



Grafton, Mark W. (2014) *New one-pot multi-reaction processes for the synthesis of highly functionalised carbocycles and heterocycles*.
PhD thesis.

<http://theses.gla.ac.uk/5864/>

Copyright and moral rights for this thesis are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the Author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the Author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given

**New One-Pot Multi-Reaction Processes for the Synthesis of
Highly Functionalised Carbocycles and Heterocycles**

By

Mark W. Grafton, M. Sci

**A thesis submitted in part fulfilment of the requirements of
the degree of Doctor of Philosophy**



School of Chemistry

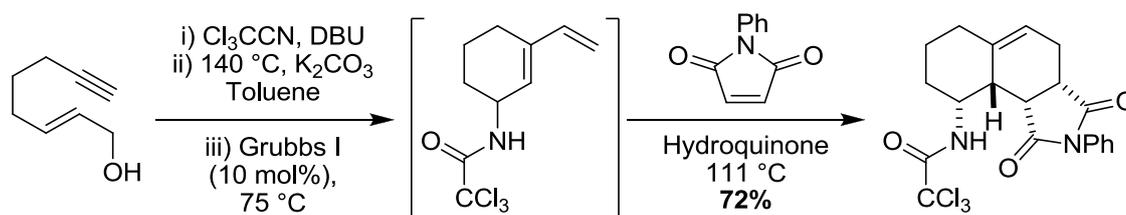
College of Science & Engineering

University of Glasgow

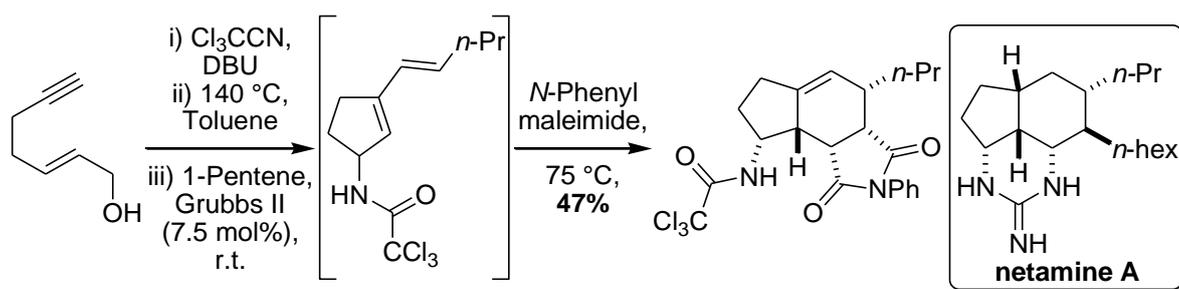
September 2014

Abstract

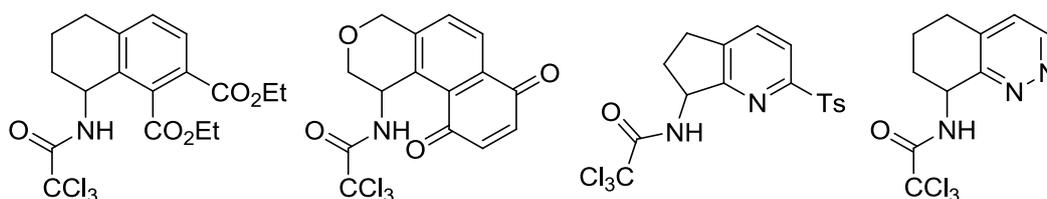
With the use of a one-pot process, a diastereoselective synthesis of bicyclononanes and decanes has been developed. Initial treatment of an allylic alcohol with trichloroacetonitrile, in the presence of DBU, afforded the corresponding allylic trichloroacetimidate. The trichloroacetimidate was then subjected to a one-pot process involving a thermal Overman rearrangement, ring-closing-enyne-metathesis and a hydrogen-bond directed Diels-Alder reaction to form polycyclic products in good isolated yields and as single diastereomers.



Research was then carried out on how this process could be extended. Through the use of Grubbs second generation catalyst, the process was extended to include a cross-metathesis reaction forming highly functionalised 1,3-dienes. These 1,3-dienes were then used in the hydrogen bond directing Diels-Alder reaction to generate highly functionalised polycycles, again as single diastereomers. This process was then employed towards the first total synthesis of the natural product, netamine A.



Further studies showed that carbo- and heterocyclic 1,3-dienes could be used in a one-pot Diels-Alder reaction and aromatisation step for the rapid preparation of partially saturated indane and tetralin motifs, which are present in biologically active molecules.



Contents

Acknowledgements	5
Author's Declaration	6
Abbreviations	7
1.0 Introduction	10
1.1.1 Enyne bond reorganisation	10
1.1.2 Pd(II)-catalysed cycloisomerisation	10
1.1.3 Other metal-catalysed enyne bond reorganisation reactions	16
1.2.1 Pauson-Khand reaction	20
1.3.1 Metathesis	23
1.3.2 Ring closing enyne metathesis	25
1.3.3 Uses for the RCEYM reaction	29
1.3.4 Tandem catalytic processes RCEYM/cross metathesis reactions	32
1.3.5 Intermolecular Enyne metathesis	34
1.3.6 Other uses of the 1,3-dienes generated from enyne metathesis	37
1.3.7 Conclusions	38
2.0 Results and Discussion	39
2.1 Development of the one-pot multi-reaction process	39
2.1.1 Proposed project aims	39
2.1.2 Overman rearrangement	40
2.1.3 Thermal Overman rearrangement	40
2.1.4 Metal catalysed Overman rearrangement	42
2.1.5 Development of the one-pot multi-step process for the synthesis of amino-substituted bicyclo[4.4.0]decanes	45

2.1.6 Exploring the scope of the one-pot process	53
2.1.7 Formation of amino-substituted bicyclo[4.3.0]nonanes	58
2.1.8 Attempted formation of the 7-membered cyclic 1,3-diene	63
2.2 Formation of C-5 substituted polycyclic compounds via a palladium(II)-catalysed Overman rearrangement	65
2.2.1 Development of Pd(II)-catalysed Overman Rearrangement	66
2.3 One-pot process tandem catalytic process for the synthesis of highly substituted polycycles	71
2.3.1 Synthesis of highly functionalised amino-substituted bicyclo[4.3.0]nonanes	73
2.3.2 Development of the one-pot process for the formation of C-6 substituted bicyclo[4.4.0]decanes	77
2.4 Total synthesis of netamine A	79
2.4.1 Towards the total synthesis of netamine A	82
2.5 Formation of partially saturated tetralins and indanes	88
2.5.1 Synthesis of heterocyclic 1,3-dienes	90
2.5.2 One-pot synthesis of quinone derivatives	95
2.5.3 Diels-Alder reaction with alkynes	99
2.5.4 Formation of heteroaromatic compounds	102
3.0 Conclusions and future work	108
4.0 Experimental	116
5.0 References	199
6.0 Appendix 1	207
7.0 Appendix 2	211

Acknowledgements

First of all I would like to express a huge thanks to my supervisor, Dr. Andrew Sutherland, for giving me the opportunity to undertake this PhD programme within his research group. I am very appreciative of all his encouragement and guidance throughout my PhD.

Thanks to my second supervisor Dr. David France for helpful discussions and to all other academic staff in the chemistry department.

Thanks also to the technical staff for their assistance over the past 4 years: Dr. L. J. Farrugia (X-ray crystallography), Dr. H. M. Senn (Computational Chemistry), Dr. D. Adam (NMR), Jim and Harry (Mass Spec), Stuart (IT) and Ted and Bruce (Stores).

Thanks go to the members of the Sutherland research group past and present: Lorna, Alistair, Fiona, Mark, Sajjad, Ahmed, Lynne, Adele, Ewen, Filip, Salaheddin, Alex, Nikki, Mohamed and Tomas for the good times both in and out of the Loudon Lab. I would like to thank members of the Hartley group for also making the lab an enjoyable place to work. I would also like to acknowledge Andrew, Michael, Julia, Craig and Stuart for their work carried out during their undergraduate studies.

Outside of the lab, I would like to thank Ally, Andy, Gordon, Mushy and Steven for all the pub quiz nights, golf and the random nights out over the past couple of years.

Finally thanks to my family: my Mum, Dad and Gran who have been a massive help and support to me through my PhD.

Financial support from the University of Glasgow scholarship is gratefully acknowledged.

Author's Declaration

This thesis represents the original work of Mark W. Grafton 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 2010 and March 2014. Aspects of the work described herein have previously been published elsewhere as stated below.

M. W. Grafton, L. J. Farrugia, H. M. Senn and A. Sutherland, *Chem. Commun.*, 2012, **48**, 7994.

M. W. Grafton, L. J. Farrugia and A. Sutherland, *J. Org. Chem.*, 2013, **78**, 7199.

E. D. D. Calder, M. W. Grafton and A. Sutherland, *Synlett*, 2014, **25**, 1068.

M. W. Grafton, S. A. Johnson, L. J. Farrugia and A. Sutherland, *Tetrahedron*, 2014, **70**, 7133.

Abbreviations

Å	angstrom(s)
Ac	acetyl
Ar	aromatic
Bn	benzyl
Bu	butyl
Boc	<i>tert</i> -butoxycarbonyl
cat.	catalyst
CI	Chemical Ionisation
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
dec	decyl
°C	degrees centigrade
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMSO	dimethyl sulfoxide
DIBAL-H	diisobutylaluminium hydride
dppb	1,4- <i>bis</i> (diphenylphosphino)butane
e.e.	enantiomeric excess
EI	Electron Impact
eq.	equivalents
ESI	Electrospray Ionisation
Et	Ethyl
g	gram(s)

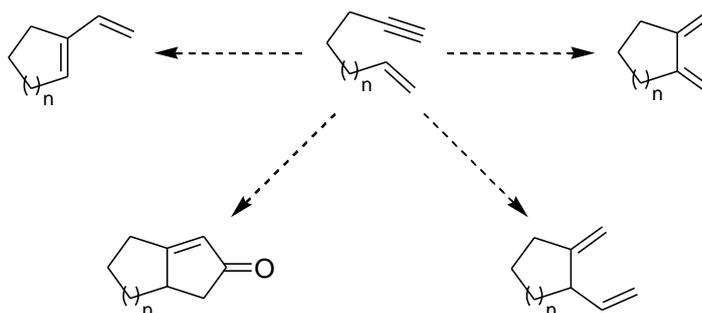
h	Hour(s)
hex	hexyl
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
M	Molar
Me	Methyl
Mes	mesityl
mg	milligram(s)
mL	millilitre(s)
mmol	millimole(s)
mol. sieves	molecular sieves
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Pd/C	Palladium on carbon
Ph	phenyl
ppm	parts per million
Pr	propyl
^1H	proton
q	quartet
quant.	quantitative
quin.	quintet
R_f	retention factor
r.b.f	round bottomed flask

RCM	Ring Closing Metathesis
RCEYM	Ring Closing Enyne Metathesis
r.t.	Room Temperature
s	singlet
t	triplet
TBDMS	<i>t</i> -butyldimethylsilyl
THF	Tetrahydrofuran
Ts	tosyl

1.0 Introduction

1.1.1 Enyne bond rearrangements

Enynes are synthetically useful intermediates that can undergo bond reorganisation reactions with a variety of metal catalysts to form a range of cyclic compounds (Scheme 1).¹⁻⁵ These cyclic compounds have been utilised in many syntheses to isolate biologically active molecules.^{6,7}

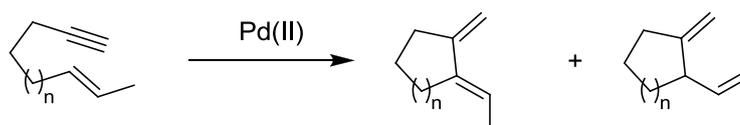


Scheme 1- Possible cyclic products formed from enyne bond reorganisation

This introduction will review how enynes have been reacted with transition metal catalysts such as Pd, Pt, Rh, Au, Co, Mo, and Ru catalysts, to bring about bond reorganisation reactions. Special attention will be made on the use of Pd and Ru catalysts to bring about cycloisomerisation and Ring Closing Enyne Metathesis (RCEYM) reactions to synthesise 1,3-diene structures, which can be used in the Diels-Alder reaction to form polycyclic products.

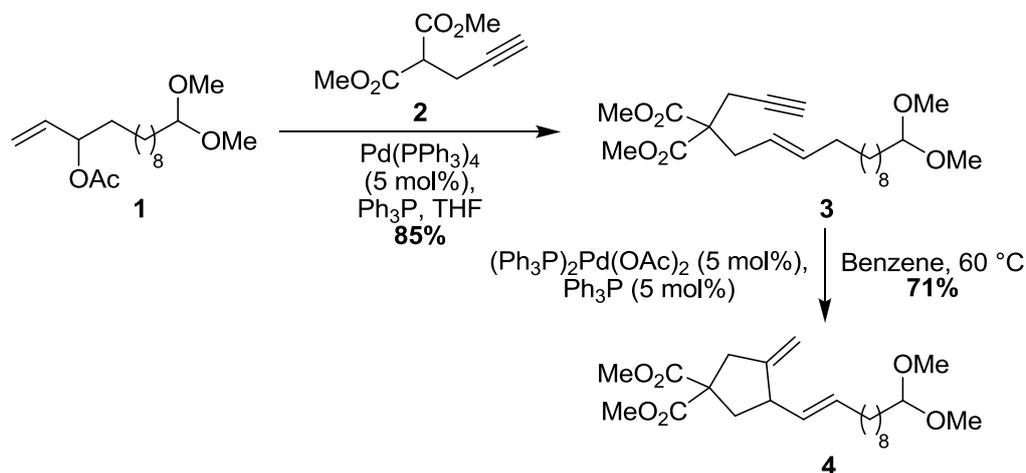
1.1.2 Pd(II)-catalysed cycloisomerisation

A cycloisomerisation reaction takes place between an enyne in the presence of a metal catalyst which causes the bonds to reorganise to form a cyclic structure (Scheme 2). This reorganisation of bonds can take place with a variety of metal catalysts such as Pd(OAc)₂.¹ Depending on the catalyst and the substitution pattern on the enyne either cyclic 1,3- or 1,4-diene structures can be formed.



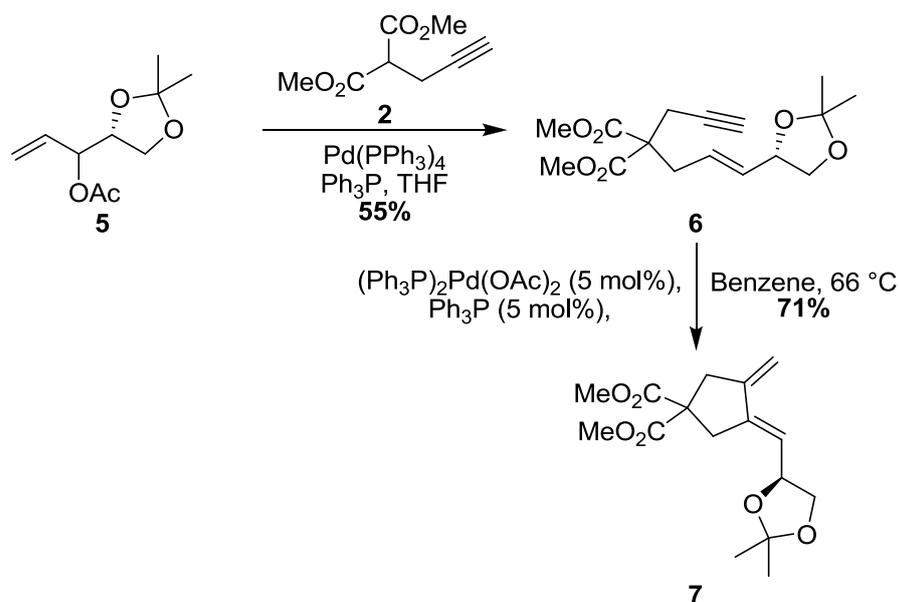
Scheme 2- Possible cycloisomerisation reactions

Pioneering work on this area was carried out by Trost and co-workers in 1985. They initially investigated a tandem Pd(0)-catalysed alkylation-Alder-ene cyclisation (Scheme 3).⁸ However, it was found that a Tsuji-Trost alkylation of alkene **1** using a Pd(0)-catalyst only generated 1,6-enyne **3**. With the addition of a Pd(II)-catalyst, a cyclisation took place forming 1,4-diene **4** in good yield.



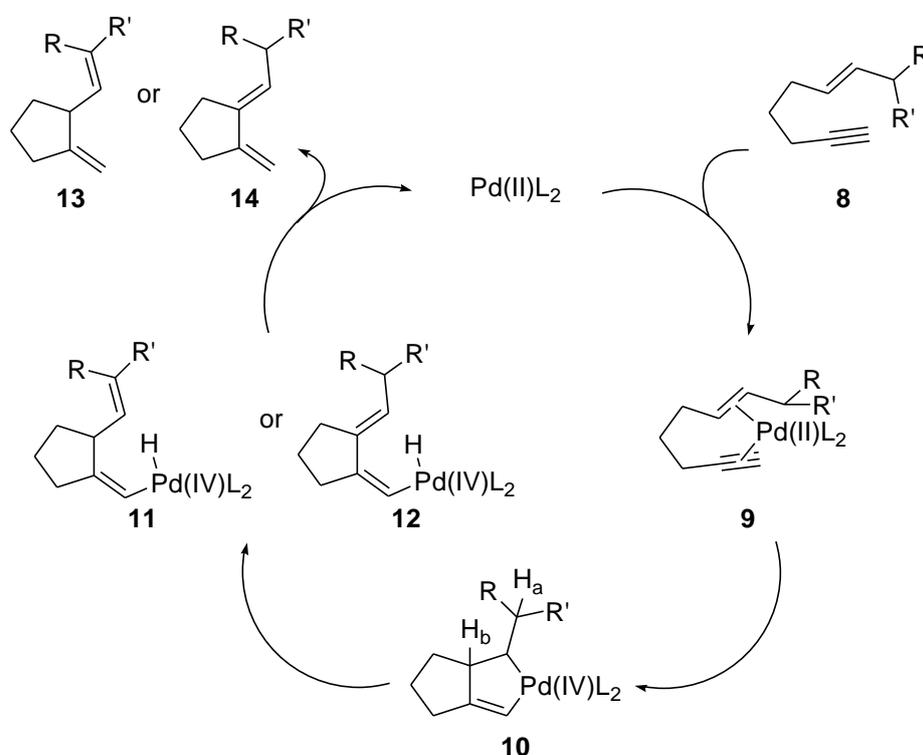
Scheme 3- Pd(II)-catalysed cycloisomerisation via Tsuji-Trost alkylation

By utilising this methodology, Trost and co-workers reported the formation of 1,3-dienes (Scheme 4). With the use of a Tsuji-Trost alkylation reaction to generate 1,6-enyne **6**, a Pd(II)-catalyst was added to the reaction mixture forming 1,3-diene **7** in good yield. It was believed that the substitution pattern of enyne **6** was responsible for the change of regiochemistry, with 1,3-diene **7** forming selectively.



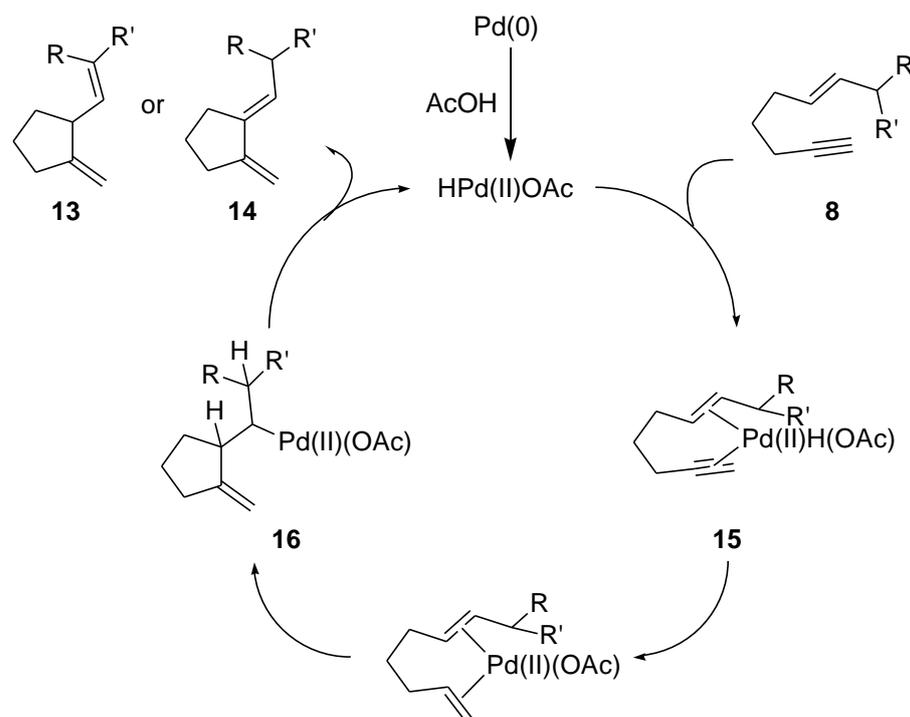
Scheme 4- Formation of 1,3-diene **7** via Pd(II)-catalysed cycloisomerisation

The formation of the 1,3- and 1,4-diene systems via a cycloisomerisation reaction is also observed with the use of Pd(0)-catalysts. The Trost group postulated two mechanisms for the cycloisomerisation reaction.^{1,8,9} The first mechanism involves a Pd(IV)-complex and the second comprises of a Pd(II)-species. The Pd(II)-catalyst first coordinates to the alkene and alkyne parts of the enyne and then undergoes an oxidative cyclisation forming palladacyclopentene **10** (Scheme 5). The formation of 1,4-diene **13** and 1,3-diene **14** is highly dependent on the substitution pattern of palladacyclopentene **10**. For Pd(IV)-species **11** to form, H_a would need to be more acidic than H_b thus allowing β-hydride elimination to occur exocyclic to the ring. Pd(IV)-species **11** can then undergo reductive elimination forming 1,4-diene **13**. The alternative elimination pathway occurs if the allylic ring hydrogen H_b is more acidic compared to H_a forming Pd(IV)-species **12**. This can then undertake a reductive elimination reaction to form 1,3-diene **14**.



Scheme 5- Proposed Pd(II)-Pd(IV)-catalytic cycle

The second postulated mechanism proceeds with the hydridopalladium(II) acetate binding to both alkene and alkyne parts of the enyne (Scheme 6). The Pd(II)-species then inserts into the alkyne moiety and undergoes β-migratory insertion across the alkene forming intermediate **16**. Complex **16** can then undergo β-hydride elimination to form 1,4-diene **13** or 1,3-diene **14** depending on the substitution of R and R' groups.

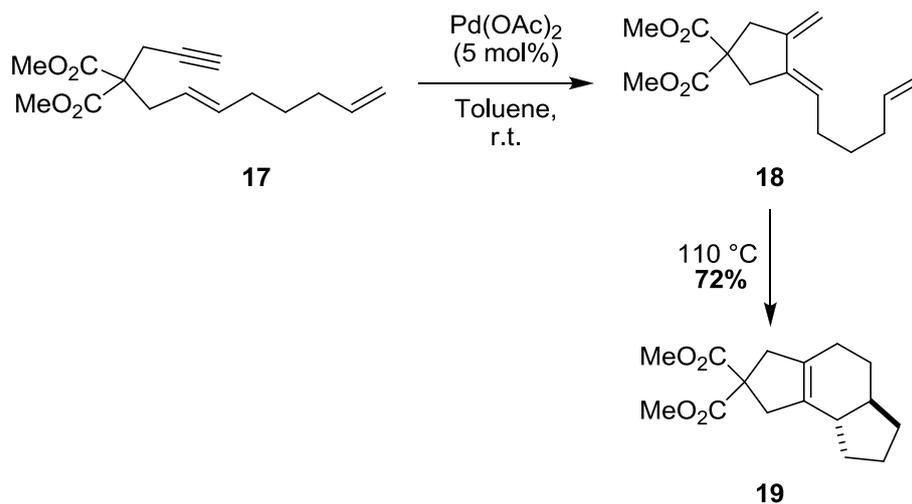


Scheme 6- Proposed Pd(II)-catalytic cycle

Trost and co-workers reasoned that both pathways were possible. The Pd(II)-Pd(IV) catalytic cycle, shown in Scheme 5, derives from similar mechanisms involving metallocyclopentenes as observed with cobalt, zirconium and titanium based catalysts.¹⁰⁻¹³ This pathway is favoured when using Pd(II)-precatalyst, such as Pd(OAc)₂, in the absence of a reducing agent.^{14,15} The alternative Pd(0)-Pd(II)-catalytic cycle is observed when using Pd(0)-precatalysts, such as [Pd₂(dba)₃.CHCl₃] with acetic acid. It is believed that this combination generates hydridopalladium acetate *in situ* which promotes the cycloisomerisation reactions.¹⁶ The choice of catalyst is also important as certain enyne substrates prefer to react with Pd(II)-catalysts over Pd(0)-catalysts.⁹

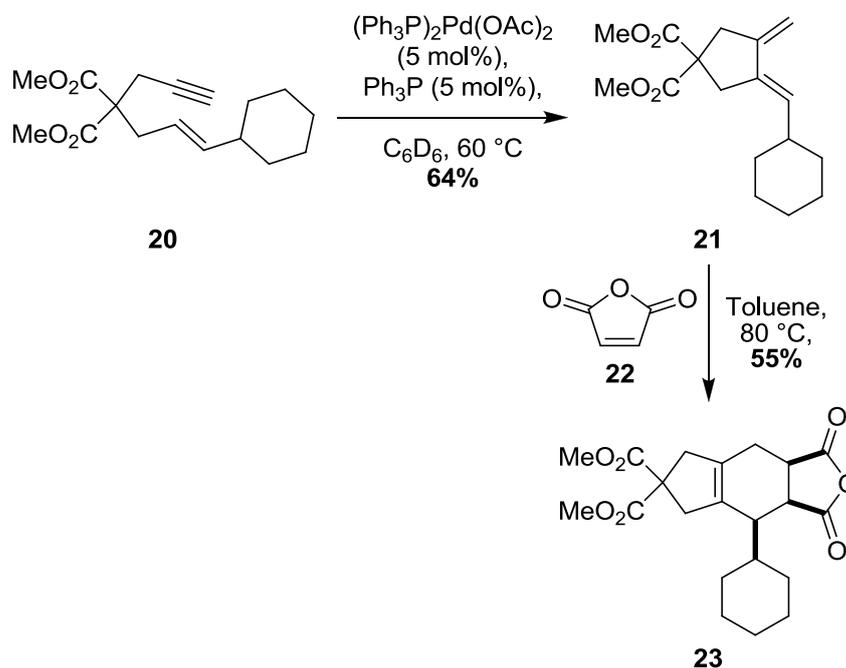
This methodology offers access to both 1,4- and 1,3-diene systems. Even though 1,4-dienes have a wide range of applications as intermediates for the synthesis of natural products and their metabolites, 1,3-dienes have got further applications as they can be used in Diels-Alder reactions.¹⁷

By utilising this methodology to form 1,3-dienes, Trost and co-workers generated a range of polycycles, which were used to form vitamin D metabolites.¹⁷ They also reported that 1,6-enyne **17** can undergo a cycloisomerisation reaction forming 1,3-diene **18** (Scheme 7). This 1,3-diene then underwent a Diels-Alder reaction forming polycycle **19** in a good yield in a one-pot process.¹



Scheme 7- One-pot process for the formation of polycycle **19**

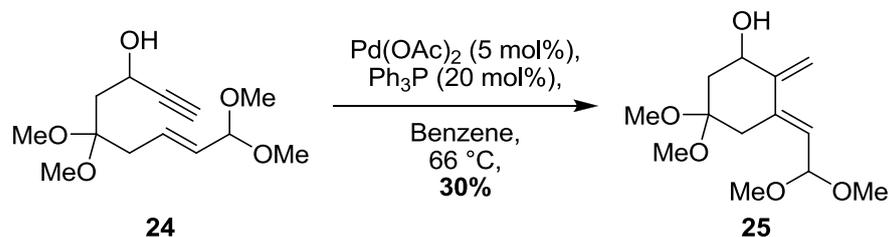
This combination of cycloisomerisation and Diels-Alder reaction is not limited to intramolecular Diels-Alder reactions. Trost was able to show that 1,3-diene **21**, formed from the cycloisomerisation reaction, can undergo a Diels-Alder reaction with maleic anhydride **22** forming polycycle **23** in a 55% yield (Scheme 8).⁸



Scheme 8- Synthesis of polycycle **23** via cycloisomerisation and Diels-Alder reaction

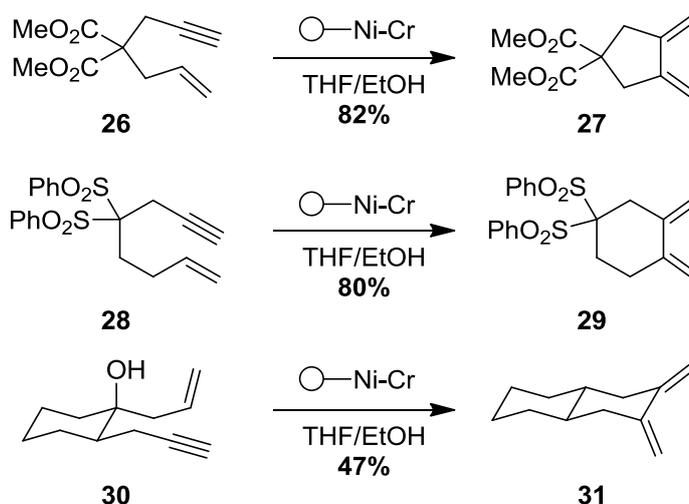
The scope of the cycloisomerisation reaction has been increased with the use of 1,7-enynes, which have been used to form 6-membered ring systems.¹⁷ However, for the reaction to proceed well, geminal substituents are needed to cause a Thorpe-Ingold effect. With the aim to synthesise metabolites of vitamin D, Trost and co-workers reported that 6-

membered 1,3-diene **25** could be isolated via a cycloisomerisation reaction using 1,7-enyne **24** (Scheme 9).



Scheme 9- Cycloisomerisation of 1,7-enyne **24**

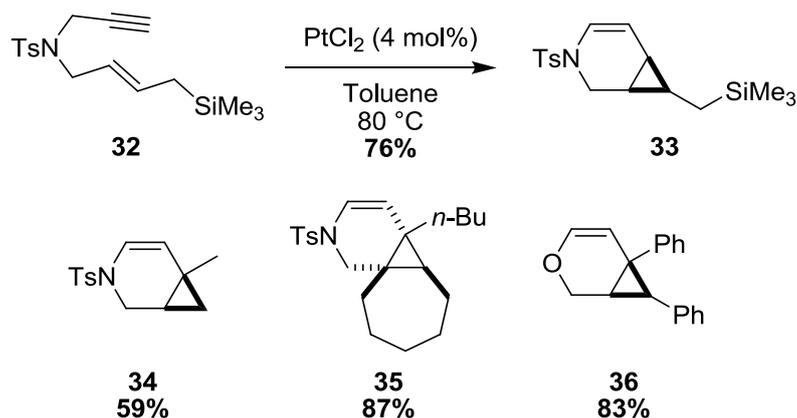
This type of cycloisomerisation is not limited to the use of palladium catalysts. Trost and co-workers described the use of a polymer bound nickel-chromium catalyst system to facilitate the isomerisation reaction.¹⁸ Initial studies in this area used Ni(II)-salts to carry out the reaction, however this did not catalyse the cycloisomerisation. With the use of chromous chloride, which acts as a one-electron reducing agent, this transformation showed promising results with 1,3-diene **27** forming in a moderate yield through a proposed Ni(I)-Ni(III)-catalytic cycle. To improve the reaction and develop a more general set of conditions, investigations were carried out to further optimise the catalyst. These issues were resolved with the use of polymer-bound Ni-Cr catalyst, where the polymer acts as a coordination site for the unstable nickel species. This led to the formation of 1,3-diene **27** in excellent yield from 1,6-enyne **26** (Scheme 10). This cycloisomerisation was not exclusive to 1,6-enynes, with 1,7-enynes **28** and **30** forming the corresponding 1,3-dienes **29** and **31** in moderate to good yields.



Scheme 10- Cycloisomerisation reaction using a polymer-bound Ni-Cr catalyst

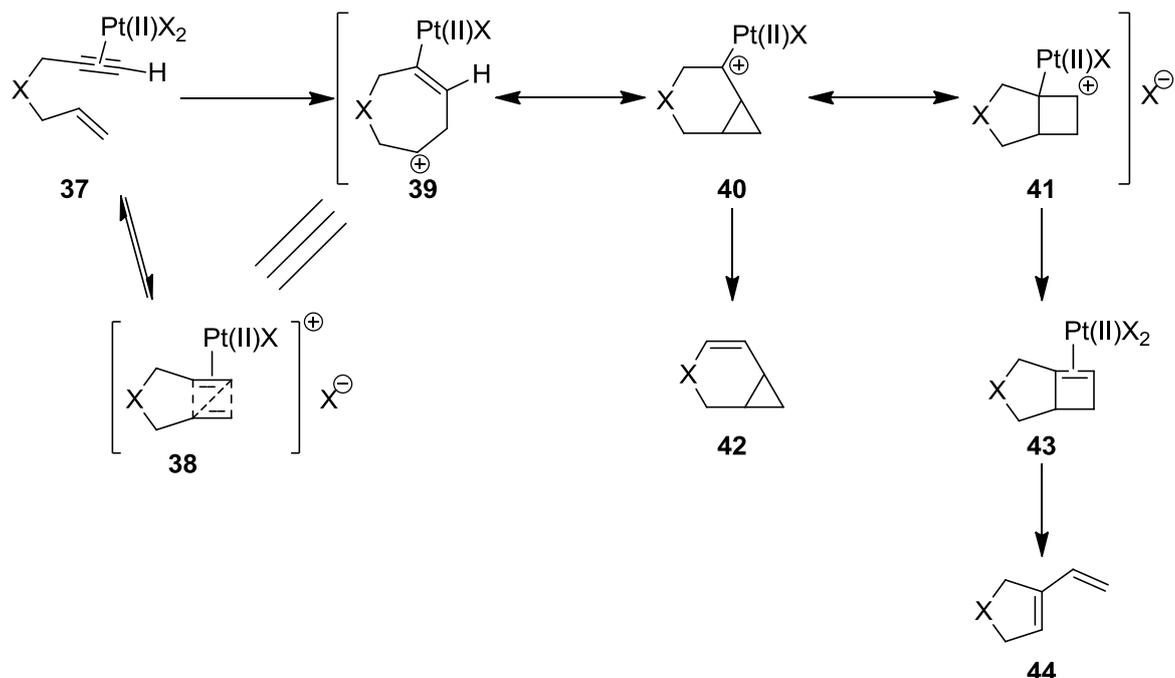
1.1.3 Other metal-catalysed enyne bond reorganisation reactions

Enyne bond rearrangements are not limited to palladium catalysts. Cycloisomerisation reactions can take place with the use of platinum(II)-catalysts leading to the formation of a diverse set of polycycles. Fürstner and co-workers observed that tosylamide- and ether-linked 1,6-enynes underwent a novel rearrangement to form cyclopropane ring systems **33–36** in excellent yield (Scheme 11).¹⁹



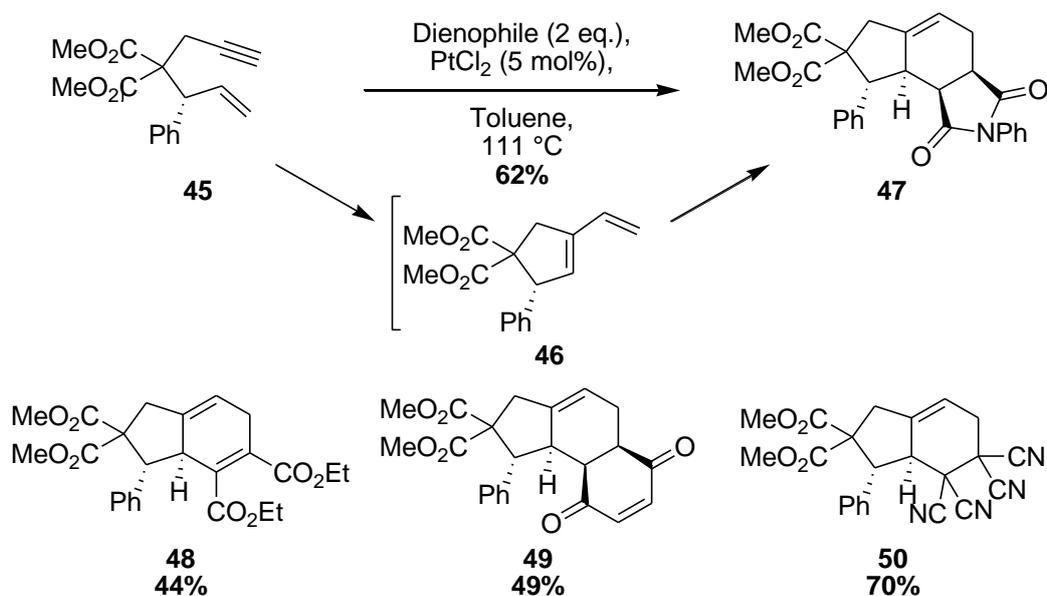
Scheme 11- Pt(II)-catalysed cycloisomerisation

This investigation led Fürstner and co-workers to consider that platinum salts function as a Lewis acid.^{3,20} They proposed that the reaction went through nonclassical carbocation **38** as represented by the canonical resonance structures **39–41** (Scheme 12). To form the cyclopropane ring systems, resonance structure **40** undergoes a 1,2-hydride shift and eliminative demetalation to afford polycycle **42**. It was also proposed that elimination of the metal from cyclobutyl cation **41** would provide cyclobutane intermediate **43** which could undergo electrocyclic ring opening to afford 1,3-diene **44**.



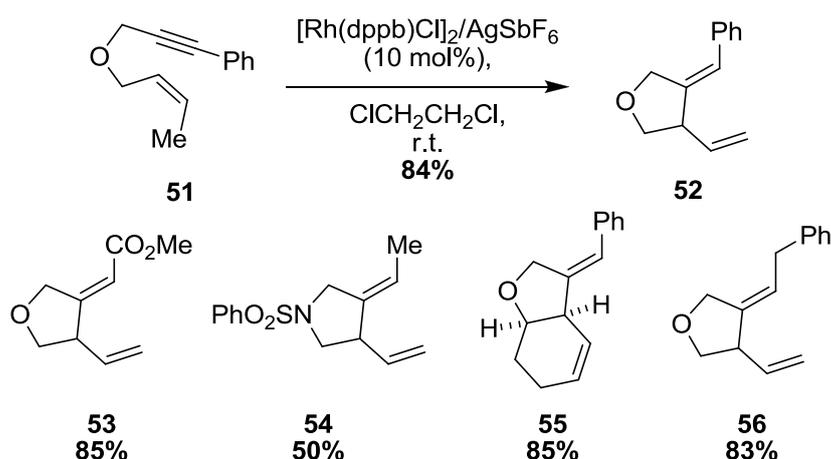
Scheme 12- Proposed mechanism for Pt(II)-catalysed cycloisomerisation

The formation of 1,3-dienes using Pt(II)-catalysts has led to reports of its use as an alternative way of performing a RCEYM reaction. In 2010, Helmchen and co-workers reported that reacting PtCl_2 with a variety of 1,6-enynes formed 1,3-dienes such as **46**, which were not accessible using other metathesis catalysts (Scheme 13).²¹ 1,3-Diene **46** was then reacted with a range of dienophiles in a one-pot tandem process to form the corresponding Diels-Alder adducts **47–50** in good yields as single diastereomers. The Diels-Alder reaction proceeded via an *endo* transition state with the dienophile attacking from the least hindered face of the diene moiety.



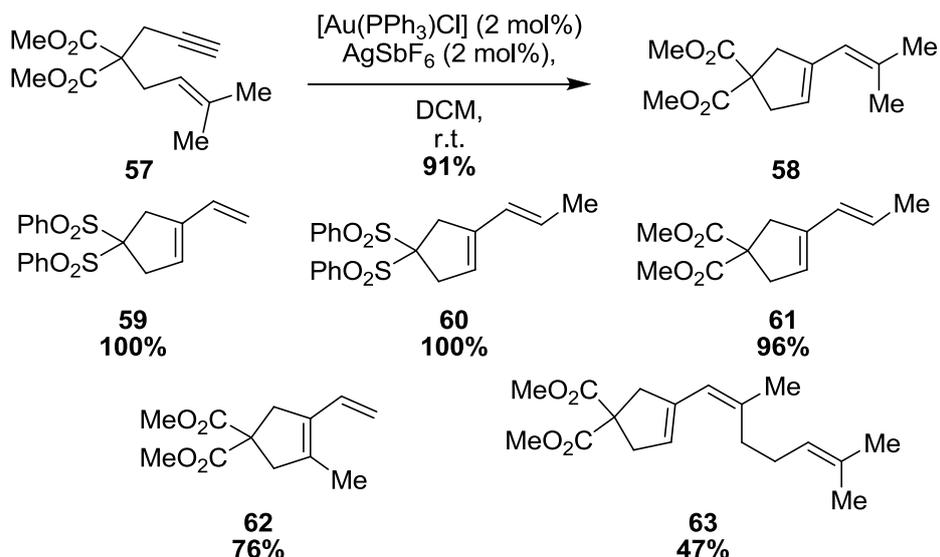
Scheme 13- One-pot tandem Pt(II)-catalysed cycloisomerisation/Diels-Alder reaction

Rhodium catalysts have also been found to be effective catalysts for enyne bond rearrangement. Zhang and co-workers reported that 1,6-enynes can be converted to the corresponding 1,4-diene systems in good yields (Scheme 14).²² This type of reaction has previously been described by Trost and co-workers with the use of Pd(II)-catalysts. The Zhang group described the use of a cationic Rh complex, which was made *in situ*, to perform the cycloisomerisation reaction forming 1,4-diene systems **52–56** selectively. The formation of 1,4-dienes can also be conducted with the use of platinum catalysts, however silyl leaving groups are required for the reaction to proceed.²³



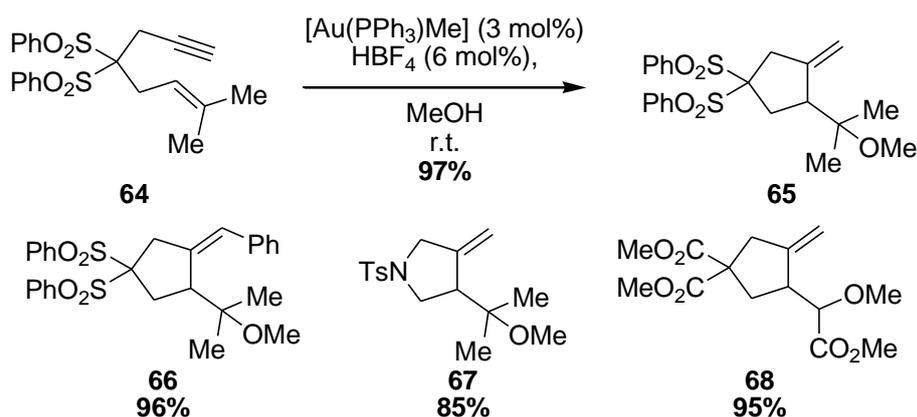
Scheme 14- Rh-catalysed cycloisomerisation

In 2004, Echavarren and co-workers demonstrated the use of Au-based catalysts as an effective way of conducting a series of 1,6-enyne cycloisomerisations for the formation of 1,3-dienes (Scheme 15).²⁴ One of the reaction pathways reported by the authors was similar to that observed for Pt-based catalysts. The catalyst was generated by treatment of Au(PPh₃)Cl with AgSbF₆, which resulted in precipitation of AgCl and formation of highly reactive cationic Au(PPh₃)⁺. In the presence of 2 mol% of this complex, enyne **57** was converted to 1,3-diene **58** in 91% yield. Notably, the reaction proceeded at room temperature, indicating that the Au-based catalyst was significantly more reactive than its Pt counterpart. This process was successfully employed for conversion of a range of 1,6-enynes to generate the corresponding 1,3-dienes **59–63** in good yields.



Scheme 15- Au-catalyzed cycloisomerisation of 1,6-enynes

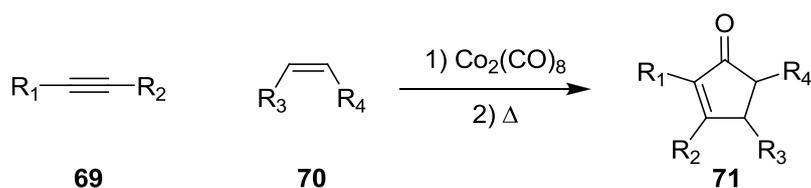
Gold catalysts can also undergo other reactions similar to that observed with platinum complexes such as cyclopropanations and alkoxy carbocyclisation. Echavarren and co-workers described the use of cationic Au complexes to promote an alkoxy carbocyclisation reaction. Utilising the alkoxy carbocyclisation reaction, the cyclic products **65–68** were generated in excellent yields from the corresponding 1,6-enynes (Scheme 16).^{24,25} It was proposed that the alkoxy carbocyclisation proceeded in a highly concerted manner involving simultaneous attack of the activated alkyne by the alkene and addition of the alcohol nucleophile followed by protodemetalation.²⁶



Scheme 16- Au-catalyzed alkoxy carbocyclizations of 1,6-enynes

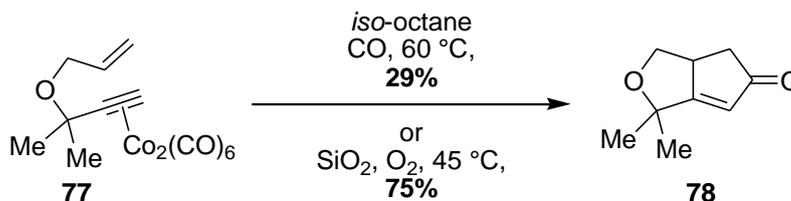
1.2.1 Pauson-Khand reaction

The Pauson-Khand reaction is a useful transformation that is routinely considered when planning the synthesis of polycyclic molecules. First described in 1971 by Pauson and Khand, the reaction relies on an alkyne and alkene coordinating to an octacarbonyldicobalt complex to form a cyclopentenone ring system (Scheme 17).^{27,28} The reaction can either be achieved intermolecularly or intramolecularly. If an intramolecular Pauson-Khand reaction is attempted, functional groups such as geminal dimethyl groups are required to facilitate a Thorpe-Ingold effect and encourage cyclisation.



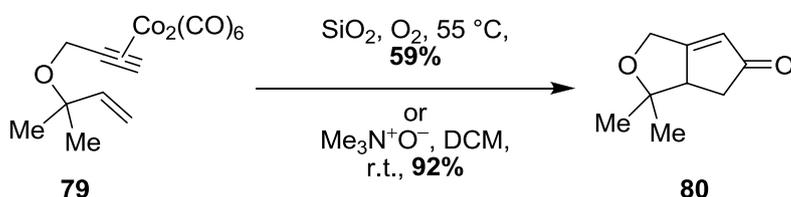
Scheme 17- Pauson-Khand reaction

The Pauson-Khand reaction is formally a [2+2+1] cycloaddition in which a triple bond, a double bond and carbon monoxide form a cyclopentenone. The mechanism of the reaction was reported by Magnus *et al.* who proposed that the reaction proceeds with alkyne **69** first, forming hexacarbonyldicobalt alkyne complex **72** (Scheme 18).^{29,30} Alkene **70** then inserts into the Co-C bond bringing about the formation of cobaltacycle **74**. Carbon monoxide then inserts into the Co-C bond constructing intermediate **75** which can then undergo two reductive elimination reactions generating cyclopentenone **71**.



Scheme 19- Oxabicyclo[3.3.0]octenone formation using normal and dry-state conditions

To further improve the reaction, Crowe and co-workers described the use of trimethylamine *N*-oxide as a useful additive to the reaction mixture (Scheme 20).³³ The *N*-oxide promotes the removal of carbon monoxide from the metal complex by oxidation to carbon dioxide, thus forming a vacant site in the cobalt cluster. This gave improved yields compared to the analogous dry state conditions.

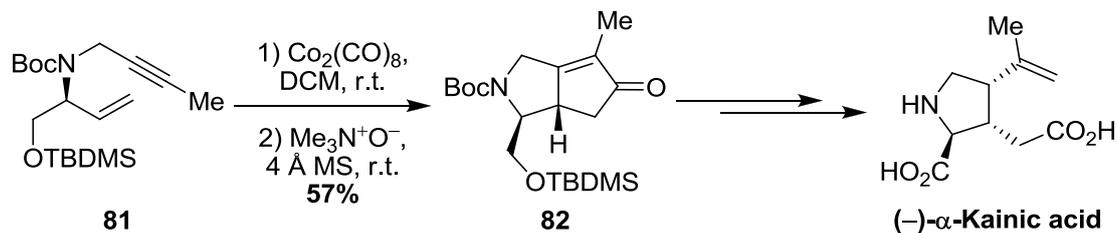


Scheme 20- Pauson-Khand reaction using dry-state and *N*-oxide promoted conditions

In a drive to further enhance the Pauson-Khand reaction, research has been carried out to perform the reaction catalytically. Using similar 1,6-enynes, Livinghouse and co-workers have shown that under a carbon monoxide atmosphere the reaction can be performed with catalytic quantities of Co₂(CO)₈ under thermal or photochemical conditions.^{34,35} Asymmetric Pauson-Khand reactions have also been reported using Rhodium catalysts. With the use of chiral ligands, the reaction is accomplished under a carbon monoxide atmosphere forming the resulting products in good yields, however, best results were observed with disubstituted alkyne substrates.^{36,37}

Since its discovery, the Pauson-Khand reaction has been utilised in the synthesis of a wide range of natural products.³⁸⁻⁴⁰ The cyclopentene rings formed in the reaction are common motifs in nature and are easily functionalised. Helmchem and co-workers reported the use of the Pauson-Khand reaction as the key step in the synthesis of the nonproteogenic amino acid (–)- α -kainic acid (Scheme 21).⁴¹ By utilising 1,6-enyne **81**, which was synthesised using an Ir-catalysed allylic amination, the hexacarbonyldicobalt alkyne complex was first synthesised. This was reacted with trimethylamine *N*-oxide to bring about a highly diastereoselective Pauson-Khand reaction with the desired polycycle **82** being obtained in

a 57% yield. Bicyclic compound **82** was then further functionalised to form (-)- α -kainic acid.

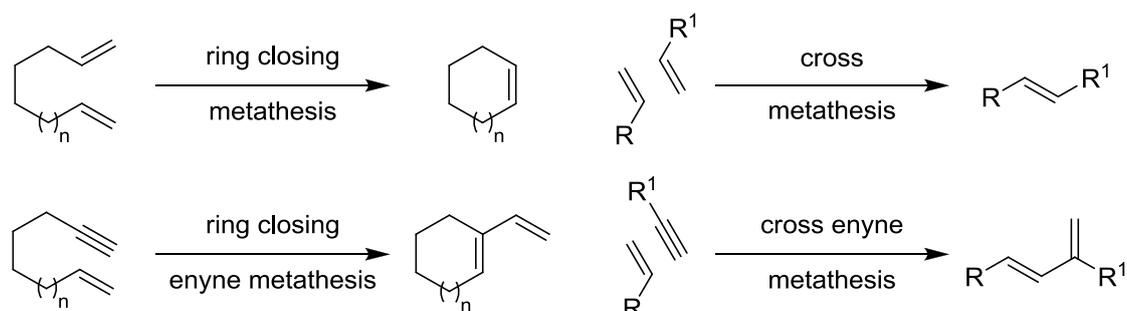


Scheme 21- *N*-Oxide promoted Pauson-Khand reaction used for the synthesis of (-)- α -kainic acid

1.3.1 Metathesis

Enyne metathesis is a type of olefin metathesis which can be described as the redistribution of covalent bonds in one or more molecules. It is one of three categories that include diene and diyne metathesis which are catalysed by metal carbene complexes. The first uses of metal carbene catalysts were in the formation of polymers.⁴² The early catalysts displayed limited scope for the formation of complex molecules and were limited to unfunctionalised substrates.

In the early 1990's, Schrock and Grubbs developed stable metal carbenes catalysts which can be used on compounds which are highly functionalised, receiving the Noble prize for this work.⁴³ Scheme 22 shows the fundamental metathesis reactions which can be carried out using metal carbene catalysts, such as, Grubbs catalyst and Schrock carbene catalysts.⁵ In diene and cross diene metathesis, ethylene is a by-product of the reaction, whereas in enyne metathesis the reaction is atom efficient. Each of the products generated from these metathesis reactions are versatile intermediates, which can be used for further manipulation.



Scheme 22- Fundamental metathesis reactions

Since the discovery of metal carbene catalysts, there has been rapid development in this area. Initially, Grubbs and Schrock synthesised a molybdenum carbene catalyst **A** which was found to be effective for olefin metathesis (Figure 1).^{44,45} While working in this area, Grubbs reported that catalyst **B** was stable and easy to handle.⁴⁶ This catalyst then became commercially available and is now known as Grubbs first generation catalyst. Grubbs first generation catalyst is a versatile catalyst and is widely used, especially for ring closing metathesis (RCM) reactions, however it is a poor catalyst for cross metathesis and for molecules with many heteroatoms present. The reactivity of this catalyst was further improved by replacing one of the tricyclohexylphosphine ligands with an *N*-heterocyclic carbene ligand leading to the development of Grubbs second generation catalyst **C** and Hoveyda-Grubbs second generation catalyst **D**.^{47,48} These catalysts are more robust and are more reactive allowing cross metathesis reactions to take place.

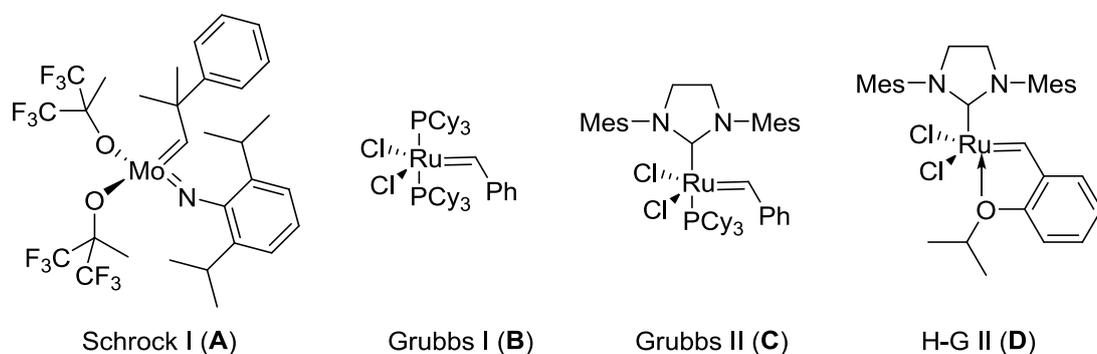
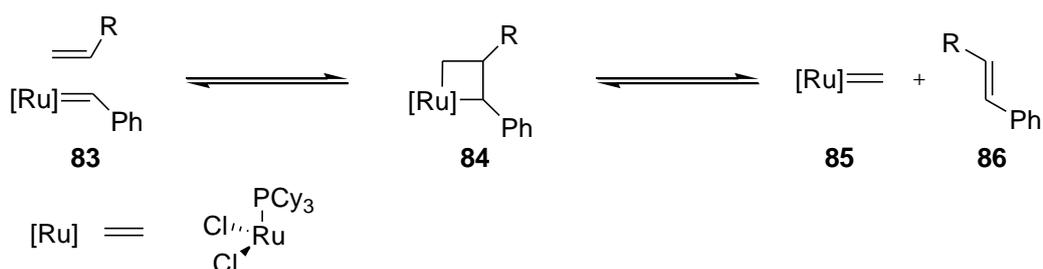


Figure 1- Structures of Schrock I catalyst (**A**), Grubbs first generation catalyst (**B**), Grubbs second generation catalyst (**C**) and Hoveyda-Grubbs second generation catalyst (**D**)

These catalysts are precatalysts and must be activated before the desired reaction occurs. This occurs *in situ*, by the catalyst first losing one of the phosphine ligands and then undergoing a [2+2] cycloaddition with an olefin present in the reaction mixture to form cycloruthenabutane intermediate **84** (Scheme 23). Ring opening of this intermediate then yields the active catalyst **85** which can then go on to be used in the main metathesis reaction.

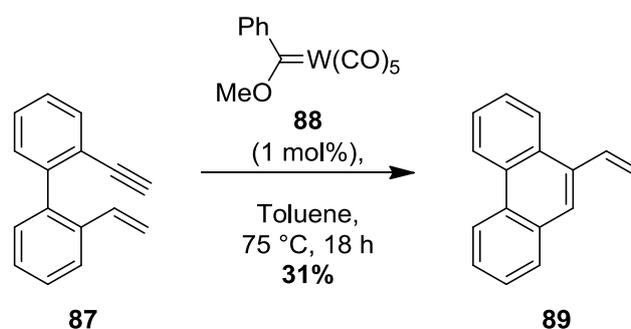


Scheme 23- Reaction pathway for the formation of active catalyst

These catalysts have been used in a wide range of metathesis reactions to form synthetically useful compounds for use in polymer chemistry and for the synthesis of natural products.^{6,7} From this point on, the introduction will focus on how enyne metathesis has been used in the formation of 1,3-dienes and how these intermediates have been used in a variety of applications.

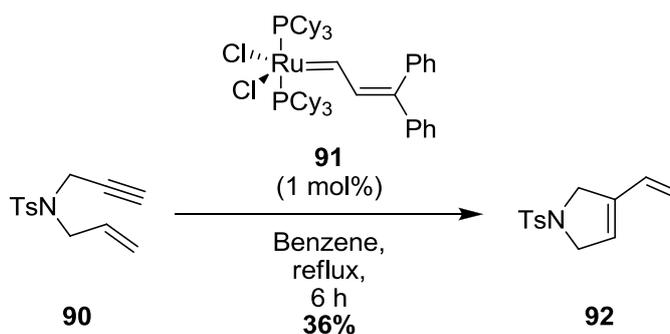
1.3.2 Ring closing enyne metathesis

The first RCEYM reaction was reported in 1985 by Katz *et al.*, who reported the use of Fischer tungsten-carbene complex **88** (Scheme 24).⁴⁹ In the reaction, 1,7-enyne **87** was reacted with a catalytic amount of tungsten carbene **88** forming 1,3-diene **89** in 31% yield. The reaction was not limited to mono-substituted alkenes as di- and tri-substituted alkenes could also be used to form the corresponding 1,3-dienes in moderate yields.



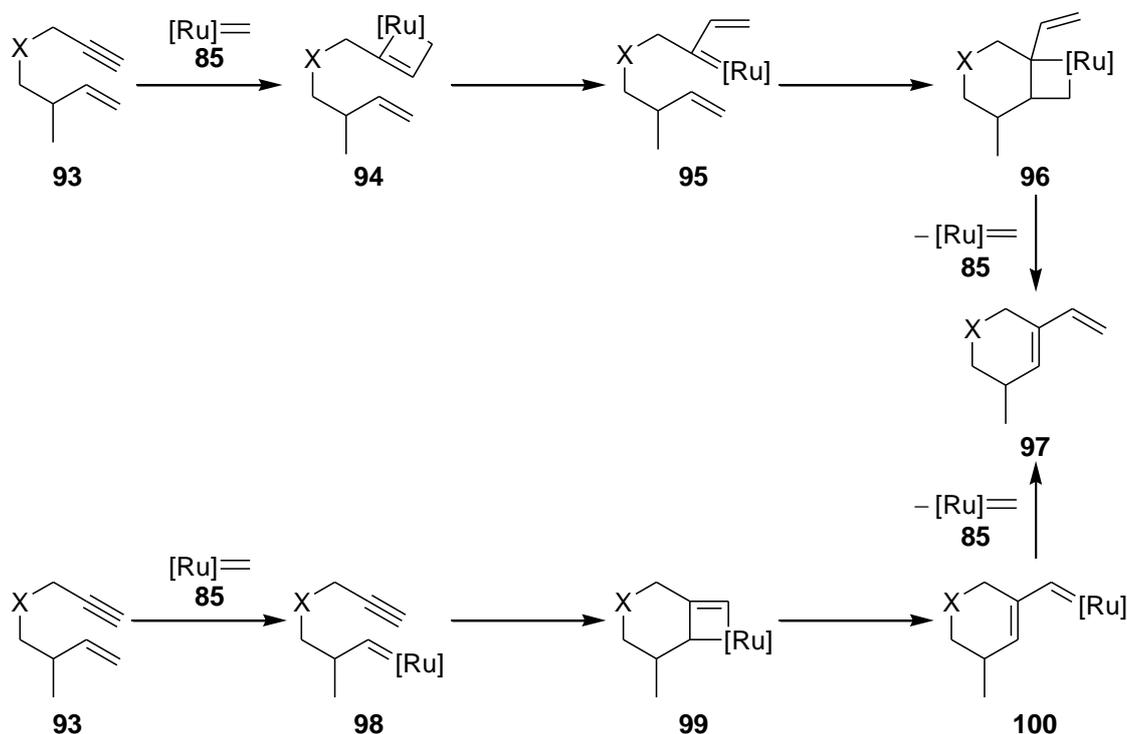
Scheme 24- RCEYM using a tungsten carbene

With the rapid development of metal carbene catalysts, the RCEYM reaction has been extensively probed with the Mori group reporting that the reaction can take place with either chromium or ruthenium based carbene catalysts.^{50,51} The Mori group reported the use of the ruthenium catalyst **91**, which is similar in reactivity to Grubbs first generation catalyst (Scheme 25).⁵¹ This generated a range of carbo- and heterocyclic 1,3-dienes in moderate yields.



