On the Synthesis of N-O bonds in Novel Heterocyclic Systems

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For my Grandad

Abstract

The origins of these investigations are in the pursuit of heterocycles containing an N-O bond. This project as a whole focusses on developing earlier chance observations made by previous members of the Knight Research Group.

Chapter 2 focusses on the synthesis of isoxazoles: 5-membered aromatic rings containing a nitrogen to oxygen bond. The origin of this project was the unexpected observation of a small percentage of isoxazole products in the Group's earlier synthesis of isoxazolines, which were thought to be the oxidation products arising from using silver nitrate as a catalyst for those cyclisations. It has now been found that by using an excess of silver nitrate, isoxazoles can be selectively formed from the same hydroxylamine precursors.

Chapter 3 centres on the viability of obtaining unusual 6-*endo*-trig products from the iodocyclisation of unsaturated *tert*-butyl carbonates. This Chapter is connected to the theme of N-O chemistry, as the *tert*-butyl carbonate starting materials were the unexpected products of a synthesis that had been designed to form hydroxylamines. The initial discovery of these unexpected 6-*endo* products on iodocyclisation was expanded upon to produce a series of cyclic carbonates with a procedure optimised to maximise the yield of this desired structural isomer.

Chapter 4 concentrates on building saturated N-O rings onto existing cyclic systems, including transannular cyclisations - investigating previous reports of rearrangement of N and O during cyclisation and working towards a synthesis of the core-structure of the natural product Histrionicotoxin. These schemes prove the utility of this acid-catalysed hydroamination methodology in building heterocycles and the chiral products that can be gleaned from them.

For the most part, this project has been concerned with methodology - solving problems and optimising key-step procedures - which can be applied to complex target molecules.

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Abbreviations and acronyms

Several abbreviations and acronyms have been used throughout this thesis that may not be familiar to the reader. They are listed below:

Δ	heat
Å	Angstrom(s)
APCI	Atmospheric Pressure Chemical Ionisation
app.	apparent
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
boc anhydride	di-*tert*-butyl dicarbonate
BOC-ON	2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile
br	broad
Bu	butyl
C	celsius
cat.	catalytic
column chromatography	flash column chromatography
d	doublet
DBN	1, 5-Diazabicyclo(4.3.0)non-5-ene
DCAD	di-(4-chlorobenzyl) azodicarboxylate
DCM	dichloromethane
dd	double doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEAD	diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DET	diethyl tartrate
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
dm	decimeter
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide

DMPU	*N*,*N'*-Dimethylpropyleneurea
DMSO	dimethylsulfoxide
dq	double quartet
dt	double triplet
e.g.	exempli gratia
EI	Electron Ionisation
EPSRC	Engineering and Physical Sciences Research Council
eq.	equivalent(s)
ES	electrospray
Et	ethyl
g	gram
h	hour(s)
HMBC	Heteronuclear Multiple Bond Correlation
HMPA	Hexamethylphosphoramide
HRMS	High Resolution Mass Spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	hertz
i.e.	*id est*
IR	infra-red
J	coupling constant
LDA	Lithium diisopropylamide
LHMDS	Lithium *bis*-(trimethylsilyl)amide
lit.	literature
m	meta
m	multiplet
M	molar
*m*CPBA	3-chloroperoxybenzoic acid
Me	methyl
mech	mechanism
MHz	megahertz
mins	minutes
ml	millilitre(s)
mmol	millimole(s)

mol%	mole percent
moldm^{-3}	moles per decimeter cubed
mp	melting point
Ms	methanesulfonyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
NOESY	nuclear Overhauser enhancement spectroscopy
nosyl or ns	*p*-nitrobenzenesulphonyl
o/n	overnight
p	para
PG	Protecting Group
Ph	phenyl
PMB	para-methoxybenzyl
ppm	parts per million
Pr	propyl
q	quartet
rt	room temperature
s	singlet
S_N2	2nd order nucleophilic substitution
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydrogen peroxide
TBS	*tert*-butyldimethylsilyl
td	triple doublet
TEA	triethylamine
tfOH/triflic acid	trifluoromethanesulphonic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	Thin Layer Chromatography
TMAD	tetramethyl azodicarboxamide
TMS	trimethylsilyl
Tosyl	toluenesulfonyl

trig	trigonal
Ts	toluenesulfonyl
UV	ultra-violet
W	watts
w/w	weight for weight

Please refer back to the above list if any terms need clarification throughout the following pages.

Chapter 1

General Introduction

1.1 General introduction

At first glance the three results chapters of this thesis may not be obviously linked. However, there are two themes that do provide continuity between these sections. These are that the origins of these investigations are in the pursuit of heterocycles containing an N-O bond, and that this project as a whole focusses on developing earlier chance observations made by previous members of the Knight Research Group.

Chapter 2 focusses on the synthesis of isoxazoles: 5-membered aromatic rings containing a nitrogen to oxygen bond. The origin of this project was the unexpected observation of a small percentage of isoxazole products in the Group's earlier synthesis of isoxazolines, which were thought to be oxidation products arising from using silver nitrate as a catalyst for those cyclisations.

Chapter 3 centres on the viability of obtaining unusual 6-*endo*-trig products from the iodocyclisation of unsaturated *tert*-butyl carbonates. A previous observation that these 6-membered products had been formed upon cyclisation of a *tert*-butyl carbonate led to the desire to pursue this project. This Chapter is connected to the theme of N-O chemistry, as the *tert*-butyl carbonates were the unexpected products of a synthesis that had been designed to form hydroxylamines.

Chapter 4 concentrates on building saturated N-O rings onto existing cyclic systems, including transannular cyclisations - investigating previous reports of rearrangement of N and O during cyclisation and working towards a synthesis of the core-structure of the natural product Histrionicotoxin. This is hoped to prove the utility of this methodology in building heterocycles and the chiral products that can be gleaned from them.

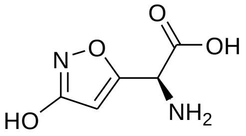
For the most part, this project has been concerned with methodology - solving problems and optimising key-step procedures - which can be applied to complex target molecules.

1.11 Heterocycles

Heterocycles are inherently important in many modern pharmaceuticals. One of the prevalent features of a heterocycle is the presence of at least one lone pair of electrons on an atom (e.g. O, N, S), which provides a basis for electron coordination, hydrogen-bonding, reactivity and resonance. Such electronic properties are crucial to the ability of a heterocycle to exhibit biological activity.

Heterocyclic targets are generally obtained either by late formation of the heteroaromatic ring from a complex acyclic precursor, or by multiple functionalisation of a simple hetereoaromatic cycle, predominantly using electrophilic substitution or metallation strategies.[1]

This project has mainly been concerned with those highly functionalised heterocycles containing both oxygen and nitrogen - the isoxazoles, isoxazolines, isoxazolidines and morpholines. An example of a natural product that has one of these systems as its core structure, Ibotenic acid **1** a secondary metabolite made by a poisonous mushroom, is shown in Figure 1.[2]



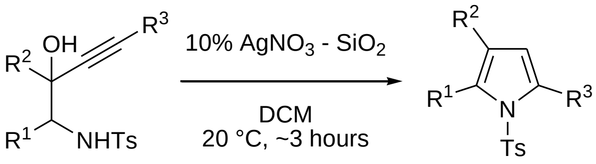
1

Figure 1: Ibotenic acid.

The Knight group has long been involved in the synthesis of such synthetically valuable heterocycles, employing silver-, iodo- and acid-catalysed cyclisations for the key ring-forming steps.

1.12 Silver-catalysed cyclisations

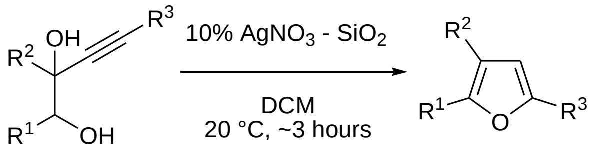
Silver(I) salts had long been known to be capable of activating allenes in cyclisation reactions,[3] and extensive work has more recently been carried out within the Knight group on silver-catalysed heterocycle formation from alkyne precursors. Preceding the isoxazoline and isoxazole chemistry that will be the focus of Chapter 2 (page 18), Sharland showed that pyrroles **3** could be formed in excellent yields from 3-alkyne-2-hydroxy-1-sulphonamides **2** on exposure to 10% silver nitrate supported on silica gel (Scheme 1).[4] This material, more often associated with the chromatographic separation of alkene stereoisomers, was especially effective and could also, in theory, be recycled.[5] In the formation of the pyrrole **3**, shown below in Scheme 1, the second double bond of the aromatic product is introduced by dehydration.



2 **3**

Scheme 1: Siver-catalysed pyrrole formation.

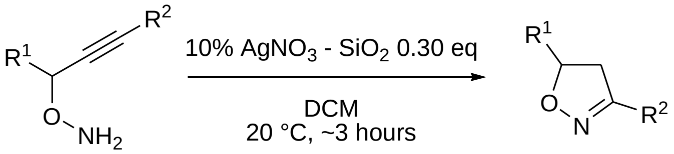
This was also the case in Menzies' synthesis of furans **5** from 3-alkyne-1,2-diols **4** using this methodology, shown in Scheme 2 below.[6]



4 **5**

Scheme 2: Silver-catalysed pyrrole formation.

In the case of Proctor's isoxazoline synthesis, shown below in Scheme 3, there was obviously no hydroxyl group present in the starting materials **6**, so dehydration could not occur and the products **7** were non-aromatic with a single double bond.[7] In the subsequent oxidative cyclisations from the same starting materials **6** to yield the isoxazoles **38** documented in Chapter 2, aromatisation would happen *via* an alternative mechanism.

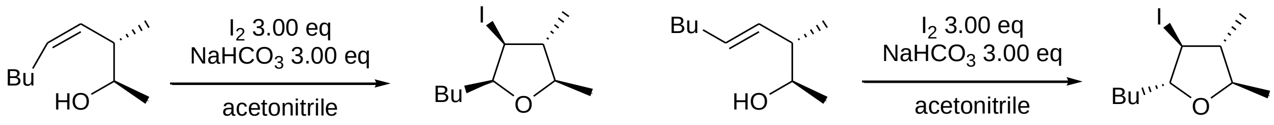


6 **7**

Scheme 3: Silver-catalysed isoxazoline formation.

1.13 Iodo-cyclisations

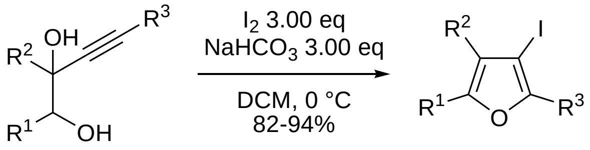
In terms of using molecular iodine within the research group, specifically to facilitate cyclisations to form heterocycles, the first reactions were 5-*endo*-trig cyclisations to synthesise tetrahydrofurans **9** and **11** (Scheme 4). A crucial feature of these reactions was that anhydrous acetonitrile had to be used as the solvent, and they yielded products in a highly stereocontrolled manner depending on the geometry of the starting materials **8** and **10**, as shown in Scheme 4 below.[8]



8 **9** **10** **11**

Scheme 4: Iodocyclisations to form tetrahydrofurans.

In a very similar reaction to that previously described in Scheme 2 that used silver nitrate, 3-alkyne-1,2-diols **4** also successfully undergo iodine-promoted 5-*endo*-dig cyclisations followed by dehydration to give β-iodofurans **12** in good to excellent yields, as shown below in Scheme 5.[9]



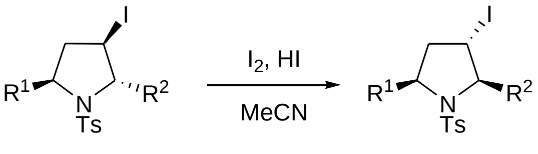
4 **12**

Scheme 5: Iodocylisation to form furans.

The above iodocyclisation could be seen as preferable to the silver-catalysed variation (Scheme 2) if a fourth substituent is required on the furan product **12**. The resulting iodine moiety can undergo regioselective metallation using halogen-metal exchange, or alternatively be displaced using a palladium-catalysed coupling method.[10]

1.14 Acid-catalysed cyclisations

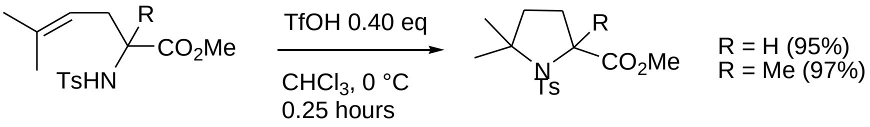
The development in acid-catalysed hydroamination cyclisations in the Knight group was actually a direct result of research into the aforementioned iodocyclisations. It had been suspected that the observed isomerisation of the iodo-pyrrolidines **13** to **14** could occur due to a proton-induced recyclisation under the conditions shown in Scheme 6 below.



13 **14**

Scheme 6: Proton induced isomerisation.

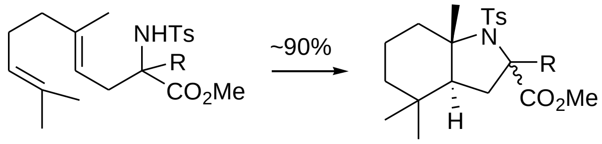
This chemistry led to speculation that it might be possible to trigger such cyclisations using acid. Haskins' demonstrated that triflic acid was an excellent catalyst for inducing overall 5-*endo*-trig cyclisations of homoallylic sulphonamides **15** to give pyrrolidines **16**.[11]



15 **16**

Scheme 7: Acid-catalysed pyrrolidine formation.

In competitive experiments, *N*-tosyl pyrrolidines are formed in preference to the corresponding piperidines, even when the latter would be obtained by trapping a tertiary carbocation. The opposite is true with methoxycarbonyl protected amine analogues, which preferentially form 6-membered products due to less steric interference. Cationic cascades terminated by a sulphonamide group are viable for the efficient formation of polycyclic systems **18**, as shown in Scheme 8 below.[12]



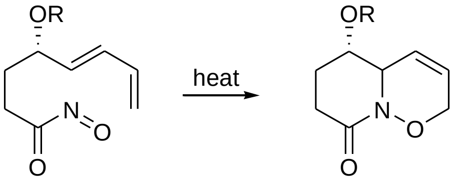
17 **18**

Scheme 8: Acid-catalysed cascade reaction.

1.15 N-O heterocycles

In recent years a large number of alkaloids, as well as other nitrogen containing compounds, have been synthesised using electrocyclic and radical pathways *via* intermediates possessing N-O bonds.[13] A brief review on some of the established reactions that yield such N-O containing cyclic intermediates follows.

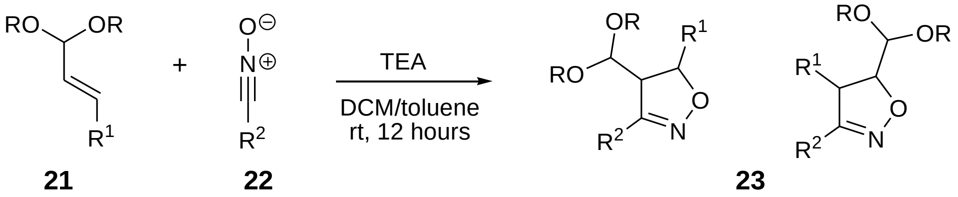
Intramolecular Diels-Alder reactions can be effected simply by pyrolysis of dilute solutions of the reactants **19** in refluxing toluene (Scheme 9).[14] This is a [4+2] cycloaddition of the dieneophilic acyl nitroso compound **19**, and gives a fused bicyclic system **20**, as shown in Scheme 9 below.



19 **20**

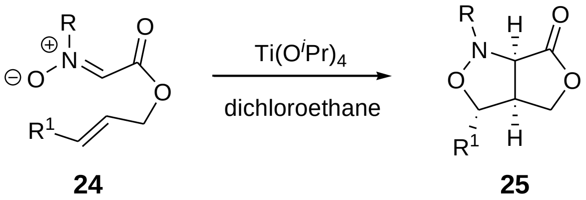
Scheme 9: Intramolecular [4+2] cycloaddition.

An intermolecular reaction can happen between the reactants **21** and **22**, shown below in Scheme 10, with the nitrile oxide **22** enabling a [1.3]-dipolar cycloaddition. In these cycloadditions, with 1,2-unsymmetrically substituted alkenes such as **21** the reaction generally proceeds non-regioselectively to give a mixture of the two possible regioisomers **23**. The example shown in Scheme 10 below however, exploits the discovery that the regiochemical course of the cycloaddition is reversed by modification of the α,β-unsaturated aldehyde precursors to either their acetal or dithioacetal derivatives **21**, allowing a single chosen structural isomer to be produced.[15]



Scheme 10: Intermolecular [1.3]-dipolar cycloaddition.

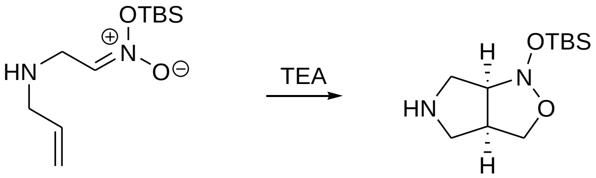
Such [1.3]-dipolar cycloadditions can also occur intramolecularly, between alkenes and nitrone groups. This cycloaddition, which is shown below in Scheme 11, features high regio- and stereo-selectivity which reflect the geometry of the olefinic moiety in the starting materials **24**.[16]



Scheme 11: Intramolecular [1.3]-dipolar cycloaddition.

In the above example (Scheme 11), cycloaddition of the α-allyloxycarbonyl nitrone **24** is attractive as it gives cycloadducts **25** in one step with a high degree of control over the relative stereochemistry.[16]

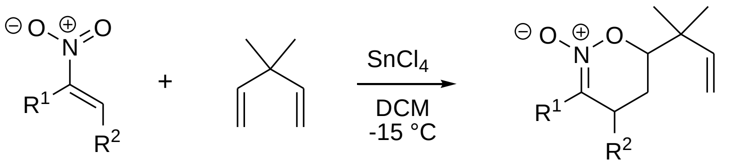
If the Michael addition product of a secondary allylamine to a nitroalkene is captured as an *O*-allylaminoalkyl nitronate, the starting material **26** (Scheme 12) is generated. The subsequent reaction is a stereoselective intramolecular silyl nitronate-olefin [1.3]-dipolar cycloaddition, to provide the highly functionalised pyrrolidine **27**.[17] This cycloaddition of *O*-silyl nitronates **26** is very similar to that shown in the preceding Scheme 11, giving an idea of the breadth of functional groups that can be tolerated in these types of reaction.



26 **27**

Scheme 12: Intramolecular [1.3]-dipolar cycloaddition.

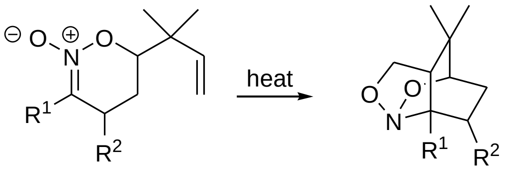
An intermolecular [4+2] cycloaddition of nitroalkenes **28** shown below in Scheme 13, to the dialkene **29**, gives the stable compounds **30**.[18]



28 **29** **30**

Scheme 13: Intermolecular [4+2] cycloaddition.

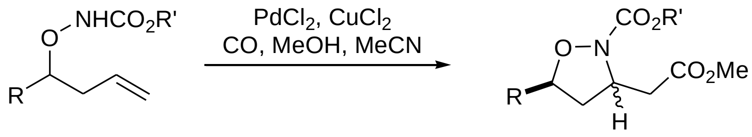
However, when the alkenes **30** are exposed to elevated temperatures, a subsequent transannular [3+2] cycloaddition is effected to give the bridged tricyclic nitroso acetals **31** (Scheme 14).[18]



30 **31**

Scheme 14: Intramolecular [3+2] cycloaddition.

Heterocycles with a direct N-O bond can be used as intermediates for the synthesis of amino alcohols following N-O bond cleavage, giving control over the regio- and stereochemistry of the final product. These heterocycles can be formed from hydroxylamines (as well as the methods given in Schemes 9-14), cyclised under various conditions according to the nature of the unsaturation in the *N*-substituent, an example of which is shown in Scheme 15 below.[19] Hydroxylamines **32** are an example of tethered nitrogen that can induce ring-closure onto an alkene. This leads to the formation of an isoxazolidine **33**, and complements the routes that rely on the preceding cycloaddition chemistry.[20]

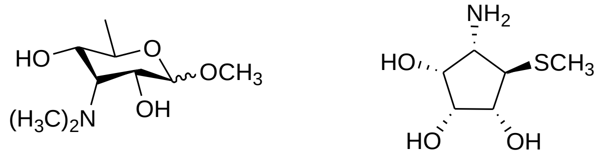


32 **33**

Scheme 15: Cyclisation to form an isoxazolidine.

A variety of nitrogen-containing natural products, including aminosugars and aminocyclitols, have been synthesised by routes that feature the intramolecular delivery of a temporarily tethered nitrogen nucleophile to an electrophilic site. This general tactic for amino group introduction frequently provides entropic advantages, as well as improved site selectivity and stereoselectivity compared to an intermolecular approach.[21] Also the resulting cyclic products can sometimes be more easily manipulated towards the desired final target than the corresponding free amine.

If, as is the case with the hydroxylamine chemistry in this project, the ‘tether’ used in the neighbouring group participation is oxygen, then on breaking the N-O bond after cyclisation, a hydroxyl group is also introduced, as was previously mentioned. Vicinal amino alcohols are a common motif in many natural products, two examples (**34** and **35**) are shown in Figure 2.[21]

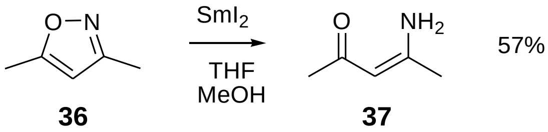


(-)-methyl ravidosaminide **34** (+)-mannostatin **35**

Figure 2: Natural products bearing vicinal amino alcohols.

The N-O bond can be selectively cleaved under mild conditions, including the use of catalytic hydrogenolysis or dissolving metals,[19] to provide nitrogen in its more common oxidation states (*i.e.* as an amine). Reductive cleavage of these N-O containing heterocycles can also be accomplished under a variety of other conditions, including: reduction with mercury amalgams of magnesium,[22] aluminium or sodium,[23] reduction using titanium trichloride[24] or reduction by molybdenum hexacarbonyl.[25]

In 1982 it was reported that the N-O bond within isoxazole **36**, related to those synthesised in Chapter 2, could be cleaved with the reducing agent samarium(II) iodide (SmI_2, also known as "Kagan’s reagent"), in the presence of a proton source such as methanol, to give the β-amino enone **37** as the product (Scheme 16 below).[26]



Scheme 16: Reductive cleavage of the N-O bond.

It has been found that this methodology can be employed for the one-step production of a variety of protected amines *via* directly quenching the reaction mixture with an acylating agent.[13]

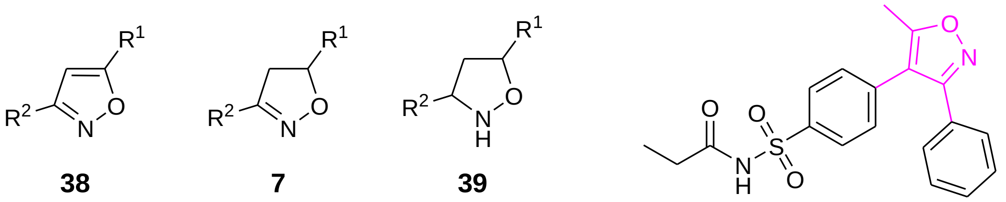
From the previous results shown in this General Introduction, the various methods of cyclisation reported by the Knight group have a great capacity to be further explored as powerful methods for the synthesis of nitrogen and oxygen containing heterocycles. Some of this potential is explored over the following chapters.

Chapter 2

A Silver Nitrate Facilitated Isoxazole Synthesis

2.1 Introduction

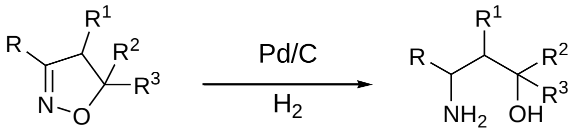
Isoxazoles **38**, and their reduced forms (including isoxazolines **7** and isoxazolidines **39** (Figure 3), are important in heterocyclic chemistry due to their frequent occurrence in compounds displaying high levels of biological activity. For example, isoxazoles have been identified as potent injectable analgesics,[27] such as Parecoxib **40** (Figure 3).



38 **7** **39** **40**

Figure 3: Isoxazoles and isoxazolines.

Furthermore, they are synthetically useful, as cleavage of the weak nitrogen-oxygen bond generates an amino-alcohol **42** with complete regioselectivity, in the case of the reduced forms **41** (Scheme 17).[28]

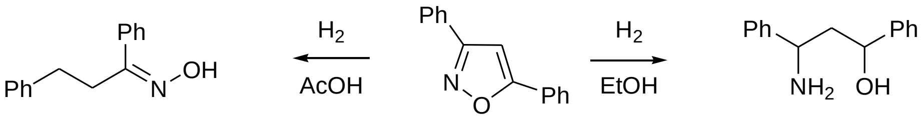


41
isoxazoline

42

Scheme 17: Amino-alcohols from isoxazolines.

Irrespective of the substituents, the N-O bond of the isoxazole ring can also be cleaved under well-controlled conditions, usually hydrogenolysis. Solvent-dependant hydrogenolysis of 3,5-diphenyl isoxazole **44** in the presence of palladium on charcoal resulted in the open chain products **43** or **45** (Scheme 18).[28]



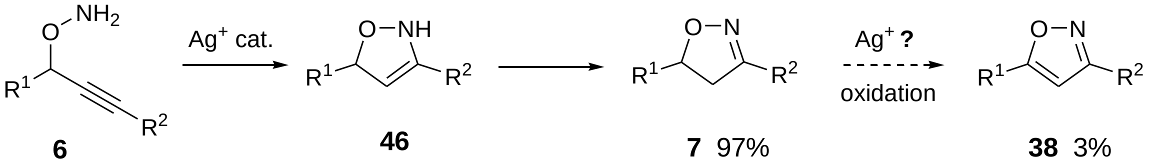
43 **44** **45**

Scheme 18: Solvent dependant hydrogenolysis.

Studies since the 1980s on isoxazole systems have been extensive, due to their versatility in the chemical syntheses of a variety of compounds, as well as their usefulness in several fields such as agriculture (herbicides), medicine (muscle relaxants and bactericides) and industry (batteries).[29]

In one of the Knight group's recent publications it was noted that during their silver nitrate-catalysed cyclisation to synthesise isoxazolines **7** from alkynyl hydroxylamines **6** (*via* the initially formed isomers **46**, Scheme 19), the only detectable impurities were small traces (2-3%)

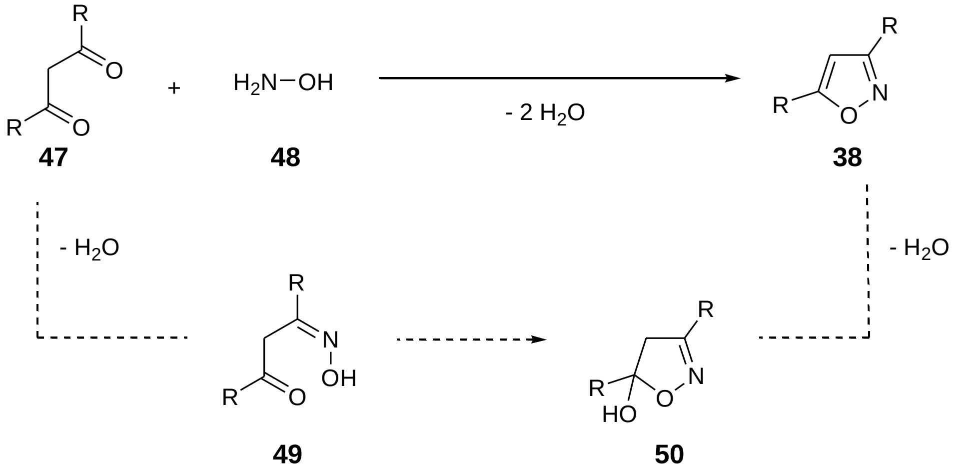
of the corresponding isoxazoles **38**, the amount of which increased if more silver nitrate was used.[30] These small impurities were easily removed by chromatography, so this was an excellent method for the catalytic formation of isoxazolines **7**. It was also a clean and straightforward procedure as the silver nitrate that was used was supported on silica gel.



Scheme 19: Proposed oxidation during isoxazoline formation.

Following on from this successful new isoxazoline **7** synthesis, the focus moved to applying similar methods to producing other significant heterocycles, namely the related isoxazoles **38**. During the silver-catalysed reactions to synthesise isoxazolines **7**, the formation of small amounts of the isoxazoles **38** was an inconvenience (Scheme 19). However, this provided the basis for the idea which was to be pursued in this present project, of developing a new and simple method of oxidising isoxazolines **7** to isoxazoles **38** – by treating them with an excess of silver nitrate, on the assumption that, as suggested in Scheme 19 this is a suitable oxidant.

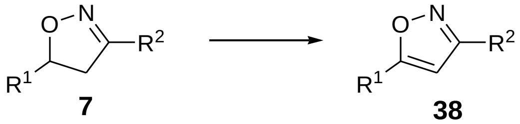
Straightforward methods for converting isoxazolines into isoxazoles are of particular interest and synthetic importance, as isoxazolines are more readily obtainable, whereas isoxazole syntheses are limited and often suffer from problems of regiochemistry.[31] In the Claisen synthesis to produce 3,5-disubstituted isoxazoles **38** from β-diketones **47** and hydroxylamine **48** (Scheme 20), if the former is unsymmetrically substituted it is only possible to control the regioselectivity by observing very strict reaction conditions,[32] unless there are extreme steric differences in the substituents ‘R’.



Scheme 20: Claisen synthesis of isoxazoles.

Other general methods include cycloadditions of alkynic derivatives with nitrile oxides that also yield 3,5-substituted isoxazoles. The analogous reaction of alkenic derivatives to nitrile oxides to give isoxazolines will be explained and utilised later in this Chapter.

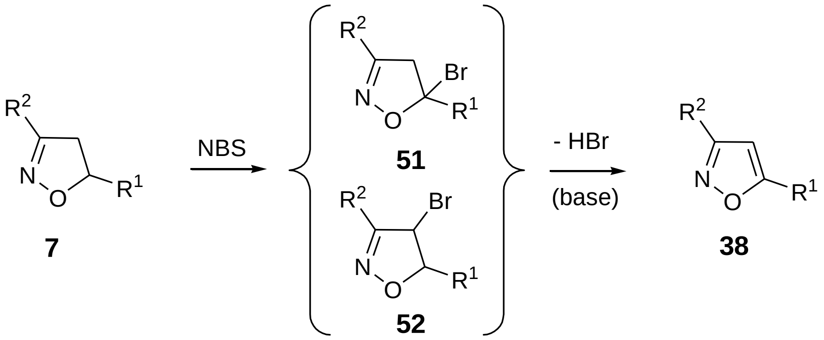
The higher stability of isoxazoles should favour the oxidative conversion of 2-isoxazolines to isoxazoles, which is achieved by either dehydrogenation or by elimination. In the literature, there are several examples of the oxidation of isoxazolines **7** to give isoxazoles **38**, however in most cases R^1 is either phenyl or alkenyl,[33] (Scheme 21), *i.e.* the 5-H is a relatively more reactive benzylic or allylic proton. Therefore, it would be significant to develop a method of oxidation which was successful for examples with more than one saturated alkyl substituent.



7 **38**

Scheme 21: Oxidation of isoxazolines to isoxazoles.

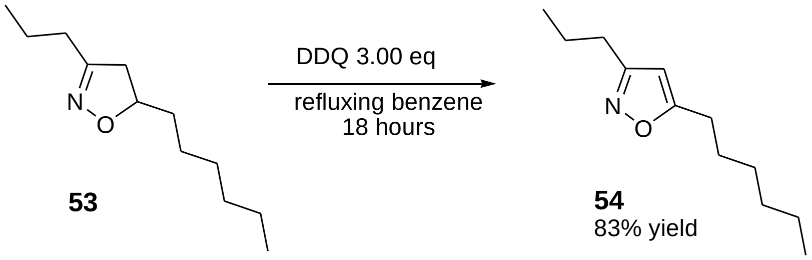
N-Bromosuccinimide can be a suitable reagent for the bromination of 2-isoxazolines **7**, to give a mixture of bromides **51** and **52**, subsequent dehydrobromination of which leads to the isoxazoles **38** (Scheme 22). However, it was observed that such brominations were often incomplete where R^1 was a simple alkyl group.[34]



Scheme 22: Isoxazoline oxidation using NBS.

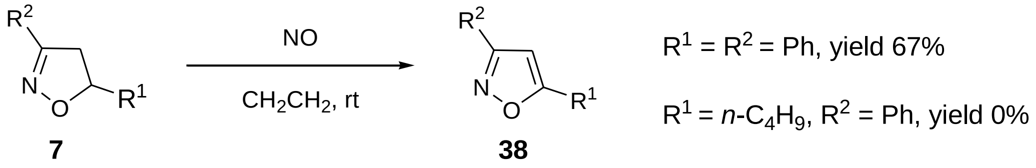
Using γ-manganese dioxide as the oxidant (normal active manganese dioxide caused only partial conversion), high yields of isoxazoles have been obtained from isoxazolines,[35] although there was no example given of an oxidation using this method where both substituents were simple alkyl groups. Furthermore, this method does have some drawbacks, as 28.75 equivalents(!) of γ-manganese dioxide were used to complete the reaction,[36] and the γ-manganese dioxide itself has to first be prepared using a time-consuming procedure.[37]

It has been claimed that a good yield of isoxazole **54** can be obtained from 3,5-dialkyl isoxazoline **53** by oxidation using three equivalents of DDQ,[38] although the reaction had to be strongly heated for 18 hours (Scheme 23), which could cause the decomposition of more sensitive substrates.



Scheme 23: Isoxazoline oxidation using DDQ.

In a recent publication on the oxidative aromatisation of 3,5-disubstituted 2-isoxazolines **7**, it was documented that, perhaps not surprisingly, R^1 exerts a larger influence than R^2 on the yield of product and the reactivity of the substrate (Scheme 24). With an aliphatic substituent at R^1, no aromatised product was obtained with the weak oxidant nitric oxide, which otherwise gave isoxazole products **38** in moderate yields. Although the conditions are conveniently mild, the reaction does take 15 hours to reach completion even when it is successful.[31]



Scheme 24: Isoxazoline oxidation using NO.

The limitations of the aforementioned reagents in oxidising a wide variety of isoxazolines highlight the need for a new universally effective method that utilises mild conditions. This encouraged the present investigation into using silver nitrate for this purpose.

2.2 Results and Discussion

2.21 Initial Trials

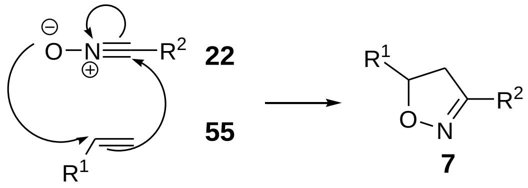
To test the suitability of silver nitrate supported on silica gel as an oxidant rather than a catalyst for cyclisation, firstly a series of isoxazolines **7** with varying substituents needed to be synthesised. It was decided to use an alternative method to the new Knight group isoxazoline synthesis, as in this case an asymmetric synthesis was not required, and forming any oxidised by-products at this stage could confuse the investigation.

This decision was in no way a reflection on the utility of the group's isoxazoline synthesis, which stands out as an extremely efficient and inherently regiospecific alternative to more traditional isoxazoline syntheses. It is a clean and simple intramolecular reaction that can yield optically pure products if the precursor propargylic alcohols are obtained as single enantiomers, which is possible using a number of approaches.[30]

The alternative method that was chosen to begin this project was a [1,3]-dipolar cycloaddition of nitrile *N*-oxides **22** to alkenes **55**, a classical approach to isoxazolines **7**.[39] Such cycloadditions to 1-alkenes proceed with essentially complete regioselectivity in the sense shown (Scheme 25).

Nitrile oxide (from treating the oxime with sodium hypochlorite)

Terminal alkene (dipolarophile)



Scheme 25: [1,3]-dipolar cycloaddition.

The first step of the synthesis was to form an oxime, by the condensation of hydroxylamine with an aldehyde. Both aryl (benzyl **56**) and alkyl (isobutyl **57**) oximes were synthesised and used in such cycloadditions (Scheme 25) to styrene **291** and 1-hexene **290** to give a total of four different isoxazolines **58-61**. The yields using this method were moderate to good for these reactions, and are shown in Table 1 below. A representative method is given in the Experimental section for both oxime formation and the cycloaddition reaction which were carried out as described in the literature.[39, 40]

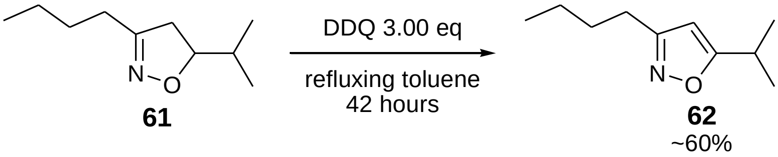
Product	Name / Substituents		% Yield
56	Benzaldoxime		68
57	Isobutylaldoxime		72
	R^1	R^2	
58	Phenyl	Phenyl	43
59	Phenyl	Isopropyl	46
60	*n*-Butyl	Phenyl	77
61	*n*-Butyl	Isopropyl	68

Table 1: Oximes and isoxazolines.

The isoxazolines **58-61** were synthesised with this variety of alkyl and aryl substituents as it was hoped that silver nitrate could then be showcased as a convenient oxidant regardless of substituents, which would set it apart from the other oxidants described in the introduction.

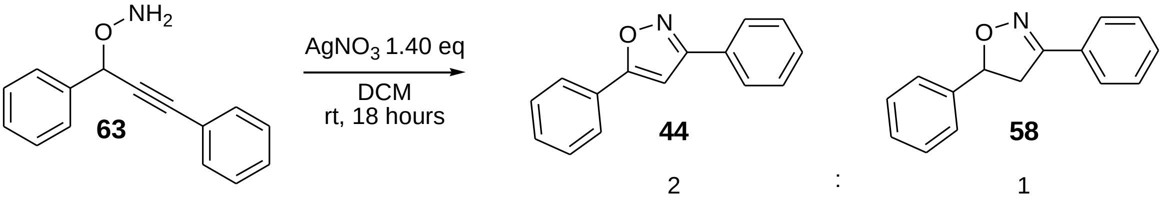
The isoxazolines **58-61** could then undergo trial oxidations utilising silver nitrate supported on silica gel, using similar procedures to those described in General Method **D** (in dichloromethane, page 111). Numerous experiments were carried out on precursors **58-61**, varying the number of mole equivalents of silver nitrate (1-2.5 mole equivalents), reaction temperature (20-70 °C, at the increased temperatures a higher boiling solvent was used), and duration (3-24 hours), but surprisingly no reaction at all was seen, even with the diphenyl isoxazoline **58**, which had previously been oxidised using very mild oxidation conditions (Scheme 24: Isoxazoline oxidation using NO. page 21).[31] In all cases although the supported silver had changed in colour to black, indicating the reduction of the silver, no product of oxidation could be seen in the ^{1}H NMR spectra of the crude reaction mixtures.

For comparison, samples were also treated with DDQ, a known oxidant of this type of compound.[38] Repeating the literature procedure (as was shown in Scheme 23 only with toluene substituted for benzene, page 21), in the case of isoxazolines that had a phenyl substituent α- to the oxygen (**58** and **59**), this oxidation was successful. However, no isoxazole products were seen from the initial trials on isoxazolines that had a simple alkyl substituent α- to the oxygen (**60** and **61**). As this contradicted the literature findings, a repeat reaction was carried out on the dialkyl isoxazoline **61** (Scheme 26) with the reaction mixture being allowed to reflux for a longer duration at the increased temperature. In this case the oxidation was partially successful: ^{1}H NMR analysis of the crude product showed that the ratio of product **62** to the starting material **61** was approximately 3:2, after a 42 hour reflux. The relevant peak integrations in the spectra of the crude product mixture that were compared to deduce this ratio, were the aromatic proton of the isoxazole **62** at 5.84 ppm (s), and one of the diastereotopic CH_2 protons of the isoxazoline ring at 2.54 ppm (dd, *J* 16.7 and 8.2 Hz). Purification was not carried out for full analysis of the isoxazoles, as the integrations within the NMR spectra of the crude products were sufficient to determine the level of oxidation that had occurred.



Scheme 26: Oxidation with DDQ.

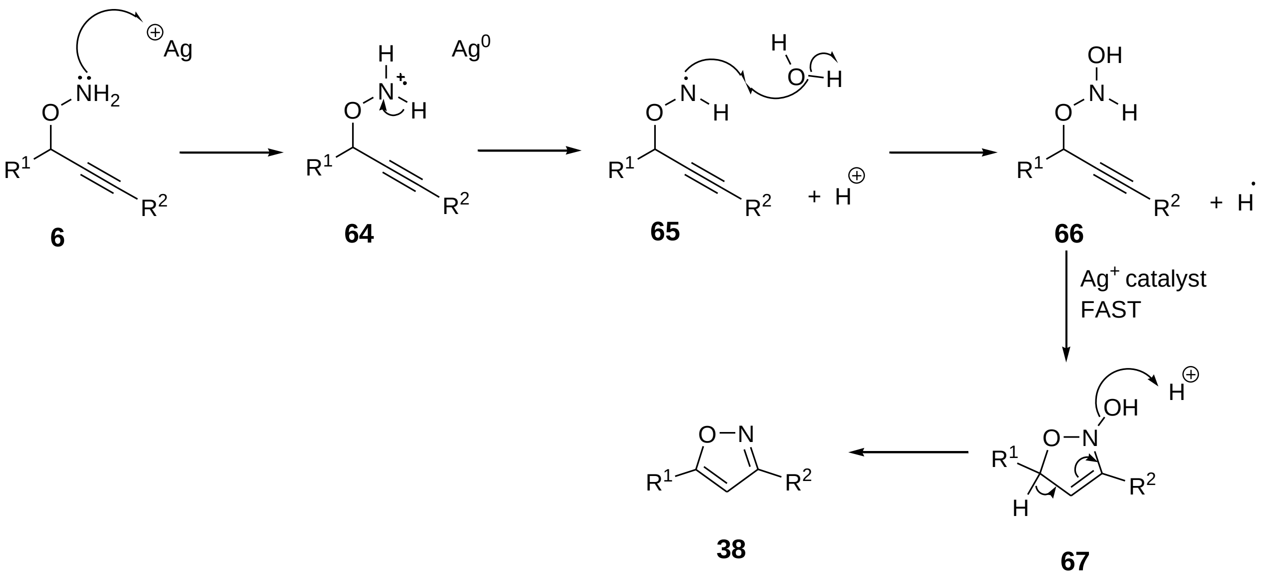
To confirm the observation by former group member Anthony Proctor that some isoxazole product had indeed been formed during his silver nitrate-catalysed cyclisations (see Scheme 19, page 19), his reaction scheme to synthesise the diphenyl substituted isoxazoline **58** was repeated.[7] The only modification to his procedure was to the final cyclisation step, where the free hydroxylamine **63** was treated with an excess of silver nitrate (see General Method **D**, page 111) instead of a catalytic amount, in the hope that this would cause a complete conversion to the isoxazole **44** (Scheme 27).



Scheme 27: Cyclisation with excess silver nitrate.

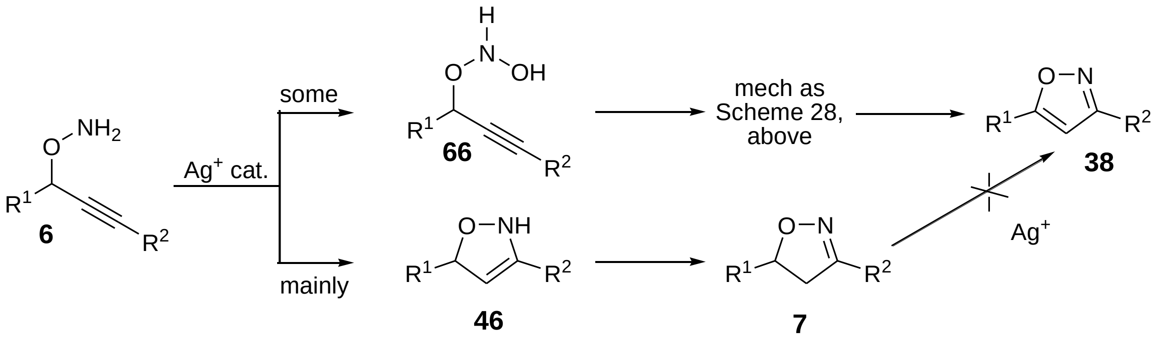
Using 1.4 equivalents of silver nitrate (10% by weight) on silica gel gave a ratio of 2:1 of isoxazole **44** : isoxazoline **58**. Though it was hoped that in using an excess of silver nitrate, complete conversion to the isoxazole would occur, the fact that it was the major product indicated that this was still a viable method to pursue for forming the oxidised product.

Furthermore, as it had been proven that silver nitrate did not oxidise pre-made isoxazolines (by all of the trials carried out on isoxazolines **58**-**61**), then the result of the cyclisation reaction shown in Scheme 27 indicated that oxidation actually happened **before** or during cyclisation. A proposed mechanism is shown below in Scheme 28, and shows how it could be oxidation of the nitrogen before cyclisation **66**, and then the loss of water **67**, that forms the second double bond of the isoxazole **38**.



Scheme 28: Proposed mechanism of oxidative cyclisation.

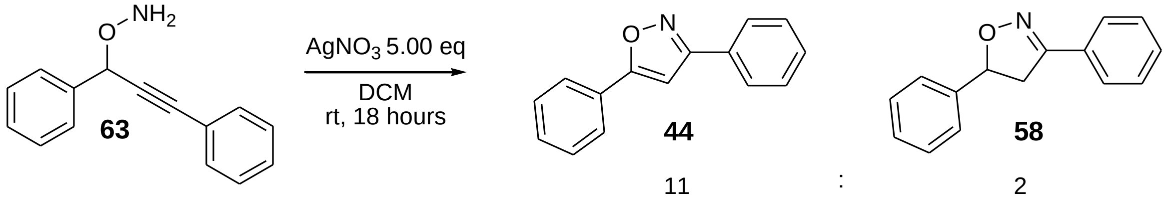
It was thought that this must be a fast process to allow it to happen before the expected silver-catalysed cyclisation to form the isoxazoline **7**, where the silver would activate the alkyne of the hydroxylamine **6** (Scheme 29). If only a catalytic amount of silver is present, the major product is the isoxazoline **7** and the minor product is the isoxazole **38**.



Scheme 29: Alternative cyclisation paths.

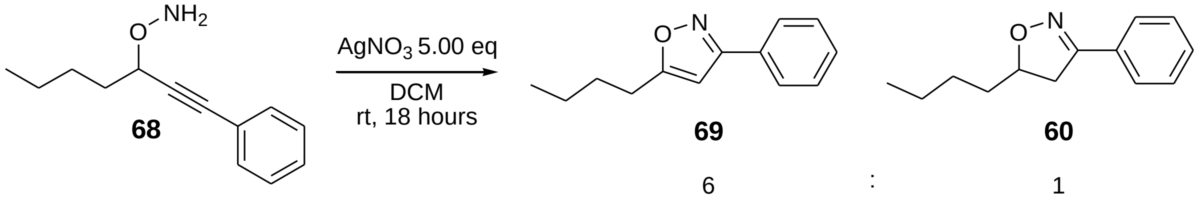
To improve this reaction by increasing the proportion of isoxazole that was formed, and to provide further evidence that this method was indeed useful for forming isoxazoles with simple alkyl substituents, further trials were carried out.

Firstly, again trying to form the oxidised product of the diphenyl substituted isoxazoline **58** (Scheme 30), five equivalents of silver nitrate were used, and the ratio of isoxazole **44** : isoxazoline **58** that was observed had increased to 11:2. The increase in mole equivalents of silver nitrate had greatly improved upon the yield of the desired product **44**.



Scheme 30: Cyclisation with 5 equivalents of silver nitrate.

The real test however, would be to form the oxidised product (an isoxazole), under these new conditions, of an isoxazoline **60** (see Scheme 31) that did not have a phenyl substituent α- to the oxygen, and which is therefore harder to oxidise with DDQ. For this cyclisation reaction, five equivalents of silver nitrate were again added at room temperature. It was pleasing to find that the desired isoxazole **69** accounted for 85% of the crude yield (Scheme 31). The isolated yield of the product mixture was lower than anticipated however, at 48%, which will be addressed later.



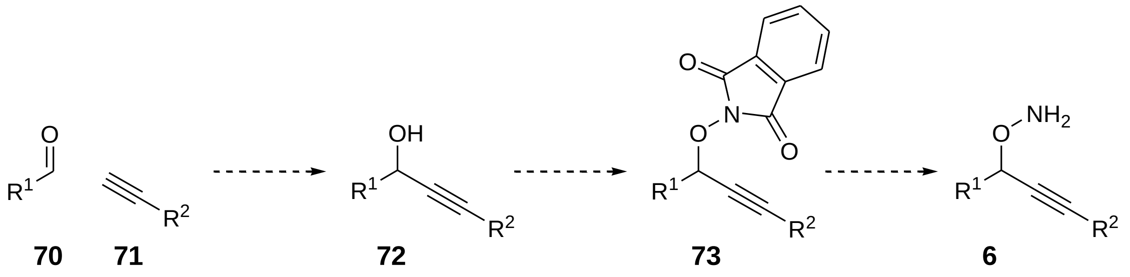
Scheme 31: Cyclisation with five equivalents of silver nitrate.

The initial aim of this preliminary investigation was to find successful conditions for oxidising ready-made isoxazolines using a simple and mild silver nitrate on silica reaction (which is not possible, as was illustrated in Scheme 29). The fact was, that instead it was found that the oxidation seemed to happen **before** cyclisation occurred, when the hydroxylamine intermediates were exposed to an excess of silver nitrate. The efficacy of this process was not affected by the substituent α- to the oxygen, which has led towards the development of conditions for a new all-in-one synthesis of isoxazoles with simple alkyl substituents, which is of synthetic significance due to the difficulty in oxidising the corresponding isoxazolines.

Further optimisation of the method was, however, required. The proportion of the desired isoxazoles, **44** and **69**, to the corresponding isozazolines, **58** and **60** (Scheme 30 and Scheme 31), had been good in the initial trials, however, as was previously mentioned the crude yields were relatively low, equalling 44 and 48% respectively. This was thought to be due to either partial decomposition (as the reactions had been allowed to run overnight), or just that the washing of the reaction mixture through celite on work-up had not been thorough enough. The full syntheses to remake the isoxazoles **44** and **69** were therefore repeated, along with schemes to form isoxazoles with other alkyl and aryl substituents to show the versatility and value of this method, and improve on the efficiency and cleanliness of the reactions at every stage of the syntheses.

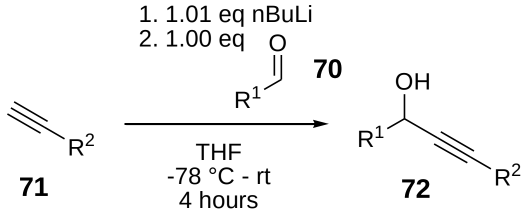
2.22 Experimental Optimisation

The synthetic sequence towards the hydroxylamine precursors **6** to this series of cyclisations is shown below in Scheme 32.



Scheme 32: Proposed synthetic sequence.

The required propargylic alcohols **72** were synthesised by the addition of a range of lithiated alkynes **71** to a selection of suitable aldehydes **70** (Scheme 33, General Method **A**, page 110).



Scheme 33: Synthesis of propargylic alcohols.

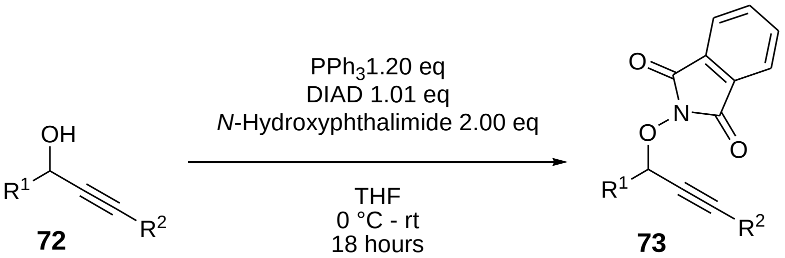
The propargylic alcohols that were synthesised are shown in Table 2 below, and in all cases there was no need for further purification.

Product	R^1	R^2	% Yield
74	Phenyl	*n*-Butyl	98
75	Phenyl	Phenyl	98
76	Isobutyl	Butyl	83
77	Butyl	Phenyl	89
78	Citronellyl	Phenyl	100

Table 2: Propargylic alcohols

The next stage of the scheme was to introduce the O-N functionality into the compounds. The method that was chosen for this purpose was the Mitsunobu reaction as this had previously been optimised within the group for exactly this type of reaction.[41] The substitution of primary or secondary alcohols with nucleophiles mediated by a redox combination of a trialkyl or triarylphosphine and a dialkyl azodicarboxylate is popularly known as the Mitsunobu reaction.[42]

The readily available reagent *N*-hydroxyphthalimide has been used as a nucleophile to couple intermolecularly with different alcohols for some time.[43] The Mitsunobu reaction was carried out on the propargylic alcohols **72** to yield the phthalimide-protected hydroxylamines **73** (Scheme 34, General Method **B**, page 110).



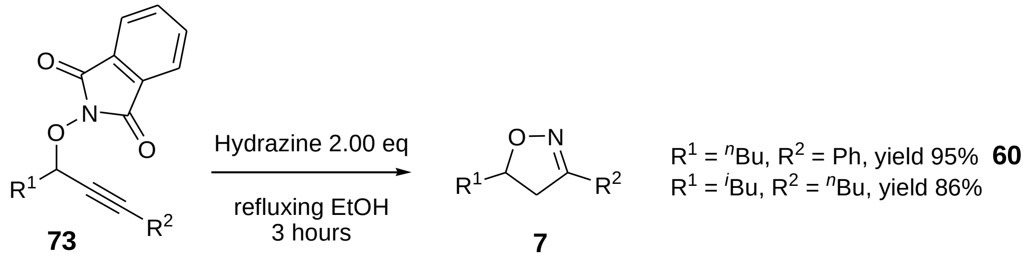
Scheme 34: Mitsunobu reaction.

