Hydrogen Atom Abstraction Pathways to Functionalised Free Radicals

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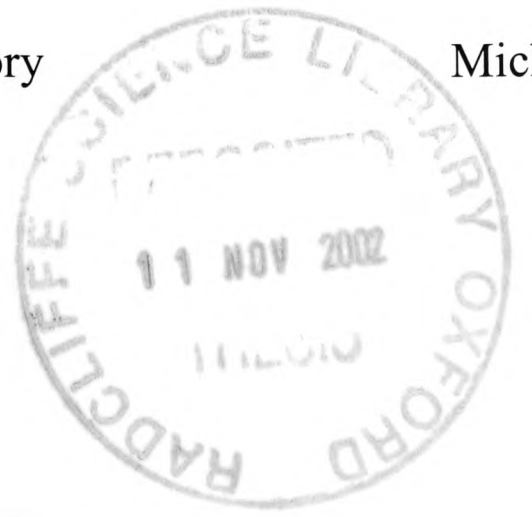
by

Rachel K. Lush

Wolfson College, Oxford

The Dyson Perrins Laboratory

Michaelmas Term 2001



ABSTRACT

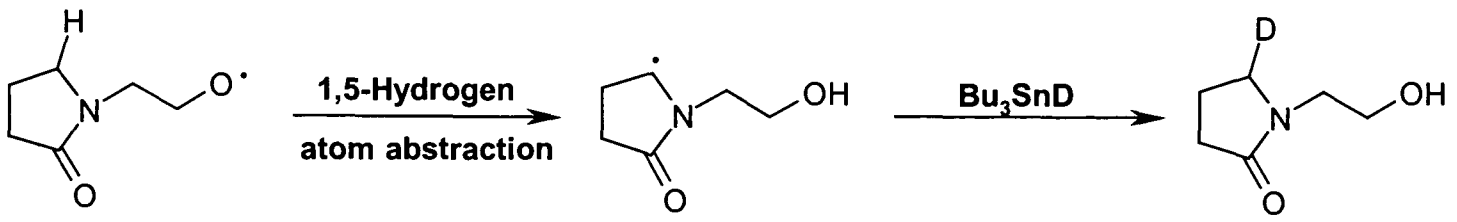
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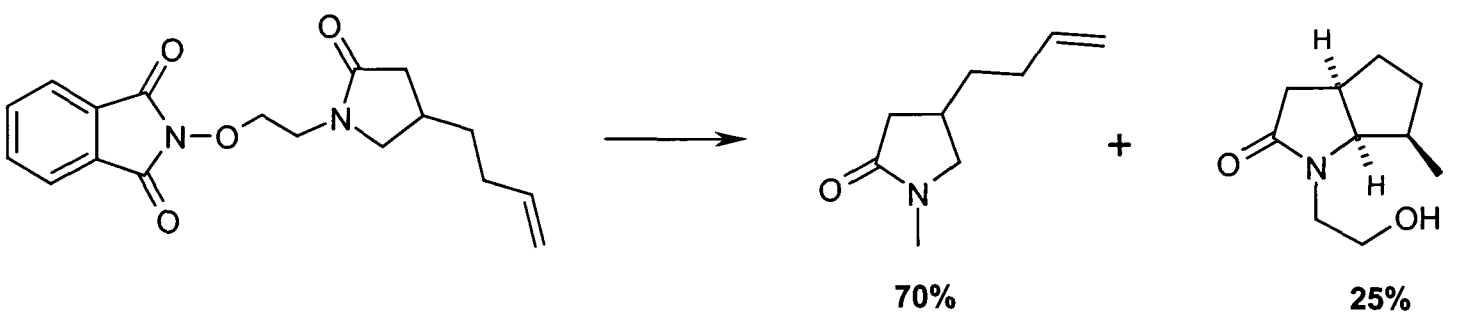
Radical translocation chemistry has classically been employed for the generation of carbon-centred radicals as a means of remotely functionalising nominally unreactive sites. Previous work within the group had investigated vinyl radicals to effect translocation and had identified a need for a more reactive abstracting radical. In this regard, the high energy of alkoxyl radicals would facilitate rapid 1,5-hydrogen abstraction as opposed to simple reduction.

This thesis describes the use of alkoxyl radicals, generated from *N*-alkoxyphthalimides, to abstract a hydrogen atom selectively from the α-position of a lactam ring.



Alkoxyl radicals generated from precursors designed to lead to intramolecular trapping of the translocated radical were prone to β-scission in preference to 1,5-hydrogen atom abstraction. This is attributed to a combination of developing π-overlap in the transition state and stabilisation of the resulting radical both by nitrogen and the attached alkyl substituents.

Incorporation of an alkenyl trap onto the lactam ring led to successful 1,5-hydrogen atom abstraction and stereoselective cyclisation, although β-scission remained the dominant pathway.



Translocation initiated by nitrogen-centred radicals was investigated and it was found that 1,5-hydrogen abstraction occurred in preference to β-scission; intramolecular trapping of the translocated radical proved impossible either because the precursors were unstable to the reaction conditions or because increased steric bulk impeded hydrogen abstraction by the less reactive aminyl radical.

Preparation of bicyclic pyrrolidinones *via* successive 5-*endo*-5-*exo*-*trig* cyclisations was investigated; the precursors were found to undergo direct reduction in preference to cyclisation. Alkyl or aryl groups attached to the α-acylamino carbon may lead to preferential 5-*endo* cyclisation by stabilisation of the developing radical in the transition state.

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CONTENTS

ABBREVIATIONS i)

Chapter 1: INTRODUCTION 1

1.1 Free Radical Chemistry 2

1.1.1 General 2

1.1.2 Polar Effects 2

1.1.3 Reactions of Radicals 4

1.2 Radical Translocation Chemistry 6

1.2.1 Alkyl Radicals 7

1.2.1.1 *Primary radicals* 7

1.2.1.2 *Secondary radicals* 9

1.2.2 Vinyl Radicals 11

1.2.2.1 *1,4-Hydrogen atom abstraction* 11

1.2.2.2 *1,5-Hydrogen atom abstraction* 12

1.2.2.3 *1,6- and 1,7-Hydrogen atom abstraction* 17

1.2.3 Aryl Radicals 18

1.2.3.1 *1,4-Hydrogen atom abstraction* 18

1.2.3.2 *1,5-Hydrogen atom abstraction* 19

1.2.3.3 *1,6- and 1,7-Hydrogen atom abstraction* 23

1.2.4 Alkoxyl Radicals 24

1.2.4.1 *Photolysis of hypoiodites* 25

1.2.4.2 *Photolysis of nitrite esters* 26

1.2.4.3 *Alkyl benzenesulfenates* 28

1.2.4.4 *N-Alkoxyphthalimides* 28

1.2.4.5 *Fragmentation of epoxides* 29

1.2.4.6 *Nitrates* 30

1.2.4.7 *Electrochemical oxidation* 30

1.2.4.8 *Homolytic cleavage of peroxides* 31

1.2.4.9 *Photolysis of carbonyls* 31

1.2.5 Nitrogen-Centred Radicals 33

1.2.5.1 *Aminyl radical cations (Hofmann-Löffler-Freytag reaction)* 33

1.2.5.2 *N-Iodo intermediates* 33

1.2.5.3 *Azides* 35

1.2.5.4 *Iminyl radicals* 35

1.2.6 Group Transfer 36

1.2.6.1 *1,n-Aryl transfer* 36

1.2.6.2 *Other group transfers* 37

1.3 Proposed Work 39

Chapter 2: RESULTS AND DISCUSSION 42

2.1 Alkoxyl Radical Precursors 43

2.1.1 Preliminary Studies 43

2.1.1.1 *Preparation of radical precursor* **115** 43

2.1.1.2 *Radical reaction of precursor* **115** 44

2.1.1.3 *Preparation of radical precursor* **120** 45

2.1.1.4 *Radical reaction of precursor* **120** 46

2.1.2 Intermolecular Trapping of the Translocated Radical 46

2.1.2.1 *Trapping with methyl acrylate* 46

2.1.2.2 *Trapping with stannyl methacrylate* **125** 47

2.1.3 Intramolecular Trapping of the Translocated Radical 48

2.1.3.1 *Preparation and radical reaction of precursor* **126** 48

2.1.3.2 *Preparation and radical reaction of precursor* **131** 51

2.1.3.3 *Attempted preparation of radical precursor* **136** 55

2.1.3.4 *Preparation and radical reaction of precursor* **140** 56

2.1.3.5 *Preparation and radical reaction of precursor* **143** 58

2.1.3.6 *Cuprate approach to precursor* **149** 60

2.1.3.7 *Radical approach to precursor* **149** 63

2.1.3.8 *Preparation and radical reaction of precursor* **168** 65

2.1.3.9 *Preparation and radical reaction of precursor* **172** 67

2.1.3.10 *Preparation and radical reaction of precursor* **149** 68

2.2 Novel Procedure for the Removal of Tin Impurities 72

2.2.1 *N*-(2-Mercaptoethyl)aminomethyl Polystyrene Resin **184** 72

2.2.2 (Thiomethyl)polystyrene Resin 75

2.2.3 Synthetic Application 75

2.3 Nitrogen-Centred Radicals 76

2.3.1 *N*-Tri-*n*-butylstannyl Substituted Aminyl Radicals 77

2.3.1.1 *Preparation and radical reaction of precursor* **187** 77

2.3.1.2 *Attempted preparation of radical precursor* **191** 78

2.3.1.3 *Preparation of radical precursor* **192** 80

2.3.1.4 *Preparation and radical reaction of precursor* **193** 81

2.3.2 Aminyl Radical Cations 82

2.3.2.1 *Preparation of radical precursor* **195** 83

2.3.2.2 *Radical reaction of precursor* **195** 85

2.3.3 Summary 86

2.4 5-*Endo-trig* Radical Cyclisations 87

2.4.1 Preparation of α-Haloacetamide Radical Precursors 87

2.4.2 Radical Reactions of α-Haloacetamide Precursors 89

2.4.3 Attempted Preparation of Trichloroacetamide **206** 91

2.4.4 Summary 92

2.5 A Radical Version of the Vinylcyclopropane-Cyclopentene Rearrangement 93

2.5.1 Original preparation of radical precursor **209** 93

2.5.2 Improved preparation of radical precursor **209** 94

2.5.3 Radical reaction of precursors **218** and **219** 95

2.5.4 Summary 96

Chapter 3: EXPERIMENTAL 97

REFERENCES 163

APPENDICES 175

ABBREVIATIONS

Å	amstrong
Ac	acetyl
ACCN	1,1′-azo*bis*(cyclohexanecarbonitrile)
AIBN	2,2′-azo*bis*(2-methylpropionitrile)
AMBN	azo*bis*methylisobutyronitrile or 2-(1-cyano-1-methyl-propylazo)-2-methylbutyronitrile
A.P.C.I.	atmospheric pressure chemical ionisation
aq.	aqueous
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
b.p.	boiling point
Bu	butyl
cat.	catalytic quantity
CI	chemical ionisation
conc.	concentrated
COSY	correlation spectroscopy
δ	chemical shift
Δ	reflux
DCE	dichloroethane
DCM	dichloromethane

DEAD	diethylazodicarboxylate
DEPT	distortionless enhancement by polarisation transfer
DIAD	diisopropylazodicarboxylate
dig	digonal
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
Ed.	editor
EI	electron impact
equiv.	equivalents
ESR	electron spin resonance
Et	ethyl
GCMS	gas chromatography mass spectrometry
h	hour
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
hν	photolysis
i	*iso* or *ipso*
IBX	iodoxybenzoic acid
In	initiator
IR	infra-red
LDA	lithium diisopropylamide
LHMDS	lithium *bis*(trimethylsilyl)amide

lit.	literature
m	*meta*
M	molar
Me	methyl
mins	minutes
mM	millimolar
MOM	methoxymethyl ether
m.p.	melting point
m/z	mass/charge
n	*normal*
N	normal
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
o	*ortho*
p	*para*
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
Pyr	pyridine
R_f	retention factor

RT	room temperature
s	second
sat.	saturated
SET	single electron transfer
S_N	nucleophilic substitution
t, *tert*	*tertiary*
TBAB	tetrabutylammonium bromide
TBS	*t*-butyldimethylsilyl
THF	tetrahydrofuran
t.l.c	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
Tosyl, Ts	*p*-toluenesulfonyl
TPAP	tetrapropylammonium perruthenate
trig	trigonal
TTMSS	*tris*(trimethylsilyl)silane
UV	ultra violet
w/v	weight:volume ratio

INTRODUCTION

1. INTRODUCTION

1.1 Free Radical Chemistry

1.1.1 General

Since the investigations into the formation and reactions of triphenylmethyl radical carried out by Gomberg[1] in 1900, free radical chemistry has undergone rapid development. In the last 20–30 years radical based chemistry has evolved into a powerful synthetic tool for the organic chemist, mainly as a result of an increased understanding of reaction rates,[2,3] radical regio- and stereoselectivities[4] and radical stabilities. The relative indifference of radical intermediates to their immediate surroundings and the ability to carry out transformations in neutral organic solvents has led to an increased popularity of radical based methodology.

1.1.2 Polar Effects

The electrophilic and nucleophilic character of free radicals is influenced by the groups attached to the radical centre.[5,6] Alkyl radicals substituted with electron-releasing groups behave like nucleophiles and react rapidly with electron poor double bonds. Conversely alkyl radicals with attached electron-withdrawing substituents are electrophilic in character and react faster with electron-rich double bonds. These tendencies have been concisely rationalised using frontier molecular orbital theory,[7] in which the singly occupied molecular orbital (SOMO) of the radical overlaps with either the highest occupied molecular orbital (HOMO) or the lowest unoccupied molecular orbital (LUMO) of the alkene in the most energetically favourable way, *i.e.* that which minimises the energy difference between them. Radicals with attached electron-donating groups

interact with an adjacent unfilled orbital to give a higher energy SOMO, whereas radicals with attached electron-withdrawing groups interact with a filled orbital to give a lower energy SOMO. Electrophilic radicals have SOMO energies so low that interaction with the HOMO of the electron-rich alkene predominates (**Figure 1.1**).

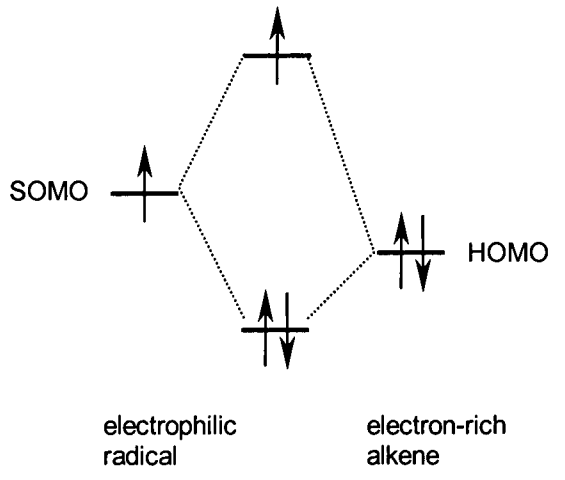


Figure 1.1 Orbital interaction between an electrophilic radical and an electron-rich double bond

Electron withdrawing substituents attached to an alkene lower the energy of the LUMO so that SOMO-LUMO interaction becomes favoured for nucleophilic radicals (**Figure 1.2**). This reduction in the SOMO-LUMO energy difference leads to an increase in addition rate to electron-poor alkenes. Therefore, the cyclohexyl radical reacts 8500 times faster with acrolein than 1-hexene.

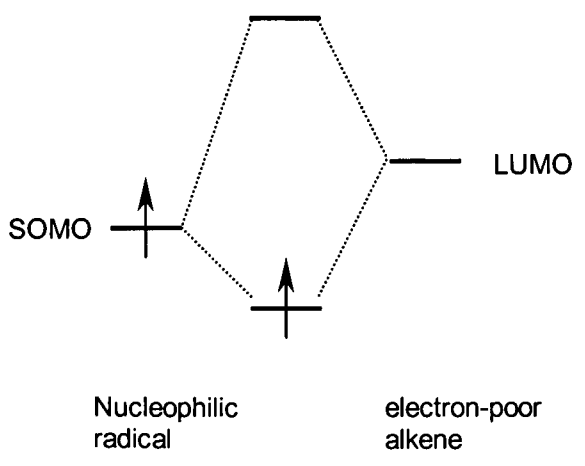


Figure 1.2 Orbital interaction between a nucleophilic radical and an electron-poor double bond

1.1.3 Reactions of Radicals

Most free radical reactions involve one of the following elementary mechanistic steps:[8]

i) addition $R^{\cdot} + AB \rightarrow RAB^{\cdot}$

ii) fragmentation $RAB^{\cdot} \rightarrow RA + B^{\cdot}$

iii) rearrangement $RAB^{\cdot} \rightarrow ARB^{\cdot}$

iv) substitution (abstraction) $R^{\cdot} + AB \rightarrow RA + B^{\cdot}$

Of radical addition reactions, perhaps the most important transformation is the intramolecular addition of a radical to a double or triple bond. The majority of these reactions proceed to give a new C–C σ bond (≈ 370 kJ mol^{-1}) at the expense of a π bond (≈ 235 kJ mol^{-1}). Cyclisations are generally faster than their intermolecular counterparts and these reactions are particularly useful for the formation of five- and six-membered rings. The additions are often regioselective; for example, in the cyclisation of 5-hexenyl radical (**Figure 1.3**), the major product is the kinetic product, arising from 5-*exo*-cyclisation. The observed preference in 5-*exo*-cyclisations for the less stable product has been shown to be due to more favourable overlap in the transition state between the incoming radical and the C=C π* orbital of the alkene leading to faster reaction rates.[4,9,10]

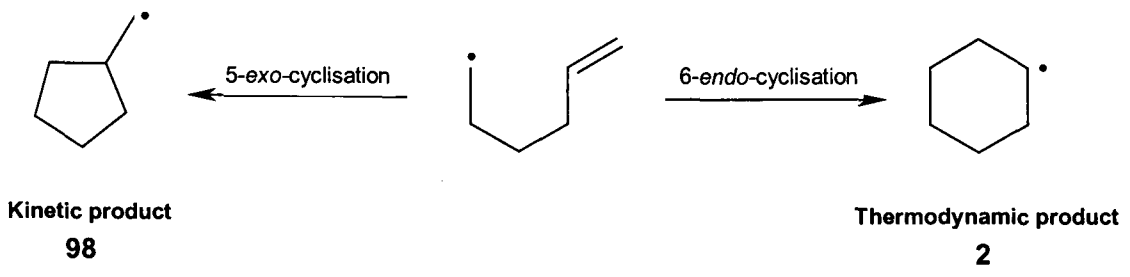


Figure 1.3. Thermodynamic vs. kinetic product of 5-hexenyl radical cyclisation

Radical fragmentation reactions involve the cleavage of an intermediate radical into two or more fragments, the reverse of an addition reaction. An unsaturated fragment is produced in the elimination reaction along with a new propagating radical. Radical ring opening reactions are also classed as fragmentations and are possibly the most important example of this reaction type, an example of which is shown in **Figure 1.4**. These reactions are generally rapid processes as they have favourable activation entropies.[8] β-Fragmentation reactions of alkoxyl radicals are also important; the generation of a strong carbonyl bond being the driving force for the fragmentation.



Figure 1.4 Reversible ring opening reaction of cyclopropylmethyl radical

Examples of radical rearrangements include intramolecular addition and elimination, the most common of which is the 1,2-shift of an aryl group (neophyl rearrangement), although vinyl, cyano or carbonyl groups can also be transferred. 1,2-Alkyl or hydrogen shifts are extremely rare, as cyclisation cannot take place onto the saturated sp^3 centre.[11]

Radical substitution reactions generally involve the removal (abstraction) of an atom, usually hydrogen or a halogen, from a non-radical precursor. The reactions are enthalpically favoured since a stronger σ bond is formed in the product than that which is broken in the precursor; for example, a strong O–H bond ($\approx$ 460 kJ mol^{-1}) being formed at the expense of a weaker C–H bond ($\approx$ 410 kJ mol^{-1}). The reactions can be inter- or intramolecular, the latter being an example of radical translocation, *vide infra*.

1.2 Radical Translocation Chemistry

Radical translocation or intramolecular abstraction reactions involve the movement of a radical centre from its site of generation to another centre, usually located five atoms away (**Figure 1.5**). The overall effect is that an unactivated C–H bond can serve indirectly as a radical precursor. Though C–H bonds are the simplest conceivable radical precursors, the direct use of C–H bonds as radical precursors in methods such as the tin hydride method is not possible because tin radicals will not abstract hydrogen atoms from C–H bonds.

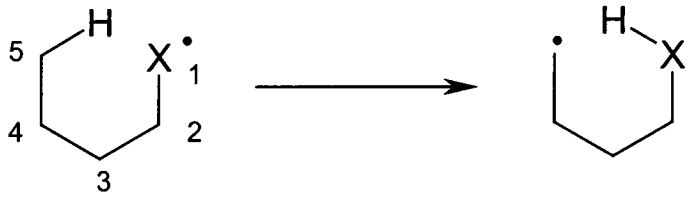


Figure 1.5 Radical translocation by 1,5-hydrogen atom abstraction; $k \approx 10^6$–10^7 s^{-1} at 25°C

The most common kind of radical translocation involves translocation from a site five positions away from the initial radical centre. The reaction proceeds by a near-linear transition state as this maximises the interaction of the radical orbital and the vacant σ* orbital of the bond to be broken.[12] A six-membered transition state is the shortest chain length that can achieve a reasonable geometry for radical translocation without suffering an excessive entropic penalty,[13] therefore 1,5-hydrogen atom abstractions (1,5-H) are the most common; although examples of 1,4-,[14-21] 1,6-,[22-34] and 1,7-hydrogen transfer[23-26,35-37] exist.

The reaction is driven by the bond strength of the forming X–H bond and additionally by the formation of a more stable radical after translocation. For example, a reactive vinyl or aryl radical will readily abstract a hydrogen atom to form an alkyl radical and the more stable the alkyl radical, the greater the driving force for the translocation. Reactions involving oxygen are strongly exothermic due to high O–H bond strength and hydrogen transfers from carbon to nitrogen are also known.

This section will be organised around the nature of the radical that initiates translocation. Since translocation methodology has been the subject of recent reviews,[38,39] coverage will mainly be confined to reports that have appeared within the past three years.

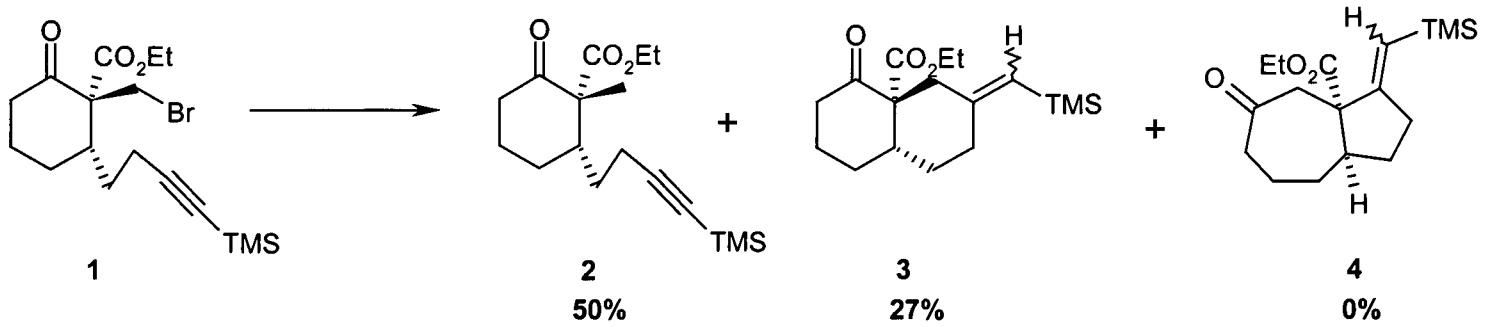
1.2.1 Alkyl Radicals

C–H transfers to alkyl radicals are less common than transfers to other carbon centred radicals, for example, aryl or vinyl, since little energy is gained in exchanging one sp^3 C–H bond for another. The majority of reported examples of hydrogen atom transfer reactions by alkyl radicals have occurred as unintentional side-reactions.

1.2.1.1 *Primary radicals*

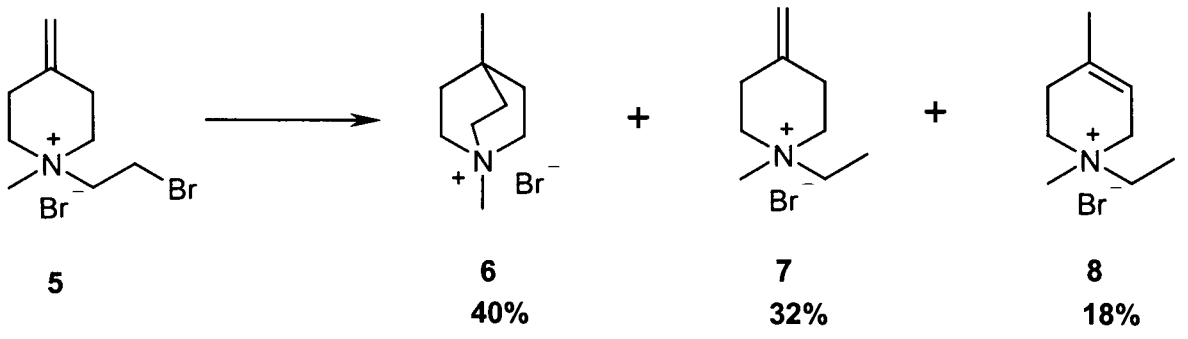
Curran and co-workers[40] were surprised to discover that when they treated the radical precursor **1** (**Scheme 1.1**) with tri-*n*-butyltin hydride, none of the desired ring expansion product **4** was formed and only the product **3** arising from 6-*exo*-cylisation was isolated along with an unusually large amount of the directly reduced product **2**. The ring expansion reaction had

proceeded efficiently in related substrates lacking the butynyl side chain, suggesting that a hydrogen atom abstraction might have occurred in competition with the 6-*exo*-cyclisation pathway. This hypothesis was supported by the observation that, when precursor **1** was treated with tri-*n*-butyltin deuteride, deuterium incorporation occurred exclusively at the propargylic carbon position. Apparently the rigid geometry of the system and stabilisation of the translocated radical by the alkyne favoured the hydrogen transfer reaction.



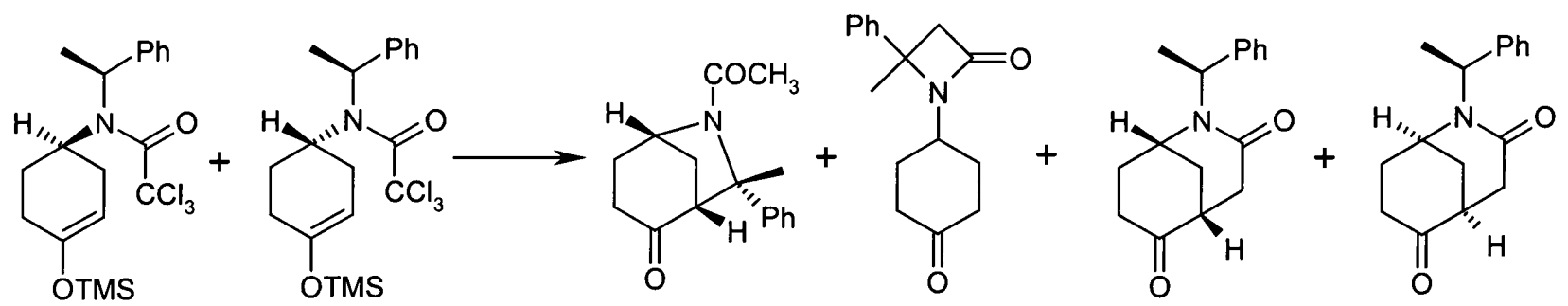
Scheme 1.1 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

During their attempts to prepare 1-azabicyclo[2.2.2]octanes, Della *et al.*[41] found that when the precursor **5** (**Scheme 1.2**) was treated with tri-*n*-butyltin hydride and AIBN three products were formed: the desired cyclisation product **6**, the directly reduced product **7**, and it's regioisomer **8**. The latter product was proposed to be derived from internal 1,5-hydrogen abstraction followed by hydrogen atom delivery by tri-*n*-butyltin hydride to the exocyclic site of the resulting allylic radical. The reduced product **7** presumably also results from the hydrogen atom abstraction pathway, but with delivery of a hydrogen atom to the internal allylic radical site.



Scheme 1.2 *Reagents and conditions*: Bu_3SnH, AIBN, 2-methylbutan-2-ol, Δ

In their attempts to prepare 2-azabicyclo[3.3.1]nonanes, Bonjoch and co-workers[20] observed an unusual 1,4-hydrogen atom transfer reaction which gave rise to two unexpected side products **9** and **10** along with the expected azabicyclic compounds **11** and **12** (**Scheme 1.3**). Isolation of **9** and **10** could be explained on the basis that the initially formed 1-(carbamoyl)dichloromethyl radical underwent 1,4-hydrogen abstraction to generate a benzylic radical which then underwent cyclisation to give normorphan **9**, or a combination reaction (after further chlorine abstraction) to give the *β*-lactam **10**. Alternatively, **10** could be formed *via* a carbenoid intermediate.

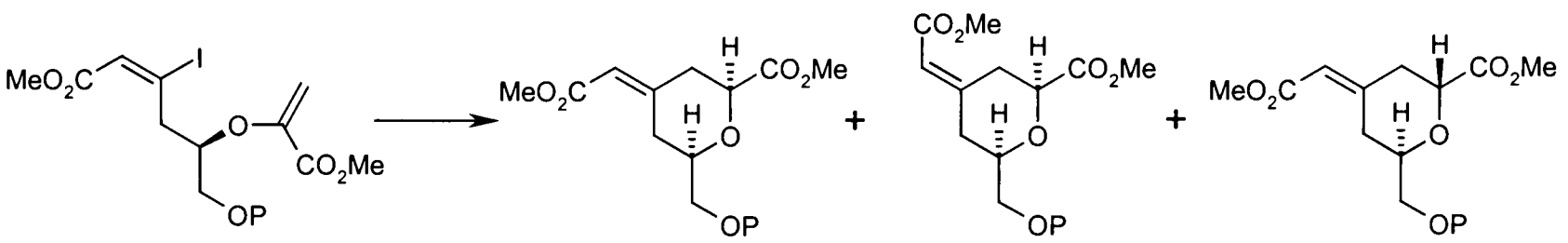


9 **10** **11** **12**
18% **7%** **10%** **21%**

Scheme 1.3 *Reagents and conditions*: TTMSS (3.5eq.), AIBN, PhH, Δ

1.2.1.2 *Secondary radicals*

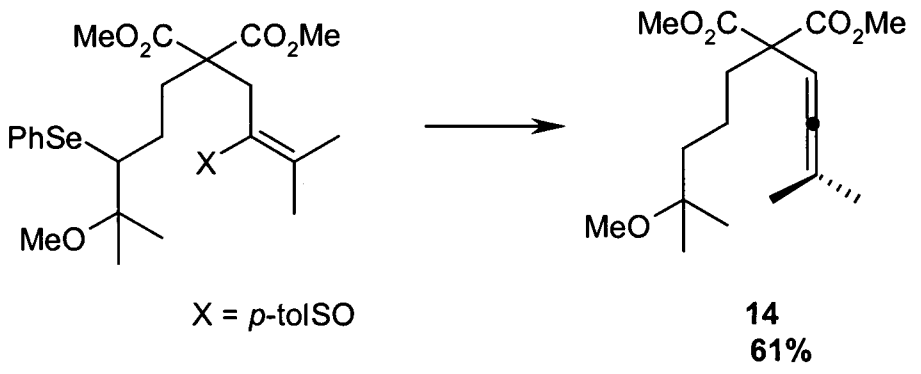
Thomas and co-workers[27] were surprised that the stereoselectivity in the cyclisation of the vinyl iodide **13** (**Scheme 1.4**) decreased when the 1°-hydroxyl protecting group was changed from *tert*-butyldimethylsilyl to *para*-methoxybenzyl. The loss of stereoselectivity in the *para*-methoxybenzyl ether case was attributed to 1,6-hydrogen atom transfer from the benzylic position of the *para*-methoxybenxyl group to the tetrahydropyranyl radical formed after initial 5-*exo*-*trig* cyclisation of the vinyl radical and ring expansion.



13	P = TBS	**85%**	**80**	:	**20**	:	**0**
	P = PMB	**73%**	**60**	:	**22**	:	**18**

Scheme 1.4 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

Radical translocations by alkyl radicals have also been used as reliable, synthetically useful processes in synthesis. For example, Malacria and co-workers[42] successfully employed 1,5-hydrogen atom transfer methodology to promote *β*-elimination of sulfinyl radical in their preparation of substituted allenes (**Scheme 1.5**). The alkyl radical generated after phenylselenyl abstraction undergoes a 1,5-hydrogen atom abstraction and the resulting stabilised allylic radical then engages in a rapid *β*-elimination to give the tri-substituted allene **14** in 61% yield along with the directly reduced vinyl sulfoxide in 18% yield.



Scheme 1.5 *Reagents and conditions*: TTMSS, AIBN, PhMe, Δ

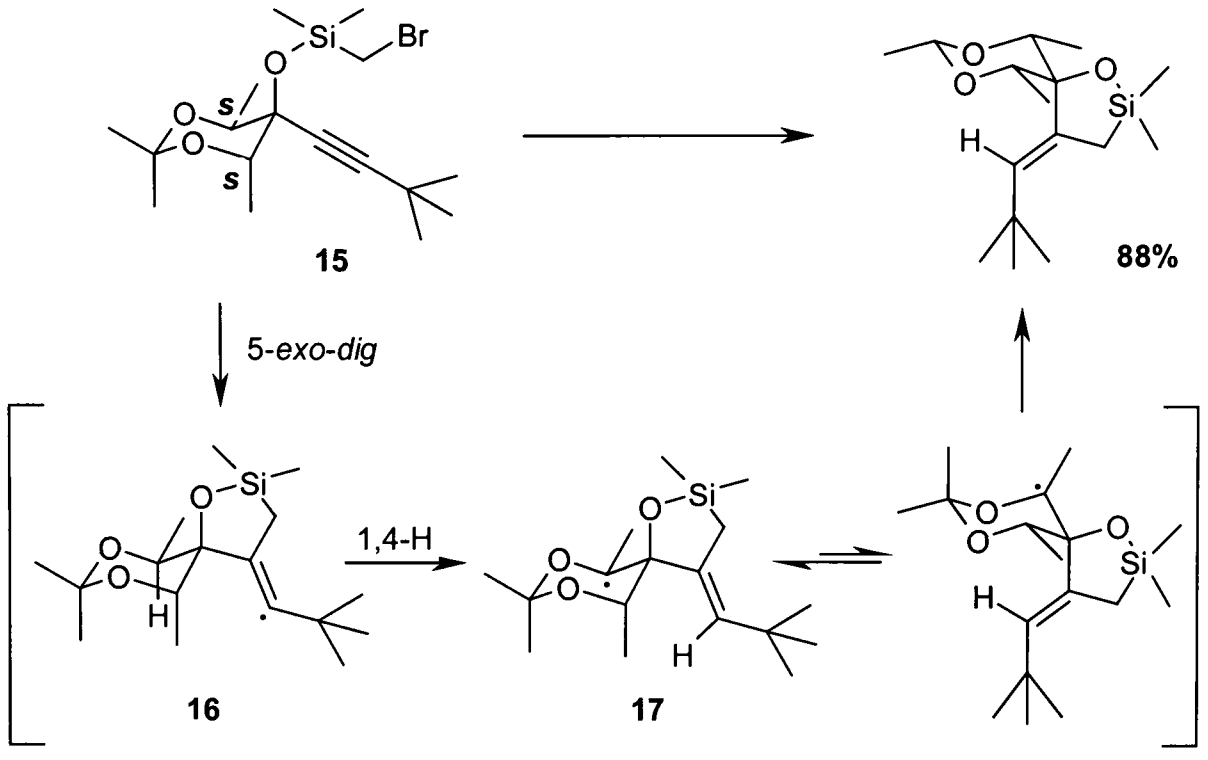
1.2.2 Vinyl Radicals

Vinyl radicals are widely used in translocation chemistry as they are highly reactive and the abstraction process is favoured both kinetically and thermodynamically. They can be generated by radical addition to alkynes or abstraction of a halogen atom from haloalkenes.

1.2.2.1 *1,4-Hydrogen atom abstraction*

1,4-Hydrogen atom transfers are observed less frequently than 1,5- and 1,6-transfers as a result of both unfavourable entropic and enthalpic factors caused by deviation from linearity in the transition state; nevertheless, examples are known that may be synthetically useful.

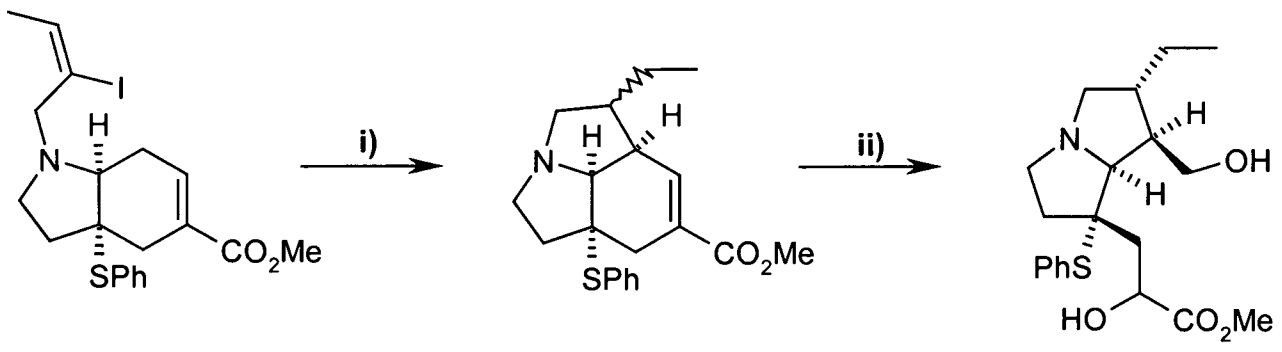
A recent example is demonstrated in the work of Malacria and co-workers,[43] in which, 1,4-hydrogen atom transfer and subsequent intermolecular trapping was employed in the preparation of enantiomerically pure 1,2,3-triol derivatives. After initial 5-*exo-dig* cyclisation of the radical generated from precursor **15** (**Scheme 1.6**), the vinyl radical **16** underwent a completely chemoselective (and diastereoselective) 1,4-hydrogen atom transfer to generate radical **17**. Preferential axial hydrogen atom delivery from the β-face led to clean inversion of configuration. This pathway was supported by labelling experiments conducted with tri-*n*-butyltin deuteride that indicated complete deuterium incorporation at the α-oxygenated position.



Scheme 1.6 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

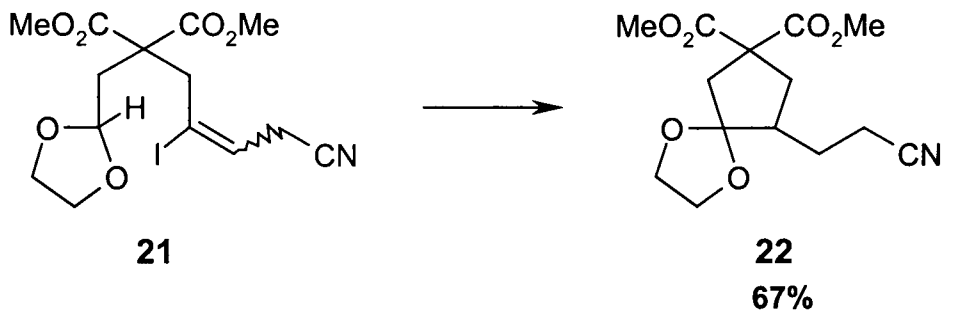
1.2.2.2 *1,5-Hydrogen atom abstraction*

An early example of radical translocation by an sp^2 carbon centre is exemplified in the work of Parsons and co-workers[44] who employed a radical translocation-cyclisation sequence for the construction of pyrrolizidine ring systems. Irradiation of the vinyl iodide precursor **18** generated a vinyl radical which underwent 1,5-hydrogen atom abstraction from the allylic position followed by 5-*exo-trig* cyclisation to give the tricyclic product **19**. Subsequent oxidative cleavage of the double bond followed by reduction with sodium borohydride afforded the pyrrolizidine **20**.



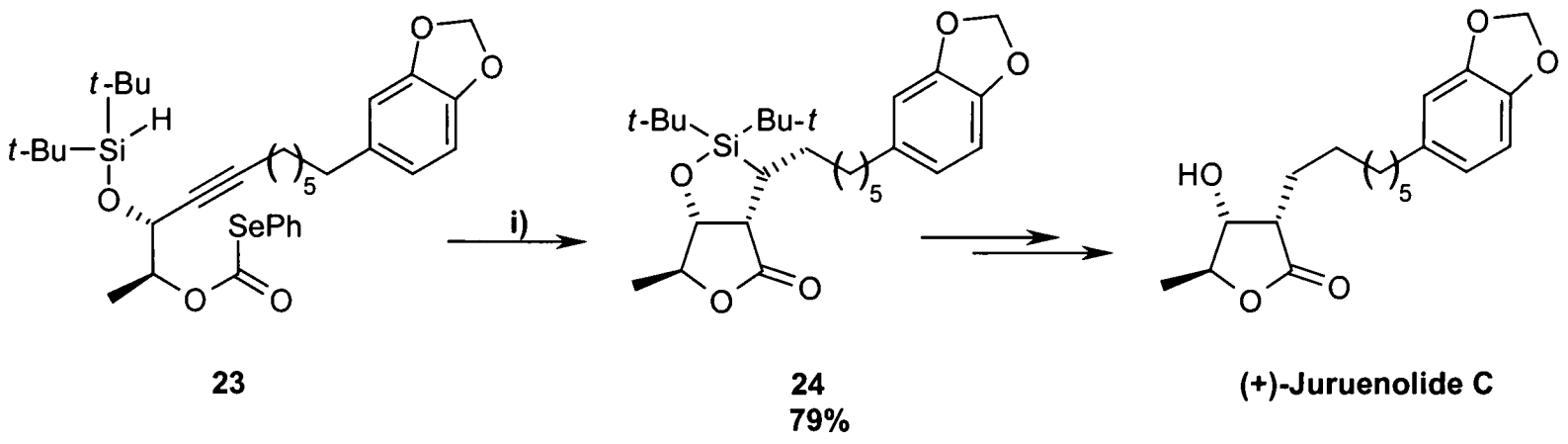
Scheme 1.7 *Reagents and conditions*: i) Bu_3SnH, PhH, *hν*; ii) O_3, then $NaBH_4$, MeOH

Other early examples of 1,5-hydrogen abstraction by a vinyl radical were provided by Curran *et al.*[45] For example, treatment of the vinyl iodide **21** (**Scheme 1.8**) with tri-*n*-butyltin hydride and AIBN gave a reactive vinyl radical which, after 1,5-hydrogen atom translocation and subsequent cyclisation, gave the cyclic ketal **22**.



Scheme 1.8 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

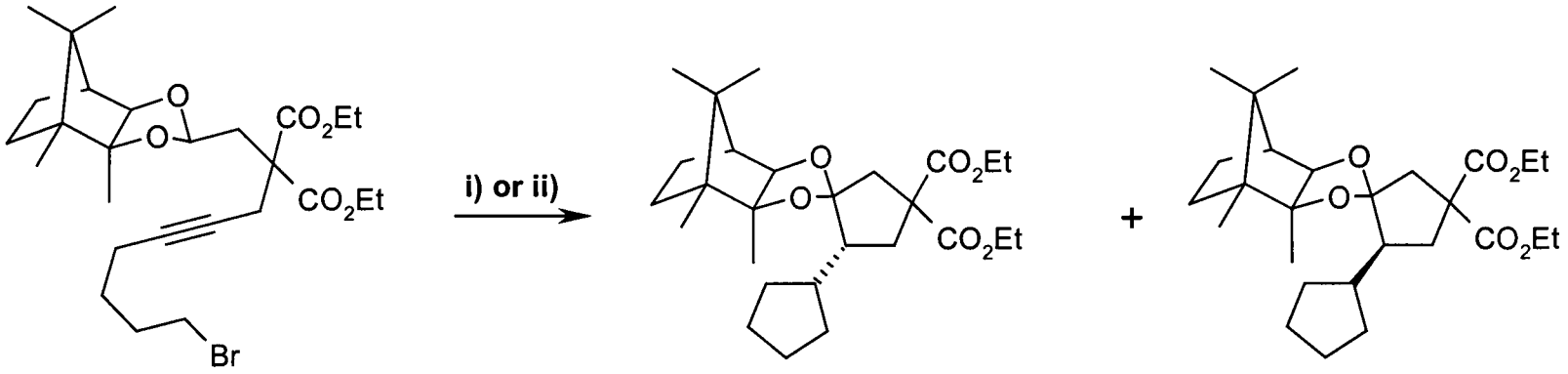
During their work on the synthesis of (+)-juruenolide C, Clive and Ardelean[46] employed a novel tandem cyclisation-translocation-cyclisation strategy to form the γ-lactone **24** (**Scheme 1.9**). Treatment of the phenylseleno carbonate **23** with triphenyltin hydride and AIBN gave the acyl radical which underwent sequential 5-*exo-dig* radical cyclisation, 1,5-hydrogen atom transfer, and 5-*endo-trig*-cyclisation, ultimately affording lactone **24**, which was further elaborated to the natural product juruenolide C. The 5-*endo-trig* ring closure in this reaction is noteworthy since 5-*endo-trig* cyclisations are encountered much less frequently than their 5-*exo* counterparts, in accordance with Baldwin's rules[47] and the Beckwith guidelines.[4] It is thought that the increased length of the bonds to silicon lowers the stereoelectronic barrier which normally hinders such *endo* cyclisations. Clive[48] also employed this tandem cyclisation-translocation-cyclisation sequence to prepare a number of other unusual silicon-containing polycyclic compounds.



23 **24** **79%** **(+)-Juruenolide C**

Scheme 1.9 *Reagents and conditions*: i) Ph_3SnH, AIBN addition over 7 hours, PhH, Δ

Crich and co-workers[49] reported an interesting 5-*exo-dig* cyclisation, 1,5-hydrogen atom transfer and 5-*exo-trig* cyclisation sequence of a chiral acyl-radical equivalent. The alkyne group in the precursor **25** (**Scheme 1.10**) served as the acceptor for both radical cyclisations and the product **26** was formed in good yield with excellent diastereomeric excess.



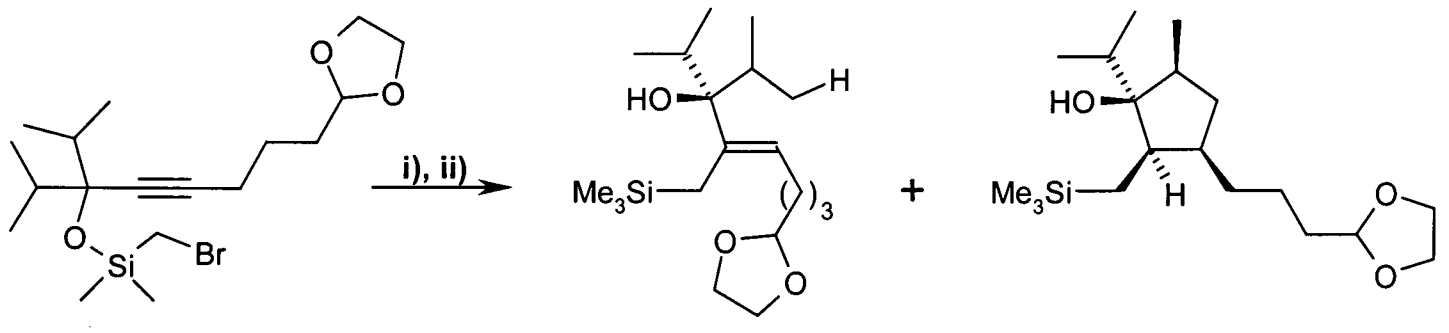
25 **26**

i) 72%	**96**	:	**4**
ii) 65%	**99**	:	**1**

Scheme 1.10 *Reagents and conditions*: i) Bu_3SnCl, $NaBH_3CN$, AIBN, *t*-BuOH, Δ; ii) Bu_3SnH, AIBN, PhH, *hν*, 20°C

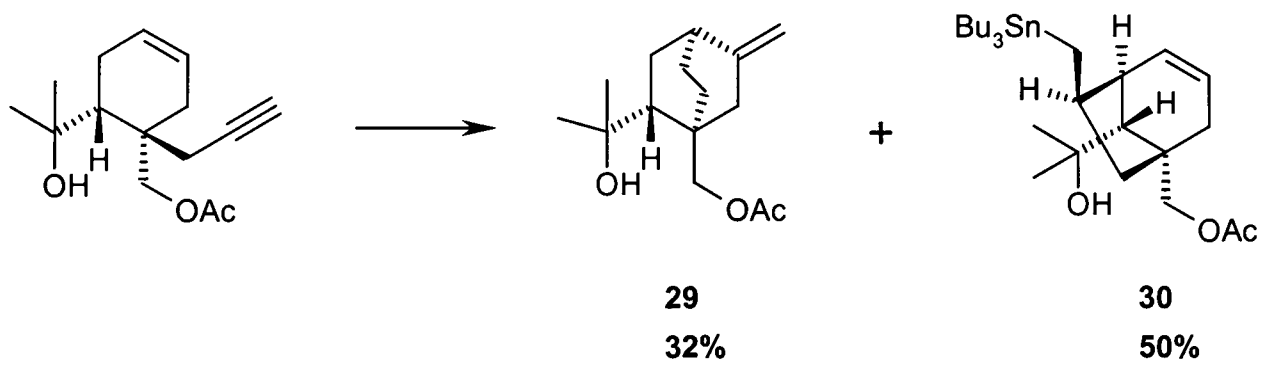
The Malacria group[50] described a similar sequence for the preparation of highly functionalised cyclopentanes. Thus, after generation of the vinyl radical by 5-*exo-dig* cyclisation, 1,5-hydrogen atom transfer followed to generate a methylene radical. This methylene radical was

either reduced by the tin hydride at this stage to give (after treatment with methyl lithium) the uncyclised product **27** (**Scheme 1.11**) or underwent an unusual, highly diastereoselective 5-*endo-trig* cyclisation to afford cyclopentane **28**, after reduction and treatment with methyl lithium.



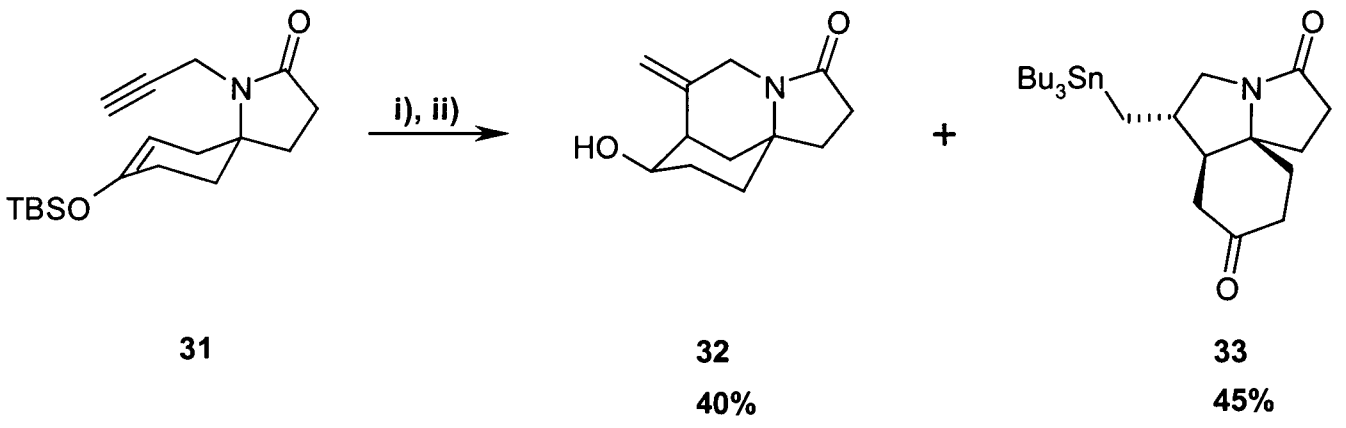
Scheme 1.11 *Reagents and conditions*: i) Bu_3SnH, AIBN, PhH, Δ; ii) MeLi, 0°C

1,5-Hydrogen atom transfer has often occurred as an unwanted side reaction. For example, during the total synthesis of (±)-methyl gummiferolate, Ihara and co-workers[51,52] discovered that a 1,5-hydrogen atom transfer pathway was a major competing process in their preparation of bicyclo[2.2.2]octane **29** (**Scheme 1.12**), the major product being the bicyclo[3.2.1]octane **30**, arising from 1,5-hydrogen abstraction by the initially formed vinyl radical followed by 5-*exo-trig* cyclisation.



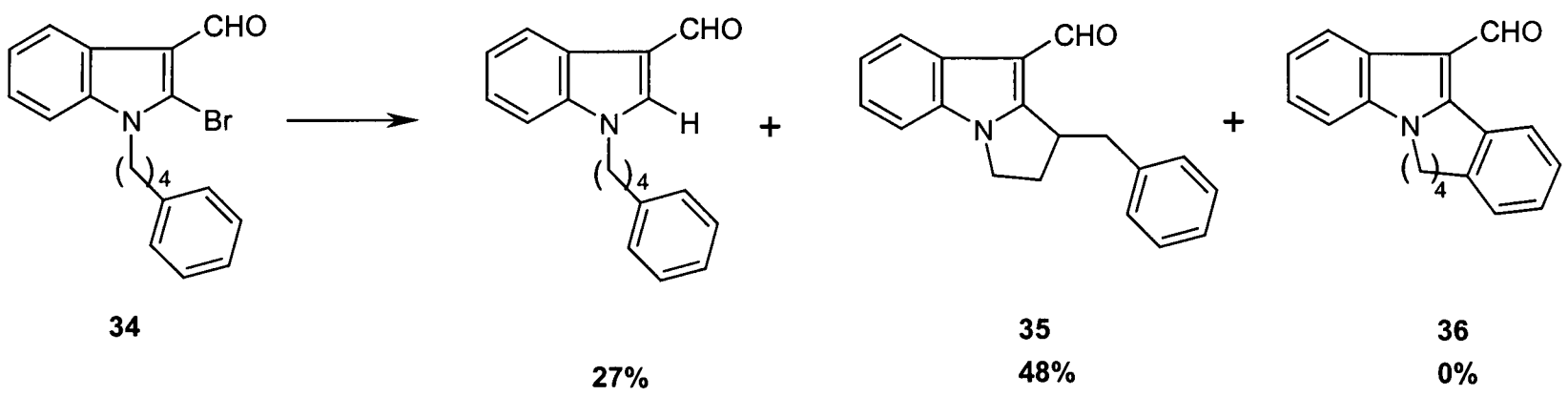
Scheme 1.12 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

During their work towards the total synthesis of (±)-desmethylamino FR901483, Wardrop and Zhang[53] assigned the major product of the radical reaction of precursor **31** (**Scheme 1.13**) to tricyclic structure **33** rather than the desired cyclisation product **32**. After initial addition of stannyl radical to the triple bond in **31**, one of the cyclohexene conformers of the resulting vinyl radical effected a preferential 1,5-hydrogen atom abstraction; subsequent diastereoselective 5-*exo-trig* cyclisation of the resulting allylic radical gave the tricyclic product **33** in 45% yield.



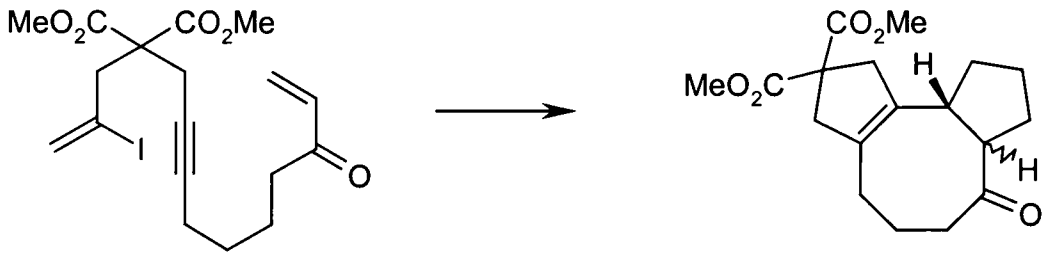
Scheme 1.13 *Reagents and conditions*: i) Bu_3SnH, AIBN, PhH, Δ; ii) MeOH, HCl, RT

In their syntheses of fused [1,2-*a*]indoles, Fiumana and Jones[54] isolated the tricyclic compound **35** (**Scheme 1.14**) as the major product in the radical reaction of indole **34** instead of the desired tetracyclic compound **36**. The tricyclic structure was proposed to arise from 1,5-hydrogen atom abstraction by the initial indole radical followed by cyclisation of the resulting alkyl radical onto the indole with subsequent oxidation to restore aromaticity.



