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Synthesis & Reactions of Cyclopropenones



University of
HUDDERSFIELD

Muhammad Ilyas Qamar

A Thesis Submitted to the University of Huddersfield
in Partial Fulfilment of the Requirements for
the Degree of Doctor of Philosophy

University of Huddersfield
Department of Chemical & Biological Sciences

September 2011

I would like to dedicate this thesis to my mother and father, for their constant love, support and encouragement, they have made many sacrifices, faced many hardships and worked countless hours so that I could have a better life. Without them none of this would be possible.

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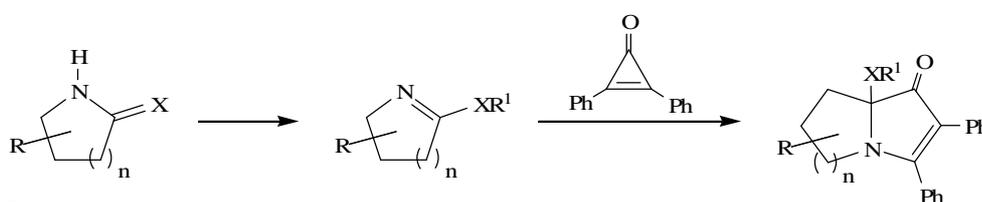
During the last four years I have had many good and bad times and I would like to say thank you to all my friends who have been there for me, knowingly or otherwise, it's been a rollercoaster of a ride and it wouldn't have been the same without them.

Lastly my family, their love, support and constant belief in me have made me who I am today, so I would like to say thank you from the bottom of my heart to my mum and dad, for never doubting me and always showing me love, to my brothers and sister for supporting me in every way they could, and to my three nephews for making me laugh and driving me crazy.

If I have missed anyone off this list I am deeply sorry, but there may be a small space at the bottom of this page, you might be able to write your name in.

Abstract

This thesis describes the synthesis of pyrrolizidines, indolizidines and pyrroloazepines from the reaction of cyclopropenones with a wide range of five, six and seven-membered cyclic imines. These three alkaloids nuclei are widespread in nature and have shown many potential pharmaceutical properties. The cyclic imines were typically synthesised by thionation and alkylation of their corresponding lactams, although other cyclic imines were investigated. The imines were then reacted with diphenylcyclopropenone (DPP), as illustrated below:¹



X = O or S

The pyrrolizidine, indolizidine and pyrroloazepine reactivity was exploited by oxidising the bridgehead group (X = S) with *m*-CPBA, giving rise to new products, including a sulfoxide elimination product, and an unexpected hydroxy compound. This was a useful discovery, given the presence of such a bridgehead OH in the jenamidine natural products. This thesis explores ways in which this may have occurred and also looks at alternative methods.

The synthesis of cyclopropenones other than DPP is described along with attempts at reacting them with 5-membered cyclic imines (1-pyrrolines).

Also included is a study of nitrile oxides as traditional 1,3-dipoles and their reaction with 1-pyrrolines. Finally, an exploration of the reactivity of diphenylcyclopropanone with acyclic imines derived from Ellman's 2-methyl-2-propanesulfinamide is included, which gave unexpected access to an indenone.

I. O'Gorman, P. A.; Chen, T.; Cross, H. E.; Naeem, S.; Pitard, A.; Qamar, M. I.; Hemming, K. *Tetrahedron Letters* **2008**, *49*, 6316-6319.

Abbreviations

Å	Ångstrom	DME	Dimethoxyethane
Ac	Acetyl	DMF	Dimethylformamide
Aq	Aqueous	DMP	Dimethoxypropane
Ar	Aryl	DPP	Diphenylcyclopropanone
b	Broad (NMR)	dt	Doublet of triplets (NMR)
bd	Broad Doublet (NMR)	dq	Doublet of quartets (NMR)
br	Broad (IR)	eq/ equiv	Equivalents
bs	Broad Singlet (NMR)	ESI+	Electron Spray Ionisation
Bu	Butyl [(CH ₂) ₃ CH ₃]	Et	Ethyl [CH ₂ CH ₃]
Conc./ c.	Concentrated	EtOAc	Ethyl Acetate
COSY	Correlation Spectroscopy	H	Proton (NMR)
d	Doublet (NMR)	h	Hour
DCM	Dichloromethane	HIV	Human Immunodeficiency Virus
dd	Doublet of doublets (NMR)	HMBC	Heteronuclear Multiple Bond Correlation
ddd	Doublet of doublets of doublets (NMR)	HMPA	Hexamethylphosphoramide
dddd	Doublet of doublets of doublets of doublets (NMR)	HRMS	High Resolution Mass Spectrometry
ddq	Doublet of doublet of quartets (NMR)	HSQC	Heteronuclear Single Quantum Coherence
DEPT	Distortionless Enhancement by Polarization Transfer	Hz	Hertz
dil.	Dilute	IR	Infrared
		J	Coupling constant (NMR)
		LDA	Lithium diisopropylamide

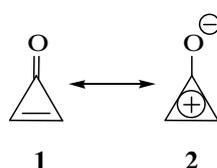
l/ liq.	Liquid	quint	Quintet (^1H NMR)
LRMS	Low Resolution Mass Spectrum	rt	Room Temperature
M	Molar (unit of concentration, moles per litre)	s	Strong (IR)/ Singlet (NMR)
m	Multiplet (NMR)/ Medium (IR)	sext	Sextet
m-CPBA	<i>meta</i> -chloroperoxybenzoic acid	t	Triplet (NMR)
Me	Methyl [CH_3]	tert/ t-	Tertiary
mg	Milligrams	Tf	Triflate [CF_3SO_2]
mmol	Millimole	THF	Tetrahydrofuran
MS	Mass Spectrum	TLC	Thin Layer Chromatography
NMR	Nuclear Magnetic Resonance	Ts	Tosyl [$\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2$]
NOE	Nuclear Overhauser Effect	tt	Triplet of triplets
NOESY	Nuclear Overhauser Effect Spectroscopy	vs	Very Strong (IR)
		vw	Very weak (IR)
p-	<i>Para</i>	w	Weak (IR)
PTSA	<i>para</i> -Toluene Sulfonic Acid	δ	Chemical shift (unit in NMR)
PE	Petroleum Ether	$^\circ\text{C}$	Degrees Celsius
Ph	Phenyl	$[\text{M}+\text{Na}]^+$	Molecular ion and sodium
ppm	Parts Per Million (NMR)	$[\text{M}+\text{H}]^+$	Molecular ion and proton
Pr	Propyl [$(\text{CH}_2)_2\text{CH}_3$]	μl	Microlitres
q	Quartet (^1H NMR)	~	Approximately
	Quaternary carbon (^{13}C NMR)	ν_{max}	Wavelength (IR)

Introduction

1 Introduction

This thesis is based on the use of cyclopropenones for the synthesis of pyrrolizidines and indolizidines. The introduction will detail past and present methods for the synthesis of cyclopropenones and their reactivity. A brief section on the pyrrolizidines and indolizidines will also be included.

1.1 Cyclopropenones

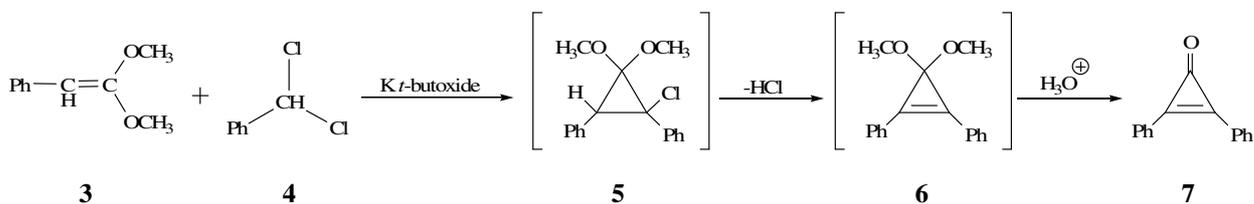


The most basic cyclopropenone **1**, consists of a three-carbon based ring with a carbonyl group. The unsubstituted cyclopropenone can be represented as its delocalised form **2**, in which the cyclopropenylum cation displays Hückel aromaticity.¹⁻⁴ The aromatic nature of cyclopropenones has been controversial,^{5,6} but recent literature suggests that the carbonyl on the ring creates a pseudo 2π system.⁴

Cyclopropenones have a large ring strain which accounts for their high reactivity.² It is also suggested by Hopkins *et al.* that it has the largest strain energy of any three-membered alicyclic compound.⁶ Cyclopropenones are amphiphilic molecules and are reactive towards nucleophilic and electrophilic reagents.²

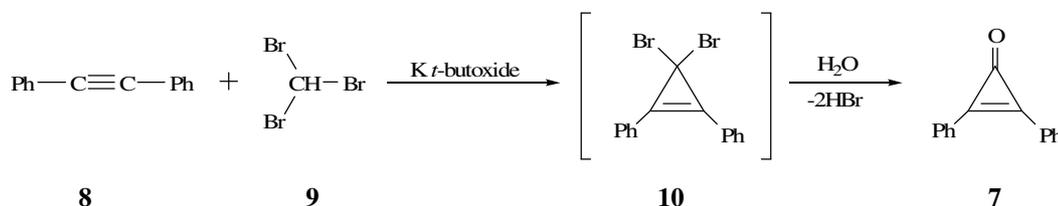
In 1959 Breslow *et al.* synthesised diphenylcyclopropenone **7**,⁷ the first synthesis of a cyclopropenone in the literature. At the time no three-membered ring with a carbonyl group attached was known to be stable, and therefore it was a very attractive challenge. Breslow *et al.* reacted benzal chloride **4** with phenyl ketene dimethyl acetal **3** in the presence of potassium *t*-butoxide. The suggested mechanism involves the addition of a carbene to the

double bond of the ketene acetal giving a cyclopropanone ketal intermediate **5**, β -elimination of HCl to give the cyclopropenone ketal **6** followed by hydrolysis to afford the diphenylcyclopropenone **7**.^{7,8}



Scheme 1.1

At a similar time Vol'pin *et al.* independently synthesised diphenylcyclopropenone **7** by reaction of tribromomethane **9** with diphenylacetylene **8** in the presence of potassium *t*-butoxide to give 3,3-dibromo-1,2-diphenylcyclopropene **10** as an intermediate, which was hydrolysed to give the cyclopropenone product in 28 % yield. The use of chloroform as the source of carbene gave a slightly lower yield of 24 %.^{9,10,11}

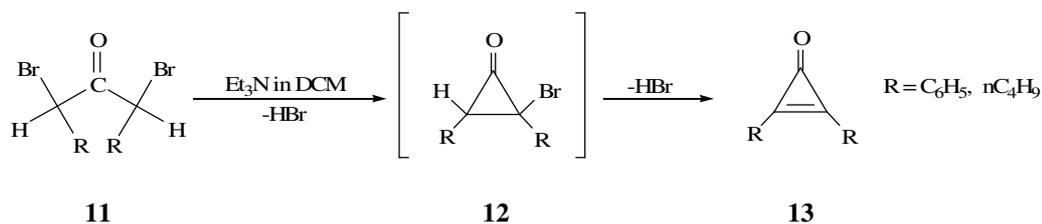


Scheme 1.2

Breslow and Peterson used Vol'pin's more convenient method of synthesis to obtain dipropylcyclopropenone by reaction of 4-octyne with dichlorocarbene which was obtained from either the reaction of sodium methoxide with ethyl trichloroacetate or from sodium trichloroacetate,¹² although this method generally gave low yields of the desired cyclopropenone.¹³

Breslow *et al.* discovered that by using a modified Favorskii reaction they could synthesise diphenyl and dialkylcyclopropenones *via* a dehydrobromination of a dibromo ketone to a

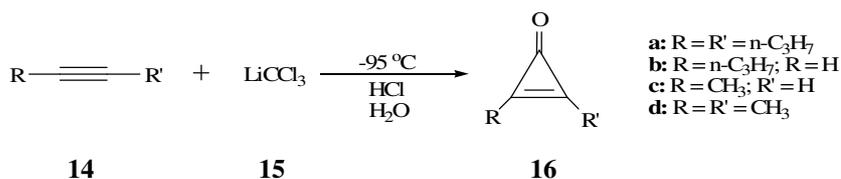
stable cyclopropenone. Synthesis of diphenylcyclopropenone was achieved by reaction of α,α' -dibromodibenzyl ketone **11** with 20 % excess triethylamine in dichloromethane at ambient temperature for 30 minutes giving a yield of ~50 % (Scheme 1.3). Dialkylcyclopropenones were synthesised in a slightly modified way, for example, dibutylcyclopropenones were prepared by reaction of α,α' -dibromodi-*n*-amyl ketone with a 40:1 mixture of chloroform and triethylamine heated at reflux for 48 hours which gave a 12 % yield.¹⁴



Scheme 1.3

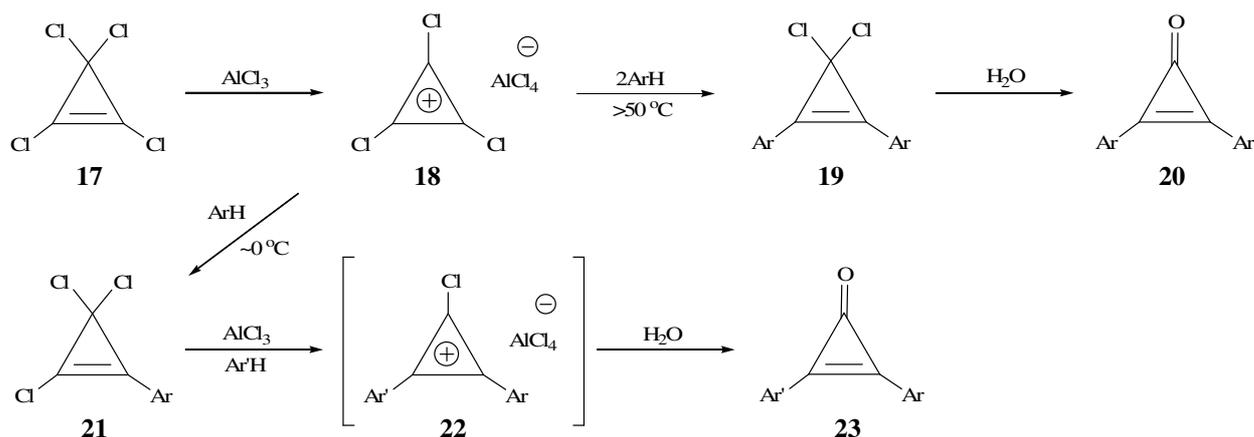
Using a similar method, Ciabattoni and Nathan synthesised di-*t*-butylcyclopropenone from the reaction of α,α' -dibromodineopentyl ketone with potassium *tert*-butoxide in THF. The cyclopropenone was afforded after sublimation at reduced pressure.^{15,13,14}

Breslow and Altman attempted the synthesis of monosubstituted cyclopropenones *via* the modified Favorskii reaction to no success, but discovered that the reaction of 4-octyne **14a** with lithium trichloromethide **15** at -95°C gave di-*n*-propylcyclopropenone **16a** after low temperature acidification and aqueous work up. Similar reactions with 1-pentyne **14b**, propyne **14c** and 2-butyne **14d** gave *n*-propylcyclopropenone **16b**, methylcyclopropenone **16c** and dimethylcyclopropenone **16d** respectively (Scheme 1.4).¹⁶



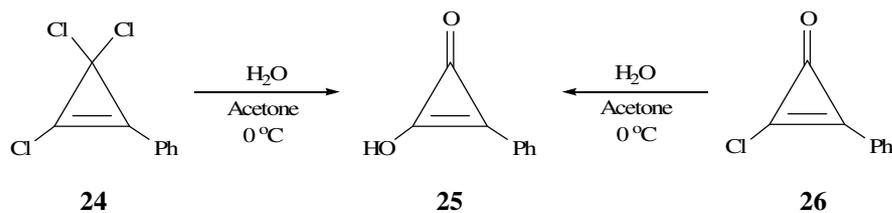
Scheme 1.4

West *et al.* first synthesised a diarylcyclopropenone using a trichlorocyclopropenium ion. The synthesis was achieved by reaction of a benzene derivative with a trichlorocyclopropenium ion **18** to give a gem-dichlorodiarylcyclopropene **19** which was then hydrolysed to provide a diarylcyclopropenone **20**.¹⁷ West *et al.* discovered that by altering reaction conditions, unsymmetrical substituted cyclopropenones could be prepared by a stepwise addition where one equivalent of trichlorocyclopropenium ion and one equivalent of an aryl compound at <0 °C gave the corresponding aryltrichlorocyclopropene **21**, which could then be further reacted with another equivalent of an alternative aryl group at ambient temperature, giving the corresponding nonsymmetric diarylcyclopropenone **23** via a hydrolysis of the intermediate diarylchlorocyclopropene ion **22**.¹⁸



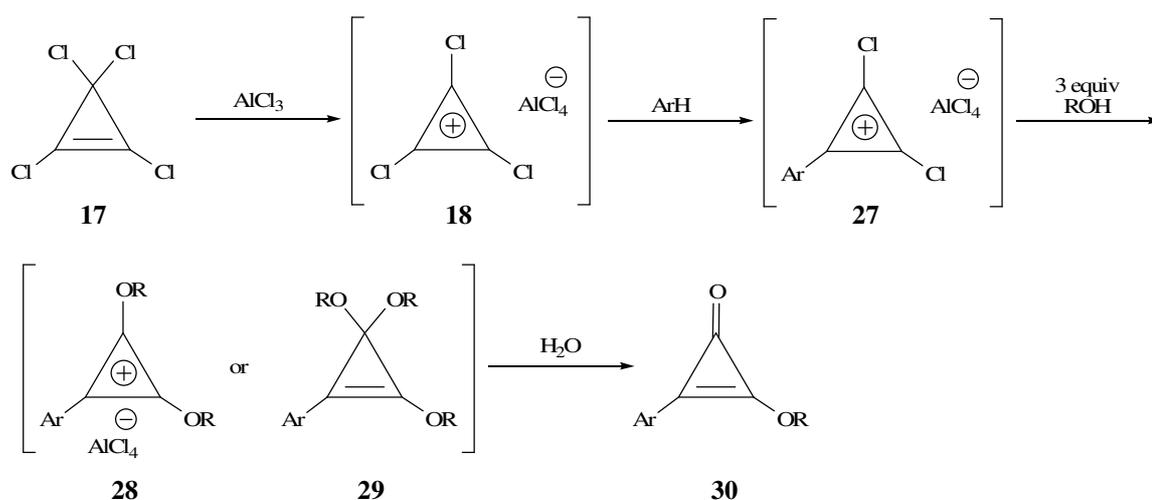
Scheme 1.5

Using a similar method West *et al.* synthesised hydroxyphenylcyclopropenone by the hydrolysis of phenyltrichlorocyclopropene **24**/ chlorophenylcyclopropenone **26** in aqueous acetone at 0 °C giving the desired product on both occasions.^{19,20} This work was extended to include other aryl groups.



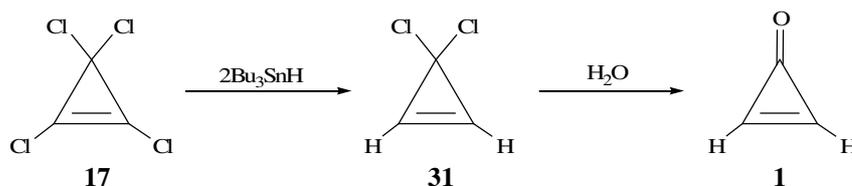
Scheme 1.6

West *et al.* also used Farnum and Thurston's²¹ method of treating phenyltrichlorocyclopropene with potassium *t*-butoxide in ether, followed by 5% HCl to obtain phenylhydroxycyclopropenone, but with very low yields and varied results.¹⁸ Weidner and Wadsworth *et al.* built upon West's earlier work by using tetrachlorocyclopropene **17** to synthesise alkoxyarylcyclopropenones **30** in a stepwise manner, the intermediate trichlorocyclopropenium tetrachloroaluminate **18** made from tetrachlorocyclopropene **17** was treated with an activated aromatic system to make intermediate aryldichlorocyclopropene tetrachloroaluminate **27** which was then reacted with three equivalents of alcohol at low temperatures to give a possible trialkoxyarylcyclopropene **29** or dialkoxyarylcyclopropenylium ion **28**, both of which undergo hydrolysis to give the alkoxyarylcyclopropenone **30**.²²



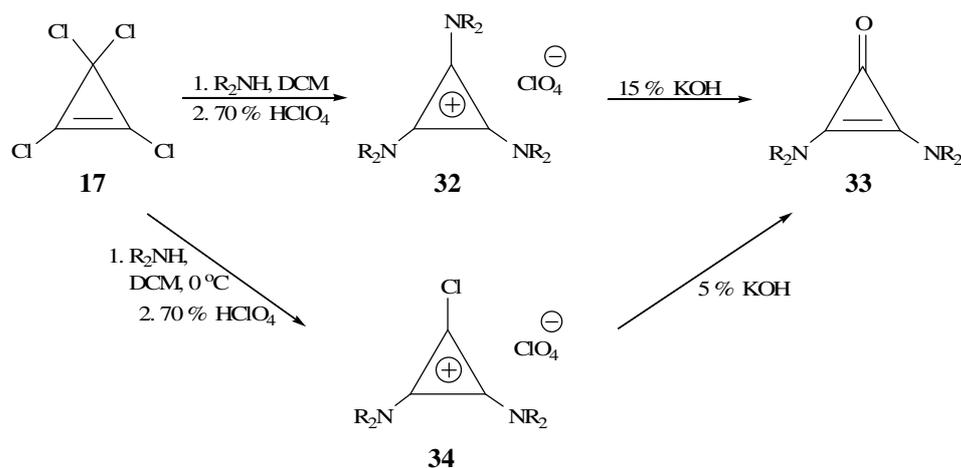
Scheme 1.7

Breslow and Ryan synthesised the parent cyclopropanone by reaction of tetrachlorocyclopropene **17** with 2 equivalents of tri-n-butyltin hydride in paraffin oil affording 3,3-dichlorocyclopropene **31**, which was then dissolved in tetrachloromethane and then hydrolyzed with cold water affording the parent cyclopropanone **1** (Scheme 1.18).²³



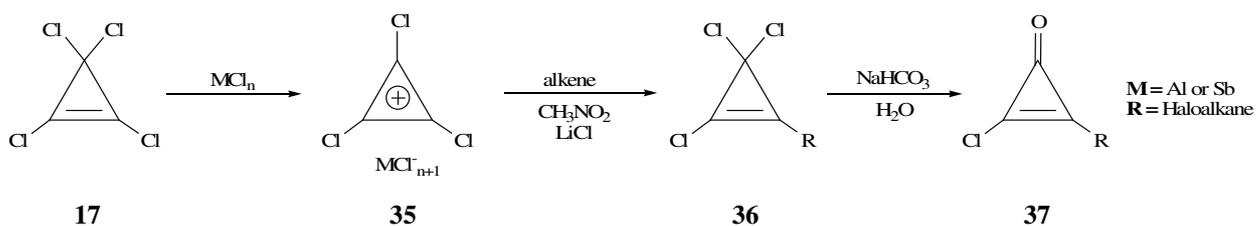
Scheme 1.8

Yoshida *et al.* investigated how secondary amines reacted with tetrachlorocyclopropene **17**. Reactions with dimethylamine, piperidine, morpholine, N-methylaniline, N-ethylaniline and diphenylamine all gave their corresponding triaminocyclopropenyl perchlorate derivatives **32**, but diethylamine and diisopropylamine both gave their corresponding 1,2-*bis*-dialkylamino-3-chlorocyclopropenyl perchlorate derivatives **34**.²⁴ The chloro substituent 1,2-*bis*-diisopropenylamino-3-chlorocyclopropenyl perchlorate was further reacted in aqueous potassium hydroxide and gave *bis*-diisopropylaminecyclopropanone **33**.²⁵ Using a slightly modified method, Breslow *et al.* synthesised *bis*-dimethyl and *bis*-diethylamino-cyclopropanone **33** from their corresponding *tris*-dialkylaminocyclopropenyl perchlorate derivatives in high yields.²⁶



Scheme 1.9

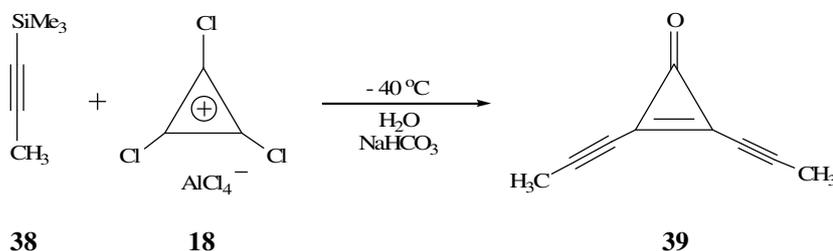
Alkenes and alkynes have also been reacted with tetrachlorocyclopropene **17** to give their cyclopropenone derivatives. Mayr *et al.* synthesised the mono substituted 1,3,3-trichlorocyclopropenes exclusively by the dropwise addition of alkenes to trichlorocyclopropenyl cation **35** in nitromethane. The trichlorocyclopropenes **36** could then be hydrolysed by aqueous sodium hydrogen carbonate to their corresponding cyclopropenones. Noteworthy was the use of sodium hydrogen carbonate in methanol which caused the ring to open.²⁷



Scheme 1.10

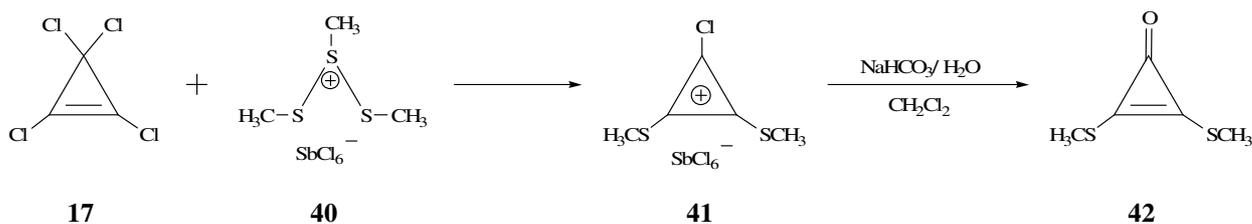
Diederich *et al.* synthesised dialkynylcyclopropenones **39** using trichlorocyclopropenyl cation **18** with 1-trimethylsilyl-1-propyne **38**. The reaction was quenched with water and the desired cyclopropenone was formed in 50 % yield after a workup with aqueous sodium

hydrogen carbonate. The parent diethynylcyclopropenone was attempted in a similar procedure, but no product was obtained.²⁸



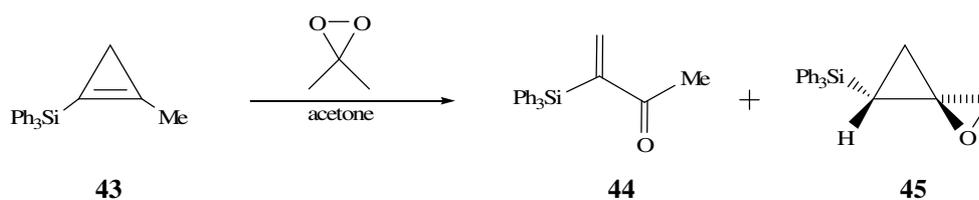
Scheme 1.11

Weiss *et al.* synthesised 1,2-dimethylthiocyclopropenone **42** using tetrachlorocyclopropene **17** and reacting it with methyl(bismethylthio)sulfonium hexachloroantimonate **40** giving dimethylthiochlorocyclopropenium salt **41**, which was converted to the cyclopropenone **42**.²⁹



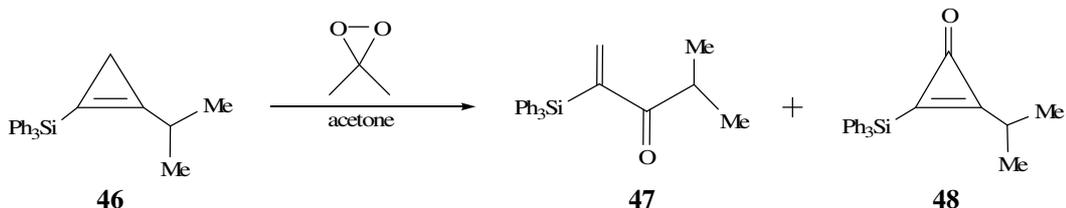
Scheme 1.12

A different route explored by Wicha and Paquette *et al.* was the oxidation of cyclopropenes to give their corresponding cyclopropenones, such as 1-methyl/ 1-isopropyl-2-triphenylsilylcyclopropene which were oxidised with dimethyldioxirane in acetone. The 1-methyl cyclopropene **43** gave a ring opened product **44** as the major product and a spiro epoxide **45** as a minor product.³⁰



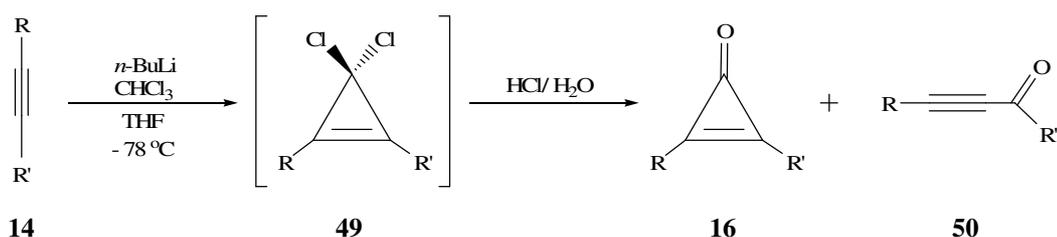
Scheme 1.13

The isopropyl cyclopropene **46** also gave a ring opened product **47** as the major product and gave the corresponding cyclopropenone **48** as the minor product. The behavioural difference seen in the two cyclopropenes is believed to be due to steric hindrance from the isopropyl group.³⁰



Scheme 1.14

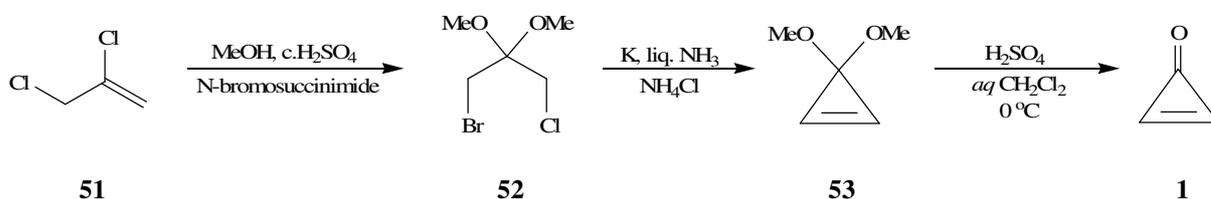
Netland *et al.* prepared dialkylcyclopropenones using an improved synthesis originally prepared by Gleiter and Merger.³¹ The reaction of the mild carbenoid reagent trichloromethyl lithium with an alkyne **14** at low temperatures in THF afforded the corresponding dichlorocyclopropene intermediate **49**, which when quenched with conc. HCl (aq) at $-78\text{ }^{\circ}\text{C}$ gave cyclopropenone **16** as the major product and a ynone **50** as a side product, but when quenched with water at $0\text{ }^{\circ}\text{C}$, gave ynone as the major product.³²



Scheme 1.15

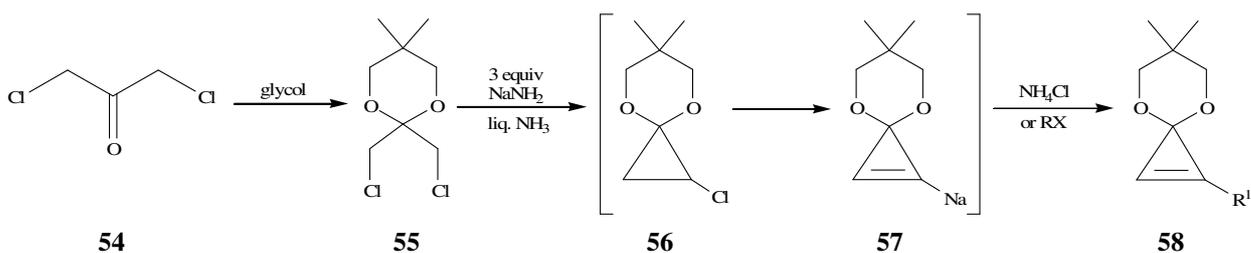
Baucom and Butler reported in 1972 the synthesis of the parent cyclopropenone. The synthesis had three steps, the initial step gave 1-bromo-3-chloro-2,2-dimethoxypropane **52** from the reaction of 2,3-dichloropropene **51**, methanol and *N*-bromosuccinimide with concentrated sulfuric acid as a catalyst, which was then cyclised with potassium amide in

liquid ammonia to give 3,3-dimethoxycyclopropene **53**. The acetal was then easily hydrolysed to the unsubstituted cyclopropenone **1**.³³ The reaction was slightly improved by Breslow by adjusting the times and conditions shown in Scheme 1.16 below.³⁴



Scheme 1.16

Nakamura *et al.* also reported a method for the synthesis of cyclopropenones and their acetals, a safer method which gave improved yields of the parent and substituted cyclopropenones. The synthesis had three steps, the acetalization of 1,3-dichloroacetone **54** with neopentyl glycol, the cyclisation of the acetal **55** with three equivalents of sodium amide in the presence of liquid ammonia, the first two equivalents of which cyclise the acetal and the third affords a sodium salt **57**. The sodium salt has either ammonium chloride or an alkyl halide added *in situ* to yield the required cyclopropenone acetal **58**.^{35,36}



RX = alkyl halide, R¹ = R or H

Scheme 1.17

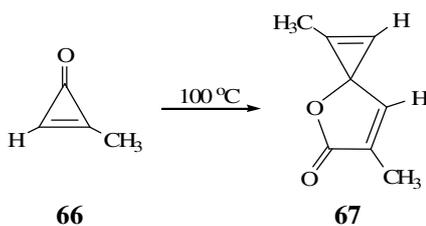
West and Eggerding synthesised dihydroxy **64** and dimethoxycyclopropenones **65** from squaric acid **59**. Earlier reactions showed that diethoxycyclopropenone **63** was synthesised from diethyl squarate **61** by photochemical extrusion of carbon monoxide. Attempted hydrolysis to deltic acid **64** was unsuccessful. Deltic acid **64** was finally synthesised by a

1.2 Reactions of Cyclopropenones

Cyclopropenones are known to react with compounds containing the carbon-nitrogen double bond but have also been shown to dimerize, react with alkynes in an overall [3+2] cycloaddition reaction, with indenes in a condensation reaction, and to undergo a variety of reactions across the carbon-carbon double bond. A summary of these processes follows.

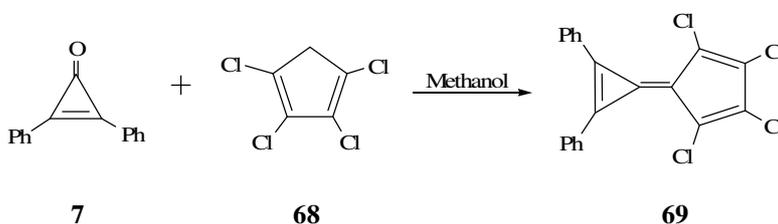
1.2.1 Reaction at the ketone double bond

Cyclopropenones at high temperatures are known to undergo decarbonylation to give an alkyne and carbon monoxide.^{14,16} However, heating cyclopropenones such as methylcyclopropenone **66** at lower temperatures, causes them to dimerize and produce a spirolactone **67**.^{2,16,13}



Scheme 1.19

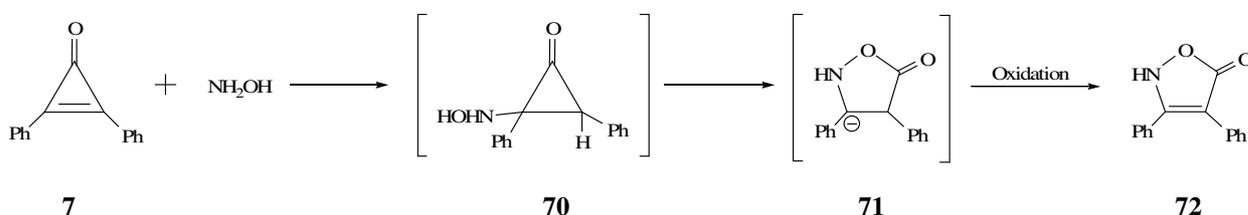
Calicenes **69** can be synthesised by the condensation of a cyclopropenone **7** with a cyclopentadiene **68** or an indene.^{38,39}



Scheme 1.20

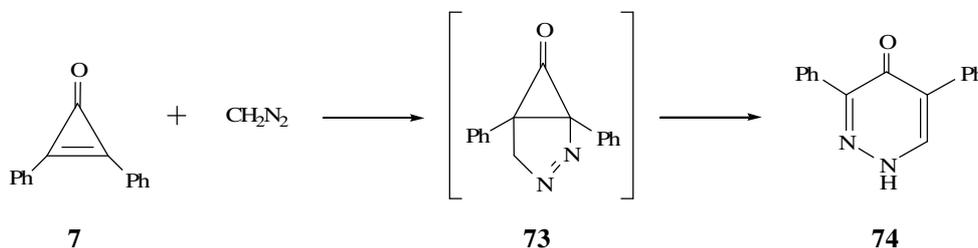
1.2.2 Reactions across carbon-carbon double bond

Cyclopropenones are known to react as an alkene across the carbon-carbon double bond. Reaction of diphenylcyclopropenone **7** with hydroxylamine resulted in two products, deoxybenzoin oxime (31 %) and 3,4-diphenylisoxazolone **72** (61 %), the latter being formed as shown in Scheme 1.21. Breslow *et al.* suggested that the first step for both products was direct attack on the cyclopropenone, as neither diphenylacetylene or 3,4-diphenylisoxazole **72** were precursors for deoxybenzoin oxime.¹³



Scheme 1.21

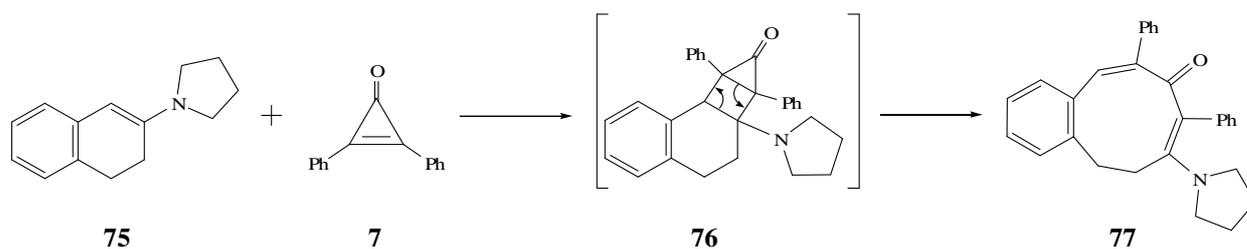
Breslow *et al.* also synthesised 3,5-diphenylpyridaz-4-one **74** from the reaction of diphenylcyclopropenone **7** with diazomethane. A suggested mechanism is the addition of diazomethane across the carbon-carbon double bond, followed by ring opening of the intermediate cyclopropanone **73**.^{13,39}



Scheme 1.22

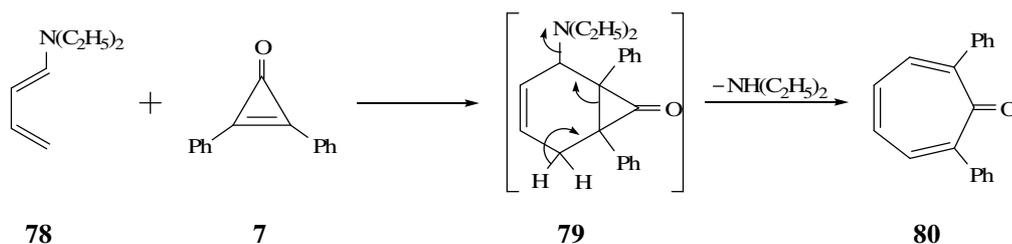
Ciabattoni and Berchtold treated diphenylcyclopropenone **7** to a number of different enamines. They suggested the addition of the enamines was across the carbon-carbon double-

bond of the diphenylcyclopropanone *via* a 1,2-cycloaddition or a 1,4-cycloaddition in the case of a dienamine. They presumed the intermediate product involved a cyclopropanone which would undergo cleavage across the C2-C3 bond to form ring enlarged products. The reaction of diphenylcyclopropanone **7** with 2-(N-pyrrolidino)-3,4-dihydronaphthalene **75** formed 4,5-benzo-2,9-diphenyl-8-(N-pyrrolidino)cyclonona-2,4,8-trienone **77** *via* a 1,2-cycloaddition followed by cleavage of the new fused ring.^{39,40}



Scheme 1.23

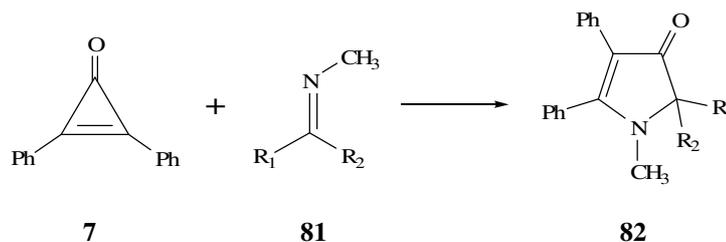
The reaction with 1-diethylamino-1,3-butadiene **78** formed 2,7-diphenyltropone **80** *via* a 1,4-cycloaddition, which was followed by cleavage of the cyclopropanone intermediate **79** and 1,4-elimination of diethylamine.^{39,40}



Scheme 1.24

1.2.3 Reactions with imines: formation of pyrroles

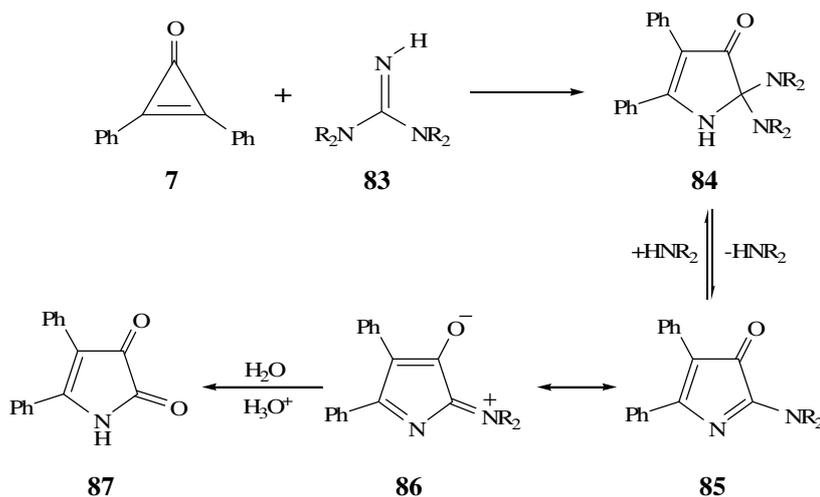
In 1974 Eicher *et al.* treated secondary ketimines **81** with diphenylcyclopropenone **7** to afford 2-pyrroline substituents **82**. The reactions presumably went *via* the equivalent of a [3+2] cycloaddition, and the majority of the products obtained were in high yields > 90%.⁴¹



a: R₁ = Ph, R₂ = CH₃, **b:** R₁ = Ph, R₂ = C₂H₅, **c:** R₁ = *p*-Tolyl, R₂ = CH₃, **d:** R₁ = R₂ = CH₃
82a = 94%, **82b** = 91%, **82c** = 98%, **82d** = 71%.

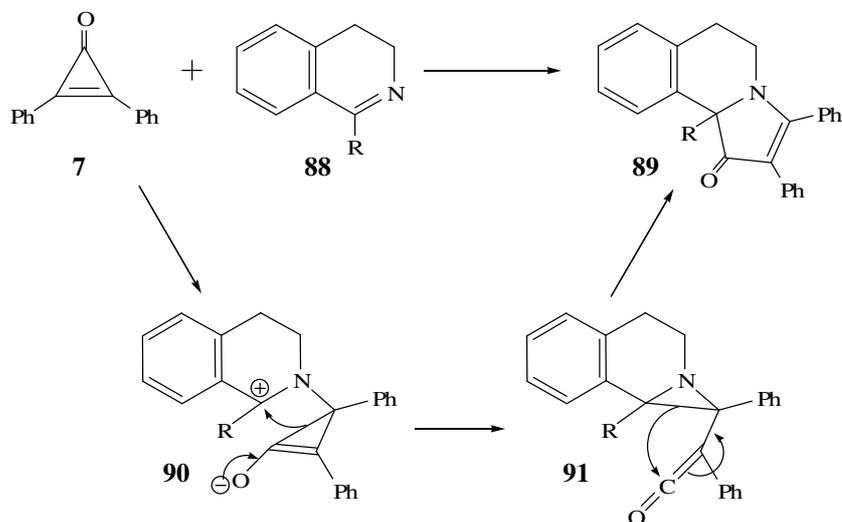
Scheme 1.25

Reactions between primary ketimines **83** and diphenylcyclopropanone **7** gave a similar pyrroline substituent **84** as an intermediate product. Removal of one of the amine side chains followed by acid hydrolysis gave 4,5-diphenyl-1H-pyrrole-2,3-dione **87** as the product.⁴²



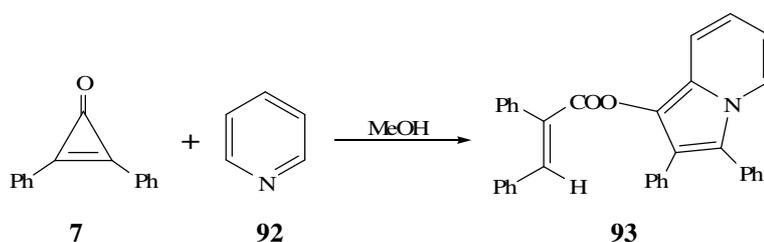
Scheme 1.26

Eicher *et al.* developed this work further by reacting diphenylcyclopropenone **7** with a 3,4-isoquinoline derivative **88** to afford pyrrolo isoquinolines **89**.



Scheme 1.27

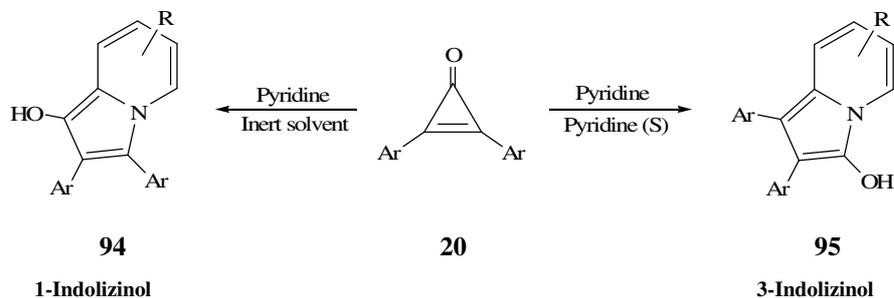
Breslow *et al.* discovered the reaction of pyridine **92** with two equivalents of diphenylcyclopropenone **7** in methanol afforded a diphenyl acrylic ester residue,¹³ the structure of which was later confirmed by Wadsworth *et al.* by X-ray crystallography as 1-[(*cis*-2,3-diphenylacryl)oxy]-2,3-diphenylindolizine **93**.



Scheme 1.28

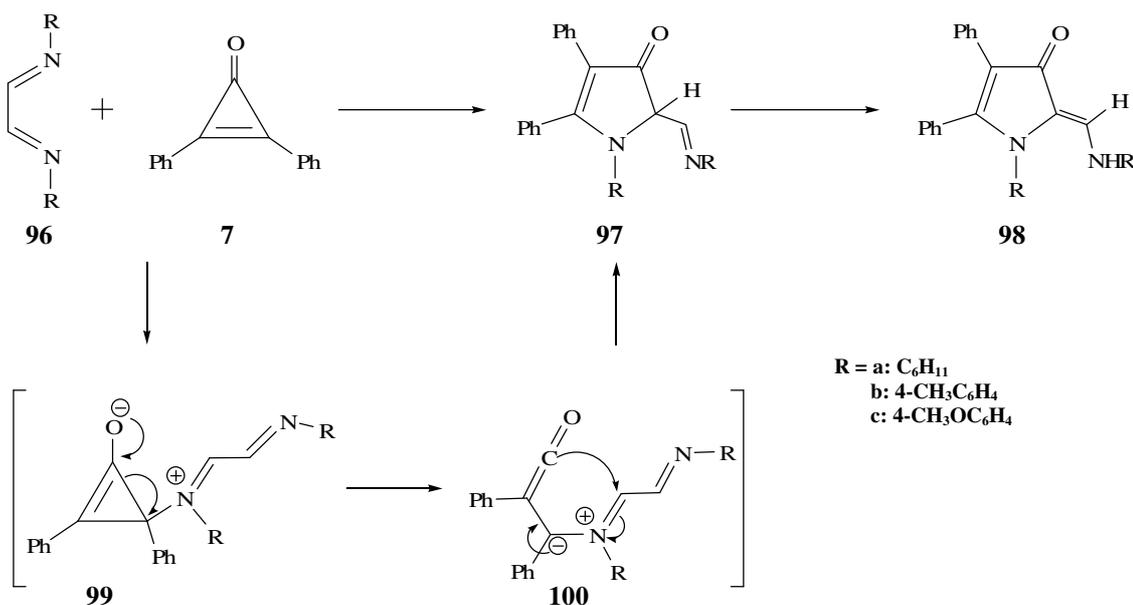
Wadsworth *et al.* continued this work by reacting substituted pyridines and diarylcyclopropenones **20** for preparation of 2,3-diaryl-1-hydroxyindolizines **94** and 1,2-diaryl-3-hydroxyindolizines **95**. The reaction of diphenylcyclopropenone in neat pyridine afforded 1,2-diphenyl-3-hydroxyindolizine **95** in 90 % yield with the remaining 10 % as the

1-indolizinol **94**. Solvent and substituent manipulation of the reaction afforded different isomer ratios,⁴³ including the isolation of the 1-indolizinol as the main product.



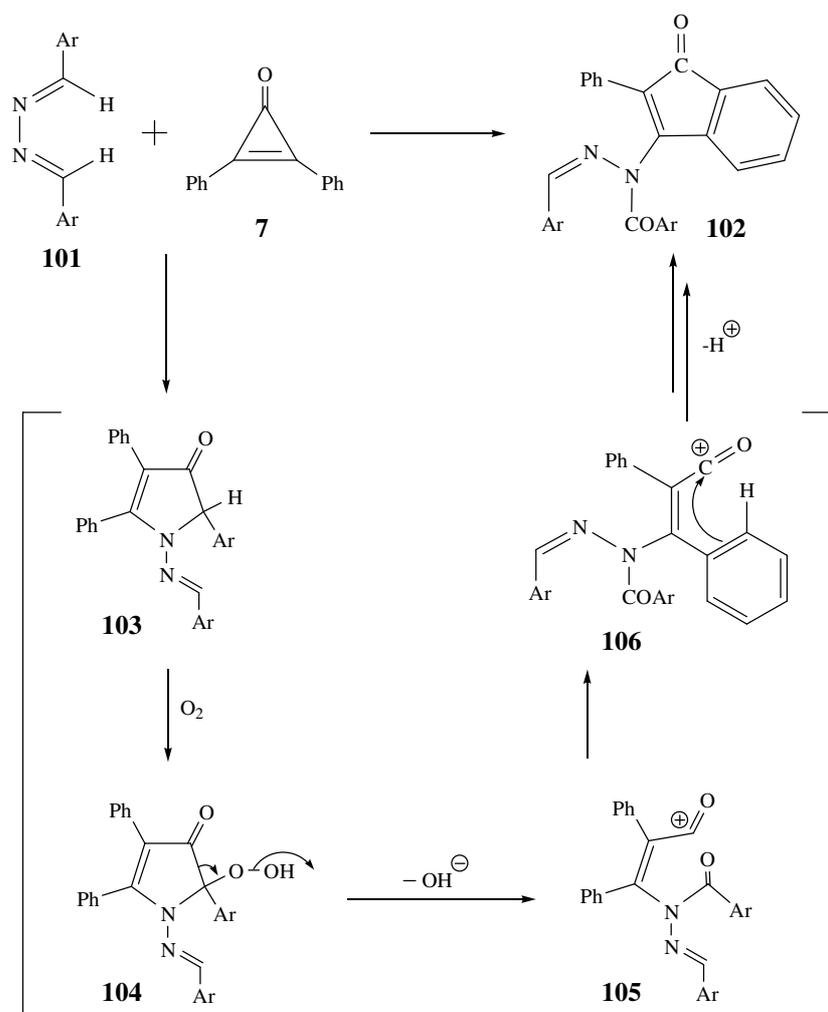
Scheme 1.29

Gomma synthesised pyrrolinone and inden-1-one derivatives from the reaction of diphenylcyclopropenone **7** with diimines **96** and azines **101** (Scheme 1.30 and Scheme 1.31, respectively). The mechanism provided for the synthesis of pyrrolinone suggests the imino nitrogen atom of the diimine attacks the C2 or C3 carbon of the diphenylcyclopropenone giving iminiumbetaine **99**, which is followed by ring opening to give ketene **100**. The iminium function is then attacked by the ketene to cyclize and afford the imines **97** which tautomerise to their more stable enaminone structure **98**.⁴⁴



Scheme 1.30

The mechanism provided for the synthesis of inden-1-one **102** suggests an initial [2+3] cycloaddition reaction of diaryldiazines **101** and diphenylcyclopropanones **7** to afford a pyrrolin-3-one derivative **103**. Oxidation leads to cleavage of the 5-membered ring to **105** followed by rearrangement to afford the inden-1-one product **102**.⁴⁴

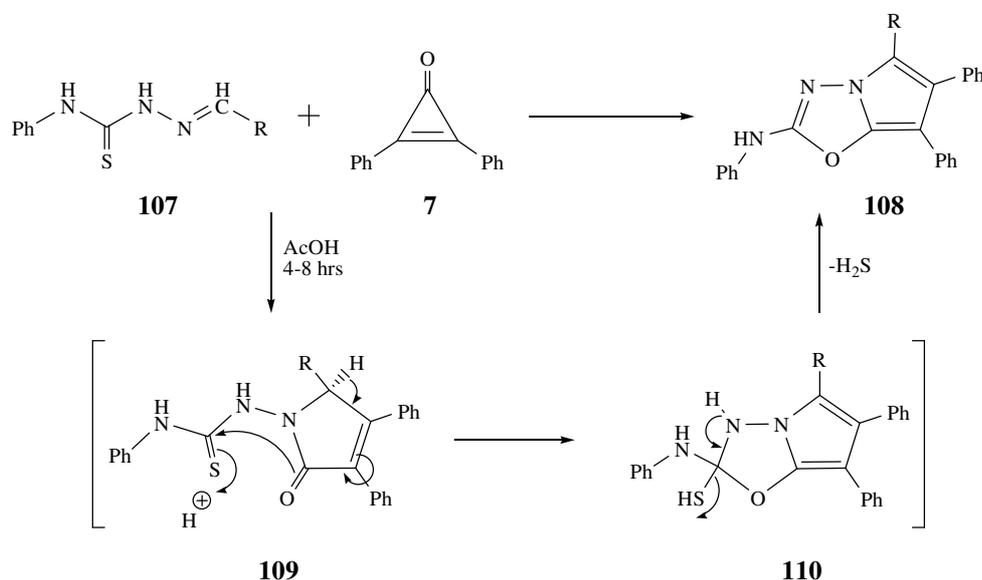


a: Ar = 4- $CH_3C_6H_4$, b: Ar = 4- $CH_3OC_6H_4$, c: Ar = 4- $(CH_3)_2NC_6H_4$

Scheme 1.31

Aly *et al.* synthesised pyrrolo[2,1-b]-1,3,4-oxadiazoles from the reaction of diphenylcyclopropanone **7** with ylidene-*N*-phenylhydrazine-carbothioamides **107**. The proposed mechanism suggests the cyclopropanone attaches across the carbon-nitrogen double bond in a [2+3]-cycloaddition giving intermediates **109a-e**. The pyrrole ring undergoes

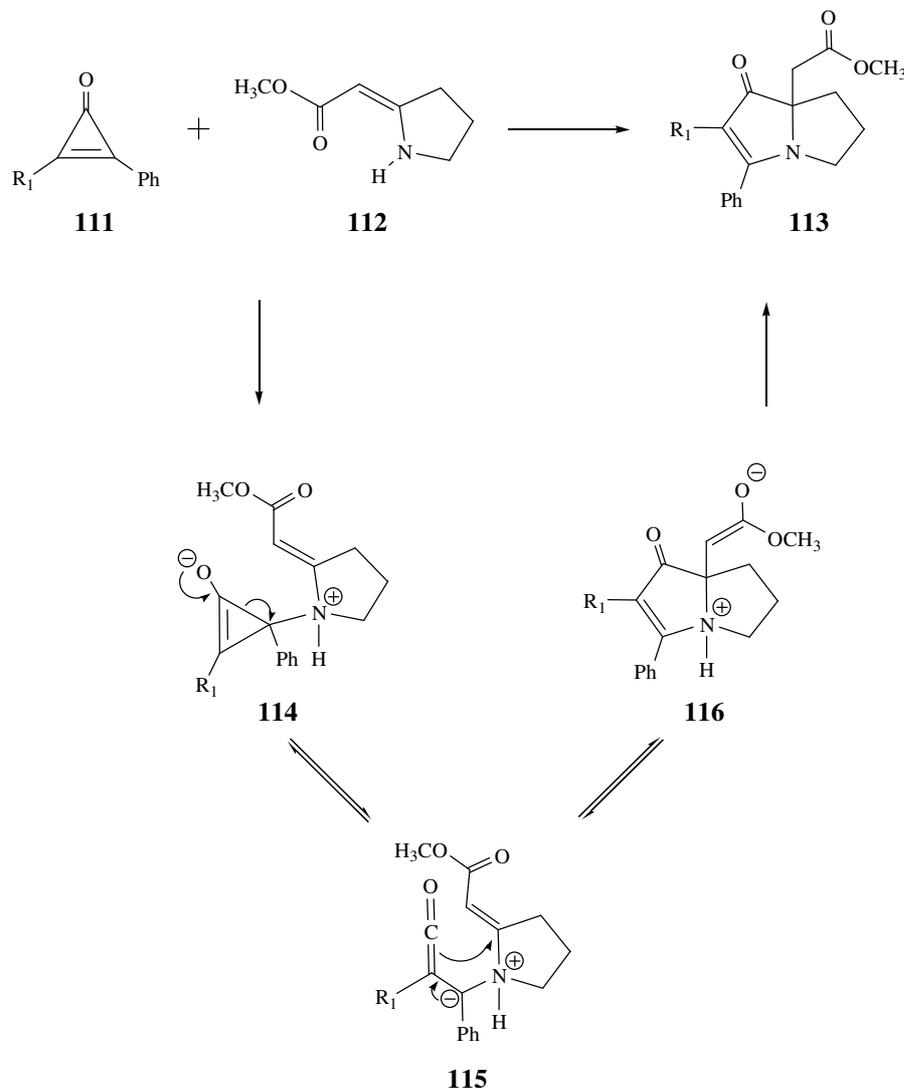
aromatization with further cyclization to form intermediates **110a-e**, and finally the loss of hydrogen sulfide provides stable 2,5,6,7-tetrasubstituted-pyrrolo[2,1-b](1,3,5-oxadiazolyl)-2-amines **108a-e**.⁴⁵



a: R = 4-H₃CO-C₆H₄, b: R = 4-HO-C₆H₄, c: R = 4-Cl-C₆H₄, d: R = 2-Thienyl, e: R = C₆H₅

Scheme 1.32

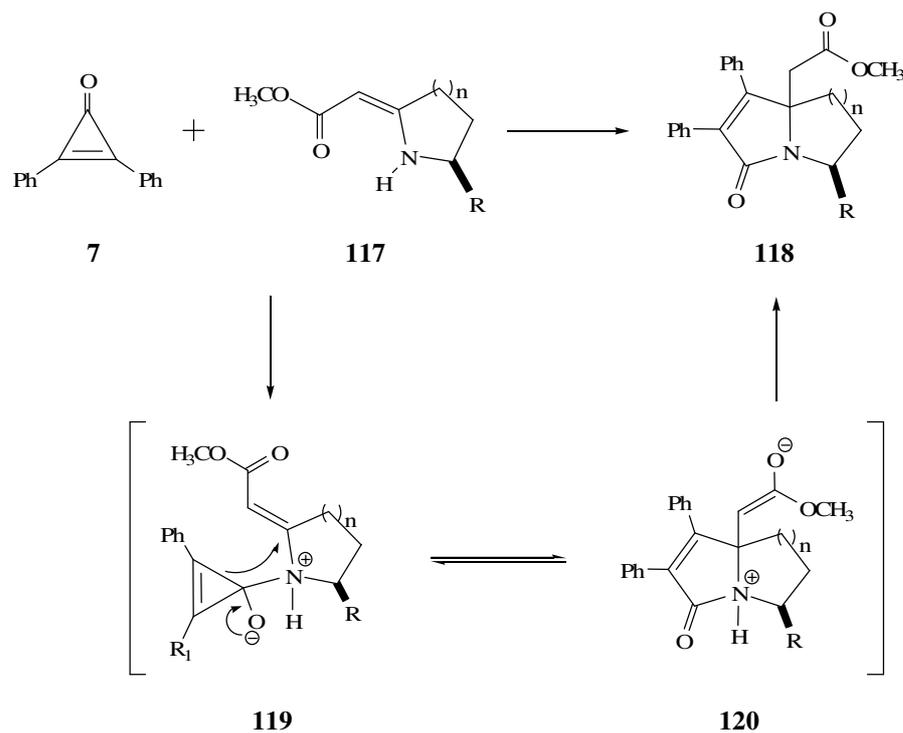
Cunha *et al.* synthesised pyrrolizidine and indolizidine derivatives from the reaction of cyclopropanones **111** with five and six-membered cyclic enaminones. Reaction of the five-membered systems **112** with **111a+b** gave pyrrolizidine derivatives **113a + b** in 70 % and 8 % yield, respectively. A rational mechanism suggested for these products and their regioselectivity was that the enaminone nitrogen attacks the C3 carbon containing the phenyl group yielding **114**. Cleavage of the cyclopropanone ring affords **115** which leads to cyclization to form enolate **116** giving the pyrrolizidine **113a+b**.⁴⁶



R_1 : a = Ph, b = CH₃

Scheme 1.33

The reaction of six-membered cyclic enaminone **117a** with diphenylcyclopropanone **7** gave indolizidine derivative **118a** in 16% yield. The reaction of **7** with chiral enaminone **117b** gave pyrrolizidine derivative **118b** and its isomer. Indolizidine **118a** and pyrrolizidine derivative **118b** both contain the carbonyl group from the cyclopropanone next to the nitrogen atom rather than next to the acetate bridgehead chain, and this is believed to be due to there being a sterically hindered environment, whereby **117a** has a six-membered ring and **117b** has a side group at C5 next to the nitrogen atom. The mechanistic rationale for products **118a** and **118b** suggests that the nitrogen attacks at the carbonyl carbon due to steric hindrance giving intermediate **119**, which cyclises to form **120** and gives the products **118a** and **118b**.⁴⁶



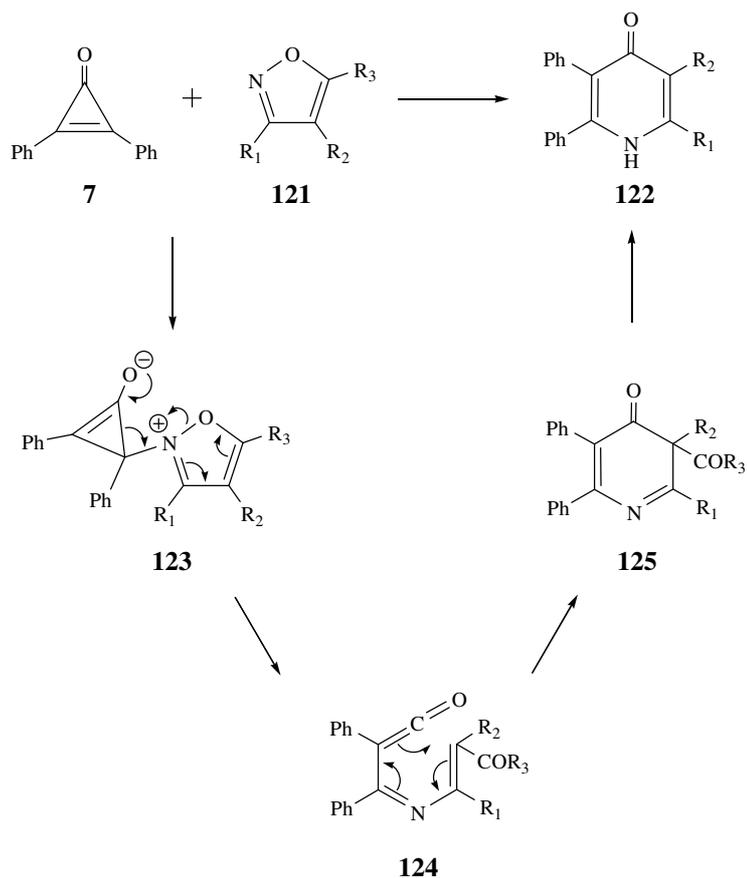
a: $n = 2$, $R = H$; b: $n = 1$, $R = CH_2OTBS$

Scheme 1.34

1.2.4 Synthesis of six-membered rings

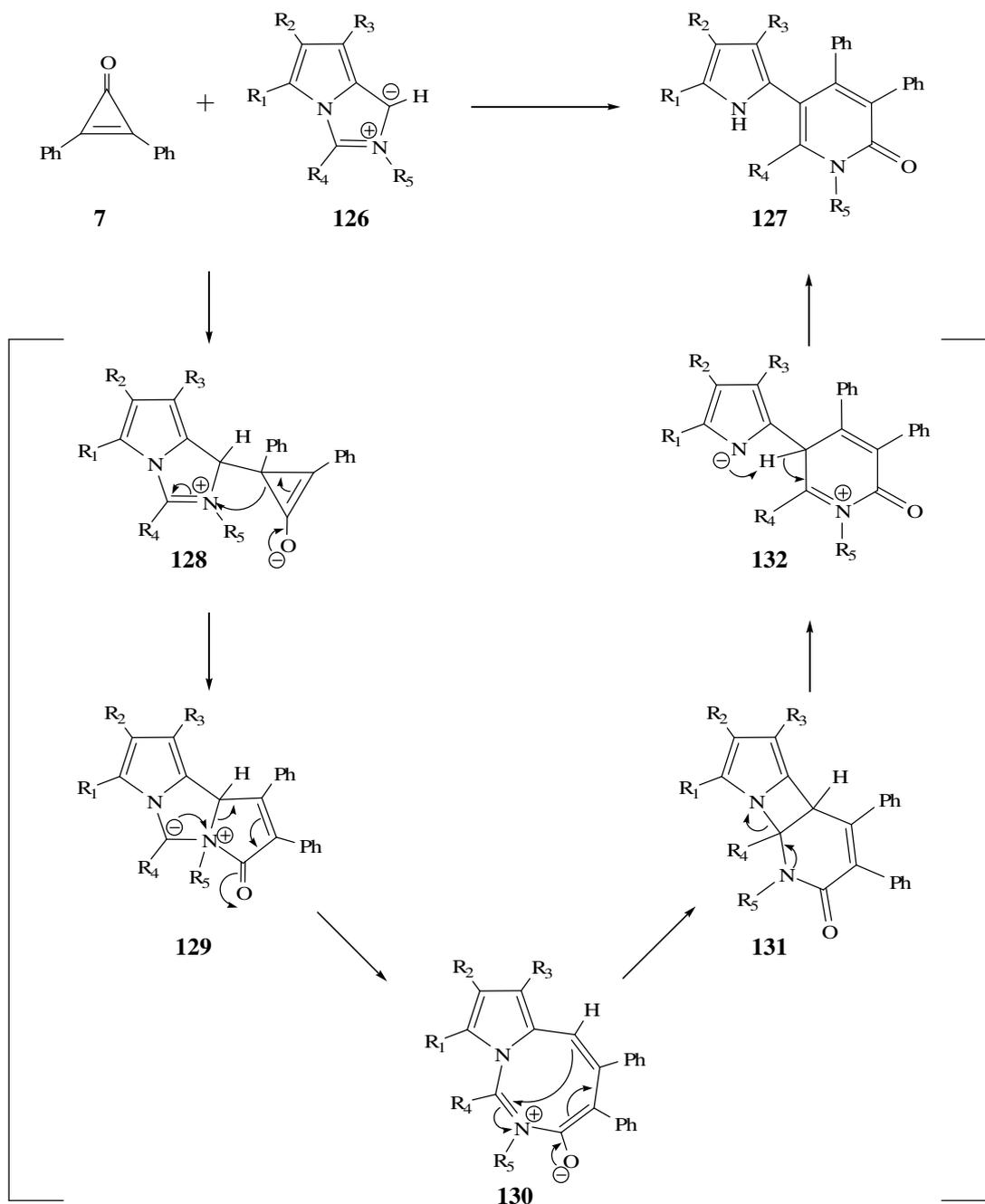
Diphenylcyclopropenones are also known to react in [4+2] and [3+3] cycloaddition reactions. Some examples are shown below, along with other reactions leading to six-membered rings.