The phthalimide-protected hydroxylamines **73** that were synthesised are shown in Table 3 below. It can be seen that the reaction was successful, and good to excellent yields of the key hydroxylamine intermediates were achieved. The yields given are those obtained after purification, which was carried out by silica gel chromatography in the case of those compounds which have a phenyl group α- to the oxygen, and quickly and conveniently by a silica plug filtration for the other products.

Product	R^1	R^2	% Yield
79	Phenyl	n-Butyl	54
80	Phenyl	Phenyl	64
81	Isobutyl	Butyl	83
82	Butyl	Phenyl	74
83	Isobutyl	Phenyl	91
84	Citronellyl	Phenyl	69

Table 3: Phthalimide-protected hydroxylamines

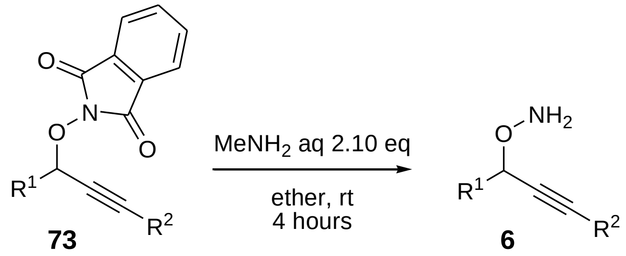
The final intermediates to be synthesised were the free hydroxylamines, which were gained by deprotecting the phthalimide products **79-84**. Although in previous trials aqueous methylamine had been used as the reagent, it was decided to examine hydrazine as an alternative, due to the inconvenience of semi-soluble organic by-products which were inherent in the former reaction. The standard conditions of treating the starting materials **73** with two equivalents of hydrazine in refluxing ethanol (the Inge-Manske procedure),[44] was used and in an interesting aside, the cyclised isoxazoline products **7** were in fact formed (Scheme 35).



Scheme 35: Hydrazine mediated deprotection and cyclisation.

When this reaction was repeated at room temperature in diethyl ether, the desired free hydroxylamine product **6** was formed and only a trace of the cyclised isoxazoline **7** was observed. Initial trials have indicated that subsequently warming a sample of this crude product mixture, consisting mainly of hydroxylamine **6** (as Scheme 36), with 5 mol% of hydrazine does not cause any further cyclisation. The preparation of 2-isoxazolines **7** from *O*-propargylic hydroxylamines *via* a tandem rearrangement-cyclisation reaction utilising potassium carbonate as the basic catalyst was published in 2006.[45] Further investigations could be undertaken to determine if this proposed one-pot deprotection and base-catalysed cyclisation (Scheme 35) is a viable complementary method of forming isoxazolines to silver cyclisation. A representative procedure to form 5-butyl-3-phenylisoxazoline **60** using hydrazine in refluxing ethanol is given in the Experimental chapter (page 120). However, as this would be beyond the remit of the current project, it was decided to revert to carrying out the deprotection reaction with aqueous methylamine and devising a more convenient solution for removing the phthalimide residue impurities.

The final deprotections were carried out by treating the phthalimide-protected hydroxylamines **73** with 2.10 equivalents of 40% w/w methylamine in water, and on work-up, the astute addition of ice-cold petroleum ether ensured that all by-products were crystalline and could be effectively removed by filtration leaving the pure hydroxylamines **6** (Scheme 36, General Method **C**, page 111).



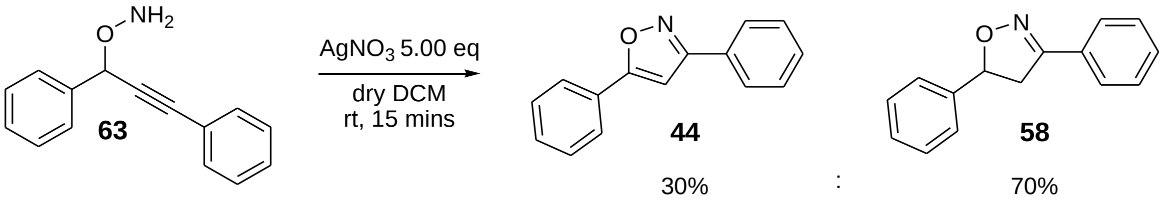
Scheme 36: Dephthaloylation reaction.

The hydroxylamines that were synthesised are shown in Table 4, and in all cases there was no need for any further purification. Only the diphenyl hydroxylamine **63** had been subjected to any form of characterisation before,[46] as these products are reported to be unstable; however proton NMR spectroscopy was successfully carried out on the compounds shown in Table 4 to confirm purity, before these intermediates were immediately taken on to the key cyclisation step.

Product	R^1	R^2	% Yield
85	Phenyl	*n*-Butyl	93
63	Phenyl	Phenyl	91
86	Isobutyl	Butyl	82
68	Butyl	Phenyl	74
87	Isobutyl	Phenyl	89
88	Citronellyl	Phenyl	90

Table 4: Free hydroxylamines.

Optimisation of the final cyclisation step began with trials to discover if five equivalents of silver nitrate (as had been used in the initial trails, Scheme 30 and Scheme 31, page 26) were actually necessary to achieve a good yield of isoxazole product. Trial cyclisations using diphenyl hydroxylamine **63** were carried out with 1.50, 3.00 and 5.00 equivalents, and progress of the reactions was monitored by TLC. After 15 minutes of reaction time had passed there was no starting material visible in the reaction mixture spots. Consequently the reactions were halted by filtering out the supported reagent, as it was assumed that as isoxazolines could not be oxidised to isoxazoles using silver nitrate, then if there was no un-cyclised starting material left, then no further isoxazole product was subsequently going to be formed. In studying the NMR spectra of the crude products from each of the trials, it was found that the cyclisations had gone to completion, but in the case of the reactions using 1.50 and 3.00 equivalents of silver nitrate there was only a trace of the oxidised product visible, and even with five equivalents the yield of isoxazole **44** was only 30% (Scheme 37), with the isoxazoline **58** accounting for the remainder of the product mixture.

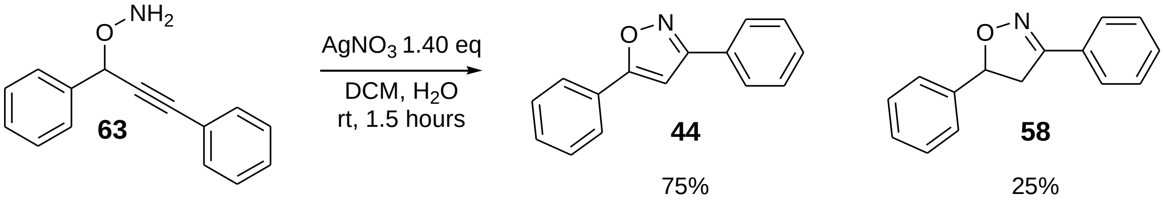


Scheme 37: Cyclisation with five equivalents of silver nitrate.

This was an unanticipated result; as previously the cyclisation of hydroxylamine **63** had yielded 85% isoxazole after an 18 hour reaction period and using five equivalents of silver nitrate (Scheme 30). As it was thought that oxidation occurred before or during cyclisation, a shorter reaction time should not have affected the ratio of products, as long as all of the starting material had been consumed.

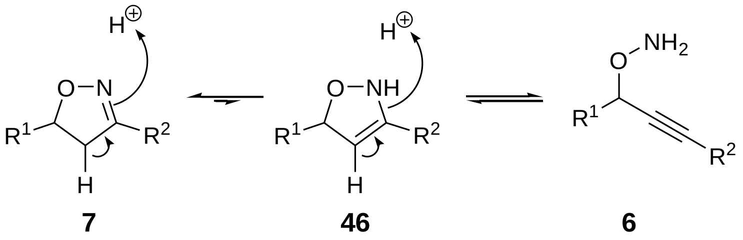
It was considered that this difference in the proportion of isoxazole product may have been because in previous trials there had been some water present due to not using thoroughly dried hydroxylamine starting material, or there having been some water adsorbed onto the silica that the silver nitrate was supported on.

There is water involved in the proposed oxidation mechanism that was outlined in Scheme 28 (page 25). To investigate this possibility, two test cyclisations were carried out, again on hydroxylamine **63** and using 1.40 equivalents of silver nitrate and stirring for 1.5 hours, one with water present and one without. There was only a small difference in the results between them; having water present seemed to increase the proportion of isoxazole **44** from 70 to 75% (Scheme 38) of the crude product mixture.



Scheme 38: Silver-cyclisation in the presence of water.

Although the addition of water had only made a very small improvement, the fact that it did not hinder the reaction meant that from then on the trials could be carried out using bench (non-anhydrous) dichloromethane, and indeed exposed to air, which was very convenient. As had been the case with the reaction shown in Scheme 37, after only 15 minutes into the reaction shown above in Scheme 38, there was no starting material remaining by TLC. A further sample was then taken after 1.5 hours for analysis by proton NMR spectroscopy. At this stage the crude product mixture was 75% isoxazole **44**, and there was no further change after leaving the reaction mixture stirring overnight. This result showed that by some means leaving the reaction mixture stirring for longer than it takes for the initial cyclisations to occur (15 minutes) does actually allow for the formation of further isoxazole by an unknown mechanism, if there is an excess of silver nitrate present. This could possibly be due to a degree of reverse cyclisation of the isoxazoline **7** occurring over time, as shown in Scheme 39 below, although no evidence of this was seen when treating isolated isoxazolines.



Scheme 39: Proposed reverse cyclisation mechanism.

The hydroxylamine **6** could then re-cyclise oxidatively to give the isoxazole product. Alternatively, rather than the oxidation mechanism that was proposed in Scheme 28 where oxidation occurred before cyclisation, it could be the case that the initially formed isoxazoline isomer **89** loses an electron to a silver cation and oxidation occurs at this stage. The proposed mechanism would then be similar to that outlined in Scheme 28, only from the intermediate **89** shown in Figure 4 below. This alternative explanation may well account for why oxidation does not occur with the isomeric pre-made isoxazolines, and why oxidation occurred after the starting material had been converted.

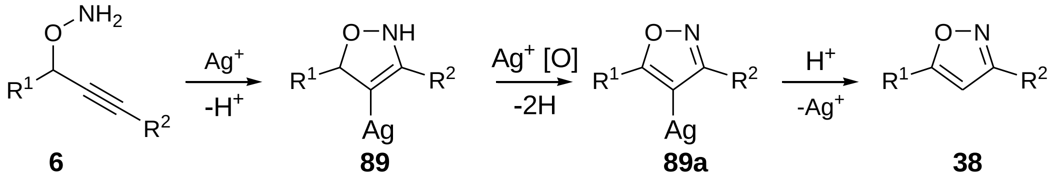
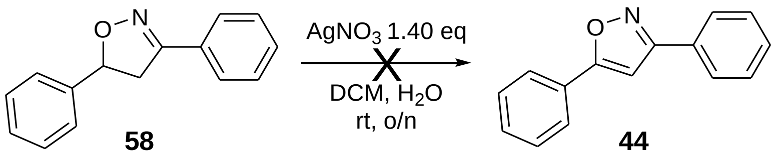


Figure 4: Oxidation intermediates.

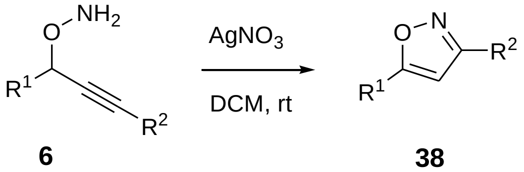
To ascertain if, with the intentional addition of water, it would be possible to oxidise a ready-made isoxazoline **58** with silver nitrate to the isoxazole **44**, the reaction shown in Scheme 40 was carried out, but still no oxidation was seen, confirming all earlier results.



Scheme 40: No oxidation.

There was one final challenge, in that when it was necessary to begin using a new bottle of commercial silver nitrate on silica (“10% by weight”), it was found that the concentration of silver between bottles was actually very inconsistent. With Sample 1 (from the batch of reagent that was used to effect the transformations in the initial trials) just 1.40 eq had yielded 75% of the diphenyl isoxazole product **44** (Scheme 38), however under otherwise identical conditions, treating precursor **63** with 3.00 equivalents of the following different batches of reagent gave: Sample 2, 59%; Sample 3, 33%; and Sample 4, 70%, of the desired isoxazole products **44** respectively (with the balance of the yield being the corresponding isoxazoline **58**). Small samples were sent off for testing for average silver content by Atomic Absorption spectroscopy, and the results confirmed the suspected irregularities - sample 2, 6.5%; sample 3, 5.5%; and sample 4, 10.6%. Furthermore, it was also noted that each individual bottle of supported reagent was not homogeneous in silver nitrate concentration throughout its contents.

Sample bottle 4 was used for the final reactions that were carried out using the optimised conditions of stirring the free hydroxylamines **6** for 4 hours at room temperature in dichloromethane with an assumed 4.00 equivalents of silver nitrate to yield the desired isoxazoles **38** (Scheme 41, General Method **D**, page 111).



6 **38**

Scheme 41: Optimised cyclisation.

The yields of the isoxazoles **38**, calculated by analysis of the NMR spectra of the crude products are given in Table 5 below, and column chromatography was carried out to glean samples for full analysis.

Product	R^1	R^2	% Yield
90	Phenyl	*n*-Butyl	64
44	Phenyl	Phenyl	74
91	Isobutyl	Butyl	74
69	Butyl	Phenyl	89
92	Isobutyl	Phenyl	90
93	Citronellyl	Phenyl	83

Table 5: Isoxazoles.

As stated beforehand, though the initial aim of this investigation was to find successful conditions for oxidising ready-made isoxazolines with silver nitrate, the fact that instead it was found that the oxidation actually happened during the cyclisation step and that this was not affected by the substituent α- to the oxygen, has led to the optimisation of conditions for a new all-in-one, quick and clean synthesis of isoxazoles with simple alkyl substituents. This is of synthetic significance due to the difficulty in oxidising the corresponding isoxazolines.

The isoxazole products shown in Table 5 were obtained in very good yields with the modified work-up that used ethyl acetate to wash the product from the silica on which the silver nitrate reagent was supported. It was also discovered that these reactions could be carried out successfully and conveniently open to the air (although still sheltered from light) and in non-anhydrous dichloromethane, in just 4 hours (the more silver nitrate is used, the faster the reaction).

It can also be seen from studying Table 5 that higher yields are gained when there is an alkyl substituent at R^1, making this complementary to the isoxazole syntheses outlined in the introduction to this chapter.

Chapter 3

A surprising propensity of *tert*-butyl carbonates to undergo 6-*endo*-trig iodocyclisations

3.1 Introduction

Although at first glance this chapter does not appear to link to the N-O chemistry described in the previous section, the route that led to this work did begin with hydroxylamine syntheses, specifically attempting to form them using a particular example of oxaziridine chemistry. The Knight group had wanted to investigate an alternative and more efficient method to the well-established Mitsunobu reaction for forming *O*-allylic hydroxylamines. Alkoxylamines are very important precursors in organic chemistry. However, there is only a narrow range of methods that have been developed to prepare these compounds.[47] Generally, these methods rely upon a specific two-step sequence consisting of nucleophilic *O*-alkylation of an *N*-protected hydroxylamine nucleophile upon an electrophilic carbon, followed by deprotection to provide the alkoxylamine product. An example of this is the Mitsunobu reaction featuring *N*-hydroxyphthalimide as extensively utilised in Chapter 2 (page 28). However, it had also been found within the group that in unsymmetrical allylic systems **94** there could be issues with unwanted S_N2' reactions (red arrows) competing with the desired S_N2 path (black arrows), as shown below in Figure 5.

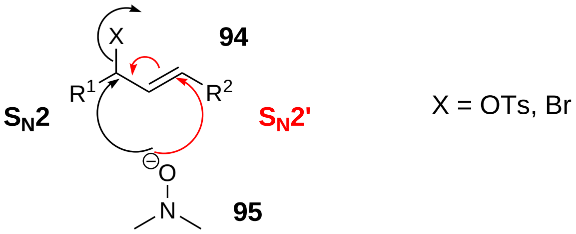
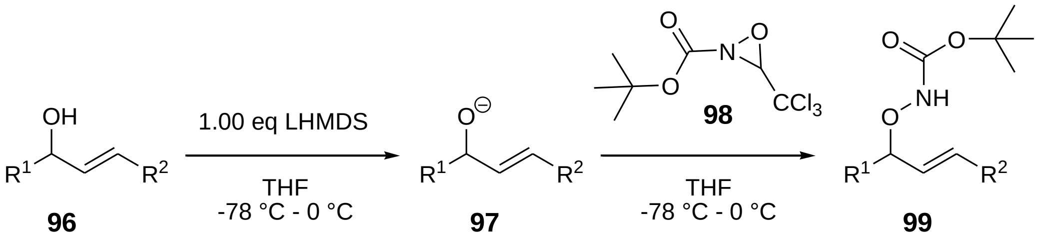


Figure 5: S_N2' *vs* S_N2

The competing reactions illustrated above led to synthetically useless mixtures of products in approximately a 1:1 ratio.

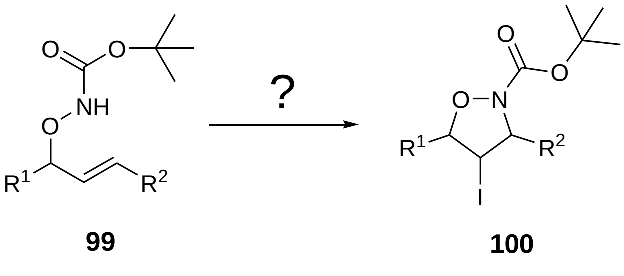
An obvious alternative to the sometimes problematic installation of a pre-formed nitrogen-oxygen bond (as in the Mitsunobu reaction) was to investigate the amination of an alcohol or alkoxide.[7] The direct electrophilic amination of alcohols should provide a more powerful and efficient approach. This would also provide the opportunity to retain the stereochemistry at the hydroxyl stereocentre, as opposed to the inversion that accompanies the S_N2 Mitsunobu reaction. This methodology of direct amination will be further discussed and applied in Chapter 4 (page 85). Previously in the literature, such transformations had been achieved using chloramine, but only with a large excess of the alkoxide and in poor yields.[48] Chloramine also has poor stability and can cause the formation of chlorine containing by-products.[49] Since then, other reagents have enjoyed a degree of success in performing this transformation, but none are without drawbacks. A method using hydroxylamine-*O*-sulphonic acid was reported in 1982 that involves handling fuming sulphuric acid, and has to be carried out in aqueous media due to insolubility of the reagent in organic solvents.[50] Another amination reagent, *O*-(mesityl sulphonyl)hydroxylamine, was found to be very unstable and explosive in its pure form.[51]

In 1999, a report was published that outlined the reaction of the easily accessible, safe and stable reactant 3,3’-di-*tert*-butyloxaziridine with a range of potassium alkoxides in DMPU and in the presence of 18-crown-6 to provide free *O*-alkylhydroxylamines in 10-86% yields.[47] This synthetically valuable procedure provided the inspiration to the Knight group for similar aminations, instead using the highly electron deficient oxaziridine **98**, to give a novel range of BOC-protected hydroxylamines **99** as shown in Scheme 42 below.[52] Reagent **98** was known to be a good source of electrophilic amine and so was thought to be set up well to react with the nucleophilic oxygen species **97**.



Scheme 42: Published alcohol amination.

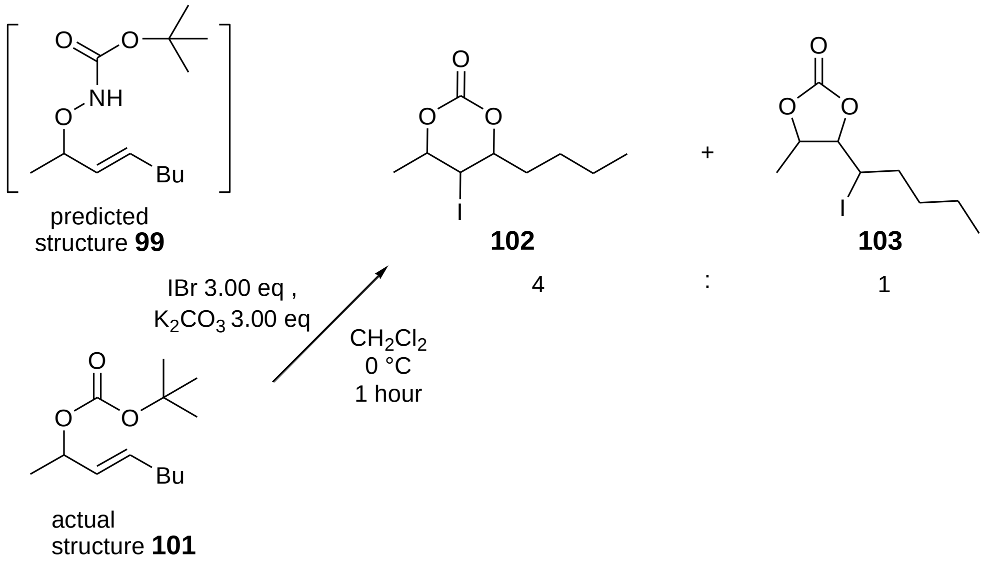
It was hoped that these protected hydroxylamines **99** could then be cyclised to form isoxazolidines **100**, to complement the innovative isoxazoline and isoxazole syntheses that had already been optimised within the group (Chapter 2 – pages 19-34). However, there were difficulties with the subsequent cyclisation (desired product **100** shown below in Scheme 43), and deprotection trials on the BOC-protected *O*-alkylhydroxylamines **99** that had been prepared using this new amination procedure. Therefore it was decided within the group to repeat the above reaction scheme (Scheme 42), to confirm the structure **99** and then resolve these concerns.



Scheme 43: Expected cyclisation products of the proposed structures.

Commercially available 1-octen-3-ol was used as the starting material for these retrials, carried out by previous group member Anthony Proctor.[7] As with the published results,[52] the hydroxylamine formation was thought to have been successful due to the disappearance of all starting material resonances and the incorporation of a *tert*-butyl peak in the ^{1}H NMR spectra of the product. However, as had been previously found within the group, the BOC moiety could not then be removed in any way to give the desired free hydroxylamine, yielding only decomposition products.[53]

It was decided to try to form the iodocyclisation product of the protected hydroxylamine, leaving the existing BOC-protection group *in situ* instead of replacing it with the initially chosen tosyl-protection group. In initial trials, standard iodocyclisation conditions using molecular iodine did not yield any product. It had been known to the group for some time that iodine monobromide could more readily facilitate iodocyclisations, as it possesses an increased level of reactivity compared to molecular iodine.[54] Using three molar equivalents of this reagent, complete iodocyclisation did occur to give a mixture of two products. However, after prolonged elemental and spectroscopic analysis it was discovered that no nitrogen was incorporated into the products and they were, in fact, cyclic carbonates **102** and **103** in the ratio given in Scheme 44 below.[7]

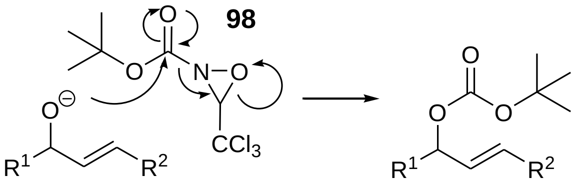


Scheme 44: Products of iodocyclisation.

As it could not be seen how these carbonates **102** and **103** could have been formed from the predicted structure **99** (Scheme 44), this strongly indicated that the initial oxaziridine reaction had not actually worked as planned, and had instead formed a *tert*-butyl carbonate **101** (had in fact simply BOC-protected the alcohol). To prove this by comparison, the suspected carbonate intermediate **101** ("actual structure" in Scheme 44 above) was synthesised from the initial starting material, 1-octen-3-ol, using a more standard transformation. There are a few different reagents available for *tert*-butyl carbonate formation: di-*tert*-butyl carbonate, di-*tert*-butyl dicarbonate and 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON). The latter was chosen in this instance as it had been reported that it gave high yields of product from similar secondary alcohol starting materials.[55] The resultant *tert*-butyl carbonate product was indeed found to be identical on full analysis to the original product of the oxaziridine reaction, proving the actual structure **101** was as shown above in Scheme 44.

On revisiting the experimental findings of the paper that had outlined the method of BOC-protected hydroxylamine formation using *tert*-butyl 3-(trichloromethyl)-1,2-oxaziridine-2-carboxylate **98** (Scheme 42),[52] it could be seen in the light of these more recent findings that the quoted product structures **99** were incorrect and had all in reality been the BOC-protected alcohols **104**.

A proposed mechanism for the formation of these carbonates **104** using the oxaziridine species **98**, due to the increased electrophilicity of the carbonyl compared to the nitrogen in the ring, is shown in Scheme 45 below.



97 **104**

Scheme 45: Unexpected mechanism of carbonate formation.

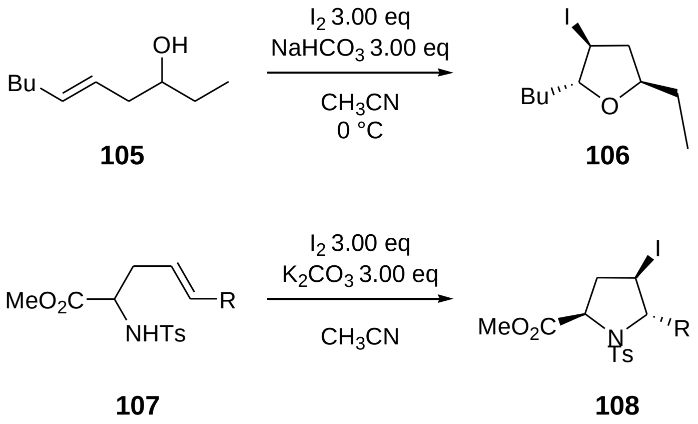
Although this was initially a disappointing finding, as it had proven the unsuitability of the oxaziridine **98** for the amination of alkoxides, the result of the subsequent iodocyclisation reaction was remarkable in that this appeared to be the first example of a 6-*endo*-trig cyclisation of this kind (Scheme 44). Directly following the refutation of the amination procedure, this unexpected result obtained by Proctor was understandably initially treated with a degree of scepticism. Not wanting to circulate any further erroneous results, it was important to prove this unusual product, which could then feature as the silver lining in a retraction of the original *O*-amination paper. As further investigation was beyond the scope of Proctor's project, this serendipitous development was pursued as part of the present project. The ratios of the 6-*endo* to 5-*exo* products on cyclisation of these carbonates **104** will be explored, along with the influence of the nature and size of the ring substituents. It can then be determined if this iodocyclisation can be used as a general synthetic method for the formation of this unusual and novel type of

6-*endo*-trig product.

3.11 Iodocyclisation.

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, some of which apparently contravene Baldwin’s rules.[56, 57] Such reactions were first documented as a versatile method for iodolactonisation, before the discovery that iodo-tetrahydrofurans were also formed in the reaction mixture.

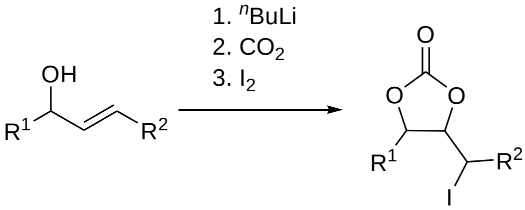
The Knight group showed an early interest in the potential applications of this methodology, as was discussed in the General Introduction (page 10). Having spent considerable time investigating iodolactonisation reactions, they had also observed the presence of iodo-tetrahydrofurans in some of the crude reaction mixtures, and resolved to develop the procedure further. The group set about developing this reaction as a means for the synthesis of a variety of iodine-substituted heterocycles, including the structures **106** and **108** shown in Scheme 46 below.[58, 59]



Scheme 46: Heterocycles formed by iodocyclisation.

Iodo-isoxazolines and -isoxazolidines have also been made by the group by utilising the above method, preceding the syntheses utilising silver catalysis that were discussed in the introduction to Chapter 2 (page 19). This previous work on iodine-facilitated cyclisations provides another link between these proposed new carbonate iodocyclisations and the formation of heterocycles which comprises the root of the present project.

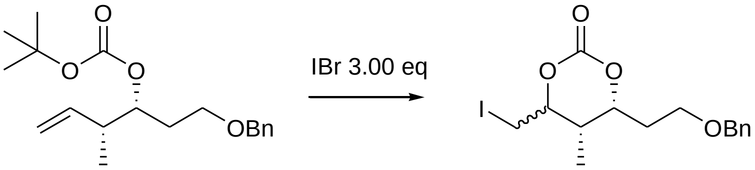
The synthesis of cyclic carbonates *via* iodocyclisation has been previously reported in the literature, where it was demonstrated that cyclic iodocarbonates **109** could be synthesised in a one-pot carboxylation of alkoxides followed by either 5-*exo*-trig or 6-*exo*-trig cyclisation of the resulting allylic carbonates, an example of which is shown in Scheme 47 below.[60]



96 **109**

Scheme 47: Carbonate formation and iodocyclisation.

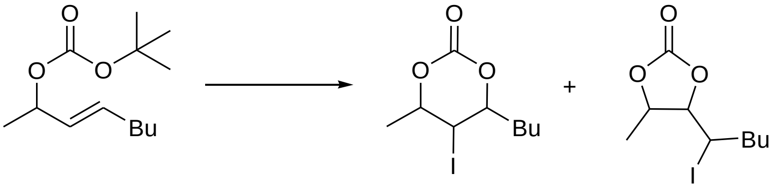
More recently, it has been reported that the unsymmetrical carbonate **110**, bearing a *tert*-butyl moiety, underwent a 6-*exo*-trig cyclisation when exposed to an excess of iodine monobromide to give the iodo-carbonate **111** as a mixture of diastereoisomers depending upon the conditions used (Scheme 48).[54]



110 **111**

Scheme 48: 6-*exo*-trig iodocyclisation.

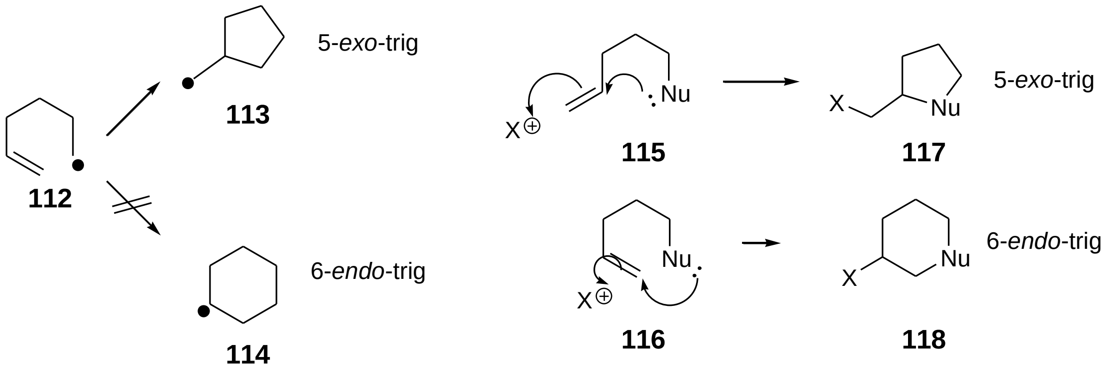
When discussing the relative facility of ring formation given the option of two different products, such as the case with the carbonates to be synthesised in this Chapter (an example is shown in Scheme 49), Baldwin's Rules can be used as a predictive tool for the ratio of products. The 5- and 6-*exo*-trig reactions shown in Scheme 47 and Scheme 48 above are types of reaction that are defined as favoured processes and have many literature precedents.[56]



101 **102** **103**

Scheme 49: Iodocyclisations to give 5- and 6-membered products.

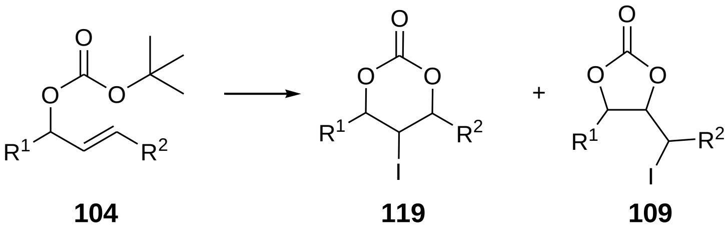
The 6-*endo*-trig cyclisation to form the above 6-membered ring **102** (Scheme 49) is also favoured, however it has been published that when 5-*exo*-trig cyclisation is also possible, the latter is preferred, as shown in Scheme 50 below.[56]



Scheme 50: Preferred radical and nucleophilic cyclisations.

The above scheme shows radical and nucleophilic reactions (Baldwin's rules also apply to homolytic and cation induced closures), that yield preferentially the cyclopentylmethyl products **113** and **117** by a 5-*exo*-trig closure rather than the 6-*endo*-trig path.[61]

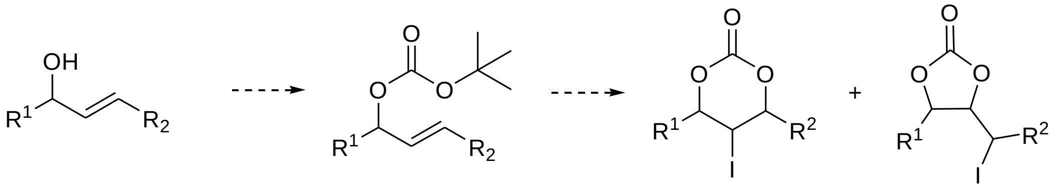
In exploring the ratio of the less common 6-*endo* **119** to the 5-*exo* **109** products on cyclisation of starting materials with varying substituents **104** (Scheme 51), it will be determined if this can be optimised into a general synthetic method to form this novel 6-*endo*-trig product type **119** by iodolactonisation.



Scheme 51: General iodolactonisation scheme.

3.2 Results and Discussion

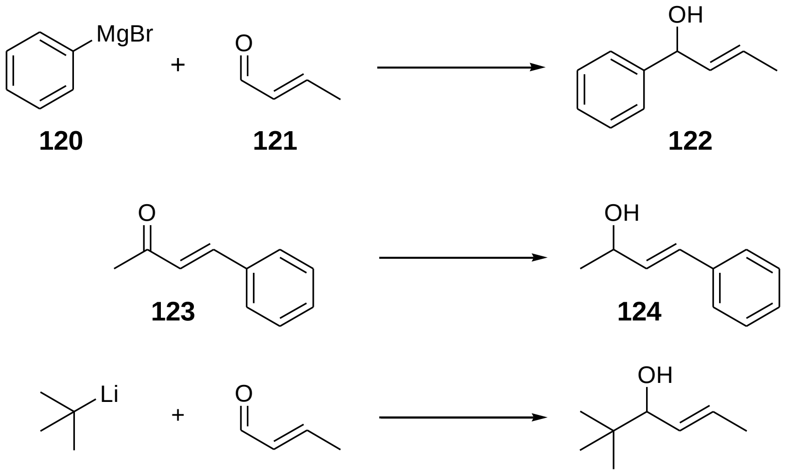
To test the suitability of iodine monobromide, a potent electrophile for alkene activation,[62] as a reagent for exploring and optimising the ratio of the 6-*endo* to 5-*exo* products on cyclisation, firstly a series of *tert*-butyl carbonates **104** with varying substituents needed to be synthesised. It could then be investigated if this ratio was affected by the size of the ring substituents, in order to determine if this is a relatively general synthetic method to form this unusual and novel 6-*endo* product **119**. The general synthetic scheme is shown in Scheme 52 below.



97 **104** **119** Major Product? **109**

Scheme 52: Proposed synthetic scheme.

Some of the secondary alcohols **97** were commercially available, but others had to be formed in one-step syntheses from alternative starting materials. The three alkenols **122**, **124** and **127** that were synthesised *via* a Grignard addition, by hydride reduction and by alkyl lithium reaction respectively are shown in Scheme 53.



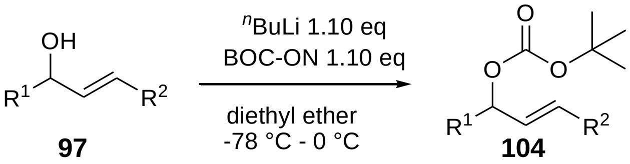
120 **121** **122**

123 **124**

125 **126** **127**

Scheme 53: Synthesising allylic alcohols.

The next step in the sequence was to carry out the BOC-protection of the secondary alcohols **97** to yield the *tert*-butyl carbonates **104** prior to cyclisation. As mentioned in the Introduction to this Chapter (page 39), there are a small number of different reagents available for *tert*-butyl carbonate formation and BOC-ON was again chosen for this transformation, as in the literature it had been said to give high yields of product with similar secondary alcohols.[55] The general reaction is shown in Scheme 54 (General Method **E**, page 111).



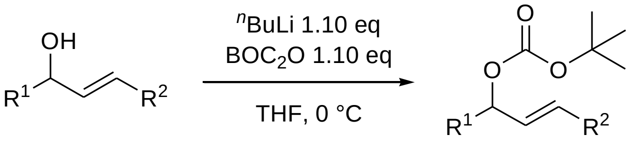
Scheme 54: BOC-ON carbonate formation.

The *tert*-butyl carbonates **128-132** that were synthesised by the above method are shown in Table 6 below. The yields not given in brackets are those obtained after purification, which was carried out by column chromatography (where the silica gel had been basified with triethylamine as these carbonates are unstable to acidic environments). It is clear to see that this reaction was not as successful as had been expected, it being a known reagent for these exact conversions. The crude yields (given in brackets) initially looked to be reasonable, however on examining the ^{1}H NMR spectra of the crude products, it was found that a proportion (~45% in the case of carbonate **129**) of this was actually BOC-ON residue, which was quantified by calculating the ratio of its five aromatic protons to an integrated peak of the product spectra. It was not trivial to remove these impurities from the crude product mixtures. Furthermore, no product at all could be formed from the diphenyl alcohol **130** using this reaction. It was thought that chromatography might not be the most appropriate method of purification due to these low isolated yields. This led to carbonate **129** being remade, and an alternative purification was attempted by triturating out the solid BOC-ON residues with a cold petroleum ether filter. The purified yield obtained was then 83% but the sample was not as clean as the previous columned material.

Product	R^1	R^2	% Yield
128	Methyl	Methyl	(86) 36
129	Phenyl	Methyl	(>100) 30
130	Phenyl	Phenyl	0
131	Methyl	Phenyl	(>100) 40
132	*tert*-Butyl	Methyl	(92) 17

Table 6: Carbonates from BOC-ON method.

Due to these unsatisfactory yields, when it was necessary to synthesise more of the above carbonates (apart from carbonate **129** as this had already been repeated), optimisation of this step was sought. In examining more recent literature, it was found that the more conventional BOC-protection agent BOC-anhydride had also been used to form carbonates from similar secondary alcohols in medium to good yields.[63] This was used as an alternative, and the new scheme to give the carbonates **104** is shown in Scheme 55 below (General Method **F**, page 111).



97

104

Scheme 55: BOC-anhydride formation of carbonates.

On carrying out these reactions with this different reagent, the yields that were obtained were much improved (See Table 7 below). This led to the conclusion that, in disagreement with the Smith paper,[55] BOC-ON is not the best compound to use to form *tert*-butyl carbonates from secondary alkenols.

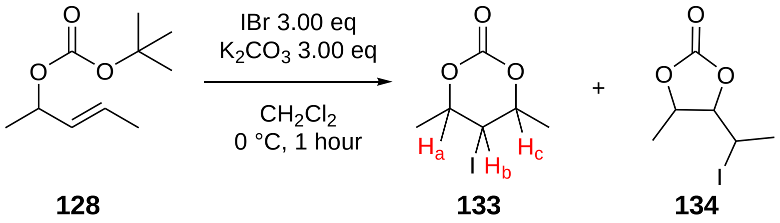
Product	R^1	R^2	% Yield
128	Methyl	Methyl	86
129	Phenyl	Methyl	Did not repeat
130	Phenyl	Phenyl	84
131	Methyl	Phenyl	53
132	*tert*-Butyl	Methyl	95

Table 7: Carbonates from BOC-anhydride method.

Additional purification steps were not needed, due to the BOC-anhydride residues being easily washed out with water during the work-ups - apart from in the case of the methyl, phenyl example **131** where some remaining starting material had to be removed using column chromatography which accounts for the lower yield in that case. The yield of the diphenyl carbonate **130** formation was most pleasing due to the previous difficulties in synthesising it at all using the BOC-ON method. The carbonate forming procedure that gave the highest yield for each product is given in the Experimental Chapter. With the carbonate syntheses having been optimised, and a range of intermediates **128-132** in hand, it was time to investigate the outcomes of the ensuing iodocyclisations.

The first trial iodocyclisation was carried out using the standardised conditions that had been previously successfully used within the group, as mentioned in the Introduction to this Chapter (page 38). A modification to the procedure was to use the iodine monobromide as a stock solution of 0.5 moldm^{-3} in anhydrous dichloromethane, to facilitate a quicker and more straightforward addition of the reagent.

The dimethyl carbonate **128** was treated with three equivalents of iodine monobromide at 0 °C for one hour (Scheme 56).



Scheme 56: Trial iodolactonisation.

Of the 89% crude yield of product material that was recovered after this initial reaction, it was calculated by studying the relevant integrations in the NMR spectra of the product mixture, that 88% of it was the desired 6-*endo* product **133** and 12% the 5-*exo* isomer **134**, which was a complex mixture of diastereomers. This meant that the overall yield of the 6-membered product **133** was 78% of the theoretical yield, by analysis of the NMR spectra (a section of which, showing $H_{a\text{-}c}$ **133** and the corresponding peaks from the 5-*exo* isomers **134** for comparison, is shown in Figure 6 below), making it the major isomer as had been hoped.

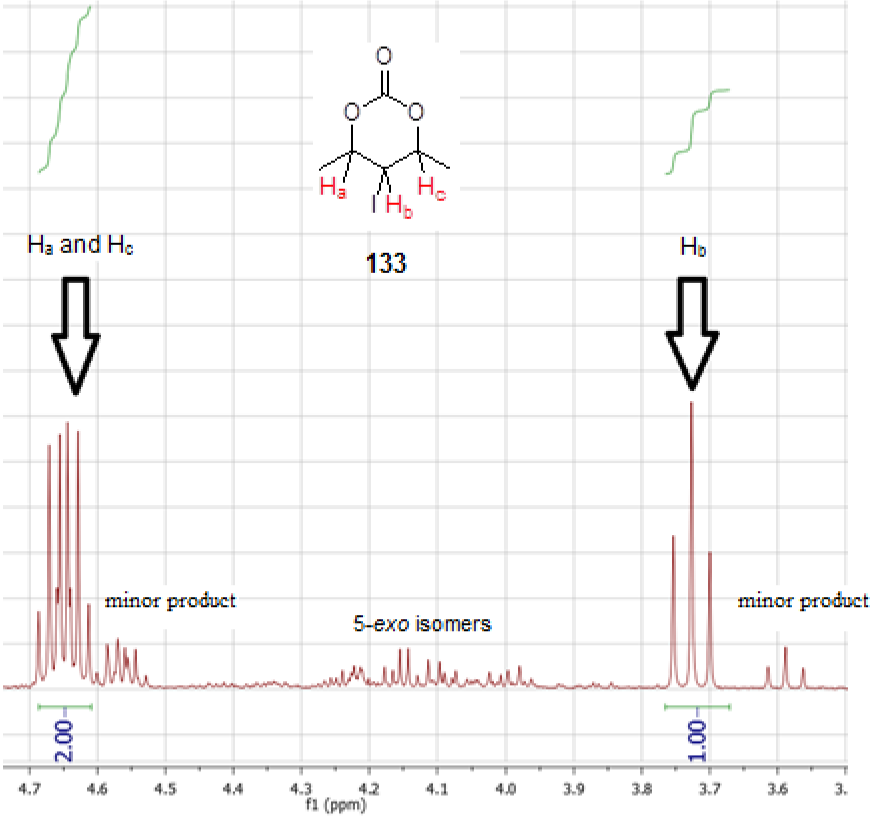


Figure 6: Section of proton NMR spectra highlighting the major iodocyclisation product.

The resonances highlighted above in Figure 6 of the three methine protons $H_{a\text{-}c}$ were consistent with those recorded by Proctor for the methyl, butyl analogue **102** - with H_a and H_c

producing the expected double quartet (2H, *J* values of 10.8 Hz and 6.2 Hz at 4.65 ppm) and H_b a triplet (1H with a *J* value of 10.8 Hz at 3.73 ppm) with a very similar *J* value to the analogous signal in Proctor's analysis.[7] A minor, assumed to be also 6-membered product, due to its matching splitting pattern, made up 15% of the total 6-membered product (seen at 4.56 ppm and 3.59 ppm in Figure 6). The identity of this unexpected minor product was hoped to be discovered after purification.

Purified samples of the isomers **133** and **134** were gleaned by column chromatography, and two dimensional NMR techniques were used to decipher and assign the structural isomers, that could then be confidently labelled in Figure 6. The key to this being possible is that the shift of a methine carbon that is also bonded to iodine appears characteristically lowfield in a ^{13}C NMR spectra (shifted ~60 ppm from the other CH resonances). This is an example of the "heavy atom effect", which can be explained in this case as a decrease in the chemical shift (δ_C) of the nucleus bound directly to the halogen substituent with increasing atomic number of the halogen.[64] After the methine shift (at ~28 ppm) that corresponded to the CHI centre had been identified in the DEPT ^{13}C NMR spectra of each isolated isomer, then the multiplicity of the paired proton shift could be examined using an HSQC experiment. HSQC links resonances from ^{13}C NMR spectra to the peaks in the corresponding proton NMR spectra from the hydrogen atoms that they are directly bonded to. Studying this allowed the structures of the stereoisomers to be assigned, as in the case of the proton NMR spectra of the major 6-membered product **133** this H-CI peak takes the form of a triplet (or double doublet), but in the case of the alternative 5-membered isomer **134** it would have a more complex splitting pattern and be dependent on the substituent (in this case, **134** Figure 7, a double quartet).

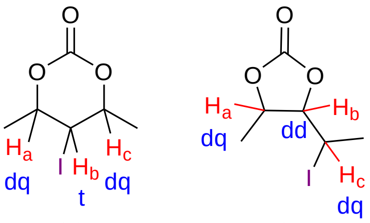


Figure 7: Protons and multiplicities. **133** **134**

The purified sample of the 6-*endo* product(s) that had been garnered by column chromatography for full analysis seemed to be more stable than the starting material, although due to the known photosensitivity of bonds to iodine, exposure to light was kept to a minimum. Assigning the structural isomer had been relatively straightforward, but to identify the specific major stereoisomer, further analysis had to be carried out. It could be tentatively concluded that the ring protons were *trans*-diaxial by the magnitude of the coupling constants (10.8 Hz). A

NOESY experiment further indicated that the alkyl substituents were *cis* to each other and *trans* to the iodo group. This was unequivocally confirmed by X-ray crystallography of the desired product **133**, as shown in Figure 8 below.

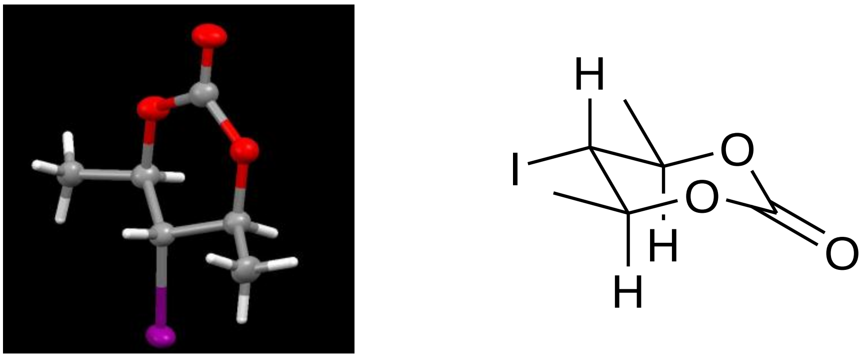


Figure 8: X-ray structure of 6-membered iodocarbonate 133.

The structure determined (**133**, Figure 8), showed a 6-membered ring containing two oxygen atoms in a 1,3 arrangement. The O-C-O bonds were 1.378 Å in length, with an internal angle between them of 116.5 ° (Full details of the data obtained are given in Appendix 1). A simple energy minimisation experiment performed using the programme Chem3D Pro calculated the same bond lengths to be 1.382 Å.

It could be seen in the NMR spectra of the purified desired product that even after column chromatography the minor 6-membered component of unknown structure had still not been separated from the major compound **133**, accounting for ~15% of the sample. It was not thought to be a stereoisomer of the main product **133** shown above, as inverting one or more of the stereocentres would have had a major effect on the magnitude of the coupling constants. Very little change in the size of the coupling constants, and only a small upfield shift could have been attributed to it being a conformer **133’**, due to flipping of the carbonyl group in the ring (Figure 9). This solution would also explain why this minor “product” could not be removed by purification.

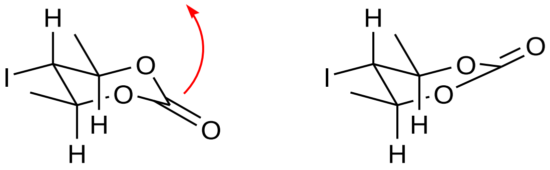


Figure 9: Conformational change 133 to 133’.

To investigate the above possibility, an increased temperature proton NMR experiment was carried out (at 55 °C), which would have caused a change in the ratio of conformers if they were present due to increasing the rate of movement in the ring. This was found to not be the case however, as there was no change in the relative integrations of the relevant signals, and other possible structures had to be taken into account.

Another potential solution was thought to be that the minor product could have arisen from an unexpected degree of bromocyclisation, due to a small amount of the iodine monobromide reacting through bromine (or the presence of molecular bromine impurities in the reagent). Although it could not be separated from the iodo-carbonate **133**, the existence of the bromo species could be proven by examining the HRMS analysis for the presence of the characteristic twinned molecular ion peaks (1:1) arising from the predicted structure and the stable isotopes of bromine (^{79}Br and ^{81}Br). These peaks were indeed found to be present, along with a set that corresponded to the molecular ion +MeCN which was echoed in the iodocarbonate high resolution spectra also. This identified the minor 6-membered product to be the bromocarbonate **135**, as pictured below with the CHI and CHBr resonances from a section of the ^{1}H NMR spectra of the purified product **133** (Figure 10).

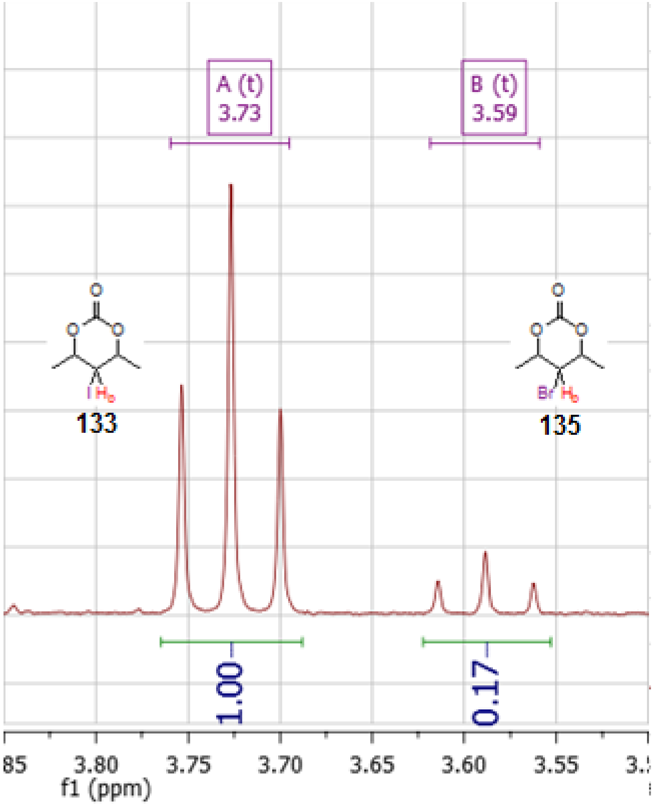
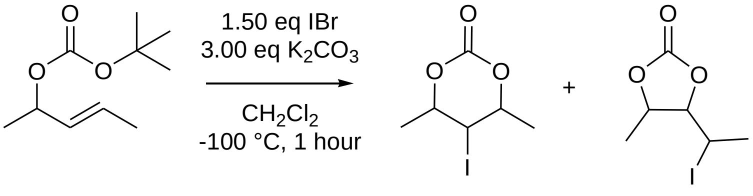


Figure 10: 3.73 (1H, t, *J* 10.8, CHI) and 3.59 (1H, t, *J* 10.3, CHBr)

Furthermore, the shift in ppm between the iodo- and bromo-cycles, shown above in Figure 10, is consistent with that between the relevant peaks in the ^{1}H NMR spectra of commercially available iodocyclohexanol and bromocyclohexanol.

Unfortunately, identifying the impurity, although interesting, did not lead to an immediate solution for preventing its production in the reaction. It was known that molecular iodine was not suitable for effecting these cyclisations, so it was decided to continue using iodine-monobromide. It was hoped that by changing the other conditions of the reaction that the incidence of bromolactonisation could be minimised, as removing the impurity after it had been formed had proved troublesome.

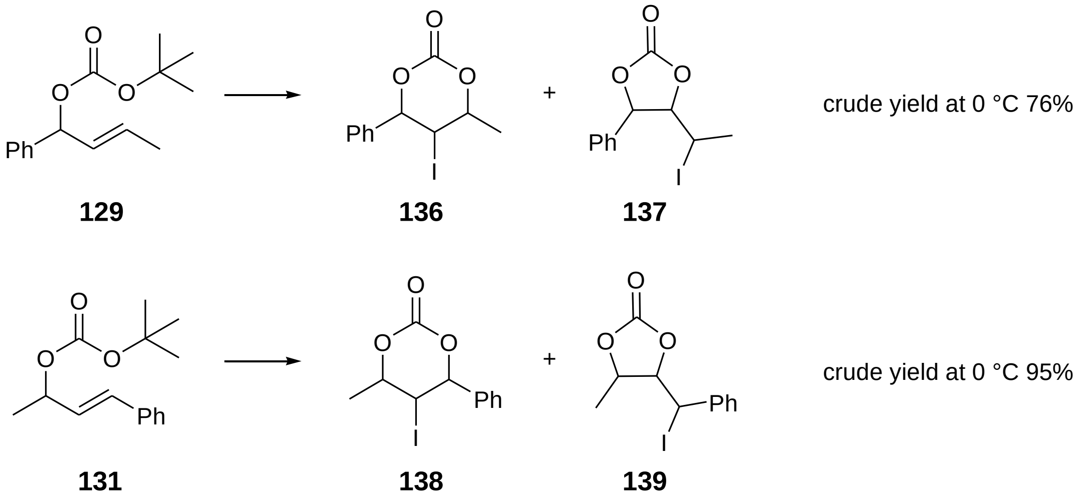
More pressingly, to try and further improve the ratio of the 6-membered to 5-membered products of iodocyclisation, the reaction was then repeated at a series of decreasing temperatures; -40 °C, -78 °C and -100 °C. After 1 hour at -40 °C, of the 87% by weight of product material that was recovered after the reaction, 83% of it was the desired 6-*endo* products (8% of which was the minor bromide product **135** - as in Figure 10) and 17% the 5-*exo* product **134**, again as a complex mixture of diastereomers. This meant that the overall yield of 6-membered products was 72%, according to the ^{1}H NMR data, but they contained less of the brominated side-product than in the 0 °C trial. At -78 °C, and for the same duration, of the 85% crude yield 84% of it was the 6-membered iodocarbonate **133** (and under these conditions no bromide product could be seen in the product mixture) and 16% the 5-membered isomer **134**, giving the yield of the desired product to be 71%. For the trial at -100 °C, the molar equivalents of iodine monobromide were reduced to 1.50, to test if the reaction would still go to completion within one hour. The best, most selective, results were found, and surprisingly still after the same short reaction time, under these conditions (Scheme 57).



