The development of one-pot tandem reactions for the synthesis of polycyclic γ-lactams

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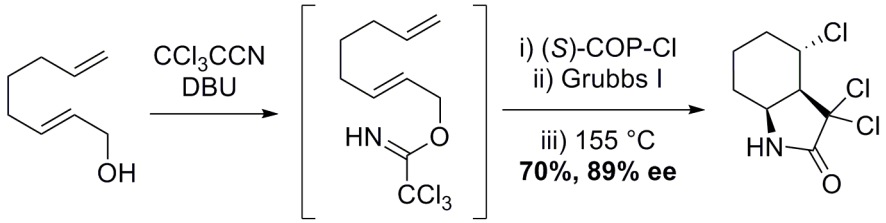
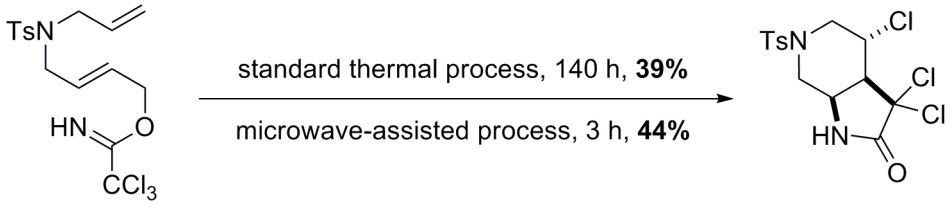
Abstract

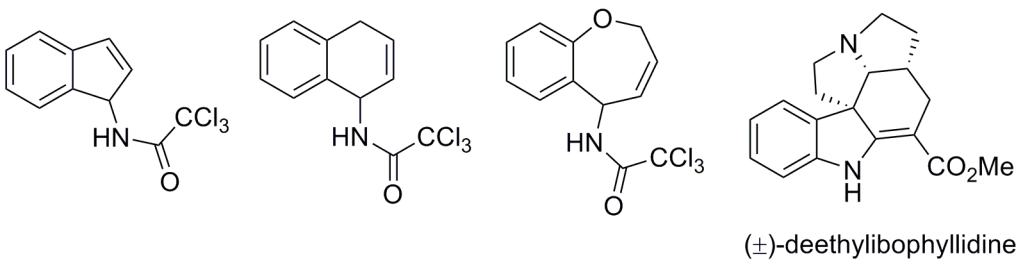
A novel tandem process has been developed for the stereoselective synthesis of bicyclic γ-lactams. Treatment of an allylic alcohol with trichloroacetonitrile, in the presence of DBU, affords the corresponding allylic trichloroacetimidate. This is then subjected to a tandem Overman rearrangement/RCM/Kharasch cyclisation, forming the desired bicyclic lactam in high yield and high enantiomeric excess. Overall, the one-pot tandem process involves three mechanistically distinct processes catalysed by palladium(II) (step 1) and Grubbs 1st generation catalyst (steps 2 and 3).



The use of a thermal Overman rearrangement in tandem with the Grubbs catalysed RCM/Kharasch cyclisation was also investigated. Furthermore, a microwave-assisted tandem process was developed which resulted in the accelerated synthesis of the desired bicyclic γ-lactams.



A two-step tandem process was then developed for the synthesis of bicyclic allylic amides, a closely related core unit to that found in a number of important commercially available drugs. Finally, progress has been made towards the total synthesis of (±)-deethylibophyllidine, which will utilise a tandem RCM/Kharasch cyclisation to construct the C and D rings of the natural product.



(±)-deethylibophyllidine

Contents

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Author's Declaration

This thesis represents the original work of Fiona I. McGonagle unless otherwise indicated in the text. The work upon which it is based was carried out at the University of Glasgow in the Loudon Laboratory under the supervision of Dr. Andrew Sutherland between October 2008 and March 2012. Aspects of the work described herein have previously been published elsewhere as stated below.

F. I. McGonagle, L. Brown, A. Cooke, A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 3418.
F. I. McGonagle, L. Brown, A. Cooke, A. Sutherland, *Tetrahedron Lett.*, 2011, **52**, 2330.

Abbreviations

°C	degrees centigrade
Δ	reflux
Å	angstrom
Ac	acetyl
Ar	aromatic
atm	atmosphere
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
Bz	benzyl
Cbz	benzyloxycarbonyl
CM	cross-metathesis
m-CPBA	*meta*-chloroperoxybenzoic acid
COP	cobaltocenyloxazoline palladacycle
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
endo	endocyclic
equiv.	equivalents
Et	ethyl
EWG	electron-withdrawing group
exo	exocyclic
Grubbs I	Grubbs 1st generation catalyst
Grubbs II	Grubbs 2nd generation catalyst
h	hour

Hex	hexyl
HLE	human leukocyte elastase
Hoveyda-Grubbs I	Hoveyda-Grubbs 1st generation catalyst
Hoveyda-Grubbs II	Hoveyda-Grubbs 2nd generation catalyst
HPLC	high-pressure liquid chromatography
hν	photon energy
Hz	hertz
IR	infrared
m-	*meta*-
M	molar
MAOS	microwave-assisted organic synthesis
Me	methyl
mech.	mechanism
Mes	mesityl
mL	millilitres
mmol	millimoles
mol	mole
mol. sieves	molecular sieves
MW	microwave
m/z	mass spectrometry
NOESY	nuclear Overhauser effect spectroscopy
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NuH	nucleophile
o-	*ortho*-
oic	octahydroindole-2-carboxylic acid
p-	*para*-
Ph	Phenyl
PHE	passive heating element
ppm	parts per million
Pr	propyl
PS	polystyrene
Py	pyridine
q	quartet
RCEYM	ring-closing enyne metathesis
RCM	ring-closing metathesis

ROM	ring-opening metathesis
ROMP	ring-opening metathesis polymerisation
rt	room temperature
s	singlet
T	temperature
t	triplet
tanδ	loss factor
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
tert	tertiary
tet	tetrahedral
Tf	triflate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
trig	trigonal
Ts	tosyl

1.0 Introduction

1.1 Background to one-pot reactions

Over the past few decades, the development of selective organic transformations using well-defined metal catalysts has revolutionised the way in which drug-like molecules are synthesised. These processes have environmental advantages over their stoichiometric counterparts as they tend to take place at reduced temperature meaning they are more energy efficient and an attractive choice from a green chemistry perspective.[1] However, due to the complexity of many pharmaceutical drug molecules, long multi-step syntheses are required to construct the final compound. This in turn means large amounts of reagents, solvents and energy are required leading to a significant quantity of waste production at each stage of the synthesis.[2] This has led to an increase in the research and development of greener tandem reactions, which combine multiple steps in a one-pot process, for the synthesis of complex organic molecules.

One-pot reactions are carried out continuously within the cells of our bodies by the involvement of well-organised enzymes. These enzymes catalyse numerous reactions in a multi-step sequence to synthesise complex molecules from simple starting materials, without the need to isolate intermediates.[3] Synthetic chemistry has long endeavoured to mimic the efficiency of biological systems and research into the development of one-pot catalytic processes has increased significantly over the past few decades.[4] One-pot reactions have several advantages over the classical step-by-step approach usually employed to synthesise complex organic molecules. The use of a one-pot system circumvents the need for large volumes of solvent both for performing the reactions and for the isolation and purification of compounds at each stage of the synthesis. Furthermore, carrying out a one-pot process lowers any loss in yield resulting from the purification of intermediates. Overall, a one-pot procedure saves time, energy and the excessive usage of solvents and other chemicals, which ultimately leads to a reduction in waste production when compared to performing a stepwise synthesis.

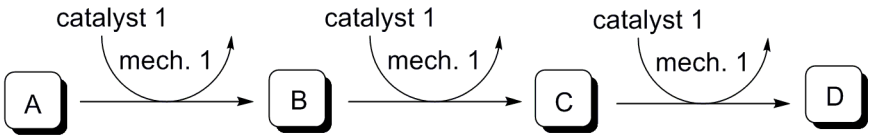
1.1.1 Definitions

As the development of one-pot processes has progressed rapidly in recent literature, the terms used to describe a reaction such as domino, cascade, tandem and sequential catalysis

have been used interchangeably to describe an array of different processes.[5] Catalytic domino and cascade reactions are related processes in which only one catalytic process is involved in the multiple transformations that take place. The term tandem process encompasses a much wider class of reactions. However, the common factor in all of these processes is that more than one catalytic cycle is involved. These can either be catalysed by the same catalyst or by mutually exclusive catalysts.

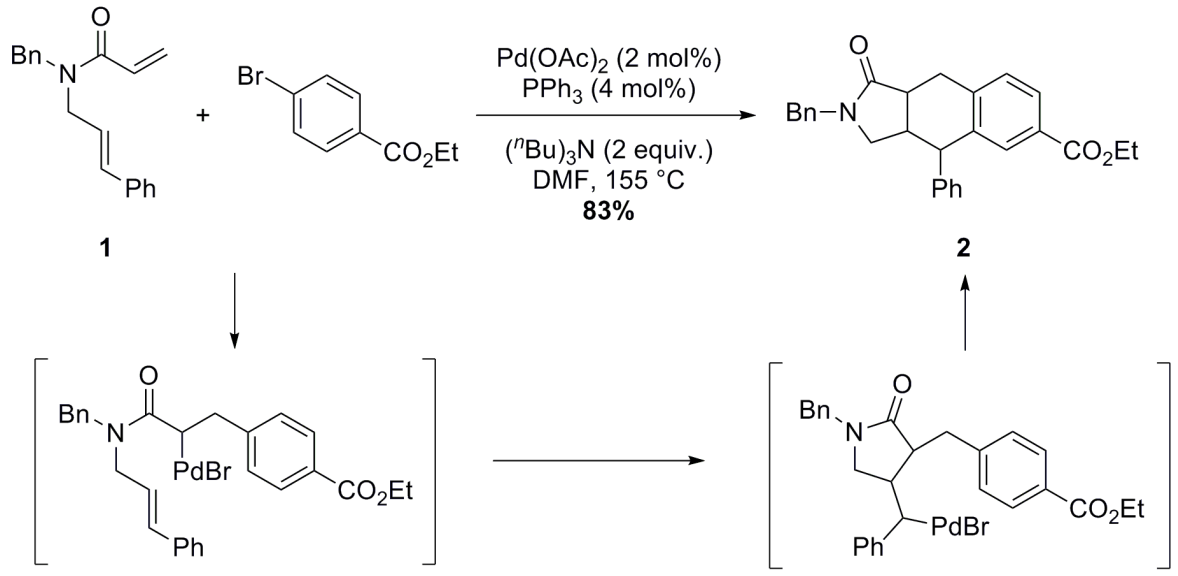
1.1.2 Domino/cascade catalysis

Tietze defines domino and cascade catalysis as "a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step".[6] Fogg added a further stipulation to this definition that all transformations involve a single catalytic mechanism (Scheme 1).[5]



Scheme 1: Illustration of a domino/cascade process

Palladium catalysed coupling reactions have become an important tool in the formation of carbon-carbon bonds and have frequently been utilised in cascade processes.[7] In 2008, Hu and co-workers reported the synthesis of the tricyclic lactam **2** *via* two consecutive Heck reactions followed by a C-H activation step using diene **1** (Scheme 2).[8] The process begins with reaction of the palladium catalyst with an aryl bromide. The first Heck reaction occurs with the α,β-unsaturated alkene and the resulting organo-palladium intermediate can undergo a second Heck reaction with the disubstituted alkene. Finally, a C-H activation step occurs with the adjacent aryl system to furnish the tricyclic product in high yield.



Scheme 2: Domino Heck reaction

In addition to palladium catalysed coupling reactions, metathesis reactions have become a valuable tool in organic synthesis. The groups of Schrock and Grubbs reported complexes of molybdenum and ruthenium respectively as well-defined metal centres for the catalysis of metathesis reactions in the 1990's (Figure 1).[9-11]

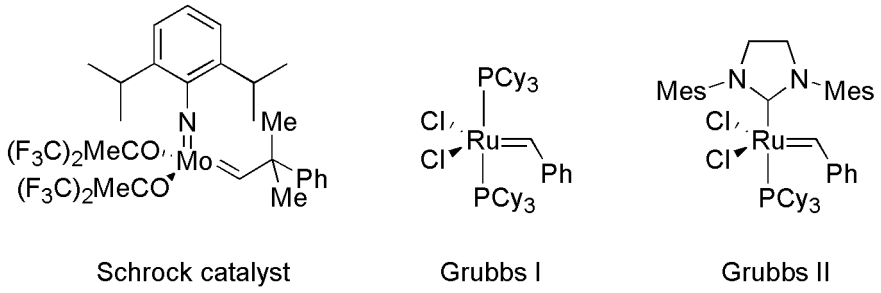
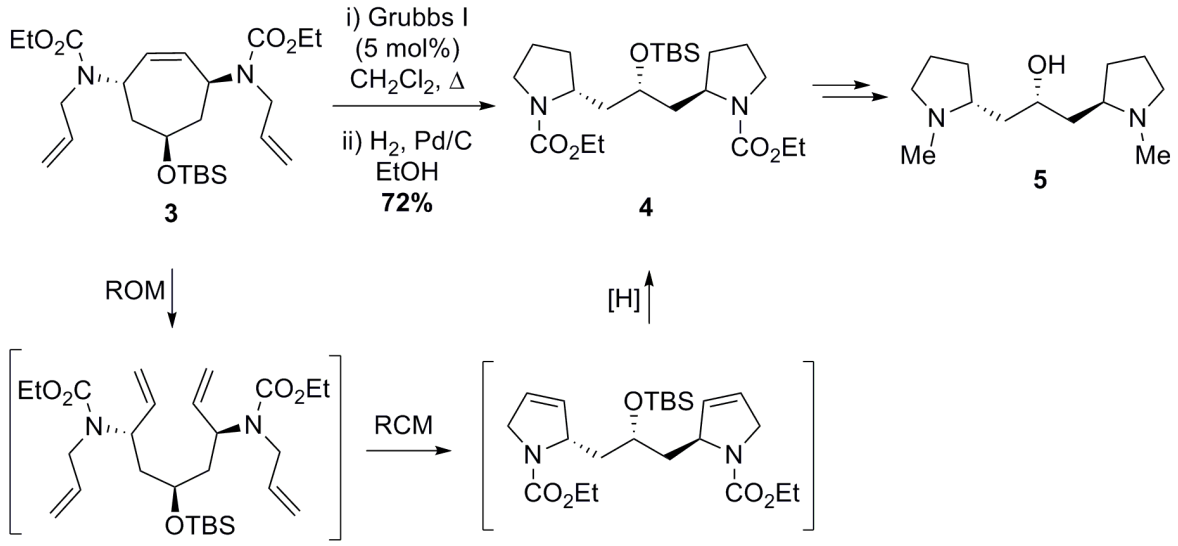


Figure 1: Commercially available metathesis catalysts

Since then, carbon-carbon bond formation using cross metathesis (CM), ring-opening metathesis (ROM) and ring-opening metathesis polymerisation (ROMP), as well the construction of cyclic systems through ring-closing metathesis (RCM) has been used extensively in organic synthesis and in the total synthesis of numerous natural products.[12] The stability of the ruthenium catalysts has made metathesis reactions a popular choice for incorporation in one-pot reactions.

In 2002, Stapper and Blechert utilised a tandem ring rearrangement, metathesis cascade towards the total synthesis of (+)-dihydrocuscohygrine **5** (Scheme 3).[13] Diamine **3** was synthesised in nine high yielding steps from tropone.[14] Treatment of **3** with Grubbs 1st generation catalyst (Grubbs I) initiated a ROM reaction of the 7-membered ring system, followed by two consecutive RCM reactions with the four alkenes. The unsaturated bicyclic product was immediately subjected to hydrogenation and bispyrrolidine **4** was yielded in 72% over the two synthetic steps, comprising of four individual transformations. Reduction of dicarbamate **4** followed by deprotection of the TBS group afforded the natural product **5**.



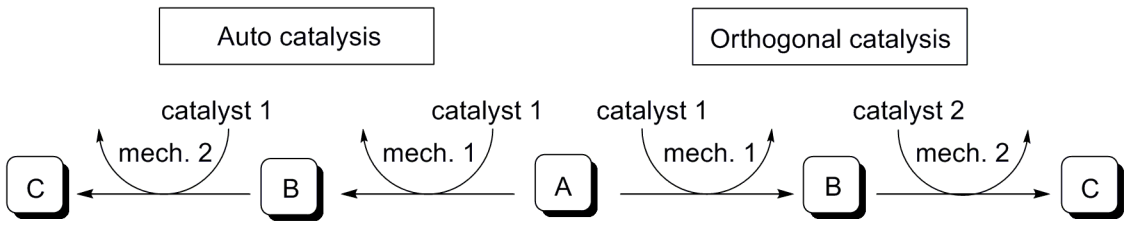
Scheme 3: Domino ROM/RCM sequence

As catalytic domino and cascade sequences utilise one catalyst and one catalytic cycle, the diversity of the process can be limited. Furthermore, as all the functionality required by the process is present in the starting material, the potential of transformations taking place out of sequence is increased and could potentially lead to poorly defined products. By designing a one-pot process that utilises two or more catalytic pathways, the directionality of the processes can be made more reliable.

1.1.3 Tandem catalysis

In Fogg's classification, he describes tandem catalysis as the "sequential transformation of the substrate *via* two (or more) mechanistically distinct processes".[5] The transformations

can be effected using the same catalyst (auto catalysis) or *via* different catalysts (orthogonal catalysis) (Scheme 4).



Scheme 4: Illustration of auto and orthogonal tandem catalysis

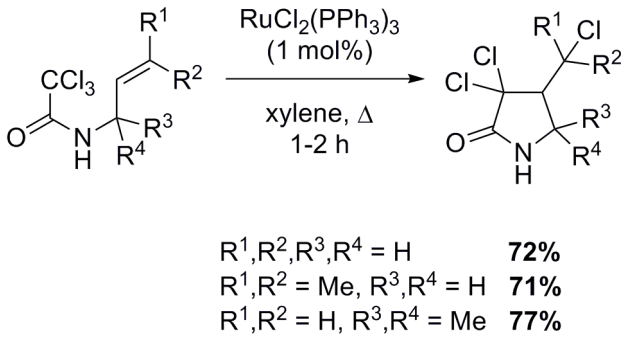
Fogg also stipulates that tandem reactions take place under the same reaction conditions and without addition of substrates or catalysts after the reaction has been initiated. One-pot reactions that require an addition of catalysts or reagents after a reaction has commenced are sometimes referred to as assisted tandem or sequential reactions.[15] These tend to be more prominent in the literature due to compatibility issues which can exist between catalysts. By allowing one catalytic process to take place before addition of the second catalyst, these issues can therefore be avoided. For clarity, the term tandem catalysis will subsequently be used to describe all one-pot catalytic processes that involve two or more distinct processes regardless of when catalysts/substrates are added or whether reaction conditions are altered during the process.

As highlighted in the previous section, metathesis reactions have been a popular tool for the construction of carbon-carbon bonds for the past two decades and many of the ruthenium complexes used to catalyse these processes are commercially available. More recently however, research into the non-metathetic uses of these catalysts has been published.[16,17] Examples include atom transfer radical additions (Kharasch addition), double bond isomerisation, oxidations, reductions, cyclopropanations, the Diels-Alder reaction and the Wittig reaction. Furthermore, by combining a metathesis reaction with these non-metathetic steps, more diverse tandem processes have been developed.

1.2 Kharasch addition

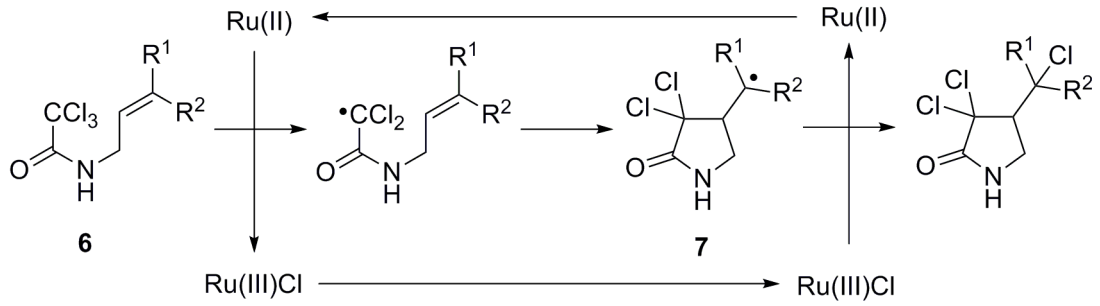
Lactams are found in an array of natural products and act as advanced intermediates for the synthesis of antibiotic and anticancer agents.[18] As a result, new methods to synthesise β-, γ- and δ-lactams are of interest in organic synthesis. Methods that form the lactam system in

ways other than through the formation of the amide linkage are particularly interesting. In 1984, Itoh and co-workers reported the synthesis of γ-lactams through a ruthenium catalysed Kharasch cyclisation of allylic trichloroacetamides.[19] In all cases only the γ-lactams were isolated in high yield showing a preference for a 5-*exo-trig* cyclisation over a 6-*endo-trig* cyclisation (Scheme 5).



Scheme 5: Kharasch cyclisation promoted by a ruthenium(II) catalyst

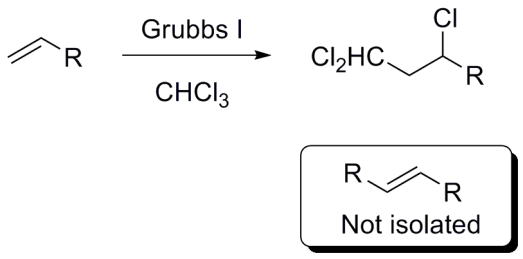
The authors went on to propose a general mechanism of the ruthenium catalysed process.[20] The ruthenium(II) catalyst initiates the process by abstracting a chlorine atom from the trichloro group of substrate **6** to form a carbon centred radical (Scheme 6). This radical then undergoes a 5-*exo-trig* cyclisation to form the 5-membered lactam ring **7**. Finally, quenching of the terminal radical occurs with reduction of ruthenium(III) to ruthenium(II) to complete the catalytic cycle.



Scheme 6: Proposed mechanism for the Kharasch cyclisation

In 1999, Snapper and co-workers reported that Grubbs 1st generation catalyst was a mild and efficient catalyst for the Kharasch addition reaction.[21] Whilst conducting a CM reaction, they isolated a product which had formed from chloroform addition across the

double bond of the parent olefin (Scheme 7). This unexpected result indicated that Grubbs 1st generation catalyst could catalyse a Kharasch addition reaction.



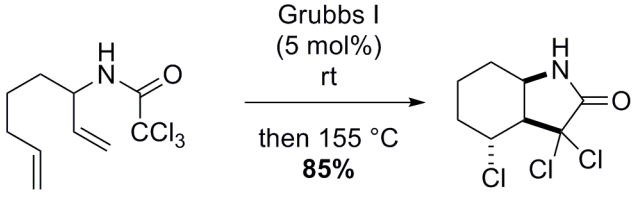
Scheme 7: Evidence that Grubbs 1st generation catalyst promotes a Kharasch addition reaction

Since this discovery, research into other non-metathetic uses of Grubbs alkylidenes has flourished and their incorporation into tandem processes has been prominent in the literature.

1.3 Tandem reactions using Grubbs catalysts

1.3.1 Ring-closing metathesis/Kharasch cyclisation

Following their initial discovery, Snapper and co-workers reported a tandem RCM/Kharasch cyclisation that used Grubbs 1st generation catalyst to effect both steps of the one-pot process.[22] RCM reaction of diene **8** with Grubbs 1st generation catalyst occurred at room temperature and once completed, an increase in reaction temperature to 155 °C initiated the ruthenium catalysed Kharasch cyclisation reaction for the formation of bicyclic lactam **9** in excellent yield (Scheme 8).

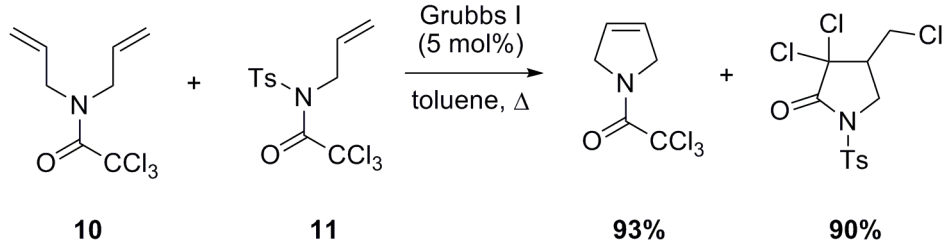


8 **9**

Scheme 8: Tandem RCM/Kharasch cyclisation

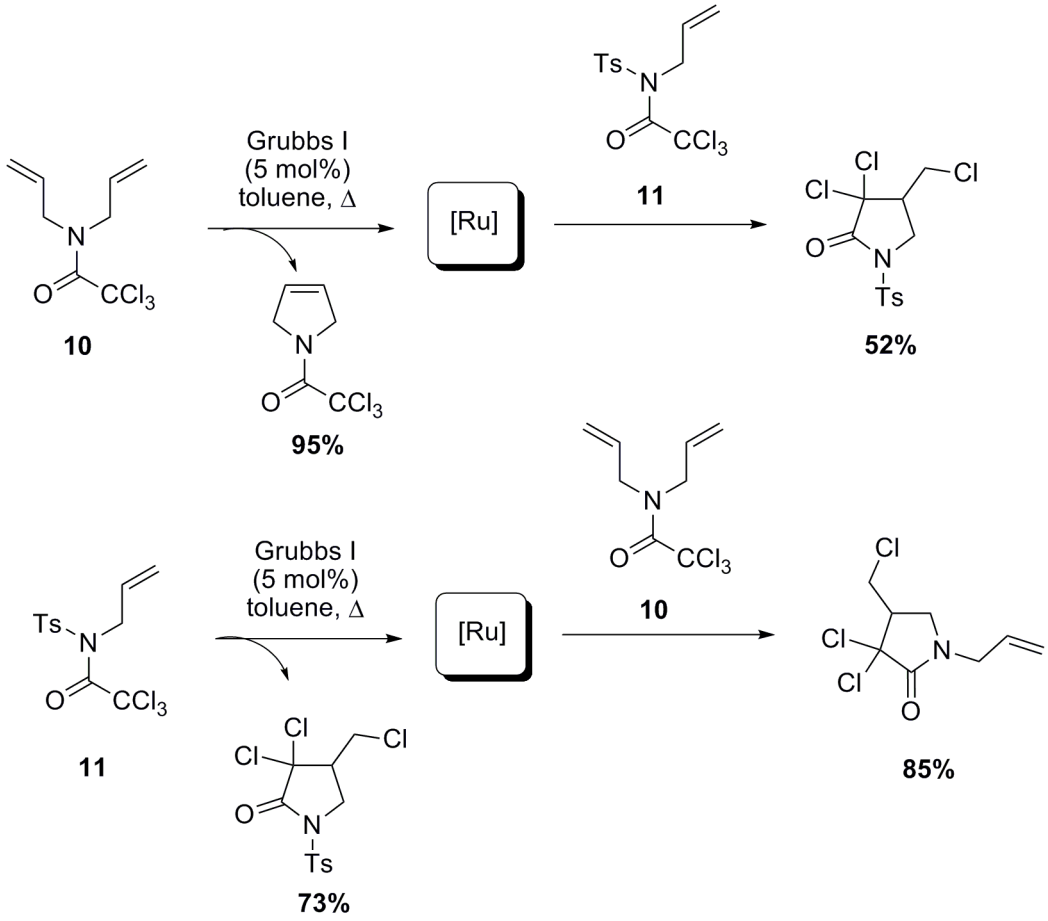
Around the same time, Quayle and co-workers carried out a series of competition reactions to further probe the rate differences between RCM reactions and Kharasch cyclisations

catalysed by Grubbs 1st generation catalyst.[23] Diene **10**, which could potentially undergo both RCM and Kharasch cyclisation, was chosen alongside allylic amide **11** which could only undergo Kharasch cyclisation (Scheme 9). When both were reacted in the same vessel with Grubbs 1st generation catalyst in toluene under reflux, diene **10** formed the corresponding RCM product in 93% yield and allylic amide **11** formed the corresponding Kharasch cyclisation product in 90% yield. ^{1}H NMR spectroscopy studies were carried out using this competition reaction and revealed that the RCM reaction initiated as soon as mixing commenced whereas the Kharasch cyclisation product formed more slowly. Furthermore, the NMR spectroscopy studies indicated that Grubbs 1st generation catalyst is denatured at elevated temperatures. The authors proposed that it was this catalyst decomposition that initiated the Kharasch reaction and would account for the difference in rates between these two reactions.



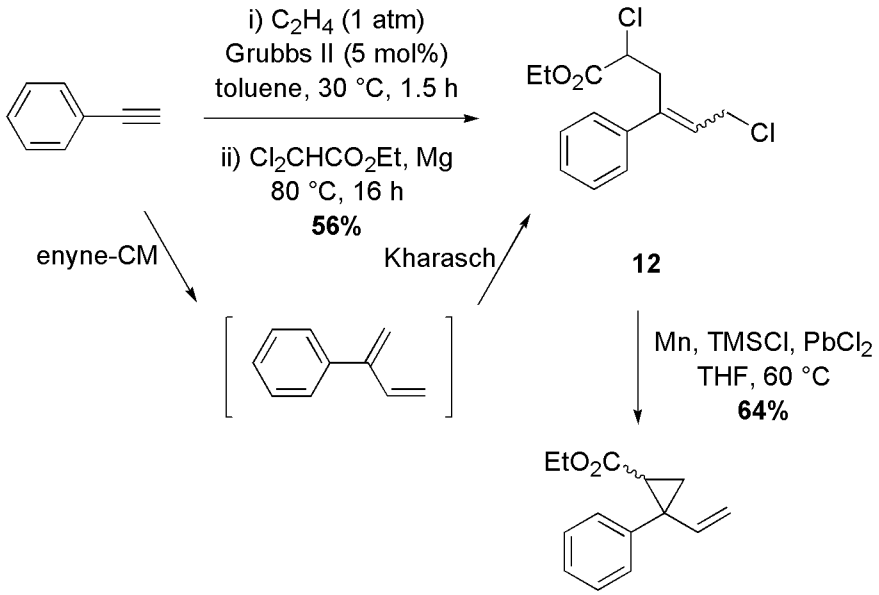
Scheme 9: Substrates and their preferred products for the competition reactions

The authors then went on to illustrate what happens when the substrates are added sequentially to the reaction vessel. By initially reacting diene **10** with Grubbs 1st generation catalyst followed by addition of allylic amide **11**, the corresponding RCM and Kharasch cyclisation products are formed respectively in 95% and 52% yield (with 45% of unreacted allylic amide **11** also recovered) (Scheme 10). When the addition of substrates is reversed, a change in reactivity is observed. Whilst the allylic amide **11** still forms the Kharasch cyclisation product in 73% yield, subsequent addition of diene **10** to the reaction mixture leads to the formation of its corresponding Kharasch cyclisation product in 85% yield rather than the RCM product observed previously. This shows that the Grubbs catalyst must undergo modifications at elevated temperatures and loses the ability to effect the metathesis reaction whilst maintaining the ability to act as a radical initiator in the Kharasch cyclisation reaction.



Scheme 10: Competition reactions to illustrate modification of Grubbs catalyst

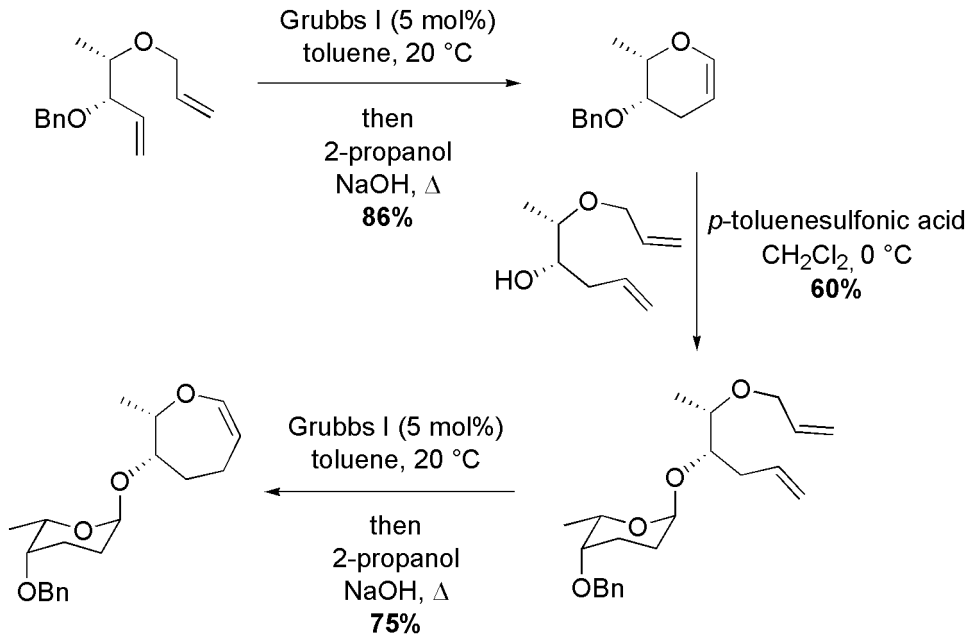
It is not only alkene metathesis that has been utilised in tandem with a Kharasch addition reaction. In 2012, Severin and co-workers reported a tandem enyne-CM/Kharasch addition reaction for the formation of 1,5-dichloropent-2-ene **12** (Scheme 11).[24] The diene formed from the enyne CM reaction of the alkyne with ethylene undergoes Kharasch addition with ethyl dichloroacetate to form compound **12** as the major regioisomer in moderate yield. The products formed from this process were shown to be suitable starting materials for the formation of vinylcyclopropanes.



Scheme 11: Tandem enyne CM/Kharasch addition

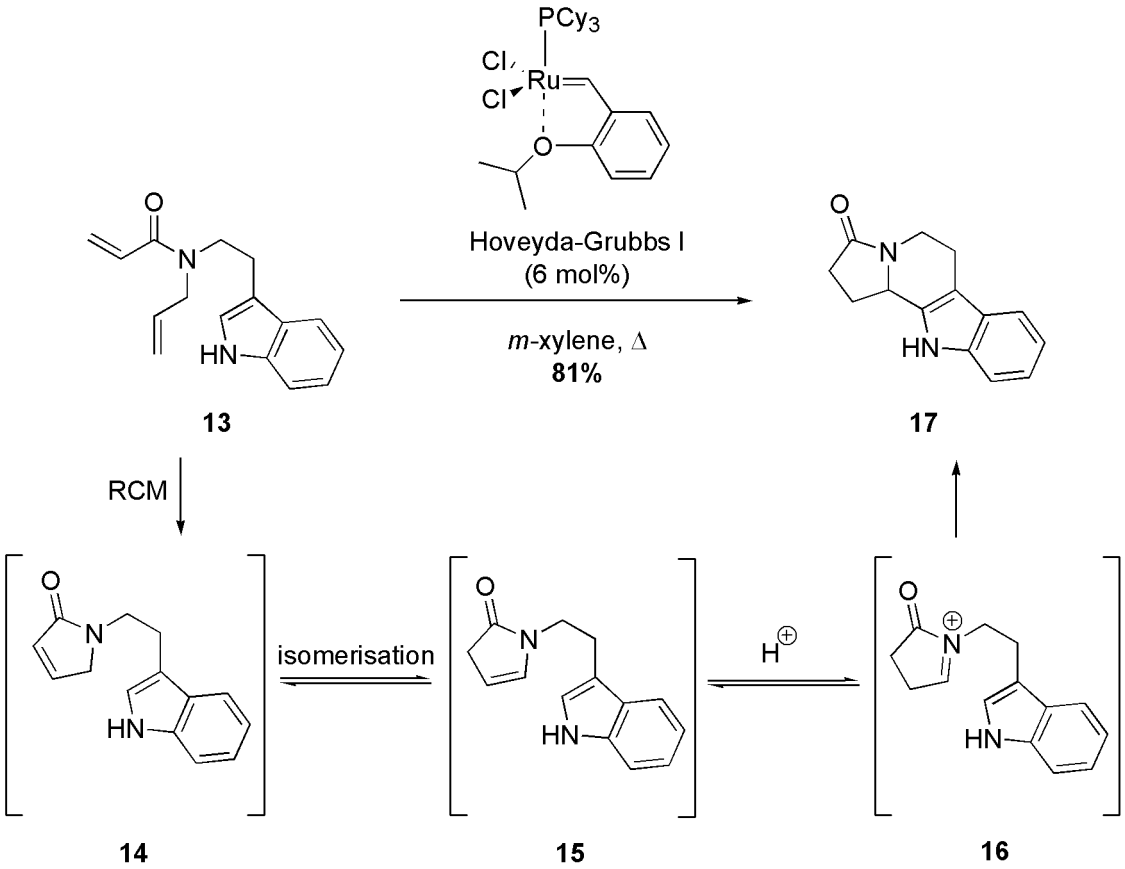
1.3.2 Ring-closing metathesis/isomerisation

Cyclic enol ethers are prevalent in a variety of bioactive compounds and as a result, methods for their synthesis are highly sought after. Direct formation of these compounds by RCM can be challenging, as vinyl ethers are poor substrates for such reactions. However, carrying out a RCM reaction using an allyl ether followed by isomerisation of the double bond, can offer easy access to these important molecules. In 2008, Schmidt and Biernat utilised a tandem RCM/isomerisation sequence towards the synthesis of deoxygenated glycols (Scheme 12).[25] Their method utilised Grubbs 1st generation catalyst to effect the RCM step before addition of 2-propanol and sodium hydroxide to convert the metathesis active ruthenium alkylidene into an isomerisation active ruthenium hydride species.[26] They showed this method was applicable for 6- and 7-membered cyclic enol ethers.



Scheme 12: Double RCM/isomerisation sequence towards disaccharides

In 2011, Nielsen and co-workers further expanded the RCM/isomerisation sequence to include a second cyclisation step, a useful method for the formation of bi-, tri- and tetracyclic lactams.[27] They proposed that the enamine **15** formed from a tandem RCM/isomerisation of amide **13** could be further isomerised into *N*-acyliminium ion **16** and undergo a second cyclisation step using a tethered nucleophile (Scheme 13). This resulted in the formation of the desired tetracyclic lactam **17**, which represents the formal synthesis of harmicine, an antiparasitic natural product.



Scheme 13: Tandem RCM-isomerisation-*N*-acyliminium cyclisation sequence

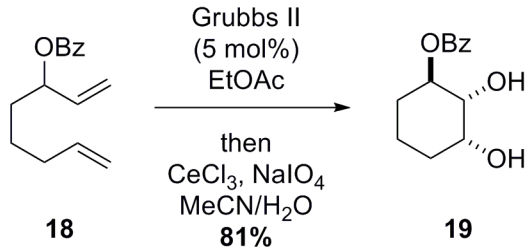
The group went on to illustrate the beneficial presence of the ruthenium catalyst for the isomerisation steps. By stirring the isolated RCM product **14** in *m*-xylene under reflux for 22 h, desired product **17** and starting material **14** were afforded as a 1:1 mixture. In comparison, treating RCM product **14** with Hoveyda-Grubbs 1st generation catalyst (6 mol%) in *m*-xylene under reflux for 5 h gave quantitative conversion to the desired tetracyclic product **17**.

As highlighted above, the formation of the carbon-carbon double bond in a metathesis reaction allows the formation of a key functionality with which to perform subsequent reactions. Oxidations and reductions can be readily carried out on alkenes and recently the use of Grubbs catalysts to effect these reactions in tandem with a metathesis step has been reported.

1.3.3 Ring-closing metathesis/oxidation

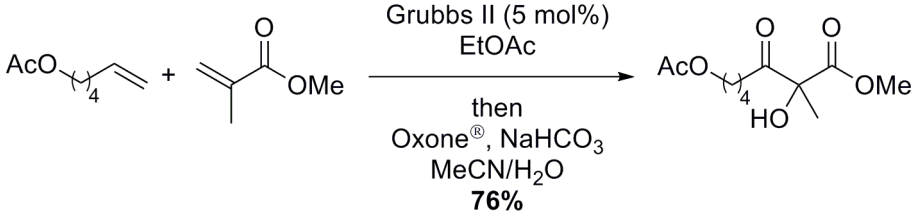
The dihydroxylation of carbon-carbon double bonds is a popular transformation in organic chemistry. Osmium reagents are the most widely used catalysts for this transformation but

some issues still need to be resolved regarding these compounds, namely the toxicity of osmium.[28] In 2005, Plietker and Niggemann reported the *in situ* formation of ruthenium tetroxide by reaction of ruthenium trichloride, sodium periodate and cerium(III) chloride for the dihydroxylation of a variety of olefins.[29] Snapper and co-workers built upon this work by applying this oxidative modification to Grubbs catalyst in order to carry out a RCM/dihydroxylation sequence (Scheme 14).[30] Grubbs 2nd generation catalyst (Grubbs II) was employed to carry out the RCM reaction using diene **18**, before addition of sodium periodate and cerium(III) chloride to transform the ruthenium alkylidene into ruthenium tetroxide, which could subsequently catalyse the dihydroxylation of the newly formed carbon-carbon double bond. The desired diol **19** was formed, as a single diastereomer, in 81% yield over the two steps.



Scheme 14: Tandem RCM/dihydroxylation

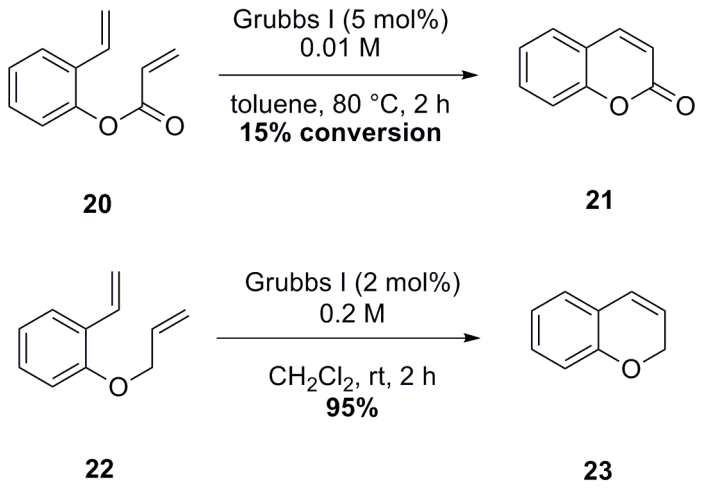
Snapper and co-workers also applied this protocol to the CM of alkenes followed by dihydroxylation with similar success. Furthermore, they showed that by changing the oxidative mixture to Oxone® and sodium hydrogen carbonate[31] they could carry out an α-ketohydroxylation, this time in tandem with a CM reaction (Scheme 15).[30]



Scheme 15: Tandem CM/α-ketohydroxylation

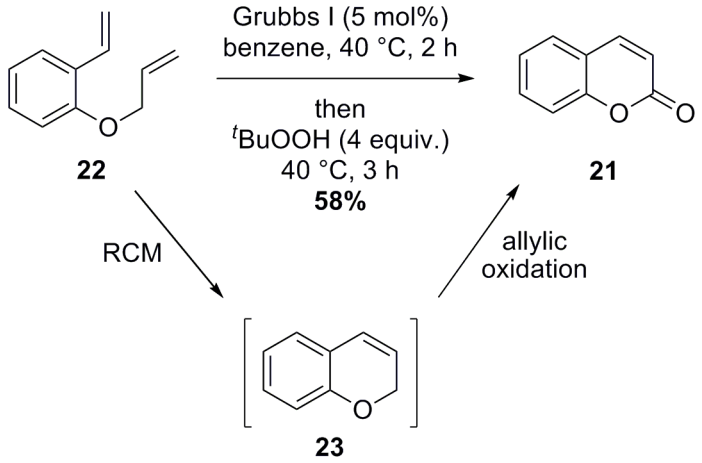
More recently, Schmidt and Krehl reported a tandem RCM/allylic oxidation for the synthesis of coumarins **21**.[32] Access to these molecules directly from styrenyl acrylate **20** using a RCM reaction requires high dilution and proceeds slowly, whereas synthesis of the

related 2*H*-chromene **23** from styrenyl allyl ether **22** proceeds rapidly under milder reaction conditions (Scheme 16).[33]



Scheme 16: Comparing RCM reactivity of styrenyl acrylates with styrenyl allyl ethers

From these significant differences in reactivity, Schmidt and co-workers developed a procedure which would allow the easy access to coumarin **21** using a tandem RCM/allylic oxidation (Scheme 17).[32] *tert*-Butyl hydroperoxide was chosen as the oxidant for the allylic oxidation instead of periodate, as the latter could potentially cause the dihydroxylation of the newly formed double bond (*c.f.* Scheme 14).

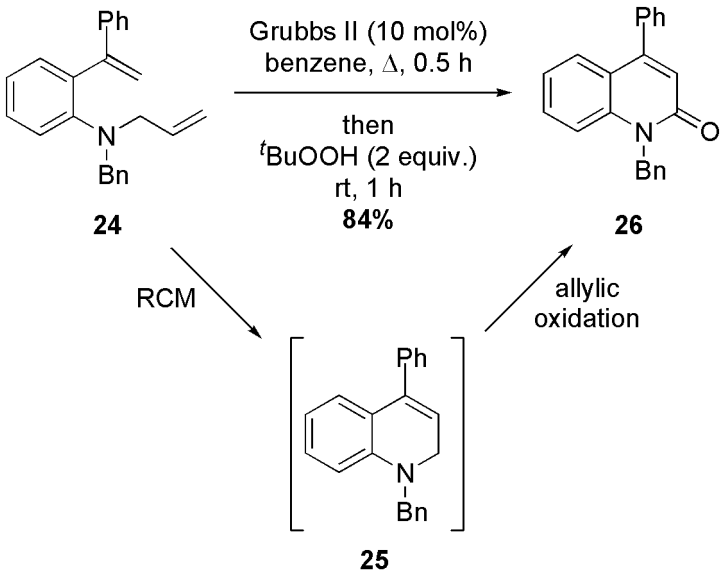


Scheme 17: Tandem RCM/allylic oxidation for the synthesis of coumarins

Furthermore, to test whether the oxidation step was being assisted by the presence of the ruthenium catalyst, the isolated 2*H*-chromene **23** was subjected to the allylic oxidation conditions with and without the addition of Grubbs 1st generation catalyst. Without the

addition of catalyst, the desired product **21** was obtained in 14% yield. In the presence of Grubbs 1st generation catalyst the yield was improved to 48%. This yield of 48% for the single allylic oxidation step also highlights the benefits of carrying out the reaction in tandem with a RCM reaction, where the yield of product was obtained in 58% yield.

Following this work, Shuto and co-workers published a similar tandem reaction for the synthesis of 2-quinolones **26** (Scheme 18).[34] In this case, the RCM reaction of diene **24** was catalysed using Grubbs 2nd generation catalyst followed by treatment with *tert*-butyl hydroperoxide to effect the oxidation step in the presence of the ruthenium catalyst. As in the coumarin synthesis, the allylic oxidation was attempted from the isolated dihydroxyquinoline **25** in the absence of Grubbs catalyst, but failed to yield any 2-quinolone product **26**. This again highlights the role of ruthenium (presumably with the *in situ* conversion of the active ruthenium alkylidene to another ruthenium species) in the allylic oxidation step of the tandem process.

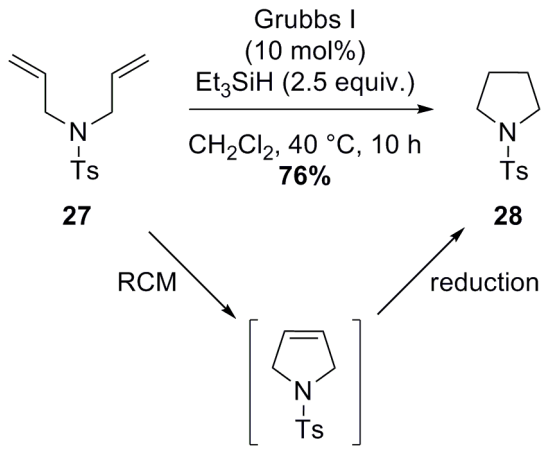


Scheme 18: Tandem RCM/allylic oxidation for the synthesis of 2-quinolones

1.3.4 Cross-metathesis/reduction

In 2005, Cossy and co-workers reported the reduction of alkenes in the absence of hydrogen. Instead, they utilised Grubbs 1st generation catalyst and triethylsilane to carry out a tandem RCM/reduction procedure (Scheme 19).[35] Treatment of diallylamine **27** with Grubbs 1st generation catalyst in the presence of triethylsilane led to the formation of saturated pyrrolidine **28** in 76% yield. Although the authors were unable to provide any

mechanistic evidence for the transformation, results suggested that the RCM step proceeds faster than the modification of the ruthenium catalyst by triethylsilane.

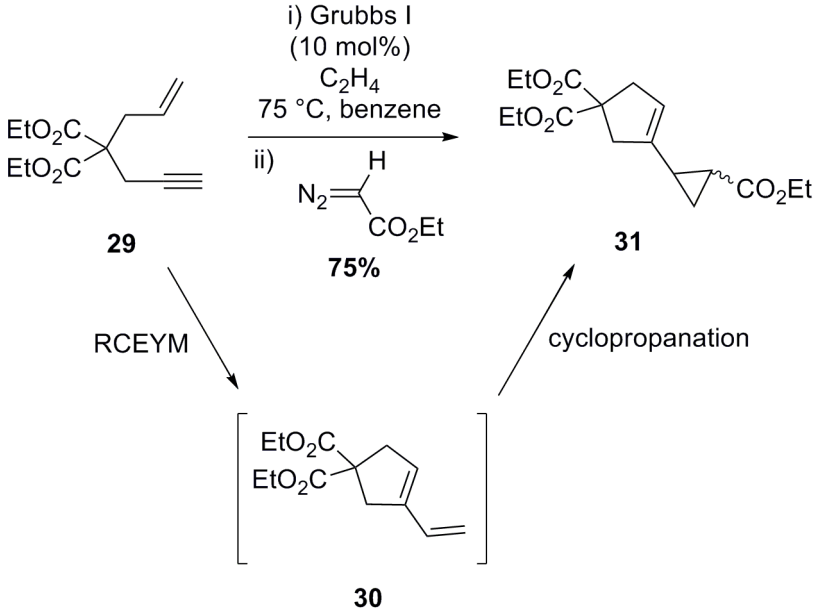


Scheme 19: RCM/reduction sequence using triethylsilane

This ability of Grubbs catalyst modified by silanes to reduce alkenes in the absence of hydrogen, provides a novel chemoselective method for this transformation.

1.3.5 Ring-closing enyne metathesis (RCEYM)

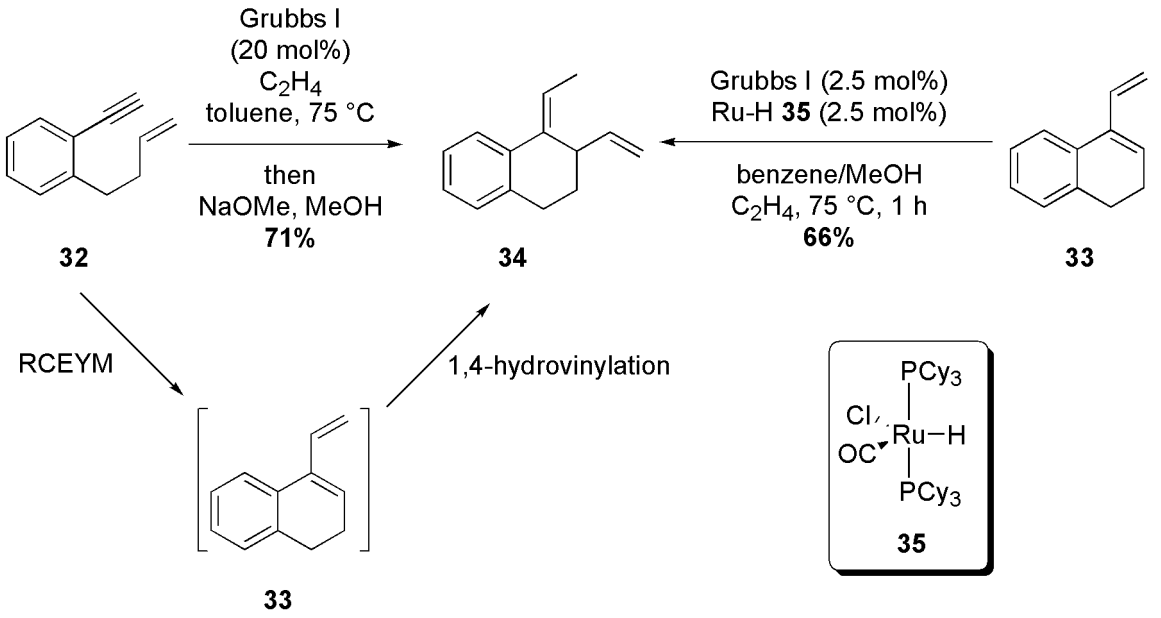
Unlike alkene metathesis, enyne metathesis is a bond reorganisation reaction and so all atoms from the substrate are present in the product making it an atom economical process.[36] The metathesis reaction forms a diene product, which was utilised in 2006 by Snapper and co-workers, in tandem with a cyclopropanation reaction, for the synthesis of vinyl cyclopropanes (Scheme 20).[37] Treatment of enyne **29** with Grubbs 1st generation catalyst under an atmosphere of ethylene formed diene **30**, to which was added ethyl diazoacetate and caused cyclopropanation of the terminal alkene to afford the desired product **31** in 75% yield and a 1:1 ratio of *E*/*Z* isomers.



