols,[87] the need for expediency led us instead to purchase a commercially available compound, to at least prove the point that asymmetry could be conserved, hopefully completely.

The availability of suitable compounds is limited, however we were able to obtain samples of both the enantiopure (S)-but-3-yn-2-ol **250** and racemic compound **252** from the Sigma Aldrich Library of Rare Chemicals (SALOR). Under the modified Mitsunobu conditions, phthalimide-protected hydroxylamines were synthesised from each substrate (Schemes 114 and 115).



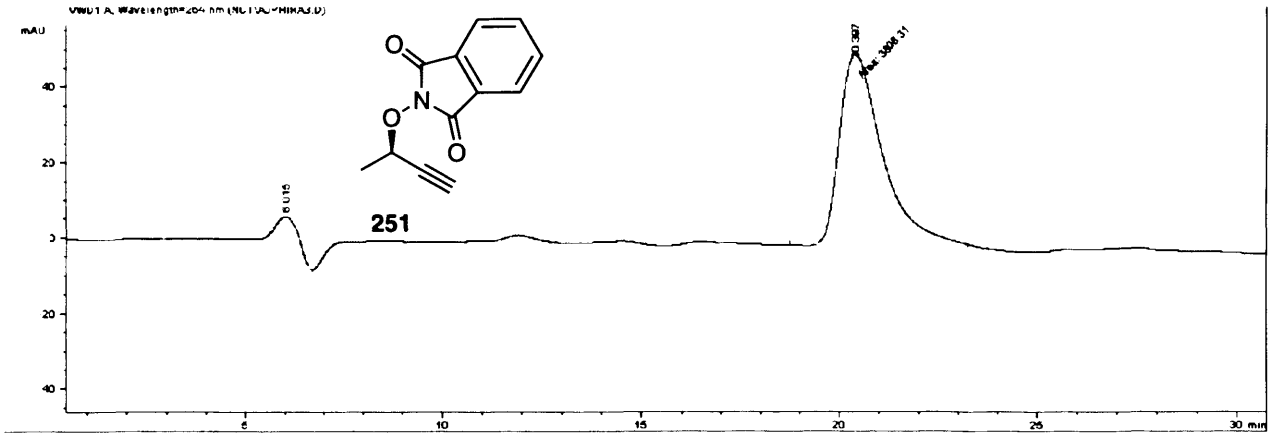
Scheme 114



Scheme 115

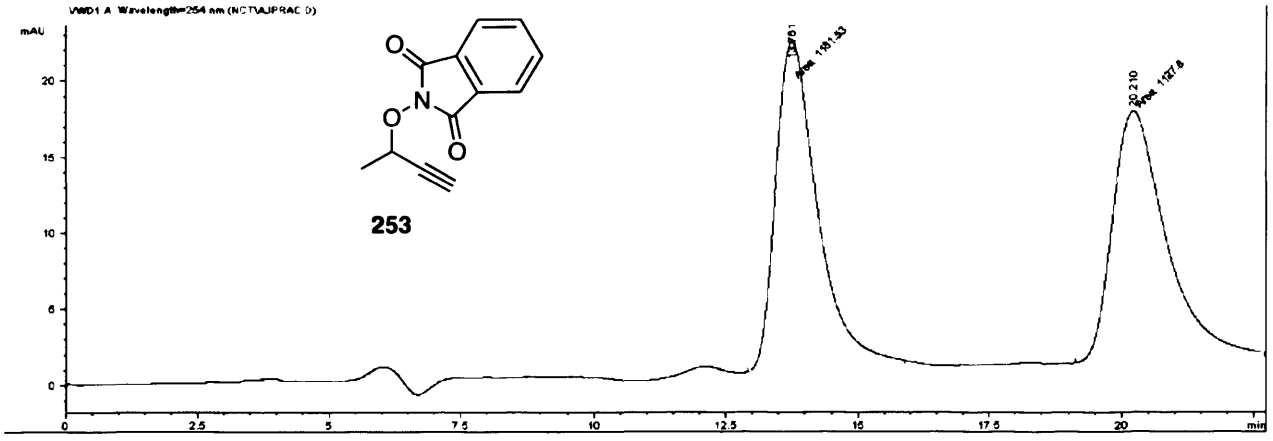
The Mitsunobu reaction was expected to proceed *via* an S_N2 pathway and thus it was assumed inversion of the stereocentre in the chiral compound had occurred, generating the (*R*)-enantiomer of the hydroxylamine. However, the reaction pathway proposed for the rearrangement of benzylic alcohols discussed previously had featured elimination of the alcohol and formation of an allene intermediate (Scheme 92, pp 51). Although such a reaction was clearly not expected in this case, the occurrence of even a minimal amount of any form of S_N1 process would clearly be to the detriment of the stereocentre present in the starting material and therefore it was vital to confirm the outcome of the Mitsunobu displacement.

Unfortunately, malfunctioning equipment meant that the optical rotation generated by the compound could not be measured, however, the optical purity of the phthalimide-protected hydroxylamine **253** was confirmed using high pressure liquid chromatography (HPLC) with a chiral stationary phase. This indicated an enantiomeric excess (ee) of ≥95% (Diagrams 9a and 9b).



Chiral HPLC analysis of compound **251**. Column: OD Chiracel. Flow: 1 ml/min. λ_{max} 254 nm. Injection volume: 5 μL. Solvent: 10% propan-2-ol, 90% hexane.

Diagram 9a



Chiral HPLC analysis of compound **253**. Column: OD Chiracel. Flow: 1 ml/min. λ_{max} 254 nm. Injection volume: 5 μL. Solvent: 10% propan-2-ol, 90% hexane.

Diagram 9b

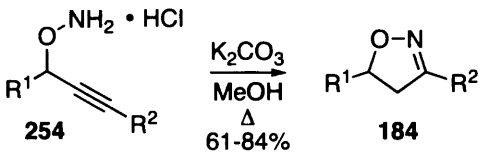
Attempts at deprotecting and either cyclising or acetylating these compounds, however, were met with continued frustration. It was suspected that unprotected hydroxylamine generated was either highly volatile or considerably less stable than other similar compounds previously encountered, hampering attempts at further reaction.

Although there appears to be no reason why a pre-formed stereogenic centre would not survive the cyclisation, the inability to obtain proof proved highly frustrating. It was with regret that, due to the time constraints of the project, we were unable to pursue such evidence further.

Further developments

During the course of these studies we were interested to observe a report by Pennicott and Lindell, detailing an alternative method for the synthesis of 4,5 dihydroisoxazoles; one that bore a distinct similarity to our own methodology.[51] Having obtained a range of *O*-propargyl hydroxylamines **254**, isolated as hydrochloride salts due to their instability, they reported that the corresponding 4,5-dihydroisoxazoles **184** could be obtained by refluxing these substrates in

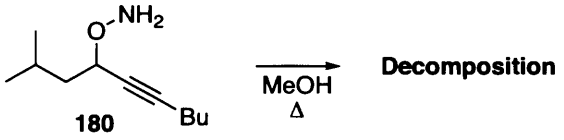
methanol, in the presence of a stoichiometric amount of potassium carbonate (Scheme 115).



Scheme 115

Although this process requires harsher conditions that the silver nitrate-catalysed cyclisations, it does nevertheless represent a viable alternative. The group also reported that in cases where R^2 = H it was not necessary to store the substrate as the hydrochloride salt and that cyclisation could be achieved by refluxing in methanol, without the presence of a base.

In order to assess the viability of the latter set of conditions in performing a wider range of cyclisations, we reproduced these conditions using the disubstituted alkyne **180** and in the absence of base; in our hands no cyclisation was observed, merely degradation of the starting material (Scheme 116).



Scheme 116

It seemed apparent, therefore, that the potassium carbonate plays a key role in the majority of the cyclisations reported, perhaps beyond simply neutralising the hydroxylamine. Whether this reagent effects the cyclisation simply by creating basic reaction conditions, or whether the potassium (or perhaps a trace transition metal contaminant in the potassium carbonate) is acting as a catalyst in a manner similar to the silver nitrate, remains unknown. This process is clearly worthy of further investigation.

Summary and future work

The use of sub-stoichiometric quantities of silver nitrate, in the form of the easily processed reagent 10% w/w silver nitrate on silica, at room temperature represents a simple and mild procedure for the synthesis of 4,5- and 2,5-dihydroisoxazoles, as single products with no need for further purification.

It also seems an attractive possibility that suitably constructed *N*-propargyl hydroxylamines may also participate in such cyclisations, with the oxygen portion of the hydroxylamine acting as a nucleophile, allowing for the synthesis of 2,3-dihydroisoxazoles. Such possibilities are clearly worthy of further investigation.

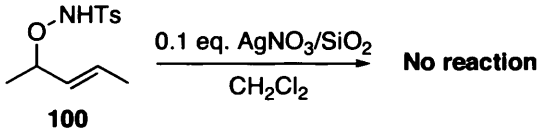
CHAPTER 4

Chapter Four

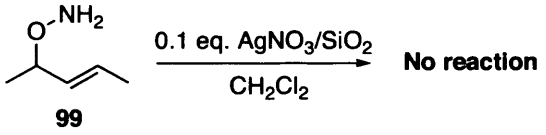
An Acid-catalysed Isoxazolidine Synthesis – "Transfer hydroamination"

Background

As discussed in the previous Chapter, the use of a silver nitrate had proven highly effective in catalysing 5-*endo*-dig cyclisations as a means for the synthesis of dihydroisoxazoles, isoxazoles, furans, dihydrofurans, pyrroles and dihydropyrroles. However, when applied to an analogous 5-*endo*-trig cyclisation, using either the *N*-tosyl-*O*-allylic hydroxylamine **100** or the unprotected analogue **99** utilised in Chapter Two of this thesis (pp 10-35), the catalyst failed to generate any product, returning only unreacted starting materials (Scheme 117 and 118).

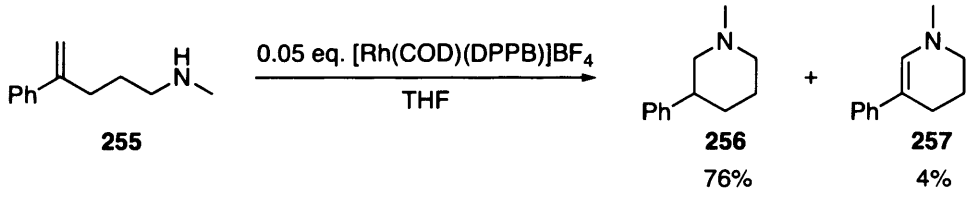


Scheme 117



Scheme 118

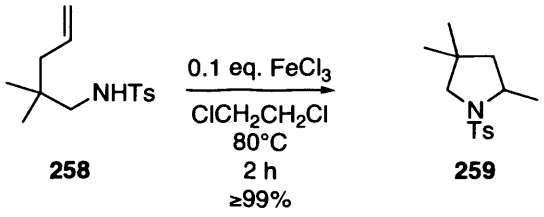
Similar observations were made in investigations into the synthesis of furans and pyrroles under the same conditions.[67] Given this, we were drawn to search for an alternative means for inducing such cyclisations. The use of various metal catalysts in effecting the addition of N-H and O-H across olefins, has recently received much attention. A significant contribution to the field has resulted from the pioneering work of Hartwig and co-workers who, over a number of years, have explored the use of a wide-range of inorganic catalysts in effecting both inter- and intra- molecular additions of amines and alcohols across a wide range of alkenes. Such work was exemplified by the recent report that, in the presence of a rhodium catalyst, secondary amines can undergo intramolecular, anti-Markovnikov addition across an olefin – effectively a hydroamination of the olefin and a highly regiospecific piperidine synthesis (Scheme 119).[88]



Scheme 119

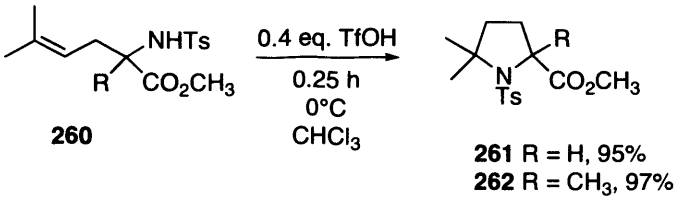
The utility of such a strategy was further underscored by the recent report of Takaki and co-workers that iron trichloride can be used to catalyse intramolecular cyclisations of tosyl-

protected amines; thus generating a range of simple, alkyl-substituted pyrrolidines (*e.g.* Scheme 120).[89]

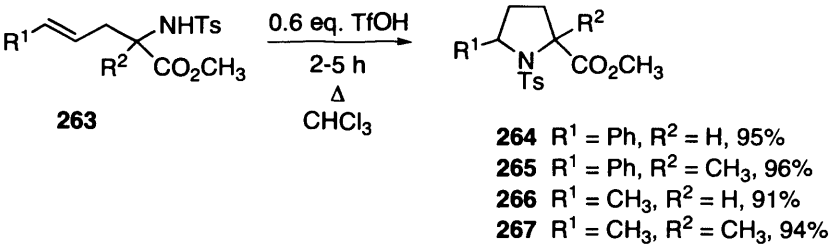


Scheme 120

Although the use of transition metal catalysts seemed an attractive proposition as a means for effecting a 5-*endo*-trig cyclisation of our *O*-allylic hydroxylamines we were, nonetheless, drawn to reports of similar cyclisations being induced by a much simpler catalyst – the proton. Perhaps surprisingly given the attention received by the use of metal catalysts in the synthesis of heterocycles, the use of acid as a cyclisation catalyst has been the subject of relatively little scrutiny. In 2002, Knight and Haskins reported the use of trifluoromethanesulphonic acid (triflic acid) in catalysing the cyclisation of sulphonamide nucleophiles onto a wide-range of triflic acid-generated, tertiary and secondary carbenium ions (Schemes 121 and 122).[90]

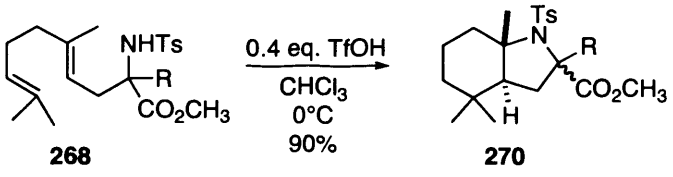


Scheme 121



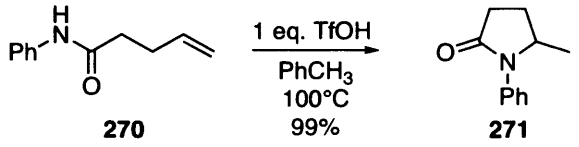
Scheme 122

Haskins and Knight also found that the same sulphonamide nucleophiles were able to act as terminators in acid-catalysed cationic cascades reactions, delivering the products as single stereoisomers at the ring junction (Scheme 123).



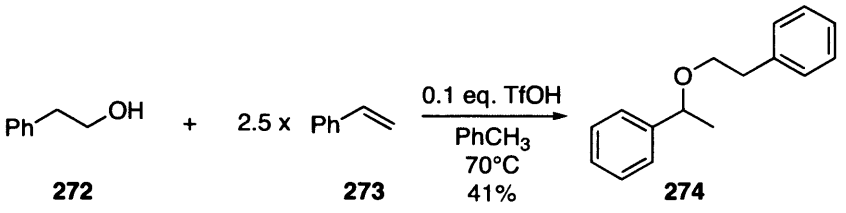
Scheme 123

Continued investigation of this versatile reaction showed that the cascade sequence could be extended further still in order to generate multiple fused rings and this methodology was applied to the total synthesis of the naturally occurring compound, Cyclopiazonic acid.[91] Coincidentally, in 2002, Hartwig also reported the use of both triflic and sulphuric acid in catalysing a similar set of cyclisations.[92] Although the work was not extended to investigate cascade reactions, the group was able to demonstrate that amides could also be induced to undergo similar cyclisations to give highly substituted lactams in excellent yield (*e.g.* Scheme 124).

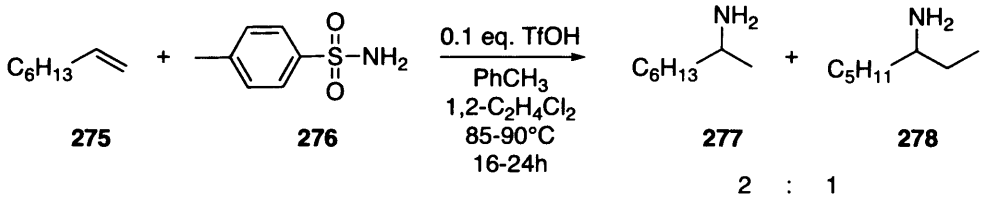


Scheme 124

More recently, Hartwig and co-workers have shown that both oxygen and nitrogen nucleophiles can, under similar conditions, also undergo intermolecular addition to acid-generated carbenium ions (Schemes 125 and 126).[93]



Scheme 125



Scheme 126

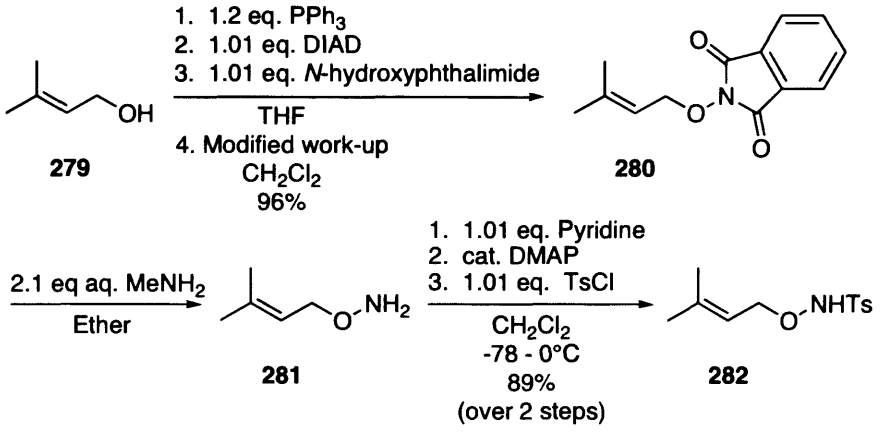
With such an excellent precedent in place we were keen to investigate whether a strong acid, such as triflic acid, could be used to catalyse analogous cyclisations of hydroxylamines.

Results and discussion

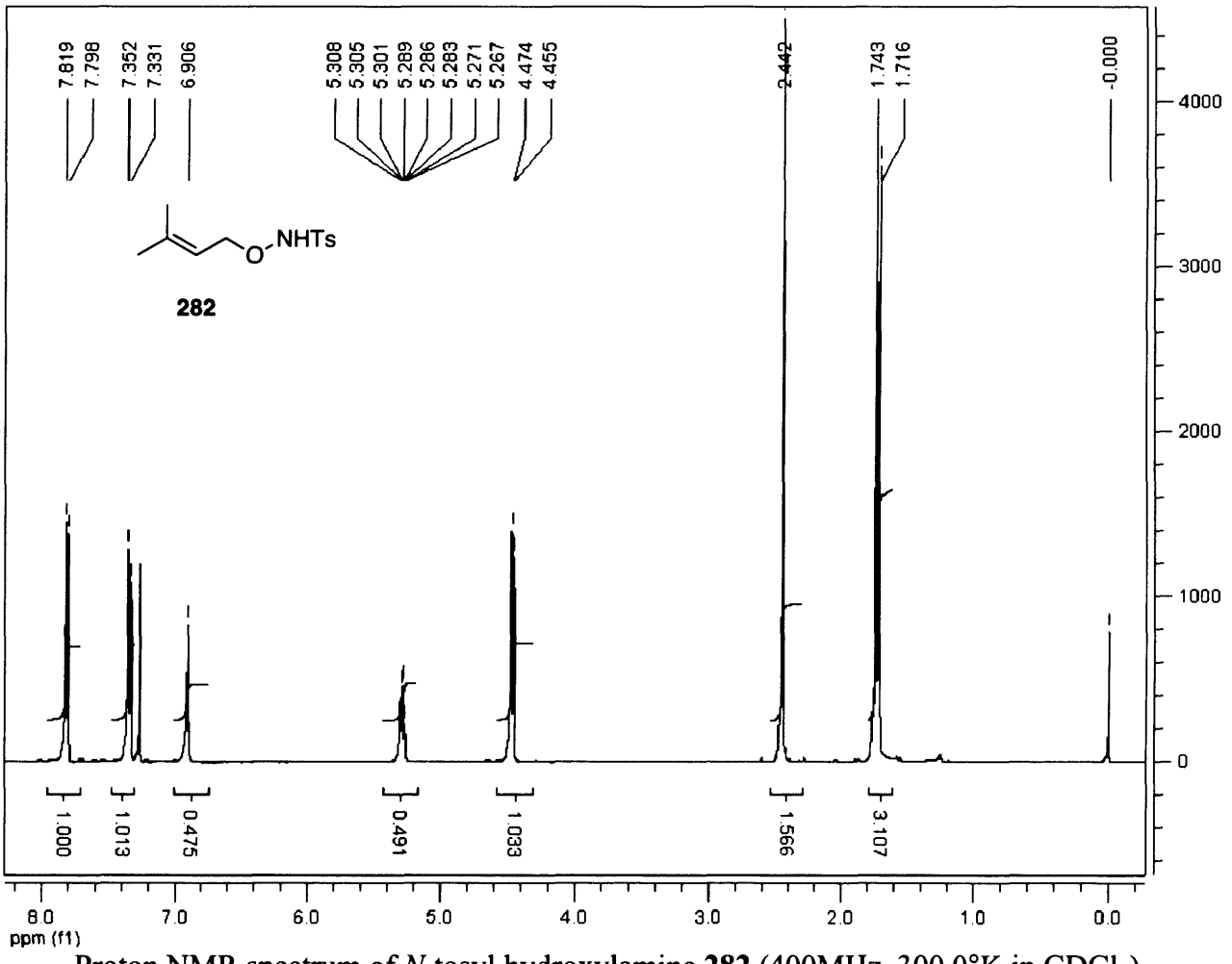
Initial findings

In order to investigate whether a suitably protected hydroxylamine could be used to trap an acid-generated carbenium ion, we required a model substrate that would allow for such a reaction, generating a substituted isoxazolidine *via* intramolecular cyclisation. Previous studies within the group had demonstrated that the required carbenium species could be generated through the interaction of triflic acid with terpene-derived substrates. The investigations into iodine- and silver-induced cyclisations described in Chapters Two and Three of this thesis (pp

10-35 and 36-65 respectively) led to the development of an efficient means for the synthesis of the required hydroxylamine precursors from suitably constructed primary and secondary alcohols. The terpenoid alcohol, 3-methylbut-2-en-1-ol **279** (commercially available from Aldrich Fine Chemicals) seemed an excellent starting point for a suitable model system. Using the procedures discussed in the aforementioned Chapters, this substrate was converted into the desired tosyl-protected hydroxylamine **282**, in excellent overall yield, 85% over 3 steps (Scheme 124, Diagram 10).



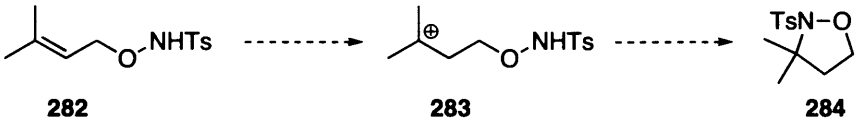
Scheme 124



Proton NMR spectrum of *N*-tosyl hydroxylamine **282** (400MHz, 300.0°K in $CDCl_3$).

Diagram 10

Although Haskins had enjoyed considerable success with the cyclisation of sulphonamides we were acutely aware that we were dealing with fundamentally different substrates. Of particular concern was the possibility that the relatively weak nitrogen-oxygen bond would simply not tolerate these conditions and that we would observe at least partial and perhaps total decomposition of either the starting material or any product formed. Moreover, several cyclisations reported by Haskins had benefited from considerable steric compression. Nonetheless, Haskins had demonstrated that tosyl-protected nitrogens have sufficient nucleophilicity to trap acid-generated carbenium species. In the case of a tosyl-protected hydroxylamine, it was hoped that this nucleophilicity would be increased further still by the so-called alpha effect, an increase in the nucleophilicity of a heteroatom generated by the presence of an adjacent heteroatom bearing a lone pair of electrons.[52] This increased nucleophilicity could, however, have a negative effect, favouring protonation of the hydroxylamine nitrogen and inhibiting its ability to act as a nucleophile. Nonetheless, we felt confident that if the application of a strong acid to the terpene-derived substrate could generate a tertiary carbenium ion, that in could in turn be trapped by the *N*-tosyl hydroxylamine to deliver a stable isoxazolidine product **284** (Scheme 125).

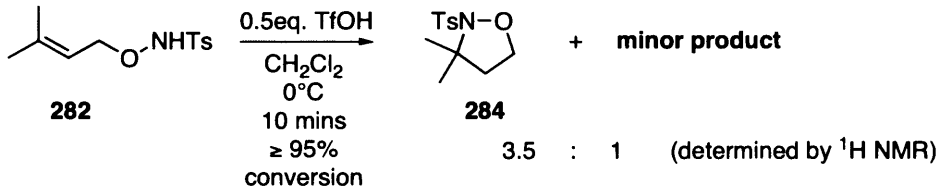


Scheme 125

Indeed if the cyclisation failed in this case, it would be difficult to imagine a simpler system upon which to test our methodology. If successful, not only would we have facilitated a highly regiospecific synthesis of an isoxazolidine, but moreover, subsequent nitrogen-oxygen bond cleavage would furnish us with an amino-alcohol, an overall regiospecific hydroamination of the alkene – a process that could be regarded as 'transfer hydroamination'.

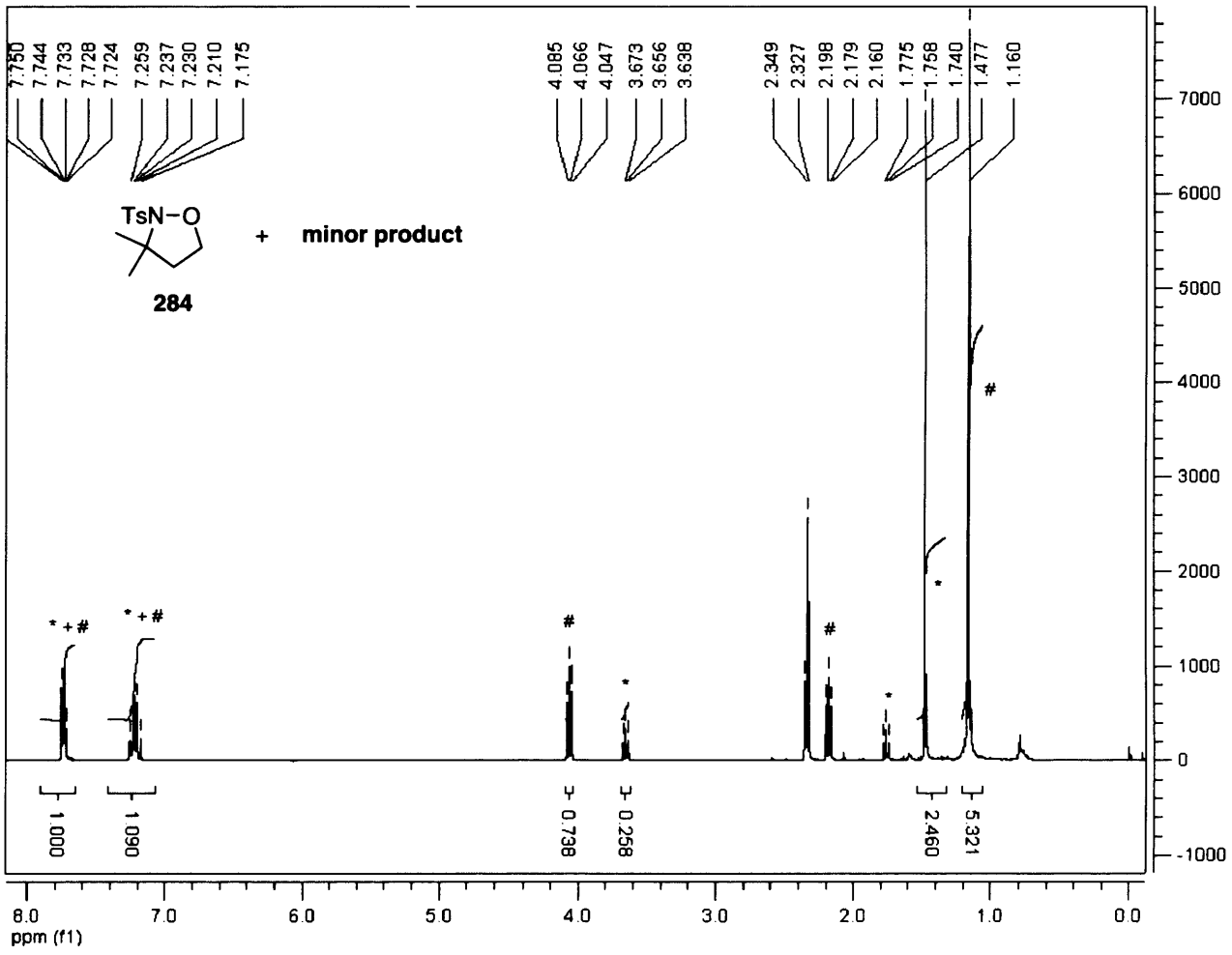
Neat triflic acid is commercially available, as a highly volatile liquid. The difficulties of handling such a reagent led to the need for its application as a diluted, stock solution. In the present study, dichloromethane was used as the reaction solvent and for the creation of the stock solution due to the ease with which it can be obtained anhydrous and also as it is easily removed at the end of the reaction. A 0.695M stock solution of triflic acid was created by the addition of 10 ml of neat triflic acid to 90 ml of anhydrous dichloromethane and was stored in a Schlenk tube, under dry nitrogen. Haskins had optimised the conditions required for the cyclisation of sulphonamides and we believed this to be an excellent starting point for the present investigations.

With the exception of a change in reaction solvent (from dry chloroform to dry dichloromethane), this set of conditions was applied to the *N*-tosyl hydroxylamine **282** (Scheme 126).



Scheme 126

To our delight, the reaction showed no signs of substrate decomposition; only complete conversion of the starting material was observed, yielding a pale yellow, crystalline solid in 96% yield (assuming no change in molecular weight between starting material and product). Upon analysis of the product it was found to contain a mixture of two compounds (Diagram 11).

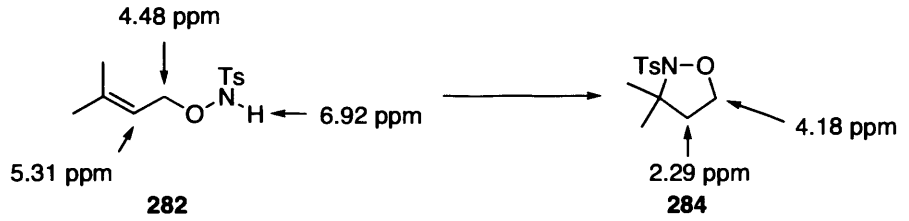


Proton NMR spectrum of crude cyclisation product (Scheme 126), isoxazolidine **284** (#) and an unidentified minor product (*) (400MHz, 300.0°K in $CDCl_3$).

Diagram 11

Careful integration of proton NMR resonances displayed by each compound indicated them to be present in an approximate ratio of 3.5 : 1. By careful silica gel chromatography, the two were separated (although the minor compound still contained traces of the major) and were isolated in an approximate ratio of 4 : 1.

The major compound displayed all of the characteristic resonances expected of the desired cyclisation product **284**. The mutually coupled proton NMR resonances corresponding to the olefinic proton at 5.31 ppm and the allylic proton α to the hydroxylamine at 4.48 ppm of the starting material **282** had disappeared, as had the resonance due to the NH proton, at 6.92 ppm and its corresponding IR absorbance at 3222 cm^{-1}. These resonances had been replaced by a set of mutually coupled resonances at 4.18 and 2.29 ppm, integrating for two protons relative to the, largely unaltered, resonances due to the tosyl group (Scheme 127).



Scheme 127

A similar set of differences were observed between the ^{13}C NMR of the starting material **282** and the product **284**. High resolution mass spectrometry (HRMS) confirmed that the product had an identical molecular formula to the starting material. These observations supported the presumption that an intramolecular addition of NH across the double bond had occurred.

Given that the major product was obtained as a crystalline solid, final confirmation of its structure was obtained through X-ray crystallography.

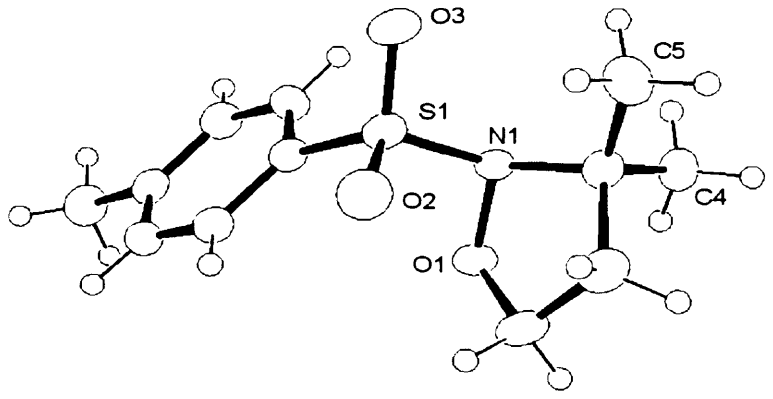
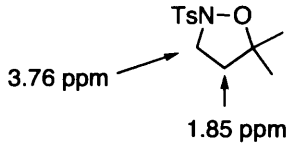


Diagram 12

The structure determined (Diagram 12) showed a five-membered ring containing a nitrogen-oxygen bond, 0.144 nm in length (Full details of the data obtained are given in the Appendix). A simple energy minimisation experiment performed using Chem 3D calculated the same bond length to be 0.135 nm.

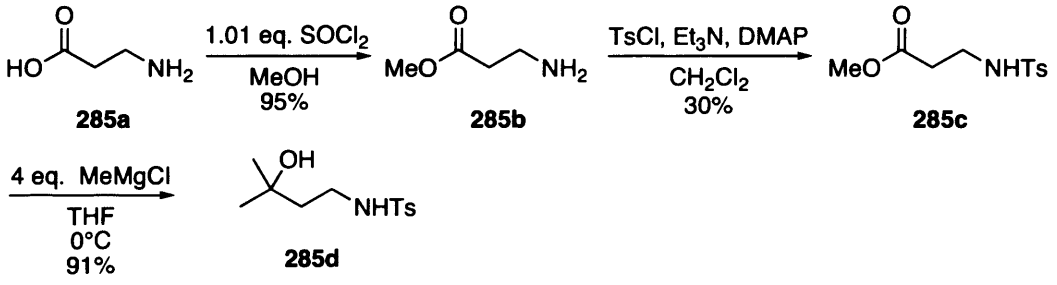
Unfortunately the minor product, when purified, did not provide a crystal suitable for X-ray analysis. The proton NMR of this compound was notable in its similarity to that of the major product **284**. The same loss of NH and olefinic resonances associated with the starting material **282** was again accompanied by the appearance of two mutually coupled resonances, each integrating for two protons, at 3.76 and 1.85 ppm. These resonances were each shifted approximately 0.4-0.5 ppm upfield compared to the corresponding resonances in the major product (See Diagram 11, pp 72). A similar effect was observed in the ^{13}C NMR and HRMS again showed that the product had the same molecular formula as both the starting material and the major product **284**. The evidence, when combined suggested that the minor product was a regioisomer of the major compound. As with the major product, the minor showed two sets of vicinal protons and two equivalent methyl groups. The significant difference between the two compounds was the chemical shifts associated with the protons on the ring. A shift upfield indicated that these protons were now α and β respectively to a less electron withdrawing functional group. The belief that the oxygen atom in the ring is more electron-withdrawing than the *N*-tosyl group led to the suggestion that the minor product was the result of an isomerisation of the nitrogen-oxygen bond, yielding the isoxazolidine **285**.



285

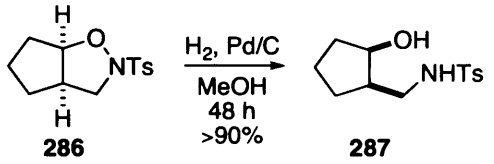
In order to confirm this proposed structural assignment, a synthesis of an authentic sample of the compound **285** was undertaken. Fearing that any alternative isoxazolidine synthesis, in particular a [1,3]-dipolar cycloaddition, would lead to the same ambiguous assignment of the regiochemistry, it was instead decided to synthesise a derivative, the corresponding amino-alcohol resulting from nitrogen-oxygen bond cleavage.

A final year project student, Alec Cox, was given the task of proving the structure of the minor product in this way.[94] Starting from commercially available β-alanine **285a** he obtained the amino-alcohol **285d** as a pure compound, through tosylation, esterification and reaction with an excess of a methyl grignard reagent (Scheme 128).



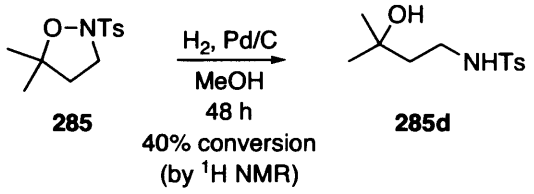
Scheme 128

Cox then set about cleaving the nitrogen-oxygen bond in the minor product. Upon consulting the literature, we found that cleavage of *N*-tosyl isoxazolines had only once been reported. Heesing and co-workers had found that the bicyclic *N*-tosyl isoxazolidine **286** could be converted into the corresponding *N*-tosyl amino-alcohol **287** under standard hydrogenation conditions, using a catalytic amount of palladium on carbon (Scheme 129).[95]



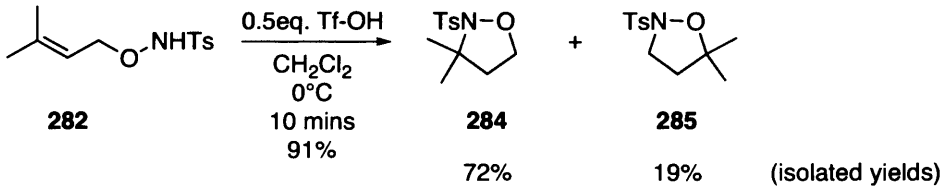
Scheme 129

Attempts made by Cox at applying these conditions to the substrate **285** proved frustrating. After 7 days, the proton NMR spectrum of the crude product revealed only 40% conversion into the amino alcohol **285d** (Scheme 130).



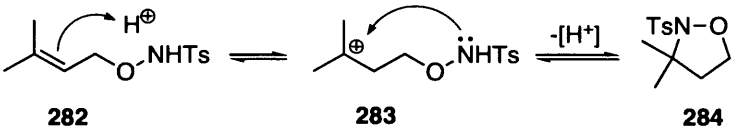
Scheme 130

Although we were not able to isolate a pure sample of the hydrogenation product, Cox found that correlation of the new peaks in the proton NMR spectrum of this mixture with those found in the authentic sample of the amino alcohol **285d** showed an exact match, providing us with excellent support for the structural assignment of the minor product and our hypothesis that the products of the cyclisation reaction were the isoxazolidine **284** and the regioisomer **285** (Scheme 131).



Scheme 131

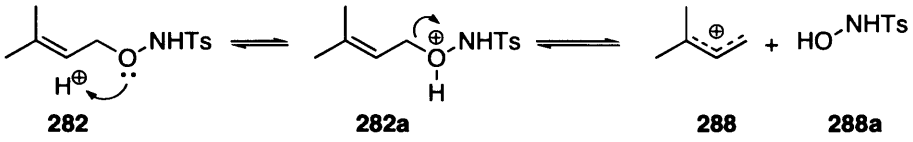
To understand how such a rearrangement might take place, we need to consider the mechanism of the cyclisation. These studies, along with observations made in previous investigations, strongly suggest that the major cyclisation products result from trapping of a carbenium ion generated by the protonation of an alkene bond in the tertiary position, under the acidic conditions (Scheme 132).



Scheme 132

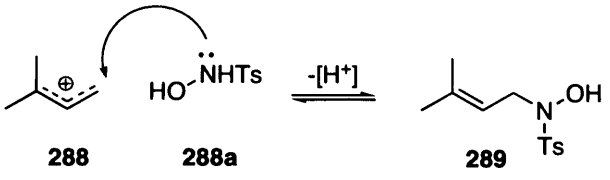
Whether or not the final, ring-closure step in the process is indeed in equilibrium is a matter of contention and will be discussed later in this Chapter. Protonation may also occur at the nitrogen nucleophile; however, although this would initially block its ability to act as a nucleophile, this may also assist in protonation of the alkene by allowing for intramolecular proton transfer.

In the case of *O*-allylic hydroxylamines, a further potential site for protonation is the hydroxylamine oxygen. Protonation at this point would result in the hydroxylamine becoming a considerably better leaving group than when in its neutral state. Loss of this would generate *N*-tosyl hydroxylamine **288a** and a relatively stabilised, allylic carbenium ion **288** (Scheme 133).



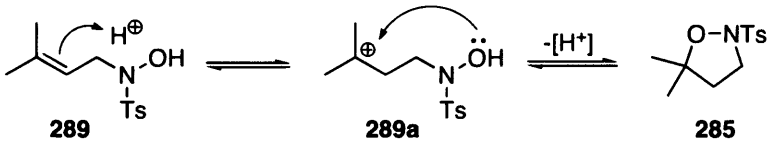
Scheme 133

It would seem highly likely that, were such a process to occur, the loss of the hydroxylamine **288a** would be a reversible process, with this portion of the molecule able to reattach through the nucleophilic oxygen and regenerate the starting material **282**, which could then cyclise to give the expected product **284**. A further possibility is that the hydroxylamine could reattach to the carbenium ion through the nitrogen instead, with regeneration of the catalytic proton yielding a rearranged starting material **289** (Scheme 134).



Scheme 134

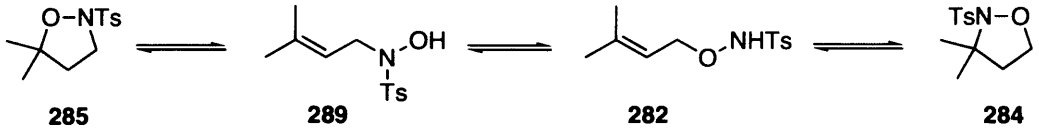
This compound **289** could then cyclise through generation of a tertiary carbenium ion **289a** followed by attack by the oxygen, yielding the minor product **285** (Scheme 135).



Scheme 135

It can reasonably be assumed that potentially both the generation and cyclisation of the rearranged starting material **289** are also in equilibrium, giving rise to the possibility that, under

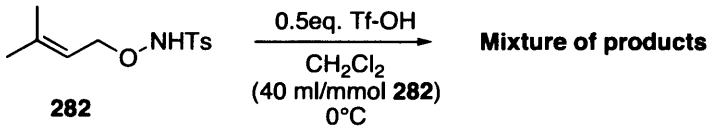
the reaction conditions, an equilibrium exists between four main compounds, in various states of protonation: the starting material **282**, the rearranged starting material **289**, the major product **284** and the minor product **285** (Scheme 136).



Scheme 136

In truth, this scheme probably represents a gross simplification of the many processes that are likely to be occurring in the rearrangement process; however, its key feature (the rearrangement forming a mixture alkenes and thus products) provides a useful illustration of how the reaction is likely to proceed.

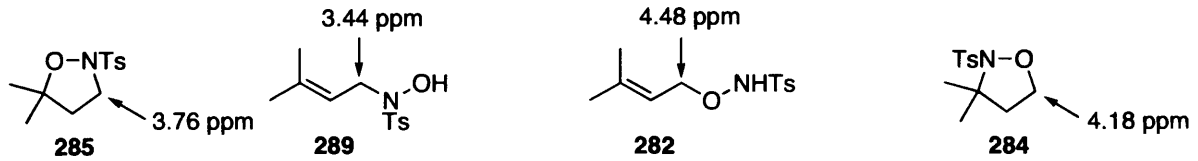
In order to more thoroughly investigate the postulated equilibrium processes, the course of the reaction was followed by taking samples at set intervals and rapidly quenching these in ice-cold, saturated aqueous sodium hydrogen carbonate. The initial cyclisation reaction had been found to be complete within 10 minutes. In order to slow its progress, the reaction was performed at increased dilution, 40 ml/mmol of dichloromethane with respect to the starting material **282** (*c.f.* 10 ml/mmol in initial cyclisation) (Scheme 137).



Scheme 137

In the proton NMR spectra of these samples, resonances corresponding to the starting material **282**, the major isoxazolidine product **284** and the minor isoxazolidine product **285** were clearly visible. The proton NMR spectra obtained also showed the presence of a novel compound, with resonances highly similar to those generated by the starting material **282** but shifted around 0.5 ppm upfield. This difference in chemical shift was roughly the same as the difference in chemical shift observed between the major and minor products. It seemed highly likely that the resonances observed corresponded to a rearranged starting material. By careful integration of resonances unique to each of the compounds it was possible to measure their abundance in the reaction mixture at intervals over the course of the reaction (Table 5).

Table 5: *Relative abundance of compounds* **282, 284, 285** *and* **289** *in reaction mixture (Scheme 137), calculated by integration of peaks indicated.*



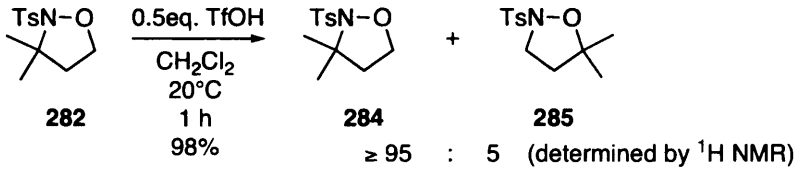
Entry	Conditions	**282** (%)	**289** (%)	**284** (%)	**285** (%)
1	<5 secs at 0°C [a]	69	7	21	3
2	5 mins at 0°C	20	11	63	6
3	10 mins at 0°C	9	9	72	10
4	20 mins at 0°C	0	7	78	15
5	30 mins at 0°C	0	4	78	18
6	1 h at 0°C	0	0	78	22
7	1 h at 0°C then 1 h at 20°C	0	0	74	26

a – A sample was taken immediately after addition of the triflic acid.

Analysis of the data revealed the following information:

- Dilution of the reaction slows the rate of cyclisation, with consumption of the alkene starting materials taking over 30 minutes (40 ml/mmol solvent, *c.f.* 10 ml/mmol standard).
- Formation of the compound postulated to be the rearranged olefin **289** is rapid, occurring immediately after addition of the triflic acid.
- The presence of the rearranged starting material **289** persists longer than the original starting material **282**, suggesting that cyclisation of this substrate occurs at a slower rate.
- Allowing the reaction to reach room temperature does not lead to decomposition of the products.
- Upon complete consumption of the starting materials, the ratio of **284** : **285** is 78 : 22.
- Allowing the reaction to proceed at room temperature for a further hour after consumption of the starting material very slightly alters the ratio of **284** : **285** to 74 : 26.

When a sample of the isoxazolidine **284** was treated with triflic acid, at room temperature, only a trace amount of the minor product **285** was generated (Scheme 138).



Scheme 138

Whilst the formation of the minor product was undoubtedly intriguing, the need for separation of the two products added unwanted complication to the process and resulted in a diminished yield of the desired major product. With this in mind, attempts were made to alter the reaction conditions in the hope of achieving a greater ratio of major product in the crude product (Table 6).

Table 6: *Effect of amount of triflic acid on ratio of products.*

Entry	Triflic acid (equivalents)	Temperature (°C)	Time [a]	Yield	Approximate Ratio (Major **284**: Minor **285**)
1	2	20	0.25 h	93%	3 : 1
2	0.1	20	0.25 h	95%	3.5 : 1
3	0.1	0	0.5 h	95%	3.5 : 1
4	0.5	-78	2 h	- [b]	-

a – The reaction was monitored by tlc and quenched upon complete consumption of the starting material.

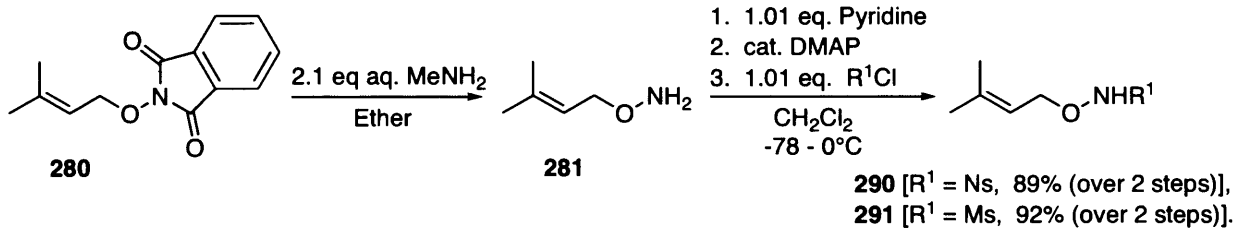
b – After 2 h the reaction mixture contained ≥95% starting material, with only trace amounts of the major and minor products and the rearranged starting material.

The results show that decreasing the amount of acid used in the reaction had little effect on the ratio of products obtained and indeed on the reaction rate. Increasing the amount of acid used, however, marginally increased the formation of the minor product, without affecting overall the yield. At -78°C, the rate of reaction was dramatically slowed (≤5% conversion); however, formation of the minor product was not abated, with trace amounts of each observed in the proton NMR of the crude product. Whilst by no means conclusive, this brief study indicated that attempting to favour the formation of a single product by altering the reaction conditions was likely to be unsuccessful given that, even under extreme conditions, formation of the major product remained predominant whilst formation of the minor product could not be significantly reduced.

An alternative protecting group

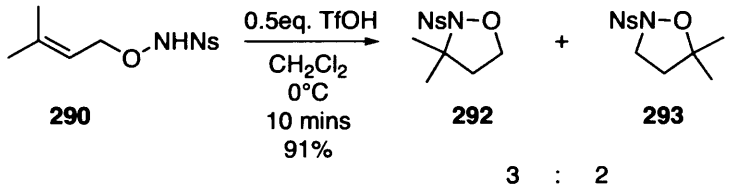
When considering the proposed rearrangement mechanism, it seemed likely that the ability of the hydroxylamine portion of the molecule to act as a leaving group under acidic conditions would be significantly affected by the electron withdrawing properties of the protecting group presently on the nitrogen. By altering these electronic properties it seemed it might be possible to control the level of isomerisation occurring under the reaction conditions.

In order to investigate this further, the *p*-nosyl (Ns) **290** and mesyl (Ms) **291** protected analogues of the model substrate were synthesised (Scheme 139).

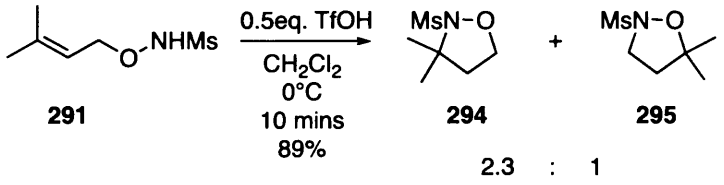


Scheme 139

These substrates **290** and **291** were then cyclised under the standard set of conditions and the approximate ratio of major to minor products calculated by integration of the corresponding resonances in the proton NMR spectra of the crude products (Schemes 140 and 141 respectively).



Scheme 140

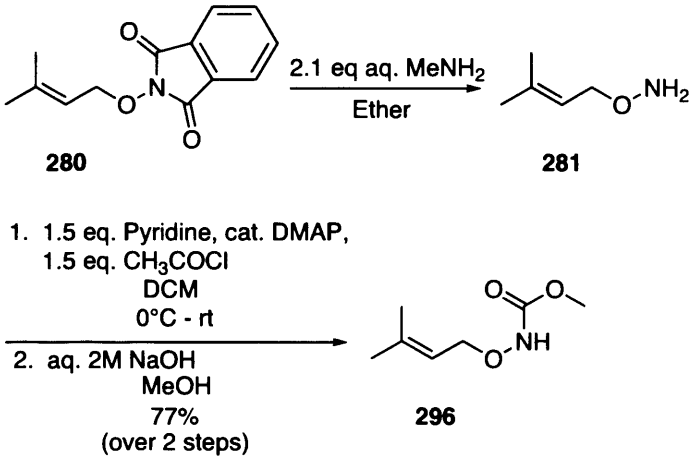


Scheme 141

The results showed that application of the more electron-withdrawing nosyl protecting group resulted in increased formation of the minor product. This seemed to support the proposed rearrangement mechanism, as an electron withdrawing protecting group would, upon protonation of the hydroxylamine oxygen, increase the likelihood of the hydroxylamine acting as a leaving group due to destabilisation of the positive charge. An electron-withdrawing protecting group would also slow the rate of formation of the major product, by reducing the nucleophilicity of the hydroxylamine nitrogen.

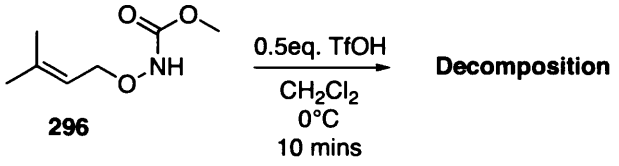
In the case of the mesyl-protected analogue, it was predicted that the less electron-withdrawing substituent would have an analogous, but opposite effect. The results, however, were arguably too similar to draw any firm conclusions. It was clear, however, that varying the nature of the sulphonamide protecting group would not be sufficient to allow for the formation of a single product.

As an alternative protection strategy, the methoxycarbonyl (Moc)-protected analogue **296** was synthesised (Scheme 142).