Scheme 57: Optimised iodocyclisation conditions.

Possibly due to there being less decomposition at this very low temperature, the crude yield was 99%. Of this, 86% was the 6-*endo* product **133**, and at this stage it was possible to carry out a quick recrystallization from cold hexane to give pure crystals of the desired compound, without having to carry out column chromatography to remove the minor structural isomer **134**. There was also, again, no trace of the minor 6-membered bromide product **135** in the product mixture of this very low temperature reaction. These were thought to be the optimal conditions for this transformation, yielding 85% of the desired novel 6-membered iodo carbonate **133**, and in this case eliminating the issue of competing bromination.

To form the cyclic iodo-carbonate with methyl and phenyl substituents, there were two isomeric starting materials **129** and **131** to trial (Scheme 58), to see if one provided more selectivity than the other. These would technically give the same 6-*endo* products due to symmetry, although the 5-*exo* products **137** and **139** have different structures.

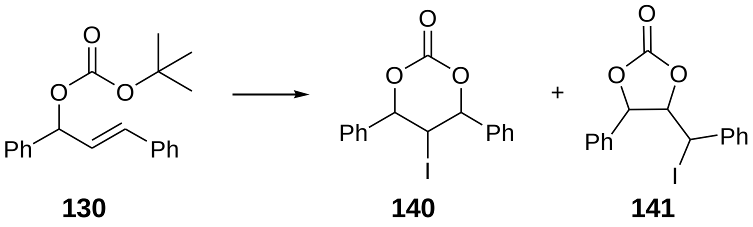


Scheme 58: Methyl, phenyl products.

After 1 hour at 0 °C, the ratio of structural isomers in each case appeared to be very similar on studying the ^{1}H NMR spectra of the crude product mixtures, with the minor 5-membered isomers being a very complex mixture that made up about 45% of the product mixtures. Again it could be seen after both reactions that the 6-membered product was a mixture of two products assumed to be from iodination and bromination respectively, with the latter this time accounting for 35% of the total amount of 6-membered products.

As there seemed to be no difference in the selectivity between the two starting materials **129** and **131** (Scheme 58), only the methyl, phenyl carbonate **131** that had given the higher crude yield above (95%) was taken on to the subsequent low temperature trials. At -78 °C, the crude yield was 69%, but with a quick recrystallisation all of the 5-membered structural isomers **139** (that accounted for ~12% of the crude product mixture) were removed. The major product was shown to be the 6-*endo* isomer **138**, using the same analytical techniques for structural assignment as with the previous dimethyl example **133**. Interestingly, even though in this case the ring is asymmetrically substituted, the CHI resonance in the ^{1}H NMR spectra of the 6-membered product **138** still took the form of a triplet. Again (as was seen in Figure 6), there was a minor 6-membered product showing a very similar coupling pattern (but shifted ~0.08 ppm upfield) that still made up 10% of the recrystallised product. At -100 °C the crude yield was 94%, which could also be purified by recrystallisation to remove the 5-membered isomers **139**. The major product (~85%) was again shown to be the product of 6-*endo*-trig cyclisation, with the recurring minor bromide product displaying the analogous coupling pattern making up 9% of the purified product even in this case. With this example, it was not possible to prevent all occurrences of cyclisation through bromine by carrying out the reaction at an extremely low temperature. Again, the identity of impurity as the bromide was proven by its characteristic presence in the HRMS of the recrystallised product.

In the case of the diphenyl intermediate **130** (Scheme 59), at -78 °C the crude yield was 99% - and it could be seen by analysing the proton NMR spectra of the crude product mixture that the 6-*endo* products accounted for ~53% - and recrystallisation from cold hexane removed the minor structural isomers **141**.



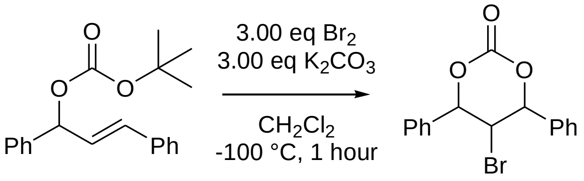
Scheme 59: Diphenyl cyclic carbonates.

The major product was the desired 6-membered cycle **140**, with the corresponding bromolactone making up 13% of the purified product. For the trial at -100 °C, the number of molar equivalents of iodine monobromide was reduced to 1.50, to test if the reaction would still go to completion within one hour, which it successfully did. After a sample had been taken to analyse the ratio of products, immediate recrystallisation of the crude product (99%) had to be carried out to prevent decomposition. It could be seen by examining the ^{1}H NMR spectra of the crude product sample that in this example the 6-*endo* products **140** accounted for an improved 79% of the overall yield. The crystalline product contained no 5-membered product **141** as desired, with the minor 6-membered bromide product accounting for only 8% of the purified yield. This result, along with the ratios of products achieved with the various substituents and at different temperatures will be summarised in a table later in the Chapter.

At this stage, due to the unwanted bromide product still being an undesirable presence, even after carrying out reactions at -100 °C, and because the diphenyl carbonate **130** had been synthesised on a large scale, it was decided to carry out further trials to investigate this unexpected but consistent side reaction. Three further investigative trials were carried out, one with molecular iodine as a control, one with NIS and one with molecular bromine to endeavour to further prove the structure of the minor product by comparison.

As had been expected, due to previous trials within the group, there was no product yielded from the attempted cyclisation with molecular iodine, and understandably none of the bromination product. The attempted cyclisation using NIS as an alternative source of iodine also only returned unreacted starting material.

After treating the starting material **130** under the usual conditions, only with molecular bromine as the reagent, it could be seen from the ^{1}H NMR spectra of the crude product mixture that the resonances of the major product matched exactly with the peaks of the recurring minor product **142** from the course of iodine monobromide reactions (Scheme 60). Bromocarbonate **142** was not purified, but it was calculated by studying the integrations from the proton NMR spectra of the crude product mixture that it accounted for ~55% of the theoretical yield after this preliminary trial reaction.

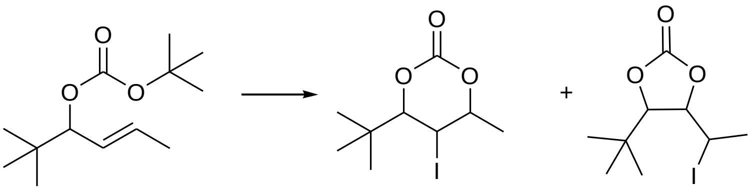


130 **142**

Scheme 60: Bromine facilitated cyclisation.

This cemented the theory that the minor 6-membered product was the result of reaction with bromine. Interestingly, when examining the literature to discover if these cyclic bromocarbonates were known compounds, it was found that this type of reaction had not been previously reported. Neither 6-*endo*, nor more surprisingly, the more common 5-*exo* reactions had been reported from treating similar starting materials with brominating agents. This opens the scope for further investigation into this type of bromo-cyclisation to produce an analogous series of bromo-substituted heterocycles. However, this was deemed to be beyond the range of the current project and remains a noteworthy initial observation.

The final carbonate example **132** showed the largest steric effects, with its very bulky tert-butyl substituent (Scheme 61).



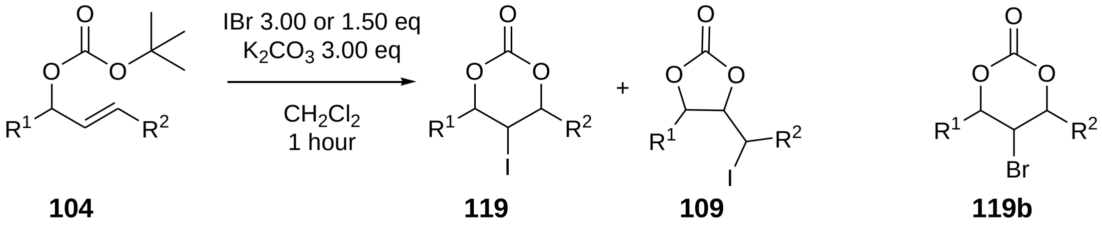
132 **143** **144**

Scheme 61: ***tert*****-Butyl, methyl cyclic carbonates.**

Even in this case though, at -100 °C, the crude product (88% yield) was comprised mostly of the 6-*endo* product **143**. However, after purification by recrystallisation, the minor

6-membered product (now known to be the bromide) did in this case account for 35% of the sample. The reaction was repeated at 0 °C to confirm that the best result had already been gleaned at the very low reaction temperature. As expected, the NMR spectra of this crude product then showed an unintelligible mixture assumed to be of numerous isomers and decomposition products.

The general reaction is shown below in Scheme 62, and below that in Table 8 all of the various cyclisations can be compared by yields and the compositions of the product mixtures.



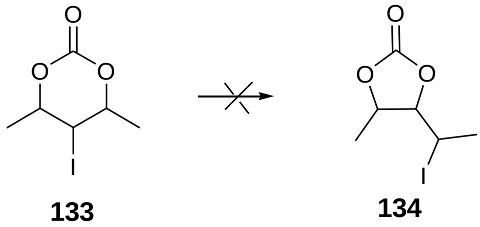
Scheme 62: General iodocyclisation scheme.

R^1, R^2	Temp (°C)	Crude yield (%)	Combined 6-*endo* (% of total)	Calculated overall yield of desired products	Major 6-*endo* iodo product (% of 6-membered)	Minor 6-*endo* bromo product (% of 6-membered)
Methyl, methyl	0	89	88	78	85	15
	-40	87	83	72	92	8
	-78	85	84	71	100	0
	-100	99	86	85	100	0
Methyl, phenyl	0	95	55	52	65	35
	-78	69	88	61	90	10
	-100	94	85	66	91	9
Phenyl, phenyl	-78	99	53	52	87	13
	-100	99	79	78	92	8
^{t}Butyl, methyl	-100	88	56	50	65	35

Table 8: Cyclisation results.

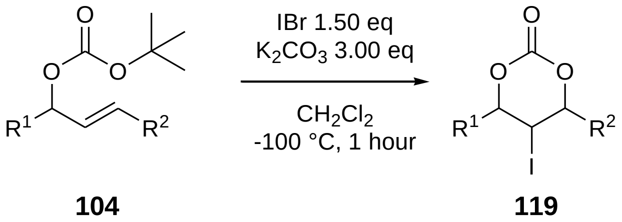
As can be seen in Table 8 above, better crude yields were consistently achieved at increasingly low temperatures of reaction. Furthermore, the overall yields of the desired 6-membered products were found to be very good, and in most cases reducing the temperature led to a decrease in the formation of the brominated product by a substantial degree.

When a pure sample of the dimethyl 6-membered cyclic carbonate **133** was exposed again to the cyclisation reagents and conditions, it was found that no equilibration occurred to give any of the 5-*exo* structural isomer **134** (Scheme 63).



Scheme 63: No isomerisation.

In conclusion, it has been found that the optimised reaction conditions are convenient and relevant as a general synthetic method for synthesising these novel products **119** of 6-*endo*-trig iodocyclisation (Scheme 64).



Scheme 64: 6-*endo*-trig iodocyclisation.

In all examples, the desired 6-membered structural isomers **119** resulting from the unprecedented 6-*endo*-trig cyclisations of the *tert*-butyl carbonate reactants **104** were the major products. This was proven in each case by thorough NMR spectroscopic investigations, and was also confirmed by X-ray crystallography. Where this had been carried out, it also verified the stereochemistry and shape of the major product. This was as expected, with the ring substituents equatorial causing the alkyl moieties to be *trans* to the large iodine atom (Figure 11).

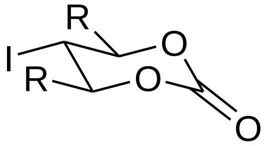


Figure 11: Chair confirmation 119.

Optimal selectivity was achieved at a decreased temperature of around -100 °C within a short reaction time. The crude yields were very good, and on average consisted of over 80% the desired novel 6-*endo* structural isomer, which could then be isolated and investigated as to its stereochemical makeup. Samples for crystallography were easily gleaned by recrystalisation, which could also be optimised for providing maximum isolated yields.

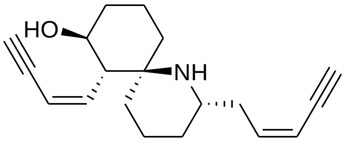
Chapter 4

Acid-catalysed hydroaminations to form fully saturated N- and O- containing heterocycles

- Working towards Histrionicotoxin

4.1 Introduction

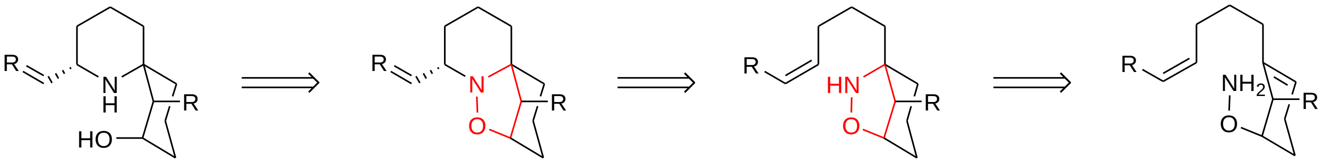
The overall theme of this Chapter is the application of novel hydroamination cyclisation methods to synthesising nitrogen and oxygen containing saturated heterocycles. Hydroamination is a highly atom-economical process in which an amine N-H functionality is added across an unsaturated carbon-carbon linkage,[65] in this case intramolecularly to induce a ring-closure. This methodology is working towards an application, focussing on a transannular cyclisation, which will ultimately introduce the chiral heterocyclic core structure of the complex natural product Histrionicotoxin **145** (Figure 12). The spirocyclic core of the Histrionicotoxin family of compounds is unique in the world of natural products, and has therefore been the subject of much study in the chemical community.[66]



145

Figure 12: Histrionicotoxin.

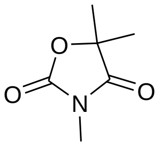
Though the final natural product itself **145** (Figure 12) does not contain an N-O heterocyclic ring, one will be formed in the synthetic scheme leading towards it (shown in red in the transannular intermediates **147** and **148** in Scheme 65 below), in order to introduce the stereospecific amino-alcohol precursor. This kind of amino-alcohol synthesis was covered in the General Introduction, outlining cyclisation methods and the subsequent reductive cleavage of the N-O bond (page 15). A proposed retrosynthesis outlining this is shown in Scheme 65.



146 **147** **148** **149**

Scheme 65: Retrosynthesis of the core structure of Histrionicotoxin.

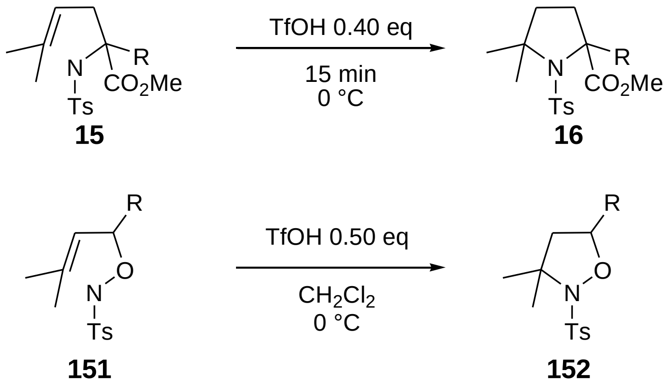
There are several other biologically active compounds which do contain a non-aromatic N-O heterocycle themselves, such as the series of oxazolidinediones one of which, Trimethadione **150**, is shown in Figure 13 below, which are anticonvulsant drugs.[67]



Trimethadione **150**

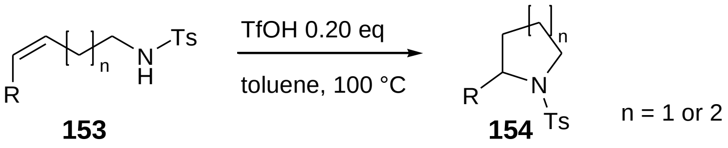
Figure 13: Oxazole-based natural product.

The work in this Chapter will be building on that previously carried out within the Knight group, such as the acid-catalysed hydroamination cyclisations to form the heterocycles **16** and **152** shown below in Scheme 66.



Scheme 66: Acid-catalysed hydroaminations.

These reactions had been found to work very well and to give high yields by previous group members.[11] Prior to this, Brønsted acids had not been extensively used as reagents for hydroamination processes involving alkenes, due to the more basic character of the amine nitrogen compared to the π-system of the alkene. This could lead to the preferential and complete formation of an ammonium salt instead of the desired carbenium ion which would result from proton addition to the carbon-carbon double bond. This, in turn, would remove the nucleophilic character of the nitrogen, preventing it from attacking the alkene. However, it has been found that catalytic amounts of Brønsted acids do trigger the inter- and intramolecular hydroaminations of alkenes and alkynes when the amine is present as a sulphonamide **153**,[68-70] as revealed by the first intramolecular example in the literature, shown in Scheme 67 below.

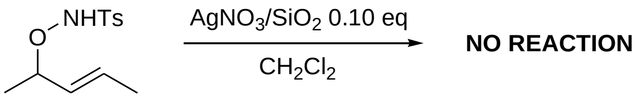


Scheme 67: Intramolecular hydroamination.

The amino-alkene starting material **153** has an electron-withdrawing group on the nitrogen, and leads to pyrrolidines and piperidines **154** in excellent yields under the conditions given in Scheme 67 above. More basic amines, however, do lead to lower rates of reaction as they drastically change the reactant–acid catalyst interaction.[71] The previous acid-catalysed cyclisations that had been optimised within the group (Scheme 66), also utilise an electron-withdrawing tosyl protecting group to decrease the basicity of the amine functionalities.

The regiochemistry of the process is determined mostly by the stability of the carbenium ion intermediate, and therefore most of the transformations are 5-*endo*-trig cyclisations. These are unfavourable according to Baldwin's rules (which were outlined in the introduction to Chapter 3 - page 40), however cation driven reactions often disobey Baldwin's Rules.[56]

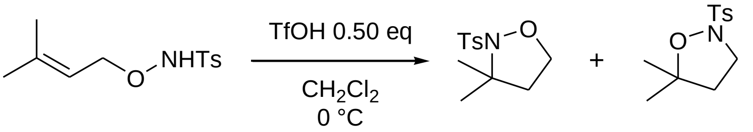
As was discussed in Chapter 2, the use of silver nitrate had proven highly effective in catalysing cyclisations as a means for the synthesis of isoxazolines and isoxazoles. However, it has been shown that when applied to the type of reaction shown below in Scheme 68, the catalyst fails to generate any of the fully saturated isoxazolidine product, returning only unreacted starting materials **155**.[7]



155

Scheme 68: Failed silver-catalysed cyclisation.

It was decided to use an acid catalyst to facilitate the addition of N-H across a double bond for this venture, following on from the Group's successful work in this area, as previously mentioned in Scheme 66. However, as the substrate is a hydroxylamine there is the added complication that the relatively weak nitrogen-oxygen bond might not tolerate such conditions and partial or even total decomposition of either the starting material or any product formed could be observed. It was also expected that there could be some possible complications with the reaction, due to the oxygen-carbon bond breaking and the resulting carbocation being attacked by the nitrogen to give the product with the positions of the oxygen and nitrogen inverted in the ring (isomerisation of the nitrogen-oxygen bond). This was thought to be a possibility as it had been observed in reactions, such as the cyclisation of **156** shown below in Scheme 69, which had been carried out by previous group member Anthony Proctor.[7]



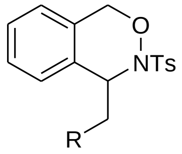
156 72% **157** 19% **158** Isolated yields

Scheme 69: Observed isomerisation in acid-catalysed cyclisations.

4.11 Benzannulation.

In order to extend the utility of such new hydroaminations, it was decided to first examine their application to the formation of Pictet-Spengler-like products **159**, as shown below in Figure 14, to optimise the cyclisation procedure before applying it transannularly to the

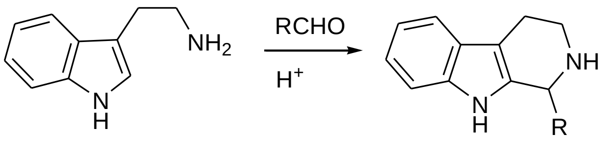
Histrionicotoxin chemistry.



159

Figure 14: Desired hydroamination products.

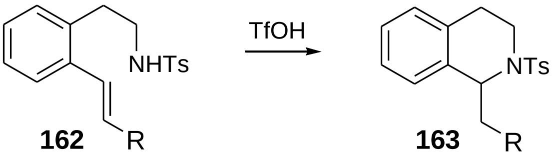
The Pictet–Spengler reaction is a chemical transformation in which a β-arylethylamine **160** undergoes ring closure after condensation with an aldehyde or ketone. Usually an acidic catalyst is employed and the reaction mixture heated. The Pictet–Spengler reaction can be considered a special case of the Mannich reaction,[72] and an example is shown in Scheme 70 below.



160 **161**

Scheme 70: Pictet-Spengler reaction.

A new synthetic approach that did not require the involvement of a carbonyl directing group had recently been optimised within the group, is now in press, and is shown in Scheme 71 below.[12]

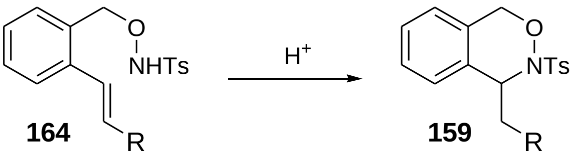


162 **163**

Scheme 71: Knight group hydroamination to give a Pictet-Spengler type product.

It was thought that synthesising the equivalent of the intermediate **162** with oxygen α to the nitrogen would be possible, so that morpholine analogues **159** (as Figure 14 above) could be synthesised using this methodology. The possibility of isomerisation of N-O could be increased in this case (compared to the result in Scheme 69), due to the fact that the carbocation that could form from cleavage of the C-O bond would be stabilised by being in the benzylic position. As shown in Scheme 71, the cyclisation had previously been catalysed by triflic acid. Triflic acid is a ‘superacid’ and is widely used, especially as a catalyst and a precursor in organic chemistry.[73] With a pKa of around -15, triflic acid is inordinately stronger than sulphuric acid (pK_a -3), and is difficult to handle.

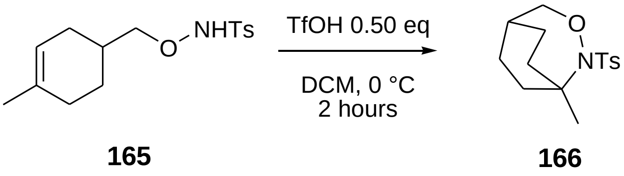
It was decided to attempt to optimise these cyclisations (Scheme 72) with the milder reagent sulphuric acid, and at 0 °C, which will be examined in the Results and Discussion segment after introducing the second section of this Chapter.



Scheme 72: Proposed cyclisation.

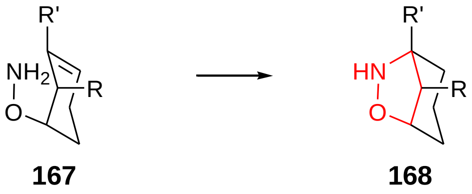
4.12 Transannulation.

Natural products containing multiple fused or bridged ring systems are regularly shown to exhibit biological activity against a wide variety of human diseases.[74] Transannular cyclisations, that form a new ring across an existing one , have been demonstrated within the group using their novel acid-catalysed hydroamination methodology,[12] as shown in Scheme 73 below.



Scheme 73: Transannular acid-catalysed hydroamination.

The transannulation precursor **165** usually has to be constructed with appropriate functionality at specific points around the ring to allow for the desired transannulation reaction to occur. Thus a single transannulation precursor **165** gives rise to a single stereospecific product **166** of a transannulation reaction.[74] This investigation will ascertain whether this transannular hydroamination methodology can be successfully used for synthesising models and precursors of the core structure of Histrionicotoxin with varying degrees of complexity. The retrosynthesis including this cyclisation step was outlined in Scheme 65 (page 58), and the transannular hydroamination step is shown below in Scheme 74, to give the bicyclic product **168** with simplified side-chains.



Scheme 74: Transannular cyclisation to give intermediate to Histrionicotoxin core.

The Histrionicotoxins are of considerable neurophysical research interest, given their biological activity as selective, non-competitive inhibitors of central neuronal, ganglionic and muscular nicotinic acetylcholine receptors.[75, 76] Non-competitive inhibition is a type of enzyme inhibition where the inhibitor reduces the activity of the enzyme, by binding not to the active site of the enzyme, but to a different (allosteric) site. The inhibitor and the substrate may both be bound at the same time, but when they are the enzyme-substrate-inhibitor complex cannot form product. Histrionicotoxin does not block interaction of acetylcholine with the nicotinic receptor, but instead interacts with a site on the associated ion channel. This type of inhibition temporarily reduces the maximum rate of a specific *in vivo* chemical reaction without changing the apparent binding affinity of the catalyst for the substrate.[77] The interaction with Histrionicotoxin appears to cause the channel to assume an inactive and non-conducting state.[78]

Histrionicotoxins are found at extremely low natural abundances, at less than 180 µg per Columbian poison arrow frog (*dendrobates histrionicus*). Captive frogs have been found not to secrete these toxins, so it has been impossible to determine a plausible biosynthetic pathway.[66] The activity of these alkaloids, combined with their scarcity and interesting structures, has led to a considerable number of synthetic approaches over the last thirty years. Some previous syntheses towards these compounds will be outlined, focussing on those methodologies where the final bond formed in order to generate the core spiropiperidine system **169** is between the nitrogen and the alkyl chain (indicated in red, Figure 15), as with the retrosynthetic scheme that was proposed for this project in Scheme 65 (page 58).

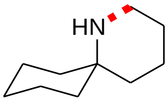
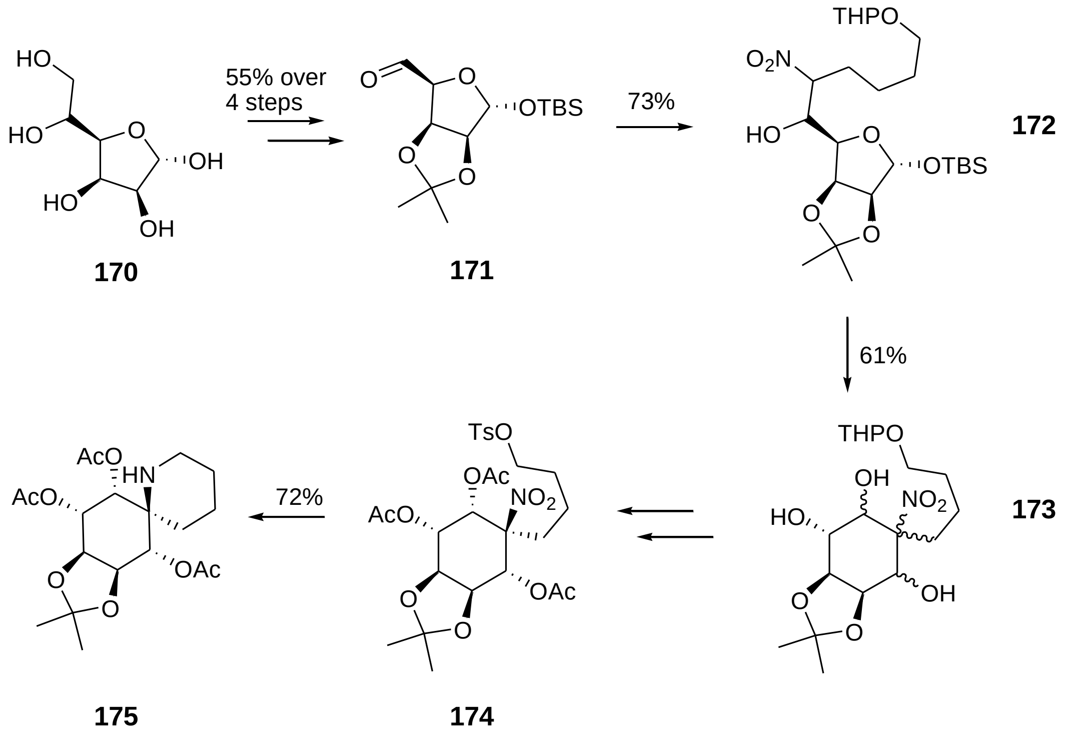

169

Figure 15: Spirocycle formation.

All of these approaches start from a functionalised carbocyclic system, to which the heterocyclic ring is fused to form the core spirocycle. A recent review by Stockman provides a comprehensive summary of many of these syntheses,[66] and reference will now be made to some of the more relevant to this project.

In 1987, the Harrison group published an enantioselective route towards the azaspirocyclic histrionicotoxin core structure, based on the use of carbohydrate starting materials, namely D-mannose **170** (Scheme 75).[79]

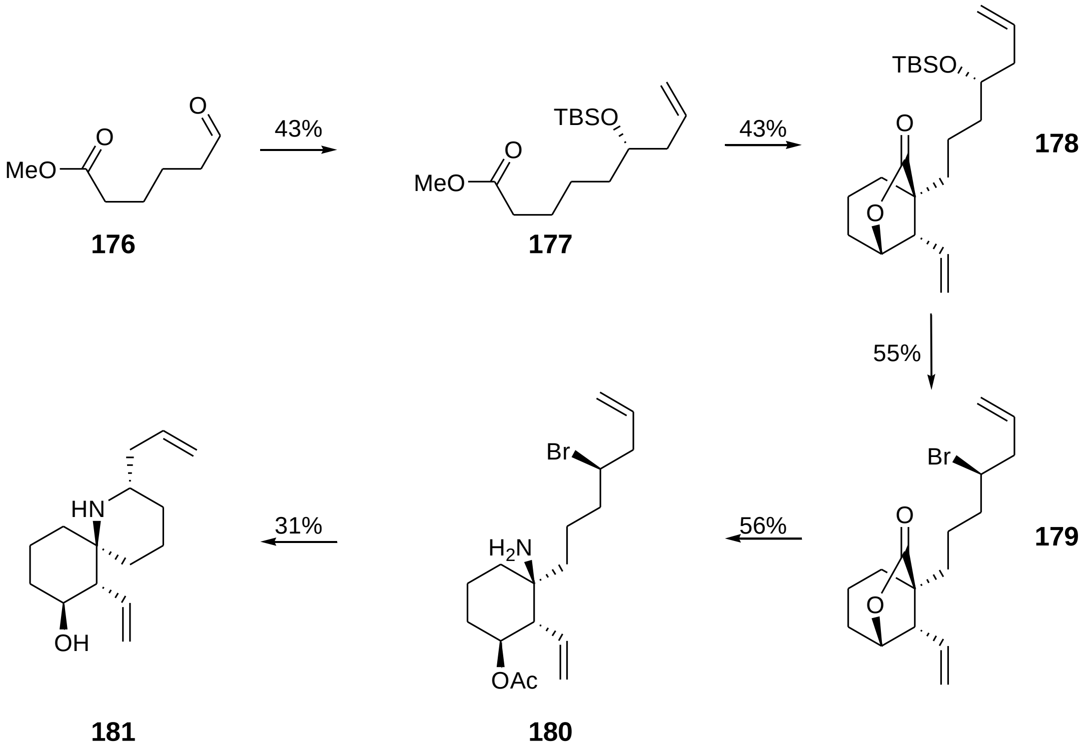


Scheme 75: Harrison's 1987 histrionicotoxin approach.

An intermolecular Henry reaction was carried out on the aldehyde **171** to generate the nitroalkane **172**. This was followed by a second intramolecular Henry reaction to generate the nitrocyclohexane as a mixture of isomers **173**, which could be separated after tosylation of the primary alcohol moiety (34% desired isomer). The Henry reaction is a base-catalysed C-C bond-forming reaction between nitroalkanes and aldehydes (or ketones). It is similar to the aldol additions, and is sometimes referred to as the Nitro-aldol reaction.[80]

Secondary alcohol protecting groups had to be introduced to form the triacetate **174**, which was then found to spontaneously cyclise on exposure to aluminium amalgam to give the desired spirocycle **175**. This route was not progressed further towards the target natural products, but demonstrated the potential for using carbohydrate starting materials in the synthesis of enantiomerically pure azospirocycles.

A few years later, the Stork group were able to develop an impressive asymmetric synthesis of the histrionicotoxin precursor **181**, commencing from the very simple starting material **176** (Scheme 76).

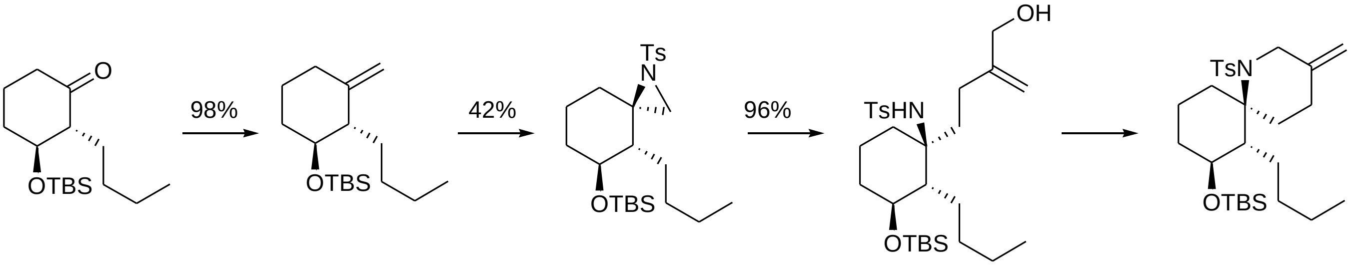


Scheme 76: Stork's 1990 histrionicotoxin approach.

The silyl ether **177** was isolated as a single enantiomer, upon reaction of the aldehyde **176** with a chiral (-)-α-pinene-derived allyl borane and a silyl protection reagent. In common with this project's proposed synthetic route, the retrosynthesis of which was given in Scheme 65, a transannular intermediate imparts the correct stereochemistry. In this case, it is a lactone **178** that is formed as a single enantiomer, in an intramolecular cyclisation, possessing three correctly set stereogenic centres. This was followed by formation of the bromide **179**.

The construction of the piperidine ring required the conversion of the lactone carbonyl into an amino function, which was carried out in two steps, to give the amine **180**. This was achieved by the action of trimethylaluminium and ammonium chloride followed by the addition of acetic anhydride, to give the crude acetoxy amide, which then underwent a Hoffmann rearrangement promoted by phenyliodonium *bis*-(trifluoroacetate) to give amine **180**. The desired cyclisation of this then required heating at 55 °C in the presence of triethylamine, to promote the key intramolecular elimination to yield the target azaspirocycle **181**.

In 2006, the Harrity group reported a formal synthesis of the spirocyclic precursor **186**, based on a stepwise [3+3] annelation strategy (Scheme 77).[81]

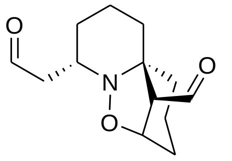


182 **183** **184** **185** **186**

Scheme 77: Harrity's 2006 histrionicotoxin approach.

Starting from the TBS-protected hydroxy ketone **182**, this was converted into the exocyclic alkene **183**. Sharpless methodology then generated the desired aziridine **184**, containing the required stereochemistry in a 42% yield. A stepwise addition sequence furnished the alcohol **185**, which cyclised in the presence of titanium isopropoxide and palladium to give the spirocycle **186**. The remainder of the synthesis to the histrionicotoxin product then involved straightforward functional group interconversions.

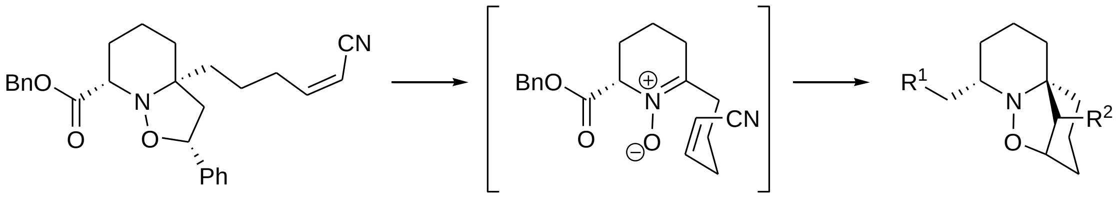
Specifically, it was Holmes' 1999 synthesis that sparked the idea of investigating the synthesis of histrionicotoxins *via* the isoxazolidine precursor **187**,[82] shown below (Figure 16).



187

Figure 16: Isoxazolidine precursor.

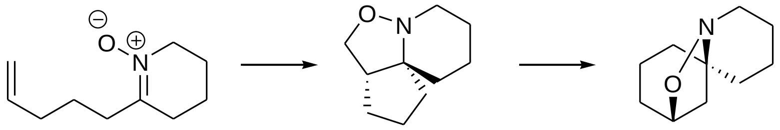
The general transannular isoxazoline intermediate **147** was formed in their route, a section of which is shown below in Scheme 78, and looked to be an excellent candidate to reach utilising the Knight group's acid-catalysed cyclisation methodology.



188 **189** **147**

Scheme 78: Section of Holmes' synthesis.

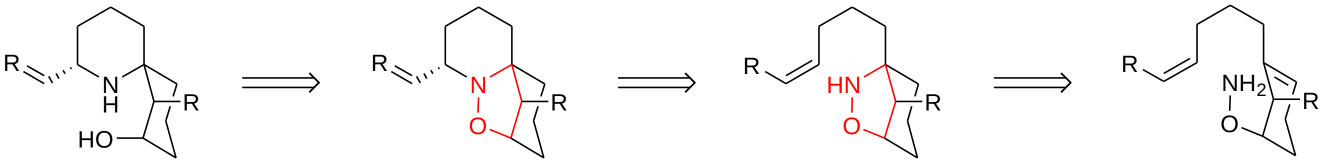
This was not, however, the first route to histrionicotoxin that went through a transannular isoxazolidine precursor. This was achieved by Gossinger, through a retro- and re-cyclisation from nitrone **190** (Scheme 79).[83]



190 **191** **192**

Scheme 79: Section of Gossinger's synthesis.

The Holmes' isoxazolidine intermediate **147** can be seen in this project's simple retrosynthetic disconnection, repeated below (Scheme 80). The spirocyclic core structure of the histrionicotoxins **146** could be obtained following N-O bond cleavage of the isoxazolidine **147** (highlighted in red). N-O bond cleavage to give amino alcohols was covered in the General Introduction (page 15), and in this specific case the heterocyle to be opened is an isoxazolidine which are cleaved particularly efficiently with hydrogenolysis catalysed by rhodium on carbon.[84] This route has been chosen, as an obvious disconnection of the C-N bond in the isoxazolidine **148** gives the substrate **149** that is set up to effect a transannular acid-catalysed cyclisation of the nitrogen on to the double bond. It is hoped that this will provide an opportunity to apply the Groups's hydroamination methodology (that was discussed in the Introduction to this Chapter, page 59) to synthesising a hydroxy amine functionalised natural product framework.



146 **147** **148** **149**

Scheme 80: Retrosynthesis of the core structure of Histrionicotoxin.

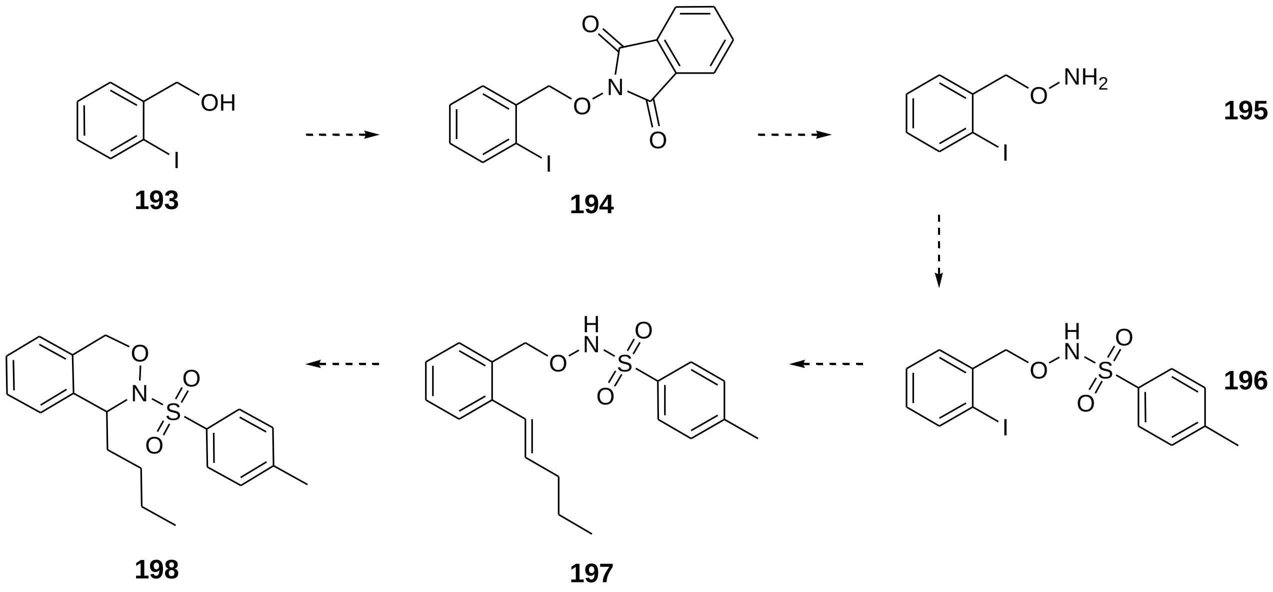
A synthetic route leading to the cyclisation precursor **149** will be devised, so that the hydroamination conditions can be investigated, and a forward synthesis planned corresponding to the proposed retrosynthesis above.

Prior to this however, the non-transannular cyclisations to synthesise morpholines (that were discussed in the benzannulation section of this introduction, page 60) will be explored, to optimise the hydroamination step, and address any issues in synthesising the precursors or with isomerisation of the N-O bond on cyclisation.

4.2 Results and Discussion

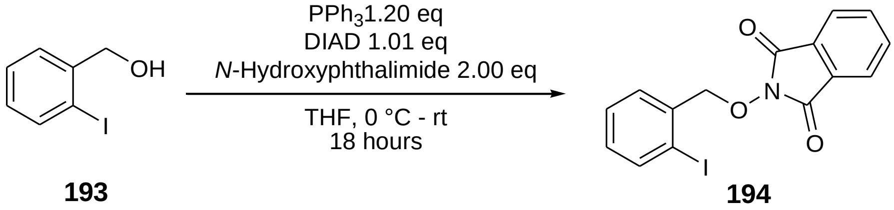
4.21 Initial route from benzyl alcohol

The synthetic sequence that was proposed for the formation of the heterocycle **198** is outlined below in Scheme 81.



Scheme 81: Proposed synthetic scheme.

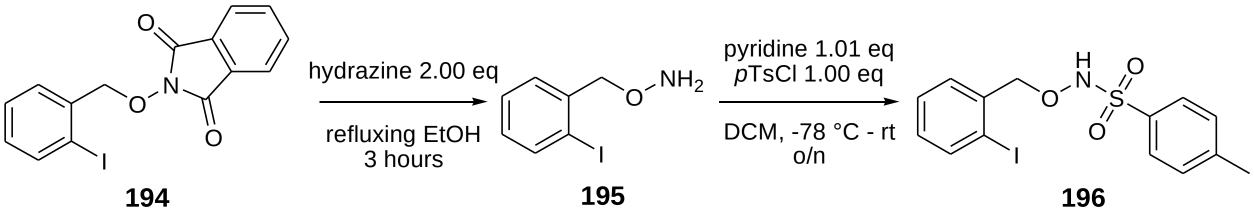
The first step in the synthesis was to carry out a Mitsunobu reaction on the benzyl alcohol **193** to yield the phthalimide protected hydroxylamine **194**. The Mitsunobu reaction was again used to introduce the O-N functionality in this case (Scheme 82), after it had been optimised for carrying out the same transformation in Chapter 2 (page 28).



Scheme 82: Mitsunobu reaction.

Carrying out General Method **B** (page 110) proceeded as a very straightforward reaction, as by using two equivalents of *N*-hydroxyphthalimide, there was no starting material **193** remaining and the cleanness of the reaction meant that purification could be carried out by washing the crude product through a plug of silica gel, rather than having to use a time-consuming column. The isolated yield of pure material **194** achieved was 71%.

The next stage of the scheme really includes two steps, as the free hydroxylamine **195** was not purified and analysed due to concerns about its stability, and so was instead taken straight through to the tosylation reaction to give the protected hydroxylamine **196** (Scheme 83).

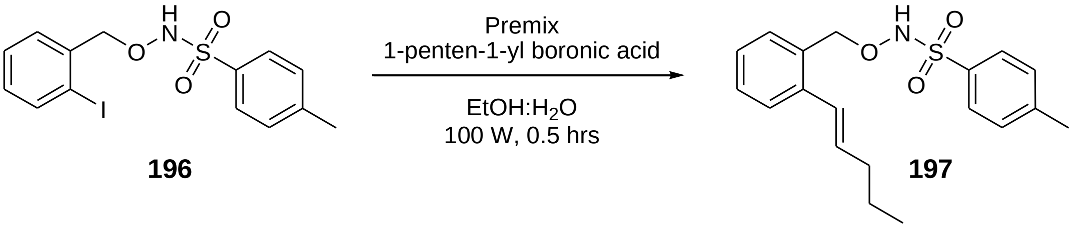


Scheme 83: Dephthaloylation and tosylation.

The deprotection of the phthalimide **194** was carried out in refluxing ethanol and went to completion within three hours (Scheme 83). Unfortunately however, the tosylation reaction did not prove to be as simple, as there were unexpected problems with what appeared to be, on careful analysis of the NMR spectra, *bis*-tosylation. This was thought to be the consequence of increased nucleophilicity of the hydroxylamine nitrogen compared to that of an amine. After many trials, varying the base, duration and temperature of the reaction, and also trialling it without the usual addition of the nucleophilic catalyst DMAP, it was found that the best conditions were with pyridine (1.01 eq) and no DMAP, with the temperature on addition at -78 °C before warming to room temperature overnight (Scheme 83). This gave an overall yield of 64% of the tosylated hydroxylamine **196**.

This was then followed by a Suzuki reaction at the iodine moiety in the *ortho*-position, using a vinyl boronic acid to introduce the required alkenyl chain substituent. The Suzuki reaction - a palladium-catalysed cross-coupling of aryl halides with boronic acids - is one of the most versatile and utilised reactions for the selective construction of carbon-carbon bonds.[85] However, in this case it was anticipated that it might have been difficult to achieve, due to both steric hindrance and the relative electron-richness of the substrate. The reaction was first tried under commonly used Suzuki conditions ($[PPh_3]_4Pd$, K_2CO_3, THF), under reflux. This only yielded a very small amount of the desired product. Transferring these same reagents to the microwave was also unsuccessful, despite recent literature showing that this could be very successful in triggering Suzuki reactions.[85]

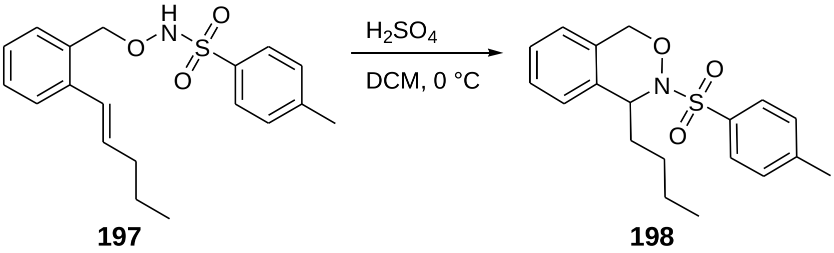
Instead, it was decided to trial using a “pre-mix” of reagents that had been optimised by previous group member Laura Henderson for her similar *ortho* Suzuki couplings.[12] Pre-mixes are different combinations of catalyst, ligand and base, which are designed to make the weighing of these components much easier and faster, especially on a small scale. This particular pre-mix contained K_3PO_4 (base), palladium acetate (catalyst) and dtbpf ligand (1,1’-*bis*(di-tert-butyl phosphino) ferrocene), and facilitated the completion of the reaction after half an hour in the 100 W microwave at 100 °C (Scheme 84), with a purified yield of the alkene **197** of 56% after column chromatography.



Scheme 84: Suzuki reaction.

This moderate yield was thought to be due to carrying out the reaction and subsequent purification on a small scale, as conversion of the starting material was complete using these reaction conditions that had been optimised within the group.

The final step in the scheme was the pivotal acid-catalysed cyclisation step. In the initial trial, concentrated sulphuric acid was simply added dropwise to the product of the Suzuki reaction **197**, at 0 °C in anhydrous dichloromethane, and the cyclisation was rapid to give the desired bicyclic product **198** (Scheme 85).



Scheme 85: Acid-catalysed cyclisation.

The reaction was only trialled on a very small scale, but it could be seen by studying the proton NMR spectra of the crude product **198** that a complete conversion had occurred. Comparing the sections of spectra below (Figure 17 - starting material **197** is shown above the cyclised product **198**), shows the disappearance of the CH_2 singlet α to oxygen from the starting material (5.00 ppm), and its replacement by the characteristic diastereotopic CH_2 pair of doublets (at 5.11 and 4.70 ppm, *J* = 14.5 Hz - axial and equatorial due to their newly fixed position on the ring) and the new tertiary C-H double doublet (at 4.93 ppm, *J* = 8.0 and 5.5 Hz).

It can be clearly seen that there is only one isomer **198** present, as the spectra is consistent with the CH_2 resonances being α to O rather than N. The formation of a single product in this reaction is evidence that there was no rearrangement of the N-O bond (unlike the earlier reaction that was shown in Scheme 69).

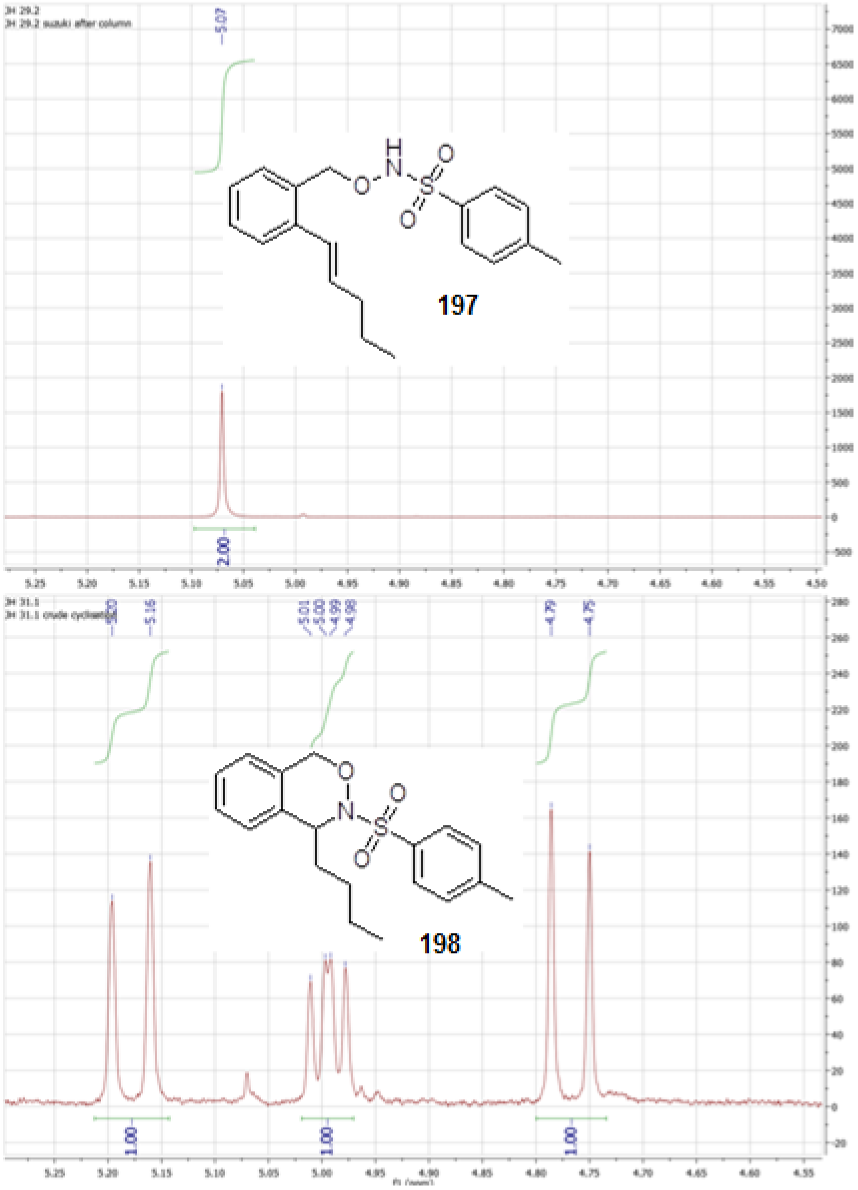
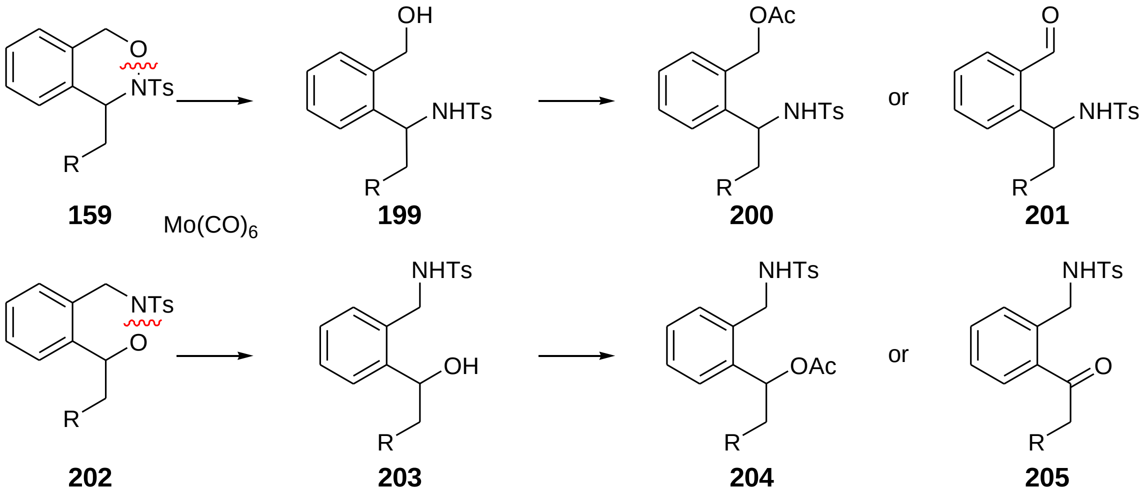


Figure 17: δ_H 4.5-5.3 Section of NMR Spectra before and after cyclisation.