Scheme 20: Tandem RCEYM/cyclopropanation reaction

Although no additives were required to significantly alter the reactivity of the catalyst after the metathesis stage, evidence from phosphorus-31 NMR spectroscopy revealed slight differences between the signals of the catalyst ligands after the tandem sequence compared to after an isolated RCEYM of enyne **29**. Furthermore, the group investigated whether the ruthenium catalyst was still metathesis active after the tandem process was complete by addition of a simple diene; however no RCM product of this compound was observed. These results suggest that small modifications of the Grubbs catalyst had taken place after addition of the diazo compound thus creating a cyclopropanation active catalyst.

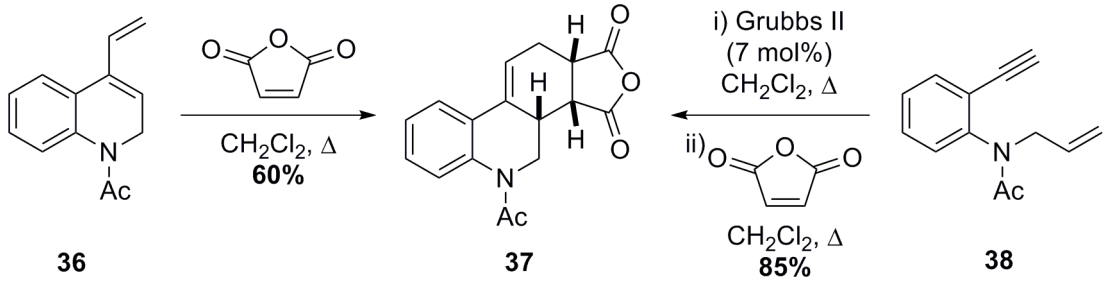
More recently, Snapper and co-workers reported a further tandem process that utilises a RCEYM step.[38] Previous work by Yi and co-workers showed that ruthenium hydride complex **35** could facilitate the hydrovinylation of 1,3-dienes.[39] Furthermore, this ruthenium hydride complex **35** can be formed by reaction of Grubbs 1st generation catalyst with a primary alcohol and an inorganic base.[40] Thus, Snapper and co-workers proposed the development of a tandem RCEYM followed by hydrovinylation reaction catalysed by Grubbs 1st generation catalyst. In the event, treatment of enyne **32** with Grubbs 1st generation catalyst under an atmosphere of ethylene, followed by addition of sodium methoxide and methanol afforded the 1,4-hydrovinylation product **34** exclusively in good yield (Scheme 21). Previous work by Yi suggested that the 1,2-hydrovinylation product would be favoured, however Snapper and co-workers showed that the presence of methanol in the reaction mixture might be responsible for the 1,4-selectivity.



Scheme 21: Tandem RCEYM/hydrovinylation

Snapper and co-workers also noted that reaction of isolated diene **33** with a 1:1 mixture of Grubbs 1st generation catalyst and the ruthenium hydride complex **35** in a benzene/methanol solvent system, gave comparable yields to the tandem process, suggesting a more complex catalytic system could be responsible for the observed reactivity (Scheme 21).[38]

As the product from a RCEYM reaction is a 1,3-diene, Perez-Castells and co-workers explored the possibility of combining this process with a Diels-Alder reaction.[41] The group showed that by carrying out an isolated Diels-Alder reaction on diene **36**, the tetracyclic product **37** was formed in 60% yield (Scheme 22). However, by carrying out a tandem RCEYM reaction catalysed by Grubbs 2nd generation catalyst, followed by the same Diels-Alder reaction, the desired tetracyclic product was afforded in 85% yield from enyne **38** under the same reaction conditions. These results would suggest that the presence of the ruthenium is assisting the Diels-Alder reaction resulting in a more efficient process.

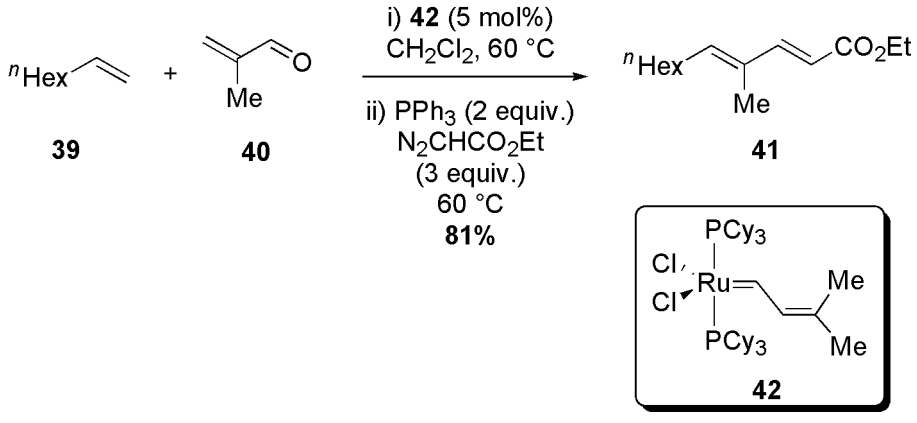


Scheme 22: Tandem RCEYM/Diels-Alder reaction

This tandem process shows the beneficial action of ruthenium within a reaction that is not traditionally known for being catalysed by ruthenium. There are examples of other named reactions, which are not commonly catalysed by ruthenium, being combined in tandem with a metathesis reaction.

1.3.6 Cross-metathesis/Wittig reaction

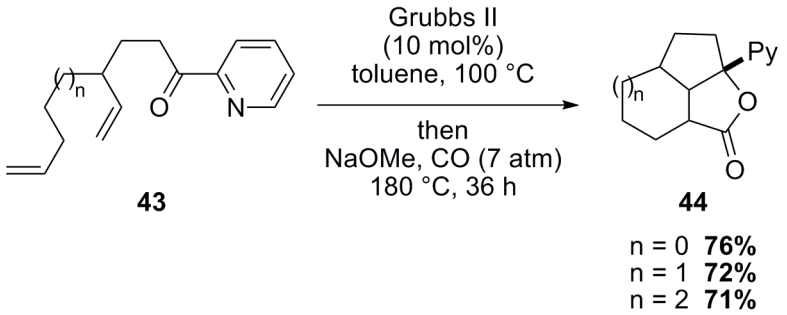
In 2007, Snapper and co-workers reported the use of cross-metathesis in tandem with a Wittig reaction.[42] Wittig reactions are traditionally performed under base mediated conditions, however some examples of ruthenium promoted Wittig reactions have been reported in the literature.[43-45] Thus, it was proposed that Grubbs-type catalysts could be utilised in tandem with a CM/Wittig reaction, for the synthesis of dienoic esters. Reaction of terminal alkenes **39** with methacrolein **40** in the presence of catalyst **42**, formed an α,β-unsaturated aldehyde, which upon treatment with triphenylphosphine and ethyl- or *tert*-butyl diazoacetate afforded the desired α,β,γ,δ-unsaturated esters **41** in good to high yield (Scheme 23). It was proposed by the authors that catalyst decomposition could lead to the formation of a phosphonium ylide capable of effecting the Wittig reaction, although the exact nature of the catalyst is not fully understood.[43,46] Catalyst **42** was chosen for this tandem process due to its efficiency and selectivity towards CM reactions. However, it was shown by the authors that Grubbs 1st generation catalyst was efficient at catalysing the Wittig reaction.



Scheme 23: Tandem CM/Wittig reaction

1.3.7 Ring-closing metathesis/hetero-Pauson-Khand reaction

In 2011, Snapper and co-workers reported a tandem RCM/hetero-Pauson-Khand reaction for the synthesis of polycyclic lactones.[47] Pauson-Khand reactions are commonly catalysed by cobalt complexes, however, ruthenium-catalysed hetero-Pauson-Khand reactions have previously been reported in the literature.[48] Snapper and co-workers found that they could modify Grubbs 2nd generation catalyst by reaction with carbon monoxide followed by reduction using sodium methoxide, to form a ruthenium species which was capable of effecting the hetero-Pauson-Khand reaction. Thus, treatment of diene **43** with Grubbs 2nd generation catalyst to effect the RCM reaction was followed by catalyst modification using sodium methoxide and carbon monoxide which initiates the hetero-Pauson-Khand reaction to form lactone product **44** (Scheme 24). Overall, the one-pot process resulted in the formation of three new carbon-carbon bonds as well as a new carbon-oxygen bond. The presence of the pyridine group adjacent to the carbonyl group was shown to be vital for the hetero-Pauson-Khand reaction to take place, as replacing it with a phenyl group lead to no lactone formation and only RCM product was isolated in 80% yield.



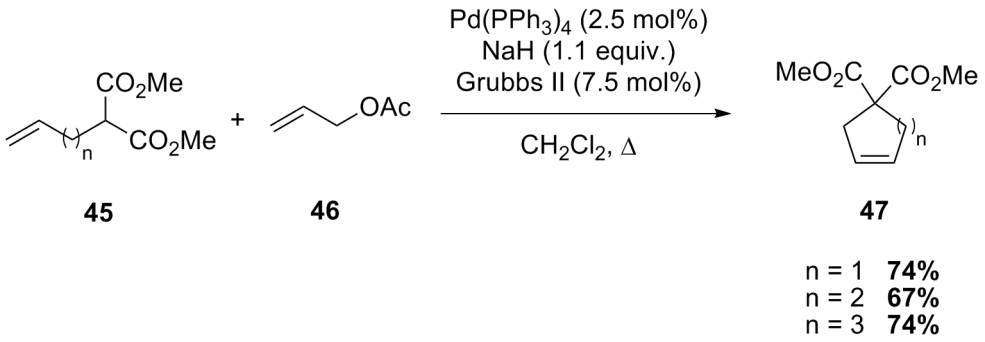
Scheme 24: Tandem RCM/hetero-Pauson-Khand reaction

In most of the examples given, with the possible exception of the tandem RCEYM/hydrovinylation reaction (section 1.4.5), only one catalytic species is present at any one time. Recent work has shown that ruthenium catalysed metathesis reactions can be used in tandem with reactions which are catalysed by other transition metal catalysts.

1.4 Bimetallic tandem reactions involving metathesis

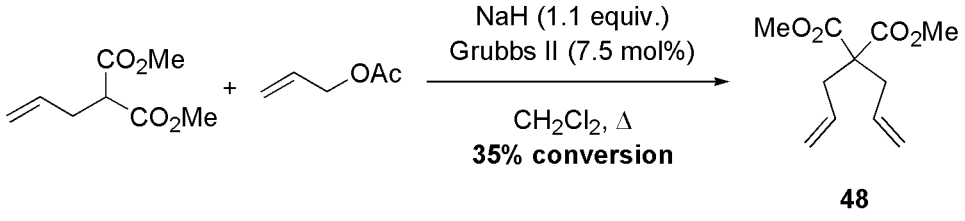
1.4.1 Ring-closing metathesis/allylic alkylation

In 2008, Poli and co-workers successfully developed a tandem process that combined a RCM reaction with a palladium catalysed allylic alkylation step.[49] Treatment of dimethyl malonates **45** and allyl acetate **46** with tetrakis(triphenylphosphine)palladium(0), sodium hydride and Grubbs 2nd generation catalyst resulted in the formation of the cycloalkene products **47** in good yield (Scheme 25). It is worth noting that both palladium and ruthenium are present in the reaction mixture from the outset of the reaction.



Scheme 25: Tandem allylic alkylation/RCM reaction

The authors showed that both catalysts are necessary for the tandem reaction to take place. In the absence of both catalysts only starting materials were observed. When only palladium was added to the reaction, only the allylation product was isolated. Interestingly, when only Grubbs 2nd generation catalyst was added to the reaction mixture, some allylated product was observed (Scheme 26). This suggests that Grubbs catalyst could promote the alkylation step to form diene **48**, however no subsequent RCM product was observed in the reaction mixture suggesting this reactivity must involve a modification of the catalyst which renders it inactive to metathesis reactions.



Scheme 26: Grubbs II catalyst promoted allylic alkylation

The tandem process was extended to a palladium catalysed double allylic alkylation of 1,3-dicarbonyl compounds followed by a Grubbs 2nd generation catalysed RCM reaction. In order to achieve high yields of the products, the Grubbs catalyst was added after completion of the double alkylation to avoid catalyst decomposition (Figure 2).

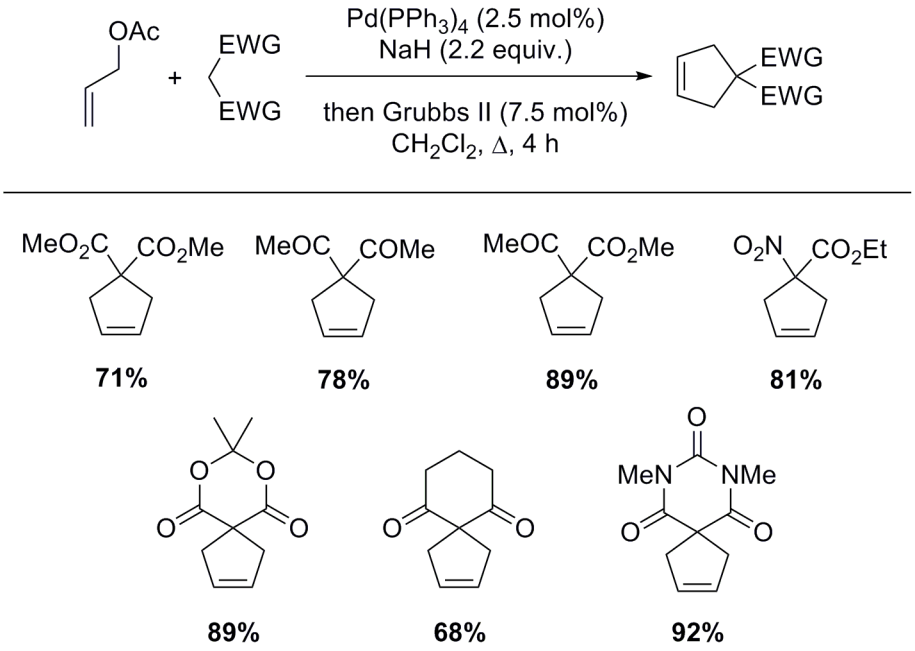
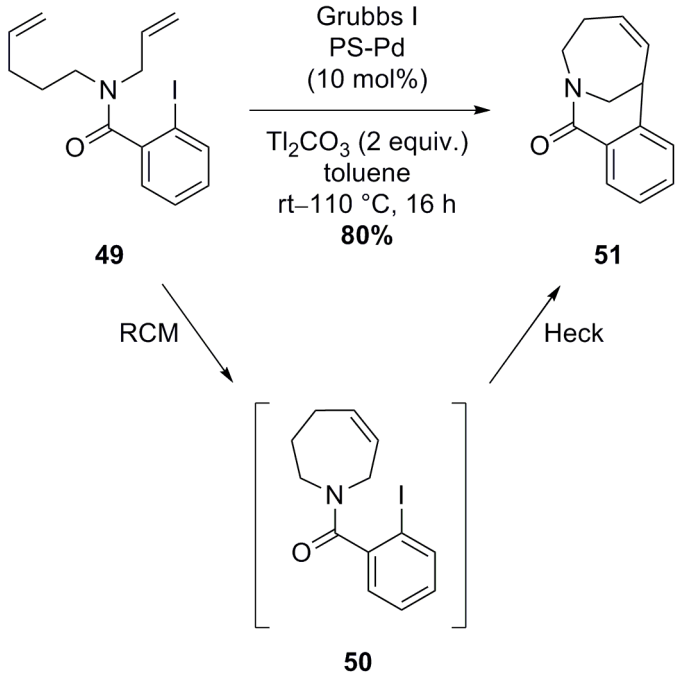


Figure 2: Products from a double allylic alkylation/RCM reaction

1.4.2 Ring-closing metathesis/Heck reaction

Catalyst compatibility can be a major issue when designing a tandem process that involves two different catalysts. To avoid this issue, Grigg and co-workers utilised a solid supported palladium catalyst along with Grubbs 1st generation catalyst in a tandem ring-closing metathesis/Heck reaction.[50] The palladium catalyst required for the Heck reaction was encapsulated within a polystyrene support, which swelled upon heating giving the substrate access to the catalyst. The RCM reaction of diene **49** with Grubbs 1st generation catalyst was initially stirred at room temperature, followed by heating of the reaction mixture to 110 ^{o}C to allow access of the RCM product **50** to the palladium catalyst within the support for the Heck reaction. The tricyclic product **51** was isolated in 80% yield (Scheme 27). It was noted in the paper that, for the example shown below, direct reaction of diene **49** with Grubbs 1st generation catalyst, palladium acetate and triphenylphosphine, resulted in no formation of the desired tricyclic product **51** and only the Heck coupled product was isolated. This was attributed to poisoning of the Grubbs catalyst by the palladium species

within the reaction mixture. It was shown that phosphine ligands in particular significantly slow down the RCM reaction by binding to the catalyst.



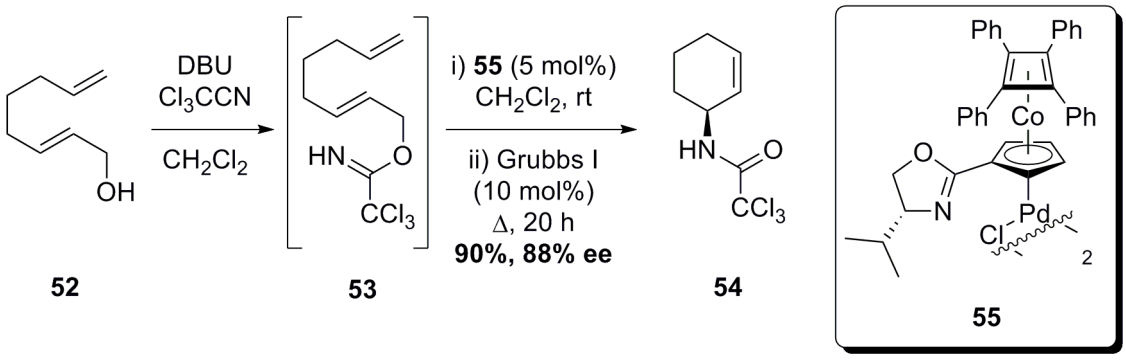
Scheme 27: Tandem RCM/Heck reaction

As seen previously, compatibility issues can also be overcome by adding the catalysts sequentially to the reaction mixture. By allowing the first catalytic process to run to completion, the second process can be initiated by a second fresh catalyst, thus reducing the time that both catalysts are present together in the reaction mixture. This approach can be useful when carrying out an asymmetric catalytic process. Most metal-catalysed asymmetric reactions rely on chiral ligands to create the chiral environment in which a reaction can occur selectively. The co-habitation of a chiral metal catalyst with another metal catalyst can result in ligand competition between metal centres, which can lead to an unpredictable chiral environment and ultimately reduce chiral induction.[51]

1.4.3 Overman rearrangement/Ring-closing metathesis

In 2007, Swift and Sutherland utilised a one-pot asymmetric Overman rearrangement/RCM reaction for the synthesis of cyclic allylic amide **54** in high enantiomeric excess (Scheme 28).[52] Starting from simple allylic alcohol **52**, treatment with DBU and trichloroacetonitrile formed the desired allylic trichloroacetimidate **53**. This intermediate then underwent an asymmetric Overman rearrangement catalysed by commercially available (*S*)-COP-Cl **55**,

followed by a RCM reaction of the resulting diene, catalysed by Grubbs 1st generation catalyst. The group had previously attempted to carry out the tandem process with both catalysts present from the outset, however, only the Overman rearrangement product was isolated, suggesting that the Grubbs catalyst had decomposed within the reaction mixture. By adding the Grubbs catalyst to the reaction mixture after the Overman rearrangement was complete, this issue could be avoided.[53]



Scheme 28: One-pot Overman rearrangement/Ring-closing metathesis

By altering the length of the carbon chain of the allylic alcohol starting material, the 5- and 7-membered rings could be formed using (*S*)-COP-Cl in excellent yield and high enantiomeric excess (Figure 3).[53] The group also illustrated that by using commercially available (*R*)-COP-Cl, the *R*-enantiomer of the product could be accessed in 75% yield and 88% enantiomeric excess.

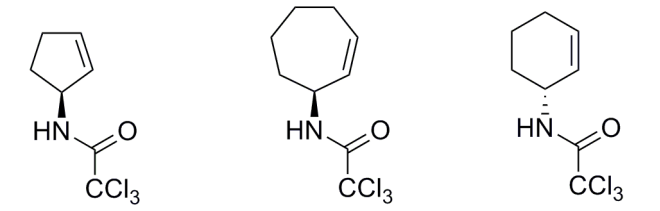
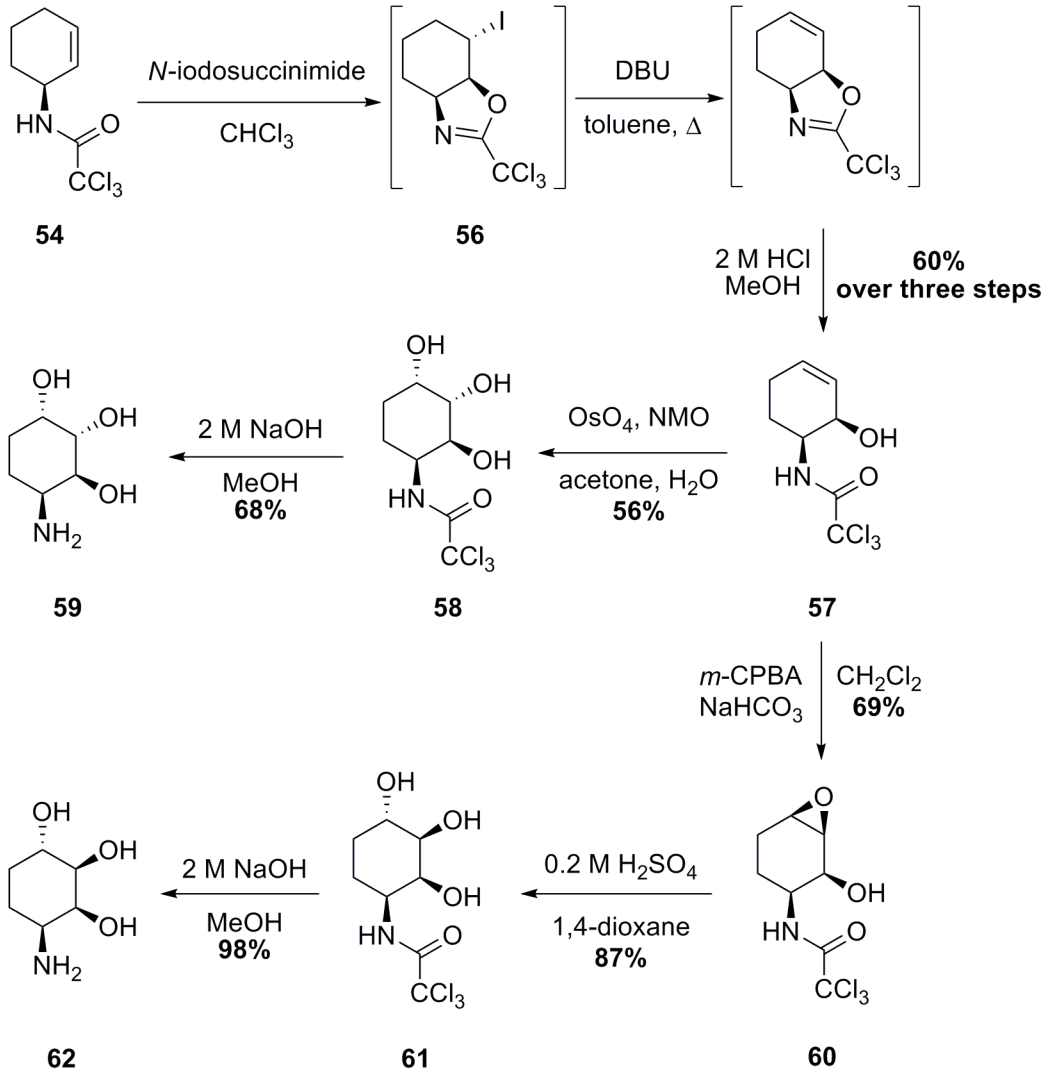


Figure 3: 5-, 6-, and 7-Membered analogues

The group went on to show that the 6-membered analogue could be further functionalised for the stereoselective synthesis of polyhydroxylated aminocyclohexanes.[54] Thus, reaction of cyclic amide **54** with *N*-iodosuccinimide formed the *syn*-bicyclic compound **56** (Scheme 29). Treatment of **56** with DBU followed by hydrolysis under acidic conditions formed the amino alcohol **57** in 60% yield over three steps. Treatment of **57** using standard Upjohn

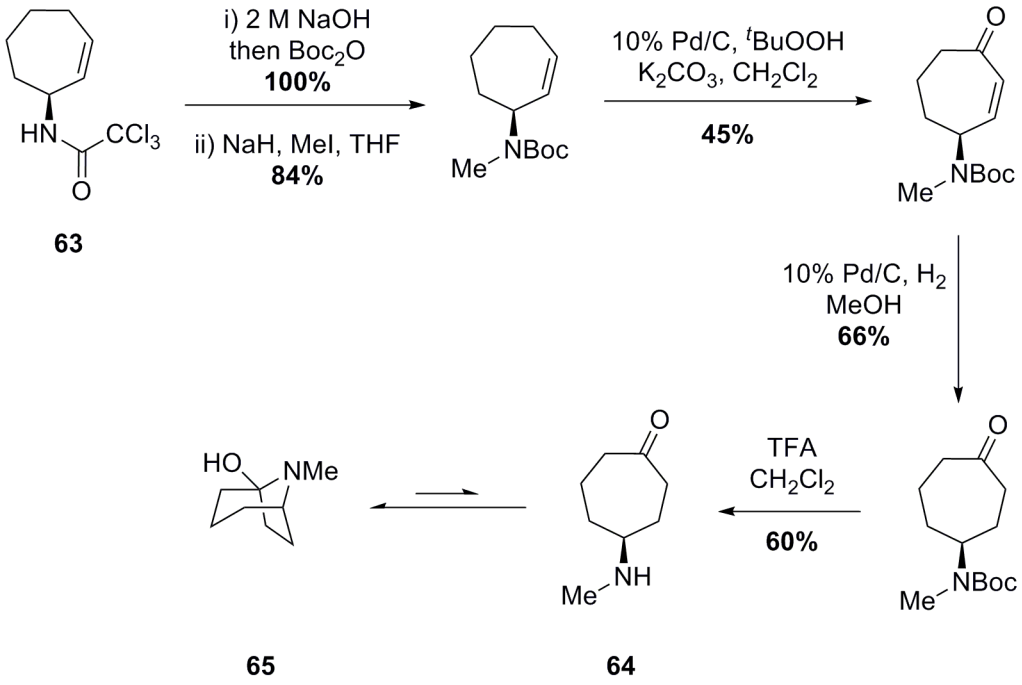
dihydroxylation conditions[55] afforded triol **58** as the sole product in 56% yield. Subsequent hydrolysis under basic conditions afforded the desired polyhydroxylated product **59** in 68% yield. Access to another diastereomer could also be achieved from amino alcohol **57**. Epoxidation of the double bond using *m*-CPBA, aided by a directing effect of the alcohol, formed the *syn*-epoxide **60** in 69% yield. Hydrolysis of the epoxide under acidic conditions affored the desired *anti*-3,4-diol **61** in 87% yield, which was deprotected under basic conditions to yield the desired product **62** in 98% yield.



Scheme 29: Functionalisation of cyclic allylic trichloroacetamide 54

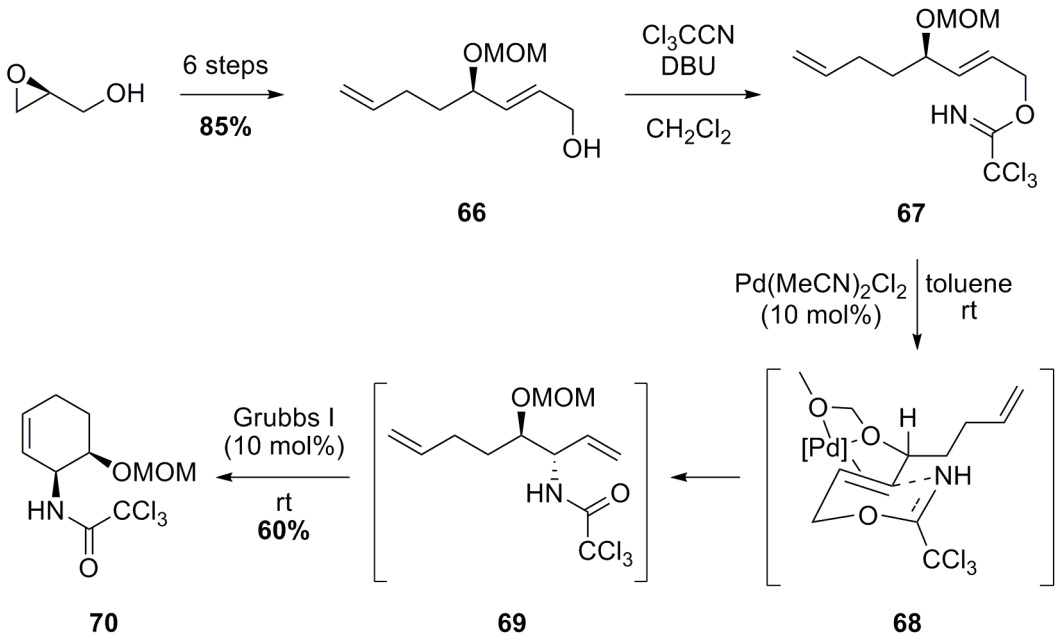
Using the 7-membered analogue **63**, this one-pot process has been utilised within the group in the total synthesis of the tropane alkaloid, (+)-physoperuvine **65** (Scheme 30).[56] Deprotection of substrate **63** under basic conditions followed by reprotection with Boc-anhydride was achieved in quantitative yield. Treatment with sodium hydride and methyl iodide introduced the required methyl moiety in 84% yield. Allylic oxidation using Pd/C

and *tert*-butyl hydroperoxide was carried out in 45% yield followed by selective hydrogenation of the alkene in 66% yield. Finally, removal of the Boc-protecting group formed the desired saturated product **64** in 60% yield, which exists almost entirely as its bicyclic tautomer **65**.



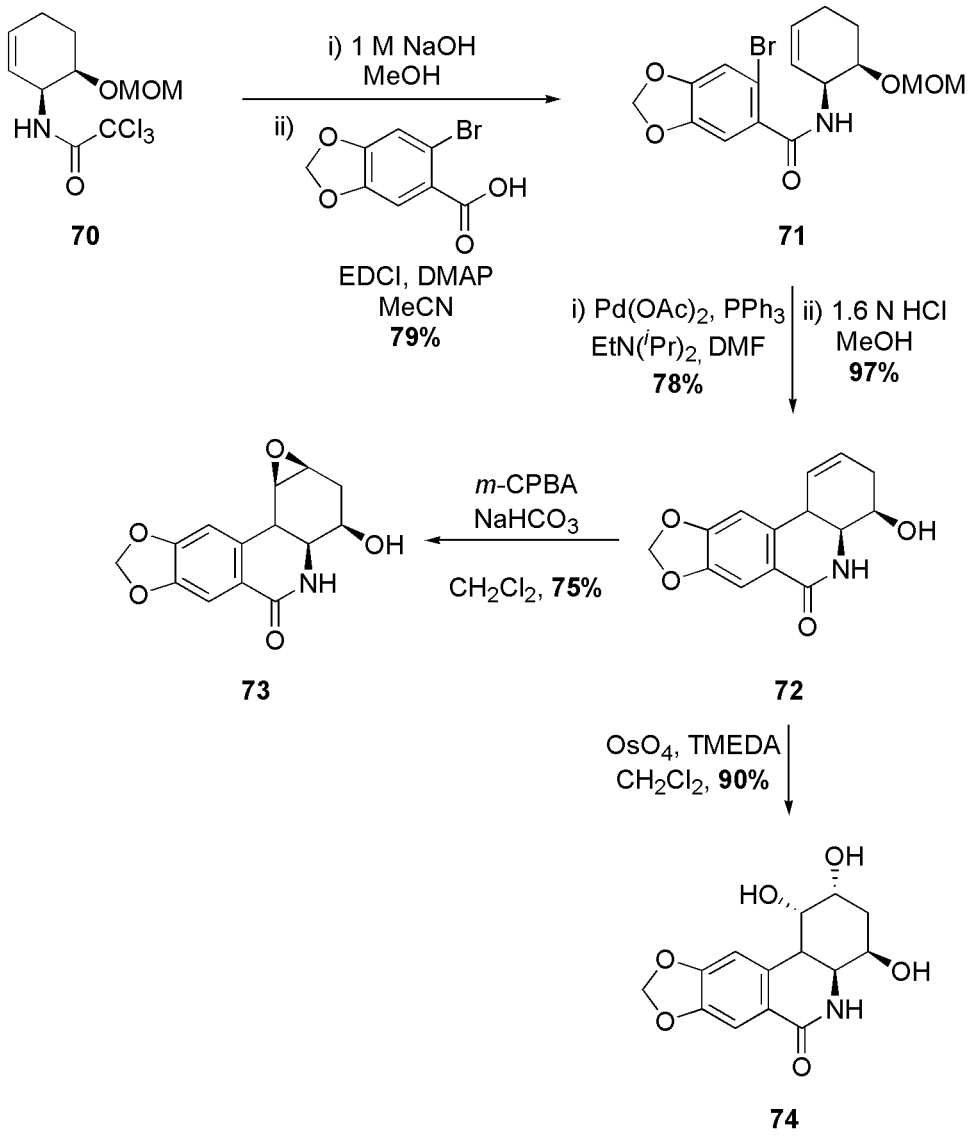
Scheme 30: Use of one-pot process in the total synthesis of (+)-physoperuvine

More recently, Sutherland and co-workers have utilised this tandem process to synthesise unnatural analogues of the Amaryllidaceae alkaloid, (+)-pancratistatin.[57] Within this work, the allylic trichloroacetamide product of the tandem process was synthesised in high diastereomeric excess by utilising a substrate-directed Overman rearrangement.[58] The MOM-ether allylic alcohol precursor **66** was synthesised in six high-yielding steps from (*S*)-glycidol and was subsequently converted into allylic trichloroacetimidate **67** as previously described (Scheme 31). In a one-pot process, allylic trichloroacetimidate was treated with an achiral palladium(II) catalyst to form amide **69** as a 10:1 ratio of diastereomers. Upon treatment of amide **69** with Grubbs 1st generation catalyst, cyclic allylic trichloroacetamide was formed as a 10:1 ratio of diastereomers, with the desired (1*R*,2*S*)-diastereomer **70** isolated in 60% yield from allylic alcohol **67**. The high diastereoselectivity can be explained by transition state **68** as coordination of palladium to the allylic double bond and the oxygen atoms of the MOM-ether lead to the preferential attack of the imidate nitrogen on the opposite face of the molecule and the formation of the *anti*- product **69**.



Scheme 31: MOM-ether directed tandem process

Cyclic trichloroacetamide **70** was subsequently deprotected and coupled with 6-bromopiperonylic acid and afforded amide **71** in 79% yield over two steps (Scheme 32). A Heck reaction proceeded in 78% yield followed by deprotection of the MOM-ether to form tetracyclic amide **72** in 97% yield. Finally, treatment of **72** with *m*-CPBA formed the *syn*-epoxide **73** in 75% yield. Alternatively, treating **72** with osmium tetroxide and TMEDA afforded diol **74** in 90% yield.



Scheme 32: Synthesis of unnatural pancratistatin analogues

1.5 Conclusion

The use of metathesis reactions, catalysed by Grubbs alkylidenes, has become a popular tool in organic synthesis for the formation of carbon-carbon double bonds. More recently, these metathesis catalysts have been found to catalyse a wide range of non-metathesis reactions including oxidations, reductions, cyclopropanations, as well as named processes including Wittig and Diels-Alder reactions. Furthermore, the combination of these novel uses in tandem with a metathesis reaction has become an active area of research and development, with many one-pot processes that utilise one catalyst to effect two mechanistically distinct processes being reported. These processes have huge environmental advantages as they allow the transformation of simple substrates into more complex products in a one-pot procedure without the need to isolate intermediates. This

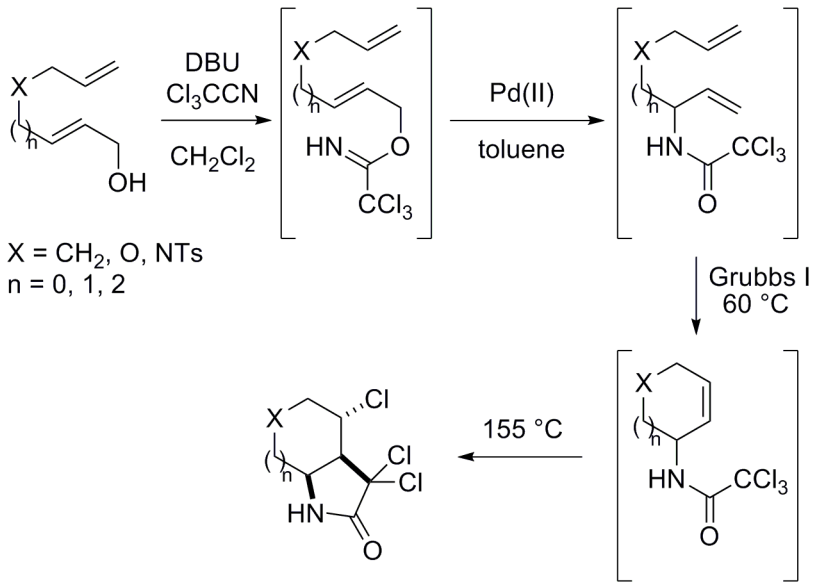
ultimately reduces the time taken to carry out the reactions, the solvent usage and the overall waste production for the tandem process.

2.0 Results and Discussion

2.1 Development of a novel tandem process for the stereoselective synthesis of bicyclic γ-lactams

2.1.1 Project Aims

The aim of this research programme was to develop a novel one-pot, three-step synthesis of bicyclic γ-lactams by utilising a palladium catalysed Overman rearrangement followed by a ruthenium catalysed RCM reaction and Kharasch cyclisation. As it has been shown that Grubbs catalyst can catalyse both the RCM reaction and Kharasch cyclisation steps,[22] this three-step process will be catalysed using two different catalysts in three separate catalytic cycles. Treatment of an allylic alcohol with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) will form the allylic trichloroacetimidate (Scheme 33). In the presence of a palladium(II) catalyst, this substrate can undergo an Overman rearrangement to form the allylic trichloroacetamide. A RCM reaction can then be carried out using Grubbs 1st generation catalyst at a temperature of 60 ºC, which when complete, will be increased to 155 ºC to initiate the ruthenium catalysed Kharasch cyclisation. Using this process, a small library of analogues will be investigated, namely by varying the length of the carbon chain to access different ring sizes and by incorporating oxygen and nitrogen into the carbon chain of the allylic alcohol to form heterocyclic analogues.

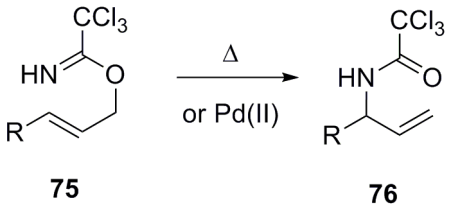


Scheme 33: Proposed tandem process for the synthesis of bicyclic γ-lactams

Due to the stereospecific nature of the Kharasch cyclisation followed by a stereoselective radical quenching by chlorine, the bicyclic γ-lactams should be obtained as single diastereomers using this process. The Overman rearrangement step will be key to the development of an asymmetric process. By utilising a chiral palladium catalyst, the allylic trichloroacetamide can be formed in high enantiomeric excess, which will allow access to enantiomerically enriched bicyclic γ-lactams from achiral starting materials.

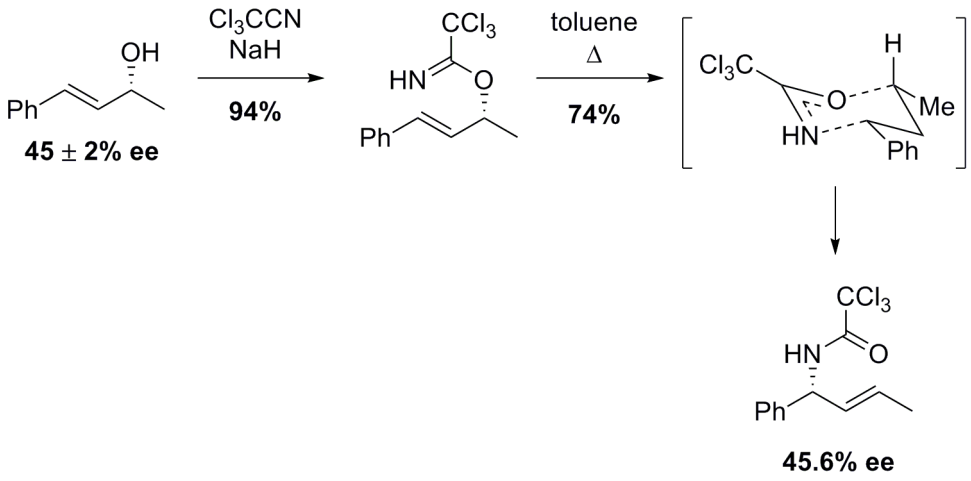
2.1.2 The Overman Rearrangement

The Overman rearrangement is the [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates **75** to form allylic trichloroacetamides **76** and was first reported in 1974 by Overman (Scheme 34).[59] The reaction has become a popular tool in organic synthesis for the formation of valuable amines from widely available alcohols. Furthermore, it can be performed under relatively mild conditions, either thermally or by metal catalysis with palladium(II) salts being the optimal catalysts for the transformation.[60]



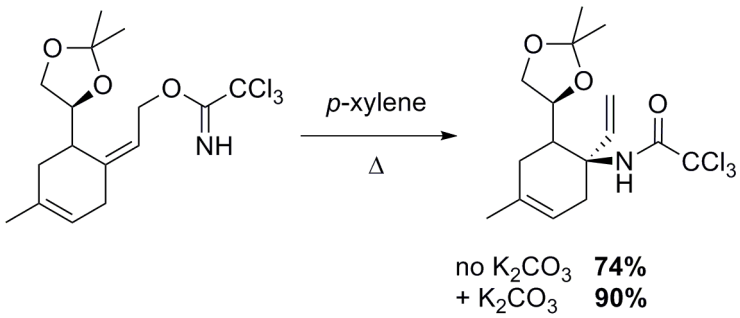
Scheme 34: The Overman rearrangement

The allylic trichloroacetimidate precursors required for the rearrangement are readily prepared by the treatment of an allylic alcohol with trichloroacetonitrile in the presence of a base, commonly sodium hydride[61] or DBU.[62] As with all sigmatropic rearrangements, the process is concerted and therefore highly stereoselective. In 1976, Shimoda and co-workers illustrated that complete chirality transfer from the carbon-oxygen bond to the newly formed carbon-nitrogen can be achieved and that the thermal process proceeds *via* a highly ordered transition state (Scheme 35).[63] By measuring the optical purity of the starting alcohol and comparing this with the optical purity of the amide product, the complete transfer of chirality was confirmed.



Scheme 35: Thermal Overman rearrangement

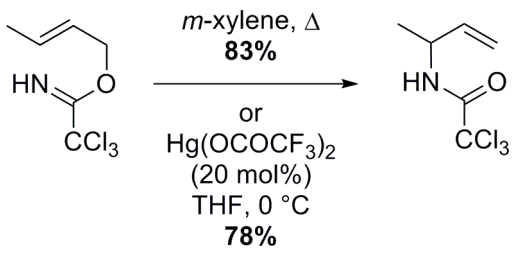
Thermal reactions are commonly carried out in xylenes at 140 ºC in the presence of potassium carbonate (2 mg/mL). Isobe and co-workers reported the beneficial addition of base to the thermal reaction in 1998 (Scheme 36).[64] They discovered that at elevated temperatures, acidic by-products were formed which could cause the decomposition of the allylic trichloroacetimidate starting material. By adding a base, they reported a significant increase in yield for a number of their complex targets, even on large-scale (~10 g) reactions.



Scheme 36: A thermal rearrangement in the absence and presence of base

The issue of decomposition can be further avoided by employing a metal salt to catalyse the transformation. These reactions can not only be carried out at or near room temperature, but the recent development of chiral palladium catalysts to effect the rearrangement means access to enantiomerically enriched products can be achieved from racemic allylic trichloroacetimidates.[65]

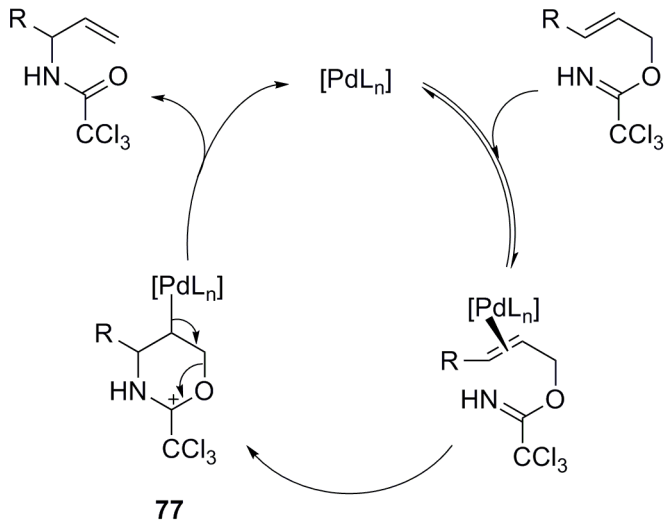
The use of mercury salts to effect the sigmatropic rearrangement was reported in the original publication by Overman and co-workers (Scheme 37).[59] They observed a dramatic increase in reaction rate (by a factor $>10^{12}$) for the rearrangement in the presence of catalytic mercuric trifluoroacetate and that the reaction could be carried out at 0 ºC without significant loss of yield in many cases.[61]



Scheme 37: Overman rearrangement catalysed by mercury(II)

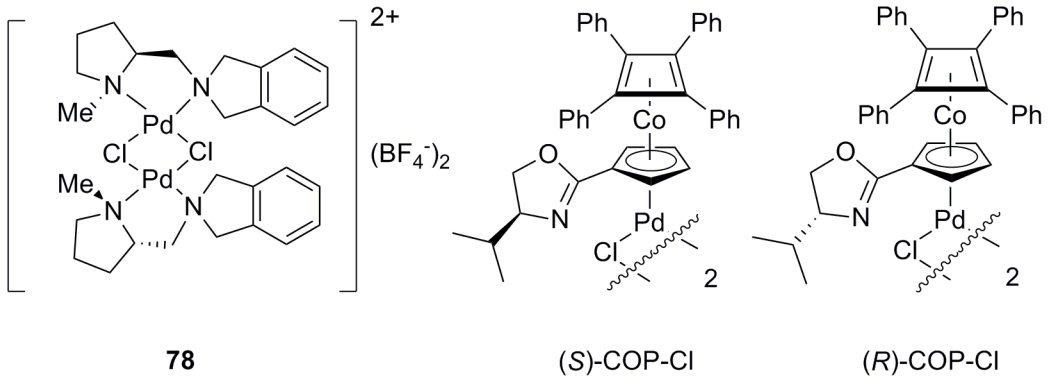
Following on from Overman's original study, other metals were found to be effective, and complexes of palladium(II) such as $Pd(MeCN)_2Cl_2$ and $Pd(PhCN)_2Cl_2$ have become the most commonly employed catalysts for the Overman rearrangement.[66]

The mechanism for the palladium(II) catalysed rearrangement is believed to occur *via* a 6-membered transition state (Scheme 38).[67] Co-ordination of the palladium to the alkene is followed by intramolecular attack by the imidate nitrogen to form a cationic intermediate **77**. Collapse of this 6-membered ring occurs rapidly, to form the stable C=O bond, the alkene and regenerates the active catalyst.



Scheme 38: Mechanism of the metal-catalysed Overman rearrangement

The use of a metal-catalysed rearrangement opened the field to the development of an asymmetric process, as the coordination of a metal catalyst bearing a chiral ligand can block the imidate attack on one face of the alkene. Early attempts at designing a chiral palladium(II) catalyst were found to be unsuitable for the rearrangement of allylic trichloroacetimidates. It was reasoned that the basic imidate nitrogen could coordinate with the cationic palladium centre of **78** (Figure 4), thus encouraging the elimination of trichloroacetamide from the molecule.[68] In 2003, Overman reported the use of COP-Cl catalysts, which were found to be more successful, and today (*S*)-COP-Cl and (*R*)-COP-Cl are commercially available.[65]



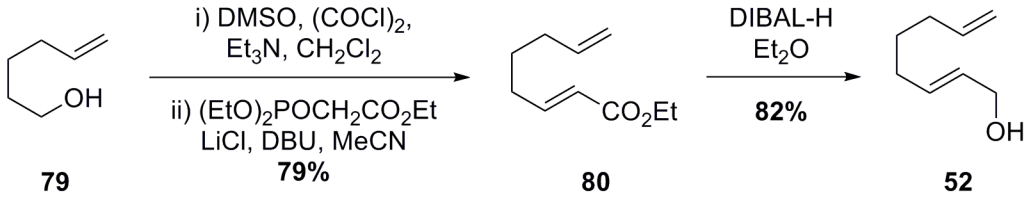
78 (*S*)-COP-Cl (*R*)-COP-Cl

Figure 4: Structures of the first asymmetric catalyst 78 and COP-Cl catalysts

For this research project, it was proposed that the novel tandem process would initially be developed using an achiral palladium(II) catalyst before utilising the COP-Cl catalysts for the synthesis of enantiomerically enriched bicyclic γ-lactams.

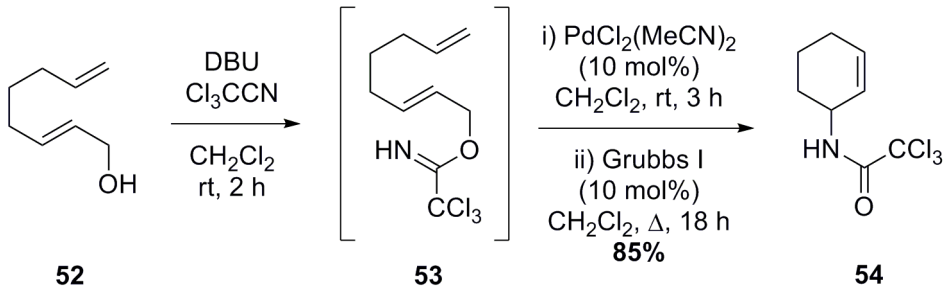
2.1.3 Development of the tandem process for the 5,6-bicyclic lactam

The first stage in the development of a novel one-pot, three-step tandem process was the synthesis of the allylic alcohol precursor. It was envisaged that the desired allylic alcohol could be accessed quickly from 5-hexen-1-ol **79**. In the event, a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction,[69,70] using the mild Masamune-Roush conditions,[71] afforded the (*E*)-α,β-unsaturated ester **80** in good yield (Scheme 39). The *E*-geometry of the alkene was confirmed by ^{1}H NMR spectroscopy with a coupling of 15.7 Hz between the protons across the double bond. The ester was then reduced using 2.2 equivalents of DIBAL-H forming the desired allylic alcohol **52** in 82% yield.



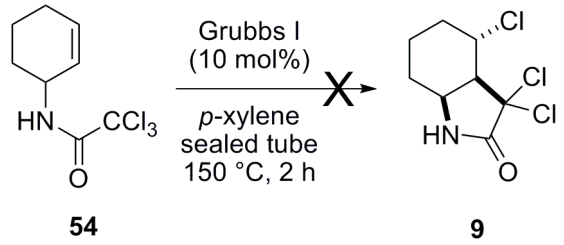
Scheme 39: Synthesis of the allylic alcohol precursor

The second stage was to optimise reaction conditions for the one-pot Overman rearrangement/RCM/Kharasch cyclisation. As the tandem Overman rearrangement/RCM reaction had previously been optimised within the Sutherland group, initial work looked at optimising the Kharasch cyclisation of amido-substituted cyclohexene **54** to form the desired bicyclic γ-lactam **9** in isolation. Thus, amide **54** was synthesised according to the procedure previously reported by Swift and Sutherland (Scheme 40).[52] Treatment of allylic alcohol **52** with trichloroacetonitrile in the presence of DBU formed allylic trichloroacetimidate **53**, which was then subjected to a tandem Overman rearrangement/RCM reaction affording trichloroacetamide **54** in 85% yield over three steps.



Scheme 40: Preparation of amido-substituted cyclohexene 54

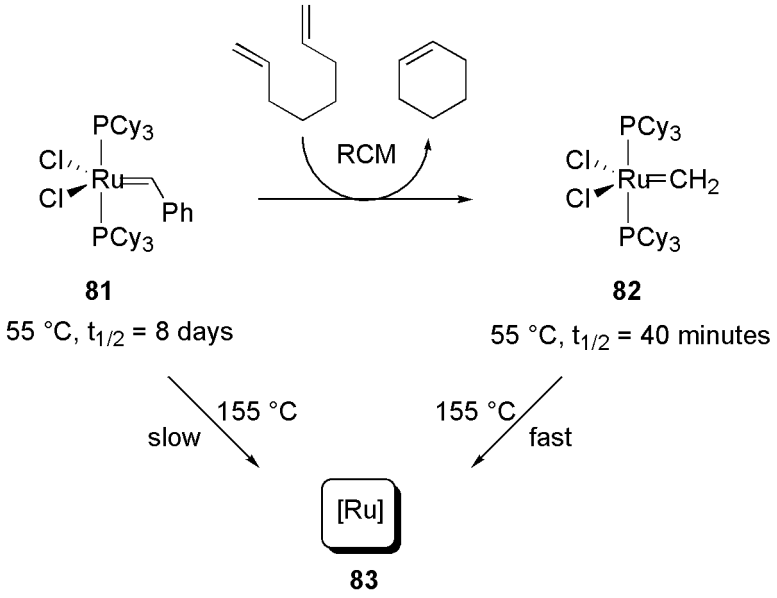
The conditions reported by Itoh and co-workers,[20] in combination with Grubbs 1st generation catalyst, were initially utilised to carry out the Kharasch cyclisation of allylic trichloroacetamide **54**. In the event, no Kharasch product was observed and only starting material was recovered (Scheme 41).