Scheme 1.14 *Reagents and conditions*: Bu_3SnH, AIBN, MeCN,

Fensterbank *et al.*[55] found that an unwanted 1,5-hydrogen atom abstraction occurred in their attempts to prepare fused 5-6-6 ring systems and sought to capitalise on this result to apply the unwanted translocation to the construction of other tricyclic systems. Thus, when precursor **37** (**Scheme 1.15**) was treated with tri-*n*-butyltin hydride and AIBN an unusual tandem cyclisation-translocation-cyclisation-cyclisation sequence followed to give tricycle **38** in 56% yield.

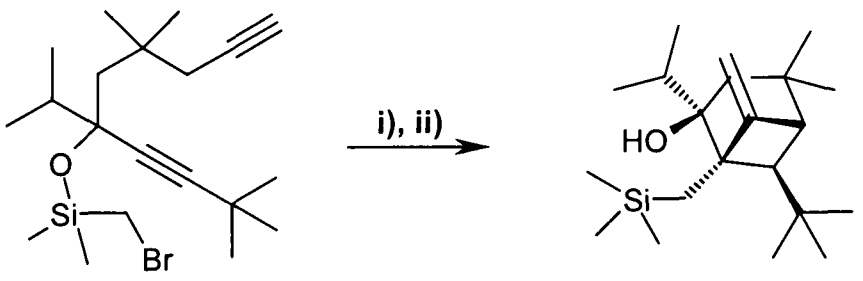


37 **38** ***cis*:*trans*** **34:66**

Scheme 1.15 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

1.2.2.3 *1,6- and 1,7-Hydrogen atom abstraction*

Malacria and co-workers[25,36] have reported both 1,6- and 1,7-hydrogen atom abstractions by vinyl radicals in their work towards the preparation of highly functionalised cyclopentanone derivatives. In a more recent example,[28] 1,6-hydrogen atom transfer operated as a key step in the preparation of bicyclo[3.1.1]heptanes (**Scheme 1.16**). Following the predicted 5-*exo-dig* cyclisation of the initially formed vinyl radical, selective 1,6-hydrogen atom translocation occurred to form a stabilised propargyl radical; in this case no 1,5-hydrogen atom transfer from the isopropyl group was seen. Subsequent 6-*endo-trig* cyclisation and an usual 4-*exo-dig* cyclisation afforded the bicyclo[3.1.1]heptane **39** upon treatment with methyl lithium.



39
85%

Scheme 1.16 *Reagents and conditions*: i) Bu_3SnH. AIBN, PhH, Δ; ii) MeLi, 0°C

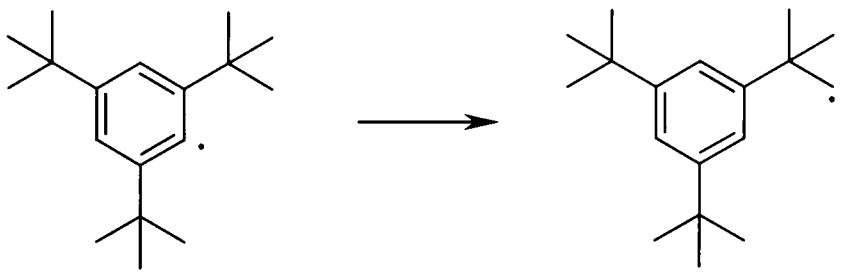
1.2.3 Aryl Radicals

The most important contribution to radical translocation chemistry comes from aryl radical precursors. This is primarily due to their ease of introduction and the high rate of hydrogen abstraction by the aryl radical ($k \approx 5 \times 10^7$–10^8 s^{-1} at 25°C).[56-58]

1.2.3.1 *1,4-Hydrogen atom abstraction*

Just as 1,4-hydrogen atom abstraction by vinyl radicals is extremely rare, examples of 1,4-hydrogen transfer by aryl radicals are also uncommon, although examples have been reported.

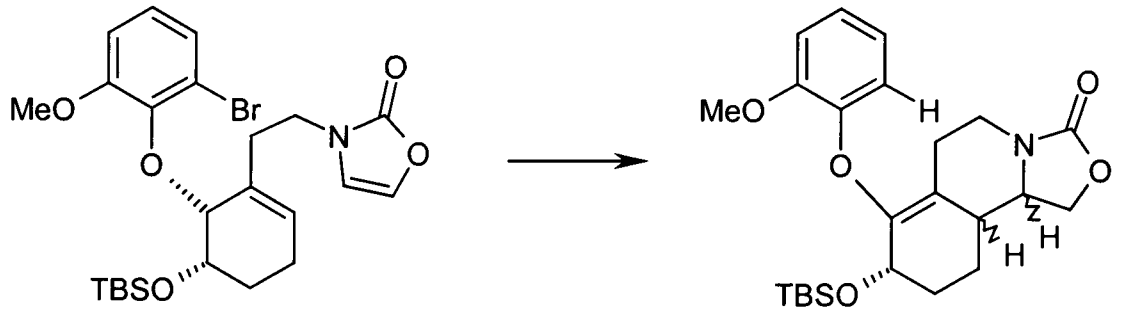
Ingold and co-workers[14,15] reported an early example of 1,4-hydrogen translocation by an aryl radical in which a sterically hindered 2,4,6-tri-*tert*-butylphenyl radical **40** (**Scheme 1.16**) underwent a rapid 1,4-hydrogen transfer from one of the *tert*-butyl groups to give the 3,5-di-*tert*-butylneophyl radical **41**, which was detected by ESR spectroscopy.



40 41

Scheme 1.16

A more recent example was published by Hudlicky and co-workers[19] during their attempted radical cyclisation approach to morphine. Thus, tricyclic compound **43** (**Scheme 1.17**) was produced, along with a complex mixture of other products, *via* competitive 1,4-hydrogen atom transfer of the radical generated from aryl bromide **42**, and subsequent 6-*exo-trig* cyclisation of the resultant allylic radical onto the oxazolidinone double bond.



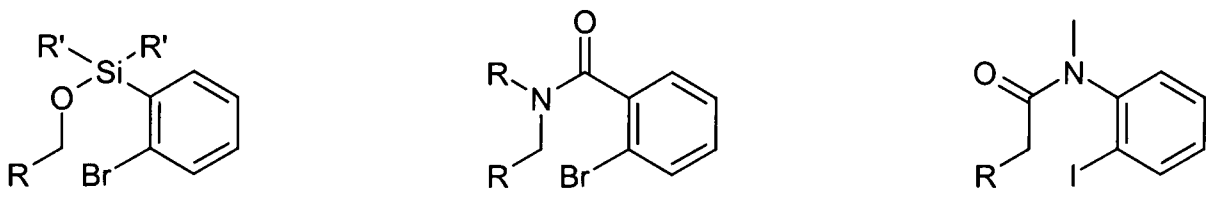
42 43

Scheme 1.17 *Reagents and conditions*: TTMSS, AIBN, PhH, sealed tube, Δ

1.2.3.2 *1,5-Hydrogen atom abstraction*

An important aspect of aryl radical precursors is their use in protecting/radical translocating (PRT) group chemistry pioneered by Curran.[59-61] Since the initial report in 1988,[45] this concept has been extensively researched by groups including Snieckus,[62] De Mesmaeker[24] and others.[63-65]

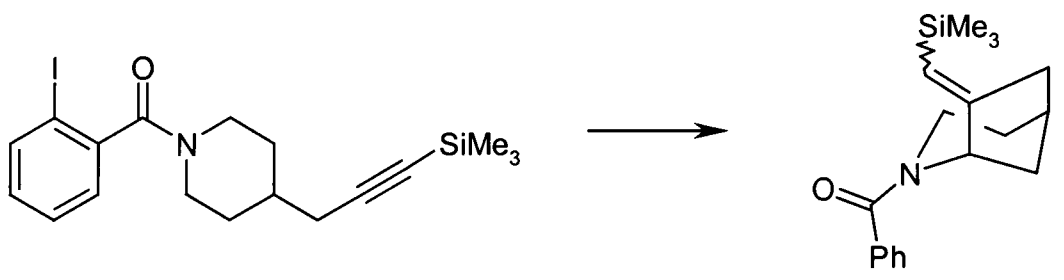
PRT groups are designed to generate selectively a radical from a C–H bond by abstraction and also to serve as a protecting group both before and after the radical reaction. They vary in both the nature of the protecting group and in the functional group to be protected, e.g. alcohols, carboxylates and amines (**Figure 1.6**).



alcohols **amines** **carboxylates**

Figure 1.6 Representative examples of PRT groups for different functionalities.

Recently PRT groups have been used by Ikeda and co-workers[66-68] to prepare bridged azabicyclic compounds. In one example,[68] treatment of the *o*-iodobenzoyl amine **44** (**Scheme 1.18**) with tri-*n*-butyltin hydride and AIBN gave two stereoisomeric 2-azabicyclo[3.2.1]octanes **45** in 85% combined yield after 1,5-hydrogen atom abstraction by the aryl radical and 5-*exo-dig* cyclisation.

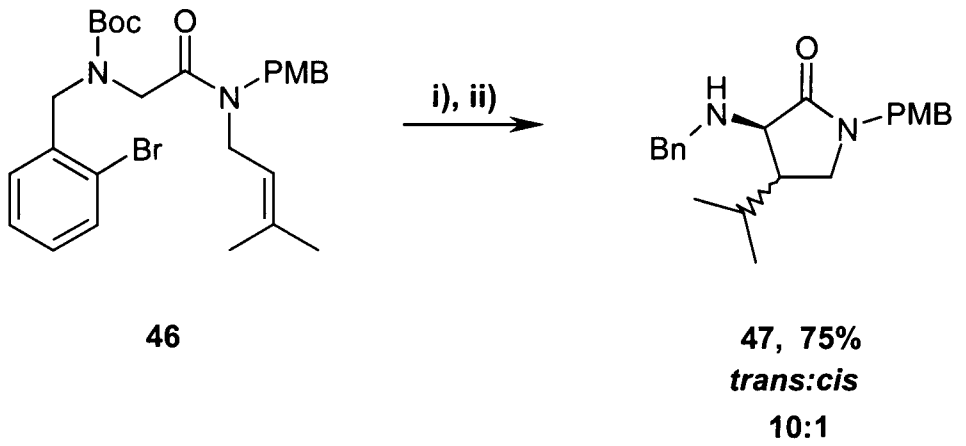


44 **45**
85%

Scheme 1.18 *Reagents and conditions*: Bu_3SnH, AIBN, PhMe, Δ

Rancourt *et al.*[69] have employed PRT methodology for the preparation of trans disubstituted γ-lactams. Thus, unsaturated glycine derivative **46** (**Scheme 1.19**) underwent tandem 1,5-hydrogen

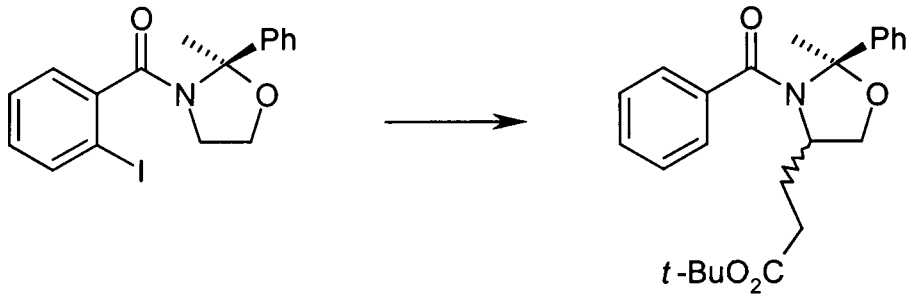
atom transfer and cyclisation, upon treatment with tri-*n*-butyltin hydride and ACCN, to give γ-lactam **47** in good yield and diastereoselectivity.



46 **47, 75%** ***trans:cis*** **10:1**

Scheme 1.19 *Reagents and conditions*: i) Bu_3SnH, ACCN, PhH, Δ; ii) 4N HCl/dioxane, aq. $NaHCO_3$

PRT methodology has been successfully employed by Wood and co-workers[70,71] to prepare functionalised *β*-aminoalcohols. For example, the aryl radical generated from aryl iodide **48** (**Scheme 1.20**) effected 1,5-hydrogen atom transfer to give an carbon-centred radical, which was trapped with *tert*-butyl acrylate to give the functionalised oxazolidine **49** in 75% isolated yield as a 2:1 mixture of diastereomers.

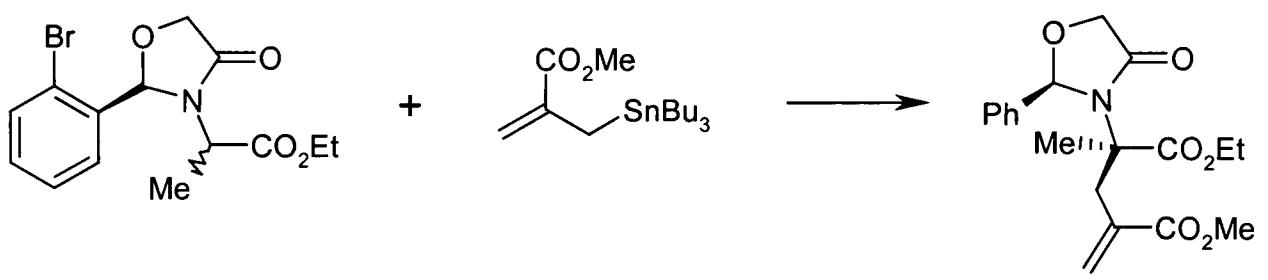


48 **49** **75%**

Scheme 1.20 *Reagents and conditions*: $CH_2{=}CHCO_2{}^tBu$, Bu_3SnCl, $NaBH_3CN$, AIBN, ^tBuOH, Δ

Giraud and Renaud[72] have extended PRT group methodology to use the PRT group as a chiral auxiliary in a useful asymmetric synthesis of cyclic amino acids. When aryl iodide **50** (**Scheme 1.21**) was treated with methyl 2-[(tributylstannyl)methyl]propenoate and AIBN, 1,5-

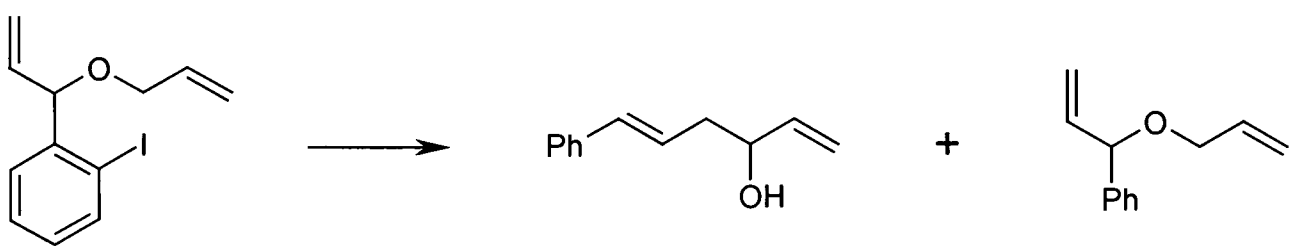
hydrogen atom transfer and subsequent intermolecular trapping occurred to give the oxazolidinone **51** in good yield and diastereoselectivity.



50 **51** **74%** **d.r. = 98:2**

Scheme 1.21 *Reagents and conditions*: AIBN, PhH, Δ

Kunishima *et al.*[73] have investigated a samarium(II) iodide-mediated [2,3]-Wittig rearrangement initiated by 1,5-hydrogen atom abstraction by an aryl radical generated from an *o*-iodophenyl group. When aryl radical precursor **52** (**Scheme 1.22**) was treated with samarium(II) iodide in an HMPA/benzene mixture, alcohol **53** was produced along with the reduced product **54**. The mechanism is thought to involve SET from samarium(II) iodide to generate the aryl radical and, after 1,5-hydrogen atom transfer, a second SET from samarium(II) iodide follows; the resulting α-allyloxy carbanion then undergoes [2,3]-Wittig rearrangement to give the alcohol in reasonable yield.

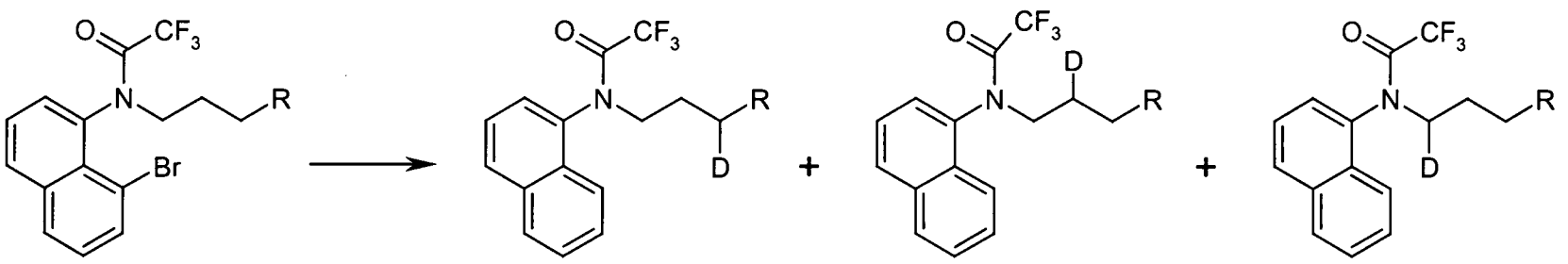


52 **53** **67%** **54** **9%**

Scheme 1.22 *Reagents and conditions*: SmI_2, PhH–HMPA, RT

1.2.3.3 *1,6- and 1,7-Hydrogen abstraction*

De Mesmaeker and co-workers[24] have investigated 1,n-hydrogen transfer (where n = 5, 6, 7) in conformationally restricted amides and found that hydrogen transfer from the *N*-alkyl side chain to the aryl radical can occur through competing 6-, 7- and 8-membered transition states. For example, on treatment of the naphthyl-derived amide **55a** (**Scheme 1.23**) with tri-*n*-butyltin deuteride and AIBN, 1,7-hydrogen atom abstraction dominated to give **56a**, along with a small amount of the 1,5-H product **58a**. However, in the absence of the stabilising phenyl group (**55b**) the reaction proceeded as expected, with the favoured product **58b** resulting from 1,5-hydrogen atom transfer, although significant amounts of the 1,6-H **57b** and 1,7-H **56b** products were observed. The products of 1,6- and 1,7-hydrogen atom abstraction are comparatively favourable in these systems because decreased conformational mobility leads to a lowering of the activation entropy for the 7- and 8-membered transition states.

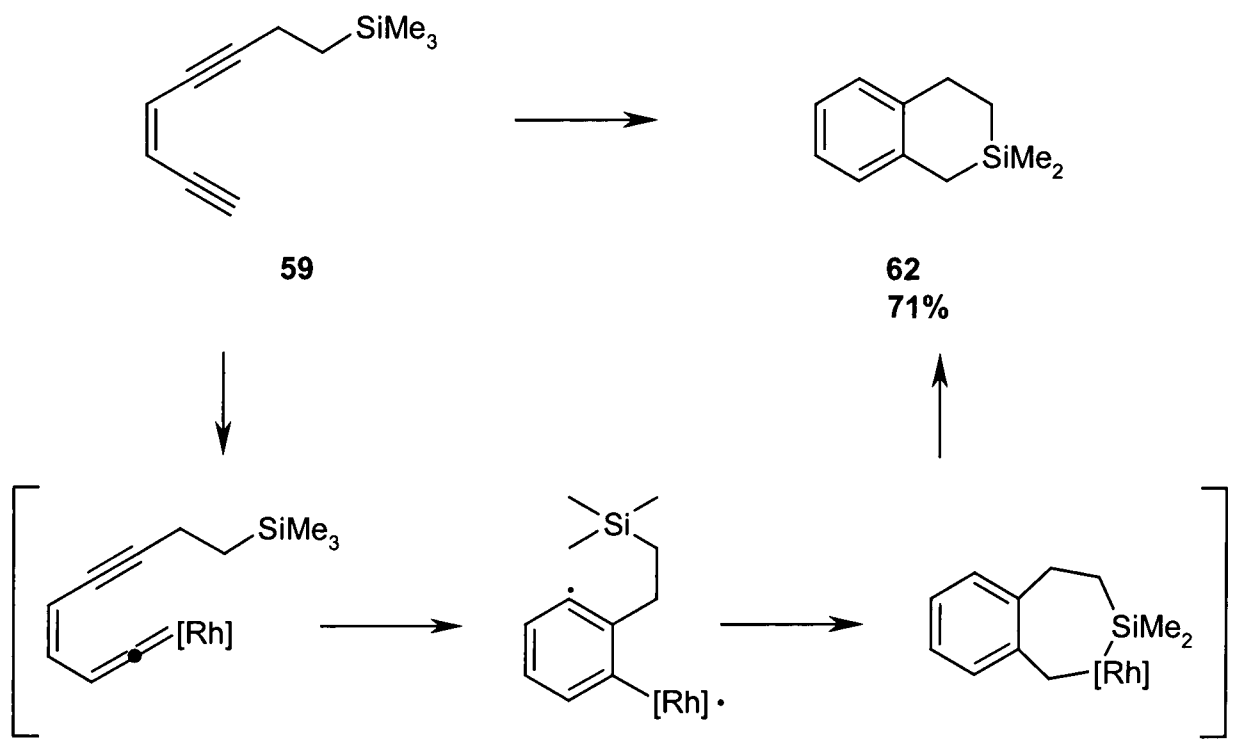


	56	:	**57**	:	**58**
55a R = Ph	78		5		17
55b R= H	10		30		40

Scheme 1.23 *Reagents and conditions*: Bu_3SnD, AIBN, PhH, Δ

A recent example of a synthetically useful 1,6-hydrogen transfer was reported by Ohe and co-workers.[26] In the rhodium(I)-catalysed radical reaction of acyclic enediyne **59** (**Scheme 1.24**)

the silacycle **62** was produced presumably by a 1,6-hydrogen transfer process. The intermediate 1,4-organorhodium diradical intermediate **60** underwent 1,6-hydrogen transfer from the methyl group to give a 1,7-diradical species. This diradical forms a rhodacycloheptane **61**, which can undergo reductive elimination to give the silacyclohexane shown.



Scheme 1.24 *Reagents and conditions*: 5 mol % $RhCl(^{i}Pr_3P)_2$, Et_3N, PhH, Δ

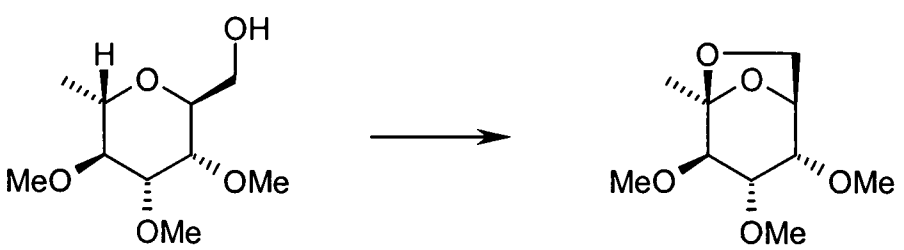
1.2.4 Alkoxyl Radicals

Alkoxyl radicals are electrophilic and preferentially attack C–H bonds with high HOMO energies, for example, C-H bonds α- to amines or ethers.[8] Although the reactions of alkoxyl radicals have been extensively reviewed,[74-76] a few recent and illustrative examples will be presented, organised around the method used to generate the reactive alkoxyl radical intermediate.

1.2.4.1 *Photolysis of hypoiodites*

The use of organohypoiodites in synthesis has recently been reviewed.[76] The alkoxyl radical precursor can be generated from the alcohol, by a number of reagents including *N*-iodosuccinimide, (diacetoxyiodo)benzene (DIB) and acyl hypoiodites. Heavy metal salts such as lead tetraacetate, mercury(II) acetate, silver acetate or mercuric oxide, in combination with iodine, generate hypoiodites *in situ* from the corresponding alcohol. Photolysis of the hypoiodite produces an alkoxyl radical, which can undergo 1,5-hydrogen transfer; the newly formed carbon radical usually captures an iodine atom and the so formed 1,4-iodohydrin generally cyclises to form a tetrahydrofuran derivative.

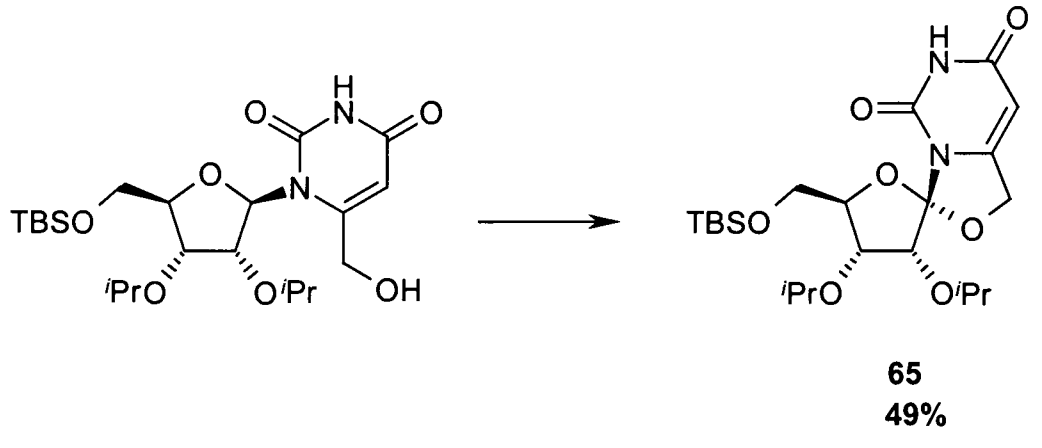
Suárez and co-workers[77] have employed the hypoiodite reaction in the synthesis of 2,7-dioxabicyclo[2.2.1]heptane and 6,8-dioxabicyclo[3.2.1]octane ring systems. In one example, the alkoxyl radical, generated *in situ* from the reaction of alcohol **63** (**Scheme 1.25**) with iodosylbenzene and iodine, effected a 1,5-hydrogen atom abstraction. The resulting anomeric radical was oxidised to a stable oxonium ion, which was subsequently trapped by the primary hydroxyl to give the 6,8-dioxabicyclo[3.2.1]octane **64** in excellent yield.



63 **64** **90%**

Scheme 1.25 *Reagents and conditions*: PhIO, I_2, DCM, *hν*

Chatgilialoglu *et al.*[78] utilised hypoiodite chemistry to prepare anomeric spironucleosides in a stereoselective manner. The key step involved 1,5-hydrogen transfer from the anomeric position to an alkoxyl radical, generated photolytically from a hypoiodite formed *in situ*. Cyclisation gave the spironucleoside **65** (**Scheme 1.26**) in moderate yield as a single diastereomer.



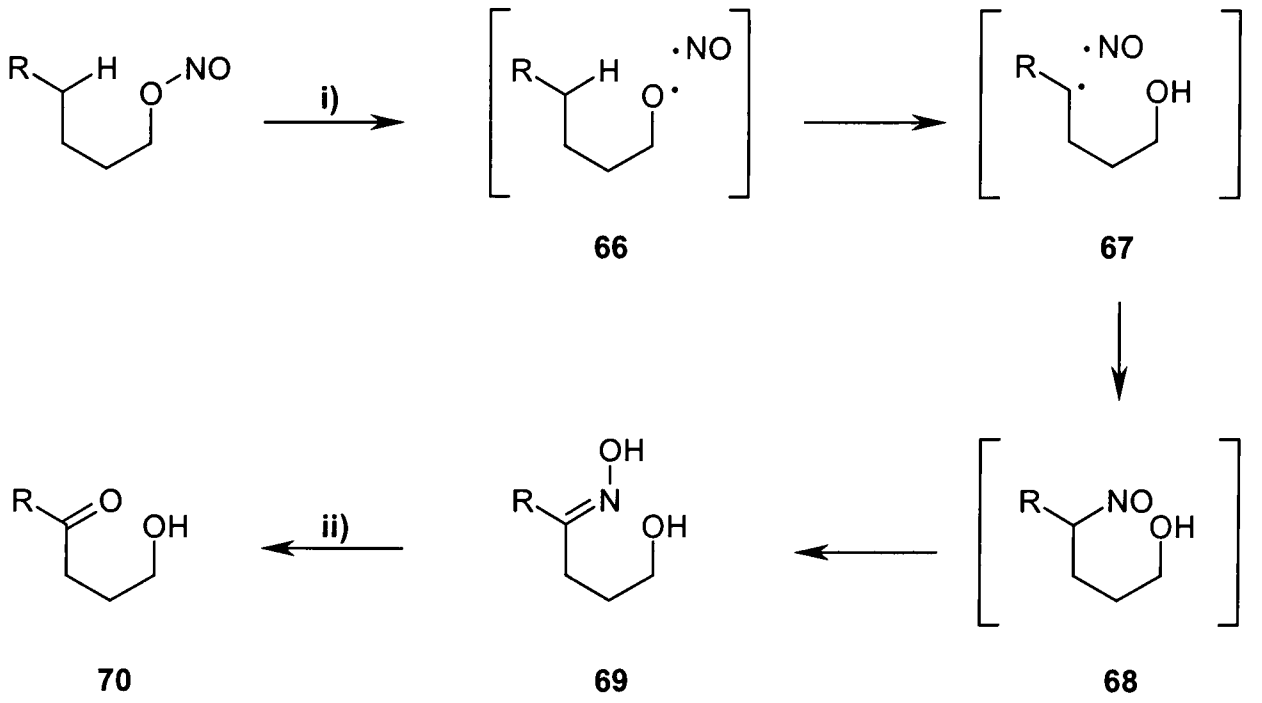
Scheme 1.26 *Reagents and conditions*: $PhI(OAc)_2$, I_2, cyclohexane, 28°C, *hν*

Ultrasonic activation instead of photolysis has also been used to generate alkoxyl radicals from hypoiodites as demonstrated in the methodology of Sá e Melo[79] for the preparation of steroidal tetrahydrofurans from 1,2-bromohydrins.

1.2.4.2 *Photolysis of nitrite esters*

The early work of Barton[80-84] on the remote functionalisation of steroidal systems by photolysis of nitrite esters was a significant achievement in the field of radical translocation. In the rigid steroidal skeleton, 1,5-hydrogen transfer is especially kinetically favourable ($k_{1,5} \approx 10^7$ s^{-1} at 25°C) and the chemistry has been widely exploited in the steroidal field[85-87] and in the synthesis of terpenes.[88] The mechanism involves the photolysis of a nitrite ester to generate an alkoxyl radical

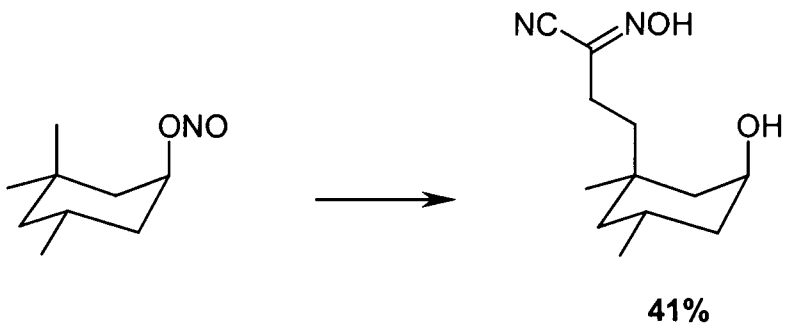
66 (**Scheme 1.27**), which undergoes rapid 1,5-hydrogen translocation to generate a more stable carbon-centred radical **67**. Trapping of this radical by the nitrosyl radical and subsequent tautomerisation of the nitroso group in **68**, results in functionalisation of the unactivated carbon as an oxime; acidic hydrolysis converts the oxime **69** to ketone **70**.



70 **69** **68**

Scheme 1.27 *Reagents and conditions*: i) *hν*; ii) H^+ / H_2O

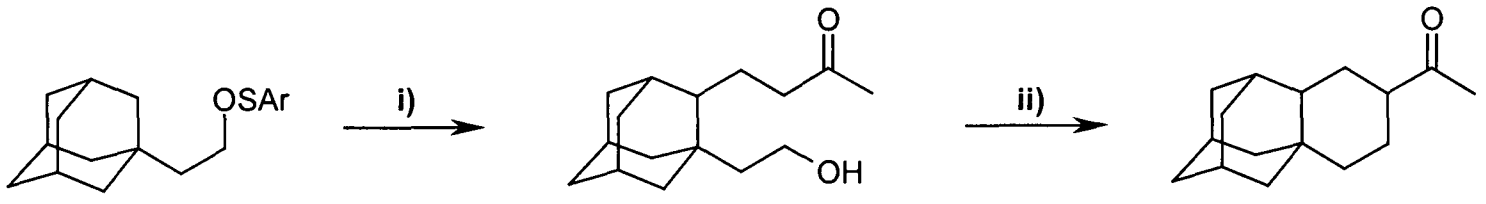
In a recent example Petrović and Čeković[89] reported that translocated alkyl radicals formed from photolysis of nitrite esters can be trapped with electron deficient alkenes, prior to quenching with the nitrosyl radical, leading to the introduction of functionalised alkyl chains (**Scheme 1.28**).



Scheme 1.28 *Reagents and conditions*: CH_2=CHCN, PhH, *hν*

1.2.4.3 *Alkyl benzenesulfenates*

The same authors[89-91] have extended the idea of trapping radicals generated from homolysis and translocation to include alkyl benzenesulfenates as precursors. In **Scheme 1.29**, a combination of radical and ionic reaction sequences operates for cyclohexane annulation. Irradiation of precursor **71** in the presence of tri-*n*-butyltin hydride and methyl vinyl ketone gave an alkoxyl radical, which underwent 1,5-hydrogen transfer and the resulting carbon-centred radical was trapped by the alkene to give alcohol **72**. Subsequent tosylation and cyclisation gave the cyclohexane ring system **73**.



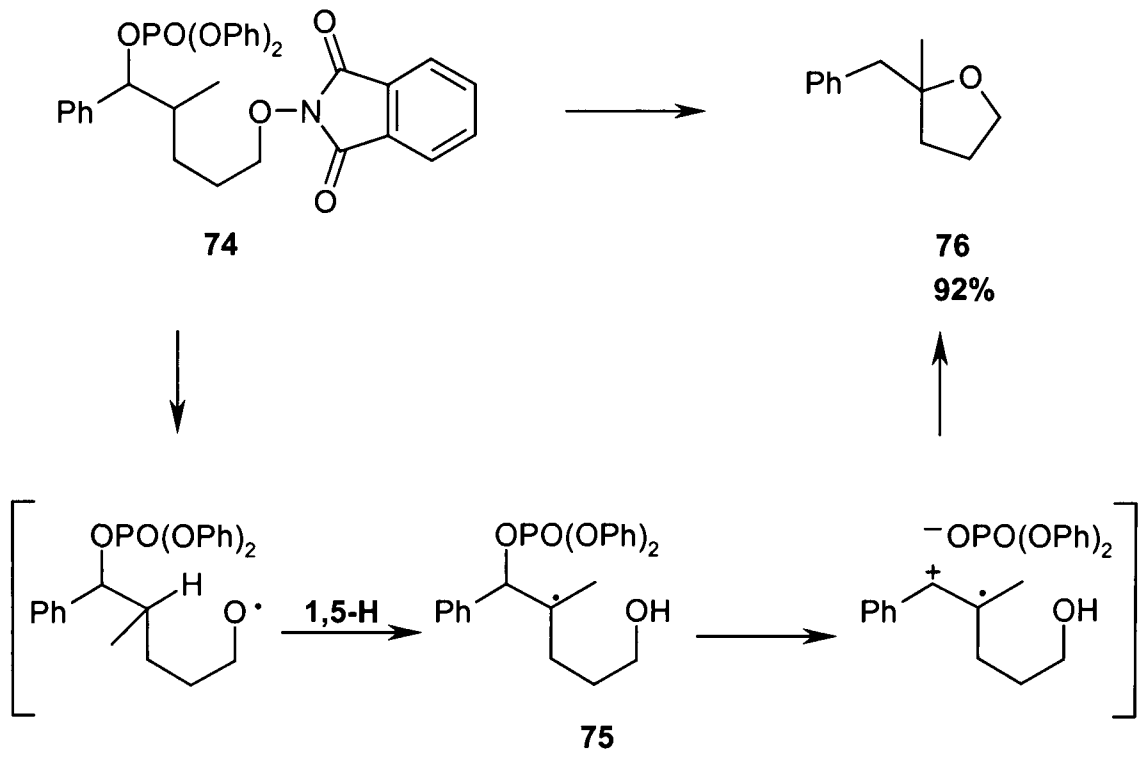
71 **72** **42%** **73** **78%**

Scheme 1.29 *Reagents and conditions*: i) Bu_3SnH, methyl vinyl ketone, PhH, *hν*; ii) TsCl, Pyr, then NaH, DME

1.2.4.4 N-*Alkoxyphthalimides*

Kim's[92] recent report of a method for the generation of alkoxyl radicals under mild conditions using *N*-alkoxyphthalimides has found application in the preparation of tetrahydrofurans. Crich and Newcomb[93,94] have employed this process in their tandem hydrogen atom abstraction/radical nucleophilic displacement sequence. Thus, when the alkoxyphthalimide **74** (**Scheme 1.30**) was treated with triphenyltin hydride and AIBN, 1,5-hydrogen atom transfer to the resulting alkoxyl radical occurred. The so-formed *β*-(phosphatoxy)alkyl radical **75** then underwent ionisation, and nucleophilic addition led to tetrahydrofuran **76** in excellent yield. The

nucleophilic displacement is thought to proceed *via* a stepwise fragmentation of the alkyl radical to give a styrene radical cation/phosphate ion pair followed by ring closure.



Scheme 1.30 *Reagents and conditions*: Ph_3SnH, AIBN, PhH/CH_3CN, Δ

1.2.4.5 *Fragmentation of epoxides*

The ring opening of an oxirane by an adjacent carbon centred radical to give an allyloxy radical is an extremely rapid process ($k \approx 1.0 \times 10^{10}$ s^{-1} at 25°C).[95] The less frequently observed cleavage of the C–C bond occurs only in the presence of stabilising groups α- to the so-formed radical (**Figure 1.7**).[96]

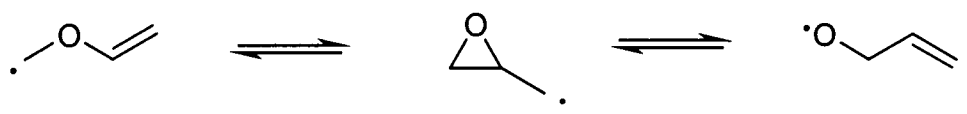
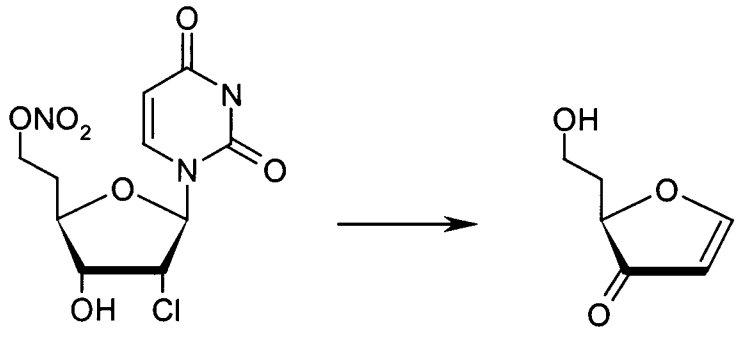


Figure 1.7 Fragmentation of an α-oxirane radical

Rawal[97-99] and Kim[100,101] have studied radical-induced epoxide fragmentation chemistry to prepare *cis*-fused bicyclic systems *via* an alkoxyl radical translocation-cyclisation sequence.

1.2.4.6 *Nitrates*

When alkyl nitrates are treated with tin hydride and AIBN, the initial stannyl radical abstracts the nitro group to generate an alkoxyl radical. In the biomimetic simulation study of Robins *et al.*[102] alkyl nitrate **77** (**Scheme 1.31**) was prepared and subjected to radical initiating conditions. 1,5-Hydrogen transfer to the resulting alkoxyl radical and subsequent elimination of chlorine atom produced an intermediate enol that ejected uracil to give the furanone **78**.



77 **78** **75%**

Scheme 1.31 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

1.2.4.7 *Electrochemical oxidation*

Alkoxyl radicals generated by electrochemical oxidation of ω-hydroxy-tetrahydropyrans have been used to prepare spiroketals.[103] The process involves loss of an electron from the alkoxide of **79** (**Scheme 1.32**), 1,5-hydrogen transfer, and further oxidation to an oxonium ion, which is finally trapped by the pendant hydroxyl to give the [5,5]spiroketal **80**.



77 **80** **60%**

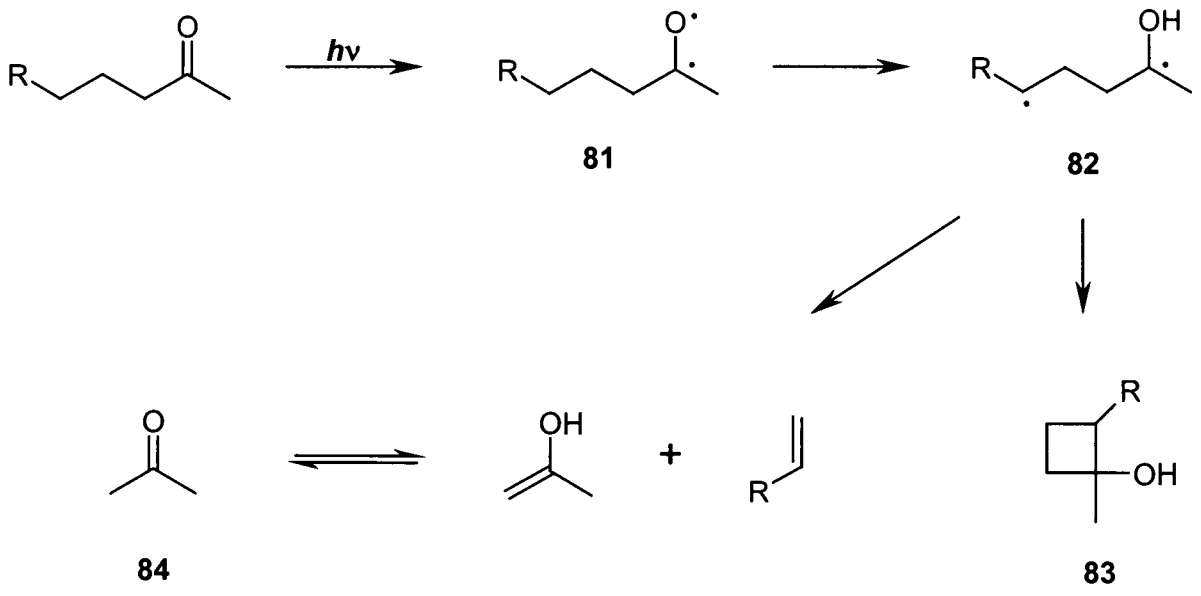
Scheme 1.32 *Reagents and conditions*: Pt–Pt, electrolysis, $LiBF_4$, NaOEt, EtOH, 20°C

1.2.4.8 *Homolytic cleavage of peroxides*

Alkoxyl radicals for 1,5-hydrogen transfer reactions have been generated by cleavage of the O–O bond in peroxides by low valent transition metals. Posner and co-workers[104] have employed iron(II) activation of peroxide bonds in the preparation of analogues of the anitimalarial artemisinin.

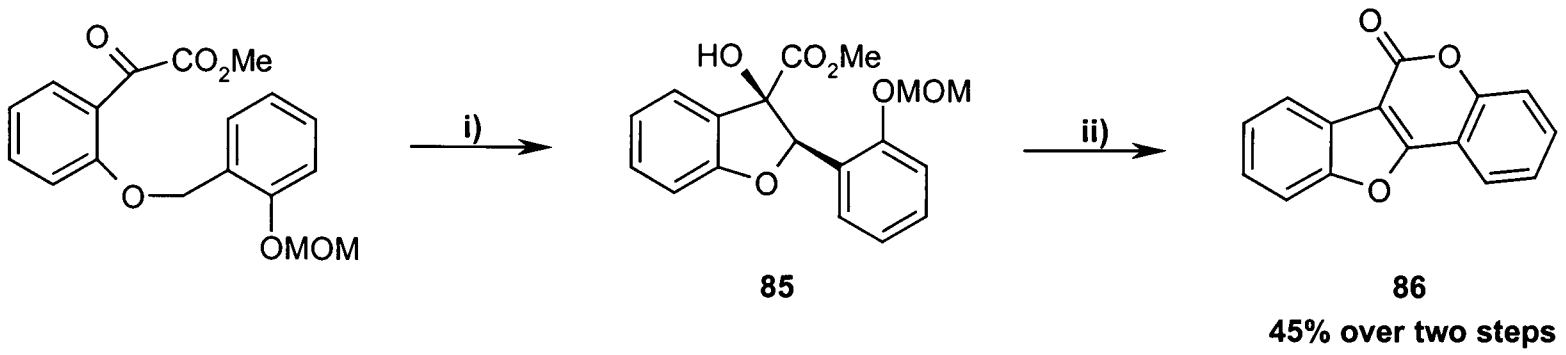
1.2.4.9 *Photolysis of carbonyls*

The intramolecular hydrogen transfer reaction of excited carbonyl compounds followed by fragmentation or recombination is known as the Norrish type II reaction. Upon irradiation the excited triplet carbonyl group **81** (**Scheme 1.33**) undergoes a hydrogen abstraction process to give the diradical **82**. This diradical species can react by two different pathways; recombination to give a cyclic alcohol **83** or fragmentation and tautomerisation to give the ketone **84**. Steric and electronic factors influence which pathway is dominant as the fragmentation involves alignment of the two SOMO's of the diradical with the C–C bond to be broken; factors that disfavour such a conformer will promote cyclisation. Although 1,5-hydrogen abstraction is the favoured pathway, abstraction of more remote hydrogen atoms is possible.[30,31,34,37]



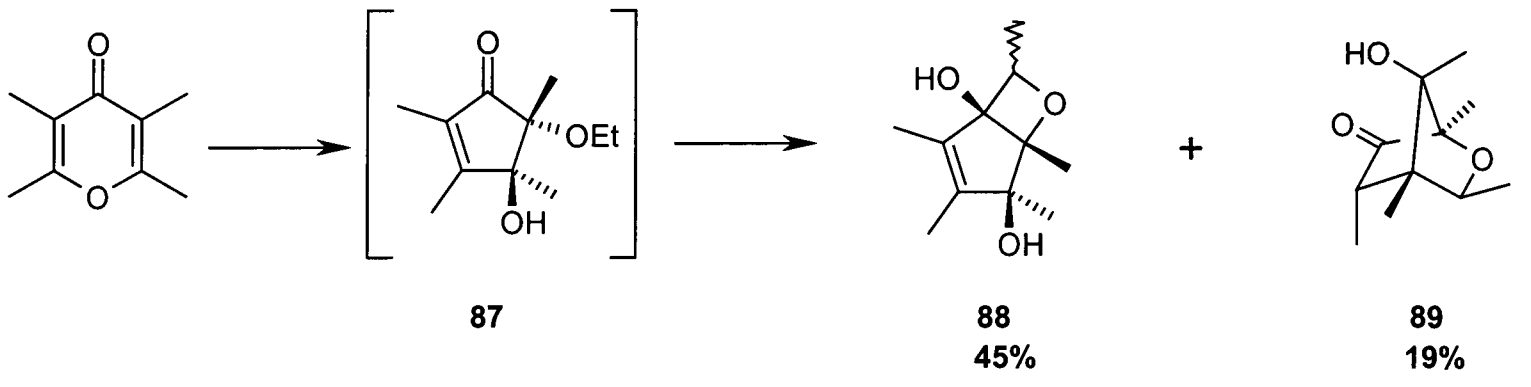
Scheme 1.33

Kraus and Zhang[30] employed this photolysis reaction in their synthesis of coumestran **86** (**Scheme 1.34**). Upon irradiation, 1,6-hydrogen abstraction and ring closure gave bicycle **85**; hydrolysis and cyclisation of the crude reaction mixture gave coumestran in 45% overall yield.



Scheme 1.34 *Reagents and conditions*: i) PhH, *hν*; ii) 6N HCl, THF, 50°C

An unusual 1,5-hydrogen abstraction (**Scheme 1.35**) was reported by West and co-workers.[21] The first-formed solvent-trapped photoadduct **87** underwent secondary photochemical processes to give the unexpected bicyclic products **88** and **89**. The mechanism is thought to proceed *via* further excitement of the cyclopentenone **87**, followed by 1,5-hydrogen abstraction, and ring closure at either of the two ring positions leading to the observed products in 64% combined yield.

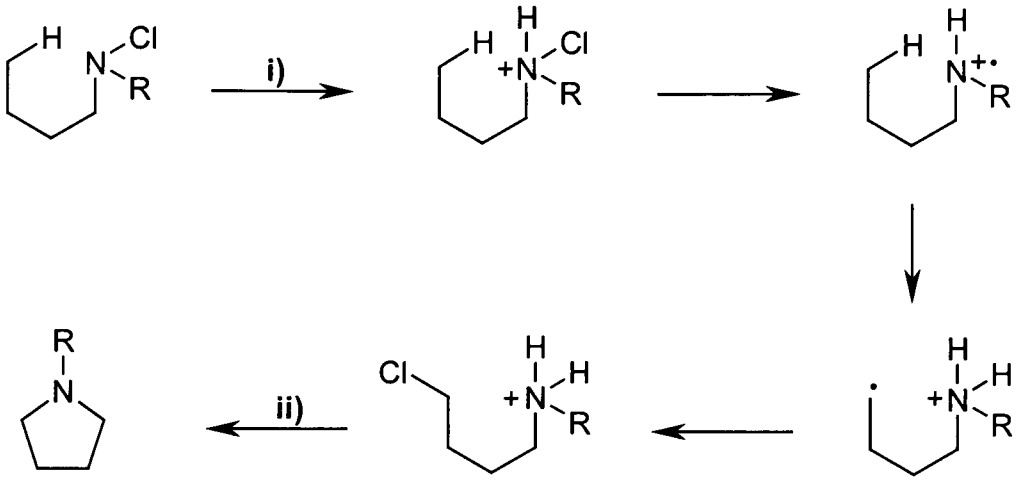


Scheme 1.35 *Reagents and conditions*: EtOH, hν

1.2.5 Nitrogen Centred Radicals[105,106]

1.2.5.1 *Aminyl radical cations (Hofmann-Löffler-Freytag reaction)*

The Hofmann-Löffler-Freytag reaction pre-dated the Barton nitrite ester photolysis (**Section 1.2.4.2**) but works on the same principle except that an electrophilic aminyl radical cation initiates hydrogen abstraction. The resulting translocated radical is trapped usually by reaction with starting material in a chain process, and the resulting alkyl chloride is cyclised in the presence of base (**Scheme 1.36**).[107,108] The reaction can be carried out photolytically, thermolytically or in the presence of a suitable reducing agent and Lewis acid.



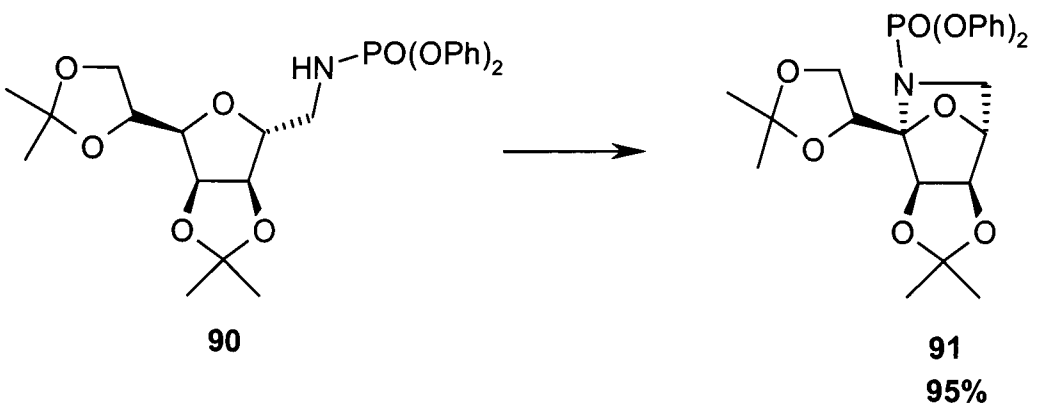
Scheme 1.36 *Reagents and conditions*: i) H^+, $h\nu$; ii) base

The reaction was extensively reviewed in 1963 by Wolff[109] and in 1995 by Majetich and Whelas.[75]

1.2.5.2 *N-Iodo intermediates*

Suárez and co-workers[110] employed conditions similar to those used to generate alkoxyl radicals for aminyl radicals. Thus, when the phosphoamidate **90** (**Scheme 1.37**) was treated with iodosylbenzene and iodine, 1,5-hydrogen transfer to the resulting aminyl radical occurred to give

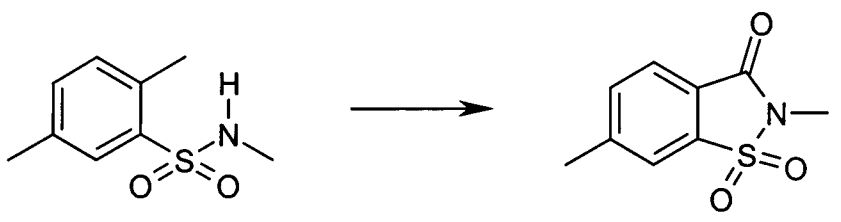
91 after one electron oxidation, and cyclisation of the amide group onto the so-formed oxonium ion.



90 **91** **95%**

Scheme 1.37 *Reagents and conditions*: PhIO, I_2, DCM/CCl_4, RT

Togo and co-workers[111] have used similar chemistry in the preparation of saccharin derivatives. A series of *N*-alkylsulfonamides was prepared and each compound was irradiated in the presence of DIB and iodine. In one particular example, *N*-methylsulfonamide **92** (**Scheme 1.38**) was irradiated and the saccharin derivative **93** was formed in excellent yield. The mechanism is thought to involve an intermediate *N*-iodo species that on photolysis undergoes successive 1,5-hydrogen transfers and subsequent trapping with iodine to give a triiodomethyl group. Cyclisation of this intermediate occurred, upon exposure to water, to give the saccharin derivative **93**.

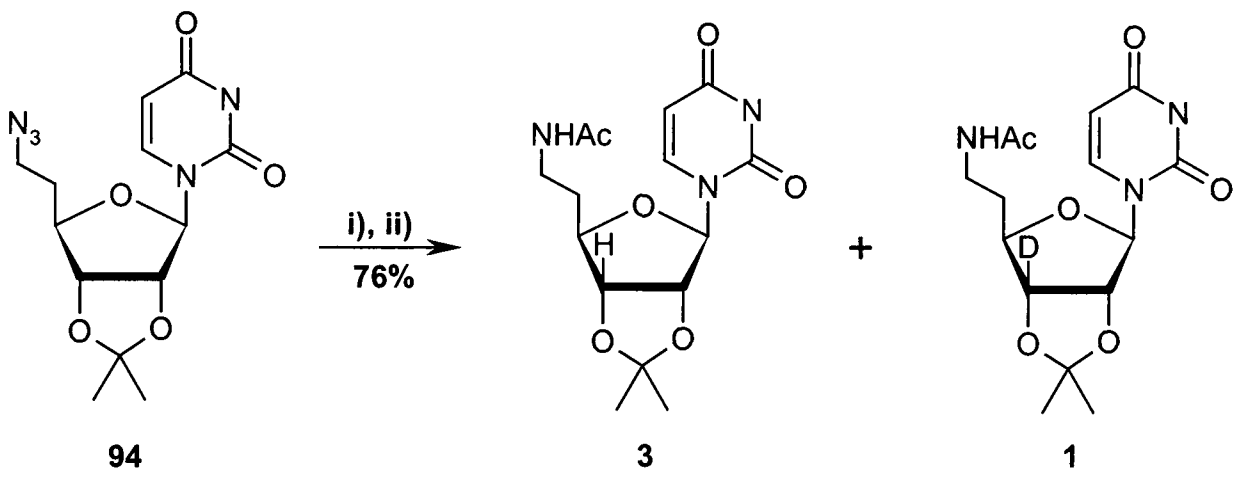


92 **93** **99%**

Scheme 1.38 *Reagents and conditions*: DIB, I_2, DCE, $h\nu$, Δ

1.2.5.3 *Azides*

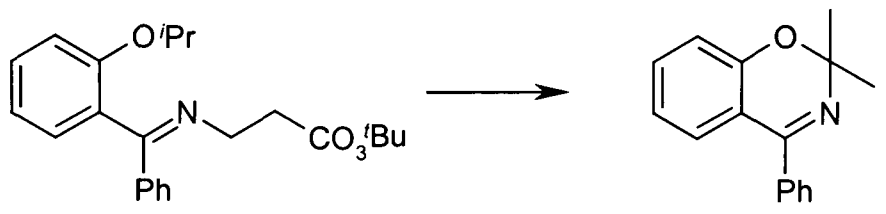
Kim's[112] recent work on tri-*n*-butylstannyl substituted aminyl radicals generated from azides has shown that these radicals are more nucleophilic than ordinary aminyl radicals and that they can participate in hydrogen abstraction processes. A recent extension of this chemistry by Robins and co-workers[113] involved the regioselective hydrogen abstraction by a tri-*n*-butylstannyl substituted aminyl radical. Thus, treatment of azide **94** with tri-*n*-butyltin deuteride and AIBN gave ~25% deuterium incorporation, after cleavage of the Sn–N bond with acetic anhydride. An analogous reaction with an alkoxyl radical precursor led to ~80% deuterium incorporation.