Grigg *et al.* synthesised 4-pyridones *via* the reaction of diphenylcyclopropenone **7** with isoxazoles **121**. One proposed mechanism is the initial addition of the nitrogen to the C2 or C3 carbon to give **123**, which then rearranges to cleave both rings to afford **124**. This is followed by an electrocyclic reaction which forms a six-membered ring **125**. The loss of ketene yields 4-pyridone **122**.⁴⁷



Scheme 1.35

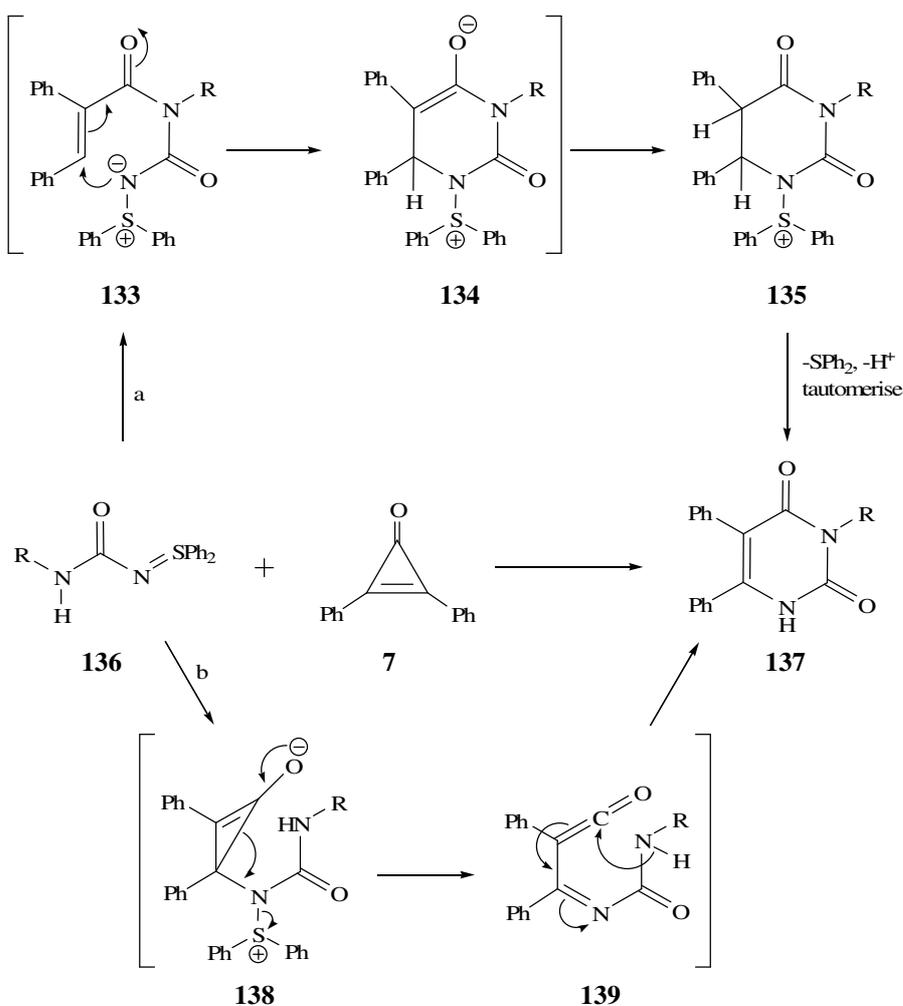
Musicki treated pyrrolo[1,2-c]imidazole mesomeric betaines **126** with diphenylcyclopropenone **7** to afford 2(1H)-pyridone **127**. The proposed mechanism suggests that the C1 of the mesomeric betaine adds to the carbon-carbon double bond by nucleophilic addition to form the zwitterionic species **128**, which rearranges to form N-ylide **129** by the opening of the cyclopropenone ring. This is followed by the formation of pyrrolo[1,2-c][1,3]diazocine derivative **130** by cleavage of the C1-N2 bond. The rearrangement of the valence tautomer **131** affords the product **127** via a zwitterion **132**.⁴⁸



Scheme 1.36

Pyrimidine-2,4-dione derivatives have been synthesised by Takahashi *et al.* in a one step synthesis from the reaction of N-carbamoylsulfilimines **136** with diphenylcyclopropanone **7**. One proposed mechanism suggests the nitrogen adjacent to the alkyl group would attack the carbonyl carbon of **7** and ring open to give intermediate **133**. A Michael addition enables cyclisation to a six-membered ring **134**, and the pyrimidine-2,4-dione **137** is formed by the

removal of diphenyl sulfide from **135**.⁴⁹ The second proposed mechanism suggests the nitrogen adjacent to the sulfonium group could attack at either C2 or C3 of **7** forming intermediate **138**, after which a rearrangement removes diphenyl sulfide to give intermediate **139**, which cyclizes to yield the product **137**.⁴⁹

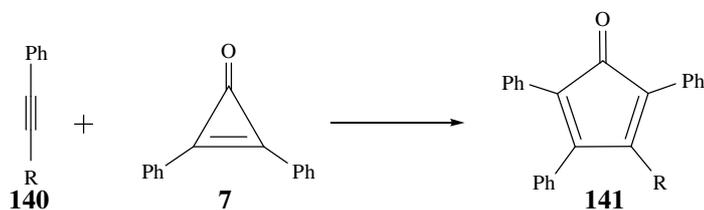


Scheme 1.37

1.2.5 Miscellaneous

Cycloproponones have also been used to synthesise cyclopentadienones **141** *via* an overall [3+2] cycloaddition with alkynes **140**. The method has also been shown to work with diaryl and arylalkylcycloproponones and with a mixture of aryl-, alkyl- and heteroaryl alkynes. The reaction takes place in toluene in the presence of a rhodium(I) catalyst, which was shown to

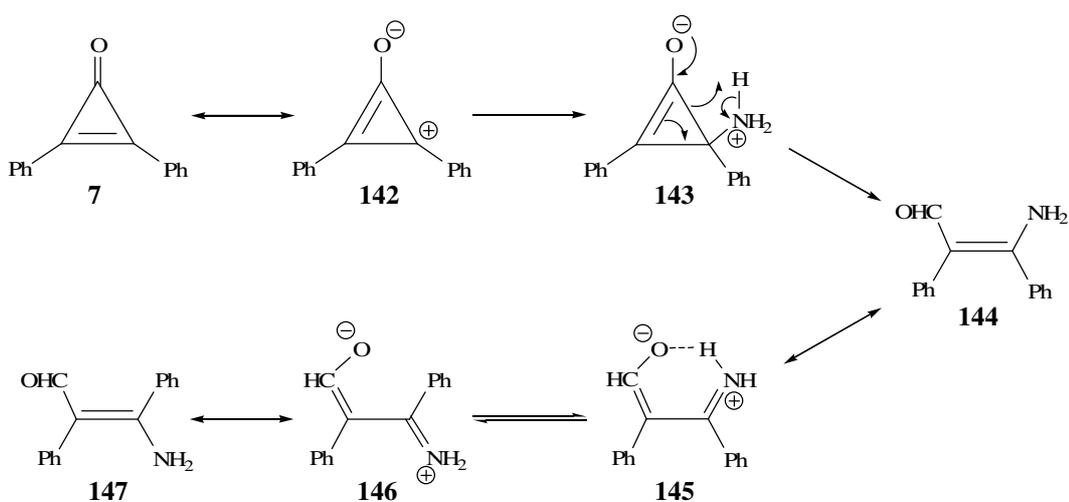
be essential to the reaction; other potential catalysts such as titanium *iso*-propoxide, palladium(II) acetate or toluenesulfonic acid only gave trace amounts of the product.⁵⁰



a: R = CH₃, b: R = CH₂OCH₃, c: R = C(O)CH₃, d: R = Cl, e: R = C(O)NH₂,
f: R = CH(OH)CH₃, g: R = CN, h: R = CHO, i: R = CC-Ph, j: R = Ph,

Scheme 1.38

Toda *et al.* synthesised α -amino- β -phenylcinnamic aldehyde from the substitution reaction of diphenylcyclopropenone **7** with liquid ammonia. The addition of ammonia at C2 or C3, followed by ring cleavage gave **144**. The *trans* isomer product **147** was shown to form when placing product **144** in potassium hydroxide/ ethanol solution and adding water. The process can be reversed when the *trans* isomer is placed in chloroform or tetrachloromethane. It was suggested the isomer is in its *cis* form when in solution due to hydrogen bonding, but forms the *trans* isomer when in an alkaline medium due to rotation of the central carbon-carbon bond.⁵¹



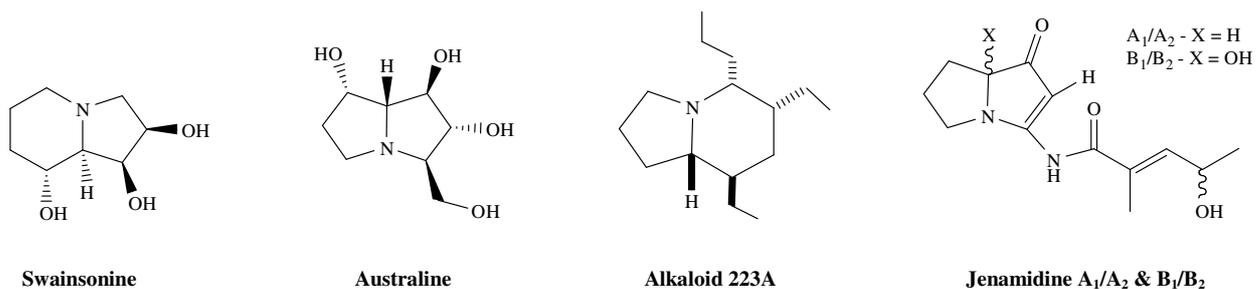
Scheme 1.39

1.3 Prologue to thesis discussion

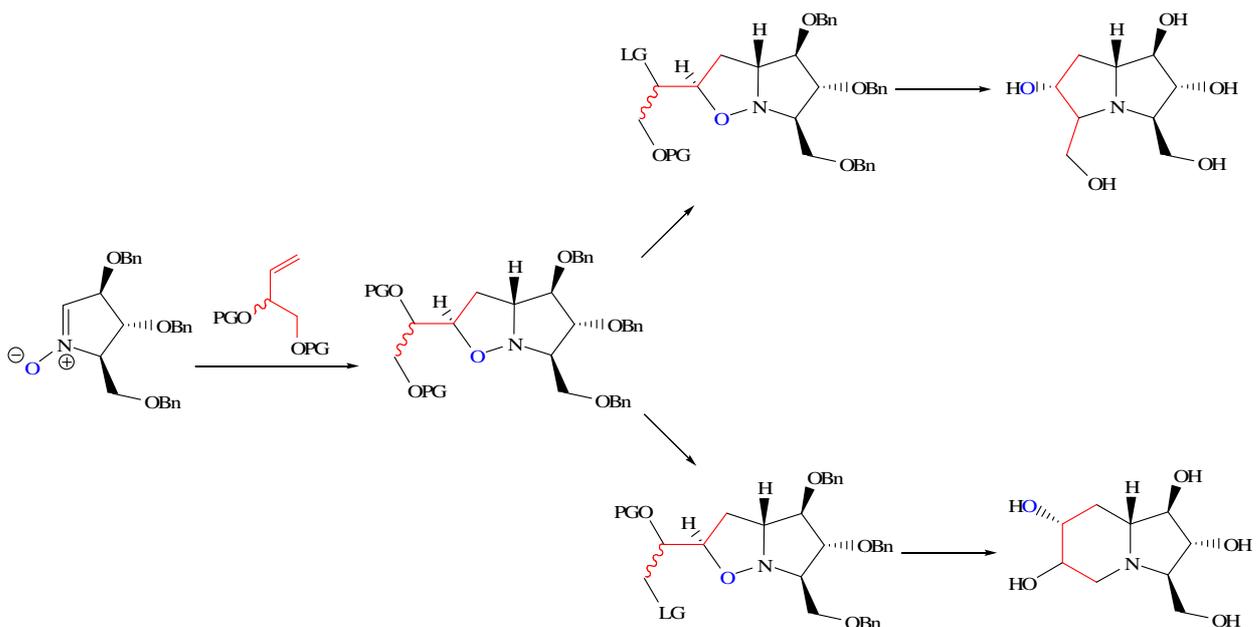
The discussion of this thesis will look at synthesising pyrrolizidines and indolizidines from the reaction of cyclopropenones with five and six-membered cyclic imines. Reactions of cyclopropenones with carbon-nitrogen double bonds are well known in the literature as shown earlier in this thesis. The interest in synthesising pyrrolizidines and indolizidines is due to the many potential pharmaceutical properties they possess, such as treatment for viral infections (treatment against HIV), activity against some cancer lines, treatment for diabetes (type II), and potential as a treatment for several neurological disorders.

The literature related to glycosidase inhibitors and to indolizidine and pyrrolizidine natural products in general is very extensive and a short review of some of it now follows, focusing on natural products of interest to our research group and to this thesis, and includes a few, selected recent total syntheses.

There are many natural pyrrolizidines and indolizidines such as the polyhydroxylated australine and swainsonine, both of which have shown glycosidase inhibitory properties which are of interest in the treatment for some cancers and viral infections,^{52,53} and therefore are great targets for synthetic chemists. There are also non-hydroxylated systems such as jenamidines A₁/A₂, B₁/B₂ and C. Jenamidines A₁/A₂ have been shown to inhibit the growth of chronic myeloid leukaemia cell lines.^{54,55} The non-hydroxylated indolizidines such as alkaloid 223A have been shown to inhibit nicotinic acetylcholine receptors and are therefore potential leads in the study of neurological disorders such as Alzheimer's disease, schizophrenia and bipolar disorders.⁵⁶

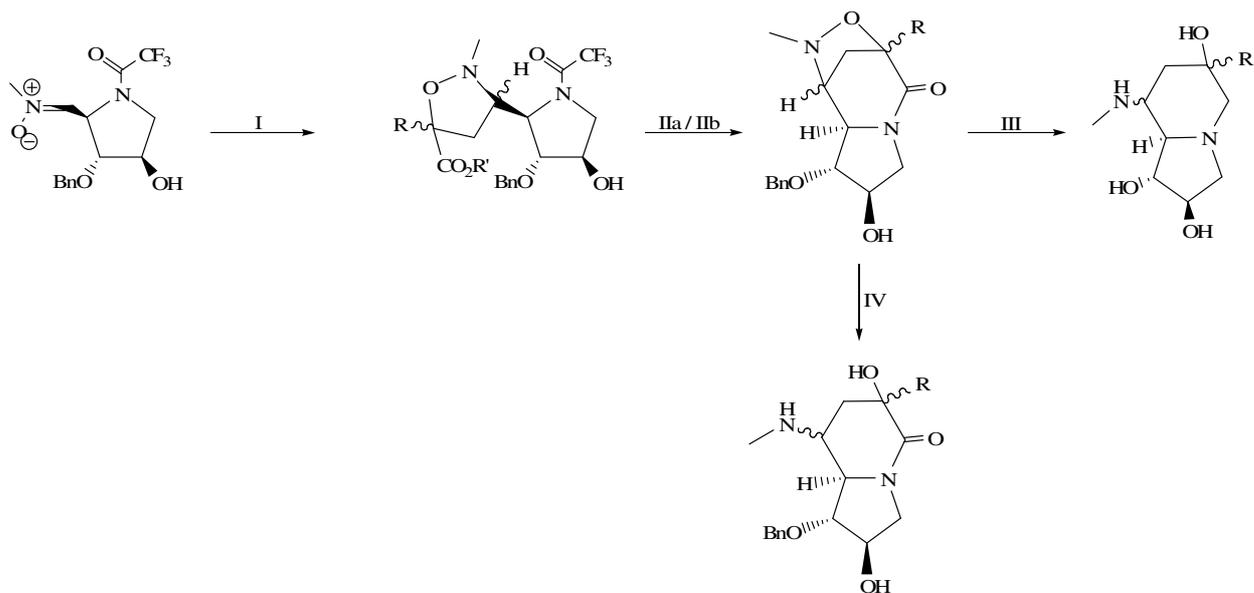


Tamayo *et al.* synthesised polyhydroxylated indolizidines and pyrrolizidines *via* a pyrroloisoxazolidine, which was synthesised *via* a 1,3-dipolar cycloaddition of a cyclic nitron with 3-buten-1,2-diol derivatives which were chemoenzymatically prepared. Protecting group manipulation, N-O cleavage of the pyrroloisoxazolidine using Zn/AcOH, cyclisation and further deprotection gave the required products⁵⁷ (see Scheme 1.40).



Scheme 1.40

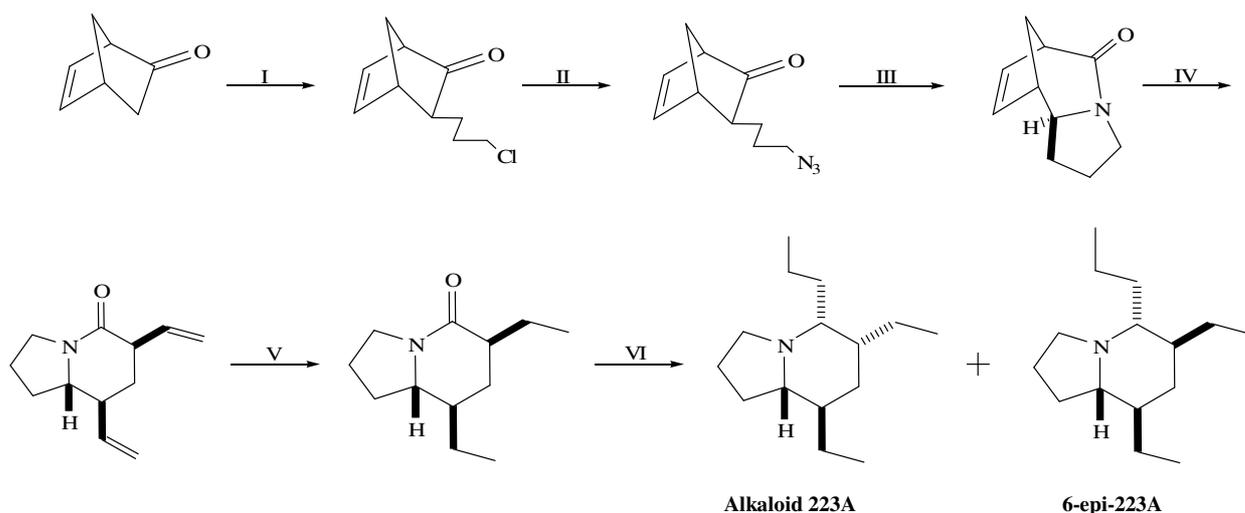
Li *et al.* used an azasugar nitron and methacrylate to synthesise a polyhydroxylated indolizidine containing an amino group *via* a microwave assisted 1,3-dipolar cycloaddition, followed by intramolecular cyclo-amidation⁵⁸ (see Scheme 1.41). Isoxazolidine cleavage gave the desired amino indolizidines.

**Conditions:**

(I) Methyl methacrylate, rt, 95 h (IIa) AcOH/ H₂O/ Zn, 70 °C, (IIb) NaOH/ MeOH/ H₂O, rt, then HCl (0.2 mol/ L) (pH = 2) (III) LiAlH₄/ THF, rt or LiAlH₄/ AlCl₃/ THF, rt then Pd(OH)₂/C, H₂, MeOH/ HCl (IV) Pd(OH)₂/C, H₂, MeOH/ HCl.

Scheme 1.41

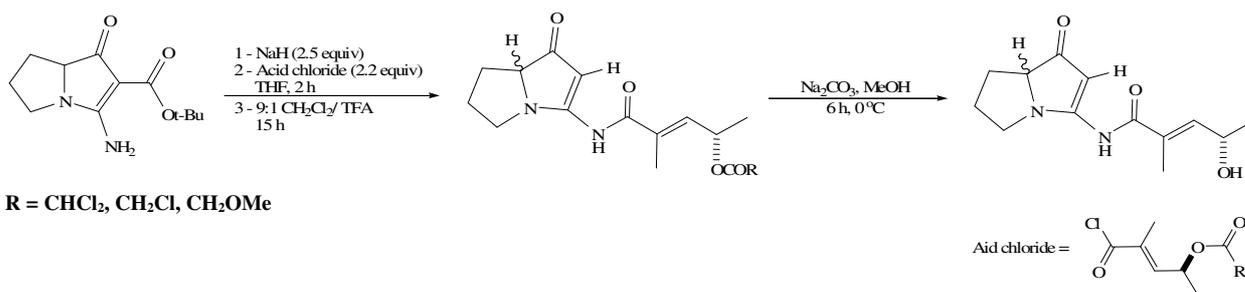
Alkylated indolizidines such as alkaloid 223A have shown promising results as inhibitors of nicotinic acetylcholine receptors. Ghosh *et al.* synthesised both alkaloids 223A and 6-epi-223A using a known norborneone derivative as the starting material (Scheme 1.42) This underwent an intramolecular Schmidt reaction; ring opening metathesis of the lactam *via* a Grubbs-Hoveyda-II catalyst, followed by hydrogenation, gave the required bicyclic amide. Addition of *n*-propyllithium and oxygen removal under neutral conditions resulted in alkaloid 223A as the major product, whereas under acidic conditions the major product was 6-epi-223A.⁵⁹

**Conditions:**

(I) LDA, THF; then HMPA, 1-chloro-3-iodopropane; (II) NaN_3 , KI, DMF; (III) TiCl_4 , CH_2Cl_2 ; (IV) ethylene, 10 mol % Grubbs-Hoveyda-II; (V) 10 % Pd/C EtOAc; (VI a): 1.5 equiv *n*-PrLi, Et_2O , $-10\text{ }^\circ\text{C}$ to rt, 2 h; then 1.5 equiv HOAc, rt, 12 h, then BH_3 , $0\text{ }^\circ\text{C}$ to rt, 2 h (Alkaloid 223A 58 %, 6-epi-223A 16 %). (VI b): 1.5 equiv *n*-PrLi, Et_2O , $-10\text{ }^\circ\text{C}$ to rt, 2 h; then 1.5 equiv TFA, $-40\text{ }^\circ\text{C}$, then BH_3 , $-40\text{ }^\circ\text{C}$ to rt, 3 h. (Alkaloid 223A 7 %, 6-epi-223A 65 %).

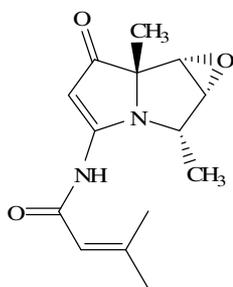
Scheme 1.42

Non-polyhydroxylated pyrrolizidines have shown similar pharmacological properties and are often scarce in nature and difficult to purify. In 1980 Doyle *et al.* published their result of the isolation and structure of bohemamine, which was discovered from a culture screen involving *Actinosporangium* sp. Strain C36145.⁶⁰ They are now believed to be inhibitors of cell adhesion which may help find new cancer treatments.⁶¹ Snider *et al.*, whilst doing a literature search involving three alkaloids that they separated from a culture broth of streptomyces sp., discovered they had the same ring structure as bohemamine, an interesting result as they originally believed they had a very different core.⁶² The compounds were the jenamidines. The main step in the synthesis of jenamide A_1/A_2 was the acylation of a vinylogous urea with an acid chloride. Hydrolysis of its ester and decarboxylation followed by another mild hydrolysis afforded the required pyrrolizidine product (Scheme 1.43).^{54,63}

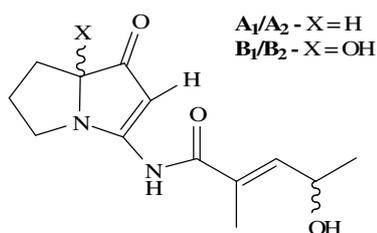
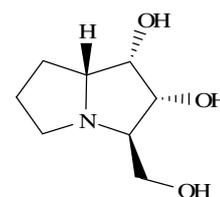


Scheme 1.43

Jenamidines B₁/B₂ differ from A₁/A₂ by having a hydroxy group at the bridgehead of the bicyclic ring. The attempted synthesis of jenamidines B₁/B₂ has been met with difficulty due to having a hydroxy group at the bridgehead and to date these systems have still not been synthesised.^{54,55} Polyhydroxylated pyrrolizidines such as hyacinthacine, again are potential glycosidase inhibitors, and therefore are also attractive targets. Donohoe *et al.* used a selection of partial reduction conditions to vary the stereochemistry around a key bicyclic ring structure which was formed *via* intramolecular S_N2 type displacement reactions to yield the natural products hyacinthacine A₁ and 1-epiaustraline.⁶⁴



Bohemamine

Jenamidine A₁/A₂ & B₁/B₂Hyacinthacine A₁

Discussion

2 Discussion

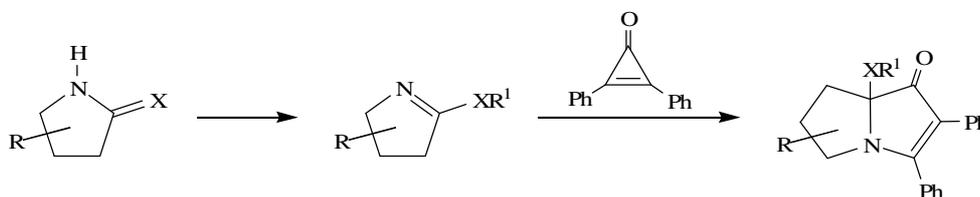
The introduction shows that there is a great demand for azasugars, indolizidines and pyrrolizidines due to the pharmaceutical properties that they possess. Therefore novel synthetic routes to these natural products and analogues of them are always needed. The work carried out in this project has been on the bicyclic ring structures of the indolizidine and pyrrolizidine types.

This research started by optimising a route developed by a previous PhD student and exploits the fact that cyclic thioimidates can be used as starting materials to generate pyrrolizidines, indolizidines and pyrroloazepines.

The first four chapters focus on the synthesis and reactivity of pyrrolizidines derived from five membered cyclic imines and their reactions with diphenylcyclopropanone. The fifth chapter presents a discussion of the synthesis and reactions of other cyclopropanones, and the sixth chapter explores the reactivity of acyclic imines towards diphenylcyclopropanone. The seventh chapter is a description of the synthesis of pyrroloazepines and indolizidines and their reactivity. The final chapter concentrates on 1,3-dipolar cycloadditions of one of these cyclic imines.

2.1 Synthesis of Pyrrolizidines

Overview:



X = O, S or Me

2.1.1 Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

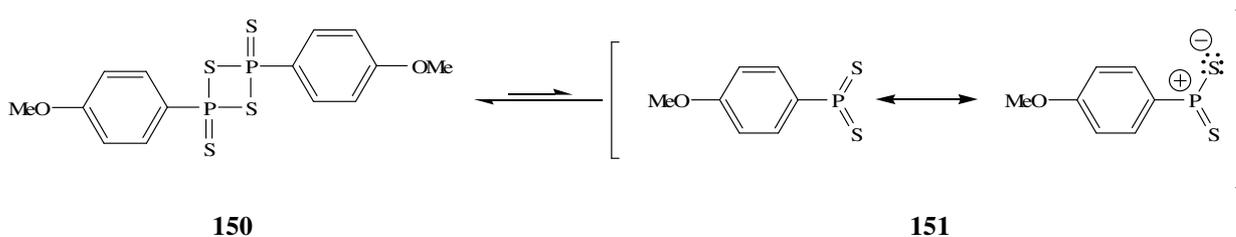
2.1.1.1 Synthesis of pyrrolidine-2-thione



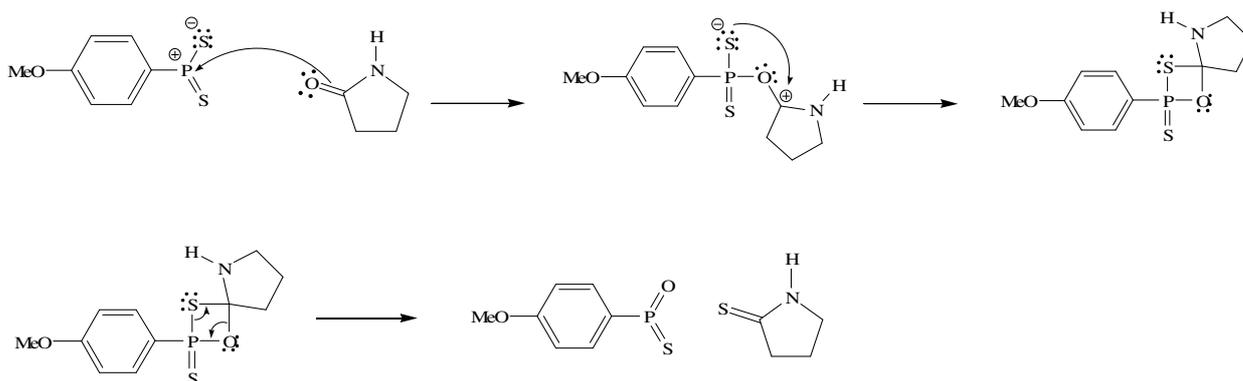
Scheme 2.1

The thiolactams were produced in 59 – 89 % yield *via* a thiation of the commercially available 2-pyrrolidone **148** with Lawesson's reagent **150**. Lawesson's reagent **150** was chosen as the thionating agent as it was commercially available, requires only very mild conditions and gave high yields. Lawesson's reagent has been widely used since 1978,⁶⁵⁻⁶⁸ the main thionating agent before this was phosphorus pentasulfide, which is still widely used today.⁶⁵

The reactivity of Lawesson's reagent **150** comes from the dithiophosphine ylide **151**, which is formed when Lawesson's reagent is in solution at reflux. A possible mechanism is shown below in Scheme 2.3 and shows that the reaction occurs *via* a Wittig type process, and forms the required thiolactam **149**.^{65,66}



Scheme 2.2



Scheme 2.3

Spectroscopic analysis confirmed the structure as pyrrolidine-2-thione **149**. The shift of all signals in the ^1H NMR spectrum showed the product had changed; the broad N-H singlet shifted from 7.03 to 8.74 ppm; the triplets at 3.37 and 2.26 ppm shifted to 3.66 and 2.91 ppm, and the remaining quintet shifted from 2.09 to 2.21 ppm. The main signal change in the ^{13}C NMR spectrum shows the carbonyl at 179 ppm shifting downfield to the thione at 206 ppm.

2.1.1.2 Synthesis of 2-ethylthio-pyrrolidine

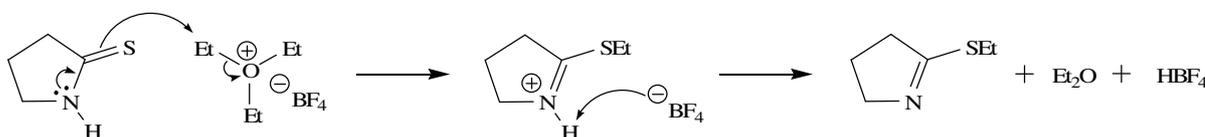


Scheme 2.4

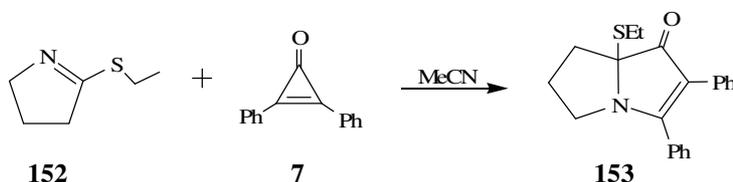
The next step was alkylation, using triethyloxonium tetrafluoroborate (Meerwein's reagent) in DCM. The imine was released from the HBF_4 salt by a work up procedure involving aqueous potassium carbonate. Very low yields were obtained (8 - 14 %) signifying possible volatility issues, as no starting material was recovered.⁶⁹

Spectroscopic analysis of ^1H and ^{13}C NMR spectra confirmed alkylation of pyrrolidine-2-thione **149**. In the ^1H NMR spectrum extra signals appear at 3.01 and 1.30 ppm, as a quartet and triplet respectively, both having a coupling constant of 7.4 Hz indicating the presence of an ethyl group. In the ^{13}C and DEPT NMR spectra a change of the $\text{C}=\text{S}$ bond to $\text{C}=\text{N}$ bond is indicated by the shift of the quaternary carbon from 206 to 172 ppm. The appearance of four CH_2 signals at 61.08, 38.89, 25.20 and 23.67 ppm, and a CH_3 signal at 14.69 ppm, confirmed the structure.

The mechanism of this simple alkylation process is shown below:



2.1.1.3 Reaction with diphenylcyclopropenone

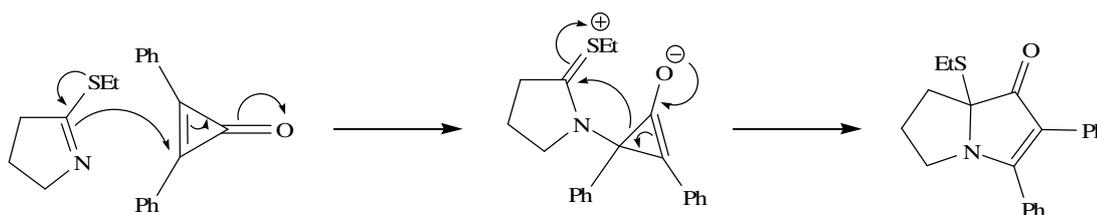


Scheme 2.5

The thioimidate **152** was reacted with diphenylcyclopropenone **7** in anhydrous acetonitrile to afford 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **153** in 50 – 55 % yield.

Analysis of ^1H and ^{13}C NMR spectra confirmed the synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **153**. In the ^1H NMR spectrum, 10 protons appear in the aromatic region between 7.48 – 7.11 ppm as multiplets, confirming the presence of the two phenyl rings. A pair of doublets of doublets of doublets appears at 3.55 and 3.08 ppm integrating to 1 proton each, with coupling constants of 6.7, 6.7 and 11.2 Hz, indicating the presence of the CH_2 group next to the nitrogen. The presence of the ethylthio moiety was provided by two doublet of quartets appearing at 2.65 and 2.55 ppm and a triplet at 1.20 ppm with coupling constants of 7.5 and 11.9 Hz and 7.5 Hz respectively. The remaining four protons appear as multiplets ranging from 2.29 - 2.17 ppm [2 protons], 2.12 – 2.03 ppm [1 proton] and 1.99 – 1.88 ppm [1 proton]. In the carbon spectra the carbonyl appears at 200.49 ppm, the unsaturated carbon of the enone in the β position appears at 175.37 ppm, whilst the unsaturated carbon of the enone in the α position appears at 116.57 ppm. The bridgehead carbon appears at 80.79 ppm with the remaining two quaternary carbons appearing in the aromatic region at 131.66 and 131.35 ppm, the six CH carbons appear between 131.44 – 126.46 ppm, four CH_2 carbons appear between 48.80 – 23.49 and one methyl group appearing at 14.61 ppm. The HRMS gave an accurate mass of 358.1235, which is within 1 ppm of the calculated value.

This reaction proceeds *via* a process that appears to be an overall three carbon 1,3-dipolar cycloaddition and a curly arrow mechanism is shown below in Scheme 2.6:



Scheme 2.6

2.1.2 Attempted synthesis of 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

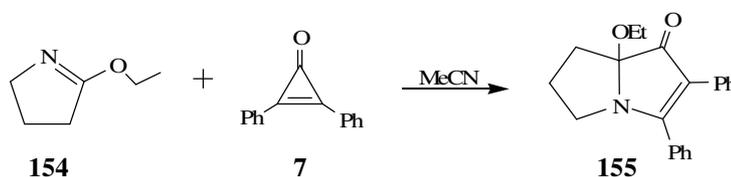
2.1.2.1 Synthesis of 2-ethoxy-1-pyrroline



Scheme 2.7

With the success of the synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one, an attempt to synthesise 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one was made starting with the alkylation of 2-pyrrolidone **148** with Meerwein's reagent.⁷⁰ This process would install an oxygen functional group directly at the bridgehead. It is notable that some natural products in the pyrrolizidine class have oxygen at the bridgehead such as the jenamidines B₁/B₂⁵⁴ and vulgarine.⁷¹ The 2-ethoxy-1-pyrroline product **154** was very volatile, therefore not all of the solvent was removed after the work up procedure and the product was used in this crude diluted form.

2.1.2.2 Attempted reaction with diphenylcyclopropanone



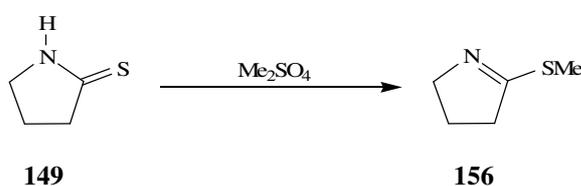
Scheme 2.8

2-Ethoxy-1-pyrroline **154** was mixed with diphenylcyclopropanone **7** in anhydrous acetonitrile. No identifiable products could be isolated. The successful installation of oxygen

at the bridgehead in a different reaction (see later) meant that this reaction was not pursued further.

2.1.3 Synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

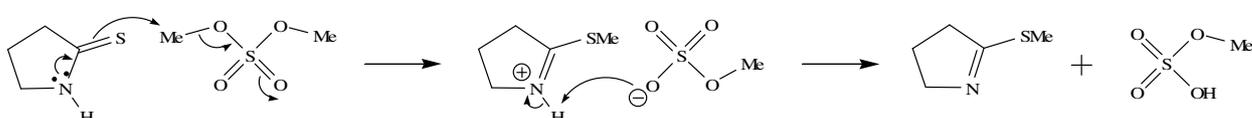
2.1.3.1 Synthesis of 2-methylthio-1-pyrroline



Scheme 2.9

The alkylation step with Meerwein's reagent gave very low yields, therefore neat dimethyl sulfate⁷² was used. The procedure with dimethyl sulfate⁷² was discovered to be higher yielding, easier to perform and superior in all ways to the use of Meerwein's reagent. The 2-methylthio-1-pyrroline⁷³ product **156** was very volatile, therefore not all of the solvent could be removed after the work up procedure and the product was used in this crude diluted form.

The mechanism for the methylation is shown below in Scheme 2.10:

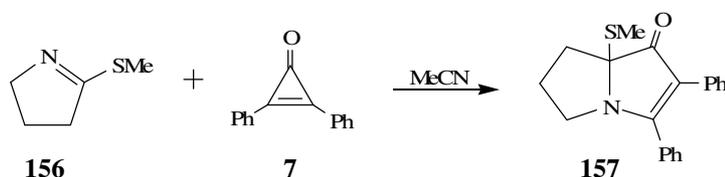


Scheme 2.10

Spectroscopic analysis of ¹H and ¹³C NMR spectra confirmed the synthesis of 2-methylthio-1-pyrroline **156**. In the proton spectrum a new methyl group is clearly visible at ~2.21 ppm. The carbon spectrum provided further evidence of the synthesis of **156**, with the appearance of the

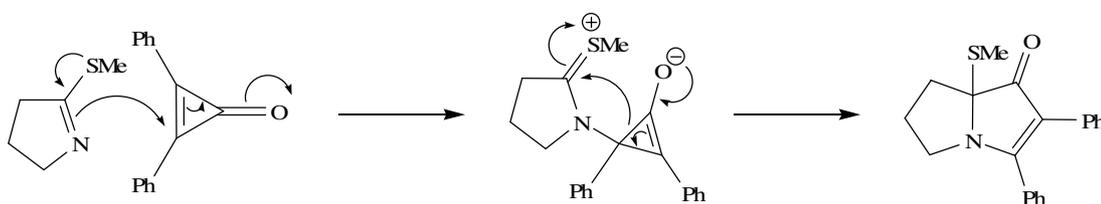
C=N bond at 172.71 ppm, three CH₂ signals appearing at 60.50, 38.18 and 23.62 ppm and a CH₃ signal appearing at 13.33 ppm.

2.1.3.2 Reaction with diphenylcyclopropenone



Scheme 2.11

The reaction of 2-methylthio-1-pyrroline **156** with DPP **7** was done in acetonitrile at ambient temperature. The product was synthesised in yields of up to 77 %. The reaction is believed to go *via* an overall [3+2] cycloaddition process with the cyclopropenone as an all-carbon 1,3-dipole equivalent; the mechanism is shown below in Scheme 2.12 and is identical to the mechanism discussed in section 2.1.1.3.



Scheme 2.12

Analysis of the ¹H and ¹³C NMR spectra confirmed the synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **157**. The proton NMR spectrum has 10 protons in the aromatic range between 7.47 – 7.10 ppm as multiplets. The CH₂ protons were seen as multiplets, the CH₂ attached to the nitrogen appeared between the ranges of 3.59 – 3.51 ppm and 3.12 – 3.04 ppm both integrating to 1 proton each. The other two CH₂ groups appeared in the range of 2.30 – 2.18 ppm, and 2.13 – 1.90 ppm. The CH₃ appears as a singlet at 2.08 ppm. The ¹³C and DEPT spectra has six quaternary carbons appearing between 200.18 – 80.34

ppm, six CHs appearing between 131.47 – 126.51, three CH₂s appearing at 48.90, 32.62 and 26.89 ppm, and the methyl group appearing at 12.04 ppm.

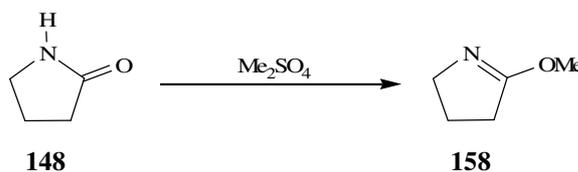
2.1.4 Synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

2.1.4.1 Attempted synthesis of 2-methoxy-1-pyrroline



Scheme 2.13

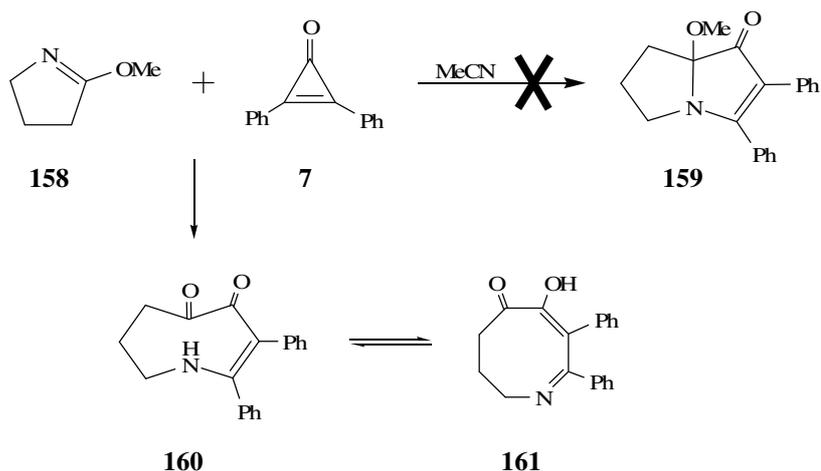
The first step was to synthesise 2-methoxy-1-pyrroline **158** to later react with DPP **7**. 2-Methylthio-1-pyrroline **156** was reacted with sodium methoxide to displace the methylthio group, but all attempts were unsuccessful.



Scheme 2.14

The next attempt to synthesise 2-methoxy-1-pyrroline **158** was by methylating 2-pyrrolidinone **148** using neat dimethyl sulfate. The mixture was stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was worked up and the solvent was removed *in vacuo* and purified by column chromatography, but no identifiable products could be observed.

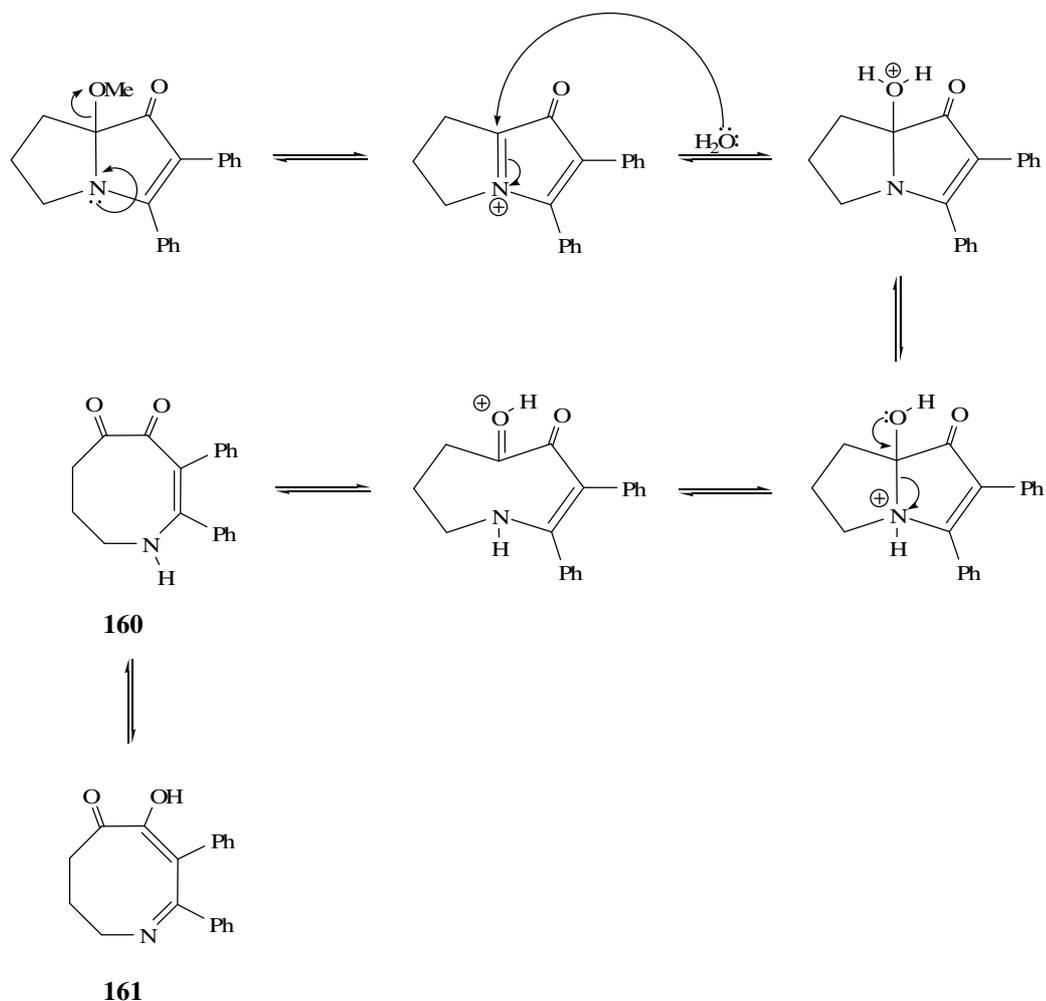
The experiment was repeated due to this being a known literature route.⁷²



Scheme 2.15

Eventually, a crude sample of 2-methoxy-1-pyrroline **158** was obtained and was dissolved in acetonitrile and reacted with diphenylcyclopropenone **7** for six days at ambient temperature under an atmosphere of dry nitrogen. The mixture changed from colourless to orange in colour and a new compound observed by TLC suggested a reaction had occurred, from which a new product was isolated by chromatography.

Whilst it was clear that the product was not the desired bicycle (Scheme 2.15), there is much evidence to suggest ring opening to the azocine **160/ 161**. Firstly a valid mechanism can be drawn as shown below in Scheme 2.16:



Scheme 2.16

Similar ring opening processes have been observed with 1-azabicyclo[3.2.0]hept-2-en-4-ones in work by Heimgartner.⁷⁴

The NMR, IR and MS spectra suggest the structure isolated is the 2,3-diphenyl-1-azocin-4,5-dione **160**. In the ¹H NMR spectrum, a proton appearing at 9.83 ppm confirmed the presence of the amine group, with 10 protons appearing in the aromatic region between 7.27 – 7.04 ppm. The aliphatic region shows three signals integrating at two protons each, two triplets at 3.50 and 2.70 ppm and a quintet at 2.17 ppm. If the bicyclic compound had been synthesised these three CH₂ groups would have been expected to be seen as more complex signals, as occurred in previous bicyclic compounds.

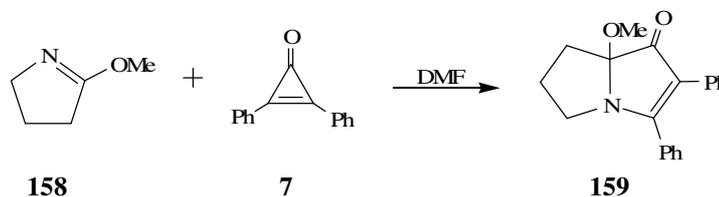
The ^{13}C NMR spectrum shows six quaternary carbons appearing between 190.17 – 133.96 ppm, six CH carbons between 131.61 – 127.89 ppm and three CH_2 carbons appearing at 49.40, 31.86 and 18.99 ppm. Significantly both ^1H and ^{13}C spectra show an absence of a methyl group.

The HRMS calculated value is within 2 ppm of the obtained value, and the IR spectrum shows two strong peaks, at 1704 cm^{-1} indicative of a diketone and 1674 cm^{-1} indicative of an α,β -unsaturated ketone. The amine NH was seen as a small signal at $\sim 3100\text{ cm}^{-1}$.

All attempts to repeat the reaction in order to allow isolation of the primary cycloadduct (the azabicyclo[3.3.0]octenone) resulted only in the isolation of the proposed azocine: it is assumed that hydrolysis is occurring upon isolation.

Other examples of the process were not encountered in this thesis and the result remains an isolated, single example. It is interesting to note that the azocine product could only be formed when crude solutions of 2-methoxy-1-pyrroline were used. We believe this may be due to the presence of water/ acid in the crude mixture.

2.1.4.2 The synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.17

The reaction of diphenylcyclopropenone **7** with pure commercially available 2-methoxy-1-pyrroline **158** in anhydrous dimethylformamide for 18 hours at an elevated temperature was found, after a long process of optimisation, to be the best conditions giving yields of up to 42

%. Other solvents, the addition of Lewis acid catalysts and shorter reaction times, gave lower yields.

Evidence for the synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **159** was provided by NMR, IR and MS spectra. The ^1H NMR displays 10 protons in the aromatic region between 7.48 – 7.10 ppm. The CH_2 adjacent to the nitrogen appears as two doublets of doublets integrating to one proton each at 3.46 and 2.98 ppm. The methyl from the methoxy group appears as a clear singlet integrating to three protons at 3.31 ppm, the methyl peak is further downfield as expected than the methyl from the methylthio group which appears at 2.08 ppm. The remaining two CH_2 groups appear as three multiplets, the first two multiplets appear between 2.34 – 2.21 ppm and 2.20 – 2.13 ppm integrating one proton each, the remaining multiplet appears between 2.00 – 1.89 ppm integrating two protons. This data is supported by the ^{13}C NMR spectrum which confirms six quaternary carbons, six CH carbons, three CH_2 carbons and a CH_3 carbon at 51.95 ppm.

The IR confirmed the presence of the carbonyl at 1683 cm^{-1} and mass spectroscopic analysis gave the correct accurate mass.

Single crystal X-ray analysis confirmed the synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **159**, as shown in Figure 1.

