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Radical mediated reactions of dithiocarbamates

by

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Abstract

Acyl radicals are versatile intermediates in organic synthesis. Methods for the generation of acyl radicals, which lead to the prior use of acyl dithiocarbamates within the Grainger group for the synthesis of functionalized 1-oxochroman-4-ones, are reviewed (Chapter 1). This work has been extended to studies which have shown that the 6-*exo trig* acyl radical cyclisation pathway adopted can be diverted to a formal 7-*endo trig* pathway through appropriate substitution on the alkene acceptor. Acyl xanthates are shown to behave differently to acyl dithiocarbamates in this respect. Substituted tetrahydrobenzoazepines and tetrahydroquinolines can also be prepared through appropriate nitrogen tethers.

Methodology for the reductive removal of the dithiocarbamate group under neutral conditions has been developed (Chapter 2). Hypophosphorus acid and triethylamine in refluxing dioxane has been shown to reduce primary and secondary dithiocarbamates in good yield. Deuterium incorporation occurs using D_3PO_2. Anomeric dithiocarbamates are reduced with varying amounts of neighbouring *O*-acyl group migration, depending on conditions.

Twisted amides display properties distinct from those of regular amides due to the lack of delocalisation between the nitrogen lone-pair and the carbon-oxygen double bond. A new approach to the synthesis of bridged twisted amides is investigated, based on a transannnular carbamoyl radical cyclisation – dithiocarbamate group transfer reaction (Chapter 3).

Stemofoline is a structurally complex, biologically active alkaloid of the *Stemona* family. Previous routes towards the synthesis of stemofoline and related compounds are reviewed (Chapter 4). Attempted formation of a dithiocarbamate-containing precursor for a tandem 7-*endo*-*trig* cyclisation - 5-*exo*-*trig* transannular cyclisation - group transfer reaction to give the azatricyclic core of stemofoline is discussed. An alternative route towards an azabicyclic fragment of stemofoline via an intermolecular cyclisation has also been investigated.

Abbreviations

Å	Angstrom
Ac	acetyl
ACCN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	2,2’-azobisisobutyronitrile
aq	aqueous
Bn	benzyl
Boc	*t*-butoxycarbonyl
b.p.	boiling point
br	broad
BTEAC	benzyltriethylammonium chloride
°C	degrees Celsius
cat.	Catalytic
cm	centimetres
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undecene
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DLP	dilauroyl peroxide
DMAP	4-dimethylaminopyridine

DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
EDCl	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
EI	electron impact
equiv.	equivalent
ESI	electrospray ionisation
FT-IR	fourier transform infrared
g	gram(s)
h	hours
HMBC	heteronuclear multiple bond correlation
HRMS	high resolution mass spectrometry
HSQC	heteronculear single quantum coherence
Hz	Hertz
i	*iso*
IBX	2-iodoxybenzoic acid
In•	initiator radical
IR	infrared
J	coupling constant (in Hz)
kJ	kilojoules

LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
m	multiplet
M	molar
MAP	4-methoxyacetophenone
*m*CPBA	*meta*-chloroperbenzoic acid
min	minute(s)
mL	millilitres
mol	moles
MOM	methylmethoxy ether
mp	melting point
m/z	mass/charge
n	normal
nm	nanometre
NMR	nuclear magnetic resonance
P	*para*
pet ether	petroleum ether (40-60 °C)
ppm	parts per million
Pr	propyl
q	quartet
qn	quintet

quant.	quantitative
R•	radical
R_f	Retention factor
RT	room temperature
s	singlet
sat.	saturated
t	tertiary
t	triplet
TBAT	tetrabutylammonium triphenydifluorosilicate
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxy
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMS	trimethylsilyl
Tol	toluene
Ts	*para*-toluenesulfonyl
UV	ultraviolet
W	Watt

Contents

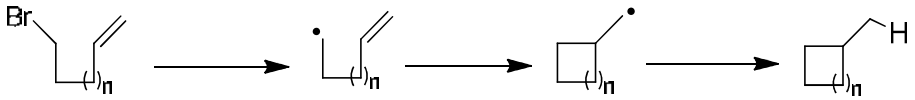
Chapter one

Acyl Radicals from Dithiocarbamate Precursors

1.1 Introduction to Radical Chemistry

Radicals were first discovered in the early 20th century[1] and since the initial work a great deal of interest has been shown in radical chemistry. However it was not until the 1970s that the potential of radicals in synthetic chemistry was appreciated,[2] as initially they were thought to be uncontrollable.

Radical chemistry is often used to form C-C bonds, making it synthetically interesting. This approach has been used to form cyclic systems as the reaction is energetically favourable; the lower energy π C-C bond (226 $kJmol^{-1}$) is replaced by a higher energy σ C-C bond (368 $kJmol^{-1}$). A wide variety of substrates can be cyclised leading to products of anything from 4 to 18 membered rings (Scheme 1).[3] Multiple ring systems can also be generated in this fashion.



Scheme 1 Radical intramolecular cyclisations

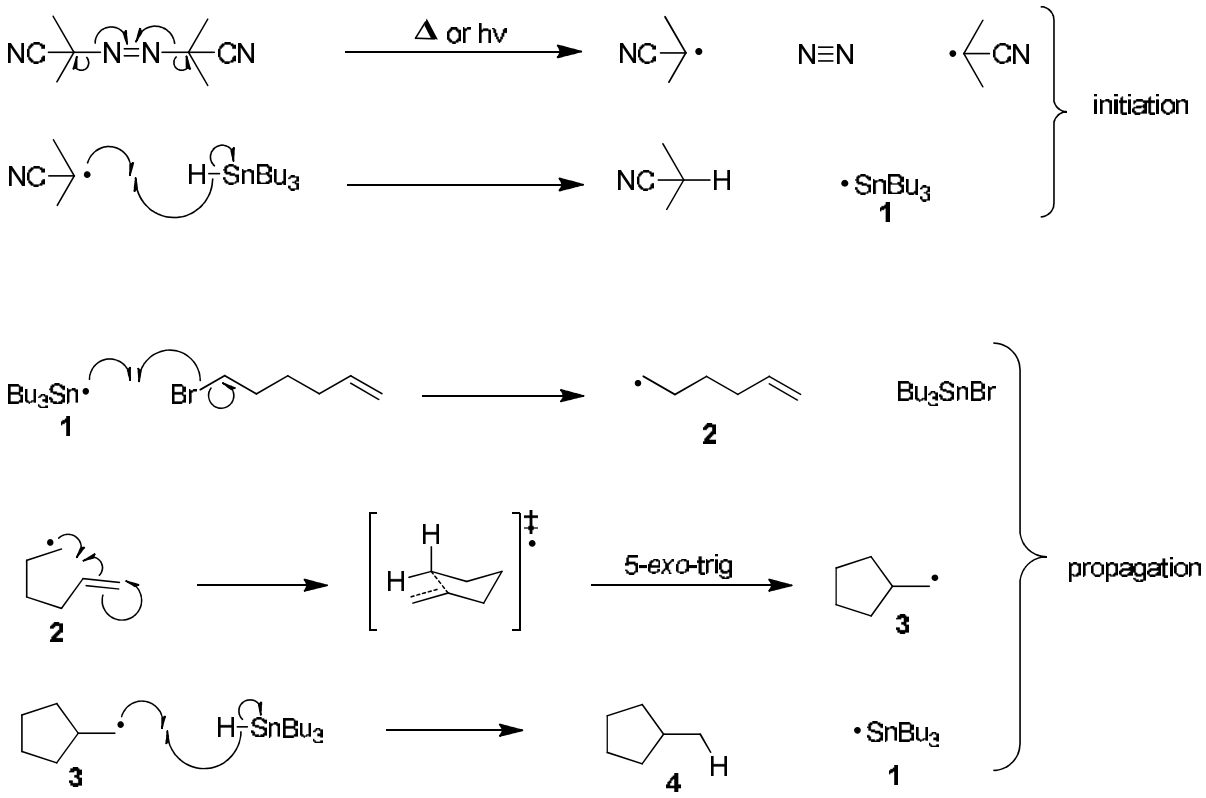
Intermolecular C-C bond formation using radical chemistry is also possible and widely used.[4] Intramolecular reactions generally proceed at a faster rate than their corresponding intermolecular reactions due to favourable entropy considerations.

In general, radical chemistry can be considered advantageous for many reasons. Most radical reactions can be run under neutral conditions. These reactions suffer less from solvation issues and are less prone to steric hindrance, polar effects, rearrangement or eliminations, which are more often observed in non-radical reactions. Carbonyl groups do

not need to be protected in radical reactions, negating the need for protection and subsequent deprotection steps, thus saving time and expense in syntheses.

However, the disadvantages commonly associated with radical chemistry are that reactions have to be run at high dilution to prevent recombination of the newly formed radicals to give starting material, slow addition by use of syringe pumps and the use of toxic tin reagents.

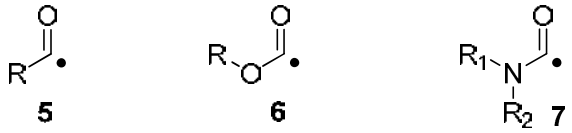
A general mechanism for a reductive radical cyclisation reaction is outlined in Scheme 2. An initiator is broken down (using heat or light) to give two radicals. Abstraction of a hydrogen atom from tributytin hydride generates the chain carrier radical **1**. This interacts with a molecule of starting material, by fission of the halogen-carbon bond, creating the carbon centred radical **2**. This step is driven by the formation of the strong tin-halogen bond. Once formed the carbon centred radical undergoes cyclisation onto the alkene giving the carbon centred radical **3**. Abstraction of hydrogen from another molecule of tributyltin hydride gives the product **4** and generates another molecule of the chain carrier **1**.



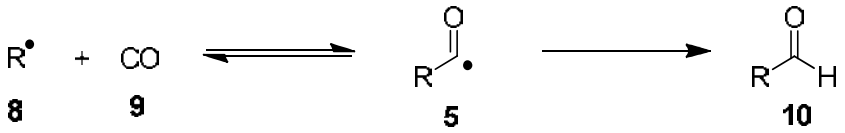
Scheme 2 Mechanism of intramolecular cyclisations

1.2 Introduction to Acyl Radicals

Carbon-carbon bond formation is one of the most important reaction types in organic synthesis. The reaction of acyl radicals with alkenes has proven to be very successful for achieving this. There are three major classes of acyl radicals; alkanoyl radicals (**5**), alkoxycarbonyl radicals (**6**) and carbamoyl radicals (**7**).[5] Generally alkanoyl radicals (**5**) are termed acyl radicals.

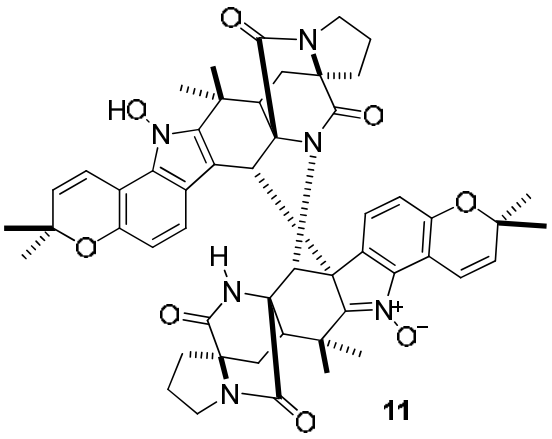


The major drawback of using alkanoyl radicals is their tendency to undergo decarbonylation (Scheme 3). Generally decarbonylation is in equilibrium with the carbonylation reaction where the alkyl radical (**8**) reacts with carbon monoxide (**9**). The position of this equilibrium is dependant on the stability of the alkyl radical and can be used advantageously in the formation of acyl radicals. Running reactions under a CO atmosphere forces the equilibrium to lie in favour of the acyl radical (**5**) by making the decarbonylation reaction unfavourable.[6,7] The acyl radical is reduced to give the aldehyde (**10**) if run in the presence of a hydride source. Alternatively the acyl radical can be trapped by a functional group that may be present.



Scheme 3 Carbonylation/decarbonylation

Alkoxylcarbonyl radicals (**6**) could also theoretically undergo fragmentation, by losing carbon dioxide to give the alkyl radical. Decarbonylation of carbamoyl radicals would result in aminyl radicals which are high energy and thus disfavoured. This suggests that carbamoyl radicals are synthetically useful and this has been demonstrated by the synthesis of the complex natural product, stephacidin B (**11**).[8] More recently the syntheses of breviones A (**12**), B (**13**) and C (**14**), which are formed utilising acyl radicals, has been reported.[9]



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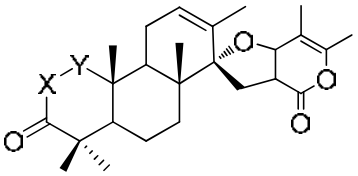
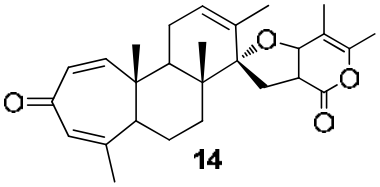


12 X-Y = CH=CH
13 X-Y = CH_2-CH_2



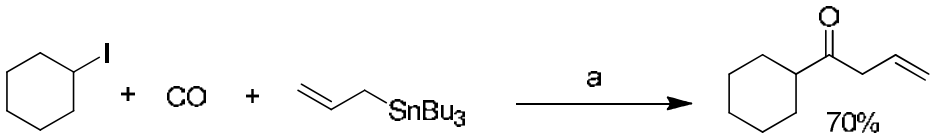
14

The formation of acyl radicals has been widely studied. Many reports have shown the synthesis of acyl radicals from a wide variety of different functional groups. Examples of these are aldehydes, acid chlorides, xanthates, oxime oxalate amides, 1-carbamoyl-1-methylcyclohexa-2,5-dienes, acyl selenides, acyl tellurides, cobalt salophens, acyl hydrazides, and from the cyclisation of aryl radicals onto sulfides. Due to the vastness of this area of research and the existence of a comprehensive review of it,[5] only the examples of most relevance to this project will be discussed herein.

1.3 Generation of Acyl Radicals

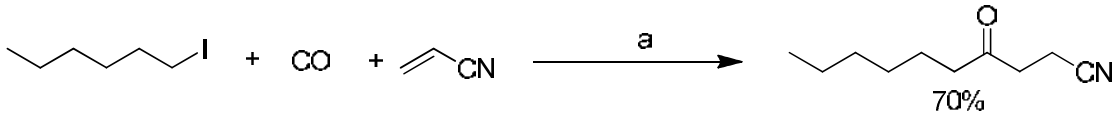
Acyl chlorides have been reduced to aldehydes, via acyl radicals, using radical mediators such as tributyltin hydride. However this method of acyl radical production is not widely used due to problems with byproduct formation[10] and the need to run these reactions at high pressures of CO. The use of alkyl halides as a source of carbonyl radicals was investigated by Ryu and Sonoda.[11] They believed that the problems previously seen could be overcome by using a more reliable method of generating the radicals. To do this they

used the Bu_3SnH conditions but also employed the use of the radical initiator AIBN in catalytic amounts (Scheme 4).[12]



Scheme 4 a) AIBN, C_6H_6, 10 atm., 80 °C, 12h, 70%

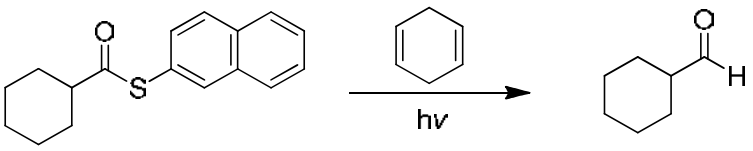
Although this method allowed for the formylation of a range of alkyl, aryl and vinyl halides, not all organohalides can be formylated in this manner. If the initial radical is particularly stable, due to the presence of electron-withdrawing groups, it is more likely to abstract a hydrogen atom from the Bu_3SnH than to undergo formylation. This can be prevented by running the reaction under very dilute conditions or by increasing the pressure of CO.[13] The use of $(TMS)_3SiH$, as the radical mediator in these reactions has been reported to give higher levels of formylation.[14] This is due to the $(TMS)_3SiH$ having a reduced ability to undergo hydrogen atom transfer (Scheme 5).



Scheme 5 a) AIBN, $(TMS)_3SiH$ (1.2 equiv.), C_6H_6, 80 °C, 2h, 70%

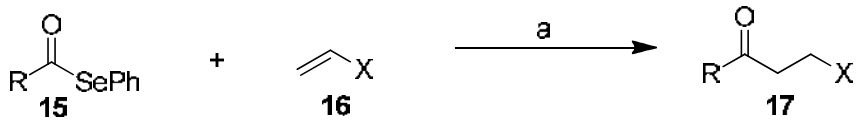
Naphthyl thioesters have been employed as a source of acyl radicals, through photolysis, and can be used to produce a wide range of aldehydes, including primary, secondary and tertiary derivatives along with aromatics (Scheme 6).[15] Simple *S*-phenyl thioesters do not

react with Bu_3Sn radicals, making these simple thioesters redundant as a source of acyl radicals.[16, 17]



Scheme 6

Unlike thioesters, selenoesters can react with Bu_3Sn radicals, due to the relatively weak RCO-SeR bond.[18, 19] This makes selenoesters useful as a source of acyl radicals. Products can be easily purified by column chromatography and the intermediate radicals do not undergo the decarbonylation or reduction reactions observed with the reactions of acyl chlorides and tin radicals.



X = electron withdarwing or radical stabilising

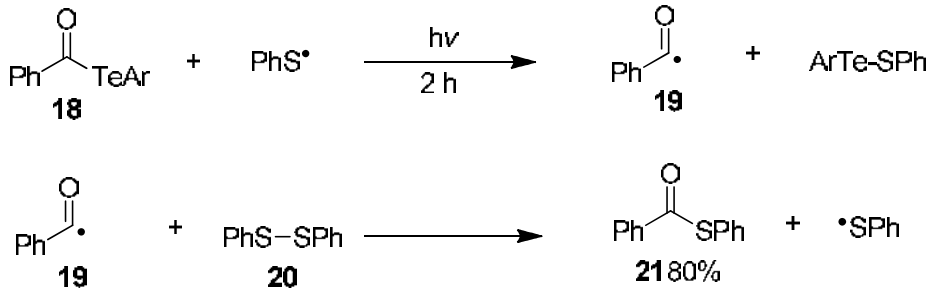
Scheme 7 a) Bu_3SnH, AIBN

Intermolecular reactions of the phenylselenoesters **15** can occur with alkenes that have electron withdrawing or radical-stabilising substituents (**16**) to give the ketone **17** (Scheme 7). Phenyl selenoesters can also be used for intramolecular addition reactions on both activated and unactivated alkenes. The rate of this addition reaction is faster than the decarbonylation or reduction reactions that could potentially compete.[10, 20]

Due to the slow rate of the phenyl selenoester radical addition reactions, there is no need to run these reactions at high dilution. This along with the ability to form primary alkyl,

vinyl and aryl substituted acyl radicals makes the phenyl selenoesters a good source of acyl radicals.

Crich et al. have shown that acyl tellurides **18** can be used as a source of acyl radicals, generated by photolysis. The generated radicals can be trapped intermolecularly by dichalcogenides or TEMPO. Crich has undertaken mechanistic studies to show the reaction pathway is as described in Scheme 8.[21, 22, 23]



Scheme 8 Generation and subsequent reaction of acyl radicals from acyl tellurides

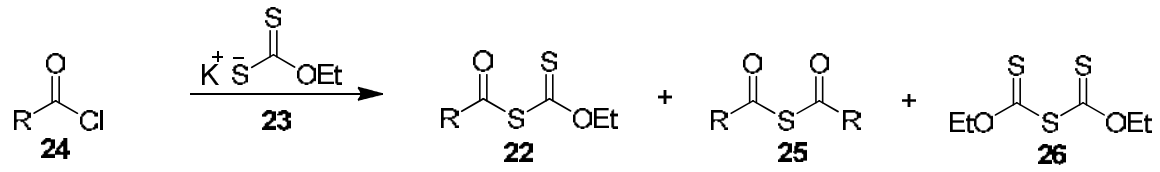
Exposure to white light induces homolytic fission of the C-Te bond to give the acyl radical **19**, which then reacts with the dichalcogenide **20** to give the product **21** in an 80% yield and another radical, which can carry the chain process. This chemistry can be used for radical cyclisations onto alkenes giving 5, 6 and 8 membered rings.

1.4 Acyl Radicals from Xanthates

The existence of xanthates and their salts have been known for a very long time, with the earliest report being in 1822.[24] They have been used as a source of alkyl radicals in the well known Barton-McCombie deoxygenation reaction (see Chapter 2).[25] Barton also

reported the earliest example of the generation of acyl radicals from xanthates in 1962.[26] It was observed that xanthate molecules can break down in the presence of visible light to provide the acyl radical. Barton's work has been extensively progressed by Zard over the past couple of decades.[27, 28, 29]

Acyl xanthates (**22**) are formed by the reaction of the xanthate salt (**23**) with the relevant acid chloride (**24**) in a simple one step procedure. These reactions, although simple in principle, were originally found to be unreproducible. This was found to be due to the production of two side products, along with the radical precursor; thioanhydride **25** and O,O-diethyl-xanthic anhydride **26** (Scheme 9).[26, 28, 30]

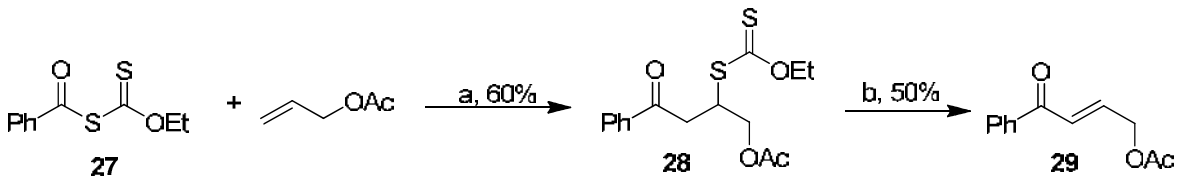


Scheme 9 Xanthate formation

Any excess xanthate salt can react with the newly formed S-acylxanthate and cause it to breakdown to give the undesired side products.[28] This can be prevented by using excess acid chloride and also ensuring the reactions are carried out in the dark.[31] This is disadvantageous as the acid chloride is more expensive and significantly less stable than the commercial available xanthate salt.

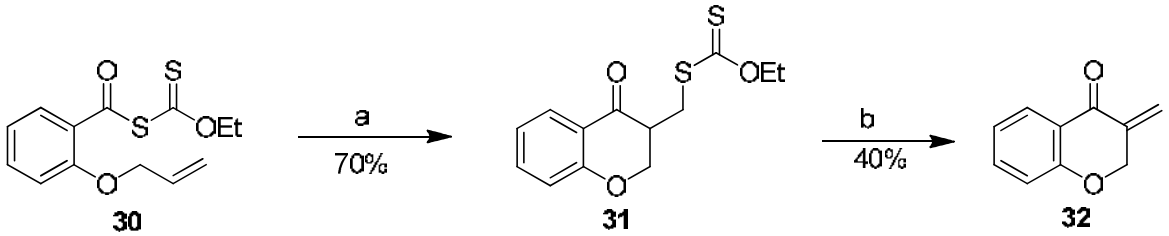
Acyl radicals generated from xanthates can be used for both intermolecular and intramolecular reactions. Olefins are used to trap the initial radical (Scheme 10). In the intermolecular example the acyl xanthate **27** is exposed to visible light in the presence of

allylacetate to give the group transfer product **28**. The xanthate in this product can be easily eliminated, as it is in the β-position relative to the carbonyl group, by heating in the presence of copper to give alkene **29**.[28]



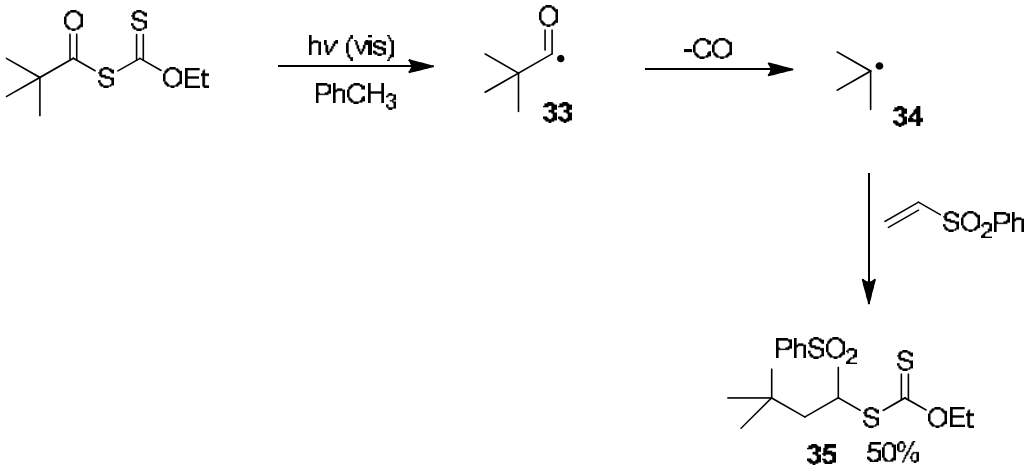
Scheme 10 a) hν (vis), $PhCH_3$; b) Cu, heat

This chemistry can also be applied to intramolecular reactions where the olefinic trap is part of the starting xanthate (**30**) (Scheme 11). Exposure to visible light in the presence of toluene gives the cyclised product (**31**) which can then be eliminated as before, to give the alkene **32**.



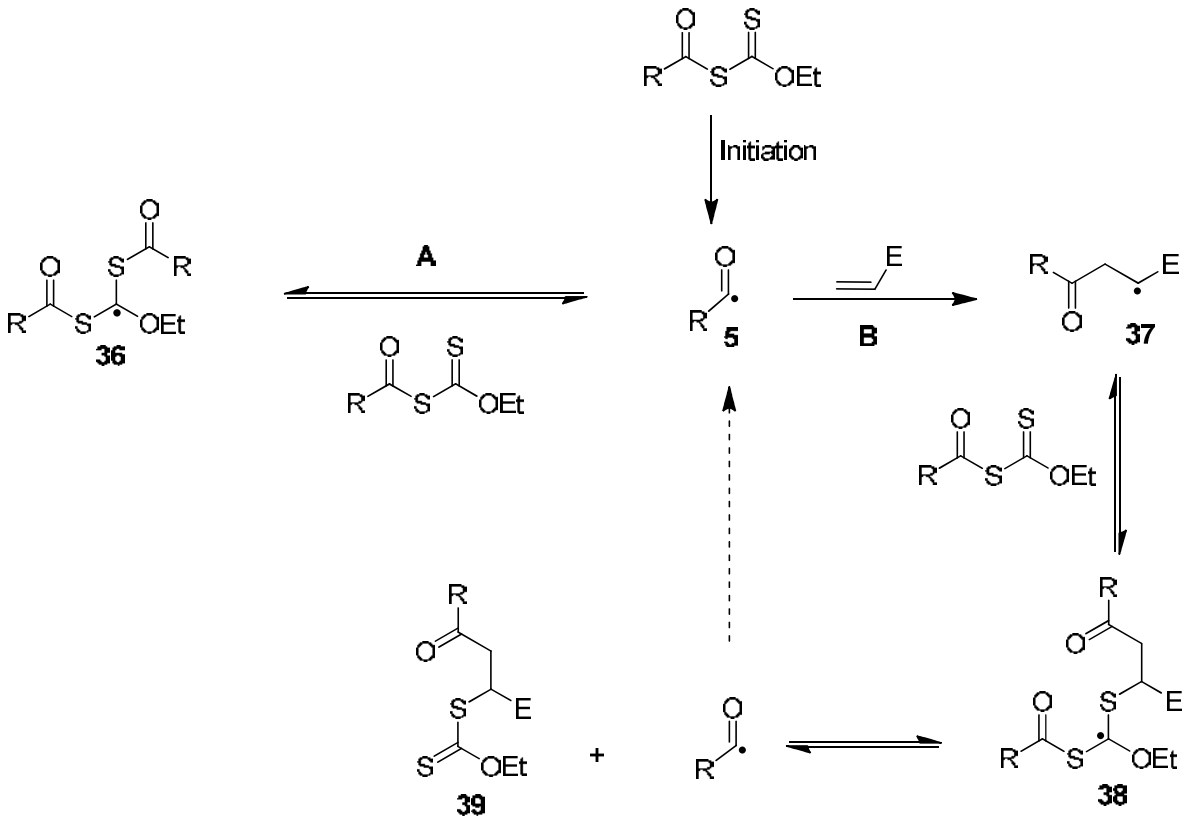
Scheme 11 a) hν (vis), $PhCH_3$; b) Cu, heat

Zard has also reported examples where carbon monoxide is lost from the acyl radical **33** to give an alkyl radical **34**. This is only observed when the alkyl radical formed has some degree of stability due to being tertiary or benzylic. After loss of carbon monoxide from radical **33** to give radical **34**, trapping with an external olefin occurs to give **35** (Scheme 12).



Scheme 12 Loss of CO from acyl radical and subsequent trapping with an alkene

The mechanism for the radical addition to the olefins is summarised in Scheme 13. Initiation produces the acyl radical **5**, which can add to the thiocarbonyl group of a further molecule of starting material (pathway A). The resultant tertiary radical **36** cannot dimerise due to steric hindrance, meaning the only pathway it can follow is fragmentation, either of the C-O bind or of the C-S bond. Breakage of the C-O bond is not observed, presumably because this bond is very strong and breaking it would result in an ethyl radical which is very high in energy.[28, 32]



Scheme 13 Radical addition to olefins

The only other possible reaction is breakage of the C-S bond which results in formation of the initial radical **5**. The degenerative nature of this pathway is key to this system, and effectively increases the lifetime of the acyl radical. This allows for reaction of the initial acyl radical with relatively unreactive olefins in an intermolecular fashion and can also be employed to allow more difficult intramolecular cyclisations to occur. Prior to this method, reactions of this kind were controlled by the slow addition of reagents or by using high dilution, to prevent a build up of radicals. However the degenerative pathway present in this system allows for better control and slow release of the radical.

When the acyl radical reacts via pathway B (attack onto an alkene), it produces the intermediate secondary radical **37**. This can undergo a reversible reaction with another molecule of starting xanthate. The resulting tertiary radical **38** can undergo a further reversible reaction to give the initial radical, propagating the chain process and also a molecule of the end product **39**.

The main drawback with using acyl xanthates is the problem associated with the formation of the radical precursors. This is because the reactions need to be carried out at low temperatures and with an excess of acid chloride. Despite the disadvantages, xanthates are extremely useful because they sustain a radical pathway without the need for toxic tin reagents and the reactions can be initiated by visible light or chemical initiators such as peroxides. This chemistry is tolerant of a wide range of functional groups allowing a considerable variety of products to be formed. The presence of the xanthate group in the product after the radical reaction has occurred allows for further functional group transformations to occur. The carbon-carbon bond forming reactions are atom economical, with all the parts of the starting olefin and xanthate being present in the product.

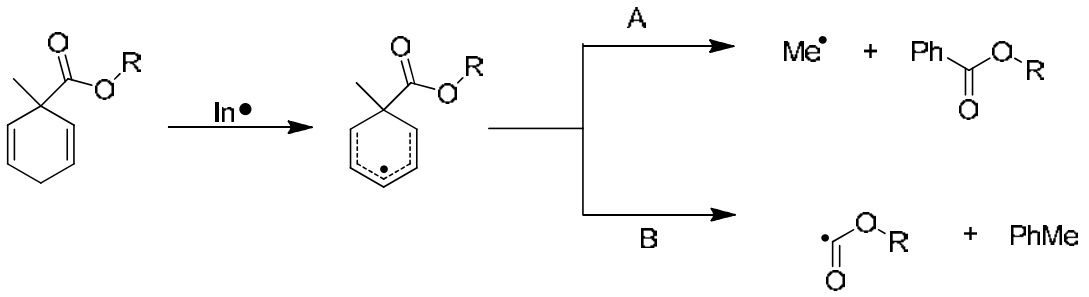
1.5 Generation of Carbamoyl Radicals

The generation of carbamoyl radicals has been successfully achieved by using precursors such as 1-carbamoyl-1-methylcyclohexa-2,5-dienes[33,34,35], oxime oxalate amides[36,37] and dithiocarbamates.[38,39] Each of these functional groups have their own advantages and drawbacks which will be discussed in turn. Overall these methods for generating radicals

can be considered useful, due to the lack of the need for toxic reagents, such as Bu_3SnH, that are often associated with radical chemistry and the formation of little or no side products.

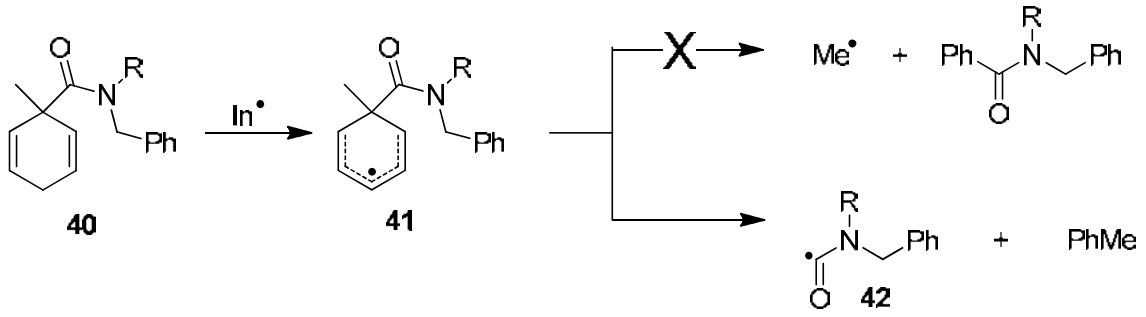
1.5.1 1-Carbamoyl-1-methylcyclohexa-2,5-dienes

The use of esters of 1-methylcyclohexa-1,5-diene-1-carboxylic acid as a source of alkoxycarbonyl radicals has been shown to be successful (Scheme 14, pathway B). However, a competing reaction was observed, where the intermediate, the radical of 1-methyl-1-carboxalatocyclohexadienyl, dissociated to give methyl radicals and benzoate esters (pathway A).[35]



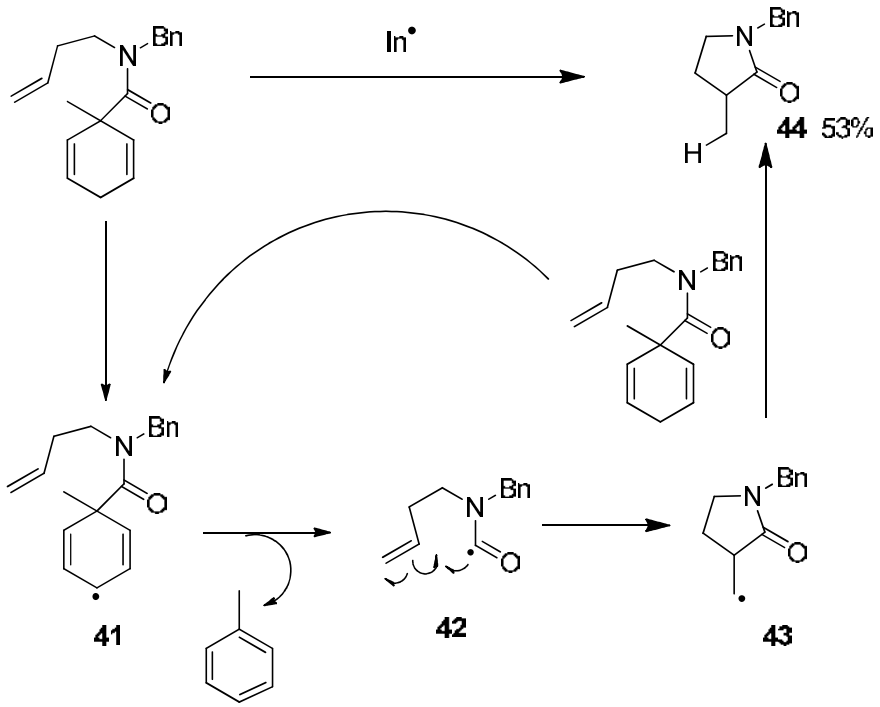
Scheme 14 Formation of radicals

The dissociation of the analogous amide to form the methyl radical was predicted to be markedly disfavoured and as expected the results showed no competing reactions (Scheme 15). The initial radical is formed by selective hydrogen abstraction on the cyclohexadiene moiety of **40** to give the radical **41** that is stabilised by delocalisation of the radical over the cyclohexadiene system. Carbon-carbon bond dissociation releases toluene and the carbamoyl radical **42**.



Scheme 15 Formation of carbamoyl radicals

The generated carbamoyl radical can potentially then undergo cyclisation, generating a new carbon centred radical **43**, which can abstract a hydrogen from another molecule of the stating material (Scheme 16). This not only gives the reduced product **44** but also generates another molecule of radical **41**, giving rise to a chain process, making this method synthetically appealing.[33,34]

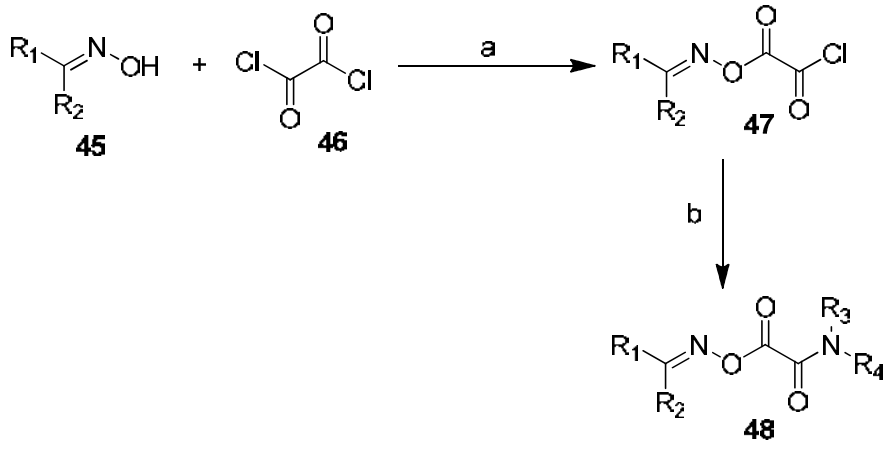


Scheme 16 Reaction mechanism of cyclisation

Another advantage of this method is that the byproduct is toluene, which can be easily removed by evaporation, rather than toxic tin reagents, often used in radical chemistry. Both β- and γ-lactams have been obtained from the ring closing reactions of the generated carbamoyl radicals. One drawback to using this method for radical cyclisations is the lack of functionality in the product, another is the potential for radical **42** to be reduced before cyclisation occurs.

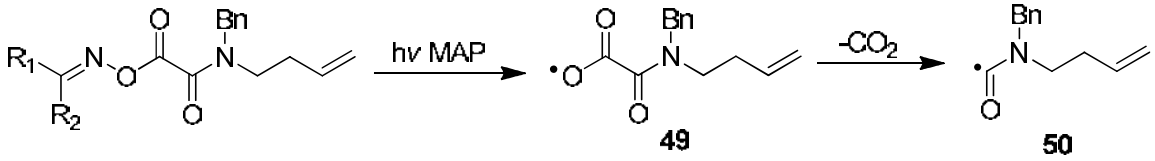
1.5.2 Oxime Oxalate Amides

Oxime oxalate amides are used as a source of carbamoyl radicals which can then undergo cyclisations to give β- or γ-lactams. The oxime oxalate amides **48** are prepared in high yields by first creating a (chlorooxallyl)oxime **47** from the reaction of the corresponding oxime **45** with oxalyl chloride **46** and subsequently treating this with a secondary amine (Scheme 17).[36,37]



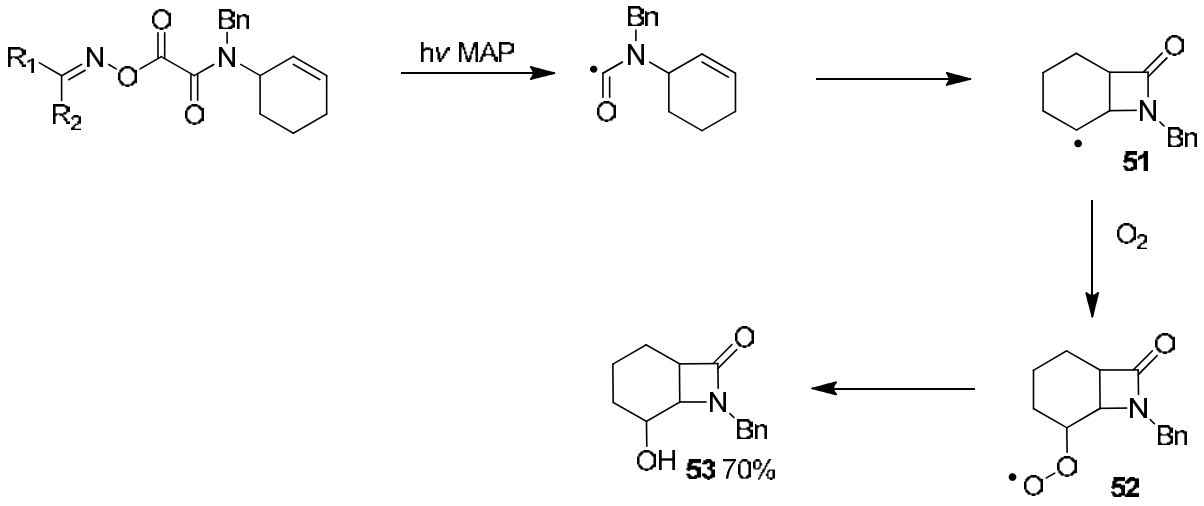
Scheme 17 a) Et_2O, -20 °C; b) Pyridine, R_3R_4NH

The formation of the radicals is initiated by UV light, in the presence of stoichiometric amounts of the photosensitiser MAP. The radical is formed by dissociation of the N-O bond of **48** to give an iminyl radical and an acyloxyl radical **49**, which rapidly loses CO_2 to give the carbamoyl radical **50** (Scheme 18). This can then undergo the relevant cyclisation reactions.



Scheme 18 Formation of radicals from oxime oxalate

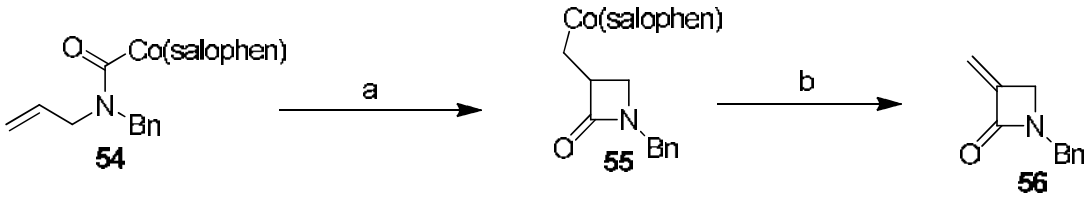
The cyclisations of secondary or benzylic radicals generated in this fashion gave rise to hydroxylated β-lactams **53**, with the hydroxyl group forming at the original radical centre (Scheme 19). This is believed to occur due to the stability of the radical **51**, formed after cyclisation, allowing it to react more readily with dissolved oxygen in the solution giving **52** and then abstract a hydrogen from the solvent. This incorporation of a hydroxy group into the product is advantageous as it allows for further functionality to be introduced into the molecule.



Scheme 19 Production of hydroxylated β-lactams

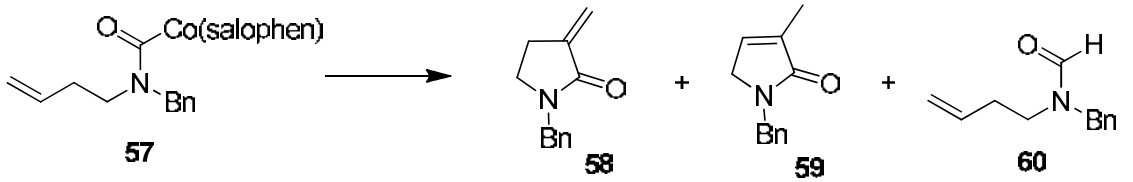
1.5.3 Cobalt Salophens

Pattenden has shown that cobalt(III) complexes can be used as a source of carbamoyl radicals, that undergo intramolecular cyclisations to give lactams (Scheme 20). The cobalt salophen complexes (**54**) are formed from the readily available carbamoyl chloride. These complexes cyclise upon exposure to visible light to give compounds of the type **55** when refluxing in the presence of pyridine.[40]



Scheme 20 a) hν, pyridine, heat, 42%; b) toluene, heat, 21%

The cobalt salophen complex can be removed from **55** by boiling in toluene to give the methylene-β-lactam **56**, albeit in modest yields. The cobalt complex can be exchanged for an alcohol by first heating with TEMPO, followed by reductive hydrogenolysis. Attempts to form the 5-membered γ-lactam system from **57** using the same method gave 3 products (Scheme 21).



Scheme 21 a) toluene, heat, **58** (59%), **59** (9%), **60** (7%)

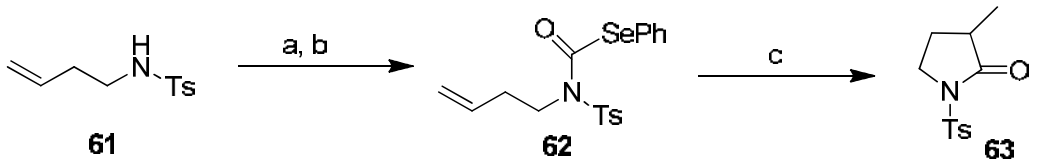
The carbamoyl radical is produced when the cobalt salophen complex **57** is irradiated in refluxing CH_2Cl_2. This radical undergoes cyclisation to give both the external alkene **58**

(41%) and internal alkene **59** (14%). A third product, the open chain alkene **60** is also formed in a low yield, which is believed to occur when a hydridocobalt species reacts with the intermediate uncyclised radical.

The attempted synthesis of δ-lactams using these cobalt complexes also resulted in a mixture of products. Despite these reactions leading to multiple products when attempting to form larger ring systems, carbamoyl cobalt salophens have been used in the racemic synthesis of an antibiotic, the β-lactam thienamicin.

1.5.4 Selenium Carbamates

The use of selenoesters as a source of acyl radicals has been known for some time. This work was extended by Rigby in 1998, by creating selenocarbamates (e.g. **62**), from which carbamoyl radicals can be generated. These reactions are mediated by the traditional tin process. Cyclisation of these radicals led to the formation of γ-lactams **63** (Scheme 22). These reactions can tolerate a variety of substituents on the alkyl chain and it is also possible to use alkyl groups on nitrogen instead of tosyl groups.[41]

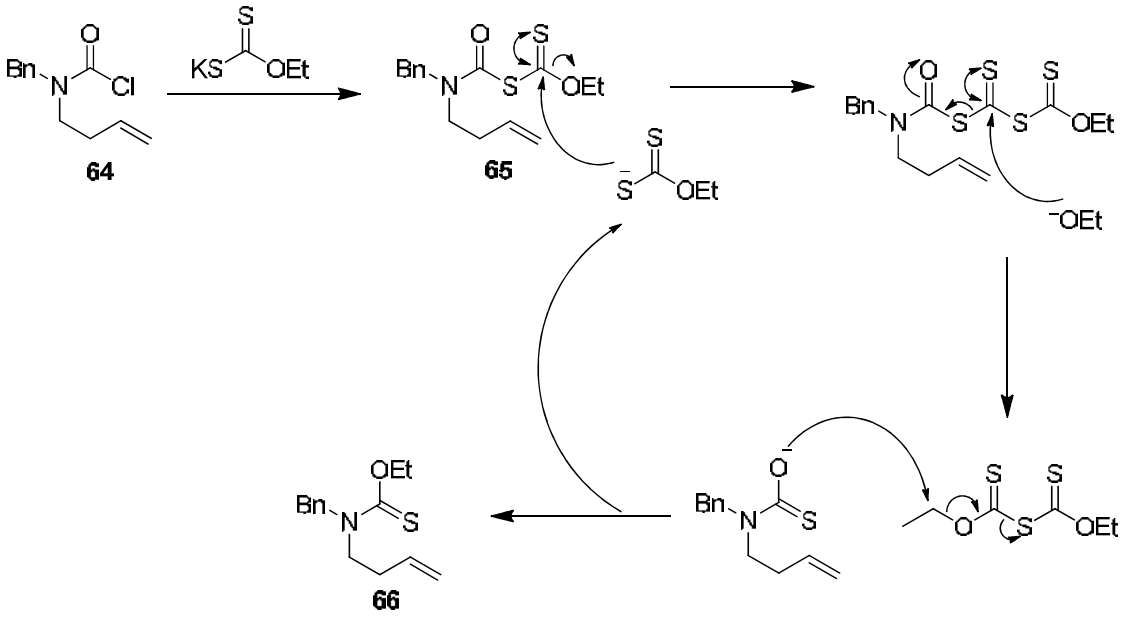


Scheme 22 a) triphosgene; b) PhSeH, pyridine, 81% over two steps; c) TMS_3SiH, AIBN, toluene, reflux, 46%

Although the cyclisation precursor is easily synthesised from tosyl amide **61**, this method gives modest yields and is only useful for the production of 5-membered rings.

1.5.5 Dithiocarbamates

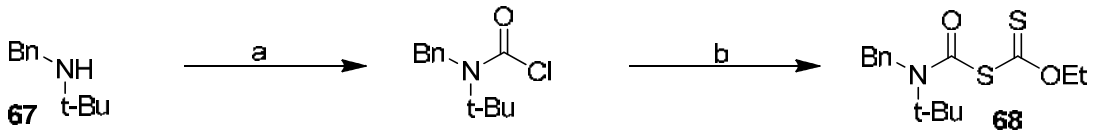
Attempts to extend Zard's work by using carbamoyl xanthates have been made. The Grainger group has reported problems linked with the formation of these substrates. Reaction of carbamoyl chloride **64** with the xanthate salt **23**, did give the expected carbamoyl xanthate **65** but in a low yield. The major product that was observed was O-ethyl thiocarbamate **66** (Scheme 23).



Scheme 23 Formation and subsequent breakdown of carbamoyl xanthates

The explanation for this is that, although the carbamoyl xanthate is believed to be formed, it then goes on to react further with the xanthate salt. A series of ionic reactions can then occur, releasing the observed product **66** and also regenerating more xanthate salt, leading to further breakdown of the carbamoyl xanthate **65**.[38,39]

Miranda et al. reported that carbamoyl xanthates of type **68** could be formed by using secondary *t*-butyl amines **67** as the starting material (Scheme 24). The presence of the *t*-butyl group is important to maintaining the stability of these molecules.[42]



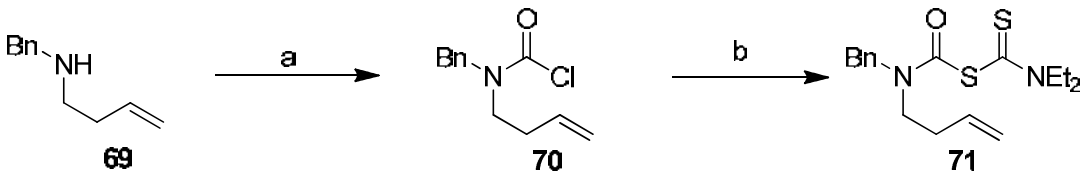
Scheme 24 a) triphosgene, Et_3N, CH_2Cl_2, rt, 10 mins; b) KSC(S)OEt, CH_3CN, 15 mins, 0 °C, 77% over two steps

All attempts at using isopropyl or methyl secondary amines, resulted in a complex mixture of products. The reason behind the stability provided by the *t*-butyl group is not supported by any evidence however it is believed to be due to either steric hindrance, or a conformation effect. The rotational energy barrier around the N-C-O bond is expected to be high and the *t*-butyl group attached to the nitrogen sits in a fixed conformation. Once formed these carbamoyl xanthates have been used to provide a variety of cyclised products, via intramolecular reactions.

To overcome the problems observed with nucleophilic attack, when attempting to synthesise carbamoyl xanthates, our group turned its attention to the formation of the related carbamoyl dithiocarbamates.

The secondary amine **69** was reacted with triphosgene in the presence of base to give the carbamoyl chloride **70** in high yields. This was reacted with the inexpensive and commercially available sodium diethyldithiocarbamate salt to give the carbamoyl dithiocarbamate **71** cleanly in high yields (Scheme 25). The carbamoyl dithiocarbamate

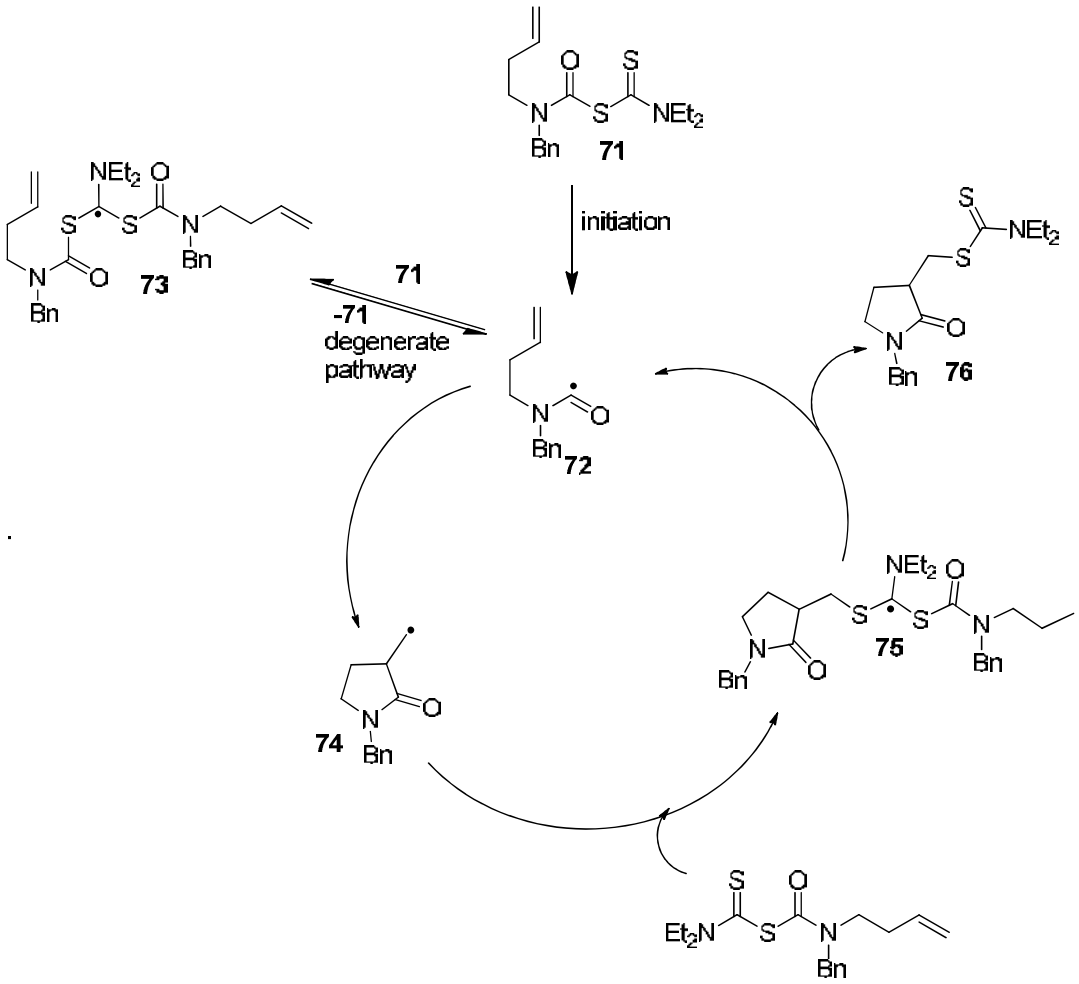
has more electron density in the thiocarbonyl group than the xanthate, making it less susceptible to nucleophilic attack and thus explaining why it is much more stable.



69 70 71

Scheme 25 a) triphosgene, pyridine, $PhCH_3$, rt, >90%; b) $Et_2NC(S)SNa.3H_2O$, acetone, >90%

The intramolecular cyclisation of this carbamoyl dithiocarbamate was achieved in a high yield, by simply exposing a solution of it to a 500 W halogen lamp that generated enough heat to bring the solution to reflux. The light causes the homolytic fission of the C-S bond to produce the carbamoyl radical **72**. This can then either cyclise or react with another molecule of starting material to produce the tertiary radical **73** (Scheme 26). As in the case of the xanthate reaction mechanism this pathway is degenerate, with the symmetrical tertiary radical only being able to fragment back to give the starting material and carbamoyl radical **72**.



Scheme 26 Cyclisation of carbamoyl radicals generated from dithiocarbamates

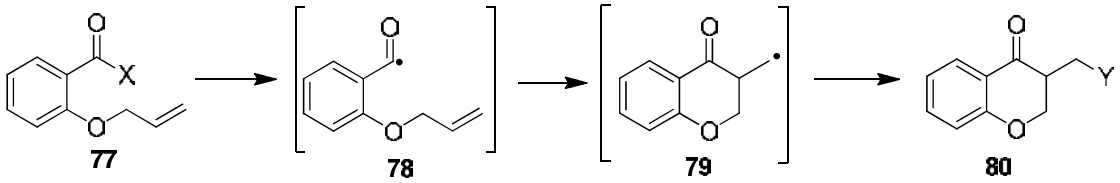
Cyclisation of carbamoyl radical **72** gives the alkyl radical **74**, which can then react another molecule of starting material to give the stable tertiary carbon centred radical **75**. Fragmentation of this gives the group transfer product **76**, in a 96% yield, and regenerates the initial carbamoyl radical, constituting a chain process.

The advantages of using dithiocarbamates are much the same as when using xanthates. The presence of the dithiocarbamate group in the product allows for further functionalisation, as will be discussed in Chapter 2. The degenerative pathway in the reaction mechanism means the more difficult cyclisations and intermolecular reactions

can occur more readily, as the lifetime of the carbamoyl radical is effectively increased. Slow addition of reagents or high dilution is not required and there is no need for toxic tin reagents.

1.6 Cyclisation of 6-Heptamoyl Radicals

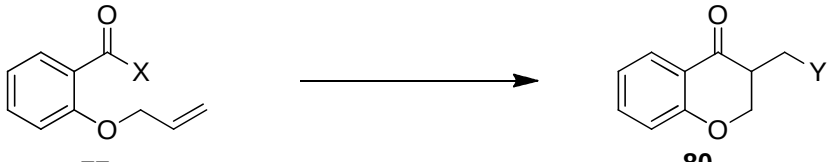
Acyl radicals can be used to form a variety of different products, including aldehydes, ketones and cyclic carbonyl compounds, by reduction and intermolecular or intramolecular alkene additions. A large number of research groups have used alkene **77** and the subsequent acyl radical **78** generated from this, as a model system to test these radicals. Once formed the radical undergoes 6-*exo*-trig cyclisation to give **79**, followed by either hydrogen atom abstraction or trapping with a functional group, to give **80** (Scheme 27).



Scheme 27 Cyclisation of 6-heptamoyl radicals

The commercially available and inexpensive salicyclic acid can be used as the starting material to yield the radical precursors via simple, well characterised reactions. This ease of formation, along with the lack of decarbonylation, makes this system particularly interesting to study. Decarbonylation would result in an aryl radical, which is high in energy and thus not formed.

Many different radical cyclisation precursors of type **77** have been used (Table 1), including xanthates,[27] thioesters,[43,44] acyl chlorides[45] and acyl selenides.[46] The use of different precursors and different initiation techniques led to either group transfer or hydrogen abstraction, in varying yields.



77 **80**

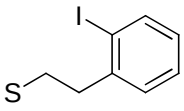
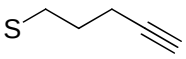
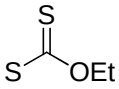
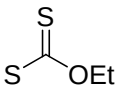
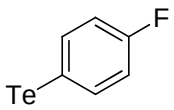
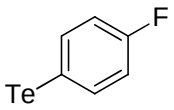
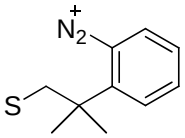
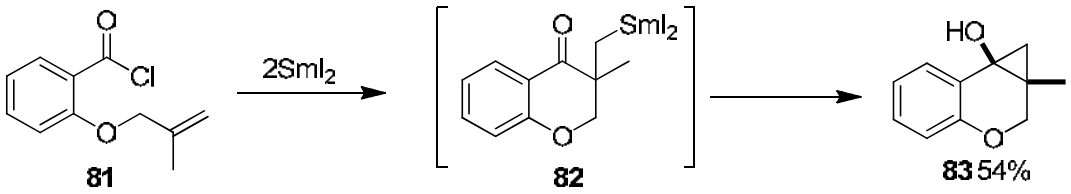
X	conditions	Y	Yield
SePh	Bu_3SnH, AIBN	H	52%
	Bu_3SnH, AIBN	H	96%
	PhS	H	78%
Cl	NEt_3, hv 350 nm	H	33%
	hv		70%
	hv		96%
	NaI	I (then elimination)	81%

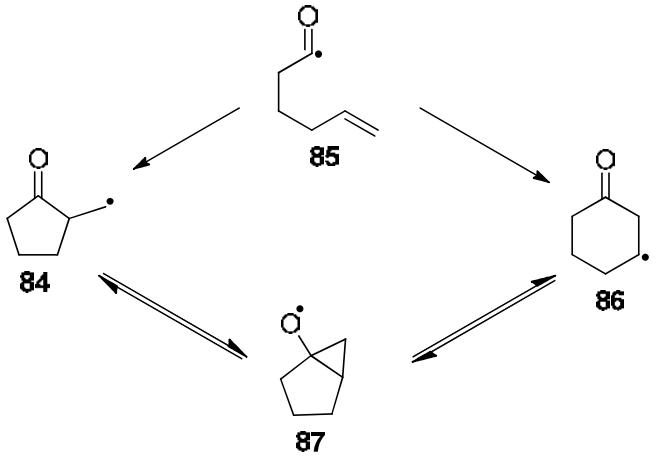
Table 1 Examples of cyclisation of 6-heptamoyl radicals

One noteworthy example is the cyclisation of acid chloride **81** with samarium (II) iodide (Scheme 28). It is believed that when the 6-*exo*-trig cyclisation occurs it is followed by trapping with SmI_2 to produce the intermediate **82**. This intermediate organometallic species then closes onto the ketone to give the alcohol **83** as the final product.[47]



Scheme 28 Cyclisations with samarium(II)iodide

The majority of the cyclisations of radicals generated from precursors of the type **77**, occur via the 6-*exo* mode. There have been some reports of products arising from the 7-*endo* mode as a side product in low yields, occurring when cyclising onto a substituted alkene. The thermodynamic equilibration of the β-acylalkyl radicals generated in 5-*exo* vs 6-*endo* cyclisations similar to this, have been studied extensively. The Beckwith[48] and Dowd[49,50] groups both thought that the mechanism of this equilibrium involves the formation of the cyclised radical **84** that undergoes a rearrangement via a 3-membered ring intermediate, with the radical centred on the oxygen. The initial acyl radical **85** can cyclise via 5-*exo*-trig cyclisation to give the radical **84**, or via 6-*endo*-trig cyclisation to give the radical **86**. Both of these species can interconvert via the oxygen centred radical **87** (Scheme 29).



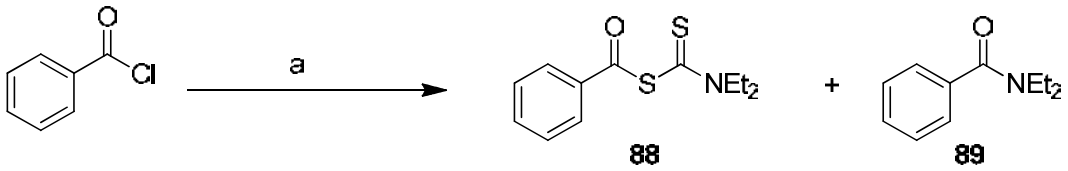
Scheme 29 6-*endo* vs 5-*exo* cyclisation

There have been extensive studies on the possibility of these cyclised products rearranging via the initial acyl radical. This has been shown to not occur, meaning the *endo* product could be formed either by direct cyclisation of the acyl radical or via the Beckwith/Dowd type rearrangement pathway.

1.7 Synthesis of Acyl Dithiocarbamates

The Grainger group has developed the use of carbamoyl dithiocarbamates as a source of carbamoyl radicals and has also carried out some initial studies on the use of acyl dithiocarbamates as a source of acyl radicals. The original work in this field, employed the chemistry to form the known xanthate systems, to create dithiocarbamates. The corresponding acid chloride was treated with the commercially available sodium diethyldithiocarbamate salt. After screening different temperatures and times, optimal conditions for the formation of these acyl dithiocarbamates **88** were found to be at 0 °C

for 15 minutes in the dark, using a slight excess of the dithiocarbamate salt (Scheme 30).[51] This gave dithiocarbamate **88** in a quantitative yield.



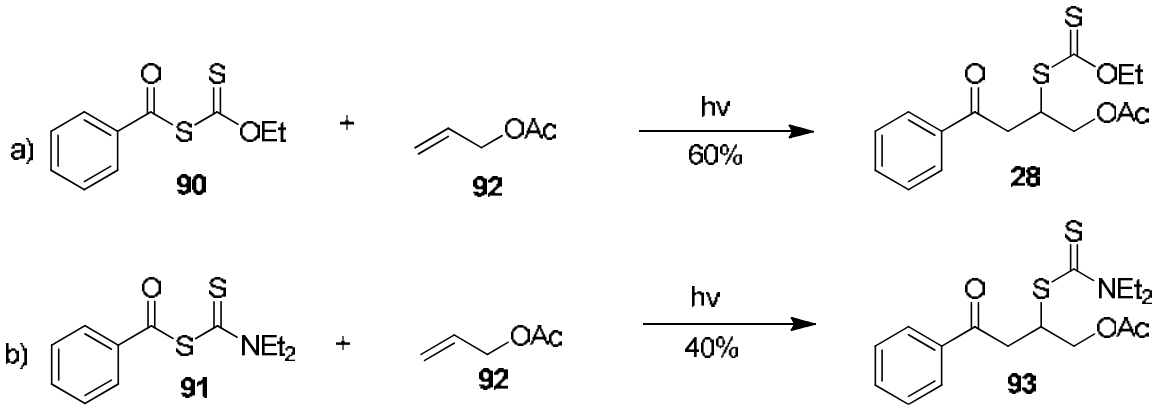
Scheme 30 a) $NaSC(S)NEt_2.3H_2O$, acetone, 0 °C

An increased reaction time led to extrusion of CS_2 and production of the colourless amide **89**, rather than the yellow dithiocarbamate **88.** The conditions used to form acyl dithiocarbamates are more favourable than those used to form acyl xanthates. Barton reported the need to run reactions at -35 °C to prevent breakdown to thioanhydride by reaction with sodium-o-ethyl xanthate.[26] Zard used excess acid chloride to prevent any side reactions or breakdown of product from excess xanthate salt.[31] This is not favourable as acid chlorides generally need to be synthesised, as opposed to the xanthate salt which is commercially available.

The ability to form the acyl dithiocarbamates at 0 °C in the presence of excess salt indicates that the acyl dithiocarbamates are more stable towards nucleophilic attack than the corresponding acyl xanthate. The nitrogen lone pairs in the dithiocarbamates can delocalise more than the oxygen lone pairs in the xanthates, accounting for their greater stability. These compounds are stable to heat and do not decompose when irradiated with a 500 W halogen lamp. However, stirring with a small amount of sodium diethyldithiocarbamate trihydrate at room temperature gave complete breakdown to the amide.

1.7.1 Intermolecular Reactions of Acyl Dithiocarbamates

Acyl dithiocarbamates can be used as a source of acyl radicals for alkene additions (Scheme 31, b), in a reaction analogous to that of the xanthate additions (Scheme 31, a).[51]

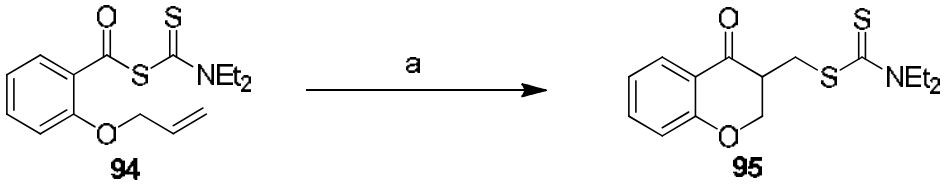


Scheme 31 Addition reactions of a) xanthates and b) acyl dithiocarbamates

In both cases the radical precursors **90** and **91** are irradiated in the presence of allylacetate (**92**), to give the addition products **28** and **93** respectively. Although the yield for the dithiocarbamate reaction is lower than that reported for the xanthate, it was the only product identified from this reaction. Both of these reactions can also be initiated by DLP.

1.7.2 Intramolecular Reactions of Acyl Dithiocarbamates

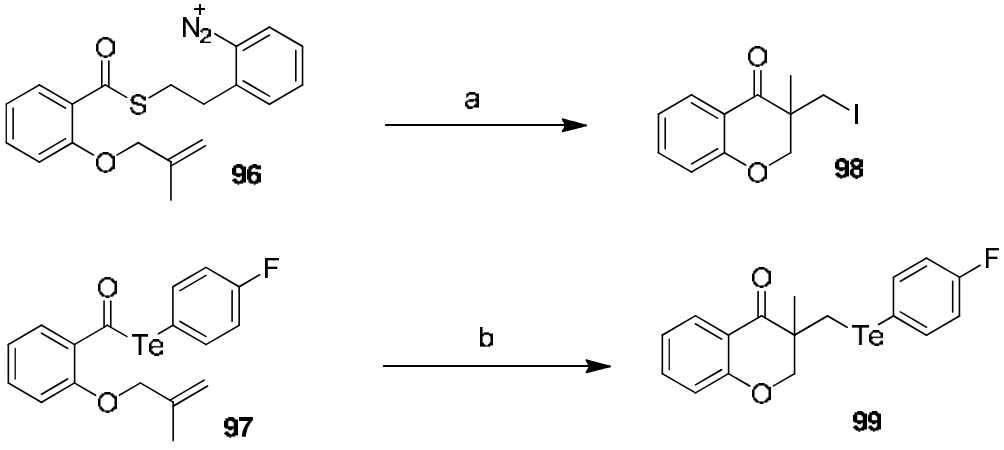
Acyl dithiocarbamates can be used as a source of acyl radicals for intramolecular cyclisations. The dithiocarbamate **94** was synthesised in four steps from salicyclic acid, because this system has been widely reported in the literature.



Scheme 32 a) cyclohexane, 500 W, 15 mins, 89%

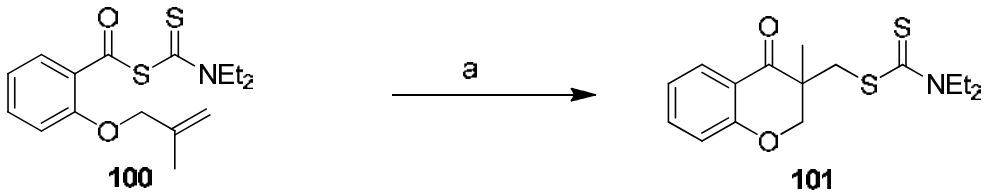
Irradiation of a solution of this acyl dithiocarbamate in cyclohexane with a 500 W lamp gave the cyclised product **95** in a high yield after just 15 minutes (Scheme 32). The corresponding xanthate was reported by Zard to cyclise in a similar fashion in a yield of 70%. This cyclisation follows the same mechanistic pathway as that for the cyclisation of carbamoyl radicals generated from dithiocarbamates previously discussed.

The cyclisation of acyl radicals generated from acyl xanthates onto more substituted alkenes has not been reported. However cyclisation of acyl radicals onto substituted alkenes have been reported, when generated from diazonium salts (**96**)[44] and acyl tellurides[23] (**97**) to give **98** and **99** respectively (Scheme 33).



Scheme 33 a) NaI (1.2 equiv.), acetone, RT, 6 h, 85%, b) hν, 4 h, 100%

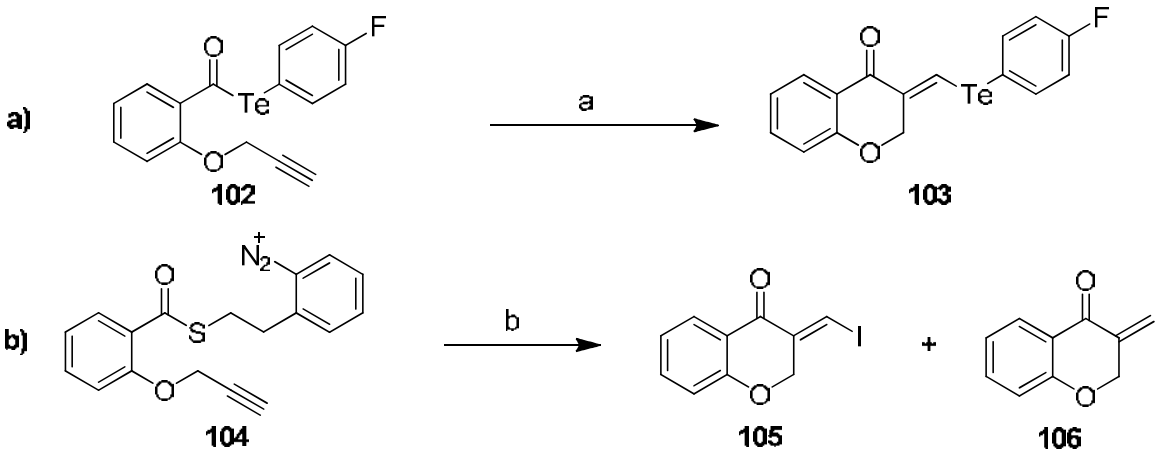
Acyl dithiocarbamate **100** was prepared in 4 steps from salicyclic acid following the same conditions used for the dithiocarbamate **94**. Upon irradiation with a 500 W halogen lamp the cyclisation to give **101** was successful in 69% yield (Scheme 34).



100 **101**

Scheme 34 a) hν, cyclohexane, reflux, 15 min, 69% or DLP (3 × 0.1 equiv.), 1,2-dichloroethane. reflux. 9 h. 59%

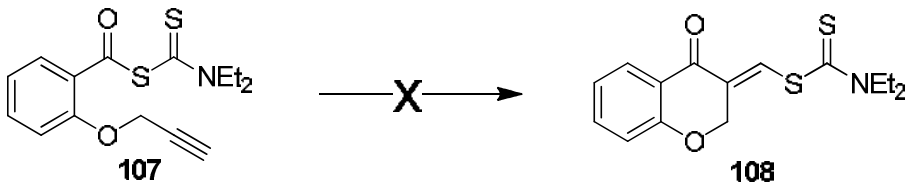
Attempts to cyclise on to alkynes via 6-*exo*-dig mechanism have been reported in the literature. Photolysis of the acyl tellurium **102** gave the alkene **103** in quantitative yield (scheme 35 a).[44] 6-*Exo*-dig cyclisation of diazonium salt **104** with sodium iodide gave two products, the iodoalkene **105** and the alkene **106** (Scheme 35 b).[23] However acyl radicals generated from acyl selenides can not be used for these cyclisations.[52]



102 **103** **104** **105** **106**

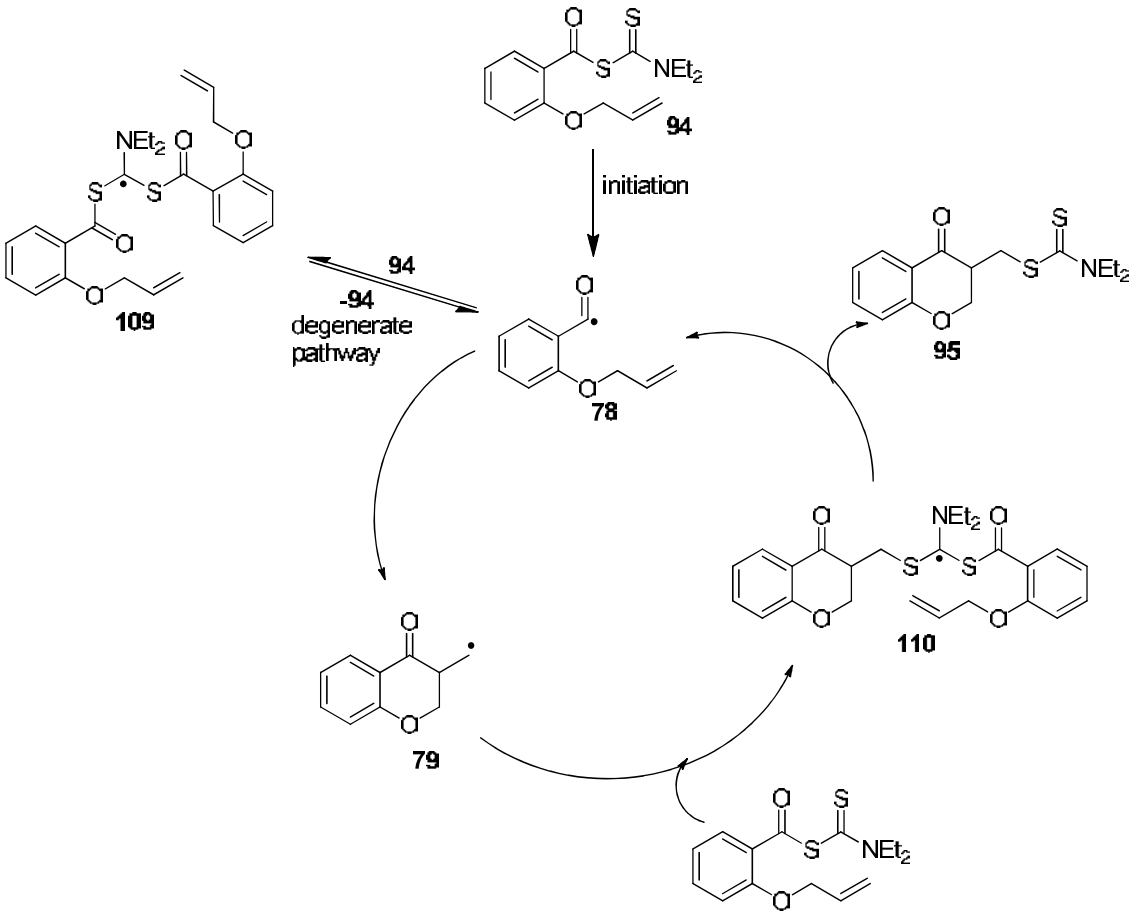
Scheme 35 a) hν, 8 °C, 4 h, 100%; b) NaI (1.2 equiv.), acetone, rt, 6 h, **105** = 50% and **106** = 25%

Investigations in the Grainger group showed that attempts to cyclise acyl dithiocarbamte **107** on to the alkyne to give vinyl dithiocarbamate **108** were unsuccessful (Scheme 36). Irradiation of a solution of acyl dithiocarbamate gave some decomposition along with recovery of unreacted starting mateial. Initiating the reaction with DLP gave the same result.[51]



Scheme 36 Attempted cyclisation of acyl radicals derived from dithiocarbamates onto alkynes

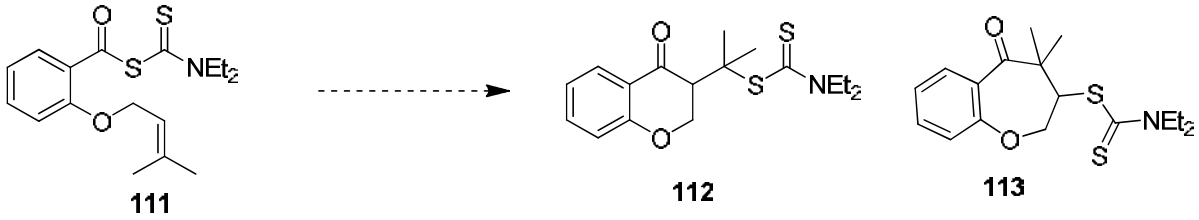
The reaction mechanism for the cyclisation of these acyl radicals (Scheme 37) follows the same pathway as the radical cyclisations of the carbamoyl radicals generated from carbamoyl dithiocarbamates. Initiation gives acyl radical **78**, which can undergo two potential reactions; cyclisation or reaction with another molecule of starting material. Reaction with a second molecule of starting material gives the symmetrical radical **109**, which can split to give starting material and the acyl radical, making this pathway degenerate. Cyclised radical **79**, can also react with a molecule of starting material to give carbon centred tertiary radical **110** which decomposes to give the product dithiocarbamate **95** and regenerates the initial acyl radical.



Scheme 37 Mechanism of acyl dithiocarbamate cyclisation

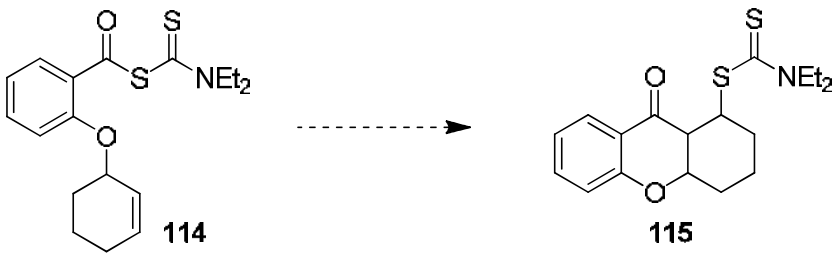
1.8 Aims and objectives

To further extend the Grainger groups research into acyl dithiocarbamates, the potential of cyclising onto trisubsituted alkenes will be investigated. Few studies have been reported in the literature on cyclisations of this type, from derivatives of salicyclic acid. It is theoretically possible to see either 6-*exo* or 7-*endo* cyclisations of the initial acyl ditiocarbamate **111**, leading to **112** or **113** respectively (Scheme 38).



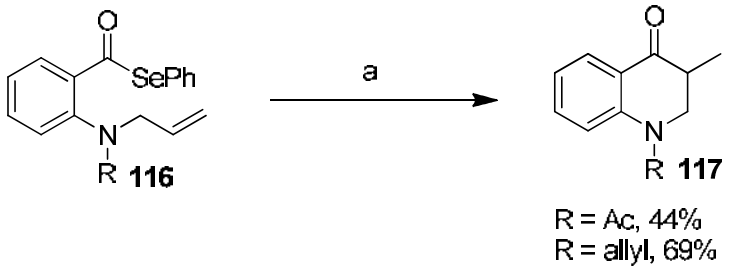
Scheme 38 Proposed cyclisation of acyl dithiocarbamate onto a trisubstituted alkene

If cyclisations on to alkenes substituted at the terminal end are successful, the possibility to create tricyclic systems will be investigated. Cyclisation of carbamoyl dithiocarbamate **114** should give the tricyclic system **115** (Scheme 39). There are currently no reports in the literature of synthesis of these ring systems utilising radical chemistry.



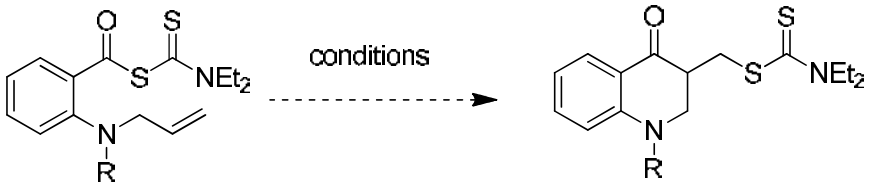
Scheme 39 Proposed cyclisation to give a tricyclic system

There have been limited reports of using allylamines that undergo the same 6-exo-trig cyclisation as the allyl esters of salicyclic acid. The only examples reported in the literature generate the acyl radical from acyl selenides **116**.[20] Intramolecular alkene addition then occurs in the expected 6-exo fashion to give the cyclised product **117** (Scheme 40).



Scheme 40 a) Bu_3SnH, AIBN

The potential of using acyl dithiocarbamates to cyclise systems derived from anthranilic acid will be investigated as outlined in Scheme 41.



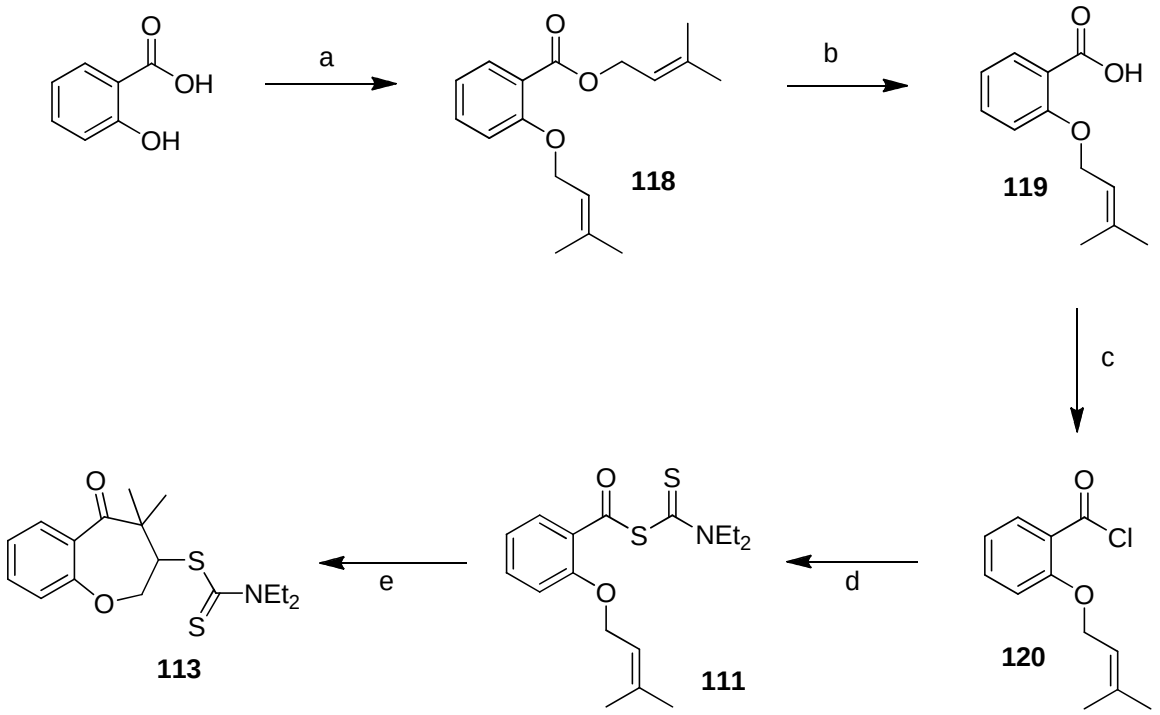
Scheme 41 Proposed 6-*exo* cyclisation of acyl dithiocarbamates derived from anthranilic acid

1.9 Results and Discussion

1.9.1 Intramolecular Cyclisations of Acyl Dithiocarbamates

Prior to this study there have been no reports of cyclisation on to alkenes substituted at the terminal position using acyl radicals generated from xanthates. In order to investigate the ability of acyl radicals to cyclise onto alkenes substituted at the terminal position the acyl dithiocarbamate **111** was synthesised (Scheme 42). Salicyclic acid was dialkylated with 3,3-dimethylallylbromide to give ester **118**, which was hydrolysed to carboxylic acid **119** by heating with NaOH, followed by an acidic work up. Treatment of the carboxylic

acid **119** with oxalyl chloride gave the corresponding acid chloride **120**, which was treated with sodium diethyldithiocarbamate trihydride to give acyl dithiocarbamate **111** in reasonable yield.



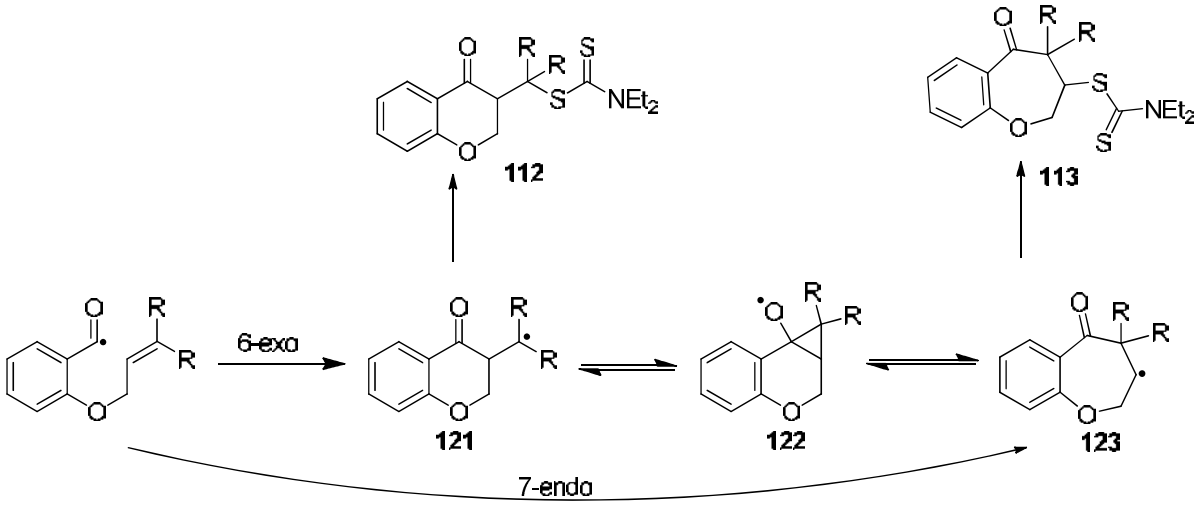
Scheme 42 a) K_2CO_3 (2.45 equiv.), acetone, reflux, 15 mins, then 3,3-dimethylallyl bromide (2.45 equiv.), reflux, 22 h, 91%; b) NaOH (3 equiv.), 90% EtOH aq., reflux 4 h, then HCl (0.1 M), c) Oxalyl Chloride (1.2 equiv.), Et_2O, RT, 1 h; d) $NaSC(S)NEt_2$ (1.05 equiv.), acetone (0.1 M), 0 °C, 15 mins, 65% over 2 steps; e) hν, cyclohexane, reflux, 2 h, 49%

Irradiation of dithiocarbamate **111** with a 500 W halogen lamp afforded the 7-*endo* product **113** in 49% yield as the only isolable product. There was no evidence of formation of the 6-*exo* product. These two products would be easily distinguishable by the ^{13}C NMR, which shows the sulfur to be bonded to a tertiary carbon as expect for the 7-*endo* product. In the case of the 6-*exo* product this sulfur would be bonded to a quarternary carbon. The formation of the 7-*endo* product is further supported by the

HMBC, which shows a correlation between the carbonyl carbon and the protons of the methyl groups. These are separated by 3 bonds. In the case of the 6-*exo* product, these would be 4 bonds apart and a correlation would not be visible in the HMBC.

The cyclisation was also carried out by initiating the reaction with DLP. Dithiocarbamate **111** was dissolved in cyclohexane and heated to reflux. DLP was added in three 20 mol% portions over 6 hours, to afford dithiocarbamate **113** after purification by column chromatography. The yield for this reaction is much lower (21%) than when using light as the initiator and can be accounted for by difficulties in isolating the dithiocarbamate from the breakdown products of the initiator by column chromatography.

The formation of the observed dithiocarbamate **113** by a direct 7-*endo*-trig cyclisation is unlikely due to steric effects. The reaction is believed to occur via a 6-*exo*-trig cyclisation to give alkyl radical **121**, followed by migration of the radical onto the oxygen to give intermediate **122** (Scheme 43). Ring expansion occurs to give the secondary alkyl radical **123** on the 7 membered ring system. All these reactions are in equilibrium. The alkyl radical **121** can be captured by group transfer from another molecule of starting dithiocarbamate to give the dithiocarbamate **112**, possessing two 6-membered rings. Capture of alkyl radical **123** by group transfer would give dithiocarbamate **111**, possessing a 7-membered ring.

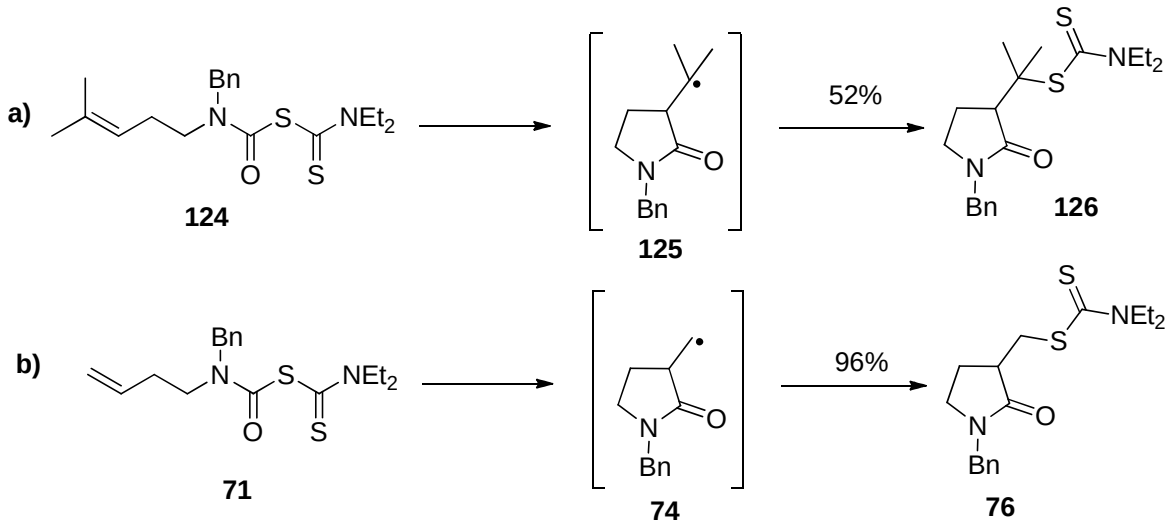


Scheme 43 Mechanism of cyclisations to give 6-*exo* and 7-*endo* products

The radical generated from the initial 6-*exo* cyclisation is a tertiary radical. The radical **123** is a less stable secondary radical, and will therefore undergo group transfer at a faster rate than the tertiary radical. Capture of this radical by group transfer yields the product **113**. The more stable tertiary radical has a longer lifetime, allowing it to rearrange to the less stable secondary radical, with subsequent group transfer yielding the dithiocarbamate **113**.