A literature search uncovered no similar structures to either the desired compound **198** or the unwanted isomerisation product **202** for comparison to the NMR spectra. However, experimental methods could be carried out to transform the product of cyclisation into intermediates that would prove its original structure, as shown below in Scheme 86.



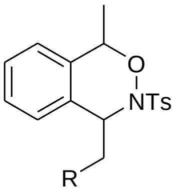
Scheme 86: Transformations to prove heterocyclic structure.

On cleavage of the N-O bond (indicated in red) of the above heterocycles **159** and **202**, the resultant amino alcohols **199** and **203** can then easily be either acylated or oxidised at the hydroxyl moiety to give the products shown above in Scheme 86. In the case of the desired structural isomer **159**; formation of the acetate **200** from the amino alcohol **199** would cause a ~1 ppm shift in the peak that corresponds to the CH_2 α to O, and oxidation would give a characteristic aldehyde **201** resonance. However, in the case of the product from the unwanted N-O bond isomerisation **202**; formation of the acetate **204** would cause a ~1 ppm shift in the peak that corresponds to the CH α to O, and oxidation would give a ketone **205**, so no aromatic aldehyde resonance would be visible around 10 ppm.

Although this was a brief initial investigation, it facilitated the optimisation of some important transformations that will be utilised in the following route towards models of the Histrionicotoxin core structure. This project of building morpholine rings onto existing cylic skeletons was then passed over to be pursued as a final year MChem assignment.

In conclusion, it was previously thought that if the hydroxylamine group was in an allylic (or similarly stabilised, in this case benzylic) position, then it could be likely that some degree of rearrangement would occur under the acidic cyclisation conditions, due to the stability of the carbocation that would form from cleavage of the carbon-oxygen bond. However, it was found that by using a less aggressive acid catalyst in a dilute reaction mixture cooled in an ice bath, this novel cyclisation method was successful, and exhibited no such rearrangement issues. It would now be possible to prove the wider utility of this particular reaction by trialling the Suzuki coupling with a selection of boronic acids, to give heterocycles with a variety of substituents. A phenyl substituent in this position has already been successfully installed. An alternative to the Suzuki couplings could also be investigated, for example the Wittig olefination.

As an extension, the scheme could be trialled with a methyl group in the benzylic position α- to the oxygen (Figure 18), to see if the cyclisation method would still be successful even with the possibility of forming a further stabilised secondary carbocation.



206

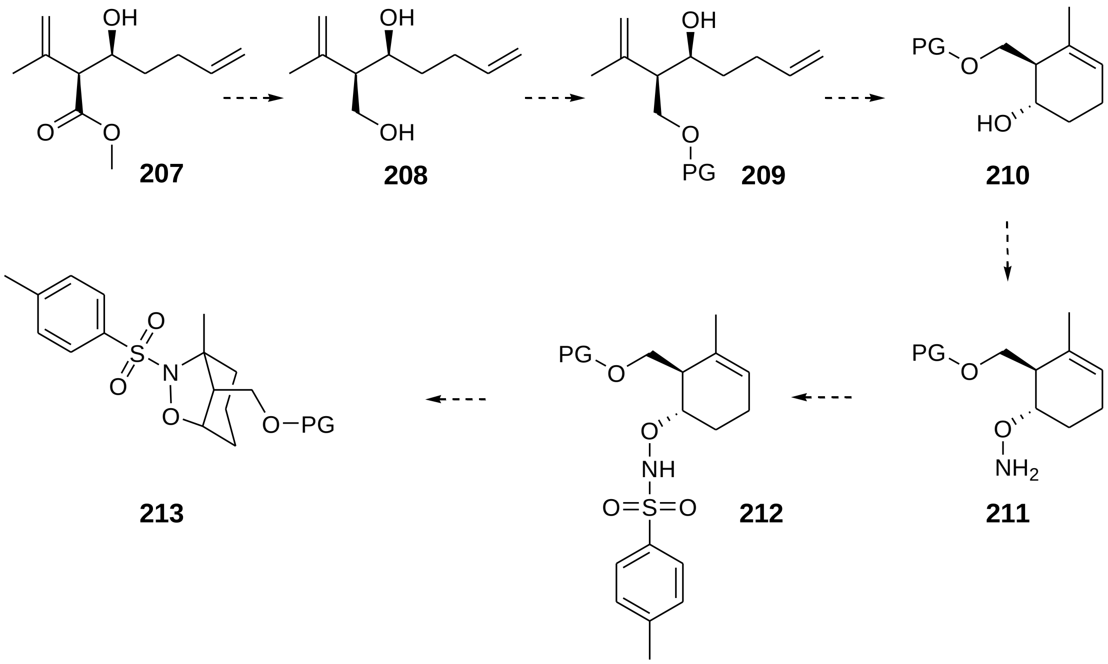
Figure 18: Proposed heterocyle

The fact that the key acid-catalysed intramolecular hydroamination step was successful provides an excellent basis for the transannular equivalents that are to be carried out. Furthermore, the perfected tosylation conditions can be used to efficiently synthesise the hydroxylamines that are protected with the electron-withdrawing group, that are required for the subsequent transannular cyclisations to give the isoxazolidine precursors to the histrionicotoxins.

4.22 Racemic model of the simplified Histrionicotoxin core.

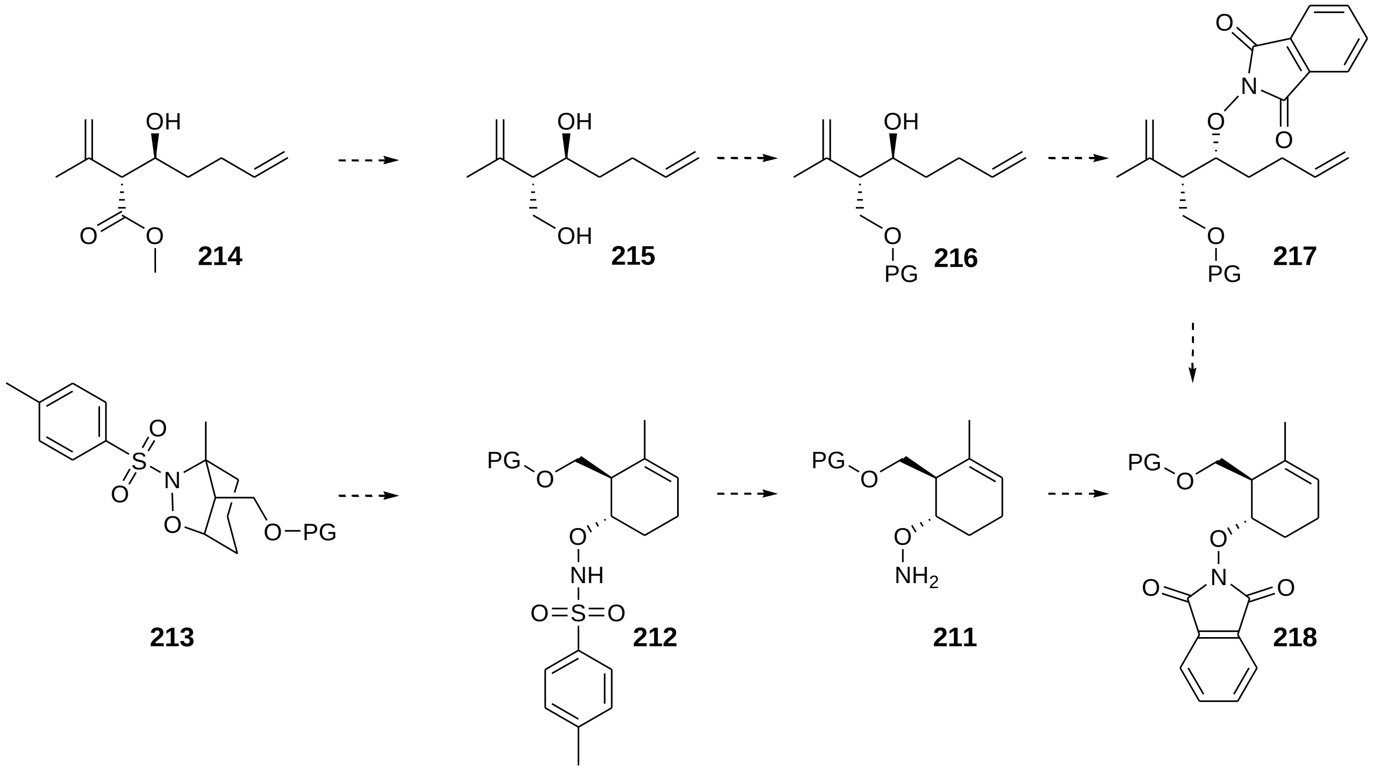
Due to the complexities involved in synthesizing a single enantiomer of a chiral natural product, especially when the key steps are being attempted for the first time, it was decided to first focus on a simplified racemic model, with one of the side chains of the transannular precursor simplified to a methyl group. Synthesising this methyl model **213** would allow all of the steps up to the formation of the spirocycle to be established, before optimising them in a chiral synthesis. The projected Schemes 87 and 88 below indicate the relative, not absolute, stereochemistry and lead to the initial target precursor **213** of the core of Histrionicotoxin. A standard disconnection of the required cyclohexene ring **211** indicated that a route utilising Grubbs' metathesis would be suitable and allow the scheme to begin from a relatively simple straight chain starting material.

In both schemes shown below, from the initial hydroxyl esters the diol functionality can be introduced with a reduction reaction, followed by selective protection of the primary alcohol moiety before the aforementioned metathesis.



Scheme 87: Proposed synthetic scheme from *syn* hydroxyl ester 207.

Starting from the *syn* hydroxyl ester **207**, as above in Scheme 87, the ring substituents have the desired relative stereochemistry after metathesis, and so a transformation to the hydroxylamine **211** that does not involve inversion of that stereocentre is required.



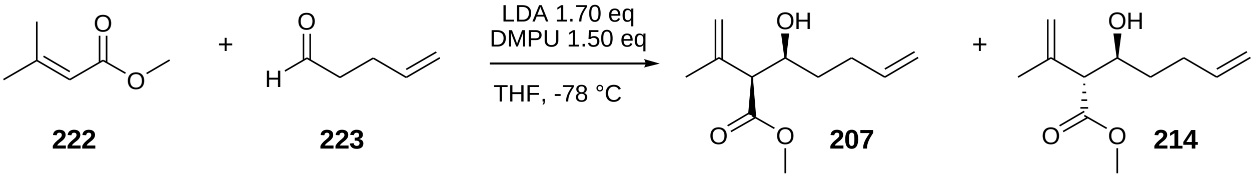
Scheme 88: Proposed synthetic scheme from *anti* hydroxyl ester 214.

In contrast, starting from the *anti* hydroxy ester **214**, as above in Scheme 88, the ring substituents would not have the desired relative stereochemistry on methathesis, so the stereocentre of the secondary alcohol **216** needs to be inverted. A Mitsunobu reaction using

N-hydroxylphthalimide would effect this, and also install the requisite hydroxylamine functionality **217**. This would, however, introduce an additional deprotection step to give the free hydroxylamine **211**.

A single reaction yields both of the starting material hydroxy esters **207** and **214**, pictured in the above schemes, which can then be separated chromatographically due to their being diastereoisomers. As this reaction was not stereocontrolled towards either the *syn*- or *anti*- product specifically it was preferable to have a purpose for both major products and incur less wastage so early on in the synthesis. Therefore it was decided to trial the above schemes concurrently, to see which methods of hydroxylamine formation and protection yielded the best results overall in reaching the immediate precursor **212** of the key cyclisation step.

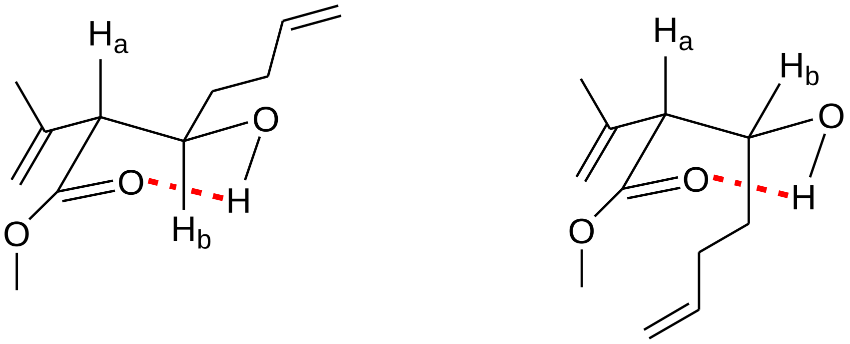
This first stage to synthesise the hydroxyl-esters **207** and **214** featured a dienolate condensation with an aldehyde **223**, as shown in Scheme 89. The deconjugative α-alkylation of α,β-unsaturated esters has been studied in simple systems.[86] In a general example, treatment of the unsaturated ester **222** with lithium diisopropylamide at -78 °C results in formation of the dienolate, which upon exposure to a carbonyl compound **223** and quenching of the reaction, results in isolation of the corresponding homoallylic alcohol esters **207** and **214**.[87] Without the 1:1 complexation of the LDA to DMPU (or HMPA) the base employed for these reactions might also act as a nucleophile and conjugatively add to the unsaturated ester **222** at a rate competitive with proton abstraction.[88] The addition of DMPU (preferable to HMPA which is carcinogenic) 30 minutes before the dienolate formation results in an essentially non-nucleophilic form of LDA, which only acts as a base towards the unsaturated ester **222** and permits high yielding mono-alkylation at the α-carbon atom of this ester. With this knowledge in hand the reaction was carried out on a multi-gram scale. In the literature, in those cases where diastereoisomers were generated, approximately a 1:1 mixture of aldols was observed.[87]



Scheme 89: Hydroxy ester diastereomers formation.

The combined isolated yields of the products **207** and **214** was 60%, which was moderate but well within the expected literature range of similar reactions of 47-91%.[87] Also, the separated diastereoisomers were very pure according to NMR spectra, despite running particularly close on the chromatography column. Initial assignment by studying the spectra identified the diastereoselectivity of the reaction, with the *syn* diastereoisomer **207** as the minor constituent of the product mixture, accounting for an isolated 13% of the entire theoretical yield. The *anti* diastereoisomer **214** was therefore the major product, with an isolated yield of 47%.

Assignment from the NMR spectra was made possible by several studies which have shown that the well-known relationship between the dihedral angle of adjacent C-H bonds and the spin-spin coupling constants of the protons can be used to obtain information about the relative conformations of a pair of diastereoisomers.[89,90] The following conclusions may be drawn for this type of diastereoisomer in non-polar aprotic solvents: (1) the two diastereoisomers exist as intramolecularly hydrogen bonded structures with a six-membered ring containing the hydrogen bond in a chair conformation, and with the maximum number of substituents equatorial; (2) in all cases the vicinal coupling constant, J_{ab}, is larger (typically 6-9 Hz) for the *anti* isomer (with trans diaxial protons H_a and H_b) than for the *syn* isomer (typically 2-4 Hz). This coupling constant difference is diminished when the hydrogen bond is disrupted by measuring the ^{1}H NMR spectrum in a protic solvent.[91] The hydrogen-bonded chair structures that would be formed by the diastereomeric products of this first reaction are shown in Figure 19 below.



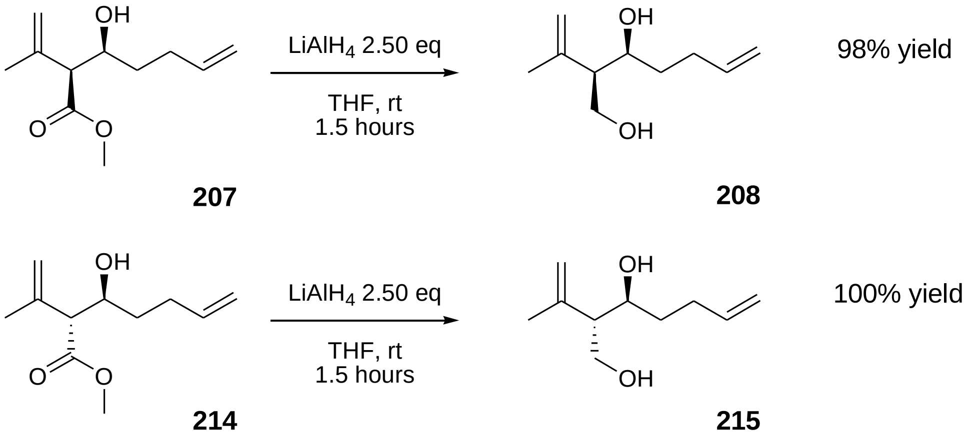
anti *syn*

Figure 19: Hydrogen bonded chair conformations of diastereoisomers 214 and 207.

It had also been observed in the ^{13}C NMR spectra that the carbinol (CH_bO) and methine (CH_a) carbons experienced an upfield shift for the *syn*-isomer relative to the *anti*-isomer.[92]

The major product was assigned as the *anti*-diastereoisomer **214** due to its larger coupling constant $^{3}J_{Ha,Hb}$ of 8.9 Hz observed at the H_a doublet, compared to the coupling constant $^{3}J_{Ha,Hb}$ of 7.1 Hz seen at the equivalent peak in the spectra of the *syn*-diastereoisomer **207**. This was a smaller difference than had initially been expected in order to confidently assign the stereochemistry, however in a similar literature example it had been shown that this resonance from the *syn*-isomer could exhibit a coupling constant as high as 8.0 Hz.[87] Furthermore, as well as the fact that in all known examples the *syn*-isomer exhibited a coupling constant less than the *anti*-isomer, the relevant comparable signals in the ^{13}C NMR spectra were also in agreement with this assignment. In the diastereoisomer assigned as *syn*, the peaks of interest were at 58.9 ppm (CH_a) and 68.8 ppm (CH_b), which were indeed shifted upfield compared to those of the *anti*-isomer which were at 59.7 ppm (CH_a) and 70.2 ppm (CH_b). Identities of the preliminary compounds of the proposed syntheses in hand, the next stage was to reduce them to their respective diols.

A straightforward lithium aluminium hydride reaction was chosen for the subsequent reductions, which are outlined in Scheme 90 below.

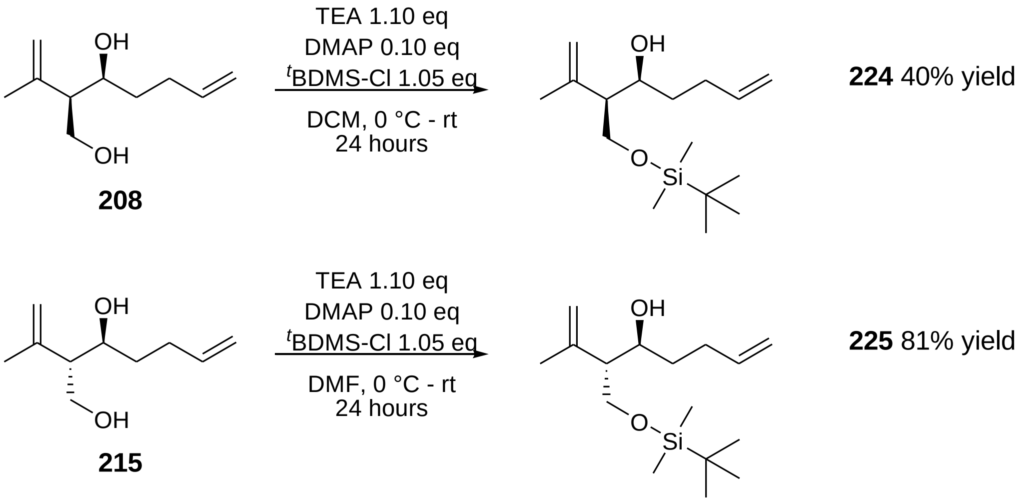


Scheme 90: Hydroxy ester reduction.

This reaction went without a hitch in both cases, as can be seen above from the excellent yields. A crossroads was then met in the syntheses, where the choice arose to either metathesise the free diols, or to first protect the primary hydroxyl function. It was decided to trial both of these scenarios in order to ascertain any differences in the overall yields and success of the reactions.

Addressing the protection of the straight chain diols first, it was thought a bulky silyl protecting group would be appropriate to ensure selectivity. The nature of the protecting group (shown in the retrosyntheses as PG) used for the protection of the primary alcohol is critical to these synthetic schemes. This group must be stable to both strongly acidic and strongly basic conditions, for the acid-catalysed cyclisation and amination steps respectively. If this group is deprotected under either of these reaction environments then either the amination or the cyclisation will not achieve the correct selectivity. A primary alcohol will be aminated faster under the conditions used, and an unprotected alcohol will be more likely to attack the olefin than the nosyl-protected nitrogen in the subsequent cyclisation.

A method for protecting group introduction was employed that had been used on a similar diol in the literature,[93] that utilised TBDMS chloride to protect the primary alcohol, leaving the secondary alcohol free to react. The conditions are shown in Scheme 91 below, with a lower isolated yield being achieved for the *syn* example **224** - possibly due to it being the first trial and not using the optimal solvent, or due to steric reasons.

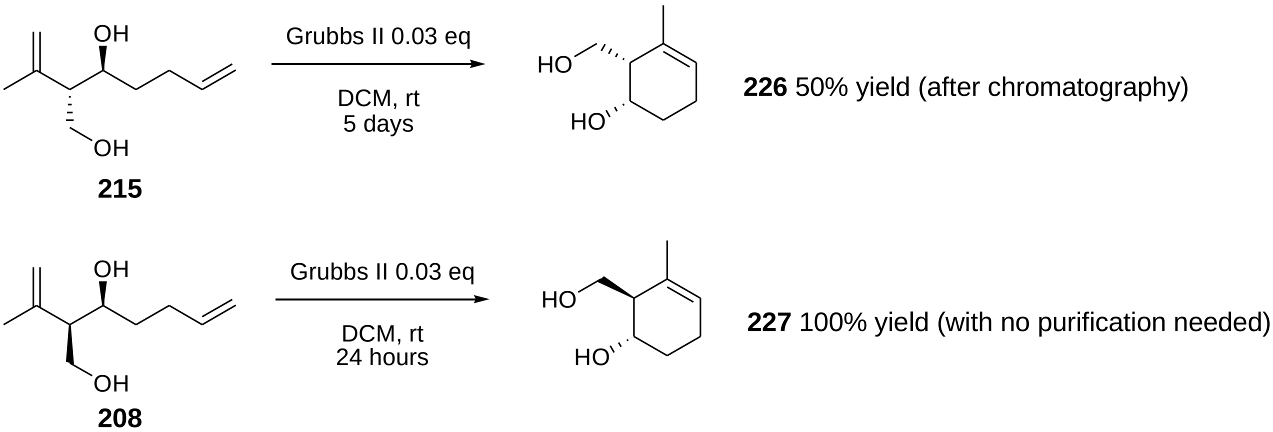


Scheme 91: Silyl protection of the primary alcohol groups.

The reactions were successful, with a good conversion to the desired products and no unwanted protection of the secondary alcohol moieties were observed. The alternative path for these straight-chain diol starting materials **208** and **215** was, as discussed, to first subject them to ring-closing metathesis.

Of the three categories of olefin metathesis, the most widely used is ring-closing metathesis.[94] Here, two terminal alkenes from the same molecule react with the catalyst to generate a cyclic olefin, releasing a smaller olefin. Ring-closing metathesis reactions can proceed to completion partly because the volatile by-product is removed (ethene), pushing the equilibrium away from the reverse process. If the catalyst used is ruthenium based, it may be used with substrates that carry an alcohol, a carboxylic acid, or an aldehyde; but can be rendered inactive in the presence of structurally exposed amines and phosphines.[94] Grubbs' catalyst is a ruthenium carbene complex, and there are two generations of the reagent available which are compatible with a wide range of solvents. For these reasons, Grubbs' Catalysts are extraordinarily versatile, with the second generation catalyst boasting both higher activity and an increased stability.[95]

With the fact that it would be compatible with diols in mind, and because it had been frequently used within the group, a simple ring closing metathesis using Grubbs' second generation catalyst was chosen to form the cyclic diastereomeric diols **226** and **227**, as shown in Scheme 92 below.



215

226 50% yield (after chromatography)

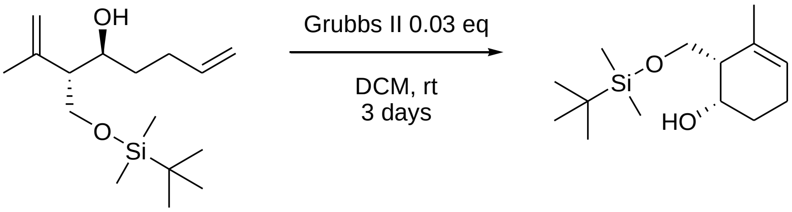
208

227 100% yield (with no purification needed)

Scheme 92: Ring closing metathesis of free diols.

The same catalyst loading of 3 mol% was used for each reaction, however the metathesis of the *anti* straight chain diol **215** did not reach completion within 24 hours and so was left to stir at room temperature whilst other reactions were carried out. The lower yield of this reaction compared to the quantitative yield achieved from the *syn* diol **208**, was due to the fact that a trace of residual starting material had to be removed using column chromatography, and unfortunately these diols were found to stick quite resolutely to the silica gel. As this reaction was not repeated, it was not ascertained whether the *anti* straight chain starting material **215** was less reactive towards the metathesis or if the lower yield had been caused by an issue with the catalyst.

Metathesis of the protected *anti* straight chain diol **225**, using the same method as above, went cleanly to completion as shown in Scheme 93 below.

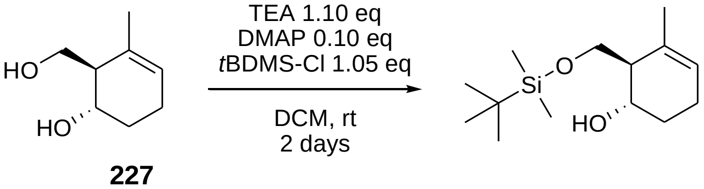


225

228 100% yield

Scheme 93: Metathesis of the protected *anti* straight chain diol.

The other diastereoisomer **229** was synthesised by protecting the cyclic *anti* diol **227**, using the same method as for the equivalent straight chain diol as shown below in Scheme 94.



227

229 40% yield

Scheme 94: Silyl protection of the *anti* cyclic diol.

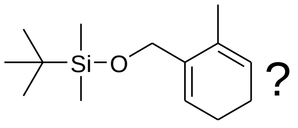
There did not seem to have been much consistent variance in the combined yields of the protection and metathesis steps depending on the order in which these transformations were carried out for either diastereomer.

The mono-silylprotected *anti* diol **229** was now ready to be taken on to the significant O-N bond forming step, leaving the relative stereochemistry of the substituents intact. As was discussed in the introduction to Chapter 3 (page 37) the most appropriate method for this was thought to be an electrophilic amination using an oxaziridine reagent. However, it was decided to first refine this reaction on a simpler model (to be discussed in section **4.23**), to obtain suitable conditions for this type of substrate. This was thought to be the best course of action as the protected diol **229** was more highly functionalized than those in the literature aminations.

The alternative mono-silylprotected *syn*-diol **228** was also ready to be taken on to the hydroxyl amine forming step, although in this case with inversion of the stereocentre at the secondary alcohol moiety. As was discussed in Chapter 2 (page 27) the most appropriate method for this was thought to be a Mitsunobu reaction. As the desired product was a free, unprotected *O*-alkyl hydroxylamine, the phthalimide protected product would then need to be deprotected. The option was also available to attempt the Mitsunobu reaction on the straight chain mono-silylprotected *anti*-diol **225** and metathesise afterwards, and this was undertaken first. The initial experiment was carried out under the conditions from General method **B** (page 110), which had been successful in several other instances within this project. These did include the transformations of secondary alcohols, however in previous reactions the alcohols had been propargylic or benzylic. Unfortunately, this conversion was not to be as straightforward, and only starting material was recovered from the reaction mixture.

It was decided to retrial the reaction using Mitsunobu conditions that had been successful in the literature for a more structurally similar substrate. Employing modifications from the literature,[96] for a similarly substituted secondary alcohol; increasing the reagent loading, and carrying out the reaction in dichloromethane with the additions at -34 °C, also led to no identifiable product being isolated from the purification column. It was found that the only ^{1}H NMR spectra of a set of column fractions that did show any peaks that may have corresponded to the desired product, was obscured by hydrazine residue from the DIAD reagent. In the next slightly larger scale trial, it was decided to utilise di(4-chlorobenzyl)azodicarboxylate (DCAD) as an alternative to DIAD. Most of the byproduct hydrazine formed in the Mitsunobu reaction when using DCAD can be precipitated from dichloromethane. The polarity of the residue is also quite different from those arising from DIAD/DEAD which facilitates separation of the products more readily during chromatography.[42] Regrettably, it could then be seen in the NMR spectra of the reaction mixture, after exposure to the reagents overnight, that the starting material was unchanged.

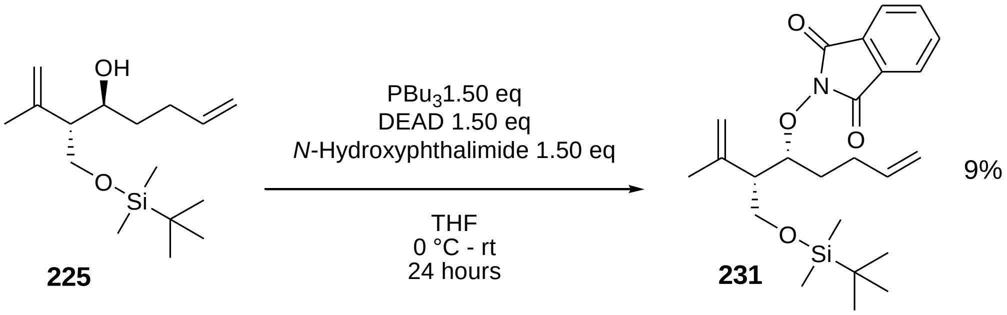
A method was found that was hoped would be suitable to trial on the corresponding metathesised cyclic protected diol **228** instead. Using conditions from the literature,[97] for a similarly substituted ring, this time employing DEAD, were initially inconclusive. Trialling the reaction again using increased reagent loading did lead to a complete conversion of the starting material. However, on detailed examination of the product analysis, it could be seen that the product of the transformation was not as desired, and it was proposed that it was the result of an unexpected elimination (Figure 20).



230

Figure 20: Suspected elimination product.

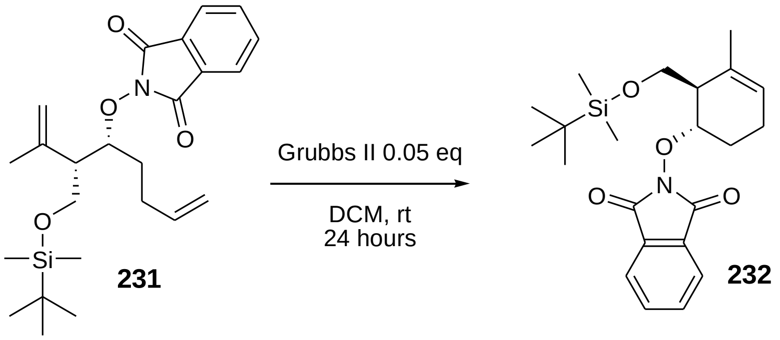
The pre-metathesis intermediate **225** was exposed to the same conditions that had provoked this elimination, and in this case no such loss of the substituent was observed. In fact, at first the proton NMR spectra of the crude product mixture seemed to show unreacted starting material and reagent residues. However, on carrying out column chromatography to recover the starting material, a small amount (5% yield) of the desired phthalimide protected hydroxylamine product **231** was recovered! This was obviously not an ideal result, but one that was seen as positive after many previous futile attempts. To endeavour to build upon this, further experiments were carried out, one with the same ratio of reagents to starting material but heated to 40 °C, and the other with five molar equivalents of each reagent. These trials did not return an increased yield of the desired product. Substituting the standard triphenylphosphine for the more reactive tributyl phosphine, did allow for a small increase in productivity, from 5 to 9% of the theoretical yield. A more modern alternative to DIAD and DEAD, called TMAD, was tested for suitability but was not appropriate in this instance.



Scheme 95: Mitsunobu reaction.

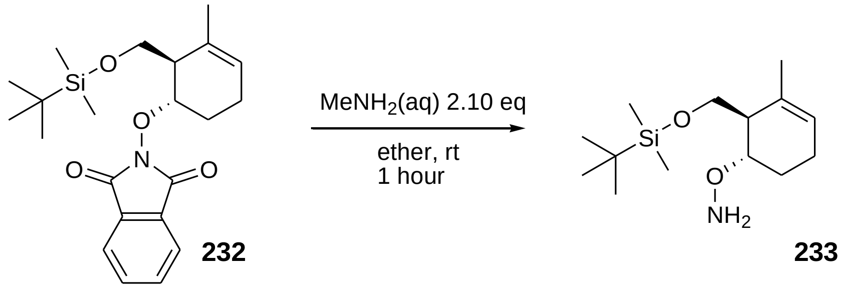
Combining the small amount of phthalimide product **231** from the most successful trial, conditions of which are given in Scheme 95 above, with that that had already been isolated, yielded enough of the hydroxylamine to continue on with this planned synthetic route.

Ring-closing metathesis of **231** was then successfully carried out as before, as shown in Scheme 96 below, to give the desired cyclohexene structure **232**.



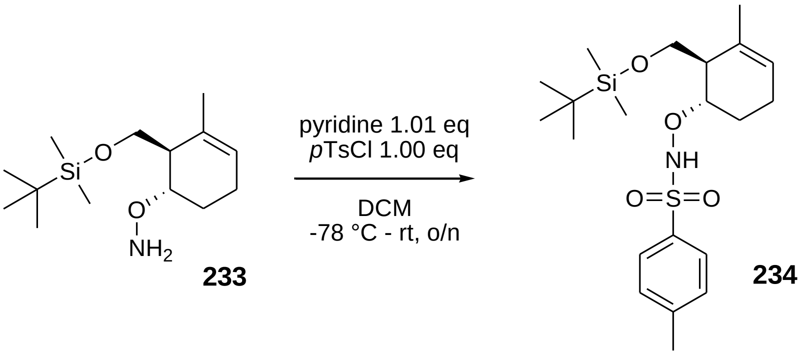
Scheme 96: Metathesis of the phthalimide protected hydroxylamine.

A quantitative yield was achieved, with no sign of the elimination product **230** that had been the unwanted result of carrying out the metathesis and Mitsunobu reaction in the reverse order. Standard dephthaloylation conditions were then employed to yield the free hydroxylamine **233** as shown in Scheme 97 below.



Scheme 97: Dephthaloylation.

The above reaction was also very high yielding, with the deprotection going to completion quickly and cleanly. The tosylation that followed utilised the method that had been optimised earlier in this Chapter (page 67), to give the intermediate **234** that was set up for the key step transannular cyclisation.



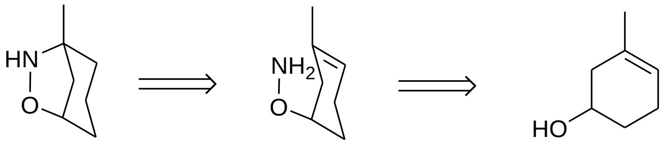
Scheme 98: Tosylation.

The product **234** did contain a small amount of excess tosyl residues, but was of sufficient purity to take on to trial acid-catalysed cyclisations. Initial trials using concentrated sulphuric acid caused partial conversion to the cyclised product, when the reaction was carried out in an ice bath for 30 minutes. This could be seen by studying the proton NMR spectra of the crude product mixture, where the alkene resonance could be seen to be diminishing to be replaced by a new CH_2 signal, along with the expected shift in the aromatic peaks of the tosyl group.

As the reaction was carried out on a very small scale (~10 mg), due to the difficulties of bringing product through to this stage, purification could not be carried out to lead to full analysis. It was decided at this juncture to revert to a simpler model of the core structure to address these issues one at a time. These racemic syntheses, the proposed schemes of which were outlined in Scheme 87 and Scheme 88, have raised some important questions and also provided significant information on the behaviour of these compounds that will be highly beneficial for the following chemistry.

4.23 Simplified model synthesis

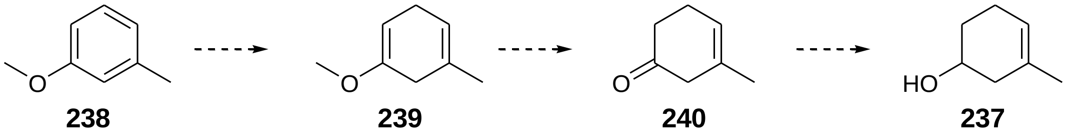
The retrosynthesis from the transannular isoxazolidine intermediate **235** (Scheme 99), follows the same disconnection as with the previous synthesis, only with the primary alcohol side-chain removed for simplicity. In synthesising the hydroxylamine **236**, conditions can be optimised for the direct amination of the alcohol using oxaziridine chemistry.



235 **236** **237**

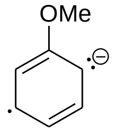
Scheme 99: Simplified model retrosynthesis.

To make the cyclohexenol intermediate **237**, instead of using the disconnection across the alkene that would again lead to a scheme utilising Grubb's metathesis, it was found that it could be synthesised in three steps from readily available 3-methyl anisole **238**, exploiting the ready-made six carbon cyclic skeleton. The proposed synthetic scheme towards the cyclohexenol intermediate **237** is shown in Scheme 100 below.



Scheme 100: Proposed synthetic scheme.

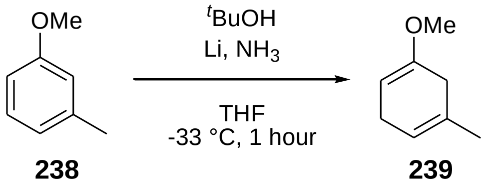
Three straightforward steps utilising well established chemistry gives the cyclohexenol reactant **237** for the key amination step. The first transformation of the above scheme was effected with a Birch Reduction, which involves the reaction of dissolving metals in ammonia with aromatic compounds to produce 1,4-cyclohexadienes, and was discovered by Arthur Birch in 1944.[98] The reaction involves an initial radical anion resulting from the introduction of an electron from the liquid ammonia solution of solvated electrons formed by dissolution of lithium or sodium metal. This radical ion **241** (Figure 21) is protonated by the *tert*-butanol co-solvent and is then further reduced to a second carbanion.



241

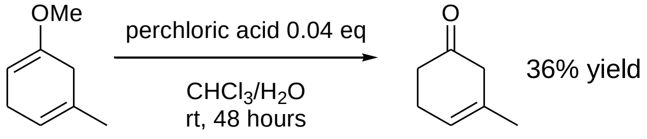
Figure 21: Anisole radical ion.

Finally, the carbanion is protonated using a second proton to afford the non-conjugated cyclohexadiene product. The regiochemistry of the final product is directed by the substituents present. In the case of electron-donating substituents such as the methoxy group (Figure 21), the dihydro-aromatic is formed with the maximum number of substituents on the residual double bond, as shown above. This avoids carbanion formation adjacent to the methoxy group and gives the correct cyclohexadiene **239**. It was decided to use lithium metal, as it had been reported that lithium leads to better yields that sodium.[99] The experimental conditions that were employed are shown in Scheme 101 below.



Scheme 101: Birch reduction.

The isolated yield of the cyclohexadiene **239** was 74%, and the product was very clean with no need for purification. Acid hydrolysis of the Birch reduction product **239** then gives the desired cyclohexene **240** with the double bond occupying the required position in the ring. Perchloric acid was used as it had been applied in the literature to the transformation of a structurally similar starting material.[100] Care is needed in carrying out the reaction in order to not produce any of the conjugated enone, and after the reaction below none was seen. However, as can be seen by the yield of the reaction shown in Scheme 102, the reaction was not as successful as had been expected.



239 **240**

Scheme 102: Acid hydrolysis.

This was the purified yield after carrying out column chromatography, so the fact that it is low could possibly be due to instability of the product on silica gel, or its volatility. However, although the yield was disappointing, as the reaction had been carried out on a multi-gram scale there was a sufficient amount of the cyclohexenone **240** to carry on with the proposed scheme.

The reduction to cyclohexenol **237** was accomplished in an isolated yield of 78% using a solution of lithium aluminium hydride as shown below in Scheme 103, followed by a another chromatographic purification.

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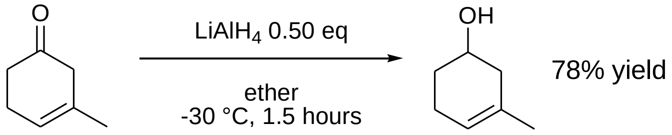
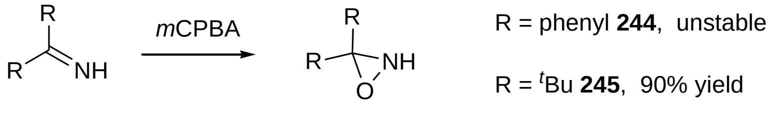


240 **237**

Scheme 103: Ketone reduction.

With the cyclohexenol intermediate **237** in hand, it was time to trial the key direct amination step with, as was previously discussed, an oxaziridine reagent. As the desired product was a free, unprotected *O*-alkyl hydroxylamine, the oxaziridine that was to be synthesized had to also have no *N*-substituent. The first example of such an oxaziridine unsubstituted at nitrogen was published in 1961,[101] and its ability to transfer its N-H group was discovered shortly afterwards.[102] The majority of known oxaziridines had been prepared from the reaction of a Schiff's base with a peracid.[49] However, a less general access to oxaziridines is possible by the electrophilic amination of carbonyl compounds.[103]

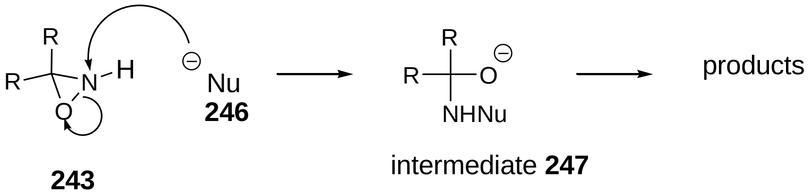
N-Unsubstituted oxaziridines are extremely reactive towards nucleophiles and are usually formed in solution and reacted further without isolation. However, in the absence of nucleophiles the *N*-unsubstituted oxaziridines are stable, even to extended heating.[49] The oxaziridines **243** in Scheme 104 below were obtained by the peracid procedure from imines **242**. The diphenyl example **244** was unstable at room temperature, but the *tert*-butyl oxaziridine **245** could be purified by high-vacuum distillation.[104]



242 **243**

Scheme 104: Oxaziridine synthesis.

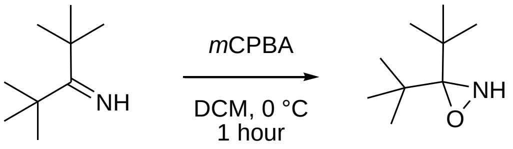
Nucleophiles **246** attack the N-H group of the 3-membered ring **243** with simultaneous bond formation and cleavage of the N-O bond, as shown below in Scheme 105.[49]



243

Scheme 105: Mechanism of amination.

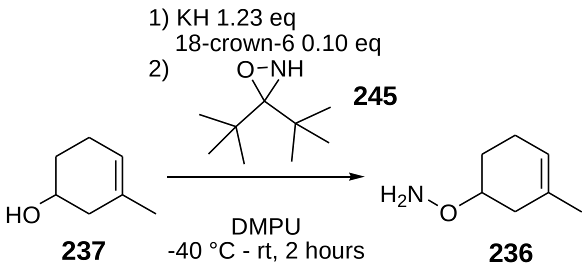
The desired outcome is that upon protonation of intermediate **247** a hemiaminal is formed which rapidly disintegrates to the corresponding ketone and aminated nucleophile product. The specific method that was chosen to synthesise the required oxaziridine **245** is shown in Scheme 106 below, and was taken from a more recent publication.[47] Since *N*-unsubstituted oxaziridines **245** react with almost every nucleophile, they must be prepared and handled in inert solvents, such as the anhydrous dichloromethane that was used in Scheme 106 below.



248 **245**

Scheme 106: Oxaziridine formation.

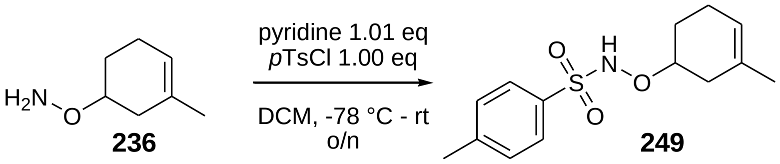
As was discussed in Chapter 3 (page 37), in 1999 a report was published that outlined the reaction of the above oxaziridine **245** with a range of potassium alkoxides in DMPU and in the presence of 18-crown-6 to provide free *O*-alkylhydroxylamines in 10-86% yields.[47] This reaction was carried out on the cyclohexenol **237** using the conditions shown in Scheme 107 below.



Scheme 107: Hydroxylamine formation.

After a work up to try and remove the majority of the high-boiling DMPU solvent, ^{1}H NMR spectroscopy could be carried out on the crude product mixture to determine the yield of hydroxylamine **236**. Apart from some residual DMPU there were no other impurities present and the transformation of the starting material to the hydroxylamine **236** was complete. As expected, there was an upfield shift observed of the methine signal α to oxygen compared with that present in the cyclohexenol starting material **237**. The calculated yield from the proton NMR spectra of the crude product was 42%, well within the literature expectation of 10-86%. This yield was moderate, possibly due to the size and polarity of the product, but no additional deprotection step was needed, as the free hydroxylamine had been formed directly. As the yield had been calculated, there was then no need to isolate the free hydroxylamine from the DMPU and it could be taken straight through to protection of the nitrogen.

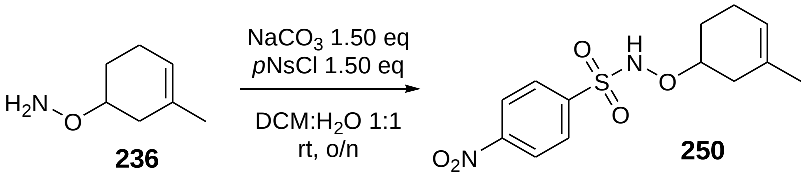
It was also thought that forming the necessary sulphonamides would not be affected by the residual DMPU that was present. Tosylation was trialled initially, using the method that had been optimised earlier in this chapter (Scheme 83), to give sulphonamide **249**.



Scheme 108: Tosylation.

The reaction went to completion overnight, although column chromatography had to be carried out to remove excess tosyl residues and the residual DMPU. The isolated yield was then 43%, which was below expectations, so it was decided to also trial nosylation to see if this delivered a better yield. Also, harsh conditions are required to remove tosyl groups from amines. The deprotection typically involves the use of reducing metals in ammonia, fluoride or electrochemical reduction, all of which show poor chemoselectivity. This issue was addressed in 1995 by the Fukuyama group. They developed the nosyl protecting groups, which have similar electron-withdrawing effects to the tosyl group, but can be selectively removed by the mild *ipso* attack of thiolate.

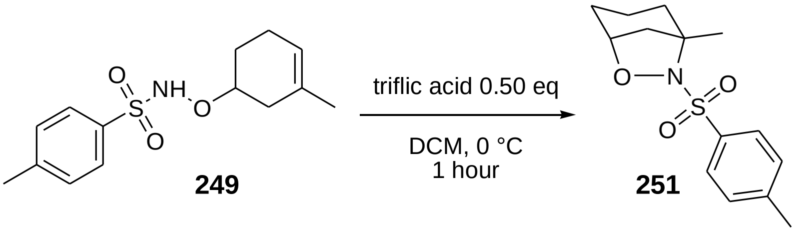
A biphasic method was chosen for nosylation of hydroxylamine **236**,[105] using *p*-nitrobenzenesulphonyl chloride as shown below in Scheme 109.



Scheme 109: Nosylation.

The reaction went to completion overnight and the residual impurities were removed by column chromatography. The isolated yield of the sulphonamide **250** in this case was 61% which was an improvement on the yield of tosyl protection. The tosyl- and nosyl-protected hydroxylamines **249** and **250** could then be exposed to the acidic hydroamination conditions to facilitate the transannular cyclisations. Comparitive studies that have been undertaken within the group to investigate nosyl and tosyl protected amines in this type of cyclisation reaction have shown that there is no significant difference in reactivity between the two.

The key transannular cyclisation of the tosyl-protected intermediate **249** was carried out by adding it to an ice-cold, anhydrous dichloromethane solution of triflic acid (0.50 molar equivalents). After one hour at 0 °C the cyclisation had gone to completion (Scheme 110), and column chromatography removed the small base-line impurities to give an isolated yield of 85% of the transannular product **251**.



Scheme 110: Transannular cyclisation.

This was an excellent result, and the novel ring system was fully characterised to prove the success of the reaction. Below are corresponding sections of the NMR spectra of the starting material **249** (top) and cyclised product **251** (bottom), for comparison. They show that the signals labelled H_a (5.34, s) and H_b (4.37-4.24, m) in the spectra of the cyclohexene **249** are no longer present in the spectra of the product **251** (indicated by the red arrows), where they have been replaced by the new CH resonance (4.64, t, *J* 5.7 Hz) which unexpectedly took the form of an apparent triplet.

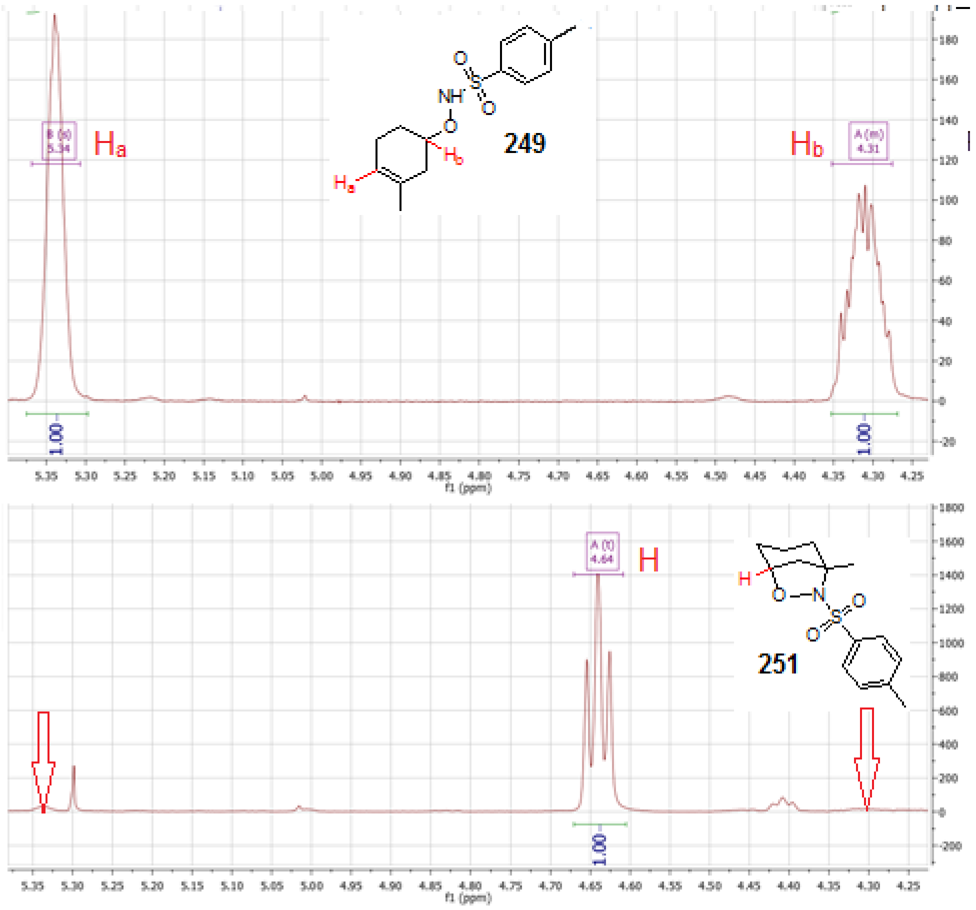
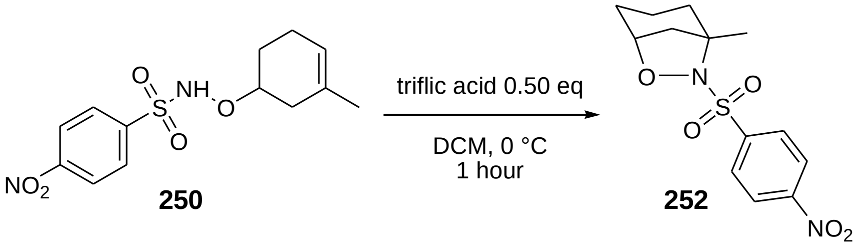


Figure 22: Spectra pre- and post-cyclisation.

The transannular cyclisation of the nosyl-protected intermediate **250** was carried out under the same conditions as the tosyl-protected equivalent above. After one hour at 0 °C the cyclisation had again gone to completion (Scheme 111), and column chromatography removed the small impurities to give an isolated yield of 77% of the transannular product **252**.



Scheme 111: Transannular cyclisation.

As expected, there was no significant difference in reactivity between the two sulphonamide intermediates **251** and **252**. The yield of the above reaction in Scheme 111 was slightly lower, however as well as carrying out the same full analysis as for the previous example (the NMR spectra was very similar to that shown in Figure 22), X-ray crystallography was also performed as this model crystallised on purification. The three dimensional picture that was generated from this is shown in Figure 23 below.