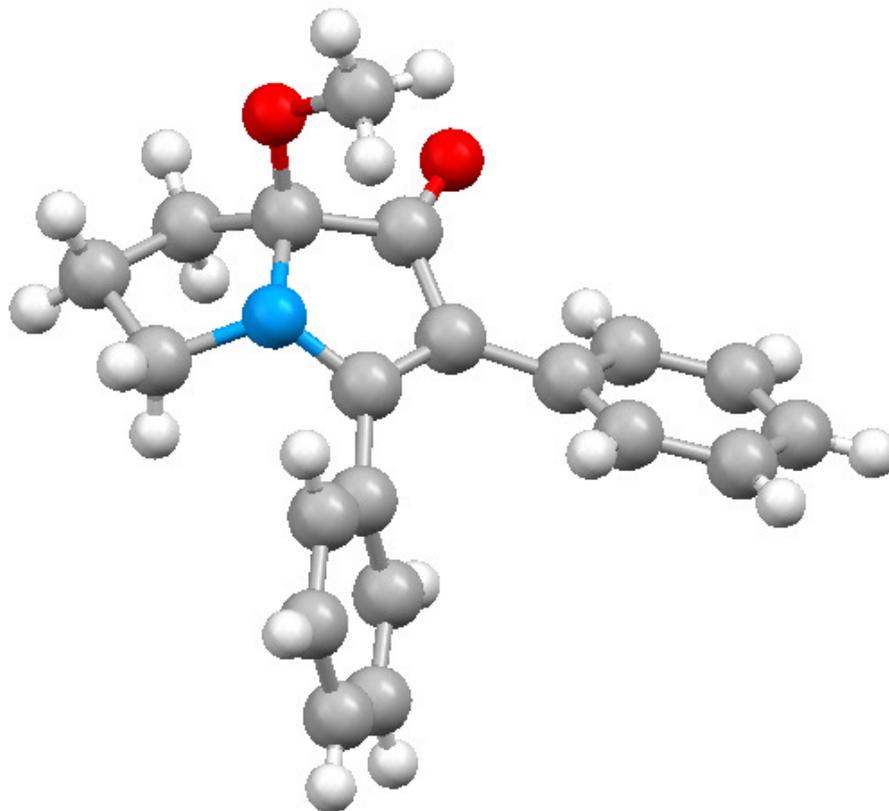
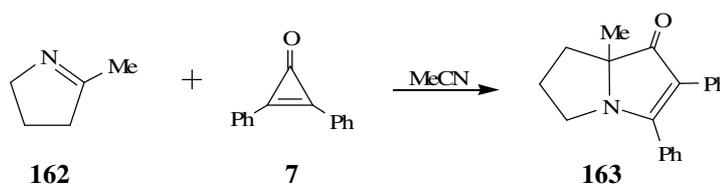


Figure 1 – Crystal Structure of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **159**

2.1.5 Synthesis of 5-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.18

5-Methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **163** was synthesised in a similar way to the pyrrolizidines shown previously. The reaction of 2-methyl-1-pyrroline **162** with diphenylcyclopropenone **7** at ambient temperature gave **163** in 57 % yield. The reaction was repeated in dimethylformamide at 100 °C and gave the desired product in 89 % yield.

The spectroscopic analysis confirmed the structure as 5-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **163**. The ^1H NMR displayed 10 protons in the aromatic region between 7.43 – 7.06 ppm. The aliphatic region of the spectrum displayed two doublets of doublets of doublets integrating to one proton each, indicative of the CH_2 neighbouring the nitrogen. The other two CH_2 s are seen as a multiplets integrating as four protons between 2.12 – 1.84 ppm and the methyl at the bridgehead appears at 1.46 ppm. The ^{13}C NMR spectrum displays six quaternary carbons, six CH carbons, three CH_2 carbons and a methyl group. HRMS was consistent with the assigned structure and the infra-red showed the expected carbonyl stretch at 1670 cm^{-1} .

2.1.6 Synthesis of 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo-[3.3.0]oct-2-en-4-one

Once a few examples of pyrrolizidines with different bridgehead groups were synthesised, the next step was to look at groups in other positions and what effect they would have on the overall process, particularly with respect to stereochemistry.

2.1.6.1 Synthesis of 5-methylpyrrolidine-2-thione

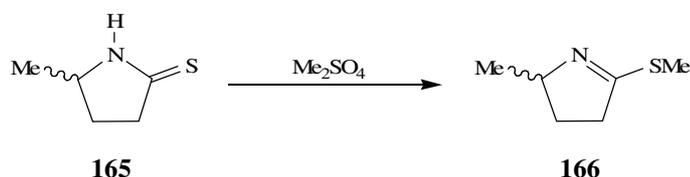


Scheme 2.19

A racemic mixture of 5-methyl-2-pyrrolidone **164** was thionated in a similar process to earlier reactions, using Lawesson's reagent in anhydrous tetrahydrofuran. Purification gave 5-methylpyrrolidine-2-thione **165** in 84 % yield as a white powder.

The structure was confirmed by spectroscopic analysis as **165**. In the ^1H NMR, several protons appear to have shifted downfield from the starting material **164**. The broad NH signal appears at 9.08 ppm, displaying a shift downfield from 7.14 ppm. A CH proton neighbouring the nitrogen appears at 4.05 ppm as a doublet of quartets, displaying a shift downfield from 3.76 ppm in the starting material. The CH_2 adjacent to the thione appears as two doublets of doublets integrating to one proton each at 2.96 and 2.86 ppm, this also displays a shift downfield, as they appeared as multiplets between 2.36 – 2.28 ppm in the starting material. The ^{13}C NMR displays one quaternary peak at 204.77 ppm, one CH peak at 58.52 ppm, two CH_2 peaks at 43.60 and 31.40 ppm, and a methyl peak at 21.07 ppm, with the most significant change being the quaternary carbon at 204.77 ppm shifting downfield from 178.90 ppm.

2.1.6.2 Synthesis of 5-methyl-2-methylthio-1-pyrroline

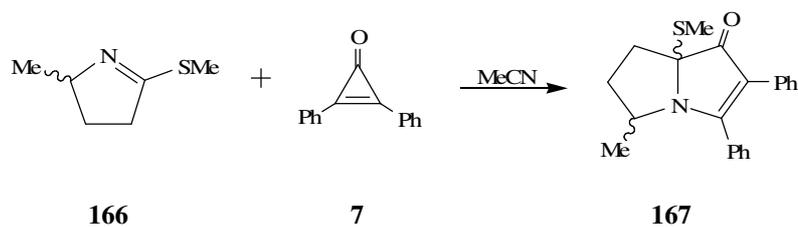


Scheme 2.20

Alkylation of 5-methylpyrrolidine-2-thione **165** using neat dimethyl sulfate yielded a volatile 2-methyl-5-methylthio-1-pyrroline **166**, all of the solvent was not removed after the work up procedure and the product was used in this crude diluted form.

Both ^1H and ^{13}C NMR spectra display the two diagnostic methyl peaks. These appear at 2.45 and 1.27 ppm in the proton NMR spectrum and at 58.93 and 22.44 ppm in the carbon NMR spectra. The ^{13}C NMR spectra also showed loss of the $\text{C}=\text{S}$ carbon at 204.77 ppm and the presence of a new peak at 172.10 ppm for the $\text{C}=\text{N}$.

2.1.6.3 Reaction with diphenylcyclopropenone



Scheme 2.21

2-Methyl-5-methylthio-1-pyrroline **166** was reacted with diphenylcyclopropenone **7** in acetonitrile to obtain the required pyrrolizidine. The reaction was performed at ambient temperature for four days affording 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one **167** as a mixture of diastereoisomers in a 1:1.3 ratio, plus a small amount of a pure single diastereoisomer. The mixture of diastereoisomers was observed by NMR for over five days and slowly showed interconversion from the more abundant isomer to the minor isomer, which was noted to be the diastereoisomer sample isolated in pure form earlier. The stereochemistry for **167** was not established as there was no diastereocontrol observed.

The ^1H NMR spectrum of the single diastereoisomer has 10 protons appearing in the aromatic region between 7.49 – 7.14 ppm, the CH at the chiral centre appears as an apparent quintet at 4.13 ppm. The CH_2 adjacent to the methylthio moiety appears as a doublet of doublets of doublets at 2.86 ppm and as a doublet of doublets at 1.88 ppm both integrating one proton each. The remaining CH_2 appears as a multiplet between 2.24 – 2.10 ppm integrating two protons. The bridgehead methyl group appears as a singlet at 2.12 ppm, and the remaining methyl group appears as a doublet at 0.70 ppm. The ^{13}C NMR spectrum displays six quaternary carbons between 199.87 - 80.37 ppm. Seven CH carbons appear

between 131.15 - 55.40 ppm. The two CH₂s appear at 35.74 and 27.77 ppm with the remaining two CH₃s appearing at 19.37 and 11.52 ppm.

The diastereoisomeric mixture showed additional peaks in both the proton and ¹³C NMR spectra.

On storage the 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one was seen to be impure, and column chromatography gave the 5-OH product (see X-ray Figure 2), presumably the product of hydrolysis in air or on the column. On further inspection of Figure 2 the cis stereochemistry is possibly a result of the methyl group directing the incoming hydroxy group onto the face of the system that reduces congestion on the “inner surface” of the bicyclic structure.

The successful synthesis of 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one **167** showed that an addition of a methyl group would not hinder the addition of diphenylcyclopropanone, although the lack of diastereocontrol was disappointing. The next step was to try starting materials with alternative side groups to get more examples of this type of reaction and to see if any other reactions out of the ordinary would occur, and to assess the level of stereocontrol that might be possible with a group larger than the methyl group.

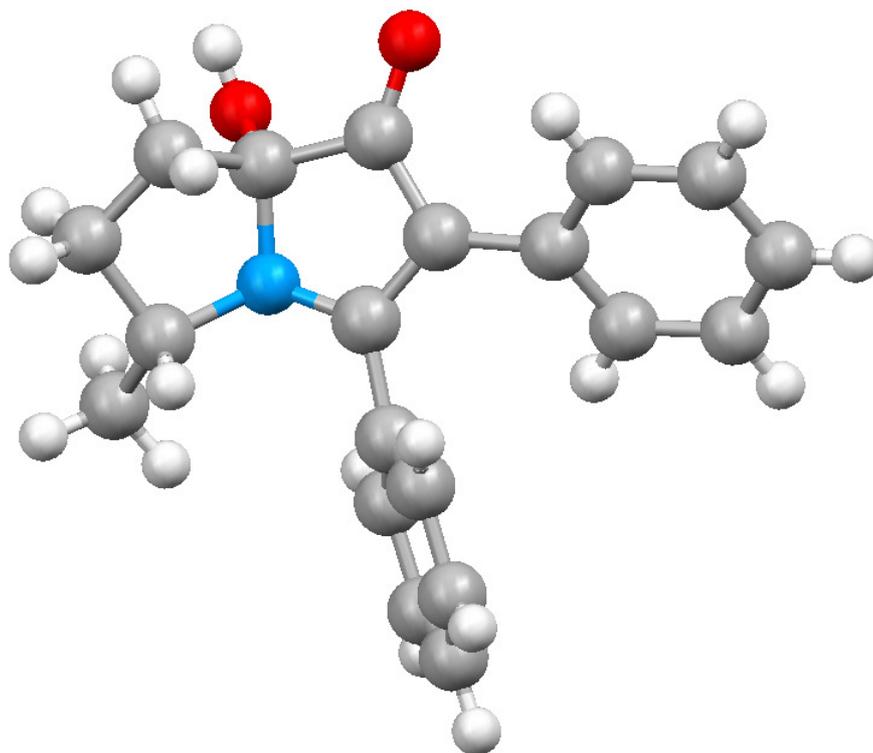


Figure 2 - Crystal Structure of 5-hydroxy-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one

2.1.7 Synthesis of 5-methylthio-2,3-diphenyl-8-ethylcarboxylate-1-azabicyclo[3.3.0]oct-2-en-4-one

2.1.7.1 Synthesis of ethyl pyrrolidine-2-thione-5-carboxylate



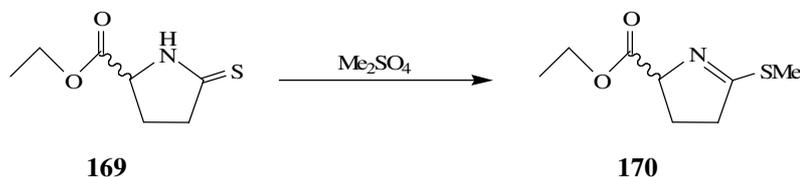
Scheme 2.22

Ethyl (R)-(-) 2-pyrrolidone-5-carboxylate **168** was reacted with Lawesson's reagent **150** in the usual manner and was found to give ethyl pyrrolidine-2-thione-5-carboxylate **169** in 95 % yield, as an orange oil.

Spectroscopic analysis confirms the product as ethyl pyrrolidine-2-thione-5-carboxylate **169**. The ^1H NMR displays a broad NH signal shifted downfield from 6.67 to 8.95 ppm. The proton at the chiral centre appears at 4.49 ppm as a doublet of doublets, and the diastereotopic CH_2 of the ethyl group appears as two doublets of quartets. The methyl group appears at 1.23 ppm, and the remaining four protons are displayed as multiplets.

The ^{13}C NMR spectrum displays a shift in a couple of peaks; the two quaternary carbons appear at 206.53 and 170.42 ppm, whereas they were displayed at 178.44 and 172.34 ppm in **168**; the chiral CH appears at 62.84 ppm whereas it appears 55.79 ppm in **168**. The three CH_2 s appear at 62.16, 42.80 and 27.06 ppm in the product, but are displayed at 61.98, 29.58 and 25.08 ppm in the starting material. The remaining CH_3 appears at 14.20 ppm whereas it is displayed at 14.44 ppm in the starting material.

2.1.7.2 Synthesis of ethyl-2-methylthio-pyrroline-5-carboxylate

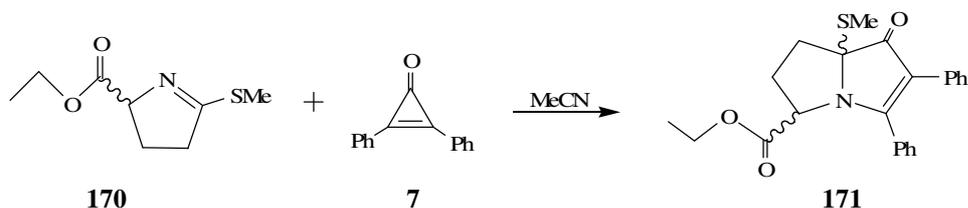


Scheme 2.23

Alkylation was achieved by adding neat dimethyl sulfate in one portion to ethyl pyrrolidine-2-thione-5-carboxylate **169**, yielding ethyl-2-methylthio-pyrroline-5-carboxylate **170** as a crude oil.

Both the ^1H NMR and ^{13}C NMR spectra displayed an extra methyl peak at 2.34 ppm and 13.72 ppm, respectively.

2.1.7.3 Reaction with diphenylcyclopropenone



Scheme 2.24

The addition of diphenylcyclopropenone **7** to 2-methylthio-5-ethylcarboxylatepyrroline **170** in anhydrous acetonitrile afforded 5-methylthio-2,3-diphenyl-8-ethylcarboxylate-1-azabicyclo[3.3.0]oct-2-en-4-one **171** in 50 % yield.

Analysis of the NMR spectra displayed the product as a mixture of diastereoisomers in a ratio of 1:1.2. In the ^1H NMR spectrum, 20 protons appear in the aromatic region between 7.46 – 7.04 ppm, with another 26 protons displayed in the aliphatic region, including two singlets at 2.11 and 2.08 ppm representing the methylthio group and two triplets at 1.27 and 0.82 ppm representing the CH_3 from the ethyl group. The ^{13}C NMR spectrum confirmed the diastereoisomer mix and displayed: 14 quaternary peaks between 199.27 – 80.20 ppm, 14 CH carbons between 131.46 – 60.31 ppm, six CH_2 carbons between 61.61 - 28.52 ppm and four CH_3 carbons appearing at 14.26, 13.79, 11.68 and 11.34 ppm.

The stereochemistry for **171** was not established as there was no diastereocontrol observed.

2.1.8 Synthesis of 5-methylthio-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one

2.1.8.1 Synthesis of (hydroxymethyl)pyrrolidin-2-thione *p*-toluenesulfonate

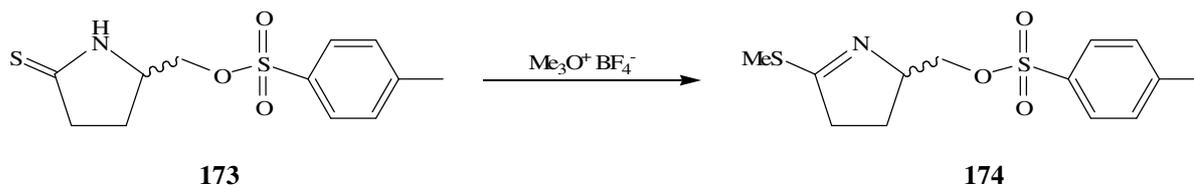


Scheme 2.25

The next substituted analogue was synthesised using (S)-(+)-(hydroxymethyl)-2-pyrrolidinone *p*-toluenesulfonate **172** as a starting material. This was thionated in the usual manner using Lawesson's reagent in anhydrous tetrahydrofuran to give product **173**.

The product was produced in 83 % yield and its structure was confirmed by NMR spectra. The ^1H NMR spectrum displayed a broad NH signal between 8.22 – 8.13 ppm, whereas the NH signal in the starting material appeared at 6.32 ppm. The ^{13}C NMR spectrum displayed three quaternary signals at 206.85, 145.93 and 132.36 ppm, whereas they appear at 178.11, 145.71 and 132.60 ppm in **172**, confirming thionation was successful.

2.1.8.2 Synthesis of (hydroxymethyl) 2-methylthio-5-*p*-toluenesulfonate pyrroline

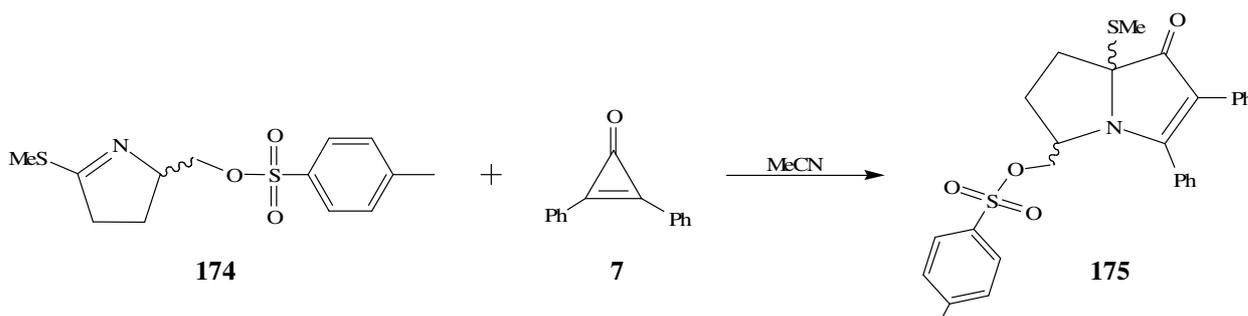


Scheme 2.26

The initial alkylation step was performed as previously described, using neat dimethyl sulfate at ambient temperature. However, on this occasion dimethyl sulfate was unsuccessful as an alkylating agent. Trimethyloxonium tetrafluoroborate was therefore used to methylate (hydroxymethyl) pyrrolidin-2-thione *p*-toluenesulfonate **173** in dichloromethane which afforded (hydroxymethyl)-2-methylthio-5-*p*-toluenesulfonate pyrroline **174**.

Methylation was confirmed by both ^1H and ^{13}C NMR spectra displaying an extra methyl peak. The ^1H NMR spectrum displays two methyl peaks at 2.44 and 2.38 ppm, and the ^{13}C NMR spectrum displays two methyl peaks at 21.97 and 14.10 ppm.

2.1.8.3 Reaction with diphenylcyclopropenone



Scheme 2.27

(Hydroxymethyl)-2-methylthio-5-*p*-toluenesulfonate pyrroline **174** was reacted with diphenylcyclopropenone **7** in anhydrous acetonitrile. The mixture was stirred at ambient temperature for three days but no reaction was observed; therefore the reaction mixture was heated at reflux for 18 hours. Purification yielded 5-methylthio-2,3-diphenyl-8(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one **175** in 48 % yield, as a single diastereoisomer.

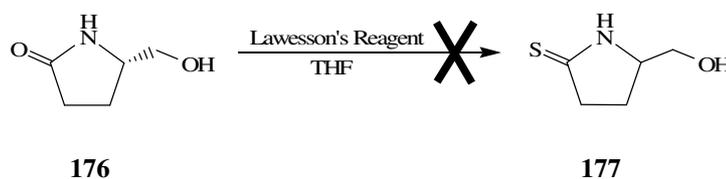
Analysis of the spectra confirmed the synthesis of **175**. The ^1H NMR spectrum displayed four protons in the aromatic region between 7.50 – 7.32 ppm and another 10 protons between 7.25

– 7.09 ppm. The ^{13}C NMR spectrum displayed eight quaternary signals, nine CH signals, three CH_2 signals and two CH_3 signals. The HRMS gave an accurate mass of 528.1274, which is within 1 ppm of the calculated value. As yet we have been unable to determine the stereochemistry outcome.

2.1.9 Attempted synthesis of 5-methylthio-2,3-diphenyl-8-hydroxymethyl-1-azabicyclo[3.3.0]oct-2-en-4-one

Many natural pyrrolizidone natural products have hydroxy/ hydroxy methyl groups attached. Therefore, the synthesis of 5-methylthio-2,3-diphenyl-8-hydroxymethyl-1-azabicyclo[3.3.0]-oct-2-en-4-one was attempted, whereby this is essentially a deprotected version of the OTs protected **175**.

2.1.9.1 Attempted synthesis of 5-(hydroxymethyl)pyrrolidin-2-thione



Scheme 2.28

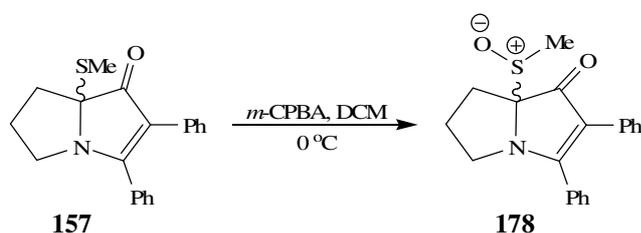
The thionation of (S)-5-(hydroxymethyl)-2-pyrrolidinone **176** with Lawesson's reagent **150** was attempted in anhydrous tetrahydrofuran under the conditions described above. On this occasion, no thionation was observed possibly due to the alcohol functional group interfering with the Lawesson's reagent. In any event none of the desired product could be isolated. However, the easy access to the OTs protected **175** meant that this failure was not an issue.

2.2 Reactivity of Pyrrolizidines

With a range of azabicyclo[3.3.0]octenones in hand, time was taken to study their reactivity.

2.2.1 Reactivity of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

2.2.1.1 Mono oxidation at sulfur



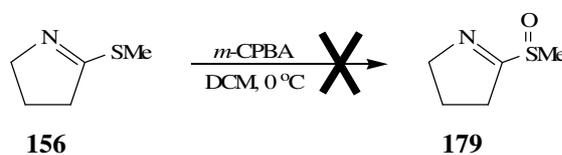
Scheme 2.29

5-Methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **157** was oxidised using *meta*-chloroperoxybenzoic acid in anhydrous dichloromethane.⁷⁵ The reaction was done at low temperature to afford the mono oxidised 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **178** in high yields of up to 90 %.

The product was formed as a mixture of diastereoisomers in a 1:1.45 ratio confirmed by both ¹H and ¹³C NMR spectra. Spectroscopic analysis by ¹H NMR displayed 20 protons in the aromatic region between 7.55 – 7.14 ppm, 12 CH₂ protons between 3.53 – 1.83 ppm and two methyl singlets at 2.69 and 2.57 ppm. The ¹³C NMR spectrum displayed ten quaternary carbon signals between 196.00 – 119.83 ppm, and two sp³ quaternary carbons at 92.75 and 91.86 ppm. There are 12 CH protons appearing in the aromatic region between 132.11 – 128.53 ppm including two CHs overlapping at 128.88 ppm. The six CH₂s appear between 60.74 – 22.15 ppm and the remaining two CH₃ carbons appear at 33.33 and 32.74 ppm.

2.2.1.2 Reactivity of 2-methylthio-1-pyrroline

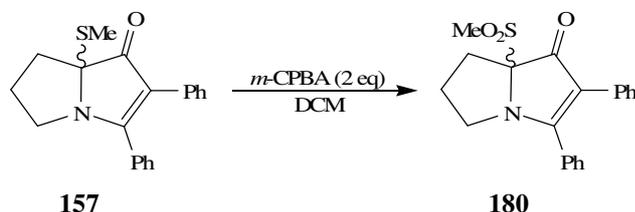
The above oxidation to produce 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **178** gave very good yields. However, there was still an obvious alternative route to **178** that had not been explored, namely the oxidation of 2-methylthio-1-pyrroline **156** followed by the reaction with diphenylcyclopropenone **7** to give access to 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **178**.



Scheme 2.30

As with the mono oxidation of **157**, 2-methylthio-1-pyrroline **156** was reacted with *meta*-chloroperoxybenzoic acid in dichloromethane, at 0 – -10 °C under an atmosphere of dry nitrogen. No identifiable products were isolated, so this route of oxidation for the synthesis of **178** was not further pursued due to the extremely high yields noted in section 2.2.1.1.

2.2.1.3 Oxidation to the sulfone



Scheme 2.31

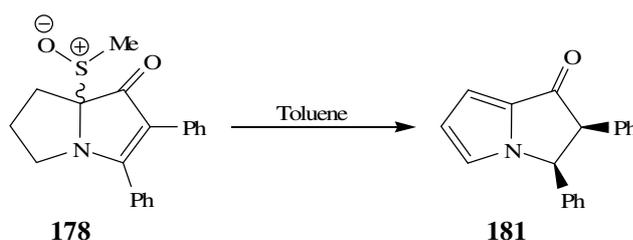
5-Methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **157** was oxidised using *meta*-chloroperoxybenzoic acid in anhydrous dichloromethane. To obtain the sulfone rather than the sulfinyl, the reaction used two equivalents of *m*-CPBA at ambient temperature for three

days, and this afforded the di-oxidised 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]-oct-2-en-4-one **180** in yields of up to 75 %.

Analysis of both ^1H and ^{13}C NMR spectra confirmed the synthesis of 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one. The ^1H NMR spectrum displayed a shift of the methyl singlet downfield from 2.08 ppm to 3.01 ppm (note that the sulfoxide displays the methyl singlets at 2.57 and 2.69 ppm). The ^{13}C NMR also displayed the methyl peak shifting downfield. This is an indication that a more electronegative group has been attached and is shifting the methyl peak further downfield. The other peaks for this product in both the ^1H and ^{13}C NMR are all present and are as described for the sulfoxide, except that there are diastereomers in this case.

The HRMS gave an accurate mass of 376.0981, which is within 3 ppm of the calculated value, confirming the uptake of the two oxygen atoms.

2.2.1.4 Reactivity of 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

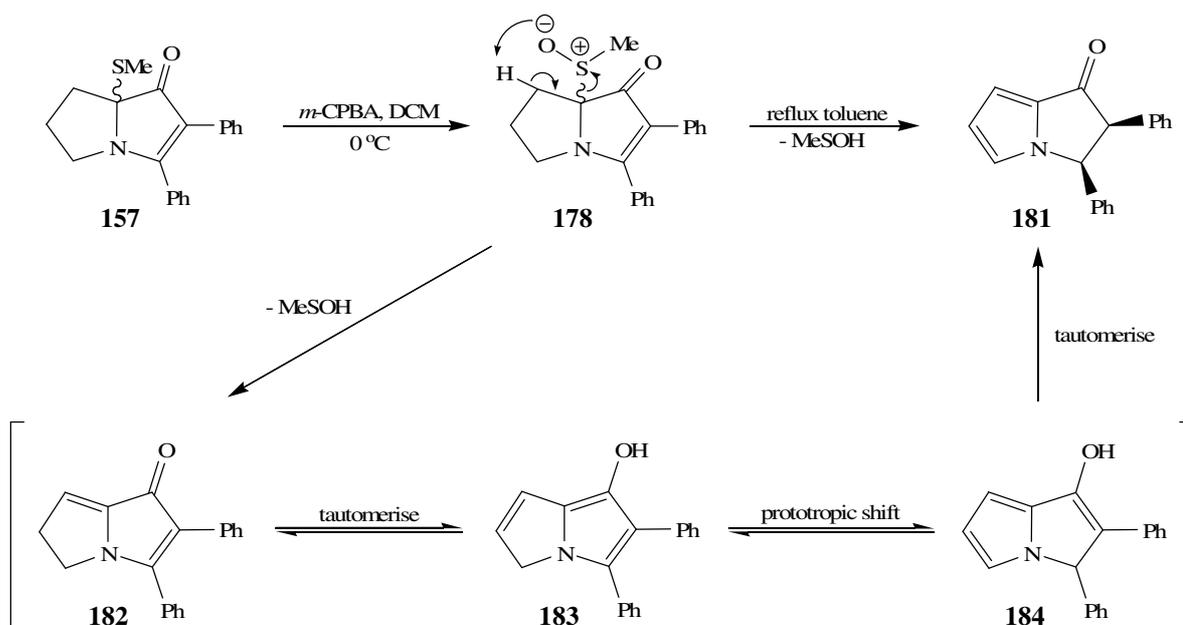


Scheme 2.32

5-Methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **178** was dissolved in toluene and heated at reflux to discover whether it would undergo β -elimination and remove methyl sulfenic acid. The immediate product of the β -elimination, **182**, was not isolated, the actual product isolated was **181** (Scheme 2.33) in 24 % yield, this was confirmed by extensive NMR studies (COSY, HSQC, HMBC, NOESY).

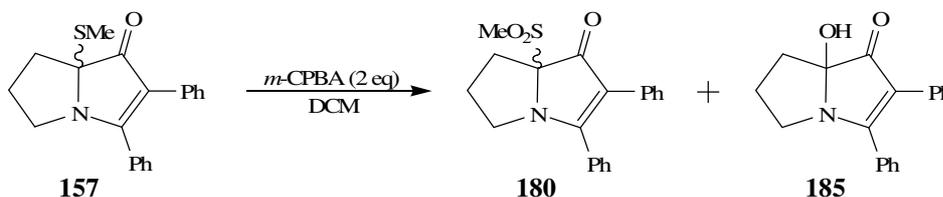
The NMR studies revealed three new CH groups appearing in the aromatic region, confirming the presence of the new pyrrole ring. Two sp^3 CHs α and β to the carbonyl appear at 5.46 and 4.11 ppm, indicative of a CO-CHPh-CHPh chain. The stereochemistry shown in Scheme 2.32 was confirmed from the strong NOE between the two sp^3 CHs, which would only be seen if both were on the same face. This, with a strong NOE between the two phenyl rings is symptomatic of a *cis* relationship between the two phenyl rings. It is also notable that there is a lack of any NOE between either of the two sp^3 CHs and the *ortho* protons of the phenyl ring on the neighbouring carbon.

The mechanistic rationale proposed in Scheme 2.33 shows a tautomerism-prototropic shift-tautomerism sequence. The loss of methyl sulfenic acid from product **178** gives the unstable product **182**, which tautomerises to **183**, undergoes a prototropic shift to give **184** and, in the final tautomerism, the incoming proton enters from the least sterically hindered face, i.e. *trans* to the existing phenyl group, resulting in the two phenyl groups sitting *cis* to each other and yielding **181**.



Scheme 2.33

2.2.1.5 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.34

5-Methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **157** as described above, was oxidised using an excess of *meta*-chloroperoxybenzoic acid in dichloromethane. In one batch, after five days of stirring, two products were isolated, the expected 5-sulfone **180**, and the unexpected 5-hydroxy compound **185**. Given the presence of such an OH in the jenamidines, this result was analysed further.

The 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185** was identified using NMR, IR and mass spectrometry, and was formed in 10 % yield.

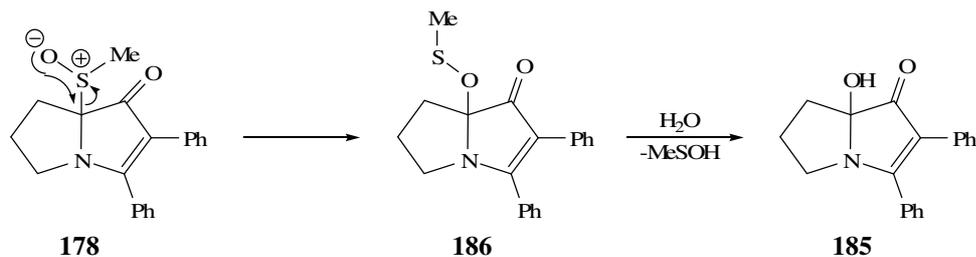
In the ¹H NMR spectrum, 10 protons appear in the aromatic region between 7.50 – 7.12 ppm, three CH₂ groups appear between 3.59 - 1.90 ppm and a new broad hydroxyl peak appears between 4.00 – 3.72 ppm. There is a distinct absence of the methyl group. In the ¹³C NMR spectrum, six quaternary peaks appear between 200.23 – 96.70 ppm, six CH carbons in the aromatic region between 131.79 – 126.63 ppm and three CH₂ peaks at 49.25, 33.34 and 26.75. The ¹³C NMR spectrum confirmed the disappearance of the methyl group. The IR spectrum shows a broad OH signal at 3348 cm⁻¹, and a very strong sharp ketone signal at 1676 cm⁻¹, consistent with an α,β-unsaturated ketone. The HRMS gave an accurate mass of 292.1336 which is within 4 ppm of the calculated value and is in agreement with the assigned structure – i.e., loss of SMe and gain of OH. All the data is consistent with the structure of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185**.

The synthesis and isolation of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185**, was a pleasant surprise as there are natural products which display an OH group in this position. A hydroxy group at the bridgehead in such systems is very difficult to obtain, and attempts at this have been met with difficulties both in our own work and in that of Snider *et al.*⁵⁴ We needed to understand more about how product **185** was formed in order that we might synthesise it deliberately. The obvious source of the OH is water, either from wet solvent or from the *m*-CPBA.

5-Methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **157** was thus reacted with *meta*-chloroperoxybenzoic acid in dichloromethane with the addition of two drops of water. The reaction was monitored by TLC and stopped after 20 hours by quenching with saturated aqueous sodium thiosulfate and washed with saturated aqueous sodium hydrogen carbonate. The results were similar to those obtained above i.e. approximately 10 % yield of the hydroxy compound. Noteworthy here is the fact that extra water did not increase the yield of the 5-hydroxy compound **185**.

In the next optimisation attempt, a solution of **157** in DCM had benzoic acid and three drops of water added to it. Benzoic acid was used as it is acidic but non-oxidising. TLC analysis showed no change had occurred after 19 hours of stirring at ambient temperature, indicating that *m*-CPBA is necessary for a successful reaction. In order to establish if the sulfone **180** was the source of **185**, a solution of **180** in DCM, benzoic acid and water (3 drops) was stirred and the mixture monitored by TLC, but no reaction was observed.

The addition of *m*-CPBA to the reaction mixtures above had no effect on their outcome. The only time the 5-hydroxy compound **185** could be produced was by treating the 5-methylthio **157** with *m*-CPBA in dichloromethane. Having looked at (and dismissed) the possibility of acid catalysed hydrolytic routes to the 5-hydroxy compound **185**, we subsequently looked at possible rearrangement process involving oxygen transfer from a sulfoxide intermediate:



Scheme 2.35

A plausible mechanism is shown above, where a rearrangement from the sulfoxide (made as shown in Scheme 2.29) gives **186** which loses methyl sulfenic acid to afford product **185**. Another possible pathway could be hydrolysis in a heterolytic or a free-radical, S-O bond cleavage. No evidence was found for these reaction pathways.

In order to see if a viable synthetic route to **185** could be established, basic aqueous media were also explored:

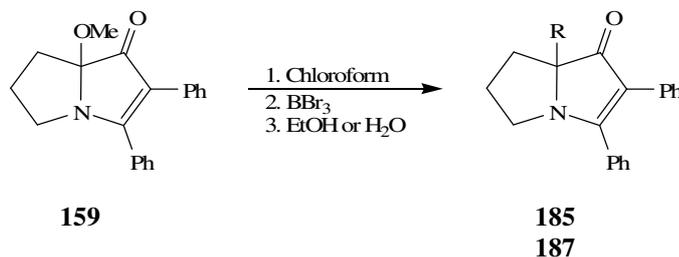


Scheme 2.36

Low yields (~20 %) of the desired 5-hydroxy compound **185** were obtained by heating a THF/DCM solution of **157** in aqueous/ethanolic sodium hydroxide for three days.

Spectroscopic analysis confirmed the structure of the isolated compound as the desired product, giving ^1H and ^{13}C NMR spectra identical to that described above. Higher yields of **185** could not be obtained *via* this route and, although further efforts are ongoing in the group, other approaches were explored in this work.

2.2.2 Reactivity of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



185: R = OH, 187: R = OEt

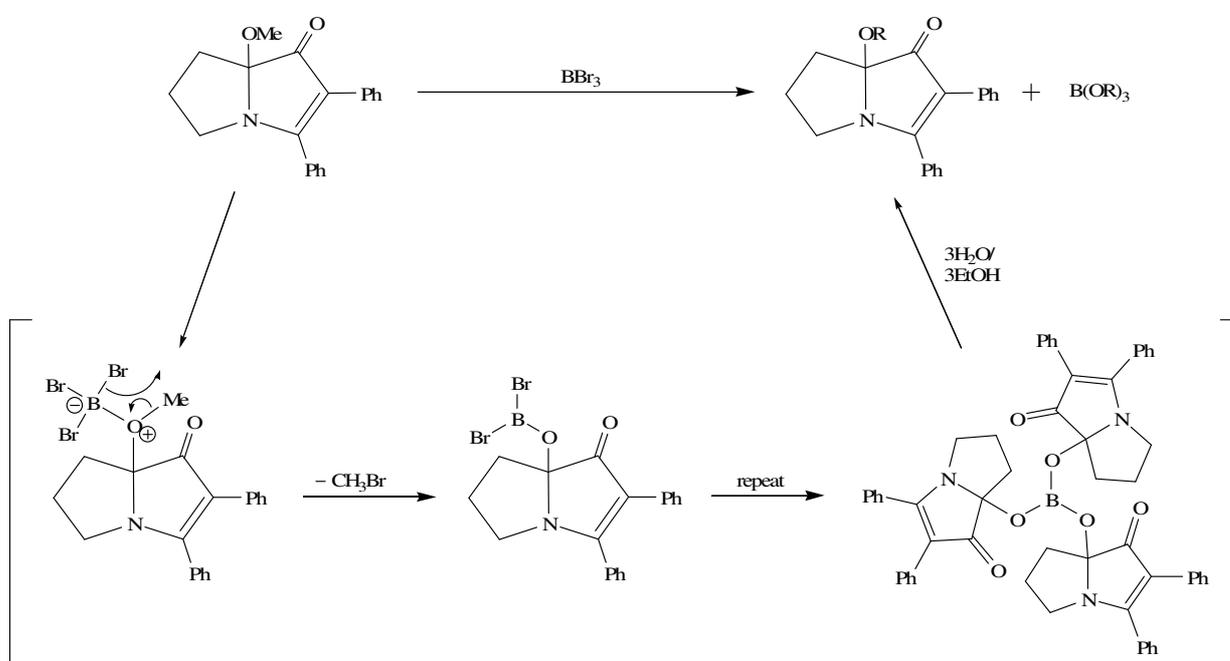
Scheme 2.37

Due to very low yields being obtained in previous attempts to gain access to the bridgehead hydroxy compound **185**, the next reaction that was performed was to cleave the methoxy group off **159** and replace it with a hydroxy group. Boron tribromide is a strong Lewis acid and is well known for cleaving methyl aryl ethers.⁷⁶⁻⁸⁰ There are a number of different cleaving methods/ reagents that can be used for the demethylation process. Hydrohalic acids are similar to Lewis acids in that they cleave at the C-O bond,⁸¹ but hydrohalic acids are not usually preferred due to the extremely high temperatures⁸² (≥ 200 °C) required. Another method is by directly attacking the methyl group using a strong nucleophile.⁸³ This method of demethylation is restricted to compounds that do not contain any other functional groups susceptible to nucleophilic attack⁸¹ and therefore **159** is not suitable as it contains an α,β -unsaturated carbonyl which could be vulnerable to a nucleophilic attack.

Boron tribromide is moisture sensitive and corrosive, but has been shown to demethylate very well.⁸⁴⁻⁸⁷ Thus after a process of optimisation, a solution of **159** in chloroform was treated with a dropwise addition of boron tribromide (0.42 eq) over two and a half hours at 0 °C, the reaction was quenched with excess ethanol. Purification gave two products which were the expected 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185** in 31 % yield and the unexpected 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **187** in 44 % yield.

The 5-hydroxy compound was identical to that obtained previously. Spectroscopic analysis also confirmed the structure of the 5-ethoxy compound as the other product. In the ^1H NMR spectrum, the appearance of the ethoxy group is displayed by two multiplets integrating to one proton each between 3.70 – 3.38 ppm representing the CH_2 protons, whilst the methyl groups appears at 1.24 ppm as a triplet. In the ^{13}C NMR spectrum, the appearance of an additional CH_2 carbon and the shift upfield of the methyl group from 51.95 to 15.80 ppm is displayed.

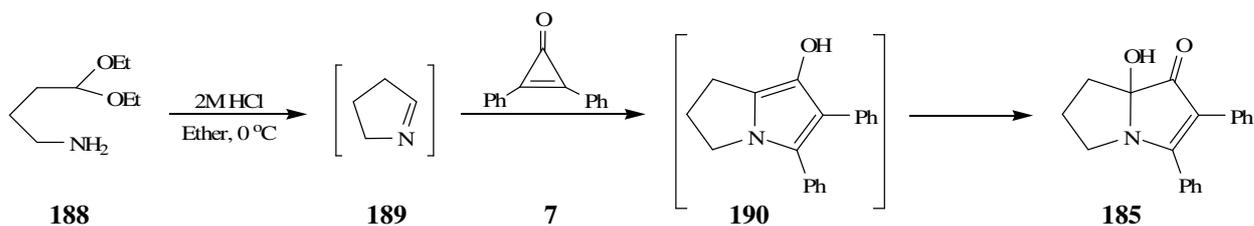
The reaction was repeated as before but instead of quenching with ethanol, water was used. This was to see if a higher yield of **185** could be synthesised. As previously **159** in chloroform had boron tribromide added dropwise and stirred for two and a half hours at 0°C . Excess water was added to quench the reaction, giving **185** in 35 % yield, and recovered **159** in 9 % yield. A possible mechanism for the BBr_3 reaction is shown below:



R = H, Et

Scheme 2.38

2.2.3 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.39

After successfully synthesising pyrrolidine compounds with hydroxy, methoxy, ethoxy, methylthio and ethylthio groups on the bridgehead, the next step was to attempt to extend the methodology to allow a proton at the bridgehead. Several pyrrolizidine and indolizidine natural products have a proton at the bridgehead, such as tylophorine,⁸⁸ castanospermine,⁸⁹ uniflorine A^{90,91} and hyacinthacine.⁹² The parent 1-pyrroline **189** was chosen as a model. 4-Aminobutylaldehyde diethyl acetal **188** was used as a starting material and was cyclised in a mixture of 2M HCl and diethyl ether at 0 °C. The mixture was basified with aqueous potassium carbonate and extracted with diethyl ether, before being concentrated down to ~10 mL. Into this solution diphenylcyclopropenone **7** was added. The only product obtained was 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185** in 8 % yield. However, given the instability of the 1-pyrroline **189**, this was an encouraging result.

Spectroscopic analysis confirmed the structure as 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one **185**.

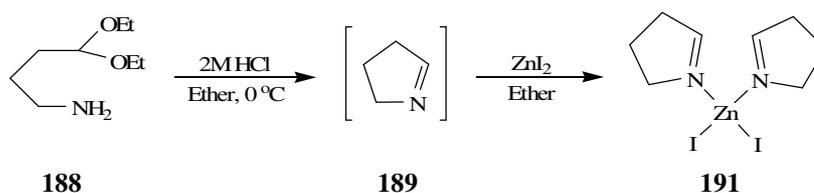
In the ¹H NMR spectrum, ten protons appear in the aromatic region between 7.47 – 7.09 ppm as multiplets, confirming the presence of the two phenyl rings. The OH proton appears at 3.86 ppm as a broad singlet. The CH₂ group adjacent to the nitrogen appears at 3.56 and 2.89 ppm as two doublets of doublets of doublets. The CH₂ protons neighbouring the bridgehead carbon

appear at 2.16 and 1.91 ppm as doublets of doublets of doublets. The remaining CH₂ group appeared as two multiplets between 2.47 – 2.36 ppm and 2.06 – 1.98 ppm. In the ¹³C NMR spectrum, six quaternary carbons appear between 199.92 – 96.61 ppm, six CH carbons appear between 131.60 – 126.50 ppm, with three CH₂s appearing at 49.26, 33.35 and 26.65 ppm. Infra-red spectrum displayed a clear presence of the hydroxy group at 3327 cm⁻¹ along, surprisingly, with a C=O at 1669 cm⁻¹.

The HRMS gave an accurate mass of 314.1152 which was exactly the calculated value of C₁₉H₁₇NNaO₂. It was somewhat surprising to note that this synthesis gave a product identical to the bridgehead OH from above suggesting oxidation at the bridgehead. A suggested mechanism is shown in Scheme 2.42 (see later).

2.2.3.1 Synthesis of bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II)

The results of the previous experiment gave a low yield which was believed to be due to the intermediate 1-pyrroline not being stable, therefore we stabilised the imine intermediate with zinc iodide using a literature method.⁹³

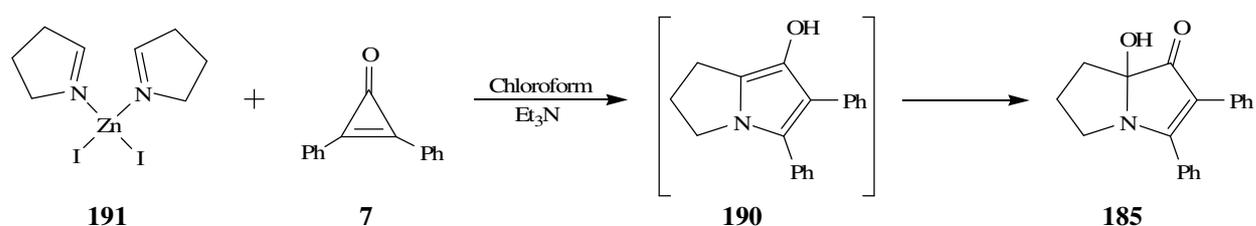


Scheme 2.40

4-Aminobutyl diethyl acetal **188** was dissolved in a mixture of 2M HCl and diethyl ether as described previously, and the resultant ethereal solution was dried over magnesium sulfate. Zinc iodide was added to the reaction mixture at 0 °C. The precipitate formed was

filtered off to yield bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) **191** in 66 % yield, identical in all aspects to that reported in the literature.⁹³

2.2.3.2 Reactivity of bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II)



Scheme 2.41

Bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) **191** in chloroform had diphenylcyclopropanone **7** and a solution of triethylamine (2 eq) in water added. The reaction mixture was stirred at ambient temperature for two and a half hours before being extracted with dichloromethane. Purification gave **185** in 43 % yield.

Spectroscopic results were identical to those described above and were confirmed unequivocally by single crystal X-ray analysis, as shown in Figure 3.

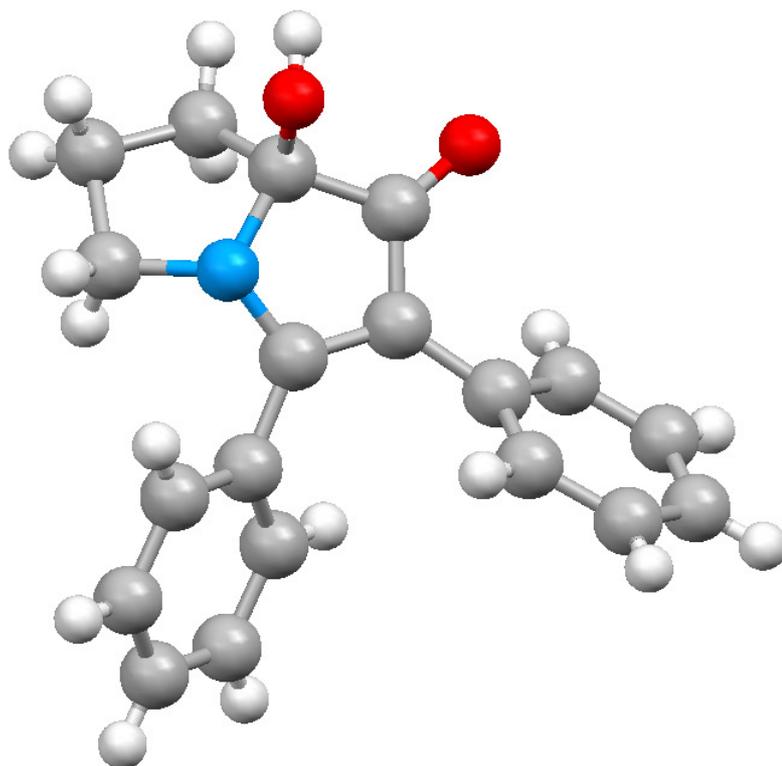
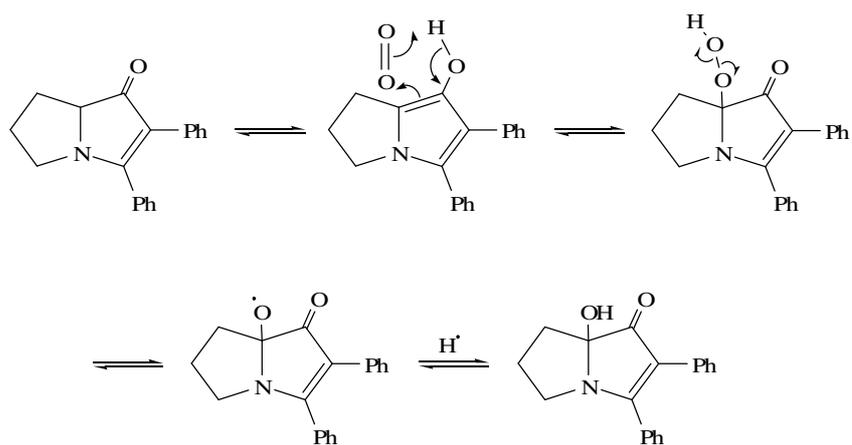


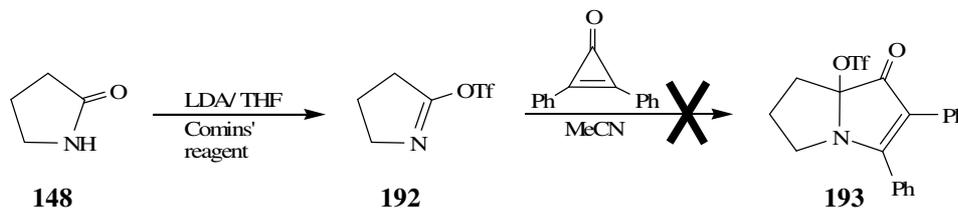
Figure 3 – Crystal Structure of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one 185.

The mechanism of this reaction is far from obvious, but a suggested pathway is shown below.



Scheme 2.42

2.2.4 Attempted synthesis of 5-triflyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.43

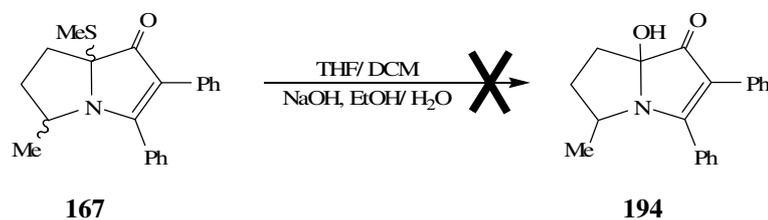
In order to extend the scope of the cyclic imine-DPP reaction further, we looked to have groups other than H, R, OR or SR (R= alkyl) at the bridgehead. Amides are easily converted into triflates; therefore the triflate group was assessed.

2-Pyrrolidinone **148** had lithium diisopropylamide (LDA) added to deprotonate the amine, followed by the addition of Comins' reagent which was used to add a triflate group. After purification the triflate **192** obtained in 10 % yield was reacted with DPP in an attempt to produce 5-triflyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one. No bicyclic products were obtained despite repeated attempts.

Spectroscopic analysis confirmed the formation of the 5-triflyl-1-pyrroline **192** intermediate.

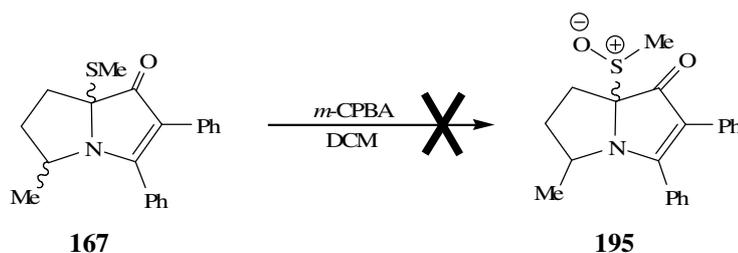
In the ^1H spectrum, all three CH_2 protons shifted downfield from those for **148** and the secondary amide proton had disappeared. In the ^{13}C NMR spectrum, all four carbon signals had shifted, along with the addition of a new quaternary carbon at 118.21 ppm, consistent with that for the CF_3 group.⁹⁴

2.2.5 Attempted formation of 5-sulfoxy and 5-hydroxy-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.44

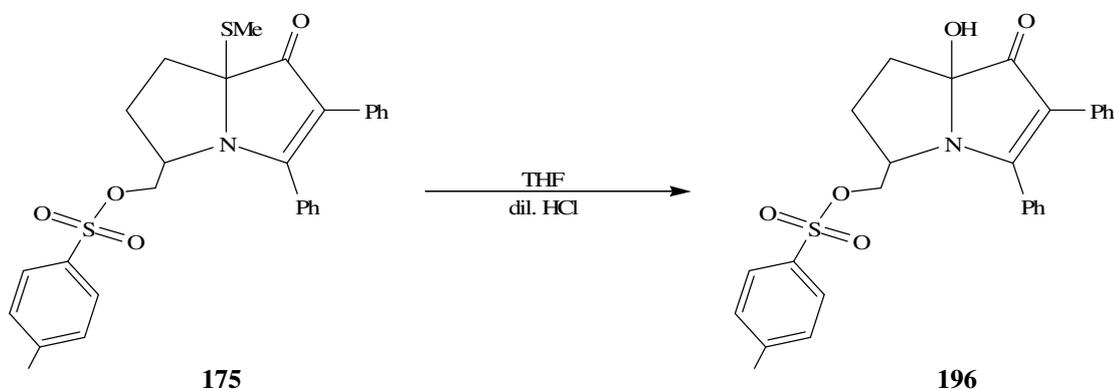
The attempt to get a hydroxy group on the bridgehead of 5-methylthio-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one was unsuccessful with basic aqueous media that was used in section 2.2.1.5.



Scheme 2.45

Similarly, attempts to oxidise the sulfide to the sulfoxide using the *m*-CPBA technique that had been used previously was also unsuccessful, with no signs of any identifiable product or starting material.

2.2.6 Hydrolysis of 5-methylthio-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one



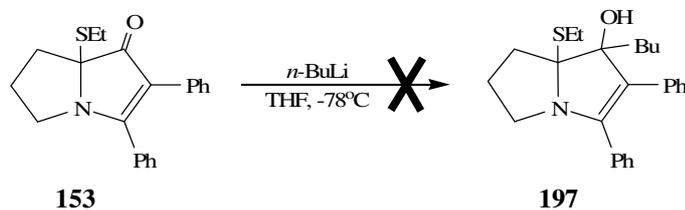
Scheme 2.46

The attempted replacement of the methylthio group in compound **175** with a hydroxy group was only successful in low yields <5 %, using THF in dilute HCl, no other product or starting material was recovered.

Spectroscopic analysis confirmed the presence of 5-hydroxy-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one **196** as the product, formed as a single diastereoisomer.

The ^1H and ^{13}C NMR spectra displayed a shift in several peaks; this observation, accompanied by the disappearance of the methyl group from both the proton spectrum at 2.07 ppm and the carbon spectra at 11.38 ppm, indicated a change had occurred. Mass spectroscopic data confirmed the structure.

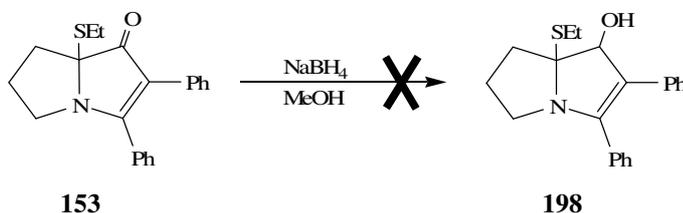
2.2.7 Attempted synthesis of 4-butyl-5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-ol



Scheme 2.47

5-Ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one was treated with ⁿBuLi under standard conditions but no identifiable products could be observed, with 90 % of the starting material being recovered unchanged.

2.2.8 Attempted synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-ol



Scheme 2.48

The same substrate also failed to react with sodium borohydride under a variety of conditions. The reaction was repeated with 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one, which also showed no signs of any identifiable product or recovery of starting material in either case.

2.3 Synthesis of polyhydroxylated pyrrolizidines

Another group of pyrrolizidines, as described in the introduction, are the polyhydroxylated pyrrolizidines also known as aza-sugars. With these in mind, the next stage of this project was to synthesise a hydroxylated pyrroline. This was done from L-arabinose as described below.

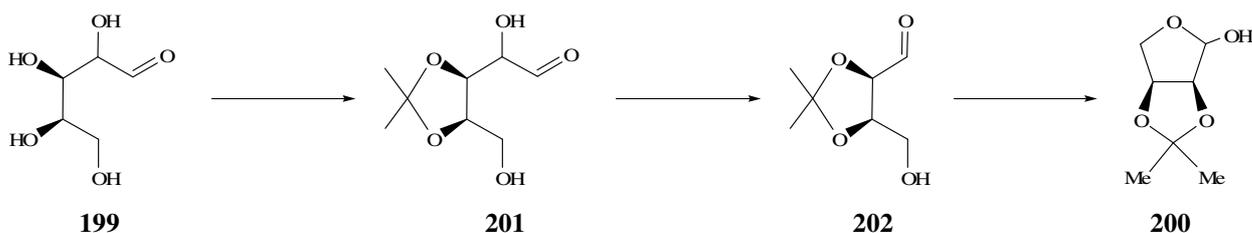
2.3.1 Synthesis of 2,3-*O*-isopropylidene-L-erythrose

The first step is summarised below:



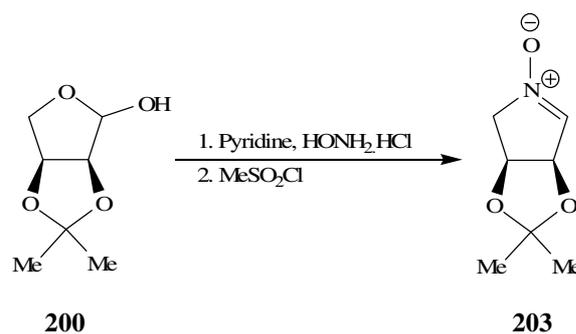
Scheme 2.49

Commercially available L-arabinose **199** in dimethylformamide had *p*-toluenesulfonic acid and 2,2-dimethoxypropane added at ambient temperature to give the protected arabinose **201** as the initial product (see Scheme 2.50). Sodium periodate was used to cleave at the C-C carbonyl bond to produce **202** which cyclises to give 2,3-*O*-isopropylidene-L-erythrose **200** in 52 % yield with data consistent with that reported in the literature⁹⁵⁻⁹⁷ together with a small quantity (3 %) of the diprotected arabinose.



Scheme 2.50

2.3.2 Synthesis of (3*S*,4*R*)-3,4-isopropylidenedioxypyrroline 1-oxide



Scheme 2.51

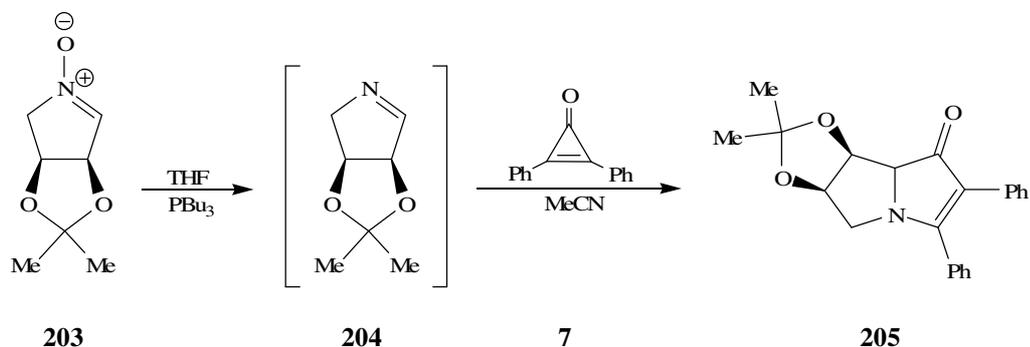
The next step was to synthesise a nitronium, again using a literature method.⁹⁸⁻¹⁰⁰

2,3-*O*-isopropylidene-*L*-erythrose **200** was dissolved in dry pyridine with 3Å activated molecular sieves, and a solution of hydroxylamine hydrochloride was added at ambient temperature under an atmosphere of dry nitrogen, followed by a solution of methanesulfonyl chloride in dry pyridine. The crude product was purified to give (3*S*,4*R*)-3,4-isopropylidenedioxypyrroline-1-oxide **203** in 13 % yield.

Spectroscopic analysis confirmed the product as **203**.