54 **9**

Scheme 41: Failed attempt of an isolated Kharasch cyclisation

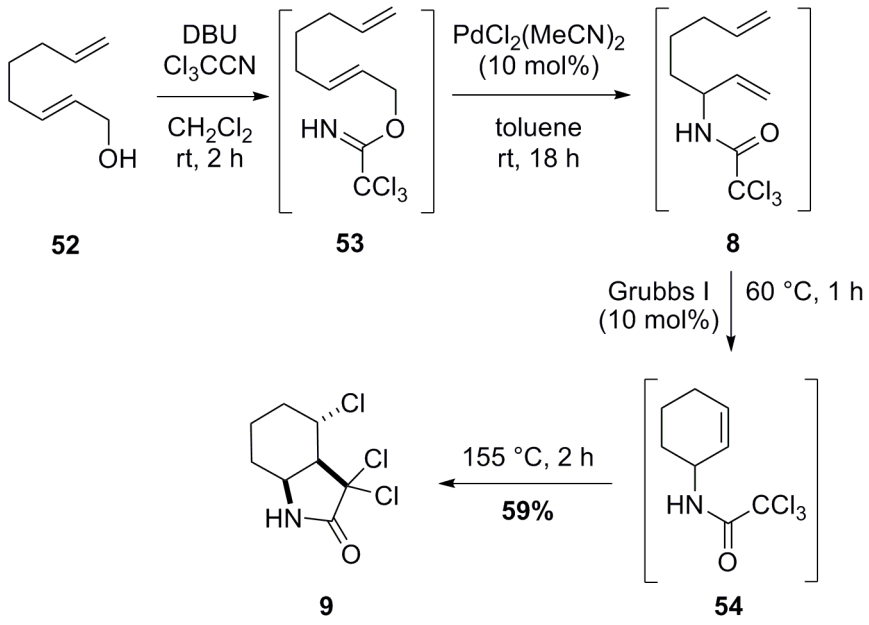
A possible reason for this may be due to the direct modification of the stable Grubbs 1st generation catalyst to the Kharasch active catalyst being too slow within the timeframe of the reaction to initiate the radical cyclisation. Grubbs and co-workers reported that the half-life of Grubbs 1st generation catalyst **81** is 8 days at 55 ºC whereas the half-life of the active ruthenium methylidene **82** formed during the RCM reaction is only 40 minutes at 55 ºC (Scheme 42).[72] Furthermore, Quayle and co-workers postulated that the active ruthenium catalyst **83** (of which the exact structure remains elusive) for the Kharasch cyclisation was formed from the decomposition of Grubbs catalyst;[23] which, based on the half lives stated, would occur more rapidly from the ruthenium methylidene **82** rather than from the more stable benzylidene **81**.



Scheme 42: Grubbs complexes for RCM and the Kharasch cyclisation

The tandem process developed by Snapper and co-workers supports this theory.[22] They showed that Grubbs catalyst could effect the Kharasch cyclisation in under 2 h at 155 ºC after being utilised in a RCM reaction (*c.f.* Scheme 8). Thus, the subsequent optimisation of

conditions for the Kharasch cyclisation, as well as for the complete tandem process, was carried out from the allylic alcohol precursor **52** (Scheme 43). Conversion of allylic alcohol **52** to allylic trichloroacetimidate **53** occurred readily at room temperature as previously described. Removal of dichloromethane was necessary at this point as the later stages of the tandem process require high temperatures to proceed. The crude trichloroacetimidate was dissolved in toluene and transferred to a Schlenk tube. Treatment with (bisacetonitrile)dichloropalladium(II) to effect the Overman rearrangement proceeded cleanly overnight at room temperature to form diene **8**. Grubbs 1st generation catalyst was then added to the reaction mixture and subsequently heated to 60 ºC for 1 h in order for the RCM reaction to take place. Once cyclic compound **54** had formed, the temperature was increased to 155 ºC for 2 h without addition of any further catalyst or reagent. Gratifyingly, the desired 5,6-bicyclic lactam was afforded in 59% yield as a single diastereomer. It is worth noting that the progress of each stage of the tandem process was monitored primarily using ^{1}H NMR spectroscopy (Figure 5).



Scheme 43: Initial attempts at performing the 3-step tandem process

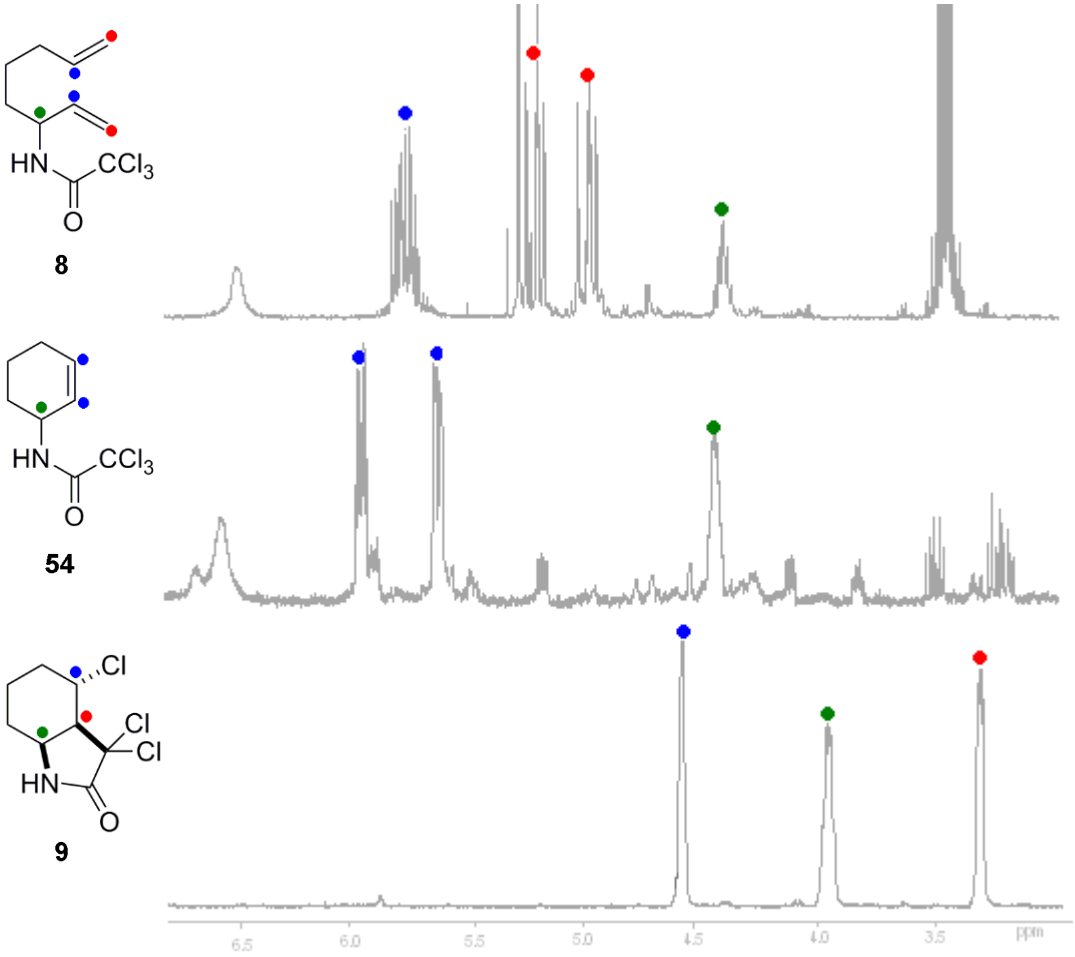
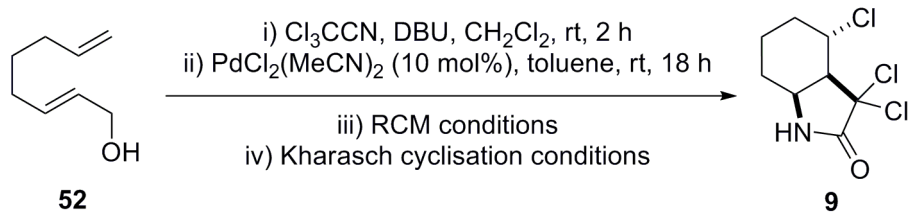


Figure 5: ^{1}H NMR spectra of crude rearrangement product 8, crude RCM product 54 and 5,6-bicyclic lactam 9

Although the ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the desired bicyclic product **9**, a significant amount of RCM product **54** was also visible and isolated as the major by-product during purification. This indicated that the final step of the tandem process had not gone to completion and there was the potential to increase the overall yield of product further (Table 1). By adding an extra quantity of Grubbs 1st generation catalyst (5 mol%) to the reaction mixture at the start of the Kharasch cyclisation step, the yield of bicyclic lactam was increased to 73% (entry 2). A comparable yield was further achieved without the need to add more catalyst, by carrying out the RCM reaction at room temperature (entry 3). The reduced temperature may prolong the lifetime of the activated catalytic intermediate. Previous work in the group had shown that molecular sieves may have a beneficial role as acid scavengers within a Kharasch cyclisation.[73,74] At such high temperature, it is possible that hydrochloric acid (HCl) could form from the decomposition of substrate **54** (or product **9**). This could in turn, cause further decomposition resulting in lower yields of the desired product. This beneficial action of the molecular sieves can be seen in entry 4 of Table 1, where addition during the RCM step of

the tandem process lead to the formation of the desired bicyclic γ-lactam **9** in 87% yield. It is worth noting that this yield of 87% for product **9** was achieved from allylic alcohol **52** *via* four chemical transformations (three of which are performed within a one-pot process) and is higher than the yield obtained by Snapper and co-workers (85%) for the synthesis of the same compound *via* a two-step tandem process.[22]



52 **9**

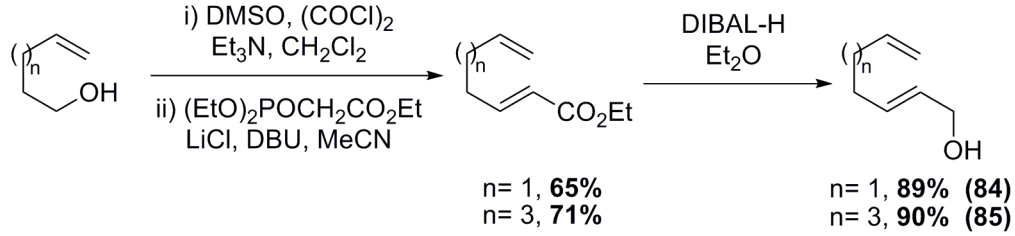
Entry	RCM reaction	Kharasch cyclisation	% yield of bicyclic lactams
1	Grubbs I (10 mol%), 60 ºC, 1 h	155 ºC, 2 h	59%
2	Grubbs I (10 mol%), 60 ºC, 1 h	155 ºC, 2 h[a]	73%
3	Grubbs I (10 mol%), rt, 1 h	155 ºC, 2 h	71%
4	Grubbs I (10 mol%), rt, 1 h[b]	155 ºC, 2 h	87%

[a] 5 mol% Grubbs I catalyst added. [b] 4 Å molecular sieves added.

Table 1: Optimisation of reaction conditions for the synthesis of 5,6-bicyclic γ-lactam 9

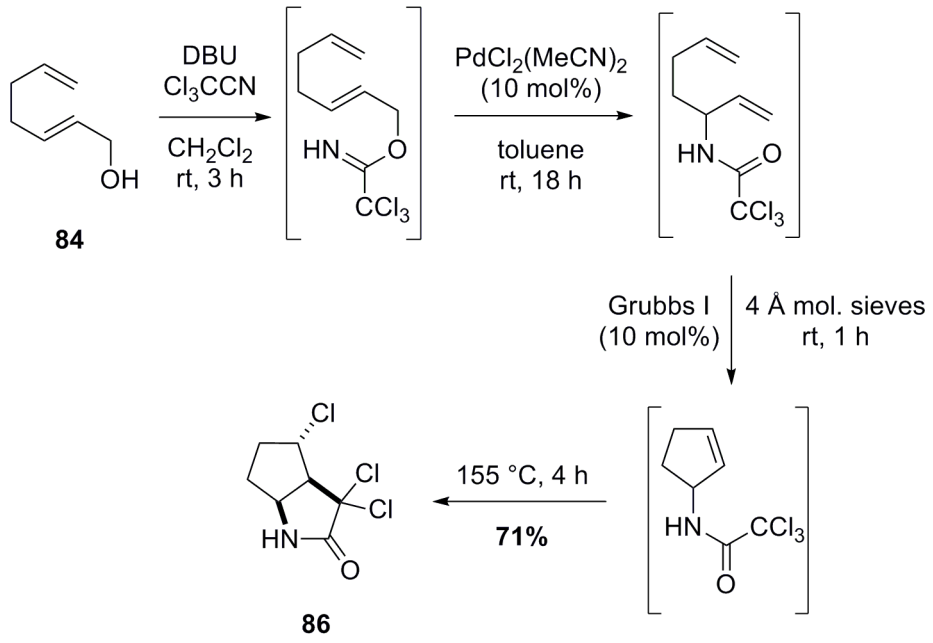
2.1.4 Application of the tandem process for the synthesis of the 5,5- and 5,7-bicyclic γ-lactams

With conditions optimised for the synthesis of the 5,6-bicyclic γ-lactam, attention was then turned to the synthesis of the 5,5- and 5,7-analogues. The allylic alcohol precursors for these analogues were prepared in good yields from the corresponding primary alcohols using a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction followed by a DIBAL-H reduction (Scheme 44).



Scheme 44: Synthesis of allylic alcohol precursors for the 5,5- and 5,7-bicyclic lactams

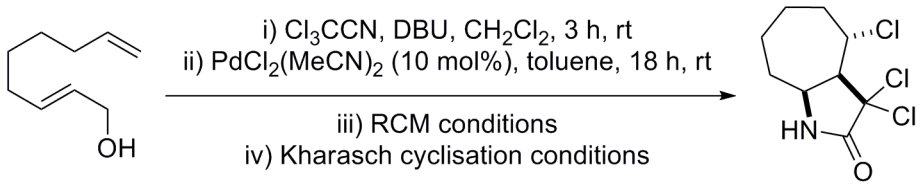
Initially, the optimised conditions developed above were applied directly to the diastereoselective synthesis of the 5,5-bicyclic γ-lactam from allylic alcohol **84**. This however, yielded only 22% of the desired product, with the RCM product identified as the major by-product in the crude reaction mixture. To overcome this and push the reaction to completion, the time for the Kharasch cyclisation step was increased from 2 h to 4 h. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy identified minimal amounts of RCM product and the desired bicyclic product was isolated in an improved 53% yield. Analysis of the reaction mixture throughout the one-pot process, however, had identified that the formation of the allylic trichloroacetimidate had not gone to completion after 2 h, resulting in a lower yield of product. By extending the trichloroacetimidate formation to 3 h, followed by the Overman rearrangement, RCM reaction and Kharasch cyclisation, the desired 5,5-bicyclic γ-lactam **87** was afforded in 71% yield (Scheme 45).



Scheme 45: Optimised conditions for the synthesis of 5,5-bicyclic γ-lactam 86

Attention then moved to the synthesis of the 5,7-bicyclic γ-lactam using allylic alcohol **85**. For this example, the optimal conditions for the 5,5-bicyclic γ-lactam **86** were used as the starting point, however only 21% of desired bicyclic product was isolated (Table 2, entry 1). The synthesis of the 5,7-analogue proved more difficult to optimise than for the smaller ring sizes. Previous work in the group had shown that the RCM reaction for the formation of the 7-membered ring was most successfully achieved under dilute reaction conditions.[52] As a result of reducing the concentration of the reaction mixture, longer reaction times were required, but a significant improvement in yield was achieved (entry 2). It is worth

noting that both the trichloroacetimidate formation and the Overman rearrangement were carried out at a concentration of 0.07 M as in the previous examples. Once the rearrangement was complete, more toluene was added to the reaction mixture thus reducing the concentration (0.005–0.009 M) in preparation for the RCM step. By increasing the loading of Grubbs 1st generation catalyst and extending the reaction time for the Kharasch cyclisation step a moderate increase in yield was observed (entry 3). As for the previous two analogues, molecular sieves were added during the RCM step. However, due to the increase in time for the RCM step as a result of reducing the concentration of the reaction mixture, the possibility of the molecular sieves interacting with the Grubbs catalyst became a factor with unknown consequences. Thus, as the molecular sieves were only needed for the Kharasch cyclisation, their addition after the RCM step allowed the completion of the final step in only 2 h. This suggested that adverse interaction of the molecular sieves with the catalyst may have occurred. In this instance the desired product **87** was isolated in a significantly improved 60% yield (entry 4).



85 **87**

Entry	Reaction concentration	RCM reaction	Kharasch cyclisation	% yield of bicyclic lactams
1	0.07 M	Grubbs I (10 mol%), rt, 1 h[a]	155 ºC, 4 h	21%
2	0.005 M	Grubbs I (15 mol%), 50 ºC, 96 h[a]	155 ºC, 4 h	32%
3	0.009 M	Grubbs I (20 mol%), 50 ºC, 96 h[a]	155 ºC, 5 h	37%
4	0.009 M	Grubbs I (25 mol%), 50 ºC, 120 h	155 ºC, 2 h[a]	60%

[a] 4 Å molecular sieves added.

Table 2: Optimisation of reaction conditions for the synthesis of 5,7-bicyclic γ-lactam 87

This completed the synthesis of the carbon analogues with varying ring sizes. It was previously proposed that due to the selective nature of the Kharasch cyclisation, this racemic synthesis would afford the bicyclic lactams as single diastereomers. In order to confirm this, nOe studies were carried out using 5,7-analogue **87**. Irradiation of H-1 showed a positive nOe signal with the adjacent H-7 but no signal was observed with H-6.

This illustrates the *syn* relationship between H-1 and H-7 and the *anti* relationship between H-1 and H-6 (Figure 6).

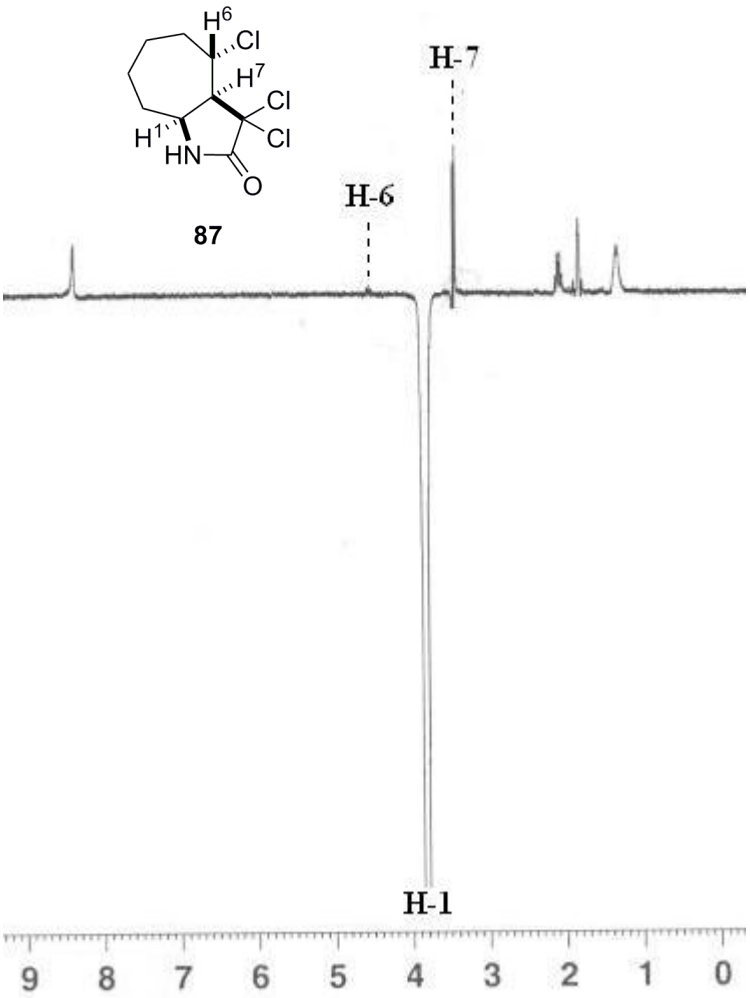


Figure 6: 1-D nOe spectrum of 5,7-bicyclic lactam 87

2.1.5 Synthesis of the oxy- and aza-5,6-bicyclic γ-lactams

Focus then moved to the incorporation of a heteroatom into the 6-membered ring fused to the γ-lactam. Both oxygen and nitrogen analogues were investigated (Figure 7), with the first stage of the development being the synthesis of the allylic alcohol precursors.

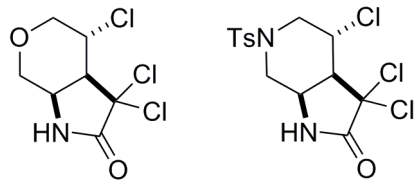
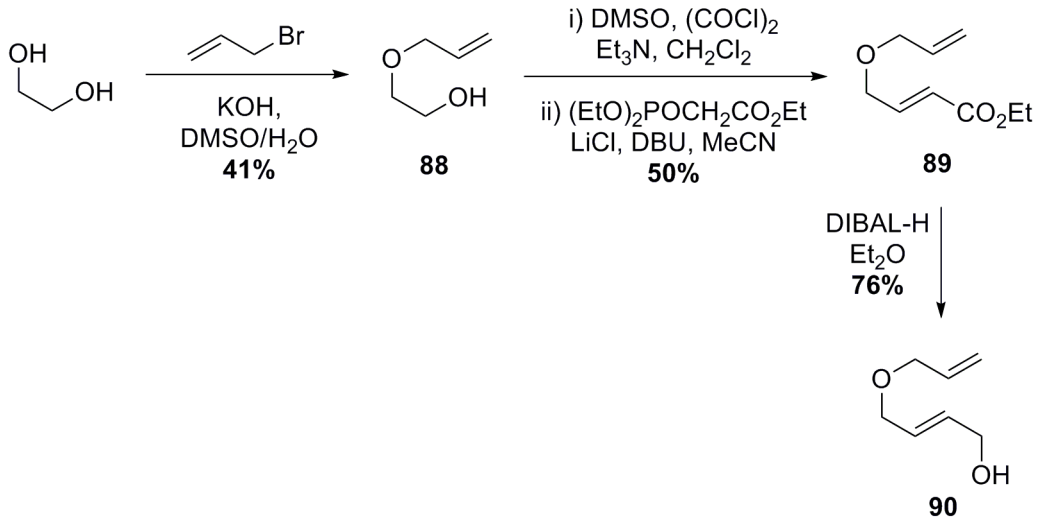


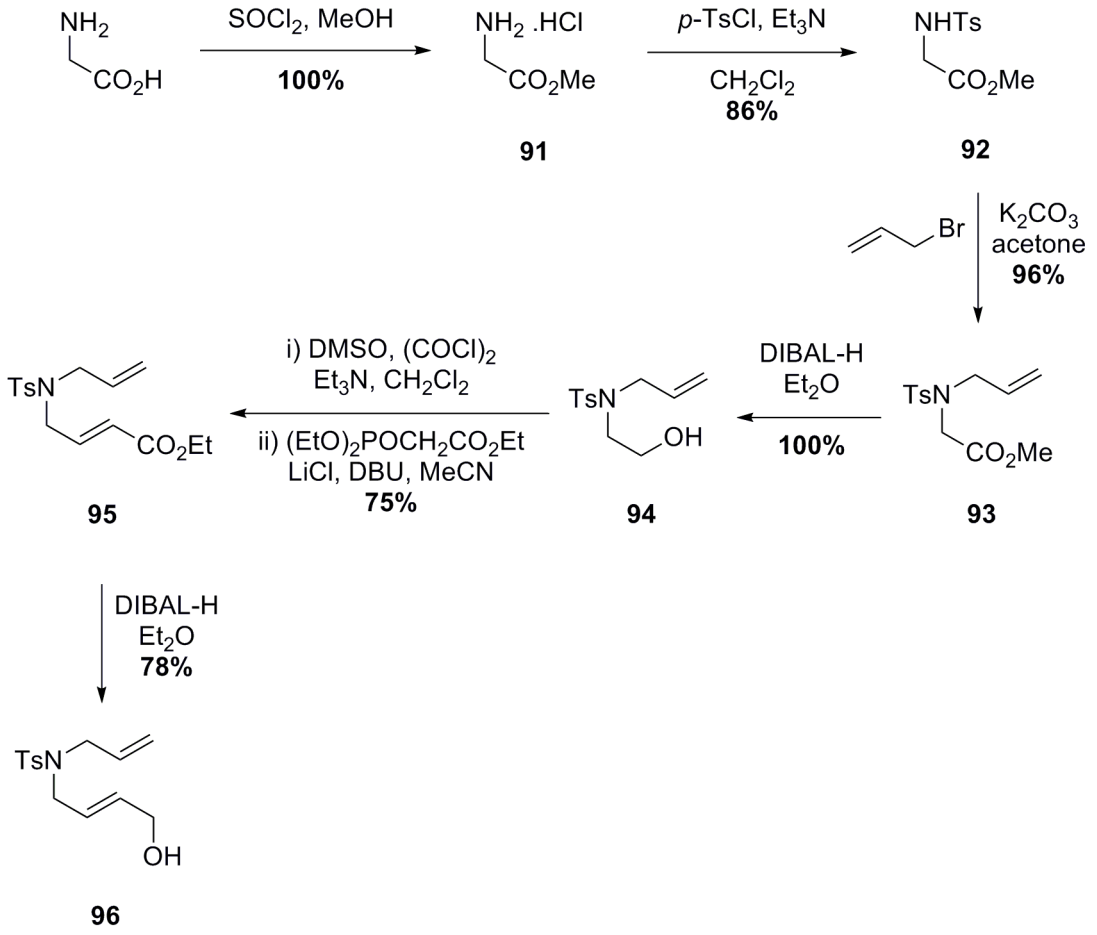
Figure 7: Structures of the oxygen- and nitrogen bicyclic lactam analogues

Starting from ethylene glycol, treatment with allyl bromide in the presence of potassium hydroxide afforded the mono-allylated product **88** in a 41% yield (Scheme 46). No double allylation product was detected in the ^{1}H NMR spectrum so the modest yield may be attributed to the volatility of the product. Alcohol **88** then underwent a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction to afford (*E*)-α,β-unsaturated ester **89** in 50% yield. Reduction of the ester moiety using DIBAL-H afforded the desired allylic alcohol precursor **90** in 76% yield.



Scheme 46: Preparation of the oxy-allylic alcohol precursor 90

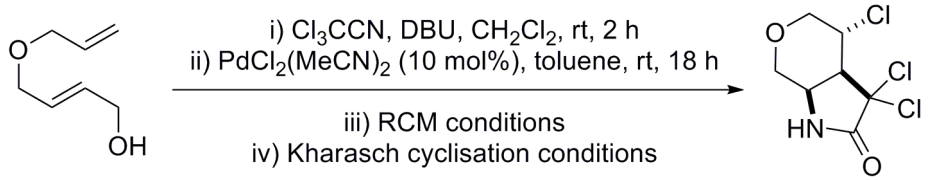
For the synthesis of the aza-allylic alcohol precursor, glycine was converted into glycine methyl ester hydrochloride **91** in a quantitative yield, using thionyl chloride in methanol (Scheme 47). Treatment of **91** with tosyl chloride and triethylamine afforded tosyl-protected amino ester **92** in 86% yield. The required allyl side chain was introduced using allyl bromide and potassium carbonate, forming alkylated product **93** in 96% yield. DIBAL-H reduction of the methyl ester afforded alcohol **94** in a quantitative yield, which was then subjected to a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction to form (*E*)-α,β-unsaturated ester **95** in a 75% yield. Finally, this compound underwent DIBAL-H reduction, with the desired allylic alcohol precursor **96** isolated in a 78% yield.



Scheme 47: Synthesis of aza-allylic alcohol precursor 96

The optimised conditions for the all-carbon 5,6-analogue **9** were used as the initial conditions for the synthesis of the oxygen-containing analogue. In the event, this failed to yield any of the desired oxy-5,6-bicyclic lactam **97** (Table 3, entry 1). By following the tandem process using ^{1}H NMR spectroscopy, it was observed that although the palladium(II) catalysed Overman rearrangement was proceeding as expected, the RCM step was not complete after 1 h at room temperature and so further investigation and optimisation was required as shown in Table 3. Increased loading of Grubbs 1st generation catalyst to 15 mol% with heating over three days was necessary for the complete conversion of the RCM step. The subsequent Kharasch cyclisation afforded the desired bicyclic lactam **97** in 23% yield (entry 2). Changing to Grubbs 2nd generation catalyst saw a dramatic reduction in time to 4 h for the RCM step, however only a modest increase in yield was observed (entry 3). As for the 5,7-analogue **87**, the RCM step was requiring more time and so the addition of the molecular sieves was delayed until after this step was completed. This again resulted in a modest increase in yield (entry 4). At this point, it was proposed that the presence of the allyl ether within the substrate could be coordinating with

the palladium(II) catalyst, which was present in the reaction mixture from the previous step of the tandem process. The palladium complexed allyl ether would therefore be less reactive towards Grubbs catalyst and thus hinder the RCM step. It was envisaged that by employing a thermal Overman rearrangement, the use of palladium(II) catalyst could be avoided which would hopefully benefit the subsequent steps of the tandem process. In the event, the thermal rearrangement proceeded cleanly and the subsequent RCM step was complete after 4 h at ambient temperature, with the desired bicyclic lactam being isolated in a significantly improved 52% yield (entry 5).



90 **97**

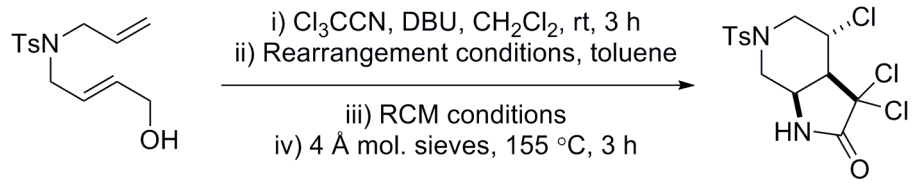
Entry	RCM reaction	Kharasch cyclisation	% yield
1	10 mol%,[a] rt, 1 h[b]	155 °C, 2 h	no product
2	15 mol%,[a] 30–60 °C, 72 h[b]	155 °C, 3 h	23%
3	10 mol%,[c] 70 °C, 4 h[b]	155 °C, 3 h	28%
4	10 mol%,[c] 70 °C, 4 h	5 mol%,[c] 155 °C, 3 h[b]	36%
5[d]	15 mol%,[a] rt, 4 h	155 °C, 3 h[b]	52%

[a] Grubbs I catalyst. [b] 4 Å molecular sieves added. [c] Grubbs II catalyst. [d] Thermal rearrangement used: K_2CO_3, toluene, 140 °C, 18 h.

Table 3: Optimisation of the synthesis of oxy-5,6-bicyclic lactam 97

The optimised conditions for the 5,6-bicyclic lactam **9** were also used as the starting point for the nitrogen analogue. Unfortunately, like the oxygen analogue, no desired product was apparent in the crude reaction mixture (Table 4, entry 1). Using ^{1}H NMR spectroscopy to analyse each step of the tandem process, it was observed that the Overman rearrangement was causing difficulties. A higher loading of palladium(II) catalyst, prolonged reaction times and higher temperatures were required to push the rearrangement to completion. The subsequent RCM reaction also proved sluggish and after the Kharasch cyclisation was complete, only 10% of the desired product was isolated (entry 2). Increasing catalyst loading and temperature for the RCM step gave a modest increase in yield of product (entry 3). At this point, it was proposed that coordination of the palladium(II) catalyst to the substrate could be occurring in a similar manner to the oxygen analogue. In this instance, it

was not only the presence of the allyl amine in the substrate that could coordinate to the metal, but also the sulfone in the tosyl protecting group. This would account for the dramatic change in reactivity observed for this particular substrate as the catalyst is no longer able to participate. This would also cause a subsequent effect to the RCM step, which is evident in entries 2 and 3 of table 4. With the implementation of a thermal Overman rearrangement being so effective for the oxygen analogue, it was envisaged that this too could be used to overcome the issues with the nitrogen analogue. Gratifyingly, the thermal Overman rearrangement proceeded cleanly, although six days were required for the reaction to go to completion. The advantage of using the thermal reaction, however, was that the subsequent RCM step proceeded smoothly in 1 h at room temperature and overall the desired bicyclic lactam **98** was isolated in a vastly improved 39% yield (entry 4).



96 **98**

Entry	Overman rearrangement	RCM reaction	% yield
1	10 mol%,[a] rt, 16 h	10 mol%,[b] rt, 1 h	no product
2	20 mol%,[a] 50 °C, 40 h	15 mol%,[b] rt-60 °C, 24 h	10%
3	20 mol%,[a] 70 °C, 20 h	20 mol%,[b] 70 °C, 20 h	19%
4	K_2CO_3, 140 °C, 136 h	15 mol%,[b] rt, 1 h	39%

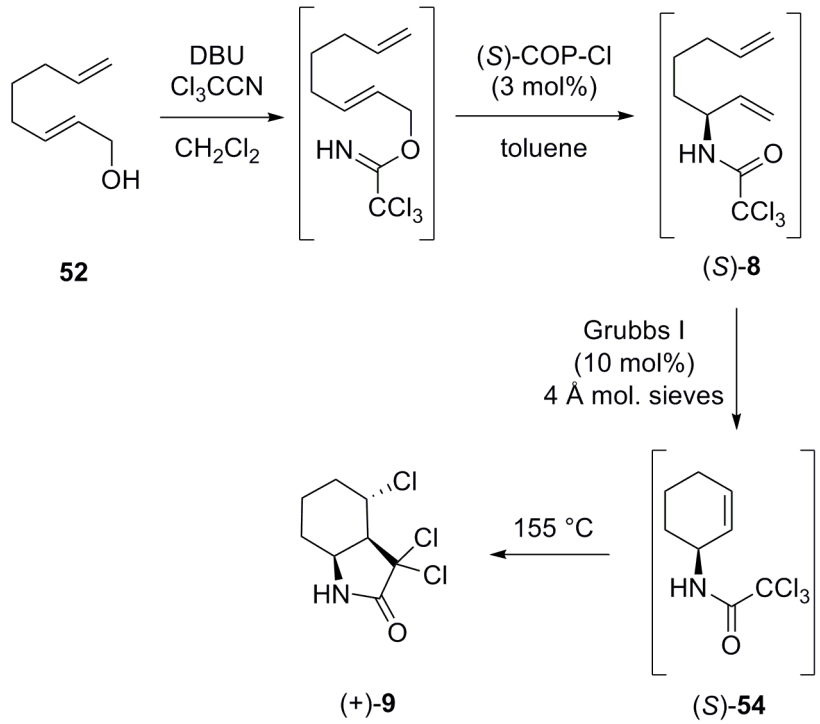
[a] $Pd(MeCN)_2Cl_2$ catalyst, [b] Grubbs I catalyst.

Table 4: Optimisation of the synthesis of aza-5,6-bicyclic lactam 98

2.1.6 Asymmetric synthesis of the 5,6- and 5,5-bicyclic γ-lactams

With the racemic syntheses of the bicyclic lactams as single diastereomers complete, focus then moved to the use of a chiral palladium(II) catalyst to effect an asymmetric Overman rearrangement. As mentioned previously, chiral palladium complexes, such as (*S*)- and (*R*)-COP-Cl, have been developed to effect the Overman rearrangement and are commercially available. Furthermore, as they have been utilised within the group in a tandem Overman rearrangement/RCM reaction,[52] it was proposed that application to this extended tandem process would be possible. By carrying out an asymmetric Overman rearrangement, allylic trichloroacetamide **8** will be formed in high enantiomeric excess, which after the RCM

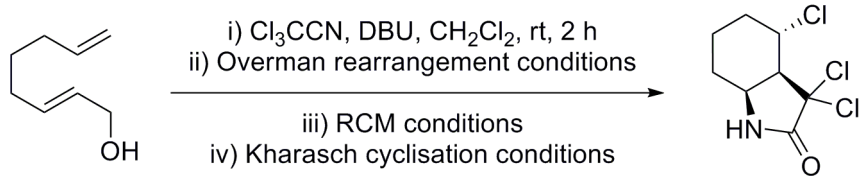
reaction to form cyclic amide **54**, the stereochemical bias within the molecule will result in the formation of enantiomerically enriched bicyclic lactam **9** (Scheme 48).



Scheme 48: Proposed asymmetric synthesis of 5,6-bicyclic lactam 9

Initially, optimised conditions previously reported in the Sutherland group were used as the starting point for the asymmetric rearrangement and RCM reaction, along with the optimised conditions for the Kharasch cyclisation developed as part of the tandem process in the current project. Allylic trichloroacetimidate, which was synthesised as previously described from allylic alcohol **52**, was treated with (*S*)-COP-Cl (3 mol%) at 38 ºC for 72 h. Grubbs 1st generation (10 mol%) and molecular sieves were then added to the reaction mixture and the mixture heated to 50 ºC for 48 h. Finally, increase of temperature to 155 ºC for 2 h resulted in formation of the desired compound (+)-**9** in 22% yield (Table 5, entry 1). Initial analysis suggested that the RCM step had not gone to completion as expected and so a further addition of Grubbs 1st generation catalyst (5 mol%) during this step resulted in an increase to 32% yield of product (entry 2). At this point it was also apparent that the rearrangement was not complete using the previously optimised conditions, so further additions of (*S*)-COP-Cl (2 × 3 mol%) were necessary to ensure that all of the allylic trichloroacetimidate underwent the Overman rearrangement. This ultimately led to an increase in product to 51% yield (entry 3). Concurrently with this optimisation, results for the 5,7-analogue showed that the presence of molecular sieves during a prolonged RCM

step at elevated temperatures was problematic. By adding the molecular sieves at the Kharasch cyclisation stage and using the RCM conditions developed in the racemic synthesis of this work, the desired product was obtained in 58% yield (entry 4). This was increased to 70% yield by extension of the Kharasch cyclisation step to ensure full conversion to bicyclic lactam (+)-**9** (entry 5).



52 (+)-**9**

Entry	Overman rearrangement	RCM reaction	Kharasch cyclisation	% yield
1	3 mol%,[a] 38 ºC, 72 h	10 mol%,[b] 50 ºC, 48 h[c]	155 °C, 2 h	22%
2	3 mol%,[a] 38 ºC, 72 h	20 mol%,[b] 50 ºC, 48 h[c]	155 °C, 2 h	32%
3	9 mol%,[d] 38 ºC, 136 h	20 mol%,[b] 50 ºC, 48 h[c]	155 °C, 2 h	51%
4	9 mol%,[d] 38 ºC, 136 h	10 mol%, rt, 1 h	155 °C, 2 h[c]	58%
5	9 mol%,[d] 38 ºC, 136 h	10 mol%, rt, 1 h	155 °C, 3 h[c]	70%

[a] (*S*)-COP-Cl catalyst. [b] Grubbs I catalyst. [c] 4 Å mol. sieves added. [d] (*S*)-COP-Cl catalyst added in 3 mol% portions at t = 0 h, t = 36 h and t = 108 h.

Table 5: Optimisation of the asymmetric 5,6-bicyclic lactam synthesis

With the yield optimised, it was important to assess the enantiomeric excess of the product obtained and to confirm whether the stereochemistry introduced in the Overman rearrangement had successfully influenced the stereochemistry of the final compound. Using chiral high-pressure liquid chromatography (HPLC) the enantiomeric excess was measured as 89% for (+)-**9** (Figure 8). For comparison, the spectrum for the racemic compound **9** has also been included and clearly shows two peaks of approximately equal area.

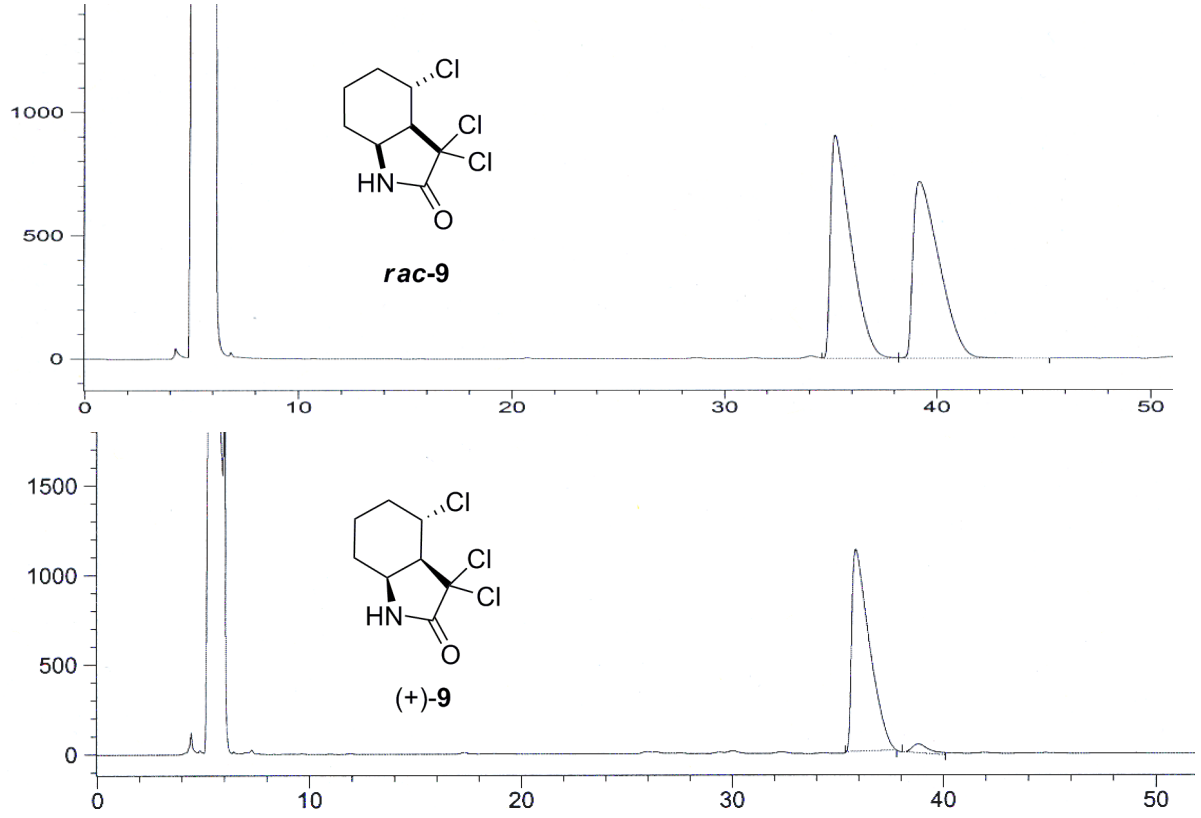
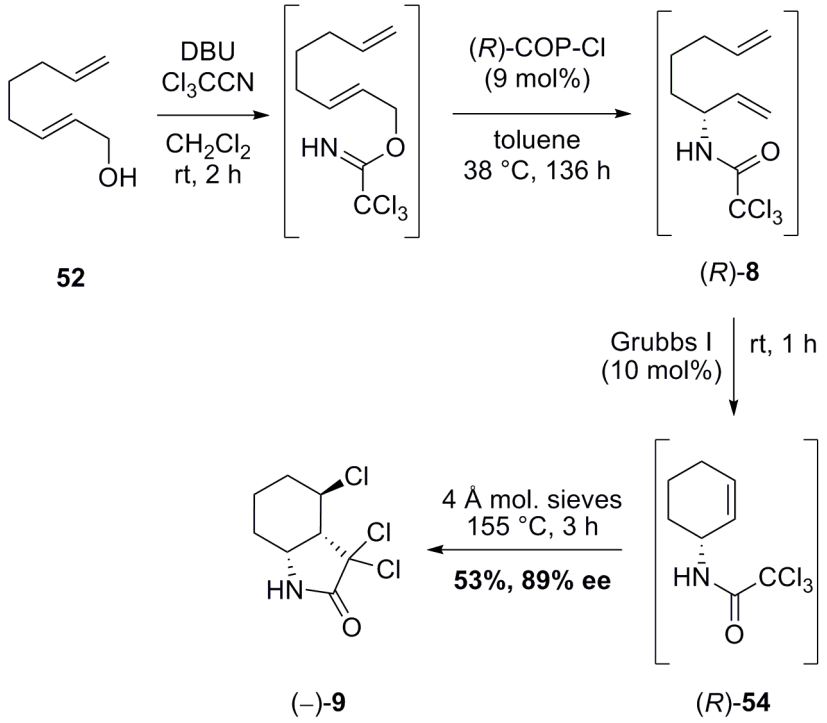


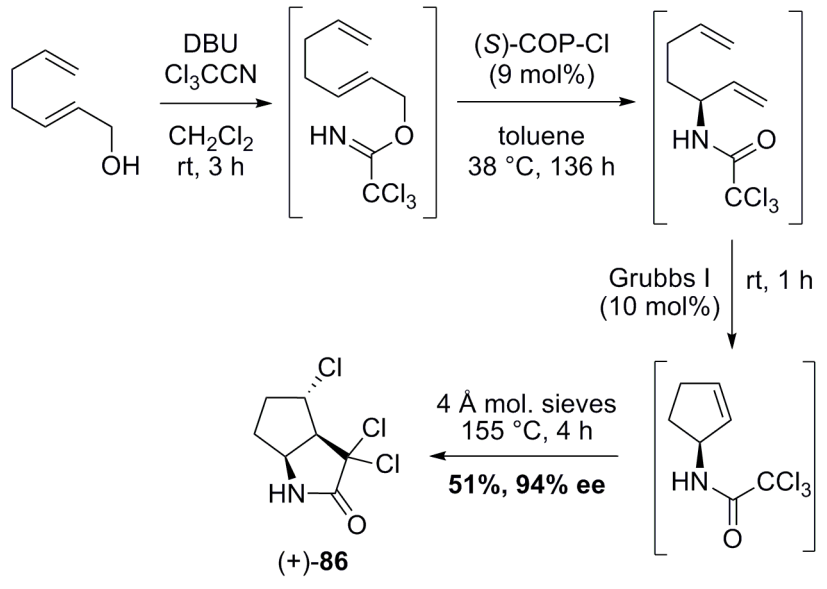
Figure 8: Chiral HPLC results for the 5,6-bicyclic lactam

The optimised conditions for accessing the *S*-enantiomer of the 5,6-bicyclic lactam **9** were successfully applied to the synthesis of the *R*-enantiomer using (*R*)-COP-Cl, affording the desired product (–)-**9** in 53% yield and 89% enantiomeric excess (Scheme 49). The reduction in yield when using (*R*)-COP-Cl may be attributed to the fact that the catalysts are *pseudo*-enantiomers of one another. Thus, the small difference in catalytic structure could cause the lower yield of product.



Scheme 49: Asymmetric synthesis of (−)-9 using (*R*)-COP-Cl

Finally, the asymmetric synthesis was applied to the synthesis of enantiomerically enriched 5,5-bicyclic lactam **86**. Applying the newly optimised conditions for the asymmetric Overman rearrangement, together with the conditions developed for the RCM reaction and Kharasch cyclisation in the racemic synthesis of this analogue, the desired product (+)-**86** was obtained in 51% yield (Scheme 50). The enantiomeric excess for this analogue was measured as 94% using chiral HPLC.

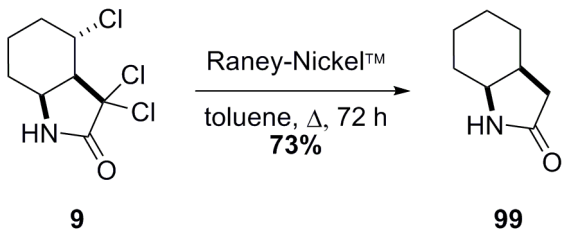


Scheme 50: Synthesis of (+)-5,5-bicyclic lactam 86

2.1.7 Modification of the 5,6-bicyclic γ-lactam

As highlighted previously (section 1.3) lactams are a common moiety found in a wide range of natural products.[18] However, many natural products tend not to contain chlorine atoms within the molecule so the ability to remove the chlorine atoms from the products synthesised using this novel tandem process will be important if this method is to be utilised within a natural product synthesis.[75] Thus, a brief study was conducted to explore such transformations.

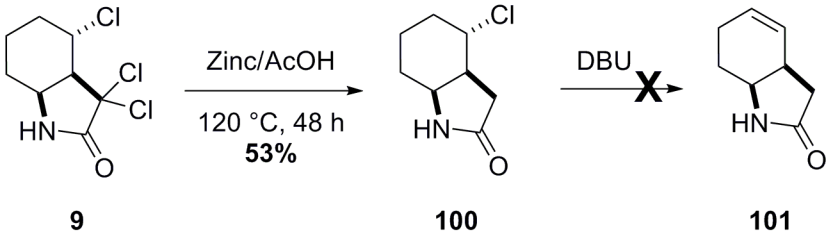
It was proposed that Raney-Nickel™ could be used to remove all three chlorine atoms from the molecule to afford the fully dechlorinated product. 5,6-Bicyclic lactam **9** was treated with activated Raney-Nickel™ under reflux conditions in toluene and after 72 h, the desired dechlorinated product **99** was obtained in 73% yield (Scheme 51).



9 **99**

Scheme 51: Removal of chlorine atoms using Raney-Nickel™

It was also envisaged that the two chlorine atoms adjacent to the carbonyl group could selectively be removed by utilising a zinc protocol described by Uda and co-workers in 1989.[76] Furthermore, if formed successfully, the monochloro compound could subsequently be treated with a base to form an alkene within the 6-membered ring by the elimination of HCl. This newly formed alkene would be an ideal handle for further functionalisation. Treatment of 5,6-bicyclic lactam **9** with activated zinc powder in glacial acetic acid at 120 ºC over 48 h, afforded the monochloro product **100** in 53% yield. Unfortunately, subsequent attempts at eliminating HCl by treating compound **100** with DBU failed to yield any of the desired unsaturated product **101**, despite employing high equivalents of DBU, prolonged reaction times and high reaction temperatures (Scheme 52).



9 100 101

Scheme 52: Selective removal of chlorine atoms using zinc in acetic acid

It was proposed that the bicyclic structure was unable to adopt the required conformation that would place the chlorine atom in an anti-periplanar position with a hydrogen atom required for elimination to occur (Figure 9).

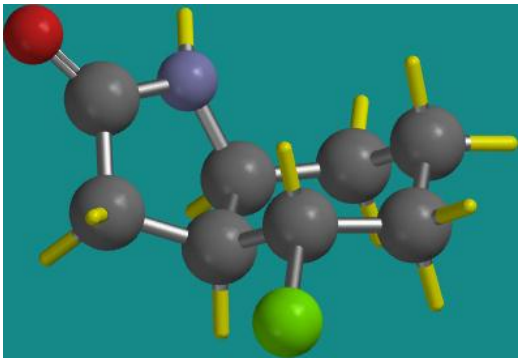


Figure 9: 3-D model of monochloro bicyclic lactam 100 using Spartan software

2.1.8 Summary

A novel one-pot tandem process has been developed for the synthesis of a small library of bicyclic γ-lactams as single diastereomers. A one-pot tandem process comprising of an Overman rearrangement, a RCM reaction and a Kharasch cyclisation follows the formation of the allylic trichloroacetimidate from a simple allylic alcohol precursor. Only two catalysts are required for the three-step tandem process as the final two steps are both catalysed using Grubbs 1st generation catalyst. Overall, the process involves the formation of carbon-carbon, carbon-nitrogen, carbon-oxygen and carbon-chlorine bonds, two ring systems as well as three new stereogenic centres. By utilising an asymmetric Overman rearrangement within the tandem process, the 5,6- and 5,5-analogues were synthesised in good yields and high enantiomeric excess. Furthermore, it was shown that the bicyclic lactams formed by this process could be modified using selective reduction protocols to enable future application of the tandem process for the synthesis of natural products.

2.1.9 Future work

A potential application of this work is for the synthesis of proline analogues containing an octahydroindole core. Octahydroindole-2-carboxylic acids (oic) have been utilised as peptidomimetics as they bring enhanced rigidity and lipophilicity to the peptide structure (Figure 10).[77] Perindopril is currently used as an antihypertensive drug and human leukocyte elastase (HLE) inhibitors give protection against the destruction of pulmonary tissue.