Scheme 142

As had been found with previous Moc-protected hydroxylamines (see Chapter Three of this thesis, pp 58), the compound **296** was unstable, with rapid decomposition hampering attempts at characterisation. Hence, unsurprisingly, even immediate application of the cyclisation conditions yielded only a small amount of an unidentified mixture of decomposition products (Scheme 143).

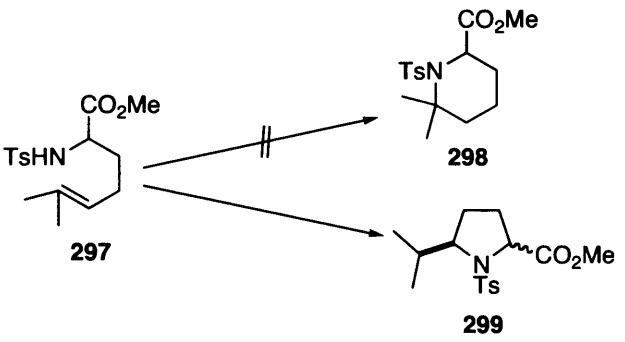


Scheme 143

With the chemistry of the rearrangement process seemingly displaying no clear pattern at this stage, we decided to accept, for now, that a mixture of products was an inevitable consequence of the reaction conditions and move on to examine their application to more complicated systems.

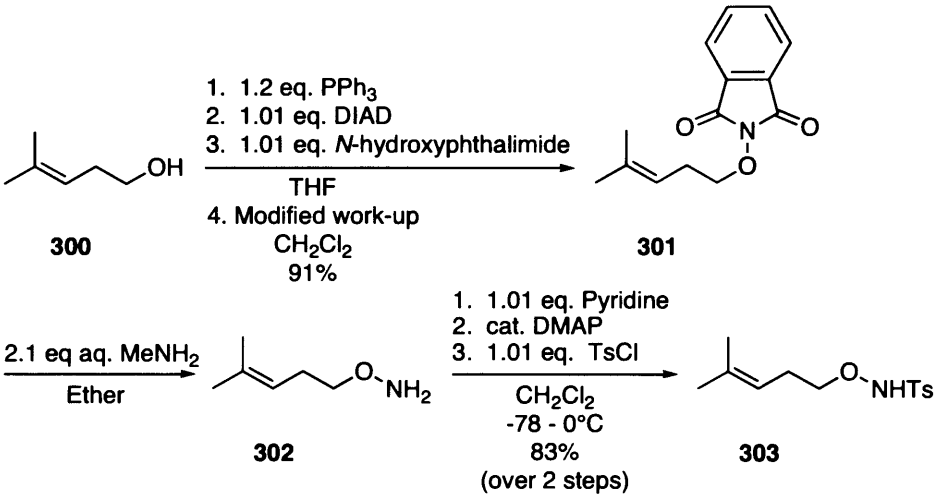
A six-membered ring

In the previously described studies into acid-catalysed cyclisation of sulphonamides, conducted by Haskins, an intriguing limitation was an apparent inability to synthesise piperidines *via* overall 6-*endo*-trig cyclisation. In one notable example, the sulphonamide **297**, designed for the synthesis of piperidine **298**, instead cyclised to the yield pyrrolidine **299**, an overall 5-*exo*-trig cyclisation, presumably occurring *via* rearrangement to a secondary carbenium ion intermediate and cyclisation through this species (Scheme 144).



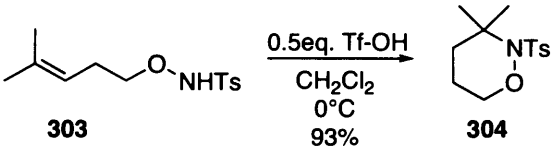
Scheme 144

In order to test whether a similar phenomenon would be observed in the cyclisation of hydroxylamines, a suitable tosyl-protected hydroxylamine **303** was synthesised from the homo-prenyl alcohol, 4-methylpent-3-en-1-ol **300**, commercially available form Aldrich Fine Chemicals (Scheme 145).



Scheme 145

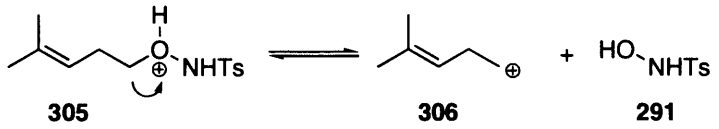
To our immense delight, application of the standard cyclisation conditions returned not only the desired six-membered cyclic product **304**, but delivered it as a single regioisomer and with no need for further purification (Scheme 146).



Scheme 146

In retrospect, when one considers the proposed mechanism for rearrangement of the hydroxylamine starting material (Schemes 133, 134 and 135, pp 76), its absence in this case is wholly consistent. The proposed rearrangement mechanism involves firstly the protonation of the hydroxylamine oxygen, thus improving its ability to act as a leaving group, and secondly, its loss, which leads to the formation of a relatively stable allylic carbenium ion. In the case of the homoprenyl analogue **303**, however, loss of the hydroxylamine portion of the molecule

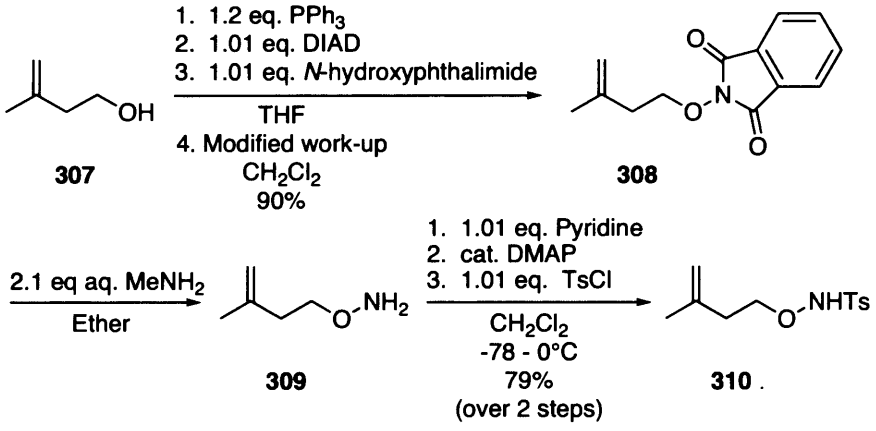
would yield a primary carbenium ion **306**, a far less stable intermediate than an allylic carbenium ion (Scheme 147).



Scheme 147

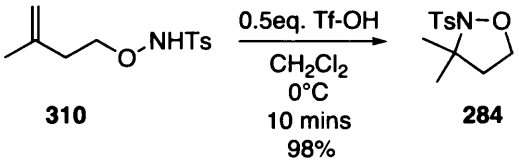
These findings suggest that if the hydroxylamine is not in an allylic (or perhaps similarly stabilised) position, the rearrangement process does not occur and a single product is obtained. We were keen to examine if such an effect could be utilised in the synthesis of isoxazolidines, *i.e.* moving the alkene bond so that the hydroxylamine oxygen was no longer in an allylic position, but repositioning it in such a manner that it would still generate the same tertiary carbenium ion.

From the commercially available, *iso*-prenyl alcohol, 3-methylbut-3-en-1-ol **307** (obtained from Aldrich Fine Chemicals), the tosyl-protected hydroxylamine **310** was synthesised (Scheme 148).



Scheme 148

To our delight, we found that exposure to triflic acid delivered the desired isoxazolidine **311**, as a single product and with no further purification required (Scheme 149).

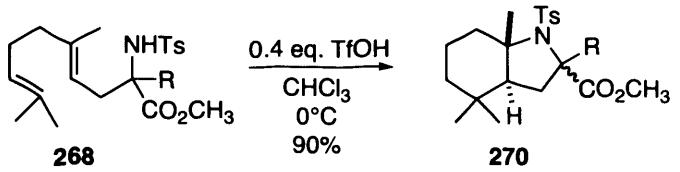


Scheme 149

With a means for eliminating the central limitation to the methodology now in place, the investigations were extended to examine the possibility for multiple fused ring synthesis *via* cascade cyclisations.

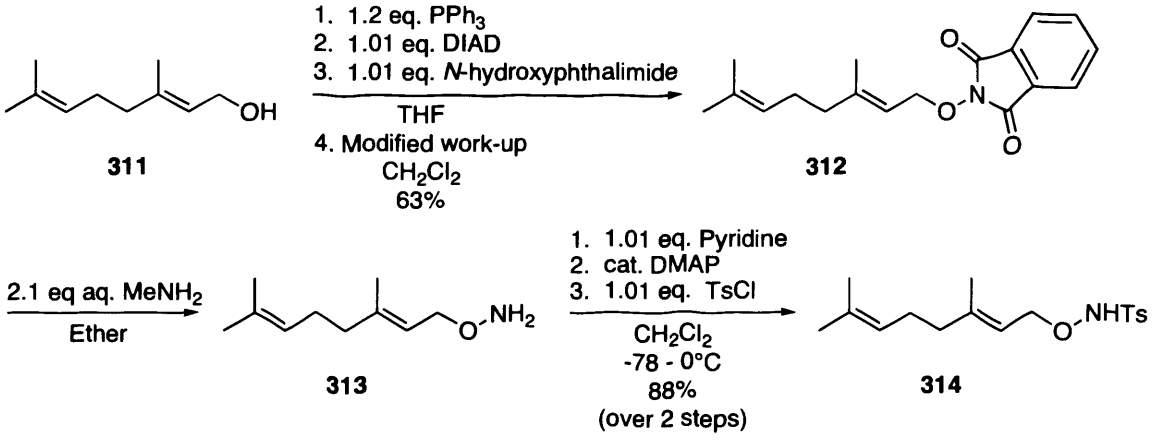
Acid-catalysed cascade reactions

As discussed in the introduction to this Chapter, Haskins and Knight demonstrated that the ability of sulphonamides to trap acid-generated carbenium ions could be extended to the synthesis of fused ring systems *via* acid-catalysed poly-ene cascade reactions, with sulphonamides acting as terminators (Scheme 123).[90]



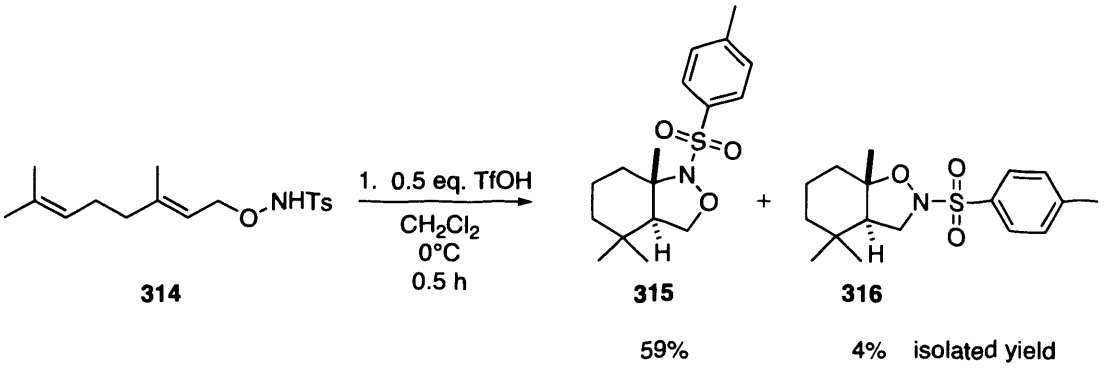
Scheme 123

Both Bronsted and Lewis acid-catalysed cascade reactions have recently received considerable interest and have found application in numerous total syntheses.[96] The synthesis of a suitable cascade precursor was achieved starting from the commercially available alcohol Geraniol **311** and using the now familiar sequence of Mitsunobu displacement followed by protecting group exchange (Scheme 150).



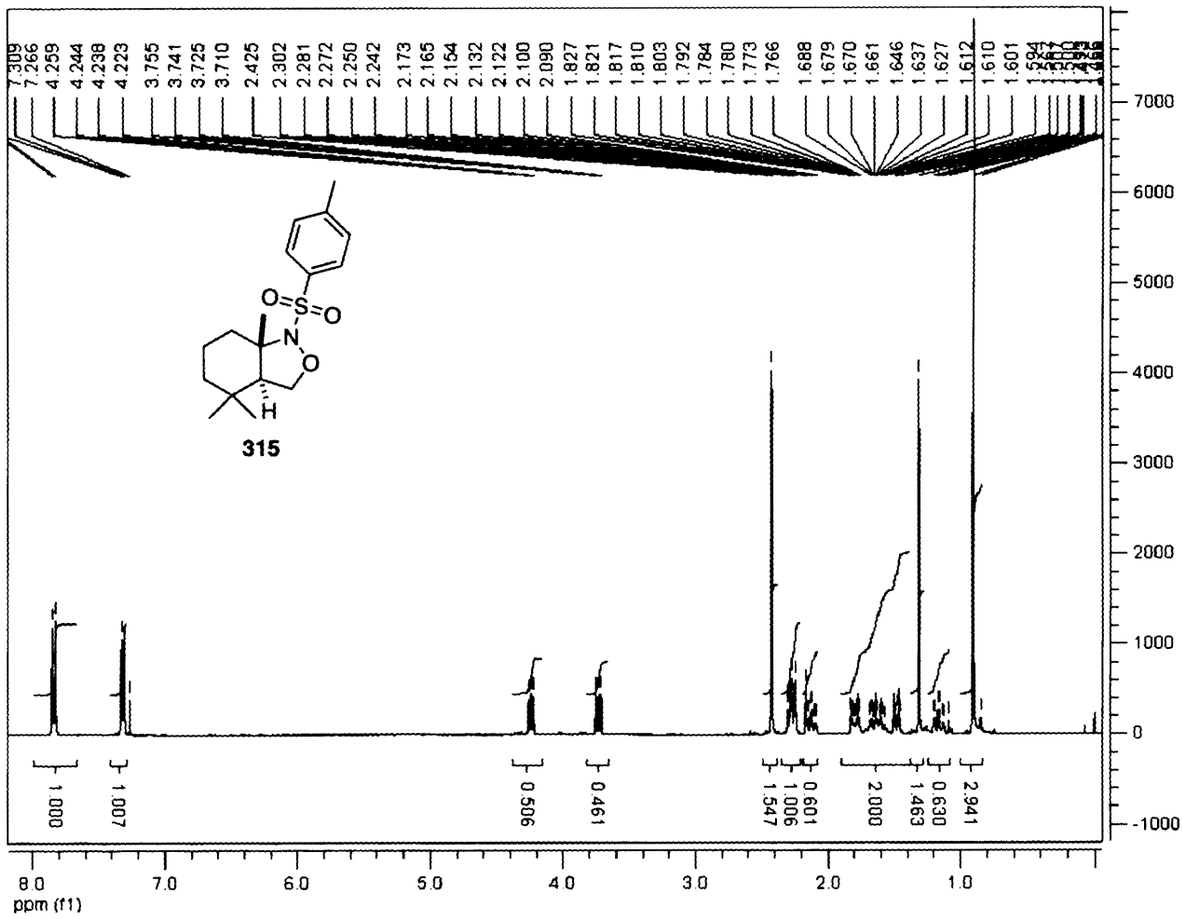
Scheme 150

Exposure to a catalytic amount of triflic acid lead to rapid consumption of the starting material and the formation of two products, in the ratio ~ 4 : 1 (adjudged by integration of resonances in the proton NMR of the crude product), which were separated by silica gel chromatography (Scheme 151).



Scheme 151

By analogy to the corresponding sulphonamide cyclisation reported by Haskins (Scheme 123) which had delivered the *trans*-fused product **269**, and to the cyclisations of prenyl alcohol-derived *N*-tosyl hydroxylamines described earlier in this Chapter, which had predominantly cyclised through the nitrogen portion of the hydroxylamine, we proposed the major product to be the 5/6 bicyclic isoxazolidine **315**. The proton NMR of the compound showed complete loss of the characteristic olefin resonances of the starting material, coupled with the apparent formation of a novel, cyclic product (Diagram 13).

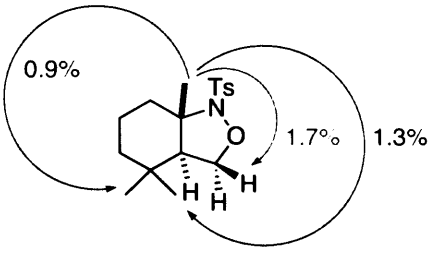


Proton NMR spectrum of bicylic isoxazolidine **315** (400MHz, 300.0°K in $CDCl_3$).

Diagram 13

In the studies conducted by Haskins, the structural assignment of the bicyclic sulphonamide **269** was confirmed using X-ray crystallography; unfortunately a suitable crystal of either isoxazolidine product could not be obtained. This regiochemical assignment, therefore, was based solely on the spectroscopic data obtained. The stereochemical assignment nonetheless remained problematic. Attempts to confirm the assignment of *trans* stereochemistry at the ring junction using nOe revealed irradiation of the methyl group at the ring junction caused enhancement of one of the protons in the 5-position of the isoxazolidine and one of the geminal methyl groups. Enhancement was also seen in an overlapping set of resonances, one of which

was thought to belong to the proton at the ring junction. The enhancement was nevertheless weaker than would be expected from a compound with *cis* geometry at the ring junction and thus we felt confident that the *trans* assignment was correct (Diagram 14).



315

Diagram 14

Attempts at structural assignment of the minor product **316** proved less conclusive. Despite repeated attempts, the amount of minor product isolated following silica gel chromatography was consistently far less than was expected given its apparent ratio to the major compound **315** in the crude product and showed persistent contamination with the major component. This led to the conclusion that the minor compound **316** was far less stable to silica gel chromatography than the major, perhaps also isomerising to this compound under chromatography conditions. Attempts at characterisation were therefore hampered; for example, with several resonances in the proton NMR obscured by resonances generated by the major product. The distinguishing feature of both compounds proved to be the resonances generated by the protons α to the hydroxylamine moiety (Diagram 15).

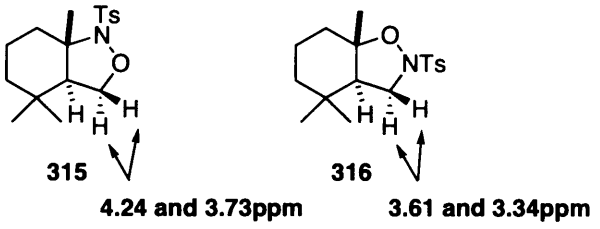
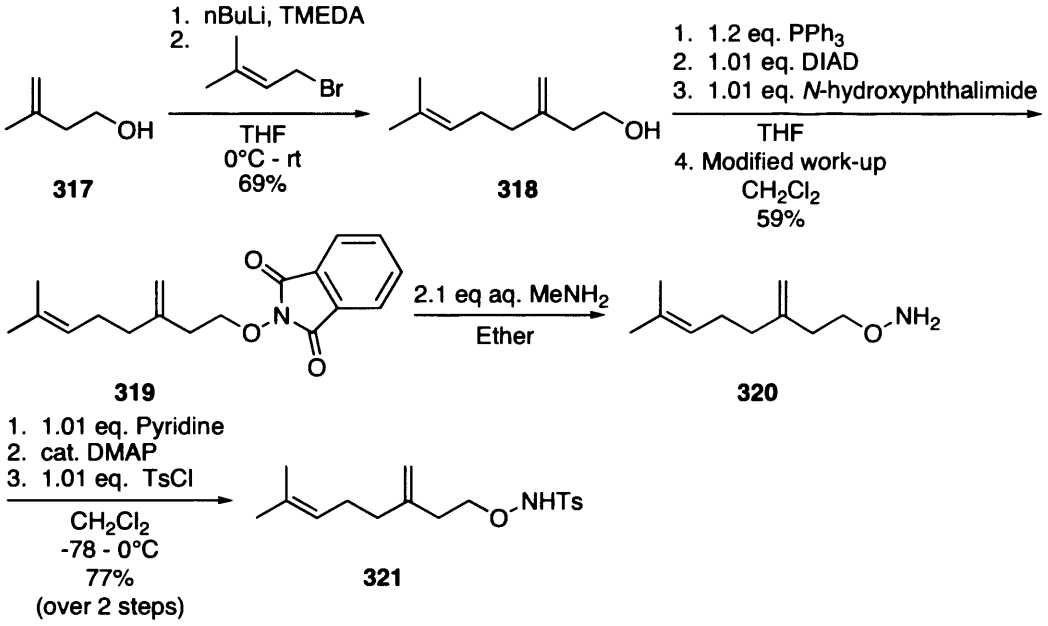


Diagram 15

The difference in chemical shift between these resonances in each compound, albeit less marked than observed in the prenyl-derived isoxazolidines **284** and **285**, was indicative of the regioisomerism observed previously (Scheme 131), confirming our belief that the minor compound **316** was indeed a regioisomer of the major. Attempts at confirming the stereochemistry by nOe enhancement proved inconclusive, due to the persistent contamination of the compound and the small quantities obtained. The *trans* stereochemistry at the ring junction is therefore proposed solely based on analogy with the major compound **315** and the belief that the product must result from a series of equilibria, favouring the thermodynamic product.

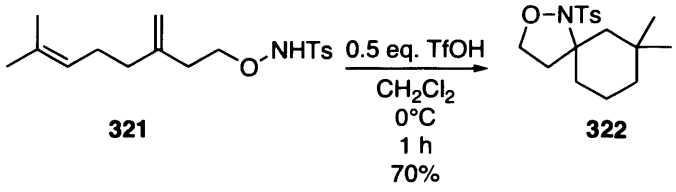
Working on the assessment that, in each of the cascade reactions described, the minor product resulted from isomerisation of the allylic *N*-tosyl hydroxylamine subunit, it seemed a logical

approach to attempt to apply the same tactic for preventing this isomerisation as had proved successful previously, *i.e.* repositioning of the double bond so that the hydroxylamine was no longer in an allylic position. The geraniol isomer **318** was synthesised using the method of Chong[97] and elaborated in the standard manner (Scheme 152).



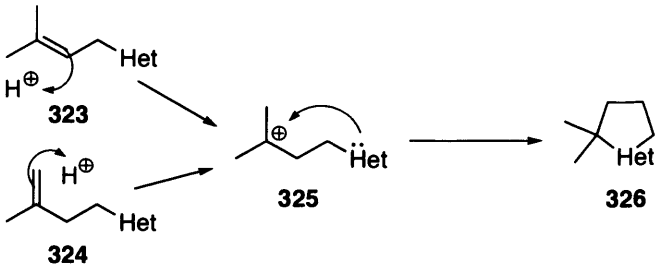
Scheme 152

Application of triflic acid, however, resulted in an initially surprising, yet in retrospect, predictable result: synthesis of the *spiro*-cyclic isoxazolidine **322** (Scheme 153).[98]



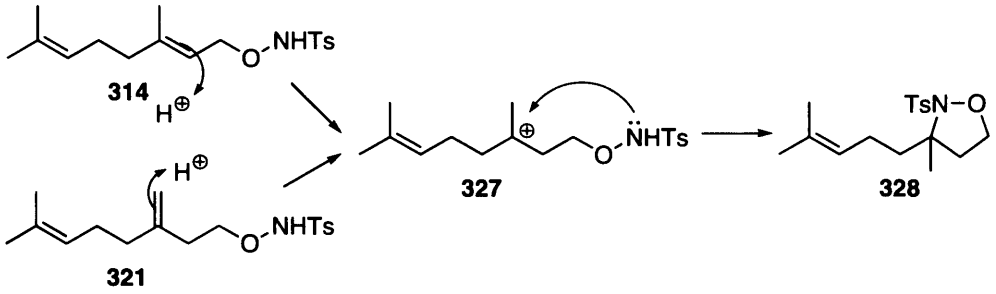
Scheme 153

Considering a possible mechanism for the formation of this product provides an intriguing insight into the cascade reaction. The viability of repositioning the double bond in such a manner results from the fact that, upon protonation, an identical tertiary carbenium species **325** is formed and subsequently attacked by the heteroatomic nucleophile (Scheme 154).



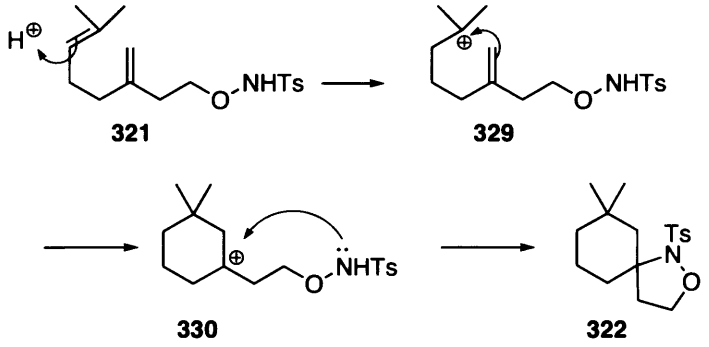
Scheme 154

In the case of the geraniol-derived *N*-tosyl hydroxylamine **314** and the regioisomer **321**, this process would result in the formation of a mono-cyclic compound **328**, leaving no available nucleophile to attack a carbenium ion formed from protonation of the second double bond (Scheme 155).



Scheme 155

For formation of the carbocyclic ring to occur, this must take place prior to the formation of the isoxazolidine ring. Protonation of the double bond furthest from the hydroxylamine moiety, followed by attack by the second double bond, leaves a tertiary carbenium species **330** that can be attacked by the hydroxylamine nucleophile to form the spirocyclic isoxazolidine **322** (Scheme 156).

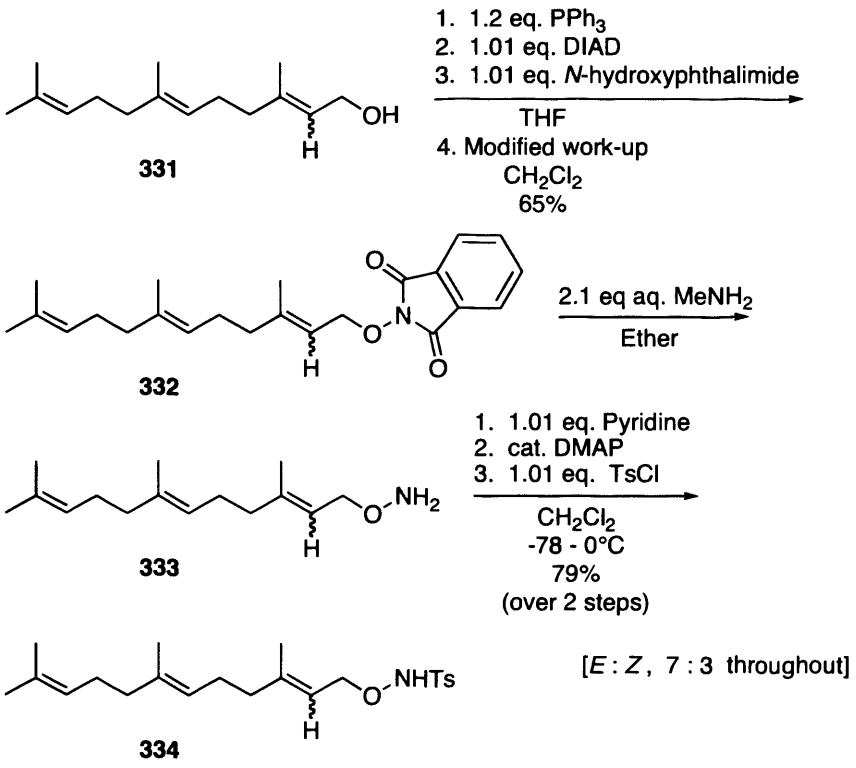


Scheme 156

As it is unlikely, however, that protonation is so regiospecific, the likelihood is of a series of rapid equilibria to give the presumably thermodynamic product **322**.

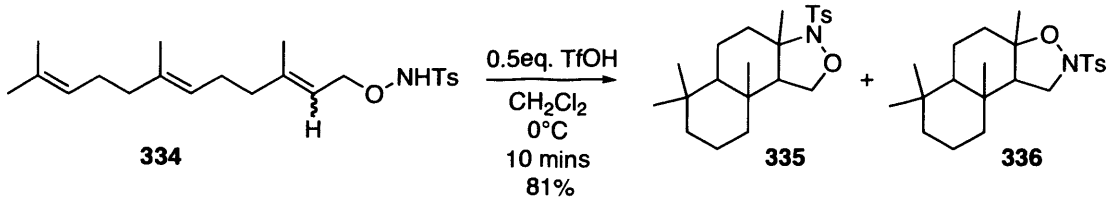
A double cascade

Enthused by these successes we decided to attempt a further extension of the acid-catalysed ring closure, incorporating three terpene subunits in a double cascade. Elaboration of commercially available farnesyl alcohol **331** (a mixture of (*E*) and (*Z*) isomers obtained from Aldrich Fine Chemicals), in the now familiar manner, yielded the required *N*-tosyl hydroxylamine **334** in excellent yield (Scheme 156).



Scheme 157

Application of our standard cyclisation conditions yielded an understandably complicated mixture of products - tentatively assigned as tricyclic system **335** and its regioisomer **336**, both present as a mixture of stereoisomers (Scheme 158).



Scheme 158

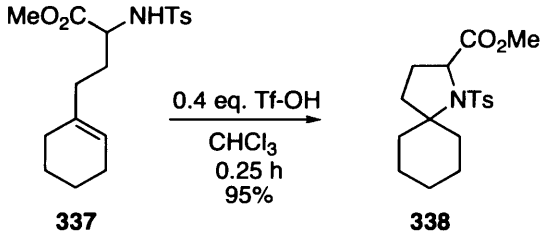
The proton NMR spectrum of the crude product clearly showed the disappearance of the resonances associated with the olefinic protons in the starting material **334**. This loss was accompanied by the appearance a series of highly complicated resonances at lower chemical shift. In the midst of these complicated resonances, four sharp resonances were observed, possibly corresponding to the expected methyl groups present in a major product. Several of these resonances were accompanied by a second, weaker resonance at a chemical shift slightly upfield of the predominant peak (around 0.03 ppm). Although these resonances could have been generated by a stereoisomer of a major product, the pattern is strongly suggestive of the formation of a minor, rearranged product, as encountered previously. The ^{13}C NMR of the product was also highly complicated, displaying far more resonances than would be expected if there was a single product. Unfortunately, repeated attempts at separation by silica gel chromatography proved unsuccessful. Based on this evidence, and previous experience, the tentative assignment was made, *i.e.* formation of major **335** and minor **336** regioisomers,

presumably obtained as a mixture of stereoisomers. Given the reaction conditions and uncertainty regarding the mechanism, the formation of further products due to Wagner-Meerwein shifts of one or more methyl groups cannot be ruled out.[99]

Whilst the stereo- and regiochemical uncertainty in the outcome of this cyclisation is clearly less than desirable, it does serve to illustrate the potential for the synthesis of a highly complex tricyclic, isoxazolidine-containing system.

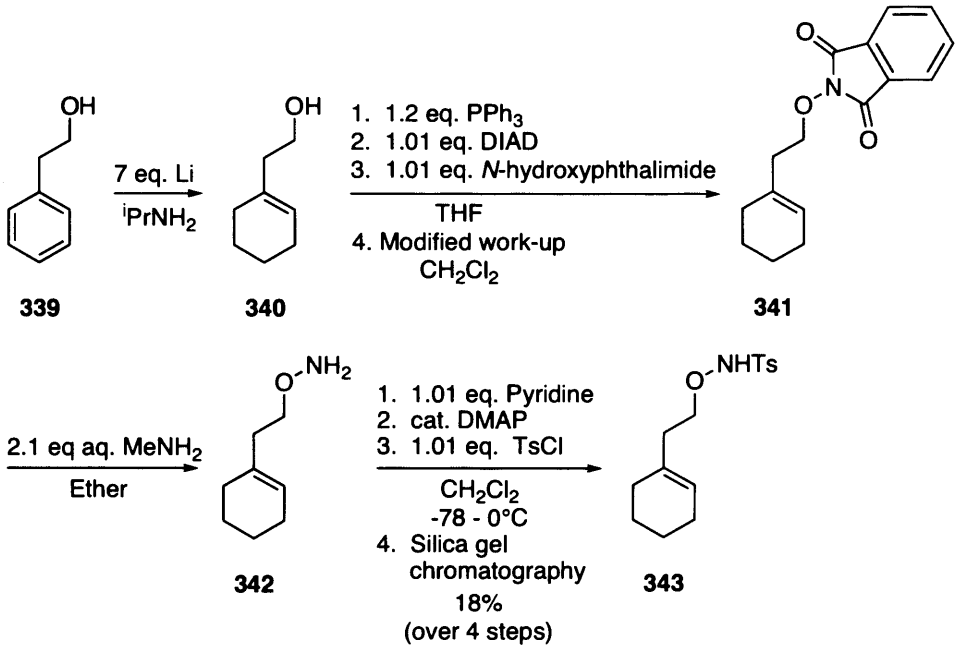
Synthesis of spiro-cycles

The unexpected synthesis of the spirocycle **322** led us to investigate further the synthesis of analogous *spiro*-cyclic compounds. Haskins previously demonstrated that the phenyl alcohol-derived sulphonamide **337** could be cyclised under the influence of triflic acid to yield a 5,6 fused spiro cycle **338** (Scheme 159).[90]



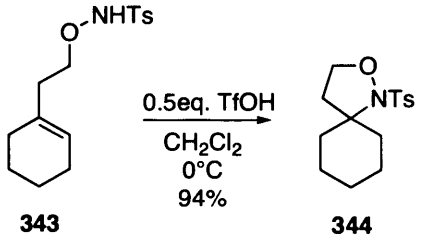
Scheme 159

The parallels drawn thus far between the cyclisation of sulphonamides and *N*-tosyl hydroxylamines suggested further investigation was certainly warranted. With a clear route to the required cyclisation precursors now firmly established, we set about exploring the potential for the creation of spirocyclic isoxazolidines. Firstly, a variation on the Birch reduction yielded the alcohol **340** as the major component in a mixture of products.[100] Repeated attempts at purification of the product through both distillation and silica gel chromatography failed to eliminate the small amounts of the starting material and various decomposition products present. Instead, given that the modified Mitsunobu process had proven itself to be highly robust, it was decided to perform this reaction on the crude reaction product in the hope that the mixture of products so obtained would be more amenable to separation. Analysis of the crude product from such a Mitsunobu reaction suggested the desired phthalimide-protected hydroxylamine **341** was the major component, however, several impurities were also present. Once again, repeated attempts at purification through both silica gel chromatography and recrystallisation failed to remove these contaminants and so again it was decided to further elaborate the compound as the major component of a crude mixture. Removal of the phthalimide-protecting group, followed by immediate tosylation and silica gel chromatography of the crude product yielded the desired *N*-tosyl hydroxylamine **343**, at last as a pure compound (Scheme 160).



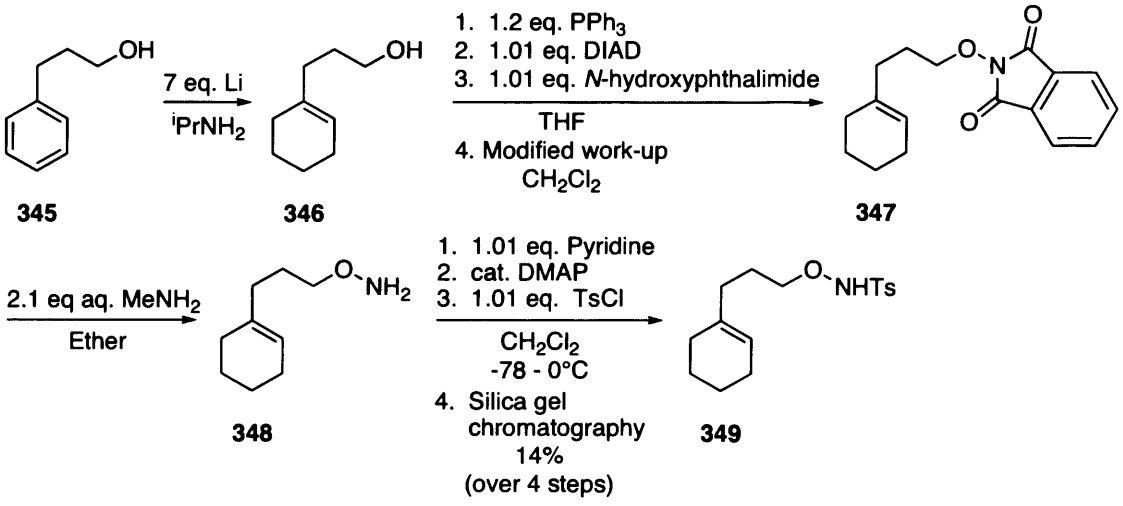
Scheme 160

Although the yield was undeniably poor (18% over 4 steps), the sequence nonetheless provided sufficient material with which to assess the viability of the cyclisation. Application of the standard set of cyclisation conditions delivered a single product, with spectroscopic data consistent with those expected for the 5,6 spiro-cycle **344** (Scheme 161).



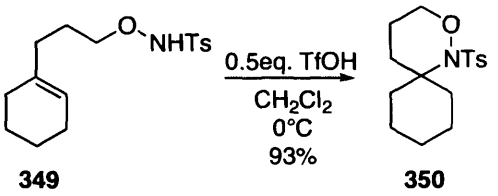
Scheme 161

Using an identical procedure, the homologous starting material **349** was synthesised, in 14% yield over 4 steps, once again isolating pure product *via* silica gel chromatography only following the final tosylation step (Scheme 162).

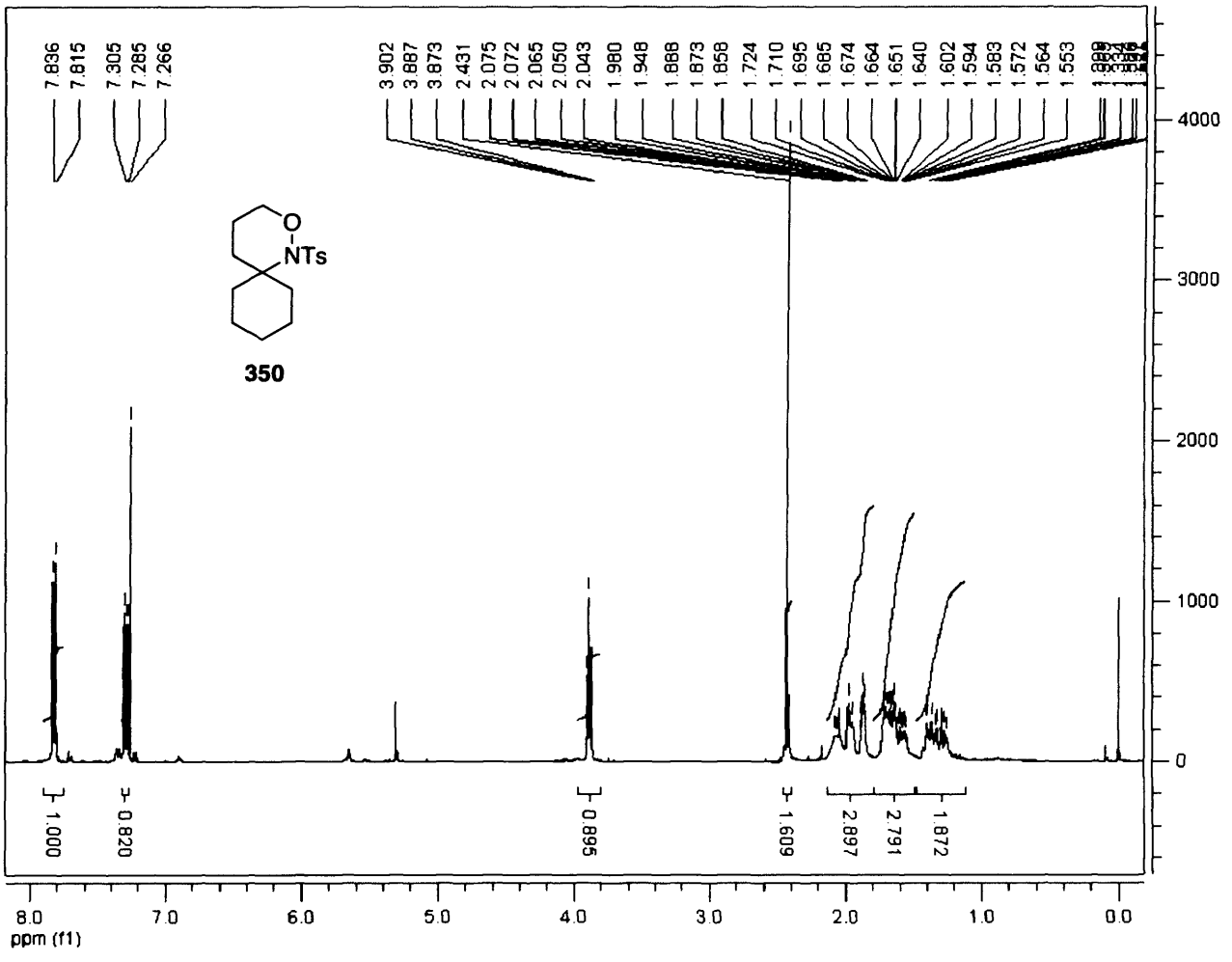


Scheme 162

Application of the standard cyclisation conditions again delivered a single compound, this time with spectroscopic data consistent with those expected for the 6,6 *spiro*-cycle **350** (Scheme 163, Diagram 16).



Scheme 163



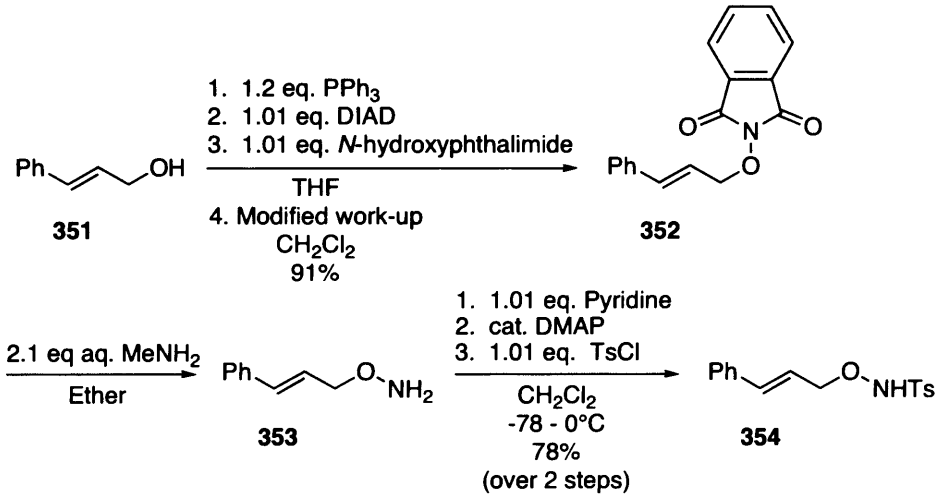
Proton NMR spectrum of crude *spiro*-cycle **350** (400MHz, 300.0°K in $CDCl_3$).

Diagram 16

This important result represented a marked contrast to the cyclisation of sulphonamides reported by Haskins, wherein an analogous substrate again failed to give the corresponding 6,6 *spiro*- cyclic product, rearranging to instead undergo an overall 5-*exo*-trig cyclisation and form a pyrrolidine, as discussed previously (pp 82).[90] No explanation for this substantial difference between the cyclisation of sulphonamides and *N*-tosyl hydroxylamines has, as of yet, been uncovered.

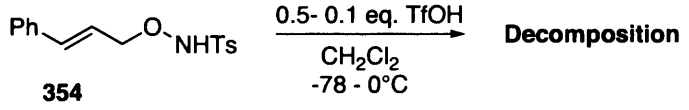
Alternative substrates for carbenium ion generation

Seeking to examine the possibility for an alternative means for carbenium ion generation, we began a brief study of suitable substrates. Generation of the required carbenium ion in a benzylic, as opposed to tertiary, position seemed to represent a promising variation. Starting with (*E*)-cinnamyl alcohol **351**, the required *N*-tosyl hydroxylamine **354** was constructed in excellent overall yield (Scheme 164).



Scheme 164

Notably, the Mitsunobu reaction involving cinnamyl alcohol **351** has the potential to deliver an alternative product *via* a competing S_N2' reaction pathway (as discussed in Chapter Two of this thesis, pp 10-35), however such products were not observed. This is probably due to the stability generated by the conjugation between the olefin and the benzene ring. Repeated attempts at applying the acid-catalysed cyclisation conditions to this substrate resulted in decomposition of the substrate (Scheme 165).



Scheme 165

This could perhaps be attributed to sensitivity of either the starting material or the reaction products to the acidic conditions. One possibility was that the same kind of regioisomerisation that had been encountered with similar allylic hydroxylamines was occurring with this substrate, in this case generating an intermediates carbenium species that was unstable. Unfortunately, in the case of this substrate, the possibility of synthesising a suitable non-allylic isomer did not exist. Due to the time restraints posed on this project these investigations were abandoned. In hindsight, further investigation into the means for carbenium ion generation is clearly warranted, as a number of promising alternatives exist. For example, the homoallylic analogue **355** would provide a substrate that is no longer easily able to participate in the isomerisation and could potentially deliver a 6-membered product by addition to a benzylic

carbenium ion. Alternatively, the tertiary alcohol **366** could potentially generate the required carbenium species through an acid-catalysed dehydration.

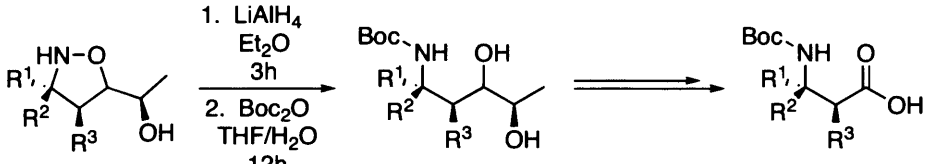
355 **356**

Attempts were made to synthesise the *N*-tosyl hydroxylamine **356**, however the required Mitsunobu process was repeatedly unsuccessful.

Cleavage of the nitrogen-oxygen bond – A route to amino-alcohols

As discussed in the introduction to this thesis, the ability to cleave the relatively labile nitrogen-oxygen bond lends isoxazolidines significant utility as precursors to highly substituted amino-alcohols. Our attempts to cleave the nitrogen-oxygen bond in the *N*-tosyl isoxazolidines resulting from our acid-catalysed cyclisations had met with little success. As discussed earlier in this Chapter, the only previously reported method for cleavage in such compounds, catalytic hydrogenation, achieved less than 50% conversion to the desired product after seven days.[95] Clearly a more efficient means for performing such transformations was required.

The use of lithium aluminium hydride in the cleavage of the isoxazolidine nitrogen-oxygen bond has been widely reported. In 2005, Mapp and co-workers reported cleavage of the bond in an unprotected isoxazolidine **357**, as a means for generating a range of *N*-Boc amino-alcohols **358**, themselves precursors to β-amino acids **359** (Scheme 166).[21]



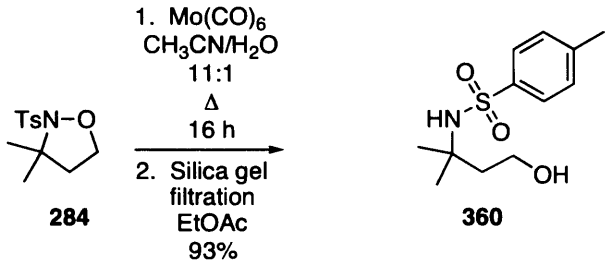
357 **358** **359**

Scheme 166

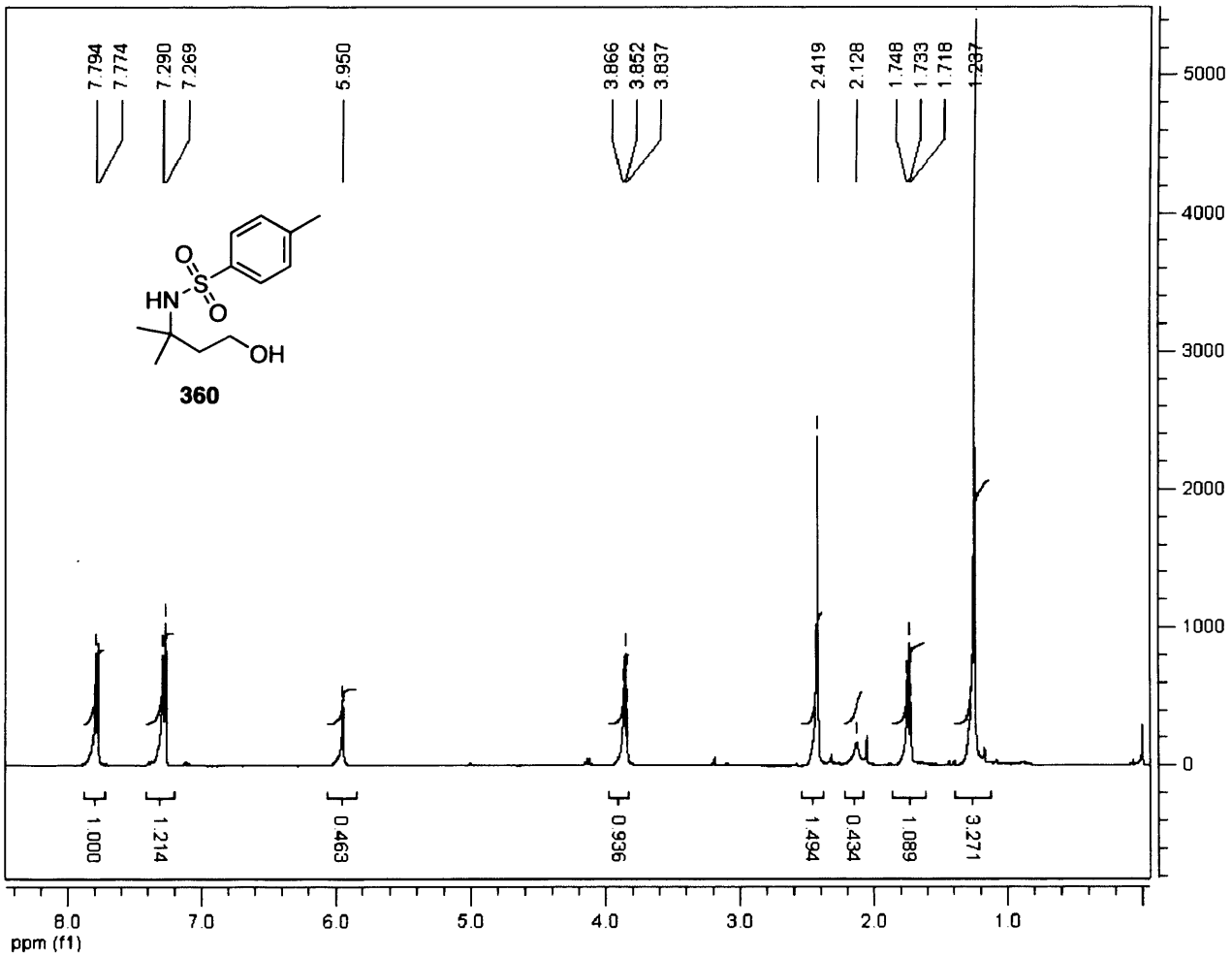
Application of these conditions to our prenyl alcohol-derived isoxazolidine **284**, however, failed to induce any cleavage of the nitrogen-oxygen bond. Even when the conditions were altered to include a prolonged reflux, the reaction returned only quantitative amounts of starting material. This surprising result suggested that the presence of a tosyl protecting group leads to a significant increase in the stability of the isoxazolidine.

In 2005, Alcaide and co-workers[101] reported selective cleavage of the isoxazolidine nitrogen-oxygen bond had been achieved, in the presence of a range of sensitive functionalities, using the popular reagent molybdenum hexacarbonyl.[102] Applying these conditions to our substrate,

we were delighted to observe complete conversion to the desired amino-alcohol **360**, which was recovered in exceptionally good yield (Scheme 167, Diagram 17).



Scheme 167

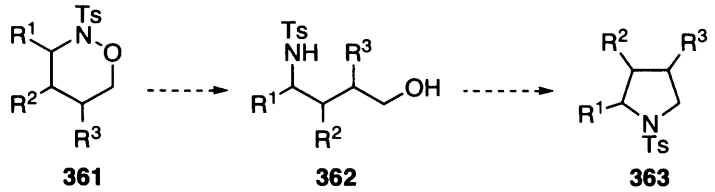


Proton NMR spectrum of amino alcohol **360** (400MHz, 300.0°K in $CDCl_3$).

Diagram 17

This key result gives rise to numerous potential applications, such as applying this acid-catalysed isoxazolidine synthesis in an effective amino-alcohol synthesis. An intriguing possibility is that cleavage of the nitrogen-oxygen bond in a 6-membered product **361** could

generate a γ-amino-alcohol **362**, which could in turn cyclise (potentially under Mitsunobu conditions) to yield a highly regiospecific pyrrolidine **363** synthesis (Scheme 168).



Scheme 168

The potential for further investigation is clear and the possible applications of the methodology are certainly exciting.

Summary and future work

The ability of a catalytic amount of triflic acid to facilitate the cyclisation of *N*-sulphonyl *O*-alkenyl hydroxylamines has been demonstrated across a broad range of substrates. The reaction is also amenable to the formation of multiple fused ring systems *via* acid-catalysed cascade reactions and, in contrast to the cyclisation of sulphonamides previously investigated by the group, to the formation of six-membered rings, *i.e.* 1,2-morpholines.

There is clearly considerable scope for further extension of this methodology. As discussed, there are several alternative substrates that will potentially allow for carbenium ion generation. The methodology can also be expanded to examine the scope for incorporation of a wider variety of functional groups in the cyclisation precursors and the possibility for the formation of highly complex multiple fused ring systems, potentially with a high degree of stereochemical control.