In the ¹H NMR, a broad singlet appearing at 6.75 ppm represents the unsaturated CH proton neighbouring the nitrogen. The protons at the ring junctions appear at 5.18 and 4.79 ppm as broad singlets. The remaining CH₂ protons from the pyrroline ring appear as two signals at 4.02 and 3.86 ppm, both as broad doublets. The two methyl groups appear at 1.30 and 1.22 ppm as singlets. The ¹³C NMR spectrum corroborates the results from the ¹H NMR. Three CH carbons appear at 133.03, 79.76 and 73.60 ppm, a quaternary carbon appears at 111.90 ppm and the CH₂ carbon appears at 29.58 ppm with the remaining CH₃ groups appearing at 27.08 and 25.56 ppm. The data was consistent with that reported in the literature.^{98,99}

2.3.3 Attempted synthesis of 2,3-diphenyl-6,7-isopropylidenedioxy-1-azabicyclo[3.3.0]oct-2-en-4-one

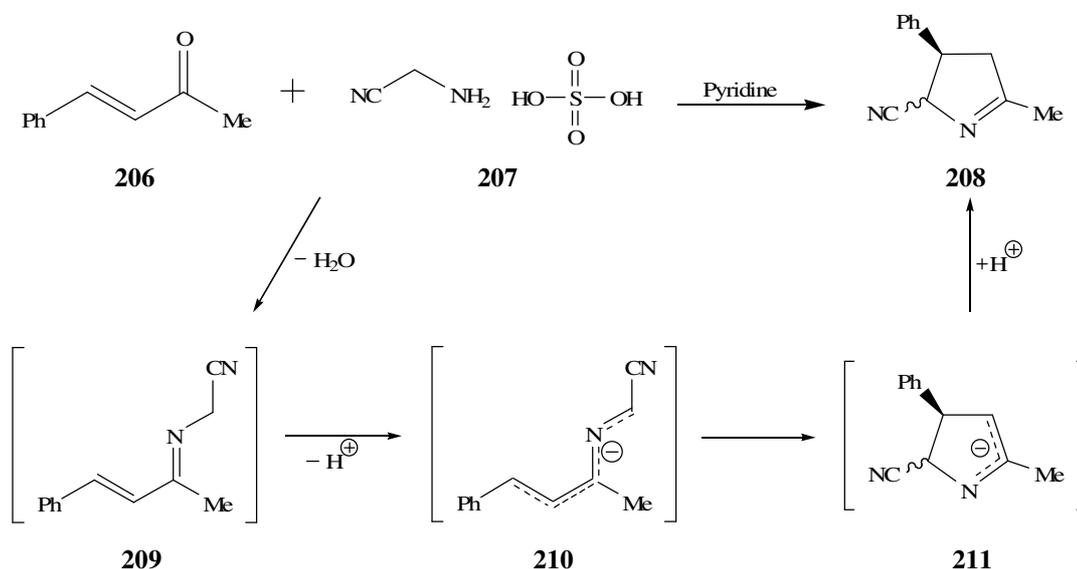


Scheme 2.52

The nitronium **203** was dissolved in anhydrous tetrahydrofuran and treated with tributylphosphine¹⁰¹ in order to deoxygenate the nitronium and hence generate the protected hydroxylated pyrroline. Diphenylcyclopropanone **7** in anhydrous acetonitrile was added and the reaction monitored for new spots by TLC. TLC and subsequent ¹H NMR indicated a change had occurred, and subsequent work by others in the group have shown that these types of reactions do work, although time constraints and difficulties in obtaining tributylphosphine in a timely fashion prevented further studies in this thesis.

2.4 Synthesis of a highly substituted, functionalised pyrrolizidine

2.4.1 Synthesis of 2-methyl-4-phenyl-5-cyano-1H-pyrroline



Scheme 2.53

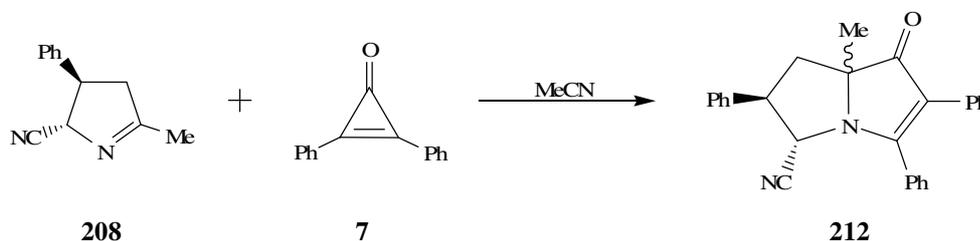
In order to produce a highly substituted functionalised pyrroline, 2-methyl-4-phenyl-5-cyano-1H-pyrroline **208** was synthesised using aminoacetonitrile bisulfate **207** and 4-phenyl-3-buten-2-one **206**. Scheme 2.53 shows a possible reaction course as suggested by Bergner *et al.*¹⁰² The intermediate imine **209** is formed by condensation of the starting materials; deprotonation of **209** then gives the 2-azapentadienyl anion **210** which undergoes electrocyclization to furnish the 1-azaallyl anion **211**. Reprotonation gives the more stable 3,4-dihydro-2H-pyrrole **208**.¹⁰² The product was only obtained as the trans isomer in low but usable yields.

The structure was confirmed by spectroscopic analysis and by comparison to the literature data.

In the ¹H NMR spectrum, five protons appear in the aromatic region between 7.39 – 7.19 ppm as multiplets, the proton neighbouring the carbonitrile appears between 4.72 – 4.66 ppm as a

multiplet, the proton neighbouring the phenyl ring appears at 3.80 ppm as a doublet of doublets of doublets and the CH₂ appears as two doublets of doublets of doublets at 3.21 and 2.83 ppm, showing some long range coupling. The ¹³C NMR spectra displays three quaternary carbons at 180.13, 140.32 and 119.56 ppm, five CH carbons between 129.37 – 49.27 ppm and the CH₂ and CH₃ carbons appear at 47.65 and 20.07 ppm, respectively.

2.4.2 Synthesis of 5-methyl-2,3,7-triphenyl-8-cyano-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.54

The next step was to react 2-methyl-4-phenyl-5-cyano-1H-pyrroline **208** with diphenylcyclopropenone **7**. This cyclopropenone was chosen as it has previously reacted well with imines as shown earlier in this thesis, and therefore would give an indication as to whether cyclopropenones can react with more complex imines of this sort.

The components were stirred in anhydrous acetonitrile at ambient temperature for three days. Purification gave back both starting materials in good recovery and the required product **212**, in 17 % yield although this reaction was not fully optimised.

Spectroscopic analysis confirmed the product to be 5-methyl-2,3,7-triphenyl-8-cyano-1-azabicyclo[3.3.0]oct-2-en-4-one **212** formed as a mixture of two diastereoisomers in a 1:1.5 ratio.

In the ^1H NMR spectrum, 30 protons, (15 per diastereoisomer) appear in the aromatic region between 7.60 – 7.16 ppm as multiplets, two of the four CH protons appear at 4.59 and 3.77 ppm, both as doublets, and the other two CH protons appear as a multiplet and a quartet between 4.25 – 4.18 ppm and at 3.71 ppm, respectively. Three of the four CH_2 protons of the two isomers appear at 2.88 ppm, 2.46 ppm, and 2.21 ppm as doublets of doublets of doublets, with the final CH_2 proton appearing as a multiplet between 2.41 – 2.27 ppm. The two methyl groups appear at 1.74 and 1.43 ppm. In the ^{13}C NMR spectrum, the 16 quaternary carbons appear between 205.03 – 74.86 ppm, the 22 CH carbons appear as 18 overlapping signals between 132.09 – 51.04 ppm. Two CH_2 carbons appear at 39.25 and 38.80 ppm with the remaining two CH_3 carbons appearing at 26.20 and 22.72 ppm. The HRMS gives an accurate mass of 413.1624 which is within 1 ppm of the calculated value.

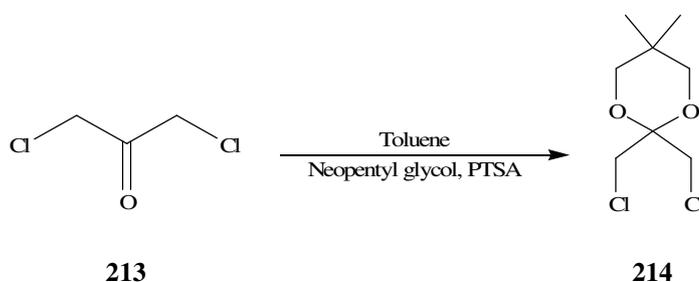
2.5 Cyclopropenones

Until now the only cyclopropenone that we have used is diphenylcyclopropenone due to it being commercially available, but most pyrrolizidine and indolizidine natural products don't contain a phenyl ring in their system. This chapter will look into the synthesis of different cyclopropenones and their reactions.

2.5.1 Unsubstituted cyclopropenones

The following sequence of syntheses looks at the production of the unsubstituted parent cyclopropenones and their reaction with cyclic imines. The first method that was attempted was reported by Isaka *et al.*^{36,35}, and uses dichloroacetone **213** to synthesise the cyclopropenone acetal **217** as described below.

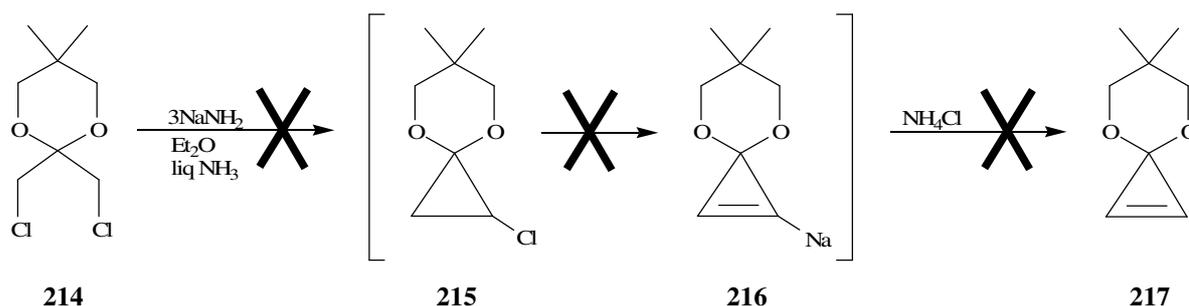
2.5.1.1 Synthesis of dichloroacetone acetal



Scheme 2.55

Dichloroacetone **213** and neopentyl glycol were reacted together in boiling toluene in the presence of PTSA with azeotropic removal of water (Dean-Stark). The acetal **214** was formed as a white solid in 88 % yield.^{36,35}

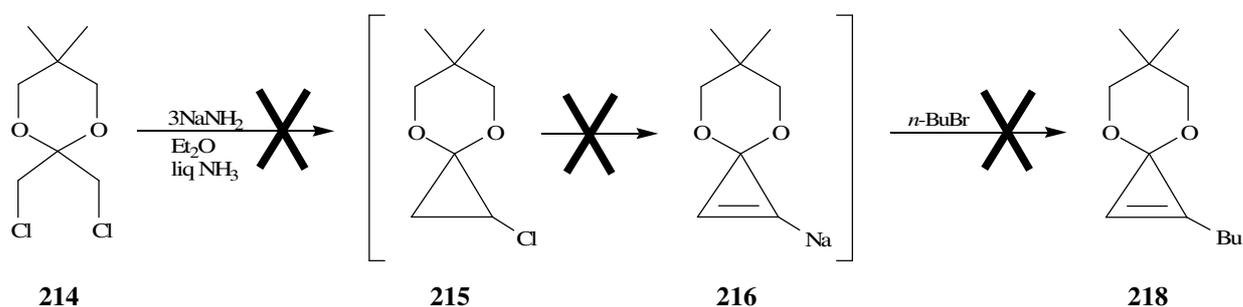
2.5.1.2 Attempted synthesis of 6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene



Scheme 2.56

The dichloroacetone acetal **214** was added to sodium amide (3 eq) in liquid ammonia at -50°C . An additional portion of sodium amide was added to the mixture to aid the formation of the sodium salt **216** from the chlorocyclopropane **215**.³⁵ Ammonium chloride was added slowly to the mixture in an attempt to form the cyclopropenone acetal **217**. Spectroscopic analysis showed no identifiable products. This reaction was extremely complex to perform and problems were encountered with the low temperature manipulation/ addition of the acetal which was found to constantly freeze. Further efforts were similarly unsuccessful (despite this being a literature procedure).

2.5.1.3 Attempted synthesis of 1-butyl-6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene

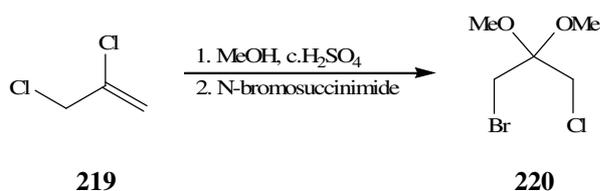


Scheme 2.57

The process described above was also repeated with the final addition of n-butylbromide rather than ammonium chloride, the idea being to quench the sodium salt **216** with butyl rather than a proton. However, spectroscopic analysis showed no reaction had occurred.

The second method attempted for the production of the unsubstituted parent cyclopropenone looks at an adaptation of Baucom and Butler's³³ synthesis, by Breslow *et al.*³⁴ The synthesis starts with 2,3-dichloro-1-propene to give 1-bromo-3-chloro-2,2-dimethoxypropane which is used to make 3,3-dimethoxycyclopropene, as described below.

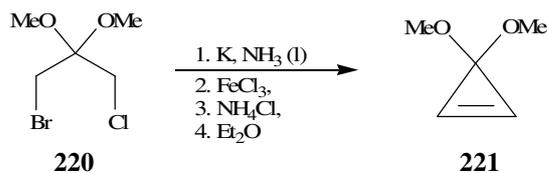
2.5.1.4 Synthesis of 1-bromo-3-chloro-2,2-dimethoxypropane



Scheme 2.58

2,3-Dichloro-1-propene in anhydrous methanol was treated with *N*-bromosuccinimide and sulfuric acid, as described in the literature,³⁴ giving 1-bromo-3-chloro-2,2-dimethoxypropane as a white crystalline solid in 36 % yield. The spectroscopic data was consistent with that of the literature.³⁴

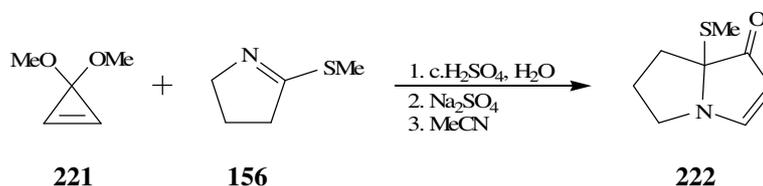
2.5.1.5 Synthesis of 3,3-dimethoxycyclopropene



Scheme 2.59

The synthesis of the protected cyclopropenone was difficult to achieve, again due to the tedious nature of the method and problems similar to those described above for the dichloro system were encountered. The bromo-chloro-acetal was treated with potassium in liquid ammonia at $-78\text{ }^{\circ}\text{C}$, and the mixture quenched with ammonium chloride. The crude product was isolated as an ethereal solution and used in this form in the next reaction. All attempts to purify the acetal were unsuccessful.

2.5.1.6 Reaction with 2-methylthio-1-pyrroline



Scheme 2.60

The crude dimethylcyclopropenone solution **221** prepared as described above was treated with sulfuric acid in water to deprotect and generate the cyclopropenone. The resulting mixture was added to a solution of 2-methylthio-1-pyrroline **156** in anhydrous acetonitrile which reacted vigorously and turned the mixture brown/ red in colour, accompanied by giving a vigorous reaction. The mixture was purified to give 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one **222** as a brown/ orange oil.

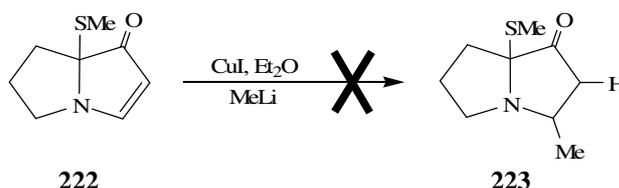
The structure was confirmed by spectroscopic analysis as **222**.

In the ¹H NMR spectrum, the protons at the β and α position of the unsaturated carbonyl appear at 7.77 and 5.30 ppm respectively, both as doublets with J values of 3.5 Hz. One of the protons from the CH₂ neighbouring the nitrogen appears at 3.52 ppm as a doublet of triplets with J values of 7.4 and 11.2 Hz, whilst the other appears at 3.32 ppm as a doublet of doublets of doublets with J values of 4.1, 7.1 and 11.2 Hz. One of the protons from the CH₂

neighbouring the bridgehead carbon appears at 1.89 ppm as doublets of doublets, the other proton along with the remaining CH₂ protons appear as a multiplet between 2.21 – 1.97 ppm. The methyl group appears as a singlet at 1.96 ppm integrating to three protons.

In the ¹³C NMR, the quaternary carbonyl carbon appears at 203.86 ppm, and the β and α carbons of the unsaturated carbonyl appear at 169.31 and 105.57 ppm, respectively. The bridgehead carbon appears at 79.78 ppm, the three sp³ carbons appear at 48.79, 33.18 and 27.38 ppm, and the methyl group appears at 12.16 ppm. The HRMS gives a value of 192.0454 which is within 1 ppm of the calculated value for this molecule. The IR displays a carbonyl peak at 1681 cm⁻¹.

2.5.1.7 Reactivity of 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one



Scheme 2.61

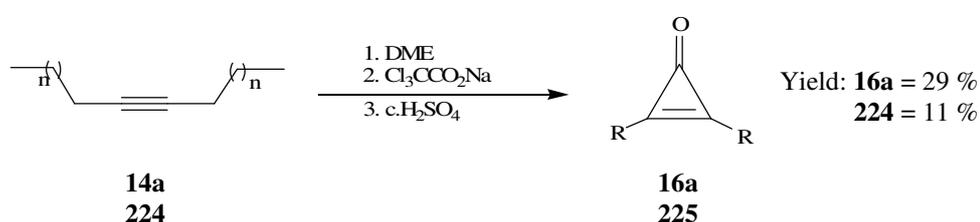
The synthesis of 2-methyl-5-methylthio-1-azabicyclo[3.3.0]octan-4-one **223** was attempted by an organocopper conjugate addition using lithium dimethylcuprate.¹⁰³ A successful model experiment was performed by reacting lithium dimethylcuprate with 2-cyclopenten-1-one. All attempts to synthesise **223** were, however, unsuccessful.

The route of using organocopper conjugate addition to add an organic group at the β position of an unsaturated carbonyl was not looked at any further due to the reaction not being successful and there being other avenues to pursue. One possible explanation of why it was unsuccessful could be due to the electron donating effect of the nitrogen, which undermines conjugate addition.

2.5.2 Synthesis of dialkylcyclopropenones

The aim of looking at different cyclopropenones was further pursued by the synthesis of dialkylcyclopropenones, and shown below are two methods used to make dipropyl and dibutyl cyclopropenones using 4-octyne **14a** and 5-decyne **224** as starting materials, respectively.

Method 1¹⁰⁴

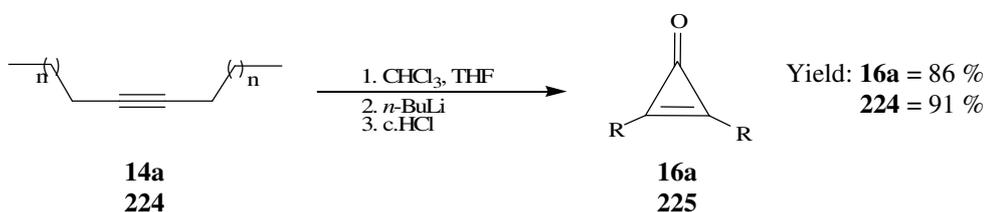


14a: n = 1, **224**: n = 2, **16a**: R = Pr, **225**: R = Bu

Scheme 2.62

The appropriate alkyne was dissolved in anhydrous DME, and treated with sodium trichloroacetate; the mixture was refluxed for 24 hours, followed by an acidic work-up. The crude product was purified giving the required dialkylcyclopropenone in 11 - 29 % yield.

Method 2³²



14a: n = 1, **224**: n = 2, **16a**: R = Pr, **225**: R = Bu

Scheme 2.63

Method 1 did successfully synthesise the required dialkylcyclopropenones, but gave very low yields. Netland *et al.* reported a method giving higher yields.³² In this method, the appropriate

alkyne was mixed with chloroform in anhydrous tetrahydrofuran and *n*-butyllithium was added. The reaction mixture was carefully maintained at $-78\text{ }^{\circ}\text{C}$ for four hours, followed by the dropwise addition of conc. aqueous HCl. The product was obtained pure (NMR) in 86 – 91 % yield.

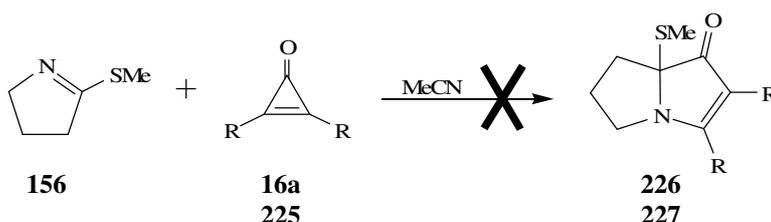
Spectroscopic analysis confirmed the structure of both dipropylcyclopropenone **16a** and dibutylcyclopropenone **225**.

For example, in the ^{13}C NMR of dipropylcyclopropenone, the alkene carbons appear at 160.68 ppm, and the carbonyl carbon appears at 160.06 ppm. The two types of CH_2 carbon appear at 28.11 and 19.61 ppm, and the remaining methyl carbon appears at 13.63 ppm. The IR showed the $\text{C}=\text{O}$ in the distinctive position of 1840 cm^{-1} with a further strong peak at 1629 cm^{-1} .

The spectroscopic data for the dibutyl system was similarly consistent with the expected structure, showing the extra CH_2 group in the ^{13}C with three peaks at 27.47, 25.16 and 21.45 ppm versus two peaks at 28.11 and 19.61 ppm.

The reactivity of these two dialkylcyclopropenones was investigated by the reaction of them with a number of different cyclic imines shown below.

2.5.2.1 Reaction with 2-methylthio-1-pyrroline



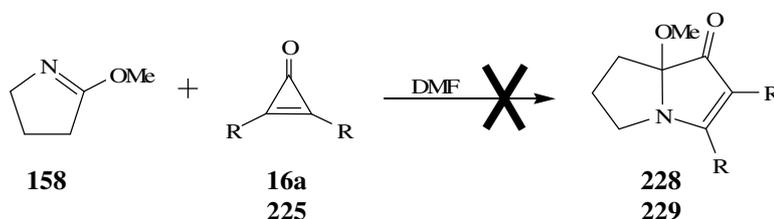
16a/ 226: R = Pr, **225/ 227:** R = Bu

Scheme 2.64

The appropriate dialkylcyclopropenone **16a/ 225** was mixed with 2-methylthio-1-pyrroline **156** in anhydrous acetonitrile. The reaction mixture was stirred overnight at ambient temperature but showed no reaction occurring. The mixture was thus heated at reflux for a week, but upon purification only the dialkylcyclopropenone was recovered.

The attempted reaction was repeated changing the solvent to dimethylformamide, and stirring at room temperature, 100 °C and higher, for up to four days. No evidence of any reaction was found.

2.5.2.2 Reaction with 2-methoxy-1-pyrroline



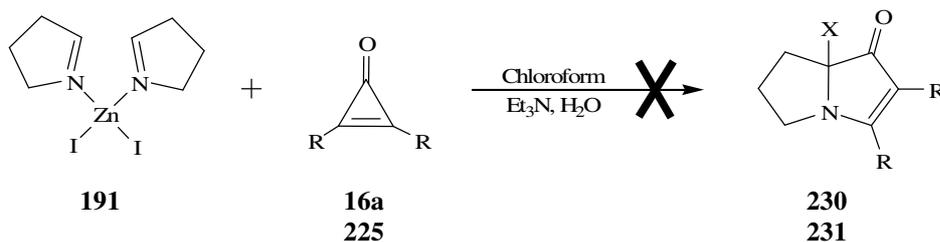
16a/228: R = Pr, **225/ 229:** R = Bu

Scheme 2.65

2-Methoxy-1-pyrroline **158** was dissolved in dimethylformamide and had dipropylcyclopropenone **16a** added. TLC showed no reaction had occurred, after 48 hours at ambient temperature, 80 °C, 130 °C, and even, finally, at reflux.

The attempted reaction was repeated using dibutylcyclopropenone **225** but no identifiable products were obtained, again under a variety of conditions.

2.5.2.3 Reaction with 1-pyrroline

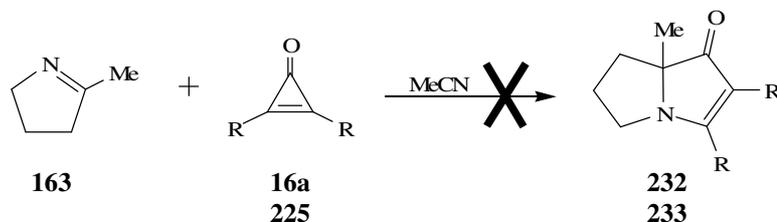


16a/230: R = Pr, **225/ 231:** R = Bu,
X = H or OH

Scheme 2.66

Bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) in chloroform was treated with an aqueous solution of triethylamine to liberate 1-pyrroline. Due to previous results with DPP, it was believed that there was a possibility that the product may have a hydroxy group at the bridgehead rather than a proton. All attempts to react 1-pyrroline with dipropyl and dibutylcyclopropanones were unsuccessful, and neither **230** or **231** could be isolated.

2.5.2.4 Reaction with 2-methyl-1-pyrroline



16a/232: R = Pr, **225/ 233:** R = Bu

Scheme 2.67

All attempts to react 2-methyl-1-pyrroline **163** with dialkylcyclopropanones **16a/ 225** were similarly unsuccessful.

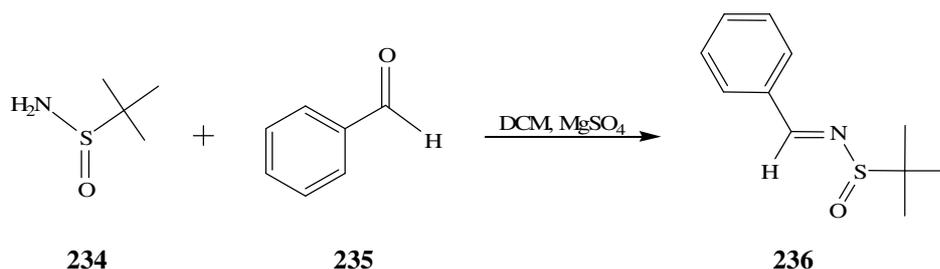
Conclusion

The synthesis of dialkylcyclopropanones **16a/ 225** was successful but they were found to be unreactive towards 5-membered ring cyclic imines. Work done by other group members have found that 6-membered ring cyclic imines are also unreactive towards these two dialkylcyclopropanones, but work done with 4-membered ring cyclic imines by others in the group have found both dialkylcyclopropanones to be reactive, and this is believed to be due to the extra strain in the four-membered ring.

2.6 Acyclic imines

The next part of this work was to explore the reactivity of some acyclic imines toward cyclopropenones. Early work by Eicher has shown that Schiff bases can react with cyclopropenones.¹⁰⁵ We were interested in seeing if imines derived from Ellman's 2-methyl-2-propanesulfonamide **234** would be reactive, particular as this might later lead to the synthesis of non-racemic pyrrolidinones, given that compound **234** is available in both enantiomeric forms. However, to start with (due to expense) we worked with the non-chiral sulfonamide. This work is described below:

2.6.1 Synthesis of *N*-(benzylidene)-*tert*-butanesulfonamide



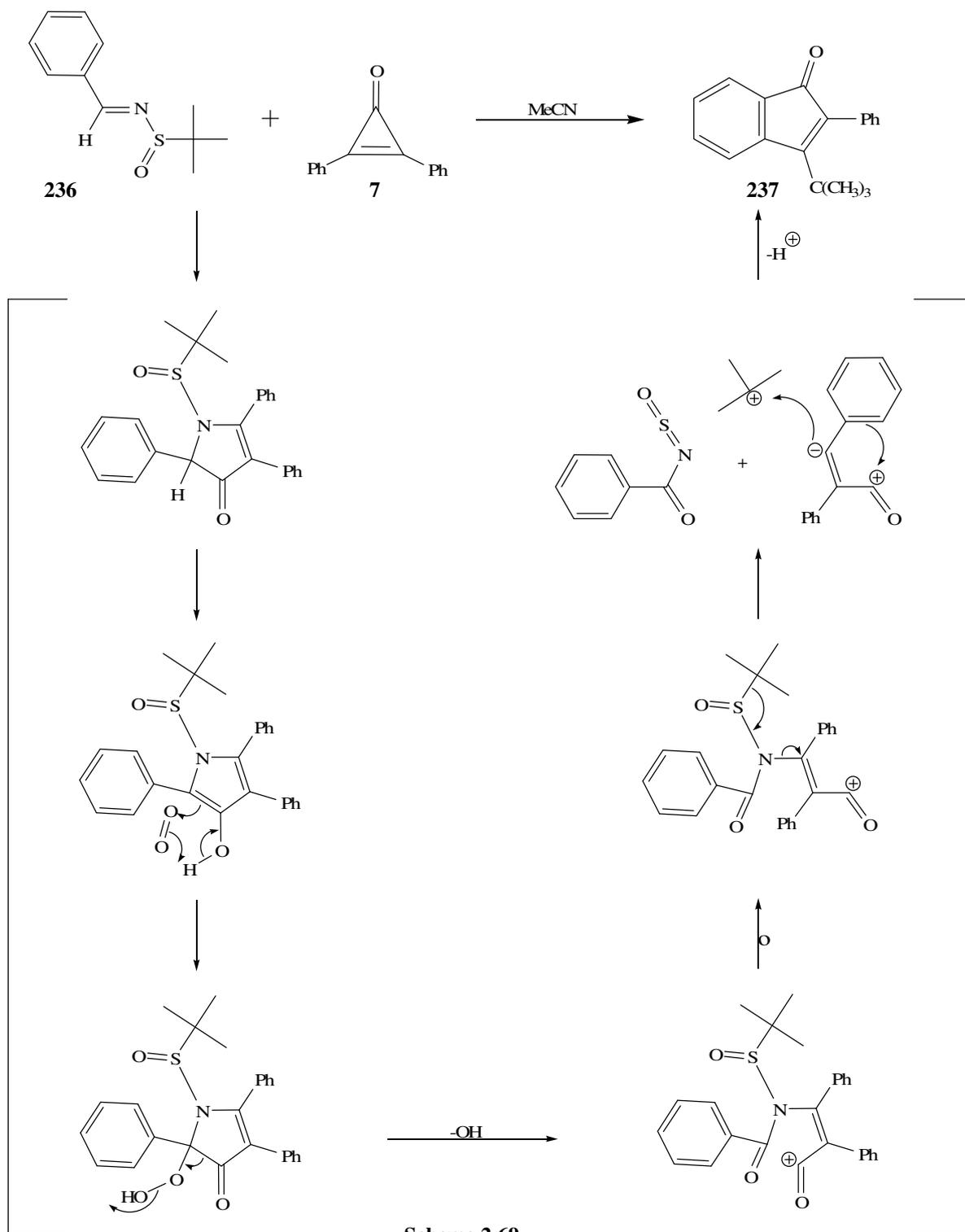
Scheme 2.68

2-Methyl-2-propanesulfonamide **234** was reacted with benzaldehyde **235** in anhydrous dichloromethane; magnesium sulfate was added to remove water produced from the condensation reaction. The product **236** was obtained in 58 % yield as an off-white oil after purification.

Spectroscopic data was as per literature,¹⁰⁶ for this standard imine-aldehyde condensation process.

2.6.2 Synthesis of 3-*tert*-butyl-2-phenyl-1-indenone

N-(benzylidene)-*t*-butanesulfonamide **236** was reacted with diphenylcyclopropenone **7** to give, unexpectedly, 3-*tert*-butyl-2-phenyl-1-indenone **237** in 13 % yield.



Ellman and Robak *et al.*¹⁰⁷ have recently written a comprehensive review on the synthesis and applications of *tert*-butanesulfinamide, and there is no mention of this type of *t*-butyl transfer reaction and no other literature precedent can be found. The structure was determined unequivocally by single crystal X-ray crystallographic studies (see Figure 4 below) and was also apparent from detailed 2D-NMR experiments. High resolution mass spectroscopy and infrared spectroscopy were in full accord.

Scheme 2.69 (above) shows a plausible route for this process.

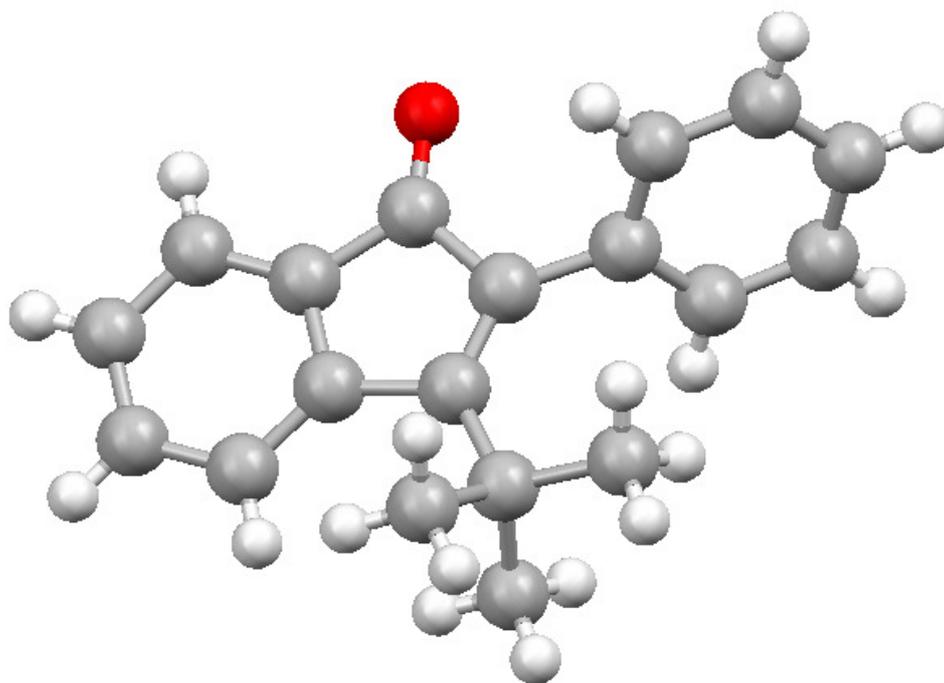
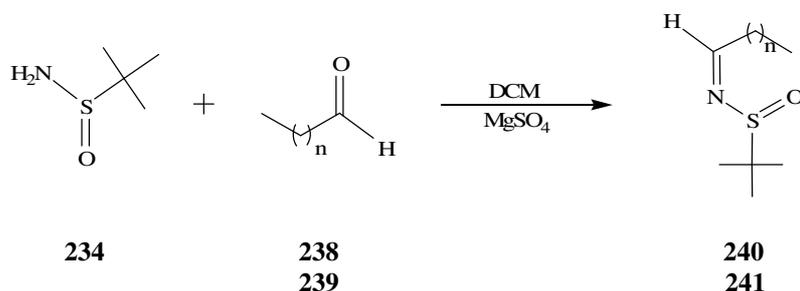


Figure 4 – Crystal Structure of 3-*tert*-Butyl-2-phenyl-1-indenone

2.6.3 Synthesis of *N*-(alkylidene)-*tert*-butanesulfinamides



238/ 240: n = 1, 239/ 241: n = 2

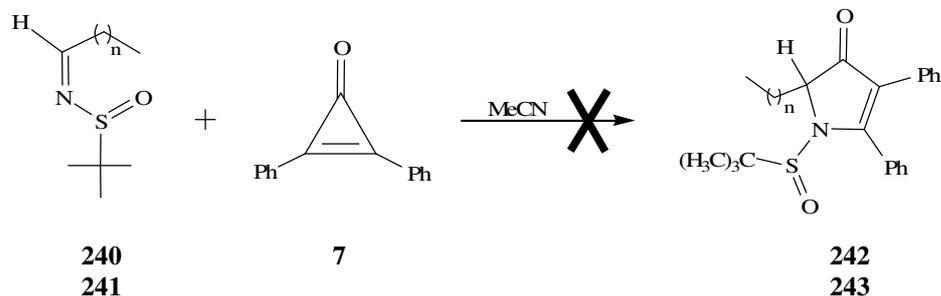
Scheme 2.70

The next step was to find out whether similar imines made from different aldehydes behaved in a similar way once reacted with diphenylcyclopropanone **7**. In order to provide some evidence that an aryl imine was necessary, two aliphatic aldehydes, propanal **238** and butanal **239** were reacted with 2-methyl-2-propanesulfinamide **234** to give *N*-(propylidene)-*t*-butanesulfinamide **240** and *N*-(butylidene)-*t*-butanesulfinamide **241** respectively, as reported in the literature.¹⁰⁶

In the ¹H NMR spectrum of the latter product, the CH proton appears at 7.84 ppm as a triplet with a J value of 7.4 Hz, the CH₂ protons next to the imine bond appear as a doublet of doublets of doublets at 2.28 ppm with J values of 4.7, 7.4, 7.4 Hz. The two CH₂ protons next to the methyl group appear as a sextet at 1.45 ppm with a J value of 7.4 Hz. The *tert*-butyl protons appear as a singlet at 0.97 ppm, the remaining methyl group appears at 0.77 ppm as a triplet with a J value of 7.4 Hz.

In the ¹³C NMR spectrum for **241**, the CH carbon appears at 169.42 ppm, the quaternary carbon appears at 56.27 ppm, the two CH₂ carbons appear at 37.89 and 18.77 ppm and the methyl groups appear at 22.17 and 13.66 ppm. The data was consistent with the literature.¹⁰⁶

2.6.4 Reaction with diphenylcyclopropenone



240/ 242: $n = 1$, 241/ 243: $n = 2$

Scheme 2.71

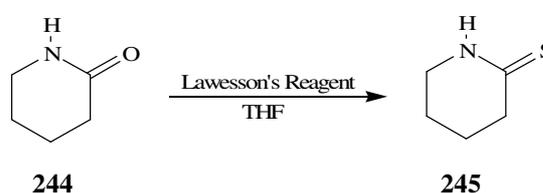
The alkyl aldehyde-derived imines were reacted with diphenylcyclopropenone **7** in anhydrous acetonitrile at ambient temperature and later heated at reflux, but neither reaction gave any new products. One possibility is that the product obtained with benzaldehyde may have had a different outcome due to its aromatic nature, as shown in the mechanism above. No further work was carried out using *t*-butanesulfinamides, but this work is being revisited by other group members: it is important, for example, that future work is done with other aromatic aldehydes in order to determine if the indenone formation above is general or not. This will tell us which benzene ring ends up in the indenone and help to provide further evidence for the mechanism tentatively put forward in Scheme 2.69.

2.7 Synthesis of Indolizidines and Pyrroloazepines

The method used for the synthesis of pyrrolizidines in section 2.1 was further used in the synthesis of both indolizidines and pyrroloazepines. The indolizidine and pyrroloazepines are also important heterocycles and hence the methodology was extended to include these.

2.7.1 Indolizidines

2.7.1.1 Synthesis of piperidone-2-thione



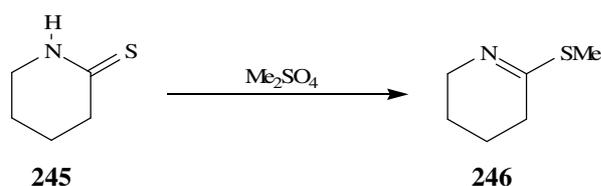
Scheme 2.72

2-Piperidone **244** and Lawesson's reagent in THF gave piperidine-2-thione **245** as white crystals in 89 % yield. The method and reaction mechanism is similar to that described in section 2.1.1.1.

Spectroscopic analysis confirmed the structure as piperidine-2-thione **245**.

In the ^1H NMR spectrum, the secondary amide proton appears at 6.90 ppm in **244** and appears at 9.23 ppm in **245**, the CH_2 neighbouring the thione appears at 2.87 ppm, whereas the CH_2 protons neighbouring the carbonyl in **244** appears at 2.33 ppm, both as triplets. The rest of the data showed no significant change. In the ^{13}C NMR spectrum, the main peak that changes from the starting material to the product is the quaternary peak, shifting downfield from 172.99 ppm to 202.75 ppm. Both the ^1H and ^{13}C NMR data showed a change had occurred.

2.7.1.2 Synthesis of 2-methylthio-1-piperidine

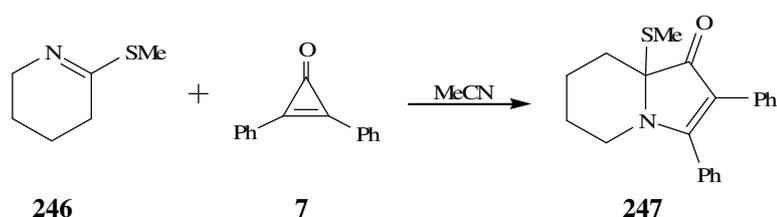


Scheme 2.73

2-Methylthio-1-piperidine^{73,108} **246** was synthesised using a similar method to that in section 2.1.3.1, which also shows the mechanism of reaction. Piperidine-2-thione **245** with dimethyl sulfate gave a volatile 2-methylthio-1-piperidine **246**. Spectroscopic analysis confirmed the structure as **246**.

In the ¹H NMR spectrum, the disappearance of the secondary amide and the appearance of the methyl group at 2.27 ppm as a singlet showed a change had occurred, and this was further confirmed by a methyl peak appearing at 12.24 ppm in the ¹³C NMR spectrum.

2.7.1.3 Reaction with diphenylcyclopropenone



Scheme 2.74

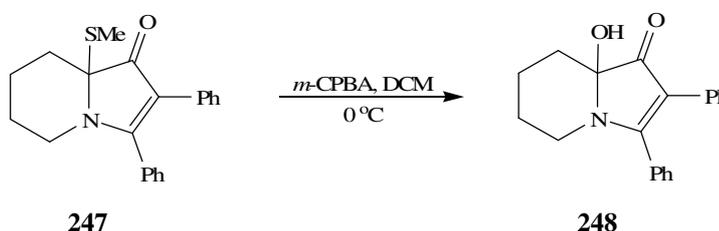
6-Methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one **247** was synthesised using 2-methylthio-1-piperidine **246** and diphenylcyclopropenone **7** giving the product in 60 % yield. The mechanism is similar to that shown in Scheme 2.12.

The structure of the product was confirmed by spectroscopic analysis as **247**.

In the ^1H NMR spectrum, 10 protons from the phenyl groups appear in the aromatic region between 7.53 - 7.00 ppm. The CH_2 protons neighbouring the nitrogen appear as a multiplet between 3.69 – 3.61 ppm and as a triplet of doublets at 3.51 ppm both integrating to one proton each. One of the CH_2 protons neighbouring the bridgehead methylthio group appears as a multiplet between 2.27 – 2.20 ppm integrating to one proton. Five protons appear as multiplets between 1.97 – 1.24ppm and the methyl group appears as a singlet integrating to three protons at 1.99 ppm.

In the ^{13}C NMR spectrum, the carbonyl appears at 199.03 ppm, the unsaturated carbons of the enone in the β and α position appear at 170.78 and 110.17 ppm, respectively. The three remaining quaternary carbons appear at 131.93, 130.63 and 72.46 ppm representing the two phenyl rings and bridgehead carbon. The six CH carbons from the two phenyl rings appear between 130.60 – 125.53 ppm. The four CH_2 s from the piperidine ring appear at 41.69, 32.89, 27.67 and 20.74 ppm and a methyl group appears at 10.86 ppm. The HRMS gives an accurate mass of 358.1234, which is within 2 ppm of the calculated value. In the IR spectrum, a peak at 1655 cm^{-1} is consistent with the carbonyl of an α, β - unsaturated ketone.

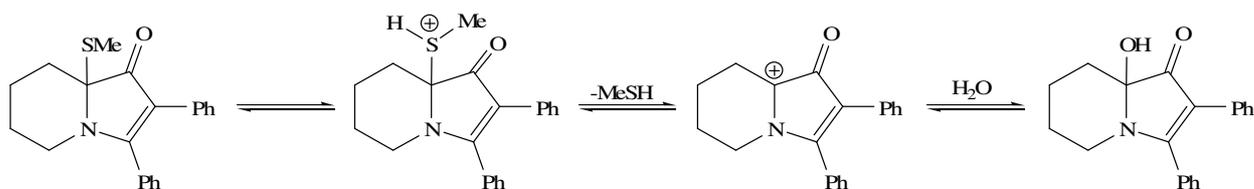
2.7.1.4 Synthesis of 6-hydroxy-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one



Scheme 2.75

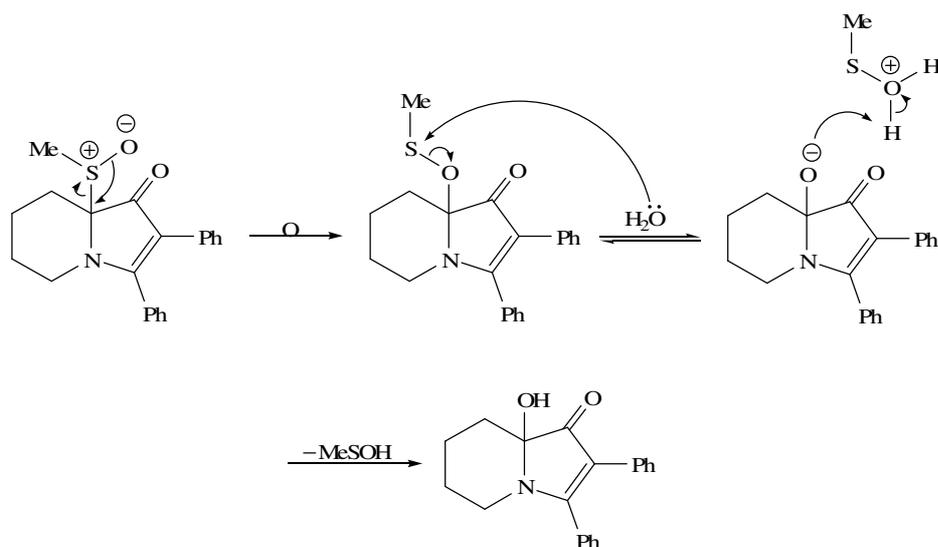
The reaction of the methylthio compound **247** with *m*-CPBA was the initial step to aid in desulfurisation by the oxidation of sulfur to attempt to gain the sulfoxide, which would then undergo loss of MeSOH to give an enone – as observed with the 5-membered rings in section

2.2. The method used was similar to that shown in section 2.2.1.1. However, the product isolated in this reaction was not the 6-sulfoxide that was desired, but was instead the 6-hydroxy compound. This may have formed by displacement of the SMe with OH in an S_N1 type process:



Scheme 2.76

Alternatively, it could arise *via* a rearrangement of the sulfoxide:



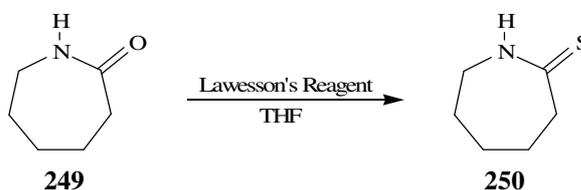
Scheme 2.77

Spectroscopic analysis confirmed the structure of the product. In the NMR spectra, most signals appear similarly to those in the starting material with some signals shifting slightly up or down field. The main difference is the absence of the methyl singlet in both the ^1H and ^{13}C NMR spectra together with a significant difference in the bridgehead carbon, which appears at

86.81 ppm in the product and 72.46 ppm in the starting material. Further evidence was provided by an OH appearing at 3295 cm^{-1} in the infra-red spectrum and a consistent HRMS measurement. In order to obtain another example of this reaction the 6-ethylthio analogue was synthesised, and a similar reaction was attempted but gave no identifiable product.

2.7.2 Pyrrolazepines

2.7.2.1 Synthesis of azepan-2-thione

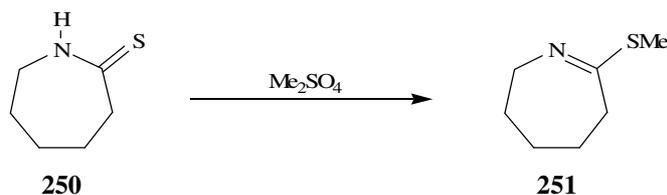


Scheme 2.78

The method and reaction mechanism is similar to that described in section 2.1.1.1. Azepan-2-one **249** and Lawesson's reagent **150** in THF gave azepan-2-thione **250** as white crystals in 73 % yield.

Spectroscopic analysis confirmed the structure. In the ^1H NMR spectrum, the secondary amide proton shifts downfield from 6.92 ppm to 9.19 ppm. The five sets of CH_2s appear in similar places to that of the starting material with a few signals shifting downfield. In the ^{13}C NMR spectrum, the main peak that shows a change is the quaternary carbonyl peak at 179.70 ppm which appears as C=S at 210.31 ppm in the product.

2.7.2.2 Synthesis of 2-methylthio-1-azepane



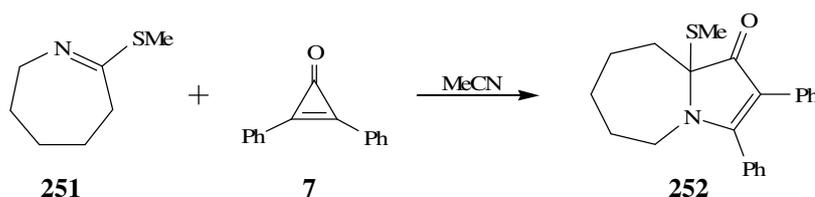
Scheme 2.79

2-Methylthio-1-azepane^{73,108} **251** was also synthesised using a similar method to that already described in section 2.1.3.1, which also shows the mechanism of reaction. The reaction of azepan-2-thione **250** with dimethyl sulfate afforded a volatile 2-methylthio-1-azepane **251**.

Spectroscopic analysis confirmed the structure as **251**.

In the ¹H NMR spectrum, the disappearance of the secondary amide and the appearance of the methyl group at 2.18 ppm as a singlet showed that the desired change had occurred, and this was further confirmed by a methyl peak appearing at 13.42 ppm in the ¹³C NMR spectrum.

2.7.2.3 Reaction with diphenylcyclopropenone



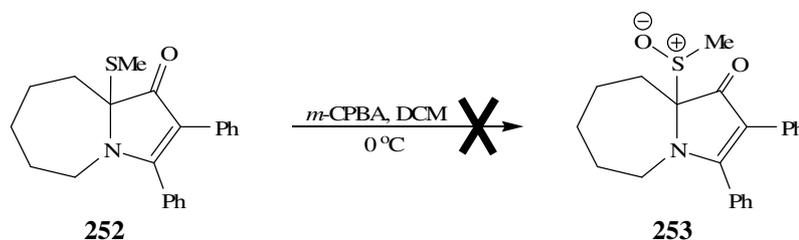
Scheme 2.80

7-Methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one **252** was synthesised as per section 2.1.1.3. The reaction of 2-methylthio-1-azepane **251** and diphenylcyclopropenone **7** afforded the desired product **252** in a low yield of 16 %.

Spectroscopic analysis confirmed the structure as 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one **252**.

In the ^1H NMR spectrum, ten protons appear in the aromatic region between 7.51– 7.01 ppm as multiplets. ten CH_2 protons appear between 3.85 – 1.01 ppm and the remaining methyl group appears at 1.97 ppm as a singlet. The ^{13}C NMR spectrum displays six quaternary carbons between 197.65 – 77.03 ppm, six CH carbons between 130.53 – 125.66 ppm, five CH_2 carbons between 43.36 – 23.97 and the remaining CH_3 carbon appears at 11.60 ppm. The HRMS gave an accurate mass of 372.1394, which is within 2 ppm of the calculated value.

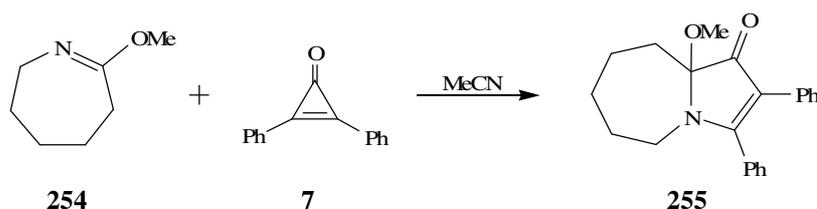
2.7.2.4 Attempted oxidation of 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one



Scheme 2.81

The reaction of 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one **252** with *m*-CPBA was to aid desulfurisation. The method used was similar to that shown in section 2.2.1.1. However, on purification the starting material was recovered and no reaction had occurred. Repeat attempts were similarly unsuccessful.

2.7.2.5 Synthesis of 7-methoxy-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one



Scheme 2.82

The attempt to synthesise 7-methoxy-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one **255** was achieved by reacting 2-methoxy-1-azacycloheptene **254** with diphenylcyclopropenone **7** in anhydrous acetonitrile to give the product in 28 % yield. The reaction was repeated in dimethylformamide to give the same product in 10 % yield.

Spectroscopic analysis confirmed the structure of the product to be 7-methoxy-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one **255**. The ^1H NMR spectrum displayed 10 protons from the two phenyl rings in the aromatic region between 7.52 – 7.01 as multiplets. The 10 CH_2 protons from the 7-membered ring appear between 3.74 – 1.04 ppm, and protons from the methoxy group appear at 3.22 ppm as a singlet. The ^{13}C NMR spectrum displays the six quaternary carbons between 198.15 – 94.92 ppm, and the six CH carbons between 130.66 – 125.76 ppm. The methoxy carbon appears at 51.43 ppm, and the five CH_2 carbons appear between 43.02 – 22.03 ppm.

Conclusion

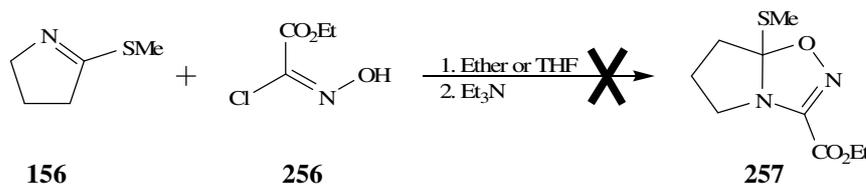
This section of the work showed that pyrroloazepines and indolizidines are accessible by this methodology, and future work in the group will look at these processes and the chemistry of the resultant adducts in more detail.

2.8 1,3-Dipolar cycloadditions

So far in this thesis, cycloaddition reactions of 1-pyrrolines have been limited to overall [3+2] cycloaddition-type processes involving cyclopropenones. In these, the cyclopropenone behaves as if it were an all-carbon 1,3-dipole equivalent and the use of cyclopropenones and their acetals in this way is gaining attention in the literature.^{2,109-113}

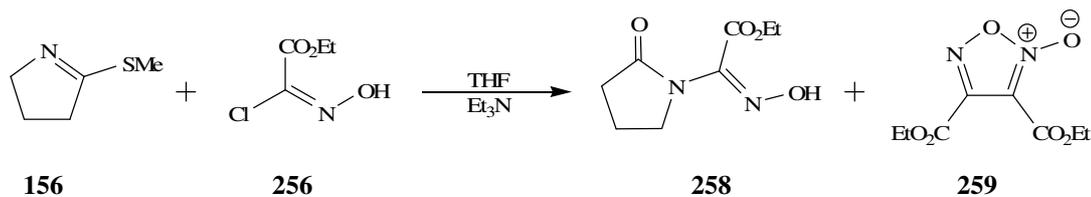
In order to explore the reaction of 1-pyrrolines, it was thought useful to see if they would react with other, traditional 1,3-dipoles. Nitrile oxides were chosen for a model study.

2.8.1 Attempted synthesis of ethyl-5-methylthio-4,1,3-oxadiazobicyclo[3.3.0]oct-2-ene-2-carboxylate



Scheme 2.83

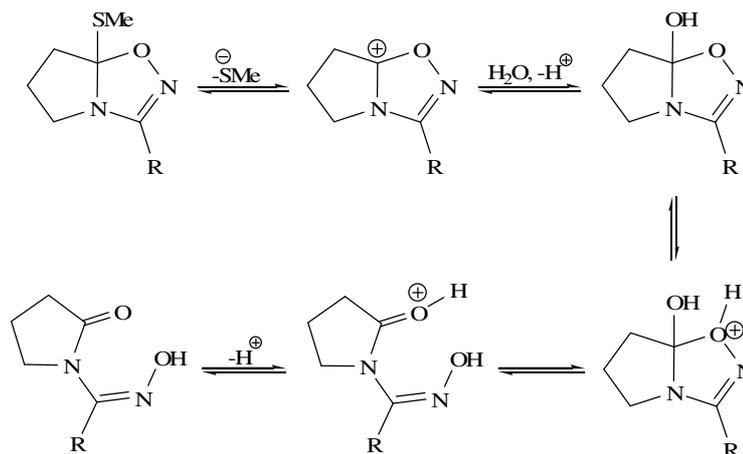
The attempt to synthesise ethyl-5-methylthio-4,1,3-oxadiazobicyclo[3.3.0]oct-2-ene-2-carboxylate **257** was carried out by the reaction of 2-methylthio-1-pyrroline **156** with ethyl chlorooximidoacetate **256** in the presence of triethylamine in either diethyl ether or THF. In both occasions product **257** was not synthesised, and instead the reaction product was the nitrile oxide dimer **259** in diethyl ether and both the nitrile oxide dimer **259** and ethyl-[N-(2-pyrrolidone)]oximidoacetate **258** in THF. Dimer **259** could be isolated in yields of up to 50 %.



Scheme 2.84

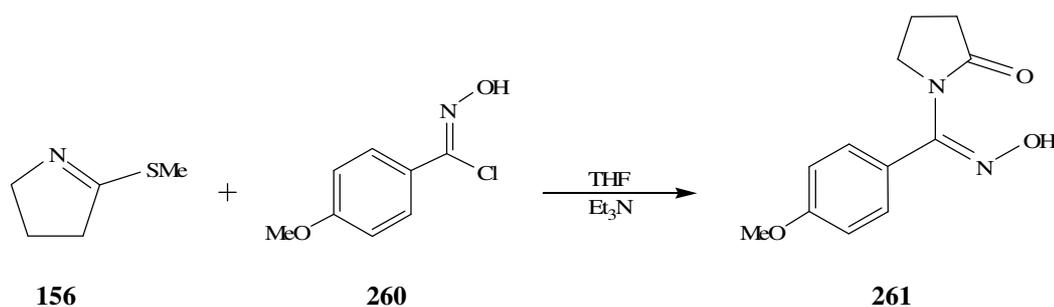
Spectroscopic analysis confirmed the product to be ethyl-[*N*-(2-pyrrolidone)]oximidoacetate **258**. In the ^1H NMR spectrum, the hydroxy proton appears at 10.81 ppm as a broad singlet. The two CH_2 protons from the ester appear at 4.27 ppm as a quartet with a *J* value of 7.1 Hz, the six CH_2 protons from the pyrrolidine ring appear at 3.79, 2.44 and 2.17 ppm. The methyl group from the ester appears at 1.28 ppm as a triplet with a *J* value of 7.1 Hz. The ^{13}C NMR spectrum displays three quaternary carbons at 176.81, 160.50, 139.67 ppm, four CH_2 carbons between 62.72 – 20.08 ppm and the methyl carbon at 14.14 ppm.

The expected product was not obtained, and this is believed to be due to the hydrolysis of the desired product **257**. In principle, hydrolysis could occur earlier, whereby compound **156** gives 2-pyrrolidone which then reacts with compound **256** to give product **258**. To investigate when the hydrolysis occurred, 2-pyrrolidone was reacted as above with ethyl chlorooximidoacetate in THF, with dropwise addition of triethylamine in THF. No product was formed apart from the nitrile oxide dimer. This provided evidence that the product of the 1,3-dipole cycloaddition underwent hydrolysis rather than the 2-methylthio-1-pyrroline starting material. A suggested mechanism for the hydrolysis is shown below in Scheme 2.85. In order to see if this was a general reaction, other nitrile oxides were utilized, as described in the next section.



Scheme 2.85

2.8.2 Synthesis of 4-methoxy-(α -[*N*-(2-pyrrolidinone)])benzaldoxime



Scheme 2.86

2-Methylthio-1-pyrroline **156** and the α -chloroxime **260** were reacted together in the presence of triethylamine as a base. The chloroxime was added slowly and dropwise to minimise nitrile oxide dimer formation. Purification gave 4-methoxy-(α -[*N*-(2-pyrrolidinone)])benzaldoxime **261** in 32 % yield. The mechanism is similar to that shown above in Scheme 2.85.