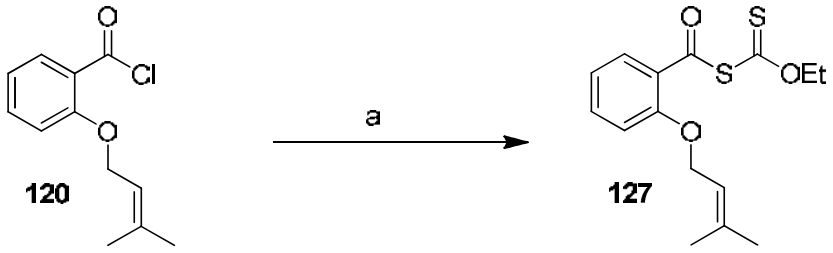
Capture of tertiary radicals by group transfer is known to be a much slower process than capture of primary radicals, as has been shown by previous work within the group on carbamoyl dithiocarbamates.[39] Radical **125** was generated from the starting ditihiocarbamate **124** by irradiation. Cyclisation occurred in a 5-*exo* fashion, followed by group transfer to give **126** in 52% yield (Scheme 44, a). The cyclisation and subsequent group transfer of dithiocarbamate **71**, which is without the two geminal methyl group, occurred in almost quantitative yield (Scheme 44, b). This suggests that the efficiency of

group transfer decreases with increasing stability of the radical after cyclisation. The formation of the 7-*endo* product **113** over the 6-*exo* is supported by this phenomenon.



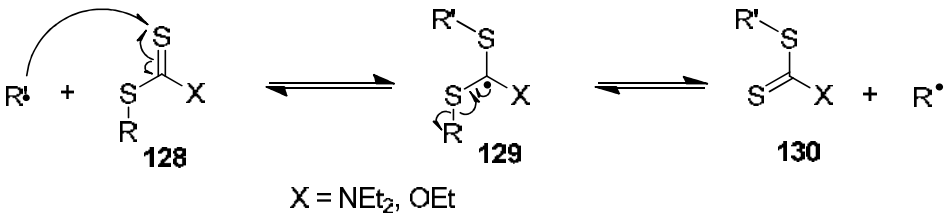
Scheme 44 a) 5-*exo* cyclisation of **124**, b) 5-*exo* cyclisation of **71**

The xanthate **127** analogous to the dithiocarbamate **111** has not previously been synthesised. In order to see if the cyclisation pathway would be different in the case of the xanthate it was first necessary to make the xanthate. This was undertaken by taking the acid chloride **120** formed in the synthesis of the dithiocarbamate and treating it with xanthate salt as opposed to the dithiocarbamate salt (Scheme 45). According with previous xanthate formation, the reaction was carried out at low temperature with excess acid chloride. This gave the product, xanthate **127**, in a reasonable yield of 78%.



Scheme 45 a) KSC(S)OEt (0.9 equiv), acetone (0.1 M), 0 °C, 15 mins

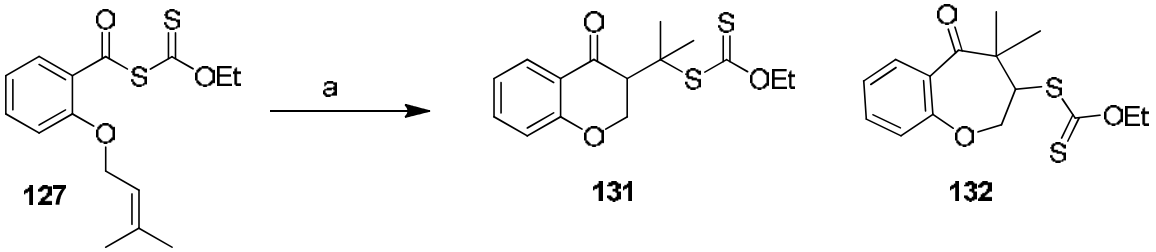
It was postulated that the group transfer rates would be different for xanthates than dithiocarbamates and this could affect the distribution of products. The group transfer reaction is depicted in Scheme 46. R' is used to represent the alkyl radical, which can interact with a molecule of starting material **128**, to generate the tertiary radical **129**, in a reversible reaction. In the case of the ditihiocarbamate, (where X = NEt_2), the carbon sulfur double bond will be more electron rich, due to the better electron donating effects of the nitrogen compared with the oxygen present in the xanthate. This should result in the reaction to form the tertiary radical **129**, being slower in the dithiocarbamate case. Conversely, the tertiary intermediate radical **129**, should be better stabilised when X=NEt_2, making this intermediate have a longer lifetime and the decomposition to give **130** slower. This theory suggests that the xanthate may have a faster rate of group transfer, favouring the 6-*exo* mode of cyclisation over the 7-*endo*.



Scheme 46 Group transfer of xanthates and dithiocarbamates

Application of the standard cyclisation conditions, using a 500 W halogen lamp, to a solution of xanthate **127** in cyclohexane, gave only one isolated product. Pleasingly this was the product from the 6-*exo* cyclisation **131** rather than that of the 7-*endo* cyclisation **132** (Scheme 47). The observed xanthate **131** can be distinguished from the other potential xanthate **132** which could be formed by using HMBC correlation. No correlation between the carbonyl carbon and the protons of the methyl group is seen in the HMBC

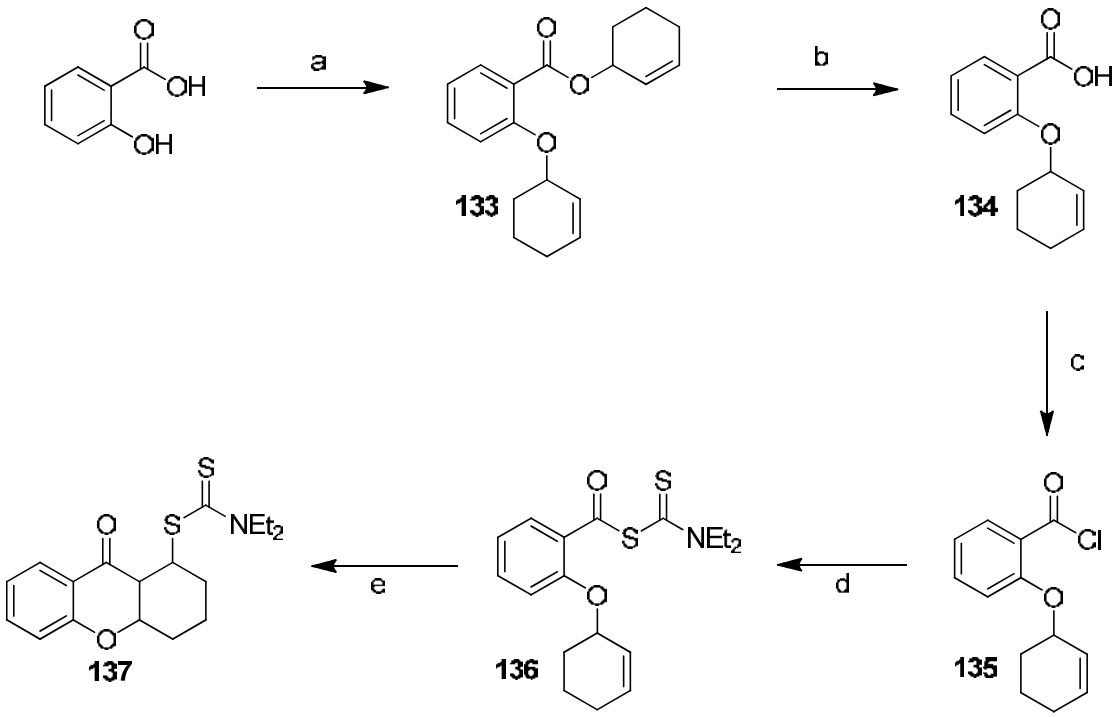
spectrum. These are four bonds apart in **131**, as such a correlation is not expected. However in **132**, the product of a 7-*endo* cyclisation, they are only 3 bonds apart, so a correlation should be observed, as for the corresponding dithiocarbamate **113**. This lack of correlation further supports the formation of the xanthate **131** over xanthate **132**.



127 **131** **132**

Scheme 47 a) 500 W, cyclohexane, **131** (47%), **132** (0%)

The use of acyl dithiocarbamates as a source of acyl radicals to form tricyclic systems was also investigated. Salicyclic acid was dialkylated with 3-bromocyclohexene to give the ester **133** as an inconsequential mixture of dithiocarbamates. Carboxylic acid **134** was formed by hydrolysis of **133** by heating with NaOH followed by an acidic work up. Treatment of this carboxylic acid with oxalyl chloride gave the corresponding acid chloride **135**, which was treated with sodium diethyldithiocarbamate trihydride to give acyl dithiocarbamate **136** in reasonable yield (Scheme 48).

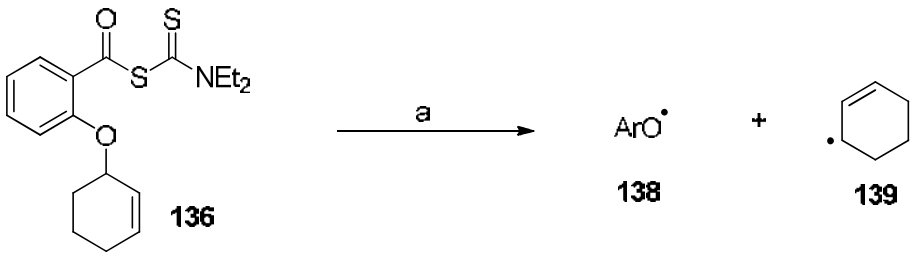


Scheme 48 a) K_2CO_3 (2.45 equiv.), acetone, reflux, 15 mins, then 3-bromocyclohexene (2.45 equiv.), reflux, 22 h, 70%; b) NaOH (3 equiv.), 90% EtOH aq., reflux 5 h, then HCl (0.1 M), 97% c) Oxalyl chloride (1.2 equiv.), Et_2O, RT, 3 h; d) $NaSC(S)NE_2$ (1.05 equiv.), acetone (0.1 M), 0 °C, 20 mins, 71% over 2 steps; e) hν, cyclohexane, reflux, 2 h, 52%

Irradiating dithiocarbamate **136** with a 500 W halogen lamp led to complete degradation of starting material after 30 minutes and no cyclised product was observed. Attempts at cyclising the product using DLP as the initiator proved to be more successful. Dithiocarbamate **136** was dissolved in cyclohexane and heated to reflux. DLP (20 mol %) was added and after 2 hours a further portion of DLP (20 mol%) was added. After 2 hours the reaction had gone to completion by TLC. Column chromatography gave the product as the expected 6-*exo*-trig cyclised dithiocarbamate **137** in a moderate yield of 52%, isolated as a single diastereomer, presumably possessing a *cis* ring junction although the stereochemistry of **137** has not been confirmed. This was the only product observed, with the rest of the starting material having degraded. There was no evidence of the 7-*endo*-

trig cyclisation, which could theoretically occur with the intermediate radical expected to be of similar stability to the radical that is formed from the 6-*exo*-trig cyclisation.

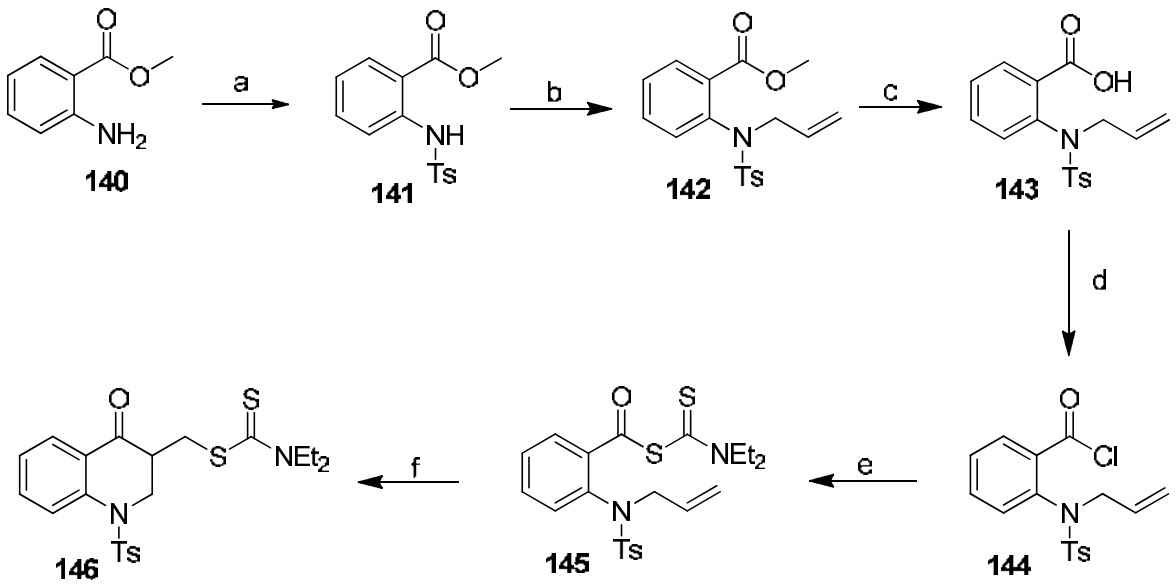
It has been postulated that photoinitation of the reaction can lead to generation of an alternative radical to that expected, by scission of the C-O bond (Scheme 49). This would generate radical **138** and a secondary allylic radical **139**. The extra stability of a secondary allylic radical over a primary allylic, is perhaps what allows for this scission to occur. This potential breakdown pathway is not available when using a chemical initiator, therefore this degradation is not observed and the 6-*exo* cyclisation occurs.



Scheme 49 a) 500 W, cyclohexane

1.9.2 Intramolecular Cyclisations to form Nitrogen Containing Heterocycles

In order to progress the acyl dithiocarbamate work, nitrogen containing equivalents of the cyclisation precursors were created. As methyl 2-aminobenzoate is commercially available, it was decided to use this reagent as the starting material, as opposed to anthranilic acid, in order to improve atom economy. It is necessary to protect the amine to prevent any unwanted reactions from occurring at this site. Tosyl was chosen as the protecting group, as its use as a protecting group for amines is widely reported and can be installed into the molecule in high yields.



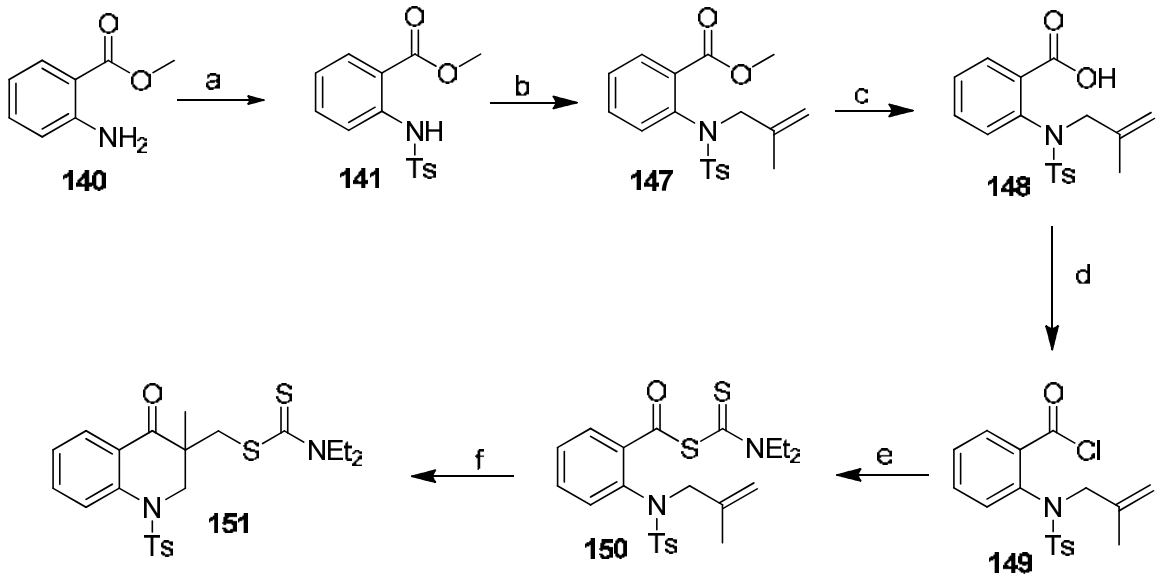
Scheme 50 a) Pyridine, CH_2Cl_2, 4-methylbenzene-1-sulfonyl chloride, RT, 20 h; b) NaH (1.5 equiv.), allylbromide (2.0 equiv.), DMF, RT, 14 h, 91%; c) MeOH:H_2O (1:1), LiOH.H_2O NaOH (5 equiv.), 70°C, 2.5 h, 85%; d) Oxalyl chloride (1.2 equiv.), CH_2Cl_2, RT, 20 mins; e) $NaSC(S)NEt_2$ (1.05 equiv.), acetone (0.1 M), 0 °C, 20 mins, 86% over 2 steps; f) hν, cyclohexane, reflux, 20 mins, 89%

Methyl 2-aminobenzoate **140** was treated with pyridine and tosyl chloride to give the tosylated amide **141**. This was alkylated to produce amide **142**, which was subsequently treated with lithium hydroxide gave the carboxylic acid **143**. The corresponding acid chloride **144** was formed by using oxalyl chloride in a solution of CH_2Cl_2, with a catalytic amount of DMF. The crude product was dissolved in acetone and sodium diethyldithiocarbamate trihydrated was added, at 0 °C in the dark, to give the corresponding acyl dithiocarbamate **145** in a high yield of 86% over 2 steps (Scheme 50).

Irradiation of **145** with a 500 W lamp gave the 6-*exo*-trig cyclised product **146** in a yield of 89%. This is directly comparable with the cyclisation of acyl dithiocarbamate **94** which gives chromanone **95**, also in 89% yield. The ability to form both of these cyclised products in high yields demonstrates the scope of this chemistry. The reaction has also

been successfully carried out using DLP as the initiator, albeit in a slightly lower yield of 72%.

To allow further comparison with the chromanone systems, cyclisations on to substituted alkenes were investigated. After tosyl protection, amine **141** was alkylated using methallyl chloride to give **147**. Treatment with lithium hydroxide gave the corresponding acid **148**. The corresponding acid chloride **149** was formed by using oxalyl chloride in a solution of CH_2Cl_2, with catalytic DMF. The crude product was dissolved in acetone and sodium diethyldithiocarbamate trihydrate was added, at 0 °C in the dark, to give the corresponding acyl dithiocarbamate **150** in high yield of 82% over 2 steps (Scheme 51).



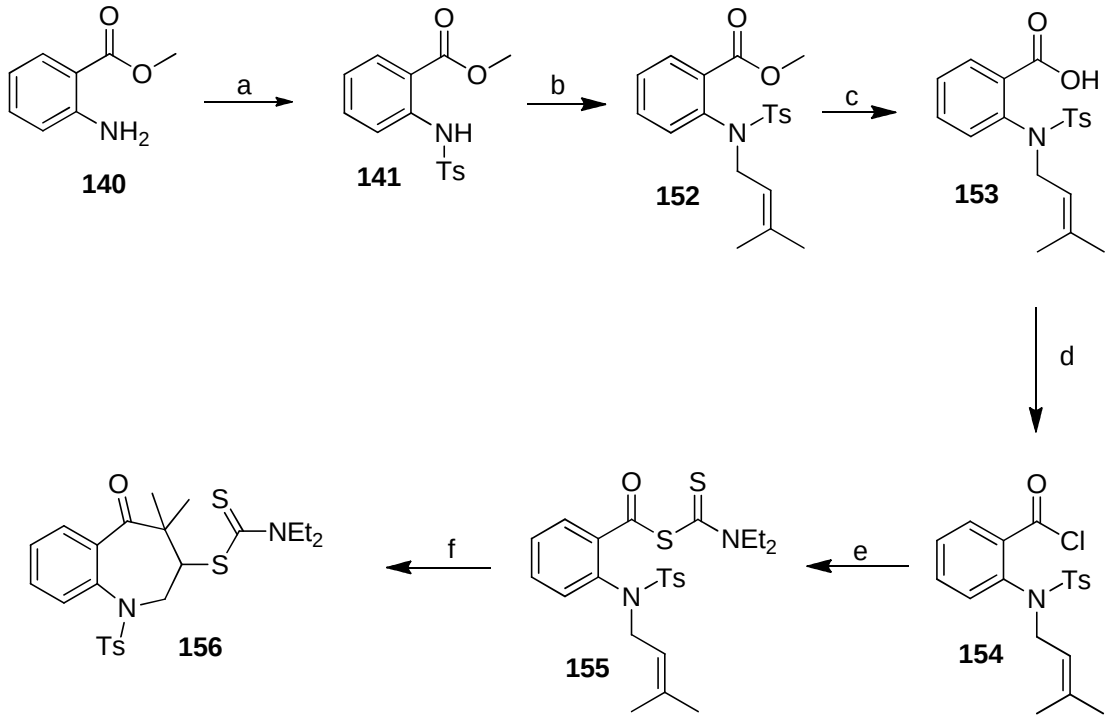
Scheme 51 a) Pyridine, CH_2Cl_2, 4-methylbenzene-1-sulfonyl chloride, RT, 20 h; b) NaH (1.5 equiv.), methallyl chloride (2.0 equiv.), DMF, RT, 14 h, 82%; c) MeOH:H_2O (1:1), LiOH.H_2O NaOH (5 equiv.), 70°C, 2.5 h, 75%; d) Oxalyl chloride (1.2 equiv.), CH_2Cl_2, RT, 15 mins; e) $NaSC(S)NEt_2$ (1.05 equiv.), acetone (0.1 M), 0 °C, 20 mins, 82% over 2 steps; f) hν, cyclohexane, reflux, 2 hours, 70%

Irradiation of **150** with a 500 W lamp, gave the 6-*exo*-trig cyclised product **151** in a yield of 70%, which is directly comparable with the cyclisation of acyl dithiocarbamate **100**

which gives chromanone **101**, also in 69% yield. There was no evidence of the 7-*endo* product, by NMR. The reaction was also attempted using DLP as the initiator. This gave the cyclised product but in a reduced yield of 57%, as also observed with the chromanone example. The lower yields when using DLP can be attributed to difficulties in removing the initiator breakdown products by column chromatography.

When using alkenes substituted at the terminal position, the acyl radical cyclisation previously discussed, gave the product containing a 7-membered ring, rather than the product arising from 6-*exo* cyclisation. The corresponding amide, dithiocarbamate **155** was synthesised and the cyclisation attempted to see if the 7 ring was the product for this system as expected.

Methyl 2-aminobenzoate was protected with a tosyl group, before alkylation to give **152**. Treatment with lithium hydroxide gave the corresponding carboxylic acid **153**, which was then reacted with oxalyl chloride and a catalytic amount of DMF, to give acid chloride **154**. The acyl dithiocarbamate **155** was obtained in high yields by treating **154** with sodium diethyldithiocarbamate trihydrate in acetone in the dark (Scheme 52).

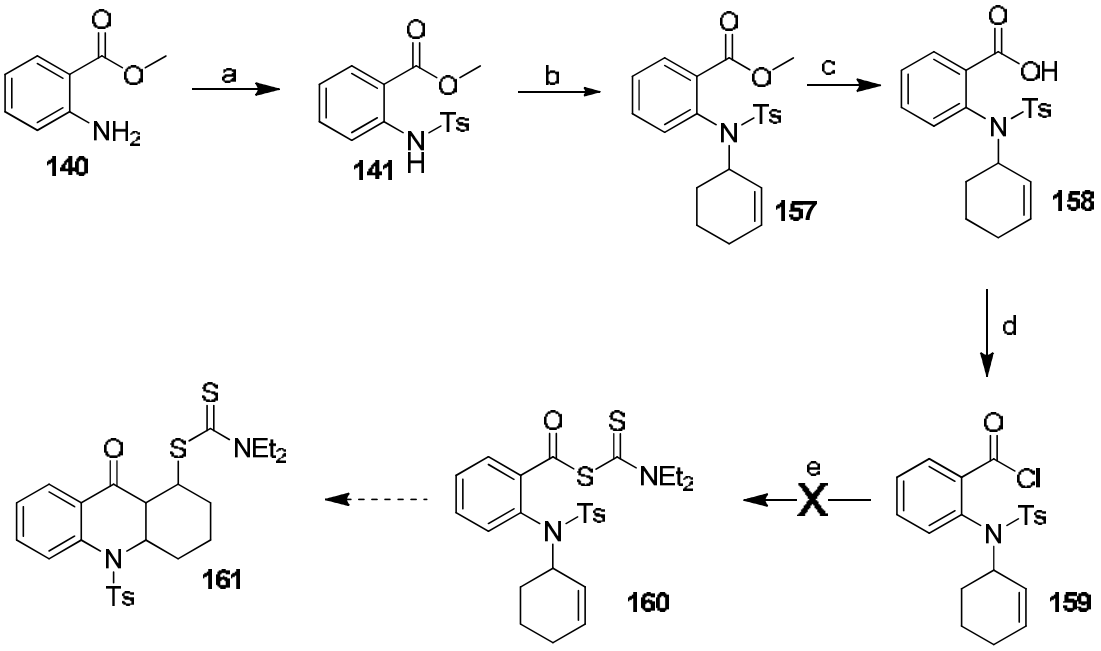


Scheme 52 a) Pyridine, CH_2Cl_2, 4-methylbenzene-1-sulfonyl chloride, RT, 20 h; b) NaH (1.5 equiv.), 3,3 dimethylallyl bromide (2.0 equiv.), DMF, RT, 14 h, 65%; c) MeOH:H_2O (1:1), LiOH.H_2O NaOH (5 equiv.), 70°C, 2.5 h, 93%; d) Oxalyl chloride (1.2 equiv.), CH_2Cl_2, RT, 15 mins; e) NaSC(S)NEt_2 (1.05 equiv.), acetone (0.1 M), 0 °C, 20 mins, 88% over 2 steps; f) hν, cyclohexane, reflux, 20 mins, 48%

Cyclisation to give dithiocarbamate **156** was achieved by irradiation of a solution of acyl dithiocarbamate **155** with a 500 W halogen lamp. The only product observed was that from the apparent 7-*endo* cyclisation. However due to steric issues, it is more likely that the 6-*exo* cyclisation occurs followed by ring expansion, as discussed previously. The yield for this reaction is moderate at 48%, but this is comparable with the oxygen containing system, which cyclised in a 49% yield. The reasoning for concluding that the 7-*endo* product is observed rather than the 6-*exo* is due to the ^{13}C NMR and HMBC spectra, which have previously been discussed for dithiocarbamate **113**.

Initiation of this cyclisation with DLP gave a reduced yield of 32%, which is also comparable with that obtained with the oxygen containing system.

As a final example of the use of acyl radicals generate from acyl dithiocarbamates, the synthesis of a tricyclic system, from methyl 2-aminobenzoate was attempted. The protected amine **141**, was alkylated with 3-bromocyclohexane to give **157**. Treatment of this with lithium hydroxide yielded the corresponding carboxylic acid **158**, which upon reaction with oxalyl chloride in the presence of catalytic DMF gives acid chloride **159**. The subsequent reaction to give the acyl dithiocarbamate **160** was unsuccessful (Scheme 53). The conditions that had successfully given all the other examples of acyl dithiocarbamates were applied. The carbamoyl chloride **159** was reacted with sodium diethyldithiocarbamate trihydrate in acetone at 0 °C in the dark. After 20 minutes the reaction mixture had turned a pale yellow colour, which showed as multiple spots by TLC. An NMR of the crude reaction mixture indicated that there may be some of acyl dithiocarbamate **160**, but in a low yield. All attempts to isolate this were unsuccessful.



Scheme 53 a) Pyridine, CH_2Cl_2, 4-methylbenzene-1-sulfonyl chloride, RT, 20 h; b) NaH (1.5 equiv.), 3-bromocyclohexene (2.0 equiv.), DMF, RT, 14 h, 91%; c) MeOH:H_2O (1:1), LiOH.H_2O NaOH (5 equiv.), 70°C, 2.5 h, 85%; d) Oxalyl Chloride (1.2 equiv.), CH_2Cl_2, RT, 20 mins; e) NaSC(S)NEt_2 (1.05 equiv.), acetone (0.1 M), 0 °C, 20 mins, 0% over 2 steps

The formation of the corresponding oxygen containing acyl dithiocarbamate proceeded with no issue. The electronics of the reactive site in this case should be almost identical to that of the oxygen containing system. However it is possible that steric hindrance plays a major role in this system. The nitrogen is protected with a reasonably large tosyl group and has been alkylated with the relatively unflexible cyclohexene group. All the other nitrogen containing systems have smaller, more flexible groups bonded to the nitrogen, along with the large tosyl group. These smaller groups are less likely to interfere sterically with the approaching dithiocarbamate moiety, hence these reactions proceed as expected. The presence of the larger, less flexible cyclohexene group will provide more of a steric clash and could potentially be what is preventing acyl dithiocarbamate **160**

forming in any appreciable yield. Without being able to form the cyclisation precursor, it was not possible to attempt any cyclisation reactions to give the tricyclic system **161**.

1.10 Conclusion

The work on the use of acyl dithiocarbamates as a source of acyl radicals has been expanded upon. Dithiocarbamates as a source of acyl radicals can be seen as advantageous over xanthates as unlike when synthesising xanthates, there is no need to use an excess of acid chloride in the formation of the dithiocarbamate acyl radical precursors. These reactions are run at 0 °C, without any observable degradation of product. Initial reports of xanthate formation required reaction temperatures of -35 °C, however it has since been reported that xanthates of this type can be successfully formed at 0 °C.

Cyclisation to give the apparent 7-*endo* product has been shown to occur when the alkene is disubstituted at the terminal position. However due to steric reasons, it is believed that the 6-*exo* cyclisation initially occurs in these cases, followed by a ring expansion. However in the case of the xanthate example the 6-*exo* product is observed. This suggests that there is a difference in the rate of group transfer, which may be due to the better electron donating ability of the nitrogen in dithiocarbamates compared with the oxygen in xanthates.

This work has enabled bicyclic nitrogen containing systems to be synthesised, an area previously given little attention in the field of acyl radical cyclisations. The rate of

cyclisation of oxygen containing systems is remarkably similar to that of the nitrogen containing sytems. This shows that the increased steric bulk of the protected nitrogen has no effect on the radical cyclisation reaction. However it may play an important role in the unsuccessful attempts to synthesise radical cyclisation precursor **160**.

All, bar one, cyclisations were successful when initiated with a 500 W halogen lamp, giving clean easily isolable products. The use of DLP as an initiator gave lower yields. This is due to the presence of initiator breakdown products making purification more difficult.

Chapter two

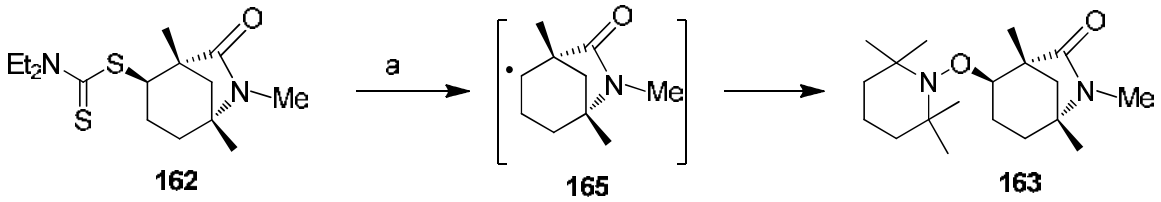
Radical-Mediated Reduction of the Dithiocarbamate Group Under Tin-Free Conditions

2.1 Dithiocarbamate Transformations

The use of dithiocarbamates as a source of both acyl and carbamoyl radicals has been discussed in Chapter 1. One of the advantages of using dithiocarbamates for radical cyclisations is the presence of the dithiocarbamate moiety in the product, as a result of group transfer occurring. The majority of target molecules, whether it be a natural product or drug, do not contain dithiocarbamate functionality, therefore transformations of dithiocarbamate groups are necessary and, as such, research into this has been undertaken in the Grainger group. Methods have been developed for oxygen exchange reactions[53] and elimination to alkenes.[38] Reduction of dithiocarbamates has previously been reported via a variety of different methods[54,55] but not as yet by the Grainger group.

2.1.1 Dithiocarbamate Oxygen Exchange Reactions

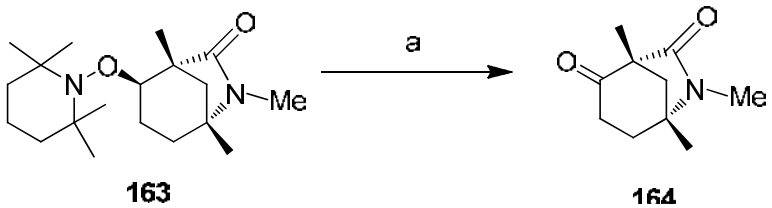
During the total synthesis of (-)-aphanorphine, it was necessary to transform the dithiocarbamate moiety of **162** into a ketone.[53] This was achieved using radical chemistry to give first the TEMPO adduct **163** (Scheme 54), which was then oxidised to yield the ketone **164**. A solution of the dithiocarbamate and TEMPO was exposed to light from a 125 W medium pressure Hg lamp using quartz glasswear to give the TEMPO adduct **163**. The intermediate radical **165** is formed by homolytic cleavage of the C-S bond, before being trapped by TEMPO. The stereochemistry of the product is the same as the starting material, due to TEMPO addition occurring on the same face as that of the dithiocarbamate group.



Scheme 54 a) hν, 125 W, medium pressure Hg lamp, TEMPO (4 equiv.), toluene, RT, 25 mins, 83%

The absorbance of the cyclised dithiocarbamate **162** is known to be at 285 nm. This information was used when optimising conditions. It was found that toluene, with an absorbance cut off of 286 nm gave the highest yield. The use of quartz, as apposed to Pyrex gave higher yields, as the cut-off point for irradiation of Pyrex is 290 nm, which is only slightly higher than that of toluene. Using quartz allows a broader wavelength of light into the solution, and therefore increases the efficiency of the initiation process.

The TEMPO adduct can easily be converted into the corresponding ketone **164** in high yield (Scheme 55), by reaction with *m*CPBA.

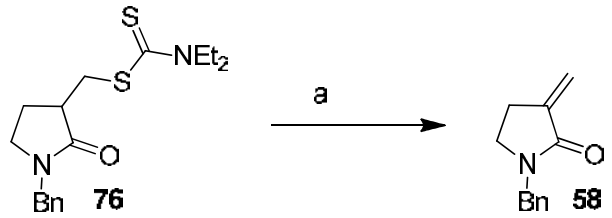


Scheme 55 a) *m*CPBA, CH_2Cl_2, 84%

2.1.2 Elimination of Dithiocarbamates to Alkenes

A general procedure for the thermal elimination of dithiocarbamates to give alkenes has been developed in the group[38] (Scheme 56). Initial investigations centred around base mediated eliminations using DBU, were completed with limited success. It was

subsequently found that simply refluxing the dithiocarbamate **76** in diphenyl ether for a few hours gave alkene **58** in high yields.



Scheme 56 a) Ph_2O, 2h, 86%

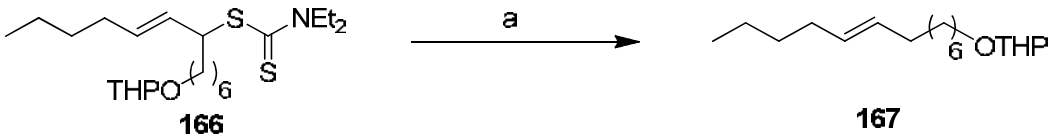
Due to the thermal stability of the starting dithiocarbamates, it was necessary to use diphenyl ether as the solvent, because it has a high boiling point of 259 °C. Experiments with lower boiling solvents showed no transformation to product. The alkene products of this elimination reactions are thermally robust.

A variety of different dithiocarbamates, containing a range of different ring sizes and also bicyclic systems, have been successfully eliminated under these conditions. In some cases a mixture of regioisomers were produced. However, most reactions gave a single isomer in high yields.

2.2 Previous Reports of Reduction of Dithiocarbamates

There have been reports of the reductive desulfurisation of dithiocarbamates in the literature, including reduction using tributytin hydride.[56] Although high yielding, this is not desirable due to the toxicity of tin and potential issues with separating products from the reagents.

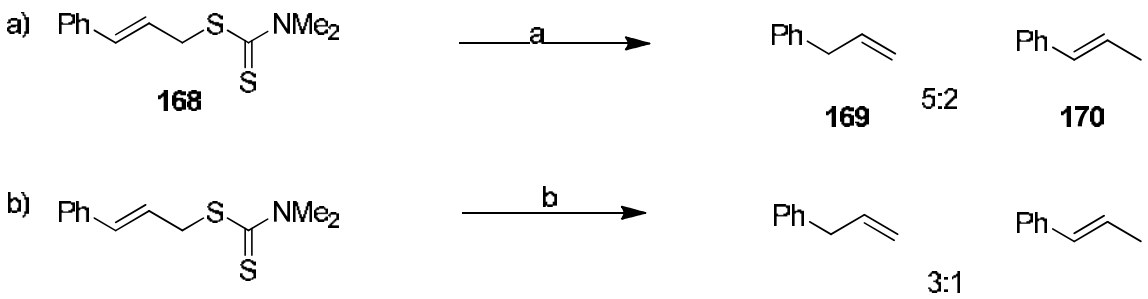
As early as 1975, the reduction of dithiocarbamates was achieved using lithium in ethylamine (Scheme 57). Dithiocarbamate **166**, was subjected to these conditions and gave the corresponding alkene **167** in 93% yield.[54]



166 **167**

Scheme 57 a) Li, $EtNH_2$, 93%

The combination of $LiAlH_4$ and $CuCl_2$ has been shown to remove the dithiocarbamate moiety from **168** to give a 5:2 mixture of alkenes **169** and **170**, when run at room temperature (Scheme 58, a). Increasing the reaction temperature of the system to reflux, results in a slight change of the ratio to give a 3:1 mixture of **169** and **170** (Scheme 58, b).[57]

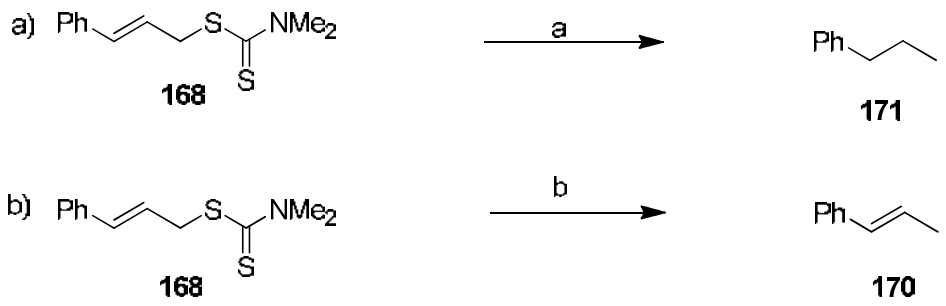


168 **169** **170**

Scheme 58 a) $LiAlH_4$-$CuCl_2$, THF, RT, 2h b) $LiAlH_4$-$CuCl_2$, THF, reflux, 2h

Raney nickel has also been used to remove the dithiocarbamate moiety. Reaction of dithiocarbamate **168** with Raney nickel in refluxing ethanol gave the alkane **171** (Scheme 59, a) in quantitative yield.[55] Deactivating the Raney nickel by heating it in refluxing

acetone for 1 hour, prior to use, led to the alkene **170** being produced in the reaction rather than the previously observed alkane **171** (Scheme 59, b).

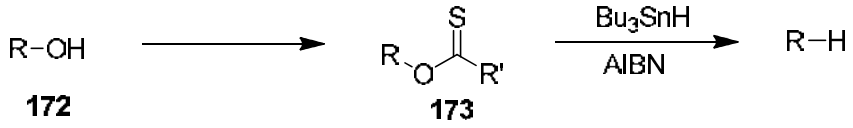


Scheme 59 a) Raney Ni, EtOH, reflux, 2h, 100% b) deactivated Raney Ni, EtOH, reflux, 2h, 100%

2.3 Barton-McCombie Reaction

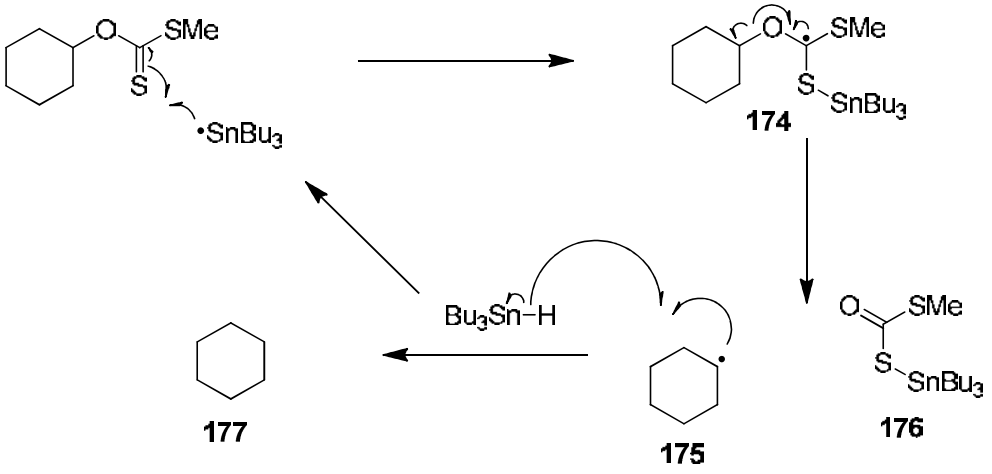
Reduction of alcohols to alkanes is important when making natural products including aminoglycosides and carbohydrates.[25] In some cases the hydroxy derivatives are not active but the deoxy derivatives display antibiotic activity.[58] Radical chemistry is the preferred method of doing this, over conventional ionic reactions, because radicals do not suffer from solvation problems making them less affected by sterics. This means that more sterically hindered alcohols can be reduced by radical methods.[58]

In 1975 Barton and McCombie first reported a radical mediated removal of alcohols via thiocarbonyl intermediates (Scheme 60).[25] The thiocarbonyl derivatives **173** are easily synthesised from the alcohol **172**, by first condensing the alcohol with an imidoyl chloride species to give an intermediate salt, which upon reaction with hydrogen sulfide and pyridine gives the thiocarbonyl. The classical reaction involves using tributyltin hydride to generate the radical chain carrier.



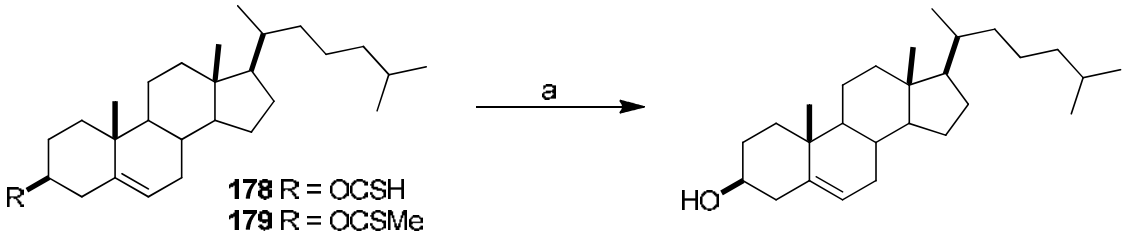
Scheme 60 Barton-McCombie deoxygenation reaction.

A typical example of the Barton-McCombie reaction is depicted in Scheme 61. Initiation of the reaction produces the tertiary carbon centred radical **174**, which then fragments to give the secondary carbon centred radical **175** and the carbonyl compound **176**. The gain in energy by going from C=S to C=O, makes this reaction favourable and creates a driving force towards the product. In addition, the S-Sn bond that is formed is very stable, further making the reaction favourable. The secondary alkyl radical **175** can easily abstract a hydrogen from another molecule of tributyltin hydride, due to the lability of the Sn-H bond, to give the reduced product **177** and another molecule of the chain carrier tin radical.



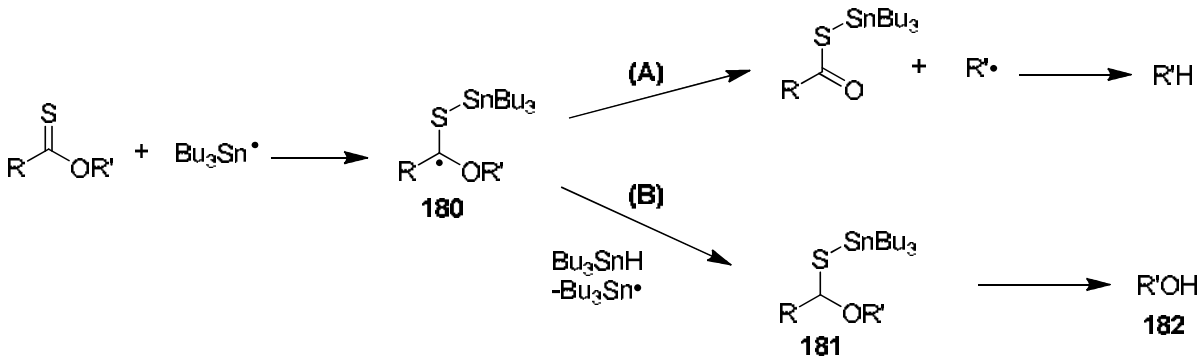
Scheme 61 Barton-McCombie mechanism

Barton and McCombie explored a range of thiocarbonyl compounds and found that thiobenzoates, thioimidazoles and xanthates gave the desired reduced product. However, when exposing thioformyl (**178**) and thioacetyl (**179**) compounds to the reaction conditions, the corresponding alcohols were obtained as the major product (Scheme 62).[59,60]



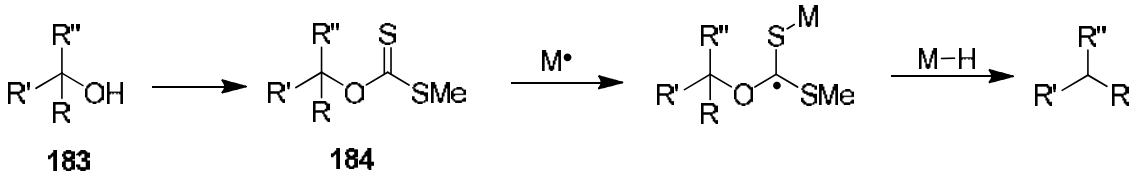
Scheme 62 a)Bu_3SnH

This is explained by considering that the initial radical **180** may follow one of two pathways (Scheme 63). Pathway A gives the classical expected reduced product. This occurs when the initial radical is stabilised (e.g. when R = Ph, Im, SMe) and thus has an extended lifetime, allowing fragmentation to occur. Additionally this can occur when R• is stabilised by neighbouring groups. Pathway B occurs when the initial radical **180** is non stabilised and high energy (e.g when R = H, Me). This can react with tributyltin hydride by 1,2 addition to give the intermediate **181** which then collapses to give the alcohol, **182**.



Scheme 63

The initial work by Barton and McCombie focused on the use of secondary alcohols and the subsequent xanthates. Barton later developed this work to include the reduction of tertiary alcohols **183** via xanthates of the type **184** (Scheme 64).[61]

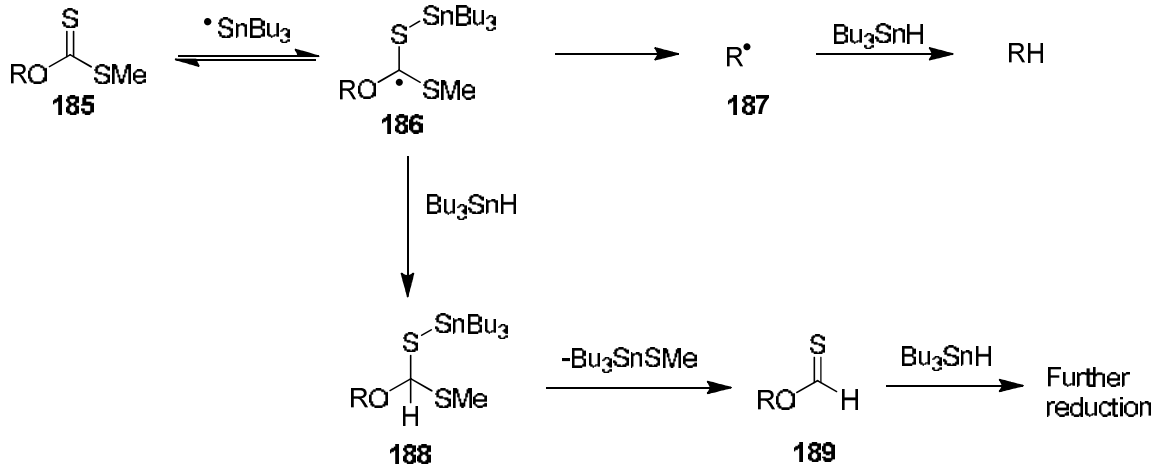


Scheme 64 Reduction of tertiary alcohols via xanthates

Tertiary xanthates were not initially looked at due to their tendency to eliminate to give olefins or rearrange to give S-alkyl dithiocarbonates. However, Barton did manage to synthesise some tertiary xanthates which successfully underwent radical deoxygenation. The best conditions found for this used Bu_3SnH as the reductant and Et_3B/O_2 as the initiator, at room temperature.[61]

Primary alcohols have also been reduced under Barton-McCombie conditions.[59] The problems with the formation of tertiary xanthates are not prevalent when forming

primary xanthates. The difficulty in these cases lies in the fragmentation step. After formation of the initial radical **186** from the primary xanthate **185**, fragmentation would result in a primary radical **187** which is unstable. This makes fragmentation relatively slow and allows for a competing pathway to occur. The initial radical can abstract a hydrogen from Bu_3SnH to give **188**, which collapses to a thioformate **189** that can then undergo further reduction (Scheme 65).

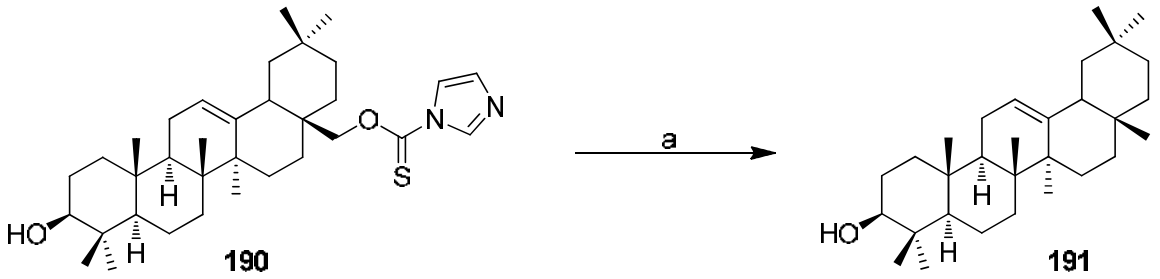


Scheme 65 Reduction of primary xanthates and competing pathway

This competing pathway is bimolecular. The difference between this and the unimolecular fragmentation, observed in the desired pathway, have been exploited to favour the reduction process. Increasing the temperature of the reaction, in the unimolecular process, allows the molecule to overcome the activation barrier, resulting in fragmentation. However, in the bimolecular process increasing the temperature has little effect. In this case, the two correct molecules need to collide for reaction to occur. Increasing the temperature gives the system more energy, thus speeding up the number collisions, but the number of incorrect collisions is also increased. Diluting the reaction

disfavours this bimolecular process, as it means the correct collisions are less likely to occur. The unimolecular fragmentation should be unaffected by concentration.

Therefore the optimal conditions for reducing xanthates derived from primary alcohol is high temperature and high dilution. An example of this is that of erythrodiol monothiocarbonyl imidazolide **190**, which was heated under reflux in xylene (b.p. 144 °C), with slow addition of Bu_3SnH, to give the reduced β-amyrin adduct **191** in a moderate yield (Scheme 66).[59]



Scheme 66 a) Bu_3SnH (added over 2h), xylene, reflux, 40%

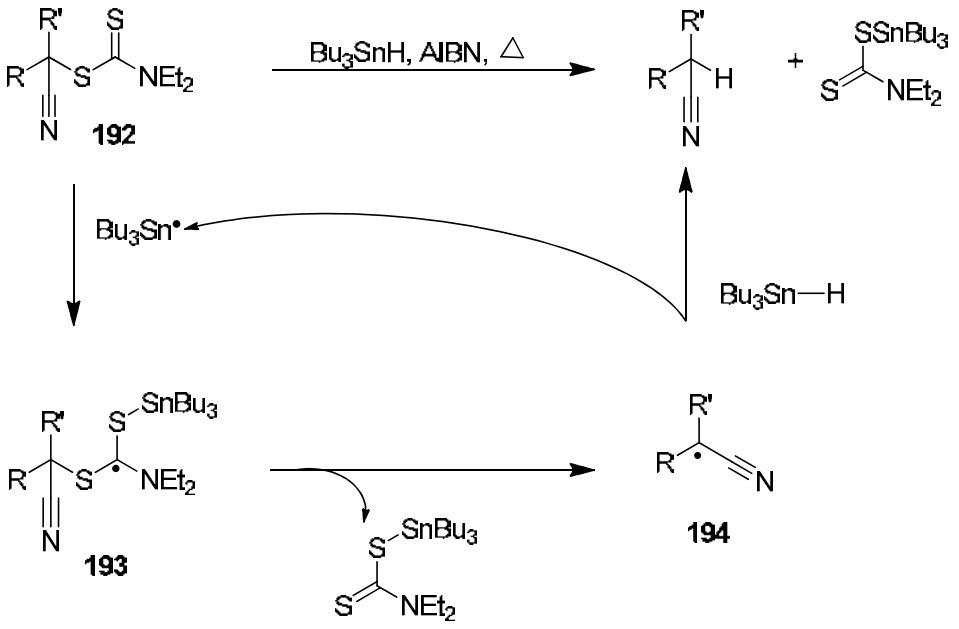
The Barton-McCombie deoxygenation of alcohols via thiocarbonyl derivatives is advantageous as it can be used for a wide variety of substrates. However the most consistent results are for secondary alcohols.[25] This radical mediated process can be run under neutral conditions and is suitable for sterically hindered alcohols. The reaction leaves functional groups such as esters, ketones, epoxides and tosylates untouched. However, halogens and isocyanide groups are reduced in the presence of the tin, which is used as the chain carrier in these reactions.

The reaction does not proceed as expected when there is a radical sensitive group in the β-position,[62] relative to the OH, of the starting alcohol. In these instances reaction with

Bu_3SnH gives the olefin. Another drawback of this reaction is that low yields have been reported in some cases, due to problems with the removal of the non-polar and non-volatile tin products during work-up and purification.

2.4 Extensions to Barton-McCombie Type Deoxygenations

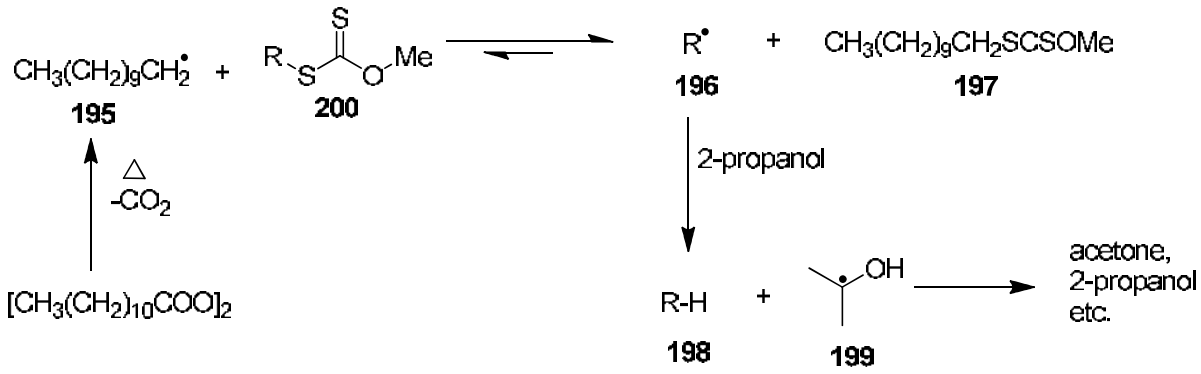
In 1988 Endo *et al.* reported the radical mediated reduction of α-cyanodithiocarbonates **192**, under the standard Barton-McCombie tin based conditions.[56] The side product of this reaction contains a C=S bond, as opposed to the C=O bond in the classical examples of the Barton-McCombie reduction. In this example the fragmentation of the intermediate radical **193** to give the stabilised α-cyano radical **194** will provide a good driving force for this reaction (Scheme 67). This work shows that fragementation to form C=O is not essential for reactions of this kind to proceed via a radical process.



Scheme 67 Reduction of α-cyanodithiocarbonates

The presence of stabilising R groups (such as a cyano group) has also been shown not to be a necessity, as Zard[63] and Boivin[64] have reported the successful reductive removal of xanthates from molecules that do not contain stabilising groups. Due to the problems associated with the use of tin, namely its toxicity, cost and difficulties in removal, there has been a desire to find a better way to mediate these reactions. Both Zard and Boivin have shown that reactions of this type can be mediated by substances other than Bu_3SnH, making this work very appealing.

Zard *et al.* reported the removal of the xanthate group by homolytic cleavage of the C-S bond using DLP in 2-propanol. This was achieved by taking advantage of the reversibility of the addition of the initiator-derived radical to the xanthate (explained in Chapter 1). The initial radical **196** can then abstract a hydrogen from 2-propanol (Scheme 68).[63]



Scheme 68 Desulfurisation using DLP in 2-propanol

Dilauroyl peroxide is broken down in the presence of heat to give an alkyl radical **195** which can then interact with the xanthate to give R• (**196**) and S- undecyl xanthate **197**. The Radical R• can abstract a hydrogen from the solvent to give the reduced product **198** and a 2-hydroxyisopropanol radical **199**. This radical is too stabilised to propagate the

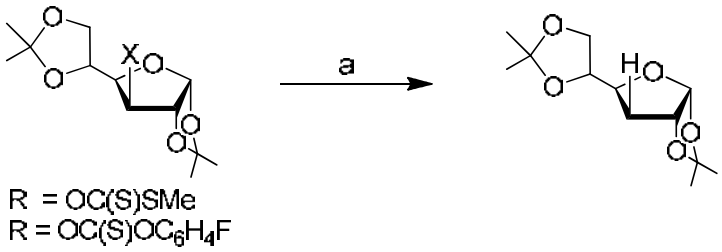
chain, so this is not a radical chain process. The DLP usually used as an initiator in the radical process, is now required in stoichiometric amounts. The radical **199** can undergo further transformations to give acetone or 2-propanol, which are easily removed from the system. For this reaction to be successful, the radical from the DLP has to react faster with xanthate **200** than it does with the solvent. The reaction of R• with another molecule of xanthate is degenerate, meaning the only reaction that provides an isolable product is that with the solvent.

The scope of this reaction has been investigated and the conditions optimised. It has been shown to work best with the addition of DLP slowly over many hours. The half-life of DLP is about 2 hours at 80 °C. 2-Propanol has a boiling point of 82-83 °C, making it a good match for the DLP, but is also a useful solvent as a hydrogen atom can be easily abstracted from it. To overcome problems with solubility that sometimes arise when using 2-propanol, it is possible to use a mixture of 2-propanol with other solvents such as diisopropylether or dichloroethane, with little effect on the yield. This method generally tolerates a range of functional groups, however there have been reports of small amounts of side products being generated in some cases. The reaction gives the best and most consistent results for secondary xanthates, which are the most synthetically useful. The use of primary xanthates has proven to be more difficult, requiring large amounts of peroxides and giving poor yields.

There have been other reported methods that do not employ the use of toxic tin reagents. The use of dialkylphosphites have been shown to work well for reductions as they are good hydrogen atom donors and chain carrier radical precursors.[65] However

reactions using these conditions tended to show formation of small amounts of side products, which would be problematic if run on a large scale. The initiator preferred for these reactions is benzoyl peroxide, which is safe to use on small scales, but on large scale the use of peroxides is disfavoured.[66] This led to the development of alternative conditions where hypophosphorus acid and triethylamine were used instead. These reactions can be initiated with AIBN, as apposed to benzoyl peroxide. The base (Et_3N) protects any acid-labile protecting groups that may be present from acid hydrolysis during the reaction, and also protects the thiocarbonate group. The main function of the base is to form the hypophosphorus acid salt, which is the hydrogen atom source.

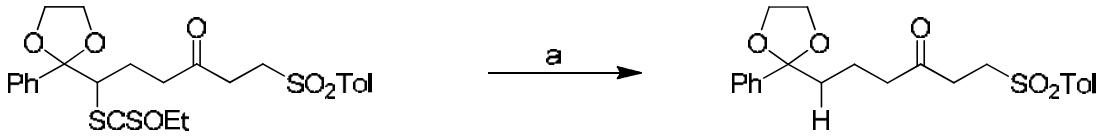
In 1992, Barton showed that a variety of different alcohols could be converted to thiocarbonates (100%) or xanthates (84%) and subsequently deoxygenated to give the reduced product under these conditions (Scheme 69). This chemistry gives reliably high yields for the cleavage of the C-O bond, from the intermediates generated from primary, secondary and tertiary alcohols.[66]



Scheme 69 a)Et_3N, H_3PO_2, AIBN, dioxane

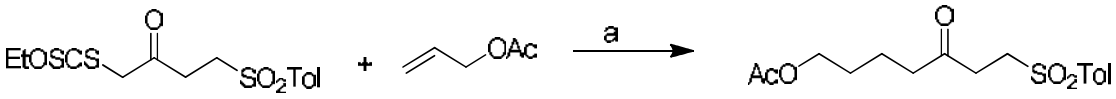
In 2003 Boivin reported a method of reductive removal of S-alkylxanthates using hypophosphorus acid or diethylphosphite to cleave the C-S bond of the xanthates.[64] The use of hypophosphorus acid (5 equiv.) and triethylamine (5.5 equiv.) in refluxing dioxane,

using AIBN as the initiator, gave high yielding reductions (Scheme 70). The use of 1-propanol, as a less toxic and cheaper alternative to dioxane was also reported and had little effect on the yield. These reactions are of particular interest as they are run under mild conditions, with water soluble by products and give good to excellent yields.



Scheme 70 a)Et_3N, H_3PO_2, AIBN, dioxane, reflux, 18 mins, 69%

Boivin also carried out the reactions using diethylphosphite in 1,2-dichloroethane, finding these conditions required longer reaction times. These longer reaction time were used as an advantage, because it allows intermolecular reactions to occur. Removal of the xanthate gives R• which can then undergo the intermolecular addition reaction onto an alkene in the reaction mixture (Scheme 71).

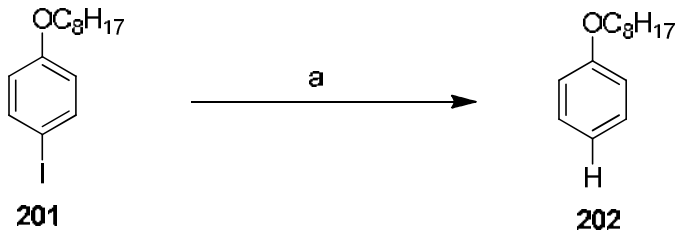


Scheme 71 a) diethylphosphite, dibenzoyl peroxide, diethylphosphite, reflux, 1,2 DCE, 18

The limitations of using diethylphosphite for intermolecular reactions onto olefins are that side reactions are often observed and yields tend to be low. However these conditions are non-toxic and the byproducts are easily removed as they are water soluble.

The use of hypophosphorus acid as the reductant in radical reactions has also been reported by Oshima *et al*. They chose to look at alternatives to dioxane in a bid to reduce

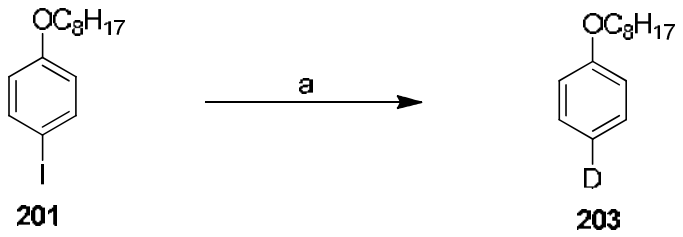
toxicity and managed to successfully carry out reactions in ethanol (Scheme 72). The iodide **201** was successfully reduced to the aromatic compound **202**. They highlighted the need for base by showing that reactions run in the absence of base gave very little product. The Inclusions of bases such as $NaHCO_3$ or Et_3N resulted in high yields, showing that the actual H-atom source in this process is a phosphonate anion.[67]



Scheme 72 a) aq. H_3PO_2, Et_3N, AIBN, EtOH, reflux, 5 h, 96%

The majority of this work focused on the reduction of arylhalides, but it was also shown that the xanthates could be reduced under these conditions.

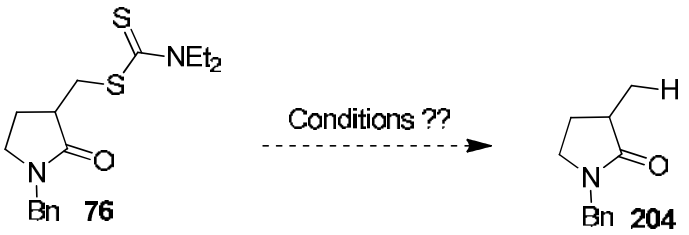
Oshima also reported a series of labelling experiments using deuterated hypophosphorus acid in D_2O. It was found that these reactions worked particularly well when using $K_2S_2O_8$ as the initiator. Although there have not been any reports of xanthates being reduced under these conditions, the reduction of a variety of iodides have been reported (Scheme 73). The iodide **201** is reduced to the deuterium containing aromatic compound **203**, with a yield of 95% with 88% D. Deuterium incorporation was also shown to occur during relevant cyclisation reactions.[67]



Scheme 73 D_3PO_2/D_2O, $K_2S_2O_8$, DBU, dioxane, reflux, 1 h, 95%, 88% D

2.5 Aims and Objectives

Previous reports of the attempted reductive removal of dithiocarbamates used relatively harsh conditions and gave mixtures of products, as discussed previously in this chapter.[54,55,57] The dithiocarbamate group contains a radiophilic thiocarbonyl group similar to that found in xanthates. As methods for the radical mediated reduction of xanthates have been reported under a few different conditions, it seemed viable that dithiocarbamates could be reduced in the same manner. The aim of this work was to find mild, neutral, tin-free conditions to give clean conversion of dithiocarbamates to alkanes (scheme 74). Initial studies focused on the reduction of the γ-lactam dithiocarbamate **76**, generated via a 5-*exo*-trig cyclisation group transfer reaction previously developed within the group, to give the γ-lactam **204**.

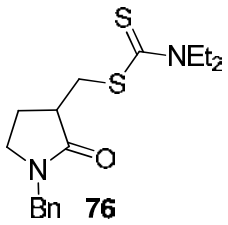


Scheme 74 Reductive desulfurisation of dithiocarbamate

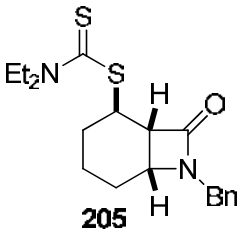
2.6 Development of Conditions for Reduction

2.6.1 Initiation Using Light Sources

Keen to avoid the use of tin, the possibility of radical reduction using different light sources was considered. The use of light to generate carbon centred radicals from dithiocarbamates is known, so it seemed logical to attempt reductions using different light sources, in the presence of a solvent with an easily abstractable hydrogen atom. The use of light as the initiator is particularly attractive as reactions of this kind require minimal work up and should convert cleanly to product.



76



205

γ-Lactam **76**, containing the primary dithiocarbamate moiety and β-lactam **205**, containing a secondary dithiocarbamate moiety, can be easily synthesised via routes previously developed within the group. Reduction initiated using light was attempted on both of these, as it was thought that the difference in substitution levels may effect the type of radical produced and ultimately provide different amounts of reduced products.

A range of different conditions were tested for the reduction of dithiocarbamates **76** and **205** as summarised in Table 2. Quartz glasswear was initially used, as it has a lower cut off point for irradiation than that of Pyrex which has a cut off point for irradiation of 290 nm, meaning quartz will allow more wavelengths of light through. Experiments previously

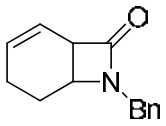
carried out on dithiocarbamates showed the absorbance of the cyclised dithiocarbamates to be 285 nm.[51]

Entry	Stariting Material	Glasstype	Solvent	Additive	Light Source	Result
1	**76**	Quartz	2-propanol	-	125 W medium pressure	degradation
2	**205**	Quartz	2-propanol	-	125 W medium pressure	alkene **206** (~10%)
3	**76**	Quartz	cyclohexane	-	125 W medium pressure	degradation
4	**205**	Quartz	cyclohexane	-	125 W medium pressure	degradation
5	**76**	Quartz	cyclohexane	-	400 W medium pressure	degradation
6	**205**	Quartz	cyclohexane	-	400 W medium pressure	degradation
7	**76**	Pyrex	cyclohexane	-	125 W medium pressure	degradation
8	**205**	Pyrex	cyclohexane	-	125 W medium pressure	degradation
9	**76**	Pyrex	2-propanol	-	125 W medium pressure	degradation
10	**205**	Pyrex	2-propanol	-	125 W medium pressure	degradation
11	**76**	Quartz	toluene	cyclohexadiene	125 W medium pressure	degradation
12	**205**	Quartz	toluene	cyclohexadiene	125 W medium pressure	degradation

Table 2 Attempted reduction with various light sources

Cyclohexane and 2-propanol have both been used as the hydrogen source in radical-mediated reduction reactions, so both solvents were experimented with under the light conditions. As a 125 W medium pressure light has previously been shown to generate carbon centred radicals from related dithiocarbamates, it seemed logical to initiate the

reductions in this manner. However the majority of results simply led to the degradation of the starting material (Table 2 entries 1, 2, 3 and 4). A small amount of the alkene **206** was observed when the reaction was carried out with β-lactam **205** in 2-propanol.



206

Reactions were also studied where a 400 W medium pressure Hg lamp was used as the initiator. Again this resulted in degradation (Table 2 entries 5 and 6).

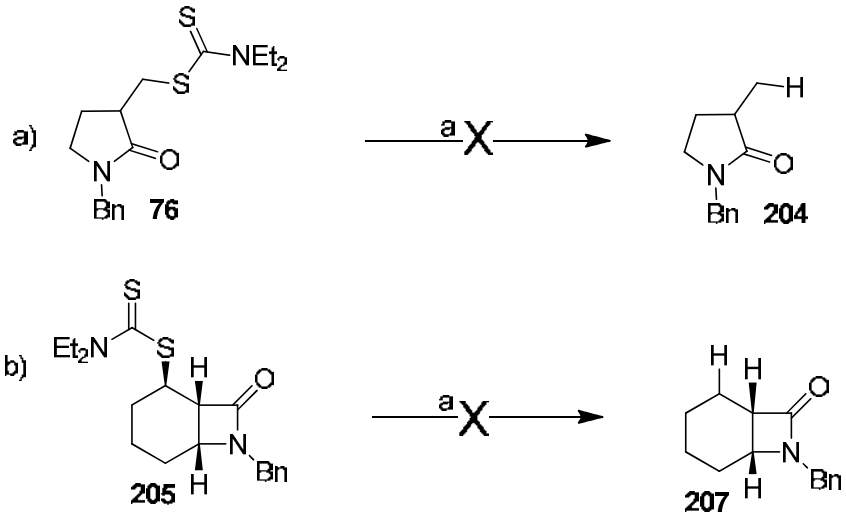
Due to consistently observing degradation, it was considered that allowing a narrower spectrum of light into the system may be preferable as it should give less degradation. As such experiments were repeated using Pyrex equipment. However this was not successful and high levels of degradation were once again observed in all experiments (Table 2 entries 7, 8, 9 and 10).

A solution of toluene containing 10 equivalents of cyclohexadiene, relative to the starting material, has been used in reactions where radicals are generated by using a 125 W medium pressure lamp. Using these conditions on dithiocarbamates **76** and **205** also gave degradation (Table 2 entries 11 and 12).

Reactions under all of the different conditions tried, where light has been used to initiate reactions, resulted in high levels of degradation. Therefore it was decided to concentrate efforts on chemical initiation.

2.6.2 Chemical initiation

As Zard has shown that the use of DLP in cyclohexane gave reliable results in the reduction of certain xanthates,[63] it was decided to apply these conditions to dithiocarbamates. A solution of dithiocarbamate **76** was dissolved in cyclohexane and DLP was added portionwise (0.2 equiv. every 2 hours) until stoichiometric amounts had been added. Unfortunately this led to degradation of starting material with little evidence of any formation of the reduced product **204** (Scheme 75, a). When the same conditions were applied to the secondary dithiocarbamate **205**, degradation was once again observed (Scheme 75, b), with no production of **207**.

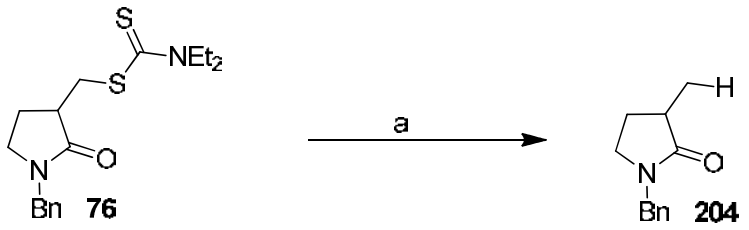


Scheme 75 a) DLP, 2-propanol, reflux

The use of diethylphosphite in 1,2-DCE and an initiator to induce reduction of dithiocarbamates **76** and **205** was also tested. In this instance degradation was also evident after a few hours and nothing could be isolated from the resultant complex mixture.

The use of hypophosphorus acid, a base and radical initiator has been reported for the reduction of xanthates.[64] The literature conditions report the use of AIBN as the radical initiator, however it was decided to use ACCN as an alternative initiator when investigating these conditions. This is due to ACCN being more readily available and safer than AIBN.

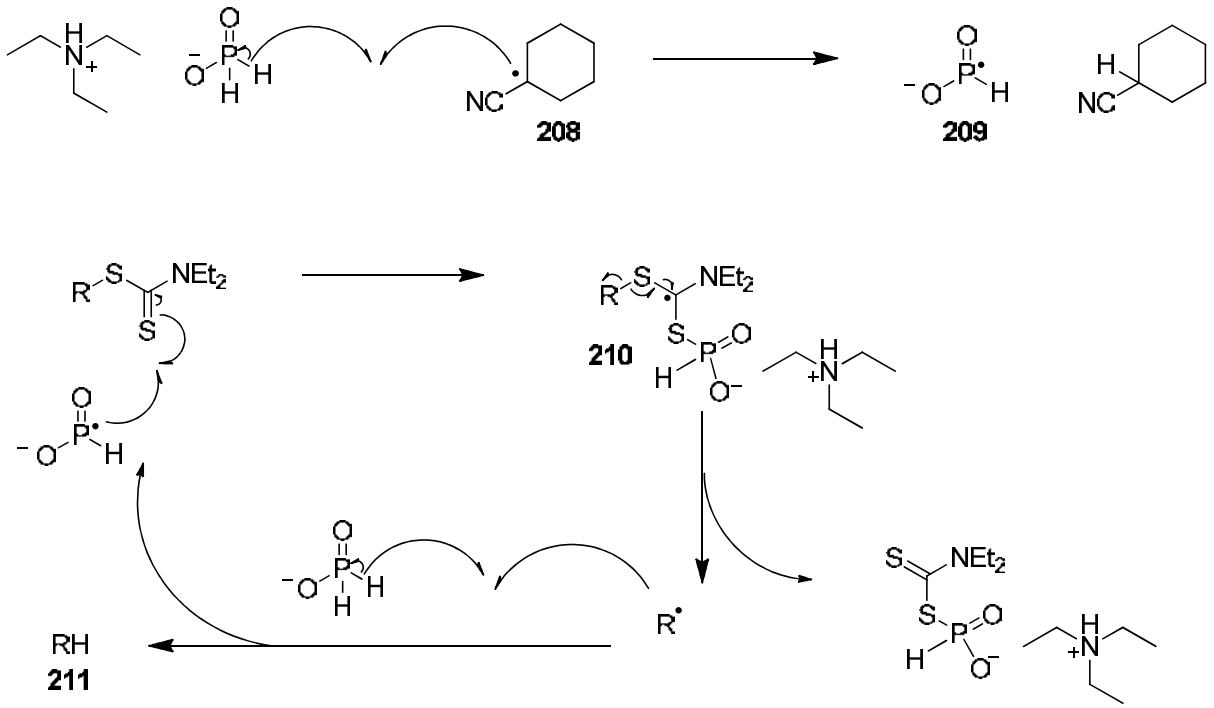
Treatment of **76** with aqueous H_3PO_2 (5 equiv.) and triethylamine (5.5 equiv.) in refluxing dioxane, initiating the reaction with sub stoichiometric amounts of ACCN (0.3 equiv.), gave the reduced γ-lactam **204** in good yield (77%) (Scheme 76). The side product arising from this reaction should be the water soluble salt $[Et_3NH]^+[HPO_2SC(S)NEt_2]^-$, and indeed after aqueous work up no products containing the dithiocarbamate moiety were observed.



Scheme 76 a) ACCN, NEt_3, H_3PO_2, dioxane, reflux, 77%

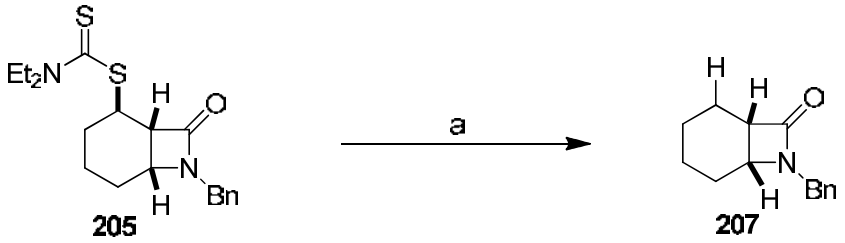
This is consistent with the mechanism for the reaction being that shown in Scheme 77. The ACCN breaks down in the presence of heat to generate the carbon centred radical **208**, which abstracts a hydrogen from the hypophosphorus acid-triethylamine salt to create the phosphorus centred radical anion **209**. This adds to the dithiocarbamate giving the tertiary carbon centred radical **210**, which breaks down to give R• and the phosphorus containing compound, stabilised by the base, which is water soluble. The

radical R• can then abstract a hydrogen from another molecule of the hypophosphorus acid, releasing the reduced product **211** and generating another phosphorus centred radical to continue the chain process.



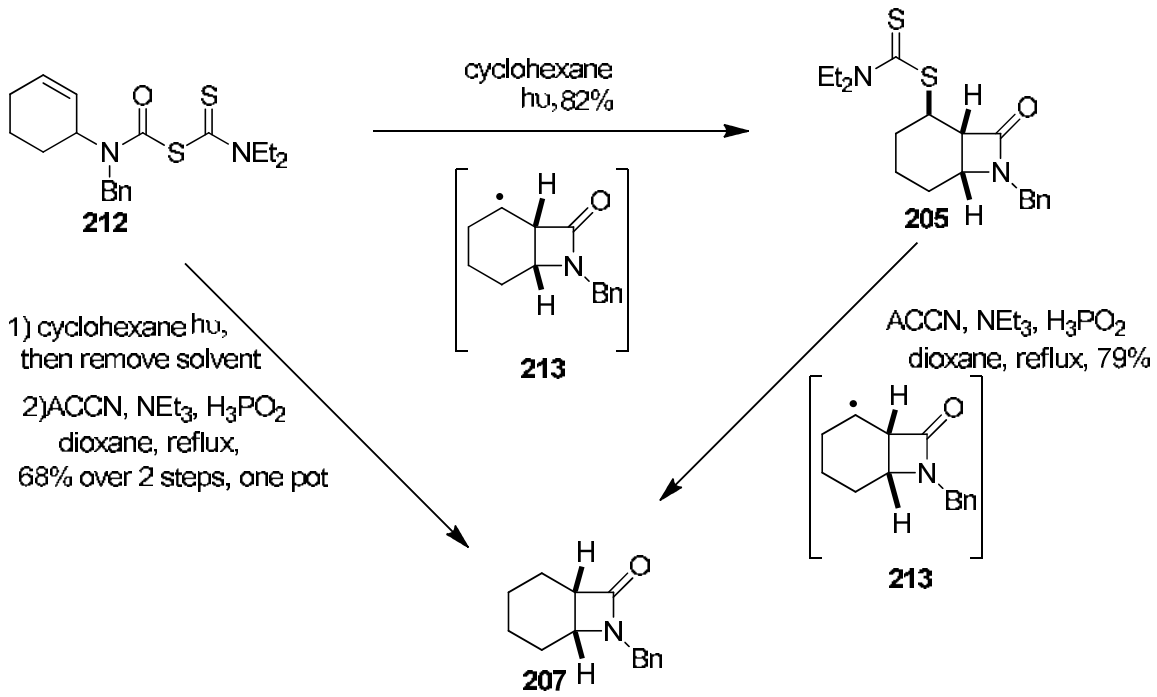
Scheme 77 Mechanism of reduction

Initial studies used 5 equivalents of hypophosphorus acid, as described for the reduction of xanthates. Running the reaction with half the number of equivalents of both hypophosphorus acid and triethylamine resulted in a substantial drop in yield to 27%. Doubling the number of equivalents of the reactants also resulted in a drop in yield to 55%. These results indicated that the original conditions are optimal.



Scheme 78 ACCN, NEt_3, H_3PO_2, dioxane, reflux, 79%

These same conditions were applied to the β-lactam **205** and again reduction occurred in good yield (Scheme 78). The cyclisation reaction to form the β-lactam **205** and its subsequent reduction to give **207** share a common radical intermediate **213**. The potential to trap the intermediate radical **213** after cyclisation, but before group transfer, was explored. The cyclisation precursor **212** was treated with H_3PO_2-Et_3N-ACCN in refluxing dioxane. It was hoped that the ACCN would first initiate the cyclisation to give radical intermediate **213**, which could then undergo H-atom abstraction with the hypophosphorus acid to give the β-lactam **207**. However this gave a complex reaction mixture, with only approximately 5% of the reduced product **207** being present.



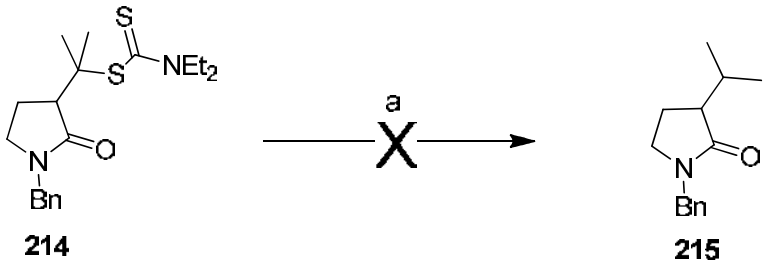
Scheme 79 Cyclisation and reduction of a β-lactam

These results made it apparent that the two reactions needed to be carried out separately. Although it was not possible to carry out the reaction in one step, it was possible to carry out the reaction in one pot. The two steps were carried out without purification of the cyclised intermediate **205**. The photomediated cyclisation is carried out under standard conditions. Once complete the solvent is simply removed and the crude **205** dissolved in dioxane. This solution is submitted to the standard reduction conditions and upon completion, work up and purification is carried out as usual. This gave an overall yield of 68% of **207**, which is comparable with the 65% overall yield from the individual transformations (Scheme 79). The advantage of the one-pot system is that only one purification is needed compared with carrying out two separate reactions, making it cheaper and practically simpler than having two separate steps.

A switch of solvents is necessary to maintain high yields. It was neither possible to cleanly cyclise **212** to **205** in dioxane (59% and 34% yields by *h*v or ACCN initiation respectively), nor reduce **205** with H_3PO_2-Et_3N-ACCN in cyclohexane. The lack of reduction in cyclohexane can be explained by the boiling point of cyclohexane (81 °C) being too low to produce efficient breakdown of ACCN, which has a half life of 10 hours at 88 °C. The higher boiling point of dioxane (101 °C), allows for formation of radicals from the initiator at a fast enough rate to allow the reaction to occur on a reasonable timescale.

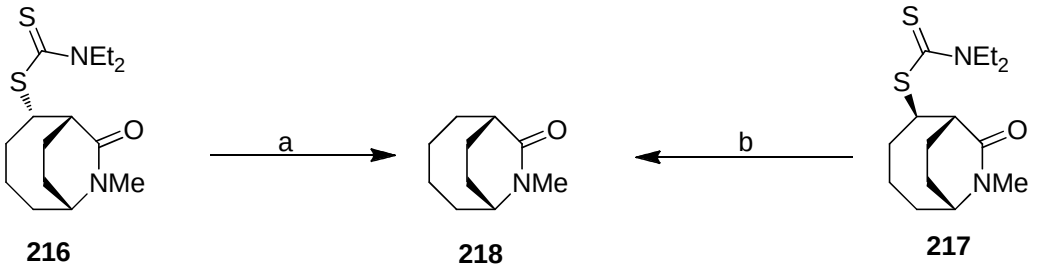
2.7 Substrate Scope

In order to probe the scope of this reaction a variety of different dithiocarbamates were synthesised. As reduction of both primary and secondary dithiocarbamates has been achieved, the next logical step was to look at the reduction of a tertiary dithiocarbamate. The tertiary dithiocarbamate **214** has been synthesised previously in the Grainger group.[39] Application of the reduction conditions did not give any isolable product, which would be expected to be **215** (Scheme 80). There was evidence of the formation of **215** in the non-purified mixture. Due to the unsuccessful outcome of this reaction, further studies concentrated on the more reliable reductions of secondary and tertiary dithiocarbamates.



Scheme 80 a) H_3PO_2, Et_3N, dioxane, ACCN, reflux

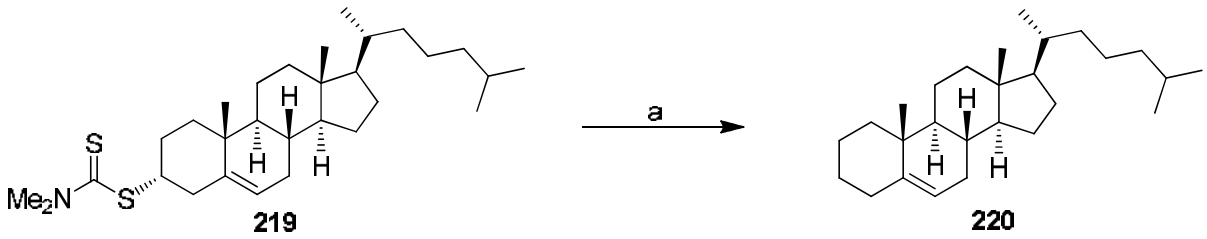
The diastereomers **216** and **217** have been synthesised previously in the Grainger group.[68] The reduction of these were attempted to see if the rate of reduction would be affected by the change in dithiocarbamate group orientation. Both these compounds underwent relatively rapid reduction in comparable yields to give **218**. However dithiocarbamate **217** underwent reduction in 2.5 hours, compared with the slightly longer reaction time of 4.5 hours for dithiocarbamate **218** (Scheme 81).



Scheme 81 a) H_3PO_2, Et_3N, ACCN, dioxane, reflux, 4.5 h, 83%; b) H_3PO_2, Et_3N, ACCN, dioxane, reflux, 2.5 h, 87%

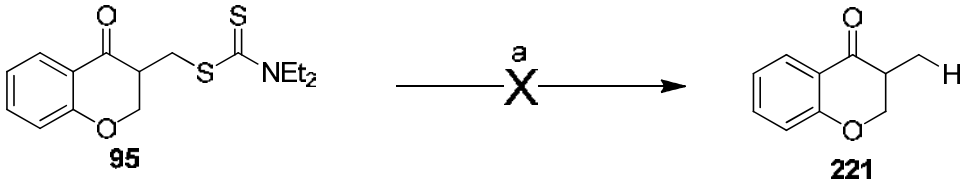
The application of this work to steroids was achieved by showing the successful reduction of the cholesterol derived dithiocarbamate **219** to give **220** under the standard conditions in an excellent yield (97%) (Scheme 82%). This steroid was chosen as it is easy to form the dithiocarbamate **219** in a simple one-step procedure from the cheap commercially

available cholesterol.[69] Gratifyingly no addition of the phosphorus centred radical to the double bond was observed, which could potentially be a competing reactions.



Scheme 82 a) H_3PO_2, Et_3N, ACCN, dioxane, reflux, 16 h, 97%

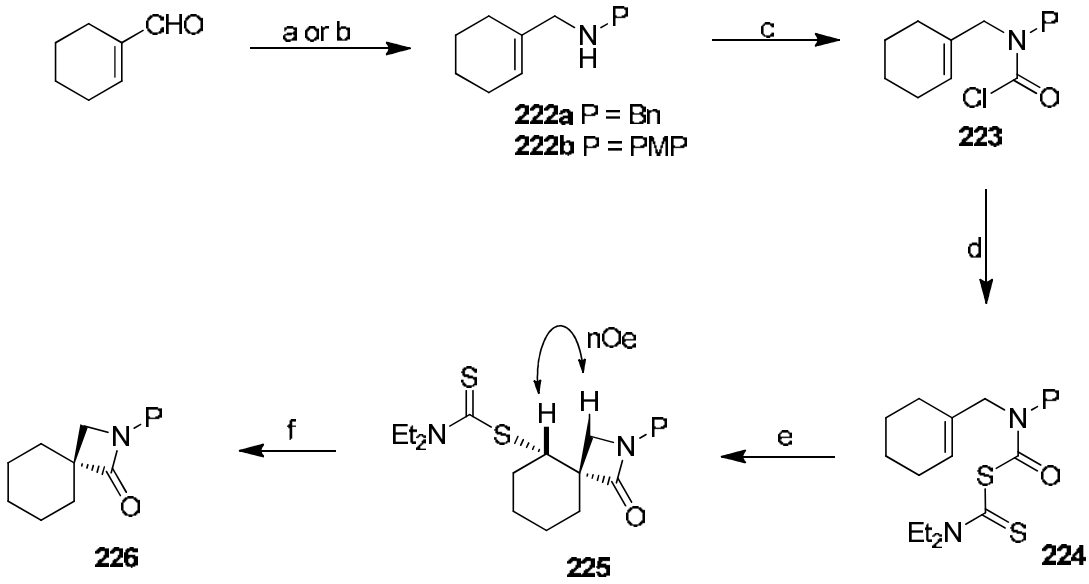
Attempted application of the reduction conditions to dithiocarbamate **95**, whose synthesis was described in Chapter 1, did not give the reduced product **221**, instead a complex mixture of products was observed (Scheme 83).



Scheme 83 a) H_3PO_2, Et_3N, ACCN, dioxane, reflux

The radical **213**, which is an intermediate in both the 4-*exo*-trig cyclisation of **212** and in the reduction of **205**, is adjacent to a 4-membered ring system (Scheme 79). In general, 4-membered ring systems with adjacent radicals are prone to ring opening, driven by the release of ring strain.[70] However, when the ring system is a β-lactam, as in this case, the ring opening is not observed.[70,71] It was envisaged that this lack of ring opening could be exploited in the synthesis of spirocyclic β-lactams via a 4-*exo-trig* cyclisation of carbamoyl

radicals. Spirocyclic β-lactams are of particular interest as they display a range of biological activities and transformations.[72]



Scheme 84 a) benzylamine, DCE, rt, 3 h, then $NaB(OAc)_3H$, rt, 16 h, 24% b) p-anisidine, CH_2Cl_2:AcOH, rt, 3h, then $NaB(OAc)_3H$, 0°C to rt, 10 h, 57% c) toluene, triphosgene, pyridine, rt, 18 h, **223a** (87%), **223b** (97%); d) $Et_2NC(S)SNa.3H_2O$, acetone, rt, 18 h, **224a** (84%), **224b** (67%); e) 500 W lamp, cyclohexane, 10 h, **225a** (59%), **225b** (60%); f) ACCN, NEt_3, H_3PO_2, reflux, **226a** (60%), **226b** (39%)

In order to investigate this approach to spirocycles, the cyclisation precursor **224a** was first synthesised. The formation of the protected amine **222a** was achieved by reductive amination of 1-cyclohexene-1-carboxaldehyde with benzylamine. The corresponding carbamoyl chloride **223a** was synthesised from this using triphosgene. Application of the conditions previously developed within the group led to dithiocarbamate **224a** via the carbamoyl chloride **223a** (Scheme 84). Exposure of a solution of dithiocarbamate **224a** in cyclohexane to a 500 W halogen lamp initiated the 4-*exo*-*trig* group transfer reaction to give a single product. Although NMR data supported the formation of **225a**, the mass spectroscopic data is inconsistent with this structure, revealing an extra oxygen to be present. With the identity of the dithiocarbamate **225a** in question, it was decided to

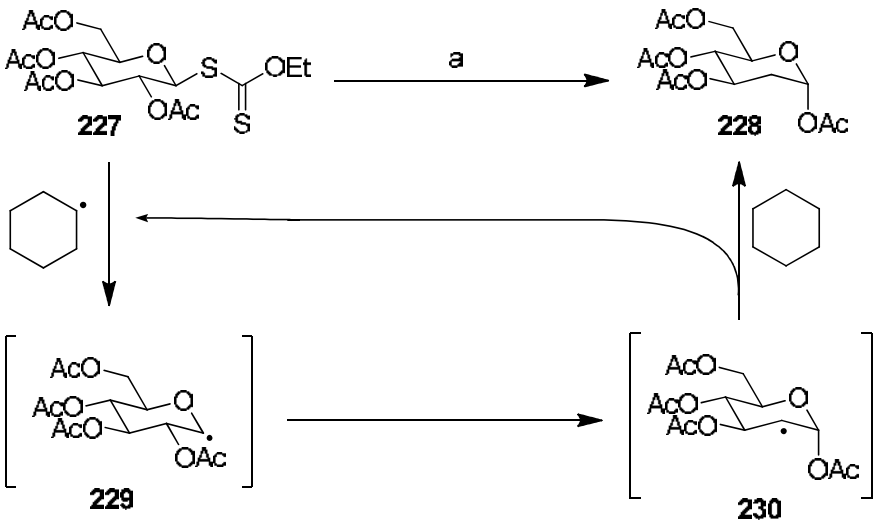
proceed with the reduction reaction, in the hope that this would allow for a clearer identification of the product to be made. Application of the reduction conditions resulted in loss of the dithiocarbamate group in an apparent 60% yield. Once again despite NMR spectra supporting formation of the spiro-lactam, discrepancies in the mass spec data have meant a firm conclusion on the production of **226a** can not be made.