Scheme 25- RCEYM of 1,6-enyne **90**

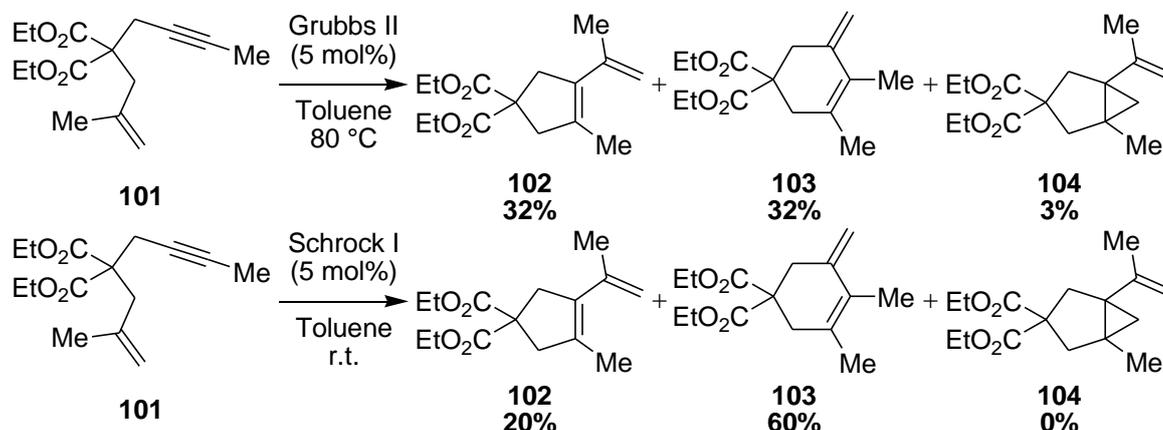
Since the discovery of metathesis reactions, their mechanisms have been extensively studied, however the mechanism for the RCEYM reaction is still not well defined.^{6,52-54} For the reaction to proceed, the activated ruthenium carbene **85** can complex to two binding sites leading to two potential mechanisms to form 1,3-diene **97** (*exo*-product). The catalyst can either react first with the alkyne part of the molecule leading to the “yne-then-ene” pathway (Scheme 26, top) or react with the alkene functional group in the “ene-then-yne” pathway (bottom). If the reaction first takes place at the alkyne moiety, the reaction would proceed via a [2+2] cycloaddition to produce ruthenacyclobutene **94** with the ruthenium attached to the internal carbon. Ring-opening of this affords ruthenium carbene complex **95**, which reacts with the alkene moiety to form ruthenacyclobutane **96**. Ring-opening of intermediate **96** affords *exo*-product **97** and the active ruthenium catalyst **85**. If the reaction were to proceed via the alkene moiety, the ruthenium carbene **98** would be generated which can undergo a [2+2] cycloaddition to produce ruthenacyclobutene **99**. Intermediate **99** would subsequently undergo ring opening, giving ruthenium carbene **100** and through an intermolecular metathesis reaction, cyclic product **97** is formed and regenerates the active catalyst **85**.



Scheme 26- Proposed “yne-then-ene” pathway and “ene-then-yne” of *exo* pathway

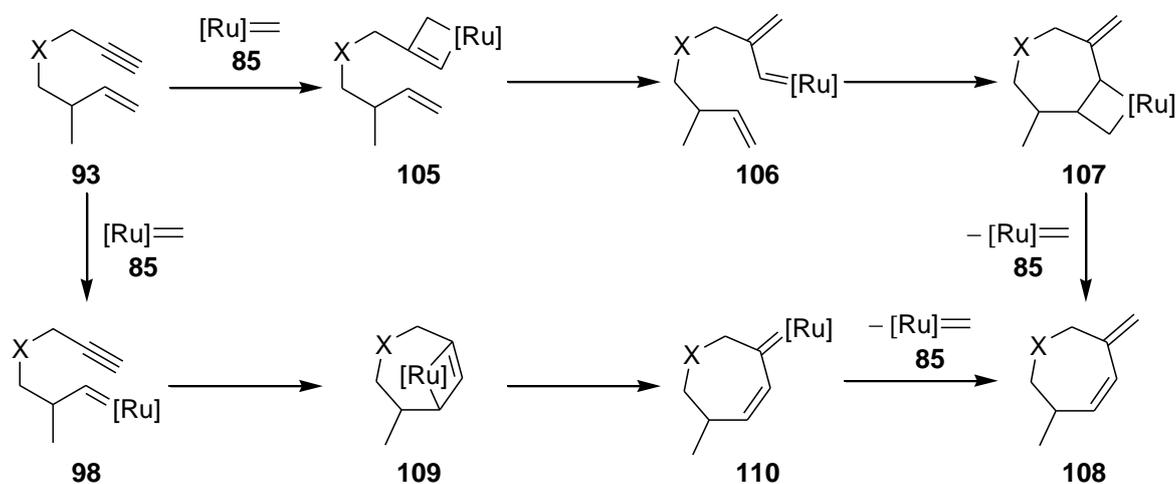
It has also been found that the RCEYM reaction can take place leading to the formation of the 1,3-diene in the sigma-*trans* geometry. This has been observed with the use of molybdenum based Schrock catalysts and second generation Grubbs catalysts.⁵⁵ Mori and

co-workers first reported that reacting Grubbs second generation catalyst with 1,6-enyne **101** led to the formation of sigma-*cis* 1,3-diene **102** with sigma-*trans* 1,3-diene (*endo*-product) **103** also forming in a 1:1 ratio (Scheme 27).⁵⁶ When this reaction was carried out using Schrock I catalyst, Schrock and co-workers observed sigma-*trans* 1,3-diene **103** formed predominantly in good yield with sigma-*cis* 1,3-diene **102** also being formed.



Scheme 27- RCEYM using Grubbs second generation and Schrock I catalysts

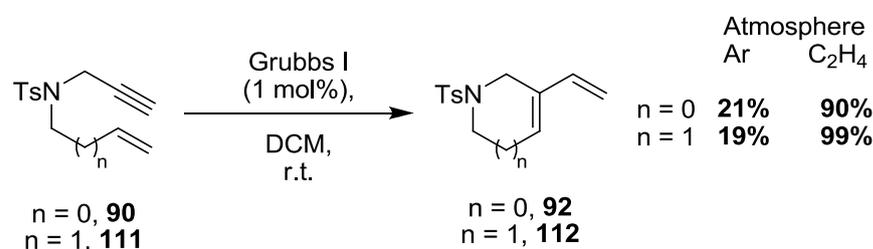
The formation of *endo*-1,3-diene **103** leads the possibility of another two pathways (Scheme 28).^{6,57} If the ruthenium catalyst reacts via the yne-then-ene pathway, the ruthenium can react at the external alkyne carbon leading to the formation of ruthenacyclobutene **105** which can ring-open to form ruthenium carbene **106**. Intermediate **106** can then undergo a RCM reaction to form *endo*-1,3-diene **108**. Alternatively, the reaction can go via the “ene-then-yne” pathway affording intermediate **98**. This can then undergo a [2+2] cycloaddition with the ruthenium reacting at the internal carbon forming the highly strained ruthenacyclobutene **109** leading to the formation of 1,3-diene **108**.



Scheme 28- Proposed *endo*-pathways for RCEYM reaction

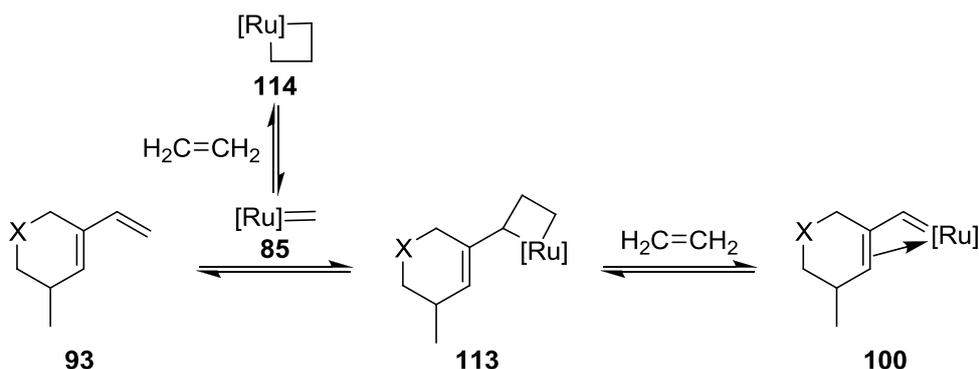
The reason why second generation ruthenium catalysts may form the *endo*-product is still not clear. The reaction is also highly substrate dependent with small- to medium-sized rings forming preferentially the *exo*-product and large ring sizes forming the *endo*-product.⁵⁴ One explanation is that Grubbs second generation catalyst is a more active catalyst than Grubbs first generation catalyst leading to the *endo*-product being formed first. Also by using highly substituted alkenes, as shown in Scheme 27, leads to the formation of the *endo*-product due to the alkene being sterically encumbered. This leads to the metal catalyst attacking the alkyne, potentially leading to the formation of two products.⁵⁶ Molybdenum catalysts form the *endo*-product predominantly. It is proposed that this is due to the more reactive molybdenum catalysts preferring to proceed through the higher energy metallacyclobutene intermediates instead of metallacyclobutane intermediates. With ruthenium based catalysts, the rate of metallacyclobutane formation is critical over metal carbene binding.^{55,58}

While investigating the effect of ethylene gas on the RCEYM reaction, Mori and co-workers also reported that reaction rates, conversions and yields were significantly increased when the reaction was carried out using an ethylene atmosphere (Scheme 29).⁵² However, when the reaction was carried out with non-terminal alkynes no increase in reaction rate or yield was observed.



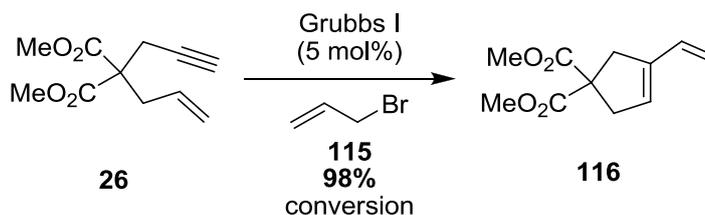
Scheme 29- RCEYM reactions using either an argon or ethylene atmosphere

The increase in reactivity is explained by the constant reactivation of the ruthenium catalyst. Mori reasoned that under standard conditions, the ruthenium carbene can further react with the vinyl group of the 1,3-diene, thus leading to the formation of less active species **100** and **113** (Scheme 30).⁵² Under ethylene conditions, the equilibrium is shifted to the formation of the active species **114** which can readily react with further starting material. It is also proposed that if the reaction proceeded via an “ene-then-yne” pathway, then ruthenium species **100** would be an intermediate. Intermediate **100** could then react with ethylene, which would lead to the formation of cyclised product **93** and active catalyst **85**.



Scheme 30- Proposed intermediate trapping during RCEYM using Mori conditions

Through the use of isotopic labelling studies, Lloyd-Jones and co-workers deduced that the RCEYM reaction proceeded through an “ene-then-yne” pathway with the involvement of a secondary catalytic cycle similar to that shown in Scheme 30.⁵⁹ They also reported that with the use of allyl bromide **115** conversions of >98% were observed whereas a conversion of 42% was achieved without any additive. This provided an alternative for the highly flammable gas ethylene (Scheme 31).⁶⁰

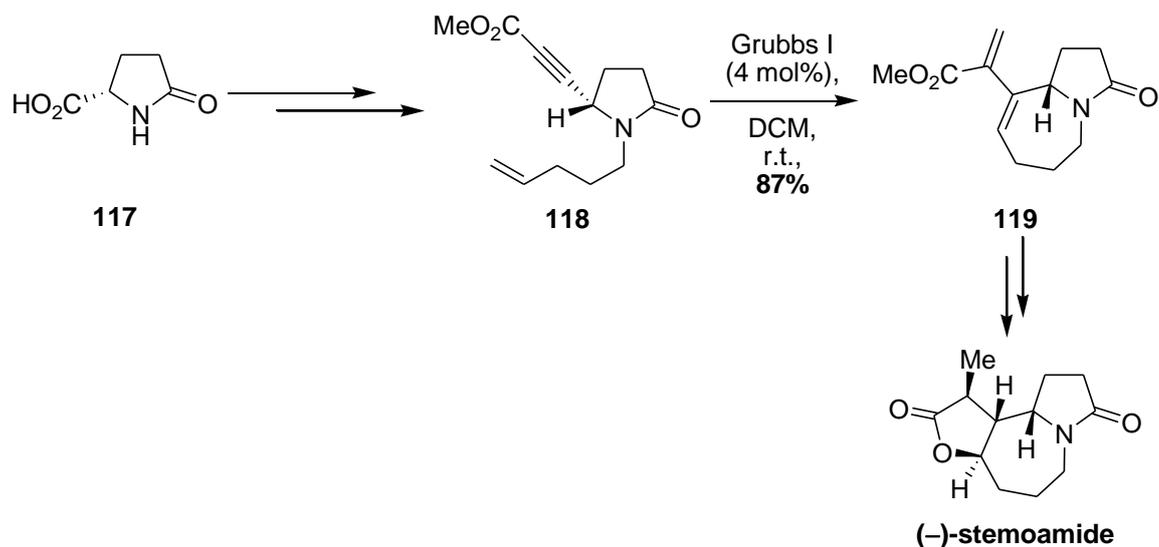


Scheme 31- RCEYM using allyl bromide as a co-catalyst

Overall the mechanism for the RCEYM is still open to debate with the reaction being highly substrate and catalyst dependent.

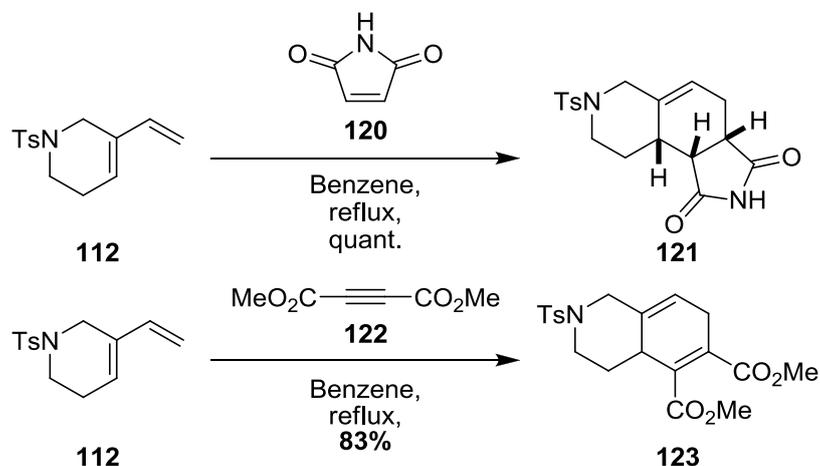
1.3.3 Uses for the RCEYM reaction

Since its discovery, the RCEYM reaction has been utilised for a wide range of applications.^{7,57} One of the first examples of the RCEYM reaction in the total synthesis of a natural product is the synthesis of (-)-stemoamide.⁶¹ 1,8-Enyne **118**, which was synthesised from (-)-pyroglutamic acid **117**, was subjected to the RCEYM reaction affording bicyclic compound **119** in 87% yield (Scheme 32). This was then converted to (-)-stemoamide in five further steps.



Scheme 32- RCEYM reaction used in the total synthesis of (-)-stemoamide

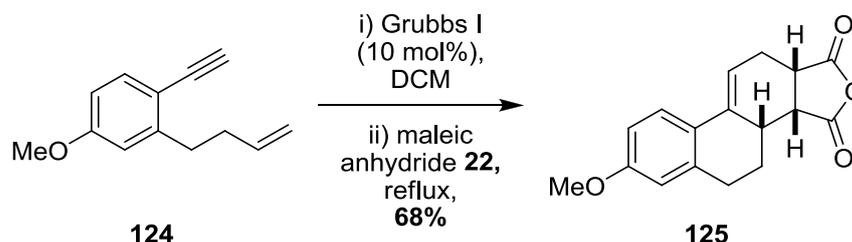
Mori and co-workers reported that the cyclic 1,3-dienes which are generated from the RCEYM reaction are useful substrates for subsequent reactions.⁵² They showed the 1,3-diene **112**, formed in the RCEYM reaction, can easily undergo a Diels-Alder reaction with alkene and alkyne dienophiles forming polycyclic products **121** and **123** in excellent yields (Scheme 33).



Scheme 33- Diels-Alder reaction using 1,3-dienes formed from the RCEYM reaction

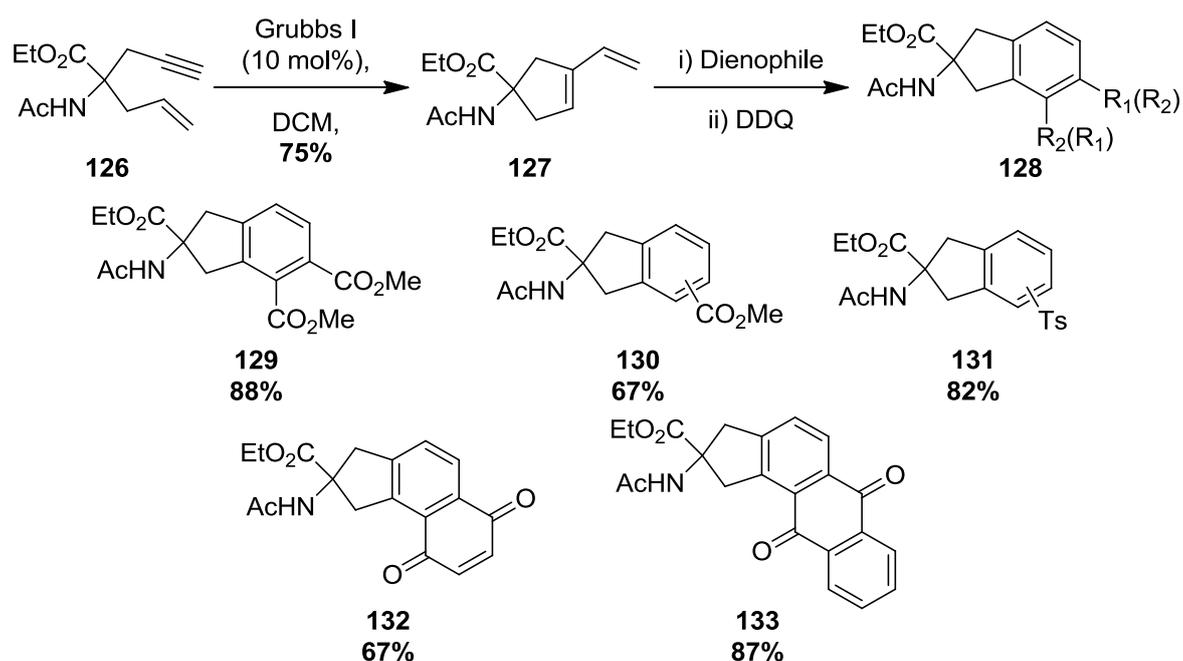
In the drive to make organic chemistry more efficient and generate less waste, there have been a number of reports on how the RCEYM reaction and Diels-Alder reaction can be combined in a one-pot/tandem process.⁷ Perez-Castells and co-workers demonstrated this by developing a one-pot RCEYM/Diels-Alder reaction to construct frameworks for natural products (Scheme 34).⁶² By subjecting 1,7-enyne **124** to a RCEYM reaction, the 1,3-diene product was generated and then reacted with maleic anhydride **22** in a one-pot process

achieving a yield of 68% of *endo*-Diels-Alder product **125**. It was noted by Perez-Castells group that if the reactions were attempted individually a poorer overall yield was achieved.



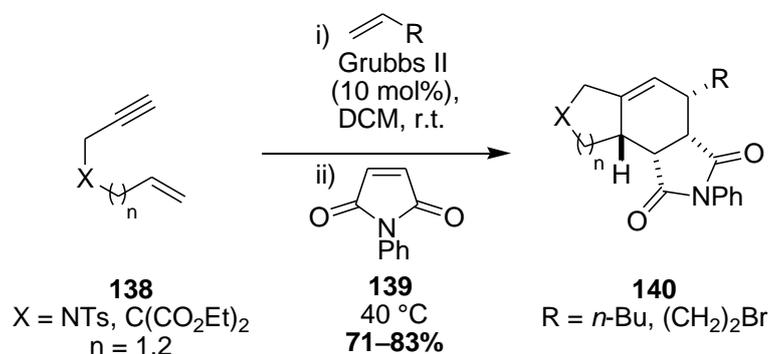
Scheme 34- One-pot RCEYM/Diels-Alder reaction

The products generated from RCEYM reactions have also been utilised in one-pot methodology involving the Diels-Alder reaction followed by an aromatisation reaction. This protocol leads to the formation of a range of natural products and biologically active compounds, containing both sp^2 and sp^3 carbons.⁶³⁻⁶⁶ Kotha and co-workers reported the combination of these reactions in the formation of amino acid derivatives of indanyl glycine which is an analogue of phenylalanine (Scheme 35).^{67,68} To achieve the formation of the indanyl glycine derivatives, Kotha and co-workers formed 1,6-enyne **126** via a double alkylation, hydrolysis and acetylation procedure. Enyne **126** was then reacted with Grubbs first generation catalyst to form 1,3-diene **127** in a 75% yield. Diene **127** was then reacted with a variety of dienophiles and the resulting 1,4-diene products were aromatised using DDQ forming polycyclic products **129–133** in good to excellent yield.



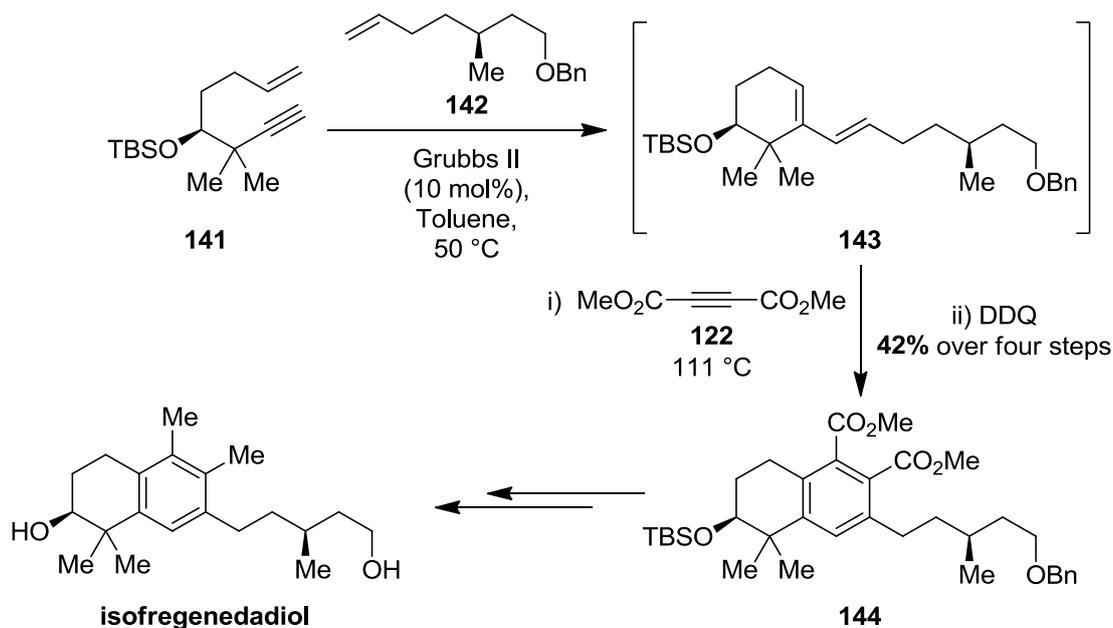
Scheme 35- Synthesis of amino acid derivatives via RCEYM and one-pot Diels-Alder/aromatisation reactions

Grubbs second generation catalyst (Scheme 37).⁷² Once the tandem catalytic process was complete, *N*-phenyl maleimide **139** was added to generate a variety of polycycles **140** in good yields over three steps.



Scheme 37- One-pot tandem catalytic process/Diels-Alder reaction

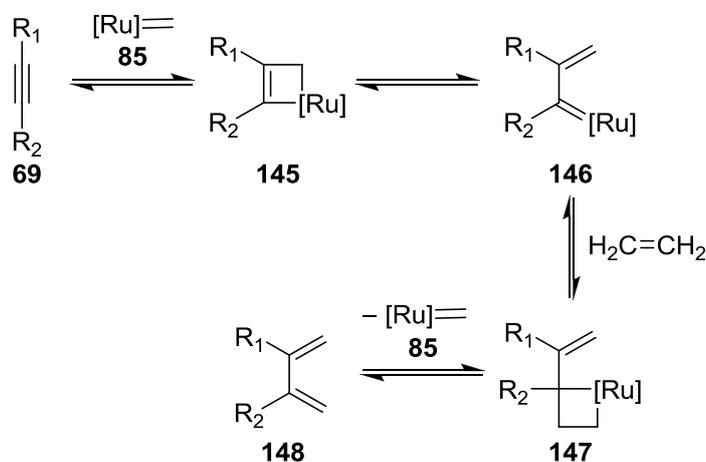
This type of one-pot process has successfully been used by Reddy and co-workers in the total synthesis of isofregenedadiol.⁷³ By utilising 1,7-enyne **141**, which was formed from (–)-pantolactone, a one-pot multi-reaction process forming 1,3-diene **143** via a RCEYM/cross metathesis reaction using olefin **142** as the cross metathesis partner was performed (Scheme 38). Once the tandem catalytic process was complete, the alkyne dienophile **122** was added to promote a Diels-Alder reaction and the resulting product was aromatised using DDQ to form polycycle **144** in a 42% yield over four steps. Reddy and co-workers also report that the one-pot process was more efficient than carrying out each step individually. Once polycycle **144** was generated, the synthesis of the natural product isofregenedadiol was completed in four further steps.



Scheme 38- One-pot process used for the synthesis of isofregenedadiol

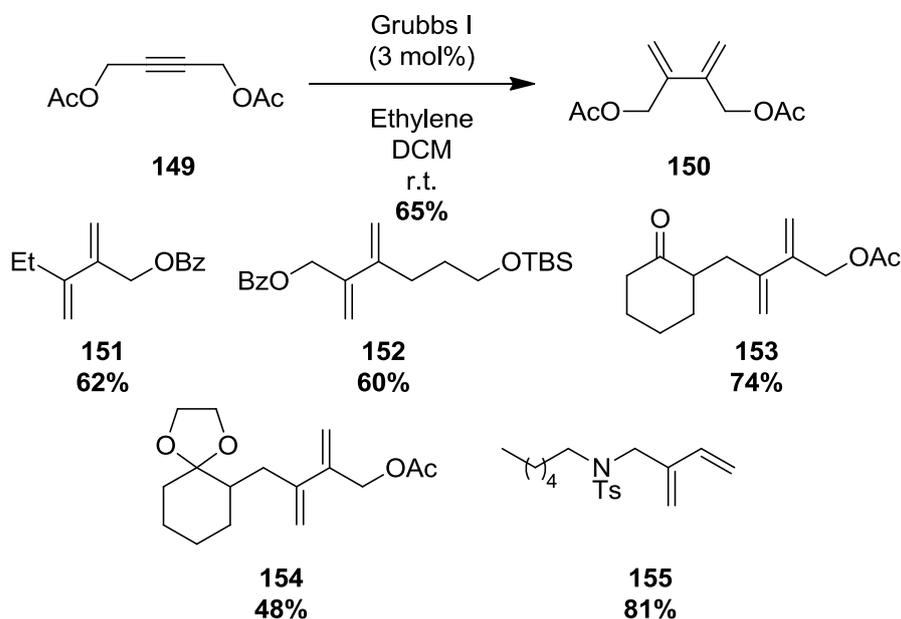
1.3.5 Intermolecular Enyne metathesis

Enyne metathesis is not limited to intramolecular reactions, as intermolecular reactions can also occur. In 1997, Mori and co-workers reported that a range of alkynes could be converted to synthetically useful 1,3-dienes with the use of ethylene gas and Grubbs first generation catalyst (Scheme 39).⁷⁴ It was envisaged that the alkyne **69** would react with activated ruthenium catalyst **85** via a [2+2] cycloaddition to form ruthenacyclobutene **145**, which converts into the vinylmethylidene ruthenium complex **146**. It was then proposed that intermediate **146** can undergo [2+2] cycloaddition with ethylene forming the ruthenacyclobutane **147**, which can then convert to the desired 1,3-diene **148** and regenerate the active catalyst.



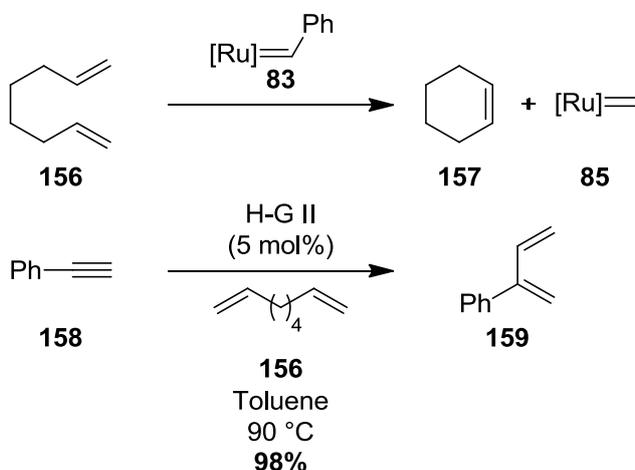
Scheme 39- Proposed mechanism for intermolecular enyne metathesis

It was shown that this procedure could be applied to a range of examples. Impressively both internal and terminal alkynes formed the respective 1,3-dienes **150–155** in good yields with low catalyst loading (Scheme 40).



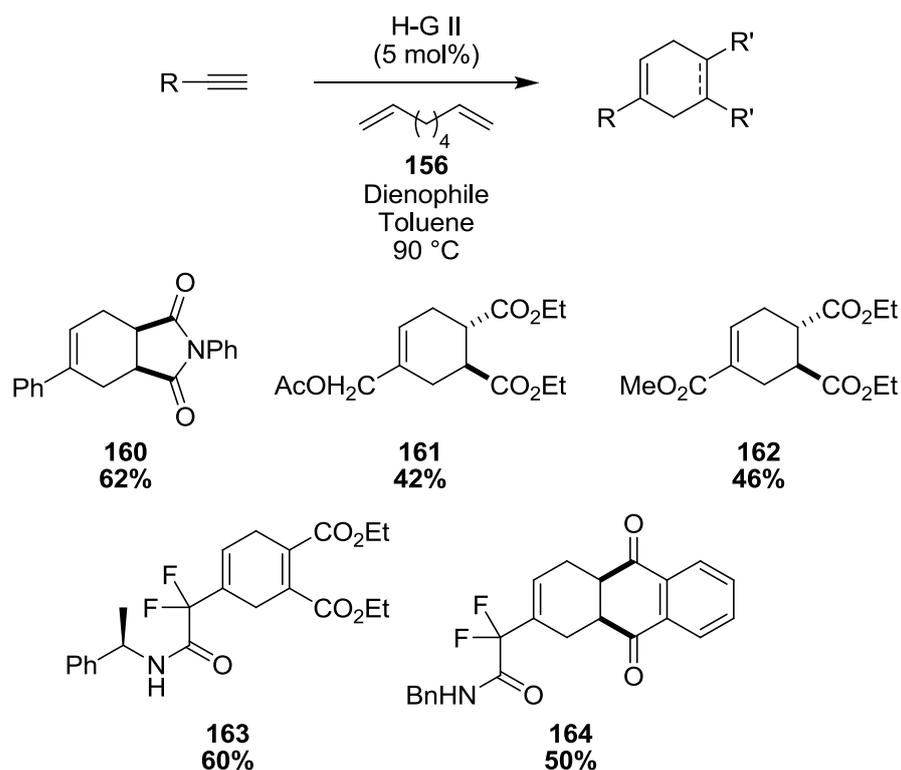
Scheme 40- Application of intermolecular enyne metathesis

One of the problems with Mori conditions is that highly flammable ethylene gas has to be used for the reaction to proceed. In 2012, Fustero and co-workers reported the use of 1,7-octadiene **156** in the cross-enyne-metathesis reaction.⁷⁵ They proposed that the 1,7-octadiene **156** would undergo a RCM reaction with the ruthenium catalyst forming cyclohexene **157** and activated ruthenium carbene **85**, thus forming ethylene *in situ* (Scheme 41). They employed this procedure using phenylacetylene **158** generating 1,3-diene **159** in excellent yield using Hoveyda-Grubbs second generation catalyst.



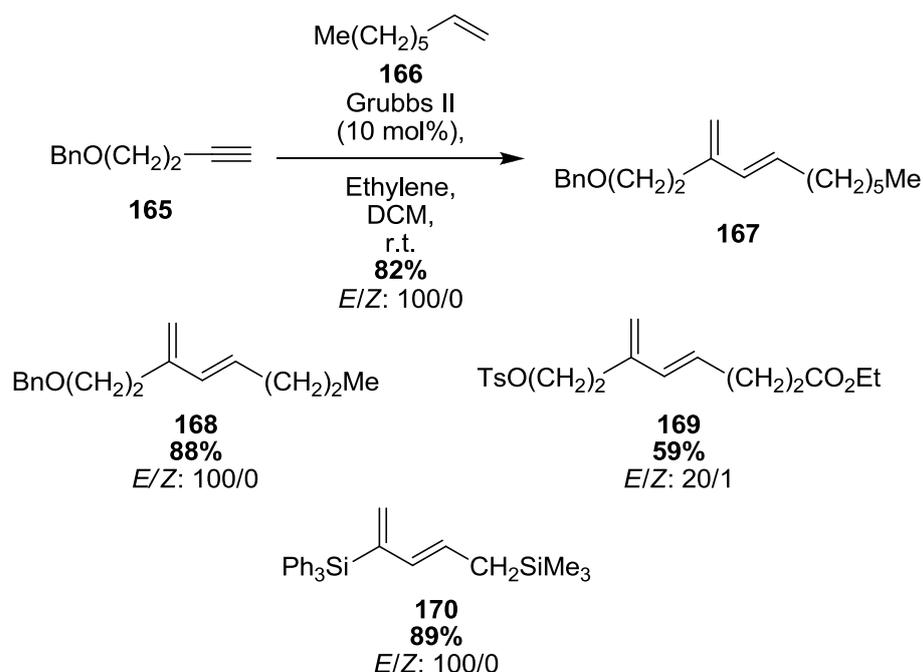
Scheme 41- Enyne metathesis generating ethylene *in situ*

Fustero and co-workers expanded the scope to include a Diels-Alder reaction (Scheme 42). With the addition of a dienophile at the beginning of the reaction, they were able to generate a range of carbocycles **160–164** in a one-pot tandem multicomponent reaction. The reaction was not limited to simple alkynes with the scope of the process being extended to include difluoropropargyl amides forming the corresponding carbocycles **163** and **164** in good yields. These can be used as fluorinated building blocks.⁷⁶



Scheme 42- Application of the *in situ* generation of ethylene for enyne metathesis

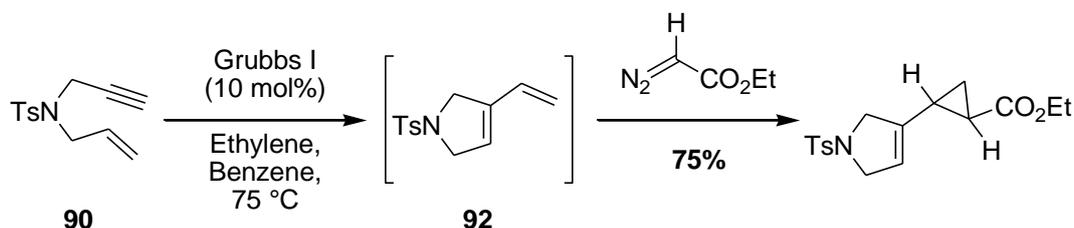
Cross enyne metathesis is not limited to the use of ethylene gas to promote the reaction as unsymmetrical alkenes can be used. However, the reaction can lead to mixtures of regio- and stereoisomers. In 2003, Lee and co-workers reported the use of a range of terminal alkenes and alkynes with ethylene to promote a stereoselective enyne cross metathesis reaction (Scheme 43).⁷⁷ Using this procedure, 1,3-dienes **167–170** were formed and in most cases forming predominantly the thermodynamically more stable *E*-alkene. They also proposed that through the use of ethylene, the unsubstituted 1,3-diene was formed first which then underwent cross metathesis to form the desired product. Also treatment of a mixture of the *E/Z* isomers led to the formation of the *E*-isomer exclusively.



Scheme 43- Stereoselective cross metathesis reaction

1.3.6 Other uses of the 1,3-dienes generated from enyne metathesis

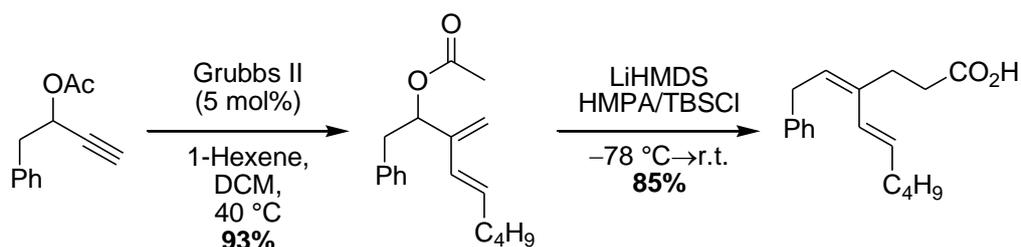
The products generated from the enyne metathesis are not limited to the Diels-Alder reaction for their use in one-pot processes. In 2005, Snapper and co-workers utilised the RCEYM reaction to form a range of cyclic 1,3-dienes which were then reacted with diazoesters (Scheme 44).⁷⁸ The ruthenium catalyst present from the RCEYM reaction enabled the catalysis of the cyclopropanation reaction, to form a range of vinylcyclopropanes in good yields with the *cis/trans* ratio in most cases greater than 2:1.



Scheme 44- One-pot RCEYM/cyclopropanation

Due to the ease of the formation of the 1,3-diene system using the RCEYM reaction, Diver and co-workers reported a [3+3] sigmatropic rearrangement to forming 1,3-diene systems inaccessible by direct intermolecular enyne metathesis (Scheme 45).⁷⁹ Once the 1,3-diene systems were generated, the Diver group utilised an Ireland-Claisen ester enolate

rearrangement to provide access to a variety of conjugated diene substitution patterns in excellent yields.



Scheme 45- Synthesis of substituted dienes via enyne metathesis and Ireland-Claisen rearrangement

1.3.7 Conclusions

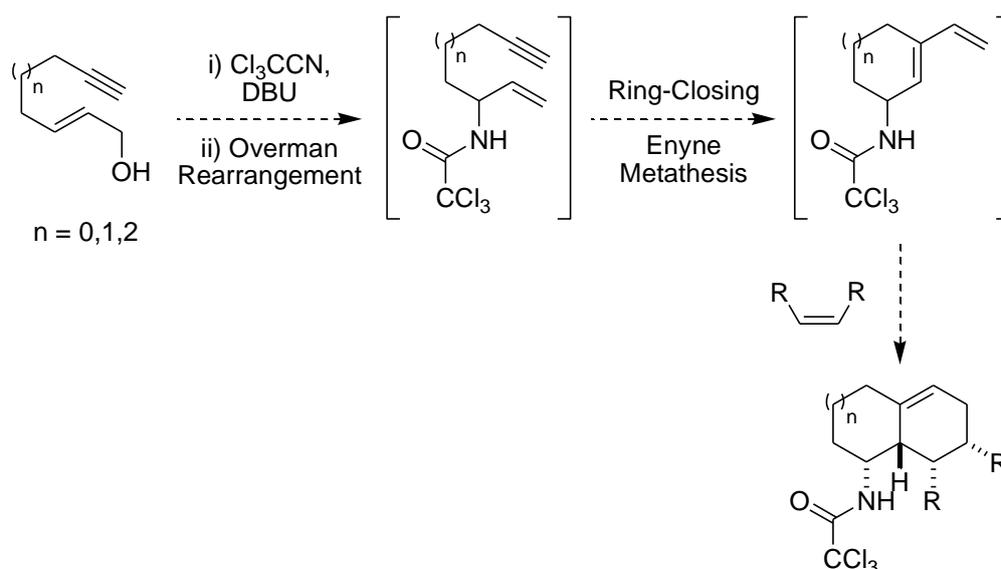
Enynes are synthetically useful intermediates which can be used to synthesise highly functionalised compounds. With the use of Pd, Pt and Au catalysts, bond reorganisation reactions can be carried out to form cyclic products, which can be utilised in further reactions. This area of organic chemistry was mainly investigated in the early 1990's with only a few examples of these bond rearrangements reported recently. With the drive to make organic reactions more efficient and to generate less waste, these reactions could be further investigated by combining them with other reactions to create a diverse set of polycyclic structures through a one-pot process. In recent years, RCEYM has led to an efficient way of generating 1,3-diene systems. Even though this reaction has been extensively developed, the usage of this reaction as part of a one-pot/tandem process is still being investigated to form highly functionalised polycyclic products from simple starting materials.

2.0 Results and discussion

2.1 Development of the one-pot multi-reaction process

2.1.1 Proposed project aims

This chapter describes research for the development of a one-pot multi-reaction process involving the Overman rearrangement, ring-closing-enyne-metathesis (RCEYM) and the Diels-Alder reaction (Scheme 46). Firstly, the development of the Overman rearrangement will be discussed where the reaction was carried out using both metal catalysed and thermal conditions. Following that, the RCEYM was examined with the use of Grubbs catalysts. The resulting 1,3-dienes were then employed in a Diels-Alder reaction using a range of dienophiles to form amino-substituted polycyclic compounds. Each reaction was then combined to form the one-pot process that allowed for the synthesis of a small library of bicyclo[4.3.0]nonanes and bicyclo[4.4.0]decanes.



Scheme 46- Proposed one-pot process

The bicyclic nonanes and decanes generated from the one-pot process have a high level of saturation within them. In recent years there has been a significant shift in the pharmaceutical industry to form more sp^3 -rich compounds for screening purposes rather than sp^2 -rich aromatic compounds.⁸⁰ It has been found that compounds with a large number of sp^3 centres have improved solubility and allow more complexity in the molecule increasing the amount of chemical space.⁸¹⁻⁸³ These nonane and decane scaffolds are present in a variety of natural products such as (+)-ptilocaulin which is an antitumour antibiotic and morphine which is a potent analgesic (Figure 2).^{84,85} Nitrogen substituted

bicyclo[4.4.0]decanes have applications in medicinal chemistry as potent antiproliferative agents.⁸⁶

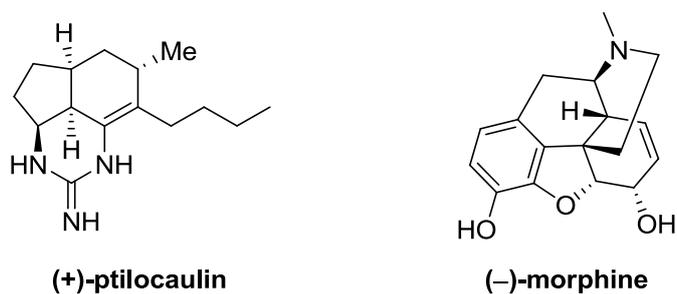
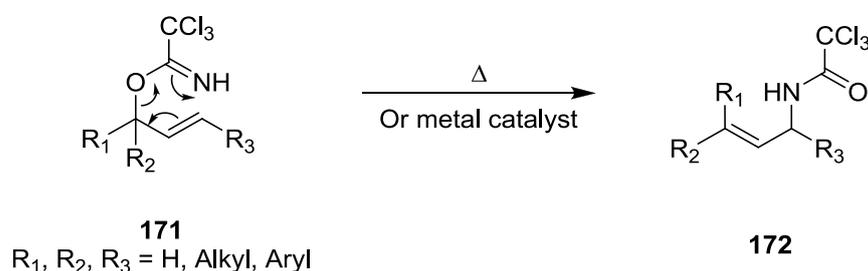


Figure 2- Structures of (+)-ptilocaulin and (-)-morphine

2.1.2 Overman rearrangement

The first key step in the one-pot process is the Overman rearrangement. This rearrangement, which was first reported by Overman in 1974, is a useful tool in organic synthesis as synthetically useful amines can be formed from simple allylic alcohols.^{87,88} Primary, secondary or tertiary allylic alcohols are first treated with trichloroacetonitrile in the presence of a base to form an allylic trichloroacetimidate **171** which can then undergo a [3,3]-sigmatropic rearrangement to form an allylic trichloroacetamide **172** (Scheme 47). To perform the reaction, thermal conditions or metal catalysts such as palladium(II) or mercury(II) salts can be used. The Overman rearrangement is not limited to the use of trichloroacetonitrile to form the imidate. Trifluoroacetonitrile can also be used to form the imidate which can then undergo rearrangement, however trifluoroacetonitrile is a highly toxic gas so is not often used.⁸⁹ The amine can then be deprotected by using acid or base hydrolysis.

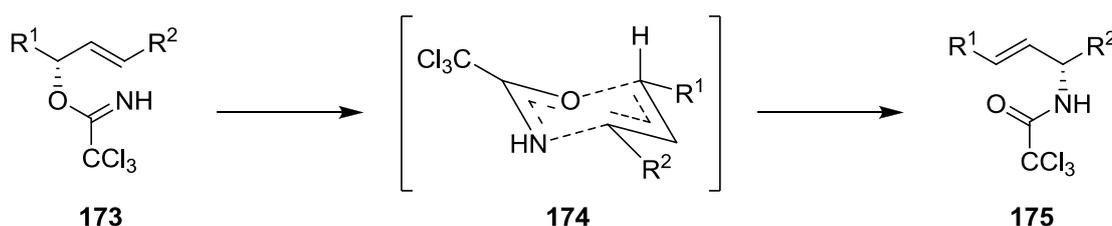


Scheme 47- Overman rearrangement

2.1.3 Thermal Overman rearrangement

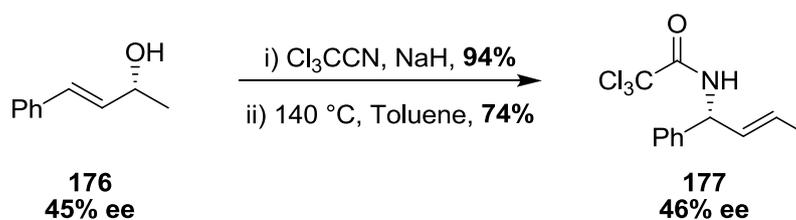
The thermal Overman rearrangement occurs at elevated temperatures; typically at 140 °C except in the case of tertiary imidates where a lower temperature of 80 °C is sufficient.⁸⁸ The imidate **173** reacts via an ordered chair-like transition state **174** to form amide **175**

(Scheme 48). Transition state **174** obeys the Woodward Hoffmann rules for thermal pericyclic rearrangements where the total number of $(4q+2)_s$ and $(4r)_q$ components must be odd.⁹⁰ The thermal rearrangement is a six electron rearrangement with the bonds forming and breaking suprafacially, thus there is one $(4q+2)_s$ component and no $(4r)_a$ component. This means that the reaction is thermally allowed in accordance with the Woodward Hoffman rules. This chair-like transition state **174** is favourable as the bulky trichloromethyl substituent is in a pseudo-equatorial position and the hydrogen atoms are in the axial position thus minimising 1,3-diaxial strain.



Scheme 48- Overman rearrangement via an ordered chair-like transition state

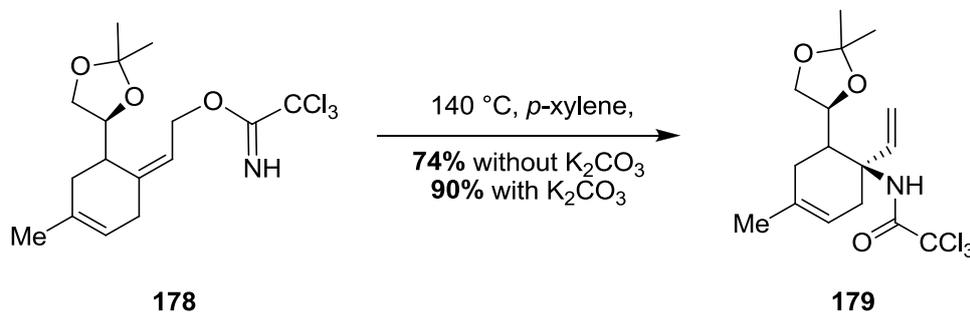
Due to the concerted nature of the reaction, it was shown by Shimoda and co-workers in 1976, that the reaction proceeds with the chirality intact.⁹¹ Evidence of this was found by measuring the optical rotation of alcohol **176** and trichloroacetamide **177**. It was found that the enantiomeric excess was not reduced, thus proving that the chirality was retained (Scheme 49).



Scheme 49- Retention of stereochemistry during thermal Overman rearrangement

A disadvantage of performing the Overman rearrangement at high temperatures is that the amide product and imidate starting material can both degrade causing low yields and unreproducible results. Isobe and co-workers demonstrated that the cause of the degradation was the formation of acids, which can cause decomposition of the imidate.⁹² To resolve this, Isobe and co-workers added a small quantity of potassium carbonate (2 mg/mL) to the reaction mixture to trap any acids generated at high temperatures. This modification had a beneficial effect on the reaction as upon heating of imidate **178** to 140 °C in the absence of potassium carbonate, the acetamide **179** was formed in a 74% yield

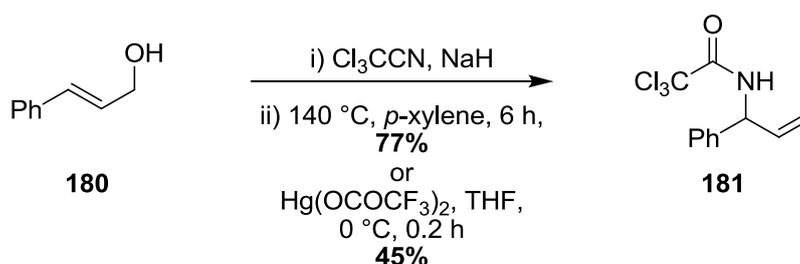
(Scheme 50). With the addition of potassium carbonate the reaction proceeded in a 90% yield and was scalable to 10 g without a reduction in yield.



Scheme 50- Overman rearrangement with and without potassium carbonate

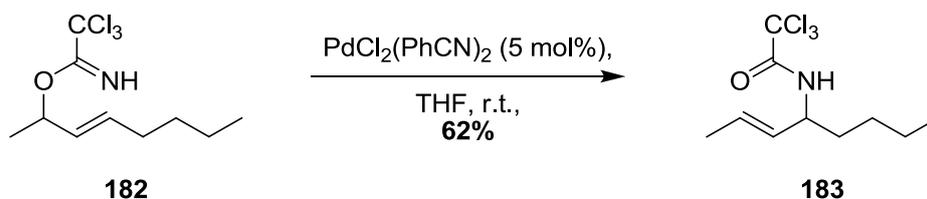
2.1.4 Metal catalysed Overman rearrangement

The alternative and most widely used way of preventing decomposition of the imidate is to perform the reaction at a lower temperature. This can typically be achieved by using metal(II) salts. Overman first reported the use of mercury(II) salts to facilitate the Overman rearrangement in 1974.^{87,88} By starting with allylic alcohol **180**, an Overman rearrangement could be facilitated by using thermal conditions to form amide **181** in a 77% yield whereas with the use of mercury trifluoroacetate, a 45% yield was achieved (Scheme 51). Although the yield of the metal catalysed reaction is lower, the reaction took significantly less time to reach completion and was carried out at a lower temperature.



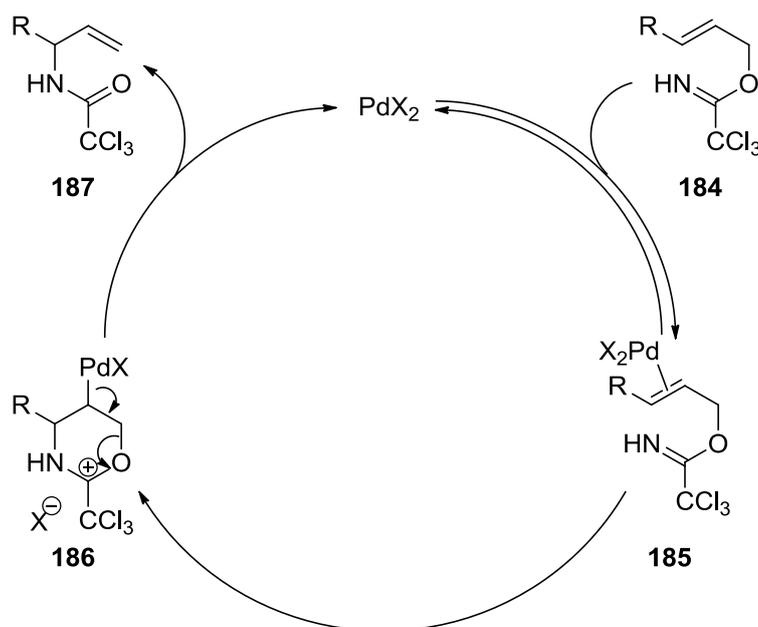
Scheme 51- Overman rearrangement using thermal and mercury(II) catalysed conditions

Palladium(II)-complexes have also been known to catalyse the Overman rearrangement. By using catalysts such as $\text{PdCl}_2(\text{MeCN})_2$ and $\text{PdCl}_2(\text{PhCN})_2$, Metz and co-workers found that these could enable the Overman rearrangement (Scheme 52).⁹³ By using a Pd(II)-catalyst at a 5 mol% loading, Metz and co-workers attained trichloroacetamide **183** in good yield.



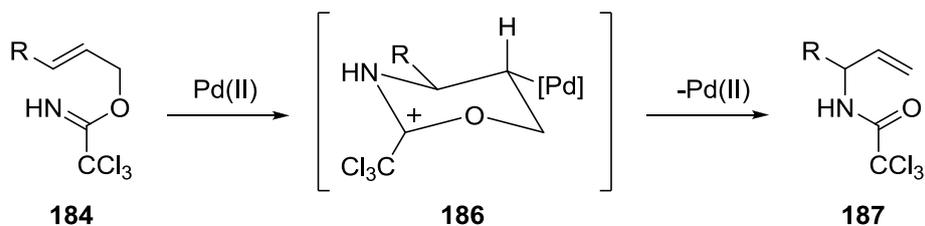
Scheme 52- Pd(II)-catalysed Overman rearrangement

Bosnich and co-workers proposed that the Pd(II)-catalysed Overman rearrangement went through a pathway similar to other metal catalysed rearrangements (Scheme 53).⁹⁴ The mechanism proceeds with the Pd(II)-catalyst coordinating to the alkene moiety of the acetimidate **185**. This activates the alkene towards nucleophilic attack from the imidate nitrogen forming the cyclic transition state **186**. Transition state **186** can then collapse, which is driven by the formation of a more stable carbonyl bond, to form the acetamide product **187** and regenerate the active catalyst.



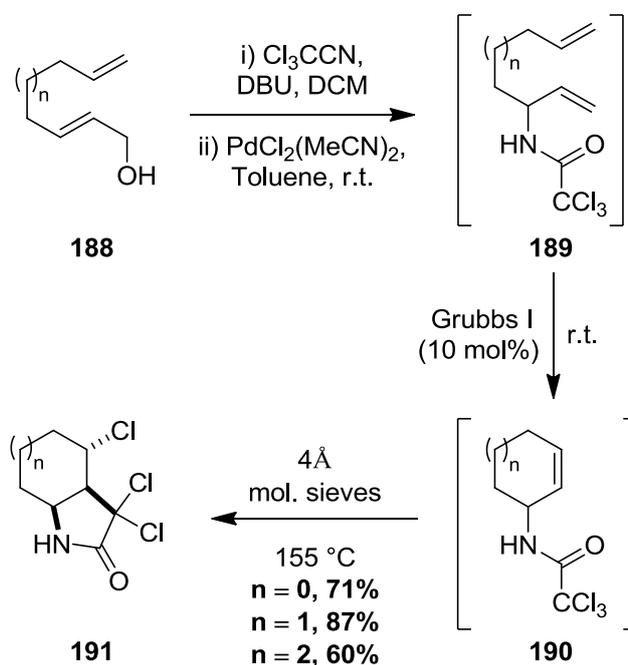
Scheme 53- Mechanism for the Pd(II)-catalysed Overman rearrangement

Bosnich and co-workers also suggested that the cyclic transition state **186** forms a similar chair-like conformation to transition state **174** found in the thermal rearrangement, with the sterically demanding metal and trichloromethyl group being in the equatorial position (Scheme 54).⁹⁴



Scheme 54- Cyclic transition state for Pd(II)-catalysed Overman rearrangement

Within the Sutherland group, the Overman rearrangement has successfully been employed in a range of processes to access structurally diverse molecules.⁹⁵⁻⁹⁷ One example of this was the development of a one-pot tandem process for the formation of bicyclic γ -lactams (Scheme 55).⁹⁸ The bicyclic γ -lactams were generated by first treating allylic alcohol **188** with trichloroacetonitrile then using a Pd(II)-catalysed Overman rearrangement to furnish diene **189**. Diene **189** was then subjected to a ring-closing-metathesis (RCM) reaction forming carbocycle **190**. The reaction mixture was then heated to bring about a Kharasch cyclisation to form bicyclic γ -lactams **191** in excellent yields as single diastereomers. With the use of chiral catalysts these bicyclic γ -lactams **191** could also be generated in high yields and high enantiomeric excess (89–94% ee).



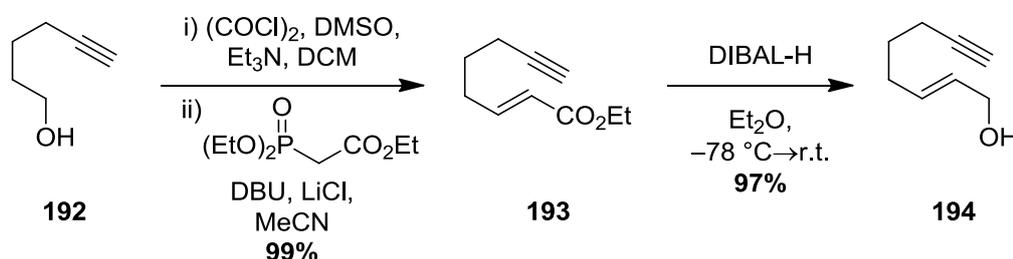
Scheme 55- One-pot process for the synthesis of bicyclic- γ -lactams

For the purpose of the PhD research described in this thesis, it was proposed that the Overman rearrangement would be the first key reaction to be developed as it gives access to the enyne moiety which can then undergo further reactions. Initially, the Overman rearrangement will be developed using palladium catalysts with the view to use the

asymmetric Pd(II)-catalysts to form optically active polycycles which will be discussed later. It was proposed to also investigate a thermally mediated Overman rearrangement as part of this process.

2.1.5 Development of the one-pot multi-step process for the synthesis of amino-substituted bicyclo[4.4.0]decanes

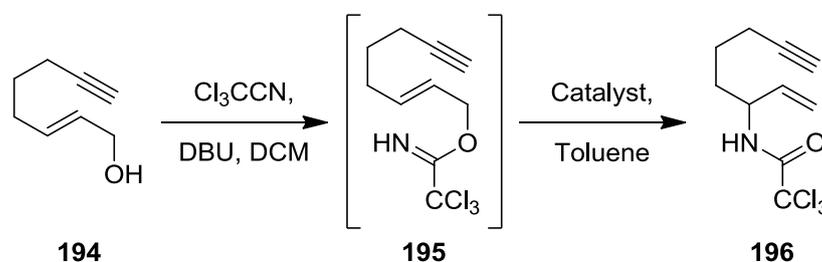
Firstly, the development of a one-pot multi-step process to form bicyclo[4.4.0]decanes will be discussed. In order to perform these reactions, the allylic alcohol precursor was first synthesised. This was achieved by subjecting 5-hexyn-1-ol **192** to a one-pot Swern Horner-Wadsworth-Emmons reaction using mild Masamune-Roush conditions which have been used previously within the Sutherland group on alkene derived alcohols (Scheme 56).^{99,100} Using these conditions, the α,β -unsaturated ester **193** was formed in a 99% yield as the *E*-isomer. The formation of the *E*-isomer was confirmed by ¹H NMR spectroscopy which showed a coupling constant of 15.6 Hz for the alkene hydrogen atoms. α,β -Unsaturated ester **193** was then reduced using DIBAL-H. Care was taken in using DIBAL-H as at elevated temperatures alkynes can also be reduced.^{101,102} By using low temperatures, allylic alcohol **194** was formed in an excellent yield.



Scheme 56- Synthesis of allylic alcohol **194**

In addition to the high yield, the formation of allylic alcohol **194** was also scalable up to 5 g. The first step of the one-pot multi-step process involving Overman rearrangement-RCEYM-Diels-Alder reaction was next investigated (Table 1). Firstly, allylic alcohol **194** was reacted with trichloroacetonitrile in the presence of DBU to form imidate **195** using previously developed conditions from the Sutherland group.⁹⁵ Imidate **195** was passed through a silica plug to remove excess DBU and trichloroacetonitrile but no further purification was required as the reaction proceeded cleanly. The imidate **195** was first reacted with 10 mol% of the Pd(II)-catalyst using conditions described by McGonagle *et al.*, for similar trichloroacetimidates.⁹⁸ Using 10 mol% PdCl₂(MeCN)₂, it was found the reaction yielded only 10% of amide product **196** after 18 h (Table 1, entry 1). This was a disappointing first attempt as the imidate **195** is similar to other imidates used within the

Sutherland group. Further optimisation of the palladium(II)-catalysed Overman rearrangement was then carried out by adding several portions of the palladium(II)-catalyst and then heating the reaction which improved the yield (entries 2 and 3). At short reaction times (< 48 h) only imidate **195** and 1,7-enyne **196** were present in the reaction mixture. When longer reaction times were employed, the formation of many side products were observed, such as the product from the 1,3-rearrangement, which forms through an ionisation pathway occurring when Pd(0) is present in the reaction mixture.^{94,103} The poor yields can be attributed to the palladium coordinating to the alkyne moiety of the molecule thus hindering the reaction. With the yield of the palladium(II)-catalysed rearrangement being unacceptable for the one-pot process, the thermal Overman rearrangement was then carried out (entry 4). By reacting the imidate at 140 °C, 1,7-enyne **196** was formed in an excellent yield.