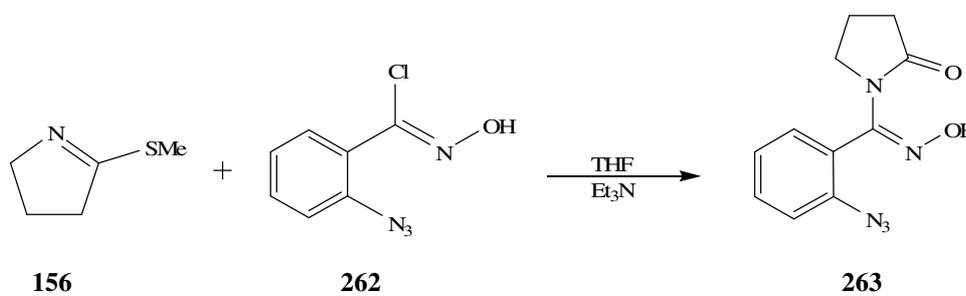
Spectroscopic analysis confirmed the product to be 4-methoxy-(α -[*N*-(2-pyrrolidinone)])benzaldoxime **261**.

The ^1H NMR spectrum displays a broad OH proton between 8.63 – 8.58 ppm, four CH protons from the phenyl ring at 7.51 and 6.90 ppm as doublets and a methyl singlet at 3.83

ppm. The three CH₂s appear at 3.73, 2.58 and 2.26 ppm as two triplets and a quintet, respectively. In the ¹³C NMR spectrum, four quaternary carbons appear between 175.53 – 123.80 ppm, two CH carbons appear at 128.50 and 114.48 ppm. The methyl carbon appears at 55.70 ppm, and the remaining three CH₂ carbons appear at 48.05, 31.07 and 20.23 ppm.

The HRMS gives an accurate mass (M+Na) consistent with the expected formula of C₁₂H₁₄N₂NaO₃.

2.8.3 Synthesis of 2-azido-(α -[N-(2-pyrrolidinone)])benzaloxime



Scheme 2.87

2-Methylthio-1-pyrroline **156** and anhydrous triethylamine in THF had α -chloroxime **262** added dropwise. Purification gave 2-azido-(α -[N-(2-pyrrolidinone)])benzaloxime **263** in 14 % yield.

Spectroscopic analysis confirmed the product to be 2-azido-(α -[N-(2-pyrrolidinone)])benzaloxime **263**.

In the ¹H NMR spectrum, the hydroxy proton appears at 9.25 ppm, four CH protons appear in the aromatic region between 7.53 – 7.15 ppm and the three CH₂s from the pyrroline ring appear at 3.89, 2.47 and 2.21 ppm as two triplets and a quintet respectively. The ¹³C NMR spectrum displays four quaternary carbons between 175.87 – 124.06 ppm, four CH carbons between 131.86 – 118.70 ppm, and three CH₂s at 48.31, 30.96 and 20.32 ppm.

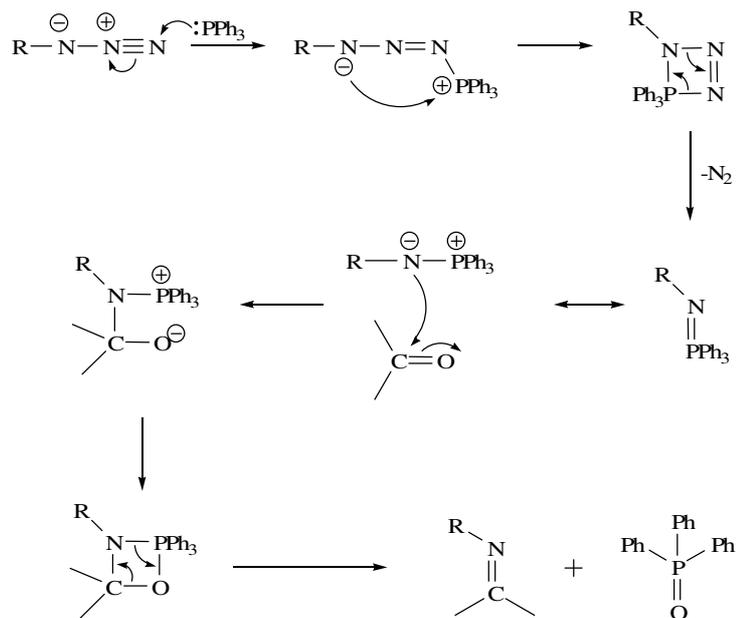
The iminophosphorane **264** in anhydrous toluene was heated at reflux, giving pyrrolo[1,2-b][1,3]benzodiazin-4-oxime **265** in 44 % yield, the product of the desired aza-Wittig reaction.

Spectroscopic analysis confirmed the product to be the pyrrolo[1,2-b][1,3]benzodiazin-4-oxime.

In the ^1H NMR spectrum, the oxime proton appears at 10.15 ppm as a broad singlet. Four CH protons appear in the aromatic region with one each at 8.17 and 7.14 ppm, and two at 7.36 ppm. The three CH_2 s appear at 4.09, 2.68 and 2.28 ppm as two triplets and a quintet, respectively. The ^{13}C NMR spectrum displays four quaternary carbons between 174.43 – 116.31 ppm, four CH carbons between 127.75 – 109.96 ppm and three CH_2 carbons at 49.32, 32.36 and 30.03 ppm. The HRMS gives an accurate mass of 224.0801 for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{NaO}$, consistent with expected structure. In the infra-red a peak at 1681 cm^{-1} showed the presence of $\text{C}=\text{N}$ and the OH appeared at 3219 cm^{-1} .

2.8.5.1 Aza-Wittig and Staudinger mechanisms

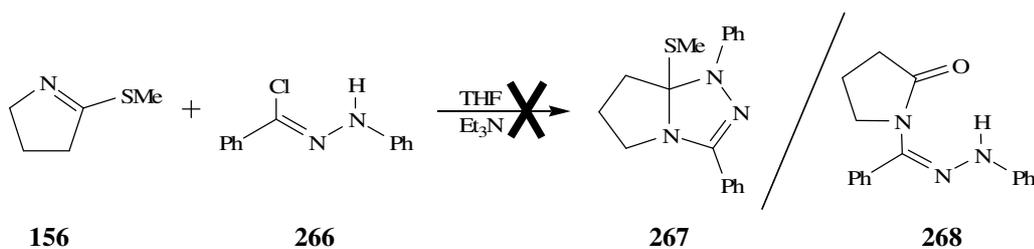
The use of the aza-Wittig reaction to construct heterocycles is very well known¹¹⁴⁻¹¹⁶ in general and has been used to make other pyrrolobenzo-fused systems.¹¹⁷⁻¹¹⁹ As shown in Scheme 2.90, the iminophosphorane (most commonly made from an azide^{120,121} – also shown in Scheme 2.90) reacts *via* a Wittig-type mechanism.



Scheme 2.90

2.8.6 Attempted reaction of 2-methylthio-1-pyrroline with a nitrilimine

An attempt was made to react 2-methylthio-1-pyrroline **156** with a nitrilimine, which was generated from the precursor **266** in the presence of anhydrous triethylamine in THF.



Scheme 2.91

This single attempt proved unfruitful and was not explored any further.

2.9 Conclusion & Future Work

Pyrrolizidines, indolizidines and pyrroloazepines have been synthesised from the reaction of cyclopropenones with five, six and seven-membered cyclic imines.

Pyrrolizidines were synthesised by the alkylation of lactams/ thio-lactams to give access to the required cyclic imines, most of which were successfully reacted with DPP. The introduction of several side groups didn't hinder the synthesis method in most cases and gave the required pyrrolizidines, a process that included the use of some highly functionalised 1-pyrrolines. Exploitation of the bridgehead group was achieved in several ways: the sulfide group of the pyrrolizidines was oxidised using *m*-CPBA which gave both the methanesulfinyl and methanesulfonyl group at the bridgehead as products. This allowed the removal of the group, which was achieved by refluxing the methanesulfinyl compound in toluene, from which the isolated product was found to contain an aromatised pyrrole ring formed by rearrangement. Unexpected bridgehead hydroxy compounds were also recovered from several reactions, which was pleasantly surprising as such a group is found in the natural jenamidines, and its installation has been met with difficulties by many researchers. The methoxy pyrrolizidines underwent BBr_3 (ethanolic work-up) cleavage to yield the hydroxy compound as a minor product along with the bridgehead ethoxy compound. In total several pyrrolizidines were obtained with the different bridgehead groups which included methoxy, ethoxy, hydroxy, methylthio, ethylthio and methyl substituents.

Indolizidines and pyrroloazepines were synthesised in a similar way to their pyrrolizidine counterpart, with methylthio groups at the bridgehead in both compounds. Upon oxidation, the indolizidine only gave the hydroxy compound, although the pyrroloazepine didn't yield any product.

Successful synthesis of three cyclopropenones was also achieved, namely the parent unsubstituted cyclopropenone, dipropylcyclopropenone and dibutylcyclopropenone. The unsubstituted cyclopropenone was difficult to make but was successfully reacted with one cyclic imine. The other two cyclopropenones were both unreactive to any cyclic imine we possessed (five, six and seven membered rings).

Nitrile oxides were reacted with 5-methylthio-1-pyrroline, in an attempt to obtain their bicyclic products, but, these products were found to be unstable and underwent hydrolysis to yield a more stable ring-opened product, one of which was cyclised using an aza-Wittig reaction.

Acyclic imines derived from Ellman's 2-methyl-2-propane sulfinamide were reacted with DPP in an attempt to give access to a pyrrolidinone compound. Unfortunately this was not the case, but did unexpectedly give access to an indenone compound. Further investigation into the reaction of Ellman's 2-methyl-2-propane sulfinamide with different aldehydes needs to take place so that further work can be done to see how this occurred and if it can occur using different acyclic imines.

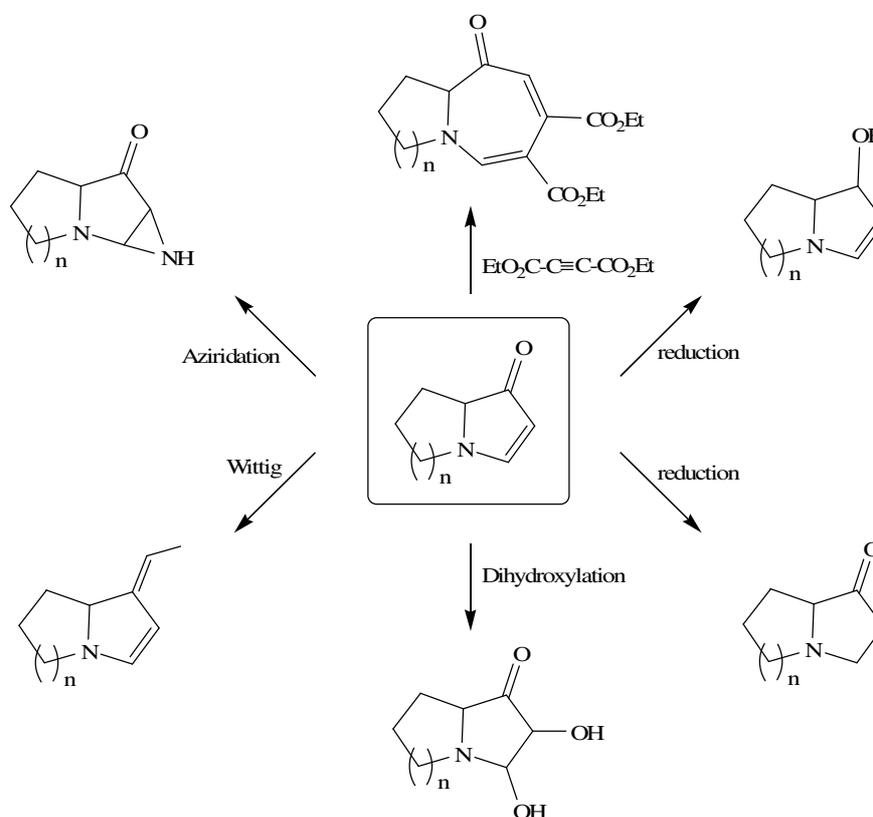
Future work

An area that could be further explored is the synthesis of imines with natural product substituents such as the polyhydroxylated imines, as there are many natural polyhydroxylated pyrrolizidines and indolizidines.

The desulfurisation process could be further investigated by reducing the sulfide moiety using a reducing agent such as Raney nickel, in order to afford a proton at the bridgehead, which many natural products such as hyacinthacine possess.

Further work with different cyclopropenones is also required, the dibutyl and dipropylcyclopropenones did not react with the five-membered imines; however, work currently undertaken in the laboratory has shown both of these cyclopropenones can react with strained four-membered cyclic imines. Synthesis of more reactive cyclopropenones may allow them to react with five, six and seven-membered imines. This may be achieved by synthesising cyclopropenones that possess electron withdrawing substituents such as nitriles, carbonyls or nitro groups. Consequently, these newly synthesised cyclopropenones will give a vast range of experiments for consideration.

The unsubstituted cyclopropenone could be synthesised in a more robust fashion by optimising the method investigated in this thesis. Other areas that could be further investigated are the elaboration of the enaminone-containing ring. For example dihydroxylation of the alkene group to give 1,2-diols, aziridation to aziridines, Wittig reaction, reduction of the alkene, ring expansion etc, as summarised below:



Experimental

General information

Unless otherwise stated, all reactions were conducted using oven dried glassware, under nitrogen delivered through a gas manifold. Work-up procedures were carried out in air. All solvents were of analytical grade and purchased from either Fisher scientific or Sigma-Aldrich.

Anhydrous solvents were freshly distilled using a continuous still under nitrogen. Tetrahydrofuran and diethyl ether were distilled over sodium wires (1-2 %, w/v) with the aid of benzophenone as an indicator. Dichloromethane and toluene were distilled over calcium hydride (5 % w/v) for ~5 hours. All other anhydrous solvents and commercially available starting materials were purchased from the following suppliers: Acros, Fisher scientific, Fluorochem Ltd and Sigma-Aldrich. Deuterated solvents were purchased from Goss scientific.

All reactions were monitored by thin layer chromatography, which was carried out on 0.20 mm Macherey-Nagel Alugram[®] Sil G/ UV₂₅₄ silica gel-60 precoated aluminium plates; analysis was achieved using ultraviolet light and/ or vanillin stain. Compounds were purified using column chromatography performed on Merck silica gel (0.063-0.200 mm, 60 Å).

NMR spectra were obtained using either a Bruker DPX-400 instrument or Bruker Avance 500. IR spectra were recorded on a Nicolet 380 FT-IR instrument as a thin film for oils or neat for solids. Mass spectra were recorded on a Bruker daltonics micrOTOF mass spectrometer operating at a positive ion mode under an electrospray ionisation (ESI +) method. Crystallographic data were recorded on a Bruker Apex Duo instrument.

3 Experimental

3.1 Synthesis of Pyrrolizidines

3.1.1 Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.1.1 Synthesis of pyrrolidine-2-thione



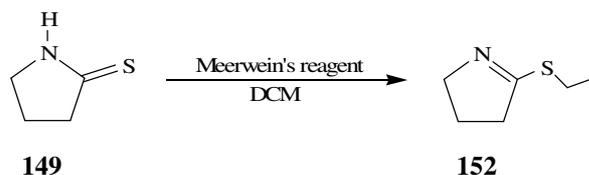
A solution of 2-pyrrolidone (1.00 – 1.40 g, 11.75 - 16.40 mmol, 1 eq) and Lawesson's reagent (2.43 – 3.98 g, 5.98 – 9.84 mmol, 0.5 – 0.6 eq) in anhydrous tetrahydrofuran (15 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC and stopped after 2 hours. The reaction mixture was left to cool to ambient temperature, concentrated and purified by column chromatography (eluent: PE: EtOAc 3:2) to yield pyrrolidine-2-thione (0.66 g – 1.16 g, 59 % - 89%) as a white crystalline powder.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 8.74 (1H, bs, NH), 3.66 (2H, t, J 7.3, NCH_2), 2.91 (2H, t, J 8.0, SCCH_2), 2.21 (2H, quint, J 7.5, $\text{CH}_2\text{CH}_2\text{CH}_2$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 206.12 (C=S), 50.02 (CH_2), 43.59 (CH_2), 23.26 (CH_2).

Data above is identical to literature values.¹²²⁻¹²⁴

3.1.1.2 Synthesis of 2-ethylthio-1-pyrroline



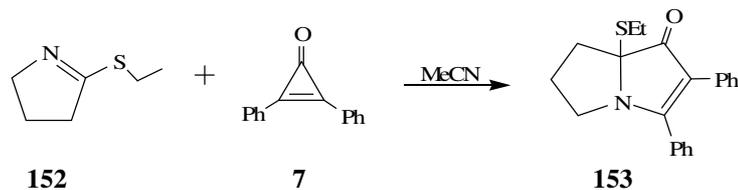
A solution of pyrrolidine-2-thione (0.40 g - 1.16 g, 3.96 - 8.99 mmol, 1 eq) in Meerwein's reagent 1M (5 - 16 mL, 1.2 - 1.8 eq) was stirred for 2-3 hours at ambient temperature under an atmosphere of dry nitrogen. Dichloromethane (10 mL) was added and the mixture was heated to reflux, monitored by TLC and stopped after two hours. The reaction mixture was left to reach ambient temperature, followed by the dropwise addition of the reaction mixture to saturated aqueous potassium carbonate (20 mL) at 0 °C over 15 minutes. The reaction mixture was filtered under vacuum through a celite plug. The filtrate was extracted with dichloromethane (5 x 20 mL), dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (eluent: PE: EtOAc, 4:1) to yield pyrrolidine-2-thione (116 - 270 mg) and 2-ethoxy-1-pyrroline (70 mg - 116 mg, 8 % - 14 %) as a yellow/ orange oil.

¹H NMR δ (400.13 MHz, CDCl₃): 3.81 (2H, tt, *J* 1.5, 7.2, NCH₂), 3.01 (2H, q, *J* 7.4, SCH₂CH₃), 2.56 (2H, tt, *J* 1.5, 8.2, SCCH₂), 1.94 (2H, quint, *J* 7.7, CH₂CH₂CH₂), 1.30 (3H, t, *J* 7.4, CH₂CH₃).

¹³C NMR δ (100 MHz, CDCl₃): 172.54 (C=N), 61.08 (CH₂), 38.89, (CH₂) 25.20 (CH₂), 23.67 (CH₂), 14.69 (CH₃).

Data above is identical to literature values.¹²⁴

3.1.1.3 Synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Diphenylcyclopropenone (DPP) (112 – 185 mg, 0.542 – 0.899 mmol, 1 eq) was added in one portion to a stirring solution of 2-ethoxy-1-pyrroline (70 – 116 mg, 0.542 – 0.899 mmol, 1 eq) in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. Monitored by TLC, the reaction mixture was concentrated *in vacuo* after two days and purified by column chromatography (eluent: PE: EtOAc, 5:1) to yield 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (100 - 150 mg, 50 - 55 %) as a bright yellow/orange oil. Data below is identical to literature values.¹²⁴

¹H NMR δ (400.13 MHz, CDCl₃): 7.48 – 7.42 (3H, m, Ar), 7.40 – 7.35 (2H, m, Ar), 7.23 - 7.19 (4H, m, Ar), 7.18 – 7.11 (1H, m, Ar), 3.55 (1H, ddd, *J* 6.7, 6.7, 11.2, NCHHCH₂), 3.08 (1H, ddd, *J* 6.7, 6.7, 11.2, NCHHCH₂), 2.65 (1H, dq, *J* 11.9 and 7.5, SCHHMe), 2.55 (1H, dq, *J* 11.9 and 7.5, SCHHMe), 2.29 – 2.17 (2H, m, SCCH₂CH₂), 2.12 – 2.03 (1H, m, SCCH₂CHH), 1.99 – 1.88 (1H, m, SCCH₂CHH), 1.20 (3H, t, *J* 7.5, SCH₂CH₃).

¹³C NMR δ (100 MHz, CDCl₃): 200.49 (C=O), 175.37 (q), 131.66 (q), 131.44 (CH), 131.35 (q), 129.92 (CH), 129.09 (CH), 129.01 (CH), 128.37 (CH), 126.46 (CH), 116.57 (q), 80.79 (q), 48.80 (CH₂), 33.23 (CH₂), 26.85 (CH₂), 23.49 (CH₂), 14.61 (CH₃).

LRMS (ESI⁺): Found 381.3 [M+2Na]⁺.

HRMS (ESI⁺): Found 358.1235 [M+Na]⁺, C₂₁H₂₁NNaOS requires 358.1236.

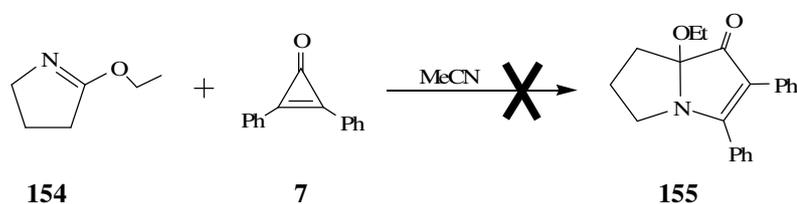
3.1.2 Attempted synthesis of 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.2.1 Synthesis of 2-ethoxy-1-pyrroline



A solution of 2-pyrrolidinone (1.02 g – 1.04 g, 11.98 mmol – 12.10 mmol, 1 eq) in Meerwein's reagent 1M (5 mL, 1.2 eq) was stirred for an hour at ambient temperature under an atmosphere of dry nitrogen. Monitored by TLC, the reaction mixture was heated at reflux for two hours and left to cool to reach ambient temperature. The reaction mixture was added dropwise to saturated aqueous potassium carbonate (20 mL) at 0 °C over 15 minutes. The reaction mixture was filtered under vacuum through a celite plug. The filtrate was extracted with dichloromethane (4 x 20 mL), dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*. The crude material was not purified due to the volatility of the product.

3.1.2.2 Attempted synthesis of 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

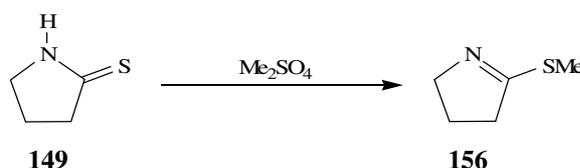


Diphenylcyclopropenone (140 mg - 456 mg, 0.681 mmol - 2.212 mmol, 1 eq) was added in one portion to a stirring solution of crude 2-ethoxy-1-pyrroline (77 mg - 250 mg, 0.681 mmol - 2.212 mmol, 1 eq) in anhydrous acetonitrile (10 mL) at ambient temperature under an

atmosphere of dry nitrogen. The reaction mixture was stirred for three days, and the crude product (green in colour) was analysed by thin layer chromatography, but no indication of any new product was observed.

3.1.3 Synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.3.1 Synthesis of 2-methylthio-1-pyrroline



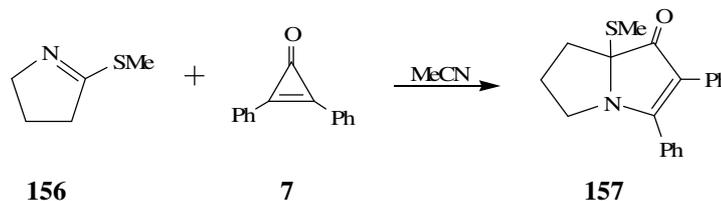
Dimethyl sulfate (0.410 - 1.127 mL, 4.33 – 11.78 mmol, 1.1 eq) was added in one portion to pyrrolidine-2-thione (398 – 1083 mg, 3.938 – 10.71 mmol, 1 eq) and the mixture was stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, but due to the volatility of the 2-methylthio-1-pyrroline⁷³, all of the solvent was not removed, and the product used in this form.

¹H NMR δ (400.13 MHz, CDCl₃): 3.65 - 3.58 (2H, m, NCH₂), 2.40 - 2.34 (2H, m, SCCH₂), 2.23 - 2.20 (3H, m, SCH₃), 1.83 - 1.72 (2H, m, CH₂CH₂CH₂).

¹³C NMR δ (100 MHz, CDCl₃): 172.71 (C=N), 60.50 (CH₂), 38.18 (CH₂), 23.62 (CH₂), 13.33 (CH₃).

IR ν_{max} (cm⁻¹): 2927 (m), 1682 (vs), 1393 (m), 1259 (s), 1218 (s), 1059 (w), 1010 (m), 748 (m).

3.1.3.2 Synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Diphenylcyclopropenone (773 mg – 1339.5 mg, 3.748 mmol – 6.495 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-pyrroline (431 mg – 747 mg, 3.748 mmol – 6.495 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for a day, concentrated and purified by column chromatography (eluent: PE: EtOAc, 5:1/ hexane: EtOAc, 3:1) to yield 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (927 mg – 1230 mg, 59 % - 77 %) as a orange/ yellow oil.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.47 – 7.43 (3H, m, Ar), 7.38 – 7.34 (2H, m, Ar), 7.20 – 7.17 (4H, m, Ar), 7.16 – 7.10 (1H, m, Ar), 3.59 – 3.51 (1H, m, NCHHCH₂), 3.12 – 3.04 (1H, m, NCHHCH₂), 2.30 – 2.18 (2H, m, SCCH₂), 2.13 – 2.03 (1H, m, CH₂CHHCH₂), 2.08 (3H, s, Me), 2.01 – 1.90 (1H, m, CH₂CHHCH₂).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 200.18 (C=O), 175.61 (q), 131.59 (q), 131.47 (CH), 131.35 (q), 129.93 (CH), 129.12 (CH), 129.02 (CH), 128.38 (CH), 126.51 (CH), 116.89 (q), 80.34 (q), 48.90 (CH₂), 32.62 (CH₂), 26.89 (CH₂), 12.04 (CH₃).

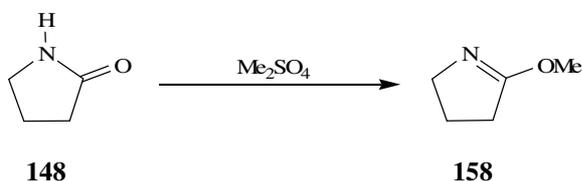
3.1.4 Attempted synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.4.1 Attempted synthesis of 2-methoxy-1-pyrroline



To a stirring solution of 2-methylthio-1-pyrroline (242 mg, 2.11 mmol, 1 eq) in methanol was added freshly-made methanolic sodium methoxide (sodium (49 mg) in methanol (5 mL)). The reaction mixture was stirred overnight at ambient temperature, but no indication of any new product was observed.

3.1.4.2 Synthesis of 2-methoxy-1-pyrroline



A:

Dimethyl sulfate (0.64 mL, 6.721 mmol, 1.2 eq) was added in one portion to 2-pyrrolidinone (0.520 mg, 6.11 mmol, 1 eq) and the mixture stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phase was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and purified by column chromatography, but no identifiable products could be observed.

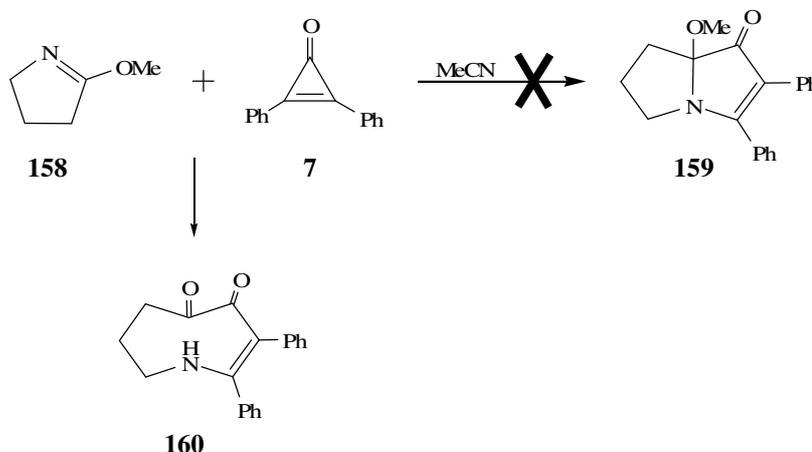
B:

Dimethyl sulfate (0.635 mL, 6.69 mmol, 1.1 eq) was added in one portion to 2-pyrrolidinone (518 mg, 6.086 mmol, 1 eq) and the mixture stirred for 16 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, but due to the volatility of the product, all of the solvent was not removed, and the crude product used in this form.

C:

Dimethyl sulfate (1.37 mL, 14.44 mmol, 1.2 eq) was added in one portion to 2-pyrrolidinone (1023.9 mg, 12.03 mmol, 1 eq) and the mixture stirred for 24 hours at 60 °C under an atmosphere of dry nitrogen. Solid sodium carbonate (1530.5 mg, 14.44 mmol, 1.2 eq) was added to the reaction mixture followed by ether (10 mL) and saturated aqueous sodium carbonate (10 mL). The solvent was decanted off and the remaining solid sodium carbonate was dissolved in water and extracted several times using dichloromethane. The combined organic phases were dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, but due to the volatility of the product, all of the solvent was not removed, and the crude product used in this form.

3.1.4.3 Attempted synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

Diphenylcyclopropanone (115 mg, 0.555 mmol, 1 eq) was added in one portion to a stirring solution of 2-methoxy-1-pyrroline (55 mg, 0.555 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for two days. The crude mixture (pale yellow in colour) was analysed by thin layer chromatography, but no identifiable products could be observed.

B:

Diphenylcyclopropanone (1.36 g, 6.60 mmol, 1.2 eq) was added in one portion to a stirring solution of 2-methoxy-1-pyrroline (0.545 g, 5.50 mmol, 1 eq) in dichloromethane/ ether (30 mL, 2:1) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for a week but showed no products. The solvent was removed under a stream of nitrogen and the remaining crude material had anhydrous acetonitrile (8 mL) added. The reaction mixture was stirred for three days, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 1:3); no identifiable products could be observed.

C:

Diphenylcyclopropenone (322.8 mg, 1.57 mmol, 1 eq) was added in one portion to a stirring solution of 2-methoxy-1-pyrroline (1.55 mg, 1.57 mmol, 1 eq) in anhydrous acetonitrile (8 mL) at ambient temperature under an atmosphere of dry nitrogen. After a few hours the reaction mixture turned pale yellow, and additional anhydrous acetonitrile (7 mL) was added due to solvent evaporation. The mixture was concentrated and purified by column chromatography, but no identifiable products were produced.

D:

Diphenylcyclopropenone (389.6 mg, 1.89 mmol, 1 eq) was added in one portion to a stirring solution of 2-methoxy-1-pyrroline (187 mg, 1.89 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for six days, and the solution (orange in colour) was concentrated and purified by column chromatography (eluent: 1:3, hexane: EtOAc) to yield 5,6,7,8-tetrahydro-4-hydroxy-2,3-diphenyl-1-azocin-5-one (15 mg, 2.7 %).

E:

Diphenylcyclopropenone (100 mg, 0.48 mmol, 1 eq) was added in one portion to a stirring solution of 2-methoxy-1-pyrroline (690 mg, 6.97 mmol, 1 eq) dissolved in anhydrous acetonitrile (10 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for three days showing no change by TLC analysis. The mixture was heated to reflux for two days. Evaporation of the solvent gave a crude product which was purified by column chromatography (eluent: 1:3, hexane: EtOAc) to yield 5,6,7,8-tetrahydro-4-hydroxy-2,3-diphenyl-1-azocin-5-one (25 mg, 18 %), as an orange oil.

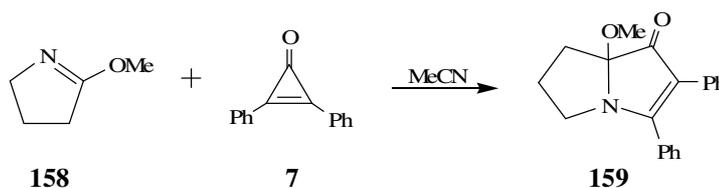
$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 9.83 (1H, s, NH), 7.27 – 7.20 (3H, m, Ar), 7.20 – 7.16 (3H, m, Ar), 7.12 – 7.04 (4H, m, Ar), 3.50 (2H, t, J 7.0, NCH_2), 2.70 (2H, t, J 8.0, OCCH_2), 2.17 (2H, quint, J 7.5, $\text{CH}_2\text{CH}_2\text{CH}_2$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 190.17 (q), 176.14 (q), 148.82 (q), 136.05 (q), 134.01 (q), 133.96 (q), 131.61 (CH), 130.06 (CH), 129.92 (CH), 128.84 (CH), 128.25 (CH), 127.89 (CH), 49.40 (CH_2), 31.86 (CH_2), 18.99 (CH_2).

HRMS (ESI+): Found 314.1154 $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{17}\text{NNaO}_2$ requires 314.1152.

IR ν_{max} (cm^{-1}): 3056 (w), 2980 (w), 2926 (w), 1704 (s), 1674 (s).

3.1.5 Synthesis of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

To a stirring solution of 2-methoxy-1-pyrroline (233 mg, 2.35 mmol, 1 eq) in anhydrous acetonitrile (7 mL) was added diphenylcyclopropenone (485.4 mg, 2.35 mmol, 1 eq) in one portion. The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for a day, whereupon the mixture turned from colourless to dark orange. The resulting mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc, 2:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (28 mg, 4 %), as a yellow/ orange oil.

B:

To a stirring solution of 2-methoxy-1-pyrroline (224 mg, 2.26 mmol, 1 eq) in anhydrous acetonitrile (8 mL) was added diphenylcyclopropenone (466 mg, 2.26 mmol, 1 eq) in one portion. The reaction mixture was heated to reflux under an atmosphere of dry nitrogen and monitored every hour by TLC. After five hours the reaction mixture was allowed to cool to ambient temperature and stirred overnight. The reaction mixture was heated at reflux for a further five hours. The resulting mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc, 2:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo-[3.3.0]oct-2-en-4-one (13 mg, 2 %), as a yellow/ orange oil.

C:

To a stirring solution of 2-methoxy-1-pyrroline (222 mg, 2.24 mmol, 4.67 eq) in anhydrous acetonitrile (4 mL) was added chlorosulfonic acid (30 mg) and diphenylcyclopropenone (100 mg, 0.48 mmol, 1 eq) in one portion. The reaction mixture was heated at reflux under an atmosphere of dry nitrogen for one day. TLC analysis showed that no reaction had occurred.

D:

To a stirring solution of 2-methoxy-1-pyrroline (218 mg, 2.24 mmol, 1 eq) in anhydrous acetonitrile (7 mL) was added zinc bromide (50 mg) and diphenylcyclopropenone (462.5 mg, 2.24 mmol, 1 eq) in one portion. The reaction mixture was heated at reflux under an atmosphere of dry nitrogen for one day. The resulting mixture was allowed to cool to ambient temperature and analysed by TLC, which showed that no reaction had occurred.

E:

To a stirring solution of 2-methoxy-1-pyrroline (240 mg, 2.42 mmol, 1 eq) in anhydrous DMF (12 mL) was added diphenylcyclopropenone (500 mg, 2.42 mmol, 1 eq) in one portion. The reaction mixture was heated at 100 °C under an atmosphere of dry nitrogen for one day. Upon completion the resulting orange/ yellow mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc, 2:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (32 mg, 4 %), as a yellow/ orange oil.

F:

To a stirring solution of 2-methoxy-1-pyrroline (250 mg, 2.53 mmol, 1 eq) in anhydrous DMF (10 mL) was added diphenylcyclopropenone (510 mg, 2.47 mmol, 0.98 eq) in one portion. The reaction mixture was rapidly heated from ambient temperature to 130 °C under an atmosphere of dry nitrogen. After three hours the reaction mixture was allowed to cool to ambient temperature, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 2:1, 1:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (56 mg, 7 %).

G:

To a stirring solution of 2-methoxy-1-pyrroline (240 mg, 2.42 mmol, 1 eq) in anhydrous DMF (10 mL) was added diphenylcyclopropenone (500 mg, 2.42 mmol, 1 eq) in one portion. The reaction mixture was heated at 130 °C under an atmosphere of dry nitrogen. After 18 hours the reaction mixture was allowed to cool to ambient temperature. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (eluent: hexane: EtOAc, 2:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (114 mg, 15 %), as a yellow/ orange oil.

H:

To a stirring solution of 2-methoxy-1-pyrroline (249 mg, 2.52 mmol, 1 eq) in anhydrous DMF (10 mL) was added diphenylcyclopropanone (519 mg, 2.52 mmol, 1 eq) in one portion. The reaction mixture was heated at 165 °C under an atmosphere of dry nitrogen. After 18 hours the reaction mixture was allowed to cool to ambient temperature. The solvent was removed *in vacuo* and the crude residue purified by column chromatography (eluent: hexane: EtOAc, 2:1) yielding 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (328 mg, 42 %), as a yellow/ orange oil.

¹H NMR δ (400.13 MHz, CDCl₃): 7.48 – 7.45 (3H, m, Ar), 7.41 – 7.35 (2H, m, Ar), 7.21 – 7.17 (4H, m, Ar), 7.16 – 7.10 (1H, m, Ar), 3.46 (1H, ddd, *J* 4.1, 7.4, 11.1, NCHH), 3.31 (3H, s, Me), 2.98 (1H, ddd, *J* 7.4, 7.4, 11.0, NCHH), 2.34 – 2.21 (1H, m, MeOCCHH), 2.20 – 2.13 (1H, m, MeOCCHH), 2.00 – 1.89 (2H, m, CH₂CH₂CH₂).

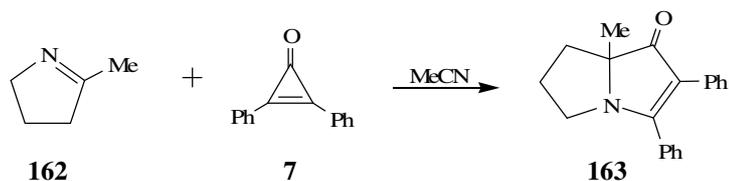
¹³C NMR δ (100 MHz, CDCl₃): 198.85 (q), 177.12 (q), 131.60 (CH), 131.21 (q), 131.10 (q), 130.00 (CH), 129.09 (CH), 128.92 (CH), 128.30 (CH), 126.49 (CH), 116.26 (q), 100.68 (q), 51.95 (CH₃), 48.96 (CH₂), 32.33(CH₂), 26.47 (CH₂).

LRMS (ESI+): 306.1 [M+H]⁺, 328.1 [M+Na]⁺, 633.3 [2M+Na]⁺.

HRMS (ESI+): 328.1307 [M+Na]⁺, C₂₀H₂₀NO₂, requires 328.1308.

IR ν_{max} (cm⁻¹): 2980 (s), 2890 (w), 1683 (vs), 1602 (m), 1580 (m), 1552 (m), 1397 (s), 1073 (s).

3.1.6 Synthesis of 5-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

Diphenylcyclopropenone (250 mg, 1.21 mmol, 1 eq) was added in one portion to a stirring solution of 2-methyl-1-pyrroline (1.15 mL, 12.12 mmol, 10 eq) in anhydrous acetonitrile (10 mL). The reaction mixture was stirred for a day at ambient temperature under an atmosphere of dry nitrogen. Evaporation of the solvent gave a crude product which was purified by column chromatography (eluent: hexane: EtOAc, 2:1) to yield 5-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (200 mg, 57 %), as a yellow solid.

B:

To a stirring solution of diphenylcyclopropenone (500 mg, 2.42 mmol, 1 eq) in DMF (10 mL) was added 2-methyl-1-pyrroline (0.23 mL, 2.42 mmol, 1 eq) and the reaction mixture was heated at reflux for one and a half hours under an atmosphere of dry nitrogen. Evaporation of the solvent gave a crude residue which was purified by column chromatography (eluent: hexane: EtOAc, 2:1) to yield 5-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (624 mg 89 %), as a yellow solid.

¹H NMR δ (400.13 MHz, CDCl₃): 7.43 – 7.40 (3H, m, Ar), 7.36 – 7.32 (2H, m, Ar), 7.24 – 7.15 (4H, m, Ar), 7.11 – 7.06 (1H, m, Ar), 3.37 (1H, ddd, *J* 1.1, 6.3, 8.8, NCHH), 2.97 (1H, dd, *J* 6.7, 8.8, NCHH), 2.12 – 1.84 (4H, m, NCH₂CH₂CH₂), 1.46 (3H, s, CH₃).

^{13}C NMR δ (100 MHz, CDCl_3): 204.24 (q), 176.12 (q), 132.26 (q), 131.78 (q), 130.88 (CH), 129.79 (CH), 128.77 (CH), 128.71 (CH), 128.05 (CH), 125.79 (CH), 115.20 (q), 74.97 (q), 48.56 (CH_2), 32.39 (CH_2), 26.67 (CH_2), 23.04 (CH_3).

LRMS (ESI+): 290.2 $[\text{M}+\text{H}]^+$, 312.1 $[\text{M}+\text{Na}]^+$, 601.3 $[2\text{M}+\text{Na}]^+$.

HRMS (ESI+): 312.1371 $[\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{19}\text{NNaO}$ requires 312.1359.

HRMS (ESI+): 290.1550 $[\text{M}+\text{H}]^+$, $\text{C}_{20}\text{H}_{20}\text{NO}$ requires 290.1539.

IR ν_{max} (cm^{-1}): 2971 (m), 1670 (vs), 1602 (m), 1581 (m), 1552 (m), 1500 (w).

3.1.7 Synthesis of 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.7.1 Synthesis of 5-methylpyrrolidine-2-thione

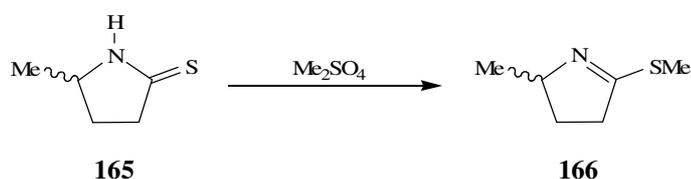


A solution of 5-methyl-2-pyrrolidinone (205 - mg, 2.07 mmol, 1 eq) and Lawesson's reagent (501.9 mg, 1.24 mmol, 0.6 eq) in anhydrous tetrahydrofuran (10 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to ambient temperature, concentrated and purified twice by column chromatography (eluent: hexane: EtOAc 1:1, then hexane: EtOAc, 3:2) to yield 5-methylpyrrolidine-2-thione (200 mg, 84 %) as a white powder.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 9.08 (1H, bs, NH), 4.05 (1H, dq, J 6.6, 13.4, CHCH₃), 2.96 (1H, ddd, J 4.8, 9.3, 18.1, SCCHH), 2.86 (1H, ddd, J 8.8, 8.8, 18.1, SCCHH), 2.38 – 2.29 (1H, m, CH₃CHCHH), 1.78 – 1.68 (1H, m, CH₃CHCHH), 1.28 (3H, d, J 6.6, CHCH₃).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 204.77 (q), 58.52 (CH), 43.60 (CH₂), 31.40 (CH₂), 21.07 (CH₃).

3.1.7.2 Synthesis of 5-methyl-2-methylthio-1-pyrroline

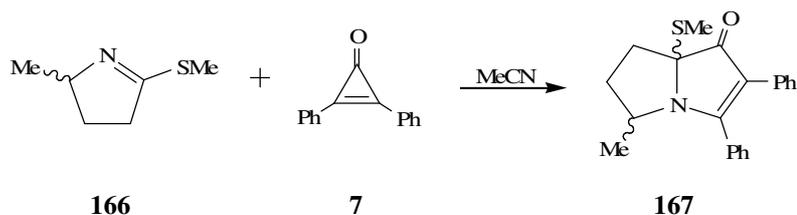


Dimethyl sulfate (0.19 mL – 0.20 mL, 1.74 mmol – 2.13 mmol, 1 eq) was added in one portion to 5-methylpyrrolidine-2-thione (200 mg – 244 mg, 1.74 mmol – 2.13 mmol, 1 eq) and the mixture stirred for 20 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave ~ 1 mL of liquid which was used directly in the next step.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 4.09 (1H, ddq, J 1.4, 6.7, 6.7, CHCH₃), 2.68 (1H, dddd, J 1.6, 5.1, 9.6, 16.4, SCCHH), 2.63 – 2.53 (1H, m, SCCH₂CHH), 2.45 (3H, s, SCH₃), 2.19 (1H, dddd, J 2.5, 4.4, 7.4, 9.6, SCCHH), 1.53 – 1.50 (1H, m, SCCH₂CHH), 1.27 (3H, d, J 6.7, CHCH₃).

^{13}C NMR δ (100 MHz, CDCl_3): 172.10 (q), 68.20 (CH), 66.20 (CH_2), 58.93 (CH_3), 38.95 (CH_2), 22.44 (CH_3).

3.1.7.3 Synthesis of 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one



Diphenylcyclopropenone (359 mg, 1.74 mmol, 1 eq) was added in one portion to a stirring solution of the 5-methyl-2-methylthio-1-pyrroline prepared above, dissolved in anhydrous acetonitrile (9 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for four days, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 2:1) to yield 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one, as a mixture of diastereoisomers (171 mg) in a ratio of 1:1.3. A small quantity (~1 mg) of one of the pure diastereoisomers was obtained, as a yellow oil.

^1H NMR δ (400.13 MHz, CDCl_3) pure sample: 7.49 – 7.40 (3H, m, Ar), 7.38 – 7.33 (2H, m, Ar), 7.26 – 7.14 (5H, m, Ar), 4.13 (1H, quint, J 6.6, NCHMe), 2.86 (1H, ddd, J 7.0, 12.4, 19.4, SCCHH), 2.24 – 2.10 (2H, m, SCCH_2CH_2), 2.12 (3H, s, SCH_3), 1.88 (1H, dd, J 5.9, 12.4, SCCHH), 0.70 (3H, d, J 6.6 CHCH_3).

^{13}C NMR δ (100 MHz, CDCl_3): 199.87 (q), 170.95 (q), 132.59 (q), 131.82 (q), 131.15 (CH), 129.31 (CH), 129.16 (CH), 129.06 (CH), 128.35 (CH), 126.42 (CH), 119.58 (q), 80.37 (q), 55.40 (CH), 35.74 (CH_2), 27.77 (CH_2), 19.37 (CH_3), 11.52 (CH_3).

The diastereoisomeric mixture showed the following extra peaks:

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.48 – 7.12 (extra peaks in aromatic region), 3.53 – 3.48, 2.36 – 2.26, 2.24 – 2.09, 2.00 – 1.92, 1.43 – 1.41.

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 200.36, 176.70, 131.74, 131.47, 131.22, 129.61, 129.00, 128.90, 128.24, 126.32, 116.59, 80.10, 57.32, 34.04, 32.28, 22.97, 12.00.

IR ν_{max} (cm^{-1}): 2971(m), 2919 (w), 1673 (vs), 1601 (m), 1500 (w), 1449 (m), 1395 (s).

On storage, the 5-methylthio-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one was seen by TLC to become impure and column chromatography of the degraded material gave a small quantity of 5-hydroxy-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one (37 %).

5-Hydroxy-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one:

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.52 – 7.35 (5H, m, Ar), 7.20 – 7.05 (5H, m, Ar), 3.38 (1H, dq, J 6.5, 13.0, $\text{NCH}(\text{Me})\text{CH}_2$), 2.26 – 2.13 (2H, m, $\text{CH}_2\text{CH}_2\text{COH}$), 2.13 – 2.02 (2H, m, $\text{CH}_2\text{CH}_2\text{COH}$), 1.40 (3H, d, J 6.5, $\text{NCH}(\text{CH}_3)\text{CH}_2$).

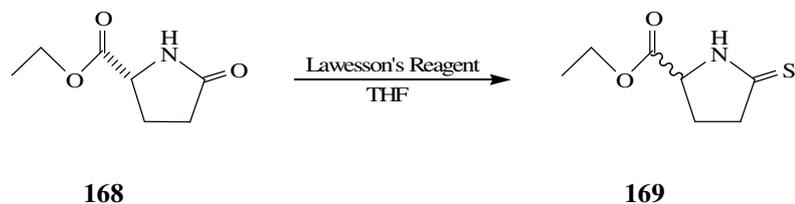
$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 199.91 (q), 177.94 (q), 131.60 (CH), 131.40 (q), 131.27 (q), 129.85 (CH), 129.09 (CH), 129.02 (CH), 128.34 (CH), 126.44 (CH), 113.78 (q), 97.39 (q), 56.87 (CH), 34.69 (CH_2), 33.66 (CH_2), 23.72 (CH_3).

LRMS (ESI+): 358.1 $[\text{M}+\text{Na}]^+$ for $\text{C}_{20}\text{H}_{19}\text{NO}_2$.

IR ν_{max} (cm^{-1}): 3331 (br), 3062 (m), 2970 (m), 2929 (w), 1664 (vs), 1602 (s), 1503 (m).

3.1.8 Synthesis of 5-methylthio-2,3-diphenyl-8-ethylcarboxylate-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.8.1 Synthesis of ethyl pyrrolidine-2-thione-5-carboxylate



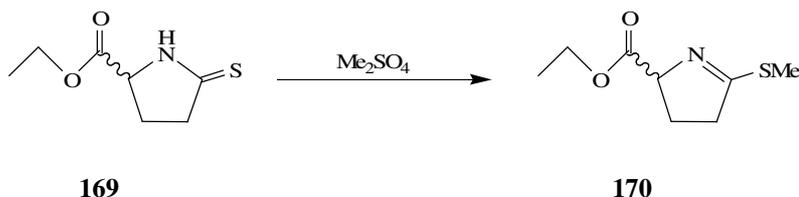
To a stirring solution of ethyl (R)-(-) 2-pyrrolidone-5-carboxylate (500 mg, 3.18 mmol, 1 eq) in anhydrous tetrahydrofuran (10 mL) was added Lawesson's reagent (772 mg, 1.91 mmol, 0.6 eq) in one portion. The reaction mixture was stirred under an atmosphere of dry nitrogen at ambient temperature for one hour, followed by heating at reflux whilst being monitored by TLC. After two and a half hours, the reaction was allowed to cool to ambient temperature. Evaporation of the solvent *in vacuo* gave a crude residue which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield ethyl pyrrolidine-2-thione-5-carboxylate (526 mg, 95 %), as an orange oil.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 8.95 (1H, s, NH), 4.49 (1H, dd, J 6.1, 8.9, HNC HCO), 4.18 (1H, dq, J 7.1, 16.1, COOCH HCH_3), 4.15 (1H, dq, J 7.1, 16.1, COOCH HCH_3), 2.96 – 2.79 (2H, m, SCCH $_2$), 2.53 – 2.43 (1H, m, SCCH $_2$ CH H), 2.29 – 2.19 (1H, m, SCCH $_2$ CH H), 1.23 (3H, t, J 7.1, COOCH $_2$ CH $_3$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 206.53 (q), 170.42 (q), 62.84 (CH), 62.16 (CH $_2$), 42.80 (CH $_2$), 27.06 (CH $_2$), 14.20 (CH $_3$).

IR ν_{\max} (cm^{-1}): 3168 (br), 2981 (m), 1735 (vs), 1496 (vs), 1422 (m), 1374 (m), 1333 (w), 1204 (vs).

3.1.8.2 Synthesis of ethyl 2-methylthio-pyrroline-5-carboxylate

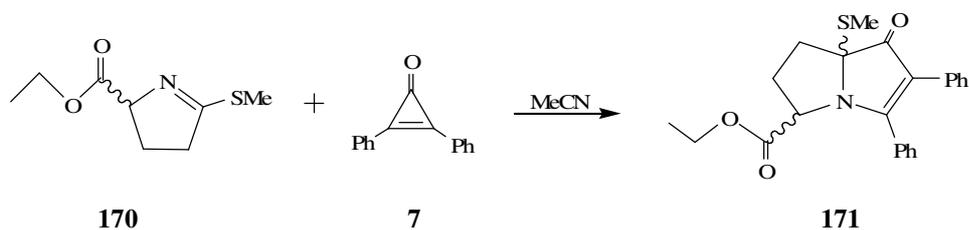


Dimethyl sulfate (0.31 mL, 3.24 mmol, 1.1 eq) was added in one portion to ethyl pyrrolidine-2-thione-5-carboxylate (510 mg, 2.95 mmol, 1 eq) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with diethyl ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic phases were dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave ~2 mL of liquid which was used without further concentration or purification.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 4.53 (1H, t, J 7.3, NCHCOO), 4.06 (2H, q, J 7.1 $\text{COOCH}_2\text{CH}_3$), 2.72 – 2.60 (1H, m, SCCHH), 2.58 – 2.47 (1H, m, SCCHH), 2.34 (3H, s, SCH_3), 2.23 – 2.12 (1H, m, SCCH_2CHH), 2.08 – 1.98 (1H, m, SCCH_2CHH), 1.15 (3H, t, J 7.1, $\text{COOCH}_2\text{CH}_3$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 176.87 (q), 172.73 (q), 60.93 (CH_2), 58.60 (CH) 38.62 (CH_2), 27.64 (CH_2), 14.13 (CH_3) 13.72 (CH_3).

3.1.8.3 Synthesis of 5-methylthio-2,3-diphenyl-8-ethylcarboxylate-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of 2-methylthio-5-ethylcarboxylatepyrroline (250 mg, 1.34 mmol, 1 eq) in acetonitrile (8 mL) was added diphenylcyclopropenone (276 mg, 1.34 mmol, 1 eq) in one portion. The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for three days. Evaporation of the solvent gave a crude residue, which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 5-methylthio-2,3-diphenyl-8-ethylcarboxylate-1-azabicyclo[3.3.0]oct-2-en-4-one (263 mg, 50%), as a yellow oil. The product was formed as a mixture of diastereoisomers in a ratio of 1:1.2.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.46 – 7.22 (10H, m, Ar), 7.21 – 7.04 (10H, m, Ar), 4.39 (1H, d, J 8.5), 4.28 – 4.10 (2H, m), 3.88 (1H, dd, J 6.9, 8.1), 3.65 – 3.51 (1H, m), 3.58 (1H, t, J 7.0), 3.01 – 2.89 (1H, m), 2.66 – 2.50 (1H, m), 2.42 – 2.32 (2H, m), 2.24 – 2.16 (2H, m), 2.17 – 2.11 (1H, m), 2.11 (3H, s, SCH_3), 2.08 (3H, s, SCH_3), 1.27 (3H, t, J 7.1, CH_2CH_3), 1.24 – 1.16 (1H, m), 0.82 (3H, t, J 7.1, CH_2CH_3).

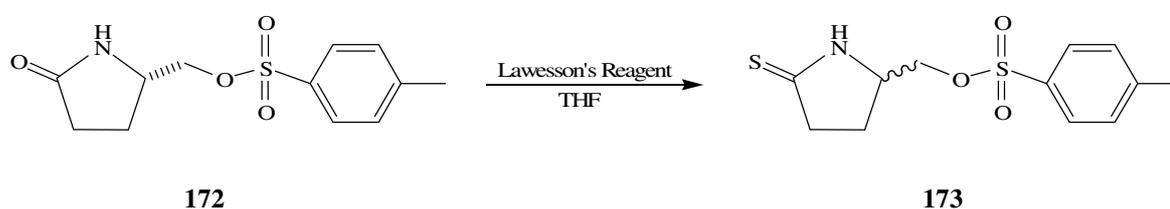
$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 199.27, 198.79, 177.20, 174.37, 172.85, 171.84, 171.16, 170.86, 131.32, 130.92, 118.63, 116.21, (12 x q), 81.02, 80.20 (2 x q), 131.46, 131.13, 130.60, 129.79, 129.60, 128.91, 128.87, 128.59, 128.09, 126.40, 126.33, (11 x CH aromatic) 61.04, 60.31 (2 x CH), 61.61, 61.17, 33.19, 32.11, 31.57, 28.52 (6 x CH_2), 14.26, 13.79, 11.68, 11.34, (4 x CH_3).

HRMS (ESI⁺): 416.1291 $[\text{M}+\text{Na}]^+$, $\text{C}_{23}\text{H}_{23}\text{NNaO}_3\text{S}$, requires 416.1291.

IR ν_{\max} (cm⁻¹): 2979 (m), 1734 (s), 1673 (vs), 1602 (m), 1582 (m), 1557 (m), 1499 (w), 1187 (s), 1025 (s).

3.1.9 Synthesis of 5-methylthio-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.9.1 Synthesis of (hydroxymethyl)pyrrolidin-2-thione *p*-toluenesulfonate



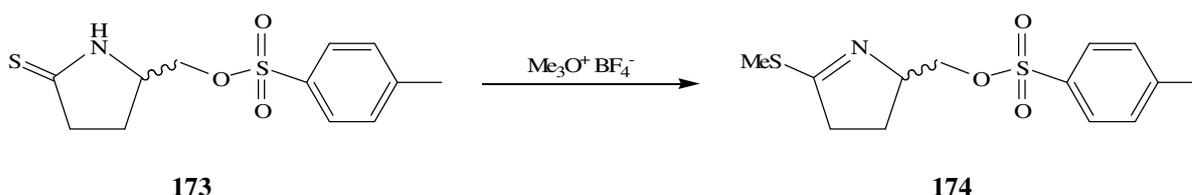
To a stirring solution of (S)-(+)-(hydroxymethyl)-2-pyrrolidinone *p*-toluenesulfonate (477 - 500 mg, 1.77 - 1.86 mmol, 1 eq) in anhydrous tetrahydrofuran (8 mL) was added Lawesson's reagent (430 - 450.6 mg, 1.06 - 1.1 mmol, 0.6 eq) in one portion. The reaction mixture was monitored by TLC and stirred under an atmosphere of dry nitrogen at ambient temperature for an hour, followed by heating at reflux. After three hours the reaction was allowed to cool to ambient temperature. Evaporation of the solvent *in vacuo* gave a crude residue which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield (hydroxymethyl)-pyrrolidin-2-thione *p*-toluenesulfonate (305 - 440 mg, 60 - 83%), as a white solid.

¹H NMR δ (400.13 MHz, CDCl₃): 8.22 – 8.13 (1H, bs, NH), 7.80 (2H, d, *J* 8.2, O₃SCCH), 7.38 (2H, d, *J* 8.2, O₃SCCHCH), 4.24 – 4.16 (1H, m, NCH), 4.13 (1H, dd, *J* 3.8, 10.4, CHHO), 3.95 (1H, dd, *J* 7.3, 10.4, CHHO), 2.99 - 2.83 (2H, m, SCCH₂)*, 2.46 (3H, s, Me), 2.38 – 2.27 (1H, m, NCHCHH)*, 1.93 – 1.83 (1H, m, NCHCHH)*.

^{13}C NMR δ (100 MHz, CDCl_3): 206.85 (q), 145.93 (q), 132.36 (q), 130.50 (CH), 128.28 (CH), 70.74 (CH_2), 60.67 (CH), 42.71 (CH_2), 25.49 (CH_2), 22.04 (CH_3).

* Assignments may be interchanged.

3.1.9.2 Synthesis of (hydroxymethyl) 2-methylthio-5-*p*-toluenesulfonate pyrroline



A:

Dimethyl sulfate (1.2 mL, 12.6 mmol, 8.2 eq) was added in one portion to (hydroxymethyl)-pyrrolidin-2-thione *p*-toluenesulfonate (440 mg, 1.54 mmol, 1 eq) and the mixture was stirred for 18 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with diethyl ether (10 mL), washed with 40 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic phases were dried over magnesium sulfate and filtered under gravity, and concentrated until ~2 mL, of liquid remained. This was used immediately in the next step.

B:

To a stirring solution of (hydroxymethyl)pyrrolidin-2-thione *p*-toluenesulfonate (300 mg, 1.05 mmol, 1 eq) in anhydrous dichloromethane (10 mL) was added a solution of $\text{Me}_3\text{O}^+ \text{BF}_4^-$ (155.52 mg, 1.05 mmol, 1 eq) in anhydrous dichloromethane (10 mL). The reaction mixture was stirred for an hour at ambient temperature under an atmosphere of dry nitrogen, followed by heating at reflux for a further hour; the mixture was cooled to ambient temperature and ice cold 50 % aqueous potassium carbonate (20 mL) was added and the mixture stirred overnight. The resulting mixture was filtered under vacuum with the aid of celite and extracted with

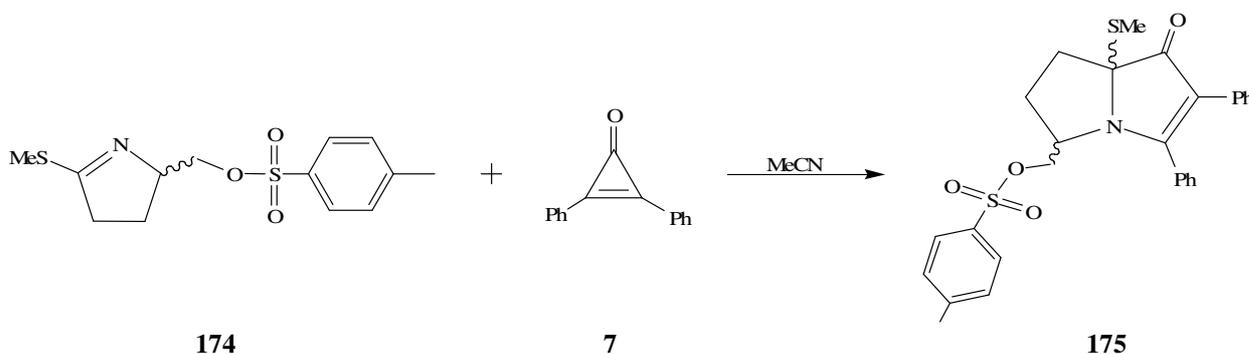
dichloromethane (4 x 10 mL). The combined organic phases were dried over magnesium sulfate, filtered under gravity and most of the solvent was removed *in vacuo*, to leave ~2 mL of liquid which was used directly in the next step.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.78 (2H, d, J 8.2, O_3SCCH), 7.34 (2H, d, J 8.2, O_3SCCHCH), 4.30 – 4.23 (1H, m, CHN), 4.21 (1H, dd, J 4.0, 9.6, CHHO), 4.03 (1H, dd, J 5.6, 9.6, CHHO), 2.72 (1H, dddd, J 1.7, 6.1, 10.1, 16.7, NCHCHH)*, 2.61 (1H, dddd, J 0.9, 6.6, 10.1, 16.7, NCHCHH)*, 2.44 (3H, s, ArCH_3), 2.38 (3H, s, SCH_3), 2.15 (1H, dddd, J 6.0, 7.5, 8.1, 15.5, NCHCH_2CHH)*, 1.86 (1H, dddd, J 5.6, 6.6, 8.1, 14.7, NCHCH_2CHH)*.