Due to the problems with identification of products, it was decided to repeat this chemistry, but using a different protecting group on the nitrogen. To achieve this, the known amine **222b** was first synthesised. This was prepared in one step by reductive amination of commercially available 1-cyclohexene-1-carboxaldehyde with *para*-methoxyaniline.[73] The dithiocarbamate **224b** was formed from this via the carbamoyl chloride **223b**. Exposure of dithiocarbamate **224b** to a 500 W halogen lamp initiated the 4-*exo*-*trig* group transfer reaction to give the spirocylic β-lactam **225b** in a reasonable yield (60%). This reaction produced a single diastereomer, with nOe analysis showing the proton adjacent to sulfur to be on the same side of the carboxylic ring as the methylene group of the β-lactam. In this instance all data gathered supports formation of the spirocyclic system.

Reduction of **225b** under standard conditions gave the spirocyclic β-lactam **226b** in a yield of 39%, somewhat lower than the yield of 79% observed for the reduction of the comparable β-lactam **205**. This suggests that competing reaction pathways are occurring, and indeed an NMR of the crude reaction mixture revealed the presence of other products. However it was not possible to isolate any other compounds from the reaction

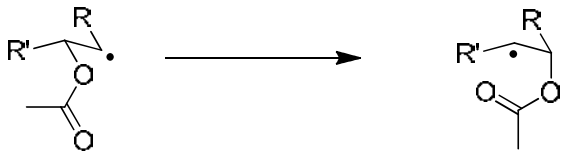
mixture in sufficient purity to allow these compounds, and subsequently alternative reaction pathways, to be identified.

To further extend this work the reduction of an anomeric sugar derivative containing an acyloxy group at C-2 was looked at. The reduction of such compounds is interesting both mechanistically and in the selective carbohydrate synthesis. The reduction of anomeric xanthate **227** has been reported by Zard, using dilauroyl peroxide as the radical initiator and cyclohexane as the solvent and hydrogen source, to give only the reduced product **228**, where the acyloxy group has migrated (Scheme 85).[74] This occurs via formation of initial radical **229**, which is nucleophilic in character, making the H-abstraction form the cyclohexane unfavourable. Migration of the acyloxy group gives the radical **230** which has sufficient electrophillic character to abstract a hydrogen from cyclohexane, giving rise to the observed product.



Scheme 85 a) cyclohexane, DLP, reflux, 6h, observed yield 86%, literature yield 65%[74]

The mechanism of this rearrangement of the β-(acyloxy)alkyl radical has been hotly disputed in the literature and is observed in many systems, not just the sugar example reported here.[75] Scheme 86 gives a simplified overview of what is occurring in these cases. The possibility of a radical type fragmentation to give an alkene and acyloxy radicals, that could then recombine, was largely dismissed as the acyloxy radicals can easily undergo decarboxylation.



Scheme 86 Rearrangement of β-(acyloxy)alkyl radicals

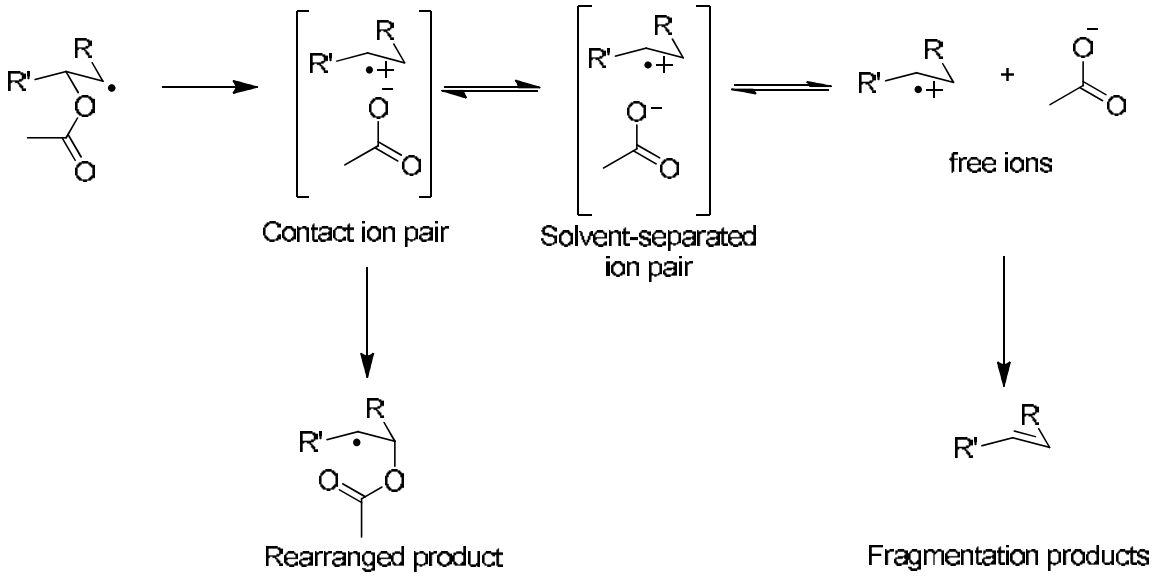
Julia *et al.* showed that the reactions were completely stereoselective and this is suggestive of an intramolecular pathway.[76] They also showed the need for a significant driving force, as rearrangement was not observed when the starting material and the radical, that would have arisen from rearrangement, would have been energetically the same.

In the case of the sugar the rearranged radical **230** is electronically less stable than the initial radical **229**. However having the ester at the 1-position means anomeric stabilisation occurs, which is believed to overcome the loss in radical stability and allows the rearranged product to form.[75]

The mechanism could theoretically proceed via a 5-centre-5-electron or a 3-centre-3-electron cyclic transition state, because both pure 2,3 shifts and pure 1,2 shifts have been observed. Substituents and solvent effects are believed to control which pathway is

followed, with mixed mechanisms being reported in some instances. Computational studies have been undertaken that supported a concerted rearrangement, possible by either of these 2 transition states.[75]

The current thinking on this mechanism centres around a radical ionic fragmentation, which gives a contact ion pair. This collapses to give the rearranged product, or in the presence of polar solvents this can lead to solvent separated ion pairs. Formation of free ions, which can then fragment to give a variety of fragmentation products, is also possible from the solvent separated ion pairs (Scheme 87).

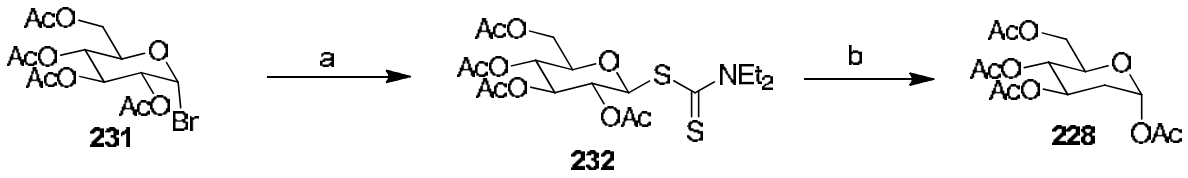


Scheme 87 General rearrangement mechanism

The use of time-resolved laser flash photolysis has shown the presence of radical cations in the closely related β-(phosphaloxy)alkyl radical rearrangement, supporting this mechanism.[77] However, there have not been any β-(acyloxy)alkyl radical cations observed by this method, which suggests that the initial contact ion pair collapses rapidly to give the product. This very short lived ion pair has no time to equilibrate to the solvent-

seperated ion pair, and hence these reactions occur in high yields with no fragmentation products observed.

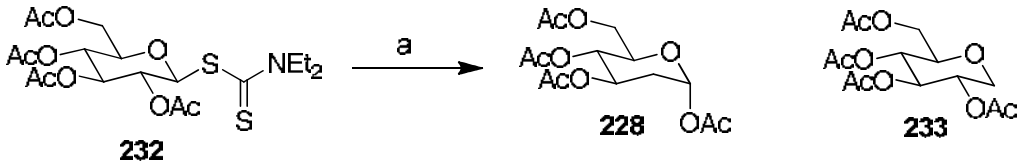
In order to allow a direct comparison between xanthates and dithiocarbamates, the ditihiocarbamate sugar **232** was first synthesised in a simple one-step procedure from the commercially available acetobromo-α-D-glucose **231**.[78] Application of the DLP and cyclohexane conditions to **232**, gave only **228**, where group migration has occurred, in a slightly higher yield and with reduced reaction times compared with the xanthate (Scheme 88).



Scheme 88 a) MeCN, $NEt_2C(S)SNa.3H_2O$, RT, 2h, 76%; b) cyclohexane DLP, 4h, 88%

Application of the standard ACCN-Et_3N-H_3PO_2 conditions in dioxane to the sugar dithiocarbamate **232** gave a mixture of 2 products **228** and **233** in a 1:1 ratio (Scheme 89) One of these arises from the acyloxy group migration as observed when initiating the reaction with DLP, the other from when hydrogen abstraction occurs prior to group migration. The same results, with comparable yields and reaction times, were observed when these conditions were applied to the xanthate (Table 5, entry 5). The ratio of **228** and **233** can be controlled through concentration effects (Table 3, entries 1-4). The rate of intermolecular H-abstraction is slower at lower concentration, allowing the

intramolecular rearrangement to compete effectively, resulting in **229** being the only product (Table 3, entry 2).



232 **228** **233**

Scheme 89 H_3PO_2, Et_3N, ACCN, dioxane

Entry	Substrate	Reagents (equiv.), solvent (substrate concentration)	Time (h)	Ratio [a] **233**:**228**	Isolated yield (%)
1	**232**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.1 M)	18	1:1	85
2	**232**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.01 M)	18	0:1	86
3	**232**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.5 M)	18	3:1	71
4	**232**	H_3PO_2 (10), Et_3N (11), ACCN (0.3), dioxane (0.5 M)	18	1:0	44
5	**227**	H_3PO_2 (5), Et_3N (5.5), ACCN (0.3), dioxane (0.1 M)	18	1:1	79
6	**232**	Dilauroyl peroxide (0.4), cyclohexane (0.1 M)	4	0:1	88
7	**227**	Dilauroyl peroxide (0.4), cyclohexane (0.1 M)	6	0:1	86[b]

[a]Determined by integration of ^1H NMR of crude reaction mixture. [b]Literature yield 65%[74]

Table 3 Concentration effects on products

At higher concentration the radical **229** undergoes H-abstraction more rapidly, as there is a higher chance of H-abstraction occurring before rearrangement can occur. This leads to a higher proportion of **233** compared to **228** in the isolated material (Table 3, entry 3). Further increasing the concentration in an attempt to yield just **233** were unsuccessful due to problems with solubility.

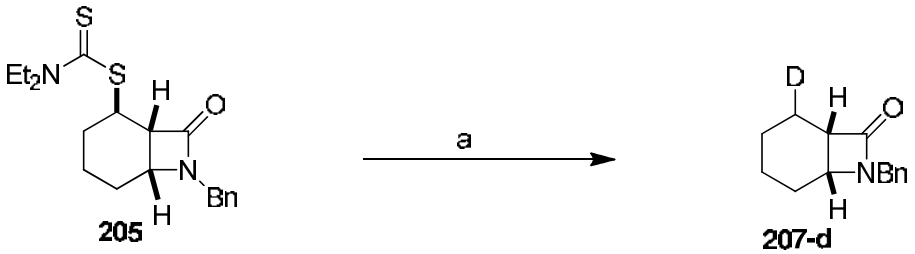
To circumvent this issue, the concentration of the reaction was increased, not by reducing the amount of solvent but instead by doubling the amount of Et_3N and H_3PO_2. This led to the non-rearranged reduction product **233** as the sole isolated product from this reaction, however the yield was lower than those previously observed (Table 3, entry 4). This low yield has been attributed to issues with the solubility of the large amounts of reactants.

The ability to steer the chemistry in the direction of one product or the other is extremely useful and easily achieved by altering the concentration at which the reaction is run. This is only achieved when using ACCN, H_3PO_2 and Et_3N as the reactants and not when using DLP in cyclohexane, where only the group migration product **228** is obtainable.

2.8 Deuterium Incorporation

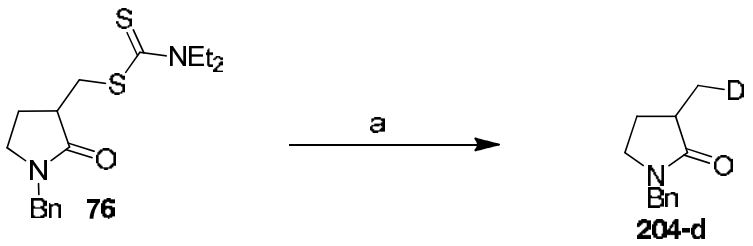
The possibility of labelling the reduced compounds with deuterium was next to be investigated. Oshima has reported the used of D_3PO_2 as a source of deuterium in the radical mediated reduction of alkyl and aryl iodides.[67] We first looked at the deuterium incorporation on the β-lactam and γ-lactam originally investigated in the reduction

chemistry (Scheme 90). The standard reduction conditions were applied to the β-lactam **205**, using the commercially available D_3PO_2 in D_2O in the place of H_3PO_2 in H_2O, giving the reduced deuterium containing compound **207-*d*** in a 32% yield with 82% deuterium incorporation.



Scheme 90 a) ACCN, NEt_3, D_3PO_2, dioxane, reflux, 32%, 82% D

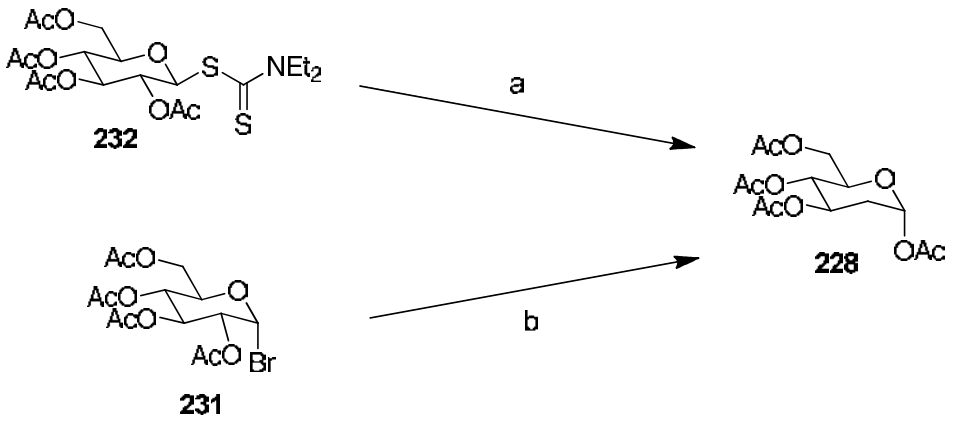
As Oshima had reported higher yields when using $K_2S_2O_8$ as the initiator, the reaction was repeated using $K_2S_2O_8$ in the place of ACCN. This gave the product in better yield with better deuterium incorporation (63% yield, 91% D). These conditions were applied to the γ-lactam **76**, which also resulted in high levels of deuterium incorporation (91%) in reasonable yield (63%) (Scheme 91).



Scheme 91 $K_2S_2O_8$, NEt_3, D_3PO_2, dioxane, reflux, 63%, 91% D

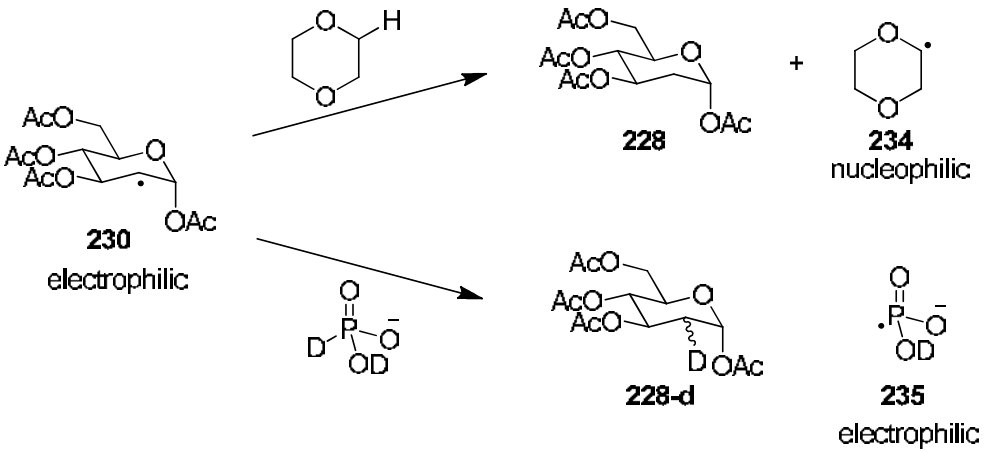
As the sugar **232** is easily accessible in one high yielding step from a commercially available starting material, deuterium incorporation studies were carried out on this

compound. Application of the $K_2S_2O_8$ conditions to the glucosyldithiocarbamate **232**, run at a concentration of 0.01 M, gave only **228**, the product from complete acyloxy group migration, with no deuterium incorporation observed. This same lack of deuterium was observed when these conditions were applied to the glucosylbromide **207** (Scheme 92).



Scheme 92 a) $K_2S_2O_8$, NEt_3, D_3PO_2, dioxane, reflux, 67%, 0% D; b) $K_2S_2O_8$, NEt_3, D_3PO_2, dioxane, reflux, 68%, 0% D

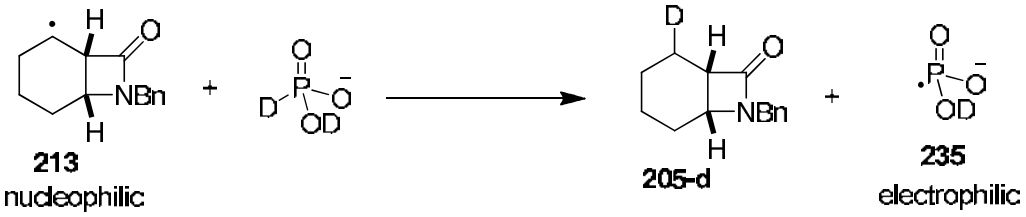
The lack of deuterium in the product can be explained by taking into account the role of polar effects in the reaction of the intermediate radical **230**.[79] This radical can be considered electrophilic in nature due to the flanking electron-withdrawing acetate groups. A polarity-matched reaction pathway is required for the reaction to be successful. Abstraction of a hydrogen from the solvent dioxane (or excess triethylamine) gives the observed product and also produces the nucleophilic α-oxo radical **234**, a polarity matched pathway (Scheme 93).



Scheme 93 Polar effects in H/D-atom abstraction

When using H_3PO_2, the mechanism predicts hydrogen abstraction from the salt of the hypophosphorus acid. Deuterium abstraction from the salt of the hypophosphorus acid is not observed. The P-D bond is stronger than the P-H bond, making deuterium abstraction less favoured. Deuterium abstraction from the salt of the hypophosphorus acid would give the electrophilic phosphorus centred radical **235**, which is a polarity mismatched pathway.

In previous cases where deuterium incorporation is observed in high yields, the reaction follows a polarity matched pathway. Radical **213** is nucleophilic, so the production of the electrophilic phosphorus centred radical **235,** and hence deuterium incorporation, is favoured (Scheme 94).



Scheme 94 Further polar effects in H/D-atom abstraction

In order to successfully incorporate deuterium, polarity effects must be considered for each individual case, as shown by this work using D_3PO_2 in D_2O. In order to incorporate deuterium, when the initial radical is not nucleophilic, the deuterium source needs to lead to the production of nucleophilic radicals. It may be possible to achieve this using deuterated dioxane, however this has not been investigated.

2.9 Conclusion

In this chapter the use of H_3PO_2-Et_3N-ACCN in refluxing dioxane has been shown to be an efficient tin-free method for the reductive removal of the dithiocarbamate group. This route is particularly attractive as the by-product is water-soluble and all products are easily isolable.

A variety of different dithiocarbamates have been produced and subsequently reduced. An efficient route to spirocyclic β-lactams via carbamoyl radical cyclisation is reported. The reduction of glucosyldithiocarbamates has been shown to give two products, the ratio of which can be controlled by altering the concentration of the reactants.

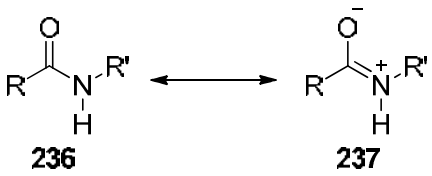
Deuterium incorporation studies have been undertaken and led to the synthesis of deuterated β- and γ-lactams. The lack of deuterium incorporation in the reduction of sugars has been explained, by consideration of polar effects. These systems abstract a hydrogen from the solvent as opposed to the hypophosphorus acid salt.

Chapter three

Twisted Amides

3.1 Introduction to Twisted Amides

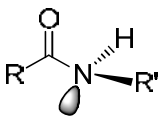
Amide bonds are commonly found in Nature.[80] They are typically flat due to the delocalisation of the lone pair of electrons from the nitrogen over the N-C-O system (Scheme 95). The amide bond can be represented as two resonance structures (**236** and **237**), whereby the electrons can delocalise over the system, giving rise to its unique properties, including the high degree of stability.[81] Amide bonds have shorter C-N bonds than amines (1.380 Å compared with 1.470 Å) and longer C=O bonds than typical ketones (1.220 Å compared with 1.213 Å).[82]



236 **237**

Scheme 95 Delocalisation effect in planar amides

Removal of this co-planarity, so that the bond angles are no longer 120°, by forcing the amide to adopt a twisted structure (**238**) should alter the properties of the amide. When this occurs the orbitals of the C=O and the C-N bonds cannot overlap, resulting in the stability normally associated with amides being lost.[81] Twisting results in not only a change in the twist angle, which can be up to 90° in a fully twisted amide, but also in pyramidalisation of the nitrogen as the delocalisation of n-π*C=O is lost.[83]



238

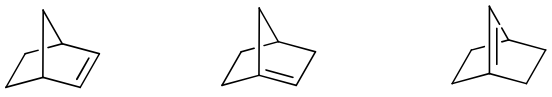
A fully twisted amide would be expected to resemble the transition state of the *cis-trans* amide bond isomerisation. Passing through this transition state is required for protein

folding,[84] which has led to the suggestion that compounds that contain twisted amides could be used as inhibitors of proline isomerases.[80] Twisted amides have also been proposed as an intermediate in amide bond cleavage.[85]

Although on initial inspection it would appear that twisted amides are very useful, they have yet to fulfil their potential. This is due to the inherent strain the molecule experiences and its lability to water, making it non-ideal for biological systems.[80, 86] Despite these issues a number of twisted amides have been successfully synthesised.[83,86,87,88] It is common to use intramolecular steric repulsion[89] as a tool in the synthesis of twisted amides or to force the twist in structure by placing the nitrogen at the bridgehead of a bicyclic system.[80,84,90] The following sections discuss the synthesis and properties of twisted amides and are arranged in chronologically, according to when the chemistry appeared in the literature.

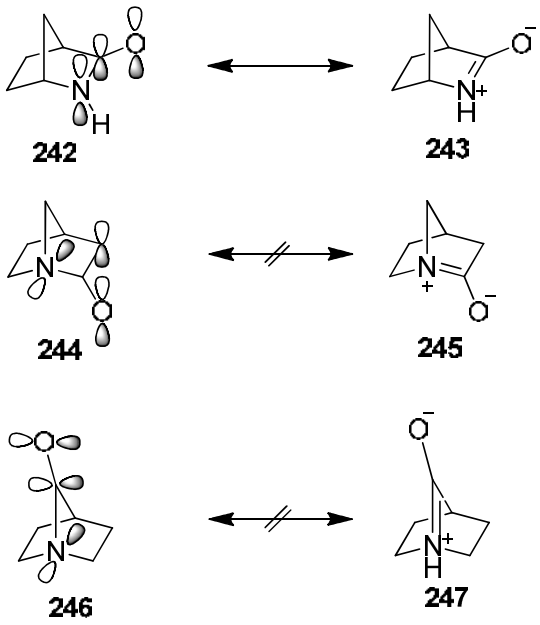
3.2 Bredt's Rule

Bredt's rule states that in bicyclic systems, it is not possible to have a C=C bond at the bridgehead carbon, unless the alkene is part of a large ring.[91] Having the alkene at this position would be the equivalent of having a *trans* double bond in the ring, which is not possible for small rings due to ring and angle strain. In the case of norbornene Bredt's rule allows for the formation of **239** but not **240** or **241**.[88]



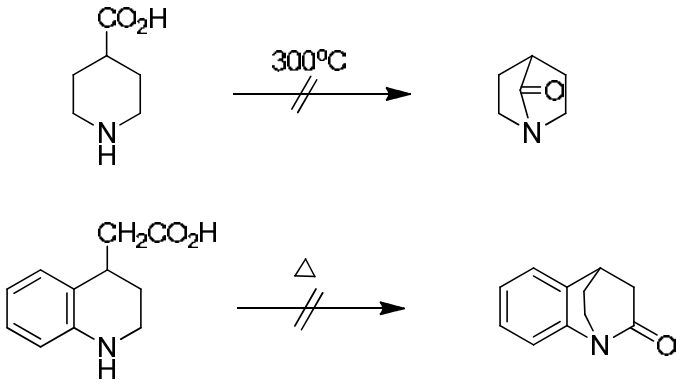
239 **240** **241**

If this principle is applied to amides, it seems feasible that **242** can form. This will be planar and can exist in its resonance form **243**. However, when the nitrogen is at the bridgehead it is not possible for delocalisation to occur. **244** can not delocalise to **245**, nor **246** to **247**, as both these transformations would create a double bond at the bridgehead (Scheme 96). Therefore molecules of this type, known as anti-Bredt molecules, can be considered twisted amides as they are forced to adopt a non-planar arrangement.



Scheme 96 Bicyclic systems containing amides

The majority of syntheses of twisted amides have centred around this principle where the nitrogen is placed at the bridgehead of a bridged bicyclic system. The first attempt at doing this was made by Lukeš in 1938, who attempted cyclisation reactions to form this type of amide (Scheme 97).[92]

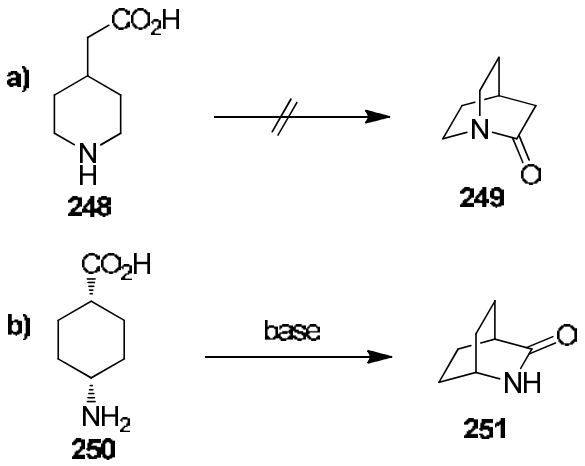


Scheme 97 Attempted synthesis of anti-Bredt amides

These attempts were unsuccessful and led to the conclusion that these amides were sterically impossible to make. Lukeš postulated that if these molecules were ever to be synthesised they would behave more like ketones than amides, presumably due to delocalisation not being expected to be able to occur.

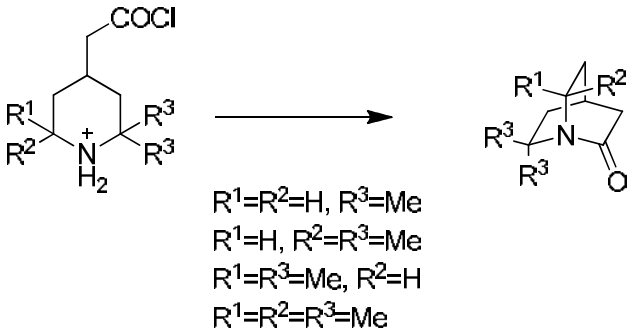
3.3 Synthesis of 2-quinuclidone

The synthesis of the twisted amide 2-quinuclidone **249**, was first attempted by Woodward in 1945.[93] However it was many years before this was unambiguously synthesised. Woodward successfully made the Bredt allowed isomer **251**, via a ring closure reaction of **250** (Scheme 98, b). The unsuccessful cyclisation of **248** to give 2-quinuclidone, **249** (Scheme 98, a), was ascribed to the target molecule being unstable, as it would have to adopt a twisted structure.



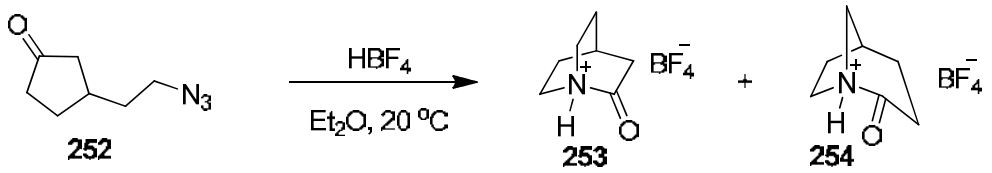
Scheme 98 Ring closing reactions to form bicylic lactams

A successful synthesis of **249** was reported in 1957,[94] however there was little evidence to support this, with only nitrogen elemental analysis being used for characterisation. This method involved the same approach as Woodward, an intramolecular amide bond formation. This route involved treatment of the corresponding acid chloride with a mild base followed by an aqueous work up. Subsequent attempts by Pracejus to repeat this work, and form **249**, were unsuccessful, although a variety of methyl-substituted 2-quinuclidones were prepared (Scheme 99).[95] This suggests that the initial report of the synthesis and isolation of 2-quinuclidone was incorrect.



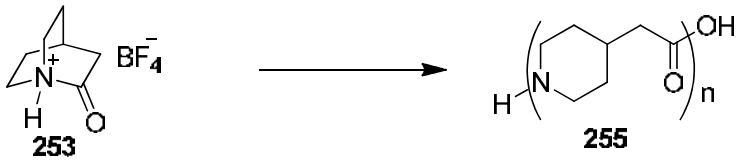
Scheme 99 Ring closing reactions to form substituted 2-quinuclidones

In 2006 Tani and Stoltz took up the challenge of the synthesis of **249**. Due to the difficulties with both the synthesis and isolation previously reported, they chose to take a non-classical route. The keto-azide **252** was prepared and after treatment with HBF_4, at room temperature for 3 hours, the 2-quinuclidonium tetrafluroborate **253** was isolated along with a side product **254** (Scheme 100). Recrystallisation led to isolation of just **253** in a 38% yield. This was fully characterised, complete with X-ray crystallography, giving the first unambiguous synthesis of 2-quinuclidone, albeit as the tetrafluroborate salt.[87]



Scheme 100 a) HBF_4, Et_2O, 20 °C, 38%

The free base of this salt was not isolated as all attempts to do this resulted in breaking of the amide bond, giving rise to a polymer **255** (Scheme 101).

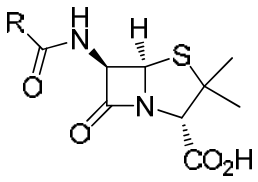


Scheme 101 Attempted isolation of of 2-quinuclidone

3.4 Penicillin

One twisted amide that has received a lot of attention is penicillin (**256**), an antibiotic that is used to treat bacterial infections. It was first discovered in 1928 by Sir Alexander Flemming.[96] However, it was not until the second world war that the efforts to produce

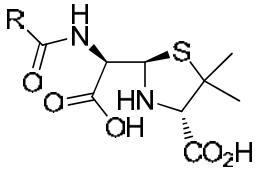
large quantities of penicillin were made. In order to do this the structure of penicillin needed to be determined.



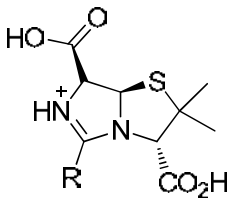
R = benzyl

256

Woodward believed the structure to contain a β-lactam fused to a five-membered ring; this later being confirmed by a crystal structure reported in 1945.[97] Although β-lactams are generally considered to be planar, in this instance there is a degree of twisting. This results in delocalisation of electrons being inhibited and accounts for the propensity for this molecule to hydrolyse. Penicillin has to be stored at low temperatures and is generally administered intravenously or intramuscularly to prevent hydrolysis to the unreactive penicilloic acid **257**, or penillic acid **258**.[98,99]



257



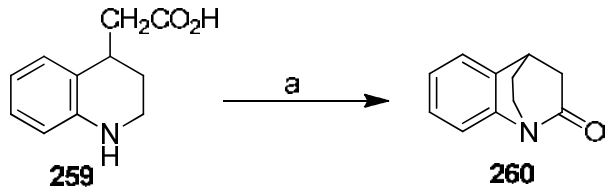
R = benzyl

258

3.5 Synthesis of Other Twisted Amides

In addition to 2-quinuclidone, other twisted amides with nitrogen at the bridgehead have been synthesised with varying yields. The instability of these twisted amides is a consequence of their enhanced lability to water. Cleavage of the amide bond in these cases releases the strain, caused by the twisting. These amides have been synthesised by intramolecular condensations,[100] cyclisations[101] and transition metal catalysis.[102]

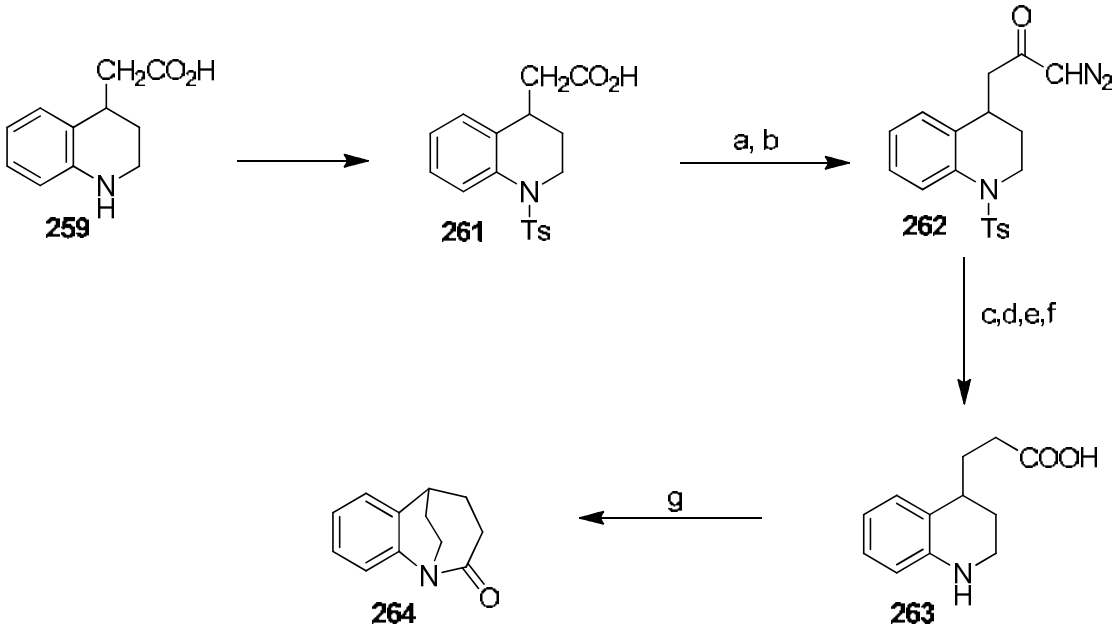
The amide **260** was synthesised in one step from the commercially available acid **259** in high yields (>90%), by dissolving the starting material in MeCN and adding DCC (dicyclohexylcarbodiimide) (Scheme 102).[85a] Previous attempts to synthesise this amide had been unsuccessful (Scheme 97).[103]



259 **260**

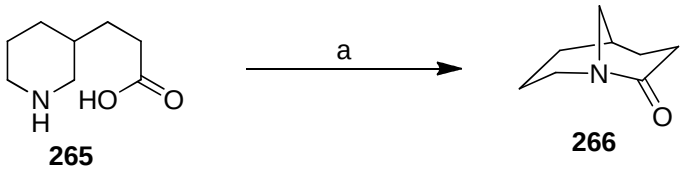
Scheme 102 MeCN, DCC, >90%

This work was extended to give a twisted amide containing a larger ring. Firstly the acid **259** was tosyl protected to give **261** and then after formation of the corresponding acid chloride, reacted in-situ with diazomethane to give the diazo ketone **262**. Following a series of reactions to give the deprotected acid **263**, the DCC conditions were applied and the twisted amide **264** was successfully synthesised (Scheme 103).[85a]



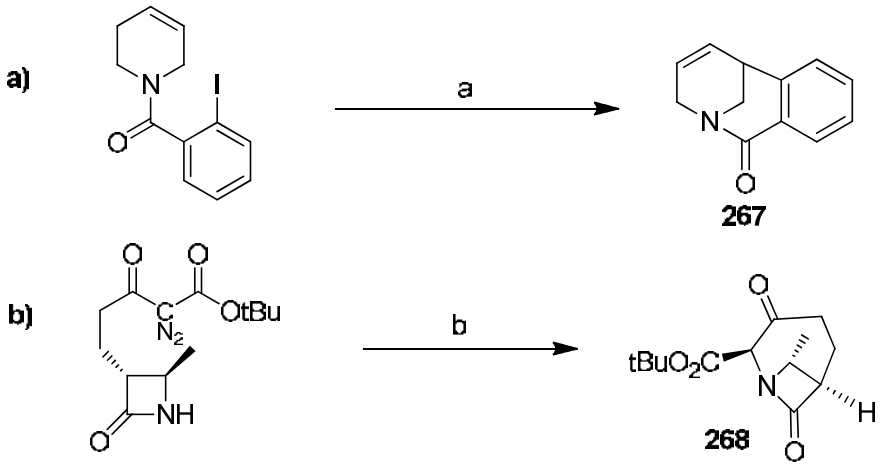
Scheme 103 a) $SOCl_2$; b) CH_2N_2; c) Ag_2O, EtOH; d) HCl, EtOH; e) KOH, EtOH; f) HCl; g) DCC,

Exposure of the acid **265** to dibutyltin oxide in refluxing toluene for 12 hours has been show to yield the twisted amide **266** in a 77% yield (Scheme 104).[104] This is a significant improvement on the yield of 7% reported a few years earlier for the synthesis of the same amide by dehydrating the amino acid **265** under high vacuum at high temperature.[105]



Scheme 104 a) Bu_2SnO, toluene, 12 h, 77%

Other transition metals have been used to synthesise twisted amides, including palladium (Scheme 105, a) where amide **267** was synthesised in high yields,[102a] and rhodium used in the synthesis of twisted amide **268** in a moderate yield (Scheme 105, b).[106]

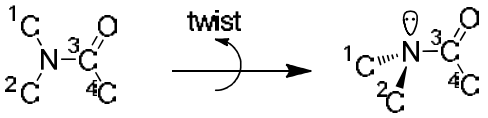


Scheme 105 a) 0.1 Pd $(OAc)_2$, 0.2 PPh_3, Et_4NCl, K_2CO_3, CH_3CN, 30-80 °C, 88%; b) cat. $Rh_2(OAc)_4$, C_6H_6, 1h, 50%

The twisted amides reported so far in this chapter still exhibit a degree of flexibility in their structures. Calculations have shown the twist angle in the 2-quinuclidone skeleton and subsequent structures derived from this to be around 90°.[107]

3.6 The Most Twisted Amide

In 1998 Kirby reported the synthesis of 1-aza-2-admantanone **269**, commonly known as the 'most twisted amide' due to its twist angle of 90.5°, which has been confirmed by an X-ray crystal structure.[108] The twist angle (τ) is calculated as shown in calculation 1.[83]

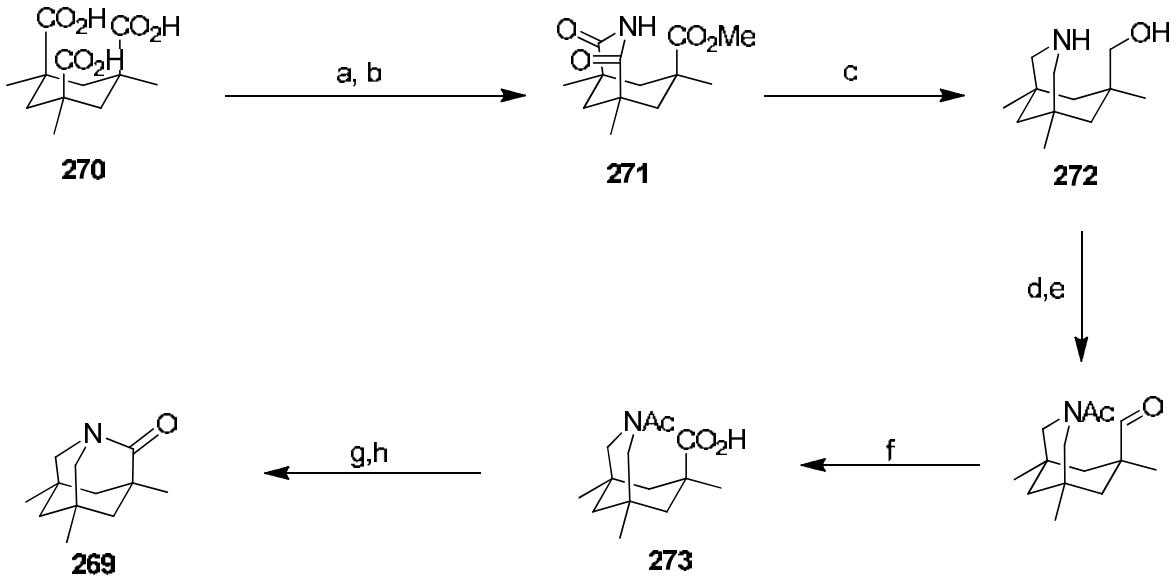


$$\tau = \frac{{}^{\omega}\text{C4-C3-N-C2} + {}^{\omega}\text{O-C3-N-C1}}{2}$$

Calculation 1 Determination of twist angle

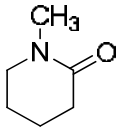
Kirby et al. first synthesised **269**, when looking into the reverse anomeric effect and found that despite the twist angle of 90.5°, this amide is relatively stable.[108] The synthesis

of **269** was achieved by first taking the commercially available Kemp triacid **270** and carrying out a series of reactions to give the known ester imide **271**, which was subsequently reduced to the amino alcohol **272** (Scheme 106). Acylation of the nitrogen, followed by oxidation gave the protected aminoacid **273**. Heating this with aqueous acid resulted in formation of the twisted amide **269**. Overall this involves 11 functional group transformations, all occurring in reasonable yields. The carbonyl group of this compound is planar and the amine nitrogen adopts a tetrahedral conformation.



Scheme 106 a) NH_3, DMAP (cat.), reflux 24 h; b) $SOCl_2$, then MeOH; c) $LiAlH_4$, Et_2O, 24 h, 82% from **270**; d) Ac_2O, MeOH, 8 h, 82%, e) CrO_3.2pyridine, CH_2Cl_2, 30 mins, 74%; f) $KMnO_4$, H_2O, acetone, 30 mins, 86%; g) 1.5 M HCl, reflux, 24 h; h) heat, 85% over 2 steps

The structural characteristics of the most twisted amide were compared with the related 1-methyl-2-piperidone **274**, which contains a planar amide bond. However it is important to note that this δ-lactam is not crystalline, so all the structural data is based on calculations.



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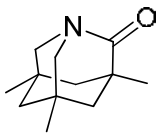
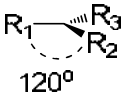


269

The sum of the bond angles in **274** are calculated to be 358.9°, which is indicative of its planar structure, whereby there should be 3 bond angles of 120°, totalling 360° for a fully flat system (**275**). In the case of **269** the bond angles are smaller with the sum being 325.7°, which means the individual bond angles are close to that of the 109° bond angles expected when the nitrogen adopts a pyramidalised conformation (**276**).[83,109]



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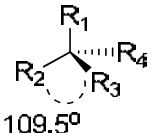


276

The sum of bond angles at the carbonyl group were measured and calculated respectively as a control and were shown to be 359.9° in both cases. The bond lengths of the C-N bonds also varied significantly between structures with the lactam **274** having a C-N length of 1.325 Å and the bond length in **269** being longer at 1.475 Å. This longer bond length is characteristic of an amine C-N single bond as apposed to normal amide C-N bond length. The C-O bond length of **269** at 1.196 Å, is much closer to that of the ketone C=O bond as apposed to that of 1.233 Å found in the non-twisted amide **274**.

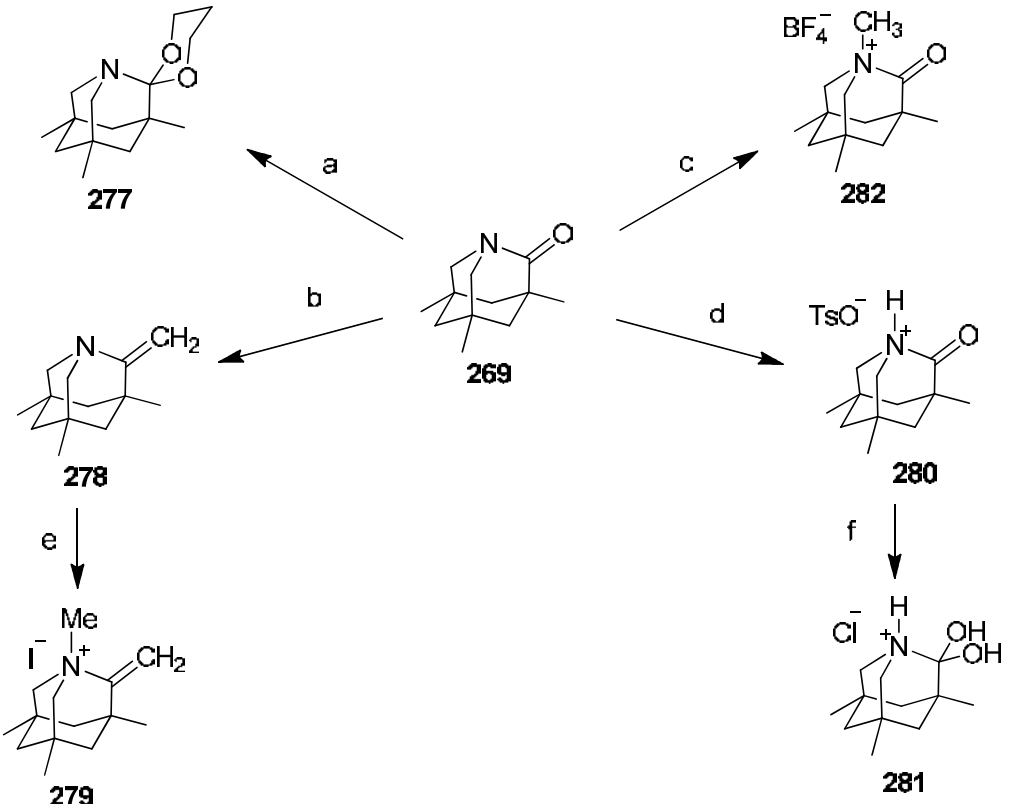
Spectroscopic properties of **269** also showed the compound to exhibit characteristics of amines and ketones as opposed to that of traditional amides. The IR stretch for **269** is much higher at 1732 cm^{-1} than that of the unconstrained amide **274**, which has a stretch

of 1653 cm^{-1}. The ^{13}C-NMR shift is 200 ppm for the twisted amide which is in the region of that expected for ketones, whereas in the amide **274**, this shift is lower at 165 ppm.

The ionisation potentials were also measured. This is the amount of energy required to remove an electron from the molecule. The value of 9.36 eV for the amide **274**, shows the removal of an electron from the n(O) lone pair. The lower value of 8.30 eV for the twisted amide shows the electron is removed first from the nitrogen lone pair n (N).

The pK_a of twisted amides (4.8 in the case of **269**, measured in H_2O:acetonitrile 1:1), is much higher than that of a standard amide (around 0.12 in water). The basicity of twisted amides is lower than that of aliphatic tertiary amines, showing that the adjacent carbonyl group in the twisted amide systems is having an electron withdrawing effect.

Both spectroscopic and structural data show that **269** displays characteristics of both carbonyl and amine groups, as opposed to that of an amide group. This is further shown by the chemical behaviour of **269** (Scheme 107).[83]



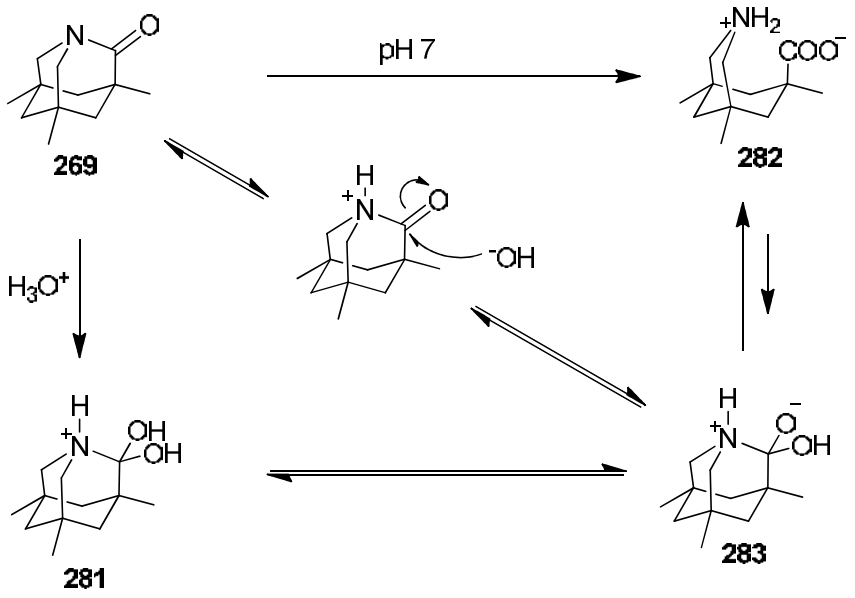
Scheme 107 Reactions of the most twisted amide a) $HO(CH_2)_3OH$, C_6H_6, TsOH (cat.), reflux, 48 h (26%); b) $Ph_3P{=}CH_2$, Et_2O, reflux 8h (64%); c) $(CH_3)_3O^+BF_4^-$, CH_2Cl_2 (100%), d) TsOH, CD_3CN; e) CH_3I, C_6H_6 (94%); f) evaporate solution in 0.1 M HCl (89% from **269**)

Acetal formation is easily achieved under standard conditions, with the amide being able to react as a ketone, to give the hemiaminal **277** when treated with propane-1,3-diol (Scheme 107). Enamine **278** can be synthesised by a Wittig reaction of **269** with a phosphorus ylide. This enamine is highly volatile, but alkylation on the nitrogen gives the stable methylated derivative **279**, whose properties were determined by X-ray crystallography.

Alkylation on the nitrogen of the twisted amide is also possible, with the *N*-methyl derivative **282** obtained in quantitative yield (Scheme 103). This product is extremely sensitive to water, so Meerwein's reagent was used, as it can remove any traces of

moisture from the reaction mixture, thus preventing hydrolysis. The conjugate acid **280** was formed by protonation on the nitrogen of **269** using TsOH in dry ether. This reaction is notable as amides are traditionally protonated on oxygen. This acid was not isolated as it readily reacts with water to give the hydrate **281**, which is sufficiently stable to allow characterisation to be carried out.

The amide **269** is extremely susceptible to hydrolysis, with rates of hydrolysis resembling those of enzymatic peptide bond cleavage. Dissolving in water gives the amino acid zwitterion **282** by ring opening. This reaction is reversible and can equilibrate back to give the twisted amide in neutral methanol. Using acidic conditions the twisted amide converts readily to the protonated orthohydrate **281**. All these reactions can occur by passing through the tetrahedral zwitterion **283** (Scheme 108).

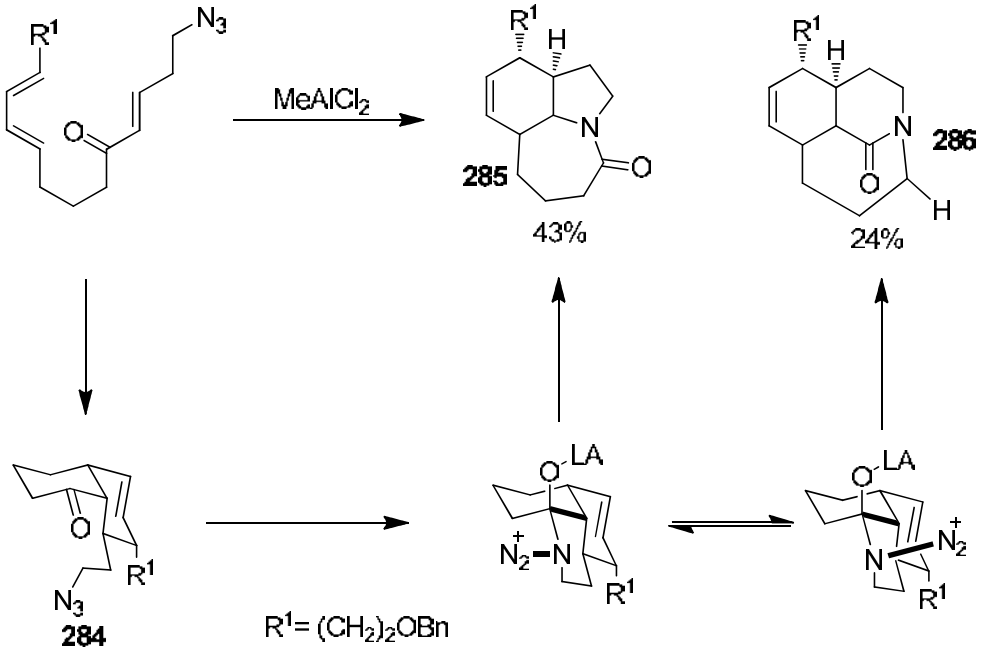


Scheme 108 Effects of hydrolysis on the most twisted amide

In summary the 'most twisted amide' **269** behaves as both an amine and a ketone. It displays remarkable stability and although, like previously reported twisted amides, it is extremely susceptible to hydrolysis, this process can be easily reversed. The presence of the methyl groups in this compound are important to give the amide the extra stability needed.

3.7 Medium–Bridged Twisted Amides

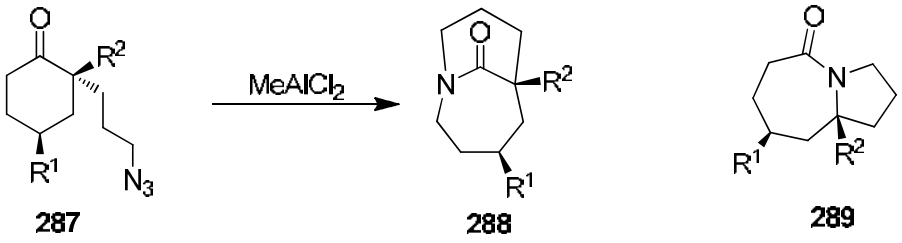
The main problems associated with the synthesis and potential application of twisted amides, is their inherent instability in water. The majority of twisted amides have nitrogen at the bridgehead of a 2-carbon bridged system. Aube *et al.* synthesised a twisted amide with a bridgehead containing only one carbon, as a side product when attempting the total synthesis of stenine (Scheme 109).[110] A Diels-Alder reaction gave the bicycle **284**, which contains an axial azidoalkyl group, with respect to the cyclohexanone ring.



Scheme 109 Production of a bridged twisted amide

C-N migration of the bond antiperiplanar to N_2^+ and subsequent loss of N_2 gave the tricyclic bridged system **286**, containing a twisted amide. When loss of N_2 occurs before C-N bond migration the fused lactam **285** is produced. The amide **286** is not fully twisted, however it is by no means planar. Later studies revealed the twist angle to be 50.7°, lying in between the 0° observed for planar amides and 90° for fully twisted amides.

After this discovery, Aube *et al.* attempted to find a general synthesis of other partially twisted amides, containing a one carbon bridgehead. A cation π-direct intramolecular Schmidt reaction on the conformationaly locked α-phenyl substituted azide **287** was shown to give the bridged amide **288** as the major product, when R^1 = *t*-butyl and R^2 = C_6H_5. The other product observed was the fused lactam **289** as expected (Scheme 110).[111]



a R^1 = *t*-Bu, R^2 = C_6H_5
b R^1 = R^2 = H
c R^1 = *t*-Bu, R^2 =H

Scheme 110 Formation of bridged bicyclic twisted amides

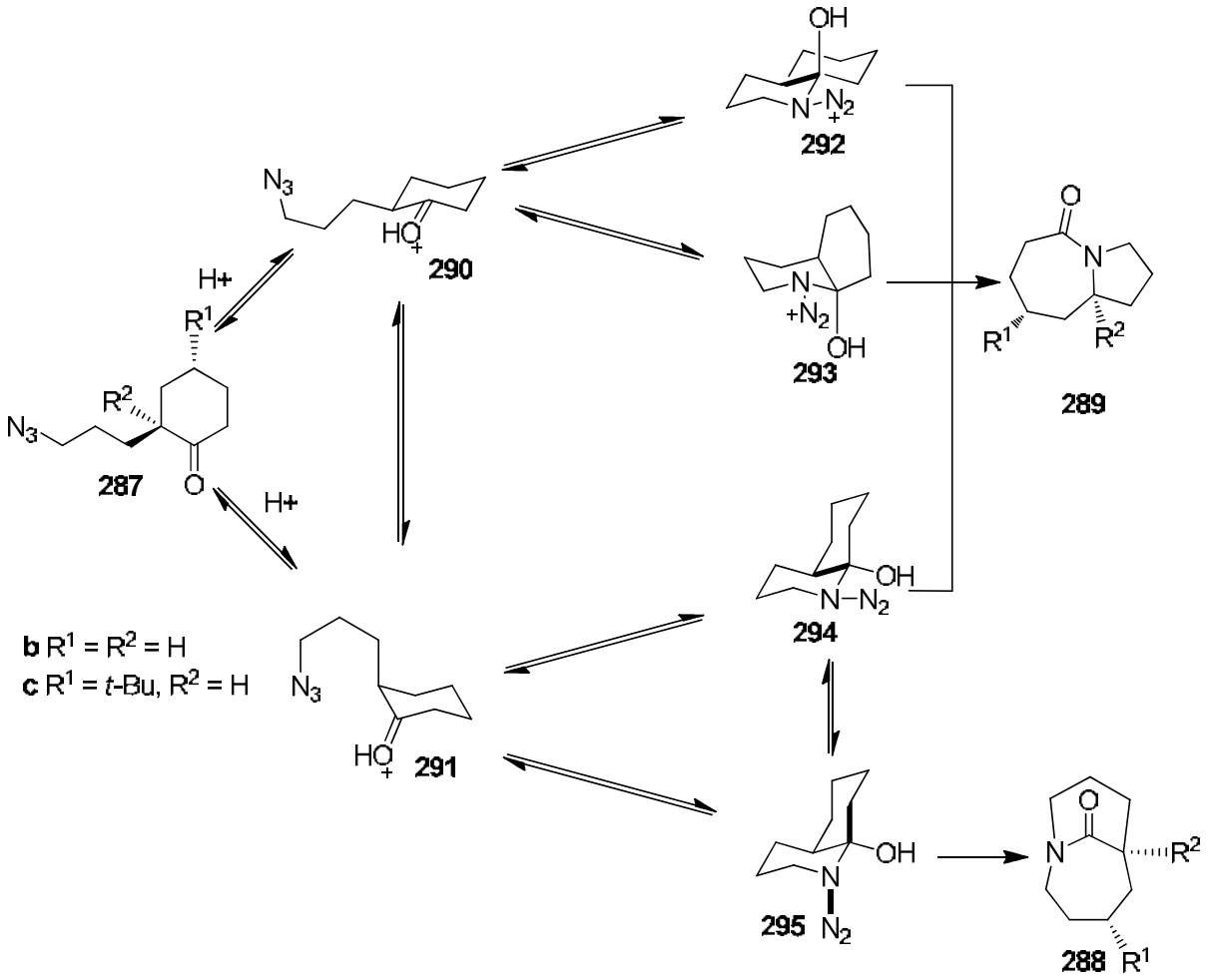
Further studies in this area showed that both the aromatic rings and *t*-butyl substituents were needed in order for the preferential formation of the bridged product over the fused product (Table 4).[112] In order to explain why this selectivity occurs, the mechanism needs to be studied in more detail.

Entry	R^1	R^2	Yield (%) Bridged (**288**)	Yield (%) Fused (**289**)
1	*t*-Bu	C_6H_5	61	22
2	*t*-Bu	4-(MeO)C_6H_4	71	11
3	*t*-Bu	4-(NO_2)C_6H_4	39	38
4	*t*-Bu	H	17	57
5	H	C_6H_5	0	96

Table 4 Ratio of products in cation-π directed Schmidt reaction outlined in Scheme 106

In 2012, Aube *et al.* reported a theoretical study on the mechanism of the Schimdt reaction used in the creation of these amides and on the influence changes in functional groups have on the ratio of products. The mechanism for the simplest form of this reaction, where R^1 and R^2 are both H (**287-b**), was probed first, the reaction proceeding

exclusively to form the fused system **289b** in 83% yield. Addition of acid can produce either the axial (**291**) or equatorial (**290**) isomers, which in this case can interconvert (Scheme 101).[113]



Scheme 111 Mechanistic considerations when forming fused and bridged amides

Upon cyclisation of these protonated azides, four different azidohydrin intermediates (**292**, **293**, **294** and **295**) are produced. This is followed by loss of N_2 and then migration of the C-C bond that is antiperiplanar to N_2. It is believed these two steps are coupled, although it is possible that they occur sequentially.

The need for antiperiplanar C-C bonds to migrate means that the intermediates **292**, **293** and **294**, will give the fused product **289**, whereas the intermediate **295** will lead to the formation of the bridged twisted amide **288**. The intermediates **292** and **293** can interconvert by ring opening to the ketoazide **290**, as shown by quantum chemical calculations. Intermediates **294** and **295** can interconvert by both ring opening and nitrogen inversion.

When the starting material **287c** contains a *t*-butyl group at the 4-position of the cyclohexanone, *trans* to the azidoalkyl chain, there is a noticable shift towards the formation of the bridged product. The intermediates **292c** and **293c** and related transition states have the *t*-butyl group in the axial position making them higher in energy than intermediates **294c** and **295c**. This results in the formation of products via intermediates **294c** and **295c**, leading to the fused product **289c** and bridge product **288c** respectively. The proportion of fused product is now reduced as there is only one route to it, as apposed to the 3 available when R^1 and R^2 = H.

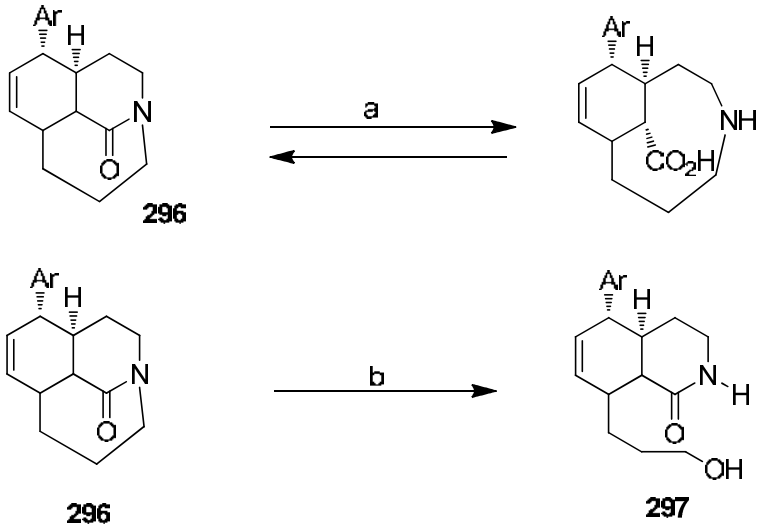
In order to increase the amount of bridged product **288**, they looked at increasing the stabilisation, and thus lowering the energy of the intermediate **295**, over the other intermediates. Ether and thioether groups were added at the R^2 position, as they can undergo lone-pair-carbon interactions with the diazonium group when in the conformation of intermediate **295**. This 1,3 diaxial arrangement stabilises this intermediate and hence gives rise to increased amounts of the bridged product. Aube successfully calculated the ratio of products, taking into account any hydrogen bonding to

water and differences in the transition state compared to that of intermediates **292**, **293**, **294** and **295**.

Having a phenyl group at the R^2 position is not sufficient on its own to stereoselectively stabilise transition state **d** by cation-π interactions. Although a combination of a trans *t*-butyl group at R^1 and a phenyl group at R^2, does increase the proportion of the bridged system (Table 4, entry 1).

Having generated a general route to the synthesis of these bridged twisted amides, Aube then went on to investigate their reactivity. Amides are traditionally stable to hydrolysis and fully twisted amides are extremely susceptible to hydrolysis. These medium bridged amides, which are only partially twisted, were found to be remarkably stable to hydrolysis. This was found to be the case for both bicyclic and tricyclic system, which are soluble and remain intact in water.[114]

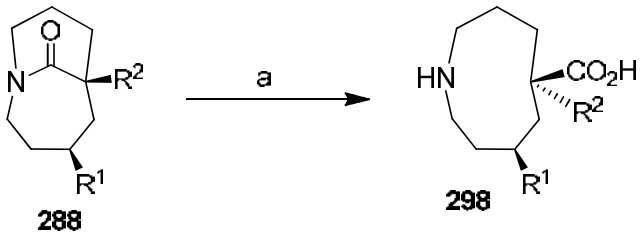
Exposure of the tricyclic system to both highly acidic and highly basic conditions resulted in no observable reaction or degradation of the amide **296**. NMR studies revealed that hydrolysis does occur in strong acid or base but this reaction is reversible and readily re-forms the amide (Scheme 112). The only conditions that gave an irreversible chemical reaction was heating in aqueous HCl and acetonitrile at 80 °C for 23 hours. This led to cleavage of the C-N bond next to the amide bond to give **297** in high yields (95%). The amide moiety remains intact.



Scheme 112 a) H^+ or OH^-; b) HCl, MeCN, 80 °C, 23 h

The reason for this stability was ascribed to scaffolding effects stabilising the medium rings. When hydrolysis does occur the carboxylic acid and the amine moieties are on opposite sides of the medium ring, meaning they will be subject to strong proximity effects.

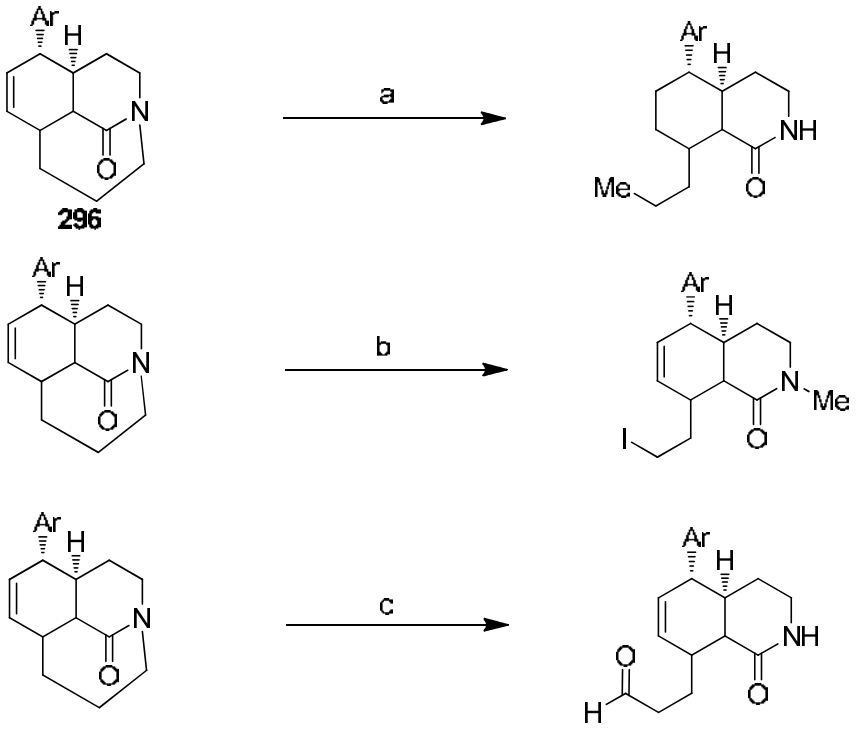
The bicyclic bridged systems **288** display different reactivity, depending on the substituents. When R^1 = *t*-butyl and R^2 = H, the compound was stable in water but upon exposure to strong acid or strong base the amide bond was cleaved, to give the amino acid **298** (Scheme 113). The carboxylic acid moiety now present can flip to outside the ring, making it too far away from the amine group for recombination to the amide to occur.



Scheme 113 a) H^+ or OH^-

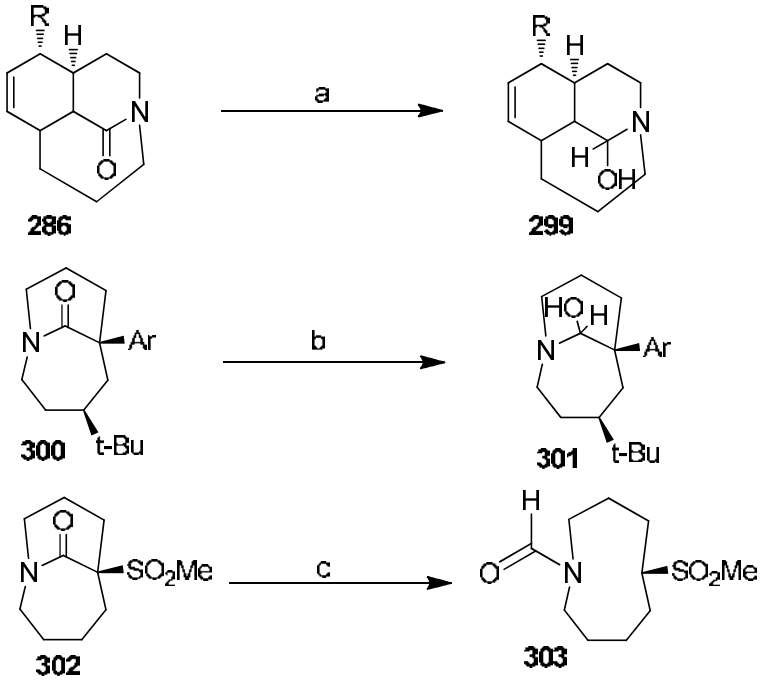
It was observed that when R^1 = H and R^2 = SMe, the compound was stable to hydrolysis even in the presence of strong acid or strong base. The stability of these partially twisted amides is due not only to the reversibility and scaffolding effects but is also dependant on the degree of twisting, and the steric effects that occur due to having the amide carbonyl in the centre of a ring system.

N-Activation of the tricyclic systems was also undertaken. In planar amides protonation typically occurs on the oxygen. The C-N bond cleavage observed in the hydrolysis studies were believed to occur by the amide bond being first activated by the nitrogen forming a hydrogen bond to the solvent. This C-N bond cleavage is also observed when exposing **296** to reduction conditions. Functionalisation was also shown to be possible when treating the system with MeI or DDQ in high yields (Scheme 114).[115]



Scheme 114 a) H_2, $Pd(OH)_2$, EtOH, 80-92%; b) MeI, 95-100%; c) DDQ, H_2O, 64-96%

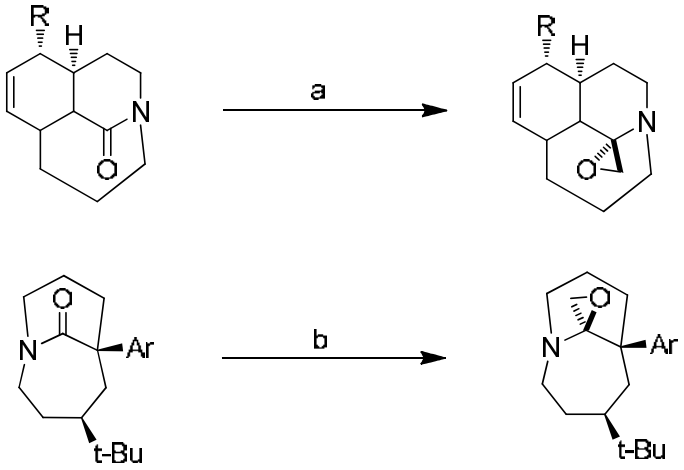
The effects of twisting the amide on the reactions of the carbonyl portion of the amide in these systems were also investigated. Reaction of the twisted amides **286** and **300** with $NaBH_4$, a mild reducing agent gave hemiaminals **299** and **301** respectively. These are stable to the reaction conditions and can be isolated. However when the bicyclic system was substituted with the electron withdrawing SO_2Me group α to the twisted amide (**302**), an unusual cleavage of a C-C bond was observed, resulting in formation of **303** (Scheme 115).[116]



Scheme 115 a) $NaBH_4$, 88-91%; b) $NaBH_4$, 90-95%; c) $NaBH_4$, 98%

Aminoketals and amidines can be formed from the tricyclic twisted amide **286**, which shows that the carbonyl group is behaving like that of a true ketone as apposed to an amide.

In order to show that these amides could form tetrahedral intermediates, significant strain was introduced to these molecules. This was done by forming aminoepoxides by Corey-Chaykovsky epoxidation of medium-bridged lactams using Me_3SI (Scheme 116). The ring opening of the epoxide, leading to degradation, forms an intermediate cation. The limited delocalisation of electrons across the amide system allows the Corey-Chaykovsky reaction to occur as the intermediate in the degradation step will no longer be stabilised.[117]

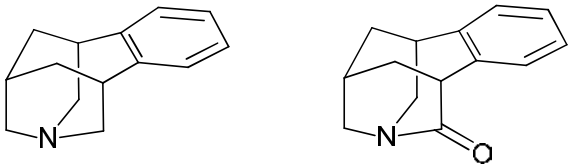


Scheme 116 a) Me_3SI, NaH, DMSO, THF, 70% b) $SiMe_3$, NaH, DMSO, THF, 88%

A range of tricyclic and bicyclic aminoepoxides were synthesised in this fashion, all in high yields. These epoxides have then been subject to further functional group transformations. This synthesis is of particular interest as epoxides can be considered one of the most useful functional groups in organic synthesis. Ring opening of epoxides to give further functionalised products can usually be sterically controlled.

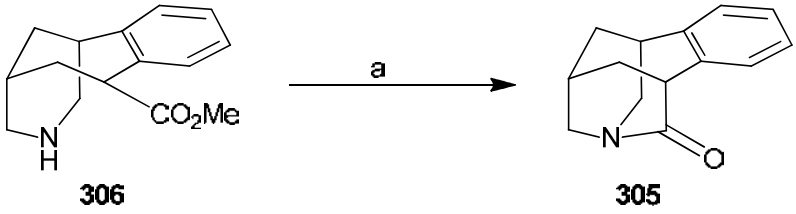
3.8 Wolff-Kishner Reduction of Twisted Amides

In 2003, in pursuit of the tricyclic amine 4,5-benzo-1-aza-tricyclo[4.3.1.1]indeane **304**, Coe *et al.* described the synthesis of a novel twisted amide **305**. This amide contains a similar tricyclic core structure as the twisted amide **269** reported by Kirby, however without the stabilising methyl groups.[118]



304 **305**

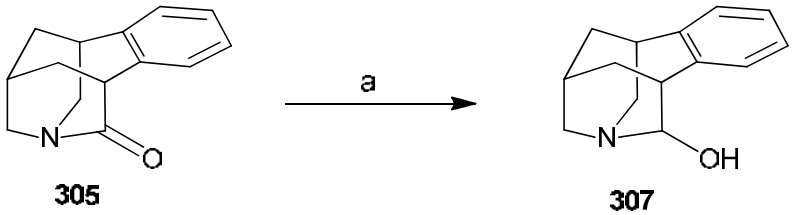
The amide forming step was achieved from the base catalysed ring closing of the corresponding amino acid **306** by using *t*-BuOK in refluxing toluene (Scheme 117).



306 **305**

Scheme 117 a) *t*-BuOK, toluene, reflux, 49-58%

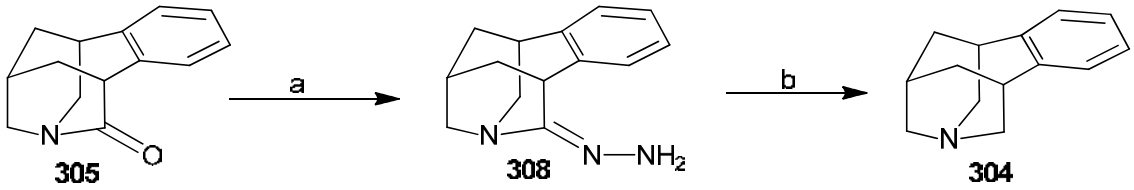
Amide **305** was expected to react as a ketone in the same fashion as Kirby's twisted amide **269** does. The desired amine could not be obtained by direct reduction of the twisted amide **305**. Treatment with $NaBH_4$ simply led to formation of hemiaminal **307** as expected (Scheme 118).



305 **307**

Scheme 118 a) $NaBH_4$, EtOH

However **305** was converted to the hydrazone **308** by application of the Wolff-Kishner reaction conditions, via a mixed ethanol-amino-hydrazine intermediate (Scheme 119). This hydrazine could easily be converted to the desired product **304**.

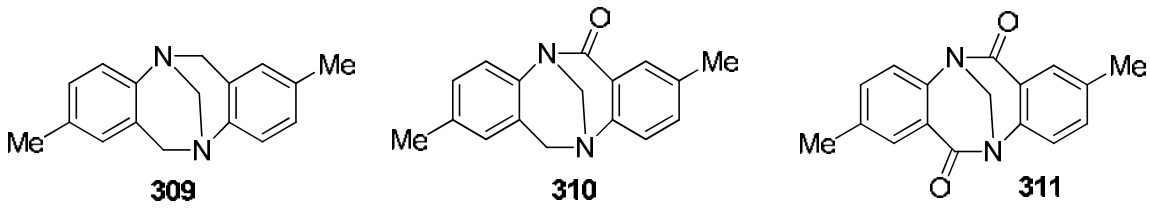


Scheme 119 a) NH_2NH_2, EtOH, 1h, 68 °C; b) KOH, $(HOCH_2)_2$, 2h, 200 °C, 68% over 2 steps

This synthesis is noteworthy as the final product **304** is a structural motif that is present in many drug candidates. This indicates that twisted amides and their unique properties could find a use in medicinal chemistry.

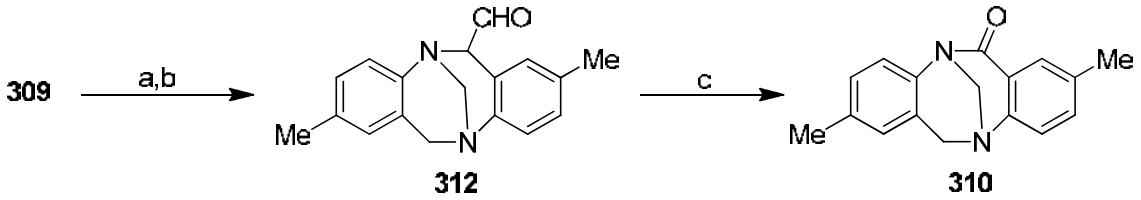
3.9 Twisted Amides Derived From Tröger's Base

Another molecule with potential for use in industry is Tröger's base **309**, which has a rigid curved shape. The unusual properties of **309** and its derivatives have made it of interest for creation of molecules for molecular recognition, catalysis and enzyme inhibition. However, the full potential of this molecule has not been reached due to limitations in functionalising the bicyclic diazocine core. In 2012 a twisted amide analogue of Tröger's base, **310** was reported along with a twisted bis-amide **311**. This if the first report of a twisted bis-amide.[119]



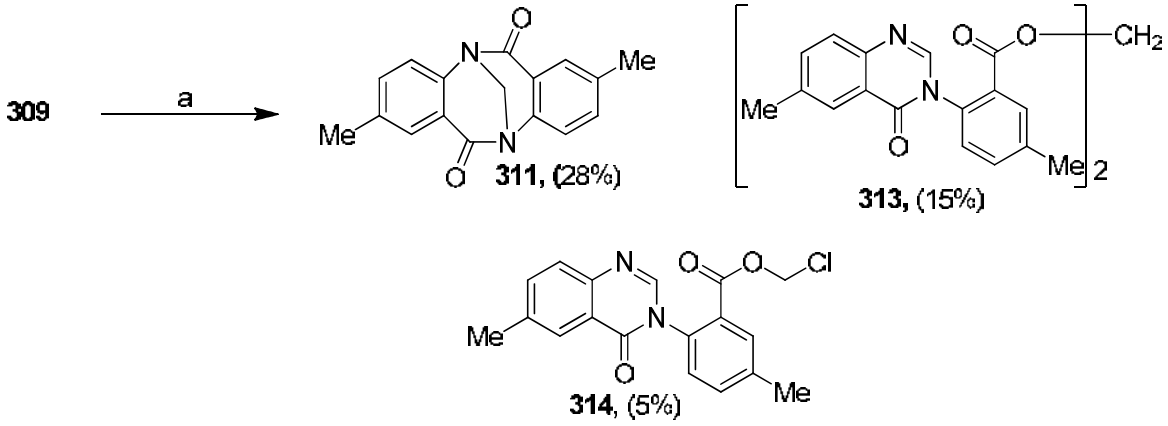
The twisted amide **310** was formed when **309** was treated with TMEDA in the presence of *s*-BuLi. Formation of the aldehyde **312** occurred albeit in poor yield. Exposure of a

solution of this to air gave the corresponding acid **310**, which is a twisted amide (Scheme 120).



Scheme 120 a) TMEDA/*s*-BuLi, THF, -78 °C; b) DMF, 10% over 2 steps; c) air

Direct oxidation of Trögers base with $KMnO_4$ and benzyl(triethyl)ammonium chloride in refluxing CH_2Cl_2 gave the twisted bis-amide **311** along with quinazoline byproducts **313** and **314** (Scheme 121). These byproducts are believed to come from the hydrolysis of the amide bond, made possible by the twist in the structure.



Scheme 121 a) $KMnO_4$, BTEAC, CH_2Cl_2, reflux, **311** (28%), **313** (15%), **314** (5%)

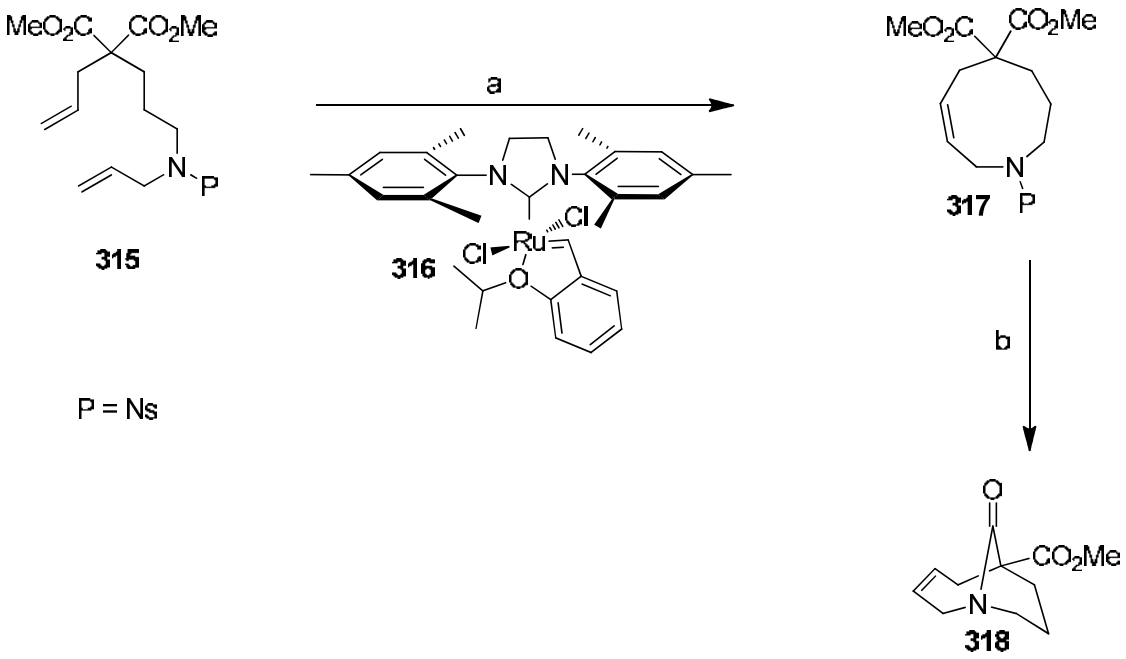
X-ray crystallography revealed the twisted bis-amide to have a twist angle of -43.7°, showing that although not fully twisted, the properties of the molecule have been suitably altered. The nitrogen centre has also been shown to display a degree of

pyramidalisation, which further indicates the compound is twisted around the amide bond.

3.10 Synthesis of Twisted Amides by Transannular Cyclisation

In 2009 Aube reported an extension to this early work on twisted amides. Previous examples had centred around specific structural types, but this new method of synthesis allows for more diversity in the structures of twisted amides. This approach involved a ring closing metathesis reaction to form medium sized rings, followed by a transannular cyclisation reaction to give the twisted amide.[90]

The initial investigations focused on making the [4.3.1] bicyclic system which they had previously synthesised (**288**) via this new approach. Malonate **315** was prepared and subjected to ring closing metathesis conditions, with the second generation Hoveyda-Grubbs' catalyst (**316**) providing the best yields of the 9-membered heterocycle **317** (Scheme 122). The deprotection of the nitrogen and the transannular cyclisation to give the twisted amide **318** was undertaken using mild conditions in one step.

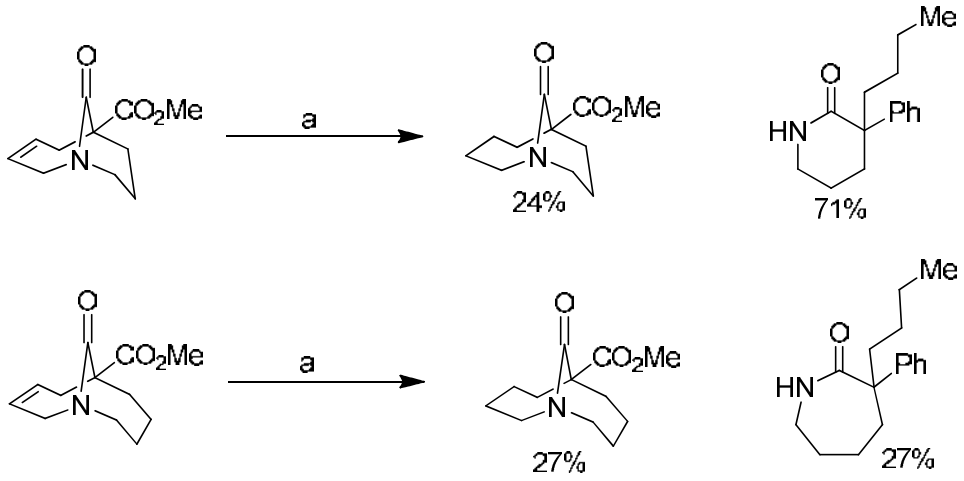


Scheme 122 a) CH_2Cl_2, 80 °C, **316** (5 mol%), 16h, 93%; b) PhSH, Cs_2CO_3, 60 °C, 87%

The geminal-diester substituent is important as it forces the ring to adopt a conformation that prevents the unwanted hydrolysis of the amide bond occurring, which is effectively the reverse of the amide bond forming reaction. A variety of 9 and 10 membered heterocycles were formed by this route, leading to the production of a variety of different ring systems.

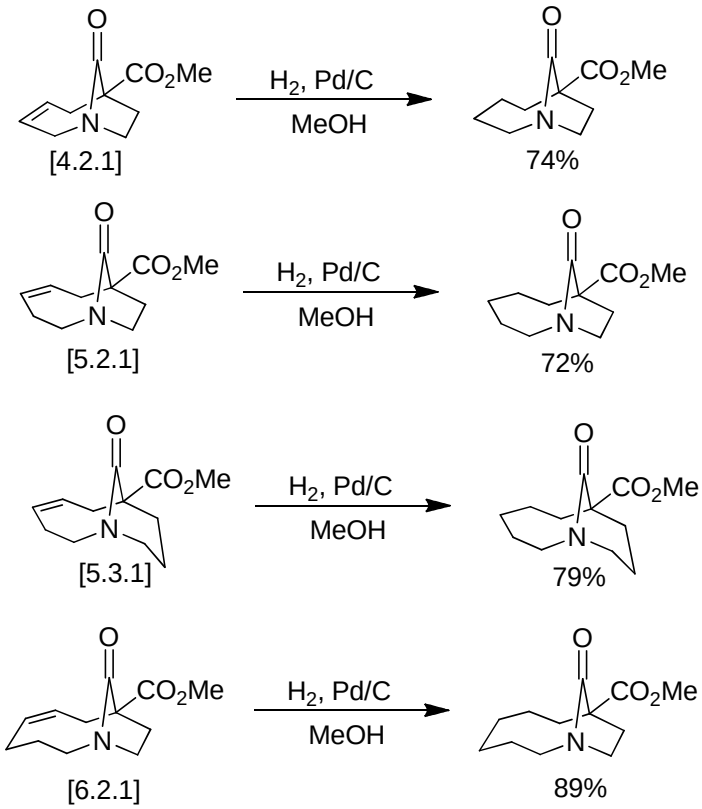
The use of Boc and Cbz protecting groups on the nitrogen was found to be tolerated for the ring closing metathesis reaction. However removal of the Cbz group was found to be problematic, and attempts to form twisted amides from these systems were hampered by the product being sensitive to the Cbz removal conditions. The protecting group removal and subsequent transannular cyclisations of the Ns and Boc protected heterocycles were effective in high yields.

To further extend this work, saturated twisted amides were synthesised. Application of standard hydrogenolysis conditions to the twisted amide with [4.3.1] and [4.4.2] systems led to the unusual cleavage of the C-N bond that had previously been observed (Scheme 123).



Scheme 123 a) H_2, Pd/C, MeOH

This bond cleavage was not observed in the twisted amides containing [4.2.1], [5.2.1], [5.3.1] and [6.2.1] structures. In these cases the desired reduction process occurs in reasonable to high yields (Scheme 124).



Scheme 124 Subjecting other twisted amides to hydrogenolysis conditions

The spectroscopic properties of this series of twisted amides revealed that the larger saturated ring systems allowed for more flexibility, thus allowing for the amide bond to become more planar and exhibit properties of standard amides. In the smaller ring systems the degree of twisting is more pronounced, with the IR stretches being in the range expected for a normal ketone. This series of compounds provides a range of twist angles, going from the almost planar like, where $\tau = 0°$, to the almost fully twisted, where $\tau = 90°$. Further chemistry on theses compounds should allow us to see what effect the degree of twisting has on the chemical and biological properties of amide bonds.

3.11 Aims and Objectives

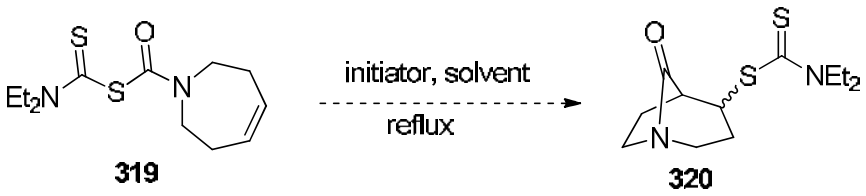
Although the existence of twisted amides has been known for many decades, it is only recently that a general synthesis of these structures has been reported. The twist in the structure prevents delocalisation of the electrons and results in the compounds having effectively amine and ketone functional groups, which react separately, in a similar manner to amino-ketones.

The unusual reactivity of twisted amides has the potential to be exploited in synthetic applications. The transition state of peptide bond cleavage has been shown to adopt a twisted amide configuration, indicating that twisted amides could be useful as enzyme inhibitors.

The use of dithiocarbamates as a source of carbamoyl radicals to form lactams, via cyclisations onto alkenes, has been well researched by the Grainger group.[38,39,53,68] It was decided to further this chemistry by creating a molecule where a radical cyclisation of this kind would produce a twisted amide. With the recent report from Aube on the formation of twisted amides by ring closing metathesis, followed by a transannular cyclisation, it seemed logical to adapt this process as a starting point for our work.

The smallest heterocyclic ring system created by ring closing metathesis reported by Aube was a 9-membered ring.[90] It was hoped that the creation of a 7-membered heterocyclic ring system, containing a dithiocarbamate group, would allow access to a twisted amide with a [3.2.1] ring system, smaller than any reported by Aube.

If formation of the dithiocarbamate **319** could be achieved, potentially by ring closing metathesis, a range of conditions to generate the carbamoyl radical and allow cyclisation on to the alkene could be investigated (Scheme 125).