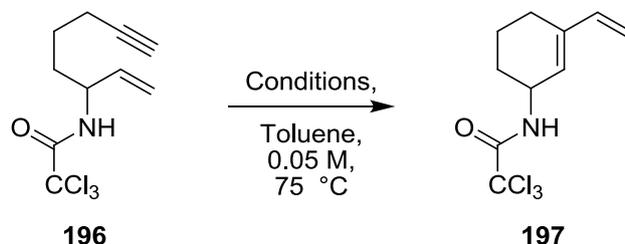


Entry	Conditions	Yield (%)
1	PdCl ₂ (MeCN) ₂ (10 mol%), r.t., 18 h	10
2	PdCl ₂ (MeCN) ₂ (10 mol%), r.t., 18 h then PdCl ₂ (MeCN) ₂ (5 mol%), r.t., 24 h	35
3	PdCl ₂ (MeCN) ₂ (10 mol%), r.t., 48 h then PdCl ₂ (MeCN) ₂ (10 mol%), 40 °C, 24 h	52
4	140 °C, K ₂ CO ₃ , 48 h	98

Table 1- Optimisation of Overman rearrangement

Since the thermal Overman rearrangement proceeded in an excellent yield and was scalable up to 2 g, the palladium(II)-catalysed method was not pursued further. The second step of the one-pot process, the RCEYM, was then developed. To carry out the metathesis reaction, Grubbs first generation catalyst was chosen as it is a commonly used catalyst in such reactions.^{52,62,104} Initially, the reaction was performed in DCM, forming desired 1,3-diene **197** in 68% yield (Table 2, entry 1). Due to the Overman rearrangement being

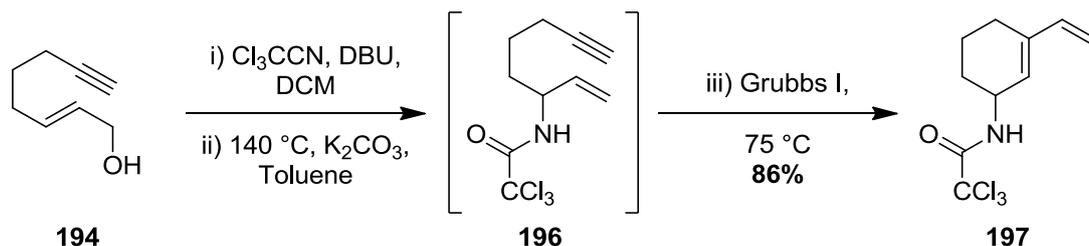
carried out in toluene the reaction was repeated using this solvent achieving a yield of 60% (entry 2). However, it was found that 1,3-diene **197** could be isolated in an improved yield of 63% yield by adding the Grubbs catalyst in two portions (entry 3). The use of Grubbs second generation catalyst was also attempted for this transformation, however this gave 1,3-diene **197** in modest yield (entry 4).



Entry	Conditions	Yield (%)
1 ^{a,b}	Grubbs I (10 mol%), 18 h	68
2	Grubbs I (10 mol%), 18 h	60
3	Grubbs I (7.5 mol%), 18 h then Grubbs I (2.5 mol%), 18 h	63
4	Grubbs II (7.5 mol%), 18 h then Grubbs II (2.5 mol%), 18 h	46

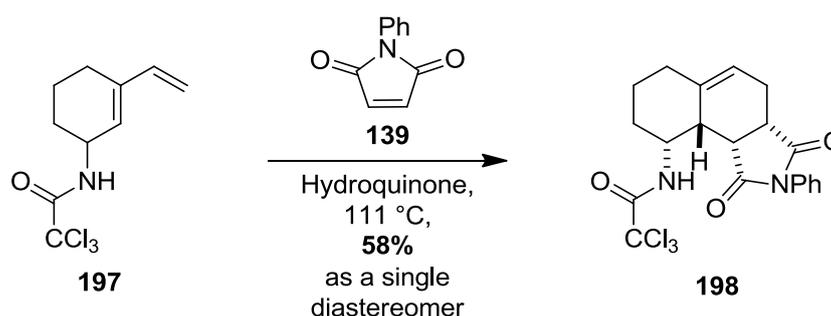
Table 2- Optimisation of RCEYM reaction. ^a Using DCM as a solvent. ^b Reaction carried out at 40 °C

After successful optimisation of the Overman rearrangement and the RCEYM, both steps were then incorporated into a one-pot multi-reaction process. To achieve this, allylic alcohol **194** was first treated with trichloroacetonitrile to form the imidate which was then reacted via a thermal Overman rearrangement forming 1,7-enyne **196** (Scheme 57). Once the Overman rearrangement was complete, as confirmed by ¹H NMR spectroscopy, Grubbs first generation catalyst was added in two batches over a period of 36 h to attain 1,3-diene **197** in excellent yield over three steps.



Scheme 57- One-pot synthesis of 1,3-diene **197**

With the optimisation of 1,3-diene **197** complete, the Diels-Alder reaction was then investigated. *N*-Phenyl maleimide **139** was chosen as the first dienophile to be investigated due to it being highly electron deficient and thus reactive towards electron-rich diene **197**. The reaction was carried out in the presence of hydroquinone to prevent polymerisation reactions which could take place at high temperature (Scheme 58).^{105,106} The Diels-Alder reaction took 18 h to reach completion at 111 °C forming polycycle **198** in a 58% yield. The yield of the reaction was slightly lower than expected but the fact that the product was isolated as a single diastereomer was of great importance.



Scheme 58- Diels-Alder reaction for the synthesis of polycycle **198**

Investigation of the stereochemical outcome of this reaction was probed by NOE difference experiments (Figure 3 and Appendix 1). The hydrogen atom on the C-9 position was irradiated showing a positive NOE for the hydrogen atom on the C-9a position meaning they are close in space to one another and thus *syn* to each other. Irradiation of the C-9b hydrogen atom also showed a positive NOE to the hydrogens on the C-3a and C-9a positions. Even though the NOE between the C-3a and 9b hydrogens was small they had to be *syn* to each other due to the *cis*-geometry of the dienophile. Finally, irradiation of the hydrogen at the C-9a position showed a positive NOE to the hydrogens on the C-9 and C-9b positions. This experiment confirms that the hydrogen atoms on the C-3a, C-9, C-9a and C-9b have a *syn*-relationship with respect to each other.

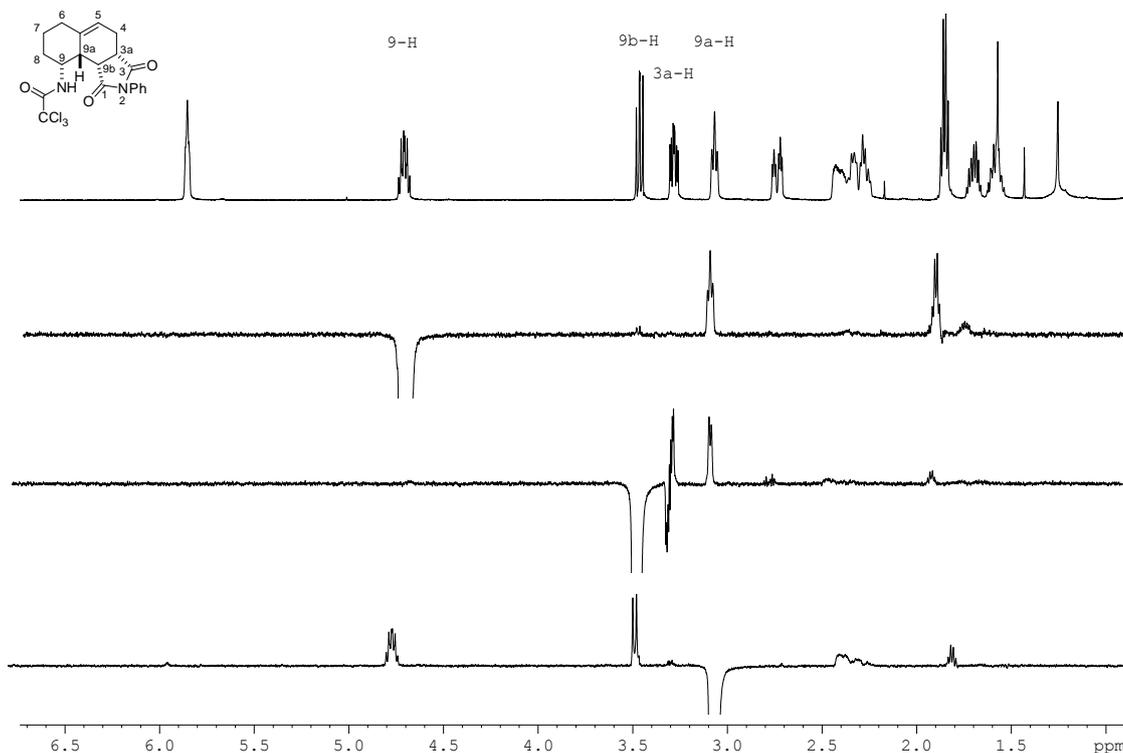
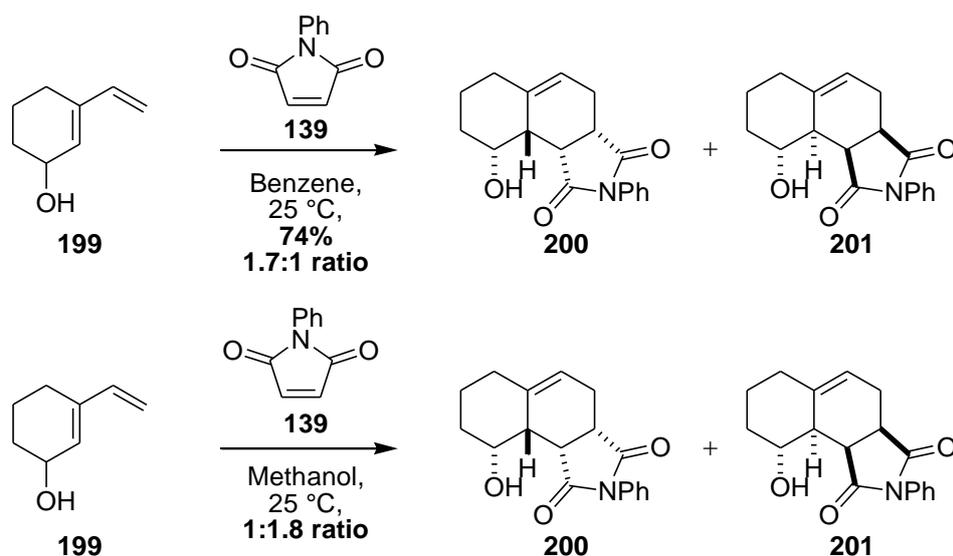


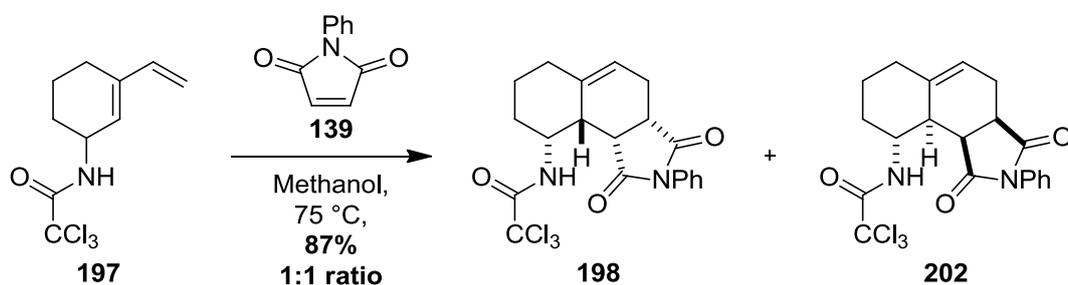
Figure 3- Comparison of NOE spectra of bicyclo[4.4.0]decane **198**

Diels-Alder product **198** is formed from the dienophile reacting on the same face as the trichloroacetamide group going through an *endo* transition state. It was suspected that the reason for the dienophile reacting from the same side as the trichloroacetamide group was due to a hydrogen bonding directing effect between the trichloroacetamide hydrogen atom and the oxygen atom on the dienophile. A similar hydrogen bonding directing effect has been reported by Franck and co-workers.¹⁰⁷ Franck and co-workers showed that the alcohol group in 1,3-diene **199** caused facial selectivity in the Diels-Alder reaction forming *syn* diastereomer **200** in 1.7:1 ratio with *anti* diastereomer **201** in non-polar solvents (Scheme 59). Both these products arise from the Diels-Alder reaction going through an *endo* transition state with the dienophile attacking from opposite faces. When the reaction was carried out in the polar protic solvent methanol the predominant product was the *anti* diastereomer **201**. This change in diastereoselectivity is due to the methanol perturbing the hydrogen bonding effect of the hydrogen on the alcohol thus causing steric repulsion of the alcohol group and dienophile in the transition state.



Scheme 59- Diels-Alder reaction showing facial selectivity using polar and non-polar solvents

To provide further evidence of this effect with diene **197**, the Diels-Alder reaction was repeated using methanol as a solvent (Scheme 60). This resulted in the formation of two diastereomers in a 1:1 ratio.



Scheme 60- Diels-Alder reaction carried out in methanol

Figure 4 shows the ^1H NMR spectrum of the crude Diels-Alder reaction mixtures which were conducted in toluene (top) and methanol (bottom) are shown. When the reaction was carried out in toluene it can clearly be observed from the ^1H NMR spectrum (top) that compound **198** is the predominant diastereomer and analysis of this mixture showed that the *syn:anti* ratio was 20:1. It is also clear from the bottom spectrum that when the reaction was carried out in methanol, the reaction forms the two diastereomers in a ratio of 1:1.

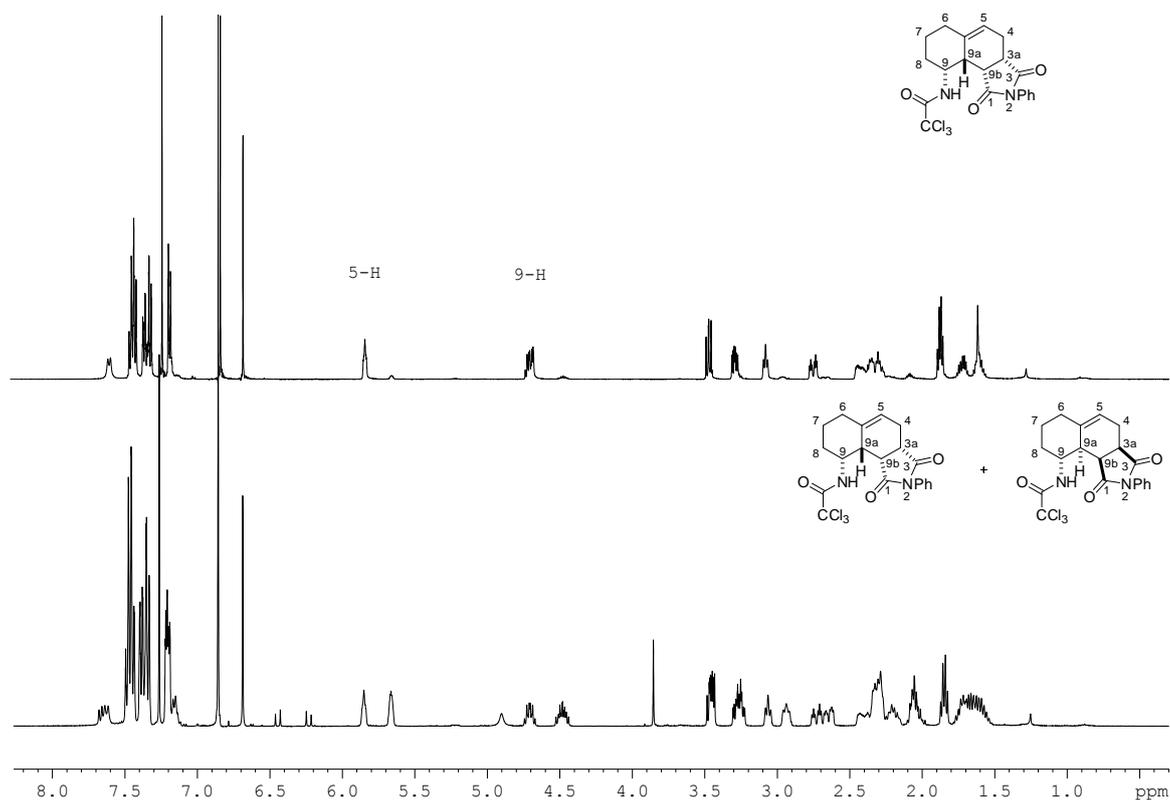


Figure 4- Comparison of ^1H NMR spectra of Diels-Alder products from toluene (top) and methanol (bottom)

To confirm the relative stereochemistry of bicyclo[4.4.0]decane **202**, NOE studies were carried out showing that the hydrogen atoms at the C-3a, C-9a and C-9b positions have a *syn*-relationship with one another (Figure 5). A NOE was not observed between the hydrogen atoms on the C-9 and C-9a positions meaning they are not close in space, and thus have an *anti*-relationship with each other.

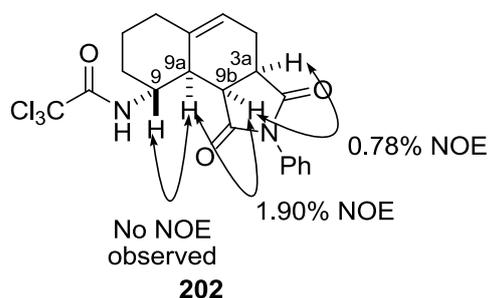


Figure 5- NOE enhancement studies for polycycle **202**

To further explore the cause of the formation of the single diastereomer, a computational study of both *endo* transition states between 1,3-diene **197** and *N*-phenyl maleimide **139** were carried out by Dr Hans Senn in the School of Chemistry (Figure 6). By employing density-functional theory at the M06-2X/def2-TZVP level, using a solvent model of

toluene at 111 °C, the *endo* transition states from the attack of the *N*-phenyl maleimide **139** from the same side as the trichloroacetamide group (*syn* attack, Figure 6, left) and the opposite side as the trichloroacetamide group (*anti* attack, right) were investigated. It can be seen from the model that the *syn*-transition state (left) is stabilised by a hydrogen bond of 2.10 Å in length between the amide NH of 1,3-diene **197** and the imide oxygen of dienophile **139**. The model of the *anti*-transition state (right) does not possess this hydrogen bond so this attack will be less favourable. *Syn*-product **198** is favoured on kinetic grounds as the calculated Gibbs free energy of activation is 115 kJ mol⁻¹ for the *syn*-attack whereas, the *anti*-attack has a calculated activation energy of 125 kJ mol⁻¹. This stabilising effect is also reflected in the Gibbs free energies of the reaction as the product from the *syn* attack has a Gibbs free energy of -93 kJ mol⁻¹ whereas the *anti*-attack product has a Gibbs free energy of -85 kJ mol⁻¹ meaning *syn*-product **198** is more thermodynamically stable. By using the calculated Gibbs free energies of the activation and assuming the reaction is both irreversible and under kinetic control, the ratio of *syn:anti* product translates to a *syn* selectivity of 23:1 at 111 °C. This correlates well with the observed result of a *syn:anti* ratio of 20:1.

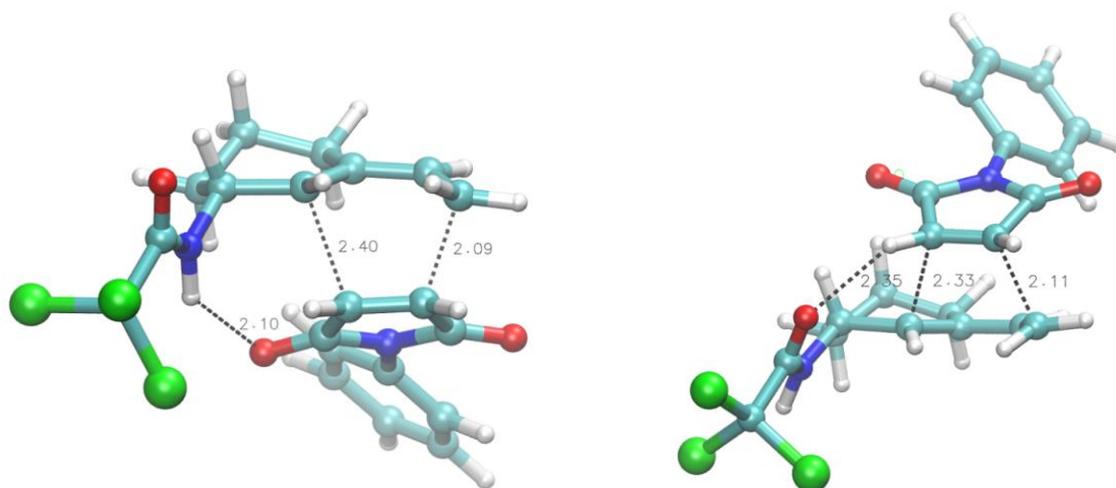
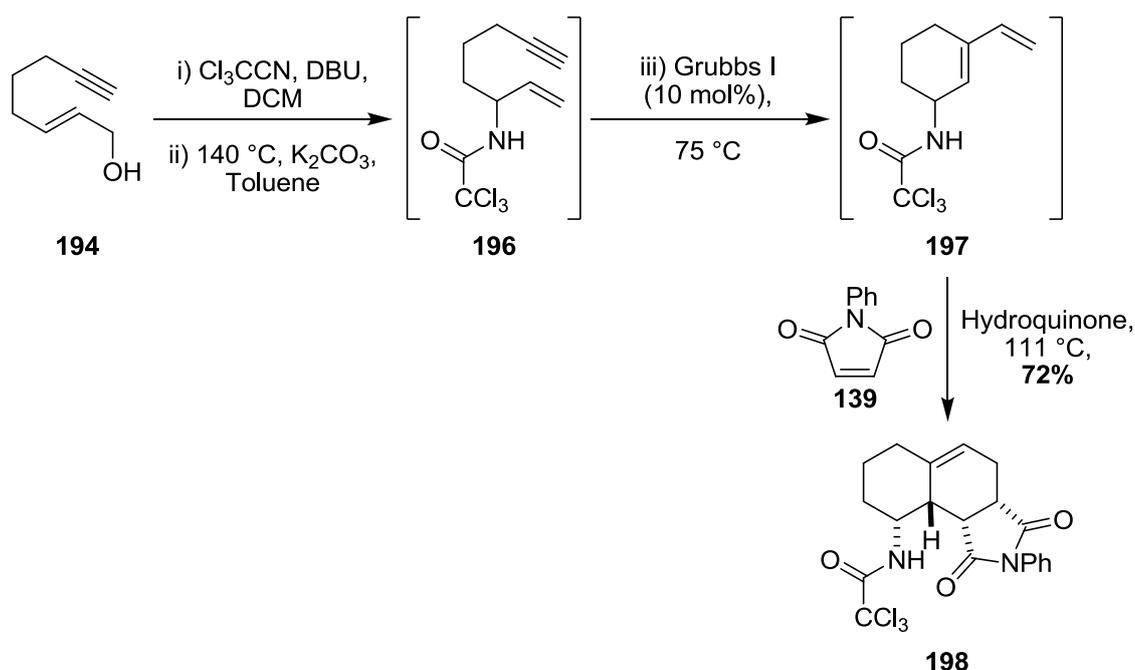


Figure 6- Modelling studies of hydrogen-bond directing transition state (left) and non-hydrogen-bond directing transition state (right)

Having optimised each step of the one-pot process, the full one-pot process was attempted (Scheme 61). By starting with allylic alcohol **194**, Overman rearrangement was employed to form 1,7-enyne **196**. Once the Overman rearrangement was complete, Grubbs first generation catalyst was added forming 1,3-diene **197**. Finally, *N*-phenyl maleimide was added generating bicyclo[4.4.0]decane **198** in a 72% yield as a single diastereomer.



Scheme 61- One-pot process for the synthesis of bicyclo[4.4.0]decane **198**

To further improve the one-pot process, *N*-phenyl maleimide **139** was added at the same time as the Grubbs catalyst, making these steps a true tandem process. However, this reaction failed, forming only small amounts of desired product.

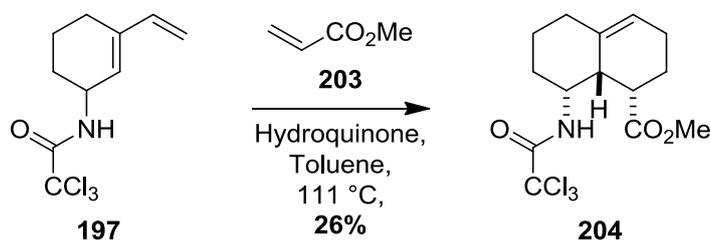
Overall a one-pot multi-reaction process has been developed forming a bicyclo[4.4.0]decane in four steps from a simple allylic alcohol with four contiguous stereogenic centres being created.

2.1.6 Exploring the scope of the one-pot process

With the conditions optimised for the synthesis of 1,3-diene **197**, attention was turned to the addition of other dienophiles to the one-pot process in order to access other substituted bicyclo[4.4.0]decanes.

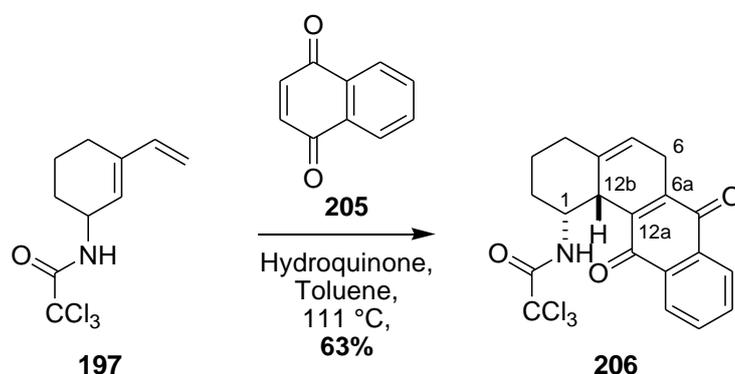
To be certain the one-pot process was compatible with other dienophiles, a short study of the Diels-Alder reaction with the dienophiles, methyl acrylate **203** and 1,4-naphthoquinone **205** was conducted. Methyl acrylate was first attempted forming amino-substituted bicyclo[4.4.0]decane **204** in 26% yield as a single diastereomer (Scheme 62). The relative stereochemistry of bicyclo[4.4.0]decane **204** was confirmed by NOE studies (Appendix 1). The low yield of this reaction could be explained by the volatility of methyl acrylate. However, the use of a sealed tube during the one-pot process overcame this issue (see later). It was important to note that the product was formed as a single diastereomer and as

a single regioisomer with three contiguous stereogenic centres. The formation of a single regioisomer is also a consequence of the Diels-Alder reaction progressing through a hydrogen bond directed *endo* transition state.



Scheme 62- Diels-Alder reaction using methyl acrylate **203**

Attention then turned to dienophile 1,4-naphthoquinone **205**. Upon reaction of 1,3-diene **197** with 1,4-naphthoquinone **205**, the desired product was not formed, however tetracyclic product **206** was generated in a 63% yield as a single diastereomer (Scheme 63). NOE studies showed that the hydrogen atoms at the C-1 and C-12b positions exhibited a *syn*-relationship thus showing that the hydrogen bond directing effect was still observed (Appendix 1).



Scheme 63- Diels-Alder reaction between 1,3-diene **197** and 1,4-naphthoquinone **205**

To confirm the structure of polycycle **206** an X-ray crystal structure was obtained (Figure 7 and Appendix 2). It can be seen that the cyclohexane ring adopts a chair conformation with the trichloroacetamide group in an axial position. The X-ray structure also clearly shows the sp^2 nature of the C-6a and C-12a positions further confirming the 1,4-diene structure. This 1,4-diene moiety can be generated via aerial oxidation which has previously been reported by Rovek and co-workers who bubbled oxygen through their reaction mixture of naphthoquinone derivatives causing partial oxidation.⁶⁶ The reaction was repeated in an oxygen free atmosphere, however 1,4-diene **206** remained. This may be due to the excess

of 1,4-naphthoquinone **205** in the reaction mixture causing the oxidation which has been reported by Su and co-workers.¹⁰⁸ This oxidation will be discussed further in Chapter 2.5.

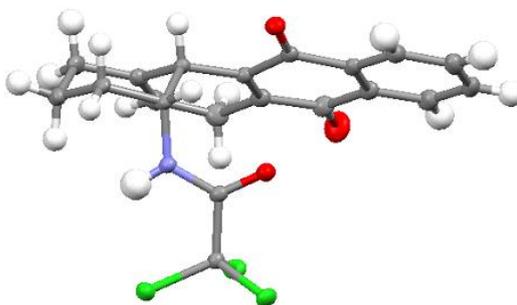
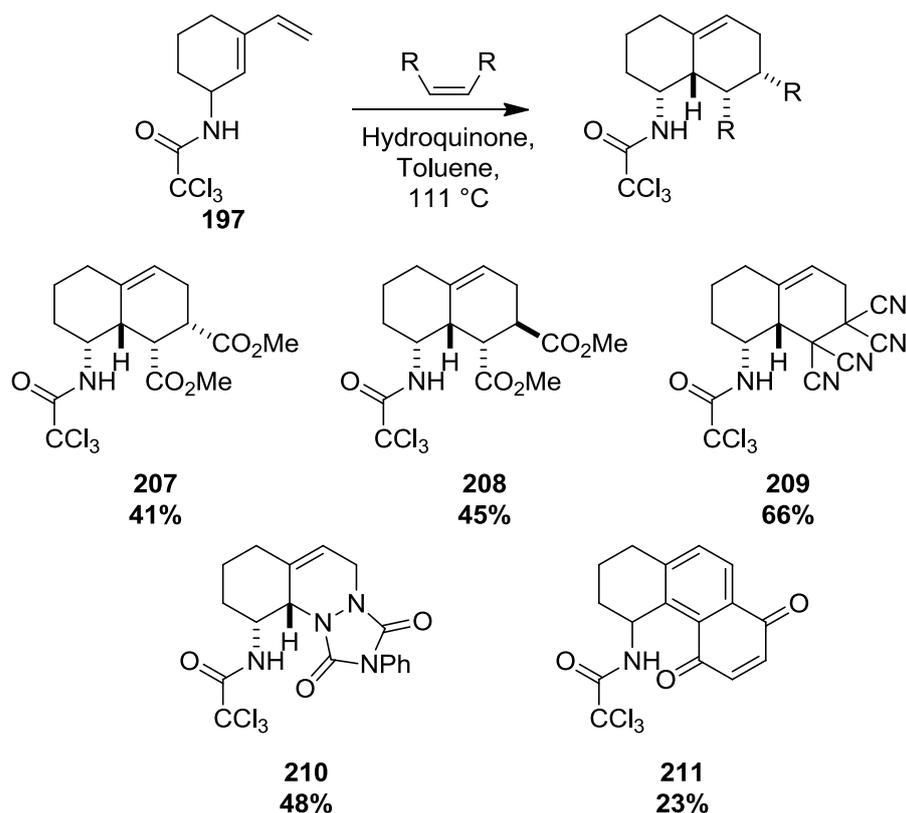


Figure 7- Ortep diagram of tetracycle **206**

The Diels-Alder reaction was then carried out on other dienophiles forming adducts **207–211** in good to moderate yields as single diastereomers, as confirmed by NOE studies (Scheme 64 and Appendix 1). Bicyclo[4.4.0]decane **209** is noteworthy as the Diels-Alder reaction generates a product with two new quaternary centres. Polycycle **210** is also an example of a hetero Diels-Alder reaction forming the heteroatom containing product in good yield as a single diastereomer. The aromatic compound **211** was formed in a low yield. The resulting aromatisation is due to the excess 1,4-benzoquinone and the presence of oxygen during the work up process leading to the oxidation reaction. This yield could be further optimised by the use of stronger oxidising agents such as DDQ. This approach will be discussed in greater detail in Chapter 2.5.



Scheme 64- Scope of Diels-Alder reaction

The dienophiles, methyl methacrylate **212** and methyl 3-methylbut-2-enoate **213**, were found to not react in the Diels-Alder reaction due to their poor electronics and being sterically encumbered (Figure 8). Furthermore, imine **214** showed no reaction with 1,3-diene **197**. Each of these examples were also attempted using more forcing conditions, such as at higher temperature and the use of a Lewis acid, however these attempts did not prove successful.

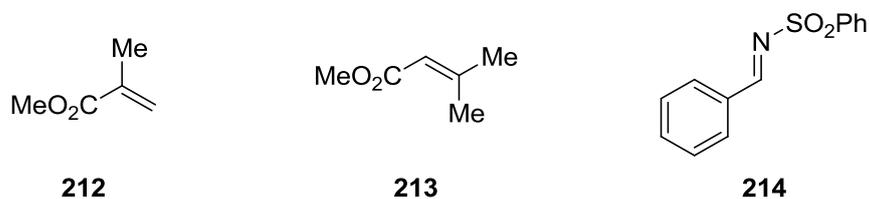
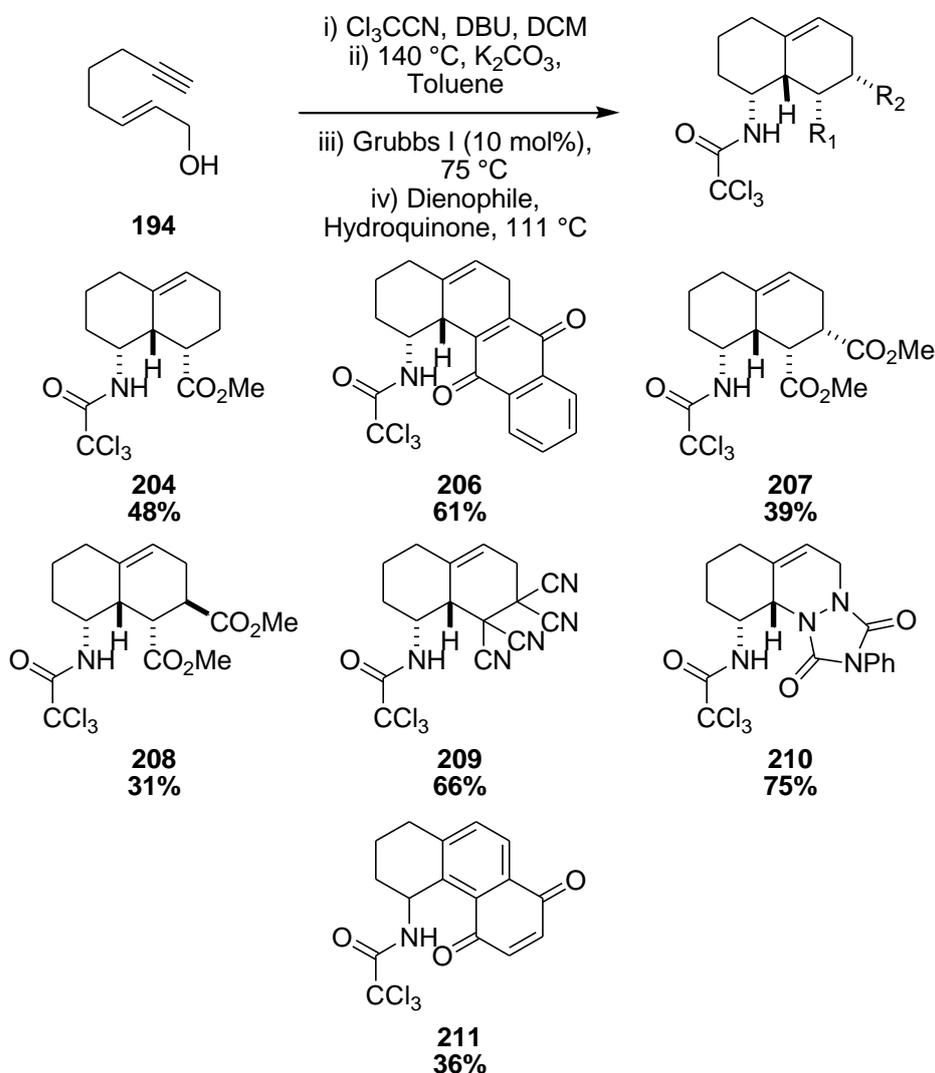


Figure 8- Unreactive dienophiles

The dienophiles discussed above were then incorporated into the one-pot multi-step process. The one-pot process was rigorously monitored by 1H NMR spectroscopy to ensure each step of the process reached completion. By starting with allylic alcohol **194**, a small library of bicyclo[4.4.0]decanes were formed in good to moderate yields over four steps (Scheme 65). In the case of the bicyclo[4.4.0]decanes **204** and **210**, the yield of the one-pot

process was better than the individual Diels-Alder step. Analysis of the crude ^1H NMR data showed that the Diels-Alder reaction formed predominantly the *syn*-diastereomer in ratios greater than 15:1.

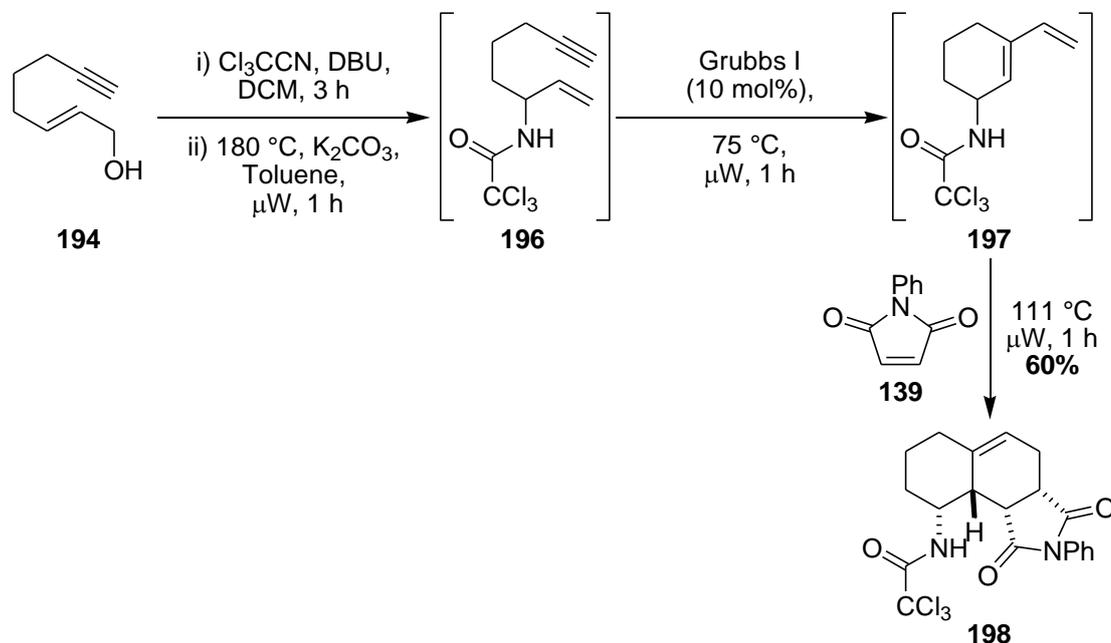


Scheme 65- Library of amino-substituted bicyclo[4.4.0]decanes

The major advantage of performing such one-pot processes is that only one purification step was needed thus substantially reducing the amount of time, handling the intermediates and reducing the amount of waste generated.

However, one disadvantage of this one-pot process was that certain steps in the process required extended reaction times resulting in the overall time taken to generate the desired product was over 5 days. To overcome this microwave reactor technology was used, which allows the reaction mixture to heat up rapidly in a uniform manner.¹⁰⁹ Following the formation of the imidate, the Overman rearrangement was carried out in the microwave at $180\text{ }^\circ\text{C}$ resulting in the formation of enyne **196** in 1 h compared to 48 h under conventional

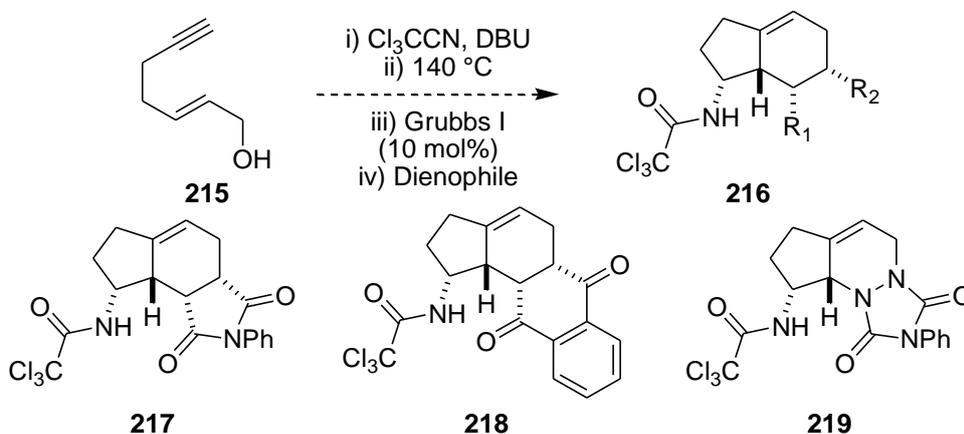
heating methods (Scheme 66). Using conditions as described before for the ring-closing-enyne-metathesis and Diels-Alder reactions, these two steps took one hour each to go to completion forming **198** in a 60% yield as a single diastereomer. Overall, this allowed the preparation of polycycle **198** in 6 h compared to 120 h using conventional heating.



Scheme 66- One-pot process carried out using microwave heating

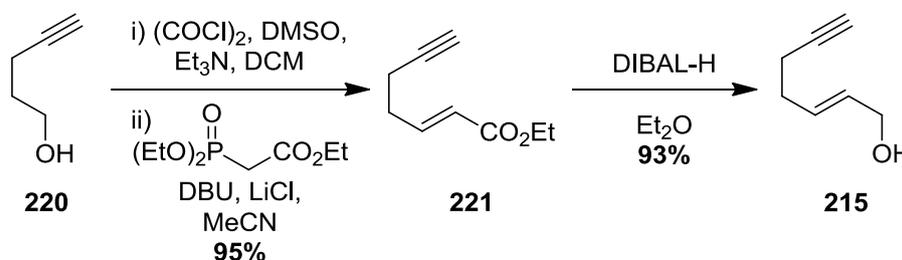
2.1.7 Formation of amino-substituted bicyclo[4.3.0]nonanes

Following the successful optimisation of the one-pot process for the formation of a small library of bicyclo[4.4.0]decanes, attention was turned to the formation of a library of bicyclo[4.3.0]nonanes **216**. The aim was to use similar conditions to those described previously to generate a small library of bicyclo[4.3.0]nonanes **216** such as those shown in Scheme 67.



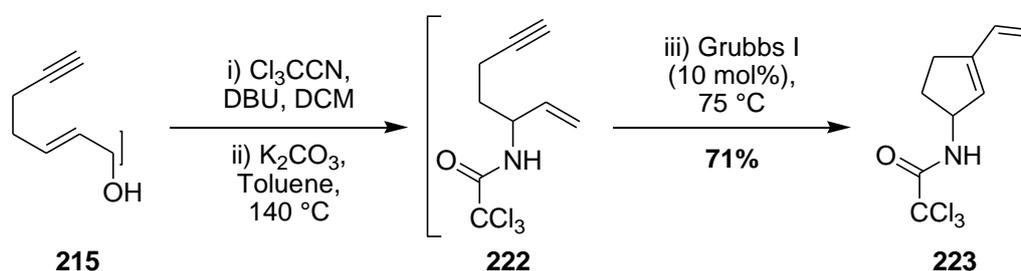
Scheme 67- Proposed one-pot process for the synthesis of bicyclo[4.3.0]nonanes **216**

In order to form the bicyclo[4.3.0]nonanes, the corresponding allylic alcohol precursor was prepared. To achieve this, allylic alcohol **215** was generated again using the one-pot Swern Horner-Wadsworth-Emmons reaction followed by a DIBAL-H reduction as described before, producing allylic alcohol **215** in excellent yield from commercially available 4-pentyn-1-ol **220** (Scheme 68).



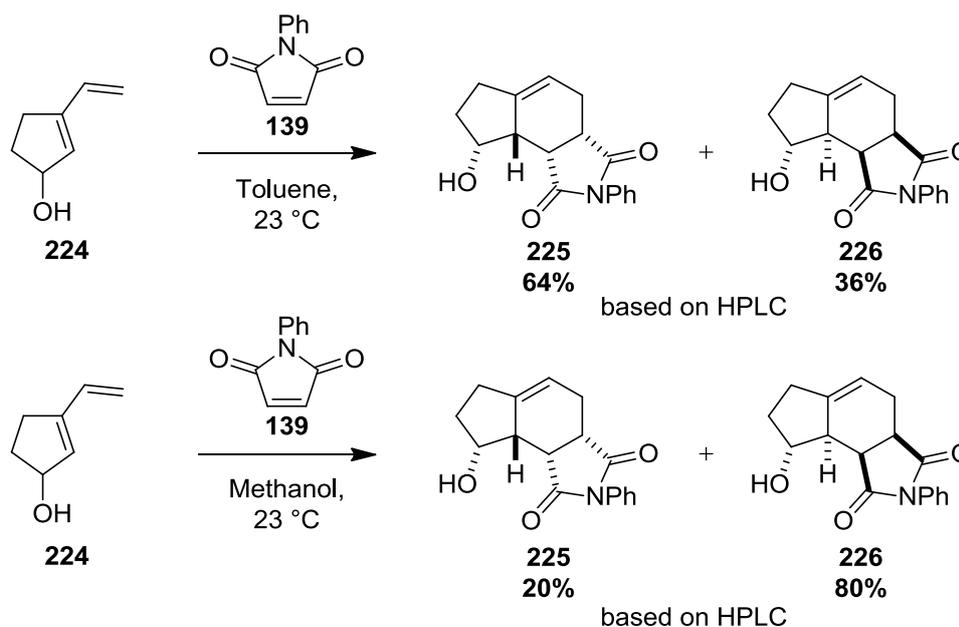
Scheme 68- Synthesis of allylic alcohol **215**

To form 5-membered cyclic 1,3-diene **223**, allylic alcohol **215** was subjected to the multi-reaction process previously developed for the synthesis of 6-membered cyclic 1,3-diene **197**. These conditions proved successful in generating 5-membered cyclic 1,3-diene **223** in good yield (Scheme 69).



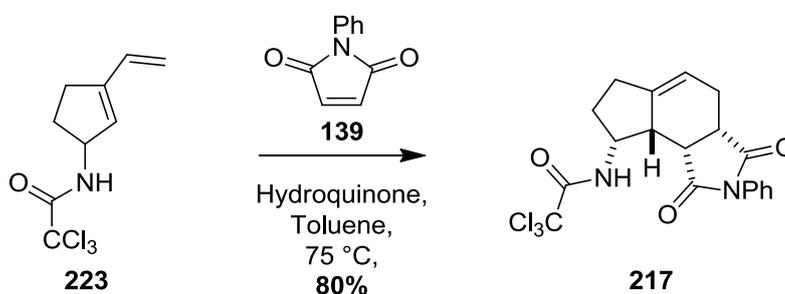
Scheme 69- One-pot synthesis of 1,3-diene **223**

With the successful formation of 1,3-diene **223**, the Diels-Alder reaction was then investigated to see if the hydrogen bonding effect was observed with the smaller ring size. Overman and co-workers had observed the same hydrogen bonding effect on alcohol functionalised cyclic 1,3-diene **224** that Franck *et al.* had observed with 6-membered analogues (Scheme 70).^{107,110} When a non-polar solvent such as toluene is used, the hydrogen bonding takes effect forming predominantly *syn*-product **225**. In the polar protic solvent methanol, the hydrogen bonding is perturbed thus, the reaction predominantly forms *anti*-product **226**.



Scheme 70- Facial selectivity of the Diels-Alder reaction of 1,3-diene **224** and *N*-phenyl maleimide **139**

It was gratifying to find that when the amino-substituted 1,3-diene **223** was reacted with *N*-phenyl maleimide **139**, compound **217** was isolated as a single diastereomer in excellent yield (Scheme 71).



Scheme 71- Diels-Alder reaction for the synthesis of polycycle **217**

Upon analysis of the ^1H NMR spectrum of the crude mixture it can clearly be seen that the *syn*-product **217** forms predominantly (18:1) when the reaction was carried out in the non-polar solvent toluene (Figure 9).

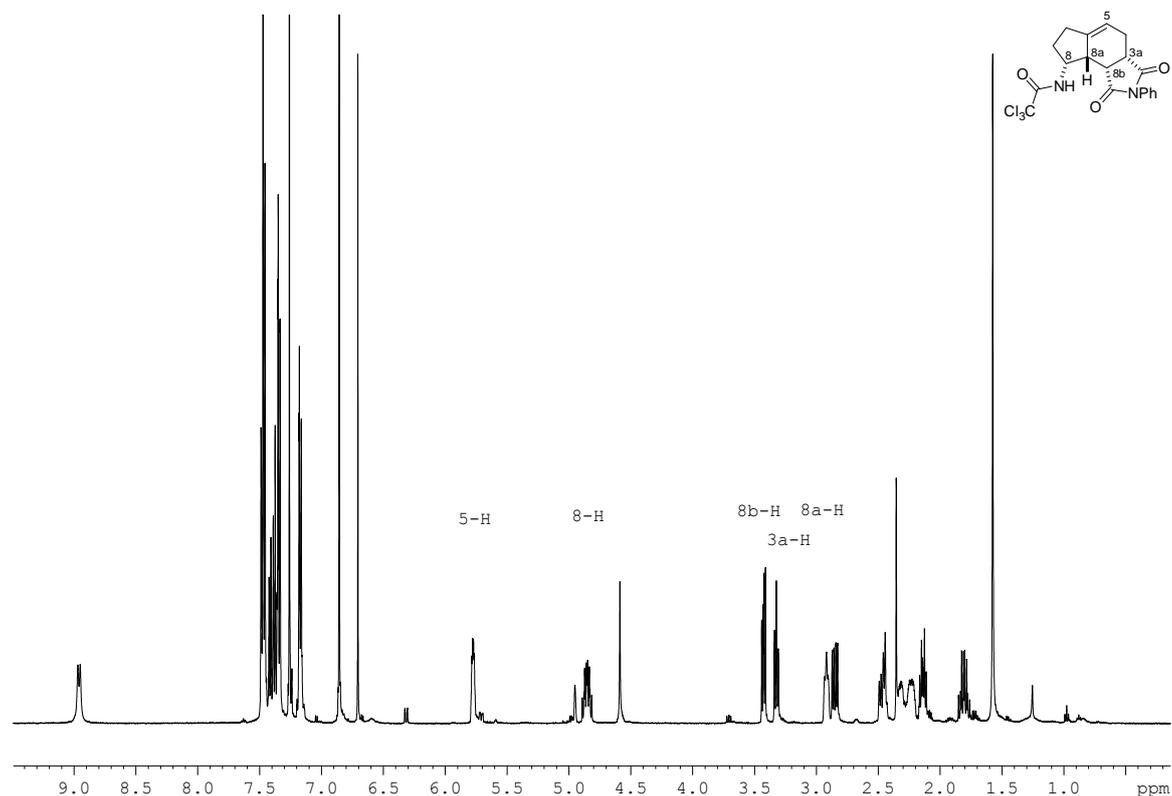
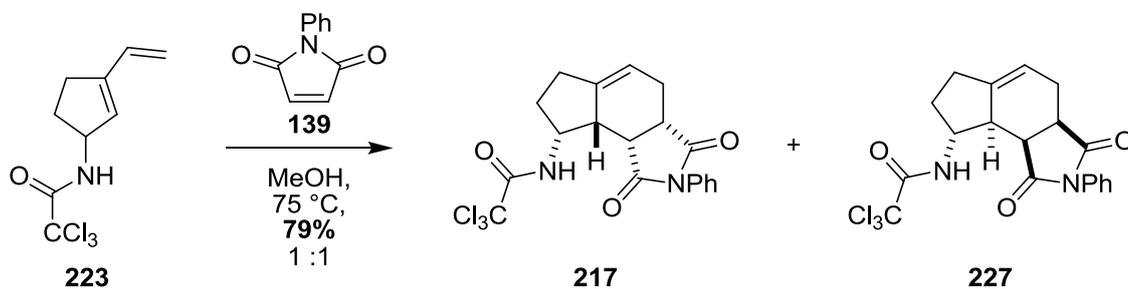


Figure 9- ^1H NMR of the crude reaction mixture of the Diels-Alder reaction between 1,3-diene **223** and *N*-phenyl maleimide **139**

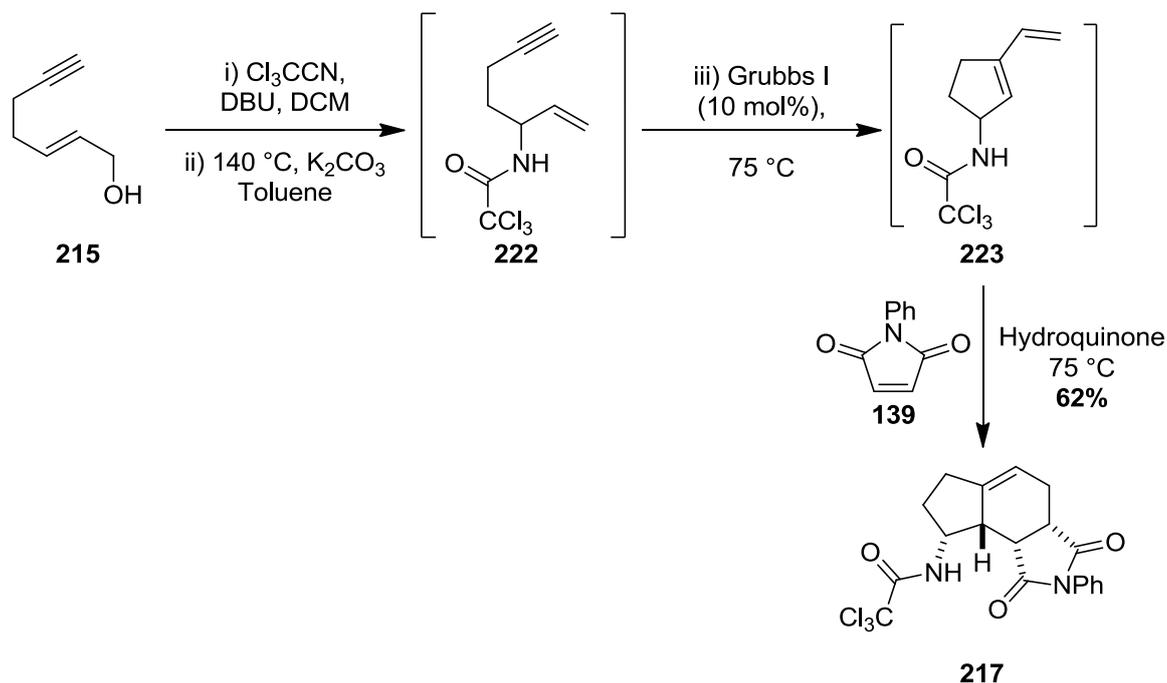
The analogous reaction between *N*-phenyl maleimide **139** and 1,3-diene **223** was carried out using methanol as the solvent (Scheme 72). It was found that once again methanol perturbed the hydrogen bonding directing effect forming both diastereomers in a 1:1 ratio with a combined yield of 79%. The relative stereochemistry of *anti*-product **227** was again confirmed by NOE studies showing no NOE between the hydrogen atoms on the C-8 and C-8a positions (Appendix 1).



Scheme 72- Diels-Alder reaction between 1,3-diene **223** and *N*-phenyl maleimide **139**

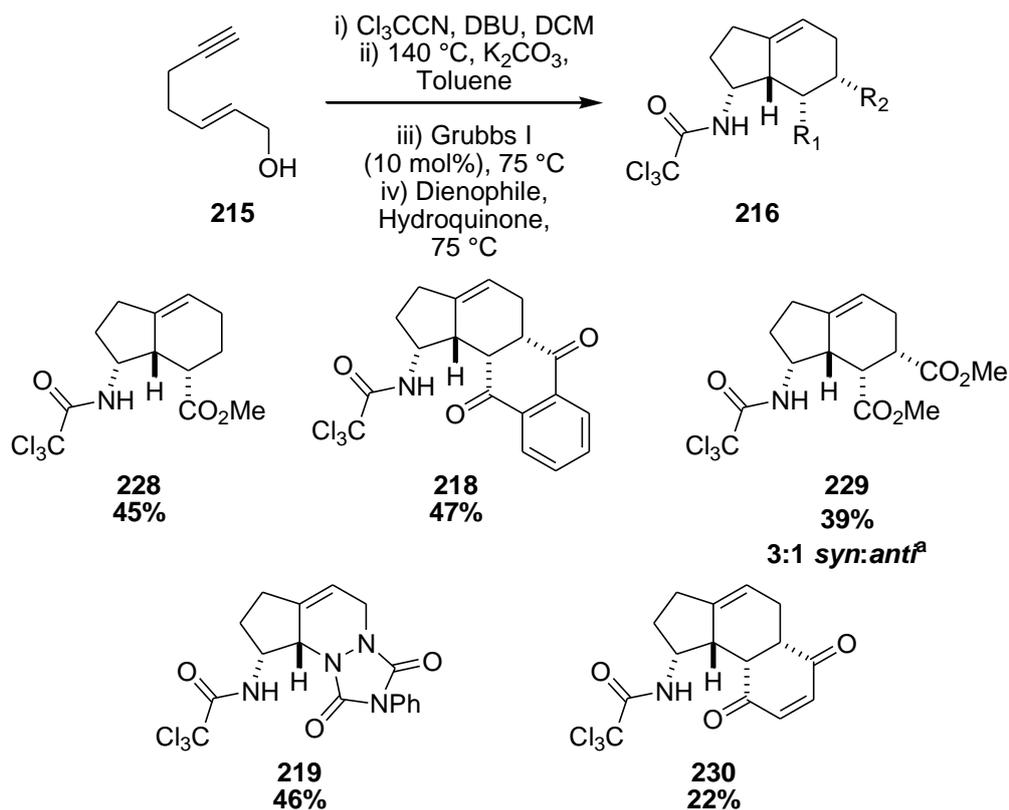
The Diels-Alder reaction was then incorporated into the one-pot process to attempt the synthesis of polycycle **217** from allylic alcohol **215** (Scheme 73). The one-pot process was carried out as previously described with rigorous monitoring to ensure each reaction went

to completion. Using these conditions, the amino-substituted bicyclo[4.3.0]nonane **217** was isolated in a 62% yield as a single diastereomer.



Scheme 73- One-pot process for the synthesis of polycycle **217**

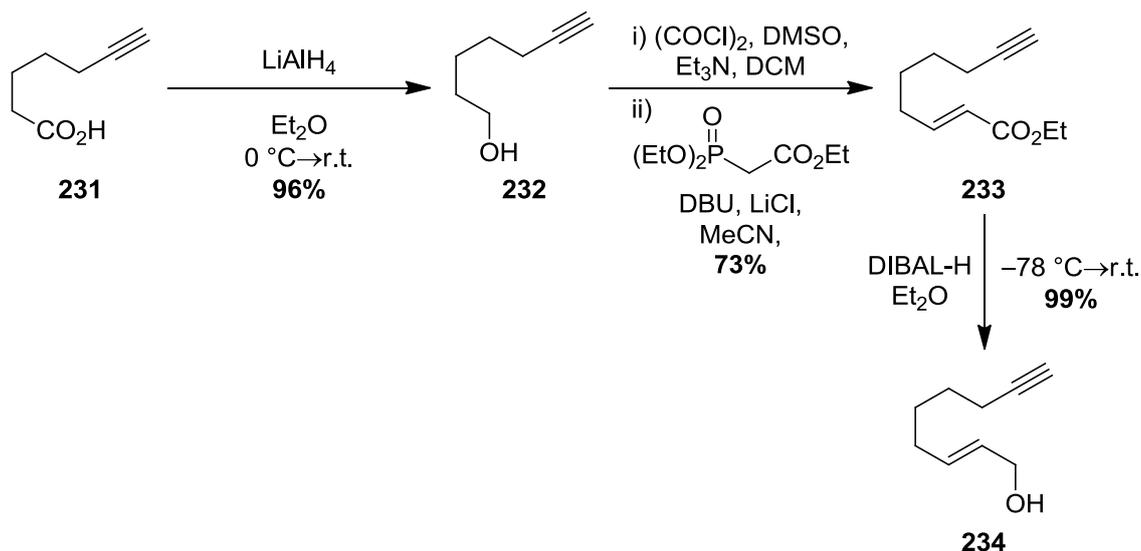
A range of dienophiles were also incorporated into the one-pot process (Scheme 74). It was gratifying to find that the bicyclo[4.3.0]nonane **228** was formed not only as a single diastereomer but also as a single regioisomer in a modest yield. Where quinones were used as dienophiles, it was found that the resulting adducts **218** and **230** did not undergo oxidation as observed with the 6,6-bicyclic analogues. However, tricycle **230** was formed in a low yield which is attributed to the oxidation of this compound upon work-up. The Diels-Alder products formed from the reaction of 5-membered dienes and 1,4-naphthoquinone **205** have been found to be more stable than their 6-membered counterparts as reported in the literature.^{7,108,111} All polycycles isolated from the one-pot process formed predominantly as the *syn*-diastereomer in greater than 16:1 based on the ^1H NMR spectra of the crude reaction mixtures. For compound **229**, it was found that the *anti*-diastereomer was also formed in significant quantities. This may be due to the Diels-Alder reaction requiring a slightly higher temperature than the other dienophiles as the reaction had to be heated to 111 °C. Heterocycle **219** was also formed in a modest yield using this one-pot process as a single diastereomer. NOE studies were again carried out on all products to confirm their relative stereochemistry (Appendix 1).