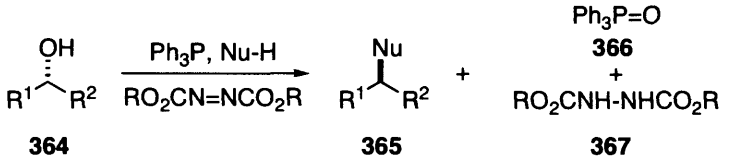
CHAPTER 5

Chapter Five

The Use of Hydrogen Peroxide in the Purification of Mitsunobu Products

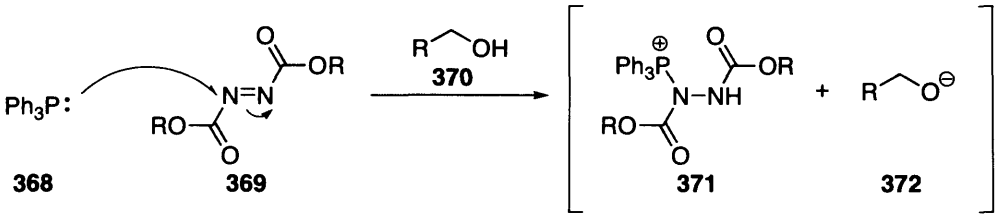
Background

In the absence of a more expedient and economical route to the various hydroxylamines required throughout this project, the Mitsunobu reaction was an ever-present feature in the approach work contained in previous Chapters of this thesis. Through activation and subsequent displacement of a primary or secondary alcohol **364**, the net effect of the Mitsunobu reaction is to create a new carbon-nucleophile bond **365** with concomitant overall dehydration and inversion of stereochemistry at the reaction centre (Scheme 169). As a powerful method for installing a wide-range of functional groups and a highly specific means for rectifying stereochemical inaccuracies in the latter stages of target synthesis, the reaction has found extensive application.[103, 104]



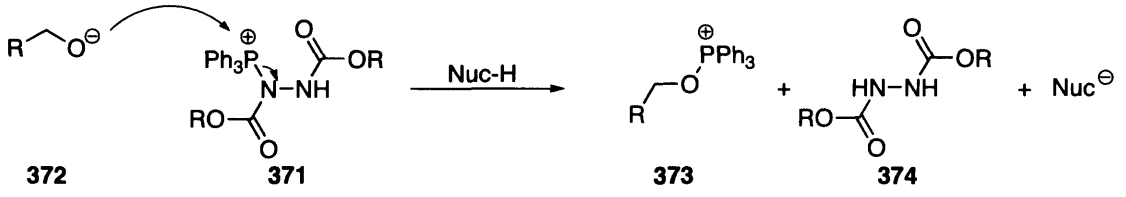
Scheme 169

Under a typical set of conditions, the reaction proceeds firstly by reaction of an azodicarboxylate **369** (usually DIAD or DEAD), with a suitable phosphine (typically triphenylphosphine), to generate an activated phosphonium adduct **371** (Scheme 170)



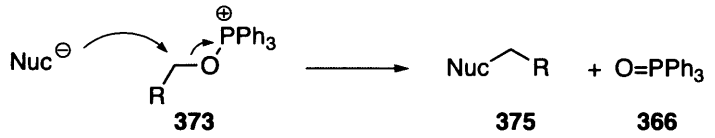
Scheme 170

This species in turn transfers the phosphonium ion, causing overall activation of alcohol **370** (Scheme 171).



Scheme 171

This is followed by a nucleophile (bearing at least, and indeed preferably, one suitably labile proton) attacking *via* an S_N2 mechanism to displace the phosphonium species and form a new carbon-nucleophile bond and a phosphine oxide (Scheme 171).



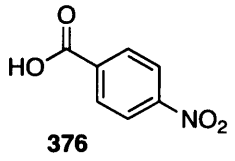
Scheme 172

This is only an overall description of the reaction intermediates and certainly does not represent all of the species likely to be formed.[103, 104]

In most cases, this nucleophile is a heteroatom although the reaction has been used to generate new carbon-carbon bonds, for example using soft nucleophiles such as 1,3-dicarbonyls. A significant driving force behind the reaction is the formation of a highly stable phosphine oxide. Prior to this, however, the heteroatom nucleophile must attack and form the S_N2 intermediate, at the same time losing its attached proton. This, rather than the associated nucleophilicity of the heteroatom, has been shown to be the key factor determining the success of the reaction, leading to the recommendation by Ragnarsson that suitable nucleophiles should bear a proton with a pK_a of less than 13.5.[105] In the case of nucleophiles bearing more than one proton, it is also crucial that only one of these is suitably labile in order to prevent the initial product going on to act as a nucleophile in further Mitsunobu displacements. In practice it is often difficult to control the reaction in this way and often more reliable to employ nucleophiles bearing only one proton on the heteroatom. This can be achieved by the incorporation of appropriate protecting groups and it is often a fortunate consequence of this that such derivitisation serves to lower the pK_a of the remaining proton, thereby increasing the efficacy of the nucleophile. It is also necessary to ensure that the starting material itself bears no unprotected heteroatoms that may participate in further intra- or intermolecular displacements, unless specifically desired.

Limitations

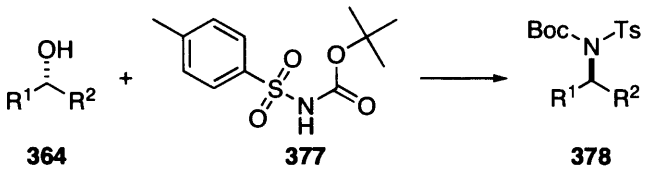
This set of preconditions has led to a relatively limited set of nucleophiles finding common use in Mitsunobu displacements. Alcohols generally have too high a pK_a to be successful, a notable exception of course being phenol. Displacement by oxygen nucleophiles is therefore best achieved using carboxylic acids, forming esters that can then be subsequently hydrolysed. The need for increased acidity has led to the recommendation by Martin and Dodge that *p*-nitrobenzoic acid **376** be employed as the nucleophile of choice in such situations.[106]



376

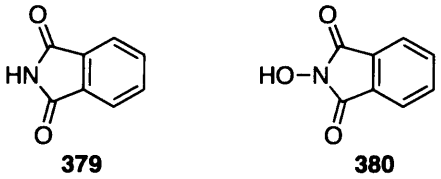
For the reasons discussed previously, amines employed as nucleophiles are limited to those that are disubstituted. This, coupled with the need for the remaining proton to be suitably labile, has

led to many of the common, electron-withdrawing protecting groups being incorporated in Mitsunobu nucleophiles. *N*-Boc *N*-tosyl amine **377**, for example, satisfies all of these criteria and allows for the synthesis of an orthogonally, *bis*-protected amine product **378** (Scheme 173).[107]



Scheme 173

The use of cyclic amines also meets the demand for a secondary amine and in particular imides, such as phthalimide, have found extensive application given that, as has been demonstrated in previous Chapters, the phthalimide group can be readily cleaved to produce the free amine. Previous Chapters also detail the use of *N*-hydroxyphthalimide **378** as a means for the synthesis of hydroxylamines from primary and secondary alcohols.



Given the many reagents involved in the reaction, the 'atom-efficiency' of such transformations is unavoidably poor. This also leads to a further, significant limitation – the presence of a plethora of contaminants in the crude reaction product. Given this, the purification required (usually silica gel chromatography) is complicated, time-consuming and often delivers product yields well below those that would be expected from the level of conversion achieved. As a consequence, much research has been undertaken towards developing improved conditions and reagents that may aid in product isolation.

Previous work towards improved product isolation

Given the degree to which the Mitsunobu reaction is hampered by the complex nature of the procedures required for product isolation, it is not surprising that there have been many attempts made at developing modifications of the reaction that may eradicate or a least greatly reduce these demands. The level of interest in this subject can be gauged by the abundance and diversity of approaches detailed in several thorough reviews of the literature, notably by Hughes,[104] Curran[108] and latterly, an excellent micro-review by Dembinski.[109] The abundance and diversity of approaches taken to limit the need for this purification step only serves to underline the frustration such limitations cause to those wishing to employ this powerful synthetic tool.

The vast majority of approaches towards practical solution have been focused on modification of the reagents utilised in the transformation. Chemical modification of these can result in the excess reagents and their respective post-reaction by-products possessing sufficient chemical differentiation from the reaction products that allows these to be selectively removed from the post-reaction mixture.

Besides the reaction product, a post-reaction mixture may contain a wide-range of contaminants:

- Excess nucleophile - In order to drive the reaction to completion, it is often necessary to employ an excess of the participating nucleophile.
- Phosphines – At least stoichiometric amounts of phosphine oxides are present as a by-product of the reaction along with excess phosphine, which is usually employed in slight excess in order to achieve high levels of conversion.
- Azodicarboxylate and derivatives - An excess of azodicarboxylate is again often present along with stoichiometric amounts of the reduced azo-derivative, the corresponding hydrazine.

An extensive and complete account of the attempts made at modifying these reagents is beyond the scope of this brief introduction and only selected highlights will be discussed here. A more detailed account can be found in the previously mentioned reviews on the subject.

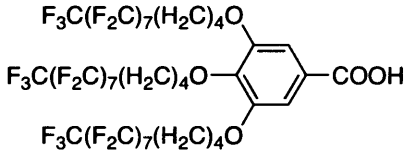
Modified nucleophiles

Modification of the nucleophile is perhaps the least used alteration to the Mitsunobu conditions since it inherently results in a similarly modified reaction product, further complicating purification and requiring additional elaboration in order to achieve the desired target. This so-called 'substrate tagging' allows only for selective purification of the reaction product and any excess nucleophile. In order to obtain pure product from the process, this excess must be dispensed with or even an excess of starting material employed, in order to ensure that the only 'tagged' compound in the crude reaction mixture is the Mitsunobu product.

The two most frequently adopted approaches towards substrate tagging appear to be those involving either polymer-supported or fluorinated nucleophiles.[109] The use of polymer-supported reagents in the Mitsunobu reaction has obvious limitations when one considers the mechanism of the transformation. Although the exact mechanism of the reaction is hotly debated, the consensus is that it follows the pattern of formation and reaction of a series of bi-molecular intermediates described previously (Schemes 170-172).[104] The need for the various reaction components to come together and form these intermediates results in steric demands dictating that only one polymer supported reagent can be present in each intermediate. Thus, in

practice, only one of the reagents in any given Mitsunobu reaction can be successfully attached to a polymer support. In the case of the nucleophile the inherent steric hindrance generated by the alcohol-derived phosphonium species leads to greatly diminished yields when polymer-supported derivatives are employed.

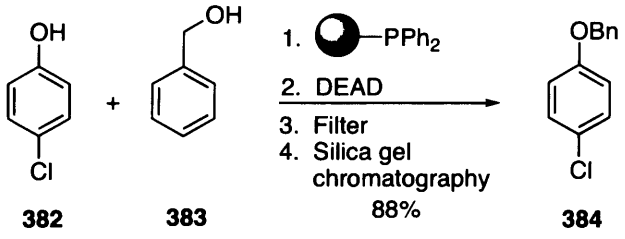
Fluorous tagging is another commonly used method to aid separation. Such 'tagged' compounds are modified to give them a high fluorous content (60% or more by weight) which can then be separated from the reaction mixture by partitioning between a fluorous and an organic solvent. Compounds with a lower fluorine content can be separated used fluorous silica gel chromatography, an adaptation of silica gel chromatography using a stationary phase that has been modified to include fluorous domains and thus have a higher affinity for fluorous tagged compounds.[110] One approach, adopted by Dembinski, involves the use of the highly fluorinated benzoic acid derivative **381** as a nucleophile which in turn generates a highly fluorinated product in high yield. Any such product can be separated using the previously described techniques and hydrolysed to yield the inverted alcohol and the recovered perfluorous carboxylic acid.[111]



381

Modified phosphines

It is often reported that the greatest complication arising from the purification of reaction products is the removal of excess phosphine and the phosphine oxide; this is certainly the experience of the author. As in the case of the nucleophile, the use of solid-supported phosphines is perhaps the most often explored means of their removal from the reaction mixture. For example, Tunoori *et al* have shown that *p*-chlorophenol **382** can be reacted with benzyl alcohol **393**, under standard Mitsunobu conditions, using a solid-supported phosphine (Scheme 174).[112]

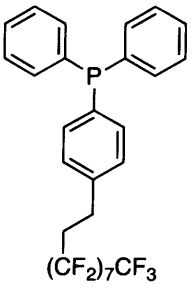


Scheme 174

Filtration of the reaction mixture results in removal of the excess phosphine and the phosphine oxide by-product to give a mixture of product, excess DEAD and the DEAD-derived hydrazine. Subsequent silica gel chromatography gives the pure ether **384**, in 88% yield. Whilst

undoubtedly simplifying the chromatography involved, the need for further purification still nonetheless limits the application of such a reagent, particularly since, as mentioned previously, only one solid-supported component can be utilised in any given Mitsunobu process. The process also suffers from the creation of large amounts of waste reagent, unless a means for the recovery and regeneration of the solid-supported reagent can be employed.

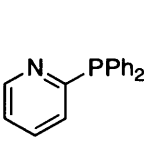
The use of fluorous-tagged phosphines can also simplify the purification of Mitsunobu products. The heavily fluorinated phosphine **385**, for example, has been utilised by Curran, who showed by HPLC analysis that this phosphine had adequate retention on a fluorous column to allow for its removal from the reaction mixture whilst at the same time returning good yields of reaction products.[113]



385

A range of other fluorinated phosphines have also been developed and many have been used in conjunction with fluorinated azodicarboxylates, allowing for complete purification after one chromatographic process.[108]

Modification of the phosphines employed in the reaction has also focused on allowing the component to be removed used simple acid/base extraction processes. Notable examples include the use by Jenkins and Camp of the basic phosphine **386** which can be removed by an aqueous acid extraction[114] and development of the *tert*-butyl ester-modified phosphine **387** by Flynn which can be unmasked using TFA and removed by ion-exchange chromatography.[115]



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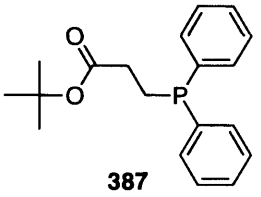
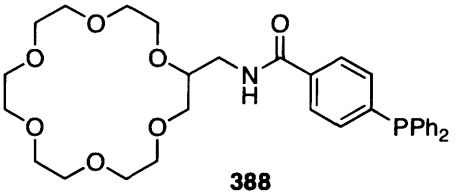


387

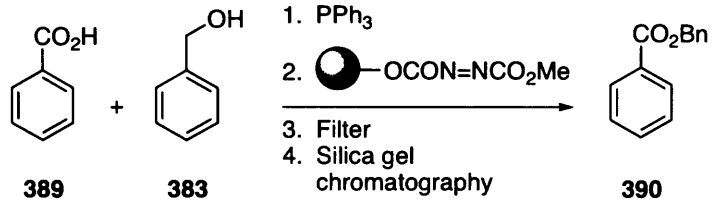
An imaginative alternative reported by Routledge and Jackson involves the use of the 18-crown-6-tagged phosphine **388**, that can be removed post-reaction by chromatography using an AgroPore™ (ammonium trifluoroacetate)-functionalized medium.[116]



388

Modified azodicarboxylates

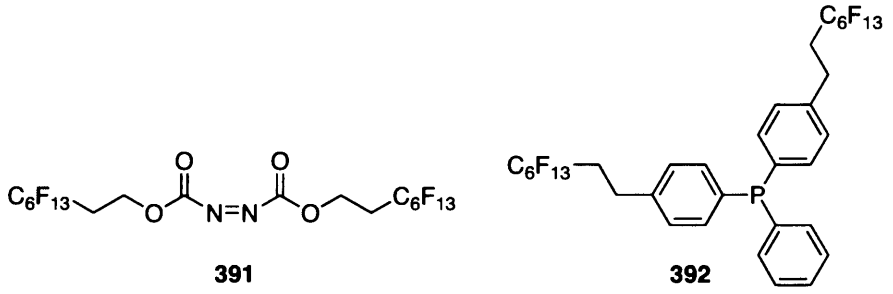
The range of strategies employed in the removal of azodicarboxylate from the reaction mixture follow roughly the same pattern of attack as those described for the removal of phosphines. A solid supported reagent, developed by Vederas and co-workers, has been utilised in a representative Mitsunobu reaction, delivering the product in 65% yield (Scheme 175).[117]



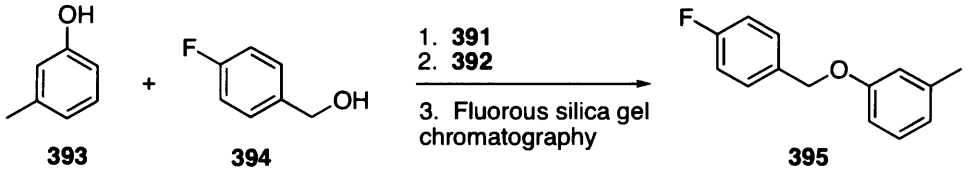
Scheme 175

As is the case with other solid-supported reagents, the modified azodicarboxylate cannot be used in conjunction with other solid-support reagents and therefore, in this case at least, there remains the need for further purification of the reaction mixture after the solid-supported reagent has been removed.

Once again, as with the phosphine component, the use of heavily fluorinated derivatives of azodicarboxylates has also been extensively investigated. The efficiency of this approach and its benefits over the solid-supported alternatives was perhaps best demonstrated by the group of Curran, combining the modified azodicarboxylate **391** with a heavily fluorinated phosphine **392**.[118]



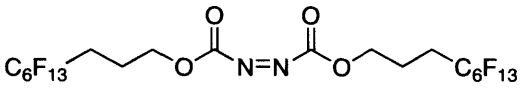
In a standard Mitsunobu coupling, they were able to achieve complete purification of the desired reaction product **395** using a single round of fluorous silica gel chromatography (Scheme 176).



Scheme 176

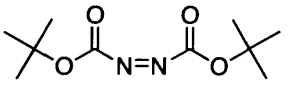
Although the overall yield was poor (19%), this is blamed on the steric demands created by the proximity of the fluorinated portion of each reagent to its respective reactive site, hardly a positive recommendation for such a tactic.

The group subsequently reported that a modified fluorous azodicarboxylate **396** participates in an identical procedure to deliver the required product in 60% yield.[108]



396

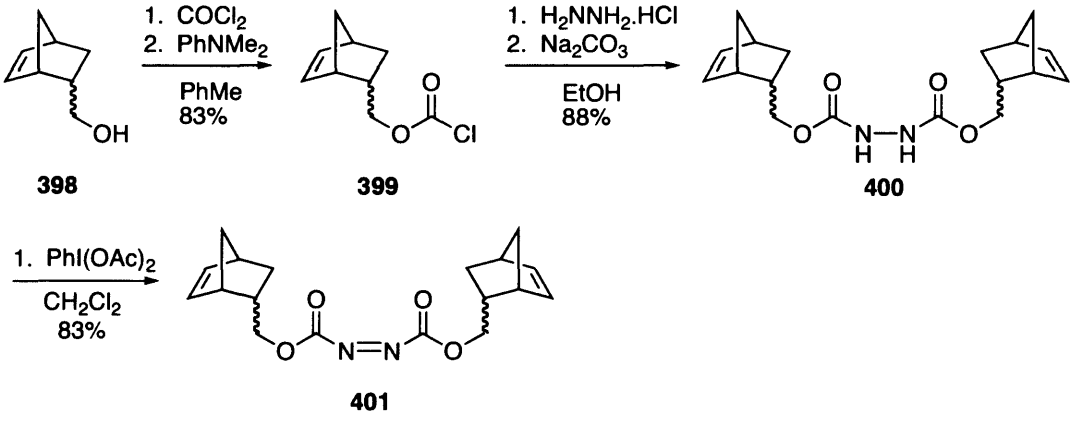
The use of an aqueous acid wash in the work up procedure can also aid in the removal of suitable azodicarboxylates and, when used in conjunction with reagents such as the basic phosphine **386** described previously, can facilitate a simple one-step process for product purification. To this end, Kiankarimi and co-workers have developed the *tert*-butyl azodicarboxylate **397** that, upon exposure to 4M HCl in the work-up procedure, decomposes to give gaseous isobutene and carbon dioxide, and hydrazine which, along with the phosphine, is removed in the aqueous layer to return pure product.[119]



397

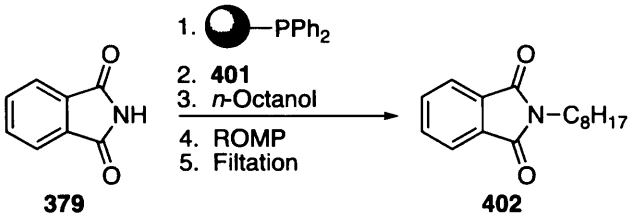
This strategy, whilst promising, does however preclude the presence of acid-sensitive functional groups or basic sites in the reaction product.

The degradation of the azodicarboxylate forms part of a radically different approach to product purification involving what has been termed 'impurity annihilation'. In this approach, the reagent is modified so that it may participate in the Mitsunobu process as required and then, post-reaction, it may be reacted further, degrading to a compound or series of compounds that may be selectively removed from the reaction mixture. Barrett has pioneered this approach and developed a synthesis of the modified azodicarboxylate **401** for use in Mitsunobu processes (Scheme 177).[120]



Scheme 177

The azodicarboxylate **401** was subsequently used in conjunction with a solid-supported phosphine in a simple Mitsunobu process (Scheme 178).



Scheme 178

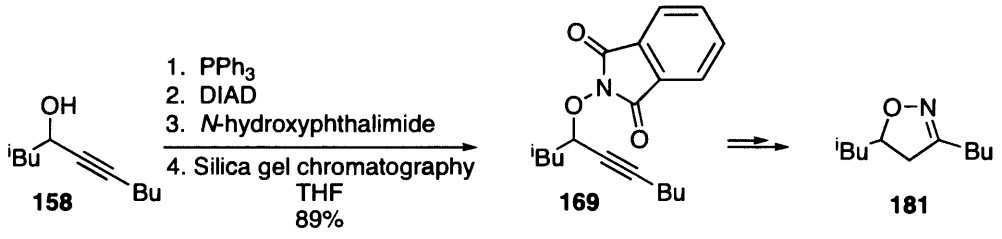
The reaction was monitored by tlc and upon completion was treated with a catalytic amount of Grubbs catalyst [PhCH=Ru(PCy$_3$)$_2$Cl$_2$], causing the azodicarboxylate **401** and the post-reaction hydrazine derivative to undergo ring-opening metathesis polymerisation (ROMP), forming an insoluble polymer. The reagent-derived polymer along with the solid supported phosphine and post-reaction phosphine oxide, were then removed from the reaction mixture by simple filtration, delivering the desired product **402** in quantitative yield.

Whilst impressive, this approach does suffer distinct limitations. The need for synthesis of the novel azodicarboxylate **401**, whilst relatively expedient and high yielding, is certainly far less preferable than the use of one the many commercially available reagents. Also, the ROMP reaction is potentially highly sensitive and could fail in the presence of free amines or non-solid-supported phosphines. Significantly, Barrett makes no mention of the degree to which the use of the ruthenium catalyst introduces additional impurities to the reaction mixture and how these impurities may be removed.[121]

Results and discussion

Initial findings

The Knight group has, for some time, held an interest in the reactions of highly functionalised hydroxylamines. Foot found that propargyl alcohols could be transformed into hydroxylamines using Mitsunobu displacements of the alcohol with *N*-hydroxyphthalimide.[37, 41] Initially suffering from low yields, a subsequent solvent study conducted by Li found that replacing the reaction solvent, ethyl acetate, with tetrahydrofuran gave significant improvements.[50] The hydroxylamines generated formed ideal stating materials for the synthesis of a wide range of dihydroisoxazoles, as described in previous Chapters of this thesis (Scheme 179).[122]



Scheme 179

Whilst the importance of the reaction as a synthetic tool cannot be overstated, the process does suffer from the need for cumbersome and time-consuming purification. As is described in the vast majority of Mitsunobu processes reported in the literature, this purification was commonly performed using silica gel chromatography and a combination of ethyl acetate and petrol as an eluent. The need for adequate separation often lead to large amounts of silica gel being required for even relatively small-scale reactions, limiting the scale on which the reaction could be performed. Further, a common requirement for gradual polarity gradients resulted in a large number of fractions being obtained, a typical purification taking up to 3 hours complete. Faced with the prospect of performing such a process on an almost daily basis, one despaired and sought means for alleviating this burden.

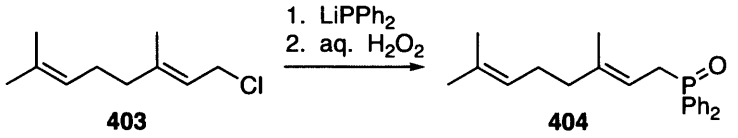
Removing the need for chromatography

A wide range of approaches have been taken to facilitate simple purification of the reaction products, however all are hindered by the need for specialist reagents obtained at greater than usual cost or requiring additional synthesis. Many of the strategies are also only able to achieve removal of one particular set of impurities leading to the need for additional, albeit simplified, chromatography. As an alternative we set about exploring the possibility of developing a process that would allow the Mitsunobu reaction to be performed under standard conditions, using the common applied set of reagents but which would allow the various impurities to be removed in one step, allowing the reaction product to be isolated in a high degree of purity.

The first breakthrough came when the conditions used in the chromatographic process were explored further. It was found that, whilst the mobility of the various reagents and their post-reaction derivatives were roughly on a par when eluting with a wide range of solvents and combinations of solvents, the situation improved greatly when neat dichloromethane was used as the eluent.

Analysis of the various impurities present in the crude product (tlc) showed that when dichloromethane was employed as an eluent the excess DIAD, the reduced DIAD derivative and the triphenylphosphine oxide present in the crude reaction mixture showed significantly reduced mobility, close to Rf 0. In contrast, all of the reaction products we had obtained for our studies in isoxazole synthesis remained highly mobile. This led us to speculate that if the reaction could be driven to completion, the vast majority of impurities in the reaction mixture could be removed using a simple filtration through silica. If this were achieved, the remaining, highly mobile impurity in the crude reaction product would be the unreacted triphenyl phosphine.

Hydrogen peroxide is often used as a reagent for the oxidation of phosphines. It can achieve quantitative oxidation at room temperature and, when used in neutral media, leaves the vast majority of other organic functional groups untouched. In this case, we were particularly inspired by the work of Clough and Pattenden, who utilised a biphasic aqueous hydrogen peroxide wash to oxidise a range of organophosphines for use in subsequent Horner-Wittig olefinations (Scheme 180).[123]



Scheme 180

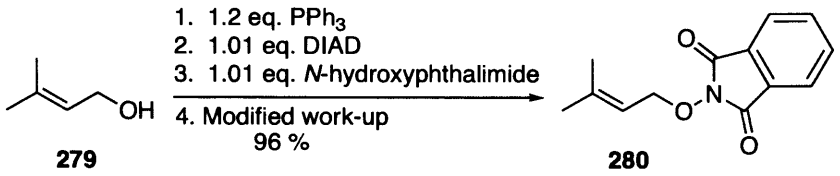
The oxidation was successfully achieved by performing a biphasic wash of a solution of the organic compound in dichloromethane with a relatively weak (15% w/w) aqueous solution of hydrogen peroxide. The excess peroxide content of the organic phase was then neutralised using a second biphasic wash with saturated aqueous sodium sulphite. This approach is particularly effective, given that the products of the reaction between the oxidant and the quenching agent (sodium sulphate and water) are non-toxic and are removed in the aqueous portion of the washings.

By combining a silica filtration with oxidation of the excess phosphine, we reasoned that we would be able to remove the main contaminants in the reaction mixture. There did, however, remain the possibility that the crude reaction product would contain an impurity in the form of unreacted starting material. Given the possibility of this component displaying similar polarity to the reaction product, we were concerned that any attempt to remove it would no doubt also result in loss of product.

In order to ensure that only minimal amounts of contaminants were present in the crude product an excess of the reagents believed to be removed by this novel oxidation and filtration strategy was employed, in an attempt to ensure complete reaction of the starting material. We also found that tlc analysis of a wide-range of nucleophiles commonly employed in the reaction, as mentioned previously, showed that they also processed close to zero mobility on silica gel when dichloromethane was used as an eluent. Given this, an excess of the nucleophile was also employed in order to achieve complete consumption of the starting material. Furthermore, due to the installation of a protected heteroatom nucleophile and the need for protection of heteroatoms not participating in the reaction (the obvious sources of polarity in the reaction) products were present as less polar, protected derivatives and thus we felt confident that a large number of Mitsunobu products would possess sufficient mobility under the filtration conditions to be eluted with relative ease.

A trial procedure

The hydroxylamine **280** was a key reagent in the development of our acid-catalysed cyclisation methodology and was routinely accessed by Mitsunobu reaction of the commercially available prenyl alcohol **279** (Scheme 181).[122]



Scheme 181

Given the large quantities of the product required for these investigations, the reaction seemed an ideal candidate for the development of a chromatography-free purification procedure. Following a number of trials, an optimised work-up procedure was defined.

The modified procedure comprised the following:

1. Perform a standard Mitsunobu reaction involving sequential addition of reagents (with nucleophile, phosphine and azodicarboxylate in slight excess) in order to allow ordered formation of intermediates and limit side reactions, as recommended by Foot and detailed in the experimental section of this thesis.[41]
2. Following the reaction, remove the reaction solvent (tetrahydrofuran) from the crude reaction mixture under reduced pressure.
3. Dissolve this crude product in a minimum amount of dichloromethane.
4. Filter this dichloromethane solution through a pad of silica, eluting with copious dichloromethane.
5. Reduce the volume of the filtrate (typically to around 1/5 original volume) under reduced pressure.
6. Wash the concentrated solution with an equal volume of 15% aqueous hydrogen peroxide, typically in a separating funnel.
7. Remove the aqueous layer and replace with an equal volume of saturated aqueous sodium sulphite. Quench the aqueous layer by addition of further saturated aqueous sodium sulphite.
8. Separate the organic layer and back extract the quenched peroxide solution using dichloromethane.
9. Dry the combined organic layers over anhydrous magnesium sulphate.
10. Filter through a second pad of silica, eluting with copious dichloromethane.
11. Remove the solvent under reduced pressure.

We were delighted to find that the trial procedure not only delivered the product in near quantitative yield (96%) but also with a high degree of purity. Analysis of the product by NMR showed there to be only one organic compound present and high resolution mass spectrometry confirmed this to be the desired phthalimide **280**. Moreover, combustion analysis of the product without recrystallisation showed it to be extremely pure.[124]

The required amounts of silica, eluent and solvent for any given reaction can be gauged from the details given in the experimental section of this thesis and a recent publication.[50] By varying the amounts of silica and dichloromethane used in the process we were able to produce up to 10 g of the product **280** in a single Mitsunobu procedure, the work up of which took some 30 minutes.

Further examples

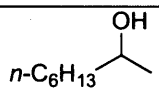
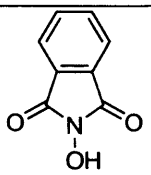
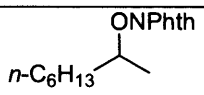
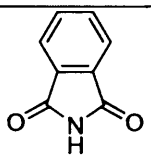
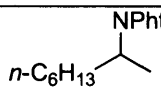
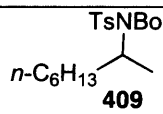
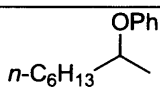
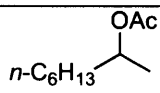
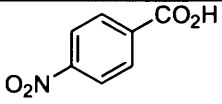
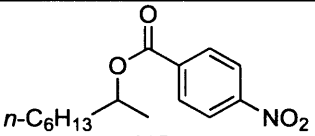
The success of this novel work-up procedure resulted in it becoming the standard procedure for all Mitsunobu reactions performed in this thesis. As a result, a wide range of examples can be found in the preceding chapters, all returning the desired products in high yield. Crucially, in those substrates where the stating alcohol and/or the product could conceivably be oxidised under the work-up procedure (*e.g.* alkenes, tertiary amines), no such reactions were observed in the proton NMR of the product.

It was brought to our attention during preparation of this work for publication that the functional groups which are perhaps the most sensitive to oxidation under the conditions used are those containing divalent sulphur. In order to assay this potential limitation, a sample of the 1, 3-dithiane **405** was subjected to the full work-up procedure. Encouragingly, the proton NMR of the returned compound showed no sign of oxidation, nor was any substantial loss of compound observed.

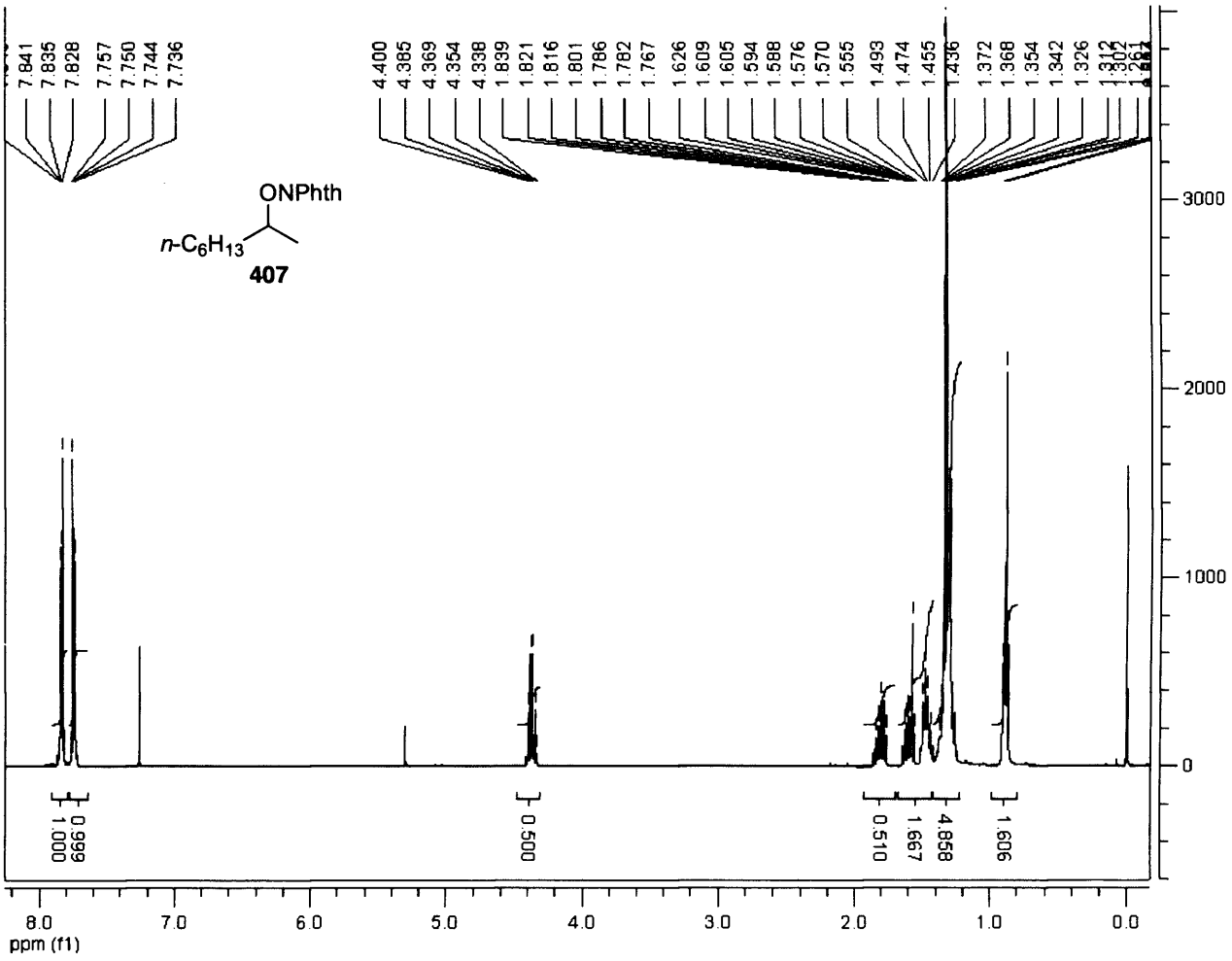
405

The range of substrates encountered during the pursuit of our novel heterocyclic synthesises were, however, understandably limited and so it remained for us to examine a broader set of reactions. Although we had examined the effect of the work-up procedure on a diverse set of primary and secondary alcohols, we had in each case used *N*-hydroxyphthalimide as the nucleophile. As discussed previously, a large number of nucleophiles have found use in the Mitsunobu reaction and so, using octan-2-ol as a standard substrate, we investigated the compatibility of examples of these nucleophiles with our novel work-up procedure (Table 7).

Table 7: *The application of alternative nucleophiles to the modified Mitsunobu procedure.*

	Electrophile	Nucleophile	Product	Yield
1	 **406**	 **379**	 **407**	81%
2	**406**	 **380**	 **408**	76%
3	**406**	TsNHBoc **377**	 **409**	79%
4	**406**	PhOH **410**	 **411**	56%
5	**406**	AcOH (2 eq.) **412**	 **413**	99%
6	**406**	 **379**	 **415**	84%

In each case the proton and ^{13}C NMR spectra of the crude product showed it to be extremely pure. For example, the proton NMR of the phthalimide **407** showed that it had been obtained as a single compound (Diagram 18). The purity of several Mitsunobu products purified in this manner (described in the preceding Chapters) was also assessed by micro-analysis and the values obtained were found to be within an acceptable margin of error of those expected, thus confirming a very high level of purity.



Proton NMR spectrum of phthalimide **407** (400MHz, 300.0°K in $CDCl_3$).

Diagram 18

Summary and future work

The results obtained thus far strongly suggest that the process described represents a practical work-up procedure for the Mitsunobu reaction, obviating the need for time-consuming and laborious chromatography of the crude product. Encouragingly, we have seen no evidence of any oxidation or degradation of the reaction product caused by the work-up procedure and in each case have returned analytically pure product in good to exceptional yields, with the majority of these being unoptimised.

We can of course envisage situations where the procedure may be less successful – particularly polar products, for example, may not have sufficient mobility at the silica filtration stage. However, due to their very nature, most or all such polar groups (OH, NH_2, CO_2H for example) will be necessarily protected and hence present in relatively less polar forms. Also, there remains the possibility that functional groups with particular susceptibility to oxidation may be disrupted, although none have been encountered by ourselves thus far. Nonetheless, we do believe the examples tested indicate that we have developed a procedure that will be applicable to the vast majority of Mitsunobu processes. The procedure has been used both on milligram

quantities and scaled up to produce around 10 g of product in one process, clearly extremely challenging if relying on conventional chromatography. The process requires only standard Mitsunobu reagents and standard laboratory reagents – all commercially available at minimal cost and requires no extra synthetic steps to be added to the process. Whilst the process does require large amounts of solvent and silica gel, it does not require the careful separation and analysis of fractions that would be required by conventional chromatography and so can be undertaken in a fraction of the time. Moreover, the large amounts of dichloromethane required can easily be recovered and recycled.

Overall, the process provides a simple and widely accessible approach to product purification in the Mitsunobu reaction – the benefits of which are apparent throughout this thesis.

CHAPTER 6

Chapter Six

The Use of Hydrogen Peroxide in the Purification of Metathesis Products

Background

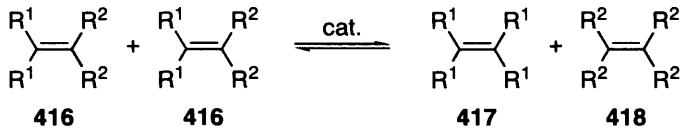
The success encountered when utilising the oxidant, aqueous hydrogen peroxide in the purification of products resulting from the Mitsunobu reaction (discussed in Chapter five of this thesis) led us to speculate whether such a purification strategy would find application elsewhere. In synthetic organic chemistry, transition metals have found widespread use as catalysts for: hydrogenation and other reductions including asymmetric reduction, oxidation, olefin metathesis and an extensive suite of coupling reactions between unsaturated carbons to name but the most popular. Without doubt, the latter two classes of reaction in particular represent highly significant paradigm shifts in the manner in which modern organic syntheses are undertaken.[125]

Where the reaction products are ultimately intended for ingestion as pharmaceutical compounds or for use in agriculture, it is important to reduce to a minimum the quantity of any transition metal residues, including spent catalyst and catalyst by-products, which may be present in the reaction product. By way of example, palladium has been used extensively on a research scale in various catalytic reactions, especially as a hydrogenation and coupling catalyst, and ruthenium is finding ever-increasing use in olefin metathesis reactions.

Nevertheless, the use of such catalysts on an industrial scale is potentially limited due to the difficulty encountered in removal of toxic catalytic residues from the reaction mixtures. Catalytically-active transition metals typically include metals of the platinum groups 8, 9 and 10, which are expensive commodities. There is therefore an economic incentive in providing a method that allows for these residues to be removed from reaction solutions in such a way that they can be recovered and reused, especially against the current background of steeply rising metal prices.

Metathesis in organic synthesis

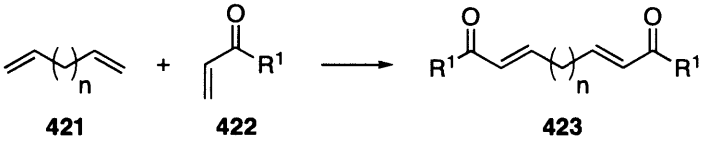
The 2005 Nobel Prize for Chemistry was awarded to Yves Chauvin, Richard Schrock and Robert H. Grubbs "for the development of the metathesis method in organic synthesis".[126] The metathesis reaction has fundamentally altered the way organic chemists consider the formation of olefinic bonds. The metathesis reaction effectively 'shuffles' the substituents on two pre-formed alkenes in order to create a novel alkene with the desired substitution pattern (Scheme 182).[126]



Scheme 182

Building on the work of Chauvin, Schrock and others, a major advancement came when Grubbs developed a set of catalysts that possessed significantly greater stability in air, rendering them highly accessible reagents for use in synthesis.[127] Perhaps the two most commonly utilised of these catalysts are referred to as the Grubbs first generation **419** and Grubbs second generation **420** metathesis catalysts.

Stable to air, effective in catalytic quantities and now widely commercially available, these compounds have become the reagent of choice for metathesis reactions. The affect that the metathesis reaction has had on the organic chemist has been profound. Indeed, when the Knight group recently required a series of symmetrical, α, β-unsaturated esters **423** for a study into the synthesis of recoverable ligands for Sharpless asymmetric epoxidation, metathesis proved to be an invaluable tool (Scheme 183).[128]



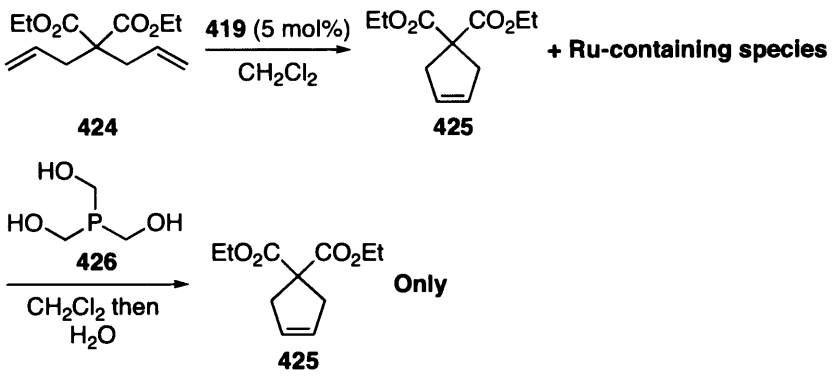
Scheme 183

Successfully delivering the desired olefins **423** in greater than 90% yield and, in contrast to various Wittig olefinations, entirely as the (*E*,*E*)-isomers, the reaction did nonetheless suffer a distinct limitation. Analysis of the product by proton and ^{13}C NMR indicated it to be extremely pure (containing greater than 95% of the desired organic compound); however, the product contained significant amounts of a highly coloured contaminant, known to result from the Ru catalyst.[129] Anxious to ensure that the olefin product was free from contaminants that might interfere with subsequent reactions, the group consulted the literature and found this to be a common problem.

Previous work

Acknowledging the significant problem posed by the presence of the ruthenium in products resulting from metathesis reactions, in 1999 Grubbs published a method for its removal.[130] Grubbs found that, following a ring closing metathesis (RCM) reaction of a diethyl malonate

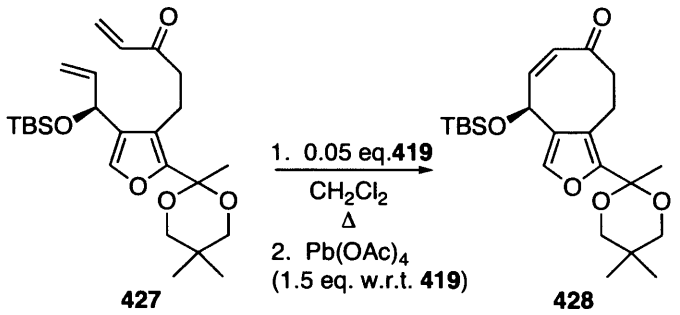
derived diene **424**, treatment of the resulting organic solution with tris(hydroxymethyl)phosphine **426**, yielding a Ru-phosphine complex that was sufficiently water-soluble to be removed upon aqueous work-up (Scheme 184).



Scheme 184

The best results were obtained when the crude reaction mixture was treated with *eighty six* equivalents of the phosphine **426** (with respect to the catalyst) and, either following or instead of an aqueous work-up, triethylamine and silica gel were added prior to filtration. Analysis of the Ru content of the product by inductively coupled plasma mass spectrometry (ICPMS) showed only 1.03 ±0.04 μg/5 mg of product, equivalent to 206.0 ±8.0 parts per million (ppm).[131] Whilst this treatment no doubt delivers an impressive level of Ru removal, it does suffer from the need for the addition of a large amount of a toxic and expensive reagent to the reaction mixture, rendering the method unacceptable to those wishing to utilise Ru catalysts in a large-scale industrial process.[132] It is also clear that in this case, cost and waste disposal issues would also arise.

An alternative process was developed by Paquette who, in 2000, reported encountering post-metathesis product contamination during a set of investigations into natural product synthesis.[133] Rather than attempting removal of the Ru by complexation with a polar ligand, Paquette decided to use oxidation of the Ru by-products to a more polar Ru compound that could be removed by silica gel chromatography. In either Grubbs 1st **419** or 2nd **420** catalysts, Ru is present as Ru(II); since the catalyst undergoes no change in oxidation state during the metathesis reaction, it is presumably in this oxidation state when it is present as any catalyst-based impurities. Paquette found that after performing a ring closing metathesis on the furan based diene **427**, the crude reaction mixture could be treated by stirring overnight with an excess (1.5 equivalents with respect to the catalyst) of lead tetra-acetate and then filtered through a pad of silica gel to give the colourless product **428** in 60% yield (Scheme 185).



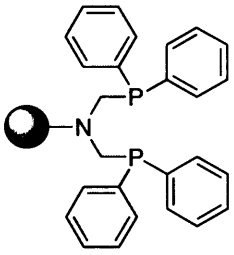
Scheme 185

ICPMS analysis showed that the process achieved excellent levels of Ru removal, down to 310.0 ±40.0 ppm. Crucially, the amount of Pb present in the sample was negligible, 1.0 ±4.0 ppm. Over a diverse set of examples, the process delivered similar Ru and Pb levels with overall yields of product ranging from quantitative to a less impressive 17%, although this can reasonably be attributed to the varying substrate complexity. Despite good yields and low levels of Ru and Pb, this process again suffers from the need for the addition to the reaction mixture of a further reagent that although readily available and relatively inexpensive, is highly toxic and would certainly pose problems on a large-scale. The oxidation is also relatively slow making it unattractive for an industrial process.[132]

In 2001, Georg reported a variation on Grubbs' addition of phosphine ligands to assist Ru removal.[129] After carrying out a representative RCM reaction on the malonate-derived diene **424**, under the conditions described by Grubbs (Scheme 184), the crude reaction mixture was treated with either triphenylphosphine oxide or dimethyl sulphoxide (DMSO), prior to silica gel chromatography. Either fifty equivalents of triphenylphosphine oxide or one hundred equivalents of DMSO (relative to the catalyst) were added to the crude reaction mixture. Subsequent silica gel chromatography returned product containing 240.0 ±2.0 and 268.0 ±4.0 ppm Ru respectively. It is worth noting that Georg describes the purification process as 'chromatography' rather than as a filtration, indicating that some level of processing is required to ensure complete removal of the additives. Clearly the drawback in this case is the requirement for a relatively huge amount of triphenylphosphine, the removal of which doesn't appear in any sense trivial. DMSO is also deeply unattractive as an additive, especially on a large scale.

The use of scavenger resins in the removal of reaction by-products has been a pervasive influence on the way reaction purification is approached both in the laboratory setting and industrially. The use of scavenger resins in metal removal has been a heavily explored application.

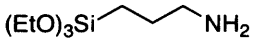
In 2004, Breinbauer reported the use of the widely available, solid supported phosphine **429** as a means for the removal of post-metathesis Ru by-products.



429

Building on the work of Georg and Grubbs and using the same representative metathesis reaction (Scheme 184), Breinbauer found that the addition to the crude reaction mixture of twenty equivalents, relative to the catalyst, of the solid supported phosphine **429**, followed by filtration through a plug of silica returned the organic product in near quantitative yield.[134] Analysis of the Ru content in the product by ICPMS showed it to contain 2400 ppm of Ru, representing 90% removal of the Ru content of the added catalyst. The decolourisation of the reaction product was accompanied by the solid-supported resin adopting a greenish-brown colour – suggesting uptake of the highly coloured Ru by-products. Addition of decolourising charcoal to the mixture at the same time as the resin had the effect of mildly increasing the level of Ru removal, although to the detriment of the product yield. Interestingly, the group also reported that a simple filtration through silica, without further measures, had little effect on the Ru content of the product, achieving only 4% removal and supporting the observation of the Knight group and many others that simple silica gel chromatography has little effect on the levels of highly-coloured Ru based contaminants.

The application of solid-supported scavengers to the removal of post-metathesis Ru was investigated further by Crudden and co-workers who, in 2006, published a series of functionalised silicates as agents for complexing of Ru.[135] The most successful of these was found to be the amino-propyltriethoxy silane **430**, immobilised on either a SiO_2 or SBA-15 solid-support.



430

Although these agents showed spectacular levels of Ru removal when applied to high concentration solutions of various Ru salts, their efficacy when applied to solutions of metathesis products was significantly diminished. The most promising results were obtained when an excess of the SiO_2-**430** scavenger was added to the product of the standard RCM reaction utilised by Grubbs (Scheme 184) and stirred for one hour prior to filtration. Under these, conditions the group were able to achieve 85% removal of Ru, reducing the level of Ru in the sample to 35 ppm.[136] The level of Ru removal was directly proportional to the initial

concentration of Ru and greater levels of Ru removal were observed when initial Ru levels were high. It was also found that a second application of the scavenger resulted in further decreased Ru levels, although this is likely to hold true for most if not all of the removal processes so far developed.

During the preparation of this thesis, several advances have been made in the area of post-metathesis Ru removal. Grubbs had reported the development of a novel PEG-supported metathesis catalyst, that can be efficiently separated from the reaction product by an aqueous extraction.[137] Furthermore, Diver has reported that the addition of a polar isocyanate to post-metathesis reaction mixtures leads to the formation of an inactive Ru-isocyanate complex, that can be removed from the reaction mixture through aqueous extraction.[138]

Whilst all of the above-mentioned methods make significant contributions to the problem of Ru removal from metathesis products they nonetheless all suffer from one or more of the following limitations:

- They require the addition of stoichiometric or greater (often far greater) amounts of an additional reagent.
- In some cases this reagent is in itself an unpleasant substance, *e.g.* $Pb(OAc)_4$.
- The need for the extra reagent generates extra cost in the process.
- Removal of the additive requires some form of chromatography.
- The process fails to achieve levels of Ru below those that are permissible in many industrial products, such as pharmaceuticals.

Permissible Ru content

The European Agency for the Evaluation of Medical Products (EMEA) enforces tough regulations on the content and purity of pharmaceuticals dispensed within the European Union.[139] The agency has placed stringent limits on the levels of metal contamination allowed in pharmaceutical products (Table 8).

Table 8: *EMEA limits on permissible metal content in pharmaceutical products.*

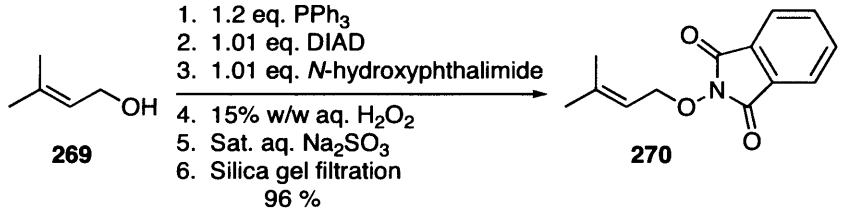
Elements	[Oral] limit (ppm)	[Parenteral] limit (ppm)
Pt, Pd, Ir, Rh, Ru, Os	5 (group)	0.5 (group)
Mo, V, Ni, Cr	10	1.0
Cu, Mn	15	1.5
Zn, Fe	20	2.0

If two or more elements derived from metal catalysts are present, the total oral concentration limit should not exceed 20 ppm and total parenteral concentration 2.0 ppm. Ppm by mass is defined as $mgkg^{-1}$.