Scheme 125 Proposed synthesis of twisted amides

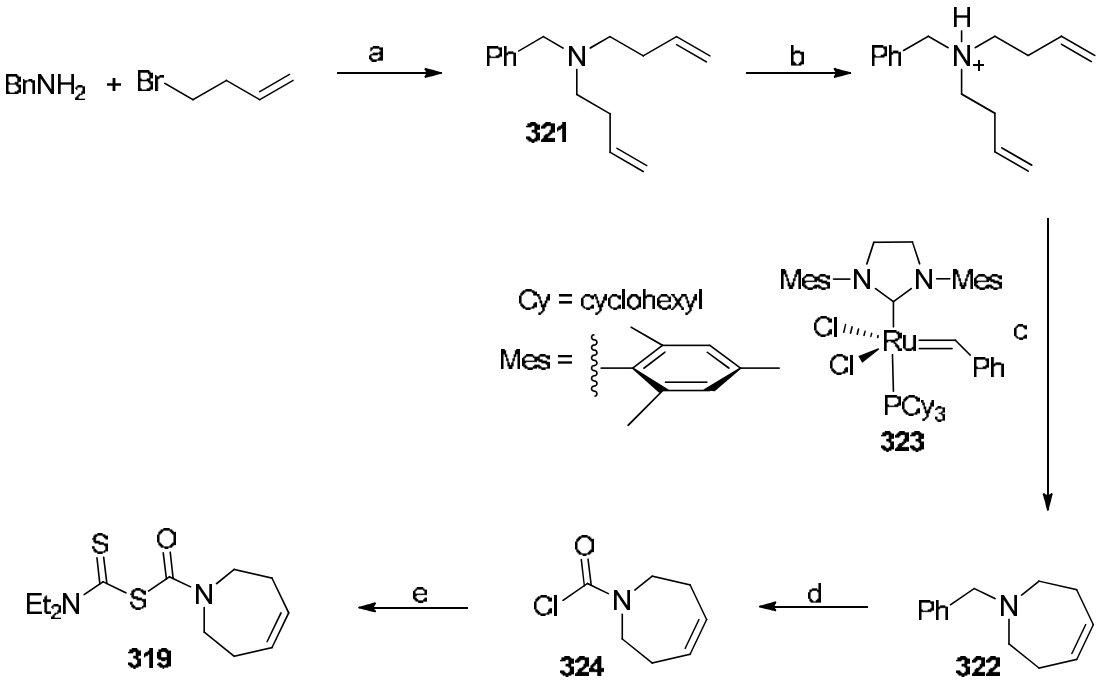
The product of this reaction **320** would afford a twisted amide containing the dithiocarbamate moiety. Further reactions could then be carried out due to the incorporation of this group as discussed previously. If successful a range of twisted amides, with varying sized rings, could be synthesised by this method.

3.12 Results and Discussion

3.12.1 Synthesis of the Radical Cyclisation Precursor

In order to create the twisted amide precursor **319**, benzylamine was dialkylated with 4-bromo-1-butene to create the tertiary amine **321**. It was necessary to protonate the nitrogen, through addition of HCl in dioxane, before application of the ring closing metathesis conditions, to give **322**. If this is not done the lone pair of the nitrogen can interact with the ruthenium of the catalyst, deactivating it and thus resulting in lower yields (10%).[120] The optimum conditions for the ring closing metathesis was found to be

using Grubbs 2nd generation catalyst (1 mol%) (**323**) in refluxing CH_2Cl_2. The reaction was successful when carried out at room temperature but the reaction times were significantly longer, making this approach less attractive.

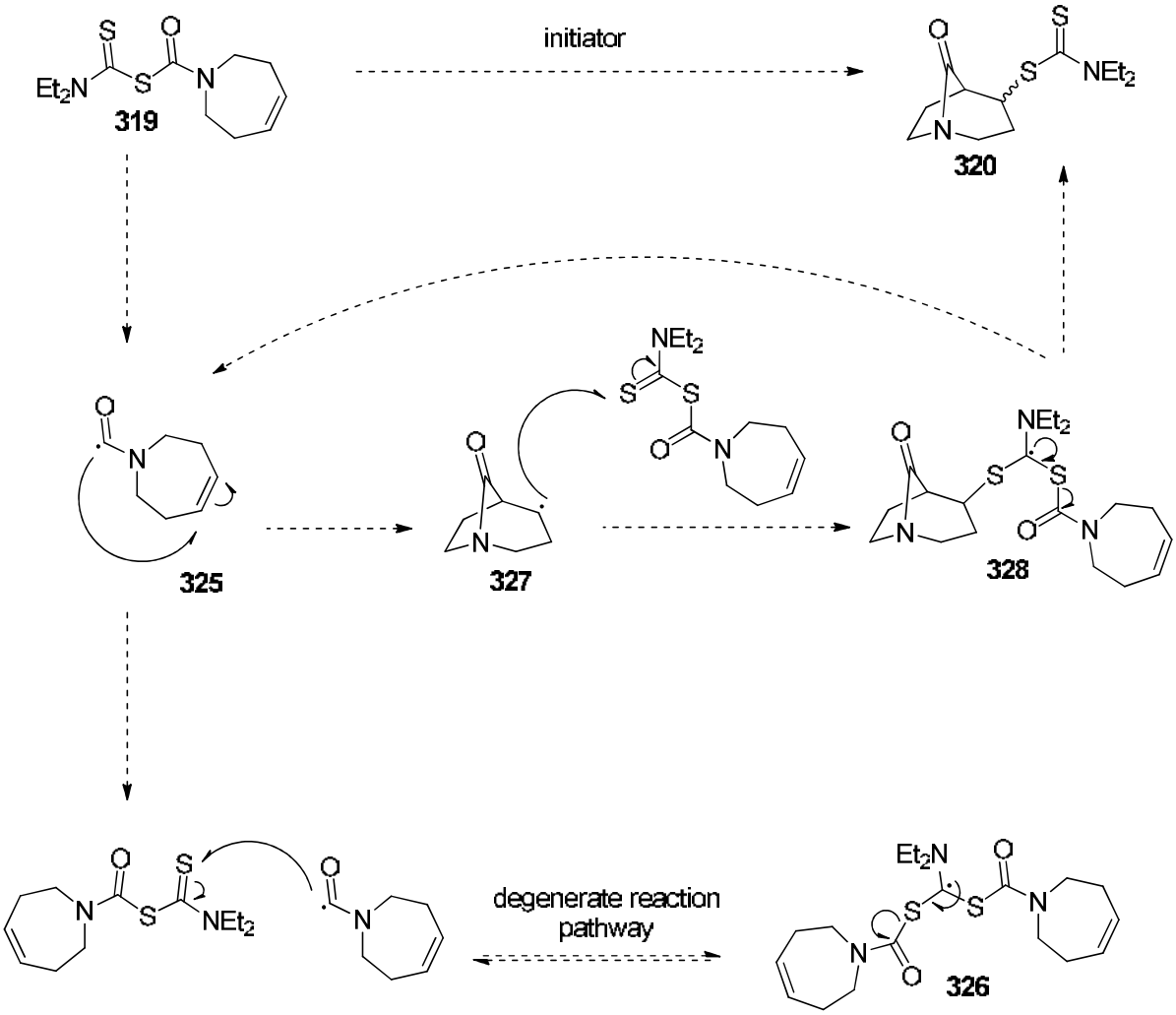


Scheme 126 a) DMF, K_2CO_3, 60 °C, 3h, rt, 16h, 61%; b) Et_2O, HCl in dioxane, rt, 30 mins; c) CH_2Cl_2, reflux, 14h, 61%, over 2 steps; d) toluene, triphosgene, pyridine, rt, 4h, 94%; e) $NaSC(S)NEt_2.3H_2O$, acetone, rt, 18h, 72%

The benzyl deprotection and the acyl chloride synthesis to give **324** were carried out in one step, using conditions previously reported in the group. This carbamoyl chloride was remarkably stable and could be purified by column chromatography, allowing it to be isolated from the side products of the reaction. Dissolving the purified carbamoyl chloride in acetone and treating with the sodium salt of diethyldithiocarbamate trihydrate generated the radical cyclisation precursor, dithiocarbamate **319**, in 72% yield (Scheme 126).

3.12.2 Radical Reactions Towards Twisted Amides

The mechanism of the proposed twisted amide formation, is the same as that previously discussed for γ-lactam and β-lactam formation (Chapter 1, Scheme 26). Initiation of the reaction will produce the carbamoyl radical **325**. This has two reaction pathways open to it. Radical **325** can react with another molecule of the starting material, producing the tertiary radical **326**. Breakdown of this radical will regenerate a molecule of starting material and also give back radical **325**, making this pathway degenerate. Alternatively carbamoyl radical **325** can react in an intramolecular fashion, cyclising onto the double bond, to produce the secondary radical **327**, and creating a twisted amide. This radical can then react with another molecule of the starting material, generating the tertiary radical **328**. Subsequent breakdown of this provides the dithiocarbamate product **320**, and also a further molecule of the carbamoyl radical **325** (Scheme 127).



Scheme 127 Proposed mechanism for twisted amide formation

In order to form the initial radical **325**, which can subsequently undergo cyclisation, various conditions were investigated. As exposure to a 500 W halogen lamp has been shown to facilitate cyclisation of other dithiocarbamates, it seemed feasible that application of these conditions to dithiocarbamate **319**, may give the cyclised product **320**.

After dissolving dithiocarbamate **319** in cyclohexane, the reaction mixture was exposed to a 500 W halogen lamp, which generated enough heat to bring the solution to reflux.

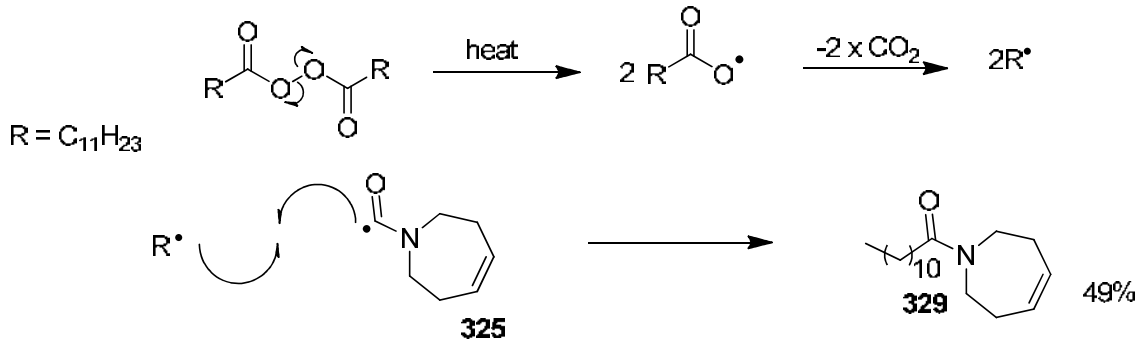
After 8 hours removal of the solvent revealed that significant degradation had occurred, although it appeared that the azacycloheptane system had been retained.

Due to concerns that the heat may be causing the degradation, as opposed to the light, the reaction was repeated at room temperature. This was done by using a piece of equipment where a stream of water is passed around the outside of the enclosed reaction vessel. This results in the heat, generated from the lamp, being removed, or at least reduced. However, reactions run under these conditions also resulted in significant degradation, indicating that this degradation was a function of the light source as opposed to the heat.

As the use of light had proved inefficient, attention turned to the use of chemical initiators, (Table 5). All these reactions were carried out at reflux and initiators were added portionwise with 0.2 equivalents being added every 2 hours, until consumption of starting material was observed.

The use of DLP to generate radicals from the related xanthate group is well precedented by Zard, and to a lesser extent the Grainger group has shown that DLP can be employed to generate carbamoyl and acyl radicals from dithiocarbamates. Use of DLP in cyclohexane for the attempted formation of the twisted amide **320** from dithiocarbamate **319** was unsuccessful, with the only isolable product (**329**) being the product of the addition of the carbamoyl radical to the carbon centred radical derived from the breakdown of DLP (Table 5, entry 1). Although this was not what was expected from the reaction, it clearly showed that the initial carbamoyl radical **325** was forming. However,

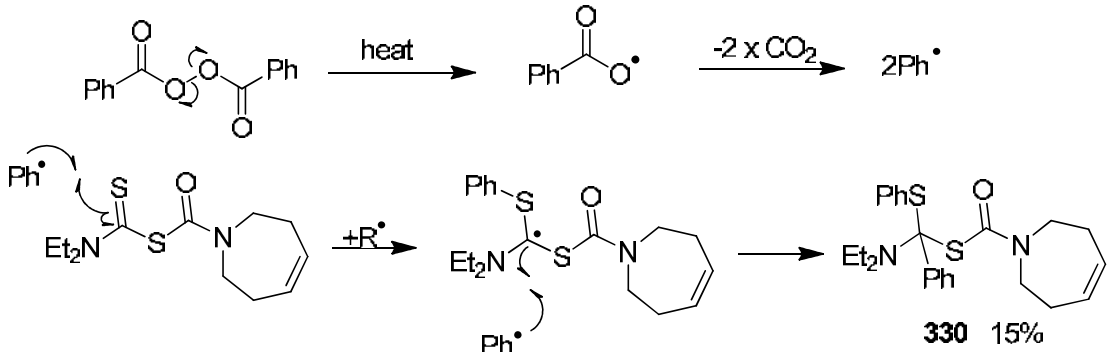
this was undergoing a intermolecular radical-radical combination reaction as opposed to the desired intramolecular reaction to give the twisted amide **320** (Scheme 128).



Scheme 128 Proposed mechanism for formation of **329**

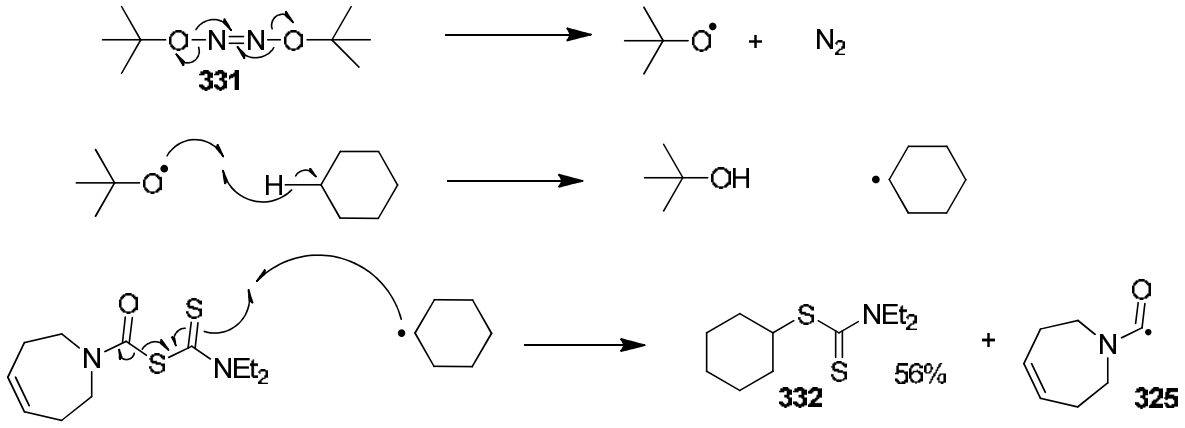
As previously noted, when there are two competing pathways, one being intramolecular and the other intermolecular, altering the concentration can afford some control over which one is followed. As a consequence the reaction was repeated in a more dilute solution, in order to give the intramolecular reaction more time to occur before the competing intermolecular could. However this had little effect on the yield and did not result in any evidence to support the formation of the twisted amide.

When the reaction was repeated using dibenzoyl peroxide instead of DLP, again the aza heptacycle was retained in the only product that was isolated from the somewhat complex reaction mixture (Table 5, entry 2). Only a small amount of this product could be obtained and the structure has been tentatively assigned to be that of **330**, the mechanism for formation of which is outline in scheme 129.



Scheme 129 Proposed mechanism for formation of **330**

The initiator **331** was prepared according to the literature procedure.[169] Once again, the use of **331** in attempted radical twisted amide formation was unsuccessful. The only product isolated from this reaction was **332** (Table 5 entry 3), which is presumed to arise from the reaction of a cyclohexyl radical with the starting carbamoyl dithiocarbamate **319**. The proposed mechanism is shown in Scheme 130. The formation of **332** again suggests formation of the carbamoyl radical, but products arising from **325** were not isolated.



Scheme 130 Proposed mechanism for formation of **332**

The results from using DLP and **331** as the initiators indicated that the carbamoyl radical **325** had been formed, yet products arising from cyclisation were not observed. Altering

the concentration of the reaction did not lead to the intramolecular reaction occurring. It was envisaged that heating the reaction should provide more energy to allow the system to adopt the required conformation for the reaction to occur. This was done by switching to the higher boiling solvent chlorobenzene.

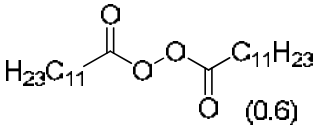
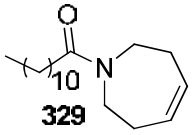
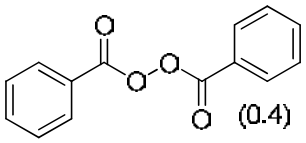
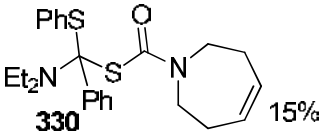
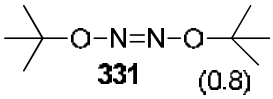
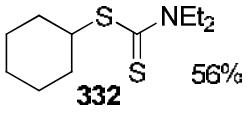
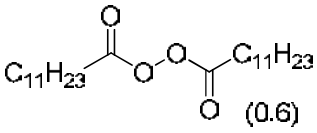
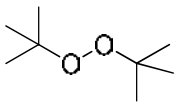
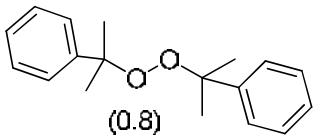
Entry	Solvent	Initiator (equiv.)	Reaction Time	Results
1	cyclohexane	 (0.6)	6 h	 **329** 49%
2	cyclohexane	 (0.4)	4 h	 **330** 15%
3	cyclohexane	 **331** (0.8)	8 h	 **332** 56%
4	chlorobenzene	 (0.6)	6 h	degradation
5	chlorobenzene	 (1.2)	12h	degradation
6	chlorobenzene	 (0.8)	8 h	degradation

Table 5 Initiators used in attempted twisted amide formation

The use of DLP in chlorobenzene led to degradation of the starting material (Table 5, entry 4). The half-life for the DLP at this increased temperature is significantly shorter, so it is perhaps not surprising that the reaction did not happen as planned. The initiators *t*-

butylperoxide and dicumylperoxide have half-lives better matched to that of the boiling point of chlorobenzene. However both of these led to degradation of the starting material and gave a complex mixture of products (Table 5, entries 5 and 6). This indicates that the increase in temperature is causing decomposition to occur, either directly from the starting material or at some other point along the reaction pathway.

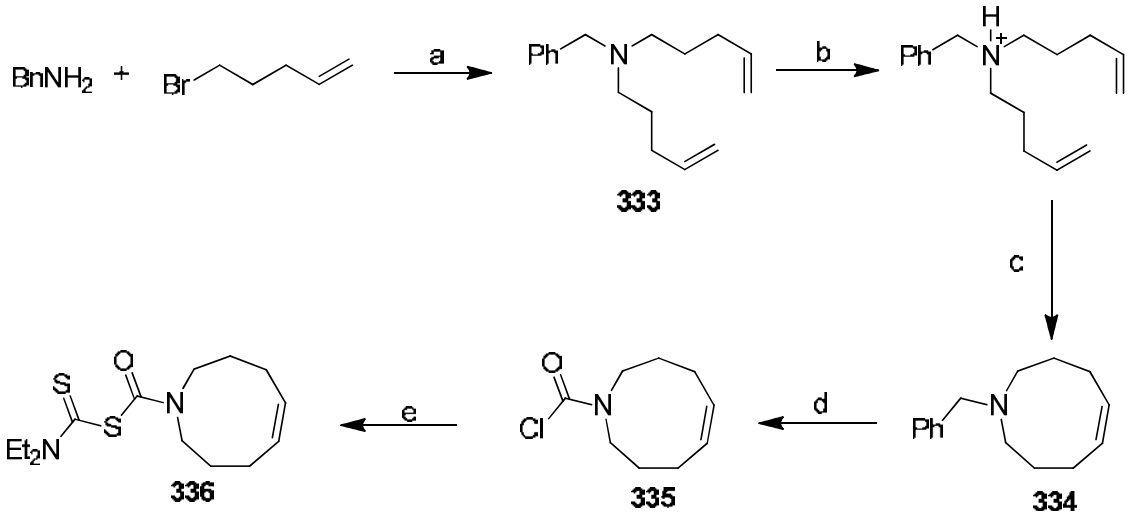
3.12.3 Reactions Towards Larger Twisted Amides

As all the attempts to form the [3.2.1] ring systems were unsuccessful, focus switched towards making the larger [4.3.1] structure. It is possible that the twist angle in the [3.2.1] system created too much strain, so that even if the molecule could form, it would not be stable enough to persist. A twisted amide containing the [4.3.1] ring system has previously been synthesised by Aube, demonstrating that this type of system can be formed and is sufficiently stable to persist without any degradation being reported.

The larger nine membered ring system, rather than an eight membered ring system was targeted, as this is more readily accessible. The chemistry used to synthesise the twisted amide precursor is the same as that for the 7-membered ring **319**, with the only difference being the use of 5-bromo-1-pentene in the first step in the sequence.

Benzylamine was dialkylated with 5-bromo-1-pentene to create the tertiary amine **333**. Protonation with HCl in dioxane followed by ring closing metathesis gave **334**. The benzyl deprotection and the carbamoyl chloride synthesis to give **335** were carried out in one step. As in the previous synthesis this carbamoyl chloride was remarkably stable, allowing

it to be purified by column chromatography. Dissolving the purified carbamoyl chloride in acetone, followed by treatment with the sodium salt of diethyldithiocarbamate trihydrate, generated the twisted amide precursor, dithiocarbamate **336**, in a 52% yield (Scheme 131).

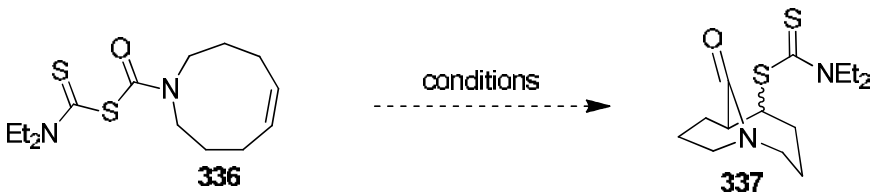


Scheme 131 a) DMF, K_2CO_3, 60 °C, 3h, 58%; b) Et_2O, HCl in dioxane, RT, 30 mins; c) Grubbs 2nd generation catalyst (1 mol%), CH_2Cl_2, reflux, 14h, 61%, over 2 steps; d) toluene, triphosgene, pyridine, RT, 4h, 84%; e) $NaSC(S)NEt_2.3H_2O$, acetone, RT, 18h, 52%

Once formed the dithiocarbamate was subjected to various conditions, in order to attempt to induce cyclisation to form the twisted amide **337** (Table 6). As when using the 7-membered ring system, application of light from a 500W halogen lamp led to degradation of the dithiocarbamate. The use of DLP in refluxing cyclohexane once again seemed to allow the formation of the initial carbamoyl radical, but cyclisation to produce the twisted amide was not apparent, with this radical reacting with the DLP to produce **338**.

The use of initiator **331**, gave **332**, the product of the reaction of the solvent derived cyclohexyl radical with the dithiocarbamate **336**. Using benzoyl peroxide to initiate the

reaction did not give any of the twisted amide product. Instead an unknown product was observed, with the azacyclononane clearly retained. An increase of the reaction temperature, by switching to the higher boiling solvent chlorobenzene, resulted in degradation of the starting material, when cumylperoxide was used to initiate the reaction.



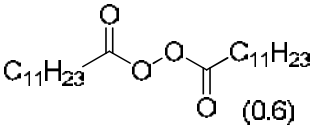
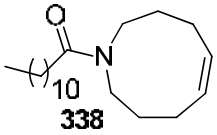
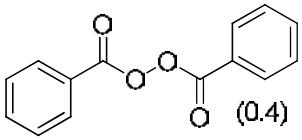
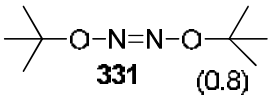
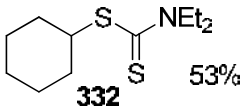
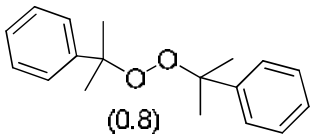
Entry	Solvent	Initiator (equiv.)	Reaction Time	Results
1	cyclohexane	500W lamp	4 h	degradation
2	cyclohexane	 (0.6)	6 h	 **338** 37%
3	cyclohexane	 (0.4)	4 h	unidentified product, containing 9-ring system
4	cyclohexane	 **331** (0.8)	8 h	 **332** 53%
5	chlorobenzene	 (0.8)	8 h	degradation

Table 6 Initiators used in attempted twisted amide formation of the larger system

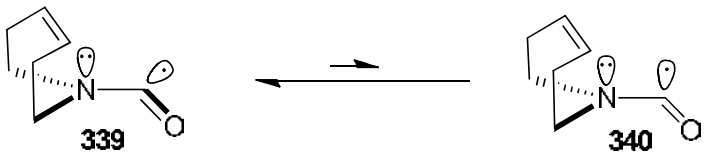
The results of attempting to cyclise the 9-membered ring closely mirror those of the attempted cyclisation of the 7-membered ring system. It was hoped that the extra flexibility available in the 9-membered system would allow for the intermediate radical to adopt the correct conformation for the intramolecular amide formation, unfortunately this proved not to be the case.

3.13 Conclusion

Twisted amides provide desirable functionality in molecules. They provide a synthetic challenge due to the propensity of the amide bond to hydrolyse relieving the strain caused by the twist angle. There are few syntheses of this type of molecule reported in the literature, with most concentrating around specific structural motifs. This work focused on using dithiocarbamates as a source of carbamoyl radicals to try and achieve the twisted amide by intramolecular cyclisaton onto the alkene.

In all examples of the attempted twisted amide formation from dithiocarbamates the reaction mixtures were generally much more complex than typically observed in dithiocarbamate group transfer carbamoyl radical cyclisations, perhaps reflecting the difficulty of the proposed cyclisation. In some cases it was possible to isolate compounds arising from reaction with initiator and/or solvent. To date it has not been possible to isolate cleanly any twisted amide from these reactions.

The difficulty in the cyclisation of **319** and **336** may be due to the requirement of the carbamoyl radical to adopt an unfavourable twisted conformation around the N-C(O) bond. The equilibrium of this system will lie heavily in favour of the planar conformation shown in **339**, as opposed to **340**, where the carbamoyl radical is twisted (Scheme 132).



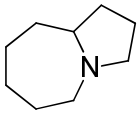
Scheme 132

Chapter four

Studies Towards the Synthesis of Stemofoline

4.1 Stemona Alkaloids

Stemona alkaloids are a group of alkaloids that contain a common structural motif, the pyrrolo[1,2-α]azepine centre **341**. A large number of these molecules have been isolated, with many having their structures determined by X-ray crystallography. All of these molecules are found in the *stemonaccae* species, a group of plants native to South-East Asia.[121]



341

They have been catagorised into 8 groups based upon their structures, stenine, stemoamide, tuberostemopironine, stemonamine, parvistemoline, stemofoline, stemocurtisine and the miscellaneous groups. The core structures of these groups are shown in Figure 3.[122]

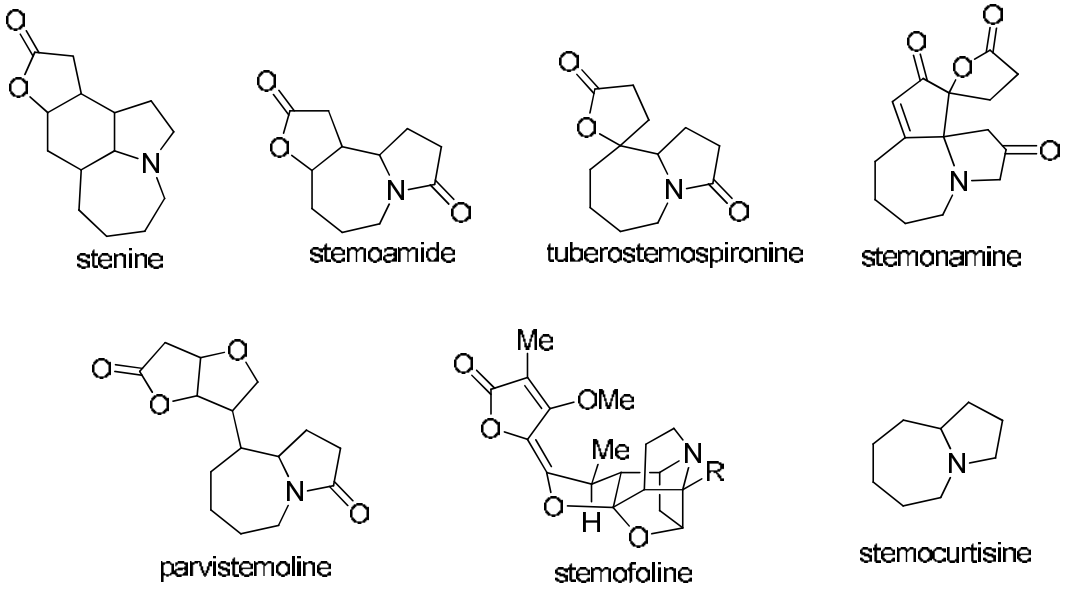
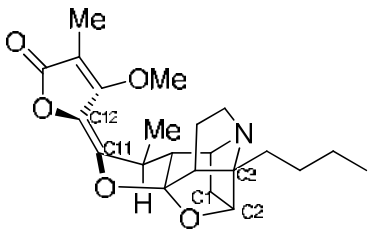


Figure 1 Stemona alkaloids

A larger number of these isolated molecules have been shown to display biological activity and have been used for centuries in traditional Chinese and Japanese medicines. The ground up roots and leaves have been used in herbal teas in order to treat coughs resulting from the respiratory disease, tuberculosis and bronchitis.[121]

4.2 Stemofoline: General Overview

Stemofoline **342** is an alkaloid that was first isolated from the stems and leaves of Stemona Japonica by Irie *et al.* in 1970.[123] The X-ray crystallography data of the isolated compound allowed the structure to be fully determined. Since then a variety of other stemofoline alkaloids have been isolated, most of which vary at either the oxidation state of the chain at C3 or in the configuration of the alkene at C11-C12.[124,125,126] Methylstemofoline **343**, where the alkyl chain at C3 is a methyl group as opposed to a butyl group, was isolated in 2005.[127]



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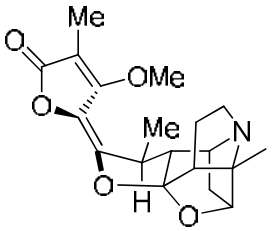
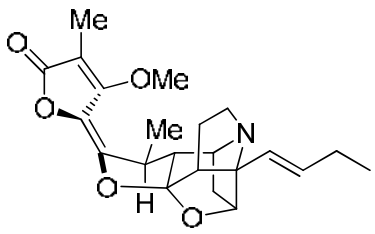


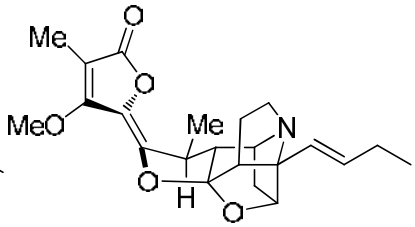
343

These molecules are of particular scientific interest because not only are they potent insecticides, with stemofoline being an agonist of the insect nicotinic acetylcholine receptor,[125,128] but also the rigid pentacyclic cage system at the centre of the molecule provides a synthetic challenge.

Didehydrostemofoline **344**, first isolated in 1994, was originally referred to as Asparagamine A, due to the incorrect reports that it was isolated from the plant *Asparagus racemosus*.[124] However, it was later discovered that the plant where this molecule was found is, in fact, *Stemona collinsae*.[125] Didehydrostemofoline also possesses biological activity, with anti-oxytocin activity reported along with activity against many human cancer cell lines.[129]



344



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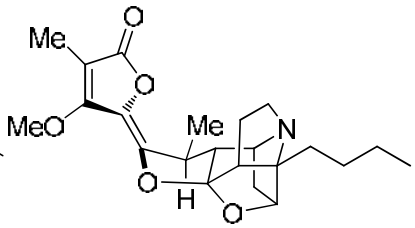


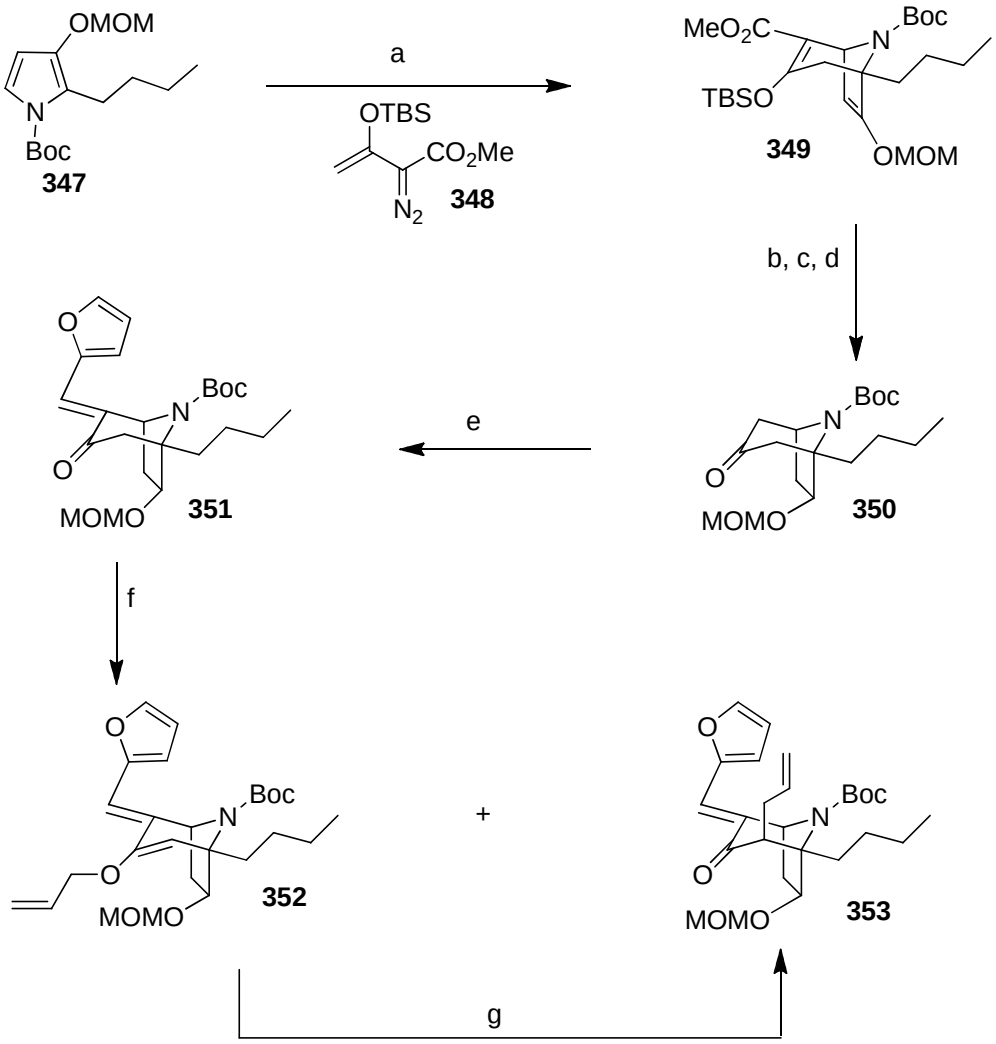
346

Many different approaches towards the synthesis of stemofoline have been undertaken, but as yet a total synthesis has not been achieved. However other stemofoline alkaloids such as (±)-didehydrostemofoline **344**,[130] (±)-isodidehydrostemofoline **345**[130] and (±)-isostemofoline **346**,[131] have been successfully synthesised.

4.3 Synthesis of Stemofoline and Related Alkaloids

4.3.1 Kende's Work Towards Stemofoline

The first total synthesis of a stemofoline alkaloid was Kende's synthesis of (±)-isostemofoline in 1999.[131] This approach began with the formation of pyrrole **347** in 5 steps from the commercially available 1,2-hexandiol.



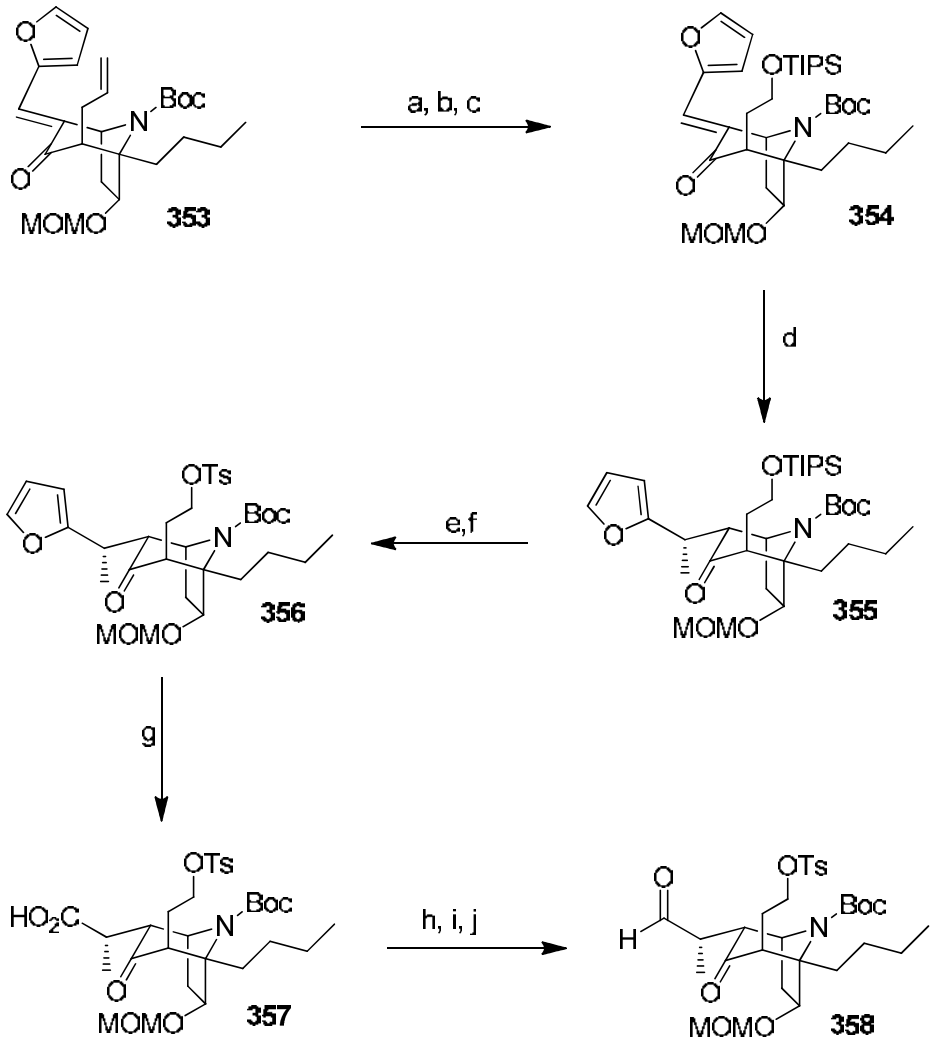
Scheme 133 a) rhodium octanone dimer, pentane, reflux, 90%; b) Bu_4NF, THF, 65%, c) H_2, 5% Pd/C, MeOH, 90%; d) H_2O, DMSO, 150 °C, 90%; e) furfural, NaOH, MeOH, H_2O, reflux, 90%; f) LiHMDS, 1.1 equiv DMPU, THF, 0 °C, then allyl iodide, RT, 91%; g) toluene, reflux 86%

A [4+3] cycloaddition of **347** with vinyl diazoester **348**, gave the bicyclic system **349**[132] which was transferred into the saturated bicycle **350** by first removal of the silicon protecting group followed by *exo*-selective hydrogenation over Pd/C. The carbomethoxy group was removed by heating with DMSO in water at 150 °C (Scheme 133).

Regio- and stereoselective base catalysed condensation of furfural with **350** gave the α-β unsaturated ketone **351** in a 90% yield. Alkylation of **351** using allyliodide and a lithium

base gave a 2.4:1 mixture of **352** and **353**. Although this mixture was not ideal, it was found that heating **352** in toluene allowed the stereoselective Claisen rearrangement to occur giving the α-β unsaturated ketone **353** in 86% yield.

The TIPS-protected keto-alcohol **354** was formed by oxidative cleavage of the terminal alkene of **353**, followed by selective reduction of the resultant aldehyde using $Zn(BH_4)_2$ to give the hemiaminal and the reduction with TIPSCl and imidazole (Scheme 134). Reaction of **354** with MeLi and DMPU in ether afforded compound **355** with the methyl group added in the correct stereochemistry. No other isomers were observed.

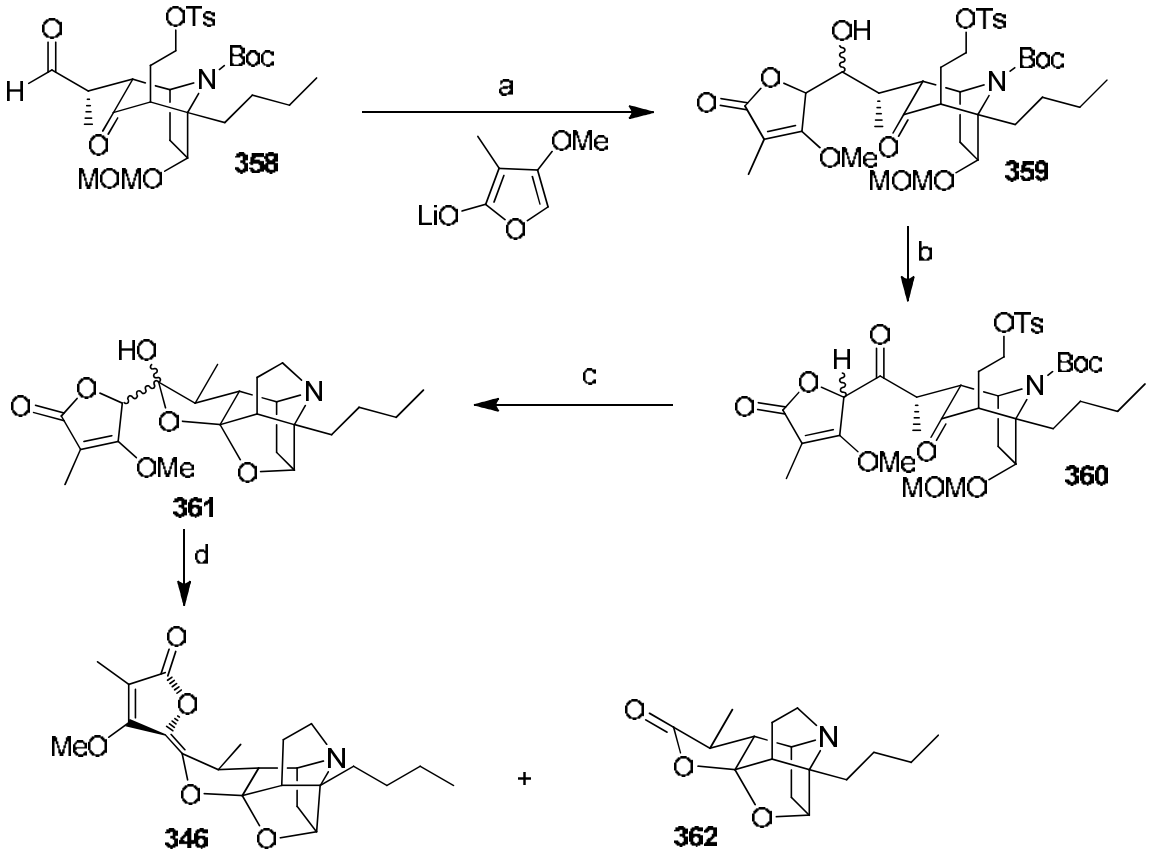


Scheme 134 a) K_2OsO_4, $NaIO_4$, Et_2O, H_2O, RT; b) $Zn(BH_4)_2$, THF, -10 °C, 52%; c) TIPSCl, imidazole, DMF, 93%; d) 2.2 MeLi, 1.1 DMPU, Et_2O, -40 °C, 85%; e) Bu_4NF, THF, 90%; f) TsCl, pyridine, $CHCl_3$, 90%; g) O_3, CH_2Cl_2, Me_2S, 65%; h) i-BuOCOCl, N-methyl-morpholine, THF, 0 °C; i) $NaBH_4$, MeOH; j) Dess-Martin periodinane, CH_2Cl_2, 30% overall yield

The protecting group on the alcohol was switched from the silylate to tosylate **356**, which was exposed to ozonolysis conditions giving the acid **357**. The transformation to the corresponding aldehyde **358** was achieved by first forming the mixed anhydride, then selective reduction and a Dess-Martin oxidation.[133]

Reaction of **358** with the lithium anion of 4-methoxy-3-methyl-2-(5H)-furanone gave a 2:1 mixture of the diastereomeric alcohols **359** which could be separated. Oxidation of these

alcohols with Dess-Martin periodinane gave the same 2:1 mixture of the diastereomeric ketone **360**. This was transferred to **361** by a triple tandem cyclisation reaction which was initiated by stirring the ketones with trifluoroacetic acid and then altering the pH to 10 by adding saturated aqueous $NaHCO_3$ (Scheme 135).



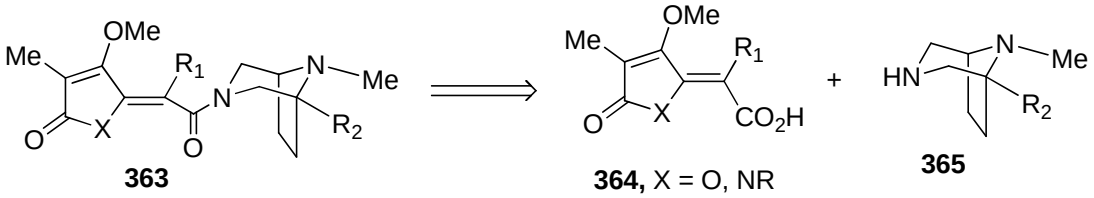
Scheme 135 a) THF, -78 °C, 56%; b) Dess-Martin periodinane, CH_2Cl_2, 61%; c) (1) CF_3CO_2H, (2) saturated aqueous $NaHCO_3$, 67%; d) Tf_2O, CH_2Cl_2, **362** 14%, **346** 12%

The final step in this synthesis required a dehydration, however this proved to be problematic with most conditions resulting in a retro-aldol bond cleavage giving the cyclic lactone **362**. Treatment of **361** with Tf_2O gave the cyclic lactone **362**, but also resulted in formation of isostemofoline **346** in 12% yield.

Although this route does provide isostemofoline, in a 26 step sequence, the low yield of the final steps results in the overall yield being only 3%. The tandem triple cyclisation of the diasteromeric ketone to give hemiacetal **361** is very elegant and the fact that this was the first reported synthesis of these stemofoline alkaloids means this work is of high importance. The problematic final step and the production of isostemofoline as opposed to stemofoline, shows that control of the double bond geometry is a particular issue that must be addressed in future synthetic efforts towards stemofoline.

4.3.2 Smith's Synthesis of 2-Subsituted Pyrrolidines

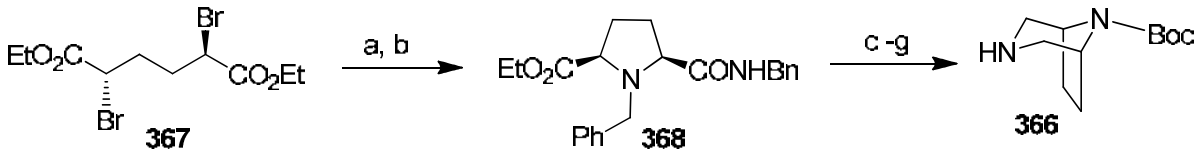
The Smith group set out to produce molecules of type **363** that are structuraly simplified variants of stemofoline, which they envisaged would have insecticidal activity.[134] In order to do this they disconnected back to the tetronate **364** (where X=O) or tetramate (where X=NR) and **365** a 3,8-diazabicyclo[3.2.1]octane. These molecules should be able to couple together to form **363** (Scheme 136).



Scheme 136 Disconnection of the stemofoline mimic

Initial work on the 3,8-diazabicyclo[3.2.1]octane ring system centred around the formation of the simple compound **366**, with no alkyl substituent. This was achieved by reacting diethyl meso-2,5-dibromoadipate (**367**) with benzylamine to allow ring closure to the pyrrolidine and then formation of the monoamide **368**. The ring closure was not fully

stereoselctive but the unwanted diasteromer was the minor product and could easily be separated from the desired *cis*-product after formation of the monoamide (Scheme 137).

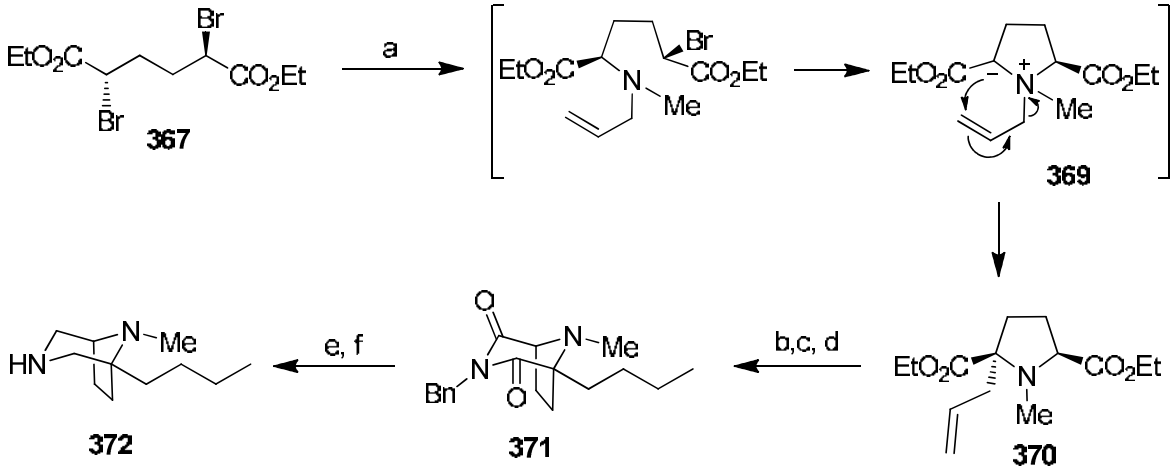


Scheme 137 a) 1) benzylamine, 3.1 equiv., toluene, 85°C, 2) filter then evaporate; b) benzylamine, xylene, reflux, 71% over 2 steps; c) 230 °C, neat, distil off EtOH; d) H_2, 1 atm, Pd/C, MeOH, HCl, 85%; e) $LiAlH_4$, Et_2O, 0 °C-reflux; f) $(Boc)_2O$, CH_2Cl_2, RT, 60% over 2 steps; g) H_2, 1 atm, Pd/C, MeOH, 72%

The bicyclic product **366** was formed by heating **368** to 230 °C and distilling off the ethanol produced[135] followed by reduction of the amide with $LiAlH_4$ then Boc protection and hydrogenolysis of the benzyl group by use of palladium on carbon.[136]

With the route to the diazabicylic system **366** being successful and high yielding, the next challenge was to incorporate an alkyl group at the 1 position (R_2=alkyl). This alkyl group was necessary in order to mimic the butyl chain in stemofoline. To facilitate the incorporation of this side chain an approach was undertaken that made use of a [2,3] Stevens rearrangement.

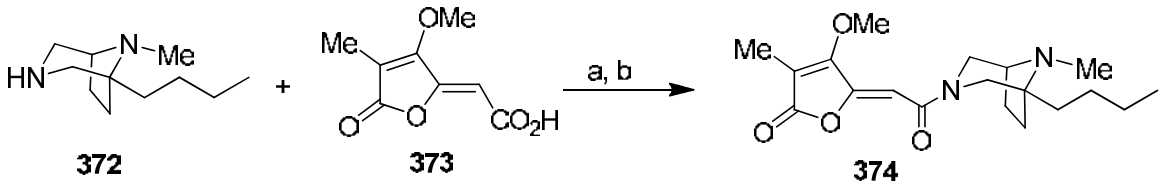
Optimisation of reaction conditions revealed that a tandem one pot cyclisation-[2,3] Stevens rearrangement gave the best results. Reaction of **367** with *N*-methylallyl amine with K_2CO_3 in DMF at 0 °C, gradually warming to room temperature, gives **370** via a quaternary ammonium ylide **369** (Scheme 138). Previous methods formed this intermediate via an intermolecular process, which was a rate limiting step and resulted in the need for higher reaction temperatures, longer reaction times and lower yields.



Scheme 138 a) N-methylallylamine, K_2CO_3, DMF, 0 °C-RT, 58%, as a 13:5 *cis*:*trans* mixture; b) benzylamine, xylene, reflux, 48h, 55%; c) H_2, Pd/C, 1 atm, EtOH, quant; d) 230 °C, neat, EtOH distilled off, 71%; e) $LiAlH_4$, Et_2O, 0 °C-reflux, 79%; f) H_2, 6.5 bar, Pd/C, EtOH, 35h 94%

The 2-allyl pyrrolidine **370** was transformed into **371** following similar reactions to that used to form **366**. The cyclisation step to give the diazabicyclic system occurred more cleanly when the alkyl chain was *n*-propyl as apposed to the allyl derivative, so reduction of this group was carried out prior to cyclisation. The 1-alkyl-3,8-diazabicyclo[3.2.1]octane **372** was formed by reduction of **371** and debenzylation.

The diazabicycle **372** was coupled with various tetronic and tetramic acid derivatives, an example of which being the reaction with **373** to give the stemofoline mimic **374** (Scheme 139).

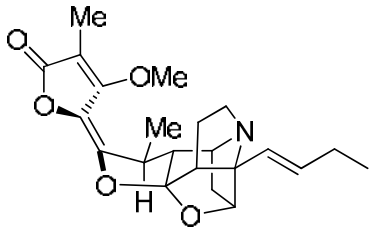


Scheme 139 a) oxalyl chloride, THF, DMF (cat.), RT, 1h; b) **372**, Et_3N, RT, 4h, 57%

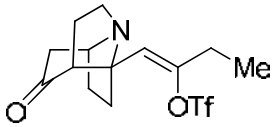
The Smith group has successfully synthesised the stemofoline mimic **374**. The use of a tandem cyclisation-[2,3]-Stevens rearrangement to give bicyclic compounds has been achieved in reasonable overall yields. This methodology is not just limited to the systems reported, it can also be applied to other 2-susbtituted pyrrolidines.

4.3.3 Gin's Work Towards Stemofoline Alkaloids

In 2002 *Gin et al.* reported the enantiospecific synthesis of **375** which contains the same bridged pyrrolizidine skeleton of didehydrostemofoline **344**. The key transformation in this route is an intramolecular 1,3-dipolar cycloaddition.[137]



344



375

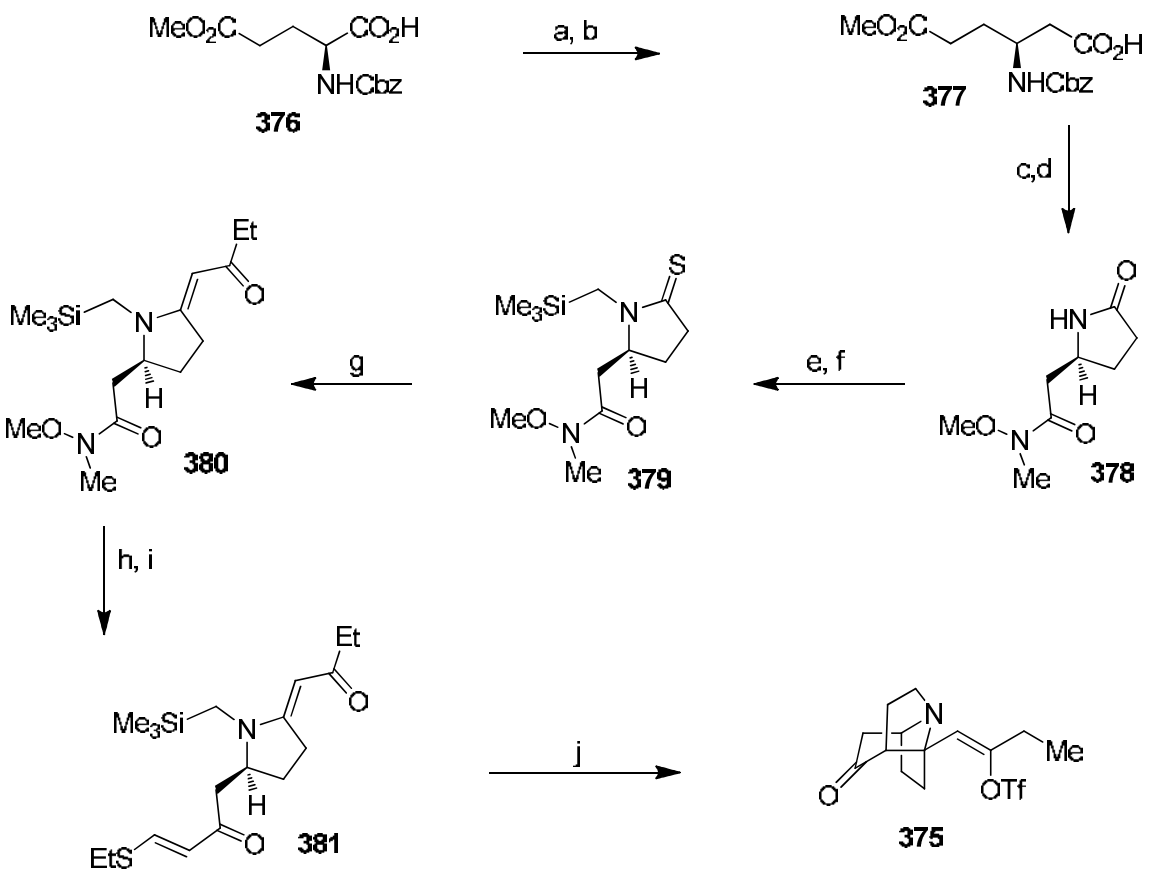
The reaction sequence began with the readily available *N*-benzyloxycarbonyl-L-glutamic acid-5-methyl ester **376**, which contains a single stereocentre that results in the control of stereochemistry in the whole reaction sequence.[138] The acid **377** was formed in 2 steps from **376** by an Arndt-Eistert reaction on the carboxylic acid moiety. Treatment of **377** with *N*-*O*-dimethylhydroxylamine gave the corresponding Weinreb amide, which was then subjected to hydrogenolysis, causing spontaneous formation of the lactam system **378** (Scheme 140).

Lactam **378** was alkylated with $TMSCH_2Cl$ and the amide was transformed to the thioamide by treatment with Lawesson's reagent to give the thiolactam **379**. Treatment

of **379** with 1-bromo-2-butanone gave the *S*-alkylated product which was transformed to the single stereoisomer of amide **380** by Eschenmosser sulfide contraction.

The next series of synthetic manipulations took place on the Weinreb amide part of the molecule. Addition of the ethynylmagnesium chloride was followed by hydrolysis and then addition of ethanethiol to give **381** in a 6:1 mixture of the *E* and *Z* isomers.

In order to afford the cyclised product **375**, the azomethine ylide intermediate was first formed by treating **381** with Tf_2O, then adding TBAT. Heating the reaction for 24 hours provided the cyclised product **375** as a single regio and stereoisomer, whose structure was confirmed by X-ray crystallography.

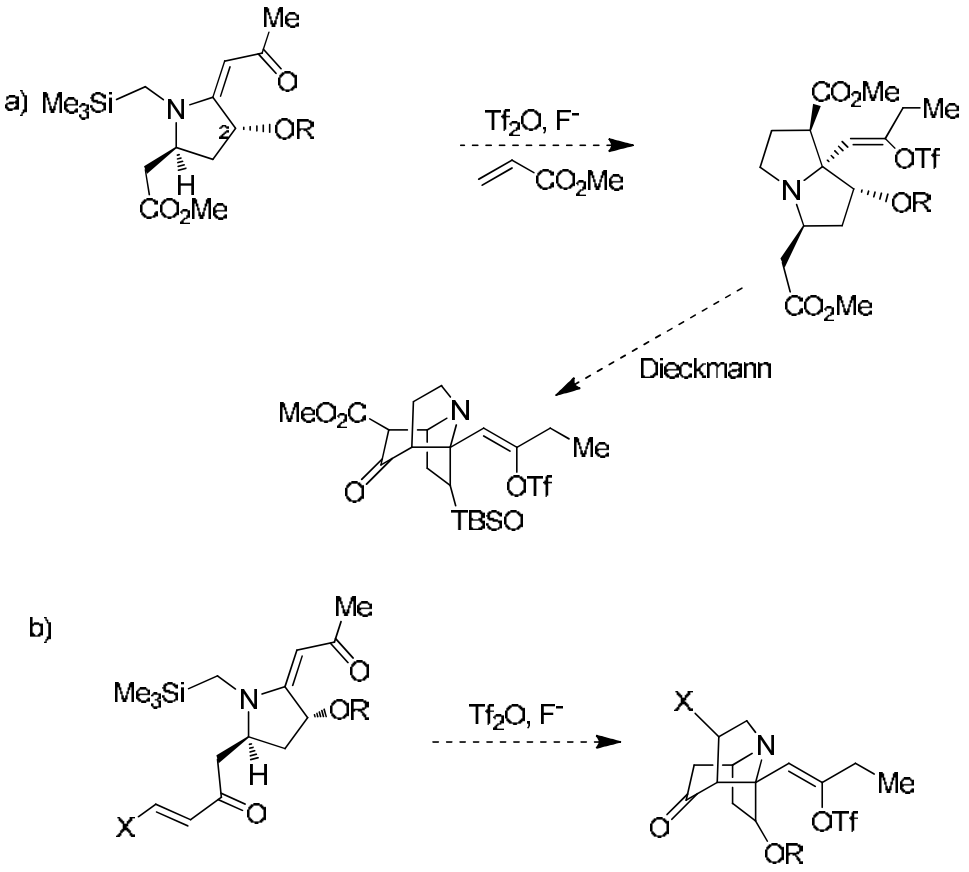


Scheme 140 a) EtOCOCl, Et_3N, THF, 0 °C, CH_2N_2, EtO, 87%; b) AgOAc, 1,4-dioxane, H_2O, 23 °C, 86%; c) EDCl, MeONHMe, Et_3N, $CHCl_3$, RT, 89%; d) H_2, 10%, Pd/C, MeOH, RT, 1 atm, 99%; e) NaH, $TMSCH_2Cl$, DMF, RT, 49%; f) Lawesson's reagent (0.51 equiv.), PhMe, RT, 88%; g) $BrCH_2COEt$, then PPh_3, Et_3N, MeCN, RT, 92%; h) HCΞCMgCl, THF 0 °C; i) EtSH, Et_3N, CH_2Cl_2, RT, 75%; j) Tf_2O (1.1 equiv.), $CHCl_3$, RT, TBAT (1.1 equiv.), 65 °C, 24 h, 51%

This 1,3-dipolar cyclisation is the key step in this sequence with the required azomethine ylide being generated from the sulfonation of a vinylogous amide. Gin *et al.* extended this work to include the synthesis of a range of highly functionalised pyrrolidines and pyrrolizidines.

In 2008 Gin reported an extension to this work which included the synthesis of compounds with an oxygen at C2, which is important in the synthesis of stemofoline alkaloids.[139] They looked at the possibility of both an intermolecular approach involving a

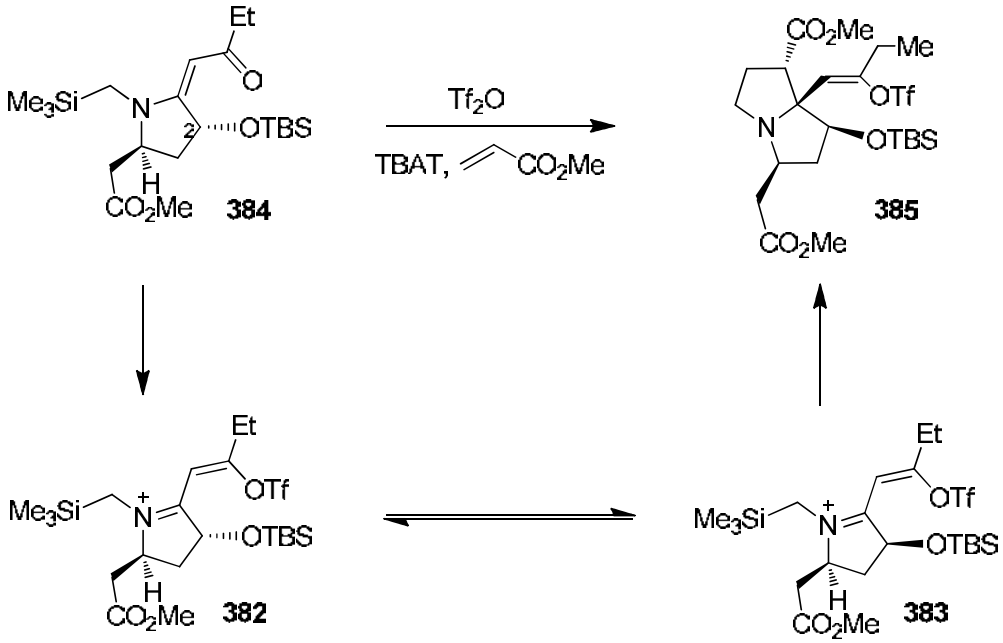
cyclisation followed by a Dieckmann condensation (Scheme 141, a), and also an intramolecular approach (Scheme 141, b), using much the same methodology as reported for the C2-deoxy bridged pyrrolizidine core.



Scheme 141 Proposed synthesis of C2 oxygenated, bridged pyrrolizidine core of stemofoline alkaloids

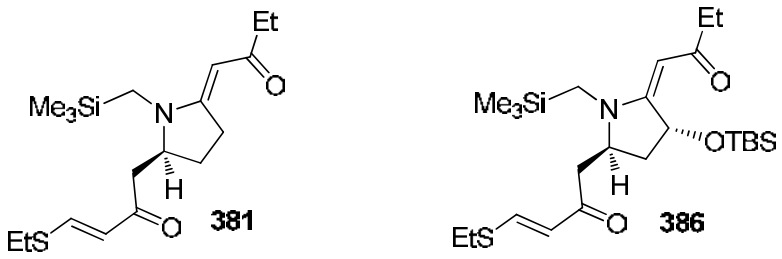
The intermolecular approach was unsuccessful due to the C2 epimerisation of the iminium triflate **382** to **383**, an intermediate in this sequence of reactions, which occurred upon treating the vinylogous amide **384** with Tf_2O and then TBAT in the presence of methyl acrylate. This problem could not be overcome by modifying the reaction conditions, or by altering the stereochemistry in other parts of the molecules. This meant

that when the cycloaddition reaction did occur the resultant bicycle **385** was in the incorrect configuration for Dieckmann condensation to happen (Scheme 142).



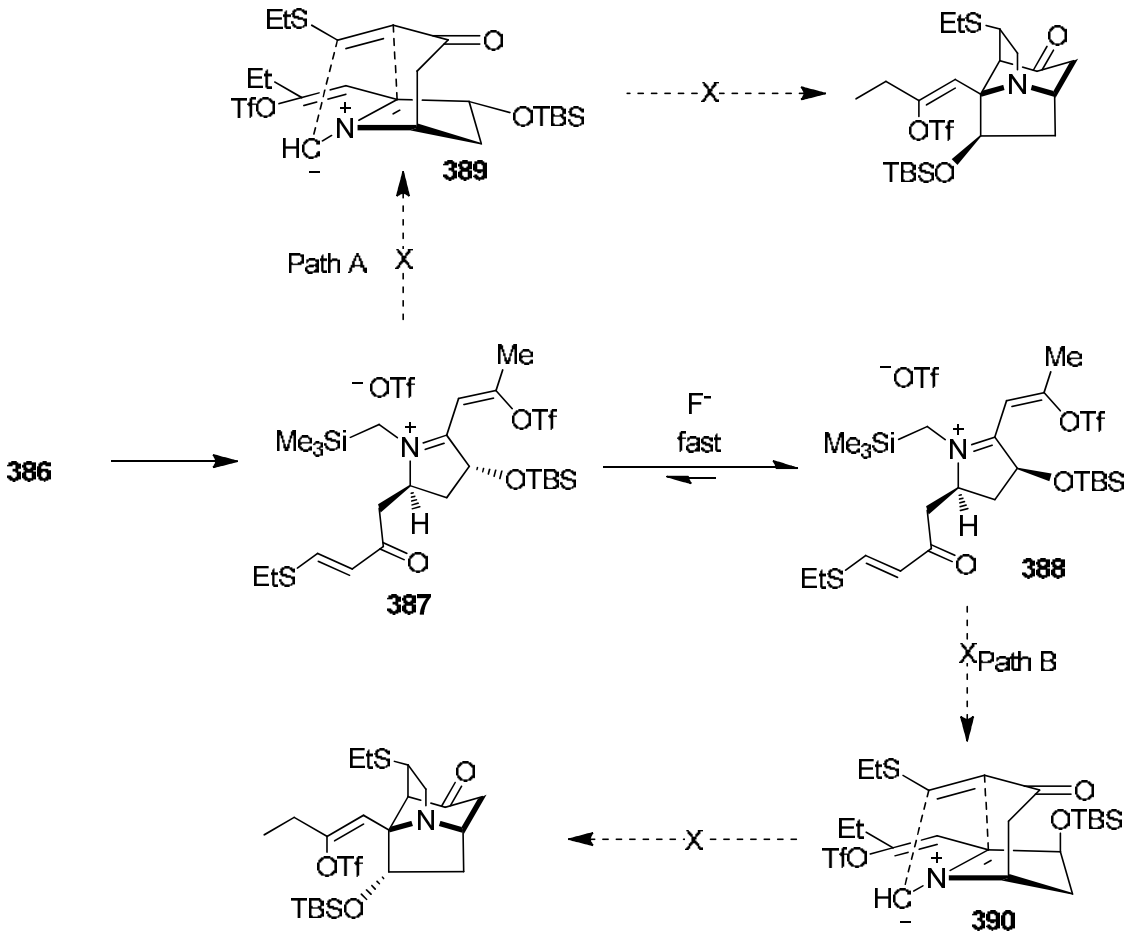
Scheme 136 Epimerisation of the iminium triflate

The intramolecular approach involved first forming the vinylogous thioester **386** which has a similar structure to that of **381**, only with oxygen incorporation at C2. Treatment under standard conditions of Tf_2O produced the imminium triflate but addition of the TBAT did not lead to the expected cycloadduct.



It was postulated that the fluoride ion could be causing epimerisation of the OTBS group at the C2 position with equilibrium favouring **388**, where the stereochemistry has been

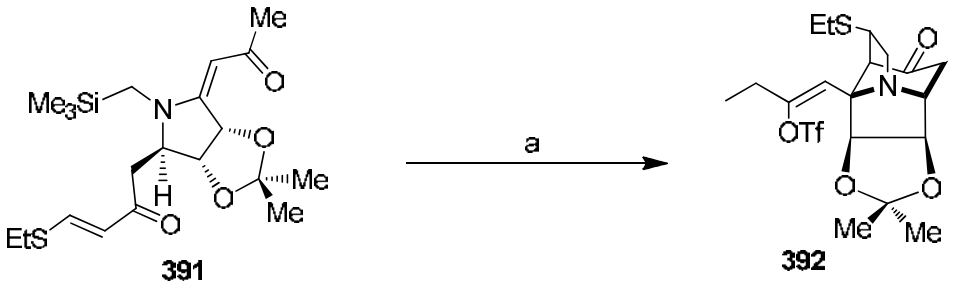
inverted. This would mean there is not enough of **387** at any given time to allow formation of the ylide **389**, so this reaction pathway could not be followed. Formation of the intermediate from **388** would result in a high energy transition state **390**, which is disfavoured due to steric clashes and thus decomposition pathway are followed instead (Scheme 143).



Scheme 143 Epimerisation of the iminium triflate at C2

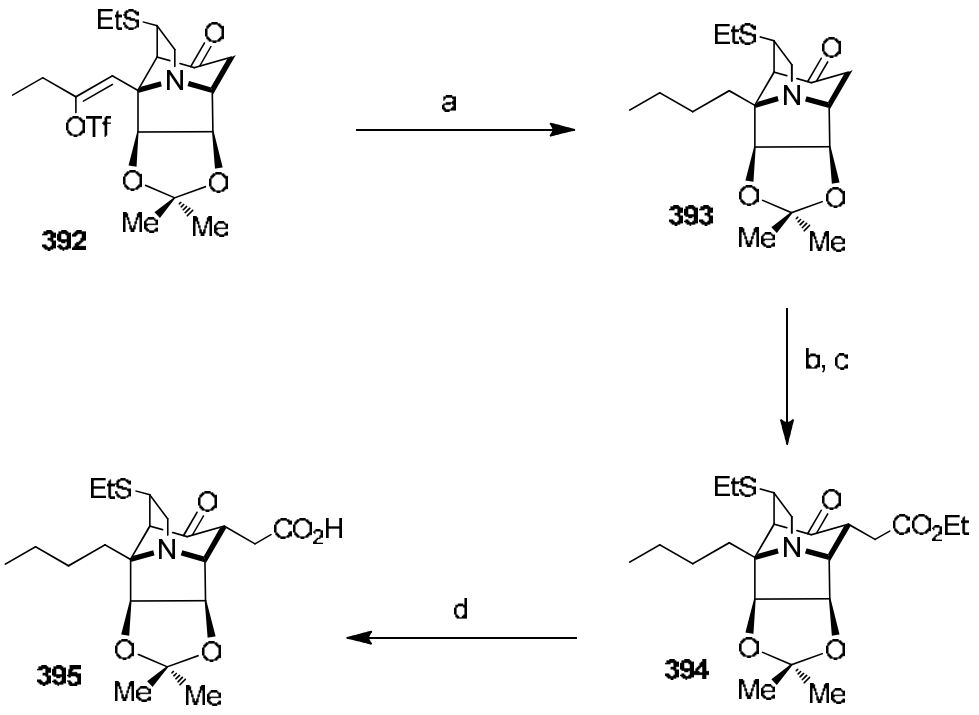
To prevent epimerisation at C2 the cyclisation precursor **391** was synthesised where C1 and C2 are oxygen substituents tethered as part of a *cis*-fused isopropylidene acetal. The intermediate is now held in the correct orientation for the cycloaddition to occur, with C2

epimerisation being prohibited, as this would result in a high energy system. Application of the Tf_2O TBAT conditions gave **392** in high yield (Scheme 144).



Scheme 144 a) Tf_2O, TBAT, $CHCl_3$, -45 to 23 °C, 71%

Further transformations on this compound allowed formation of pyrrolizidine **393**, with the butyl side chain in place which is present in stemofoline. Functionality could then be introduced at C9 by enolate alkylation, followed by use of DBU to equilibrate to the ethylester **394**. The isopropylidine group was deprotected with HCl, which also resulted in hydrolysis of the ester giving compound **395** (Scheme 145).



Scheme 145 a) 1 atm. H_2, 10% Pd/C, MeOH, 23 °C, 89%; b) LDA, ICH_2CO_2Et, THF, HMPA, 0 °C; c) DBU, PhMe, 80 °C, 58% (over 2 steps); d) 2.5 M HCl, THF, 60 °C, 96%

In summary this intramolecular route can be extremely useful in the synthesis of stemofoline alkaloids. The formation of compound **395** not only provides a molecule where the butyl side chain is already in place, it also contains a lot of functionality to allow further chemistry to be carried out.

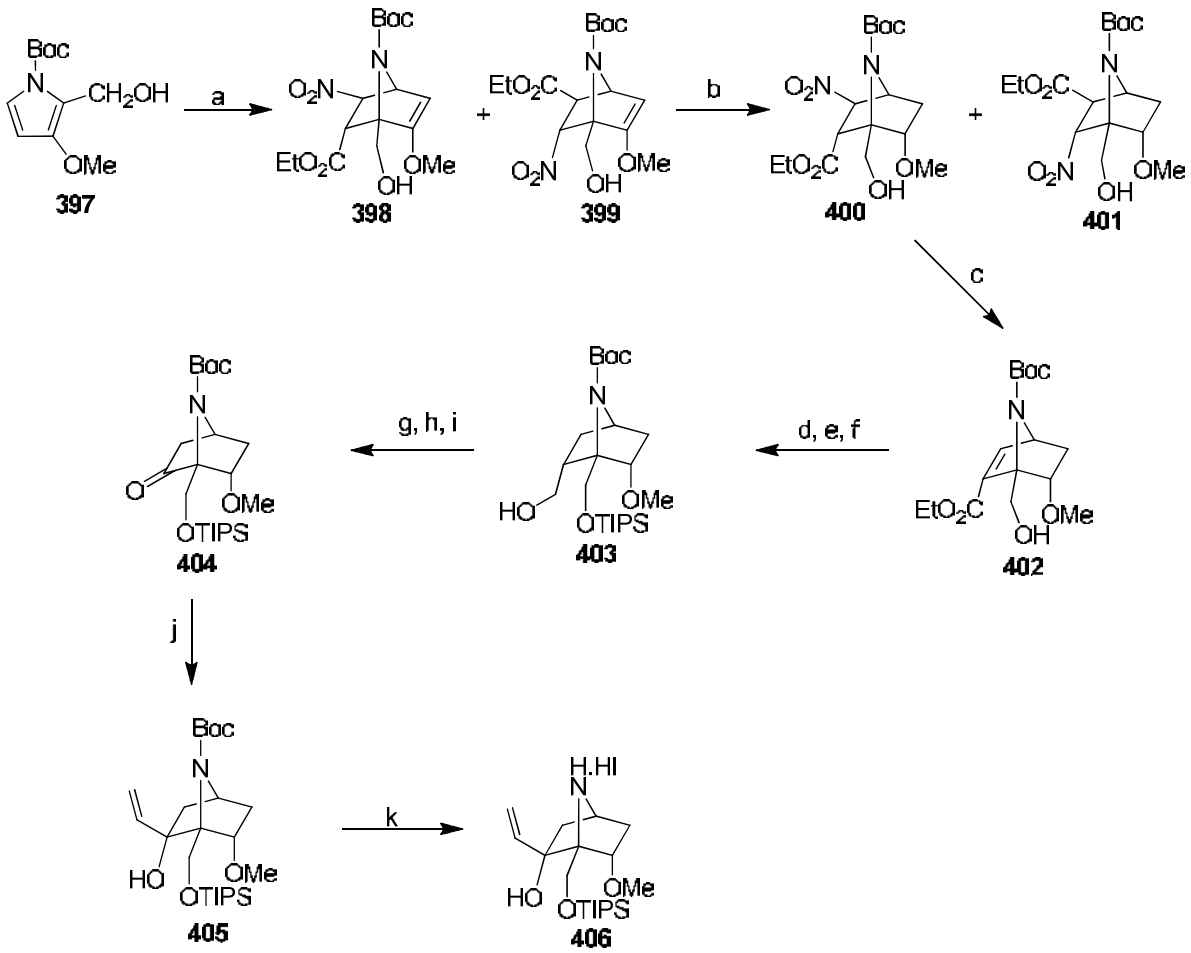
4.3.4 Overman's Synthesis

In 2003 Overman and co-workers reported the total synthesis of (±)-didehydrostemofoline and (±)-isodidehydrostemofoline.[130] The synthetic route to both of these molecules follows the same pathway with the penultimate step being where the divergence occurs. Two diastereomers were produced at this point which both could be cleanly converted into the desired products in reasonable yields. This report was the first

of a total synthesis of a stemofoline alkaloid with the *Z*-configuration at the tetrahydrofuranylidene butenolide (C11-C12) junction.

The initial studies focused on forming the tricyclic system **396**. This was achieved by reacting the readily available Boc protected pyrrole **397**, acting as the diene, with ethyl (*E*)-3-nitroacrylate acting as the dienophile. The [4+2] Diels-Alder cycloaddition of these two compounds gave two cycloadducts **398** and **399**, which were directly hydrogenated over Pd/C resulting in the steroselective formation of azabicycloheptanes **400** (73%) and **401** (13%). This direct hydrogenation is necessary as the cycloadducts **398** and **399** are not stable to the column chromatography conditions.

The presence of the nitro group in 3-nitroacrylate is crucial for the cycloaddition as it lowers the energy level of the LUMO of the dienophile, making the reaction more favourable. After cyclisation the nitro groups is no longer required, so it is removed from azabicycloheptane **400** using DBU to give the α-β unsaturated ester **402** (Scheme 146).

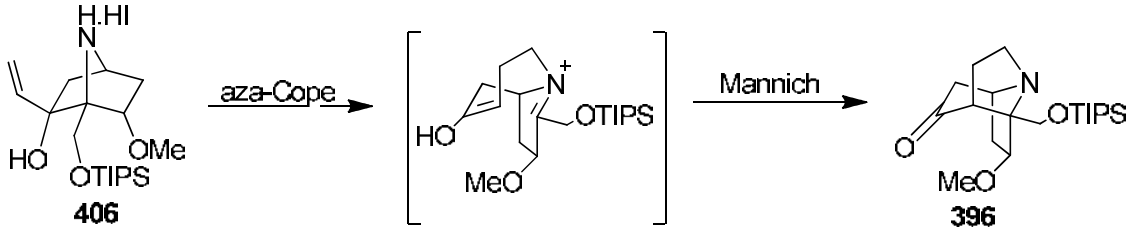


Scheme 146 a) (*E*)-$O_2NCHCHCO_2Et$, RT; b) H_2, Pd/C, EtOAc, RT; c) DBU, CH_2Cl_2, RT; d) H_2, Pd/C, EtOAc, RT; e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, RT; f) DIBALH, MePh, -78 °C, 51%; g) DMP oxid., CH_2Cl_2, RT; h) TIPSOTf, Et_3N, CH_2Cl_2, -78 °C; i) O_3, MeOH, CH_2Cl_2, -78 °C; j) $CH_2CHMgBr$, $CeCl_3$, THF, -78 °C; k) TMSI, 2,6-lutidine, 0 °C- rt, MeOH 85%

After hydrogenation of alkene **402** with Pd/C, the resultant primary alcohol was protected with a TIPS group. The ester could then be selectively reduced using DIBAL to give the alcohol **403**. This was subsequently oxidised to the aldehyde which was treated with TIPSOTf and Et_3N at -78 °C to give the enolsilane. Subsequent ozonolysis of this gave ketone **405** in 37% overall yield from **398**. Addition of the vinyl Grignard using Luche conditions gave the allylic alcohol **405** as a single isomer due to the highly stereoselective

addition occurring from the top face. The Boc group was chemoselectively removed by treatment with TMSI to give the hydroiodide salt **406** in 85% yield.

The next step was crucial for formation of the 1-azatricyclo[5.3.0.0]decane moiety seen in stemofoline. This was achieved in 94% yield by heating the salt **406** with excess paraformaldehyde at 80 °C, allowing a aza-Cope-Mannich reaction to occur giving the desired tricyclic system **396** (Scheme 147).[140]

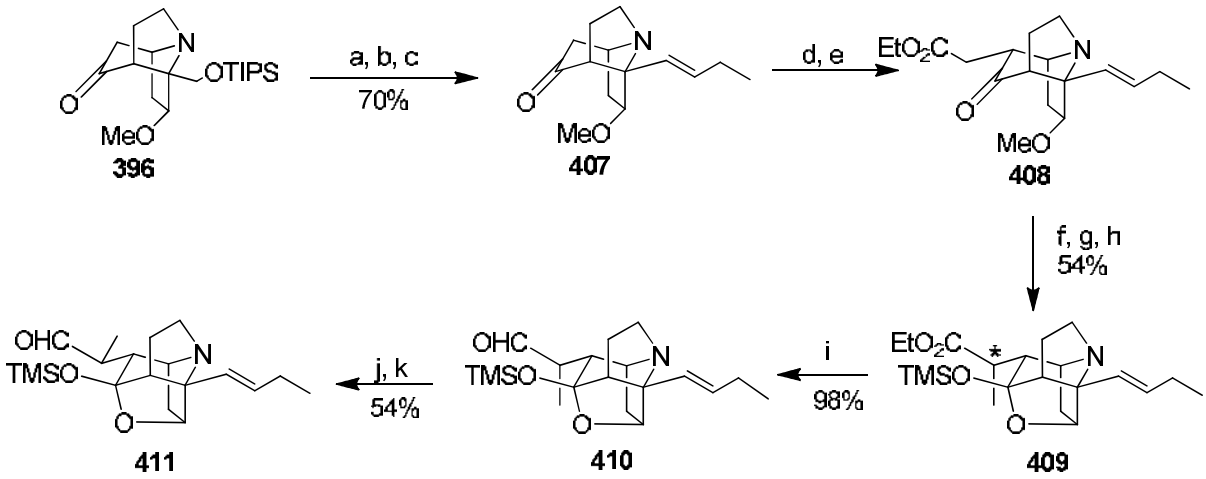


Scheme 147 $(CH_2O)_n$, 80 °C, PhMe-MeCN, 94%

The TIPS protected alcohol was deprotected using TBAF and the resultant alcohol oxidised to the aldehyde, which was treated under Julia-Kocienski olefination conditions[141] to give **407** as an isomerically pure compound in 70% overall yield. LDA was then used to form the lithium salt of **407**, which was alkylated under kinetically controlled conditions to give a mixture of stereoisomers. The desired equatorial keto-ester configuration of **408** was achieved by epimerising the stereoisomers under basic conditions with DBU.

The methyl ester of **408** was deprotected with BBr_3, which resulted in lactol formation. This was silylated using TMS-imidazole, and the ester enolate deprotected then treated with MeI to give the α-methyl ester **409**. This ester had the incorrect configuration for the stemofoline alkaloids at C*. However this configuration could be altered by forming the

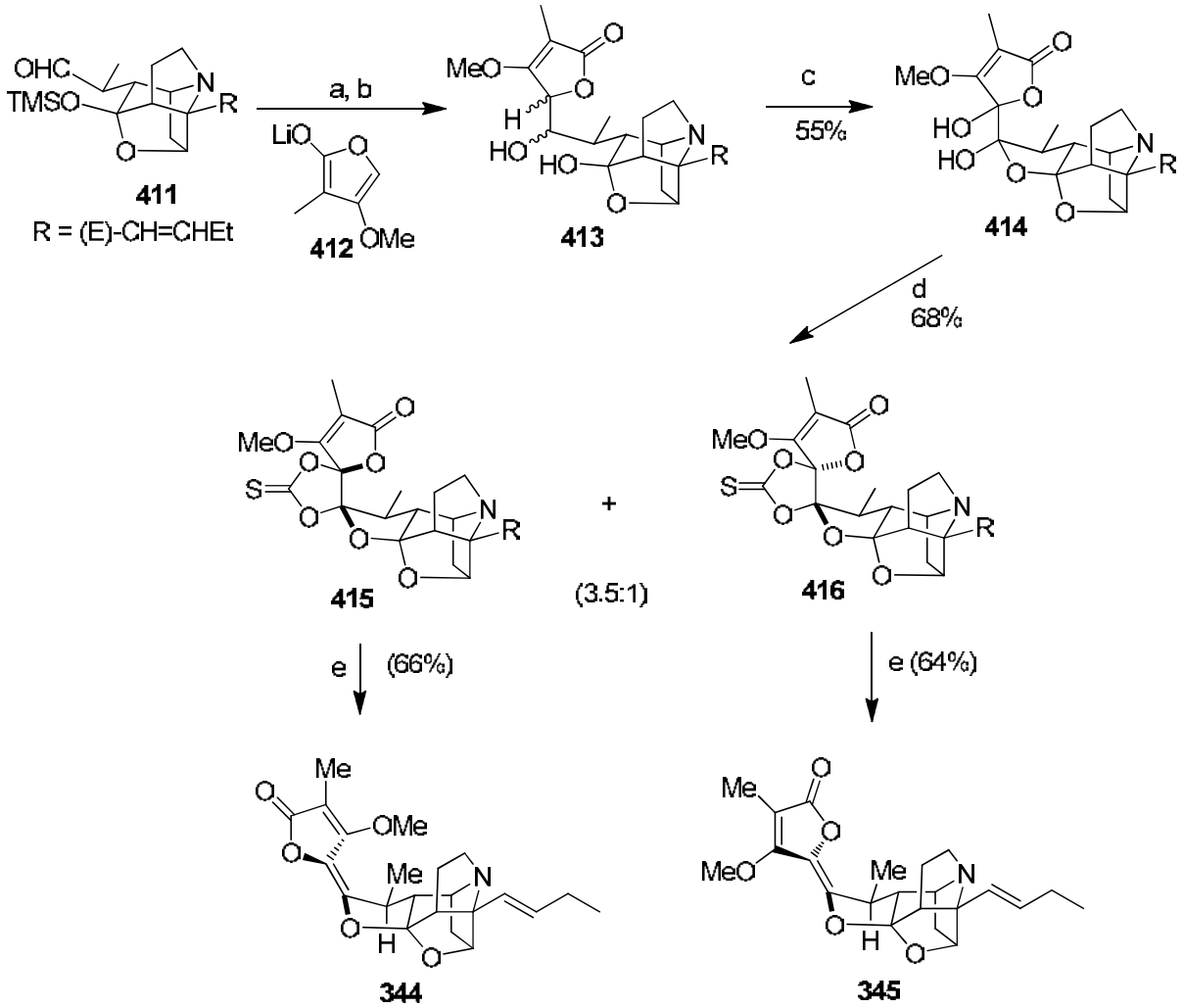
corresponding primary alcohol using DIBAL then Dess-Martin oxidation to the aldehyde **410**. Basic conditions allowed epimerisation to give **411** as the major epimer (94:6) which could be separated by column chromatography (Scheme 148).



Scheme 148 a)TBAF, THF, RT; b) SO_3.Py, NEt_3, DMSO, RT; c) $C_7H_5N_4SO_2$n-Pr, KHMDS, DME, -55 °C; d) LDA, THF, ICH_2CO_2Et, -10 °C; e) DBU, MePh, 130 °C; f) BBr_3, CH_2Cl_2, -78 °C to -10 °C; aq NaOH; g) TMS-imid., 130 °C; h) LDA, MeI, THF-DMPU, -45 °C; i) DIBALH, CH_2Cl_2, -78 °C; j) DMP oxid., rt; k) SiO_2, $CHCl_3$, RT

With the tetracyclic unit **411** in hand, the next task was to add on the furanone unit. This was achieved by reacting the lithium anion of 4-methoxy-3-metyl-2(5H)furanone (**412**) with the aldehyde **411**. The silyl protecting group was then removed under acidic conditions to give the hemiacetal **413**. Treatment of **413** with excess IBX in DMSO gave the oxidised diol **414** as one of four possible isomers. This diol was condensed with thiophosgene to give a separable mixture of the cyclic thionocarbanates **415** and **416**. The ratio of these products could be altered by changing the temperature of the reaction, with an increase in temperature favouring **416**.

Heating both of these cyclic thiocarbonates with excess trimethylphosphite caused fragmentation of **415** and **416** to didehydrostemofoline **344** and isodidehydrostemofoline **345** respectively (Scheme 149).



Scheme 149 a) **414**, n-BuLi, THF, -78 °C; b) aq HCl, $CHCl_3$-MeOH, RT; c) IBX, DMSO, 55 °C; d) $CSCl_2$, DMAP, CH_2Cl_2, -50 °C; e) $(MeO)_3P$, 120 °C

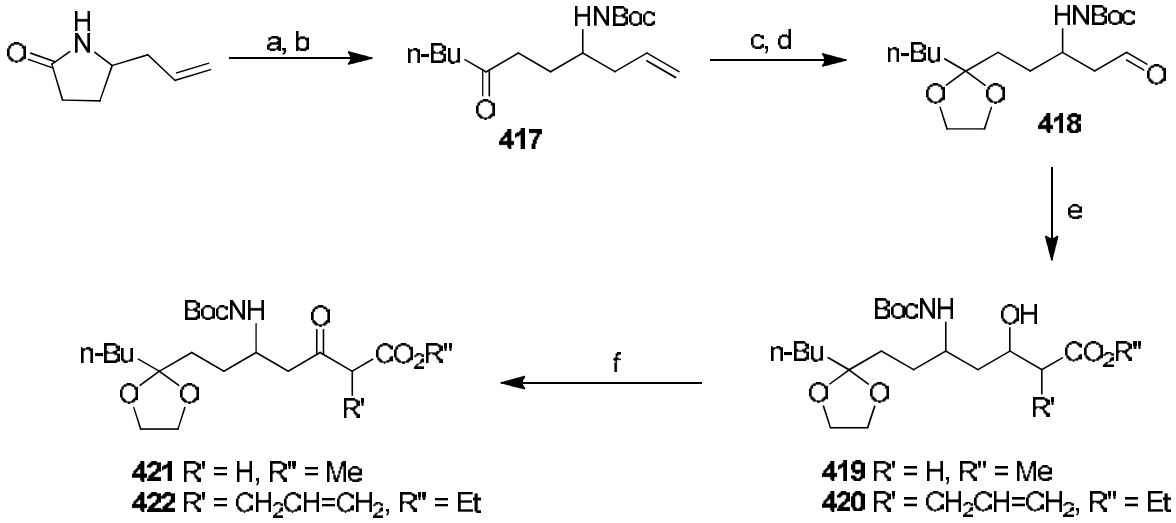
In conclusion the total syntheses of **344** and **345** were achieved in 27 steps from the Boc protected pyrrole **397**. The key steps in this route are the Diels-Alder reaction using (*E*)-3-nitroacrylate to give **398**, and the aza-Cope-Mannich cyclisation to give the tricyclic

system. Although the product is racemic the two products are cleanly separated at the penultimate step.

4.3.5 Thomas' Approaches Towards Stemofoline

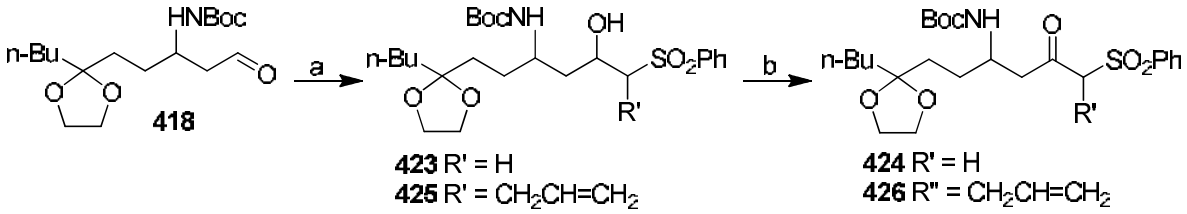
In 2007 Thomas *et al.* reported their latest approach towards the synthesis of stemofoline.[142] This route involved a stereoselective cyclisation to give aza-bicyclic adducts, with the tricyclic system being introduced by cyclising an organolithium species onto the carbonyl carbon of a carbamate.