Scheme 74- Library of bicyclo[4.3.0]nonane generated from allylic alcohol **215**. ^a Reaction carried out at $111\text{ }^\circ\text{C}$

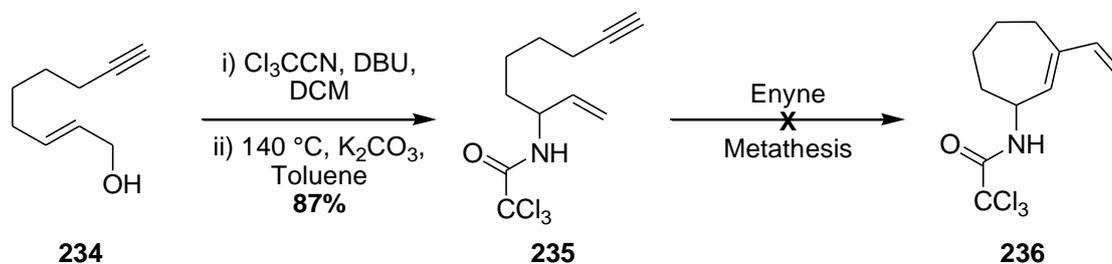
2.1.8 Attempted formation of the 7-membered cyclic 1,3-diene

Another aim of this project was the application of the one-pot process for the synthesis of bicyclo[5.4.0]undecanes. To achieve this, corresponding allylic alcohol **234** was first synthesised. Commercially available 6-heptyn-1-oic acid **231** was reduced using lithium aluminium hydride, forming alcohol **232** in a 96% yield, with no reduction of the alkyne being observed (Scheme 75).¹¹² Allylic alcohol **234** was synthesised using the previously developed reaction sequence in good yield.



Scheme 75- Synthesis of allylic alcohol **234**

The thermal Overman rearrangement was then applied to allylic alcohol **234** forming the corresponding enyne **235** in good yield (Scheme 76). A RCEYM reaction was then attempted using 1,8-enyne **235**. A range of conditions were tested, including various catalysts (GI, GII and HGII), but unfortunately no metathesis product was observed. To try and promote the metathesis reaction, the reaction was attempted at both higher and lower concentrations but to no effect.



Scheme 76- Attempted synthesis of 1,3-diene **236**

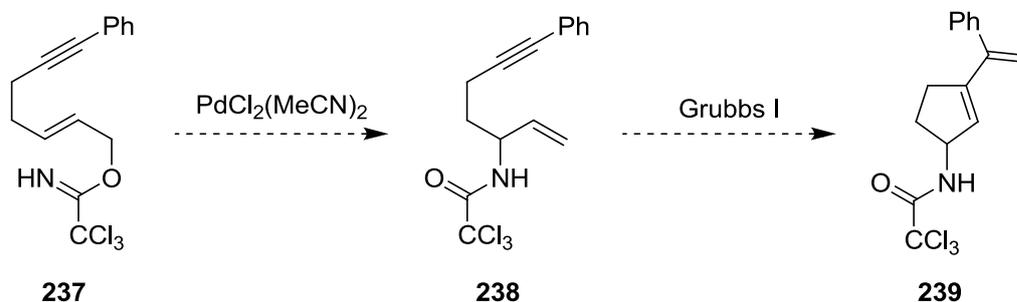
Within the literature, there have been reports of performing RCEYM on 1,8-enyne systems.¹¹³⁻¹¹⁶ However, all of these examples contained heteroatoms or geminal dimethyl groups which, due to a Thorpe-Ingold effect, promote the ring closing metathesis reaction.

2.2 Formation of C-5 substituted polycyclic compounds via a palladium(II)-catalysed Overman rearrangement

A novel one-pot multi-reaction process has been developed which comprises of an Overman rearrangement, a RCEYM reaction and a Diels-Alder reaction. This one-pot process has been used to generate a library of bicyclo[4.4.0]decanes and [4.3.0]nonanes. The products from the Diels-Alder reaction were isolated as single diastereomers due to a hydrogen bond directing effect, which in some cases led to the formation of products with up to four new contiguous stereogenic centres.

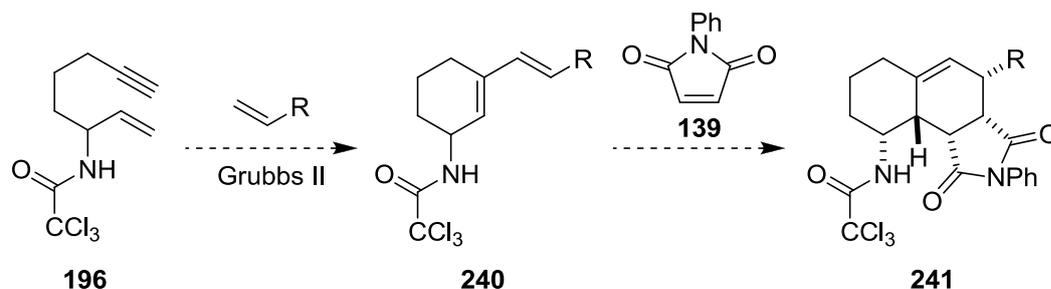
The one-pot process raised three issues.

- 1) The Overman rearrangement did not proceed as expected when Pd(II)-catalysts were used, thus work on an asymmetric Overman rearrangement would not be recommended. The sluggish reactivity was attributed to the Pd(II)-catalyst binding to the alkyne. To hinder the binding, the alkyne could be disubstituted to facilitate a more efficient Pd(II)-catalysed Overman rearrangement with the potential for the use of asymmetric catalysts (Scheme 77). Care would have to be taken as the disubstituted alkyne may then be unreactive toward RCEYM.



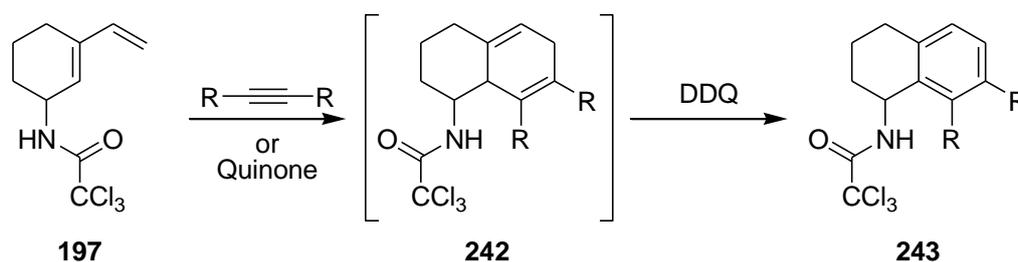
Scheme 77- Proposed palladium(II)-catalysed one-pot process

- 2) The dienes formed during the RCEYM reaction could be further functionalised. As shown in Scheme 78, this could be achieved by adding an alkene with the Grubbs catalyst to initiate a cross-metathesis reaction after the RCEYM reaction, to form substituted 1,3-diene **240**, which could undergo a Diels-Alder reaction. By adding different cross-metathesis partners the scope of the one-pot process could be expanded forming more structurally divergent multicycles which could be used as scaffolds for natural product synthesis.



Scheme 78- Proposed one-pot process involving tandem catalysis

3) It was found that Diels-Alder products of quinone dienophiles would undergo an oxidation reaction forming 1,4-dienes **242**, or in the presence of excess quinone starting material, fully aromatised products. To further optimise the yields, a stronger oxidising agent such as DDQ could be added to the reaction mixture to further promote the aromatisation process (Scheme 79). In addition, 1,4-dienes **242** could be formed by reacting 1,3-diene **197** with alkyne dienophiles. These Diels-Alder products could be aromatised to form other aromatic analogues. This will be elaborated upon in Chapter 2.5.

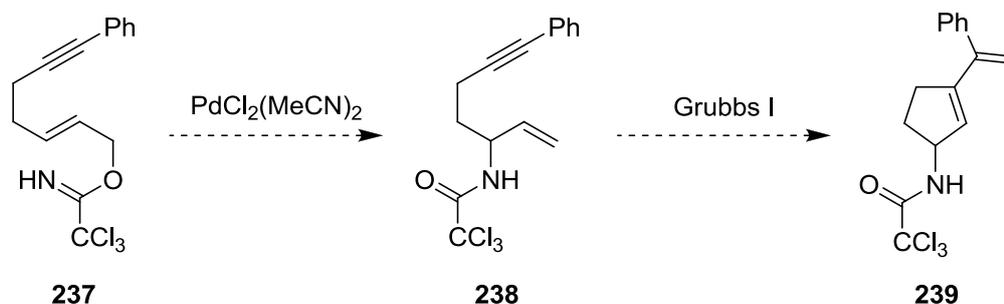


Scheme 79- Proposed one-pot process for the synthesis of aromatic scaffolds

As highlighted previously, the Overman rearrangement did not proceed as expected when Pd(II)-catalysts were used. This slow reactivity was attributed to the Pd(II)-catalyst binding to the alkyne as reported in the literature.^{1,117} The use of a palladium catalysed Overman rearrangement is important, as once developed chiral palladium catalysts could be applied to the one-pot process to form polycycles as single enantiomers.

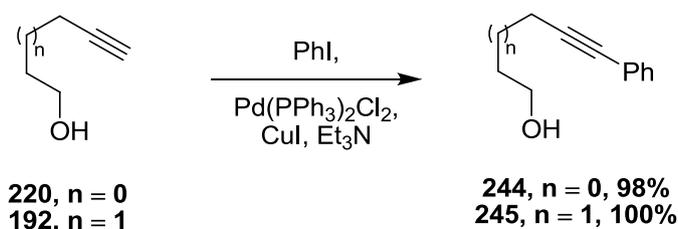
2.2.1 Development of Pd(II)-catalysed Overman Rearrangement

It was thought that using a disubstituted alkyne would hinder the binding of the palladium to the alkyne, thus allowing for a more efficient Pd(II)-catalysed Overman rearrangement. This could be achieved by attaching a phenyl group at one end of the alkyne which would hinder the catalyst access but still allow the RCEYM reaction to proceed (Scheme 80).



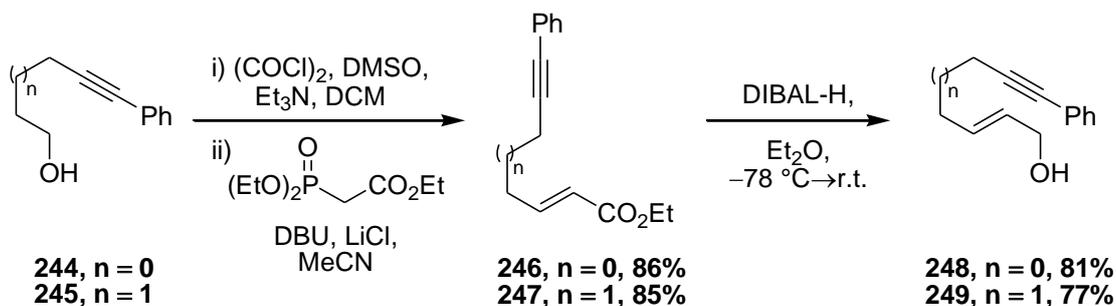
Scheme 80- Proposed synthesis of 1,3-diene **239** utilising a Pd(II)-catalysed Overman rearrangement

To install the phenyl group, a Sonogashira reaction could be employed to couple the alkyne to the phenyl group.^{118,119} This coupling reaction could be performed either before the formation of the allylic alcohols, or at the allylic alcohol stage of the route. It was decided that the Sonogashira reaction would be carried out on commercially available alkyne derived alcohols, 4-pentyn-1-ol **220** and 5-hexyn-1-ol **192**.¹²⁰ Palladium(0) is required for the Sonogashira reaction to proceed and this was generated *in situ* by reacting a Pd(II)-complex with triethylamine. Using iodobenzene as the coupling partner and copper iodide as a co-catalyst, disubstituted alkynes **244** and **245** were generated in excellent yields from the commercially available starting material and could be prepared on a multigram scale (Scheme 81).



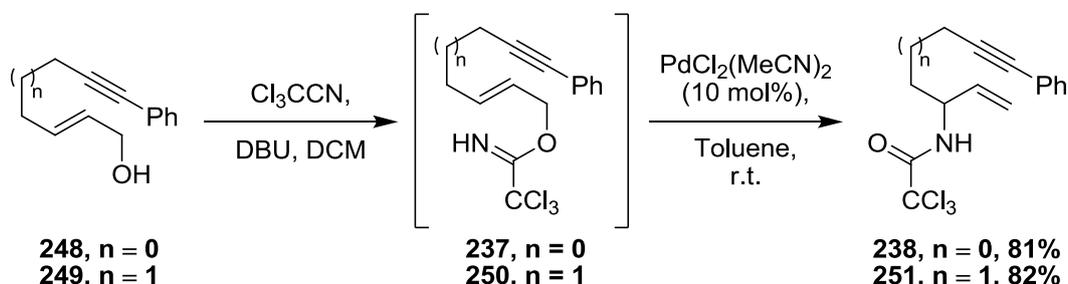
Scheme 81- Sonogashira reaction

The disubstituted alkynes were then subjected to the one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction developed previously, giving the (*E*)- α,β -unsaturated esters in excellent yields (Scheme 82). Subsequent DIBAL-H reduction, using standard conditions, gave allylic alcohols **248** and **249** in high yields.



Scheme 82- Synthesis of allylic alcohols **248** and **249**

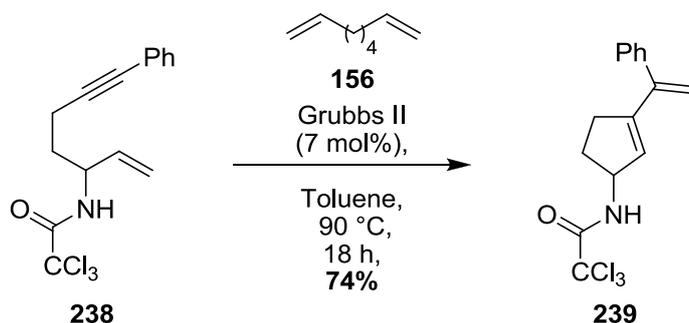
Before attempting the one-pot multi-reaction process, key steps were first optimised starting with the Overman rearrangement. Following the formation of allylic trichloroacetimidates **237** and **250**, it was found that the Overman rearrangement proceeded extremely well using 10 mol% bis(acetonitrile)palladium(II) chloride taking only 18 hours to go to completion (Scheme 83). The reaction produced allylic acetamides **238** and **251** in excellent yields over the two steps. Yields of the analogous Pd(II)-catalysed reactions with the unsubstituted alkyne were 34% and 52% for the formation of 1,6-enyne **222** and 1,7-enyne **196** respectively with the reaction taking up to 48 h to go to completion. These results strongly suggest that the coordination of the Pd(II)-catalyst to the alkyne was hindering the previous Pd(II)-catalysed Overman rearrangements.



Scheme 83- Pd(II)-catalysed Overman rearrangement

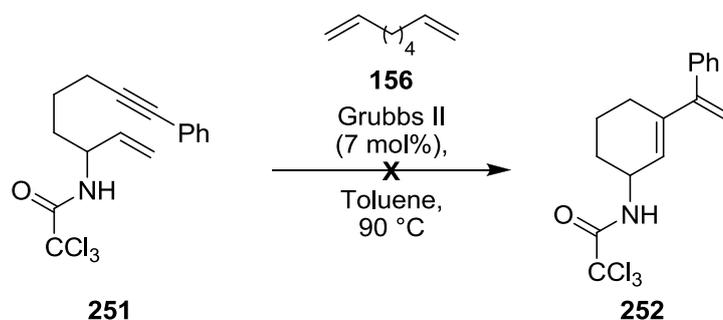
Attention then focussed on the RCEYM reaction of 1,6-enyne **238**. As expected, using Grubbs first generation catalyst for this reaction at 75 °C proceeded with a low conversion. This was also observed with Grubbs second generation catalyst. To accelerate this transformation, the reaction was repeated using 1,7-octadiene **156** and at a higher temperature (90 °C) in the presence of Grubbs second generation catalyst (Scheme 84). 1,7-Octadiene **156** undergoes a RCM reaction with the catalyst forming cyclohexene and ethylene *in situ*, which accelerates the reaction.⁷⁵ This methodology is safer than employing the conventional Mori conditions where ethylene gas, which is highly

flammable, is bubbled through the reaction mixture.⁵² With the addition of 1,7-octadiene **156**, the RCEYM reaction proceeded well, forming 1,3-diene **239** in a 74% yield.



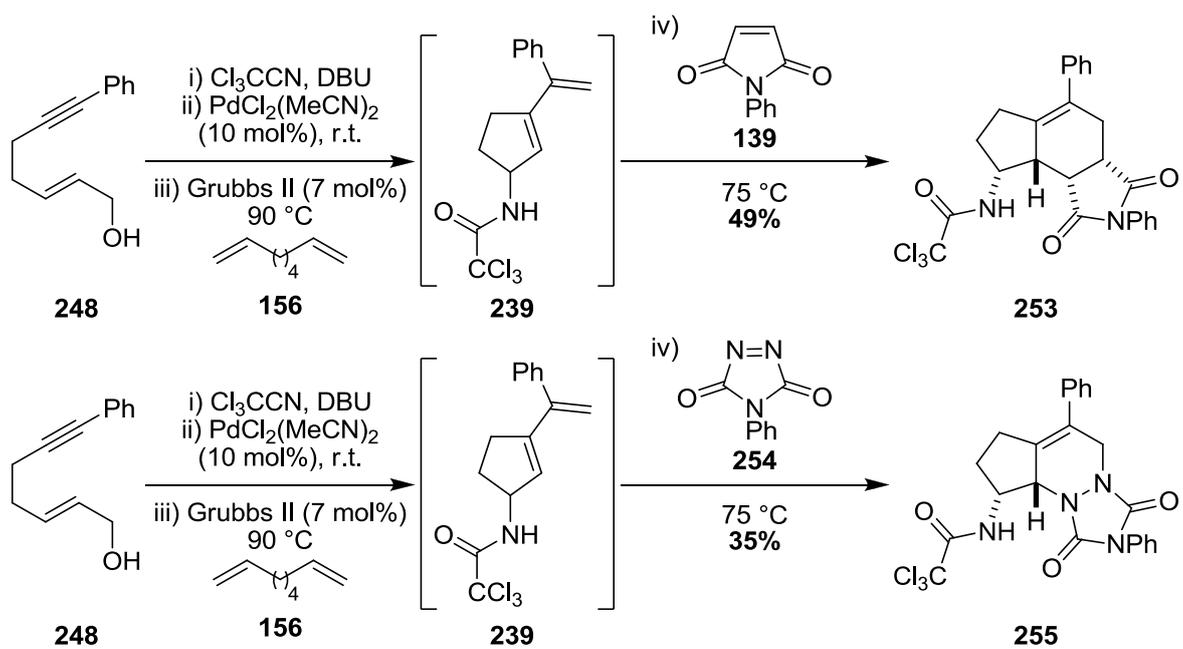
Scheme 84- RCEYM reaction using 1,7-octadiene for the formation of 1,3-diene **239**

The analogous RCEYM reaction with 1,7-enyne **251** was also attempted. However, only minimal conversion to 1,3-diene **252** was observed (Scheme 85). A range of conditions were carried out to further optimise the reaction. This involved using Hoveyda-Grubbs second generation catalyst and heating the reaction to higher temperatures. The best results were achieved when the reaction was heated to 125 °C, using Grubbs second generation catalyst in the presence of 1,7-octadiene **156**. Unfortunately, this only resulted in a 50% conversion and 1,3-diene **252** could not be separated from 1,7-enyne **251**. Due to the poor conversion this part of the project was not continued.



Scheme 85- Attempted RCEYM reaction using 1,7-octadiene **156** for the formation of 1,3-diene **252**

Using the optimised conditions for the formation of 1,3-diene **239**, a one-pot process was attempted, which included the Diels-Alder reaction. The one-pot process proceeded well using the dienophiles, *N*-phenyl maleimide **139** and *N*-phenyl-1,2,3-triazoline-3,5-dione **254**, generating amino-substituted bicyclo[4.3.0]nonanes **253** and **254** as single diastereomers in modest yields from allylic alcohol **248** (Scheme 86). The relative stereochemistry was confirmed by NOE studies showing the hydrogen bond directing effect of the Diels-Alder reaction (Appendix 1).



Scheme 86- One-pot process for the synthesis of bicyclo[4.3.0]nonanes **253** and **255**

2.3 One-pot process tandem catalytic process for the synthesis of highly substituted polycycles

Having developed two one-pot multi-reaction processes, one comprising of a thermal Overman rearrangement and the other a palladium(II)-catalysed Overman rearrangement, attention focused on the application of these processes to form biologically active compounds. Within the literature two natural products both of which had biological activity were of interest. These related natural products were netamine A and (+)-ptilocaulin which both contain an amino-substituted bicyclo[4.3.0]nonane core that could potentially be formed using the one-pot processes developed (Figure 10).^{84,121}

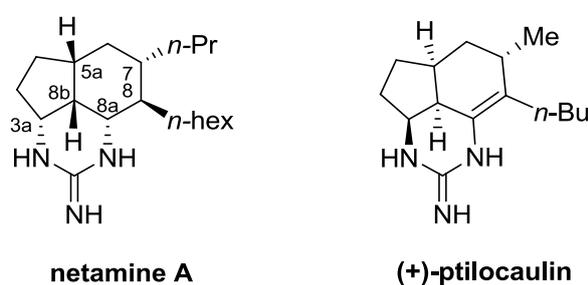
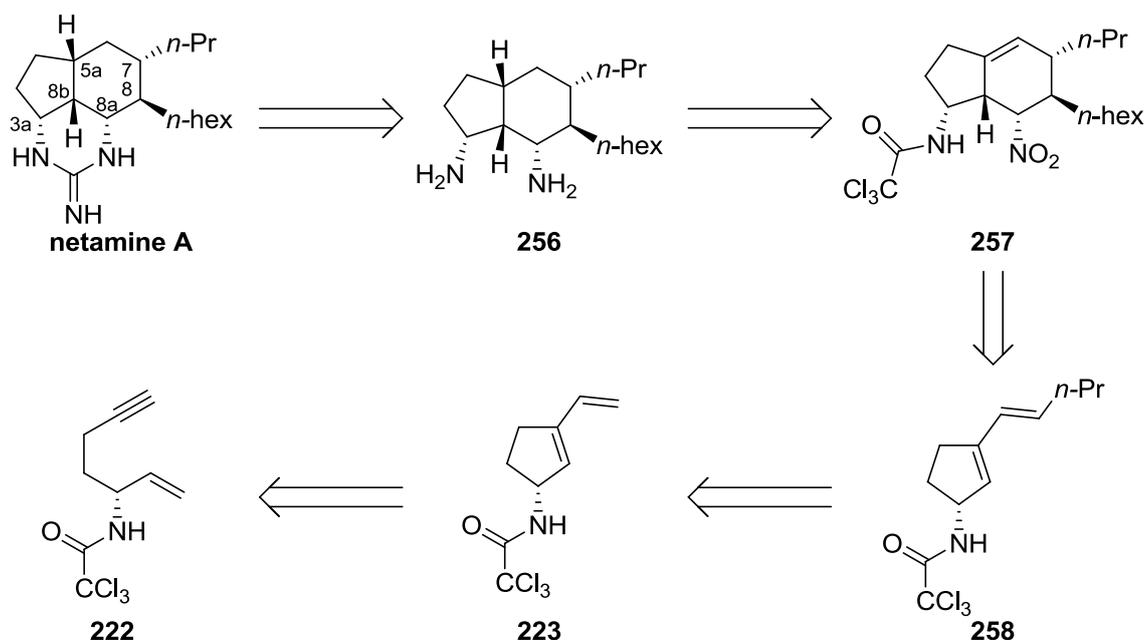


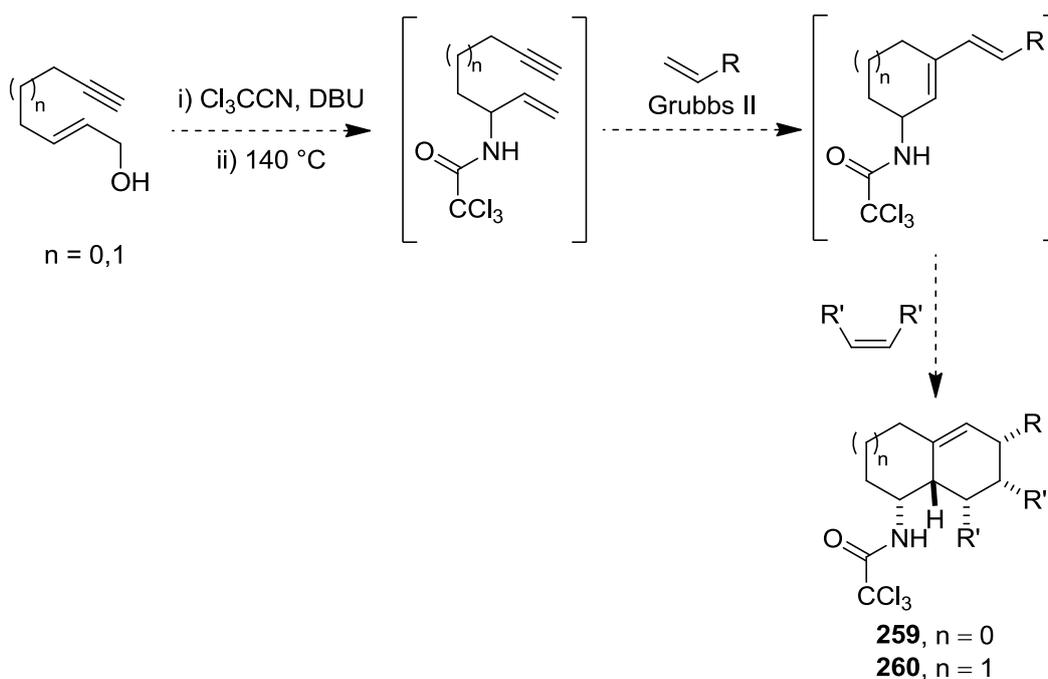
Figure 10- Structures of netamine A and (+)-ptilocaulin

Examining the structure of netamine A, the generation of the stereogenic centres could be controlled by the use of a Diels-Alder reaction and a hydrogenation reaction (Scheme 87). The synthesis of polycycles **256** and **257** will be further discussed in Chapter 2.4. The substituent in the C-7 position would then need to be part of the initial 1,3-diene **258**. To synthesise diene **258**, a cross metathesis reaction could be achieved using 1,3-diene **223** and an alkyl substituted alkene. Using the Grubbs selectivity model for cross metathesis, 1,3-diene **223** would be classed as a type II olefin and an alkyl substituted alkene would be a type I olefin, thus leading to a selective cross metathesis reaction forming the (*E*)-diene **258**.¹²² Since metathesis catalyst would be present in the reaction mixture from the previous RCEYM reaction with 1,6-enyne **222**, there would be the possibility of carrying out both reactions consecutively and with the same catalyst.



Scheme 87- Retrosynthesis of netamine A

Combining the RCEYM and cross metathesis reactions would be an example of a tandem catalytic process. Within the literature there have been many reports of this tandem catalytic process taking place to form 1,3-dienes as discussed earlier (Chapter 1.3.4).^{71-73, 123-125} By utilising a tandem catalytic process, it was proposed that the one-pot process developed previously could be further extended to include the cross metathesis step (Scheme 88). Initially the RCEYM/cross metathesis steps were investigated by using Grubbs second generation catalyst to facilitate both the RCEYM step and cross metathesis reaction forming substituted cyclic 1,3-dienes similar in structure to 1,3-diene **258**. A range of olefins and dienophiles would then be used to form a small library of highly substituted bicyclo[4.3.0]nonanes **259** and [4.4.0]decanes **260**. Following development of the one-pot process, the methodology will be applied to the synthesis of netamine A.



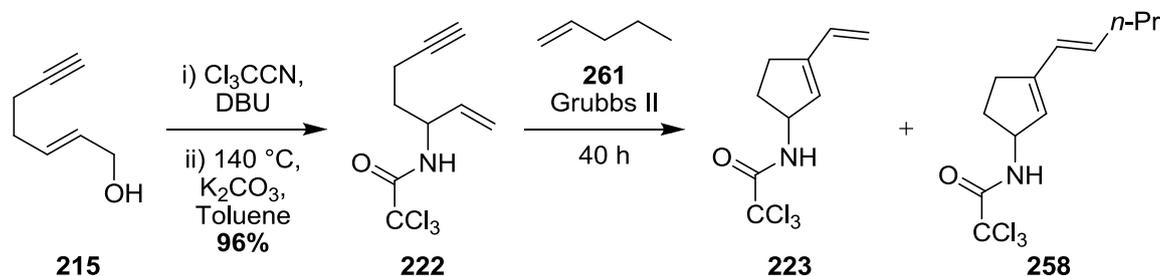
Scheme 88- Proposed one-pot tandem catalytic process

2.3.1 Synthesis of highly functionalised amino-substituted bicyclo[4.3.0]nonanes

Before proceeding with the development of the tandem catalytic process, 1,6-enyne **222** was first synthesised. This was easily achieved using the previously developed thermal Overman rearrangement conditions, obtaining 1,6-enyne **222** in excellent yield from allylic alcohol **215** (Table 3). The first tandem catalytic process that was developed was for the synthesis of 1,3-diene **258** from 1,6-enyne **222**. This was chosen due to the fact 1,3-diene **258** could be used for the synthesis of the natural product netamine A.

Initially, the previous conditions for the RCEYM were carried out using Grubbs first generation catalyst (7.5 and then 2.5 mol%) with 1-pentene **261** (5 eq. and then 2.5 eq.) added. As expected only 1,3-diene **223** was formed (Table 3, entry 1). The catalyst was then replaced with Grubbs second generation catalyst (5 and then 2.5 mol%) which promoted both the RCEYM and cross metathesis forming RCEYM/CM product **258** in a 41% yield with 16% of intermediate 1,3-diene **223** also being isolated (entry 2). It was thought that the volatility of the cross metathesis partner, 1-pentene **261**, was hindering the cross metathesis reaction at elevated temperatures, therefore the reaction was repeated at room temperature which resulted in an improved yield of 74% of 1,3-diene **258** with only a small amount of intermediate 1,3-diene **223** being isolated (entry 3). Changing the concentration of the reaction and increasing the catalyst loading was also investigated which led to no further improvement of the yield of RCEYM/CM product **258** (entries 4, 5

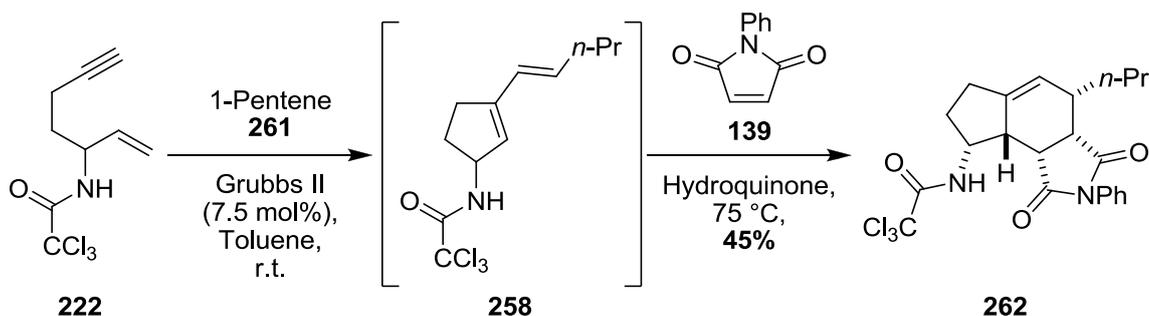
and 6). Due to Grubbs second generation catalyst being used for the cross metathesis reaction the reaction proceeded with complete selectivity for the *E*-alkene product. This was confirmed by ^1H NMR experiments where the alkene protons exhibited a coupling constant of 15.7 Hz.



Entry	Reaction Concentration (M)	Catalyst Loading (mol%) ^a	Temperature ($^\circ\text{C}$)	Yield (%) of 223	Yield (%) of 258
1 ^b	0.05	10	75	57	0
2	0.05	7.5	75	16	41
3	0.05	7.5	r.t.	9	74
4	0.025	7.5	r.t.	22	65
5	0.1	7.5	r.t.	30	53
6	0.05	10	r.t.	14	65

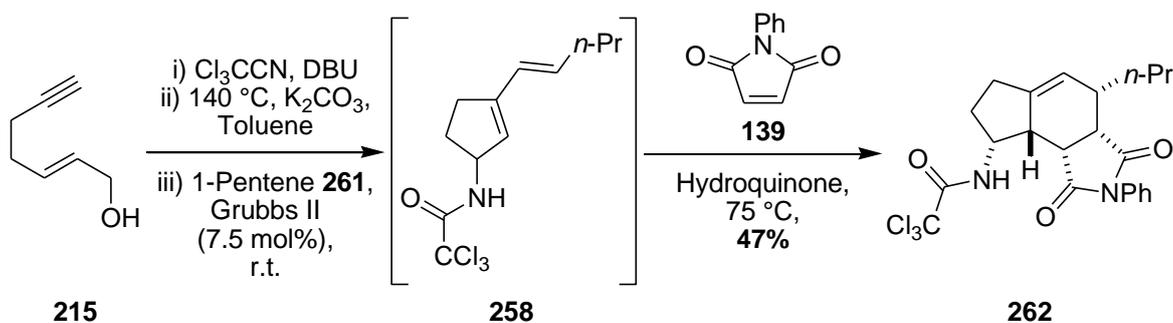
Table 3- Optimisation of the one-pot RCEYM/CM process. ^a Grubbs second generation catalyst added in two batches (5 and 2.5 mol% for entries 2–5 and 7.5 and 2.5 mol% for entries 1 and 6). ^b Grubbs first generation catalyst was used.

Having optimised the tandem catalytic process to form the 1,3-diene **258**, attention was then drawn to the addition of the Diels-Alder reaction to the one-pot process. *N*-Phenyl maleimide **139** was again chosen as the dienophile and the reaction was carried out at 75°C forming polycycle **262** in a modest yield from enyne **222** (Scheme 89). As expected, the Diels-Alder reaction went through a hydrogen bond directed *endo* transition state, with bicyclo[4.3.0]nonanes **262** being isolated as a single diastereomer with the relative stereochemistry confirmed by NOE studies (Appendix 1).



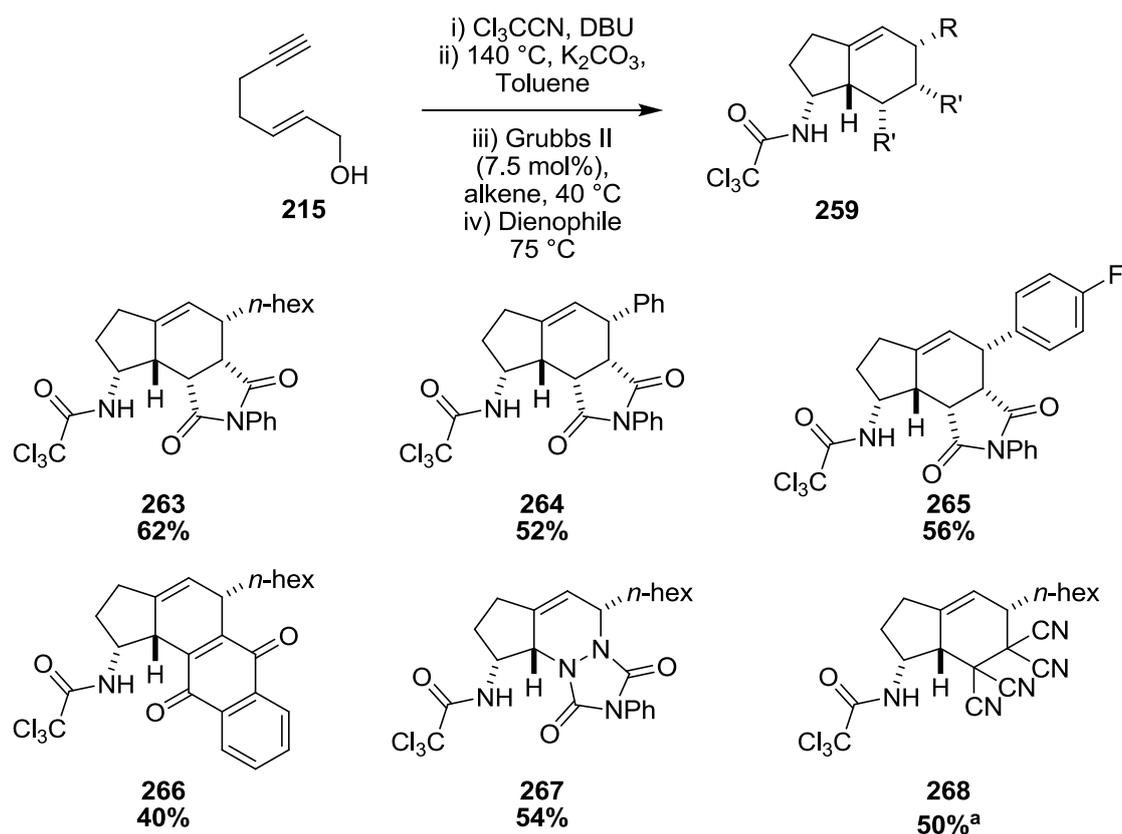
Scheme 89- One-pot three-step process for the synthesis of bicyclo[4.3.0]nonanes **262**

The development of the one-pot multi-reaction tandem catalytic process was then completed with the inclusion of the Overman rearrangement generating aminobicyclo[4.3.0]nonane **262** in a 47% yield from allylic alcohol **215** as a single diastereomer (Scheme 90).



Scheme 90- One-pot process for the formation of polycycle **262** from allylic alcohol **215**

With the one-pot process optimised, the scope of this methodology was explored. To achieve this, the one-pot process was repeated using 1-octene **166**, styrene and 4-fluorostyrene as cross metathesis partners (Scheme 91). These olefins are less volatile than 1-pentene **261**, which allowed the RCEYM/CM reaction to be carried out at slightly higher temperatures to further promote the reaction. This resulted in the formation of bicyclo[4.3.0]nonanes **263–265** in good yields over five steps. The scope of the Diels-Alder reaction was also investigated, using dienophiles 1,4-naphthoquinone **205**, 4-phenyl-1,2,4-triazole-3,5-dione **254** and tetracyanoethylene. Using these dienophiles and 1-octene **166** as the cross metathesis partner gave amino-substituted bicyclo[4.3.0]nonanes **266–268** in modest yields isolated as single diastereomers.



Scheme 91- One-pot synthesis of bicyclo[4.3.0]nonanes **263–268**. ^a Diels-Alder reaction was performed at $50\text{ }^\circ\text{C}$

The relative stereochemistry of bicyclo[4.3.0]nonanes **263–265** and **267–268** were confirmed by NOE studies, however the stereochemistry of polycycle **266** could not be confirmed as a NOE was not observed between the hydrogen atoms on the C-5 and C-11b positions. However, it can be assumed that based on the outcome of the other reactions that the hydrogen atoms in the C-5 and C-11b positions are *syn* to one another. An X-ray structure of bicyclo[4.3.0]nonane **264** was found to be crystallise in the monoclinic group $\text{P2}_1/\text{n}$ and as shown in Figure 11, the hydrogen atoms of the five stereogenic centres can clearly be seen to have a *syn*-relationship to one another (Appendix 2).

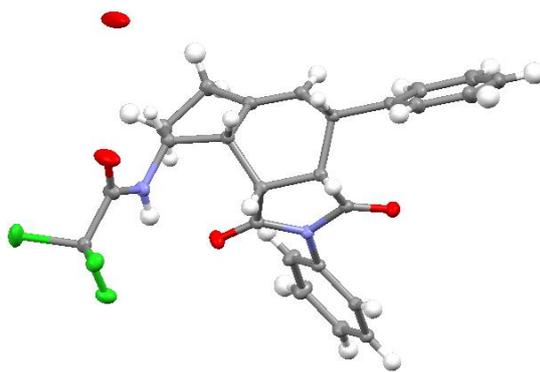
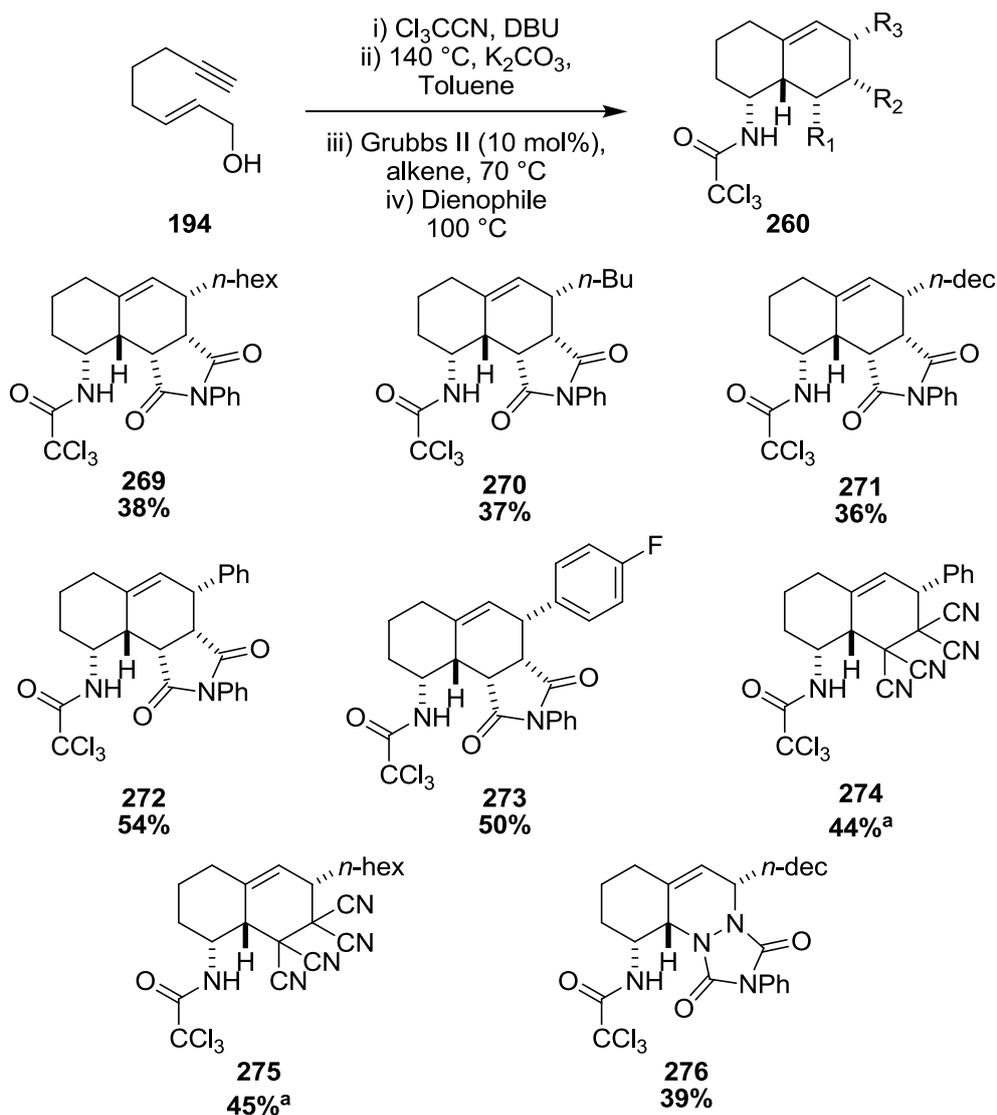


Figure 11- Ortep diagram of bicyclo[4.3.0]nonane **264**

2.3.2 Development of the one-pot process for the formation of C-6 substituted bicyclo[4.4.0]decane

With the formation of a small library of C-5 substituted bicyclo[4.3.0]nonanes complete, the focus was then turned to the preparation of a library of C-6 substituted bicyclo[4.4.0]decane systems. Initial development of the one-pot process to form these systems was carried out by an undergraduate MSci student Stuart Johnson, who found that when performing the RCEYM/CM reaction at 40 °C, conversions of less than 30% were observed, with a range of alkene cross metathesis partners. This was resolved by increasing the reaction temperature and catalyst loading to 10 mol%. Consequently, conversions of greater than 80% were achieved.¹²⁶

By using these optimised conditions, a small library was then generated. Firstly, the overall process was carried out using *N*-phenyl maleimide **139** as the dienophile and various olefinic cross metathesis partners were tested (Scheme 92). Alkyl substituted alkenes were first tested forming amino-substituted bicyclo[4.4.0]decanes **269–271** in modest yields as single diastereomers. With the more reactive cross metathesis partners, styrene and 4-fluorostyrene improved yields were observed with the corresponding compounds **272** and **273** being isolated in 54% and 50% yields respectively. Other dienophiles were then employed to further expand the scope of the multi-reaction process generating bicyclo[4.4.0]decanes **274–276** in good yields over five steps. All products from the one-pot process were isolated as single diastereomers with the ratio of *syn:anti* products in the crude reaction mixture being greater than 16:1 in favour of the *syn* product. Again NOE studies were carried out confirming the relative stereochemistry of each product (Appendix 1).



Scheme 92- One-pot synthesis of bicyclo[4.4.0]decanes **269–276**. ^a Diels-Alder reaction carried out at $50\text{ }^\circ\text{C}$

With the successful formation of a library of highly substituted bicyclo[4.3.0]nonanes and [4.4.0]decanes complete, attention was then drawn to the application of this process to form a biologically active molecule.

2.4 Total synthesis of netamine A

Netamines are a family of tricyclic compounds isolated by Kashman and co-workers from the Poeciloscleridae marine sponge *Biemna lboutei*.¹²¹ These natural products have proven to be cytotoxic and are thought to have similar biological activities to other tricyclic guanidine alkaloids, such as the mirabilin and ptilocaulin families of natural products which are cytotoxic against L1210 leukemia cells and antifungal.^{127,128}

The initial isolation of the netamine natural products produced seven tricyclic guanidine alkaloids of similar structure netamine A-G (Figure 12). The all carbon bicyclic core of netamine A-D has a saturated *cis*-fused ring system with six stereogenic centres. Netamine E-G are partially unsaturated at the *N*-heterocycle, and contain two alkyl chains *cis* to each other.

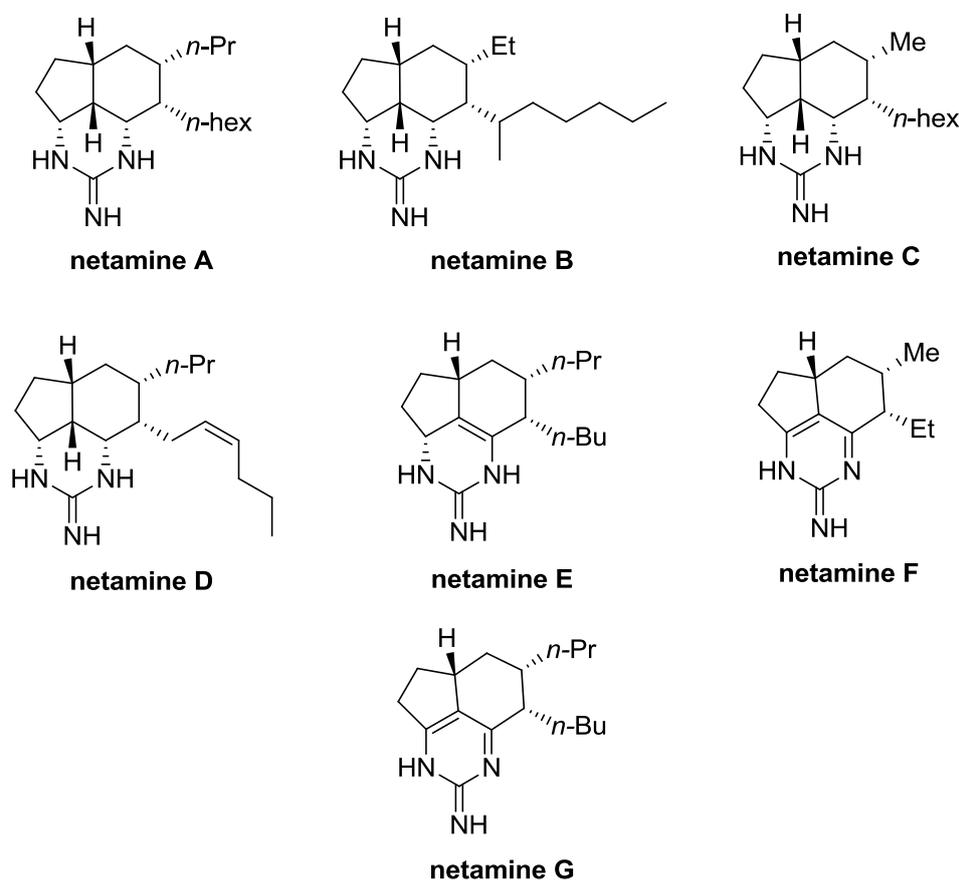
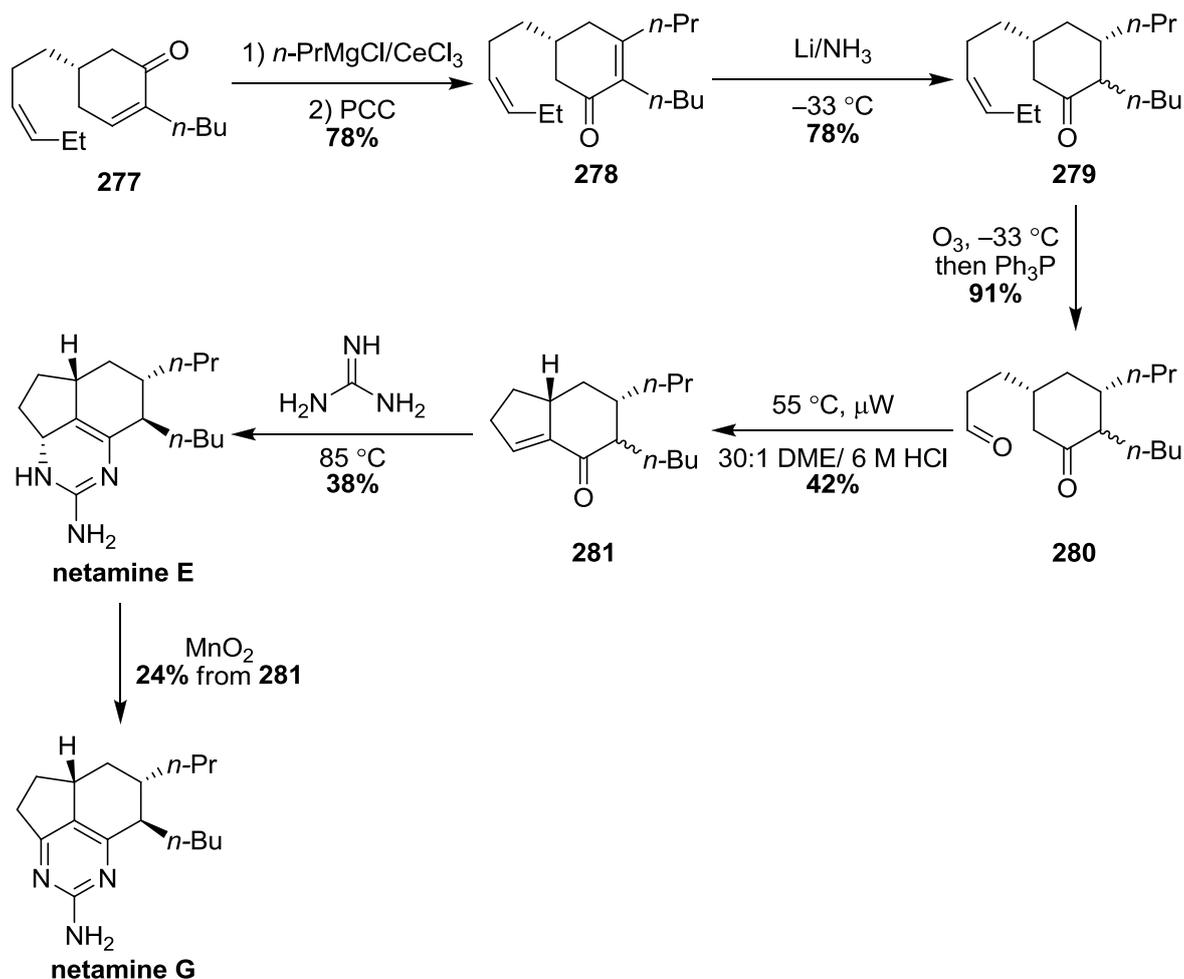


Figure 12- Structures of guanidine alkaloids netamine A-G

When working on the synthesis of the mirabilin and ptilocaulin families of natural products, Snider and co-workers found that 7-epineoptilocaulin and mirabilin B were of similar structure to netamine E and G.¹²⁹ Using similar methodology to that employed in the synthesis of mirabilin B, Snider and co-workers were able to prepare netamine E from cyclohexenone **277** in six steps through a 1,2-addition, oxidation, Birch reduction,

ozonolysis, aldol reaction and finally addition of guanidine (Scheme 93). Netamine E could then be oxidised with MnO_2 to form netamine G in a 24% yield from **281**. It was found that the synthesised netamine G matched the published spectra for the naturally occurring netamine G, in which the alkyl substituents were assigned as being *cis* in relation to one another. The optical rotations of the synthesised and naturally occurring compounds were also identical. Therefore, the structures of netamine E and G were revised to have a *trans* relationship between the alkyl groups.



Scheme 93- Synthesis of netamine G

With the stereochemistry of netamine E and G defined, Snider and co-workers revised the structures of netamine A and C using samples obtained from Kashman and co-workers.^{121,129} Snider and co-workers used NOE studies to confirm the two alkyl chains were *trans* to each other and the hydrogen atoms on the C-3a, C-5a, C-7, C-8a and C-8b positions have a *syn* relationship (Figure 13).

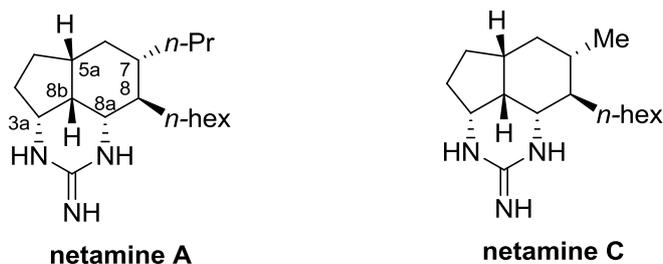
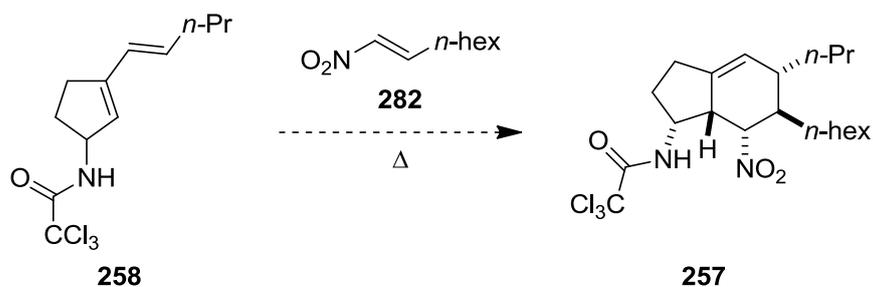


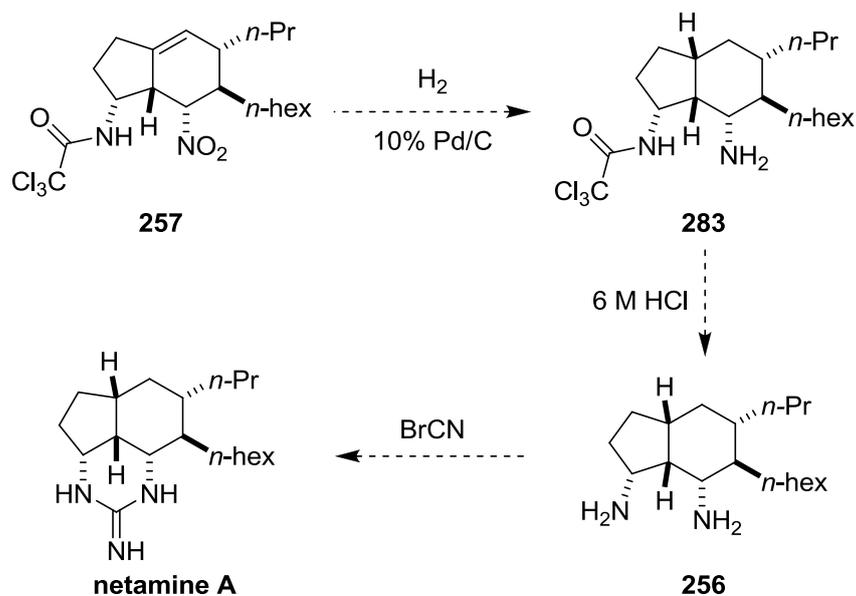
Figure 13- Revised structures of netamine A and netamine C

Using the previously developed methodology (Chapter 2.3), a synthetic route for the first racemic synthesis of netamine A was proposed. It was planned to use a one-pot process to form substituted diene **258**, followed by a hydrogen bond-directed Diels-Alder reaction involving nitroalkene **282** to generate compound **257**, incorporating five of the six stereogenic centres of the natural product netamine A (Scheme 94).



Scheme 94- Proposed Diels-Alder reaction

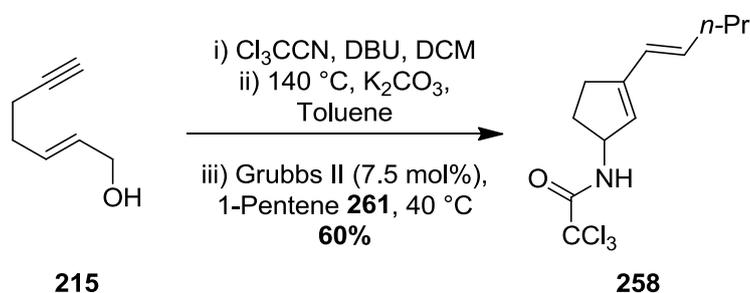
It was then proposed that hydrogenation of polycycle **257**, would form compound **283**. The hydrogenation should proceed on the least substituted and convex face of the molecule and at the same time reducing the nitro group (Scheme 95). Deprotection would follow, and finally addition of cyanogen bromide would complete the first racemic synthesis of netamine A.¹³⁰⁻¹³³



Scheme 95- Proposed synthesis of netamine A

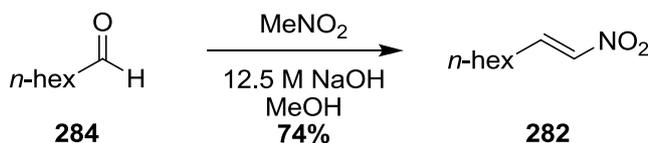
2.4.1 Towards the total synthesis of netamine A

From previous work, the substituted 1,3-diene **258** was generated from allylic alcohol **215** using a one-pot multi-step process involving the tandem catalysed RCEYM/CM process (Scheme 96).



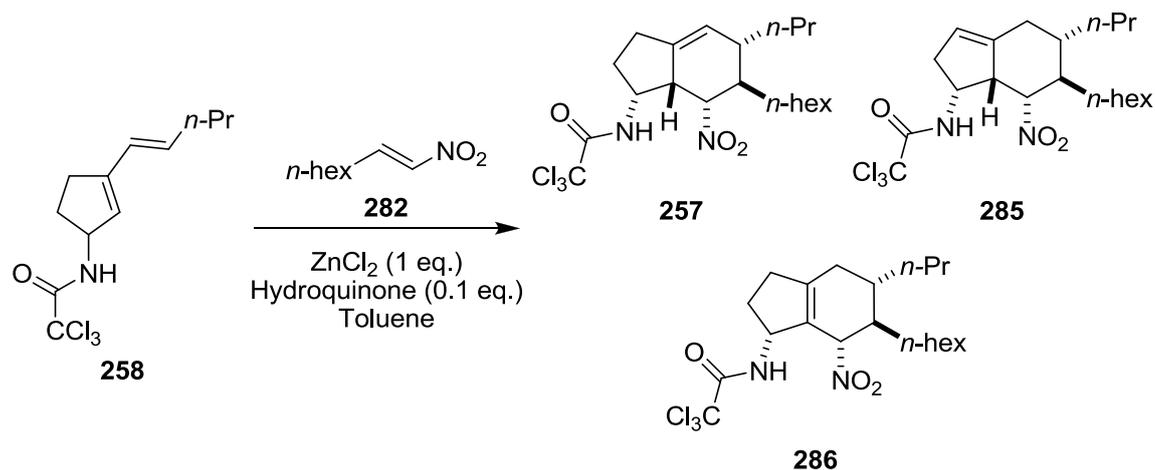
Scheme 96- Formation of 1,3-diene **258**

Having formed 1,3-diene **258**, it was proposed that by utilising a Diels-Alder reaction with a nitroalkene, bicyclo[4.3.0]nonane **257** could be generated. With the use of the nitroalkene, (*E*)-1-nitrooct-1-ene **282**, an attempt at the synthesis of netamine A could be performed. The nitroalkene synthesis was initially attempted using a procedure by Ballini and co-workers where heptaldehyde **284**, was treated with nitromethane and alumina to promote the Henry reaction and subsequent dehydration.¹³⁴ This method was unsuccessful in producing any product. Using conditions by Zhang, heptaldehyde **284** and nitromethane were stirred in the presence of sodium hydroxide, and the desired nitroalkene was formed in a good yield (Scheme 97).¹³⁵



Scheme 97- Synthesis of (*E*)-1-nitrooct-1-ene **282**

The Diels-Alder reaction was then optimised using conditions as shown in Table 4. The initial attempt was carried out using conditions developed previously for simpler alkenes, and these did not yield any product (Table 4, entry 1). However, when the Lewis acid ZnCl_2 was added and higher temperatures were used, polycycles **285** and **286** were generated (entries 2, 3, 4, 6 and 7). Both polycyclic products **285** and **286** showed that the double bond has migrated from its initial position in the product **257**. This migration was possibly instigated by the use of the Lewis acid and the higher temperatures. In the case of compound **286**, formation of the more stable tetrasubstituted alkene is likely the driving force. Both polycycles **285** and **286** could be used in the formation of netamine A as subsequent hydrogenation would still occur on the least hindered face. When the reaction was carried out with the nitroalkene **282** as the solvent, desired product **257** was formed in a 34% yield (entry 5). To further optimise this reaction, it was proposed that using ZnCl_2 would accelerate the Diels-Alder reaction and allow a lowering of the temperature which would slow the migration of the alkene. By lowering the temperature to 50 °C, an improved yield of 46% of **257** was observed, with a 28% yield of bicyclononane **285** (entry 6). Finally, lowering the temperature to 40 °C and monitoring the reaction until all starting material was consumed meant a shorter reaction time could be used, forming compound **257** in a 70% yield with only a small amount of **285** being generated (entry 7).