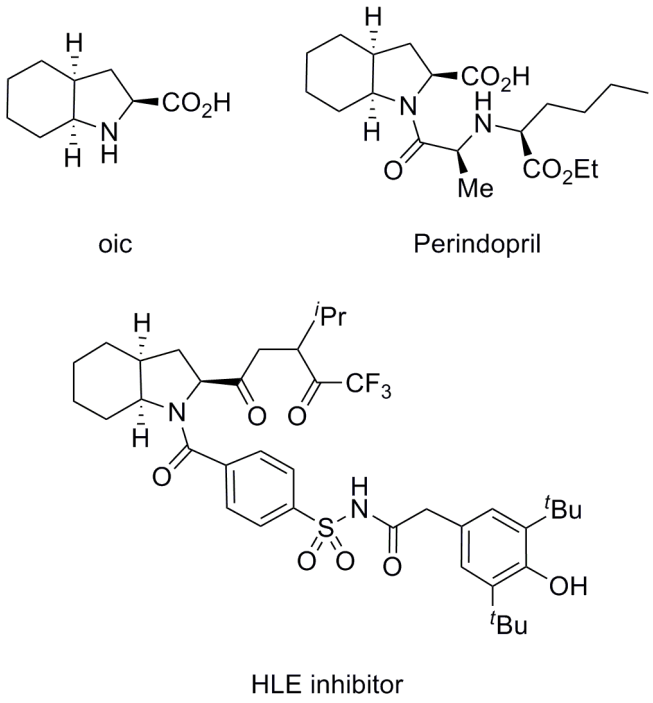
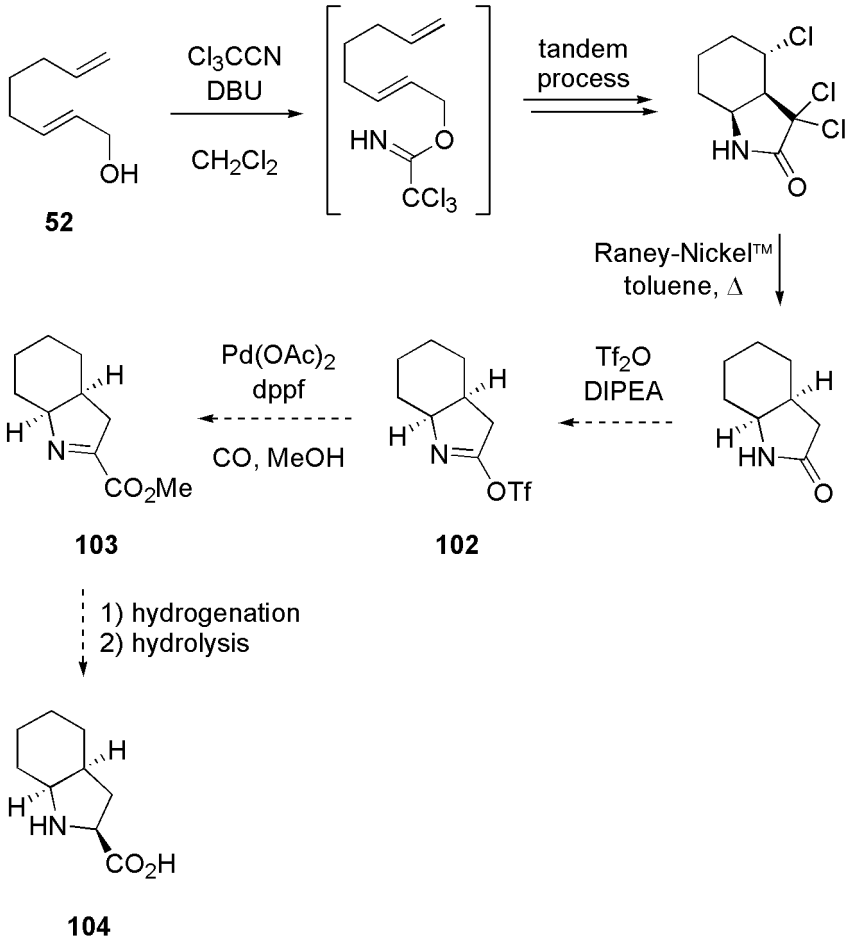


Figure 10: Structure of octahydroindole-2-carboxylic acid (oic) and examples of oic-containing peptidomimetics with important pharmacological activity

The tandem process developed would allow the synthesis of the required octahydroindole core, bearing the *cis*-ring junction, from allylic alcohol **52** (Scheme 53). The Raney-Nickel™ protocol can be used to remove the chlorine atoms, followed by formation of the imino triflate **102**. A palladium mediated carbonylation reaction[78] would subsequently yield imino methyl ester **103**, which upon hydrogenation and hydrolysis would afford the desired oic product **104**.



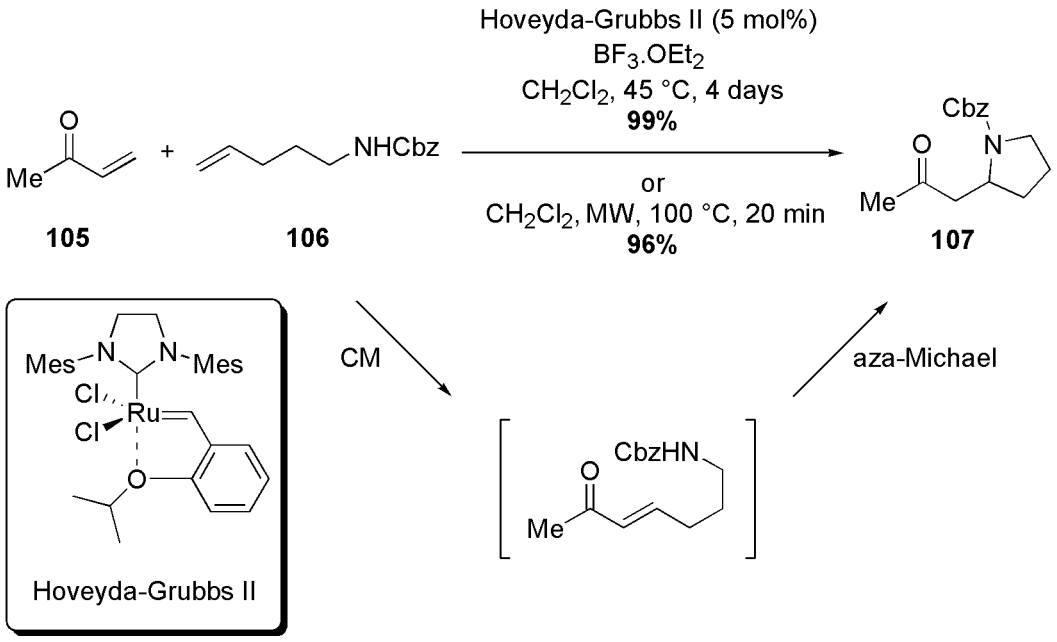
Scheme 53: Possible application of the tandem process for the synthesis of octahydroindole-2-carboxylic acid 104

2.2 Microwave-assisted tandem process for the synthesis of bicyclic γ-lactams

2.2.1 Introduction to microwave chemistry

Many chemical processes require energy in the form of heat to be initiated. Traditional heat sources such as oil baths, hot plates and isomantles have been used extensively in synthesis laboratories for many years; however, the use of microwave reactors to drive reactions is becoming an increasingly popular tool. Early reports utilised standard domestic microwaves to heat reactions in a sealed Teflon or Pyrex vessel.[79,80] Although useful, the accurate temperature could not be controlled and the presence of compounds of known melting points were required to crudely determine the temperature within the reaction vessel. It has only been in the last 15 years, when dedicated microwave reactors for chemical synthesis were developed, that the field of microwave-assisted organic synthesis (MAOS) has flourished.

In 2007, Fustero and co-workers highlighted the advantages of utilising microwave irradiation for the acceleration of a tandem CM/intramolecular aza-Michael reaction.[81] Reaction of methyl vinyl ketone **105** with Cbz-protected amine **106** in the presence of Hoveyda-Grubbs 2nd generation catalyst and $BF_3.OEt_2$ afforded the desired cyclic amine **107** in 99% yield (Scheme 54). However, the reaction took 4 days at 45 ^{o}C to go to completion. In comparison, by heating the reaction mixture in a microwave reactor at 100 ^{o}C, the product was isolated in 96% yield after only 20 minutes. This example illustrates the dramatic increase in rate of a reaction that can be achieved using microwave heating.



Scheme 54: Microwave-assisted tandem cross-metathesis/aza-Michael reaction

This increase in reaction rate can be explained by considering the different heating methods. The heating effect for a microwave reaction is the result of energy absorption by the molecules in the bulk solution, therefore the mixture will heat up rapidly in a uniform manner.[82] In contrast, the temperature of a reaction mixture heated by an external heat source (e.g. an oil bath) will increase rapidly around the wall of the vessel but more slowly towards the centre of the reaction mixture. Furthermore, when heating in a microwave reactor, solvent can be superheated to above their boiling point; thus, enhancing the rate of reaction *via* an increased thermal effect.[83]

The heating mechanism for a chemical reaction is the same as for domestic cooking. A solvent absorbs the microwave energy and converts it into heat energy. When a sample is irradiated, the dipole of the molecules aligns itself with the electromagnetic field. As the field oscillates, the dipoles realign and it is this motion, together with some molecular friction, which causes the conversion of electromagnetic energy into heat energy.[83,84] The efficiency with which this occurs depends on the ability of the solvent to absorb the microwave energy and subsequently convert it into heat energy. Polar solvents with high dielectric constants tend to be highly efficient at absorbing microwave radiation, whereas solvents that lack a permanent dipole are microwave transparent. The "loss factor" or tanδ (which combines absorption ability with conversion to heat efficiency) is commonly used as a guide to how rapidly a reaction mixture will heat under microwave irradiation (Table 6).[85] Solvents which possess a high tanδ value (> 0.5) absorb and convert microwave

radiation into heat energy efficiently, whereas solvents with a low tanδ (< 0.1) do not heat as efficiently under microwave irradiation.

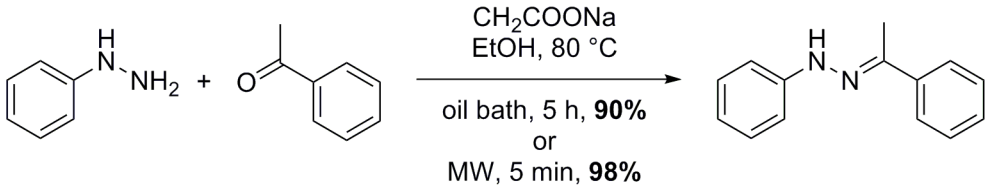
Solvent	tanδ	Solvent	tanδ
Ethylene glycol	1.350	Chlorobenzene	0.101
Ethanol	0.941	Acetonitrile	0.062
DMSO	0.825	Ethyl acetate	0.059
Methanol	0.659	Dichloromethane	0.042
Acetic acid	0.174	Toluene	0.040
Water	0.123	Hexane	0.020

Table 6: Tanδ values for common organic solvents

It is important to consider the tanδ of the reaction mixture as a whole when determining the potential heating ability in a microwave reactor, as a solvent with low tanδ can still be used in MAOS if the substrates/catalysts within the reaction mixture possess a high tanδ.[85] Furthermore, the addition of a heating aid, such as a more polar solvent or an ionic liquid, can also be used to increase the absorption (and therefore heating) ability of a poorly absorbing reaction mixture.

It has been argued that it is not only thermal effects which result in the enhanced rate of reaction in MAOS.[83] By considering the Arrhenius equation [$k = A\exp(-\Delta G^{\ddagger}/RT)$], which defines the rate constant (and hence the overall rate) for a given reaction, two factors other than temperature could be affected under microwave irradiation. The pre-exponential factor, *A*, represents the probability of molecular collisions for a given reaction. This factor could be enhanced by the specific orientation of the molecules in the microwave field resulting in an increase in the rate of a reaction. Furthermore, the activation energy, $\Delta G^{\ddagger}$ (where $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$), could be reduced for a microwave-assisted reaction as a resulting increase of entropy ($\Delta S^{\ddagger}$) within the molecule. This too would lead to an increase in the rate of reaction. In spite of these rationalisations, the presence of "specific" microwave effects on a reaction remains a highly debated area of microwave-enhanced chemistry and may only influence the rate of specific types of reaction. In 2011, La Regina and co-workers reported the microwave-accelerated synthesis of hydrazones which did not appear to rely on the enhanced thermal ability of microwave irradiation.[86] By using a continuous flow of air through the microwave reactor, the desired product was formed in high yield in 5 minutes at 80 ºC, whereas the reaction took 5 h at the same temperature in

an oil bath (Scheme 55). The cooling effect of the airflow meant that more microwave energy was required to maintain the 80 ºC of the reaction mixture, which would indicate a non-thermal microwave effect upon the reaction itself.



Scheme 55: Possible non-thermal microwave effect

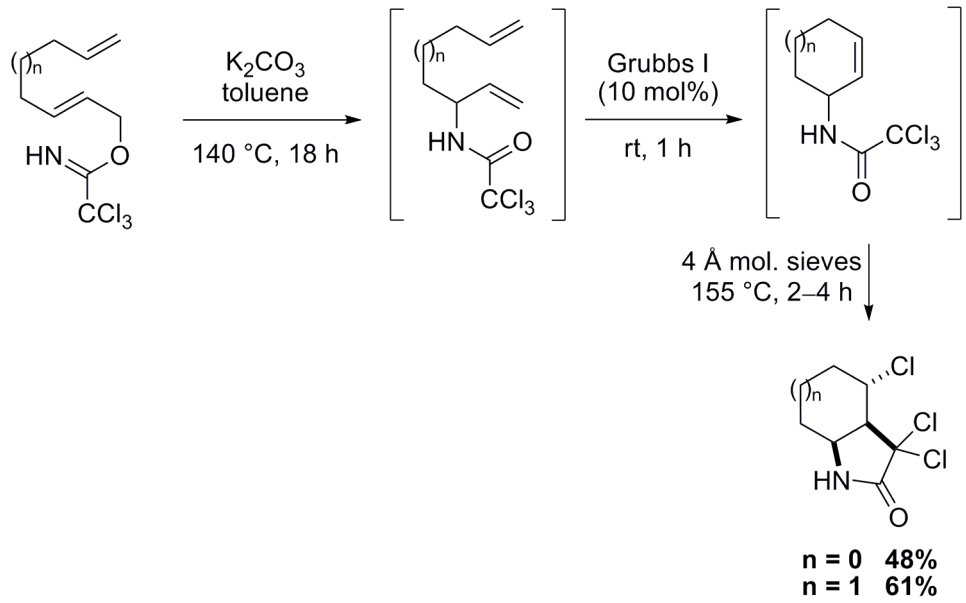
As it was illustrated previously (section 2.1.5) that a thermal Overman rearrangement could be utilised in the tandem process for the synthesis of the oxy- and aza-analogues, it was proposed that microwave heating could be exploited to accelerate both the Overman rearrangement step as well as the Kharasch cyclisation step. It was envisaged that the rapid heating ability of the microwave-assisted process could reduce the reaction times of these steps for all the analogues illustrated previously, and overall allow the rapid synthesis of the bicyclic γ-lactams.

2.2.2 Synthesis of the 5,5- and 5,6-bicyclic γ-lactams using a tandem thermal Overman rearrangement/RCM/Kharasch cyclisation

Before proceeding with investigations into the application of microwave irradiation to promote the tandem process, the 5,5-bicyclic γ-lactam **86** and 5,6-bicyclic γ-lactam **9** were synthesised using a thermal Overman rearrangement within the tandem process. These results, along with those gained for the heteroatom analogues, could then be used for comparison with the microwave-assisted tandem process results. It is worth noting that the synthesis of the 5,7-analogue **87** using the microwave-assisted approach was not considered due to the constraints regarding maximum solvent volume within the microwave vial. This meant that the ability to mimic the low concentrations required for this analogue was not possible.

The allylic trichloroacetimidates required for the tandem process were synthesised from the corresponding allylic alcohols as previously described. For both substrates, the thermal Overman rearrangement was complete after 18 h at 140 ºC (Scheme 56). The subsequent RCM reaction and Kharasch cyclisation were carried out using the optimal conditions

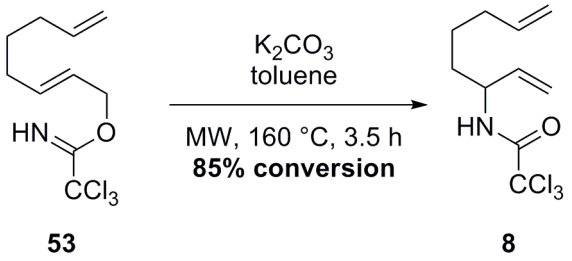
previously described for both substrates and afforded the desired products in good yield over four steps.



Scheme 56: Synthesis of the 5,5- and 5,6-bicyclic lactams using a tandem thermal Overman rearrangement/RCM/Kharasch cyclisation process

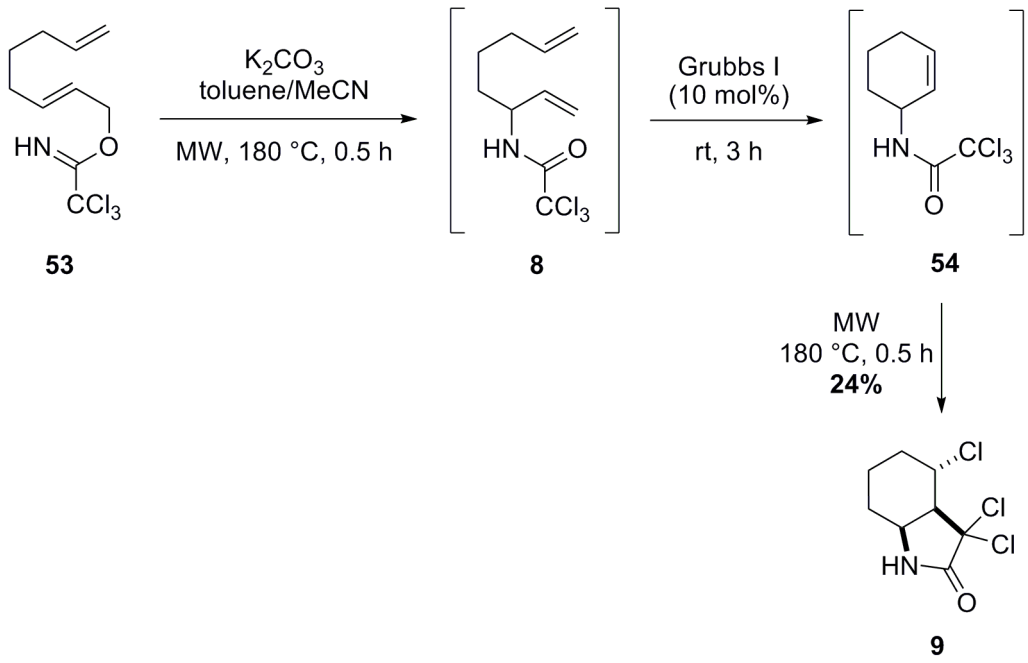
2.2.3 Development of a microwave-assisted tandem Overman rearrangement/RCM/Kharasch cyclisation

The first stage in the development of this microwave-assisted tandem process was the optimisation of conditions for each step of the synthesis. Although a poor solvent for microwave irradiation (*c.f.* table 6), toluene was initially tested as it had been utilised previously for the tandem process. As expected, the rate of heating was slow despite the presence of ionic potassium carbonate within the reaction mixture. The reaction was heated to 160 ºC and the progress of the Overman rearrangement was measured by ^{1}H NMR spectroscopy every 30–60 minutes. After a total of 3.5 h at 160 ºC, only 85% of the allylic trichloroacetimidate **53** had been converted to desired allylic trichloroacetamide **8** (Scheme 57).



Scheme 57: Initial attempts at carrying out the microwave assisted Overman rearrangement in toluene

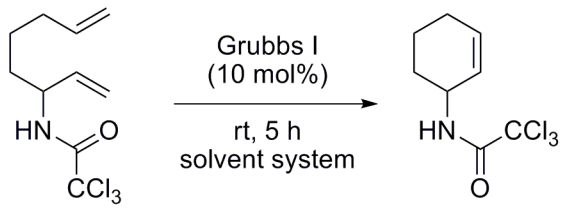
In order to increase the rate of heating and allow access to higher temperatures, acetonitrile was tested as a co-solvent for the transformation. This indeed increased the rate of heating and after 30 minutes at 180 ºC the Overman rearrangement of allylic trichloroacetimidate **53** was complete (Scheme 58 and Table 8, entry 1). Grubbs 1st generation catalyst was subsequently added with stirring at room temperature for 3 h, followed by heating in the microwave reactor for a further 30 minutes at 180 ºC to effect the RCM reaction and Kharasch cyclisation respectively. Unfortunately this yielded only 24% of the desired bicyclic lactam product **9** with allylic trichloroacetamide **8** isolated as the major by-product. This suggested that acetonitrile might be an unsuitable co-solvent which can interact with the Grubbs catalyst resulting in the low conversion of the RCM reaction.



Scheme 58: Initial results for the microwave-assisted tandem process

A quick screen of potential co-solvents was then carried out to identify a solvent that would be suitable for assisting the microwave heating but which would not adversely interact with

the Grubbs catalyst. The allylic trichloroacetamide **8** was synthesised from the corresponding allylic trichloroacetimidate **53** using traditional thermal conditions (see section 2.2.2). The crude reaction mixture was split into 5 × 2 mL batches and to this was added 1 mL of polar co-solvent (1 mL of toluene was added to one reaction vessel as a control experiment). Grubbs 1st generation catalyst was added immediately and the reactions were stirred at room temperature for 5 h before analysing the crude reaction mixtures by ^{1}H NMR spectroscopy. After 5 h at room temperature, the ^{1}H NMR spectrum of the crude reaction mixture indicated that a 90% conversion to the desired RCM product **54** had been achieved for the control reaction (Table 7, entry 1). As expected, acetonitrile performed poorly as the co-solvent, with the RCM reaction only 20% complete after 5 h (entry 2). It has been reported that acetonitrile can coordinate to Grubbs catalyst resulting in the formation of a hexacoordinate adduct.[87] This coordination would slowly retard the activity of the catalyst towards the RCM reaction resulting in low conversion to the cyclised product **54**. Dimethyl sulfoxide proved even worse with no desired RCM product visible in the crude mixture after 5 h (entry 3). This result is somewhat unsurprising as dimethyl sulfoxide has been reported as a convenient reagent with which to remove traces of Grubbs catalyst after a RCM reaction.[88] This presumably occurs by the coordination of dimethyl sulfoxide to the catalyst which, when added before a RCM reaction, would render the catalyst inactive to a metathesis reaction. More encouraging results were obtained by using acetic acid and chlorobenzene as co-solvents. Taylor and co-workers have previously illustrated that acetic acid and chlorobenzene are suitable solvents for RCM reactions as they promote high catalytic turnover.[89] Although the results of 70% and 85% conversion for acetic acid and chlorobenzene respectively were encouraging (entries 4 and 5), they were still lower than the 90% obtained for the control experiment using only toluene. Taylor and co-workers also noted that although catalytic turnover was higher for acetic acid and chlorobenzene compared to toluene, the subsequent rate of decomposition of the active catalyst was also higher. As Grubbs catalyst is required for both the RCM reaction and subsequent Kharasch cyclisation of the tandem process, this decomposition of catalyst by solvent needed to be avoided. Instead, a non-invasive method of assisting the microwave heating of toluene was explored.



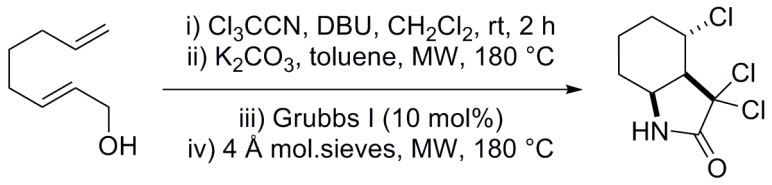
8 **54**

Entry	Solvent system[a]	% Conversion[b]
1	Toluene	90%
2	Toluene/acetonitrile	20%
3	Toluene/DMSO	0%
4	Toluene/acetic acid	70%
5	Toluene/chlorobenzene	85%

[a] Total volume of solvent = 3 mL (2:1 ratio of mixtures), [b] % conversion was calculated from ^{1}H NMR spectrum

Table 7: Screen of co-solvents for the RCM step

In 2006, Kremsner and Kappe reported that passive heating elements (PHE's), such as sintered silicon carbide (SiC) bars, could assist the microwave heating of non-polar solvents.[90] SiC bars are strongly microwave absorbing but chemically inert and can be used as an alternative for performing microwave-assisted reactions in a solvent with a low tanδ, where the addition of polar solvents or ionic liquids as heating aids is not possible for a given reaction. In the event, the SiC bar was employed successfully in toluene, with the microwave-assisted Overman rearrangement of allylic trichloroacetimidate **53** complete after 1 h at 180 ºC. The reaction mixture was subsequently stirred with Grubbs 1st generation catalyst at room temperature for 1 h before heating the reaction mixture in the microwave reactor for 30 minutes at 180 ºC. The desired 5,6-bicyclic lactam **9** was isolated in a much-improved 42% yield (Table 8, entry 2). The use of microwave heating for the RCM step was subsequently explored in an attempt to reduce reaction times further whilst hopefully improving the yield of product. By heating the RCM step at 60 ºC for 30 minutes, a comparable yield of 44% was obtained (entry 3). Slight adjustment of reaction times for both the RCM step and the Kharasch cyclisation resulted in the formation of the desired 5,6-bicyclic lactam **9** in 64% yield (entry 4).



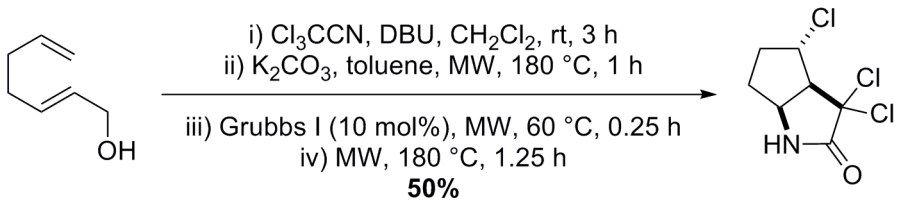
52 **9**

Entry	Overman rearrangement	RCM reaction	Kharasch cyclisation	% yield of bicyclic lactam
1	MeCN (10%), 0.5 h	rt, 3 h	0.5 h	24%
2	SiC PHE, 1 h	rt, 1 h	0.5 h	42%
3	SiC PHE, 1 h	MW, 60 ºC, 0.5 h	0.5 h	44%
4	SiC PHE, 1 h	MW, 60 ºC, 0.25 h	0.75 h	64%

Table 8: Optimisation of reaction conditions for the synthesis of 5,6-bicyclic γ-lactam 9

2.2.4 Synthesis of the 5,5-, oxy-5,6- and aza-5,6-bicyclic γ-lactams

With conditions optimised for the 5,6-bicyclic lactam **9**, focus was then turned to the 5,5- and oxy-5,6- and aza 5,6-analogues. As for the previous tandem methods, the synthesis of the 5,5-analogue **86** proceeded well using the newly optimised conditions, with only minor changes to the Kharasch cyclisation step required to afford the desired product in 50% yield (Scheme 59). It is worth noting that due to the shorter time required for the Kharasch cyclisation, it was found that the addition of molecular sieves was not necessary during the microwave-assisted process.

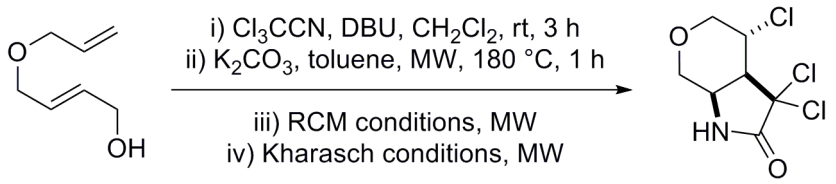


84 **86**

Scheme 59: Microwave-assisted synthesis of 5,5-bicyclic lactams 86

Focus then moved to the synthesis of the oxy- and aza-bicyclic lactams. Initial attempts at the microwave-assisted tandem process of the oxy-5,6-analogue **97** showed that although the Overman rearrangement was complete after 1 h at 180 ºC, low conversion of the RCM step with Grubbs 1st generation catalyst was apparent by ^{1}H NMR spectroscopy after 15 minutes at 60 ºC. By increasing the loading of catalyst and reaction time for the RCM step,

the desired product **97** was isolated in 21% yield (Table 9, entry 1). Grubbs 2nd generation catalyst was explored for the RCM and Kharasch cyclisation under these conditions, however only a small improvement in yield was achieved (entry 2). By increasing the time to 5 h for the Kharasch cyclisation using Grubbs 2nd generation catalyst, the desired product **97** was afforded in 30% yield (entry 3). Finally, Hoveyda-Grubbs 2nd generation catalyst was tested, and using the prolonged Kharasch reaction time, the desired product **97** was afforded in 43% yield (entry 4). Despite requiring a longer reaction time for the Kharasch cyclisation, overall the microwave-assisted synthesis of oxy-5,6-bicyclic lactam is significantly shorter compared to the standard thermal process.

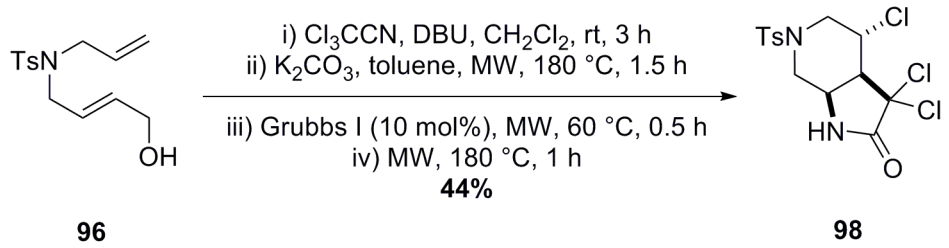


90 **97**

Entry	RCM reaction	Kharasch cyclisation	% yield of bicyclic lactam
1	Grubbs I (15 mol%), 60 ºC, 0.5 h	180 ºC, 1 h	21%
2	Grubbs II (10 mol%), 60 ºC, 0.5 h	180 ºC, 1 h	23%
3	Grubbs II (10 mol%), 60 ºC, 0.5 h	180 ºC, 5 h	30%
4	Hoveyda-Grubbs II (10 mol%), 60 ºC, 0.5 h	180 ºC, 5 h	43%

Table 9: Optimisation of conditions for the microwave-assisted synthesis of oxygen-analogue

The synthesis of the aza-bicyclic lactam **98** proved more straightforward. It was anticipated that a prolonged reaction time for the Overman rearrangement step would be required due to the length of time (5 days) required for the thermal Overman rearrangement. In the event, heating the allylic trichloroacetimidate in the microwave reactor at 180 ºC for 90 minutes was sufficient to complete the rearrangement step (Scheme 60). The reaction was subsequently stirred with Grubbs 1st generation catalyst in the microwave reactor at 60 ºC for 30 minutes followed by 1 h at 180 ºC and afforded the desired product **98** in 44% yield.

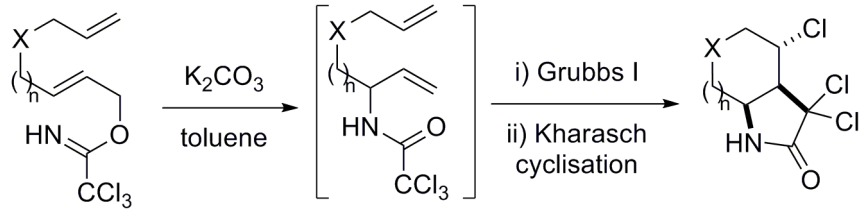


96 **98**

Scheme 60: Synthesis of the aza-bicyclic lactams 98 using the microwave protocol

2.2.5 Summary

The use of microwave irradiation has been successfully utilised to effect all three steps of the tandem Overman rearrangement/RCM/Kharasch cyclisation process. The 5,5-, 5,6-, oxy-5,6- and aza-5,6-bicyclic γ-lactams were all successfully synthesised using this approach. The major advantage of this microwave-assisted tandem process is that the products can be obtained in significantly shorter times and, in most cases, in higher yields when compared to the thermal approach (Table 10). In particular, the reaction time for the Overman rearrangement is significantly reduced and allows the synthesis of the products in a cleaner and more reproducible manner. This is especially highlighted in the synthesis of the amino-bicyclic γ-lactam **98**, which takes 5.5 days to synthesise in 39% yield using the standard thermal reaction conditions due to a lengthy Overman rearrangement step. In comparison, using the microwave-assisted synthesis, the desired product can be synthesised in 44% yield in only 6 hours over 4 steps from the corresponding allylic alcohol.



Product	Overman rearrangement	RCM reaction	Kharasch cyclisation	yield
X = CH_2	140 °C, 18 h	rt, 1 h	4 Å MS, 155 °C, 3 h	48%
n = 0, **86**	SiC PHE, 180 °C, 1 h	60 °C, 0.25 h	180 °C, 1.25 h	50%
X = CH_2	140 °C, 18 h	rt, 1 h	4 Å MS, 155 °C, 2 h	61%
n = 1, **9**	SiC PHE, 180 °C, 1 h	60 °C, 0.25 h	180 °C, 0.75 h	64%
X = O	140 °C, 72 h	rt, 4 h	4 Å MS, 155 °C, 3 h	52%
n = 1, **97**	SiC PHE, 180 °C, 1 h	60 °C, 0.5 h[a]	180 °C, 5 h[a]	43%
X = NTs	140 °C, 136 h	rt, 1 h	4 Å MS, 155 °C, 3 h	39%
n = 1, **98**	SiC PHE, 180 °C, 1.5 h	60 °C, 0.5 h	180 °C, 1 h	44%

[a] Hoveyda-Grubbs II.

Table 10: Results for the standard thermal tandem process versus the microwave-assisted tandem process for the synthesis of the bicyclic γ-lactams

2.3 Application of the three-step tandem process for the synthesis of benzannulated γ-lactams

2.3.1 Targets and proposed synthesis

It was envisaged that the three-step tandem process developed, could be utilised for the synthesis of tricyclic γ-lactams, which contain an aromatic system fused to the basic 5,5- and 5,6-lactam core (Figure 11). Such structures have previously been prepared for a range of applications, for example as hypoglycemic agents and as the core unit for complex natural products.[91,92] Thus, the ability to synthesise such compounds from simple substrates in a rapid and efficient manner is of interest within a number of areas of organic chemistry.

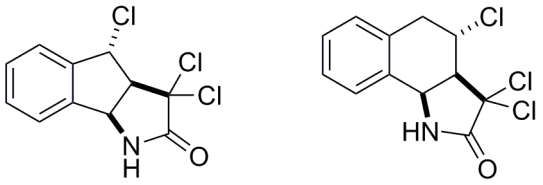
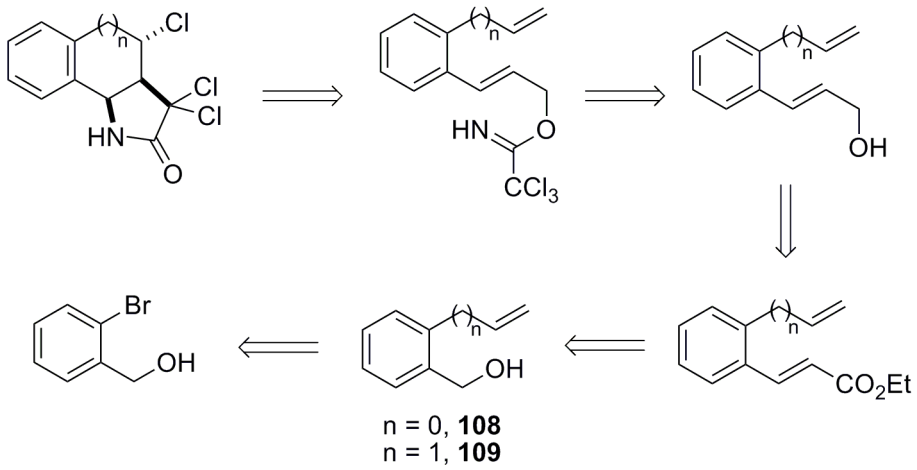


Figure 11: Benzannulated-5,5- and 5,6-targets

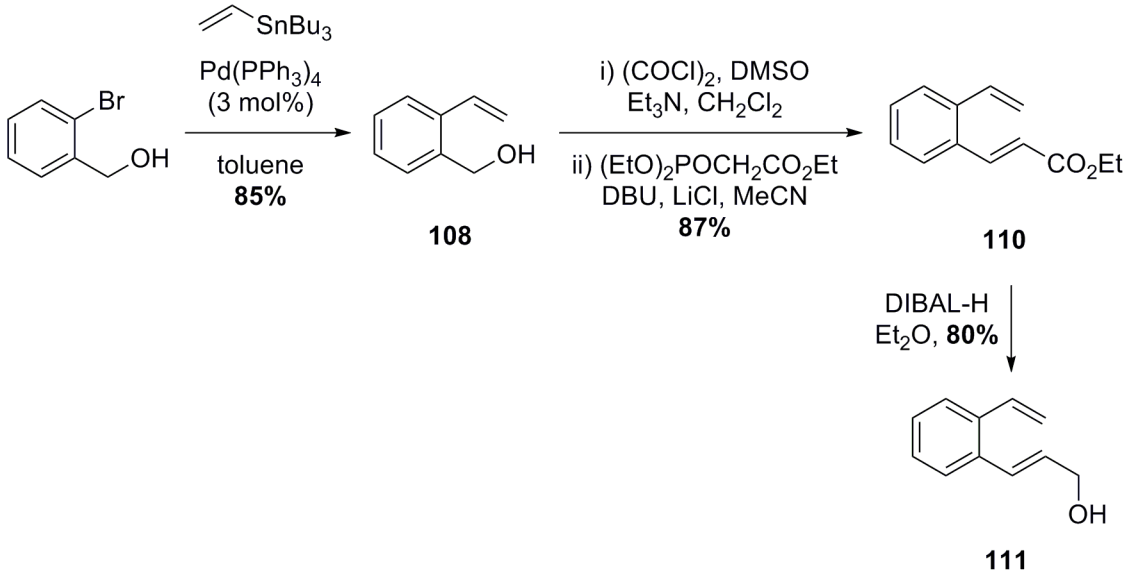
The proposed retrosynthesis for these targets is given in Scheme 61. A Stille coupling of 2-bromobenzyl alcohol with vinyl or allyl tri-*n*-butyltin would yield alcohols **108** and **109**. Subsequent one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction followed by DIBAL-H reduction would give the desired allylic alcohol precursors.



Scheme 61: Retrosynthesis of target molecules

2.3.2 Synthesis of the benzannulated-5,5- and 5,6-lactams

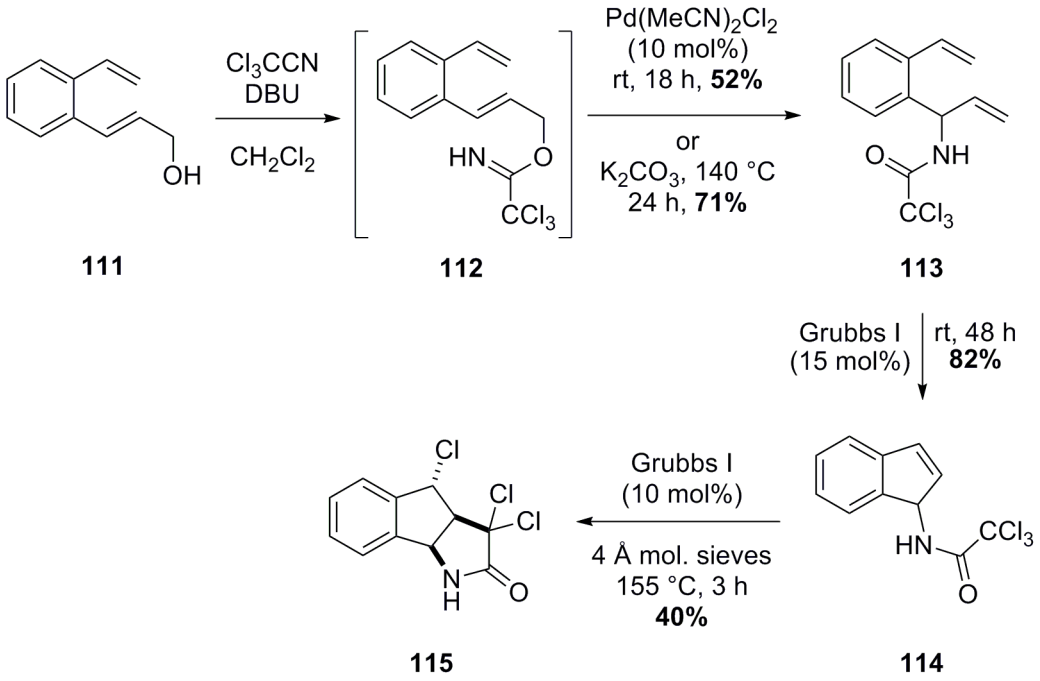
Initially, the application of the tandem process for the synthesis of the benzannulated-5,5-lactam was studied. The Stille coupling of 2-bromobenzyl alcohol with tri-*n*-butyl(vinyl)tin in the presence of tetrakis(triphenylphosphine)palladium(0) proceeded well, forming the desired vinylated product **108** in 85% yield (Scheme 62).[93] The subsequent one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction gave the (*E*)-α,β-unsaturated ester **110** in 87% yield. DIBAL-H reduction of the ester formed the desired allylic alcohol precursor **111** in 80% yield.



Scheme 62: Synthesis of allylic alcohol 111

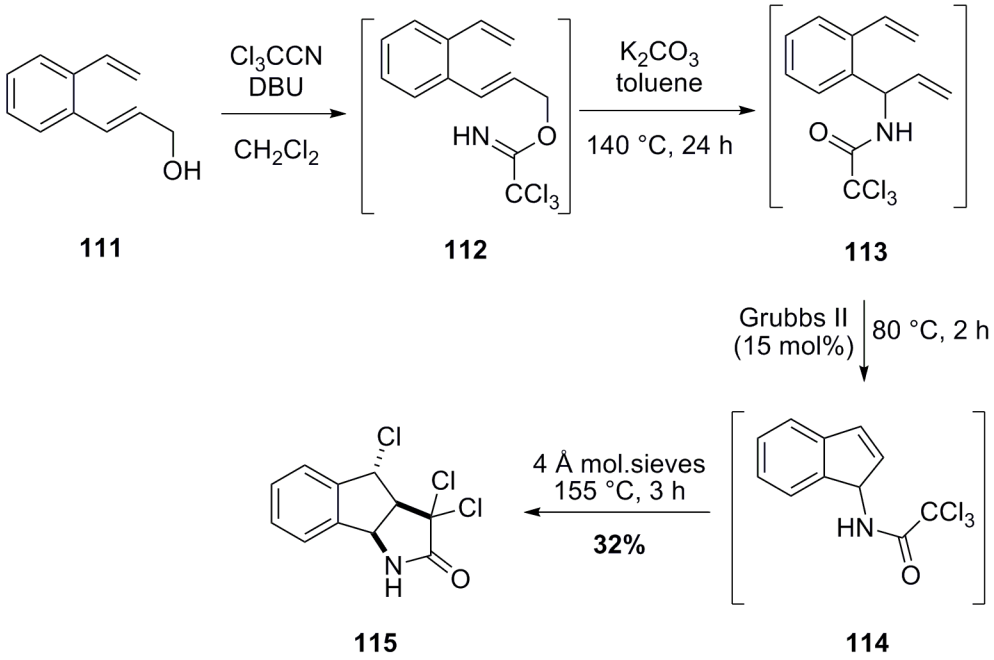
Before proceeding with the full tandem process, each step of the process was carried out individually to gauge the optimal conditions for each step. Furthermore, the ^{1}H NMR spectra of these products could subsequently be used as a reference during the development of the tandem process. Treatment of allylic alcohol **111** with trichloroacetonitrile and DBU formed the desired allylic trichloroacetimidate **112** in 3 h at room temperature (Scheme 63). Initially, a palladium(II)-catalysed Overman rearrangement was performed, however the desired allylic trichloroacetamide **113** was only obtained in 52% yield. By switching to a thermal Overman rearrangement the desired amide was formed in an improved 71% yield. The RCM reaction of diene **113** with Grubbs 1st generation catalyst proceeded slowly over 48 h, requiring 15 mol% of catalyst, however the desired bicyclic product **114** was isolated in 82% yield. Finally, the reaction of cyclic amide **114** with Grubbs 1st generation catalyst at 155 ºC afforded the target tricyclic lactam **115** in a modest 40% yield. The low

yield of Kharasch product was perhaps unsurprising as it was observed previously that the conversion of Grubbs catalyst to the Kharasch active ruthenium complex may be slow (Scheme 42).[23,72]



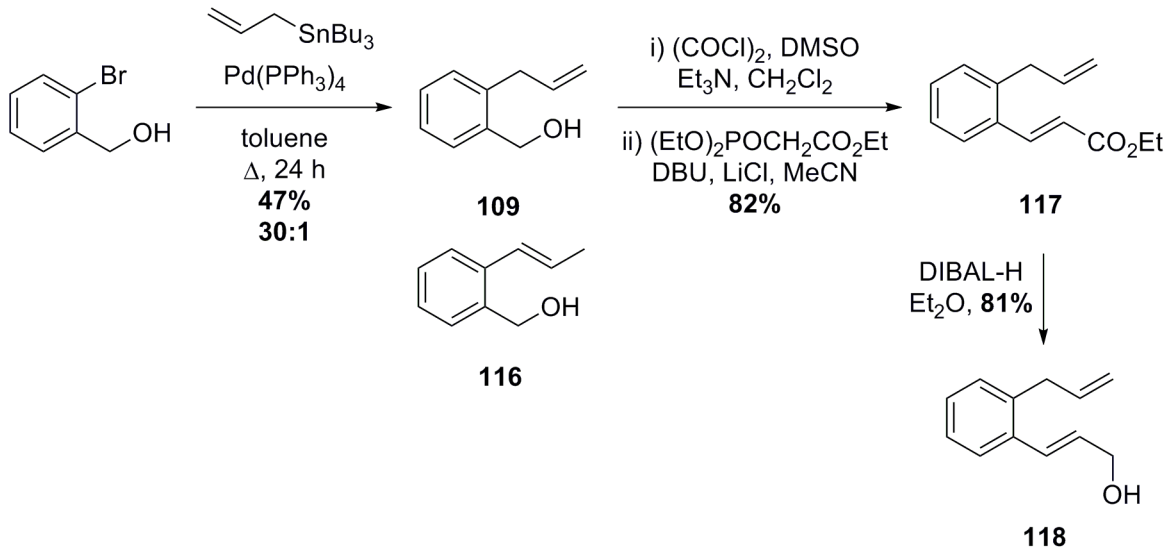
Scheme 63: Synthesis of the benzannulated-5,5-γ-lactam using a stepwise process

Next, the tandem process was carried out in full starting from allylic alcohol **111** (Scheme 64). Using a palladium(II)-catalysed Overman rearrangement along with the conditions for the RCM reaction and Kharasch cyclisation shown above, the desired tricyclic product **115** was formed in 27% yield over the four steps. Following this, a switch to a thermal Overman rearrangement and the use of Grubbs 2nd generation catalyst were implemented; however, after a number of attempts the highest yield achieved for the benzannulated-5,5-lactam **115** was a modest 32% yield.



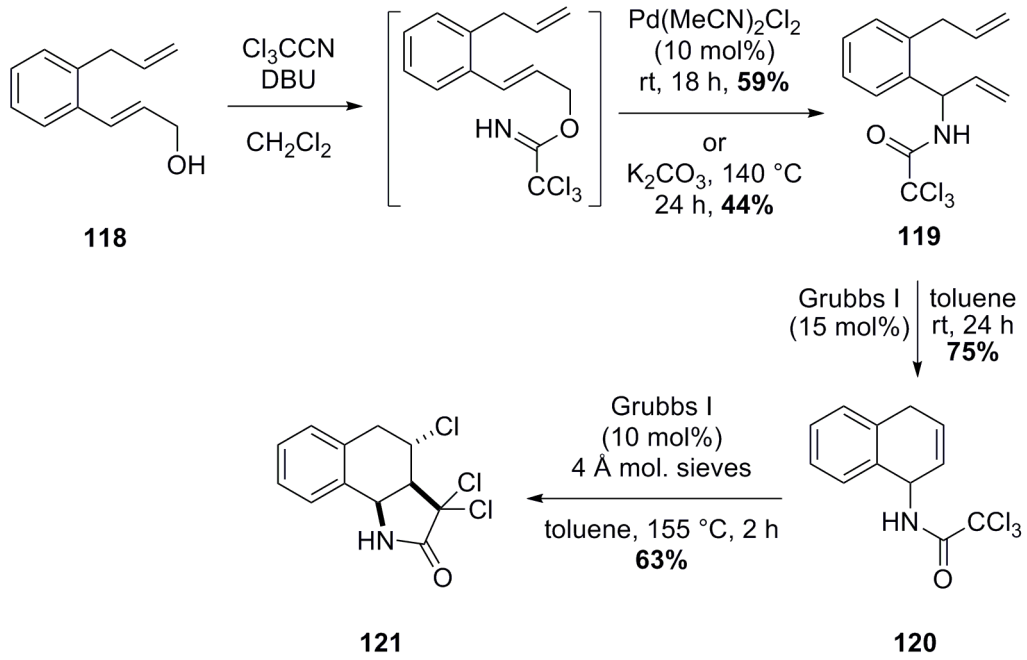
Scheme 64: Optimised result for the synthesis of benzannulated-5,5-γ-lactam 115

Attention then focused on the synthesis of the benzannulated-5,6-analogue. The Stille coupling of 2-bromobenzyl alcohol with tri-*n*-butyl(allyl)tin gave mixed results. The reaction required 24 h of heating under reflux with tetrakis(triphenylphosphine)palladium(0) to ensure that all the starting material had reacted with the organostannane, thus avoiding separation issues of starting material and product. However, it was discovered that prolonged heating (> 24 h) of the reaction mixture led to the isomerisation of the newly introduced allyl group. The ratios of desired product **109** to isomerised product **116** ranged from 30:1 to 2:1 and were inseparable (Scheme 65). It was proposed that the presence of palladium(0) could form an η^3-complex with the allyl group, which when dissociated would form the more stable conjugated product. With the presence of the allyl group vital for the tandem process, a compromise in yield had to be accepted with the desired product afforded in 47% yield and a 30:1 ratio. The subsequent Swern oxidation/Horner-Wadsworth-Emmons reaction and DIBAL-H reduction proceeded as expected with the (*E*)-α,β-unsaturated ester **117** and allylic alcohol **118** isolated in 82% and 81% yield, respectively.



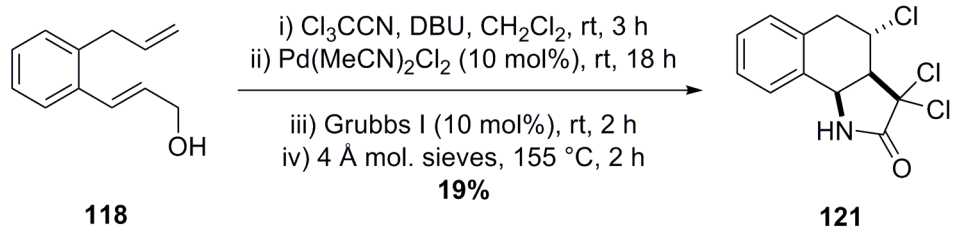
Scheme 65: Synthesis of the allylic alcohol precursor for the benzannulated-5,6-analogue

As for the previous analogue, each step was carried out individually before progressing with the tandem process. The Overman rearrangement product **119** was isolated in 59% yield using palladium(II) catalysis and 44% yield using thermal conditions (Scheme 66). The RCM step proceeded well using Grubbs 1st generation catalyst, with the desired bicyclic amide **120** isolated in 75% yield. Finally the Kharasch cyclisation using Grubbs 1st generation catalyst formed the desired tricyclic lactam in 63% yield.



Scheme 66: Synthesis of the benzannulated-5,6-γ-lactam using a stepwise process

The complete tandem process was then attempted using a palladium(II)-catalysed Overman rearrangement and a Grubbs 1st generation catalysed RCM/Kharasch cyclisation. Unfortunately, the benzannulated-5,6-lactam **121** was isolated in a disappointing 19% yield, a lower yield than the combined individual steps (Scheme 67). Traces of the benzannulated-5,5-analogue **115** was also visible due to the presence of the isomerised product from the Stille coupling.



118 **121**

Scheme 67: Synthesis of the benzannulated-5,6-γ-lactam using the tandem process

It was apparent that the presence of the aromatic unit was hindering the three-step tandem process, with the individual steps progressing slower and in lower yield compared to the bicyclic systems. Furthermore, with the low yield achieved for the benzannulated-5,6-analogue together with the modest yield achieved for the benzannulated-5,5-analogue, alternative products were targeted using the tandem process.

2.3.3 Tandem Overman rearrangement/RCM reaction for the synthesis of C-1 amino substituted indenes and dihydronaphthalenes

Indanes and tetralins which possess an amine functionality at the C-1 position are of interest within medicinal chemistry due to their potential pharmacological activity.[94] Examples of such compounds, which are currently on the market, are shown in Figure 12. (+)-Sertraline (Zoloft™) is currently used as an antidepressant drug,[95] (+)-indatraline has potential as a treatment for cocaine addiction[96] and rasagiline (Azilect™) is used in the treatment of Parkinson's disease.[97]

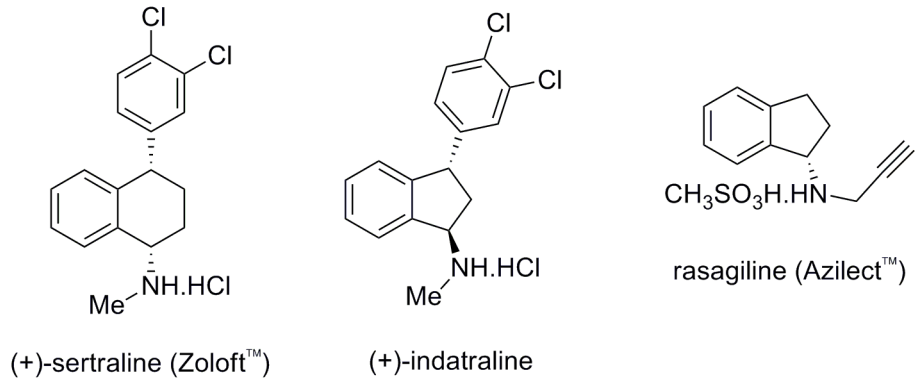


Figure 12: Pharmaceutical agents containing 1-aminoindane and 1-aminotetralin core

As the product of the RCM reaction for the aromatic substrates is a bicyclic allylic trichloroacetamide, it was proposed that a tandem Overman rearrangement/RCM reaction could be developed for the rapid synthesis of 1-aminoindene and 1-aminodihydronaphthalene units. Furthermore, the presence of the alkene within both systems would offer a handle for further functionalisation of the molecule if desired. Initially five targets were proposed upon which to develop the tandem process as shown in Figure 13.