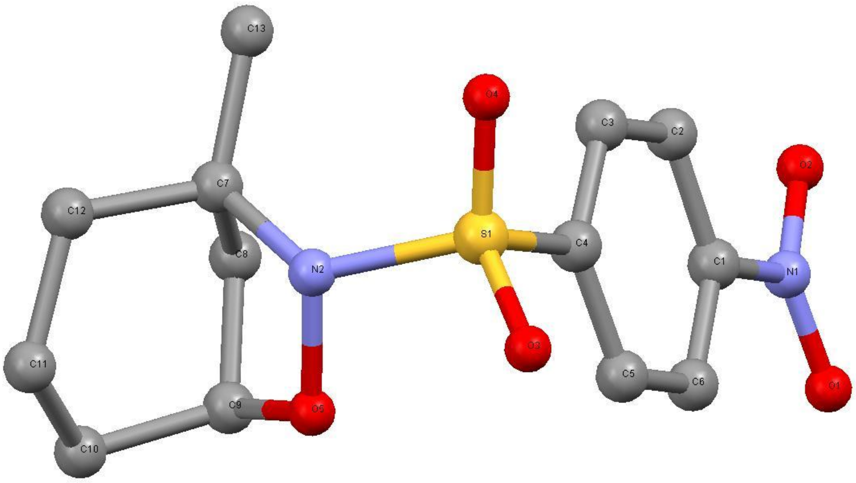


Figure 23: Nosyl-protected transannular cyclisation product 252.

The structure determined (Figure 23), showed the transannular 5-membered ring **252** containing an N-O linkage. The N-O bond was 1.456 Å in length, with the new N-C bond 1.506 Å long (Full details of the data obtained are given in Appendix 2).

This is a novel heterocyclic system, and exemplifies the ease, selectivity and scope of this new transannular acid-catalysed hydroamination methodology.

Using all of the information learnt from the syntheses of the racemic models and the simplified transannular core with no functionalized side chains, it was possible to embark upon a full chiral synthesis towards the target with the option of increasing the complexity of the methyl side chain.

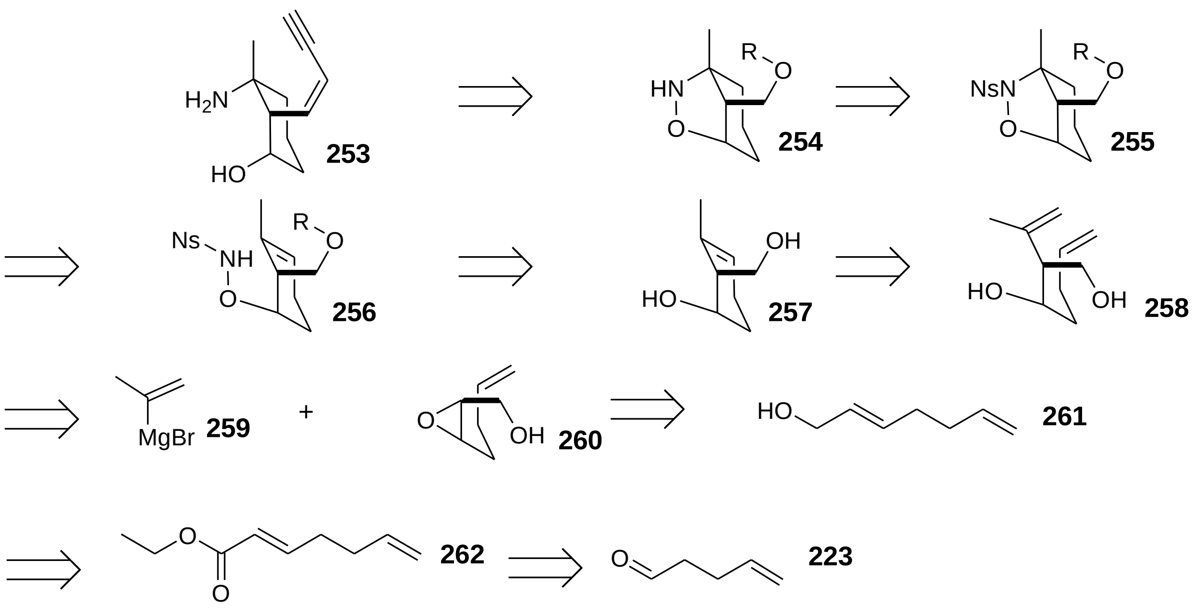
4.24 Chiral core synthesis.

As the previous model substrate **252** (successfully synthesised for the first time as shown in Scheme 111**)** contained no competing functional groups for the acid-catalysed cyclisation, the next model was designed to allow incorporation of another of the side chains needed in the final intermediate. This increased the complexity of synthesis in a stepwise fashion to allow it to be possible to see at which stage, if any, difficulties could arise with the synthetic scheme that needed to be dealt with. As seen previously, Stockman has published a short total synthesis of the precursor (±)-HTX *via* Holmes' isoxazolidine intermediate **147**. It therefore seemed sensible to again use an analogue of Holmes' isoxazolidine **154** as an intermediate in the synthesis of our next model, target **253**, utilising the same retrosynthesis as for the racemic schemes - up until how to form the chiral straight-chain diol **258**.

The retrosynthetic analysis of (±)-HTX model **253** is shown below in Scheme 112. The first step (retrosynthetically) is to synthesise the side chain from the protected alcohol **254** using the Stockman method.[66] The key acid-catalysed cyclisation requires nosyl protection of the amine which is disconnected to expose an *O*-hydroxylamine and olefin in compound **256**, as with the disconnections of the previous substrate models.

The primary alcohol must be chemoselectively protected (R = protecting group in Scheme 112) before the amination step to prevent amination of the primary alcohol in compound **257**. The olefin is then disconnected using a ring closing metathesis to give the di-unsaturated compound **258**. This can be disconnected to give isopropenylmagnesium bromide **259** (in Scheme 112 where only a methyl substituent is desired in this position) and Sharpless epoxidation product **260**. Using an epoxide is an obvious disconnection as it will allow for the correct absolute stereochemistry to be introduced to the synthesis. Also, at this stage, opening the epoxide to form the enantiomeric diol allows for the introduction of a variety of side-chains depending on the Grignard reagent that is used and therefore the degree of complexity that is desired. An alternative to introduce the more complex side-chain that will allow the core spirocycle to be formed onto the nitrogen will be discussed later.

The allylic alcohol **261** is required to produce epoxide **260** by the Sharpless epoxidation, which can be synthesised from the DIBAL-H reduction of α,β-unsaturated ester **262**. The α,β-unsaturated ester **262** can then be synthesised from a Horner-Wadsworth-Emmons type Wittig reaction from commercially available 4-pentenal **223**.

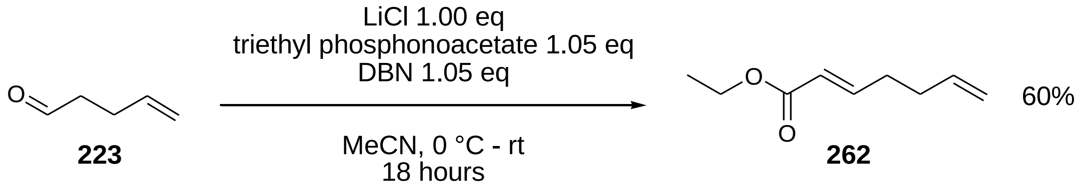


Scheme 112: Retrosynthesis.

The straight-chain diol **258** is structurally the same as in the racemic synthesis. However, in this chiral synthesis the stereochemistry of this intermediate must be absolute, with the diol being obtained as a single isomer. It was for this reason that asymmetric Sharpless epoxidation was chosen as the tool to introduce the correct stereochemistry. The forward synthesis corresponding to the above retrosynthesis (Scheme 112) was chosen as the route begins from commercially available 4-pentenal **223**, and uses well known and reliable reactions to reach the amination precursor.

The first step of this route was to synthesise the diene **262**, and it was decided to use the Masamune-Roush modification of the Horner-Wadsworth-Emmons reaction. In 1958, Horner published a modified Wittig reaction using phosphate-stabilised carbanions, which was further defined by Wadsworth and Emmons, resulting in the Horner-Wadworth-Emmons reaction that reliably transforms aldehydes in to *E*-alkenes.[106] Masamune and Roush went on to develop mild conditions using lithium chloride and DBN,[107] which were employed in this case as these conditions had been successfully used within the group for very similar chemistry.[108]

The reaction was carried out as shown in Scheme 113 below, and went completion after stirring overnight.

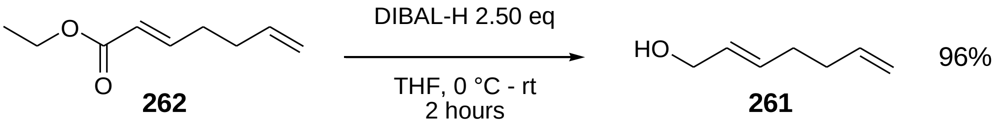


Scheme 113: Diene formation.

As a known compound, it could be seen that the ^{1}H NMR spectra of the ester product **262** was exactly as expected and no further purification was needed after the aqueous work-up. The isolated yield of this multi-gram reaction was 60%, and the product **262** was taken on to the subsequent reduction step.

Due to the desired product **261** being an allylic alcohol, the reducing agent had to be chosen carefully so that complete reduction to the saturated alcohol did not occur. The mild reducing agent sodium borohydride was not suitable as it is not reactive enough to reduce ester groups. Lithium aluminium hydride on the other hand is much more reactive, and although there are examples of it being cautiously applied to this type of reaction in the literature,[109] it was decided to go for a more common reagent. Diisobutylaluminium hydride (DIBAL-H) was chosen as it had been successfully used in the literature for this exact transformation.[110]

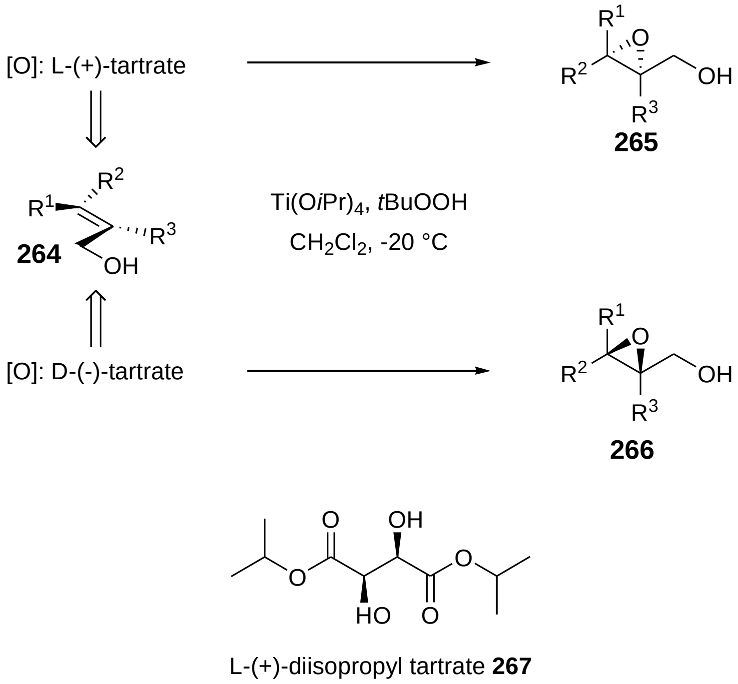
The conditions for this straightforward reduction are shown in Scheme 114 below, and an excellent isolated yield of 96% was achieved.



Scheme 114: DIBAL-H reduction.

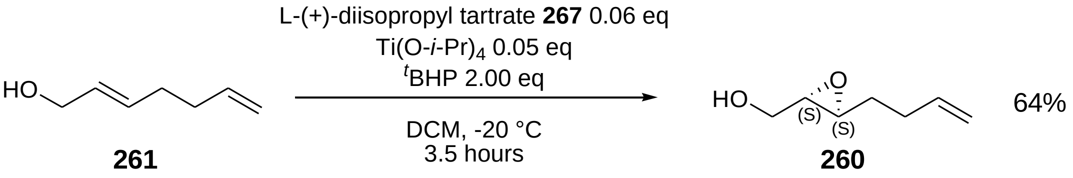
This allylic alcohol **261** was the starting material for the chirality-inducing epoxidation reaction. The reaction of an allylic alcohol with *tert*-butyl hydroperoxide (TBHP) in the presence of Ti(O-*i*-Pr)$_4$ and diethyl tartrate (DET) to form an epoxy alcohol of high enantiomeric purity was introduced in 1980 by the Sharpless group.[111] More recently they reported a simple modification of the original procedure which allowed the asymmetric epoxidation to be carried out with just 5-10% catalyst. The key feature of the catalytic modification was the use of molecular sieves to remove water from the reaction mixture.[112] In carrying out the retrosynthesis it had been calculated which tartrate was required to introduce the correct stereochemistry.

It can be seen in Scheme 115 below that it is L-(+)-diisopropyl tartrate that will lead to the correct product under these conditions.



Scheme 115: Stereoselectivity of epoxidation.

The multipart reaction was carried out under the conditions shown in Scheme 116 below, and an isolated purified yield of 64% was achieved. The very detailed preparation from a Sharpless paper on catalytic asymmetric epoxidation was followed,[112] as it included numerous guidelines on the best way to carry out the additions and complex reaction workup.



Scheme 116: Sharpless epoxidation.

The purified epoxide **260**, for which there was no analytical data in the literature, was fully characterised and found to be very stable to storing for long periods of time. With the desired epoxide available, the regiospecific ring-opening reaction of the epoxide **260** to give the 1,3-diol **258** and invert the stereocenter in the 2-position could be attempted.

At this stage, a sample of the epoxide **260** was also taken to determine the specific rotation of the compound. In stereochemistry, the specific rotation of a chemical compound [α] is defined as the observed angle of optical rotation α, when plane-polarized light is passed through a sample with a path length of 1 dm and a sample concentration of 1 g per ml. It is the main property used to quantify the chirality of a molecular species or a mineral. The specific rotation of a pure material is an intrinsic property of that material at a given wavelength and temperature.

A polarimeter was used to measure the optical rotation of solutions of known concentrations of the novel chiral molecules made in this synthesis, including this epoxide **260**, to contribute to the full analysis, and to allow some comparisons to be drawn to stereochemically similar compounds if the relevant analysis was available in the literature.

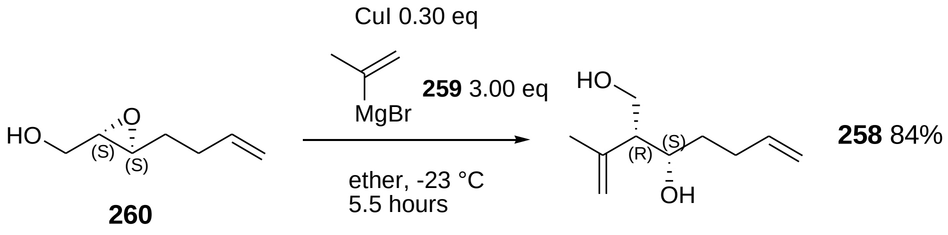
For solutions, the equation below is used:

$$[\alpha]_D^{20} = \frac{\alpha}{l \times c}$$

In this equation, l is the path length in decimeters and c is the concentration in g ml^{-1}, for a sample at a temperature T (given here as 20 °C) and wavelength λ (589 nm, sodium D line). When using this equation, the concentration and the solvent are provided in parentheses after the rotation. The rotation is reported using degrees, and no units of concentration are given (it is assumed to be g/100 ml). The $[\alpha]_D^{20}$ value calculated for the (*S*,*S*) epoxide **260** was -105.3° (c = 3.8, MeOH). A negative value means levorotatory rotation, and this correlates with the literature optical rotation of a similar epoxide, (2*S*-*trans*)-3-propyloxiranemethanol $[\alpha]_D^{25}$ -46.6° (c = 1.0, $CHCl_3$).[112] $[\alpha]_D^{20}$ values will also be calculated for the subsequent chiral intermediates of this synthetic scheme.

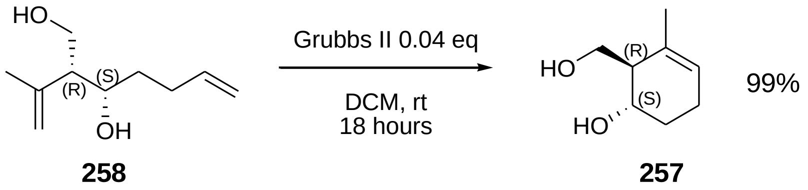
In the next stage of the synthesis it was imperative to ensure that the epoxide opening occurred at the 2- and not the 3-position, to give the desired diol **258** and not a mixture of isomers. A literature method was found where the cuprous iodide catalysed addition of Grignard reagents under carefully controlled conditions took place selectively at C-2, and inverted the stereochemistry at that centre.[113] This method had been shown to provide selectivity even with sterically unbiased epoxides, as it seems likely that the epoxy alcohol group directs the nucleophilic attack at C-2.[114] The selectivity of the reaction is maintained only within a narrow range of conditions. Lower temperatures favoured the 1,3-diol but diminished the reaction rate.

A compromise between selectivity and an acceptable rate can be reached by conducting reactions with vinylic Grignard reagents at -20 to -25 °C. Tetrahydrofuran was found to be an essential cosolvent (although large amounts were found to be inhibitory), which was convenient as in this case the commercial reagent that was to be used was a one molar isopropenyl Grignard solution in tetrahydrofuran. A small percentage of complexing solvent may be necessary to solubilize the reagent.[115] The copper (I) mediated epoxide opening reaction that was carried out using the aforementioned conditions is shown in Scheme 117 below.



Scheme 117: Regioselective epoxide opening.

It can be seen that with this judicious choice of reaction conditions, a selective reaction occurred even though there was a lack of stereochemical bias for attack of the epoxide **260**. The yield of 84% was that of the purified product **258** after column chromatography. It was confirmed as the 1,3-diol (rather than the 1,2-) by spectral comparison to the previously made racemic diols **208** and **215**. This novel chiral diol **258** was of sufficient purity to take on to the subsequent metathesis reaction, again using Grubb's 2nd catalyst (Scheme 118).



Scheme 118: Grubb's metathesis.

A near quantitative yield was achieved, and the lack of impurities from the reaction allowed full analysis of the crystalline product **257** to be carried out without a need for purification. As the cyclic diol **257** was crystalline, it was possible to carry out X-ray crystallography on the sample. The three dimensional picture that was generated from this is shown in Figure 24 below.

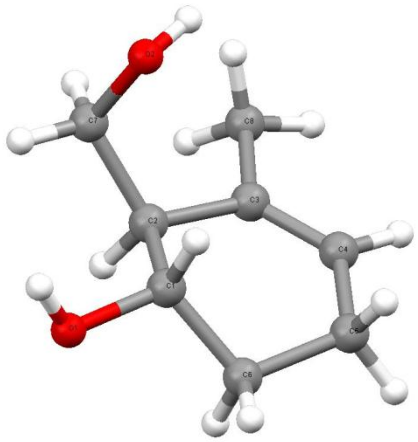
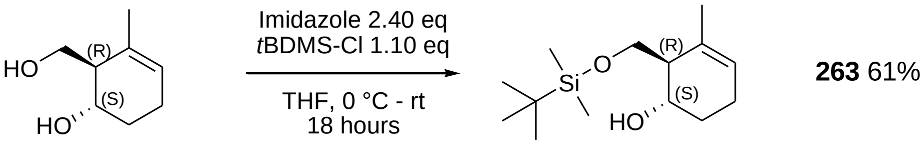


Figure 24: Chiral cyclic diol 257.

It can be seen from the trans-diaxial protons at the C-2 and C-3 positions that the alcohol ring-substituents are *anti* to each other in their relative stereochemistry as desired. The stereocentres at the secondary alcohol and primary alcohol can be deduced to be (*S*) and (*R*) respectively due to the known outcome of the Sharpless asymmetric epoxidation. This proves the reputed configuration of the cyclic diol **257** and therefore the stereochemistry of the preceding straight-chain diol **258** and epoxide **260**. The structure determined (Figure 24), showed the 6-membered ring containing the C=C double bond. The new endocyclic double bond was 1.328 Å in length (Full details of the data obtained are given in Appendix 3). A simple energy minimisation experiment performed using the programme Chem3D Pro calculated the same bond length to be 1.345 Å.

The nature of the protecting group (shown in the retrosynthetic Scheme 112 as R) used for the protection of the primary alcohol is critical to this synthetic scheme. This group must be stable to both strongly basic and strongly acidic conditions, for the amination and acid-catalysed cyclisation steps respectively. If this group is deprotected under either of these reaction conditions then either the amination or the cyclisation will not achieve the correct selectivity. As, previously mentioned, a primary alcohol will be aminated faster under the conditions used, and an unprotected alcohol will be more likely to attack the olefin than the nosyl-protected nitrogen in the cyclisation.

As it had been chosen for the previous analogous racemic syntheses, the protecting group strategy that was trialled first was again to form the TBDMS ether of the primary alcohol moiety. However, in employing the same conditions (as in Scheme 94, page 79), the extent of conversion of the starting material was deemed unsatisfactory, and so a different literature preparation was utilised.[116] Silyl derivative **263** was then obtained in a 61% yield, starting from compound **257**, by treatment with TBDMS chloride and imidazole in anhydrous tetrahydrofuran (Scheme 119).



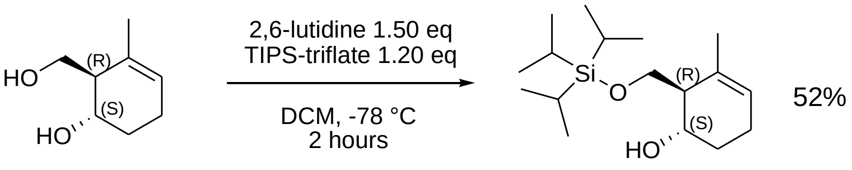
257

Scheme 119: TBDMS protection of primary alcohol.

This isolated yield was an improvement, and a sample of the mono-protected diol **263** was subjected to the amination conditions that had proved successful on the simplified model **237** in Scheme 107 (page 84).

This method was trialled on the mono-silylprotected chiral diol **263**, but unfortunately, due to a presumed deprotection under the reaction conditions to return the diol, the highly polar compound could not be retrieved from the water that is necessary in the work-up to remove the DMPU solvent, and the reaction was unsuccessful. It was decided that this step would be retrialled at a later date, employing a more durable protecting group, as it was later found that deprotection even occurred during storage with the compound under an atmosphere of nitrogen.

The bulky isopropyl substituents on silicon in the triisopropylsilyl (TIPS) protecting group are known to slow down reactions at silicon compared to TMS or TBDMS ethers.[117] It was hoped that this would mean that the protecting group would survive the conditions of the direct amination on the neighbouring secondary alcohol. Obviously the bulkiness of the TIPS group also makes it sensitive to the steric demands of reaction partners, thus rendering TIPS-chloride and -triflate selective silylating agents for primary hydroxyl moieties in the presence of secondary alcohols. TIPS triflate and 2,6-lutidine were chosen as the reagents for the protection of diol **257**, the conditions of which are shown in Scheme 120 below.[80]



257 **268**

Scheme 120: TIPS protection.

The isolated yield of 52% was lower than that desired for a reaction that simply introduced a protecting group. It was thought that this might have been due to carrying out the reaction and subsequent purification on a small scale.

This mono-TIPS protected diol **268** could then be exposed to exactly the same amination conditions that had been previously successfully trialled on the simplified model **236** (Scheme 107, page 87). However, on studying the proton NMR spectra of the crude product mixture in residual DMPU (a section of which is shown at the bottom of Figure 25), it was apparent that again unwanted deprotection had occurred as there was no longer the large characteristic triisopropyl resonance visible (at 1.07 ppm (18H, d, *J* 5.6 Hz, 6 × CH_3)). On comparison to the analysis of the free diol **257** (top of Figure 25), it could be seen that some degree of reaction had occurred as well as the deprotection, as the peaks of the protons α to the alcohol groups had shifted. However, the degree of the shifts was not as had been observed in previous hydroxylamine formation (~0.15 ppm upfield) and the reaction was deemed unsuccessful, as it was not known at what centre and to what degree the reaction had occurred.

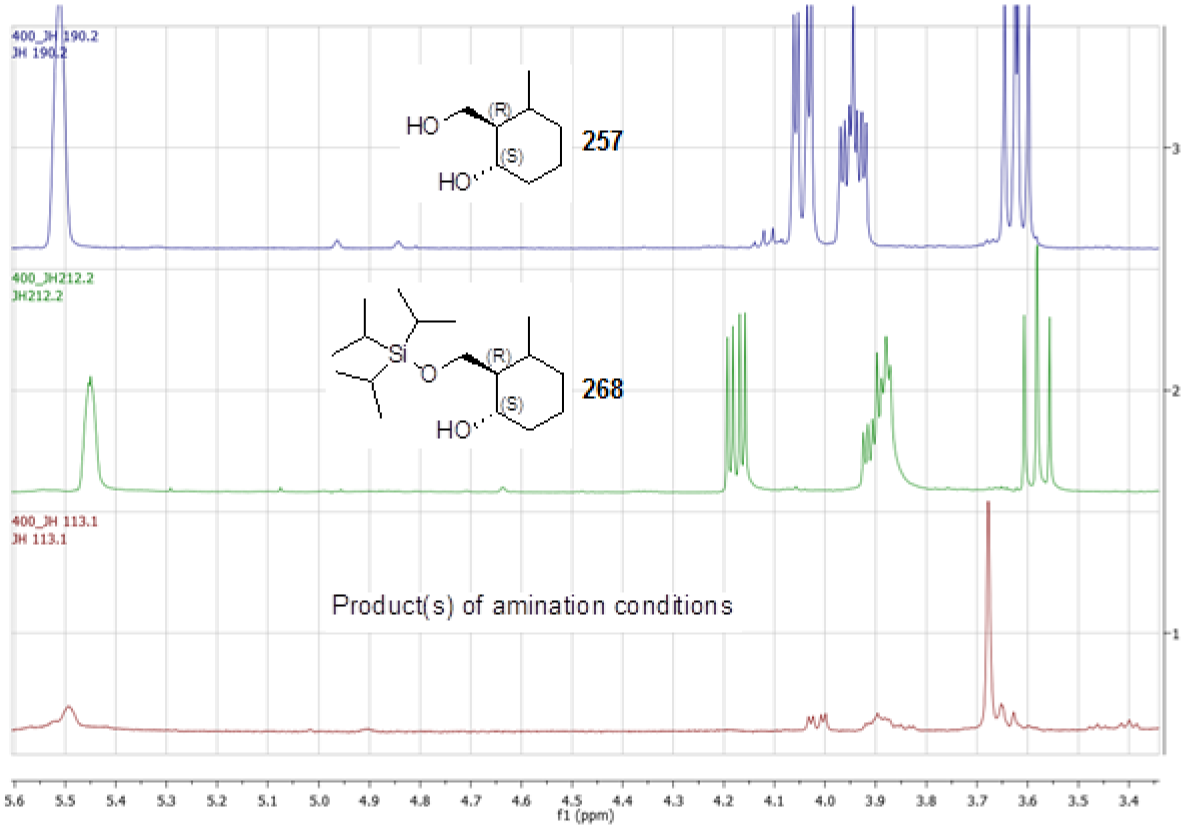
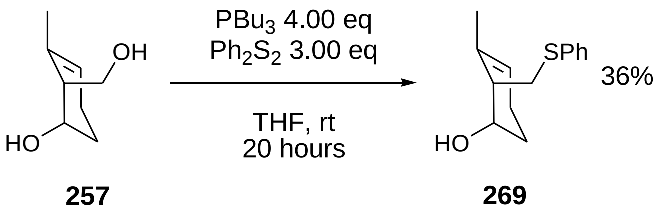


Figure 25: NMR spectra comparison of diol, protected diol and amination reaction product mixture.

A complete rethink was needed at this stage of the synthesis, to overcome these recurring issues with protecting group instability and the complications caused to the ensuing amination reaction. This was assigned to an MChem student, William Dean, as his fourth year project, under my guidance.

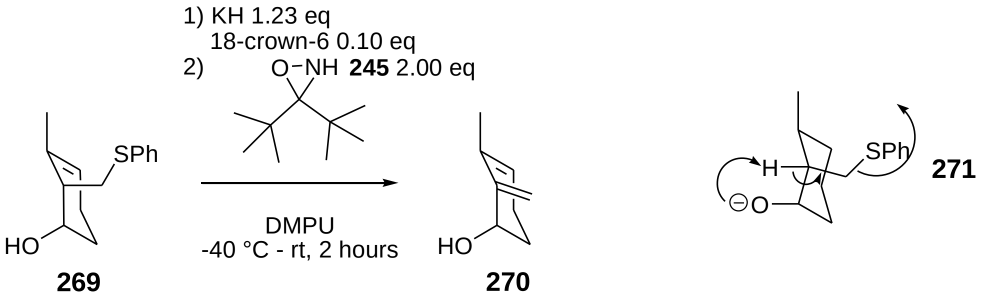
Another possible protecting methodology would be to convert the primary hydroxyl group into a thiophenol ether. These groups are much less common than the silyl protecting groups, but are able to chemoselectively protect primary alcohols and can then later be removed by oxidation to the sulfoxide and Pummerer rearrangement.

Primary alcohols such as **257** can be selectively substituted for a thiophenol benzyl ether by stirring with tributylphosphine and diphenyl disulfide overnight at room temperature.[118] An isolated yield of 36% of the thiophenol ether **269** was attained by Dean (Scheme 121), which was attributed to a slower conversion of the starting material than had been expected from literature precedents.



Scheme 121: Thioether formation.

The amination was then performed on the thiophenol ether **269**, which produced a mixture of unchanged starting material and a product which was eventually assigned as diene **270** (Scheme 122). Unfortunately this once more showed that the amination had not worked, instead eliminating thiophenol under the basic conditions rendered by the potassium hydroxide. While it is surprising that this should have happened, with the pKa of the removed proton being several orders of magnitude higher than the pKa of KH, it is proposed that the stability of the PhSH leaving group has a role to play in this outcome, or that it was the proximity of the oxygen anion to the proton in question (intermediate **271** Scheme 122), that facilitated the elimination.



Scheme 122: Thioether elimination with possible mechanism.

It was also unexpected that the exocyclic olefin stayed in the *exo*-position, rather than migrating to form a more thermodynamically stable cyclohexadiene compound. A section of the ^{1}H NMR spectra of the reaction mixture showing the 1:1 ratio of the starting material **269** and the diene **270** makes up Figure 26, where the relevant resonances are highlighted.

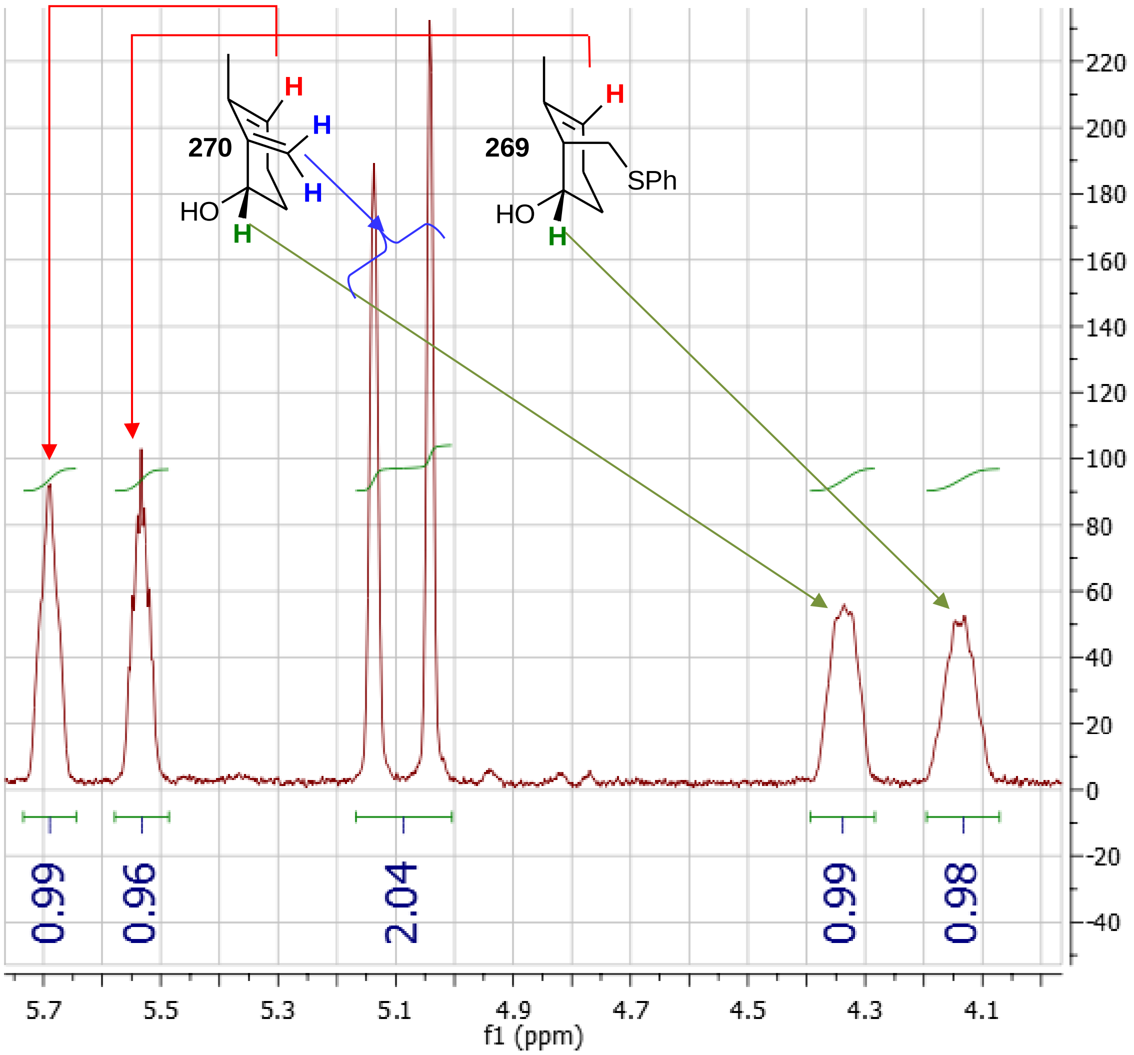
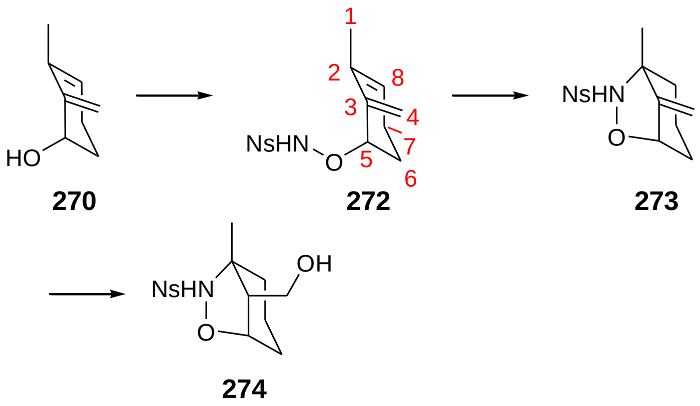


Figure 26: Elimination of thioether.

While the synthesis of diene **270** was not planned, the stability of this compound opened up a possible new avenue for synthesising the oxygen containing side-chain later in the synthesis, and after the contentious amination step. It is proposed that if diene **270** was aminated and nosylated, to form the protected *O*-hydroxylamine **272**, then an acid-catalysed cyclisation would ring-close at carbon 2 due to its proximity when compared to carbons 8 and 4, and the strained ring formation if it attacked at carbon 3 (Scheme 123).

If this is the case, then the correct stereochemistry of carbon 3 could then be regained through the hydroboration of isoxazolidine **273**. The heteroatoms of the isoxazolidine ring could be used guide the hydroboration agent, such as 9-BBN, to give the correct stereochemistry. Oxidative cleavage of the borane to the alcohol will then give a building block from which the rest of the side chain can be synthesised.

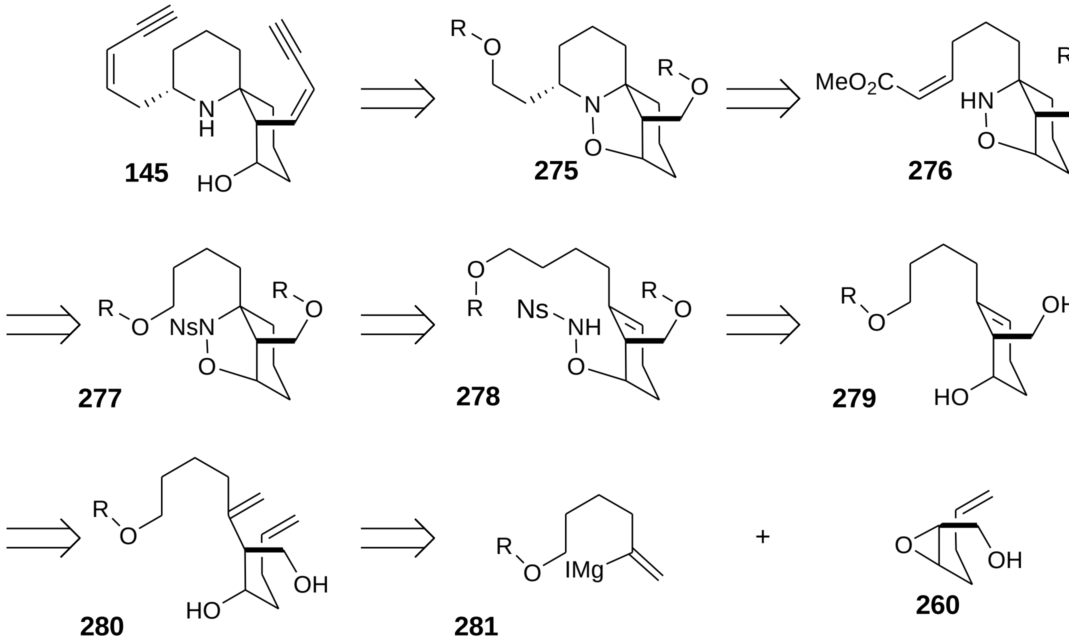


Scheme 123: Proposed scheme from exocyclic alkene.

If this alternative scheme worked, then a route could be developed to reliably reach the diene **270**. At this juncture, Dean's assignment came to a close and it was decided to focus on the introduction of the final side-chain as the concluding investigation of this research project.

4.25 Full synthesis.

As was previously discussed, a convenient consequence of using the route proposed in Scheme 112 (page 92) is the ability to easily synthesise the full Histrionicotoxin molecule by changing isopropenylmagnesium bromide **281** for a more complex vinyl-Grignard that will go on to synthesise the spirocyclic piperidine ring **275**. The retrosynthesis for Histrionicotoxin **145** using this approach is shown below in Scheme 124, and will introduce a further level of complexity to the synthesis in the form of another hydroxyl-containing side-chain and the inherent complications that this may introduce to the amination with the possibility of subsequent competitive cyclisation.

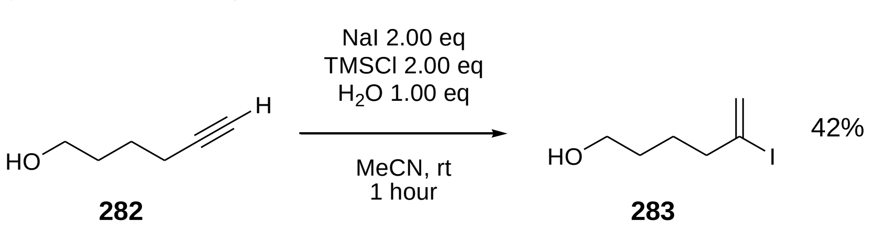


Scheme 124: Retrosynthesis.

The retrosynthesis of Histrionicotoxin **145** starts with the conversion back to the protected alcohol side chains of isoxazolidine **275** from their highly unsaturated counterparts using Stockman's route.[66] The piperidine ring is then disconnected to the corresponding α,β-unsaturated ester **276**, which can be synthesised by the oxidation and Horner-Wadsworth-Emmons type Wittig reaction of compound **277**. Both the acid-catalysed cyclisation of **278** and the selective amination of **279** require both primary alcohols to be protected with complementary protecting groups. The disconnection of the cyclohexene ring of compound **280** at the olefin and the addition of the Grignard reagent **281** to epoxide **260** is similar to the previous retrosynthesis (Scheme 112, page 92).

As the asymmetric epoxidation reaction to form epoxide **260** could be reliably repeated on a large scale, and the product itself was conveniently stable, plenty of the epoxide **260** was available to attempt an opening with the complex Grignard **281**.

The Grignard reagent **281** or its corresponding bromo- or iodo-compounds were not commercially available, so this needed to be synthesised by a concise route. Formation of the iodoalkene **283** was attempted by the Markovnikov addition of hydrogen iodide to commercially available 5-hexyn-1-ol **282**, using a literature preparation,[119] as shown below in Scheme 125.

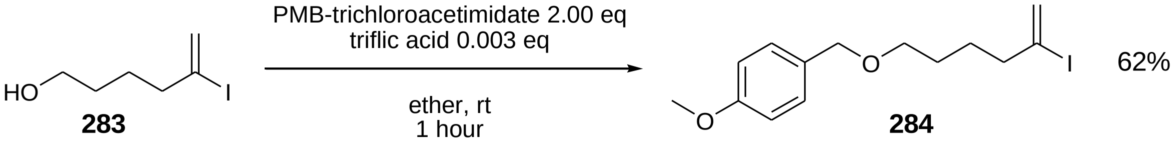


Scheme 125: Hydroiodination of alkyne.

The reaction appeared to have proceeded as desired on studying the ^{1}H NMR spectra of the crude product, despite the risk of terminal- or di-iodination. However, to remove the minor impurities column chromatography was carried out and this led to the isolated yield being 42%. On carrying out the chromatography it became apparent that there were several different compounds present and the reaction was not as selective as had been first thought. Nonetheless, the desired product **283** did account for the largest fraction of the product mixture, and as it was a known compound the structure could be confidently assigned on comparison of the analysis.

The appropriate protection of the alcohol moiety of the iodoalkene **283** was important as, referring back to intermediate **278** in Scheme 124, if R was removed under acidic conditions then cyclisation through the oxygen to give a 6-membered spirocyclic ring would be a real threat to the desired transannular cyclisation through nitrogen. Also, a protecting group was required that would be complementary to that on the hydroxyl moiety of the other primary alcohol substituent on the cyclohexene ring structure **278**.

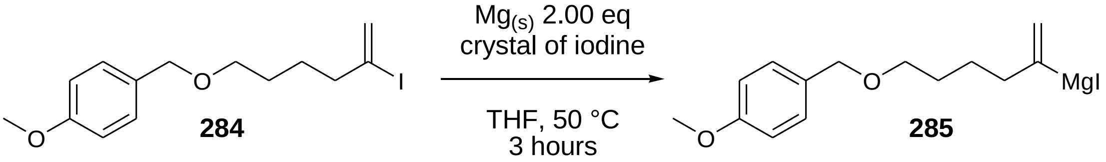
Methoxybenzyl groups are widely used as a convenient way of protecting hydroxyl groups in multi-step syntheses of complex natural products, as they can be selectively cleaved under specific oxidative environments. The *p*-methoxybenzyl group is by far the most widespread methoxybenzyl protecting group, as it is more stable to a variety of reaction conditions. This solution was chosen to mask the reactivity of the alcohol **283**, and a common method for benzyl ether protection was employed where the alcohol **283** (Scheme 126) was reacted with benzyltrichloroacetimidate, in a reaction promoted by triflic acid.[120]



Scheme 126: PMB-protection.

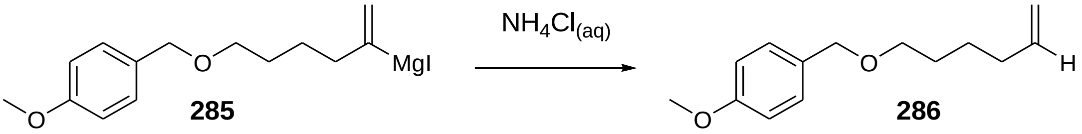
On studying the proton NMR spectra of the crude product mixture from the above reaction, it could be seen that there had only been around a 75% conversion of the starting material **283** to the PMB-protected product **284**. This residual starting material and the other more minor impurities were removed by column chromatography to give an isolated yield of 62%. It was important to successfully remove all of the unreacted alcohol as this could have caused side-reactions in the subsequent Grignard forming step. Furthermore, in doing so the remaining starting material was recovered to be used at a later date. The suitably protected iodoalkene could then be exposed to Grignard reagent-forming conditions.

Grignard reagents form *via* the reaction of an alkyl (or aryl) halide with magnesium metal, and it is important to exclude water and air which rapidly destroy the reagent by protonolysis or oxidation.[121] There was not much detail in the literature about exactly how to form a Grignard reagent from this type of vinyl compound. A typical preparation was trialled by adding the organic halide **284** to a suspension of magnesium in an ethereal solvent (Scheme 127), as this provides the ligands required to stabilize the organomagnesium compound.[122] Also, rapid stirring of the magnesium turnings under nitrogen prior to the reaction weakens the passivating layer of magnesium oxide on the surfaces to expose the highly reactive magnesium beneath.



Scheme 127: Grignard formation.

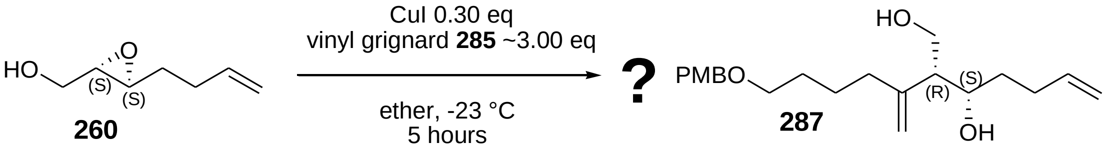
The progress of the magnesium insertion reaction could be monitored by quenching samples of the reaction mixture with ammonium chloride (Scheme 128), and if the Grignard **285** had been formed then it would be hydrolysed to give the monosubstituted alkene **286**.



Scheme 128: Quenching the Grignard reagent.

The reaction was carried out as shown in Scheme 127, and after the three hour reflux the ^{1}H NMR spectra of the sample of reaction mixture that was quenched as above did show that the monosubstituted alkene **286** had been formed, and no iodo starting material **285** was remaining. The alkene **286** is a known compound,[123] and its proton NMR spectra matched exactly to that in the literature, proving that the Grignard reagent had been successfully formed. The remaining vinyl magnesium iodide **285** solution in anhydrous tetrahydrofuran could then be used to trial the opening of the epoxide **260**.

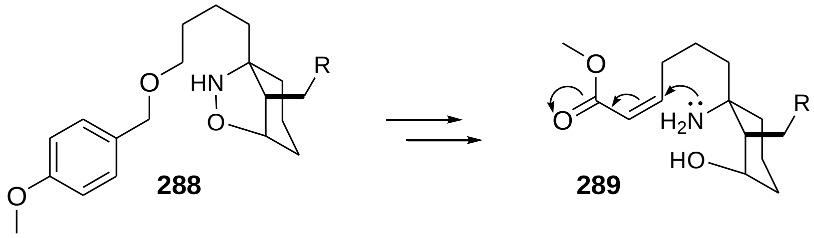
The same conditions that had been successful for the previous regioselective epoxide opening using the commercially available Grignard reagent (Scheme 117, page 96), were employed for this next step as proposed in Scheme 129 below.



Scheme 129: Epoxide opening using synthesised side-chain.

It was unfortunate that three equivalents of the Grignard reagent were necessary at this stage, as it meant sacrificing two equivalents of a reactant that had taken three steps to make. The solution of Grignard reagent **285** had been kept under nitrogen overnight before its addition to the suspension of copper (I) iodide. Following the work-up after the five hours of reaction time had passed, it was found on studying the proton NMR spectra of the crude reaction mixture that the epoxide **260** had, in fact, remained intact. As it was known that the Grignard reagent **285** had been formed, it was thought that the reason for this failure to react could be either due to an insufficient reaction time as the side-chain being introduced was much bulkier, or that the Grignard reagent was short-lived and should have been utilised directly after formation.

If, after retrialling the Grignard addition, it was possible to reach the transannular intermediate **288** shown below, then the PMB group could be removed from the primary alcohol using DDQ. The resulting hydroxyl group could then be simply oxidised up to an aldehyde, which would be able to undergo a Wittig reaction to install the required ester functionality. As can be seen in Scheme 130 below, the spirocyclic nitrogen containing ring can then be formed by Michael addition **289**.



Scheme 130: Proposed final steps of synthesis.

Despite falling short of the full model synthesis that had been designed, it can be concluded from this Chapter that this chemistry is well suited to this type of complex synthesis.

Taking this project as a whole, numerous compounds have been made that have not been previously published, and the methods optimised within this thesis have been shown to be reliably repeatable. These are the main achievements of this project, and I hope that through the subsequent publication of some of these novel methods that they could go on to be used in the synthesis of other compounds and play a small part in future discoveries.

Chapter 5

Experimental

5.1 Experimental

5.11 General Details

Reagents were obtained from Aldrich, Alfa Aesar and Lancaster chemical suppliers and used as received unless otherwise specified. Dichloromethane was dried by refluxing over, and distilling from, calcium hydride. Anhydrous tetrahydrofuran was obtained by refluxing over sodium with sodium benzophenone ketyl as indicator, followed by distillation. Diethyl ether and acetonitrile were used in their anhydrous state directly from an MBRAUN SPS solvent purification system. All aqueous solutions were saturated unless otherwise stated. “Dried” refers to the addition of dried magnesium sulphate ($MgSO_4$) to remove trace amounts of water. “Filtered” refers to the removal of solid residues by gravity filtration of organic solutions through filter paper. “Evaporated” refers to the distillation of volatiles using a Büchi rotary evaporator attached to a 20 L Charles Austen pump at approx. 8 mbar, heated with a water bath typically between 20 and 40 °C.

All reactions using air/moisture sensitive reagents were performed in oven-dried apparatus, under a nitrogen atmosphere. Solid carbon dioxide and an acetone bath (-78 °C) or an ice-water bath (0 - 5 °C) were used to obtain low temperatures unless otherwise stated. “m.p.” stands for melting point. Heated reactions were conducted in a stirred oil bath heated on a magnetically stirred hotplate. Reactions were followed and monitored by TLC, ^{1}H NMR, ^{13}C NMR and mass spectrometry as appropriate.

TLC analysis refers to analytical thin layer chromatography, using aluminium-backed plates coated with Merck Kieselgel 60 GF254. Product spots were viewed either by UV fluorescence, or by staining with a suitable staining solution. Column chromatography refers to flash column chromatography using head pressure by means of compressed air, and using Merck Kieselgel 60 H silica or Matrix silica 60.

Melting points were recorded using a Kofler Heated Stage Micro Melting Point Apparatus and are uncorrected.

Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1600 series FTIR instrument as a thin film between sodium chloride plates unless otherwise stated, in which case samples were run dissolved in dichloromethane (DCM) between sodium chloride plates. All absorptions are quoted in wave numbers (cm^{-1}).

^{13}C NMR spectra (δ_C) were recorded at 125MHz on an Avance Bruker DPX 500 instrument (500 MHz) unless otherwise stated. ^{1}H NMR spectra (δ_H) were recorded using an

Avance Bruker DPX 400 instrument (400 MHz) or an Avance Bruker DPX 250 instrument (250 MHz). Spectra were obtained as dilute solutions in deuterated chloroform, unless otherwise stated. Chemical shifts are expressed in parts per million (ppm, δ) and were recorded relative to residual chloroform (7.26 or 77.0 ppm) as an internal standard unless otherwise stated. All NMR spectra were measured at room temperature unless otherwise stated. Abbreviations used for the multiplicities are s (singlet), d (doublet), t (triplet), q (quartet), br. s (broad singlet), dd (doublet of doublets), dt (doublet of triplets), td (triplet of doublets), m (unresolved multiplet), app. (apparent) or as a combination of these multiplicities. All coupling constants (*J*) are recorded in Hertz (Hz). Assignments were made on the basis of chemical shift and coupling constant data using DEPT-90, DEPT-135, COSY, NOESY, HSQC and HMBC experiments where required.

Mass spectrometric data was determined using a Waters GCT Premier instrument using electron ionisation (EI) unless otherwise stated. In which case mass spectrometric data was determined by a Waters LCT Premier XE instrument (LRMS) or Agilent 5975C Series GC/MSD (GC-MS) using pressure chemical ionisation (APCI) or electrospray ionisation (ES). High resolution mass spectrometric data were determined with the molecular formula corresponding to the observed signal using the most abundant isotopes of each element.

5.12 General Methods

General Method A – Addition of an alkyne to an aldehyde

The alkyne (1.00 equivalent) was taken up in dry tetrahydrofuran (2.00 ml/mmol of alkyne) and the solution 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 hours at this temperature. The resulting solution of metallated alkyne was transferred to a solution of the aldehyde (1.00 equivalent) in dry tetrahydrofuran (1.00 ml/mmol of aldehyde) at -78 °C, and the resulting mixture allowed to warm to room temperature over a period of 4 hours, then quenched by the addition of saturated aqueous ammonium chloride (equal volume to the reaction mixture) and extracted with dichloromethane (3 × volume of the reaction mixture). The combined organic extracts were washed with water (3 × volume of the combined extracts), and saturated sodium chloride solution (equal volume to the combined extracts) then dried, filtered and evaporated to give the product, which was used without further purification.

General Method B – Mitsunobu reaction[108]

To a solution of triphenylphosphine (1.20 equivalents) in dry tetrahydrofuran (10.00 ml/mmol of alcohol) at 0 °C was added diisopropyl azodicarboxylate (1.01 equivalents) *via* syringe. The resulting orange solution was stirred until it became colourless and opaque (about 15 minutes). The alcohol (1.00 equivalent) was added dropwise *via* syringe and the resulting solution stirred for 20 minutes. *N*-Hydroxyphthalimide (2.00 equivalents) was then added portionwise and the solution allowed to warm to room temperature overnight. The solvent was evaporated and replaced with a minimum amount of dichloromethane. The resulting solution was washed with a 1:1 solution of water and 30% w/w hydrogen peroxide (20.00 ml/g triphenylphosphine), and the aqueous layer was extracted with dichloromethane (3 × volume of aqueous layer). The combined organic extracts were then washed with saturated sodium sulphite solution (equal volume to the combined extracts – added slowly as reaction with residual hydrogen peroxide can be vigorous), and the aqueous layer was extracted with dichloromethane (3 × 5.00 ml/mmol product). The combined organic extracts were then washed with water (equal volume to the combined extracts) then dried, filtered and evaporated to give the crude product.