For a purification process to have significant industrial potential it must be clean, cheap, safe and most importantly, it must bring the levels of contaminant in the sample down to those allowed under the relevant regulations. Of the various removal procedures discussed thus far, the scavenger resin **430** reported by Crudden appears to come closest to achieving this aim.

Purification of Mitsunobu products

During a study into the development of recoverable ligands for Sharpless asymmetric epoxidation, Morgan found, somewhat serendipitously, that vigorously stirring a solution of the crude reaction mixture under air, for an extended period of time, prior to silica gel chromatography significantly reduced the level of highly coloured catalyst by-products contained in the product.[128] It was postulated that the exposure of the solution to atmospheric oxygen had resulted in oxidation of the Ru residue. This tallied with the observation of Paquette that such by-products could be oxidised to more polar derivatives that were no longer mobile on silica gel.[133] Around this time we were in the final stages of developing the method for the purification of reaction products arising from the Mitsunobu reaction (Scheme 181).



Scheme 181

As discussed in Chapter Five of this thesis, the procedure proved highly effective and routinely delivered Mitsunobu products in good yield and with a high degree of purity.[50] It seemed to be a logical progression of this work to consider whether the use of hydrogen peroxide as a selective oxidant may find applications in the purification of products arising from other procedures. The removal of post-metathesis Ru seemed an attractive candidate.

Oxidation of ruthenium

There are two commonly occurring oxides of Ru that could reasonably be expected to result from oxidation of the Ru(II)-containing Grubbs Catalysts. Ruthenium(IV) oxide, RuO_2, also known as ruthenium dioxide is a blue-black, high melting point solid that has little effect as an oxidant on organic compounds. Ruthenium(VIII) tetraoxide is a yellow crystalline solid that is volatile at room temperature and is an extremely powerful oxidant of organic compounds.[140] Ruthenium tetraoxide would clearly be an unfavourable product to form in the crude reaction solution since it would have the potential to oxidise the reaction product, however, the conditions required for the formation of Ru in this oxidation state are harsh, with the oxidation

strength of hydrogen peroxide probably being insufficient. Given this, Ruthenium(IV) oxide seemed the more likely product to arise from any oxidation of Ruthenium(II) by hydrogen peroxide.

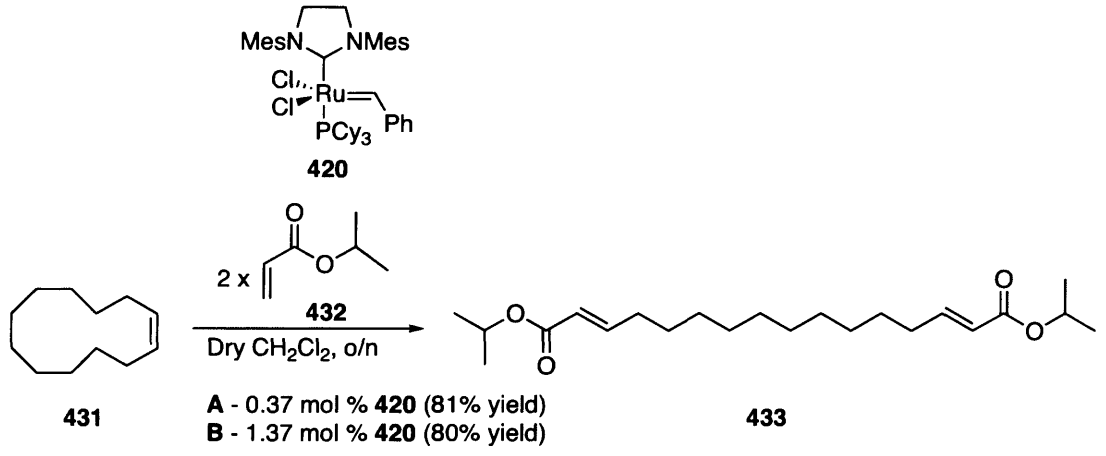
Results and discussion

Removal of Grubbs 2nd generation catalyst

In order to investigate the applicability of the modified Mitsunobu work-up procedure to the removal of ruthenium, a series of representative metathesis reactions were conducted. The application of the Grubbs 2nd generation catalyst **420** to the synthesis of a series of symmetrical, long-chain, α,β-unsaturated esters had been the driving force behind the desire to investigate the process of Ru removal from reaction products and thus seemed ideal candidates for trial metathesis purifications. Specifically, it was decided to perform a ring-opening metathesis of cyclodecene **431** followed by cross-metathesis with *iso*-propyl acrylate **432** to yield the long-chain ester **433**, under the catalytic effect of:

A – A low loading Grubbs second generation catalyst **420** (0.37 mol%)

B – A high loading of the catalyst (1.37 mol%)



Scheme 186

Our experience with metathesis reactions had indicated that Grubbs 2nd generation catalyst **420** was highly effective in performing these kinds of transformations and that 0.37 mol% was the minimum amount required to achieve complete conversion. We were nonetheless aware that more complicated metathesis reactions often require larger amounts of catalyst and so considered it prudent to also conduct the reaction with a higher loading of catalyst, 1.37 mol%. Monitoring the reaction by tlc indicated that, after heating at reflux overnight, the starting materials had been completely consumed leaving a single, highly mobile organic compound. At this point we applied the 'Mitsunobu' work-up procedure.

When conducting the procedure on Mitsunobu reaction products, it was thought prudent to conduct an initial filtration through a plug of silica, in order to remove as much as possible of

the highly polar contaminants, prior to exposing the mixture to the oxidant. In the case of the metathesis product, however, previous experience had shown that silica gel chromatography of the crude reaction mixture had little effect on the levels of contaminants present. Given this, it was decided to omit this step and proceed directly to the peroxide oxidation. The reaction flask containing the crude reaction mixture was opened to air and a large excess of hydrogen peroxide (5000 equivalents relative to the amount of catalyst used) was added as a 15% w/w aqueous solution (created by dilution of a commercially available 30% w/w solution, obtained from Sigma Aldrich). Our intention had initially been to transfer this bi-phasic mixture to a separating funnel so that it could be thoroughly mixed. However, upon addition of the peroxide solution, the aqueous layer began to effervesce in a vigorous and mildly exothermic manner. We instead added a magnetic stirrer to the biphasic mixture and stirred this at maximum speed until the effervescence subsided (around 15 minutes). Suspecting the release of gas had been a result of decomposition of the peroxide, we performed a starch-iodide test on the aqueous layer and indeed found it to contain no peroxide. The organic layer was observed to contain a significant amount of a blue-black precipitate leading us to speculate that the Ru(II) content of the catalyst had undergone oxidation to ruthenium(IV) oxide. Upon consulting the literature we found that the decomposition of aqueous hydrogen peroxide by ruthenium (IV) oxide had been previously reported. In 1999, Prakash and co-workers reported that an alkali solution of hydrogen peroxide could be decomposed to water and oxygen using a catalytic amount of RuO_2 (Scheme 187).[141]

$$HOO^- \xrightarrow{RuO_2} HO^- + {}^1/_2\, O_2$$

Scheme 187

Although Prakash conducted no studies on solutions of peroxide at neutral pH, these findings, coupled with the observation of the colour of precipitate present after oxidation, led to the speculation that the ruthenium content of the catalyst was being oxidised to ruthenium(IV) oxide and that this is then in turn decomposing the excess peroxide to oxygen and water. This was an entirely unexpected side-reaction, although, nevertheless, an extremely welcome one. The autocatalytic quenching of the peroxide by the oxidation product eliminated the need for neutralisation of the excess, thereby eliminating a time-consuming step in the process. Instead, upon completion of the peroxide decomposition (which could easily be assessed by the level of effervescence), the organic layer was separated, the aqueous layers back extracted with fresh dichloromethane and the combined organic solutions dried over magnesium sulphate. This solution was then passed through a plug of silica (eluting with copious dichloromethane) and the solvent removed to give the product as a colourless oil. The plug of silica used to filter the organic solution had become noticeably blackened on the upper surface and, although no tests

were undertaken in order to confirm this, it seems probable that this was due to the removal of the ruthenium(IV) oxide from the solution onto the silica. This plug of silica was disposed of with care, due to the suspected toxicity of ruthenium oxides. It is worth noting that the silica used in the filtration essentially represents a highly concentrated source of ruthenium. Given that ruthenium is a precious metal that is becoming ever more scarce, it may be desirable, especially on an industrial scale, to examine means for the recovery of the ruthenium from this highly enriched source. This should be a simple enough task.

The organic product obtained from each work-up procedure was analysed by NMR, IR and mass spectrometry and found to contain only the desired ester **433**, with no visible sign of any oxidation having occurred. This corresponds to the investigations into the purification of Mitsunobu products (Chapter five, pp 97-113), where no oxidation of organic functional groups was observed under these work-up conditions. There is of course a possibility that the presence of ruthenium in the sample may alter the reactivity of the peroxide towards organic functionality. However, having observed no effect on a substrate that was assumed to be highly vulnerable to such oxidation (*via* Michael addition) we felt confident that this would not prove to be the case. It was also encouraging to note that not only were no catalyst-derived organic contaminants detected in the proton NMR spectrum of the product, suggesting that as a result of the oxidation the ligands had been converted to derivatives that were sufficiently polar to be removed in the work up procedure. Given our previous experience, we thought it reasonable to postulate that the phosphine ligand had been oxidised to the corresponding tricyclohexylphosphine oxide. The carbene ligand could also be reasonably supposed to have been oxidised by the hydrogen peroxide solution, presumably to a polar cyclic urea. Additionally, we were encouraged to note that the colourless product obtained was in stark contrast to the blue-black, untreated products obtained previously.

The analysis of the ruthenium content of the products was conducted by digesting a known amount of product in aqua regia for 48 h and then diluting to a known volume with distilled water. The ruthenium content was then analysed using inductively coupled plasma mass spectrometry (ICMPS), a background level from a blank sample deducted and the amount of ruthenium in the reaction product calculated in parts per million (ppm). The ruthenium levels present in metathesis products formed with a high loading of catalyst (1.37 mol%) and a low loading of catalyst (0.37 mol%) were analysed, along with a sample produced with a high loading of catalyst that had been treated by the work-up procedure twice. These results were compared to a those obtained for a sample that had been stirred vigorously under air for 48 h prior to standard silica gel chromatography. For each sample, a percentage of ruthenium removal achieved by the process was calculated by comparing the level of ruthenium in the

sample to that in a sample taken from the respective pre-treatment reaction product that had been reduced under vacuum, weighed accurately and analysed in the same manner (Table 9).

Table 9: *Analysis of ruthenium levels in metathesis products (Scheme 186).*

Entry	Catalyst (mol%)	Treatment	[Ru] (ppm)	% Removal
1	2nd Gen. (0.37)	Air	132.00	85.76
2	2nd Gen. (0.37)	Peroxide	1.33	99.95
3	2nd Gen. (0.37)	Peroxide	2.05	99.55
4	2nd Gen. (1.37)	Peroxide	12.46	99.28
5	2nd Gen. (1.37)	Peroxide (2 treatments)[a]	2.53	99.88

a – In this case the product was subjected to the work-up procedure, isolated and then subjected to a second, identical work-up procedure.

The results obtained were spectacular, especially when considered against the far poorer levels of ruthenium removal achieved by previously reported processes. When a sample synthesised using a low loading of Grubbs second generation catalyst was treated under the peroxide oxidation (Table 9, Entry 2), we were delighted to find that virtually all of the ruthenium present in the untreated sample had been removed. This result was verified by a repeat reaction (Table 9, Entry 3), which delivered virtually identical results.

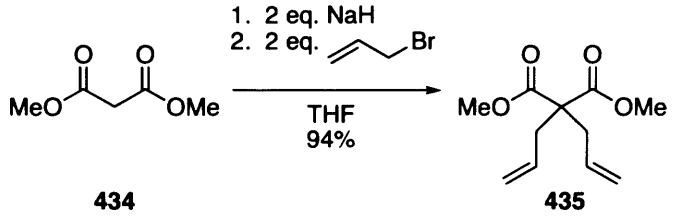
These preliminary sets of data confirmed the original hypothesis – that hydrogen peroxide could be used to selectively oxidise the ruthenium content of Grubbs 2nd generation catalyst to a polar derivative that could be removed by filtration through silica gel. Particularly encouraging was that this unoptimised study had managed to reduce ruthenium levels in the product to below those required by EMEA guidelines (5 ppm). Upon widening the study to examine reactions employing higher loadings of catalyst, the procedure again achieved virtually quantitative removal of ruthenium. In such cases the levels of ruthenium in the product were found to be slightly above those permissible by EMEA guidelines but it was found that by repeating the process on the same sample the ruthenium content could be reduced further still, to within acceptable levels (Entry 5, Table 9). The results obtained during this brief study were highly encouraging. The process was simple to perform, had no undesired effect on the reaction product and achieved levels of ruthenium removal within the requirements of the pharmaceutical industry.

Whilst we had employed Grubbs 2nd generation catalyst **420** in the metathesis reaction (Scheme 186, pp 122) due to its well-documented effectiveness in cross-metathesis reactions of this kind we were, however, conscious of the fact that comparison of these levels of ruthenium removal to those achieved by other groups were perhaps unfair, given that these processes focused on

removal of Grubbs 1st generation catalyst **419** rather than the second generation catalyst **420**, favoured by ourselves.

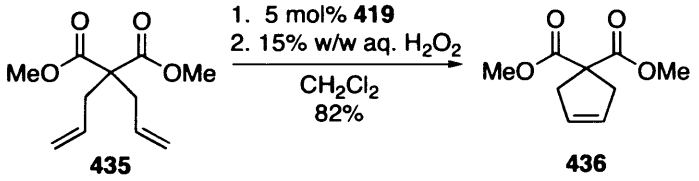
Removal of Grubbs 1st generation catalyst

Whilst the use of Grubbs 2nd generation catalyst **420** has largely superseded that of Grubbs 1st generation **419** in cross-metathesis reactions, it is still a popular and highly effective agent for performing ring closing metathesis (RCM) reactions.[142] A suitable substrate for such a procedure was synthesised by the double alkylation of dimethylmalonate to give the diene **435**, in excellent yield (Scheme 188).



Scheme 188

This substrate **435** was then subjected to the standard set of RCM conditions utilised previously by Grubbs, using a significantly higher loading of catalyst (5 mol%) than had been employed in the reactions using Grubbs 2nd generation catalyst (Scheme 189).[130]



Scheme 189

The preparation of cyclopentenes in this manner has routinely been used as a model reaction for investigating alternative metathesis conditions or reagents. The reaction was monitored by tlc and, upon completion, 5000 equivalents of hydrogen peroxide were added as a 15% w/w aqueous solution. The biphasic mixture was then stirred at maximum speed. As before, the solution effervesced vigorously and was left to stir until this subsided (around 30 minutes). At this time, the aqueous portion of the solution was again tested for peroxide content and was found to contain none. The organic portion was then separated, the aqueous portion extracted and the combined organic extracts dried over magnesium sulphate, as described previously. Filtration through a pad of silica, eluting with copious dichloromethane, followed by removal of the solvent gave a colourless oil. All spectroscopic analysis indicated this to be the desired cyclic alkene **436** and showed no other organic compound to be present. As before the silica used for the filtration process had adopted a blue-black colouration on the surface, inferring the removal of ruthenium(IV) oxide from the solution.

Finally, the ruthenium content of the sample was analysed by ICPMS (Table 10).

Table 10: *Analysis of ruthenium level in metathesis product (Scheme 189).*

Entry	Catalyst loading (mol%)	Treatment	[Ru] (ppm)	% Removal
1	1st Gen. (5.00)	Peroxide	2116	84.89

Clearly these initial results are far less impressive than those obtained for the removal of the 2nd generation catalyst **420**, however, in compassion to those achieved by others working in the field, however, they are certainly comparable and it is worth noting, that these were achieved using a far more amenable process. Unfortunately, due to difficulties in obtaining ICPMS measurements, no further studies were conducted. It seems likely, however, that were a second treatment to be applied to the sample (Entry 1, Table 10) then a further reduction in the ruthenium content could be achieved. In the studies into the removal of Grubbs 2nd generation catalyst **420**, a sample exposed to a second treatment process (Table 9,Entry 5) had shown a *ca* 5 x reduction in ruthenium content. Were such a result to be repeated here it would clearly have a dramatic effect on the ruthenium content of the product. Regardless, it seemed certain that optimisation of the process would greatly improve its efficacy.

Summary and future work

By modifying the process developed for the purification of Mitsunobu products, we have been able to develop a means for the oxidation and removal of catalyst-derived contaminants in metathesis products. The process is simple to perform and utilises a cheap and readily available oxidant, H_2O_2. In each case, the product is returned with only minimal reduction in yield compared to untreated samples. Analysis of the ruthenium content of the products shows that in the case of removal of Grubbs 2nd generation catalyst, ruthenium levels can be reduced to within acceptable limits, with respect to pharmaceutical standards. In the case of Grubbs 1st generation catalyst, the process is less effective, however, we are confident that an optimisation of the process would yield significantly improved results.

Although the results obtained were extremely encouraging, it must be stressed that this process is in a very early stage of development. There is also clear potential to extend the process and investigate the removal of a broad range of other transition metal catalysts.

EXPERIMENTAL

Experimental

General Details

All non-aqueous reactions were, unless otherwise stated, conducted using oven or flame-dried glassware and under an atmosphere of dry nitrogen. Reactions conducted at "-78°C" were cooled using an acetone-solid carbon dioxide bath. Reactions conducted at "0°C" were cooled using an ice-water bath. Heated reactions were conducted in a stirred oil bath heated on a hotplate. Unless otherwise stated, reactions were stirred magnetically. Dry tetrahydrofuran was obtained by fresh distillation from sodium wire and a benzophenone indicator. Dry dichloromethane was obtained by fresh distillation from calcium hydride. All other dry solvents were obtained commercially from Fisher Scientific Ltd.

Silica gel chromatography and filtration was performed using Matrex Silica (35-70 μm). All reactions were monitored by tlc, using Merck silica gel 60 F254 pre-coated aluminium-backed plates and were visualised using ultraviolet light, potassium permanganate or ammonium molybdate. All melting points (mp °C) were determined on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 1600 series Fourier Transform Infrared Spectrometer, as nujol mulls on sodium chloride plates [nujol], as liquid films on sodium chloride plates [film] or as a solution in dichloromethane [DCM].

Unless otherwise stated, NMR spectra were recorded on a Bruker DPX 400 instrument with proton (^{1}H) NMR spectra recorded at 400 MHz and ^{13}C spectra recorded at 100 MHz. Proton (^{1}H) NMR spectra recorded at 500 MHz and ^{13}C spectra recorded at 125 MHz were obtained using a Bruker DRX500 instrument. Unless otherwise stated, spectra were obtained from dilute solutions in deuteriochloroform and at 298 K. Abbreviations used for the multiplicities are: singlet (s), doublet (d), triplet (t), quartet (q), pentet (pent.), septet (sept.), unresolved multiplet (m) or combinations thereof. Apparent (app.) refers to overlapping peaks appearing to display a given multiplicity. Chemical shifts are reported relative to residual, undeuterated solvent (*e.g.* residual chloroform, 7.27 ppm in proton NMR). Mass spectra were recorded on a Fisons VG Platform II Mass Spectrometer using atmosphere pressure chemical ionisation [APcI]. Accurate high resolution mass spectral data were either obtained at Cardiff University, using a Micromass Q-ToF Micromass Mass Spectrometer, Swansea University, using various instruments, or at the University of Nottingham using a Waters 2795 Micromass LCT platform. Microanalytical data were obtained on a Perkin Elmer Elemental Analyser and are quoted as atom percentages. Unless otherwise stated, all compounds in organic solution were dried over anhydrous magnesium sulphate. "Evaporated" refers to solvent removal using a Buchi rotary evaporator with water pump vacuum and water bath at 25°C.

General methods

General method A – Chromatography-free Mitsunobu reaction

To a solution of triphenylphosphine (1.2 equivalents) in dry tetrahydrofuran (10 ml/mmol of alcohol) at 0°C was added diisopropyl azodicarboxylate (1.01 equivalents) *via* syringe. The resulting, bright orange solution was stirred for 15 minutes during which time it became colourless and opaque. The alcohol (1 equivalent) was added (dropwise, *via* syringe in the case of liquids or in small portions in the case of solids) and the resulting solution stirred for 20 minutes. The nucleophile (*e.g.* *N*-hydroxyphthalimide) was then added (dropwise, *via* syringe in the case of liquids or in small portions in the case of solids) and the solution allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and replaced with a minimum amount of dichloromethane. This solution was passed through a plug of silica gel (~ 10 g/mmol of product), eluting with dichloromethane until such time as the brightly coloured orange band became mobile. The filtrate was concentrated, *in vacuo*, to a volume of *ca.* 100 ml/mmol, before being transferred to a separating funnel. Water (50 ml/mmol of product) and 30% w/w hydrogen peroxide (50 ml/mmol of product) were added and the biphasic mixture vigorously shaken, with frequent release of pressure. The layers were separated and the aqueous layer replaced with saturated aqueous sodium sulphite (100 ml/mmol of product) and mixed as before. The separated organic solution was dried and filtered through a fresh plug of silica gel (~ 10 g/mmol of product), eluting with copious dichloromethane. Evaporation of the filtrate left the product, which generally required no further purification.

General method B – Phthalimide deprotection

The phthalimide (1 equivalent) was taken up in ether (10 ml/mmol of phthalimide) and 40% w/w aqueous methylamine (2.1 equivalents) added in one portion. The resulting solution was stirred for 4 h, over which time a white precipitate formed, then cooled in an ice-water bath to 0°C and filtered under vacuum. The solid residue was washed with ice-cold ether and the combined organic filtrates dried (over sodium sulphate), filtered and evaporated to give the hydroxylamine, which was typically used immediately without further purification.

General method C – A modified tosylation of hydroxylamines

The crude hydroxylamine (1 equivalent) was dissolved in dry dichloromethane (20 ml/mmol of hydroxylamine) and the resulting solution stirred at -78°C. Pyridine (1.01 equivalents) and DMAP (0.005 g) were added and the resulting solution stirred for 5 minutes then *p*-toluenesulphonyl chloride (1 equivalent) was added in one portion and the resulting mixture stirred overnight without any further addition of coolant. The reaction was quenched by the

addition of water (an equal volume to that of the reaction mixture) and the products extracted into dichloromethane (3 x volume of reaction mixture). The combined organic solutions were washed with saturated aqueous copper sulphate (an equal volume to that of the reaction mixture), saturated aqueous sodium hydrogen carbonate (an equal volume to that of the reaction mixture) and water (3 x volume of the reaction mixture), dried, filtered and evaporated to leave the sulphonamide.

General method D – Addition of an alkyne to an aldehyde

The alkyne (1 equivalent) was dissolved in dry tetrahydrofuran (10 ml/mmol of alkyne) and stirred at -78°C. n-Butyl lithium (1.01 equivalents of a 2.5 M solution in hexanes) was added, dropwise *via* syringe and the resulting solution stirred for 0.5 h at this temperature. The aldehyde (1 equivalent) was taken up in dry tetrahydrofuran (5 ml/mmol of aldehyde) and stirred at -78°C. The solution of metallated alkyne was transferred to the aldehyde solution and the resulting solution allowed to warm to room temperature over 4 h, then quenched by the addition of saturated, aqueous ammonium chloride (~ equal volume to the reaction mixture) and extracted with dichloromethane (3 x volume of the reaction mixture). The combined organic solutions were washed with water (3 x volume of the combined extracts), then dried, filtered and evaporated to give the product, which was typically used without further purification.

General method E – Silver nitrate-catalysed cyclisation

The hydroxylamine (1 equivalent) was dissolved in dry dichloromethane and the reaction vessel shrouded in aluminium foil so as to exclude light. 10% w/w Silver nitrate on silica (0.05 equivalents of a 10% w/w dispersion on silica gel; Aldrich) was added in one portion and the resulting mixture stirred and monitored by tlc until reaching completion. The mixture was passed through a plug of celite, eluting with copious dichloromethane, and the solvent evaporated *in vacuo* to give the product.

General method F – Synthesis of hydroxylamine-derived amides

The crude hydroxylamine (1 equivalent; General Method **B**) was dissolved in dry dichloromethane (20 ml/mmol of hydroxylamine) and the solution stirred at 0°C. Pyridine (1.01 equivalents) and DMAP (0.005 g) were added and the resulting solution stirred for 5 minutes. The protecting agent (*e.g.* an acid chloride, 1.5 equivalents) was added in one portion and the reaction allowed to warm to room temperature over 4 h, then quenched by the addition of water (an equal volume to that of the reaction mixture) and extracted into dichloromethane (3 x volume of the reaction mixture). The combined organic extracts were washed with saturated aqueous copper sulphate (an equal volume to that of the reaction mixture) and water (3 x

volume of the reaction mixture). The solvent was evaporated and the crude residue taken up in methanol (equal volume to dichloromethane used previously) and 2M aqueous NaOH (0.5 ml/mmol product) added. The reaction was monitored by tlc and, upon completion, quenched by the addition of water (equal amount to that of reaction mixture), extracted into dichloromethane (3 x volume of the reaction mixture), washed with saturated aqueous sodium hydrogen carbonate (2 x volume of the reaction mixture) and water (3 x volume of the reaction mixture). The organic solution was dried, filtered and evaporated to give the amide, which routinely did not require further purification.

General method G – Triflic acid-catalysed cyclisations

The sulphonamide (1 equivalent; General Method **C**) was dissolved in dry dichloromethane (10 ml/mmol of sulphonamide) and stirred at 0°C. Trifluoromethanesulphonic acid (0.5 equivalents) was added, dropwise, as a 0.695 M solution in dry dichloromethane (preformed by the addition of 10 ml of neat triflic acid to 90 ml of dry dichloromethane and stored under dry nitrogen). The resulting solution was stirred and the reaction monitored by tlc. Upon completion, the reaction was quenched by the addition of ice-cold saturated aqueous sodium hydrogen carbonate (an equal volume to that of the reaction mixture), the products extracted into dichloromethane (3 x volume of the reaction mixture) and the combined organic solutions washed with water (3 x volume of the reaction mixture), dried, filtered and evaporated to give the product.

Chapter 2 compounds

tert-Butyl azidoformate 104 [39]

103 104

CAUTION: EXPLOSIVE AZIDE

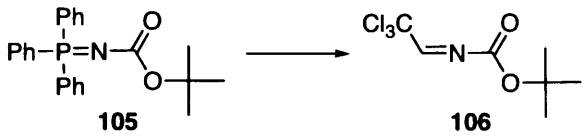
tert-Butyl carbazate **103** (110.00 g, 0.756 mol), acetic acid (86 ml) and water (122 ml) were stirred together at 0°C. Solid sodium nitrite (57.43 g, 0.83 mol) was added, gradually over 3 h, ensuring the reaction mixture was maintained between 10-15°C. Following the addition the resulting mixture was allowed to stand in an ice bath for 0.5 h prior to the addition of water (120 ml). The resulting mixture was extracted with ether (4 x 150 ml) and the combined organic solutions washed with water (2 x 150 ml) and 1 M sodium hydrogen carbonate (4 x 150 ml), until no longer acidic. The organic solution was then filtered and used directly in the next step without further purification.

tert-Butyl triphenylphosphoranylidenecarbamate 105 [39]

104 105

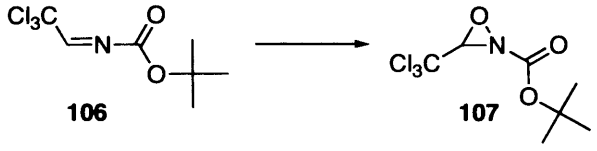
The foregoing solution of *tert*-butyl azidoformate **104** (~108 g, ~0.756 mol) in ether (~560 ml) was stirred at room temperature and a solution of triphenylphosphine (155.7 g, 0.59 mol) in ether (430 ml) added dropwise, over 3 h (N_2 liberated). The resulting mixture was allowed to stand overnight over which time a white precipitate was formed. The precipitate was collected by filtration, dissolved in a minimum of hot ethyl acetate and the solution allowed to cool over 1 h. The solid was again collected by filtration. The mother liquors were concentrated *in vacuo* and the residue recrystallised again from hot ethyl acetate. The combined solid fractions gave the *title compound* **105** (166 g, 60% over 2 steps), as a colourless solid. The data obtained were in accordance with those previously reported in the literature[39] : mp 148-149°C [lit.[39] 148°C]; δ_H 1.37 (9H, s, ^{t}Bu-Me), 7.43-7.47 (6H, m, 6 x ArH), 7.50-7.54 (3H, m, 3 x ArH) and 7.70-7.74 (6H, m, 3 x 2 ArH); *m/z* [APcI] 378 (M^+ + H, 100%).

***tert*-Butyl 2,2,2-trichloroethylidenecarbamate 106** [39]



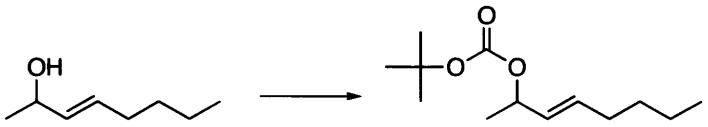
tert-Butyl triphenylphosphoranylidenecarbamate **105** (50 g, 0.137 mol) was dissolved in dry toluene (100ml). Freshly distilled anhydrous chloral (15.34 ml, 0.157 mol) was added *via* syringe and the mixture heated at reflux for 1 h, then cooled and evaporated to give a pale yellow residue. The residue was triturated with hexane (200 ml) and the resulting solution collected by filtration and evaporated to give the *title compound* **106** (31.9 g, 94%) as a colourless solid. The data obtained was in accordance with that previously reported in the literature[39] and showed: δ_H 1.50 (9H, s, ^{t}Bu-Me) and 8.00 (1H, s, CH).

***tert*-Butyl 3-trichloromethyl-2-oxaziridinecarboxylate 107** [39]



The foregoing *tert*-butyl trichloroethylidenecarbamate **106** (40.1 g, ~0.123 mmol) was dissolved in dry chloroform (400 ml) and the resulting solution stirred at 0°C. An ice-cold solution of potassium carbonate (61.92 g, 0.45 mol) in water (465 ml) was added followed by an ice-cold solution of Oxone® (77.4 g, 0.126 mmol) in water (775 ml). The resulting biphasic mixture was stirred vigorously for 1 h. The aqueous layer was separated, discarded and replaced with fresh potassium carbonate and Oxone® solutions. This procedure was performed a total of 8 times. The solution was separated and the organic layer washed with water (3 x 200 ml), dried over sodium sulphate and the solvent removed *in vacuo* in an ice-cold water bath. The crude product was then immediately purified by column chromatography (using dichloromethane as the eluent) to yield the *title compound* **107** as a colourless oil (18.0 g, 51% over 2 steps). All data obtained were in accordance with those previously reported in the literature[39] and showed: δ_H 1.53 (9H, s, ^{t}Bu-CH_3) and 4.95 (1H, s, 3-H); δ_C 27.8 (CH_3), 81.2 (CH), 87.2 (C), 93.7 (CCl_3) and 158.0 (CO).

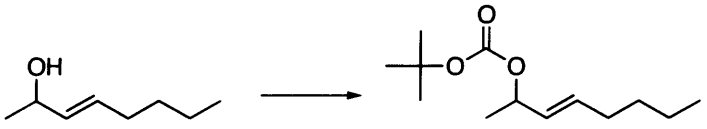
(*E*)-*tert*-Butyl-pent-3-en-2-yl carbonate 120



109 **120**

Oct-3-en-2-ol **109** (1.000 g, 7.797 mmol) was stirred in dry tetrahydrofuran (80 ml) at -78°C. Lithium *bis*-(trimethylsilyl)amide (3.40 ml, 8.577 mmol as a 2.5 M in hexanes) was added dropwise *via* syringe. The resulting mixture was stirred for 0.5 h prior to the dropwise addition of *oxaziridine* **107** (2.035 g, 7.797 mmol) as a solution in dry tetrahydrofuran (80 ml). The reaction mixture was stirred for 1h and then allowed to warm to room temperature over a further 2h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (160 ml) and the volatile solvents removed under reduced pressure. The resulting brown oil was dissolved into dichloromethane (100 ml) and the solution washed with saturated aqueous ammonium chloride (3 x 100 ml). The combined aqueous washings were extracted with dichloromethane (2 x 100 ml) and the combined organic solutions dried over sodium sulphate, filtered and evaporated to give the *title compound* **120** (1.391 g, 78%) as pale yellow oil characterised by: [Found: C, 65.76; H, 10.11; N, 0.36. $C_{13}H_{24}O_3$ requires C, 68.38; H, 10.59%]; ν_{max}/cm^{-1} [film] 1739, 1673 and 1457; δ_H 0.81 (3H, t, *J* 7.1, 8-CH_3), 1.32-1.17 (4H, m, 6- and 7-CH_2), 1.26 (3H, d, *J* 6.8, 1-CH_3), 1.41 (9H, s, Boc-CH_3), 1.98-1.93 (2H, m, 5-CH_2), 5.02 (1H, dq, *J* 7.0 and 6.8, 2-H), 5.39 (1H, ddt, *J* 15.4, 7.0 and 1.4, 3-H) and 5.65 (1H, dt, *J* 15.4 and 6.8, 4-H); δ_C 13.9 (CH_3), 20.5 (CH_3), 22.1 (CH_2), 27.8 (3 x CH_3), 31.0 (CH_2), 31.8 (CH_2), 74.4 (CH), 81.7 (C), 129.2 (CH) and 134.0 (CH).

(*E*)-*tert*-Butyl-pent-3-en-2-yl carbonate 120 (Alternative Synthesis)

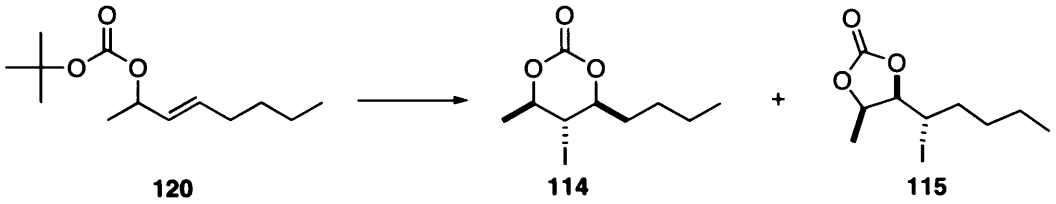


109 **120**

Oct-3-en-2-ol **109** (1.000 g, 7.797 mmol) was stirred in dry tetrahydrofuran (80 ml) at -78°C. n-Butyl lithium (3.40 ml, 8.577 mmol as a 2.5 M in hexanes) was added dropwise *via* syringe. The resulting mixture was stirred for 0.5 h prior to the dropwise addition of BOC-ON (1.920 g, 7.797 mmol) as a solution in dry tetrahydrofuran (80 ml). The reaction mixture was stirred for 1 h and then allowed to warm to room temperature over a further 2 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (160 ml) and the volatile solvents removed under reduced pressure. The resulting brown oil was dissolved in dichloromethane (100 ml) and the solution washed with saturated aqueous ammonium chloride (3 x 100 ml). The combined aqueous washings were extracted with dichloromethane (2 x 100

ml) and the combined organic solutions dried over sodium sulphate, filtered and evaporated to give the *title compound* **120** (1.599 g, 78%) as pale yellow oil. All data displayed were identical to those obtained for the foregoing sample.

(4*SR*,5*RS*,6*RS*)-4-Butyl-5-iodo-6-methyl-1,3-dioxan-2-one 114 and (4*RS*,5*RS*)-4-[(*SR*)-1-iodopentyl]-5-methyl-1,3-dioxolan-2-one 115

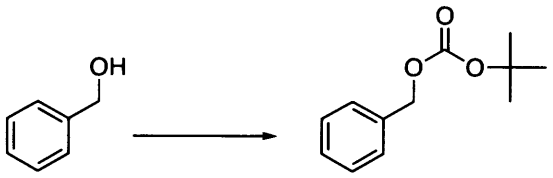


A solution of the foregoing carbonate **120** (0.100 g, 0.438 mmol) in dry dichloromethane (45 ml) was stirred at 0°C prior to the addition of potassium carbonate (0.182 g, 1.314 mmol) and iodine monobromide (0.815 g, 1.314 mmol). The resulting solution was stirred for 1 h, quenched by the addition of saturated aqueous sodium thiosulphate (45 ml) and extracted with dichloromethane (3 x 45 ml). The combined organic layers were washed with saturated aqueous sodium thiosulphate (45 ml) and water (2 x 45 ml) then dried, filtered and evaporated to give the a pale yellow solid, which was separated by chromatography (10-20% ethyl acetate/petrol) to yield two products:

(4SR,5RS,6RS)-4-Butyl-5-iodo-6-methyl-1,3-dioxan-2-one **114** (0.098 g, 75%) as a pale yellow solid showing: mp 71-72°C; ν_{max}/cm^{-1} [nujol] 1715, 1330, 1131 and 1080; δ_H 0.87 (3H, t, *J* 14.4, 4'-CH_3), 1.41-1.24 (4H, m, 2'- and 3'-CH_2), 1.58 (3H, d, *J* 6.2, CH_3), 1.75-1.66 (1H, m, 1'-H_a), 2.12-2.04 (1H, m, 1'-H_b), 3.72 (1H, app. t, *J* 10.6, 5-H), 4.47 (1H, ddd, *J* 10.6, 7.9 and 2.5, 4-H) and 4.57 (1H, dq, *J* 10.6 and 6.2, 6-H); δ_C 13.8 (CH_3), 20.9 (CH_3), 22.2 (CH_2), 25.5 (CH), 25.8 (CH_2), 33.5 (CH_2), 80.1 (CH), 83.4 (CH) and 148.5 (CO); *m/z* [APcI] 299 (M^+ + H, 100%) and 237 (30%); [Found M^+ + H: 299.0174. $C_9H_{16}IO_3$ requires *M*, 299.0144].

(4RS,5RS)-4-[(SR)-1-Iodopentyl]-5-methyl-1,3-dioxolan-2-one **115** (0.021 g, 16%) as a colourless solid showing: mp 75-76°C; ν_{max}/cm^{-1} [nujol] 1810, 1456 and 1382; δ_H 0.87 (3H, t, *J* 7.1, 5'-CH_3), 1.39-1.21 (6H, m, 2'-, 3'- and 4'-CH_2), 1.53 (3H, d, *J* 6.3, 5-CH_3), 1.74-1.64 (1H, m, 2'-H_a), 1.93-1.83 (1H, m, 2'H_b), 3.98 (1H, td, *J* 9.4 and 3.3, 1'-H), 4.20 (1H, dd, *J* 9.4 and 5.1, 4-H) and 4.54 (1H, qd, *J* 6.3 and 5.1, 5-H); δ_C 13.9 (CH_3), 21.0 (CH_3), 21.8 (CH_2), 30.9 (CH_2), 34.6 (CH_2), 35.6 (CH), 79.2 (CH), 84.5 (CH) and 153.6 (CO); *m/z* [APcI] 299 (M^+ + H, 100%) and 237 (80%); [Found M^+ + H: 299.0119. $C_9H_{16}IO_3$ requires *M*, 299.0114].

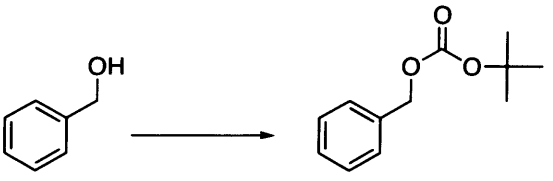
***tert*-Butyl benzyl carbonate 128** [143]



127 **128**

Benzyl alcohol **127** (1.000 g, 9.254 mmol) was stirred in dry tetrahydrofuran (90 ml) at -78°C. Lithium *bis*-(trimethylsilyl)amide (4.07 ml, 10.179 mmol as a 2.5 M in hexanes) was added dropwise *via* syringe. The resulting mixture was stirred for 0.5 h prior to the dropwise addition of oxaziridine **107** (2.415 g, 9.254 mmol) as a solution in dry tetrahydrofuran (90 ml). The reaction mixture was stirred for 1h and then allowed to warm to room temperature over a further 2h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (180 ml) and the volatile solvents removed under reduced pressure. The resulting brown oil was dissolved into dichloromethane (100 ml) and washed with saturated aqueous ammonium chloride (3 x 100 ml). The combined aqueous washings were extracted with dichloromethane (2 x 100 ml) and the combined organic layers dried over sodium sulphate, filtered and evaporated to give the *title compound* **128** (1.561 g, 81%) as pale yellow oil. All data obtained were in accordance with those reported in the literature[143] and showed: δ_H 1.50 (H, s, ^{t}Bu), 5.11 (2H, s, CH_2), 7.32-7.39 (5H, m, Ar-H); δ_C 28.3 (3 x ^{t}Bu-CH_3), 70.0 (CH_2), 82.6 (^{t}Bu-C), 128.6 (Ar-H), 128.8 (Ar-H), 129.0 (Ar-H), 135.6 (Ar-C) and 154.1 (CO).

***tert*-Butyl benzyl carbonate 128 (Alternative Synthesis)**

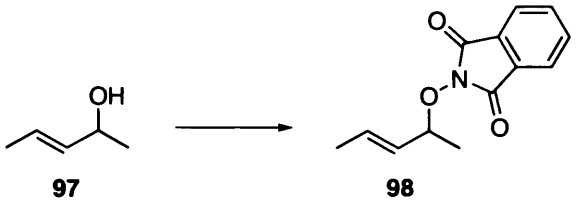


127 **128**

Benzyl alcohol **127** (1.000g, 9.247mmol) was taken up in dry tetrahydrofuran (90ml) and stirred at 0°C. n-Butyl lithium (3.74ml, 9.340mmol as a 2.5M solution in hexanes) was added, dropwise *via* syringe and the resulting solution stirred for 10 minutes, over which time it became orange in colour. BOC-ON (2.300g, 9.340mmol) was added as a solution in dry tetrahydrofuran (10ml) and the resulting solution stirred at room temperature for 4 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (100 ml) and the volatile solvents removed under reduced pressure. The resulting brown oil was dissolved into dichloromethane (100 ml) and washed with saturated aqueous ammonium chloride (3 x 100 ml). The combined aqueous washings were extracted with dichloromethane (2 x 100 ml) and the combined organic layers dried over sodium sulphate, filtered and evaporated to give the

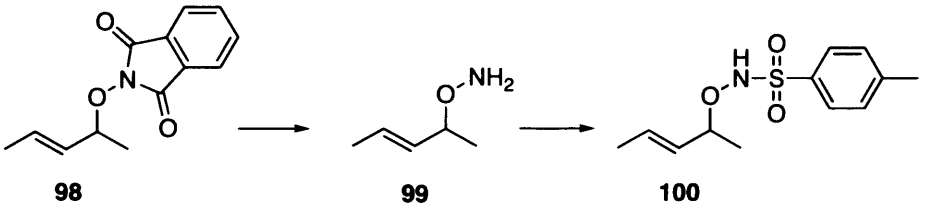
title compound **128** (1.924g, 99%) as a pale yellow oil. All data obtained were identical with those reported for the foregoing sample.

(*E*)-*N*-(Pent-3-en-2-yloxy)phthalimide 97 [41]



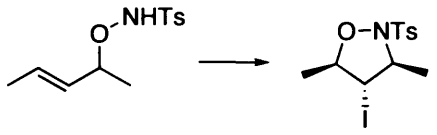
(*E*)-Pent-3-en-2-ol **97** (1.000 g, 11.610 mmol) was reacted with *N*-hydroxyphthalimide (1.913 g, 11.730 mmol) according to general method **A** to yield the *title compound* **98** (2.480 g, 92%) as a colourless solid. The data obtained were in accordance with those previously reported in the literature[41] : mp 61-62°C [lit.[41] mp 61.5-62.5°C]; δ_H 1.47 (3H, d, *J* 6.7, 1-CH_3), 1.61 (3H, d, *J* 5.1, 5-CH_3), 4.80 (1H, dq, *J* 8.0 and 6.7, 2-H), 5.55-5.75 (2H, m, 3- and 4-H), 7.76 (2H, dd, *J* 5.5 and 3.0, Ar-H) and 7.83 (2H, dd, *J* 5.5 and 3.0, Ar-H); δ_C 18.0 (CH_3), 19.0 (CH_3), 85.5 (CH), 123.5 (Ar-CH), 129.0 (Ar-C), 130.0 (CH), 132.9 (CH), 134.4 (Ar-CH) and 164.3 (CO).

(*E*)-*O*-(Pent-3-en-2-yl)-*N*-(*p*-toluenesulphonyl)hydroxylamine 100 [41]



The foregoing alkoxyphthalimide **98** (1.000 g, 4.327 mmol) was deprotected according to general method **B** to give the crude hydroxylamine **99** (0.430 g, 4.240 mmol) as a colourless oil. The crude intermediate was immediately tosylated by the procedure detailed in general method **C** to yield the *title compound* **100** (0.961 g, 87% over 2 steps) as a colourless solid. All data obtained were in accordance with those previously obtained in the literature[41] including: mp 88-89°C [lit.[41] mp 90.5-91.5°C]; δ_H 1.21 (3H, d, *J* 6.4, 1-CH_3), 1.68 (3H, dd, *J* 6.5 and 1.5, 5-CH_3), 2.45 (3H, s, Ar-CH_3), 4.45 (1H, app. pentet, *J* 6.9, 2-H), 5.33 (1H, ddq, *J* 15.0, 6.9 and 1.5, 3-H), 5.74 (1H, dq, *J* 15.0 and 6.5, 4-H), 6.67-6.70 (1H, br s, NH), 7.35 (2H, d, *J* 8.2, 2 x ArH) and 7.80 (2H, d, *J* 8.2, 2 x ArH); δ_C 18.0 (CH_3), 19.1 (CH_3), 22.0 (Ar-CH_3), 83.3 (2-CH), 128.9 (2 x Ar-CH), 130.0 (2 x Ar-CH), 130.5 (CH), 130.7 (CH), 134.0 (Ar-C) and 144.9 (Ar-C); *m/z* (APcI) 256 (M^+ + H, 100%).

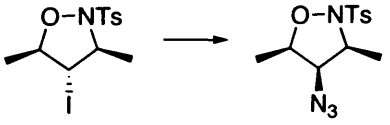
(3*SR*, 4*SR*, 5*RS*)-*N*-(*p*-toluenesulphonyl)-3,5-dimethyl-4-iodo-isoxazolidine 101 [41]



100 **101**

The sulphonamide **100** (0.400 g, 1.57 mmol) was stirred at room temperature in dry acetonitrile (15 ml). Potassium carbonate (0.650 g, 4.70 mmol) was added followed by solid iodine (1.193 g, 4.70 mmol) in one portion. The resulting mixture was stirred for 20 min and then quenched by the addition of saturated aqueous sodium thiosulphate (10 ml) and extracted with dichloromethane (3 x 20 ml). The combined extracts were dried over sodium sulphate and evaporated to give the *title compound* **101** (0.483 g, 81%) as a yellow solid. An analytical sample was obtained by column chromatography (10-20% ethyl acetate-petrol). All data obtained were in accordance with those previously reported in the literature,[41] including: mp 110-111°C [lit.[41] mp 112°C]; δ_H 1.25 (3H, d, *J* 6.0, 5-CH_3), 1.56 (3H, d, *J* 6.3, 3-CH_3), 2.47 (3H, s, Ar-CH_3), 3.44 (1H, dd, *J* 10.2 and 9.3, 4-H), 3.92 (1H, dq, *J* 10.2 and 6.0, 5-H), 4.13 (1H, dq, *J* 9.1 and 6.3, 3-H), 7.38 (2H, d, *J* 8.2, 2 x Ar-H) and 7.86 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 14.7 (CH_3), 18.8 (CH_3), 22.1 (Ar-CH_3), 29.4 (CH), 65.4 (CH), 84.1 (CH), 129.6 (Ar-CH), 130.2 (Ar-CH), 132.3 (Ar) and 145.8 (Ar); *m/z* [APcI] 382 (M^+ + H, 100%).

(3*SR*,4*RS*,5*RS*)-4-Azido-3,5-dimethyl-2-(*p*-toluenesulphonyl)isoxazolidine 132



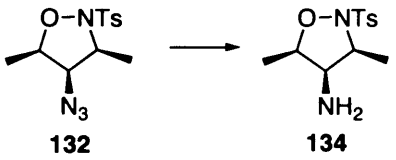
101 **132**

CAUTION: TOXIC AND EXPLOSIVE

A solution of isoxazolidine **101** (0.300 g, 0.787 mmol) was stirred in dry dimethylformamide (8 ml) and sodium azide (0.077 g, 1.180 mmol) added in one portion. The resulting mixture was stirred at 120°C for 16 h, behind a blast-proof shield. The reaction mixture was allowed to cool, quenched by the addition of water (10 ml), extracted with dichloromethane (3 x 10 ml), and the extracts washed with water (3 x 10 ml) and dried over sodium sulphate. The solvent was evaporated to provide the *title compound* **132** as a brown oil (0.151 g, 66%). An analytical sample was obtained by column chromatography (10-30% ethyl acetate/petrol) and showed: ν_{max}/cm^{-1} [film] 2108, 1718, 1674, 1597, 1453, 1356, 1273 and 1169; δ_H (500 MHz) 1.31 (3H, d, *J* 6.2, 3-CH_3), 1.59 (3H, d, *J* 7.5, 5-CH_3), 2.47 (3H, s, Ar-CH_3), 4.04 (1H, dd, *J* 5.6 and 3.5, 4-H), 4.31 (1H, dq, *J* 6.2 and 3.5, 3-H), 4.42 (1H, qd, *J* 7.5 and 5.6, 5-H), 7.38 (2H, d, *J* 8.2, 2 x Ar-H) and 7.88 (2H, d, *J* 8.2, 2 x Ar-H); δ_C (125 MHz) 12.9 (CH_3), 16.4 (CH_3), 21.8 (Ar-CH_3), 60.4 (CH), 69.6 (CH), 79.7 (CH), 129.3 (Ar-CH), 129.8 (Ar-CH) 132.5 (Ar) and 145.2 (Ar);

m/z [APcI] 297 (M^+ + H, 100%); [Found M^+ + H: 297.1009. $C_{12}H_{17}N_4O_3S$ requires *M*, 297.1021].

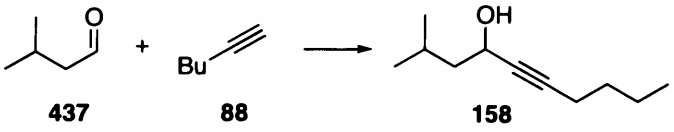
(3*SR*,4*RS*,5*RS*)-3,5-Dimethyl-2-(*p*-toluenesulphonyl)isoxazolidin-4-amine 134



To a solution of the foregoing isoxazolidine **132** (0.131 g, 0.442 mmol) in methanol (8 ml) was added 10% w/w Pd/Carbon (0.046 g, 0.044 mmol). The resulting mixture was stirred under an atmosphere of hydrogen for 16 hours then filtered through a pad of celite, eluting with hot methanol (10 ml). The filtrate was passed through a pad of silica gel using methanol as an eluent and the solvent evaporated to give the *title compound* **134** as a yellow solid (0.101 g, 84%): mp 68-69°C; ν_{max}/cm^{-1} [nujol] 3394, 3110, 1597, 1492, 1378, 1305 and 1186; δ_H 1.16 (3H, d, *J* 6.2, 3-CH_3), 1.47 (3H, d, *J* 6.4, 5-CH_3), 2.45 (3H, s, Ar-CH_3), 3.32 (1H, dd, *J* 5.0 and 3.3, 4-H), 3.86 (1H, dq. *J* 6.2 and 3.2, 3-H), 4.01 (1H, app pentet, *J* 6.4, 5-H), 7.36 (2H, d, *J* 8.2, 2 x Ar-H) and 7.87 (2H, d, *J* 8.2, 2 x Ar-H); δ_C (125 MHz) 12.3 (CH_3), 15.8 (CH_3), 21.7 (CH_3), 60.4 (CH), 61.2 (CH), 79.5 (CH), 129.4 (Ar-H), 129.7 (Ar-H), 132.2 (Ar) and 144.9 (Ar); *m/z* [APcI] 271 (M^+ + H, 100%); [Found M^+ + H: 271.1122. $C_{12}H_{19}N_2O_3S$ requires *M*, 271.1116].

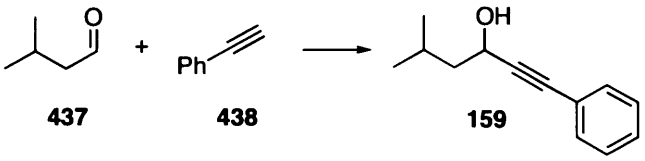
Chapter 3 compounds

2-Methyldec-5-yn-4-ol 158 [144]



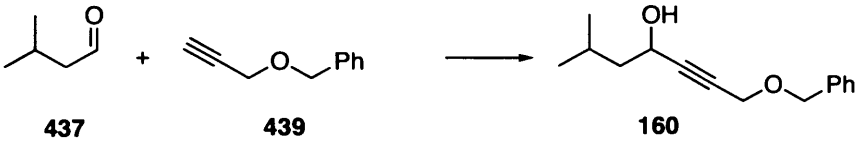
Isovaleraldehyde **437** (1.93 ml, 0.018 mol) was reacted with hexyne **88** (2.48 ml, 0.022 mol) under the conditions described in general method **D** to give the *title compound* **158** (2.991 g, 99%) as a colourless oil. All data obtained were consistent with those previously reported in the literature[144] and showed: δ_H 0.78 (3H, t, *J* 8.0, CH_3), 0.81 (6H, d, *J* 8.0, 2 x CH_3), 1.64-1.36 (7H, m, 2-H, 3-H_a, 8-CH_2 and 9-CH_2), 1.90-1.77 (1H, m, 3-H_b), 2.21 (2H, td, *J* 7.0 and 2.0, 7-CH_2) and 4.40 (1H, app. br. t, *J* 7.0, 4-CH); δ_C 13.6 (CH_3), 18.4 (CH_2), 21.9 (CH_2), 22.5 (CH_3), 24.8 (CH), 30.8 (CH_2), 47.3 (CH_2), 61.3 (CH), 81.5 (C) and 85.4 (C); *m/z* [APcI] 169.4 (M^+ + H, 100%) and 151.0 (80%).