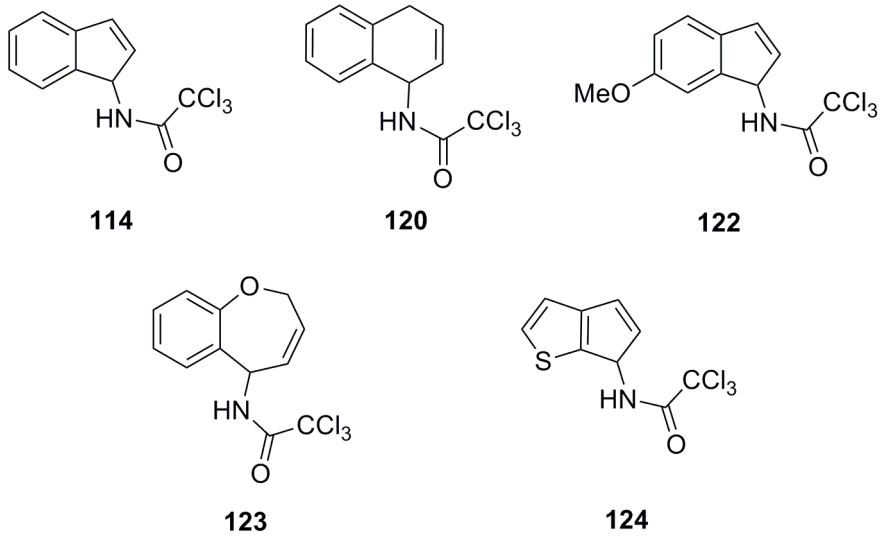
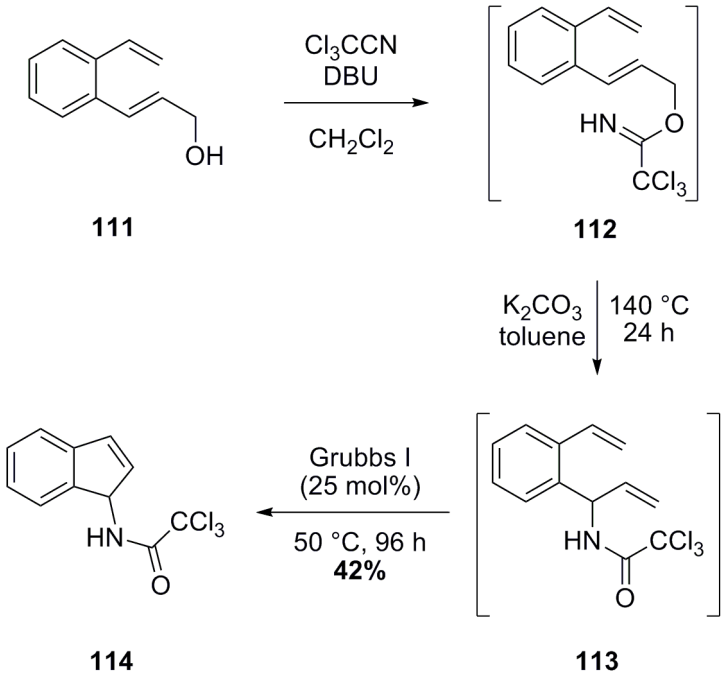


Figure 13: Initial targets for tandem Overman rearrangement/RCM process

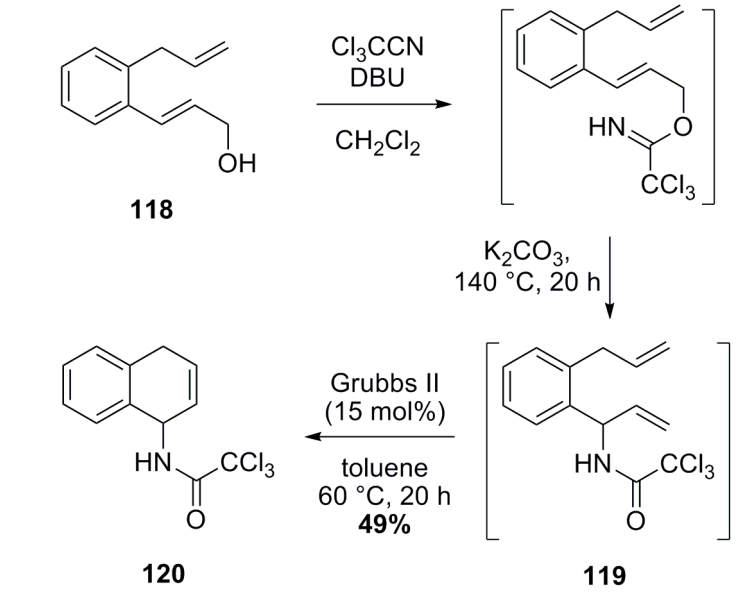
As the Overman rearrangement and subsequent RCM reaction had previously been performed individually on the benzannulated-5- and benzannulated-6-analogues, the two-step tandem process was initially used to synthesise these targets. The indene analogue **114** was successfully synthesised in 42% yield from allylic alcohol **111** using a tandem thermal

Overman rearrangement/RCM reaction (Scheme 68). A 25 mol% loading of Grubbs 1st generation catalyst was necessary for the RCM reaction possibly due to an increased rate of catalyst decomposition at 50 ºC. The elevated temperature was necessary to accelerate a sluggish RCM reaction.



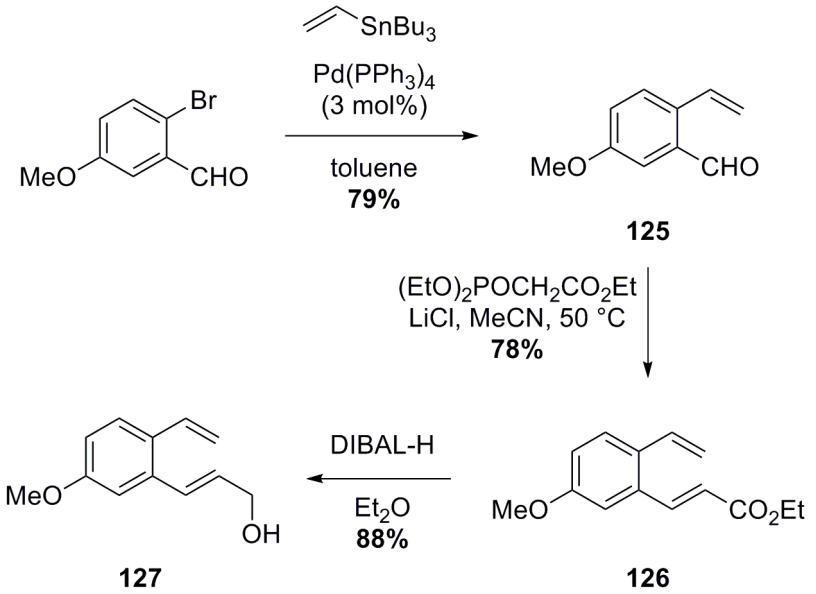
Scheme 68: Synthesis of 1-aminoindene analogue 114

Using the optimal conditions of metal-catalysed Overman rearrangement and Grubbs 1st generation catalysed RCM reaction, the desired 1-aminodihydronaphthalene product **120** was isolated in 38% yield from allylic alcohol **118**. By employing a thermal Overman rearrangement and switching to Grubbs 2nd generation catalyst for the RCM step, the yield was improved to 49% (Scheme 69).



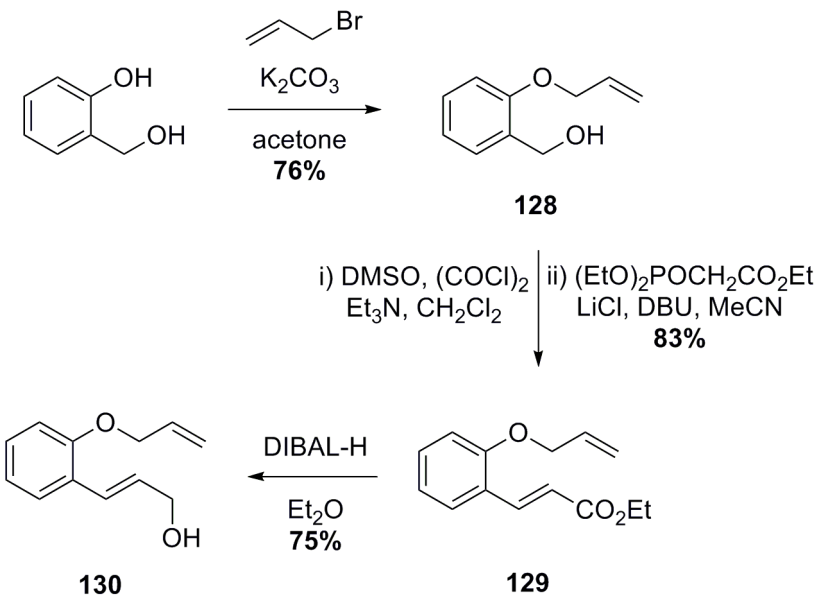
Scheme 69: Synthesis of the 1-aminodihydronapthalene analogue 120

With the synthesis of the basic structures optimised, focus was then turned to the synthesis of the precursors for the other targets. For the methoxyindene analogue **122**, a palladium(0)-catalysed Stille coupling of 2-bromo-5-methoxybenzaldehyde with tri-*n*-butyl(vinyl)tin formed the desired product **125** in 79% yield (Scheme 70). The subsequent Horner-Wadsworth-Emmons reaction afforded (*E*)-α,β-unsaturated ester **126** in 78%, which was reduced to allylic alcohol **127** using DIBAL-H in 88% yield.



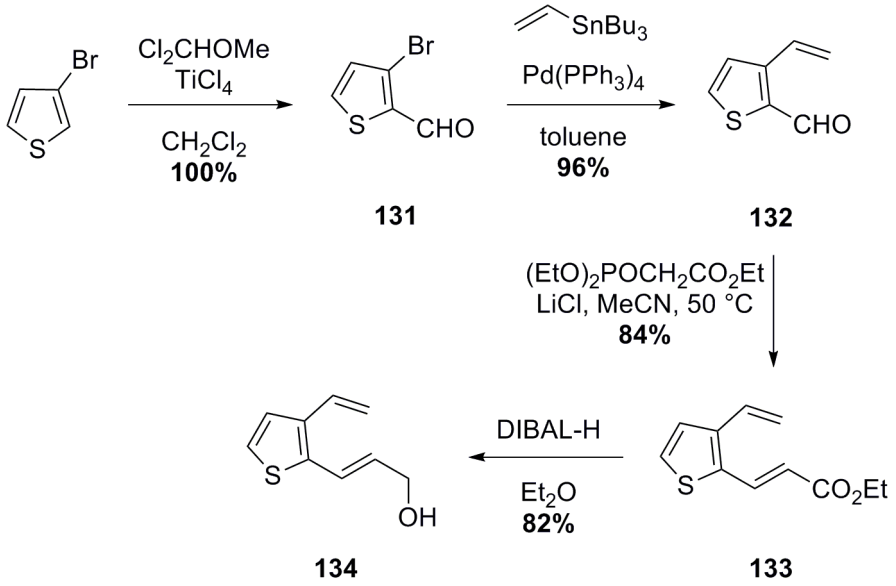
Scheme 70: Synthesis of the methoxyindene allylic alcohol precursor

The allylic alcohol precursor for the benzoxepine analogue **123** was synthesised from 2-hydroxybenzyl alcohol (Scheme 71). 2-Hydroxybenzyl alcohol was reacted with allyl bromide in the presence of potassium carbonate, forming allylated product **128** in 76% yield. A one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction afforded (*E*)-α,β-unsaturated ester **129** in 83% yield and DIBAL-H reduction of the ester moiety gave allylic alcohol **130** in 75% yield.



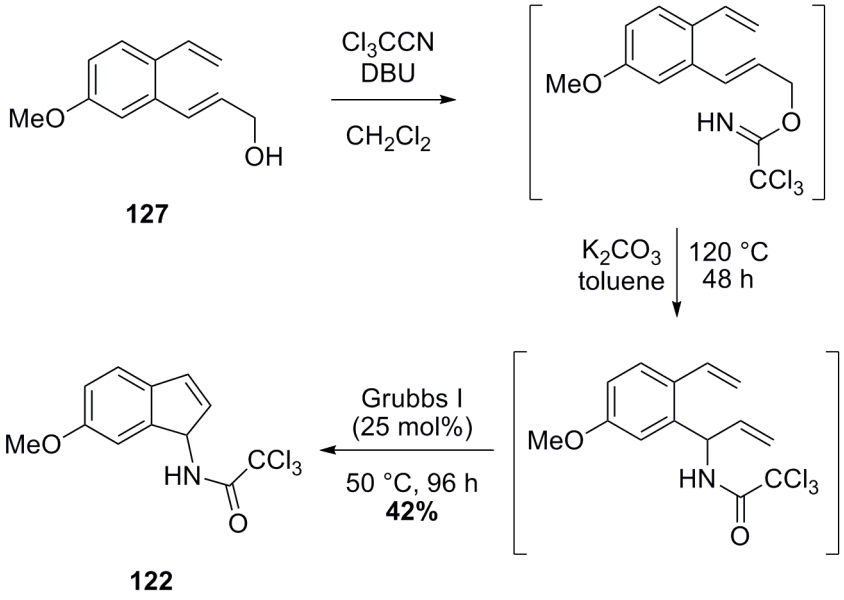
Scheme 71: Synthesis of the benzoxepine allylic alcohol precursor

For the thiophene analogue, 2-bromothiophene was formylated using Rieche conditions in quantitative yield (Scheme 72).[98] Stille coupling of bromide **131** with tri-*n*-butyl(vinyl)tin formed the desired coupled product **132** in 96% yield which subsequently underwent a Horner-Wadsworth-Emmons reaction to give (*E*)-α,β-unsaturated ester **133** in 84% yield. DIBAL-H reduction of the ester moiety formed allylic alcohol **134** in 82% yield. It is worth noting that intermediates **132**, **133** and **134** were reasonably unstable and had to be used within ca. two days of being synthesised before significant decomposition was observed.



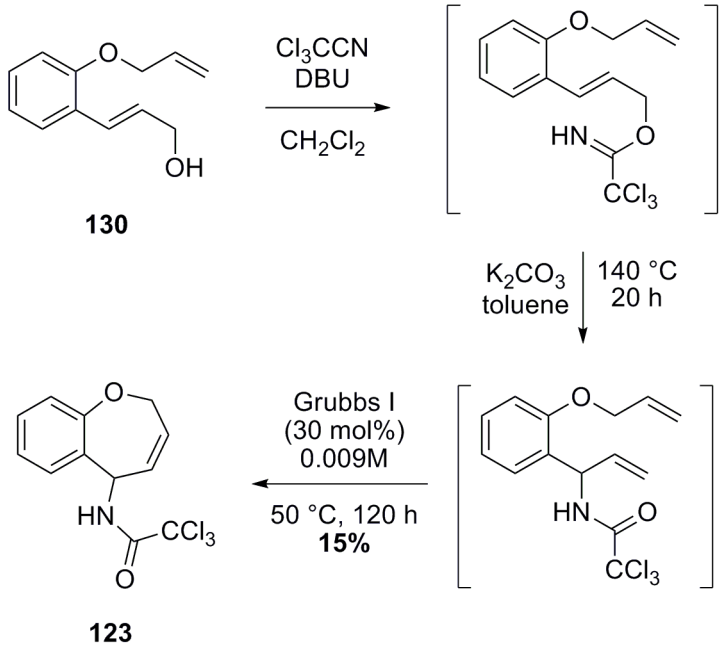
Scheme 72: Synthesis of the thiophene allylic alcohol precursor

The optimal conditions for indene analogue **114** were utilised for the methoxyindene analogue **122**, however it was apparent that decomposition of the substrate was occurring during the thermal Overman rearrangement. To overcome this, the temperature for the thermal rearrangement was reduced to 120 °C and the reaction time increased to 48 h (Scheme 73). This reduced the extent of the decomposition observed in the ^{1}H NMR spectrum of the crude reaction mixture. The subsequent RCM was catalysed by Grubbs 1st generation catalyst, forming the desired product **122** in 42% yield. Again, elevated temperatures were required to push the RCM step to completion, which in turn would lead to faster catalyst decomposition resulting in the need for high catalyst loading.



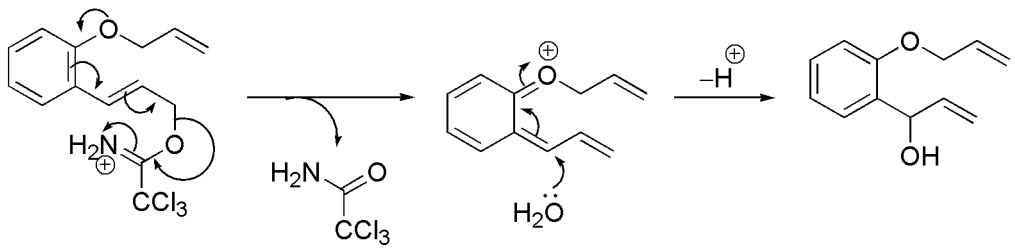
Scheme 73: Synthesis of the methoxyindene analogue 122

The synthesis of the benzoxepine and thiophene analogues proved more challenging than the previous examples. For the benzoxepine analogue **123**, some of the issues encountered for previous related analogues had to be taken into account. Firstly, the presence of the allyl ether meant that a thermal Overman rearrangement would be more favourable compared to a metal-catalysed rearrangement due to the issues of palladium(II) complexation observed for the oxy-5,6-bicyclic lactam **97** (Section 2.1.5). Secondly, due to the formation of a 7-membered ring, a reduced reaction mixture concentration would be necessary to achieve the highest possible yield of product. Despite taking these factors into account, a disappointing 15% yield of desired benzoxepine product **123** was isolated form allylic alcohol **130** (Scheme 74).



Scheme 74: First attempt at the synthesis of benzoxepine analogue 123

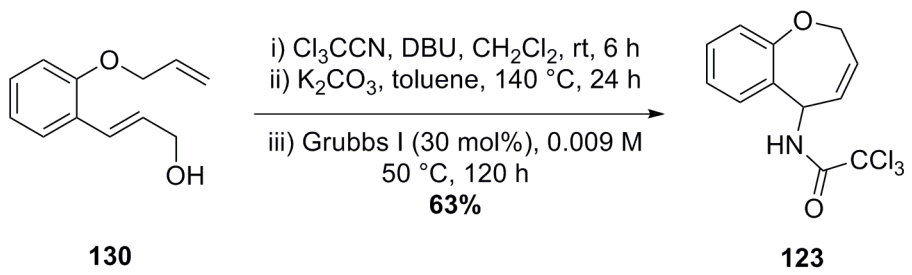
It was evident from the ^{1}H NMR spectrum that loss of the trichloroacetimidate unit from the allylic trichloroacetimidate substrate was occurring. An attempt to purify the allylic trichloroacetimidate by flash column chromatography resulted in increasing the amount of hydrolysis product present. It was suspected that the hydrolysis was promoted by the presence of the *ortho*-ether unit and it was being catalysed by the acidic silica (Scheme 75). The ^{1}H NMR spectrum indicated the presence of a substituted allyl group, which could be formed by the addition of water to the cationic intermediate during rearomatisation. Full analysis was carried out and the structure of the major side-product was confirmed by comparison to the literature data.[99]



Scheme 75: Proposed mechanism for the acid catalysed hydrolysis

To overcome this issue, it was proposed that neutral alumina could be used for the purification of the allylic trichloroacetimidate prior to the tandem process. Gratifyingly, the ^{1}H NMR spectrum of the alumina purified trichloroacetimidate showed no evidence of the

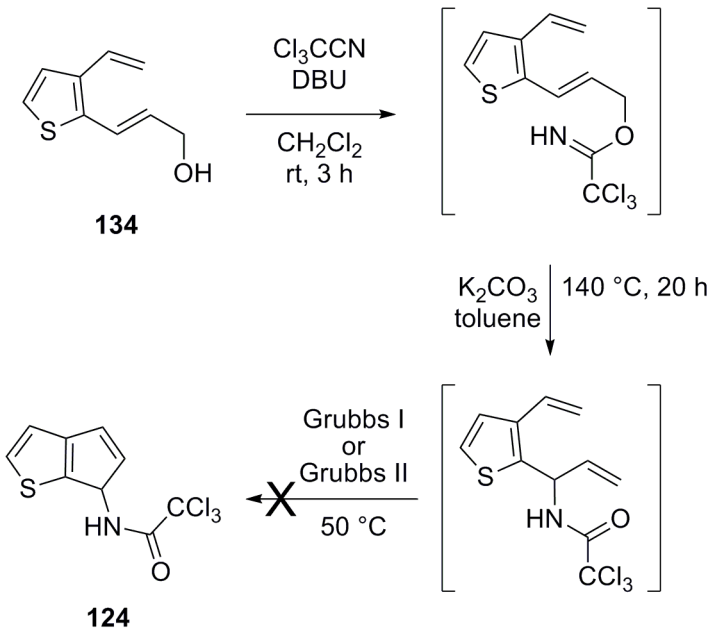
hydrolysis product and the subsequent thermal Overman rearrangement was complete in 24 h at 140 °C (Scheme 76). The concentration of the reaction mixture was then reduced to 0.009 M before the addition of Grubbs 1st generation catalyst. After stirring for 120 h at 50 °C the desired oxepine product was isolated in 63% yield over three steps.



130 **123**

Scheme 76: Synthesis of the oxepine analogue 123

Similar issues were encountered for the thiophene analogue **124**, however unlike the benzoxepine analogue no clear evidence of hydrolysis was observed by ^{1}H NMR spectroscopy. Instead, broad peaks were visible between 5–7 ppm in the ^{1}H NMR spectrum indicating that some adverse interaction of the allylic trichloroacetimidate substrate with the acidic silica was occurring. To test this, alumina was again employed to purify the allylic trichloroacetimidate prior to a thermal Overman rearrangement. This resulted in the successful isolation of the allylic trichloroacetimidate, which was then subjected to the tandem Overman rearrangement/RCM reaction (Scheme 77). Although the thermal Overman rearrangement appeared to progress as expected when analysed by ^{1}H NMR spectroscopy, the subsequent RCM reaction failed to yield any desired product when catalysed by either Grubbs 1st or 2nd generation catalysts. Unfortunately, at this stage of the project, time restraints meant that further investigation into the synthesis of the thiophene analogue was not possible.



Scheme 77: Attempted synthesis of the thiophene analogue 124

2.3.4 Summary

A one-pot tandem Overman rearrangement/RCM has successfully been utilised for the synthesis of bicyclic allylic trichloroacetamides. This process utilises simple allylic alcohol substrates, which are readily synthesised from commercially available starting materials. The tandem process developed allows the rapid synthesis of pharmacologically important 1-aminoindene and 1-aminodihydronaphthalene units as well as related compounds.

2.3.5 Future work

The two-step tandem process developed within this project will be used to complete the synthesis of thiophene analogue **124** as well as expand the library of target compounds (Figure 14). It is anticipated that the use of neutral alumina for the purification of the allylic trichloroacetimidate could be beneficial for the synthesis of all aromatic fused analogues and lead to improved yields for these targets.

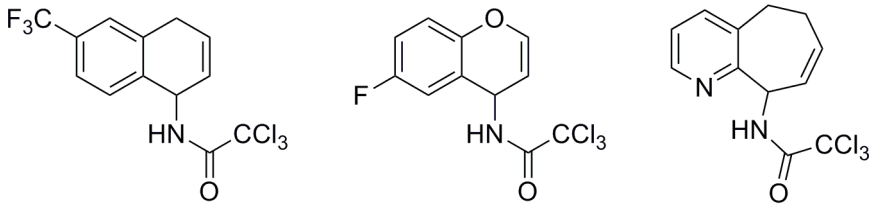
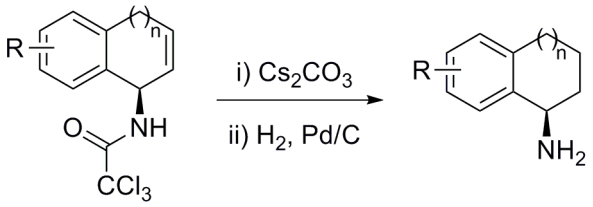


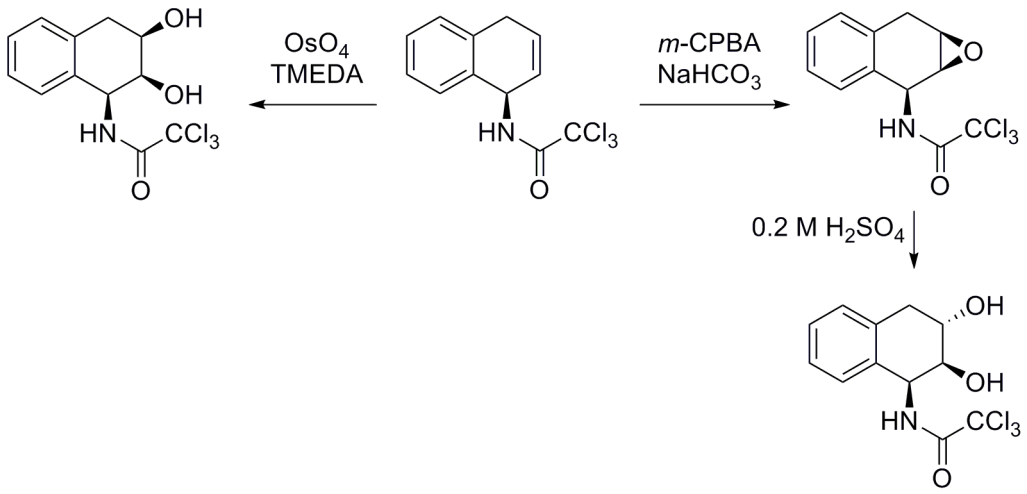
Figure 14: Potential targets for the application of the tandem process

Furthermore, it is proposed that an asymmetric Overman rearrangement could be employed to access enantiomerically enriched products. Once formed, the deprotection[100] and hydrogenation of the products would generate a number of targets with potential biological activity (Scheme 78).



Scheme 78: Deprotection and hydrogenation of the allylic trichloroacetamides

In addition, the functionalisation of the cyclic allylic amides will be investigated. The *syn*-diol can be accessed using a directed dihydroxylation reported by Donohoe and co-workers (Scheme 79).[55,101] A directed epoxidation followed by acid-mediated ring-opening will lead to the formation of the *anti*-diol.[54]

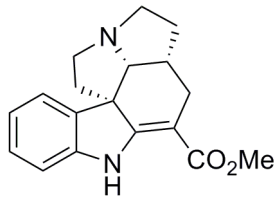


Scheme 79: Functionalisation of the cyclic allylic amide

2.4 Studies towards the total synthesis of deethylibophyllidine

2.4.1 Background and previous synthetic strategies

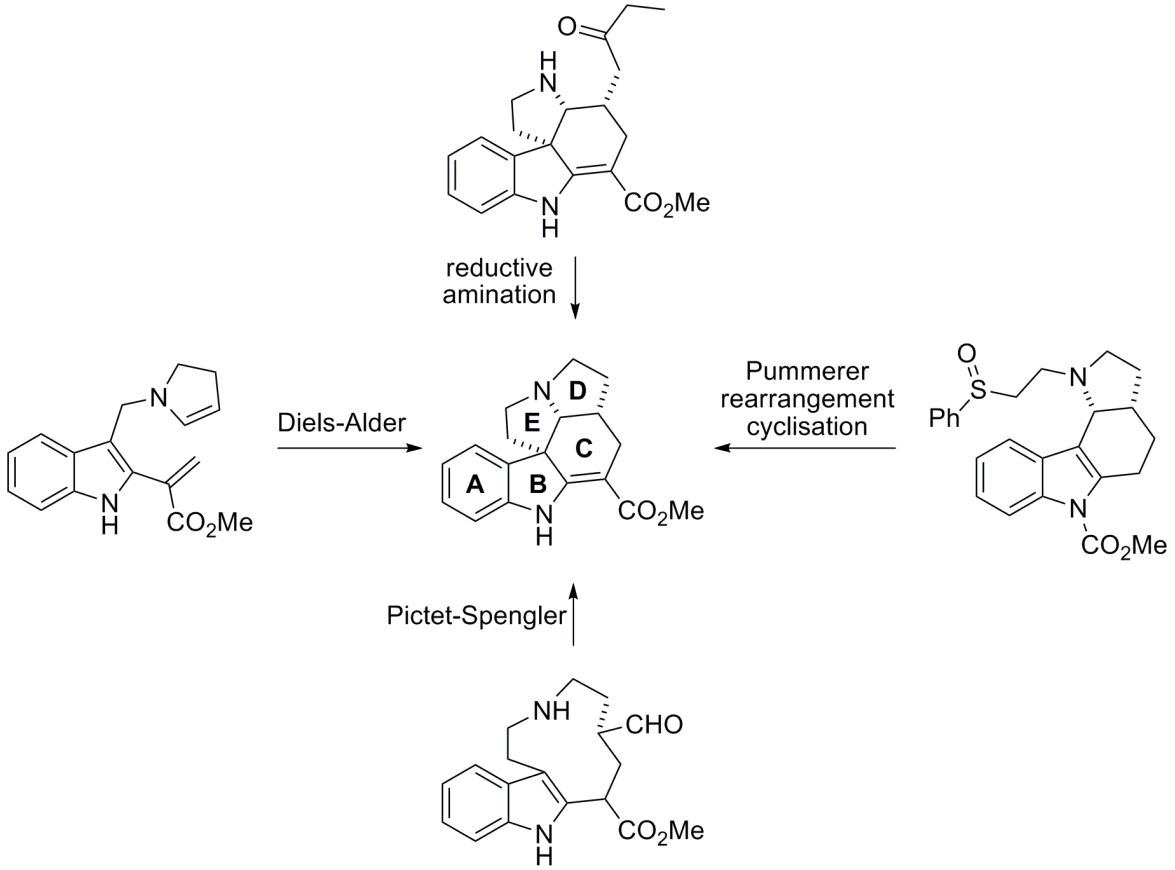
Deethylibophyllidine is a natural product and was isolated from the leaves of *Tabernanthe Iboga* in 1976 (Figure 15).[102,103] Alkaloids isolated from this plant have been shown to possess psychoactive properties, some of which have been reported as potential treatments for substance addiction including heroin, cocaine and methamphetamine.[104,105] Thus, there has been interest in synthesising various alkaloids within this class to further explore their pharmacological activity.



(+)-deethylibophyllidine

Figure 15: Structure of (+)-deethylibophyllidine

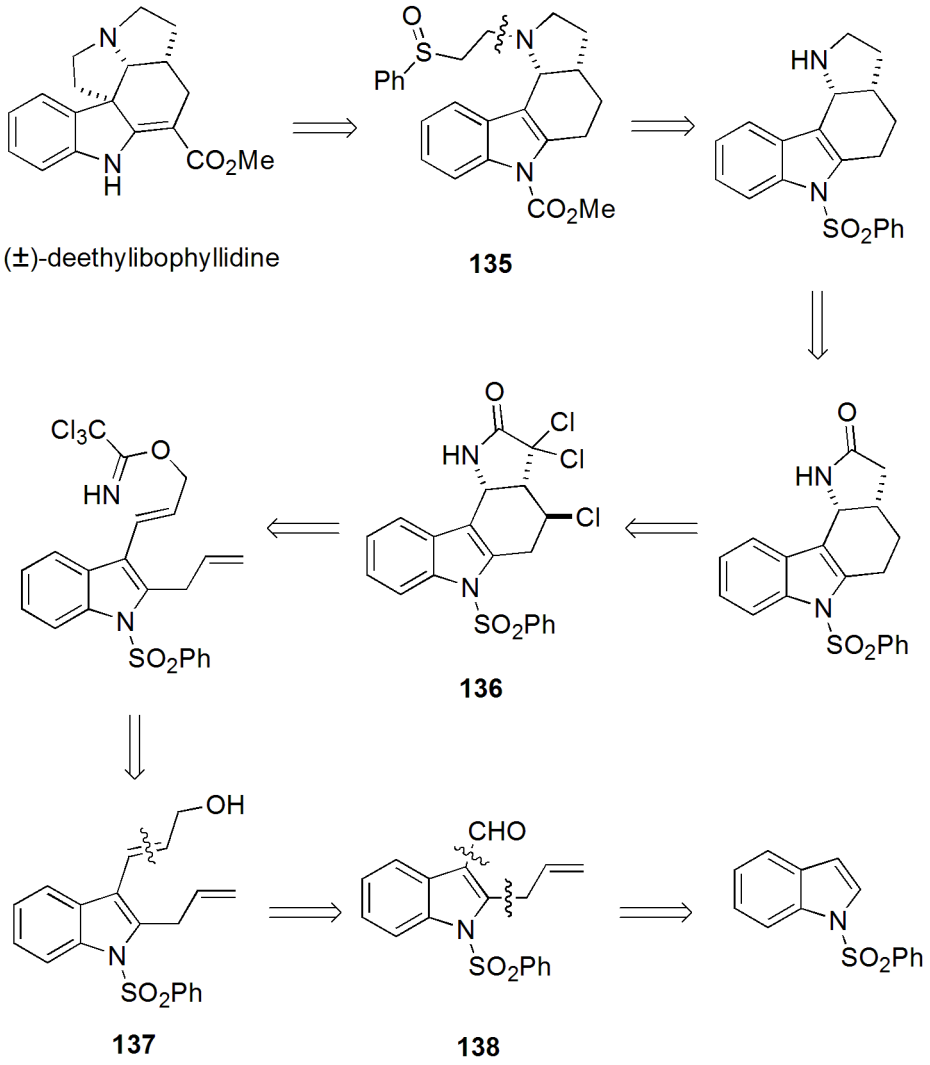
There have been several previous syntheses of (±)-deethylibophyllidine which use various strategies to form the desired pentacyclic core. The key cyclisations include an intramolecular Diels-Alder reaction to form the C and E rings,[106] reductive amination to form the D ring,[107] Pummerer rearrangement-cyclisation to form the E ring[108] and an intramolecular Pictet-Spengler reaction to form the C, D and E rings simultaneously (Scheme 80).[109] It was envisaged that the tandem process developed in Section 2.1, as well as information gained in Section 2.3, could be utilised in the formation of the required *cis*-fused C and D rings of deethylibophyllidine.



Scheme 80: Previous approaches to the synthesis of (±)-deethylibophyllidine

2.4.2 Proposed retrosynthesis

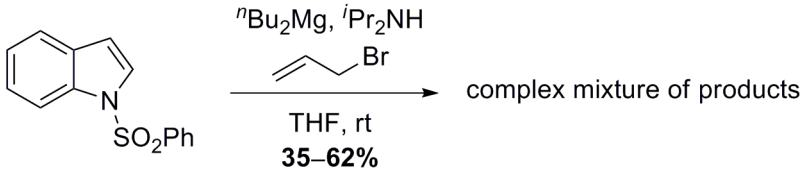
Synthesis of advanced intermediate **135** would complete the formal synthesis of deethylibophyllidine, with three further steps required to furnish the natural product (Scheme 81).[108] Disconnection of the *N*-alkyl chain, functional group interchange and introduction of three chlorines leads to compound **136**. This is the product of the one-pot tandem process and can be synthesised from allylic alcohol **137**. Disconnection of the alkene affords aldehyde **138** which can be formed from the C-2 alkylation and C-3 formylation of commercially available 1-phenylsulfonyl indole. Initially, a racemic synthesis will be developed for the synthesis of (±)-deethylibophyllidine. If successful, an asymmetric approach would also be explored to form enantiomerically enriched (+)-deethylibophyllidine.



Scheme 81: Proposed retrosynthesis of deethylibophyllidine

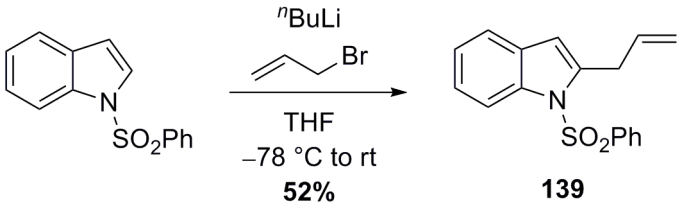
2.4.3 Attempted synthesis of (2*E*)-3-[2-allyl-1-(phenylsulfonyl)-1*H*-indole]prop-2-en-1-ol 137

The first stage was the synthesis of the allylic alcohol precursor **137** from commercially available 1-phenylsulfonyl indole. Initially, a magnesium amide base and allyl bromide were tested for the introduction of the required allyl side chain at the C-2 position of the indole system.[110] The reaction proved more difficult than expected as both mono- and dialkylated products were formed during the course of the reaction which were difficult to separate (Scheme 82). As none of the product formed was pure enough to be used for the subsequent transformations, an alternative approach using a lithium base was considered.



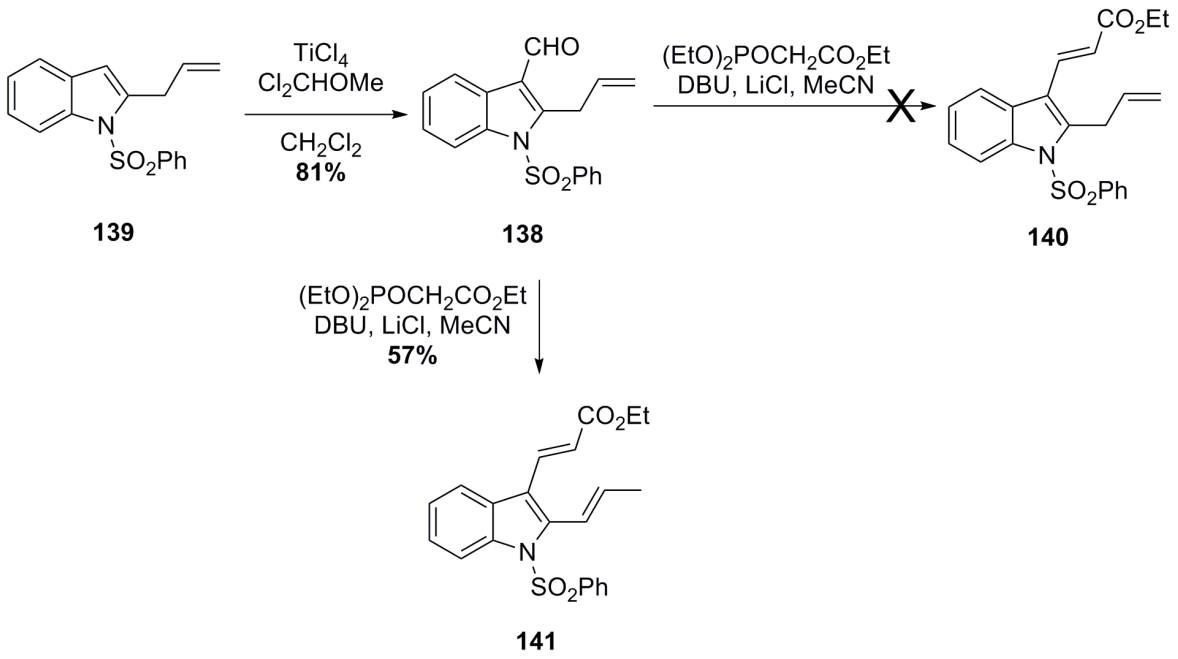
Scheme 82: Attempted allylation of the indole ring using a magnesium base

The use of *n*-butyl lithium and allyl bromide gave more consistent results and after some optimisation the desired allylated product **139** was isolated in 52% yield (Scheme 83). In all cases, a significant amount of starting material was also recovered from the reaction mixture, which accounted for the low yield of product.



Scheme 83: Allylation of the indole ring using butyl lithium

The next step was the introduction of a formyl group at the C-3 position of the indole. Using Rieche formylation conditions of titanium tetrachloride and dichloromethyl methyl ether at –78 ºC, the desired formylated indole **138** was formed in 81% yield (Scheme 84).[98] Aldehyde **138** was subsequently used in a Horner-Wadsworth-Emmons reaction and initial analysis suggested that the desired (*E*)-α,β-unsaturated ester **140** had been formed. On closer inspection of the ^{1}H NMR spectrum, it was discovered that isomerisation of the allyl chain had occurred forming compound **141**. It was proposed that the presence of the base in the Horner-Wadsworth-Emmons reaction could cause a 1,5-proton shift to form the more stable fully conjugated system.[111]

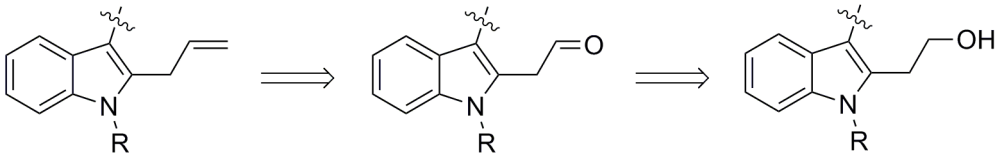


Scheme 84: Formylation followed by a Horner-Wadsworth-Emmons reaction

As the presence of the allyl group is essential for the formation of the C ring of the target product, a new strategy was necessary to avoid the isomerisation of the allyl side chain.

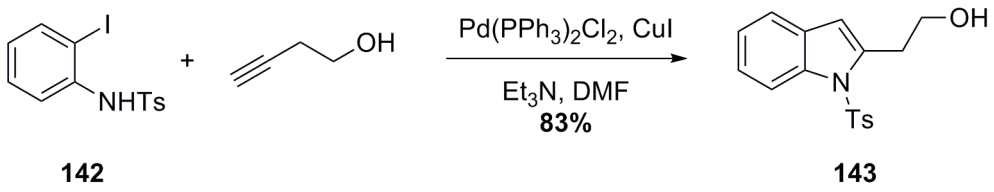
2.4.4 Alternative strategy using a Larock indole synthesis

The use of an oxygenated side chain, which could be converted into the required allyl side chain, was proposed. As allylic trichloroacetimidate formation prior to the three-step tandem process requires a base, it would not be possible to convert the oxygenated side chain to the desired allyl group until after the Overman rearrangement step. Once the rearrangement is complete, the side chain would be transformed into the allyl group, followed by a two-step tandem RCM/Kharasch cyclisation. An ethanol side chain was proposed for the new strategy (Scheme 85). Oxidation of the alcohol followed by a methylenation of the aldehyde group would form the desired allyl substituted compound.



Scheme 85: Proposed retrosynthesis of the indole C-2 chain

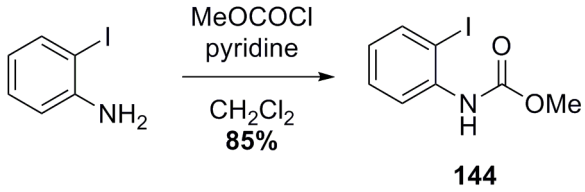
Jacobsen and co-workers have previously reported the formation of indoles bearing an ethanol side chain using a Larock heteroannulation reaction.[112,113] They showed that reaction of tosyl protected iodoaniline **142** with 3-butyn-1-ol in the presence of bis(triphenylphosphine)palladium(II) dichloride, copper(I) iodide and triethylamine afforded the tosyl protected indole **143** in 83% yield (Scheme 86).



142 **143**

Scheme 86: Jacobsen's synthesis of indole 143 using a Larock heteroannulation

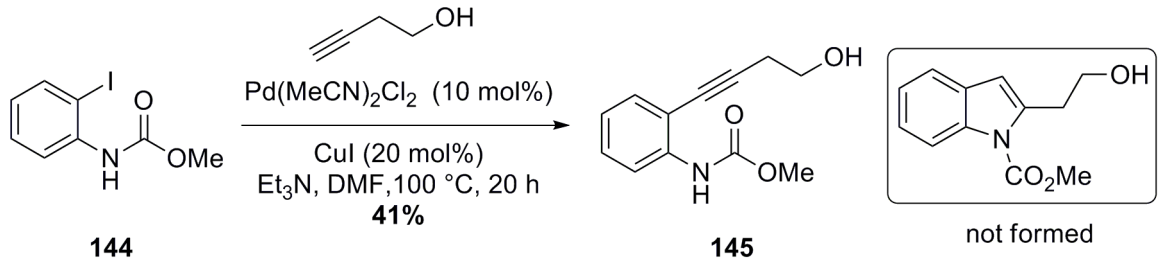
For application to the current synthesis, a methyl carbamate protected iodoaniline was initially explored. This was due to the presence of this group in the final product. Reaction of 2-iodoaniline with methyl chloroformate in the presence of pyridine formed the desired protected aniline **144** in 85% yield (Scheme 87).



144

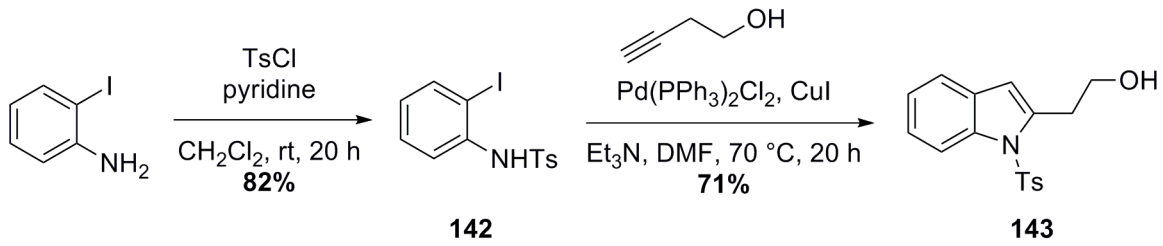
Scheme 87: Methyl carbamate protection of 2-iodoaniline

The subsequent indole formation using the methyl carbamate protected aniline proved difficult. Different palladium(II) catalysts including $PdCl_2$, $Pd(MeCN)_2Cl_2$ and $Pd(PPh_3)_2Cl_2$ were tested and the reaction was carried out at elevated temperatures; however, no desired product was detected in the crude reaction mixture. Instead, the Sonogashira coupled product **145** was isolated in 41% yield (Scheme 88). It has previously been reported that a strong electron-withdrawing group is required to activate the amine and facilitate the one-pot coupling and cyclisation under mild conditions.[114] In contrast, compounds bearing an alkoxycarbonyl substituent require a strong base to induce the cyclisation after the coupling reaction has taken place.[115]



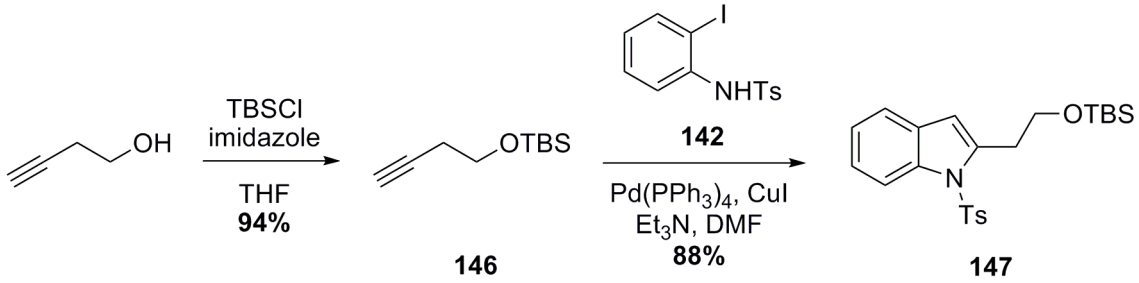
Scheme 88: Formation of the Sonogashira product 145

Despite the requirement of the methyl carbamate for the final product, the tosyl group used by Jacobsen and co-workers was instead utilised. As expected, the tosyl protected aniline **142** was afforded in 82% yield with the subsequent indole **143** formed successfully in 71% yield (Scheme 89).



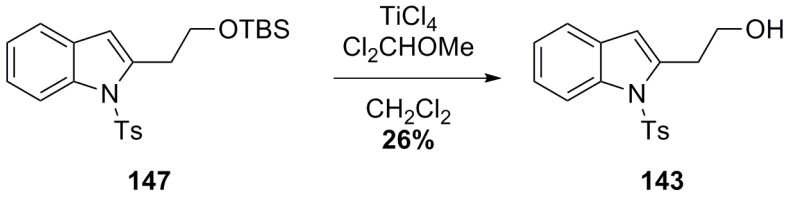
Scheme 89: Synthesis of tosyl-protected indole 143

In order to avoid any unwanted side reaction of the primary alcohol in the subsequent reaction sequence, a protecting group for the alcohol was required. It was envisaged that by carrying out a silyl protection of the primary alcohol before indole formation, the number of linear steps of the synthesis could be reduced. In the event, the *tert*-butyldimethylsilyl (TBS) protection of 3-butyn-1-ol proceeded well affording desired siloxy ether **146** in 94% yield (Scheme 90). The subsequent indole **147** was afforded in 88% yield. It is worth noting that this reaction was subjected to a quick screen of palladium catalysts and tetrakis(triphenylphosphine)palladium(0) was found to be as efficient as bis(triphenylphosphine)palladium(II) dichloride for the indole synthesis.



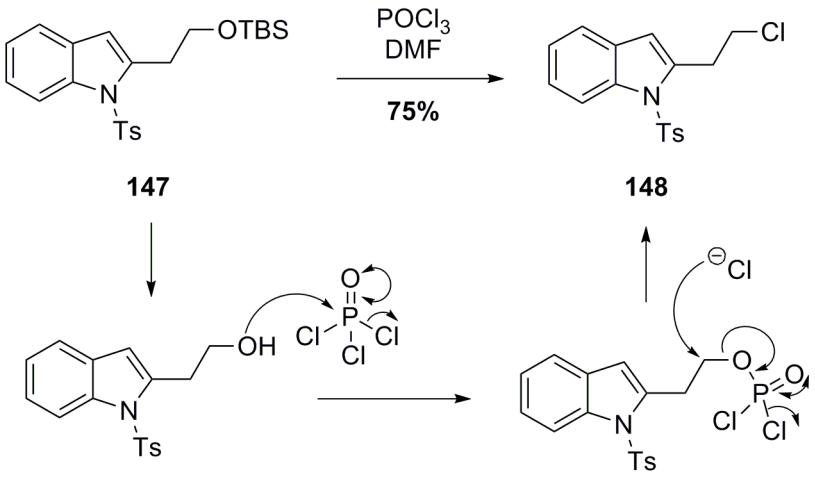
Scheme 90: Formation of indole 147 from but-3-yn-1-ol

The next step was C-3 formylation of the indole ring. Initially the Rieche formylation using titanium tetrachloride and dichloromethyl methyl ether was attempted, however no formylated product was detected (Scheme 91).[98] Instead, the silyl deprotected starting material **143** was isolated as the main product. As titanium tetrachloride is highly moisture sensitive, small amounts of moisture within the reaction mixture could lead to the formation of titanium oxide and HCl. It is this acid which could subsequently deprotect the alcohol.



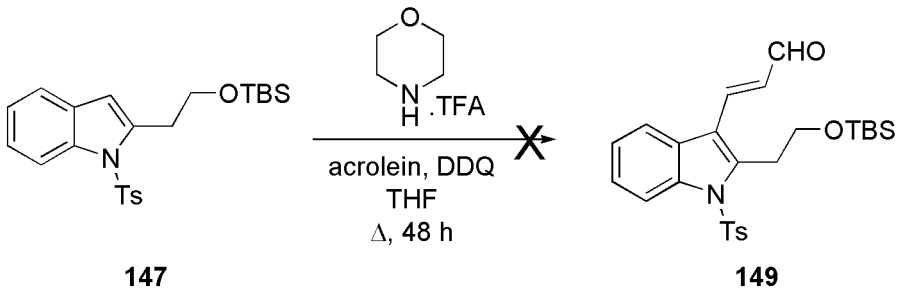
Scheme 91: Failed attempt at a Rieche formylation reaction

A Vilsmeier formylation using phosphorous oxychloride and *N*,*N*-dimethylformamide was also attempted but again none of the desired product was formed (Scheme 92).[116] Mass spectrometry analysis of the product isolated from this reaction indicated the formation of chloride **148**. This could have resulted from the removal of the TBS group (from the *in situ* formation of HCl), activation of the alcohol by the phosphorous oxychloride and finally displacement by a chloride ion.



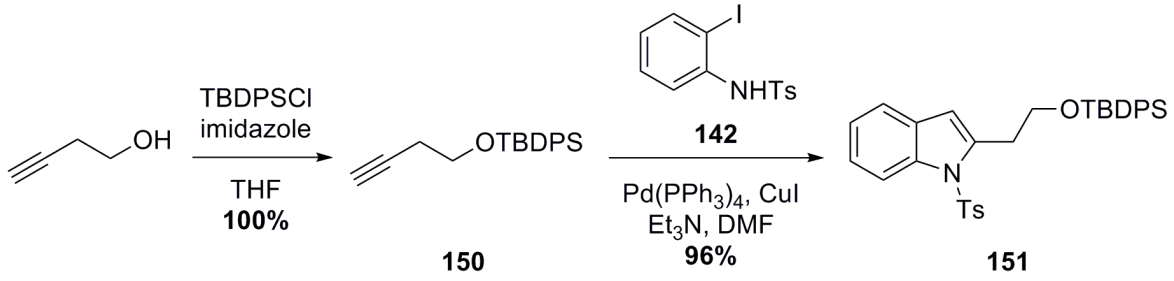
Scheme 92: Failed attempt at a Vilsmeier formylation

Jiao and co-workers recently reported the introduction of an alkenyl group at the C-3 position of an indole using an organocatalysed reaction.[117] This procedure was also attempted but unfortunately none of the desired α,β-unsaturated aldehyde **149** was formed, with only starting material recovered (Scheme 93).