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 176.71 (q), 145.14 (q), 133.10 (q), 130.16 (CH), 128.28 (CH), 72.54 (CH_2), 70.57 (CH), 38.93 (CH_2), 26.45 (CH_2), 21.97 (CH_3), 14.10 (CH_3).

* Assignments may be interchanged.

3.1.9.3 Synthesis of 5-methylthio-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of the pyrroline (415 mg, 1.39 mmol, 1 eq) in acetonitrile (10 mL) was added diphenylcyclopropenone (286 mg, 1.39 mmol, 1 eq) in one portion. The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for three days. Analysis by TLC showed no reaction had taken place; therefore the mixture was heated at reflux, whilst being monitored by TLC. After 18 hours no reaction was observed.

To a stirring solution of the pyrroline (283.2 mg, 0.95 mmol, 1 eq) in acetonitrile (10 mL) was added diphenylcyclopropenone (195.1 mg, 0.95 mmol, 1 eq) in one portion. The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for three days. Analysis by TLC showed no reaction had taken place; therefore the mixture was heated at reflux for 18 hours. The mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 5-methylthio-2,3-diphenyl-8-(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one (228 mg, 48%), as an orange/ yellow oil. The product was formed as a single diastereoisomer.

¹H NMR δ (400.13 MHz, CDCl₃): 7.48 (2H, d, *J* 8.3, Ar), 7.40 – 7.32 (2H, m, Ar), 7.25 – 7.09 (10H, m, Ar), 4.14 – 4.07 (1H, m, NCH), 3.54 (1H, dd, *J* 2.6, 10.3, CHHO), 3.35 (1H, dd, *J* 5.8, 10.3, CHHO), 2.84 (1H, ddd, *J* 7.7, 15.0, 22.5 (gem), CH₃SCCHH)*, 2.38 (3H, s, CHCHCH₃), 2.25 – 2.14 (2H, m, NCHCH₂CH₂)*, 2.10 – 2.03 (1H, m, CH₃SCCHH)*, 2.07 (3H, s, SCH₃).

¹³C NMR δ (100 MHz, CDCl₃): 198.72 (q), 168.49 (q), 145.24 (q), 132.27 (q), 131.31 (CH), 131.14 (q), 131.07 (q), 130.08 (CH), 129.09 (CH), 128.94 (CH), 128.72 (CH), 128.14 (CH), 127.77(CH), 126.51 (CH), 119.44 (q), 80.31 (q), 68.65 (CH₂), 56.88 (CH), 31.85 (CH₂), 28.21 (CH₂), 21.75 (CH₃) 11.38 (CH₃).

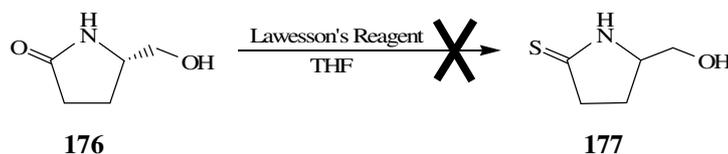
HRMS (ESI+): 528.1274 [M+Na]⁺, C₂₈H₂₇NNaO₄S₂, requires 528.1274.

IR ν_{\max} (cm⁻¹): 3062 (w), 2920 (w), 1672 (vs), 1599 (s), 1582 (m), 1556 (s), 1497 (w), 1482 (w), 1364 (s), 1306 (w), 1189 (m), 1176 (vs).

* Assignments may be interchanged.

3.1.10 Attempted synthesis of 5-methylthio-2,3-diphenyl-8-hydroxymethyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.1.10.1 Attempted synthesis of 5-(hydroxymethyl)pyrrolidin-2-thione



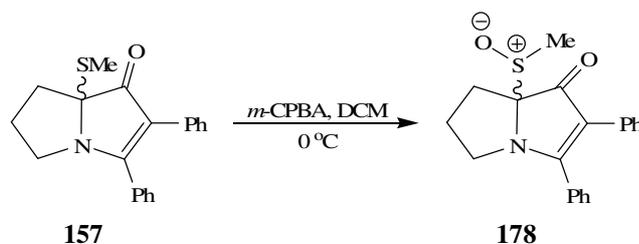
Typical Procedure:

To a stirring solution of (S)-5-(hydroxymethyl)-2-pyrrolidinone (506 mg, 4.4 mmol, 1 eq) in anhydrous tetrahydrofuran (10 mL) was added Lawesson's reagent (1.07 g, 2.64 mmol, 0.6 eq) in one portion. The reaction mixture was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour, followed by heating at reflux. After 18 hours the reaction mixture was allowed to cool to ambient temperature, concentrated and purified by column chromatography, no indication of any new product or recovery of starting material was observed by TLC.

3.2 Reactivity of Pyrrolizidines

3.2.1 Reactivity of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

3.2.1.1 Synthesis of 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (110 mg, 0.343 mmol, 1 eq) in anhydrous dichloromethane (7 mL) was added a solution of *meta*-chloroperoxybenzoic acid (60 mg, 0.343 mmol, 1 eq) in anhydrous dichloromethane (4 mL) at 0 °C – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for four and a half hours at 0 °C – -10 °C, before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extraction with dichloromethane (3 x 10 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: PE: EtOAc, 1:3) to yield 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (104 mg, 90 %), as a orange solid.

B:

To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (570 mg, 1.78 mmol, 1 eq) in anhydrous dichloromethane (10 mL) at 0 – -10 °C was added a

solution of *meta*-chloroperoxybenzoic acid (600 mg, 3.48 mmol, 2 eq) in anhydrous dichloromethane (6 mL) under an atmosphere of dry nitrogen. The reaction mixture was stirred for six hours at 0 – -10 °C before being quenched with saturated aqueous sodium thiosulfate (15 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: PE: EtOAc, 1:3) to yield 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (275 mg, 46 %), as a orange solid.

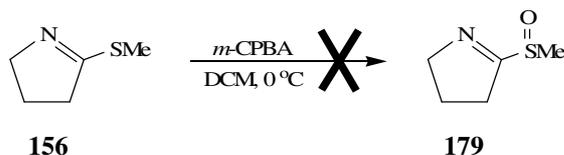
The product was formed as a mixture of diastereoisomers in a ratio of 1:1.45.

¹H NMR δ (400.13 MHz, CDCl₃): [mixture of diastereoisomers]: 7.55 – 7.43 (3H, m, Ar), 7.41 (2H, m, Ar), 7.27 – 7.14 (5H, m, Ar), 3.53 (2H, 2 x dd, *J* 6.8, 8.0, 11.1, m, NCH₂), 3.41 (1H, td, *J* 5.7, 11.1, CHH) 3.27 – 3.18 (2H, m, CH₂), 2.86 (1H, dt, *J* 7.5, 13.8, CHH), 2.83 – 2.75 (1H, m, CHH), 2.69 (3H, s, CH₃), 2.58 – 2.51 (1H, m, CHH), 2.57 (3H, s, CH₃), 2.37 – 2.18 (2H, m, CH₂), 2.03 – 1.83 (2H, m, CH₂).

¹³C NMR δ (100 MHz, CDCl₃): [mixture of diastereoisomers]: 196.00, 195.94, 178.05, 177.37, 120.12, 119.83 (6 x q), 131.03, 130.76, 130.62, 130.38 (4 x q, aromatic), 132.11, 131.93, 130.14, 129.95, 129.23, 129.09, 128.65, 128.53 (8 x CH aromatic), 128.88 (CH), 92.75, 91.86 (2 x q), 60.74, 51.20, 50.81, 28.91, 26.26, 22.15 (6 x CH₂), 33.33, 32.74 (2 x CH₃).

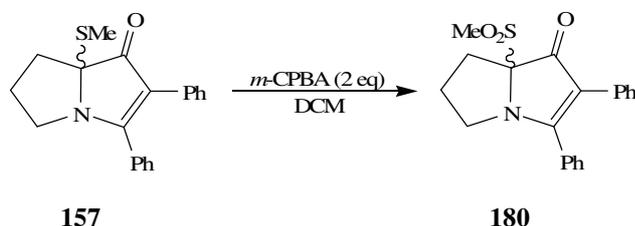
IR ν_{max} (cm⁻¹): 2917 (m), 1737 (vs), 1603 (w), 1558 (w), 1447 (w), 1373 (s), 1237 (vs), 1140 (w), 1097 (w), 1044 (s), 938 (w), 846 (w), 701 (m).

3.2.1.2 Attempted Synthesis of 2-methanesulfinyl-1-pyrroline



To a stirring solution of 2-methylthio-1-pyrroline (235 - 495 mg, 2.05 - 2.87 mmol, 1 eq) in anhydrous dichloromethane (5 mL) was added a solution of *meta*-chloroperoxybenzoic acid (353 - 742.8 mg, 2.05 - 2.87 mmol, 1 eq) in anhydrous dichloromethane (6 mL) at 0 °C – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was maintained at 0 °C – -10 °C for 5-6 hours, and warmed to 5 °C after seven hours. The reaction was quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. The resulting mixture had saturated aqueous sodium hydrogen carbonate (10 mL) added and was stirred for ten minutes followed by extraction with dichloromethane (3 x 20 mL). The combined organic layers were dried over magnesium sulfate and filtered under gravity. The crude material was subjected to column chromatography (eluent: hexane: EtOAc, 1:1), but no identifiable products were isolated.

3.2.1.3 Synthesis of 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (86 mg, 0.268 mmol, 1 eq) in anhydrous dichloromethane (6 mL) was added a solution of *meta*-chloroperoxybenzoic acid (92.5 mg, 0.536 mmol, 2 eq) in anhydrous dichloromethane (5

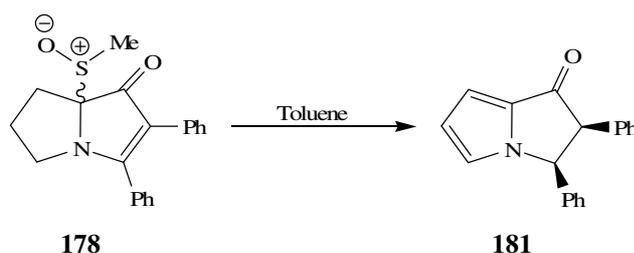
mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred at ambient temperature for three days, before being quenched and stirred for ten minutes with saturated aqueous sodium thiosulfate (10 mL). Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture and the mixture was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: hexane: EtOAc, 4:3) to yield 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (71.2 mg, 75 %), as a yellow solid.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.53 – 7.47 (3H, m, Ar), 7.40 (2H, t, J 7.6, Ar), 7.27 – 7.18 (5H, m, Ar), 3.57 (1H, ddd, J 6.4, 9.4, 11.4, NCHH), 3.24 (1H, dd, J 3.9, 11.4 NCHH), 3.01 (3H, s, CH_3), 2.72 (1H, dt, J 8.2, 13.9 CHH), 2.47 (1H dd, J 3.9, 13.9, CHH), 2.28 – 2.18 (1H, m, CHH), 1.99 – 1.87 (1H, m, CHH).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 195.33 (q), 178.74 (q), 132.19 (CH), 130.63 (q), 130.46 (q), 130.10 (CH), 129.17 (CH), 129.03 (CH), 128.60 (CH), 127.29 (CH), 119.53 (q), 91.64 (q), 35.57 (CH_3), 30.04 (CH_2), 28.08 (CH_2), 25.99 (CH_2).

HRMS (ESI+): Found 376.0981, $[\text{M}+\text{Na}]^+$, $\text{C}_{20}\text{H}_{19}\text{NNaO}_3\text{S}$ requires 376.0978.

3.2.1.4 Synthesis of 2,3-diphenyl-1-azabicyclo[3.3.0]oct-5,7-dien-4-one



A solution of 5-methanesulfinyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (100 mg, 0.297 mmol) in anhydrous toluene (5 mL) was warmed to reflux under an atmosphere of dry nitrogen. The reaction mixture was monitored by TLC and stopped after four hours, concentrated and purified by column chromatography twice (eluent: hexane: EtOAc, 10:1) to yield 2,3-diphenyl-1-azabicyclo[3.3.0]oct-5,7-en-4-one (19.5 mg, 24 %), as a orange/ yellow oil.

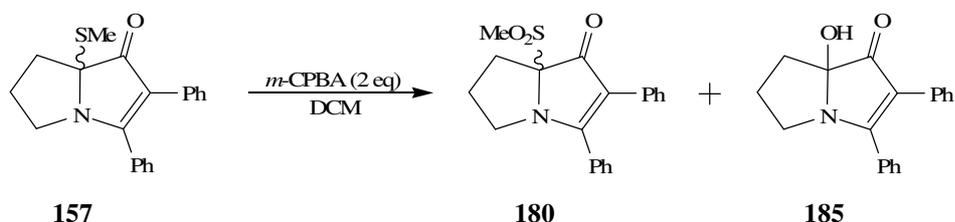
$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.42 – 7.31 (6H, m, Ar), 7.17 – 7.15 (2H, m, Ar), 7.10 – 7.07 (2H, m, Ar), 6.94 – 6.92 (2H, m, Ar), 6.65 (1H, dd, J 2.5, 3.8 pyrrole NCH), 5.46 (1H, d, J 4.4 CHPh), 4.11 (1H, d, J 4.4 CHPh).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 188.76 (q), 139.82 (q), 137.53 (q), 133.22 (q), 129.63 (CH), 129.47 (CH), 129.08 (CH), 128.61 (CH), 128.13 (CH), 126.50 (CH), 123.26 (CH), 118.09 (CH), 109.10 (CH), 67.86 (CH), 67.78 (CH).

HRMS (ESI+): Found 296.1046, $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{15}\text{NNaO}$ requires 296.1055.

IR ν_{max} (cm^{-1}): 3058 (w), 2924 (m), 2854 (w), 2360 (m), 2338 (m), 1673 (vs), 1498 (m), 1448 (m), 1392 (s), 1296 (m), 1219 (w), 1184 (m), 1093 (m), 1029 (w).

3.2.1.5 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (1.79 g, 5.58 mmol, 1 eq) in DCM (10 mL) was added *m*-CPBA (1.92 g, 11.15 mmol, 2 eq). The reaction mixture was stirred for five days at ambient temperature under an atmosphere of dry nitrogen. Evaporation of the solvent followed by purification of the residue by column chromatography (eluent: 1:1, hexane: EtOAc) yielded pure 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (667 mg), pure 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (170 mg) and a mixture of both (140 mg).

B:

To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (343 mg, 1.07 mmol, 1 eq) in DCM (10 mL) was added *m*-CPBA (184.4 mg, 1.07 mmol, 1 eq) followed by two drops of water (70 mg). The reaction mixture was stirred for 20 hours at ambient temperature under an atmosphere of dry nitrogen, before being quenched and stirred for ten minutes with saturated aqueous sodium thiosulfate (10 mL), followed by saturated aqueous sodium hydrogen carbonate (10 mL). The mixture was stirred for ten minutes before extraction with dichloromethane (5 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (22.5 mg), 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (80 mg) and a mixture of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one/ 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (210 mg), all as yellow/ orange oils.

5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one – *data as above*.

5-Hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one:

$^1\text{H NMR } \delta$ (500.13 MHz, CDCl_3): 7.47 – 7.40 (3H, m, Ar), 7.38 – 7.32 (2H, m, Ar), 7.21 – 7.09 (5H, m, Ar), 3.86 (1H, bs, OH), 3.56 (1H, ddd, J 3.8, 7.6, 11.0, NCHH), 2.89 (1H, ddd, J 7.6, 7.9, 10.6, NCHH), 2.47 – 2.36 (1H, m, $\text{CH}_2\text{CHHCH}_2$), 2.16 (1H, ddd, J 3.2, 6.7, 13.1, CCHH), 2.06 – 1.98 (1H, m, $\text{CH}_2\text{CHHCH}_2$), 1.91 (1H, ddd, J 7.6, 10.6, 13.1, CCHH).

$^{13}\text{C NMR } \delta$ (125 MHz, CDCl_3): 199.92 (q), 176.70 (q), 131.60 (CH), 131.49 (q), 131.28 (q), 130.21 (CH), 129.24 (CH), 128.93 (CH), 128.36 (CH), 126.50 (CH), 114.22 (q), 96.61 (q), 49.26 (CH_2), 33.35 (CH_2), 26.65 (CH_2).

HRMS (ESI+): Found 292.1336, $[\text{M}+\text{H}]^+$, $\text{C}_{19}\text{H}_{18}\text{NO}_2$ requires 292.1332.

HRMS (ESI+): Found 314.1153 $[\text{M}+\text{Na}]^+$, $\text{C}_{19}\text{H}_{17}\text{NNaO}_2$ requires 314.1152.

IR ν_{max} (cm^{-1}): 3370 (br), 3061 (m), 2923 (m), 2851 (w), 1678 (vs), 1601 (s), 1580 (m), 1549 (s), 1501 (w).

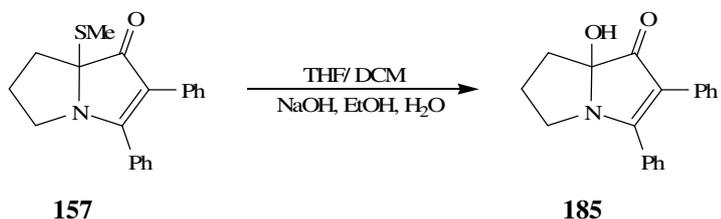
3.2.1.6 Attempted synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (80 mg, 0.249 mmol, 1 eq) in DCM (10 mL) was added three drops of water (72 mg) and benzoic acid (30 mg, 0.249 mmol, 1 eq). The reaction mixture was stirred for 19 hours at ambient temperature. TLC analysis showed no change, whereupon *meta*-chloroperoxybenzoic acid (43 mg, 0.249 mmol, 1 eq) was added to the mixture which was stirred at 0 – -10 °C for five hours and allowed to warm to ambient temperature. TLC analysis showed no reaction had occurred.



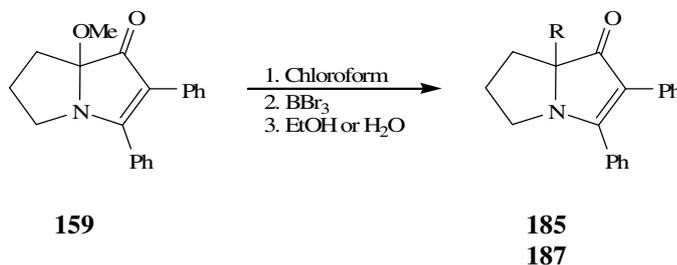
To a stirring solution of 5-methanesulfonyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (200 mg, 0.566 mmol, 1 eq) in DCM (10 mL) was added three drops of water (85 mg) and benzoic acid (70 mg, 0.566 mmol, 1 eq). The reaction mixture was stirred for 19 hours at ambient temperature. TLC analysis showed no change, whereupon *m*-CPBA (98 mg, 0.566 mmol, 1 eq) was added and the mixture was stirred at 0 – -10 °C for five hours and allowed to warm to ambient temperature. TLC analysis showed no reaction had occurred.

3.2.1.7 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (250 mg, 0.779 mmol, 1 eq) in tetrahydrofuran/ dichloromethane (6 mL, 1:1) was added sodium hydroxide (250 mg), ethanol (7 mL) and water (2 mL). The reaction mixture was stirred for two days at ambient temperature. TLC analysis showed no change, and so the reaction mixture was heated to reflux for three days. Evaporation of the solvent gave a crude product which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (42 mg, 18 %), as a yellow solid. Spectroscopy results were identical to those mentioned in section 3.2.1.5.

3.2.2 Demethylation of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



R= OEt, OMe, OH

A:

To a stirring solution of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (328 mg, 1.075 mmol, 1eq) in chloroform (10 mL) was added boron tribromide (1 M solution in DCM, 0.18 mL, 0.18 mmol, 0.17 eq)¹²⁵ dropwise over an hour at 0 °C under an atmosphere of dry nitrogen. After the addition was complete, ethanol (8 mL) was added to quench the reaction. Large amounts of starting material remained; therefore the crude material in chloroform (10 mL) had boron tribromide (1 M solution in DCM, 0.9 mL, 0.9 mmol) added dropwise, and the mixture was stirred for an hour at 0 °C under an atmosphere of dry nitrogen. After the addition was complete, ethanol (9 mL) was added to quench the reaction. Evaporation of the volatile components gave a crude residue which was purified by column chromatography (eluent: hexane: EtOAc, 3:1) to yield 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (35 mg, 10 %), as an orange oil.

B:

To a stirring solution of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (102 mg, 0.33 mmol, 1 eq) in chloroform (10 mL) was added boron tribromide (1 M solution in DCM, 0.14 mL, 0.14 mmol, 0.42 eq) dropwise and the mixture was stirred for two and a half hours at 0 °C under an atmosphere of dry nitrogen. Ethanol (8 mL) was added to quench the reaction. Evaporation of the volatile components gave a crude residue which was purified by

column chromatography (eluent: hexane: EtOAc, 3:1) to yield 5-ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (47 mg, 44 %) and 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (30 mg, 31 %) both as orange/ yellow oils.

5-Ethoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one:

¹H NMR δ (400.13 MHz, CDCl₃): 7.50 – 7.44 (3H, m, Ar), 7.41 – 7.36 (2H, m, Ar), 7.26 – 7.17 (4H, m, Ar), 7.16 – 7.11 (1H, m, Ar), 3.70 – 3.61 (1H, m, OCHHCH₃), 3.50 – 3.38 (2H, m, OCHHCH₃, NCHH), 3.02 – 2.94 (1H, m, NCHH), 2.36 – 2.25 (1H, m, OCCHHCH₂), 2.24 – 2.15 (1H, m, OCCHHCH₂), 2.00 – 1.89 (2H, m, NCH₂CH₂CH₂), 1.24 (3H, t, *J* 7.0 OCH₂CH₃).

¹³C NMR δ (100 MHz, CDCl₃): 199.31 (q), 176.78 (q), 131.57 (CH), 131.41 (q), 131.28 (q), 130.08 (CH), 129.16 (CH), 128.97 (CH), 128.36 (CH), 126.50 (CH), 116.08 (q), 100.51 (q), 60.08 (CH₂), 48.93 (CH₂), 32.63 (CH₂), 26.56 (CH₂), 15.80 (CH₃).

HRMS (ESI+): 342.1463 [M+H]⁺, C₂₁H₂₁NO₂, requires 342.1465.

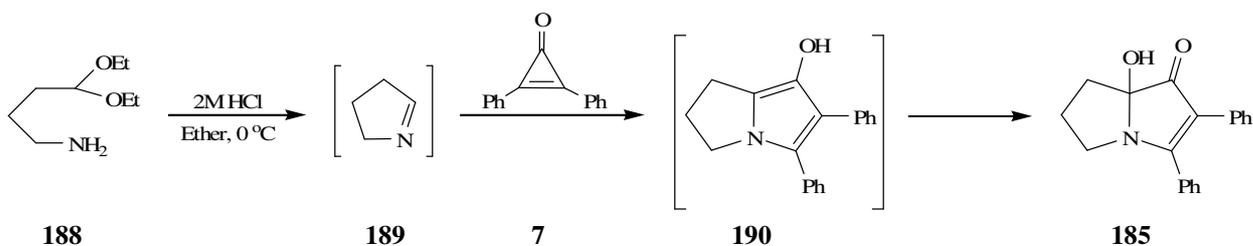
IR ν_{max} (cm⁻¹): 3056 (w), 2973m (m), 2926 (w), 2889 (w), 1678 (vs), 1601 (s), 1581 (m), 1552 (s), 1500 (m).

C:

To a stirring solution of 5-methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (100 mg, 0.33 mmol, 1 eq) in chloroform (10 mL) was added boron tribromide (1.0M solution in DCM, 0.15 mL, 0.15 mmol, 0.45 eq) dropwise and stirred for two and a half hours at 0 °C under an atmosphere of dry nitrogen. Water (10 mL) was added to quench the reaction. Evaporation of the solvents gave a crude residue which was purified by column chromatography (eluent: hexane: EtOAc, 3:1) to yield 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (33 mg, 35%), as a orange/ yellow oil and recovered 5-methoxy-2,3-diphenyl-1-azabicyclo-

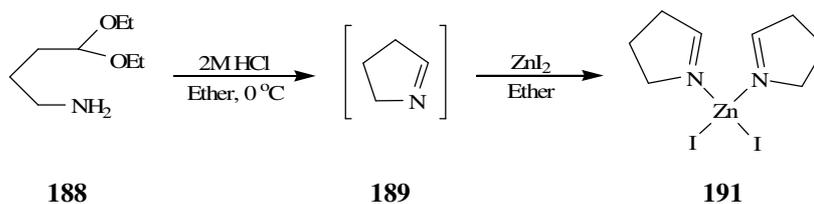
[3.3.0]oct-2-en-4-one. The spectroscopy results for 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one were comparable to those mentioned in section 3.2.1.5.

3.2.3 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



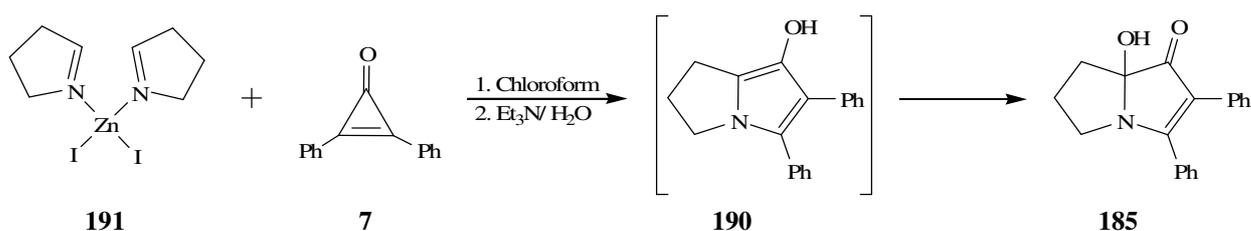
A solution of 4-aminobutylaldehyde diethyl acetal (250 mg, 1.55 mmol, 1 eq) in a mixture of 2 M aqueous HCl (2 mL) and diethyl ether (5 mL) at 0 °C was stirred for 20 minutes, after which it was basified with solid potassium carbonate and extracted with diethyl ether (4 x 7 mL) pre-cooled to 0 °C. The combined organic phases were dried over magnesium sulfate and filtered under gravity at 0 °C. The solvent was evaporated *in vacuo* using an ice slush bath to give an ethereal solution of 1-pyrroline (~10 mL). The resulting mixture was stirred at 0 °C and diphenylcyclopropenone (319.7 mg, 1.55 mmol, 1 eq) was added in one portion under an atmosphere of dry nitrogen and the mixture was stirred for five hours. The mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc, 1:1) yielding 4-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2,4-ene (162 mg, 38 %). Spectroscopic results were comparable to those mentioned in section 3.2.1.5.

3.2.3.1 Synthesis of bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II)



A solution of 4-aminobutylaldehyde diethyl acetal (2.34 g, 14.5 mmol, 1 eq) in a mixture of 2 M aqueous HCl (20 mL) and diethyl ether (50 mL) at 0 °C was stirred for 20 minutes, after which it was basified with solid potassium carbonate and extracted with cold diethyl ether (3 x 50 mL) at 0 °C. The combined organic phases were dried over magnesium sulfate and filtered under gravity at 0 °C. Zinc iodide (2.08 g, 7.2 mmol) was added to the reaction mixture and the whole was stirred at 0 °C under an atmosphere of dry nitrogen. After 30 minutes the precipitate formed was filtered off and washed with diethyl ether to yield bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) (2.2 g, 66 %), as a white solid.⁹³

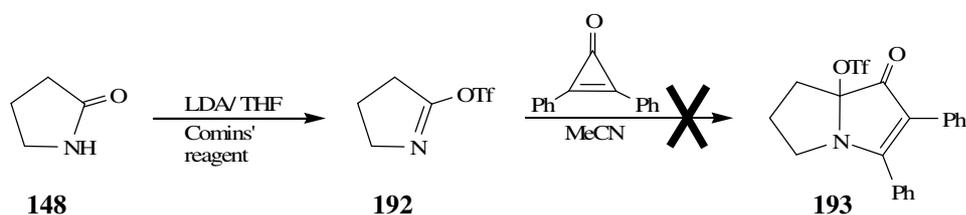
3.2.3.2 Synthesis of 5-hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2,4-diene



To a stirring solution of bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) (500 mg, 1.04 mmol, 1 eq) in chloroform (10 mL) was added diphenylcyclopropenone (214 mg, 1.04 mmol, 1 eq) and a solution of triethylamine (0.29 mL, 2.08 mmol, 2 eq) in water (2 mL). The reaction mixture was stirred at ambient temperature and was monitored by TLC and stopped after two and a half hours. Extraction with dichloromethane (4 x 10 mL), gave the organic layers which

were dried over magnesium sulfate and filtered under gravity. Evaporation of the solvent *in vacuo* gave a crude product which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2,4-ene (123 mg, 43%), as a yellow solid. Spectroscopic results were comparable to those mentioned in section 3.2.1.5.

3.2.4 Attempted synthesis of 5-triflyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A stirring solution of LDA (0.05 mL, 2 M in THF) in anhydrous tetrahydrofuran (2 mL) was cooled to $-78\text{ }^{\circ}\text{C}$. A solution of 2-pyrrolidinone (85.11 mg, 1 mmol) in anhydrous tetrahydrofuran (17 mL) was added, followed after 15 minutes by a solution of Comins' reagent (392.69 mg, 1 mmol) in anhydrous tetrahydrofuran (2 x 3 mL). LDA (0.5 mL, 2 M in THF, 1 mmol) was added and the temperature was maintained at $-78\text{ }^{\circ}\text{C}$ for another hour and allowed to warm to ambient temperature over three hours. The reaction mixture was diluted with hexane (20 mL) and washed with saturated aqueous sodium carbonate solution (10 mL). The organic layer was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was subjected to column chromatography (eluent: hexane: EtOAc, 2:1, 3:2, 1:1) which yielded the crude triflate (22 mg) which was divided into two fractions, to each of which was added anhydrous acetonitrile (7 mL) and diphenylcyclopropenone (11 mg, 1 eq) in one portion at ambient temperature under an atmosphere of dry nitrogen. Both mixtures were stirred for five days, but neither showed any reaction occurring, and produced only recovered triflate.

Triflate:

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 3.98 (2H, t, J 7.0, NCH_2), 2.68 (2H, t, J 8.0, OCCH_2), 2.23 (2H, quint, J 7.6, $\text{CH}_2\text{CH}_2\text{CH}_2$).

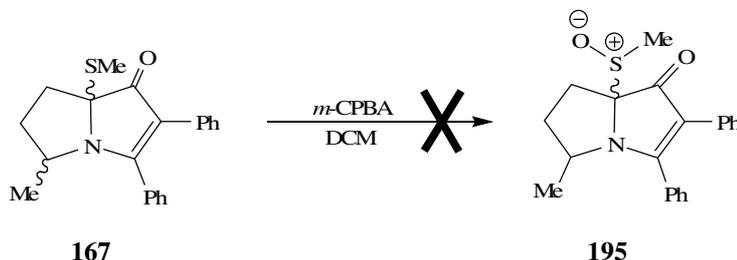
$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 172.56 (q), 118.21 (q, CF_3), 48.97 (CH_2), 32.37 (CH_2), 18.96 (CH_2).

3.2.5 Attempted synthesis of 5-hydroxy-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of 5-methylthio-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (85 mg, 0.254 mmol, 1 eq) in tetrahydrofuran/ dichloromethane (4 mL, 1:1) was added sodium hydroxide (85 mg), in ethanol/ water (4 mL, 3:1). The reaction mixture was stirred for two hours at ambient temperature, followed by heating to reflux for three days. Upon completion, water (10 mL) was added turning the mixture from orange to bright yellow. Evaporation of the solvent gave a mixture which was subjected to column chromatography but no identifiable products were obtained.

3.2.6 Attempted synthesis of 5-methanesulfinyl-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

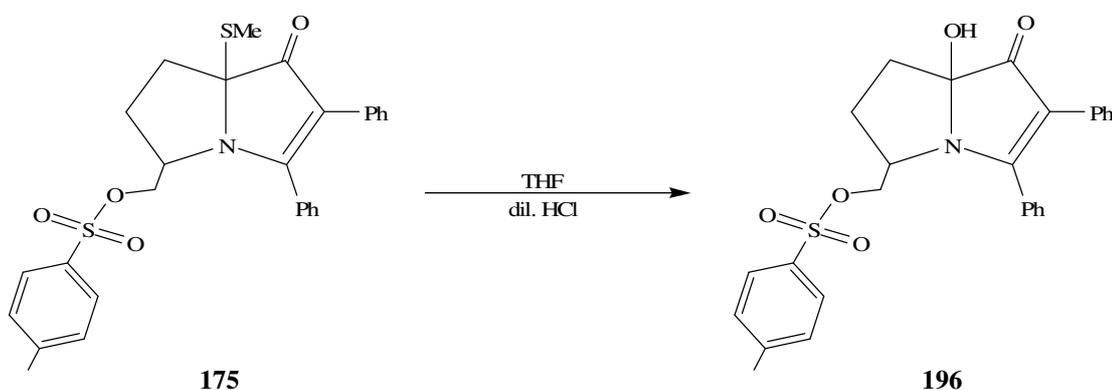
To a stirring solution of 5-methylthio-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (85 mg, 0.254 mmol, 1 eq) in anhydrous dichloromethane (5 mL) was added a solution of *meta*-chloroperoxybenzoic acid (43.8 mg, 0.254 mmol, 1 eq) in anhydrous dichloromethane (4 mL) at 0 – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for five and a half hours, before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (4 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was subjected to column chromatography but no identifiable products were obtained.

B:

To a stirring solution of 5-methylthio-8-methyl-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (62 mg, 0.185 mmol, 1 eq) in anhydrous dichloromethane (10 mL) was added a solution of *meta*-chloroperoxybenzoic acid (32 mg, 0.185 mmol, 1 eq) in anhydrous dichloromethane (5 mL) at 0 – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for four and a half hours, before being quenched with saturated aqueous sodium thiosulfate (15

mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and replaced with toluene (5 mL) and the mixture heated at reflux for four hours at which point TLC analysis showed a complex inseparable mixture.

3.2.7 Synthesis of 5-hydroxy-2,3-diphenyl-8(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one



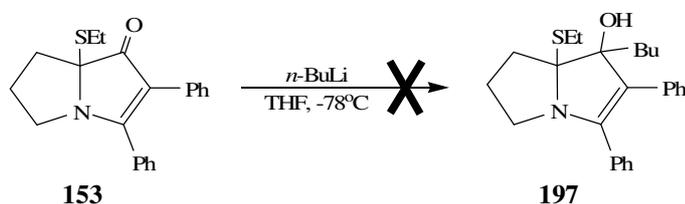
To a stirring solution of 5-methylthio-2,3-diphenyl-8(4-methylbenzenesulfonate)-1-azabicyclo[3.3.0]oct-2-en-4-one (228 mg, 0.45 mmol, 1 eq) in tetrahydrofuran (10 mL) was added water (0.5 mL) and concentrated HCl (0.5 mL). The resulting mixture was heated at reflux for four hours, after which time a complex multi-spot mixture was revealed by TLC. Purification by column chromatography yielded the title compound (<10 mg) as an orange oil.

¹H NMR δ (500.13 MHz, CDCl₃): 7.77 (2H, d, *J* 8.0, Ar), 7.40 – 7.30 (6H, m, Ar), 7.25 – 7.08 (4H, m, Ar), 7.05 (2H, bd, *J* 8.0, Ar), 4.26 (1H, dd, *J* 6.4, 10.1, OCHH), 4.06 (1H, dd, *J* 7.3, 10.1, OCHH), 3.55 - 3.51 (1H, m, NCHCH₂CH₂), 2.46 (3H, s, Me), 2.14 – 2.07 (4H, m, NCHCH₂CH₂).

^{13}C NMR δ (125 MHz, CDCl_3): 199.61 (q), 176.03 (q), 145.42 (q), 133.07 (q), 131.60 (CH), 130.90 (q), 130.80 (q), 130.27 (CH), 129.68 (CH), 129.25 (CH), 129.14 (CH), 128.36 (CH), 128.24 (CH), 126.78 (CH), 114.87 (q), 97.31 (q), 71.58 (CH_2), 58.50 (CH), 33.02 (CH_2), 29.70 (CH_2), 21.98 (CH_3).

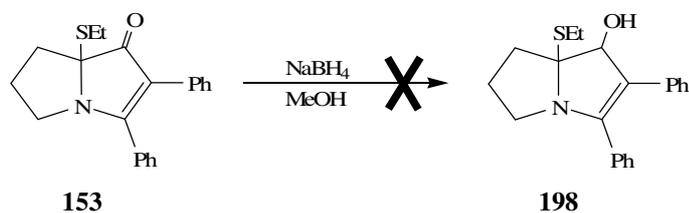
LRMS (ESI+): Found 498.1 $[\text{M}+\text{Na}]^+$, $\text{C}_{27}\text{H}_{25}\text{NNaO}_5\text{S}$, requires 498.

3.2.8 Attempted synthesis of 4-butyl-5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-ol



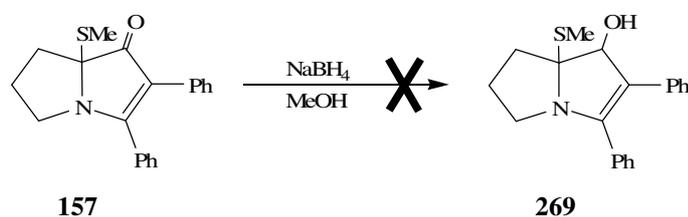
To a stirring solution of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (100 mg, 0.299 mmol, 1 eq) in anhydrous THF (5 mL) was added dropwise $n\text{BuLi}$ (1.6 M in hexane, 0.35 mL, 1.32 mmol, 0.89 eq) at -78°C under an atmosphere of dry nitrogen. The reaction mixture was stirred for an hour at -78°C and allowed to reach ambient temperature, before being quenched with saturated aqueous ammonium chloride (2 mL) and stirred for ten minutes, followed by the addition of water (5 mL) and ethyl acetate (10 mL). The resulting mixture was extracted using further portions of ethyl acetate (2 x 10 mL), dried over magnesium sulfate and filtered under gravity. The crude product was analysed by thin layer chromatography, but no indication of any new product could be observed, the starting material (~90 mg) was recovered.

3.2.9 Attempted synthesis of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-ol



To a stirring solution of 5-ethylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (162 mg, 0.484 mmol, 1 eq) in methanol (5 mL) at 0 °C was added sodium borohydride (84 mg, 2.21 mmol, 4.6 eq) in one portion under an atmosphere of dry nitrogen. The reaction mixture was maintained between 0 – -10 °C for three and a half hours and allowed to reach ambient temperature. The reaction had a mixture of dichloromethane (10 mL) and saturated sodium hydrogen carbonate (5 mL) added and was further stirred for 20 minutes. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), dried over magnesium sulfate and filtered under gravity. The crude product was analysed by thin layer chromatography, but no indication of any new product or starting material was observed.

3.2.10 Attempted synthesis of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-ol

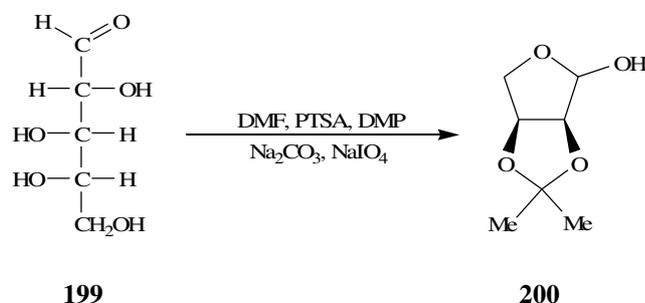


To a stirring solution of 5-methylthio-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one (101 mg, 0.315 mmol, 1 eq) in methanol (5 mL) at 0 °C was added sodium borohydride (48 mg, 1.26 mmol, 4.6 eq) in one portion under an atmosphere of dry nitrogen. The reaction mixture

was maintained between 0 – -10 °C for three and a half hours and allowed to reach ambient temperature. Dichloromethane (10 mL) and saturated sodium hydrogen carbonate (5 mL) were added and the mixture was further stirred for 20 minutes. The resulting mixture was extracted with ethyl acetate (3 x 10 mL), dried over magnesium sulfate and filtered under gravity. The crude product was analysed by thin layer chromatography, but no indication of any new product or starting material could be observed.

3.3 Synthesis of polyhydroxylated pyrrolizidines

3.3.1 Synthesis of 2,3-*O*-isopropylidene-L-erythrose

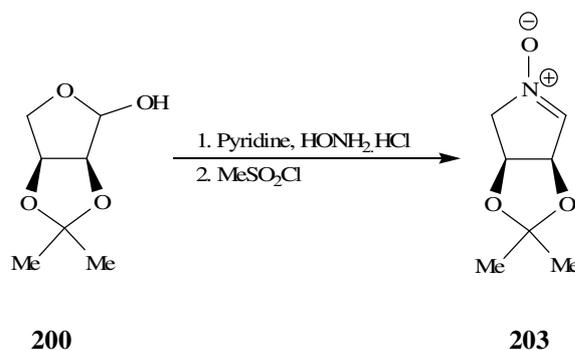


To a stirring solution of L-arabinose (10.15 g, 67.7 mmol, 1 eq), in dimethylformamide (130 mL) was added p-toluenesulfonic acid (150 mg, 0.79 mmol) and 2,2-dimethoxypropane (27 mL) at ambient temperature and the mixture was stirred overnight. Anhydrous sodium carbonate was used to neutralise the mixture, the excess removed by filtration and the solution then concentrated. The crude product was partitioned between water (120 mL) and 40-60 petroleum ether (60 mL), the aqueous layer was separated and placed in a round bottom flask, wrapped in foil and had sodium periodate (35.6 g) added in small aliquots (3 g) every ten minutes at 0 °C. Upon completion, the reaction yielded a white slurry in a colourless solution. The reaction mixture was neutralised with anhydrous sodium carbonate and stirred for an hour. The aqueous layer was decanted off and extracted with ethyl acetate (3 x 100 mL), whilst the remaining white slurry was dissolved in ethyl acetate (100 mL) and stirred for an hour. The combined ethyl acetate layers were dried over magnesium sulfate, filtered under gravity and concentrated and purified by column chromatography (eluent: hexane, EtOAc, 3:1) to yield 2,3-*O*-isopropylidene-L-erythrose (5.59 g, 52 %) as a yellow oil, with data consistent with that reported in the literature⁹⁵⁻⁹⁷ and a quantity (455 mg, 3 %) of the diprotected arabinose given as a white solid, the data for which is:-

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 5.50 (1H, d, J 5.0, OCCHCHCHCH_2), 4.56 (1H, dd, J 2.3, 7.9, OCCHCHCHCHCHH), 4.30 (1H, dd, J 2.3, 5.0, OCCHCHCHCHCHH), 4.22 (1H, bd, OCCHCHCHCHCH_2), 3.82 (1H, dd, J 1.9, 13.0, OCCHCHCHCHCH_2), 3.66 (1H, bd, OCCHCHCHCHCH_2), 1.52 (3H, s, O_2CCH_3), 1.48 (3H, s, O_2CCH_3), 1.34 (3H, s, O_2CCH_3), 1.33 (3H, s, O_2CCH_3).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 109.19 (q), 108.70 (q), 96.17 (CH), 71.04 (CH), 70.80 (CH), 70.13 (CH), 60.44 (CH_2), 26.34 (CH_3), 26.31 (CH_3), 25.24 (CH_3), 24.50 (CH_3).

3.3.2 Synthesis of (3S,4R)-3,4-isopropylidenedioxypyrroline 1-oxide



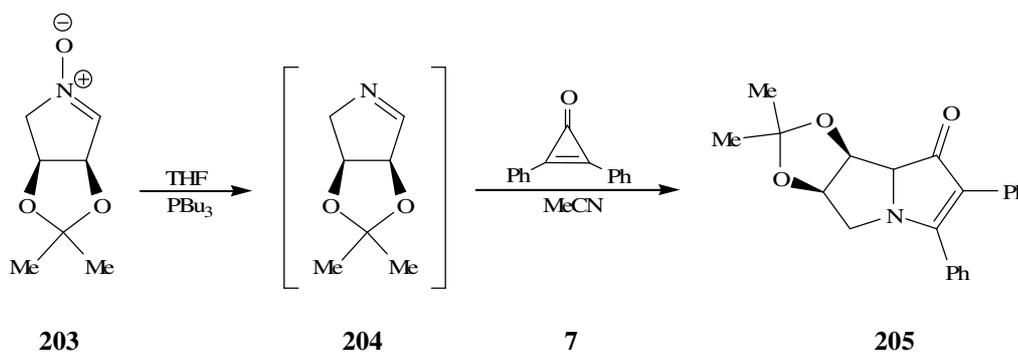
To a solution of 2,3-*O*-isopropylidene-*L*-erythrose (1.01 g, 6.3 mmol, 1 eq) in dry pyridine (12 mL) with 3Å activated molecular sieves (5 g) was added a solution of hydroxylamine hydrochloride (5.264 mg, 7.6 mmol, 1.2 eq) at ambient temperature under an atmosphere of dry nitrogen and the mixture was stirred overnight. A solution of methanesulfonyl chloride (585 μL , 7.56 mmol, 1.2 eq) in dry pyridine (12.6 mL) was added to the reaction mixture which was stirred for 24 hours. Dichloromethane (12 mL) was added and the mixture was filtered under vacuum with the aid of a celite plug.⁹⁸⁻¹⁰⁰ The solvent was removed *in vacuo* and purified by column chromatography (eluent: hexane: EtOAc, 2:1) to yield (3S,4R)-3,4-isopropylidenedioxypyrroline 1-oxide (133 mg, 13 %) as a orange solid, with NMR data comparable with that quoted in the literature.^{98,100}

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 6.75 (1H, b, $\text{ON}=\text{CHCH}$), 5.18 (1H, b, ONCHCH), 4.79 (1H, b, ONCH_2CH), 4.02 (1H, bd, J 13.0, ONCHHCH), 3.86 (1H, bd, J 14.6, ONCHHCH), 1.30 (3H, s, CH_3), 1.22 (3H, s, CH_3).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 133.03 (CH), 111.90 (q), 79.76 (CH), 73.60 (CH), 29.58 (CH_2), 27.08 (CH_3), 25.56 (CH_3).

$\text{IR } \nu_{\text{max}}$ (cm^{-1}): 2964 (s), 2932 (s), 2875 (m), 1846 (s), 1683 (w), 1599 (m).

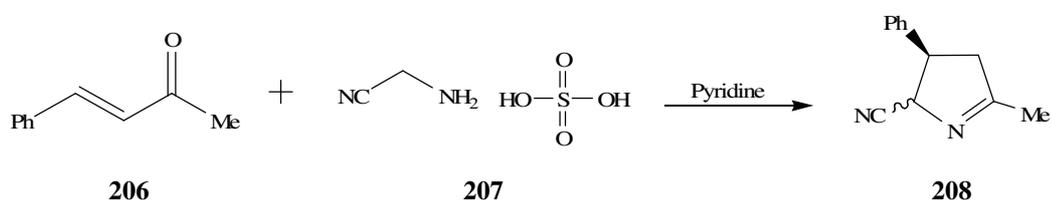
3.3.3 Attempted synthesis of 2,3-diphenyl-5,6-isopropylidenedioxy-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of (3S,4R)-3,4-isopropylidenedioxypyrroline 1-oxide (26 mg, 0.166 mmol, 1 eq) in dry tetrahydrofuran (2 mL) was added tributylphosphine (0.1 mL, 2 eq) [caution pyrophoric] at 65 °C under an atmosphere of dry nitrogen. These conditions were maintained for 48 hours. The mixture was allowed to cool to ambient temperature and a solution of diphenylcyclopropenone (34 mg, 0.166 mmol, 1 eq) in anhydrous acetonitrile (15 mL) was added. The resulting mixture was stirred for four days under an atmosphere of dry nitrogen, after which TLC showed a clear new product. The solvent was removed *in vacuo* and the crude product was purified by column chromatography (eluent: PE: EtOAc, 1:1)[see discussion – the very late arrival of tributylphosphine (due to shipping restrictions) prevented a more thorough investigation of the process].

3.4 Synthesis of a highly substituted, functionalised pyrrolizidine

3.4.1 Synthesis of 2-methyl-4-phenyl-5-cyano-1*H*-pyrroline



A:

To a stirring solution of aminoacetonitrile bisulfate (494 mg, 3.21 mmol) in anhydrous pyridine (25 mL) was added 4-phenyl-3-buten-2-one (854 mg, 5.84 mmol) and the mixture was heated at reflux for two hours under an atmosphere of dry nitrogen. A further aliquot of aminoacetonitrile bisulfate (494 mg, 3.21 mmol) was added due to the presence of 4-phenyl-3-buten-2-one as judged by TLC and the mixture was heated at reflux for a further two hours. TLC analysis showed the remaining presence of 4-phenyl-3-buten-2-one therefore another aliquot of aminoacetonitrile bisulfate (250 mg, 1.62 mmol) was added and the mixture was heated at reflux for two hours. The reaction mixture was diluted with ethyl acetate (15 mL), washed with sodium hydrogen carbonate (25 mL), dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluent: hexane: EtOAc, 1:1) yielding the title compound (15 mg, 1.4 %), as a brown oil, with data consistent with that previously reported for the *trans* isomer.¹⁰²

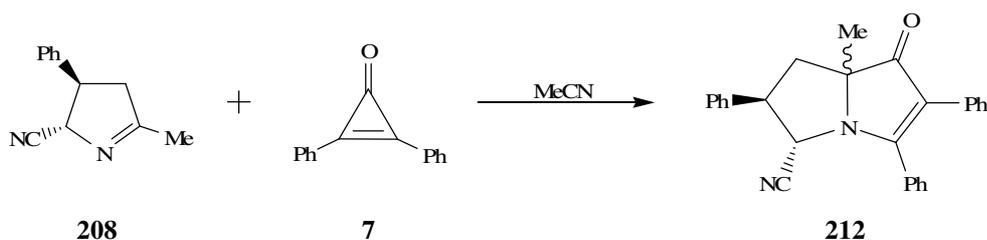
¹H NMR δ (400.13 MHz, CDCl₃): 7.39 – 7.27 (3H, m, Ar), 7.24 – 7.19 (2H, m, Ar), 4.72 – 4.66 (1H, m, NCHCN), 3.80 (1H, ddd, *J* 7.5, 7.6, 9.5, NCHCHCH₂C), 3.21 (1H, ddd, *J* 1.0, 9.5, 17.9, NCHCHCHHC), 2.83 (1H, ddd, *J* 1.0, 7.6, 17.9, NCHCHCHHC), 2.18 (3H, s, CH₃).

^{13}C NMR δ (100 MHz, CDCl_3): 180.13 (q), 140.32 (q), 129.37 (CH), 127.92 (CH), 126.85 (CH), 119.56 (q), 68.95 (CH), 49.27 (CH), 47.65 (CH_2), 20.07 (CH_3).

B:

To a stirring solution of aminoacetonitrile bisulfate (1.04 g, 6.75 mmol) in anhydrous pyridine (20 mL) was added 4-phenyl-3-buten-2-one (1.08 g, 7.43 mmol) and the mixture was heated at reflux for two hours under an atmosphere of dry nitrogen. The reaction mixture was allowed to cool to ambient temperature before being diluted with ethyl acetate (15 mL) washed with saturated aqueous sodium hydrogen carbonate (25 mL), dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude product was purified by column chromatography to yield the title compound (630 mg, 51 %) as a dark brown oil, identical to that described above.

3.4.2 Synthesis of 5-methyl-2,3,7-triphenyl-8-cyano-1-azabicyclo[3.3.0]oct-2-en-4-one



Diphenylcyclopropenone (80 mg, 0.39 mmol, 1 eq) was added to a stirring solution of the pyrroline (72 mg, 0.39 mmol, 1 eq) in anhydrous acetonitrile (10 mL). The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for three days. The solvent was removed *in vacuo* and the mixture was purified by column chromatography (eluent: hexane: EtOAc, 1:1), to give both starting materials plus the required product (2 mg, 1 %). The recovered starting materials were redissolved in anhydrous acetonitrile (10 mL) and

the mixture was heated at reflux for two days, after which it was concentrated and the residue subjected to column chromatography (eluent: hexane: EtOAc, 1:1) to give 5-methyl-2,3,7-triphenyl-8-cyano-1-azabicyclo[3.3.0]oct-2-en-4-one (26 mg, 17 %), as a mixture of two diastereoisomers in a 1:1.5 ratio.

¹H NMR δ (500.13 MHz, CDCl₃): 7.60 – 7.16 (both diastereoisomers, 30H, m, Ar), 4.59 (1H, d, *J* 6.8, CH), 4.25 – 4.18 (1H, m, CH), 3.77 (1H, d, *J* 8.3, CH), 3.71 (1H, q, *J* 7.2, CH), 2.88 (1H, dd, *J* 7.6, 13.6, CHH), 2.46 (1H, dd, *J* 6.5, 13.0, CHH), 2.41 – 2.27 (1H, m, CHH), 2.21 (1H, dd, *J* 7.3, 13.6, CHH), 1.74 (3H, s, CH₃), 1.43 (3H, s, CH₃).

¹³C NMR δ (125 MHz, CDCl₃): 205.03 (q), 202.24 (q), 174.16 (q), 172.67 (q), 137.63 (q), 137.16 (q), 132.09 (CH), 131.92 (CH), 131.72 (q), 131.04 (q), 131.00 (q), 130.47 (q), 130.28 (CH), 130.24 (CH), 129.53 (CH), 129.45 (CH), 129.27 (CH), 129.18 (CH), 128.69 (CH), 128.52 (CH), 128.44 (CH), 127.35 (CH), 127.29 (CH), 127.10 (CH), 122.66 (q), 119.74 (q), 117.47 (q), 115.38 (q), 76.27 (q), 74.86 (q), 56.99 (CH), 56.05 (CH), 53.38 (CH), 51.04 (CH), 39.25 (CH₂), 38.80 (CH₂), 26.20 (CH₃), 22.72 (CH₃).

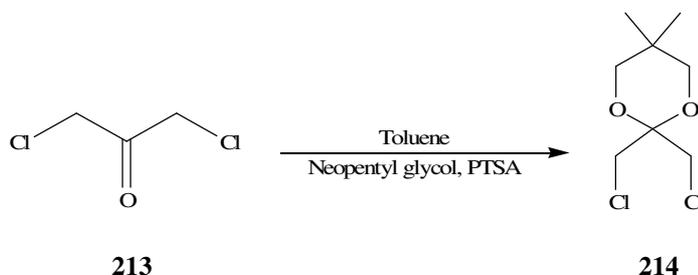
HRMS (ESI+): Found 413.1624 [M+Na]⁺, requires C₂₇H₂₂N₂NaO 413.1624.

IR ν_{\max} (cm⁻¹): 3400 (br), 3063 (w), 3017 (m), 2926 (s), 2853 (m), 2250 (vw), 1683 (vs), 1603(s).

3.5 Cyclopropenones

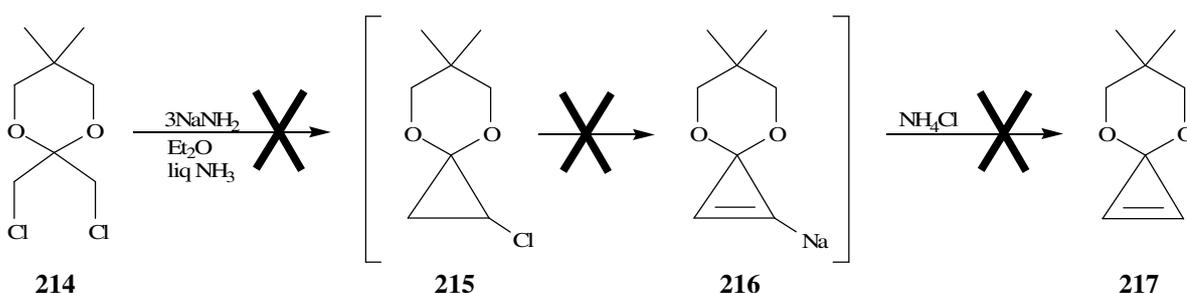
3.5.1 Unsubstituted cyclopropenones

3.5.1.1 Synthesis of dichloroacetone acetal



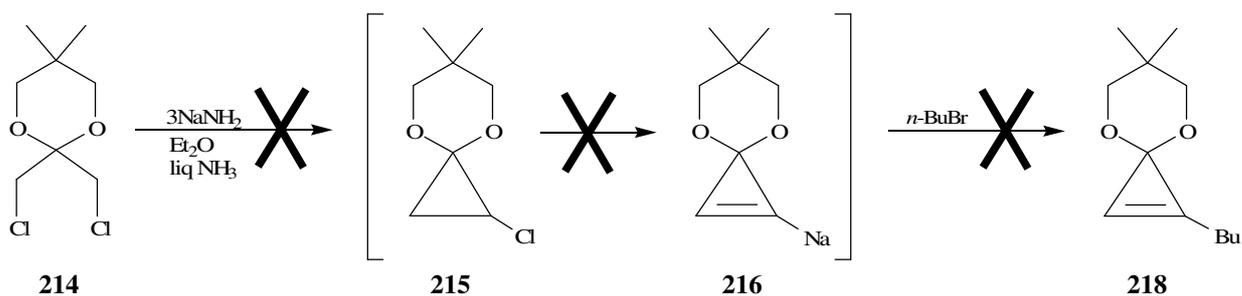
To a stirring solution of 1,3-dichloroacetone (25 g, 0.197 mol, 1 eq) in toluene (150 mL) was added neopentyl glycol (22.6 g, 0.2166 mol, 1.1 eq) followed by *p*-toluene sulfonic acid (0.75 g, 3.94 mmol, 0.02 eq). The reaction mixture was warmed to reflux for 24 hours with azeotropic removal of water (Dean-Stark trap) followed by extraction with hexane (120 mL) and washing with saturated aqueous sodium hydrogen carbonate (50 mL). The organic phase was washed with water (50 mL) followed by saturated sodium chloride (50 mL) and dried over magnesium sulfate and filtered under gravity. The solvent was removed under vacuum and the crude material yielded dichloroacetone acetal (37 g, 88 %), as a white solid with data as reported in the literature.^{36,35}

3.5.1.2 Attempted synthesis of 6,6-trimethyl-4,8-dioxaspiro[2.5]oct-1-ene



To a stirring solution of sodium amide (6.51 g, 166.8 mmol, 3.55 eq) in dry liquid ammonia (70 mL) at $-70\text{ }^{\circ}\text{C}$ was added dichloroacetone acetal (10 g, 46.9 mmol, 1 eq) in freshly distilled ether (25 mL) dropwise over 40 minutes. The reaction was stirred for an hour below $-50\text{ }^{\circ}\text{C}$. An additional portion of sodium amide (1 g) was added and the reaction was stirred below $-50\text{ }^{\circ}\text{C}$ for a further 30 minutes. Ammonium chloride (3.13 g, 58.41 mmol, 1.2 eq) in dry ether (20 mL) was added slowly over 45 minutes to the reaction mixture which was maintained at $-70\text{ }^{\circ}\text{C}$, and stirred for an additional 10 minutes. Once the cooling bath had reached $-50\text{ }^{\circ}\text{C}$, ammonium chloride (6 g) was added slowly over 30 minutes. The cooling bath was removed and dry ether (70 mL) was added slowly to the mixture. The resulting mixture was stirred overnight, but analysis showed no identifiable products.