5-Methyl-1-phenylhex-1-yn-3-ol 159 [144]



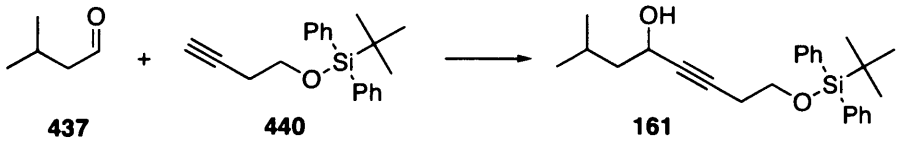
Isovaleraldehyde **437** (1.93 ml, 0.018 mol) was reacted with phenylacetylene **438** (1. 98 ml, 0.018 mol) under the conditions described in general method **D** to give the *title compound* **159** (3.330 g, 98%) as a colourless oil. All data obtained were consistent with those previously reported in the literature,[144] showing: δ_H 0.84 (3H, d, *J* 5.8, CH_3), 0.86 (3H, d, *J* 5.9, CH_3), 1.65-1.50 (2H, m, 4-H_a and 5-H), 1.80 (1H, app. heptet, *J* 6.7, 4-H_b), 4.51 (1H, dd, *J* 7.1, and 5.8, 3-H), 7.20-7.16 (2H, m, 2 x Ar-H) and 7.32-7.28 (2H, m, 2 x Ar-H); δ_C 22.5 (CH_3), 22.6 (CH_3), 24.9 (CH), 46.9 (CH_2), 61.5 (CH), 84.8 (C), 90.4 (C), 122.7 (Ar), 128.3 (Ar-H), 128.4 (Ar-H) and 131.7 (Ar-H); *m/z* [APcI] 189.3 (M^+ + H, 100%).

1-(Benzyloxy)-6-methylhept-2-yn-4-ol 160 [145]



Isovaleraldehyde **437** (0.73 ml, 6.840 mmol) was reacted with 1-[(prop-2-ynyloxy)methyl]benzene **439** (1.000 g, 6.840 mmol) under the conditions described in general method **D** to yield the *title compound* **160** (1.430 g, 90%) as a colourless oil. All data obtained were consistent with those previously reported in the literature,[145] showing: δ_H 0.81 (3H, d, *J* 5.8, CH_3), 0.83 (3H, d, *J* 5.8, CH_3), 1.56-1.41 (2H, m, 6- and 5-H_a), 1.78-1.68 (1H, m, 5-H_b), 4.09 (2H, d, *J* 1.6, 1-CH_2), 4.34 (1H, ddt, *J* 12.8, 7.2 and 1.6, 4-H), 4.46 (2H, s, Ar-CH_2) and 7.23-7.16 (5H, m, 5 x Ar-H); δ_C 22.5 (CH_3), 22.6 (CH_3), 24.8 (CH), 46.8 (CH_2), 57.5 (CH_2), 61.1 (CH), 71.7 (CH_2), 80.7(C), 87.9 (C), 128.1 (Ar-H), 128.2 (Ar-H), 128.5 (Ar-H) and 137.4 (Ar-C); *m/z* [APcI] 233.3 (M^+ + H, 100%).

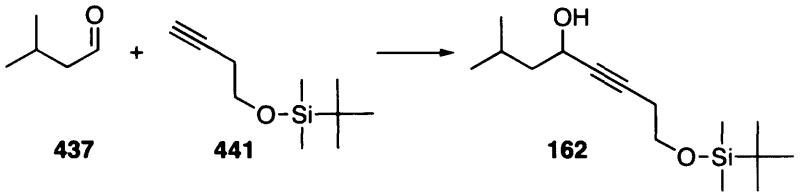
1-(*tert*-Butyldiphenylsilyloxy)-7-methyloct-3-yne-5-ol 161



Isovaleraldehyde **437** (0.71 ml, 6.655 mmol) was reacted with alkyne **440** (2.000 g, 6.655 mmol) under the conditions described in general method **D** to give the *title compound* **161** (2.570 g, 99%) as a colourless oil: ν_{max}/cm^{-1} [thin film] 3392, 1473, 1390 and 1008; δ_H 0.76 (3H, d, *J* 6.4, CH_3), 0.78 (3H, d, *J* 6.4, CH_3), 0.92 (9H, s, 3 x CH_3), 1.50-1.33 (2H, m, 7-H and

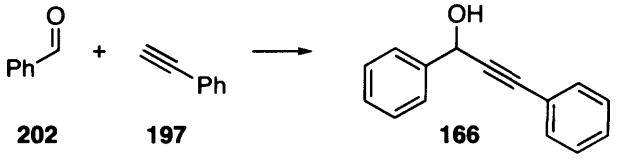
6-H_a), 1.74-1.64 (1H, m, 6-H_b), 2.35 (2H, dt, *J* 6.9 and 1.9, 2-CH_2), 3.63 (2H, t, *J* 6.9, 1-CH_2), 4.23 (1H, ddt, *J* 12.6, 7.3 and 1.9, 5-H), 7.30-7.23 (6H, m, 6 x Ar-H) and 7.55 (4H, d, *J* 7.9, 4 x Ar-H); *m/z* [APcI] 395.5 (M^+ + H, 100%).

1-(*tert*-Butyldimethylsilyloxy)-7-methyloct-3-yne-5-ol 162



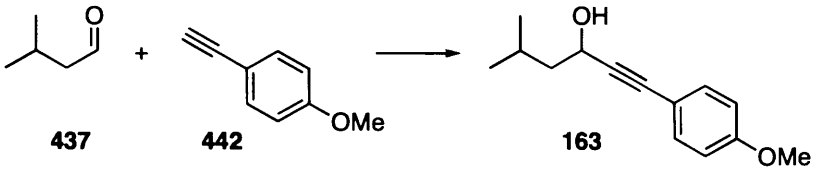
Isovaleraldehyde **437** (0.486 g, 5.432 mmol) was reacted with alkyne **441** (1.000 g, 5.432 mmol) under the conditions described in general method **D** to yield the *title compound* **162** (1.438 g, 98%) as a colourless oil: ν_{max}/cm^{-1} [film] 3401, 1469 and 1398; δ_H 0.01 (6H, s, 2 x Si-CH_3), 0.84 (9H, s. tBu-CH_3), 0.96 (3H, d, *J* 6.4, CH_3), 1.04 (3H, d, *J* 6.3, CH_3), 1.76-1.69 (1H, m, 2-H), 2.05-1.89 (2H, m, 3-H_a and H_b), 2.35 (2H, td, *J* 7.4 and 1.8, 2-CH_2), 3.63-3.54 (2H, m, 1-CH_2), 4.31 (1H, app. tt, *J* 6.8 and 1.8, 5-H); δ_C -5.3 (CH_3), 18.4 (C), 22.5 (CH_3), 22.6 (CH_3), 23.1 (CH_2), 24.8 (CH), 25.9 (3 x CH_3), 47.2 (CH_2), 61.2 (CH), 61.9 (CH_2), 82.3 (C) and 82.6 (C); [Found M^+ + H: 271.2112. $C_{15}H_{31}O_2Si$ requires *M*, 271.2093].

1,3-Diphenylprop-2-yn-1-ol 166 [146]



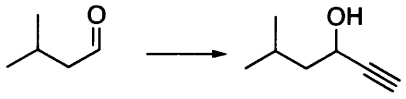
Phenylacetylene **197** (1.000 g, 9.434 mmol) was reacted with benzaldehyde **202** (0.962 g, 9.434 mmol) under the conditions described in general method **D** to yield the *title compound* **166** (1.941 g, 99%) as a yellow oil. All data obtained was in accordance with that previously reported in the literature[146] and showed: δ_H 2.40 (1H, br. s, OH), 5.70 (1H, s, 1-H) and 7.25-7.66 (10H, m, 10 x Ar-H); δ_C 65.4 (CH), 87.2 (C), 90.0 (C), 122.6 (Ar), 127.0, 128.4, 128.9, 129.0 and 132.0 (all Ar-H), 140.2 (Ar); *m/z* [APcI] 191 (M^+ - H_2O + H, 100%).

1-(4-Methoxyphenyl)-5-methylhex-1-yn-3-ol 163



Isovaleraldehyde **437** (0.652 g, 7.570 mmol) was reacted with *p*-methoxyphenylacetylene **442** (1.000 g, 7.570 mmol) under the conditions described in general method **D** to yield the crude product which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to give the *title compound* **163** (1.582 g, 96%) as a pale yellow oil showing: ν_{max}/cm^{-1} [film] 3359, 1345, 1066 and 945; δ_H 0.99 (6H, app. t, *J* 6.4, 2 x CH_3), 1.77-1.63 (2H, m, 4-H_a and 5-H), 1.97-1.88 (1H, m, 4-H_b), 3.83 (3H, s, OCH_3), 4.69-4.64 (1H, m, 3-H), 6.85 (2H, br. d, *J* 8.9, 2 x Ar-H) and 7.38 (2H, br. d, *J* 8.9, 2 x Ar-H); δ_C 22.6 (CH_3), 22.7 (CH_3), 24.9 (CH), 47.0 (CH_2), 55.3 (CH_3), 61.6 (CH), 84.7 (C), 89.0 (C), 113.9 (Ar-H), 114.8 (Ar), 133.1 (Ar-H) and 159.6 (Ar); [Found M^+ + H: 219.1389. $C_{14}H_{19}O_2$ requires *M*, 219.1385].

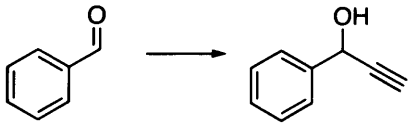
5-Methylhex-1-yn-3-ol 167



437 167

Isovaleraldehyde **437** (1.000 g, 11.614 mmol) was taken up in dry tetrahydrofuran (120 ml) and stirred at 0°C. Ethynylmagnesium bromide (27.87 ml, 13.937 mmol as a 0.5M solution in tetrahydrofuran) was added, dropwise and the resulting solution allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of water and the reaction mixture extracted into dichloromethane (3 x 120 ml). The combined organic extracts were washed with water (3 x 120 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the *title compound* **167** (1.290 g, 99%) as a pale yellow oil. All data obtained were identical to those obtained for a commercially available sample (Sigma Aldrich).

1-Phenylprop-2-yn-1-ol 168

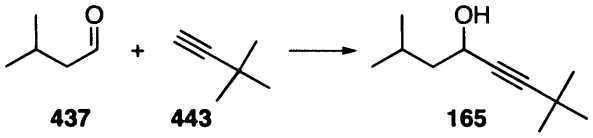


202 168

Benzaldehyde **202** (1.000 g, 9.422 mmol) was taken up in dry tetrahydrofuran (120 ml) and stirred at 0°C. Ethynyl magnesium bromide (22.61 ml, 11.306 mmol as a 0.5M solution in tetrahydrofuran) was added, dropwise and the resulting solution allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of water and the

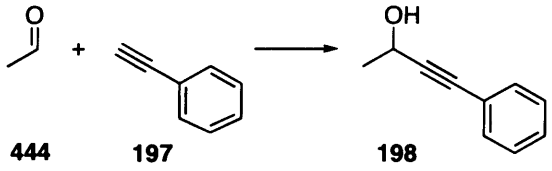
reaction mixture extracted into dichloromethane (3 x 120 ml). The combined organic extracts were washed with water (3 x 120 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the *title compound* **168** (1.230 g, 99%) as a pale yellow oil. All data obtained were identical to those obtained for a commercially available sample (Sigma Aldrich).

2,7,7-Trimethyloct-5-yn-4-ol 165



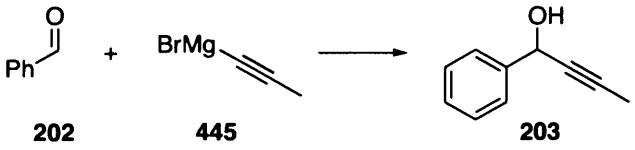
Isovaleraldehyde **437** (1.000 g, 11.614 mmol) was reacted with 3,3-dimethylbut-1-yne **443** (0.954 g, 11.614 mmol) under the conditions described in general method **D** to yield the *title compound* **165** (1.915 g, 98%) as a colourless oil: ν_{max}/cm^{-1} [film] 3382, 2210, 1460, 1321 and 1112; δ_H 0.92 (3H, d *J* 6.7, CH_3), 0.94 (3H, d, *J* 6.7, CH_3), 1.21 (9H, s, ^tBu-CH_3), 1.54-1.47 (1H, m, 2-H), 1.66-1.57 (1H, m, 3-H_a), 1.87-1.77 (1H, m, 3-H_b) and 4.39 (1H, app. t, *J* 7.1, 4-H); δ_C 22.5 (CH_3), 22.6 (CH_3), 24.8 (CH), 27.3 (C), 31.0 (CH_3), 47.3 (CH_2), 61.2 (CH), 79.9 (C) and 93.7 (C); [Found M^+ + H: 169.1559. $C_{11}H_{21}O$ requires *M*, 169.1592].

4-Phenylbut-3-yn-2-ol 198 [147]



Phenylacetylene **197** (1.000 g, 9.804 mmol) was reacted with freshly distilled acetaldehyde **444** (0.431 g, 9.804 mmol) under the conditions described in general method **D** to yield the *title compound* **198** as a pale yellow oil (1.411 g, 98%). All data obtained were in accordance with those previously reported in the literature[147] and showed: δ_H 1.56 (3H, d, *J* 6.6, CH_3), 1.96 (1H, d, *J* 5.4, OH), 4.76 (1H, dq, *J* 6.6 and 5.4, 2-H), 7.33-7.30 (2H, m, 2 x Ar-H) and 7.44-7.42 (2H, m, 2 x Ar-H); δ_C 24.4 (CH_3), 58.9 (CH), 84.0 (C), 90.9 (C), 122.6 (Ar), 128.3 (Ar-H), 128.4 (Ar-H) and 131.7 (Ar-H); *m/z* [APcI] 147.2 (M^+ + H, 100%).

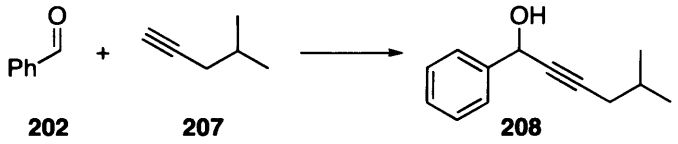
1-Phenylbut-2-yn-1-ol 203 [148]



To a solution of benzaldehyde **202** (1.000 g, 9.434 mmol) in dry tetrahydrofuran (95 ml) at 0°C was added propynylmagnesium bromide **445** (11.32 ml, 11.320 mmol as a 1M solution in

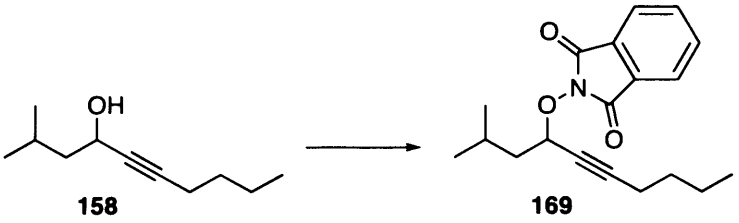
tetrahydrofuran; Sigma Aldrich), dropwise *via* syringe. The resulting solution was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (100 ml) and reaction mixture extracted with dichloromethane (3 x 100 ml). The combined organic portions were washed with water (3 x 100 ml) and dried. The solution was filtered and the solvent removed *in vacuo* to yield the *title compound* **203** (1.352 g, 98%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature,[148] showing: ν_{max}/cm^{-1} [film] 3418, 2206, 1450 and 1136; δ_H 7.55-7.52 (2H, m, 2 x Ar-H), 7.40-7.31 (3H, m, 3 x Ar-H), 5.43 (1H, dq, *J* 5.9 and 3.1, 1-H), 2.21 (1H, d, *J* 5.9, OH) and 1.91 (3H, d, *J* 2.2, 3-CH_3); δ_C 29.7 (CH_3), 64.9 (CH), 79.1 (C), 83.2 (C), 126.6 (Ar-H), 128.3 (Ar-H), 128.6 (Ar-H) and 141.2 (Ar); *m/z* [APcI] 147.4 (M^+ + H, 100%).

5-Methyl-1-phenylhex-2-yn-1-ol 208



Benzaldehyde **202** (1.000 g, 9.434 mmol) was reacted with 4-methylpent-1-yne **207** (0.775 g, 9.434 mmol) under the conditions described in general method **D** to yield the *title compound* **208** (1.655 g, 89%) as a pale yellow oil: ν_{max}/cm^{-1} [film] 3352, 2277, 2228, 1493, 1454 and 1453; δ_H 7.48 (2H, d, *J* 7.5, 2 x Ar-H), 7.30 (2H, app. t, *J* 7.5, 2 x Ar-H), 7.25 (1H, d, *J* 7.5, Ar-H), 5.39 (1H, br. s, 1-H), .2.12 - 2.09 (2H, m, 4-CH_2), 1.80-1.74 (1H, m, 5-H) and 0.92 (6H, d, *J* 6.6, 2 x CH_3); δ_C 22.06 (CH_3), 28.0 (CH), 28.1 (CH_2), 64.9 (CH), 80.8 (C), 86.6 (C), 126.7 (Ar-H), 128.2 (Ar-H), 128.6 (Ar-H) and 141.3 (Ar); *m/z* [APcI] *No molecular ion present due to decomposition in solution.*

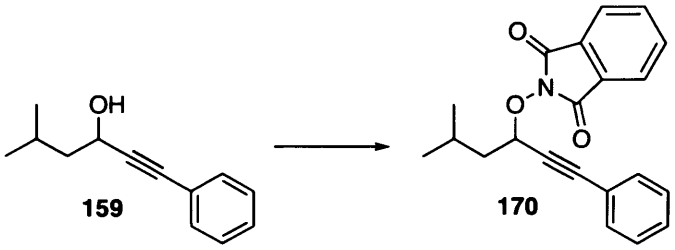
2-(2-Methyldec-5-yn-4-yloxy)isoindoline-1,3-dione 169



The propargyl alcohol **158** (1.000g, 5.945 mmol) was reacted with *N*-hydroxyphthalimide (0.979 g, 6.004 mmol) under the conditions described in general procedure **A** to give the *title compound* **169** (1.655 g, 89%) as a thick, colourless oil showing: ν_{max}/cm^{-1} [film] 2240, 1850, 1791, 1736, 1610, 1467 and 1371; δ_H 0.71 (3H, t, *J* 7.2, 10-CH_3), 0.89 (3H, d, *J* 6.4, CH_3), 0.98 (3H, d, *J* 6.5, CH_3), 1.22-1.13 (2H, m, 9-CH_2), 1.32-1.24 (2H, m, 8-CH_2), 1.70-1.63 (1H, m, 2-

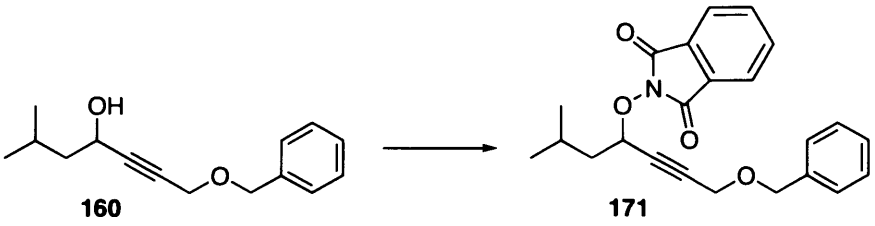
H), 1.95-1.83 (2H, m, 3-H_a and 3-H_b), 2.05 (2H, dt, *J* 7.1 and 2.0, 7-CH_2), 5.06 (1H, app. tt, *J* 6.9 and 2.0, 4-H), 7.68 (2H, dd , *J* 5.5 and 3.1, 2 x Ar-H) and 7.78 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 13.5 (CH_3), 18.4 (CH_2), 21.8 (CH_2), 22.4 (CH_3), 22.5 (CH_3), 25.0 (CH), 30.2 (CH_2), 42.9 (CH_2), 76.4 (CH), 89.9 (C), 123.4 (Ar-H), 129.0 (Ar), 134.3 (Ar-H) and 163.7 (CO) *Missing one quaternary carbon*; *m/z* [APcI] 314 (M^+ + H, 30%) and 151 (100%); [Found M^+ + Na: 336.1581. $C_{19}H_{23}NNaO_3$ requires *M*, 336.1576].

2-(5-Methyl-1-phenylhex-1-yn-3-yloxy)isoindoline-1,3-dione 170



The propargyl alcohol **159** (1.000 g, 5.316 mmol) was reacted with *N*-hydroxyphthalimide (0.875 g, 5.369 mmol) under the procedure described in general method **A** to give the *title compound* **170** (1.540 g, 87%) as a chalky, white solid showing: mp 111-112°C; ν_{max}/cm^{-1} [nujol] 2235, 1789, 1732, 1610, 1490, 1467 and 1370; δ_H 0.95 (3H, d, *J* 6.3, CH_3), 1.03 (3H, d, *J* 6.4, CH_3), 1.84-1.76 (1H, m, 5-H), 2.05-1.96 (2H, m, 4-H_a and 4-H_b), 5.26 (1H, app. t, *J* 6.9, 3-H), 7.23-7.19 (3H, m, 3 x Ar-H), 7.28 (2H, dd, *J* 7.7 and 1.9, 2 x Ar-H), 7.67 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.78 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 22.5 (CH_3), 22.6 (CH_3), 25.0 (CH), 42.6 (CH_2), 76.9 (CH), 85.5 (C), 88.3 (C), 122.0 (Ar), 123.5 (Ar-H), 128.2 (Ar-H), 128.7 (Ar-H), 128.9 (Ar), 131.6 (Ar-H), 134.5 (Ar-H) and 163.8 (CO); *m/z* [APcI] 334 (M^+ + H, 100%); [Found M^+ + Na: 356.1339. $C_{21}H_{19}NNaO_3$ requires *M*, 356.1263].

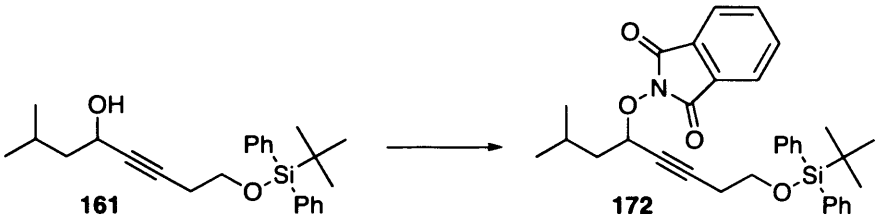
2-(1-(Benzyloxy)-6-methylhept-2-yn-4-yloxy)isoindoline-1,3-dione 171



The propargyl alcohol **160** (1.000 g, 4.308 mmol) was reacted with *N*-hydroxyphthalimide (0.709 g, 4.351 mmol) under the conditions described in general method **A** to give the *title compound* **171** (1.280 g, 79%) as a thick, colourless oil characterised by: ν_{max}/cm^{-1} [film] 2231, 1790, 1732 and 1469; δ_H 0.99 (3H, d, *J* 6.4, CH_3), 1.07 (3H, d, *J* 6.5, CH_3), 1.81-1.75 (1H, m, 6-H), 2.07-1.96 (2H, m, 3-H_a and -H_b), 4.16 (2H, d, *J* 1.6, 1-CH_2), 4.48 (2H, s, Ar-CH_2), 5.18 (1H, app. tt, *J* 7.0 and 1.6, 4-H), 7.32-7.25 (5H, m, 5 x Ar-H), 7.73 (2H, dd, *J* 5.5 and 3.1, 2 x

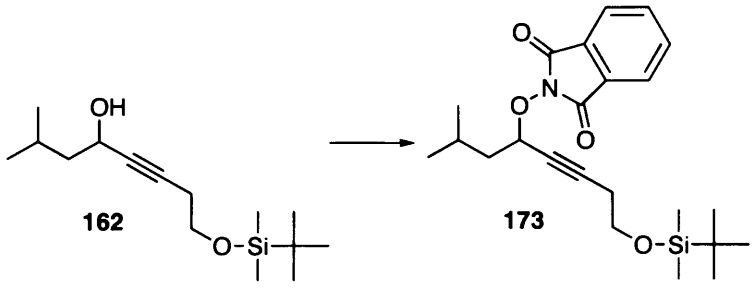
Ar-H) and 7.82 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 22.4 (CH_3), 22.5 (CH_3), 24.9 (CH), 42.6 (CH_2), 57.2 (CH_2), 71.5 (CH_2), 76.3 (CH), 83.0 (C), 84.7 (C), 123.5 (Ar-H), 128.1 (Ar-H), 128.3 (Ar-H), 128.5 (Ar-H), 129.0 (Ar), 133.7 (Ar-H), 137.3 (Ar) and 163.6 (CO); [Found M^+ + Na: 400.1530. $C_{23}H_{23}NNaO_4$ requires *M*, 400.1525].

2-[8-(*tert*-Butyldiphenylsilyloxy)-2-methyloct-5-yn-4-yloxy]isoindoline-1,3-dione 172



The propargyl alcohol **161** (1.000 g, 2.537 mmol) was reacted with *N*-hydroxyphthalimide (0.418 g, 2.562 mmol) under the conditions described in general method **A** to give the *title compound* **172** (1.010 g, 74%) as a thick, colourless oil showing: ν_{max}/cm^{-1} [film] 2243, 1791, 1737, 1468, 1428 and 1372; δ_H 0.87 (3H, d, *J* 6.5, CH_3), 0.91 (9H, s, ^{t}Bu-CH_3), 0.95 (3H, d, *J* 6.5, CH_3), 1.67-1.61 (1H, m, 2-H), 1.94-1.80 (2H, m, 3-H_a and 3-H_b), 2.34 (2H, dt, *J* 7.1 and 1.9, 7-CH_2), 3.57 (2H, t, *J* 7.1, 8-CH_2), 5.00 (1H, app. tt, *J* 7.0 and 1.9, 5-H), 7.37-7.26 (6H, m, 6 x Ar-H), 7.56-7.51 (4H, m, 4 x Ar-H), 7.61 (2H, dd, *J* 5.6 and 3.0, 2 x Ar-H) and 7.68 (2H, dd, *J* 5.6 and 3.0); δ_C 14.2 (CH_3), 19.1 (C), 22.5 (CH_3), 22.9 (CH_2), 24.9 (CH), 26.7 (3 x CH_3), 42.8 (CH_2), 62.0 (CH_2), 76.6 (CH), 77.7 (C), 86.4 (C), 123.4 (Ar-H), 127.7 (Ar-H), 128.9 (C), 129.7 (Ar-H), 133.5 (C), 134.3 (CH), 135.5 (CH) and 163.7 (CO); *m/z* [APcI] 540 (M^+ + H, 30%) and 462 (100%); [Found M^+ + H: 540.2555. $C_{33}H_{38}NO_4Si$ requires *M*, 540.2570].

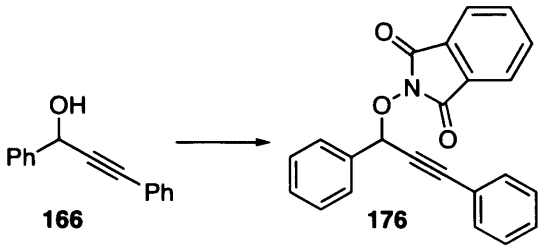
2-[8-(*tert*-Butyldimethylsilyloxy)-2-methyloct-5-yn-4-yloxy]isoindoline-1,3-dione 173



The propargyl alcohol **162** (1.000 g, 3.701 mmol) was reacted with *N*-hydroxyphthalimide (0.610 g, 3.738 mmol) under the conditions described in general method **A** to yield the *title compound* **173** (1.122 g, 73%) as a thick, colourless oil: ν_{max}/cm^{-1} [film] 2240, 1790, 1723, 1459 and 1378; δ_H 0.01 (6H, s, 2 x Si-CH_3), 0.84 (9H, s. ^{t}Bu-CH_3), 0.96 (3H, d, *J* 6.5, CH_3), 1.04 (3H, d, *J* 6.5, CH_3), 1.76-1.69 (1H, m, 2-H), 2.05-1.89 (2H, m, 3-H_a and H_b), 2.35 (2H, td, *J* 7.4 and 1.9, 7-CH_2), 3.63-3.54 (2H, m, 8-CH_2), 5.08 (1H, app. tt, *J* 6.8 and 1.9, 4-H), 7.75 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.84 (2H, dd, *J* 5.5 and 3.1); δ_C -5.4 (CH_3), 18.3 (C), 21.6

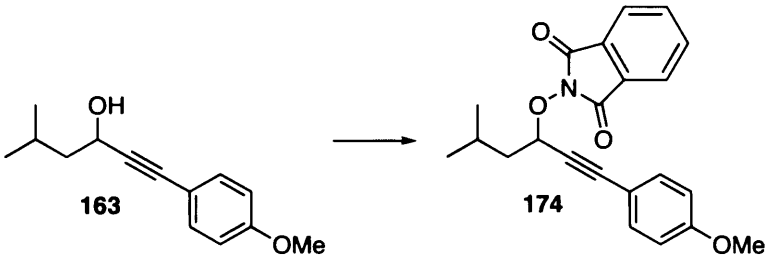
(CH_3), 22.5 (CH_3), 23.1 (CH_2), 24.9 (CH), 25.8 (3 x CH_3), 42.8 (CH_2), 61.2 (CH_2), 69.3 (C), 77.7 (CH), 86.4 (C), 123.5 (Ar-H), 128.9 (Ar), 134.5 (Ar-H) and 163.7 (CO); [Found M^+ + Na: 438.2069. $C_{23}H_{33}NNaO_4Si$ requires *M*, 438.2077].

2-(1,3-Diphenylprop-2-ynyloxy)isoindoline-1,3-dione 176 [41]



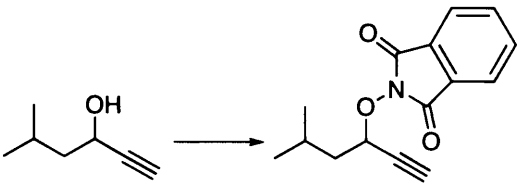
The propargyl alcohol **166** (1.000 g, 4.805 mmol) reacted with *N*-hydroxyphthalimide (0.791 g, 4.853 mmol) under the conditions described in general method **A** (with the exception that the delay between the sequential addition of reagents was omitted) to yield the *title compound* **176** (0.696 g, 41%) as a colourless solid. All data obtained were in accordance with those previously reported in the literature[41] and showed: mp 122-123°C [lit.[41] 124°C]; δ_H 6.20 (1H, s, 1-H), 7.12-7.18 (3H, m, 3 x Ar-H), 7.30-7.35 (5H, m, 5 x Ar-H), 7.64-7.65 (2H, m, 2 x Ar-H), 7.70-7.75 (4H, m, 4 x Ar-H); δ_C 79.5 (CH), 84.0 (C), 90.6 (C), 122.0 (Ar-C), 123.9, 128.4, 128.9 (all Ar-H), 129.0 (Ar), 129.2, 129.4, 130.2, 131.9, 134.7 (all Ar-H), 134.8 (Ar), 164.0 (CO); *m/z* [APcI] 354 (M^+ + H, 100%).

2-(1-(4-Methoxyphenyl)-5-methylhex-1-yn-3-yloxy)isoindoline-1,3-dione 174



The propargyl alcohol **163** (1.000 g, 4.585 mmol) reacted with *N*-hydroxyphthalimide (0.755 g, 4.630 mmol) under the conditions described in general method **A** to yield the *title compound* **174** (1.347 g, 81%) as a colourless solid: mp 119-121°C; ν_{max}/cm^{-1} [film] 2123, 1741, 1724 and 1399; δ_H 0.94 (3H, d, *J* 6.3, ^iBu-CH_3), 1.02 (3H, d, *J* 6.4, ^iBu-CH_3), 1.82-1.75 (1H, m, 5-H), 2.04-1.94 (2H, m, 4- H_a and H_b), 3.71 (3H, s, OCH_3), 5.26-5.23 (1H, m, 3-H), 6.71 (2H, br. d, *J* 8.8, 2 x Ar-H), 7.21 (2H, br. d, *J* 8.8, 2 x Ar-H), 7.67 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.77 (2H, dd, *J* 5.5 and 3.2, 2 X Ar-H); δ_C 22.5 (CH_3), 22.6 (CH_3), 25.1 (CH), 42.7 (CH_2), 55.3 (CH_3), 84.1 (C), 88.4 (C), 113.8 (Ar-H), 123.6 (Ar-H), 129.0 (Ar), 133.2 (Ar-H), 134.4 (Ar-H), 135.0 (Ar), 159.8 (Ar) and 163.8 (CO); [Found M^+ + Na: 386.1373. $C_{22}H_{21}NNaO_4$ requires *M*, 386.1368].

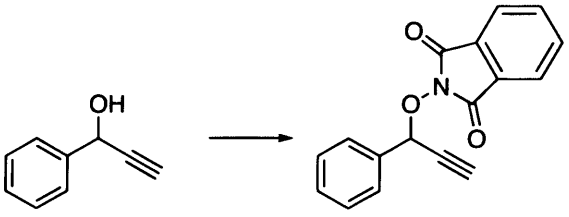
2-(5-Methylhex-1-yn-3-yloxy)isoindoline-1,3-dione 167



167 **177**

The propargyl alcohol **167** (1.000 g, 8.921 mmol) was reacted with *N*-hydroxyphthalimide (1.469 g, 9.010 mmol) under the conditions described in general method **A** to give the *title compound* **177** (1.949 g, 85%) as a colourless solid: mp 84-85°C; [Found: C, 69.92; H, 5.90; N, 5.31%. $C_{15}H_{15}O_3N$ requires C, 70.02; H, 5.88; N, 5.44%]; ν_{max}/cm^{-1} [film] 2119, 1732, 1719, 1611, 1468 and 1373; δ_H 0.99 (3H, d, *J* 6.4, CH_3), 1.07 (3H, d, *J* 6.4, CH_3), 1.79-1.76 (1H, m, 5-H), 2.07-1.96 (2H, m, 4-H_a and H_b), 2.46 (1H, d, *J* 2.1, 1-H), 5.11 (1H, dt, *J* 7.0 and 2.1, 3-H), 7.77 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H) and 7.86 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C (125 MHz) 22.4 (CH_3), 22.5 (CH_3), 24.9 (CH), 42.5 (CH_2), 76.0 (CH), 76.6 (C), 80.3 (CH), 123.6 (Ar-H), 128.9 (Ar), 134.5 (Ar-H) and 163.6 (CO); [Found M^+ + H: 258.1124. $C_{15}H_{16}NO_3$ requires *M*, 258.1125].

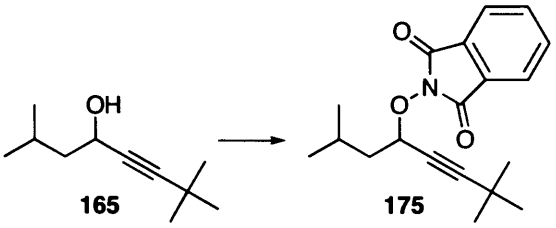
2-(1-Phenylprop-2-ynyloxy)isoindoline-1,3-dione 178



168 **178**

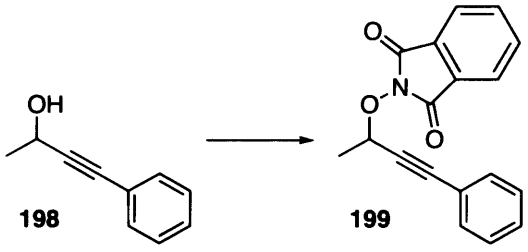
The propargyl alcohol **168** (1.000 g, 7.570 mmol) was reacted with *N*-hydroxyphthalimide (1.246 g, 7.646 mmol) under the conditions described in general method **A** (with the exception that the delay between the sequential addition of reagents was omitted) to yield the *title compound* **178** (1.444 g, 69%) as a pale yellow solid: mp 120-121°C; ν_{max}/cm^{-1} [nujol] 2221, 1790, 1732, 1495, 1467 and 1373; δ_H 2.78 (1H, d, *J* 2.2, 1-H), 6.10 (1H, d, *J* 2.2, 3-H), 7.44-7.42 (3H, m, 3 x Ar-H), 7.76 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H), 7.78-7.74 (2H, m, 2 x Ar-H) and 7.86 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 22.4 (CH_3), 22.5 (CH_3), 24.8 (CH), 42.5 (CH_2), 75.9 (CH), 80.2 (C), 123.6 (Ar-H), 128.9 (Ar), 134.5 (Ar-H) and 163.6 (CO); [Found M^+ + Na: 300.0636. $C_{17}H_{11}NNaO_3$ requires *M*, 300.0637].

2-(2,7,7-Trimethyloct-5-yn-4-yloxy)isoindoline-1,3-dione 175



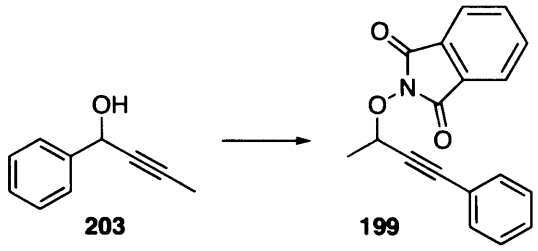
The propargyl alcohol **165** (1.000 g, 5.945 mmol) was reacted with *N*-hydroxyphthalimide (0.980 g, 6.005 mmol) under the conditions described in general method **A** to give the *title compound* **175** (1.657 g, 89%) as a thick, colourless oil: ν_{max}/cm^{-1} [thin film] 2241, 1790, 1737, 1611, 1468, 1370, 1264; δ_H 0.97 (3H, d, *J* 6.4, CH_3), 1.05 (3H, d, *J* 6.5, CH_3), 1.07 (9H, s, ^{t}Bu-CH_3), 1.76-1.69 (1H, m, 3-H_a), 2.03-1.90 (2H, m, 2-H and 3-H_b), 5.14 (1H, t, *J* 6.9, 4-H), 7.75 (2H, d, *J* 5.4 and 3.1, 2 x Ar-H) and 7.85 (2H, d, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 22.4 (CH_3), 22.6 (CH_3), 25.0 (CH), 27.3 (C), 30.5 (CH_3), 42.8 (CH_2), 74.9 (C), 77.2 (CH), 97.9 (C), 123.4 (Ar-H), 128.9 (Ar), 134.3 (Ar-H) and 163.7 (CO); [Found M^+ + Na: 336.1573. $C_{19}H_{23}NNaO_3$ requires *M*, 336.1576].

2-(4-Phenylbut-3-yn-2-yloxy)isoindoline-1,3-dione 199



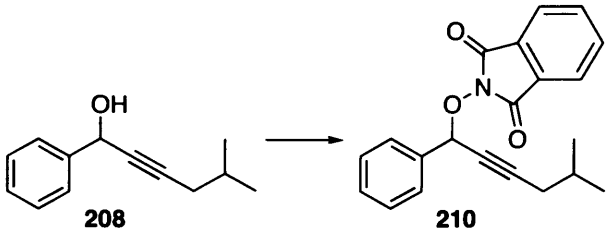
The propargyl alcohol **198** (1.000 g, 6.845 mmol) was reacted with *N*-hydroxyphthalimide (1.127 g, 6.913 mmol) under the conditions described in general method **A** to yield the *title compound* **199** (1.616 g, 81%) as a pale yellow solid, characterised by: mp 67-68°C; ν_{max}/cm^{-1} [thin film] 1790, 1738, 1490, 1466, 1443 and 1376; δ_H 1.77 (3H, d, *J* 6.6, CH_3), 5.39 (1H, q, *J* 6.6, 2-H), 7.30-7.25 (3H, m, 3 x Ar-H), 7.38-7.35 (2H, m, 2 x Ar-H), 7.75 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.86 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 20.2 (CH_3), 74.0 (CH), 85.9 (C), 87.7 (C), 121.9 (Ar), 123.6 (Ar-H), 128.3 (Ar-H), 128.7 (Ar-H), 128.9 (Ar), 131.7 (Ar-H), 134.5 (Ar-H) and 163.8 (CO); *m/z* [APcI] 291 (M^+ + H, 100%); [Found M^+ + Na: 314.1619. $C_{18}H_{13}NNaO_3$ requires *M*, 314.0793].

2-(4-Phenylbut-3-yn-2-yloxy)isoindoline-1,3-dione 199 (Alternative Synthesis)



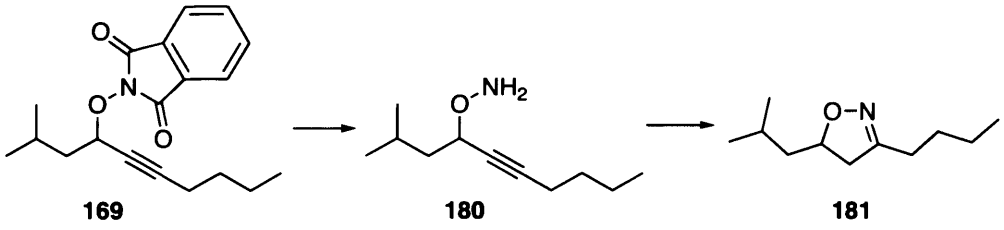
The propargyl alcohol **203** (1.000 g, 6.845 mmol) was reacted with *N*-hydroxyphthalimide (1.127 g, 6.913 mmol) under the conditions described in general method **A** (with the exception that the delay between the sequential addition of reagents was omitted) to yield the *title compound* **199** (1.413 g, 72%) as a colourless solid. All data obtained were identical to those obtained for the foregoing sample.

2-(5-Methyl-1-phenylhex-2-ynyloxy)isoindoline-1,3-dione 210



The propargyl alcohol **208** (1.000 g, 5.316 mmol) was reacted with *N*-hydroxyphthalimide (0.875 g, 5.369 mmol) under the conditions described in general method **A** (with the exception that the delay between the sequential addition of reagents was omitted) to yield the *title compound* **210** (1.222 g, 69%) as a thick, colourless oil: ν_{max}/cm^{-1} [film] 2243, 1790, 1732, 1643, 1467 and 1372; δ_H 0.82 (3H, br. t, *J* 7.2, CH_3), 1.69 (1H, app. heptet., *J* 6.6, 5-H), 2.05 (2H, dd, *J* 6.5 and 1.9, 4-CH_2), 6.05 (1H, br. t, *J* 1.9, 1-H), 7.36-7.33 (3H, m, 3 x Ar-H), 7.70-7.66 (4H, m, 4 x Ar-H) and 7.77 (2H, dd, *J* 5.2 and 3.2, 2 x Ar-H); δ_C 21.9 (CH_3), 27.7 (CH), 28.1 (CH_2), 79.3 (CH), 91.4 (C), 123.5 (Ar-H), 128.6 (Ar-H), 129.1 (Ar-H), 129.8 (Ar-H), 134.4 (Ar-H), 135.2 (Ar) and 165.5 (CO) *Missing some quaternary carbons*; *m/z* [APcI] 351.2 (M^+ + H, 100%); [Found M^+ + NH_4: 351.1699. $C_{21}H_{23}N_2O_3$ requires *M*, 351.1709].

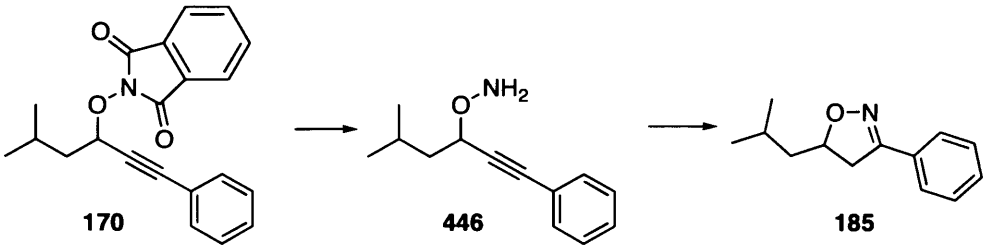
3-Butyl-4,5-dihydro-5-isobutylisoxazole 181



The phthalimide **169** (0.500 g, 1.596 mmol) was deprotected under the conditions described in general procedure **B** to yield the hydroxylamine **180** (0.283 g, 1.548 mmol) a colourless oil,

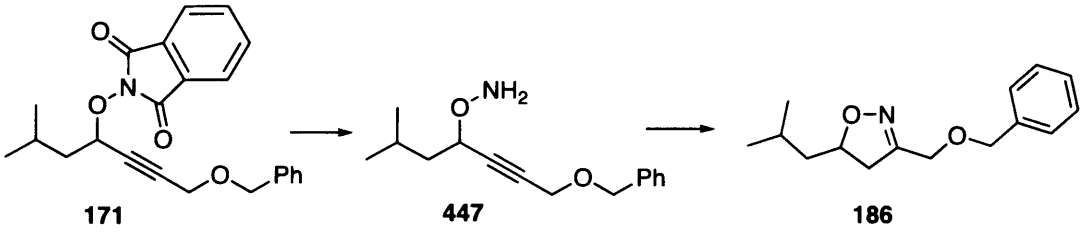
which was treated as unstable and cyclised immediately under the conditions described in general method **E** to give the *title compound* **181** (0.279 g, 95% over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 1639, 1467 and 1368; δ_H 0.86 (3H, d, *J* 6.4, ^{i}Bu-CH_3), 0.87 (3H, t, *J* 7.4, Bu-CH_3), 0.88 (3H, d, *J* 6.3, ^{i}Bu-CH_3), 1.33-1.23 (4H, m, 2 x Bu-CH_2), 1.51-1.43 (1H, m, ^{i}Bu-H), 1.63-1.55 (1H, m, ^{i}Bu-H_a), 1.74-1.65 (1H, m, ^{i}Bu-H_b), 2.27 (2H, t, *J* 7.7, Bu-CH_2), 2.44 (1H, dd, *J* 16.7 and 8.2, 4-H_a), 2.90 (1H, dd, *J* 16.7 and 9.9, 4-H_b) and 4.51 (1H, app. dtd, *J* 9.9, 8.2 and 5.7, 4-H); δ_C 13.8 (CH_3), 22.3 (CH_2), 22.4 (CH_3), 23.0 (CH_3), 25.3 (CH), 27.6 (CH_2), 28.5 (CH_2), 42.7 (CH_2), 44.4 (CH_2), 78.6 (CH) and 159.3 (CN); [Found M^+ + H: 184.1699. $C_{11}H_{22}NO$ requires *M*, 184.1701].

4,5-Dihydro-5-isobutyl-3-phenylisoxazole 185



The phthalimide **170** (0.500 g, 1.501 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **446** (0.280 g, 1.381 mmol) as a colourless oil which was treated as unstable and cyclised immediately under the conditions described in general method **E** to give the *title compound* **185** (0.274 g, 90 % over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 1717, 1645, 1447 and 1357; δ_H 0.97 (3H, d, *J* 6.9, ^{i}Bu-CH_3), 0.99 (3H, d, *J* 7.2, ^{i}Bu-CH_3), 1,48-1.42 (1H, m, ^{i}Bu-H), 1.91-1.74 (2H, m, ^{i}Bu-CH_2), 2.94 (1H, dd, *J* 16.3 and 8.2, 4-H_a), 3.41 (1H, dd, *J* 16.3 and 10.2, 4-H_b), 4.80 (1H, app. dtd, *J* 10.2, 8.2 and 5.7, 5-H), 7.41-7.37 (3H, m, 3 x Ar-H) and 7.68-7.66 (2H, m, 2 x Ar-H); δ_C 22.4 (CH_3), 22.9 (CH_3), 25.4 (CH), 40.5 (CH_2), 44.5 (CH_2), 80.0 (CH), 126.6 (Ar-H), 128.7 (Ar-H), 129.9 (Ar-H), 133.9 (Ar) and 156.5 (CN); *m/z* [APcI] 204.4 (M^+ + H, 100%) and 174.7 (40%); [Found M^+ + H: 204.1386. $C_{13}H_{18}NO$ requires *M*, 204.1388].

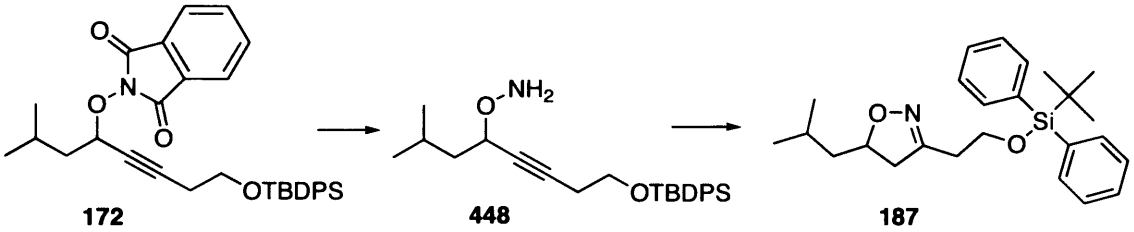
3-[(Benzyloxy)methyl]-5-*iso*butyl-4,5-dihydroisoxazole 186



The phthalimide **171** (0.500 g, 1.326 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **447** (0.307 g, 1.246 mmol) as a colourless oil

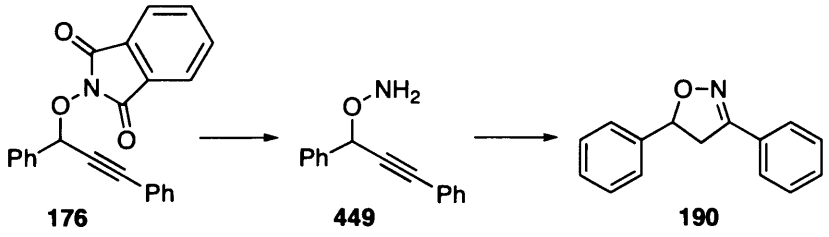
which was treated as unstable and cyclised immediately under the conditions described in general method **E** to give the *title compound* **186** (0.302 g, 92% over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 1722, 1658, 1360 and 1126; δ_H 0.93 (3H, d, *J* 6.5, ^{i}Bu-CH_3), 0.95 (3H, d, *J* 6.4, ^{i}Bu-CH_3), 1.40-1.33 (1H, m, ^{i}Bu-H), 1.83-1.65 (2H, m, ^{i}Bu-CH_2), 2.63 (1H, dd, *J* 17.1 and 8.3, 4-H_a), 3.10 (1H, dd, *J* 17.1 and 10.1, 4-H_b), 4.29 (2H, s, CH_2), 4.53 (2H, s, Ar-CH_2), 4.65 (1H, app. dtd, *J* 10.1, 8.3 and 5.8, 5-H) and 7.36-7.32 (5H, m, 5 x Ar-H); δ_C 22.3 (CH_3), 22.9 (CH_3), 25.3 (CH), 40.9 (CH_2), 44.4 (CH_2), 64.8 (CH_2), 72.6 (CH_2), 79.7 (CH), 127.9 (Ar-H), 128.2 (Ar-H), 128.5 (Ar-H), 137.4 (Ar) and 156.5 (CN); *m/z* [APcI] 248.3 (M^+ + H, 100%); [Found M^+ + H: 248.1652. $C_{15}H_{22}NO_2$ requires *M*, 248.1651].

3-(*t*-Butyldiphenylsilyloxyethyl)-4,5-dihydro-5-isobutylisoxazole 187



The phthalimide **172** (0.500 g, 0.927 mmol) was deprotected under the conditions described in general procedure **B** to yield the hydroxylamine **448** (0.361 g, 0.881 mmol) as a colourless oil which was treated as unstable and cyclised immediately under the conditions described in general method **E** to give the *title compound* **187** (0.345 g, 91% over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 1717, 1661, and 1117; δ_H 0.92 (3H, d, *J* 6.3, ^{i}Bu-CH_3), 0.94 (3H, d, *J* 6.4, ^{i}Bu-CH_3), 1.05 (9H, s, ^{t}Bu-CH_3), 1.35-1.25 (1H, m, ^{i}Bu-H), 1.79-1.63 (2H, m, ^{i}Bu-CH_2), 2.62-2.55 (3H, m, 4-H_a and CH_2), 3.01 (1H, dd, *J* 16.9 and 10.1, 4-H_b), 3.87 (2H, t, *J* 6.2, CH_2), 4.57 (1H, dtd, *J* 10.1, 8.2 and 5.7, 5-H), 7.44 (6H, m, 6 x Ar-H) and 7.66 (4H, m, 4 x Ar-H); δ_C 19.2 (tBu-C), 22.3 (CH_3), 22.9 (CH_3), 25.3 (CH), 26.8 (tBu-CH_3), 31.1 (CH_2), 43.2 (CH_2), 44.4 (CH_2), 61.4 (CH_2), 78.8 (CH), 127.7 (Ar-H), 129.8 (Ar-H), 133.3 (Ar), 135.6 (Ar-H) and 157.4 (CN); *m/z* [APcI] 410.1 (M^+ + H, 100%); [Found M^+ + H: 410.2513. $C_{25}H_{36}NO_2Si$ requires *M*, 410.2515].