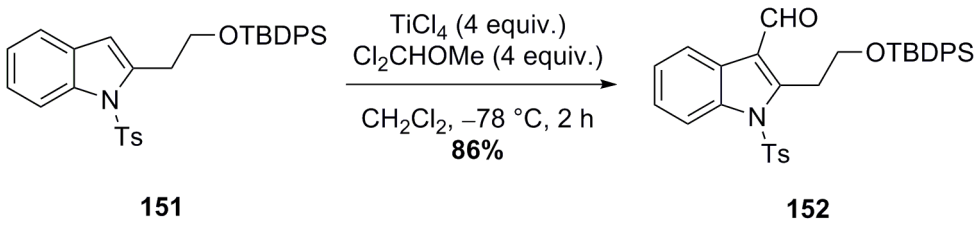
Scheme 93: Attempt at performing an alkenylation reaction

It was evident from the first two attempts that the TBS group was not robust enough to cope with the *in situ* formation of acid from the formylation reactions. It was envisaged that this could be overcome by introducing a bulkier silyl group and so the use of a *tert*-butyldiphenylsilyl (TBDPS) group was explored. Silyl protection of 3-butyn-1-ol with *tert*-butyldiphenylsilyl chloride formed the desired silyloxy ether **150** in quantitative yield and subsequent reaction with the tosyl-protected iodoaniline **142** afforded the desired indole **151** in 96% yield (Scheme 94).



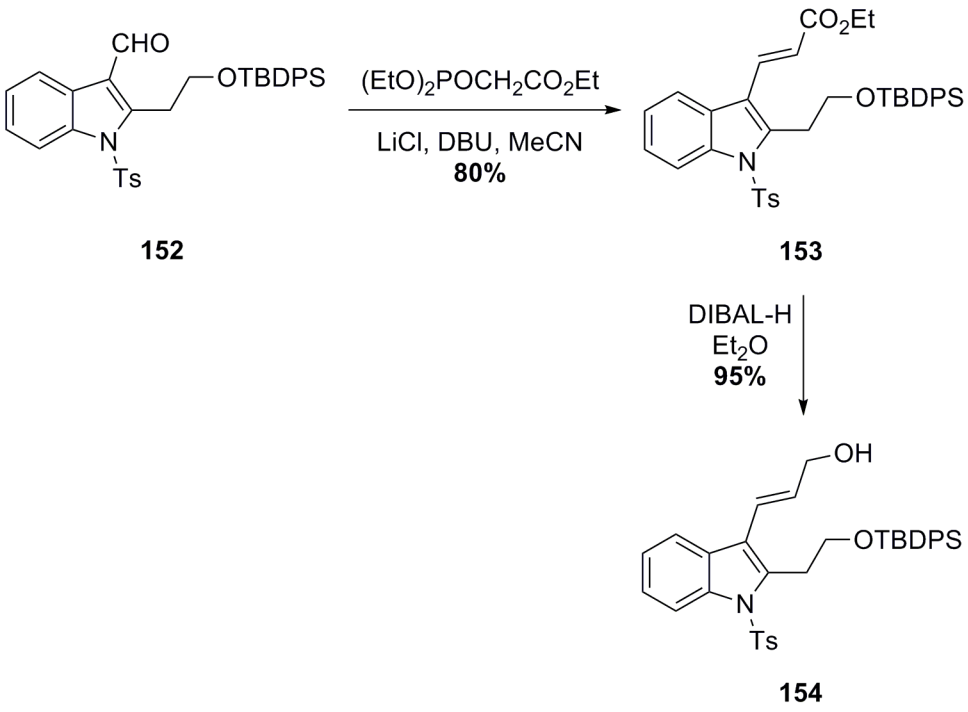
Scheme 94: TBDPS-protection of 3-butyn-1-ol and subsequent indole formation

Attempts at performing the organocatalysed alkenylation and the Vilsmeier formylation failed with only starting material recovered in both cases. Although disappointing, the fact that the TBDPS group remained in place after the Vilsmeier formylation was encouraging, suggesting that this bulkier silyl group could withstand small amounts of *in situ* HCl formation within the reaction mixture. The subsequent attempt using a Rieche formylation proved successful, giving the desired formylated product **152** in 86% yield (Scheme 95).



Scheme 95: Synthesis of formylated indole 152

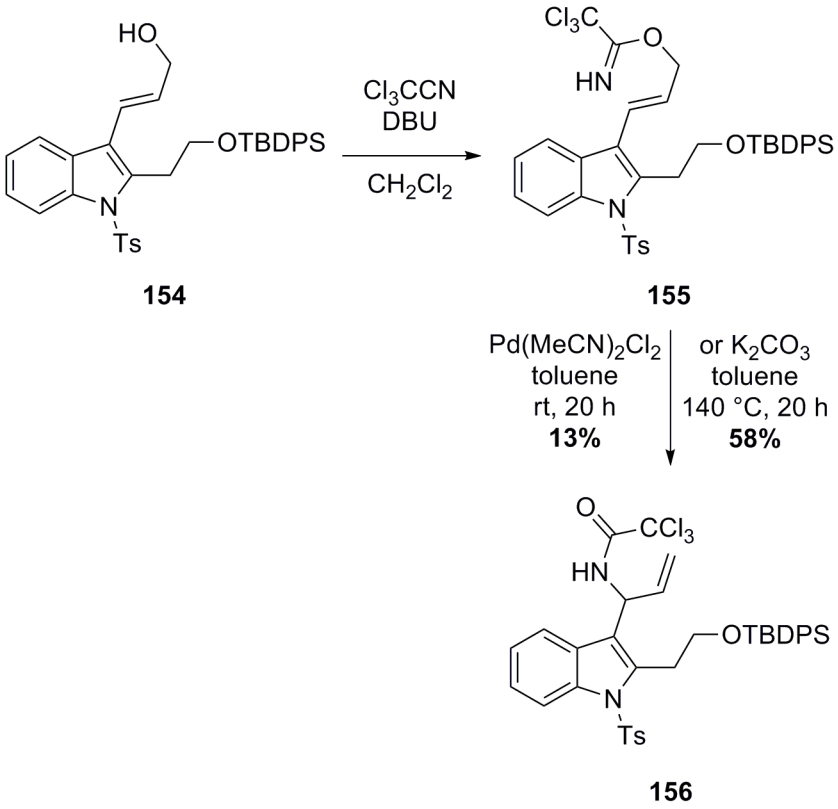
The next step was a Horner-Wadsworth-Emmons reaction using the newly introduced aldehyde. This proceeded well forming the (*E*)-α,β-unsaturated ester **153** in 80% yield and reduction of the ester using DIBAL-H gave the desired allylic alcohol **154** in 95% yield (Scheme 96).



152 **153** **154**

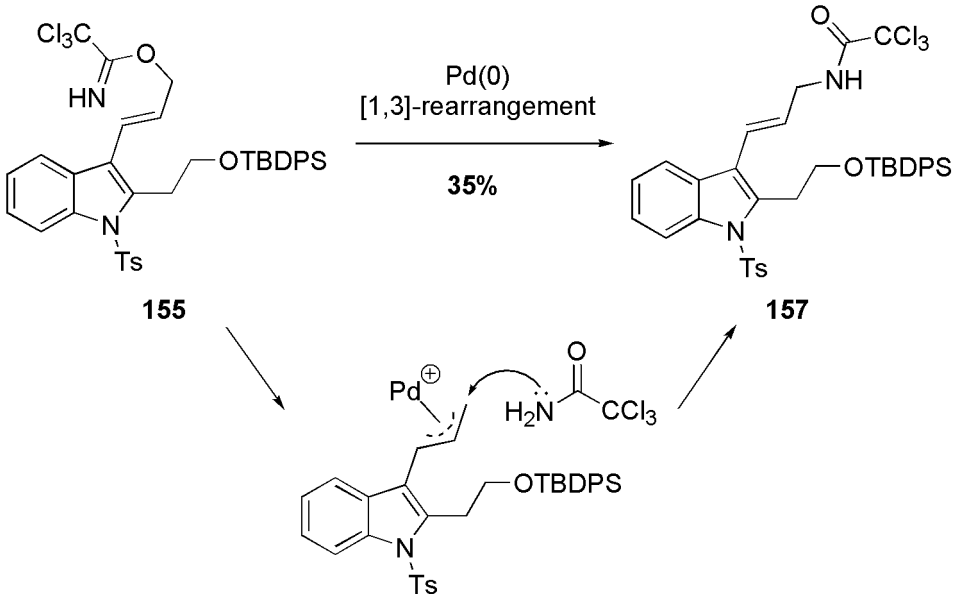
Scheme 96: Formation of allylic alcohol 154

The next stage of the synthesis was formation of the allylic trichloroacetimidate **155** followed by the Overman rearrangement. Once complete, this would be followed by the transformation of the oxygenated side chain to the desired allyl group for the subsequent tandem RCM/Kharasch cyclisation. In the event, the initial attempts at carrying out allylic trichloroacetimidate formation and subsequent Overman rearrangement proceeded in modest yields with the allylic trichloroacetamide **156** afforded in 13% yield using a palladium(II)-catalysed rearrangement and 58% yield for a thermal rearrangement (Scheme 97).



Scheme 97: Initial results for the formation of allylic trichloroacetamide 156

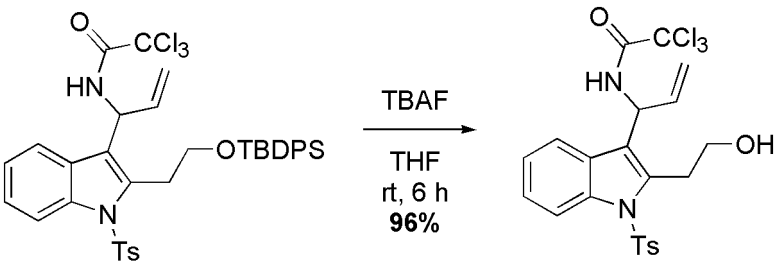
For the palladium catalysed rearrangement, a significant amount of the [1,3]-rearrangement (anti-Claisen) product was recovered which accounts for the low yield of desired [3,3]-rearranged product. This can arise from a competing palladium(0)-catalysed pathway (Scheme 98). Bosnich and co-workers proposed that in the presence of palladium(0), π-allyl complex formation can undergo nucleophilic attack by the eliminated trichloroacetamide forming the anti-Claisen product **157**.[67]



Scheme 98: [1,3]-rearrangement catalysed by Pd(0)

Unfortunately, subsequent attempts at the Overman rearrangement failed to improve the yield of allylic trichloroacetamide **156**. ^{1}H NMR spectroscopy indicated the presence of olefinic hydrogen atoms that did not match the chemical shift of the desired allylic trichloroacetamide group. Concurrently with this work, results from the benzoxepine analogue **123** (Section 2.3.3), showed that the presence of a lone pair of electrons in conjugation with the aromatic system and the allylic trichloroacetimidate could result in the elimination of trichloroacetamide from the molecule. This elimination could occur in the presence of acid from the silica during the purification of the allylic trichloroacetimidate. Considering the presence of the lone pair of electrons on the indole nitrogen, it was envisaged that neutral alumina could be employed thus avoiding compound decomposition. In the event, NMR spectroscopy analysis of the allylic trichloroacetimidate **155** after washing through alumina, showed clean product with no sign of decomposition. The subsequent Overman rearrangement formed the desired allylic trichloroacetamide **156** in 37% yield. It is worth noting that the 58% yield of desired product **156** afforded during the initial attempt might have been due to the amount of silica used and/or the rate of filtration during the allylic trichloroacetimidate purification. Both a smaller amount of silica and a quicker rate of filtration would have resulted in less decomposition of allylic trichloroacetimidate, therefore resulting in the 58% yield of product isolated after the Overman rearrangement. Unfortunately, due to time constraints, this reaction was only attempted once after the implementation of alumina. Some further optimisation will be required to improve the yield of allylic trichloroacetamide product.

The next stage in the synthesis was the manipulation of the oxygenated side chain into the desired allyl group. The strategy for this was illustrated previously in Scheme 84, with TBDPS removal followed by oxidation of the primary alcohol to the aldehyde. Methylenation of the aldehyde using a Wittig olefination or Tebbe reaction would form the desired terminal alkene. Again, due to time constraints, only the silyl deprotection was carried out. In the presence of tetra-*n*-butylammonium fluoride, the desired deprotected primary alcohol **158** was afforded in 96% yield (Scheme 99).



156 **158**

Scheme 99: Siloxy deprotection of the primary alcohol

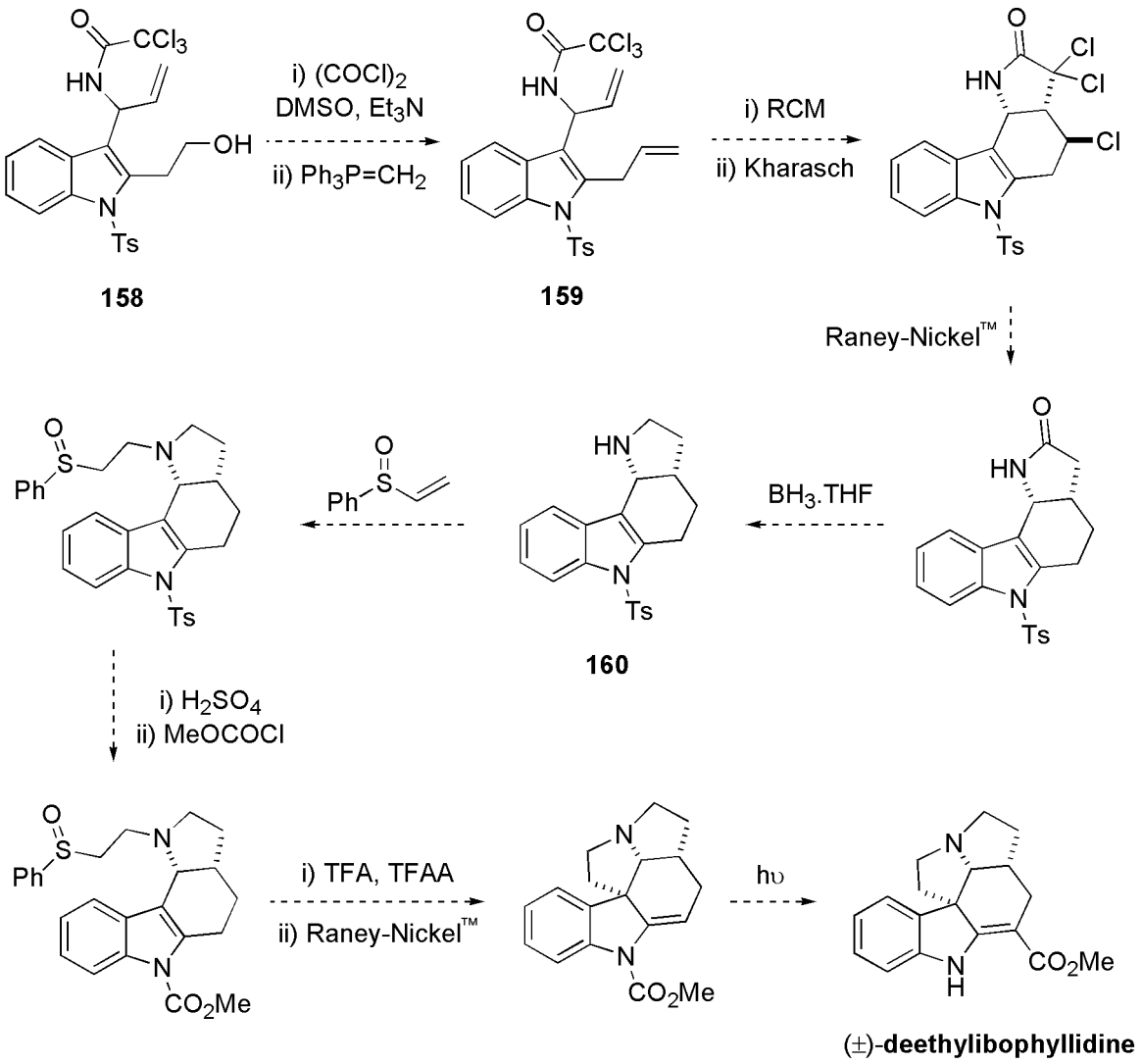
2.4.5 Summary

Significant progress has been made towards the total synthesis of deethylibophyllidine. Some problems were encountered early in the synthesis which unfortunately prevented progression to the tandem reaction stage of the project. A Larock heteroannulation reaction was successfully employed to form the desired indole system more efficiently than the originally proposed strategy involving the introduction of the allyl chain onto a preformed indole ring. The construction of the allylic alcohol proceeded well and although decomposition of the allylic trichloroacetimidate on silica prevented full optimisation of the Overman rearrangement, a solution to stop this decomposition has been implemented and so future work should allow the successful completion of the natural product.

2.4.6 Future work

With the oxygenated side chain deprotected, the next stage of the synthesis is the oxidation of the primary alcohol **158** to the aldehyde followed by a methylenation reaction (Scheme 100). This will afford the desired diene **159** which will then be subjected to a tandem RCM/Kharasch cyclisation catalysed by Grubbs 1st generation catalyst. Removal of the chlorine atoms using Raney-Nickel™ will be followed by reduction of the lactam to form

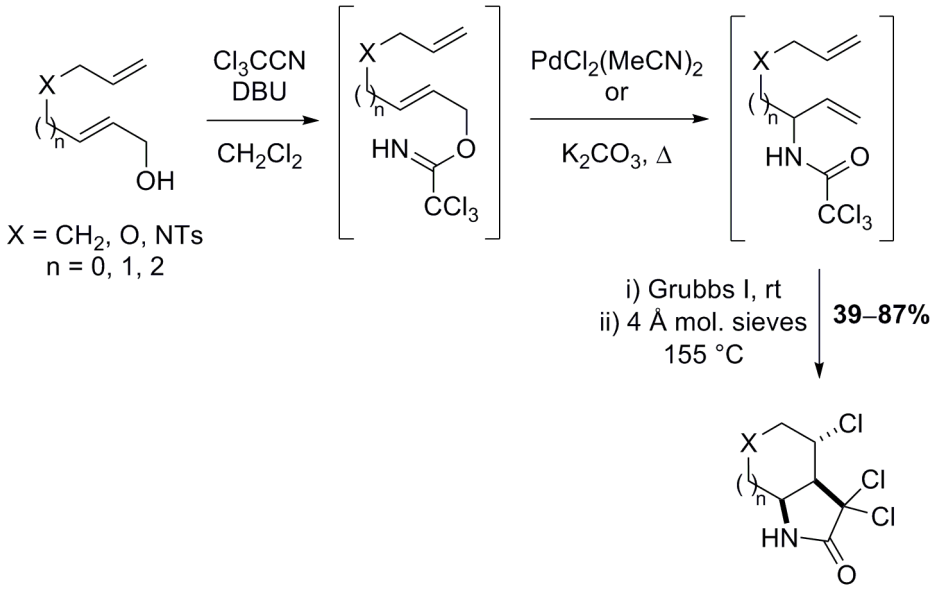
cyclic amine **160**. Alkylation of the amine with phenyl vinyl sulfoxide followed by exchange of the tosyl group for a methyl ester will complete the formal synthesis of the natural product.[108] To complete the total synthesis an acid catalysed Pummerer rearrangement-cyclisation followed by desulfurisation using Raney-Nickel™ would form the desired pentacyclic system. Finally, UV irradiation of this compound would furnish the target molecule.



Scheme 100: Future work to complete the synthesis of (±)-deethylibophyllidine

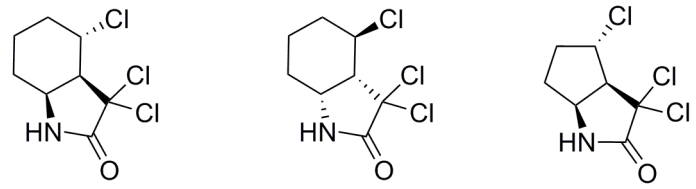
2.5 Conclusions

During the course of this research programme, a novel tandem process has been developed for the fast and efficient synthesis of bicyclic γ-lactams (Scheme 101). Treatment of an allylic alcohol with trichloroacetonitrile in the presence of DBU formed the required allylic trichloroacetimidate. This was then subjected to a one-pot tandem Overman rearrangement/RCM/Kharasch cyclisation to form the desired bicyclic γ-lactam as a single diastereomer, in good to high yields over four steps. Overall, the process involves the formation of carbon-carbon, carbon-nitrogen, carbon-oxygen and carbon-chlorine bonds, two ring systems and three new stereogenic centres.



Scheme 101: Synthesis of the bicyclic γ-lactams

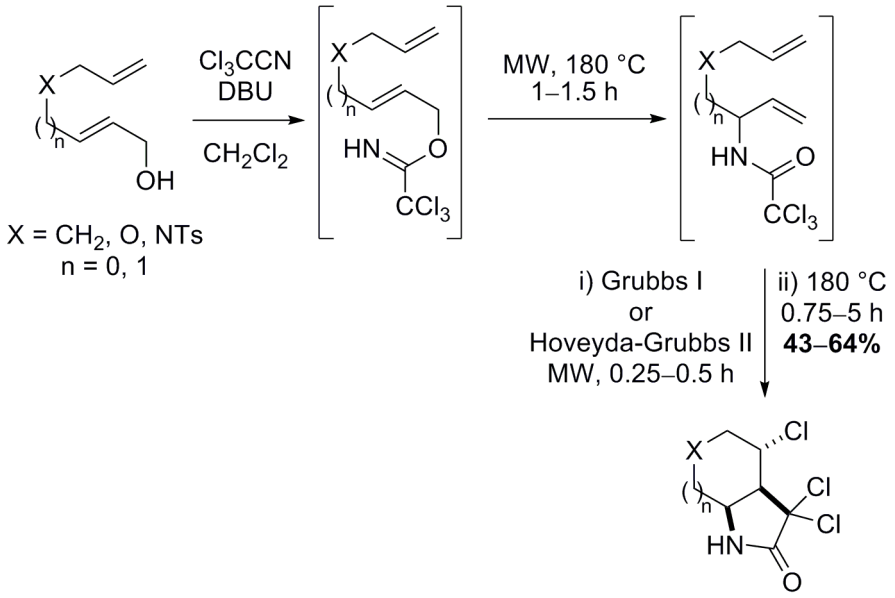
By utilising chiral palladium catalysts (*S*)- and (*R*)-COP-Cl to effect an asymmetric Overman rearrangement within the tandem process, the 5,6- and 5,5-analogues were synthesised in good yields and high enantiomeric excess (Figure 16).



70%, 89% ee **53%, 89% ee** **51%, 94% ee**

Figure 16: Results for the asymmetric synthesis of the 5,5- and 5,6-analogues

With the implementation of a thermal Overman rearrangement necessary for the oxy- and aza-analogues, the use of microwave irradiation to accelerate all three steps of the tandem process was investigated (Scheme 102). Compared to the standard thermal process, the microwave assisted process resulted in the synthesis of the desired bicyclic lactams in a quicker and more reproducible manner.



Scheme 102: Microwave-assisted synthesis of the bicyclic γ-lactams

The application of a two-step tandem Overman rearrangement/RCM reaction for the synthesis of bicyclic allylic amides was investigated (Figure 17). This class of compound have potentially interesting pharmacological properties due to the prominence of the related 1-aminoindane and tetralin core within important drugs currently on the market.

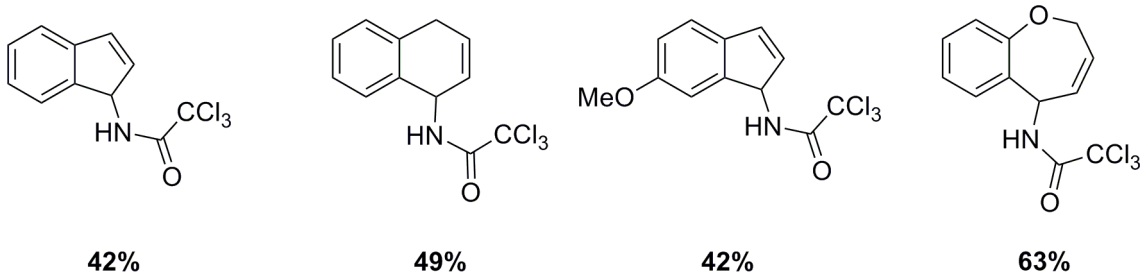
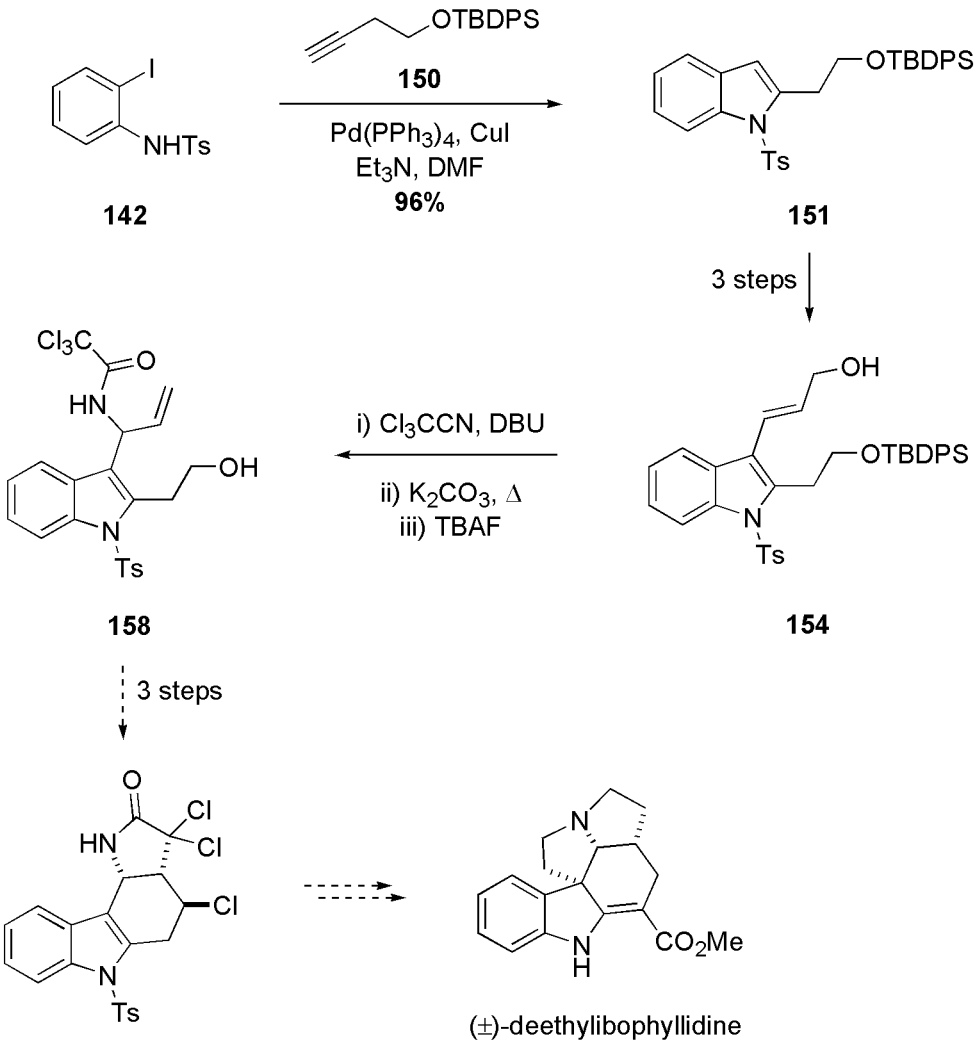


Figure 17: Results from the two-step tandem process for the synthesis of bicyclic allylic amides

Finally, significant progress has been made towards the application of the tandem process to the total synthesis of deethylibophyllidine. Some issues were encountered and successfully overcome early on in the synthesis. Indole **151** was formed using the Larock indole synthesis and was further elaborated into allylic alcohol **154** in three high yielding steps (Scheme 103). Acetimidate formation followed by a thermal Overman rearrangement and finally protecting group removal afforded alcohol **158**. Future work on this project will utilise a tandem Grubbs catalysed RCM/Kharasch cyclisation to construct the C and D rings of the target molecule, followed by completion of the total synthesis as outlined in Scheme 100.



Scheme 103: Progress towards the total synthesis of (±)-deethylibophyllidine

3.0 Experimental

General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to tetramethylsilane as the standard. Infrared spectra were recorded on a Shimazdu FTIR 8400S spectrometer and mass spectra were obtained using a JEOL JMS-700 spectrometer. Microwave reactions were performed in a 300 W Biotage initiator. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC methods were calibrated with their corresponding racemic mixtures. (*S*)-COP-Cl, di-μ-chlorobis[η^5-(*S*)-($_\rho$*R*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium and (*R*)-COP-Cl, di-μ-chlorobis[η^5-(*R*)-($_\rho$*R*)-2-(2'-(4'-methylethyl)oxazolinyl)cyclopentadienyl, 1-*C*, 3'-*N*)(η^4-tetraphenylcyclobutadiene)cobalt]dipalladium were purchased from Aldrich Chemical Co.

General procedure 1: One-Pot Swern Oxidation/Horner-Wadsworth-Emmons reaction. To a stirred solution of oxalyl chloride (1.4 equiv.) in dichloromethane (0.54 M) at –78 °C, was added dimethyl sulfoxide (2.5 equiv.). The reaction was stirred at –78 °C for 0.3 h before slow addition of the alcohol (1.0 equiv.) in dichloromethane (0.58 M). After a further 0.3 h at –78 °C, triethylamine (5.0 equiv.) was added. The reaction mixture was stirred for a further 0.5 h, then allowed to warm to room temperature and stirred for 2 h. The Horner-Wadsworth-Emmons solution was prepared by dissolving lithium chloride (1.8 equiv.) in acetonitrile (0.70 M) followed by addition of triethyl phosphonoacetate (1.5 equiv.) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.5 equiv.). The mixture was stirred at room temperature for 1 h. The Swern solution was concentrated *in vacuo* and the Horner-Wadsworth-Emmons solution was added to the crude residue before stirring at room temperature overnight. The reaction was quenched with saturated aqueous ammonium

chloride solution (50 mL) and concentrated *in vacuo*. The product was extracted using diethyl ether (4 × 50 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using an eluent of petroleum ether/diethyl ether to afford the desired (*E*)-α,β-unsaturated ester.

General procedure 2: Reduction of α,β-unsaturated ester using DIBAL-H. (*E*)-α,β-Unsaturated ester (1.0 equiv.) was dissolved in diethyl ether (0.12 M) and cooled to –78 °C. DIBAL-H (1 M in hexanes) (2.2 equiv.) was added dropwise and the reaction mixture allowed to stir at –78 °C for 3 h. The reaction mixture was then allowed to warm to room temperature before stirring overnight. The reaction mixture was cooled to 0 °C and quenched with saturated aqueous ammonium chloride solution (20 mL) before stirring rapidly for 1 h at room temperature to produce a white precipitate. The mixture was filtered through a short plug of Celite® and washed with diethyl ether (400 mL). The organic solvent was dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using an eluent of petroleum ether/diethyl ether to afford the desired allylic alcohol.

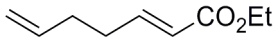
General procedure 3: Synthesis of allylic trichloroacetimidate followed by a one-pot metal catalysed Overman rearrangement/ring-closing metathesis/Kharasch cyclisation. Allylic alcohol (1.0 equiv.) was dissolved in dichloromethane (0.08 M) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv) and trichloroacetonitrile (1.5 equiv.). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (0.08 M) and transferred to a Schlenk tube containing bis(acetonitrile)dichloropalladium(II) (10 mol%). The tube was then sealed under argon and the reaction mixture stirred at room temperature overnight. Grubbs 1st generation catalyst (10 mol%) was added along with 4 Å molecular sieves (1.00 g) and the reaction mixture was stirred at room temperature for 1 h with degassing of the mixture. The reaction mixture was sealed under argon and stirred at 155 °C for 2 h. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Purification was carried out by flash column chromatography using an eluent of petroleum ether/ethyl acetate to afford the desired bicyclic lactam.

General procedure 4: Synthesis of allylic trichloroacetimidate followed by a one-pot thermal Overman rearrangement/ring-closing metathesis/Kharasch cyclisation. Allylic alcohol (1.0 equiv.) was dissolved in dichloromethane (0.08 M) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv.) and trichloroacetonitrile (1.5 equiv.). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (0.08 M) and transferred to a Schlenk tube containing potassium carbonate (3 mg/mL). The tube was then sealed under argon and the reaction mixture stirred at 140 °C for 20 h. Grubbs 1st generation catalyst (10 mol%) was added along with 4 Å molecular sieves (1.00 g) and the reaction mixture was stirred at room temperature for 1 h with degassing of the mixture. The reaction mixture was sealed under argon and stirred at 155 °C for 2 h. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Purification was carried out by flash column chromatography using an eluent of petroleum ether/ethyl acetate to afford the desired bicyclic lactam.

General procedure 5: Synthesis of allylic trichloroacetimidate followed by a one-pot microwave assisted Overman rearrangement/ring-closing metathesis/Kharasch cyclisation. Allylic alcohol (1.0 equiv.) was dissolved in dichloromethane (0.08 M) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv.) and trichloroacetonitrile (1.5 equiv.). The reaction mixture was allowed to warm to room temperature before stirring for 3 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in degassed toluene (0.08 M) and transferred to a microwave vial containing potassium carbonate (3 mg/mL) and a silicon carbide (SiC) bar. The vial was then sealed under argon and the reaction mixture heated in a microwave reactor at 180 °C for 1 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture was heated in the microwave at 60 °C for 0.25 h. The temperature was then raised to 180 °C for 0.75 h. Purification was carried out by flash column chromatography using an eluent of petroleum ether/ethyl acetate to afford the desired bicyclic lactam.

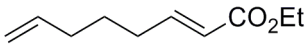
General procedure 6: Synthesis of allylic trichloroacetimidate followed by a one-pot Overman rearrangement/ring-closing metathesis. Allylic alcohol (1.0 equiv.) was dissolved in dichloromethane (0.06 M) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.5 equiv.) and trichloroacetonitrile (1.5 equiv.). The reaction mixture was allowed to warm to room temperature before stirring for 6 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (0.06 M) and transferred to a Schlenk tube containing potassium carbonate (3 mg/mL). The tube was then sealed under argon and the reaction mixture stirred at 140 °C overnight. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture was stirred at 50 °C for 24 h. An additional quantity of Grubbs 1st generation catalyst (5 mol%) was then added every 24 h for a further 72 h at 50 °C. Purification was carried out by flash column chromatography using an eluent of petroleum ether/diethyl ether to afford the desired allylic trichloroacetamide.

Ethyl (2*E*)-hepta-2,6-dienoate (161)[118]



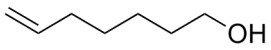
Ethyl (2*E*)-hepta-2,6-dienoate **161** was synthesised according to general procedure 1, using 4-penten-1-ol (1.00 g, 11.6 mmol). Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **161** (1.17 g, 65%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2986 (CH), 2932 (CH), 1721 (CO), 1651 (C=C), 1443, 1265, 1173, 1042, 988, 918; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.18–2.26 (2H, m, 5-H_2), 2.27–2.35 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.99–5.09 (2H, m, 7-H_2), 5.75–5.86 (2H, m, 2-H and 6-H), 6.96 (1H, dt, *J* 15.6, 6.7 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.5 (CH_2), 32.1 (CH_2), 60.3 (CH_2), 115.6 (CH_2), 121.8 (CH), 137.2 (CH), 148.4 (CH), 166.7 (C); *m/z* (CI) 155 (MH^+, 100%), 95 (4), 81 (10), 69 (12).

Ethyl (2*E*)-octa-2,7-dienoate (80)[119]



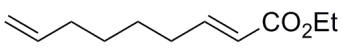
Ethyl (2*E*)-octa-2,7-dienoate **80** was synthesised according to general procedure 1, using 5-hexen-1-ol (3.00 g, 30.0 mmol). Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded the desired compound **80** (3.96 g, 79%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2978 (CH), 2932 (CH), 2862 (CH), 1721 (CO), 1651 (C=C), 1442, 1265, 1173, 1042, 980, 910, 733; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.56 (2H, quin., *J* 7.2 Hz, 5-H_2), 2.05–2.13 (2H, m, 6-H_2), 2.18–2.26 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.95–5.06 (2H, m, 8-H_2), 5.73–5.84 (2H, m, 2-H and 7-H), 6.96 (1H, dt, *J* 15.7, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 27.1 (CH_2), 31.5 (CH_2), 33.0 (CH_2), 60.1 (CH_2), 115.1 (CH_2), 121.5 (CH), 138.0 (CH), 148.8 (CH), 166.6 (C); *m/z* (CI) 169 (MH^+, 100%), 141 (11), 123 (33), 95 (68), 81 (21).

6-Hepten-1-ol (162)[120]



6-Hepten-1-ol **162** was synthesised according to general procedure 2, using ethyl 6-heptenoate (1.50 g, 9.62 mmol). Flash column chromatography (petroleum ether/diethyl ether 7:3) afforded the desired product **162** (1.10 g, 100%) as a colourless oil. Spectroscopic data in accordance with literature values. δ_H (400 MHz, $CDCl_3$) 1.32–1.47 (4H, m, 3-H_2 and 4-H_2), 1.53–1.61 (2H, m, 5-H_2), 1.70 (1H, br s, OH), 2.03–2.10 (2H, m, 2-H_2), 3.63 (2H, t, *J* 6.6 Hz, 1-H_2), 4.91–5.04 (2H, m, 7-H_2), 5.81 (1H, ddt, *J* 17.1, 10.1, 6.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 28.7 (CH_2), 32.6 (CH_2), 33.7 (CH_2), 62.9 (CH_2), 114.4 (CH_2), 138.9 (CH); *m/z* (CI) 115 (MH^+, 68%), 97 (100), 69 (23).

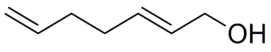
Ethyl (2*E*)-nona-2,8-dienoate (163)[121]



Ethyl (2*E*)-nona-2,8-dienoate **163** was synthesised according to general procedure 1, using 6-hepten-1-ol **162** (1.00 g, 8.77 mmol). Flash column chromatography (petroleum

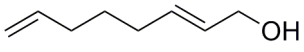
ether/diethyl ether 97:3) afforded the desired compound **163** (1.14 g, 71%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2978 (CH), 2932 (CH), 2862 (CH), 1721 (CO), 1651 (C=C), 1442, 1265, 1180, 1042, 980, 910, 733; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.37–1.53 (4H, m, 5-H_2 and 6-H_2), 2.06 (2H, q, *J* 6.9 Hz, 7-H_2), 2.21 (2H, q, *J* 6.9 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.92–5.04 (2H, m, 9-H_2), 5.73–5.85 (2H, m, 2-H and 8-H), 6.96 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.5 (CH_2), 28.4 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 60.2 (CH_2), 114.6 (CH_2), 121.4 (CH), 138.6 (CH), 149.2 (CH), 166.8 (C); *m/z* (EI) 182 (M^+, 15%), 137 (50), 109 (44), 84 (100), 67 (83), 55 (43), 41 (27).

(2*E*)-Hepta-2,6-dien-1-ol (84)[122]



(2*E*)-Hepta-2,6-dien-1-ol **84** was synthesised according to general procedure 2, using ethyl (2*E*)-hepta-2,6-dienoate **161** (2.22 g, 14.4 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **84** (1.43 g, 89%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3325 (OH), 3078 (CH), 2924 (CH), 2847 (CH), 1643 (C=C), 1443, 1088, 972, 910, 633; δ_H (400 MHz, $CDCl_3$) 1.35 (1H, br s, OH), 2.13–2.18 (4H, m, 4-H_2 and 5-H_2), 4.09 (2H, d, *J* 4.8 Hz, 1-H_2), 4.95–5.07 (2H, m 7-H_2), 5.62–5.75 (2H, m, 2-H and 3-H), 5.76–5.88 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 31.6 (CH_2), 33.3 (CH_2), 63.8 (CH_2), 114.9 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); *m/z* (CI) 113 (MH^+, 6%), 95 (100), 81 (15), 69 (18).

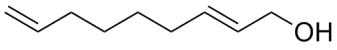
(2*E*)-Octa-2,7-dien-1-ol (52)[119]



(2*E*)-Octa-2,7-dien-1-ol **52** was synthesised according to general procedure 2, using ethyl (2*E*)-octa-2,7-dienoate **80** (3.88 g, 23.1 mmol). Flash column chromatography (petroleum ether/diethyl ether 1:1) afforded the desired compound **52** (2.39 g, 82%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3325 (OH), 3078 (CH), 2924 (CH), 2855 (CH), 1643 (C=C), 1435, 1088, 972, 910, 633; δ_H (400 MHz, $CDCl_3$) 1.36 (1H, br s, OH), 1.49 (2H, quin, *J* 7.2 Hz, 5-H_2), 2.03–2.11 (4H, m, 4-H_2 and 6-H_2), 4.10 (2H, d, *J* 4.6 Hz, 1-H_2), 4.93–5.05 (2H, m, 8-H_2), 5.60–5.74 (2H, m, 2-H and 3-H),

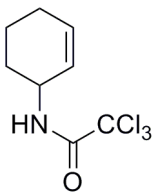
5.80 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 7-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 63.6 (CH_2), 114.6 (CH_2), 129.2 (CH), 132.9 (CH), 138.6 (CH); *m/z* (CI) 127 (MH^+, 4%), 125 (15), 109 (100), 95 (9), 67 (18).

(2*E*)-Nona-2,8-dien-1-ol (85)[121]



(2*E*)-Nona-2,8-dien-1-ol **85** was synthesised according to general procedure 2, using ethyl (2*E*)-nona-2,8-dienoate **163** (1.05 g, 5.77 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **85** (0.73 g, 90%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3341 (OH), 3078 (CH), 2924 (CH), 2855 (CH), 1643 (C=C), 1435, 1088, 972, 910, 633; δ_H (400 MHz, $CDCl_3$) 1.33 (1H, br s, OH), 1.36–1.44 (4H, m, 5-H_2 and 6-H_2), 2.01–2.10 (4H, m, 4-H_2 and 7-H_2), 4.09 (2H, d, *J* 4.9 Hz, 1-H_2), 4.91–5.03 (2H, m, 9-H_2), 5.59–5.74 (2H, m, 2-H and 3-H), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 8-H); δ_C (100 MHz, $CDCl_3$) 28.4 (CH_2), 28.6 (CH_2), 32.1 (CH_2), 33.6 (CH_2), 68.9 (CH_2), 114.4 (CH_2), 129.0 (CH), 133.3 (CH), 138.9 (CH); *m/z* (CI) 141 (MH^+, 3%), 123 (100), 97 (13), 81 (34), 67 (12).

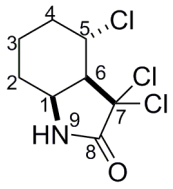
1-(2',2',2'-Trichloromethylcarbonylamino)cyclohexa-2-ene (54)[52]



(2*E*)-Octa-2,7-dien-1-ol **52** (0.50 g, 4.00 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.30 mL, 2.00 mmol) and trichloroacetonitrile (0.60 mL, 6.00 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 2 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in dichloromethane (50 mL) and to this was added bis(acetonitrile)dichloropalladium(II) (0.10 g, 0.40 mmol). The reaction mixture was stirred at room temperature for 3 h. Grubbs 1st generation catalyst (0.33 g, 0.4 mmol) was

then added and the reaction mixture was stirred under reflux overnight. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Flash column chromatography (petroleum ether/diethyl ether 97:3) afforded the desired compound **54** (0.83 g, 85%) as a white solid. Mp 83–84 °C, *lit.*[52] 85–86 °C; δ_H (400 MHz, $CDCl_3$) 1.60–1.73 (3H,m, 5-H_2 and 6-H), 1.94–2.10 (3H, m, 4-H_2 and 6-H), 4.42–4.50 (1H, m, 1-H), 5.65 (1H, ddt, *J* 10.0, 3.3, 2.3 Hz, 2-H), 5.98 (1H, dtd, *J* 10.0, 3.7, 1.8 Hz, 3-H), 6.59 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 24.7 (CH_2), 28.6 (CH_2), 46.9 (CH), 92.8 (C), 125.7 (CH), 132.7 (CH), 161.1 (C); *m/z* (CI) 242 (MH^+, 78%), 210 (65), 208 (100), 174 (36), 107 (73), 81 (80), 71 (79).

(1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (9)[20]**



(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **9** was synthesised according to general procedure 3, using (2*E*)-octa-2,7-dien-1-ol **52** (0.10 g, 0.80 mmol). Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **9** (0.17 g, 87%) as a white solid. Mp 135–137 °C, *lit.*[20] 142–143.5 °C; ν_{max}/cm^{-1} 3256 (NH), 2924 (CH), 2870 (CH), 1689 (CO), 1427, 1273, 1049, 741, 664; δ_H (400 MHz, $CDCl_3$) 1.63–1.84 (3H, m, 3-H_2 and 4-*H*H), 1.91–2.01 (2H, m, 2-*H*H and 4-H*H*), 2.31–2.41 (1H, m, 2-H*H*), 3.34 (1H, dd, *J* 7.0, 3.7 Hz, 6-H), 3.99 (1H, q, *J* 7.0 Hz, 1-H) 4.62 (1H, q, *J* 3.7 Hz, 5-H), 7.30 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 17.5 (CH_2), 28.4 (CH_2), 32.2 (CH_2), 50.0 (CH), 55.2 (CH), 57.1 (CH), 82.5 (C), 168.5 (C); *m/z* (CI) 242 (MH^+, 89%), 208 (100), 172 (32), 157 (71), 113 (24), 81 (43).

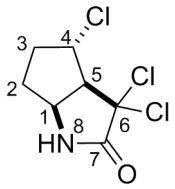
Synthesis of (1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane 9 using thermal Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 4, using (2*E*)-octa-2,7-dien-1-ol **52** (0.10 g, 0.80 mmol). Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **9** (0.12 g, 61%) as a white solid. Spectroscopic data as described above.

Synthesis of (1*S,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane 9 using microwave assisted Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 5, using (2*E*)-octa-2,7-dien-1-ol **52** (0.05 g, 0.40 mmol). Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **9** (0.06 g, 64%) as a white solid. Spectroscopic data as described above.

(1*S,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (86)[22]**



(1*S**,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane **86** was synthesised according to general procedure 3, using (2*E*)-hepta-2,6-dien-1-ol **84** (0.10 g, 0.90 mmol). The final stage of the reaction was stirred for 4 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **86** (0.14 g, 71%) as a white solid. Mp 172–174 °C, *lit*.[22] 175–176 °C dec.; ν_{max}/cm^{-1} 3264 (NH), 2932 (CH), 2870 (CH), 1690 (CO), 1427, 1273, 1049, 741, 664; δ_H (400 MHz, $CDCl_3$) 1.87–1.95 (1H, m, 2-*H*H), 2.00–2.09 (1H, m, 2-H*H*), 2.18–2.36 (2H, m, 3-H_2), 3.66 (1H, dd, *J* 6.4, 3.4 Hz, 5-H), 4.41–4.46 (1H, m, 1-H), 4.59–4.64 (1H, m, 4-H), 7.75 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 30.6 (CH_2), 34.7 (CH_2), 56.6 (CH), 61.0 (CH), 65.8 (CH), 83.1 (C), 169.0 (C); *m/z* (EI) 227 (M^+, 26%), 192 (16), 149 (100), 113 (73), 77 (68), 65 (18).

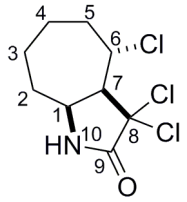
Synthesis of (1*S,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane 86 using thermal Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 4, using (2*E*)-hepta-2,6-dien-1-ol **84** (0.10 g, 0.90 mmol). The final stage of the reaction was stirred for 4 h at 155 °C. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **86** (0.10 g, 48%) as a white solid. Spectroscopic data as described above.

Synthesis of (1*S,4*S**,5*S**)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane 86 using microwave assisted Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

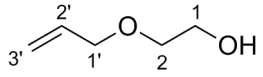
The reaction was carried out according to general procedure 5, using (2*E*)-hepta-2,6-dien-1-ol **84** (0.05 g, 0.05 mmol). The reaction was initially heated at 180 °C for 1 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture heated at 60 °C for 0.25 h. The temperature was then raised to 180 °C and heating continued for a further 1.25 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **86** (0.05 g, 50%) as a white solid. Spectroscopic data as described above.

(1*S,6*S**,7*S**)-6,8,8-Trichloro-9-oxo-10-azabicyclo[5.3.0]decane (87)[22]**



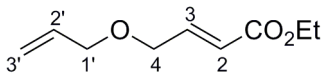
(1*S**,6*S**,7*S**)-6,8,8-Trichloro-9-oxo-10-azabicyclo[5.3.0]decane **87** was synthesised according to general procedure 3 (at a concentration of 0.009 M), using (2*E*)-nona-2,8-dien-1-ol **85** (0.05 g, 0.36 mmol). The reaction was stirred with Grubbs 1st generation catalyst (10 mol%) for 48 h at 50 °C. Grubbs 1st generation catalyst (5 mol%) was then added every 24 h for a further 72 h and the reaction mixture was stirred at 50 °C throughout. To the cooled reaction, 4 Å molecular sieves (1.00 g) were added and the reaction mixture degassed for 1 h at room temperature, before sealing under argon and stirring at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **87** (0.06 g, 60%) as a white solid. Mp 208–210 °C, *lit.*[22] 206–208 °C dec.; ν_{max}/cm^{-1} 3194 (NH), 2932 (CH), 2862 (CH), 1705 (CO), 1443, 1281, 1049, 849, 710; δ_H (400 MHz, $CDCl_3$) 1.22–1.35 (1H, m, 3-*H*H), 1.45–1.59 (1H, m, 4-*H*H), 1.73–1.84 (2H, m, 2-H_2), 1.85–1.97 (2H, m, 3-H*H* and 4-H*H*), 1.98–2.09 (1H, m, 5-*H*H), 2.32–2.40 (1H, m, 5-H*H*), 3.41 (1H, dd, *J* 10.1, 8.3 Hz, 7-H), 3.75–3.82 (1H, m, 1-H), 4.47–4.53 (1H, m, 6-H), 7.69 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 27.4 (CH_2), 29.0 (CH_2), 31.7 (CH_2), 38.7 (CH_2), 57.1 (CH), 59.0 (CH), 60.2 (CH), 83.9 (C), 168.8 (C); *m/z* (CI) 256 (MH^+, 100%), 222 (49), 186 (12), 157 (7), 123 (8), 95 (12), 81 (44).

2-Allyloxyethan-1-ol (88)[123]



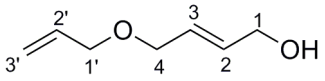
To a solution of ethylene glycol (5.50 mL, 99.0 mmol) and potassium hydroxide (1.67 g, 29.8 mmol) in dimethyl sulfoxide (40 mL) and water (10 mL) at 0 °C, was added a solution of allyl bromide (2.15 mL, 24.8 mmol) in dimethyl sulfoxide (10 mL). The reaction mixture was stirred at 0 °C for 1 h followed by stirring at room temperature for 5 h. The solution was diluted with diethyl ether (100 mL) and water (50 mL) and the product extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 7:3) afforded the desired compound **88** (1.03 g, 41%) as a colourless oil. Spectroscopic data in accordance with literature values. δ_H (400 MHz, $CDCl_3$) 2.09 (1H, br s, OH), 3.57 (2H, t, *J* 4.5 Hz, 2-H_2), 3.75 (2H, t, *J* 4.5 Hz, 1-H_2), 4.04 (2H, d, *J* 5.6 Hz, 1'-H_2), 5.21 (1H, d, *J* 10.4 Hz, 3'-*H*H), 5.29 (1H, d, *J* 17.2 Hz, 3'-H*H*), 5.87–5.99 (1H, m, 2'-H); δ_C (100 MHz, $CDCl_3$) 61.8 (CH_2), 71.4 (CH_2), 72.1 (CH_2), 117.3 (CH_2), 134.5 (CH); *m/z* (CI) 103 (MH^+, 79%), 69 (4).

Ethyl (2*E*)-4-allyloxybut-2-enoate (89)



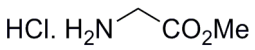
Ethyl (2*E*)-4-allyloxybut-2-enoate **89** was synthesised according to general procedure 1, using 2-allyloxyethan-1-ol **88** (1.73 g, 17.0 mmol). Flash column chromatography (petroleum ether/diethyl ether 98:2) afforded the desired compound **89** (1.43 g, 50%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2982 (CH), 1720 (CO), 1662 (C=C), 1447, 1368, 1302, 1178, 1040, 930; δ_H (400 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.03 (2H, d, *J* 5.5 Hz, 1'-H_2), 4.15 (2H, dd, *J* 4.3, 1.9 Hz, 4-H_2), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.21 (1H, d, *J* 10.4 Hz, 3'-*H*H), 5.31 (1H, d, *J* 17.2 Hz, 3'-H*H*), 5.85–5.97 (1H, m, 2'-H), 6.09 (1H, dt, *J* 15.7, 1.9 Hz, 2-H), 6.96 (1H, dt, *J* 15.7, 4.3 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 60.4 (CH_2), 68.6 (CH_2), 71.7 (CH_2), 117.4 (CH_2), 121.3 (CH), 134.2 (CH), 144.3 (CH), 166.4 (C); *m/z* (CI) 171.1022 (MH^+. $C_9H_{15}O_3$ requires 171.1021), 163 (6%), 131 (10), 125 (11), 115 (31), 69 (10).

(2*E*)-4-Allyloxybut-2-en-1-ol (90)



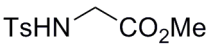
(2*E*)-4-Allyloxybut-2-en-1-ol **90** was synthesised according to general procedure 2, using ethyl (2*E*)-4-allyloxybut-2-enoate **89** (0.79 g, 4.7 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **90** (0.49 g, 76%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3433 (OH), 2855 (CH), 1645 (C=C), 1451, 1423, 1358, 1094, 1005; δ_H (400 MHz, $CDCl_3$) 1.49 (1H, br s, OH), 3.98–4.02 (4H, m, 4-H_2 and 1'-H_2), 4.16–4.18 (2H, m, 1-H_2), 5.17–5.22 (1H, m, 3'-*H*H), 5.26–5.32 (1H, m, 3'-H*H*), 5.79–5.97 (3H, m, 2-H, 3-H and 2'-H); δ_C (100 MHz, $CDCl_3$) 63.0 (CH_2), 70.0 (CH_2), 71.3 (CH_2), 117.2 (CH_2), 127.8 (CH), 132.2 (CH), 134.6 (CH); *m/z* (CI) 129.0918 (MH^+. $C_7H_{13}O_2$ requires 129.0916), 111 (98%), 93 (35), 79 (100), 71 (66).