In order to create cyclisation precursors, the reaction pathway outlined in Scheme 150 was followed. Racemic 5-prop-2-enyl-pyrrolidine was reacted to give the Boc carbamate, and subsequent reaction with butylmagnesium bromide gave the butyl ketone **417**. Acetylisation of the ketone followed by ozonolysis gave the aldehyde **418**. An aldol condensation gave **419** which was then oxidised to yield the corresponding ketoester **420** (Scheme 150).



Scheme 150 a) $(t\text{-}BuCO_2)_2O$, DMAP, Et_3N, 76%; b) n-BuMgBr, THF, 91%; c) $(CH_7OH)_2$, pyH-OTS, toluene, 81%; d) O_3, MeOH, then Ph_3P, 90%; e) $MeCO_2Me$, LDA, -78 °C, (**419**, 95%) or ethyl pent-4-enoate, LDA, -78 °C, (**420**, 92%); f) PDC (**421**, 73%) Or Dess Martin (**422**, 59%)

Production of the ketosulfone equivalent **420** of **417** was achieved by treating **418** with lithiated methylphenyl sulfone to give the alcohol **423**. This was subsequently oxidised under Dess-Martin conditions giving the ketosulfone **424** (Scheme 151). The alkylated analogues **422** and **426** of the ketoester (**421**) and the ketosulfone (**422**) respectively were prepared under similar conditions.

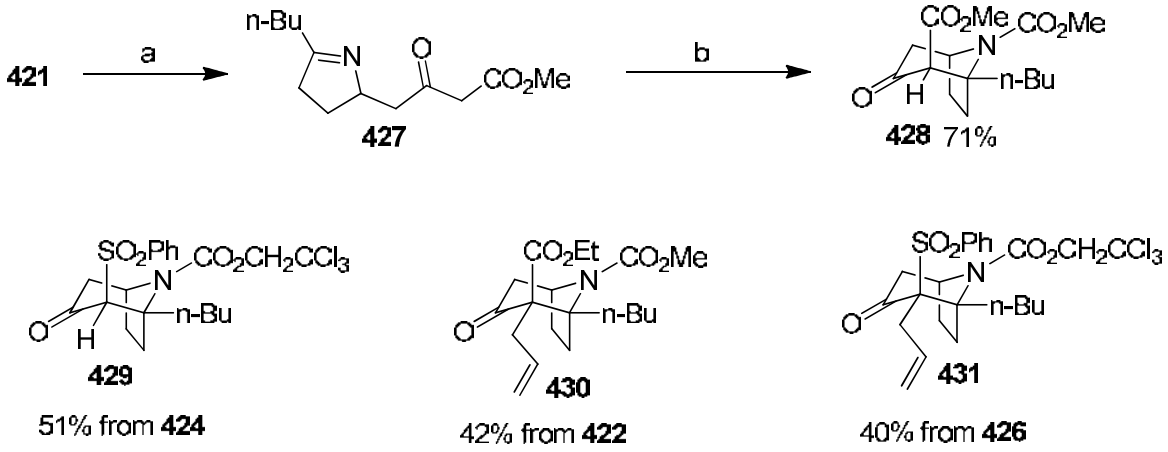


423 R' = H
425 R' = $CH_2CH{=}CH_2$

424 R' = H
426 R" = $CH_2CH{=}CH_2$

Scheme 151 a) $PhSO_2Me$, LDA -78 °C (**423**, 58%) or but-3-enyl phenyl sulfone, LDA, -78 °C (**425**, 80%); b) Dess Martin (**424** 72%), (**426**, 66%)

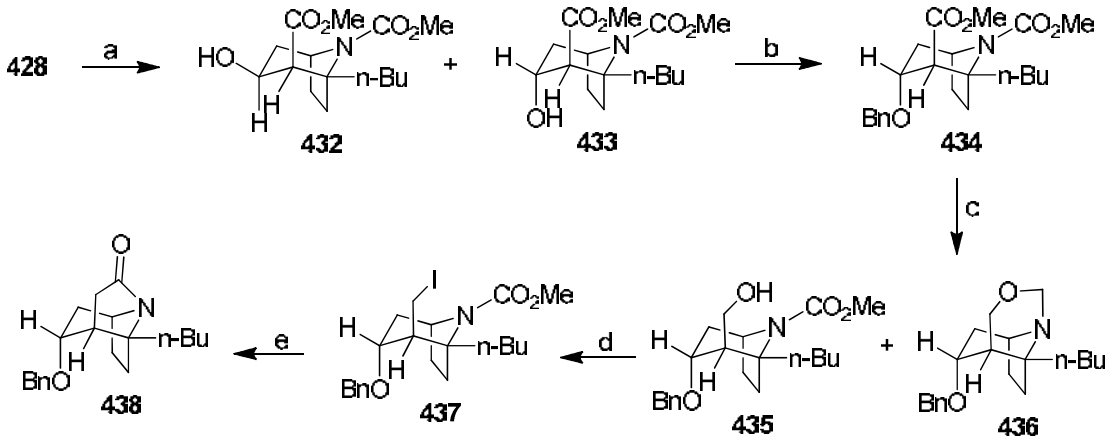
Now that the cyclisation precursors had been prepared, the azabicyclic fragment of stemofoline could be synthesised. The first cyclisation was achieved by treating ketoester **421** with TFA, which resulted in deprotection of both the Boc amide and the acetal and then spontaneous formation of the imine **427**. This was transformed to the azabicylic system **428** by reacting the imine with methyl chloroformate, then triethylamine. Azabicycles **429**, **430** and **431** were also obtained in a similar fashion (Scheme 152).



Scheme 152 a) TFA, CH_2Cl_2; b) $ClCO_2Me$, Et_3N, 71%

Compounds **430** and **431** contain allyl substiuents, which sit in the axial position, making further cyclisations to give the third ring of the stemofoline core unfavourable. As such the focus for further elaboration of compounds towards the stemofoline core was centred around the azabicycle **428**.

The ketone moiety of **428** was reduced to give alcohols **432** and **433** using zinc cyanoborahydride. Although this reaction was not completely selective the equatorial alcohol in **432** could be re-oxidised back to the ketone. The alcohol **433** was protected using benzyl trichloroacetimidate under acidic conditions to give benzylether **434**.

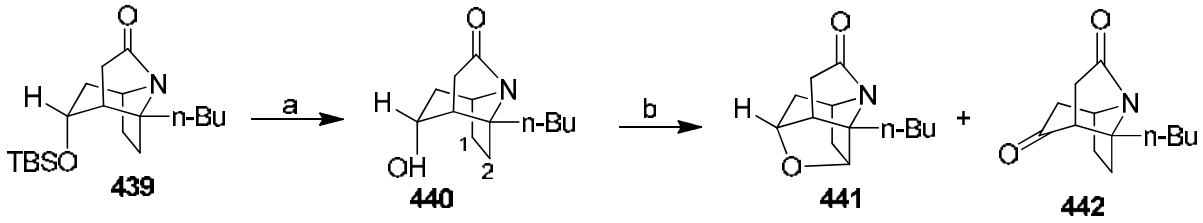


Scheme 153 a) $ZnCl_2$, $NaBH_3CN$, Et_2O (**432**:**433** = 1:3, 91%); b) benzyl trichloroacetimidate, TfOH (99%); c) DIBAL-H, hexane, 0 °C (**435**, 59%, **436**, 18%); d) I_2, PPh_3, imid., 81%; e) t-BuLi, -78 °C to rt 71%

Reduction conditions gave the expected primary alcohol **435** along with the tricylic side product aminoacetal **436**. Formation of this side product was believed to have occurred by an iminium ion, derived from the methyl carbamate, being captured by the alkoxide which would have formed when the ester was reduced. This indicated that the third ring of stemofoline could be formed by incorporating the carbonyl carbon of the carbamate. The alcohol **435** was treated with I_2 in the presence of PPh_3 and imidazole to give the iodide **437**. The corresponding organolithium species, resulted in formation of the tricyclic lactam **438** (Scheme 153).

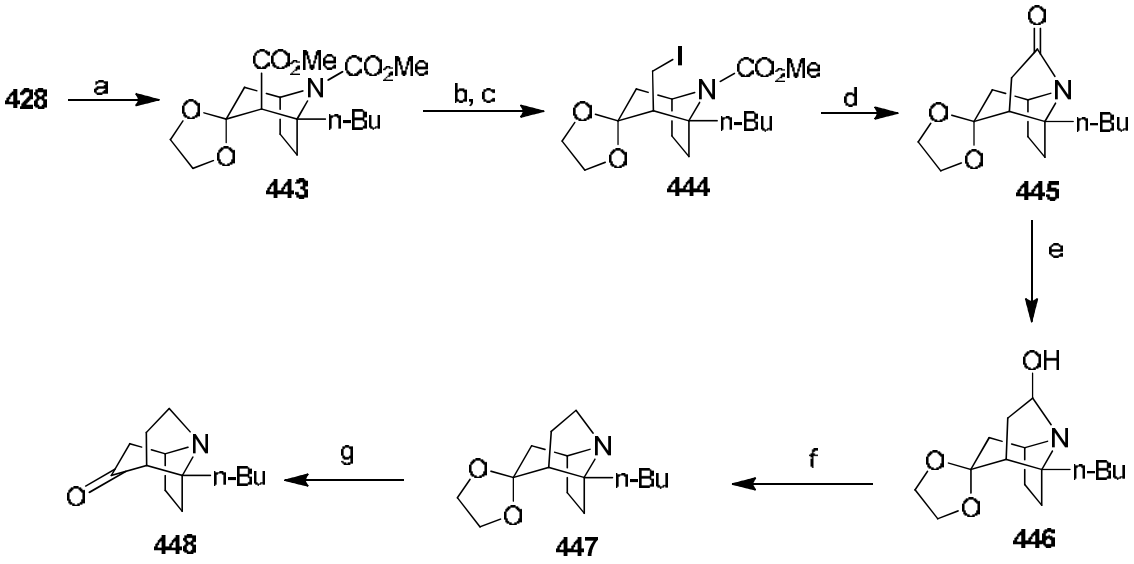
The analogous TBS protected tricyclic lactam **439** was also synthesised in a similar fashion. Deprotection gave the alcohol **440**, the X-ray crystal structure of which, revealed a twist in the structure. This twist resulted in the distance between the endo hydrogens at C1 and C2 being different distances away from the oxygen of the alcohol group, with that at C2 being closer.

Treatment of alcohol **440** with lead acetate gave **441**, occurring from ring closure onto C2; no ring closure onto C1 was observed. Although the tetracyclic ester **441** was the major product (35%), the ketone **442** was also observed (16%) along with some unreacted starting material (12%).



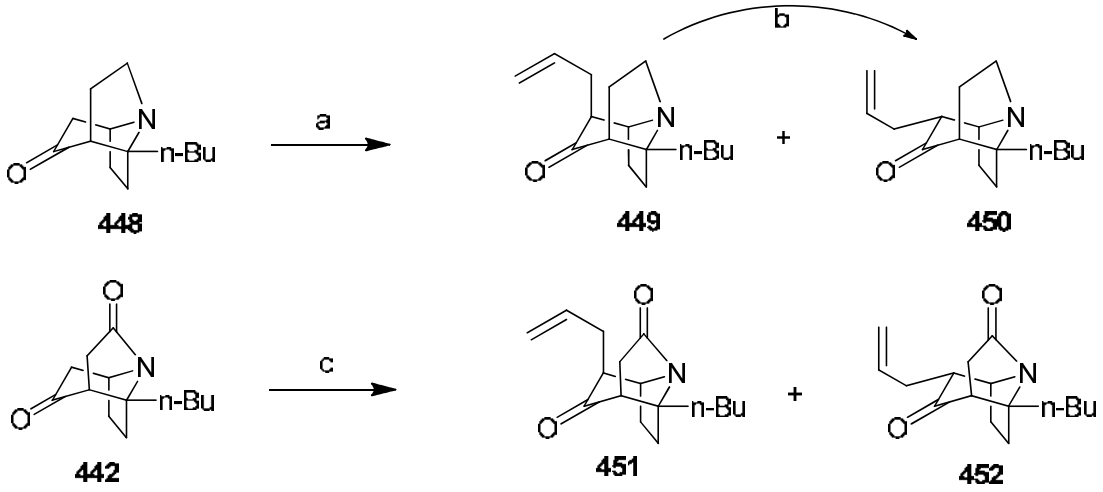
Scheme 154 a) TBAF, THF, RT, 99%; b) $Pb(OAc)_4$, benzene, reflux (**441**, 35%, **442**, 16%)

In order to afford stemofoline, the tricyclic keto-amide **448** needed to be synthesised. This was done by first acetal protecting **428**, to give **443**. The ester moiety of this compound was reduced to the primary alcohol then subsequently converted to the iodide **444**. Cyclisation using the conditions previously developed gave the tricyclic lactam **445**, which was reduced via the aminol **446** to give the acetal **447**. Deprotection of the acetal under mildly acidic conditions gave the aminoketone **448** (Scheme 155).



Scheme 155 a) 2-methoxy-1.3-dioxolane, TsOH, MeOH, toluene, 50 °C, 87%; b) DIBAL-H, 55%; c) I_2, PPh_3, imid., 78%; d) t-BuLi, THF, -78 °C, 74%; e) $LiAlH_4$, Et_2O, 83%; f) $SOCl_2$ then $LiAlH_4$, 75%; g) 1% aq. H_2SO_4, 90%

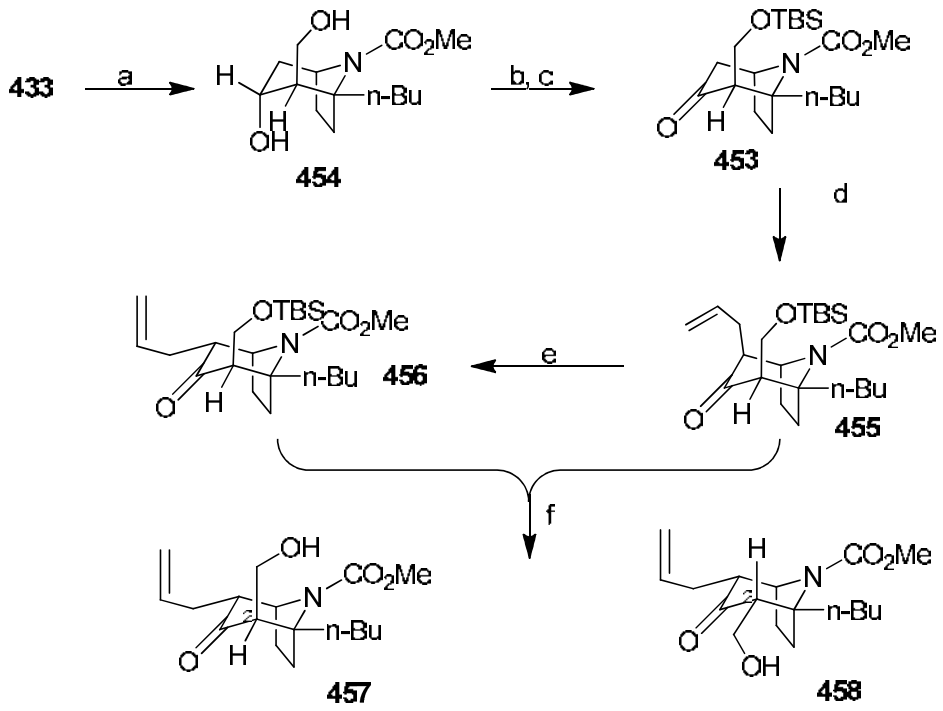
Having successfully synthesised part of the stemofoline core, Thomas *et al.* then went on to attempt a complete synthesis of pentacyclic core by looking at formation of the C10 and C11 fragment. This was first attempted by alkylation of ketoamine **448** and ketolactam **442**. The ketoamine **448** was alkylated with allyliodide and hexamethyldisilazide which gave an 8:2 mixture of epimers **449** and **450**. The desired equatorial product was achieved exclusively by treating **449** with potassium *t*-butoxide, which caused epimerisation to **450**. Allylation of the ketolactam with allylbromide gave a mixture of the axial (**451**) and equatorial (**452**) products in a substantially lower yield than seen for the ketoamine (Scheme 156).



Scheme 156 a) KHMDS, allyl iodide, -78 °C, **449**:**450** 4:1 56%; b) KOt-Bu, CH_2Cl_2, methanol, RT, 88%; c) LDA, allyl bromide, -78 °C to RT, **451**:**452** 65:35, 39%

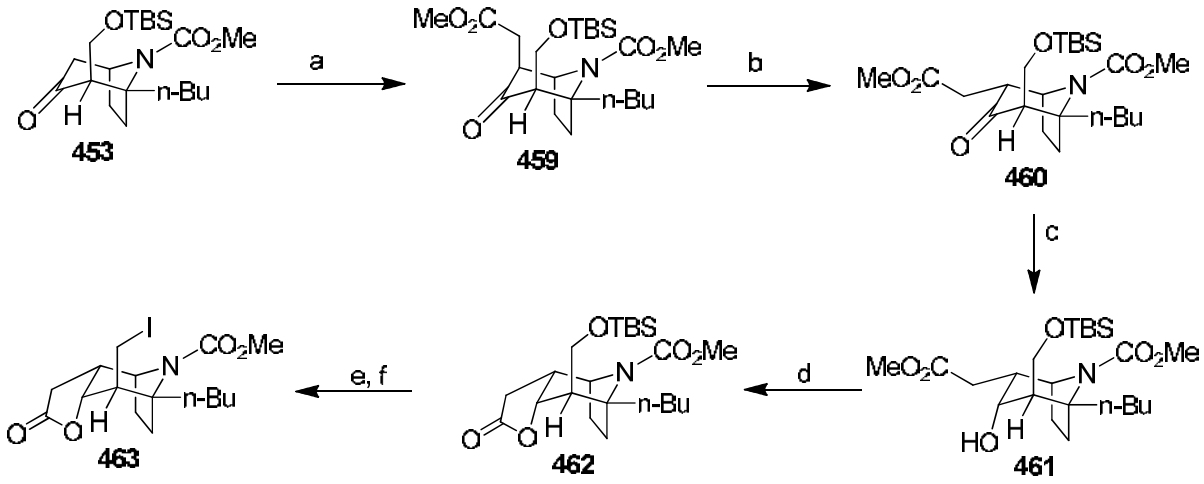
Further elaboration of the allylated molecules produced was unsuccessful, with all attempts to do oxidative cleavage of the terminal alkene of **450** not giving the desired products. Due to this, the possibility of introducing the alkyl chain earlier in the synthesis by alkylating the previously reported bicyclic ketones was investigated.

Ketone **453** was synthesised by reducing the bicyclic lactam **433** to the alcohol **454**, then regioselectively protecting with TBS, before oxidation to the ketone. Alkylation at this stage gave the axial allylated product **455** which was epimerised to the equatorial allylated product **456** using potassium *t*-butoxide. Desilylation of both these epimers gave the alcohols **457** and **458**, where epimerisation around C2 is observed (Scheme 157).



Scheme 157 a) DIBAl-H, CH_2Cl_2, -78 °C, than $NaBH_4$, 63%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 94%; c) PDC, CH_2Cl_2, 98%; d) KHMDS, allyl iodide, -78 °C, 63%; e) KO*t*-Bu, CH_2Cl_2, methanol, 56%; e) TBAF, THF, (**457**:**459** = 3:2, 56% from **455**), (**457**:**458** = 1:1, 36% from **456**)

Alkylation of ketone **453** using methyl bromoacetate and potassium hexamethyldisilylazide gave the unfavorable axial product **459** in modest yield. Epimerisation to the equatorial product **460** using potassium *t*-butoxide was achieved in 66% yield. Reduction to the alcohol **461** was followed by removal of the silyl protecting group using TBAF, which also resulted in cyclisation to give the hydroxylactone **462** (Scheme 158). This was converted into the iodide **463**, but attempts to cyclise this to create the top ring via halogen-metal exchange were unsuccessful, with complex mixtures of products being observed.



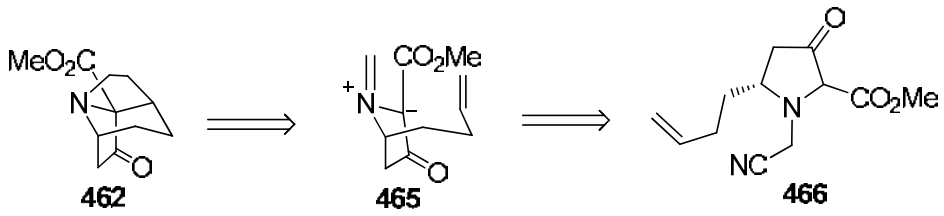
Scheme 158 a) KHMDS, $BrCH_2CO_2Me$, -78 °C to RT, 58%; b) KOt-Bu, CH_2Cl_2, MeOH, 66%; c) $ZnCl_2$, $NaCNBH_3$, 74%; d) TBAF, THF, 84%; e) Ac_2O, DMAP, Et_3N, 69%; f) I_2, PPh_3, imid, 80%

In summary, Thomas and co-workers have advanced the synthesis of stemofoline by successfully synthesising the tetracyclic core in a stereoselective manner. The azabicycles were formed in modest yields by stereoselective cyclisations, with the synthesis of the lactam achieved by a lithium-halogen exchange reaction of an alkyl iodide and subsequent onto a carbamate. The final ring was installed by oxidation of an alcohol to give the tetracycle ether regioselectively. Allylation of tricyclic intermediates to install the C10-C11 fragment of stemofoline was not very efficient. However there is potential to install this portion before cyclisations to give more complex analogues of **427**.

4.3.6 Martin's Work Towards Stemofoline

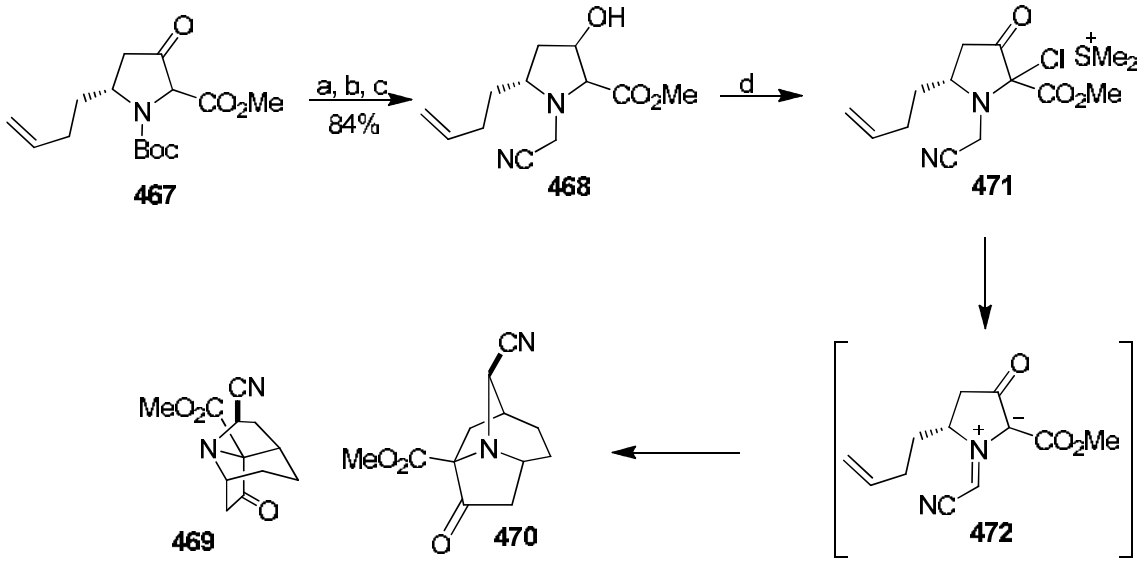
In 2011 Martin reported his attempts towards the tricyclic core of stemofoline. This approach involved formation of the functionalised tricyclic core, seen in **464**, by an intramolecular 3+2 cycloaddition reaction of an azomethine ylide such as **465**. It was envisaged that these ylides could be synthesised by addition of silver ions to the chiral

amino nitrile **466**, resulting in decyanation and deprotonation to give the ylide (Scheme 159).[143]



Scheme 159 Disconnection of the tricyclic core of stemofoline

In order to test this chemistry, the amino nitrile species **466** first needed to be synthesised. The precursor to this, the Boc protected pyrrolidine **467** was formed with relative ease. However upon removal of the Boc protecting group an unstable keto ester intermediate was formed that could not be reacted further. To continue the work towards the tricyclic core of stemofoline, the ketone of **467** was reduced to the alcohol, allowing for subsequent removal of the Boc group followed by cyanomethylation to give **468**. Attempts to reoxidise the alcohol at this stage to give **466** were unsuccessful with most conditions leading to complex mixtures of products.



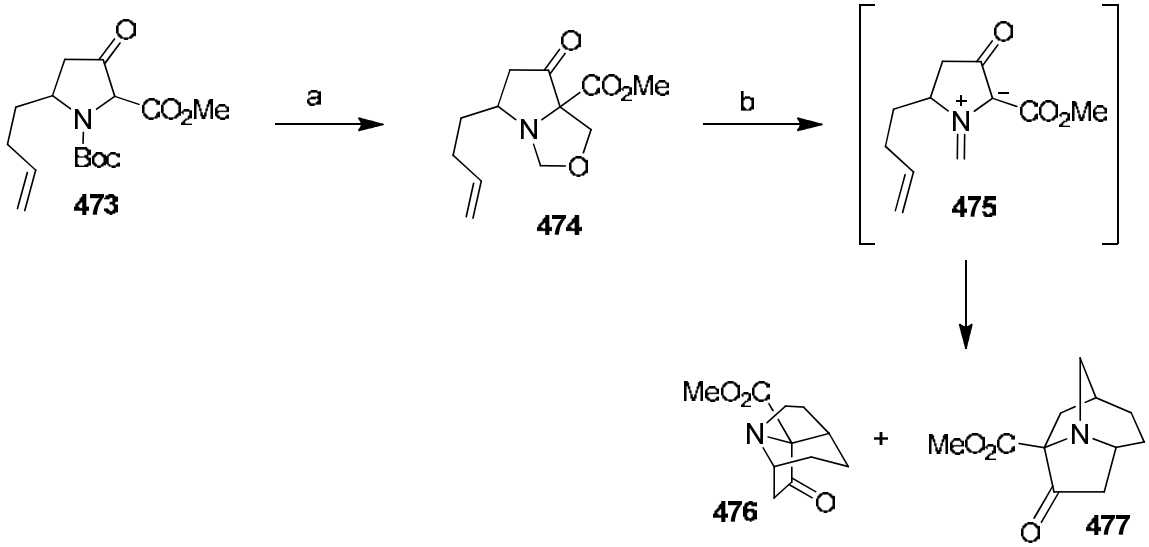
Scheme 160 a) $NaBH_4$, MeOH, 0 °C; b) CF_3CO_2H, CH_2Cl_2, 0 °C; c) formalin, HCl, NaCN; d) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, then Et_3N, 69% (**469**:**470** 5:1)

Oxidising **468** under Swern conditions led to production of the tricyclic compounds **469** and **470**, which could be separated by column chromatography. It is believed that the mechanism operating here involved initial oxidation to the ketone, which can react with the electrophillic species generated during the Swern oxidation to give the intermediate **471**. Loss of HCl from this would result in formation of the azomethine ylide **472** and subsequent cyclisation would give the tricyclic systems observed (Scheme 160).

Further elaboration of **469** was possible, with the ketone being first reduced to the alcohol, or by transformation of the ester to the aldehyde and subsequent olefination to introduce the butenyl side chain observed in didehydrostemofoline. However, all attempts at removing the cyanogroup were unsuccessful.

Due to the difficultied observed in the decyanation of products, the approach towards stemofoline and its analogues was modified to produce the intermediate azomethine ylides by a different method.[144] Oxazolidine **474** was synthesised by reaction of

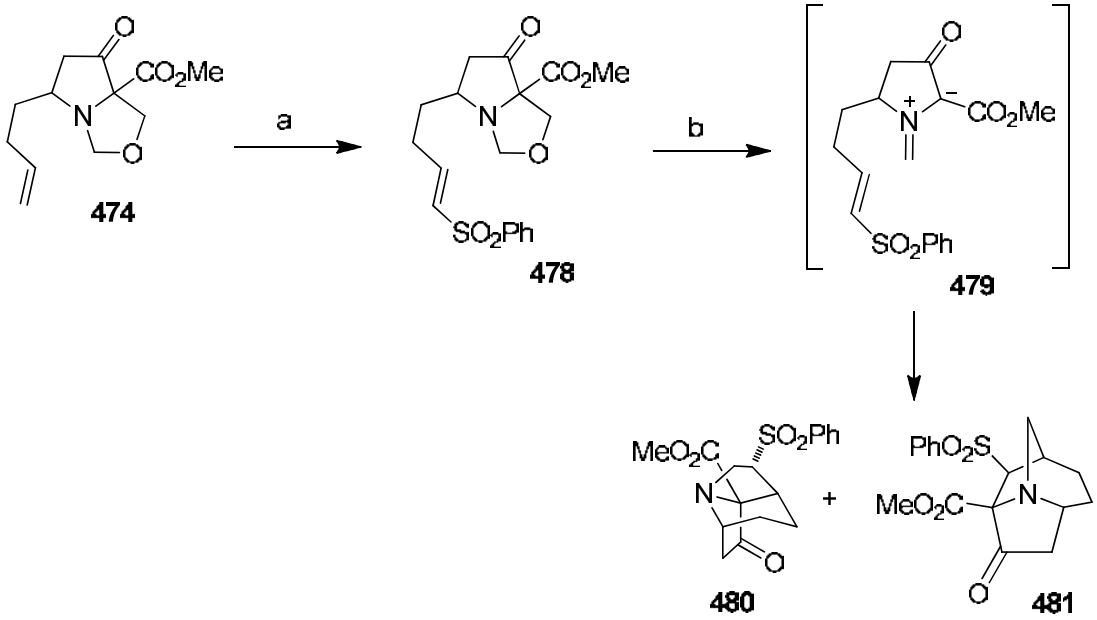
pyrrolidinone **473** with CF_3CO_2H and dimethoxymethane. This was attempted due to previous literature reports that azomethine ylides could be prepared by thermolysis of 2,2-unsubstituted oxazolidines. Thermolysis of oxazolidine **474** did indeed result in formation of the azomethine ylide **475**, which could then undergo cyclisation to give **476** and **477** (Scheme 161). Althought this method did give the tricyclic core of stemofoline the ratio of the products was not desirable with **477** being favoured over **476**. This is the reverse of that observed for the cyano product, where formation of **469** with the correct configuration was the major product.



Scheme 161 a) $(MeO)_2CH_2$ (10 equiv.), 10% CF3CO2H in CH_2Cl_2, rt, 7 h, 75%; b) 160 °C, PhMe, 96% (**476**:**477** 1:3)

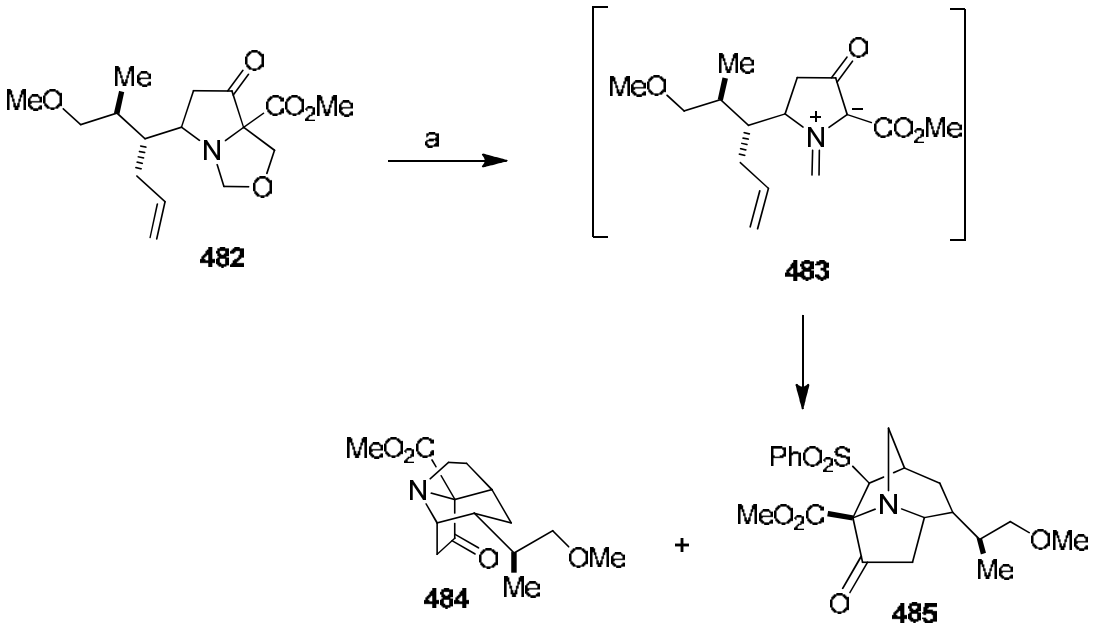
The reason behind this shift in selectivity was thought to partially be due to electronic factors. The oxazolidine **474** was further elaborated to contain a sulfone group, by reaction with vinyl sulfone to give **478**. This group is electron withdrawing so should make the dipolarophile electron deficient, resulting in a better match with the polarisation of the azomethine ylide and thus render the cyclisation more regioselective. Thermolysis of

478, led to production of the ylide **479** and then gave the expected two products **480** and **481**, but with little change in the ratio (Scheme 162).



Scheme 162 a) phenyl vinyl sulfone, Grubbs 2nd generation catalyst (5 mol%), CH_2Cl_2, reflux, 50%; b) 160 °C, PhMe, 97% (**480**:**481** 1:2)

As altering the electronic properties of the molecule did not result in the desired shift in regioselectivity, Martin and co-workers decided to concentrate on possible steric effects. This was done by installing a side chain, at the eventual C9 position of stemofoline. A series of reactions allowed for formation of the oxazolidine **482**, as a mixture of diastereomers. Application of the thermolysis conditions resulted in formation of the azomethine ylide **483**, which subsequently underwent cyclisation to give the two products **484** and **485** in a 1:1 ratio (Scheme 163). Although this is an improvement in regioselesctivity, it is still does not lie in favour of the desired product.



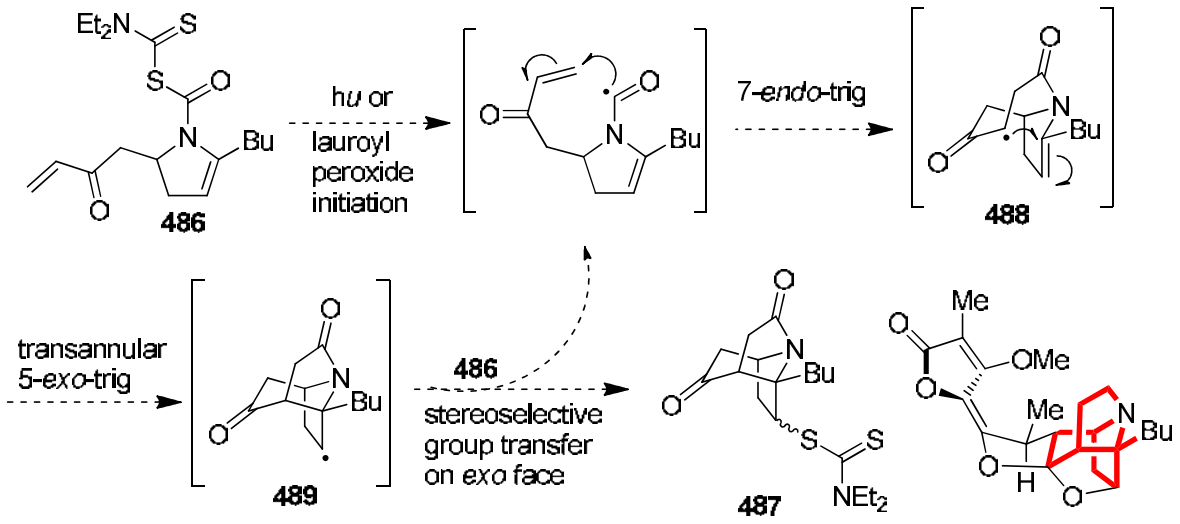
Scheme 163 a) 160 °C, PhMe, 95% (**484**:**485** 1:1)

In summary Martin and co-workers have been able to produce the tricyclic core of stemofoline, by generating enantomerically pure **484** in a 7% overall yield in 15 steps from a commercially available starting material. They use an azomethine ylides to facilitate an intramolecular 3+2 dipolar cycloaddition reaction to form the tricyclic system. If the selectivity of the dipolar cyclisation could be improved, this method may be useful in the synthesis of stemofoline and related alkaloids.

4.4 Previous Work in the Grainger Group Towards Stemofoline

Previous work in the Grainger group towards stemofoline focused on the synthesis of carbamoyl dithiocarbamate **486**. It was predicted that generation of the carbamoyl radical from **486** would result in a tandem 7-*endo*-trig cyclisation, 5-*exo*-trig transannular

cyclisation and group transfer of the dithiocarbamate to give the tricyclic system **487**, analogous to the tricyclic core of stemofoline.[145]

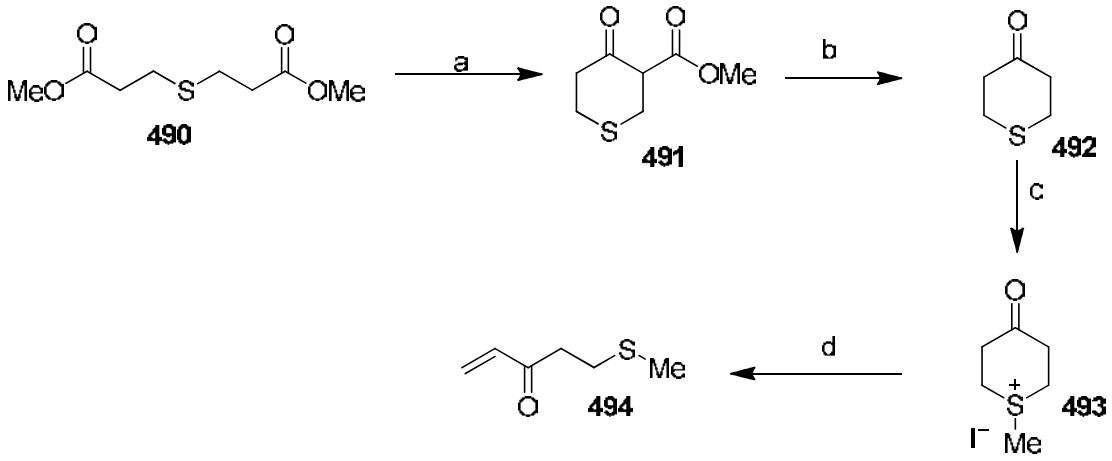


Scheme 164 Proposed route to the tricyclic core of stemofoline

It was postulated that the 7-*endo*-trig cyclisation pathway would be followed, as opposed to the 6-*exo*-trig, due to the carbamoyl radical preferentially reacting at the less hindered end of the electron deficient alkene. This 7-*endo*-trig cyclisation is also electronically preferred, with the nucleophillic carbamoyl radical adding to the most electron deficient end of the alkene. The carbon centred secondary radical **488** can then undergo a 5-*exo*-*trig* cyclisation onto the enamide double bond to give a new secondary radical **489**. Dithiocarbamate group transfer should then give the tricylic system **487** which has the butyl side chain of stemofoline already in place. The presence of the dithiocarbamate moiety in **487** should allow further elaboration towards stemofoline (Scheme 164).

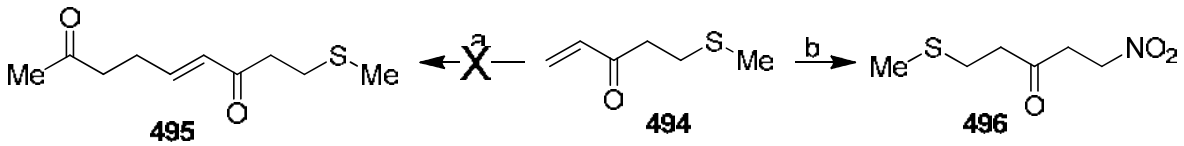
The first route investigated into the synthesis of the cyclisation precursor, commenced with a Deickmann condensation of dimethyl 3,3-thiodipropionate (**490**) with sodium

methoxide giving the dicarbonyl compound **491**. This was converted to the tetrahdrothiopyranone **492** by inducing decarboxylation by heating in refluxing aqueous acid.[146] Treatment of **492** with iodomethane gave the sulfonium salt **493**, which upon reaction with Hunig's base gave the conjugated enone **494** (Scheme 165).



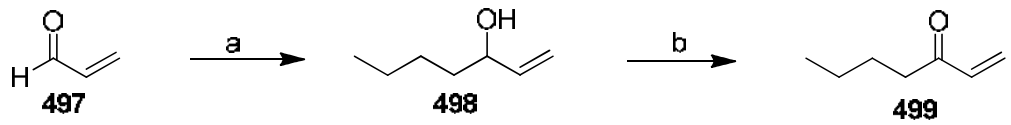
Scheme 165 a) NaOMe, THF, RT, 4h, 92%; b) H_2SO_4 (10%), reflux 1h, 80%; c) MeI (20 equiv.), RT, 3 d, 93%; d) DIPEA (3 equiv.), MeCN/H_2O (9:1), RT, 2 d, 78%

A cross metathesis reaction of **494** with 5 hexen-2-one was unsuccessful, with none of the desired **495** compound being observed. This was put down to the lone pair of the sulfur interacting with the ruthenium at the centre of the metathesis catalyst, thus poisoning it. As this route towards stemofoline now seemed inaccessible, an alternative route involving a 1,4-conjugate addition was looked into. The enone **494** was reacted with sodium nitrate and acetic acid to give β-nitro ketone **496** (Scheme 166).[147]



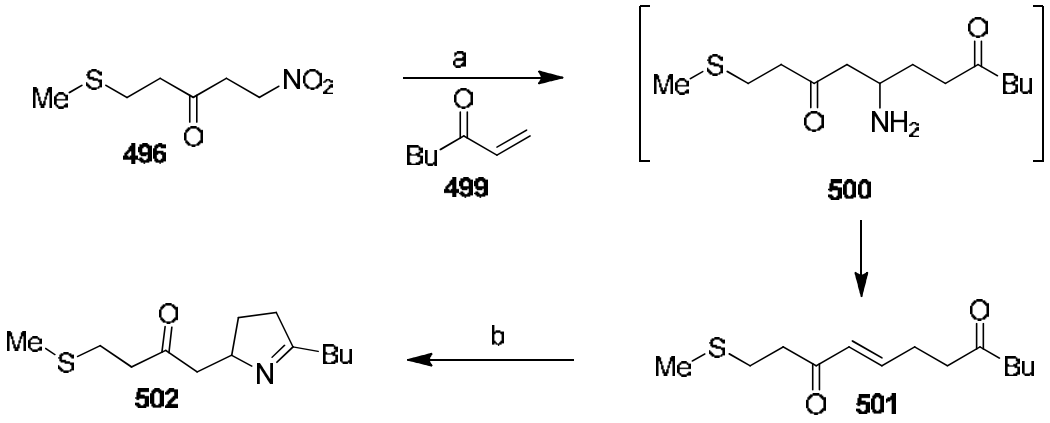
Scheme 166 a) 5-hexene-2-one, Grubbs II (5-10 mol%), CH_2Cl_2, reflux; b) $NaNO_2$ (2 equiv.), AcOH (2 equiv.), THF, RT, 2 d, 75%

In order to attempt the conjugate addition, to give first **501** and ultimately **502**, the butyl enone **499** was required. This was formed by first generating the butyl allylic alcohol **498** by treating the commercially available acrolein **497** with BuLi in THF. Oxidation with IBX in DMSO gave the required butyl enone **499** in 88% yield (Scheme 167).[148]



Scheme 167 a) BuLi, -78 °C, THF, RT, 16 h, 92%; b) IBX (2 equiv.), DMSO, RT, 3h, 88%

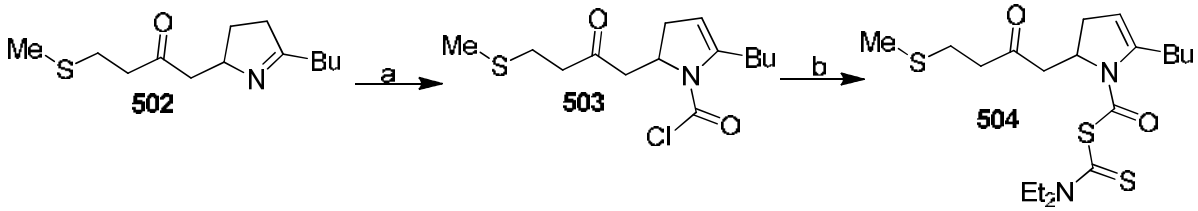
The reaction of butyl enone **499** with the β-nitro ketone **496**, produced first the intermediate **500**, from a 1,4 Michael addition of the nitronate anion onto the enone. This intermediate undergoes rapid loss of HNO_2, giving the observed enone **501**. Reacting this with ammonia led to addition of the ammonia onto the enone and immediate cyclisation to give the butylimine **502** (Scheme 168).



Scheme 168 a) basic Al_2O_3 (40 equiv.), CH_2Cl_2, rt, 16h, 15%; b) NH_3 (aq), MeOH, rt, 16h, 88%

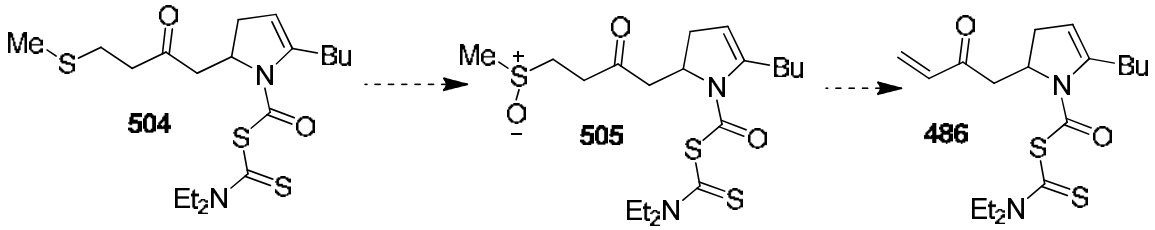
Although the conversion of **496** to **501** was low yielding, all attempts at improving this by altering the base were unsuccessful. This route towards the cyclisation precursor was continued with the hope of being able to test the key cyclisation-group transfer reaction.

The cyclic imine **502** was treated with triphosgene and pyridine to give the corresponding carbamoyl chloride **503**. The chloride was displaced with sodium diethyldithiocarbamate trihydrate salt by heating in acetone for 4 hours to give the carbamoyl dithiocarbamate **504** in a 44% isolated yield over the two steps (Scheme 169).



Scheme 169 a) triphosgene (0.33 equiv.), Py (1.5 equiv.) toluene, RT, 16 h; b) sodium diethyldithiocarbamate trihydrate(4 equiv.), acetone, reflux 44%

In order to convert **504** to the cyclisation precursor **486**, attempts were made to oxidise the sulfide to the sulfoxide **505** and then eliminate to give the desired product. The use of mCPBA, $NaIO_4$ and DMDO as the oxidants all gave the same result, that being a complex mixture of unidentifiable products (Scheme 170).

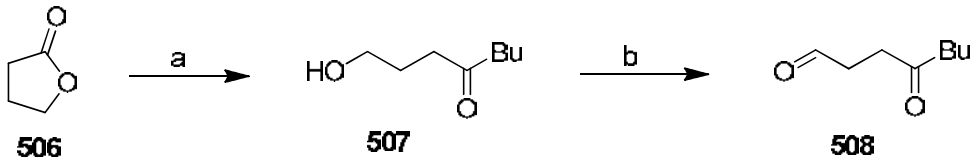


Scheme 170 Proposed formation of cyclisation precursor

With this route proving ineffective an alternative method of synthesising **486** was attempted, with the key step being a Wittig olefination. It was envisaged that this route might be more successful as the somewhat sensitive dithiocarbamate group would be

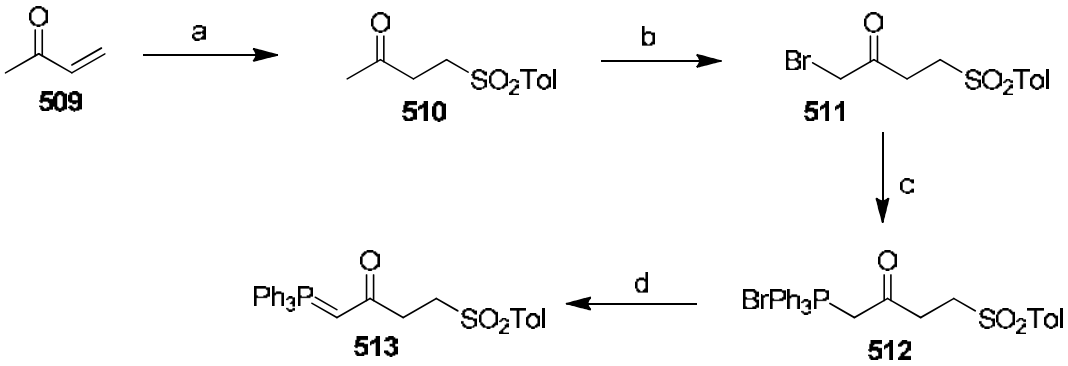
introduce in the last step of the sequence. The coupling of a triphenylphosphonium ylide with a dicarbonyl species was required to produce an enone via the Wittig olefination.

The dicarbonyl species **508** was prepared in two steps from the commercially available γ-butyrolactone **506**. Treatment of **506** with BuLi resulted in ring opening to give alcohol **507**,[149] which was subsequently oxidised to the ketone **508** under Swern conditions (Scheme 171).[150]



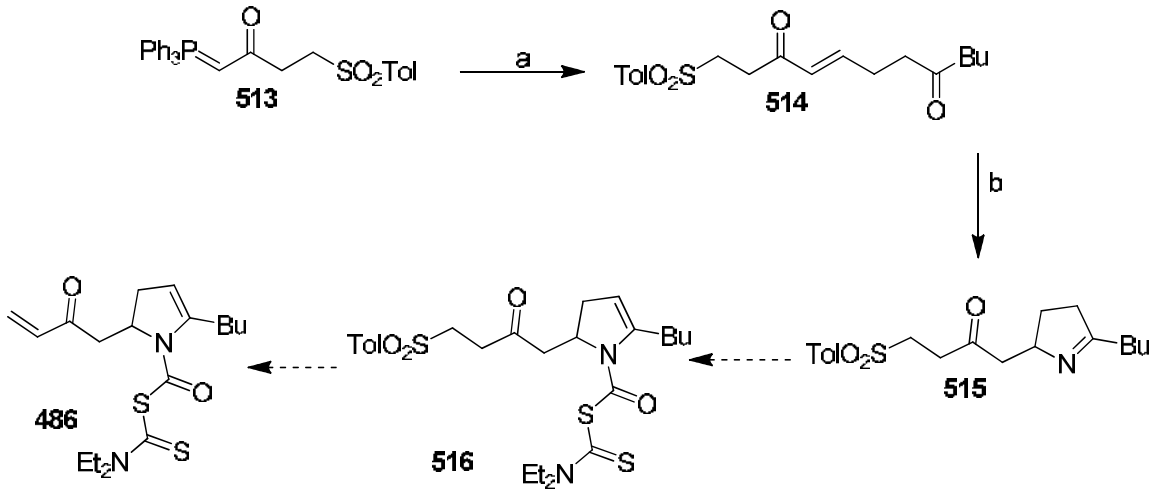
Scheme 171 a) BuLi, Et_2O, -78 °C to RT, 16 h, 65%; b) DMSO (2 equiv.), $(COCl)_2$, Et_3N, CH_2Cl_2, -78 °C, 16%

The phosphonium ylide **513** was synthesised by the initial addition of methyl vinyl ketone **509** with sodium tosylate hydrate to give the β-tosyl ketone **510**.[151] This was followed by bromination of the ketone with pyridinium perbromide to give **511**.[152] Formation of the bromide salt **512** followed by deprotonation with sodium hydroxide gave the phosphonium ylide **513** in a high yield (Scheme 172).[153]



Scheme 172 a) a) $NaSO_2Tol$, THF, RT, 16 h, 90%; b) $PyHBr_3$, AcOH, 70 °C, 16 h, 45%; c) PPh_3, toluene, 40 °C, 6 h, 87%; d) NaOH, MeOH, 0 °C, 30 min, 95%

The Wittig olefination of **513** and its coupling partner **508** led to formation of the enone **514** in 67% yield. However attempts to further elaborate this structure towards the cyclisation precursor did not succeed. Treatment with aqueous ammonia in methanol led to decomposition rather than production of butyl imine **515**. This meant that the carbamoyl dithiocarbamte **516** could not be formed. Tosyl elminiation of this should have resulted in the cyclisation precursor **486** (Scheme 173).

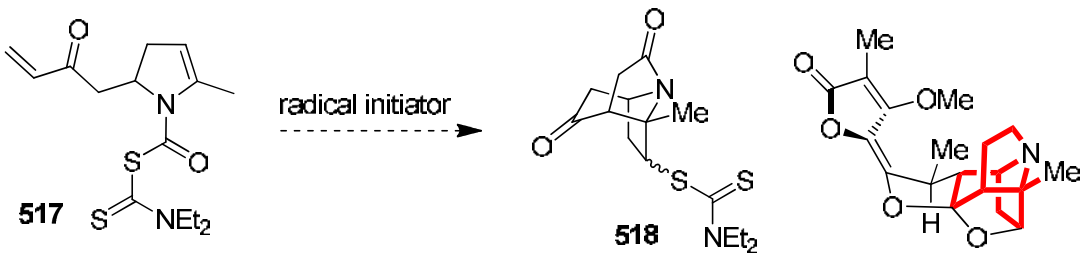


Scheme 173 a) **508**, toluene, 70 °C, 4 d, 67%; b) NH_3, MeOH, RT, decomposition

In summary, the work completed up to this point in the Grainger group had not yielded the tricyclic core of stemofoline. However significant progress had been made towards the synthesis of the cyclisation precursor. If this precursor could be synthesised, this would provide a novel tandem cyclisation group transfer reaction to give the tricyclic core of stemofoline and related alkaloids.

4.5 Aims and Objectives

With initial studies towards stemofoline, within the group, having failed to provide the tricyclic core (Scheme 164), the aim of this project was to find an alternative route into the cyclisation precursor **486**. If this could be achieved then further elaboration towards stemofoline would be attempted. The isolation of methylstemofoline in 2005, provided another synthetic target,[127] with no need to introduce a butyl group. The formation of the tricyclic core of methylstemofoline **518**, would require a tandem 7-*endo*-trig, 5-*exo*-trig, group transfer reaction of the cyclisation precursor **517** (Scheme 174).

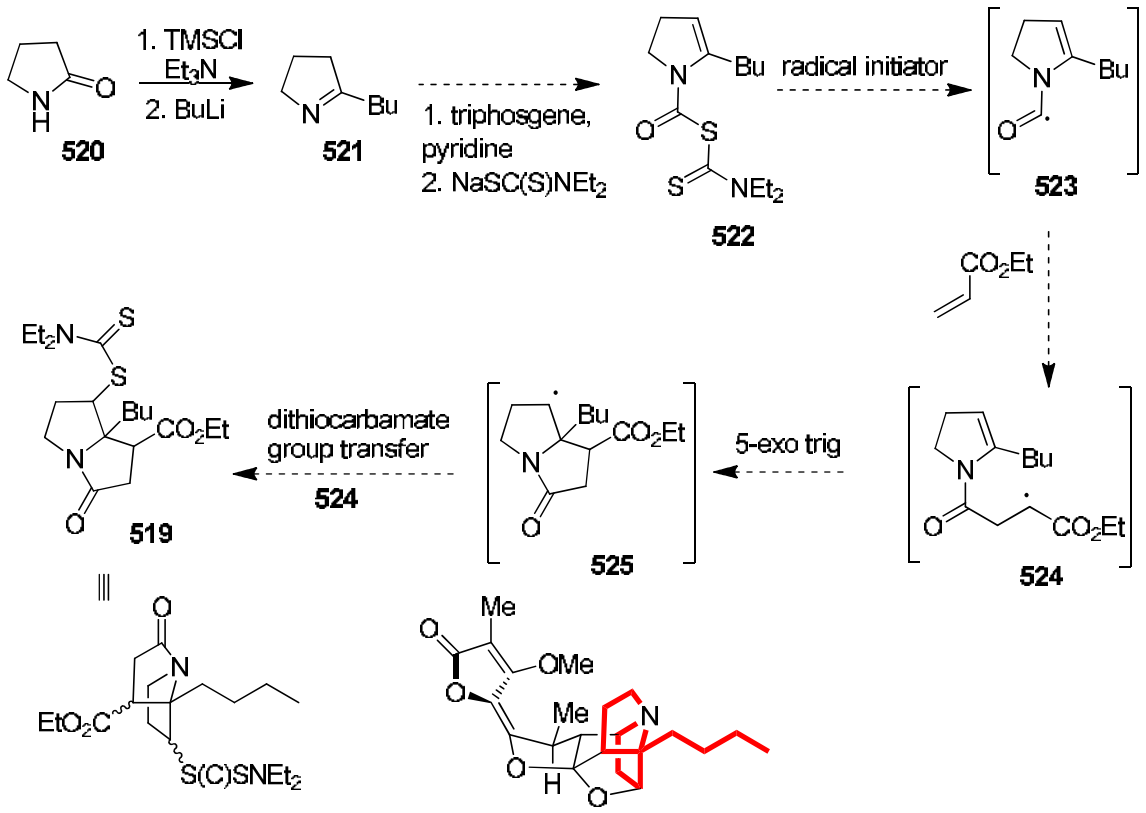


Scheme 174 Proposed route to the tricyclic core of methylstemofoline

With the inherent difficulties in the production of the cyclisation precursor alternative approaches towards stemofoline will also be undertaken. In this case the bicyclic system **519** would be obtained, with the intention of carrying out further chemistry on this to produce stemofoline. The proposed synthesis of this bicycle begins with the *N*-silylation of the commercially available pyrrolidine **520**, which upon reaction with BuLi should give the butylpyrroline **521**.[154]

Application of conditions previously developed within the group should allow formation of the dithiocarbamate **522**. The carbamoyl radical **523** should be produced using either a

chemical radical initiator or a light source. An intermolecular addition reaction of the carbamoyl radical with ethylacrylate would generate the carbon centred secondary radical **524**. It is proposed that this will be followed by a 5-*exo-trig* cyclisation, giving intermediate radical **525**, which upon group transfer of the dithiocarbamate will yield the bicyclic system **519** (Scheme 175).



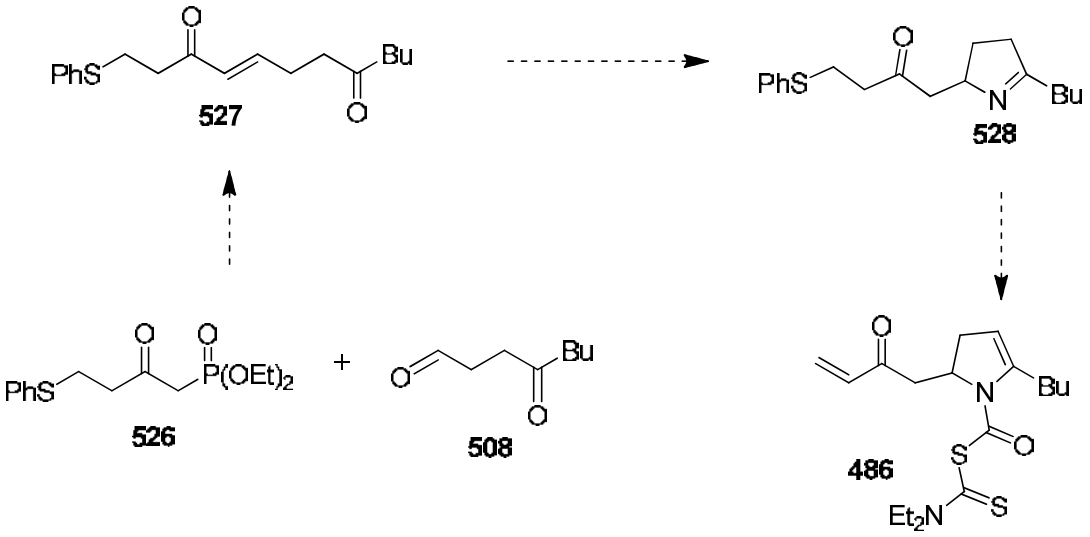
Scheme 175 Proposed formation of the bicyclic fragment of stemofoline

4.6 Studies Towards the Tricyclic System

4.6.1 Horner-Wadsworth-Emmons Approach

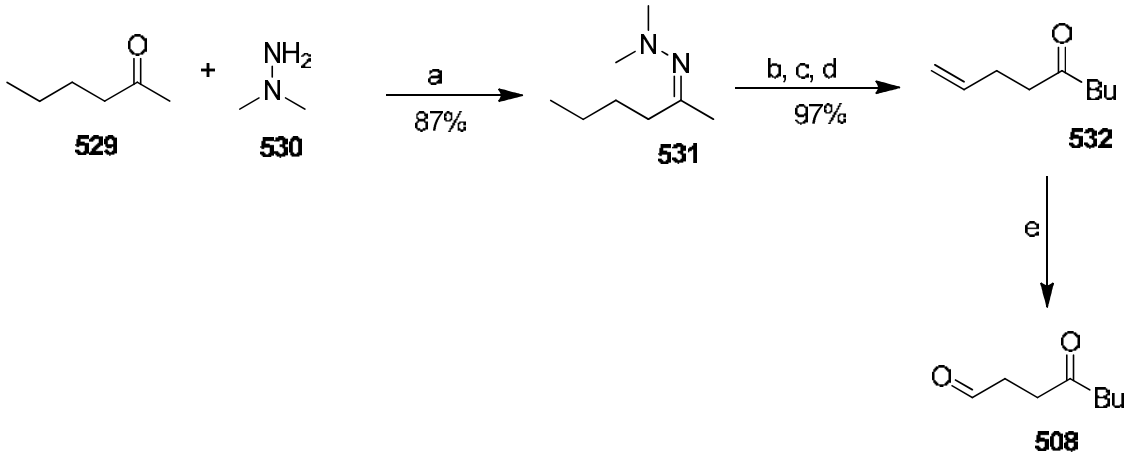
In order to create the cyclisation precursor **486**, studies began with the synthesis of enone **527** via a Horner-Wadsworth-Emmons type reaction of coupling partners

phosphonate **526** and keto-aldehyde **508**. Once formed, it should be possible to convert enone **527** to the butylimine **528** by treatment with aqueous ammonia in methanol. Subsequent dithiocarbamate formation and elimination of the thiophenol would give the cyclisation precusor **486** (Scheme 176).



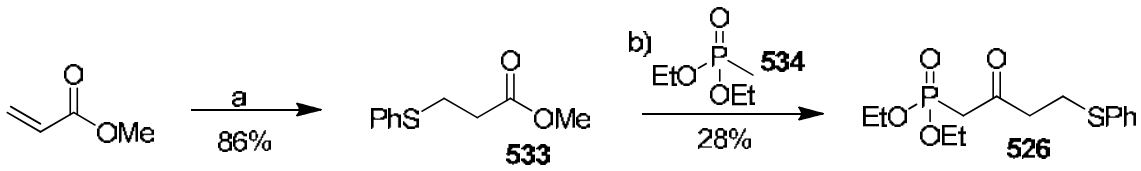
Scheme 176 Proposed formation of cyclisation precursor using a Horner-Wadsworth-Emmons reaction as the key step

The synthesis of keto-aldehyde **508** had already been described within the group, albeit in a poor yield. As such an alternative route into this was developed. The reaction of the commercially available 2-hexanone **529** with dimethylhydrazine **530** in refluxing ethanol gave the corresponding hydrazine **531**. Allylation of this with allybromide, followed by removal of the hydrazine group using copper chloride gave the alkene **532** in a pleasing 97% yield. Oxidation of this using O_3 gave the keto-aldehyde **508** in 98% yield (Scheme 177). The overall yield for the synthesis of the **508** has thus been significantly improved.



Scheme 177 a) EtOH, reflux, 18 h, 87%; b) BuLi, THF, 0 °C, 40 mins; c) allylbromide, 0 °C to RT, 16 h; d) $CuCl_2$, H_2O, 2.5 h, 97%; e) O_3, CH_2Cl_2:MeOH, 98%

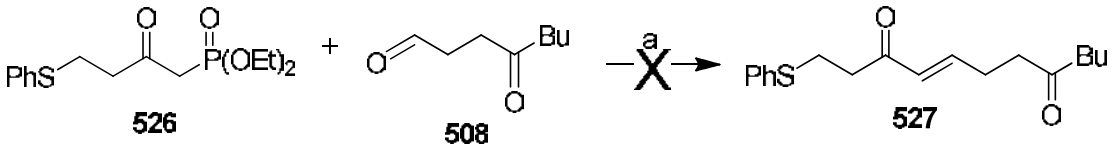
Formation of the coupling partner **526** was achieved by the reaction of methylacrylate with thiophenol in the presence of pyridine to give **533**. Treatment of this with *n*-BuLi followed by diethylmethylphosphonate **534** gave the desired keto-phosphonate **526** in a modest yield of 28% (Scheme 178). Although the unpurified compound appeared to be clean all attempts to remove any slight impurities by column chromatography were unsuccessful. As such the compound was used crude.



Scheme 178 a) PhSH, Py, RT, 1.5 h, 86%; b) *n*-BuLi, 487, -78 °C to RT, 3h, 28%

With the keto-phosphonate **526** in hand, a Horner-Wadsworth-Emmons type reaction was attempted onto the keto-aldehyde **508**. Sodium hydride was used to deprotonate the phosphonate and the resulting anion was reacted with the aldehyde. However this resulted in no observable reaction. Due to the problems with purification of **526** and the

instability of the aldehyde **508** the starting materials could not be separated from the reaction mixture, although they appeared to be unchanged (Scheme 179). The reaction was repeated using a range of different bases including KO*t*-Bu in THF, MeMgBr in THF and DBU in MeCN. None of these conditions led to the production of **527**. This prevented any further attempts at synthesising stemofoline via this route.



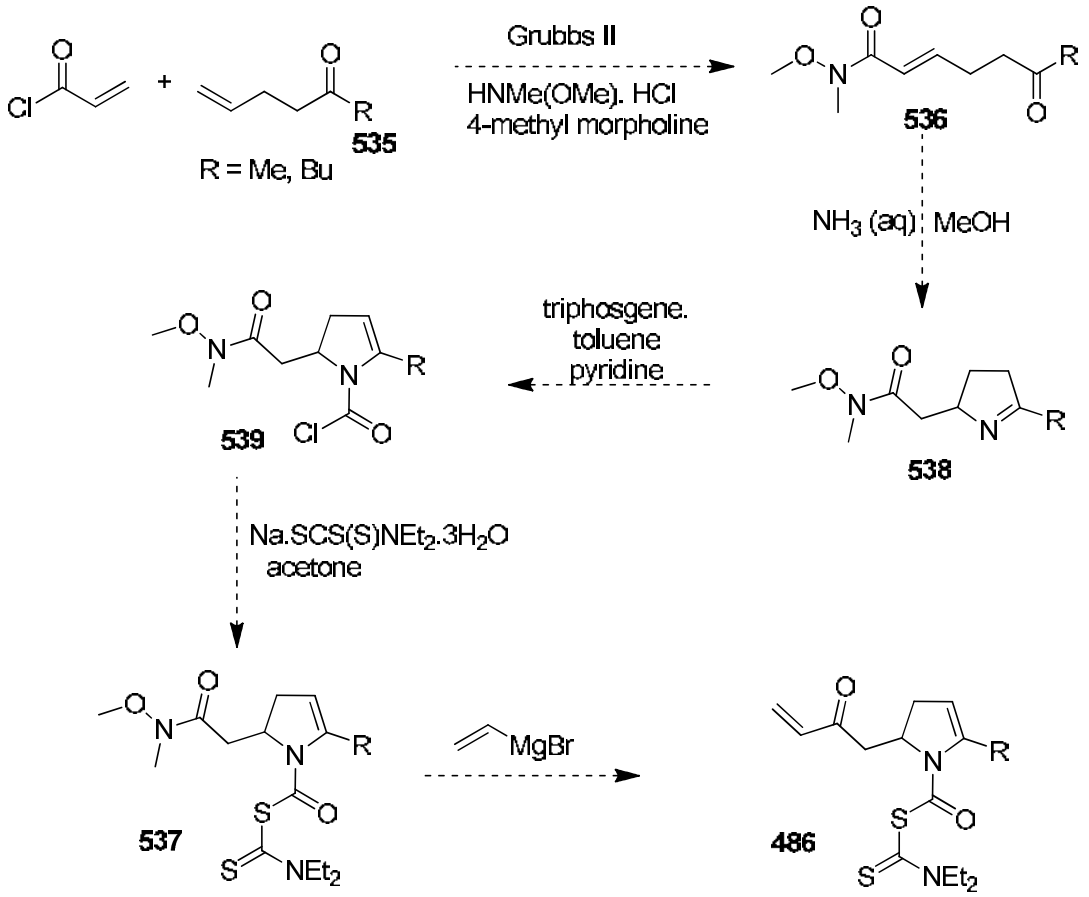
Scheme 179 a) NaH, THF, 2h, 0 °C

4.6.2 Cross-Metathesis Approach

The 2009 report from the Cossy research group on the use of acryloyl chloride as a substrate for cross-metathesis to give α,β-unsaturated carbonyl derivatives[155] led to the idea of using a cross-metathesis in pursuit of the cyclisation precursor needed to from the tricyclic core of stemofoline. This route could potentially be used to synthesise stemofoline or methylstemofoline as the side-chain (butyl in the case of stemofoline) is present from the very start of the synthesis.

A cross metathesis of acryloyl chloride with the alkene **535** would be expected to produce the enamide **536**, which would form upon addition of the alkoxyamine to the intermediate acyl chloride compound. Application of the conditions previously developed within the group should allow access to the dithiocarbamate **537**, via treatment of **536** with aqueous ammonia in methanol to give the pyrroline **538**. This would be followed by reaction with triphosgene to give the carbamoyl chloride **539** and

subsequent treatment with sodium diethyldithiocarbamate trihydrate should give **537**. Reaction of this with vinylmagesium bromide should then afford the cyclisation precursor **486** (Scheme 180).



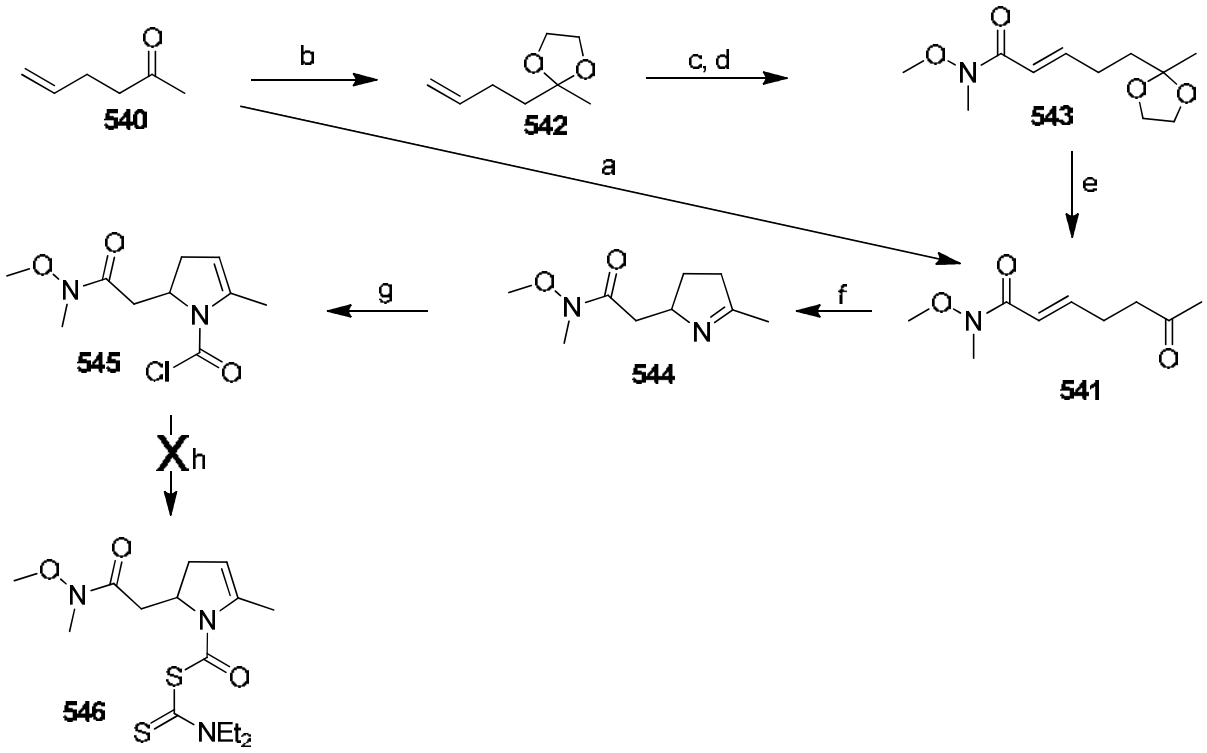
Scheme 180 Proposed access to the cyclisation precursor using cross metathesis as the key step

Studies on this proposed route to the cyclisation precursor began with the use of 5-hexen-2-one **540**, due to this alkene being commercially available. To create stemofoline, as opposed to methylstemofoline, the reaction sequence would begin with the use of alkene **532**, the synthesis of which having previously been achieved in high yield (Scheme 177).

Reaction of **540** with acryloyl chloride in the presence of the Grubbs 2nd generation catalyst, followed by treatment with the alkoxyamine, provided the desired enamide **541**, but in very low yields of 10%. This poor yield was ascribed to the lone pairs of the oxygen of the ketone interacting with the ruthenium of the catalyst, resulting in the catalyst being effectively poisoned. In order to increase the yield, it was decided to protect the ketone fragment as an acetal, hopefully preventing it from poisoning the catalyst. The protection was carried out by reaction of ethylene glycol with **540** under Dean-Stark conditions in the presence of *p*-toluenesulfonic acid, resulting in the protected ketone **542**. Reaction of **542** with acryloyl chloride under cross-metathesis conditions gave the expected enamide **543** in a much improved 83% yield. This product was formed as a result of the addition of dimethyldihydroxylamine hydrochloride to the intermediate acyl chloride that is formed upon the reaction of acryloyl chloride with the alkene **543**. The ketone **541** was formed by heating **543** in the presence of acid to remove the protecting group. Although this requires two extra steps, the yields are all reasonable, making the overall yield of the transformation of **540** to **541** much improved (Scheme 181).

The reaction of **541** with aqueous ammonia in methanol gave the pyrroline **544**. The formation of the dithiocarbamate **546** was attempted by first creating the carbamoyl chloride **545**. This was done by treatment of **544** with triphosgene and pyridine in toluene. Carbamoyl chlorides of this type are known to be unstable and as such this intermediate was reacted immediately, after a simple aqueous work up, with sodium deithyldithiocarbamate trihydrate. Unfortunately the dithiocarbamate **546** was not observed, with only a mixture of unidentifiable products being obtained (Scheme 181). Full analysis data on the carbamoyl chloride was not available due to the product

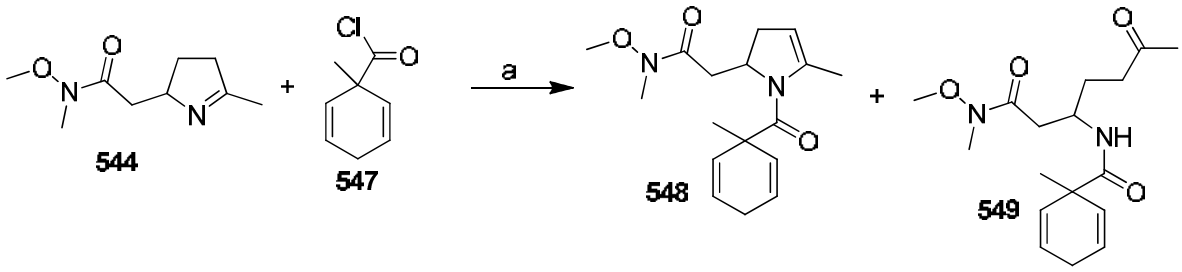
breaking down before analytical techniques could be carried out, however the data that was obtained suggested that the carbamoyl chloride has been successfully synthesised and the problem lies in the formation of the dithiocarbamate.



Scheme 181 a) acryloyl chloride, Grubbs 2nd generation catalyst (5 mol%), CH_2Cl_2, reflux 36h, then HNMe(OMe).HCl, RT, 2h, 10% over 2 steps; b) *p*-toluenesulfonic acid, toluene, ethylene glycol, reflux, 16h, 59%; c) acryloyl chloride, Grubbs 2nd generation catalyst (5 mol %), CH_2Cl_2, reflux, 40h; d) HNMe(OMe).HCl, RT, 2h, 83% over 2 steps; e) AcOH, MeOH, reflux, 14h, 99%; f) MeOH, NH3 (aq), rt, 18h, 90%; g) toluene, triphosgene, pyridine, RT, 16h, 70%; h) sodium diethyldithiocarbamate trihydrate, acetone, RT, 24h

With this route providing access to **544** in reasonable yields, it was decided to attach a different group, other than the carbamoyl dithiocarbamate, to provide a source of the carbamoyl radical. The use of esters of 1-methylcyclohexa-1,5-diene-1-carboxylic acid as a source of carbamoyl radicals is known and has been discussed in chapter 1. These are formed from the reaction of an amine with 3-methylcyclohexa-1,4-diene-3-carbonylchloride **547**. The reaction of imine **544** with the carbonyl chloride in the

presence of triethylamine and DMAP, did not give the expected product **548**. Instead the ring opening hydrolysis product **549** was cleanly isolated from the reaction mixture in 60% yield (Scheme 182). Attempts were made to cyclise **549** to **548** by removal of water, but all efforts to this end proved to be unsuccessful.

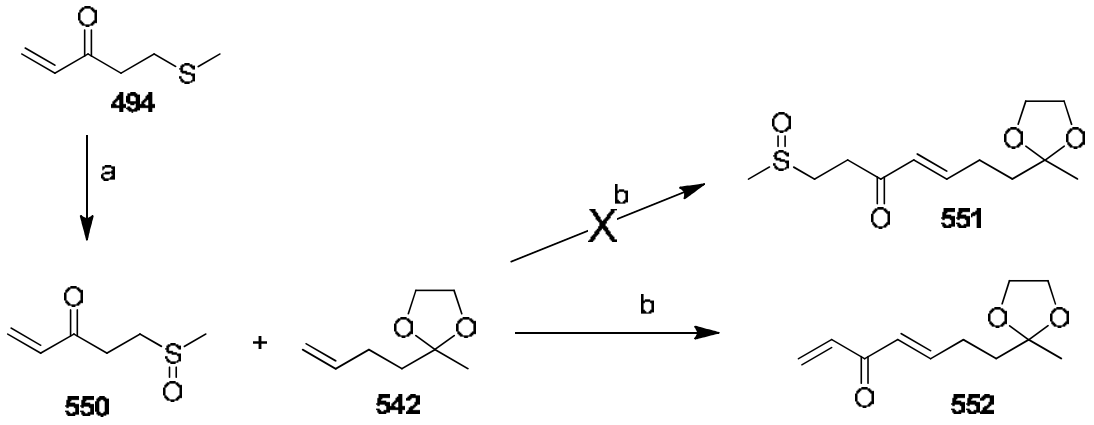


Scheme 182 a) CH_2Cl_2, DMAP, Et_3N, 18 h, reflux, **549** 60%

4.6.3 Sulfur Cross-Metathesis Approach

The pleasing results from the cross metathesis of the acetal protected 5-hexene-2-one with acryloyl chloride prompted the revision of an early route towards the cyclisation precursor that had not been progressed due to problems with the cross metathesis step. Previous work within the group had revealed the reaction of 5-hexen-2-one with the sulfur containing enone **494** gave no reaction.[145] With both the lone pairs of the ketone in 5-hexen-2-one and the sulfur of the enone being able to poison the metathesis catalyst, this observation is perhaps not unexpected. It was postulated that if these two functional groups could be masked during the cross metathesis reaction, the result may be more favourable. The protection of 5-hexen-2-one has already been shown to give a dramatic increase in yield of the cross-metathesis with acryloyl chloride.

A route to the enone **494** had already been established. This was converted to the sulfoxide **550** by oxidation with sodium metaperiodate. Reaction of **550** with **542** in the presence of Grubbs' 2nd generation catalyst did not afford the expected enone **551**. Instead **552** was isolated as a pale yellow oil (Scheme 183).



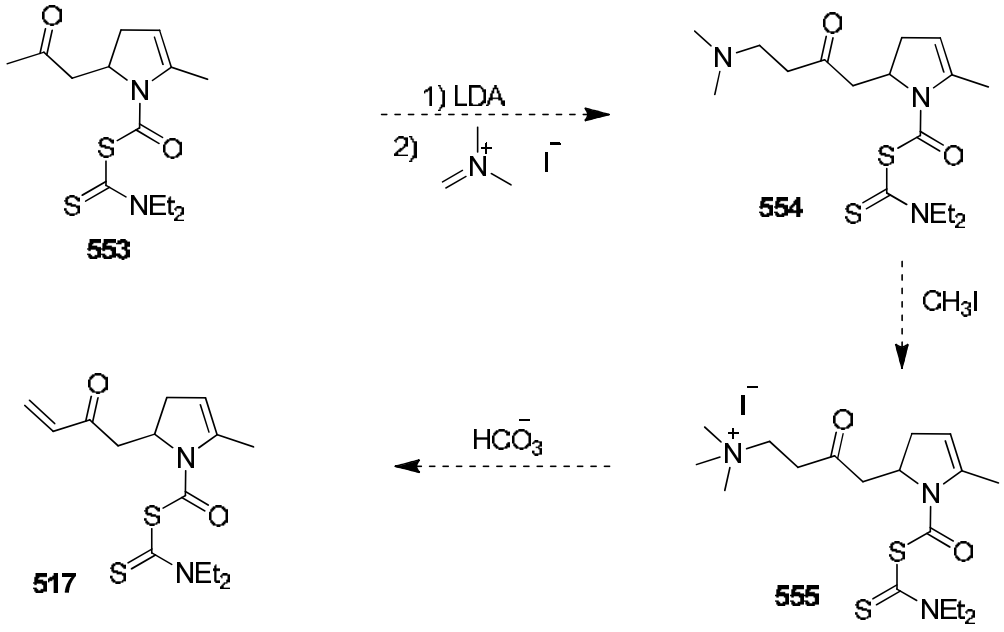
Scheme 183 a) sodium metaperiodate, MeOH:H_2O 9:1, 0 °C 4h, RT, 14h, 42%; b) Grubbs' 2nd generation catalyst; CH_2Cl_2 reflux, 72h, 60%

Refluxing **550** in CH_2Cl_2 led to loss of the sulfoxide, showing that **550** was not stable to the reaction conditions used for the cross-metathesis. Unfortunately heat is required for the cross-metathesis reaction, with all attempts at running the reaction at lower temperatures giving no product. The loss of the sulfoxide, observed in this reaction, meant that work on this route towards stemofoline was short lived.

4.6.4 Mannich Reaction Approach

The synthesis of dithiocarbamate **553**, had previously been undertaken in the group as a test system to show the reactivity of imines towards triphosgene to give carbamoyl chlorides and subsequent reaction with sodium diethyldithiocarbamate. Originally there were no attempts to further elaborate this molecule, due to the side chain being a methyl

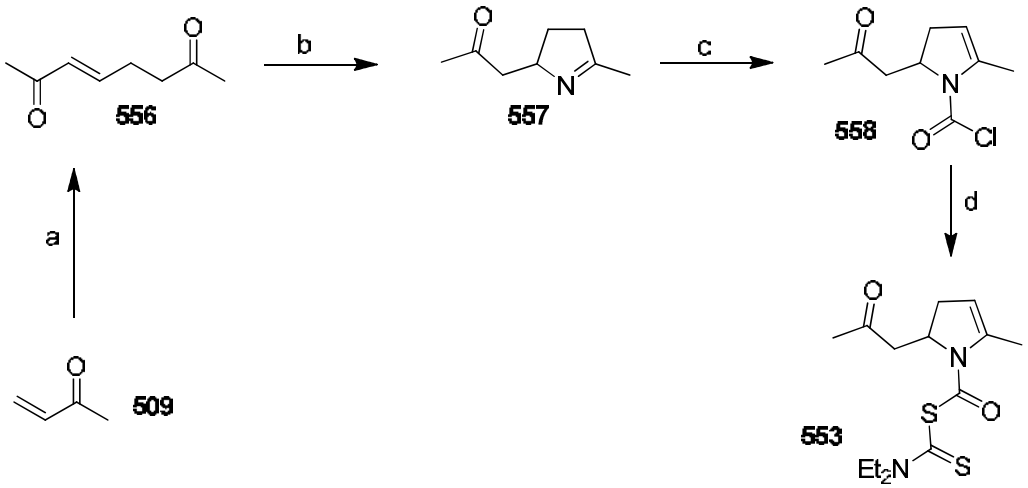
group as opposed to the butyl group seen in stemofoline. However now that methylstemofoline has become a target, further elaboration of this molecule could provide access to the cyclisation precursor **517**. A Mannich reaction of **553** with an imine salt should give the β-aminoketone **554**. Reaction of this with methyl iodide should produce the iodide salt **555**, and subsequent treatment with a base should then afford the cyclisation precursor **517** (Scheme 184).



Scheme 184 Proposed use of a Mannich reaction to give cyclisation precursor **517**

The synthesis of **553** was achieved by treating methyl vinyl ketone **509** with sodium nitrate and acetic acid to induce dimerisation to the diketone **556**. Reaction of **556** with aqueous ammonia in methanol gave the cyclic imine **557**. Acylation of this imine was achieved by reaction with triphosgene in the presence of excess pyridine in toluene to give the carbamoyl chloride **558**. Treatment with sodium diethyldithiocarbamate

trihydrate in refluxing acetone resulted in displacement of the chloride to give the dithiocarbamate **553** in 63% yield over 2 steps (Scheme 185).



Scheme 185 a) acetic acid, $NaNO_2$, DMSO, RT, 16 h, 80%; b) NH_3 (aq), MeOH, RT, 16 h, 93%; c) triphosgene (0.33 equiv), pyridine, toluene, 16 h, RT; d) sodium diethyldithiocarbamate trihydrate, acetone, reflux 2h, 63% over 2 steps

With dithiocarbamate **553** in hand, attempts towards its conversion to the cyclisation precursor **517** were undertaken. However reaction of **553** with *N,N*-dimethylmethyleneiminium iodide and subsequent reaction with methyl iodide did not occur as expected, with degradation being observed. Initial attempts involved a one pot synthesis of **555**, however due to only observing a complex mixture of unidentifiable products, the product of reaction of **553** with *N,N*-dimethylmethyleneiminium iodide was isolated. This revealed that the formation of **554** was the problematic step in this route. Despite numerous attempts to form **554** its synthesis could not be achieved, making this route redundant.

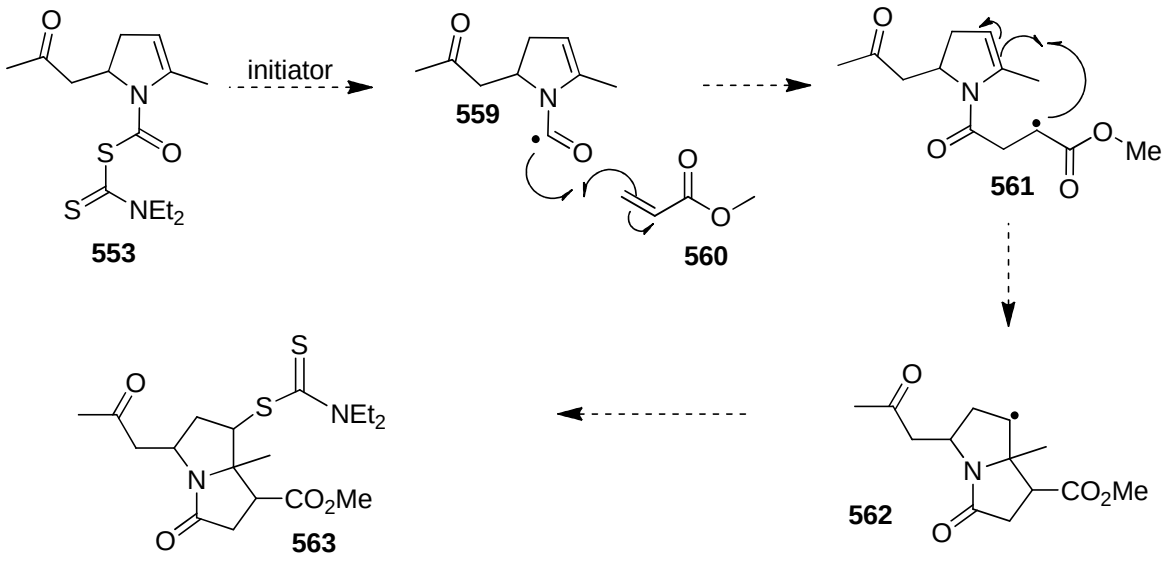
4.7 Studies Towards the Bicyclic System

With the synthesis of cyclisation precursors for the formation of the tricyclic core currently proving elusive, it was decided to look into the possibility of forming the bicyclic system. As the formation of dithiocarbamate **553** had already been achieved, the possibility of forming bicyclic systems via a tandem intermolecular addition-cyclisation reaction was investigated.

The initiation of **553**, using either a chemical initiator or a light source, should result in formation of the carbamoyl radical **559**. This can then react with methylacrylate **560** to give the carbon-centred secondary radical **561**. The intramolecular reaction of the carbamoyl radical **559** onto the enamide double bond is unlikely to occur as the bond angles are unfavourable and the resultant bicyclic system would be unstable. Radical **561** can undergo an intramolecular reaction onto the alkene of the pyrroline system to form a new carbon-centred radical **562**. The resultant group transfer of the dithiocarbamate should furnish the desired dithiocarbamate **563** by reaction with another molecule of **553**, also generating another molecule of the carbamoyl radical **559**, thus completing a chain process (Scheme 186).

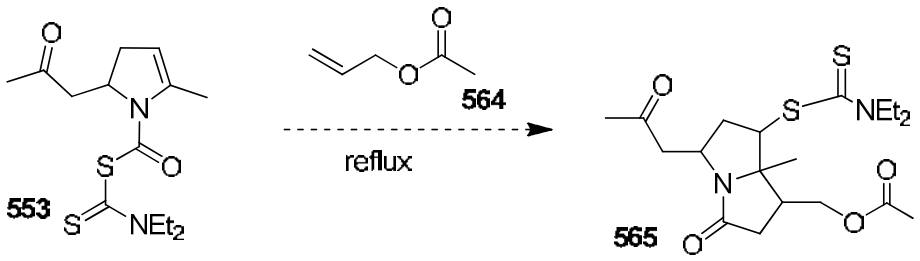
A solution of **553** and methylacrylate in cyclohexane was exposed to a 500W halogen lamp that generated enough heat to bring the solution to reflux. Ater 2 hours, no starting material remained, with only a complex mix of unidentifiable compounds being produced. Repeating the reaction using DLP as the initiator also resulted in degradation of the starting materials. As it is known that radicals can be generated from a 500W light source at room temperature, the reaction was repeated using a room temperature

photo-apparatus. This resulted in no observable reaction, indicating that in this case light alone was not enough to generate the initial carbamoyl radical **559**.



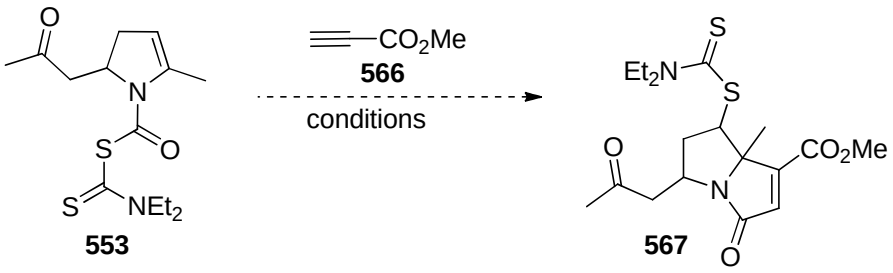
Scheme 185 Proposed route to the bicylic dithiocarbamate **563**

Attention then switched to the possibility of using allylacetate **564** as the coupling partner in this reaction to give **565** (Scheme 186). Dithiocarbamate **553** was dissolved in allylacetate and the resultant solution exposed to the 500W halogen lamp. When carried out at reflux the reaction mixture again led to a mixture of unidentifiable products. The same result was observed when using the chemical initiator DLP. The use of photochemistry at room temperature led to some observable degradation after many hours, with starting material also being present.



Scheme 186 Proposed reaction to give **565**

Due to the lack of any identifiable products arising from the intermolecular reaction of **553** on to alkenes, it was decided to investigate the possibility of reacting alkynes. The dithiocarbamate **553** and methylpropiolate **566** were dissolved in cyclohexane and the resultant solution exposed to the light of a 500W lamp, which generated enough heat to bring the solution to reflux. This led to degradation of the starting material, rather than production of the desired dithiocarbamate **567** (Scheme 187). Repeating the reaction using a room temperature photo-apparatus resulted in no reaction, as observed in all other previous attempts at reacting the carbamoyl radical **553**. The initiation of the reaction by use of DLP was also investigated and resulted only in the production of a complex mixture of products. Due to experiencing some problems with solubilising the mixture of **553** and **566** in cyclohexane, the use of chlorobenzene as the solvent was investigated. However it was discovered that dithiocarbamate **553** was unstable in chlorobenzene. A solution of **553** in chlorobenzene swiftly degraded when exposed to a 500W lamp, both at room temperature and also at reflux.