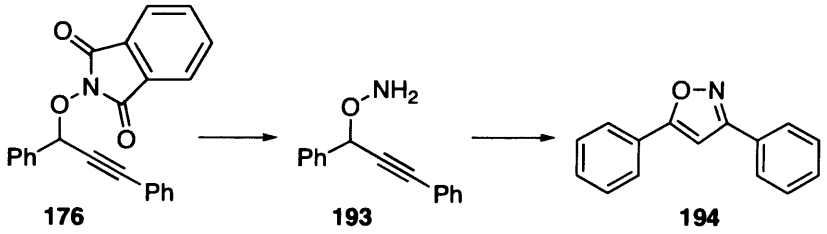
3,5-Diphenyl-4,5-dihydroisoxazole 190 [149]



The phthalimide **176** (0.500 g, 1.416 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **449** (0.295 g, 1.331 mmol) as a pale yellow oil

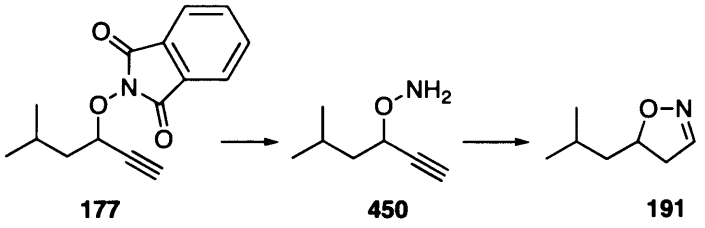
which was treated as an unstable intermediate and cyclised immediately under the conditions described in general method **E** to give the *title compound* **190** (0.281 g, 89% over 2 steps) as a pale yellow oil. All data obtained was in accordance with that previously reported in the literature[149] and showed: δ_H 3.35 (1H, dd, *J* 8.7 and 6.8, 4-H_a), 3.78 (1H, dd, *J* 10.8 and 16.8, 4-H_b), 5.74 (1H, dd, *J* 8.7 and 10.8, 5-H), 7.42-7.30 (8H, m, 8 x Ar-H) and 7.68-7.70 (2H, m, 2 x Ar-H); δ_C 43.0 (CH_2), 82.5 (CH), 125.8 (Ar-H), 126.7 (Ar-H), 128.7 (Ar-H), 129.4 (Ar-H), 130.1 (Ar), 140.9 (Ar) and 156.0 (CN); [Found M^+ + H: 224.1070. $C_{15}H_{14}NO$ gives 224.1075].

3,5-Diphenylisoxazole 194 [75]



The phthalimide **176** (0.500 g, 1.416 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **193** (0.290 g, 1.330 mmol) as a pale yellow oil which was treated as an unstable intermediate that was taken up in dry dichloromethane (10 ml) and stirred in the dark (as described in general method **E**). 10% w/w silver nitrate on silica (3.371 g, 1.995 mmol) was added and the resulting mixture stirred overnight. The reaction was filtered through a pad of celite and the solvent removed *in vacuo* to give the crude product, which was purified *via* silica gel chromatography (5% ethyl acetate/petrol) to yield the *title compound* **194** (0.213 g, 68% over 2 steps) as a pale yellow solid. All data obtained was in accordance with that previously reported in the literature[75] and showed: mp 143-144 [Lit.[75] 140-141°C]; δ_H 6.83 (1H, s, 4-H), 7.51-7.44 (6H, m, 6 x Ar-H) and 7.88-7.82 (4H, m, 4 x Ar-H); δ_C 97.4 (CH), 125.7, 126.7, 127.3, 128.8, 128.9, 130.1 (All Ar-H), 162.9 (Ar) and 170.3 (Ar); *m/z* [APcI] 222.3 (M^+ + H, 100%).

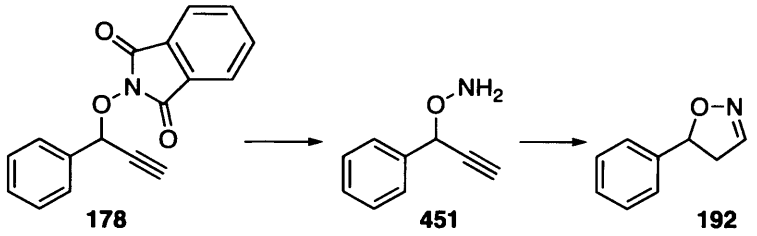
4,5-Dihydro-5-isobutylisoxazole 191



The phthalimide **177** (0.500 g, 1.945 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **450** (0.240 g, 1.906 mmol) as a colourless oil which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (20 ml) and stirred in the dark (as described in general

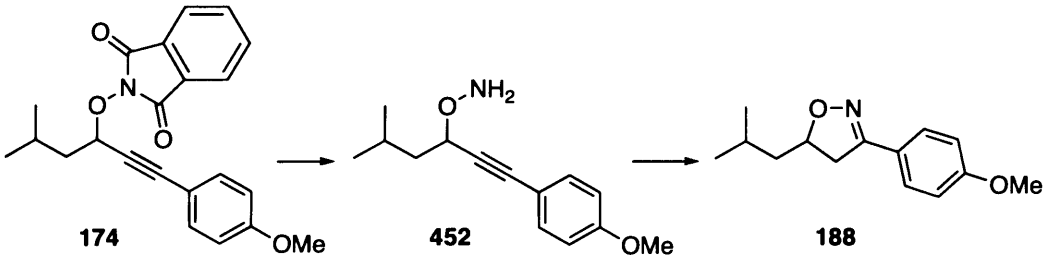
method **E**). 10% w/w silver nitrate on silica (0.330 g, 0.194 mmol) was added and the resulting mixture stirred overnight. The reaction was filtered through a pad of celite and the solvent removed *in vacuo* to give the *title compound* **191** (0.236 g, 96% over 2 steps) as a sweet smelling, pale yellow oil characterised by: ν_{max}/cm^{-1} [film] 1759, 1715, 1594, 1435 and 1383; δ_H 0.96 (6H, app. t, *J* 6.9, 2 x CH_3), 1.38-1.31 (1H, m, ^{i}Bu-H), 1.70-1.63 (1H, m, ^{i}Bu-H_a), 1.85-1.75 (1H, m, ^{i}Bu-H_b), 2.59 (1H, ddd, *J* 17.3, 8.2 and 1.7, 4-H_a), 3.06 (1H, ddd, *J* 17.3, 10.3 and 1.7, 4-H_b), 4.58 (1H, app. ddt, *J* 10.3, 8.2 and 5.6, 5-H) and 7.12 (1H, app. t, *J* 1.7, 3-H); δ_C 22.2 (CH_3), 22.9 (CH_3), 25.3 (CH), 41.0 (CH_2), 44.3 (CH_2), 77.3 (CH) and 146.0 (CN); [Found M^+ + H: 128.1073. $C_7H_{14}NO$ requires *M*, 128.1075].

4,5-Dihydro-5-phenylisoxazole 192 [150]



The phthalimide **178** (0.500 g, 1.804 mmol) deprotected under the conditions described in general method **B** to yield the hydroxylamine **451** (0.246 g, 1.678 mmol) which was treated as an unstable intermediate and cyclised immediately under the conditions described in general method **E** to yield the *title compound* **192** (0.238 g, 90% over 2 steps) as a yellow oil. All data obtained were in accordance with those previously reported in the literature[150] and showed: ν_{max}/cm^{-1} [film] 1758, 1718, 1600, 1493, 1434, 1383, 1291 and 1253; δ_H 2.99 (1H, ddd, *J* 17.6, 8.1 and 1.8, 4-H_a), 3.44 (1H, ddd, *J* 17.6, 11.2 and 1.8, 4-H_b), 5.53 (1H, dd, *J* 11.2 and 8.1, 5-H), 7.21 (1H, br. t, *J* 1.8, 3-H), 7.39-7.31 (5H, m, 5 x Ar-H), 7.71 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H) and 7.84 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 43.8 (CH_2), 79.9 (CH), 125.5 (Ar-H), 128.5 (Ar-H), 127.9 (Ar-H), 140.9 (Ar) and 145.6 (CN); [Found M^+ + H: 148.0755. $C_9H_{10}NO$ requires *M*, 148.0762].

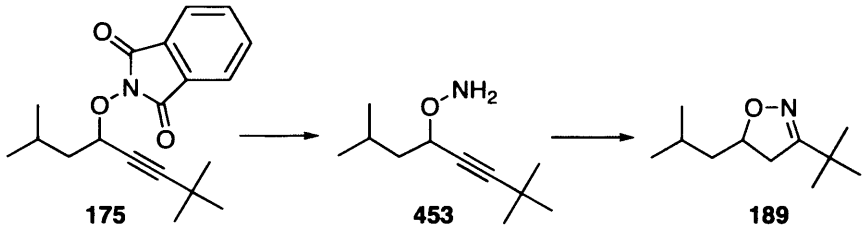
4,5-Dihydro-5-isobutyl-3-(4-methoxyphenyl)isoxazole 188



The phthalimide **174** (0.500 g, 1.377 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **452** (0.312 g, 1.336 mmol) as a pale yellow oil

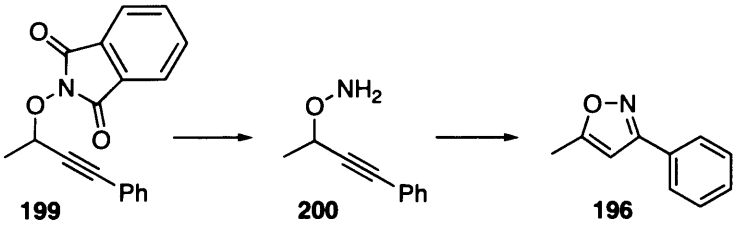
which was treated as an unstable intermediate and cyclised immediately under the conditions described in general method **E** to give the *title compound* **188** (0.294 g, 91% over 2 steps) as a colourless solid showing: mp 79-80°C; ν_{max}/cm^{-1} [film] 1719, 1647, 1372, 1126, 1034 and 999; δ_H 0.90 (3H, d, *J* 6.7, ^{i}Bu-CH_3), 0.92 (3H, d, *J* 6.7, ^{i}Bu-CH_3), 1.40-1.33 (1H, m, ^{i}Bu-H), 1.81-1.65 (1H, m, ^{i}Bu- H_a and H_b), 2.85 (1H, dd, *J* 8.3 and 16.2, 4-H_a), 3.32 (1H, dd, *J* 10.0 and 16.2, 4-H_b), 3.77 (3H, s, OCH_3), 4.70 (1H, app. dtd, *J* 5.7, 8.3 and 10.0, 5-H), 6.84 (2H, br. d, *J* 8.9, 2 x Ar-H) and 7.54 (2H, br. d, *J* 8.9, 2 x Ar-H); δ_C (125 MHz) 22.4 (CH_3), 22.9 (CH_3), 25.4 (CH), 40.8 (CH_2), 44.5 (CH_2), 55.4 (CH_3), 79.7 (CH), 114.1 (Ar-H), 128.1 (Ar-H) and 158.0 (CN); [Found M^+ + H: 234.1496. $C_{14}H_{20}NO_2$ requires *M*, 234.1494].

3-*tert*-Butyl-4,5-dihydro-5-isobutylisoxazole 189



The phthalimide **175** (0.500 g, 1.596 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **453** (0.287 g, 1.564 mmol) as a colourless oil which was treated as an unstable intermediate and cyclised immediately under the conditions described in general method **E** to yield the *title compound* **189** (0.281 g, 96% over 2 steps) as a colourless oil: ν_{max}/cm^{-1} [film] 1721, 1467, 1367 and 1255; δ_H 0.87 (6H, app. t, *J* 6.4, 2 x CH_3), 1.12 (9H, s, 3 x ^{t}Bu-CH_3), 1.28-1.21 (1H, m, ^{i}Bu-H), 1.62-1.55 (1H, m, ^{i}Bu-H_a), 1.76-1.66 (1H, m, ^{i}Bu-H_b), 2.47 (1H, dd, *J* 16.4 and 8.4, 4-H_a), 2.94 (1H, dd, *J* 16.4 and 9.9, 4-H_b) and 4.50 (1H, app. ddt, *J* 9.9, 8.4 and 5.7, 5-H); δ_C 22.4 (CH_3), 22.9 (CH_3), 25.4 (CH), 28.1 (3 x CH_3), 33.0 (C), 39.9 (CH_2), 44.3 (CH_2), 79.0 (CH) and 166.1 (CN); [Found M^+ + H: 184.1708. $C_{11}H_{22}NO$ requires *M*, 184.1701].

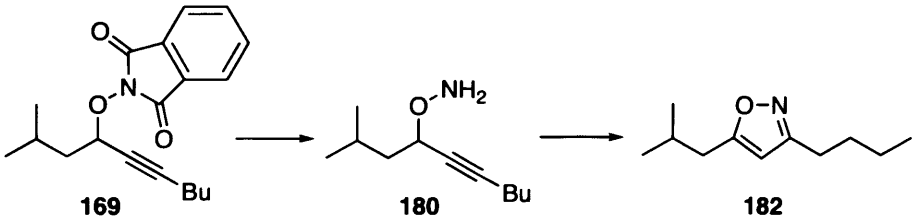
5-Methyl-3-phenylisoxazole 196 [74]



The phthalimide **199** (0.500 g, 1.718 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **200** (0.270 g, 1.683 mmol) as a colourless oil which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (20 ml) and stirred in the dark (as described in general method

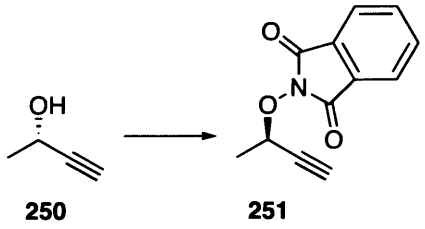
E). 10% w/w silver nitrate (0.286 g, 0.168 mmol) was added and the resulting mixture stirred overnight. The reaction was filtered through a pad of celite and the solvent removed *in vacuo* to yield the crude product which was purified by silica gel chromatography (5% ethyl acetate/petrol) to give the *title compound* **196** (0.174 g, 64% over 2 steps) as a pale yellow oil. All data obtained was in accordance with that previously reported in the literature[74] and showed: δ_H 2.44 (3H, s, CH_3), 6.28 (1H, s, 4-H), 7.50-7.35 (3H, m, 3 x Ar-H) and 7.82-7.78 (2H, m, 2 x Ar-H); *m/z* [APcI] 160.2 (M^+ + H, 100%).

3-Butyl-5-isobutylisoxazole 182



The phthalimide **169** (0.500 g, 1.596 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.282 g, 1.548 mmol) as a colourless oil which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (15 ml) and stirred in the dark (as described in general method **E**). 10% w/w silver nitrate on silica (0.262 g, 0.155 mmol) was added and the resulting mixture stirred overnight. The reaction was filtered through a pad of celite and the solvent evaporated. The crude product was purified by silica gel chromatography (5% ethyl acetate/petrol) to give the *title compound* **182** (0.212 g, 73% over 2 steps) as a pale yellow oil: ν_{max}/cm^{-1} [film] 1586, 1470, 1390 and 1188; δ_H 0.93 (3H, t, *J* 7.3, Bu-CH_3), 0.96 (6H, d, *J* 6.7, 2 x ^{i}Bu-CH_3), 1.43-1.34 (2H, m, Bu-CH_2), 1.70-1.59 (2H, m, Bu-CH_2), 2.09-1.96 (1H, m, ^{i}Bu-H), 2.58 (2H, d, *J* 7.1, ^{i}Bu-CH_2), 2.63 (2H, t, *J* 7.7, Bu-CH_2) and 5.82 (1H, s, 4-H); δ_C 13.7 (CH_3), 22.3 (CH_3), 25.8 (CH_2), 27.7 (CH), 30.5 (CH_2), 30.6 (CH_2), 35.8 (CH_2), 101.1 CH), 164.0 (CN) and 172.3 (CO); *m/z* [APcI] 182.2 (M^+ + H, 100%); [Found M^+ + NH_4: 199.1812. $C_{11}H_{23}N_2O$ requires *M*, 199.1807].

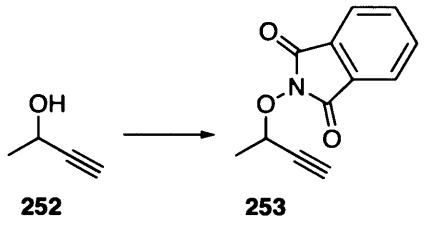
2-[(*R*)-But-3-yn-2-yloxy]isoindoline-1,3-dione 251



(*S*)-But-3-yn-2-ol **250** (0.500 g, 7.143 mmol) was reacted with *N*-hydroxyphthalimide (1.176 g, 7.214 mmol) under the conditions described in general method **A** to yield the *title compound*

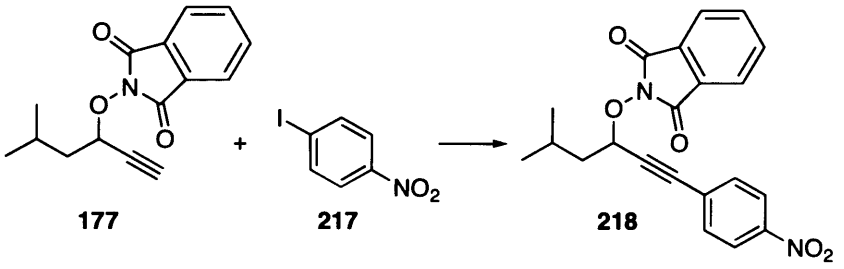
251 (1.412 g, 92%) as a colourless solid: mp 102-103°C; ν_{max}/cm^{-1} [DCM] 3296, 1795, 1720, 1630 and 1366; δ_H 1.62 (3H, d, *J* 6.7, 1-CH_3), 2.47 (1H, d, *J* 2.1, 4-H), 5.10 (1H, qd, *J* 6.7 and 2.1, 2-H), 7.70 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H) and 7.79 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); 20.1 (CH_3), 73.1 (CH), 76.1 (C), 80.7 (CH), 123.7 (Ar-H), 128.8 (Ar), 134.6 (Ar-H) and 163.6 (CO); *m/z* [APcI] 216.1 (M^+ + H, 100%); [Found M^+ + H: 216.0673. $C_{12}H_{10}N_3O$ requires *M*, 216.0661].

2-(But-3-yn-2-yloxy)isoindoline-1,3-dione 253



But-3-yn-2-ol **252** (0.500 g, 7.143 mmol) was reacted with *N*-hydroxyphthalimide (1.176 g, 7.214 mmol) under the conditions described in general method **A** to yield the *title compound* **253** (1.428 g, 93%) as a colourless solid. All data obtained were identical to those obtained for the foregoing, optically pure sample with the exception of: mp 119-120°C.

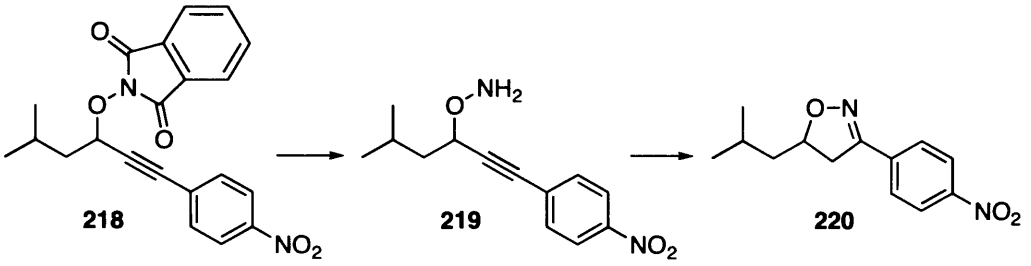
2-[5-Methyl-1-(4-nitrophenyl)hex-1-yn-3-yloxy]isoindoline-1,3-dione 218



To a solution of *p*-nitro-iodobenzene **217** (0.329 g, 1.321 mmol) in dry tetrahydrofuran (15 ml) was added dichloro-bis(triphenylphosphine)palladium (0.050 g, 0.132 mmol) and copper iodide (0.025 g, 0.132 mmol). The resulting mixture was heated at reflux for 5 min before being allowed to cool to room temperature. Over the course of this the mixture was observed to adopt a pale green colour. Dry diisopropylamine (1.85 ml, 13.210 mmol) was added *via* syringe, immediately followed by the alkyne **177** (0.340 g, 1.321 mmol) in one portion. The mixture was heated at reflux for one hour and then allowed to stir at room temperature overnight. The solvent mixture was evaporated to give a thick black oil, which was taken up in dichloromethane (20 ml) and washed with water (3 x 20 ml). A small amount of decolourising charcoal was added to the organic layer, followed by magnesium sulphate as a drying agent. The mixture was filtered and the solvent evaporated to give the crude product, which was purified by silica gel chromatography to yield the *title compound* **218** (0.163 g, 33%) as a thick,

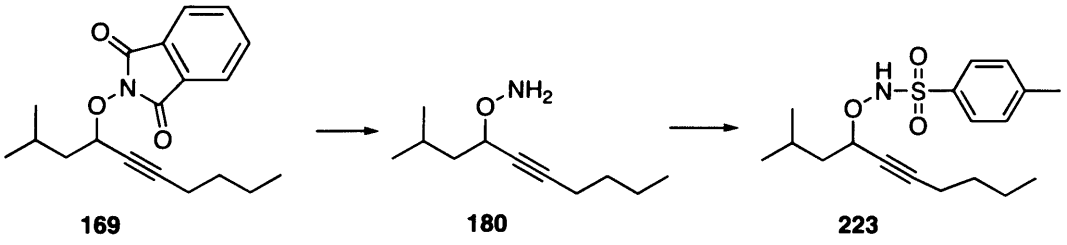
yellow oil: ν_{max}/cm^{-1} [film] 1791, 1737, 1594, 1520, 1492, 1468, 1344; δ_H 1.04 (3H, d, *J* 6.3, CH_3), 1.11 (3H, d, *J* 6.4, CH_3), 1.91-1.83 (1H, m, 5-H), 2.14-2.05 (2H, m, 4- H_a and H_b), 5.30 (1H, app. t, *J* 6.9, 3-H), 7.54-7.51 (2H, m, 2 x Ar-H), 7.77 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H), 7.87 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 8.17-8.14 (2H, m, 2 x Ar-H); δ_C 22.4 (CH_3), 22.6 (CH_3), 25.0 (CH), 42.4 (CH_2), 86.1 (C), 91.1 (C), 123.6 (Ar-H), 123.7 (Ar-H), 128.8 (Ar), 132.4 (Ar-H), 134.7 (Ar-H) and 163.7 (CO); [Found M^+ + H: 379.1292. $C_{21}H_{19}N_2O_5$ requires *M*, 379.1294].

4,5-Dihydro-5-isobutyl-3-(4-nitrophenyl)isoxazole 220



The phthalimide **218** (0.150 g, 0.397 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **219** (0.096 g, 0.385 mmol) as a pale yellow oil which was treated as an unstable intermediate and immediately cyclised under the conditions described in general method **E** to give the *title compound* **220** (0.092 g, 94% over 2 steps) as a pale yellow oil characterised by: ν_{max}/cm^{-1} [film] 1727, 1529, 1517, 1429, 1320, 1233, 1138 and 1090; δ_H 0.99 (3H, d, *J* 6.6, CH_3), 1.01 (3H, d, *J* 6.5, CH_3), 1.52-1.45 (1H, m, ^{i}Bu-H), 1.91-1.77 (2H, m, ^{i}Bu-H_a and H_b), 2.97 (1H, dd, *J* 16.4 and 8.4, 4-H_a), 3.45 (1H, dd, *J* 16.4 and 10.4, 4-H_b), 4.90 (1H, app. ddt, *J* 10.4, 8.4 and 5.7, 5-H), 7.84-7.81 (2H, m, 2 x Ar-H) and 8.28-8.25 (2H, m, 2 x Ar-H); δ_C 22.4 (CH_3), 22.9 (CH_3), 25.3 (CH), 39.9 (CH_2), 44.5 (CH_2), 81.3 (CH), 124.0 (Ar-H), 127.2 (Ar-H), 136.0 (Ar) and 155.0 (CN); *m/z* [APcI] 249.4 (M^+ + H, 100%); [Found M^+ + H: 249.1236. $C_{13}H_{17}N_2O$ requires *M*, 249.1239].

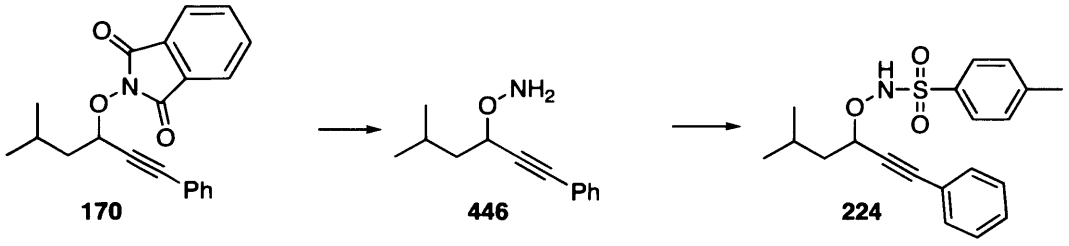
***O*-(2-Methyldec-5-yn-4yl)-*N*-(*p*-toluenesulphonyl)hydroxylamine 223**



The phthalimide **169** (0.500 g, 1.596 mmol) was deprotected under the conditions described in general procedure **B** to yield the hydroxylamine **180** (0.282 g, 1.533 mmol) as a colourless oil which was treated as unstable and tosylated immediately under the conditions described in general method **C** to give the *title compound* **223** (0.463 g, 86% over 2 steps) as a colourless

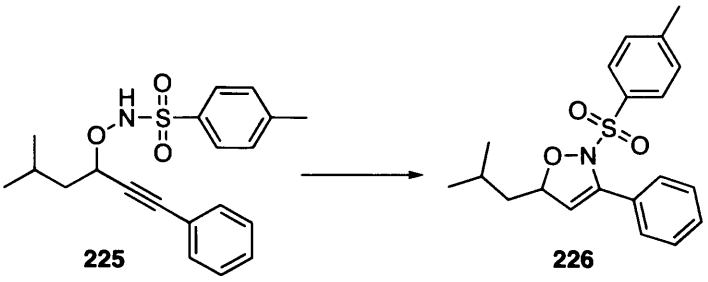
solid. An analytical sample was obtained by silica gel chromatography (10-20% ethyl acetate/petrol) and showed: mp 122-123°; ν_{max}/cm^{-1} [thin film] 3225, 1561, 1461, 1340 and 1161; δ_H 0.91 (9H, m, 3 x CH_3), 1.50-1.36 (5H, m, 2-H, 8- and 9-CH_2), 1.65-1.55 (1H, m, 3-H_a), 1.84-1.73 (1H, m, 3-H_b), 2.20 (2H, td, *J* 7.0 and 1.9, 7-CH_2), 2.45 (3H, s, Ar-CH_3), 4.66 (1H, app. tt, *J* 7.2 and 1.9, 4-H), 7.26, 1H, br. s, NH), 7.34 (2H, d, *J* 8.2, 2 x Ar-H) and 7.80 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 13.6 (CH_3), 18.4 (CH_2), 21.7 (CH_3), 21.9 (CH_2), 22.5 (CH_3), 24.7 (CH), 30.6 (CH_2), 43.0 (CH_2), 76.0 (CH), 77.7 (C), 87.5 (C), 128.6 (Ar-H), 129.7 (Ar-H), 133.8 (Ar) and 144.8 (Ar); *m/z* [APcI] 338.4 (M^+ + H, 100%); [Found M^+ + H: 338.1786. $C_{18}H_{28}N_2O_3S$ requires *M*, 338.1790].

***O*-[(2-Methyl-6-phenyl-hex-5-ynyl)4-yl]-*N*-(*p*-toluenesulphonyl)hydroxylamine 224**



The phthalimide **170** (0.500 g, 1.501 mmol) was deprotected under the conditions described in general procedure **B** to yield the hydroxylamine **446** (0.294 g, 1.456 mmol) as a colourless oil which was treated as unstable and tosylated immediately under the conditions described in general method **C** to give the *title compound* **224** (0.434 g, 81% over 2 steps) as a colourless solid. An analytical sample was obtained by silica gel chromatography (10-20% ethyl acetate/petrol) and showed: mp 129-130°C; ν_{max}/cm^{-1} [nujol] 3221, 1569, 1351, 1238 and 1160; δ_H 0.94 (3H, d, *J* 6.6, CH_3), 0.99 (3H, d, *J* 6.6, CH_3), 1.63-1.56 (1H, m, 2-H), 1.78-1.71 (1H, m, 3-H_a), 1.90-1.82 (1H, m, 3-H_b), 2.45 (3H, s, Ar-CH_3), 4.91 (1H, app. t, *J* 7.2, 4-H), 7.05 (1H, s, NH), 7.33-7.29 (3H, m, 3 x Ar-H), 7.35 (2H, d, *J* 8.2, 2 x Ar-H), 7.43-7.41 (2H, m, 2 x Ar-H) and 7.83 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 22.2 (CH_3), 22.6 (CH_3), 25.0 (CH), 42.6 (CH_2), 76.9 (CH), 85.5 (C), 88.3 (C), 122.0 (Ar), 128.2 (Ar-H) 128.8 (Ar-H), 128.7 (Ar-H), 129.6 (Ar-H), 131.6 (Ar-H), 133.8 (Ar) and 144.5 (Ar); *m/z* [APcI] 358.1 (M^+ + H, 100%), 114.4 (20 %).

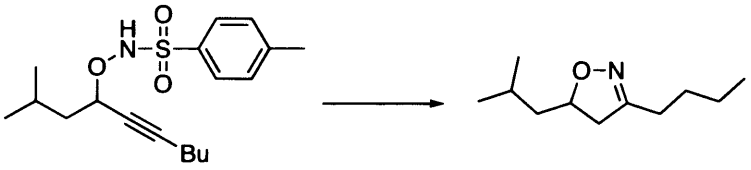
5-Isobutyl-3-phenyl-2-(*p*-toluenesulphonyl)-2,5-dihydroisoxazole 226



225 **226**

To a solution of the sulphonamide **225** (0.250 g, 0.700 mmol) in dry dichloromethane (7 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.120 g, 0.070 mmol). The resulting mixture was stirred for 4h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **226** (0.241 g, 96%) as a pale, yellow oil characterised by: ν_{max}/cm^{-1} [film] 1590, 1493, 1390, 1382, 1173 and 1076; δ_H 0.98 (3H, d, *J* 6.6, CH_3), 1.01 (3H, d, *J* 6.6, CH_3), 1.38-1.31 (1H, m, ^iBu-H), 1.69-1.62 (1H, m, ^iBu-H_a), 1.89-1.82 (1H, m, ^iBu-H_b), 2.41 (3H, s, Ar-CH_3), 4.75 (1H, d, *J* 3.0, 4-H), 5.31 (1H, ddd, *J* 8.7, 6.0 and 3.0, 5-H), 7.22 (2H, d, *J* 8.2, 2 x Ar-H), 7.46-7.38 (3H, m, 3 x Ar-H), 7.50 (2H, d, *J* 8.2, 2 x Ar-H) and 7.72-7.70 (2H, m, 2 x Ar-H); δ_C 21.8 (CH_3), 22.3 (CH_3), 22.6 (CH_3), 24.5 (CH), 43.4 (CH_2), 83.2 (CH), 127.7 (Ar-H), 128.7 (Ar-H), 129.2 (Ar-H), 129.6 (Ar-H), 130.5 (Ar-H), 132.1 (Ar), 132.7 (Ar) and 145.8 (Ar) *Missing some quaternary carbons*; *m/z* [APcI] 358.1 (M^+ + H, 100%); [Found M^+ + H: 358.1479. $C_{20}H_{24}NO_3S$ requires *M*, 358.1477].

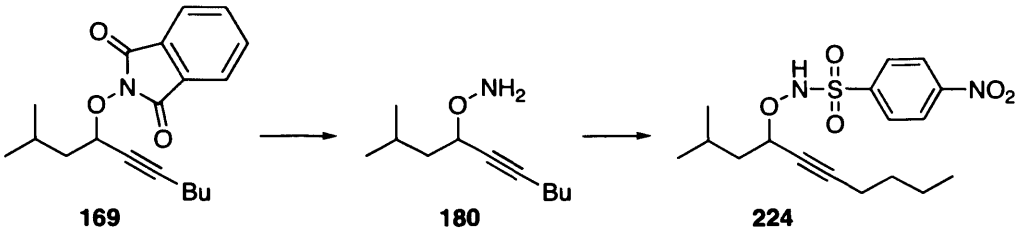
3-Butyl-4,5-dihydro-5-isobutylisoxazole 181 (Alternative Synthesis)



223 **181**

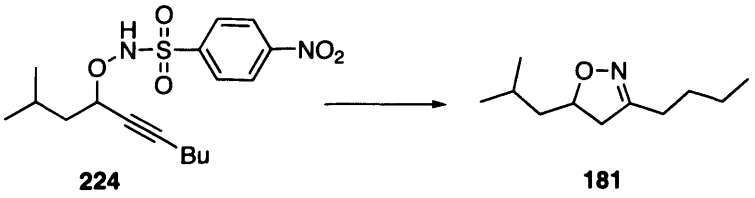
To a solution of the sulphonamide **223** (0.250 g, 0.741 mmol) in dry dichloromethane (7 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.126 g, 0.074 mmol). The resulting mixture was stirred for 4h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **181** (0.111 g, 81%) as a pale, yellow oil. All data obtained were identical to those obtained for the foregoing sample.

O-(2-Methyldec-5-yn-4yl)-N-((p-nitrophenyl)sulphonyl)hydroxylamine 224



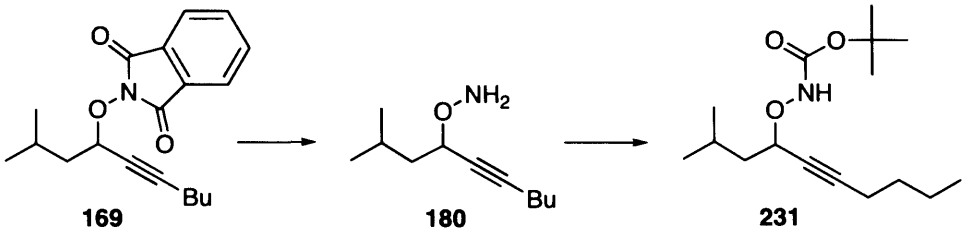
The phthalimide **169** (0.250 g, 0.798 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.233 g, 1.271 mmol) as a colourless oil, which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (12 ml) and stirred at 0°C. Pyridine (0.10 ml, 1.271 mmol) and DMAP (0.005 g) were added and the resulting solution stirred for 5 mins. *p*-Nitrobenzenesulphonylchloride (0.282 g, 1.271 mmol) was added in one portion and the solution allowed to warm to room temperature overnight. The reaction was quenched by the addition of water (10 ml) and extracted into dichloromethane (3 x 10 ml). The organic portions were combined and washed with sat. aq. copper sulphate solution (30 ml) and water (3 x 30 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield the crude product as a brown solid which was purified *via* silica gel chromatography (10-20% ethyl acetate/petrol) to yield the *title compound* **224** (0.252 g, 86% over 2 steps) as a yellow solid: mp 119-120°C; ν_{max}/cm^{-1} [nujol] 1712, 1512, 1320 and 1256; δ_H 0.89 (3H, t, *J* 6.6, 10-CH_3), 0.91 (3H, d, *J* 7.2, CH_3), 0.96 (3H, d, *J* 6.6, CH_3), 1.52-1.36 (5H, m, 8- and 9-CH_2 and 2-H), 1.67-1.60 (1H, m, 3-H_a), 1.83-1.73 (1H, m, 3-H_b), 2.21 (2H, td, *J* 7.1 and 1.9, 7-CH_2), 4.73 (1H, app. tt, *J* 7.2 and 1.9, 4-H), 8.14-8.10 (2H, m, 2 x Ar-H) and 8.42-8.39 (2H, m, 2 x Ar-H); δ_C 13.6 (CH_3), 18.4 (CH_2), 21.7 (CH_3), 21.9 (CH_2), 24.7 (CH), 30.6 (CH_2), 43.0 (CH_2), 77.9 (CH), 78.7 (C), 87.9 (C), 124.4 (Ar-H), 129.9 (Ar-H), 142.1 (Ar) and 150.6 (Ar); *m/z* [APcI] 369.3 (M^+ + H, 100%); [Found M^+ + H: 369.1481. $C_{17}H_{25}N_2O_5S$ requires *M*, 369.1484].

3-Butyl-4,5-dihydro-5-isobutylisoxazole 181 (Alternative Synthesis)



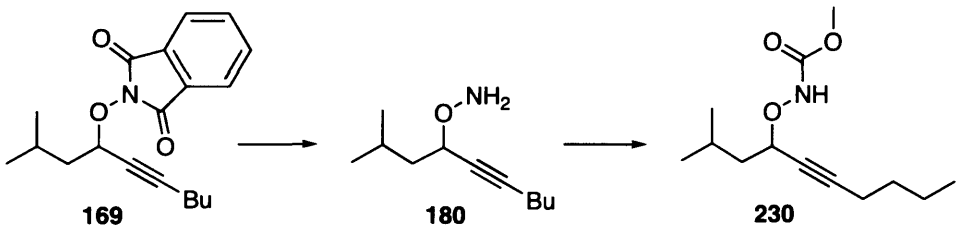
To a solution of the sulphonamide **224** (0.250 g, 0.679 mmol) in dry dichloromethane (7 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.115 g, 0.068 mmol). The resulting mixture was stirred for 4h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **181** (0.109 g, 89%) as a pale, yellow oil. All data obtained were identical to those obtained for the foregoing sample.

***N*-(2-Methyldec-5-yn-4-oxy)-*tert*-butyl carbamate 231**



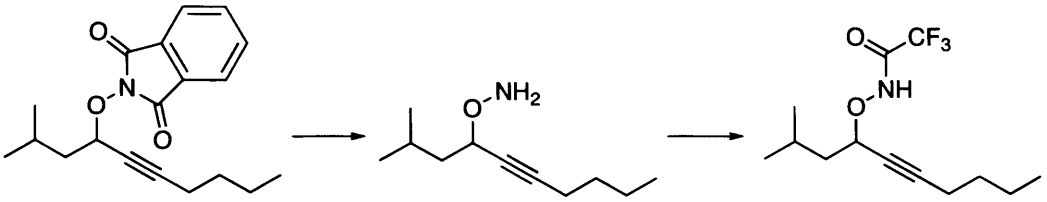
The phthalimide **169** (0.180 g, 0.575 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.103 g, 0.562 mmol) which was treated as an unstable intermediate as reacted immediately. The crude product was reacted with BOC-ON (0.140 g, 0.568 mmol) under the conditions described in general method **F** to give the crude product which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to yield the *title compound* **231** (0.132 g, 81% over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3312, 2237, 1714, 1469, 1368; δ_H 0.91 (3H, d, *J* 6.6, CH_3), 0.92 (3H, t, *J* 7.2, 10-CH_3), 0.97 (3H, d, *J* 6.6, CH_3), 1.49 (9H, s, tBu-CH_3), 1.55-1.38 (5H, m, 2-H and 8- and 9-CH_2), 1.73-1.66 (1H, m, 3-H_a), 1.93-1.85 (1H, m, 3-H_b), 2.23 (2H, td, *J* 7.0 and 1.8, 7-CH_2), 4.53 (1H, br. t, *J* 7.1, 4-H) and 7.23 (1H, s, NH); δ_C 13.6 (CH_3), 18.5 (CH_2), 22.0 (CH_2), 22.6 (CH_3), 22.7 (CH_3), 24.8 (CH), 28.3 (CH_3), 30.7 (CH_2), 42.9 (CH_2), 74.9 (CH), 77.9 (C), 81.7 (C), 87.3 (C), 156.3 (CO); [Found M^+ + Na: 306.2031. $C_{16}H_{29}NNaO_3$ requires *M*, 306.2045].

***N*-(2-Methyldec-5-yn-4-oxy)-methyl carbamate 230**



The phthalimide **169** (0.500 g, 1.596 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.281 g, 1.533 mmol) as a colourless oil which was treated as an unstable intermediate and reacted immediately. The crude product was reacted with methylchloroformate (0.216 g, 2.300 mmol) under the conditions described in general method **F** to give the crude product which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to give the *title compound* **230** (0.065 g, 17% over 2 steps) as a colourless oil. *N.B. The compound obtained was highly unstable; hampering attempts at characterisation.*

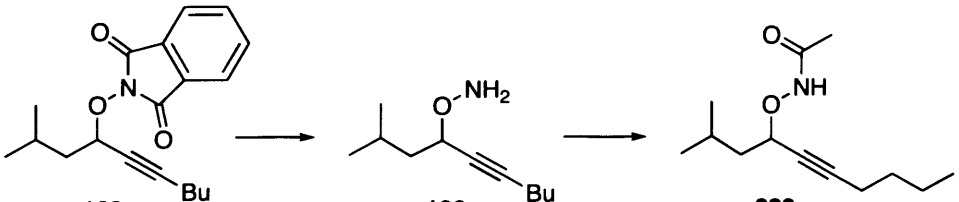
N-(2-Methyldec-5-yn-4-yloxy)-2,2,2-trifluoroacetamide 232



169 180 232

The phthalimide **169** (0.407 g, 1.300 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.235 g, 1.282 mmol) as a colourless oil, which was treated as an unstable intermediate and reacted immediately. The crude product was reacted with trifluoroacetic anhydride (0.410 g, 1.950 mmol) under the conditions described in general method **F** to give the *title compound* **232** (0.308 g, 85% over 2 steps) as a colourless oil, characterised by: ν_{max}/cm^{-1} [film] 3220, 2229, 1720, 1387, 1125 and 998; δ_H (DMSO) 0.92 (3H, t, *J* 6.6, 10-CH_3), 0.94 (3H, d, *J* 6.7, CH_3), 0.99 (3H, d, *J* 6.6, CH_3), 1.45-1.38 (2H, m, 9-CH_2), 1.54-1.47 (2H, m, 8-CH_2), 1.62-1.55 (1H, m, 2-H), 1.79-1.72 (1H, m, 3-H_a), 1.94-1.86 (1H, m, 3-H_b), 2.25 (2H, td, *J* 7.0 and 1.9, 7-CH_2), 4.75 (1H, app. tt, *J* 7.0 and 1.9, 4-H) and 8.87 (1H, br. s, NH); δ_C (DMSO) 13.5 (CH_3), 18.4 (CH_2), 21.9 (CH_2), 22.4 (CH_3), 22.5 (CH_3), 24.8 (CH), 30.5 (CH_2), 42.6 (CH_2), 76.0 (CH), 76.1 (C), 89.9 (C) and 165.3 (CO); *m/z* [APcI] 280.3 (M^+ + H, 100%); [Found M^+ + H: 280.1525. $C_{13}H_{21}F_3NO_2$ requires *M*, 280.1524].

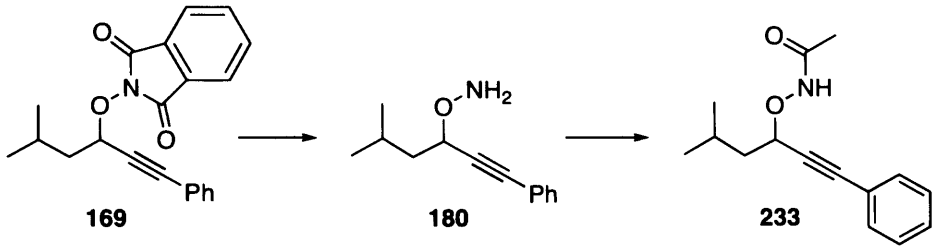
N-(2-Methyldec-5-yn-4-yloxy)acetamide 228



169 180 228

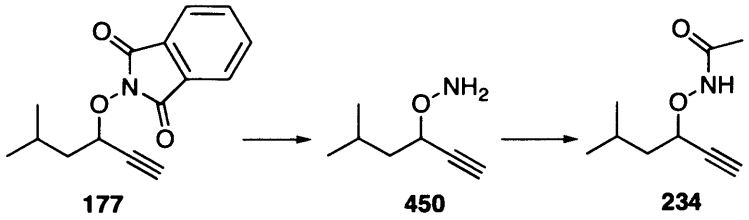
The phthalimide **169** (0.550 g, 1.756 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.309 g, 1.686 mmol) which was treated as an unstable intermediate and reacted immediately with acetyl chloride (0.197 g, 2.529 mmol) under the conditions described in general method **F** to give the *title compound* **228** (0.365 g, 92% over 2 steps) as a colourless oil: ν_{max}/cm^{-1} [film] 3194, 2221, 1667 and 1469; δ_H (DMSO) 0.90 (3H, d, *J* 6.6, CH_3), 0.92 (3H, t, *J* 7.3, 10-CH_3), 0.97 (3H, d, *J* 6.6, CH_3), 1.50-1.38 (5H, m, 2-H and 8- and 9-CH_2), 1.67-1.60 (1H, m, 3-H_a), 1.77 (3H, br. s, CH_3CO), 1.89-1.81 (1H, m, 3-H_b), 2.26 (2H, br. t, *J* 6.1, 7-CH_2), 4.49 (0.1H, br. s, 4-H) and 4.57 (0.9H, br. t, *J* 6.9, 4-H); δ_C (DMSO) 13.9 (CH_3), 18.1 (CH_2), 20.0 (CH_3), 21.7 (CH_2), 22.7 (CH_3), 23.0 (CH_3), 24.9 (CH), 30.6 (CH_2), 43.1 (CH_2), 73.3 (CH), 79.1 (C), 87.2 (C) and 166.9 (CO); *m/z* [APcI] 226.3 (M^+ + H, 100%); [Found M^+ + Na: 248.1629. $C_{13}H_{23}NO_2Na$ requires *M*, 248.1626].

N-(5-Methyl-1-phenylhex-1-yn-3-yloxy)acetamide 233



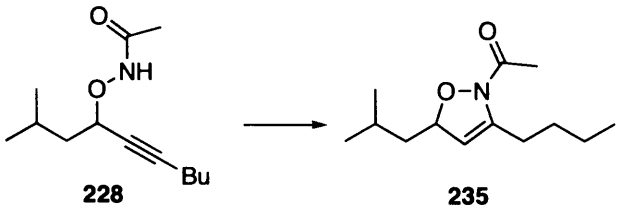
The phthalimide **169** (0.305 g, 0.916 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **180** (0.177 g, 0.870 mmol) as a colourless oil which was treated as an unstable intermediate and immediately reacted with acetyl chloride (0.102 g, 1.305 mmol) under the conditions described in general method **F** to give the *title compound* **233** (0.202 g, 90% over 2 steps) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3221, 2218, 1667, 1490; δ_H (DMSO) 0.92 (3H, d, *J* 6.6, CH_3), 0.98 (3H, d, *J* 6.6, CH_3), 1.63-1.54 (1H, m, 5-H), 1.77 (3H, s, Ac-CH_3), 1.81-1.70 (1H, m, 4-H_a), 1.94-1.85 (1H, m, 4-H_b), 4.80 (1H, app. t, *J* 6.6, 3-H), 7.41-7.40 (3H, m, 3 x Ar-H) and 7.47-7.45 (2H, m, 2 x Ar-H); δ_C (DMSO) 20.1 (CH_3), 22.9 (CH_3), 25.0 (CH), 42.8 (CH_2), 73.6 (CH), 129.1 (Ar-H), 129.3 (Ar-H) and 132.0 (Ar-H); *m/z* [APcI] 246.3 (M^+ + H, 100%) and 172.8 (40%); [Found M^+ + H: 246.1491. $C_{15}H_{20}NO_2$ requires *M*, 246.1494].

N-(5-Methylhex-1-yn-3-yloxy)acetamide 234



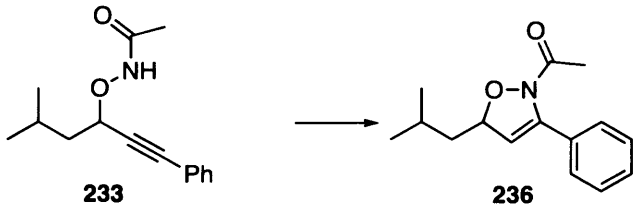
The phthalimide **177** (0.500 g, 1.945 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **450** (0.242 g, 1.906 mmol) as a colourless oil which was treated as an unstable intermediate and immediately reacted with acetyl chloride (0.223 g, 2.859 mmol) under the conditions described in general method **F** to give the *title compound* **234** (0.289 g, 88% over 2 steps) as a colourless oil: ν_{max}/cm^{-1} [film] 3260, 2110, 1669, 1468 and 1232; δ_H 0.87 (3H, d, *J* 6.6, CH_3), 0.94 (3H, d, *J* 6.6, CH_3), 1.50-1.43 (1H, m, 5-H), 1.66-1.59 (1H, m, 4-H_a), 1.74 (3H, s, CH_3CO), 1.86-1.78 (1H, m, 4-H_b), 3.55 (1H, d, *J* 1.7, 1-H), 4.55 (1H, app. td, *J* 7.0 and 1.7, 3-H) and 11.05 (1H, br. s, NH); δ_C 20.0 (CH_3), 22.7 (CH_3), 22.8 (CH_3), 24.8 (CH), 42.6 (CH_2), 72.9 (CH), 77.8 (CH), 82.8 (C) and 167.1 (CO); [Found M^+ + Na: 192.1003. $C_9H_{15}NNaO_2$ requires *M*, 192.1000].

1-[3-Butyl-5-isobutylisoxazol-2(5*H*)-yl]ethanone 235



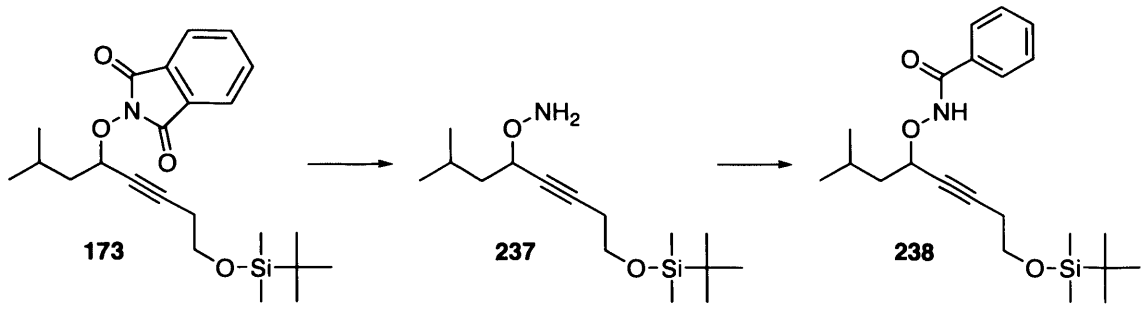
To a solution of the amide **228** (0.250 g, 1.110 mmol) in dry dichloromethane (11 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.188 g, 0.111 mmol). The resulting mixture was stirred for 4 h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **235** (0.244 g, 98%) as a colourless oil: ν_{max}/cm^{-1} [film] 1732, 1469, 1371, 1230; δ_H 0.92 (3H, t, *J* 7.3, Bu-CH_3), 0.95 (6H, d, *J* 2.4, 2 x CH_3), 1.83-1.33 (9H, m, 4 x CH_2 and ^{i}Bu-H), 2.13 (3H, s, CH_3), 2.63 (2H, br. t, *J* 2.6, Bu-CH_2), 4.89 (1H, dt, *J* 1.8 and 1.5, 4-H) and 5.09 (1H, ddd, *J* 8.0, 4.4 and 1.8, 5-H); δ_C 13.9 (CH_3), 22.2 (CH_3), 22.4 (CH_3), 22.6 (CH_2), 23.1 (CH_3), 25.1 (CH), 27.8 (CH_2), 29.7 (CH_2), 44.7 (CH_2), 82.2 (CH), 107.1 (CH), 140.4 (C), 166.0 (CO); *m/z* [APcI] 226.0 (M^+ + H, 100%); [Found M^+ + Na: 248.1630. $C_{13}H_{23}NNaO_2$ requires *M*, 248.1626].

1-(5-Isobutyl-3-phenylisoxazol-2(5*H*)-yl)ethanone 236



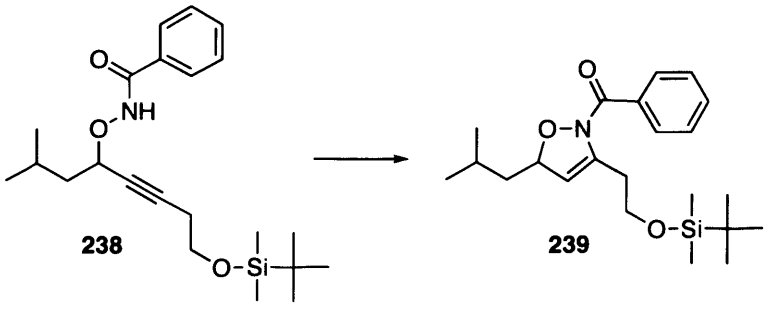
To a solution of the amide **233** (0.200 g, 0.816 mmol) in dry dichloromethane (8 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.140 g, 0.082 mmol). The resulting mixture was stirred for 4 h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **236** (0.192g, 97%) as a pale yellow oil: ν_{max}/cm^{-1} [film] 1732.0, 1667, 1468, 1449, 1370; δ_H 0.99 (6H, d, *J* 6.6, 2 x CH_3), 1.52-1.47 (1H, m, ^{i}Bu-H), 1.72-1.62 (1H, m, ^{i}Bu-H_a), 1.90-1.82 (1H, m, ^{i}Bu-H_b), 2.20 (3H, s, CH_3), 5.20 (1H, ddd, *J* 8.0, 4.8 and 2.2, 5-H), 5.54 (1H, d, *J* 2.2, 4-H), 7.35-7.33 (3H, m, 3 x Ar-H) and 7.43-7.41 (2H, m, 2 x Ar-H); δ_C (500 MHz) 22.1 (CH_3), 23.0 (CH_3), 25.0 (CH_3), 25.5 (CH), 41.4 (CH_2), 80.0 (C), 81.9 (CH), 87.5 (CH), 127.0 (Ar-H), 128.8 (Ar-H), 132,1 (Ar), 133.4 (Ar) and 157.6 (CO); [Found M^+ + Na: 268.1310. $C_{15}H_{19}NNaO_2$ requires *M*, 268.1314].