Methyl 2-aminoethanoate hydrochloride (91)[124]



Glycine (0.50 g, 6.7 mmol) was dissolved in methanol (20 mL) and the solution cooled to 0 °C. To this was added thionyl chloride (1.22 mL, 16.7 mmol) and the reaction mixture heated under reflux for 2 h. The reaction mixture was cooled and concentrated *in vacuo* to afford the desired compound **91** (0.84 g, 100%) as a white solid. Mp 173–174 °C, *lit.*[124] 174–175 °C; δ_H (400 MHz, $CDCl_3$) 3.85 (3H, s, OCH_3), 3.94 (2H, s, 2-H_2); δ_C (100 MHz, $CDCl_3$) 39.9 (CH_2), 53.3 (CH_3), 168.7 (C); *m/z* (CI) 90 (MH^+, 98%), 81 (100), 78 (85).

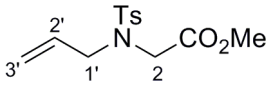
Methyl 2-[*N*-(4-methylbenzene)sulfonyl]ethanoate (92)[125]



To a solution of methyl 2-aminoethanoate hydrochloride **91** (0.83 g, 6.6 mmol) in dichloromethane (20 mL), was added triethylamine (2.02 mL, 14.6 mmol) and the mixture cooled to 0 °C. In a separate flask, *p*-toluenesulfonyl chloride (1.51 g, 7.94 mmol) was dissolved in dichloromethane (10 mL) and added slowly to the cooled mixture. The resulting solution was stirred at room temperature overnight. The reaction was diluted with water (20 mL) and the product extracted with diethyl ether (3 × 50 mL). The combined

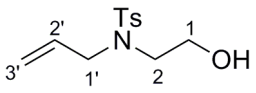
organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 3:2) afforded the desired compound **92** (1.38 g, 86%) as a white crystalline solid. Mp 88–90 °C, *lit.*[125] 92–93 °C; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, Ar-CH_3), 3.64 (3H, s, OCH_3), 3.79 (2H, d, *J* 5.3 Hz, 2-H_2), 5.05 (1H, br t, *J* 5.3 Hz, NH), 7.31 (2H, d, *J* 8.1 Hz, ArH), 7.75 (2H, d, *J* 8.1 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 44.0 (CH_2), 52.6 (CH_3), 127.3 (2 × CH), 129.8 (2 × CH), 136.2 (C), 143.8 (C), 169.3 (C); *m/z* (EI) 243 (M^+, 48%), 184 (100), 155 (99), 118 (18), 91 (99), 85 (98), 65 (57), 47 (79).

Methyl 2-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]ethanoate (93)[126]



To a solution of methyl 2-[*N*-(4-methylbenzene)sulfonyl]ethanoate **92** (0.50 g, 2.1 mmol) in acetone (40 mL), was added potassium carbonate (0.31 g, 2.3 mmol) and allyl bromide (0.20 mL, 2.3 mmol) and the reaction mixture heated under reflux overnight. The solution was cooled, diluted with water (20 mL) and the acetone was removed *in vacuo*. The product was extracted with diethyl ether (3 × 50 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 4:1) afforded the desired compound **93** (0.55 g, 96%) as a colourless oil. Spectroscopic data in accordance with literature values. δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, Ar-CH_3), 3.64 (3H, s, OCH_3), 3.89 (2H, d, *J* 6.4 Hz, 1'-H_2), 4.02 (2H, s, 2-H_2), 5.14–5.22 (2H, m, 3'-H_2), 5.62–5.74 (1H, m, 2'-H), 7.31 (2H, d, *J* 8.1 Hz, ArH), 7.74 (2H, d, *J* 8.1 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 46.8 (CH_2), 50.8 (CH_2), 52.1 (CH_3), 120.0 (CH_2), 127.4 (2 × CH), 129.6 (2 × CH), 132.2 (CH), 136.7 (C), 143.5 (C), 169.4 (C); *m/z* (CI) 284 (MH^+, 99%), 224 (15), 197 (100), 128 (51), 89 (80).

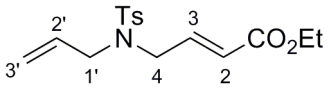
2-[*N*-Allyl-*N*-(4-methylbenzene)sulfonyl]ethan-1-ol (94)[127]



2-[*N*-Allyl-*N*-(4-methylbenzene)sulfonyl]ethan-1-ol **94** was synthesised according to general procedure 2, using methyl 2-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]ethanoate **93**

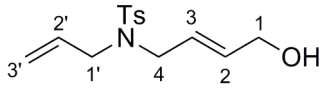
(2.55 g, 9.01 mmol). Flash column chromatography (petroleum ether/diethyl ether 7:3) afforded the desired compound **94** (2.30 g, 100%) as a pale yellow oil. Spectroscopic data in accordance with literature values. δ_H (400 MHz, $CDCl_3$) 2.34 (1H, br s, OH), 2.44 (3H, s, Ar-CH_3), 3.24 (2H, t, *J* 5.2 Hz, 2-H_2), 3.73 (2H, t, *J* 5.2 Hz, 1-H_2), 3.85 (2H, d, *J* 6.4 Hz, 1'-H_2), 5.15–5.22 (2H, m, 3'-H_2), 5.68 (1H, ddt, *J* 16.7, 10.2, 6.4 Hz, 2'-H), 7.32 (2H, d, *J* 8.0 Hz, ArH), 7.72 (2H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_3), 49.8 (CH_2), 52.2 (CH_2), 61.1 (CH_2), 119.4 (CH_2), 127.3 (2 × CH), 129.8 (2 × CH), 133.0 (CH), 136.2 (C), 143.6 (C); *m/z* (CI) 256 (MH^+, 100%), 157 (10), 113 (11), 102 (41), 73 (15).

Ethyl (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-enoate (95)



Ethyl (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-enoate **95** was synthesised according to general procedure 1, using 2-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]ethan-1-ol **94** (0.40 g, 1.6 mmol). Flash column chromatography (petroleum ether/diethyl ether 7:3) afforded the desired compound **95** (0.38 g, 75%) as a pale yellow oil. ν_{max}/cm^{-1} (NaCl) 2982 (CH), 2920 (CH), 1719 (CO), 1661 (C=C), 1598, 1347, 1161, 1039, 762; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.44 (3H, s, Ar-CH_3), 3.80 (2H, d, *J* 6.4 Hz, 1'-H_2), 3.92 (2H, d, *J* 5.6 Hz, 4-H_2), 4.18 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.10–5.19 (2H, m, 3'-H_2), 5.53–5.66 (1H, m, 2'-H), 5.90 (1H, d, *J* 15.6 Hz, 2-H), 6.70 (1H, dt, *J* 15.6, 5.6 Hz, 3-H), 7.31 (2H, d, *J* 8.0 Hz, ArH), 7.71 (2H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 21.6 (CH_3), 47.3 (CH_2), 50.4 (CH_2), 60.6 (CH_2), 119.8 (CH_2), 124.0 (CH), 127.2 (2 × CH), 129.9 (2 × CH), 132.2 (CH), 136.8 (C), 142.3 (CH), 143.7 (C), 166.7 (C); *m/z* (FAB^+) 324.1275 (MH^+. $C_{16}H_{22}NO_4S$ requires 324.1270), 322 (24%), 278 (54), 224 (8), 168 (56), 155 (58), 122 (13), 91 (63), 85 (10).

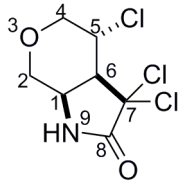
(2*E*)-4-[*N*-Allyl-*N*-(4-methylbenzene)sulfonyl]but-2-en-1-ol (96)



(2*E*)-4-[*N*-Allyl-*N*-(4-methylbenzene)sulfonyl]but-2-en-1-ol **96** was synthesised according to general procedure 2, using ethyl (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-enoate **95** (1.50 g, 4.64 mmol). Flash column chromatography (petroleum ether/diethyl

ether 3:2) afforded the desired compound **96** (1.01 g, 78%) as viscous oil. ν_{max}/cm^{-1} (NaCl) 3513 (OH), 2922 (CH), 1643 (C=C), 1597, 1443, 1338, 1158, 1091, 662; δ_H (400 MHz, $CDCl_3$) 1.79 (1H, br s, OH), 2.43 (3H, s, Ar-CH_3), 3.78–3.83 (4H, m, 4-H_2 and 1'-H_2), 4.08 (2H, d, *J* 4.9 Hz, 1-H_2), 5.11–5.19 (2H, m, 3'-H_2), 5.48–5.66 (2H, m, 3-H and 2'-H), 5.74 (1H, dt, *J* 15.4, 4.9 Hz, 2-H), 7.30 (2H, d, *J* 8.1 Hz, ArH), 7.70 (2H, d, *J* 8.1 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 48.2 (CH_2), 49.6 (CH_2), 62.7 (CH_2), 119.1 (CH_2), 125.7 (CH), 127.2 (2 × CH), 129.7 (2 × CH), 132.7 (CH), 133.7 (CH), 137.2 (C), 143.4 (C); *m/z* (CI) 282.1169 (MH^+. $C_{14}H_{20}NO_3S$ requires 282.1164), 264 (100%), 212 (11), 157 (8), 128 (6), 69 (7).

(1*R,5*R**,6*S**)-3-Oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (97)**



(1*R**,5*R**,6*S**)-3-Oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **97** was synthesised according to general procedure 3, using (2*E*)-4-allyloxybut-2-en-1-ol **90** (0.10 g, 0.78 mmol). The reaction mixture was stirred with Grubbs 1st generation catalyst (10 mol%) at 70 ºC for 4 h. A second quantity of Grubbs 1st generation catalyst (5 mol%) was added along with 4 Å molecular sieves (1.00 g) and the reaction mixture was degassed for 1 h before stirring at 155 °C for 2 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **97** (0.07 g, 36%) as a white solid. Mp 188–190 °C; ν_{max}/cm^{-1} 3139 (NH), 2864 (CH), 1752 (CO), 1711, 1367, 1096, 1033, 909, 834, 763; δ_H (400 MHz, $CDCl_3$) 3.21 (1H, dd, *J* 8.0, 5.3 Hz, 6-H), 3.42 (1H, dd, *J* 12.0, 9.3 Hz, 4-*H*H), 3.77 (1H, dd, *J* 12.9, 2.8 Hz, 2-*H*H), 3.98–4.05 (1H, m, 5-H), 4.05–4.11 (2H, m, 1-H and 2-H*H*), 4.16 (1H, dd, *J* 12.0, 5.1 Hz, 4-H*H*), 7.59 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 50.1 (CH), 51.1 (CH), 56.7 (CH), 67.3 (CH_2), 70.7 (CH_2), 84.0 (C), 168.7 (C); *m/z* (CI) 243.9695 (MH^+. $C_7H_9{}^{35}Cl_3NO_2$ requires 243.9699), 210 (68%), 174 (38), 140 (18), 107 (42).

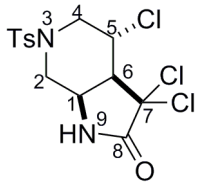
Synthesis of (1*R,5*R**,6*S**)-3-oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane 97 using thermal Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 4, using (2*E*)-4-allyloxybut-2-en-1-ol **90** (0.10 g, 0.78 mmol). The allylic trichloroacetimidate was dissolved in toluene (10 mL) and stirred with potassium carbonate (0.03 g) in a sealed tube at 140 °C for 72 h. Grubbs 1st generation catalyst (10 mol%) was added and after degassing of the solvent, the reaction mixture was stirred at room temperature for 3 h. A second quantity of Grubbs 1st generation catalyst (5 mol%) was added and the reaction stirred for a further 1 h at room temperature with degassing of the solvent. 4 Å Molecular sieves (1.00 g) were then added and the reaction was sealed under argon and heated at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **97** (0.10 g, 52%) as a white solid. Spectroscopic data as described above.

Synthesis of (1*R,5*R**,6*S**)-3-oxa-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane 97 using microwave assisted Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 5, using (2*E*)-4-allyloxybut-2-en-1-ol **90** (0.05 g, 0.39 mmol). The allylic trichloroacetimidate was dissolved in toluene (5 mL) and stirred with potassium carbonate (0.02 g) in a microwave vial at 180 °C for 1 h. Hoveyda-Grubbs 2nd generation catalyst (10 mol%) was added and the reaction mixture heated at 60 °C for 0.5 h. The temperature was then raised to 180 °C and heating continued for a further 5 h. Flash column chromatography (petroleum ether/ethyl acetate 8:2) afforded the desired compound **97** (0.04 g, 43%) as a white solid. Spectroscopic data as described above.

(1*R,5*R**,6*S**)-3-(4-Methylbenzenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane (98)**



(1*R**,5*R**,6*S**)-3-(4-methylbenzenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane **98** was synthesised according to general procedure 3, using (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-en-1-ol **96** (0.10 g, 0.36 mmol). The

reaction mixture was stirred with bis(acetonitrile)dichloropalladium(II) (10 mol%) at 40 °C for 28 h. An additional quantity of the palladium(II) catalyst (5 mol%) was added and the reaction continued to stir at 40 °C for 24 h. A final quantity of the palladium(II) catalyst (5 mol%) was added and the reaction mixture stirred for a final 24 h at 40 °C. Grubbs 1st generation catalyst (10 mol%) was then added and after degassing the solvent, the reaction mixture was stirred at 70 °C for 24 h. An additional quantity of Grubbs 1st generation catalyst (5 mol%) was added and the reaction stirred at 70 °C for 24 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 4 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **98** (0.03 g, 19%) as a white solid. Mp 184–186 °C; ν_{max}/cm^{-1} 3193 (NH), 2915 (CH), 2898 (CH), 1740 (CO), 1712, 1343, 1237, 1171, 1090, 869, 744; δ_H (400 MHz, $CDCl_3$) 2.45 (3H, s, Ar-CH_3), 3.11 (1H, dd, *J* 13.0, 7.4 Hz, 4-*H*H), 3.18 (1H, t, *J* 5.8 Hz, 6-H), 3.28 (1H, dd, *J* 13.0, 4.2 Hz, 2-*H*H), 3.48 (1H, dd, *J* 13.0, 5.8 Hz, 2-H*H*), 3.81 (1H, dd, *J* 13.0, 4.3 Hz, 4-H*H*), 4.16–4.21 (1H, m, 1-H), 4.27–4.33 (1H, m, 5-H), 7.06 (1H, br s, NH), 7.36 (2H, d, *J* 8.2 Hz, ArH), 7.67 (2H, d, *J* 8.2 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 46.5 (CH_2), 49.3 (CH), 50.8 (CH_2), 51.4 (CH), 56.4 (CH), 82.6 (C), 127.5 (2 × CH), 130.2 (2 × CH), 133.4 (C), 144.6 (C), 167.5 (C); *m*/*z* (FAB) 398.9912 (MH^+. $C_{14}H_{16}{}^{35}Cl_2{}^{37}ClN_2O_3S$ requires 398.9919), 363 (6%), 307 (7), 243 (5), 155 (89), 137 (100), 121 (14), 109 (11).

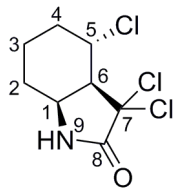
Synthesis of (1*R,5*R**,6*S**)-3-(4-methylbenzenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane 98 using thermal Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

The reaction was carried out according to general procedure 4, using (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-en-1-ol **96** (0.10 g, 0.36 mmol). The allylic trichloroacetimidate was dissolved in toluene (10 mL) and stirred with potassium carbonate (0.03 g) in a sealed tube at 140 °C for 136 h. Grubbs 1st generation catalyst (15 mol%) was added and after degassing the solvent, the reaction mixture was stirred at room temperature for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **98** (0.06 g, 39%) as a white solid. Spectroscopic data as described above.

Synthesis of (1*R,5*R**,6*S**)-3-(4-methylbenzenesulfonyl)-5,7,7-trichloro-8-oxo-3,9-diazabicyclo[4.3.0]nonane 98 using microwave assisted Overman rearrangement/ring-closing metathesis/Kharasch cyclisation.**

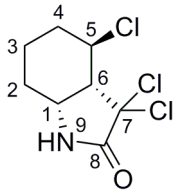
The reaction was carried out according to general procedure 5, using (2*E*)-4-[*N*-allyl-*N*-(4-methylbenzene)sulfonyl]but-2-en-1-ol **96** (0.10 g, 0.36 mmol). The allylic trichloroacetimidate was dissolved in toluene (5 mL) and stirred with potassium carbonate (0.02 g) in a microwave vial at 180 °C for 1.5 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture heated at 60 °C for 0.5 h. The temperature was then raised to 180 °C and heating continued for a further 1 h. Flash column chromatography (petroleum ether/ethyl acetate 8:2) afforded the desired compound **98** (0.06 g, 44%) as a white solid. Spectroscopic data as described above.

(1*S*,5*S*,6*S*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (9)



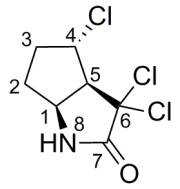
(1*S*,5*S*,6*S*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **9** was synthesised according to general procedure 3, using (2*E*)-octa-2,7-dien-1-ol **52** (0.10 g, 0.80 mmol). The reaction mixture was stirred with (*S*)-COP-Cl (3 mol%) at 38 °C for 40 h. A second quantity of (*S*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*S*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture was stirred at room temperature, with degassing of the reaction mixture, for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **9** (0.20 g, 70%) as a white solid. Chiral HPLC (Chiralcel IB column, λ= 220 nm) analysis using 4% isopropanol in hexane (0.75 mL/min) as the elution solvent indicated 89% ee. Retention times: t = 35.8 min (major enantiomer), t = 38.8 min (minor enantiomer). $[\alpha]_D^{24}$ +59.2 (*c* 1.2, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane.

(1*R*,5*R*,6*R*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (9)



(1*R*,5*R*,6*R*)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **9** was synthesised according to general procedure 3, using (2*E*)-octa-2,7-dien-1-ol **52** (0.10 g, 0.80 mmol). The reaction mixture was stirred with (*R*)-COP-Cl (3 mol%) at 38 °C for 40 h. A second quantity of (*R*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*R*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture was stirred at room temperature for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 3 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **9** (0.10 g, 53%) as a white solid. Chiral HPLC (Chiralcel IB column, λ= 220 nm) analysis using 4% isopropanol in hexane (0.75 mL/min) as the elution solvent indicated 89% ee. Retention times: t = 35.8 min (minor enantiomer), t = 37.2 min (major enantiomer). $[\alpha]_D^{24}$ –63.5 (*c* 1.3, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane.

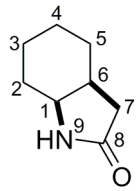
(1*S*,4*S*,5*S*)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane (86)



(1*S*,4*S*,5*S*)-4,6,6-Trichloro-7-oxo-8-azabicyclo[3.3.0]octane **86** was synthesised according to general procedure 3, using (2*E*)-hepta-2,6-dien-1-ol **84** (0.10 g, 0.90 mmol). The reaction mixture was stirred with (*S*)-COP-Cl (3 mol%) at 38 °C for 40 h. A second quantity of (*S*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for 72 h. A final quantity of (*S*)-COP-Cl (3 mol%) was added and the solution stirred at 38 °C for a further 24 h. Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture

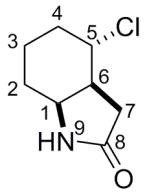
was stirred at room temperature for 1 h. 4 Å Molecular sieves (1.00 g) were then added, the reaction sealed under argon and stirred at 155 °C for 4 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **86** (0.10 g, 51%) as a white solid. Chiral HPLC (Chiralcel IB column, λ= 220 nm) analysis using 4% isopropanol in hexane (0.75 mL/min) as the elution solvent indicated 94% ee. Retention times: t = 32.4 min (major enantiomer), t = 35.9 min (minor enantiomer). $[\alpha]_D^{24}$ +45.5 (*c* 0.5, $CHCl_3$). All other spectroscopic data matched that previously reported for (1*S**,4*S**,5*S**)-4,6,6-trichloro-7-oxo-8-azabicyclo[3.3.0]octane.

(1*S,6*S**)-8-Oxo-9-azabicyclo[4.3.0]nonane (99)[128]**



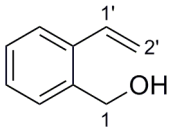
(1*S**,5*S**,6*S**)-5,7,7-Trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **9** (0.29 g, 1.18 mmol) was dissolved in tetrahydrofuran (5 mL) and added to the slurry of activated Raney-Nickel™ (1.00 g).[129] The reaction was heated under reflux for 24 h. A second portion of Raney-Nickel™ (1.00 g) was added and the reaction mixture was heated under reflux for a further 24 h. A final portion of Raney-Nickel™ (1.00 g) was added and the reaction mixture was heated under reflux for a final 24 h. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through a short silica plug. The plug was washed with diethyl ether (100 mL), the organic filtrate dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (ethyl acetate/methanol 9:1) afforded the desired compound **99** (0.12 g, 73%) as a colourless oil. Spectroscopic data in accordance with literature values. δ_H (400 MHz, $CDCl_3$) 1.28–1.69 (8H, m, 2-H_2, 3-H_2, 4-H_2 and 5-H_2), 2.02–2.09 (1H, m, 6-H), 2.32–2.41 (2H, m, 7-H_2), 3.68 (1H, q, *J* 5.1 Hz, 1-H), 5.62 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 20.6 (CH_2), 22.7 (CH_2), 27.3 (CH_2), 28.8 (CH_2), 34.4 (CH), 37.8 (CH_2), 53.2 (CH), 178.6 (C); *m/z* (EI) 139 (M^+, 55%), 96 (100), 83 (21), 57 (55), 44 (48).

(1*S,5*S**,6*S**)-5-Chloro-8-oxo-9-azabicyclo[4.3.0]nonane (100)**



To a solution of (1*S**,5*S**,6*S**)-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **9** (0.04 g, 0.17 mmol) in acetic acid (4 mL), was added activated zinc powder[130] (0.06 g, 0.87 mmol) and the reaction mixture heated at 120 ºC for 20 h. An additional portion of activated zinc powder (0.06 g, 0.87 mmol) was added and the reaction mixture heated at 120 ºC for a further 24 h. The reaction mixture was cooled and quenched with saturated sodium hydrogen carbonate solution (5 mL) and saturated sodium carbonate (5 mL). The product was extracted using diethyl ether (4 × 20 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 1:1) afforded the desired compound **100** (0.02 g, 53%) as a colourless oil. ν_{max}/cm^{-1} 3537 (NH), 2937 (CH), 1723 (CO), 1457, 1324, 706; δ_H (400 MHz, $CDCl_3$) 1.46–1.86 (6H, m, 2-H_2, 3-H_2 and 4-H_2), 2.08–2.17 (1H, m, 6-H), 2.43–2.51 (2H, m, 7-H_2), 3.81–3.94 (2H, m, 1-H and 5-H), 6.43 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 27.4 (CH_2), 34.0 (CH_2), 37.4 (CH_2), 44.6 (CH), 54.1 (CH), 60.7 (CH), 177.8 (C); *m/z* (CI) 174.0685 (MH^+. $C_8H_{13}{}^{35}ClNO$ requires 174.0686), 138 (5%), 69 (8).

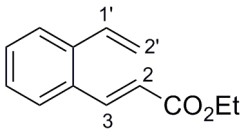
2-Vinylbenzyl alcohol (108)[131]



To a solution of 2-bromobenzyl alcohol (1.00 g, 5.35 mmol) in toluene (30 mL), was added tetrakis(triphenylphosphine)palladium(0) (0.19 g, 0.16 mmol) followed by tri-*n*-butyl(vinyl)tin (1.88 mL, 6.42 mmol) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was quenched with saturated potassium fluoride solution (15 mL) and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash

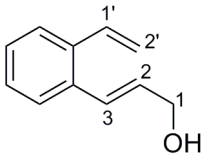
column chromatography (petroleum ether/ethyl acetate 3:2) afforded the desired compound **108** (0.61 g, 85%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3334 (OH), 3065 (CH), 2883 (CH), 1626 (C=C), 1484, 1453, 1006, 914, 773, 731; δ_H (400 MHz, $CDCl_3$) 1.58 (1H, br s, OH), 4.77 (2H, s, 1-H_2), 5.37 (1H, dd, *J* 11.0, 1.3 Hz, 2'-*H*H), 5.71 (1H, dd, *J* 17.4, 1.3 Hz, 2'-H*H*), 7.06 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 7.27–7.39 (3H, m, ArH), 7.53–7.56 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 63.5 (CH_2), 116.6 (CH_2), 126.0 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 133.8 (CH), 136.7 (C), 137.5 (C); *m/z* (EI) 134 (M^+, 27%), 105 (33), 91 (24), 77 (25), 44 (100).

Ethyl (2*E*)-3-(2-vinylphenyl)prop-2-enoate (110)[132]



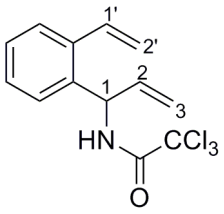
Ethyl (2*E*)-3-(2-vinylphenyl)prop-2-enoate **110** was synthesised according to general procedure 1, using 2-vinylbenzyl alcohol **108** (1.05 g, 7.84 mmol). The Horner-Wadsworth-Emmons reaction was stirred at 50 °C for 20 h. A second amount of deprotonated triethyl phosphonoacetate (1.5 equiv.) was added to the reaction mixture and the mixture stirred for a further 24 h at 50 °C. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **110** (1.38 g, 87%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2986 (CH), 1705 (CO), 1628 (C=C), 1304, 1265, 1165, 1034, 980, 756; δ_H (400 MHz, $CDCl_3$) 1.35 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 4.27 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 5.43 (1H, dd, *J* 11.0, 1.2 Hz, 2'-*H*H), 5.64 (1H, dd, *J* 17.4, 1.2 Hz, 2'-H*H*), 6.35 (1H, d, *J* 15.9 Hz, 2-H), 7.07 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 7.37–7.40 (3H, m, ArH), 7.47–7.55 (1H, m, ArH), 8.04 (1H, d, *J* 15.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 60.5 (CH_2), 118.0 (CH_2), 120.4 (CH), 127.0 (2 × CH), 127.9 (CH), 130.0 (CH), 132.5 (C), 134.2 (CH), 138.0 (C), 142.3 (CH), 166.9 (C); *m/z* (CI) 203 (MH^+, 100%), 177 (4), 114 (11), 97 (11), 85 (22), 71 (27).

(2*E*)-3-(2-Vinylphenyl)prop-2-en-1-ol (111)



(2*E*)-3-(2-Vinylphenyl)prop-2-en-1-ol **111** was synthesised according to general procedure 2, using ethyl (2*E*)-3-(2-vinylphenyl)prop-2-enoate **110** (1.38 g, 6.83 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **111** (0.88 g, 80%) as a colourless oil. ν_{max}/cm^{-1} 3362 (OH), 2919 (CH), 2861 (CH), 1625 (C=C), 1476, 1414, 1099, 988, 767; δ_H (400 MHz, $CDCl_3$) 1.46 (1H, t, *J* 5.8 Hz, OH), 4.35 (2H, td, *J* 5.8, 1.5 Hz, 1-H_2), 5.34 (1H, dd, *J* 11.0, 1.4 Hz, 2'-*H*H), 5.63 (1H, dd, *J* 17.4, 1.4 Hz, 2'-H*H*), 6.24 (1H, dt, *J* 15.8, 5.8 Hz, 2-H), 6.92 (1H, dt, *J* 15.8, 1.5 Hz, 3-H), 7.02 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 7.24–7.27 (2H, m, ArH), 7.41–7.48 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 63.9 (CH_2), 116.4 (CH_2), 126.3 (CH), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.8 (CH), 131.0 (CH), 134.8 (CH), 135.0 (C), 136.2 (C); *m/z* (CI) 143.0860 (MH^+–H_2O. $C_{11}H_{11}$ requires 143.0861), 97 (8%), 81 (9), 69 (9).

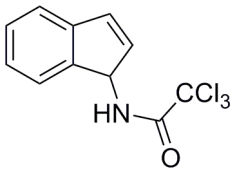
1-(2',2',2'-Trichloromethylcarbonylamino)-1-(2-vinylphenyl)prop-2-ene (113)



(2*E*)-3-(2-Vinylphenyl)prop-2-en-1-ol **111** (0.05 g, 0.31 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.16 mmol) and trichloroacetonitrile (0.05 mL, 0.47 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 5 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (5 mL) and transferred to a Schlenk tube containing potassium carbonate (0.02 g). The tube was then sealed under argon and the reaction mixture stirred at 140 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired

compound **113** (0.07 g, 71%) as a white solid. Mp 78–80 °C; ν_{max}/cm^{-1} 3435 (NH), 2975 (CH), 2881 (CH), 2837 (CH), 1728 (CO), 1455, 1377, 722; δ_H (400 MHz, $CDCl_3$) 5.27 (1H, dd, *J* 17.2, 1.9 Hz, 3-*H*H), 5.37 (1H, dd, *J* 10.5, 1.9 Hz, 3-H*H*), 5.41 (1H, dd, *J* 10.9, 1.3 Hz, 2'-*H*H), 5.66 (1H, dd, *J* 17.2, 1.3 Hz, 2'-H*H*), 5.80–5.85 (1H, m, 1-H), 6.08 (1H, ddd, *J* 17.2, 10.5, 4.4 Hz, 2-H), 6.88 (1H, br d, *J* 4.4 Hz, NH), 7.01 (1H, dd, *J* 17.2, 10.9 Hz, 1'-H), 7.27–7.38 (3H, m, ArH), 7.51–7.55 (1H, m, ArH); δ_C (125 MHz, $CDCl_3$) 54.0 (CH), 92.6 (C), 116.7 (CH_2), 118.2 (CH_2), 127.2 (CH), 127.3 (CH), 128.2 (CH), 128.7 (CH), 133.7 (CH), 135.4 (CH), 135.5 (C), 137.6 (C), 160.8 (C); *m/z* (CI) 304.0069 (MH^+. $C_{13}H_{13}{}^{35}Cl_3NO$ requires 304.0063), 270 (45%), 236 (30), 200 (100), 143 (88), 117 (21), 85 (63), 69 (94).

1-(2',2',2'-Trichloromethylcarbonylamino)-1*H*-indene (114)

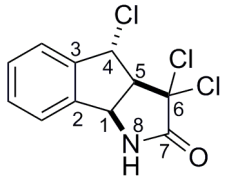


To a solution of 1-(2',2',2'-trichloromethylcarbonylamino)-1-(2-vinylphenyl)prop-2-ene **113** (0.06 g, 0.2 mmol) in toluene (10 mL), was added Grubbs 1st generation catalyst (0.02 g, 0.02 mmol) and the reaction mixture was stirred at room temperature for 24 h. An additional amount of Grubbs 1st generation catalyst (0.01 g, 0.01 mmol) was added and the reaction mixture stirred for a further 24 h at room temperature. The reaction mixture was filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **114** (0.05 g, 82%) as a light brown solid. Mp 73–75 °C; ν_{max}/cm^{-1} 3433 (NH), 2894 (CH), 2840 (CH), 1723 (CO), 1465, 1377, 722; δ_H (400 MHz, $CDCl_3$) 5.66 (1H, m, 1-H), 6.42 (1H, dd, *J* 5.6, 1.9 Hz, 2-H), 6.66 (1H, br s, NH), 6.91 (1H, ddd, *J* 5.6, 1.9, 0.8 Hz, 3-H), 7.23–7.28 (1H, m, ArH), 7.33–7.36 (2H, m, ArH), 7.47–7.51 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 58.4 (CH), 92.4 (C), 121.9 (CH), 123.6 (CH), 126.6 (CH), 128.9 (CH), 133.9 (CH), 134.7 (CH), 142.8 (C), 143.1 (C), 162.7 (C); *m/z* (CI) 275.9753 (MH^+. $C_{11}H_9{}^{35}Cl_3NO$ requires 275.9750), 242 (62%), 208 (32), 172 (10), 85 (17), 69 (27).

Synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene 114 using a one-pot thermal Overman rearrangement/ring-closing metathesis.

The reaction was carried out according to general procedure 6, using (2*E*)-3-(2-vinylphenyl)prop-2-en-1-ol **111** (0.10 g, 0.63 mmol). Flash column chromatography (petroleum ether/ethyl acetate 19:1) afforded the desired compound **114** (0.07 g, 42%) as a light brown solid. Spectroscopic data as described above.

(1*S,4*S**,5*S**)-2,3-Benzo-4,6,6-trichloro-7-oxo-8-azabicyclo[3.3.0]octane (115)**



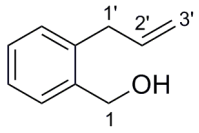
To a Schlenk tube containing 1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene **114** (0.04 g, 0.14 mmol) dissolved in degassed toluene (5 mL) was added Grubbs 1st generation catalyst and 4 Å molecular sieves (1.00 g) and the reaction mixture was heated to 155 °C for 3 h. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **115** (0.02 g, 40%) as a brown solid. Mp 205–207 °C dec.; ν_{max}/cm^{-1} 3202 (NH), 2924 (CH), 1728 (CO), 1458, 972, 864, 741; δ_H (400 MHz, $CDCl_3$) 4.02 (1H, t, *J* 6.0 Hz, 2-H), 5.21 (1H, d, *J* 6.0 Hz, 1-H), 5.50 (1H, d, *J* 6.0 Hz, 3-H), 6.78 (1H, br s, NH), 7.35–7.43 (2H, m, ArH), 7.45–7.51 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 58.5 (CH), 61.0 (CH), 66.4 (CH), 81.8 (C), 124.7 (CH), 126.0 (CH), 130.1 (CH), 130.7 (CH), 137.6 (C), 142.1 (C), 167.5 (C); *m/z* (CI) 275.9767 (MH^+. $C_{11}H_9{}^{35}Cl_3NO$ requires 275.9750), 242 (75%), 208 (53), 172 (11), 113 (13), 85 (55), 58 (65).

Synthesis of (1*S,4*S**,5*S**)-2,3-benzo-4,6,6-trichloro-7-oxo-8-azabicyclo[3.3.0]octane 115 using thermal Overman rearrangement/RCM/Kharasch cyclisation.**

(1*S**,4*S**,5*S**)-2,3-Benzo-4,6,6-trichloro-7-oxo-8-azabicyclo[3.3.0]octane **115** was synthesised according to general procedure 4 using (2*E*)-3-(2-vinylphenyl)prop-2-en-1-ol **111** (0.05 g, 0.31 mmol). Grubbs 2nd generation catalyst was added the reaction mixture degassed for 0.5 h before stirring at 80 °C for 2 h. 4 Å molecular sieves (1.00 g) were then added and the mixture stirred at 155 °C for 2 h. Flash column chromatography (petroleum

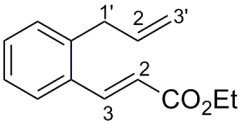
ether/ethyl acetate 7:3) afforded the desired compound **115** (0.03 g, 32%) as a brown solid. Spectroscopic data as described above.

2-Allylbenzyl alcohol (109)[133]



To a solution of 2-bromobenzyl alcohol (1.00 g, 5.35 mmol) in toluene (40 mL), was added tetrakis(triphenylphosphine)palladium(0) (0.19 g, 0.16 mmol) followed by tri-*n*-butyl(allyl)tin (2.49 mL, 8.02 mmol) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was quenched with saturated potassium fluoride solution (15 mL) and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **109** (0.37 g, 47%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3333 (OH), 3075 (CH), 2889 (CH), 1637 (C=C), 1454, 1040, 999, 915, 752; δ_H (400 MHz, $CDCl_3$) 1.59 (1H, t, *J* 6.0 Hz, OH), 3.48 (2H, dt, *J* 6.2, 1.6 Hz, 1'-H_2), 4.71 (2H, d, *J* 6.0 Hz, 1-H_2), 5.00 (1H, dq, *J* 17.1, 1.6 Hz, 3'-*H*H), 5.08 (1H, dq, *J* 10.1, 1.6 Hz, 3'-H*H*), 6.01 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, 2'-H), 7.19–7.22 (1H, m, ArH), 7.24–7.28 (2H, m, ArH), 7.37–7.41 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 36.8 (CH_2), 63.3 (CH_2), 115.9 (CH_2), 126.7 (CH), 128.1 (CH), 128.4 (CH), 130.0 (CH), 137.5 (CH), 137.8 (C), 138.7 (C); *m/z* (CI) 149 (MH^+, 4%), 131 (100), 113 (12), 97 (18), 85 (39), 71 (52).

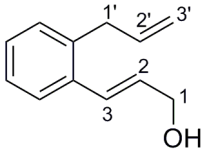
Ethyl (2*E*)-3-(2-allylphenyl)prop-2-enoate (117)[134]



Ethyl (2*E*)-3-(2-allylphenyl)prop-2-enoate **117** was synthesised according to general procedure 1, using 2-allylbenzyl alcohol **109** (0.60 g, 4.1 mmol). The Horner-Wadsworth-Emmons reaction was stirred at 50 °C for 20 h. A second amount of deprotonated triethyl phosphonoacetate (1.5 equiv.) was added to the reaction mixture and the mixture stirred for

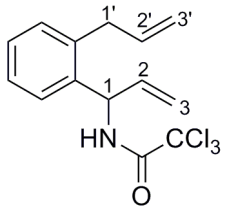
a further 24 h at 50 °C. Flash column chromatography (petroleum ether/diethyl ether 49:1) afforded the desired compound **117** (0.72 g, 82%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2979 (CH), 1714 (CO), 1635 (C=C), 1483, 1366, 1314, 1268, 1175, 1037, 981, 916, 765; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.53 (2H, dt, *J* 6.2, 1.5 Hz, 1'-H_2), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.99 (1H, dq, *J* 17.1, 1.5 Hz, 3'-*H*H), 5.09 (1H, dq, *J* 10.1, 1.5 Hz, 3'-H*H*), 5.96 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, 2'-H), 6.36 (1H, d, *J* 15.8 Hz, 2-H), 7.20–7.23 (1H, m, ArH), 7.24–7.27 (1H, m, ArH), 7.33 (1H, td, *J* 7.5, 1.4 Hz, ArH), 7.58 (1H, dd, *J* 7.5, 1.2 Hz, ArH), 7.99 (1H, d, *J* 15.8 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 37.5 (CH_2), 60.5 (CH_2), 116.4 (CH_2), 119.6 (CH), 126.6 (CH), 126.9 (CH), 130.1 (CH), 130.3 (CH), 133.4 (C), 136.6 (CH), 139.2 (C), 142.2 (CH), 167.0 (C); *m/z* (EI) 216 (M^+, 37%), 143 (100), 128 (95), 115 (69), 84 (92), 46 (14).

(2*E*)-3-(2-Allylphenyl)prop-2-en-1-ol (118)[135]



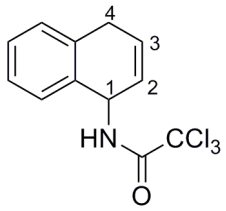
(2*E*)-3-(2-Allylphenyl)prop-2-en-1-ol **118** was synthesised according to general procedure 2, using ethyl (2*E*)-3-(2-allylphenyl)prop-2-enoate **117** (0.70 g, 3.2 mmol). A second addition of DIBAL-H solution (1 M in hexanes) (2.2 equiv.) was added at –78 °C after 24 h and the reaction stirred for a further 24 h at room temperature. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **118** (0.46 g, 81%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3330 (OH), 3062 (CH), 2913 (CH), 1637 (C=C), 1482, 1449, 998, 967, 916, 749; δ_H (400 MHz, $CDCl_3$) 1.48 (1H, t, *J* 5.4 Hz, OH), 3.45 (2H, dt, *J* 6.2, 1.7 Hz, 1'-H_2), 4.30–4.35 (2H, m, 1-H_2), 4.97 (1H, dq, *J* 17.1, 1.7 Hz, 3'-*H*H), 5.06 (1H, dq, *J* 10.1, 1.7 Hz, 3'-H*H*), 5.96 (1H, ddt, *J* 17.1, 10.1, 6.2 Hz, 2'-H), 6.26 (1H, dt, *J* 15.7, 5.7 Hz, 2-H), 6.85 (1H, dt, *J* 15.7, 1.5 Hz, 3-H), 7.14–7.17 (1H, m, ArH), 7.19–7.23 (2H, m, ArH), 7.46–7.49 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 37.5 (CH_2), 64.0 (CH_2), 115.9 (CH_2), 126.1 (CH), 126.6 (CH), 127.8 (CH), 128.8 (CH), 129.8 (CH), 130.2 (CH), 135.7 (C), 136.8 (CH), 137.2 (C); *m/z* (CI) 175 (MH^+, 6%), 157 (100), 143 (13), 129 (53), 117 (10), 69 (8).

1-(2-Allylphenyl)-1-(2',2',2'-trichloromethylcarbonylamino)prop-2-ene (119)



(2*E*)-3-(2-Allylphenyl)prop-2-en-1-ol **118** (0.06 g, 0.34 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.03 mL, 0.17 mmol) and trichloroacetonitrile (0.05 mL, 0.52 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 5 h. The reaction mixture was filtered through a short pad of silica gel and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (5 mL) and transferred to a Schlenk tube containing potassium carbonate (0.02 g). The tube was then sealed under argon and the reaction mixture stirred at 140 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **119** (0.05 g, 44%) as a white solid. Mp 62–64 °C; ν_{max}/cm^{-1} 3248 (NH), 3024 (CH), 1682 (CO), 1520, 1265, 988, 926, 817, 725; δ_H (400 MHz, $CDCl_3$) 3.41–3.57 (2H, m, 1'-H_2), 5.00 (1H, dq, *J* 17.1, 1.6 Hz, 3'-*H*H), 5.10 (1H, dq, *J* 10.1, 1.6 Hz, 3'-H*H*), 5.27 (1H, dd, *J* 17.2, 1.4 Hz, 3-*H*H), 5.35 (1H, dd, *J* 10.4, 1.4 Hz, 3-H*H*), 5.79 (1H, m, 1-H), 5.93–6.08 (2H, m, 2-H and 2'-H), 6.79 (1H, br s, NH), 7.23–7.33 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 35.8 (CH_2), 52.3 (CH), 91.6 (C), 115.2 (CH_2), 115.5 (CH_2), 126.1 (CH), 126.2 (CH), 127.6 (CH), 129.7 (CH), 134.8 (CH), 135.6 (CH), 135.7 (C), 137.3 (C), 159.8 (C); *m/z* (CI) 318.0217 (MH^+. $C_{14}H_{15}{}^{35}Cl_3NO$ requires 318.0219), 284 (30%), 248 (86), 214 (78), 157 (100), 129 (12), 85 (28), 69 (32).

1-(2',2',2'-Trichloromethylcarbonylamino)-1,4-dihydronaphthalene (120)

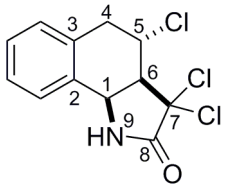


To a solution of 1-(2-allylphenyl)-1-(2',2',2'-trichloromethylcarbonylamino)prop-2-ene **119** (0.05 g, 0.2 mmol) in toluene (5 mL), was added Grubbs 1st generation catalyst (0.01 g, 0.02 mmol) and the reaction mixture was stirred for 6 h at room temperature. An additional amount of Grubbs 1st generation catalyst (0.01 g, 0.01 mmol) was added and the reaction mixture stirred for a further 18 h at room temperature. The reaction mixture was filtered through a short pad of Celite® and washed with diethyl ether (80 mL). The solvent was removed *in vacuo* to give a brown residue. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **120** (0.04 g, 75%) as a light brown solid. Mp 85–87 °C; ν_{max}/cm^{-1} 3256 (NH), 3036 (CH), 1686 (CO), 1524, 1250, 1011, 818, 741, 652; δ_H (400 MHz, $CDCl_3$) 3.38–3.55 (2H, m, 4-H_2), 5.70–5.78 (1H, m, 1-H), 5.93 (1H, ddt, *J* 10.1, 3.6, 2.2 Hz, 2-H), 6.20 (1H, dq, *J* 10.1, 2.4 Hz, 3-H), 6.83 (1H, br s, NH), 7.18–7.22 (1H, m, ArH), 7.25–7.30 (2H, m, ArH), 7.37–7.41 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 29.3 (CH_2), 47.9 (CH), 92.8 (C), 124.3 (CH), 127.2 (CH), 128.0 (CH), 128.3 (CH), 128.5 (CH), 128.6 (CH), 133.1 (C), 134.0 (C), 161.5 (C); *m/z* (CI) 289.9900 (MH^+. $C_{12}H_{11}{}^{35}Cl_3NO$ requires 289.9906), 256 (36%), 222 (14), 162 (100), 129 (97), 73 (10).

Synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene 120 using a one-pot thermal Overman rearrangement/ring-closing metathesis.

The reaction was carried out according to general procedure 6, using (2*E*)-3-(2-allylphenyl)prop-2-en-1-ol **118** (0.05 g, 0.28 mmol). Grubbs 2nd generation catalyst (15 mol%) was added and the reaction mixture was stirred at 60 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **120** (0.04 g, 49%) as a light brown solid. Spectroscopic data as described above.

(1*S,5*S**,6*S**)-2,3-Benzo-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane (121)**

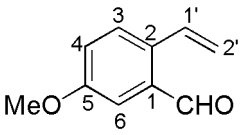


To a Schlenk tube containing 1-(2',2',2'-trichloromethylcarbonylamino)-1,4-dihydronaphthalene **120** (0.03 g, 0.11 mmol) dissolved in degassed toluene (5 mL) was added Grubbs 1st generation catalyst and 4 Å molecular sieves (1.00 g) and the reaction mixture was heated to 155 °C for 2 h. The reaction mixture was cooled, filtered through a short pad of Celite® and washed with diethyl ether (150 mL). The solvent was removed *in vacuo* to give a brown residue. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **121** (0.02 g, 63%) as a brown solid. Mp 163–165 ºC dec.; ν_{max}/cm^{-1} 3283 (NH), 2928 (CH), 1707 (CO), 1499, 1265, 820, 735; δ_H (400 MHz, $CDCl_3$) 3.11 (1H, dd, *J* 14.9, 9.9 Hz 4-*H*H), 3.34 (1H, dd, *J* 14.9, 4.4 Hz, 4-H*H*), 3.81 (1H, dd, *J* 8.3, 5.7 Hz, 2-H), 4.63–4.69 (1H, m, 3-H), 4.91 (1H, d, *J* 8.3 Hz 1-H), 6.98 (1H, br s, NH), 7.20–7.34 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 38.2 (CH_2), 52.2 (CH), 53.0 (CH), 59.2 (CH), 82.6 (C), 124.7 (CH), 128.1 (CH), 128.3 (CH), 128.6 (CH), 133.0 (C), 133.3 (C), 168.5 (C); *m/z* (CI) 289.9911 (MH^+. $C_{12}H_{11}{}^{35}Cl_3NO$ requires 289.9906), 276 (15%), 256 (24), 242 (6), 184 (4).

Synthesis of (1*S,5*S**,6*S**)-2,3-benzo-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane 121 using metal-catalysed Overman rearrangement/RCM/Kharasch cyclisation.**

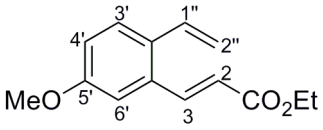
(1*S**,5*S**,6*S**)-2,3-Benzo-5,7,7-trichloro-8-oxo-9-azabicyclo[4.3.0]nonane **121** was synthesised according to general procedure 3 using (2*E*)-3-(2-allylphenyl)prop-2-en-1-ol **118** (0.05 g, 0.28 mmol). Grubbs 1st generation catalyst (10 mol%) was added and the reaction mixture was stirred for 2 h at room temperature, with degassing of the solution during the first hour. 4 Å molecular sieves (1.00 g) were added and the mixture was stirred at 155 ºC for 2 h. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **121** (0.02 g, 19%) as a brown solid. Spectroscopic data as described above.

5-Methoxy-2-vinylbenzaldehyde (125)[136]



To a solution of 2-bromo-5-methoxybenzaldehyde (1.00 g, 4.65 mmol) in toluene (30 mL), was added tetrakis(triphenylphosphine)palladium(0) (0.16 g, 0.14 mmol) followed by tributyl(vinyl)tin (1.63 mL, 5.58 mmol) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was quenched with saturated cesium fluoride solution (20 mL) and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 9:1) afforded the desired compound **125** (0.60 g, 79%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2839 (CH), 1686 (CO), 1604, 1493, 1316, 1246, 1611, 1022, 918, 829, 787; δ_H (400 MHz, $CDCl_3$) 3.87 (3H, s, OCH_3), 5.45 (1H, dd, *J* 10.9, 1.1 Hz, 2'-*H*H), 5.61 (1H, dd, *J* 17.3, 1.1 Hz, 2'-H*H*), 7.13 (1H, dd, *J* 8.6, 2.8 Hz, 4-H), 7.34 (1H, d, *J* 2.8 Hz, 6-H), 7.42 (1H, dd, *J* 17.3, 10.9 Hz, 1'-H), 7.51 (1H, d, *J* 8.6 Hz, 3-H), 10.32 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 55.6 (CH_3), 112.8 (CH), 118.2 (CH_2), 121.2 (CH), 128.9 (CH), 122.3 (CH), 133.8 (C), 133.9 (C), 159.4 (C), 191.7 (CH); *m/z* (CI) 163 (MH^+, 100%), 161 (95), 147 (11), 85 (12), 69 (19).

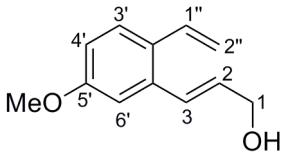
Ethyl (2*E*)-3-(5-methoxy-2-vinylphenyl)prop-2-enoate (126)



To a suspension of lithium chloride (0.39 g, 9.26 mmol) in acetonitrile (50 mL), was added triethyl phosphonoacetate (1.47 mL, 7.41 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.11 mL, 7.41 mmol). The mixture was stirred at room temperature for 1 h before addition to a flask containing 5-methoxy-2-vinylbenzaldehyde **125** (0.60 g, 3.70 mmol). The reaction mixture was then stirred at 50 °C overnight. The reaction was quenched with saturated ammonium chloride solution (20 mL) and concentrated *in vacuo*. The product was extracted using diethyl ether (4 × 30 mL), the organic layers combined, dried ($MgSO_4$)

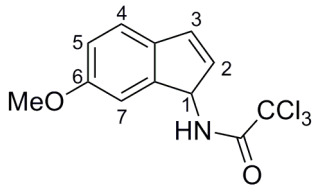
and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded the desired compound **126** (0.67 g, 78%) as a colourless oil. ν_{max}/cm^{-1} 2980 (CH), 1707 (CO), 1632 (C=C), 1491, 1314, 1234, 1163, 1026, 978; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 3.83 (3H, s, OCH_3), 4.27 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.32 (1H, dd, *J* 11.0, 1.2 Hz, 2"-*H*H), 5.54 (1H, dd, *J* 17.3, 1.2 Hz, 2"-H*H*), 6.33 (1H, d, *J* 15.8 Hz, 2-H), 6.92 (1H, dd, *J* 8.6, 2.3 Hz, 4'-H), 7.00 (1H, dd, *J* 17.3, 11.0 Hz, 1"-H), 7.02 (1H, d, *J* 2.3 Hz, 6'-H), 7.43 (1H, d, *J* 8.6 Hz, 3-H), 8.01 (1H, d, *J* 15.8 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 55.4 (CH_3), 60.6 (CH_2), 111.2 (CH), 116.2 (CH_2), 116.5 (CH), 120.5 (CH), 128.2 (CH), 130.9 (C), 133.5 (CH), 133.6 (C), 142.3 (CH), 159.2 (C), 166.8 (C); *m/z* (EI) 232.1095 (M^+. $C_{14}H_{16}O_3$ requires 232.1099), 203 (49%), 187 (42), 159 (100), 144 (92), 115 (82), 77 (22).

(2*E*)-3-(5-Methoxy-2-vinylphenyl)prop-2-en-1-ol (127)



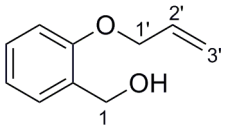
(2*E*)-3-(5-Methoxy-2-vinylphenyl)prop-2-en-1-ol **127** was synthesised according to general procedure 2, using ethyl (2*E*)-3-(5-methoxy-2-vinylphenyl)prop-2-enoate **126** (0.63 g, 2.7 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **127** (0.46 g, 88%) as a colourless oil. ν_{max}/cm^{-1} 3325 (OH), 2835 (CH), 1601, 1489, 1288, 1242, 1165, 1103, 1022, 964, 907, 822; δ_H (400 MHz, $CDCl_3$) 1.71 (1H, s, OH), 3.81 (3H, s, OCH_3), 4.33 (2H, dd, *J* 5.7, 1.5 Hz, 1-H_2), 5.22 (1H, dd, *J* 11.0, 1.4 Hz, 2"-*H*H), 5.52 (1H, dd, *J* 17.4, 1.4 Hz, 2"-H*H*), 6.22 (1H, dt, *J* 15.7, 5.7 Hz, 2-H), 6.81 (1H, dd, *J* 8.6, 2.7 Hz, 4'-H), 6.89 (1H, dt, *J* 15.7, 1.5 Hz, 3-H), 6.90–6.94 (1H, m, 6'-H), 6.94 (1H, dd, *J* 17.4, 11.0 Hz, 1"-H), 7.40 (1H, d, *J* 8.6 Hz, 3'-H); δ_C (100 MHz, $CDCl_3$) 55.3 (CH_3), 63.7 (CH_2), 111.2 (CH), 113.9 (CH), 114.5 (CH_2), 127.5 (CH), 128.7 (CH), 129.2 (C), 131.2 (CH), 134.1 (CH), 136.2 (C), 159.2 (C); *m/z* (CI) 191.1073 (MH^+. $C_{12}H_{15}O_2$ requires 191.1072), 189 (37%), 173 (100), 163 (29), 147 (12), 85 (5), 69 (6).