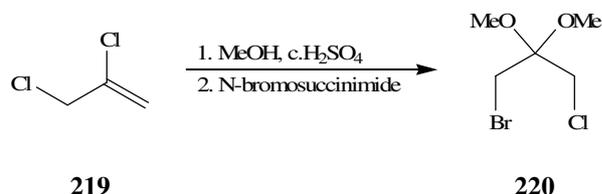
3.5.1.3 Attempted synthesis of 1-butyl-6,6-dimethyl-4,8-dioxaspiro[2.5]oct-1-ene



To a stirring solution of sodium amide (5.20 g, 130 mmol, 3.07 eq) in dry ammonia (35 mL) at $-70\text{ }^{\circ}\text{C}$ was added dichloroacetone acetal (9 g, 42.3 mmol, 1 eq) in freshly distilled ether (25 mL) dropwise over 40 minutes. The reaction was stirred for an hour below $-50\text{ }^{\circ}\text{C}$. An additional portion of sodium amide (1 g) was added and the mixture was stirred below $-50\text{ }^{\circ}\text{C}$ for a further 30 minutes. 1-Bromobutane (4.6 mL, 42.3 mmol, 1 eq) in dry ether (20 mL) was added slowly over 45 minutes to the reaction mixture which was maintained at $-70\text{ }^{\circ}\text{C}$, and stirred for an additional ten minutes. Once the cooling bath had warmed to $-50\text{ }^{\circ}\text{C}$, ammonium chloride (6 g) was added slowly over 30 minutes. The cooling bath was removed and dry

ether (70 mL) was added slowly to the mixture. The resulting mixture was stirred overnight, but analysis showed no identifiable products.

3.5.1.4 Synthesis of 1-bromo-3-chloro-2,2-dimethoxypropane

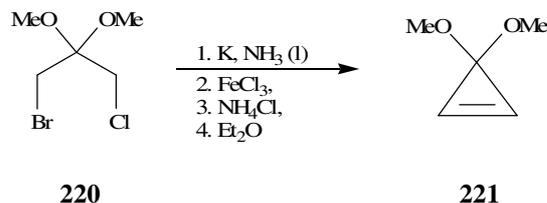


To a stirring solution of 2,3-dichloro-1-propene (9.1 mL, 99.13 mmol, 1 eq) in anhydrous methanol (30 mL) with conc. sulfuric acid (two drops) was added *N*-bromosuccinimide (18 g, 1 eq) in small portions over one and a half hours. The reaction mixture was stirred for an hour at ambient temperature followed by the addition of anhydrous sodium carbonate (500 mg) to neutralize the catalyst. After a further 20 minutes of stirring the mixture was washed with water (30 mL), followed by the extraction of the aqueous layer with pentane (2 x 50 mL). The organic phases were combined and washed twice with an equimolar amount of water, dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* to give a semi-crystalline mass which was dissolved in refluxing pentane (25 mL) and cooled in an acetone/ liquid nitrogen bath for 30 minutes. The mixture was filtered under vacuum to yield a white crystalline solid (4.67 - 7.60 g, 22 - 36 %), with NMR data as reported in the literature.³⁴

¹H NMR δ (400.13 MHz, CDCl₃): 3.70 (2H, s, ClCH₂), 3.55 (2H, s, BrCH₂), 3.30 (6H, s, 2 x OCH₃).

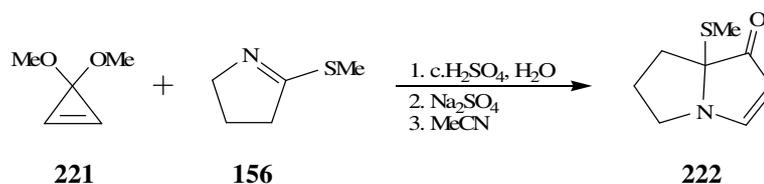
¹³C NMR δ (100 MHz, CDCl₃): 100.65 (q), 49.49 (CH₃), 41.75 (CH₂), 29.91 (CH₂).

3.5.1.5 Synthesis of 3,3-dimethoxycyclopropene



Potassium metal (125 mg) was added to liquid ammonia (~90 mL) condensed from a commercial cylinder at -78 °C. Upon the solution turning blue, the cooling bath was removed and anhydrous iron (III) chloride (~13 mg) was added to the reaction mixture. As the reaction started to reflux the colour changed to light grey and potassium metal (2.93 g) was added in small portions over 15 minutes maintaining the temperature to give a gentle reflux. 1-Bromo-3-chloro-2,2-dimethoxypropane (5.43 g, 24.97 mmol, 1 eq) in anhydrous ether (15 mL) was added dropwise over ten minutes maintaining the mixture at -60 °C for three hours. Solid ammonium chloride (2.7 g) was added and the mixture was allowed to stir for ten minutes; the liquid ammonia was evaporated by removing the cooling bath, whilst simultaneously adding anhydrous diethyl ether (~90 mL). The mixture was filtered from its inorganic salts upon reaching ~0 °C. The ethereal solution was cooled to 0 °C and concentrated by applying a vacuum (50 – 80 mm) through a condenser held at -25 °C. The ethereal solution was held at 0 °C and concentrated by applying a vacuum (50 – 80 mm) through a condenser cooled at -25 °C until ~20 mL of solution was present (2-3 hours). The cyclopropenone acetal was used in this form; further concentration resulted in significant loss of material. A small amount was concentrated and analysed – the NMR data was as reported in the literature.³⁴

3.5.1.6 Synthesis of 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring mixture of dimethylcyclopropenone acetal in dichloromethane (20 mL) was added a solution of conc. sulfuric acid (three drops) in water (5 mL) dropwise at 0 °C. The reaction mixture was stirred for three hours followed by the addition of anhydrous sodium sulfate (30 g) added in small portions. The mixture was filtered and the solvent evaporated at 50 – 80 mm with a water bath maintained at 0 – 10 °C. The brown viscous residue of crude cyclopropenone was dissolved in anhydrous acetonitrile (6 mL) and was added to a solution of 2-methylthio-1-pyrroline (2.048 g) in dry acetonitrile (4 x 3 mL) turning the solution a brown/ red colour (exothermic). The mixture was allowed to stir over three nights, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 1:1), yielding a crude mixture of products (335 mg). A small sample (40 mg) was further purified by flash chromatography (hexane: EtOAc, 1:1) yielding 5-methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one (36 mg), as a brown/ orange oil.

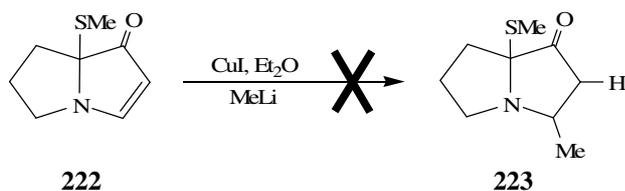
$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.77 (1H, d, J 3.5, NCHCH), 5.30 (1H, d, J 3.5, NCHCH), 3.52 (1H, dt, J 7.4, 11.2, NCHH) 3.32 (1H, ddd, J 4.1, 7.1, 11.2, NCHH), 2.21 – 1.97 (3H, m, CHH + CH_2), 1.96 (3H, s, CH_3), 1.89 (1H, dd, J 6.6, 12.5, CHH).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 203.86 (q), 169.31 (CH), 105.57 (CH), 79.78 (q), 48.79 (CH_2), 33.18 (CH_2), 27.38 (CH_2), 12.16 (CH_3).

HRMS (ESI+): Found 192.0454, $\text{C}_8\text{H}_{11}\text{NOSNa}$, requires 192.0454.

IR ν_{max} (cm^{-1}): 3454 (br), 2980 (m), 2920 (w), 2889 (w), 1681 (vs), 1533 (s).

3.5.1.7 Attempted synthesis of 2-methyl-5-methylthio-1-azabicyclo[3.3.0]octan-4-one

**A:**

To a stirring suspension of copper iodide (81.1 mg, 0.426 mmol, 1.2 eq) in anhydrous diethyl ether (15 mL) at 0 °C was added methyllithium (1.6 M, 0.44 mL, 0.71 mmol, 2 eq). Upon addition the colour changes to yellow and quickly fades to a straw yellow. 5-Methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one (60 mg, 0.36 mmol, 1 eq) in anhydrous diethyl ether (2 x 5 mL) was added over three minutes at -78 °C and the mixture was allowed to warm up slowly in the cooling bath overnight. Saturated aqueous ammonium chloride (5 mL) was added to the mixture which was allowed to stir for an hour in the cooling bath followed by the addition of brine (10 mL). The resulting mixture was extracted with ethyl acetate (4 x 10 mL), dried over magnesium sulfate and filtered under gravity. No identifiable products or starting material could be observed.

B:

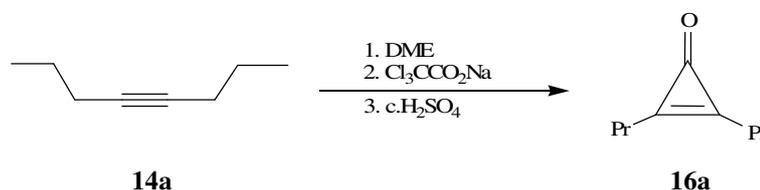
To a stirring suspension of copper iodide (81.1 mg, 0.426 mmol, 1.2 eq) in anhydrous diethyl ether (15 mL) at 0 °C was added methyllithium (1.6 M, 0.44 mL, 0.71 mmol, 2 eq). Upon addition the colour changes to yellow and quickly fades to a straw yellow. 5-Methylthio-1-azabicyclo[3.3.0]oct-2-en-4-one (60 mg, 0.36 mmol, 1 eq) in anhydrous tetrahydrofuran (20 mL) was added to the reaction mixture over three minutes at -78 °C and the mixture was allowed to warm up slowly to -20 °C in the cooling bath over 80 minutes. Saturated aqueous ammonium chloride (5 mL) at 0 °C was added and the mixture stirred overnight. Brine (10 mL) was added and the mixture was allowed to stir for 15 minutes, and extracted with ethyl

acetate (4 x 10 mL), dried over magnesium sulfate and filtered under gravity. No identifiable products or starting material could be observed.

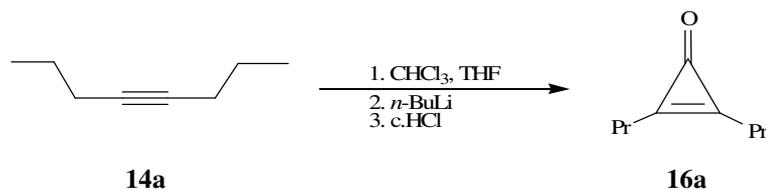
3.5.2 Synthesis of dialkylcyclopropenone

3.5.2.1 Synthesis of dipropylcyclopropenone

Method 1¹⁰⁴



To a stirring solution of 4-octyne (3 mL, 20.4 mmol, 1 eq) in anhydrous 1,2-dimethoxyethane (100 mL) was added sodium trichloroacetate (18.5 g, 100 mmol, 4.9 eq). The reaction mixture was heated at reflux for 24 hours under an atmosphere of dry nitrogen and allowed to cool to ambient temperature, whereupon 50 % aqueous sulfuric acid (200 mL) was added and the mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were neutralised by washing with saturated aqueous sodium hydrogen carbonate and washed with saturated aqueous sodium chloride. The resulting organic layer was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and purified by column chromatography (eluent: hexane, with slow addition of EtOAc) to yield dipropylcyclopropenone (840 mg, 29 %). Spectroscopic data was as shown after Method 2, below.

Method 2³²

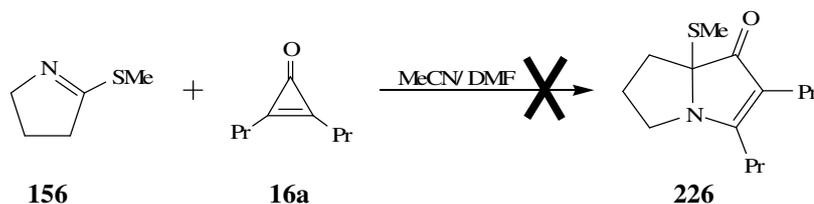
To a stirring solution of 4-octyne (0.29mL, 2 mmol, 1 eq) and chloroform (0.4 mL, 5 mmol, 2.5 eq) in anhydrous tetrahydrofuran (25 mL) was added *n*-butyllithium, (1.6 M in hexane, 2.8 mL, 4.4 mmol, 2.2 eq) dropwise over 100 minutes at -78 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred and maintained at -78 °C for four hours. Conc. HCl (2 mL) was added dropwise over ten minutes. The cooling bath was removed and the mixture had a further ten minutes stirring followed by the addition of water (25 mL). The resulting mixture was extracted using dichloromethane (5 x 25 mL), and the combined organic extracts were dried over magnesium sulfate and filtered under gravity, to give the pure dipropylcyclopropenone (238 mg, 86 %).

¹H NMR δ (400.13 MHz, CDCl₃): 2.47 – 2.38 (4H, m, CCH₂CH₂CH₃), 1.61 – 1.50 (4H, m, CCH₂CH₂CH₃), 0.86 (6H, t, *J* 7.2, CCH₂CH₂CH₃).

¹³C NMR δ (100 MHz, CDCl₃): 160.68 (q), 160.06 (q), 28.11 (CH₂), 19.61 (CH₂), 13.63(CH₃).

IR ν_{max} (cm⁻¹): 3468 (br), 2963 (m) 2934 (w), 2875 (w), 1840 (vs), 1629 (s), 1461 (m), 1382 (w).

3.5.2.2 Attempted synthesis of 5-methylthio-2,3-dipropyl-1-azabicyclo[3.3.0]oct-2-en-4-one



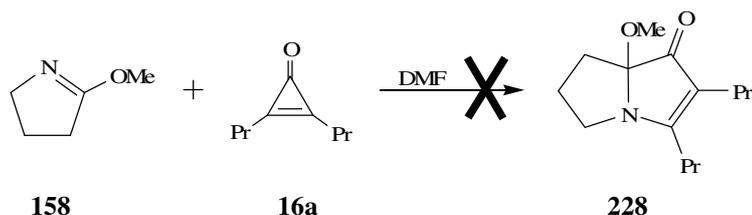
A:

To a stirring solution of 2-methylthio-1-pyrroline (57.5 mg, 0.5 mmol, 1 eq) in acetonitrile (10 mL) was added dipropylcyclopropenone (71.4 mg, 0.52 mmol, 1.04 eq). The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen overnight, but yielded no identifiable products. The mixture was thus heated at reflux for a week, concentrated but only the dipropylcyclopropenone was recovered.

B:

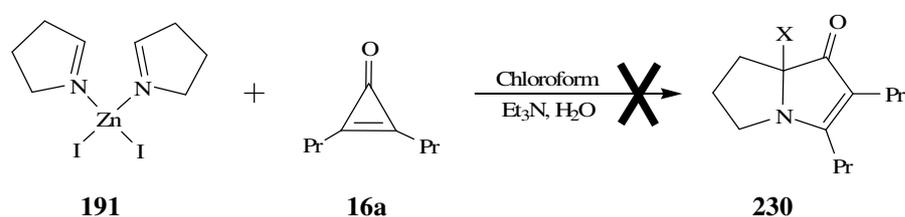
To a stirring solution of dipropylcyclopropenone (71.4 mg, 0.52 mmol, 1.04 eq) in dimethylformamide (15 mL) was added 2-methylthio-1-pyrroline (57.5 mg, 0.5 mmol, 1 eq) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for 24 hours, but showed no reaction. Therefore the reaction mixture was heated at 100 °C for four days, concentrated but only the dipropylcyclopropenone was recovered.

3.5.2.3 Attempted synthesis of 5-methoxy-2,3-dipropyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A solution of dipropylcyclopropenone (149 mg, 1.08 mmol, 1 eq), and 2-methoxy-1-pyrroline (0.1 mL, 1.10 mmol, 1 eq) in dimethyl formamide (10 mL) was stirred at ambient temperature under an atmosphere of dry nitrogen for four days. TLC showed no reaction. The temperature was increased to 80 °C then 130 °C and finally to reflux. No identifiable products were observed.

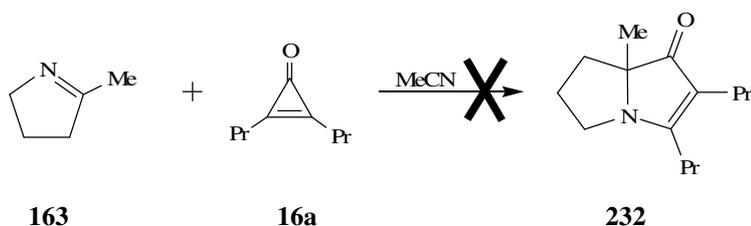
3.5.2.4 Attempted synthesis of 5-hydroxy-2,3-dipropyl-1-azabicyclo[3.3.0]oct-2-en-4-one/ 2,3-dipropyl-1-azabicyclo[3.3.0]oct-2-en-4-one



X = H/ OH

Dipropylcyclopropanone (152 mg, 1.10 mmol, 1 eq), triethylamine (0.15 mL, 1.10 mmol, 1 eq) and water (2 mL) was added to a stirring solution of bis(3,4-dihydro-2H-pyrrol-1-yl)diiodozinc (II) (251.8 mg, 0.551 mmol, 0.5 eq) in chloroform (8 mL). The reaction mixture was stirred at ambient temperature for four days. No identifiable products were observed.

3.5.2.5 Attempted synthesis of 5-methyl-2,3-dipropyl-1-azabicyclo[3.3.0]oct-2-en-4-one

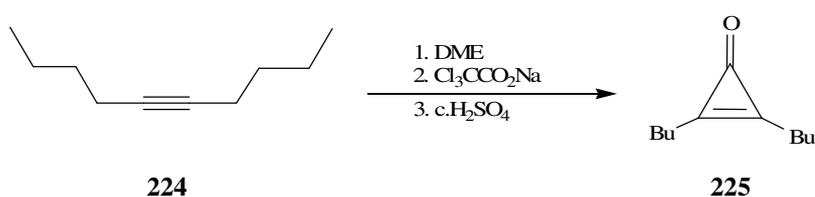


To a stirring solution of dipropylcyclopropanone (152 mg, 1.10 mmol, 1 eq) in anhydrous acetonitrile (10 mL) was added 2-methyl-1-pyrroline (0.1 mL, 1.10 mmol, 1 eq) at ambient

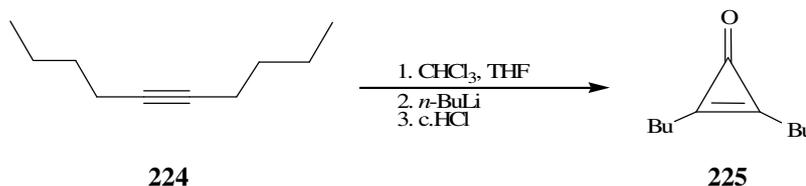
temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for four days. No identifiable products were observed. The mixture was heated at reflux for a further three days. No identifiable products were observed.

3.5.2.6 Synthesis of dibutylcyclopropenone

Method 1¹⁰⁴



To a stirring solution of 5-decyne (3 mL, 16.6 mmol, 1 eq) in anhydrous 1,2-dimethoxyethane (100 mL) was added sodium trichloroacetate (15.4 g, 83.14 mmol, 5 eq). The reaction mixture was heated at reflux for 48 hours under an atmosphere of dry nitrogen and allowed to cool to ambient temperature overnight, whereupon 50 % aqueous sulfuric acid (200 mL) was added and the mixture was extracted with dichloromethane (3 x 100 mL). The combined organic extracts were neutralised with saturated aqueous sodium hydrogen carbonate and washed with saturated aqueous sodium chloride. The resulting organic layer was dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and purified by column chromatography (gradient eluent: hexane: EtOAc 1:1, EtOAc, EtOAc: MeOH 10:1, 1:1) to yield dibutylcyclopropenone (290 mg, 11 %). Spectroscopic data was as shown after Method 2.

Method 2³²**A:**

To a stirring solution of 5-decyne (0.18 mL, 1 mmol, 1 eq) and chloroform (0.2 mL, 2.5 mmol, 2.5 eq) in anhydrous tetrahydrofuran (20 mL) was added *n*-butyllithium, (1.6 M in hexane, 1.4 mL, 2.2 mmol) dropwise over 80 minutes at -78 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred and maintained at -78 °C for four hours. Conc. HCl (1 mL) was added dropwise over ten minutes. The cooling bath was removed and the mixture allowed to stir for a further ten minutes followed by the addition of water (20 mL). The resulting mixture was extracted using dichloromethane (5 x 20 mL), and the combined organic extracts were dried over magnesium sulfate and filtered under gravity to give the pure product dibutylcyclopropenone (133 mg, 80 %).

B:

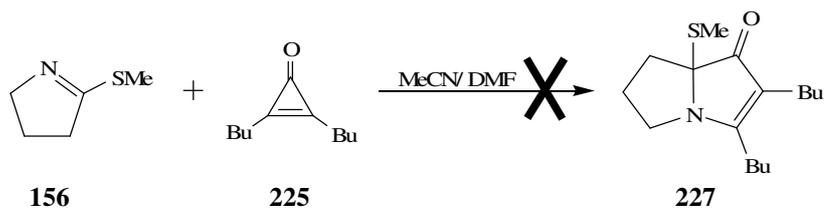
To a stirring solution of 5-decyne (0.9 mL, 5 mmol, 1 eq) and chloroform (1 mL, 12.5 mmol, 2.5 eq) in anhydrous tetrahydrofuran (20 mL) was added *n*-butyllithium, (1.6 M in hexane, 7 mL, 11 mmol, 2.2 eq) dropwise over 80 minutes at -78 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred and maintained at -78 °C for four hours. Conc. HCl (5 mL) was added dropwise over ten minutes. The cooling bath was removed and the mixture allowed to stir for a further ten minutes followed by the addition of water (20 mL). The resulting mixture was extracted using dichloromethane (5 x 20 mL), and the combined organic extracts were dried over magnesium sulfate and filtered under gravity to give the pure product dibutylcyclopropenone (758 mg, 91 %).

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 2.61 (4H, t, J 7.3, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.67 (4H, quint, J 7.3, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.42 (4H, sext, J 7.4, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.94 (6H, t, J 7.3, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 159.89 (q), 159.08 (q), 27.47 (CH_2), 25.16 (CH_2), 21.45 (CH_2), 12.73 (CH_3).

IR ν_{max} (cm^{-1}): 2957 (m) 2932 (m), 2872 (m), 2209 (w), 1840 (vs), 1672 (w), 1635 (s), 1465 (m).

3.5.2.7 Attempted synthesis of 5-methylthio-2,3-dibutyl-1-azabicyclo[3.3.0]oct-2-en-4-one



A:

To a stirring solution of 2-methylthio-1-pyrroline (115 mg, 1 mmol, 1 eq) in acetonitrile (10 mL) was added dibutylcyclopropenone (166 mg, 1 mmol, 1 eq). The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen for a week, but showed no identifiable products. The mixture was heated at reflux for a week, concentrated and purified by column chromatography but only the dibutylcyclopropenone was recovered.

B:

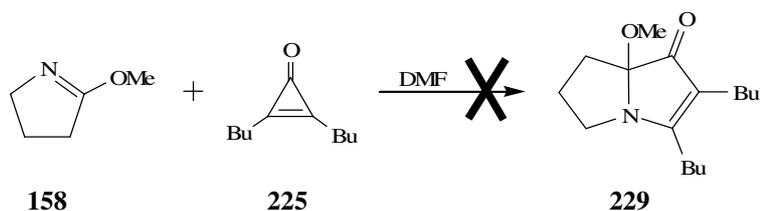
To a stirring solution of 2-methylthio-1-pyrroline (57.5 mg, 0.5 mmol, 1 eq) in acetonitrile (10 mL) was added crude dibutylcyclopropenone (66.5 mg, 0.4 mmol, 0.8 eq). The reaction mixture was stirred at ambient temperature under an atmosphere of dry nitrogen overnight,

but showed no change. The mixture was thus heated at reflux for a week, concentrated and purified by column chromatography but only the dibutylcyclopropenone was recovered.

C:

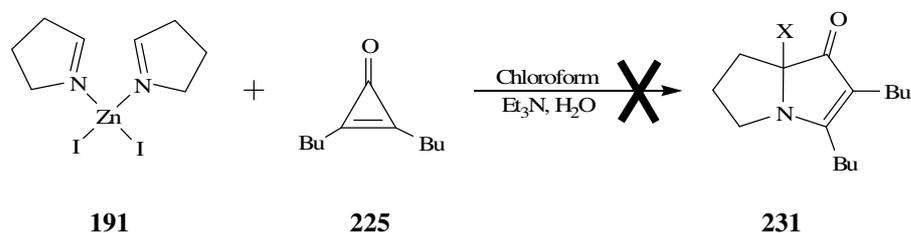
To a stirring solution of 2-methylthio-1-pyrroline (57.5 mg, 0.5 mmol, 1 eq) in dimethylformamide (15 mL) was added dibutylcyclopropenone (66.5 mg, 0.4 mmol, 0.8 eq) at ambient temperature under an atmosphere of dry nitrogen. The mixture was stirred for 24 hours, but showed no reaction occurring, and therefore the mixture was heated at 100 °C for four days, concentrated and purified by column chromatography but only the dibutylcyclopropenone was recovered.

3.5.2.8 Attempted synthesis of 5-methoxy-2,3-dibutyl-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of 2-methoxypyrroline (108 mg, 1.1 mmol, 1.9 eq) in dimethylformamide (10 mL) was added crude dibutylcyclopropenone (100 mg, 0.6 mmol, 1 eq) at ambient temperature and the mixture was stirred for 30 minutes under an atmosphere of dry nitrogen, followed by heating at reflux for 24 hours. No products could be identified.

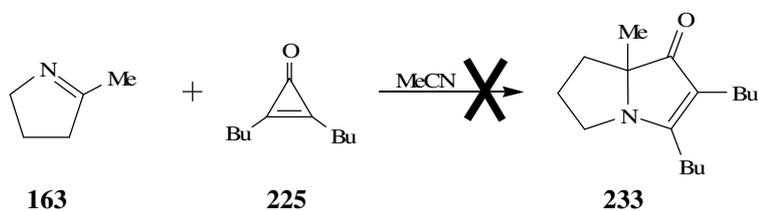
3.5.2.9 Attempted synthesis of 5-hydroxy-2,3-dibutyl-1-azabicyclo[3.3.0]oct-2-en-4-one/ 2,3-dibutyl-1-azabicyclo[3.3.0]oct-2-en-4-one



X = H/ OH

To a stirring solution of dibutylcyclopropanone (100 mg, 0.6 mmol, 1 eq) in chloroform (15 mL) was added bis(3,4-dihydro-2H-pyrrol-1-yl)di-iodozinc (II) (275 mg, 0.6 mmol, 1 eq) and a solution of triethylamine (0.167 mL, 1.2 mmol, 2 eq) in water (2 mL). The reaction mixture was stirred at ambient temperature for five days but only the dibutylcyclopropanone was recovered.

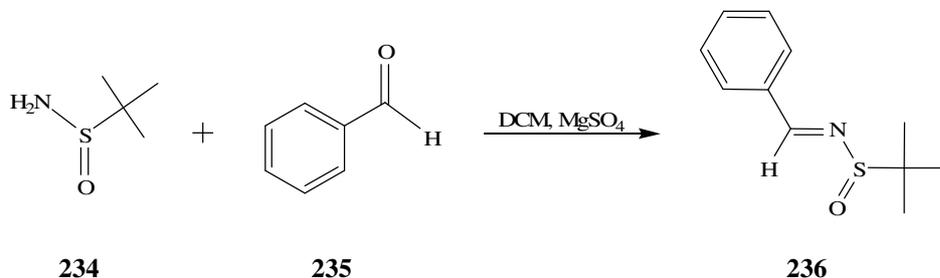
3.5.2.10 Attempted synthesis of 5-methyl-2,3-dibutyl-1-azabicyclo[3.3.0]oct-2-en-4-one



To a stirring solution of dibutylcyclopropanone (150 mg, 0.9 mmol, 1 eq) in anhydrous acetonitrile (10 mL) was added 2-methyl-1-pyrroline (86 μ L, 0.9 mmol, 1 eq) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for four days. No identifiable products were observed. The mixture was heated at reflux for a further three days. No identifiable products were observed.

3.6 Acyclic imines

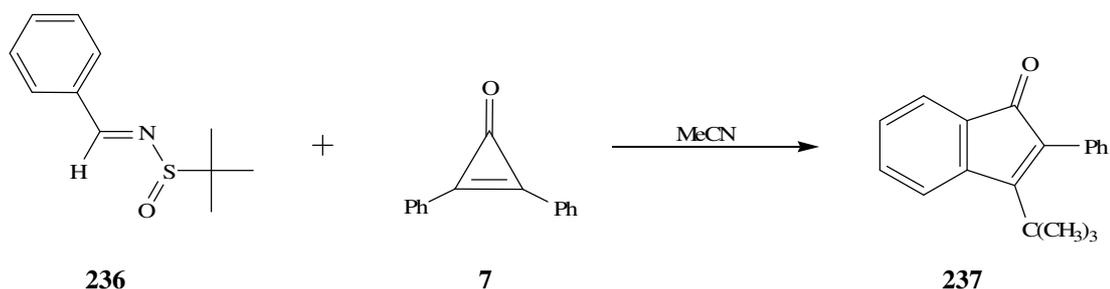
3.6.1 Synthesis of *N*-(benzylidene)-*t*-butanesulfinamide



To a stirring solution of 2-methyl-2-propanesulfinamide (252 mg, 2.08 mmol, 1 eq) in anhydrous dichloromethane (15 mL) was added magnesium sulfate (1.25 g, 10.4 mmol, 5 eq) and benzaldehyde (661 mg, 6.24 mmol, 3 eq) at ambient temperature under an atmosphere of dry nitrogen. Upon completion (24 hours) the reaction was filtered, concentrated and purified by column chromatography (hexane: EtOAc, 1:10) yielding *N*-(benzylidene)-*t*-butanesulfinamide (250 mg, 58 %), as an off white oil.¹⁰⁶

¹H NMR δ (400.13 MHz, CDCl₃): 8.63 (1H, s, NCH), 7.86 (2H, dd, *J* 1.7, 8.1, Ar) 7.50 – 7.45 (3H, m, Ar), 1.28 (9H, s (CH₃)₃).

¹³C NMR δ (100 MHz, CDCl₃): 163.29 (CH), 134.27 (q), 132.75 (CH), 129.19 (CH), 128.64 (CH), 58.11 (q), 22.84 (CH₃).

3.6.2 Synthesis of 3-*tert*-butyl-2-phenyl-1-indenone

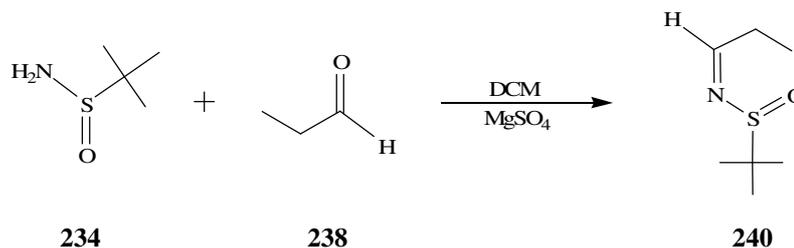
A solution of the imine (250 mg, 1.2 mmol, 1 eq) and diphenylcyclopropenone (247 mg, 1.2 mmol, 1 eq) in anhydrous acetonitrile (10 mL) was stirred at ambient temperature under an atmosphere of dry nitrogen for 48 hours, at which point a significant new spot was present. The reaction mixture was concentrated and purified by column chromatography (eluent: hexane: EtOAc 1:1) to give 3-*tert*-butyl-2-phenyl-1-indenone (41 mg, 13 %) as a yellow oil, a crystal was formed by slow evaporation of DCM.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.44 – 7.39 (2H, m, Ar), 7.42 (1H, td, J 1.2, 7.6, Ar), 7.38 – 7.33 (3H, m, Ar), 7.27 – 7.23 (1H, m, Ar), 7.18 – 7.15 (2H, m, Ar), 1.31 (9H, s, $\text{SC}(\text{CH}_3)_3$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 198.41 (q), 164.74 (q), 145.44 (q), 134.50 (q), 134.26 (q), 133.54 (CH), 131.70 (q), 130.53 (CH), 128.33 (CH), 127.91 (CH), 127.80 (CH), 124.22 (CH), 122.77(CH), 36.54 (q), 30.79 (CH_3)₃.

HRMS (ESI+): Found 285.1240 [$\text{M}+\text{Na}$]⁺, $\text{C}_{19}\text{H}_{18}\text{NNaO}$ requires 285.1250. [Structure was confirmed by X-ray crystallographic analysis].

3.6.3 Synthesis of *N*-(propylidene)-*tert*-butanesulfinamide

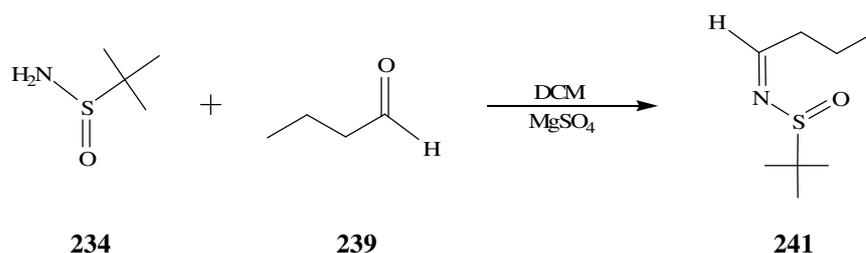


To a stirring solution of 2-methyl-2-propanesulfonamide (294 mg, 2.43 mmol, 1 eq) in anhydrous dichloromethane (15 mL) was added magnesium sulfate (1.46 g, 12.15 mmol, 5 eq) and propionaldehyde (0.53 mL, 7.29 mmol, 3 eq) at ambient temperature under an atmosphere of dry nitrogen. Upon completion (48 hours) the reaction was filtered under vacuum through a celite plug, the solvent was removed *in vacuo* and purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield the title compound (257 mg, 71 %) as a pale yellow oil.

¹H NMR δ (400.13 MHz, CDCl₃): 7.97 (1H, t, *J* 4.2, NCH), 2.41 (1H, q, *J* 7.4, NCHCHHCH₃), 2.40 (1H, q, *J* 7.4, NCHCHHCH₃), 1.06 (9H, s, SC(CH₃)₃), 0.90 – 0.71 (3H, m, NCHCH₂CH₃).

¹³C NMR δ (100 MHz, CDCl₃): 170.53 (CH), 56.53 (q), 29.57 (CH₂), 22.28 (CH₃), 9.57 (CH₃).

Consistent with data reported.¹⁰⁶

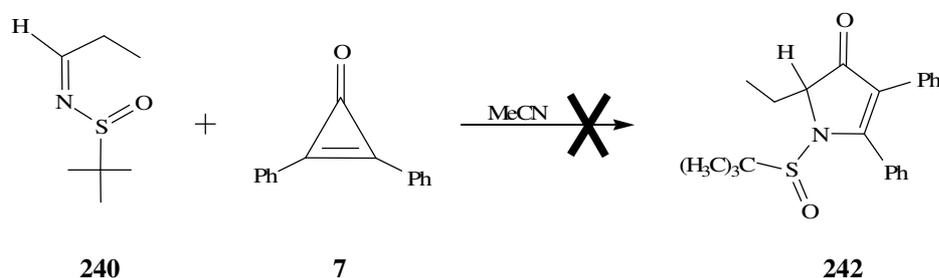
3.6.4 Synthesis of *N*-(butylidene)-*tert*-butanesulfinamide

To a stirring solution of 2-methyl-2-propanesulfonamide (304 mg, 2.51 mmol, 1 eq) in anhydrous dichloromethane (15 mL) was added magnesium sulfate (1.51 g, 12.55 mmol, 5 eq) and butyraldehyde (0.66 mL, 7.53 mmol, 3 eq) at ambient temperature under an atmosphere of dry nitrogen. Upon completion (48 hours) the reaction was filtered under vacuum through a celite plug, the solvent was removed *in vacuo* and purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield the title compound (329 mg, 75 %), as a pale yellow oil.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.84 (1H, t, J 4.7, NCH), 2.28 (2H, ddd, J 4.7, 7.4, 7.4 NHCH₂CH₂CH₃), 1.45 (2H, sext, J 7.4, NHCH₂CH₂CH₃), 0.97 (9H, s, C(CH₃)₃) 0.77 (3H, t, J 7.4, NHCH₂CH₂CH₃).

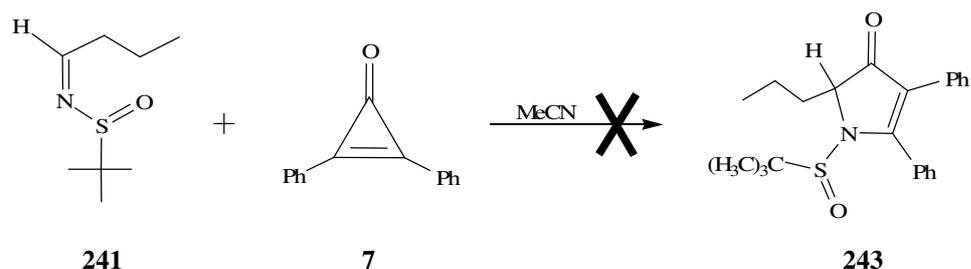
$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 169.42 (CH), 56.27 (q), 37.89 (CH₂), 22.17 (CH₃), 18.77 (CH₂), 13.66 (CH₃).

3.6.5 Attempted synthesis of 2-ethyl-1-(2'-methyl-2'-propanesulfinyl)-4,5-diphenyl-2-pyrrolin-3-one



To a stirring solution of the imine (257 mg, 1.59 mmol, 1 eq) in anhydrous acetonitrile (15 mL) was added diphenylcyclopropenone (328 mg, 1.59 mmol, 1 eq) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for five days at ambient temperature (no reaction was observed), and then heated at reflux for one day, but no new products were observed.

3.6.6 Attempted synthesis of 1-(2'-methyl-2'-propanesulfinyl)-4,5-diphenyl-2-propyl-pyrrolin-3-one

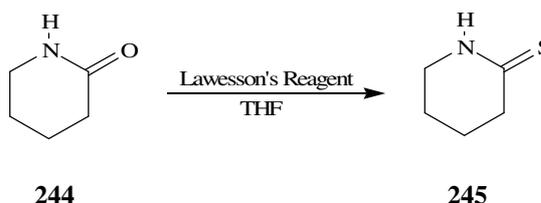


To a stirring solution of the imine (329 mg, 1.88 mmol, 1 eq) in anhydrous acetonitrile (15 mL) was added diphenylcyclopropenone (388 mg, 1.88 mmol, 1 eq) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for five days at ambient temperature (no reaction was observed), and then heated at reflux for one day, but no new products were observed.

3.7 Synthesis of Indolizidines and Pyrroloazepines

3.7.1 Indolizidines

3.7.1.1 Synthesis of piperidone-2-thione

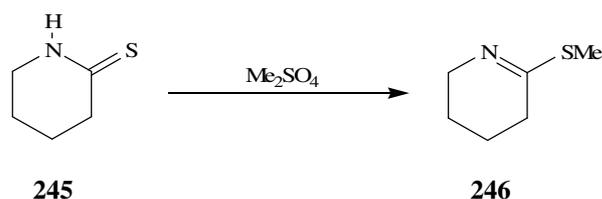


A solution of 2-piperidone (520 mg, 5.247 mmol, 1 eq) and Lawesson's reagent (1.27 g, 3.147 mmol, 0.6 eq) in anhydrous tetrahydrofuran (15 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to reach ambient temperature, concentrated and purified by column chromatography (eluent: hexane: EtOAc 3:2) to yield piperidine-2-thione (540 mg, 89 %) as white crystals. Data below is identical to literature values.¹²⁴

¹H NMR δ (400.13 MHz, CDCl₃): 9.23 (1H, s, NH), 3.36 – 3.32 (2H, m, NCH₂), 2.87 (2H, t, SCCH₂), 1.83 – 1.70 (4H, m, CH₂CH₂CH₂CH₂).

¹³C NMR δ (100 MHz, CDCl₃): 202.75 (q), 44.98 (CH₂), 39.38 (CH₂), 21.00 (CH₂), 20.39 (CH₂).

3.7.1.2 Synthesis of 2-methylthio-1-piperidine

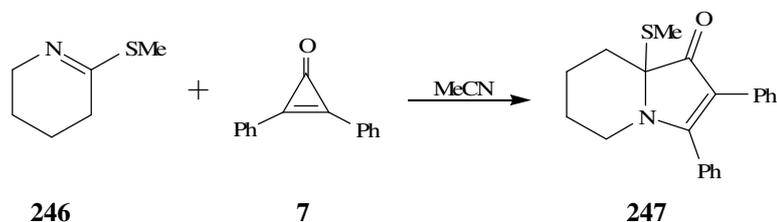


Dimethyl sulfate (0.34 mL, 3.612 mmol, 1.1 eq) was added in one portion to piperidine-2-thione (378 mg, 3.28 mmol, 1 eq) and the mixture was stirred for 15 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with ether (10 mL), washed with 10 % potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave ~2 mL of liquid which was used crude in the next step. (Note that 2-methylthio-1-piperidine^{73,108} was found to be volatile).

¹H NMR δ (400.13 MHz, CDCl₃): 3.68 – 3.63 (2H, m, NCH₂), 2.32 – 2.27 (2H, m, SCCH₂), 2.27 (3H, s, CH₃), 1.76 – 1.68 (2H, m, CH₂), 1.67 – 1.61 (2H, m, CH₂).

¹³C NMR δ (100 MHz, CDCl₃): 166.00 (q), 50.84 (CH₂), 31.78 (CH₂), 22.91 (CH₂), 20.39 (CH₂), 12.24 (CH₃).

3.7.1.3 Synthesis of 6-methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one



Diphenylcyclopropenone (609.5 mg, 2.955 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-piperidine (381.6 mg, 2.955 mmol, 1 eq) dissolved in anhydrous

acetonitrile (8 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for a week, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 3:1) to yield 6-methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (596 mg, 60 %) as an orange/ yellow oil.

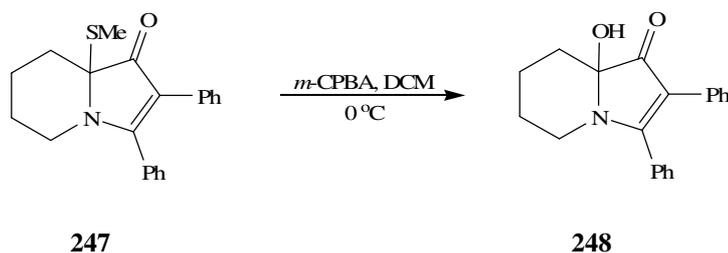
$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.53 – 7.41 (3H, m, Ar), 7.36 – 7.24 (2H, m, Ar), 7.14 – 7.09 (4H, m, Ar), 7.06 – 7.00 (1H, m, Ar). 3.69 – 3.61 (1H, m, NCHH), 3.51 (1H, td, J 3.3, 13.1, NCHH), 2.27 – 2.20 (1H, m, SCCHH), 1.99 (3H, s, CH_3), 1.97 – 1.74 (3H, m, CHH, CH_2), 1.73 – 1.65 (1H, m, CHH), 1.38 – 1.24 (1H, m, CHH).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 199.03 (q), 170.78 (q), 131.93 (q), 130.63 (q), 130.60 (CH), 129.44 (CH), 128.47 (CH), 128.09 (CH), 125.53 (CH), 110.17 (q), 72.46 (q), 41.69 (CH_2), 32.89 (CH_2), 27.67 (CH_2), 20.74 (CH_2), 10.86 (CH_3).

HRMS (ESI+): Found 358.1234 [$\text{M}+\text{H}$] $^+$, $\text{C}_{20}\text{H}_{19}\text{NO}_2$ requires 358.1236.

IR ν_{max} (cm^{-1}): 3056 (w), 2941 (m), 2859 (w), 1655 (vs), 1599 (m), 1578 (w), 1537 (m).

3.7.1.4 Synthesis of 6-hydroxy-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one



A:

To a stirring solution of 6-methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (576 mg, 1.719 mmol, 1 eq) in anhydrous dichloromethane (5 mL) was added a solution of *meta*-chloroperoxybenzoic acid (296.6 mg, 1.719 mmol, 1 eq) in anhydrous dichloromethane (4

mL) at 0 – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for four and a half hours, before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture and the whole was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: PE: EtOAc, 1:3) to yield 6-hydroxy-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (224 mg, 43 %) as an orange solid.

B:

To a stirring solution of 6-methylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (172 mg, 0.513 mmol, 1 eq) in anhydrous dichloromethane (7 mL) was added a solution of meta-chloroperoxybenzoic acid (88.57 mg, 0.513 mmol, 1 eq) in anhydrous dichloromethane (4 mL) at 0 – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for three hours, before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: PE: EtOAc, 1:3) to yield 6-hydroxy-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (70 mg, 45 %) as an orange solid.

¹H NMR δ (400.13 MHz, CDCl₃): 7.51 – 7.40 (5H, m, Ar), 7.13 – 7.00 (5H, m, Ar), 3.63 (1H, dd, *J* 4.6, 13.4, NCHH), 3.46 (1H, ddd, *J* 3.3, 12.6, 13.4, NCHH), 2.21 (1H, d, *J* 13.4, HOCCHH), 2.05 (1H, ddd, *J* 3.5, 3.5, 13.2, HOCCHH), 2.00 (1H, dd, *J* 6.0, 11.6,

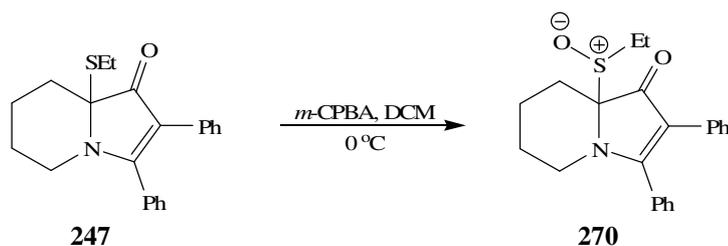
NCH₂CHH), 1.77 – 1.71 (1H, m, NCH₂CHH), 1.66 (1H, dd, *J* 4.1, 13.6, NCH₂CH₂CHH), 1.28 (1H, ddd *J* 4.1, 4.2, 13.2, NCH₂CH₂CHH).

¹³C NMR δ (100 MHz, CDCl₃): 200.62 (q, C=O), 172.31 (q), 131.93(q), 130.62 (CH), 130.40 (q), 129.37 (CH), 128.72 (CH), 128.54 (CH), 128.09 (CH), 125.45 (CH), 107.58 (q), 86.81 (q), 42.23 (CH₂), 34.56 (CH₂), 27.76 (CH₂), 19.46 (CH₂).

HRMS (ESI+): Found 306.1493 [M+H]⁺, C₂₀H₁₉NO₂ requires 306.1489.

IR ν_{max} (cm⁻¹): 3295 (br) 2929 (m), 1639 (s), 1600 (m), 1527 (m).

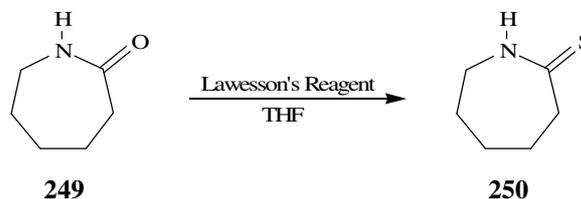
3.7.1.5 Attempted synthesis of 6-ethanesulfinyl-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one



To a stirring solution of 6-ethylthio-8,9-diphenyl-1-azabicyclo[4.3.0]non-8-en-7-one (96 mg, 0.275 mmol, 1 eq) in anhydrous dichloromethane (7 mL) at 0 – -10 °C was added a solution of *meta*-chloroperoxybenzoic acid (47.5 mg, 0.275 mmol, 1 eq) in anhydrous dichloromethane (4 mL) under an atmosphere of dry nitrogen. The reaction mixture was stirred for six hours before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL). The organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was subjected to column chromatography (eluent: hexane: EtOAc, 1:1), but NMR and TLC showed no identifiable products.

3.7.2 Pyrrolazepines

3.7.2.1 Synthesis of Azepan-2-thione

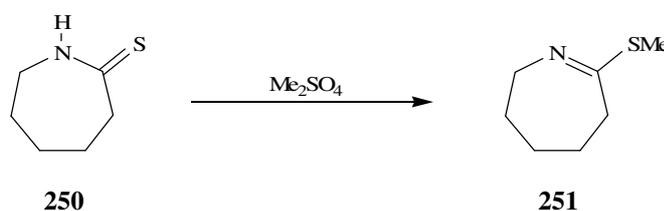


A solution of azepan-2-one (780 mg, 6.89 mmol, 1 eq) and Lawesson's reagent (1672 mg, 4.14 mmol, 0.6 eq) in anhydrous tetrahydrofuran (20 mL) was stirred under an atmosphere of dry nitrogen at ambient temperature for an hour. The mixture was then heated at reflux and monitored by TLC. Upon completion of the reaction (two hours) the mixture was left to cool to ambient temperature, concentrated and purified by column chromatography (eluent: hexane: EtOAc, 3:2) to yield azepan-2-thione (650 mg, 73 %) as white crystals. Data below is identical to literature values.¹²⁴

¹H NMR δ (400.13 MHz, CDCl₃): 9.19 (1H, s, NH), 3.36 (2H, dd, *J* 6.0, 10.2, NCH₂), 2.97 (2H, t, *J* 5.5, SCCH₂) 1.81 – 1.74 (2H, m, CH₂), 1.73 – 1.68 (2H, m, CH₂), 1.67 – 1.61 (2H, m, CH₂).

¹³C NMR δ (100 MHz, CDCl₃): 210.31 (q), 47.27 (CH₂), 45.13 (CH₂), 30.53 (CH₂), 28.20 (CH₂), 24.64 (CH₂).

3.7.2.2 Synthesis of 2-methylthio-1-azepane

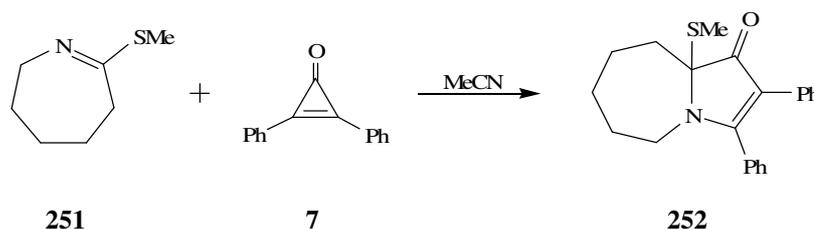


Dimethyl sulfate (0.525 mL, 5.536 mmol, 1.1 eq) was added in one portion to azepan-2-thione (650 mg, 5.033 mmol, 1 eq) and the mixture was stirred for 15 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was diluted with diethyl ether (10 mL), washed with 10 % aqueous potassium carbonate (20 mL) and extracted with dichloromethane (3 x 20 mL). The organic phase was dried over magnesium sulfate and filtered under gravity. Most of the solvent was removed *in vacuo*, to leave ~2 mL of crude liquid which was used in the next step. (Note that 2-methylthio-1-azepane^{73,108} was found to be volatile).

¹H NMR δ (400.13 MHz, CDCl₃): 3.60 – 3.58 (2H, m, NCH₂), 2.39 – 2.35 (2H, m, SCCH₂), 2.18 (3H, s, CH₃), 1.73 – 1.67 (2H, m, CH₂), 1.49 – 1.41 (4H, m, 2 x CH₂).

¹³C NMR δ (100 MHz, CDCl₃): 172.44 (q), 52.86 (CH₂), 37.04 (CH₂), 31.34 (CH₂), 27.13 (CH₂), 24.41 (CH₂), 13.42 (CH₃).

3.7.2.3 Synthesis of 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one



Diphenylcyclopropenone (923.4 mg, 4.478 mmol, 1 eq) was added in one portion to a stirring solution of 2-methylthio-1-azepane (641 mg, 4.478 mmol, 1eq) dissolved in anhydrous acetonitrile (15 mL) at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for three weeks, concentrated and purified by column

chromatography (eluent: hexane: EtOAc, 1:1) to yield 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one (257 mg, 16 %) as a yellow oil.

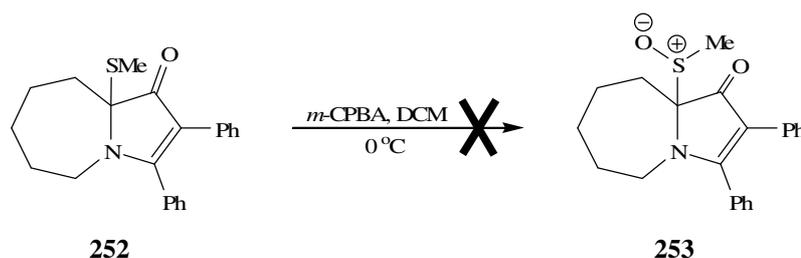
$^1\text{H NMR } \delta$ (500.13 MHz, CDCl_3): 7.51 – 7.45 (3H, m, Ar), 7.38 – 7.33 (2H, m, Ar), 7.13 – 7.10 (4H, m, Ar), 7.07 – 7.01 (1H, m, Ar), 3.85 – 3.78 (1H, m, NCH_2), 3.44 – 3.37 (1H, m, NCH_2), 2.78 (1H, dd, J 7.8, 14.4, CH_2CSMe), 1.97 (3H, s, Me), 1.83 – 1.74 (2H, m, CH_2), 1.71 (1H, dd, J 11.4, 14.4, CH_2CSMe), 1.52 – 1.45 (1H, dd, J 1.7, 14.1, CHH), 1.30 – 1.19 (1H, m, CHH), 1.18 – 1.10 (1H, m, CHH), 1.10 – 1.01 (1H, m, CHH),

$^{13}\text{C NMR } \delta$ (125 MHz, CDCl_3): 197.65 (q, C=O), 174.31 (q), 131.73 (q), 130.95 (q), 130.53 (CH), 129.38 (CH), 128.83 (CH), 128.55 (CH), 128.06 (CH), 125.66 (CH), 113.27 (q), 77.03 (q), 43.36 (CH_2), 37.31 (CH_2), 29.71 (CH_2), 29.51 (CH_2), 23.97 (CH_2), 11.60 (CH_3).

HRMS (ESI+): Found 372.1394 [$\text{M}+\text{Na}$] $^+$, $\text{C}_{22}\text{H}_{23}\text{NNaOS}$ requires 372.1392.

IR ν_{max} (cm^{-1}): 3053 (w) 2920 (m), 2851 (m), 1656 (vs), 1599 (s), 1577 (w), 1540 (s).

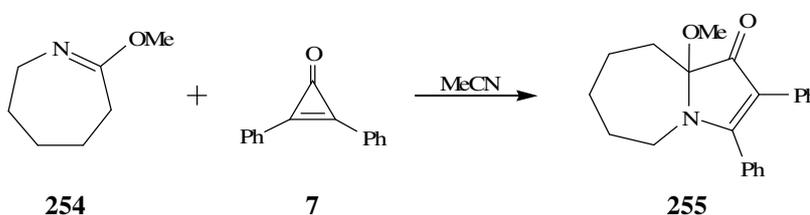
3.7.2.4 Attempted synthesis of 7-methanesulfonyl-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one



To a stirring solution of 7-methylthio-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one (257 mg, 0.738 mmol, 1 eq) in anhydrous dichloromethane (7 mL) was added a solution of *meta*-chloroperoxybenzoic acid (128 mg, 0.738 mmol, 1 eq) in anhydrous dichloromethane (4 mL) at 0 – -10 °C under an atmosphere of dry nitrogen. The reaction mixture was stirred for five hours, before being quenched with saturated aqueous sodium thiosulfate (10 mL) and allowed

to warm to ambient temperature. Saturated aqueous sodium hydrogen carbonate (10 mL) was added to the mixture which was stirred for a further ten minutes before extracting with dichloromethane (3 x 10 mL), the organic phases were dried over magnesium sulfate and filtered under gravity. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (eluent: PE: EtOAc, 1:3) to give only the starting material (51 mg, 20 %).

3.7.2.5 Synthesis of 7-methoxy-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one



Diphenylcyclopropenone (324.3 mg, 1.572 mmol, 1 eq) was added in one portion to a stirring solution of 2-methoxy-1-azepane (200 mg, 1.572 mmol, 1 eq) in anhydrous acetonitrile (6 mL). The reaction mixture was stirred for two days at ambient temperature under an atmosphere of dry nitrogen. TLC analysis showed little or no change, and so the mixture was heated to reflux for five days, changing in colour from light yellow to dark orange. Evaporation of the solvent gave a crude product which was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 7-methoxy-9,10-diphenyl-1-azabicyclo[5.3.0]dec-9-en-8-one (145 mg, 28 %) as a yellow/ orange oil.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.52 – 7.43 (3H, m, Ar), 7.40 – 7.35 (2H, m, Ar), 7.15 – 7.01 (5H, m, Ar), 3.74 (1H, ddd, J 3.2, 3.2, 14.9, NCHH), 3.22 (3H, s, Me), 3.28 (1H, ddd, J 1.8, 12.5, 14.9, NCHH), 2.53 (1H, dd, J 8.6, 14.4, MeOCCHH), 1.87 (1H, dd, J 10.9, 14.4,

MeOCCHH), 1.80 – 1.69 (2H, m, CH₂), 1.47 – 1.38 (1H, m, CHH), 1.37 – 1.25 (1H, m, CHH), 1.20 – 1.04 (2H, m, CH₂).

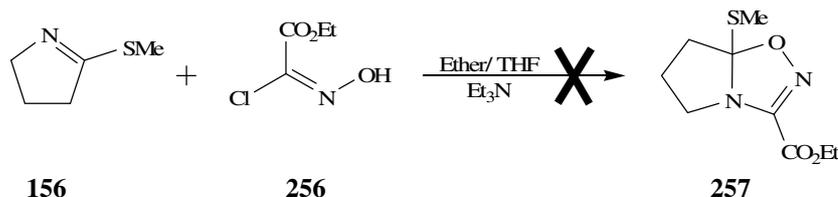
¹³C NMR δ (100 MHz, CDCl₃): 198.15 (q), 176.63 (q), 131.23 (q), 130.93 (q), 130.66 (CH), 129.31 (CH), 128.77 (CH), 128.64 (CH), 128.07 (CH), 125.76 (CH), 112.88 (q), 94.92 (q), 51.43 (CH₃), 43.02 (CH₂), 37.09 (CH₂), 29.59 (CH₂), 29.07 (CH₂), 22.03 (CH₂).

HRMS (ESI+): Found 356.1625 [M+Na]⁺, C₂₂H₂₃NNaO₂, requires 356.1621.

3.8 1,3-Dipolar cycloadditions

3.8.1 Attempted synthesis of ethyl-5-methylthio-4,1,3-oxadiazobicyclo[3.3.0]oct-2-ene-2-carboxylate

Method 1:

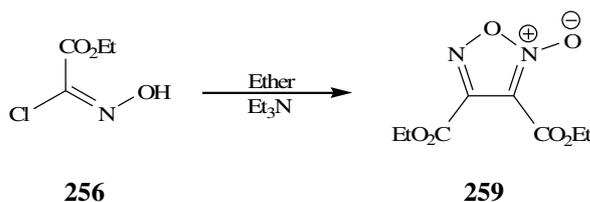


A:

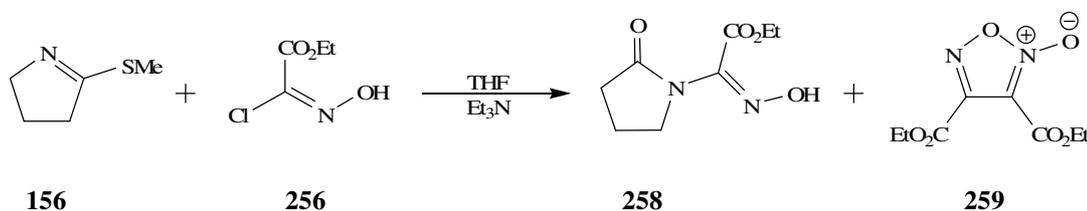
To a stirring solution of 2-methylthio-1-pyrroline (260 mg, 2.26 mmol, 1 eq) and ethyl chlorooximidoacetate (342.5 mg, 2.26 mmol, 1 eq) in ether (5 mL) was added triethylamine (0.32 mL, 2.26 mmol, 1 eq) diluted in ether (5 mL) dropwise over four to five hours at ambient temperature using a syringe pump. The reaction was purified by column chromatography, but only the nitrile oxide dimer was formed with no other identifiable products.