Scheme 1.39 *Reagents and conditions*: i) Bu_3SnD, AIBN, PhH, Δ; ii) Ac_2O, DMAP

1.2.5.4 *Iminyl radicals*

McNab and co-workers[33] employed iminyl radicals generated by flash vacuum pyrolysis (FVP) or thermally in solution to effect hydrogen atom transfer processes. When imine **95** (**Scheme 1.40**) was heated in bromobenzene at 156°C an iminyl radical was generated, which underwent 1,6-hydrogen transfer and subsequent cyclisation and oxidation to give the bicyclic product **96** in 40% yield.



95 **96**
40%

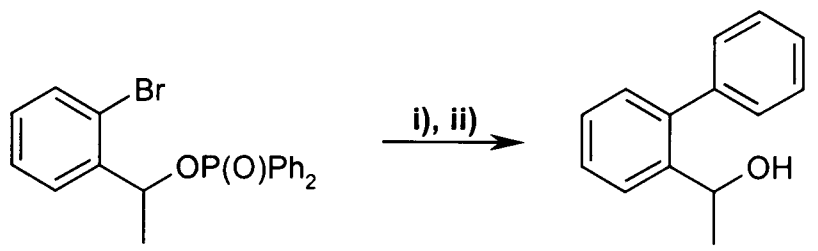
Scheme 1.40 *Reagents and conditions*: PhBr, 156°C

1.2.6 Group Transfer

1.2.6.1 *1,n-Aryl transfers*

Although hydrogen transfers are by far the most common processes, 1,n-transfers of other functional groups have also been observed and, within these, the transfer of a phenyl group predominates; examples of 1,2-, 1,4-, 1,5- and 1,6- transfer are known. The mechanism is thought to proceed by *ipso*-substitution onto the phenyl group with subsequent fragmentation to give the 'translocated' radical. Examples include transfer from carbon to carbon,[114-119] phosphorus to carbon,[120,121] silicon to carbon,[122,123] tin to carbon[124] and sulfur to carbon.[125]

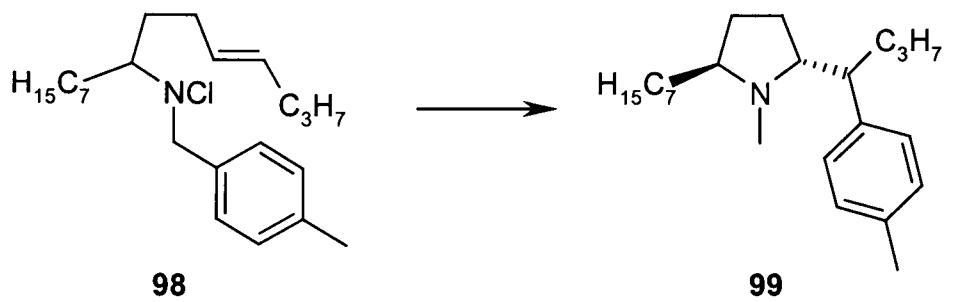
Clive *et al.*[120,121] reported a 1,5-aryl transfer from phosphorus to carbon in their syntheses of biaryls (**Scheme 1.41**). The reaction proceeds *via ipso*-attack of the initially formed aryl radical on one of the phenyl rings attached to phosphorus. Fragmentation of the resulting radical leads to a phosphinate radical, which is quenched by triphenyltin hydride. Subsequent hydrolysis gave biphenyl **97** in 64% yield.



97
64%

Scheme 1.41 *Reagents and conditions*: i) Ph_3SnH, AIBN, xylene, Δ; ii) K_2CO_3, MeOH

Tokuda and co-workers[118] found that treatment of the *N*-chloroamine **98** (**Scheme 1.42**) with tri-*n*-butyltin hydride and AIBN afforded the pyrrolidine **99** *via* 1,4-aryl group transfer.



98 **99**
62%

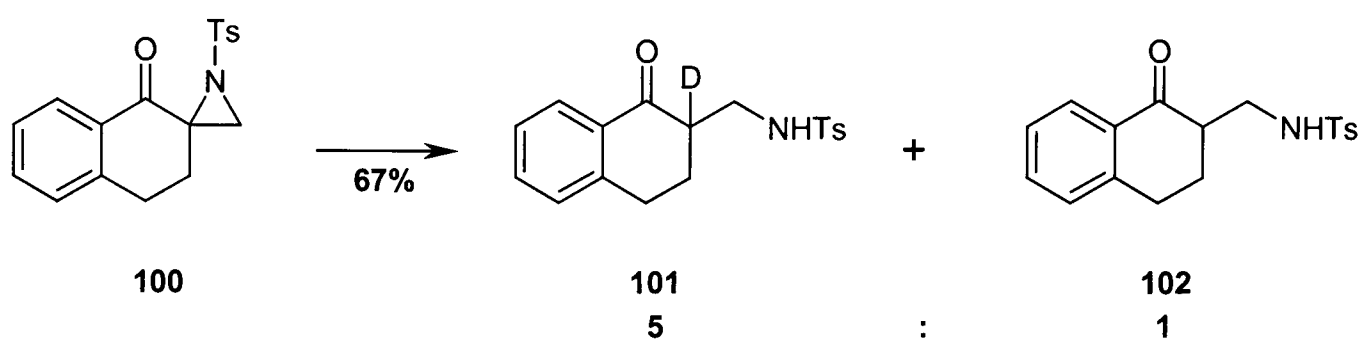
Scheme 1.42 *Reagents and conditions*: Bu_3SnH, AIBN, PhMe, Δ

1.2.6.2 *Other group transfers*

Although aryl transfer is the most common kind of group transfer, it is possible to transfer other functional groups. Transfers of acyloxy,[126] stannyl,[100,127-131] nitrile,[132,133] germanyl[134] and silyl[129] groups are also known.

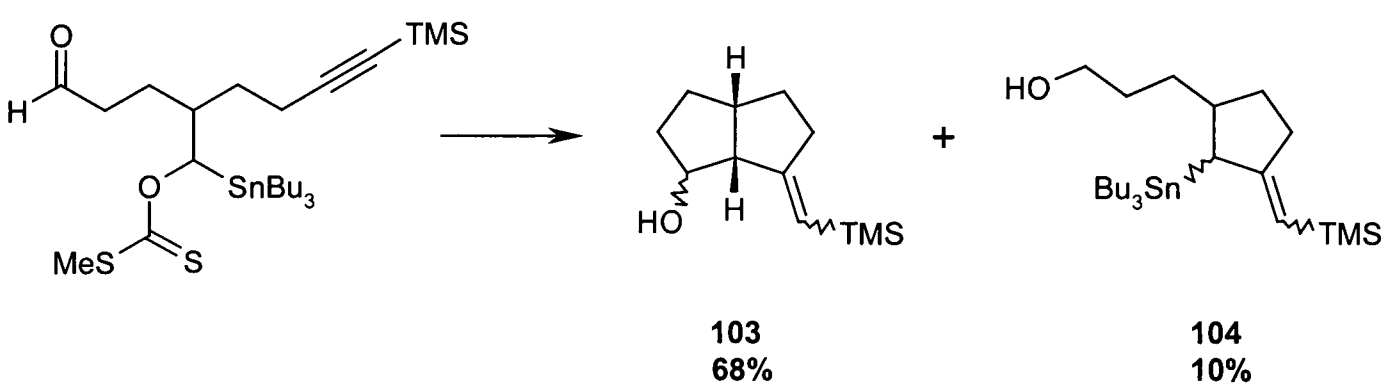
Tri-*n*-butylstannyl group transfer from carbon to oxygen has been investigated by Kim *et al.*[100,129] A recent extension of this chemistry involved the 1,5-transfer of a tri-*n*-butylstannyl group from oxygen to nitrogen (**Scheme 1.43**).[131] When keto-aziridine **100** was treated with tri-*n*-butyltin

deuteride and AIBN, ring opening of the aziridine occurred after addition of the stannyl radical to the carbonyl group. The nitrogen-centred radical then abstracted the tri-*n*-butylstannyl group from oxygen to give, after hydrolysis, deuterated product **101**. The undeuterated product **102** was thought to arise from direct reduction of the aminyl radical after fragmentation and subsequent hydrolysis and proton exchange.



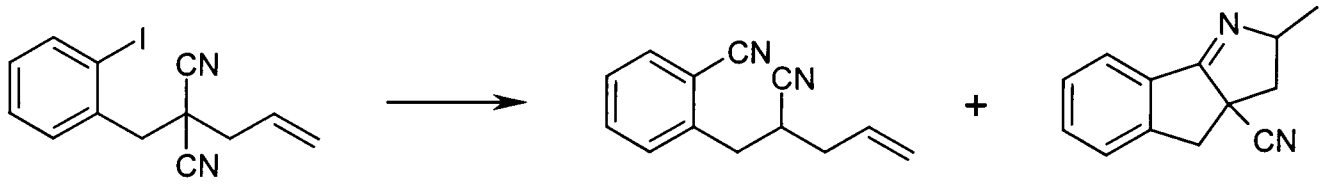
Scheme 1.43 *Reagents and conditions*: Bu_3SnD, AIBN, PhH, Δ

Tsai and co-workers[130] observed an unusual 1,3-stannyl shift from carbon to oxygen in their investigations into cyclisations of α-stannyl radicals onto formyl groups (**Scheme 1.44**). After the initial cyclisation of α-stannyl radical onto the formyl group the tri-*n*-butylstannyl group undergoes a 1,3-shift to oxygen. Subsequent cyclisation of the resulting carbon-centred radical onto the triple bond gave the bicyclic alcohol **103** as a mixture of four diastereomers in 68% combined yield. Competing cyclisation of the α-stannyl radical onto the triple bond led to monocyclic alcohol **104**.



Scheme 1.44 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ, 4 h

Bowman *et al.*[133] reported a recent example of nitrile group transfer in their studies towards the synthesis of bicyclic nitrogen heterocycles. The aryl radical generated from iodide **105** (**Scheme 1.45**) underwent cyclisation onto the cyano group and subsequent *β*-fragmentation to give the 1,4-nitrile group transfer product **106**. The rate of *β*-scission of the iminyl radical was faster than 5-*exo-trig* cyclisation onto the terminal double bond and thus no tricyclic product **107** was observed.



105 **106** **70%** **107** **0%**

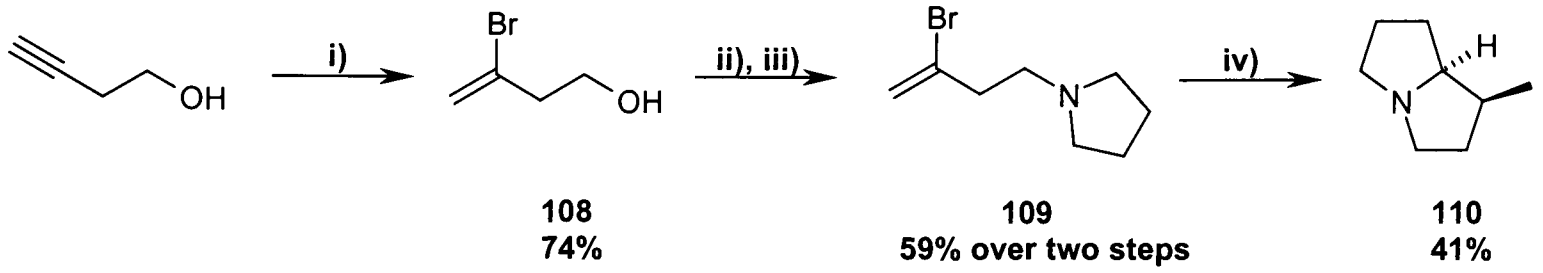
Scheme 1.45 *Reagents and conditions*: Bu_3SnH, AMBN, cyclohexane, Δ, 9 h

1.3 Proposed work

Previous work within the group had focused on the use of radical translocation chemistry to prepare pyrrolizidine ring systems.[38,135,136] Pyrrolizidine alkaloids occur in a wide variety of plants and have a core structure consisting of two fused five membered rings with a nitrogen atom at the bridgehead. The related indolizidines consist of one five and one six membered ring fused together with nitrogen at the bridgehead.

Heliotridane **110** was synthesised in the group by the method outlined in **Scheme 1.46**. Thus, 3-butyn-1-ol was treated with hydrogen bromide in the presence of tetraethylammonium bromide to give the alcohol **108** in reasonable yield. Tosylation and reaction with pyrrolidine gave

the radical precursor **109** in good yield. Treatment with tri-*n*-butyltin hydride and AIBN gave heliotridane **110** as a 13:1 mixture with its epimer pseudoheliotridane.



108
74%

109
59% over two steps

110
41%

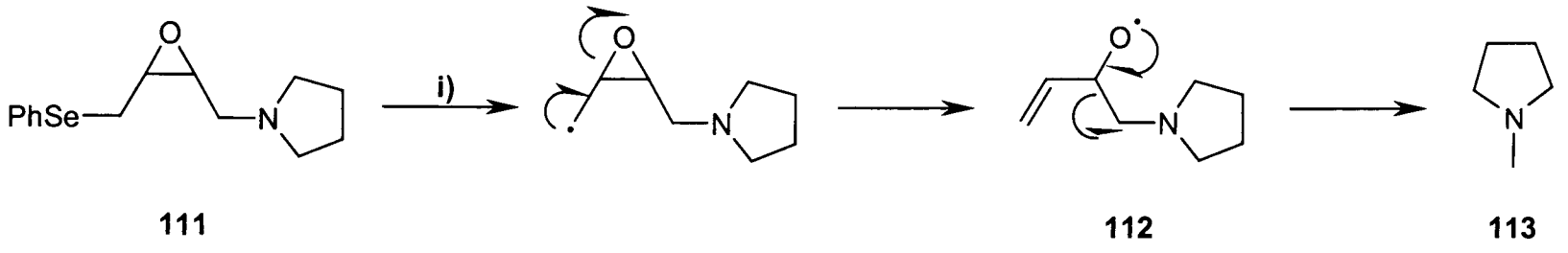
Scheme 1.46 *Reagents and conditions*: i) HBr (g), Et_4NBr, DCM, 38°C, 4h; ii) Ts_2O, Pyr, DCM, 0°C → RT; iii) pyrrolidine, Δ; iv) Bu_3SnH, AIBN, PhH, Δ

Unfortunately, when this radical translocation methodology was applied to other nitrogen heterocycles, for example, pyrrolidinones and oxazolidines, little or no evidence of 1,5-translocation and cyclisation was observed; the vinyl radical was found to be too unreactive. When attempts were made to incorporate extra functionality into the pyrrolizidine systems problems arose and oxygenation of the final methylene radical was not possible.

Alkoxyl radicals were then investigated to effect the translocation (*cf.* **Section 1.2.4**). The increased reactivity of alkoxyl radicals means that they are much more likely to undergo 1,5-hydrogen atom abstraction as opposed to reduction. Furthermore, using this approach extra oxygen functionality could be incorporated into the side-chain and there would be the potential for enantiospecific routes to pyrrolizidines.

In a preliminary experiment precursor **111** (**Scheme 1.47**) was treated with tri-*n*-butyltin hydride and AIBN but it was found that *β*-scission of the alkoxyl radical **112** occurred preferentially to lead to *N*-methylpyrrolidine **113**; no translocation and cyclisation product was observed. It was thought

that the β-scission pathway may be favoured due to favourable polarity and developing π-overlap in the transition state and stabilisation from nitrogen of the resulting *N*-methyl radical.



111 **112** **113**

Scheme 1.47 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

The immediate aim of this project was to prepare a series of alkoxyl radical precursors in order to investigate the factors that contributed to the undesired fragmentation pathway. The intention was to apply the alkoxyl radical translocation methodology to other nitrogen-containing heterocycles and use this approach in the synthesis of a range of functionalised alkaloidal ring systems.

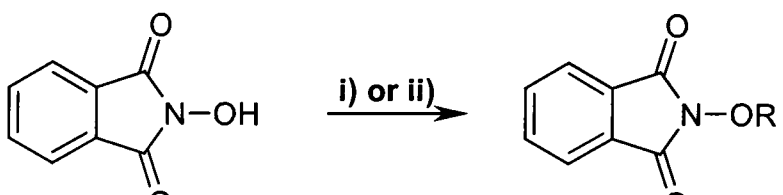
RESULTS AND DISCUSSION

2. RESULTS AND DISCUSSION

2.1 Alkoxyl Radical Precursors

2.1.1 Preliminary Studies

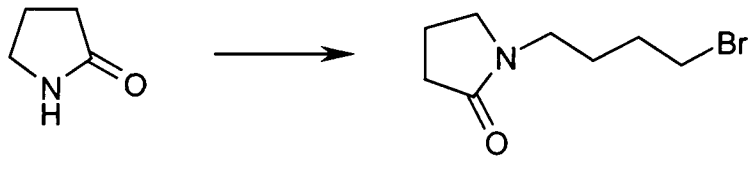
A suitable alkoxyl radical precursor was required that would generate the necessary alkoxyl radical using relatively mild conditions. Following work published by Kim *et al.*[92] *N*-alkoxyphthalimides were chosen as the precursors as they are reasonably stable yet the relatively weak N–O bond (≈ 160 kJ mol^{-1}) can be cleaved readily under mild initiating conditions, for example, tri-*n*-butyltin hydride and AIBN. Alkoxyphthalimides are readily accessible from alcohols and alkyl halides *via* nucleophilic displacement chemistry or Mitsunobu[137] conditions (**Scheme 2.1**).



Scheme 2.1 *Reagents and conditions*: i) RX, NaH, DMF, RT; ii) ROH, PPh_3, DEAD, THF, RT

2.1.1.1 *Preparation of radical precursor* **115**

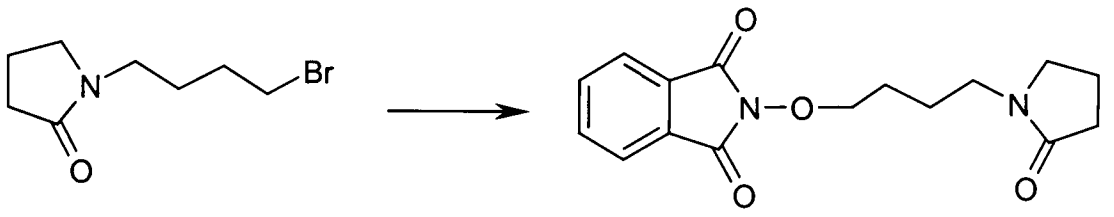
To investigate whether hydrogen abstraction α-to the lactam nitrogen was possible, precursor **115** was prepared. Treatment of 2-pyrrolidinone with 1,4-dibromobutane under phase transfer conditions gave the bromide **114** (**Scheme 2.2**).



114
53%

Scheme 2.2 *Reagents and conditions*: $Br(CH_2)_4Br$, TBAB, KOH, THF, RT, 18 h

Nucleophilic displacement of bromide from **114** by the sodium salt of *N*-hydroxyphthalimide gave the radical precursor **106** in moderate yield (**Scheme 2.3**).

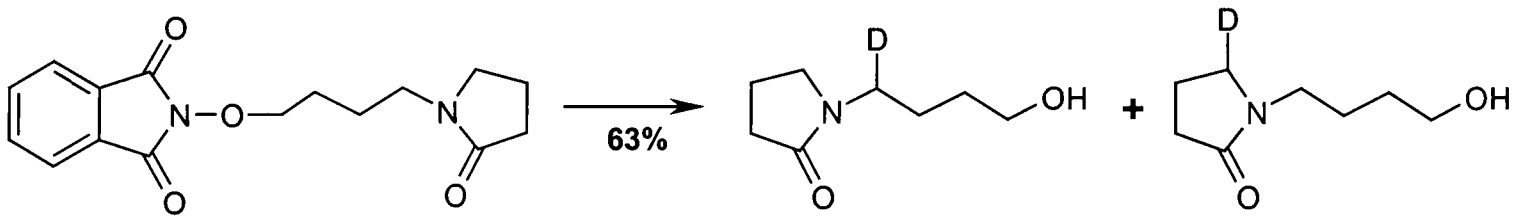


114 **115** **58%**

Scheme 2.3 *Reagents and conditions*: *N*-hydroxyphthalimide, NaH, DMF, 60°C, 16 h

2.1.1.2 *Radical reaction of precursor* **115**

Treatment of precursor **115** with tri-*n*-butyltin deuteride and AIBN in degassed benzene gave the expected 1,5-hydrogen transfer product **116** but unexpectedly the 1,7-hydrogen transfer product **117** was also obtained in approximately equal proportion (as determined by ^{1}H NMR analysis) (**Scheme 2.4**).

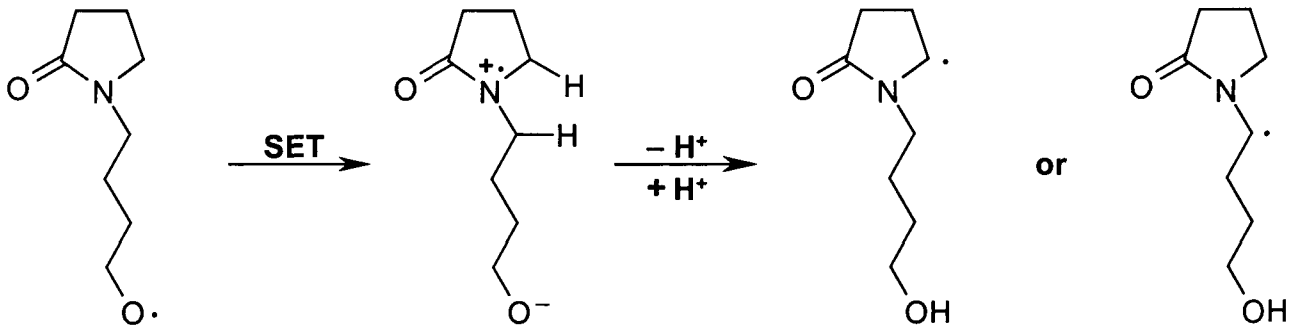


115 **116** **117**
1 **1**

Scheme 2.4 *Reagents and conditions*: Bu_3SnD, AIBN, PhH, Δ, 3 h

Although 1,7-hydrogen translocations are rare,[23-26,35-37] De Mesmaeker and co-workers[24] have investigated hydrogen transfer processes in conformationally restricted amides and found that 1,7-hydrogen abstraction can compete efficiently with 1,5-transfer (ratio of 82:18) (**Scheme 1.23**).

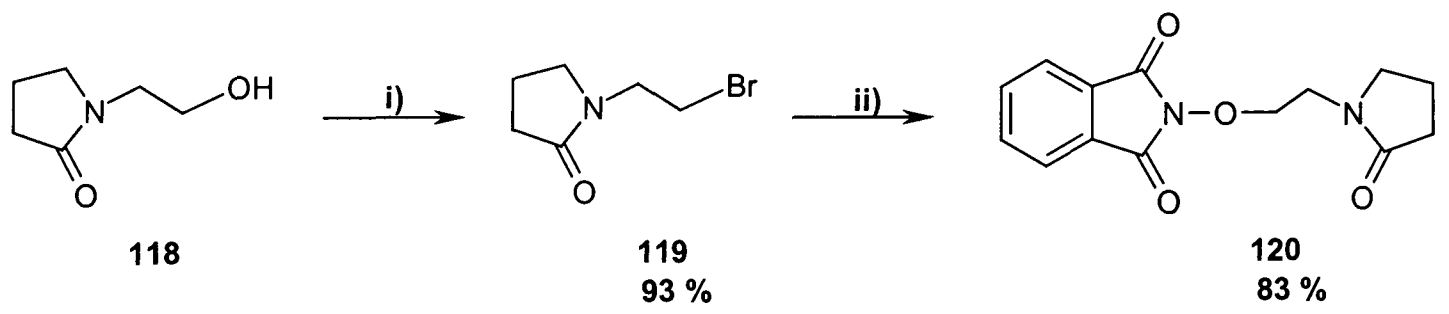
An alternative explanation for the efficiency of the 1,7- hydrogen transfer is the possibility that the reaction could proceed through a single electron transfer (SET) process from nitrogen to oxygen. Proton loss can then occur at either position α- to the nitrogen leading to the observed ~1:1 product ratio (**Scheme 2.5**).



Scheme 2.5

2.1.1.3 *Preparation of radical precursor* **120**

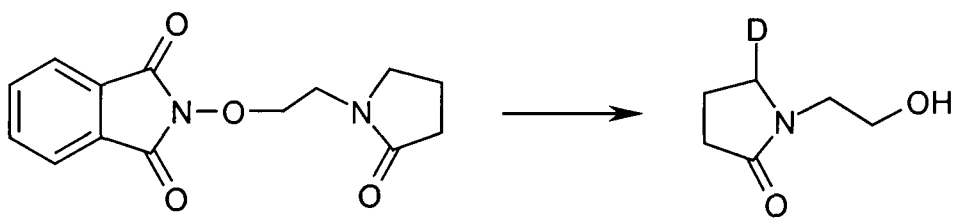
Precursor **120** was prepared in order to determine whether selective 1,5-hydrogen transfer α- to the lactam ring nitrogen was possible. Thus, commercially available alcohol **118** was converted into the bromide **119** with phosphorus tribromide.[138] Treatment of **119** with the sodium salt of *N*-hydroxyphthalimide then gave the radical precursor **120** in excellent overall yield (**Scheme 2.6**).



Scheme 2.6 *Reagents and conditions*: i) PBr_3, PhMe, 60°C, 16 h; ii) *N*-hydroxyphthalimide, NaH, DMF, 60°C, 16 h

2.1.1.4 *Radical reaction of precursor* **120**

Treatment of a 50 mM solution of precursor **120** in degassed benzene with tri-*n*-butyltin deuteride and AIBN afforded the 1,5-transfer product **121** in good yield (**Scheme 2.7**). No evidence of *β*-scission of the alkoxyl radical was observed in the crude ^{1}H NMR spectrum and the translocation product was the only compound isolated from the reaction mixture. ^{2}H NMR spectroscopy showed that the *α*-position was the only site of deuterium incorporation and it was concluded that the 1,5-hydrogen transfer from carbon to oxygen was an efficient process.



120 **121**
74%

Scheme 2.7 *Reagents and conditions*: Bu_3SnD, AIBN, PhH, Δ, 18 h

2.1.2 Intermolecular Trapping of the Translocated Radical

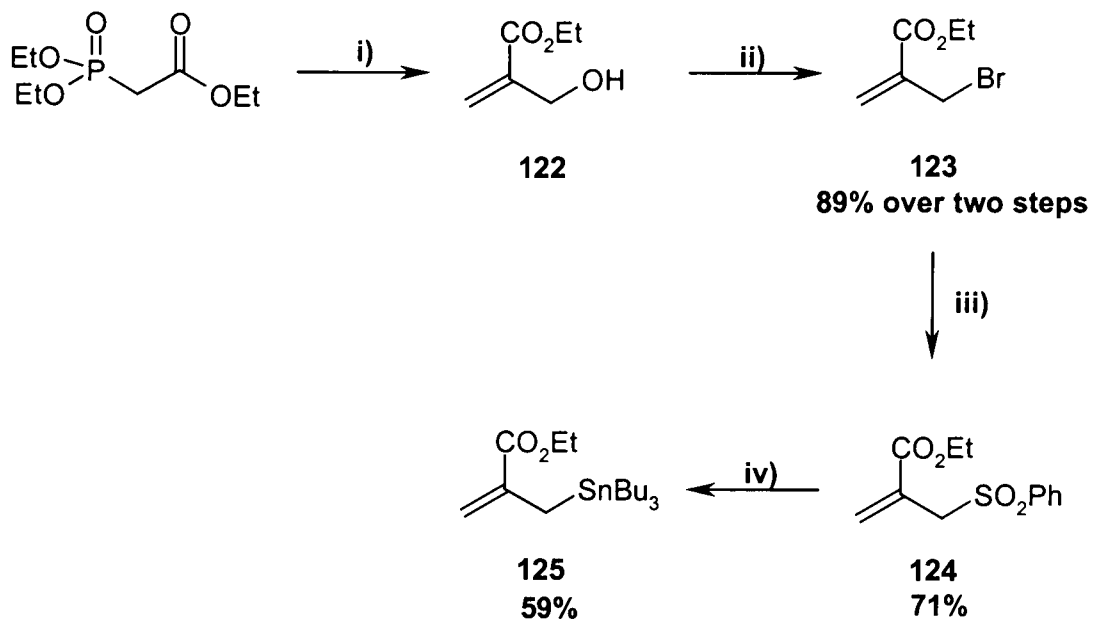
2.1.2.1 *Trapping with methyl acrylate*

Since it had been shown that 1,5-hydrogen transfer *α*- to a lactam ring nitrogen was a viable process, attempts were made to trap the translocated radical intermolecularly. Thus, treatment of a 50 mM solution of precursor **111** and 10 equivalents of methyl acrylate in benzene with a solution of tri-*n*-butyltin hydride and AIBN in benzene added *via* syringe pump over 6 h to reduce the

concentration of tin hydride present did not result in intermolecular trapping. Starting material was recovered, along with uncharacterisable tin-containing polymeric material. Since propagation of the radical chain seemed to have been hampered, the reaction was repeated with a reduced tin hydride addition time (syringe pump over 2 h). No starting material was isolated from this experiment; therefore propagation seemed to be efficient. Mass spectrometric analysis (CI^+) of the crude reaction mixture showed peaks at *m/z* 186 (67%), 272 (13), 358 (12), and 444 (5) suggesting *β*-fragmentation of the alkoxyl radical and successive trapping of the *N*-methyl radical with methyl acrylate. A small signal consistent with the translocated and trapped product appeared at *m/z* 216 (10%). A major signal was obseved at *m/z* 130 (100%) corresponding to the product of direct reduction of the alkoxyl radical. However, after column chromatography no products could be isolated and, again, contamination with tin was a problem. In the ^1H NMR spectrum, apart from the peaks corresponding to the tri-*n*-butyl peaks and the phthalimide unit, only two other significant peaks appeared at δ_H 2.20–2.50 (m), and 3.70 (bs) suggesting oligomerisation of the acrylate was a problem.

2.1.2.2 *Trapping with stannyl methacrylate* **125**

An attempt was also made to trap the translocated radical with the stannyl acrylate **125**, prepared in four steps from triethyl phosphonoacetate (**Scheme 2.8**).[38] With this trapping agent, catalytic conditions could be employed.



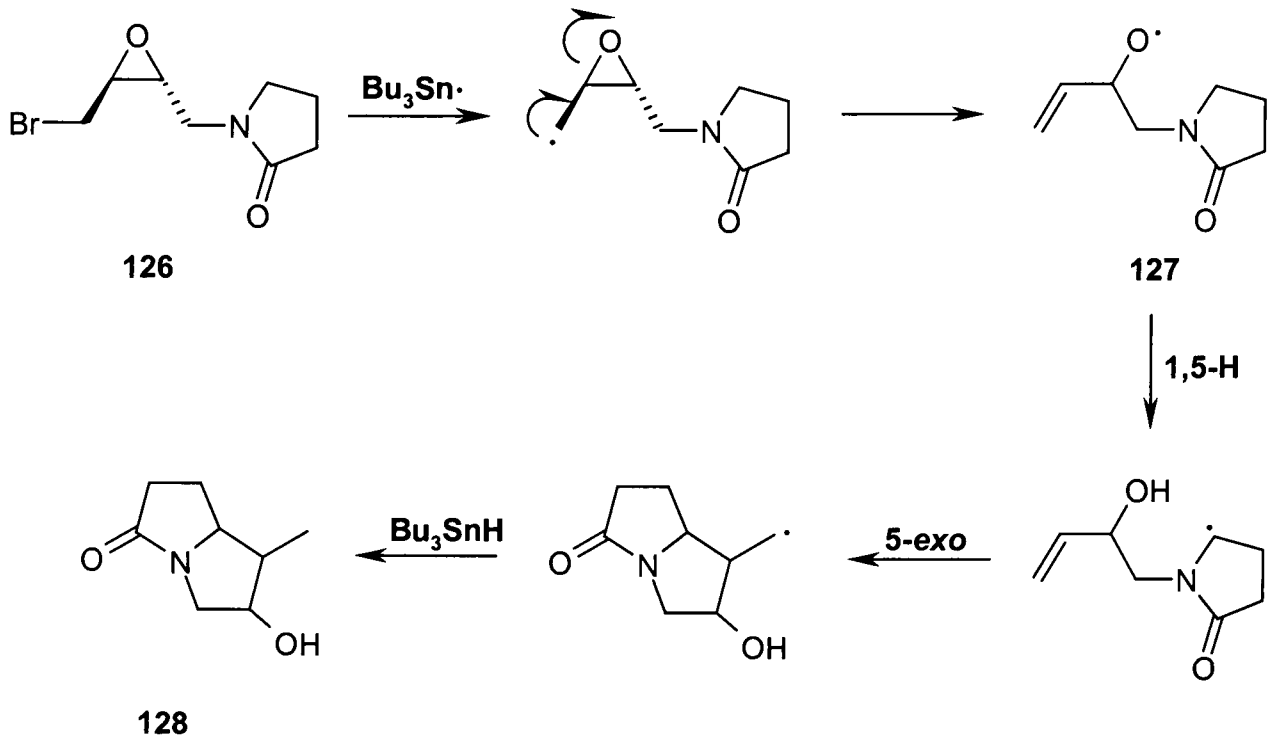
Scheme 2.8 *Reagents and conditions*: i) aq. formaldehyde, K_2CO_3, 1 h; ii) PBr_3, ether, −10°C→RT, 3 h; iii) $PhSO_2Na$, MeOH, Δ, 15 h; iv) Bu_3SnH, AIBN, PhH, Δ, 0.75 h

Treatment of precursor **120** with the acrylate **125** and AIBN in benzene led to a complex mixture of products. T.l.c. analysis of the crude mixture indicated a number of products from the reaction; column chromatography on silica proved difficult and no identifiable products could be isolated from the complex mixture. No conclusive results could be obtained from this reaction.

2.1.3 Intramolecular Trapping of the Translocated Radical

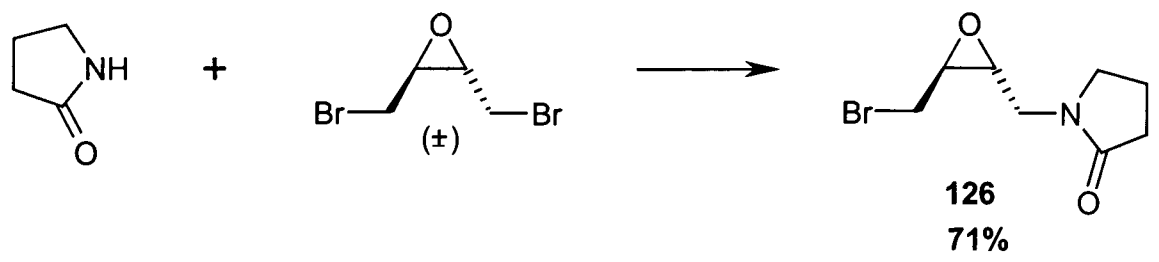
2.1.3.1 *Preparation and radical reaction of precursor* **126**

Since attempts to trap the translocated radical intermolecularly had failed it was decided to attempt intramolecular trapping and thus, radical precursor **126** was chosen as the next target. Fragmentation of the epoxide would result in the allylic alkoxyl radical **127**, which was expected to undergo 1,5-hydrogen transfer and cyclisation onto the double bond that resulted from the fragmentation process, to give pyrrolizidinone **128** (**Scheme 2.9**)



Scheme 2.9

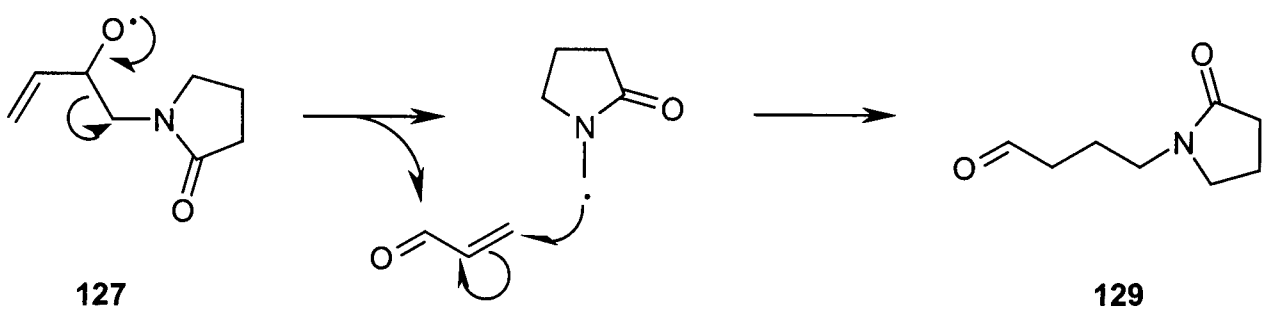
Precursor **126** was prepared in good yield by treatment of 2-pyrrolidinone with sodium hydride and (*E*)-2,3-*bis*(bromomethyl)oxirane[38] (**Scheme 2.10**).



Scheme 2.10 *Reagents and conditions*: NaH, DMF, 0°C→RT, 16 h

Under the usual initiating conditions, precursor **126** gave a number of products in the reaction, which could not be isolated free of tin residues. The difficulty of removal of tin from reaction mixtures is well documented,[139-141] the tin species present are unstable to silica, tending to hydrolyse slowly on the column leading to contamination of all fractions. Synthetic methods for tin removal are discussed in depth in **Section 2.2**.

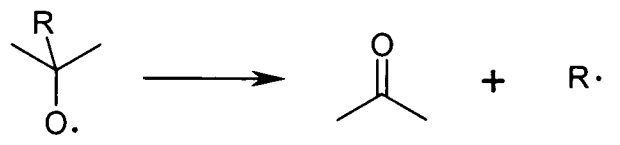
From the crude 1H NMR spectrum, the major component of the mixture was assigned as aldehyde **129** (**Scheme 2.11**) δ_H 9.76 (s) and the hydrate of **129** δ_H 5.47 (t, *J* 6.4). A plausible explanation for the formation of **129** involves β-scission of the alkoxyl radical **127** to give acrolein and *N*-methyl-2-oxopyrrolidinyl radical, which could recombine to give the aldehyde **129**. Peaks corresponding to an *N*-methyl group were also observed in the ^{1}H NMR spectrum δ_H 2.85 (s); no evidence of translocation or cyclisation was seen. This outcome of the reaction was consistent with that observed previously with the pyrrolidine alkoxyl radical precursor **111** (**Scheme 1.47**)[38]



127 **129**

Scheme 2.11

In our system fragmentation of the alkoxyl radical may predominate because of the increased α- stabilisation by nitrogen of the resulting radical. Nakamura *et al.*[142] estimated that the rate constants (at 25°C) for β-fragmentation of *tert*-alkoxyl radicals **130a–c** (**Scheme 2.12**) were in the order **130a** (8.9×10^6 s^{-1}) < **130b** (1.2×10^8 s^{-1}) < **130c** (3.1×10^9 s^{-1}). These estimates were in good agreement with the proposal of Kochi[143] that rates of β-scission are influenced by the stability of the leaving alkyl radical. In radical **130a** 1,5-hydrogen transfer competed with β-scission; the ratio of $k_{1,5\text{-H}}/k_\beta$ (in cumene at 60°C) was estimated to be 1.3, indicating that β-scission of alkoxyl radicals can compete with 1,5-hydrogen abstraction in certain systems.

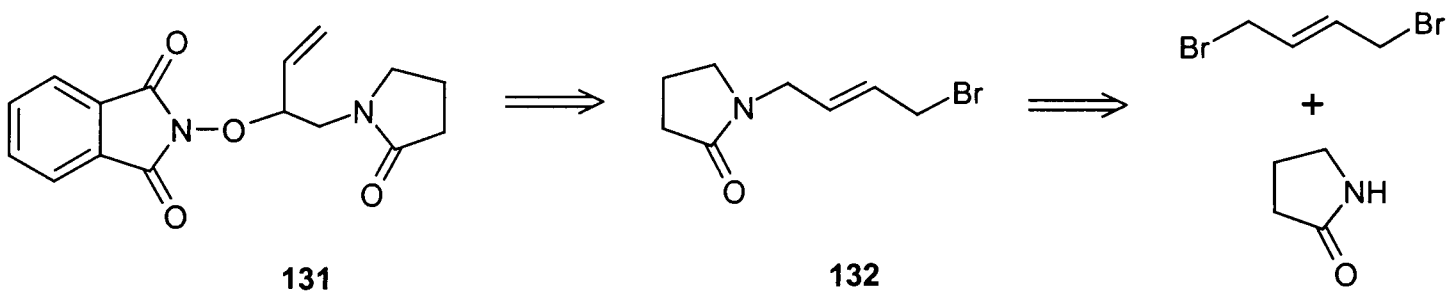


130a R = Pr
130b R = ^{i}Pr
130c R = ^{t}Bu

Scheme 2.12

2.1.3.2 *Preparation and radical reaction of precursor* **131**

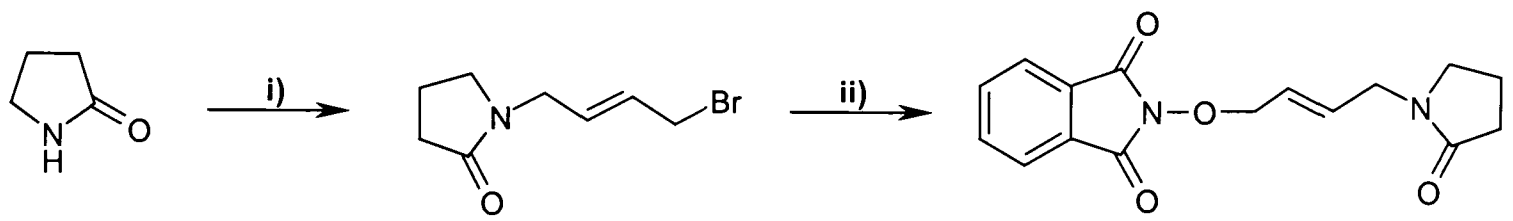
Since tri-*n*-butyltin bromide is an excellent electrophile/Lewis acid it might potentially influence the outcome of the reaction by promoting the *β*-scission pathway. To remove this possibility, precursor **131** was prepared; the alkoxyl radical would be generated from the alkoxyphthalimide and thus, no tri-*n*-butyltin bromide would be present in the reaction mixture (**Figure 2.1**). Initially, retrosynthetic analysis led back to allylic bromide **132**, which could be prepared from 1,4-dibromo-2-butene and 2-pyrrolidinone.



131 **132**

Figure 2.1

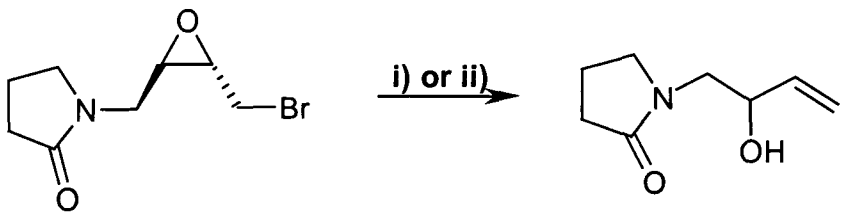
Allylic bromide **132** was prepared in moderate yield from 2-pyrrolidinone and 1,4-dibromo-2-butene, but treatment of the bromide **132** with *N*-hydroxyphthalimide and silver(I) acetate led not to allylic (S_N2') displacement of the bromide but attack at the primary position to give alkoxyphthalimide **133** in 88% yield (**Scheme 2.13**). The same result was obtained in the absence of silver(I) acetate.



132 **133**
64% **88%**

Scheme 2.13 *Reagents and conditions*: i) 1,4-dibromo-2-butene, NaH, DMF, 0°C→RT, 16 h; ii) *N*-hydroxyphthalimide, NaH, DMF, 60°C, 16 h

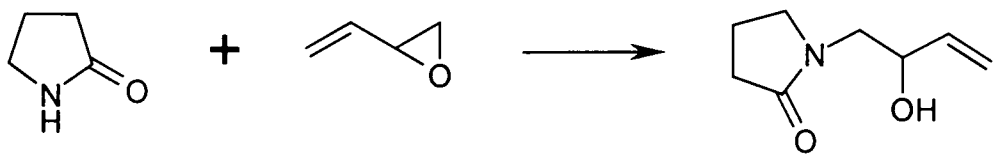
The next strategy required the preparation of alcohol **134** with the intention of subjecting the alcohol **134** to Mitsunobu conditions. Treatment of epoxide **126** with zinc dust and sodium iodide led to fragmentation of the epoxide but, after aqueous work-up and chromatography, only a 5% yield of the alcohol was obtained. The use of lithium iodide to promote fragmentation led to a slight increase in the yield of **134** (25%), but this was considered insufficient for pursuing the projected chemistry (**Scheme 2.14**). It was thought that the high polarity of allylic alcohol **134** resulted in loss of material during aqueous work-up.



126 **134**
i) **5%**
ii) **25%**

Scheme 2.14 *Reagents and conditions*: i) NaI, Zn dust, MeOH, Δ, 18 h; ii) LiI, THF, Δ, 3.5 h

Success was eventually achieved by regioselective ring opening of butadiene monoxide with 2-pyrrolidinone, to give the alcohol **134** in a more workable yield (**Scheme 2.15**).[144]

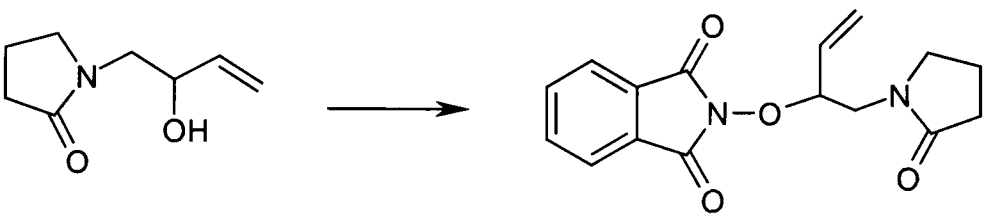


134
66%

Scheme 2.15 *Reagents and conditions*: 30% aq. KOH, sealed tube, 150°C, 20 h.

The Mitsunobu preparation of the alkoxyphthalimide precursor **131** was then attempted using the Volante modification;[145] *i.e.*, with DIAD instead of DEAD and pre-forming the DIAD–triphenylphosphine complex prior to addition of the alcohol.

In practice, separation of the product **131** from the triphenylphosphine oxide produced in the reaction proved difficult. Substituting tributylphosphine for triphenylphosphine allowed the alkoxyphthalimide precursor **131** to be isolated in moderate yield, although material was still being lost by contamination with phosphine oxide (**Scheme 2.16**).

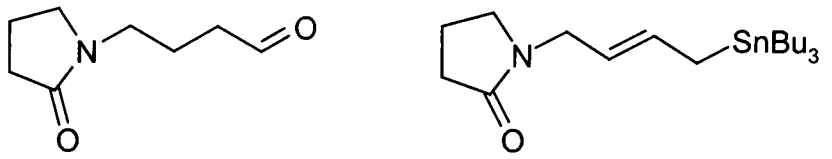


134 **131**
52%

Scheme 2.16 *Reagents and conditions*: *N*-hydroxyphthalimide, PBu_3, DIAD, THF, 0°C→RT, 4 h

Treatment of precursor **131** with tri-*n*-butyltin deuteride under the usual conditions gave a mixture of products, within which it could be seen (^{1}H NMR) that the product of *β*-scission and the aldehyde **129** had formed (ratio ~ 1:1, 40%). Chromatographic separation of the product mixture again proved difficult due to presence of the tin species. ^{1}H NMR analysis of some of the fractions

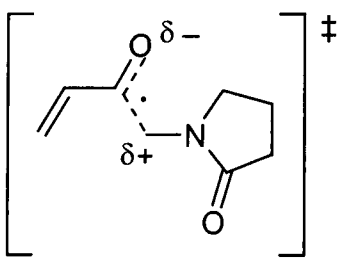
indicated the presence of the allyl stannane **135** (**Figure 2.2**) [δ_H 3.80 (d), 5.00–5.02 (m) and 5.70–5.85 (m)] (from integration ~ 12% yield) and mass spectrometry (CI^+) showed peaks at *m/z* 429 (10%), 427 (8), 425 (4) for the molecular ion. The formation of **135** presumably involves direct addition of the stannyl radical to the terminal double bond and subsequent elimination of the alkoxyphthalimide moiety. Repeating the reaction with slow addition of tri-*n*-butyltin hydride and AIBN *via* syringe pump gave the same result, as determined by ^1H NMR analysis of the crude mixture.



129 **135**

Figure 2.2

The β-scission pathway is probably favoured for this substrate by a combination of favourable polarity and developing π-overlap in the transition state (**Figure 2.3**). Furthermore, the nitrogen lone pair stabilises the resulting *N*-methyl radical, which may contribute to the rapid fragmentation of the alkoxyl radical.

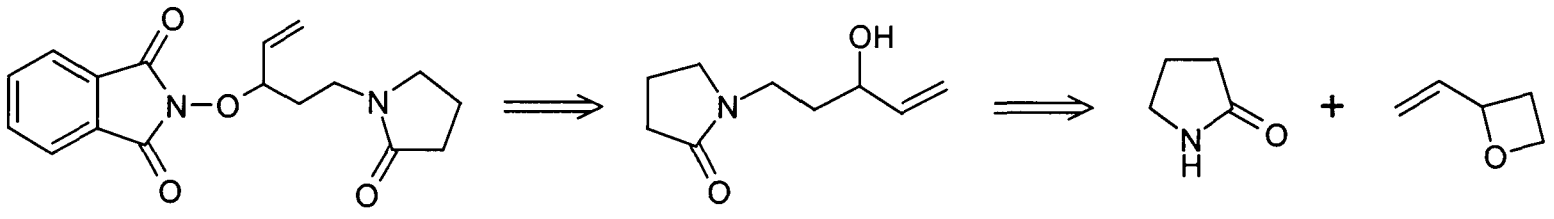


127

Figure 2.3

2.1.3.3 *Attempted preparation of radical precursor* **136**

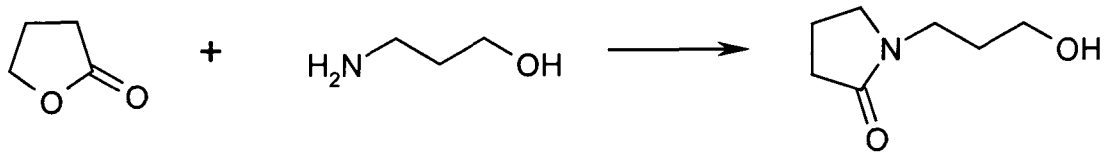
The synthesis of precursor **136** was briefly explored in order to determine whether β-scission occurred more readily as a consequence of stabilisation from nitrogen or from the developing overlap (or both). In this homologous precursor the alkoxyl radical is situated one position further from the pyrrolidinone nitrogen, although remaining allylic to the double bond. A route directly analogous to that used for **131** was not pursued because the vinyl oxetane proved difficult to prepare and, in any case, was less likely to react in the desired sense (**Figure 2.4**).



136

Figure 2.4

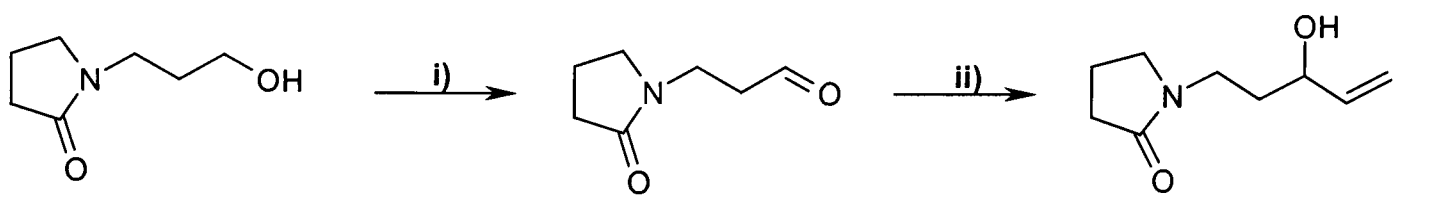
A partially successful strategy proceeded *via* oxidation of alcohol **137** and treatment of the resulting aldehyde with vinyl magnesium bromide. Alcohol **137** was prepared in excellent yield by condensation of γ-butyrolactone with 3-amino-1-propanol at 210°C (**Scheme 2.17**).



137
93%

Scheme 2.17 *Reagents and conditions*: $-H_2O$, 210°C, 26 h.

Oxidation of alcohol **137** proved problematic; many conditions were attempted (*e.g.* PDC, PCC, Swern, IBX) but all resulted in mostly recovered starting material with only small amounts of aldehyde **138** being isolated (**Scheme 2.18**). Finally TPAP oxidation gave the aldehyde as an inseparable mixture with NMO, which was used without purification in the next step. Treatment of crude **138** with vinyl magnesium bromide gave the alcohol **139** in poor yield. Alcohol **139** is very polar [R_f 0.09 (3:97 MeOH:DCM)] and presumably material was lost during the aqueous work-up; consequently the route was abandoned.

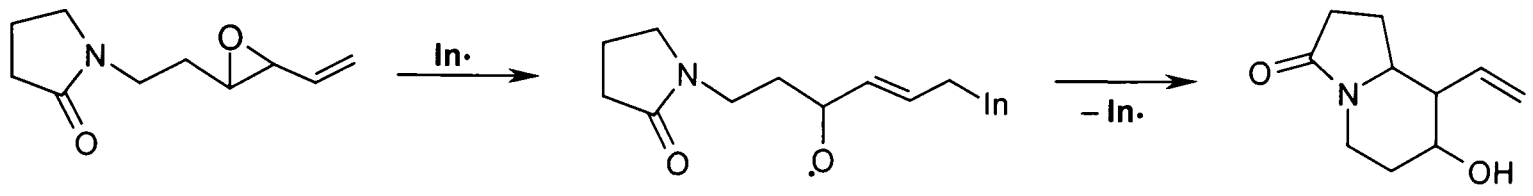


137 **138** **139**
3% over two steps

Scheme 2.18 *Reagents and conditions*: i) TPAP, NMO, 4Å molecular sieves, DCM, RT, 3 h; ii) vinyl magnesium bromide, THF, 0°C→RT, 1.5 h

2.1.3.4 *Preparation and radical reaction of precursor* **140**

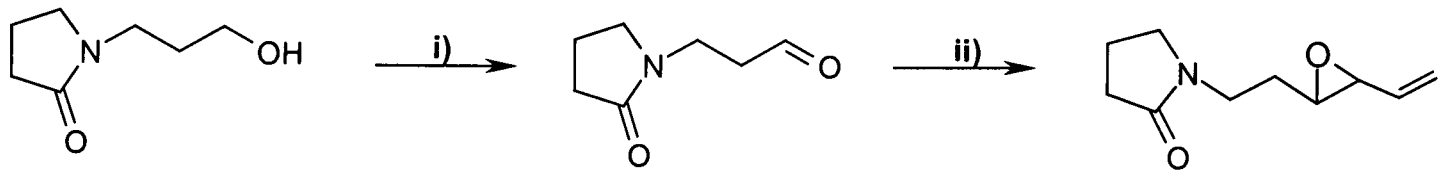
Since attempts to prepare the allylic alcohol required for the Mitsunobu reaction had proved unsuccessful an alternative alkoxyl radical precursor was considered. Epoxide **140**, when treated with a catalytic amount of tri-*n*-butyltin hydride or thiophenol, was expected to undergo fragmentation to give alkoxyl radical **141** (**Scheme 2.19**). This alkoxyl radical would resemble that produced from the fragmentation of precursor **136**. 1,6-Hydrogen transfer and 6-*exo-trig* cyclisation would then lead to indolizidinone **142**.



140 141 142

Scheme 2.19

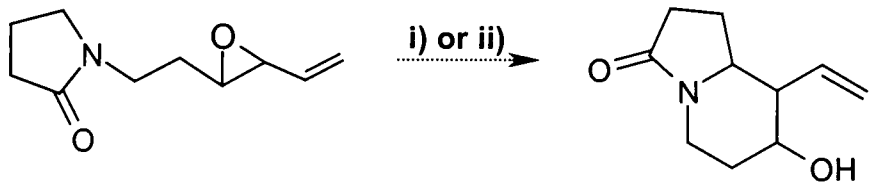
Epoxide **140** was prepared in excellent yield by treatment of the crude aldehyde mixture (~ 45% aldehyde) with allyldiphenylsulfonium tetrafluoroborate[146] and *tert*-butyllithium (**Scheme 2.20**).



137 138 140
57% over two steps

Scheme 2.20 *Reagents and conditions*: i) TPAP, NMO, 4Å molecular sieves, DCM, RT, 3 h; ii) allyldiphenylsulfonium tetrafluoroborate, ^{t}BuLi, THF, −78°C→RT, 1 h

Initially epoxide **140** was treated with a catalytic amount of tri-*n*-butyltin hydride and AIBN, but ^{1}H NMR analysis showed mostly starting material remained in the crude spectrum. Repeating the experiment with 1.0 equivalents of tri-*n*-butyltin hydride and AIBN led to a complex mixture of inseparable products. From the crude ^{1}H NMR spectrum there was no evidence of cyclisation to indolizidinone **131** (no terminal alkene peaks at $\delta_H \sim 5.8$) (**Scheme 2.21**). β-scission of the alkoxyl radical could not be ruled out, although no clear evidence was observed in the ^{1}H NMR spectrum [$\delta_H \sim 3.3–3.5$ (q)]. The use of thiophenol as initiator also afforded a complex mixture of products, with no evidence of cyclisation (or β-scission) being apparent in the crude ^{1}H NMR spectrum.