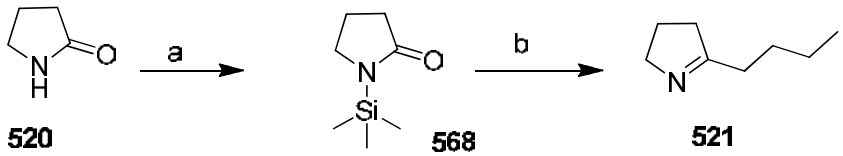


Scheme 187 Proposed reaction to give dithiocarbamate **567**

With the tandem intermolecular addition-intramolecular cyclisation-dithiocarbamate group transfer of **553** to the bicyclic core of methyl stemofoline not being fruitful, attention turned back towards the related synthesis of the bicylic core of stemofoline

(Scheme 175). The proposed synthesis for this involves formation of the dithiocarbamate **522**, which is a simplified version of **553**. It was thought that the presence of the ketone in **553** could be causing problems with the intermolecular addition and subsequent radical reactions. The simplified analogue **522** may have less competing pathways and should therefore have a higher chance of success.

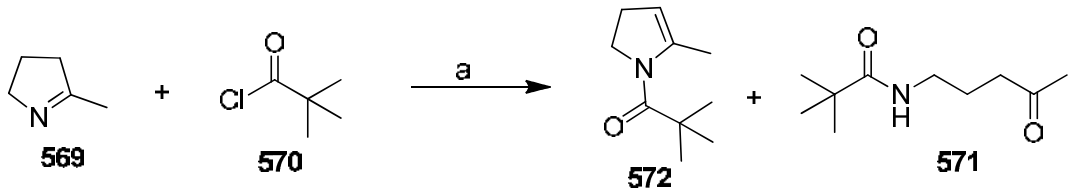
The synthesis began with formation of the TMS protected amide **568**, formed from the reaction of **520** with trimethylsilyl chloride in 72% yield, as reported in the literature.[154] The next step in this pathway, addition of the butyl group followed by an intramolecuar Peterson elimination, did afford the required dihydropyrrole **521** but in a very low yield of 3% (Scheme 188).



Scheme 188 a) trimethlsilylchloride, Et_3N, 60 °C, 2h, then RT, 17h, 72%; b) BuLi, -20 °C, 30 mins, RT, 1h

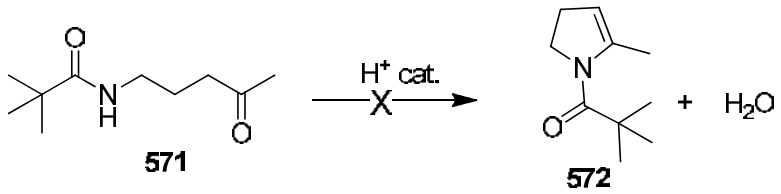
To investigate the reactions of this type of molecule with acid chlorides, pyrroline **569** was first reacted with the simple trimethylacetylchloride (**570**). Initial studies used pyridine as the base to initiate the reaction, followed by addition of the acetyl chloride at 0 °C. However, the product of this reaction was seen to be the hydrolysed compound **571** as opposed to the expected **572** (Scheme 189). The reaction was repeated using Et_3N as the base, and reaction times were lowered from 3.5 hours to 2 hours, but no change in the result was observed with yields only differing slightly (between 52 and 63%). The

formation of the desired **572** was only observed in a 2% yield, when the reaction was run at -78 °C, with an excess of the pyrroline.



Scheme 189 a) Et_3N, -78 °C to rt, 16 h, **572** 2%. **571** 73%

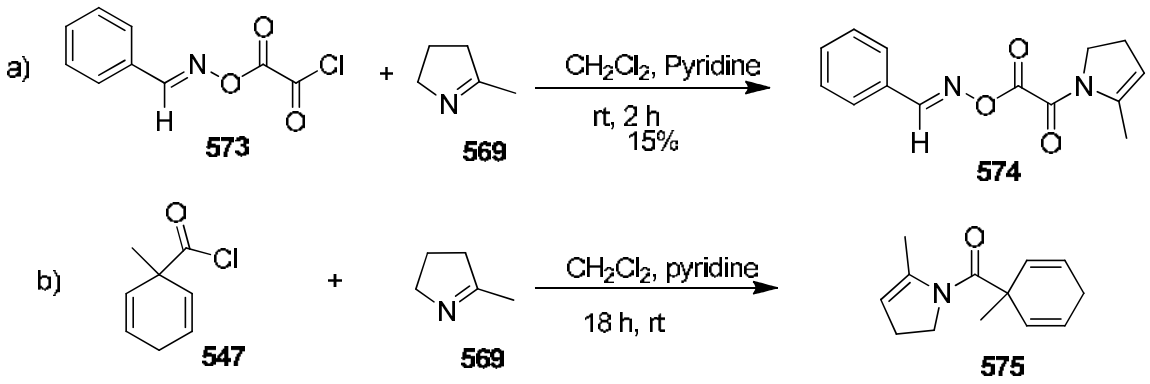
As large quantities of the ring opened form were readily available attempts to re-close the ring via a dehydration reaction were made. If the system is in equilibrium between the two states (**572** and **571**), removal of the water should force the equilibrium in favour of the cyclised product **572**. Therefore reactions were carried out by dissolving **571** in toluene, adding a catalytic amount of acid and heating to reflux, firstly in the presence of $MgSO_4$ and then under Dean-Stark conditions. Both of these sets of conditions led to no observable reaction (Scheme 190).



Scheme 190 Attempts at ring closure

Although the reactions with the simple acid chloride did not produce the desired results, the reactions of the pyrroline **569** with more complex acid chlorides **573** and **547** were investigated. These acid chlorides were chosen as they have been shown to add successfully to open chain amines, creating carbamoyl radical precursors.

The reaction of pyrroline **569** with the acid chloride **573** (Scheme 191, a) did give the desired oxime oxalate amide **574** as a mixture of 2 non-seperable isomers in a modest yield of 15%. The reaction of **569** with acid chloride **547** to give **575** was successful in an estimated 50% yield (Scheme 191 b). However problems with purification of this compound meant that the two isomers produced could not be separated from another impurity that was seen in the system.



Scheme 191 Reactions of pyrroline **569** with acid chlorides

Due to the associated problems with formation of acyl chlorides from the reaction of pyrroline **569** with various acid chlorides, namely the low yields and purification issues, this route towards stemofoline was not continued.

4.8 Conclusion

The work towards the synthesis of the tricyclic core of stemofoline alkaloids has been progressed inasmuch as various routes can now be eliminated. The problems associated with a number of different synthetic strategies have been exposed by this work. Attempts to synthesise the tricyclic precursor to stemofoline by a Horner-Wadsworth-Emmons approach were made. Cross metathesis reaction using acryloyl chloride appeared promising, however difficulties in the formation of the dithiocarbamate from the acid chloride were problematic. A cross metathesis onto the sulfoxide containing species was unsuccessful due to the starting material being unstable to reaction conditions.

Attempts at forming the bicyclic system seen in the core of stemofoline and methyl stemofoline were also made via an intermolecular addition. However when reactions did occur only complex mixtures were observed.

Chapter five

Experimental

General Experimental

All solvents and reagents were obtained from commercial sources and used as received with the following exceptions:

THF, toluene, CH_2Cl_2 and CH_3CN were dried by passing through activated alumina columns. Dry pyridine was obtained by stirring with CaH_2 followed by fractional distillation, and stored over Linde type 4Å molecular sieves.

Solvents were degassed by bubbling nitrogen or argon through a needle immersed in the solvent for the stated length of time. *n*-BuLi was purchased as either 2.5 M or 1.6 M solutions in hexanes and the solutions were titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene or 1,10-phenanthroline.

Unless otherwise stated all aqueous solutions used in work ups were saturated and all water used was deionised. All reactions in non-aqueous solutions were carried out under argon in oven-dried glassware. Reactions were monitored by analytical TLC. Room temperature generally indicates a reaction temperature of 17-25 °C. Concentration *in vacuo* was performed at pressures of 30-350 mmHg. Residual solvent was removed at 0.1-1 mmHg.

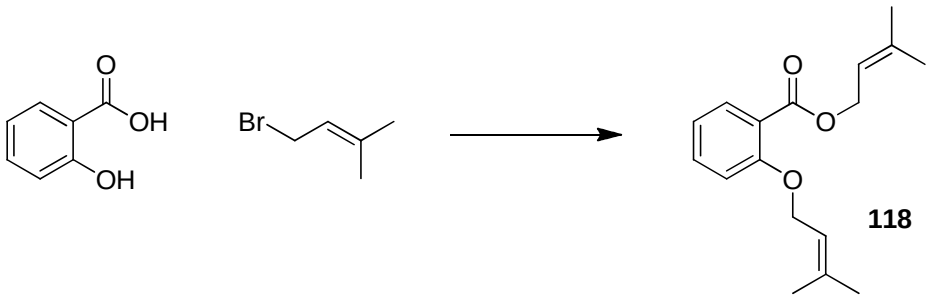
Analytical TLC was carried out on Merck 60 F_{245} aluminum backed silica gel plates using short wave (254 nm) UV light, Vanillin or $KMnO_4$ were used to visualise components. Column chromatography was performed using laboratory grade solvents on Merck silica gel 60 (0.043-0.063 mm) under gentle pressure applied using hand bellows. Distillation was performed using a Buchi Kugelrohr distillation B-585 oven.

Infra-red spectra were all recorded neat on a Perkin Elmer Spectrum 100 FT-IR Spectrometer. All NMR spectra were recorded in deuterated chloroform unless otherwise stated. ^{1}H-NMR spectra were recorded on a Bruker AC300 (at 300.13 MHz), a Bruker AV300 (at 300.07 MHz) or a Bruker AVIII300 (at 300.13MHz) and referenced relative to residual $CDCl_3$ (^{1}H, 7.26 ppm). ^{13}C-NMR spectra were recorded on a Bruker AV300 (at 75.46 MHz) or a Bruker AV400 (at 100.60 MHz) using the PENDANT pulse sequence and referenced relative to $CDCl_3$ (^{13}C, 77.16 ppm). Chemical shifts (δ) were measured in parts per million (ppm). Coupling constants (*J*) were measured in Hertz (Hz). The following abbreviations are used; s-singlet, d-doublet, t-triplet, q-quartet, qn-quintet, br-broad, ap. apparent. Mass spectra were obtained on a Jeol AX505W spectrometer using EI or CI or a Micromass LCT spectrometer utilising electrospray (ESI) ionisation (and a MeOH mobile phase), or on a VG ProSpec mass spectrometer utilising electron impact (EI) ionisation. High resolution ES spectra were obtained using a lock-mass to adjust the calibrated mass scale.

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected.

Chapter 1 - Experimental

3-Methylbut-2-en-1-yl 2-((3-methylbut-2-en-1-yl)oxy)benzoate

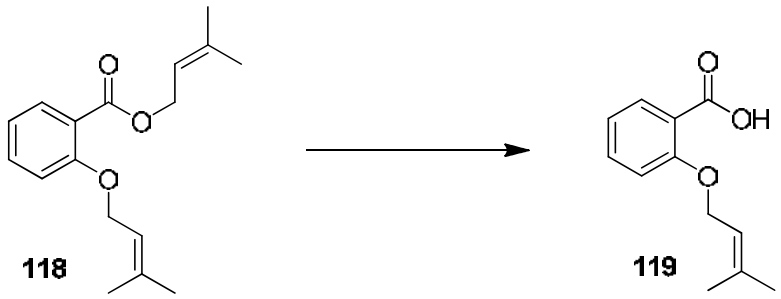


118

Prepared according to the general literature procedure.[156]

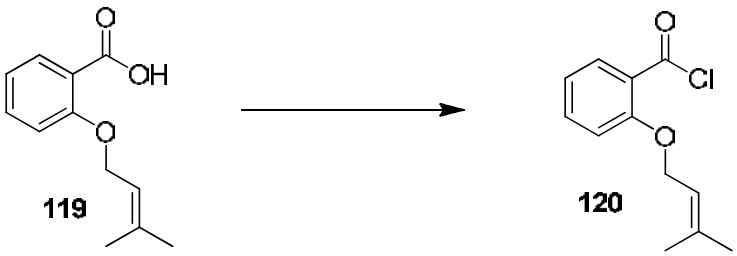
K_2CO_3 (4.83 g, 35 mmol) was added to a solution of salicyclic acid (2.00 g, 14 mmol) in acetone (27 mL) and the resulting solution heated to reflux for 20 minutes. After cooling to room temperature a solution of 3,3-dimethylallylbromide (4.04 mL, 35 mmol) in acetone (16 mL) was added dropwise. The resultant reaction mixture was heated to reflux for 20 hours. The cooled reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resultant brown/yellow oil was dissolved in CH_2Cl_2 (50 mL), washed with water (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* as a clear oil (3.48 g, 91%). R_f 0.29 (4:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2972, 2914, 1724, 1702, 1487, 1449, 1295, 1239; δ_H (300 MHz; $CDCl_3$) 1.70 (3H, s, CH_3), 1.74 (3H, s CH_3), 1.77 (3H, s, CH_3), 1.81 (3H, s, CH_3), 4.61 (2H, d, *J* = 6.5 Hz, CH_2), 4.79 (2H, d, *J* =7.2 Hz, CH_2), 5.42-5.54 (2H, m, 2 x CH), 6.95 (2H, dd, *J* = 7.8, 5.3 Hz, 2 x CH), 7.37-7.46 (1H, m, CH), 7.77 (1H, dd, *J* =7.9, 1.8 Hz, CH); δ_c (100 MHz; $CDCl_3$); 18.1 (2 x CH_3), 25.8 (2 x CH_3), 61.7 (CH_2), 66.1 (CH_2), 113.8 (CH), 118.9 (CH), 119.8 (CH), 120.1 (CH), 131.6 (CH), 133.1 (CH), 137.4 (C), 138.8 (2 x C), 157.5 (C) 166.5 (C=O); *m/z* (ESI) 297 ($[M+Na]^+$ 100 %); HRMS calculated for $C_{17}H_{22}O_3Na$ $[M+Na]^+$ 297.1467, found 297.1460.

2-((3-Methylbut-2-en-1-yl)oxy)benzoic acid



A solution of **118** (0.6 g, 2.12 mmol) in ethanol (90%, 10 mL), was treated with NaOH (0.26 g, 6.56 mmol) and subsequently heated to reflux for 4 hours. The cooled reaction mixture was treated with HCl (1 M, 10 mL), extracted with toluene (3 x 15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* as a clear oil. R_f 0.27 (4:1 petroleum ether:EtOAc); ν_{max} (neat)/cm^{-1}: 3331, 2971, 2929, 1736, 1601, 1456, 1217, 969; δ_H (300 MHz; $CDCl_3$); 1.68 (3H, s, CH_3), 1.84 (3H, s, CH_3) 4.76 (2H, d, *J* = 7.1 Hz, CH_2), 5.32-5.71 (1H, t, *J* =7.1 Hz, CH), 6.96-7.18 (2H, m, 2 x CH), 7.55 (1H, ddd, *J* = 8.5, 7.4, 1.8 Hz, CH), 8.20 (CH, d, *J* = 7.8 Hz, CH); δ_c (100 MHz; $CDCl_3$) 18.5 (CH_3), 26.0 (CH_3), 67.0 (CH_2), 113.1 (CH), 117.3 (CH), 118.1 (C), 122.3 (CH), 133.9 (CH), 135.1 (CH), 142.1 (C), 156.6 (C) 165.7 (C=O); *m/z* (ESI) 229 ($[M+Na]^+$ 100 %); HRMS calculated for $C_{12}H_{14}O_3Na$ $[M+Na]^+$ 229.0841, found 229.0848.

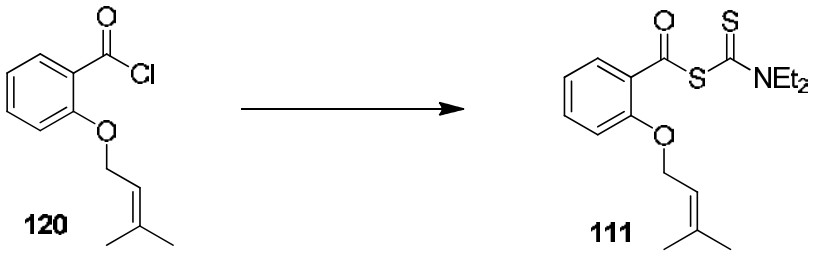
2-((3-Methylbut-2-en-1-yl)oxy)benzoyl chloride



Prepared as according to the general literature procedure. [156]

Oxalyl chloride (0.05 mL, 0.58 mmol) was added to a solution of **119** (0.10 g, 0.48 mmol) in diethylether (6 mL) and allowed to stir at room temperature for 1 hour. Removal of the solvent and excess oxalyl chloride under reduced pressure gave the acid chloride **120** that was used without further purification. δ_H (300 MHz; $CDCl_3$) ; 1.67 (3H, s, CH_3) 1.90 (3H, s, CH_3), 4.67 (2H, m, CH_2), 5.39-5.59 (1H, m, CH), 6.94-7.14 (2H, m, 2 x CH), 7.50-7.68 (1H, m, CH), 8.08 (1H, d, *J* = 8.0 Hz, CH); δ_c (100 MHz; $CDCl_3$) 18.3 (CH_3), 25.8 (CH_3), 66.1 (CH_2), 113.5 (CH), 118.9 (CH), 120.2 (CH), 122.8 (C), 134.4 (CH), 135.9 (CH), 138.5 (C), 158.1 (C) 158.9 (C=O).

Diethylcarbamothioic 2-(2- cyclohex-2-en-1-yloxy)benzoic thioanhydride

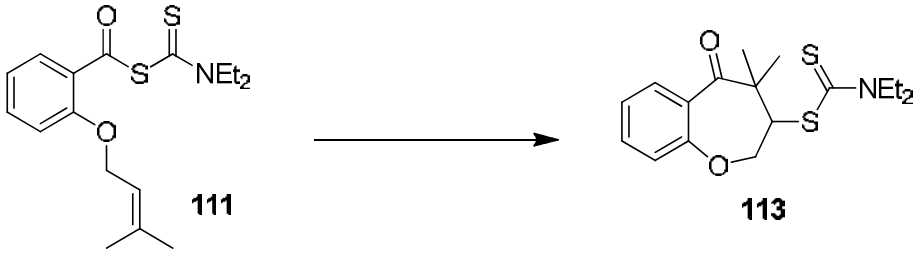


Prepared according to the general literature procedure.[51]

Acid chloride **120** was dissolved in acetone (5 mL) and cooled to 0 °C. Sodium diethyldithiocarbamate trihydrate (0.10 g, 0.48 mmol) was added in one portion and the solution was stirred at 0 °C for 20 minutes in the dark. Saturated $NaHCO_3$ (5 mL) was added followed by water (10 mL) until the inorganic salts dissolved. Et_2O (50 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 20 mL) and the combined organic extracts were washed with water (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 petroleum ether:EtOAc) to afford the *title compound* as a

yellow oil (65% over 2 steps, 0.12 g). R_f 0.23 (2:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2974, 2933, 1738, 1644, 1594, 1483, 1448, 1271, 1188, 971; δ_H (300 MHz; $CDCl_3$); 1.26-1.38 (6H, m, 2 x CH_3), 1.73 (3H, s, CH_3), 1.77 (3H, s, CH_3), 3.95 (4H, d, *J* = 6.5 Hz, 2 x CH_2), 4.66 (2H, d, *J* = 6.6 Hz, CH_2), 5.54 (1H, t, *J* = 6.6 Hz, CH), 6.96 (2H, dd, *J* = 12.0, 5.1 Hz, 2 x CH), 7.37-7.51 (1H, m, CH), 7.81 (1H, d, *J* = 7.8 Hz, CH); δ_c (100 MHz; $CDCl_3$); 12.5 (2 x CH_3), 18.4 (CH_3), 25.8 (CH_3), 49.5 (2 x CH_2), 66.2 (CH_2), 113.3 (CH), 119.0 (CH), 129.6 (CH), 125.5 (C), 130.0 (CH), 134.5 (CH), 138.4 (C), 158.1 (C), 184.4 (C=O), 185.3 (C=S); *m/z* (ESI) 360 ([M+Na]$^+$ 100 %); HRMS calculated for $C_{17}H_{23}O_2S_2NNa$ [M+Na]$^+$ 360.1068, found 360.1077.

(4,4 Dimethyl-5-oxo-2,3,4,5-tetrahydro-1-benzoxepine)-diethylcarbamodithioate

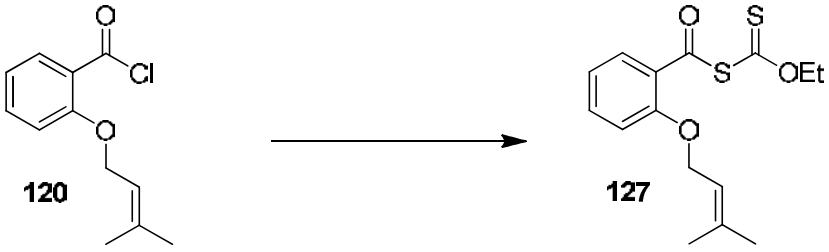


A solution of acyl dithiocarbamate **111** (0.2 g, 0.59 mmol) in cyclohexane (6 mL) was degassed for 15 min. The yellow solution was stirred vigorously and irradiated for 2 hours with a 500 W halogen lamp from a distance of approximately 15 cm, the heat generated by the lamp being sufficient to bring the solution to reflux. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (2:1 petroleum ether:EtOAc) afforded the *title compound* (0.09 g, 49%) as a pale yellow oil. R_f 0.39 (2:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2974, 2932, 1679, 1603, 1478, 1411, 1263; δ_H (300 MHz; $CDCl_3$); 1.18-1.36 (6H, m, 2 x $CH_2C\mathit{H}_3$), 1.40 (3H, s, $CC\mathit{H}_3$), 2.00

(3H, s, CCH_3), 3.64-4.17 (4H, m, 2 x CH_2), 4.68-4.80 (3H, m, CH_2 and SCH), 6.91-7.01 (2H, m, 2 x CH), 7.41-7.44 (1H, m, CH), 7.88 (1H, dd, *J* = 7.9, 1.7 Hz, CH); δ_c (100 MHz; $CDCl_3$) 11.8 (CH_3), 12.9 (CH_3), 25.8 (CH_3), 27.9 (CH_3), 47.2 (CH_2), 47.7 (CH_2), 49.2 (SCH), 56.3 (C), 70.8 (CH_2), 117.8 (CH), 121.3 (CH), 122.4 (C), 127.2 (CH), 135.7 (CH), 161.7 (C), 193.2 (C=O), 193.4 (C=S); *m/z* (ESI) 360 ($[M+Na]^+$ 100 %); HRMS calculated for $C_{17}H_{23}O_2S_2NNa$ $[M+Na]^+$ 360.1068, found 360.1079.

A solution of acyl dithiocarbamate **111** (0.2 g, 0.59 mmol) in cyclohexane (6 mL) was degassed for 15 min. Dilauroyl peroxide (0.047 g, 0.12 mmol) was added and the resultant solution heated to reflux for 2 hours. A further portion of dilauroyl peroxide (0.047 g, 0.12 mmol) was added, and after two more hours at reflux a further portion of dilauroyl peroxide (0.047 g, 0.12 mmol) was added. After a further 2 hours of heating at reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (2:1 petroleum ether:EtOAc) afforded the *title compound* **113** (0.042 g, 21%), whose analytical data was as reported above.

(*O*-Ethyl carbonthioic) 2-((3-methylbut-2-en-1-yl)oxy)benzoic thioanydride

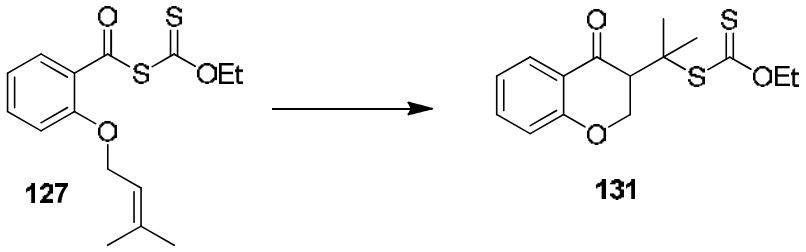


Prepared according to the general literature procedure.[51]

Acid chloride **120** (0.2 g, 0.9 mmol, 1 equiv.) was dissolved in acetone (10 mL) and cooled to 0 °C. Potassium ethyl xanthate (0.13 g, 0.8 mmol) was added in one portion and the

solution was stirred at 0 °C for 15 minutes in the dark. Saturated $NaHCO_3$ (10 mL) was added followed by water (20 mL) until the inorganic salts dissolved. Et_2O (80 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 40 mL) and the combined organic extracts were washed with water (60 mL) and brine (60 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (8:1 petroleum ether:EtOAc) to afford the *title compound* as a yellow oil (0.14 g, 78%). R_f 0.18 (8:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 1742, 1689, 1623, 1436, 1271, 1043,; δ_H (300 MHz; $CDCl_3$); 1.35 (3H, t, *J* = 7.2 Hz, CH_3), 1.67 (6H, s, CH_3), 1.72 (3H, s, CH_3), 4.51-4.62 (4H, m, 2 x CH_2), 5.43-5.48 (1H, m, CH), 6.89-6.94 (2H, m, 2 x CH), 7.32-7.42 (1H, m, CH), 7.61 (1H, d, *J* = 7.7 Hz, CH); δ_c (100 MHz; $CDCl_3$); 13.5 (CH_3), 18.4 (CH_3), 25.8 (CH_3), 66.1 (CH_2), 70.9 (CH_2), 113.4 (CH), 119.0 (CH), 120.6 (CH), 126.0 (C), 130.0 (CH), 134.6 (CH), 138.5 (C), 157.7 (C), 184.9 (C=O), 206.3 (C=S); *m/z* (ESI) 311 ($[M]^+$ 100 %); HRMS (ESI) calculated for $C_{15}H_{19}O_3S_2$ $[M]^+$ 311.0776, found 311.0771.

_O_-Ethyl _S_-(2-(4-oxochroman-3-yl)propan-2-yl) carbanodithioate

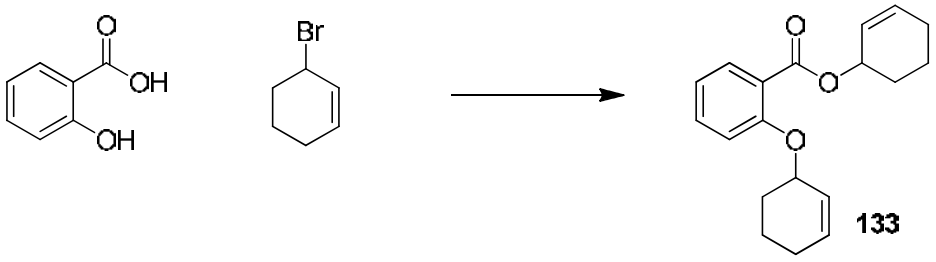


A solution of acyl xanthate **127** (0.1 g, 0.32 mmol) in cyclohexane (3 mL) was degassed for 15 min. The yellow solution was stirred vigorously and irradiated for 1 hour with a 500 W halogen lamp from a distance of approximately 15 cm, the heat generated by the lamp being sufficient to bring the solution to reflux. The solution was cooled to room

temperature and concentrated *in vacuo*. Purification by column chromatography (10:1 petroleum ether:EtOAc) afforded the *title compound* **131** (0.05 g, 47%) as a pale yellow oil. R_f 0.27 (10:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 1747, 1679, 1587, 1473, 1274, 964; δ_H (300 MHz; $CDCl_3$); 1.21 (3H, s, CH_3), 1.41 (3H, t, *J* = 7.2 Hz, CH_3), 1.81 (3H, s, CH_3), 3.48 (1H, t, *J* = 6.3 Hz, CH), 4.51-4.71 (4H, m, 2 x OCH_2), 6.87-7.00 (2H, m, 2 x CH), 7.38-7.47 (1H, m, CH), 7.76 (1H, dd, *J* = 7.7, 1.7 Hz, CH); δ_c (100 MHz; $CDCl_3$) 13.8 (CH_3), 24.0 (CH_3), 28.8 (CH_3), 51.5 (CH), 56.0 (CS), 69.6 (CH_2), 69.9 (CH_2), 117.8 (CH), 121.5 (CH), 121.9 (C), 127.3 (CH), 136.1 (CH), 161.4 (C), 191.9 (C=O), 212.3 (C=S); *m/z* (ESI) 311 ($[M]^+$ 100 %); HRMS (ESI) calculated for $C_{15}H_{19}O_3S_2$ $[M]^+$ 360.1068, found 360.1077.

A solution of acyl xanthate **127** (0.1 g, 0.3 mmol) in cyclohexane (3 mL) was degassed for 15 min. Dilauroyl peroxide (0.024 g, 0.06 mmol) was added and the resultant solution heated to reflux for 2 hours. A further portion of dilauroyl peroxide (0.024 g, 0.06 mmol) was added. After a further 2 hours of heating to reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (10:1 petroleum ether:EtOAc) afforded the *title compound* **131** (0.026 g, 26%). Analytical data as reported above.

Cyclohex-2-en-1-yl 2-(cyclohex-2-en-1-yloxy)benzoate

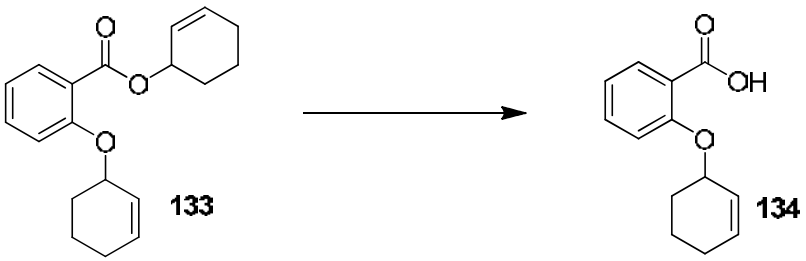


133

Prepared according to the general literature procedure.[156]

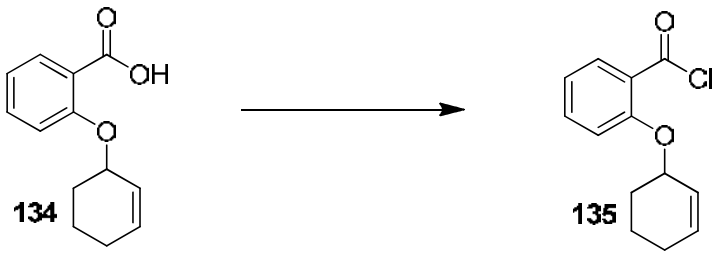
K_2CO_3 (0.95 g, 6.9 mmol) was added to a solution of salicyclic acid (0.5 g, 3.6 mmol) in acetone (7 mL) and heated to reflux for 20 minutes. After cooling to room temperature a solution of 3-bromo-cyclohexene (0.79 mL, 6.9 mmol) in acetone (4 mL) was added dropwise. The resultant reaction mixture was heated to reflux for 20 hours. The cooled reaction mixture was filtered and the filtrate concentrated under reduced pressure. The resultant brown/yellow oil was dissolved in CH_2Cl_2 (10 mL), washed with water (8 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (6:1 petroleum ether:EtOAc) gave the *title compound* as a pale yellow oil **133** (0.72 g, 70%). R_f 0.31 (6:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 3032, 2938, 1720, 1697, 1669. 1484, 1292, 1242; δ_H (300 MHz; $CDCl_3$) (mixture of diastereomers)1.57-2.23 (12H, m, 3 x CH_2) 4.80-4.86 (1H, m, CH), 5.47-5.53 (1H, m, CH), 5.80-6.01 (4H, m, 4 x CH), 6.92-7.06 (2H, m, 2 x CH), 7.37-7.48 (1H, m, CH), 7.75 (1H, d, *J* = 7.8 Hz, CH); δ_c (100 MHz; $CDCl_3$) 18.8 (CH_2), 19.0 (CH_2), 25.0 (CH_2), 25.2 (CH_2), 28.3 (CH_2), 28.4 (CH_2), 68.4 (CH), 72.2 (CH), 115.3 (CH), 119.0 (CH), 120.2 (CH), 122.6 (C), 126.1 (CH), 130.0 (CH), 131.5 (CH), 132.7 (CH), 135.0 (CH), 157.3 (C), 166.5 (C=O); *m/z* (ESI) 321 [M^+] 100%; HRMS (ESI) calculated for $C_{19}H_{22}O_3Na$ $[M+Na]^+$ 321.1467, found 321.1477.

2-(Cyclohex-2-en-1-yloxy)benzoic acid



A solution of **133** (3.00 g, 10.0 mmol) in ethanol (90%, 50 mL), was treated with NaOH (1.2 g, 30.2 mmol) and subsequently heated to reflux for 5 hours. The cooled reaction mixture was treated with HCl (1 M, 30 mL), extracted with toluene (3 x 30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound* as a clear oil **134** (2.10 g, 97%). ν_{max}(neat)/cm^{-1}: 3231, 2939, 1662, 1611, 1441, 1291, 1246; δ_H (300 MHz; $CDCl_3$) 1.68-2.32 (6H, m, 3 x CH_2), 5.07-5.12 (1H, m, CH), 5.84-5.96 (1H, m, CH), 6.08-6.18 (1H, m, CH), 7.07-7.17 (2H, m, 2 x CH), 7.54 (1H, t, *J* = 7.5 Hz, CH), 8.21 (1H, d, *J* = 7.5 Hz, CH), 11.03 (1H, br s, OH); δ_c (100 MHz; $CDCl_3$) 18.5 (CH_2), 24.9 (CH_2), 28.0 (CH_2) 74.0 (CH_2), 114.0 (CH), 118.6 (C), 122.2 (CH), 123.7 (CH), 133.9 (CH), 134.9 (CH), 135.0 (CH), 156.6 (C), 165.7 (C=O); *m/z* (EI) 218 ([M^+] 26%), 200 (100%), 172 (73%), 79 (100%); HRMS (EI) calculated for $C_{13}H_{14}O_3$ $[M]^+$ 218.0943, found 218.0948.

2-(Cyclohex-2-en-1-yloxy)benzoyl chloride

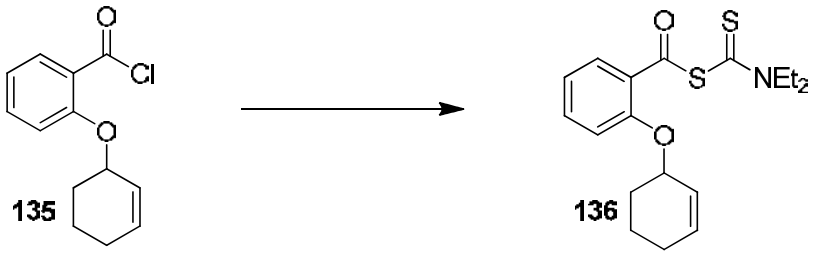


Prepared according to the general literature procedure.[156]

Oxalyl chloride (0.73 mL, 8.4 mmol) was added to a solution of **134** (1.5 g, 6.97 mmol) in diethylether (70 mL) and allowed to stir at room temperature for 3 hours. Removal of the solvent and excess oxalyl chloride under reduced pressure gave acid chloride **135** as a milky oil that was used directly without further purification. δ_H (300 MHz; $CDCl_3$) 1.61-2.27 (6H, m, 3 x CH_2), 4.91 (1H, s, CH), 5.78-6.22 (2H, m, CH), 7.01-7.16 (2H, m, 2 x CH),

7.59-7.64 (1H, m, CH), 8.26 (1H, d, *J* = 8.00 Hz, CH); δ_c (100 MHz; $CDCl_3$) 18.7 (CH_2), 25.1 (CH_2), 28.4 (CH_2), 72.5 (CH_2), 114.0 (CH), 120.1 (CH), 125.0 (CH), 133.3 (CH), 134.3 (CH), 135.6 (CH), 163.8 (C=O).

Diethylcarbamothioic 2-(2- cyclohex-2-en-1-yloxy)benzoic thioanhydride

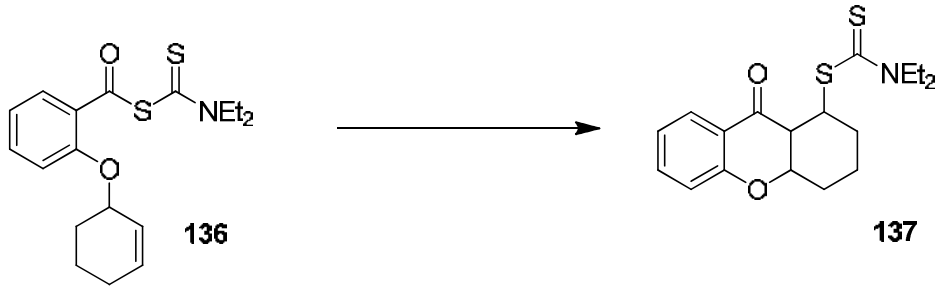


Prepared according to the general literature procedure.[51]

Acid chloride **135** (1.64 g, 6.97 mmol) was dissolved in acetone (70 mL) and cooled to 0 °C. Sodium diethyldithiocarbamate trihydrate (1.57 g, 6.97 mmol) was added in one portion and the solution was stirred at 0 °C for 20 minutes in the dark. Saturated $NaHCO_3$ (30 mL) was added followed by water (60 mL) until the inorganic salts dissolved. Et_2O (200 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 50 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 petroleum ether:EtOAc) to afford the *title compound* as a yellow oil (1.72 g, 71% over 2 steps). R_f 0.19 (2:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2973, 2932, 1642, 1592, 1478, 1448, 1271, 889; δ_H (300 MHz; $CDCl_3$) 1.25-1.40 (6H, t, *J* = 5.6 Hz, 2 x CH_3), 1.60-2.21 (6H, m, 3 x CH_2), 3.84-4.10 (4H, m, 2 x CH_2), 4.89-5.02 (1H, m, CH), 5.88-6.04 (2H, m, 2 x CH), 6.94-7.02 (2H, m, 2 x CH), 7.43 (1H, ddd, *J* = 8.8, 7.3, 1.8 Hz, CH), 7.83 (1H, dd, *J* = 7.3, 1.8 Hz, CH); δ_c (100 MHz; $CDCl_3$); 12.6 (2 x

CH_3), 19.2 (CH_2), 25.2 (CH_2), 28.5 (CH_2), 49.6 (2 x NCH_2), 72.8 (CH), 113.8 (CH), 120.5 (CH), 125.3 (CH), 126.1 (C), 130.4 (CH), 133.0 (CH), 134.5 (CH), 157.3 (C), 184.6 (C=O), 185.5 (C=S); *m/z* (ESI) 372 ($[M+Na]^+$ 100 %); HRMS (ESI) calculated for $C_{18}H_{23}O_2S_2NNa$ $[M+Na]^+$ 372.1068, found 372.1061.

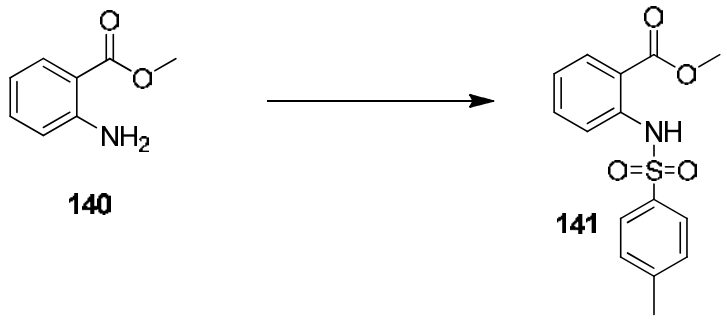
9-Oxo-2,3,4,4a,9,9a-hexahydro-1H-xanthen-1-yl-diethylcarbamodithioate



A solution of acyl dithiocarbamate **136** (0.05 g, 0.14 mmol) in cyclohexane (2 mL) was degassed for 15 min. Dilauroyl peroxide (0.01 g, 0.03 mmol) was added and the resultant solution heated to reflux for 2 hours. A further portion of dilauroyl peroxide (0.01 g, 0.03 mmol) was added. After a further 2 hours of heating to reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (2:1 petroleum ether:EtOAc) afforded the *title compound* (0.026 g, 52%) as a white solid. R_f 0.41 (2:1 petroleum ether:EtOAc); m.p. 126-130 °C; ν_{max}(neat)/cm^{-1}: 2942, 2916, 1684, 1603, 1460, 1300, 1271; δ_H (300 MHz; $CDCl_3$) 1.21-1.35 (8H, m, 2 x CH_3 and 1 x CH_2), 1.52-1.68 (2H, m, CH_2) 1.88-2.08 (2H, m, CH_2), 3.07 (1H, br s, SCH), 3.61-4.10 (4H, m, 2 x CH_2), 4.64-4.74 (2H, m, 2 x CH), 6.89-7.70 (2H, m, 2 x CH), 7.39-7.55 (1H, m, 2H), 7.85 (1H, dd, *J* = 7.8, 1.7 Hz, CH); δ_c (100 MHz; $CDCl_3$); 11.7 (CH_3), 12.7 (CH_3), 21.3 (CH_2), 28.5 (CH_2), 29.7 (CH_2), 46.8 (CH_2), 47.0 (2 x CH), 49.4 (CH_2), 51.6 (SCH), 118.0 (CH), 120.1 (C), 121.3 (CH), 127.5 (CH), 136.1 (CH), 158.7 (C), 192.3 (C=O), 193.5 (C=S); *m/z* (ESI)

372 ([M+Na]$^+$ 100 %); HRMS (ESI) calculated for $C_{18}H_{23}O_2S_2NNa$ [M+Na]$^+$ 372.1068, found 372.1060.

Methyl 2-(4-methylphenylsulfonamido)benzoate[157]

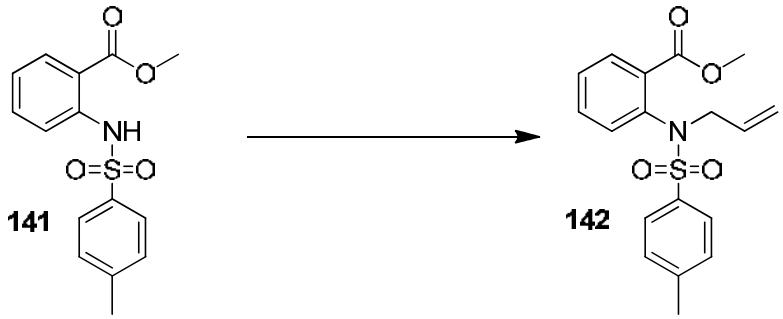


Prepared according to the literature procedure.[157]

Pyridine (0.97 mL, 12 mmol) was added dropwise to a solution of methyl 2-aminobenzoate (1.51 g, 10 mmol) in CH_2Cl_2 (15 mL). After stirring at room temperature for 25 minutes, a solution of 4-methylbenzene-1-sulfonyl chloride (2.28 g, 12 mmol) in CH_2Cl_2 (30 mL) was added dropwise to the reaction mixture. The resultant mixture was allowed to stir at room temperature overnight, before being quenched with saturated aqueous NH_4Cl (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified buy column chromatography (8:1 Hexane:EtOAC) to give the *title compound* as a white solid (2.3 g, 76%) whose analytical data was in accordance with that reported in the literature.[157] δ_H (300 MHz; $CDCl_3$) 2.38 (3H, s, CH_3), 3.89 (3H, s, CH_3), 7.03-7.06 (1H, m, CH), 7.23-7.24 (2H, m, 2 x CH), 7.29 (1H, m, CH), 7.45-7.47 (1H, m, CH), 7.70-7.77 (2H, m, 2 x CH), 7.92-7.94 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 21.5 (CH_3), 52.5 (CH_3), 115.8 (C),

118.9 (CH), 122.9 (CH), 127.2 (2 x CH), 129.6 (2 x CH), 131.2 (CH), 134.5 (CH), 136.5 (C), 140.6 (C), 144.0 (C), 168.3 (C=O); *m/z* (ESI) 328 ($[M+Na]^+$ 100%).

Methyl 2-(*N*-allyl-4-methylphenylsulfonamido)benzoate

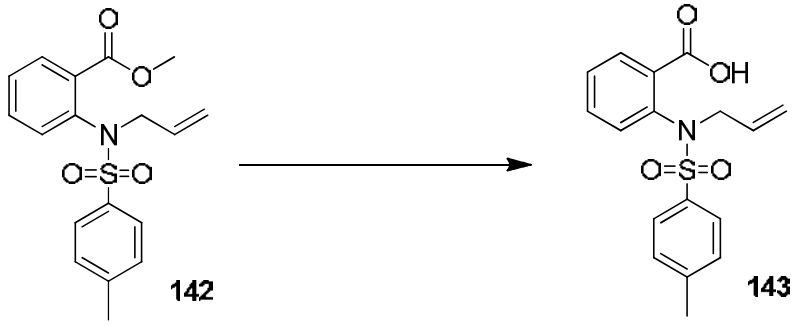


Prepared according to the literature procedure.[158]

Sodium hydride (60% dispersion in mineral oil, 0.39 g, 9.84 mmol) was added to a stirred solution of **141** (2.00 g, 6.56 mmol) and allyl bromide (1.13 mL, 13.1 mmol) in DMF (12 mL). After stirring for 14 hours at room temperature, the reaction mixture was diluted with Et_2O (80 mL), washed with 1M HCl (3 x 40 mL) then brine (2 x 40 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (3:1 petroleum ether:EtOAc) gave the product as a white solid (2.26 g, 91%). ν_{max} (neat)/cm^{-1}: 2869, 2657, 1669, 1634, 1524, 1411; δ_H (300 MHz; $CDCl_3$) 2.44 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.29 (2H, d, *J* = 6.7 Hz, CH_2), 4.97-5.12 (2H, m, CH_2), 5.86-5.99 (1H, m, CH), 6.90-6.71 (2H, m, 2 x CH), 7.23-7.30 (2H, m, 2 x CH), 7.39-7.43 (2H, m, 2 x CH), 7.53 (2H, d, *J* = 8.3 Hz, 2 x CH), 7.81-7.90 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 21.5 (CH_3), 52.1 (CH_3), 54.6 (CH_2), 118.9 (CH_2), 127.6 (CH), 128.2 (CH), 129.4 (CH), 131.0 (2 x CH), 131.3 (CH), 131.9 (CH), 132.6 (CH), 133.1 (C), 133.4 (CH), 136.8 (C), 137.9 (C), 143.2

(C), 166.6 (C=O). *m/z* (ESI) 368 $[M+Na]^+$, 354; HRMS calculated for $C_{18}H_{19}O_4SNNa$ $[M+Na]^+$ 368.0932, found 368.0937.

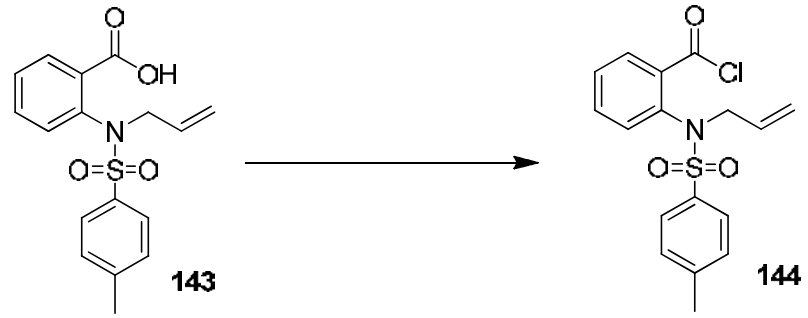
2-(*N*-Allyl-4-methylphenylsulfonamido)benzoic acid[158]



Prepared according to the literature procedure.[158]

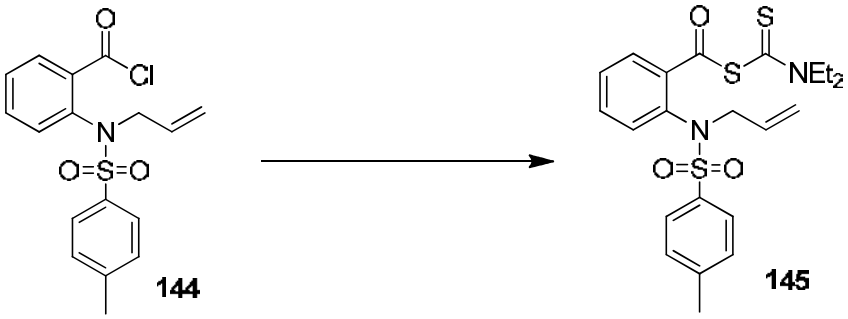
142 (2.26 g 6.56 mmol) was dissolved in MeOH:H_2O (1:1, 20 mL) and LiOH•H_2O (1.36 g, 32.8 mmol) was added. The reaction mixture was heated at 70 °C for 2.5 h then cooled to room temperature. HCl (2 M, 25 mL) and Et_2O (60 mL) were added. The layers were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. After washing with cold pentane (1 x 25 mL), the product was obtained as a white solid (1.85 g, 85%), whose analytical data was in accordance with that reported in the literature.[158] m.p. = 166–168 °C; δ_H (300 MHz; $CDCl_3$) 2.83 (3H, s, CH_3), 4.29 (1H, br s, CH_2), 5.08 (1H, d, *J* = 12.0 Hz, CH), 5.87-5.96 (1H, m, CH), 6.97 (1H, d, *J* = 7.8 Hz, CH), 7.26 (2H, d, *J* = 5.4 Hz, 2 x CH), 7.44 (2H, dt, *J* = 9.1, 7.5 Hz, 2 x CH), 7.54 (2H, d, *J* = 8.3 Hz, 2 x CH), 8.00 (1H, dd, *J* = 7.6 Hz, 1.7 Hz, CH); δ_c (100 MHz; $CDCl_3$) 21.7 (CH_3), 54.9 (CH_2), 119.6 (CH_2), 127.9 (CH), 128.7 (CH), 129.7 (2 x CH), 131.4 (2 x CH), 131.6 (2 x CH), 132.2 (C), 133.1 (CH), 135.9 (C), 138.3 (C), 144.0 (C), 170.8 (C=O); *m/z* (ESI) 354 ($[M+Na]^+$ 100 %).

2-(*N*-Allyl-4-methylphenylsulfonamido)benzoyl chloride



Freshly distilled oxalyl chloride (0.12 mL, 1.45 mmol) was added to a stirred solution of **143** (0.40 g, 1.20 mmol) and one drop of DMF in CH_2Cl_2 (5 mL) at room temperature. After 20 minutes the solvent and excess oxalyl chloride was removed under reduced pressure, to give the *title compound* as white solid, which was used without further purification. δ_H (300 MHz; $CDCl_3$); 2.41 (3H, d, *J* = 8.6 Hz, CH_3), 4.29 (2H, br s, CH_2), 4.91-5.19 (2H, m, CH_2), 5.78-6.02 (1H, m, CH), 6.94 (1H, td, *J* =7.6, 1.4 Hz, CH), 7.27 (2H, dd, *J* = 8.1, 1.7 Hz, 2 x CH), 7.37-7.67 (4H, m, 4 x CH), 8.02 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 21.6 (CH_3), 54.4 (CH_2), 119.6 (CH_2), 127.7 (CH), 127.8 (CH), 128.5 (CH), 128.6 (CH), 129.6 (CH), 130.5 (CH), 130.9 (C), 131.6 (CH), 132.0 (CH), 132.5 (CH), 135.6 (C), 138.1 (C), 143.9 (C), 170.1 (C=O).

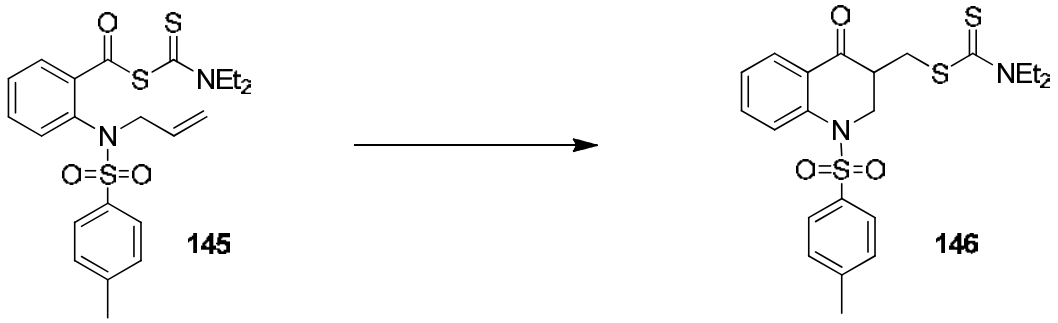
2-(*N*-Allyl-4-methylphenylsulfonamido)benzoic diethylcarbamothioic thioanyhydride



Prepared according to the general literature procedure.[51]

Acid chloride **144** (1.20 mmol) was dissolved in acetone (12 mL) and the resultant solution cooled to 0 °C. Sodium diethyldithiocarbamate trihydrate (0.27 g, 1.20 mmol) was added in one portion and the solution was stirred at 0 °C for 20 minutes in the dark. Saturated $NaHCO_3$ (10 mL) was added followed by water (20 mL) until the inorganic salts dissolved. Et_2O (100 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 50 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether:EtOAc) to afford the *title compound* as a pale yellow oil (0.47 g, 86% over 2 steps). R_f 0.32 (1:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2983, 1689, 1488, 1341, 1162, 1061; δ_H (300 MHz; $CDCl_3$); 1.41 (6H, t, *J* = 6.9 Hz, 2 x CH_2CH_3), 2.42 (3H, s, ArCH_3), 4.10 (4H, d, *J* = 6.4 Hz, 2 x CH_2CH_3), 4.91-5.18 (2H, m, CH_2), 5.87-5.99 (1H, m, CH), 6.61 (1H, d, *J* = 7.7 Hz, CH), 7.13-7.59 (6H, m, 6 x CH), 7.87 (1H, d, *J* = 7.6 Hz, CH); δ_c (400 MHz; $CDCl_3$, -30°C) 11.1 (CH_3), 14.4 (CH_3), 21.7 (CH_3), 49.0 (CH_2), 51.2 (CH_2), 54.5 (CH_2), 120.1 (CH_2), 128.1 (2 x CH), 128.5 (CH), 128.7 (CH), 129.6 (2 x CH), 129.9 (CH) 132.1 (CH), 132.3 (CH), 134.7 (C), 136.6 (C), 139.0 (C), 144.0 (C), 181.8 (C=O), 186.4 (C=S); *m/z* (ESI) 485 ([M+Na]$^+$ 100%), 354 (48%); HRMS (ESI) calculated for $C_{22}H_{26}O_3S_3N_2Na$ [M+Na]$^+$ 485.1003, found 485.1011.

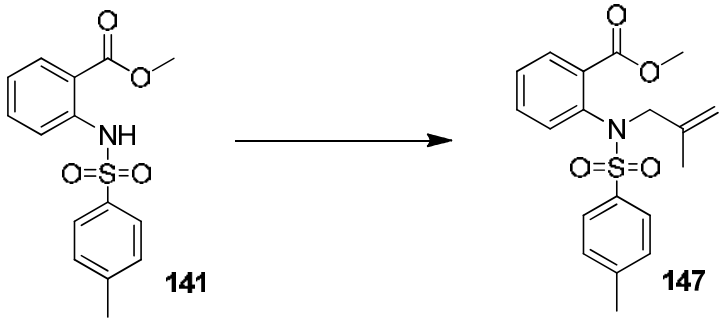
(4-Oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)methyl diethylcarbamoditioate



A solution of acyl dithiocarbamate **145** (0.44 g, 0.95 mmol) in cyclohexane (10 mL) was degassed for 1 hour. The yellow solution was stirred vigorously and irradiated for 20 min. with a 500 W halogen lamp from a distance of approximately 15 cm, the heat generated by the lamp being sufficient to bring the solution to reflux. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (1:1 petroleum ether:EtOAc) provided the *title compound* **146** (0.39 g, 89%) as a pale yellow solid. R_f 0.27 (1:1 petroleum ether:EtOAc); m.p. 96-98 °C; ν_{max}(neat)/cm^{-1}: 2977, 2932, 2873, 1687, 1598, 1418, 1352, 1269, 1164; δ_H (300 MHz; $CDCl_3$) 1.19-1.36 (6H, m, 2 x CH_3), 2.24-2.40 (3H, s, CH_3), 2.84 (1H, ddt, *J* = 10.1, 7.3, 5.0 Hz, (O)CC*H*), 3.29 (1H, dd, *J* = 14.3, 7.4 Hz, SCH_aH$_b$) 3.67-3.80 (1H, m, CH$_c$H$_d$), 3.88 (1H, dd, *J* = 14.3, 5.1 Hz, SCH$_a$$H_b$), 3.94-4.12 (4H, m, CH_2), 4.75 (1H, dd, *J* = 14.1, 5.0 Hz, CH$_c$$H_d$), 7.11-7.25 (3H, m, 3 x CH), 7.46-7.64 (3H, m, 3 x CH), 7.81-8.04 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$) 11.5 (CH_3), 12.5 (CH_3), 21.5 (CH_3), 33.7 (CH_2), 44.8 (CH), 46.7 (CH_2), 49.7 (CH_2), 49.8 (CH_2), 123.2 (CH), 124.5 (C), 125.0 (CH), 126.9 (2 x CH), 127.9 (CH), 130.0 (2 x CH), 134.6 (CH), 136.3 (C), 142.1 (C), 144.4 (C), 193.6 (C), 194.1 (C); *m/z* (ESI) 485 ([M+Na]$^+$ 100%); HRMS calculated for $C_{22}H_{26}O_3S_3N_2Na$ [M+Na]$^+$ 485.1003, found 485.0991.

A solution of acyl dithiocarbamate **145** (0.437 g, 0.95 mmol) in cyclohexane (10 mL) was degassed for 15 min. Dilauroyl peroxide (0.075 g, 0.19 mmol) was added and the resultant solution heated to reflux. A further two portions of dilauroyl peroxide (2 x 0.075 g, 0.19 mmol) were added after 2 hours and 4 hours. After a further 2 hours of heating to reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (1:1 petroleum ether:EtOAc) afforded the *title compound* (0.315 g, 72%) as a pale yellow solid. Analytical data as reported above.

Methyl 2-(4-methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoate

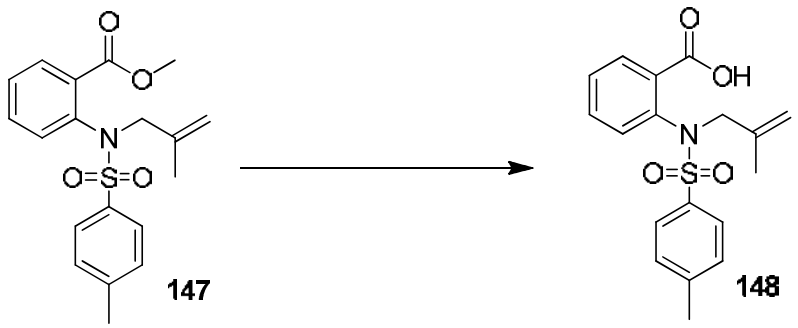


Prepared according to the general literature procedure.[158]

Sodium hydride (0.20 g, 4.92 mmol) was added to a stirred solution of **141** (1.00 g, 3.28 mmol) and methallyl chloride (0.65 mL, 6.56 mmol) in DMF (15 mL). After stirring for 14 hours at room temperature, the reaction mixture was diluted with Et_2O (100 mL), washed with 1M HCl (3 x 50 mL) then brine (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (2:1 petroleum ether:ether) gave the *title compound* **147** as a clear oil (0.97 g, 82%). ν_{max}(neat)/cm^{-1}: 2984, 1734, 1687, 1491, 1256, 1158; δ_H (300 MHz; $CDCl_3$)

1.82 (3H, s, CH_3), 2.40 (3H, s, CH_3), 3.79 (3H, s, CH_3), 4.21 (2H, s, NCH_2), 4.65 (1H, s, C=CH_aH$_b$), 4.87 (1H, s, C=CH$_a$$H_b$), 6.87-7.06 (1H, m, CH), 7.15-7.55 (6H, m, 6 x CH), 7.87 (1H, d, *J* = 7.6 Hz, CH); δ_c (100 MHz; $CDCl_3$) 20.5 (CH_3), 21.6 (CH_3), 52.2 (CH_3), 57.7 (CH_2), 116.0 (CH_2), 127.4 (2 x CH), 127.8 (CH), 129.4 (2 x CH), 129.7 (CH), 130.4 (CH), 131.6 (CH), 132.1 (C), 136.3 (C), 138.0 (C), 140.4 (C), 143.2 (C), 166.7 (C=O); *m/z* (ESI) 382 ($[M+Na]^+$ 100%); HRMS (ESI) calculated for $C_{19}H_{21}O_4SNNa$ $[M+Na]^+$ 382.1089, found 382.1095.

2-(4-Methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoic acid

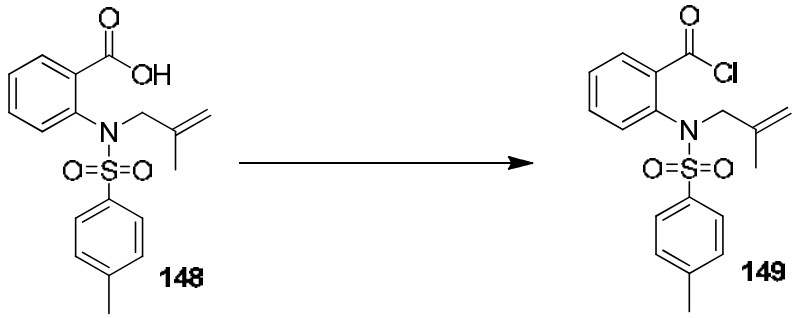


Prepared according to the general literature procedure.[158]

147 (0.97 g, 2.7 mmol) was dissolved in MeOH/H_2O (1:1, 26 mL) and LiOH•H_2O (0.32 g, 13.5 mmol) was added. The reaction mixture was heated at 70 °C for 2.5 h then cooled to room temperature. HCl (2 M, 25 mL) and Et_2O (60 mL) were added. The layers were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. After washing with cold pentane (1 x 25 mL), the product **148** was obtained as a yellow solid (0.7 g, 75%). m.p. 166-168 °C; ν_{max} (neat)/cm^{-1}: 2930, 1702, 1671, 1343, 1158, 1089; δ_H (300 MHz; $CDCl_3$); 1.84 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.92 (1H, s, NCH_aH$_b$), 4.51 (1H, s, NCH$_a$$H_b$), 4.68 (1H, s, C=C$H_cH_d$), 4.74 (1H, s, C=CH$_c$$H_d$), 6.82-6.98 (1H, m, CH), 7.27-7.33 (2H, m, 2 x CH), 7.41-7.49 (2H, m, 2 x CH), 7.54 (2H, d, *J* = 8.3 Hz, CH), 7.90-8.05 (CH); δ_c (100 MHz; $CDCl_3$) 20.5 (CH_3), 21.8 (CH_3), 58.6 (CH_2), 107.4 (C),

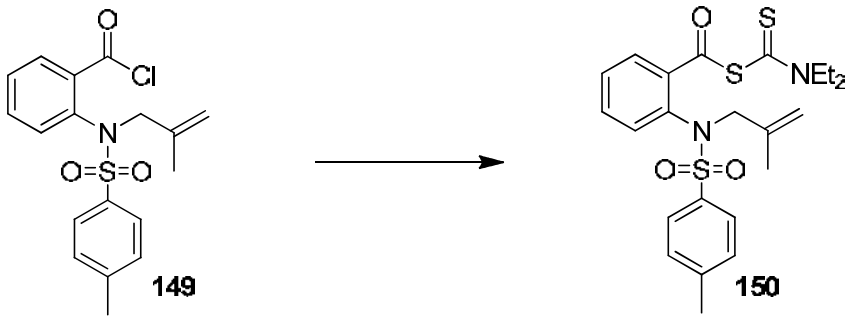
116.8 (CH_2), 128.3 (2 x CH), 128.7 (CH), 129.7 (2 x CH), 130.0 (CH), 132.2 (CH), 132.7 (CH), 134.8 (C), 137.8 (C), 139.7 (C), 144.3 (C), 169.1 (C=O); *m/z* (ESI) 485 $[M+Na]^+$; HRMS (ESI) calculated for $C_{18}H_{19}O_4SNNa$ $[M+Na]^+$ 368.0932, found 368.0923.

2-(4-Methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoyl chloride



Freshly distilled oxalyl chloride (0.15 mL, 1.60 mmol) was added to a stirred solution of **148** (0.5 g, 1.45 mmol) and one drop of DMF in CH_2Cl_2 (6 mL) at room temperature. After 15 minutes the solvent and excess oxalyl chloride were removed under reduced pressure, to give the product as a white semi-solid which was used without further purification.

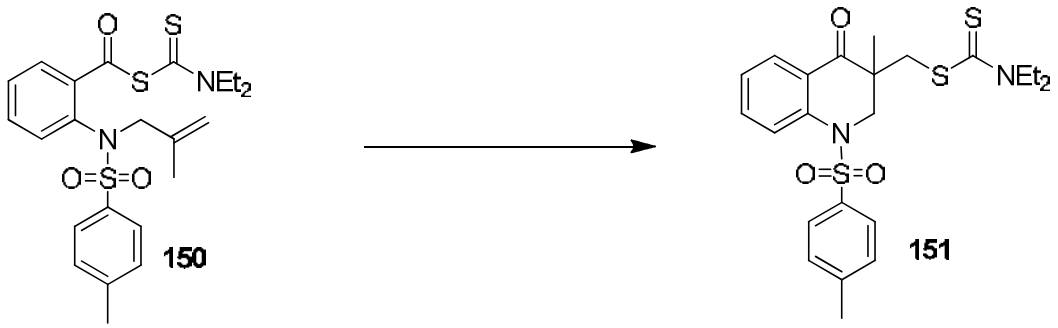
2-(4-Methyl-*N*-(2-methylallyl)phenylsulfonamido)benzoicdiethylcarbamothioic thioanyhydride



Prepared according to the general literature procedure.[51]

Acid chloride **149** (1.45 mmol) was dissolved in acetone (14 mL) and cooled to 0 °C. Sodium diethyldithiocarbamate trihydrate (0.32 g, 1.45 mmol) was added in one portion and the solution was stirred at 0 °C for 20 minutes in the dark. Saturated $NaHCO_3$ (10 mL) was added followed by water (20 mL) until the inorganic salts dissolved. Et_2O (100 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 50 mL) and the combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether:EtOAc) to afford the *title compound* as a yellow oil (0.54 g, 82% over 2 steps). R_f 0.32 (1:1 petroleum ether:EtOAc); ν_{max} (neat)/cm^{-1}: 2900, 2834, 1698, 1463, 1168; δ_H (300 MHz; $CDCl_3$); 1.30-1.47 (6H, m, 2 x CH_3), 1.78 (1H, s, CH_3), 2.47 (3H, s, CH_3), 3.90-4.30 (6H, m, 3 x CH_2), 4.68 (1H, s, CH_aH_b), 4.77 (1H, s, CH_aH_b), 6.76-6.80 (1H, m, CH) 7.24-7.30 (2H, m, 2 x CH), 7.37-7.42 (2H, m, 2 x CH), 7.48 (2H, d, *J* = 8.3 Hz, 2 x CH), 7.91-7.96 (CH); δ_c (100 MHz; $CDCl_3$, -30 °C); 11.1 (CH_3), 14.2 (CH_3), 21.1 (CH_3), 21.8 (CH_3), 48.9 (CH_2), 51.0 (CH_2), 57.2 (CH_2), 117.1 (CH2), 127.8 (CH), 127.9 (CH), 128.1 (CH), 129.5 (CH), 129.6 (CH), 129.7 (CH), 130.2 (CH), 132.1 (CH), 133.5 (C), 136.0 (C), 137.8 (C), 139.3 (C), 144.1 (C), 181.2 (C=O), 186.5 (C=S); *m/z* (ESI) 499 ($[M+Na]^+$ 100%); HRMS (ESI) calculated for $C_{23}H_{28}O_3S_3N_2Na$ $[M+Na]^+$ 499.1160, found 499.1173.

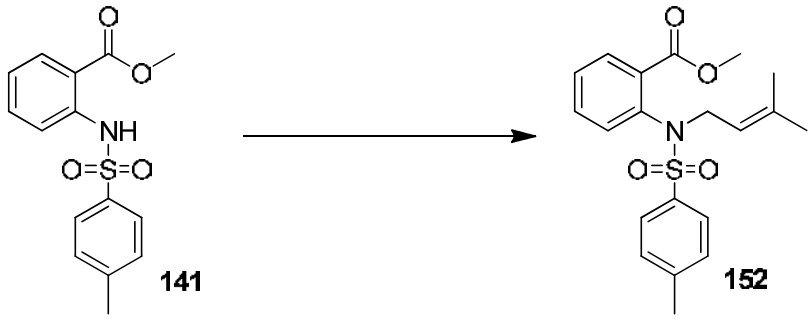
(3-Methyl-4-oxo-1-tosyl-1,2,3,4-tetrahydroquinolin-3-yl)methyl diethylcarbamodithioate



A solution of acyl dithiocarbamate **150** (0.20 g, 0.4 mmol) in cyclohexane (4 mL) was degassed for 15 min. The yellow solution was stirred vigorously and irradiated for 2 hours with a 500 W halogen lamp from a distance of approximately 15 cm, the heat generated by the lamp being sufficient to bring the solution to reflux. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (1:1 petroleum ether:EtOAc) provided the *title compound* (0.14 g, 70%) as a yellow oil. R_f 0.32 (1:1 petroleum ether:EtOAc); ν_{max} (neat)/cm^{-1}: 2917, 2834, 1709, 1608, 1437, 1348, 1168; δ_H (300 MHz; $CDCl_3$); 1.28 (6H, t, *J* = 7.1 Hz, 2 x CH_3), 1.43 (3H, s, CH_3), 2.44 (3H, s, CH_3), 3.71-4.12 (7H, m, 2 x CH_2, CH_aH_b, SCH_2), 4.45 (1H, d, *J* =13.0 Hz, CH_aH_b), 7.08-7.16 (1H, m, CH), 7.35 (2H, d, *J* = 8.1 Hz, 2 x CH), 7.45 (1H, ddd, *J* = 8.7, 7.2, 1.7 Hz, CH), 7.66 (1H, d, *J* = 8.4 Hz, CH), 7.84 (2H, d, *J* = 8.3 Hz, 2 x CH), 8.03 (1H, dd, *J* = 7.9, 1.7 Hz, CH); δ_c (100 MHz; $CDCl_3$); 11.6 (CH_3), 12.7 (CH_3), 20.5 (CH_3), 21.7 (CH_3), 41.3 (CH_2), 46.9 (CH_2), 47.5 (C), 50.3 (CH_2), 54.7 (CH_2), 118.6 (CH), 122.0 (C), 123.5 (CH), 127.2 (2 x CH), 129.3 (CH), 130.2 (2 x CH), 134.8 (CH), 136.8 (C), 142.4 (C), 144.5 (C), 195.2 (C=O), 196.4 (C=S); *m/z* (ESI) 499 ($[M+Na]^+$ 100%); HRMS (ESI) calculated for $C_{23}H_{28}O_3S_3N_2Na$ $[M+Na]^+$ 499.1160, found 499.1150.

A solution of acyl dithiocarbamate **150** (0.20 g, 0.4 mmol) in cyclohexane (4 mL) was degassed for 15 min. Dilauroyl peroxide (0.03 g, 0.08 mmol) was added and the resultant solution heated to reflux. A further two portions of dilauroyl peroxide (2 x 0.03 g, 0.08 mmol) were added after 2 hours and 4 hours. After a further 2 hours of heating to reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (1:1 petroleum ether:EtOAc) afforded the title compound (0.11 g, 57%) as a yellow oil. Analytical data as reported above.

Methyl 2-(4-methyl-*N*-(3-methylbut-2-en-1-yl)phenylsulfonamido)benzoate

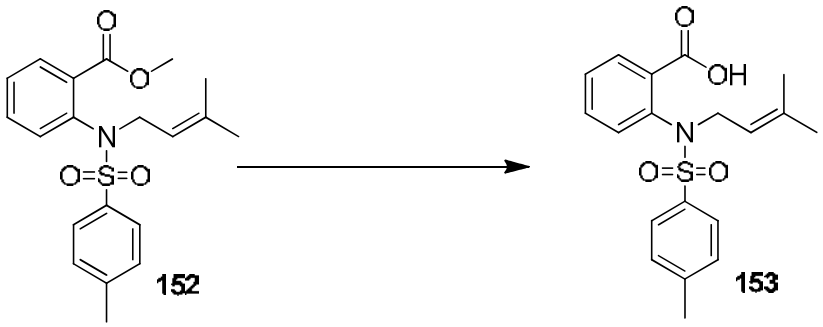


Prepared according to the general literature procedure.[158]

Sodium hydride (60%, 0.2 g, 4.92 mmol) was added to a stirred solution of **141** (1.00 g, 3.28 mmol) and 3,3 dimethylallyl bromide (0.75 mL, 6.56 mmol) in anhydrous DMF (15 mL). After stirring for 14 hours at room temperature, the reaction mixture was diluted with Et_2O (100 mL), washed with 1M HCl (3 x 50 mL) then brine (2 x 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by column chromatography (2:1 petroleum ether:EtOAc) gave the *title compound* as a clear oil (0.80 g, 65%). R_f = 0.21 (2:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2912, 1738, 1342, 1295, 1256 1087; δ_H (300 MHz; $CDCl_3$); 1.40 (3H, s, CH_3), 1.62 (3H, s, CH_3),

2.43 (3H, s, CH_3), 3.81 (3H, s, CH_3), 4.28 (2H, d, *J* =7.3 Hz, CH_2), 5.13-5.36 (1H, m, CH), 6.89-7.05 (1H, m, CH), 7.21-7.31 (2H, m, 2 x CH), 7.33-7.46 (2H, m, 2 x CH), 7.55 (2H, d, *J* = 8.3 Hz, 2 x CH), 7.76-7.95 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 17.7 (CH_3), 21.6 (CH_3), 25.8 (CH_3), 49.5 (CH_2), 52.3 (CH_3), 118.4 (CH), 119.2 (CH), 127.7 (2 x CH), 128.2 (CH), 129.4 (2 x CH), 131.2 (CH), 131.3 (CH), 132.9 (C), 137.3 (C), 137.4 (C), 138.3 (C), 143.1 (C), 166.8 (C=O); *m/z* (ESI) 396 ($[M+Na]^+$ 100%); HRMS calculated for $C_{20}H_{22}O_4SNNa$ $[M+Na]^+$ 396.1061, found 396.1064.

2-(4-Methyl-*N*-(3-methylbut-2-en-1-yl)phenylsulfonamido)benzoic acid

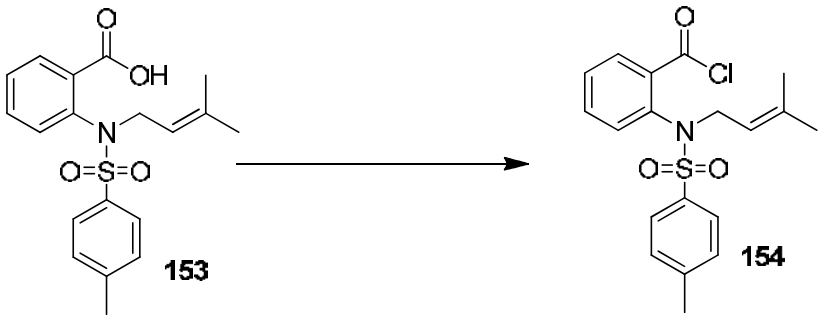


Prepared as according to the general literature procedure.[158]

152 (0.96 g, 2.56 mmol) was dissolved in MeOH/H_2O (1:1, 24 mL) and LiOH•H_2O (0.30 g, 12.8 mmol) was added. The reaction mixture was heated at 70 °C for 2.5 h then cooled to room temperature. HCl (2 M, 30 mL) and Et_2O (70 mL) were added. The layers were separated and the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure. After washing with cold pentane (1 x 25 mL), the *title compound* was obtained as a white solid (0.85 g, 93%). m.p. = 122-124 °C; ν_{max}(neat)/cm^{-1}: 2974, 2933, 1678, 1597, 1412, 1297, 1269, 1159; δ_H (300 MHz; $CDCl_3$) ; 1.43 (3H, s, CH_3), 1.61 (3H, s,

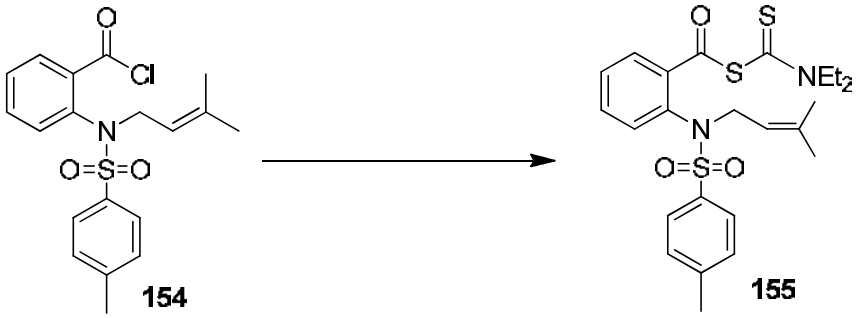
CH_3), 2.47 (3H, s, CH_3), 4.04 (1H, br s, CH_aH_b), 4.43 (1H, s, CH_aH_b), 4.95-5.25 (1H, m, CH), 6.75-6.97 (1H, m, CH), 7.33 (2H, d, *J* = 8.1 Hz, 2 x CH), 7.40-7.52 (2H, m, 2 x CH), 7.62 (2H, d, *J* =8.3 Hz, 2 x CH), 7.91-8.20 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 17.7 (CH_3), 21.8 (CH_3), 25.8 (CH_3), 49.9 (CH_2), 117.1 (CH), 118.4 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH), 129.9 (CH), 132.3 (CH), 132.4 (CH), 132.7 (CH), 134.2 (C), 134.5 (C), 137.9 (C), 140.1 (C), 144.7 (C), 167.4 (C=O); m/z (ESI) 382 ($[M+Na]^+$ 100%); HRMS (ESI) calculated for $C_{19}H_{21}O_4SNNa$ $[M+Na]^+$ 382.1089*,* found 382.1079.

2-(4-Methyl-*N*-(3-methylbut-2-en-1-yl)phenylsulfonamido)benzoyl chloride



Freshly distilled oxalyl chloride (0.067 mL, 0.77 mmol) was added to a stirred solution of **153** (0.25 g, 0.70 mmol) and one drop of DMF in CH_2Cl_2 (2.5 mL) at room temperature. After 15 minutes the solvent and excess oxalyl chloride were removed under reduced pressure, to give the *title compound* as a white semi-solid which was used without further purificaction.

2-(4-Methyl-*N*-(3-methylbut-2-en-1-yl)phenylsulfonamido)benzoic diethylcarbamothioic thioanyhydride

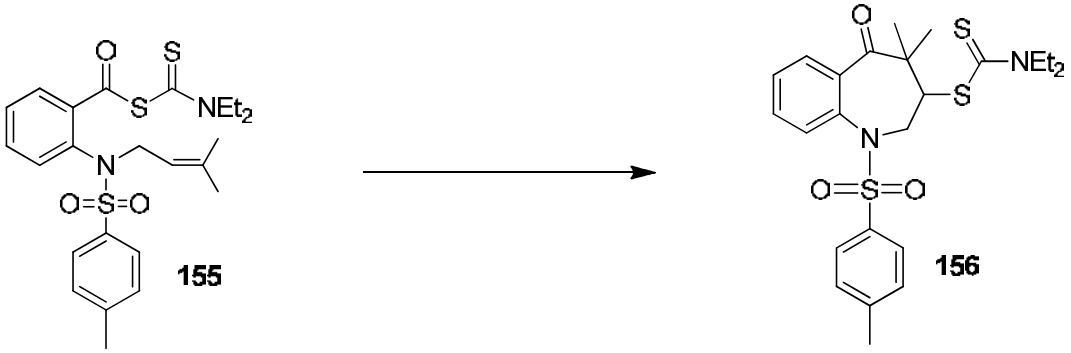


Prepared according to the general literature procedure.[51]

Acid chloride **154** (0.7 mmol) was dissolved in acetone (5 mL) and cooled to 0 °C. Sodium diethyldithiocarbamate trihydrate (0.157 g, 0.7 mmol) was added in one portion and the solution was stirred at 0 °C for 20 minutes in the dark. Saturated $NaHCO_3$ (5 mL) was added followed by water (10 mL) until the inorganic salts dissolved. Et_2O (50 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 25 mL) and the combined organic extracts were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 petroleum ether:EtOAc) to afford the *title compound* as a yellow oil (0.30 g, 88% over 2 steps). R_f 0.25 (1:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2972, 2929, 1667, 1493, 1345, 1160, 1089; δ_H (300 MHz; $CDCl_3$); 1.38 (6H, t, *J* = 7.6 Hz, 2 x CH_2CH_3), 1.45 (3H, s, CH_3), 1.54 (3H, s, CH_3), 2.34 (3H, s, CH_3) 3.96-4.39 (6H, m, 3 x CH_2), 5.10-5.24 (1H, m, CH), 6.60 (1H, dd, *J* = 7.6, 1.4 Hz, CH), 7.23 (2H, d, *J* = 8.4 Hz, 2 x CH), 7.28-7.39 (2H, m, 2 x CH), 7.43 (2H, d, *J* =8.3 Hz, 2 x CH), 7.79 (1H, dd, *J* = 7.5 Hz, 1.9 Hz, CH); δc (100 MHz; $CDCl_3$), 17.8 (CH_3), 21.5 (CH_3), 25.6 (CH_3), 49.2 (CH_2), 117.8 (CH), 127.9 (2 x CH), 128.3 (CH), 128.5 (CH), 129.4 (2 x CH), 129.7 (CH), 131.9 (CH), 134.9 (C), 136.8

(C), 137.9 (C), 138.9 (C), 143.7 (C), 181.9 (C=O), 186.4 (C=S); δ_c (100 MHz; $CDCl_3$, - 30 °C): 10.9 (CH_3), 13.9 (CH_3), 17.9 (CH_3), 21.6 (CH_3), 25.7 (CH_3), 48.4 (CH_2), 48.7 (CH_2), 50.8 (CH_2), 117.0 (CH), 127.2 (2 x CH), 127.6 (CH), 128.2 (CH), 129.4 (2 x CH), 129.5 (CH), 132.0 (CH), 133.2 (C), 136.3 (C), 138.1 (C), 138.3 (C), 143.9 (C), 181.6 (C=O), 186.7 (C=S); *m/z* (ESI) 513 ($[M+Na]^+$ 100%); HRMS calculated for $C_{24}H_{30}O_3S_3N_2Na$ $[M+Na]^+$ 513.1316, found 513.1304.

(4,4)dimethyl-5-oxo-1-tosyl-2,3,4,5-tetrahydro-1H-benzene)azepin-3-yl diethylcarbamodithioate



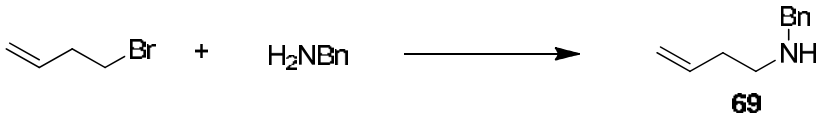
A solution of acyl dithiocarbamate **155** (0.1 g, 0.2 mmol) in cyclohexane (2 mL) was degassed for 15 min. The yellow solution was stirred vigorously and irradiated for 20 min. with a 500 W halogen lamp from a distance of approximately 15 cm, the heat generated by the lamp being sufficient to bring the solution to reflux. The solution was cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (1:1 petroleum ether:EtOAc) provided the *title compound* (0.048 g, 48%) as a viscous yellow oil. R_f 0.29 (1:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2924, 2854, 1707, 1598, 1457, 1357, 1166; δ_H (300 MHz; $CDCl_3$); 1.25-1.40 (9H, m, 3 x CH_3), 2.09 (3H, s, CH_3), 2.39 (3H, s, CH_3), 3.73-4.08 (7H, m, 3 x CH_2, CHS), 4.62 (1H, dd, *J* = 11.8, 5.5 Hz, CH_aH_b), 4.87

(1H, dd, *J* =13.9, 5.5 Hz, CH_aH_b), 7.17-7.26 (3H, m, 3 x CH), 7.47-7.53 (1H, m, CH), 7.68-7.75 (2H, m, 2 x CH), 7.82-7.91 (2H, m, 2 x CH); δc (100 MHz; $CDCl_3$); 11.9 (CH_3), 12.9 (CH_3), 21.7 (CH_3), 24.7 (CH_3), 27.9 (CH_3), 47.4 (CH_2), 47.9 (CH_2) 49.1 (CH_2), 49.5 (CH), 56.1 (C), 122.4 (CH), 124.8 (CH), 127.3 (C), 127.7 (2 x CH), 128.0 (CH), 129.9 (2 x CH), 134.4 (CH), 135.9 (C), 142.0 (C), 144.4 (C), 193.1 (C=O), 195.0 (C=S); *m/z* (ESI) 513 ($[M+Na]^+$ 100%); HRMS calculated for $C_{24}H_{30}O_3S_3N_2Na$ $[M+Na]^+$ 513.1316, found 513.1300.

A solution of acyl dithiocarbamate **155** (0.1 g, 0.2 mmol) in cyclohexane (2 mL) was degassed for 15 min. Dilauroyl peroxide (0.016 g, 0.04 mmol) was added and the resultant solution heated to reflux. A further two portions of dilauroyl peroxide (2 x 0.016 g, 0.04 mmol) were added after 2 hours and 4 hours. After a further 2 hours of heating to reflux the solution was cooled to room temperature and concentrated under reduced pressure. Purification by column chromatography (1:1 petroleum ether:EtOAc) afforded the *title compound* (0.032g, 32%) as a yellow oil. Analytical data as reported above.

Chapter 2 – Experimental

***N*-Benzylbut-3-en-1-amine**[159]



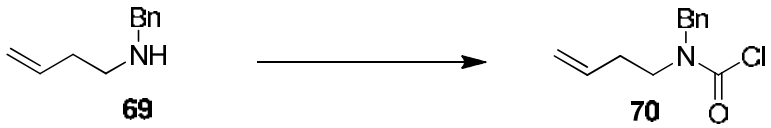
69

Prepared according to the literature procedure.[159]

A solution of 4-bromo-1-butene (1.35 g, 10.0 mmol) in ethanol (15 mL) was treated with benzylamine (5.4 g, 50.5 mmol) and sodium iodide (110 mg, 0.7 mmol) and the resultant

mixture heated to reflux for 4 hours. The reaction was quenched with 10% sodium hydroxide solution and extracted with diethyl ether (3 x 15 mL). The organic extracts were combined, washed with water then brine, dried ($MgSO_4$) and concentrated under reduced pressure. The resulting crude product was purified by column chromatography (2:1 petroleum ether:EtOAc) to give the amine (1.40 g, 87%) as a yellow oil, whose analytical data were in agreement with literature values;[159] ν_{max} (neat)/cm^{-1}: 1640, 1451, 1110, 912, 732, 696; δ_H (300 MHz; $CDCl_3$) 1.29 (1H, br s, NH), 2.25-2.32 (2H, m, =CHC*H*$_2$), 2.71 (2H, t, *J* = 6.8 Hz, NC*H*$_2$CH$_2$), 3.80 (2H, s, PhC*H*$_2$N), 5.02-5.13 (2H, m, C*H*$_2$=CH), 5.74-5.85 (1H, m, CH$_2$=C*H*), 7.23-7.37 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) 34.5 (CH_2), 48.5 (NCH_2), 54.1 ($PhNCH_2$), 116.4 (CH_2), 127.1 (CH), 128.3 (2 x CH), 128.6 (2 x CH), 136.6 (CH), 140.6 (C).

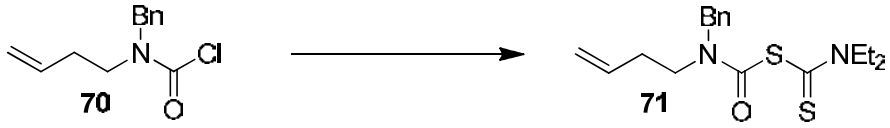
Benzyl(but-3-enyl)carbamic chloride



A solution of triphosgene (0.496 g, 1.7 mmol) in toluene (43 mL) was treated with pyridine (0.45 mL, 5.5 mmol), and subsequently with a solution of amine **69** (0.803 g, 5.0 mmol) in toluene (7 mL). The reaction was stirred at room temperature overnight, quenched with saturated Na_2CO_3 and extracted with diethylether (3 x 20 mL). The combined extracts were washed with hydrochloric acid (0.25M, 20 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **70** (1.0 g, 90 %) as a yellow oil; δ_H (300 MHz; $CDCl_3$) 2.31-2.39 (2H, m, =CHC*H*$_2$), 3.39-3.47 (2H, m, =CHCH$_2$C*H*$_2$), 4.59 (1H, s, 0.5 x PhC*H*$_2$), 4.72 (1H, s, 0.5

x PhCH_2), 5.06-5.11 (2H, m, CH_2=CH), 5.67-5.80 (1H, m, CH_2=C*H*), 7.25-7.40 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) (mixture of rotamers) 31.7 (CH_2), 32.7 (CH_2), 48.9 (NCH_2), 49.8 (NCH_2), 52.7 ($PhNCH_2$), 54.7 ($PhNCH_2$), 117.7 (CH_2), 117.9 (CH_2), 127.2 (CH), 128.2 (CH), 129.0 (CH), 133.9 (CH), 134.2 (CH), 135.6 (CH), 135.8 (CH_2), 149.6 (C=O), 150.3 (C=O); m/z (EI) 223 (M^+; 17), 182 (77), 132 (9), 91 (100), 65 (27).

Diethylthiocarbamic aicd-[benzyl(but-3-enyl)carbamic acid]-thioanyhdride[160]

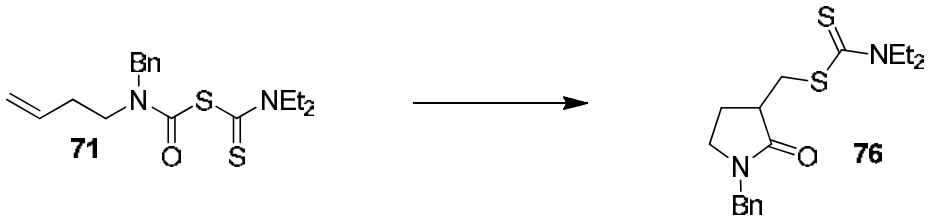


Prepared according to the general procedure.[160]

A solution of carbamoyl chloride **70** (0.981 g, 4.4 mmol) in acetone (30 mL) was treated with sodium diethyldithiocarbamate trihydrate (4.0g, 17.8 mmol). The reaction mixture was stirred at room temperature for 16 hours, quenched with saturated Na_2CO_3 and extracted with diethylether (3 x 20 mL). The combined extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl dithiocarbamate **71** (1.40 g, 95 %) as a bright yellow oil, whose analytical data was in accordance with that previously reported;[160] ν_{max} (neat)/cm^{-1}: 2976, 1668, 1493, 1420, 1271, 1189, 918, 732; δ_H (300 MHz; $CDCl_3$) 1.30-1.36 (6H, m, 2 x CH_2CH_3), 2.34 (2H, br s, =CHCH_2), 3.33-3.47 (2H, br m, CH_2N), 3.79 (2H, br m, CH_2CH_3), 4.03 (2H, q, *J* = 6.9 Hz, CH_2CH_3), 4.63 (2H, s, CH_2), 5.03-5.09 (2H, br m, CH_2), 5.72-5.74 (1H, br m, CH), 7.26-7.31 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) (mixture of rotamers) 11.1 (CH_3), 13.3 (CH_3), 31.5 (CH_2), 32.6 (CH_2), 47.1 (CH_2), 47.7 (CH_2), 48.8 (CH_2), 49.9 (CH_2), 50.1 (CH_2), 50.4 (CH_2), 53.1 (CH_2), 117.0 (CH_2), 117.5 (CH_2), 127.0 (CH), 127.8 (CH), 128.1 (CH), 128.6

(CH), 134.0 (CH), 134.7 (CH), 135.9 (C), 136.2 (C), 162.0 (C=O), 162.7 (C=O), 184.7 (C=S), 184.9 (C=S); *m/z* (EI) 336 (M^+; 11), 188 (40), 147 (42), 91 (100), 72 (17); HRMS (ESI) calcd for $C_{17}H_{24}N_2OS_2Na$ (M+Na): 359.1222; found 359.1220

(1-Benzyl-2-oxopyrrolidin-3-yl)methyl diethylcarbamodithioate[160]



Prepared according to the literature procedure.[160]

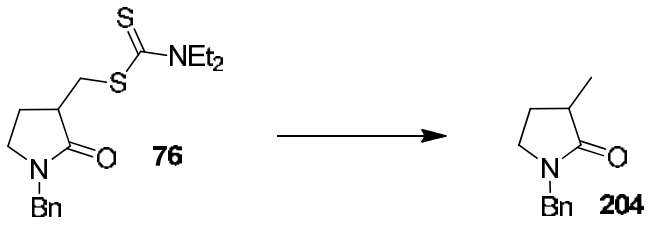
A solution of carbamoyl dithiocarbamate **71** (0.87 g, 2.6 mmol) in cyclohexane (30 mL) was degassed and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 3 hours the solvent was removed under reduced pressure and the crude product purified by column chromatography (hexane:EtOAc 3:1) to give lactam **76** (0.836 g, 96%) as a yellow solid, whose analytical data was consistent with that previously reported;[160] mp 57-61 °C; ν_{max} (neat)/cm^{-1}: 2967, 1682, 1489, 1269, 1206, 1143, 1076, 985, 917, 832, 702; δ_H (300 MHz; $CDCl_3$) 1.25-1.31 (6H, m, 2 x CH_3), 1.84-1.95 (1H, m, CH_2), 2.19-2.22 (1H, m, CH_2), 2.94-3.02 (1H, m, CH), 3.17-3.21 (2H, m, CH_2), 3.66 (1H, dd, *J* = 13.7 Hz and 6.7 Hz, CH_2), 3.71-3.85 (2H, m, CH_2), 3.91 (1H, dd, *J* = 13.7 Hz and 5.2 Hz, CH_2), 3.95-4.14 (2H, m, CH_2), 4.41 (1H, d, J = 14.7 Hz, CH_2), 4.53 (1H, d, J = 14.7 Hz, CH_2), 7.23-7.35 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) 11.5 (CH_3), 12.5 (CH_3), 23.6 (CH_2), 37.8 (CH_2), 41.7 (CH), 44.7 (CH_2), 46.6 (CH_2), 46.7 (CH_2), 49.7 (CH_2), 127.5 (CH), 128.0 (2 x CH), 128.6 (2 x CH), 136.4 (C), 174.7 (C=O), 195.5 (C=S); *m/z* (EI) 337 (M^+ +1; 5),

188 (100), 116 (36), 91 (29); HRMS (ESI) calcd for $C_{17}H_{24}N_2O_2S_2Na$ (M+Na): 359.1222; found 359.1225

General procedure for reduction of dithiocarbamates using H_3PO_2–Et_3N–ACCN

A solution of dithiocarbamate (1 equiv.), triethylamine (5.5 equiv.) and hypophosphorous acid (50 wt% in water, 5.0 equiv.) in dioxane (0.08 M dithiocarbamate in dioxane) was heated to reflux for 20 min under an argon atmosphere. ACCN (0.15 equiv.) was added to the solution, and the resultant reaction mixture was heated to reflux. An additional portion of ACCN (0.15 equiv.) was added if required, typically after 4 h of reflux. Upon completion (by t.l.c. analysis) the reaction mixture was cooled to room temperature. EtOAc and H_2O were added, and the aqueous layer extracted a further two times with EtOAc (approximately equal volumes of H_2O and EtOAc as dioxane were used). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography.