B:

To a stirring solution of 2-methylthio-1-pyrroline (209 mg, 1.817 mmol, 1 eq) and triethylamine (0.25 mL, 1.817 mmol, 1 eq) in ether (5 mL) was added ethyl chlorooximidoacetate (275.4 mg, 1.817 mmol, 1 eq) diluted in ether (15 mL) dropwise over 30 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction was purified by column chromatography, but only the nitrile oxide dimer was formed with no other identifiable products.

Nitrile oxide dimer:

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 4.43 (2H, q, J 7.1, CH_2CH_3), 4.36 (2H, q, J 7.1, CH_2CH_3), 1.36 (3H, t, J 7.1, CH_2CH_3), 1.31 (3H, t, J 7.1, CH_2CH_3).

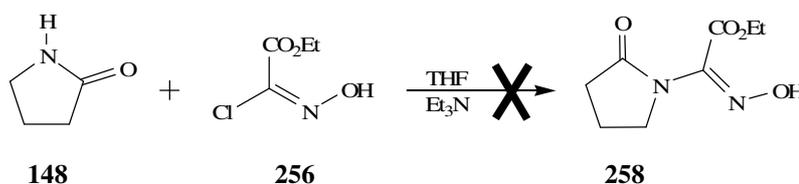
Method 2:

To a stirring solution of 2-methylthio-1-pyrroline (232 mg, 2.017 mmol, 1 eq) and triethylamine (0.28 ml, 2.017 mmol, 1 eq) in THF (5 mL) was added ethyl chlorooximidoacetate (305.7 mg, 2.017 mmol, 1 eq) diluted in THF (20 mL) dropwise over 20 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was filtered, concentrated and the residue purified by column chromatography (eluent: 10:1, 7:1, 5:1, 2:1, 1:1 hexane: EtOAc) to give ethyl-[*N*-(2-pyrrolidone)]oximidoacetate (231.9 mg, 50%), as an orange/ yellow oil and the nitrile oxide dimer.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 10.81 (1H, bs, OH), 4.27 (2H, q, J 7.1, $\text{COOCH}_2\text{CH}_3$), 3.79 (2H, t, J 7.0, NCH_2), 2.44 (2H, t, J 8.0, OCCH_2), 2.17 (2H, quint, J , 7.5, OCCH_2CH_2), 1.28 (3H, t, J 7.1, CH_2CH_3).

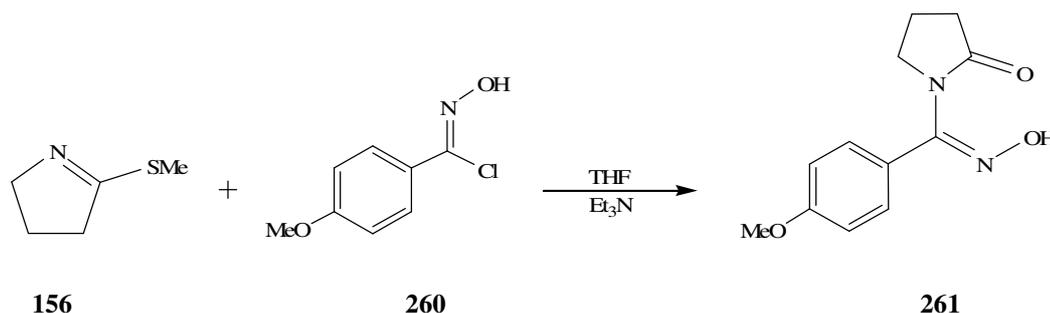
^{13}C NMR δ (100 MHz, CDCl_3): 176.81 (q), 160.50 (q), 139.67 (q), 62.72 (CH_2), 47.56 (CH_2), 30.16 (CH_2), 20.08 (CH_2), 14.14 (CH_3).

3.8.1.1 Attempted synthesis of ethyl-[N-(2-pyrrolidone)]oximidoacetate



To a stirring solution of 2-pyrrolidinone (213 mg, 2.503 mmol, 1 eq) and triethylamine (0.35 mL, 2.503 mmol, 1 eq) in THF (7 mL) was added ethyl chlorooximidoacetate (379.3 mg, 2.503 mmol, 1 eq) in THF (23 mL), dropwise over 12 hours at ambient temperature under an atmosphere of dry nitrogen. The reaction was purified by column chromatography, to give the nitrile oxide dimer (150 mg, 33 %) as the only identifiable product.

3.8.2 Synthesis of 4-methoxy-(α -[N-(2-pyrrolidinone)])benzaldoxime



To a stirring solution of 2-methylthio-1-pyrroline (217 mg, 1.89 mmol, 1 eq) and anhydrous triethylamine (0.27 mL, 1.89 mmol, 1 eq) in THF (7 mL) was added the α -chlorooxime (351 mg, 1.89 mmol, 1 eq) diluted in THF (25 mL) dropwise over 30 hours under an atmosphere of dry nitrogen. The reaction mixture was filtered, concentrated and the residue was purified by

column chromatography (eluent: hexane: EtOAc, 10:1, 8:1, 6:1, 3:2, 1:1) to give 4-methoxy-(α -[N-(2-pyrrolidinone)])benzaldoxime (141.8 mg, 32 %), as an orange oil.

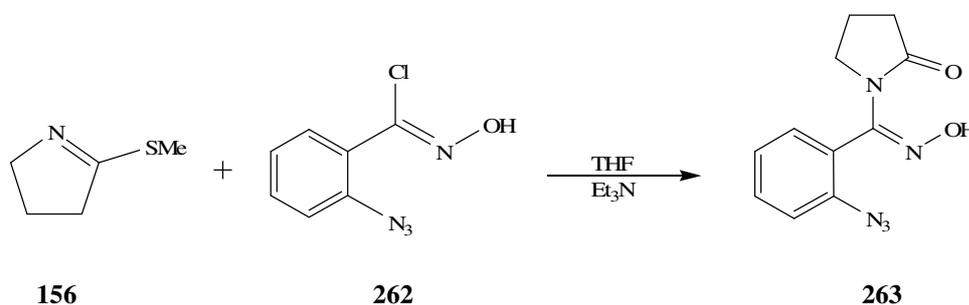
$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 8.63 – 5.58 (1H, bs, OH), 7.51 (2H, d, J 8.9, MeOCCH), 6.90 (2H, d, J 8.9, MeOCCHCH), 3.83 (3H, s, CH_3), 3.73 (2H, t, J 7.0 NCH₂), 2.58 (2H, t, J 8.0, OCCH₂), 2.26 (2H, quint, J 7.5, CH₂CH₂CH₂).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 175.53 (q), 161.58 (q), 147.39 (q), 128.50 (CH), 123.80 (q), 114.48 (CH), 55.70 (CH₃), 48.05 (CH₂), 31.07 (CH₂), 20.23 (CH₂).

HRMS (ESI⁺): Found 257.0900 [M+Na]⁺, C₁₂H₁₄N₂NaO₃ requires 257.0894.

IR ν_{max} (cm⁻¹): 3167 (m) 3024 (w), 2960 (w), 2899 (w), 2838 (w) 1660 (s), 1601 (s) 1513 (s).

3.8.3 Synthesis of 2-azido-(α -[N-(2-pyrrolidinone)])benzaldoxime

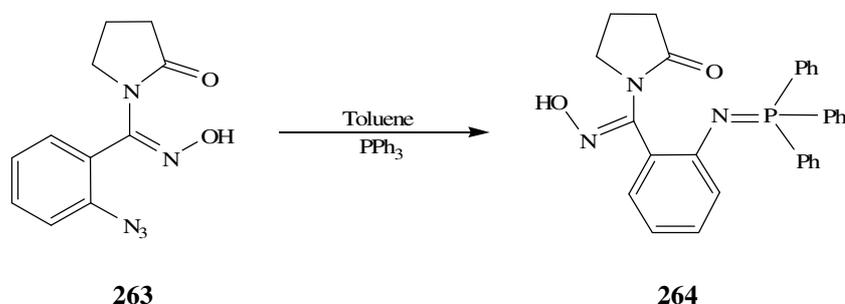


To a stirring solution of 2-methylthio-1-pyrroline (217 mg, 1.89 mmol, 1 eq) and anhydrous triethylamine (0.27 mL, 1.89 mmol, 1 eq) in THF (7 mL) was added the α -chloroxime (342 mg, 1.89 mmol, 1 eq) in THF (15 mL) dropwise over 20 hours *via* a reservoir at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was filtered, concentrated and the residue was purified by column chromatography (eluent: hexane: EtOAc, 1:1) to yield 2-azido-(α -[N-(2-pyrrolidinone)])benzaldoxime (66 mg, 14 %) as a pale orange solid.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 9.25 (1H, bs, OH), 7.53 – 7.51 (1H, m, Ar), 7.45 (1H, td, J 1.4, 15.6, Ar), 7.20 – 7.15 (2H, m, Ar), 3.89 (2H, t, J 7.0, NCH_2), 2.47 (2H, t, J 8.0, OCCH_2), 2.21 (2H, quint, J 7.5, $\text{OCCH}_2\text{CH}_2\text{CH}_2$).

$^{13}\text{C NMR } \delta$ (100 MHz, CDCl_3): 175.87 (q), 146.26 (q), 138.22 (q), 131.86 (CH), 131.41 (CH), 125.42 (CH), 124.06 (q), 118.70 (CH), 48.31 (CH_2), 30.96 (CH_2), 20.32 (CH_2).

3.8.4 Synthesis of 2-[triphenylphosphoranylimino]- α -[*N*-(2-pyrrolidinone)]-benzaldoxime



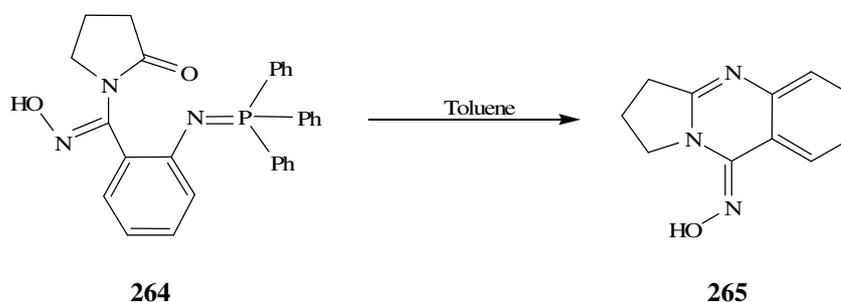
A stirring solution of the azide (66 mg, 0.269 mmol, 1 eq) in anhydrous toluene (15 mL) had triphenylphosphine (70.7 mg, 0.269 mmol, 1 eq) added in one portion at ambient temperature under an atmosphere of dry nitrogen. The reaction mixture was stirred for three days, concentrated and purified by column chromatography (eluent: 1:1 hexane: EtOAc) to yield 2-[triphenylphosphoranylimino]- α -[*N*-(2-pyrrolidinone)]benzaldoxime (120 mg, 93 %) as an orange solid.

$^1\text{H NMR } \delta$ (400.13 MHz, CDCl_3): 7.72 – 7.64 (6H, m, Ar), 7.57 – 7.51 (3H, m, Ar), 7.49 – 7.43 (6H, m, Ar), 7.36 (1H, ddd, J 2.1, 2.1, 7.5, Ar), 6.90 (1H, ddd, J 1.7, 7.7, 8.1, Ar), 6.65 (1H, t, J 7.5, Ar), 6.40 (1H, d, J 8.1, Ar), 3.55 (2H, t, J 7.0, NCH_2) 2.19 (2H, t, J 8.1, NCOCH_2), 1.84 (2H, quint, J 7.5, $\text{NCH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR δ (100 MHz, CDCl_3): 177.10 (q), 151.33 (q), 150.30 (q), 142.00 (q), 133.08 (CH), 132.79 (CH), 132.69 (CH), 132.37 (CH), 132.34 (CH), 132.31 (CH), 132.27 (CH), 132.24 (CH), 132.04 (q), 130.37 (CH), 129.14 (CH), 129.02 (CH), 128.84 (CH), 128.72 (CH), 128.44 (q), 110.34 (q), 48.83 (CH_2), 31.75 (CH_2), 19.72 (CH_2).

HRMS (ESI+): Found 480.1838 $[\text{M}+\text{H}]^+$, $\text{C}_{29}\text{H}_{27}\text{N}_3\text{O}_2\text{P}$ requires 480.1835.

3.8.5 Synthesis of pyrrolo[1,2-b][1,3]benzodiazin-4-oxime



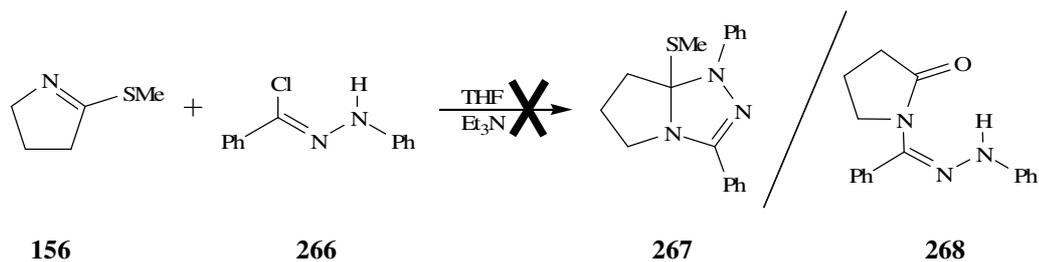
A stirring solution of the iminophosphorane (120 mg, 0.251 mmol) in anhydrous toluene (10 mL) was warmed to reflux under an atmosphere of dry nitrogen. The reaction mixture was stirred for 17 hours, concentrated and purified by column chromatography (eluent: 1:4, hexane: EtOAc) to yield pyrrolo[1,2-b][1,3]benzodiazin-4-oxime (22 mg, 44 %) as a pale yellow solid.

^1H NMR δ (400.13 MHz, CDCl_3): 10.15 (1H, bs, OH), 8.17 (1H, d, J 8.3, Ar), 7.36 (2H, dd, J 0.7, 3.8 Ar), 7.14 (1H, ddd, J 3.2, 4.8, 8.3, Ar), 4.09 (2H, t, J 7.1, NCH_2), 2.68 (2H, t, J 8.1, NCCH_2), 2.28 (2H, quint, J 7.6, $\text{CH}_2\text{CH}_2\text{CH}_2$).

^{13}C NMR δ (100 MHz, CDCl_3): 174.43 (q), 142.70 (q), 142.06 (q), 127.75 (CH), 123.91 (CH), 120.90 (CH), 116.31 (q), 109.96 (CH), 49.32 (CH_2), 32.36 (CH_2), 30.03 (CH_2).

HRMS (ESI+): Found 224.0801 $[\text{M}+\text{Na}]^+$, $\text{C}_{11}\text{H}_{11}\text{N}_3\text{NaO}$ requires 224.0794.

IR ν_{max} (cm^{-1}): 3219 (br), 2923 (m), 2854 (w), 1681 (vs), 1508 (vs), 1174 (m).

3.8.6 Attempted reaction of 2-methylthio-1-pyrroline with a nitrilimine

To a stirring solution of 2-methylthio-1-pyrroline (241 mg, 2.096 mmol, 1 eq) and anhydrous triethylamine (0.3 mL, 2.096 mmol, 1 eq) in THF (4 mL) was added the nitrile imine precursor (483 mg, 2.096 mmol, 1 eq) diluted in THF (25 mL) dropwise over 30 hours under an atmosphere of dry nitrogen. The reaction was purified by column chromatography but no identifiable products were isolated.

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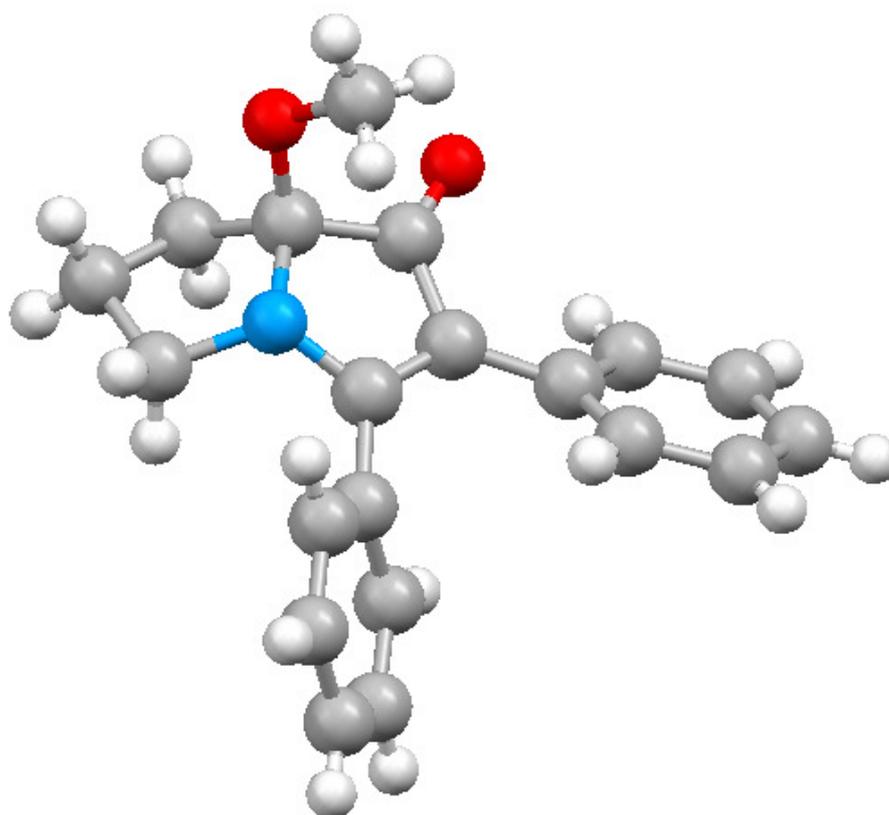
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Appendix

Crystal Data for

5-Methoxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

(159)



```

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?
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_atom_type_scatter_dispersion_imag
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'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'N' 'N' 0.0061 0.0033
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O' 'O' 0.0106 0.0060
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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loop_
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'-x+y, -x, z+1/3'
'-x, -y, z+1/2'
'y, -x+y, z+1/6'
'x-y, x, z+5/6'

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_cell_length_b                  9.316(3)
_cell_length_c                  33.188(9)
_cell_angle_alpha               90.00
_cell_angle_beta               90.00
_cell_angle_gamma              120.00
_cell_volume                    2494.6(12)
_cell_formula_units_Z           6
_cell_measurement_temperature   296(2)
_cell_measurement_reflns_used   ?
_cell_measurement_theta_min     ?
_cell_measurement_theta_max     ?

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?
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Refinement of F2 against ALL reflections. The weighted R-factor wR
and
goodness of fit S are based on F2, conventional R-factors R are
based
on F, with F set to zero for negative F2. The threshold expression
of
F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is

```

not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

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P=(Fo^2^+2Fc^2^)/3'
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C14 C 0.0352(2) 0.4150(2) 0.07508(6) 0.0417(4) Uani 1 1 d . . .
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H6 H -0.1953 0.1065 0.0564 0.063 Uiso 1 1 calc R . .
C16 C 0.3312(2) 0.5984(2) 0.07280(6) 0.0450(4) Uani 1 1 d . . .
C7 C 0.0467(2) 0.1824(2) 0.11397(5) 0.0435(4) Uani 1 1 d . . .
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 H8 H -0.1143 0.2126 0.1485 0.064 Uiso 1 1 calc R . .
 C12 C 0.1059(2) 0.0747(2) 0.10699(8) 0.0622(5) Uani 1 1 d . . .
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 C17 C 0.4268(3) 0.7126(3) 0.10728(7) 0.0636(6) Uani 1 1 d . . .
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 H17B H 0.5013 0.8242 0.0978 0.076 Uiso 1 1 calc R . .
 C19 C 0.3964(2) 0.4505(3) 0.12296(6) 0.0553(5) Uani 1 1 d . . .
 H19A H 0.4504 0.3858 0.1186 0.066 Uiso 1 1 calc R . .
 H19B H 0.3338 0.4148 0.1479 0.066 Uiso 1 1 calc R . .
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 H20B H 0.4553 0.5666 -0.0146 0.098 Uiso 1 1 calc R . .
 H20C H 0.2897 0.5683 -0.0077 0.098 Uiso 1 1 calc R . .
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 C9 0.0489(12) 0.0764(15) 0.0634(16) 0.0264(12) 0.0057(10) 0.0085(11)
 C20 0.0584(12) 0.0839(15) 0.0437(14) 0.0035(11) -0.0021(10) 0.0275(11)

C18 0.0531(12) 0.0805(15) 0.0470(14) -0.0022(10) -0.0134(10) 0.0137(11)
 C3 0.0629(13) 0.112(2) 0.0667(17) 0.0044(14) 0.0033(11) 0.0623(15)
 C11 0.0714(15) 0.0555(13) 0.113(2) 0.0200(13) -0.0100(15) 0.0325(11)
 C4 0.0428(11) 0.120(2) 0.0614(17) 0.0123(14) 0.0017(10) 0.0398(14)
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 O2 0.0411(6) 0.0575(8) 0.0422(9) 0.0100(6) -0.0002(6) 0.0120(6)
 O1 0.0720(10) 0.0622(9) 0.1035(14) 0.0307(8) 0.0002(9) 0.0389(8)
 N1 0.0387(7) 0.0469(8) 0.0391(9) 0.0093(6) 0.0004(6) 0.0214(6)

_geom_special_details

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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 C13 N1 1.381(2) . ?
 C13 C7 1.475(2) . ?
 C14 C15 1.453(3) . ?
 C6 C5 1.395(3) . ?
 C16 O2 1.410(2) . ?
 C16 N1 1.476(2) . ?
 C16 C17 1.512(3) . ?
 C16 C15 1.539(3) . ?
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 C7 C12 1.384(3) . ?
 C2 C3 1.386(3) . ?
 C15 O1 1.218(2) . ?
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 C12 C11 1.385(3) . ?
 C17 C18 1.514(3) . ?
 C19 N1 1.487(2) . ?
 C19 C18 1.512(3) . ?
 C5 C4 1.376(3) . ?
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C14 C13 C7 128.82(15) . . ?
N1 C13 C7 117.28(14) . . ?
C13 C14 C15 106.72(14) . . ?
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C15 C14 C1 124.32(15) . . ?
C1 C6 C5 120.85(19) . . ?
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O2 C16 C17 107.80(15) . . ?
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C17 C16 C15 117.05(17) . . ?
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C12 C7 C13 120.66(17) . . ?
C3 C2 C1 120.7(2) . . ?
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O1 C15 C16 122.49(17) . . ?
C14 C15 C16 107.44(14) . . ?
C9 C8 C7 120.1(2) . . ?
C7 C12 C11 120.4(2) . . ?
C16 C17 C18 102.68(17) . . ?
N1 C19 C18 104.16(15) . . ?
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C10 C9 C8 120.8(2) . . ?
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C10 C11 C12 119.9(2) . . ?
C3 C4 C5 120.3(2) . . ?
C9 C10 C11 120.1(2) . . ?
C16 O2 C20 114.96(14) . . ?
C13 N1 C16 108.18(13) . . ?
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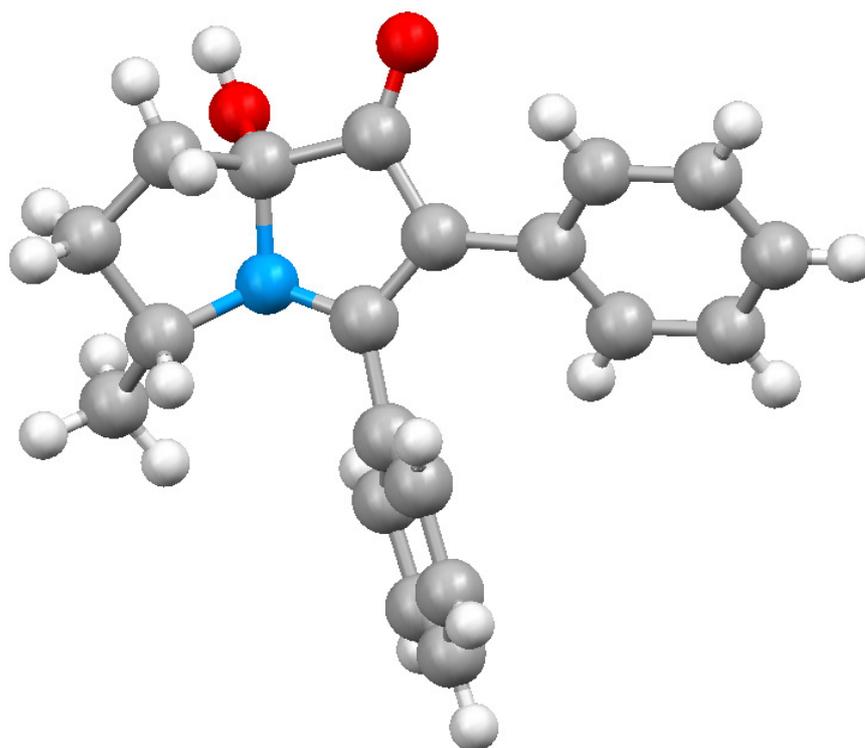
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Crystal Data for

5-Hydroxy-2,3-diphenyl-8-methyl-1-azabicyclo[3.3.0]oct-2-en-4-one

(167)



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'-x, -y, -z'

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_cell_angle_gamma               63.916(2)
_cell_volume                    784.87(12)
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_refine_special_details
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Refinement of F2 against ALL reflections. The weighted R-factor wR
and goodness of fit S are based on F2, conventional R-factors R are
based on F, with F set to zero for negative F2. The threshold expression
of F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is not relevant to the choice of reflections for refinement. R-factors
based

```

on F^2 are statistically about twice as large as those based on F ,
and R -
factors based on ALL data will be even larger.

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P=(Fo^2^+2Fc^2^)/3'
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_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
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H3 H -0.0249 0.8139 0.2006 0.025 Uiso 1 1 calc R . .
C6 C 0.28142(17) 0.71050(17) 0.38145(14) 0.0200(3) Uani 1 1 d . . .
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C2 C 0.12691(16) 0.64179(16) 0.27740(14) 0.0184(3) Uani 1 1 d . . .
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C8 C 0.00359(17) 0.66123(16) 0.67757(14) 0.0195(3) Uani 1 1 d . . .
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C4 C 0.09494(18) 0.89334(17) 0.28105(15) 0.0233(3) Uani 1 1 d . . .
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C9 C -0.10656(17) 0.75780(17) 0.80384(15) 0.0222(3) Uani 1 1 d . . .
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C12 C 0.19954(17) 0.51148(17) 0.78709(15) 0.0218(3) Uani 1 1 d . . .
H12 H 0.3038 0.4277 0.7824 0.026 Uiso 1 1 calc R . .
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 C10 C -0.06510(18) 0.73247(18) 0.92284(15) 0.0243(3) Uani 1 1 d . . .
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 C13 C 0.30152(16) 0.45421(16) 0.39501(14) 0.0171(3) Uani 1 1 d . . .
 C14 C 0.27396(16) 0.42726(16) 0.53554(14) 0.0181(3) Uani 1 1 d . . .
 C20 C 0.47265(19) 0.32324(19) 0.03342(15) 0.0273(3) Uani 1 1 d . . .
 H20A H 0.4387 0.2437 0.0323 0.041 Uiso 1 1 calc R . . .
 H20B H 0.5691 0.3110 -0.0575 0.041 Uiso 1 1 calc R . . .
 H20C H 0.3730 0.4212 0.0470 0.041 Uiso 1 1 calc R . . .
 C16 C 0.45563(17) 0.19811(16) 0.37366(15) 0.0196(3) Uani 1 1 d . . .
 C17 C 0.65349(17) 0.14216(18) 0.30278(16) 0.0248(3) Uani 1 1 d . . .
 H17A H 0.6897 0.2042 0.3421 0.030 Uiso 1 1 calc R . . .
 H17B H 0.7170 0.0359 0.3142 0.030 Uiso 1 1 calc R . . .
 C15 C 0.36693(17) 0.26764(16) 0.53096(15) 0.0198(3) Uani 1 1 d . . .
 C18 C 0.68292(18) 0.16085(18) 0.14659(16) 0.0260(3) Uani 1 1 d . . .
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 H18B H 0.7964 0.1617 0.0928 0.031 Uiso 1 1 calc R . . .
 C19 C 0.53027(17) 0.31365(17) 0.15490(14) 0.0216(3) Uani 1 1 d . . .
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 O3 O 0.40367(13) 0.09216(12) 0.35296(11) 0.0242(2) Uani 1 1 d . . .
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 C4 0.0226(6) 0.0142(8) 0.0280(7) 0.0043(6) -0.0079(5) -0.0063(5)
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 C5 0.0251(7) 0.0152(8) 0.0278(7) 0.0007(5) -0.0080(5) -0.0120(6)
 C11 0.0261(7) 0.0273(9) 0.0244(7) 0.0046(6) -0.0119(6) -0.0121(6)
 C10 0.0223(6) 0.0219(8) 0.0250(7) -0.0005(6) -0.0057(5) -0.0096(6)
 C13 0.0144(5) 0.0138(7) 0.0254(6) 0.0025(5) -0.0090(5) -0.0076(5)
 C14 0.0169(6) 0.0148(8) 0.0246(6) 0.0041(5) -0.0097(5) -0.0077(5)
 C20 0.0212(6) 0.0303(9) 0.0238(7) 0.0019(6) -0.0049(5) -0.0094(6)
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 C17 0.0176(6) 0.0196(8) 0.0346(8) 0.0002(6) -0.0123(6) -0.0044(5)
 C15 0.0185(6) 0.0168(8) 0.0276(7) 0.0034(5) -0.0120(5) -0.0086(5)
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 N1 0.0173(5) 0.0142(6) 0.0232(5) 0.0030(4) -0.0083(4) -0.0063(4)
 O1 0.0306(5) 0.0161(6) 0.0320(5) 0.0077(4) -0.0179(4) -0.0092(4)

O3 0.0272(5) 0.0149(6) 0.0371(6) 0.0046(4) -0.0187(4) -0.0101(4)

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All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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C1 C2 1.4013(17) . ?

C1 C13 1.4780(18) . ?

C3 C4 1.385(2) . ?

C3 C2 1.3881(19) . ?

C3 H3 0.9500 . ?

C6 C5 1.392(2) . ?

C6 H6 0.9500 . ?

C2 H2 0.9500 . ?

C8 C9 1.383(2) . ?

C8 C7 1.4085(18) . ?

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C9 C10 1.392(2) . ?

C9 H9 0.9500 . ?

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C12 C7 1.4025(18) . ?

C12 H12 0.9500 . ?

C7 C14 1.472(2) . ?

C5 H5 0.9500 . ?

C11 C10 1.391(2) . ?

C11 H11 0.9500 . ?

C10 H10 0.9500 . ?

C13 N1 1.3639(19) . ?

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C20 C19 1.517(2) . ?

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C20 H20C 0.9800 . ?

C16 O3 1.4010(18) . ?

C16 N1 1.4722(17) . ?

C16 C17 1.5329(18) . ?

C16 C15 1.537(2) . ?
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 C5 C4 H4 119.8 . . ?
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 C10 C9 H9 119.8 . . ?
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 C10 C11 H11 119.5 . . ?
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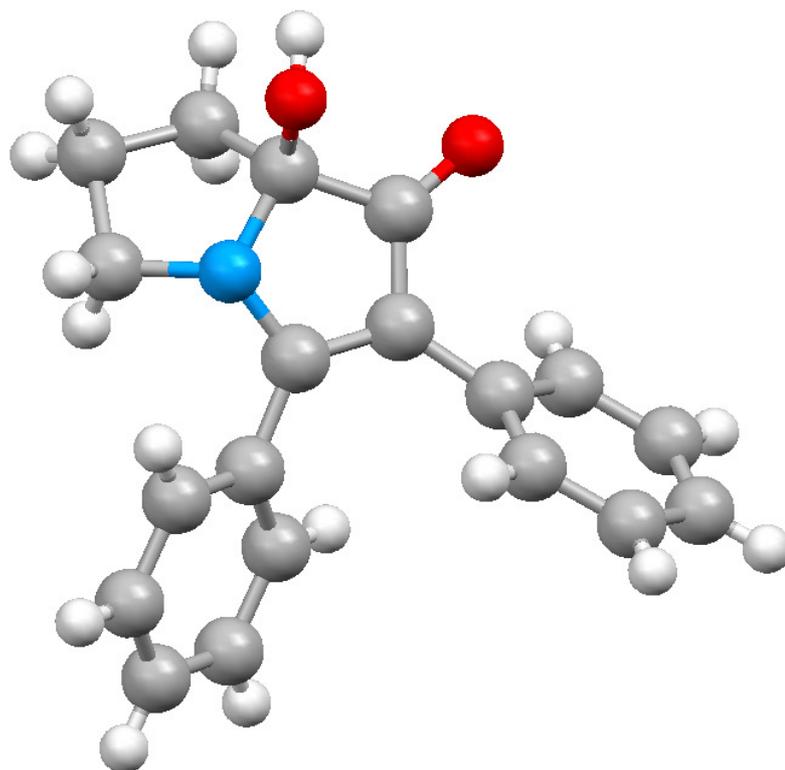
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 H20A C20 H20B 109.5 . . ?
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 H20A C20 H20C 109.5 . . ?
 H20B C20 H20C 109.5 . . ?
 O3 C16 N1 109.66(10) . . ?
 O3 C16 C17 113.28(12) . . ?
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 C18 C17 C16 101.71(10) . . ?
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 H18A C18 H18B 109.0 . . ?
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Crystal Data for

5-Hydroxy-2,3-diphenyl-1-azabicyclo[3.3.0]oct-2-en-4-one

(185)



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_exptl_absorpt_correction_T_min   0.9751
_exptl_absorpt_correction_T_max   0.9833
_exptl_absorpt_process_details    multi-scan

_exptl_special_details
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?
;

_diffn_ambient_temperature        240(2)
_diffn_radiation_wavelength       0.71073
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_diffn_radiation_monochromator    graphite
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_diffn_reflns_av_R_equivalents    0.0306
_diffn_reflns_av_sigmaI/netI     0.0279
_diffn_reflns_limit_h_min         -12
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_diffn_reflns_limit_k_min         -24
_diffn_reflns_limit_k_max         24
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_diffn_reflns_limit_l_max         13
_diffn_reflns_theta_min           2.46
_diffn_reflns_theta_max           30.03
_reflns_number_total              4345
_reflns_number_gt                 3077
_reflns_threshold_expression       >2sigma(I)

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_computing_cell_refinement        ?
_computing_data_reduction         ?
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_computing_structure_refinement   'SHELXL-97 (Sheldrick, 2008)'
_computing_molecular_graphics     ?
_computing_publication_material   ?

_refine_special_details
;
Refinement of F2 against ALL reflections. The weighted R-factor wR
and
goodness of fit S are based on F2, conventional R-factors R are
based
on F, with F set to zero for negative F2. The threshold expression
of
F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-factors
based

```

on F^2 are statistically about twice as large as those based on F ,
and R -
factors based on ALL data will be even larger.

;

```

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
'calc w=1/[\s^2^(Fo^2)+(0.0620P)^2^+0.1244P] where
P=(Fo^2+2Fc^2)/3'
_atom_sites_solution_primary      direct
_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     mixed
_refine_ls_extinction_method       SHELXL
_refine_ls_extinction_coef         0.000(5)
_refine_ls_extinction_expression
'Fc^*=kFc[1+0.001xFc^2\l^3^/sin(2\q)]^-1/4^'
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_refine_ls_number_parameters       201
_refine_ls_number_restraints       0
_refine_ls_R_factor_all            0.0668
_refine_ls_R_factor_gt             0.0436
_refine_ls_wR_factor_ref           0.1245
_refine_ls_wR_factor_gt           0.1113
_refine_ls_goodness_of_fit_ref     1.037
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_refine_ls_shift/su_max            1.719
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  _atom_site_fract_x
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  _atom_site_fract_z
  _atom_site_U_iso_or_equiv
  _atom_site_adp_type
  _atom_site_occupancy
  _atom_site_symmetry_multiplicity
  _atom_site_calc_flag
  _atom_site_refinement_flags
  _atom_site_disorder_assembly
  _atom_site_disorder_group
C1 C 0.44969(13) 0.14391(6) 0.34828(11) 0.0324(2) Uani 1 1 d . . .
C2 C 0.57979(13) 0.09956(6) 0.36248(11) 0.0358(3) Uani 1 1 d . . .
C3 C 0.55346(14) 0.05396(7) 0.23568(12) 0.0396(3) Uani 1 1 d . . .
C4 C 0.39647(14) 0.07683(6) 0.13648(11) 0.0364(3) Uani 1 1 d . . .
C5 C 0.26617(16) 0.01888(7) 0.11433(14) 0.0471(3) Uani 1 1 d . . .
H5A H 0.2775 -0.0131 0.1992 0.056 Uiso 1 1 calc R . .
H5B H 0.2609 -0.0145 0.0325 0.056 Uiso 1 1 calc R . .
C6 C 0.12525(16) 0.07072(8) 0.08714(15) 0.0523(3) Uani 1 1 d . . .
H6A H 0.0397 0.0436 0.1079 0.063 Uiso 1 1 calc R . .
H6B H 0.0932 0.0885 -0.0119 0.063 Uiso 1 1 calc R . .
C7 C 0.17888(14) 0.13816(8) 0.18943(14) 0.0453(3) Uani 1 1 d . . .
H7A H 0.1335 0.1867 0.1461 0.054 Uiso 1 1 calc R . .
H7B H 0.1516 0.1301 0.2782 0.054 Uiso 1 1 calc R . .

```

C8 C 0.41045(12) 0.19123(6) 0.45789(11) 0.0324(2) Uani 1 1 d . . .
 C9 C 0.32798(14) 0.25951(7) 0.42091(13) 0.0404(3) Uani 1 1 d . . .
 H9 H 0.3015 0.2771 0.3263 0.048 Uiso 1 1 calc R . .
 C10 C 0.28500(16) 0.30147(8) 0.52395(15) 0.0488(3) Uani 1 1 d . . .
 H10 H 0.2291 0.3474 0.4987 0.059 Uiso 1 1 calc R . .
 C11 C 0.32361(16) 0.27637(8) 0.66237(14) 0.0517(3) Uani 1 1 d . . .
 H11 H 0.2943 0.3052 0.7315 0.062 Uiso 1 1 calc R . .
 C12 C 0.40528(15) 0.20888(8) 0.70080(13) 0.0485(3) Uani 1 1 d . . .
 H12 H 0.4312 0.1919 0.7957 0.058 Uiso 1 1 calc R . .
 C13 C 0.44899(14) 0.16622(7) 0.59904(12) 0.0389(3) Uani 1 1 d . . .
 H13 H 0.5047 0.1204 0.6252 0.047 Uiso 1 1 calc R . .
 C14 C 0.72767(13) 0.10436(7) 0.47413(11) 0.0370(3) Uani 1 1 d . . .
 C15 C 0.79769(15) 0.17544(8) 0.51502(13) 0.0466(3) Uani 1 1 d . . .
 H15 H 0.7458 0.2210 0.4779 0.056 Uiso 1 1 calc R . .
 C16 C 0.94317(16) 0.17968(10) 0.60995(16) 0.0590(4) Uani 1 1 d . . .
 H16 H 0.9895 0.2279 0.6357 0.071 Uiso 1 1 calc R . .
 C17 C 1.02009(16) 0.11340(12) 0.66665(15) 0.0634(4) Uani 1 1 d . . .
 H17 H 1.1187 0.1164 0.7308 0.076 Uiso 1 1 calc R . .
 C18 C 0.95161(17) 0.04290(11) 0.62879(16) 0.0601(4) Uani 1 1 d . . .
 H18 H 1.0034 -0.0023 0.6681 0.072 Uiso 1 1 calc R . .
 C19 C 0.80607(15) 0.03795(9) 0.53269(14) 0.0488(3) Uani 1 1 d . . .
 H19 H 0.7606 -0.0105 0.5073 0.059 Uiso 1 1 calc R . .
 N1 N 0.34733(11) 0.13871(5) 0.21562(10) 0.0350(2) Uani 1 1 d . . .
 O1 O 0.63820(12) 0.00693(6) 0.20131(10) 0.0581(3) Uani 1 1 d . . .
 O2 O 0.41219(12) 0.10612(5) 0.00720(9) 0.0479(2) Uani 1 1 d . . .
 H2 H 0.4018 0.0706 -0.0515 0.072 Uiso 1 1 calc R . .

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 _atom_site_aniso_U_13
 _atom_site_aniso_U_12
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 C2 0.0385(6) 0.0386(6) 0.0296(5) -0.0044(4) 0.0086(4) 0.0030(5)
 C3 0.0485(7) 0.0381(6) 0.0325(5) -0.0045(5) 0.0122(5) 0.0042(5)
 C4 0.0480(7) 0.0330(5) 0.0271(5) -0.0052(4) 0.0088(4) -0.0015(5)
 C5 0.0592(8) 0.0397(6) 0.0415(6) -0.0090(5) 0.0130(6) -0.0094(6)
 C6 0.0489(7) 0.0555(8) 0.0459(7) -0.0119(6) 0.0028(6) -0.0093(6)
 C7 0.0379(6) 0.0471(7) 0.0450(7) -0.0083(5) 0.0019(5) 0.0016(5)
 C8 0.0331(5) 0.0341(5) 0.0301(5) -0.0052(4) 0.0089(4) -0.0026(4)
 C9 0.0451(7) 0.0383(6) 0.0374(6) -0.0029(5) 0.0110(5) 0.0027(5)
 C10 0.0504(7) 0.0410(6) 0.0571(8) -0.0106(6) 0.0186(6) 0.0052(6)
 C11 0.0529(8) 0.0601(8) 0.0494(7) -0.0182(6) 0.0262(6) -0.0036(6)
 C12 0.0510(7) 0.0648(8) 0.0335(6) -0.0048(6) 0.0182(5) -0.0075(7)
 C13 0.0396(6) 0.0429(6) 0.0341(6) 0.0001(5) 0.0102(5) -0.0013(5)
 C14 0.0354(6) 0.0485(6) 0.0289(5) -0.0033(5) 0.0120(4) 0.0047(5)
 C15 0.0441(7) 0.0548(7) 0.0415(6) -0.0096(6) 0.0131(5) 0.0000(6)
 C16 0.0442(7) 0.0781(10) 0.0535(8) -0.0196(8) 0.0119(6) -0.0094(7)
 C17 0.0373(7) 0.1072(13) 0.0429(7) -0.0090(8) 0.0069(6) 0.0036(8)
 C18 0.0473(8) 0.0867(11) 0.0456(7) 0.0126(8) 0.0121(6) 0.0217(8)
 C19 0.0454(7) 0.0565(8) 0.0443(7) 0.0039(6) 0.0124(5) 0.0089(6)
 N1 0.0387(5) 0.0330(5) 0.0297(4) -0.0049(4) 0.0042(4) 0.0016(4)
 O1 0.0649(6) 0.0628(6) 0.0444(5) -0.0160(4) 0.0119(4) 0.0217(5)
 O2 0.0680(6) 0.0464(5) 0.0295(4) -0.0027(4) 0.0143(4) -0.0054(4)

```

_geom_special_details
;
  All esds (except the esd in the dihedral angle between two l.s.
  planes)
  are estimated using the full covariance matrix. The cell esds are
  taken
  into account individually in the estimation of esds in distances,
  angles
  and torsion angles; correlations between esds in cell parameters are
  only
  used when they are defined by crystal symmetry. An approximate
  (isotropic)
  treatment of cell esds is used for estimating esds involving l.s.
  planes.
;

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C1 N1 1.3707(13) . ?
C1 C2 1.3866(15) . ?
C1 C8 1.4744(14) . ?
C2 C3 1.4349(15) . ?
C2 C14 1.4768(16) . ?
C3 O1 1.2343(14) . ?
C3 C4 1.5354(17) . ?
C4 O2 1.4094(14) . ?
C4 N1 1.4673(14) . ?
C4 C5 1.5237(17) . ?
C5 C6 1.528(2) . ?
C6 C7 1.5286(18) . ?
C7 N1 1.4816(16) . ?
C8 C9 1.3953(16) . ?
C8 C13 1.3960(15) . ?
C9 C10 1.3884(16) . ?
C10 C11 1.3720(19) . ?
C11 C12 1.382(2) . ?
C12 C13 1.3880(17) . ?
C14 C15 1.3950(18) . ?
C14 C19 1.3915(18) . ?
C15 C16 1.388(2) . ?
C16 C17 1.380(2) . ?
C17 C18 1.376(2) . ?
C18 C19 1.394(2) . ?

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  _geom_angle_site_symmetry_3
  _geom_angle_publ_flag
N1 C1 C2 112.98(9) . . ?
N1 C1 C8 119.16(10) . . ?

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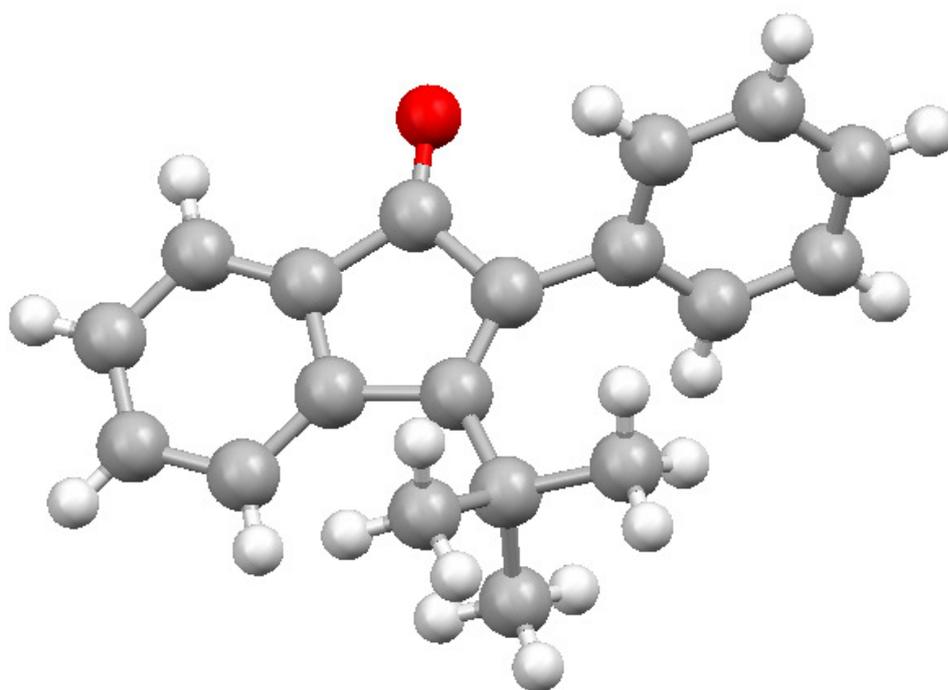
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C2 C1 C8 127.82(10) . . ?
C1 C2 C3 106.95(10) . . ?
C1 C2 C14 128.07(10) . . ?
C3 C2 C14 124.45(10) . . ?
O1 C3 C2 129.61(11) . . ?
O1 C3 C4 122.71(10) . . ?
C2 C3 C4 107.59(9) . . ?
O2 C4 N1 109.54(9) . . ?
O2 C4 C5 112.58(10) . . ?
N1 C4 C5 102.54(9) . . ?
O2 C4 C3 110.39(10) . . ?
N1 C4 C3 102.92(8) . . ?
C5 C4 C3 117.83(10) . . ?
C4 C5 C6 102.54(10) . . ?
C5 C6 C7 103.94(10) . . ?
N1 C7 C6 103.95(10) . . ?
C9 C8 C13 119.15(10) . . ?
C9 C8 C1 120.55(10) . . ?
C13 C8 C1 120.22(10) . . ?
C10 C9 C8 119.95(11) . . ?
C11 C10 C9 120.39(12) . . ?
C10 C11 C12 120.40(11) . . ?
C11 C12 C13 119.93(12) . . ?
C12 C13 C8 120.18(11) . . ?
C15 C14 C19 118.41(12) . . ?
C15 C14 C2 120.60(11) . . ?
C19 C14 C2 120.80(11) . . ?
C16 C15 C14 120.73(14) . . ?
C17 C16 C15 120.30(15) . . ?
C18 C17 C16 119.62(13) . . ?
C17 C18 C19 120.54(14) . . ?
C14 C19 C18 120.38(14) . . ?
C1 N1 C4 108.79(9) . . ?
C1 N1 C7 123.83(10) . . ?
C4 N1 C7 111.08(9) . . ?

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_refine_diff_density_rms                0.032

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Crystal Data for
3-Tert-butyl-2-phenyl-1-indenone
(237)



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data_mo_ilyas_iq161_0ma

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;
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;
_chemical_name_common           ?
_chemical_melting_point         ?
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_atom_type_scatter_dispersion_imag
_atom_type_scatter_source
'C' 'C' 0.0033 0.0016
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'H' 'H' 0.0000 0.0000
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'
'O' 'O' 0.0106 0.0060
'International Tables Vol C Tables 4.2.6.8 and 6.1.1.4'

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_symmetry_space_group_name_H-M ?

loop_
_symmetry_equiv_pos_as_xyz
'x, y, z'
'-x, -y, -z'

_cell_length_a                  8.8973(4)
_cell_length_b                  9.8539(4)
_cell_length_c                  10.0315(7)
_cell_angle_alpha               106.0860(10)
_cell_angle_beta                113.2970(10)
_cell_angle_gamma               103.9330(10)
_cell_volume                    712.36(7)
_cell_formula_units_Z           1
_cell_measurement_temperature   150(2)
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_cell_measurement_theta_min     ?
_cell_measurement_theta_max     ?

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_exptl_crystal_density_meas    ?
_exptl_crystal_density_diffn   0.649
_exptl_crystal_density_method  'not measured'
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_exptl_absorpt_coefficient_mu  0.041

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_exptl_absorpt_process_details      ?

_exptl_special_details
;
?
;

_diffn_ambient_temperature          150(2)
_diffn_radiation_wavelength         0.71073
_diffn_radiation_type               MoK\alpha
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_diffn_radiation_monochromator       graphite
_diffn_measurement_device_type       ?
_diffn_measurement_method           ?
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_reflns_threshold_expression         >2sigma(I)

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_computing_cell_refinement           ?
_computing_data_reduction            ?
_computing_structure_solution        'SHELXS-97 (Sheldrick, 2008)'
_computing_structure_refinement      'SHELXL-97 (Sheldrick, 2008)'
_computing_molecular_graphics        ?
_computing_publication_material      ?

_refine_special_details
;
Refinement of F2 against ALL reflections. The weighted R-factor wR
and
goodness of fit S are based on F2, conventional R-factors R are
based
on F, with F set to zero for negative F2. The threshold expression
of
F2 > 2sigma(F2) is used only for calculating R-factors(gt) etc.
and is
not relevant to the choice of reflections for refinement. R-factors
based
on F2 are statistically about twice as large as those based on F,
and R-
factors based on ALL data will be even larger.
;

```

```

_refine_ls_structure_factor_coef  Fsqd
_refine_ls_matrix_type            full
_refine_ls_weighting_scheme       calc
_refine_ls_weighting_details
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P=(Fo^2^+2Fc^2^)/3'
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_atom_sites_solution_secondary    difmap
_atom_sites_solution_hydrogens    geom
_refine_ls_hydrogen_treatment     mixed
_refine_ls_extinction_method      none
_refine_ls_extinction_coef        ?
_refine_ls_number_reflns          4942
_refine_ls_number_parameters      184
_refine_ls_number_restraints      0
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_refine_ls_R_factor_gt            0.0421
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_refine_ls_wR_factor_gt           0.1353
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_refine_ls_restrained_S_all       1.107
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_refine_ls_shift/su_mean          0.000

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loop_

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_atom_site_fract_y
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_atom_site_occupancy
_atom_site_symmetry_multiplicity
_atom_site_calc_flag
_atom_site_refinement_flags
_atom_site_disorder_assembly
_atom_site_disorder_group
C1 C 0.88952(10) 0.71503(9) 0.47950(9) 0.01705(16) Uani 1 1 d . . .
C10 C 0.67715(11) 0.77400(9) 0.10134(9) 0.01729(16) Uani 1 1 d . . .
C9 C 0.67062(10) 0.75426(9) 0.24348(9) 0.01605(15) Uani 1 1 d . . .
C8 C 0.82721(10) 0.74819(9) 0.33700(9) 0.01644(15) Uani 1 1 d . . .
C16 C 0.51411(10) 0.75361(9) 0.27069(10) 0.01818(16) Uani 1 1 d . . .
O1 O 1.10424(9) 0.78994(9) 0.32878(9) 0.02939(17) Uani 1 1 d . . .
C11 C 0.84707(11) 0.79348(9) 0.12105(10) 0.01840(16) Uani 1 1 d . . .
C7 C 0.95035(11) 0.77874(9) 0.27066(10) 0.01854(16) Uani 1 1 d . . .
C2 C 1.04122(11) 0.82369(10) 0.62253(10) 0.02127(17) Uani 1 1 d . . .
H2 H 1.1006 0.9217 0.6297 0.026 Uiso 1 1 calc R . .
C12 C 0.89709(12) 0.81685(10) 0.01315(11) 0.02334(18) Uani 1 1 d . . .
H12 H 1.0144 0.8321 0.0316 0.028 Uiso 1 1 calc R . .
C15 C 0.55120(12) 0.77266(10) -0.03652(10) 0.02174(17) Uani 1 1 d . . .
H15 H 0.4339 0.7571 -0.0548 0.026 Uiso 1 1 calc R . .
C18 C 0.34878(12) 0.60515(11) 0.14401(11) 0.02550(19) Uani 1 1 d . . .
H18A H 0.3272 0.5943 0.0372 0.038 Uiso 1 1 calc R . .
H18B H 0.2448 0.6104 0.1537 0.038 Uiso 1 1 calc R . .
H18C H 0.3692 0.5163 0.1605 0.038 Uiso 1 1 calc R . .
C6 C 0.80779(12) 0.57012(10) 0.47023(11) 0.02234(17) Uani 1 1 d . . .
H6 H 0.7053 0.4944 0.3733 0.027 Uiso 1 1 calc R . .

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C13 C 0.76981(14) 0.81756(11) -0.12497(11) 0.02651(19) Uani 1 1 d . . .
H13 H 0.8002 0.8337 -0.2017 0.032 Uiso 1 1 calc R . .
C14 C 0.59995(13) 0.79466(10) -0.14881(10) 0.02504(19) Uani 1 1 d . . .
H14 H 0.5140 0.7938 -0.2433 0.030 Uiso 1 1 calc R . .
C5 C 0.87498(13) 0.53548(11) 0.60169(12) 0.0273(2) Uani 1 1 d . . .
H5 H 0.8191 0.4363 0.5939 0.033 Uiso 1 1 calc R . .
C19 C 0.47733(13) 0.89687(11) 0.25950(12) 0.02583(19) Uani 1 1 d . . .
H19A H 0.5838 0.9902 0.3405 0.039 Uiso 1 1 calc R . .
H19B H 0.3773 0.8982 0.2779 0.039 Uiso 1 1 calc R . .
H19C H 0.4476 0.8930 0.1531 0.039 Uiso 1 1 calc R . .
C17 C 0.54920(13) 0.76444(12) 0.43657(11) 0.02577(19) Uani 1 1 d . . .
H17A H 0.5559 0.6689 0.4444 0.039 Uiso 1 1 calc R . .
H17B H 0.4520 0.7801 0.4528 0.039 Uiso 1 1 calc R . .
H17C H 0.6622 0.8513 0.5185 0.039 Uiso 1 1 calc R . .
C3 C 1.10625(13) 0.78992(12) 0.75460(11) 0.0275(2) Uani 1 1 d . . .
H3 H 1.2076 0.8657 0.8523 0.033 Uiso 1 1 calc R . .
C4 C 1.02336(14) 0.64568(13) 0.74382(12) 0.0290(2) Uani 1 1 d . . .
H4 H 1.0684 0.6225 0.8339 0.035 Uiso 1 1 calc R . .

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loop_

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_atom_site_aniso_U_12
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C10 0.0186(3) 0.0165(3) 0.0170(3) 0.0068(3) 0.0088(3) 0.0073(3)
C9 0.0163(3) 0.0149(3) 0.0170(3) 0.0061(3) 0.0088(3) 0.0060(3)
C8 0.0162(3) 0.0171(3) 0.0172(3) 0.0077(3) 0.0090(3) 0.0068(3)
C16 0.0164(3) 0.0198(4) 0.0212(4) 0.0093(3) 0.0106(3) 0.0083(3)
O1 0.0198(3) 0.0440(4) 0.0343(4) 0.0228(3) 0.0158(3) 0.0164(3)
C11 0.0192(4) 0.0184(3) 0.0187(3) 0.0079(3) 0.0105(3) 0.0072(3)
C7 0.0175(3) 0.0200(4) 0.0208(3) 0.0093(3) 0.0110(3) 0.0079(3)
C2 0.0188(4) 0.0202(4) 0.0205(4) 0.0068(3) 0.0076(3) 0.0069(3)
C12 0.0251(4) 0.0252(4) 0.0235(4) 0.0114(3) 0.0153(3) 0.0085(3)
C15 0.0218(4) 0.0229(4) 0.0205(4) 0.0106(3) 0.0088(3) 0.0100(3)
C18 0.0188(4) 0.0253(4) 0.0280(4) 0.0098(4) 0.0105(3) 0.0055(3)
C6 0.0211(4) 0.0212(4) 0.0246(4) 0.0108(3) 0.0111(3) 0.0074(3)
C13 0.0343(5) 0.0261(4) 0.0227(4) 0.0131(3) 0.0165(4) 0.0100(4)
C14 0.0308(5) 0.0236(4) 0.0202(4) 0.0117(3) 0.0105(3) 0.0109(3)
C5 0.0316(5) 0.0301(5) 0.0351(5) 0.0224(4) 0.0213(4) 0.0166(4)
C19 0.0276(4) 0.0252(4) 0.0365(5) 0.0158(4) 0.0209(4) 0.0167(4)
C17 0.0254(4) 0.0355(5) 0.0248(4) 0.0141(4) 0.0169(4) 0.0157(4)
C3 0.0246(4) 0.0346(5) 0.0191(4) 0.0098(4) 0.0065(3) 0.0145(4)
C4 0.0327(5) 0.0425(5) 0.0272(4) 0.0227(4) 0.0177(4) 0.0242(4)

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_geom_special_details

;

All esds (except the esd in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell esds are taken into account individually in the estimation of esds in distances, angles and torsion angles; correlations between esds in cell parameters are only

used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell esds is used for estimating esds involving l.s. planes.

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C1 C6 1.3962(11) . ?
C1 C8 1.4754(10) . ?
C10 C15 1.3876(11) . ?
C10 C11 1.4015(11) . ?
C10 C9 1.5127(11) . ?
C9 C8 1.3646(10) . ?
C9 C16 1.5202(11) . ?
C8 C7 1.5042(11) . ?
C16 C17 1.5338(12) . ?
C16 C18 1.5406(12) . ?
C16 C19 1.5472(12) . ?
O1 C7 1.2194(10) . ?
C11 C12 1.3757(11) . ?
C11 C7 1.4873(11) . ?
C2 C3 1.3897(12) . ?
C12 C13 1.4037(13) . ?
C15 C14 1.4073(12) . ?
C6 C5 1.3918(12) . ?
C13 C14 1.3828(14) . ?
C5 C4 1.3848(15) . ?
C3 C4 1.3866(15) . ?
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  _geom_angle_site_symmetry_3
  _geom_angle_publ_flag
C2 C1 C6 118.67(7) . . ?
C2 C1 C8 120.36(7) . . ?
C6 C1 C8 120.73(7) . . ?
C15 C10 C11 118.40(8) . . ?
C15 C10 C9 132.79(8) . . ?
C11 C10 C9 108.79(7) . . ?
C8 C9 C10 108.14(7) . . ?
C8 C9 C16 129.85(7) . . ?
C10 C9 C16 121.89(7) . . ?
C9 C8 C1 132.72(7) . . ?
C9 C8 C7 109.05(7) . . ?
C1 C8 C7 118.22(7) . . ?
C9 C16 C17 113.58(7) . . ?
C9 C16 C18 109.59(7) . . ?
C17 C16 C18 108.39(7) . . ?
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C9 C16 C19 108.73(7) . . ?
C17 C16 C19 106.01(7) . . ?
C18 C16 C19 110.49(7) . . ?
C12 C11 C10 123.21(8) . . ?
C12 C11 C7 129.25(8) . . ?
C10 C11 C7 107.52(7) . . ?
O1 C7 C11 127.09(8) . . ?
O1 C7 C8 126.71(8) . . ?
C11 C7 C8 106.21(7) . . ?
C3 C2 C1 120.63(8) . . ?
C11 C12 C13 118.08(8) . . ?
C10 C15 C14 118.96(8) . . ?
C5 C6 C1 120.63(8) . . ?
C14 C13 C12 119.67(8) . . ?
C13 C14 C15 121.64(8) . . ?
C4 C5 C6 119.99(9) . . ?
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C5 C4 C3 120.01(8) . . ?

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