N-[8-(*tert*-Butyldimethylsilyloxy)-2-methyloct-5-yn-4-yloxy]benzamide 238



The phthalimide **173** (0.300 g, 0.723 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **237** (0.193 g, 0.679 mmol) as a colourless oil which was treated as an unstable intermediate and immediately reacted with benzoyl chloride (0.142 g, 1.019 mmol) under the conditions described in general method **F** to yield the crude product which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to give the *title compound* **238** (0.219 g, 78% over 2 steps) as a colourless oil: ν_{max}/cm^{-1} [film] 3216, 1651, 1581, 1516, 1471; δ_H (DMSO) 0.01 (6H, s, 2 x $SiCH_3$), 0.82 (9H, s, ^tBu-CH_3), 0.87 (3H, d, *J* 6.6, CH_3), 0.95 (3H, d, *J* 6.6, CH_3), 1.54-1.47 (1H, m, 2-H), 1.71-1.64 (1H, m, 3-H_a), 1.92-1.82 (1H, m, 3-H_b), 2.39 (2H, td, *J* 6.5 and 1.7, 2-CH_2), 3.63 (2H, br. t, *J* 6.3, 1-CH_2), 4.71 (1H, app. br. t, *J* 7.0, 5-H), 7.45 (2H, br. t, *J* 7.4, 2 x Ar-H), 7.54 (1H, t, *J* 7.3, Ar-H), 7.76 (2H, br. d, *J* 7.1, 2 x Ar-H) and 11.77 (1H, br. s, NH); δ_C (DMSO) -4.9 (CH_3), 18.4 (C), 22.6 (CH_3), 23.1 (CH_3), 24.9 (CH), 26.2 (CH_3), 31.5 (CH_2), 43.2 (CH_2), 61.7 (CH_2), 79.9 (CH), 85.4 (C), 89.4 (C), 127.6 (Ar-H), 128.9 (Ar-H), 132.1 (Ar-H), 132.7 (Ar) and 166.7 (CO); *m/z* [APcI] 390.3 (M^+ + H, 100%); [Found M^+ + H: 390.2475. $C_{22}H_{36}NO_3Si$ requires *M*, 390.2464].

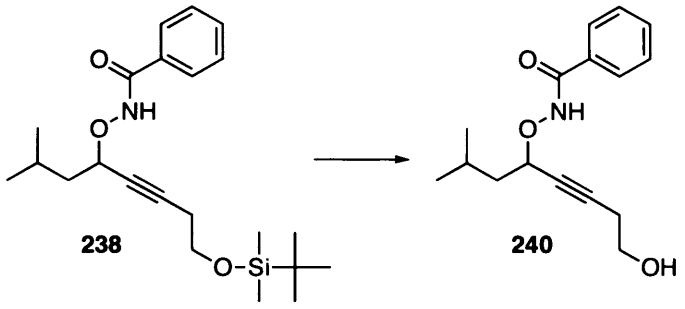
3-[2-(*tert*-Butyldimethylsilyloxy)ethyl)-5-isobutylisoxazol-2(5*H*)-yl]phenylmethanone 239



To a solution of the amide **238** (0.204 g, 0.524 mmol) in dry dichloromethane (5 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.089 g, 0.052 mmol). The resulting mixture was stirred for 4 h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **239** (0.916 g, 96%) as a colourless oil: ν_{max}/cm^{-1} [film] 1714, 1604, 1580, 1531, 1470, 1450, 1388; δ_H 0.04 (6H, s, Si-CH_3), 0.78 (3H, d, *J* 6.6, CH_3), 0.81 (3H, d, *J* 6.6, CH_3), 0.83 (9H, s, ^tBu-CH_3), 1.37-1.31 (1H, m, ^iBu-H), 1.62-1.46 (2H, m, ^iBu-H_a and H_b), 2.89 (2H, br. t, *J* 5.9, 1'-CH_2), 3.81 (2H, t, *J* 6.0,

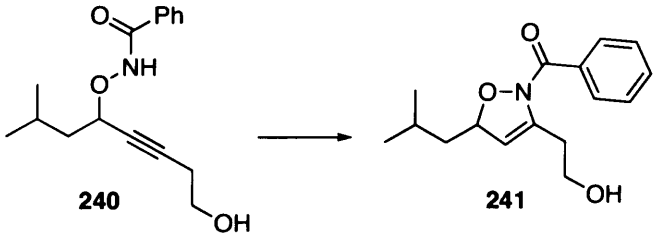
2'-CH_2), 5.05 (1H, br. t, *J* 5.4, 5-H), 5.13 (1H, br. s, 4-H), 7.32 (2H, app. br. t, *J* 7.4, 2 x Ar-H), 7.41-7.37 (1H, m, Ar-H) and 7.73 (2H, br. d, *J* 7.1, 2 x Ar-H); δ_C 0.01 (6H, s, 2 x $SiCH_3$), 0.80 (9H, s, ^{t}Bu-CH_3), 22.4 (CH_3), 22.8 (CH_3), 25.5 (CH), 32.9 (CH_2), 44.8 (CH_2), 61.0 (CH_2), 84.1 (CH), 111.5 (CH), 127.8 (Ar-H), 129.1 (Ar-H), 131.3 (Ar-H), 133.8 (C(Ar)), 138.1 (Ar(C)) and 165.5 (CO); *m/z* [APcI] 390.2 (M^+ + H, 100%); [Found M^+ + H: 390.2469. $C_{22}H_{36}NO_3Si$ requires *M*, 390.2464].

N-(8-Hydroxy-2-methyloct-5-yn-4-yloxy)benzamide 240



The phthalimide **238** (0.500 g, 1.285 mmol) was taken up in tetrahydrofuran (12 ml) and TBAF (7.71 ml, 7.710 mmol as a 1M solution in tetrahydrofuran) added in one portion. The resulting solution was stirred overnight. The reaction was quenched by the addition of water (20 ml) and extracted into dichloromethane (3 x 20 ml). The combined organic portions were washed with water (3 x 60 ml) and dried over magnesium sulphate. The solvent was evaporated to give the *title compound* **240** (0.219 g, 62%) as a colourless oil: ν_{max}/cm^{-1} [film] 3264, 3205, 1664, 1520 and 1472; δ_H (DMSO) 0.94 (3H, d, *J* 6.6, CH_3), 1.01 (3H, d, *J* 6.6, CH_3), 1.60-1.53 (1H, m, 2-H), 1.77-1.70 (1H, m, 3-H_a), 1.97-1.87 (1H, m, 3-H_b), 2.41 (2H, td, *J* 7.0 and 1.9, 2-CH_2), 3.51 (2H, td, *J* 7.0 and 5.6, 1-CH_2), 4.78 (1H, app. br. t, *J* 7.0, 5-H), 4.83 (1H, t, *J* 5.6, OH), 7.51 (2H, br. t, *J* 7.4, 2 x Ar-H), 7.59 (1H, br. d, *J* 7.3, Ar-H), 7.81 (2H, d, *J* 7.1, 2 x Ar-H) and 11.74 (1H, br. s, NH); *m/z* [APcI] 276.3 (M^+ + H, 100%).

3-[2-Hydroxyethyl-5-isobutylisoxazol-2(5*H*)-yl]phenylmethanone 241

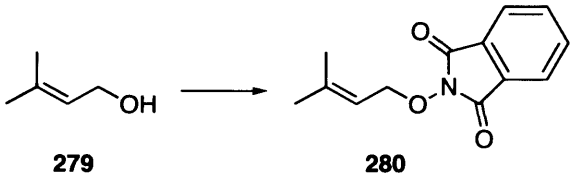


To a solution of the amide **240** (0.200 g, 0.727 mmol) in dry dichloromethane (7 ml), in the dark (as described in general method **E**), was added 10% w/w silver nitrate on silica (0.123 g, 0.072 mmol). The resulting mixture was stirred for 4h. The mixture was passed through a pad of celite and the solvent evaporated to give the *title compound* **241** (0.162 g, 81%) as a

colourless oil: ν_{max}/cm^{-1} [film] 3358, 1721, 1667, 1403 and 1273; δ_H (500 MHz) 0.86 (3H, d, *J* 6.6, ^{i}Bu-CH_3), 0.89 (3H, d, *J* 6.6, ^{i}Bu-CH_3), 1.46-1.40 (1H, m, ^{i}Bu-H), 1.71-1.57 (^{i}Bu- H_a and H_b), 3.06 (2H, dt, *J* 6.7 and 6.3, 2'-CH_2), 3.92 (2H, td, *J* 6.3 and 2.2, 1'-CH_2), 5.17 (1H, ddd, *J* 7.9, 4.0 and 2.0, 5-H), 5.25 (1H, td, *J* 2.2 and 2.0, 4-H), 7.41 (2H, br. t, *J* 7.4, 2 x Ar-H), 7.48 (1H, br. t, *J* 7.3, Ar-H) and 7.82 (2H, br. d, *J* 7.1, 2 x Ar-H); δ_C (500 MHz) 22.6 (CH_3), 22.7 (CH_3), 25.2 (CH), 31.3 (CH_2), 44.2 (CH_2), 61.4 (CH_2), 84.1 (CH), 111.5 (CH), 127.8 (Ar-H), 129.1 (Ar-H), 131.3 (Ar-H), 133.8 (C(Ar)), 138.1 (Ar(C)) and 165.5 (CO); *m/z* [APcI] 276.2 (M^+ + H, 100%) and 171.3 (60%); [Found M^+ + H: 276.1591. $C_{16}H_{22}NO_3$ requires *M*, 276.1600].

Chapter 4 compounds

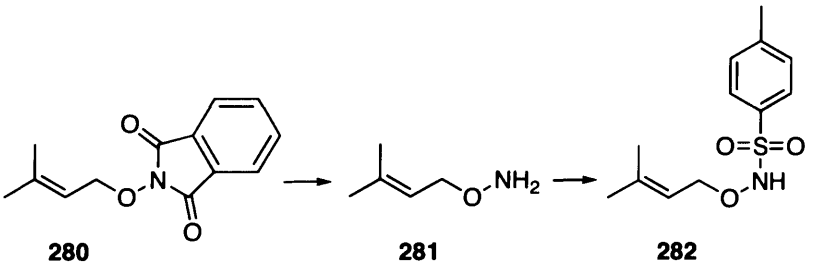
2-(3-Methylbut-2-enyloxy)isoindoline-1,3-dione 280



279 **280**

3-Methylbut-2-en-1-ol **279** (3 g, 34.843 mmol) was reacted with *N*-hydroxyphthalimide (5.737 g, 35.191 mmol) under the conditions described in general method **A** to give the *title compound* **280** (7.735 g, 96%) as a powdery, colourless solid: mp 94-95°C; [Found C, 67.38; H, 5.61; N, 6.02%. $C_{13}H_{13}NO_3$ requires C, 67.52; H, 5.67; N, 6.06%]; ν_{max}/cm^{-1} [thin film] 1783, 1728, 1673, 1464, 1392 and 1358; δ_H 1.74 (3H, s, CH_3), 1.77 (3H, s, CH_3), 4.73 (2H, d, *J* 7.7, CH_2), 5.54 (1H, t, *J* 7.7, 2-H), 7.75 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.84 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 18.1 (CH_3), 26.0 (CH_3), 74.1 (CH_2), 117.1 (CH), 123.5 (Ar-H), 128.9 (C), 134.4 (Ar-H), 143.7 (Ar) and 163.9 (CO); *m/z* [APcI] 232.0 (M^+ + H, 100%); [Found M^+ + H: 232.0984. $C_{13}H_{14}NO_3$ requires *M*, 232.0974].

***N*-(3-Methylbut-2-enyloxy)-*p*-toluenesulphonamide 282**

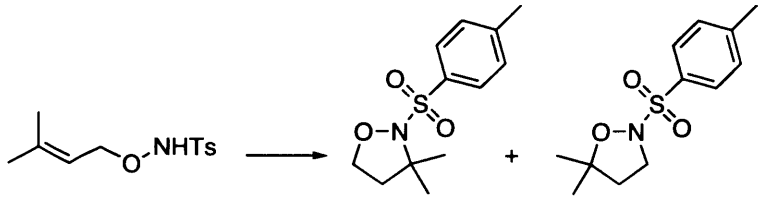


280 **281** **282**

The phthalimide **280** (1.000 g, 4.327 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **281** (0.424 g, 4.197 mmol) as a colourless solid which was treated as an unstable intermediate and immediately tosylated under the conditions

described in general method **C** to give the *title compound* **282** (0.984 g, 89% over 2 steps) as a colourless solid: mp 71-72°C; ν_{max}/cm^{-1} [DCM] 3222, 1598, 1379, 1334, 1197 and 1167; δ_H 1.68 (3H, s, CH_3), 1.72 (3H, s, CH_3), 2.44 (3H, s, Ar-CH_3), 4.48 (2H, d, *J* 7.5, CH_2), 5.31 (1H, br. t, *J* 7.5, 2-H), 6.92 (1H, s, NH), 7.33 (2H, d, *J* 8.3, 2 x Ar-H) and 7.85 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 18.2 (CH_3), 21.7 (CH_3), 25.9 (CH_3), 73.5 (CH_2), 117. 9 (CH), 128.5 (Ar-H), 129.7 (Ar-H), 133.7 (C(Ar)), 141.4 (Ar(C)) and 144.8 (Ar-H); *m/z* [APcI] 256.2 (M^+ + H, 100%); [Found M^+ + Na: 278.0834. $C_{12}H_{17}NaNO_3S$ requires 278.0827].

3,3-Dimethyl-2-(*p*-toluenesulphonyl)isoxazolidine 284 and
5,5-dimethyl-2-(*p*-toluenesulphonyl)isoxazolidine 285



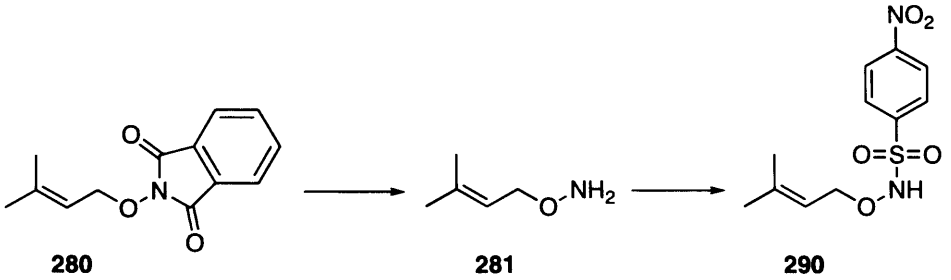
282 **284** **285**

The sulphonamide **282** (0.500 g, 1.960 mmol) was cyclised under the conditions described in general method **G** and the crude product chromatographed (10-20% ethyl acetate/petrol) to yield 2 products:

3,3-Dimethyl-2-(p-toluenesulphonyl)isoxazolidine **284** (0.359 g, 72%) as a colourless solid showing: mp 96-97 °C; ν_{max}/cm^{-1} [thin film] 1717, 1596, 1456, 1372, 1326 and 1160; δ_H 1.58 (6H, s, 2 x CH_3), 2.29 (2H, t, *J* 7.6, 4-CH_2), 2.43 (3H, s, Ar-CH_3), 4.18 (2H, t, *J* 7.6, 5-CH_2), 7.32 (2H, d, *J* 8.3, 2 x Ar-H) and 7.84 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 21.7 (CH_3), 26.7 (CH_3), 42.5 (CH_2), 67.7 (C), 69.9 (CH_2), 128.8 (Ar-H), 129.4 (Ar-H), 135.5 (Ar) and 144.5 (Ar); [Found M^+ + Na: 278.0825. $C_{12}H_{17}NNaO_3S$ requires *M*, 278.0827].

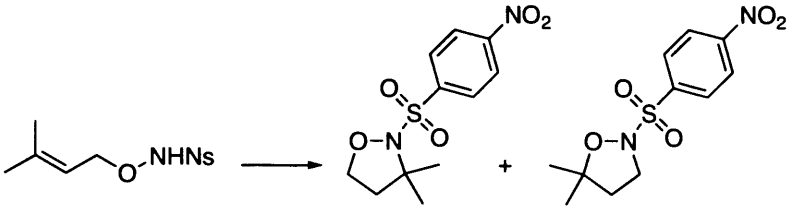
5,5-Dimethyl-2-(p-toluenesulphonyl)isoxazolidine **285** (0.095 g, 19%) as a colourless solid showing: mp 92-93°C; ν_{max}/cm^{-1} [thin film] 1717, 1598, 1451, 1355, 1331 and 1164; δ_H 1.26 (6H, s, 2 x CH_3), 1.85 (2H, app. t, *J* 7.0, 4-CH_2), 2.45 (3H, s, Ar-CH_3), 3.76 (2H, t, *J* 7.0, 3-CH_2), 7.35 (2H, d, *J* 8.2, 2 x Ar-H) and 7.84 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 21.8 (CH_3), 27.0 (CH_3), 40.3 (CH_2), 49.3 (CH_2), 85.6 (C), 129.6 (Ar-H), 129.7 (Ar-H), 131.7 (Ar) and 145.0 (Ar); [Found M^+ + H: 256.1015. $C_{12}H_{18}NO_3S$ requires *M*, 256.1007].

***N*-(3-Methylbut-2-enyloxy)-*p*-nitrobenzenesulphonamide 290**



The phthalimide **280** (0.500 g, 2.164 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **281** (0.208 g, 2.077 mmol) which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (20 ml) and cooled to -78°C in a carbon dioxide/acetone bath. Pyridine (0.17 ml, 2.098 mmol) and DMAP (0.005 g) were added and the solution stirred for 5 mins. *p*-Nitrobenzenesulphonyl chloride (0.464 g, 2.098 mmol) was added in one portion and the solution left in the cold bath and allowed to warm gradually, overnight. The reaction was quenched by the addition of water (20 ml) and extracted into dichloromethane (3 x 20 ml). The combined organic portions were washed with sat. aq. copper sulphate (60 ml) and water (3 x 60 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the *title compound* **290** (0.551 g, 89%) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 3421, 1715, 1532 and 1349; δ_H 1.73 (3H, s, CH_3), 1.76 (CH_3), 4.49 (2H, d, *J* 7.5, 1-CH_2), 5.31-5.26 (1H, br. t, *J* 7.6, 2-H), 6.45 (1H, s, NH), 8.12 (2H, app. dt, *J* 8.9 and 2.1, 2 x Ar-H) and 8.38 (2H, dt, *J* 8.9 and 2.0, 2 x Ar-H); δ_C 18.2 (CH_3), 25.9 (CH_3), 60.5 (CH_2), 117.5 (CH), 124.2 (Ar-H), 129.8 (Ar-H), 142.0 (C(Ar)), 142.8 (C(Ar)) and 150.6 (Ar); *m/z* [APcI] 287.1 (M^+ + H, 100%); [Found M^+ + H: 287.0705. $C_{11}H_{15}N_2O_5S$ requires *M*, 287.0702].

3,3-Dimethyl-2-(*p*-nitrobenzenesulphonyl)isoxazolidine 292 and 5,5-dimethyl-2-(*p*-nitrobenzenesulphonyl)isoxazolidine 293

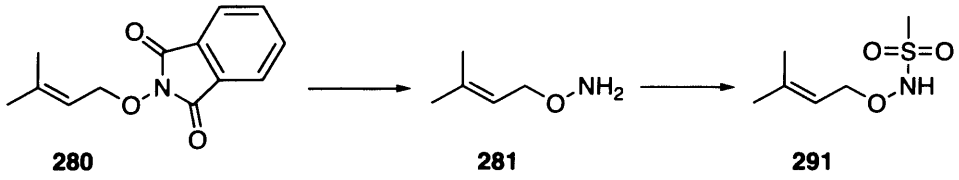


The sulphonamide **290** (0.200 g, 0.699 mmol) was cyclised under the conditions described in general method **G** and the crude product chromatographed (10-20% ethyl acetate/petrol) to give 2 products:

3,3-Dimethyl-2-(p-nitrobenzenesulphonyl)isoxazolidine **292** (0.114 g, 56%) as a pale yellow solid: mp 89-90°C; ν_{max}/cm^{-1} [thin film] 1607, 1532, 1466, 1351, 1254 and 1178; δ_H 1.61 (6H, s, 2 x CH_3), 2.35 (2H, t, *J* 7.5, 4-CH_2), 4.21 (2H, t, *J* 7.5, 5-CH_2), 8.15 (2H, br. d, *J* 8.6, 2 x Ar-H) and 8.37 (2H, br. d, *J* 8.8, 2 x Ar-H); δ_C 26.6 (CH_3), 42.8 (CH_2), 68.4 (C), 69.8 (CH_2), 123.9 (Ar-H), 130.1 (Ar-H), 141.3 (Ar) and 144.3 (Ar); *m/z* [APcI] 287.0 (M^+ + H, 100%); [Found M^+ + H: 287.0712. $C_{11}H_{15}N_2O_5S$ requires *M*, 287.0702].

5,5-Dimethyl-2-(p-nitrobenzenesulphonyl)isoxazolidine **293** (0.072 g, 35%) as pale yellow solid: mp 90-91°C; ν_{max}/cm^{-1} [thin film] 1612, 1529 and 1362; δ_H 1.34 (6H, s, 2 x CH_3), 2.05 (2H, t, *J* 7.0, 4-CH_2), 3.85 (2H, t, *J* 7.0, 3-CH_2), 8.15 (2H, br. d, *J* 8.7, 2 x Ar-H) and 8.40 (2H, br. d, *J* 8.40, 2 x Ar-H); δ_C 27.1 (CH_3), 40.7 (CH_2), 42.8 (CH_2), 86.6 (C), 124.0 (Ar-H), 130.8 (Ar-H), 141.3 (Ar) and 144.3 (Ar); *m/z* [APcI] 287.1 (M^+ + H, 100%); [Found M^+ + H: 287.0705. $C_{11}H_{15}N_2O_5S$ requires *M*, 287.0702].

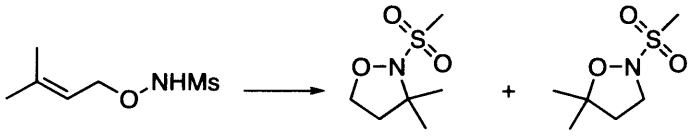
***N*-(3-Methylbut-2-enyloxy)-methylsulphonamide 280**



The phthalimide **280** (1.000 g, 4.327 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **281** (0.422 g, 4.154 mmol) which was treated as an unstable intermediate and reacted immediately. The crude product was taken up in dry dichloromethane (40 ml) and cooled to -78°C in a carbon dioxide/acetone bath. Pyridine (0.34 ml, 4.120 mmol) and DMAP (0.005 g) were added and the solution stirred for 5 mins. Methanesulphonyl chloride (0.478 g, 4.120 mmol) was added in one portion and the solution

left in the cold bath and allowed to warm gradually, overnight. The reaction was quenched by the addition of water (40 ml) and extracted into dichloromethane (3 x 40 ml). The combined organic portions were washed with sat. aq. copper sulphate (120 ml) and water (3 x 120 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the *title compound* **291** (0.711 g, 92%) as a thick, colourless oil: ν_{max}/cm^{-1} [film] 3221, 1709, 1326, 1197 and 1165; δ_H 1.74 (3H, s, CH_3), 1.79 (3H, s, CH_3), 3.07 (3H, s, S-CH_3), 4.50 (2H, d, *J* 7.5, 1-CH_2), 5.37 (1H, br. t, *J* 7.5, 2-H) and 7.03 (1H, br. s, NH); δ_C 18.2 (CH_3), 25.9 (CH_3), 36.8 (CH_3), 73.7 (CH_2), 117.7 (CH), 142.0 (C); [Found M^+ + Na: 202.0512. $C_6H_{13}NNaO_3S$ requires *M*, 202.0514].

***N*-(3,3-Dimethylisoxazolidine)methylsulphonamide 294 and *N*-(5,5-dimethylisoxazolidine)methylsulphonamide 295**

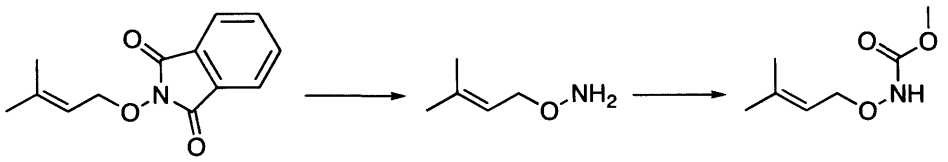


The sulphonamide **291** (0.250 g, 1.396 mmol) was cyclised under the conditions described in general method **G** and the crude product chromatographed (10-20% ethyl acetate/petrol) to give 2 products:

N-(3,3-Dimethylisoxazolidine)methylsulphonamide **294** (0.148 g, 60%) as a pale yellow oil: ν_{max}/cm^{-1} [film] 1716, 1467, 1373, 1321 and 1144; δ_H 1.54 (6H, s, 2 x CH_3), 2.29 (2H, t, *J* 7.6, 4-CH_2), 3.09 (3H, s, CH_3) and 4.28 (2H, t, *J* 7.6, 5-CH_2); δ_C 26.6 (CH_3), 39.8 (CH_3), 42.4 (CH_2), 67.7 (C) and 69.9 (CH_2); [Found M^+ + H: 180.0699. $C_6H_{14}NO_3S$ requires *M*, 180.0694].

N-(5,5-Dimethylisoxazolidine)methylsulphonamide **295** (0.066 g, 26%) as pale yellow oil: ν_{max}/cm^{-1} [film] 1719, 1373, 1253, 1196 and 1139; δ_H 1.45 (6H, s, 2 x CH_3), 2.18 (2H, t, *J* 7.0, 4-CH_2), 3.00 (3H, s, CH_3) and 3.81 (2H, t, *J* 7.0, 5-CH_2); δ_C 27.4 (CH_3), 37.3 (CH_3), 41.0 (CH_2), 47.4 (CH_2) and 86.9 (C); [Found M^+ + H: 180.0696. $C_6H_{14}NO_3S$ requires *M*, 180.0694].

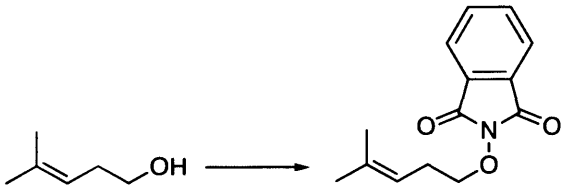
N-(3-Methylbut-2-enyloxy)-methyl carbamate 296



280 **281** **296**

The phthalimide **280** (0.500 g, 2.164 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **281** (0.205 g, 2.034 mmol) as a colourless oil which was treated as an unstable intermediate and reacted immediately. The crude product was reacted with methyl chloroformate (0.287 g, 3.051 mmol) under the conditions described in general method **F** to give the *title compound* **296** (0.248 g, 77%) as a colourless oil showing: ν_{max}/cm^{-1} [film] 3280, 1729, 1455, 1379, 1256 and 1196; δ_H 1.73 (3H, s, CH_3), 1.78 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 4.37 (2H, d, *J* 7.4, 1-CH_2), 5.38 (1H, br. t, *J* 7.4, 2-H) and 7.33 (1H, s, NH); δ_C 18.1 (CH_3), 25.9 (CH_3), 52.8 (CH_3), 72.8 (CH_2), 118.0 (CH), 141.4 (C) and 158.0 (CO); [Found M^+ + H: 160.0966. $C_7H_{14}NO_3$ requires *M*, 160.0974].

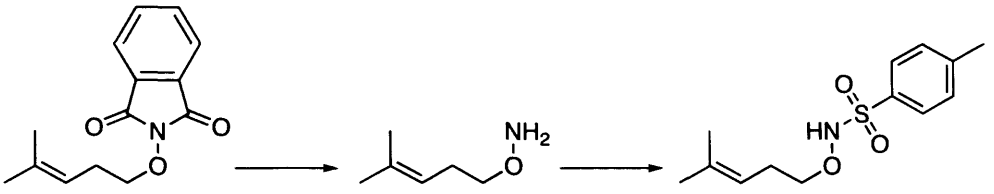
2-(4-Methylpent-3-enyloxy)isoindoline-1,3-dione 301



300 **301**

4-Methyl-3-penten-1-ol **300** (1.000 g, 9.990 mmol) was reacted with *N*-hydroxyphthalimide (1.645 g, 10.090 mmol) under the conditions described in general method **A** to yield the phthalimide **301** (2.226 g, 91%) as a colourless solid: mp 123-124°C; ν_{max}/cm^{-1} [DCM] 1782, 1732, 1467, 1399, 1375, 1186 and 1131; δ_H 1.65 (3H, s, CH_3), 1.70 (3H, s, CH_3), 2.52 (2H, app. q, *J* 7.1, 2-CH_2), 4.18 (2H, t, *J* 7.3, 1-CH_2), 5.20-5.16 (1H, m, 3-H), 7.76 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H) and 7.85 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 17.9 (CH_3), 25.7 (CH_3), 27.3 (CH_2), 77.8 (CH_2), 118.3 (CH), 123.5 (Ar-H), 128.9 (Ar), 134.5 (Ar-H), 135.0 (C) and 163.7 (CO); [Found M^+ + H: 246.1082. $C_{14}H_{16}NO_3$ requires *M*, 246.1130].

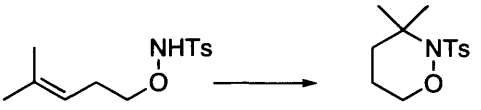
N-(4-Methylpent-3-en-1-oxy)-p-toluenesulphonamide 303



301 **302** **303**

The phthalimide **301** (1.000 g, 4.080 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **302** (0.455 g, 3.958 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to give the *title compound* **303** (0.913 g, 83% over 2 steps) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 3421, 1597, 1332 and 1164; δ_H 1.58 (3H, br. s, CH_3), 1.70 (3H, br. s, CH_3), 2.28 (2H, app. q, *J* 6.9, 2-CH_2), 2.45 (3H, s, Ar-CH_3), 3.96 (2H, t, *J* 6.8, 1-CH_2), 5.09-5.04 (1H, m, 3-H), 7.34 (2H, d, *J* 8.3, 2 x Ar-H) and 7.81 (2H, d, *J* 8.3, 2 x Ar-H); 17.8 (CH_3), 21.7 (CH_3), 25.8 (CH_3), 27.1 (CH_2), 76.9 (CH_2), 119.5 (CH), 128.6 (Ar-H), 129.7 (Ar-H), 133.5 (C(Ar)), 134.3 (C(Ar)) and 144.9 (Ar); *m/z* [APcI] 270.2 (M^+ + H, 100%) and 115.6 (55%); [Found M^+ + Na: 292.0972. $C_{13}H_{19}NNaO_3S$ requires *M*, 292.0983].

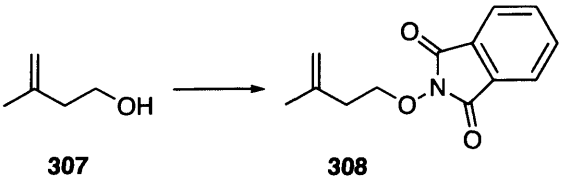
3,3-Dimethyl-2-(p-toluenesulphonyl)-1,2-morpholine 304



303 **304**

The sulphonamide **303** (0.200 g, 0.743 mmol) was cyclised under the conditions described in general method **G** to yield the *title compound* **304** (0.186 g, 93%) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 1718, 1599, 1454, 1355, 1335 and 1172; δ_H 1.42 (6H, s, 2 x CH_3), 1.69-1.64 (4H, m, 4- and 5-CH_2), 2.43 (3H, s, Ar-CH_3), 3.86 (2H, t, *J* 5.2, 6-CH_2), 7.30 (2H, d, *J* 8.2, 2 x Ar-H) and 7.82 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 21.6 (2 x CH_3), 21.7 (CH_2), 21.9 (CH_3), 39.2 (CH_2), 62.1 (C), 72.2 (CH_2), 128.5 (Ar-H), 129.3 (Ar-H), 136.2 (Ar) and 143.9 (Ar); *m/z* [APcI] 270.2 (M^+ + H, 100%); [Found M^+ + H: 270.1169. $C_{13}H_{20}NO_3S$ requires *M*, 270.1164].

2-(3-Methylbut-3-enyloxy)isoindoline-1,3-dione 308

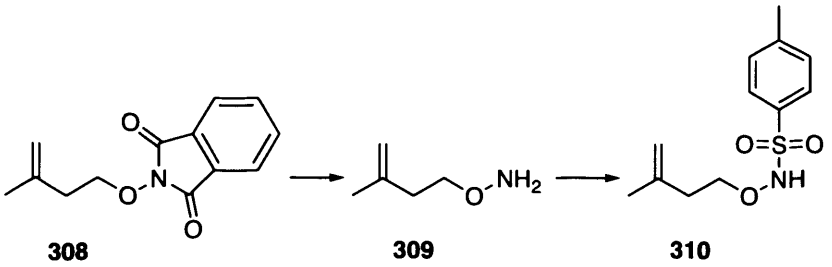


307 **308**

3-Methylbut-3-en-1-ol **307** (1.000 g, 11.614 mmol) was reacted with *N*-hydroxyphthalimide (1.912 g, 11.730 mmol) under the conditions described in general method **A** to yield the *title*

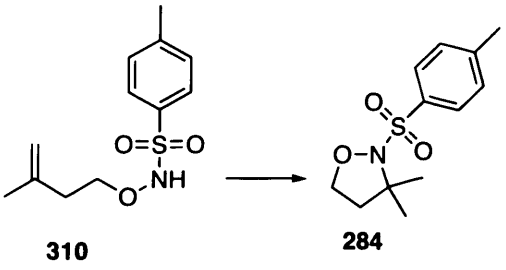
compound **308** (2.414 g, 90%) as a colourless solid: mp 89-90°C; ν_{max}/cm^{-1} [film] 1790, 1732, 1651, 1610, 1468, 1374 and 1187; δ_H 1.83 (3H, s, CH_3), 2.55 (2H, t, *J* 7.0, 1-CH_2), 4.33 (2H, t, *J* 7.0, 2-CH_2), 4.86 (2H, br. s, 4- H_{cis} and H_{trans}), 7.76 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.85 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 22.7 (CH_3), 36.1 (CH_2), 76.4 (CH_2), 112.5 (CH_2), 123.6 (Ar-H), 128.9 (Ar), 134.5 (Ar-H), 141.0 (C) and 163.6 (CO); [Found M^+ + Na: 254.0791. $C_{13}H_{13}NNaO_3$ requires 254.0793].

N-(3-Methylbut-3-en-1-oxy)-*p*-toluenesulphonamide 310



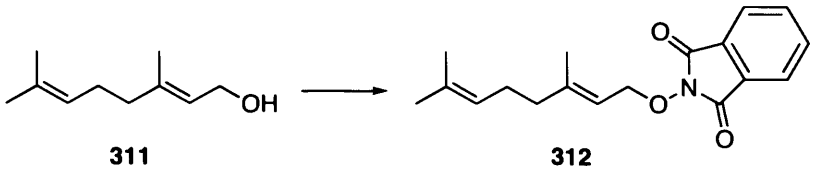
The phthalimide **308** (1.000 g, 4.327 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **309** (0.421 g, 4.197 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to yield the *title compound* **310** (0.915 g, 83%) as a pale yellow solid, showing: mp 72-74°C; ν_{max}/cm^{-1} [nujol] 3220, 1709, 1597, 1452, 1376, 1331 and 1169; 1.74 (3H, s, CH_3), 2.32 (2H, t, *J* 6.7, 2-CH_2), 2.45 (2H, s, Ar-CH_3), 4.12 (2H, t, *J* 6.7, 2-CH_2), 4.72 (1H, br. s, CH), 4.79 (1H, br. s, CH), 6.97 (1H, s, NH), 7.34 (2H, d, *J* 8.3, 2 x Ar-H) and 7.81 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 21.7 (CH_3), 22.4 (CH_3), 36.3 (CH_2), 112.2 (CH_2), 128.6 (Ar-H), 129.7 (Ar-H), 133.5 (C), 141.9 (Ar) and 144.9 (Ar); [Found M^+ + Na: 278.0823. $C_{12}H_{17}NNaO_3S$ requires *M*, 278.0827].

3,3-Dimethyl-2-(*p*-toluenesulphonyl)isoxazolidine 284 (Alternative Synthesis)



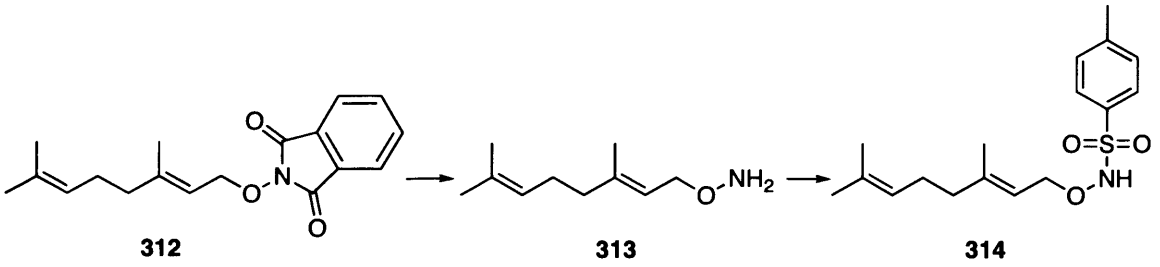
The sulphonamide **310** (0.500 g, 1.960 mmol) was cyclised under the conditions described in general method **G** to give the *title compound* **284** (0.488 g, 98%) as a pale yellow solid, with no need for further purification. All data obtained were identical to those obtained for the foregoing sample, with the exception of: mp 97-98°C.

2-[(*E*)-3,7-Dimethylocta-2,6-dienyloxy]isoindoline-1,3-dione 312



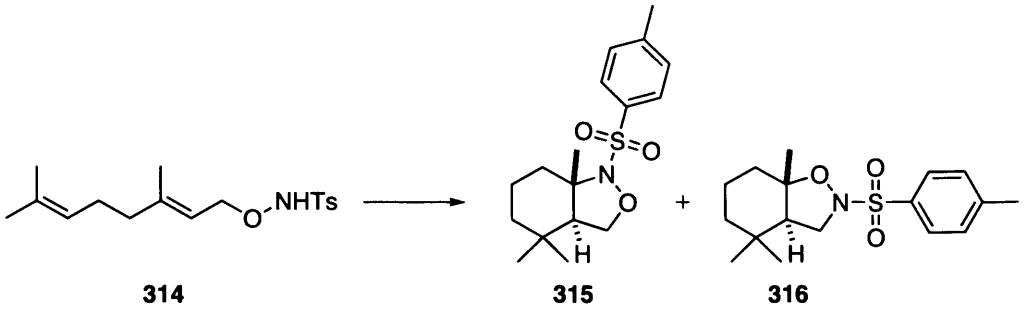
Geraniol **311** (2.000 g, 12.979 mmol) was reacted with *N*-hydroxyphthalimide (2.137 g, 13.110 mmol) under the conditions described in general method **A** to give the *title compound* **312** (2.444 g, 63%) as a powdery, colourless solid: mp 81-82°C; [Found C, 72.23; H, 7.09; N, 4.64%. $C_{18}H_{21}NO_3$ requires C, 72.22; H, 7.07; 4.68%]; ν_{max}/cm^{-1} [film] 1784, 1723, 1463, 1396 and 1371; δ_H 1.57 (3H, s, CH_3), 1.65 (3H, s, CH_2), 1.72 (3H, s, CH_3), 2.05 (4H, d, *J* 2.9, 4- and 5-CH_2), 4.76 (2H, d, *J* 7.6, 1-CH_2), 5.05 (1H, br. s, 3-H), 5.55 (1H, t, *J* 7.5, 7-H), 7.75 (2H, dd. *J* 5.4 and 3.1, 2 x Ar-H) and 7.84 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 16.6 (CH_3), 17.7 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 39.7 (CH_2), 74.0 (CH_2), 116.7 (CH), 123.4 (Ar-H), 123.6 (CH), 128.9 (C), 132.0 (C), 134.4 (Ar-H), 147.1 (Ar) and 163.9 (CO); [Found M^+ + Na: 322.1424. $C_{18}H_{21}NNaO_3$ requires *M*, 322.1419].

***N*-[(*E*)-3,7-dimethylocta-2,6-dienyloxy]-*p*-toluenesulphonamine 314**



The phthalimide **312** (0.500 g, 1.671 mmol) was deprotected under the conditions described in general method **B** to yield the hydroxylamine **313** (0.271 g, 1.588 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to give the *title compound* **314** (0.475 g, 88% over 2 steps) as a thick, colourless oil: ν_{max}/cm^{-1} [film] 3227, 1665, 1598, 1446, 1378 and 1336; δ_H 1.60 (3H, s, CH_3), 1.68 (3H, d, *J* 0.9, CH_3), 1.71 (3H, d, *J* 1.2, CH_3), 2.12-2.01 (4H, m, 4- and 5-CH_2), 2.44 (3H, s, Ar-CH_3), 4.49 (2H, d, *J* 7.4, 1-CH_2), 5.08-5.05 (1H, m, 6-H), 5.29 (1H, tq, *J* 7.4 and 1.2, 2-H), 6.87 (1H, s, NH), 7.34 (2H, d, *J* 8.3, 2 x Ar-H) and 8.33 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 16.6 (CH_3), 17.7 (CH_3), 21.7 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 39.6 (CH_2), 73.5 (CH_2), 177.5 (CH), 123.7 (CH), 128.8 (Ar-H), 129.7 (Ar-H), 131.9 (C), 133.7 (C), 144.6 (C) and 144.8 (C); *m/z* [APcI] 324.2 (M^+ + H, 20%) and 154.1 (100%); [Found M^+ + H: 324.1635. $C_{17}H_{26}NO_3S$ requires *M*, 324.1633].

(3a*S*,7a*S*)-Octahydro-4,4,7a-trimethyl-1-(*p*-toluenesulphonyl)benzo[*c*]isoxazole 315 and (3a*R*,7a*S*)-octahydro-4,4,7a-trimethyl-2-(*p*-toluenesulphonyl)benzo[*d*]isoxazole 316

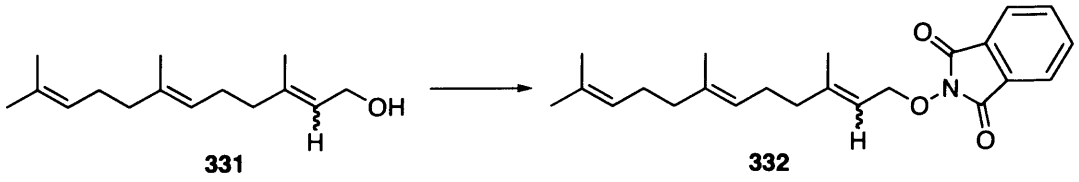


The sulphonamide **314** (0.400 g, 1.237 mmol) was cyclised under the conditions described in general method **G** to give the crude product, which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to give 2 products:

(3aS,7aS)-Octahydro-4,4,7a-trimethyl-1-(p-toluenesulphonyl)benzo[c]isoxazole **315** (0.237 g, 59%) as a colourless solid showing: mp 74-75°C; ν_{max}/cm^{-1}[nujol] 1722, 1604, 1341, 1222, 1187 and 1099; δ_H 0.91 (6H, s, 2 x CH_3), 1.16 (1H, app. td, *J* 13.5 and 4.5), 1.32 (3H, s, CH_3), 1.48 (1H, app. dt, *J* 13.5 and 2.8), 1.70-1.56 (2H, m), 1.82-1.76 (1H, m), 2.13 (app. td, *J* 12.8 and 4.2), 2.28 (1H, dd, *J* 12.3 and 8.4, 3a-H), 3.73 (1H, dd, *J* 12.3 and 5.9, 3-H_a), 4.24 (1H, dd, *J* 8.4 and 5.9, 3-H_b), 7.32 (2H, d, *J* 8.3, Ar-H) and 7.84 (2H, d, *J* 8.3, Ar-H); δ_C 20.5 (CH_2), 20.9 (CH_3), 21.5 (CH_3), 21.7 (CH_3), 32.9 (C), 33.6 (CH_3), 34.8 (CH_2), 40.4 (CH_2), 57.7 (CH), 68.9 (CH_2), 69.4 (C), 128.8 (Ar-H), 129.4 (Ar-H), 135.9 (Ar) and 144.3 (Ar); [Found M^+ + H: 324.1644. $C_{17}H_{26}NO_3S$ requires 324.1633].

(3aR,7aS)-Octahydro-4,4,7a-trimethyl-2-(p-toluenesulphonyl)benzo[d]isoxazole **316** (0.016 g, 4%) as a thick, colourless oil showing: ν_{max}/cm^{-1} [nujol] 1715, 1597, 1459, 1357 and 1168; δ_H 0.74 (3H, s, CH_3), 0.79 (3H, s, CH_3), 1.07 (1H, app, td, *J* 12.4 and 4.3), 1.14 (3H, s, CH_3), 1.41-1.22 (4H, m), 1.66-1.59 (1H, m), 1.89 (1H, dd, *J* 13.2 and 6.9, 3a-H), 2.47 (3H, s, CH_3), 3.34 (1H, dd, *J* 13.2 and 10.1, 3-H_a), 3.61 (1H, dd, *J* 10.1 and 6.9, 3-H_a), 7.36 (2H, d, *J* 8.3, Ar-H) and 7.84 (2H, d, *J* 8.3, Ar-H); [Found M^+ + H: 324.1671. $C_{17}H_{26}NO_3S$ requires 324.1633]

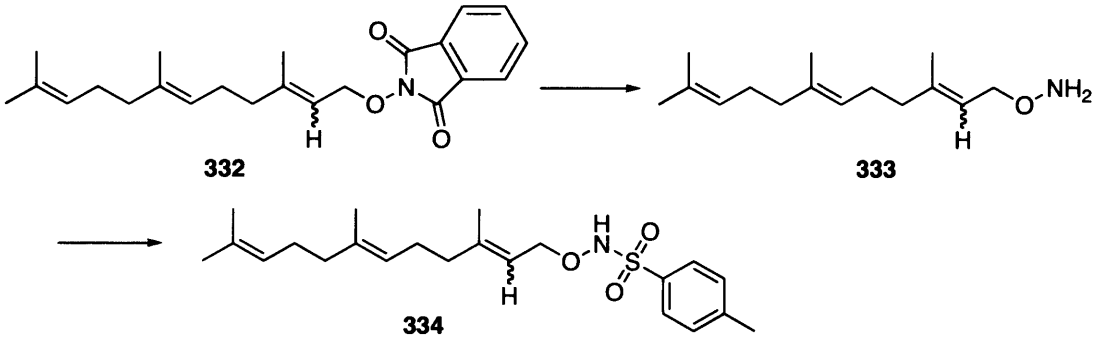
2-[(2*EZ*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trienyloxy]isoindoline-1,3-dione 332



Farnesol **XX** (1.000 g, 4.500 mmol) was reacted with *N*-hydroxyphthalimide (0.741 g, 4.545 mmol) under the conditions described in general method **A** to yield the *title compound* **50**

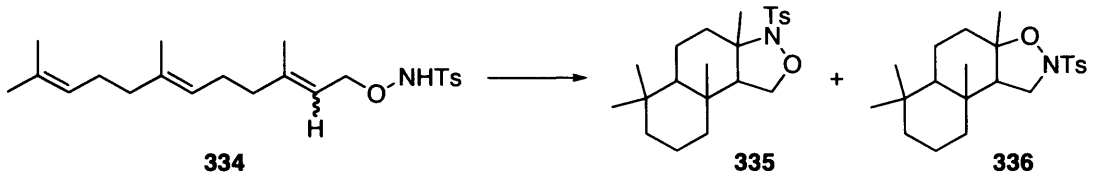
(1.072 g, 65%) as a colourless gel: ν_{max}/cm^{-1} [film] 1780, 1731, 1469, 1461, 1389, 1369 and 1212; δ_H 1.57 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.68 (3H, s, 6-CH_3), 1.73 (2.1H, s, 3-CH_3), 1.79 (0.9H, s, 3-CH_3), 1.95 (2H, t, *J* 8.0, CH_2), 2.10-2.00 (4H, m, 2 x CH_2), 2.16 (2H, t, *J* 7.2, CH_2), 4.73 (0.6H, d, *J* 7.6, 1-CH_2), 4.77 (1.4H, d, *J* 7.8, 1-CH_2), 5.08 (2H, br. s, 2- and 6-H), 5.55 (1H, br. t, *J* 7.2, CH), 7.75 (2H, dd, *J* 5.6 and 3.1, Ar-H) and 7.84 (2H, dd, *J* 5.6 and 3.2, Ar-H) ; δ_C 15.9 (CH_3), 16.6 (CH_3), 17.7 (CH_3), 23.7 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 26.7 (CH_2), 31.9 (CH_2), 39.9 (CH_2), 73.9 (CH_2), 116.7 (CH), 117.8 (CH), 123.4 (Ar-H), 124.3 (CH), 129.0 (Ar), 131.3 (C), 134.4 (Ar-H), 135.5 (C), 146.6 (C), 147.1 (C) and 163.8 (CO); *m/z* [APcI] 368.2 (M^+ + H, 100%), 206.3 (40%); [Found M^+ + H: 368.2256. $C_{23}H_{30}NO_3$ requires *M*, 368.2226].

N-((2*EZ*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-ol)-*p*-toluenesulphonamide 334



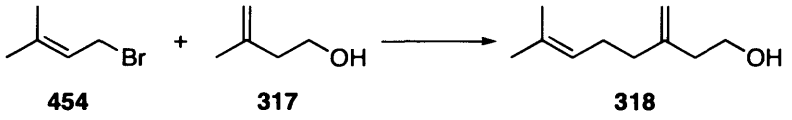
The phthalimide **332** (0.500 g, 1.362 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **333** (0.300 g, 1.266 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to give the *title compound* **334** (0.419 g, 79 %) as a thick, pale yellow oil characterised by: ν_{max}/cm^{-1} [film] 3222, 1665, 1598, 1447, 1378, 1338 and 1167; δ_H 1.59 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.68 (3H, s, CH_3), 1.72 (2.1H, s, 3-CH_3), 1.74 (0.9H, s, 3-CH_3), 1.97 (2H, t, *J* 8.1, CH_2), 2.11-2.03 (6H, m, 3 x CH_2), 2.44 (3H, s, Ar-CH_3), 4.46 (0.6H, d, *J* 7.5, 1-CH_2), 4.49 (1.4H, d, *J* 7.5, 1-CH_2), 5.10-5.07 (2H, br. m, 2 x CH), 5.29 (1H, t, *J* 7.4, CH), 6.88 (1H, s, NH), 7.34 (2H, d, *J* 8.2, 2 x Ar-H) and 7.81 (2H, d, *J* 8.1, 2 x Ar-H); δ_C 16.0 (CH_3), 16.7 (CH_3), 17.7 (CH_3), 21.7 (CH_3), 23.6 (CH_3), 25.7 (CH_3), 26.2 (CH_2), 26.7 (CH_2), 32.1 (CH_2), 39.6 (CH_2), 73.3 (CH_2), 73.5 (CH_2), 117.6 (CH), 118.6 (CH), 123.4 (CH), 123.6 (CH), 124.3 (CH), 128.5 (Ar-H), 129.7 (Ar-H), 131.4 (C(Ar)), 133.7 (C(Ar)), 135.5 (C(Ar)), 135.7 (C(Ar)), 144.5 (C(Ar)), 144.7 (C(Ar)) and 144.8 (C(Ar)); [Found M^+ + H: 392.2263. $C_{22}H_{34}NO_3S$ requires *M*, 392.2259].

Dodecahydro-3a,6,6,9a-tetramethyl-3-(*p*-toluenesulphonyl)naphtho[2,1-*c*]isoxazole 335 and dodecahydro-3a,6,6,9a-tetramethyl-2-tosylnaphtho[1,2-*d*]isoxazole 336



The sulphonamide **334** (0.200 g, 0.511 mmol) was cyclised under the conditions described in general method **G** to give the *title compounds* **335** and **336** (0.161 g, 81%) as an inseparable mixture containing multiple stereoisomers, showing: ν_{max}/cm^{-1} [film] 1598, 1446, 1343 and 1167; $\delta_{H\ (WHOLE\ SAMPLE)}$ 1.89-0.79 (m), 2.34-2.23 (m), 2.44 (br. s), 3.72 (app. dd, *J* 12.2 and 5.8), 3.80 (app. dd, *J* 12.3 and 5.8), 4.02-3.95 (m), 4.18 (app. dd, *J* 8.4 and 5.9), 4.32-4.25 (m), 4.36 (app, dd, *J* 10.0 and 7.1), 7.35-7.31 (m) and 7.86-7.80 (m); $\delta_{C\ (WHOLE\ SAMPLE)}$ 15.9, 18.2, 19.1, 19.2, 20.9, 21.1, 21.7, 28.8, 28.9, 32.6, 32.7, 32.9, 36.2, 36.2, 36.3, 38.6, 40.1, 41.0, 42.6, 46.8, 52.4, 54.1, 56.6, 60.1, 60.9, 61.6, 68.1, 69.4, 70.4, 72.7, 123.4, 126.4, 127.5, 129.4, 129.5, 136.1 and 144.2 *Predominant resonances only*; *m/z* [APcI] 392.2 (M^+ + H, 100%), 255.2 (60%) and 207.6 (40%).