Entry	Conditions	Yield (%)
1 ^a	nitroalkene (2 eq.), 111 °C, 48 h	No reaction
2	nitroalkene (3 eq.), 140 °C, 72h	285 (17) + 286 (9)
3	nitroalkene (5 eq.), 160 °C, 72 h	286 (20)
4	nitroalkene (20 eq.), 111 °C, 120 h	285 (18)
5 ^{a,b}	nitroalkene (20 eq.), 80 °C, 48 h	257 (34)
6 ^b	nitroalkene (20 eq.), 50 °C, 48 h	257 (46) + 285 (28)
7 ^b	nitroalkene (20 eq.), 40 °C, 20 h	257 (70) + 285 (17)

Table 4- Optimisation of Diels-Alder reaction. ^a ZnCl_2 was not added. ^b Reactions were performed neat.

The stereochemistry of polycycle **257** was confirmed by difference NOE experiments. Positive NOEs were observed showing 1-H, 7-H and 7a-H have a *syn* relationship with each other (Figure 14). This product arises from the Diels-Alder reaction being hydrogen bond directed, and progressing via an *endo* transition state as observed with previous Diels-Alder reactions of allylic trichloroacetamides.

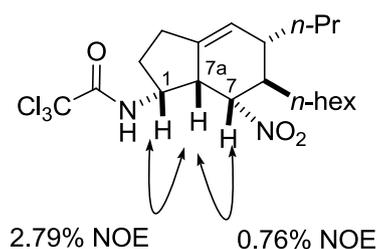
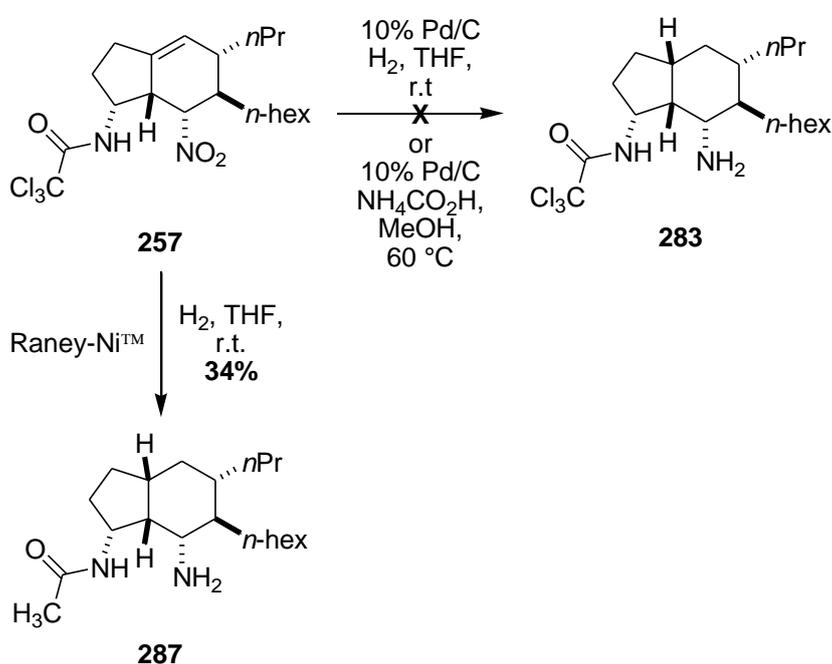


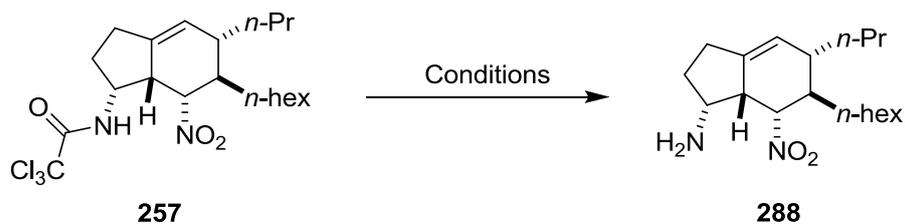
Figure 14- NOE studies of polycycle **257**

Having synthesised polycycle **257**, the hydrogenation of this compound was then investigated. By using standard hydrogenation conditions expected product **283** was not isolated (Scheme 98). However, it was observed that the starting material was being consumed, as the olefinic hydrogen on the ^1H NMR spectrum disappeared but the CHNO_2 signal remained. More forcing conditions were then carried out by using an *in situ* source of hydrogen gas, which would allow the reaction to be heated, but this proved unsuccessful.¹³⁶ Finally, Raney-NickelTM, which is often used to reduce nitro groups, was added to facilitate the hydrogenation and proved successful, providing amine **287** in a 34% yield. By using Raney-NickelTM not only were the nitro group and alkene reduced, but the trichloroacetamide was dechlorinated to form an acetyl group.



Scheme 98- Hydrogenation of polycycle **257**

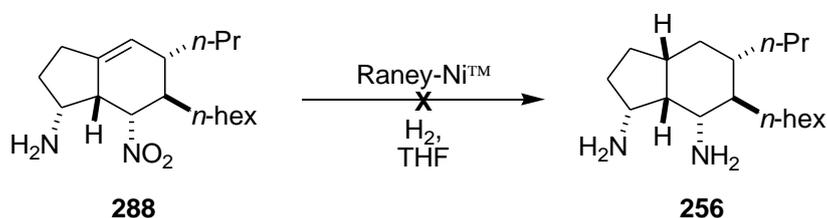
The stereochemistry of amine **287** was confirmed, as positive NOEs were observed for 1-H and 7-H. However, due to their chemical shift overlapping, an NOE could not be used to elucidate the stereochemistry of 3a-H (Figure 15). The synthesis of netamine A was continued at this stage as it was proposed that when the natural product was isolated, by comparing the ^1H NMR spectrum of the synthesised sample and the literature ^1H NMR spectra would confirm the stereochemistry of the C-3a position.



Entry	Conditions	Yield
1	2 M LiOH, MeOH, 35 °C, 72 h	No product isolated
2	6 M HCl, 60 °C, 48 h	No product isolated
3	NaBH ₄ (2 eq.), MeOH, r.t., 18 h	No reaction
4	DIBAL-H (2.2 eq.), Et ₂ O, -78 °C→r.t., 3 h	No reaction
5	DIBAL-H (6 eq.), Et ₂ O, -78 °C→r.t., 3 h	58%

Table 5- Conditions for deprotection

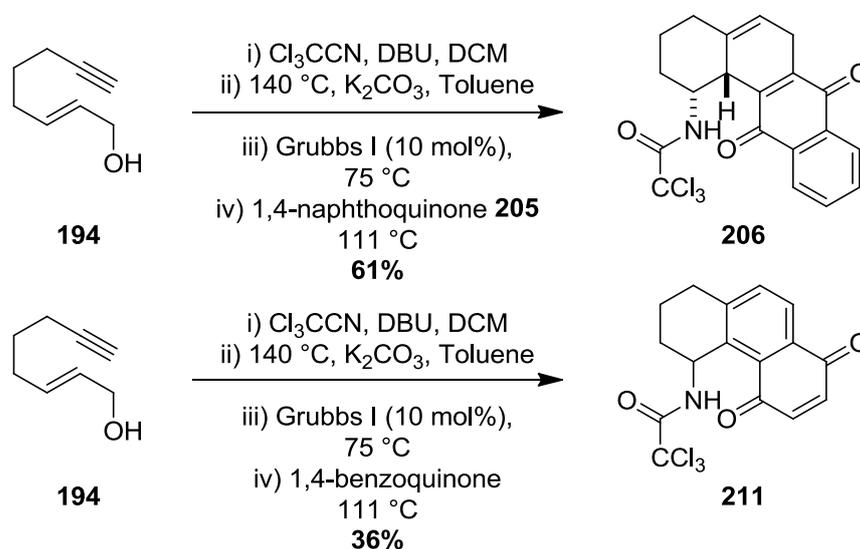
The next stage was for amine **288** to undergo the hydrogenation reaction. Using Raney-Nickel™ conditions employed previously proved unsuccessful in forming the diamino nonane **256** (Scheme 100). It was clear from the ¹H NMR spectrum of the crude reaction mixture that the reduction of the nitro group was complete, however, peaks were observed in the olefinic region of the spectrum indicating that the alkene was not reduced. This was surprising, as previously the Raney-Nickel™ was able to reduce the nitro group and the alkene. Another attempt was made by using more equivalents of Raney-Nickel™ and a longer reaction time, but this also proved unsuccessful. Due to time constraints no further reactions were performed on this project.



Scheme 100- Attempted hydrogenation using Raney-Nickel™

2.5 Formation of partially saturated tetralins and indanes

During the initial development of the one-pot process involving Overman rearrangement, RCEYM and Diels-Alder reaction, certain examples displayed unexpected reactivity. This reactivity was observed when the 1,3-dienes were reacted with quinones in the Diels-Alder reaction. When 1,4-naphthoquinone **205** was used, the partially aromatised 1,4-diene **206** was formed in good yield from allylic alcohol **194** (Scheme 101). A more oxidised product was observed with 1,4-benzoquinone, with tricyclic tetralin **211** being isolated in a modest yield. This partial and complete aromatisation was attributed to the presence of excess quinone and air in the reaction mixture.^{66,108} Interestingly, the corresponding indane systems did not display the same reactivity, with aromatisation only being observed after extended reaction times.



Scheme 101- One-pot process using quinone dienophiles

To further improve the yields of this one-pot process, the focus of our interest was on refining the aromatisation step by using a stronger oxidant to allow a more general procedure which would allow access to other aromatic motifs. By using a Diels-Alder reaction followed by aromatisation as described previously, it was envisaged that C-1 amino-substituted indane and tetralin scaffolds could be generated with ease from the corresponding 1,3-dienes.^{67,68} C-1 Amino-substituted indane and tetralins are of interest as they display a wide range of pharmacological activity. (+)-Sertraline (ZoloftTM) is used as an antidepressant, rasagiline (AzilectTM) is used for the treatment of Parkinson's disease and indinavir (CrixivanTM) is being used in the therapy of HIV and AIDS (Figure 16).¹³⁸⁻¹⁴⁰

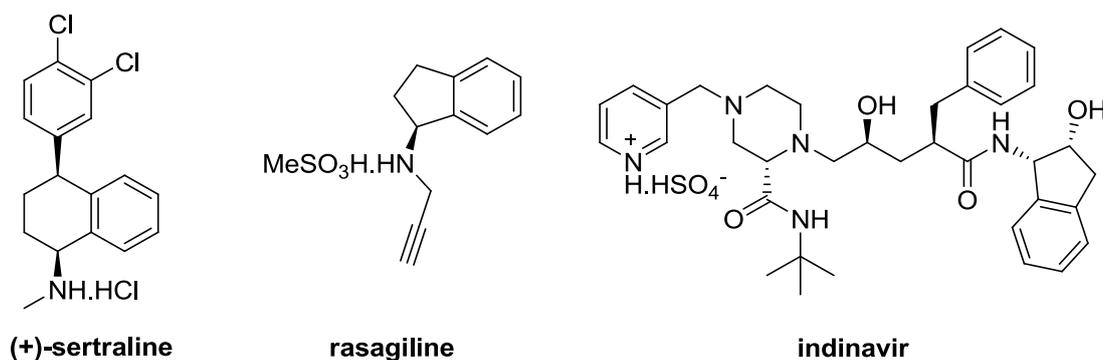
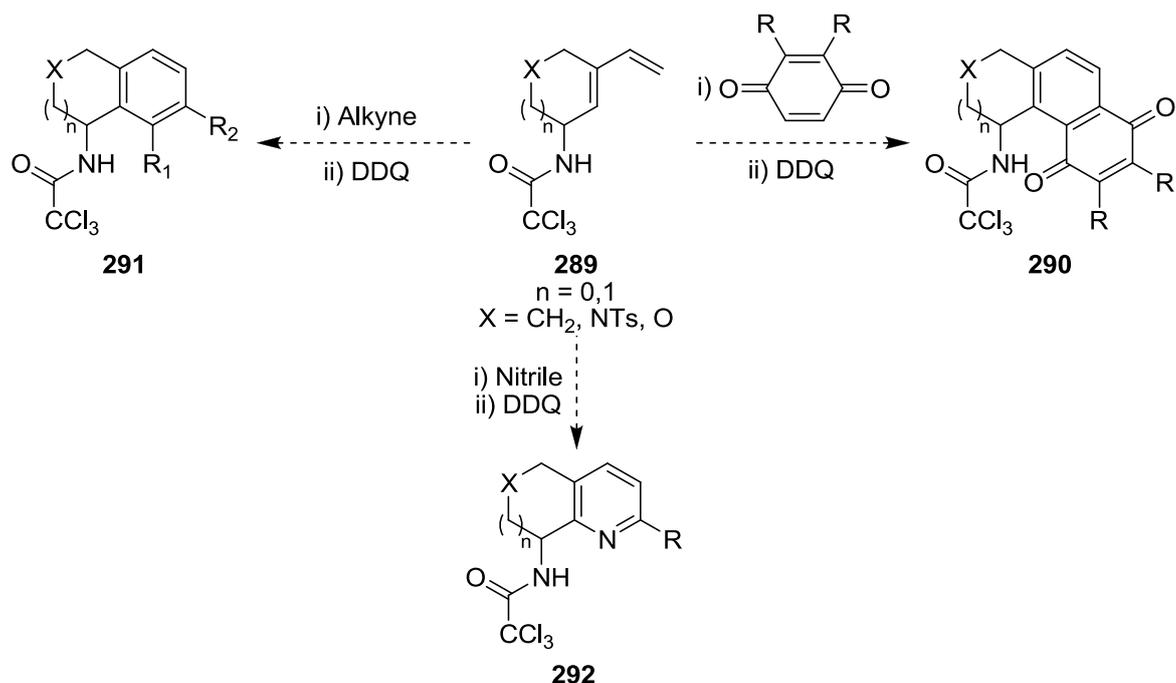


Figure 16- Structures of (+)-sertraline, rasagiline and indinavir

Current approaches towards these compounds involve a stepwise construction of the carbocyclic ring systems via Friedel-Crafts alkylation/acylation followed by reductive amination to introduce the amino moiety.^{141,142} Other methods also focus on the formation of the partially saturated ring system, which include a CAN-mediated Ritter-type cyclodimerisation and an aryne Diels-Alder reaction with acyclic dienes.^{143,144} These approaches, although elegant, are generally limited to a particular bicyclic ring system and are restricted in scope by the starting material.

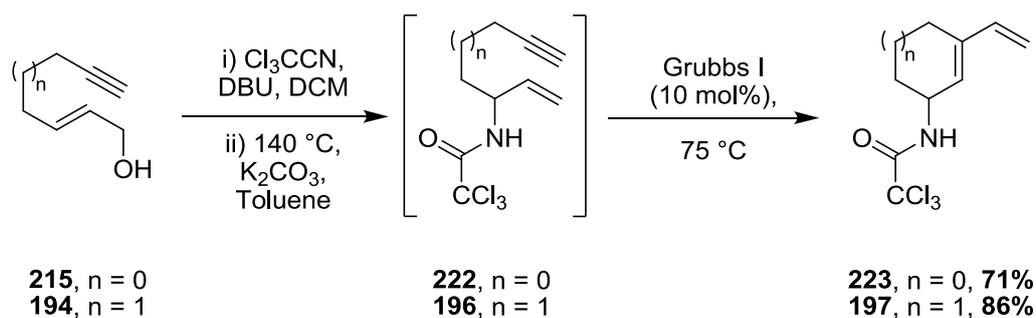
To further expand on previous methodologies, it was envisaged that by using 1,3-dienes, generated from a one-pot process, a flexible approach for the generation to these bicyclic motifs could allow late stage introduction of various aryl ring substitutions. This approach would use two consecutive one-pot multi-bond forming processes. The first process will form 1,3-dienes **289** from simple allylic alcohols. It was envisaged that the 1,3-dienes **289** generated, would contain a heteroatom further expanding the scope. As shown in Scheme 102, a Diels-Alder reaction with commercially available quinones and alkynes could be used to prepare a variety of carbocyclic aromatic scaffolds **290** and **291**, respectively. It was also envisaged that by using nitriles, the resulting products could be aromatised to form heteroaromatic scaffold **292** to further diversify the set of compounds generated using this methodology. Once the methodology was developed an attempt would be made in achieving a one-pot five step process.



Scheme 102- Proposed one-pot process to form various amino-substituted aromatic motifs

2.5.1 Synthesis of heterocyclic 1,3-dienes

Before focusing on the formation of the aromatic motifs, attention was concentrated on a concise method for generating 1,3-dienes. As discussed in Chapter 2.1, 5- and 6-membered cyclic 1,3-dienes **223** and **197** were isolated in good yields over a three step process from the corresponding allylic alcohol (Scheme 103).



Scheme 103- Three step one-pot synthesis of carbocyclic 1,3-dienes

Focus then moved to the incorporation of a heteroatom into the ring of the 1,3-diene. It was envisaged that both nitrogen and oxygen 1,3-diene analogues, such as **293** and **294** (Figure 17) could be easily generated using a similar approach as described above.

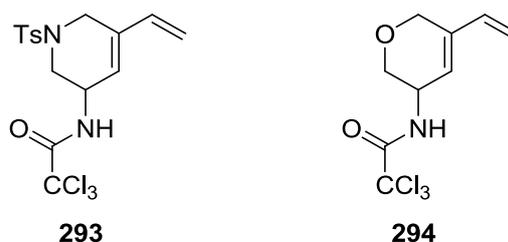
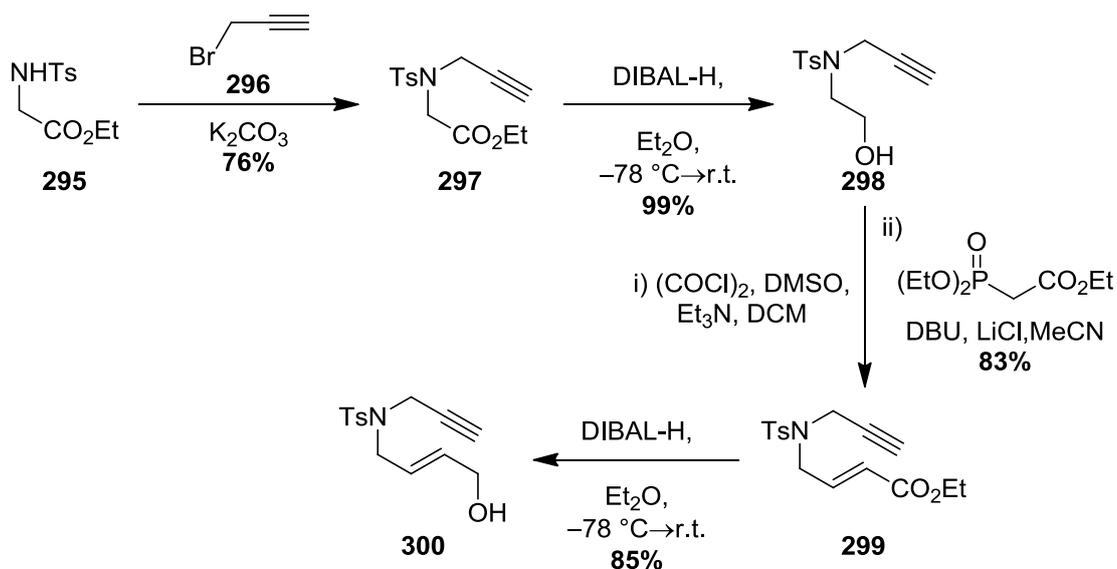


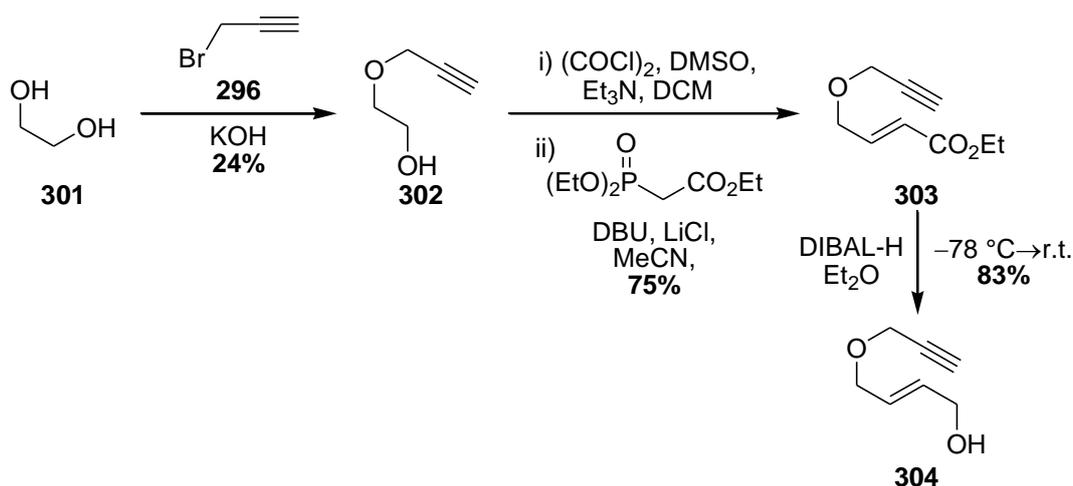
Figure 17- Proposed heterocyclic containing 1,3-dienes

The first part of the formation of these 1,3-dienes was the synthesis of the allylic alcohol precursors. The nitrogen containing allylic alcohol **300** was synthesised by first treating tosylated ethyl glycine **295** with propargyl bromide **296** to form the propargylated product **297** in good yield (Scheme 104). DIBAL-H reduction of ethyl ester afforded alcohol **298** which was then subjected to a one-pot Swern Horner-Wadsworth-Emmons reaction to generate the α,β -unsaturated ester **299** in excellent yield as the *E*-isomer. Finally, a DIBAL-H reduction was used to form allylic alcohol **300** also in excellent yield.



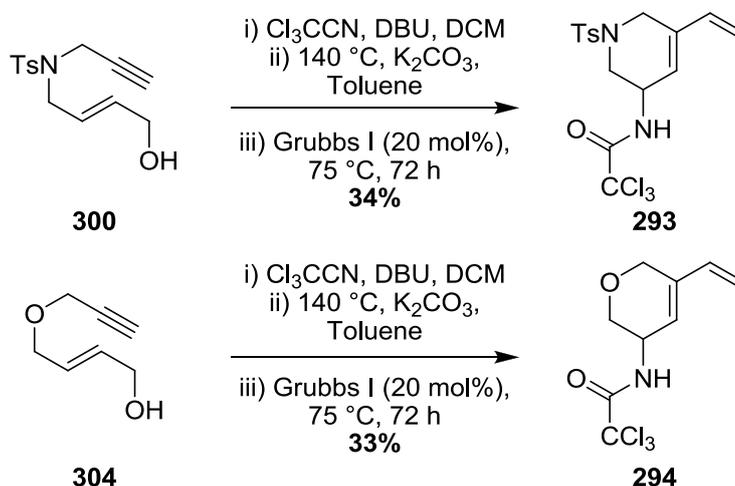
Scheme 104- Synthesis of allylic alcohol **300**

The corresponding oxygen containing allylic alcohol **304** was generated using a similar approach. Firstly, reacting ethylene glycol **301** with propargyl bromide **296** afforded the mono-propargylated alcohol in a 24% yield (Scheme 105). This low yield is attributed to the formation of the di-propargylated product, however, this result was consistent with the yield given in the literature for this reaction.¹⁴⁵ Alcohol **302** was then subjected to the one-pot Swern Horner-Wadsworth-Emmons reaction followed by DIBAL-H reduction to form the oxygen containing allylic alcohol **304** in good overall yield for these steps.



Scheme 105- Synthesis of allylic alcohol **304**

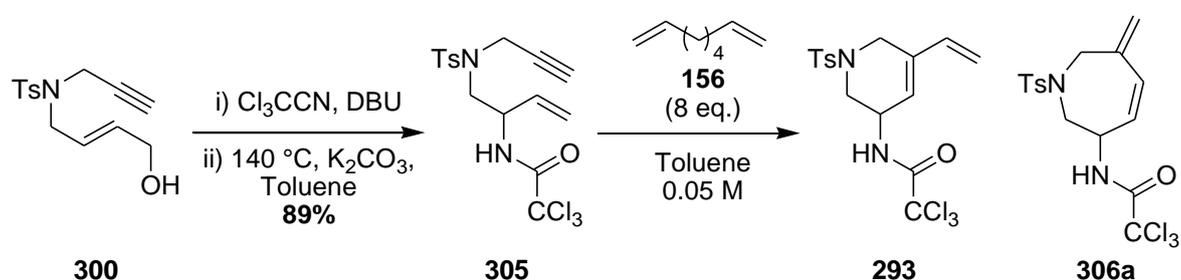
With the heteroatom containing allylic alcohol precursors synthesised, the one-pot process to form the 1,3-dienes was investigated. Using the previously optimised conditions for the synthesis of **197** and **223**, 1,3-dienes **293** and **294** were isolated in poor yields over the three steps. To achieve even modest yields, longer reaction times and higher catalyst loading were required for the RCEYM step (Scheme 106). These poor results were attributed to the Grubbs first generation catalyst not being robust enough to undergo a RCEYM reaction, with coordination to the additional heteroatom being a possible issue.



Scheme 106- Initial one-pot process for the synthesis of 1,3-dienes **293** and **294**

To resolve the issues of long reaction times and the high catalyst loading, the reaction was repeated using other Grubbs catalysts. Firstly, 1,7-enyne **305** was generated using previously optimised thermal Overman rearrangement conditions to furnish the desired product in excellent yield from allylic alcohol **300**. By using Grubbs and Hoveyda-Grubbs second generation catalysts, the problem with the catalyst loading was solved as only 10 mol% of catalyst was required for the reaction to go to completion, however poor isolated

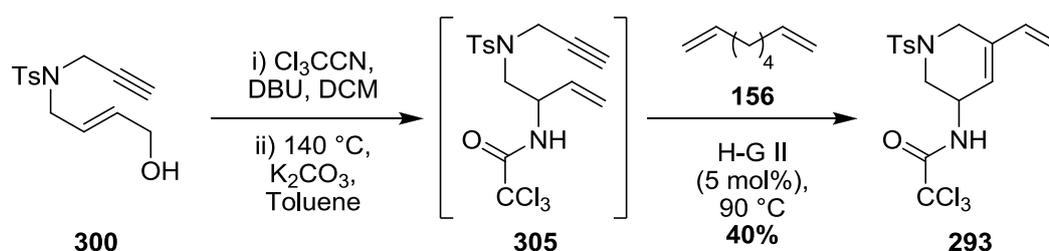
yields of 1,3-diene **293** were still obtained (Table 6, entry 1 and 2). At this point in the project a paper in the literature, which reported the *in situ* generation of ethylene using 1,7-octadiene **156** and a metathesis catalyst, was published. It was reported by Fustero and co-workers that by adding 1,7-octadiene **156** to a reaction mixture of Hoveyda-Grubbs second generation catalyst would generate ethylene *in situ* and the resulting methane-activated catalyst intermediate allowing an accelerated RCEYM reaction.⁷⁵ By using this method of generating ethylene *in situ*, enyne **305** was subjected to these RCEYM reaction conditions with the addition of 1,7-octadiene **156** affording desired 1,3-diene **293** in a 37% yield, with a lower catalyst loading being achieved as compared to Scheme 106 (entry 3). Changing the catalyst to Grubbs second generation catalyst improved the yield slightly, lowered the catalyst loading and reaction time, however, 1,3-diene **306a** was also formed (entry 4). 1,3-Diene **306a** is the *endo*-product from the RCEYM reaction which occurs when the ruthenium attaches to the external carbon of the alkyne that then ring closes to form the seven membered ring as discussed in Chapter 1.3.2.⁵⁵ This product was deduced as it had two singlet peaks in the olefinic region of the ¹H NMR spectrum characteristic of geminal methylene hydrogen atoms. Finally, Hoveyda-Grubbs second generation catalyst was tested and using this catalyst, desired 1,3-diene **293** was isolated in good yield with a quantity of the *endo*-diene **306a** also being formed (entry 5).



Entry	Conditions	Yield (%) of 293	Yield (%) of 306a
1 ^a	Grubbs II (10 mol%), 75 °C, 72 h	39	0
2 ^a	H-G II (10 mol%), 75 °C, 96 h	25	0
3	Grubbs I (10 mol%), 75 °C, 72 h	37	0
4	Grubbs II (5 mol%), 90 °C, 24 h	45	15
5	H-G II (5 mol%), 90 °C, 24 h	67	23

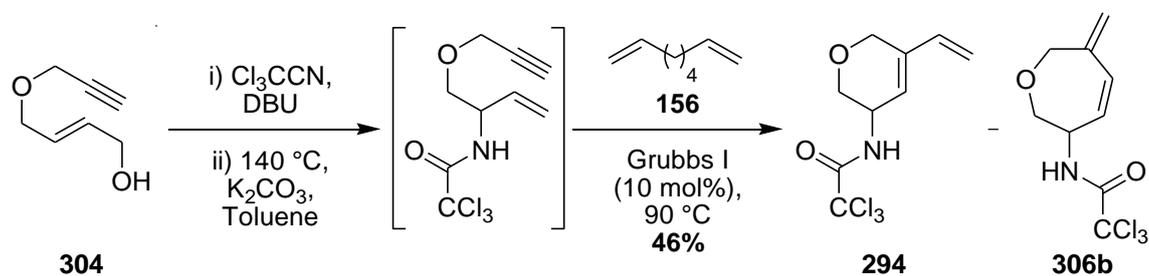
Table 6- Optimisation of RCEYM reaction. ^a 1,7-Octadiene **156** was not added.

Using these optimised RCEYM conditions, the one-pot process was repeated with 1,3-diene **293** being isolated in a 40% yield from allylic alcohol **300** (Scheme 107). This optimised method has many advantages over the previous one-pot process (Scheme 106). With the use of 1,7-octadiene **156**, the catalyst loading was lowered from 20 mol% of Grubbs first generation to 5 mol% of Hoveyda-Grubbs second generation catalyst and the time for the RCEYM reaction was shortened from 72 h to 24 h.



Scheme 107- One-pot process for the synthesis of 1,3-diene **293**

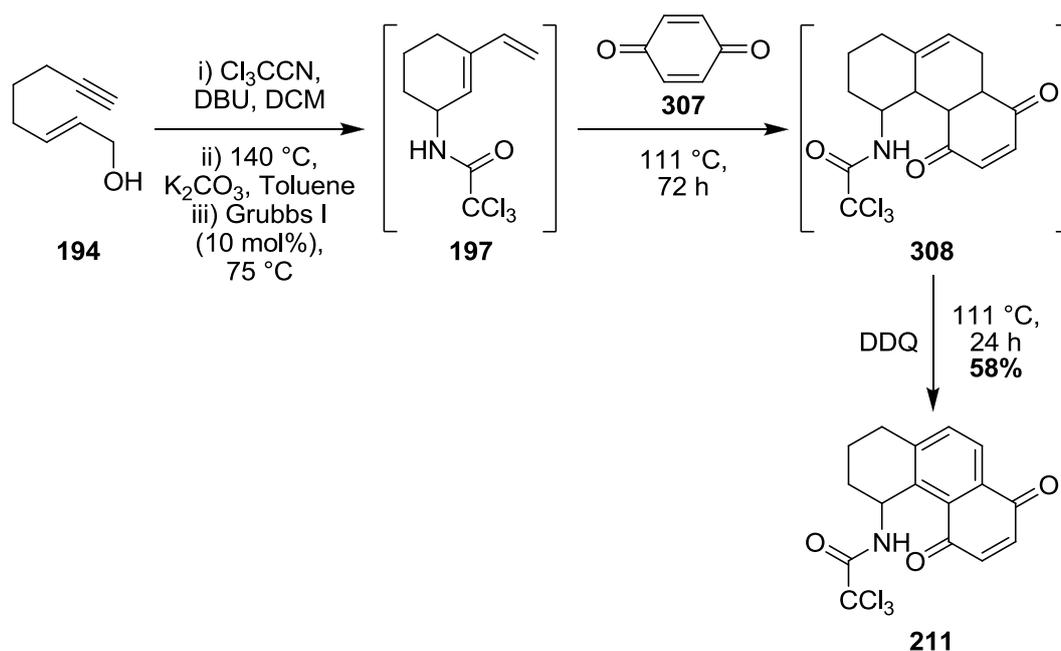
With the formation of aza-1,3-diene **293** complete, attention was then drawn to using these conditions and applying them to the oxygen containing 1,3-diene **294**. Initially the optimised conditions, where Hoveyda-Grubbs second generation catalyst and 1,7-octadiene **156** were used, worked well to form desired 1,3-diene **294**. However, *endo*-1,3-diene **306b** was also formed in a 1:1 ratio and could not be removed by column chromatography. The formation of the *endo*-1,3-diene **306b** is not surprising and has been reported before when Grubbs second generation catalyst is used with ethylene gas.^{55,146} This reactivity is not observed with Grubbs first generation catalyst which is less reactive so forms only the *exo*-diene product **294**. The one-pot process was then repeated using Grubbs first generation catalyst generating desired 1,3-diene **294** in an isolated yield of 46% from the allylic alcohol **304** (Scheme 108).



Scheme 108- One-pot process for the synthesis of 1,3-diene **294**

2.5.2 One-pot synthesis of quinone derivatives

With the development of an efficient one-pot procedure to form carbocyclic and heterocyclic containing 1,3-dienes complete, attention was turned to using these 1,3-diene in a Diels-Alder reaction with quinones. As previously shown in Chapter 2.1.6, a one-pot multi-reaction process was attempted using 1,4-benzoquinone **307**. Surprisingly, the desired product **308** from this reaction was not isolated, however the aromatised product **211** was isolated in a modest yield. The formation of this product was attributed to 1,4-benzoquinone **307** acting as an oxidant, causing aromatisation to take place. To improve the yield of this process, it was proposed that by adding a stronger oxidant such as DDQ, after the Diels-Alder reaction with 1,4-benzoquinone **307** was complete, would lead to a more efficient synthesis of polycycle **211**. Thus by adding DDQ after the Diels-Alder reaction was complete, the overall yield of the reaction was improved to 58% of the aromatised product **211** over five steps from allylic alcohol **194** (Scheme 109).



Scheme 109- Synthesis of tricyclic tetralin **211**

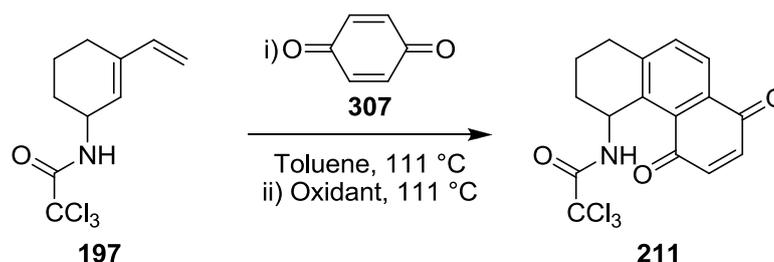
While this one-pot procedure worked well, forming tricyclic tetralin **211** in a good yield over five steps, it was not applicable to other examples. As such attention focused on developing an efficient process to form these products. It was decided that the best course of action was to first carry out the one-pot process to generate the 1,3-dienes, then in a separate one-pot process, use the Diels-Alder reaction followed by aromatisation to form the aromatic scaffolds.

Separating the one-pot process allowed further optimisation of the Diels-Alder reaction and aromatisation steps. With each of the steps being heated, it was proposed that the entire process could be performed using microwave reactor technology which may allow faster access to these compounds.

Over the past 15 years, microwave technology has become popular within chemistry due to increased reaction rates compared with conventional heat sources. Within academia, microwave reactor technologies have been applied to a wide range of applications.^{147,148} This increase in reaction rate is due to the reaction mixture being heated in a rapid uniform manner whereas, in conventional heating, the walls of the flask are heated quicker than the centre of the flask.¹⁴⁹⁻¹⁵¹ Also, due to the reaction vessel being held under pressure, the reaction mixture can be heated above the solvent boiling point, further accelerating the reaction.^{152,153}

One problem of using microwave reactors is that solvents with a small dielectric constant, such as toluene, are unable to absorb the microwave irradiation as well as solvents with large dielectric constants such as acetonitrile. This means that the reaction mixture is unable to heat to the required temperature. To overcome this, a passive heating element (silicon carbide bar) is added to the reaction mixture.¹⁵⁴ The silicon carbide bar absorbs the microwave radiation and transfers it to the solvent molecules allowing it to heat to the required temperature.

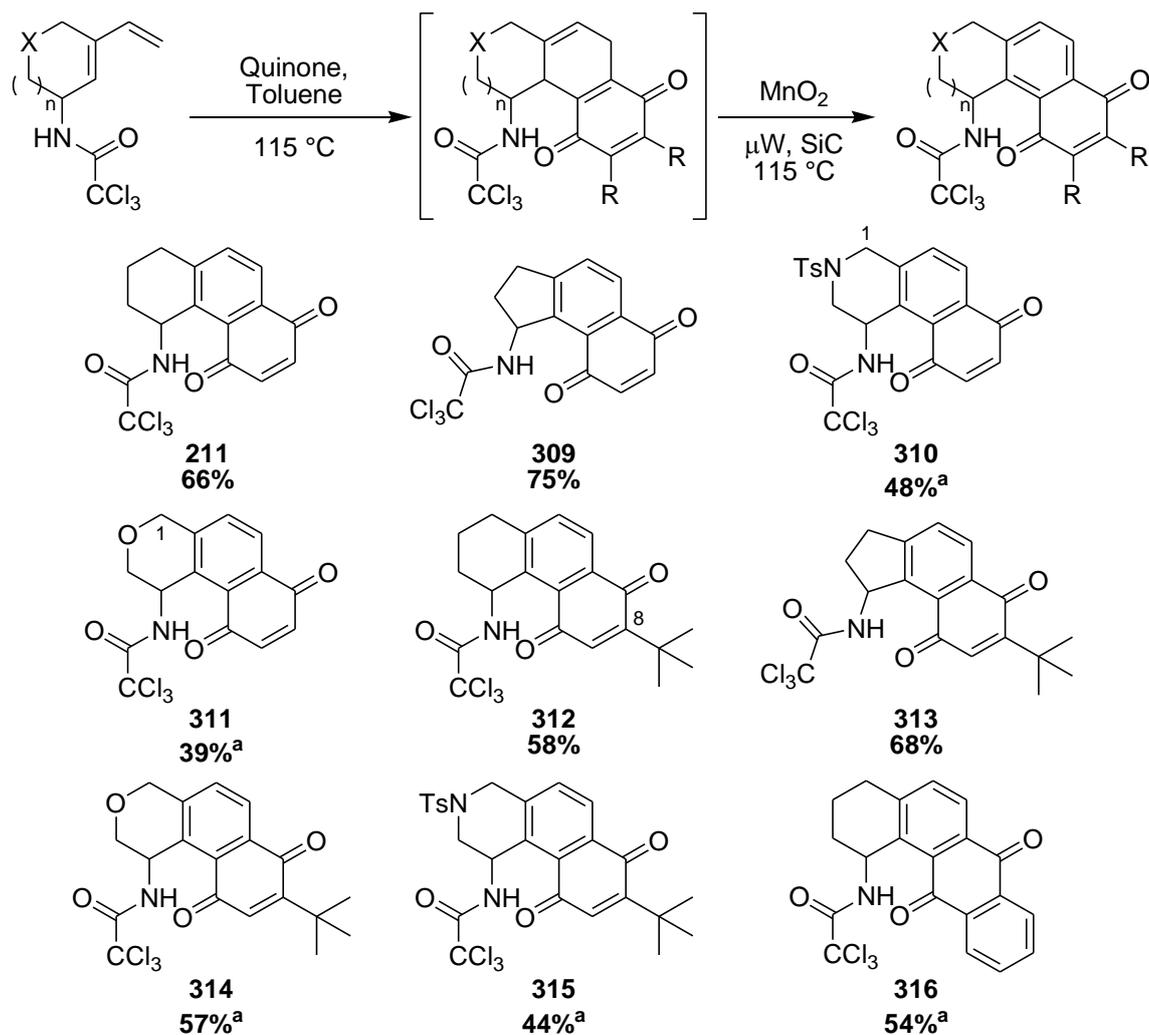
Initial optimisation under non-microwave conditions was accomplished by reacting 1,3-diene **197** with 1,4-benzoquinone **307** to promote the thermal Diels-Alder reaction and then when complete as judged by ¹H NMR spectroscopy, DDQ was added and heated thermally forming quinone derivative **211** in a good yield over the two steps (Table 7, entry 1). Repeating the process using microwave technology did enhance the rate of the reaction with the product formed in 5 h, however a lower yield was obtained (entry 2). Due to the lower yield, the oxidant manganese dioxide was used to perform the aromatisation and when both steps were performed using conventional heating a 44% yield was obtained (entry 3). This yield was improved by first carrying out the Diels-Alder reaction using conventional heating then repeating the aromatisation reaction in the microwave which formed polycycle **211** in a 66% yield over two steps with the aromatisation stage only taking 2 h to go to completion (entry 4).



Entry	Diels-Alder reaction conditions	Aromatisation reaction conditions	Yield (%)
1	Δ , 72 h	Δ , DDQ, 24 h	49
2	μ W, 4 h	μ W, DDQ, 1 h	40
3	Δ , 72 h	Δ , MnO ₂ (10 eq.), 24 h	44
4	Δ , 72 h	μ W, MnO ₂ (10 eq.), 2 h	66

Table 7- Optimisation of one-pot process using 1,4-benzoquinone **307**

Using the optimised conditions, a small library of quinone derivatives were synthesised in good to modest yields over two steps (Scheme 110). The scope of the reaction was expanded to include 2-*tert*-butyl-1,4-benzoquinone and 1,4-naphthoquinone **205** forming the corresponding tri- and tetracyclic indanes and tetralins **312–316** in good overall yield. When the one-pot process was applied to the nitrogen and oxygen containing 1,3-diene, trace amounts of the lactam and lactone products formed from benzylic oxidation at the C-1 position were also isolated. In these cases, DDQ provided the aromatic products in higher yields with the use of microwave heating.



Scheme 110- Library of quinone derivatives. ^a Oxidation performed using DDQ

It should be noted that products isolated from the one-pot process with 2-*tert*-butyl-1,4-benzoquinone were isolated as single regioisomers. The regiochemical outcome of this reaction was determined by X-ray analysis of polycycle **312** (Figure 18 and Appendix 2). The structure shows the *tert*-butyl group in the C-8 position. This suggests that the Diels-Alder reaction was sterically controlled.

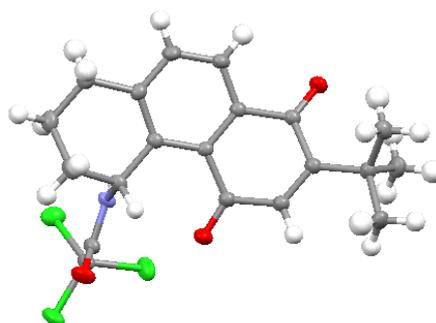
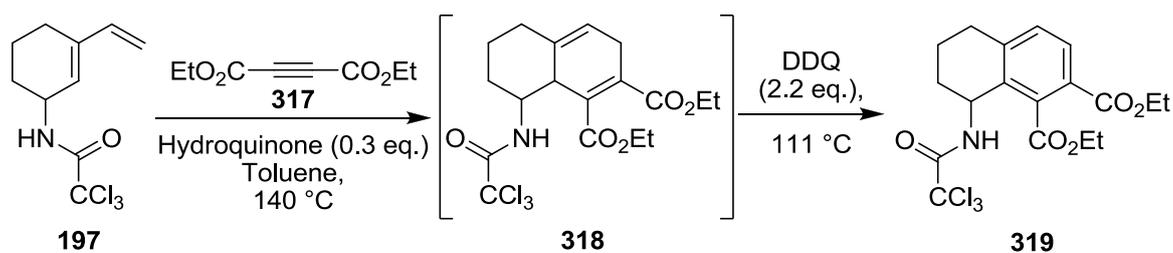


Figure 18- Ortep diagram of polycycle **312**

2.5.3 Diels-Alder reaction with alkynes

With the synthesis of the quinone derivatives complete, attention was then focused on the formation of other indane and tetralin systems. As shown earlier, Kotha and co-workers were able to form indanes ring systems, by reacting 1,3-diene with alkyne dienophiles, such as dimethyl acetylenedicarboxylate **122** (Chapter 1.3.3, Scheme 35).^{67,68}

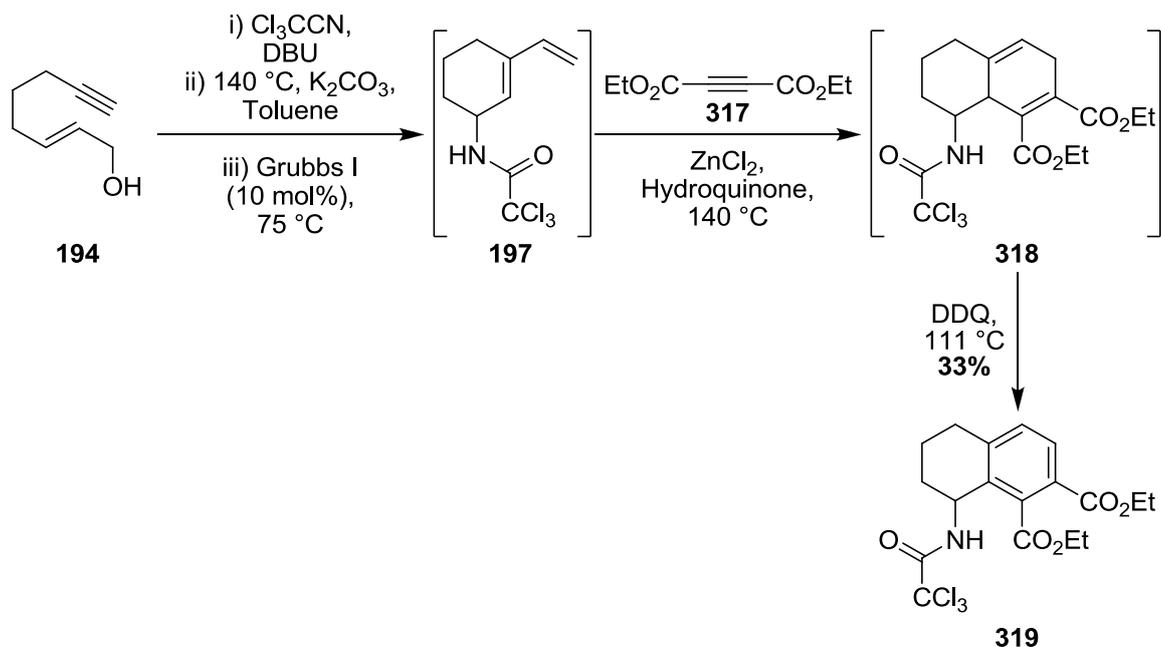
It was envisaged that 1,3-diene **197** could participate in a Diels-Alder reaction forming 1,4-diene **318**. 1,4-Diene **318** would then be aromatised using DDQ to form the tetralin **319**. Initial results showed that 1,3-diene **197** did not react with diethyl acetylenedicarboxylate **317** even when elevated temperatures were used (Table 8, entry 1). With the addition of hydroquinone, which perturbs polymerisation reactions occurring at high temperatures, more promising results were observed with tetralin **319** being isolated in a modest yields after DDQ was added to 1,4-diene **318** (entry 2 and 3).¹⁰⁶ Due to the poor reactivity of 1,3-diene **197** it was decided that a Lewis acid would be added to the reaction mixture to lower the energy of the LUMO of the dienophile and thus catalyse the reaction. With the addition of zinc chloride, to act as the Lewis acid, the Diels-Alder reaction proceeded at a slightly lower temperature (120 °C instead of 140 °C) and took 72 h to go to completion. With the addition of DDQ, tetralin **319** was formed in a good yield over the two steps (entry 4). One disappointing aspect of this process was the fact that the Diels-Alder reaction took 72 h to go to completion and a further 24 h was needed for the aromatisation reaction. To resolve this, the reaction was repeated in a microwave reactor at 140 °C with the Diels-Alder reaction taking 3 h to go to completion. Microwave heating was also employed in the aromatisation reaction taking only 2 h to go to completion. With the use of these conditions, tetralin **319** was synthesised in 58% yield with the overall process taking only 5 h to go to completion (entry 5).



Entry	Conditions for Diels-Alder reaction	Yield (%)
1 ^a	317 (3 eq.), 120 h	0
2	317 (1.5 eq.), 120 h	34
3	317 (3 eq.), 120 h	39
4 ^b	317 (3 eq.), ZnCl ₂ (1 eq.), 72 h	50
5 ^c	317 (3 eq.), ZnCl ₂ (1 eq.), 3 h	58

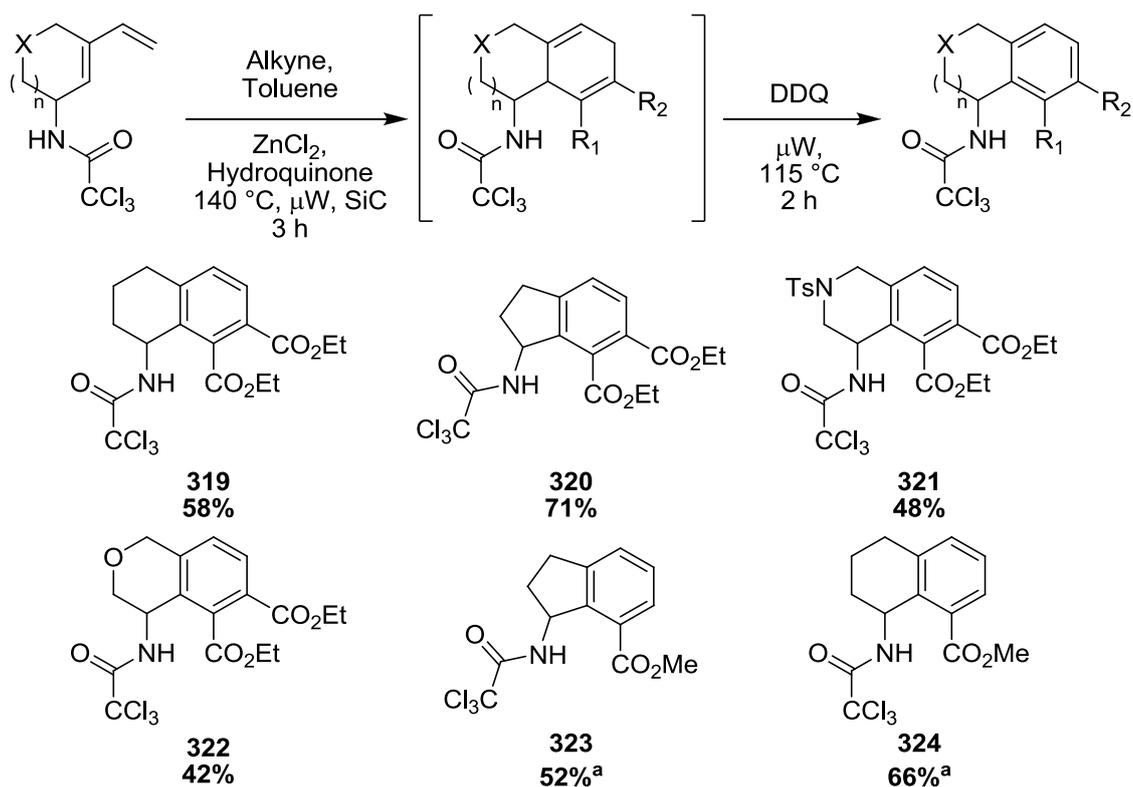
Table 8- Optimisation of Diels-Alder reaction towards the formation of tetralin **319**. ^a Hydroquinone was not added. ^b Reaction carried out at 120 °C. ^c Diels-Alder and aromatisation reaction carried out in microwave reactor (300 W).

With the two step process optimised, it was proposed that this Diels-Alder/aromatisation reaction could be combined with the three step process used to synthesise 1,3-diene **197** to form a five-step process (Scheme 111). Due to the small scale required for microwave reactions, it was deemed more practical to carry out the multi-step process using conventional heating, with tetralin **319** being isolated in a low yield of 33% over five steps. The low yield was attributed to there being too many reagents in the reaction mixture, thus having a detrimental effect on the Diels-Alder reaction, which had to be carried out at 140 °C.



Scheme 111- One-pot process for synthesis of tetralin **319**

Due to the poor yield achieved for this five step process, it was decided that the best course of action was again to split the process into two one-pot processes and carry out the Diels-Alder reaction followed by aromatisation as a separate process. The scope of the one-pot Diels-Alder reaction aromatisation was then investigated (Scheme 112). Using diethyl acetylenedicarboxylate **317**, indanes and tetralins **319–322** were isolated in good yields over two steps using microwave heating. Both microwave and conventional heating methods were attempted in the formation of indane **323** and tetralin **324**. Using standard thermal conditions, indane **323** and tetralin **324** were isolated in 52% and 66% yields respectively compared to yields of 30% and 54% recorded when microwave conditions were used. It was also found that indane and tetralin **323** and **324** were isolated as single regioisomers through a highly regioselective Diels-Alder reaction with the use of methyl propiolate. This provides further evidence for the hydrogen bond directing effect as observed with previous Diels-Alder reactions.



Scheme 112- One-pot synthesis of indanes and tetralins. ^a Reaction performed under standard thermal conditions.

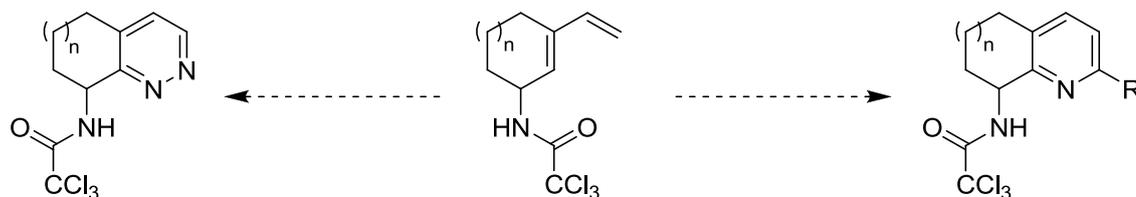
The scope of the Diels-Alder reaction was further explored with the use of other alkyne dienophiles. The alkynes, ethyl 3-phenylpropiolate **325** and methyl non-2-ynoate **326** which both contain an electron withdrawing group, were applied to the Diels-Alder reaction using the previously optimised conditions, however no reaction was observed (Figure 19). Elevated temperatures and higher equivalents were also attempted with no success.



Figure 19- Unreactive alkyne dienophiles

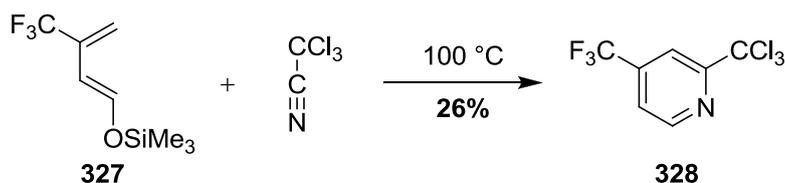
2.5.4 Formation of heteroaromatic compounds

Having investigated the Diels-Alder reaction using quinone and alkyne dienophiles, attention was turned to applying the 1,3-dienes to a hetero Diels-Alder reaction to further expand the scope by forming pyridine and pyridazine derivatives (Scheme 113). Amino-substituted heteroatom containing polycyclic scaffolds are common in the literature and have medicinal applications.¹⁵⁵⁻¹⁵⁸



Scheme 113- Proposed heteroaromatic compounds

To achieve the synthesis of pyridine derivatives it was decided that electron-deficient nitriles would be required for a normal electron demand Diels-Alder reaction to occur. The hetero Diels-Alder reaction of this type is not uncommon, however most reactions require forcing conditions.¹⁵⁹⁻¹⁶² Schlosser and co-workers reported the preparation of pyridine derivatives using trichloroacetonitrile as the dienophile and an electron-rich diene **327** (Scheme 114).¹⁶³ It was found that when the Diels-Alder reaction took place, the trimethylsilyloxy group would spontaneously eliminate to rapidly form the pyridine product **328**.

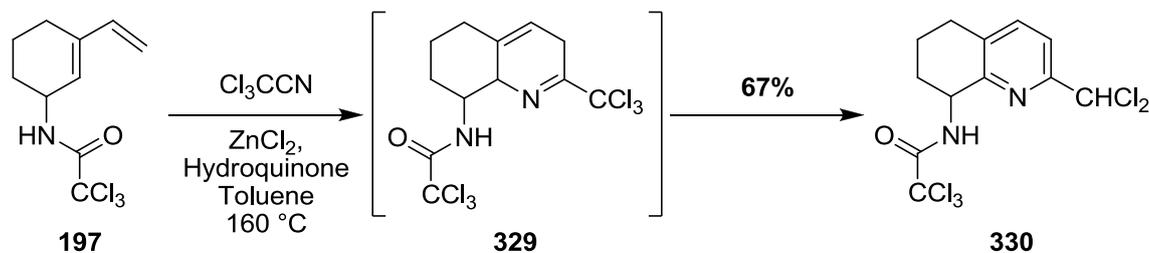


Scheme 114- Hetero Diels-Alder reaction of a nitrile to form pyridine by elimination of leaving group

This method of using an elimination reaction to form the pyridine products have been used in many examples.^{161,162,164} Another method of using a hetero Diels-Alder reaction which would lead to the formation of substituted pyridines is by carrying out a nickel catalysed dehydrogenative [4+2] cycloaddition.¹⁶⁵

Initial work on this area was carried out by an undergraduate MSci student Craig Donoghue. It was found that, by using similar 1,3-dienes and toluenesulfonyl cyanide as the dienophile, the resulting 1,4-dihydropyridine from the Diels-Alder reaction would undergo spontaneous aromatisation at temperatures of 160 °C forming a pyridine product in modest yield.¹⁶⁶

By utilising these conditions, 1,3-diene **197** was reacted with trichloroacetonitrile and using the elevated temperature of 160 °C, pyridine **330** was isolated in good yield as a single regioisomer (Scheme 115).



Scheme 115- Diels-Alder reaction using trichloroacetonitrile

The structure of pyridine **330** was elucidated by using NMR spectroscopy. Firstly, the ^1H NMR spectrum showed an extra CH signal at 6.67 ppm which was a singlet and combining that information with the CH signal at 71.2 ppm in the ^{13}C NMR spectra indicated the presence of the CHCl_2 group. The CHCl_2 signal also allowed NOE studies of pyridine **330**. This showed a NOE between the hydrogen on the CHCl_2 group and the hydrogen on the C-3 position confirming the regiochemistry of the product (Figure 20). The product is also formed as a single regioisomer.

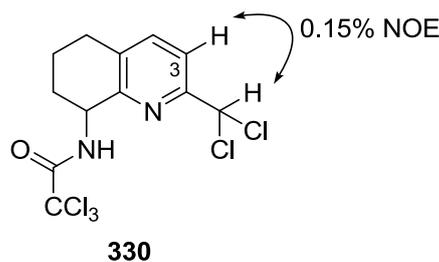
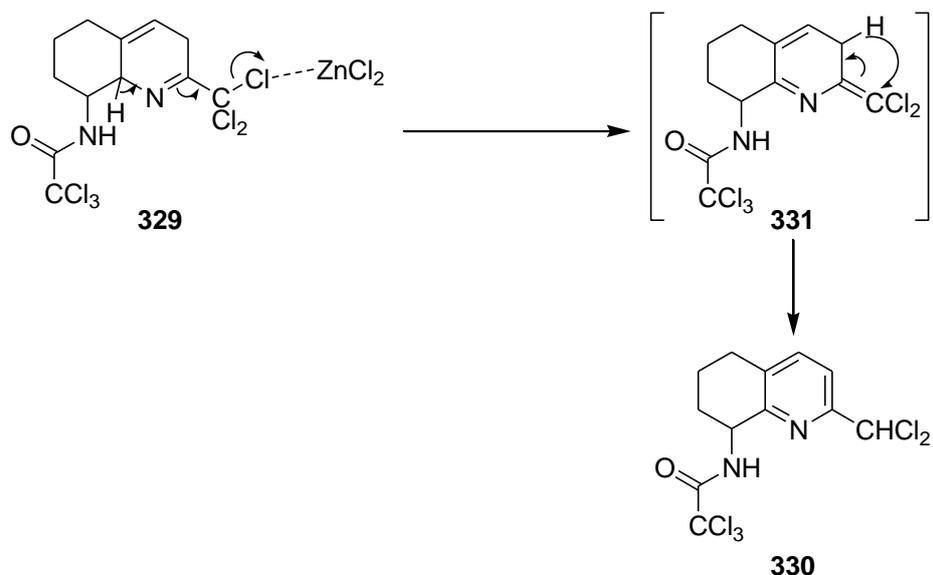


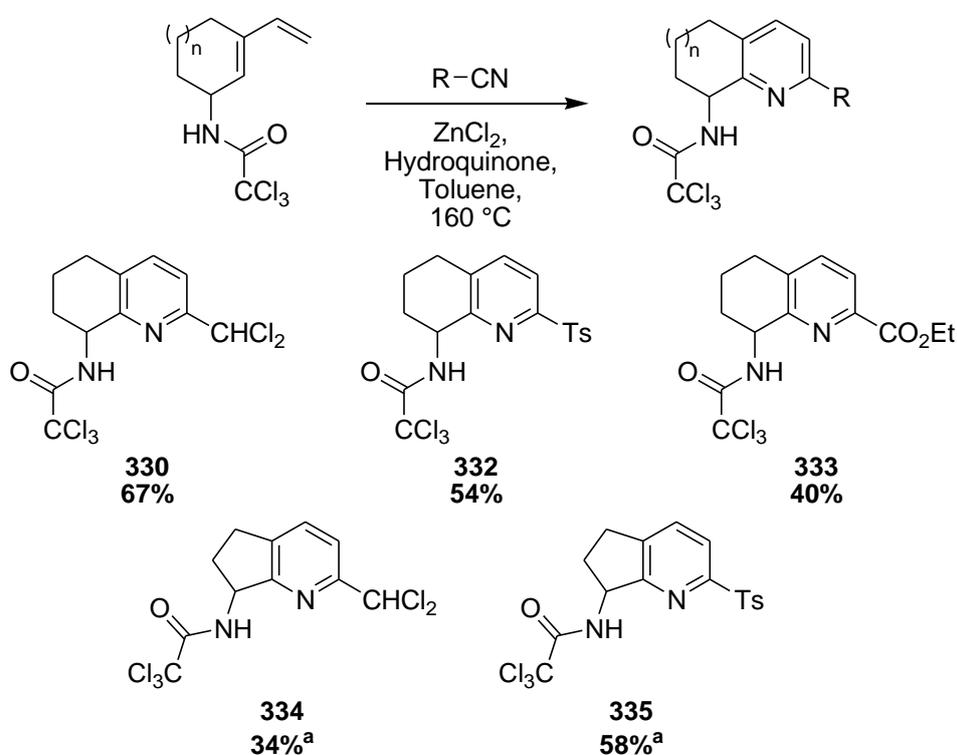
Figure 20- NOE studies of pyridine **330**

A possible mechanism for the formation of this product would be that the Lewis acid can coordinate to a chlorine atom on the 1,4-diene **329** (Scheme 116). This can lead to an elimination reaction to occur forming partially aromatised product **331**. Intermediate **331** can then aromatised via a 1,3-hydride shift forming the CHCl_2 group and the pyridine ring.