1-Benzyl-3-methylpyrrolidin-2-one



The reduced product **204** was prepared according to the general experimental. Dithiocarbamate **76** (0.25 g, 0.74 mmol) was dissolved in dioxane (9.3 mL) and treated

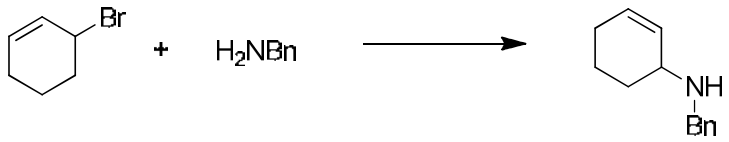
with triethlamine (0.56 mL, 4.07 mmol) and hypophosphorus acid (0.38 mL, 3.72 mmol). After 20 minutes at reflux ACCN (0.027 g, 0.11 mmol) was added. After a further 4 hours at reflux, a further portion of ACCN (0.027 g, 0.11 mmol) was added to the reaction mixture and the reaction continued for a further 14 hours. The work up was completed according to the general procedure. The crude product was purified by column chromatography (1:1 hexane:EtOAc) to afford the reduced product **204** as a yellow oil (0.108g, 77%) whose analytical data were consistent with that reported in the literature;[36] ν_{max} (neat)/cm^{-1}: 2972 (br), 1740 (C=O), 1671, 1418, 1219, 1205, 1044; δ_H (300 MHz; $CDCl_3$) 1.23 (3H, d, *J* = 7.0 Hz, CH_3), 1.52-1.65 (1H, m, CH_2), 2.14-2.25 (1H, m, CH_2), 2.44-2.57 (1H, m, CH), 3.14-3.20 (2H, m, CH_2), 4.39-4.50 (2H, m, CH_2), 7.20-7.34 (5H, m, 5 x CH); δc (100 MHz; $CDCl_3$) 16.4 (CH_3), 27.1 (CH_2), 36.7 (CH), 44.6 (CH_2), 46.7 (CH_2), 127.5, 128.1, 128.6 (5 × CH), 136.7 (C), 177.4 (C=O); HRMS (ESI) calculated for $C_{12}H_{15}NONa$ $[M+Na]^+$ 212.1051, found 212.1048.

Deuterated 1-Benzyl-3-methylpyrrolidin-2-one

The reduced product was prepared according to the general experimental. Dithiocarbamate **76** (0.40 g, 1.20 mmol) was dissolved in dioxane (15 mL) and treated with triethlamine (0.92 mL, 6.6 mmol) and deuterated hypophosphorus acid (0.60 mL, 5.95 mmol). After 20 minutes at reflux ACCN (0.04 g, 0.18 mmol) was added. After a further 4 hours at reflux, a further portion of ACCN (0.04 g, 0.18 mmol) was added to the

reaction mixture and the reaction continued for a further 14 hours. The work up was completed according to the general procedure. The crude product was purified by column chromatography (1:1 hexane:EtOAc) to afford the reduced product as a yellow oil (0.1484 g, 65%); R_f 0.24 (1:1 Hexane:EtOAc); v_{max} (neat)/cm^{-1}: 2972 (br), 1740 (C=O), 1671, 1418, 1219, 1205, 1044; δ_H (300 MHz; $CDCl_3$) 1.18-1.29 (3H, m, CH_3 and CH_2D), 1.49-1.63 (1H, m, CH_2), 2.14-2.25 (1H, m, CH_2), 2.44-2.57 (1H, m, CH), 3.14-3.20 (2H, m, CH_2), 4.31-4.50 (2H, m, CH_2), 7.20-7.34 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$) 16.1 (t, *J* = 17.6 Hz, CH_2D), 16.4 (CH_3), 27.0 (CH_2), 36.7 (CH), 44.6 (CH_2), 46.7 (CH_2), 127.5 (CH), 128.0 (2 x CH), 128.6 (2 × CH), 136.6 (C), 177.4 (C=O); HRMS (EI) calculated for $C_{12}H_{14}DNO[M]^+$ 190.1216, found 190.1215. 53% D by MS analysis.

_N_-Benzylcyclohex-2-enamine[161]

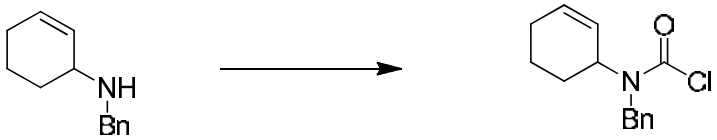


Prepared according to the general literature procedure.[161]

A solution of benzylamine (9.7 ml, 89.1 mmol, 2.7 equiv.) in acetonitrile (90 ml) was treated with 3-bromocyclohexene (3.8 ml, 33.0 mmol) and potassium carbonate (4.79 g, 34.7 mmol). After stirring for 2 hours at room temperature, the reaction mixture was quenched with water (50 ml) and extracted with EtOAc (2 x75 ml). The combined organic extracts were washed with brine (50 ml), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (CH_2Cl_2 increasing to CH_2Cl_2: EtOH 9:1) to give *N*-benzylcyclohex-2-enamine as a colourless oil. Analytical data was consistent with that reported in the literature;[161] v_{max}(neat)/cm^{-1}: 3063, 2926, 1452,

1106,723, 696; δ_H (300 MHz; $CDCl_3$) 1.38 (1H, br s, NH), 1.47-1.63 (2H, m, CH_2), 1.73-1.81 (1H, m, CH_2), 1.89-1.97 (1H, m, CH_2), 1.99-2.06 (2H, m, CH_2), 3.20-3.26 (1H, m, CH), 3.84 (1H, d, *J* = 13.0 Hz, CH_2), 3.88 (1H, d, *J* = 13.0 Hz, CH_2), 5.75-5.82 (2H, m, CH), 7.23-7.38 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) 20.3 (CH_2), 25.5 (CH_2), 29.6 (CH_2), 51.1 (CH_2), 52.5 (CH), 126.9 (CH), 128.3 (CH), 128.4 (CH), 129.1 (CH), 130.1 (CH), 140.9 (C); *m/z* (ESI) 188 ($[M+H]^+$, 100 %)

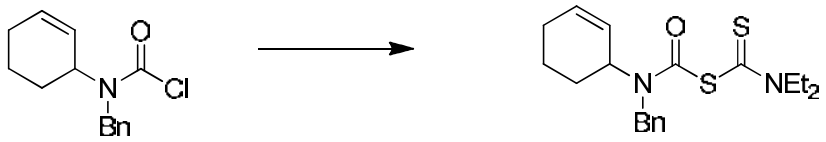
Benzyl(cyclohex-2-enyl)carbamic chloride[160]



A solution of triphosgene (0.85 g, 2.87 mmol) in toluene (50 mL) was treated with pyridine (0.75 mL, 9.3 mmol) and subsequently with a solution of *N*-benzylcyclohex-2-enamine (1.46 g, 7.78 mmol) in toluene (5 mL). The reaction was stirred for 18 h, quenched with saturated sodium bicarbonate (40 mL, and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with hydrochloric acid (0.25 M, 40 mL), water (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give benzyl(cyclohex-2-enyl)carbamic chloride (1.85 g, 95%) as a white solid. Analytical data was consistent with that previously reported.[160] mp 73-75 °C; R_f 0.55 (pet ether: EtOAc 85:15); V_{max} neat/cm^{-1}: 2920, 1607, 1477, 1419, 727, 697; δ_H (300 MHz; $CDCl_3$) 1.57-1.71 (2H, m, CH_2), 1.80-1.92 (2H,m, CH_2), 2.02 (2H, br s, CH_2), 4.16-4.37 (2H, m, CH_2), 4.48-4.50 (1H, m, CH), 5.52-5.54 (1H, m, CH), 5.88-5.91 (1H, m, CH), 7.21-7.32 (5H, m, 5 x CH); δ_c (75 MHz; $CDCl_3$) 22.0 (CH_2), 24.7 (CH_2), 28.0 (CH_2), 47.0 (CH_2),

57.2 (CH), 126.6 (CH), 127.2 (CH), 128.2 (CH), 129.0 (CH), 129.1 (CH), 131.5 (CH), 140.3 (C), 164.9 (C=O).

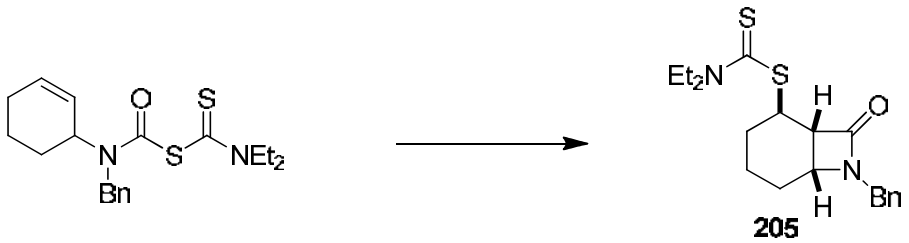
Diethyldithiocarbamic acid-[benzyl(cyclohex-2-enyl)carbamic acid]-thioanhydride[160]



Prepared according to the general literature procedure.[160]

A solution of benzyl(cyclohex-2-enyl)carbamic chloride (4.27 g, 15.0 mmol) in acetone (100 ml) was treated with sodium diethyldithiocarbamate trihydrate (13.52 g, 60.0 mmol). The solution was stirred at room temperature for 18 h quenched with water (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether:EtOAc 95:5 increasing to 85:15) gave the product as a yellow oil (4.88 g, 90%), whose analytical data was consistent with that previously reported;[160] ν_{max} neat/cm^{-1}: 2931, 1663, 1492, 1418, 1271, 916, 725; δ_H (300 MHz; $CDCl_3$) 1.19-1.34 (6H, m, 2 x CH_2CH_3), 1.42-1.74 (6H, m, 3 x CH_2), 3.62-3.94 (4H, m, 2 x CH_2), 4.38-5.13 (3H, m, CH and CH_2), 5.43-5.46 (1H, m, CH), 5.80-5.82 (1H, m, CH), 7.08-7.33 (5H ,m, 5 x CH); δ_c (75 MHz; $CDCl_3$) 11.3 (CH_3), 13.4 (CH_3), 21.4 (CH_2), 24.5 (CH_2), 27.5 (CH_2), 48.9 (CH_2), 50.0 (CH_2), 52.1 (CH_2), 54.8 (CH), 126.2 (CH). 127.1 (CH), 128.5 (CH), 132.5 (CH), 138.4 (C), 163.0 (C=O), 185.3 (C=S); *m/z* (ESI) 385 ($[M+Na]^+$.

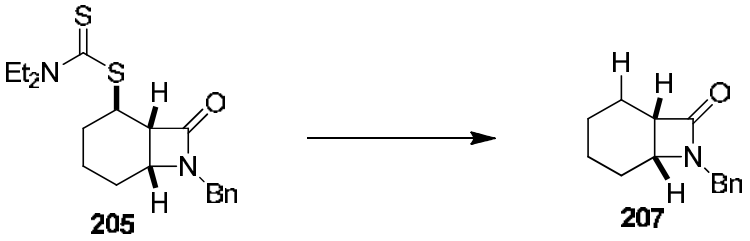
(1*RS*,2*SR*,6*SR*)-7-Benzyl-8-oxo-7-aza-bicyclo[4.2.0]octan-2-yl diethylcarbamodithioate[160]



Prepared according to the general literature procedure.[160]

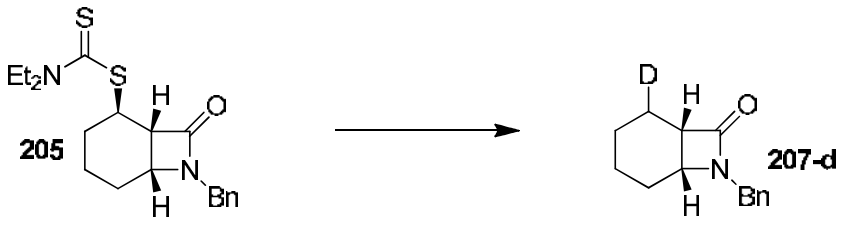
A solution of carbamoyl dithiocarbamate (3.86 g, 10.6 mmol) in cyclohexane (120 mL) was degassed and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 3 hours the solvent was removed under reduced pressure and the crude product purified by column chromatography (hexane:EtOAc 3:1) to give lactam **205** (2.91 g, 76%) as a yellow solid. The analytical data was consistent with that previously reported.[160] mp 86-89 °C; ν_{max} neat/cm^{-1}: 2926, 1729, 1208, 722; δ_H (300 MHz; $CDCl_3$) 1.27 (6H, t, *J* = 7.2 Hz, 2 x CH_3) 1.45-1.54 (2H, m, CH_2), 1.65-1.83 (3H, m, 0.5 x CH_2 and CH_2), 2.24-2.34 (1H, m, 0.5 x CH_2), 3.59-3.61 (1H, m, CH), 3.64-3.74 (3H, m, CH and CH_2), 3.92-4.06 (2H, m, CH_2), 4.15 (1H, d, *J* = 15.1 Hz, 1 x CH_2), 4.50-4.54 (1H, m, CH), 4.59 (1H, d, *J* = 15.1 Hz, 1 x CH_2), 7.23-7.36 (5H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$) 11.6 (CH_3), 12.5 (CH_3), 15.1 (CH_2), 22.1 (CH_2), 25.1 (CH_2), 44.3 (CH), 44.5 (CH_2), 46.7 (CH_2), 49.1 (CH_2), 50.2 (CH), 52.1 (CH), 127.7 (CH) 128.3 (2 x CH), 128.8 (2 x CH), 136.0 (C), 167.9 (C=O), 193.5 (C=S).

(1*S*,6*R*)-7-Benzyl-7-azabicyclo[4.2.0]octan-8-one



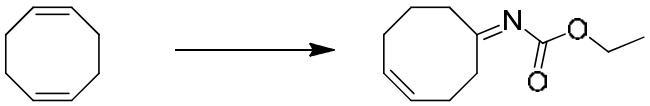
The reduced product **207** was prepared according to the general experimental. **205** (0.15 g, 0.4 mmol) was dissolved in dioxane (5 mL) and treated with triethylamine (0.31 mL, 2.2 mmol) and hypophosphorus acid (0.21 ml, 2.0 mmol). After 20 minutes at reflux ACCN (0.015 g, 0.06 mmol) was added. After a further 4 hours at reflux, another portion of ACCN (0.015 g, 0.06 mmol) was added to the reaction mixture and the reaction continued for a further 14 hours. The work up was completed according to the general procedure. The crude product was purified by column chromatography (1:2 hexane:EtOAc) to afford the reduced product as a yellow oil (0.068 g, 79%). R_f 0.32 (1:2 hexane:EtOAc); ν_{max}(neat)/cm^{-1}: 2935 (br), 1734 (C=O), 1400; δ_H (300 MHz; $CDCl_3$) 1.26-1.91 (8H, m, 4 x CH_2), 3.20 (1H, q, *J* = 5.3 Hz, CH), 3.65 (1H q, *J* = 5.3 Hz, CH), 4.10 (1H, d, *J* = 15.0 Hz, NCH_2), 4.60 (1H, d, *J* = 15.0 Hz, NCH_2), 7.26-7.37 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$) 16.8 (CH_2), 18.8 (CH_2), 19.6 (CH_2), 22.8 (CH_2), 44.4 (NCH_2), 46.9 (CH), 50.0 (CH), 127.2 (CH), 128.3 (2 x CH_3), 128.5 (2 x CH_3), 136.2 (C), 170.8 (C=O); *m/z* (EI) 215.1 ([M]$^+$, 75%), 134.1 (28%), 124.1 (36%), 91.1 (100%), 82.1 (62%), 67.1 (63%); HRMS (EI) calculated for $C_{14}H_{17}NO$ [M]$^+$ 215.1310, found 215.1318.

Deuterated (1*S*,6*R*)-7-Benzyl-7-azabicyclo[4.2.0]octan-8-one



205 (0.05 g, 0.14 mmol) was dissolved in dioxane (2 mL) and treated with triethylamine (0.1 mL, 0.8 mmol) and deuterated hypophosphorus acid (0.07 ml, 0.69 mmol). After 20 minutes at reflux $K_2S_2O_8$ (0.006 g, 0.02 mmol) was added. After a further 4 hours at reflux, another portion of $K_2S_2O_8$ (0.006 g, 0.02 mmol) was added to the reaction mixture and the reaction continued for a further 14 hours. The work up was completed according to the general procedure. The crude product was purified by column chromatography (1:2 hexane:EtOAc) to afford the reduced product as a clear oil (0.019 g, 63%). R_f 0.28 (1:2 hexane:EtOAc); ν_{max}(neat)/cm^{-1}: 2935 (br), 1734 (C=O), 1400; δ_H (300 MHz; $CDCl_3$) 1.15-2.18 (8H, m, 4 x CH_2), 3.15-3.23 (1H, m, CHCO), 3.65 (1H q, *J*= 4.0 Hz, NCH), 4.10 (1H, d, *J* = 15.2 Hz, NCH_2), 4.60 (1H, d, *J* = 15.2 Hz, NCH_2), 7.26-7.37 (5H, m, Ph); δ_c (100 MHz; $CDCl_3$) 16.8 (CH_2), 18.8 (CH_2), 19.3 (CHD, t, *J* = 19.4 Hz), 22.9 (CH_2), 44.4 (NCH_2), 46.9 (CH), 50.0 (CH), 127.6 (CH), 128.3 (2 x CH_3), 128.7 (2 x CH_3), 136.2 (C), 170.8 (C=O); *m/z* (EI) 216.1 ([M]$^+$, 71%), 125.1 (7%), 91.1 (100%), 82.1 (95%); HRMS (EI) calculated for $C_{14}H_{16}NOD$ [M]$^+$ 216.1373, found 216.1376. 91% D by MS analysis.

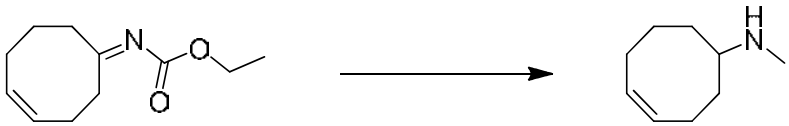
Ethyl-cyclooct-4-enyldiene-carbamate[162]



Prepared according to the literature procedure.[162]

A solution of ethyl azidoformate (5.70 g, 49.56 mmol) and cyclooctadiene (20 mL) was heated at 100 °C for 16 hours. The reaction mixture was cooled to room temperature, concentrated under reduced pressure and purified by reduced pressure distillation (0.02 mmHg, 142-146 °C) to afford ethyl-cyclooct-4-enyldiene-carbomate (6.55 g, 68%) as a colourless oil whose data were in agreement with those reported in the literature;[162] ν_{max} neat/cm^{-1}: 2936, 2864, 1718, 1663, 1539; δ_H (300 MHz; $CDCl_3$) 1.32 (3H, t, *J* = 7.1 Hz, CH_3), 1.64 (5H, m), 2.15-2.42 (5H m), 4.20-4.27 (2H, q, J = 6.2 Hz, CH_2), 5.70-5.74 (2H, m, CH); *m/z* (EI) 195 (60 %), 194 (100%), 180 (25%).

5-Methylaminocyclooctene[162]

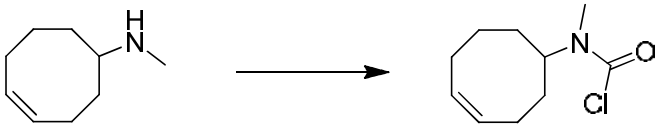


Prepared according to the literature procedure.[162]

A suspension of $LiAlH_4$ (0.15 g, 3.94 mmol) in dry diethylether (4 mL) was added dropwise to a solution of ethyl-cyclooct-4-enyldiene-carbomate (0.512 g, 2.63 mmol) in dry diethylether (5 mL) and the resulting mixture was heated to reflux for 4 h. The solution was allowed to cool to room temperature and quenched with a solution of saturated sodium potassium tartrate (10 mL) to leave two clear layers. The resulting solution was filtered and the residue was washed with diethyl ether (3 x 20 mL). The organic layer was

separated and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure at 0 °C to afford the volatile 5-methylaminocyclooctene as a colourless oil (0.32 g, 87%). The analytical data were in agreement with those reported in the literature;[162] ν_{max} neat/cm^{-1}: 2930, 2855, 1705, 1650, 1540, 1466, 1367; δ_H (300 MHz; $CDCl_3$) 1.18-1.42 (2 H, m, CH_2), 1.52-1.84 (6 H, m, 3 x CH_2), 2.02-2.20 (3 H, m), 2.36 (3 H, s, NCH_3), 2.44-2.48 (1H, m, NCH), 5.56-5.70 (2H, m, CH); δc (75 MHz; $CDCl_3$) 23.6 (CH_2), 25.8 (CH_2), 26.6 (CH_2), 32.2 (CH_2), 33.9 (CH_3), 35.1 (CH_2), 60.0 (CH), 129.5 (CH), 130.0 (CH); *m/z* (EI) 140.6 (100%).

_N_-Methyl-_N_-cyclooct-4-enylcarbamoyl chloride[145]

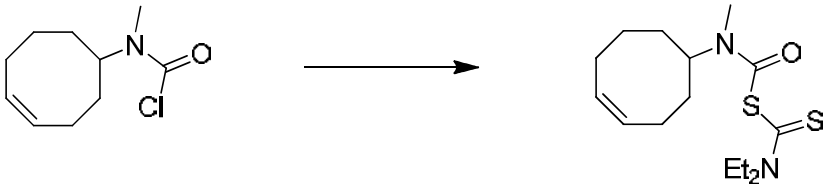


Prepared according to the general literature procedure.[145]

A solution of triphosgene (0.38 g, 1.29 mmol) in toluene (38 mL) was treated with pyridine (0.38 mL, 4.73 mmol), and subsequently with a solution of 5-Methylaminocyclooctene (0.6 g, 4.3 mmol) in toluene (5 mL). The reaction was stirred at room temperature overnight, quenched with saturated Na_2CO_3 and extracted with diethylether (3 x 20 mL). The combined extracts were washed with hydrochloric acid (0.25M, 20 ml), water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give *N*-methyl-*N*-cyclooct-4-enylcarbamoyl chloride (0.64 g, 74 %) as a yellow oil. The analytical data was consistent with that previously reported;[145] ν_{max}neat/cm^{-1}: 2391, 2857, 1732 (CO), 1468, 1396, 1358; δ_H(300

MHz; $CDCl_3$) 1.58-1.77 (6H, m, 3 x CH_2), 2.13-2.35 (4H, m, 2 x CH_2), 2.88 & 2.96 (mixture of rotamers, 3H, s, NC*H*$_3$), 4.18-4.40 (1H, m), 5.65-5.72 (2H, m); δ_C (100 MHz; $CDCl_3$) 23.0 (CH_2), 25.4 (CH_2), 26.3 (CH_2),32.1 (CH_2), 32.6 (CH_2), 33.8 (CH_3), 59.1 (CH), 129.0 (CH), 130.3 (CH).

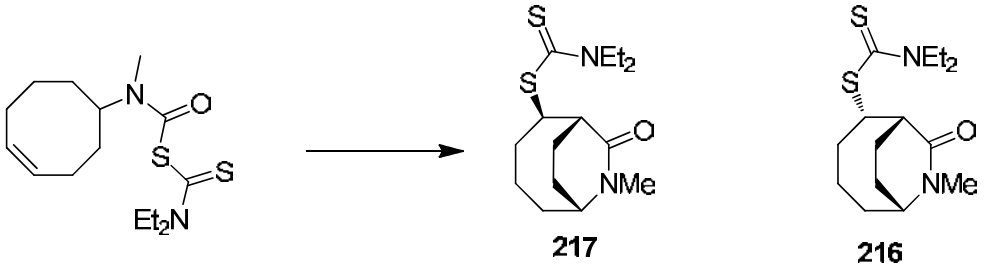
_N_-Methyl-_N_-cyclooctyl-4-enylcarbamoylcarbodithioate[145]



A solution of *N*-methyl-*N*-cyclooct-4-enylcarbamoyl chloride (0.64 g, 3.17 mmol) in acetone (40 mL) was treated with sodium diethyldithiocarbamate trihydrate (2.80 g, 12.6 mmol). The solution was stirred at room temperature for 18 h, quenched with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (pet ether:EtOAc 4:1 increasing to 2:1) to give the product as a yellow oil (0.58 g, 59%), whose analytical data was consistent with that previously reported;[145] ν_{max}neat/cm^{-1}: 2932, 2857, 1667 (C=O), 1489, 1463, 1418; δ_H(300 MHz, $CDCl_3$); 1.30 (6 H, t, *J* = 7.2 Hz, CH_3), 1.69-1.72 (6H, m, 3 x CH_2), 2.14-2.29 (4H, m, 2 x CH_2), 2.87 (3H, s, N*CH*$_3$), 3.76-4.01 (4H, m, 2 x NC*H*$_2$$CH_3$), 4.37-4.43 (1 H, m, CH), 5.63-5.69 (2H, m, CH); δ_C(75 MHz, $CDCl_3$) mixture of rotamers, 10.7 (CH_3), 12.9 (CH_3), 22.5 (CH_2), 22.8 (CH_2), 25.0 (CH_2), 25.4 (CH_2), 25.8 (CH_2), 26.0 (CH), 29.6 (CH_3), 31.1 (CH_3), 31.7 (CH_2), 31.9 (CH_2), 32.6 (CH_2), 32.8 (CH_2), 48.3 (CH_2), 49.5 (CH_2), 56.2 (CH), 58.4 (CH), 128.4 (CH),

128.8 (CH), 129.7 (CH), 130.1 (CH), 160.6 (C), 184.7 (C); *m/z* (ESI) 337 ($[M]^+$, 100%); HRMS (ESI) calculated for $C_{15}H_{26}N_2ONaS_2$ [M+] 337.1384, found 337.1377.

rac-(1R, 2R, 5R)-6-Methyl-7-oxo-6-azabicyclo[4.2.2]nonan-2-yldiethylcarbamodithioate and *rac*-(1*R*, 2*S*, 5*R*)-6-Methyl-7-oxo-6-azabicyclo[4.2.2]nonan-2-yldiethylcarbamodithioate[68]



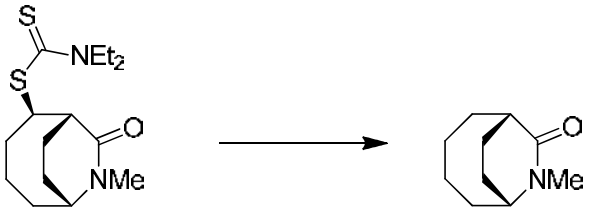
Prepared according to the literature procedure.[68]

A solution of *N*-methyl-*N*-cyclooctyl-4-enylcarbamoylcarbodithioate (0.27 g, 0.85 mmol) in cyclohexane (8 ml) was degassed and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 5 hours the solvent was removed under reduced pressure and the crude product purified by column chromatography (EtOAc) to give lactam **217** (0.0523 g, 19 %), and lactam **216** (0.1219 g, 45%) as a yellow solid, whose analytical data was consistent with that reported in the literature;[68] **216** R_f 0.40 (EtOAc); ν_{max}(neat)/cm^{-1} 2932, 2817, 1634 (C=O), 1486, 1442, 1417, 1356; δ_H (300 MHz; $CDCl_3$) 1.24 (6H, t, *J* = 6.9 Hz, 2 x CH_3,), 1.50-1.54 (1H, m, 1 x CH_2), 1.73-1.80 (3 H, m, 1 x CH_2 and CH_2), 1.96-2.27 (5 H, m, 2 x CH_2 and CH), 2.93 (3 H, s, NCH_3), 3.12-3.17 (1 H, m, CH), 3.65-3.74 (4 H, m 2 x CH_2), 3.96-4.03 (2 H, m, CH_2), 4.45-4.51 (1 H, m, 1 x CHS); δ_C (75 MHz; $CDCl_3$) 11.5 (CH_3), 12.5 (CH_3), 20.4 (CH_2), 21.5 (CH_2), 25.6 (CH_2), 31.6 (CH_2), 34.0 (CH), 34.7 (CH_2), 44.4 (CH), 46.5 (CH_2), 49.1 (CH_2), 56.1 (CH),

173.0 (C=O), 193.4 (C=S); *m/z* (ESI) 337.2 (100%); HRMS (ESI) calculated for $C_{15}H_{26}N_2ONaS_2$ $[M]^+$ 337.1384, found 337.1375.

217 R_f 0.20; ν_{max}(neat)/cm^{-1} 2932, 1633 (C=O), 1487, 1417, 1268; δ_H (300 MHz; $CDCl_3$) 1.26 (6 H, t, *J* = 7.1 Hz, 2 x CH_3), 1.76-1.79 (6 H, m), 2.07-2.32 (4 H, m), 3.01 (3 H, s, NCH_3), 3.14-3.18 (1 H, m), 3.85-3.96 (4 H, m), 4.04-4.13 (1 H, m), 4.31-4.36 (1 H, m, 1 x CHS); δ_C(75 MHz; $CDCl_3$) 11.5 (CH_3), 12.4 (CH_3), 23.0 (CH_2), 23.5 (CH_2), 26.0 (CH_2), 31.44 (CH_2), 33.0 (CH_2), 33.9 (CH), 44.8 (CH), 46.5 (CH_2), 49.2 (CH_2), 58.7 (CH_2), 171.5 (C=O), 195.2 (C=S) *m/z m/z* (ESI) 337.1 (100%); HRMS (ESI) calculated for $C_{15}H_{26}N_2ONaS_2$ $[M]^+$ 337.1384, found 337.1376.

(±)-(1R*,6R*)-7-Methyl-8-oxo-7-azabicyclo[4.2.2]decane

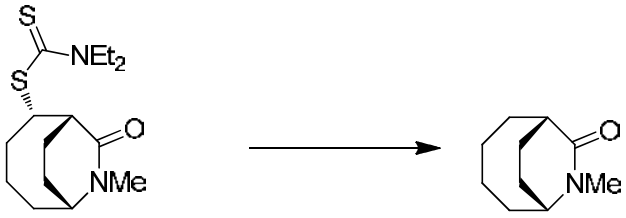


217 **218**

The reduced product was prepared according to the general experimental procedure. **217** (0.05 g, 0.16 mmol) was dissolved in dioxane (2 mL) and treated with triethylamine (0.12 mL, 0.88 mmol) and hypophosphorus acid (0.08 mL, 0.80 mmol). After 20 minutes at reflux ACCN (0.006 g, 0.024 mmol) was added. After a further 2 hours at reflux another portion of ACCN (0.006 g, 0.0024 mmol) was added. The reaction was complete after 4.5 hours and the workup completed in accordance with the general experimental. The crude product was purified by column chromatography (EtOAc followed by CH_2Cl_2:MeOH 9:1) to give a white solid (0.022 g, 83%). ν_{max}(neat)/cm^{-1}: 2925, 1634 (C=O), 1451, 1369; δ_H (300

MHz; $CDCl_3$); 1.37-1.84 (8H, m, 4 x CH_2), 1.98-2.25 (4H, m, 2 x CH_2), 2.75-2.84 (1H, m, CH), 2.96 (3H, s, NCH_3), 3.62-3.71 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 23.4 (CH_2), 23.8 (CH_2), 24.8 (CH_2), 25.1 (CH_2), 34.0 (CH_3), 34.7 (CH_2), 35.9 (CH_2), 39.4 (CH), 57.0 (CH), 175.5 (C=O); *m/z* (EI) 167.1 ($[M]^+$, 71%), 139.1 (26%), 124.1 (36%), 96.1 (100%); HRMS (EI) calculated for $C_{10}H_{17}NO$ $[M]^+$ 167.1310 found 167.1318.

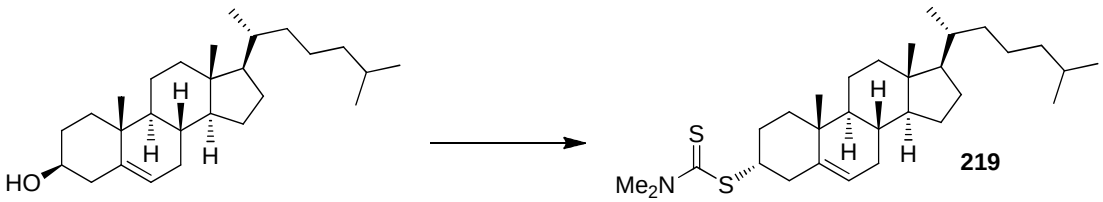
(±)-(1R*,6R*)-7-Methyl-8-oxo-7-azabicyclo[4.2.2]decane



216 **218**

The reduced product was prepared according to the general experimental procedure. **216** (0.05 g, 0.16 mmol) was dissolved in dioxane (2 mL) and treated with triethylamine (0.12 mL, 0.88 mmol) and hypophosphorus acid (0.08 mL, 0.80 mmol). After 20 minutes at reflux ACCN (0.006 g, 0.024 mmol) was added. The reaction was complete after 2.5 hours. The crude product was purified by column chromatography (EtOAc followed by CH_2Cl_2:MeOH 9:1) to give a white solid (0.023 g, 87%). ν_{max} (neat)/cm^{-1}: 2925, 1634 (C=O), 1451, 1369; δ_H (300 MHz; $CDCl_3$); 1.37-1.84 (8H, m, 4 x CH_2), 1.98-2.25 (4H, m, 2 x CH_2), 2.75-2.84 (1H, m, CH), 2.96 (3H, s, NCH_3), 3.62-3.71 (1H, m, CH); δ_c (100 MHz; $CDCl_3$) 23.4 (CH_2), 23.8 (CH_2), 24.8 (CH_2), 25.1 (CH_2), 34.0 (CH_3), 34.7 (CH_2), 35.9 (CH_2), 39.4 (CH), 57.0 (CH), 175.5 (C=O); *m/z* (EI) 167.1 ($[M]^+$, 71%), 139.1 (26%), 124.1 (36%), 96.1 (100%); HRMS calculated for $C_{10}H_{17}NO$ $[M]^+$ 167.1310 found 167.1318.

3 α-Cholestanyl *N*,*N*-dimethyldithiocarbamate[69]

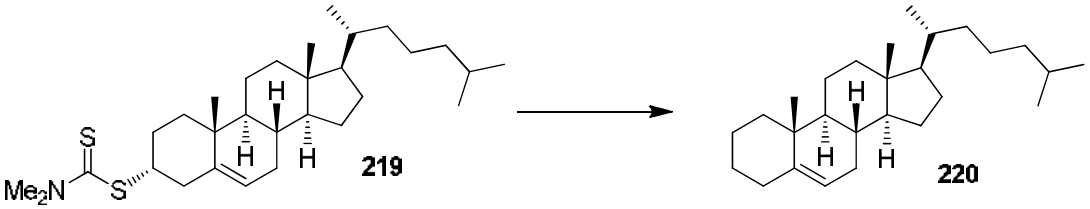


219

Prepared according to the general literature procedure.[69]

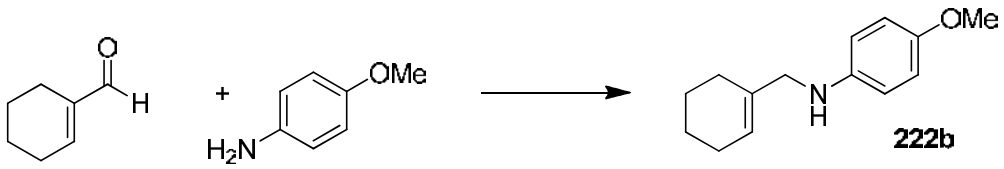
A suspension of cholesterol (1 g, 2.59 mmol), triphenylphosphine (1.35 g, 5.17 mmol) and zinc dimethyldithiocarbamate (1.19 g, 3.89 mmol) in toluene (26 mL) was stirred at 0 °C. DIAD (1.02 mL, 5.17 mmol) was added dropwise and the solution allowed to warm to room temperature. After 18 hours the solvent was removed under reduced pressure and the crude product obtained was purified by column chromatography (petroleum ether: EtOAc 3:1) to give the product as a white solid (0.84 g, 68 %) whose analytical data were in accordance with that reported in the literature;[69] m.p. 161-162 °C; δ_H (300 MHz; $CDCl_3$); 0.70-2.23 (42H, m, CH, CH_2 and CH_3), 2.81-2.94 (1H, m, CH), 3.38 (3H, s, NCH_3), 3.55 (3H, s, NCH_3), 4.39-4.46 (1H, m, SCH), 5.32-5.38 (1H, m, CH); δc (100 MHz; $CDCl_3$) 11.7 (CH_3), 18.7 (CH_3), 19.2 (CH_3), 20.8 (CH_2), 21.0 (CH), 22.8 (CH_3), 23.1 (CH_3), 23.9 (CH_2), 24.3 (CH_2), 27.3 (CH_2), 28.0 (CH), 28.2 (CH_2), 30.9 (CH_2), 31.8 (CH_2) 35.8 (CH_2), 36.2 (CH_2), 37.2 (C), 37.7 (CH_2), 39.5 (CH_2), 39.8 (CH_2), 41.6 (CH), 42.3 (C), 45.1 (CH), 50.1 (NCH_3), 51.6 (NCH_3), 56.2 (CH), 56.8 (SCH), 122.1 (CH), 139.6 (C), 197.5 (C=S).

Cholest-5-ene



The reduced product was prepared according to the general experimental procedure. 3 α-Cholestanyl *N*,*N*-dimethyldithiocarbamate (0.40 g, 0.84 mmol) was dissolved in dioxane (10 mL) and treated with triethylamine (0.64 mL, 4.62 mmol) and hypophosphorus acid (0.44 mL, 4.2 mmol). After 20 minutes at reflux ACCN (0.03 g, 0.12 mmol) was added. The reaction was complete after 5 hours and the crude product purified by column chromatography to give a white solid (0.30 g, 97%). The literature data were in accordance with that reported in the literature;[163] m.p. 86-88 °C; δ_H (400 MHz; $CDCl_3$); 0.68 (3H, s, CH_3), 0.86-2.08 (41H, m), 2.20-2.41 (1H, m, CH), 5.27 (1H, m, C=CH); δc (100 MHz; $CDCl_3$) 11.9 (CH or CH_3), 18.8 (CH or CH_3), 19.5 (CH or CH_3), 20.8 (CH_2), 22.6 (CH or CH_3), 22.6 (CH_2), 22.9 (CH or CH_3), 23.9 (CH_2), 24.3 (CH_2), 28.0 (CH or CH_3), 28.1 (CH_2), 28.3 (CH_2), 31.8 (CH or CH_3), 31.9 (CH_2), 32.9 (CH_2), 35.8 (CH or CH_3), 36.3 (CH_2), 37.5 (C), 39.6 (CH_2), 39.9 (CH_2), 42.3 (C), 50.6 (CH or CH_3), 56.2 (CH or CH_3), 56.9 (CH or CH_3), 119.0 (CH), 143.6 (C).

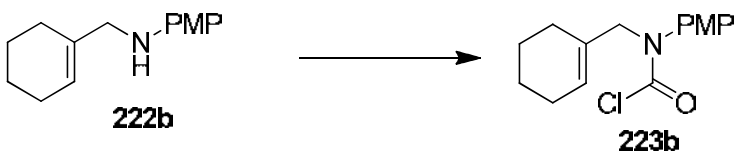
(4-Methoxyphenyl)cyclohex-1-enylmethylamine[73]



Prepared according to the literature procedure[73]

To a solution of 1-cyclohexene-1-carboxaldehyde (2.0 g, 18.2 mmol) in 99:1 CH_2Cl_2:AcOH (60 mL) was added *p*-anisidine (2.46 g, 19.9 mmol). The reaction mixture was stirred at room temperature for 3 hours and then cooled to 0 °C. Sodiumtriacetoxy borohydride ($NaB(OAc)_3H$) (9.64 g, 45.5 mmol) was added to the reaction mixture. The reaction mixture was warmed to room temperature and allowed to stir for 10 hours. Upon completion of the reaction the excess $NaB(OAc)_3H$ was quenched with ice-water (20 mL). The solution was poured into CH_2Cl_2 (40 mL) and washed with H_2O (40 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 60 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product as a red oil, which was purified by column chromatography (10:1 petroleum ether:EtOAc) to give (4-methoxyphenyl)cyclohex-1-enylmethylamine (**222b**) as a light yellow oil (2.25 g, 57%), whose analytical data were in accordance with that reported in the literature.[73] δ_H (300 MHz; $CDCl_3$); 1.56-1.72 (4H, m, 2 x CH_2), 2.02-2.10 (4H, m, 2 x CH_2), 3.56 (1H, br s, NH), 3.60 (2H, s, CH_2NH), 3.76 (3H, s, $PhOCH_3$), 5.69-5.71 (1H, m, CH=C), 6.58-6.62 (2H, m, 2 x CH), 6.79- 6.83 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$) 22.4 (CH_2), 22.6 (CH_2), 24.9 (CH_2), 26.7 (CH), 51.4 (CH_2), 55.7 (CH_3), 114.1 (2 x CH), 114.7 (2 x CH), 122.9 (CH), 135.3 (C), 142.6 (C), 151.9 (C); *m/z* (EI) 217 (80%).

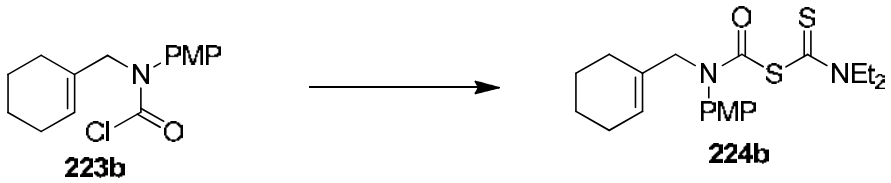
(4-Methoxyphenyl)cyclohex-1-enylmethyl carbamic chloride



222b **223b**

A solution of triphosgene (0.50 g, 1.70 mmol) in toluene (43 mL) was treated with pyridine (0.45 ml, 5.50 mmol), and subsequently with a solution of amine **222b** (1.0 g, 4.6 mmol) in toluene (7 mL). The reaction was stirred at room temperature overnight, quenched with saturated Na_2CO_3 and extracted with diethylether (3 x 25 ml). The combined extracts were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and evaporated under reduced pressure to give carbamoyl chloride **223b** (1.24 g, 97%) as a yellow oil; δ_H (300 MHz; $CDCl_3$); 1.51-1.70 (4H, m, 2 x CH_2), 1.91-2.08 (4H, m, 2 x CH_2), 3.83 (3H, s, $PhOCH_3$), 4.19 (2H, s, $C\underline{H}_2NH$), 5.41-5.43 (1H, m, CH=C), 6.89-6.97 (2H, m, 2 x CH), 7.17- 7.23 (2H, m, 2 x CH);

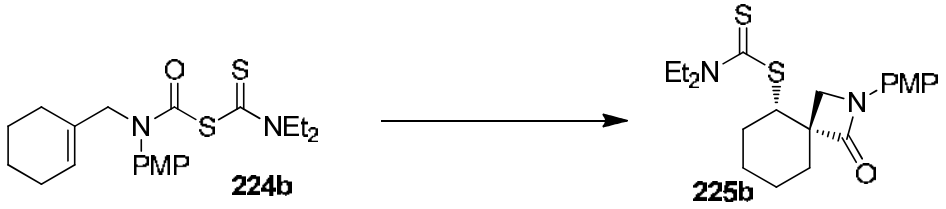
Diethylthiocarbamic acid-[4-methoxyphenyl (cyclohex-2-enyl) carbamic acid]-thioanhydride



A solution of carbamoyl chloride **223b** (2.20 g, 7.87 mmol) in acetone (79 mL) was treated with sodium diethyldithiocarbamate trihydrate (7.09 g, 31.4 mmol). The solution was stirred at room temperature for 18 hours quenched with water (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (70 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (4:1 petroleum ether:EtOAc) gave the *title compound* as a yellow oil (2.05 g, 67%). R_f 0.27 (4:1 hexane:EtOAc); ν_{max}neat/cm^{-1}: 2929, 1669 (C=O), 1508, 1418, 1237, 1194; δ_H (300 MHz; $CDCl_3$); 1.28-1.39 (6H, t, J = 7.1 Hz, 2 x CH_3), 1.48-1.68 (4H, m, 2

x CH_2), 1.89-2.07 (4H, m, 2 x CH_2), 3.72-3.89 (5H, m, NCH_2 + $PhOCH_3$), 3.99-4.10 (2H, m, CH_2), 4.19 (2H, s, CH_2), 5.37-5.41 (1H, m, CH=C), 6.88-6.98 (2H, m, 2 x CH), 7.12- 7.20 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$)11.0 (CH_3), 13.5 (CH_3), 22.3 (CH_2), 25.1 (CH_2), 26.4 (CH_2), 26.8 (CH_2), 48.6 (NCH_2), 50.3 (NCH_2), 55.4 (OCH_3), 57.9 (NCH_2), 113.4 (CH), 114.7 (CH), 122.7 (CH), 128.2 (CH),130.5 (CH), 132.5 (C), 134.5 (C-N), 137.7 (C-O), 156.9 (C=O), 185.4 (C=S); *m/z* (EI) 393 ($[M]^+$ 22%), 331 (100%), 244 (33%), 218 (25%); HRMS (EI) calculated for $C_{20}H_{29}N_2O_2S_2$ $[M]^+$ 393.1670, found 393.1652.

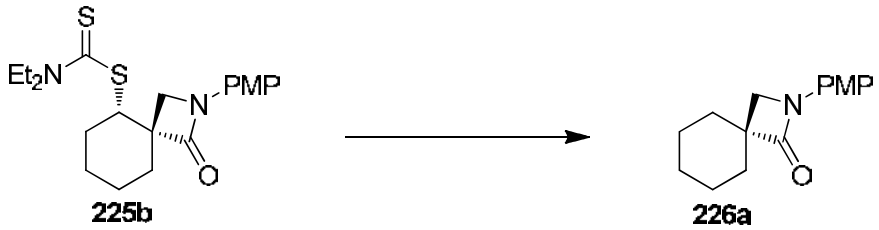
2-(4-Methoxyphenyl)-1-oxo-2-azaspiro[3.5]nonan-5-yl diethylcarbamodithioate



A solution of carbamoyl dithiocarbamate **224** (0.32 g, 0.83 mmol) in cyclohexane (8.3 mL) was degassed for 15 minutes and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 8 hours the solvent was removed under reduced pressure and the crude product purified by column chromatography (petroleum ether:EtOAc 3:1) to give the *title compound* as a white solid (0.19 g, 60%). R_f 0.21 (3:1 petroleum ether:EtOAc); m.p. 147-148 °C; ν_{max}(neat)/cm^{-1}: 2929, 1671 (C=O), 1509, 1415, 1243; δ_H (300 MHz; $CDCl_3$); 1.27 (6H, t, 2 x CH_3), 1.48-2.11 (7H, m, CH_2), 2.36-2.48 (1H, m, CH_2), 3.31 (1H, d, *J* = 5.8 Hz, 0.5 x NCH_2), 3.64 (1H, d, *J* = 5.8 Hz, 0.5 x NCH_2), 3.70-3.77 (2H, m, NCH_2), 3.80 (3H, s, $PhOCH_3$) 3.98-4.05 (2H, m, CH_2), 4.76-4.80 (1H, m, SCH), 6.88 (2H, d, *J* = 12.6 Hz, 2 x CH), 7.31 (2H, d, *J* = 12.0 Hz, 2 x CH); δc (100 MHz; $CDCl_3$) 11.6 (CH_3), 12.6 (CH_3), 22.7 (CH_2), 23.4 (CH_2), 30.7 (CH_2), 31.9 (CH_2), 46.8 (CH_2), 49.8 (CH_2), 50.5 (CH_2),

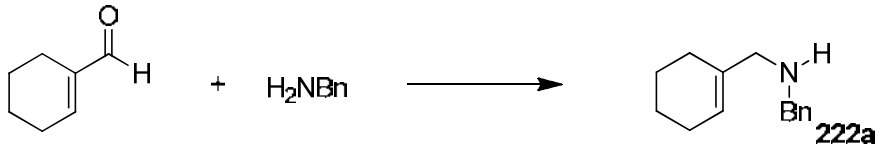
53.0 (SCH), 55.8 (OCH_3), 58.6 (C), 114.3 (2 x CH), 117.6 (2 x CH), 132.2 (C-N), 156.0 (C-O), 167.6 (C=O), 193.7 (C=S); *m/z* (ESI) 415 $[M+Na]^+$; HRMS (ESI) calculated for $C_{21}H_{28}N_2O_2S_2Na$ $[M]^+$ 415.490; found 415.1490.

2-(4-Methoxyphenyl)-2-azaspiro[3.5]nonan-1-one



The reduced product was prepared according to the general experimental procedure. Dithiocarbamate **225** (0.29 g, 0.74 mmol) was dissolved in dioxane (9.25 mL) and treated with triethylamine (0.56 mL, 4.07 mmol) and hypophosphorus acid (0.38 mL, 3.70 mmol). After 20 minutes at reflux ACCN was added (0.027 g, 0.11 mmol). The reaction was complete after 6 hours and the product purified by column chromatography (6:1 petroleum ether:EtOAc) to give a white solid (0.069 g, 39%). R_f 0.24 (6:1 petroleum ether:EtOAc); m.p. 119-122°C; ν_{max}(neat)/cm^{-1}: 2928, 1733 (C=O), 1511, 1392, 1243; δ_H (300 MHz; $CDCl_3$); 1.28-1.44 (2H, m, CH_2), 1.56-1.71 (2H, m, CH_2), 1.73-1.97 (6H, m, 3 x CH_2), 3.40 (2H, s, NCH_2), 3.81 (3H, s, $PhOCH_3$), 6.89 (2H, d, *J* = 12.6 Hz, CH), 7.31 (2H, d, *J* = 12.0 Hz, CH); δc (100 MHz; $CDCl_3$) 23.4 (2 x CH_2), 25.2 (CH_2), 31.2 (2 x CH_2), 51.8 (NCH_2), 55.3 (C), 55.5 (OCH_3), 114.4 (2 x CH), 117.4 (2 x CH), 132.6 (C-N), 155.8 (C-O), 170.5 (C=O); *m/z* (EI) 245 ($[M^+]$ 52%), 149 (100%), 135 (22%); HRMS (EI) calculated for $C_{15}H_{19}NO_2$ [M+] 245.1416, found 245.1417.

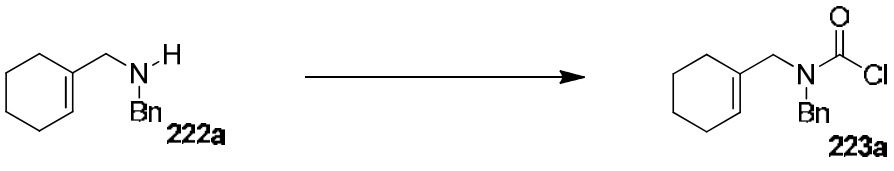
***N*-Benzyl-*N*-cyclohex-1-enylmethylamine**[164]



Prepared according to the literature procedure.[164]

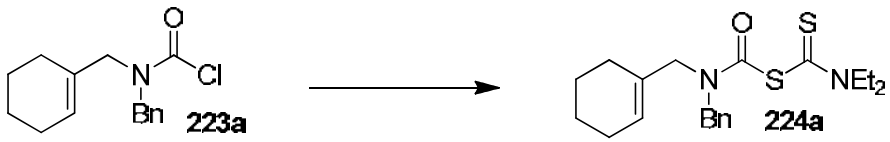
Benzylamine (0.99 mL, 9.2 mmol) was added to a solution of 1-cyclohexene-1-carboxaldehyde (1.0 mL, 8.76 mmol) in dichloroethane (10 mL) with 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 3 hours. Sodium triacetoxyborohydride (2.4 g, 11.4 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction was quenched with aqueous sodium bicarbonate, and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. Purification by column chromatography (1:1 hexane:EtOAc) gave amine **222a** as a pale yellow oil (0.42 g, 24%) whose analytical data was consistent with that reported in the literature.[164] ν_{max} neat/cm^{-1}: 3326, 3026, 2924, 2830, 1496, 1201; δ_H (300 MHz; $CDCl_3$); 1.42 (1H, br, s, NH), 1.56-1.67 (4H, m, 2 x CH_2), 2.00-2.04 (4H, m, 2 xCH_2), 3.14 (2H, s, CH_2), 3.76 (2H, s, CH_2), 5.60-5.62 (1H, m, CH), 7.24-7.27 (1H, m, CH), 7.31-7.37 (4H, m, 4 x CH); δ_c (100 MHz; $CDCl_3$) 22.7 (CH_2), 22.8 (CH_2), 25.2 (CH_2), 27.0 (CH_2), 53.22 (CH_2), 55.7 (CH_2), 122.8 (CH), 126.9 (CH), 128.2 (2 x CH), 128.4 (2 x CH), 136.2 (C), 140.7 (C).

Benzyl(cyclohex-1-en-1-ylmethyl)carbamic chloride



A solution of triphosgene (0.06 g, 0.20 mmol) in toluene (5 mL) was treated with pyridine (0.06 mL, 0.74 mmol), and subsequently with a solution of *N*-benzyl-*N*-cyclohex-1-enylmethylamine (0.12 g, 0.62 mmol) in toluene (1 mL). The reaction was stirred at room temperature for 18 hours, quenched with saturated Na_2CO_3 (3 mL) and extracted with Et_2O (3 x 5 mL). The combined extracts were washed with water (3 mL) and brine (3 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the *title compound* (0.14 g, 87%) as a yellow oil. This was used directly in the next step without any further purification; δ_H (300 MHz; $CDCl_3$); 1.51-1.75 (4H, m, 2 x CH_2), 1.88-2.13 (4H, m, 2 x CH_2), 3.93 (2H, d, *J* = 17.8 Hz, CH_2), 4.54 (1H, s, CH_2), 4.66 (1H, s, CH_2) 5.54-5.64 (1H, m, CH), 7.25-7.44 (5H, m, 5 x CH).

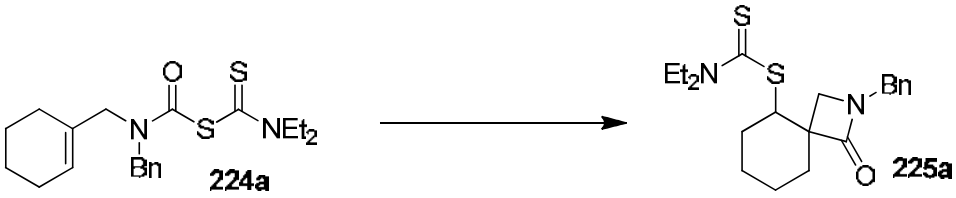
Diethylthiocarbamic acid-[*N*-benzyl (cyclohex-2-enyl) carbamic acid]-thioanhydride



A solution of carbamoyl chloride **223a** (0.18 g, 0.7 mmol) in acetone (10 mL) was treated with sodium diethyldithiocarbamate trihydrate (0.65 g, 2.8 mmol). The solution was stirred at room temperature for 18 hours quenched with water (7 mL) and extracted with Et_2O (3 x 7 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by column chromatography (7:1 petroleum ether:EtOAc) gave the product as a yellow oil (0.22 g, 84%); R_f 0.19 (7:1 petroleum ether:EtOAc); ν_{max} neat/cm^{-1}: 2929, 1661 (C=O), 1488, 1418, 1269, 1185; δ_H (300 MHz; $CDCl_3$); 1.21-1.41 (6H, t, *J* = 7.3 Hz, 2 xCH_3), 1.49-1.68 (4H, m, 2 x CH_2), 1.89-2.10 (4H, m, 2 x CH_2), 3.73-3.90 (3H, m, CH_2), 3.96-4.11 (3H, m, CH_2), 4.55

(2H, s, CH_2), 5.55 (1H, s, CH=C), 7.20- 7.50 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$) 11.2 (CH_3), 13.2 (CH_3), 22.2 (CH_2), 22.4 (CH_2), 25.1 (CH_2), 26.1 (CH_2), 48.9 (NCH_2), 50.0 (NCH_2), 50.2 (NCH_2), 54.4 (NCH_2), 126.2 (CH), 126.9 (CH), 127.6 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 132.3 (CH_2), 136.3 (C), 185.0 (C=O), 192.7 (C=S); *m/z* (ESI) 399 $[M+Na]^+$; HRMS (ESI) calculated for $C_{20}H_{28}N_2OS_2Na$ $[M]^+$ 399.1541, found 399.1529.

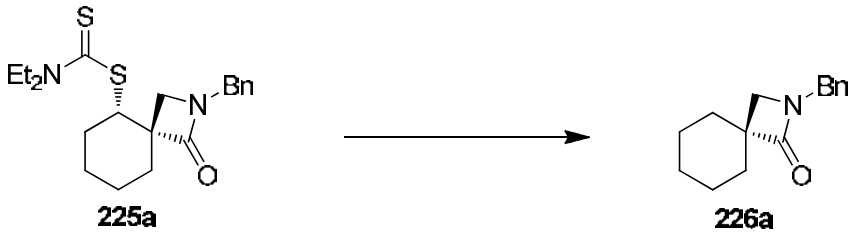
2-Benzyl-1-oxo-2-azaspiro[3.5]nonan-5-yl diethylcarbamodithioate



A solution of carbamoyl dithiocarbamate **224a** (0.20 g, 0.53 mmol) in cyclohexane (5.3 mL) was degassed for 15 minutes and irradiated with a 500 W halogen lamp that generated enough heat to bring the solvent to reflux. After 8 hours the solvent was removed under reduced pressure and the crude product purified by column chromatography (petroleum ether:EtOAc 4:1) to give the *title compound* as a white solid (0.12 g, 59%). R_f 0.33 (4:1 petroleum ether:EtOAc); m.p. 61-63 °C; ν_{max} (neat)/cm^{-1}: 2933, 1675 (C=O), 1487, 1416, 1268; δ_H (300 MHz; $CDCl_3$); 1.11-1.26 (6H, m, 2 x CH_3), 1.43-1.70 (5H, m, CH_2), 1.79-2.05 (3H,m, CH_2), 3.05 (1H, d, *J* = 10.6 Hz, NCH_2), 3.53 (1H, d, *J* = 10.6 Hz, NCH_2), 3.66 (2H, q, *J* = 7.0 Hz, NCH_2), 3.94 (2H, q, *J* = 6.55, NCH_2), 4.14 (1H, d, *J* = 15.0 Hz, CH_2), 4.60 (1H, d, *J* = 15.0 Hz, CH_2), 4.76 (1H, m, SCH), 7.14-7.30 (5H, m, 5 x CH); δc (100 MHz; $CDCl_3$) 11.6 (CH_3), 12.7 (CH_3), 22.7 (CH_2), 22.9 (CH_2), 30.7 (CH_2), 37.3 (CH_2), 46.8 (CH_2), 48.4.8 (CH_2), 50.1 (CH_2), 57.8 (CH_2), 58.2 (SCH), 127.6 (C), 128.0 (2 x CH), 128.7 (2 x CH), 136.2 (C), 170.6 (C=O), 193.4 (C=S); *m/z* (ESI) 415 ($[M+Na+O]^+$, 100 %); HRMS (ESI)

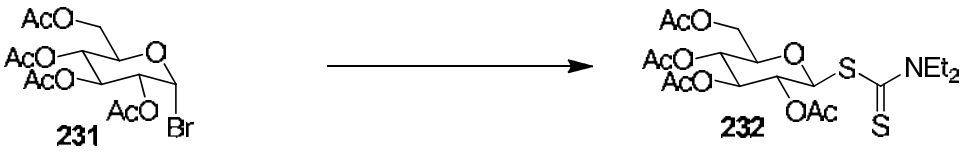
calculated for $C_{20}H_{28}N_2O_2S_2Na$ $[M]^+$ 415.490; found 415.1490. The mass spec data indicates that a different compound to that shown has been synthesised, containing an extra oxygen.

2-Benzyl-2-azaspiro[3.5]nonan-1-one



The reduced product was prepared as according to the general experimental procedure. Dithiocarbamate **225a** (0.08 g, 0.21 mmol) was dissolved in dioxane (2.70 mL) and treated with triethylamine (0.16 mL, 1.15 mmol) and hypophosphorus acid (0.10 mL, 1.05 mmol). After 20 minutes at reflux ACCN was added (0.01 g, 0.04 mmol). The reaction was complete after 6 hours and the product purified by column chromatography (4:1 petroleum ether:EtOAc) to give a clear oil (0.029 g, 60%). R_f 0.23 (4:1 petroleum ether:EtOAc); ν_{max} (neat)/cm^{-1}: 3275, 2927, 1737 (C=O), 1648, 1537, 1259; δ_H (300 MHz; $CDCl_3$); 0.83-1.85 (10H, m, 5 x CH_2), 3.18-3.24 (1H, m, NCH_2), 3.64-3.69 (1H, m, NCH_2), 4.09-4.14 (1H, d, *J* = 19.2 Hz , CH_2), 4.59-4.64 (1H, m, *J* = 19.2 Hz, CH_2), 7.24-7.21 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$) 16.8 (CH_2), 19.3 (CH_2), 22.0 (CH_2), 22.9 (CH_2), 25.6 (CH_2), 29.4 (CH_2), 35.4 (NCH_2), 44.5 (NCH_2), 127.6 (C), 128.3 (2 x CH), 128.7 (2 x CH), 136.2 (C), 170.9 (C=O); *m/z* (ESI) 245 ($[M+O]^+$ 52%), 149 (100%), 135 (22%); HRMS (ESI) calculated for $C_{15}H_{19}NO_2$ [M+] 245.1416, found 245.1417. The mass spec data indicates that a different compound to that shown has been synthesised, containing an extra oxygen.

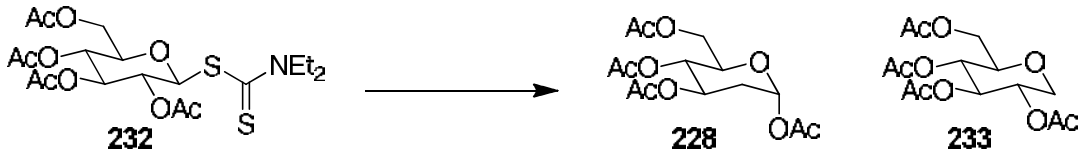
***S*-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)*N*,*N*-diethyldithiocarbamate[78]**



Prepared according to the literature procedure.[78]

A solution of acetylated glucosyl bromide (1.00 g, 2.43 mmol) in CH_3CN (10 mL) was treated with sodium diethyldithiocarbamate trihydrate (0.55 g, 2.43 mmol). After stirring at room temperature for 2 hours, the reaction mixture was quenched with $CHCl_3$ (10 mL), washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give the crude compound. This was purified by column chromatography (petroleum ether:EtOAc:methanol 70:25:5) to afford the *title compound* (0.88 g, 76%) as a yellow solid, whose analytical data were in agreement with that reported in the literature;[78] m.p. 77-78 °C; δ_H (300 MHz; $CDCl_3$): 1.24-1.30 (6H, m, CH_3), 2.02 (3H, s, OCH_3), 2.03 (3H, s, OCH_3), 2.04 (3H, s, OCH_3), 2.07 (3H, s, OCH_3), 3.57-3.65 (1H, m, CH_2), 3.74-3.81 (1H, m, CH_2), 3.90-3.97 (2H, m, CH_2), 4.05-4.11 (1H, m, NCH_2), 4.13 (1H, dd, *J* = 12.0 Hz and *J* = 2.0 Hz), 4.29 (1H, dd, *J* = 12.0 Hz, *J* = 4.5 Hz), 5.10-5.16 (1H, m, CH), 5.29-5.37 (2H, m, 2 x CH_3), 5.87 (1H, d, *J* = 10.0 Hz, CH); HRMS (ESI) *m/z* found $[M+Na]^+$ 502.1192, $C_{19}H_{29}O_9NaS_2$ calculated 502.1181.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol and Tetra-*O*-acetyl-α-D-arabino-2-deoxy-hyexopyranose, formed under standard conditions



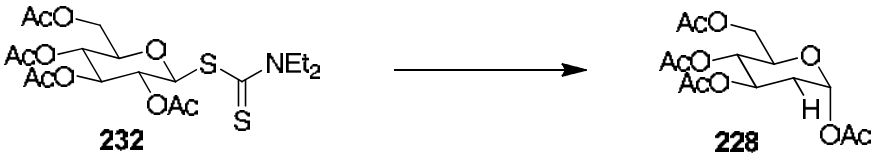
The reduced product was prepared according to the general experimental from, *S*-(2',3',4',6'-tetra-*O*-acetyl-β-D-glucopyranosyl)*N*,*N*-diethyldithiocarbamate (0.50 g, 1.04 mmol)**.** After 4 hours at reflux, a further portion of ACCN (0.15 eq) was added to the reaction mixture and the reaction was continued for a further 14 hours. The work up was completed according to the general procedure. Purification by column chromatography (hexane:EtOAc 9:1) gave a mixture of compounds **228** and **233**. The ratio of the products was determined by ^{1}H NMR and varied depending on the concentration of the solution.

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol

S-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)*N*,*N*-diethyldithiocarbamate (0.25 g, 0.52 mmol) was dissolved in dioxane (1 mL, 0.5 M) and treated with triethylamine (0.79 mL, 5.72 mmol) and hypophosphorus acid (0.54 mL, 5.20 mmol). The solution was heated to reflux for 20 minutes before the addition of ACCN (0.019 g, 0.08 mmol). After heating to reflux for 4 hours a further portion of ACCN (0.019 g, 0.08 mmol) was added and the reaction continued for a further 14 hours. The reaction mixture was cooled to room temperature and the work up completed in accordance with the general experimental.

Purification by column chromatography (hexane:EtOAc 9:1) gave **233** as a white solid (0.037 g, 44%), whose analytical data were consistent with that reported in the literature;[165] δ_H (300 MHz; $CDCl_3$) 2.03 (3H, s, CH_3), 2.04 (6H, s, 2 x CH_3), 2.10 (3H, s, CH_3), 3.31 (1H, t, *J* = 12.0 Hz, CH), 3.58-3.62 (1H, m, CH), 4.25-4.09 (3H, m), 4.98-5.06 (2H, m), 5.21 (1H, t, *J* = 9.5 Hz, CH); δc (100 MHz; $CDCl_3$) 20.6 (2 x CH_3), 20.7 (2 x CH_3), 62.2 (CH_2), 66.9 (CH_2), 68.5 (CH), 68.9 (CH), 73.7 (CH), 76.5 (CH), 169.5 (C=O), 169.7 (C=O), 170.3 (C=O), 170.6 (C=O); HRMS (ESI) calculated for $C_{14}H_{20}O_9Na$ $[M+Na]^+$ 355.1005, found 355.1003.

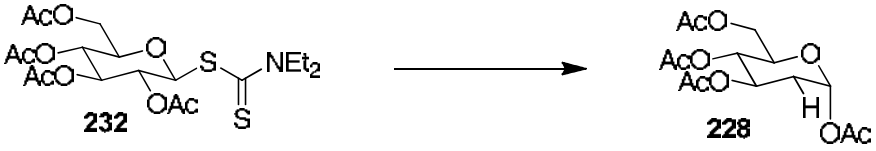
Tetra-*O*-acetyl-α-D-arabino-2-deoxy-hyexopyranose using ACCN



S-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)*N*,*N*-diethyldithiocarbamate (0.50 g, 1.04 mmol) was dissolved in dioxane (104 mL, 0.01 M) and treated with triethylamine (0.79 mL, 5.72 mmol) and hypophosphorus acid (0.54 mL, 5.20 mmol). The solution was heated to reflux for 20 minutes before the addition of ACCN (0.038 g, 0.16 mmol). After heating to reflux for 4 hours a further portion of ACCN (0.038 g, 0.16 mmol) was added and the reaction continued for a further 14 hours. The reaction mixture was cooled to room temperature and the work up completed in accordance with the general experimental. Purification by column chromatography (hexane:EtOAc 9:1) gave **228** as a white solid (0.29 g, 85%) whose analytical data were consistent with that reported in the literature:[166] δ_H (300 MHz; $CDCl_3$) 2.04 (3H, s, CH_3), 2.06 (3H, s, CH_3), 2.09 (3H, s, CH_3),

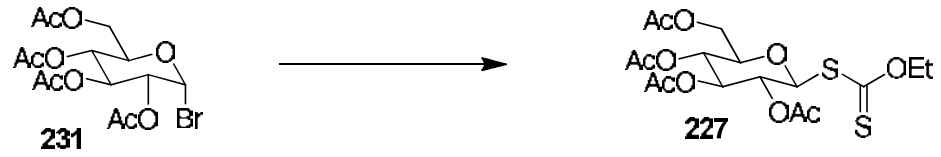
2.14 (3H, s, CH_3), 2.24-2.30 (1H, m), 2.95-2.99 (1H, m), 4.03-4.09 (1H, m), 4.29-4.35 (2H, m, CH_2), 5.09 (1H, t, *J* = 9.7 Hz, CH), 5.27-5.36 (1H, m, CH), 6.25-6.28 (1H, m); δc (100 MHz; $CDCl_3$) 20.6 (CH_3), 20.7 (CH_3), 20.9 (CH_2), 21.0 (CH_2), 33.9 (CH_2), 61.9 (CH_2), 68.5 (CH), 68.7 (CH), 70.2 (CH), 90.9 (CH), 168.9 (C=O), 169.7 (C=O), 170.2 (C=O), 170.7 (C=O); HRMS (ESI) calculated $C_{14}H_{20}O_9Na$ $[M+Na]^+$ 355.1005, found 355.0999.

Tetra-*O*-acetyl-α-D-arabino-2-deoxy-hyexopyranose using $K_2S_2O_8$



S-(2',3',4',6'-Tetra-*O*-acetyl-β-D-glucopyranosyl)*N*,*N*-diethyldithiocarbamate (0.25 g, 0.52 mmol) was dissolved in dioxane (52 mL, 0.01 M) and treated with triethylamine (0.40 mL, 2.86 mmol) and deuterated hypophosphorus acid (0.27 mL, 2.60 mmol). The solution was heated to reflux for 20 minutes before the addition of $K_2S_2O_8$ (0.02 g, 0.08 mmol).[67] After heating to reflux for 4 hours a further portion of $K_2S_2O_8$ (0.02 g, 0.08 mmol) was added and the reaction continued for a further 14 hours. The reaction mixture was cooled to room temperature and the work up completed in accordance with the general experimental. Purification by column chromatography (hexane:EtOAc 9:1) gave the product without any deuterium incorporation as a white solid (0.17 g, 67%) whose analytical data was consistent with that reported in the literature.[166]

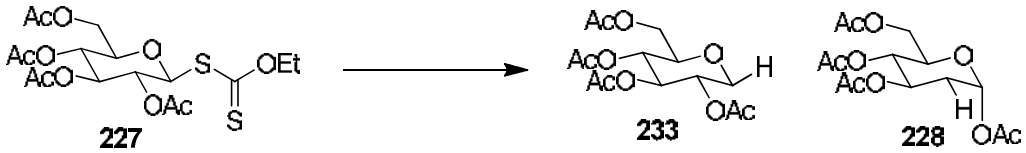
3,5-bis-(Acetyloxy)-2-[(acetyloxy)methyl]-6-[(ethoxycarbothioyl)-sulfanyl]tetrahydro-2H-pyran-4-yl-acetate



Prepared according to the literature procedure.[74]

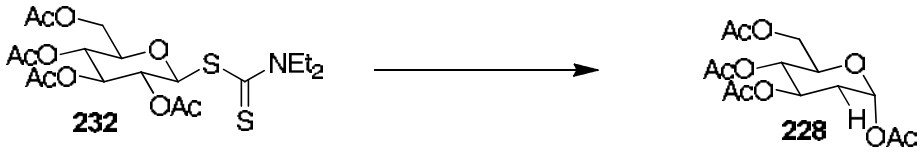
Acetobromo-α-D-glucose (1.0 g, 2.43 mmol) was treated with ethylxanthic acid potassium salt (0.58 g, 3.65 mmol) in CH_3CN (12 mL) at room temperature under argon. After stirring for 4 hours, water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a sticky yellow oil. Purification by column chromatography (petroleum ether:EtOAc 3:1) gave the product as a yellow syrup (0.63 g, 57%), whose analytical data were consistent with that reported in the literature.[74] m.p. 77-79 °C; ν_{max} (neat)/cm^{-1}: 1737, 1365, 1211, 1036, 911; δ_H (300 MHz; $CDCl_3$); 1.37 (3H, t, *J* = 7.1 Hz, CH_3), 1.95 (3H, s, CH_3), 1.97 (6H, s, 2 x CH_3), 2.01 (3H, s, CH_3), 3.77 (1H, m, SCH), 4.07 (1H, dd, *J* = 2.1 Hz and *J* = 12.5 Hz, CH), 4.20 (1H, dd, *J* = 4.8 Hz and *J* = 12.5 Hz, CH), 4.61 (2H, q, *J* =7.1 Hz, CH_2), 5.09-5.22 (2H, m, CH_2), 5.28 (1H, t, *J* = 9.2 Hz, CH), 5.40 (1H, d, *J* = 10.5 Hz, CH).

1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol and Tetra-*O*-acetyl-α-D-arabino-2-deoxy-hyexopyranose, from reduction of xanthate



227 (0.25 g, 0.55 mmol) was dissolved in dioxane (6.9 mL, 0.08 M) and treated with triethylamine (0.42 mL, 3.03 mmol) and hypophosphorus acid (0.29 mL, 2.76 mmol). The solution was heated to reflux for 20 minutes before the addition of ACCN (0.02 g, 0.08 mmol). After heating to reflux for 6 hours the reaction mixture was cooled to room temperature and the work up completed in accordance with the general experimental. Purification by column chromatography (hexane:EtOAc 9:1) gave a mixture of the 2 reduced products **233** and **228** in a 1:1 ratio (0.14 g, 79%) whose analytical data were consistent with that reported in the literature.[165,166]

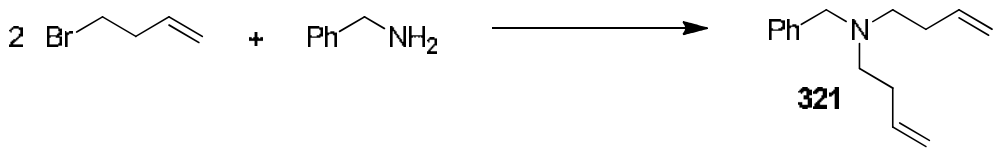
Tetra-*O*-acetyl-α-D-arabino-2-deoxy-hyexopyranose using alternative conditions



A solution of **232** (0.48 g, 1.00 mmol) in cyclohexane (10 mL), was heated to reflux under argon for 15 minutes. Dilauroyl peroxide (0.08 g, 0.2 mmol) was added. After 1 hour a further portion of dilauroyl peroxide (0.08 g, 0.2 mmol) was added. After 4 hours, the solvent was removed under reduced pressure to give the crude compound. Purification by column chromatography (hexane:EtOAc 9:1) gave the *title compound* **228** (0.30 g, 88%), whose analytical data were consistent with that reported in the literature.[166]

Chapter 3-Experimental

***N*-Benzyl-*N*-(but-3-en-1-yl)but-3-en-1-amine**

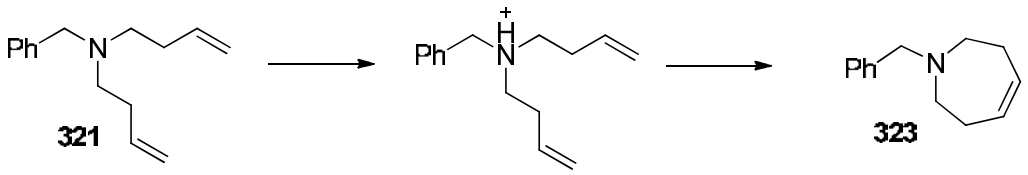


321

Prepared according to the literature procedure.[167]

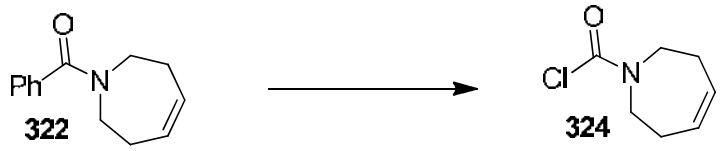
To a stirred solution of K_2CO_3 (2.76 g, 22 mmol) and benzylamine (1.1 mL, 10 mmol) in DMF (60 mL) was added 4-bromo-1-butene (2.0 mL, 20 mmol) in DMF (15 mL). The resultant solution was heated at 60 °C for 3 hours then continued with stirring for 16 hours. The reaction mixture was diluted with ether and quenched with water. The organic layer was extracted with ether (2 x 40 mL), washed with water (60 mL), then brine (60 mL), dried ($MgSO_4$), filtered and evaporated under reduce pressure. The crude product was purified by column chromatography (3:1 hexane:EtOAc) to give the *title compound* as a yellow oil (1.3 g, 61%), whose analytical data was in accordance with that reported in the literature.[167] δ_H (300 MHz; $CDCl_3$); 2.23 (4 H, m, 2 x CH_2), 4.13-4.19 (2H, m, CH_2), 4.35-4.37 (2H, m, CH_2), 4.89-5.02 (2H, m, CH_2), 5.03-5.12 (4H, m, 2 x CH_2), 5.59-6.02 (2H, m, 2 x CH), 7.22-7.46 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$); 31.7 (2 x CH_2), 53.2 (2 x CH_2), 58.5 (CH_2), 115.5 (2 x CH_2), 126.9 (2 x CH), 128.3 (2 x CH), 128.9 (2 x CH), 137.2 (CH), 139.9 (C); HRMS (EI) calculated for $C_{15}H_{21}N$ $[M]^+$ 215.1674, found 215.1676.

1-Benzyl-2,3,6,7-tetrahydro-1*H*-azepine[168]



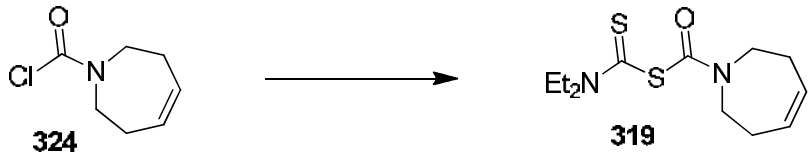
321 (0.88 g, 4.12 mmol) was dissolved in ether (2 mL) and HCl in dioxane (4 M) added until the solution became acidic. The resultant solution was stirred at room temperature for 30 minutes, before the solvent was removed under reduced pressure to yield the salt. This was dissolved in CH_2Cl_2 (41 mL) and Grubbs 2nd generation catalyst (0.035 g, 0.04 mmol) was added. The resultant solution was heated to reflux for 14 hours. After cooling to room temperature a saturated solution of $NaHCO_3$ (40 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with water (60 mL), brine (60 mL), dried ($MgSO_4$) filtered and evaporate under reduced pressure. Purification by column chromatography (5:1 petroleum ether:EtOAC) gave the product as a pale yellow oil (0.53 g, 61%), whose data was in accordance with that reported in the literature.[168] R_f 0.19 (5:1 petroleum ether:EtOAc); δ_H (300 MHz; $CDCl_3$); 2.22-2.36 (4H, m, 2 x CH_2), 2.56-2.75 (4H, m, 2 x CH_2), 3.69 (2H, s, CH_2), 5.80-5.84 (2H, m, 2 x CH), 7.25-7.68 (5H, m, 5 x CH); δ_c (100 MHz; $CDCl_3$); 28.8 (2 x CH_2), 54.8 (2 x CH_2), 62.3 (CH_2), 127.0 (CH), 128.3 (2 x CH), 129.2 (2 x CH), 131.6 (2 x CH), 138.9 (C); HRMS (EI) calculated for $C_{13}H_{17}N$ $[M]^+$ 187.1361, found 187.1359.

2,3,6,7-Tetrahydro-1*H*-azepine-1-carbonyl chloride



A solution of triphosgene (0.056 g, 0.19 mmol) and pyridine (0.06 mL, 0.7 mmol) in toluene (1.5 mL) was stirred at room temperature for 15 minutes. To this was added a solution of amide **322** (0.05 g, 0.27 mmol) in toluene (0.5 mL). The resultant solution was stirred at room temperature for 3 hours before addition of saturated sodium bicarbonate solution (2 mL). The organic layer was separated and the aqueous layer extracted with ether. The combined organic portions were washed with 0.3 M HCl, water, the brine, dried ($MgSO_4$), filtered and concentrate under reduced pressure to yield the crude product. This was purified by column chromatography (3:1 petroleum ether:EtOAc) to give the *title compound* as a yellow oil (0.37 g, 90%). R_f 0.27 (3:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 1721, 1402, 1167, 700; δ_H (300 MHz; $CDCl_3$); 2.30-2.50 (4H, m, 2 x CH_2), 3.61-3.74 (4H, m, 2 x CH_2), 5.71-5.81 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$); 28.8 (CH_2), 29.6 (CH_2), 49.7 (CH_2), 51.3 (CH_2), 128.3 (CH), 129.2 (CH), 148.8 (C=O); m/z (EI) 159 ($[M]^+$ 100%), 144 (74%), 124 (97%), 67 (72%); HRMS (EI) calculated for $C_7H_{10}ONCl$ $[M]^+$ 159.0451, found 159.0454.

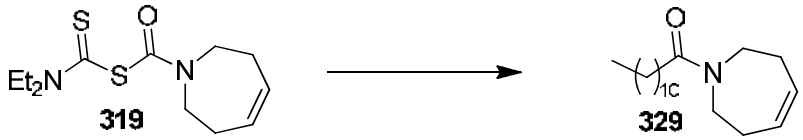
Diethylcarbamthioic 2,3,6,7-tetrahydro-1*H*- azepine-1-carboxylic thioanhydride



Prepared according to the general literature procedure.[160]

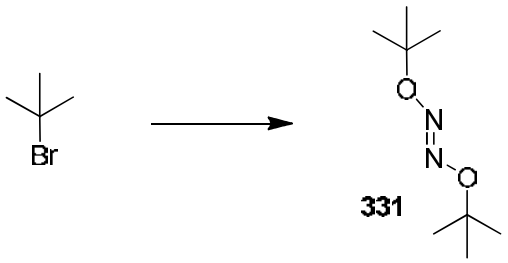
Acid chloride **324** (1.9 mmol, 0.31 g) was dissolved in acetone (12 mL) at room temperature. Sodium diethyldithiocarbamate trihydrate (7.8 mmol, 1.75 g) was added in one portion and the solution was stirred for 16 hours. Saturated $NaHCO_3$ (10 mL) was added followed by water (10 mL) until the inorganic salts dissolved. Et_2O (40 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 25 mL) and the combined organic extracts were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 petroleum ether:EtOAc) to afford the title compound as a yellow oil (0.39 g. 76%). R_f 0.34 (4:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2972, 1659, 1418, 1404, 1269, 1170, 1142; δ_H (300 MHz; $CDCl_3$); 1.30 (3H, t, *J* = 7.2 Hz, CH_3), 1.34 (3H, t, *J* = 7.2 Hz, CH_3), 2.35-2.42 (4H, m, 2 x CH_2), 3.55-3.71 (4H, m, 2 x CH_2), 3.80 (2H, q, *J* = 7.1 Hz, NCH_2), 4.03 (2H, q, J = 7.1 Hz, NCH_2), 5.82-5.85 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$); 11.1 (CH_3), 13.4 (CH_3). 29.0 (CH_2), 29.7 (CH_2), 47.7 (CH_2), 48.9 (CH_2), 49.3 (CH_2), 50.1 (CH_2), 128.6 (CH), 129.0 (CH), 173.3 (C=O), 193.3 (C=S); *m/z* (ESI) 295 ($[M+Na]^+$); HRMS (ESI) calculated for $C_{12}H_{20}OS_2N_2Na$ $[M+Na]^+$ 295.0915, found 295.0906.

1-(2,3,6,7-Tetrahydro-1*H*-azepin-1-yl)dodecan-1-one



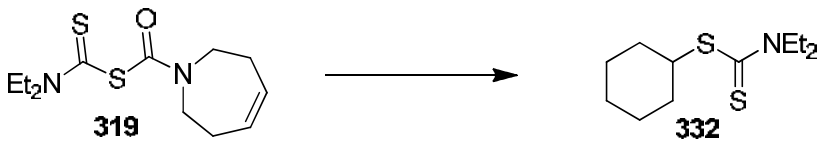
A solution of **319** (0.2 g, 0.74 mmol) was dissolved in cyclohexane (7.4 mL) and the resultant solution degassed for 15 minutes. After heating to reflux, dilauroyl peroixde (0.058 g, 0.15 mmol) was added. After 2 hours a further portion of dilauroyl peroixde (0.058 g, 0.15 mmol) was added. After 2 more hours, another portion of dilauroyl peroxide was added (0.058 g, 0.15 mmol). The reaction mixture was heated to reflux for two more hours then cooled to room temperature. The solvent was removed under reduced pressure and the crude product purified by column chromatography (14:1 petroleum ether:EtOAc) to give the *title compound* as a yellow oil (0.09 g, 56%)**.** R_f 0.34 (14:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}:2921, 2852, 1641, 1423, 699; δ_H (300 MHz; $CDCl_3$); 0.88 (3H, t, *J* = 6.9 Hz, CH_3), 1.22-1.38 (20H, m, 10 x CH_2), 1.61-1.69 (4H, m, 2 x CH_2), 3.52 (2H, t, *J* = 5.5 Hz, CH_2), 3.62 (2H, t, *J* = 5.5 Hz, CH_2), 5.62-5.91 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$); 14.3 (CH_3), 22.8 (CH_2), 25.6 (CH_2), 29.5 (CH_2), 29.6 (3 xCH_2), 29.7 (CH_2), 29.8 (3x CH_2), 30.5 (CH_2), 33.7 (CH_2), 45.6 (CH_2), 48.2 (CH_2), 128.31 (CH), 130.7 (CH), 172.4 (C=O); *m/z* (ESI) 288 $[M+Na]^+$ 100%; HRMS (ESI) calculated for $C_{18}H_{33}ONNa$ $[M+Na]^+$ 288.2429*,* found 288.2437.

(E)-1,2-di-*tert*-butoxydiazene[169]



(E)-1,2-di-tert-butoxydiazene was prepared according to the literature procedure.[169] $Na_2N_2O_{21}$ (0.805 g, 7.6 mmol) was added over a 5 minute period to a mixture of $FeCl_3$ (1.20 g, 7.40 mmol) and t-BuBr (8.00 mL, 80.0 mmol) in Et_2O (8.00 mL). The temperature was maintained below -45 °C and allowed to stand for 75 minutes and then at 5 °C overnight in the fridge. The inorganic precipitate was removed by suction filtration and washed with ice cold Et_2O (3 x 3mL). The filtrate was washed with water (3 x 3 mL) and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Recrystaillisation from pentane (7 mL) afforded the *title compound* (201 mg, 16%) as clear crystals, whose data was in accordance with that reported in the literature.[169] m.p. 82-83 °C (pentane); δ_H (300 MHz; $CDCl_3$) 1.39 (18H, s, 6 x CH_3); δc (100 MHz; $CDCl_3$); 27.8 (6 x CH_3), 81.2 (C).

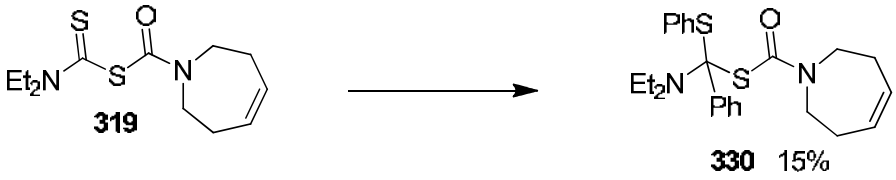
Cyclohexyl diethylcarbamodithioate



A solution of **319** (0.2 g, 0.74 mmol) was dissolved in cyclohexane (7.4 mL) and the resultant solution degassed for 15 minutes. After heating to reflux (E)-1,2-di-*tert*-

butoxydiazene (0.023 g, 0.15 mmol) was added. After 2 hours a further portion of (E)-1,2-di-*tert*-butoxydiazene (0.023 g, 0.15 mmol) was added. This was repeated a further two times. The reaction mixture was heated to reflux for two hours after the final addition, then cooled to room temperature. The solvent was removed under reduced pressure and the crude reaction mixture purified by column chromatography (19:1 petroleum ether:EtOAc) to give the *title compound* **332** as a yellow oil (0.09 g, 56%)**.** R_f 0.27 (19:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}:2928, 1483, 1412, 1261, 1208, 982, 914; δ_H (300 MHz; $CDCl_3$); 1.17-1.35 (7H, m, 2 x CH_3, CH_2), 1.39-1.51 (4H, m, 2 x CH_2), 1.56-1.62 (1H, m, CH_2), 1.71-1.83 (2H, m, CH_2), 1.99-2.21 (2H, m, CH_2), 3.71 (2H, q, *J* = 7.0 Hz, CH_2), 3.85-3.94 (1H, m, CHS), 4.01 (2H, q, *J* = 7.1 Hz, CH_2); δc (100 MHz; $CDCl_3$); 11.7 (CH_3), 12.4 (CH_3), 25.7 (CH_2), 26.2 (2 x CH_2), 32.9 (2 x CH), 46.6 (CH_2), 49.0 (CH_2), 50.2 (CH), 195.3 (C=S); *m/z* (EI) 231 ($[M]^+$ 24%), 149 (63%), 116 (100%); HRMS (EI) calculated for $C_{11}H_{21}S_2N$ $[M]^+$ 231.1115, found 231.1118.

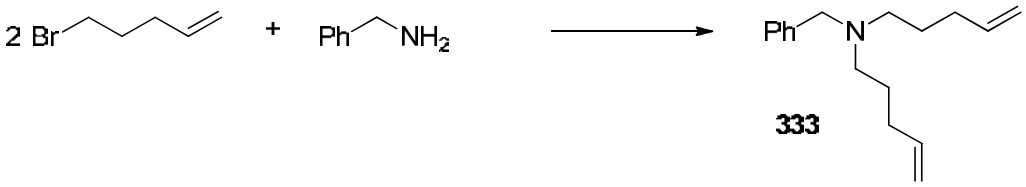
_S_-((Dimethylamino)(phenyl)(phenylthio)methyl) 2,3,6,7-tetrahydro-1H-azepine-1-carbothioate



A solution of **319** (0.2 g, 0.74 mmol) in cyclohexane (7.4 mL) and was degassed for 15 minutes. After heating to reflux dibenzoyl peroxide (0.036 g, 0.15 mmol) was added. After 2 hours a further portion of dibenzoyl peroxide (0.036 g, 0.15 mmol) was added. This was repeated a further two times. The reaction mixture was heated to reflux for two hours

after the final addition, then cooled to room temperature. The solvent was removed under reduced pressure and the crude reaction mixture purified by column chromatography (3:1 petroleum ether:EtOAc) to give a single product as a yellow oil (0.05 g, 15%), whose structure has tentatively been assigned to that of **332**. R_f 0.34 (3:1 petroleum ether:EtOAc) ν_{max}(neat)/cm^{-1}: 2933, 1782, 1721, 1208, 117, 991; δ_H (300 MHz; $CDCl_3$); 0.99-1.29 (6H, m, 3 x CH_3), 2.11-2.49 (4H, m, 2 x CH_2), 3.12-3.79 (8H, m, 4 x CH_2), 5.62-5.83 (2H, m, 2 x CH), 7.27-7.47; δ_c (100 MHz; $CDCl_3$); 12.9 (CH_3), 13.2 (CH_3), 28.9 (CH_2), 30.5 (CH_2), 38.9 (CH_2), 43.2 (CH_2), 45.7 (CH_2), 49.4 (CH_2), 126.3 (2 x CH), 126.5 (3 x CH), 128.4 (2 x CH), 129.1 (C), 129.2 (2 x CH), 130.6 (3 x CH), 137.2 (C), 137.3 (C),171.2 (C=O); m/z (ESI) 426 $[M]^+$.