General Method C – Phthalimide deprotection

The phthalimide (1.00 equivalent) was taken up in diethyl ether (10.00 ml/mmol of phthalimide) and 40% w/w aqueous methylamine (2.10 equivalents) was added in one portion at room temperature. The resulting solution was stirred for 4 hours at this temperature, over which time a white precipitate formed, then a small amount of petroleum ether was added and the solution was cooled in an ice-water bath to 0 °C and filtered under vacuum. The solid residue was washed with petroleum ether and the combined organic filtrates dried, filtered and evaporated to give the hydroxylamine, which was used without further purification.

General Method D – Silver nitrate cyclisations

The hydroxylamine (1.00 equivalent) was taken up in dichloromethane (30.00 ml/mmol of hydroxylamine) and the reaction flask was covered with aluminium foil to exclude all light. 10% w/w Silver nitrate on silica gel (see specific procedures for suitable number of equivalents) was added in one portion and the resulting mixture stirred for 4 hours. The mixture was passed through a plug of celite, eluting with ethyl acetate until filtrate runs clear, and the solvent evaporated to give the product.

General Method E – Carbonate formation with BOC-ON[55]

A solution of the alcohol (1.00 eq) in dry diethyl ether (1.00 ml/mmol) at -78 °C was treated with *n*-butyl lithium (2.5 molar solution in hexane, 1.10 eq) and stirred for 0.5 hours at this temperature. The resultant alkoxide solution was transferred *via* syringe to a solution of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (BOC-ON, 1.00 eq), in dry tetrahydrofuran (2.00 ml/mmol) at 0 °C. After stirring for 4 hours at room temperature the mixture was washed successively with 2 M aqueous sodium hydroxide (2 x volume of reaction mixture) and saturated aqueous sodium chloride (equal to volume of reaction mixture). The combined aqueous washings were back extracted with diethyl ether (2 x 3.00 ml/mmol), and the combined organic extracts were dried, filtered and evaporated to give the carbonate product.

General Method F – Carbonate formation with BOC-anhydride[63]

A solution of the alcohol (1.00 eq) in dry tetrahydrofuran (1.00 ml/mmol) at 0 °C was treated with *n*-butyl lithium (2.5 molar solution in hexane, 1.10 eq) and stirred for 10 minutes at this temperature. Di-*tert*-butyl dicarbonate (BOC-anhydride, 1.05 eq) in dry tetrahydrofuran

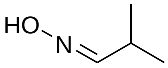
(2.00 ml/mmol) was added to the alkoxide solution at 0 °C and the reaction mixture was allowed to warm to room temperature and stir for 24 hours. Water (3.00 ml/mmol) was added to form a biphasic mixture which was left to stir to decompose any residual BOC-anhydride for 1 hour. The tetrahydrofuran was removed under reduced pressure, and diethyl ether (3.00 ml/mmol) was added. The organic layer was washed with brine (equal volume to organic layer), then dried, filtered and evaporatred to give the carbonate product.

General Method G - Optimised iodocyclisation

A solution of the carbonate (1.00 eq) in dry dichloromethane (30.00 ml/mmol) was stirred at -100 °C (in a CO_2/diethyl ether cooling bath) prior to the addition of potassium carbonate (3.00 eq) and iodine monobromide (0.50 molar solution in dry dichloromethane, 1.50 eq). The resulting solution was stirred at this temperature for 1 hour in a foil wrapped flask to maintain a darkened environment. The reaction mixture was then quenched by the addition of saturated aqueous sodium sulphite (equal to half the volume of reaction mixture), and extracted with dichloromethane (3 x equal volume to aqueous layer). The combined organic layers were washed with saturated aqueous sodium sulphite (equal volume to organic layer), then water (equal volume to organic layer) and dried, filtered and evaporated to give the cyclised product.

5.13 Chapter 2 compounds

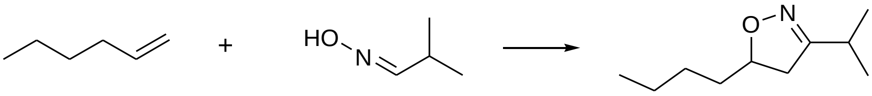
Isobutylaldoxime 57



57

A solution of sodium hydroxide (14.00 g, 0.35 mol) in water (40.00 ml) was mixed with isobutanal (14.00 g, 0.20 mol). Hydroxylamine hydrochloride (15.00 g, 0.22 mol) was added portionwise causing an exotherm, and on cooling crystals of the sodium derivative precipitated out of solution. The solution was acidified with 2 M hydrochloric acid (125.00 ml, to pH 3), and the aqueous layer was extracted with dichloromethane (2 × 50.00 ml). The combined organic extracts were dried, and the solvent was evaporated to yield the crude product which was purified by vacuum distillation (35 °C, 1 mmHg,) [Lit.[124]bp 141-142 °C] to give the *oxime* **20** (5.29 g, 30%) as a colourless oil. All data obtained were in accordance with those reported in the literature[124] and showed: δ_H 7.35 (1H, d, *J* 5.9, CH), 2.56-2.44 (1H, m, CH), 1.20 (6H, d, *J* 7.0, 2 × CH$_3$).

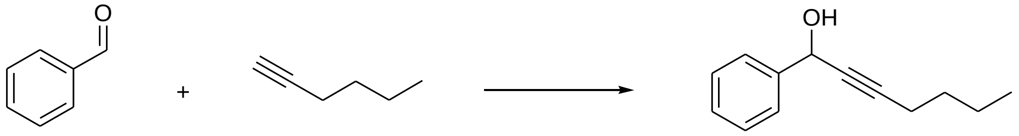
3-Isobutyl-5-butylisoxazoline 61



290 **57** **61**

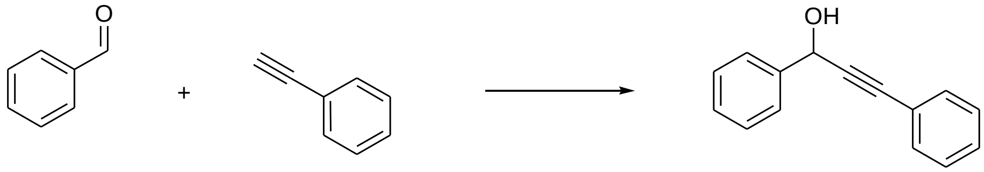
To a flask containing 1-hexene **290** (2.61 ml, 21.00 mmol), triethylamine (0.20 g, 0.28 ml, 1.98 mmol), dichloromethane (15.00 ml) and sodium hypochlorite solution (20.00 ml, available chlorine 10-13%), was added isobutylaldoxime **57** (1.83 g, 21.00 mmol) in dichloromethane (10.00 ml) dropwise at 0 °C. After stirring for 2 hours the layers were separated and the aqueous layer was extracted with dichloromethane (2 × 10.00 ml). The combined organic extracts were dried, and the solvent was evaporated to yield the crude product which was purified by vacuum distillation (80 °C, 1 mmHg) to give the *isoxazoline* **61** (1.09 g, 31%) as a yellow oil, showing: ν_{max}/cm^{-1} [thin film] 2966, 2874, 1595, 1466, 1387, 1108; δ_H 4.54-4.45 (1H, m, CH), 2.99-2.90 (1H, m, CH), 2.76-2.64 (1H, m, CH$_a$), 2.50 (1H, dd, *J* 16.7, 8.1, CH$_b$), 1.74-1.62 (1H, m, CH$_{a'}$), 1.55-1.44 (1H, m, CH$_{b'}$), 1.41-1.28 (4H, m, 2 × CH$_3$), 1.15 (6H, d, *J* 7.0, 2 × CH$_3$), 0.87 (3H, t, *J* 7.0, CH$_3$).

1-Phenylhept-2-yn-1-ol 74


291 **292** **74**

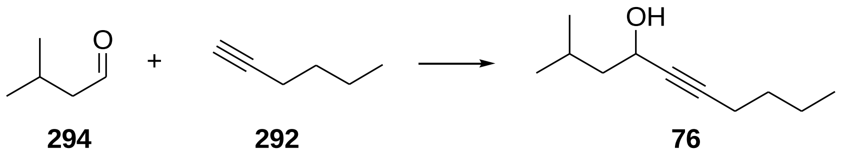
Benzaldehyde **291** (1.24 ml, 12.17 mmol) was reacted with 1-hexyne **292** (1.40 ml, 12.17 mmol) under the conditions described in General Method **A** to give the *alkynol* **74** (2.24 g, 98%) as a colourless oil. All data obtained were in accordance with those reported in the literature[125] and showed: ν_{max}/cm^{-1} [thin film] 3399, 2958, 2203, 1644, 1451, 1267; δ_H 7.55 (2H, d, *J* 7.1, 2 × ArH), 7.38 (2H, app. t, *J* 7.1, 2 × ArH), 7.30 (1H, d, *J* 7.1, ArH), 5.45 (1H, s, CH), 2.28 (2H, td, *J* 7.0, 2.0, CH_2), 2.15 (1H, br. s, OH), 1.54 (2H, tt, *J* 7.0, 5.9, CH_2) 1.43 (2H, app. q, *J* 7.2, CH_2), 0.92 (3H, t, *J* 7.2, CH_3); δ_C 136.4 (ArC). 133.4 (ArC), 129.1 (2 × ArCH), 128.0 (2 × ArCH), 96.4 (C), 79.2 (C), 64.4 (CH), 29.3 (CH_2), 21.6 (CH_2), 18.4 (CH_2), 13.0 (CH_3); HRMS *m/z* [EI] $C_{13}H_{16}O$ requires 188.1201, found 188.1200.

1,3-Diphenylprop-2-yn-1-ol 75


291 **293** **75**

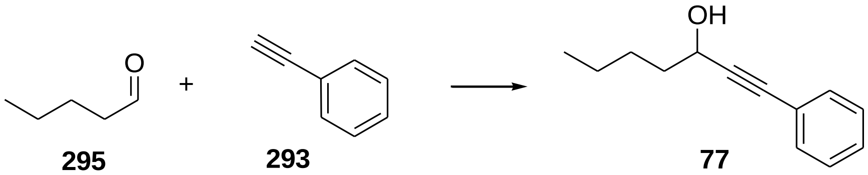
Benzaldehyde **291** (0.92 ml, 9.43 mmol) was reacted with phenylacetylene **293** (1.08 ml, 9.43 mmol) under the conditions described in General Method **A** to give the *alkynol* **75** (1.92 g, 98%) as a colourless oil. All data obtained were in accordance with those reported in the literature[126] and showed: ν_{max}/cm^{-1} [thin film] 3411, 2198, 1640, 1032, 757; δ_H 7.65-7.61 (2H, m, ArH), 7.50-7.47 (2H, m, 2 × ArH), 7.44-7.40 (2H, m, 2 × ArH), 7.36-7.31 (4H, m, 4 × ArH), 5.70 (1H, s, CH), 2.43 (1H, br. s, OH); δ_C 140.5 (ArC), 131.6 (2 × ArCH), 128.5 (3 × ArCH), 128.3 (ArCH), 128.2 (2 × ArCH), 126.6 (2 × ArCH), 122.2 (ArC), 88.6 (C), 86.5 (C), 65.0 (CH); HRMS *m/z* [EI] $C_{15}H_{12}O$ requires 208.0888, found 208.0884.

2-Methyldec-5-yn-4-ol 76



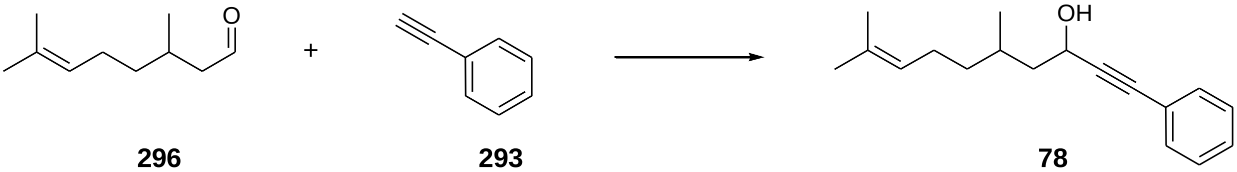
Isovaleraldehyde **294** (2.61 ml, 24.35 mmol) was reacted with 1-hexyne **292** (2.80 ml, 24.35 mmol) under the conditions described in General Method **A** to give the *alkynol* **76** (3.39 g, 83%) as a colourless oil. All data obtained were in accordance with those reported in the literature[127] and showed: ν_{max}/cm^{-1} [thin film] 3608, 3583, 2360, 441; δ_H 4.37 (1H, t, *J* 7.1, CH), 2.18 (2H, td, *J* 7.0, 1.9, CH_2), 1.90 (1H, br. s, OH), 1.81 (1H, app. p, *J* 6.8, CH), 1.63-1.32 (6H, m, 3 × CH_2), 0.92 (6H, d, *J* 6.8, 2 × CH_3), 0.89 (3H, t, *J* 7.1, CH_3); δ_C 85.1 (C), 81.2 (C), 61.0 (CH), 47.0 (CH_2), 30.5 (CH_2), 24.6 (CH), 22.3 (CH_3), 22.2 (CH_3), 21.6 (CH_2), 18.1 (CH_2), 13.3 (CH_3); HRMS *m/z* [EI] $C_{11}H_{20}O - H_2O$ requires 150.1409, found 150.1406.

1-Phenyl-3-hydroxyl-hept-1-yne 77



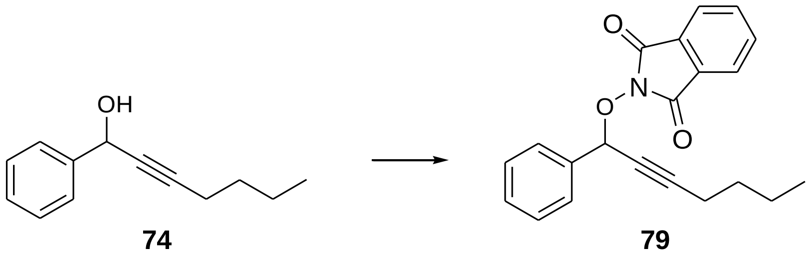
Valeraldehyde **295** (2.08 ml, 19.58 mmol) was reacted with phenylacetylene **293** (2.15 ml, 19.58 mmol) under the conditions described in General Method **A** to give the *alkynol* **77** (3.27 g, 89%) as a colourless oil. All data obtained were in accordance with those reported in the literature[128] and showed: ν_{max}/cm^{-1} [thin film] 3349, 2956, 2362, 1490, 1028, 755; δ_H 7.43 (2H, dd, *J* 6.7, 3.0, 2 × ArH), 7.24-7.17 (3H, m, 3 × ArH), 4.59 (1H, t, *J* 6.5, CH), 2.47 (1H, br. s, OH), 1.79-1.64 (2H, m, CH_2), 1.46-1.36 (2H, m, CH_2), 1.35-1.23 (2H, m, CH_2), 0.94 (3H, t, *J* 7.3, CH_3); δ_C 131.5 (ArCH), 128.2 (2 × ArCH), 128.1 (2 × ArCH), 122.5 (ArC), 90.1 (C), 84.6 (C), 62.8 (CH), 37.5 (CH_2), 27.2 (CH_2), 22.2 (CH_2), 13.9 (CH_3); HRMS *m/z* [EI] $C_{13}H_{16}O$ requires 188.1201, found 188.1203.

(3*RS*,5*RS*) and (3*RS*,5*SR*) 5,9-Dimethyl-1-phenyldec-8-en-3-ol 78



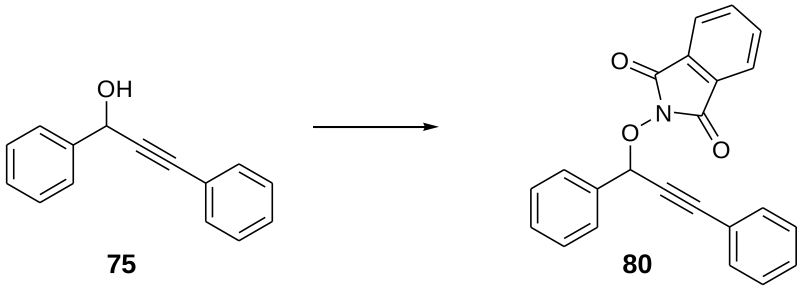
Citronellal **296** (0.28 ml, 1.58 mmol) was reacted with phenylacetylene 293 (0.18 ml, 1.58 mmol) under the conditions described in General Method **A** to give the *alkynol* **78** as a 1:1 diastereomeric mixture – multiplets could not be resolved to separate resonances for each diastereomer (0.41 g, 100%) as a yellow oil. All data obtained were in accordance with those reported in the literature[46] and showed: ν_{max}/cm^{-1} [thin film] 3390, 2930, 1602, 1443, 768; δ_H 7.46-7.39 (2H, m, 2 × ArH), 7.33-7.28 (3H, m, 3 × ArH), 5.17-5.05 (1H, m, C=CH), 4.67 (1H, dd, *J* 7.7, 6.3, CH), 2.11-1.93 (2H, m, CH_2), 1.90-1.82 (1H, m, CH), 1.81-1.70 (2H, m, CH_2), 1.68 (3H, s, CH_3), 1.61 (3H, s, CH_3), 1.47-1.33 (1H, m, CH_a), 1.31-1.17 (1H, m, CH_b), 0.98 (3H, app. dd, *J* 6.5, 5.5, CH_3); δ_C 131.5 (CH), 129.7 (ArCH), 129.6 (ArC), 129.5 (2 × ArCH), 128.1 (C), 126.6 (2 × ArCH), 90.1 (C), 84.6 (C), 98.6 (CH), 62.8 (CH), 29.4 (CH_2), 26.3 (CH_2), 22.0 (CH_2), 13.9 (2 × CH_3), 13.5 (CH_3).

2-(1-Phenylhept-2-yn-1-yloxy)isoindoline-1,3-dione 79



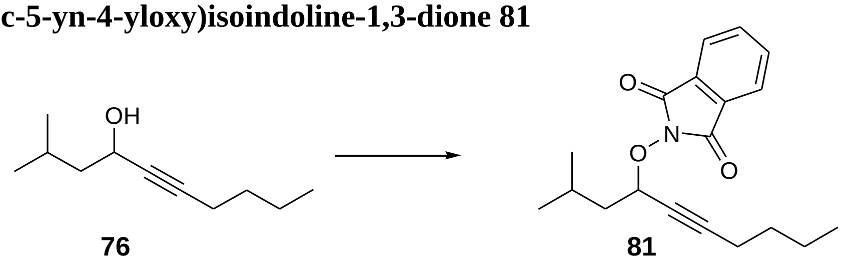
The propargyl alcohol **74** (2.24 g, 11.90 mmol) was reacted with *N*-hydroxyphthalimide (3.88 g, 23.80 mmol) under the conditions described in General Method **B**, except that the propargyl alcohol and *N*-hydroxyphthalimide were added at the same time. The crude product was purified by eluting 100.00 ml fractions of dichloromethane through a silica plug with the second fraction yielding the *phthalimide* **79** (2.13 g, 54%) as a yellow oil, showing: ν_{max}/cm^{-1} [thin film] 2958, 2235, 1735, 1374, 1186, 970; δ_H 7.82 (2H, dd, *J* 5.5, 3.1, 2 × ArH), 7.77-7.70 (4H, m, 4 × ArH), 7.43-7.38 (3H, m, 3 × ArH), 6.08 (1H, t, *J* 2.1, CH), 2.20 (2H, td, *J* 7.0, 2.1, CH_2), 1.45-1.37 (2H, m, CH_2), 1.34-1.24 (2H, m, CH_2), 0.79 (3H, t, *J* 7.3, CH_3); δ_C 163.4 (2 × CO), 135.0 (ArC), 134.1 (2 × ArCH), 129.5 (ArCH), 128.8 (2 × ArC), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 123.3 (2 × ArCH), 92.2 (C), 79.1 (CH), 74.9 (C), 30.0 (CH_2), 21.7 (CH_2), 18.4 (CH$_2$), 13.3 (CH$_3$); HRMS *m/z* [EI] $C_{21}H_{19}NO_3$ requires 333.1365, found 333.1369.

2-(1,3-Diphenylprop-2-yn-1-yloxy)isoindoline-1,3-dione 80



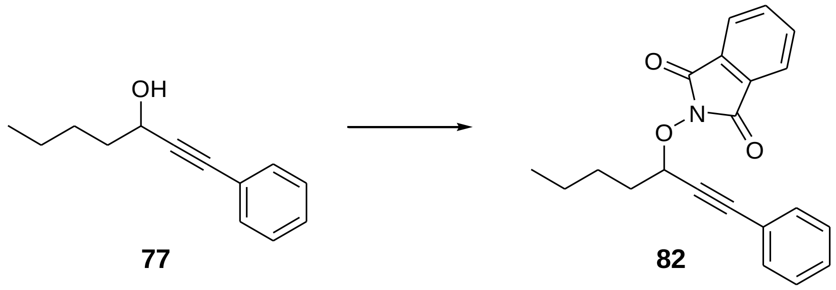
The propargyl alcohol **75** (1.88 g, 9.03 mmol) was reacted with *N*-hydroxyphthalimide (2.94 g, 18.06 mmol) under the conditions described in General Method **B**, except that the propargyl alcohol and *N*-hydroxyphthalimide were added at the same time. The crude product was chromatographed (10-40% diethyl ether in petroleum ether) to give the *phthalimide* **80** (2.04 g, 64%) as a pale yellow solid (the title compound had been reported in the literature[30] but with no analysis), showing: mp 43-46 °C; ν_{max}/cm^{-1} [film] 3583, 3064, 2358, 2228, 1735, 698; δ_H 7.85 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.83-7.78 (2H, m, 2 × ArH), 7.74 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.48-7.40 (5H, m, 5 × ArH), 7.35-7.27 (3H, m, 3 × ArH), 6.31 (1H, s, CH); δ_C 163.6 (CO), 134.6 (ArC), 134.5 (2 × ArCH), 131.8 (2 × ArCH), 130.0 (ArCH), 129.2 (2 × ArCH), 129.0 (ArCH), 128.9 (ArC), 128.7 (2 × ArCH), 128.3 (2 × ArCH), 123.6 (2 × ArCH), 121.8 (ArC), 90.5 (C), 83.9 (C), 79.5 (CH); HRMS *m/z* [APCI] $C_{23}H_{15}NO_3 + H^+$ requires 354.1130, found 354.1129.

2-(2-Methyldec-5-yn-4-yloxy)isoindoline-1,3-dione 81



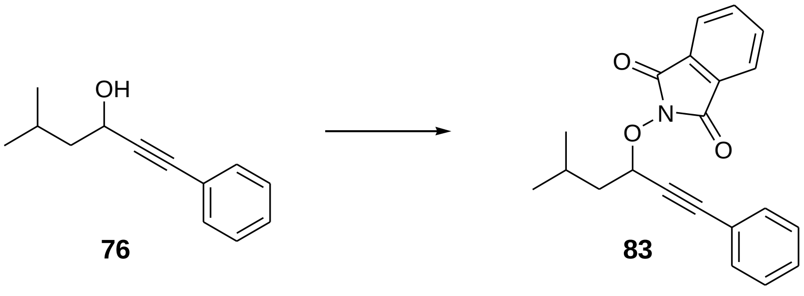
The propargyl alcohol **76** (1.00 g, 5.94 mmol) was reacted with *N*-hydroxyphthalimide (1.94 g, 11.88 mmol) under the conditions described in General Method **B**, and the crude product was purified by elution through a silica plug with copious amounts of dichloromethane to give the *phthalimide* **81** (1.54 g, 96%) as a colourless oil (the title compound had been reported in the literature[30] but with no analysis), showing: ν_{max}/cm^{-1} [thin film] 2958, 2241, 1735, 1375, 1187, 975; δ_H 7.83 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.74 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 5.11 (1H, tt, *J* 6.9, 2.0, CH), 2.11 (2H, td, *J* 7.0, 2.0, CH_2), 1.97 (1H, sept., *J* 6.6, CH), 1.91 (1H, dt, 14.3, 7.1, CH_a), 1.72 (1H, dt, *J* 14.2, 7.1, CH_b), 1.37-1.28 (2H, m, CH_2), 1.27-1.17 (2H, m, CH_2), 1.03 (3H, d, *J* 6.6, CH_3), 0.94 (3H, d, *J* 6.6, CH_3), 0.76 (3H, t, *J* 7.2, CH_3); δ_C 163.5 (2 × CO), 134.1 (2 × ArCH), 128.8 (2 × ArC), 123.2 (2 × ArCH), 89.6 (C), 76.5 (CH), 76.2 (C), 42.7 (CH_2), 30.0 (CH_2), 24.8 (CH), 22.3 (2 × CH_3), 21.6 (CH_2), 18.2 (CH_2), 13.3 (CH_3).

2-(1-Phenyl-1-hept-1-yn-3-yloxy)isoindoline-1,3-dione 82



The propargyl alcohol **77** (0.50 g, 2.63 mmol) was reacted with *N*-hydroxyphthalimide (0.86 g, 5.26 mmol) under the conditions described in General Method **B**, and the crude product was purified by elution through a silica plug with copious amounts of dichloromethane to give the *phthalimide* **82** (0.64 g, 86%) as a pale yellow waxy solid, showing: mp 43-46 °C; ν_{max}/cm^{-1} [film] 3434, 2360, 1734, 1645, 1375, 1187, 700; δ_H 7.85 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.74 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.35 (2H, d, *J* 7.7, 2 × ArH), 7.29-7.23 (3H, m, 3 × ArH), 5.27 (1H, t, *J* 6.7, CH), 2.16-1.95 (2H, m, CH_2), 1.71-1.59 (2H, m, CH_2), 1.49-1.39 (2H, m, CH_2), 0.97 (3H, t, *J* 7.3, CH_3); δ_C 163.5 (CO), 134.2 (2 × ArCH), 131.5 (2 × ArCH), 128.8 (ArC), 128.5 (ArCH), 128.1 (2 × ArCH), 123.4 (2 × ArCH), 121.8 (ArC), 88.2 (C), 85.1 (C), 78.0 (CH), 33.4 (CH_2), 27.1 (CH_2), 22.2 (CH_2), 13.8 (CH_3); HRMS *m/z* [APCI] $C_{21}H_{19}NO_3 + H^+$ requires 334.1443, found 334.1433.

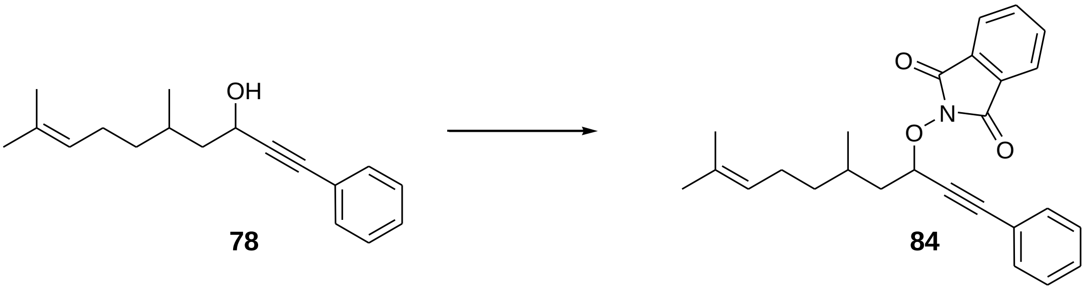
2-(5-Methyl-1-phenylhex-1-yn-3-yloxy)isoindoline-1,3-dione 83



The propargyl alcohol **76** (1.96g, 10.41 mmol) was reacted with *N*-hydroxyphthalimide

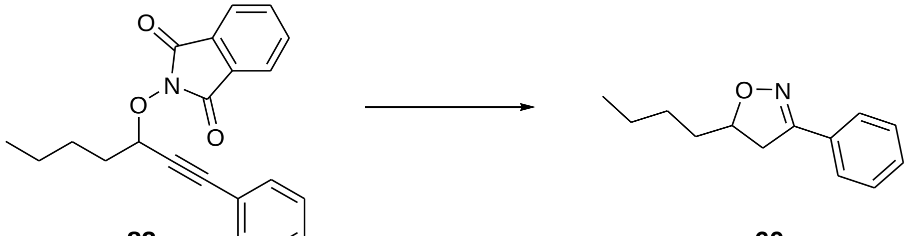
(3.40 g, 20.82 mmol) under the conditions described in General Method **B**, and the crude product was purified by elution through a silica plug with copious amounts of dichloromethane to give the *phthalimide* **83** (3.16 g, 91%) as a pale yellow solid (the title compound had been reported in the literature[30] but with no analysis), showing: mp 87-90 °C; ν_{max}/cm^{-1} [film] 2958, 2235, 1791, 1738, 1371, 1187; δ_H 7.83 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.72 (2H, dd, *J* 5.4, 3.1, 2 × ArH), 7.37-7.32 (2H, m, 2 × ArH), 7.30-7.23 (3H, m, 3 × ArH), 5.31 (1H, t, *J* 6.9, CH), 2.15-2.01 (2H, m, CH_2), 1.92-1.82 (1H, m, CH), 1.08 (3H, d, *J* 6.4, CH_3), 1.01 (3H, d, *J* 6.4, CH_3); δ_C 163.7 (CO), 134.4 (2 × ArCH), 131.6 (2 × ArCH), 129.0 (2 × ArC), 128.6 (ArCH), 128.3 (2 × ArCH), 123.5 (2 × ArCH), 122.1 (ArC), 88.3 (C), 85.5 (C), 76.9 (CH), 42.7 (CH_2), 25.0 (CH), 22.6 (CH_3), 22.5 (CH_3); HRMS *m/z* [EI] $C_{21}H_{19}NO_3 + H^+$ requires 334.1443, found 334.1458.

(3*RS*,5*RS*) and (3*RS*,5*SR*) 2-(5,9-Dimethyl-1-phenyldec-8-en-1-yn-3-yloxy)isoindoline-1,3-dione 84



The propargyl alcohol **78** (1.00g, 3.90 mmol) was reacted with *N*-hydroxyphthalimide (1.27 g, 7.80 mmol) under the conditions described in General Method **B**, and the crude product was purified by elution through a silica plug with copious amounts of dichloromethane to give the *phthalimide* **84** (1.09 g, 69%) as a pale yellow viscous oil, showing: ν_{max}/cm^{-1} [thin film] 3449, 3062, 2958, 1735, 1376, 1187, 973; δ_H 7.88-7.82 (2H, m, 2 × ArH), 7.74 (2H, dd, *J* 5.5, 3.3, 2 × ArH), 7.37-7.31 (2H, m, 2 × ArH), 7.29-7.24 (3H, m, 3 × ArH), 5.38-5.31 (1H, m, CH), 5.16-5.10 (1H, m, CH), 2.24-2.13 (1H, m, CH_a), 2.09-1.90 (4H, m, 2 × CH_2), 1.79 (1H, ddd, *J* 14.1, 8.4, 5.9, CH_b), 1.67 (3H, d, *J* 0.8, CH_3), 1.61 (3H, s, CH_3), 1.36-1.22 (1H, m, CH), 1.11 (3H, d, *J* 6.6, CH_3); δ_C 163.7 (2 × CO), 134.5 (2 × ArCH), 131.6 (2 × ArCH), 131.5 (C), 129.0 (2 × ArC), 128.6 (ArCH), 128.3 (2 × ArCH), 124.5 (CH), 123.5 (2 × ArCH), 122.1 (ArC), 85.7 (C), 82.1 (C), 76.6 (CH), 41.2 (CH_2), 37.0 (CH_2), 29.3 (CH), 25.7 (CH_3), 25.3 (CH_2), 19.3 (2 × CH_3).

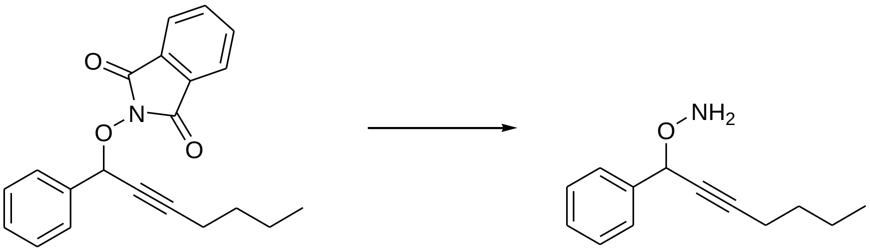
5-Butyl-3-phenylisoxazoline 60



82 **60**

The phthalimide **82** (1.00 g, 3.00 mmol) was taken up in ethanol (50.00 ml) and hydrazine hydrate (0.30 g, 0.29 ml, 6.00 mmol) was added. The reaction was heated to reflux for 3 hours. The reaction mixture was then allowed to cool to room temperature and cooled in ice, before the solid was filtered off and the filtrate was evaporated to yield the *isoxazoline* **60** (0.58 g, 95%) as a colourless solid. All data obtained were in accordance with those reported in the literature[129] and showed: mp 42-44 °C [Lit.[23] 40-42 °C]; δ_H 7.69-7.63 (2H, m, 2 × ArH), 7.48-7.39 (3H, m, 3 × ArH), 4.66 (1H, ddd, *J* 14.6, 10.3, 6.5, CH), 3.47 (1H, dd, *J* 16.9, 10.4, CH_a), 3.04 (1H, dd, *J* 16.9, 8.2, CH_b), 1.66-1.51 (2H, m, CH_2), 1.37-1.24 (4H, m, 2 × CH_2), 0.88 (3H, t, *J* 6.9, CH_3).

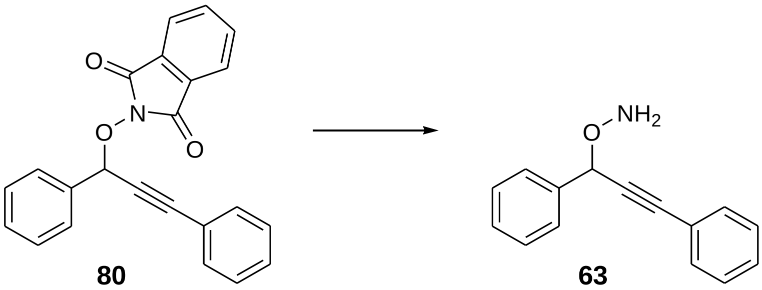
O-(1-Phenylhept-2-ynyl)hydroxylamine 85



79 **85**

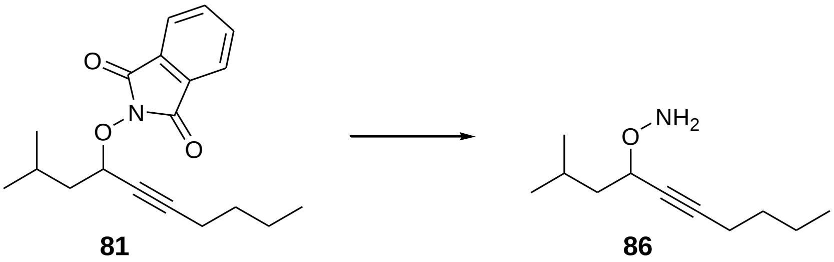
The phthalimide **79** (1.12 g, 3.37 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **85** (0.64 g, 93%) as a yellow oil (the title compound had been reported in the literature[130] but with no analysis), showing: δ_H 7.53 (2H, dd, *J* 8.0, 1.5, 2 × ArH), 7.45-7.27 (3H, m, 3 × ArH), 5.36 (1H, t, *J* 1.9, CH), 2.35-2.23 (2H, m, CH_2), 1.60-1.50 (2H, m, CH_2), 1.49-1.38 (2H, m, CH_2), 0.92 (3H, t, *J* 7.3, CH_3).

O-(1,3-Diphenylprop-2-yn-1-yl)hydroxylamine 63



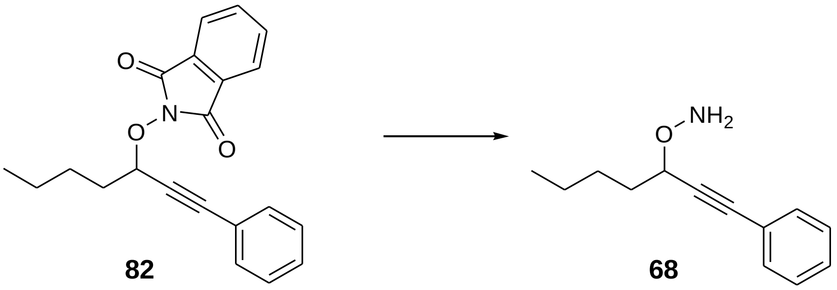
The phthalimide **80** (0.56 g, 1.58 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **63** (0.32 g, 91%) as an orange oil. All data obtained were in accordance with those reported in the literature[131] and showed: δ_H 7.61 (2H, dd, *J* 8.0, 1.4, 2 × ArH), 7.55-7.49 (2H, m, 2 × Ar-H), 7.45-7.37 (3H, m, 3 × ArH), 7.37-7.31 (3H, m, 3 × ArH), 5.61 (1H, s, CH), 5.27 (2H, br s, NH_2).

O-(2-Methyldec-5-yn-4-yl)hydroxylamine 86



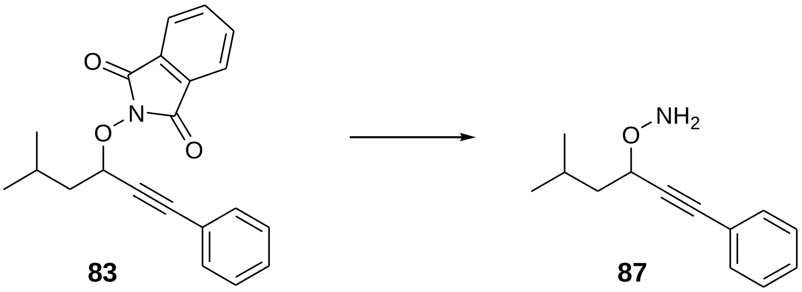
The phthalimide **81** (0.52 g, 1.66 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **86** (0.25 g, 82%) as a yellow oil (the title compound had been reported in the literature[30] but with no analysis), showing: δ_H 5.38 (2H, br s, NH_2), 4.28 (1H, tt, *J* 7.2, 1.9, CH), 2.23 (2H, td, *J* 7.0, 1.9, CH_2), 1.82 (1H, tt, *J* 13.4, 6.7, CH_a), 1.61 (1H, dt, *J* 14.4, 7.2, CH_b), 1.53-1.45 (3H, m, CH + CH_2), 1.44-1.37 (2H, m, CH_2), 0.94-0.89 (9H, m, 3 × CH_3).

O-(1-Phenylhept-1-yn-3-yl)hydroxylamine 68



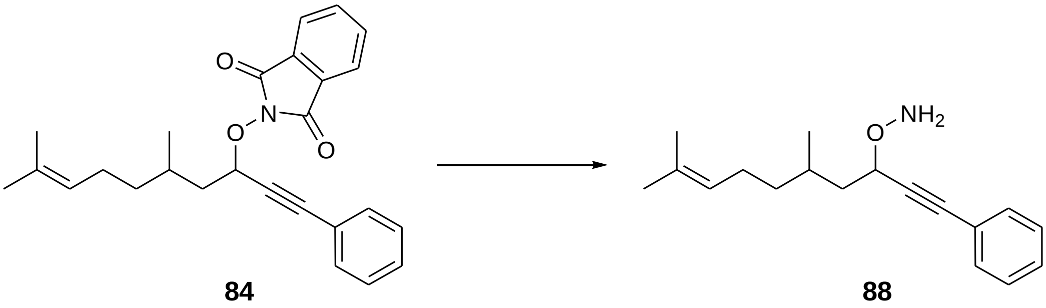
The phthalimide **82** (0.45 g, 1.35 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **68** (0.20 g, 74%) as a yellow oil, showing: δ_H 7.46 (2H, dd, *J* 6.7, 3.0, 2 × ArH), 7.35-7.27 (3H, m, 3 × ArH), 5.51 (2H, br s, NH_2), 4.48 (1H, t, *J* 6.7, CH), 1.86-1.71 (2H, m, CH_2), 1.52-1.45 (2H, m, CH_2), 1.43-1.29 (2H, m, CH_2), 0.93 (3H, t, *J* 7.3, CH_3).

O-(5-Methyl-1-phenylhex-1-yn-3-yl)hydroxylamine 87



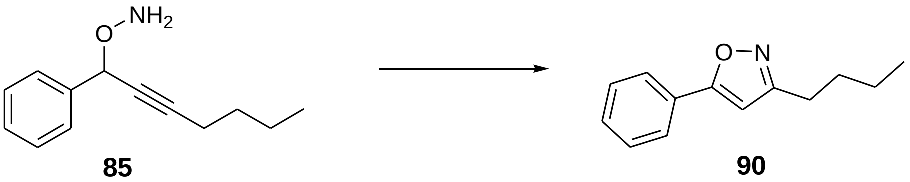
The phthalimide **83** (2.90 g, 8.69 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **87** (1.57 g, 89%) as a yellow oil (the title compound had been reported in the literature[30] but with no analysis), showing: δ_H 7.46 (2H, dd, *J* 6.7, 3.0, 2 × ArH), 7.33-7.29 (3H, m, 3 × ArH), 5.51 (2H, br s, NH_2), 4.52 (1H, t, *J* 7.2, CH), 1.98-1.83 (1H, m, CH), 1.74 (1H, dt, *J* 14.4, 7.2, CH_a), 1.63 (1H, dt, *J* 13.6, 7.2, CH_b), 0.98 (3H, d, *J* 6.6, CH_3), 0.96 (3H, d, *J* 6.6, CH_3).

(3*RS*,5*RS*) and (3*RS*,5*SR*) *O*-(5,9-Dimethyl-1-phenyldec-8-en-1-yn-3-yl)hydroxylamine 88



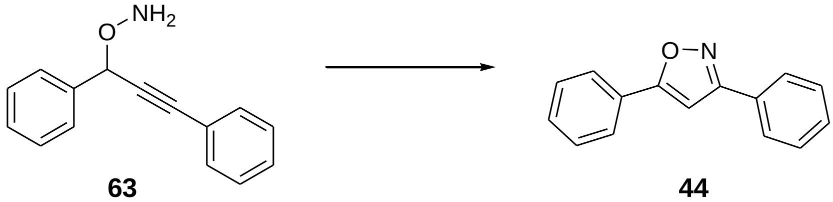
The phthalimide **84** (1.02 g, 2.55 mmol) was deprotected under the conditions described in General Method **C** to yield the *hydroxylamine* **88** (0.62 g, 90%) as a yellow oil, showing: δ_H 7.45 (2H, dd, *J* 6.7, 3.0, 2 × ArH), 7.33-7.28 (3H, m, 3 × ArH), 5.51 (2H, br s, NH_2), 5.13-5.08 (1H, m, C=CH), 4.63-4.51 (1H, m, CH), 2.08-1.95 (2H, m, CH_2), 1.93-1.83 (1H, m, CH), 1.82-1.72 (2H, m, CH_2), 1.67 (3H, s, CH_3), 1.60 (3H, s, CH_3), 1.46-1.34 (1H, m, CH_a), 1.28-1.19 (1H, m, CH_b), 0.97 (3H, d, *J* 6.5, CH_3).

3-Butyl-5-phenylisoxazole 90



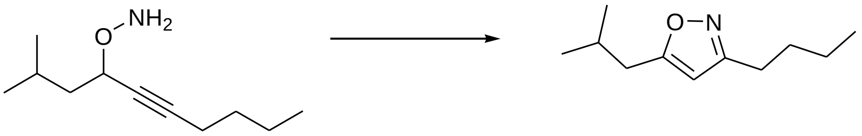
The hydroxylamine **85** (0.20 g, 0.98 mmol) was treated with 10% w/w silver nitrate on silica gel (6.69 g, 3.94 mmol) as described in General Method **D** to yield the title compound as 64% of the crude product (0.19 g, 96%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (5% diethyl ether/hexane) to give a sample of the *isoxazole* **90** as a viscous yellow oil. All data obtained were in accordance with those reported in the literature[132] and showed: ν_{max}/cm^{-1} [thin film] 3065, 2958, 2201, 1576, 1451, 765; δ_H 7.78-7.73 (2H, m, 2 × ArH), 7.48-7.40 (3H, m, 3 × ArH), 6.37 (1H, s, 4-H), 2.63 (2H, t, *J* 7.6, CH_2), 1.70 (2H, dt, *J* 15.3, 7.4, CH_2), 1.42 (2H, dq, *J* 14.7, 7.4, CH_2), 0.88 (3H, t, *J* 7.4, CH_3); δ_C 169.7 (ArC), 164.9 (ArC), 130.1 (ArCH), 129.1 (2 × ArCH), 127.9 (ArC), 125.7 (2 × ArCH), 99.3 (ArCH), 30.7 (CH_2), 26.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS *m/z* [APCI] $C_{13}H_{15}NO + H^+$ requires 202.1232, found 202.1231.

3,5-Diphenylisoxazole 44


63 **44**

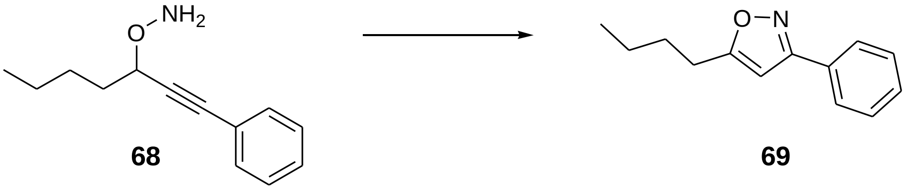
The hydroxylamine **63** (0.18 g, 0.80 mmol) was treated with 10% w/w silver nitrate on silica gel (1.90 g, 1.12 mmol) as described in General Method **D** to yield the title compound as 74% of the crude product (0.17 g, 96%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (5% diethyl ether/hexane) to give a sample of the *isoxazole* **44** as a pale yellow solid. All data obtained were in accordance with those reported in the literature[132] and showed: mp 136-139 °C [Lit.[132] 139-140 °C]; ν_{max}/cm^{-1} [film] 3583, 3114, 3049, 2358, 1463, 1451, 763; δ_H 7.90-7.82 (4H, m, 4 × ArH), 7.52-7.44 (6H, m, 6 × ArH), 6.84 (1H, s, 4-H); δ_C 170.2 (ArC), 162.8 (ArC), 130.0 (ArCH), 129.8 (ArCH), 129.0 (ArC), 128.8 (4 × ArCH), 127.3 (ArC), 126.6 (2 × ArCH), 125.7 (2 × ArCH), 97.3 (ArCH); HRMS *m/z* [APCI] $C_{15}H_{11}NO + H^+$ requires 222.0919, found 222.0919.

3-Butyl-5-isobutylisoxazole 91


86 **91**

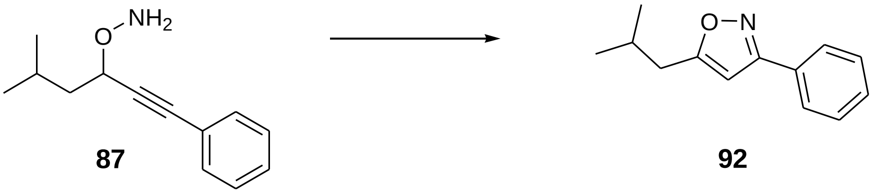
The hydroxylamine **86** (0.90 g, 0.49 mmol) was treated with 10% w/w silver nitrate on silica gel (3.34 g, 1.96 mmol) as described in General Method **D** to yield the title compound as 74% of the crude product (0.88 g, 99%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (5% diethyl ether/hexane) to give a sample of the *isoxazole* **91** as a yellow oil, showing: ν_{max}/cm^{-1} [thin film] 2959, 2360, 1602, 1467, 797; δ_H 5.81 (1H, s, 4-H), 2.65-2.55 (4H, m, CH_2), 2.06 (1H, m, CH), 1.62 (2H, m, CH_2), 1.38 (2H, dq, *J* 14.6, 7.3, CH_2), 0.97-0.91 (9H, m, 3 × CH_3); δ_C 172.0 (ArC), 163.7 (ArC), 100.8 (ArCH), 35.5 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 27.4 (CH), 25.5 (CH_2), 22.1 (2 × CH_3), 13.5 (CH_3); HRMS *m/z* [APCI] $C_{11}H_{19}NO + H^+$ requires 182.1545, found 182.1554.

5-Butyl-3-phenylisoxazole 69



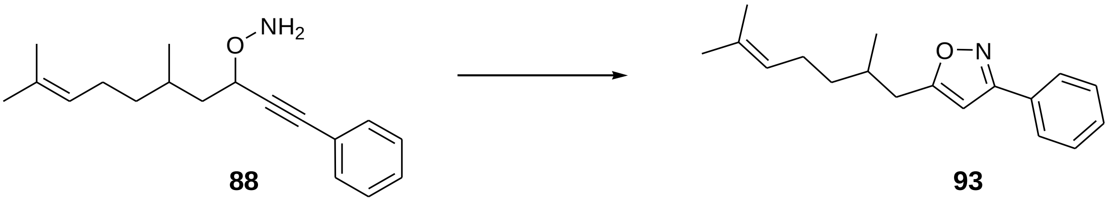
The hydroxylamine **68** (0.17 g, 0.82 mmol) was treated with 10% w/w silver nitrate on silica gel (3.48 g, 2.05 mmol) as described in General Method **D** to yield the title compound as 89% of the crude product (0.14g, 85%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (5-15% diethyl ether/hexane) to give a sample of the *isoxazole* **69** as a colourless oil. All data obtained were in accordance with those reported in the literature[133] and showed: ν_{max}/cm^{-1} [thin film] 3434, 2958, 2086, 1642, 1408, 767; δ_H 7.81-7.77 (2H, m, 2 × ArH), 7.47-7.41 (3H, m, 3 × ArH), 6.29 (1H, s, 4-H), 2.80 (2H, t, *J* 7.6, CH_2), 1.73 (2H, m, CH_2), 1.43 (2H, tq, *J* 14.7, 7.4, CH_2), 0.99-0.93 (3H, t, *J* 7.4, CH_3); δ_C 174.1 (ArC), 162.1 (ArC), 129.6 (ArCH), 129.28 (ArC), 128.6 (2 × ArCH), 126.6 (2 × ArC), 98.6 (ArCH), 29.4 (CH_2), 26.3 (CH_2), 22.0 (CH_2), 13.5 (CH_3); HRMS *m/z* [EI] $C_{13}H_{15}NO$ requires 201.1154, found 201.1154.

5-Isobutyl-3-phenylisoxazole 92



The hydroxylamine **87** (0.54 g, 2.66 mmol) was treated with 10% w/w silver nitrate on silica gel (13.69 g, 8.06 mmol) as described in General Method **D** to yield the title compound as 90% of the crude product (0.50 g, 94%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (10% diethyl ether/hexane) to give a sample of the *isoxazole* **92** as a yellow oil. All data obtained were in accordance with those reported in the literature[133] and showed: ν_{max}/cm^{-1} [thin film] 3127, 2960, 1602, 1470, 1408, 768; δ_H 7.82-7.77 (2H, m, 2 × ArH), 7.48-7.41 (3H, m, 3 × ArH), 6.29 (1H, s, 4-H), 2.68 (2H, d, *J* 7.1, CH_2), 2.15-2.04 (1H, m, CH), 1.00 (6H, d, *J* 6.7, 2 × CH_3); δ_C 173.5 (ArC), 162.5 (ArC), 130.0 (ArCH), 129.7 (ArC), 129.1 (2 × ArCH), 127.0 (2 × ArCH), 99.8 (ArCH), 36.0 (CH_2), 28.0 (CH), 22.6 (2 × CH_3); HRMS *m/z* [EI] $C_{13}H_{17}NO$ requires 201.1154, found 201.1158.

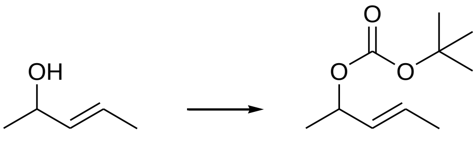
5-(2,6-Dimethylhept-5-enyl)-3-phenylisoxazole 93



The hydroxylamine **88** (0.25 g, 0.91 mmol) was treated with 10% w/w silver nitrate on silica gel (3.85 g, 2.27 mmol) as described in General Method **D** to yield the title compound as 83% of the crude product (0.23 g, 94%), the rest of which was the corresponding isoxazoline by ^{1}H NMR analysis. The crude product was chromatographed (5% diethyl ether/hexane) to give a sample of the *isoxazole* **93** as a colourless oil, showing: ν_{max}/cm^{-1} [thin film] 3126, 2925, 1601, 1471, 1408, 768; δ_H 7.80 (2H, d, *J* 7.0, 2 × ArH), 7.49-7.39 (3H, m, 3 × ArH), 6.29 (1H, s, 4-H), 5.10 (1H, t, *J* 6.5, C=CH), 2.80 (1H, dd, *J* 14.8, 5.6, CH$_a$), 2.63 (1H, dd, *J* 14.8, 7.9, CH$_b$), 2.04-1.90 (3H, m, CH + CH$_2$), 1.69 (3H, s, CH$_3$), 1.61 (3H, s, CH$_3$), 1.48-1.38 (1H, m, CH$_{a'}$), 1.31-1.21 (1H, m, CH$_{b'}$), 0.97 (3H, d, *J* 6.4, CH$_3$); δ_C 173.5 (ArC), 162.5 (ArC), 131.9 (C), 130.0 (ArCH), 129.7 (ArC), 129.1 (2 × ArCH), 127.0 (2 × ArCH), 124.4 (CH), 99.9 (ArCH), 36.8 (CH$_2$), 34.3 (CH$_2$), 32.2 (CH), 25.9 (CH$_3$), 25.7 (CH$_2$), 19.7 (CH$_3$), 17.9 (CH$_3$); HRMS *m/z* [APCI] $C_{18}H_{23}NO + H^+$ requires 270.1858, found 270.1867.