Scheme 116- Proposed mechanism for pyridine formation

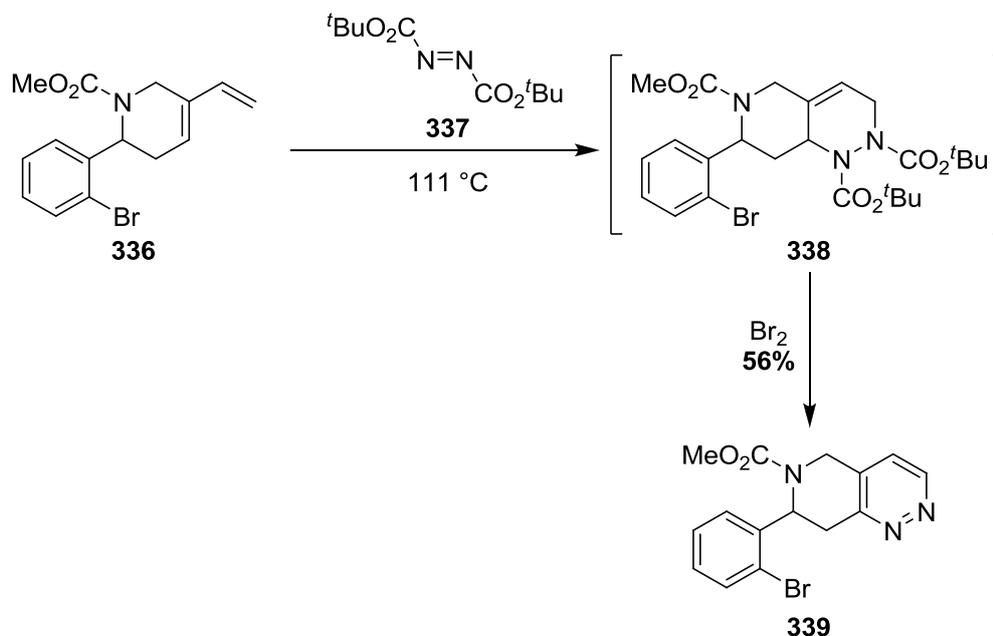
This methodology was extended with the use of other electron-deficient nitriles such as, *p*-toluenesulfonyl cyanide and ethyl cyanoformate forming the corresponding pyridines **332** and **333** in good yield as single regioisomers (Scheme 117). The process was then applied to the 5-membered cyclic 1,3-diene **223** with pyridines **334** and **335** being isolated in modest yields again as single regioisomers.



Scheme 117- Preparation of pyridine derivatives. ^a Reaction was performed at 125 °C

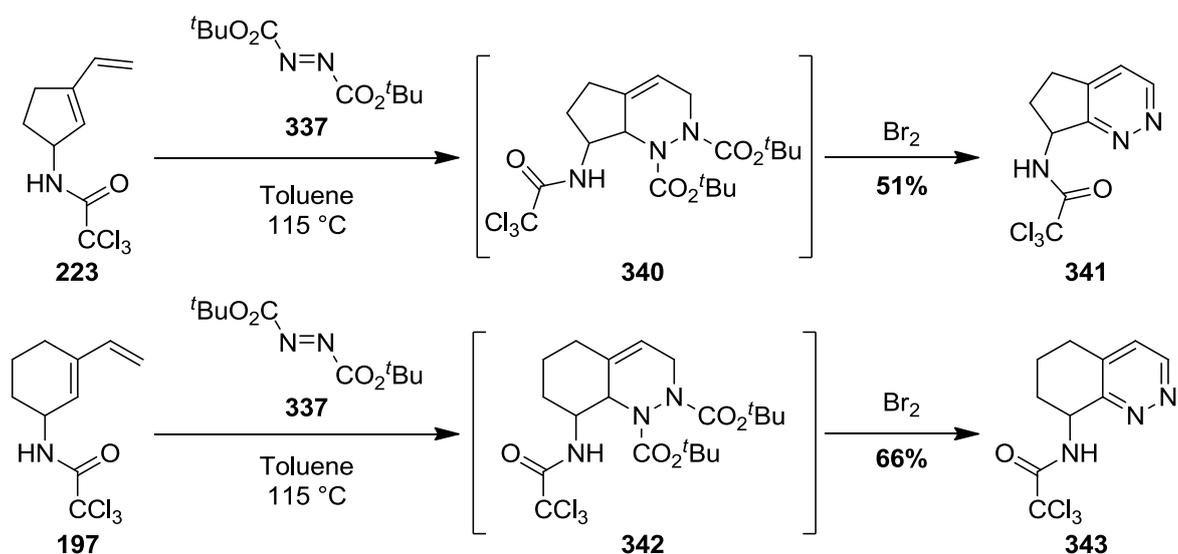
With the formation of pyridines complete, this approach was then utilised for the formation of pyridazine derivatives. Pyridazines derivatives display a wide range of biological activities such as 11β -HSD1 inhibitors for treating type II diabetes and are known to be effective antitumor agents.^{167,168} Pyridazines can also be used as key intermediates in total synthesis as they can be used in a [4+2]cycloaddition with alkynes, which can then aromatise with the loss of nitrogen gas.¹⁶⁹

To form pyridazine structures through a Diels-Alder reaction is uncommon in the literature. Martin and co-workers showed that by reacting the 1,3-diene **336** with di-*tert*-butyl azodicarboxylate **337**, cycloadduct **338** was formed as a mixture of diastereomers (Scheme 118).¹⁷⁰ Upon treatment of cycloadduct **338** with bromine, it was proposed that this led to a tandem sequence of bromination, *N*-Boc deprotection followed by aromatisation to provide desired pyridazine **339** in good yield over the two steps.



Scheme 118- Pyridazine formation via a Diels-Alder reaction followed by a tandem bromination, deprotection, aromatisation sequence

The 1,3-dienes **223** and **197** were reacted with di-*tert*-butyl azodicarboxylate **337**, which afforded the cycloadducts **340** and **342** as a mixture of diastereomers (Scheme 119). Bromine was then added to the reaction mixture resulting in the formation of pyridazines **341** and **343** in good yields over the two steps.

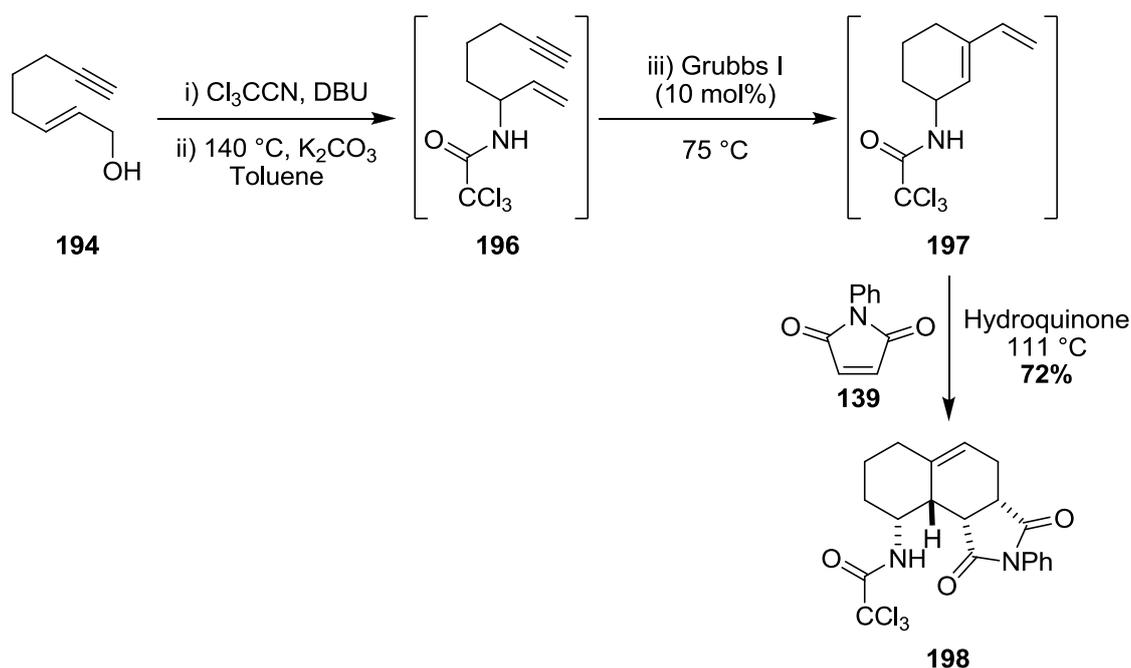


Scheme 119- Synthesis of pyridazines **341** and **343**

Two one-pot processes have been developed, the first generating novel C-1 amino-substituted indane and tetralin scaffolds and the second the formation of C-1 amino-substituted heteroaromatic structures. These processes are currently being investigated to generate a variety of medicinally important compounds.

3.0 Conclusions and future work

During the course of this research project, a novel one-pot multi-reaction process has been developed which comprises of an Overman rearrangement, a RCEYM reaction and a Diels-Alder reaction (Scheme 120). The product was isolated as a single diastereomer due to a hydrogen bond directed Diels-Alder reaction, which led to the formation of product **198** in 72% yield from allylic alcohol **194**. The structure of polycycle **198** was elucidated using NOE studies with the Diels-Alder reaction creating four contiguous stereogenic centres due to the hydrogen bond directing effect.



Scheme 120- One-pot process for the synthesis of polycycle **198**

The scope of this process was expanded by changing the dienophile. Diels-Alder products such as **206** and **209** were again isolated again as a single diastereomers in good yield (Figure 21). An X-ray crystal structure of product **206** proved the relative stereochemistry of the C-1 and C-12b hydrogen atoms. The one-pot process was then further expanded using allylic alcohol **215** to generate amino-substituted bicyclo[4.3.0]nonanes. Using hetero-Diels-Alder and Diels-Alder reactions generated polycycles **219** and **228** in moderate to good yields and as single diastereomers. Bicyclo[4.3.0]nonane **228** was also isolated as a single regioisomer giving further evidence of the hydrogen bond directing effect observed in the Diels-Alder reaction.

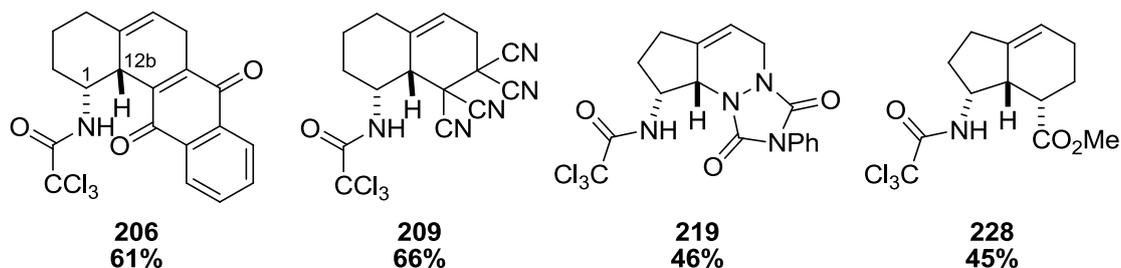
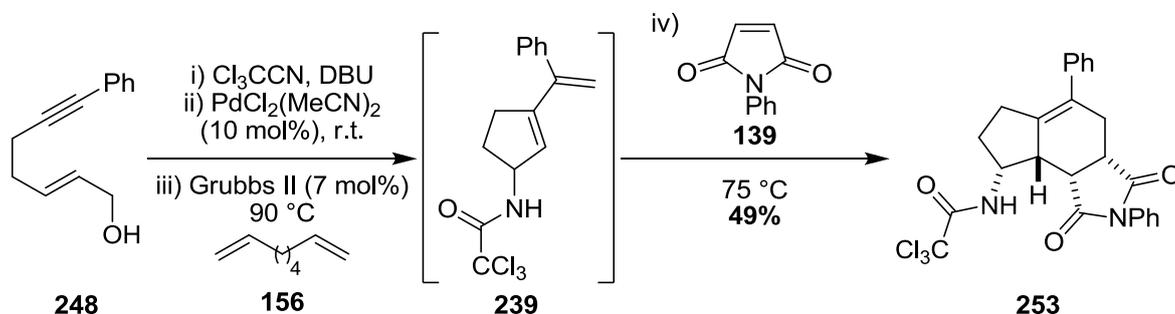


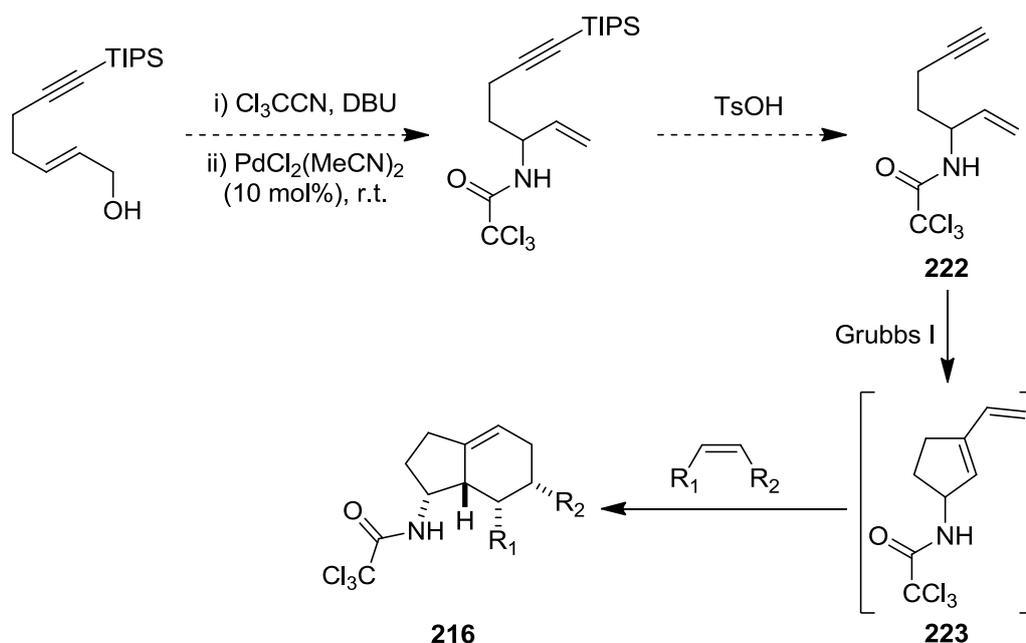
Figure 21- Structures of isolated bicyclo[4.4.0]decanes **206** and **209** and [4.3.0]nonanes **219** and **228**

In an attempt to carry out the one-pot process asymmetrically, work was then carried out to instigate a Pd(II)-catalysed Overman rearrangement. Through the use of a phenyl substituted alkyne, a Pd(II)-catalysed Overman rearrangement was achieved forming 1,6- and 1,7-enynes in excellent yields. Overall, a one-pot multi-reaction process was developed to form 5-aryl aminobicyclo[4.3.0]nonane **253** in a 49% yield and isolated as a single diastereomer (Scheme 121). Work is currently underway to examine the scope of disubstituted alkyne derived allylic alcohols and the use of chiral Pd(II)-catalysts in these one-pot multi-reaction processes for the asymmetric synthesis of medicinally important compounds and natural products.



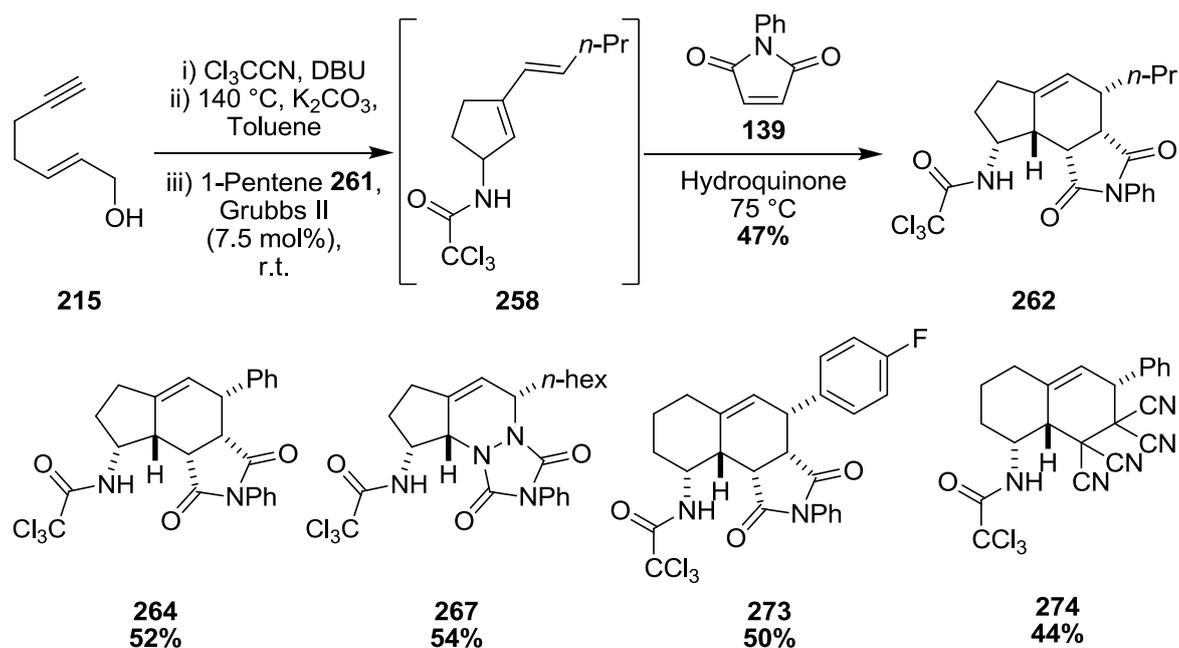
Scheme 121- One-pot process involving a Pd(II)-catalysed Overman rearrangement

Alternatively, the substituent on the alkyne could be changed to a labile protecting group that could be cleaved after the rearrangement. For example, a silyl protecting group could easily be cleaved after the Overman rearrangement forming enyne **222** which can then participate in the developed one-pot procedure (Scheme 122).



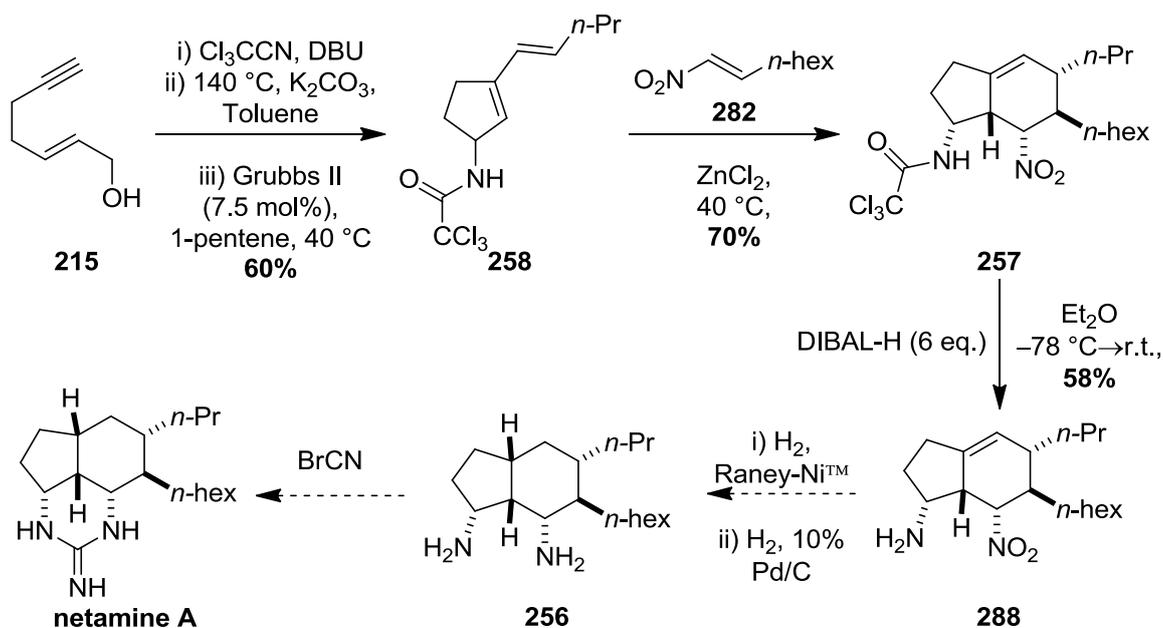
Scheme 122- Proposed one-pot process using silyl protected alkynes

The next stage of the research programme was to apply the developed one-pot process for the first total synthesis of the natural product netamine A, which has an amino-substituted bicyclo[4.3.0]nonane core. Unlike the previously synthesised compounds from this work, netamine A has further functionality in the C-7 position. It was proposed that this functionality could be introduced by utilising a tandem catalytic process involving RCEYM/cross metathesis. A one-pot multi-step process was then developed and by using a variety of cross metathesis partners and dienophiles, highly functionalised amino-substituted bicyclo[4.3.0]nonanes and [4.4.0]decanes were synthesised in good yields as single diastereomers (Scheme 123).



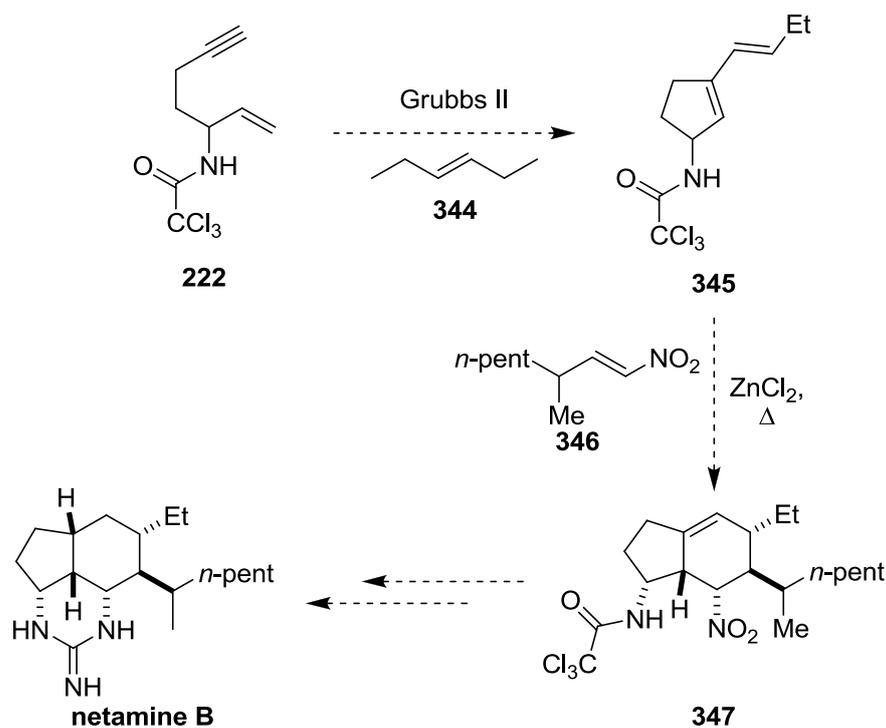
Scheme 123- One-pot multi-reaction process involving a tandem catalytic process

Significant progress has been made towards the total synthesis of netamine A. By exploiting a tandem catalytic process and a hydrogen bond directed Diels-Alder reaction, the bicyclo[4.3.0]nonane **257** was successfully formed with the desired relative stereochemistry for the synthesis of netamine A (Scheme 124). The deprotection of polycycle **257** generated bicyclo[4.3.0]nonane **288**, however a subsequent hydrogenation reaction was only able to reduce the nitro group, not the olefin. It is proposed that future work will be to complete the synthesis of netamine A by repeating the hydrogenation step using a combination of both Raney-NiTM and Pd/C catalysts. Once diamine **256** has been generated, cyanogen bromide would then be added to the reaction mixture to complete the first total synthesis of netamine A.¹³⁰⁻¹³³



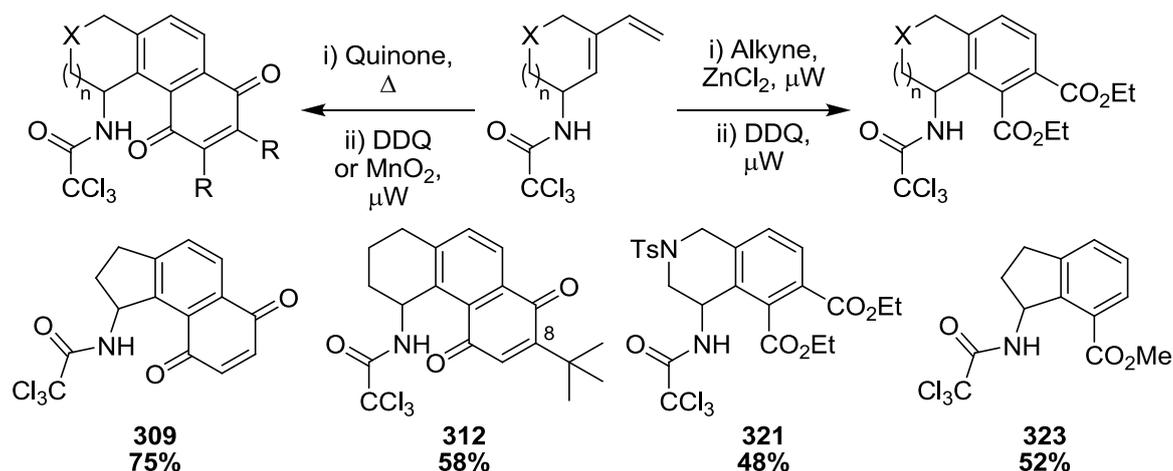
Scheme 124- Attempted route towards the synthesis of netamine A

Further work on this project could be done to exploit the usefulness of the cross metathesis and the Diels-Alder step to produce netamine B. This would involve changing the alkyl chain length on the cross coupling partner and employing a different dienophile in the Diels-Alder reaction. To form netamine B, 1-butene, which is a highly flammable gas, would be required to perform the ring-closing-ene-yne-metathesis cross metathesis reaction. By using the homodimerisation product of 1-butene, as used by Grubbs and co-workers as an alternative way of performing cross metathesis, the olefin 3-hexene **344** could be used as an alternative to form substituted 1,3-diene **345** (Scheme 125).¹²² Using nitroalkene **346**, a Diels-Alder reaction could be used to form polycycle **347** which would then be transformed to netamine B. A total synthesis of this compound would allow the elucidation of its structure.



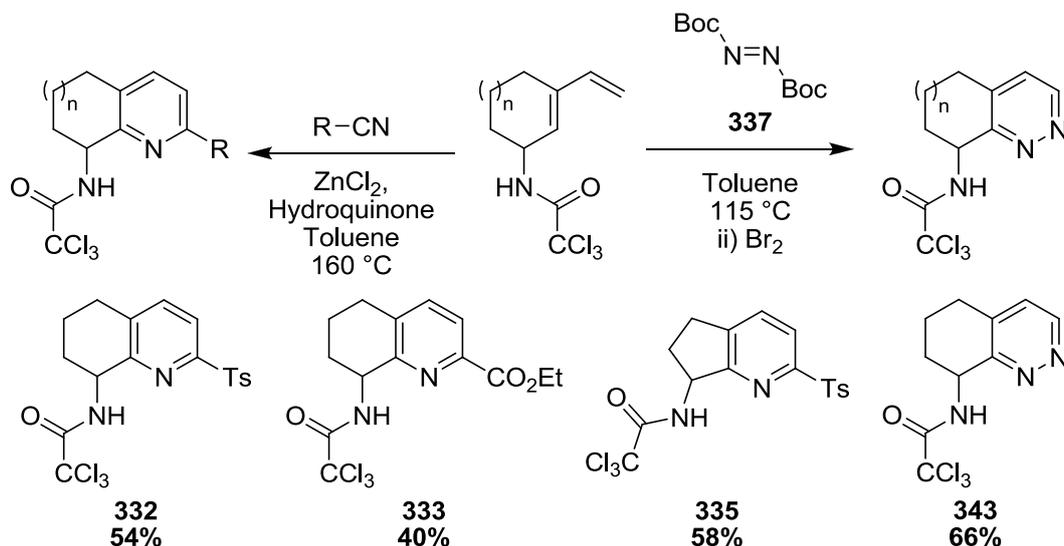
Scheme 125- Proposed synthesis of netamine B

Finally, a novel approach for the synthesis of a diverse library of compounds containing partially saturated amino-substituted indanes and tetralins was developed (Scheme 126). These privileged structures are found within a range of pharmaceutically important agents. Utilising both carbo- and heterocyclic 1,3-dienes in a Diels-Alder reaction with quinone and alkyne dienophiles, resulted in the formation of 1,4-diene products. These 1,4-dienes were then aromatised using DDQ or manganese dioxide resulting in the formation of aromatic products such as **309**, **312**, **321** and **323** in a one-pot process. All aromatic products were generated in moderate to good yields with the products from the reaction with 2-*tert*-butyl-1,4-benzoquinone and methyl propiolate being isolated as single regioisomers. Tricycle **312** formed as a single regioisomer due to a sterically controlled Diels-Alder reaction with the *tert*-butyl group being in the C-8 position which was confirmed by X-ray crystallography. In the case of methyl propiolate, the Diels-Alder reaction was highly regioselective due to a hydrogen bond directing effect, yielding compound **323** as a single regioisomer.



Scheme 126- One-pot process for the synthesis of partially saturated indenes and tetralins

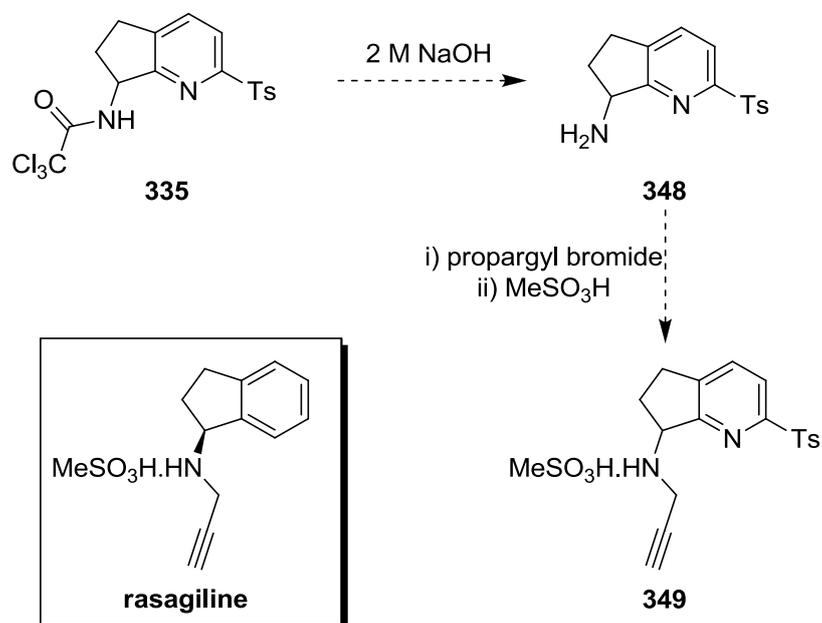
This one-pot process involving a Diels-Alder reaction followed by aromatisation was extended for the synthesis of pyridine and pyridazine ring systems (Scheme 127). Reacting the cyclic-1,3-dienes with nitrile dienophiles at temperatures of 160 °C, facilitated the Diels-Alder reaction and at the same time aromatising the resulting 1,4-dihydropyridines. The pyridazine scaffold **343** was also formed in good yields. Compound **343** was produced via a Diels-Alder reaction followed by treatment of the resulting Diels-Alder adduct with bromine. This led to a tandem sequence of bromination, *N*-Boc deprotection followed by aromatisation.



Scheme 127- One-pot process for the synthesis of pyridine and pyridazine scaffolds

A range of drug-like derivatives could be prepared by employing the developed one-pot process. One example would be to synthesise derivatives of rasagiline (Scheme 128). This could be achieved by deprotecting indene **335** and the resulting product **348** could then be

treated with propargyl bromide and methanesulfonic acid to form the rasagiline derivative **349**.



Scheme 128- Proposed synthesis of rasagiline derivatives

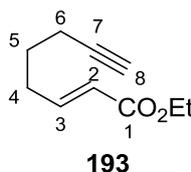
4.0 Experimental

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. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV₂₅₄) were used for thin layer chromatography and were visualised by staining with KMnO₄. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_{H} 0.00 and δ_{C} 0.0) or residual chloroform (δ_{H} 7.26 and δ_{C} 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer for EI and CI or Bruker Microtof-q for ESI. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Melting points were determined on a Reichert platform melting point apparatus. Microwave reactions were conducted using a CEM DiscoverTM Synthesis Unit (CEM Corp., Matthews, NC) and performed in glass vessels (capacity 10 mL) sealed with a septum.

Experimental Procedures and Spectroscopic Data for All Compounds

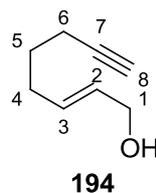
Ethyl (2*E*)-oct-2-en-7-ynoate (**193**).¹⁷¹



Dimethyl sulfoxide (5.42 mL, 76.5 mmol) was added to a stirred solution of oxalyl chloride (29.5 mL, 42.8 mmol) in dichloromethane (150 mL) at -78 °C. The mixture was stirred for 0.3 h before 5-hexyn-1-ol (**192**) (3.00 g, 30.6 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (21.3 mL, 153 mmol) was added. This reaction mixture was stirred for 0.5 h at -78 °C and then allowed to warm to room temperature and stirred for a further 2 h. A solution of lithium chloride (2.34 g, 55.1 mmol), triethyl phosphonoacetate (10.9 mL, 55.1 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (8.22 mL, 55.1 mmol) in acetonitrile (150 mL) was then prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo*, then the Horner-Wadsworth-Emmons solution was added and the reaction mixture was stirred at

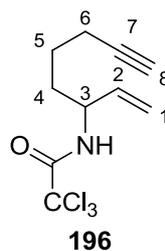
room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried (MgSO₄) and concentrated to give an orange oil. Flash column chromatography using silica (diethyl ether/petroleum ether, 1:9) gave ethyl (2*E*)-oct-2-en-7-ynoate (**193**) (4.99 g, 99%) as a yellow oil. Spectroscopic data was consistent with the literature.¹⁷¹ *R_f* (50% diethyl ether/petroleum ether) 0.74; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3295 (C≡C–H), 2940 (CH), 1713 (CO), 1651 (C=C), 1265, 1188, 1150, 1042, 979, 756, 633; δ_{H} (400 MHz, CDCl₃) 1.29 (3H, t, *J* 7.1 Hz, OCH₂CH₃), 1.70 (2H, quin, *J* 6.9 Hz, 5-H₂), 1.98 (1H, s, 8-H), 2.23 (2H, t, *J* 6.9 Hz, 6-H₂), 2.33 (2H, q, *J* 6.9 Hz, 4-H₂), 4.18 (2H, q, *J* 7.1 Hz, OCH₂CH₃), 5.86 (1H, d, *J* 15.6 Hz, 2-H), 6.94 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_{C} (101 MHz, CDCl₃) 14.3 (CH₃), 17.9 (CH₂), 26.7 (CH₂), 30.9 (CH₂), 60.2 (CH₂), 69.0 (CH), 83.5 (C), 122.1 (CH), 147.8 (CH), 166.6 (C); *m/z* (CI) 167 (MH⁺, 100%), 139 (42), 113 (10), 97 (12), 81 (25), 71 (30).

(2*E*)-Oct-2-en-7-yn-1-ol (194).¹⁷²



Ethyl (2*E*)-oct-2-en-7-ynoate (**193**) (4.10 g, 24.7 mmol) was dissolved in diethyl ether (50 mL) and cooled to –78 °C. DIBAL-H (1 M in hexane) (54.3 mL, 54.3 mmol) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 50 mL). The filtrate was then dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography using silica (diethyl ether/petroleum ether, 1:1) gave (2*E*)-oct-2-en-7-yn-1-ol (**194**) (2.95 g, 97% yield) as a yellow oil. Spectroscopic data was consistent with the literature.¹⁷² *R_f* (50% petroleum ether/diethyl ether) 0.29; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3361 (OH), 3302 (C≡C–H), 2932 (CH), 1674 (C=C), 1435, 1219, 1088, 972; δ_{H} (400 MHz, CDCl₃) 1.29 (1H, br s, OH), 1.63 (2H, quin, *J* 6.9 Hz, 5-H₂), 1.96 (1H, t, *J* 2.6 Hz, 8-H), 2.15–2.25 (4H, m, 4-H₂ and 6-H₂), 4.09–4.15 (2H, m, 1-H₂), 5.63–5.74 (2H, m, 2-H and 3-H); δ_{C} (101 MHz, CDCl₃) 17.8 (CH₂), 27.8 (CH₂), 31.1 (CH₂), 63.7 (CH₂), 68.5 (CH), 84.2 (C), 129.9 (CH), 131.9 (CH); *m/z* (CI) 125 (MH⁺, 20%), 107 (95), 97 (40), 81 (80), 71 (100).

3-(2',2',2'-Trichloromethylcarbonylamino)oct-1-en-7-yne (196).

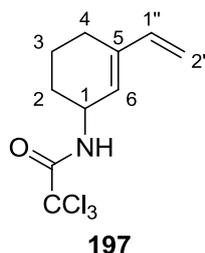


Method A- (*E*)-Octa-2-en-7-yn-1-ol (**194**) (0.50 g, 4.03 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 0.81 mmol) and trichloroacetonitrile (0.61 mL, 6.05 mmol). The reaction mixture was allowed to warm to 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 (40 mL) under an argon atmosphere. Bis(acetonitrile)palladium chloride (0.10 g, 0.40 mmol) was then added to the solution and the reaction mixture was stirred at room temperature for 48 h. To the reaction mixture, an additional portion of bis(acetonitrile)palladium chloride (0.10 g, 0.40 mmol) was added and the reaction mixture was stirred at 40 °C for 24 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 10:1) gave 3-(2',2',2'-trichloromethylcarbonylamino)oct-1-en-7-yne (**196**) (0.57 g, 52%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.61; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3425 (NH), 3309 (C≡C-H), 2947 (CH), 2114 (C≡C), 1697 (CO), 1512, 1242, 817; δ_{H} (400 MHz, CDCl_3) 1.62 (2H, quin., J 6.8 Hz, 5- H_2), 1.76–1.81 (2H, m, 4- H_2), 1.99 (1H, t, J 2.6 Hz, 8-H), 2.25 (2H, td, J 6.8, 2.6 Hz, 6- H_2), 4.45 (1H, quin., J 6.2 Hz, 3-H), 5.23 (1H, d, J 10.4 Hz, 1-*HH*), 5.28 (1H, d, J 17.7 Hz, 1-*HH*), 5.82 (1H, ddd, J 17.7, 10.4, 6.2 Hz, 2-H), 6.48 (1H, br s, NH); δ_{C} (101 MHz, CDCl_3) 18.2 (CH_2), 24.5 (CH_2), 33.3 (CH_2), 53.2 (CH), 69.5 (CH), 83.6 (C), 92.8 (C), 116.5 (CH_2), 136.3 (CH), 161.3 (C); m/z (CI) 268.0067 (MH^+ . $\text{C}_{10}\text{H}_{13}^{35}\text{Cl}_3\text{NO}$ requires 268.0063), 234 (30%), 198.3 (100), 162 (15), 121 (68), 105 (30).

Method B- (*E*)-Octa-2-en-7-yn-1-ol (**194**) (0.42 g, 3.40 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.095 mL, 0.68 mmol) and trichloroacetonitrile (0.51 mL, 5.09 mmol). 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 48 h, before cooling to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 10:1) gave 3-(2',2',2'-trichloromethylcarbonylamino)oct-1-en-7-yne (**196**) (0.890 g, 98%) as a colourless oil. Spectroscopic data as described above.

5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (197**).**

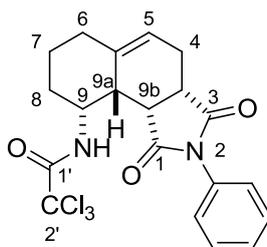


Method A- 3-(2',2',2'-Trichloromethylcarbonylamino)-oct-1-en-7-yne (**196**) (0.20 g, 0.75 mmol) was dissolved in dichloromethane (20 mL) and Grubbs first generation catalyst (0.062 g, 0.075 mmol) was then added. The reaction mixture stirred at 40 °C for 24 h. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 7:1) gave 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.14 g, 68%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.86; Mp 77–79 °C; ν_{\max} / cm^{-1} (neat) 3258 (NH), 2942 (CH), 1703, 1684 (CO), 1535, 1310, 1273, 1248, 1157, 1073, 993, 907, 824; δ_{H} (400 MHz, CDCl_3) 1.57–1.68 (1H, m, 2-HH), 1.70–1.83 (2H, m, 3-H₂), 1.96–2.07 (1H, m, 2-HH), 2.16–2.26 (2H, m, 4-H₂), 4.53–4.63 (1H, m, 1-H), 5.10 (1H, d, J 10.6 Hz, 2''-HH), 5.26 (1H, d, J 17.7 Hz, 2''-HH), 5.65 (1H, br s, 6-H), 6.36 (1H, dd, J 17.7, 10.6 Hz, 1''-H), 6.60 (1H, br s, NH); δ_{C} (126 MHz, CDCl_3) 19.4 (CH₂), 23.5 (CH₂), 28.7 (CH₂), 47.7 (CH), 92.7 (C), 113.7 (CH₂), 126.4 (CH), 138.6 (CH), 140.5 (C), 161.1 (C); m/z (CI) 268.0059 (MH⁺. $\text{C}_{10}\text{H}_{13}^{35}\text{Cl}_3\text{NO}$ requires 268.0063), 234 (38%), 200 (9), 164 (3), 107 (100), 87 (22), 69 (33).

Method B- (2E)-Oct-2-en-7-yn-1-ol (**194**) (0.050 g, 0.40 mmol) was dissolved in dichloromethane (15 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.011 mL, 0.080 mmol) and trichloroacetonitrile (0.060 mL, 0.61 mmol) was added. 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 24 h. Grubbs first generation catalyst (0.024 g, 0.030 mmol) was added and the reaction mixture was heated for 18 h at 75 °C. A further portion of Grubbs first generation catalyst (0.010 g, 0.010 mmol) was added and the reaction mixture was stirred at 75 °C for 4 h. The reaction mixture was then cooled to rt and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 7:1) gave 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.092 g, 86%) as a white solid. Spectroscopic data as described above.

(3aS*,9R*,9aS*,9bR*)-3a,4,6,7,8,9,9a,9b-Octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (198**).**



198

Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) was dissolved in toluene (10 mL) and *N*-phenyl maleimide (**139**) (0.096 g, 0.56 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The flask was stirred at 111 °C for 18 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 2:3) gave (3aS*,9R*,9aS*,9bR*)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (0.095 g, 58%) as a white solid. R_f (70% diethyl ether/petroleum ether) 0.33; Mp 152–154 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3567 (NH), 3056 (ArH), 2944 (CH), 1712 (CO), 1501, 1385, 1265, 1188; δ_{H} (500 MHz, CDCl_3) 1.57–1.62 (1H, m, 7-*HH*), 1.68–1.73 (1H, m, 7-*HH*), 1.86 (2H, q, J 7.6 Hz, 8- H_2), 2.24–2.47 (3H, m, 6- H_2 and 4-*HH*), 2.75 (1H, dt, J 16.5, 4.4 Hz, 4-*HH*), 3.08 (1H, t, J 7.6 Hz, 9a-H), 3.29 (1H, ddd, J 9.4, 8.1, 4.4 Hz, 3a-H), 3.47 (1H, dd, J 9.4, 7.6 Hz, 9b-H), 4.72 (1H, dq, J 9.3, 7.6 Hz, 9-H), 5.84–5.89 (1H, m, 5-H), 7.20–7.24 (2H, m, $2 \times$ ArH), 7.40 (1H, t, J 7.5 Hz, ArH), 7.46 (2H, t, J 7.5 Hz, $2 \times$ ArH), 7.63 (1H, d, J 9.3 Hz, NH); δ_{C} (126 MHz, CDCl_3) 22.7 (CH_2), 23.4 (CH_2), 29.5 (CH_2), 32.4 (CH_2), 38.1

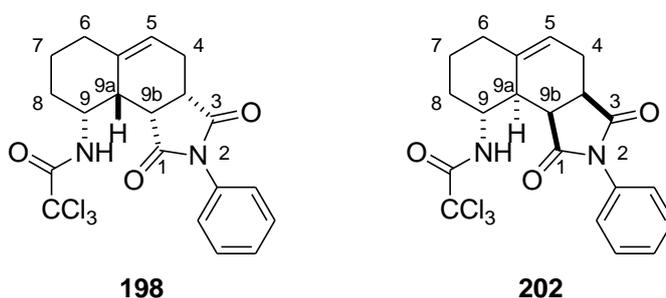
(CH), 38.9 (CH), 40.3 (CH), 48.8 (CH), 91.8 (C), 121.1 (CH), 126.4 (2 × CH), 128.8 (CH), 129.2 (2 × CH), 131.5 (C), 138.1 (C), 161.1 (C), 178.1 (C), 178.3 (C); *m/z* (EI) 440.0450 (M^+ . $C_{20}H_{19}^{35}Cl_3N_2O_3$ requires 440.0461), 403 (5%), 323 (5), 279 (100), 241 (10), 132 (65), 91 (32), 77 (11).

Method B- (*E*)-Oct-2-en-7-yn-1-ol (**194**) (0.050 g, 0.40 mmol) was dissolved in dichloromethane (15 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.011 mL, 0.08 mmol) and trichloroacetonitrile (0.060 mL, 0.60 mmol) was added. 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 24 h. Grubbs first generation catalyst (0.025 g, 0.030 mmol) was added and the reaction mixture was heated for 18 h at 75 °C. A further portion of Grubbs first generation catalyst (0.0082 g, 0.010 mmol) was added and the reaction mixture was stirred at 75 °C for 4 h. *N*-Phenyl maleimide (**139**) (0.10 g, 0.60 mmol) was added with hydroquinone (0.013 g, 0.12 mmol). The reaction mixture was stirred for 48 h at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 2:3) gave (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (0.13 g, 72%) as a white solid. Spectroscopic data as described above

Method C- (*E*)-Oct-2-en-7-yn-1-ol (**194**) (0.025 g, 0.20 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.0056 mL, 0.04 mmol) and trichloroacetonitrile (0.030 mL, 0.30 mmol) was added. 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 (5 mL) and transferred to a microwave vial containing potassium carbonate (0.025 g) and purged with Ar and sealed. The reaction mixture was then heated in a microwave reactor to 180 °C and stirred for 1 h (300W). Grubbs first generation catalyst (0.017 g, 0.020 mmol) was added and the reaction mixture was stirred in a microwave reactor for 1 h at 75 °C. *N*-Phenyl maleimide (**139**) (0.052 g, 0.30 mmol) was added and

the mixture was stirred at 111 °C in a microwave reactor for 1 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 2:3) gave (3a*S**,9*R**,9a*S**,9b*R**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (0.053 g, 60%) as a white solid. Spectroscopic data as described above.

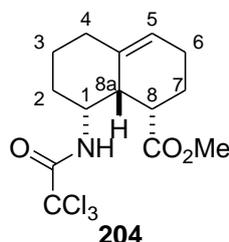
(3a*S,9*R**,9a*S**,9b*R**)-3a,4,6,7,8,9,9a,9b-Octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (198) and (3a*R**,9*R**,9a*R**,9b*S**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (202).**



5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.083 g, 0.31 mmol) was dissolved in methanol (5 mL) and *N*-phenyl maleimide (**139**) (0.078 g, 0.46 mmol) was added with hydroquinone (0.005 g, 0.05 mmol). The flask was stirred at 75 °C for 18 h. The solution was then cooled to room temperature and solvent evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 2:3) gave the product as a 1:1 mixture of two diastereomers. Elution with 2:3 diethyl ether/petroleum ether gave (3a*S**,9*R**,9a*S**,9b*R**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (0.060 g, 44%) as a white solid. Spectroscopic data as described above. Elution with 1:1 diethyl ether/petroleum ether gave (3a*R**,9*R**,9a*R**,9b*S**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**202**) (0.059 g, 43%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.28; Mp 156–158 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3402 (NH), 3043 (ArH), 2925 (CH), 1711 (CO), 1502, 1385, 1305, 1248, 927; δ_{H} (500 MHz, CDCl_3) 1.58–1.79 (1H, m, 7- H_2), 2.03–2.11 (2H, m, 6-*HH* and 8-*HH*), 2.16–2.24 (1H, m, 4-*HH*), 2.26–2.38 (2H, m, 4-*HH* and 6-*HH*), 2.65 (1H, d, J 16.1 Hz, 9a-H), 2.96 (1H, t, J 8.8 Hz, 8-*HH*), 3.26 (1H, td, J 8.5, 3.5 Hz, 3a-H), 3.45 (1H, dd, J 8.5, 6.6 Hz, 9b-H), 4.43–4.51 (1H, m, 9-H), 5.64–5.69 (1H, m, 5-H), 7.14 (1H, d, J 7.0 Hz, NH), 7.18–7.22 (2H, m, 2 \times ArH), 7.36–7.41 (1H, m, ArH), 7.46 (2H, t, J 7.7 Hz, 2 \times ArH); δ_{C} (126 MHz, CDCl_3) 21.3 (CH_2), 24.8 (CH_2), 28.0 (CH_2), 29.7 (CH_2), 39.3 (CH),

39.8 (CH), 41.1 (CH), 51.1 (CH), 93.0 (C), 119.8 (CH), 126.4 (2 × CH), 128.7 (CH), 129.1 (2 × CH), 131.7 (C), 139.2 (C), 161.7 (C), 177.3 (C), 178.5 (C); m/z (ESI) 463.0352 (MNa^+ . $C_{20}H_{19}^{35}Cl_3N_2O_3$ requires 463.0353).

Methyl (1*R,8*S**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (204).**

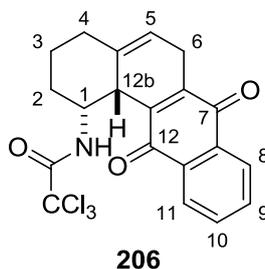


Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.12 g, 0.45 mmol) was dissolved in toluene (10 mL) and methyl acrylate (**203**) (0.048 mL, 0.54 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The reaction was stirred at 111 °C for 72 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:2) gave methyl (1*R**,8*S**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (**204**) (0.042 g, 26%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.39; ν_{max}/cm^{-1} (neat) 3416 (NH), 2938 (CH), 1713 (CO), 1501, 1435, 1265, 1152, 1020, 952, 816; δ_H (500 MHz, $CDCl_3$) 1.35 (1H, qt, J 13.3, 4.4 Hz, 3-*HH*), 1.59 (1H, tdd, J 13.3, 4.4, 3.0 Hz, 2-*HH*), 1.65–1.72 (1H, m, 3-*HH*), 1.74–1.88 (3H, m, 2-*HH* and 7- H_2), 1.93–2.04 (2H, m, 4-*HH* and 6-*HH*), 2.05–2.13 (1H, m, 6-*HH*), 2.24 (1H, ddt, J 13.3, 4.4, 2.2 Hz, 4-*HH*), 2.63–2.67 (1H, m, 8*a*-H), 2.72 (1H, ddd, J 12.8, 7.1, 4.4 Hz, 8-H), 3.66 (3H, s, OCH_3), 4.11 (1H, dq, J 9.2, 3.0 Hz, 1-H), 5.69–5.72 (1H, m, 5-H), 6.76 (1H, br d, J 9.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 20.7 (CH_2), 22.9 (CH_2), 23.5 (CH_2), 31.5 (CH_2), 35.5 (CH_2), 40.9 (CH), 42.8 (CH), 50.2 (CH), 52.1 (CH_3), 93.0 (C), 123.8 (CH), 134.4 (C), 160.1 (C), 173.7 (C); m/z (CI) 354.0431 (MH^+ . $C_{14}H_{19}^{35}Cl_3NO_3$ requires 354.0431), 320 (60%), 291 (20), 257 (15), 193 (15), 107 (23), 69 (53).

Method B- Methyl (1*R**,8*S**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (**204**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.050 g, 0.40 mmol). The reaction mixture was

stirred with Grubbs first generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before methyl acrylate (**203**) (0.22 mL, 2.41 mmol) was added. The reaction mixture was stirred for 6 days at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:2) gave methyl (1*R**,8*S**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (**204**) (0.068 g, 48%) as a colourless oil. Spectroscopic data as described above.

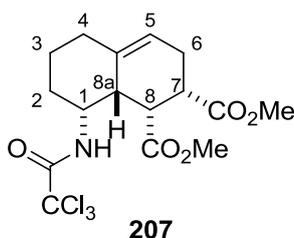
(1*R,12*bR**)-1,2,3,4,6,12*b*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**206**).**



Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.16 g, 0.60 mmol) was dissolved in toluene (10 mL) and 1,4-naphthoquinone (**205**) (0.14 g, 0.90 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The reaction mixture was stirred at 115 °C for 24 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 7:3) gave (1*R**,12*bR**)-1,2,3,4,6,12*b*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**206**) (0.16 g, 63%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.51; Mp 176–178 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3418, 3333 (NH), 3073 (ArH), 2935 (CH), 1705 (CO), 1661 (CO), 1591, 1506, 1330, 1293, 821; δ_{H} (500 MHz, CDCl_3) 1.43 (1H, qt, J 13.6, 3.6 Hz, 3-*HH*), 1.84–1.94 (2H, m, 2-*HH* and 3-*HH*), 1.99 (1H, qt, J 13.6, 3.6 Hz, 2-*HH*), 2.12 (1H, m, 4-*HH*), 2.34–2.40 (1H, m, 4-*HH*), 3.15 (1H, dddd, J 24.9, 6.4, 2.6, 1.9 Hz, 6-*HH*), 3.24 (1H, dddd, J 24.9, 6.4, 3.6, 2.6 Hz, 6-*HH*), 3.78 (1H, td, J 6.4, 3.6 Hz, 12*b*-H), 4.62 (1H, dq, J 9.3, 3.6 Hz, 1-H), 5.78–5.82 (1H, m, 5-H), 6.83 (1H, br d, J 9.3 Hz, NH), 7.62 (1H, td, J 7.4, 1.3 Hz, ArH), 7.66 (1H, td, J 7.4, 1.3 Hz, ArH), 7.96 (1H, dd, J 7.4, 1.3 Hz, ArH), 8.07 (1H, dd, J 7.4, 1.3 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 23.6 (CH_2), 25.3 (CH_2), 30.3 (CH_2), 34.7 (CH_2), 41.5 (CH), 51.1 (CH), 92.6 (C), 118.5 (CH), 126.1 (CH), 126.7 (CH), 131.7 (C), 132.2 (C), 133.5 (CH and C), 133.9 (CH), 140.4 (C), 142.7 (C), 161.4 (C), 183.7 (C), 184.3 (C); m/z (CI) 426.0245 (MH^+ . $\text{C}_{20}\text{H}_{17}^{35}\text{Cl}_2^{37}\text{ClNO}_3$ requires 426.0247), 390 (85%), 356 (30), 279 (35), 261 (30), 162 (10), 130 (7), 85 (33), 69 (48).

Method B- (1*R**,12*bR**)-1,2,3,4,6,12*b*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**206**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.060 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C, before 1,4-naphthoquinone (**205**) (0.15 g, 0.10 mmol) was added. The reaction mixture was stirred for 48 h at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether 7:3) gave (1*R**,12*bR**)-1,2,3,4,6,12*b*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**206**) (0.12 g, 61%) as a yellow solid. Spectroscopic data as described above.

Dimethyl (1*R,7*S**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**207**).**

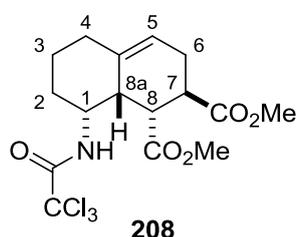


Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) and hydroquinone (0.012 g, 0.11 mmol) was dissolved in toluene (10 mL) and transferred to a Schlenk tube. Dimethyl maleate (0.14 mL, 1.11 mmol) was then added. The tube was purged with Ar and sealed. The sealed tube was stirred at 120 °C for 6 days. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 11:9) gave dimethyl (1*R**,7*S**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**207**) (0.063 g, 41%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.37; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3395 (NH), 2951 (CH), 2939 (CH), 1730 (CO), 1710 (CO), 1502, 1436, 1201, 1173, 1162, 819, 734; δ_H (500 MHz, CDCl_3) 1.46–1.57 (2H, m, 2-*HH* and 3-*HH*), 1.60–1.67 (1H, m, 3-*HH*), 2.05–2.17 (2H, m, 2-*HH* and 4-*HH*), 2.33–2.42 (2H, m, 4-*HH* and 6-*HH*), 2.65 (1H, dt, J 11.3, 4.6 Hz, 7-H), 2.85–2.95 (2H, m, 6-*HH* and 8*a*-H), 3.43 (1H, dd, J 8.6, 4.6 Hz, 8-H), 3.64 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 4.41–4.47 (1H, m, 1-H), 5.80–5.85 (1H, m, 5-H), 6.88 (1H, d, J 7.5 Hz, NH); δ_C (126 MHz, CDCl_3) 20.3 (CH_2), 23.9 (CH_2), 29.5 (CH_2), 33.5 (CH_2), 41.3 (CH), 41.6 (CH), 41.8 (CH), 50.1 (CH), 52.0 (CH_3), 52.1 (CH_3), 92.5 (C),

124.2 (CH), 132.8 (C), 160.7 (C), 173.3 (C), 173.5 (C); m/z (CI) 412.0475 (MH^+). $C_{16}H_{21}^{35}Cl_3NO_5$ requires 412.0485), 378 (100%), 344 (40), 310 (10), 235 (55), 193 (10), 113 (12), 69 (42).

Method B- Dimethyl (1*R**,7*S**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**207**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B), using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.050 g, 0.40 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before dimethyl maleate (0.15 mL, 1.20 mmol) was added. The reaction mixture was stirred for 120 h at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave dimethyl (1*R**,7*S**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**207**) (0.065 g, 39%) as a colourless oil. Spectroscopic data as described above.

Dimethyl (1*R,7*R**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**208**).**

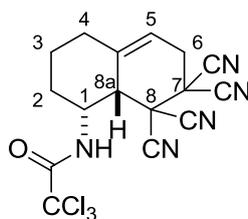


Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.11 g, 0.41 mmol) and hydroquinone (0.012 g, 0.11 mmol) was dissolved in toluene (10 mL) and transferred to a Schlenk tube. Dimethyl fumarate (0.088 g, 0.61 mmol) was then added. The tube was purged with Ar and sealed. The sealed tube was stirred at 111 °C for 48 h. The solution was then cooled to room temperature and the solvent was then evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave dimethyl (1*R**,7*R**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**208**) (0.075 g, 45%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.41; ν_{max}/cm^{-1} (neat) 3347 (NH), 2951 (CH), 1715 (CO), 1505, 1437, 1173, 910; δ_H (500 MHz, $CDCl_3$) 1.36–1.47 (1H, m, 3-*HH*), 1.66–1.74 (1H, m, 3-*HH*), 1.77–1.85 (1H, m, 2-*HH*), 1.88–1.94 (1H, m, 2-*HH*), 2.02–2.15 (1H, m, 4-*HH*), 2.30–2.39 (1H, m, 4-*HH*), 2.47 (1H, ddd, J 16.9, 6.3, 5.7 Hz, 6-*HH*), 2.74–2.87 (2H, m, 7-H and 8*a*-H), 3.06 (1H, ddd, J 12.7, 11.2, 5.7 Hz, 8-

H), 3.14 (1H, dd, J 12.7, 7.1 Hz, 6-HH), 3.67 (3H, s, OCH₃), 3.71 (3H, s, OCH₃), 4.10 (1H, dq, J 9.4, 3.1 Hz, 1-H), 5.72–5.79 (1H, m, 5-H), 6.67 (1H, d, J 9.4 Hz, NH); δ_C (126 MHz, CDCl₃) 22.8 (CH₂), 27.6 (CH₂), 35.0 (CH₂), 37.6 (CH₂), 41.2 (CH), 41.6 (CH), 44.4 (CH), 50.2 (CH), 52.1 (CH₃), 52.3 (CH₃), 92.8 (C), 121.5 (CH), 134.7 (C), 160.1 (C), 172.2 (C), 172.4 (C); m/z (CI) 412.0469 (MH⁺. C₁₆H₂₁³⁵Cl₃NO₅ requires 412.0485), 378 (75%), 344 (100), 310 (30), 235 (23), 193 (18), 113 (32).