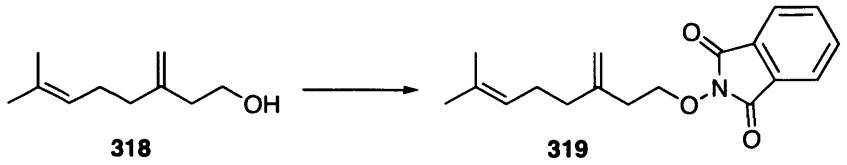
7-Methyl-3-methyleneoct-6-en-1-ol 318 [97]



An oven-dried, 3-neck 100 ml flask was charged with dry ether (20 ml) and TMEDA (4.53 ml, 30.186 mmol) and stirred at 0°C. Butyl lithium (9.29 ml, 23.220 mmol) was added, dropwise and the resulting solution allowed to warm to room temperature and stirred for 1 h. The solution was cooled to 0°C and 3-methylbut-3-en-1-ol **317** (1.000 g, 11.610 mmol) added, dropwise. The solution was allowed to warm to room temperature and stirred for 6h. The solution was cooled to -78°C and 1-bromo-3-methylbut-2-ene **454** (1.730 g, 11.610 mmol) added, dropwise. The solution was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (20 ml) and extracted into ether (3 x 20ml). The combined organic portions were washed with water (3 x 20 ml) and brine (20 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to yield the *title compound* **318** (1.228 g, 69%) as a colourless oil which was used directly, without further purification. All data obtained were in accordance with those previously reported in the literature[97] and showed: δ_H 1.59 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.15-2.00 (4H, m, 2 x CH_2), 2.29 (2H, t, *J* 6.3, 2-CH_2), 3.69 (2H, t, *J* 6.3, 1-CH_2), 4.82 (1H, br. s, CH), 4.86 (1H, br. s, CH) and 5.13-5.05 (1H, m, 6-H); δ_C 17.8 (CH_3), 27.5 (CH_3), 26.3

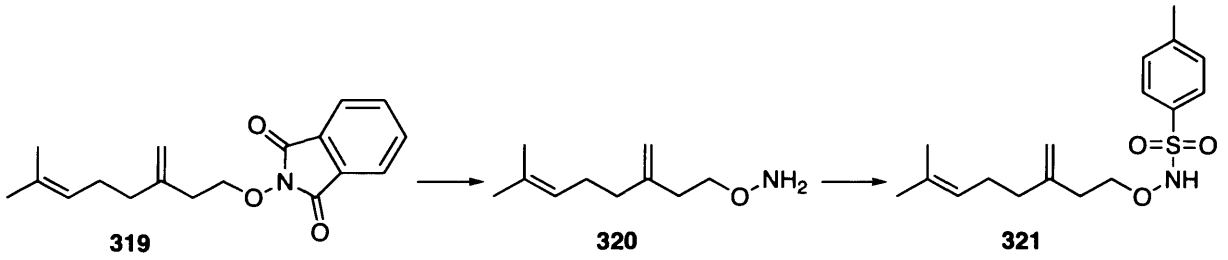
(CH_2), 35.7 (CH_2), 39.3 (CH_2), 60.3 (CH_2), 111.8 (CH_2), 123.8 (CH), 132.0 (C) and 145.9 (C); *m/z* [APcI] 137.1 (M^+ + H, 100%).

2-(7-Methyl-3-methyleneoct-6-enyloxy)isoindoline-1,3-dione 318



The crude alcohol **318** (1.000 g, 6.489 mmol) was reacted with *N*-hydroxyphthalimide (1.068 g, 6.554 mmol) under the conditions described in general method A to give the crude product which was purified by silica gel chromatography (5-10% ethyl acetate/petrol) to yield the *title compound* **319** (1.147 g, 59%) as a colourless solid: mp 74-75°C; ν_{max}/cm^{-1} [thin film] 1789, 1735, 1468, 1375, 1246 and 1188; δ_H 1.61 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.14-2.12 (4H, m, 2 x CH_2), 2.56 (2H, t, *J* 7.1, 2-CH_2), 4.33 (2H, t, *J* 7.1, 1-CH_2), 4.88 (1H, br. s, CH), 4.91 (1H, br. s, CH), 5.13-5.10 (1H, m, 6-H), 7.76 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H) and 7.85 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 17.8 (CH_3), 25.7 (CH_3), 26.3 (CH_2), 34.5 (CH_2), 36.3 (CH_2), 76.9 (CH_2), 111.4 (CH_2), 123.6 (Ar-H), 123.8 (CH), 128.9 (Ar), 131.9 (C), 134.5 (Ar-H), 144.6 (C) and 163.6 (CO); [Found M^+ + Na: 322.1414. $C_{18}H_{21}NNaO_3$ requires *M*, 322.1419].

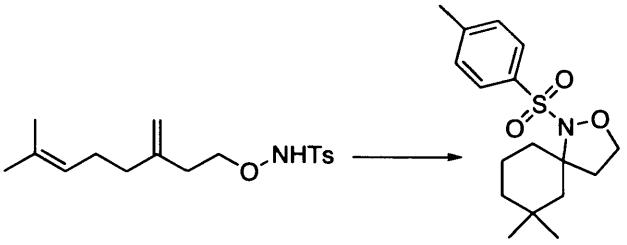
***N*-(7-Methyl-3-methyleneoct-6-en-1-ol)-*p*-toluenesulphonamide 321**



The phthalimide **319** (0.500 g, 1.671 mmol) was deprotected under the conditions described in general method **A** to yield the hydroxylamine **320** (0.262 g, 1.554 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to give the crude product which was purified by silica gel chromatography (5-20% ethyl acetate/petrol) to yield the *title compound* **321** (0.414 g, 77%) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 3221, 1670, 1459 and 1341; δ_H 1.60 (3H, s, CH_3), 1.68 (3H, s, CH_3), 2.10-2.00 (4H, m, 4- and 5-CH_2), 2.32 (2H, t, *J* 6.8, 2-CH_2), 2.44 (3H, s, Ar-CH_3), 4.10 (2H, t, *J* 6.8, 1-CH_2), 4.76 (1H, br. s, CH), 4.80 (1H, br. s, CH), 5.08 (1H, br. t, *J* 6.7, 6-H), 7.12 (1H, br. s, NH), 7.33 (2H, d, *J* 8.3, 2 x Ar-H) and 7.80 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 17.7 (CH_2), 21.7 (CH_3), 25.7 (CH_3), 26.3 (CH_3), 34.6 (CH_2), 36.0 (CH_2), 75.6 (CH_2), 111.1 (CH),

123.8 (CH_2), 128.6 (2 x Ar-H), 129.7 (2 x Ar-H), 131.8 (C), 133.6 (C), 144.8 (2 x Ar) and 145.5 (2 x Ar); [Found M^+ + H: 324.1636. $C_{17}H_{26}NO_3S$ requires *M*, 324.1633].

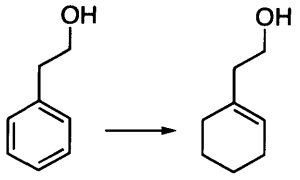
1-[(*p*-toluenesulphonyl)aza]-2-oxa-8,8-dimethyl-*spiro*-[4,5]-decane 322



321 **322**

The sulphonamide **321** (1.410 g, 4.379 mmol) was cyclised under the conditions described in general method **G** to give the *title compound* **322** (0.960 g, 70%) as a colourless solid showing: ν_{max}/cm^{-1} [DCM] 1598, 1455, 1327, 1156, 1089 and 814; δ_H 0.93 (3H, s, 8-CH_3), 1.07 (3H, s, 8-CH_3), 1.40-1.29 (2H, m), 1.49 (1H, d, *J* 13.4, 9-H_a), 1.57-1.51 (1H, m), 1.77 (1H, dddd, *J* 0.9, 3.6, 7.9 and 13.7), 1.97-1.88 (1H, m), 2.01 (1H, d, *J* 13.4, 9-H_b), 2.17-2.09 (1H, m), 2.21 (1H, ddd, *J* 5.9, 9.2 and 11.7), 2.43 (3H, s, Ar-CH_3), 2.47 (1H, ddd, *J* 6.2, 9.4 and 11.8), 4.23-4.11 (2H, m, 3-H_a and –H_b), 7.32 (2H, d, *J* 8.4, Ar-H) and 7.83 (2H, d, *J* 8.4, Ar-H); δ_C 20.0 (CH_2), 21.6 (2 x CH_3), 21.7 (Ar-CH_3), 31.4 (C), 33.8 (CH_2), 38.7 (CH_2), 40.7 (CH_2), 47.1 (CH_2), 69.5 (C), 71.2 (CH_2), 128.6 (Ar-H), 129.3 (Ar-H), 136.0 (Ar) and 144.2 (Ar); [Found M^+ + H: . $C_{17}H_{26}NO_3S$ requires *M*, 324.1633].

2-Cyclohexenylethanol 340

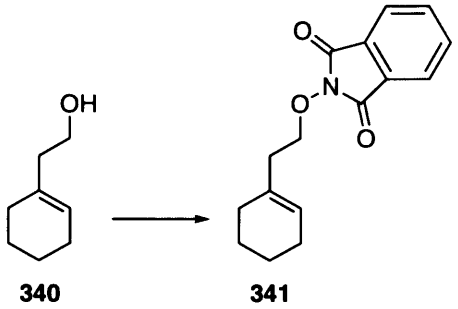


339 **340**

A dry, three neck flask was fitted with a cold finger and flushed with dry nitrogen. Lithium shot (3.980 g, 0.573 mol) was added to the flask followed by freshly distilled n-propylamine (90 ml). 2-Phenylethanol **339** (10.000 g, 81.900 mmol) was added, dropwise over 10 minutes over which time the solution became warm and adopted a deep blue colour. The resulting mixture was stirred, at room temperature for 8 h over which time it became light brown. The reaction was quenched by the gradual addition of saturated, aqueous ammonium sulphate until the resulting effervescence subsided. The propylamine was removed under reduced pressure to leave a thick, brown solid which was taken up in water (100 ml) and extracted into ether (3 x 100 ml). The combined organic portions were washed with saturated, aqueous ammonium sulphate (300 ml) and water (3 x 300 ml) and dried over magnesium sulphate. The solvent was

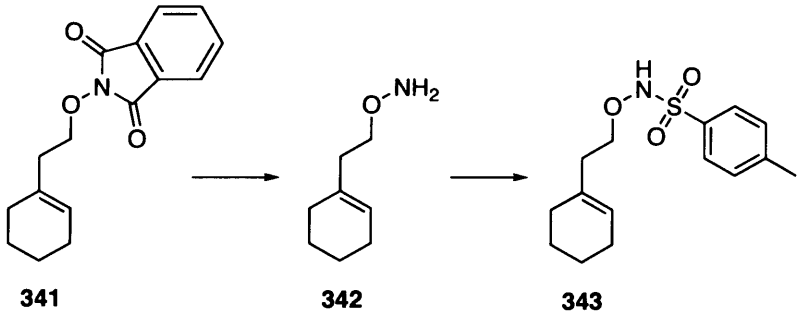
removed *in vacuo* to give the crude *title compound* **340** (11.206 g) [δ_H 1.59-1.54 (2H, m, CH_2), 1.67-1.61 (2H, m, CH_2), 1.95 (2H, br. s, CH_2), 2.02 (2H, br. s, CH_2), 2.21 (2H, t, *J* 6.0, 2-CH_2), 3.66 (2H, app. q, *J* 6.0, 1-CH_2) and 5.53 (1H, br. s, CH)], as the major component in an inseparable mixture of compounds. The product was used directly, without further purification.

2-(2-Cyclohexenylethoxy)isoindoline-1,3-dione 341



The crude alcohol **340** (1.000 g, 7.924 mmol if pure) was reacted with *N*-hydroxyphthalimide (1.305 g, 8.003 mmol) under the conditions described in general method **A** to give the crude *title compound* **341** (0.997 g), as the major component in a inseparable mixture of compounds. The product was used directly, without further purification.

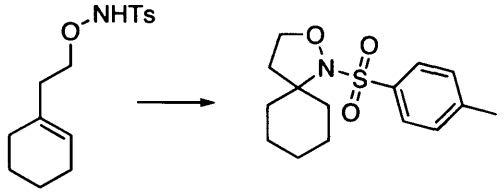
***N*-(2-Cyclohexenylethanol)-*p*-toluenesulphonamide 343**



The crude phthalimide **341** (0.997 g, 3.678 mmol if pure) was deprotected under the conditions described in general method **B** to yield the crude hydroxylamine **342** (0.475 g, 3.383 mmol if pure), presumed to be the major component in a mixture of compounds. The crude mixture was treated as an unstable intermediate and immediately tosylated under the conditions described in general method **C** to give the crude product which was purified by silica gel chromatography (5-20% ethyl acetate/petrol) to yield the *title compound* **343** (0.388 g, 18% over 4 steps with respect to 2-phenylethanol **339**) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 3222, 1598, 1335 and 1167; δ_H 1.58-1.45 (4H, m, 2 x CH_2), 1.87-1.84 (2H, m, CH_2), 1.93-1.90 (2H, m, CH_2), 2.15 (2H, t, *J* 6.7, 2-CH_2), 2.38 (3H, s, Ar-CH_3), 4.00 (2H, t, *J* 6.7, 1-CH_2), 5.37 (1H, br .s, CH), 6.87 (1H, br. s, NH), 7.27 (2H, d, *J* 8.3, 2 x Ar-H) and 7.74 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 21.7 (CH_3), 22.3 (CH_2), 22.8 (CH_2), 25.3 (CH_2), 28.2 (CH_2), 36.6 (CH_2), 75.5 (CH_2), 123.3 (CH), 128.6

(Ar-H), 129.7 (Ar-H), 133.6 (C(Ar)), 133.8 (C(Ar)) and 144.8 (C(Ar)); [Found M^+ + Na: 318.1155. $C_{15}H_{21}NO_3SNa$ requires 318.1140].

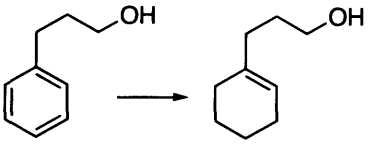
1-[(*p*-Toluenesulphonyl)aza]-2-oxa-*spiro*-[4,5]-decane 344



343 **344**

The sulphonamide **343** (0.200 g, 0.678 mmol) was cyclised under the conditions described in general method **G** to give the *title compound* **344** (0.187 g, 94%) as an orange solid: mp 61-62 °C; ν_{max}/cm^{-1} [film] 1598, 1453, 1325 and 1159; δ_H 1.35-1.32 (2H, m, CH_2), 1.49-1.43 (2H, m, CH_2), 1.77-1.70 (2H, m, CH_2), 2.02-1.95 (2H, m, CH_2), 2.24 (2H, t, *J* 7.7, 4-CH_2), 2.33 (3H, s, Ar-CH_3), 4.07 (2H, t, *J* 7.7, 3-CH_2), 7.22 (2H, d, *J* 7.5, 2 x Ar-H) and 7.75 (2H, d, *J* 7.5, 2 x Ar-H); δ_C 21.7 (CH_3), 23.7 (CH_2), 25.5 (CH_2), 34.8 (CH_2), 38.7 (CH_2), 69.4 (CH_2), 72.0 (C), 128.8 (Ar-H), 129.4 (Ar-H), 135.8 (Ar) and 144.3 (Ar); *m/z* [APcI] 296.1 (M^+ + H, 100%); [Found M^+ + Na: 318.1148. $C_{15}H_{21}NNaO_3S$ requires *M*, 318.1140].

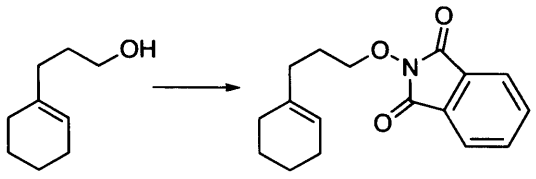
3-Cyclohexenylpropan-1-ol 346



345 **346**

A dry, three neck flask was fitted with a cold finger and flushed with dry nitrogen. Lithium shot (3.570 g, 0.514 mol) was added to the flask followed by freshly distilled n-propylamine (90 ml). 3-Phenylpropanol **345** (10.000 g, 73.475 mmol) was added, dropwise over 10 minutes over which time the solution became warm and adopted a deep blue colour. The resulting mixture was stirred, at room temperature for 8 h over which time it became light brown. The reaction was quenched by the gradual addition of saturated, aqueous ammonium sulphate until the resulting effervescence subsided. The propylamine was removed under reduced pressure to leave a thick, brown solid which was taken up in water (100 ml) and extracted into ether (3 x 100 ml). The combined organic portions were washed with saturated, aqueous ammonium sulphate (300 ml) and water (3 x 300 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the crude *title compound* **346** (10.559 g) [*m/z* [APcI] 141.1 (M^+ + H, 80%) and 123.1 (100%)], as the major component in a inseparable mixture of compounds. The product was used directly, without further purification.

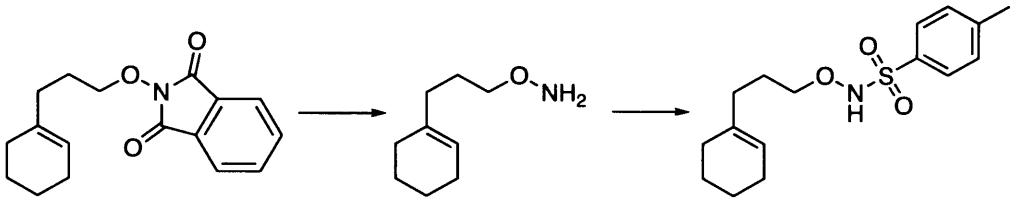
2-(3-Cyclohexenylpropoxy)isoindoline-1,3-dione 347



346 **347**

The crude alkene **346** (1.000 g, 7.138 mmol if pure) was reacted with *N*-hydroxyphthalimide (1.175 g, 7.210 mmol) under the conditions described in general method **A** to yield the crude *title compound* **347** (1.092 g), as the major component in a mixture of compounds. The product was used directly, without further purification.

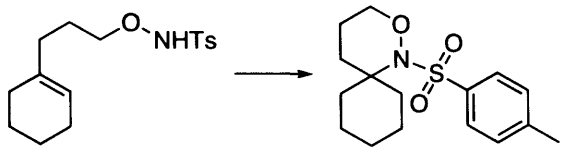
***N*-(3-Cyclohexenylpropan-1-ol)-*p*-toluenesulphonamide 349**



347 **348** **349**

The phthalimide **347** (1.092 g, 3.830 mmol if pure) was deprotected under the conditions described in general method **B** to give the hydroxylamine **348** (0.542 g, 3.485 mmol if pure) as a colourless oil which was treated as an unstable intermediate which was immediately tosylated under the conditions described in general method **C** to yield the crude product which was purified by silica gel chromatography (10-20% ethyl acetate/petrol) to give the *title compound* **349** (0.305g, 14% over 4 steps with respect to 3-phenylpropanol **345**) as a thick, yellow oil: ν_{max}/cm^{-1} [film] 3222, 1598, 1446, 1383, 1335, 1189 and 1168; δ_H 1.71-1.50 (6H, m, 3 x CH_2), 1.97-1.86 (6H, m, 3 x CH_2), 2.45 (3H, s, Ar-CH_3), 3.96 (2H, t, *J* 6.7, 1-CH_2), 5.37 (1H, br. s, CH), 6.93 (1H, br. s, NH), 7.35 (2H, d, *J* 8.2, 2 x Ar-H) and 7.81 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 21.7 (CH_3), 22.5 (CH_2), 22.9 (CH_2), 25.2 (CH_2), 26.1 (CH_2), 28.2 (CH_2), 34.0 (CH_2), 77.4 (CH_2), 121.4 (CH), 128.6 (2 x Ar-H), 129.7 (2 x Ar-H), 133.6 (C), 136.7 (Ar) and 144.9 (Ar); [Found M^+ + Na: 332.1305. $C_{16}H_{23}NNaO_3S$ requires *M*, 332.1296].

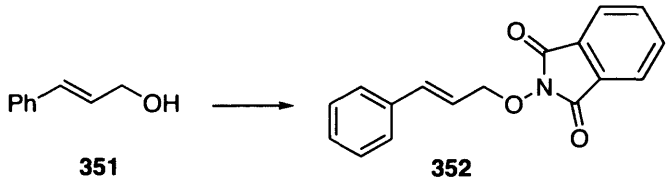
1-[(*p*-Toluenesulphonyl)aza]-2-oxa-*spiro*-[5,6]-undecane 350



349 **350**

The *title compound* **349** (0.250 g, 0.809 mmol) was cyclised under the conditions described in general method **G** to yield the *title compound* **350** (0.232 g, 93%) as a crystalline, orange solid: mp 63-64°C; ν_{max}/cm^{-1} [DCM] 1597, 1448, 1321 and 1165; δ_H 1.31-1.16 (4H, m, 2 x CH_2), 1.63-1.45 (4H, m, 2 x CH_2), 1.79-1.76 (2H, m, CH_2), 1.88-1.85 (2H, m, CH_2), 1.98-1.95 (2H, m, CH_2), 2.35 (3H, s, Ar-CH_3), 3.79 (2H, app. t, *J* 5.8, 3-CH_2); 7.20 (2H, d, *J* 8.2, 2 x Ar-H) and 7.73 (2H, d, *J* 8.2, 2 x Ar-H); δ_C 20.4 (CH_2), 21.6 (CH_3), 22.4 (CH_2), 25.8 (CH_2), 30.5 (CH_2), 33.3 (CH_2), 66.6 (C), 71.0 (CH_2), 128.2 (Ar-H), 129.3 (Ar-H), 137.2 (Ar) and 143.7 (Ar); [Found M^+ + H: 310.1474. $C_{16}H_{24}NO_3S$ requires *M*, 310.1477].

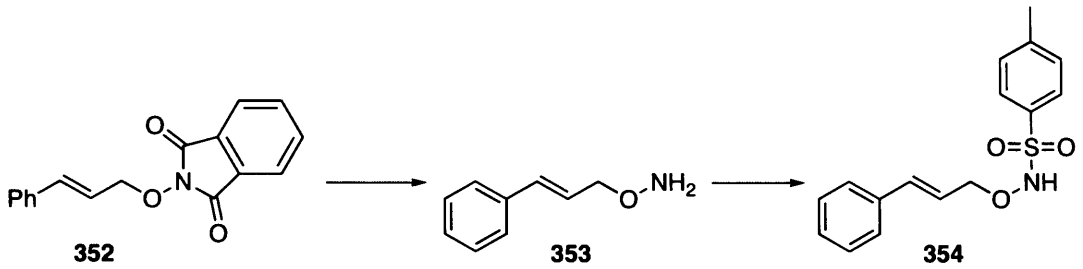
2-[(*E*)-3-Phenylprop-2-en-1-oyl]isoindoline-1,3-dione 351



351 **352**

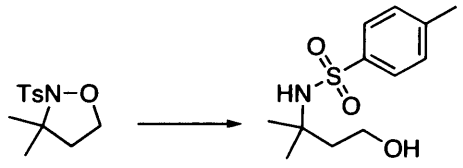
(*E*)-Cinnamyl alcohol **351** (1.000 g, 7.457 mmol) was reacted with *N*-hydroxyphthalimide (1.228 g, 7.532 mmol) under the conditions described in general method **A** to yield the *title compound* **352** (1.891 g, 91%) as a colourless solid: mp 146-147°C; ν_{max}/cm^{-1} [nujol] 1728, 1464, 1453 and 1392; δ_H 4.80 (2H, d, *J* 7.1, 1-CH_2), 6.39 (1H, td, *J* 15.8 and 7.1, 2-H), 6.60 (1H, d, *J* 15.8, 3-H), 7.26-7.19 (3H, m, 3 x Ar-H), 7.32-7.30 (2H, m, 2 x Ar-H), 7.65 (2H, dd, *J* 5.5 and 3.0, 2 x Ar-H) and 7.74 (2H, dd, *J* 5.4 and 3.2 , 2 x Ar-H) ; δ_C 78.7 (CH_2), 122.0 (C(Ar)-H), 123.6 (C(Ar)-H), 126.9 (C(Ar)-H), 128.5 (C(Ar)-H), 128.6 (C(Ar)-H), 128.8 (Ar), 134.5 (C(Ar)-H), 135.8 (Ar), 137.6 (C(Ar)-H) and 163.9 (CO); [Found M^+ + Na: 302.0786. $C_{17}H_{13}NNaO_3$ requires *M*, 302.0793].

N-[(E)-3-Phenylprop-2-en-1-oyl]-p-toluenesulphonamide 354



The phthalimide **352** (1.000 g, 3.583 mmol) was deprotected under the conditions described in general method **B** to give the hydroxylamine **353** (0.517 g, 3.476 mmol) as a colourless oil which was treated as an unstable intermediate and tosylated immediately under the conditions described in general method **C** to yield the *title compound* **354** (0.849 g, 78%) as a pale yellow solid showing: mp 92-93°C; ν_{max}/cm^{-1} [film] 3425, 1654, 1597, 1334 and 1168; δ_H 2.43 (3H, s, Ar-CH_3), 4.61 (2H, d, *J* 6.8, 1-CH_2), 6.22 (1H, dt, *J* 15.9 and 6.8, 2-H), 6.63 (1H, d, *J* 15.9, 3-H), 6.96 (1H, s, NH), 7.40-7.26 (7H, m, 7 x Ar-H) and 7.83 (2H, d, *J* 8.3, 2 x Ar-H); δ_C 21.7 (CH_3), 77.9 (CH_2), 122.8 (C(Ar)-H), 126.6 (C(Ar)-H), 127.1 (C(Ar)-H), 128.2 (C(Ar)-H), 128.6 (C(Ar)-H), 129.8 (C(Ar)-H), 133.5 (Ar), 135.9 (C(Ar)-H), 136.1 (Ar) and 145.0 (Ar); *m/z* [APcI] 304.1 (M^+ + H, 100 %); [Found M^+ + H: 304.1001. $C_{18}H_{18}NO_3S$ requires *M*, 304.1007].

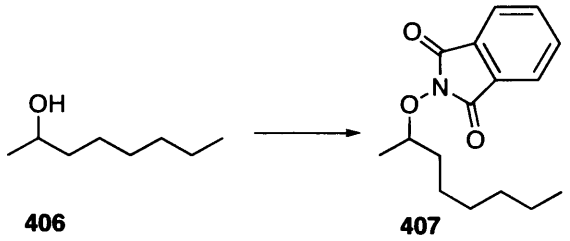
3-Methyl-3-(p-toluenesulphonamide)butan-1-ol 360



The isoxazolidine **284** (0.186 g, 0.728 mmol) was taken up in acetonitrile (11 ml) and water (1 ml) and stirred under an atmosphere of nitrogen. Molybdenum hexacarbonyl (0.192 g, 0.728 mmol) was added in one portion and the resulting mixture heated at reflux for 16 h. The mixture was cooled and passed through a pad of celite, eluting with ethyl acetate. The solvent was removed *in vacuo* and the resulting crude product taken up in the minimum amount of ethyl acetate. The solution was then passed through a pad of silica gel, eluting with copious ethyl acetate and the solvent removed *in vacuo* to yield the *title compound* **360** (0.174 g, 93%) as a thick, orange oil characterised by: ν_{max}/cm^{-1} [film] 3423, 3277, 1707, 1599, 1427 and 1320; δ_H 1.24 (6H, s, 2 x CH_3), 1.73 (2H, t, *J* 5.9, 2-CH_2), 2.13 (1H, br. s, OH), 2.42 (3H, s, Ar-CH_3), 3.85 (2H, t, *J* 5.9, 1-CH_2), 5.95 (1H, br. s, NH), 7.28 (2H, br. d, *J* 8.3, 2 x Ar-H) and 7.78 (2H, br. d, *J* 8.3, 2 x Ar-H); δ_C 21.5 (CH_3), 27.8 (2 x CH_3), 44.3 (CH_2), 56.6 (C), 59.4 (CH_2), 126.9 (Ar-H), 129.5 (Ar-H), 140.7 (Ar) and 142.8 (Ar); [Found M^+ + Na: 280.0974. $C_{12}H_{19}NNaO_3S$ requires *M*, 280.0983].

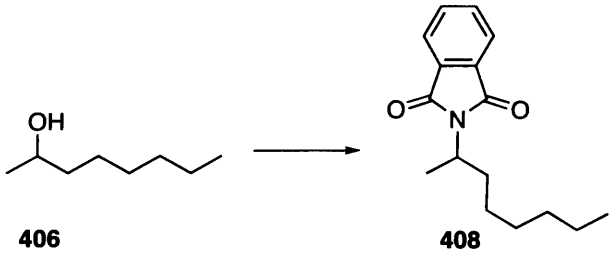
Chapter 5 compounds

2-(Octan-2-yloxy)isoindoline-1,3-dione 407 [120]



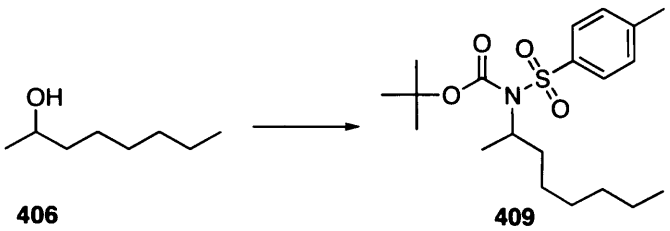
Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with *N*-hydroxyphthalimide (1.266 g, 7.763 mmol) under the conditions described in general method **A** to yield the *title compound* **407** (1.711 g, 81%) as a thick, colourless oil. All data obtained were in accordance with those previously reported in the literature[120] and references contained therein: δ_H 0.89 (3H, t, *J* 6.5, 8-CH_3), 1.33 (3H, d, *J* 6.3, 1-CH_3), 1.35-1.26 (6H, m, 5-, 6- and 7-CH_2), 1.51-1.42 (2H, m, 4-CH_2), 1.64-1.56 (1H, m, 3-H_a), 1.86-1.77 (1H, m, 3-H_b), 4.38 (1H, app. sextet, *J* 6.3, 2-H), 7.75 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H) and 7.84 (2H, dd, *J* 5.5 and 3.1, 2 x Ar-H); δ_C 14.1 (CH_3), 18.8 (CH_3), 22.6 (CH_2), 25.3 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 34.9 (CH_2), 84.5 (CH), 123.4 (Ar-H), 129.1 (Ar), 134.4 Ar-H) and 164 .4 (CO); *m/z* [APcI] 276.3 (M^+ + H, 100%).

2-(Octan-2-yl)isoindoline-1,3-dione 408 [120]



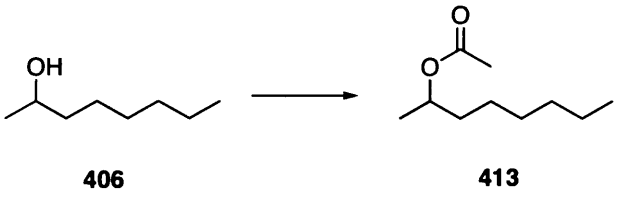
Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with phthalimide (1.141 g, 7.763 mmol) under the conditions described in general method **A** to yield the *title compound* **408** (1.515 g, 76%) as a thick, colourless oil. All data obtained were in accordance with those previously reported in the literature[120] and references contained therein, showing: 0.84 (3H, t, *J* 6.9, 8-CH_3), 1.31-1.18 (8H, m, 4-, 5-, 6- and 7-CH_2), 1.46 (3H, d, *J* 6.9, 1-CH_3), 1.77-1.70 (1H, m, 3-H_a), 2.09-2.00 (1H, m, 3-H_b), 4.39-4.30 (1H, m, 2-H), 7.70 (2H, dd, *J* 5.4 and 3.1, 2x Ar-H) and 7.82 (2H, dd, *J* 5.4 and 3.1, 2 x Ar-H); δ_C 14.0 (CH_3), 18.7 (CH_3), 22.6 (CH_2), 26.8 (CH_2), 28.9 (CH_2), 31.7 (CH_2), 33.8 (CH_2), 47.5 (CH), 123.0 (Ar-H), 132.1 (Ar), 133.8 (Ar-H) and 168.6 (CO); *m/z* [APcI] 260.2 (M^+ + H, 100%).

N-(p-toluenesulphonyl)-*tert*-butyl octan-2-ylcarbamate 409 [151]



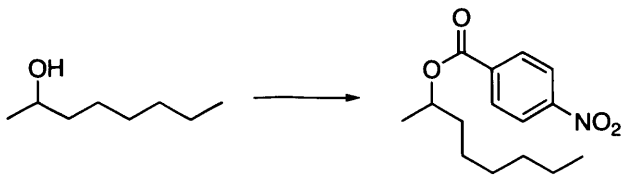
Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with N-Boc-p-toluenesulphonamide (2.105 g, 7.763 mmol) under the conditions described in general method **A** to yield the *title compound* **409** (2.325 g, 79%) as a thick, colourless oil. All data obtained were in accordance with those previously reported in the literature[151] and showed: δ_H 0.88 (3H, t, J 6.9, 8-CH_3), 1.31-1.26 (8H, m, 4-, 5-, 6- and 7-CH_2), 1.36 (9H, s, 3 x tBu-CH_3), 1.44 (3H, d, J 6.8, 1-CH_3), 1.71-1.61 (1H, m, 3-H_a), 1.98-1.89 (1H, m, 3-H_b), 2.44 (3H, s, Ar-CH_3), 4.58-4.49 (1H, m, 2-H), 7.29 (2H, d, J 8.2, 2 x Ar-H) and 7.80 (2H, d, J 8.2, 2 x Ar-H); δ_C 14.1 (CH_3), 19.9 (CH_3), 21.6 (CH_3), 22.6 (CH_2), 27.0 (CH_2), 28.0 (tBu-CH_3), 29.1 (CH_2), 31.7 (CH_2), 34.9 (CH_2), 55.6 (CH), 83.8 (C), 127.8 (Ar-H), 129.1 (Ar-H), 138.0 (Ar), 143.7 (Ar) and 150.8 (CO); *m/z* [APcI] 406.3 (M^+ + Na, 50%) and 155.0 (100%).

Octan-2-yl acetate 413 [152]



Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with acetic acid (0.970 g, 16.141 mmol) under the conditions described in general method **A** to yield the *title compound* **413** (1.321 g, 99%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature[152] and showed: δ_H 0.88 (3H, t, J 6.7, 8-CH_3), 1.20 (3H, d, J 6.3, 1-CH_3), 1.32-1.27 (8H, m, 4-, 5-, 6- and 7-CH_2), 1.49-1.42 (1H, m, 3-H_a), 1.62-1.53 (1H, m, 3-H_b), 2.03 (3H, s, CH_3) and 4.89 (1H, app. sextet, J 6.3, 2-H); δ_C 14.1 (CH_3), 20.0 (CH_3), 21.5 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 29.1 (CH_2), 31.8 (CH_2), 35.9 (CH_2), 71.1 (CH) and 170.9 (CO); *m/z* [APcI] 195.3 (M^+ + H, 100%).

Octan-2-yl 4-nitrobenzoate 415 [153]



406 **415**

Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with *p*-nitrobenzoic acid (2.167 g, 7.763 mmol) under the conditions described in general method **A** to yield the *title compound* **415** (1.803 g, 84%) as a thick, colourless oil. All data obtained were in accordance with those previously reported in the literature[153] and showed: δ_H 0.88 (3H, t, *J* 6.9, 8-CH_3), 1.37 (3H, d, *J* 6.3, 1-CH_3), 1.41-1.29 (8H, m, 4-, 5-, 6- and 7-CH_2), 1.68-1.60 (1H, m, 3-H_a), 1.81-1.72 (1H, m, 3-H_b), 5.19 (1H, app. sextet, *J* 6.2, 2-H), 8.20 (2H, app. dt, *J* 9.0 and 2.0, 2 x Ar-H) and 8.29 (2H, app. dt, *J* 9.0 and 2.0, 2 x Ar-H); δ_C 14.0 (CH_3), 20.0 (CH_3), 22.6 (CH_2), 25.4 (CH_2), 29.1 (CH_2), 31.7 (CH_2), 35.9 (CH_2), 73.2 (CH), 123.5 (Ar-H), 130.6 (Ar-H), 136.3 (Ar), 150.4 (Ar) and 164.3 (C_); _/z OAPcm] 2[0.4I(M^+8+ H 100%).

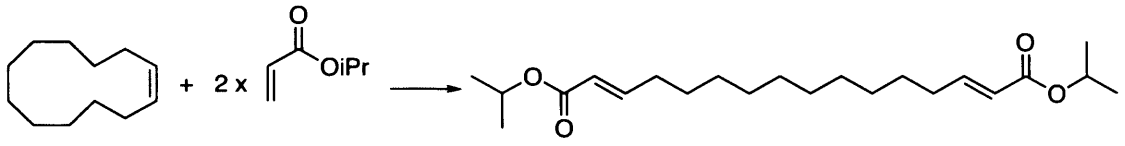
1-(Octan-2-yloxy)benzene 411 [152]

406 **411**

Octan-2-ol **406** (1.000 g, 7.686 mmol) was reacted with phenol (0.730 g, 7.763 mmol) under the conditions described in general method **A** to yield the *title compound* **411** (0.888 g, 56%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature[152] and showed: δ_H 0.88 (3H, t, *J* 6.9, 8-CH_3), 1.29 (3H, d, *J* 6.1, 1-CH_3), 1.60-1.30 (8H, m, 4 x CH_2), 1.78-1.69 (2H, m, 3-CH_2), 4.35 (1H, app. sextet, *J* 6.1, 2-H), 6.93-6.87 (3H, m, 3 x Ar-H) and 7.29-7.25 (2H, m, 2 x Ar-H); δ_C 14.1 (CH_3), 19.8 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 29.3 (CH_2), 31.8 (CH_2), 36.5 (CH_2), 73.8 (CH), 115.3 (2 x Ar-H), 120.8 (Ar-H), 129.7 (2 x Ar-H) and 158.2 (Ar); *m/z* [APcI] 229.2 (M^+ + Na, 100%).

Chapter 6 compounds

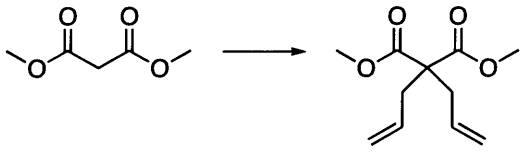
(2*E*,14*E*)-Isopropyl hexadeca-2,14-dienedioate 433 [128]



431 432 433

Cyclododecane **431** (1.85 ml, 9.020 mmol) was added to dry dichloromethane (90 ml) and isopropyl acrylate **432** (2.31 ml, 18.040 mmol) added dropwise, *via* syringe. Grubb's Second Generation Catalyst **420** (0.028 g, 0.033 mmol) was added in one portion and the solution heated at reflux for 16 h. The solution was cooled to 0°C and stirred whilst open to air. Water (17 ml) was added followed by 30% aq. hydrogen peroxide (17 ml, 0.165 mol). The biphasic solution was stirred vigorously for 1 h. The solution was seen to effervesce with slowly increasing vigour before gradually subsiding. CAUTION: FLAMMABLE GAS RELEASED. The mixture was transferred to a separating funnel and the organic portion removed. The aqueous portion extracting with dichloromethane (2 x 30 ml) and quenched by addition to sat. aq. sodium sulphate (100 ml). The combined organic portions were dried over magnesium sulphate and passed through a pad of silica. The silica pad was washed through with dichloromethane (300 ml) and the organic portions combined and the solvent removed *in vacuo* to yield the *title compound* **433** (2.669 g, 81%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature[128] and showed: δ_H 1.26 (12H, d, *J* 6.2, 4 x CH_3), 1.20-1.30 (12H, m, 6 x CH_2), 1.40-1.50 (4H, m, 2 x CH_2), 2.20 (4H, app. qd, *J* 6.9 and 1.4, 4- and 13-CH_2), 5.05 (2H, app. heptet, *J* 6.2, 2 x CH), 5.88 (2H, dt, *J* 15.6 and 1.4, 2- and 15-H) and 6.95 (2H, dt, *J* 15.6 and 6.3, 3- and 14-H); *m/z* [APcI] 367.4 (M^+ + H, 100%).

Dimethyl 2,2-diallylmalonate 435

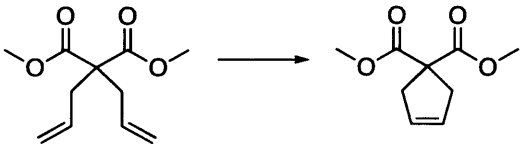


434 435

Sodium hydride (60% dispersion in mineral oil) (3.176 g, 0.0794 mol) was stirred in dry hexane (250 ml) for 0.5 h. The hexane was removed *via* syringe and replaced with dry tetrahydrofuran (500 ml) and the resulting mixture stirred at 0°C. Dimethyl malonate **434** (4.55 ml, 37.800 mmol) was added and the reaction stirred for 0.5 h. Allyl bromide (6.78 ml, 79.400 mmol) was added *via* syringe and the reaction allowed to warm to room temperature over 4 h. The reaction was cooled to 0°C and was quenched by the careful, dropwise addition of water (200 ml). The

product was extracted into dichloromethane (3 x 200 ml) and the combined organic portions washed with water (3 x 600 ml) and dried over magnesium sulphate. The solvent was removed *in vacuo* to give the crude product, which was distilled under reduced pressure (bp ~60°C, 1 mmHg) to yield the *title compound* **435** (7.534 g, 94%) as a colourless oil. All data obtained were in accordance with those previously reported in the literature[154] and showed: δ_H 2.65 (4H, d, *J* 6.8, 2 x 1'-CH_2), 3.68 (6H, s, CH_3), 5.02 (2H, dd, *J* 10.0 and 1.6, 3'-H-*cis*), 5.08 (2H, dd, *J* 17.1 and 1.6, 3'-H-*trans*) and 5.67 (2H, ddt, *J* 17.1, 10.0 and 6.8, 2'-H); δ_C 36.9 (2 x CH_3), 52.4 (2 x CH_2), 57.7 (C), 119.3 (CH), 132.2 (CH_2) and 171.2 (CO); *m/z* [APcI] 213.3 (M^+ + H, 100%).

Dimethyl cyclopent-3-ene-1,1-dicarboxylate 436 [155]



435 **436**

A solution of the dicarboxylate **435** (0.250 g, 1.178 mmol) in dry dichloromethane (250 ml) was degassed by bubbling through a stream of dry nitrogen for 0.5 h whilst stirring. Grubbs First Generation Catalyst (0.049 g, 0.059 mmol) was added in one portion and the progress of the reaction monitored by tlc [**77** Rf = 0.44 and **91** Rf = 0.40 (20% ethyl acetate/petrol)]. After was 1 h the solution was opened to air. Water (30.1 ml) and 30% aq. hydrogen peroxide (30.1 ml, 0.295 mol) added were added and the biphasic solution stirred vigorously for 1 h. The solution was seen to effervesce with slowly increasing vigour before gradually subsiding. CAUTION: FLAMMABLE GAS RELEASED. The mixture was transferred to a separating funnel and the organic portion removed. The aqueous portion was extracted with dichloromethane (2 x 250 ml) and quenched by addition to saturated aqueous sodium sulphate (500 ml). The combined organic portions were dried over magnesium sulphate and passed through a pad of silica. The silica pad was washed through with dichloromethane (600 ml) and the organic portions combined and the solvent removed *in vacuo* to yield the *title compound* **436** (0.177 g, 82%) as a colourless oil. All data obtained was in accordance with that previously reported in the literature[155] and showed: δ_H 3.00 (4H, s, 2- and 5-CH_2), 3.72 (6H, s, 2 x CH_3), 5.61 (2H, s, 3- and 4-H).

An example of the calculation of Ru levels in reaction products

A sample of both treated and untreated reaction product was accurately weighed and added to a volumetric flask. Each sample was digested overnight with 20 ml of aqua regia and then diluted to 100ml in volume with distilled water. This solution was analysed by ICPMS and the Ru content recorded as ppb in the solution.

Untreated sample:
Total Ru content (^{99}Ru and ^{101}Ru) by ICPMS = 1542.8 ppb
This equates to 1.5428 ppm or 1.5428 μg/ml. Thus in 100 ml there are 154.28 μg.
This must originate from the sample added; therefore the sample contains 154.28 μg of Ru.
The sample weighed 58 mg. 154.28 μg/ 58 mg = 2660 μg/g or 2660 ppm.

Treated sample:
Total Ru content (^{99}Ru and ^{101}Ru) by ICPMS = 0.984 ppb
This equates to 0.000984 ppm or 0.000984 μg/ml. Thus in 100 ml there are 0.0984 μg.
This must originate from the sample added; therefore the sample contains 0.0984 μg of Ru.
The sample weighed 74 mg. 0.0984 μg/ 74 mg = 1.330 μg/g or 1.330 ppm.

1.330 ppm / 2660 ppm = 0.0005 or 0.05%
Thus, 95.95% removal of Ru is achieved in the treated sample when compared to the untreated sample.

A similar calculation was performed for each of the Ru content values.

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APPENDIX

X-ray crystal structure data for 3,3-Dimethyl-2-(*p*-toluenesulphonyl)isoxazolidine 284

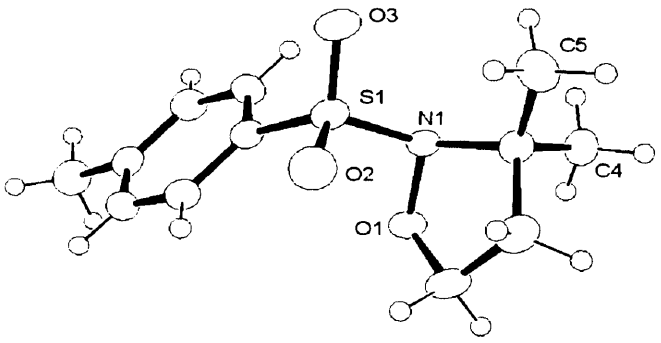

Table 1. Crystal data and structure refinement for asDK01.

Identification code	asDK01
Empirical formula	C12 H17 N O3 S
Formula weight	255.33
Temperature	150(2) K
Wavelength	0.71073 A
Crystal system, space group	orthorhombic, Pbca
Unit cell dimensions	a = 8.1125(16) A alpha = 90 deg.
b = 14.098(3) A beta = 90 deg.	
c = 22.448(5) A gamma = 90 deg.	
Volume	2567.4(9) A^3
Z, Calculated density	8, 1.321 Mg/m^3
Absorption coefficient	0.249 mm^-1
F(000)	1088
Crystal size	0.50 x 0.35 x 0.20 mm
Theta range for data collection	3.04 to 26.00 deg.
Limiting indices	-9<=h<=10, -17<=k<=17, -27<=l<=27
Reflections collected / unique	4645 / 2491 [R(int) = 0.0222]
Completeness to theta = 26.00	99.1 %
Max. and min. transmission	sortav 0.955 and 0.730
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2491 / 0 / 157
Goodness-of-fit on F^2	1.037
Final R indices [I>2sigma(I)]	R1 = 0.0329, wR2 = 0.0822
R indices (all data)	R1 = 0.0400, wR2 = 0.0863
Largest diff. peak and hole	0.234 and -0.339 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for asDK01. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

x	y	z	U(eq)	
S(1)	410(1)	6434(1)	4065(1)	27(1)
O(1)	2679(1)	5295(1)	3803(1)	29(1)
N(1)	2301(2)	6288(1)	3748(1)	24(1)
C(1)	3752(2)	6779(1)	4030(1)	30(1)
O(2)	385(1)	6148(1)	4678(1)	38(1)
C(2)	4200(2)	6117(1)	4551(1)	42(1)
O(3)	-93(1)	7377(1)	3916(1)	39(1)
C(3)	3600(2)	5146(1)	4353(1)	38(1)
C(4)	5108(2)	6769(1)	3557(1)	37(1)
C(5)	3379(2)	7792(1)	4223(1)	40(1)
C(6)	-732(2)	5615(1)	3646(1)	25(1)
C(7)	-980(2)	5783(1)	3043(1)	29(1)
C(8)	-1889(2)	5139(1)	2714(1)	32(1)
C(9)	-2563(2)	4336(1)	2978(1)	30(1)
C(10)	-2326(2)	4195(1)	3588(1)	31(1)
C(11)	-1404(2)	4825(1)	3923(1)	29(1)
C(12)	-3477(2)	3612(1)	2612(1)	43(1)

Table 3. Bond lengths [A] and angles [deg] for asDK01.

S(1)-O(3)	1.4307(12)
S(1)-O(2)	1.4344(11)
S(1)-N(1)	1.7037(13)
S(1)-C(6)	1.7536(15)
O(1)-N(1)	1.4390(15)
O(1)-C(3)	1.4587(18)
N(1)-C(1)	1.5047(19)
C(1)-C(5)	1.523(2)
C(1)-C(4)	1.528(2)
C(1)-C(2)	1.541(2)
C(2)-C(3)	1.520(2)
C(6)-C(11)	1.387(2)
C(6)-C(7)	1.3904(19)
C(7)-C(8)	1.382(2)
C(8)-C(9)	1.390(2)

C(9)-C(10)	1.397(2)
C(9)-C(12)	1.507(2)
C(10)-C(11)	1.384(2)
O(3)-S(1)-O(2)	118.77(7)
O(3)-S(1)-N(1)	105.69(7)
O(2)-S(1)-N(1)	112.34(6)
O(3)-S(1)-C(6)	109.62(7)
O(2)-S(1)-C(6)	108.81(7)
N(1)-S(1)-C(6)	99.95(6)
N(1)-O(1)-C(3)	108.75(10)
O(1)-N(1)-C(1)	104.14(10)
O(1)-N(1)-S(1)	105.85(8)
C(1)-N(1)-S(1)	118.29(9)
N(1)-C(1)-C(5)	113.25(13)
N(1)-C(1)-C(4)	105.49(11)
C(5)-C(1)-C(4)	110.48(14)
N(1)-C(1)-C(2)	103.05(12)
C(5)-C(1)-C(2)	113.44(13)
C(4)-C(1)-C(2)	110.64(14)
C(3)-C(2)-C(1)	104.29(12)
O(1)-C(3)-C(2)	106.43(12)
C(11)-C(6)-C(7)	121.13(14)
C(11)-C(6)-S(1)	119.73(11)
C(7)-C(6)-S(1)	119.12(11)
C(8)-C(7)-C(6)	119.05(14)
C(7)-C(8)-C(9)	121.09(14)
C(8)-C(9)-C(10)	118.72(14)
C(8)-C(9)-C(12)	120.80(14)
C(10)-C(9)-C(12)	120.44(14)
C(11)-C(10)-C(9)	121.05(14)
C(10)-C(11)-C(6)	118.95(13)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for asDK01.

The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S(1)	30(1)	27(1)	24(1)	-4(1)	-1(1)	5(1)
O(1)	33(1)	22(1)	30(1)	0(1)	-3(1)	6(1)
N(1)	27(1)	20(1)	24(1)	-1(1)	-4(1)	3(1)

C(1)	31(1)	31(1)	27(1)	-1(1)	-9(1)	-2(1)
O(2)	45(1)	47(1)	21(1)	-6(1)	4(1)	2(1)
C(2)	43(1)	50(1)	33(1)	7(1)	-15(1)	0(1)
O(3)	39(1)	27(1)	52(1)	-6(1)	-7(1)	11(1)
C(3)	40(1)	40(1)	34(1)	8(1)	-6(1)	12(1)
C(4)	30(1)	40(1)	41(1)	1(1)	-3(1)	-4(1)
C(5)	46(1)	34(1)	41(1)	-11(1)	-5(1)	-7(1)
C(6)	23(1)	27(1)	25(1)	0(1)	1(1)	4(1)
C(7)	31(1)	29(1)	27(1)	4(1)	0(1)	-1(1)
C(8)	34(1)	36(1)	27(1)	1(1)	-4(1)	1(1)
C(9)	24(1)	30(1)	36(1)	-1(1)	-3(1)	2(1)
C(10)	27(1)	28(1)	38(1)	6(1)	3(1)	1(1)
C(11)	27(1)	34(1)	26(1)	5(1)	3(1)	4(1)
C(12)	39(1)	38(1)	53(1)	-5(1)	-11(1)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for asDK01.

x	y	z	U(eq)	
H(2A)	5405	6113	4621	50
H(2B)	3638	6319	4922	50
H(3A)	4545	4717	4283	45
H(3B)	2882	4862	4662	45
H(4A)	5314	6114	3430	55
H(4B)	6120	7038	3724	55
H(4C)	4758	7147	3213	55
H(5A)	2976	8155	3880	61
H(5B)	4385	8087	4377	61
H(5C)	2534	7785	4535	61
H(7)	-531	6332	2859	35
H(8)	-2056	5247	2301	38
H(10)	-2806	3657	3776	37
H(11)	-1234	4718	4337	35
H(12A)	-3812	3897	2232	65
H(12B)	-4457	3400	2829	65
H(12C)	-2756	3068	2534	65