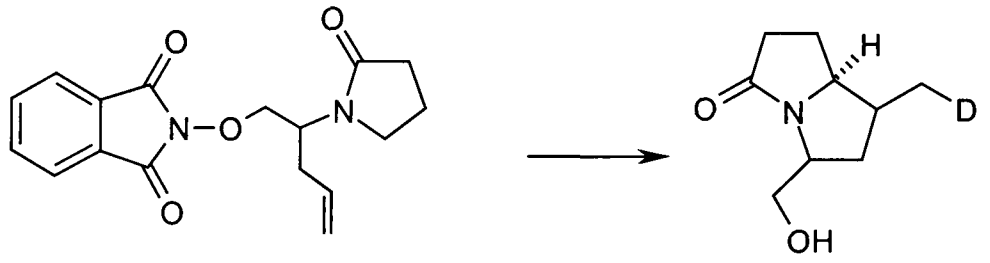


140 **142**

Scheme 2.21 *Reagents and conditions*: i) Bu_3SnH, AIBN, PhH, Δ; ii) PhSH, AIBN, PhH, Δ

2.1.3.5 *Preparation and radical reaction of precursor* **143**

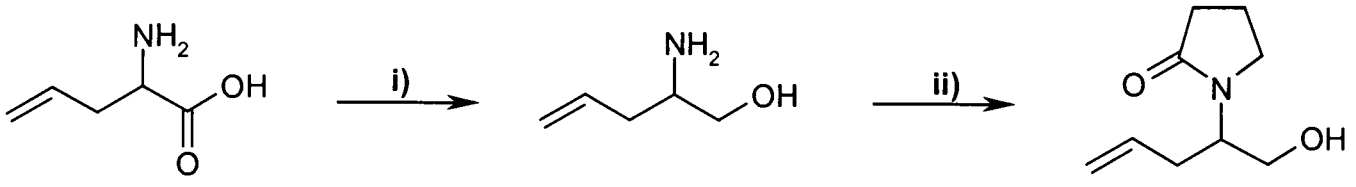
The next target, precursor **143** (**Scheme 2.22**), was designed to probe whether the stabilisation conferred by nitrogen was sufficient to lead to *β*-scission. If not, hydrogen abstraction and subsequent cyclisation would lead to pyrrolizidinone **144**.



143 **144**

Scheme 2.22

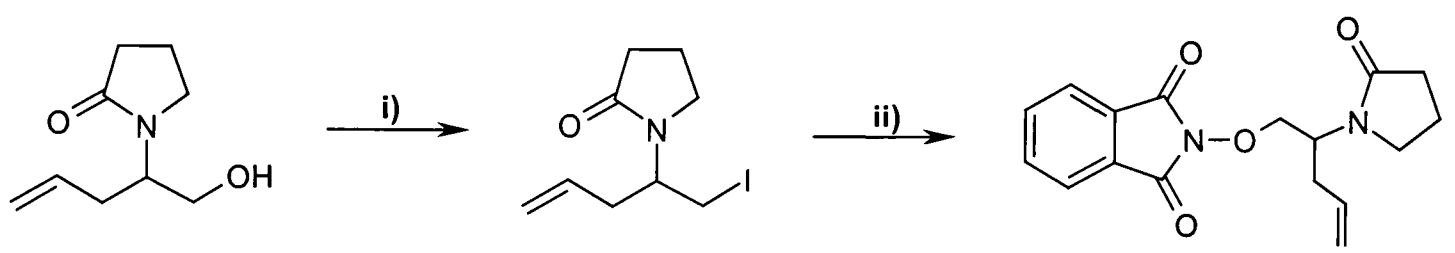
Reduction of allylglycine with lithium aluminium hydride gave amino alcohol **145**,[147] which was condensed in a sealed tube at 220°C with *γ*-butyrolactone to give alcohol **146** (**Scheme 2.23**).



145 **146**
83% **45%**

Scheme 2.23 *Reagents and conditions*: i) $LiAlH_4$, THF, Δ, 16 h; ii) *γ*-butyrolactone, 220°C, 20 h

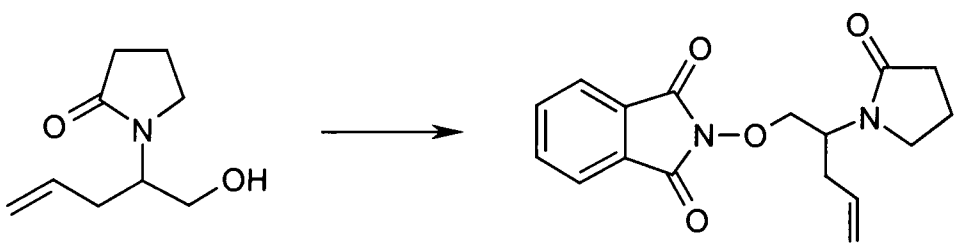
Attempted activation of the alcohol **146** by tosylation failed, but conversion to the iodide **147** and treatment with *N*-hydroxyphthalimide gave the radical precursor **143** in good yield (**Scheme 2.24**).



146 **147** **79%** **143** **81%**

Scheme 2.24 *Reagents and conditions*: i) I_2, PPh_3, imidazole, MeCN/ether, 0°C→RT, 3 h; ii) *N*-hydroxyphthalimide, NaH, DMF, 60°C, 16 h

An alternative route to precursor **143** was achieved by direct Mitsunobu conversion from alcohol **135**. Polymer-supported triphenylphosphine was used in the preparation for ease of purification of the alkoxyphthalimide (**Scheme 2.25**).[148] The overall yield of the previous synthesis was slightly higher (64%) however, the convenience of the modified Mitsunobu reaction proved advantageous as the product could be more readily isolated free from impurities.

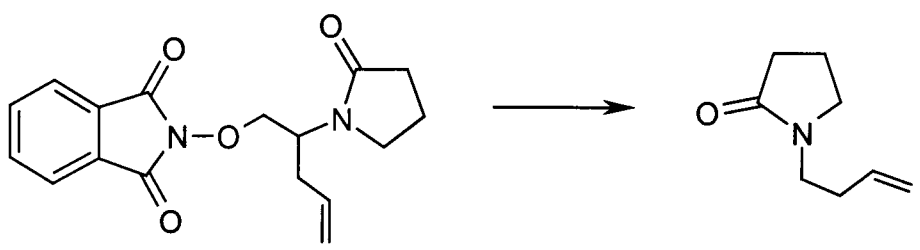


146 **143** **44%**

Scheme 2.25 *Reagents and conditions*: *N*-hydroxyphthalimide, polymer supported PPh_3, DIAD, RT, 16 h

Treatment of a 5 mM solution of precursor **143** in chlorobenzene with tri-*n*-butyltin hydride and AIBN led to complete β-scission of the alkoxyl radical; pyrrolidinone **148** was isolated in 56%

yield along with 43% of the starting alkoxyphthalimide **143**. No β-scission of the alkoxyl radical derived from precursor **120** had occurred therefore it seems that the extra stabilisation imparted by the attached alkyl group in **143** is sufficient to tip the balance in favour of the fragmentation pathway (**Scheme 2.26**). In order for 1,5-hydrogen abstraction to occur in preference, the *N*-hydroxyethyl substituent must not possess additional substitution.



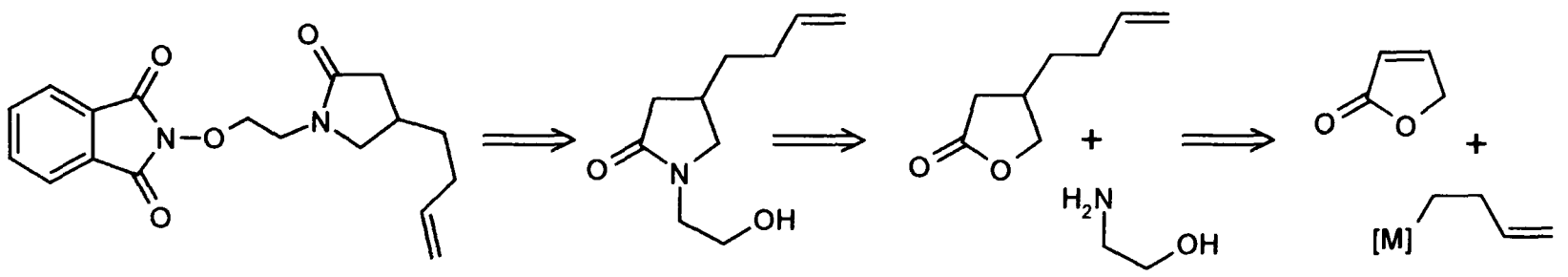
143 **148** **56%**

Scheme 2.26 *Reagents and conditions*: Bu_3SnH, AIBN, PhCl, 90°C, 16 h

2.1.3.6 *Cuprate approach to precursor* **149**

Since intermolecular trapping of the translocated radical had failed, and the previous experiments had shown branching of the *N*-alkyl substituent led to competing β-scission, the only alternative was to append a trapping alkene onto the pyrrolidinone ring. Thus, target **149** was chosen since we had already demonstrated that, in the absence of an alkyl group attached to the exocyclic carbon α- to nitrogen, 1,5-translocation of the alkoxyl radical occurred more rapidly than β-scission (**Scheme 2.7**). Therefore it seemed unlikely that β-fragmentation of the alkoxyl radical generated from **149** would occur in preference to translocation and cyclisation.

Initial retrosynthetic analysis led back to lactone **150**, to be prepared from cuprate addition to commercially available 2-(5*H*)furanone followed by condensation with ethanolamine (**Figure 2.5**).



149 150

Figure 2.5

Although there is literature precedent for cuprate addition to a similar lactone[149] in practice the addition to 2-(5*H*)furanone proved to be problematic. All attempts to add organocuprates derived from 4-lithiobutene **151** or butyllithium, employing a range of reaction conditions and work-up procedures, failed (**Table 2.1**). In all attempts, either starting material or the 1,2-addition product were recovered.

RLi	Reagents	Conditions	Work-up
BuLi	CuI, PBu_3,	–78°C→ –50°C→ –30°C, ether	conc. aq. NH_3/NH_4Cl, –30°C→RT
CH_2=$CHCH_2CH_2Li$	CuI, HMPT	–78°C→ –50°C→ RT, ether	conc. aq. NH_3/NH_4Cl, RT
CH_2=$CHCH_2CH_2Li$	CuI, HMPT	–78°C→ –50°C→ RT, ether	0.025 M HCl, RT
CH_2=$CHCH_2CH_2Li$	CuI, HMPT	–78°C→ –50°C→ RT, ether	0.025 M HCl then sat. aq. NH_4Cl, RT
BuLi	CuCN	–78°C→ –50°C→ –78°C→ –50°C, ether	conc. aq. NH_3/NH_4Cl, –30°C→RT

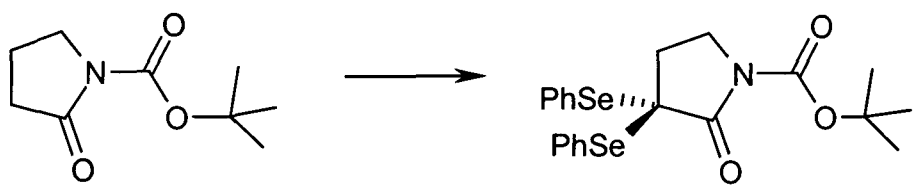
Table 2.1

At this stage the route was abandoned, however, more recently the cuprate addition to 2-(5*H*)furanone was repeated in the presence of boron trifluoride etherate and the 1,4-addition product was isolated in 62% yield (**Section 2.3.2.1**).

The next strategy involved cuprate addition to an α,β-unsaturated lactam. Hagen[150] reported that conjugate addition to normally unreactive α,β-unsaturated lactams was facilitated by the introduction of a *tert*-butoxycarbonyl group on nitrogen. A similar observation was described by Nagashima *et al.*[151] concerning *N*-tosylated lactams. The attached electron withdrawing group reduces the donating ability of the nitrogen to the carbonyl, thus enhancing the electrophilicity of the carbonyl functionality and activating the system towards conjugate addition.

However, attempted tosyl or *t*-Boc protection of 1,5-dihydropyrrol-2-one[152] gave no protected α,β-unsaturated lactam, only excess reagents being recovered from polymeric residues.

α,β-Unsaturated lactams can be conveniently prepared *via* the α-phenylselenyl lactam and subsequent oxidation and elimination.[152] Although, treatment of the *t*-Boc protected lactam **152**[153] with phenylselenenyl chloride and LHMDS at −78°C gave only the di-selenated product **154** (**Scheme 2.27**) indicating that enolate exchange is fast.

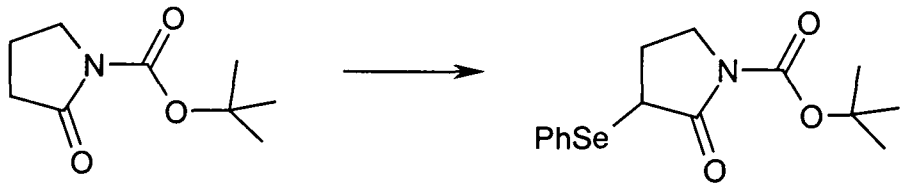


141 **142** **27%**

Scheme 2.27 *Reagents and conditions*: PhSeCl, LHMDS, THF, −78°C→RT, 3h

Treatment of the *N*-tosyl protected pyrrolidinone **153**[154] with either phenylselenenyl chloride or bromide and LDA gave only recovered starting material.

Finally, conditions were found that gave acceptable amounts of the mono-selenated product **155**. Thus, a solution of the enolate of lactam **152** in THF at −78°C was added to a solution of phenylselenenyl chloride in THF at −78°C and the reaction allowed to warm to −20°C and then quenched at −78°C with pH 6.8 buffer solution (**Scheme 2.28**). The reverse addition of the enolate to the phenylselenenyl chloride solution resulted in immediate quenching therefore, the previously observed enolate exchange did not occur.



152 **155** **46%**

Scheme 2.28 *Reagents and conditions*: PhSeCl, LHMDS, THF, −78°C→ −20°C→ −78°C, then pH 6.8 buffer

Although conditions had been found that gave the mono-selenide in moderate yield the elimination and subsequent cuprate chemistry was not attempted as an alternative parallel route appeared more promising.

2.1.3.7 *Radical approach to precursor* **149**

It was envisaged that alcohol **156** could be prepared by 5-*exo-trig* cyclisation of the unsaturated haloamide. The radical precursor **157**, derived from ethanolamine, an alkenyl halide and bromoacetyl bromide (**Figure 2.6**).

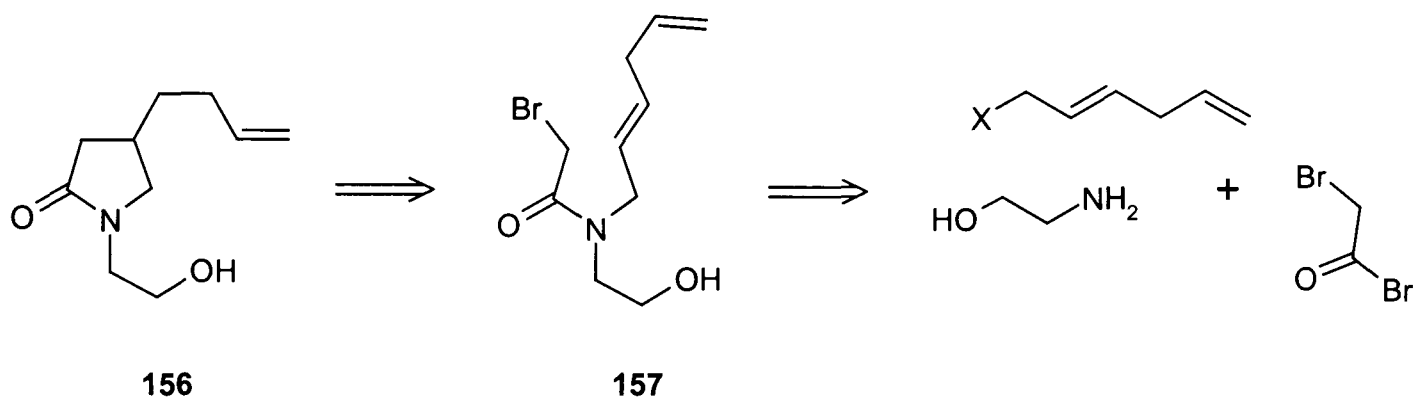
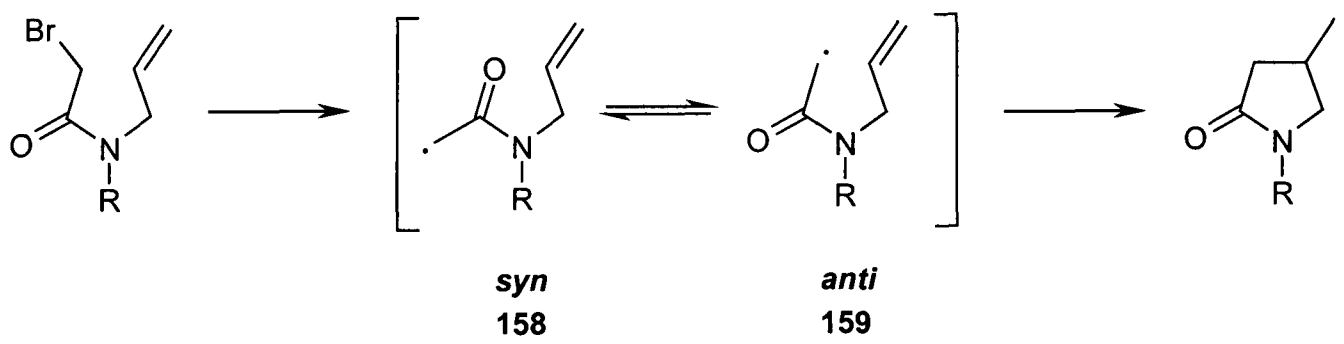


Figure 2.6

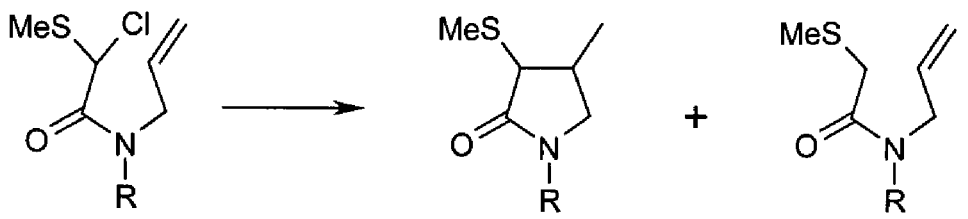
5-*Exo-trig* cyclisation of unsaturated haloamides is dependent on a reasonable population of the appropriate conformer of the intermediate carbamoylmethyl radical (**Scheme 2.29**). The *syn*-conformer **158** is unable to effect cyclisation but the *anti*-conformer **159** is able to undergo cyclisation for which the rate constant has been estimated to be in the range of $0.5–1.0 \times 10^6\ s^{-1}$ at ambient temperature.[155] As rotation around the N–CO bond is ten times slower than reduction by tin hydride at 20°C the reaction needs to be carried out at elevated temperatures with a low concentration of tin hydride to prevent premature reduction.



Scheme 2.29

Rotamer population can be influenced by the substituent attached to nitrogen.[156] The presence of bulky protecting groups on nitrogen favour the desired *anti*-conformer. For example, when the benzyl protected chloroacetamide **160a** (**Scheme 2.30**) was treated with tri-*n*-butyltin hydride and AIBN the cyclised product **161a** was obtained in 80% yield. In contrast, the

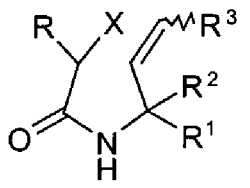
corresponding unprotected amide **160b** gave only the product of direct reduction **162b** when subjected to the same conditions.[157]



	161	162
160a R = Bn	80%	12%
160b R = H	0%	36%

Scheme 2.30 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ

Parsons and co-workers[158] found that varying the substituents on a series of haloamides **163** at the site of radical generation (R), α- to the nitrogen (R^1, R^2) and at the acceptor double bond (R^3) could alter conformer population, favouring cyclisation without the need for a large protecting group (**Figure 2.7**).



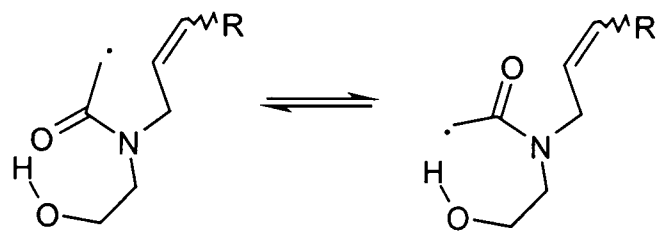
163

R = Ph, Cl
R^1 = ^{i}Pr, R^2 = H
R^1 = R^2 = $(CH_2)_5$
R^3 = CO_2Et
X = Cl

Figure 2.7

2.1.3.8 *Preparation and radical reaction of precursor* **168**

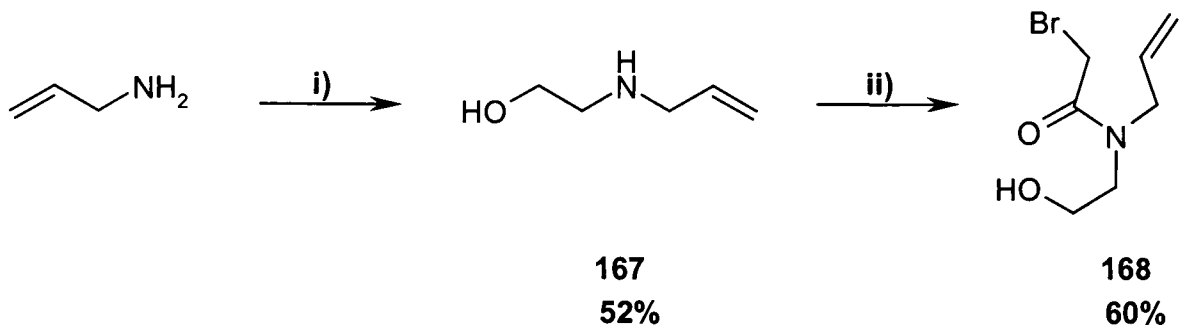
In our system it was hoped[159] that hydrogen bonding between the hydroxyl group and the carbonyl functionality would favour the *anti*-conformer **164** over the *syn*-conformer **165** (**Figure 2.8**).



164 **165**

Figure 2.8

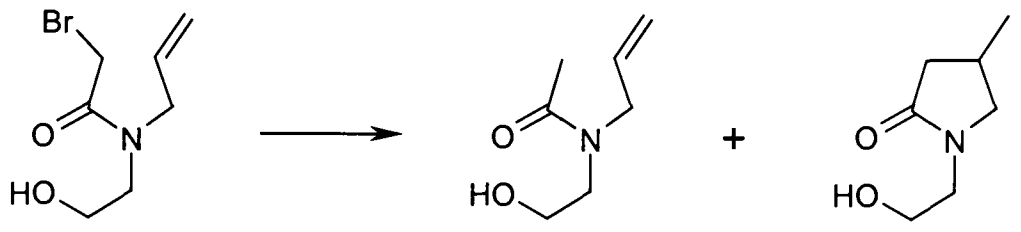
To test this hypothesis, precursor **168** was prepared by treatment of allylamine with 2-chloroethanol, under modified conditions to prevent formation of *N,N*-diallylethanolamine **166**, to give amino alcohol **167** in moderate yield. Acetylation with bromoacetyl bromide gave the radical precursor **168** as a 31:69 ratio of rotamers at 25°C (from ^{1}H NMR integration) (**Scheme 2.31**).



167 **168**
52% **60%**

Scheme 2.31 *Reagents and conditions*: i) 2-chloroethanol, Δ, 2 h, then NaOH; ii) bromoacetyl bromide, Et_3N, $CHCl_3$, 0°C→RT, 1.5 h

A 10 mM solution of precursor **168** in chlorobenzene was treated with a solution of tri-*n*-butyltin hydride and AIBN in chlorobenzene added *via* syringe pump over 2 h to afford the reduced (**169**) and cyclised (**170**) products in 34% and 56% yields respectively (**Scheme 2.32**). After completion of the reaction, *N*-(2-mercaptoethyl)aminomethyl polystyrene resin was added to the reaction mixture to remove the tri-*n*-butyltin bromide present.



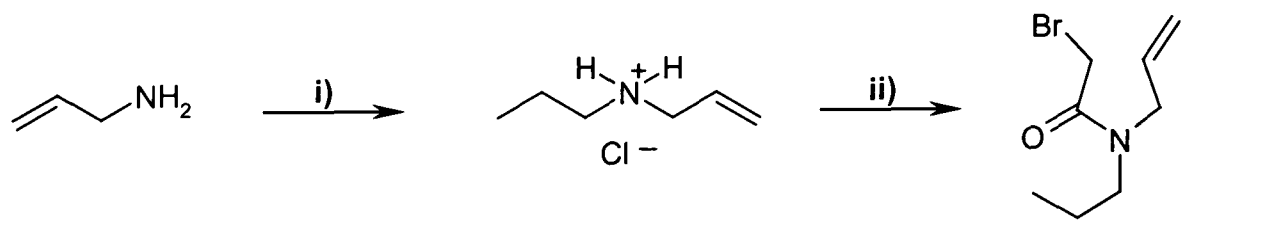
168 **169** **170**
34% **56%**

Scheme 2.32 *Reagents and conditions*: Bu_3SnH, AIBN, PhCl, 90°C, 3h, then *N*-(2-mercaptoethyl)aminomethyl polystyrene resin, RT, 16 h

The application of resin-bound scavenging agents to the removal of tin impurities has not been reported previously. Optimal conditions required for tin removal were investigated and the results are discussed in **Section 2.2**.

2.1.3.9 *Preparation and radical reaction of precursor* **172**

Precursor **172** was prepared to determine whether the hydroxyl group was influencing the outcome of the reaction (**Scheme 2.33**). (From ^1H NMR integration – a 45:55 ratio of rotamers at room temperature).

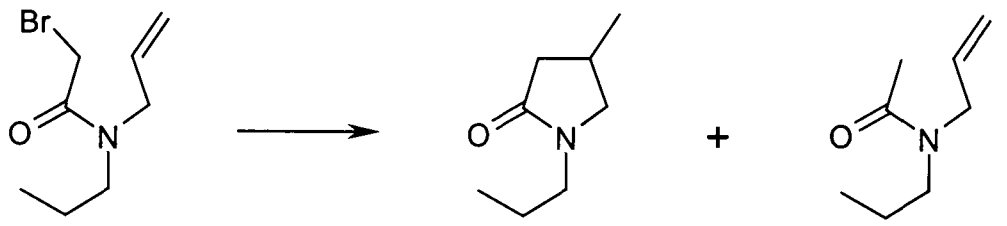


171 **172**
25% over two steps

Scheme 2.33 *Reagents and conditions*: i) 1-chloropropane, Δ, 4h then Paar Pressure Vessel, 100°C, 10 h; ii) bromoacetyl bromide, *N*,*N*-diisopropylaminoethyl polystyrene, $CDCl_3$, RT, 20 h

Subjecting precursor **172** to the same reaction conditions as those used for precursor **168** gave a 1:1 (unseparated) mixture of the cyclised (**173**) and reduced (**174**) products (as determined

by ^{1}H NMR integration) (**Scheme 2.34**). Therefore, it can be concluded that the hydroxyl group may influence rotamer population of the acetamide but only weakly.

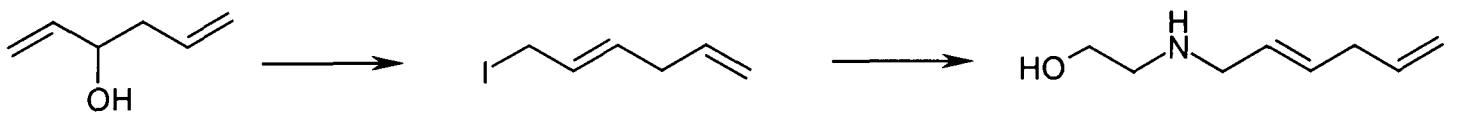


172 **173** **174**

Scheme 2.34 *Reagents and conditions*: Bu_3SnH, AIBN, PhCl, 90°C, 3h, then *N*-(2-mercaptoethyl)aminomethyl polystyrene resin, RT, 16 h

2.1.3.10 *Preparation and radical reaction of precursor* **149**

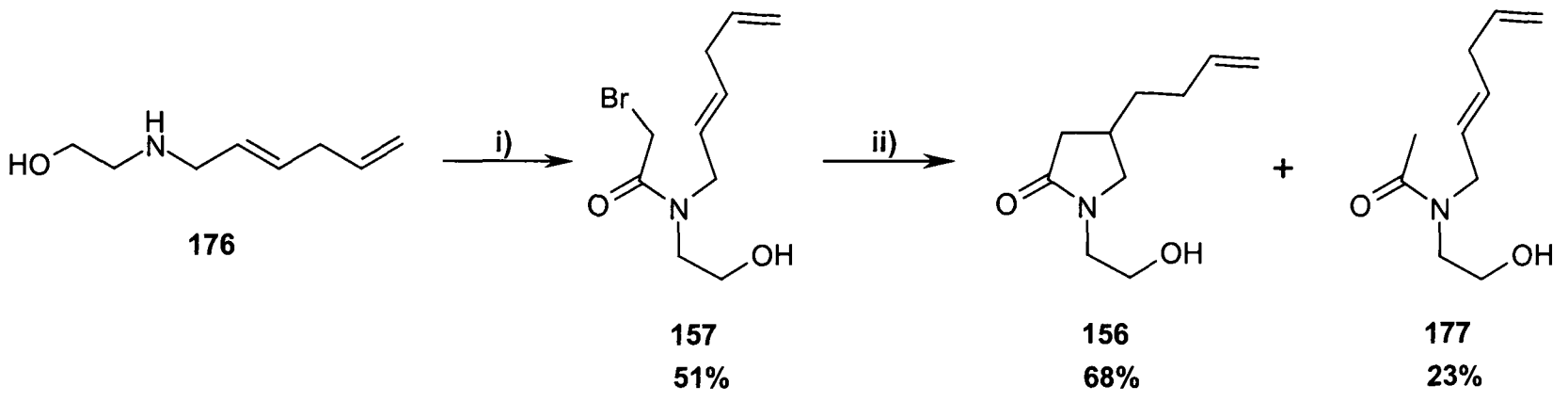
Since this work had established that radical cyclisation of bromacetamides could be achieved in reasonable yield, attention turned to the preparation of the precursor **149** The iodide **175**, generated *in situ* from 1,5-hexadien-3-ol,[160] was treated with ethanolamine to give the *N*-alkylated product **176** (**Scheme 2.35**).



175 **176** **57%**

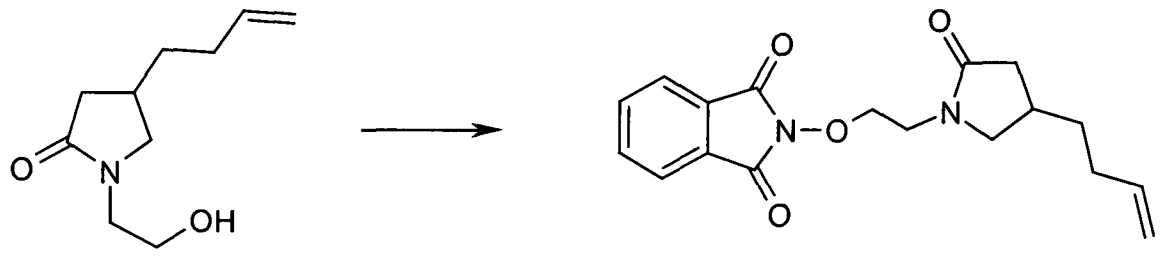
Scheme 2.35 *Reagents and conditions*: TMSCl, NaI, H_2O, MeCN, 3 h, RT then ethanolamine, DIPEA, 16 h, RT

Amino alcohol **176** was treated with bromoacetyl bromide to give the radical precursor **157** as a 35:65 ratio of rotamers at room temperature (from ^{1}H NMR integration), which when subjected to radical initiating conditions gave the cyclised **156** and directly reduced product **177** in 68% and 23% yields respectively (**Scheme 2.36**).



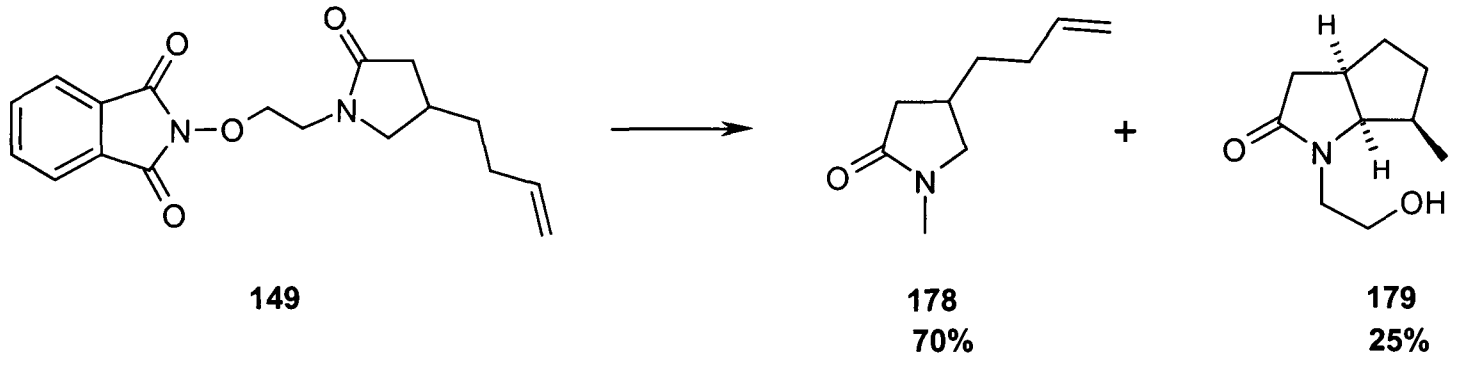
Scheme 2.36 *Reagents and conditions*: i) bromoacetyl bromide, Et_3N, $CHCl_3$, 0°C→RT, 2 h; ii) Bu_3SnH, AIBN, PhCl, 90°C, 5h, then *N*-(2-mercaptoethyl)aminomethyl polystyrene resin, RT, 1 h

With the lactam **156** in hand, the modified Mitsunobu reaction was attempted using DIAD and polymer-supported triphenylphosphine to give the alkoxyphthalimide **149** (**Scheme 2.37**).



Scheme 2.37 *Reagents and conditions*: *N*-hydroxyphthalimide, DIAD, polymer supported PPh_3, DCM, 16 h, RT

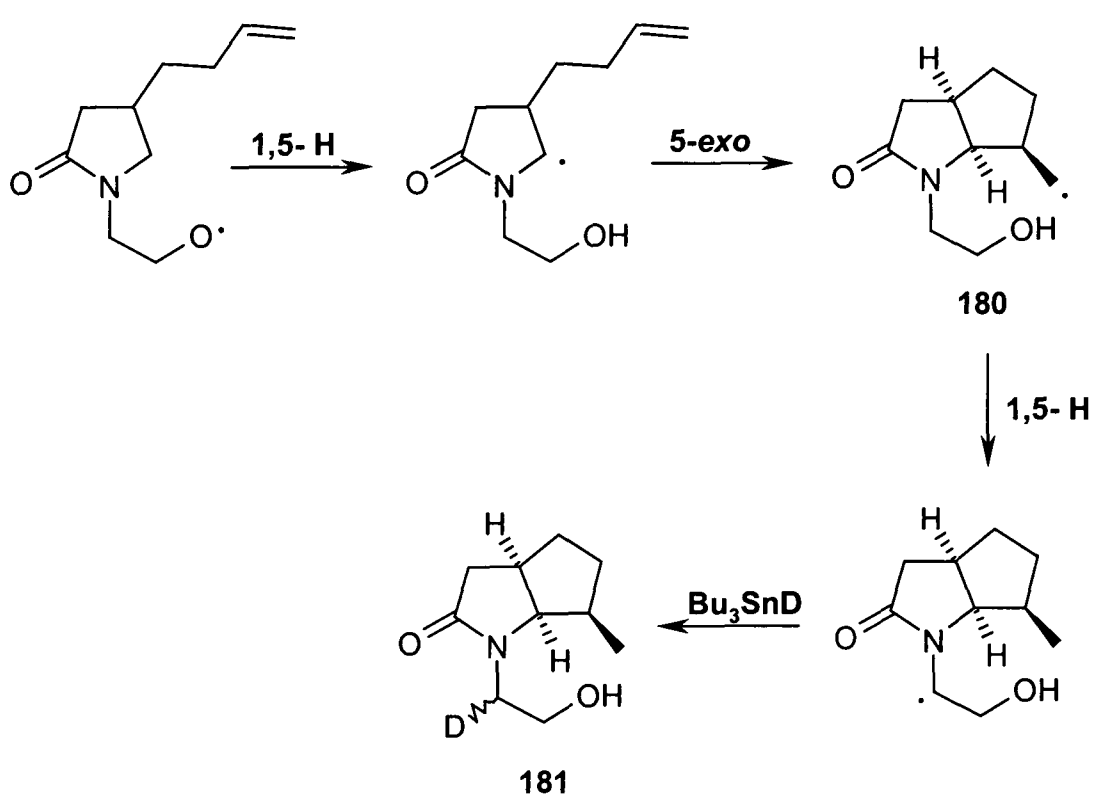
A 5mM solution of precursor **149** in chlorobenzene was treated with tri-*n*-butyltin hydride and AIBN. Although the major product from the reaction was the product resulting from *β*-scission **178**, the translocated and cyclised product **179** was obtained in 25% yield (**Scheme 2.38**), the first case of successful 1,5-hydrogen transfer and trapping by an alkene.



Scheme 2.38 *Reagents and conditions*: Bu_3SnH, AIBN, PhCl, 90°C, 16 h

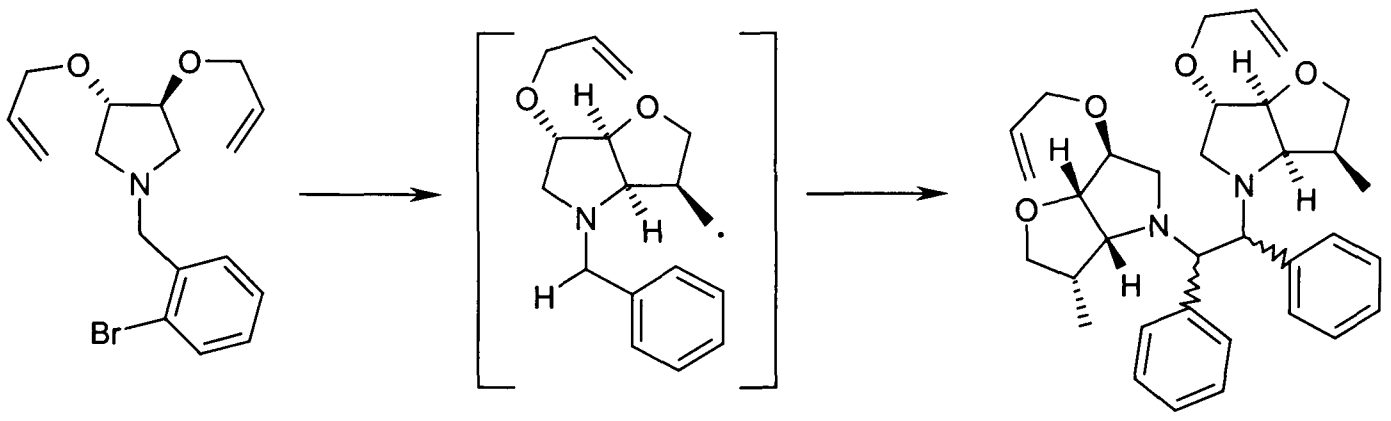
Although, in this system translocation of the alkoxyl radical had been possible, β-scission still dominated; this had not been the case in the system devoid of the alkenyl side chain and it was thought that the alkenyl side chain might provide a steric influence to reduce the rate of translocation relative to fragmentation.

Interestingly, when the reaction was repeated using tri-*n*-butyltin deuteride, the major diastereomer underwent a further 1,5-hydrogen transfer to the methyl radical **180** leading to deuterium incorporation in the hydroxyethyl side-chain to give the bicyclic pyrrolidinone **181** as a mixture of 63:37 diastereomers (**Scheme 2.39**).



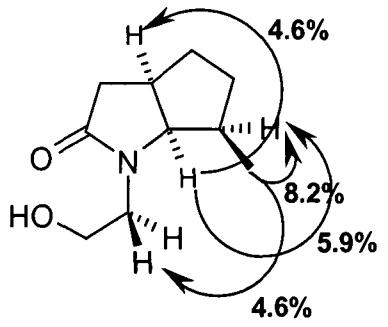
Scheme 2.39

Hoshino and co-workers[161] observed a similar 1,5-hydrogen transfer to radical **182** from the benzylic position leading to hexahydrofuro[3,2-*b*]pyrrole **183**, after *in situ* dimerisation (**Scheme 2.40**).



Scheme 2.40 *Reagents and conditions*: Bu_3SnH, AIBN, PhMe, Δ, 5 h

The stereochemistry of the major diastereomer of the translocation-cyclisation product **179** was assumed to be that shown in **Figure 2.9**, since only one of the diastereomers can undergo the final 1,5-hydrogen transfer process (ratio of diastereomers 8:1 as determined by ^1H NMR integration). This assumption was supported by n.O.e. experiments (Appendix 1) and **Table 2.2** shows the important enhancements.



179

Figure 2.9

	Enhancement						
Irradiated	CH_3	$CH_3CHCH_aH_b$	CH_3CH	$COCH_2CH$	$COCH_aCH_b$	NCH_aCH_b	NCH
CH_3		4.5%	8.2%		2.1%	4.6%	
NCH			5.9%	4.6%		2.4%	

Table 2.2

2.2 Novel Procedure for the Removal of Tin Impurities

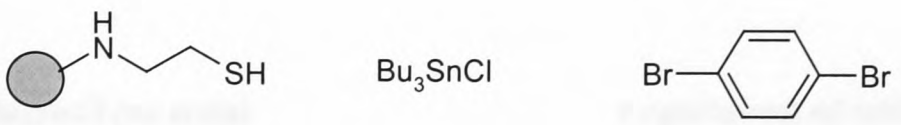
Organotin residues are notoriously difficult to remove from the desired end products of radical reactions.[141] Since organotin compounds are neurotoxins, the necessity for their complete removal from reaction products, especially in the pharmaceutical industry, is essential. Numerous approaches for tin removal have appeared in the literature over the past two decades and the use of catalytic amounts of tin reagent with recycling *in situ* by means of borohydride reagents is common.[162,163] Other methods include the use of water-soluble tin hydrides,[164] fluorous organotin reagents combined with extraction into an immiscible fluorous phase,[165] partitioning between hexane and acetonitrile,[166] the addition of polar groups to assist chromatography[167] or conversion to polar[168] or non-polar species[139] prior to chromatography, and conversion to insoluble polymeric tin fluorides.[140,169] Polymer-supported tin hydrides have also been successfully employed.[170-173] However, polymer-supported scavenging agents have not previously been employed in this context.

2.2.1 *N*-(2-Mercaptoethyl)aminomethyl Polystyrene Resin **184**

The concept originated from the observation that (thiophenol)tri-*n*-butylstannane passes rapidly through silica gel without significant degradation, facilitating chromatography. The conversion of stannyl residues to thiophenylstannanes *in situ* had previously been made use of within the group to remove the majority of tin impurities from a crude reaction mixture.[38,174]

As an extension of this idea, the use of *N*-(2-mercaptoethyl)aminomethyl polystyrene resin **184** (**Figure 2.10**) to remove tin residues was investigated. The resin combines the required thiol

functionality with a basic site to remove the liberated hydrogen halide. Although the resin is commercially available, it can also be prepared in two steps from Merrifield resin.[175] Experiments were performed to determine optimal conditions for tin removal. In a typical experiment known equimolar quantities of tri-*n*-butyltin chloride **185** and 1,4-dibromobenzene **186** (used as an internal standard) were shaken with varying molar ratios of the resin in $CDCl_3$. ^1H NMR spectra were recorded at varying intervals and comparison of the 1,4-dibromobenzene integral with that of the tri-*n*-butyltin chloride gave an estimate of the extent of tin removal from the mixture; the results of which are summarised in **Table 2.3**.



184 185 186

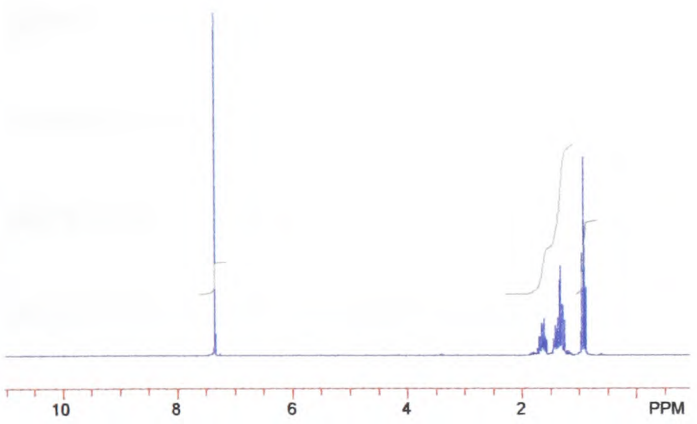
Figure 2.10

Run	Molar equivalent of resin	Ratio of **185**:**186** (based on ^1H NMR integration)						
		0 h	**0.5 h**	**1 h**	**3 h**	**5 h**	**7 h**	**20 h**
1	**1.5**	50:50	37:63	34:66	43:57	44:56	36:64	41:59
2	**4.0**	50:50	9:91	11:89	13:87	13:87	11:89	15:85
3	**8.0**	50:50	7:93	9:91	10:90	10:90	12:88	15:85

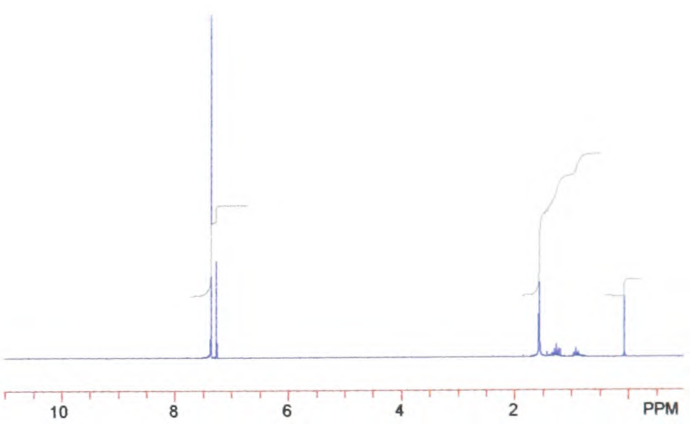
Table 2.3

From the results in **Table 2.3** it can been seen that the optimal equivalents for tin removal were four molar equivalents of thiol resin shaken for 0.5 h (Run 2) (**Figure 2.11**). Longer reaction times did not result in a significant increase in the quantity of tin removed; in fact some

degradation from the resin appeared to be occurring. Eight molar equivalents of resin gave comparable results (Run 3); however, due to the expense of the resin, four equivalents was considered optimal.



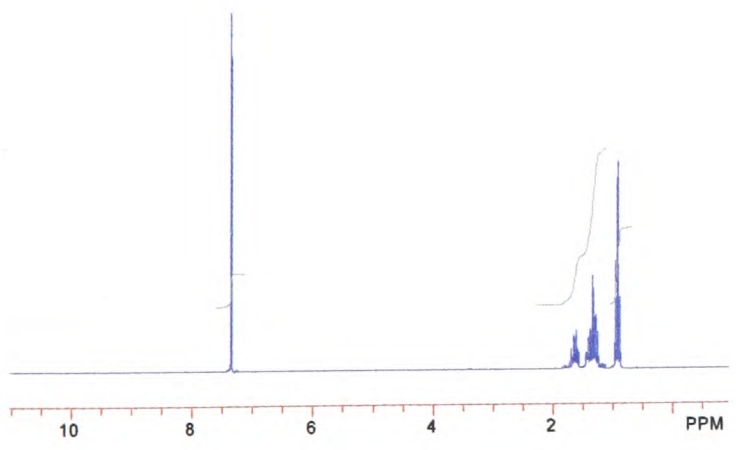
1,4-dibromobenzene & Bu_3SnCl (no resin)



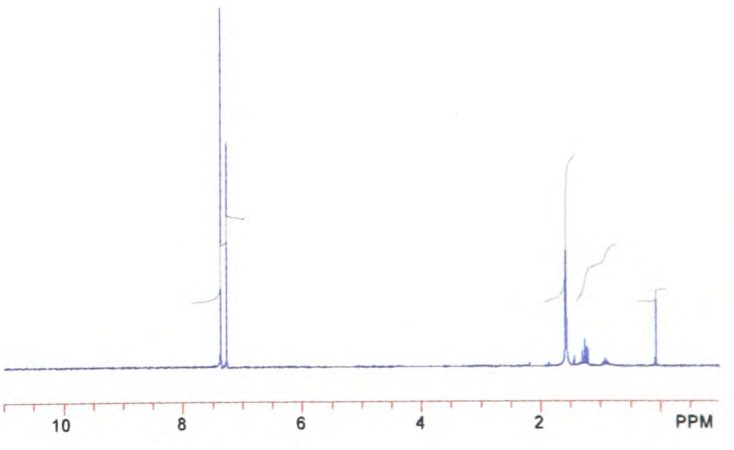
4 equivalents of resin added after 30 mins

Figure 2.11

In further experiments four equivalents of resin was added to the 1:1 mixture. After shaking for 30 minutes a further four equivalents of resin was added; however, no further quantity of tin was removed (**Figure 2.12**). Addition of 1.0 M solution of iodine in ether to the mixture and further shaking for 30 minutes did not result in increased removal.



1,4-dibromobenzene & Bu_3SnCl (no resin)

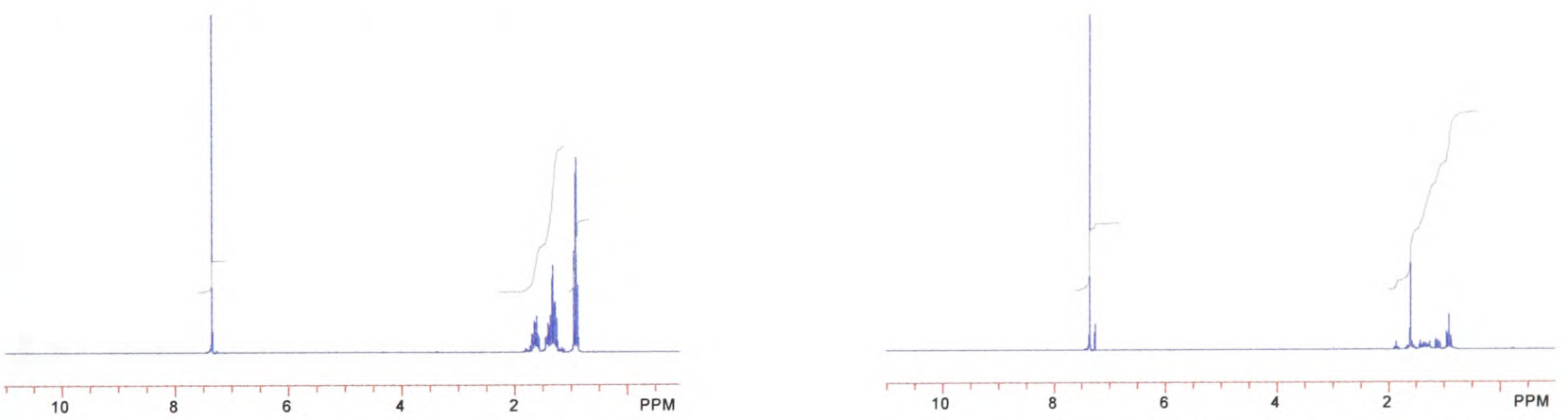


8 equivalents of resin added after 60 mins

Figure 2.12

2.2.2 (Thiomethyl)polystyrene Resin

Similar experiments were conducted using the less expensive (thiomethyl)polystyrene resin. Under the conditions described above this resin failed to remove any tin residues from a 1,4-dibromobenzene/tri-*n*-butyltin chloride mixture. Fortunately, addition of an external base, for example, sodium hydrogen carbonate, resulted in significant amounts (~ 60%) of tin removal, although overall, this resin appears less effective than *N*-(2-mercaptoethyl)aminomethyl polystyrene resin (**Figure 2.13**).



1,4-dibromobenzene & Bu_3SnCl (no resin)

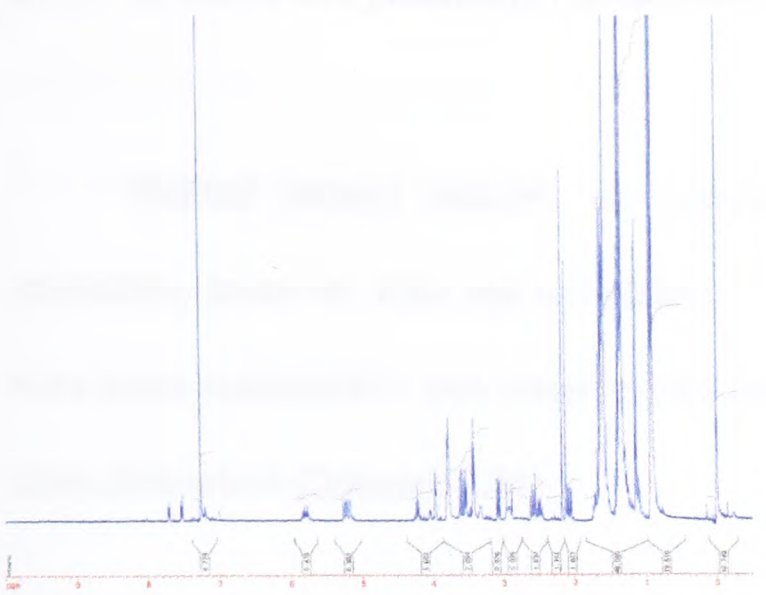
4 equivalents of thiomethyl resin added

+ 2 equivalents $NaHCO_3$ after 30 mins

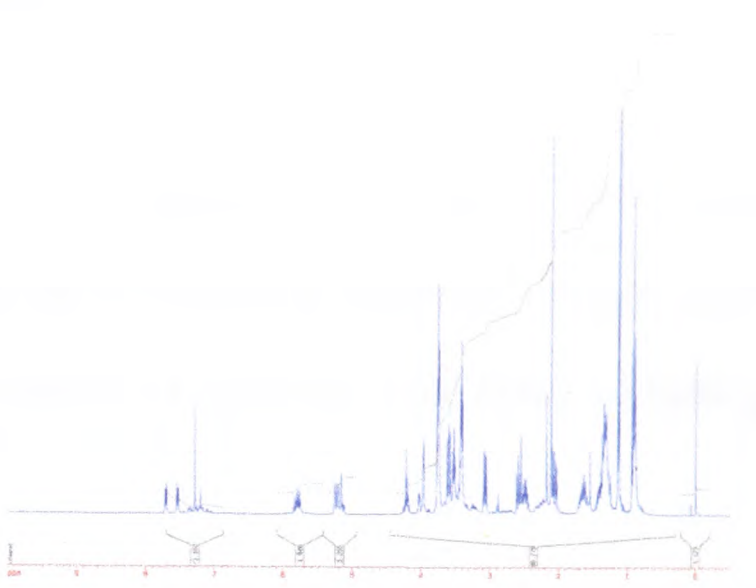
Figure 2.13

2.2.3 Synthetic Application

This work-up was applied in the preparation of lactam **170** (**Scheme 2.31**) leading to a 90% combined yield of the reduced product **169** and cyclised product **170**. **Figure 2.14** shows the ^{1}H NMR spectra from the crude reaction mixture before and after addition of 4.0 equivalents of *N*-(2-mercaptoethyl) aminomethyl polystyrene resin.