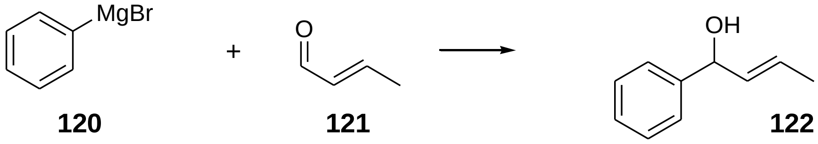
5.14 Chapter 3 compounds

tert-Butyl (*E*)-pent-3-en-2-yl carbonate 128



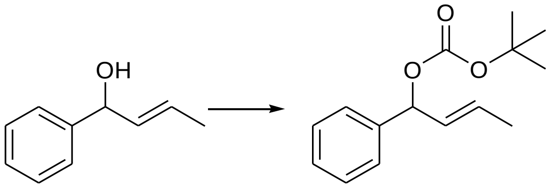
The alcohol **297** (1.00 g, 1.19 ml, 11.61 mmol) was treated with BOC-anhydride (2.66 g, 12.19 mmol) under the conditions described in General Method **F** to give the *carbonate* **128** (1.86 g, 86%) as a yellow oil, which was used without further purification. All data obtained were in accordance with those reported in the literature[134]: ν_{max}/cm^{-1} [thin film] 2981, 2935, 1739; δ_H 5.78-5.69 (1H, m, C=CH), 5.48 (1H, dd, *J* 15.3, 7.1, HC=C), 5.11-5.04 (1H, m, CH), 1.68 (3H, d, *J* 6.5, CH$_3$), 1.47 (9H, s, ^{t}Bu), 1.31 (3H, d, *J* 6.5, CH$_3$); δ_C 152.9 (CO), 130.6 (CH), 128.5 (CH), 81.6 (C), 74.2 (CH), 27.6 (^{t}Bu), 20.37 (CH$_3$), 17.60 (CH$_3$).

(*E*)-1-Phenylbut-2-en-1-ol 122


120 **121** **122**

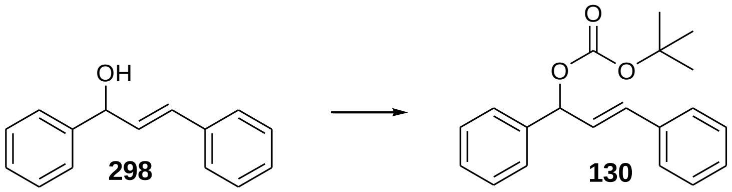
Crotonaldehyde **121** (0.90 ml, 11.00 mmol) was diluted in dry tetrahydrofuran (6.00 ml) and phenyl magnesium bromide **120** (1.00 molar solution in tetrahydrofuran, 15.00 ml, 15.00 mmol) was added slowly at 0 °C. The resulting solution was allowed to warm to room temperature over 4 hours, then quenched by the addition of saturated aqueous ammonium chloride (20.00 ml) and extracted with diethyl ether (3 × 10.00 ml). The combined organic extracts were dried over magnesium sulphate, filtered and evaporated to give the *alcohol* **122** (1.47 g, 90%) as a colourless oil, which was used without further purification. All data obtained were in accordance with those reported in the literature[135]: ν_{max}/cm^{-1} [thin film] 3360, 3029, 2916, 2855, 1675, 699; δ_H 7.27-7.22 (4H, m, 4 × ArH), 7.19-7.14 (1H, m, ArH), 5.69-5.53 (2H, m, 2 × C=CH), 5.02 (1H, d, *J* 6.4, CH), 2.25 (1H, br s, OH), 1.62 (3H, d, *J* 5.7, CH_3); δ_C 143.5 (ArC), 133.7 (ArCH), 128.5 (2 × ArCH), 127.5 (CH), 127.3 (CH), 126.2 (2 × ArCH), 75.2 (CH), 17.7 (CH_3).

tert-Butyl (*E*)-1-phenylbut-2-enyl carbonate 129


122 **129**

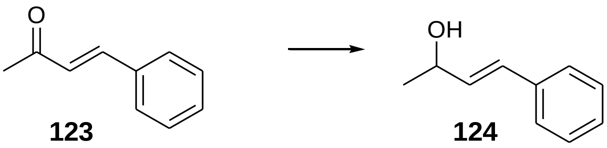
The alcohol **122** (0.50 g, 3.38 mmol) was treated with BOC-ON (0.83 g, 3.38 mmol) under the conditions described in General Method **E**, and the crude product was purified by trituration in cold petroleum ether to give the *carbonate* **129** (0.70 g, 83%) as a pale yellow oil, showing: ν_{max}/cm^{-1} [thin film] 2935, 1739, 1678, 754; δ_H 7.40-7.37 (2H, m, 2 × ArH), 7.35-7.28 (3H, m, 3 × ArH), 6.62 (1H, d, *J* 7.0, CH), 6.20 (1H, dd, *J* 16.0, 7.0, HC=C), 5.32 (1H, m, C=CH), 1.49 (9H, s, ^{t}Bu), 1.45 (3H, d, *J* 6.5, CH_3); δ_C 152.9 (CO), 136.4 (ArC), 131.8 (CH), 128.6 (2 × ArCH), 127.9 (CH), 126.6 (2 × ArCH), 126.5 (CH), 82.0 (C), 74.11 (CH), 27.9 (^{t}Bu), 20.6 (CH_3).

***tert*-Butyl (*E*)-1,3-diphenylallyl carbonate 130**



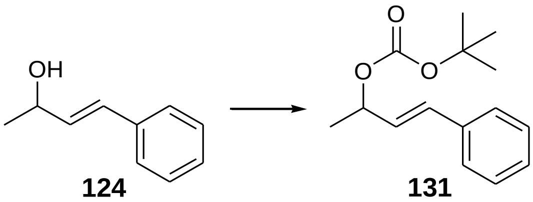
Alcohol **298** (2.00 g, 9.51 ml, 11.61 mmol) was treated with BOC-anhydride (2.18 g, 9.99 mmol) under the conditions described in General Method **F** to give the *carbonate* **130** (12.47 g, 84%) as a white crystalline solid, which was used without further purification. All data obtained were in accordance with those reported in the literature[136]: mp 98-99 °C [Lit.[63] 94-94.5 °C]; ν_{max}/cm^{-1} [thin film] 3030, 1740, 791, 742, 695; δ_H 7.50-7.44 (2H, m, 2 × ArH), 7.43-7.38 (4H, m, 4 × ArH), 7.37-7.30 (3H, m, 3 × ArH), 7.29-7.25 (1H, m, ArH), 6.70 (1H, d, *J* 15.8, C=CH), 6.41 (1H, dd, *J* 15.8, 7.0, HC=C), 6.24 (1H, d, *J* 7.0, CH), 1.52 (9H, s, ^{t}Bu).

(*E*)-4-Phenyl-3-buten-2-ol 124



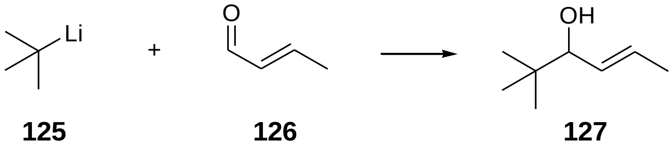
4-Phenyl-3-butene-2-one **123** (2.04 g, 14.00 mmol) was dissolved in methanol (20.00 ml), and sodium borohydride (0.56 g, 14.00 mmol) was added in one portion at 0 °C. The reaction was stirred at this temperature for 4 hours, before being neutralised with 2 M aqueous hydrochloric acid and extracted with ethyl acetate (3 × 20.00 ml). The combined organic extracts were dried, filtered and evaporated to give the *alcohol* **124** (2.00 g, 96%) as a white solid, which was used without further purification. All data obtained were in accordance with those reported in the literature[137]: mp 44-46 °C [Lit.[137] 40-43 °C]: ν_{max}/cm^{-1} [thin film] 3399, 3027, 2927, 1657, 749; δ_H 7.42-7.38 (2H, m, 2 × ArH), 7.37-2.32 (2H, m, 2 × ArH), 7.30-7.25 (1H, m, ArH), 6.58 (1H, d, *J* 15.9, C=CH), 6.29 (1H, dd, *J* 15.9, 6.4, HC=C), 4.50 (1H, dp, *J* 6.4, 1.1, CH), 2.41 (1H, br s, OH), 1.40 (3H, d, *J* 6.4, CH_3); δ_C 136.7 (ArC), 133.6 (CH), 129.4 (ArCH), 128.6 (2 × ArCH), 127.7 (CH), 126.5 (2 × ArCH), 69.0 (CH), 23.4 (CH_3); HRMS *m/z* [EI] $C_{10}H_{12}O$ requires 148.0888, found 148.0887.

tert-Butyl (*E*)-4-phenylbut-3-en-2-yl carbonate 131



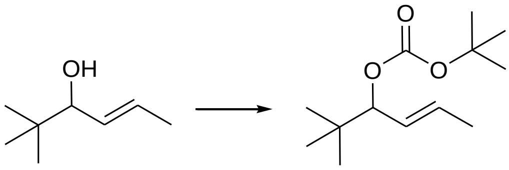
The alcohol **124** (0.10 g, 0.68 mmol) was treated with BOC-anhydride (0.15 g, 0.68 mmol) under the conditions described in General Method **F**, and the crude product was chromatographed (35% diethyl ether in hexane) to give the *carbonate* **131** (0.09 g, 53%) as a yellow oil, showing: ν_{max}/cm^{-1} [thin film] 2932, 1739, 1277, 851, 793, 757; δ_H 7.32-7.29 (2H, m, 2 × ArCH), 7.26-7.21 (2H, m, 2 × ArH), 7.19-7.14 (1H, m, ArH), 6.55 (1H, d, *J* 16.0, C=CH), 6.13 (1H, dd, *J* 16.0, 7.0, HC=C), 5.27 (1H, dq, *J* 7.0, 6.5, CH), 1.42 (9H, s, ^{t}Bu), 1.37 (3H, d, *J* 6.5, CH_3); δ_C 152.9 (CO), 136.4 (ArC), 131.8 (CH), 128.5 (2 × ArCH), 128.6 (ArCH), 127.9 (CH), 126.6 (2 × ArCH), 82.0 (C), 74.1 (CH), 27.9 (^{t}Bu), 20.6 (CH_3); HRMS *m/z* [EI] $C_{15}H_{20}O$ requires 248.1412, found 248.1414.

(*E*)-2,2-Dimethylhex-4-en-ol 127



To anhydrous diethyl ether (10.00 ml) was added crotonaldehyde **126** (14.27 mmol, 1.00 g, 1.18 ml) and the solution was cooled to -30 °C, before the dropwise addition of *tert*-butyl lithium **125** (1.70 molar solution in pentane, 7.81 ml, 13.27 mmol). The reaction mixture was allowed to stir and warm to room temperature overnight before being cooled in an ice bath, then quenched by the dropwise addition of water (0.50 ml) followed by 2 M aqueous sulphuric acid (10.00 ml). The layers were separated and the organic portion was washed with saturated aqueous sodium bicarbonate (15.00 ml), and brine (15.00 ml). The organic extracts were dried, filtered and evaporated to give the *alcohol* **127** (1.45 g, 79%) as a yellow oil, which was used without further purification. All data obtained were in accordance with those reported in the literature[138]: ν_{max}/cm^{-1} [thin film] 3419, 2961, 2870; δ_H 5.67-5.58 (1H, m, C=CH), 5.55-5.47 (1H, m, HC=C), 3.63 (1H, d, *J* 7.5, CH), 1.94 (1H, br s, OH), 1.69 (3H, dd, *J* 6.3, 0.8, CH_3), 0.87 (9H, s, ^{t}Bu); δ_C 131.1 (CH), 128.1 (CH), 81.0 (CH), 34.7 (C), 29.5 (CH_3), 25.7 (^{t}Bu).

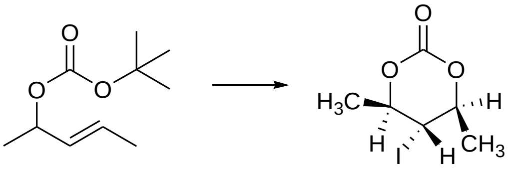
tert-Butyl (*E*)-2,2-dimethylhex-4-en-3-yl carbonate 132



127 **132**

The alcohol **127** (1.39 g, 10.84 mmol) was treated with BOC-anhydride (2.48 g, 11.38 mmol) under the conditions described in General Method **F** to give the *carbonate* **132** (2.36 g, 95%) as a colourless oil, which was used without further purification and which showed: ν_{max}/cm^{-1} [thin film] 2964, 2871, 1739, 1279, 1254, 969; δ_H 5.74-5.65 (1H, m, C=CH), 5.44 (1H, ddq, *J* 15.3, 8.1, 1.5, HC=C), 4.69 (1H, d, *J* 8.1, CH), 1.69 (3H, dd, *J* 6.5, 1.5, CH_3), 1.46 (9H, s, ^{t}Bu), 0.89 (9H, s, ^{t}Bu); δ_C 153.5 (C), 130.5 (CH), 126.6 (CH), 81.3 (C), 74.6 (CH), 34.4 (C), 27.9 (3 × CH_3), 25.8 (3 × CH_3), 20.5 (CH_3).

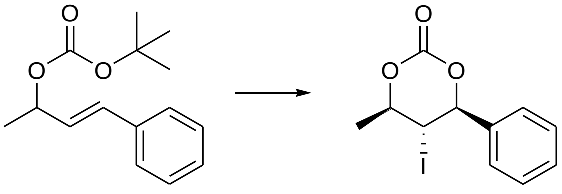
(4*SR*,6*RS*)-4,6-Dimethyl-5-iodo-1,3-dioxan-2-one 133



128 **133**

The carbonate **128** (0.50 g, 2.68 mmol) was treated with potassium carbonate (1.11 g, 8.05 mmol) and iodine monobromide solution (8.06 ml, 4.03 mmol) under the conditions described in General Method **G** to yield the title compound as 85% of the crude product (0.683 g, 99%), the rest of which was the corresponding 5-membered isomer by ^{1}H NMR analysis. The crude product was recrystallised from warm hexane to give a sample of the cyclic *carbonate* **133** as a pale grey crystals, showing: mp 114-116 °C; ν_{max}/cm^{-1} [thin film] 2979, 1740, 1273; δ_H 4.65 (2H, dq, *J* 10.8, 6.2, 2 × CHMe), 3.73 (1H, t, *J* 10.8, CHI), 1.65 (6H, d, *J* 6.2, 2 × CH_3); δ_C 148.1 (CO), 80.5 (2 × CH), 27.1 (CHI), 20.8 (2 × CH_3); HRMS *m/z* [APCI] $C_6H_9O_3I + H^+$ requires 256.9675, found 256.9663.

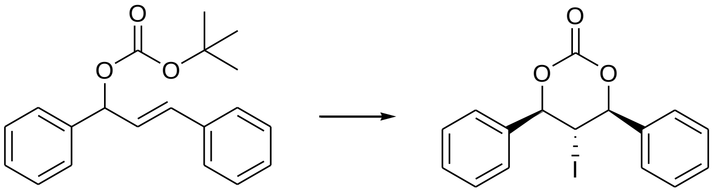
(4*SR*,6*RS*)-4-Methyl-6-phenyl-5-iodo-1,3-dioxan-2-one 138



131 **138**

The carbonate **131** (1.37 g, 5.52 mmol) was treated with potassium carbonate (2.29 g, 16.55 mmol) and 1M iodine monobromide solution (16.6 ml, 16.6 mmol) under the conditions described in General Method **G** (except with 3 equivalents of iodine monobromide) to yield the title compound as 85% of the crude product (1.84, 94%), the rest of which was the corresponding 5-membered isomer by ^{1}H NMR analysis. The crude product was recrystallised from warm hexane to give a sample of the *cyclic carbonate* **138** as a brown solid, showing; mp 120-122 °C; ν_{max}/cm^{-1} [film] 1755, 1614, 1460, 1389, 1203, 757; δ_H 7.44-7.41 (3H, m, 3 × ArCH), 7.39-7.36 (2H, m, 2 × ArCH), 5.46 (1H, d, *J* 10.8, CHPh), 4.82 (1H, dq, *J* 10.8, 6.2, CHMe), 4.06 (1H, t, *J* 10.8, CHI), 1.74 (3H, d, *J* 6.2, CH_3); δ_C 148.0 (CO), 135.5 (ArC), 130.1 (ArCH), 128.8 (2 × ArCH), 127.6 (2 × ArCH), 85.7 (CH), 80.5 (CH), 27.3 (CHI), 21.0 (CH_3); HRMS *m/z* [EI] $C_{11}H_{11}IO_3$ requires 317.9753, found 317.9747.

(4*SR*,6*RS*)-4,6-Diphenyl-5-iodo-1,3-dioxan-2-one 140

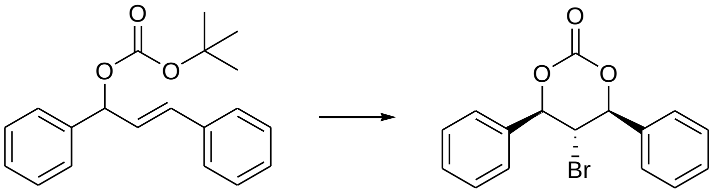


130 **140**

The carbonate **130** (143 mg, 0.46 mmol) was treated with potassium carbonate (0.19 g, 1.38 mmol) and iodine monobromide solution (2.76 ml, 0.69 mmol) under the conditions described in General Method **G** to yield the title compound as 78% of the crude product (0.173 g, 99%), the rest of which was the corresponding 5-membered isomer by ^{1}H NMR analysis. The crude product was recrystallised from warm hexane to give a sample of the cyclic *carbonate* **140** as a white solid, showing: mp 170-173 °C; ν_{max}/cm^{-1} [thin film] 3434, 2101, 1738, 1641, 1087; δ_H 7.50-7.40 (10H, m, 10 × ArCH), 5.64 (2H, d, *J* 10.9, 2 × CH), 4.38 (1H, t, *J* 10.9, CHI); δ_C 148.1 (CO), 135.4 (2 × ArC), 130.1 (2 × ArCH), 128.7 (4 × ArCH), 127.6 (4 × ArCH), 85.9 (2 × CH), 27.8 (CHI); HRMS *m/z* [APCI] $C_{16}H_{13}O_3I$ +H requires 380.9988, found

380.9977.

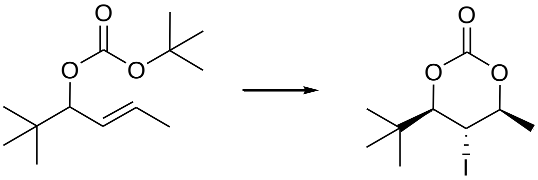
(4*SR*,6*RS*)-5-Bromo-4,6-diphenyl-1,3-dioxan-2-one 142



130 **142**

The carbonate **130** (200 mg, 0.64 mmol) in anhydrous dichloromethane (20.00 ml) at -78 °C, was treated with potassium carbonate (0.27 g, 1.92 mmol) and bromine (0.05 ml, 1.92 mmol) and the reaction mixture was allowed to stir at this temperature for one hour. The work-up was carried out as described in General Method **G** to yield the title compound as ~50% of the crude product (0.211 g, 99%), the rest of which was thought to be the corresponding 5-membered isomer by ^{1}H NMR analysis. The crude product was recrystallised from warm hexane to give a sample of the cyclic *carbonate* **142** as a white solid, showing: mp 182-185 °C; ν_{max}/cm^{-1} [film] 1745, 1611, 1461, 1242, 751; δ_H 7.51-7.38 (10H, m, 10 × ArCH), 5.55 (2H, d, *J* 10.4, 2 × CH), 4.23 (1H, t, *J* 10.4, CHBr); δ_C 142.1 (CO), 134.6 (2 × ArC), 130.0 (2 × ArCH), 128.7 (4 × ArCH), 127.4 (4 × ArCH), 84.2 (2 × CH), 47.8 (CHBr); HRMS *m/z* [APCI] $C_{16}H_{13}O_3Br$ +H requires 333.0126, found 333.0136.

(4*SR*,6*RS*)-4-*tert*-Butyl-5-iodo-6-methyl-1,3-dioxan-2-one 143



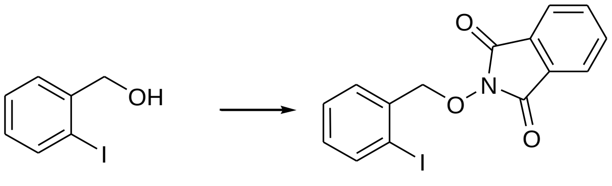
132 **143**

The carbonate **132** (0.67 g, 2.94 mmol) was treated with potassium carbonate (1.22 g, 8.82 mmol) and iodine monobromide solution (8.82 ml, 4.41 mmol) under the conditions described in General Method **G** to yield the title compound as 56% of the crude product (0.73 g, 88%), the rest of which was the corresponding 5-membered isomer by ^{1}H NMR analysis. The crude product was chromatographed (20% ethyl acetate in hexane) to give the *cyclic carbonate* **143** as a brown oil, showing: ν_{max}/cm^{-1} [thin film] 2871, 1800, 1364, 1158, 735; δ_H 4.73 (1H, d, *J* 7.4, CH), 4.52 (1H, dq, *J* 10.6, 6.2, CH), 3.88 (1H, dd, *J* 10.6, 7.4, CHI), 1.63 (3H, d, *J* 6.2,

CH_3), 1.10 (9H, s, ^{t}Bu); δ_C 153.9 (CO), 87.8 (CH), 80.4 (CH), 34.3 (C), 24.6 (3 × CH_3), 23.0 (CHI), 21.6 (CH_3); HRMS *m/z* [EI] $C_9H_{15}O_3I$ requires 298.0066, found 298.0058.

5.15 Chapter 4 compounds

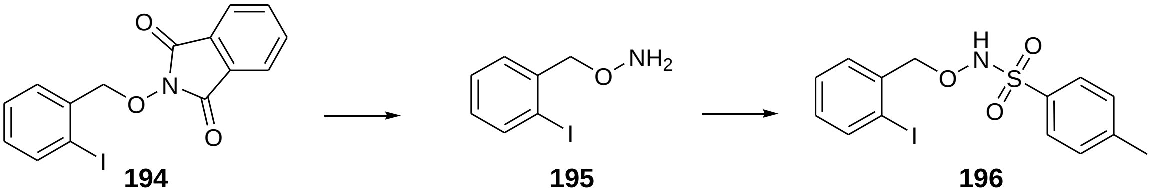
2-(2-Iodobenzyloxy)isoindoline-1,3-dione 194



193 **194**

The benzyl alcohol **193** (5.00 g, 21.36 mmol) was reacted with *N*-hydroxyphthalimide (6.79 g, 42.73 mmol) under the conditions described in General Method **B**, and the crude product was purified by elution through a silica plug with copious amounts of dichloromethane to give the *phthalimide* **194** (5.72 g, 71%) as a yellow oil, showing: ν_{max}/cm^{-1} [film] 1730, 1466, 1387, 1186, 752, 518; δ_H 7.86 (1H, dd, *J* 7.9, 1.1, ArH), 7.81 (2H, dd, *J* 5.2, 2.0, 2 × ArH), 7.75 (2H, dd, *J* 5.2, 2.0, 2 × ArH), 7.62 (1H, dd, *J* 7.7, 1.6, ArH), 7.38 (1H, dt, *J* 7.5, 1.1, ArH), 7.06 (1H, dt, *J* 7.7, 1.6, ArH), 5.31 (2H, s, CH_2); δ_C 163.3 (2 × C), 143.5 (C), 139.6 (CH), 134.5 (2 × CH), 131.1 (CH), 130.7 (CH), 128.9 (2 × C), 128.5 (CH), 123.5 (2 × CH), 86.0 (C), 82.9 (CH_2); HRMS *m/z* [APCI] $C_{15}H_{10}NO_3I$ +H requires 379.9784, found 379.9766.

2-Iodobenzyloxy-4-toluenesulfonamide 196

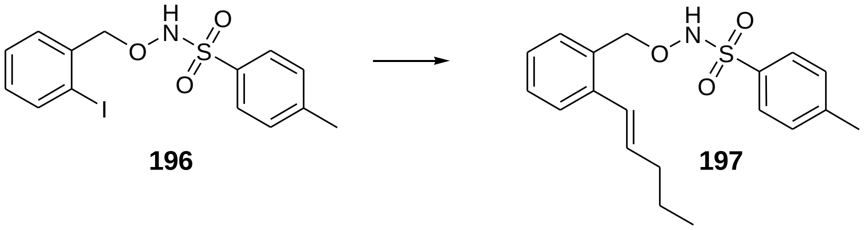


194 **195** **196**

The phthalimide **194** (3.47 g, 9.15 mmol) was taken up in ethanol (120.00 ml) and hydrazine hydrate (0.92 g, 0.89 ml, 18.30 mmol) was added and the reaction was heated to reflux for 3 hours. The reaction mixture was allowed to cool to room temperature and then cooled in ice, before the solid was filtered off and the filtrate was evaporated to yield the *hydroxylamine* **195** (2.21 g, 97%) which was immediately taken on to the tosylation step. The crude free hydroxylamine **195** (2.21 g, 8.88 mmol) was taken up in anhydrous dichloromethane (180.00 ml) and the resulting solution was stirred at -78 °C. Pyridine (0.71 g, 0.73 ml, 8.97 mmol) was added and the reaction mixture was stirred for 5 minutes at this temperature before *p*-tosyl chloride

(1.69 g, 8.88 mmol) was added in one portion. The resulting reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of water (100.00 ml), and the aqueous layer was extracted with dichloromethane (3 × 50.00 ml). The combined organic extracts were washed with saturated aqueous copper sulphate (150.00 ml) and water (3 × 50 ml), before being dried, filtered and evaporated to yield the crude product which was purified by column chromatography (50% diethyl ether in hexane) to give the *tosyl protected hydroxylamine* **196** (2.38 g, 67%) as a yellow oil, showing: ν_{max}/cm^{-1} [film] 1641, 1620, 1475, 1467, 1381, 1016, 735; δ_H 7.85-7.84 (2H, m, 2 × ArH), 7.83 (2H, dd, *J* 3.1, 1.3, 2 × ArH), 7.38 (1H, dd, *J* 7.6, 1.9, ArH), 7.36-7.31 (2H, m, 2 × ArH), 7.02 (1H, dt, *J* 7.7, 1.9, ArH), 6.95 (1H, s, NH), 5.06 (2H, s, CH_2), 2.44 (3H, s, CH_3); HRMS *m/z* [EI] $C_{14}H_{14}NO_3SI$ -H requires 401.9661, found 401.9656.

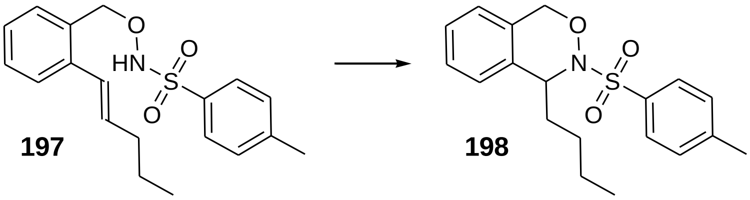
(E)-*N*-[(2-Pent-1-en-1-yl)benzyloxy]4-toluenesulfonamide 197



The tosyl protected hydroxylamine **196** (73 mg, 0.18 mmol), Premix[12] (400 mg, corresponds to: $Pd(OAc)_2$ 4.44 mg, 1,1'-bis(di-*tert*-butyl phosphino)ferrocine 5.56 mg and K_2CO_3 390 mg) and 1-penten-1-yl boronic acid (20 mg, 0.18 mmol) were taken up in ethanol and water 1:1 (1.00 ml of each) and heated with 100 W power to 100 °C in the microwave for 0.5 hours. The reaction mixture was partitioned between diethyl ether (10.00 ml) and water (10.00 ml). The organic layer was washed with water (10.00 ml), and then saturated aqueous sodium chloride (10.00 ml), then again with water (10.00 ml). The combined aqueous washings were extracted with diethyl ether (3 x 10.00 ml), and the combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by column chromatography (40% diethyl ether in hexane) to give the *title compound* **197** (35 mg, 56%) as a pale yellow viscous oil, showing: ν_{max}/cm^{-1} [film] 1691, 1641, 1620, 1475, 1467, 1431, 1381, 1016, 735; δ_H 7.74 (2H, d, *J* 8.4, 2 × ArH), 7.34 (1H, d, *J* 7.6, ArH), 7.23 (2H, d, *J* 8.4, 2 × ArH), 7.21 (2H, dd, *J* 4.0, 2.4, 2 × ArH), 7.12 (1H, dt, *J* 7.6, 1.2, ArH), 6.86 (1H, s, NH), 6.68 (1H, d, *J* 15.6, HC=C), 6.09 (1H, dt, *J* 15.6, 7.2, C=CH), 5.00 (2H, s, CH_2), 2.35 (3H, s, tosyl CH_3), 2.17 (2H, dq, *J* 7.2, 1.2, CH_2), 1.44 (2H, q, *J* 7.2, CH_2), 0.88 (3H, t, *J* 7.2, CH_3); δ_C 146.5 (ArC), 144.9 (ArC), 138.4

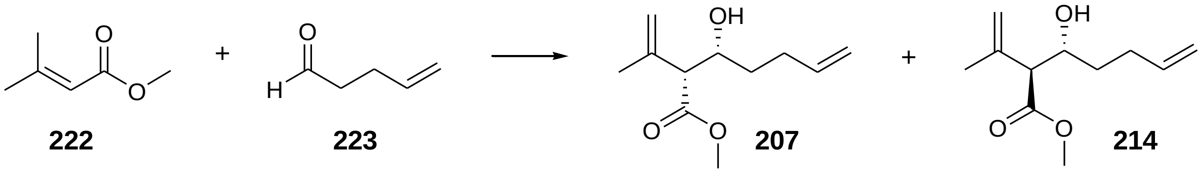
(ArC), 138.3 (ArC), 133.7 (ArCH), 131.2 (ArCH), 129.8 (2 × ArCH), 129.1 (CH), 128.3 (2 × ArCH), 126.8 (ArCH), 126.7 (ArCH), 126.0 (CH), 77.2 (CH_2), 35.4 (CH_2), 22.6 (CH_2), 21.8 (CH_3), 13.7 (CH_3).

4-Butyl-3-tosyl-3,4-dihydro-1H-benzo[1,2]oxazine 198



(*E*)-4-Methyl-*N*-(2-(pent-1-enyl)benzyloxy)benzenesulfonamide **197** (0.087 mmol, 30 mg) was taken up in anhydrous dichloromethane (10.00 ml) and the solution was cooled to 0 °C in an ice bath. Concentrated sulphuric acid (5 drops) was added and the reaction mixture was left to stir for 2 hours with no further addition of coolant. The reaction was then quenched with saturated aqueous potassium carbonate (10.00 ml) and a small amount of solid potassium carbonate was also added. The aqueous layer was extracted with dichloromethane (3 x 5.00 ml) and the combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by column chromatography (60% diethyl ether in hexane) to give the *cyclised product* **198** (10 mg, 33%) an orange viscous oil, showing: ν_{max}/cm^{-1} [film] 2956, 2928, 2871, 1166, 814, 744; δ_H 7.76 (2H, d, *J* 8.0, 2 × ArH), 7.22 (2H, d, *J* 8.0, 2 × ArH), 7.18-7.11 (2H, m, 2 × ArH), 7.07 (1H, d, *J* 7.0, ArH), 6.85 (1H, d, *J* 7.0, ArH), 5.11 (1H, d, *J* 14.5, CH_a), 4.93 (1H, dd, *J* 8.0, 5.5, CH), 4.70 (1H, d, *J* 14.5, CH_b), 2.35 (3H, s, tosyl CH_3), 1.96-1.90 (1H, m, $CH_{a'}$), 1.80-1.74 (1H, m, $CH_{b'}$), 1.39-1.34 (2H, m, CH_2), 1.27-1.22 (2H, m, CH_2), 0.81 (3H, t, *J* 7.3, CH_3); δ_C 141.2 (ArC), 141.1 (ArC), 136.3 (ArC), 136.2 (ArC), 129.5 (2 × ArCH), 128.5 (2 × ArCH), 126.8 (ArCH), 126.7 (ArCH), 124.1 (ArCH), 124.0 (ArCH), 70.0 (CH_2), 56.7 (CH), 35.4 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 21.5 (CH_3), 13.9 (CH_3); HRMS *m/z* [ES] $C_{19}H_{23}NO_3S$ +H requires 346.148, found 346.146.

(2*SR*, 3*SR*)- and (2*RS*, 3S*R*)-Methyl 3-hydroxy-2-(prop-1-en-2-yl)hept-6-enoate 207 and 214

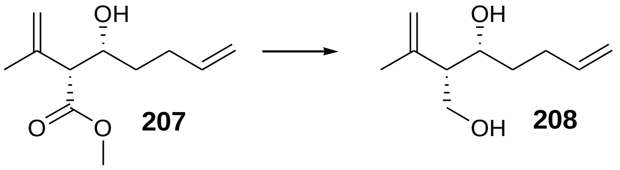


To a solution of diisopropylamine (2.49 g, 3.45 ml, 24.60 mmol) in anhydrous tetrahydrofuran (15.00 ml) at 0 °C was added *n*-butyl lithium (2.50 molar in hexane, 8.68 ml, 21.71 mmol). The solution was stirred at this temperature for 15 minutes. The reaction mixture was then cooled to -78 °C and 1,3-dimethyl-3,4,5,6-tetranhydro-2(1H)-pyrimidinone (2.78 g, 2.62 ml, 21.71 mmol) was added, before stirring for another 0.5 hours at -78 °C. A solution of methyl-3,3-dimethylacrylate **222** (1.65 g, 1.75 ml, 14.47 mmol) in anhydrous tetrahydrofuran (5.00 ml) was then added to the reaction mixture, before stirring for a further 0.5 hours at -78 °C to allow the dienolate to form. A solution of 4-pentenal **223** (1.70 g, 2.00 ml, 20.26 mmol) in anhydrous tetrahydrofuran (5.00 ml) was then added to the solution, before stirring at -78 °C for a final 1.5 hours. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution (10.00 ml). The aqueous layer was extracted with diethylether (3 x 25.00 ml). The combined organic extracts were washed with saturated aqueous sodium chloride (50.00 ml) before being dried, filtered and evaporated to yield the crude products which were separated by column chromatography (12% diethyl ether in hexane) to give:

i) the *syn-hydroxyl ester* **207** (0.355 g, 25% of the theoretical 50% yield) as a colourless oil, showing: δ_H 5.82 (1H, ddt, *J* 17.0, 10.2, 6.7, HC=C), 5.04 (2H, m, $H_2C=C$), 4.96 (2H, m, $C=CH_2$), 4.03 (1H, dt, *J* 7.1, 5.6, CH), 3.69 (3H, s, OCH_3), 3.07 (1H, d, *J* 7.1, CH), 2.32-2.23 (1H, m, CH_a), 2.20-2.10 (1H, m, CH_b), 1.82 (3H, dd, *J* 1.4, 0.8, CH_3), 1.56-1.50 (2H, m, CH_2); δ_C 173.0 (C=O), 140.1 (C), 138.2 (CH), 116.8 (CH_2), 114.9 (CH_2), 69.8 (CH), 58.9 (CH), 52.0 (CH_3), 34.1 (CH_2), 30.0 (CH_2), 21.4 (CH_3)

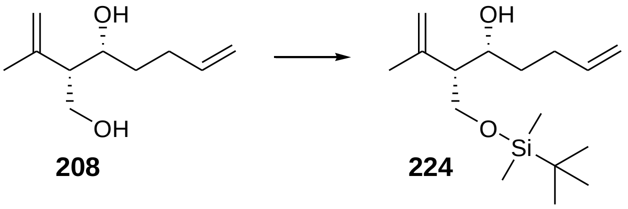
ii) the *anti-hydroxyl ester* **214** (0.771 g, 54% of the theoretical 50% yield) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3455, 3079, 2977, 2950, 1736, 1642, 1196, 1165, 909; δ_H 5.85-5.74 (1H, m, HC=C), 5.04 (1H, ddd, *J* 17.1, 3.5, 1.7, $C=CH_a$), 4.98-4.90 (3H, m, $C=CH_b$ + $H_2C=C$), 4.00 (1H, dt, *J* 8.9, 2.8, CH), 3.71 (3H, s, OCH_3), 3.06 (1H, d, *J* 8.9, CH), 2.70 (1H, br s, OH), 2.33-2.22 (1H, m, $CH_{a'}$), 2.19-2.08 (1H, m, $CH_{b'}$), 1.72 (3H, dd, *J* 1.3, 0.9, CH_3), 1.57 (1H, dddd, *J* 14.0, 9.5, 7.1, 2.8, $CH_{a''}$), 1.47-1.36 (1H, m, $CH_{b''}$); δ_C 173.9 (C=O), 140.0 (C), 138.2 (CH), 115.8 (CH_2), 115.0 (CH_2), 70.2 (CH), 59.7 (CH), 52.1 (CH_3), 33.2 (CH_2), 29.8 (CH_2), 21.1 (CH_3); HRMS *m/z* [APCI] $C_{11}H_{18}O_3$ +H requires 199.1334, found 199.1325.

(2*SR*, 3*RS*)-2-(Prop-1-en-2-yl)hept-6-ene-1,3-diol 208



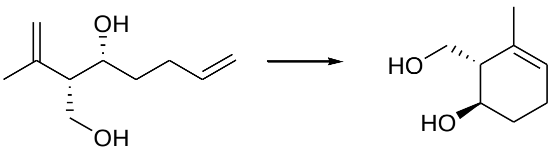
To a solution of the *syn*-hydroxyl ester **207** (226 mg, 1.14 mmol) in anhydrous tetrahydrofuran (10.00 ml) was added lithium aluminium hydride powder (108 mg, 2.85 mmol) at room temperature. The resulting solution was stirred at this temperature for 1.5 hours. The reaction mixture was then cooled in an ice bath before being quenched by the addition of 2.00 M aqueous sodium hydroxide (1.00 ml). Excess magnesium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to give the *syn-diol* **208** (190 mg, 98%) as a colourless oil (which was used without further purification), showing: ν_{max}/cm^{-1} [film] 3359, 3076, 2920, 1642, 1027, 910; δ_H 5.88-5.76 (1H, m, HC=C), 5.10-4.75 (4H, m, 2 × C=CH_2), 3.77 (1H, dd, *J* 10.9, 6.5, CH_a), 3.75-3.70 (1H, m, CH), 3.67 (1H, dd, *J* 10.9, 7.2, CH_b), 2.48 (2H, br s, 2 × OH), 2.35 (1H, dd, 13.1, 6.6, CH), 2.31-2.19 (1H, m, $CH_{a'}$), 2.18-2.07 (1H, m, $CH_{b'}$), 1.79 (3H, s, CH_3), 1.66-1.41 (2H, m, CH_2); δ_C 148.4 (C), 138.3 (CH), 115.4 (2 ×CH_2), 70.4 (CH), 62.6 (CH_2), 54.9 (CH), 34.0 (CH_2), 30.2 (CH_2), 21.4 (CH_3).

(2*SR*, 3*RS*)-2-(*tert*-Butyldimethylsilyloxymethyl)-prop-1-en-2-yl-hept-6-ene-3-ol 224



To a solution of the *syn*-diol **208** (134 mg, 0.79 mmol) in anhydrous dichloromethane (5.00 ml) at 0 °C, were added triethylamine (0.09 g, 0.12 ml, 0.87 mmol), DMAP (10 mg, 0.08 mmol) and TBDMS chloride (125 mg, 0.83 mmol).The reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of water (5.00 ml). The aqueous layer was extracted with dichloromethane (3 × 10.00 ml), and the combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by eluting through a plug of silica with dichloromethane to give the *protected syn-diol* **224** (90 mg, 40%) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3368, 2925, 2854, 1641, 1034, 910; δ_H 5.90-5.76 (1H, m, HC=C), 5.08-4.71 (4H, m, 2 × C=CH_2), 3.82 (1H, dd, *J* 9.9, 7.3, CH_a), 3.79-3.75 (1H, m, CH), 3.74 (1H, dd, *J* 9.9, 5.4, CH_b), 2.36-2.23 (2H, m, CH_2), 2.19-2.09 (1H, m, CH), 1.79 (3H, s, CH_3), 1.65-1.54 (2H, m, CH_2), 0.89 (9H, s, ^{t}Bu), 0.06 (6H, s, 2 × CH_3); δ_C 143.5 (C), 138.4 (CH), 115.4 (2 × CH_2), 70.5 (CH), 62.2 (CH_2), 54.8 (CH), 33.8 (CH_2), 29.7 (CH_2), 25.8 (3 × CH_3), 21.9 (CH_3), 14.1 (C), -3.6 (2 × CH_3); HRMS *m/z* [APCI] $C_{16}H_{32}O_2Si$ +H requires 285.2250, found 285.2245.

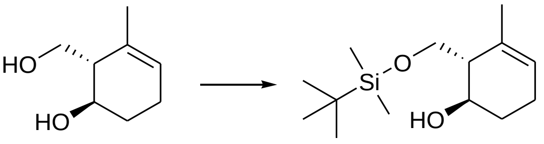
(1*SR*, 2*RS*)-2-(Hydroxymethyl)-3-methylcyclohex-3-en-1-ol 227



208 **227**

A solution of the *syn*-diol **208** (68 mg, 0.40 mmol) and Grubbs II catalyst (10 mg, 0.012 mmol) in dry dichloromethane (10.00 ml) was stirred at room temperature overnight. The solvent was evaporated to give the *cyclic anti-diol* **227** (57 mg, 100%) as a brown oil (which was used without further purification), showing: ν_{max}/cm^{-1} [film] 3350, 2934, 1670, 1379, 1051; δ_H 5.42 (1H, t, *J* 3.5, C=CH), 4.13 (1H, dt, 9.3, 4.6, CH), 3.90-3.72 (2H, m, CH_2), 3.55 (2H, br s, 2 × OH), 2.42 (1H, br app s, CH), 2.19-1.94 (2H, m, CH_2), 1.80-1.71 (2H, m, CH_2), 1.69 (3H, d, *J* 1.8, CH_3); δ_C 131.0 (C), 123.7 (CH), 71.4 (CH), 62.6 (CH_2), 46.0 (CH), 27.2 (CH_2), 23.4 (CH_2), 21.9 (CH_3); HRMS *m/z* [EI] $C_8H_{14}O_2$ -H_2O requires 124.0888, found 124.0885.

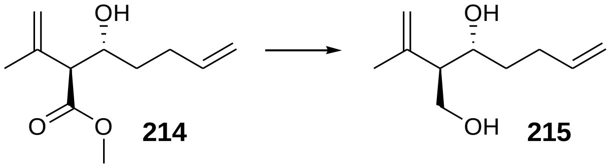
(1*SR*, 2*RS*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohex-3-enol 229



227 **229**

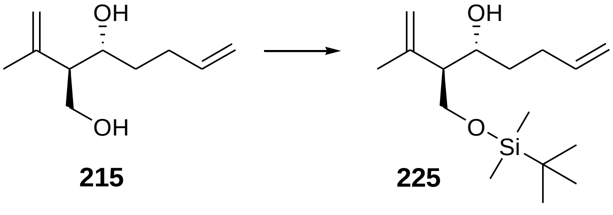
To a solution of the cyclic *anti*-diol **227** (80 mg, 0.56 mmol) in anhydrous dimethylformamide (5.00 ml) at 0 °C, were added triethylamine (62 mg, 0.09 ml, 0.62 mmol), DMAP (8 mg, 0.062 mmol) and TBDMS chloride (89 mg, 0.59 mmol). The reaction mixture was allowed to warm to room temperature and stir for 24 hours. The reaction was quenched by the addition of water (5.00 ml), and the aqueous layer was extracted with ethyl acetate (3 × 10.00 ml). The combined organic extracts were washed with water (2 × 10.00 ml), then dried, filtered and evaporated to yield the crude product which was purified by column chromatography (10% ethyl acetate in hexane) to give the *protected cyclic anti-diol* **229** (57 mg, 40%) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3381, 2929, 1654, 1257, 1079, 839; δ_H 5.43 (1H, t, *J* 3.4, C=CH), 4.08-3.96 (2H, m, CH + OH), 3.90 (1H, dd, *J* 10.4, 8.7, CH_a), 3.85 (1H, dd, *J* 10.4, 3.7, CH_b), 2.47-2.40 (1H, m, CH), 2.18-2.08 (2H, m, CH_2), 1.80-1.72 (2H, m, CH_2), 1.69 (3H, d, *J* 1.5, CH_3), 0.91 (9H, s, ^{t}Bu), 0.10 (6H, s, 2 × CH_3).

(2*SR*, 3*SR*)-2-(Prop-1-en-2-yl)hept-6-ene-1,3-diol 215



To a solution of the *anti*-hydroxyl ester **214** (590 mg, 2.98 mmol) in anhydrous tetrahydrofuran (20.00 ml) was added lithium aluminium hydride powder (283 mg, 7.45 mmol) at room temperature. The resulting solution was stirred at this temperature for 1.5 hours. The reaction mixture was then cooled in an ice bath before being quenched by the addition of 2.00 M aqueous sodium hydroxide solution (1.00 ml). Excess magnesium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to give the *anti-diol* **215** (507 mg, 100%) as a colourless oil (which was used without further purification), showing: ν_{max}/cm^{-1} [film] 3359, 3076, 2974, 2919, 1642, 1376, 1043, 1000, 910; δ_H 5.87-5.76 (1H, m, HC=C), 5.04 (1H, dtd, *J* 17.2, 3.8, 1.6, C=CH_a), 4.96 (1H, ddt, *J* 10.2, 3.0, 1.6, C=CH_b), 4.90-4.85 (1H, m, $H_{a'}$C=C), 4.80-4.74 (1H, m, $H_{b'}$C=C), 3.87-3.80 (1H, m, CH), 3.75-3.70 (2H, m, CH_2), 2.70 (2H, br s, 2 × OH), 2.29-2.20 (2H, m, CH_2), 2.17-2.07 (1H, m, CH), 1.68 (3H, dd, *J* 1.4, 0.9, CH_3), 1.67-1.59 (1H, m, $CH_{a''}$), 1.50-1.39 (1H, m, $CH_{b''}$); δ_C 143.6 (C), 138.5 (CH), 115.0 (CH_2), 113.5 (CH_2), 73.7 (CH), 62.2 (CH_2), 54.4 (CH), 34.7 (CH_2), 29.8 (CH_2), 21.7 (CH_3).

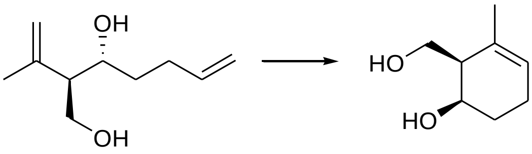
(2*SR*, 3*SR*)-2-(*tert*-Butyldimethylsilyloxymethyl)-prop-1-en-2-yl-hept-6-ene-3-ol 225



To a solution of the *anti*-diol **215** (134 mg, 0.79 mmol) in anhydrous dimethylformamide (5.00 ml) at 0 °C, were added triethylamine (0.09 g, 0.12 ml, 0.87 mmol), DMAP (10 mg, 0.08

mmol) and TBDMS chloride (125 mg, 0.83 mmol). The reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition on water (5.00 ml). The aqueous layer was extracted with dichloromethane (3 × 10.00 ml), and the combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by eluting through a plug of silica with dichloromethane to give the *protected anti-diol* **225** (90 mg, 81%) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 3497, 2929, 2857, 1642, 1472, 1256, 1103, 895; δ_H 5.83 (1H, ddt, *J* 17.0, 10.2, 6.7, HC=C), 5.03 (1H, ddd, *J* 17.1, 3.6, 1.6, C=CH$_a$), 4.94 (1H, ddt, *J* 10.2, 2.2, 1.6, C=CH$_b$), 4.86-4.81 (1H, m, C=CH$_{a'}$), 4.73 (1H, d, *J* 0.7, C=CH$_{b'}$), 4.03 (1H, br s, OH), 3.88-3.76 (3H, m, CH + CH$_2$), 2.35-2.25 (1H, m, CH$_{a''}$), 2.22 (1H, td, *J* 8.8, 4.3, CH), 2.18-2.08 (1H, m, CH$_{b''}$), 1.68 (3H, dd, *J* 1.3, 0.9, CH$_3$), 1.62-1.54 (1H, m, CH$_{a'''}$), 1.48-1.38 (1H, m, CH$_{b'''}$), 0.90 (9H, s, ^{t}Bu), 0.09 (6H, s, 2 × CH$_3$); δ_C 143.9 (C), 139.9 (CH), 114.4 (CH$_2$), 113.0 (CH$_2$), 74.4 (CH), 67.1 (CH$_2$), 54.1 (CH), 34.6 (CH$_2$), 29.5 (CH$_2$), 25.8 (3 × CH$_3$), 22.07 (CH$_3$), 18.2 (C), -5.5 (2 × CH$_3$); HRMS *m/z* [APCI] $C_{16}H_{32}O_2Si + H^+$ requires 285.2250, found 285.2237.

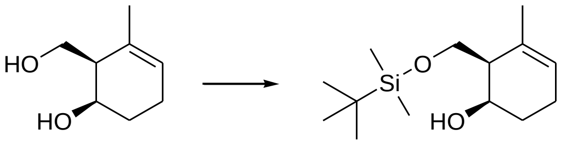
(1*SR*, 2*SR*)-2-(Hydroxymethyl)-3-methylcyclohex-3-enol 226



215 **226**

A solution of the *anti*-diol **215** (430 mg, 2.53 mmol) and Grubbs 2nd catalyst (68 mg, 0.08 mmol) in dry dichloromethane (25.00 ml) was stirred at room temperature for 5 days. The solvent was evaporated to yield the crude product which was purified by column chromatography (40% ethyl acetate in hexane) to give the *cyclic syn-diol* **226** (176 mg, 50%) as an off-white viscous oil, showing: ν_{max}/cm^{-1} [film] 3337, 2928, 1665, 1379, 1049, 809; δ_H 5.48 (1H, d, *J* 1.4, C=CH), 4.01 (1H, dd, *J* 10.6, 3.4, CH$_a$), 3.92 (1H, ddd, *J* 10.1, 7.1, 3.3, CH), 3.58 (1H, dd, *J* 10.6, 8.3, CH$_b$), 3.21 (2H, br s, 2 × OH), 2.19 (1H, app br s, CH), 2.11-1.99 (2H, m, CH$_2$), 1.85 (1H, ddd, *J* 12.9, 8.4, 4.9, CH$_{a'}$), 1.65 (3H, s, CH$_3$), 1.62-1.52 (1H, m, CH$_{b'}$); δ_C 130.9 (C), 124.6 (CH), 71.4 (CH), 64.2 (CH$_2$), 49.5 (CH), 29.5 (CH$_2$), 23.2 (CH$_2$), 21.3 (CH$_3$); HRMS *m/z* [EI] $C_8H_{14}O_2$ -H_2O requires 124.0888, found 124.0884.

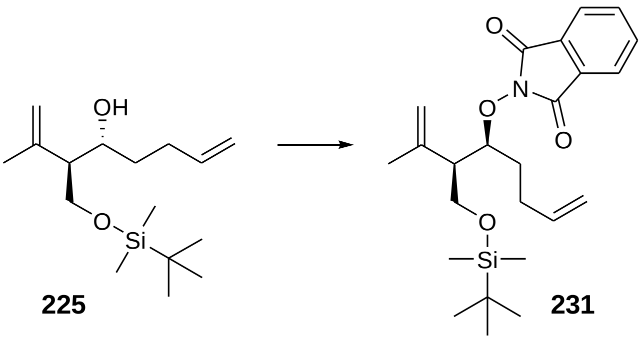
(1*SR*, 2*SR*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohex-3-enol 228



226 **228**

A solution of the protected *anti*-diol **226** (248 mg, 0.87 mmol) and Grubbs II catalyst (22 mg, 0.026 mmol) in anhydrous dichloromethane (10.00 ml) was stirred at room temperature for 3 days. The solvent was evaporated to give the *cyclic protected syn-diol* **228** (224 mg, 100%) as a brown solid (which was used without further purification), showing: decomposes 110 °C; ν_{max}/cm^{-1} [film] 3399, 2955, 2928, 2857, 1661, 1472, 1389, 1257, 1098, 836; δ_H 5.45-5.40 (1H, m, C=CH), 4.03 (1H, dd, *J* 9.8, 4.2, CH$_a$), 3.85 (1H, ddd, *J* 10.2, 6.8, 3.4, CH), 3.46 (1H, t, *J* 9.8, CH$_b$), 2.25-2.17 (1H, m, CH), 2.06-1.96 (2H, m, CH$_2$), 1.84 (1H, ddd, *J* 9.2, 8.5, 4.0, CH$_{a'}$), 1.60 (3H, d, *J* 1.2, CH$_3$), 1.56-1.47 (1H, m, CH$_{b'}$), 0.88 (9H, s, ^{t}Bu), 0.07 (6H, s, 2 × CH$_3$); δ_C 130.9 (C), 124.2 (CH), 72.1 (CH), 66.3 (CH$_2$), 49.3 (CH), 28.8 (CH$_2$), 25.8 (3 × CH$_3$), 23.3 (CH$_2$), 21.3 (CH$_3$), 18.1 (C), -5.8 (2 × CH$_3$); HRMS *m/z* [APCI] $C_{14}H_{28}O_2Si$ +H requires 257.1937, found 257.1944.

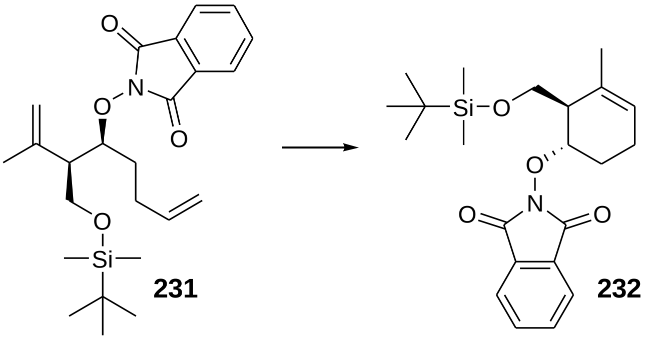
(2*SR*,3*RS*)-2-((Prop-1-en-2-yl)hept-6-ene-1-*tert*-butyldimethylsilyloxy-3-yloxy)isoindoline-1,3-dione 231



225 **231**

The protected *anti*-diol **225** (100 mg, 0.35 mmol), tributylphosphine (106 mg, 0.13 ml, 0.53 mmol) and *N*-hydroxyphthalimide (86 mg, 0.53 mmol) were successively dissolved in anhydrous tetrahydrofuran (5.00 ml) with stirring at 0 °C, before diethyl azodicarboxylate (92 mg, 0.08 ml, 0.53 mmol) was added to the solution. After 10 minutes, the reaction mixture was allowed to warm to room temperature and stir for 24 hours. The solvent was removed under reduced pressure to yield the crude product which was purified by column chromatography (5% ethyl acetate in hexane) to give the *syn protected hydroxlamine* **231** (14 mg, 9%) as a colourless oil, showing: ν_{max}/cm^{-1} [film] 2958, 2924, 2851, 1737, 1463, 1260, 1098; δ_H 7.81 (2H, dd, *J* 5.5, 3.1, 2 × ArH), 7.73 (2H, dd, 5.5, 3.1, 2 × ArH), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.6, HC=C), 5.04 (1H, ddd, *J* 17.0, 3.3, 1.6, C=CH_a), 4.97-4.89 (2H, m, C=CH_b + C=$CH_{a'}$), 4.90 (1H, d, *J* 0.7, C=$CH_{b'}$), 4.53 (1H, dd, *J* 11.0, 6.0, CH), 4.01 (1H, dd, *J* 10.2, 5.8, $CH_{a''}$), 3.86 (1H, dd, *J* 10.2, 6.9, $CH_{b''}$), 2.57 (1H, dd, *J* 11.0, 5.8, CH), 2.36-2.27 (1H, m, $CH_{a'''}$), 2.22-2.14 (1H, m, $CH_{b'''}$), 1.87 (3H, s, CH_3), 1.85-1.80 (2H, m, CH_2), 0.86 (9H, s, ^{t}Bu), 0.04 (6H, s, 2 × CH_3); HRMS *m/z* [APCI] $C_{24}H_{35}NO_4Si$ +H requires 430.2412, found 430.2402.