Method B- Dimethyl (1*R**,7*R**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**208**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B), using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.060 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C, before dimethyl fumarate (0.11 g, 0.73 mmol) was added. The reaction mixture was stirred for 120 h at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave dimethyl (1*R**,7*R**,8*R**,8*aS**)-1,2,3,4,6,7,8,8*a*-octahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**208**) (0.061 g, 31%) as a colourless oil. Spectroscopic data as described above.

(1*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-Octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**209**).



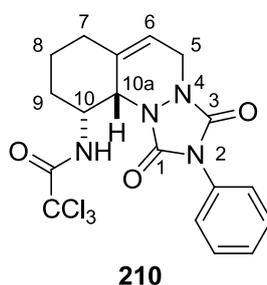
209

Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) was dissolved in toluene (8 mL) in a Schlenk tube, and hydroquinone (0.012 g, 0.11 mmol) and tetracyanoethylene (0.28 g, 2.22 mmol) were added. The reaction mixture was stirred at 75 °C for 44 h. The reaction mixture was concentrated *in vacuo*. Flash column chromatography using silica (petroleum ether/ethyl acetate 3:1) gave (1*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**209**) (0.097 g, 66%) as an orange oil. R_f (50% ethyl acetate/petroleum ether) 0.56; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3313 (NH), 2945 (CH), 2359 (CN), 2342 (CN), 1699 (CO), 1514, 1275, 910, 733; δ_H (500 MHz, CDCl₃) 1.53 (1H, qt, J 12.7,

3.9 Hz, 3-*HH*), 1.82 (1H, qd, *J* 12.7, 3.9 Hz, 2-*HH*), 1.92–1.99 (1H, m, 3-*HH*), 2.13–2.25 (2H, m, 2-*HH* and 4-*HH*), 2.49–2.56 (1H, m, 4-*HH*), 3.06 (1H, ddt, *J* 18.1, 6.2, 2.1 Hz, 6-*HH*), 3.15 (1H, ddd, *J* 18.1, 5.3, 2.1 Hz, 6-*HH*), 3.37 (1H, dd, *J* 11.5, 1.3 Hz, 8a-H), 4.11–4.20 (1H, m, 1-H), 5.70–5.74 (1H, m, 5-H), 7.11 (1H, d, *J* 9.6 Hz, NH); δ_{C} (126 MHz, CDCl_3) 23.4 (CH_2), 31.4 (CH_2), 32.3 (CH_2), 34.1 (CH_2), 39.7 (C), 42.6 (C), 47.1 (CH), 54.4 (CH), 91.9 (C), 108.5 (C), 110.3 (C), 110.9 (C), 112.1 (C), 115.8 (CH), 135.0 (C), 161.9 (C); *m/z* (CI) 396.0197 (MH^+ . $\text{C}_{16}\text{H}_{13}^{35}\text{Cl}_3\text{N}_5\text{O}$ requires 396.0186), 362 (100%), 328 (20), 292 (25), 264 (30), 237 (25), 183 (42), 167 (50), 147 (25), 107 (65), 69 (74).

Method B- (1*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-Octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**209**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.060 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C before tetracyanoethylene (0.37 g, 2.88 mmol) was added. The reaction mixture was stirred for 24 h at 111 °C. Flash column chromatography using silica (petroleum ether/ethyl acetate, 3:1) gave (1*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**209**) (0.13 g, 66%) as an orange oil. Spectroscopic data as described above.

(10*R**,10*aS**)-5,7,8,9,10,10*a*-Hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**210**).

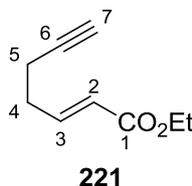


Method A- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) was dissolved in toluene (10 mL) and 4-phenyl-1,2,4-triazole-3,5-dione (**254**) (0.10 g, 0.56 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The reaction mixture was stirred at 111 °C for 18 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica

(petroleum ether/ethyl acetate, 1:3) gave (10*R**,10*aS**)-5,7,8,9,10,10*a*-hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**210**) (0.079 g, 48%) as a brown oil. R_f (75% ethyl acetate/petroleum ether) 0.46; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3418 (NH), 3055 (ArH), 2940 (CH), 2361, 1775, 1705 (CO), 1505, 1420, 819, 733; δ_{H} (500 MHz, CDCl_3) 1.45–1.55 (1H, m, 8-*HH*), 1.89–1.99 (2H, m, 9-*HH* and 8-*HH*), 2.04–2.11 (1H, m, 9-*HH*), 2.22–2.31 (1H, m, 7-*HH*), 2.59 (1H, dtd, J 13.5, 4.2, 2.1 Hz, 7-*HH*), 3.96 (1H, ddd, J 16.3, 5.6, 2.7 Hz, 5-*HH*), 4.30 (1H, dd, J 16.3, 4.9 Hz, 5-*HH*), 4.59–4.63 (1H, m, 10*a*-H), 5.04 (1H, dq, J 8.5, 3.3 Hz, 10-H), 5.93–5.97 (1H, m, 6-H), 6.85 (1H, d, J 8.5 Hz, NH), 7.36–7.41 (1H, m, ArH), 7.45–7.53 (4H, m, 4 \times ArH); δ_{C} (126 MHz, CDCl_3) 22.4 (CH_2), 28.7 (CH_2), 33.8 (CH_2), 43.0 (CH_2), 49.4 (CH), 56.3 (CH), 92.7 (C), 116.6 (CH), 126.2 (CH), 128.4 (2 \times CH), 129.2 (2 \times CH), 131.0 (C), 132.0 (C), 150.8 (C), 152.5 (C), 161.3 (C); m/z (EI) 442.0358 (M^+ . $\text{C}_{18}\text{H}_{17}^{35}\text{Cl}_3\text{N}_4\text{O}_3$ requires 442.0366), 408 (10%), 325 (5), 281 (100), 253 (10), 162 (5), 119 (20), 91 (20).

Method B (10*R**,10*aS**)-5,7,8,9,10,10*a*-Hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**210**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.050 g, 0.40 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.033 g, 0.040 mmol) for 48 h at 75 °C before 4-phenyl-1,2,4-triazole-3,5-dione (**254**) (0.11 g, 0.60 mmol) was added. The reaction mixture was stirred for 24 h at 111 °C. Flash column chromatography using silica (petroleum ether/ethyl acetate, 1:3) gave (10*R**,10*aS**)-5,7,8,9,10,10*a*-hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (**210**) (0.13 g, 75%) as a brown oil. Spectroscopic data as described above.

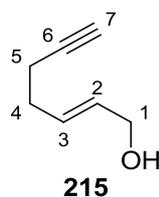
Ethyl (2*E*)-hept-2-en-6-ynoate (221**).**¹⁷³



Dimethyl sulfoxide (3.60 mL, 50.8 mmol) was added to a stirred solution of oxalyl chloride (2.49 mL, 28.4 mmol) in dichloromethane (100 mL) at –78 °C. The mixture was stirred for 0.3 h before 4-pentyn-1-ol (**220**) (1.70 g, 20.3 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (14.1 mL, 102 mmol) was added. This reaction mixture was stirred for 0.5 h at –78 °C and

then allowed to warm to room temperature and stirred for a further 3 h. A solution of lithium chloride (1.55 g, 36.5 mmol), triethyl phosphonoacetate (7.24 mL, 36.5 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (5.14 mL, 36.5 mmol) in acetonitrile (70 mL) was then prepared and stirred for 1.0 h. The Swern solution was concentrated *in vacuo*, then the Horner-Wadsworth-Emmons solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with a saturated solution of ammonium chloride (50 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 75 mL). The organic layers were combined, dried (MgSO₄) and concentrated to give an orange oil. Flash column chromatography using silica (diethyl ether/petroleum ether, 1:9) gave ethyl (2*E*)-hept-2-en-6-ynoate (**221**) (2.93 g, 95%) as a yellow oil. Spectroscopic data consistent with literature.¹⁷³ *R_f* (25% diethyl ether/petroleum ether) 0.63; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3302 (C≡C-H), 2984 (CH), 1715 (CO), 1657 (C=C), 1445, 1368, 1267, 1155, 1038, 756; δ_{H} (400 MHz, CDCl₃) 1.30 (3H, t, *J* 7.1 Hz, OCH₂CH₃), 2.01 (1H, t, *J* 2.5 Hz, 7-H), 2.34–2.39 (2H, m, 5-H₂), 2.41–2.48 (2H, m, 4-H₂), 4.20 (2H, q, *J* 7.1 Hz, OCH₂CH₃), 5.90 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.97 (1H, dt, *J* 15.7, 6.7 Hz, 3-H); δ_{C} (126 MHz, CDCl₃) 14.3 (CH₃), 17.4 (CH₂), 31.0 (CH₂), 60.3 (CH₂), 69.4 (CH), 82.7 (C), 122.6 (CH), 146.3 (CH), 166.4 (C); *m/z* (CI) 153 (MH⁺, 100%), 139 (5), 113 (10), 97 (5), 81 (15), 69 (15).

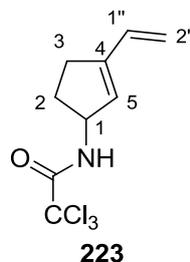
(2*E*)-Hept-2-en-6-yn-1-ol (215).¹⁷⁴



Ethyl (2*E*)-hept-2-en-6-ynoate (**221**) (1.50 g, 9.87 mmol) was dissolved in diethyl ether (50 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. DIBAL-H (1 M in hexane) (21.7 mL, 21.7 mmol) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, before warming to room temperature overnight. The solution was cooled to $0\text{ }^{\circ}\text{C}$ and quenched by the addition of a saturated solution of ammonium chloride (10 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite® and washed with diethyl ether (3 × 50 mL). The filtrate was then dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography using silica (diethyl ether/petroleum ether, 1:1) gave (2*E*)-hept-2-en-6-yn-1-ol (**215**) (1.01 g, 93%) as a yellow oil. Spectroscopic data consistent with literature.¹⁷⁴ *R_f* (50% diethyl ether/petroleum ether) 0.33; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3360 (OH), 3295 (C≡C-H), 2915 (CH), 1670 (C=C), 1433,

1084, 997, 968; δ_{H} (500 MHz, CDCl_3) 1.42 (1H, br s, OH), 1.99 (1H, t, J 2.5 Hz, 7-H), 2.28–2.33 (4H, m, 4- H_2 and 5- H_2), 4.14 (2H, d, J 4.0 Hz, 1- H_2), 5.70–5.81 (2H, m, 2-H and 3-H); δ_{C} (126 MHz, CDCl_3) 18.5 (CH_2), 31.1 (CH_2), 63.5 (CH_2), 68.8 (CH), 83.7 (C), 130.5 (CH), 130.6 (CH); m/z (CI) 111 (MH^+ , 3%), 107 (15), 93 (100), 81 (10), 69 (10).

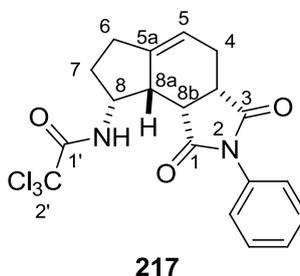
4-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (223).



(*2E*)-Hept-2-en-6-yn-1-ol (**215**) (0.40 g, 3.64 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.10 mL, 0.728 mmol) and trichloroacetonitrile (0.55 mL, 5.45 mmol) was added. 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 (10 mL) containing potassium carbonate (0.05 g) and purged with argon. The reaction mixture was then heated to 140 °C in a sealed tube for 24 h. The reaction mixture was then cooled to room temperature and toluene (68 mL) was added to achieve a concentration of 0.048 M of starting material. Grubbs first generation catalyst (0.225 g, 0.273 mmol) was added and the reaction mixture was heated for 18 h at 75 °C. A further portion of Grubbs first generation catalyst (0.070 g, 0.085 mmol) was added and the reaction mixture was stirred at 75 °C for 24 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 7:1) gave 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.66 g, 71%) as a yellow oil. R_f (50% diethyl ether/petroleum ether) 0.81; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3320 (NH), 2930 (CH), 2855 (CH), 1690 (CO), 1508, 1236, 1065, 908, 818; δ_{H} (500 MHz, CDCl_3) 1.66–1.74 (1H, m, 2-*HH*), 2.35–2.52 (2H, m, 2-*HH* and 3-*HH*), 2.54–2.62 (1H, m, 3-*HH*), 4.92–4.99 (1H, m, 1-H), 5.18 (1H, d, J 10.5 Hz, 2''-*HH*), 5.19 (1H, d, J 17.6 Hz, 2''-*HH*), 5.61 (1H, d, J 1.7 Hz, 5-H), 6.51 (1H, dd, J 17.6, 10.5 Hz, 1''-H), 6.54 (1H, br s, NH); δ_{C} (126 MHz, CDCl_3) 28.4 (CH_2), 30.0 (CH_2), 56.8 (CH), 91.7 (C), 116.6 (CH_2), 126.7 (CH),

131.4 (CH), 146.3 (C), 160.1 (C); m/z (CI) 253.9906 (MH^+ . $C_9H_{11}^{35}Cl_3NO$ requires 253.9906), 220 (58%), 184 (17), 132 (5), 85 (23), 69 (37).

(3a*S,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (217).**

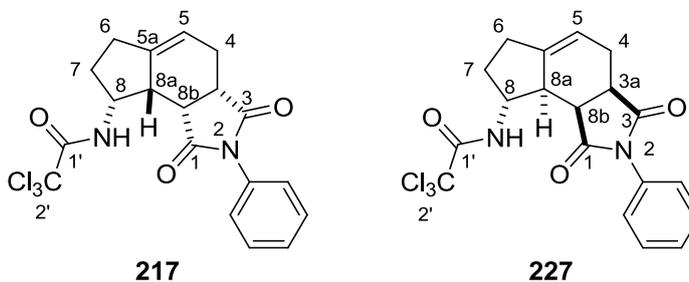


Method A- 4-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.064 g, 0.25 mmol) was dissolved in toluene (10 mL) and *N*-phenyl maleimide (**139**) (0.064 g, 0.37 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The flask was stirred at 75 °C for 24 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:7) gave (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) (0.086 g, 80%) as a white solid. R_f (70% diethyl ether/petroleum ether) 0.44; Mp 174–176 °C; ν_{max}/cm^{-1} (neat) 3304 (NH), 2955 (CH), 2924 (CH), 1695 (CO), 1516, 1388, 1288, 1202, 1182, 822, 750; δ_H (500 MHz, $CDCl_3$) 1.81 (1H, qd, J 12.5, 7.6 Hz, 7-*HH*), 2.10–2.18 (1H, m, 7-*HH*), 2.19–2.38 (2H, m, 6-*HH* and 4-*HH*), 2.47 (1H, dd, J 16.2, 7.6 Hz, 6-*HH*), 2.85 (1H, ddd, J 15.1, 7.2, 1.1 Hz, 4-*HH*), 2.89–2.96 (1H, m, 8a-H), 3.33 (1H, ddd, J 8.7, 7.2, 1.1 Hz, 3a-H), 3.43 (1H, dd, J 8.7, 6.4 Hz, 8b-H), 4.80–4.91 (1H, m, 8-H), 5.75–5.81 (1H, m, 5-H), 7.15–7.20 (2H, m, 2 × ArH), 7.39–7.51 (3H, m, 3 × ArH), 8.95 (1H, d, J 9.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 26.1 (CH_2), 28.6 (CH_2), 31.7 (CH_2), 39.4 (CH), 41.2 (CH), 41.5 (CH), 52.9 (CH), 92.9 (C), 117.1 (CH), 126.5 (2 × CH), 129.2 (CH), 129.3 (2 × CH), 131.5 (C), 145.8 (C), 162.3 (C), 178.6 (C), 179.7 (C); m/z (CI) 427.0373 (MH^+ . $C_{19}H_{18}^{35}Cl_3N_2O_3$ requires 427.0383), 393 (65%), 359 (100), 325 (65), 311 (20), 266 (25), 174 (25), 113 (25), 71 (73).

Method B- (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) was synthesised as described for (3a*S**,9*R**,9a*S**,9b*R**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (*2E*)-hept-2-en-6-yn-1-ol (**215**) (0.050 g, 0.48 mmol). The reaction

mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C before *N*-phenyl maleimide (**139**) (0.13 g, 0.73 mmol) was added. The reaction mixture was stirred for 72 h at 75 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:7) gave (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) (0.13 g, 62%) as white solid. Spectroscopic data as described above.

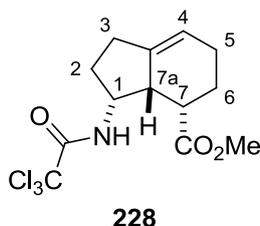
(3a*S,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) and (3a*R**,8*R**,8a*R**,8b*S**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**).**



4-Ethyl-1''-ene1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.075 g, 0.30 mmol) was dissolved in methanol (10 mL) and *N*-phenyl maleimide (**139**) (0.076 g, 0.44 mmol) was added with hydroquinone (0.012 g, 0.11 mmol). The flask was stirred at 75 °C for 24 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography on silica (petroleum ether/diethyl ether, 2:3) gave the product as a 1:1 mixture of two diastereomers (0.10 g, 79%). Elution with 3:7 diethyl ether/petroleum ether gave (3a*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**217**) (0.049 g, 39%) as a white solid. Spectroscopic data as described above. Elution with 6:4 diethyl ether/petroleum ether) gave (3a*R**,8*R**,8a*R**,8b*S**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**227**) (0.050 g, 40%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.17; Mp 161–163 °C; ν_{\max} / cm^{-1} (neat) 3331 (NH), 2951 (CH), 2908 (CH), 1777 (CO), 1652 (CO), 1527, 1498, 1180, 1150; δ_{H} (500 MHz, CDCl_3) 1.81–1.89 (1H, m, 7-*HH*), 2.05–2.21 (2H, m, 7-*HH* and 4-*HH*), 2.27–2.48 (2H, m, 6- H_2), 2.61 (1H, m, 8a-H), 2.77 (1H, ddd, J 15.5, 7.2, 1.3 Hz, 4-*HH*), 3.25 (1H, td, J 8.9, 1.3 Hz, 3a-H), 3.64 (1H, dd, J 8.9, 7.2 Hz, 8b-H), 4.88–4.95 (1H, m, 8-H), 5.65–5.72 (1H, m, 5-H), 6.74 (1H, d, J 5.1 Hz, NH), 7.10–7.15 (1H, m, 2 × ArH), 7.28–7.33 (1H, m, ArH), 7.35–7.41 (2H, m, 2 ×

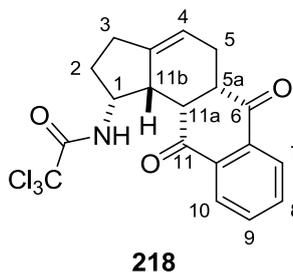
ArH); δ_C (126 MHz, $CDCl_3$) 25.5 (CH_2), 29.0 (CH_2), 31.4 (CH_2), 40.3 (CH), 41.5 (CH), 45.9 (CH), 54.7 (CH), 92.6 (C), 117.3 (CH), 126.4 (CH), 128.7 ($2 \times CH$), 129.1 ($2 \times CH$), 131.8 (C), 144.4 (C), 162.0 (C), 177.2 (C), 178.8 (C); m/z (CI) 427.0379 (MH^+ . $C_{19}H_{18}^{35}Cl_3N_2O_3$ requires 427.0383), 393 (55%), 359 (100), 325 (62), 311 (15), 266 (30), 174 (24), 113 (21).

Methyl (1*R,7*S**,7*aS**)-2,3,5,6,7,7*a*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (228).**



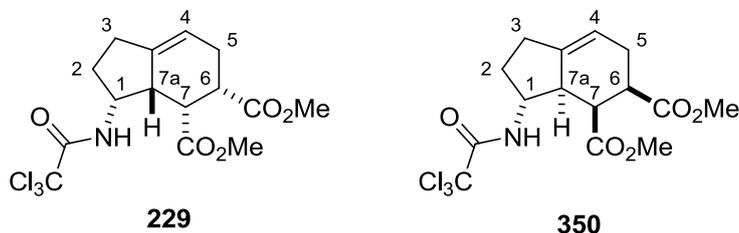
Methyl (1*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**228**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.050 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.041 g, 0.050 mmol) for 48 h at 75 °C, before methyl acrylate (**203**) (0.13 mL, 1.44 mmol) was added. The reaction mixture was stirred for 13 days at 111 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 20:7) gave methyl (1*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**228**) (0.074 g, 45%) as a colourless oil. R_f (50% petroleum ether/ diethyl ether) 0.66; ν_{max}/cm^{-1} (neat) 3410 (NH), 2953 (CH), 1709 (CO), 1508, 1198, 1171, 818, 735; δ_H (500 MHz, $CDCl_3$) 1.69–1.83 (2H, m, 2-*HH* and 3-*HH*), 1.95–2.11 (4H, m, 2-*HH*, 5-*HH* and 6- H_2), 2.15–2.25 (1H, m, 3-*HH*), 2.32 (1H, dd, J 15.2, 6.3 Hz, 5-*HH*), 2.79–2.89 (2H, m, 7-H and 7*a*-H), 3.60 (1H, s, OCH_3), 4.51 (1H, dq, J 8.7, 7.2 Hz, 1-H), 5.45 (1H, br s, 4-H), 7.51 (1H, d, J 7.2 Hz, NH); δ_C (126 MHz, $CDCl_3$) 22.6 (CH_2), 26.0 (CH_2), 30.2 (CH_2), 31.7 (CH_2), 39.3 (CH), 42.5 (CH), 52.0 (CH), 53.3 (CH_3), 92.9 (C), 117.7 (CH), 140.1 (C), 161.7 (C), 175.7 (C); m/z (CI) 342.0247 (MH^+ . $C_{13}H_{17}^{35}Cl_2^{37}ClNO_3$ requires 342.0246), 324 (60%), 306 (29), 257 (8), 230 (11), 195 (49), 179 (28), 157 (50), 141 (16), 73 (24).

(1*R,5*aS**,11*aR**,11*bS**)-1,2,3,5,11*a*,11*b*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11(5*aH*)-dione (218).**



(1*R**,5*aS**,11*aR**,11*bS**)-1,2,3,5,11*a*,11*b*-Hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11(5*aH*)-dione (**218**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.055 g, 0.50 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.041 g, 0.050 mmol) for 48 h at 75 °C, before 1,4-naphthoquinone (**205**) (0.12 g, 0.75 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. Flash column chromatography using silica (petroleum ether/ diethyl ether, 1:1) gave (1*R**,5*aS**,11*aR**,11*bS**)-1,2,3,5,11*a*,11*b*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11(5*aH*)-dione (**218**) (0.097 g, 47%) as white solid. R_f (50% diethyl ether/petroleum ether) 0.40; Mp 153–155 °C; ν_{\max} /cm⁻¹ (neat) 3364 (NH), 2940 (CH), 2847 (CH), 2338, 1682 (CO), 1589, 1512, 1281, 1247, 810, 741; δ_H (500 MHz, CDCl₃) 1.95–2.15 (2H, m, 2-*HH* and 5-*HH*), 2.15–2.30 (2H, m, 2-*HH* and 3-*HH*), 2.35–2.48 (2H, m, 3-*HH* and 5-*HH*), 2.91–2.97 (1H, m, 11*b*-H), 3.33 (1H, ddd, J 11.3, 7.2, 4.4 Hz, 5*a*-H), 3.51 (1H, t, J 4.4 Hz, 11*a*-H), 4.65 (1H, m, 1-H), 5.31–5.36 (1H, m, 4-H), 7.44 (1H, d, J 8.8 Hz, NH), 7.60–7.72 (2H, m, 2 × ArH), 7.84 (1H, dd, J 7.3, 1.6 Hz, ArH), 7.99 (1H, dd, J 7.3, 1.6 Hz, ArH); δ_C (126 MHz, CDCl₃) 26.9 (CH₂), 31.4 (CH₂), 32.0 (CH₂), 41.5 (CH), 48.6 (CH), 49.5 (CH), 52.9 (CH), 93.0 (C), 114.2 (CH), 126.4 (CH) 127.4 (CH), 132.6 (C), 134.6 (CH), 134.8 (CH), 135.0 (C), 141.7 (C), 161.8 (C), 198.2 (C), 199.9 (C); m/z (EI) 413.0159 (M⁺. C₁₉H₁₆³⁵Cl₂³⁷ClNO₃ requires 413.0169), 376 (5%), 324 (5) 294 (5), 250 (100), 232 (40), 205 (25), 165 (18), 117 (70), 91 (32), 77 (22).

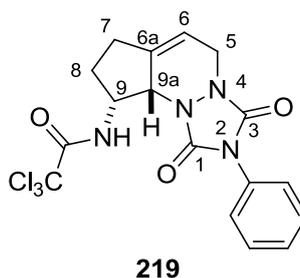
Dimethyl (1*R,6*S**,7*R**,7*aS**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (229) and dimethyl (1*R**,6*R**,7*S**,7*aR**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (350).**



Dimethyl (1*R**,6*S**,7*R**,7*aS**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (**229**) and dimethyl (1*R**,6*R**,7*S**,7*aR**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (**350**) were synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.050 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C before dimethyl maleate (0.18 mL, 1.44 mmol) was added. The reaction mixture was stirred for 24 h at 120 °C. Flash column chromatography using silica afforded the product as a 3:1 mixture of two diastereomers as colourless oils. Elution with 11:9 petroleum ether/diethyl ether gave dimethyl (1*R**,6*S**,7*R**,7*aS**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (**229**) (0.065 g, 34%) as the major diastereomer as a colourless oil. R_f (50% petroleum ether/diethyl ether) 0.51; $\nu_{\max}/\text{cm}^{-1}$ 2955 (CH), 1709 (CO), 1508 (C=C), 1435, 1204, 1026; δ_{H} (400 MHz, CDCl_3) 1.61–1.73 (1H, m, 2-*HH*), 1.95–2.05 (1H, m, 2-*HH*), 2.13–2.25 (1H, m, 3-*HH*), 2.27–2.46 (3H, m, 3-*HH* and 5- H_2), 2.80 (1H, ddd, J 10.3, 7.1, 3.4 Hz, 6-H), 2.90–2.99 (1H, m, 7*a*-H), 3.37 (1H, dd, J 4.6, 3.4 Hz, 7-H), 3.57 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 4.58 (1H, dq, J 9.7, 6.6 Hz, 1-H), 5.47 (1H, s, 4-H), 7.85 (1H, br s, NH); δ_{C} (126 MHz, CDCl_3) 25.3 (CH_2), 30.2 (CH_2), 32.0 (CH_2), 41.7 (CH), 42.6 (CH), 43.7 (CH), 52.1 (CH_3), 52.3 (CH_3), 53.1 (CH), 92.8 (C), 117.2 (CH), 139.9 (C), 161.9 (C), 173.3 (C), 173.7 (C); m/z (ESI) 420.0137 (MNa^+ . $\text{C}_{15}\text{H}_{18}^{35}\text{Cl}_3\text{NNaO}_5$ requires 420.0143). Further elution with 9:11 petroleum ether/diethyl ether gave dimethyl (1*R**,6*R**,7*S**,7*aR**)-2,3,5,6,7,7*a*-hexahydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (**350**) (0.022 g, 11%) as the minor diastereomer as a colourless oil. R_f (50% petroleum ether/diethyl ether) 0.45; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2961 (CH), 1713 (CO), 1513, 1440, 1223, 1029; δ_{H} (500 MHz, CDCl_3) 1.65–1.73

(1H, m, 2-*HH*), 1.99–2.09 (1H, m, 2-*HH*), 2.25–2.34 (4H, m, 3-*H*₂ and 5-*H*₂), 2.75–2.82 (1H, m, 7a-*H*), 2.90 (1H, q, *J* 7.1 Hz, 6-*H*), 3.30 (1H, t, *J* 7.1 Hz, 7-*H*), 3.64 (3H, s, OCH₃), 3.66 (3H, s, OCH₃), 4.47–4.55 (1H, m, 1-*H*), 5.58 (1H, s, 4-*H*), 7.02 (1H, d, *J* 9.0 Hz, NH); δ_c (126 MHz, CDCl₃) 25.8 (CH₂), 28.4 (CH₂), 31.3 (CH₂), 40.5 (CH), 40.6 (CH), 41.6 (CH), 52.1 (CH₃), 52.3 (CH₃), 53.1 (CH), 92.8 (C), 117.7 (CH), 139.6 (C), 161.2 (C), 173.6 (C), 174.4 (C); *m/z* (ESI) 420.0135 (MNa⁺. C₁₅H₁₈³⁵Cl₃NNaO₅ requires 420.0143).

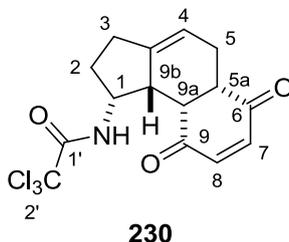
(9*R,9a*S**)-2-Phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (219).**



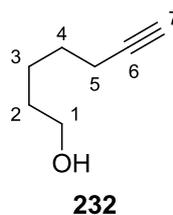
(9*R**,9a*S**)-2-Phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**219**) was synthesised as described for (3a*S**,9*R**,9a*S**,9b*R**)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (*2E*)-hept-2-en-6-yn-1-ol (**215**) (0.054 g, 0.48 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.040 g, 0.048 mmol) for 48 h at 75 °C, before 4-phenyl-1,2,4-triazole-3,5-dione (**254**) (0.13 g, 0.73 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. Flash column chromatography using silica (dichloromethane/methanol, 19:1) gave (9*R**,9a*S**)-2-phenyl-7,8,9,9a-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]-triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**219**) (0.095 g, 46%) as a white solid. *R_f* (10% methanol/dichloromethane) 0.58; Mp 55–57 °C; ν_{\max} /cm⁻¹ (neat) 3396 (NH), 3057 (ArH), 2359, 2342, 1773 (CO), 1699 (CO), 1516, 1503, 1419, 1265, 1140, 820, 731; δ_H (500 MHz, CDCl₃) 2.13–2.22 (1H, m, 8-*HH*), 2.31 (1H, dt, *J* 15.0, 5.6 Hz, 8-*HH*), 2.53–2.61 (2H, m, 7-*H*₂), 4.11 (1H, dquin., *J* 16.4, 2.8 Hz, 5-*HH*), 4.32–4.41 (2H, m, 5-*HH* and 9a-*H*), 4.89 (1H, q, *J* 5.6 Hz, 9-*H*), 5.93–5.98 (1H, m, 6-*H*), 6.75 (1H, d, *J* 5.6 Hz, NH), 7.38–7.53 (5H, m, 5 × ArH); δ_c (126 MHz, CDCl₃) 24.9 (CH₂), 27.8 (CH₂), 42.5 (CH₂), 53.3 (CH), 59.9 (CH), 92.6 (C), 115.6 (CH), 125.4 (2 × CH), 128.4 (CH), 129.2 (2 × CH), 130.9 (C), 137.0 (C), 151.5 (C), 153.2 (C), 161.4 (C); *m/z* (EI) 428.0208 (M⁺. C₁₇H₁₅³⁵Cl₃N₄O₃

requires 428.0210), 393 (5%), 343 (10), 311 (20), 267 (100), 241 (5), 192 (8), 148 (23), 119 (83), 91 (70), 66 (29).

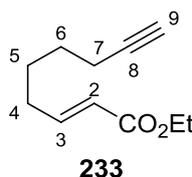
(1*R,5*aS**,9*aR**,9*bS**)-1,2,3,5,5*a*,9*a*,9*b*-Heptahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]naphthalene-6,9-dione (**230**).**



(1*R**,5*aS**,9*aR**,9*bS**)-1,2,3,5,5*a*,9*a*,9*b*-Heptahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]naphthalene-6,9-dione (**230**) was synthesised as described for (3*aS**,9*R**,9*aS**,9*bR**)-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**198**) (Method B) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.055 g, 0.50 mmol). The reaction mixture was stirred with Grubbs first generation catalyst (0.041 g, 0.050mmol) for 48 h at 75 °C, before *p*-benzoquinone (0.16 g, 1.50 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave (1*R**,5*aS**,9*aR**,9*bS**)-1,2,3,5,5*a*,9*a*,9*b*-heptahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]naphthalene-6,9-dione (**230**) (0.040 g, 22%) as yellow oil. R_f (50% diethyl ether/petroleum ether) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3346 (NH), 2953 (CH), 2927 (CH), 1699 (CO), 1662 (CO), 1509, 1298, 1074; δ_{H} (500 MHz, CDCl_3) 2.02–2.33 (4H, m, 2- H_2 and 3- H_2), 2.40–2.51 (2H, m, 5- H_2), 2.88–2.94 (1H, m, 9*b*-H), 3.21–3.27 (1H, m, 5*a*-H), 3.41 (1H, t, J 4.6 Hz, 9*a*-H), 4.62–4.72 (1H, m, 1-H), 5.39–5.43 (1H, m, 4-H), 6.61 (2H, s, 7-H and 8-H), 7.34 (1H, d, J 9.2 Hz, NH); δ_{C} (126 MHz, CDCl_3) 26.8 (CH₂), 29.7 (CH₂), 31.7 (CH₂), 41.1 (CH), 48.5 (CH), 48.8 (CH), 52.9 (CH), 92.3 (C), 114.3 (CH), 138.3 (CH), 139.9 (CH), 141.7 (C), 161.9 (C), 200.4 (C), 201.2 (C); m/z (CI) 364.0089 (MH^+ . $\text{C}_{15}\text{H}_{15}^{35}\text{Cl}_2^{37}\text{ClNO}_3$ requires 364.0090), 328 (8%), 243 (12), 217 (40), 187 (60), 113 (20), 73 (100).

6-Heptyn-1-ol (232).¹¹²

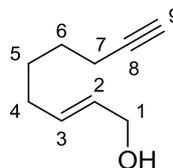
Lithium aluminium hydride (0.90 g, 23.8 mmol) was dissolved in diethyl ether (100 mL) and cooled to 0 °C. A solution of 6-heptyn-1-oic acid (**231**) (1.50 g, 11.9 mmol) in diethyl ether was then added slowly. The reaction mixture was then warmed to room temperature and stirred for 1 h. The reaction was then quenched with 1 M hydrochloric acid (40 mL) and the mixture was stirred for 0.5 h. The product was extracted using diethyl ether (4 × 50 mL), the organic layers were combined, dried (MgSO₄), filtered and concentrated to give a colourless oil. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave 6-heptyn-1-ol (**232**) (1.28 g, 96%) as a colourless oil. Spectroscopic data consistent with literature.¹¹² *R_f* (50% diethyl ether/petroleum ether) 0.28; δ_{H} (500 MHz, CDCl₃) 1.25 (1H, s, OH), 1.38–1.57 (6H, m, 2-H₂, 3-H₂ and 4-H₂), 1.88 (1H, t, *J* 2.7 Hz, 7-H), 2.14 (2H, td, *J* 6.9, 2.7 Hz, 5-H₂), 3.59 (2H, t, *J* 6.5 Hz, 1-H₂); δ_{C} (126 MHz, CDCl₃) 18.4 (CH₂), 24.9 (CH₂), 28.2 (CH₂), 32.2 (CH₂), 62.8 (CH₂), 68.3 (CH), 84.4 (C); *m/z* (CI) 113 (MH⁺, 85%), 95 (52), 73 (100), 69 (35).

Ethyl (2*E*)-non-2-en-8-ynoate (233).

Ethyl (2*E*)-non-2-en-8-ynoate (**233**) was synthesised as described for the synthesis of ethyl (2*E*)-hept-2-en-6-ynoate (**221**) using 6-heptyn-1-ol (**232**) (0.30 g, 2.70 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 9:1) gave ethyl (2*E*)-non-2-en-8-ynoate (**233**) (0.35 g, 73%) as a colourless oil. *R_f* (50% diethyl ether/petroleum ether) 0.69; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3300, 2940 (CH), 1715 (CO), 1653 (C=C), 1368, 1182, 1145, 1041; δ_{H} (500 MHz, CDCl₃) 1.29 (3H, t, *J* 7.1 Hz, OCH₂CH₃), 1.52–1.64 (4H, m, 5-H₂ and 6-H₂), 1.95 (1H, t, *J* 2.7 Hz, 9-H), 2.18–2.27 (4H, m, 4-H₂ and 7-H₂), 4.19 (2H, q, *J* 7.1 Hz, OCH₂CH₃), 5.85 (1H, dt, *J* 15.6, 1.6 Hz, 2-H), 6.96 (1H, dt, *J* 15.6, 7.1 Hz, 3-H); δ_{C} (126 MHz, CDCl₃) 14.3 (CH₃), 18.2 (CH₂), 27.0 (CH₂), 27.8 (CH₂), 31.6 (CH₂), 60.2

(CH₂), 68.5 (CH), 84.0 (C), 121.7 (CH), 148.6 (CH), 166.6 (C); *m/z* (CI) 181.1232 (MH⁺. C₁₁H₁₇O₂ requires 181.1229), 171 (5%), 113 (15), 81 (27), 69 (45).

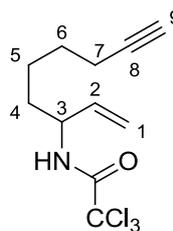
(2E)-Non-2-en-8-yn-1-ol (234).¹⁷⁵



234

(2E)-Non-2-en-8-yn-1-ol (**234**) was synthesised as described for the synthesis of (2E)-hept-2-en-6-yn-1-ol (**215**) using ethyl (2E)-nona-2-en-8-ynoate (**233**) (0.35 g, 1.94 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 9:11) gave (2E)-nona-2-en-8-yn-1-ol (**234**) (0.26 g, 99%) as a yellow oil. Spectroscopic data consistent with literature.¹⁷⁵ *R_f* (50% petroleum ether/diethyl ether) 0.33; *v*_{max}/cm⁻¹ (neat) 3296 (OH), 2934 (CH), 1670 (C=C), 1460, 1088; *δ*_H (500 MHz, CDCl₃) 1.14–1.19 (1H, m, OH), 1.40–1.52 (4H, m, 5-H₂ and 6-H₂), 1.88 (1H, t, *J* 2.7 Hz, 9-H), 2.01 (2H, q, *J* 6.2 Hz, 4-H₂), 2.13 (2H, td, *J* 6.8, 2.7 Hz, 7-H₂), 4.03 (2H, dd, *J* 5.6, 4.9 Hz, 1-H₂), 5.55–5.65 (2H, m, 2-H and 3-H); *δ*_C (126 MHz, CDCl₃) 18.3 (CH₂), 27.9 (CH₂), 28.1 (CH₂), 31.6 (CH₂), 63.8 (CH₂), 68.3 (CH), 84.4 (C), 129.3 (CH), 133.8 (CH); *m/z* (CI) 139.1122 (MH⁺. C₉H₁₅O requires 139.1123), 121 (100%), 107 (10), 93 (45), 79 (40).

3-(2',2',2'-Trichloromethylcarbonylamino)non-1-en-8-yne (235).

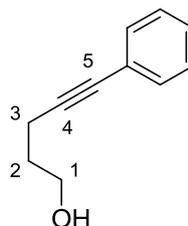


235

(2E)-Non-2-en-8-yn-1-ol (**234**) (0.15 g, 1.11 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.041 mL, 0.29 mmol) and trichloroacetonitrile (0.168 mL, 1.67 mmol). 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction

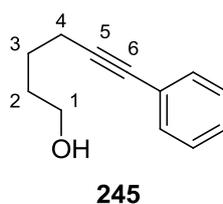
mixture was then heated to 140 °C and stirred for 48 h, before cooling to room temperature. The solvent was then evaporated. Flash column chromatography on silica (petroleum ether/diethyl ether, 3:2) gave 3-(2',2',2'-trichloromethylcarbonylamino)non-1-en-8-yne (**235**) (0.27 g, 87%) as a yellow oil. R_f (50% diethyl ether/petroleum ether) 0.60; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3310 (NH), 2940 (CH), 1697 (CO), 1512, 1435, 1242, 817; δ_{H} (500 MHz, CDCl_3) 1.37–1.68 (6H, m, 4-H₂, 5-H₂ and 6-H₂), 1.88 (1H, t, J 2.7 Hz, 9-H), 2.15 (2H, td, J 6.8, 2.7 Hz, 7-H₂), 4.37 (1H, quin, J 5.7 Hz, 3-H), 5.15 (1H, d, J 10.5 Hz, 1-HH), 5.19 (1H, d, J 17.2 Hz, 1-HH), 5.74 (1H, ddd, J 17.2, 10.5, 5.7 Hz, 2-H), 6.48 (1H, s, NH); δ_{C} (126 MHz, CDCl_3) 18.2 (CH₂), 24.5 (CH₂), 27.9 (CH₂), 33.9 (CH₂), 53.4 (CH), 68.7 (CH), 83.9 (C), 92.8 (C), 116.3 (CH₂), 136.5 (CH), 161.2 (C); m/z (CI) 284.0196 (MH^+ . $\text{C}_{11}\text{H}_{15}^{35}\text{Cl}_2^{37}\text{ClNO}$ requires 284.0191), 248 (18%), 212 (60), 146 (20), 113 (28), 73 (100).

5-Phenylpent-4-yn-1-ol (**244**).¹⁷⁶

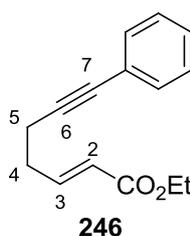


244

Bis(triphenylphosphine)palladium(II) dichloride (0.022 g, 0.031 mmol) and copper iodide (0.012 g, 0.062 mmol) were dissolved in triethylamine (43 mL) and iodobenzene (0.42 mL, 3.75 mmol) was added and stirred at room temperature for 0.1 h. 4-Pentyn-1-ol (**220**) (0.26 g, 3.12 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo* and flash column chromatography using silica (petroleum ether/ethyl acetate, 3:1) gave 5-phenylpent-4-yn-1-ol (**244**) (0.49 g, 98%) as a colourless oil. The spectroscopic data was consistent with the literature.¹⁷⁶ R_f (50% petroleum ether/ethyl acetate) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3380 (OH), 2950 (CH), 1700, 1490, 1442, 1217, 1031, 752; δ_{H} (500 MHz, CDCl_3) 1.63 (1H, s, OH), 1.85 (2H, quin., J 6.5 Hz, 2-H₂), 2.53 (2H, t, J 6.5 Hz, 3-H₂), 3.81 (2H, t, J 6.5 Hz, 1-H₂), 7.24–7.29 (3H, m, 3 × ArH), 7.36–7.40 (2H, m, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 16.0 (CH₂), 31.4 (CH₂), 61.8 (CH₂), 81.2 (C), 89.3 (C), 123.7 (C), 127.7 (CH), 128.2 (2 × CH), 131.6 (2 × CH); m/z (EI) 160 (M^+ . 39%), 141 (100), 128 (38), 115 (71), 104 (32), 85 (35).

6-Phenylhex-5-yn-1-ol (245).¹²⁰

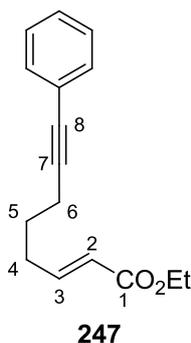
Bis(triphenylphosphine)palladium(II) dichloride (0.110 g, 0.156 mmol) and copper iodide (0.060 g, 0.312 mmol) were dissolved in triethylamine (160 mL) and iodobenzene (2.10 mL, 18.8 mmol) was added and stirred at room temperature for 0.1 h. 5-Hexyn-1-ol (**192**) (1.50 g, 15.6 mmol) was added and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was concentrated *in vacuo* and flash column chromatography using silica (petroleum ether/ethyl acetate, 2:1) gave 6-phenylhex-5-yn-1-ol (**245**) (2.69 g, 100%) as a colourless oil. The spectroscopic data was consistent with the literature.¹²⁰ R_f (50% petroleum ether/diethyl ether) $\nu_{\max}/\text{cm}^{-1}$ (neat) 3360 (OH), 2938 (CH), 1597 (C=C), 1489, 1441, 1063, 754, 691; δ_{H} (400 MHz, CDCl_3) 1.43 (1H, s, OH), 1.69–1.84 (4H, m, 2- H_2 and 3- H_2), 2.49 (2H, t, J 6.7 Hz, 4- H_2), 3.71–3.79 (2H, m, 1- H_2), 7.28–7.34 (3H, m, 3 \times ArH), 7.40–7.46 (2H, m, 2 \times ArH); δ_{C} (101 MHz, CDCl_3) 19.2 (CH_2), 25.0 (CH_2), 31.9 (CH_2), 62.5 (CH_2), 81.0 (C), 89.9 (C), 123.9 (C), 127.6 (CH), 128.2 (2 \times CH), 131.6 (2 \times CH); m/z (CI) 174 (M^+ , 32%), 145 (15), 130 (64), 115 (100), 102 (15), 91 (22), 73 (18).

Ethyl (2E)-7-phenylhept-2-en-6-ynoate (246).¹⁷⁷

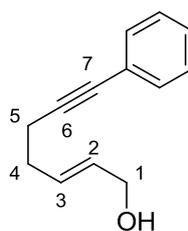
Ethyl (2E)-7-phenylhept-2-en-6-ynoate (**246**) was synthesised as described for ethyl (2E)-hept-2-en-6-ynoate (**221**) using 5-phenylpent-4-yn-1-ol (**244**) (1.62 g, 10.1 mmol). Flash column chromatography using silica (diethyl ether/petroleum ether, 1:6) gave ethyl (2E)-7-phenylhept-2-en-6-ynoate (**246**) (1.97 g, 86%) as a yellow oil. The spectroscopic data was consistent with the literature.¹⁷⁷ R_f (50% petroleum ether/diethyl ether) 0.66; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2982 (CH), 1717 (CO), 1655 (C=C), 1491, 1443, 1368, 1315, 1153; δ_{H} (500 MHz, CDCl_3) 1.30 (1H, t, J 7.1 Hz, OCH_2CH_3), 2.48–2.55 (4H, m, 4- H_2 and 5- H_2), 4.20 (2H, q, J

7.1 Hz, OCH_2CH_3), 5.93 (1H, dt, J 15.7, 1.5 Hz, 2-H), 7.04 (1H, dt, J 15.7, 6.6 Hz, 3-H), 7.26–7.31 (3H, m, $3 \times \text{ArH}$), 7.36–7.41 (2H, m, $2 \times \text{ArH}$); δ_{C} (126 MHz, CDCl_3) 14.3 (CH_3), 18.4 (CH_2), 31.4 (CH_2), 60.3 (CH_2), 81.6 (C), 88.3 (C), 122.5 (CH), 123.6 (C), 127.8 (CH), 128.2 ($2 \times \text{CH}$), 131.6 ($2 \times \text{CH}$), 146.7 (CH), 166.5 (C); m/z (ESI) 251.1040 (MNa^+ . $\text{C}_{15}\text{H}_{16}\text{NaO}_2$ requires 251.1043).

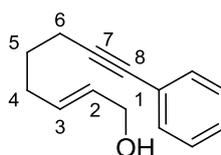
Ethyl (2E)-8-phenyloct-2-en-7-ynoate (247).



Ethyl (2E)-8-phenyloct-2-en-7-ynoate (**247**) was synthesised as described for ethyl (2E)-hept-2-en-6-ynoate (**221**) using 6-phenylhex-5-yn-1-ol (**245**) (1.73 g, 10.1 mmol). Flash column chromatography using silica (diethyl ether/petroleum ether, 3:17) gave ethyl (2E)-8-phenyloct-2-en-7-ynoate (**247**) (2.06 g, 85%) as a yellow oil. R_f (50% petroleum ether/diethyl ether) 0.68; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 2938 (CH), 2360, 1717 (CO), 1654 (C=C), 1490, 1369, 1267, 1151; δ_{H} (500 MHz, CDCl_3) 1.29 (1H, t, J 7.2 Hz, OCH_2CH_3), 1.77 (2H, quin., J 7.0 Hz, 5- H_2), 2.36–2.42 (2H, m, 4- H_2), 2.45 (2H, t, J 7.0 Hz, 6- H_2), 4.19 (2H, q, J 7.2 Hz, OCH_2CH_3), 5.88 (1H, dt, J 15.7, 1.6 Hz, 2-H), 6.99 (1H, dt, J 15.7, 7.0 Hz, 3-H), 7.26–7.31 (3H, m, $3 \times \text{ArH}$), 7.37–7.41 (2H, m, $2 \times \text{ArH}$); δ_{C} (126 MHz, CDCl_3) 14.3 (CH_3), 18.9 (CH_2), 27.0 (CH_2), 31.2 (CH_2), 60.2 (CH_2), 81.4 (C), 89.1 (C), 122.1 (CH), 123.8 (C), 127.7 (CH), 128.2 ($2 \times \text{CH}$), 131.6 ($2 \times \text{CH}$), 148.1 (CH), 166.6 (C); m/z (CI) 243.1387 (MH^+ . $\text{C}_{16}\text{H}_{19}\text{O}_2$ requires 243.1385), 215 (5%), 197 (8), 169 (12), 123 (10).

(2E)-7-Phenylhept-2-en-6-yn-1-ol (248).**248**

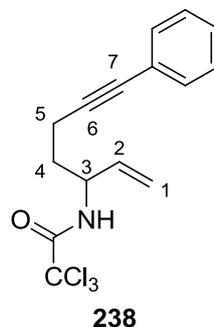
(2E)-7-Phenylhept-2-en-6-yn-1-ol (**248**) was synthesised as described for (2E)-hept-2-en-6-yn-1-ol (**215**) using ethyl (2E)-7-phenylhept-2-en-6-ynoate (**246**) (1.97 g, 8.64 mmol). Purification by flash column chromatography (ethyl acetate/petroleum ether, 7:13) gave (2E)-7-phenylhept-2-en-6-yn-1-ol (**248**) (1.30 g, 81%) as a colourless oil. R_f (50% petroleum ether/diethyl ether) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3329 (OH), 2918 (CH), 2324, 2110, 1597 (C=C), 1489, 1441, 1084, 966; δ_{H} (500 MHz, CDCl_3) 1.36 (1H, br s, OH), 2.36 (2H, dt, J 7.2, 6.8 Hz, 4-H₂), 2.50 (2H, t, J 6.8 Hz, 5-H₂), 4.13 (2H, t, J 4.5 Hz, 1-H₂), 5.72–5.85 (2H, m, 2-H and 3-H), 7.25–7.31 (3H, m, 3 × ArH), 7.36–7.42 (2H, m, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 19.5 (CH₂), 31.5 (CH₂), 63.6 (CH₂), 81.2 (C), 89.4 (C), 123.8 (C), 127.6 (CH), 128.2 (2 × CH), 130.4 (CH), 131.0 (CH), 131.6 (2 × CH); m/z (CI) 169.1018 ($\text{MH}^+ - \text{H}_2\text{O}$. $\text{C}_{13}\text{H}_{13}$ requires 169.1017), 143 (14%), 123 (46), 105 (17), 91 (6).

(2E)-8-Phenyloct-2-en-7-yn-1-ol (249).**249**

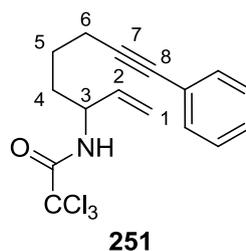
(2E)-8-Phenyloct-2-en-7-yn-1-ol (**249**) was synthesised as described for (2E)-hept-2-en-6-yn-1-ol (**215**) using ethyl (2E)-8-phenyloct-2-en-7-ynoate (**247**) (1.52 g, 6.26 mmol). Flash column chromatography using silica (ethyl acetate/petroleum ether, 3:7) gave (2E)-8-phenyloct-2-en-7-yn-1-ol (**249**) (0.97 g, 77%) as a colourless oil. R_f (50% petroleum ether/ethyl acetate) 0.62; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3428 (OH), 2937 (CH), 2361, 1717, 1691, 1490, 1442, 1270, 1216, 972; δ_{H} (500 MHz, CDCl_3) 1.30 (1H, br s, OH), 1.70 (2H, quin., J 7.2 Hz, 5-H₂), 2.20–2.26 (2H, m, 4-H₂), 2.42 (2H, t, J 7.2 Hz, 6-H₂), 4.11 (2H, br s, 1-H₂), 5.70–5.74 (2H, m, 2-H and 3-H), 7.26–7.31 (3H, m, 3 × ArH), 7.37–7.41 (2H, m, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 18.8 (CH₂), 28.1 (CH₂), 31.3 (CH₂), 63.7 (CH₂), 81.0 (C),

89.8 (C), 123.9 (C), 127.6 (CH), 128.2 (2 × CH), 129.9 (CH), 131.5 (CH), 132.1 (2 × CH); m/z (CI) 183.1171 ($MH^+ - H_2O$. $C_{14}H_{16}$ requires 183.1174), 173 (11%), 123 (33), 105 (10).

7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (238).

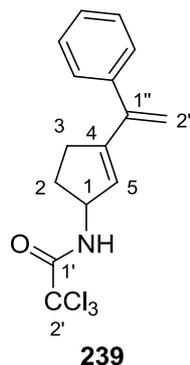


(*2E*)-7-Phenylhept-2-en-6-yn-1-ol (**248**) (0.081 g, 0.44 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.012 mL, 0.088 mmol) and trichloroacetonitrile (0.066 mL, 0.66 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 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 (10 mL) and bis(acetonitrile)palladium chloride (0.012 g, 0.044 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave 7-phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**238**) (0.118 g, 81%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.86; ν_{max}/cm^{-1} (neat) 3304 (NH), 3055 (CH), 2362, 1714 (CO), 1511, 1265, 1175; δ_H (400 MHz, $CDCl_3$) 1.90–2.09 (2H, m, 4- H_2), 2.50–2.59 (2H, m, 5- H_2), 4.60–4.69 (1H, m, 3-H), 5.27 (1H, d, J 10.4 Hz, 1- HH), 5.32 (1H, d, J 17.2 Hz, 1- HH), 5.85 (1H, ddd, J 17.2, 10.4, 5.6 Hz, 2-H), 6.98 (1H, d, J 7.4 Hz, NH), 7.26–7.31 (3H, m, 3 × ArH), 7.37–7.43 (2H, m, 2 × ArH); δ_C (101 MHz, $CDCl_3$) 15.9 (CH_2), 32.8 (CH_2), 53.2 (CH), 82.0 (C), 88.4 (C), 92.7 (C), 116.9 (CH_2), 123.4 (C), 128.0 (CH), 128.3 (2 × CH), 131.7 (2 × CH), 135.6 (CH), 161.4 (C); m/z (ESI) 352.0019 (MNa^+ . $C_{15}H_{14}^{35}Cl_3NNaO$ requires 352.0033).

8-Phenyl-3-(2',2',2'-trichloromethylcarbonylamino)oct-1-en-7-yne (251).

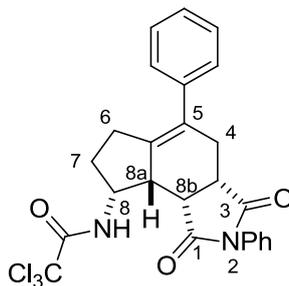
(*2E*)-8-Phenyloct-2-en-7-yn-1-ol (**249**) (0.105 g, 0.53 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.015 mL, 0.11 mmol) and trichloroacetonitrile (0.079 mL, 0.79 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 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 (10 mL) and bis(acetonitrile)palladium chloride (0.014 g, 0.053 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave 8-phenyl-3-(2',2',2'-trichloromethylcarbonylamino)oct-1-en-7-yne (**251**) (0.148 g, 82%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.95; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3325 (NH), 2932 (CH), 2361, 1691 (CO), 1512, 1491, 1441, 1238, 1071; δ_{H} (500 MHz, CDCl_3) 1.65–1.83 (3H, m, 4-*HH* and 5- H_2), 1.85–1.94 (H, m, 4-*HH*), 2.48 (2H, t, J 6.8 Hz, 6- H_2), 4.45–4.53 (1H, m, 3-H), 5.23 (1H, d, J 10.5 Hz, 1-*HH*), 5.28 (1H, d, J 17.2 Hz, 1-*HH*), 5.83 (1H, ddd, J 17.2, 10.5, 5.7 Hz, 2-H), 6.55 (1H, d, J 7.6 Hz, NH), 7.26–7.31 (3H, m, 3 \times ArH), 7.36–7.42 (2H, m, 2 \times ArH); δ_{C} (126 MHz, CDCl_3) 19.1 (CH_2), 24.8 (CH_2), 33.6 (CH_2), 53.0 (CH), 81.4 (C), 89.1 (C), 92.8 (C), 116.5 (CH_2), 123.7 (C), 127.7 (CH), 128.3 (2 \times CH), 131.6 (2 \times CH), 136.4 (CH), 161.3 (C); m/z (ESI) 366.0179 (MNa^+ . $\text{C}_{16}\text{H}_{16}^{35}\text{Cl}_3\text{NNaO}$ requires 366.0190).

4-(1''-Phenylethyl-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (239).



7-Phenyl-3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**238**) (0.050 g, 0.15 mmol) was dissolved in toluene (3 mL) and Grubbs second generation catalyst (0.009 g, 0.011 mmol) with 1,7-octadiene (**156**) (0.095 mL, 0.60 mmol) was then added. The reaction mixture was stirred at 90 °C for 18 h. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 17:3) gave 4-(1''-phenylethyl-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**239**) (0.037 g, 74%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.78; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3291 (NH), 2945 (CH), 1686 (CO), 1520, 1242, 1175, 1069, 895; δ_{H} (500 MHz, CDCl_3) 1.78–1.88 (1H, m, 2-*HH*), 2.57–2.67 (2H, m, 2-*HH* and 3-*HH*), 2.77–2.86 (1H, m, 3-*HH*), 5.02–5.09 (1H, m, 1-H), 5.26 (1H, s, 2''-*HH*), 5.34 (1H, s, 2''-*HH*), 5.54 (1H, br s, 5-H), 6.61 (1H, d, J 6.0 Hz, NH), 7.27–7.38 (5H, m, $5 \times \text{ArH}$); δ_{C} (126 MHz, CDCl_3) 31.4 (CH_2), 31.6 (CH_2), 58.2 (CH), 92.6 (C), 117.0 (CH_2), 127.6 (CH), 128.1 (CH), 128.2 ($2 \times \text{CH}$), 128.4 ($2 \times \text{CH}$), 141.0 (C), 145.5 (C), 147.9 (C), 161.1 (C); m/z (ESI) 352.0020 (MNa^+ . $\text{C}_{15}\text{H}_{14}^{35}\text{Cl}_3\text{NNaO}$ requires 352.0033).

(3a*S,8*R**,8a*S**,8b*R**)-2,5-Diphenyl-4,6,7,8,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (253).**

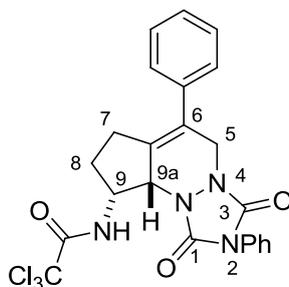


253

(*2E*)-7-Phenylhept-2-en-6-yn-1-ol (**248**) (0.075 g, 0.40 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.011 mL, 0.080 mmol) and trichloroacetonitrile (0.062 mL, 0.60 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 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 (10 mL) and bis(acetonitrile)palladium chloride (0.011 g, 0.040 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. Grubbs second generation catalyst (0.024 g, 0.028 mmol) was added with 1,7-octadiene (**156**) (0.24 mL, 1.60 mmol) and the reaction mixture was stirred for 18 h at 90 °C. *N*-Phenyl maleimide (**139**) (0.104 g, 0.60 mmol) was added with hydroquinone (0.005 g, 0.005 mmol). The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 1:1) gave (3a*S**,8*R**,8a*S**,8b*R**)-2,5-diphenyl-4,6,7,8,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**253**) (0.099 g, 49%) as a yellow solid. R_f (50% petroleum ether/ethyl acetate) 0.76; Mp 151–153 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3358 (NH), 2936 (CH), 1695 (CO), 1517, 1498, 1387, 1154, 822; δ_{H} (400 MHz, CDCl_3) 1.75 (1H, dq, J 12.3, 10.2 Hz, 7-*HH*), 2.10–2.20 (1H, m, 7-*HH*), 2.53–2.66 (3H, m, 4-*HH* and 6- H_2), 3.12 (1H, dd, J 9.1, 5.8 Hz, 8a-H), 3.30 (1H, dd, J 15.2, 1.4 Hz, 4-*HH*), 3.46–3.56 (2H, m, 3a-H and 8b-H), 4.88–5.01 (1H, m, 8-H), 7.06–7.10 (2H, m, 2 \times ArH), 7.23–7.47 (8H, m, 8 \times ArH), 8.96 (1H, d, J 9.6 Hz, NH); δ_{C} (126 MHz, CDCl_3) 28.4 (CH_2), 29.9 (CH_2), 31.6 (CH_2), 40.3 (CH), 41.7 (CH), 43.7 (CH), 52.8 (CH), 92.9 (C), 126.5 (2 \times CH), 127.2 (CH), 127.5 (2 \times CH), 128.5 (2 \times CH), 129.2 (CH), 129.4 (2 \times CH), 130.3 (C), 131.4 (C), 139.0 (C), 139.6 (C), 162.3 (C), 178.5 (C), 179.7 (C); m/z (ESI)

525.0497 (MNa^+ . $C_{25}H_{21}^{35}Cl_3N_2NaO_3$ requires 525.0510), 481 (18%), 454 (7), 413 (7), 345 (24), 323 (21), 297 (9), 236 (11), 218 (7), 196 (6).