Before addition of N-*(2-mercaptoethyl) aminomethyl polystyrene resin*



After addition of N-*(2-mercaptoethyl) aminomethyl polystyrene resin*

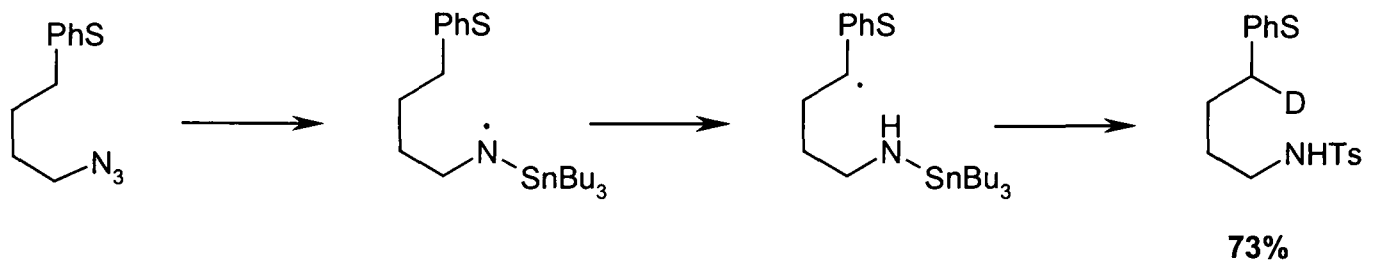
Figure 2.14

2.3 Nitrogen-Centred Radicals

Although it had been shown that 1,5-hydrogen abstraction by an alkoxyl radical α-to a lactam nitrogen was possible, it seemed that alkoxyl radicals are too reactive and induce unwanted side reactions in preference to 1,5-hydrogen abstraction when extra functionality was present in the precursor. To overcome the problem of preferential β-scission, the use of nitrogen centred radicals as the abstracting species was investigated as they are much less prone to fragmentation as the resulting C=N bond ($\approx$ 610 kJ mol^{-1}) provides less of a driving force than the C=O bond ($\approx$ 740 kJ mol^{-1}) formed during fragmentation of an alkoxyl radical.

2.3.1 *N*-Tri-*n*-butylstannyl Substituted Aminyl Radicals

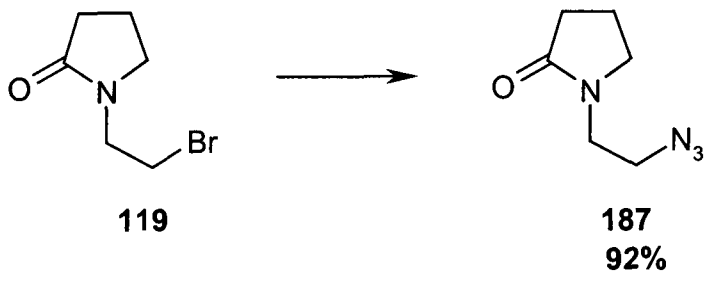
Neutral aminyl radicals are considered to be electrophilic in nature and relatively unreactive; however, Kim and co-workers[112] found that *N*-tributyltin substituted nitrogen radicals were more nucleophilic and reactive than ordinary aminyl radicals and could effect 1,5-hydrogen atom abstraction (**Scheme 2.41**).



Scheme 2.41 *Reagents and conditions*: Bu_3SnD, AIBN, PhH, Δ, 4 h then TsCl, Pyr, 1 h

2.3.1.1 *Preparation and radical reaction of precursor* **187**

To determine whether 1,5-hydrogen abstraction α- to a lactam nitrogen by a tri-*n*-butylstannyl aminyl radical was possible precursor **187** was prepared in excellent yield by treatment of bromide **119** with sodium azide (**Scheme 2.42**).

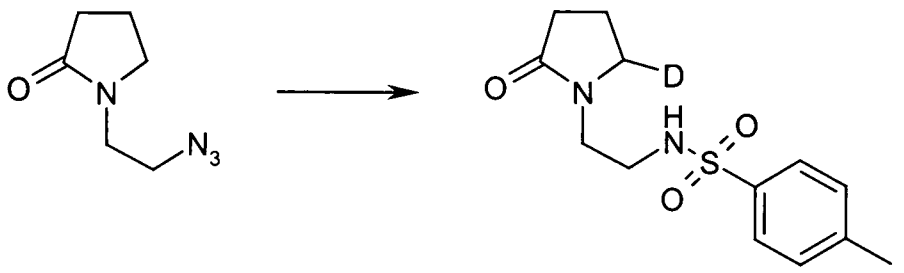


119 **187** **92%**

Scheme 2.42 *Reagents and conditions*: NaN_3, DMF, 70°C, 24 h

When precursor **187** was treated with tri-*n*-butyltin deuteride and AIBN (followed by *p*-toluenesulfonyl chloride and pyridine to cleave the tin–nitrogen bond), pyrrolidinone **188** (**Scheme**

2.43) was isolated with ≥90% deuterium incorporation α- to the lactam nitrogen; the non-deuterated proportion presumably arose from direct reduction of the aminyl radical followed by hydrogen exchange during chromatography.



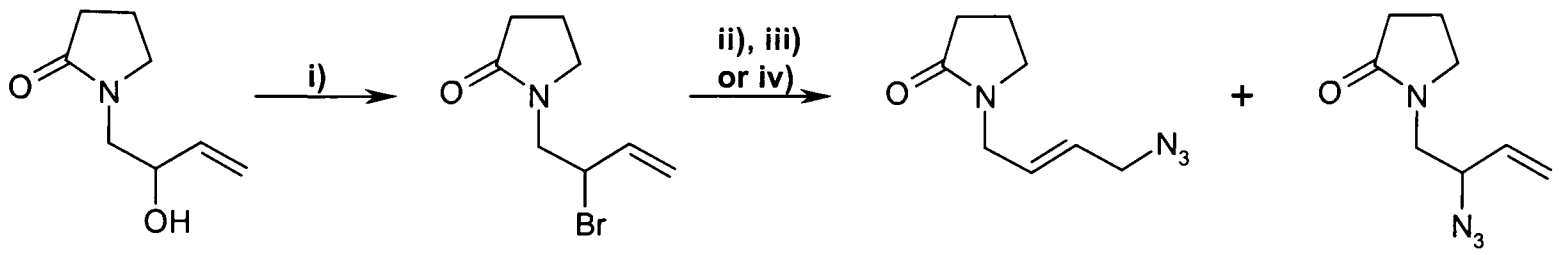
187 **188** **41%**

Scheme 2.43 *Reagents and conditions*: Bu_3SnD, AIBN, PhCl, 90°C, 16 h then TsCl, Pyr, 90°C, 2 h

Attempts were then made to trap the translocated radical intramolecularly, however, the preparation of the precursors proved difficult.

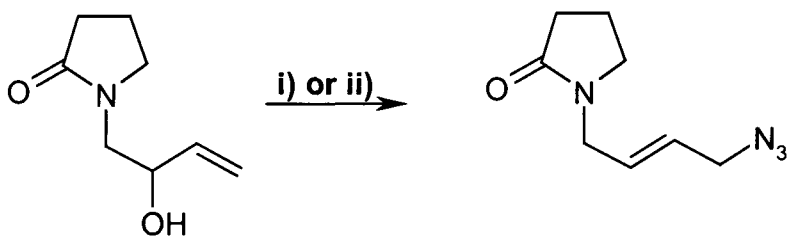
2.3.1.2 *Attempted preparation of radical precursor* **191**

Bromide **189** was prepared from alcohol **134** using polymer-supported triphenylphosphine to aid purification.[176] When bromide **189** was treated with sodium azide in DMF as before, allylic displacement (S_N2') of the bromide occurred in preference to direct S_N2 reaction, to give the primary azide **190** as the major product along with the desired secondary azide **191** (**Scheme 2.44**). Using acetone or THF as solvent did not achieve significant variation of the ratio of primary azide to secondary azide.



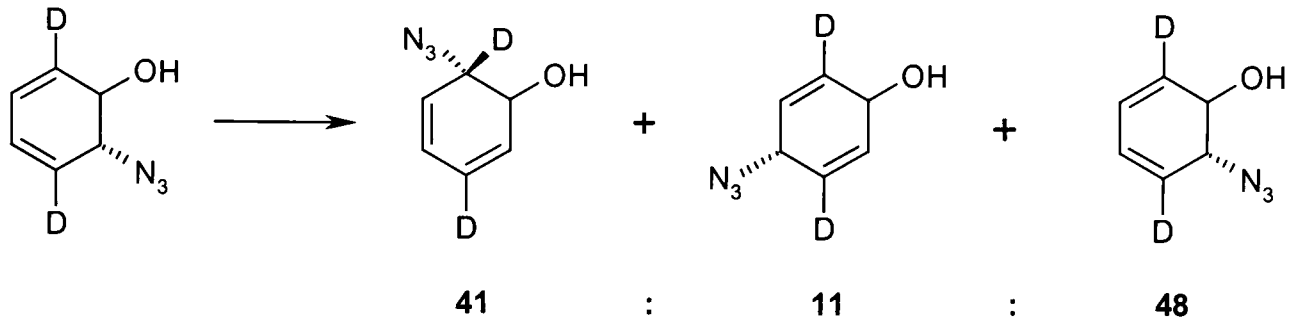
Scheme 2.44 *Reagents and conditions*: i) CBr_4, polymer supported PPh_3, $CHCl_3$, RT, 16 h; ii) NaN_3, DMF, 70°C, 16 h; iii) NaN_3, acetone, Δ, 16 h; iv) NaN_3, THF, Δ, 16 h

Using a modified Mitsunobu procedure[177] in an attempt to prepare the azide **191** directly from the alcohol **134** resulted in complete conversion to the unwanted primary azide **190** (as determined by ^{1}H NMR analysis of the crude reaction mixture) (**Scheme 2.45**).



Scheme 2.45 *Reagents and conditions*: i) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, 0°C→RT, 16 h; ii) $(PhO)_2P(O)N_3$, DIAD, PBu_3, THF, 0°C→RT, 16 h

This result was somewhat surprising as the previous modified Mitsunobu reaction[145] between alcohol **134** and *N*-hydroxyphthalimide (**Scheme 2.16**) had yielded only the secondary alcohol. Possibly the secondary azide formed during both reactions is able to rearrange to the more stable primary azide, *cf.* the work of McManus *et al.*[178] (**Scheme 2.46**).

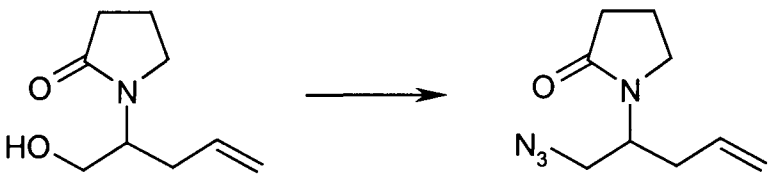


Scheme 2.46 *Conditions*: H_2O, RT

As the secondary azide **191** had proved difficult to prepare it was decided to investigate the chemistry with an alternative precursor.

2.3.1.3 *Preparation of radical precursor* **192**

Precursor **192** was prepared from the alcohol **146** using the modified Mitsunobu reaction with diphenylphosphoryl azide in 40% yield (**Scheme 2.47**). However, when a thermal stability test was attempted on this precursor (heating at 80°C in chlorobenzene) it was found that decomposition occurred. At 40°C in chlorobenzene significant amounts of decomposition occurred and even at room temperature in $CDCl_3$ decomposition occurred (over 24 h) leading to a complex mixture of products, presumably by intramolecular cycloaddition.



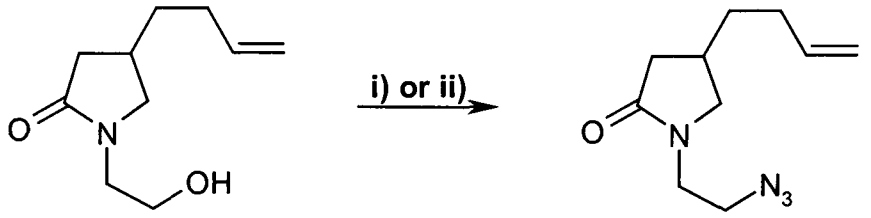
Scheme 2.47 *Reagents and conditions*: $(PhO)_2P(O)N_3$, DEAD. PPh_3, THF, 0°C→RT, 16 h

As thermal rearrangement of the azide **192** occurred even at room temperature, the substrate was not considered suitable to attempt the radical chemistry.

2.3.1.4 *Preparation and radical reaction of precursor* **193**

In precursor **193** the double bond is positioned sufficiently remote from the azide that rearrangement or cycloaddition reactions were thought to be unlikely. Also, it had already been shown that the alkoxyl radical analogue of this precursor had undergone translocation and cyclisation to give bicycle **166** (**Scheme 2.38**).

Precursor **193** was prepared from the alcohol **156**, previously prepared by radical cyclisation, either by the modified Mitsunobu conditions[177] or *via in situ* generation of the alkyl bromide and subsequent treatment with sodium azide[179] (**Scheme 2.48**).



156 **193**

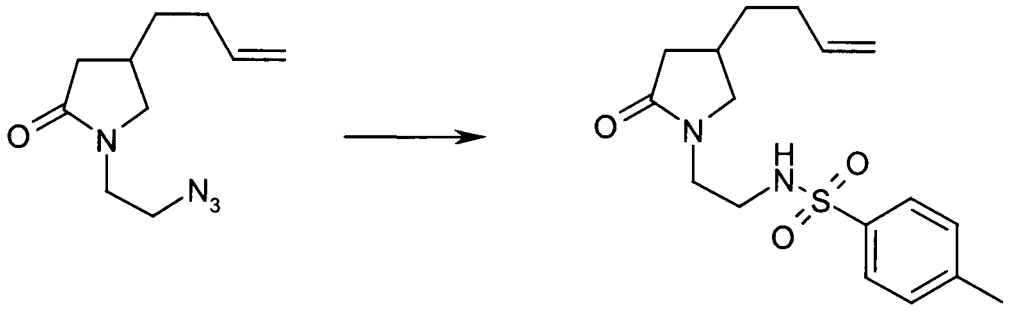
i) 33%

ii) 64%

Scheme 2.48 *Reagents and conditions*: i) $(PhO)_2P(O)N_3$, DEAD, PPh_3, THF, 0°C→RT, 16 h; ii) PPh_3, CBr_4, NaN_3, DMF, RT, 16 h

A thermal stability test of precursor **193** showed that no decomposition occurred at 80°C, therefore the radical reaction was attempted at this temperature. However, treatment of azide **193** with tri-*n*-butyltin deuteride and AIBN followed by *p*-toluenesulfonyl chloride and pyridine did not lead to translocation and cyclisation of the resulting radical; only the directly reduced product **194** was isolated, after proton exchange on silica gel chromatography (**Scheme 2.49**). It was thought

that direct reduction of the stannyl substituted aminyl radical occurred preferentially to translocation as the steric influence of the side-chain now dominated leading to failure of the translocation by the less reactive aminyl radical. On the plus side, no fragmentation had occurred and it was decided to persist with potentially more reactive nitrogen-centred radicals.



180 **181** **31%**

Scheme 2.49 *Reagents and conditions*: Bu_3SnD, AIBN, PhCl, 90°C, 16 h then TsCl, Pyr, 90°C, 2 h

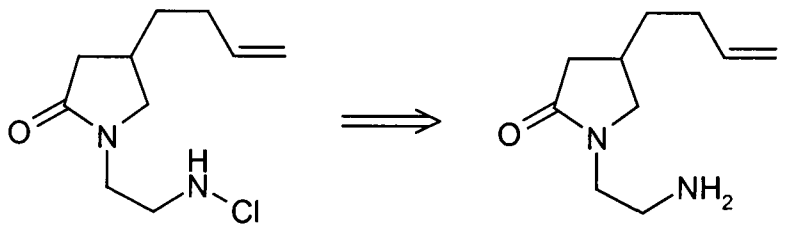
2.3.2 Aminyl Radical Cations

Since the *N*-tributylstannyl substituted aminyl radical proved too unreactive to promote hydrogen abstraction in the more complex substrate it was decided to investigate a more reactive aminyl radical system.

Aminyl radical cations are more reactive than their neutral aminyl radical counterparts[180,181] and have been shown to undergo hydrogen atom abstraction processes; this is the basis of the well-known Hofmann-Löffler-Freytag reaction (**Section 1.2.5.1**). The electrophilic cationic radical can be generated from the corresponding *N*-chloroamine by thermolysis in the presence of a strong acid (commonly H_2SO_4), irradiation in acidic media, or by treatment with a redox couple or a reducing agent and suitable Lewis acid.

2.3.2.1 *Preparation of radical precursor* **195**

To investigate the methodology, precursor **195** became the next target, which could, in principle, be prepared from the corresponding amine **196** by treatment with a suitable chlorinating agent (**Figure 2.15**).

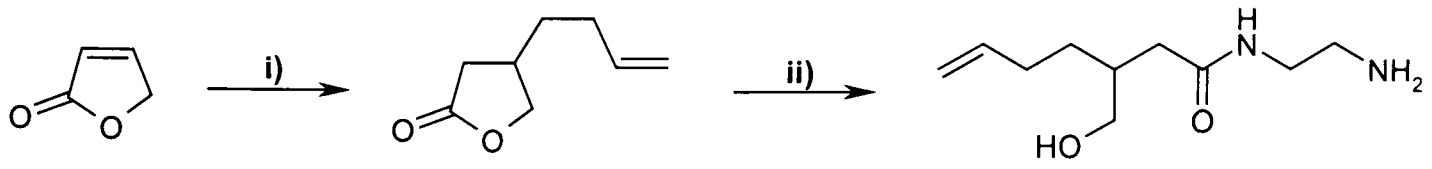


195 **196**

Figure 2.15

Ongoing work within the group had shown that cuprate addition to lactones could be promoted by boron trifluoride etherate. With this in mind cuprate addition to 2-(5*H*)furanone (**Section 2.1.3.6**) was reinvestigated in the presence of the Lewis acid as this would lead to a more convenient synthesis of precursor **196** by condensation of the resulting β-substituted γ-lactone with ethylenediamine.

Treatment of 2-(5*H*)furanone[182] with the cuprate derived from 4-iodobutene in the presence of boron trifluoride etherate did, indeed, give the substituted lactone **150** in moderate yield. However, condensation with ethylenediamine could not be achieved, even at 230°C, the acyclic amino alcohol **197** being the sole product from the reaction (**Scheme 2.50**).

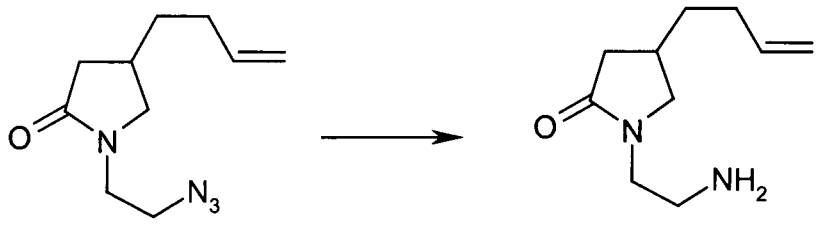


150
62%

197
61%

Scheme 2.50 *Reagents and conditions*: i) 4-iodobutene, ^{t}BuLi, CuI, $BF_3{\cdot}Et_2O$, ether, THF, −78°C→RT, 2 h; ii) ethylenediamine, 230°C, sealed tube, 20 h

An alternative route to amine **196** *via* reduction of the azide **193** proved successful affording the amine **196** in excellent yield (**Scheme 2.51**).

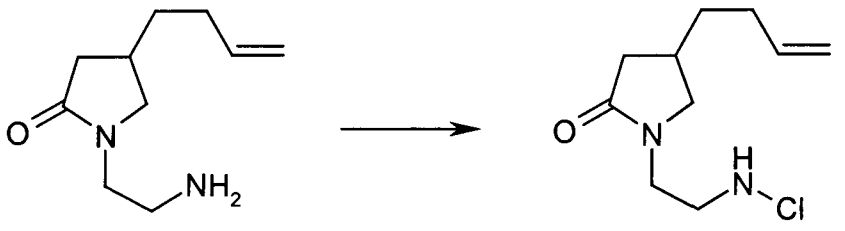


193

196
97%

Scheme 2.51 *Reagents and conditions*: PPh_3, H_2O, THF, RT, 16 h

Treatment of this precursor with freshly prepared *tert*-butyl hypochlorite[183] using the procedure of Duhamel *et al.*[184] gave the radical precursor, which was unstable to silica gel chromatography and therefore used immediately without purification (**Scheme 2.52**).



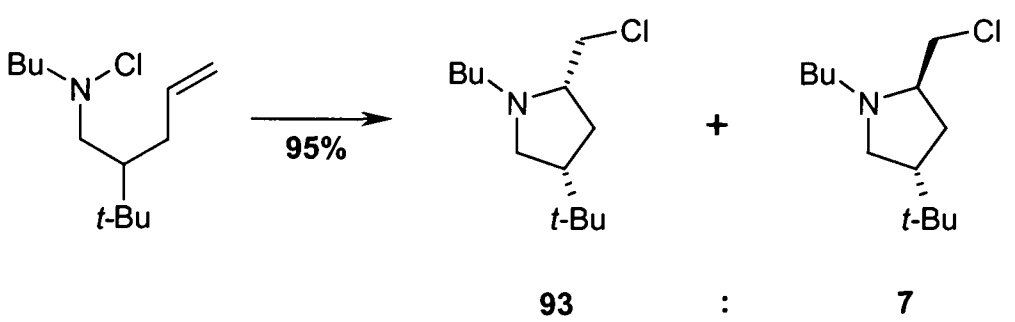
196

195
99%

Scheme 2.52 *Reagents and conditions*: ^{t}BuOCl, MeOH, 0°C, 45 mins

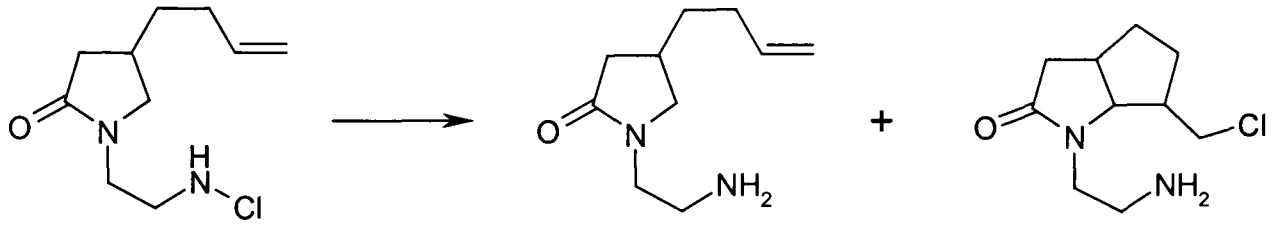
2.3.2.2 *Radical reaction of precursor* **195**

Recent work by Somfai and co-workers[185] investigated Lewis acid-promoted aminyl radical cyclisations in the presence of titanium(III) chloride leading to pyrrolidines. In this work, complexation of the aminyl radical with a Lewis acid gave a cationic electrophilic radical which readily added to the double bond. A range of Lewis acids was screened and optimal results were obtained when a combination of titanium(III) chloride and boron trifluoride etherate was used to initiate cyclisation (**Scheme 2.53**).



Scheme 2.53 *Reagents and conditions*: $TiCl_3$, $BF_3{\cdot}Et_2O$, DCM, −78°C, 55 mins then 30% aq. NaOH solution

Precursor **195** was subjected to identical conditions to those used by Somfai. Initial chromatographic separation of the crude reaction mixture gave what appeared to be one major highly polar component. However, from the ^{1}H NMR spectrum it was clear that other products were present in the sample and t.l.c. analysis of the mixture using a more polar solvent system (60:30:5:3 $CHCl_3$:MeOH:water:AcOH) revealed the presence of other compounds. Further chromatography gave an apparent mixture of reduced product **196** and an unidentified compound. Peaks in the ^{1}H NMR spectrum [400 MHz, D_2O, 3.76 (d, *J* 5.6), 4.15–4.18 (m)] supported the presence of cyclised product **198**, although further separation of the components of the mixture proved impossible due to their identical polarity (**Scheme 2.54**).



195 **196** **198**

Scheme 2.54 *Reagents and conditions*: $TiCl_3$, $BF_3{\cdot}Et_2O$, DCM, −78°C, 55 mins then 30% aq. NaOH solution

2.3.3 Summary

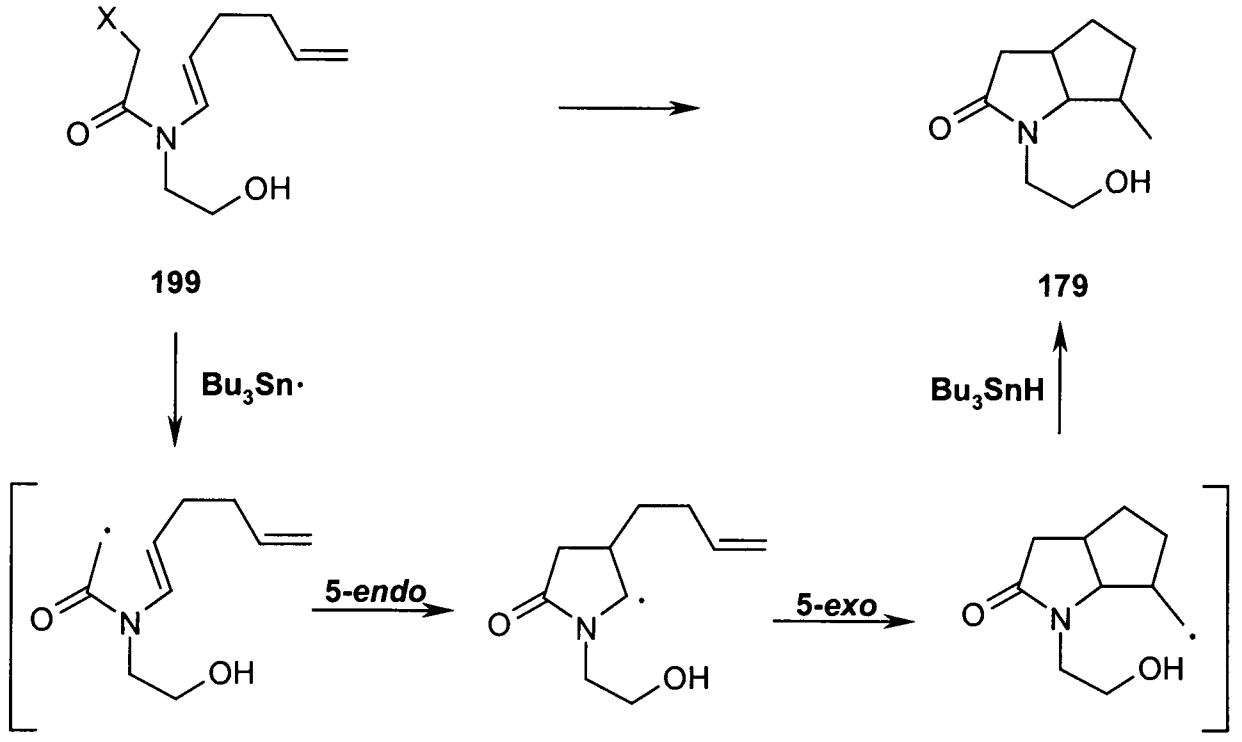
It has been shown that an alkoxyl radical is capable of abstracting a hydrogen atom α- to a lactam nitrogen however β-scission of the alkoxyl radical became a significant or dominant pathway when extra functionality was incorporated into the precursor. Although developing π-overlap in the transition state certainly contributes to favourable β-scission, it is thought that stabilisation of the resulting radical by nitrogen and the attached alkyl substituents contributes to a greater extent. Extra functionality incorporated into the pyrrolidinone ring also favours β-fragmentation, the effect probably arising from increased steric bulk around the abstractable hydrogen which retards the rate of translocation relative to fragmentation.

When less reactive nitrogen-centred radicals are employed as translocation initiators, β-fragmentation does not seem to be the problem but translocation fails in potentially cyclisable substrates. The use of aminyl radical cations to effect translocation was briefly investigated and this type of electrophilic radical shows potential as an abstracting species, however, product isolation proved difficult and may limit the scope of the reaction. These extensive restrictions mean that the chemistry will not be followed up as a method for hydrogen translocation.

2.4 5-*Endo-trig* Radical Cyclisations

2.4.1 Preparation of α-Haloacetamide Radical Precursors

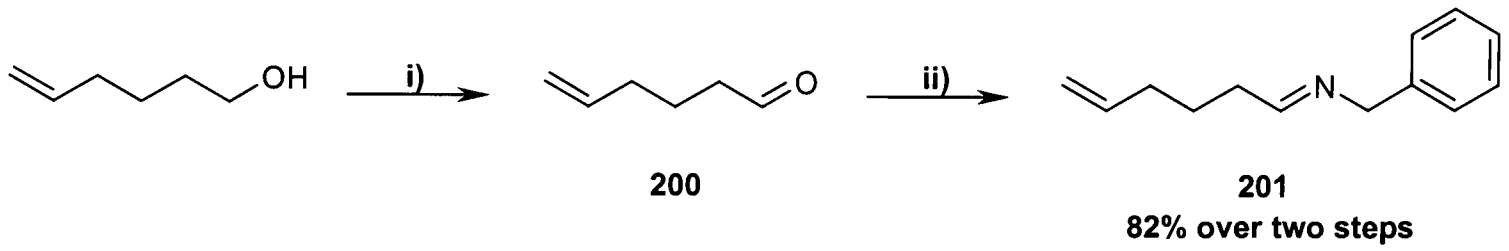
It was envisaged that bicyclic product **179** (**Scheme 2.38**) could be more readily prepared in a cascade radical cyclisation process from a suitable enamine precursor such as **199** (**Scheme 2.55**) *via* a 5-*endo-trig*/5-*exo-trig* sequence.



Scheme 2.55

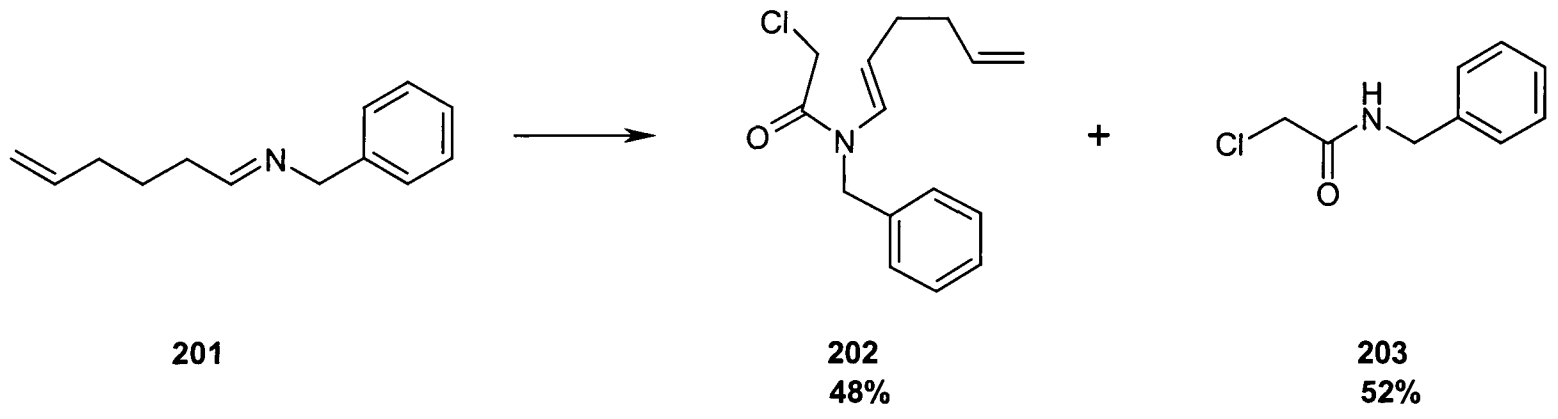
5-*Endo-trig* cyclisations are disfavoured by Baldwin's guidelines[47] as significant distortion from the normal geometry of a five-membered ring is necessary to achieve good orbital overlap in the transition state introduces strain, consequently the activation energy for the cyclisation is high and kinetically disavoured. However, Ikeda[186-191] and Parsons[192-200] amongst others have demonstrated that certain α-haloacetamides can undergo 'disfavoured' radical cyclisations *via* a 5-*endo-trig* process.

Precursor **202** (**Scheme 2.57**) was prepared in order to determine the feasibility of the 5-*endo* cyclisation. Thus treatment of 5-hexen-1-ol with PCC gave the crude aldehyde **200**,[201] which was condensed with benzylamine to afford the imine **201** in good overall yield (**Scheme 2.56**).



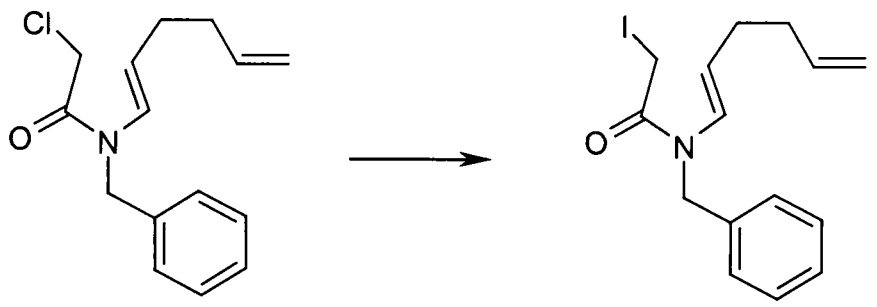
Scheme 2.56 *Reagents and conditions*: i) PCC, silica gel, DCM, RT, 4 h; ii) benzylamine, $MgSO_4$, DCM, RT, 3 h

Acetylation with chloroacetyl chloride gave the radical precursor **202** along with the hydrolysed product **203** (**Scheme 2.57**).



Scheme 2.57 *Reagents and conditions*: chloroacetyl chloride, $PhNEt_2$, DCM, 0°C→RT, 4 h

Iodoacetamide **204** was also prepared, by Finkelstein reaction between the chloride **202** and NaI (**Scheme 2.58**).



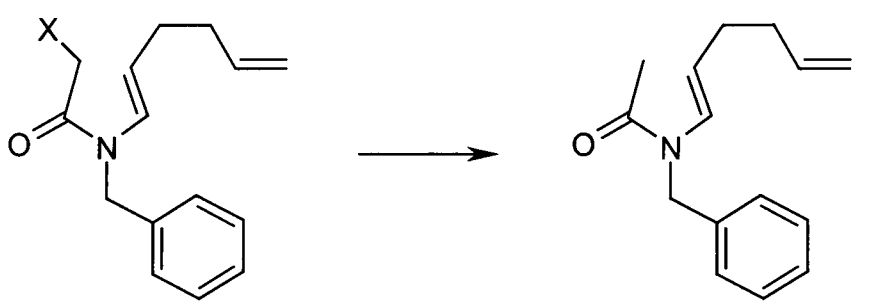
202 **204**
83%

Scheme 2.58 *Reagents and conditions*: NaI, acetone, RT, 1.5 h

2.4.2 Radical Reactions of α-Haloacetamide Precursors

Both precursors were subjected to a variety of radical initiating conditions (**Table 2.3**) however, no cyclised product was observed in any of these reactions.

With extended addition time (Entries 1 and 3) propagation of the radical chain was inefficient and significant quantities of starting material were isolated along with the directly reduced product **205** (**Scheme 2.59**). The amount of unreacted starting material could be decreased with shorter addition time (Entry 2), although no evidence of cyclisation was observed and only the directly reduced product **205** resulted.



202 X=Cl **205**
204 X=I

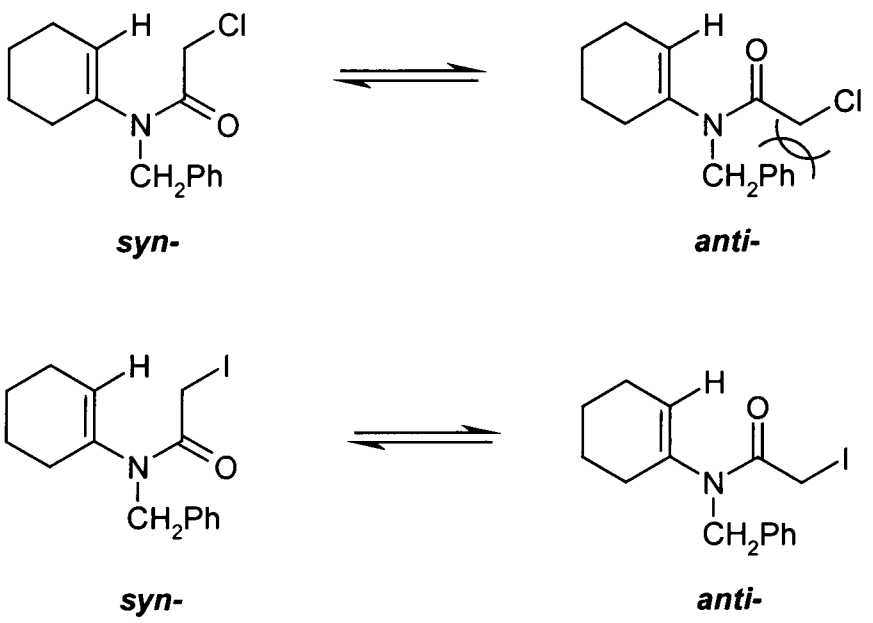
Scheme 2.59 *Reagents and conditions*: Bu_3SnH, AIBN, PhCl, 90°C then 10% aq. KF solution, 3 h

Entry	Precursor	[Precursor]/mM	Conditions	Results
1	**202**	20	Bu_3SnH, AIBN, 90°C, 6 h[a]+16 h	**202**, 40%; **205**, 46%
2	**202**	20	Bu_3SnH, AIBN, 90°C, 0.5 h[a]+16 h	**202**, 7%; **205**, 75%
3	**204**	20	Bu_3SnH, AIBN, 90°C, 5 h[a]+16 h	**204**, 24%; **205**, 59%
4	**204**	8	Bu_3SnH, Bu_3SnCl, AIBN, 90°C, 16 h	**205**, 88%

[a]Syringe pump addition

Table 2.3

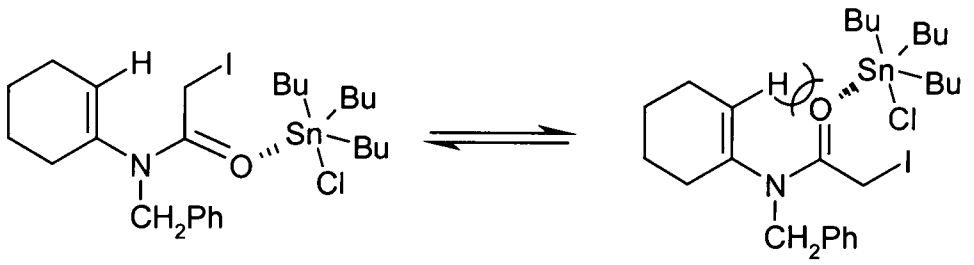
Ishibashi *et al.*[202] recently reported that 5-*endo-trig* radical cyclisation of α-halo amides promoted by tri-*n*-butyltin hydride gave a higher degree of direct reduction when the iodide precursor was used instead of the chloride. They suggested that the longer length of the carbon–iodine bond meant that the *anti*-conformer of the amide was less disfavoured than in the chloride. As only the *syn*-conformer of the amide can cyclise, the iodide led to decreased amounts of cyclised product (**Scheme 2.60**).



Scheme 2.60

Addition of tri-*n*-butyltin chloride to the reaction mixture led to an increased amount of cyclisation in the case of the iodide. The tri-*n*-butyltin chloride is thought to act as a Lewis acid,

coordinating to the carbonyl oxygen of the amide. This results in severe steric interaction in the *anti*-conformer and leads to an increased amount of the cyclised product (**Scheme 2.61**).



syn- ***anti-***

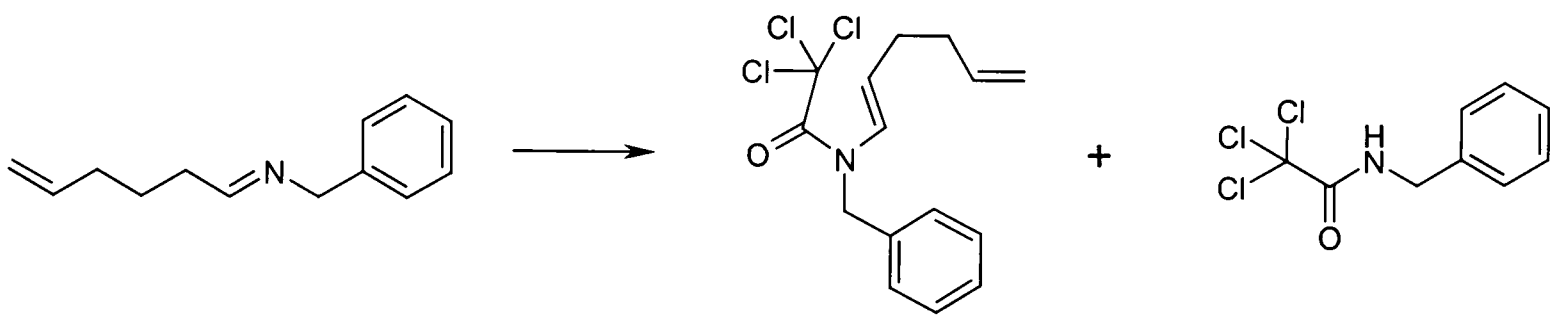
Scheme 2.61

In the case of iodide **204**, addition of tri-*n*-butyltin chloride to the reaction mixture (Entry 4) did not induce cyclisation; again, only the directly reduced product **205** was isolated along with unreacted starting material.

2.4.3 Attempted Preparation of Trichloroacetamide **206**

Attempts were made to prepare the trichloroacetamide **206** because it was thought that the radical generated from this precursor would be more electrophilic in nature and thus, more likely to undergo 5-*endo* cyclisation onto the electron rich double bond.[203]

However, when the imine **201** was treated with trichloroacetyl chloride in the presence of base, all conditions led to the hydrolysed product **207** even after extensive drying of all the reagents (**Scheme 2.62**). The acetamide **206** may hydrolyse on silica gel chromatography and repetition of the experiment in $CDCl_3$ suggested that this might be the case since none of the aldehyde **200** was observed in the ^1H NMR spectrum after 4 h.

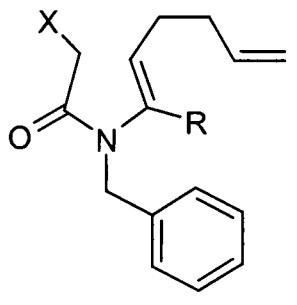


201 **206** **0%** **207** **90%**

Scheme 2.62 *Reagents and conditions*: trichloroacetyl chloride, $PhNEt_2$, DCM, 0°C→RT, 4 h

2.4.3 Summary

Although 5-*endo*-cyclisation of precursors **202** and **204** did not occur, there is some potential for this route to be developed. Ikeda[189] suggested that in order for 5-*endo-trig* cyclisations of acetamides to proceed effectively, a stabilising alkyl or aryl group α- to the amide nitrogen is necessary. Future work will involve investigation of the radical methodology on a modified bromoacetamide of type **208**, where R = alkyl or aryl group (**Figure 2.17**). The additional stabilisation from the alkyl/aryl group of the resulting radical could prove to be of fundamental importance to the success of the tandem cyclisation sequence and influence the stability of the precursor.



208

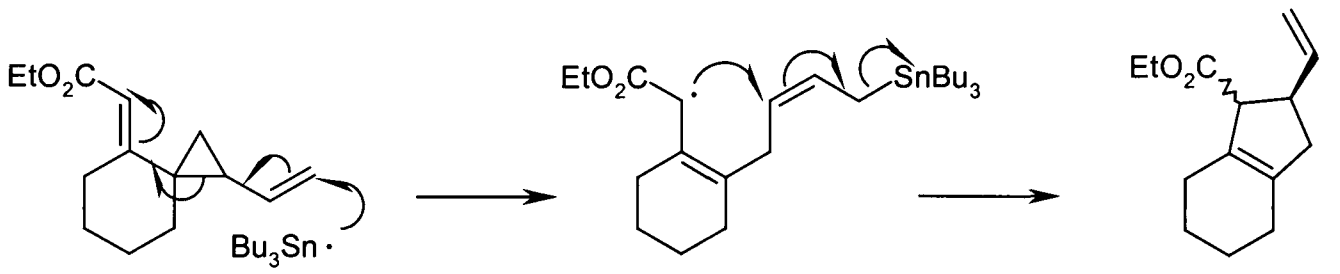
Figure 2.16

2.5 A Radical Version of the Vinylcyclopropane-Cyclopentene Rearrangement

As an aside to radical translocation methodology, a radical-mediated vinylcyclopropane-cyclopentene rearrangement was investigated.[204]

2.5.1 Original preparation of radical precursor **209**

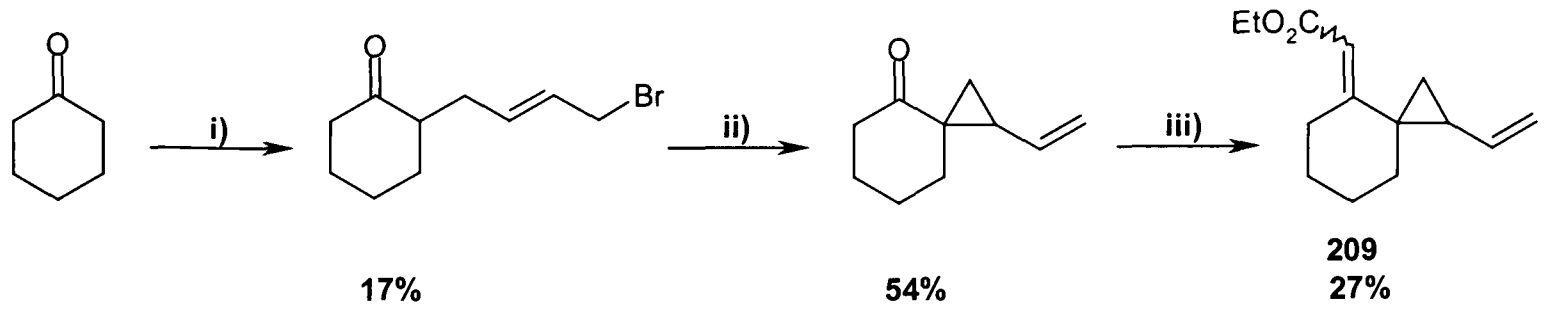
Previous work within the group had investigated the course of a radical rearrangement process published by Rajagopalan.[205] During the course of this investigation, precursor **209** was prepared, which was shown to undergo rearrangement to give the bicyclic ester **210** (**Scheme 2.63**).[146]



209 **210** **53%**

Scheme 2.63 *Reagents and conditions*: Bu_3SnH, AIBN, PhH, Δ, 5 h

Unfortunately, the route to the precursor **209** involved a number of poor yielding steps that required optimisation in order for the reaction to be of synthetic use. Alkylation of cyclohexanone with 1,4-dibromo-2-butene proceeded in only 17% yield and, after vinylcyclopropane formation, the Horner-Wadsworth-Emmons (HWE) reaction gave only 27% of the desired precursor **209** (**Scheme 2.64**).



Scheme 2.64 *Reagents and conditions*: i) LDA, 1,4-dibromo-2-butene, THF, −78°C→RT, 16.5 h; ii) KO^{t}Bu, THF, ^{t}BuOH, RT, 4 h; iii) triethyl phosphonoacetate, NaH, THF, RT, 15 h

2.5.2 Improved preparation of radical precursor **209**

We attempted to improve the initial alkylation of cyclohexanone with 1,4-dibromo-2-butene: e.g. by alkylation of imine **211** or hydrazones **212** and **213** (**Figure 2.17**), but all attempts proved unsuccessful with only poor yields being obtained.

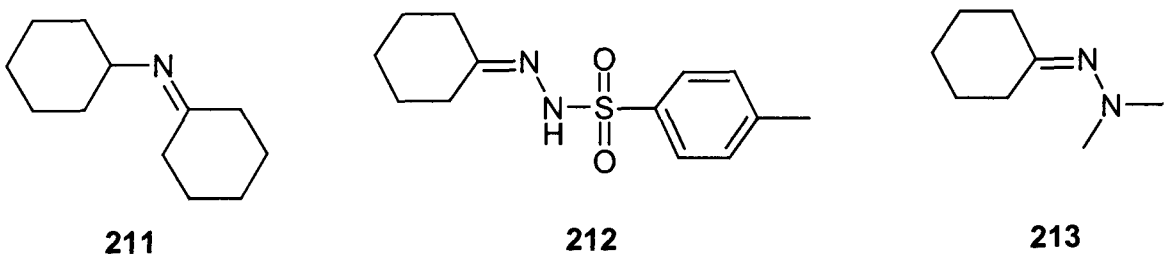
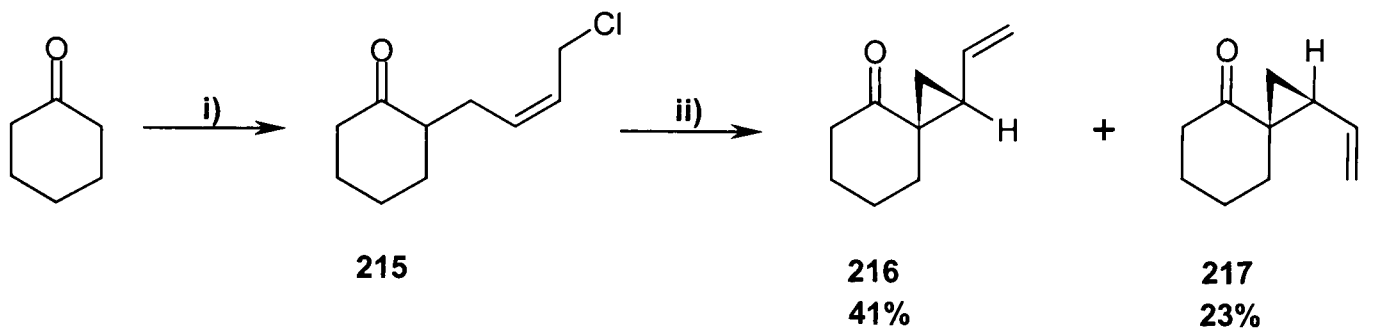


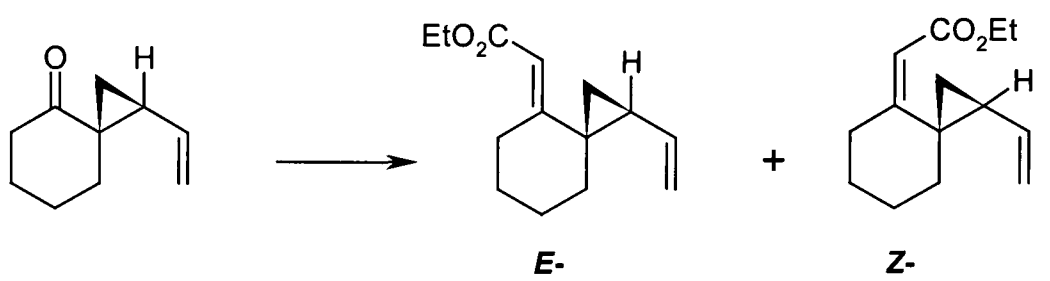
Figure 2.17

Fortunately, treatment of cyclohexanone enolate with *cis*-1-chloro-4-iodo-2-butene **214** and treatment of the so-formed chloride **215** with potassium *tert*-butoxide yielded the two separable diastereomeric cyclopropanes **216** and **217** in reasonable overall yield (1:1 mixture by ^{1}H NMR integration) (**Scheme 2.65**).



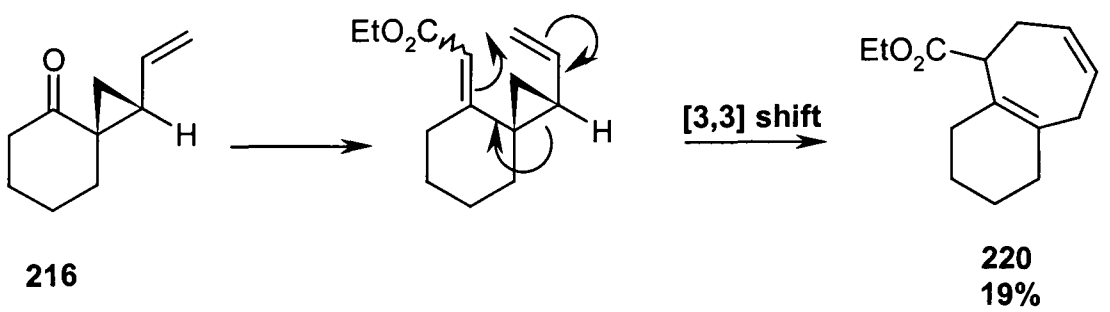
Scheme 2.65 *Reagents and conditions*: i) LDA, 4-chloro-1-iodo-2-butene, THF, 0°C→RT, 3.5 h; ii) KO^{t}Bu, THF, ^{t}BuOH, RT, 6 h

The olefination of the unseparated mixture afforded only low yields of the radical precursor **209** using a variety of reaction conditions and olefinating reagents. When each of the diastereomers **216** and **217** was subjected to HWE conditions separately it was found that the *exo* isomer **217** afforded the radical precursor as a 3:1 ratio of alkene diastereomers **218** and **219** (**Scheme 2.66**).



Scheme 2.66 *Reagents and conditions*: triethyl phosphonoacetate, NaH, DME, RT, 40 h

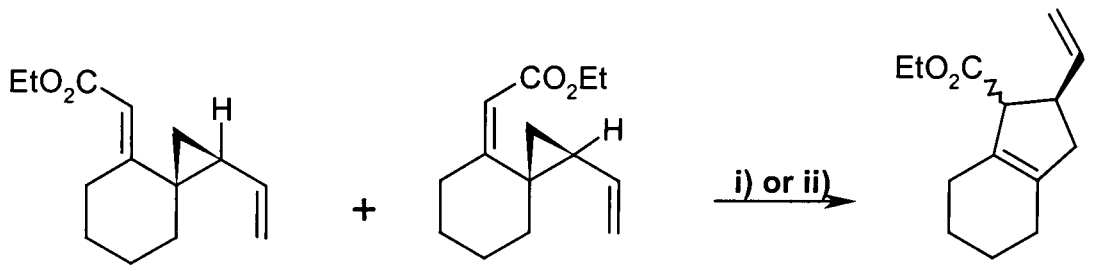
Interestingly the *endo* isomer **216** underwent an unexpected divinylcyclopropane rearrangement[206] after olefination to give bicyclic ester **220** and recovered starting material (**Scheme 2.67**). This unexpected side reaction accounts for the previous poor yield from the reaction when both the vinylcyclopropane diastereomers were used without prior separation.



Scheme 2.67 *Reagents and conditions*: triethyl phosphonoacetate, NaH, DME, RT, 40 h

2.5.3 Radical reaction of precursors **218** and **219**

Treatment of a 5 mM benzene solution of the diastereomeric mixture of vinylcyclopropanes **218** and **219** with a solution of tri-*n*-butyltin hydride and AIBN in benzene, added *via* syringe pump over 4 h, gave the bicyclic ester **210** as an inseparable 1:1 mixture of diastereomers in excellent yield (**Scheme 2.68**).



Scheme 2.68 *Reagents and conditions*: i) Bu_3SnH, AIBN, PhH (syringe pump 4 h), Δ, 1 h; ii) 25 mol % Bu_3SnH, AIBN, PhH, Δ, 5 h

The proposed mechanism for this rearrangement implies that the reaction should, in principle, be catalytic in the stannyl radical and in practice this was found to be the case. Treatment of a 5 mM solution of vinylcyclopropanes **218** and **219** with 0.25 equiv. of tri-*n*-butyltin hydride gave the bicyclic product **210** in almost the same yield and diastereomeric ratio

2.5.3 Summary

As a result of the divinylcyclopropane rearrangement outlined in **Scheme 2.66** the route to the precursor has a maximum yield of 50%. Ongoing work within the group has focused on a higher yielding diastereoselective preparation of the precursor to fully explore the synthetic utility of the rearrangement chemistry.

EXPERIMENTAL

GENERAL EXPERIMENTAL

NMR Spectra: Proton NMR spectra were run on one of the following machines: Varian Gemini 200 (200 MHz), Bruker DPX200 (200 MHz), Bruker DPX400 (400 MHz) and Bruker AMX500 (500 MHz) spectrometers. Chemical shifts (δ_H) are quoted in parts per million (ppm) downfield of tetramethylsilane, spectra being recorded in deuteriochloroform or deuterium oxide and referenced to residual protonated solvent. Assignments were made on the basis of chemical shift and coupling data, using $^1H-^{13}C$ correlation and $^1H-^1H$ COSY where appropriate. Where the product is obtained as a mixture of diastereomers the two isomers are assigned as separate compounds where possible. Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), app (apparent) and b (broad). Coupling constants (J) are quoted to the nearest 0.5 Hz (200 MHz spectrometers) and 0.1 Hz (400 MHz and 500 MHz spectrometers).

Carbon-13 (δ_C) NMR spectra were recorded on Bruker DPX200 (50.3 MHz), Bruker DPX400 (100.6 MHz) and Bruker AMX500 (125.8 MHz). *C* (4°) refers to a quaternary carbon. Chemical shifts (δ_C) are quoted in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal standard. Assignments were made on the basis of chemical shift using the DEPT sequence and $^1H-^{13}C$ correlation where appropriate.

Infra-red spectra: Infra-red spectra were recorded on either a Perkin-Elmer 1750 or a Perkin-Elmer Paragon 1000 Fourier Transform spectrometer as a thin film on sodium chloride plates or in the form of a potassium bromide disc. Absorptions (ν_{max}) are reported in wavenumbers (cm^{-1}) with the abbreviations: w (weak), m (medium), s (strong) and b (broad).