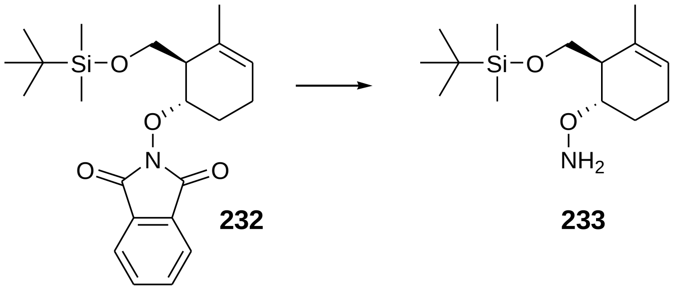
(1*SR*,2*RS*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohexen-3-yloxy)isoindoline-1,3-dione 232



231 **232**

A solution of the *syn* protected hydroxylamine **231** (21 mg, 0.049 mmol) and Grubbs II catalyst (2 mg, 0.002 mmol) in anhydrous dichloromethane (5.00 ml) was stirred at room temperature overnight. The solvent was evaporated to give the *cyclised anti protected hydroxylamine* **232** (20 mg, 100%) as a brown oil (which was used without further purification or sampling for analysis), showing: δ_H 7.83 (2H, dd, *J* 5.5, 3.0, 2 × ArH), 7.74 (2H, dd, 5.5, 3.0, 2 ×ArH), 5.43 (1H, d, *J* 1.6, C=CH), 4.45 (1H, ddd, *J* 11.0, 5.1, 3.5, CH), 4.14-4.05 (2H, m, CH_2), 2.55-2.50 (1H, m, CH), 2.31 (1H, d, *J* 15.2, CH_a), 2.19-2.05 (2H, m, CH_2), 1.92-1.84 (1H, m, CH_b), 1.76 (3H, d, *J* 1.6, CH_3), 0.89 (9H, s, ^{t}Bu), 0.07 (6H, s, 2 × CH_3).

(1*SR*,2*RS*)-*O*-(2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohexen-3-yl) hydroxylamine 233

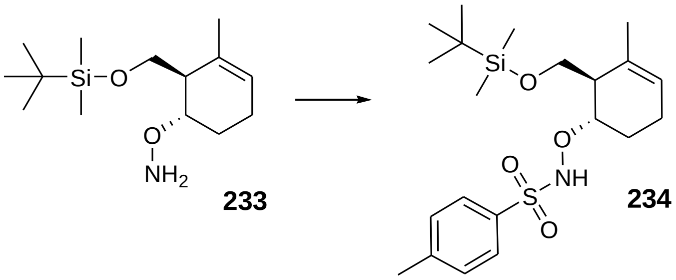


232 **233**

To the cyclised *anti* protected hydroxylamine **232** (20 mg, 0.0489 mmol) in diethyl ether

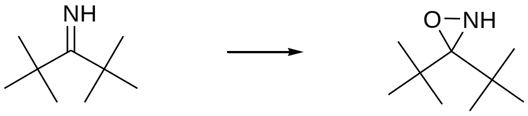
(1.00 ml) was added methylamine (40% w/w solution in water, 0.0009 ml, 0.10 mmol) at room temperature. After 1 hour of stirring at this temperature, the reaction mixture was cooled in an ice bath before the addition of petroleum ether (1.00 ml). The solution was filtered through magnesium sulphate, and the filtrate was evaporated to give the *free anti hydroxylamine* **233** (19 mg, 99%) as a brown oil (which was used without further purification or sampling for analysis), showing: δ_H 5.50 (2H, br s, NH_2), 5.40 (1H, app br s, C=CH), 3.91-3.86 (1H, m, CH), 3.76 (1H, dd, *J* 10.2, 7.0, CH_a), 3.63 (1H, dd, *J* 10.2, 3.5, CH_b), 2.58 (1H, m, CH), 2.06 (2H, m, CH_2), 1.72 (3H, d, *J* 1.4, CH_3), 1.71-1.61 (2H, m, CH_2), 0.91 (9H, s, ^{t}Bu), 0.06 (6H, s, 2 × CH_3).

(1*SR*,2*RS*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohexen-3-yloxy-4-toluenesulfonamide 234



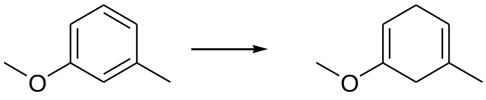
The crude free *anti* hydroxylamine **233** (13 mg, 0.0489 mmol) was dissolved in anhydrous dichloromethane (1.00 ml) and the resulting solution was stirred at -78 °C. Pyridine (4 mg, 0.049 mmol) was added and the reaction mixture was stirred for 5 minutes at this temperature before the addition of *p*-tosyl chloride (9 mg, 0.047 mmol). The resulting reaction mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched by the addition of saturated aqueous copper sulphate (1.00 ml), and the aqueous layer was extracted with dichloromethane (3 × 5.00 ml). The combined organic extracts were dried, filtered and evaporated to give the *tosyl protected anti hydroxylamine* **234** (31 mg, 100% - including excess tosyl residues) as a brown oil (which was used without further purification or sampling for analysis), showing: δ_H 7.74 (2H, d, *J* 8.2, 2 × ArH), 7.25 (2H, d, *J* 8.2, 2 × ArH), 5.38 (1H, app br s, C=CH), 4.28-4.20 (1H, m, CH), 3.63 (1H, dd, *J* 10.6, 7.5, CH_a), 3.52 (1H, dd, *J* 10.6, 2.4, CH_b), 2.69-2.59 (1H, m, CH), 2.37 (3H, s, CH_3), 2.11-1.98 (2H, m, CH_2), 1.80-1.72 (1H, m, $CH_{a'}$), 1.71 (3H, s, CH_3), 1.57 (1H, dd, *J* 14.6, 6.2, $CH_{b'}$), 0.78 (9H, s, ^{t}Bu), 0.00 (6H, s, 2 × CH_3).

3,3-Di-*tert*-butyl-1,2-oxaziridine 245[47]


248 **245**

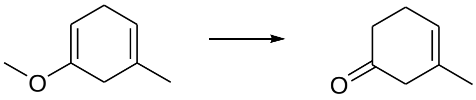
To a solution of 2,2,4,4-tetramethyl-3-pentanone imine **248** (5.00 g, 0.0354 mol) in anhydrous dichloromethane (17.00 ml) over molecular sieves, was added dropwise a dried solution of *m*CPBA (8.73 g of the 77% pure solid, 0.0389 mol) in dichloromethane (78.00 ml) at 0 °C. The reaction mixture was stirred at this temperature for 1 hour before the solvent was evaporated to yield the crude product, which was purified by filtering off the solid impurities which were insoluble in cold hexane, to give the *oxaziridine* **245** (4.55 g, 82%) as a pale green oil. All data obtained were in accordance with those reported in the literature[47] and showed: δ_H 3.72 (1H, br s, NH), 1.05 (18H, s, 2 × ^{t}Bu); δ_C 85.1 (C), 37.5 (2 × C), 28.0 (6 × CH_3).

1-Methoxy-5-methylcyclohexa-1,4-diene 239


238 **239**

Methyl anisole **238** (23.21 g, 23.95 ml, 0.19 mol) was dissolved in anhydrous tetrahydrofuran (50.00 ml) and *t*-butanol (80.00 ml) and cooled to -78 °C. Liquid ammonia (approx 500 ml) was then introduced. Lithium metal (3.68 g, 0.53 mol) was added portion-wise to the solution. Stirring was continued for 1 hour at -33 °C before the addition of methanol (20.00 ml) to the reaction mixture. The reaction was quenched by the slow addition of water (60.00 ml), and then left to warm to room temperature overnight so that the ammonia evaporated. The mixture was extracted with diethyl ether (3 × 80.00 ml) and the combined organic extracts were washed with water (4 × 50.00 ml) before being dried, filtered and evaporated to give the *diene* **239** (17.56 g, 74%) as a colourless oil (which was used without further purification). All data obtained were in accordance with those reported in the literature[139] and showed: δ_H 5.38 (1H, app d, J 1.1, HC=C), 4.60 (1H, app s, C=CH), 3.52 (3H, s, OCH_3), 2.77-2.72 (2H, m, CH_2), 2.58 (2H, t, J 7.6, CH_2), 1.67 (3H, s, CH_3).

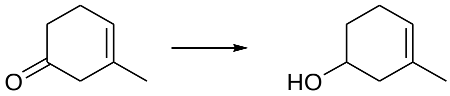
3-Methylcyclohex-3-enone 240



239 **240**

The diene **239** (5.27 g, 0.042 mol) was dissolved in chloroform (25.00 ml), and to this solution was added perchloric acid (0.242 g of 70% w/w aqueous solution, 0.241 mmol) in water (50.00 ml) which had been cooled in an ice bath. The reaction mixture was then stirred for 2 days at room temperature. The chloroform was removed under reduced pressure and diethyl ether was added (50.00 ml). Sodium chloride was added to the biphasic solution until the aqueous layer was saturated, which was then extracted with diethyl ether (3 × 50.00 ml). The combined organic extracts were washed with water (50.00 ml) before being dried, filtered and evaporated to yield the crude product which was purified by column chromatography (4% ethyl acetate in hexane) to give the *ketone* **240** (1.66 g, 36%) as a colourless oil (the title compound had been reported in the literature[140] but with no analysis), showing: δ_H 5.58-5.54 (1H, m, HC=C), 2.74 (2H, app s, CH_2), 2.42-2.34 (4H, m, 2 × CH_2), 1.69 (3H, s, CH_3); δ_C 210.5 (C=O), 132.2 (C), 121.0 (CH), 44.5 (CH_2), 38.3 (CH_2), 25.0 (CH_2), 22.7 (CH_3).

3-Methylcyclohex-3-enol 237

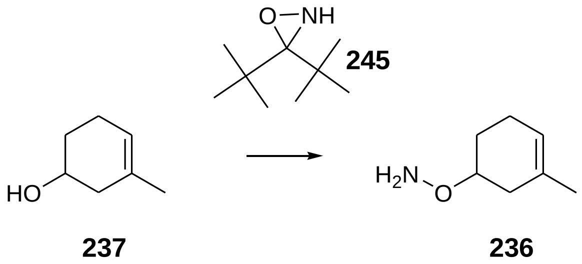


240 **237**

The ketone **240** (1.64 g, 14.89 mmol) was dissolved in anhydrous diethyl ether (100.00 ml) and the solution was cooled to -30 °C. Lithium aluminium hydride solution (1.00 molar in hexane, 7.45 ml, 7.45 mmol) was added and the reaction mixture was left to stir in the cooling bath for 1.5 hours. The reaction was quenched by the addition of 2.00 M aqueous sodium hydroxide (1.00 ml). Excess magnesium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to yield the crude product which was purified by column chromatography (60% diethyl ether in hexane) to give the *alcohol* **237** (1.31 g, 78% yield) as a colourless oil. All data obtained were in accordance with those reported in the literature[141] and showed: δ_H 5.37-5.33 (1H, m, HC=C), 3.97-3.91 (1H, m, CH), 2.23 (1H, dd, *J* 16.7, 3.8, CH_a), 2.17-2.10 (1H, m, $CH_{a'}$), 2.08-1.99 (1H, m, $CH_{b'}$), 1.92 (1H, dd, *J* 16.7, 6.5, CH_b), 1.85 (1H, br s, OH), 1.82-1.75 (1H, m, $CH_{a''}$), 1.64 (3H, d, *J* 0.4, CH_3), 1.54 (1H, m, $CH_{b''}$); δ_C 131.3 (C), 120.5 (CH), 67.3 (CH), 39.1 (CH_2), 30.5

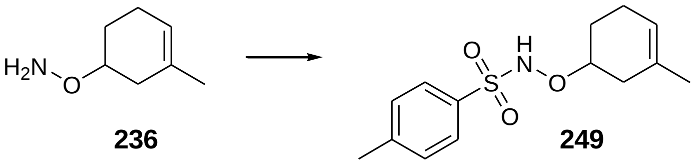
(CH_2), 23.5 (CH_3), 23.2 (CH_2).

O-(3-Methylcyclohexenyl)hydroxylamine 236



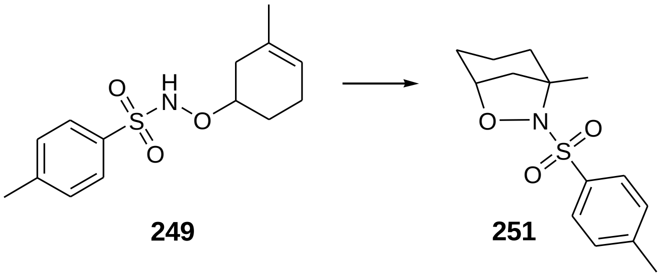
To a suspension of potassium hydroxide (that had been rinsed twice with anhydrous hexane and blown dry under a stream of nitrogen, 0.73 g of 30% w/w suspension in mineral oil, 5.49 mmol) in *N*,*N'*-dimethylpropyleneurea (5.90 ml), was added dropwise a solution of the alcohol **237** (0.50 g, 4.46 mmol) and 18-crown-6 (0.118 g, 0.446 mmol) in *N*,*N'*-dimethylpropyleneurea (5.90 ml) at room temperature. The reaction mixture was stirred for 1 hour at this temperature. This alkoxide solution was then added dropwise to a solution of the oxaziridine **245** (1.40 g, 8.92 mmol) in *N*,*N'*-dimethylpropyleneurea (5.90 ml) at -40 °C. The reaction mixture was then allowed to warm to room temperature and stirred for 2 hours. 1.00 M aqueous hydrochloric acid was added to acidify to solution, which was then washed with dichloromethane (3 × 10.00 ml). The aqueous layer was then made alkali with 2.00 M aqueous sodium hydroxide to pH 12, and extracted with diethyl ether (3 × 20.00 ml). The combined organic extracts were dried, filtered and evaporated to give the *free hydroxylamine* **236** (calculated from the ^{1}H NMR spectrum as 238 mg, 42%) as a yellow oil in residual *N*,*N'*-dimethylpropyleneurea (which was used without further purification), showing: ν_{max}/cm^{-1} [film] 3456, 2932, 2863, 1252, 1217; δ_H 5.29 (1H, app d, *J* 1.0, HC=C), 5.24 (2H, br s, NH_2), 3.82-3.68 (1H, m, CH), 2.17 (1H, d, *J* 16.4, CH_a), 2.09-1.93 (2H, m, $CH_{a'}$ + $CH_{b'}$), 1.90 (1H, m, CH_b), 1.85-1.75 (1H, m, $CH_{a''}$), 1.58 (3H, s, CH_3), 1.54-1.43 (1H, m, $CH_{b''}$); δ_C 131.6 (C), 121.0 (CH), 79.4 (CH), 35.3 (CH_2), 26.5 (CH_2), 23.7 (CH_3), 23.5 (CH_2).

3-Methylcyclohexenyloxy-4-toluenesulfonamide 249


236 **249**

The crude free hydroxylamine **236** (38 mg, 0.299 mmol, calculated as a percentage by weight from the NMR spectra due to residual *N,N'*-dimethylpropyleneurea) was dissolved in anhydrous dichloromethane (10.00 ml) and the resulting solution was stirred at -78 °C. Pyridine (24 mg, 0.03 ml, 0.302 mmol) was added and the reaction mixture was stirred for 5 minutes. *p*-tosyl chloride (57 mg, 0.299 mmol) was added in one portion and the reaction mixture was stirred overnight without any further addition of coolant. The reaction was quenched by the addition of water (10.00 ml), and the aqueous layer was extracted with dichloromethane (3 × 10.00 ml). The combined organic extracts were successively washed with saturated aqueous copper sulphate (10.00 ml), saturated aqueous sodium bicarbonate (10.00 ml) and water (10.00 ml), before being dried, filtered and evaporated to yield the crude product which was purified by column chromatography (20% diethyl ether in hexane) to give the *tosyl protected hydroxylamine* **249** (36 mg, 43%) as a yellow oil, showing: ν_{max}/cm^{-1} [film] 1678, 1641, 1620, 1475, 1467, 1414, 1392, 1076; δ_H 7.81 (2H, d, *J* 8.2, 2 × ArH), 7.34 (2H, d, *J* 8.2, 2 × ArH), 6.82 (1H, s, NH), 5.34 (1H, app s, HC=C), 4.37-4.24 (1H, m, CH), 2.45 (3H, s, CH_3), 2.33-2.21 (2H, m, CH_2), 2.03 (2H, app s, CH_2), 2.00-1.93 (1H, m, CH_a), 1.92-1.83 (1H, m, CH_b), 1.64 (3H, s, CH_3); HRMS m/z [EI] $C_{14}H_{19}NO_3$ requires 281.1086, found 281.1080.

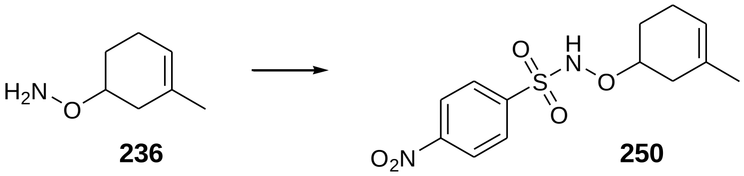
N-(4-methylphenylsulfonyl)-3-methyl-2-aza-1-oxabicyclo[3.2.1]octane 251


249 **251**

The tosyl protected hydroxylamine **249** (17 mg, 0.0604 mmol) in anhydrous dichloromethane (1.00 ml) was added to triflic acid (4.5 mg, 2.7 µl, 0.0302 mmol) in anhydrous dichloromethane (0.10 ml) in an ice bath, and the reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous potassium carbonate (0.10 ml).

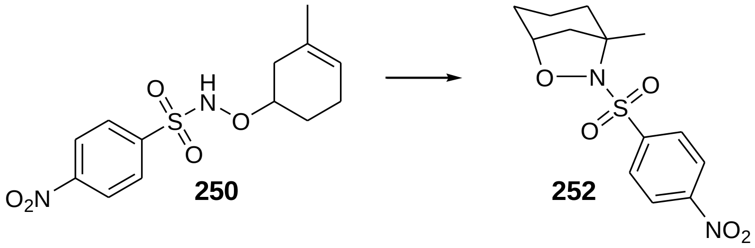
Excess magnesium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to give the *protected cyclised product* **251** (14 mg, 85%) as a yellow oil (a sample was further purified by column chromatography (30% diethyl ether in hexane) for analysis), showing: ν_{max}/cm^{-1} [thin film] 2924, 1353, 1165, 1089, 814; δ_H 7.85 (2H, d, *J* 8.2, 2 × ArH), 7.32 (2H, d, *J* 8.2, 2 × ArH), 4.64 (1H, app t, *J* 5.7, CH), 2.43 (3H, s, CH_3), 2.35-2.16 (1H, m, CH_a), 2.05-1.86 (3H, m, CH_2 + CH_b), 1.82-1.77 (1H, m, $CH_{a'}$), 1.68 (3H, s, CH_3), 1.55 (2H, m, $CH_{b'}$ + $CH_{a''}$), 1.34 (1H, dd, *J* 14.7, 5.8, $CH_{b''}$); δ_C 144.3 (ArC), 135.4 (ArC), 129.4 (2 × ArCH), 129.1 (2 × ArCH), 77.8 (CH), 67.8 (C), 44.9 (CH_2), 39.7 (CH_2), 30.2 (CH_2), 22.0 (CH_3), 21.7 (CH_3), 18.4 (CH_2); HRMS *m/z* [EI] $C_{14}H_{19}NO_3S$ requires 281.1084, found 281.1086.

3-Methylcyclohexenyloxy-4-nitrobenzenesulfonamide 250



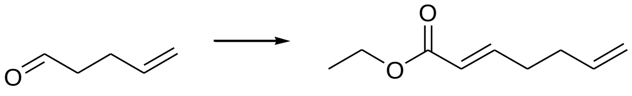
p-Nitrobenzenesulphonyl chloride (0.62 g, 2.81 mmol) was added to a solution of the crude free hydroxylamine **236** (38 mg, 0.299 mmol, calculated as a percentage by weight from the NMR spectra due to residual *N*,*N'*-dimethylpropyleneurea) in a 1:1 mixture of dichloromethane:water (6.00 ml of each). Sodium carbonate (0.30 g, 2.81 mmol) was added and the biphasic reaction mixture was stirred at room temperature overnight. The organic layer was washed with saturated aqueous sodium chloride solution (2 × 6.00 ml), and the combined aqueous layers were back extracted with dichloromethane (20.00 ml). The combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by column chromatography (30% diethyl ether in hexane) to give the *nosyl protected hydroxylamine* **250** (0.356 g, 61%) as an off-white solid, showing: mp 144-147 °C; ν_{max}/cm^{-1} [thin film] 3820, 2924, 2853, 1532, 1175, 855; δ_H 8.40 (2H, d, *J* 8.9, 2 × ArH), 8.12 (2H, d, *J* 8.9, 2 × ArH), 6.96 (1H, s, NH), 5.36 (1H, dd, *J* 3.2, 1.7, HC=C), 4.42-4.33 (1H, m, CH), 2.33-2.25 (1H, m, CH_a), 2.08-1.97 (3H, m, CH_2 + CH_b), 1.96-1.86 (1H, m, $CH_{a'}$), 1.65 (3H, s, CH_3), 1.64-1.58 (1H, m, $CH_{b'}$); δ_C 150.8 (ArC), 142.5 (ArC), 130.6 (C), 130.0 (2 × ArCH), 124.2 (2 × ArCH), 120.7 (CH), 82.2 (CH), 34.4 (CH_2), 26.0 (CH_2), 23.3 (CH_3), 22.8 (CH_2); HRMS *m/z* [ES] $C_{13}H_{16}N_2O_5S$ -H requires 311.0702, found 311.0705.

N-(4-nitrophenylsulfonyl)-3-methyl-2-aza-1-oxabicyclo[3.2.1]octane 252


250 **252**

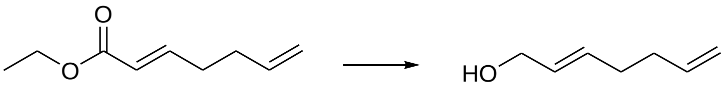
The nosyl protected hydroxylamine **250** (226 mg, 0.977 mmol) in anhydrous dichloromethane (10.00 ml) was added to triflic acid (0.40 molar solution in anhydrous dichloromethane, 1.21 ml, 0.489 mmol) in an ice bath, and the reaction mixture was stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous potassium carbonate (1.00 ml). Excess sodium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to give the protected cyclised product **252** (173 mg, 77%) as an off-white solid, showing: mp 165-168 °C; ν_{max}/cm^{-1} [film] 2952, 1532, 1349, 1171, 740, 644; δ_H 8.35 (2H, d, *J* 8.9, 2 × ArH), 8.15 (2H, d, *J* 8.9, 2 × ArH), 4.75-4.64 (1H, m, CH), 2.24-2.16 (1H, m, CH_a), 1.94 (1H, dd, *J* 13.0, 4.7, CH_b), 1.90-1.79 (1H, m, $CH_{a'}$), 1.72 (3H, s, CH_3), 1.62-1.55 (1H, m, $CH_{b'}$), 1.41 (2H, td, *J* 12.9, 5.9, CH_2), 1.34-1.26 (2H, m, CH_2); δ_C 155.1 (C), 154.0 (C), 130.4 (2 × CH), 123.9 (2 × CH), 78.2 (CH), 68.9 (C), 45.6 (CH_2), 39.4 (CH_2), 29.9 (CH_2), 22.0 (CH_3), 18.4 (CH_2); HRMS *m/z* [EI] $C_{13}H_{16}N_2O_5S$ requires 312.0780, found 312.0775.

(*E*)-Ethyl hepta-2,6-dienoate 262


223 **262**

To lithium chloride (2.52 g, 0.0594 mol) in anhydrous acetonitrile (250.00 ml) was added triethyl phosphonoacetate (13.98 g, 12.37 ml, 0.0624 mol) and 1,5-diazabicyclo[4.3.0]non-5-ene (7.75 g, 7.71 ml, 0.0624 ml) at room temperature. The resulting solution was cooled in an ice bath before the dropwise addition of 4-pentenal **223** (5.00 g, 0.0594 mol). The reaction mixture was stirred at room temperature overnight. Water (125.00 ml) was added to dissolve the precipitate, and the mixture was extracted with a 1:99 mixture of diethyl ether:hexane (4 × 100.00 ml, desired extract is the top layer of the 3). The combined organic extracts were washed successively with saturated aqueous ammonium chloride (250.00 ml), saturated aqueous potassium carbonate (250.00 ml), water (250.00 ml) and saturated aqueous sodium chloride (250.00 ml), before being dried, filtered and evaporated to give the *ester* **262** (5.50 g, 60%) as a colourless oil (which was used without further purification). All data obtained were in accordance with those reported in the literature[142] and showed: δ_H 6.92 (1H, dt, *J* 15.7, 6.7, HC=C), 5.79 (1H, dt, *J* 15.7, 1.6, C=CH), 5.80-5.70 (1H, m, HC=C), 5.01 (1H, ddd, *J* 17.2, 3.0, 1.6, C=CH$_a$), 4.97 (1H, ddd, *J* 10.2, 3.0, 1.2, C=CH$_b$), 4.14 (2H, q, *J* 7.1, CH$_2$), 2.30-2.23 (2H, m, CH$_2$), 2.22-2.14 (2H, m, CH$_2$), 1.24 (3H, t, *J* 7.1, CH$_3$).

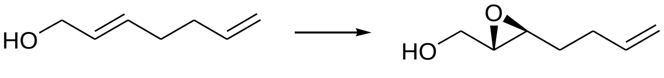
(*E*)-Hepta-2,6-dien-1-ol 261



262 **261**

A solution of the ester **262** (1.07 g, 6.94 mmol) in anhydrous tetrahydrofuran (10.00 ml) was cooled to 0 °C and diisobutylaluminium hydride (1.00 molar solution in hexane, 17.35 ml, 17.35 mmol) was added. The cooling bath was removed and the solution was stirred at room temperature for 2.5 hours. To quench the reaction it was cooled in an ice bath before the sequential addition of sodium hydroxide solution (15% w/w in water, 0.73 ml), diethyl ether (0.73 ml) and water (1.71 ml). The mixture was stirred at room temperature for 15 minutes. Excess magnesium sulphate was added to remove the water, and was then removed by filtration, washing with dichloromethane. The solvent was evaporated to give the alcohol **261** (0.747 g, 96%) as a colourless oil (which was used without further purification). All data obtained were in accordance with those reported in the literature[142] and showed: δ_H 5.84-5.72 (1H, m, HC=C), 5.74-5.56 (2H, m, 2 × C=CH), 4.99 (1H, dd, *J* 17.0, 1.8, C=CH$_a$), 4.94 (1H, dd, *J* 10.1, 1.8, C=CH$_b$), 4.04 (2H, d, *J* 4.6, CH$_2$), 2.26 (1H, br s, OH), 2.13-2.09 (4H, m, 2 × CH$_2$).

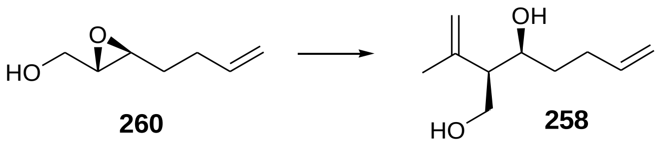
((2*S*, 3*S*)-3-(But-3-enyl)oxiran-2-yl)methanol 260



261 **260**

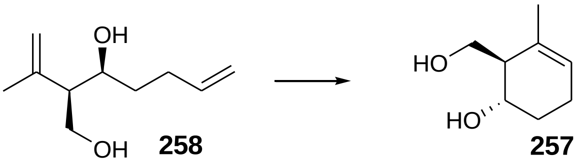
Activated molecular sieves (1.00 g) and anhydrous dichloromethane (30.00 ml) were cooled to -20 °C. L-(+)-diisopropyl tartrate (0.125 g, 0.535 mmol) and titanium (IV) isopropoxide (0.127 g, 0.13 ml, 0.446 mmol) were added with stirring at this temperature. *tert*-Butyl hydroperoxide (5.5 molar in decane, 3.24 ml, 17.84 mmol) was added dropwise at -20 °C, and the reaction mixture was stirred at this temperature for 0.5 hours. The alcohol **261** (1.00 g, 8.92 mmol) was dissolved in anhydrous dichloromethane (5.00 ml) and added dropwise to the reaction mixture, keeping the temperature below -15 °C. The reaction mixture was then stirred for an additional 3.5 hours between -20 °C and -15 °C. To quench the reaction it was added to a freshly prepared stirring solution of iron (II) sulphate (3.30 g) and tartaric acid (1.00 g) in deionised water (10.00 ml) at 0 °C. The mixture was stirred for 10 minutes, before the aqueous layer was extracted with diethyl ether (2 × 20.00 ml). The combined organic extracts were treated with a solution of 30% w/v sodium hydroxide in saturated aqueous sodium hydroxide (1.00 ml), and stirred vigorously for 1 hour at 0 °C. Water (20.00 ml) was added, and the aqueous layer was extracted with diethyl ether (2 × 20.00 ml). The combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by column chromatography (30% ethyl acetate in hexane) to give the *epoxy alcohol* **260** (748 mg, 64%) as a colourless oil (the title compound had been reported in the literature[143] but with no analysis), showing: $[\alpha]_D^{20}$ = -105.3° (c = 3.8, MeOH); ν_{max}/cm^{-1} [thin film] 3419, 3078, 2979, 2927, 2863, 1642, 997, 913;δ_H 5.80 (1H, ddt, J 17.0, 10.2, 6.0, HC=C), 5.03 (1H, ddd, J 17.0, 3.0, 1.6, C=CH_a), 4.97 (1H, ddd, J 10.2, 3.0, 1.2, C=CH_b), 3.87 (1H, ddd, J 12.6, 5.8, 2.4, CH), 3.63-3.48 (1H, m, CH), 3.00-2.85 (2H, m, CH_2), 2.51 (1H, t, J 6.3, OH), 2.27-2.05 (2H, m, CH_2), 1.65 (2H, td, J 7.5, 6.0, CH_2); δ_C 137.8 (CH), 115.1 (CH_2), 61.7 (CH_2), 58.7 (CH), 55.5 (CH), 31.0 (CH_2), 29.9 (CH_2).

(2*R*, 3*S*)-2-(Prop-1-en-2-yl)hept-6-ene-1,3-diol 258



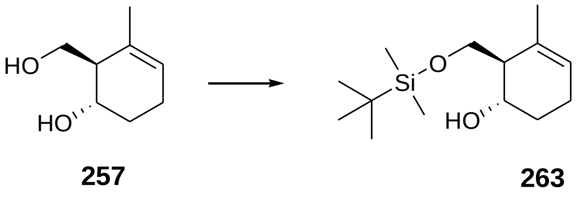
To a stirred suspension of copper (I) iodide (0.218 g, 1.15 mmol) in anhydrous diethyl ether (20.00 ml) at -8 °C was added isoprenyl magnesium bromide (0.5 molar in tetrahydrofuran, 22.90 ml, 11.46 mmol). The resulting suspension was immediately cooled to -23 °C and the epoxy alcohol **260** (490 mg, 3.82 mmol) in anhydrous diethyl ether (5.00 ml) was added dropwise. The reaction mixture was then stirred between -25 °C and -20 °C for 5.5 hours. The solution was partitioned between diethyl ether (25.00 ml) and saturated aqueous ammonium chloride that had been basified with concentrated sodium bicarbonate to pH 8 (25.00 ml). The ethereal extract was washed with saturated aqueous sodium chloride (25.00 ml), before being dried, filtered and evaporated to yield the crude product which was purified by column chromatography (60% diethyl ether in hexane) to give the *diol* **258** (545 mg, 84%) as a colourless oil, showing: $[\alpha]_D^{20}$ = +1.6° (c = 0.5, MeOH); ν_{max}/cm^{-1} [thin film] 3369, 3076, 2923, 1641, 1376, 1033, 911;δ_H 5.83 (1H, ddt, J 17.0, 10.1, 6.7, HC=C), 5.07 (1H, ddd, J 17.0, 3.2, 1.5, C=CH$_a$), 4.99 (1H, ddd, J 10.1, 2.4, 1.5, C=CH$_b$), 4.93-4.83 (1H, m, C=CH$_{a'}$), 4.80 (1H, d, J 0.5, C=CH$_{b'}$), 3.85-3.77 (2H, m, CH + CH$_a$), 3.74 (1H, dd, J 10.9, 5.1, CH$_b$), 2.79 (2H, br s, 2 × OH), 2.29-2.19 (2H, m, CH$_2$), 2.18-2.08 (1H, m, CH), 1.71 (3H, d, J 0.9, CH$_3$), 1.69-1.61 (1H, m, CH$_{a''}$), 1.52-1.40 (1H, m, CH$_{b''}$); δ_C 143.6 (C), 138.4 (CH), 115.1 (CH$_2$), 113.6 (CH$_2$), 73.8 (CH), 64.9 (CH$_2$), 54.6 (CH), 34.7 (CH$_2$), 29.9 (CH$_2$), 21.7 (CH$_3$); HRMS *m/z* [APCI] $C_{10}H_{18}O_2$ +H requires 171.1385, found 171.1378.

(1*S*, 2*R*)-2-(Hydroxymethyl)-3-methylcyclohex-3-enol 257



A solution of the diol **258** (184 mg, 1.08 mmol) and Grubbs II catalyst (46 mg, 0.054 mmol) in anhydrous dichloromethane (20.00 ml) was stirred at room temperature overnight. The solvent was evaporated to give the *cyclic diol* **257** (152 mg, 99%) as pale brown crystals, showing: mp 76-77 °C ; $[\alpha]_D^{20}$ = +23.0° (c = 0.6, EtOH); ν_{max}/cm^{-1} [thin film] 3349, 1652, 1379, 1050, 809; δ_H 5.51 (1H, app d, J 1.4, C=CH), 4.04 (1H, dd, J 10.5, 3.4, CH$_a$), 3.94 (1H, ddd, J 10.2, 7.0, 3.3, CH), 3.62 (1H, dd, J 10.5, 8.3, CH$_b$), 2.54 (2H, br s, 2 × OH), 2.22 (1H, app s, CH), 2.16-1.98 (2H, m, CH$_2$), 1.88 (1H, ddd, J 9.6, 8.4, 4.3, CH$_{a'}$), 1.67 (3H, s, CH$_3$), 1.65-1.55 (1H, m, CH$_{b'}$); δ_C 130.9 (C), 124.6 (CH), 71.5 (CH), 64.3 (CH$_2$), 49.5 (CH), 29.6 (CH$_2$), 23.2 (CH$_2$), 21.3 (CH$_3$); HRMS *m/z* [EI] $C_8H_{14}O_2$ -H_2O requires 124.0888, found 124.0887.

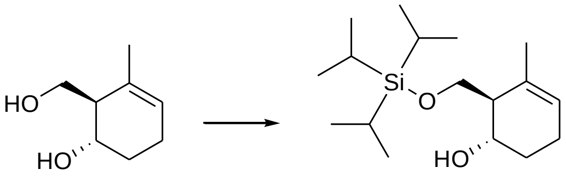
(1*S*, 2*R*)-2-(*tert*-Butyldimethylsilyloxymethyl)-3-methylcyclohex-3-enol 263



TBDMS chloride (181 mg, 1.20 mmol) was slowly added to a solution of the cyclic diol **257** (155 mg, 1.09 mmol) and imidazole (178 mg, 2.62 mmol) in anhydrous tetrahydrofuran

(10.00 ml) at 0 °C. The reaction mixture was allowed to slowly warm to room temperature and stir overnight. The solvent was removed under reduced pressure, and the residue taken up in diethyl ether (20.00 ml). The organic layer was washed with water (3 × 20.00 ml), before being dried, filtered and evaporated to give the *TBDMS protected cyclic diol* **263** (170 mg, 61%) as a colourless oil (which was used without further purification), showing: ν_{max}/cm^{-1} [thin film] 3433, 2955, 2928, 2857, 1472, 1389, 1253, 1099, 836; δ_H 5.46 (1H, app d, *J* 0.9, C=CH), 4.07 (1H, dd, *J* 9.8, 4.3, CH_a), 3.86 (1H, ddd, *J* 10.2, 6.9, 3.4, CH), 3.48 (1H, t, *J* 9.8, CH_b), 2.35-2.15 (2H, m, CH_2), 2.05 (1H, app s, CH), 1.91-1.81 (1H, m, $CH_{a'}$), 1.62 (3H, s, CH_3), 1.58-1.50 (1H, m, $CH_{b'}$), 0.91 (9H, s, ${}^tBu$), 0.09 (6H, s, 2 × CH_3); δ_C 131.3 (C), 124.5 (CH), 72.5 (CH), 66.7 (CH_2), 49.4 (CH), 29.1 (CH_2), 26.3 (3 × CH_3), 23.7 (CH_2), 21.6 (CH_3), 18.7 (C), -5.5 (2 × CH_3); HRMS *m/z* [APCI] $C_{14}H_{28}O_2Si$ +H requires 257.1937, found 257.1925.

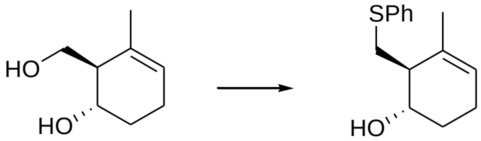
(1*S*, 2*R*)-2-(Triisopropylsilyloxymethyl)-3-methylcyclohex-3-enol 268



A solution of the cyclic diol **257** (0.120 g, 0.841 mmol) in anhydrous dichloromethane (5.00 ml) was treated with 2,6-lutidine (0.126 g, 0.127 ml, 1.27 mmol) and triisopropylsilyl trifluoromethanesulphonate (0.309 g, 0.272 ml, 1.01 mmol) at -78 °C. The reaction mixture was stirred at this temperature for 2 hours and then quenched by the addition of saturated aqueous sodium bicarbonate (10.00 ml). The aqueous layer was extracted with diethyl ether (3 × 20.00 ml), and the combined organic extracts were dried, filtered and evaporated to yield the crude product which was purified by column chromatography (10% ethyl acetate in hexane) to give the *TIPS protected diol* **268** (133 mg, 52%) as a colourless oil, showing: $[\alpha]_D^{20}$ = +28.0° (*c* = 0.9, MeOH); ν_{max}/cm^{-1} [thin film] 3434, 2866, 1464, 1383, 1257, 1099, 794; δ_H 5.48-5.42 (1H, m, C=CH), 4.18 (1H, dd, *J* 9.6, 4.2, CH_a), 3.93-3.88 (1H, m, CH), 3.87 (1H, d, *J* 3.3, OH), 3.58 (1H, dd, *J* 10.2, 9.6, CH_b), 2.33-2.24 (1H, m, CH), 2.12-1.96 (2H, m, CH_2), 1.88 (1H, ddd, *J* 12.4, 8.7, 3.7, $CH_{a'}$), 1.61 (3H, s, CH_3), 1.58-1.49 (1H, m, $CH_{b'}$), 1.17-1.09 (3H, m, 3 × CH), 1.07 (18H, d, *J* 5.6, 6 × CH_3); δ_C 130.9 (C), 124.3 (CH), 72.5 (CH), 67.1 (CH_2), 49.44 (CH), 29.0 (CH_2), 23.4 (CH_2), 21.3 (CH_3), 17.9 (6 × CH_3), 11.8 (3 × CH); HRMS *m/z* [APCI] $C_{17}H_{34}O_2Si$ +H requires

299.2406, found 299.2408.

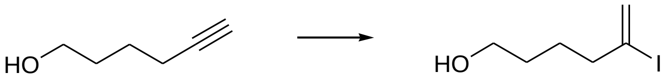
(1*S*,2*S*)-3-methyl-2-((phenylthio)methyl)cyclohex-3-enol 269



257 **269**

To the cyclic diol **257** (78 mg, 0.55 mmol) in dry tetrahydrofuran (2.00 ml) was added Bu_3P (0.54 ml, 2.20 mmol) and Ph_2S_2 (361 mg, 1.65 mmol). The reaction mixture was stirred overnight at room temperature before the solvent was evaporated to yield the crude product which was purified by column chromatography (40% ethyl acetate in hexane) to give the *thio ether* **269** (46 mg, 36 %) as a green solid, showing: mp 29-31 °C; $[\alpha]_D^{20}$ = +12.7° (c = 0.17, MeOH); ν_{max}/cm^{-1} [thin film] 3391, 2919, 2849, 1583, 1481, 1438, 1377, 1063, 1025, 804, 739, 690; δ_H 7.43-7.13 (5H, m, 5 × Ar-H), 5.58-5.48 (1H, m, H-5), 4.19-4.09 (1H, m, H-2), 3.38 (1H, dd, *J* 12.9, 3.3, H-9), 2.84 (1H, dd, *J* 12.9, 8.3, H-9), 2.29 (1H, s, H-8), 2.17-2.02 (1H, m, H-1), 1.87-1.55 (4H, m, H-3 and -4), 1.72 (3H, s, H-7); δ_C 136.9 (C), 132.4 (C), 129.2 (CH), 129.1 (CH), 126.1 (CH), 124.0 (CH), 69.0 (CH), 46.8 (CH), 35.4 (CH_2), 27.3 (CH_2), 22.1 (CH_2), 22.0 (CH_3).

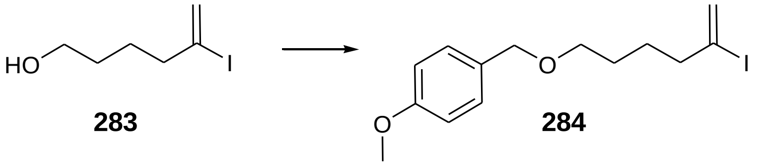
5-Iodohex-5-en-1-ol 283



282 **283**

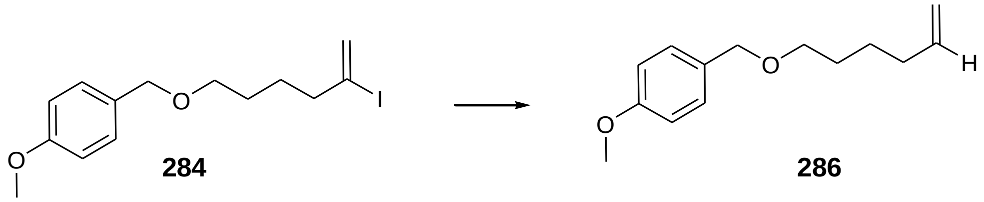
Sodium iodide (18.33 g, 122.26 mmol) was dissolved in acetonitrile (90.00 ml) at room temperature, and to this was added TMS chloride (13.28 g, 15.52 ml, 122.26 mmol) followed by water (1.10 ml, 61.13 mmol). After 20 minutes a solution of 5-hexyn-1-ol **282** (6.00 g, 61.13 mmol) in acetonitrile (15.00 ml) was added to the mixture and the reaction mixture was stirred for 1 hour at room temperature. Water (100.00 ml) was added to dissolve the precipitate, and the aqueous layer was extracted with diethyl ether (3 × 100.00 ml). The combined organic extracts were washed with water (100.00 ml), before being dried, filtered and evaporated to yield the crude product which was purified by column chromatography (50% ethyl acetate in hexane) to give the *iodoalcohol* **283** (5.81 g, 42%) as a yellow oil. All data obtained were in accordance with those reported in the literature[144] and showed: δ_H 6.04 (1H, q, *J* 1.4, C=CH$_a$), 5.71-5.70 (1H, m, C=CH$_b$), 3.67 (2H, t, *J* 6.2, CH$_2$), 2.42 (2H, t, *J* 6.2, CH$_2$), 1.62-1.55 (4H, m, 2 × CH$_2$).

1-((5-Iodohex-5-enyloxy)methyl)-4-methoxybenzene 284



To a stirred solution of the iodoalcohol **283** (330 mg, 1.46 mmol) in anhydrous diethyl ether (6.00 ml) over molecular sieves was added *p*-methoxybenzyl-2,2,2-trichloroacetimidate (825 mg, 0.61 ml, 2.92 mmol) followed by triflic acid (0.657 mg, 0.4 µl, 0.004338 mmol). The reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous sodium bicarbonate (1.00 ml), and the organic layer was dried, filtered and evaporated to yield the crude product which was purified by column chromatography (15% ethyl acetate in hexane) to give the *PMB protected iodoalcohol* **284** (311 mg, 62%) as a yellow oil, showing: δ_H 7.27 (2H, d, *J* 8.6, 2 × ArH), 6.88 (2H, d, *J* 8.6, 2 × ArH), 6.02-6.00 (1H, m, C=CH$_a$), 5.69 (1H, d, *J* 0.6, C=CH$_b$), 4.44 (2H, s, CH$_2$), 3.81 (3H, s, OCH$_3$), 3.48-3.43 (2H, m, CH$_2$), 2.39 (2H, t, *J* 6.1, CH$_2$), 1.62-1.57 (4H, m, 2 × CH$_2$).

1-((Hex-5-enyloxy)methyl)-4-methoxybenzene 286



A sample from the reaction to try and form a Grignard reagent from *iodoalkene* **284** was quenched to check the progress of the transformation, to give the *hydrolysed product* **286** as a colourless oil. All data obtained were in accordance with those reported in the literature[123] and showed: δ_H 7.26 (2H, d, *J* 8.7, 2 × ArH), 6.88 (2H, d, *J* 8.7, 2 × ArH), 5.80 (1H, ddt, *J* 16.9, 10.1, 6.7, C=CH), 5.05-4.90 (2H, m, C=CH$_2$), 4.43 (2H, s, CH$_2$), 3.80 (3H, s, OCH$_3$), 3.45 (2H, t, *J* 6.4, CH$_2$), 2.06 (2H, dd, *J* 14.2, 7.1, CH$_2$), 1.64-1.59 (2H, m, CH$_2$), 1.51-1.42 (2H, m, CH$_2$).

References

1. A. R. Katritzky, C. A. Ramsden, E. V. F. Scriven and R. J. K. Taylor, *Comprehensive Heterocyclic Chemistry*, 3rd edn., Pergamon, Oxford, 2008.
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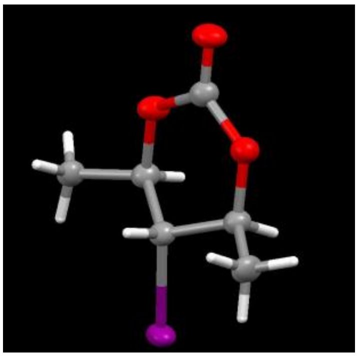
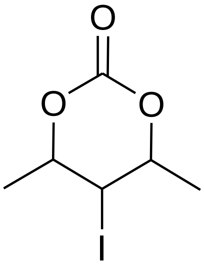
Appendix 1

Crystallographic data for iodocarbonate **133**





133

CCDC 878231

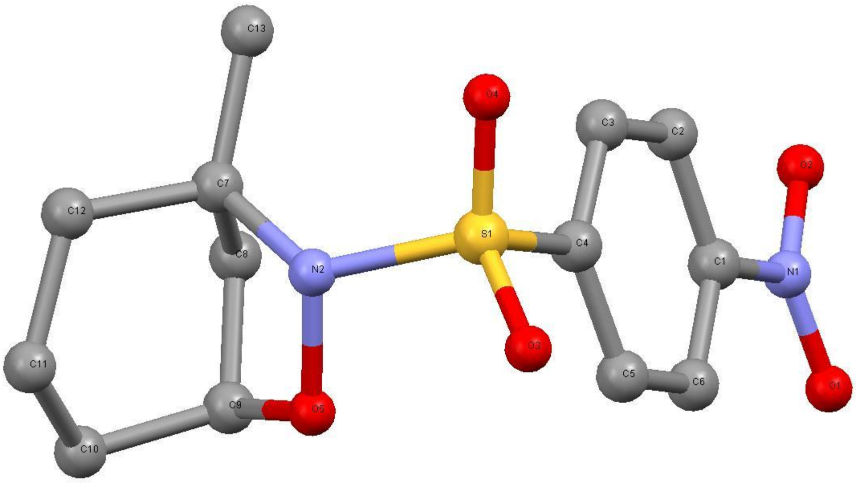
Table 1. Crystal data and structure refinement for iodocarbonate **133**.

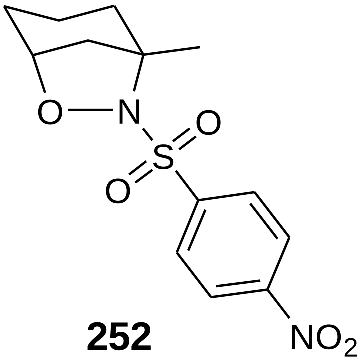
Identification code	dwk0902	
Empirical formula	C6 H9 I O3	
Formula weight	256.03	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna21	
Unit cell dimensions	a = 9.0743(15) Å	α= 90°.
	b = 7.3931(10) Å	β= 90°.
	c = 12.306(2) Å	γ = 90°.
Volume	825.6(2) Å^3	
Z	4	
Density (calculated)	2.060 Mg/m^3	
Absorption coefficient	3.829 mm^{-1}	
F(000)	488	
Crystal size	? x ? x ? mm^3	
Theta range for data collection	3.21 to 27.50°.	
Index ranges	-11<=h<=11, -9<=k<=9, -12<=l<=15	
Reflections collected	3385	
Independent reflections	1422 [R(int) = 0.0638]	
Completeness to theta = 27.50°	97.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1422 / 429 / 183	
Goodness-of-fit on F^2	1.061	
Final R indices [I>2sigma(I)]	R1 = 0.0470, wR2 = 0.1254	
R indices (all data)	R1 = 0.0677, wR2 = 0.1416	
Absolute structure parameter	0.01(18)	
Extinction coefficient	0.0105(16)	
Largest diff. peak and hole	1.237 and -0.731 e.Å^{-3}	

CCDC 878231

Appendix 2

Crystallographic data for transannular product **252**





252

CCDC 878232

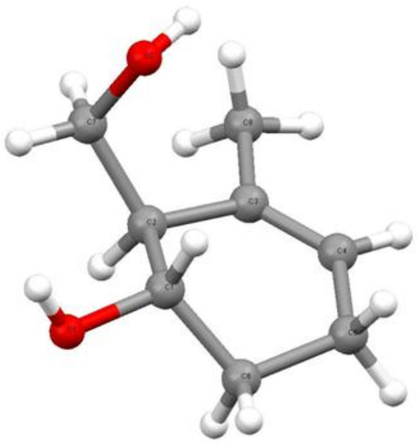
Table 1. Crystal data and structure refinement for transannular product **252**.

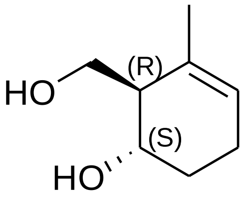
Identification code	dwk1103	
Empirical formula	C13 H16 N2 O5 S	
Formula weight	312.34	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P21/c	
Unit cell dimensions	a = 6.8684(2) Å	α= 90°.
	b = 16.8474(8) Å	β= 99.858(2)°.
	c = 12.2469(3) Å	γ = 90°.
Volume	1396.22(8) Å^3	
Z	4	
Density (calculated)	1.486 Mg/m^3	
Absorption coefficient	0.256 mm^{-1}	
F(000)	656	
Crystal size	0.25 x 0.25 x 0.15 mm^3	
Theta range for data collection	2.95 to 27.50°.	
Index ranges	-8<=h<=8, -21<=k<=21, -15<=l<=15	
Reflections collected	6149	
Independent reflections	3192 [R(int) = 0.0384]	
Completeness to theta = 27.50°	99.7 %	
Max. and min. transmission	0.9626 and 0.9388	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3192 / 0 / 191	
Goodness-of-fit on F^2	1.035	
Final R indices [I>2sigma(I)]	R1 = 0.0530, wR2 = 0.1234	
R indices (all data)	R1 = 0.0766, wR2 = 0.1389	
Largest diff. peak and hole	0.276 and -0.493 e.Å^{-3}	

CCDC 878232

Appendix 3

Crystallographic data for chiral diol **257**





257

CCDC 878233

Table 1. Crystal data and structure refinement for chiral diol **257**

Identification code	dwk1104	
Empirical formula	C8 H14 O2	
Formula weight	142.19	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P212121	
Unit cell dimensions	a = 5.3321(2) Å	α= 90°.
	b = 6.2335(2) Å	β= 90°.
	c = 23.0851(9) Å	γ = 90°.
Volume	767.29(5) Å^{3}	
Z	4	
Density (calculated)	1.231 Mg/m^{3}	
Absorption coefficient	0.086 mm^{-1}	
F(000)	312	
Crystal size	0.30 x 0.22 x 0.20 mm^{3}	
Theta range for data collection	3.92 to 27.48°.	
Index ranges	-6<=h<=6, -6<=k<=8, -21<=l<=29	
Reflections collected	3118	
Independent reflections	1710 [R(int) = 0.0306]	
Completeness to theta = 27.48°	98.6 %	
Max. and min. transmission	0.9829 and 0.9745	
Refinement method	Full-matrix least-squares on F^{2}	
Data / restraints / parameters	1710 / 0 / 95	
Goodness-of-fit on F^{2}	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0397, wR2 = 0.0923	
R indices (all data)	R1 = 0.0448, wR2 = 0.0963	
Absolute structure parameter	0.4(13)	
Extinction coefficient	0.23(2)	
Largest diff. peak and hole	0.199 and -0.168 e.Å^{-3}	

CCDC 878233