_N_-Benzyl-_N_-(pent-4-en-1-yl)pent-4-en-1-amine



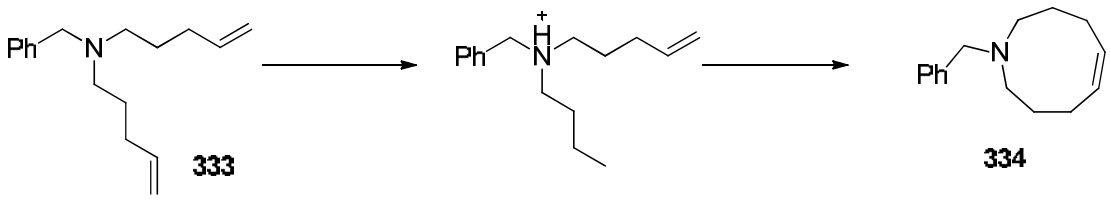
333

Prepared according to the general literature procedure.[167]

To a stirred solution of K_2CO_3 (2.76 g, 22 mmol) and benzylamine (1.1 mL, 10 mmol) in DMF (60 mL) was added 5-bromo-1-pentene (2.4 mL, 20 mmol) in DMF (15 mL). The resultant solution was heated at 60 °C for 3 hours then continued with stirring for 16 hours. The reaction mixture was diluted with ether and quenched with water. The aqueous layer was extracted with ether (2 x 40 mL). The combined organic extracts were washed with water (60 mL), then brine (60 mL), dried ($MgSO_4$), filtered and evaporated

under reduce pressure. The crude product was purified by column chromatography (4:1 hexane:EtOAc) to give the *title compound* as a yellow oil (1.4 g, 58%). R_f 0.26 (4:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2933, 2797, 1452, 991, 908; δ_H (300 MHz; $CDCl_3$); 1.59 (4H, qn, *J* = 7.5 Hz, 2 x CH_2), 2.07 (4H, q, *J* = 8.1 Hz, 2 x CH_2), 2.45 (4 H, t, *J* = 7.4 Hz, 2 x CH_2), 3.57 (2H, s, CH_2), 4.82-5.11 (4H, m, 2 x CH_2), 5.73-5.90 (2H, m, 2 x CH), 7.03-7,48 (5 x CH); δ_c (100 MHz; $CDCl_3$); 26.6 (2 x CH_2), 31.7 (2 x CH_2), 53.5 (2 x CH_2), 58.8 (CH_2), 114.5 (2 x CH_2), 126.8 (CH), 128.2 (2 x CH), 139.0 (2 x CH), 139.5 (C), 140.4 (2 x CH); m/z (EI) 243 ([M]$^+$ 22%), 188 (100%), 91 (76%); HRMS (EI) calculated for $C_{17}H_{25}N$ [M]$^+$ 243.1987, found 243.1980.

(Z)-1-Benzyl-2,3,4,7,8,9-hexahydro-1*H*-azonine

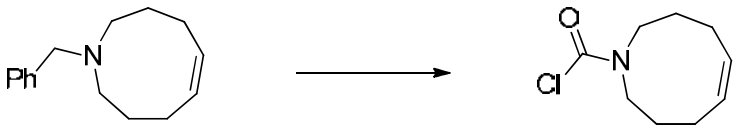


Prepared according to the general literature procedure.[168]

N-Benzyl-*N*-(pent-4-en-1-yl)pent-4-en-1-amine (1.0 g, 4.1 mmol) was dissolved in ether (3 mL) and HCl in dioxane (4 M) added until the solution became acidic. The resultant solution was stirred at room temperature for 30 minutes, before the solvent was removed under reduced pressure to yield the salt. This was dissolved in CH_2Cl_2 (80 mL) and Grubbs 2nd generation catalyst (0.035 g, 0.04 mmol) was added. The resultant solution was heated to reflux for 14 hours. After cooling to room temperature a saturated solution of $NaHCO_3$ (40 mL) was added. The organic phase was separated and the

aqueous phase was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were washed with water (60 mL), brine (60 mL), dried ($MgSO_4$) filtered and evaporate under reduced pressure. Purification by column chromatography (5:1 petroleum ether:EtOAC) gave the product as a pale yellow oil (0.53 g, 61%). R_f 0.19 (5:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2974, 1658, 1412, 1398, 1273, 1166, 1140; δ_H (300 MHz; $CDCl_3$); 1.51-1.74 (4H, m, 2 x CH_2), 1.96-2.17 (4H, m, 4 x CH_2), 2.39-2.63 (4H, m, 4 x CH_2), 3.60 (2H, s, CH_2), 5.39-5.58 (2H, m, 2 x CH), 7.20-7.51 (5 x CH); δ_c (100 MHz; $CDCl_3$); 26.5 (CH_2), 26.9 (CH_2), 29.7 (CH_2), 34.3 (CH_2), 52.1 (CH_2), 53.2 (CH_2), 58.6 (CH_2), 126.7 (2 x CH), 128.1 (2 x CH), 128.8 (2 x CH), 130.47 (CH), 139.9 (C); *m/z* (ESI) 216 (M^+ 100%); HRMS (ESI) calculated for $C_{15}H_{22}N$ $[M]^+$ 216.1752, found 216.1756.

(Z)-2,3,4,7,8,9-Hexahydro-1*H*-azonine-1-carbonyl chloride

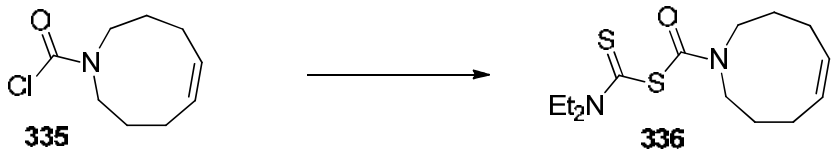


334 **335**

A solution of triphosgene (0.19 g, 0.65 mmol) and triethylamine (0.19 mL, 2.42 mmol) in toluene (6 mL) was stirred at room temperature for 15 minutes. To this was added a solution of amide (0.20 g, 0.93 mmol) in toluene (4 mL). The resultant solution was stirred at room temperature for 16 hours before addition of saturated sodium bicarbonate solution (10 mL). The organic layer was separated and the aqueous layer extracted with Et_2O (2 x 10 mL). The combined organic portions were washed with HCl (0.3 M, 15 mL), water (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield the crude product. This was purified by column chromatography (5:1

petroleum ether:EtOAc) to give the product as a yellow oil (0.12 g, 70%). R_f 0.34 (5:1 petroleum ether:EtOAc); δ_H (300 MHz; $CDCl_3$); 1.52-1.61 (4H, m, 2 x CH_2), 1.89-1.93 (4H, m, 2 x CH_2), 2.94-2.97 (4H, m, 2 x CH_2), 5.39-5.46 (2H, m, 2 x CH).

Diethylcarbamothioic(Z)-2,3,4,7,8,9-hexahydro-1H-azonine-1-carboxylicthioanhydride

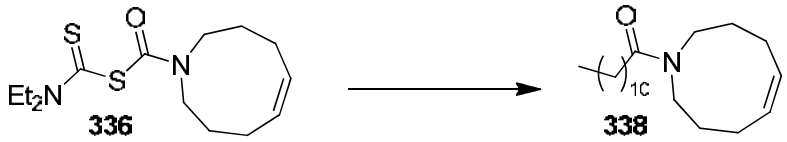


Prepared according to the general literature procedure.[160]

Acid chloride **335** (0.33g, 1.76 mmol) was dissolved in acetone (18 mL) at room temperature. Sodium diethyldithiocarbamate trihydrate (1.58 g, 1.76 mmol) was added in one portion and the solution was stirred for 16 hours. Saturated $NaHCO_3$ (15 mL) was added followed by water (20 mL) until the inorganic salts dissolved. Et_2O (50 mL) was added and the phases were separated. The aqueous portion was washed with Et_2O (3 × 25 mL) and the combined organic extracts were washed with water (25 mL) and brine (25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 petroleum ether:EtOAc) to afford the *title compound* as a yellow oil (52%, 0.27 g). R_f 0.14 (5:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2933, 1732, 1664, 1418, 1402, 1268, 1142, 969; δ_H (300 MHz; $CDCl_3$); 1.29 (3H, t, *J* = 7.1 Hz, CH_3), 1.32 (3H, t, *J* = 7.1 Hz, CH_3), 1.63-1.74 (4H, m, 2 x CH_2), 1.98-2.14 (4H, m, 2 x CH_2), 3.23-3.47 (4H, m, 2 x CH_2), 3.78 (2H, q, *J* = 7.1, CH_2), 4.01 (2H, q, *J* = 7.1 Hz, CH_2), 5.37-5.48 (2H, m, 2 x CH); δ_c (100 MHz; $CDCl_3$); 11.3 (CH_3), 13.5 (CH_3), 27.1 (CH_2), 27.3 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 49.0 (CH_2), 49.4 (CH_2), 50.2 (CH_2), 50.7 (CH_2), 130.0 (CH), 130.3 (CH), 161.9 (C=O),

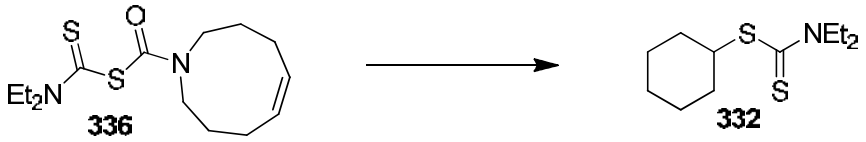
185.1 (C=S). *m/z* (ESI) 323 ([M+Na]$^+$ 100%); HRMS (ESI) calculated for $C_{14}H_{24}OS_2N_2Na$ [M+Na]$^+$ 323.1228*,* found 323.1234.

(Z)-1-(2,3,4,7,8,9-hexahydro-1H-azonin-1-yl)dodecan-1-one



A solution of **336** (0.03 g, 0.1 mmol) was dissolved in cyclohexane (2 mL) and the resultant solution degassed for 15 minutes. After heating to reflux, dilauroyl peroixde (0.008 g, 0.02 mmol) was added. After 2 hours a further portion of dilauroyl peroixde (0.008 g, 0.02 mmol) was added. After 2 more hours, another portion of dilauroyl peroxide was added (0.058 g, 0.02 mmol). The reaction mixture was heated to reflux for two more hours then cooled to room temperature. The solvent was removed under reduced pressure and the crude mixture purified by column chromatography (14:1 petroleum ether:EtOAc) to give the *title compound* as a yellow oil (37%, 0.01 g)**.** R_f 0.29 (14:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 2919, 2853, 1641, 1420, 701; δ_H (300 MHz; $CDCl_3$); 0.83 (3H, t, *J* = 6.7 Hz, CH_3), 1.22-1.38 (20H, m, 10 x CH_2), 1.51-1.63 (4H, m, 2 x CH_2), 3.18 (4H, t, *J* = 5.5 Hz, 2 x CH_3), 3.52-3.56 (2H, m, CH_2), 3.683-3.88 (2H, m, CH_2), 5.68-5.97 (2H, m, 2 x CH); δc (100 MHz; $CDCl_3$); 14.2 (CH_3), 22.9 (CH_2), 25.5 (CH_2), 29.4 (CH_2), 29.5 (3 x CH_2), 29.7 (CH_2), 29.8 (3 x CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (CH_2) 33.7 (CH_2), 45.6 (CH_2), 48.2 (CH_2), 128.31 (CH), 130.7 (CH), 172.4 (C=O); *m/z* (ESI) 316 [M+Na]$^+$ 100%; HRMS (ESI) calculated for $C_{20}H_{37}ONNa$ [M+Na]$^+$ 316.2742*,* found 316.2749.

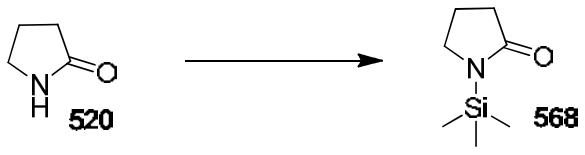
Cyclohexyl diethylcarbamodithioate



A solution of **336** (0.1 g, 0.34 mmol) was dissolved in cyclohexane (4 mL) and the resultant solution degassed for 15 minutes. After heating to reflux (E)-1,2-di-*tert*-butoxydiazene (0.012 g, 0.07 mmol) was added. After 2 hours a further portion of (E)-1,2-di-*tert*-butoxydiazene (0.012 g, 0.07 mmol) was added. This was repeated a further two times. The reaction mixture was heated to reflux for two hours after the final addition, then cooled to room temperature. The solvent was removed under reduced pressure and the crude product purified by column chromatography (19:1 petroleum ether:EtOAc) to give the *title compound* **332** as a yellow oil (0.04 g, 53%). Analytical data as reported previously.

Chapter 4-Experimental

1-(trimethylsilyl)pyrrolidin-2-one[154]

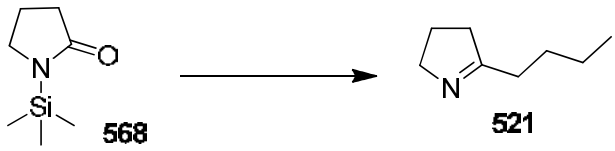


Prepared according to the literature procedure.[154]

Trimethylsilylchloride (11.2 mL, 88 mmol) was added to a solution of 2-pyrrolidinone (6 mL, 80 mmol) and triethylamine (14 mL, 100 mmol) in toluene (80 ml). The resulting solution was stirred at 60 °C for 2 hours then at room temperature for 17 hours. The

reaction mixture was cooled on ice, diluted with hexane:diethyl ether (1:1, 80 mL), filtered through celite and the filtrate concentrated under reduced pressure. Purification by column chromatography (diethyl ether) resulted in a yellow oil (9.1 g, 72%), whose analytical data was in accordance with that reported in the literature.[154] R_f 0.66 (diethylether); ν_{max}(neat)/cm^{-1} 2947, 2847, 1638, 1400, 987; δ_H (300 MHz; $CDCl_3$) 0.21 (9H, s, 3 x CH_3), 2.09 (2H, qn, *J* = 7.2 Hz, CH_2), 2.25 (2H, t, *J* = 7.2 Hz, CH_2CO), 3.35 (2H, t, *J* = 7.2 Hz, CH_2N); δ_C (75 MHz; $CDCl_3$) -0.9 (3 x CH_3), 22.4 (CH_2), 33.5 (CH_2), 47.2 (CH_2), 184.1 (C=O).

5-butyl-3,4-dihydro-2*H*-pyrrole[154]

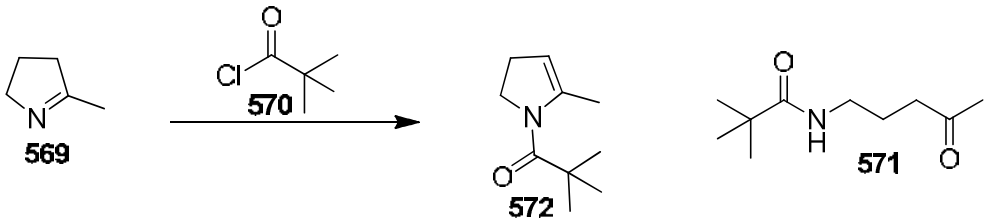


Prepared according to the general literature procedure.[154]

To a cold (-20 °C), stirred solution of butyllithium was added **568** (2 g, 12.7 mmol) in diethyl ether (20 mL). The solution was stirred at –20 °C for 30 minutes and then at room temperature for 1 hour. A solution of NH_4Cl (0.68 g) in water (25 mL) was added and the reaction allowed to continue for 30 minutes. The organic layer was removed and the aqueous later extracted with CH_2Cl_2 (3 x 25 mL). The organic extracts were combined, washed with brine and dried ($MgSO_4$). The solvents were removed under reduced pressure. Purification by column chromatography (diethyl ether) resulted in a colourless oil (1.03 g, 65%), whose analytical data was in accordance with that reported in the literature.[154] R_f = 0.46 (acetone); δ_H (300 MHz; $CDCl_3$) 0.84 (3H, t, *J* = 7.8 Hz, CH_3), 1.26

(2H, m, CH_2), 1.50 (2H, qn, *J* = 7.8 Hz, CH_2), 1.77 (2H, qn, *J* = 6.9 Hz, CH_2), 2.26 (2H, t, *J* = 6.9 Hz, CH_2) 2.37 (2H, t, *J* = 7.8 Hz, CH_2), 3.70 (2H, t, *J* = 6.9 Hz, CH_2N); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 22.6 (CH_2), 22.7 (CH_2), 28.7 (CH_2), 32.6 (CH_2), 37.1 (CH_2), 60.7 (CH_2), 178.8 (C); *m/z* (ESI) 125 ($[M]^+$ 100%).

1-trimethylacetyl(5-methyl-2,3-dihydro-1*H*-pyrrol-1-yl) and *N*-(4-oxypentyl)pivalamide



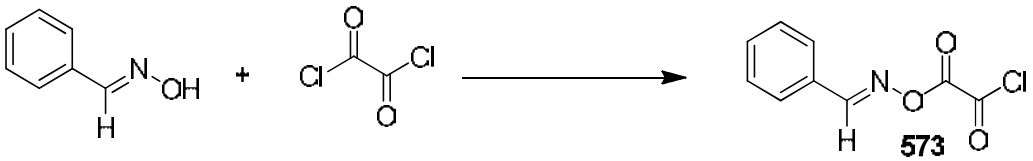
Triethylamine (1.4 mL, 10 mmol) in THF (5 mL) was added to a solution of 2-methyl-1-pyrroline (1.42 mL, 15 mmol) in THF (30 mL) at -78 °C, followed by trimethylacetylchloride (1.2 mL, 10 mmol) in THF (5 mL). The solution was allowed to warm to room temperature for 16 hours. Pentane (20 mL) was added and the resulting precipitate removed by filtration. Evaporation of the filtrate lead to a mixture of products which were separated by column chromatography (2:1 hexane:ethylacetate). This resulted in an orange oil (1-trimethylacetyl(5-methyl-2,3-dihydro-1*H*-pyrrol-1-yl)) (0.05 g, 2%) and also a white solid (1.44 g, 52 %) (*N*-(4-oxypentyl)pivalamide).

1-trimethylacetyl(5-methyl-2,3-dihydro-1*H*-pyrrol-1-yl); R_f = 0.66 (2:1 hexane:EtOAc); δ_H (300 MHz; $CDCl_3$) 1.28 (9H, s, CH_3), 2.18 (3H, m, CH_3), 2.45 (2H, m, CH_2), 3.97 (2H, t, *J* = 8.2, CH_2), 4.92 (1H, m, CH); δ_C (75 MHz; $CDCl_3$) 19.4 (CH_3), 28.7 (CH_3), 38.9 (CH_2), 47.1

(CH_2), 53.9 (C), 109.7 (CH), 134.6 (C), 179 (C=O). *m/z* (EI) 176 $(M+Na)^+$; HRMS (EI) $C_{10}H_{17}O$ calculated for M^+ 153.1279, found 153.1277.

N-(4-oxypentyl)pivalamide; R_f = 0.21 (4:1 hexane:EtOAc); m.p. 38-40 °C; ν_{max} (neat)/cm^{-1} 3341, 2955, 1712, 1631, 1536, 1367, 1217; δ_H (300 MHz; $CDCl_3$) 1.16 (9 H, s, CH_3), 1.78 (2 H, qn, *J* = 6.8, CH_2), 2.14 (3 H, s, CH_3), 2.49 (2 H, t, *J* = 6.8, CH_2), 3.21-3.23 (2H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 25.7 (CH_2), 30.1 (3 x CH_3), 32.5 (CH_3), 41.8 (CH_2), 43.8 (CH_2), 164.0 (2 x C), 168.2 (C); *m/z* (EI) 185 (M^+), 142 (80%), 128 (24%), 100 (27%), 85 (12%); HRMS (EI) $C_{10}H_{19}NO_2$ calculated for M^+ 185.1416, found 185.1415.

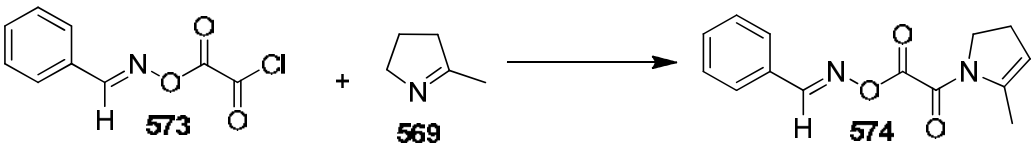
2-(benzylideneaminooxy)-2-oxyacetyl chloride [36]



Prepared according to the literature procedure.[36]

A solution of benzaldozime (1.20 g, 10 mmol) in diethylether (10 mL) was added dropwise to a cold (-40 °C), stirred solution of oxalylchloride (1.9 g, 15 mmol) in diethylether (10 mL). After stirring for 1 hour at – 20 °C, the solvent was evaporated to give a white, temperature sensitive, powder (1.60 g, 76%), whose analytical data was consistent with that reported in the literature;[36] δ_H (300 MHz; $CDCl_3$) 7.23-7.49 (5H, m, CH), 8.56 (1H, s, CH); δ_C (75 MHz; $CDCl_3$) 128.2 (CH), 128.8 (2 x CH), 129.2 (2 x CH), 132.9 (C), 159.2 (C=N), 160.4 (C=O), 162.4 (C=O); EI *m/z* 211 (M^+, 20%).

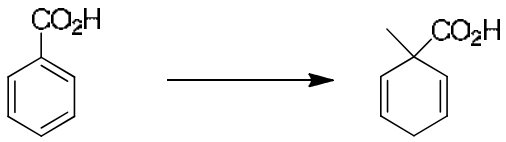
Benzaldehyde *O*-2-(5-methyl-2,3-dihydro-1-H-pyrrol-1yl)-2oxoacetyl oxime



Prepared according to the general literature procedure.[36]

Pyridine (0.4 mL, 5mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of **573** (1.06 g, 5 mmol) in CH_2Cl_2 (11 mL) at 0 °C, followed by 2-methyl-1-pyrroline (0.4 ml, 5 mmol) in CH_2Cl_2 (6 mL). The mixture was allowed to reach room temperature and then stirred at room temperature for 3 hours. After this time pentane (10 mL) was added to promote the formation of the pyridine hydrochloride precipitate. The precipitate was filtered off and the filtrate evaporated to dryness. The resulting oil was purified by column chromatography (petroleum ether:EtOAc 4:1) to give a clear oil (15%) as 2 non separable isomers (0.19 g, 15%). R_f = 0.35 (4:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1} 3347, 1759, 1675, 1369, 1177; δ_H (300 MHz; $CDCl_3$) 2.00-2.29 (3H, m, CH_3), 2.52-2.61 (2H, m, CH_2), 4.00-4.07 (2H, m, CH_2), 5.10-5.15 (1H, m, CH), 7.37-7.76 (5H, m, CH), 8.46-8.50 (1H, m, NCH); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3), 16.2 (CH_3), 26.6 (CH_2), 28.1 (CH_2), 47.8 (CH_2), 48.9 (CH_2), 113.3 (CH), 114.5 (CH), 127.5 (CH), 129.1 (CH), 129.2 (CH), 129.5 (CH), 130.4 (CH), 132.7 (CH), 158.2 (HC=N), 158.5 (HC=N); *m/z* (EI) 258 (M^+) 43%, 155 (30%), 110 (68%), 104 (65%), 77 (100%); HRMS (EI) $C_{14}H_{14}N_2O_3$ calculated for M^+ 260.1168, found 260.1174

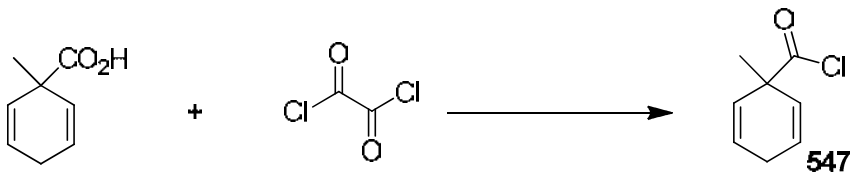
3- Methylcyclohexa-1,4-diene-3-carboxylic acid[170]



Prepared according to the literature procedure.[170]

Benzoic acid (10 g, 82 mmol) was dissolved in liquid ammonia (600 mL) and lithium wire (2.1 g) was added in small portions until a deep-blue colour appeared. Methyliodide (16.6 mL, 267 mmol) was then added dropwise, leading to a discharge of colour and formation of a white solid. The ammonia was evaporated and the suspension acidified with 50% H_2SO_4. The mixture was extracted with diethyl ether (4 x 100 mL). The organic extracts were combined, washed with saturated sodium thiosulfate solution (100 mL), water (100 mL), brine (100 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a yellow oil (7.87 g, 70%), whose analytical data was in accordance with that reported in the literature.[170] ν_{max}(neat)/cm^{-1} 1694 (C=O), 1637 (C=C), 980, 976; δ_H (300 MHz; $CDCl_3$) 1.38 (3H, s, CH_3), 2.62-2.66 (2H, m, CH_2), 5.81-5.85 (4H, m, 4 x CH), 12.31 (1H, br, s); δ_C (75 MHz; $CDCl_3$) 26.6 (CH_3), 27.7 (CH_2), 44.1 (C), 125.4 (CH), 128.5 (CH), 182.6 (C=O).

3- Methylcyclohexa-1,4-diene-3-carbonylchloride[171]

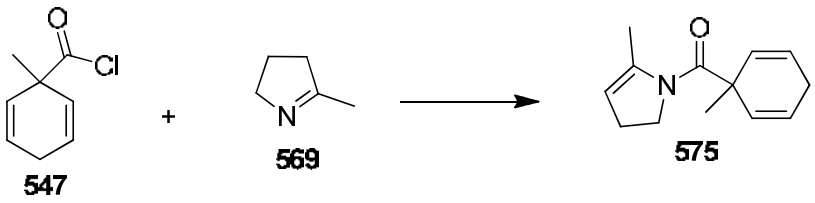


547

Prepared according to the literature procedure.[171]

A solution of oxalylchloride (2.21 g, 17.5 mmol) in diethylether (13 mL), was added dropwise to a stirred solution of 3-methylcyclohexa-1,4-diene-3-carboxylic acid (2 g, 15 mmol) in diethylether (15 mL). The solution was stirred at room temperature for 18 hours then heated at reflux for 2 hours. The solvent was removed under reduced pressure to give a temperature sensitive white powder (2.0 g, 85%), whose analytical data was consistent with that reported in the literature.[171] R_f = 0.73 (petroleum ether); δ_H (300 MHz; $CDCl_3$) 1.43 (3 H, s, CH_3), 2.71 (2H, m, CH_2), 5.68-5.72 (2 H, m, CH), 5.92-6.06 (2H, m, CH).

(5-methyl-2,3-dihydro-1-H-pyrrol-1yl)(1-methylcyclohexa-2,5-dienyl)methanone



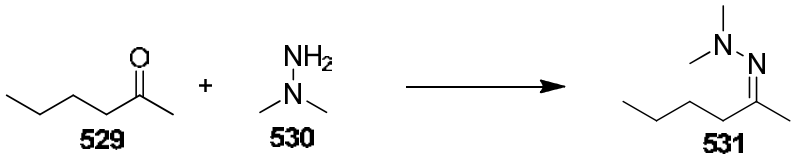
547 **569** **575**

Prepared according to the general literature procedure.[171]

To a cold (0 °C), stirred, solution of the carbonyl chloride **547** (5 mmol, 0.78 g) in CH_2Cl_2 (11 mL) was added pyridine (0.4 mL, 5 mmol) in CH_2Cl_2 (6 mL), followed by 2-methyl-1-pyrroline (5 mmol, 0.47 mL) in CH_2Cl_2 (6 mL). The reaction was allowed to reach room temperature and continued for 18 hours. After this time pentane was added and the resulting precipitate removed by filtration. The solvent was removed by evaporation to give the crude product. Purification by column chromatography (2:1 petroleum ether: diethyl ether) gave a mixture of 2 isomers. ν_{max}(neat)/cm^{-1} 2928, 1710, 1647, 1516, 1363, 708; δ_H (300 MHz; $CDCl_3$) 1.29 (1.5H, s, CH_3), 1.33 (1.5H, s, CH_3), 2.11 (1.5H, s, CH_3), 2.19 (1.5H, s, CH_3), 2.02-2.08 (1H, m, CH_2), 2.11-2.19 (1H, m, CH_2), 2.69-2.72 (2H, m, CH_2), 3.79

(1H, t, *J* = 7.2 Hz, CH_2), 3.92 (1H, t, J = 7.3 Hz, CH_2), 4.54 (0.5H, m, CH) 4.84 (0.5H, m, CH), 5.62-5.81 (4H, m, CH_2); δ_C (75 MHz; $CDCl_3$) 16.9 (CH_3), 19.6 (CH_3), 26.1 (CH_2), 39.9 (C), 40.7 (CH_2), 55.0 (CH_2), 127.5 (CH), 129.2 (CH), 129.5 (CH), 133.9 (C), 207.7 (C); *m/z* (EI) 203.1 (M^+), 128.1 (22%), 91.1 (100%), 77.0 (23%); HRMS (EI) $C_{13}H_{17}NO$ calculated for M^+ 203.1310, found 203.1314.

2-(hexan-2-ylidene)-1,1-dimethylhydrazine[172]

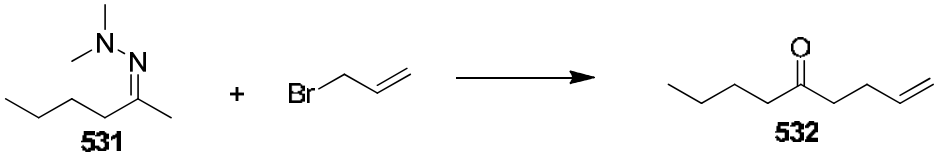


529 530 531

Prepared according to the literature procedure.[175]

To a solution of 2-hexanone (6.12 mL, 50 mmol) in ethanol (20 ml) was added dimethylhydrazine (12 mL, 150 mmol) and the reaction mixture heated at reflux for 18 hours. The reaction mixture was cooled on ice and the solvent removed under reduced pressure to give a clear oil (6.2 g, 87%) whose analytical data was consistent with that reported in the literature.[172] ν_{max}(neat)/cm^{-1} 1640, 1467, 910; δ_H (300 MHz; $CDCl_3$) 0.89 (3H, t, *J* = 7.2, CH_3), 1.09-1.71 (4H, m, 2 x CH_2), 1.93 (3H, s, CH_3), 2.12-2.29 (2H, m, CH_2), 2.43 (6H, s, CH_3); δ_C (75 MHz; $CDCl_3$) 16.4 (CH_3), 22.4 (CH_2), 29.2 (CH_2), 30.9 (CH_3), 38.8 (CH_2), 47.0 (CH_3), 47.5 (CH_3), 158.2 (C).

Non-1-en-5-one[175]

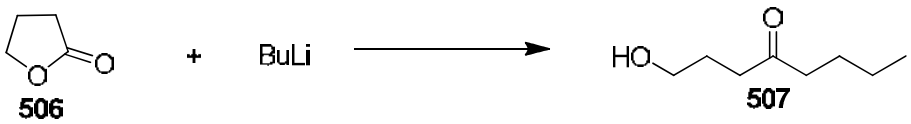


531 532

Prepared according to the general literature procedure.[175]

n-BuLi (3.1 mL, 5.16 mmol) was added to a stirred solution of 2-(hexan-2-ylidene)-1,1-diemthylhydrazine (0.6 g, 4.3 mmol) in THF (20 mL) at 0 °C. After stirring for 40 minutes, allylbromide (0.67 g, 5.16 mmol) was added and the reaction was slowly allowed to reach temperature overnight. Water was added and the product extracted with ethylacetate (3 x 20 mL). The organic phases were combined and concentrated under reduced pressure.[173] The resulting hydrazine was added to a solution of copper chloride (1.1 equiv.) in water and the solution stirred for 2 hours and 30 minutes. The reaction was quenched with NH_4OH, extracted with ethylacetate (3 x 20 mL), washed with brine (60 mL) and dried ($MgSO_4$).[174] The solvents were removed under reduced pressure before purification by distillation (100 °C) gave a yellow oil (97%, 0.58 g), whose analytical data was consistent with that reported in the literature.[175] ν_{max}(neat)/cm^{-1} 3077, 1714, 1640, 1411, 1361, 995, 910; δ_H (300 MHz; $CDCl_3$) 0.93 (3H, t, *J* =7.1 Hz, CH_3), 1.21-1.42 (2H, m, CH_2), 1.49-1.63 (2H, m, CH_2), 2.15-2.49 (6H, m, 3 xCH_2), 4.89-5.00 (2H, m, =CH_2), 5.68-5.92 (1H, m, CH); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3), 22.3 (CH_2), 25.9 (CH_2), 27.8 (CH_2), 41.8 (CH_2), 42.6 (CH_2), 115.1 (CH_2), 135.5 (CH), 209.3 (C).

1-Hydroxyoctan-4-one[176]



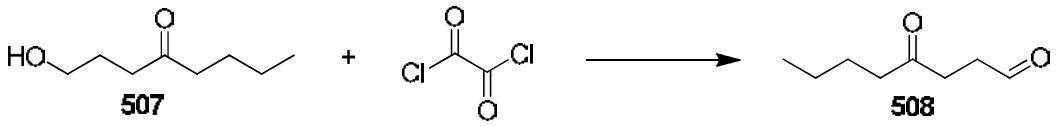
Prepared according to the general literature procedure.[176]

Butyllithium (8 mL, 12.5 mmol) was added dropwise over 10 minutes to a stirred solution of γ-butyra-lactone (1.00 g, 11.6 mmol) in THF (24 mL) at –78 ° C. After stirring for 2 hours

at this temperature, the solution was warmed to room temperature overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and the aqueous phase extracted with Et_2O (3 x 15 mL). The organic portions were combined, washed with brine, dried ($MgSO_4$) and concentrated under *vacuo* to give a colourless oil (1.37 g, 82%), whose analytical data was consistent with that reported in the literature.[176] ν_{max}(neat)/cm^{-1} 3400, 2933, 1711, 1467, 1378, 1059, 996; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, t, CH_3), 1.28-1.89 (6H, m, 3 x CH_2), 2.45-2.60 (4H, m, CH_2), 3.66 (2H, t, CH_2OH); δ_C (75 MHz; $CDCl_3$) 14.1 (CH_3), 23.3 (CH_2), 25.8 (CH_2), 26.8 (CH_2), 36.0 (CH_2), 39.0 (CH_2), 63.5 (CH_2), 162.1 (C); *m/z* (EI) 143 (M^+), 127 (100%), 85 (24%), 69 (16%), 57 (56%).

4-Oxooctanal

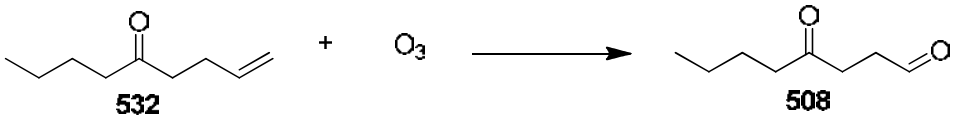
Approach 1



A stirred solution of oxalyl chloride (0.24 mL, 2.78 mmol) in CH_2Cl_2 (12 mL) at –78 °C was treated with DMSO (0.42 mL, 5.96 mmol), followed after ten minutes by ketoalcohol **507** (0.2 g, 1.38 mmol). After stirring for 30 minutes, triethylamine (1.92 mL, 13.8 mmol) was added and the reaction slowly allowed to reach room temperature. Stirring for 5 hours was followed by quenching with water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the organic extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil (0.03 g, 16%), whose analytical data was consistent with that reported in the literature.[177]

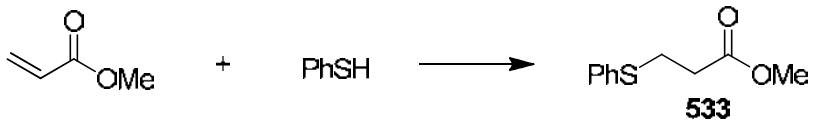
Approach 2

Alternative method for formation of keto-alcohol.



Ozone was bubbled through a solution of non-1en-5-one (0.22 g, 1.6 mmol) in CH_2Cl_2:MeOH (3 mL) containing $NaHCO_3$ (0.26 g, 3.1 mmol) at –78 °C for 15 minutes, when a blue colour persisted. Addition of Me_2S (1.1 mL, 15.7 mmol) was followed by removal of DMSO by evaporation. The resultant solution was diluted with brine, extracted with diethylether, dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil (0.22 g, 98%), whose analytical data was consistent with that reported in the literature.[177] ν_{max} (neat)/cm^{-1} 2959, 2873, 1712, 1466, 1411; δ_H (300 MHz; $CDCl_3$) 0.91 (3H, t, *J* = 7.6 Hz, CH_3), 1.22-1.39 (2H, m, CH_2), 1.52-1.63 (2H, m, CH_2), 2.47 (2H, t, *J* = 7.6 Hz, CH_2), 2.69-2.75 (4H, m, 2 x CH_2), 9.80 (lH, s, CH=O); δ_C (75 MHz; $CDCl_3$) 13.8 (CH_3), 22.3 (CH_2), 25.9 (CH_2), 34.6 (CH_2), 37.5 (CH_2), 42.5 (CH_2), 200.5 (COH), 208.7 (C).

Methyl 3-(phenothiol)propanoate[178]

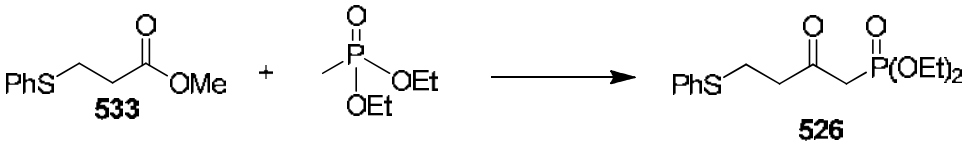


Prepared according to the literature procedure.[178]

Methyl acrylate (4.5 mL, 50 mmol) was added dropwise to a cold (0 °C) solution of thiophenol (3.8 mL, 38 mmol) in dry pyridine (20 mL). After stirring for 1.5 hours, CH_2Cl_2 (20 mL) was added and the resultant solution washed with 10% HCl (4 x 20 mL). The

organic phase was dried ($MgSO_4$) and the solvent evaporated to give lead a yellow/brown oil (6.5 g, 86%) whose analytical data was consistent with that reported in the literature.[178] ν_{max} (neat)/cm^{-1} 1733, 1480, 1437, 1244, 737; δ_H (300 MHz; $CDCl_3$) 2.62 (2H, t, *J* =7.3 Hz, CH_2), 3.19 (2H, t, *J* = 7.3 Hz, CH_2), 3.68 (3H, s, CH_3), 7.20-7.41 (5H, m, CH); δ_C (75 MHz; $CDCl_3$) 29.1 (CH_2), 34.3 (CH_2), 51.8 (CH_3), 126.6 (CH), 129.0 (CH), 130.2 (CH), 132.5 (C), 165.7 (C=O); *m/z* (EI) 196 (M^+ 100%), 165 (34%), 136 (48%), 123 (87%), 109 (50%).

Diethyl 2-oxo-4-(phenylthio)butylphosphonate[179]

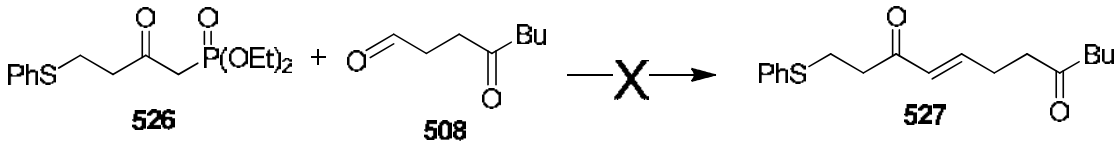


Prepared according to the literature procedure.[179]

n-Butyllithium (7.7 mL, 12 mmol) was added over ten minutes to a stirred solution of diethylmethylphosphonate (1.75 mL, 12 mmol) in THF (1.5 mL) at –78 °C. Methyl 3-(phenothiol)propanoate (1.96 g, 10 mmol) in THF (15 mL) was added and the solution gradually warmed to room temperature with stirring for 3 hours. The reaction was quenched with aqueous NH_4Cl then extracted with ethylacetate (3 x 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (0.89 g, 28%), whose analytical data was consistent with that reported in the literature.[179] ν_{max}(neat)/cm^{-1} 1713, 1583, 1481, 1250, 1015, 959; δ_H (300 MHz; $CDCl_3$) 1.32 (6H, t, CH_3), 2.98 (2H, t, CH_2), 3.07 (2H, s, CH_2), 3.20 (2H, t, CH_2), 4.15 (4H, q, 2xCH_2), 7.28-7.40 (5H, m, CH); δ_C (75 MHz; $CDCl_3$) 16.3 (2 x CH_3),

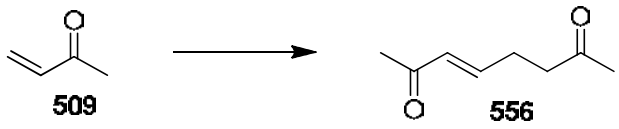
27.4 (CH_2), 42.6 (CH_2), 43.7 (CH_2), 62.7 (2 x CH_2), 126.4 (CH), 129.1 (CH), 129.7 (CH), 135.9 (C), 200.1 (C=O).

(*E*)-1-(phenylthio)dodec-4-ene-3,8-dione



A solution of phosphonoacetate (220 mg, 0.7 mmol) in THF (2 mL) was added dropwise to a stirred solution of NaH (34 mg, 0.77 mmol) in THF (2 mL) at 0 °C and the resultant mixture stirred for 20 minutes. A solution of 4-oxoocetenal (0.1 g, 0.7 mmol) in THF (6 mL) was added and the reaction mixture stirred for a further 2 hours at 0 °C. The reaction was quenched with aqueous NH_4Cl (2 mL) and the resultant solution extracted with diethylether. The ether extracts were combined, washed with water and dried ($MgSO_4$) and concentrated under reduced pressure. This resulted in no observable reaction.

Oct-3-ene-2,7-dione[180]

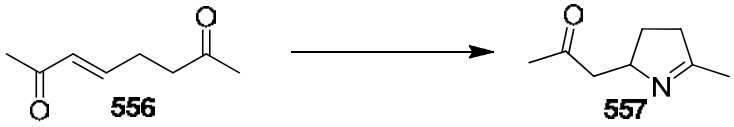


Prepared according to the literature procedure.[180]

Acetic acid (0.60 g, 0.01 mmol) was added dropwise to a stirred solution of sodium nitrate (0.69 g, 0.10 mmol) and 3-buten-2-one (3.5 g, 46.1 mmol) in DMSO (10 mL) at room temperature. After stirring for 16 hours the reaction mixture was acidified with HCl (0.1 M, 10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were

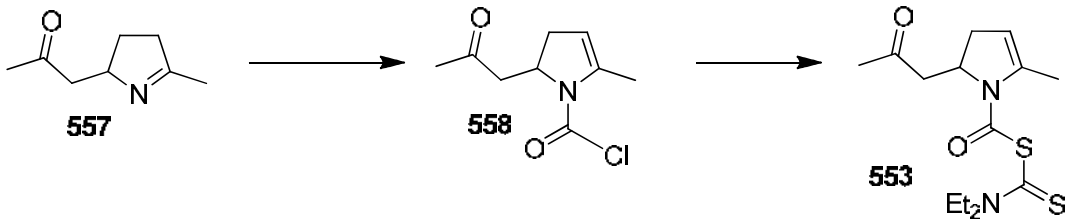
washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and concentrated under educed pressure. The resultant brown oil was purified by fractional distillation to give the enone **556** (2.02 g, 80%), as a pale yellow oil, whose analytical data is in agreement with that reported in the literature.[180] ν_{max}(neat)/cm^{-1}: 2920, 1718, 1672, 1556, 1424; δ_H (300 MHz; $CDCl_3$); 2.17 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.45-2.65 (4H, m, 2 x CH_2), 6.03-6.09 (1H, m, CH), 6.73-6.83 (1H, m, CH); δ_c (100 MHz; $CDCl_3$); 26.0 (CH_2), 26.8 (CH_3), 30.1 (CH_3), 131.5 (CH), 146.3 (CH), 198.5 (C=O), 206.7 (C=O).

1-(5-Methyl-3,4-dihydro-2*H*-pyrrole-2-yl)-propan-2-one



A solution of aqueous ammonia (35%, 7.6 mL) was added to a solution of enone **556** (0.38 g, 2.7 mmol) in MeOH (27 mL) and the resultant mixture was stirred at room temperature for 16 hours. Dilution with water (35 mL) was followed by removal of MeOH under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic phases were washed with water (30 mL), brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the product as a pale yellow oil (93%, 0.35 g). R_f 0.45 (Et_2O); ν_{max}(neat)/cm^{-1}: 2955, 1712, 1650, 1431; δ_H (300 MHz; $CDCl_3$); 2.02 (3H, s, CH_3), 2.15-2.17 (1H, m, C$H_a$$H_b$), 2.19 (3H, s, CH_3), 2.44-2.54 (4H, m, 2 x CH_2), 2.87-2.95 (1H, m, $CH_a$$H_b$), 4.29-4.35 (1H, m, CH); δ_c (100 MHz; $CDCl_3$); 19.8 (CH_3), 29.5 (CH_2), 30.6 (CH_3), 39.1 (CH_2), 50.5 (CH_2), 68.4 (CH), 175.1 (C), 207.6 (C); *m/z* (EI) 139 ($[M]^+$ 18%); 96 (90%), 82 (100%); HRMS calculated for $C_8H_{13}ON$ $[M]^+$ 139.0455, found 139.0452.

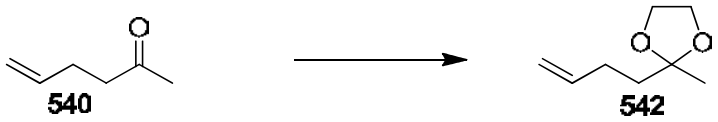
Diethylcarbamothioic-5-methyl-2-(2-oxopropyl)-2,3-dihydro-1*H*-pyrrole-1-carboxylic thioanhydride



Pyridine (0.17 ml, 2.18 mmol) was added to a solution of triphosgene (0.14 g, 0.48 mmol) in toluene (12 mL). The resultant mixture was stirred at room temperature for ten minutes before the addition of a solution of imine **557** (0.2 g, 1.45 mmol) in toluene (8 mL). After stirring for 16 hours at room temperature the reaction mixture was quenched with water (15 mL). The aqueous phase was separated and extracted with Et_2O (3 x 20 mL). The combined organic phases were washed with water (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the carbamoyl chloride **558** (0.27 g, 1.37 mmol). The crude product was dissolved in acetone (14 mL), and sodium diethyldithiocarbamate trihydrate (0.62 g, 2.74 mmol) was added in one portion. The resultant mixture was heated at reflux for 2 hours. After cooling to room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL). The aqueous phase was separated and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with water (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* **553** as a bright yellow oil (0.31 g, 63% over two steps). R_f 0.25 (1:1 petroleum ether:Et_2O); ν_{max}(neat)/cm^{-1}: 2980, 2253, 1712, 1678, 1651, 1492, 1456; δ_H (300 MHz; $CDCl_3$); 1.26-1.35 (6H, m, 2 x CH_3), 2.16 (3H, s, CH_3), 2.17 (3H, s, CH_3), 2.55-3.19 (3H, m, CH_2), 3.68-4.17 (5H, m, 2 x CH_2), 4.57-4.63 (1H, m, CH), 4.91-4.92 (1H, m, CH); δc (100 MHz; $CDCl_3$); 11.1 (CH_3), 13.5 (CH_3), 16.0 (CH_3), 30.5 (CH_3),

34.3 (CH_2), 48.4 (CH_2), 48.9 (CH_2), 50.2 (CH_2), 57.3 (CH), 110.3 (CH), 139.9 (C), 157.6 (C=O), 184.0 (C=S), 206.1 (C=O); *m/z* (ESI) 337 ($[M+Na]^+$ 100%); HRMS (ESI) calculated for $C_{14}H_{22}O_2S_2N_2Na$ $[M+Na]^+$ 337.1020, found 337.1027.

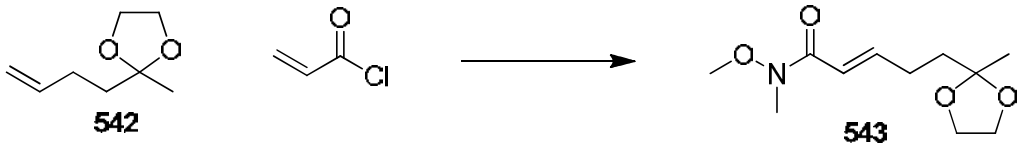
2-(But-3-en-1-yl)-2-methyl-1,3-dioxolane[181]



Prepared according to the general literature procedure.[181]

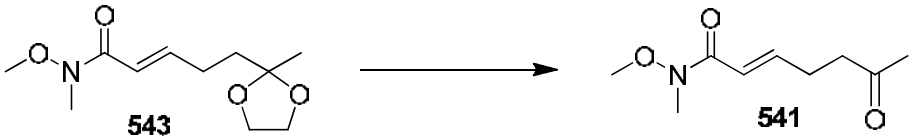
Ethylene glycol (11 mL, 190 mmol) was heated to reflux in toluene (17 mL) with p-toluenesulfonic acid (0.025 g, 0.013 mmol) under Dean-Stark conditions for 3 hours. 5-hexen-2-one (0.58 mL, 5 mmol) was added and the reaction continued for 16 hours. After cooling to room temperature saturated aqueous K_2CO_3 (15 mL) was added followed by Et_2O (30 mL). The organic phase was washed with water (15 mL), brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. Purification by distillation (40 °C, 0.1 Torr) gave the *title compound* as a colourless viscous oil (59%, 0.42 g), whose analytical data was consistent with that reported in the literature.[181] δ_H (300 MHz; $CDCl_3$); 1.29 (3H, s, CH_3), 1.67-1.76 (2H, m, CH_2), 2.09-2.14 (2H, m, CH_2), 3.87-3.95 (4H, m, 2 x CH_2), 4.91 (1H, dd, *J* = 10.3, 1.2 Hz), 4.99 (1H, dd, *J* = 17.2 Hz, 1.2 Hz, CH), 5.81 (ddt, *J* = 17.2, 10.3, 1.0 Hz, CH); δ_c (100 MHz; $CDCl_3$); 23.8 (CH_3), 28.3 (CH_2), 38.2 (CH_2), 64.6 (2 x CH_2), 109.7 (C), 114.1 (CH), 138.4 (CH_2); *m/z* (ESI) 165 ($[M+Na]^+$ 100%).

(*E*)-*N*-Methoxy-*N*-methyl-5-(2-methyl-1,3-dioxolan2-yl)pent-2-enamide



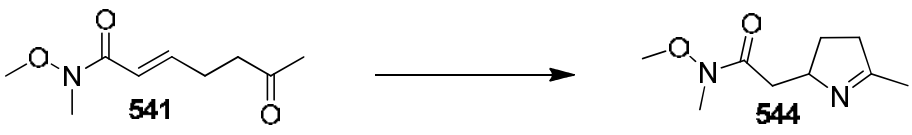
Grubbs 2nd generation catalyst (0.448 g, 0.53 mmol, 0.05 equiv.) was added to a stirred solution of **542** (1.5 g, 10.5 mmol) and freshly distilled acryloyl chloride (1.27 mL, 15.7 mmol) in CH_2Cl_2 (50 mL). The resultant solution was heated to reflux for 40 hours. After cooling to room temperature, dimethyldihydroxylamine hydrochloride (1.63 g, 16.8 mmol) was added followed by 4-methylmorpholine (6.9 mL, 63 mmol) and the reaction mixture stirred for 2 hours. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography (2:1 hexane:diethyl ether increasing to ether) to give the product as a yellow oil (2.4 g, 83%). R_f 0.34 (diethyl ether); ν_{max}(neat)/cm^{-1}: 2980, 2938, 1661, 1629, 1377, 1054, 998; δ_H (300 MHz; $CDCl_3$); 1.38 (3H, m, CH_3), 1.72-1.89 (2H, m, CH_2), 2.31-2.42 (2H, m, CH_2), 3.30 (3H, s, CH_3), 3.72 (3H, s, CH_3), 3.92-4.02 (4H, m, 2 x CH_2), 6.44 (1H, d, *J* = 12 Hz, CH), 6.88-7.11 (1H, m, CH); δ_c (100 MHz; $CDCl_3$); 24.1 (CH_3), 27.2 (CH_2), 32.5 (CH_3), 37.7 (CH_2), 61.8 (CH_3), 64.9 (2 x CH_2), 118.7 (CH), 147.3 (CH), 204.3 (C=O); *m/z* (EI) 229 ($[M]^+$ 20%); 214 (100%), 184 (76%), 169 (35%); HRMS (EI) calculated for $C_{11}H_{19}O_4N$ $[M]^+$ 229.1314, found 229.1307.

(*E*)-*N*-Methoxy-*N*-methyl-6-oxohept-2-enamide



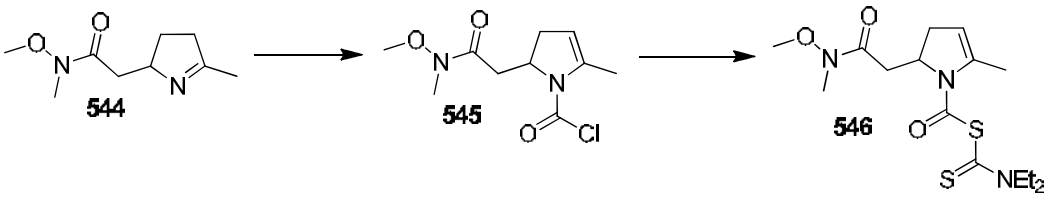
Acetic acid (13 mL) was added to a solution of **543** (2.00 g, 8.7 mmol) in MeOH (60 mL) and the resultant mixture heated to reflux for 14 hours. After cooling to room temperature, the solution was concentrated under reduced pressure. Water (50 mL) was added and the reaction mixture extracted with CH_2Cl_2 (3 x 40 mL). The organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the *title compound* as a clear oil (1.61 g, 99%). R_f 0.20 (diethyl ether); ν_{max}(neat)/cm^{-1}: 2938, 1713, 1661, 1629, 1378, 1161, 981; δ_H (300 MHz; $CDCl_3$); 2.18 (3H, s, CH_3), 2.43-2.51 (2H, m, CH_2), 2.56-2.64 (2H, m, CH_2), 3.26 (3H, s, CH_3), 3.72 (3H, s, CH_3), 6.46 (1H, d, J = 12.3 Hz, CH), 6.88-6.99 (1H, m, CH); δc (100 MHz; $CDCl_3$); 26.5 (CH_2), 30.1 (CH_3), 32.4 (CH_3), 41.9 (CH_2), 61.8 (CH_3), 119.8 (CH), 145.6 (CH), 166.8 (C=O), 207.1 (C=O); *m/z* (EI) 185 ($[M]^+$ 15%), 125 (100%), 97 (63%); HRMS (EI) calculated for $C_9H_{15}O_3N$ $[M]^+$ 185.1052, found 185.1051.

***N*-Methoxy-*N*-methyl-2-(5-methyl-3,4-dihydro-2H-pyrrol-2-yl)acetamide**



541 (1.6 g, 8.0 mmol) was dissolved in a solution of MeOH (100 mL) and aqueous ammonia (35%, 30 mL) and stirred at room temperature for 18 hours. Water (60 mL) was added and the MeOH removed under reduced pressure. The remaining solution was extracted with CH2Cl2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (MgSO4) and concentrated under reduced pressure to give the product as a brown oil (90%, 1.34 g); R_f 0.12 (EtOAc); ν_{max}(neat)/cm^{-1}: 2942, 1646, 1430, 1382, 1178, 995; δ_H (300 MHz; $CDCl_3$); 1.48-1.52 (1H, m, CH_2), 2.12 (3H, s, CH_3), 2.19-2.27 (1H, m, CH_2), 2.31-2.56 (3H, m, CH_2), 2.94-3.07 (1H, m, CH_2), 3.18 (3H, s, CH_3), 3.73 (3H, s, CH_3), 4.30-4.48 (1H, m, CHS); δ_c (100 MHz; $CDCl_3$); 19.9 (CH_3), 29.5 (CH_2), 32.2 (CH), 38.8 (CH_2), 39.2 (CH_2), 61.3 (CH_3), 69.0 (CH_3), 122.8 (C), 175.1 (C=O); *m/z* (ESI) 207 ($[M+Na]^+$); HRMS (ESI) calculated for $C_9H_{16}O_2N_2Na$ $[M+Na]^+$ 207.1109, found 207.1107.

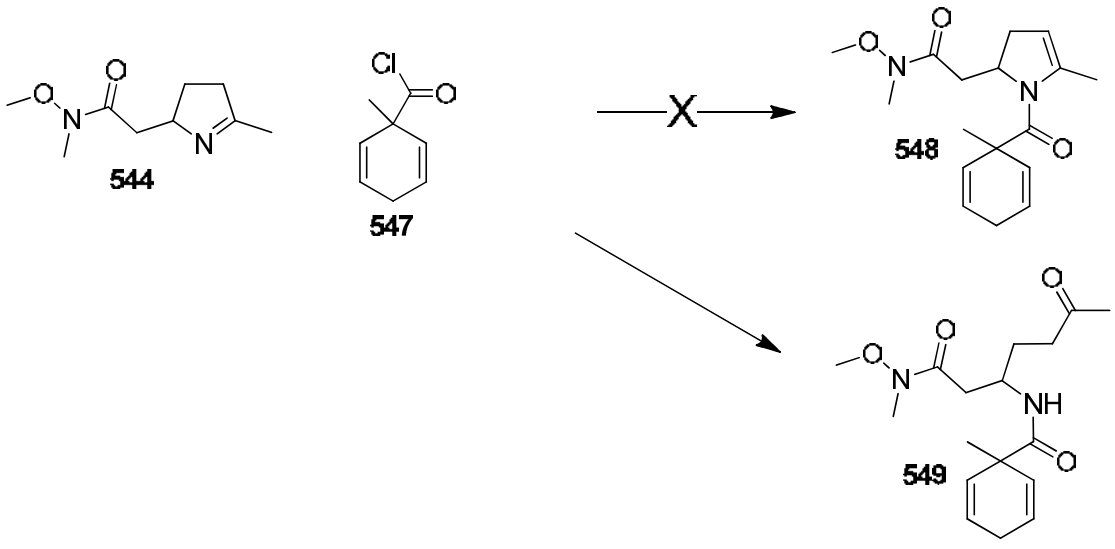
Attempted synthesis of Diethylcarbamothioc 2-(2-(methoxy(methyl)amino)-2-oxoethyl)-5-methyl-2,3-dihydro-1-H-pyrrole-1-carboxylic thioanhydride



Pyridine (0.80 ml, 10.0 mmol) was added to a solution of triphosgene (0.66 g, 2.22 mmol) in toluene (50 mL). The resultant mixture was stirred at room temperature for ten minutes before the addition of a solution of imine **544** (1.23 g, 6.68 mmol) in toluene (20 mL). After stirring for 16 hours at room temperature the reaction mixture was quenched with water (40 mL). The aqueous phase was separated and extracted with Et_2O (3 x 40

mL). The combined organic phases were washed with water (80 mL), brine (80 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give the carbamoyl chloride **545** (70%, 1.17 g, 4.68 mmol). The crude product was dissolved in acetone (14 mL), and sodium diethyldithiocarbamate trihydrate (4.21 g, 18.70 mmol) was added in one portion. The resultant mixture was stirred at room temperature for 24 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (45 mL). The aqueous phase was separated and extracted with Et_2O (3 x 45 mL). The combined organic extracts were washed with water (45 mL), brine (45 mL), dried ($MgSO_4$) and concentrated under reduced pressure, to give a yellow oil. This oil was a combination of unidentifiable breakdown products.

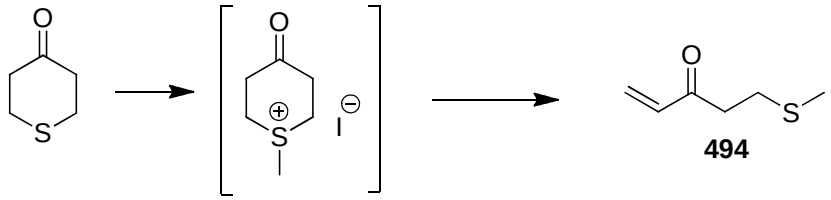
Attempted synthesis of N-methoxy-N-methyl-2-(5-methyl-1-(1-methylcyclohexan-2,5-dienecarbonyl)-2,3-dihydro-1H-pyrrol-2yl)acetamide



To a stirred solution of the carbonyl chloride **547** (0.86 mmol, 0.14 g) in CH_2Cl_2 (8 mL) was added triethylamine (0.1 mL, 0.7 mmol) and DMAP (0.009 g, 0.7 mmol), followed by

amine **544** (0.7 mmol, 0.13 g) in CH_2Cl_2 (1 mL). The reaction was heated to reflux and continued for 18 hours. After this time the reaction was cooled to room temperature, before washing with water (8 mL), drying ($MgSO_4$) and the solvent was removed by evaporation to give the crude product. Purification by column chromatography (30:1 CH_2Cl_2:MeOH) gave the product, **549** as a yellow oil (60%, 0.21 g). R_f 0.25 (30:1 CH_2Cl_2:MeOH); ν_{max}(neat)/cm^{-1}: 2975, 1611, 1607, 1437, 1386, 1108, 997; δ_H (300 MHz; $CDCl_3$); 1.22 (3H, s, CH_3), 1.71-1.80 (2H, m, CH_2), 2.08 (3H, s, CH_3), 2.3-2.48 (3H, m, CH_2 and CH_aH_b), 2.61-2,78 (3H, m, CH_2 and CH_aH_b), 3.09 (3H, s, CH_3), 3.61 (3H, s, CH_3), 4.01-4.12 (1H, m, CH), 5.53-5.62 (2H, m, 2 x CH), 5.71-5.84 (2H, m, 2 x CH), 6.80-6.88 (NH); δc (100 MHz; $CDCl_3$); 25.5 (CH_3), 26.0 (CH_2), 28.1 (CH_2), 30.1 (CH_3), 31.9 (CH_3), 35.8 (CH_2), 40.3 (CH_2), 44.9 (C), 46.0 (CH), 61.4 (CH_3), 125.1 (CH), 125.4 (CH), 129.7 (CH), 130.1 (CH), 172.1 (C=O), 174.8 (C=O), 208.4 (C=O); *m/z* (ESI) 345 [M+Na]; HRMS (ESI) calculated for $C_{17}H_{26}O_4N_2Na$ $[M+Na]^+$ 345.1770, found 345.1779.

5-(Methylthio)pent-1-en-3-one[145]



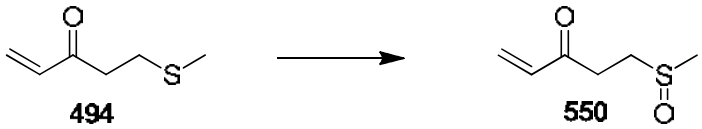
494

Prepared according to the general literature procedure.[145]

Methyl iodide (10.3 mL, 166 mmol) was added portionwise to a solution of dihydro-2H-thiopyran-4(3H)-one (1.93 g, 16.6 mmol) in acetone (20 mL). The reaction mixture was stirred together at room temperature in the dark for 3 days. The resulting white

precipitate was filtered off and washed with acetone (3 x 20 mL). Drying under vacuum gave the sulfonium salt (3.7 g, 92%). This was dissolved in a solution of acetonitrile and water (9:1, 45 mL). DIPEA (7.5 mL, 43 mmol) was added and the reaction mixture stirred at room temperature for 2 days. The aqueous phase was extracted with EtOAc (3 x 30 mL), and the combined organic phases were washed with water (30 mL), brine (300 mL), dried ($MgSO_4$) and concentrated under pressure. Purification by column chromatography (4:1 hexane:EtOAc) gave **494** as a yellow oil (1.85 g, 86% over two steps), whose data was consistent with that previously reported.[145] R_f 0.47 (1:1 hexane:diethyl ether); ν_{max}(neat)/cm^{-1}: 2919, 2253, 1679, 1617, 1403, 1094; δ_H (300 MHz; $CDCl_3$); 2.13 (3H, s, CH_3), 2.75-2.82 (2H, m, CH_2), 2.89-2.92 (2H, m, CH_2), 5.88 (1H, dd, J = 10.2, 1.4 Hz, CH*a*Hb), 6.25 (1H, dd, J = 17.7, 1.4 Hz, CHaH*b*), 6.38 (1H, dd, J = 17.7, 10.2 Hz, CH); δ_c (100 MHz; $CDCl_3$); 15.8 (CH_3), 28.2 (CH_2), 39.4 (CH_2), 128.5 (CH_2), 136.3 (CH), 198.8 (C=O); m/z (EI) 130 ($[M]^+$ 20%), 82 (90%), 55 (100%).

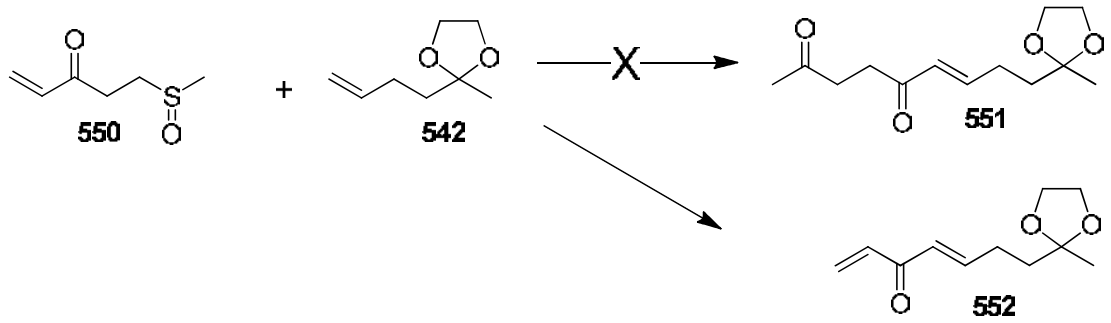
5-(Methylsulfinyl)pent-1-en-3-one



Sodium metaperiodate (0.65 g, 3.06 mmol) was added to a solution of **494** (0.2 g, 1.53 mmol) in methanol:water (9:1) at 0 °C. The reaction mixture was stirred at this temperature for 4 hours then allowed to warm to room temperature for 14 hours. CH_2Cl_2 was added and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the product as a yellow oil (0.09 g, 42%). ν_{max}(neat)/cm^{-1}: 2918, 1677, 1404, 1025, 971, 942; δ_H (300

MHz; $CDCl_3$); 2.53 (3H, s, CH_3), 2.79-2.91 (2H, m, CH_2), 3.01-3.14 (2H, m, CH_2), 5.89 (1H, dd, J = 10.3, 1.4 Hz, CH*a*Hb), 6.26-6.41 (2H, m, CH and, CHaH*b*); δ_c (100 MHz; $CDCl_3$); 31.7 (CH_2), 39.0 (CH_3), 47.4 (CH_2), 129.6 (CH_2), 135.9 (CH), 197.4 (C=O); *m/z* (EI) 146 ($[M]^+$ 46%), 91 (43%), 55 (100%); HRMS (EI) calculated for $C_6H_{10}O_2S$ $[M]^+$ 146.0402, found 146.0398.

Attempted synthesis of (E)-9-(2-methyl-1,3-dioxolan-2-yl)non-6-ene-2,5-dione



Grubbs' 2nd generation catalyst (0.058 g, 0.07 mmol, 0.05 equiv.) was added to a stirred solution of **550** (0.2 g, 1.37 mmol) and protected alcohol **542** (0.194 g, 1.37 mmol) in CH_2Cl_2 (7 mL). The resultant solution was heated to reflux for 72 hours. After cooling to room temperature a saturated solution of $NaHCO_3$ (7 mL) was added. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) filtered and evaporate under reduced pressure. Purification by column chromatography (3:1 petroleum ether:EtOAC) did not give the expected product (**551**) but led to the formation of **552** instead, as a pale yellow oil (60%, 0.16 g). R_f 0.17 (3:1 petroleum ether:EtOAc); ν_{max}(neat)/cm^{-1}: 1709, 1689, 1603, 1204, 987, 603; δ_H (300 MHz; $CDCl_3$); 1.22 (3H, s, CH_3), 1.71-1.79 (2H, m, CH_2), 2.22-2.34 (2H, m, CH_2), 3.79-4.02 (4H, m, 2 x CH_2), 5.21 (1H, dd, *J* = 10.2, 1.2 Hz, CH), 6.17-6.34 (2H, m, CH_2), 6.47-6.53 (1H, m, CH),

6.80-6.97 (1H, m, CH); δ_c (100 MHz; $CDCl_3$); 21.2 (CH_2), 23.8 (CH_3), 33.7 (CH_2), 64.3 (2 x CH_2), 120.1 (C),123.5 (CH_2), 132.0 (CH), 137.9 (CH), 157.4 (CH), 189.3 (C=O); *m/z* (ESI) 219 [M+Na]; HRMS (ESI) calculated for $C_{11}H_{16}O_3Na$ $[M+Na]^+$ 219.0997, found 219.0993.

Chapter six

References

1 C. S. Schoepple and W. E. Bachmann, *J. Am. Chem. Soc.*, 1947, **69**, 2921-2925

2 M. Julia, *Acc. Chem. Res.,* 1971, **4**, 386-392

3 W. R. Bowman, C. F. Bridge and P. Brookes, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1-14

4 S. Murai, N. Sonda and S. Tsutsumi, *J. Org. Chem.*, 1964, **29**, 2104-2105

5 C. Chatgilialoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991-2069

6 I. Ryu and N. Sonoda, *Angew. Chem. Int. Ed.*, 1996, **35**, 1050-1066

7 S. Kim, S. Kim, N. Otsuka and I. Ryu, *Angew. Chem., Int. Ed.*, 2005, **44**, 6183-6186

8 S. B. Herzon and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 5342-5344

9 H. Yokoe, C. Mitsuhasi, Y. Matsuoka, T. Yoshimura, M. Yoshida and K. Shishido, *J. Am. Chem. Soc.*, 2011, **133**, 8854–8857

10 J. Lusztyk, E. Lusztyk, B. Maillard and K. U. Ingold, *J. Am. Chem. Soc.*, 1984, **106**, 2923-2931

11 K. Nagahara, I. Ryu, M. Komatsu and N. Sonoda, *J. Am. Chem. Soc.*, 1997, **119**, 5464-5466

12 I. Ryu, K. Kusano, A. Ogawa, N. Kambe and N. Sonda, *J. Am. Chem. Soc.*, 1990, **112**, 1295-1297

13 I. Ryu, M. Hasegawa, A. Kurihara, A. Ogawa, S. Tsunoi and N. Sonada, *Synlett*, 1993, 143-144

14 C. Chatgilialoglu, *Acc. Chem. Res.*, 1992, **25**, 188-194

15 H. J. Penn and F. Liu, *J. Org. Chem.*, 1994, **59**, 2608-2612

16 D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1988, **53**, 3377-3379

17 D. Crich and S. M. Fortt, *Tetrahedron*, 1989, **45**, 6581-6593

18 M. S. Kharasch, W. H. Urry and B. M. Kuderna, *J. Org. Chem.*, 1949, **14**, 248-253

19 T. M. Patrick Jr., *J. Org. Chem.*, 1952, **17**, 1269-1275

20 D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1992, **57**, 1429-1443

21 C. Chen and D. Crich, *Tetrahedron Lett.*, 1993, **34**, 1545-1548

22 C. Chen, D. Crich and A. Papadatos, *J. Am. Chem. Soc.*, 1992, **114**, 8313-8314

23 D. Crich, C. Chen, J.-T. Hwang, H. Yuan, A. Papadatos and R. I. Walter, *J. Am. Chem. Soc.*, 1994, **116**, 8937-8951

24 W. C. Zeise, *J. Chem. Phys.*, *1822*, **35**, 173

25 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans.1*, 1975, 1574–1585

26 D. H. R. Barton, M. V. George and M. Tomoeda, *J. Chem. Soc.*, 1962, 1967-1974

27 P. Delduc, C. Tailhan and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 1988, 308

28 S. Z. Zard, *Angew. Chem., Int. Ed.*, 1997, **36**, 672-685

29 M. E. Briggs, M. El Qacemi, C. Kalai and S. Z. Zard, *Tetrahedron Lett.*, 2004, **45**, 6017-6020

30 G. Bulmer and F. G. Mann, *J. Chem. Soc.*, 1945, 677-680

31 M. R. Heinrich and S. Z. Zard, *Org. Lett.*, 2004, **6**, 4969-4972

32 B. Quiclet-Sire and S. Z. Zard, *Chem. Eur. J.*, 2006, **12**, 6002-6016

33 A. Franco Bella, L. V. Jackson and J. C. Walton, *Org. Bimol. Chem.*, 2004, **2**, 421-428

34 L. V. Jackson and J. C. Walton, *Chem. Commun.*, 2000, 2327-2328

35 G. Binmore, L. Cardellini and J. C. Walton, *J. Chem. Soc., Perkin Trans. 2*, 1997, 757-762

36 E. M. Scanlan, A. M. Z. Slawin and J. C. Walton, *Org. Biomol. Chem.*, 2004, **2**, 716-724

37 E. M. Scanlan and J. C. Walton, *Org. Biomol. Chem.*, 2002, 2086-2087

38 R. S. Grainger, P. Innocenti, *Angew. Chem., Int. Ed., 2004*, **43**, 3445-3448

39 R. S. Grainer, P. Innocenti, *Heteroatom Chem.*, 2007, **18**, 568-571

40 G. B. Gill, G. Pattenden and S. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1994, 369-378

41 J. H. Rigby, D. M. Danca and J. H. Horner, *Tetrahedron Lett.*, 1998, **39**, 8413-8416

42 G. Lopez-Valdez, S. Olguin-Uribe and L. D. Miranda, *Tetrahedron Lett.*, 2007, **48**, 8285-8289

43 D. Crich and Q. W. Yao, *J. Org. Chem.*, 1996, **61**, 3566-3570

44 D. Crich and X. L. Hao, *J. Org. Chem.*, 1997, **62**, 5982-5988

45 S. Das, C. S. Rajesh, T. L. Thanulingam, D. Ramaiah and M. V. George, *J. Chem. Soc., Perkin Trans. 2*, 1994, 1545-1547

46 D. Crich, K. A. Eustace, S. M. Fortt and T. J. Ritchie, *Tetrahedron*, 1990, **46**, 2135-2148

47 M. Sasaki, J. Collin and H. B. Kagan, *Tetrahderon Lett.*, 1988, **29**, 6105-6106

48 A. L. B. Beckwith, D. M. O'Shea, S. Gerba and S. W. Westwood, *J. Chem. Soc., Chem. Commun.*, 1987, 666-667

49 P. Dowd and S. C. Choi, *J. Am. Chem. Soc.*, 1987, **109**, 3493-3494

50 P. Dowd and W. Zhang, *Chem. Rev.*, 1993, **93**, 2091-2115

51 E.J. Welsh, PhD Thesis, University of Birmingham, Edgbaston, Birmingham, B15 2TT

52 D. Crich and S. M. Fortt, *Tetrahedron Lett.*, 1987, **28**, 2895-2898

53 R. S. Grainger and E. J. Welsh, *Angew. Int. Ed.*, 2007, **46**, 5377-5380

54 T. Hayashi and H. Midorikawa, *Synthesis*, 1975, 100-102

55 H. G. Fletcher, *J. Am. Chem. Soc.*, 1947, **69**, 706-707

56 M. Yanagawa, O. Moriya, Y. Watanabe, Y. Ueno and T. Endo, *Bull. Chem. Soc. Jpn.*, 1988, **61**, 2203-2204

57 T. Nakai, H. Shiono and M. Okawara, *Chem. Lett.*, 1975, 249-252

58 W. Hartwig, *Tetrahedron*, 1983, **39**, 2609-2645

59 D. H. R. Barton, W. B, Motherwell and A. Strange, *Synthesis*, 1981, 743-745

60 D. H. R. Barton, D. Crich, A. Lobberding and S. Z. Zard, *Tetrahedron*, 1986, **42**, 2329-2338

61 D. H. R. Barton, S. I. Parekh and C.-L. Tse, *Tetrahderon*, 1993, **34**, 2733-2736

62 R. H. Nace, *Org. React.*, 1962, **12**, 57-100

63 A. Liard, B. Quiclet-Sire and S. Z. Zard, *Tetrahedron Lett.*, 1996, **37**, 5877-5880

64 J. Biovin, R. Jrad, S. Juge and V. T. Nguyen, *Org. Lett.*, 2003, **5**, 1645-1648

65 D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahderon Lett.*, 1992, **33**, 2311-2314

66 D. H. R. Barton, D. O. Jang and J. C. Jaszberenyi, *Tetrahedron Lett.*, 1992, **33**, 5709-5712

67 H. Yorimitsu, H. Shinokubo and K. Oshima, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 225-235

68 S. Ahmed, L. A. Baker, R. S. Grainger, P. Innocenti and C. E. Quevedo, *J. Org. Chem.*, 2008, **73**, 8116-8119

69 P. Rollin, *Tetrahedron Lett.*, 1986, **27**, 4169-4170

70 a) J. Shi, S.-S Chong, Y. Fu, Q. –X. Guo and L. Liu, *J. Org. Chem.*, 2008, **73**, 974-972; b) A. Gansäuer, T. Lauterbach and S. Narayan, *Angew. Chem., Int. Ed.*, 2003, **42**, 5556-5573 and references therein.

71 G. A. DiLabio, E. M. Scanlan and J. C. Walton, *Org. Lett.*, 2005, **7**, 155-158

72 For a review see: G. S. Singh, M. D'hooghe and N. De Kimpe, *Tetrahedron*, 2011, **67**, 1989-2012

73 D. D. Kim, S. J. Lee and P. Beak, *J. Org. Chem.*, 2005, **70**, 5376-5386

74 a) B. Quiclet-Sire and S. Z. Zard, *J. Am. Chem. Soc.*, 1996, **118**, 9190-9191, b) J. Biovin, B. Quiclet-Sire, L. Ramos and S. Z. Zard, *Chem. Commun.*, 1997, 353-354

75 a) For a review see: A. L. J. Beckwith, D. Crich, P. J. Duggan and Q. Yao, *Chem. Rev.*, 1997, **97**, 3273-3312; b) D. Crich Radicals rearrangements in esters. In *Radicals in organic synthesis*, Vol 2, (ed. P. Renaud and M. P. Sibi) Wiley-VCH, Weinheim, 2001

76 a) S. Julia and R. Lorne, *C. R. Acad. Sci. Fr. Ser. C*, 1971, **119**, 8740, b) S. Julia and R. Lorne, *Tetrahedron*, 1986, **42**, 5011-5017

77 G. Behrens, E. Bothe, G. Koltzenberg, D. Schulte-Frohlinde, *J. Chem. Soc., Perkin Trans. 2*, 1980, 883-889

78 B. –H. Lee, B. Bertram, P. Schmezer, N. Frank and M. Wiessler, *J. Med. Chem.*, 1994, **37**, 3154-3162

79 For a discussion of polar effects in free radical reactions see: a) B. P. Roberts, *Chem. Soc. Rev.*, 1999, **28**, 25-25; b) D. Crich, D. Grant, V. Krishnamurthy and M. Patel, *Acc. Chem. Res.*, 2007, **40**, 453-463

80 A. Greenberg, C. Breneman and J. F. Liebman (editors). The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Material Structure, Wiley-Interscience, New York, 2000

81 a) A. J. Bennet, Q. P. Wang, H. Slebocka-Tilk, V. Somayaji, R. S. Brown and B. Santarsiero, *J. Am. Chem. Soc.*, 1990, **112**, 6383-6385; b) H. Slebocka-Tilk and R. S. Brown, *J. Org. Chem.*, 1987, **52**, 805-808

82 H. Ishida, *Z. Naturforsch*, 2000, **55a**, 769-771

83 A. J. Kirby, I. R. Komarov and N. Feeder, *J. Chem. Soc., Perkin Trans. 2*, 2001, 522-529

84 a) H. Shao, X. Jiang, P. Gantzel and M. Goodman, *Chem. Biol.*, 1994, **1**, 231-234; b) F. X. Schmid, *Adv. Protein Chem.*, 2002, **59**, 243-282

85 a) V. Somoayaji and R. S. Brown, *J. Org. Chem.*, 1986, **51**, 2676-2686; b) J. I. Mujika, J. M. Mercero and X. Lopez, *J. Am. Chem. Soc.*, 2003, **127**, 4445-4453

86 G. M. Blackburn, C. J. Skaife and L. T. Kay, *J. Chem. Res. Miniscript*, 1980, 3650-3669

87 K. Tani and B. M. Stoltz, *Nature*, 2006, **441**, 731-734

88 H. K. Hall. Jnr. and A. El-Shekeil, *Chem. Rev.*, 1983, **83**, 549-555

89 a) S. Yamada, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 1083-1085; b) S. Yamada, *Rev. Heteroat. Chem.*, 1999, **19**, 203

90 M. Szostak and J. Aube, *Org. Lett.*, 2009, **11**, 3878-3881

91 J. Bredt, H. Thouet and J. Schnitz, *Leibigs Ann.*, 1924, **437**, 1-13

92 R. Lukeš, *Coll. Czech Chem. Commun.*, 1938, **10**, 148-152

93 R. B. Woodward and W. E. Doering, *J. Am. Chem. Soc.*, 1945, **67**, 860-874

94 L. N. Yakhontov and M. V. Rubsitov, *J. Gen. Chem. USSR*, 1957, **7**, 1-15

95 H. Pracejus, M. Kehlen, H. Kehlen and H. Matschiner, *Tetrahedron*, 1965, **21**, 2257-2270

96 A. Fleming, *Brit. J. Exp. Pathol.,* 1929, **10**, 226-236

97 H. T. Clark, J. R. Johnson and R. Robinson (editors), The Chemistry of Penicillin, Princeton University Press, Princeton, 1949

98 R. G. Benedict, W. H. Schmidt, R. D. Coghill and A. P. Oleson, *J. Bacteriol.*, 1945, **49**, 85-95

99 M. J. Golden and F. M. Neumeier, *Science*, 1946, **104**, 102-104

100 a) N. F. Albertson, *J. Am. Chem. Soc.*, 1950, **72**, 2594-2599; b) H. Pracejus, *Chem. Ber.*, 1959, **92**, 988-993; c) Q. P. Wang, A. J. Bennet, R. S. Brown, and B. D. Santarsiero, *J. Am. Chem. Soc.*, 1991, **113**, 5757-5765; d) A. Greenberg, G. L. Wu, J. C. Tsai and Y. Y. Chiu, *Struct. Chem.*, 1993, **4**, 127-132

101 T. G. Lease and K. J. Shea, *J. Am. Chem. Soc.*, 1993, **115**, 2248-2260

102 a) R. Grigg, V. Sridharan, P. Stevenson and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1986, 1697-1699; b) R. M. Williams, B. H. Lee, M. M. Miller and O. P. Anderson*, J. Am. Chem. Soc.*, 1989, **111**, 1073-1081

103 J. C. Sheehan and K. R. Henery-Logan, *J. Am. Chem. Soc.*, 1957, **79**, 1262-1263

104 H. K. Hall Jnr., R. R. Shaw and A. Deustchmann, *J. Org. Chem.*, 1980, **45**, 3722-3724

105 K. Steliou and M.-A. Poupart, *J. Am. Chem. Soc.*, 1983, **105**, 7130-7138

106 R. M. Williams and B. H. Lee, *J. Am. Chem. Soc.*, 1986, **108**, 6431-6433

107 A. Greenberg and C. A. Venanzi, *J. Am. Chem. Soc.*, 1993, **115**, 6951-6957

108 a) P. G. Jones, A. J. Kirby, I. V. Komarov and P. D. Worthers, *Chem. Commun.*, 1998, 1695-1696; b) A. J. Kirby, I. V. Komarov, P. D. Worthers and N. Feeder, *Angew. Chem. Int. Ed.*, 1998, **37**, 785-786; c) A. J. Kirby, I. V. Komarov and N. Feeder, *J. Am. Chem. Soc.*, 1998, **120**, 7101-7102

109 A. J. Kirby, I. V. Komarov, K. Kowski and P. Rademacher, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1313-1316

110 J. E. Golden and J. Aube, *Angew. Int. Ed.*, 2002, **41**, 4316-4318

111 L. Yao and J. Aube, *J. Am. Chem. Soc.*, 2007, **129**, 2766-2767

112 M. Szostak, L. Yao and J. Aube, *J. Org. Chem.*, 2010, **75**, 1235-1243

113 O. Gutierrez, J. Aube and D. J. Tantillo, *J. Org. Chem.*, 2012, **77**, 640-647

114 M. Szostak, L. Yao and J. Aube, *J. Org. Chem.*, 2009, **74**, 1869-1875

115 Y. Lei, A. D. Wrobleski, J. E. Golden, D.R. Powell and J. Aube, *J. Am. Chem. Soc.*, 2005, **127**, 4552-4553

116 M. Szostak, L. Yao and J. Aube, *J. Am. Chem. Soc.*, 2010, **132**, 2078-2084

117 M. Szostak and J. Aube, *J. Am. Chem. Soc.*, 2009, **131**, 13246-13247

118 C. G. Bashore, I. J. Samardjiev, J. Bordner and J. W. Coe, *J. Am. Chem. Soc.*, 2003, **125**, 3268-3272

119 J. Artacho, E. Ascic, T. Rantanen, J. Karlsson, C.-J. Wallentin, R. Wang, O. F. Wendt, M. Harmata, V. Snieckus and K. Wärnmark, *Chem. Eur. J.*, 2012, **18**, 1038-1042

120 G. C. Fu, S. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856-9859

121 R. A. Pilli and M. C. Ferreira de Oliveira, *Nat. Prod. Rep.,* 2000, **17**, 117–127

122 Y. Ye, G.-W. Qin and R.-S. Xu, *J. Nat. Prod.*, 1994, **57**, 665-669

123 H. Irie, N. Masaki, K. Ohno, K. Osaki, T. Taga and S. Uyeo*, Chem. Commun.*, 1970, 1066-1068

124 T. Sekine, N. Fukasawa, Y. Kashiwagi, N. Ruangrungsi and I. Murakoshi, *Chem. Pharm. Bull.*, 1994, **42**, 1360-1362

125 B. Brem, C. Seger, T. Pacher, O. Hofer, S. Vajrodaya and H. Greger, *J. Agric. Food Chem.*, 2002, **50**, 6383-6388

126 C. Seger, K. Mereiter, E. Kaltenegger, T.Pacher, H. Greger and O. Hofer, *Chem. Biodiv.*, 2004, **1**, 265-279

127 T. Sastraruji, A. Jatisatienr, S. G. Pyne, A. T. Ung, W. Lie and M. C. Williams, *J. Nat. Prod.*, 2005, **68***,* 1763–1767

128 E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchhauser, H. Kahlig, O. Hofer, S. Vajrodaya and H. Greger, *Phytochemistry*, 2003, **63**, 803-816

129 T. Sekine, F. Ikegami, N. Fukasawa, Y. Kashiwagi, T. Aizawa, Y. Fujii, N. Ruangrungsi and I. Murakoshi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 391-393

130 M. Brüggermann, A. I. McDonald, L. E. Overman, M. D. Rosen, L. Schwink and J. P. Scott, *J. Am. Chem. Soc.*, 2003, **125**, 15284-15285

131 A. S. Kende, T. L. Smalley and H. Huang, *J. Am. Chem. Soc.*, 1999, **121**, 7431-7432

132 H. M. L. Davies, G. Ahmed and M. R. Churchill, *J. Am. Chem. Soc.*, 1996, **118**, 10774-10782

133 P. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155-4156

134 S. C. Smith and P. D. Bentley, *Tetrahderon Lett.*, 2002, **43**, 899-902

135 G. Cignarella and G. Nathanson, *J. Org. Chem.*, 1961, **26**, 1500-1504

136 D. Barlocco, G. Cignarella, D. Tondi, P. Vianello, S. Villa, A. Bartolini, C. Ghelardini, N. Galeotti, D. J. Anderson, T. A. Kuntzweiler, D. Colombo, L. Toma, *J. Med. Chem.*, 1998, **41**, 674-681

137 M. T. Epperson and D. Y. Gin, *Angew. Chem. Int. Ed.*, 2002, **41**, 1778-1780

138 X. Feng and E. D. Edstrom, *Tetrahedron Asymmetry*, 1999, **10**, 99-105

139 R. J. Carra, M. T. Epperson and D. Y. Gin, *Tetrahedron*, 2008, **64**, 3629-3641

140 L. E. Overman, *Acc. Chem. Res.*, 1992, **25**, 352-359

141 a) P. R. Blakemore, W. J. Cole, P. J. Kocienski and A. Morley, *Synlett.*, 1998, 26-28; b) J. B. Baudin, G. Hareau, S. A. Julia and O. Ruel, *Tetrahdron Lett.*, 1991, **32**, 1175-1178

142 A. M. Baylis, M. P. H. Davies and E. J. Thomas, *Org. Biomol. Chem.*, 2007, **5**, 3139-3155

143 J. Dietz and S. F. Martin, *Tetrahedron Lett.*, 2011, **52**, 2048-2050

144 C. S. Shanahan, N. O. Fuller, B. Ludolph and S. F. Martin, *Teterahderon Lett.*, 2011, **52**, 4076-4079

145 S. A. Ahmed, PhD Thesis, University of Birmingham, Edgbaston, Birmingham, B15 2TT

146 D. E. Ward, M. A. Rasheed, H. M. Gillis, G. E. Beye, V. Jheengut and G. T. Achonduh, *Synthesis* 2007, **10**, 1584-1586

147 T. Miyakoshi, S. Saito and J. Kumanotani, *Chem. Lett.* 1981, *16*77-1678

148 K. C. Nicolaou, T. Montagnon, P. S. Baran and Y. L. Zhong, *J. Am. Chem. Soc*., 2002, **124**, 2245-2258

149 G.R. Takeoka, R. G. Buttery and C. T. Perrino, *J. Agric. Food Chem*., 1995, **43**, 22-26

150 M. Kawanishi, *Bioorg*. *Med*. *Chem*., 2004, **12**, 5297-5307

151 J. Fayos, J. Clardy, L. J. Dolby and T. Farnham, *J. Org. Chem.* 1977, **42**, 1349-1352

152 S. F. Macdonald, *Can. J. Chem*., 1974, **52**, 3257-3258

153 A. Barco, S. Benetti, C. Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Eur. J. Org. Chem.,* 2001, 975-986

154 D. H. Hua, S. W. Miao, S. N. Bharathi, T. Katsuhira and A. A. Bravo, *J. Org. Chem.*, 1990, **55**, 3682-3684

155 L. Ferrie, S. Bouzbouz and J. Cossy, *Org. Lett.*, 2009, **11**, 5446-5448

156 T. Ye, C. F. Garcia and M. A. Mckervey, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1373-1379

157 F. Li, J. Nie, J.-W. Wu, Y. Zheng and J.-A. Ma, *J. Org. Chem.*, 2012, **77**, 2398 - 2406

158 N. T. Barczak and E. R. Jarvo, *Chem. Eur. J.*, 2011, **17**, 12912 - 12916

159 S. F. McCann and L. E. Overman, *J. Am. Chem. Soc.*, 1987, **109**, 6107-6114

160 P. Innocenti, PhD Thesis, King's College, University of London, London, UK

161 J. Pawlas, Y. Nakao, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 3669-3679

162 J. W. Bastable, J. D. Hobson and W. D. Riddell, *J. Chem. Soc. Perkin Trans. 1.*, 1972, 2205-2213

163 D. R. Prudhomme, Z. Wang and C. J. Rizzo, *J. Org. Chem.*, 1997, **62**, 8257–8260

164 S. E. Steinhardt and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2009, **131**, 7546–7547

165 B. Ruttens, P. Blom, S. Van Hoof, I. Hubrecht and J. Van der Eycken, *J. Org. Chem.*, 2007, **72**, 5514–5522

166 M. G. Beaver and K. A. Woerpel, *J. Org. Chem.*, 2010, **75**, 1107–1118

167 S. M. Sarkar, Y. Taira, A. Nakano, K. Takahashi, J. Ishihara and S. Hatakeyama, *Tetrahedron Lett.,* 2011, **52**, 923-927

168 B. Guyot, J. Pornet and L. Miginiac, *J. Org. Chem.*, 1990, **386**, 19-28

169 G. D. Mendenhall, *Tetrahedron Lett.*, **1983**, 24, 451 - 452

170 N. Nelson, J. H. Fassnacht and J. U. Piper, J. Am. Chem. Soc., 1961, 83, 206

171 A. Franco Bella, A. M. Z. Slawin and J. C. Walton, *J. Org. Chem.*, 2004, **69**, 5926-5933

172 a) H. Muratake, M. Watanabe, K. Goto and M. Natsume, *Tetrahedron*, 1990, **46**, 4179-4192; b) A. C. Cope, D. S. Smith and R. J. Cotter, *Organic Syntheses Coll.,* 1963, **4**, 377

173 G. A. Molander and K. O. Cameron, *J. Am. Chem. Soc.*, 1993, **115**, 830-846

174 T. Mino, S. Fukui and M. Yamashita, *J. Org. Chem.*, 1997, **62**, 734-735

175 P. Wijkens and P. Vermer, *J. Organomet. Chem.*, 1986, **301**, 247-256

176 S. Cavicchiola, D. Savoia, C. Trombini and A. Umani-Ronchi, J. Org. Chem., 1984, **49**, 1246-1251

177 G. R. Takeoka, R. G. Buttery and C. T. Perrino Jr., J. Agric. Food Chem., 1995, **43**, 22-26

178 H. O. Fong, W. R. Hardstaff, D. G. Kay, R. F. Langer, R. H. Morse and D.-N. Sandoval, *Can. J. Chem.*, 1979, **57**, 1206-1213

179 a) E. Wada, J. Funakashi and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2456-2464; b) E. Wada, S. Kanemasa and O. Tsuge, Bull. Chem. Soc. Jpn., 1989, **62**, 860-868

180 T. Miyakoshi, S. Saito and J. Kumantani, *Chem. Lett.*, 1982, 83-84

181 K. A. M. Kremer and P. Helquist, *J. Organomet. Chem.*, 1985, **285**, 231-252