Mass spectra: Low resolution mass spectra were recorded on a Masslab Trio-1 GCMS spectrometer or a Micromass Autospec 500, using direct chemical ionisation (CI) with ammonia as the reagent gas or electron impact (EI) or on a Micromass Platform 1 spectrometer using atmospheric pressure chemical ionisation (A.P.C.I.) from a mixed solvent system [MeOH:MeCN:water, 40:40:20]. High resolution mass spectra were recorded by the EPSRC National Mass Spectrometry Service in Swansea. *m/z* values are reported in Daltons and are followed by their percentage abundance in parentheses. For peaks other than MH^+ and MNH_4^+, only those with a percentage abundance greater than 10 % are quoted.

Chromatography techniques: Thin layer chromatography (t.l.c) was performed on Merck DC-Alufolien $60F_{254}$ 0.2 mm pre-coated plates or Polygram® SIL G/UV_{254} 0.2 mm pre-coated plates. Product spots were visualised by the quenching of UV fluorescence (λ_{max}= 254 nm) and subsequently developed using either 5% (w/v) *dodeca*-molybdophosphoric acid in ethanol, 5% (w/v) potassium permanganate in 0.5% aq. K_2CO_3 solution, 5% (w/v) ammonium molybdate and 0.2% (w/v) ceric sulfate in 5% aq. H_2SO_4 solution, 0.3% (w/v) ninhydrin and 3% (v/v) acetic acid in *n*-butanol, or 6% (w/v) vanillin and 1% (v/v) conc. H_2SO_4 in ethanol as appropriate. Retention factors (R_f) are reported with the solvent system used in parentheses.

Flash column chromatography was carried out on silica gel [Merck silica gel 60 (230-400 mesh ASTM)] employing the method of Still *et al.*[207]

Solvents: DCM, DMF, benzene, toluene and methanol were obtained by distillation from calcium hydride under argon. DME and ether were distilled from calcium hydride under argon followed by lithium aluminium hydride and stored over sodium wire. Chloroform was distilled from

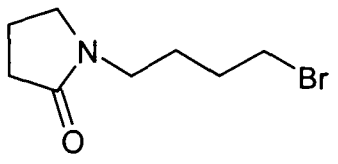
phosphorous pentoxide and stored over potassium hydroxide. *tert*-Butanol was distilled from potassium carbonate under argon. THF was obtained dry and oxygen free by distillation from sodium benzophenone ketyl under argon. 'petrol' refers to that fraction of light petroleum ether boiling in the range 30-40 °C and was distilled before use. Benzene for radical reactions, was degassed by passing a rapid flow of argon through it for 30–90 minutes, depending on scale.

Reagents: *N*,*N*-Diisopropylamine, pyridine and triethylamine were distilled from and stored over potassium hydroxide. Sodium hydride was washed with 3 × THF and dried under high vacuum prior to use unless otherwise stated. Cyclohexanone was passed through a short column of silica gel and distilled under reduced pressure prior to use. *N*,*N*-Diethylaniline was dried by heating with acetic anhydride at reflux for 4 h and then distilled under argon. 4Å powdered molecular sieves were activated under high vacuum at 200°C for 2h prior to use. The purity of tri-*n*-butyltin hydride was determined by ^{1}H NMR spectroscopy (200 MHz, C_6D_6), by examination of the relative integration of the Sn**H** peak (at δ_H 4.68) and the butyl peaks. All other reagents were used as supplied by the manufacturer.

Reactions: Reactions were conducted under an inert atmosphere of argon, unless otherwise stated.

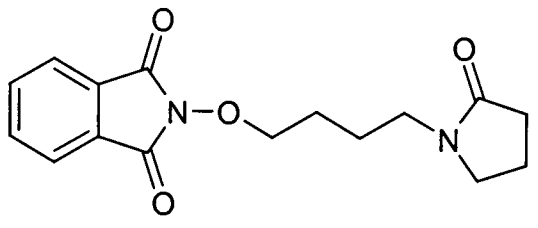
Melting points: Melting points were measured on a Griffin Melting Point Apparatus and are uncorrected.

1-(4-Bromobutyl)-2-pyrrolidinone 114



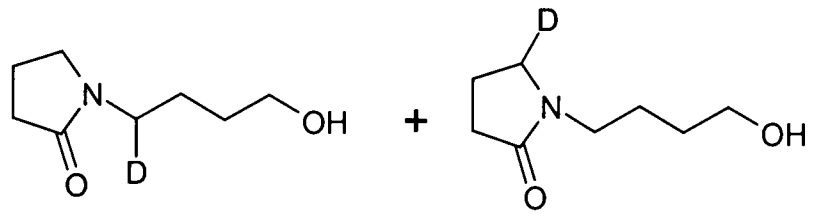
A solution of 1,4-dibromobutane (7.62 mL, 62.5 mmol) and 2-pyrrolidinone (1.94 mL, 25 mmol) in THF (10 mL) was added dropwise over 0.75 h to a suspension of pulverised KOH (1.59 g, 27.5 mmol) and tetrabutylammonium bromide (1.63 g, 5 mmol) in THF (25 mL) and the mixture stirred at RT for 18 h. After filtering, the filtrate was concentrated *in vacuo* to leave a colourless oil. The residue was re-dissolved in DCM (35 mL) and washed successively with water (35 mL) and brine (35 mL) re-extracting between washings with DCM (3 × 35 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (3:97 MeOH:chloroform) gave the bromide **114** as a colourless oil (2.93 g, 53%). R_f 0.57 (1:9 MeOH:chloroform); Accurate mass: Found 220.0338, $C_8H_{15}{}^{79}BrNO$ (MH^+) requires 220.0337; ν_{max}/cm^{-1} (thin film) 3465bm, 2935m, 2867m, 1682s (C=O), 1495m, 1463s, 1427s, 1290s, 1267s, 736m; δ_H (400 MHz, $CDCl_3$) 1.65 (2H, app. quin., *J* 7.1, C**H**$_2$CH$_2$Br), 1.82 (2H, app. quin., *J* 7.1, C**H**$_2$CH$_2$CH$_2$Br), 2.00 (2H, app. quin., *J* 7.3, COCH$_2$C**H**$_2$), 2.35 (2H, t, *J* 8.1, COC**H**$_2$), 3.28 (2H, t, *J* 7.1, C**H**$_2$Br), 3.36 (2H, t, *J* 7.1, NC**H**$_2$(CH$_2$)$_2$Br), 3.41 (2H, t, *J* 6.5, CO(CH$_2$)$_2$C**H**$_2$); δ_C (100.6 MHz, $CDCl_3$) 17.9 (COCH$_2$**C**H$_2$), 25.6, 29.7 (2 × **C**H$_2$), 31.0 (CO**C**H$_2$), 33.4 (**C**H$_2$Br), 41.3 (N**C**H$_2$(CH$_2$)$_2$Br), 46.9 CO(CH$_2$)$_2$**C**H$_2$), 175.0 (C=O); *m/z* (CI, NH_3) 222 ($M^{81}BrH^+$, 100%), 220 ($M^{79}BrH^+$, 98), 158 (50), 140 (41), 98 (27).

4-(2-Oxopyrrolidin-1-yl)butyloxyphthalimide 115



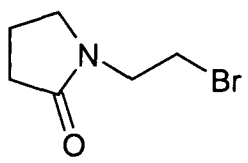
To a solution of *N*-hydroxyphthalimide (1.01 g, 6 mmol) and NaH (0.24 g of a 60% dispersion in mineral oil, 6 mmol) in DMF (13 mL) at RT was added a solution of the bromide **114** (1.10 g, mmol) in THF (2 mL) *via* cannula. The mixture was heated at 60°C for 18 h and then diluted with water (25 mL) and the aqueous layer extracted with EtOAc (3 × 25 mL). The combined organics were washed with sat. aq. $NaHCO_3$ solution (30 mL) and the separated aqueous layer extracted with EtOAc (2 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product as a yellow oil. Column chromatography on silica (1:6 → 1:8 → 1:10 petrol:EtOAc → EtOAc) yielded a colourless oil, which still contained excess DMF. Heating at 60°C under reduced pressure (0.05 mmHg) for 4 h gave the title compound **115** as a pale yellow solid (1.15 g, 76%). R_f 0.12 (1:4 petrol:EtOAc, UV active); m.p. 61–62 °C; Accurate mass: Found 303.1341, $C_{16}H_{19}N_2O_4$ (MH^+) requires 303.1345; ν_{max}/cm^{-1} (KBr disk) 3470m, 2940m, 1785s, 1744s, 1662s, 1469s, 1361s, 1286s, 1188s, 1124s, 995s, 879s; δ_H (400 MHz, $CDCl_3$) 1.72–1.83 (4H, m, C**H₂**C**H₂**CH_2O), 2.02 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.37 (2H, t, *J* 8.1, CO**CH₂**), 3.35 (2H, t, *J* 6.8, N**CH₂**$(CH_2)_2O$), 3.43 (2H, t, *J* 7.1, $CO(CH_2)_2C\mathbf{H_2}$), 4.21 (2H, t, *J* 5.8, O**CH₂**), 7.71–7.84 (4H, m, ArC**H**); δ_C (100.6 MHz, $CDCl_3$) 17.8, 23.5, 25.5 (3 × **C**H_2), 31.0 ($COCH_2$), 41.9 ($NCH_2(CH_2)_2O$), 47.0 ($CO(CH_2)_2CH_2$), 77.8 (OCH_2), 123.4 (*m*-Ar**C**H), 128.8 (*i*-Ar**C**), 134.4 (*o*-Ar**C**H), 163.5 (**C**ON**C**O), 175.0 (**C**=O); *m/z* (CI, NH_3) 303 (MH^+, 100%), 158 (61), 156 (37).

1-[1-d_1-(4-Hydroxybutyl)]-2-pyrrolidinone 116 and 1-(4-hydroxybutyl)-5-d_1-2-pyrrolidinone 117



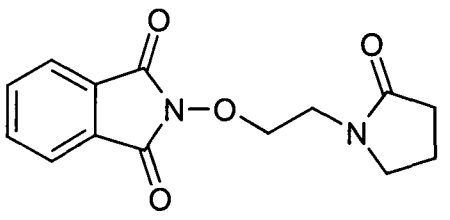
A degassed solution the alokoxyphthalimide **115** (100 mg, 0.33 mmol), AIBN (8.3 mg, 0.05 mmol) and tri-*n*-butyltin deuteride (97 μL, 0.36 mmol) in benzene (6.6 mL) was heated at reflux for 3 h and then concentrated *in vacuo*. Column chromatography on silica (3:97 MeOH:chloroform) gave the deuterated products **116** and **117** as a 1:1 inseparable mixture (33 mg, 63%). R_f 0.30 (1:9 MeOH:DCM); Accurate mass: Found 159.1240, $C_8H_{15}DNO_2$ (MH^+) requires 159.1244; ν_{max}/cm^{-1} (thin film) 3388bm, 2936m, 2868m, 1667s, 1464m, 1426m, 1292m, 1061m, 753s; δ_H (400 MHz, $CDCl_3$) 1.47–1.61 (4H, m, C**H₂**C**H₂**CH_2OH), 1.99 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.35 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.27 (H/2, app. quin., *J* 8.0, N**H**D$(CH_2)_3OH$) overlays 3.28 (2H/2, t, *J* 7.1, $NC\mathbf{H_2}(CH_2)_3OH$), 3.35 (H/2, app. quin., *J* 7.0, $CO(CH_2)_2C\mathbf{H}D$) overlays 3.36 (2H/2, t, *J* 7.0, $CO(CH_2)_2C\mathbf{H_2}$), 3.61 (2H, t, *J* 6.1, $OC\mathbf{H_2}$); δ_D (38.4 MHz, $CHCl_3$) 3.32 (NCH**D**$(CH_2)_3OH$ and $CO(CH_2)_2CH\mathbf{D}$); δ_C (100.6 MHz, $CDCl_3$) 17.8 ($COCH_2\mathbf{C}H_2$), 23.6, 29.5 (2 × $\mathbf{C}H_2$), 31.1 ($CO\mathbf{C}H_2$), 41.9 (t, *J* 21.1, N**C**HD$(CH_2)_3$), 42.2 (N**C**$H_2(CH_2)_3$), 46.8 (t, *J* 21.6, $CO(CH_2)_2\mathbf{C}HD$), 47.1 ($CO(CH_2)_2\mathbf{C}H_2$), 62.0 (**C**H_2OH), 175.2 (**C**=O) [also shows peaks at 17.7, 23.7] ; *m/z* (CI, NH_3) 160 (15%), 159 (MH^+, 100), 158 (21), 99 (20).

1-(2-Bromoethyl)-2-pyrrolidinone[138] 119



To a solution of 1-(2-hydroxyethyl)-2-pyrrolidinone (3.00 g, 22.76 mmol) in toluene (45 mL) was added PBr_3 (0.91 mL, 9.39 mmol) and the mixture stirred at 60°C for 16 h. After concentrating *in vacuo* the mixture was dissolved in DCM (100 mL) and washed with sat. aq. $NaHCO_3$ solution (100 mL). The separated aqueous phase was extracted with DCM (2 × 100 mL) and the combined organics dried ($MgSO_4$) and concentrated *in vacuo* to give the bromide **119** as a colourless oil (4.03 g, 93%). R_f 0.59 (1:9 MeOH:chloroform); ν_{max}/cm^{-1} (thin film) 3442bm, 2974m, 1690s, 1494s, 1463s, 1425s, 1288s, 1141m, 1048m, 976m, 753s; δ_H (200 MHz, $CDCl_3$) 2.00–2.20 (2H, m, $COCH_2CH_2$), 2.44 (2H, t, *J* 8.1, $COCH_2$), 3.46–3.56 (4H, m, 2 × NCH_2), 3.70 (2H, t, *J* 6.4, CH_2Br); *m/z* (EI) 193 ($M^{81}Br^+$, 3%), 191 ($M^{79}Br^+$, 3%), 98 (100), 71 (24), 69 (25).

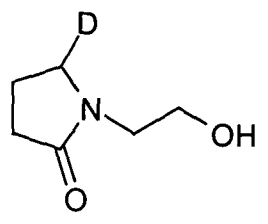
2-(2-Oxopyrrolidin-1-yl)ethoxyphthalimide 120



To a stirred solution of *N*-hydroxyphthalimide (2.10 g, 12.50 mmol) and NaH (300 mg, 12.50 mmol) in DMF (30 mL) was added a solution of the bromide **119** (2.00 g, 10.41 mmol) in DMF (5 mL) *via* cannula. After 16 h at 60°C the mixture was diluted with water (100 mL) and the aqueous

phase extracted with EtOAc (3 × 100 mL). The combined organics were washed with sat. aq. $NaHCO_3$ solution (250 mL), and the separated aqueous phase extracted with EtOAc (2 × 200 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Heating at 60°C under reduced pressure (0.03 mmHg) for 3.5 h gave the title compound **120** as a yellow solid (2.36 g, 83%). R_f 0.64 (1:9 MeOH:chloroform, UV active); m.p. 98–99 °C; Accurate mass: Found 275.1035, $C_{14}H_{15}N_2O_4$ (MH^+) requires 275.1032; ν_{max}/cm^{-1} (KBr disk) 2929m, 1794s, 1728s, 1690s, 1494m, 1465m, 1376s, 1296s, 1188s, 1131s, 987s, 874s; δ_H (400 MHz, $CDCl_3$) 2.11 (2H, app. quin., *J* 7.6, $COCH_2CH_2$), 2.44 (2H, t, *J* 8.1, $COCH_2$), 3.68 (2H, t, *J* 4.9,OCH_2CH_2), 3.73 (2H, t, *J* 7.0, $CO(CH_2)_2CH_2$), 4.36 (2H, t, *J* 4.9, OCH_2), 7.73–7.85 (4H, m, 4 × ArCH); δ_C (100.6 MHz, $CDCl_3$) 18.3 ($COCH_2CH_2$), 30.8 ($COCH_2$), 41.2 (NCH_2CH_2O), 48.8 ($CO(CH_2)_2CH_2$), 77.6 (OCH_2), 123.6 (*m*-ArCH), 128.8 (*i*-ArC), 134.6 (*o*-ArCH), 163.3 (CONCO), 175.6 (C=O); *m/z* (CI, NH_3) 275 (MH^+, 15%), 151 (19), 134 (89), 130 (30), 128 (45), 117 (14), 114 (32), 103 (19), 100 (100), 86 (46), 70 (11).

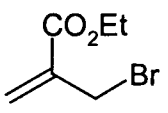
1-(2-Hydroxyethyl)-5-d_1-2-pyrrolidinone 121



A degassed solution of the alkoxyphthalimide **120** (85 mg, 0.31 mmol), AIBN (7.7 mg, 0.05 mmol) and tri-*n*-butyltin deuteride (0.089 mL, 0.33 mmol) in benzene (6.2 mL) was heated at reflux for 16 h. A further portion of AIBN (5.1 mg, 0.03 mmol) was added and after one hour tri-*n*-butyltin

deuteride (0.045 mL, 0.17 mmol) was added and the mixture stirred for a further 2 h and then concentrated *in vacuo*. After evaporation of the solvent column chromatography on silica (chloroform → 1:99 MeOH:chloroform → 1:49 MeOH:chloroform) gave the deuterated product **121** as a colourless oil (30 mg, 74%) still contaminated with some tin species. R_f 0.48 (1:9 MeOH:DCM); Accurate mass: Found 131.0928, $C_6H_{11}DNO_2$ (MH^+) requires 131.0931; ν_{max}/cm^{-1} (thin film) 3382bm, 2956s, 2923s, 2851s, 1664s, 1464m, 1376m, 1340w, 1261m, 1168w, 1074m, 1022m, 866w, 801w; δ_H (400 MHz, $CDCl_3$) 2.07 (2H, app. q, *J* 8.0, $COCH_2C\mathbf{H_2}$), 2.44 (2H, t, *J* 8.0, $COC\mathbf{H_2}$), 2.95 (1H, bs, O**H**), 3.44 (2H, t, *J* 5.1, $NC\mathbf{H_2}$), 3.47–3.50 (1H, m, NC**H**D), 3.78 (2H, t, *J* 5.1, $OC\mathbf{H_2}$); δ_D (38.4 MHz, $CHCl_3$) 3.52 (NCH**D**); δ_C (100.6 MHz, $CDCl_3$) 18.1 ($COCH_2\mathbf{C}H_2$), 31.0 ($COCH_2$), 46.4 (NCH_2), 48.3 (m, N**C**HD), 61.0 (OCH_2), 176.7 (**C**=O); *m/z* (CI, NH_3) 131 (MH^+, 100%), 130 (35), 99 (27).

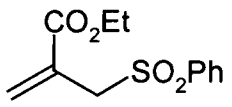
Ethyl 2-(bromomethyl)acrylate[38] 123



To a mixture of triethyl phosphonoacetate (11.0 g, 49.10 mmol) and aq. formaldehyde (20 mL of a 37% solution) at RT was slowly added sat. aq. K_2CO_3 solution (12 g in 20 mL). When the addition of base was complete, the mixture was stirred for a further hour, then sat. aq. NH_4Cl solution (25 mL) was carefully added to quench the reaction. The resulting mixture was partitioned between brine (15 mL) and ether (15 mL). The collected organic portions were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude hydroxyacrylate **122** as a colourless liquid.

To the crude hydroxyacrylate **122** in dry ether (25 mL) at −10°C was added in one portion PBr_3 (4.70 mL, 49.5 mmol) *via* syringe; the solution became turbid immediately. The reaction mixture was allowed to warm to RT and stirred for a further 16 h then was re-cooled to −10°C and water (25 mL) added carefully *via* syringe. The resulting mixture was extracted with hexane (3 × 25 mL) and the combined organic layers washed with brine (15 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give the bromide **123** as a pale yellow oil (8.44 g, 89%). R_f 0.52 (1:2 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2982m, 1724s, 1370m, 1330s, 1310s, 1187s, 1118m, 1026m, 960m, 811m, 722m; δ_H (200 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1, CH_3), 4.20 (1H, s, CH_2Br), 4.29 (2H, q, *J* 7.1, CH_2CH_3), 5.96 (1H, s, H_ZHC=), 6.35 (1H, s, H_EHC=); *m/z* (CI, NH_3) 212 ($M^{81}BrNH_4^+$, 95%), 210 ($M^{79}BrNH_4^+$, 100), 149 (23), 147 (23), 132 (68), 130 (16), 115 (28), 114 (23), 113 (21), 69 (54).

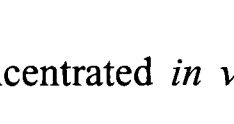
Ethyl 2-(phenylsulfonylmethyl)acrylate[38] 124



A mixture of the bromide **123** (3.25 g, 16.80 mmol) and sodium benzene sulfinate (5.55 g, 33.1 mmol) in dry MeOH (27 mL) was heated at reflux for 15 h. Concentration of the cooled mixture *in vacuo* gave a white slush which was dissolved in a mixture of water (25 mL), 5% aq. $NaHCO_3$ solution (50 mL) and chloroform (25 mL). The layers were separated and the aqueous layer extracted with chloroform (3 × 25 mL). The combined organic portions were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:4 ether:petrol) gave the sulfone **124** as a colourless viscous oil (3.03 g, 71%). R_f 0.08 (1:2 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film)

2987m, 1719s, 1631m, 1586w, 1448s, 1414m, 1370m, 1309s, 1248s, 1193s, 1147s, 1086s, 1025m, 967m, 901m, 858m, 793m; δ_H (200 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, C**H**$_3$), 4.02 (2H, q, *J* 7.1, C**H**$_2$CH$_3$), 4.18 (2H, s, C**H**$_2$SO$_2$Ph), 5.94 (1H, s, **H**$_Z$HC=), 6.53 (1H, s, **H**$_E$HC=), 7.56–7.70 (3H, m, Ar), 7.85–7.90 (2H, m, Ar); *m/z* (CI, NH_3) 272 (MNH_4^+, 100%), 255 (MH^+, 35).

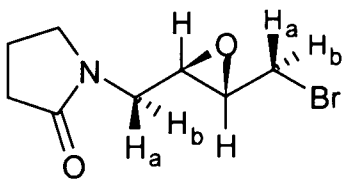
Ethyl 2-(tributylstannylmethyl)acrylate[38] 125



A solution of the sulfone **124** (2.04 g, 8.02 mmol), tri-*n*-butyltin hydride (5.53 mL, 16.00 mmol) and AIBN (50 mg, 0.30 mmol) in degassed benzene (11 mL) was heated at reflux. After 45 mins the reaction mixture was cooled and concentrated *in vacuo*. Column chromatography on silica (1:99 DCM:petrol) gave the stannyl methacrylate **125** as a colourless oil (1.91g, 59%). R_f 0.67 (1:2 EtOAc:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2925s, 1713s, 1614s, 1464s, 1320s, 1299s, 1179s, 1096s, 909m, 693m; δ_H (200 MHz, $CDCl_3$) 0.82–0.98 (15H, m, 3 × SnC**H**$_2$(CH$_2$)$_2$C**H**$_3$), 1.24–1.61 (15H, m, 3 × SnCH$_2$(C**H**$_2$)$_2$CH$_3$, OCH$_2$C**H**$_3$), 1.98[1] (2H, s, C**H**$_2$SnBu$_3$), 4.20 (2H, q, *J* 7.1, C**H**$_2$CH$_3$), 5.30[1] (1H, d, *J* 1.6, **H**$_Z$HC=), 5.83[1] (1H, d, *J* 1.6, **H**$_E$HC=); *m/z* (EI) 351 ($M^{124}Sn - C_4H_9$, 25%), 349 ($M^{122}Sn - C_4H_9$, 26), 347 ($M^{120}Sn - C_4H_9$, 100), 346 ($M^{119}Sn - C_4H_9$, 51), 345 ($M^{118}Sn - C_4H_9$, 82), 343 ($M^{116}Sn - C_4H_9$, 55), 233 (27), 177 (33), 121 (15).

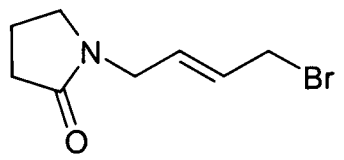
[1] These resonances displayed ^{119}Sn satellites

(*E*)-2-Bromomethyl-3-(2-oxopyrrolidinyl)methyloxirane 126



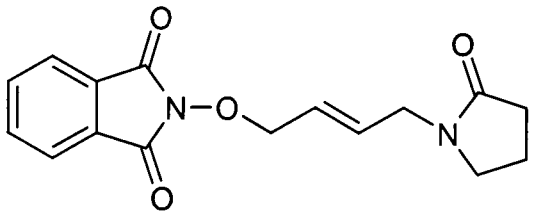
To a suspension of NaH (35 mg, 1.45 mmol) in DMF (1 mL) at 0°C was added a solution of 2-pyrrolidinone (87 μL, 1.09 mmol) in DMF (1 mL) and the mixture was stirred for 0.33 h. A solution of (*E*)-2,3-*bis*(bromomethyl)oxirane[38] (500 mg, 2.17 mmol) in DMF (1 mL) was added. After 16 h at RT the mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (4:1 → 6:1 → 8:1 EtOAc:petrol → EtOAc) on half of the crude product gave epoxide **126** as a yellow solid (90 mg, 71% based on 0.55 mmol of crude product). R_f 0.30 (1:9 MeOH:DCM); m.p. 73–74°C; Accurate mass: Found 234.0133, $C_8H_{13}{}^{79}BrNO_2$ (MH^+) requires 234.0130; ν_{max}/cm^{-1} [1] (KBr disk) 2926m, 1682s (C=O), 1505m, 1463s, 1443s, 1368m, 1286m, 1226m, 943w, 904s, 727m; δ_H (400 MHz, $CDCl_3$) 2.04 (2H, app. quin., *J* 7.5, $COCH_2C\mathbf{H_2}$), 2.38 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.02 (1H, ddd, *J* 6.1, 3.4, 2.0, $OC\mathbf{H}CH_2N$), 3.09 (1H, ddd, *J* 5.8, 5.8, 2.0, $OC\mathbf{H}CH_2Br$), 3.22 (1H, dd, *J* 14.6, 6.1, $NCH_a\mathbf{H_b}$), 3.35 (1H, d, *J* 11.1, 5.8, $C\mathbf{H_a}H_bBr$), 3.38 (1H, d, *J* 11.1, 5.8, $CH_a\mathbf{H_b}Br$), 3.43–3.54 (2H, m, $CO(CH_2)_2C\mathbf{H_2}$), 3.73 (1H, dd, *J* 14.6, 3.4, $NC\mathbf{H_a}H_b$); δ_C (100.6 MHz, $CDCl_3$) 18.0 ($COCH_2\mathbf{C}H_2$), 30.5 ($CO\mathbf{C}H_2$), 31.5 ($\mathbf{C}H_2Br$), 43.7 ($N\mathbf{C}H_2CH$), 48.3 ($N\mathbf{C}H_2CH_2$), 55.1 , 58.1 (2 × $OC\mathbf{H}$), 175.3 ($\mathbf{C}$=O); *m/z* (CI, NH_3) 236 ($M^{81}BrH^+$, 39%), 234 ($M^{79}BrH^+$, 41), 156 (28), 140 (100), 138 (27), 100 (61), 86 (37).

(*E*)-1-(4-Bromo-2-butenyl)-2-pyrrolidinone 132



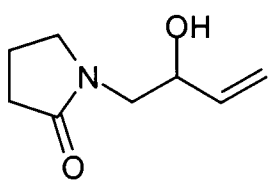
To a suspension of NaH (0.37 g, 15.31 mmol) in DMF (25 mL) at 0°C was added a solution of 2-pyrrolidinone (0.91 mL, 11.51 mmol) in DMF (5 mL). After 20 mins (*E*)-1,4-dibromo-2-butene (4.98 g, 23.03 mmol) was added. After 16 h at RT the mixture was diluted with water (150 mL) and extracted with EtOAc (3 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:1 EtOAc:petrol) gave the product contaminated with DMF. Heating at 60°C under reduced pressure (0.03 mmHg) for 6 h gave the title compound allylic bromide **132** a yellow oil (1.62 g, 64%). R_f 0.55 (1:9 MeOH:chloroform, UV active); Accurate mass: Found 218.0181, $C_8H_{13}{}^{79}BrNO$ (MH^+) requires 218.0179; ν_{max}/cm^{-1} (thin film) 3459w, 2950w, 1682s, 1495w, 1463m, 1424m, 1360w, 1289m, 1207m, 970m; δ_H (400 MHz, $CDCl_3$) 2.03 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.41 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.35 (2H, t, *J* 7.1, $CO(CH_2)_2C\mathbf{H_2}$), 3.91 (2H, d, *J* 6.1, $C\mathbf{H_2}Br$), 3.94 (2H, d, *J* 7.5, $NC\mathbf{H_2}CH$), 5.68 (1H, dt, *J* 15.2, 6.1, $C\mathbf{H}CH_2Br$), 5.84 (1H, dt, *J* 15.2, 7.5, $NCH_2C\mathbf{H}$); δ_C (100.6 MHz, $CDCl_3$) 17.8 ($COCH_2\mathbf{C}H_2$), 30.8 ($CO\mathbf{C}H_2$), 31.6 ($\mathbf{C}H_2Br$), 43.6 ($N\mathbf{C}H_2CH$), 46.8 ($N\mathbf{C}H_2CH_2$), 129.5 ($\mathbf{C}HCH_2Br$), 129.6 ($NCH_2\mathbf{C}H$), 174.8 ($\mathbf{C}$=O); *m/z* (CI, NH_3) 220 ($M^{81}BrH^+$, 98%), 218 ($M^{79}BrH^+$, 100), 156 (17), 138 (82).

4-(2-Pyrrolidin-1-yl)-2-butenyloxyphthalimide 133



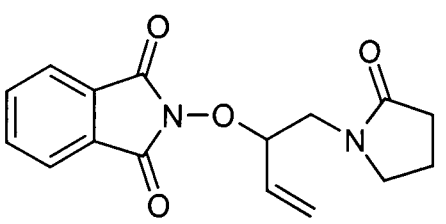
To a stirred solution of *N*-hydroxyphthalimide (463 mg, 2.75 mmol) in DMF (3 mL) was added AgOAc (502 mg, 2.98 mmol). After 5 mins a solution of the allylic bromide **132** (500 mg, 2.29 mmol) in DMF (2 mL) was added and the mixture heated at 60°C for 16 h. The deep red solution formed a yellow precipitate. The mixture was then diluted with water (50 mL) and extracted with EtOAc (3 × 25 mL). The combined organics were washed with sat. aq. $NaHCO_3$ solution (100 mL), back-extracting with EtOAc (2 × 75 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound **133** as a yellow solid (626 mg, 91%). R_f 0.37 (1:9 MeOH:EtOAc, UV active); m.p. 68–72°C; Accurate mass: Found 301.1193, $C_{16}H_{17}N_2O_4$ (MH^+) requires 301.1188; ν_{max}/cm^{-1} (KBr disk) 3054m, 2952m, 1787s, 1728s, 1671s, 1488m, 1422m, 1373s, 1287s, 1262s, 1187s, 1136s, 991s, 961s, 882s; δ_H (400 MHz, $CDCl_3$) 1.95 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.35 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.26 (2H, t, *J* 7.1, $CO(CH_2)_2C\mathbf{H_2}$), 3.85 (2H, d, *J* 5.7, $NC\mathbf{H_2}CH$), 4.66 (2H, d, *J* 7.0, $OC\mathbf{H_2}$), 5.71 (1H, dt, *J* 15.5, 5.7, $OCH_2C\mathbf{H}$), 5.88 (1H, dt, *J* 15.5, 7.0, $NCH_2C\mathbf{H}$), 7.71–7.83 (4H, m, 4 × ArC**H**); δ_C (100.6 MHz, $CDCl_3$) 17.7 ($COCH_2\mathbf{C}H_2$), 30.7 ($CO\mathbf{C}H_2$), 43.7 ($N\mathbf{C}H_2CH$), 46.8 ($N\mathbf{C}H_2CH_2$), 77.6 ($O\mathbf{C}H_2$), 123.5 (*m*-Ar**C**H), 126.0 ($NCH_2\mathbf{C}H$), 128.7 (*i*-Ar**C**), 133.0 ($OCH_2\mathbf{C}H$), 134.6 (*o*-Ar**C**H), 163.6 (**C**ON**C**O), 174.9 (**C**=O); *m/z* (CI, NH_3) 318 (MNH_4^+, 17%), 302 (32), 301 (MH^+, 100), 154 (13), 138 (50).

1-(2-Hydroxy-3-butenyl)-2-pyrrolidinone[144] 134



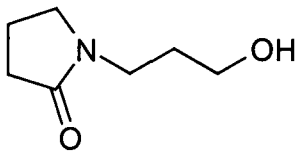
To butadiene monoxide (2.93 mL, 35.7 mmol) was added 2-pyrrolidinone (2.77 mL, 35.5 mmol) and 1 drop of 30% aq. KOH. The mixture was heated in a sealed tube at 150°C for 20 h. After cooling to room temperature the crude mixture was fractionally distilled (collecting the fraction that boiled between 115–135°C @ 0.6 mmHg) to give the allylic alcohol **134** as a colourless oil (3.64 g, 66%). R_f 0.09 (3:97 MeOH:chloroform); ν_{max}/cm^{-1} (thin film) 3356bm, 2881m, 1665s, 1495m, 1466m, 1424m, 1289m, 1135m, 1077m, 995m, 926m; δ_H (400 MHz, $CDCl_3$) 2.06 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.42 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.39 (2H, app. d, *J* 5.5, $NC\mathbf{H_2}CH$), 3.51 (2H, t, *J* 7.1, $NC\mathbf{H_2}CH_2$), 4.36 (1H, ddd, *J* 5.5, 5.5, 5.5, C**H**OH), 5.19 (1H, d, *J* 10.5, $CH{=}C\mathbf{H}_{E}CH_Z$), 5.37 (1H, d, *J* 17.2, $CH{=}CH_EC\mathbf{H}_Z$), 5.87 (1H, ddd, *J* 17.2, 10.5, 5.5, C**H**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 18.3 ($COCH_2\mathbf{C}H_2$), 30.9 ($CO\mathbf{C}H_2$), 49.4 , 49.6 (2 × $N\mathbf{C}H_2$), 71.8 (**C**HOH), 116.0 ($CH{=}\mathbf{C}H_2$), 138.0 **C**H=CH_2), 176.9 (**C**=O); *m/z* (CI, NH_3) 156 (MH^+, 100%), 138 (13), 98 (11), 86 (68).

1-Ethenyl-2-(2-oxopyrrolidin-1-yl)ethoxyphthalimide 131



To a solution of tributylphosphine (0.53 mL, 2.13 mmol) in THF (8 mL) at 0°C was added diisopropylazodicarboxylate (0.40 mL, 1.93 mmol). After 1 h a solution of the allylic alcohol **134** (150 mg, 0.97 mmol) in THF (2 mL) was added, followed by *N*-hydroxyphthalimide (326 mg, 1.93 mmol). The reaction mixture was stirred at 0°C for 1 h, then at RT for 3 h and then concentrated *in vacuo*. Column chromatography on silica (1:2 petrol:EtOAc) gave the alkoxyphthalimide **131** as a yellow oil (152 mg, 52%). R_f 0.14 (1:4 petrol:EtOAc, UV active); Accurate mass: Found 301.1187, $C_{16}H_{17}N_2O_4$ (MH^+) requires 301.1188; ν_{max}/cm^{-1} (thin film) 3503m, 3086w, 2979m, 1787s, 1732s, 1682s, 1493w, 1467m, 1425m, 1380s, 1288s, 1268m, 1188s, 1127m, 1082m, 1016m, 973s, 959s, 878s, 702s; δ_H (400 MHz, $CDCl_3$) 2.01–2.08 (2H, m, $COCH_2C\mathbf{H_2}$), 2.35–2.49 (2H, m, $COC\mathbf{H_2}$), 3.64 (2H, app. d, *J* 5.6, $NC\mathbf{H_2}CH$) overlays 3.62–3.74 (2H, m, $NC\mathbf{H_2}CH_2$), 4.80 (1H, ddd, *J* 9.1, 5.6, 5.6, OC**H**), 5.28 (1H, d, *J* 10.2, $CH{=}C\mathbf{H}_{E}CH_Z$), 5.31 (1H, d, *J* 17.2, $CH{=}CH_EC\mathbf{H}_Z$), 5.92 (1H, ddd, *J* 17.2, 10.1, 9.1, C**H**=CH_2), 7.70–7.80 (4H, m, 4 × ArC**H**); δ_C (100.6 MHz, $CDCl_3$) 18.3 ($COCH_2\mathbf{C}H_2$), 30.8 ($CO\mathbf{C}H_2$), 45.0 ($N\mathbf{C}H_2CH$), 48.9 ($N\mathbf{C}H_2CH_2$), 88.3 (O**C**H), 122.7 (=$\mathbf{C}H_2$), 123.5 (*m*-Ar**C**H), 128.6 (*i*-Ar**C**), 132.8 (**C**H=CH_2), 134.5 (*o*-Ar**C**H), 163.6 (**C**ON**C**O), 175.7 (**C**=O); *m/z* (CI, NH_3) 301 (MH^+, 100), 156 (12), 154 (12), 138 (11), 100 (17), 86 (11).

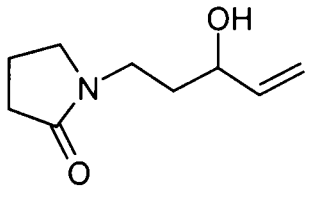
1-(3-Hydroxypropyl)-2-pyrrolidinone 137



γ-Butyrolactone (3.84 mL, 0.05 mol) and 3-amino-1-propanol (4.67 g, 0.06 mol) were heated at 210°C for 26 h with continuous removal of water by distillation. Column chromatography of the

crude mixture (3:97 MeOH:DCM) gave the alcohol **137** as a yellow oil (6.66 g, 93%). R_f 0.10 (3:97 MeOH:DCM); ν_{max}/cm^{-1} (thin film) 3396bs, 2938s, 1668s, 1497s, 1427s, 1299s, 1162m, 1063s, 946w, 853w; δ_H (200 MHz, $CDCl_3$), 1.68 (2H, app. quin., *J* 5.8, C**H**$_2$CH$_2$OH), 2.04 (2H, app. quin., *J* 7.6, COCH$_2$C**H**$_2$), 2.41 (2H, t, *J* 8.2, COC**H**$_2$), 3.36–3.44 (4H, m, 2 × NC**H**$_2$), 3.52 (2H, t, *J* 5.8, C**H**$_2$OH); *m/z* (CI, NH_3) 144 (MH^+, 100%), 98 (12), 76 (41).

1-(3-Hydroxy-4-butenyl)-2-pyrrolidinone 139

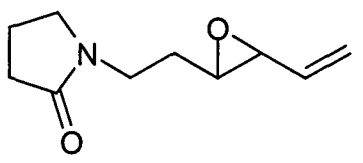


To a mixture of the alcohol **137** (1.00 g, 7 mmol), *N*-methylmorpholine *N*-oxide (1.26 g, 10.5 mmol) and activated powdered 4Å molecular sieves (3.50 g) in DCM (14 mL) was added TPAP (0.063 g, 0.175 mmol) in one portion. After 2 h at RT the mixture was filtered through a short pad of silica (14 mL) using DCM then EtOAc as eluent. The solution was concentrated *in vacuo* to give the crude aldehyde **138** as a yellow oil (475 mg). R_f 0.37 (1:9 MeOH:DCM) δ_H (400 MHz, $CDCl_3$) 1.94 (2H, app. quin., *J* 7.6, COCH$_2$C**H**$_2$), 2.27 (2H, t, *J* 8.1, COC**H**$_2$), 2.66 (2H, t, *J* 6.5, C**H**$_2$CHO), 3.34 (2H, t, *J* 7.1, CO(CH$_2$)$_2$C**H**$_2$), 3.52 (2H, t, *J* 6.5, NC**H**$_2$CH$_2$CHO), 9.71 (1H, t, *J* 1.4, C**H**O).

To a solution of the crude aldehyde **138** (400 mg, ≤ 5.89 mmol) in THF (3 mL) at 0°C was added vinyl magnesium bromide (5.7 mL of a 1.0 M solution in THF, 5.70 mmol) and the mixture was allowed to warm to RT over 1.5 h. The solvent was removed *in vacuo* and sat. aq. NH_4Cl solution (25 mL) was added to the residue. The aqueous solution was extracted with EtOAc (5 × 25 mL)

and the combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (3:97 MeOH:DCM) gave the allylic alcohol **139** compound as a colourless oil (27 mg, 3% over two steps). R_f 0.09 (3:97 MeOH:DCM); ν_{max}/cm^{-1} (thin film) 3388bm, 2917s, 2849s, 1652s, 1464m, 1292m, 923w, 668w; δ_H (400 MHz, $CDCl_3$) 1.56–1.64 (1H, m, C**H**HCH), 1.71–1.79 (1H, m, CH**H**CH), 2.05 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.41 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.16 (1H, ddd, *J* 14.4, 4.9, 4.9, NC**H**HCH_2CH), 3.35–3.49 (2H, m, $NC\mathbf{H_2}(CH_2)_2$) 3.72 (1H, ddd, *J* 14.4, 9.9, 4.9, NCH**H**CH_2CH), 4.01–4.05 (1H, m, C**H**OH), 5.09 (1H, d, *J* 10.5, CH=C$\mathbf{H}_E$$CH_Z$), 5.26 (1H, d, *J* 17.0, CH=CH_EC$\mathbf{H}_Z$), 5.87 (1H, ddd, *J* 17.0, 10.5, 5.5, C**H**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 17.9 ($COCH_2\mathbf{C}H_2$), 30.8 ($CO\mathbf{C}H_2$), 34.3 ($\mathbf{C}H_2$CHOH), 39.5 ($N\mathbf{C}H_2CH_2CH$), 47.6 ($N\mathbf{C}H_2(CH_2)_2$), 68.8 (**C**HOH), 114.2 (=$\mathbf{C}H_2$), 140.1 **C**H=CH_2), 176.2 (**C**=O); *m/z* (CI, NH_3) 170 (MH^+, 45%), 152 (100), 142 (93), 133(18).

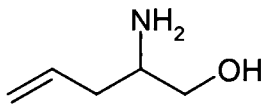
2-Vinyl-3-(2-oxopyrrolidinyl)ethyl oxirane 140



To a solution of the alcohol **137** (1.00 g, 7 mmol), *N*-methylmorpholine *N*-oxide (1.26 g, 10.5 mmol) and activated powdered 4Å molecular sieves (3.5 g) in DCM (14 mL) was added TPAP (0.063 g, 0.175 mmol) in one portion. After 2 h at RT the mixture was filtered through a short pad of silica (14 mL) using DCM then EtOAc as eluent. The solution was concentrated *in vacuo* to give the crude aldehyde **138** and NMO as a 1:1 mixture (2.02 g). Data as above.

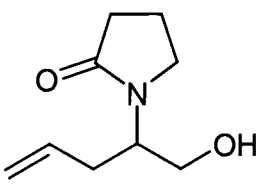
To a suspension of diphenylsulfonium tetrafluoroborate (200 mg, 0.64 mmol) in THF (10 mL) at –78°C was added *tert*-butyl lithium (0.38 ml of a 1.7 M solution in pentane, 0.65 mmol). After 15 mins a solution of the crude aldehyde **138** (314 mg of a 45% mixture with NMO, 1.09 mmol) in THF (1 mL) was added and the mixture was stirred at –78°C for 15 mins, then allowed to warm to RT over 1 h. The reaction mixture was diluted with water (7 mL) and extracted with ether (4 × 10 mL). The combined organics were dried (K_2CO_3), filtered and concentrated *in vacuo* to give the crude product (292 mg). Column chromatography (3:97 MeOH:DCM) gave the epoxide **140** as a colourless oil (113 mg, 57% over two steps) and as an inseparable 85:15 mixture of diastereomers. R_f 0.56 (1:9 MeOH:DCM); Accurate mass: Found 182.1180, $C_{10}H_{16}NO_2$ (MH^+) requires 182.1181; ν_{max}/cm^{-1} (thin film) 3467m, 2928m, 1670s (C=O), 1496m, 1466m, 1426m, 1367w, 1290m, 1184w, 989m, 930m, 873m, 802w; δ_H (400 MHz, $CDCl_3$) 1.68–1.94 (2H, m, OCHC**H**$_2$), 1.95–2.06 (2H, m, COCH$_2$C**H**$_2$), 2.32–2.42 (2H, m, COC**H**$_2$), 2.87 (0.3H, ddd, *J* 6.7, 4.6, 2.1, NC**H**$_2$CH$_2$CH, minor diastereomer), 3.08–3.14 (0.85H, m, OC**H**CH$_2$, major diastereomer), 3.35–3.46 (3.85H, m, OC**H**CH$_2$ minor diastereomer, OC**H**CH, NC**H**$_2$(CH$_2$)$_2$, NC**H**$_2$CH$_2$CH major diastereomer) 5.25–5.29 (0.3H, m, CH=C**H**$_2$ minor diastereomer), 5.36 (0.85H, dd, *J* 10.5, 0.7, CH=C**H**$_E$CH$_Z$ major diastereomer), 5.43–5.59 (1H, m, C**H**=CH$_2$ minor diastereomer, CH=CH$_E$C**H**$_Z$ major diastereomer), 5.69 (0.85H, ddd, *J* 17.4, 10.5, 7.0, C**H**=CH$_2$ major diastereomer); δ_C (100.6 MHz, $CDCl_3$) 17.8 (COCH$_2$**C**H$_2$), 26.0 (OCH**C**H$_2$), 30.9 (CO**C**H$_2$), 39.8 (N**C**H$_2$CH$_2$CH), 47.3 (N**C**H$_2$(CH$_2$)$_2$), 56.6 (O**C**H), 58.2 (O**C**H), 120.6 (=**C**H$_2$), 132.1 (**C**H=CH$_2$), 175.1 (**C**=O), peaks are also visible for the minor diastereomer at 18.0 (COCH$_2$**C**H$_2$), 30.4 (CO**C**H$_2$), 39.6 (N**C**H$_2$-CH$_2$CH), 47.3 (N**C**H$_2$(CH$_2$)$_2$), 58.1(O**C**H), 119.5 (=**C**H$_2$), 135.8 (**C**H=CH$_2$); *m/z* (CI, NH_3) 204 (MNa^+, 15%), 182 (MH^+, 100%).

2-Amino-4-penten-1-ol[147] 145



To a suspension of $LiAlH_4$ (3.07 g, 76.9 mmol) in dry THF (125 mL) was added carefully 2-amino-4-pentenoic acid (3.60 g, 31.3 mmol) and the mixture was heated at reflux for 16 h. After cooling to RT the mixture was diluted with ether (375 mL) and water (25 mL) carefully added to precipitate the aluminium salts. The supernatant liquid was decanted and the remaining aluminium residues washed with THF (5 × 50 mL). The combined organics were filtered, concentrated *in vacuo* and then distilled under reduced pressure (78°C @ 3 mmHg) to give the amino alcohol **145** as a colourless oil (2.62 g, 83%). R_f 0.10 (1:4 MeOH:DCM); ν_{max}/cm^{-1} (thin film) 3280bs, 3076bs, 2914s, 1640s, 1589s, 1438s, 1360m, 1254w, 1118m, 1060s, 995s, 917s, 843s; δ_H (400 MHz, $CDCl_3$) 1.96–2.03 (1H, m, CH_2=CHC**H**H), 2.17–2.23 (1H, m, CH_2=CHCH**H**), 2.63 (3H, bs, N**H**$_2$, O**H**), 2.86–2.91 (1H, m, NC**H**), 3.28–3.33 (1H, m, C**H**HOH), 3.54–3.58 (1H, m, CH**H**OH), 5.06–5.10 (2H, m, CH=C**H**$_2$), 5.69–5.80 (1H, m, C**H**=CH_2); *m/z* (CI, NH_3) 103 (13%), 102 (MH^+, 100%).

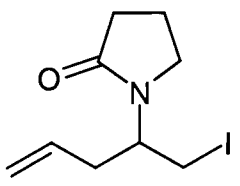
1-(1-Hydroxy-4-penten-2-yl)-2-pyrrolidinone 146



A mixture of γ-butyrolactone (5.22 mL, 67.23 mmol) and the alcohol **145** (1.36 g, 13.45 mmol) was heated in a sealed tube at 220°C for 20 h. Reduced pressure distillation (138–142°C @ 0.3

mmHg), followed by column chromatography on silica (1:9 MeOH:EtOAc) gave the alcohol **146** as a pale yellow oil (1.02 g, 45%). R_f 0.42 (1:4 MeOH:EtOAc); Accurate mass: Found 170.1184, $C_9H_{16}NO_2$ (MH^+) requires 170.1181; ν_{max}/cm^{-1} (thin film) 3382bs, 2948m, 1661s, 1492w, 1463m, 1440m, 1426m, 1290m, 1057w, 999w, 921w; δ_H (400 MHz, $CDCl_3$) 1.92–2.19 (2H, m, $COCH_2C\mathbf{H_2}$), 2.21–2.42 (4H, m, $COC\mathbf{H_2}$, $CH_2{=}CHC\mathbf{H_2}$), 3.34 (1H, dt, *J* 8.0, 5.5, NC**H**H), 3.76 (1H, dt, 8.0, 6.0, NCH**H**), 3.58–3.73 (2H, m, $C\mathbf{H_2}OH$), 4.05–4.12 (1H, m, NC**H**), 5.03–5.11 (2H, m, $CH{=}C\mathbf{H_2}$), 5.73 (1H, dddd, *J* 17.5, 10.4, 6.2, 6.2, C**H**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 18.3 ($COCH_2\mathbf{C}H_2$), 31.5 ($CO\mathbf{C}H_2$), 32.8 ($CH_2{=}CH\mathbf{C}H_2$), 44.3 ($N\mathbf{C}H_2$), 54.0 ($\mathbf{C}H_2OH$), 62.9 (N**C**H), 117.4 ($CH{=}\mathbf{C}H_2$), 134.3 (**C**H=CH_2), 176.5 (**C**=O); *m/z* (CI, NH_3) 172 (30%) 171 (17), 170 (MH^+, 100), 152 (81), 128 (28).

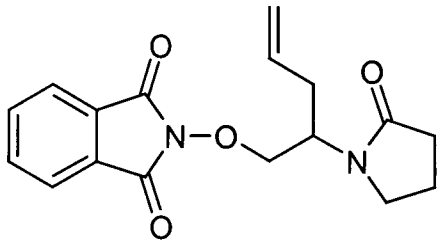
1-(1-Iodo-4-penten-2-yl)-2-pyrrolidinone 147



To a solution of the alcohol **146** (500 mg, 2.95 mmol), triphenylphosphine (939 mg, 3.54 mmol) and imidazole (284 mg, 4.14 mmol) in a 3:1 ether:CH_3CN mixture (40 mL) at 0°C was added iodine (974 mg, 3.84 mmol) in one portion and the reaction was allowed to warm to RT. After 3 h at RT the mixture was diluted with water (100 mL) and extracted with EtOAc (3 × 100 mL). The organic layers were washed with sat. aq. $Na_2S_2O_4$ solution (150 mL) and water (150 mL), re-extracting between washings with EtOAc. The combined organics were dried ($MgSO_4$) and

concentrated *in vacuo*. Column chromatography on silica (1:99 MeOH:EtOAc) gave the iodide **147** as a yellow oil (650 mg, 79%). R_f 0.57 (1:4 MeOH:EtOAc); Accurate mass: Found 280.0199, $C_9H_{15}INO$ (MH^+) requires 280.0198; ν_{max}/cm^{-1} (thin film) 2975w, 2951w, 1682s, 1642m, 1489w, 1460m, 1422s, 1286s, 1269m, 1228w, 1185w, 934w, 919m; δ_H (400 MHz, $CDCl_3$) 1.94–2.11 (2H, m., $COCH_2CH_2$), 2.29–2.48 (4H, m, $COCH_2$, $CH_2=CHCH_2$), 3.22 (1H, dd, *J* 10.4, 9.2, CHHI), 3.28–3.41 (3H, m, CHHI, NCH_2), 4.27 (1H, dddd, *J* 9.2, 9.2, 5.5, 5.5, NCH), 5.05–5.12 (2H, m, $CH=CH_2$), 5.69 (1H, dddd, *J* 17.0, 10.0, 6.5, 6.5, $CH=CH_2$); δ_C (100.6 MHz, $CDCl_3$) 6.4 (CH_2I), 18.3 ($COCH_2CH_2$), 31.3 ($COCH_2$), 36.5 ($CH_2=CHCH_2$), 42.9 (NCH_2), 52.1 (NCH), 118.0 ($CH=CH_2$), 133.7 ($CH=CH_2$), 175.4 (C=O); *m/z* (CI, NH_3) 282 (16%) 280 (MH^+, 100), 238 (24), 170 (23) 152 (60).

2-(2-Oxopyrrolidin-1-yl)-4-pentenyloxyphthalimide 143



Method 1

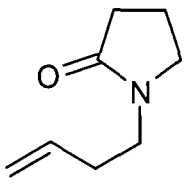
To a suspension of NaH (22 mg of a 60 % dispersion in mineral oil, 0.54 mmol) in DMF (0.5 mL) was added *N*-hydroxyphthalimide (90 mg, 0.54 mmol). After 1.5 h at room temperature a solution of the iodide **147** (75 mg, 0.27 mmol) in DMF (0.5mL) was added and the mixture heated at 60°C. After 16 h sat. aq. $NaHCO_3$ solution (10 mL) was added and the mixture extracted with EtOAc (3 × 10 mL). The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* and the mixture

placed on a high vacuum line at 40°C to remove the excess DMF. Column chromatography on silica (1:4 petrol:EtOAc → 1:99 MeOH:EtOAc) gave the alkoxyphthalimide **143** as a yellow oil (69 mg, 81%). R_f 0.54 (1:4 MeOH:EtOAc, UV active); Accurate mass: Found 315.1341, $C_{17}H_{19}N_2O_4$ (MH^+) requires 315.1345; ν_{max}/cm^{-1} (thin film) 2950w, 1789m, 1732s, 1682s, 1466m, 1424m, 1392m, 1372m, 1288m, 1187m, 1130m, 1082m, 1019m, 994m, 923w; δ_H (400 MHz, $CDCl_3$) 1.97–2.08 (1H, m, $COCH_2CHH$), 2.10–2.20 (1H, m, $COCH_2CHH$), 2.36–2.56 (4H, m, $COCH_2$, CH_2=$CHCH_2$), 3.46 (1H, dt, *J* 8.8, 5.5, $NCHH$), 3.76 (1H, dt, 8.8, 6.0, $NCHH$), 4.32 (2H, app. d, *J* 5.6, OCH_2), 4.50 (1H, dddd, *J* 9.2, 5.6, 5.6, 5.6, NCH), 5.09–5.19 (2H, m, CH_2=CH), 5.79 (1H, dddd, *J* 17.0, 10.1, 7.2, 7.2, CH_2=CH), 7.73–7.85 (4H, m, Ar); δ_C (100.6 MHz, $CDCl_3$) 18.4 ($COCH_2CH_2$), 31.3 ($COCH_2$), 32.8 (CH_2=$CHCH_2$), 44.3 (NCH_2), 49.5 (OCH_2), 78.0 (NCH), 118.0 (CH=CH_2), 123.5 (*m*-ArCH), 128.8 (*i*-ArC), 133.7 (CH=CH_2), 134.5 (*o*-ArCH), 163.2 (CONCO), 175.7 (C=O); *m/z* (CI, NH_3) 337 (MNa^+, 20%), 317 (20), 316 (28), 315 (MH^+, 100), 152 (25).

Method 2

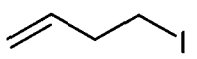
To the alcohol **146** (140 mg, 0.83 mmol) in DCM (7 mL) was added successively polymer supported triphenylphosphine (690 mg, capacity: ~3.0 mmol g^{-1}, 2.07 mmol) and diisopropylazodicarboxylate (420 μL, 2.07 mmol). After 30 mins at RT *N*-hydroxyphthalimide (153 mg, 0.91 mmol) was added and the mixture stirred for 16 h at RT. The mixture was filtered and the resin washed successively with DCM (3 × 5 mL), ether (3 × 5 mL) and DCM (3 × 5 mL). The combined filtrates were concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (1:4 petrol:EtOAc) gave the alkoxyphthalimide **143** as a yellow solid (115 mg, 44%). M.p. 68–72°C.