6-Methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene (122)



6-Methoxy-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-indene **122** was synthesised according to general procedure 6, using (2*E*)-3-(5-methoxy-2-vinylphenyl)prop-2-en-1-ol **127** (0.10 g, 0.43 mmol). The allylic trichloroacetimidate was dissolved in toluene (10 mL) and stirred at 120 °C for 48 h. Grubbs 1st generation catalyst (10 mol%) was then added and the reaction mixture was stirred at 50 °C for 24 h. An additional quantity of Grubbs 1st generation catalyst (5 mol%) was then added every 24 h for a further 72 h and the mixture stirred at 50 °C throughout. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **122** (0.06 g, 42%) as a light brown solid. Mp 68–70 °C; ν_{max}/cm^{-1} 3314 (NH), 2940 (CH), 1697 (CO), 1504, 1234, 1026, 818, 737; δ_H (400 MHz, $CDCl_3$) 3.82 (3H, s, OCH_3), 5.58–5.63 (1H, m, 1-H), 6.27 (1H, dd, *J* 5.6, 2.1 Hz, 2-H), 6.67 (1H, br d, *J* 6.8 Hz, NH), 6.82–6.88 (2H, m, 3-H and 5-H), 7.06–7.08 (1H, m, 7-H), 7.23 (1H, d, *J* 8.2 Hz, 4-H); δ_C (125 MHz, $CDCl_3$) 55.7 (CH_3), 58.3 (CH), 92.4 (C), 110.5 (CH), 113.8 (CH), 122.3 (CH), 131.6 (CH), 134.4 (CH), 135.7 (C), 144.8 (C), 159.1 (C), 162.7 (C); *m/z* (EI) 306.9742 (M^+. $C_{12}H_{10}{}^{35}Cl_2{}^{37}ClNO_2$ requires 306.9749), 270 (88%), 234 (100), 192 (30), 160 (66), 145 (75), 130 (33), 102 (62), 77 (47).

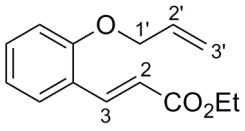
2-Allyloxybenzyl alcohol (128)[137]



To a solution of 2-hydroxybenzyl alcohol (0.50 g, 4.0 mmol) in acetone (2 mL), was added allyl bromide (0.35 mL, 4.0 mmol) and potassium carbonate (0.58 g, 4.2 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was concentrated *in vacuo*, diluted with diethyl ether (20 mL) and washed with a saturated aqueous sodium carbonate solution (5 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **128** (0.50 g, 76%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3349 (OH), 2870 (CH), 1597, 1489, 1234, 995,

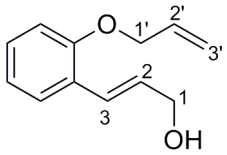
926, 748; δ_H (400 MHz, $CDCl_3$) 2.35 (1H, t, *J* 6.5 Hz, OH), 4.60 (2H, dt, *J* 5.2, 1.5 Hz, 1'-H_2), 4.72 (2H, d, *J* 6.5 Hz, 1-H_2), 5.31 (1H, dq, *J* 10.6, 1.5 Hz, 3'-*H*H), 5.42 (1H, dq, *J* 17.3, 1.5 Hz, 3'-H*H*), 6.07 (1H, ddt, *J* 17.3, 10.6, 5.2 Hz, 2'-H), 6.88 (1H, d, *J* 8.2 Hz, ArH), 6.96 (1H, td, *J* 7.4, 1.0 Hz, ArH), 7.23–7.31 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 62.2 (CH_2), 68.7 (CH_2), 111.5 (CH), 117.7 (CH_2), 120.9 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 133.0 (C), 156.5 (C); *m/z* (CI) 165 (MH^+, 2%), 147 (100), 135 (2), 107 (3), 81 (3), 69 (4).

Ethyl (2*E*)-3-(2-allyloxyphenyl)-prop-2-enoate (129)[135]



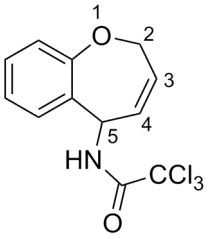
Ethyl (2*E*)-3-(2-allyloxyphenyl)-prop-2-enoate **129** was synthesised according to general procedure 1, using 2-allyloxybenzyl alcohol **128** (1.20 g, 7.32 mmol). Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded the desired compound **129** (1.41 g, 83%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 2982 (CH), 1705 (CO), 1630 (C=C), 1487, 1316, 1267, 1240, 1159, 988, 748; δ_H (400 MHz, $CDCl_3$) 1.34 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.62 (2H, dt, *J* 5.1, 1.5 Hz, 1'-H_2), 5.31 (1H, dq, *J* 10.6, 1.5 Hz, 3'-*H*H), 5.43 (1H, dq, *J* 17.3, 1.5 Hz, 3'-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.6, 5.1 Hz, 2'-H), 6.53 (1H, d, *J* 16.2 Hz, 2-H), 6.90 (1H, d, *J* 8.3 Hz, ArH), 6.96 (1H, td, *J* 7.7, 0.5 Hz, ArH), 7.29–7.35 (1H, m, ArH), 7.52 (1H, dd, *J* 7.7, 1.7 Hz, ArH), 8.05 (1H, d, *J* 16.2 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 60.3 (CH_2), 69.2 (CH_2), 112.5 (CH), 117.7 (CH_2), 118.8 (CH), 120.9 (CH), 123.8 (C), 128.8 (CH), 131.3 (CH), 132.9 (CH), 139.9 (CH), 157.3 (C), 167.5 (C); *m/z* (EI) 232.1104 (M^+. $C_{14}H_{16}O_3$ requires 232.1099), 187 (42%), 158 (78), 144 (59), 129 (61), 118 (97), 84 (100), 77 (19), 49 (99).

(2*E*)-3-(2-allyloxyphenyl)-prop-2-en-1-ol (130)[135]



(2*E*)-3-(2-Allyloxyphenyl)-prop-2-en-1-ol **130** was synthesised according to general procedure 2, using ethyl (2*E*)-3-(2-allyloxyphenyl)-prop-2-enoate **129** (1.20 g, 5.17 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **130** (0.74 g, 75%) as a white solid. Spectroscopic data in accordance with literature values. Mp 41–43 °C; ν_{max}/cm^{-1} 3271 (OH), 2862 (CH), 1597, 1481, 1451, 1420, 1234, 1111, 1011, 972, 933, 748; δ_H (400 MHz, $CDCl_3$) 1.41 (1H, t, *J* 6.0 Hz, OH), 4.33 (2H, td, *J* 6.0, 1.4 Hz, 1-H_2), 4.58 (2H, dt, *J* 5.2, 1.5 Hz, 1'-H_2), 5.29 (1H, dq, *J* 10.5, 1.5 Hz, 3'-*H*H), 5.42 (1H, dq, *J* 17.3, 1.5 Hz, 3'-H*H*), 6.08 (1H, ddt, *J* 17.3, 10.5, 5.2 Hz, 2'-H), 6.40 (1H, dt, *J* 16.0, 6.0 Hz, 2-H), 6.86 (1H, dd, *J* 8.3, 0.7 Hz, ArH), 6.90–6.96 (1H, m, ArH), 6.97 (1H, dt, *J* 16.0, 1.4 Hz, 3-H), 7.20 (1H, m, ArH), 7.46 (1H, dd, *J* 7.6, 1.6 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 64.3 (CH_2), 69.2 (CH_2), 111.4 (CH), 117.5 (CH_2), 120.9 (CH), 126.0 (C), 126.3 (CH), 127.0 (CH), 128.7 (CH), 129.2 (CH), 133.4 (CH), 155.8 (C); *m/z* (EI) 190.0992 (M^+. $C_{12}H_{14}O_2$ requires 190.0994), 149 (93%), 131 (95), 121 (90), 91 (92), 77 (47), 41 (34).

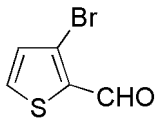
5-(2',2',2'-Trichloromethylcarbonylamino)-2,5-dihydrobenzo[b]oxepine (123)



5-(2',2',2'-Trichloromethylcarbonylamino)-2,5-dihydrobenzo[b]oxepine **123** was synthesised according to general procedure 6 (at a concentration of 0.009 M), using (2*E*)-3-(2-allyloxyphenyl)prop-2-en-1-ol **130** (0.05 g, 0.26 mmol) and alumina for the purification of the allylic trichloroacetimidate. The reaction mixture was stirred with Grubbs 1st generation catalyst (10 mol%) for 24 h at 50 °C. An additional quantity of Grubbs 1st generation catalyst (5 mol%) was then added every 24 h for a further 96 h and

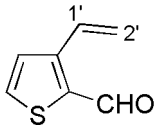
the mixture was stirred at 50 °C throughout. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **123** (0.05 g, 63%) as a white solid. Mp 95–97 ºC; ν_{max}/cm^{-1} 3260 (NH), 3055 (CH), 1686 (CO), 1539, 1269, 1227, 1072, 822, 725; δ_H (400 MHz, $CDCl_3$) 4.41–4.48 (1H, m, 2-*H*H), 4.82 (1H, ddd, *J* 17.7, 3.5, 2.2 Hz, 2-H*H*), 5.37–5.44 (1H, m, 5-H), 5.71 (1H, ddd, *J* 11.5, 3.5, 2.1 Hz, 3-H), 6.08–6.14 (1H, m, 4-H), 7.10–7.15 (1H, m, ArH), 7.14 (1H, d, *J* 7.7 Hz, ArH), 7.27–7.34 (2H, m, ArH), 7.62 (1H, br d, *J* 7.1 Hz, NH); δ_C (125 MHz, $CDCl_3$) 51.5 (CH), 71.1 (CH_2), 92.7 (C), 122.1 (CH), 125.1 (CH), 126.0 (CH), 128.3 (CH), 130.1 (CH), 131.6 (CH), 134.9 (C), 157.3 (C), 160.7 (C); *m/z* (CI) 307.9830 (MH^+. $C_{12}H_{11}{}^{35}Cl_2{}^{37}ClNO_2$ requires 307.9827), 272 (37%), 257 (62), 197 (13), 157 (28), 145 (64), 113 (35), 71 (53).

3-Bromo-2-formylthiophene (131)[138]



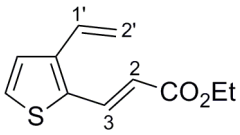
To a solution of titanium tetrachloride (1 M in dichloromethane) (12.3 mL, 12.3 mmol) in dichloromethane (50 mL) at –78 °C, was added dichloromethyl methyl ether (1.11 mL, 12.3 mmol) followed by 3-bromothiophene (0.29 mL, 3.0 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at –78 °C for 2 h then warmed to 0 °C before quenching with water (20 mL) and a 10% aqueous sodium carbonate solution (10 mL). The product was extracted with dichloromethane (3 × 20 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **131** (0.56 g, 100%) as a yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3104 (CH), 1710 (CO), 1661, 1498, 1416, 1210, 887, 738; δ_H (400 MHz, $CDCl_3$) 7.16 (1H, d, *J* 5.2 Hz, ArH), 7.72 (1H, dd, *J* 5.2, 1.2 Hz, ArH), 9.99 (1H, br d, *J* 1.2 Hz, CHO); δ_C (100 MHz, $CDCl_3$) 120.3 (C), 132.0 (CH), 134.8 (CH), 137.0 (C), 183.0 (CH); *m/z* (CI) 191 (MH^+, 100%), 137 (15), 113 (4), 81 (7), 69 (9).

2-Formyl-3-vinylthiophene (132)[139]



To a solution of 3-bromo-2-formylthiophene **131** (0.55 g, 2.9 mmol) in toluene (20 mL), was added tetrakis(triphenylphosphine)palladium(0) (0.10 g, 0.09 mmol) followed by tributyl(vinyl)tin (1.00 mL, 3.44 mmol) and the reaction mixture was heated under reflux for 24 h. The reaction mixture was quenched with saturated aqueous cesium fluoride solution (10 mL) and stirred at room temperature for 1 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 19:1) afforded the desired compound **132** (0.38 g, 96%) as a pale yellow oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3094 (CH), 1643 (CO), 1427, 1204, 918, 764; δ_H (400 MHz, $CDCl_3$) 5.58 (1H, dd, *J* 10.9, 0.9 Hz, 2'-*H*H), 5.84 (1H, dd, *J* 17.4, 0.9 Hz, 2'-H*H*), 7.26 (1H, dd, *J* 17.4 Hz, 1'-H), 7.34 (1H, d, *J* 5.1 Hz, ArH), 7.65 (1H, d, *J* 5.1 Hz, ArH), 10.14 (1H, br d, *J* 1.0 Hz CHO); δ_C (100 MHz, $CDCl_3$) 120.1 (CH_2), 126.8 (CH), 127.7 (CH), 134.3 (CH), 137.9 (C), 147.0 (C), 182.2 (CH); *m/z* (CI) 139 (MH^+, 100%), 85 (2), 69 (3).

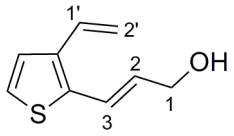
Ethyl (2*E*)-3-(3-vinylthiophen-2-yl)prop-2-enoate (133)



To a suspension of lithium chloride (0.46 g, 11.0 mmol) in acetonitrile (30 mL), was added triethyl phosphonoacetate (1.64 mL, 8.26 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.23 mL, 8.26 mmol). The mixture was stirred at room temperature for 1 h before addition to a flask containing 2-formyl-3-vinylthiophene **132** (0.38 g, 2.8 mmol). The reaction mixture was then stirred at 50 °C overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (10 mL) and concentrated *in vacuo*. The product was extracted using diethyl ether (3 × 30 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **133** (0.48 g, 84%) as a colourless oil. ν_{max}/cm^{-1} 2978 (CH),

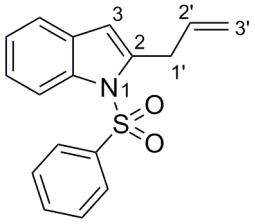
1705 (CO), 1613, 1273, 1157, 1034, 964, 910, 848, 709; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 4.25 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.40 (1H, dd, *J* 11.0, 1.0 Hz, 2'-*H*H), 5.66 (1H, dd, *J* 17.3, 1.0 Hz, 2'-H*H*), 6.22 (1H, d, *J* 15.5 Hz, 2-H), 6.94 (1H, dd, *J* 17.3, 11.0 Hz, 1'-H), 7.21 (1H, d, *J* 5.3 Hz, ArH), 7.27 (1H, d, *J* 5.3 Hz, ArH), 7.96 (1H, d, *J* 15.5 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 60.5 (CH_2), 117.0 (CH_2), 117.3 (CH), 126.2 (CH), 127.2 (CH), 128.3 (CH), 134.6 (CH), 134.9 (C), 141.8 (C), 166.8 (C); *m/z* (CI) 209.0640 (MH^+. $C_{11}H_{13}O_2S$ requires 209.0636), 163 (4%), 135 (7), 85 (4), 69 (8).

(2*E*)-3-(3-Vinylthiophen-2-yl)prop-2-en-1-ol (134)



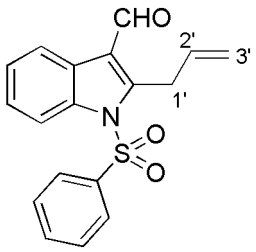
(2*E*)-3-(3-Vinylthiophen-2-yl)prop-2-en-1-ol **134** was synthesised according to general procedure 2, using ethyl (2*E*)-3-(3-vinylthiophen-2-yl)prop-2-enoate **133** (0.49 g, 2.3 mmol). Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **134** (0.32 g, 82%) as a colourless oil. ν_{max}/cm^{-1} 3349 (OH), 2859 (CH), 1366, 1173, 1084, 818, 737; δ_H (400 MHz, $CDCl_3$) 1.71–1.75 (1H, m, OH), 4.27–4.32 (2H, m, 1-H_2), 5.27 (1H, dd, *J* 11.0, 1.2 Hz, 2'-*H*H), 5.56 (1H, dd, *J* 17.4, 1.2 Hz, 2'-H*H*), 6.18 (1H, dt, *J* 15.6, 5.7 Hz, 2-H), 6.83 (1H, dd, *J* 17.4, 11.0 Hz, 1'-H), 6.87–6.93 (1H, m, 3-H), 7.08 (1H, d, *J* 5.3 Hz, ArH), 7.15 (1H, d, *J* 5.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 63.5 (CH_2), 114.8 (CH_2), 122.1 (CH), 123.8 (CH), 125.6 (CH), 128.8 (CH), 129.1 (CH), 136.8 (C), 137.3 (C); *m/z* (CI) 149.0420 (MH^+–H_2O. C_9H_9S requires 149.0425), 139 (15%), 123 (5), 95 (6), 81 (16), 69 (20).

2-Allyl-1-benzenesulfonyl-1*H*-indole (139)[111]



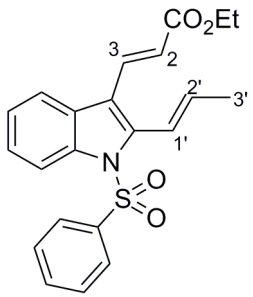
To a solution of 1-benzenesulfonyl-1*H*-indole (0.50 g, 2.0 mmol) in tetrahydrofuran (25 mL) at –78 °C, was added *n*-butyl lithium (2 M in hexanes) (0.88 mL, 1.8 mmol) and the reaction stirred for 1 h. To the reaction mixture was added allyl bromide (0.15 mL, 1.75 mmol) dissolved in tetrahydrofuran (5 mL) and the reaction warmed to –50 °C before stirring for a further 0.5 h. The reaction mixture was then warmed to room temperature and quenched with a saturated aqueous ammonium chloride solution (10 mL). The product was extracted using diethyl ether (3 × 20 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **139** (0.27 g, 52%) as a white solid. Spectroscopic data in accordance with literature values. Mp 84–86 °C; ν_{max}/cm^{-1} 3079 (CH), 1445, 1365, 1336, 1167, 1139, 1091, 1043, 996, 913, 810, 739, 719; δ_H (400 MHz, $CDCl_3$) 3.75–3.79 (2H, m, 1'-H_2), 5.16–5.22 (2H, m, 3'-H_2), 6.03 (1H, ddt, *J* 17.6, 10.7, 6.7 Hz, 2'-H), 6.39–6.42 (1H, m, 3-H), 7.18–7.30 (2H, m, ArH), 7.38–7.45 (3H, m, ArH), 7.50–7.55 (1H, m, ArH), 7.74–7.78 (2H, m, ArH), 8.14–8.18 (1H, m, ArH); δ_C (125 MHz, $CDCl_3$) 33.4 (CH_2), 109.6 (CH), 114.7 (CH), 117.9 (CH_2), 120.3 (CH), 123.6 (CH), 124.1 (CH), 126.3 (2 × CH), 129.3 (2 × CH), 129.6 (C), 133.7 (CH), 134.1 (CH), 137.2 (C), 139.1 (C), 140.1 (C); *m/z* (EI) 297 (M^+, 62%), 156 (42), 128 (19), 84 (100), 49 (90).

2-Allyl-1-benzenesulfonyl-3-formyl-1*H*-indole (138)[111]



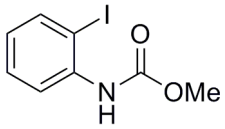
To a solution of titanium tetrachloride (1 M in dichloromethane) (3.77 mL, 3.77 mmol) in dichloromethane (30 mL) at –78 °C, was added dichloromethyl methyl ether (0.34 mL, 3.77 mmol) followed by 2-allyl-1-benzenesulfonyl-1*H*-indole **139** (0.56 g, 1.9 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at –78 °C for 2 h then warmed to 0 °C before quenching with water (10 mL) and a 10% aqueous sodium carbonate solution (10 mL). The product was extracted with dichloromethane (3 × 20 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **138** (0.50 g, 81%) as a viscous oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3063 (CH), 1667 (CO), 1450, 1373, 1173, 1088, 995, 918, 725; δ_H (400 MHz, $CDCl_3$) 4.21 (2H, dt, *J* 5.8, 1.5 Hz, 1'-H_2), 5.07 (1H, dq, *J* 17.1, 1.5 Hz, 3'-*H*H), 5.13 (1H, dq, *J* 10.1, 1.5 Hz, 3'-H*H*), 6.07 (1H, ddt, *J* 17.1, 10.1, 5.8 Hz, 2'-H), 7.33–7.41 (2H, m, ArH), 7.44–7.50 (2H, m, ArH), 7.59 (1H, tt, *J* 7.5, 1.2 Hz, ArH), 7.84–7.87 (2H, m, ArH), 8.16–8.19 (1H, m, ArH), 8.26–8.30 (1H, m, ArH), 10.29 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 29.5 (CH_2), 114.4 (CH), 117.8 (CH_2), 119.6 (C), 121.5 (CH), 125.2 (CH), 125.8 (CH), 126.1 (C), 126.7 (2 × CH), 129.6 (2 × CH), 134.3 (CH), 134.5 (CH), 136.0 (C), 138.5 (C), 148.9 (C), 185.8 (CH); *m/z* (CI) 326 (MH^+, 29%), 186 (100), 143 (42), 127 (12), 85 (11), 69 (17).

Ethyl (2*E*)-3-[1-benzenesulfonyl-2-prop-1-enyl)-1*H*-indol-3-yl]prop-2-enoate (141)



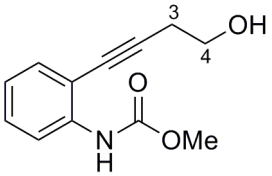
To a suspension of lithium chloride (0.02 g, 0.43 mmol) in acetonitrile (5 mL), was added triethyl phosphonoacetate (0.07 mL, 0.36 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.05 mL, 0.36 mmol). The mixture was stirred at room temperature for 1 h before addition to a flask containing 2-allyl-1-benzenesulfonyl-3-formyl-1*H*-indole **138** (0.08 g, 0.24 mmol). The reaction mixture was then stirred at 50 °C overnight. The reaction was quenched with saturated aqueous ammonium chloride solution (2 mL) and concentrated *in vacuo*. The product was extracted using diethyl ether (4 × 5 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded compound **141** (0.05 g, 57%) as a white solid. Mp 114–116 °C; ν_{max}/cm^{-1} 2984 (CH), 1711 (CO), 1625 (C=C), 1303, 1269, 1169, 967, 744, 722; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.07 (3H, dd, *J* 6.6, 1.5 Hz, 3'-H_3), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 5.83 (1H, dq, *J* 15.6, 6.6 Hz, 2'-H), 6.50 (1H, d, *J* 16.2 Hz, 2"-H), 6.89–6.96 (1H, m, 1'-H), 7.29–7.41 (4H, m, ArH), 7.49–7.54 (1H, m, ArH), 7.70–7.81 (4H, m, 1"-H and ArH), 8.29 (1H, d, *J* 8.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 14.4 (CH_3), 19.3 (CH_3), 60.4 (CH_2), 115.1 (CH), 117.0 (C), 118.6 (CH), 120.4 (CH), 120.6 (CH), 124.5 (CH), 125.5 (CH), 126.8 (2 × CH), 127.8 (C), 129.1 (2 × CH), 134.0 (CH), 136.5 (C), 137.1 (CH), 138.3 (CH), 138.4 (C), 141.4 (C), 167.5 (C); *m/z* (EI) 395.1195 (M^+. $C_{22}H_{21}NO_4S$ requires 395.1191), 322 (10%), 252 (17), 210 (12), 180 (100), 167 (29), 152 (8), 77 (20).

2-(Methoxycarbonylamino)iodobenzene (144)



To a solution of 2-iodoaniline (1.50 g, 6.85 mmol) in dichloromethane (30 mL), was added methyl chloroformate (0.64 mL, 8.2 mmol) and pyridine (1.66 mL, 20.5 mmol) and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with chloroform (20 mL) and washed with water (20 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded the desired compound **144** (1.61 g, 85%) as a white solid. Mp 49–51 °C; ν_{max}/cm^{-1} 3372 (NH), 2955 (CH), 1735 (CO), 1582, 1520, 1435, 1304, 1204, 1011, 941, 748; δ_H (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.78–6.83 (1H, m, ArH), 6.96 (1H, br s, NH), 7.31–7.37 (1H, m, ArH), 7.76 (1H, dd, *J* 8.0, 1.5 Hz, ArH), 8.05 (1H, d, *J* 8.0 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 52.6 (CH_3), 88.9 (C), 120.3 (CH), 125.1 (CH), 129.3 (CH), 138.4 (C), 138.9 (CH), 153.9 (C); *m/z* (EI) 276.9603 (M^+. $C_8H_8INO_2$ requires 276.9600), 245 (10%), 218 (6), 150 (100), 135 (30), 91 (23), 49 (8).

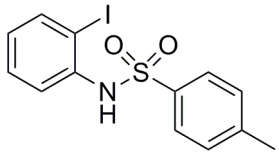
2-(4-Hydroxybut-1-yn-1-yl)methoxycarbonylaminobenzene (145)



To a solution of 2-(methoxycarbonylamino)iodobenzene **144** (0.10 g, 0.36 mmol) in *N*,*N*-dimethylformamide (5 mL), was added 3-butyn-1-ol (0.16 mL, 2.2 mmol), triethylamine (1.55 mL, 11.2 mmol), copper iodide (0.01 g, 0.07 mmol) and bis(acetonitrile)dichloropalladium(II) (0.01 g, 0.04 mmol) and the reaction mixture was heated at 100 °C overnight. The mixture was cooled, diluted with ethyl acetate (20 mL) and washed with water (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 4:1) afforded compound **145** (0.03 g, 41%) as a colourless oil. ν_{max}/cm^{-1} 3395 (NH), 3333 (OH), 2951 (CH), 1721 (CO), 1582, 1520, 1450, 1304, 1215, 1061, 756; δ_H (400 MHz, $CDCl_3$) 2.05 (1H, br s, OH), 2.76 (2H, t, *J* 6.2 Hz, 3-H_2), 3.79 (3H, s, OCH_3), 3.86 (2H, t, *J*

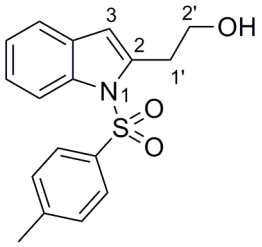
6.2 Hz, 4-H_2), 6.96 (1H, td, *J* 7.7, 1.0 Hz, ArH), 7.27–7.32 (1H, m, ArH), 7.35 (1H, dd, *J* 7.7, 1.4 Hz, ArH), 7.53 (1H, br s, NH), 8.11 (1H, d, *J* 8.2 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2), 52.4 (CH_3), 61.0 (CH_2), 77.7 (C), 94.0 (C), 111.7 (C), 117.7 (CH), 122.5 (CH), 129.3 (CH), 131.6 (CH), 139.2 (C), 153.8 (C); *m/z* (CI) 220.0972 (MH^+. $C_{12}H_{14}NO_3$ requires 220.0974), 188 (100%), 170 (22), 158 (8).

2-(4-Methyl-benzenesulfonyl)iodobenzene (142)[140]



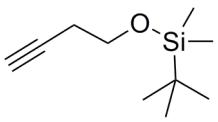
To a solution of 2-iodoaniline (3.00 g, 13.7 mmol) in dichloromethane (50 mL), was added *p*-toluenesulfonyl chloride (3.13 g, 16.4 mmol) and pyridine (3.32 mL, 41.1 mmol) and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with chloroform (30 mL) and washed with water (30 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 9:1) afforded the desired compound **142** (4.12 g, 82%) as a white solid. Mp 86–88 °C, *lit.*[140] 90–92 °C; ν_{max}/cm^{-1} 3287 (NH), 3063 (CH), 1589, 1466, 1389, 1327, 1157, 1088, 1011, 910, 818, 756, 710, 656; δ_H (400 MHz, $CDCl_3$) 2.38 (3H, s, Ar-CH_3), 6.79 (1H, br s, NH), 6.81–6.86 (1H, m, ArH), 7.20–7.23 (2H, m, ArH), 7.28–7.33 (1H, m, ArH), 7.61–7.67 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 92.3 (C), 122.5 (CH), 126.8 (CH), 127.5 (2 × CH), 129.5 (CH), 129.6 (2 × CH), 135.9 (C), 137.5 (C), 139.1 (CH), 144.2 (C); *m/z* (EI) 373 (M^+, 100%), 218 (39), 155 (31), 139 (28), 91 (82), 84 (19), 44 (96).

2-(2-Hydroxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indole (143)[112]



To a solution of 2-(4-methylbenzene-1-sulfonyl)iodobenzene **142** (0.10 g, 0.27 mmol) in *N*,*N*-dimethylformamide (5 mL), was added 3-butyn-1-ol (0.12 mL, 1.6 mmol), triethylamine (1.16 mL, 8.37 mmol), copper iodide (0.01 g, 0.05 mmol) and bis(benzonitrile)dichloropalladium(II) (0.02 g, 0.03 mmol) and the reaction mixture was heated at 70 °C overnight. The mixture was cooled, diluted with ethyl acetate (20 mL) and washed with water (30 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate 7:3) afforded the desired compound **143** (0.06 g, 71%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3383 (OH), 2943 (CH), 1450, 1366, 1219, 1173, 1146, 1092, 1045, 814, 748, 664; δ_H (400 MHz, $CDCl_3$) 1.70 (1H, br s, OH), 2.32 (3H, s, Ar-CH_3), 3.28 (2H, td, *J* 6.0, 0.6 Hz, 1'-H_2), 4.00 (2H, t, *J* 6.0 Hz, 2'-H_2), 6.50 (1H, m, 3-H), 7.15–7.30 (4H, m, ArH), 7.40–7.44 (1H, m, ArH), 7.59–7.63 (2H, m, ArH), 8.14–8.18 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 32.6 (CH_2), 61.8 (CH_2), 110.6 (CH), 114.9 (CH), 120.3 (CH), 123.7 (CH), 124.3 (CH), 126.3 (2 × CH), 129.7 (C), 129.9 (2 × CH), 135.9 (C), 137.3 (C), 138.1 (C), 144.9 (C); *m/z* (CI) 316 (MH^+, 100%), 298 (58), 203 (6), 161 (5), 85 (4), 69 (8).

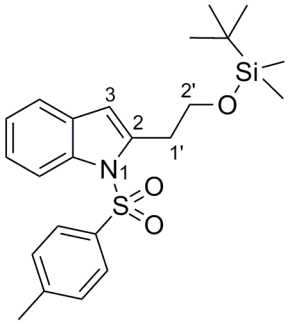
1-(*tert*-Butyldimethylsilyloxy)but-3-yne (146)[141]



To a solution of 3-butyn-1-ol (2.15 mL, 28.6 mmol) in tetrahydrofuran (80 mL), was added *tert*-butyldimethylsilyl chloride (6.50 g, 42.9 mmol) and imidazole (2.90 g, 42.9 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was filtered through a short pad of Celite® and washed with diethyl ether (100 mL). The organic filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column

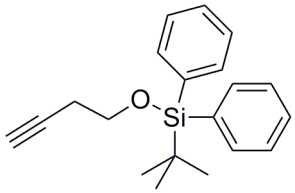
chromatography (petroleum ether/diethyl ether 49:1) afforded the desired compound **146** (4.96 g, 94%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3310 (CH), 2932 (CH), 1258, 1103, 918, 833, 779, 633; δ_H (400 MHz, $CDCl_3$) 0.08 (6H, s, 2 × CH_3), 0.90 (9H, s, ^{t}Bu), 1.96 (1H, t, *J* 2.7 Hz, 4-H), 2.40 (2H, td, *J* 7.2, 2.7 Hz, 2-H_2), 3.74 (2H, t, *J* 7.2 Hz, 1-H_2); δ_C (100 MHz, $CDCl_3$) –5.3 (2 × CH_3), 18.3 (C), 22.9 (CH_2), 25.9 (3 × CH_3), 61.7 (CH_2), 69.3 (CH), 81.5 (C); *m/z* (CI) 185 (MH^+, 100%), 127 (10), 113 (15), 81 (29), 71 (39).

2-(2-*tert*-Butyldimethylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indole (147)



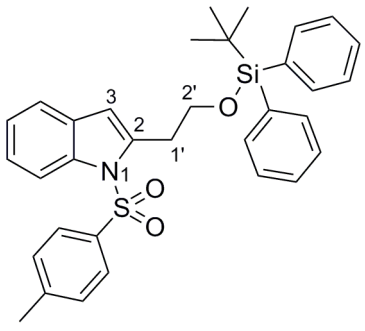
To a solution of 2-(4-methyl-benzenesulfonyl)iodobenzene **142** (0.40 g, 1.1 mmol) in *N*,*N*-dimethylformamide (15 mL), was added 1-(*tert*-butyldimethylsilyloxy)but-3-yne **146** (1.19 g, 6.43 mmol), triethylamine (4.60 mL, 33.2 mmol), copper iodide (0.04 g, 0.2 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.12 g, 0.11 mmol) and the reaction mixture was heated at 70 °C overnight. The mixture was cooled, diluted with ethyl acetate (30 mL) and washed with water (50 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 49:1) afforded the desired compound **147** (0.40 g, 88%) as a white solid. Mp 70–72 °C; ν_{max}/cm^{-1} 2932 (CH), 1458, 1358, 1250, 1165, 1088, 1049, 903, 810, 748, 687, 656; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, 2 × CH_3), 0.87 (9H, s, ^{t}Bu), 2.32 (3H, s, Ar-CH_3), 3.22 (2H, td, *J* 6.6, 0.7 Hz, 1'-H_2), 3.98 (2H, t, *J* 6.6 Hz, 2'-H_2), 6.45 (1H, br d, *J* 0.7 Hz, 3-H), 7.15–7.28 (4H, m, ArH), 7.39–7.42 (1H, m, ArH), 7.57–7.63 (2H, m, ArH), 8.15–8.18 (1H, m, ArH); δ_C (100 MHz, $CDCl_3$) –5.4 (2 × CH_3), 18.3 (C), 21.6 (CH_3), 25.9 (3 × CH_3), 32.8 (CH_2), 62.3 (CH_2), 110.5 (CH), 114.9 (CH), 120.1 (CH), 123.5 (CH), 123.9 (CH), 126.2 (2 × CH), 129.8 (2 × CH), 129.9 (C), 136.1 (C), 137.1 (C), 138.7 (C), 144.6 (C); *m/z* (CI) 430.1874 (MH^+. $C_{23}H_{32}NO_3SSi$ requires 430.1872), 332 (40%), 276 (100), 197 (12), 157 (68), 141 (32), 85 (17), 71 (24).

1-(*tert*-Butyldiphenylsilyloxy)but-3-yne (150)[142]



To a solution of 3-butyn-1-ol (2.15 mL, 28.6 mmol) in tetrahydrofuran (80 mL), was added *tert*-butyldiphenylsilyl chloride (11.2 mL, 42.9 mmol) and imidazole (2.90 g, 42.9 mmol) and the reaction mixture was stirred at room temperature overnight. The mixture was filtered through a short pad of Celite® and washed with diethyl ether (100 mL). The organic filtrate was dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 49.1) afforded the desired compound **150** (8.80 g, 100%) as a colourless oil. Spectroscopic data in accordance with literature values. ν_{max}/cm^{-1} 3302 (CH), 2932 (CH), 1103, 918, 702, 617; δ_H (400 MHz, $CDCl_3$) 1.06 (9H, s, ^{t}Bu), 1.94 (1H, t, *J* 2.6 Hz, 4-H), 2.45 (2H, td, *J* 7.1, 2.6 Hz, 2-H_2), 3.78 (2H, t, *J* 7.1 Hz, 1-H_2), 7.35–7.45 (6H, m, ArH), 7.66–7.70 (4H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 22.6 (CH_2), 26.8 (3 × CH_3), 62.3 (CH_2), 69.4 (CH), 81.5 (C), 127.7 (4 × CH), 129.7 (2 × CH), 133.6 (2 × C), 135.6 (4 × CH); *m/z* (CI) 309 (MH^+, 100%), 269 (12), 251 (22), 231 (21), 167 (6), 85 (10), 69 (18).

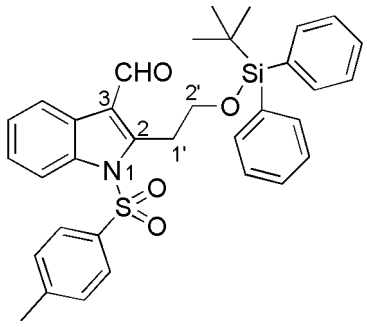
2-(2-*tert*-Butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indole (151)



To a solution of 2-(4-methyl-benzenesulfonyl)iodobenzene **142** (0.35 g, 0.94 mmol) in *N*,*N*-dimethylformamide (40 mL), was added 1-(*tert*-butyldiphenylsilyloxy)but-3-yne **150** (0.88 g, 2.8 mmol), triethylamine (4.05 mL, 29.1 mmol), copper iodide (0.04 g, 0.19 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.11 g, 0.09 mmol) and the reaction mixture was heated at 70 °C overnight. The mixture was cooled, diluted with ethyl acetate

(40 mL) and washed with water (100 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 97:3) afforded the desired compound **151** (0.50 g, 96%) as a white solid. Mp 108–110 °C; ν_{max}/cm^{-1} 2940 (CH), 1443, 1366, 1165, 1080, 910, 810, 741, 694, 617; δ_H (400 MHz, $CDCl_3$) 1.02 (9H, s, ^{t}Bu), 2.31 (3H, s, Ar-CH_3), 3.26 (2H, t, *J* 6.3 Hz, 1'-H_2), 4.02 (2H, t, *J* 6.3 Hz, 2'-H_2), 6.42 (1H, br s, 3-H), 7.13 (2H, d, *J* 8.3 Hz, ArH), 7.17–7.28 (2H, m, ArH), 7.30–7.35 (4H, m, ArH), 7.37–7.43 (3H, m, ArH), 7.54–7.62 (6H, m, ArH), 8.15 (1H, d, *J* 8.3 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 21.5 (CH_3), 26.8 (3 × CH_3), 32.5 (CH_2), 62.7 (CH_2), 110.6 (CH), 114.9 (CH), 120.1 (CH), 123.5 (CH), 123.9 (CH), 126.2 (2 × CH), 127.7 (4 × CH), 129.6 (2 × CH), 129.8 (2 × CH), 129.9 (C), 133.7 (2 × C), 135.6 (4 × CH), 136.2 (C), 137.2 (C), 138.7 (C), 144.6 (C); *m/z* (CI) 554.2183 (MH^+. $C_{33}H_{36}NO_3SSi$ requires 554.2185), 456 (32%), 400 (100), 342 (12), 257 (13), 157 (25), 141 (25), 69 (32).

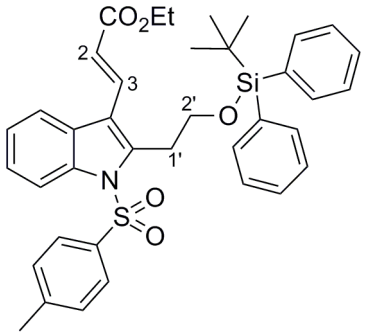
2-(2-*tert*-Butyldiphenylsilyloxyethyl)-3-formyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (152)



To a solution of titanium tetrachloride (1 M in dichloromethane) (8.68 mL, 8.68 mmol) in dichloromethane (90 mL) at –78 °C, was added dichloromethyl methyl ether (0.79 mL, 8.68 mmol) followed by 2-(2-*tert*-butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indole **151** (1.20 g, 2.17 mmol) in dichloromethane (10 mL). The reaction mixture was stirred at –78 °C for 2 h then warmed to 0 °C before quenching with water (30 mL) and a 10% aqueous sodium carbonate solution (30 mL). The product was extracted with dichloromethane (3 × 40 mL) and the organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **152** (1.08 g, 86%) as a white solid. (Found: C, 70.1; H, 6.1; N, 2.5. $C_{34}H_{35}O_4NSSi$ requires C, 70.2; H, 6.1; N, 2.4%); Mp 128–130 °C; ν_{max}/cm^{-1} 2940 (CH), 1667 (CO), 1443, 1373, 1165, 1072, 1011, 957, 910, 748, 694; δ_H (400 MHz, $CDCl_3$) 0.96 (9H, s, ^{t}Bu), 2.33 (3H, s, Ar-CH_3), 3.63 (2H, t, *J* 5.8

Hz, 1'-H_2), 4.02 (2H, t, *J* 5.8 Hz, 2'-H_2), 7.16–7.19 (2H, m, ArH), 7.23–7.27 (4H, m, ArH), 7.33–7.39 (4H, m, ArH), 7.45–7.49 (4H, m, ArH), 7.60–7.64 (2H, m, ArH), 8.14–8.18 (1H, m, ArH), 8.29–8.33 (1H, m, ArH), 10.19 (1H, s, CHO); δ_C (100 MHz, $CDCl_3$) 19.0 (C), 21.6 (CH_3), 26.8 (3 × CH_3), 29.2 (CH_2), 63.3 (CH_2), 114.4 (CH), 121.5 (C), 121.8 (CH), 125.1 (CH), 125.6 (CH), 126.2 (C), 126.4 (2 × CH), 127.6 (4 × CH), 129.7 (2 × CH), 130.1 (2 × CH), 133.0 (2 × C), 135.5 (4 × CH), 135.6 (C), 136.1 (C), 145.7 (C), 148.5 (C), 186.7 (CH); *m/z* (CI) 582.2136 (MH^+. $C_{34}H_{36}NO_4SSi$ requires 582.2134), 470 (22%), 428 (100), 370 (44), 284 (29), 257 (12), 157 (52), 141 (16), 69 (7).

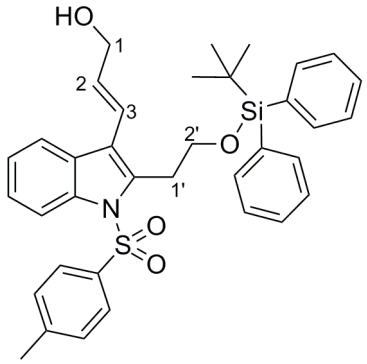
Ethyl (2*E*)-3-[2-(2-*tert*-butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]prop-2-enoate (153)



To a suspension of lithium chloride (1.01 g, 24.1 mmol) in acetonitrile (150 mL), was added triethyl phosphonoacetate (3.59 mL, 18.1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2.70 mL, 18.1 mmol). The mixture was stirred at room temperature for 1 h before addition to a flask containing 2-(2-*tert*-butyldiphenylsilyloxyethyl)-3-formyl-1-(4-methylbenzenesulfonyl)-1*H*-indole **152** (3.20 g, 5.50 mmol). The reaction mixture was then stirred at 50 °C overnight. The reaction was quenched with a saturated aqueous ammonium chloride solution (30 mL) and concentrated *in vacuo*. The product was extracted using diethyl ether (4 × 50 mL), the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. The product was recrystallised (ethyl acetate/petroleum ether) and afforded the desired compound **153** (2.88 g, 80%) as a white solid. Mp 115–117 °C; ν_{max}/cm^{-1} 2940 (CH), 1713 (CO), 1628 (C=C), 1442, 1366, 1288, 1157, 1072, 1026, 964, 694; δ_H (400 MHz, $CDCl_3$) 0.94 (9H, s, ^{t}Bu), 1.32 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.31 (3H, s, Ar-CH_3), 3.47 (2H, t, *J* 5.5 Hz, 1'-H_2), 4.00 (2H, t, *J* 5.5 Hz, 2'-H_2), 4.26 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 6.55 (1H, d, *J* 16.2 Hz, 2-H), 7.10–7.15 (2H, m, ArH), 7.19–7.27 (4H, m, ArH), 7.30–7.39 (4H, m, ArH), 7.46–7.49 (4H, m, ArH), 7.52–7.55 (2H, m, ArH), 7.78–7.82 (1H, m, ArH), 7.97 (1H, d, *J* 16.2 Hz, 3-H), 8.24 (1H, d, *J* 7.8 Hz, ArH); δ_C (100

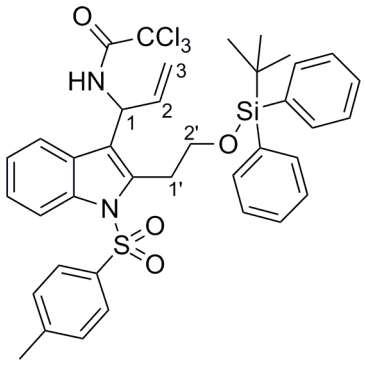
MHz, $CDCl_3$) 14.4 (CH_3), 19.0 (C), 21.6 (CH_3), 26.7 (3 × CH_3), 29.8 (CH_2), 60.4 (CH_2), 63.6 (CH_2), 115.3 (CH), 118.7 (C), 119.0 (CH), 120.1 (CH), 124.3 (CH), 125.0 (CH), 126.3 (2 × CH), 127.5 (4 × CH), 127.6 (C), 129.5 (2 × CH), 129.9 (2 × CH), 133.3 (2 × C), 135.5 (4 × CH), 135.7 (C), 136.3 (CH), 136.9 (C), 141.0 (C), 145.1 (C), 167.2 (C); *m/z* (FAB) 652.2554 (MH^+. $C_{38}H_{42}NO_5SSi$ requires 652.2553), 594 (73%), 497 (30), 439 (100), 273 (15), 197 (12), 168 (17), 135 (54), 84 (40), 69 (61), 56 (89).

(2*E*)-3-[2-(2-*tert*-Butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]prop-2-en-1-ol (154)



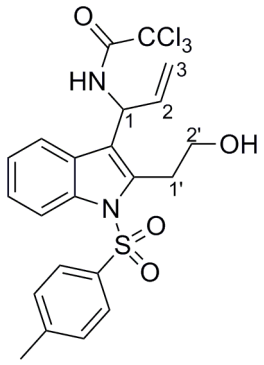
(2*E*)-3-[2-(2-*tert*-Butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]prop-2-en-1-ol **154** was synthesised according to general procedure 2, using ethyl (2*E*)-3-[2-(2-*tert*-butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]prop-2-enoate **153** (1.00 g, 1.54 mmol) and DIBAL-H (1 M in hexanes) (3.5 eq). Flash column chromatography (petroleum ether/ethyl acetate 4:1) afforded the desired compound **154** (0.89 g, 95%) as a viscous oil. ν_{max}/cm^{-1} 3403 (OH), 3071 (CH), 2859 (CH), 1450, 1362, 1173, 1088, 810, 737, 702, 656; δ_H (500 MHz, $CDCl_3$) 0.98 (9H, s, ^{t}Bu), 1.30 (1H, br s, OH), 2.29 (3H, s, Ar-CH_3), 3.38 (2H, t, *J* 6.2 Hz, 1'-H_2), 4.00 (2H, t, *J* 6.2 Hz, 2'-H_2), 4.24 (2H, m, 1-H_2), 6.38 (1H, dt, *J* 16.2, 5.8 Hz, 2-H), 6.69 (1H, dt, *J* 16.2, 1.4 Hz, 3-H), 7.09–7.11 (2H, m, ArH), 7.24–7.38 (8H, m, ArH), 7.51–7.54 (6H, m, ArH), 7.70–7.73 (1H, m, ArH), 8.22 (1H, d, *J* 8.2 Hz, ArH); δ_C (125 MHz, $CDCl_3$) 19.2 (C), 21.5 (CH_3), 26.8 (3 × CH_3), 29.9 (CH_2), 63.8 (CH_2), 64.5 (CH_2), 115.3 (CH), 119.9 (CH), 120.0 (C), 122.8 (CH), 123.9 (CH), 124.5 (CH), 126.2 (2 × CH), 127.6 (4 × CH), 128.6 (C), 129.6 (2 × CH), 129.8 (2 × CH), 130.9 (CH), 133.6 (2 × C), 135.5 (4 × CH), 135.9 (C), 136.1 (C), 137.0 (C), 144.7 (C); *m/z* (FAB) 592.2340 (MH^+–H_2O. $C_{36}H_{38}NO_3SSi$ requires 592.2342), 437 (21%), 380 (17), 310 (22), 197 (44), 135 (100), 91 (6).

1-[2-(2-*tert*-Butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]-1-(2',2',2'-trichloromethylcarbonylamino)prop-2-enyl (156)



(2*E*)-3-[2-(2-*tert*-butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indole]prop-2-en-1-ol **154** (0.15 g, 0.25 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.04 mL, 0.25 mmol) and trichloroacetonitrile (0.05 mL, 0.49 mmol). The reaction mixture was allowed to warm to room temperature before stirring for 6 h. The reaction mixture was filtered through a short pad of alumina, washed with ethyl acetate (50 mL) and the filtrate concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (5 mL) and transferred to a Schlenk tube containing potassium carbonate (0.02 g). The tube was then sealed under argon and the reaction mixture stirred at 140 °C for 24 h. Flash column chromatography (petroleum ether/diethyl ether 19:1) afforded the desired compound **156** (0.07 g, 37%) as a white solid. Mp 102–104 °C; ν_{max}/cm^{-1} 3356 (NH), 2858 (CH), 1712 (CO), 1506, 1357, 1160, 1109, 1067, 816, 766, 702; δ_H (400 MHz, $CDCl_3$) 1.04 (9H, s, ^{t}Bu), 2.96 (3H, s, Ar-CH_3), 3.42–3.59 (2H, m, 1'-H_2), 3.85–3.93 (1H, m, 2'-*H*H), 4.02–4.10 (1H, m, 2'-H*H*), 5.12 (1H, dd, *J* 17.3, 2.2 Hz, 3-*H*H), 5.14 (1H, dd, *J* 10.5, 2.2 Hz, 3-H*H*), 5.67–5.72 (1H, m, 1-H), 5.87 (1H, ddd, *J* 17.3, 10.5, 3.8 Hz, 2-H), 6.97 (1H, br d, *J* 7.6 Hz, NH), 7.09–7.11 (2H, m, ArH), 7.18–7.23 (1H, m, ArH), 7.26–7.32 (5H, m, ArH), 7.34–7.42 (3H, m, ArH), 7.49–7.53 (2H, m, ArH), 7.55–7.59 (4H, m, ArH), 8.22 (1H, d, *J* 8.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 21.5 (CH_3), 26.9 (3 × CH_3), 29.8 (CH_2), 49.7 (CH), 64.1 (CH_2), 92.5 (C), 115.8 (CH), 116.4 (CH_2), 118.9 (CH), 119.0 (C), 123.7 (CH), 124.6 (CH), 126.2 (2 × CH), 127.7 (4 × CH), 127.8 (C), 129.6 (2 × CH), 129.8 (2 × CH), 133.5 (2 × C), 135.0 (CH), 135.5 (4 × CH), 135.6 (C), 136.7 (C), 137.1 (C), 144.8 (C), 160.9 (C); *m/z* (CI) 755.1533 (MH^+. $C_{38}H_{40}{}^{35}Cl_2{}^{37}ClN_2O_4SSi$ requires 755.1523), 592 (5%), 400 (6), 307 (4), 257 (100), 199 (15), 157 (75), 141 (22), 69 (9).

1-[2-(2-Hydroxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]-1-(2',2',2'-trichloromethylcarbonylamino)-prop-2-enyl (158)



To a solution of 1-[2-(2-*tert*-butyldiphenylsilyloxyethyl)-1-(4-methylbenzenesulfonyl)-1*H*-indol-3-yl]-1-(2',2',2'-trichloromethylcarbonylamino)-prop-2-enyl **156** (0.02 g, 0.03 mmol) in tetrahydrofuran (4 mL) at 0 °C, was added tetra-*n*-butylammonium fluoride (1 M in tetrahydrofuran) (0.05 mL, 0.05 mmol). The reaction mixture was warmed to room temperature and stirred for 6 h. The reaction was quenched with a saturated aqueous ammonium chloride solution (1 mL) and the mixture was concentrated *in vacuo*. The product was extracted with diethyl ether (3 × 10 mL), organic layers separated, dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether 4:1) afforded the desired compound **158** (0.01 g, 96%) as a colourless oil. ν_{max}/cm^{-1} 3221 (OH), 2901 (CH), 1693 (CO), 1520, 1265, 1169, 1126, 1057, 822, 733, 679, 656; δ_H (400 MHz, $CDCl_3$) 1.98 (1H, br s, OH), 2.27 (3H, s, Ar-CH_3), 3.33–3.39 (2H, m, 1'-H_2), 3.94–4.05 (2H, m, 2'-H_2), 5.18–5.28 (1H, m, 3-H_2), 5.85–5.98 (2H, m, 1-H and 2-H), 7.13 (2H, d, *J* 8.2 Hz, ArH), 7.17–7.28 (2H, m, ArH), 7.45–7.52 (3H, m, ArH), 8.13 (1H, d, *J* 8.2 Hz, ArH), 8.18 (1H, br d, *J* 7.4 Hz, NH); δ_C (100 MHz, $CDCl_3$) 21.6 (CH_3), 29.5 (CH_2), 48.3 (CH), 62.3 (CH_2), 92.7 (C), 115.4 (CH), 116.1 (CH_2), 118.5 (CH), 120.4 (C), 124.0 (CH), 125.0 (CH), 126.2 (2 × CH), 128.7 (C), 129.9 (2 × CH), 135.3 (CH), 135.7 (C), 136.6 (C), 136.8 (C), 145.1 (C), 161.7 (C); *m/z* (EI) 516.0259 (M^+. $C_{22}H_{21}{}^{35}Cl_2{}^{37}ClN_2O_4S$ requires 516.0261), 484 (12%), 449 (10), 359 (8), 323 (53), 284 (32), 220 (11), 198 (94), 168 (100), 155 (19), 91 (58), 65 (10).

4.0 References

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