1-(3-butenyl)-2-pyrrolidinone 148



A degassed solution of the alkoxyphthalimide **143** (98 mg, 0.31 mmol), AIBN (5 mg, 0.031 mmol) and tri-*n*-butyltin hydride (93 μL, 0.34 mmol) in benzene (6.2 mL) was heated at reflux for 16 h and then concentrated *in vacuo*. Column chromatography on silica (1:4 petrol:EtOAc) gave the product of β-scission **148** as colourless oil (24 mg, 56%) and recovered starting material (42 mg, 43%). R_f 0.20 (1:4 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2961m, 2868m, 1735m, 1682s, 1495m, 1464m, 1426m, 1289m, 1265m, 999w, 918m; δ_H (400 MHz, $CDCl_3$) 2.00 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.29 (2H, dt, *J* 7.1, 1.3, CH_2=$CHC\mathbf{H_2}$), 2.38 (2H, t, *J* 8.1, $CO\mathbf{CH_2}$), 3.36 (2H, t, *J* 7.1, $NC\mathbf{H_2}CH_2CH$), 3.38 (2H, t, *J* 7.1, $CO(CH_2)_2C\mathbf{H_2}$), 5.02–5.06 (1H, m, CH=$C\mathbf{H}_E CH_Z$), 5.09 (1H, ddt, *J* 17.0, 1.3, 1.3, CH=$CH_E C\mathbf{H}_Z$), 5.77 (1H, dddd, *J* 17.0, 10.2, 7.1, 7.1, CH_2=$C\mathbf{H}$); δ_C (100.6 MHz, $CDCl_3$) 17.9 ($COCH_2\mathbf{C}H_2$), 31.0 ($CO\mathbf{C}H_2$), 31.8 (CH_2=$CH\mathbf{C}H_2$), 41.8 ($N\mathbf{C}H_2CH_2CH$), 47.2 ($CO(CH_2)_2\mathbf{C}H_2$), 116.8 ($\mathbf{C}H_2$=CH), 135.1 (CH_2=$\mathbf{C}H$), 175.0 ($\mathbf{C}$=O); *m/z* (CI, NH_3) 140 (MH^+, 100%).

4-Iodo-1-butene 151



Method 1

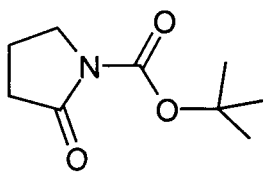
To a solution of triphenylphosphine (10.80 g, 40.8 mmol) in DCM (185 mL) was added imidazole (2.80 g, 40.8 mmol) followed by iodine (10.35 g, 40.8 mmol). A solution of 3-buten-1-ol (2.00 g, 27.2 mmol) in DCM (30 mL) was then added slowly *via* cannula and the resulting solution stirred

at RT for 2.5 h. The crude mixture was then diluted with water (100 mL) and washed successively with sat. aq. $Na_2S_2O_4$ solution (150 mL) and brine (150 mL), extracting between washings with DCM. The combined organics were dried ($MgSO_4$) and carefully concentrated *in vacuo*. Distillation under reduced pressure (68°C @ 160 mmHg) gave the iodide **151** as a colourless oil (3.11 g, 63%). ν_{max}/cm^{-1} (thin film) 3078m, 2978m, 2956m, 1639s, 1425s, 1303m, 1248s, 1178s, 991s, 920s; δ_H (400 MHz, $CDCl_3$) 2.63 (2H, tdddd, *J* 7.1, 7.1, 1.5, 1.5, C**H**$_2$CH$_2$I), 3.19 (2H, t, *J* 7.1, C**H**$_2$I), 5.13 (1H, ddt, *J* 10.6, 1.5, 1.5, CH=C**H**$_E$CH$_Z$), 5.15 (1H, ddt, *J* 16.5, 1.5, 1.5, CH=CH$_E$C**H**$_Z$), 5.72–5.82 (1H, m, C**H**=CH$_2$); *m/z* (EI) 182 (M^+, 23%), 127 (13), 56 (11), 55 (M^+–I, 100).

Method 2

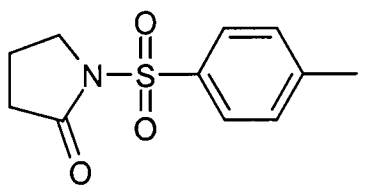
To a saturated solution of NaI (28.31 g, 188.9 mmol) in acetone (113 mL) was added a solution of 4-bromo-1-butene (5.10 g, 37.8 mmol) in acetone (5 mL) and the mixture was heated at reflux for 16 h. After filtration the solvent was removed by distillation and the crude iodide distilled under reduced pressure (68°C @ 160 mmHg) to give the iodide **151** as a colourless oil (2.87 g, 42%). Data as above.

1-*tert*-butoxycarbonyl-2-pyrrolidinone[153] 152



To a solution of 2-pyrrolidinone (2.00 g, 23 mmol) in DCM (46 mL) was added triethylamine (3.21 mL, 23 mmol), di-*tert*-butyl dicarbonate (10.91 mL, 46.1 mmol) and 4-dimethylaminopyridine (2.84 g, 23 mmol) and the resulting yellow solution was stirred at RT for 6.5 h. Concentrating *in vacuo* gave the crude product as a red oil, which after column chromatography on silica (1:19 MeOH:DCM), gave the protected lactam **152** as a yellow oil (4.25 g, 100%). R_f 0.40 (1:1 EtOAc:petrol); ν_{max}/cm^{-1} (thin film) 2980m, 2934m, 1784s, 1750s, 1716s, 1478m, 1459m, 1393m, 1367s, 1312s, 1255s, 1153s, 1045m, 1019m, 940m; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, $C(CH_3)_3$), 1.98 (2H, app. quin., *J* 7.6, $COCH_2CH_2$) 2.49 (2H, t, *J* 8.1, $COCH_2$), 3.73 (2H, t, *J* 7.1, NCH_2); δ_C (100.6 MHz, $CDCl_3$) 17.3 ($COCH_2CH_2$), 28.0 ($C(CH_3)_3$), 32.9 ($COCH_2$), 46.4 (NCH_2), 82.7 ($C(CH_3)_3$), 150.2 (OC=O) 174.2 (C=O); *m/z* (CI, NH_3) 203 (MNH_4^+, 17%), 186 (MH^+, 15), 171 (13), 147 (47), 130 (13), 107 (42), 95 (11), 94, 100).

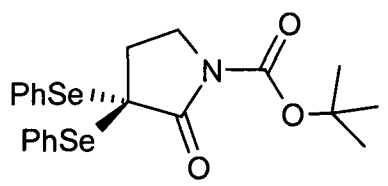
N-*p*-Toluenesulfonyl-2-pyrrolidinione[154] 153



To a suspension of NaH (576 mg, 14.4 mmol) in ether (60 mL) was added 2-pyrrolidinone (890 μL, 12 mmol). The mixture was stirred for 1h at RT and *p*-toluenesulfonylchloride (2.80 g, 14.4 mmol) added. After 16h at RT the mixture was filtered and concentrated *in vacuo*. Column chromatography on silica (1:99 MeOH:DCM → EtOAc) gave the tosylated lactam **153** as a white solid (1.21 g, 34%). R_f 0.28 (1:1 EtOAc:petrol); m.p. 139–140°C [lit.,[154] 141–142°C] ν_{max}/cm^{-1} (KBr disk) 3099m, 3058m, 2996m, 2914m, 1732s, 1687m, 1595s, 1491m, 1459m, 1420m 1355s,

1300s, 1221s, 1173s, 1087s, 1069s, 1021m, 962s,; δ_H (400 MHz, $CDCl_3$) 2.04–2.11 (2H, app. quin., *J* 7.5, $COCH_2CH_2$), 2.43 (2H, t, *J* 8.0, $COCH_2$) overlaying 2.44 (3H, s, CH_3), 3.90 (2H, t, *J* 7.0, NCH_2), 7.34 (2H, d, *J* 8.5, ArCH), 7.93 (2H, d, *J* 8.5, ArCH); *m/z* (CI, NH_3) 262 (11%), 242 (11), 240 (MH^+, 100), 155 (24)

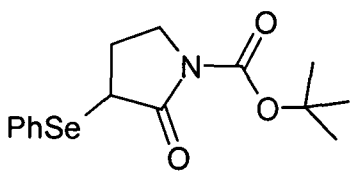
4-4-*Bis*-phenylselanyl-2-oxopyrrolidine-1-carboxylic acid *tert*-butyl ester 154



To a stirred solution of the lactam **152** (250 mg, 1.35 mmol) in THF (6 mL) at –78°C was added LHMDS (2.16 mL of a 1.0M solution in hexanes, 2.16 mmol). After 20 mins phenylselenenyl chloride (289 mg, 1.48 mmol) was added and the resulting solution stirred at –78°C for a further 40 mins then allowed to warm to room temperature over 120 mins. The mixture was then diluted with ether (15 mL) and washed successively with water (15 mL) and brine (30 mL), re-extracting between washings with ether (3 × 15 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give a green oil. Column chromatography on silica (1:9 ether:petrol) gave the di-selenide **154** as a pale pink solid (100 mg, 27% based on PhSeCl). R_f 0.69 (1:2 EtOAc:petrol); m.p. 89.5–90.5°C; ν_{max}/cm^{-1} (KBr disk) 2975w, 1725s, 1708s, 1474m, 1436m, 1364s, 1325s, 1297m, 1256m, 1201m, 1151s, 1080m, 983m; δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, $C(CH_3)_3$), 2.23 (2H, t, *J* 6.8, $COCH_2$), 3.28 (2H, t, *J* 6.8, NCH_2), 7.31–7.44 (6H, m, *m*-Ar, *p*-Ar), 7.72 (4H, d, *J* 7.3, *o*-Ar); δ_C (100.6 MHz, $CDCl_3$) 28.0 ($C(CH_3)_3$), 32.8 ($COCH_2$), 43.7 (NCH_2),

51.4 **C**SePh, 83.1 (**C**$(CH_3)_3$), 127.8 (*i*-Ar**C**), 129.1 (Ar**C**H), 129.7 (Ar**C**H), 137.3 (Ar**C**H), 149.9 (O**C**=O) 171.0 (**C**=O); *m/z* (CI, NH_3) 398 ($M^{80}Se^{80}SeH^+$–^{t}BuOCO, 15%), 396 ($M^{80}Se^{78}SeH^+$–^{t}BuOCO, 13), 303 (12), 289 (13), 272 (27), 257 (44), 242 (47), 240 (100), 219 (14), 123 (36), 87 (48), 85 (38).

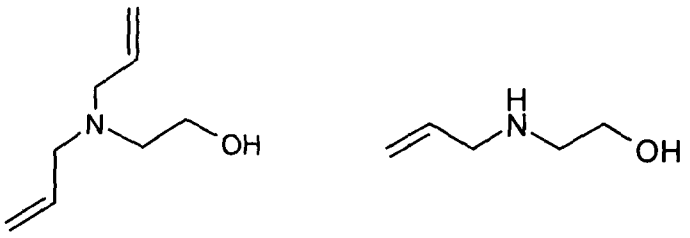
4-phenylselanyl-2-oxopyrrolidine-1-carboxylic acid *tert*-butyl ester 155



To a stirred solution of the lactam **152** (93 mg, 0.5 mmol) in THF (2.0 mL) at –78°C was added LHMDS (0.55 mL of a 1.0M solution in THF, 0.55 mmol). After 1 h at –78°C a solution of phenylselenenyl chloride (117 mg, 0.6 mmol) in THF (1.2 mL) was added *via* cannula and the resulting solution stirred at –78°C for 2 h, allowed to warm to –20°C over 1 h and then re-cooled to –78°C. After quenching with pH 6.8 buffer solution (3.2 mL) the mixture was allowed to warm until the ice had just melted and then poured into EtOAc (25 mL) . The organic phase was separated and the aqueous extracted with EtOAc (2 × 10 mL). The combined organics were washed with brine (15 mL), re-extracting with EtOAc (2 × 10mL), then dried (Na_2SO_4) and concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (1:4 ether:petrol) gave the mono-selenide **155** as a colourless oil (79 mg, 46%). R_f 0.51 (1:1 EtOAc:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2979m, 2932w, 1779s, 1742s, 1716s, 1578w, 1478m, 1438m, 1367s, 1311s, 1255s, 1151s, 1022m, 1000m; δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, C(C**H**$_3$)$_3$), 2.07 (1H, dddd, *J* 13.9, 7.8,

4.0, 4.0, COCHCHH) 2.46 (1H, dddd, *J* 13.9, 8.4, 8.4, 8.4 COCHCHH), 3.42 (1H, ddd, *J* 10.9, 8.4, 7.8, NCHH) 3.62 (1H, ddd, *J* 10.9, 8.4, 4.0, NCHH) 3.94 (1H, dd, *J* 8.4, 4.0, COCH) 7.28–7.38 (3H, m, *m*-Ar, *p*-Ar), 7.68 (2H, d, *J* 7.2, *o*-Ar); δ_C (100.6 MHz, $CDCl_3$) 26.1 ($COCH_2$), 28.0 ($C(CH_3)_3$), 42.0 CSePh, 44.8 (NCH_2), 83.0 ($C(CH_3)_3$), 126.9 (*i*-ArC), 128.8 (ArCH), 129.2 (ArCH), 135.8 (ArCH), 149.9 (OC=O) 172.5 (C=O); *m/z* (CI, NH_3) 340 ($M^{80}SeH^+$, 7%), 341 (11), 340 ($M^{78}SeH^+$, 7), 303 ($M^{80}SeNH_4^+$–^{t}Bu, 37), 301 ($M^{78}SeNH_4^+$–^{t}Bu, 18), 244 ($M^{82}SeH^+$–^{t}BuOCO, 18), 242 ($M^{80}SeH^+$–^{t}BuOCO, 100), 240 ($M^{78}SeH^+$–^{t}BuOCO, 53), 238 ($M^{76}SeH^+$–^{t}BuOCO, 21), 218 (54), 192 (21), 147 (26), 103 (15), 87 (72). Also isolated di-selenide (24 mg, 16%)

N,N-Diallylethanolamine 166 and *N*-Allylethanolamine 167



Method 1

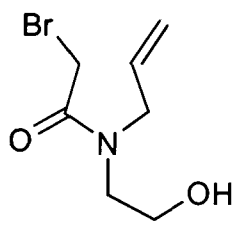
To a solution of ethanolamine (2.52 mL, 41.33 mmol) in DCM (20 mL) was added allylbromide (1.37 mL, 8.27 mmol) and *N,N*-diisopropylethylamine (1.54 mL, 8.68 mmol). After 4 h at RT the mixture was concentrated *in vacuo* and the residue suspended in EtOAc for 1 h, filtered and concentrated *in vacuo*. Column chromatography on silica (1:9 MeOH:EtOAc) gave *N,N*-Diallylethanolamine **166** (579 mg, 50%) and *N*-Allylethanolamine **167** (286 mg, 34%) both as colourless oils. Data for **166**: R_f 0.46 (1:4 MeOH:EtOAc); ν_{max}/cm^{-1} (thin film) 3390bs, 3078s,

2925s, 2883s, 2815s, 1644m, 1447m, 1418s, 1353m, 1333m, 1260m, 1150m, 1052s, 996s, 919s; δ_H (400 MHz, $CDCl_3$) 2.62 (2H, t, *J* 5.5, NC**H**$_2$CH$_2$), 2.74 (1H, bs, O**H**), 3.13 (4H, app. d, *J* 6.5, NC**H**$_2$CH), 3.57 (2H, t, *J* 5.5, C**H**$_2$OH), 5.14–5.20 (4H, m, CH=C**H**$_2$), 5.82 (2H, dddd, *J* 16.8, 10.3, 6.5, 6.5, C**H**=CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 54.3 (N**C**H$_2$CH$_2$), 56.5 (NCH$_2$**C**H), 58.4 (**C**H$_2$OH), 117.9 (CH=**C**H$_2$), 135.2 (**C**H=CH$_2$); *m/z* (CI, NH_3) 142 (MH^+, 100%), 100 (49). Data for **167**: R_f 0.14 (1:4 MeOH:EtOAc); ν_{max}/cm^{-1} (thin film) 3304bs, 3079s, 2917s, 2835s, 1644m, 1456s, 1419m, 1338m, 1151m, 1115s, 1057s, 996s, 920s; δ_H (400 MHz, $CDCl_3$) 2.68 (2H, t, *J* 5.2, NC**H**$_2$CH$_2$), 3.19 (1H, bs, O**H**) overlaying 3.20 (2H, ddd, *J* 6.3, 1.5, 1.5, NC**H**$_2$CH), 3.60 (2H, t, *J* 5.2, C**H**$_2$OH), 5.05 (1H, dddd, 10.4, 1.5, 1.5, 1.5, CH=C**H**$_E$CH$_Z$), 5.13 (1H, dddd, *J* 17.0, 1.5, 1.5, 1.5, CH=CH$_E$C**H**$_Z$), 5.83 (1H, dddd, *J* 17.0, 10.4, 6.3, 6.3, C**H**=CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 50.5 (N**C**H$_2$CH$_2$), 51.9 (NCH$_2$**C**H), 60.9 (**C**H$_2$OH), 116.1 (CH=**C**H$_2$), 136.6 (**C**H=CH$_2$); *m/z* (CI, NH_3) 102 (MH^+, 100%).

Method 2

To allylamine (22.5 mL, 0.2 mol) at reflux was added 2-chloroethanol (6.7 mL, 0.1 mol) and the mixture heated at reflux for 2h. After cooling to RT, NaOH (4.0g, 0.1 mol) was added and the mixture was stirred at RT for 10 mins and then filtered to remove the precipitated NaCl. After concentrating *in vacuo*, the yellow oil was distilled under reduced pressure (34°C @ 0.06 mmHg) to give the *N*-allylethanolamine **167** as a colourless oil (5.29 g, 52%). Data as above.

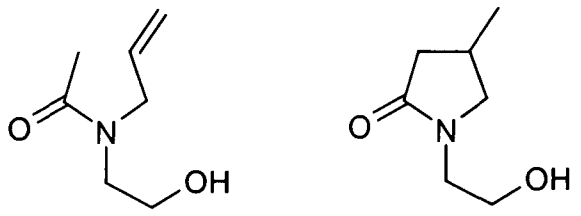
N-Allyl-*N*-(2-hydroxyethyl)-2-bromoacetamide 168



To a solution of the amino alcohol **167** (2.00 g, 19.78 mmol) and triethylamine (4.40 mL, 31.64 mmol) in chloroform (120 mL) at 0°C was added a solution of bromoacetyl bromide (2.16 mL, 24.72 mmol) in chloroform (26 mL) over a period of 20 mins. After warming to RT the mixture was stirred for 90 mins and then water (60 mL) was added and the organic phase separated. The aqueous phase was extracted with chloroform (2 × 60 mL) and the combined organic phases washed with 1N HCl (100 mL) and brine (100 mL), re-extracting between washings with chloroform. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:2 EtOAc:petrol) gave the bromoacetamide **168** as a yellow oil (2.63 g, 60%). R_f 0.28 (1:2 EtOAc:petrol, UV active); Accurate mass: Found 222.0123, $C_7H_{13}{}^{79}BrNO_2$ (MH^+) requires 222.0130; ν_{max}/cm^{-1} (thin film) 3391bm, 2936w, 1749w, 1634s, 1463m, 1418m, 1362w, 1288m, 1210m, 1073m, 995m, 928m; δ_H (400 MHz, $CDCl_3$) major rotamer 1.85 (1H, bs, CH_2OH), 3.55 (2H, app. quin., *J* 5.5, NCH_2CH_2), 3.79–3.82 (2H, m, CH_2OH), 3.87 (2H, s, CH_2Br), 4.08 (2H, ddd, *J* 5.5, 1.5, 1.5, NCH_2CH), 5.19–5.30 (2H, m, $CH=CH_2$), 5.87 (1H, dddd, *J* 17.0, 9.9, 5.5, 5.5, $CH=CH_2$) [peaks for the minor rotamer were observed at: 4.03 (2H, app. d, *J* 5.5, NCH_2CH), 4.06 (2H, s, CH_2Br), 5.73–5.86 (1H, m $CH=CH_2$)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 26.1 (CH_2Br), 49.9 (NCH_2CH_2), 52.5 (NCH_2CH), 61.2 (CH_2OH), 117.6 ($CH=CH_2$), 132.5 ($CH=CH_2$), 168.8 (C=O) [peaks for the minor rotamer were observed at: 27.0 (CH_2Br), 48.2 (NCH_2CH), 50.1 (NCH_2CH_2), 59.7 (CH_2OH), 117.4 ($CH=CH_2$), 132.3 ($CH=CH_2$), 167.7 (C=O)];

m/z (CI, NH_3) 224 ($M^{81}BrH^+$, 68%), 222 ($M^{79}BrH^+$, 66), 206 (24), 204 (24), 167 (20), 166 (28), 165 (25), 164 (29), 144 (12), 142 (45), 126 (12), 114 (35), 102 (100).

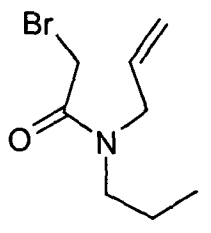
_N_-Allyl-_N_-(2-hydroxyethyl)-acetamide 169 and 1-(2-Hydroxyethyl)-4-methyl-2-pyrrolidinone 170



To a degassed solution of the bromoacetamide **168** (100 mg, 0.45 mmol) in chlorobenzene (45 mL) at 90°C was added a degassed solution of tri-*n*-butyltin hydride (135 μL, 0.50 mmol) and AIBN (7.5 mg, 0.045 mmol) in chlorobenzene (10 mL) *via* syringe pump over a period of 2 h. After a further 1 h the reaction mixture was cooled to RT and *N*-(2-mercaptoethyl)aminomethyl polystyrene resin (200-400 mesh) (1.43 g, capacity: 1.26 mmol g^{-1}, 1.8 mmol) was added and the mixture slowly stirred for 16 h. After filtering, the resin was washed successively with DCM (3 x 6 mL), ether (3 x 6 mL) and DCM (3 x 6 mL) and the combined filtrates were concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (1:4 petrol:EtOAc) gave the directly reduced product **169** (22 mg, 34 %) and cyclised product **170** (36 mg, 56 %) both as colourless oils. Data for **169**: R_f 0.46 (1:4 MeOH:EtOAc); Accurate mass: Found 144.1027, $C_7H_{14}NO_2$ (MH^+) requires 144.1025; ν_{max}/cm^{-1} (thin film) 3390bm, 2934m, 1624s, 1481s, 1419s, 1364m, 1246m, 1187w, 1061m, 1029m, 985m, 925m, 860w; δ_H (400 MHz, $CDCl_3$) major rotamer 2.10 (3H, s, CH_3), 3.51 (2H, t, *J* 5.1, NCH_2CH_2), 3.75 (2H, t, *J* 5.1, CH_2OH), 3.95 (2H, ddd, *J* 5.0, 1.3, 1.3, NCH_2CH), 5.18 (1H, dd, *J* 17.1, 1.3, $CH{=}CH_ECH_Z$), 5.23 (1H, dd, *J* 10.2, 1.3, $CH{=}CH_ECH_Z$), 5.81 (1H, dddd, *J* 17.1, 10.2, 5.0, 5.0, $CH{=}CH_2$) [peaks for the minor rotamer were observed at: 2.17

(3H, s, C**H**$_3$) 3.24 (2H, t, *J*=5.6 Hz, NC**H**$_2$CH$_2$), 4.01 (2H, app. d, *J*=5.9, NC**H**$_2$CH), 5.11–5.16 (2H, m, CH=C**H**$_2$), 5.74–5.81 (1H, m, C**H**=CH$_2$)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 21.4 (**C**H$_3$), 49.6 (N**C**H$_2$CH$_2$), 52.5 (N**C**H$_2$CH), 62.0 (**C**H$_2$OH), 116.9 (CH=**C**H$_2$), 132.3 (**C**H=CH$_2$), 173.2 (**C**=O) [peaks for the minor rotamer were observed at 21.7 (**C**H$_3$), 48.0 (N**C**H$_2$CH), 50.0 (N**C**H$_2$CH$_2$), 59.9 (**C**H$_2$OH), 117.1 (CH=**C**H$_2$), 133.3 (**C**H=CH$_2$), 171.3 (**C**=O)]; *m/z* (CI, NH_3) 144 (MH^+, 100%), 125 (75). Data for **170**: R_f 0.35 (1:4 MeOH:EtOAc); Accurate mass: Found 144.1024, $C_7H_{13}NO_2$ (MH^+) requires 144.1025; ν_{max}/cm^{-1} (thin film) 3380bs, 2962s, 2939s, 2874s, 1668s, 1494s, 1455s, 1427m, 1380m, 1360m, 1304m, 1275s, 1065s, 1010m, 864w; δ_H (400 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.6, C**H**$_3$), 2.08 (1H, dd, *J* 16.4, 6.9, COC**H**H), 2.45–2.54 (1H, m, COCH$_2$C**H**), 2.59 (1H, dd, *J* 16.4, 8.5, COCH**H**), 3.08 (1H, dd, *J* 9.6, 6.1, NC**H**HCH), 3.43 (2H, t, *J* 5.0, NC**H**$_2$CH$_2$), 3.60 (1H, dd, *J* 9.6, 7.8, NCH**H**CH), 3.78 (2H, t, *J* 5.0, C**H**$_2$OH); δ_C (100.6 MHz, $CDCl_3$) 19.7 (**C**H$_3$), 26.7 (**C**H), 39.4 (CO**C**H$_2$), 45.9 (N**C**H$_2$CH$_2$), 55.9 (N**C**H$_2$CH), 60.4 (**C**H$_2$OH), 176.0 (**C**=O); *m/z* (CI, NH_3) 144 (MH^+, 100%), 125 (75).

_N_-Allyl-_N_-propyl-2-bromoacetamide 172

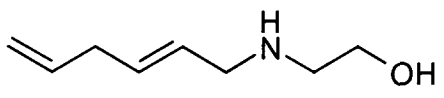


To allylamine (22.5 mL, 0.2 mol) at reflux was added 1-chloropropane (9.0 mL, 0.1 mol) and the mixture was heated at reflux for a further 4 h. ^{1}H NMR analysis showed that no reaction had occurred so the reaction mixture was transferred to a Parr Pressure Vessel and heated at 100°C for

10 h. After cooling to RT, NaOH (4.0 g, 0.1 mol) was added and the mixture atirred at RT for 5 mins and then filtered to remove the precipitated NaCl. Heating at 110°C to remove excess allylamine gave the crude hydrochloride salt **171** as a yellow crystalline solid. δ_H (400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.0, C**H**$_3$), 1.87 (2H, app. sextet, *J* 7.5, $CH_3C\mathbf{H}_2$), 2.85 (2H, t, *J* 8.0, $NC\mathbf{H}_2CH_2$), 3.58 (2H, d, *J* 7.5, $NC\mathbf{H}_2CH$), 5.42–5.49 (2H, m, CH=C**H**$_2$), 6.07 (1H, dddd, *J* 17.0, 10.0, 7.5, 7.5, C**H**=CH_2).

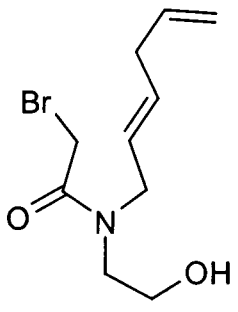
To a suspension of the crude hydrochloride salt **171** (500 mg, ~3.69 mmol) and *N*,*N*-diisopropylaminoethyl polystyrene resin (4.0 g, capacity: 3.72 mmol g^{-1}, 14.88 mmol) in $CDCl_3$ (25 mL) was added a solution of bromoacetyl bromide (401 μL, 4.61 mmol) in $CDCl_3$ (5 mL). After 20 h the reaction mixture was filtered and the resin washed successively with DCM (3 × 25 mL), ether (3 × 25 mL) and DCM (3 × 25 mL) and the combined organics concentrated *in vacuo*. Column chromatography on silica (1:6 EtOAc:petrol) gave the bromoacetamide **172** as a yellow oil (196 mg, 25% based on 3.69 mmol starting material). R_f 0.08 (1:2 petrol:EtOAc, UV active); Accurate mass: Found 219.0254, $C_8H_{15}{}^{79}BrNO$ (MH^+) requires 219.0259; ν_{max}/cm^{-1} (thin film) 3084w, 2967m, 2935m, 2876, 1652s, 1456s, 1382m, 1345m, 1248m, 1225m, 1205m, 1124m, 993m, 925m; δ_H (400 MHz, $CDCl_3$) major rotamer 0.89–0.96 (3H, m, C**H**$_3$), 1.55–1.69 (2H, m, $CH_3C\mathbf{H}_2$), 3.25–3.34 (2H, m, $NC\mathbf{H}_2CH_2$), 3.97–4.01 (2H, m, $NC\mathbf{H}_2CH$), 4.04 (2H, s, C**H**$_2$Br), 5.16–5.26 (2H, m, CH=C**H**$_2$), 5.73–5.88 (1H, m C**H**=CH_2) [peaks for the minor rotamer were observed 4.10 (2H, s, C**H**$_2$Br)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 11.2 (**C**H_3), 20.6 ($CH_3\mathbf{C}H_2$), 41.3 (**C**H_2Br), 48.2 ($N\mathbf{C}H_2CH_2$), 50.4 ($N\mathbf{C}H_2CH$), 117.1 (CH=**C**H_2), 132.9 (**C**H=CH_2), 166.7 (**C**=O) [peaks for the minor rotamer were observed at 11.2 (**C**H_3), 22.1 ($CH_3\mathbf{C}H_2$), 41.1 (**C**H_2Br), 48.1 ($N\mathbf{C}H_2CH_2$), 49.4 ($N\mathbf{C}H_2CH$), 117.4 (CH=**C**H_2), 132.6 (**C**H=CH_2), 166.7 (**C**=O)]; *m/z* (CI, NH_3) 222 ($M^{81}BrH^+$, 24%), 220 ($M^{79}BrH^+$, 24), 178 (44), 176 (100), 100 (50).

2-Hexa-2,5-dienylaminoethanol 176



To a solution of NaI (7.72 g, 0.051 mol) in acetonitrile (75 mL) was added successively chlorotrimethylsilane (6.60 mL, 0.051 mol), water (459 μL, 0.026 mol) and 1,5-hexadien-3-ol (6.00 mL, 0.051 mol). After 3 h at RT ethanolamine (31.09 mL, 0.51 mol) and diisopropylethylamine (10.69 mL, 0.061 mol) were added and the mixture stirred for a further 16 h. The reaction mixture was then diluted with EtOAc (125 mL) and washed with 10% aq. $Na_2S_2O_4$ solution (200 mL). The organic layer was separated and the aqueous layer extracted with EtOAc (4 × 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:10:90 conc. aq. NH_3:MeOH:EtOAc) gave the amino alcohol **176** as a yellow oil (4.08g, 57%). R_f 0.25 (1:20:79 conc. aq. NH_3:MeOH:EtOAc); Accurate mass: Found 142.1230, $C_8H_{16}NO$ (MH^+) requires 142.1232; ν_{max}/cm^{-1} (thin film) 3306bs, 2916s, 1638m, 1454m, 1051s, 973s, 912s; δ_H (400 MHz, $CDCl_3$) 2.72–2.78 (4H, m, NC**H**$_2$CH$_2$, CH$_2$=CHC**H**$_2$), 2.89 (2H, bs, O**H**, N**H**), 3.21 (2H, d, *J* 5.9, NC**H**$_2$CH), 3.64 (2H, t, *J* 5.3, C**H**$_2$OH), 4.96–5.04 (2H, m, C**H**$_2$=CH), 5.49–5.64 (2H, m, NCH$_2$C**H**=C**H**), 5.80 (1H, dddd, *J* 16.7, 10.3, 6.4, 6.4, CH$_2$=C**H**); δ_C (100.6 MHz, $CDCl_3$) 36.4 (CH$_2$=CH**C**H$_2$), 50.5 (N**C**H$_2$CH$_2$), 51.1 (N**C**H$_2$CH), 60.7 (**C**H$_2$OH), 115.3 (**C**H$_2$=CH), 128.9 (NCH$_2$**C**H=), 130.5 (NCH$_2$CH=**C**H), 136.6 (CH$_2$=**C**H); *m/z* (CI, NH_3) 142 (MH^+, 100%).

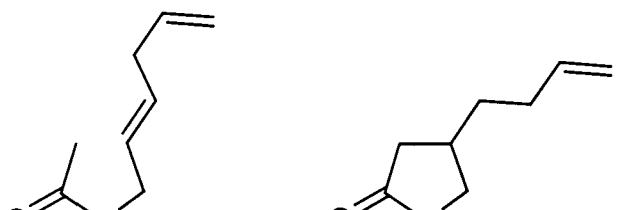
2-Bromo-*N*-hexa-1,5-dienyl-*N*-(2-hydroxyethyl)acetamide 157



To a solution of the amino alcohol **176** (5.00 g, 35.4 mmol) and triethylamine (7.90 mL, 56.7 mmol) in chloroform (210 mL) at 0°C was added a solution of bromoacetyl bromide (3.93 mL, 44.2 mmol) in chloroform (50 mL) over 10 mins. After warming to RT the mixture was stirred for 2 h and then diluted with water (200 mL). The separated organic phase was washed with 1N HCl (200 mL), and brine (200 mL), extracting between washings with chloroform. The combined organics were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (1:3 petrol:EtOAc) gave the bromoacetamide **157** as a yellow solid (4.91g, 53%). R_f 0.37 (1:4 petrol:EtOAc, UV active); m.p. 31–32°C; Accurate mass: Found 262.0440, $C_{10}H_{17}{}^{79}BrNO_2$ (MH^+) requires 262.0443; ν_{max}/cm^{-1} (KBr disk) 3332bm, 2920m, 1634s, 1462s, 1427s, 1361m, 1283m, 1261m, 1165m, 1118m, 1083s, 1064s, 978m, 915m; δ_H (400 MHz, $CDCl_3$) major rotamer 2.76–2.86 (2H, m, CH_2=CHC**H$_2$**), 3.12 (1H, bs, O**H**), 3.52 (2H, t, *J* 5.1, NC**H$_2$**CH_2), 3.74–3.78 (2H, m, C**H$_2$**OH), 3.87 (2H, s, C**H$_2$**Br), 4.02 (2H, dd, *J* 5.5, 1.5, NC**H$_2$**CH), 4.98–5.06 (2H, m, C**H$_2$**=CH), 5.39–5.53 (1H, m, NCH_2C**H**), 5.60–5.70 (1H, m, NCH_2CH=C**H**), 5.74–5.84 (1H, m, CH_2=C**H**) [peaks for minor rotamer were observed at 3.31 (1H, bs, O**H**), 3.49 (2H, t, *J* 5.2, NC**H$_2$**CH_2), 3.97 (2H, d, *J* 6.3, NC**H$_2$**CH) 4.04 (1H, s, C**H$_2$**Br)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 26.2 (**C**H_2Br), 36.1 (CH_2=CH**C**H_2), 49.6 (N**C**H_2CH_2), 51.9 (N**C**H_2CH), 61.2 (**C**H_2OH), 116.1 (**C**H_2=CH), 125.2 (NCH_2**C**H), 132.1 (NCH_2CH=**C**H), 135.6 (CH_2=**C**H),

168.6 (**C**=O) [peaks for the minor rotamer were observed at 27.2 (**C**H_2Br), 36.2 (CH_2=CH**C**H_2), 47.4 (N**C**H_2CH), 49.7 (N**C**H_2CH_2), 59.6 (**C**H_2OH), 115.6 (**C**H_2=CH), 125.0 (N**C**H_2CH), 131.8 (NCH_2CH=**C**H), 136.1 (CH_2=**C**H), 167.7 (**C**=O)]; *m/z* (CI, NH_3) 264 ($M^{81}BrH^+$, 72%), 262 ($M^{79}BrH^+$, 70), 184 (99), 182 (100), 166 (49), 164 (45), 142 (13), 104 (13).

_N_-Hexa-2,5-dienyl-_N_-(2-hydroxyethyl)acetamide 177 and 4-But-3-enyl-1-(2-hydroxyethyl)-2-pyrrolidinone 156

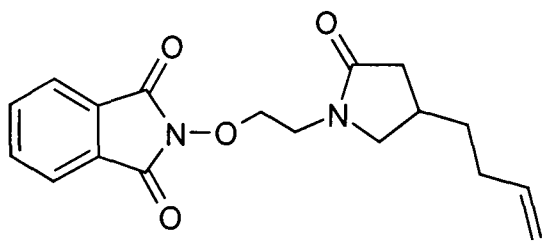


To a degassed solution of the bromoacetamide **157** (250 mg, 0.95 mmol) at 90°C in chlorobenzene (95 mL) was added a degassed solution of tri-*n*-butyltin hydride (280 μL, 1.05 mmol) and AIBN (16 mg, 0.095 mmol) in chlorobenzene (21 mL) *via* syringe pump over a period of 3 h. After a further 2 h the reaction mixture was concentrated *in vacuo* to give a yellow oil which was dissolved in DCM (50 mL) and *N*-(2-mercaptoethyl)aminomethyl polystyrene resin (200–400 mesh) (3.33 g, capacity: 1.26 mmol g^{-1}, 4.20 mmol) was added; the mixture was stirred for 1 h then filtered and the resin washed successively with DCM (3 × 10 mL), ether (3 × 10 mL) and DCM (3 × 10 mL). The combined filtrates were concentrated *in vacuo* to give a yellow oil. Column chromatography

on silica (1:2:98 conc. aq. NH_3:MeOH:EtOAc) gave the directly reduced product **177** (40 mg, 23%) and cyclised product **156** (118 mg, 68%) both as colourless oils. Data for **177**: R_f 0.37 (1:5:95 conc. aq. NH_3:MeOH:EtOAc); Accurate mass: Found 184.1337, $C_{10}H_{18}NO_2$ (MH^+) requires 184.1337; ν_{max}/cm^{-1} (thin film) 3382bs, 2931m, 1623s, 1480m, 1424s, 1365m, 1239m, 1175w, 1058m, 1023m, 973m, 915m, 860w; δ_H (400 MHz, $CDCl_3$) major rotamer 2.12 (3H, s, C**H**$_3$), 2.76–2.83 (2H, m, CH_2=CHC**H**$_2$), 3.51 (2H, t, *J* 5.1, NC**H**$_2$$CH_2$), 3.74 (2H, t, *J* 5.1, C**H**$_2$OH), 3.91 (2H, dd, *J* 5.4, 1.2, NC**H**$_2$CH), 4.99–5.05 (2H, m, C**H**$_2$=CH), 5.39–5.47 (1H, m, NCH_2C**H**), 5.56–5.66 (1H, m, NCH_2CH=C**H**), 5.74–5.84 (1H, m, CH_2=C**H**) [peaks for minor rotamer were also observed at 2.15 (3H, s, C**H**$_3$), 3.42 (2H, t, *J* 5.6, NC**H**$_2$$CH_2$), 3.98 (2H, d, *J* 5.7, NC**H**$_2$CH)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 21.4 (**C**H_3), 36.1 (CH_2=CH**C**H_2), 49.7 (N**C**H_2CH_2), 51.9 (N**C**H_2CH), 62.0 (**C**H_2OH), 115.9 (**C**H_2=CH), 125.1 (NCH_2**C**H=), 131.4 (NCH_2CH=**C**H), 135.8 (CH_2=**C**H), 172.9 (**C**=O) [peaks for the minor rotamer were observed at 21.8 (**C**H_3), 36.3 (CH_2=CH**C**H_2), 47.1 (N**C**H_2CH), 49.3 (N**C**H_2CH_2), 59.8 (**C**H_2OH), 115.5 (**C**H_2=CH), 126.1 (NCH_2**C**H), 131.4 (NCH_2CH=**C**H), 136.3 (CH_2=**C**H), 171.2 (**C**=O)]; *m/z* (CI, NH_3) 184 (MH^+, 95%), 142 (16), 104 (100). Data for **156**: R_f 0.30 (1:5:95 conc. aq. NH_3:MeOH:EtOAc); Accurate mass: Found 184.1338, $C_{10}H_{18}NO_2$ (MH^+) requires 184.1337; ν_{max}/cm^{-1} (thin film) 3384bs, 2926m, 2859m, 1668s, 1494m, 1455m, 1425m, 1279m, 1064m, 1007m, 912m; δ_H (400 MHz, $CDCl_3$) 1.53 (2H, app. q, *J* 7.8, CH_2=$CHCH_2$C**H**$_2$), 2.02–2.09 (2H, m, CH_2=CHC**H**$_2$) overlays 2.09 (1H, dd, *J* 16.5, 8.0, COC**H**H), 2.37 (1H, app. sept., *J* 7.8, $COCH_2$C**H**), 2.52 (1H, dd, *J* 16.5, 8.8, COCH**H**), 3.12 (1H, dd, *J* 9.7, 7.2, NC**H**HCH), 3.38 (2H, t, *J* 5.1, NC**H**$_2$$CH_2$), 3.55 (1H, dd, *J* 9.7, 8.4, NCH**H**CH), 3.71 (2H, t, *J* 5.1, C**H**$_2$OH), 4.94–5.03 (2H, m, C**H**$_2$=CH), 5.75 (1H, dddd, *J* 16.8, 10.1, 6.6, 6.6, CH_2=C**H**); δ_C (100.6 MHz, $CDCl_3$) 31.5 ($COCH_2$**C**H), 31.6 (CH_2=CH**C**H_2), 33.8 (CH_2=$CHCH_2$**C**H_2), 37.6 (CO**C**H_2), 45.9 (N**C**H_2CH_2),

54.3 (NCH_2CH), 60.4 (CH_2OH), 115.9 (CH_2=CH), 137.6 (CH_2=CH), 175.8 (C=O); *m/z* (CI, NH_3) 184 (MH^+, 100%), 166 (59).

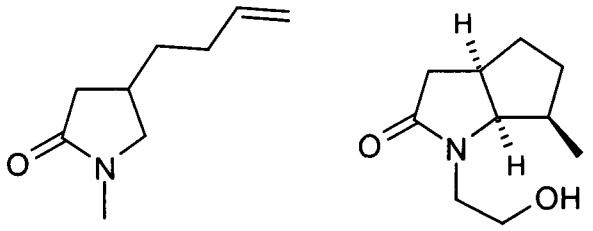
2-(4-But-3-enyl-2-oxopyrrolidin-1-yl)ethoxyphthalimide 149



To the alcohol **156** (700 mg, 3.82 mmol) in DCM (40 mL) was added successively polymer supported triphenylphosphine (3.18 g, capacity: ~3.0 mmol g^{-1}, 9.55 mmol) and diisopropylazodicarboxylate (1.94 mL, 9.55 mmol). After 30 mins at RT *N*-hydroxyphthalimide (707 mg, 4.20 mmol) was added and the mixture stirred for 16 h at RT. The mixture was filtered and the resin washed successively with DCM (3 × 40 mL), ether (3 × 40 mL) and DCM (3 × 40 mL). The combined filtrates were concentrated *in vacuo* to give a yellow oil. Column chromatography on silica (1:4 petrol:EtOAc) gave the alkoxyphthalimide **149** as a yellow oil (947 mg, 75%). R_f 0.32 (1:2 petrol:EtOAc, UV active); Accurate mass: Found 329.1491, $C_{18}H_{21}N_2O_4$ (MH^+) requires 329.1501; ν_{max}/cm^{-1} (thin film) 3075w, 2975m, 2925m, 2853m, 1790s, 1732s, 1682s, 1641m, 1492m, 1467m, 1445m, 1370s, 1278m, 1187s, 1130s, 1083m, 1017m, 997m, 915m, 878s; δ_H (400 MHz, $CDCl_3$) 1.56–1.69 (2H, m, CH_2=$CHCH_2C\mathbf{H}_2$), 2.09–2.18 (3H, m, CH_2=$CHC\mathbf{H}_2$, COC**H**H), 2.46 (1H, app. sept., *J* 7.7, $COCH_2C\mathbf{H}$), 2.57 (1H, dd, *J* 16.4, 8.6, COCH**H**), 3.39 (1H, dd, *J* 9.6, 6.8, NC**H**HCH), 3.61–3.73 (2H, t, *J* 4.9, $NC\mathbf{H}_2CH_2$), 3.81 (1H, dd, *J*

9.6, 7.9, NCH**H**CH), 4.35 (2H, t, *J* 4.9, OC**H**$_2$), 4.98-5.08 (2H, m, C**H**$_2$=CH), 5.82 (1H, dddd, *J* 17.0, 10.2, 6.7, 6.7, CH$_2$=C**H**), 7.74–7.86 (4H, m, ArC**H**); δ_C (100.6 MHz, $CDCl_3$) 31.5 (COCH$_2$**C**H), 31.6 (CH$_2$=CH**C**H$_2$), 33.7 (CH$_2$=CHCH$_2$**C**H$_2$), 37.4 (CO**C**H$_2$), 41.2 (N**C**H$_2$CH$_2$), 54.5 (N**C**H$_2$CH), 77.6 (O**C**H$_2$), 115.1 (**C**H$_2$=CH), 123.6 (Ar**C**H), 128.8 (*i*-Ar**C**), 134.6 (Ar**C**H), 137.8 (CH$_2$=**C**H), 163.3 (**C**ON**C**O), 174.9 (**C**=O); *m/z* (CI, NH_3) 330 (30%), 329 (MH^+, 100), 166 (13).

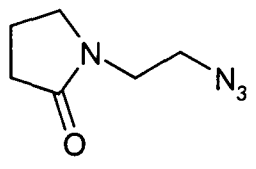
4-But-3-enyl-1-methyl-2-pyrrolidinone 178 and 1-(2-Hydroxyethyl)-6-methylhexahydro-cyclopenta[b]pyrrol-2-one 179



A degassed solution of the alkoxyphthalimide (500 mg, 1.52 mmol), tri-*n*-butyltin hydride (450 μL, 1.67 mmol) and AIBN (38 mg, 0.23 mmol) in chlorobenzene (304 mL) were heated at 90°C for 16 h and then concentrated *in vacuo* to give a yellow oil (1.699 g). Column chromatography on silica (1:2 petrol:EtOAc) gave the product of β-scission **178** (163 mg, 70%) and the cyclised product **179** (69 mg, 25%) both as yellow oils. Data for **178**: R_f 0.20 (1:4 petrol:EtOAc); Accurate mass: Found 154.1232, $C_9H_{16}NO$ (MH^+) requires 154.1232; ν_{max}/cm^{-1} (thin film) 2925m, 2855m, 1690s, 1501m, 1426m, 1403m, 1288m, 995m, 911m, 668m; δ_H (400 MHz, $CDCl_3$) 1.55 (2H, app. q, *J* 7.5, CH$_2$=CHCH$_2$C**H**$_2$), 2.02–2.11 (3H, m, CH$_2$=CHC**H**$_2$, COC**H**H), 2.36 (1H, app. sept., *J* 7.6, COCH$_2$C**H**), 2.52 (1H, dd, *J* 16.5, 8.4, COCH**H**), 2.83 (3H, s, NC**H**$_3$), 3.02 (1H, dd, *J* 9.6, 5.5,

NC**H**H), 3.47 (1H, dd, *J* 9.6, 6.0, NCH**H**), 4.97–5.06 (2H, m, C**H**$_2$=CH) 5.79 (1H, dddd, *J* 17.2, 10.2, 7.0, 7.0, CH$_2$=C**H**); δ_C (100.6 MHz, $CDCl_3$) 29.5 (**C**H$_3$), 31.0 (NCH$_2$**C**H), 31.6 (CH$_2$=CH**C**H$_2$), 33.9 (CH$_2$=CHCH$_2$**C**H$_2$), 37.3 (CO**C**H$_2$), 55.2 (N**C**H$_2$), 115.2 (**C**H$_2$=CH), 137.7 (CH$_2$=**C**H), 174.4 (**C**=O); *m/z* (CI, NH_3) 155 (20%), 154 (MH^+, 100). Data for **179**: R_f 0.08 (1:4 petrol:EtOAc); Accurate mass: Found 184.1339, $C_{10}H_{18}NO_2$ (MH^+) requires 184.1337; ν_{max}/cm^{-1} (thin film) 3387bs, 2955s, 2873s, 1660s, 1652s, 1462s, 1421s, 1361m, 1299m, 1261m, 1061m, 1008m; δ_H (500 MHz, C_6D_6) 0.64 (3H, d, *J* 7.0, C**H**$_3$), 1.17–1.39 (4H, m, CH$_3$CHC**H**$_2$C**H**$_2$), 1.59–1.68 (1H, m, CH$_3$C**H**), 1.85 (1H, dd, *J* 17.5, 6.5, COC**H**H), 2.27–2.34 (1H, m, COCH$_2$C**H**), 2.44 (1H, dd, *J* 17.5, 11.2, COCH**H**), 2.87–2.92 (1H, m, NC**H**H), 3.67 (1H, app. t, *J* 7.7, NC**H**), 3.74–3.84 (3H, m, NCH**H**, C**H**$_2$OH) [peaks for minor diastereomer were also observed at 0.69 (3H, d, *J* 7.2, C**H**$_3$) and 3.27 (1H, dd, *J* 8.1, 2.8, NC**H**)]; δ_C (100.6 MHz, $CDCl_3$) 15.0 (**C**H$_3$), 31.5 (CH$_3$CH**C**H$_2$), 32.5 (CH$_3$CHCH$_2$**C**H$_2$), 35.6 (COCH$_2$**C**H), 38.5 (CH$_3$**C**H), 38.9 (CO**C**H$_2$), 47.8 (N**C**H$_2$), 61.7 (**C**H$_2$OH), 67.9 (N**C**H), 178.1 (**C**=O); *m/z* (CI, NH_3) 185 (19%), 184 (MH^+, 100), 166 (20). Repetition of the experiment with tri-*n*-butyltin deuteride gave deuterium incorporation at δ_D (76.7 MHz, $CHCl_3$) 1.03 (CH$_2$**D**), 3.21 (NC**D**H), 3.74 (NCH**D**).

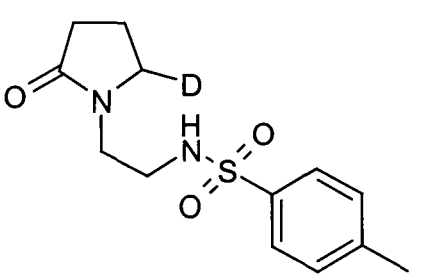
1-(2-Azidoethyl)-2-pyrrolidinone 187



To a stirred solution of the bromide **119** (1.00 g, 5.20 mmol) in DMF (12 mL) was added NaN_3 ((384 mg, 5.85 mmol) and the mixture heated at 70°C for 24 h. The reaction mixture was then diluted with brine (50 mL) and extracted with DCM (3 ×50 mL). The combined organics were

dried ($MgSO_4$) and concentrated *in vacuo*. Heating at 60°C under reduced pressure (0.03 mmHg) for 4 h gave the azide **187** as an orange oil (734 mg, 92%). R_f 0.22 (1:6 petrol:EtOAc); Accurate mass: Found 155.0929, $C_6H_{11}N_4O$ (MH^+) requires 155.0933; ν_{max}/cm^{-1} (thin film) 2929m, 2100s, 1683s, 1495m, 1463m, 1425m, 1288s, 1099w, 1003w, 973w, 928w, 826w; δ_H (400 MHz, $CDCl_3$) 2.10 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.43 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 3.49–3.55 (6H, m, 3 × $NC\mathbf{H_2}$); δ_C (100.6 MHz, $CDCl_3$) 18.2 ($COCH_2\mathbf{C}H_2$), 30.7 ($CO\mathbf{C}H_2$), 42.2 ($N\mathbf{C}H_2$), 48.2 ($N\mathbf{C}H_2$), 49.3 ($N\mathbf{C}H_2$), 175.5 (**C**=O); *m/z* (CI, NH_3) 155 (MH^+, 19%), 129 (24), 127 (79), 112 (100).

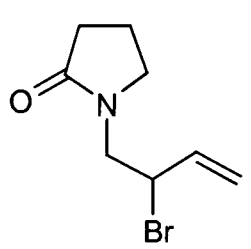
_N_-(2-Oxo-5-_d_$_1$-pyrrolidin-1-yl)ethyl]-4-methylbenzenesulfonamide 188



To a degassed solution of the azide **187** (154 mg, 1 mmol) and AIBN (17 mg, 0.1 mmol) in chlorobenzene (15 mL) at 90°C was added a degassed solution of tri-*n*-butyltin deuteride (329 μL, 1.25 mmol) and AIBN (17 mg, 0.1 mmol) in chlorobenzene (5 mL) *via* syringe pump over 1 h. After 16 h at 90°C *p*-toluenesulfonyl chloride (210 mg, 1.1 mmol) and pyridine (89 μL, 1.1 mmol) were added and the mixture heated at 90°C for a further 2 h. After concentrating *in vacuo* the brown oil was purified by column chromatography on silica (3:97 MeOH:chloroform) to give the pyrrolidinone **188** as a white solid (117 mg, 41%). Deuterium incorporation, ~90%. R_f 0.11 (1:6 petrol:EtOAc, UV active); m.p. 103–107 °C; Accurate mass: Found 284.1177, $C_{13}H_{18}DN_2O_3S$

(MH^+) requires 284.1179; ν_{max}/cm^{-1} (KBr disk) 3139m, 2957s, 2909s, 2870s, 1679s, 1593m, 1465s, 1429m, 1415m, 1362m, 1321s, 1285m, 1155s, 1092s, 908m, 821m; δ_H (400 MHz, $CDCl_3$) 1.97 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.34 (2H, t, *J* 8.1, $COC\mathbf{H_2}$), 2.43 (3H, s, $C\mathbf{H_3}$), 3.13 (2H, app. q, *J* 5.6, $NHC\mathbf{H_2}$), 3.33–3.39 (3H, m, NC**H**D, $NHCH_2C\mathbf{H_2}$), 5.49 (1H, t, *J* 5.6, N**H**), 7.31 (2H, d, *J* 8.1, ArC**H**), 7.74 (2H, d, *J*, 8.1 (ArC**H**); δ_D (250MHz, $CHCl_3$) 3.38 (bs, NCH**D**); δ_C (100.6 MHz, $CDCl_3$) 17.9 ($COCH_2\mathbf{C}H_2$), 21.5 ($\mathbf{C}H_3$), 30.8 ($CO\mathbf{C}H_2$), 41.1 ($NH\mathbf{C}H_2$), 42.2 ($NHCH_2\mathbf{C}H_2$) 47.3 (t, *J* 21.1, **C**HD), 47.7 ($N\mathbf{C}H_2(CH_2)_2$), 127.0 (Ar**C**H), 129.6 (Ar**C**H), 137.0 (Ar**C**), 143.2 (Ar**C**), 176.4 (**C**=O); *m/z* (CI, NH_3) 285 (19%), 284 (MH^+, 100), 283 (69), 112 (14).

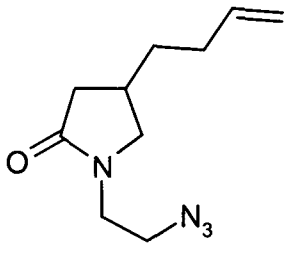
1-(2-Bromo-3-butenyl)-2-pyrrolidinone 189



A mixture of the alcohol **134** (466 mg, 3 mmol), carbon tetrabromide (1.12 g, 3.3 mmol) and polymer supported triphenylphosphine (2.20 g, capacity: 3 mmol g^{-1}, 6.6 mmol) in MeCN (24 mL) was stirred at RT for 16 h. After filtering, the resin was washed with chloroform (10 × 50 mL) and the combined filtrates were concentrated *in vacuo* to give an orange oil. Column chromatography on silica (1:2 petrol:EtOAc) gave the allylic bromide **189** as a colourless oil (404 mg, 62%). R_f 0.15 (1:2 petrol:EtOAc); ν_{max}/cm^{-1} (thin film) 2980m, 2890m, 1683s, 1493m, 1462m, 1422s, 1289s, 1268s, 1227m, 1158m, 1132m, 987m, 932m; δ_H (400 MHz, $CDCl_3$) 2.02 (2H, app. quin., *J* 7.6, $COCH_2C\mathbf{H_2}$), 2.37 (2H, t, *J* 8.0, $COC\mathbf{H_2}$), 3.35 (1H, dt, *J* 9.5, 7.1, NC**H**HCH_2) 3.51 (1H, dt, *J* 9.5, 7.1, $NCH\mathbf{H}CH_2$), 3.64 (1H, dd, *J* 14.2, 7.5, NC**H**HCH), 3.68 (1H, dd, *J* 14.2, 7.5, NCH**H**CH),

4.66 (1H, dt, *J* 9.9, 7.5, $NCH_2C\mathbf{H}$), 5.16 (1H, d, *J* 9.9, $CH{=}C\mathbf{H}_{E}CH_{Z}$), 5.32 (1H, d, *J* 16.9, $CH{=}CH_{E}C\mathbf{H}_{Z}$), 5.96 (1H, ddd, *J* 16.9, 9.9, 9.9, $C\mathbf{H}{=}CH_2$); δ_C (100.6 MHz, $CDCl_3$) 18.2 ($COCH_2\mathbf{C}H_2$), 30.7 ($CO\mathbf{C}H_2$), 48.2 ($N\mathbf{C}H_2CH_2$), 49.1 ($N\mathbf{C}H_2CH$), 50.3 ($NCH_2\mathbf{C}H$), 118.7 ($CH{=}\mathbf{C}H_2$), 136.5 ($\mathbf{C}H{=}CH_2$), 175.4 ($\mathbf{C}{=}O$); *m/z* (CI, NH_3) 220 ($M^{81}BrH^+$, 91%), 218 ($M^{79}BrH^+$, 90), 156 (21), 139 (18), 138 (100).

1-(2-Azidoethyl)-4-but-3-enyl-2-pyrrolidinone 193



Method 1

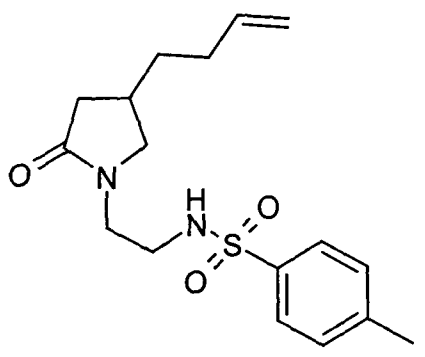
To a solution of the alcohol **156** (150 mg, 0.82 mmol) and triphenylphosphine (434 mg, 1.64 mmol) at 0°C was added dropwise diethylazodicarboxylate (258 μL, 1.64 mmol) followed by diphenylphosphoryl azide (364 μL, 1.64 mmol). The reaction mixture was stirred at 0°C for 20 mins, allowed to warm to RT and stirred for 16 h and then concentrated *in vacuo*. Column chromatography on silica (1:2 petrol:EtOAc) gave the azide **193** as a yellow oil (57 mg, 33%). R_f 0.44 (1:6 petrol:EtOAc); Accurate mass: Found 209.1402, $C_{10}H_{17}N_4O$ (MH^+) requires 201.1402; ν_{max}/cm^{-1} (thin film) 2926m, 2854m, 2101s, 1692s, 1641m, 1492m, 1426m, 1350m, 1277m, 1203w, 997w, 914m; δ_H (400 MHz, $CDCl_3$) 1.56 (2H, app. q, *J* 7.5, $CH_2{=}CHCH_2C\mathbf{H_2}$), 2.05–2.11 (2H, m, $CH_2{=}CHC\mathbf{H_2}$) overlays 2.08 (1H, dd, *J* 16.7, 7.8, $COC\mathbf{H}H$), 2.38 (1H, app. sept., *J* 7.9,

$COCH_2CH$), 2.53 (1H, dd, *J* 16.7, 8.7, COCH**H**), 3.12 (1H, dd, *J* 9.5, 7.0, NC**H**HCH), 3.43–3.47 (4H, m, NCH_2CH_2), 3.56 (1H, dd, *J* 9.5, 7.9, NCH**H**CH), 4.97–5.06 (2H, m, CH_2=CH), 5.78 (1H, dddd, *J* 16.8, 10.1, 6.6, 6.6, CH_2=C**H**); δ_C (100.6 MHz, $CDCl_3$) 31.5 ($COCH_2CH$), 31.6 (CH_2=$CHCH_2$), 33.7 (CH_2=$CHCH_2CH_2$), 37.4 ($COCH_2$), 42.1, 49.3 (NCH_2CH_2), 54.0 (NCH_2CH), 115.3 (CH_2=CH), 137.6 (CH_2=CH), 174.9 (C=O); *m/z* (CI, NH_3) 209 (MH^+, 93%), 152 (100), 122 (10).

Method 2

To a stirred solution of the alcohol **156** (0.50 g, 2.73 mmol) in DMF (15 mL) was added triphenylphosphine (0.94 g, 3.55 mmol), carbon tetrabromide (1.39 g, 4.09 mmol) and NaN_3 (0.36 g, 5.46 mmol). After 16 h at RT the mixture was concentrated *in vacuo* and placed on a high vacuum line (40°C @ 0.03 mmHg) for 3h to remove DMF. Column chromatography on silica (1:1 petrol:EtOAc) gave the azide **193** as a yellow oil (362 mg, 64%). Data as above.

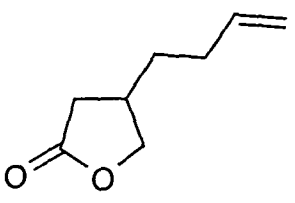
N-[2-(4-But-3-enyl-2-oxopyrrolidin-1-yl)-ethyl]-4-methyl-benzenesulfonamide 194



To a degassed solution of the azide **193** (50 mg, 0.24 mmol) and AIBN (4 mg, 0.024 mmol) in chlorobenzene (3 mL) at 80°C was added a degassed solution of tri-*n*-butyltin hydride (71 μL, 0.26

mmol) and AIBN (4 mg, 0.024 mmol) in chlorobenzene (1.8 mL) *via* syringe pump over 1 h. After 16 h at 80°C *p*-toluenesulfonyl chloride (50 mg, 0.26 mmol) and pyridine (21 μL, 0.26 mmol) were added and the mixture stirred at 80°C for a further 2 h and then concentrated *in vacuo*. Column chromatography on silica (1:3 petrol:EtOAc) gave the pyrrolidinone **194** as a yellow oil (25 mg, 31 %). R_f 0.33 (1:6 petrol:EtOAc, UV active); Accurate mass: Found 337.1582, $C_{17}H_{24}N_2O_3S$ (MH^+) requires 337.1586; ν_{max}/cm^{-1} (thin film) 3259m, 3167s, 3079m, 2926s, 2869m, 1668s, 1599m, 1494s, 1455s, 1329s, 1306s, 1160s, 1095s, 1020w, 997w, 914s, 816s; δ_H (400 MHz, $CDCl_3$) 1.49 (2H, app. q, *J* 7.5, CH_2=CHCH$_2$C**H$_2$**), 1.99–2.07 (3H, m, CH_2=CHC**H$_2$**, COC**H**H), 2.29 (1H, app. sept., *J* 7.9, COCH$_2$C**H**), 2.42 (3H, s, C**H$_3$**), 2.47 (1H, dd, *J* 16.6, 8.7, COCH**H**), 2.99 (1H, dd, *J* 9.4, 7.2, NC**H**HCH), 3.10 (2H, app. q, *J* 5.8, NHC**H$_2$**), 3.36 (2H, t, *J* 5.8, NC**H$_2$**CH$_2$), 3.43 (1H, dd, *J* 9.4, 8.1, NCH**H**CH), 4.97–5.05 (2H, m, C**H$_2$**=CH), 5.66 (1H, t, *J* 5.8, N**H**), 5.77 (1H, dddd, *J* 17.0, 10.3, 6.7, 6.7, CH_2=C**H**), 7.30 (2H, d, *J* 8.2, ArC**H**), 7.73 (2H, d, *J*, 8.2 (ArC**H**); δ_C (100.6 MHz, $CDCl_3$) 21.5 (**C**H$_3$), 31.4 (COCH$_2$**C**H), 31.6 (CH_2=CH**C**H$_2$), 33.6 (CH_2=CHCH$_2$**C**H$_2$), 37.4 (CO**C**H$_2$), 41.3 (NH**C**H$_2$), 42.1 (N**C**H$_2$CH$_2$), 53.4 (N**C**H$_2$CH), 115.3 (**C**H$_2$=CH), 127.0 (Ar**C**H), 129.7 (Ar**C**H), 136.9 (Ar**C**), 137.6 (CH_2=**C**H), 143.3 (Ar**C**), 175.8 (**C**=O); *m/z* (CI, NH_3) 338 (21%), 337 (MH^+, 100).

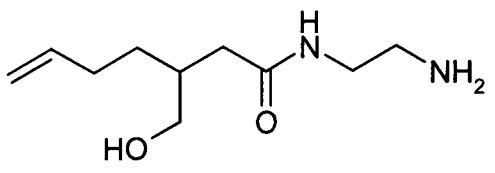
4-But-3-enyldihydrofuran-2-one 150



To a solution of 4-iodo-1-butene (1.62 g, 8.92 mmol) in ether (30 mL) at −78°C was added *tert*-butyllithium (10.50 mL of a 1.7 M solution in hexanes, 17.84 mmol). After 30 mins the solution

was added to a slurry of CuI (1.70 g, 8.92 mmol) in THF (30 mL) at −78°C. The reaction mixture was allowed to warm to −25°C over 20 mins and then re-cooled to −78°C. $BF_3{\cdot}OEt_2$ (1.10 mL, 8.92 mmol) was added followed by a solution of 2-(5*H*)furanone[182] (250 mg, 2.97 mmol) in THF (7.5 mL). After 1 h at −78°C the reaction was quenched with sat. aq. NH_4Cl solution and ether and filtered through celite®. After washing with brine (100 mL) the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:5 EtOAc:petrol) gave the lactone **150** as a yellow oil (259 mg, 62%). R_f 0.44 (1:6 EtOAc:petrol); Accurate mass: Found 158.1179, $C_8H_{16}NO_2$ (MNH_4^+) requires 158.1181; ν_{max}/cm^{-1} (thin film) 3077w, 2970w, 2922m, 2855m, 1774s, 1641m, 1480w, 1454w, 1419m, 1379w, 1340w, 1259w, 1170s, 1018m, 999m, 913m; δ_H (400 MHz, $CDCl_3$) 1.59 (2H, app. q, *J* 7.6, $CH_2{=}CHCH_2C\mathbf{H_2}$), 2.06–2.12 (2H, m, $CH_2{=}CHC\mathbf{H_2}$), 2.19 (1H, dd, *J* 16.2, 7.5, COC**H**H), 2.54–2.67 (2H, m, $COCH_2C\mathbf{H}$, COCH**H**), 3.93 (1H, dd, *J* 9.1, 7.2, OC**H**H), 4.42 (1H, dd, *J* 9.1, 7.5, OCH**H**), 4.99–5.07 (2H, m, $C\mathbf{H_2}{=}CH$), 5.77 (1H, dddd, *J* 16.9, 10.3, 6.6, 6.6, $CH_2{=}C\mathbf{H}$); δ_C (100.6 MHz, $CDCl_3$) 31.5 ($CH_2{=}CHCH_2\mathbf{C}H_2$), 32.1 ($CH_2{=}CH\mathbf{C}H_2$), 34.4 ($CO\mathbf{C}H_2$), 35.1 ($COCH_2\mathbf{C}H$), 73.2 ($O\mathbf{C}H_2$), 115.7 ($\mathbf{C}H_2{=}CH$), 137.1 ($CH_2{=}\mathbf{C}H$), 177.1 (**C**=O); *m/z* (CI, NH_3) 160 (10%), 158 (MNH_4^+, 100), 81 (20).

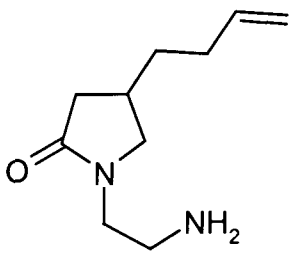
N-(2-Aminoethyl)-3-hydroxymethyl-6-heptenamide 197



The lactone **150** (200 mg, 1.43 mmol) and ethylenediamine (477 μL, 7.13 mmol) were heated in a sealed tube for 20 h at 230°C and then cooled and concentrated *in vacuo*. Column chromatography

on silica (1:20:80 conc. aq. NH_3:MeOH:EtOAc) gave the amino alcohol **197** as a yellow solid (174 mg, 61%). R_f 0.08 (1:20:80 conc. aq. NH_3:MeOH:EtOAc); m.p. 182°C; Accurate mass: Found 201.1599, $C_{10}H_{21}N_2O_2$ (MH^+) requires 201.1603; ν_{max}/cm^{-1} (KBr disk) 3353bs, 3080m, 2919s, 1641s, 1553s, 1443m, 1369m, 1195m, 1048m, 993m, 914m; δ_H (400 MHz, $CDCl_3$) 1.32–1.41 (1H, m, CH_2=CHCH$_2$C**H**H), 1.43–1.52 (1H, m, CH_2=CHCH$_2$CH**H**), 1.97–2.12 (3H, m, CH_2=CHC**H$_2$**, C**H**CH$_2$OH), 2.27 (1H, dd, *J* 8.9, 2.3, COC**H**H), 2.31 (1H, d, *J* 8.9, COCH**H**), 2.82 (2H, ddd, *J* 7.5, 5.5, 2.0, CONHC**H$_2$**), 3.20–3.39 (2H, m, C**H$_2$**NH$_2$), 3.47 (1H, dd, *J* 11.0, 6.5, C**H**HOH), 3.65 (1H, dd, *J* 11.0, 3.8, CH**H**OH), 4.93–5.04 (2H, m, C**H$_2$**=CH), 5.78 (1H, dddd, *J* 16.8, 10.1, 6.6, 6.6, CH_2=C**H**), 6.69 (1H, t, *J* 5.5, N**H**); δ_C (100.6 MHz, $CDCl_3$) 30.6 (CH_2=CHCH$_2$**C**H$_2$), 31.2 (CH_2=CH**C**H$_2$), 37.6 (**C**HCH$_2$OH), 39.7 (CO**C**H$_2$), 41.2 (CONH**C**H$_2$), 41.7 (**C**H$_2$NH$_2$), 64.9 (**C**H$_2$OH), 114.8 (**C**H$_2$=CH), 138.3 (CH_2=**C**H), 173.6 (**C**=O); *m/z* (CI, NH_3) 201 (MH^+, 22%), 185 (47), 184 (75), 183 (100), 166 (31), 123 (16).

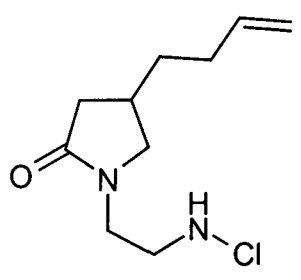
1-(2-Aminoethyl)-4-but-3-enyl-2-pyrrolidinone 196



To a stirred solution of the azide **193** (362 mg, 1.74 mmol) in THF (10 mL) was added triphenylphosphine (517 mg, 1.91 mmol). After 1 h water (63 μL, 3.48 mmol) was added and the mixture stirred at RT for 16 h and then concentrated *in vacuo*. Column chromatography on silica (1:20:80 conc. aq. NH_3:MeOH:EtOAc) gave the amine **196** as a yellow oil (309 mg, 97%). R_f 0.08

(1:20:80 conc. aq. NH_3:MeOH:EtOAc); Accurate mass: Found 183.1502, $C_{10}H_{19}N_2O$ (MH^+) requires 183.1497; ν_{max}/cm^{-1} (thin film) 3471bs, 3363s, 3298s, 3075m, 2923s, 2853s, 1678s, 1492s, 1431s, 1364m, 1276s, 1098w, 996m, 910m; δ_H (400 MHz, $CDCl_3$) 1.51 (2H, app. q, *J* 7.5, CH_2=CHCH$_2$C**H$_2$**), 1.72 (2H, bs, N**H$_2$**), 2.00–2.06 (2H, m, CH_2=CHC**H$_2$**) overlays 2.06 (1H, dd, *J* 16.7, 7.7, COC**H**H), 2.33 (1H, app. sept., *J* 7.8, COCH$_2$C**H**), 2.50 (1H, dd, *J* 16.7, 8.7, COCH**H**), 2.79 (2H, t, *J* 5.9, C**H$_2$**NH$_2$), 3.01 (1H, dd, *J* 9.6, 6.8, NC**H**HCH), 3.22–3.34 (2H, m, NC**H$_2$**CH$_2$), 3.47 (1H, dd, *J* 9.6, 8.1, NCH**H**CH), 4.92–5.00 (2H, m, C**H$_2$**=CH), 5.74 (1H, dddd, *J* 16.8, 10.1, 6.6, 6.6, CH_2=C**H**); δ_C (100.6 MHz, $CDCl_3$) 31.8 (COCH$_2$**C**H), 32.0 (CH_2=CH**C**H$_2$), 34.2 (CH_2=CHCH$_2$**C**H$_2$), 38.0 (CO**C**H$_2$), 40.1 (**C**H$_2$NH$_2$), 46.1 (**C**H$_2$CH$_2$NH$_2$), 53.8 (N**C**H$_2$CH), 115.7 (**C**H$_2$=CH), 138.1 (CH_2=**C**H), 175.5 (**C**=O); *m/z* (CI, NH_3) 183 (MH^+, 83%), 167 (15), 166 (100).

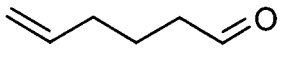
1-[2-(*N*-Chloroamino)ethyl]-4-but-3-enyl-2-pyrrolidinone 195



To a stirred solution of the amine **196** (50 mg, 0.27 mmol) in MeOH (400 μL) at 0°C was added freshly prepared *tert*-butylhypochlorite[183] (30 μL, 0.27 mmol). After 45 mins the reaction mixture was concentrated *in vacuo*. The crude chloroamine **195** (58 mg, 99%) was unstable and was used immediately without further purification. R_f 0.38 (1:19 MeOH:chloroform); δ_H (200 MHz, $CDCl_3$) 1.57 (2H, app. q, *J* 7.4, CH_2=CHCH$_2$C**H$_2$**), 2.04–2.15 (3H, m, CH_2=CHC**H$_2$**, COC**H**H), 2.32–2.60 (3H, m, COCH$_2$C**H**, COCH**H**), 3.11–3.29 (3H, m, NHC**H$_2$**, NC**H**HCH), 3.48–3.63 (3H, m,

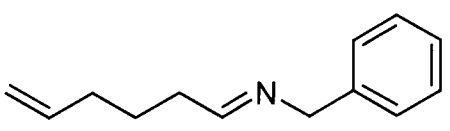
NCH_2CH_2, $NCHHCH$), 4.48 (1H, t, *J* 5.5, N**H**) 4.96–5.05 (2H, m, CH_2=CH), 5.79 (1H, dddd, *J* 17.1, 10.1, 6.7, 6.7, CH_2=C**H**); δ_C (100.6 MHz, $CDCl_3$) 31.5 ($COCH_2CH$), 31.6 (CH_2=$CHCH_2$), 33.6 (CH_2=$CHCH_2CH_2$), 37.2 ($COCH_2$), 41.2 (NCH_2CH_2), 54.2 (NCH_2CH), 54.6 ($NHCH_2$), 115.3 (CH_2=CH), 137.6 (CH_2=CH), 176.6 (C=O).

5-Hexenal[201] 200



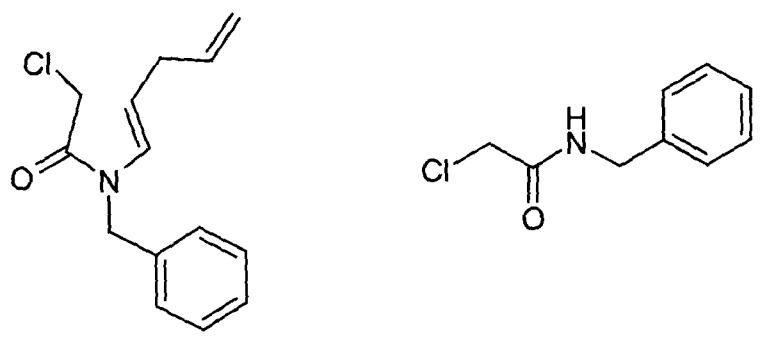
To a suspension of PCC (2.42 g, 11 mmol) and silica gel (500 mg) in DCM (40 mL) was added 5-hexen-1-ol (1.21 mL, 10 mmol) and the mixture stirred at RT for 4 h. Ether (50 mL) was added and the supernatant liquid decanted. The insoluble residue was washed with further portions of ether (3 × 50 mL) and the organics filtered through a short plug of silica. The majority of the solvent was removed by distillation and the remaining green liquid distilled by short path distillation (0.1 mmHg, 10 cm Vigreux column) collecting the ethereal aldehyde **200** solution in a flask cooled by solid CO_2. The colourless solution was used crude in the next reaction. δ_H (200 MHz, $CDCl_3$) 1.74 (2H, app. quin, *J* 7.3, CH_2=$CHCH_2CH_2$), 2.10 (2H, app. q., *J* 7.0, CH_2=$CHCH_2$), 2.46 (2H, t, *J* 7.3, CH_2CHO), 4.98–5.07 (2H, m, CH_2=CH), 5.78 (1H, dddd, *J* 16.9, 10.2, 6.7, 6.7, CH_2=C**H**), 9.78 (1H, s, C**H**O).

***N*-(5-Hexenylidine)benzylamine 201**



To a solution of the crude ethereal aldehyde **200** (≤10 mmol) in DCM (10 mL) was added benzylamine (1.09 mL, 10 mmol) and $MgSO_4$ (2.00 g) and the reaction stirred at RT. After 3h the reaction mixture was filtered and concentrated *in vacuo* to give the crude imine **201** (1.54 g, 82% over two steps) that was used without further purification. δ_H (200 MHz, $CDCl_3$) 1.68 (2H, app. quin, *J* 7.5, CH_2=CHCH$_2$C**H$_2$**), 2.13 (2H, app. q., *J* 7.2, CH_2=CHC**H$_2$**), 2.33–2.35 (2H, m, NCHC**H$_2$**), 4.58 (2H, s, C**H$_2$**Ph), 4.95–5.09 (2H, m, C**H$_2$**=CH), 5.82 (1H, dddd, *J* 17.0, 10.2, 6.9, 6.9, CH_2=C**H**), 7.21–7.45 (5H, m, ArC**H**), 7.80 (1H, t, *J* 4.8, NC**H**).

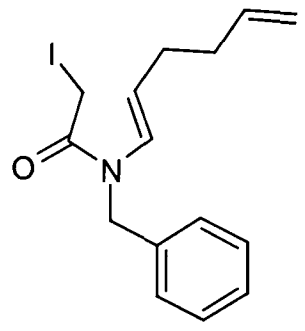
_N_-Benzyl-_N_-hexa-1,5-dienyl-2-chloroacetamide 202 and _N_-Benzyl-2-chloroacetamide 203



To a solution of the crude imine **201** (1.20 g, 6.39 mmol) in DCM (100 mL) at 0°C was added chloroacetyl chloride (519 μL, 6.39 mmol) and *N*,*N*-diethylaniline (1.04 mL, 6.39 mmol) and the mixture allowed to warm to RT. After 4 h the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ether (100 mL) and washed with brine (100 mL). The aqueous layer was extracted with further portions of ether (2 × 100 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave *N*-benzyl-*N*-hexa-1,5-dienyl-2-chloroacetamide **202** (812 mg, 48%) and *N*-benzyl-2-chloracetamide **203** (612 mg, 52%) both as yellow oils. Data for **202**: R_f 0.38 (1:9 EtOAc:petrol, UV active); Accurate mass: Found 264.1153, $C_{15}H_{19}ClNO$ (MH^+) requires 264.1155; ν_{max}/cm^{-1}

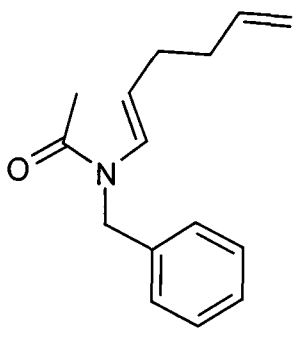
(thin film) 3066w, 3032w, 2977w, 2927m, 2846w, 1677s, 1652s, 1496m, 1437m, 1410s, 1333m, 1260m, 1191m, 1141m, 1080w, 1029w, 944w, 918m; δ_H (400 MHz, $CDCl_3$) major rotamer 2.07–2.18 (4H, m, CH_2=CHC**H**$_2$C**H**$_2$), 4.27 (2H, s, C**H**$_2$Cl), 4.85 (2H, s, C**H**$_2$Ph), 4.91–4.97 (2H, m, C**H**$_2$=CH), 5.21 (1H, ddd, *J* 13.8, 6.9, 6.9, NCHC**H**), 5.65–5.75 (1H, m, CH_2=C**H**), 6.49 (1H, d, *J* 13.8, NC**H**), 7.15–7.38 (5H, m, ArC**H**) [peaks for minor rotamer were also observed at 4.06 (2H, s, C**H**$_2$Cl), 4.84 (2H, s, C**H**$_2$Ph), 5.05 (1H, ddd, *J* 14.0, 7.4, 6.7, NC**H**)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 29.6, 33.7 (CH_2=CH**C**H$_2$, CH_2=CHCH$_2$**C**H$_2$), 41.5 (**C**H$_2$Cl), 48.0 (**C**H$_2$Ph), 115.4 (**C**H$_2$=CH), 118.1 (NCH**C**H), 126.8, 127.1, 127.2, 128.5 (3 × Ar**C**H, N**C**H), 136.4 (*i*-Ar**C**), 137.4 (CH_2=**C**H), 165.3 (**C**=O) [peaks for the minor rotamer were observed at 29.6, 34.1 (CH_2=CH**C**H$_2$, CH_2=CHCH$_2$**C**H$_2$), 41.8 (**C**H$_2$Cl), 49.0 (**C**H$_2$Ph), 113.8 (**C**H$_2$=CH), 115.1 (NCH**C**H), 125.5, 126.4, 127.6, 129.0 (3 × Ar**C**H, N**C**H), 135.6 (*i*-Ar**C**), 137.7 (CH_2=**C**H), 165.1 (**C**=O)]; *m/z* (CI, NH_3) 266 ($M^{37}ClH^+$, 28%), 264 ($M^{35}ClH^+$, 100), 230 (12), 188 (19), 186 (10), 129 (19), 106 (18). Data for **203**: R_f 0.13 (1:9 EtOAc:petrol); m.p. 93 °C [lit.,[208] m.p. 92–93°C]; ν_{max}/cm^{-1} (KBr disk) 3279s, 3063m, 3006m, 2952m, 1649s, 1557s, 1499m, 1454s, 1426s, 1366m, 1334m, 1237s, 1173m, 1063m, 1031m, 1002m, 925m; δ_H (200 MHz, $CDCl_3$) 4.12 (2H, s, C**H**$_2$Cl), 4.51 (2H, d, *J* 5.7, C**H**$_2$Ph), 6.89 (1H, bs, N**H**), 7.29–7.43 (5H, m, ArC**H**); *m/z* (CI, NH_3) 186 ($M^{37}ClH^+$, 8%), 184 ($M^{35}ClH^+$, 22), 150 (100), 148 (10), 128 (48), 122 (25), 106 (13).

_N_-Benzyl-_N_-hexa-1,5-dienyl-2-iodoacetamide 204



To a stirred solution of the chloride **202** (100 mg, 0.38 mmol) in acetone (1 mL) was added NaI (171 mg, 1.14 mmol). After 90 mins at RT the mixture was concentrated *in vacuo*. The residue was diluted with EtOAc (10 mL) and washed with brine (10 mL). After separation, the aqueous layer was extracted with further portions of EtOAc (2 × 10 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave the iodide **204** as a yellow oil (112 mg, 83%). R_f 0.38 (1:9 EtOAc:petrol, UV active); Accurate mass: Found 356.0504, $C_{15}H_{19}INO$ (MH^+) requires 356.0511; ν_{max}/cm^{-1} (thin film) 3064m, 2924m, 2846m, 1645s, 1496m, 1453m, 1430m, 1400s, 1332m, 1290m, 1220m, 1163m, 1099m, 1076m, 952m, 915m; δ_H (400 MHz, $CDCl_3$) major rotamer 2.04–2.17 (4H, m, CH_2=CHC**H$_2$**C**H$_2$**), 3.93 (2H, s, C**H$_2$**I), 4.84 (2H, s, C**H$_2$**Ph), 4.91–4.98 (2H, m, C**H$_2$**=CH), 5.18–5.25 (1H, ddd, *J* 14.0, 6.9, 6.9, NCHC**H**), 5.67–5.77 (1H, m, CH_2=C**H**), 6.46 (1H, d, *J* 14.0, NC**H**), 7.16–7.39 (5H, m, ArC**H**) [peaks for the minor rotamer were also observed at 3.69 (2H, s, C**H$_2$**I), 4.81 (2H, s, C**H$_2$**Ph), 5.05 (1H, ddd, *J* 14.0, 7.1, 7.1, NC**H**)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer –3.3 (**C**H_2I), 29.7, 33.7 (CH_2=CH**C**H_2**C**H_2), 47.8 (**C**H_2Ph), 115.4 (**C**H_2=CH), 117.4 (NCH**C**H), 126.9, 127.1, 127.9, 128.5 (3 × Ar**C**H, N**C**H), 136.7 (*i*-Ar**C**), 137.5 (CH_2=**C**H), 166.7 (**C**=O) [peaks for the minor rotamer were observed at –3.1 (**C**H_2I), 29.7, 34.1 (CH_2=CH**C**H**C**H_2), 50.1 (**C**H_2Ph), 113.5 (**C**H_2=CH), 115.1 (NCH**C**H), 125.4, 126.8, 127.6, 129.0 (3 × Ar**C**H, N**C**H), 135.7 (*i*-Ar**C**), 137.7 (CH_2=**C**H), 166.6 (**C**=O)]; *m/z* (CI, NH_3) 357 (16%), 356 (MH^+, 100), 228 (12), 188 (35), 122 (38).

_N_-Benzyl-_N_-hexa-1,5-dienyl-2-iodoacetamide 205



Method 1

To a degassed solution of the chloride **202** (100 mg, 0.38 mmol) in chlorobenzene (19 mL) at 90°C was added a degassed solution of tri-*n*-butyltin hydride (113 μL, 0.41 mmol) and AIBN (6 mg, 0.038 mmol) in chlorobenzene (20 mL) *via* syringe pump over a period of 5 h. After a further 16 h at 90°C the reaction mixture was concentrated *in vacuo*. Ether (10 mL) and 10% aq. KF solution (10 mL) were added and the mixture stirred at RT for 3 h. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave the directly reduced product **205** (40 mg, 46%) as a colourless oil and unreacted starting material **202** (40 mg, 40%). R_f 0.25 (1:9 EtOAc:petrol, UV active); Accurate mass: Found 230.1540, $C_{15}H_{20}NO$ (MH^+) requires 230.1545; ν_{max}/cm^{-1} (thin film) 3066m, 2976m, 2926m, 2847m, 1674s, 1652m, 1496m, 1403s, 1360m, 1330s, 1279m, 1216s, 987m, 934m, 913m; δ_H (400 MHz, $CDCl_3$) major rotamer 2.03–2.14 (4H, m, CH_2=CHC**H$_2$**C**H$_2$**), 2.30 (3H, s, C**H$_3$**), 4.86 (2H, s, C**H$_2$**Ph), 4.88–5.03 (3H, m, C**H$_2$**=CH, NCHC**H**), 5.65–5.76 (1H, m, CH_2=C**H**), 6.56 (1H, d, *J* 13.7, NC**H**), 7.15–7.41 (5H, m, ArC**H**) [peaks for minor rotamer were also observed at 2.15 (3H, s, C**H$_3$**) and 4.75 (2H, s, C**H$_2$**Ph)]; δ_C (100.6 MHz, $CDCl_3$) major rotamer 22.2 (**C**H$_3$), 29.8, 34.2 (CH_2=CH**C**H$_2$**C**H$_2$), 46.5 (**C**H$_2$Ph), 113.5 (**C**H$_2$=CH), 115.2 (NCH**C**H), 125.6, 126.9, 128.4, 128.7 (3 × Ar**C**H, N**C**H), 137.1 (*i*-Ar**C**), 137.6 (CH_2=**C**H), 169.3 (**C**=O) [peaks for the minor rotamer

were observed at 22.3 (**C**H_3), 29.7, 34.3 (CH_2=CH**C**H_2**C**H_2), 49.6 (**C**H_2Ph), 111.7 (**C**H_2=CH), 114.9 (NCH**C**H), 126.3, 127.3, 127.8, 128.8 (3 × Ar**C**H, N**C**H), 136.2 (*i*-Ar**C**), 137.9 (CH_2=**C**H), 169.4 (**C**=O)]; *m/z* (CI, NH_3) 231 (15%), 230 (MH^+, 100), 188 (87), 150 (14), 112 (12).

Method 2

To a degassed solution of the chloride **202** (100 mg, 0.38 mmol) in chlorobenzene (19 mL) at 90°C was added a degassed solution of tri-*n*-butyltin hydride (113 μL, 0.41 mmol) and AIBN (6 mg, 0.038 mmol) in chlorobenzene (20 mL) *via* syringe pump over a period of 0.5 h. After a further 16 h at 90°C the reaction mixture was concentrated *in vacuo*. Ether (10 mL) and 10% aq. KF solution (10 mL) were added and the mixture stirred at RT for 3 h. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave the directly reduced product **205** (65 mg, 75%) as a colourless oil and unreacted starting material **202** (7 mg, 7%). Data as above.

Method 3

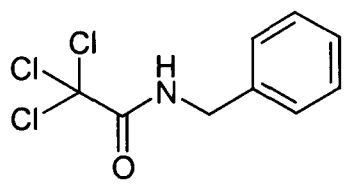
To a degassed solution of the iodide **204** (50 mg, 0.14 mmol) in chlorobenzene (7 mL) at 90°C was added a degassed solution of tri-*n*-butyltin hydride (42 μL, 0.15 mmol) and AIBN (2.5 mg, 0.014 mmol) in chlorobenzene (10 mL) *via* syringe pump over a period of 5 h. After a further 16 h at 90°C the reaction mixture was concentrated *in vacuo*. Ether (5 mL) and 10% aq. KF solution (5 mL) were added and the mixture stirred at RT for 3 h. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave the

directly reduced product **205** (19 mg, 59%) as a colourless oil and unreacted starting material **204** (12 mg, 24%). Data as above.

Method 4

A degassed solution of the iodide **204** (50 mg, 0.14 mmol), tri-*n*-butyltin hydride (42 μL, 0.15 mmol), tri-*n*-butyltin chloride (199 μL, 0.70 mmol) and AIBN (2.5 mg, 0.014 mmol) in chlorobenzene (17 mL) were heated at 90°C for 16 h and then concentrated *in vacuo*. Ether (15 mL) and 10% aq. KF solution (15 mL) were added and the mixture stirred at RT for 3 h. The organic layer was separated and dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) gave the directly reduced product **205** (28 mg, 88%) as a colourless oil. Data as above.

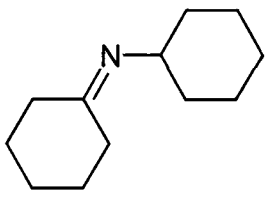
N-Benzyl-2,2,2-trichloroacetamide 207



To a solution of the crude imine **201** (144 mg, 0.77 mmol) in DCM (15 mL) at 0°C was added trichloroacetyl chloride (87 μL, 0.77 mmol) and *N*,*N*-diethylaniline (125 μL, 0.77 mmol) and the mixture allowed to warm to RT. After 4 h the mixture was filtered and the filtrate concentrated *in vacuo*. The residue was dissolved in ether (25 mL) and washed with brine (25 mL). The aqueous layer was extracted with further portions of ether (2 × 25 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography on silica (1:9 ether:petrol) the trichloride **207** as a white solid (174 mg, 90%). R_f 0.34 (1:9 EtOAc:petrol); m.p. 92°C [lit.,[209] m.p.

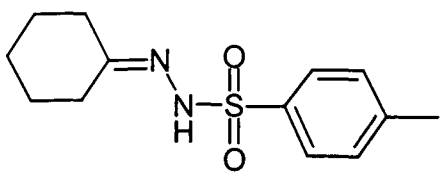
90–92°C]; ν_{max}/cm^{-1} (KBr disk) 3303m, 3274m, 3033m, 1704s, 1686s, 1530s, 1496m, 1454m, 1425m, 1357m, 1236m, 1082m, 1031m, 820s; δ_H (200 MHz, $CDCl_3$) 4.57 (2H, d, *J* 5.8, C**H**$_2$Ph), 6.95 (1H, bs, N**H**), 7.29–7.45 (5H, m, ArC**H**); *m/z* (CI, NH_3) 273 ($M^{37}Cl^{37}Cl^{35}ClNH_4^+$, 51%), 271 ($M^{37}Cl^{35}Cl^{35}ClNH_4^+$, 93), 269 ($M^{35}Cl^{35}Cl^{35}ClNH_4^+$, 95), 256 ($M^{37}Cl^{37}Cl^{35}ClH^+$, 18), 254 ($M^{37}Cl^{35}Cl^{35}ClH^+$, 48), 252 ($M^{35}Cl^{35}Cl^{35}ClH^+$, 50), 220 (25), 219 (17), 218 (71), 217 (30), 216 (100), 215 (12), 182 (14), 180 (27), 109 (45), 107 (34), 94 (11), 93 (68).

_N_-cyclohexylidene cyclohexylamine 211



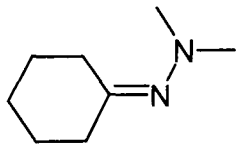
A stirred solution of cyclohexanone (2.57 mL, 23.8 mmol) and cyclohexylamine (2.78 mL, 23.8 mmol) in benzene (25 mL) was heated at reflux under a Dean-Stark water separator for 18 h. The resulting imine **211** was freed from the more volatile starting materials by concentrating *in vacuo* to give a yellow oil (3.52 g, 82%) R_f 0.28 (1:2 ether:petrol); ν_{max}/cm^{-1} (thin film) 2927s, 2853s, 1716m, 1657s, 1448s, 1345m, 1311w, 1226m, 1127w, 954w, 890w, 775w; δ_H (400 MHz, $CDCl_3$) 0.99–1.43 (6H, m) 1.87 (10H, m), 2.21–2.33 (4H, m, C**H**$_2$C(N)C**H**$_2$), 3.23–3.31 (1H, m, NC**H**); *m/z* (CI, NH_3) 180 (MH^+, 100%).

_N_-Cyclohexylidene _p_-toluenesulphonylhydrazine 212



To a stirred solution of cyclohexanone (2.16 mL, 20.38 mmol) in AcOH (35 mL) was added *p*-toluenesulfonylhydrazine (7.59 g, 40.75 mmol) in one portion. After 1 h the thick white precipitate that had formed was collected and washed with water (3 × 50 mL). The solid was then dissolved in DCM and dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the tosyl hydrazine **212** as a white solid (4.00 g, 74%). R_f 0.45 (1:2 EtOAc:petrol, UV active); m.p. 152–153 °C [lit.,[210] m.p. 153 °C]; ν_{max}/cm^{-1} (KBr disk) 3265s, 2932s, 2852s, 1634s, 1596s, 1492s, 1446s, 1430s, 1399s, 1324s, 1290s, 1166s, 1094s, 1042s, 944s, 815s; δ_H (400 MHz, $CDCl_3$) 1.55–1.63 (6H, m, N=CCH$_2$(C**H$_2$**)$_3$), 2.22 (4H, t, *J* 6.0, C**H$_2$**CC**H$_2$**), 2.42 (3H, s, C**H$_3$**), 7.30 (2H, d, *J* 8.0, ArC**H**), 7.84 (2H, d, *J* 8.0, ArC**H**); *m/z* (CI, NH_3) 267 (MH^+, 100%) 111 (46).

_N_-Cyclohexylidine-_N'_,_N'_-dimethylhydrazine 213



A stirred solution of cyclohexanone (2.16 mL, 20 mmol), *N,N*-dimethylhydrazine (1.86 mL, 24 mmol) and trifluoroacetic acid (0.001 mL) in benzene (10 mL) was heated at reflux under a Dean-Stark water separator for 5 h and then cooled to room temperature. The reaction mixture was then diluted with water (10 mL) and extracted with ether (3 × 20 mL). The organic layer was then washed successively with water (10 mL) and brine (10 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Reduced pressure distillation (74°C @ 19 mmHg) gave the *N,N*-dimethylhydrazine **213** as a colourless oil (1.80 g, 64%). R_f 0.27 (1:4 petrol:EtOAc); ν_{max}/cm^{-1}

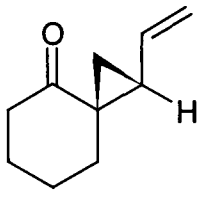
(thin film) 2982s, 2932s, 2856s, 2815s, 2771m, 1635s, 1468s, 1449s, 1347w, 1200m, 1021m, 995s, 964s, 850w; δ_H (400 MHz, $CDCl_3$) 1.56–1.72 (6H, m, $N{=}CCH_2(CH_2)_3$), 2.23 (2H, t, *J* 6.3, CH_2CCH_2), 2.42 (6H, s, $N(CH_3)_2$), 2.49 (2H, t, *J* 6.0, CH_2CCH_2); *m/z* (CI, NH_3) 141 (MH^+, 100%), 139 (13) 124 (15).

1-Chloro-4-iodo-2-butene 214

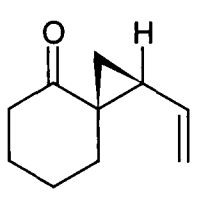


To a stirred solution of *cis*-1,4-dichloro-2-butene (10 mL, 90 mmol) in acetone (20 mL) was added in one portion NaI (8.12 g, 54 mmol). A thick brown precipitate formed so a further portion of acetone (10 mL) was added to assist with stirring. After 2 h the reaction mixture was diluted with petrol (100 mL) and washed with sat. aq. $NaHSO_3$ solution (50 mL) to remove the iodine present. The aqueous phase was extracted with further portions of petrol (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The crude product was then distilled under reduced pressure (10 mmHg), collecting the fraction that boiled between 86–88°C to give the title compound **214** as a pale green liquid (5.84 g, 50%). R_f 0.53 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 3035m, 2955m, 1656w, 1439m, 1314m, 1250s, 1151s, 1084m, 961s, 782m, 684s; δ_H (200 MHz, $CDCl_3$) 3.87 (2H, d, *J* 7.6, CH_2I), 4.05 (2H, d, *J* 6.7, CH_2Cl), 5.84 (1H, dt., *J* 7.4, 6.7, $CHCH_2Cl$), 6.05 (1H, dt, *J* 7.6, 7.4, $CHCH_2I$); *m/z* (EI) 218 ($M^{37}Cl^+$, 8%), 216 ($M^{35}Cl^+$, 16), 181 (22), 127 (20), 92 (49), 91 (15), 90 (100).

1-Vinyl-spiro[2.5]octan-4-one 216 and 217



216



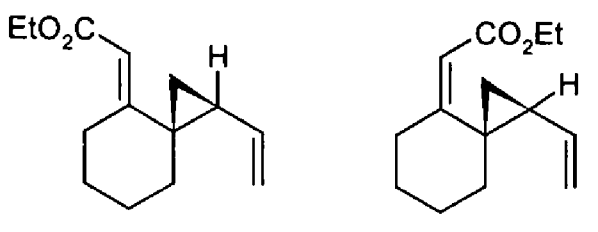
217

To a stirred solution of diisopropylamine (3.24 mL, 23 mmol) in THF (88 mL) at 0°C was added *n*-butyllithium (9.24 mL of a 2.5M solution in hexanes, 23 mmol) followed, after 30 mins, by the addition of cyclohexanone (2.28 mL, 22 mmol). After stirring for a further 30 mins at 0°C *Z*-4-chloro-1-iodo-2-butene **214** (2.68 mL, 23 mmol) was added and the mixture allowed to warm to RT slowly over 2.5 h. The reaction was quenched by the addition of sat. aq. NH_4Cl solution (150 mL) and extracted with ether (3 × 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude chloride **215** (5.301 g) which was used crude in the next reaction. R_f 0.20 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2936m, 2862m, 1710s, 1448m, 1312w, 1252w, 1129m, 972m, 733w; δ_H (400 MHz, $CDCl_3$) 1.31–1.44 (1H, m), 1.53–1.72 (2H, m), 1.82–1.93 (1H, m), 1.97–2.18 (3H, m), 2.27–2.44 (3H, m) 2.53 (1H, dt, *J* 14.3, 5.9, COC**H**), 4.02 (2H, d, *J* 6.9, C**H**$_2$Cl), 5.59–5.68 (1H, m, C**H**=), 5.70–5.80 (1H, m, C**H**=); δ_C (125 MHz, $CDCl_3$) 25.0 (**C**H_2), 27.9 (**C**H_2), 32.0 (**C**H_2), 33.5 (**C**H_2), 42.1 (**C**H_2), 45.2 (**C**H_2), 50.2 (CO**C**H), 127.7 (**C**H=), 133.5 (**C**H=) 212.2 (**C**=O); *m/z* (CI, NH_3) 152 (11), 151 (MH^+–Cl, 100%).

The a stirred solution of the crude chloride **215** from the previous reaction (≤22 mmol) in THF (50 mL) and *tert*-butanol (50 mL) at RT was added potassium KO^{t}Bu (2.60 g, 23 mmol) and stirring was continued for 6 h. Sat. aq. NH_4Cl solution (100 mL) was added and the aqueous layer

extracted with ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow/brown oil. Column chromatography on silica (1:40 ether:petrol) gave the two diastereomers **216** (1.35 g, 41% over two steps) and **217** (0.77 g, 23% over two steps) as colourless oils. Data for **216**: R_f 0.28 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2933m, 1697s, 1634w, 1448m, 1362m, 1118m, 996w, 901m; δ_H (400 MHz, $CDCl_3$) 0.70–0.88 (1H, m, CC**H**HCH), 1.35 (1H, dd, *J* 14.0, 2.6, CC**H**HCH_2), 1.64–1.88 (5H, m, CCH**H**C**H**, CCH**H**C**H₂**), 1.98–2.13 (3H, m, COC**H**HC**H₂**), 2.46 (1H, app. dd, *J* 13.3, 3.2, COCH**H**), 4.95 (1H, app. dt, *J* 9.8, 1.4, CH=C**H**$_E$CH$_Z$), 5.15 (1H, app. dt, *J* 17.6, 1.4, CH=CH$_E$C**H**$_Z$), 5.31 (1H, ddddd, *J* 17.6, 9.8, 7.2, 1.4, 1.4, C**H**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 17.9 (**C**H_2), 23.9 (**C**H_2), 25.4 (**C**H_2), 35.0 (**C**H), 35.8 (**C**H_2), 37.4 (**C**°), 41.7 (CO**C**H_2), 115.6 (=**C**H_2), 135.6 (**C**H=CH_2), 208.4 (**C**=O); *m/z* (CI, NH_3) 168 (MNH_4^+, 10%), 152 (13) 151 (MH^+, 100). Data for **217**: R_f 0.21 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 3082w, 2940m, 2863m, 1692s, 1635m, 1449m, 1360m, 1136m, 987m, 904m; δ_H (400 MHz, $CDCl_3$) 0.68 (1H, dd, *J* 6.5, 4.1, CC**H**HCH), 1.65 (1H, dd, *J* 9.0, 4.1, CCH**H**CH) overlays 1.60–1.82 (4H, m, CC**H₂**C**H₂**), 1.84–1.95 (2H, m, COCH$_2$C**H₂**), 2.01 (1H, app. q, *J* 7.9, CCH$_2$C**H**), 2.33–2.46 (2H, m, COC**H₂**), 5.14 (1H, ddd, *J* 10.3, 1.6, 0.8, CH=C**H**$_E$CH$_Z$), 5.19 (1H, ddd, *J* 17.1, 1.6, 0.8, CH=CH$_E$C**H**$_Z$), 5.59 (1H, ddd, *J* 17.1, 10.3, 8.2, C**H**=CH_2); δ_C (100.6 MHz, $CDCl_3$) 22.0 (C**C**H$_2$CH), 23.4 (**C**H_2), 24.0 (**C**H_2), 28.5 (**C**H_2), 32.2 (CH_2=CHC**H**), 35.0 (**C**°), 39.8 (CO**C**H_2), 117.4 (=**C**H_2), 135.1 (**C**H=CH_2), 190.0 (**C**=O); *m/z* (CI, NH_3) 168 (MNH_4^+, 10%), 152 (12), 151 (MH^+, 100).

4-Carboethoxymethylene-1-vinylspiro[2.5]octane 218 and 219



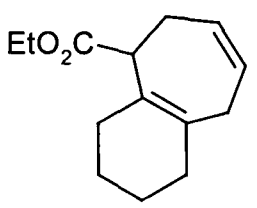
E-
218

Z-
219

To a suspension of NaH (88 mg of a 60% dispersion in mineral oil, 2.20 mmol) in dry DME (3 mL) at RT was slowly added triethyl phosphonoacetate (0.46 mL, 2.20 mmol). After 1 h a solution of vinylcyclopropane **217** (220 mg, 1.46 mmol) in dry DME (1 mL) was added and the mixture stirred for 40 h. After quenching with sat. aq. NH_4Cl solution (15 mL) and extracting with ether (3 × 10 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography on silica (1:40 ether:petrol) gave the two vinylcyclopropane diastereomers **218** (168 mg, 52%) and **219** (59 mg, 19%) as colourless oils. Data for **218**: R_f 0.41 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2981m, 2932s, 2857m, 1716s, 1642s, 1447m, 1372m, 1305m, 1178s, 1038s, 901m; δ_H (400 MHz, $CDCl_3$) 0.60 (1H, app. t, *J* 5.5, CC**H**HCH), 1.22 (1H, dd, *J* 8.7, 5.1, CC**H**HCH$_2$), 1.28 (3H, t, *J* 7.1, C**H$_3$**), 1.43–1.71 (6H, m, =CCH$_2$CH**H**C**H$_2$**C**H$_2$**CCH$_2$C**H**), 1.76–1.83 (1H, m, =CCH$_2$C**H**H), 2.36–2.43 (1H, m, =CC**H**H) 3.42 (1H, app. dt, *J* 13.4, 4.2, =CCH**H**), 4.14 (2H, q, *J* 7.1, OC**H$_2$**), 5.08 (1H, ddd, *J* 10.2, 1.8, 0.7, CH=C**H$_E$**CH$_Z$), 5.16 (1H, ddd, *J* 17.0, 1.8, 0.7, CH=CH$_E$C**H$_Z$**), 5.52 (1H, s, C=C**H**), 5.62 (1H, ddd, *J* 17.0, 10.2, 8.4, C**H**=CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 14.3 (**C**H$_3$), 18.5 (**C**H$_2$), 24.7 (**C**H$_2$), 27.1 (**C**H$_2$), 29.2 (CH$_2$=CH**C**H), 29.5 (**C**H$_2$), 32.3 (**C**H$_2$), 33.3 (**C**°), 59.6 (O**C**H$_2$), 110.9 (C=**C**H), 115.7 (=**C**H$_2$), 136.5 (**C**H=CH$_2$), 165.7 (**C**=CH), 167.3 (**C**=O); *m/z* (CI, NH_3) 221 (MH^+, 100%), 175 (12), 147 (15). Data for **219** R_f 0.36 (1:9 ether:petrol, UV active); ν_{max}/cm^{-1} (thin film) 2981m, 2934s, 2857m, 1721s, 1644s, 1445m,

1336w, 1228s, 1179s, 1116m, 1037s, 901m; δ_H (400 MHz, $CDCl_3$) 0.78 (1H, app. t, *J* 5.7, CC**H**HCH), 1.09 (1H, dd, *J* 8.7, 5.4, CC**H**HCH$_2$), 1.29 (3H, t, *J* 7.1, C**H**$_3$), 1.42–1.85 (7H, m, =CCH$_2$C**H**$_2$C**H**$_2$C**H**$_2$CCH$_2$C**H**) 2.25–2.29 (2H, m, =CC**H**$_2$), 4.08–4.22 (2H, m, OC**H**$_2$), 5.06 (1H, dd, *J* 10.3, 1.8, CH=C**H**$_E$CH$_Z$), 5.14 (1H, ddd, *J* 17.0, 1.8, 0.7, CH=CH$_E$C**H**$_Z$), 5.57 (1H, s, C=C**H**), 5.74 (1H, ddd, *J* 17.0, 10.3, 8.2, C**H**=CH$_2$); δ_C (100.6 MHz, $CDCl_3$) 14.2 (**C**H$_3$), 21.1 (**C**H$_2$), 24.8 (**C**H$_2$), 29.2 (**C**H$_2$), 29.5 (CH$_2$=CH**C**H), 30.9 (**C**°), 32.7 (**C**H$_2$), 37.9 (**C**H$_2$), 60.0 (O**C**H$_2$), 112.9 (C=**C**H), 115.0 (=**C**H$_2$), 137.1 (**C**H=CH$_2$), 162.2 (**C**=CH), 166.5 (**C**=O); *m/z* (CI, NH_3) 238 (MNH_4^+, 4%), 222 (18), 221 (MH^+, 100), 147 (15).

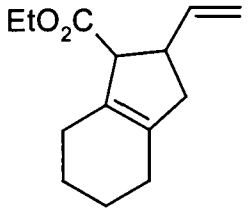
2-Carboethoxybicyclo[5.4.0]undeca-1(7),4(5)-diene 220



To a suspension of NaH (44 mg of a 60% dispersion in mineral oil, 1.10 mmol) in dry DME (2 mL) at RT was slowly added triethyl phosphonoacetate (0.23 mL, 1.10 mmol). After 1 h a solution of 1-vinyl-spiro[2.5]octan-4-one **216** (150 mg, 1.00 mmol) in dry DME (1 mL) was added and the mixture stirred for 40 h. After quenching with sat. aq. NH_4Cl solution (15 mL) and extracting with ether (3 × 10 mL), the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Column chromatography on silica (1:40 ether:petrol) gave the bicyclic ester **220** as a colourless oil (41 mg, 19%). R_f 0.56 (1:2 ether:petrol); Accurate mass: Found 221.1542, $C_{14}H_{21}O_2$ (MH^+) requires 221.1542; ν_{max}/cm^{-1} (thin film) 2928s, 1735s, 1439m, 1370m, 1310m, 1195m, 1155s,

1096m, 1027m; δ_H (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, C**H**$_3$), 1.49–1.68 (4H, m, C=CCH$_2$C**H**$_2$C**H**$_2$) 1.87–2.08 (4H, m, C=CC**H**$_2$CH$_2$CH$_2$C**H**$_2$), 2.32–2.49 (3H, m, C(O)CHC**H**HCH=CHC**H**$_2$), 3.02 (1H, bd, *J* 19.2 C(O)CHCH**H**) 3.60 (1H, dd, *J* 9.7, 2.8, COC**H**), 4.17 (2H, q, *J* 7.1, OC**H**$_2$), 5.54–5.64 (2H, m, C**H**=C**H**); δ_C (100.6 MHz, $CDCl_3$) 14.3 (**C**H$_3$), 22.8, 22.8 (C=CCH$_2$**C**H$_2$**C**H$_2$), 27.7 (CHC=**C**CH$_2$), 28.4 (C=**C**CH$_2$CH), 32.3 (CH**C**CH$_2$), 33.5 (COCH**C**H$_2$), 47.2 (CO**C**H), 60.3 (O**C**H$_2$), 126.9, 128.1 (H**C**=**C**H), 129.9, 134.7 (**C**=**C**), 173.9 (**C**=O); *m/z* (CI, NH_3) 222 (29%), 221 (MH^+, 100), 147 (16), 146 (10).

3-Carboethoxy-2-ethenyl-2,3,4,5,6,7-hexahydro-1*H*-indene 210



Method 1

To a degassed solution of vinylcyclopropane diastereomers **218** and **219** (40 mg, 0.18 mmol) and AIBN (3 mg, 0.018 mmol) in benzene (60 mL) was added a degassed solution of tri-*n*-butyltin hydride (0.049 mL, 0.18 mmol) and AIBN (3 mg, 0.018 mmol) in benzene (4 mL) *via* syringe pump over a period of 4 h. The resulting solution was then stirred for a further 1 h and then concentrated *in vacuo*. Column chromatography on silica (1:40 ether:petrol) gave the bicyclic ester **210** as a colourless oil (38 mg, 95%) and as an inseparable 1:1 mixture of diastereomers. R_f 0.42 (1:9 ether:petrol); Accurate mass: Found 221.1537, $C_{14}H_{21}O_2$ (MH^+) requires 221.1542; ν_{max}/cm^{-1}

(thin film) 2929s, 1734s, 1641w, 1445m, 1368m, 1336m, 1162s, 1035m, 913m; δ_H (400 MHz, $CDCl_3$) 1.21–1.28 (3H, m, C**H**$_3$), 1.55–1.68 (4H, m, C=CCH$_2$C**H**$_2$C**H**$_2$), 1.86–2.05 (4H, m, C**H**$_2$C=CC**H**$_2$), 2.11–2.18 (0.5H, m, CH$_2$=CHCHC**H**H diastereomer **A**), 2.37 (1H, dd, *J* 7.8, 1.1, CH$_2$=CHCHCH**H**), 2.52–2.58 (0.5H, m, CH$_2$=CHCHC**H**H diastereomer **B**), 3.12–3.22 (1.5H, m, CH$_2$=CHC**H**, COC**H** diastereomer **A**), 3.41 (1H, app. d, *J* 8.7, COC**H** diastereomer **B**), 4.06–4.20 (2H, m, OC**H**$_2$), 4.94–5.10 (2H, m, C**H**$_2$=CH), 5.8 (1H, ddd, *J* 17.1, 10.2, 7.7, CH$_2$=C**H**); δ_C (100.6 MHz, $CDCl_3$) (doubling due to two diastereomers) 14.4, 14.4 (**C**H$_3$), 22.5, 22.7, 22.7, 22.8 (C=CCH$_2$**C**H$_2$**C**H$_2$), 24.2, 24.6, 25,7, 25.7 (**C**H$_2$C=**C**CH$_2$), 41.2, 41.6 (CH$_2$=CHCH**C**H$_2$), 44.9, 45.4 (CH$_2$=CH**C**H), 58.3, 59.6 (CO**C**H), 59.9, 60.3 (O**C**H$_2$), 113.8, 115.3 (**C**H$_2$=CH), 131.4, 132.1 (**C**=CCH), 137.2, 138.3 (C=**C**CH), 139.1, 141.5 (CH$_2$=**C**H), 173.3, 174.6 (**C**=O); *m/z* (CI, NH_3) 238 (MNH_4^+, 17%), 222 (18), 221 (MH^+, 100), 147 (29).

Method 2

A degassed solution of vinylcyclopropane diastereomers **218** and **219** (40 mg, 0.18 mmol), tri-*n*-butyltin hydride (0.012 mL, 0.045 mmol) and AIBN (6.0 mg, 0.036 mmol) in benzene (36 mL) was heated at reflux for 5 h and then concentrated *in vacuo*. Column chromatography on silica (40:1 petrol:ether) gave the bicyclic ester **210** as a colourless oil (36 mg, 90%). Data as above.

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APPENDICES

APPENDIX 1: n.O.e. SPECTRUM FOR 179