(9*R,9*aS**)-2,6-Diphenyl-7,8,9,9*a*-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (255).**



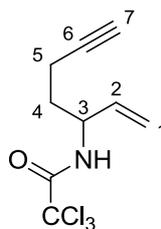
255

(*2E*)-7-Phenylhept-2-en-6-yn-1-ol (**248**) (0.087 g, 0.47 mmol) was dissolved in dichloromethane (15 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.013 mL, 0.080 mmol) and trichloroacetonitrile (0.071 mL, 0.71 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction mixture was filtered through a short pad of silica gel with diethyl ether (300 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 (10 mL) and bis(acetonitrile)palladium chloride (0.012 g, 0.047 mmol) was then added and the reaction mixture was stirred at room temperature for 18 h. Grubbs second generation catalyst (0.029 g, 0.047 mmol) was added with 1,7-octadiene (**156**) (0.28 mL, 1.88 mmol) and the reaction mixture was stirred for 18 h at 90 °C. 4-Phenyl-1,2,4-triazole-3,5-dione (**254**) (0.099 g, 0.56 mmol) was added with hydroquinone (0.005 g, 0.005 mmol). The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (dichloromethane/methanol, 99:1) gave

(*9R**,*9aS**)-2,6-diphenyl-7,8,9,9*a*-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (**255**) (0.083 g, 35%) as a colourless oil. R_f (10% methanol/dichloromethane) 0.86; ν_{max}/cm^{-1} (neat) 3402 (NH), 2939 (CH), 1701 (CO), 1512, 1486, 1387, 1246, 1152, 928; δ_H (400 MHz, $CDCl_3$) 2.07–2.23 (2H, m, 8- H_2), 2.37–2.48 (1H, m, 7-*HH*), 2.52–2.64 (1H, m, 7-*HH*), 4.33 (1H, ddd, *J* 16.6, 5.3, 2.3 Hz, 5-*HH*), 4.46 (1H, ddd, *J* 16.6, 5.3, 2.9 Hz, 5-*HH*), 4.48–4.53 (1H, m, 9*a*-H), 4.82–4.88 (1H, m, 9-

H), 6.66 (1H, d, J 6.0 Hz, NH), 7.28–7.33 (2H, m, $2 \times$ ArH), 7.36–7.56 (8H, m, $8 \times$ ArH); δ_{C} (101 MHz, CDCl_3) 24.4 (CH_2), 27.8 (CH_2), 45.7 (CH_2), 52.5 (CH), 59.9 (CH), 92.7 (C), 125.5 ($2 \times$ CH), 127.6 ($2 \times$ CH), 128.4 (CH), 128.7 (CH), 128.8 (C), 128.9 ($2 \times$ CH), 129.2 ($2 \times$ CH), 131.0 (C), 132.4 (C), 136.3 (C), 151.7 (C), 152.7 (C), 161.3 (C); m/z (ESI) 527.0409 (MNa^+ . $\text{C}_{23}\text{H}_{19}^{35}\text{Cl}_3\text{N}_4\text{NaO}_3$ requires 527.0415).

3-(2',2',2'-Trichloromethylcarbonylamino)hept-1-en-6-yne (**222**).



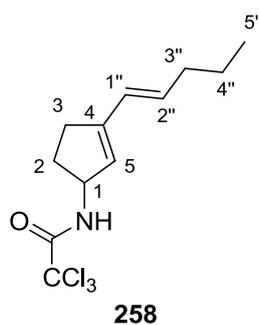
222

Method A- (*E*)-Hept-2-en-6-yn-1-ol (**215**) (0.388 g, 3.53 mmol) was dissolved in dichloromethane (25 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.099 mL, 0.706 mmol) and trichloroacetonitrile (0.530 mL, 5.29 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then warmed to 140 °C and stirred for 36 h. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 10:1) gave 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**222**) (0.866 g, 96%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.95; Mp 35–37 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3304 (NH), 3055 (CH), 2361, 1713 (CO), 1510, 1265, 822, 733; δ_{H} (500 MHz, CDCl_3) 1.84–2.00 (2H, m, 4- H_2), 2.05 (1H, t, J 2.7 Hz, 7-H), 2.26–2.39 (2H, m, 5- H_2), 4.56–4.63 (1H, m, 3-H), 5.27 (1H, d, J 10.5 Hz, 1- HH), 5.30 (1H, d, J 17.2 Hz, 1- HH), 5.82 (1H, ddd, J 17.2, 10.5, 5.6 Hz, 2-H), 6.93 (1H, br s, NH); δ_{C} (126 MHz, CDCl_3) 14.8 (CH_2), 32.5 (CH_2), 53.0 (CH), 69.9 (CH), 83.1 (C), 92.7 (C), 116.9 (CH_2), 135.4 (CH), 161.3 (C); m/z (CI) 253.9901 (MH^+ . $\text{C}_9\text{H}_{11}^{35}\text{Cl}_3\text{NO}$ requires 253.9906), 220 (55%), 186 (42), 184 (37), 132 (12), 89 (100), 69 (27).

Method B- (*E*)-Hept-2-en-6-yn-1-ol (**215**) (0.11 g, 1.00 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution was added 1,8-

diazabicyclo[5.4.0]undec-7-ene (0.028 mL, 0.20 mmol) and trichloroacetonitrile (0.15 mL, 1.50 mmol). 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 (21 mL) under an argon atmosphere. Bis(acetonitrile)palladium chloride (0.026 g, 0.10 mmol) was then added to the solution and the reaction mixture was stirred at room temperature for 18 h. To the reaction mixture an additional portion of bis(acetonitrile)palladium chloride (0.026 g, 0.1 mmol) was added and the reaction was stirred at room temperature for 24 h and solvent evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 10:1) gave 3-(2',2',2'-trichloromethylcarbonylamino)hept-1-en-6-yne (**222**) (0.086 g, 34%) as a white solid. Spectroscopic data as described above.

4-(*n*-Pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (258**).**

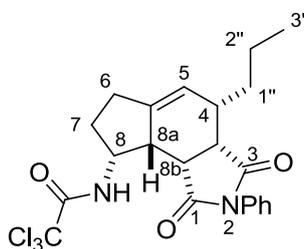


Method A- 3-(2',2',2'-Trichloromethylcarbonylamino)hept-1-en-6-yne (**222**) (0.11 g, 0.42 mmol) was dissolved in toluene (8 mL) and Grubbs second generation catalyst (0.016 g, 0.019 mmol) with 1-pentene (**261**) (0.204 mL, 1.87 mmol) was then added. The reaction mixture was stirred at room temperature for 18 h. Further addition of Grubbs second generation catalyst (0.008 g, 0.010 mmol) with 1-pentene (**261**) (0.11 mL, 1.01 mmol) was then added and the reaction mixture stirred at room temperature for 22 h. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 9:1) gave 4-(*n*-pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**258**) (0.091 g, 74%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.82; Mp 56–58 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3285 (NH), 2957 (CH), 2930, 1701, 1686 (CO), 1524, 1258, 1067, 964; δ_H (500 MHz, CDCl_3) 0.92 (3H, t, J 7.4 Hz, 5''-H₃), 1.44 (2H, sextet, J 7.4 Hz, 4''-H₂), 1.75 (1H, ddt, J 13.0, 8.5, 4.1 Hz, 2''-HH), 2.11 (2H, q, J 7.4 Hz, 3''-H₂), 2.40–2.55 (2H, m, 2''-HH and 3''-HH), 2.58–2.67 (1H, m, 3''-HH), 4.96–5.03 (1H, m, 1''-H), 5.53 (1H, br s, 5''-H), 5.75 (1H, dt, J 15.7, 7.4 Hz, 2''-

H), 6.27 (2H, d, J 15.7 Hz, 1''-H₂), 7.63 (1H, d, J 9.3 Hz, NH); δ_C (126 MHz, CDCl₃) 13.7 (CH₃), 22.4 (CH₂), 30.0 (CH₂), 31.1 (CH₂), 34.9 (CH₂), 57.8 (CH), 92.8 (C), 124.8 (CH), 125.9 (CH), 135.3 (CH), 147.3 (C), 161.1 (C); m/z (ESI) 318.0182 (MNa⁺. C₁₂H₁₆³⁵Cl₃NNaO requires 318.0190), 296 (10%), 236 (24), 184 (16), 135 (21).

Method B- (2*E*)-Hept-2-en-6-yn-1-ol (**215**) (0.060 g, 0.55 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.015 mL, 0.11 mmol) and trichloroacetonitrile (0.082 mL, 0.82 mmol) was added. 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 (11 mL) and transferred to a Schlenk tube containing potassium carbonate (0.055 g), purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 36 h. Grubbs second generation catalyst (0.023 g, 0.027 mmol) was added with 1-pentene (**261**) (0.30 mL, 2.75 mmol) and the reaction mixture was stirred for 24 h at room temperature. A further portion of Grubbs second generation catalyst (0.014 g, 0.016 mmol) and 1-pentene (**261**) (0.30 mL, 2.75 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 9:1) gave 4-(*n*-pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**258**) (0.098 g, 60%) as a white solid. Spectroscopic data as described above.

(3*aS**,4*S**,8*R**,8*aS**,8*bR**)-4,6,7,8,8*a*,8*b*-Hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3*aH*)-dione (**262**).

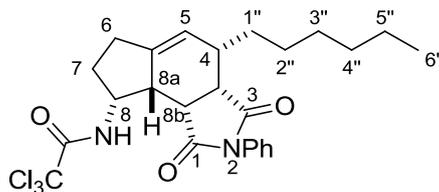


262

(2*E*)-Hept-2-en-6-yn-1-ol (**215**) (0.027 g, 0.24 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.007 mL, 0.048 mmol) and trichloroacetonitrile (0.036 mL, 0.36 mmol) was added. 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 (5 mL) and transferred to a Schlenk tube containing potassium carbonate (0.025 g, 0.18 mmol), purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 36 h. Grubbs second generation catalyst (0.012 g, 0.014 mmol) was added with 1-pentene (**261**) (0.13 mL, 1.21 mmol) and the reaction mixture was stirred for 24 h at room temperature. A further portion of Grubbs second generation catalyst (0.005 g, 0.006 mmol) and 1-pentene (**261**) (0.067 mL, 0.61 mmol) was added and the reaction mixture was stirred at room temperature for 18 h. *N*-Phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added with hydroquinone (0.005 g, 0.005 mmol). The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 4:1) gave (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**262**) (0.054 g, 47%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.59; Mp 145–147 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3304 (NH), 2957 (CH), 1695 (CO), 1516, 1499, 1389, 1182; δ_{H} (500 MHz, CDCl_3) 0.91 (3H, t, J 7.3 Hz, 3''-H₃), 1.37–1.50 (2H, m, 2''-H₂), 1.61–1.71 (1H, m, 1''-HH), 1.74–1.91 (2H, m, 1''-HH and 7-HH), 2.08 (1H, dt, J 12.4, 7.2 Hz, 7-HH), 2.23–2.33 (2H, m, 4-H and 6-HH), 2.39 (1H, dd, J 15.4, 8.1 Hz, 6-HH), 2.83–2.90 (1H, m, 8a-H), 3.20 (1H, dd, J 8.4, 6.9 Hz, 3a-H), 3.35 (1H, dd, J 8.4, 6.5 Hz, 8b-H), 4.75–4.85 (1H, m, 8-H), 5.52 (1H, br s, 5-H), 7.05–7.10 (2H, m, 2 × ArH), 7.30–7.35 (1H, m, ArH), 7.36–7.42 (2H, m, 2 × ArH), 8.90 (1H, d, J 9.7 Hz, NH); δ_{C} (126 MHz, CDCl_3) 14.1 (CH₃), 21.4 (CH₂), 28.2 (CH₂), 31.7 (CH₂), 33.2 (CH₂), 38.3 (CH), 42.1 (CH), 42.2 (CH), 42.8 (CH), 52.9 (CH), 92.9 (C), 123.1 (CH), 126.5 (2 × CH), 129.0 (CH), 129.3 (2 × CH), 131.5 (C), 145.1 (C), 162.3 (C), 175.7 (C), 179.3 (C); m/z (ESI) 491.0649 (MNa⁺. C₂₂H₂₃³⁵Cl₃N₂NaO₃ requires 491.0666), 413 (6%), 301 (4), 236 (11), 228 (100).

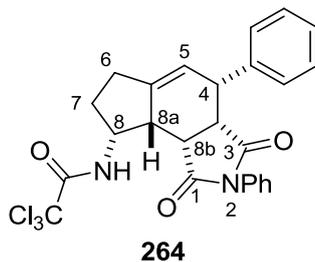
(3a*S,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-4-*n*-hexyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (263).**



263

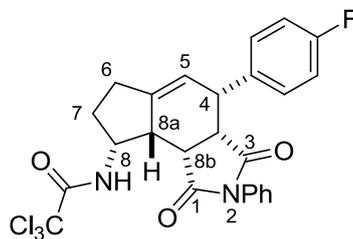
(3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-Hexahydro-4-*n*-hexyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**263**) was synthesised as described for (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**262**) using (*2E*)-hept-2-en-6-yn-1-ol (**215**) (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and 1-octene (**166**) (0.28 mL, 1.82 mmol) for 48 h at 40 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:1) gave (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-4-*n*-hexyl-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**263**) (0.076 g, 62%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.62; Mp 145–147 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3310 (NH), 2928 (CH), 1697 (CO), 1516, 1499, 1389, 1186; δ_{H} (500 MHz, CDCl_3) 0.86–0.92 (3H, m, 6''-H₃), 1.25–1.53 (8H, m, 2''-H₂, 3''-H₂, 4''-H₂ and 5''-H₂), 1.73 (1H, dtd, J 14.1, 9.4, 5.4 Hz, 1''-HH), 1.86 (1H, qd, J 12.3, 7.8 Hz, 7-HH), 1.99–2.01 (1H, m, 1''-HH), 2.14 (1H, dt, J 12.3, 7.2 Hz, 7-HH), 2.25–2.39 (2H, m, 4-H and 6-HH), 2.46 (1H, dd, J 16.0, 7.8 Hz, 6-HH), 2.90–2.96 (1H, m, 8a-H), 3.27 (1H, dd, J 8.4, 6.9 Hz, 3a-H), 3.41 (1H, dd, J 8.4, 6.5 Hz, 8b-H), 4.81–4.92 (1H, m, 8-H), 5.57–5.61 (1H, m, 5-H), 7.13–7.17 (2H, m, 2 × ArH), 7.37–7.42 (1H, m, ArH), 7.43–7.48 (2H, m, 2 × ArH), 8.98 (1H, d, J 9.7 Hz, NH); δ_{C} (126 MHz, CDCl_3) 14.1 (CH₃), 22.7 (CH₂), 28.2 (CH₂), 28.3 (CH₂), 29.3 (CH₂), 31.0 (CH₂), 31.7 (CH₂), 31.8 (CH₂), 38.6 (CH), 42.1 (CH), 42.2 (CH), 42.8 (CH), 52.9 (CH), 92.2 (C), 123.1 (CH), 126.6 (2 × CH), 129.0 (CH), 129.3 (2 × CH), 131.5 (C), 145.0 (C), 162.2 (C), 175.7 (C), 179.4 (C); m/z (ESI) 533.1120 (MNa⁺. C₂₅H₂₉³⁵Cl₃N₂NaO₃ requires 533.1136), 413 (4%), 301 (15), 236 (28), 228 (22), 218 (6), 141 (3).

(3a*S,4*S**,8*R**,8a*S**,8b*R**)-2,4-Diphenyl-4,6,7,8,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (264).**



(3a*S**,4*S**,8*R**,8a*S**,8b*R**)-2,4-Diphenyl-4,6,7,8,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**264**) was synthesised as described for (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**262**) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and styrene (0.21 mL, 1.82 mmol) for 48 h at 40 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 48 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-2,4-diphenyl-4,6,7,8,8a,8b-hexahydro-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (**264**) (0.063 g, 52%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.32; Mp 154–156 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3318 (NH), 2940 (CH), 1697 (CO), 1512, 1501, 1383, 1196, 1177, 822; δ_{H} (500 MHz, CDCl₃) 1.99 (1H, qd, J 12.4, 7.9 Hz, 7-*HH*), 2.23 (1H, dq, J 12.4, 7.3 Hz, 7-*HH*), 2.38–2.49 (1H, m, 6-*HH*), 2.60 (1H, dd, J 16.5, 7.9 Hz, 6-*HH*), 3.08–3.16 (1H, m, 8a-H), 3.49–3.55 (1H, m, 3a-H and 8b-H), 3.75 (1H, br s, 4-H), 4.90–5.01 (1H, m, 8-H), 6.13–6.17 (1H, m, 5-H), 7.13 (2H, t, J 7.6 Hz, 2 × ArH), 7.25–7.32 (3H, m, 3 × ArH), 7.35–7.40 (3H, m, 3 × ArH), 7.41–7.46 (2H, m, 2 × ArH), 8.91 (1H, d, J 9.6 Hz, NH); δ_{C} (126 MHz, CDCl₃) 28.8 (CH₂), 31.8 (CH₂), 41.9 (CH), 42.1 (CH), 43.5 (CH), 46.1 (CH), 52.9 (CH), 92.9 (C), 120.3 (CH), 126.3 (2 × CH), 127.3 (CH), 128.4 (2 × CH), 128.7 (2 × CH), 128.9 (CH), 129.2 (2 × CH), 131.4 (C), 138.7 (C), 146.5 (C), 162.3 (C), 174.3 (C), 178.7 (C); m/z (ESI) 501.0533 ([*M*-H]⁻. C₂₅H₂₀³⁵Cl₃N₂O₃ requires 501.0545), 383 (100%), 312 (15), 212 (22).

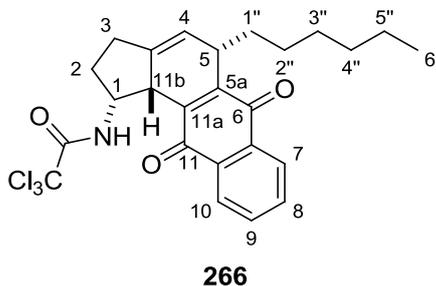
(3a*S,4*S**,8*R**,8a*S**,8b*R**)-4-(4-Fluorophenyl)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (265).**



265

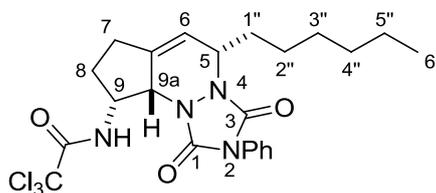
(3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4-(4-Fluorophenyl)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (265) was synthesised as described for (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4,6,7,8,8a,8b-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (262) using (*2E*)-hept-2-en-6-yn-1-ol **215** (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and 4-fluorostyrene (0.22 mL, 1.82 mmol) for 48 h at 40 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave (3a*S**,4*S**,8*R**,8a*S**,8b*R**)-4-(4-fluorophenyl)-4,6,7,8,8a,8b-hexahydro-2-phenyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3a*H*)-dione (265) (0.070 g, 56%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.24; Mp 146–148 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3307 (NH), 2925 (CH), 1696 (CO), 1510, 1388, 1214, 1200, 1158, 822; δ_{H} (500 MHz, CDCl₃) 2.00 (1H, qd, J 12.3, 7.9 Hz, 7-*HH*), 2.26 (1H, dq, J 12.3, 7.4 Hz, 7-*HH*), 2.39–2.52 (1H, m, 6-*HH*), 2.62 (1H, dd, J 16.4, 7.9 Hz, 6-*HH*), 3.09–3.16 (1H, m, 8a-H), 3.47 (1H, dd, J 15.5, 8.3 Hz, 3a-H), 3.54 (1H, dd, J 8.3, 6.0 Hz, 8b-H), 3.71–3.79 (1H, m, 4-H), 4.91–5.04 (1H, m, 8-H), 6.08–6.12 (1H, m, 5-H), 7.06–7.10 (2H, m, 2 × ArH), 7.13–7.16 (2H, m, 2 × ArH), 7.22–7.27 (2H, m, 2 × ArH), 7.38–7.43 (1H, m, ArH), 7.44–7.50 (2H, m, 2 × ArH), 8.92 (1H, d, J 9.6 Hz, NH); δ_{C} (126 MHz, CDCl₃) 28.7 (CH₂), 31.7 (CH₂), 41.8 (CH), 42.2 (CH), 42.8 (CH), 46.0 (CH), 52.8 (CH), 92.8 (C), 115.3 (d, $J_{\text{C-C-F}}$ 21.6 Hz, 2 × CH), 120.2 (CH), 126.3 (2 × CH), 129.0 (CH), 129.3 (2 × CH), 130.2 (d, $J_{\text{C-C-F}}$ 8.0 Hz, 2 × CH), 131.3 (C), 134.5 (C), 146.8 (C), 162.0 (d, $J_{\text{C-F}}$ 245.9 Hz, C), 162.3 (C), 174.4 (C), 178.6 (C); m/z (ESI) 543.0410 (MNa⁺. C₂₅H₂₀³⁵Cl₃FN₂NaO₃ requires 543.0416), 449 (6%), 413 (7), 352 (4), 227 (6), 159 (4).

(1*R,5*S**,11*bR**)-5-*n*-Hexyl-1,2,3,5,11*b*-pentahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11-dione (**266**).**



(1*R**,5*S**,11*bR**)-5-*n*-Hexyl-1,2,3,5,11*b*-pentahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11-dione (**266**) was synthesised as described for (3*aS**,4*S**,8*R**,8*aS**,8*bR**)-4,6,7,8,8*a*,8*b*-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3*aH*)-dione (**262**) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and 1-octene (**166**) (0.28 mL, 1.82 mmol) for 48 h at 40 °C before 1,4-naphthoquinone (**205**) (0.057 g, 0.36 mmol) was added. The reaction mixture was stirred for 48 h at 111 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 4:1) gave (1*R**,5*S**,11*bR**)-5-*n*-hexyl-1,2,3,5,11*b*-pentahydro-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*a*]anthracene-6,11-dione (**266**) (0.048 g, 40%) as a yellow oil. R_f (50% diethyl ether/petroleum ether) 0.54; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2928 (CH), 1709 (CO), 1667 (CO), 1593 (C=C), 1510, 1346, 1281, 1267, 820; δ_{H} (500 MHz, CDCl_3) 0.87 (3H, t, J 6.5 Hz, 6''-H₃), 1.29–1.48 (8H, m, 2''-H₂, 3''-H₂, 4''-H₂ and 5''-H₂), 1.55–1.66 (1H, m, 1''-HH), 1.78–1.88 (2H, m, 1''-HH and 2-HH), 2.35–2.52 (3H, m, 2-HH and 3-H₂), 3.62–3.70 (2H, m, 5-H and 11*b*-H), 5.07–5.13 (1H, m, 1-H), 5.76 (1H, br s, 4-H), 6.35 (1H, d, J 8.4 Hz, NH), 7.68–7.73 (2H, m, 2 × ArH), 8.01–8.11 (2H, m, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 14.1 (CH₃), 22.7 (CH₂), 26.6 (CH₂), 26.8 (CH₂), 29.3 (CH₂), 30.2 (CH₂), 31.6 (CH₂), 36.6 (CH), 36.9 (CH₂), 43.8 (CH), 53.8 (CH), 92.6 (C), 122.2 (CH), 126.3 (CH), 126.4 (CH), 131.8 (C), 132.4 (C), 133.6 (CH), 133.7 (CH), 136.2 (C), 140.0 (C), 148.9 (C), 160.9 (C), 184.0 (C), 184.4 (C); m/z (ESI) 520.0788 (MNa⁺. C₂₅H₂₆³⁵Cl³⁷Cl₂NNaO₃ requires 520.0811).

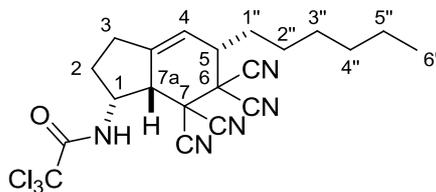
(5*S,9*R**,9*aS**)-5-*n*-Hexyl-7,8,9,9*a*-tetrahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (267).**



267

(5*S,9*R**,9*aS**)-5-*n*-Hexyl-2-phenyl-7,8,9,9*a*-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (267)** was synthesised as described for **(3*aS**,4*S**,8*R**,8*aS**,8*bR**)-4,6,7,8,8*a*,8*b*-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3*aH*)-dione (262)** using **(2*E*)-hept-2-en-6-yn-1-ol (215)** (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and 1-octene **(166)** (0.28 mL, 1.82 mmol) for 48 h at 40 °C before *N*-phenyl-1,2,4-triazoline-3,5-dione **(254)** (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 18 h at 75 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 7:3) gave **(5*S**,9*R**,9*aS**)-5-*n*-hexyl-2-phenyl-7,8,9,9*a*-tetrahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*,5*H*-cyclopent[*c*][2,4,10]triazolo[1,2-*a*]pyridazine-1,3(2*H*)-dione (267)** (0.066 g, 54%) as a brown oil. R_f (50% diethyl ether/petroleum ether) 0.33; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3412 (NH), 2928 (CH), 1775 (CO), 1711 (CO), 1503, 1416, 1265, 1140, 820; δ_{H} (400 MHz, CDCl_3) 0.88 (3H, t, J 6.9 Hz, 6''-H₃), 1.19–1.47 (8H, m, 2''-H₂, 3''-H₂, 4''-H₂ and 5''-H₂), 1.73–1.94 (2H, m, 1''-H₂), 2.07–2.20 (1H, m, 8-*HH*), 2.34–2.43 (1H, m, 8-*HH*), 2.52–2.62 (2H, m, 7-H₂), 4.23–4.29 (1H, m, 9*a*-H), 4.62–4.68 (1H, m, 5-H), 4.87 (1H, br q, J 5.4 Hz, 9-H), 5.88–5.94 (1H, m, 6-H), 6.80 (1H, d, J 5.4 Hz, NH), 7.35–7.41 (1H, m, ArH), 7.45–7.50 (2H, m, 2 × ArH), 7.51–7.56 (2H, m, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 14.0 (CH₃), 22.6 (CH₂), 24.9 (CH₂), 24.9 (CH₂), 27.7 (CH₂), 29.1 (CH₂), 31.5 (CH₂), 33.2 (CH₂), 52.6 (CH), 53.9 (CH), 60.7 (CH), 92.7 (C), 120.4 (CH), 125.2 (2 × CH), 128.2 (CH), 129.2 (2 × CH), 131.0 (C), 136.5 (C), 150.0 (C), 154.6 (C), 161.3 (C); m/z (ESI) 535.1023 (MNa^+). $\text{C}_{23}\text{H}_{27}^{35}\text{Cl}_3\text{N}_4\text{NaO}_3$ requires 535.1041).

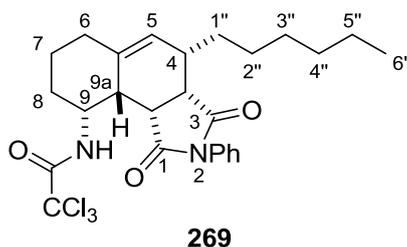
(1*R,5*S**,7*aR**)-2,3,5,6,7,7*a*-Hexahydro-5-*n*-hexyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (268).**



268

(1*R**,5*S**,7*aR**)-2,3,5,6,7,7*a*-Hexahydro-5-*n*-hexyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (**268**) was synthesised as described for (3*aS**,4*S**,8*R**,8*aS**,8*bR**)-4,6,7,8,8*a*,8*b*-hexahydro-2-phenyl-4-*n*-propyl-8-(2',2',2'-trichloromethylcarbonylamino)cyclopent[*e*]isoindole-1,3(2*H*,3*aH*)-dione (**262**) using (2*E*)-hept-2-en-6-yn-1-ol (**215**) (0.027 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.015 g, 0.018 mmol) and 1-octene (**166**) (0.28 mL, 1.82 mmol) for 48 h at 40 °C before tetracyanoethylene (0.046 g, 0.36 mmol) was added. The reaction mixture was stirred for 18 h at 50 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 4:1) gave (1*R**,5*S**,7*aR**)-2,3,5,6,7,7*a*-hexahydro-5-*n*-hexyl-6,6,7,7-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)indene (**268**) (0.057 g, 50%) as a white solid. R_f (50% ethyl acetate/petroleum ether) 0.80; Mp 163–165 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3316 (NH), 2930 (CH), 1688 (CO), 1530, 1458, 1265, 841, 822; δ_{H} (500 MHz, CDCl_3) 0.90 (3H, t, J 8.7 Hz, 6''-H₃), 1.25–1.49 (7H, m, 2''-HH, 3''-H₂, 4''-H₂ and 5''-H₂), 1.53–1.65 (1H, m, 2''-HH), 1.86–2.03 (2H, m, 1''-HH and 2-HH), 2.05–2.16 (1H, m, 1''-HH), 2.39–2.49 (1H, m, 2-HH), 2.51–2.64 (1H, m, 3-HH), 2.69–2.80 (1H, m, 3-HH), 2.97–3.06 (1H, m, 5-H), 3.29–3.37 (1H, m, 7*a*-H), 4.41–4.52 (1H, m, 1-H), 5.84–5.89 (1H, m, 4-H), 6.91 (1H, d, J 10.2 Hz, NH); δ_{C} (126 MHz, CDCl_3) 14.0 (CH₃), 22.5 (CH₂), 27.0 (CH₂), 27.9 (CH₂), 28.7 (CH₂), 28.8 (CH₂), 31.5 (CH₂), 32.8 (CH₂), 39.3 (C), 43.3 (CH), 44.5 (C), 49.0 (CH), 55.2 (CH), 91.8 (C), 109.1 (C), 110.1 (C), 110.9 (C), 111.6 (C), 119.8 (CH), 134.6 (C), 162.3 (C); m/z (ESI) 464.0806 ([M-H]⁻. C₂₁H₂₁³⁵Cl₃N₅O requires 464.0817), 400 (2%), 346 (10), 303 (22), 276 (8), 265 (4), 249 (4).

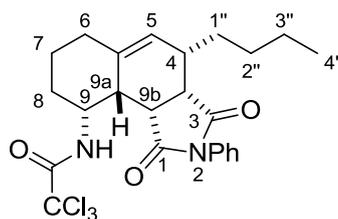
(3a*S,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-Hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (269).**



(2*E*)-Oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. To the solution 1,8-diazabicyclo[5.4.0]undec-7-ene (0.007 mL, 0.048 mmol) and trichloroacetonitrile (0.036 mL, 0.36 mmol) was added. 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 (5 mL) and transferred to a Schlenk tube containing potassium carbonate (0.025 g, 0.18 mmol), purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 36 h. Grubbs second generation catalyst (0.010 g, 0.012 mmol) was added with 1-octene (**166**) (0.19 mL, 1.21 mmol) and the reaction mixture was stirred for 24 h at 70 °C. A further portion of Grubbs second generation catalyst (0.005 g, 0.006 mmol) and 1-octene (**166**) (0.096 mL, 0.61 mmol) was added and the reaction mixture was stirred at 70 °C for 18 h. A further portion of Grubbs second generation catalyst (0.005 g, 0.006 mmol) and 1-octene (**166**) (0.096 mL, 0.61 mmol) was added and the reaction mixture was stirred at 70 °C for 18 h. *N*-Phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added with hydroquinone (0.005 g, 0.005 mmol). The reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:1) gave (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) (0.048 g, 38%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.63; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3327 (NH), 2927 (CH), 2856 (CH), 1700 (CO), 1512, 1500, 1387, 1191, 845; δ_{H} (400 MHz, CDCl_3) 0.89 (3H, t, J 6.8 Hz, 6''-H₃), 1.25–1.50 (8H, m, 2''-H₂, 3''-H₂, 4''-H₂ and 5''-H₂), 1.52–1.63 (1H, m, 7-HH), 1.64–1.78 (2H, m, 1''-HH and 7-HH), 1.81–2.00 (3H, m, 1''-HH and 8-H₂), 2.08–2.20 (1H, m, 6-HH), 2.25–2.36 (1H, m, 4-H), 2.46–2.56 (1H, m, 6-HH), 3.06 (1H, t, J 8.5 Hz, 9a-H), 3.27 (1H, dd, J 8.5, 6.0 Hz, 3a-H), 3.46 (1H, dd, J 8.5, 6.0 Hz, 9b-H), 4.58–4.69 (1H, m, 9-H),

5.61–5.66 (1H, m, 5-H), 7.13–7.19 (2H, m, 2 × ArH), 7.37–7.43 (1H, m, ArH), 7.44–7.51 (2H, m, 2 × ArH), 8.40 (1H, d, *J* 9.4 Hz, NH); δ_{C} (126 MHz, CDCl₃) 13.1 (CH₃), 20.9 (CH₂), 21.6 (CH₂), 27.2 (CH₂), 28.0 (CH₂), 28.2 (CH₂), 28.7 (CH₂), 29.8 (CH₂), 30.8 (CH₂), 36.1 (CH), 36.7 (CH), 41.1 (CH), 43.4 (CH), 47.3 (CH), 91.9 (C), 125.4 (2 × CH), 127.4 (CH), 127.9 (CH), 128.2 (2 × CH), 130.5 (C), 136.9 (C), 160.7 (C), 175.3 (C), 178.2 (C); *m/z* (ESI) 523.1319 ([M-H]⁻. C₂₆H₃₀³⁵Cl₃N₂O₃ requires 523.1327).

(3a*S,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-Butyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (270).**

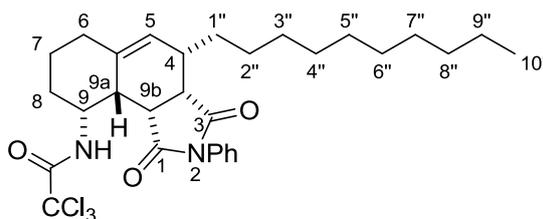


270

(3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-Butyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**270**) was synthesised as described for (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and 1-hexene (0.30 mL, 2.41 mmol) for 72 h at 70 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:1) gave (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-butyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**270**) (0.045 g, 37%) as a colourless oil. *R_f* (50% diethyl ether/petroleum ether) 0.59; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3328 (NH), 2929 (CH), 1698 (CO), 1499, 1387, 1191, 820; δ_{H} (500 MHz, CDCl₃) 0.93 (3H, t, *J* 7.1 Hz, 4''-H₃), 1.33–1.49 (4H, m, 2''-H₂ and 3''-H₂), 1.51–1.62 (1H, m, 7-HH), 1.65–1.77 (2H, m, 1''-HH and 7-HH), 1.82–2.01 (3H, m, 1''-HH and 8-H₂), 2.09–2.19 (1H, m, 6-HH), 2.26–2.35 (1H, m, 4-H), 2.48–2.54 (1H, m, 6-HH), 3.06 (1H, t, *J* 8.5 Hz, 9a-H), 3.27 (1H, dd, *J* 8.5, 6.0 Hz, 3a-H), 3.45 (1H, dd, *J* 8.5, 6.0 Hz, 9b-H), 4.58–4.69 (1H, m, 9-H), 5.61–5.66 (1H, m, 5-H), 7.13–7.18 (2H, m, 2 × ArH), 7.37–7.42 (1H, m, ArH), 7.43–7.49 (2H, m, 2 × ArH), 8.39 (1H, d, *J* 9.4 Hz, NH); δ_{C} (126 MHz, CDCl₃) 14.1 (CH₃), 21.9 (CH₂), 22.6 (CH₂), 29.0 (CH₂), 29.7 (CH₂), 30.5 (CH₂), 30.6 (CH₂), 37.1 (CH), 37.8 (CH),

42.1 (CH), 44.4 (CH), 48.3 (CH), 92.9 (C), 126.4 (2 × CH), 128.4 (CH), 128.9 (CH), 129.3 (2 × CH), 131.5 (C), 138.0 (C), 161.7 (C), 176.3 (C), 179.2 (C); m/z (CI) 497.1167 (MH⁺. C₂₄H₂₈³⁵Cl₃N₂O₃ requires 497.1166), 463 (100%), 429 (41), 379 (32), 335 (39), 174 (38), 122 (12), 69 (40).

(3a*S,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-Decyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (271).**

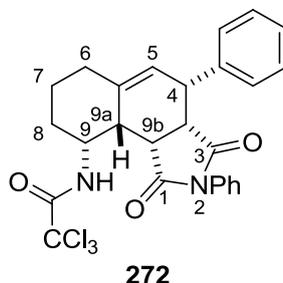


271

(3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-Decyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**271**) was synthesised as described for (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and 1-dodecene (0.54 mL, 2.41 mmol) for 72 h at 70 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:1) gave (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-decyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**271**) (0.051 g, 36%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.68; Mp 152–154 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3327 (NH), 2924 (CH), 2853 (CH), 1700 (CO), 1500, 1386, 1192; δ_{H} (500 MHz, CDCl₃) 0.88 (3H, t, J 7.0 Hz, 10''-H₃), 1.25–1.50 (14H, m, 2''-H₂, 3''-H₂, 4''-H₂, 5''-H₂, 6''-H₂, 7''-H₂ and 8''-H₂, 9''-H₂), 1.52–1.62 (1H, m, 7-*HH*), 1.65–1.76 (2H, m, 1''-*HH* and 7-*HH*), 1.81–1.99 (3H, m, 1''-*HH* and 8-H₂), 2.09–2.19 (1H, m, 6-*HH*), 2.25–2.35 (1H, m, 4-H), 2.47–2.55 (1H, m, 6-*HH*), 3.06 (1H, t, J 8.5 Hz, 9a-H), 3.27 (1H, dd, J 8.5, 5.7 Hz, 3a-H), 3.45 (1H, dd, J 8.5, 6.5 Hz, 9b-H), 4.58–4.68 (1H, m, 9-H), 5.61–5.65 (1H, m, 5-H), 7.13–7.18 (2H, m, 2 × ArH), 7.37–7.49 (3H, m, 3 × ArH), 8.39 (1H, d, J 9.4 Hz, NH); δ_{C} (126 MHz, CDCl₃) 14.1 (CH₃), 21.9 (CH₂), 22.7 (CH₂), 28.3 (CH₂), 29.0 (CH₂), 29.3 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 29.7 (CH₂), 30.9 (CH₂), 31.9 (CH₂), 37.1 (CH), 37.8 (CH), 42.1 (CH), 44.4 (CH), 48.3 (CH), 92.9 (C), 126.4 (2 × CH),

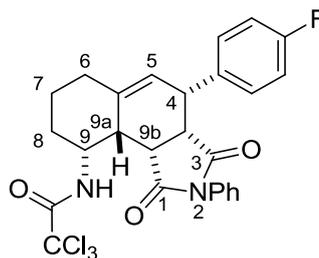
128.4 (CH), 128.9 (CH), 129.3 (2 × CH), 131.6 (C), 138.0 (C), 161.7 (C), 176.3 (C), 179.2 (C); m/z (ESI) 603.1889 (MNa^+ . $C_{30}H_{39}^{35}Cl_3N_2NaO_3$ requires 603.1918).

(3a*S,4*S**,9*R**,9a*S**,9b*R**)-2,4-Diphenyl-3a,4,6,7,8,9,9a,9b-octahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (272).**



(3a*S**,4*S**,9*R**,9a*S**,9b*R**)-2,4-Diphenyl-3a,4,6,7,8,9,9a,9b-octahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**272**) was synthesised as described for (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (*2E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and styrene (0.27 mL, 2.41 mmol) for 72 h at 70 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 13:7) gave (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-2,4-diphenyl-3a,4,6,7,8,9,9a,9b-octahydro-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**272**) (0.067 g, 54%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.47; Mp 153–155 °C; ν_{max}/cm^{-1} (neat) 3336 (NH), 2937 (CH), 1698 (CO), 1511, 1499, 1386, 1192, 819; δ_H (500 MHz, $CDCl_3$) 1.61–1.86 (3H, m, 7- H_2 and 8- HH), 2.01 (1H, dq, J 12.5, 5.6 Hz, 8- HH), 2.23–2.34 (1H, m, 6- HH), 2.58–2.66 (1H, m, 6- HH), 3.21–3.28 (1H, m, 9a-H), 3.53–3.60 (2H, m, 3a-H and 9b-H), 3.70 (1H, br s, 4-H), 4.66–4.76 (1H, m, 9-H), 6.23–6.28 (1H, m, 5-H), 7.11–7.16 (2H, m, 2 × ArH), 7.26–7.46 (8H, m, 8 × ArH), 8.43 (1H, d, J 9.4 Hz, NH); δ_C (126 MHz, $CDCl_3$) 21.7 (CH_2), 28.7 (CH_2), 29.9 (CH_2), 38.2 (CH), 41.8 (CH), 41.9 (CH), 47.3 (CH), 48.2 (CH), 92.9 (C), 125.2 (CH), 126.3 (2 × CH), 127.2 (CH), 128.3 (2 × CH), 128.8 (2 × CH), 128.9 (CH), 129.2 (2 × CH), 131.4 (C), 138.6 (C), 139.1 (C), 161.9 (C), 175.1 (C), 178.6 (C); m/z (ESI) 539.0652 (MNa^+ . $C_{26}H_{23}^{35}Cl_3N_2NaO_3$ requires 539.0666), 413 (10%), 383 (8), 301 (6), 236 (3).

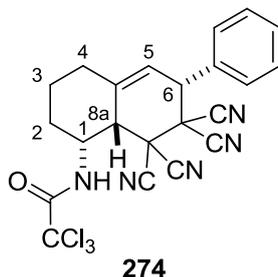
(3a*S,4*S**,9*R**,9a*S**,9b*R**)-4-(4-Fluorophenyl)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (273).**



273

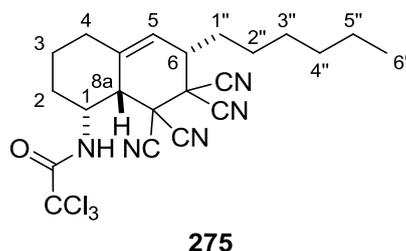
(3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-(4-Fluorophenyl)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**273**) was synthesised as described for (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-*n*-hexyl-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and 4-fluorostyrene (0.29 mL, 2.41 mmol) for 72 h at 70 °C before *N*-phenyl maleimide (**139**) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 48 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:2) gave (3a*S**,4*S**,9*R**,9a*S**,9b*R**)-4-(4-fluorophenyl)-3a,4,6,7,8,9,9a,9b-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**273**) (0.065 g, 50%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.35; Mp 144–146 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3324 (NH), 2927 (CH), 1699 (CO), 1510, 1386, 1264, 1188, 820; δ_{H} (500 MHz, CDCl_3) 1.61–1.86 (3H, m, 7- H_2 and 8-*HH*), 2.02 (1H, dq, J 11.8, 5.4 Hz, 8-*HH*), 2.22–2.33 (1H, m, 6-*HH*), 2.58–2.66 (1H, m, 6-*HH*), 3.24 (1H, t, J 6.8 Hz, 9a-H), 3.51 (1H, dd, J 8.5, 5.7 Hz, 3a-H), 3.57 (1H, dd, J 8.5, 6.8 Hz, 9b-H), 3.68 (1H, br s, 4-H), 4.65–4.76 (1H, m, 9-H), 6.15–6.21 (1H, m, 5-H), 7.02–7.08 (2H, m, 2 \times ArH), 7.11–7.15 (2H, m, 2 \times ArH), 7.29–7.47 (5H, m, 5 \times ArH), 8.41 (1H, d, J 9.7 Hz, NH); δ_{C} (126 MHz, CDCl_3) 21.7 (CH_2), 28.7 (CH_2), 29.8 (CH_2), 38.2 (CH), 41.2 (CH), 41.8 (CH), 47.3 (CH), 48.2 (CH), 92.9 (C), 115.2 (d, $J_{\text{C-C-F}}$ 21.4 Hz, 2 \times CH), 125.1 (CH), 126.3 (2 \times CH), 129.0 (CH), 129.3 (2 \times CH), 130.3 (d, $J_{\text{C-C-F}}$ 8.0 Hz, 2 \times CH), 131.3 (C), 134.3 (C), 139.4 (C), 161.9 (C), 162.0 (d, $J_{\text{C-F}}$ 245.9 Hz, C), 175.1 (C), 178.5 (C); m/z (ESI) 557.0586 (MNa^+ . $\text{C}_{26}\text{H}_{22}^{35}\text{Cl}_3\text{FN}_2\text{NaO}_3$ requires 557.0572), 413 (23%), 345 (8), 242 (34), 142 (3).

(1*R,6*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-Octahydro-6-phenyl-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (274).**



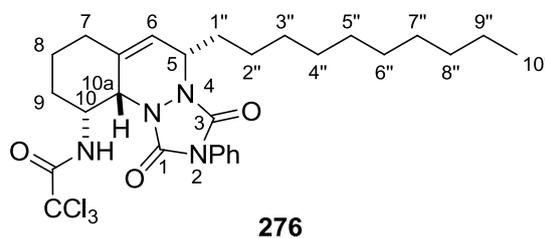
(1*R**,6*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-Octahydro-6-phenyl-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**274**) was synthesised as described for (3*aS**,4*S**,9*R**,9*aS**,9*bR**)-4-*n*-hexyl-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and styrene (0.27 mL, 2.41 mmol) for 72 h at 70 °C before tetracyanoethylene (0.046 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 50 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 7:3) gave (1*R**,6*R**,8*aR**)-1,2,3,4,6,7,8,8*a*-octahydro-6-phenyl-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**274**) (0.050 g, 44%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.68; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3332 (NH), 2946 (CH), 2254 (CN), 1696 (CO), 1513, 1455, 1275, 1082, 820; δ_{H} (500 MHz, CDCl_3) 1.57–1.70 (1H, m, 3-*HH*), 1.95–2.10 (2H, m, 2-*HH* and 3-*HH*), 2.21–2.35 (2H, m, 2-*HH* and 4-*HH*), 2.63 (1H, br d, J 13.2 Hz, 4-*HH*), 3.68 (1H, d, J 11.3 Hz, 8*a*-H), 4.21–4.31 (1H, m, 1-H), 4.32–4.37 (1H, m, 6-H), 5.85–5.90 (1H, m, 5-H), 7.10–7.18 (1H, m, NH), 7.44–7.49 (5H, m, 5 × ArH); δ_{C} (126 MHz, CDCl_3) 24.2 (CH_2), 32.1 (CH_2), 35.2 (CH_2), 40.3 (C), 44.3 (C), 46.2 (CH), 46.4 (CH), 54.6 (CH), 92.0 (C), 108.9 (C), 110.2 (C), 111.5 (C), 112.4 (C), 119.8 (CH), 129.0 (2 × CH), 130.5 (CH), 130.7 (2 × CH), 131.3 (C), 136.1 (C), 161.9 (C); m/z (ESI) 470.0332 ($[\text{M}-\text{H}]^-$. $\text{C}_{22}\text{H}_{15}^{35}\text{Cl}_3\text{N}_5\text{O}$ requires 470.0348), 352 (21%), 309 (20), 282 (15), 257 (8), 212 (4).

(1*R,6*S**,8*aR**)-6-*n*-Hexyl-1,2,3,4,6,7,8,8*a*-octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**275**).**

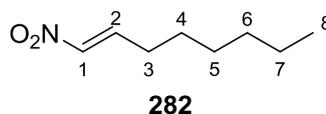


(1*R**,6*S**,8*aR**)-6-*n*-Hexyl-1,2,3,4,6,7,8,8*a*-octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**275**) was synthesised as described for (3*aS**,4*S**,9*R**,9*aS**,9*bR**)-4-*n*-hexyl-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (**269**) using (2*E*)-oct-2-en-7-yn-1-ol (**194**) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and 1-octene (**166**) (0.38 mL, 2.41 mmol) for 72 h at 70 °C before tetracyanoethylene (0.046 g, 0.36 mmol) was added. The reaction mixture was stirred for 18 h at 50 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 5:1) gave (1*R**,6*S**,8*aR**)-6-*n*-hexyl-1,2,3,4,6,7,8,8*a*-octahydro-7,7,8,8-tetracyano-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene (**275**) (0.052 g, 45%) as a colourless oil. R_f (25% ethyl acetate/petroleum ether) 0.50; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3332 (NH), 2929 (CH), 1690 (CO), 1512, 1457, 1277, 1215, 823; δ_{H} (500 MHz, CDCl_3) 0.91 (3H, t, J 7.0 Hz, 6''-H₃), 1.27–1.66 (9H, m, 2''-H₂, 3-HH, 3''-H₂, 4''-H₂ and 5''-H₂), 1.83–1.99 (3H, m, 2-HH, 3-HH and 1''-HH), 2.04–2.27 (3H, m, 2-HH, 4-HH and 1''-HH), 2.45–2.54 (1H, m, 4-HH), 2.91–2.99 (1H, m, 6-H), 3.42 (1H, d, J 11.4 Hz, 8*a*-H), 4.09–4.19 (1H, m, 1-H), 5.82–5.86 (1H, m, 5-H), 6.98 (1H, d, J 9.1 Hz, NH); δ_{C} (126 MHz, CDCl_3) 14.0 (CH₃), 22.5 (CH₂), 23.6 (CH₂), 27.8 (CH₂), 28.8 (CH₂), 31.5 (CH₂), 32.2 (CH₂), 32.2 (CH₂), 34.7 (CH₂), 40.1 (C), 42.0 (CH), 44.2 (C), 46.6 (CH), 54.5 (CH), 91.9 (C), 109.6 (C), 110.3 (C), 111.5 (C), 112.5 (C), 120.8 (CH), 132.8 (C), 161.8 (C); m/z (ESI) 502.0928 (MNa⁺. C₂₂H₂₄³⁵Cl₃N₅NaO requires 502.0939), 413 (7%), 345 (48), 336 (37), 323 (8), 236 (6).

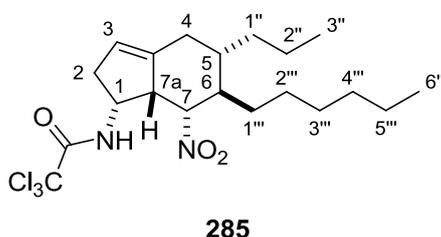
(5*S,10*R**,10*aS**)-5-*n*-Decyl-5,7,8,9,10,10*a*-hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (276).**



(5*S**,10*R**,10*aS**)-5-*n*-Decyl-5,7,8,9,10,10*a*-hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (276) was synthesised as described for (3*aS**,4*S**,9*R**,9*aS**,9*bR**)-4-*n*-hexyl-3*a*,4,6,7,8,9,9*a*,9*b*-octahydro-2-phenyl-9-(2',2',2'-trichloromethylcarbonylamino)-1*H*-benz[*e*]isoindole-1,3(2*H*)-dione (269) using (2*E*)-oct-2-en-7-yn-1-ol (194) (0.030 g, 0.24 mmol). The reaction mixture was stirred with Grubbs second generation catalyst (0.020 g, 0.024 mmol) and 1-dodecene (0.54 mL, 2.41 mmol) for 72 h at 75 °C before *N*-phenyl-1,2,4-triazoline-3,5-dione (254) (0.063 g, 0.36 mmol) was added. The reaction mixture was stirred for 24 h at 100 °C. The reaction mixture was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 7:3) gave (5*S**,10*R**,10*aS**)-5-*n*-decyl-5,7,8,9,10,10*a*-hexahydro-2-phenyl-10-(2',2',2'-trichloromethylcarbonylamino)-1*H*-[2,4,11]-triazolo[1,2-*a*]cinnoline-1,3(2*H*)-dione (276) (0.055 g, 39%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.49; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3415 (NH), 2923 (CH), 1709 (CO), 1503, 1416, 1141, 818; δ_{H} (500 MHz, CDCl_3) 0.88 (3H, t, J 7.0 Hz, 10''-H₃), 1.15–1.59 (17H, m, 8-HH, 2''-H₂, 3''-H₂, 4''-H₂, 5''-H₂, 6''-H₂, 7''-H₂, 8''-H₂ and 9''-H₂), 1.77–1.91 (3H, m, 8-HH, 9-HH and 1''-HH), 2.14–2.28 (3H, m, 7-HH, 9-HH and 1''-HH), 2.49–2.57 (1H, m, 7-HH), 4.31–4.38 (1H, m, 5-H), 4.49 (1H, br s, 10*a*-H), 5.11–5.18 (1H, m, 10-H), 5.88–5.93 (1H, m, 6-H), 6.79 (1H, d, J 8.1 Hz, NH), 7.33–7.39 (1H, m, ArH), 7.44–7.53 (4H, m, 4 × ArH); δ_{C} (126 MHz, CDCl_3) 14.1 (CH₃), 21.6 (CH₂), 22.7 (CH₂), 25.2 (CH₂), 28.0 (CH₂), 29.3 (CH₂), 29.5 (CH₂), 29.5 (CH₂), 29.6 (CH₂), 29.6 (CH₂), 31.9 (CH₂), 33.2 (CH₂), 33.5 (CH₂), 50.0 (CH), 54.4 (CH), 57.5 (CH), 92.8 (C), 122.7 (CH), 125.8 (2 × CH), 128.2 (CH), 128.3 (C), 129.1 (2 × CH), 131.1 (C), 151.6 (C), 151.9 (C), 161.2 (C); m/z (ESI) 605.1796 (MNa⁺. C₂₈H₃₇³⁵Cl₃N₄NaO₃ requires 605.1823), 413 (9%), 301 (4), 236 (5).

(*E*)-1-Nitrooct-1-ene (282).¹³⁴

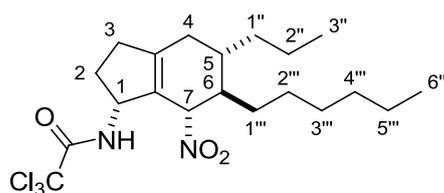
Heptaldehyde (**284**) (10.0 mL, 71.5 mmol) was dissolved in methanol (100 mL) and nitromethane (3.87 mL, 71.5 mmol) was added. The solution was cooled to 0 °C and a solution of 12.5 M sodium hydroxide (7.2 mL) was then added dropwise. Further methanol (50 mL) was added and the reaction mixture was stirred at room temperature for 18 h. Water (30 mL) was added and the clear yellow solution was poured into 5 M hydrochloric acid (40 mL) and stirred for 0.2 h. The resulting mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried (MgSO₄) and the solvent removed under reduced pressure. Flash column chromatography using silica (petroleum ether/diethyl ether 10:1) gave (*E*)-1-nitrooct-1-ene (**282**) (8.28 g, 74%) as a yellow oil. Spectroscopic data was consistent with literature.¹³⁴ *R_f* (50% diethyl ether/petroleum ether) 0.86; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2930 (CH), 2861, 1649, 1524, 1466, 1350, 959; δ_{H} (500 MHz, CDCl₃) 0.90 (1H, t, *J* 6.9 Hz, 8-H₃), 1.26–1.39 (6H, m, 5-H₂, 6-H₂ and 7-H₂), 1.51 (2H, quin., *J* 7.4 Hz, 4-H₂), 2.27 (2H, qd, *J* 7.4, 1.5 Hz, 3-H₂), 6.98 (1H, dt, *J* 13.4, 1.5 Hz, 1-H), 7.28 (1H, dt, *J* 13.4, 7.4 Hz, 2-H); δ_{C} (126 MHz, CDCl₃) 14.0 (CH₃), 22.5 (CH₂), 27.7 (CH₂), 28.5 (CH₂), 28.8 (CH₂), 31.4 (CH₂), 139.6 (CH), 142.8 (CH); *m/z* (CI) 158 (MH⁺, 72%), 142 (43), 113 (40), 85 (100), 69 (92).

(1*R,5*S**,6*R**,7*S**,7*aS**)-2,4,5,6,7,7*a*-Hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (285).**

4-(*n*-Pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**258**) (0.051 g, 0.17 mmol) was dissolved in (*E*)-1-nitrooct-1-ene (**282**) (0.54 g, 3.44 mmol) with anhydrous zinc chloride (0.047 g, 0.34 mmol) and hydroquinone (0.002 g, 0.002 mmol). The reaction mixture was stirred at 111 °C for 120 h. The solution was then cooled to room temperature. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave (1*R**,5*S**,6*R**,7*S**,7*aS**)-2,4,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-

(2',2',2'-trichloromethylcarbonylamino)indene (**285**) (0.014 g, 18%) as a yellow oil. R_f (50% diethyl ether/petroleum ether) 0.40; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3341 (NH), 2928 (CH), 1697 (CO), 1518, 1464, 1264, 820; δ_{H} (500 MHz, CDCl_3) 0.88 (3H, t, J 6.9 Hz, 3''-H₃), 0.91 (3H, t, J 6.9 Hz, 6'''-H₃), 1.20–1.54 (15H, m, 5-H, 1''-H₂, 2''-H₂, 1'''-H₂, 2'''-H₂, 3'''-H₂, 4'''-H₂ and 5'''-H₂), 1.90–2.03 (1H, m, 6-H), 2.13–2.22 (1H, m, 4-HH), 2.27 (1H, dd, J 16.4, 6.1 Hz, 2-HH), 2.52–2.62 (2H, m, 4-HH and 7a-H), 2.87 (1H, dd, J 16.4, 8.3 Hz, 2-HH), 4.36 (1H, dq, J 7.5, 6.1 Hz, 1-H), 4.69 (1H, dd, J 8.0, 6.1 Hz, 7-H), 5.52 (1H, s, 3-H), 6.72 (1H, d, J 7.5 Hz, NH); δ_{C} (126 MHz, CDCl_3) 14.0 (CH₃), 14.1 (CH₃), 20.3 (CH₂), 22.6 (CH₂), 25.9 (CH₂), 29.5 (CH₂), 31.6 (CH₂), 32.3 (CH₂), 33.5 (CH₂), 37.3 (CH₂), 38.7 (CH₂), 38.8 (CH), 41.1 (CH), 42.5 (CH), 51.1 (CH), 90.8 (CH), 92.5 (C), 120.1 (CH), 141.5 (C), 161.5 (C); m/z (ESI) 475.1278 (MNa^+ . $\text{C}_{20}\text{H}_{31}^{35}\text{Cl}_3\text{N}_2\text{NaO}_3$ requires 475.1292).

(1*R,5*S**,6*R**,7*S**)-2,3,4,5,6,7-Hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**286**).**

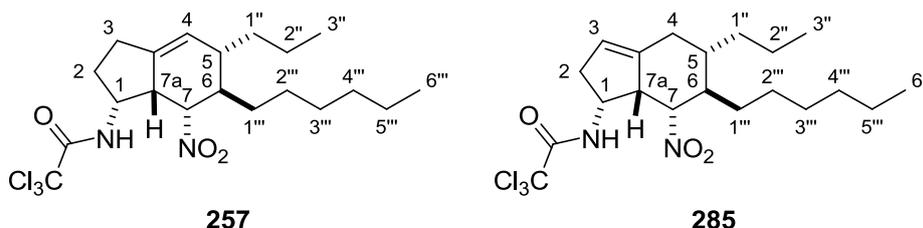


286

4-(*n*-Pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**258**) (0.073 g, 0.25 mmol) was dissolved in *p*-xylene (4 mL). (*E*)-1-Nitrooct-1-ene (**282**) (0.19 g, 1.23 mmol), anhydrous zinc chloride (0.033 g, 0.25 mmol) and hydroquinone (0.003 g, 0.003 mmol) were added. The reaction mixture was stirred at 160 °C for 76 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:3) gave (1*R**,5*S**,6*R**,7*S**)-2,3,4,5,6,7-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**286**) (0.023 g, 20%) as a yellow oil. R_f (50% diethyl ether/petroleum ether) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 2927 (CH), 1708 (CO), 1546, 1507, 1466, 1263, 1086, 1012; δ_{H} (500 MHz, CDCl_3) 0.89 (3H, t, J 6.9 Hz, 3''-H₃), 0.93 (3H, J 6.9 Hz, 6'''-H₃), 1.20–1.48 (14H, m, 1''-H₂, 2''-H₂, 1'''-H₂, 2'''-H₂, 3'''-H₂, 4'''-H₂ and 5'''-H₂), 1.92–2.30 (5H, m, 2-HH, 3-HH, 4-H₂ and 5-H), 2.63 (1H, br s, 6-H), 2.80 (1H, dd, J 16.3, 7.5 Hz, 2-HH), 2.92–3.00 (1H, m, 3-HH), 4.51–4.58 (1H, m, 1-H), 4.67–4.70 (1H, m, 7-H), 6.85 (1H, d, J 7.5 Hz, NH); δ_{C} (126 MHz, CDCl_3) 13.0 (CH₃), 13.0 (CH₃), 21.6 (CH₂), 26.2 (CH₂), 27.3 (CH₂), 28.2 (CH₂), 28.7 (CH₂), 30.6 (CH₂), 31.3 (CH₂), 32.6 (CH₂), 33.2 (CH), 39.1 (CH), 40.4 (CH₂), 41.6 (CH₂), 49.6 (CH), 87.0 (CH), 91.6 (C),

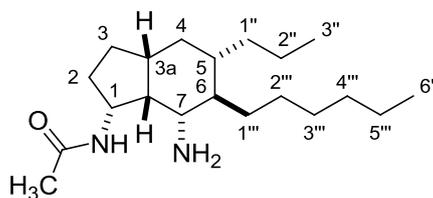
131.0 (C), 131.5 (C), 160.5 (C); m/z (ESI) 475.1270 (MNa^+ . $C_{20}H_{31}^{35}Cl_3N_2NaO_3$ requires 475.1292).

(1*R,5*R**,6*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-Hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (257) and (1*R**,5*S**,6*R**,7*S**,7*aS**)-2,4,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (285).**



4-(*n*-Pent-1''-ene)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**258**) (0.140 g, 0.48 mmol) was dissolved in (*E*)-1-nitrooct-1-ene (**282**) (1.50 g, 9.58 mmol) with anhydrous zinc chloride (0.065 g, 0.48 mmol) and hydroquinone (0.005 g, 0.005 mmol). The reaction mixture was stirred at 40 °C for 24 h. The solution was then cooled to room temperature. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave (1*R**,5*R**,6*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**257**) (0.150 g, 70%) as a white solid. R_f (25% diethyl ether/petroleum ether) 0.45; Mp 138–140 °C; ν_{max}/cm^{-1} (neat) 3287 (NH), 2957 (CH), 1681 (CO), 1537, 1466, 1375, 1284, 1230, 1080; δ_H (500 MHz, $CDCl_3$) 0.86 (3H, J 6.8 Hz, 6'''-H₃), 0.92 (3H, J 6.8 Hz, 3''-H₃), 1.19–1.40 (10H, m, 2''-H₂, 2'''-H₂, 3'''-H₂, 4'''-H₂ and 5'''-H₂), 1.42–1.52 (2H, m, 1''-HH and 1'''-HH), 1.57–1.72 (3H, m, 2-HH, 1''-HH and 1'''-HH), 2.14–2.21 (1H, m, 2-HH), 2.22–2.32 (2H, m, 3-HH and 7*a*-H), 2.35–2.43 (1H, m, 5-H), 2.45–2.56 (2H, m, 3-HH and 6-H), 4.12 (1H, quin., J 8.5 Hz, 1-H), 4.70 (1H, dd, J 7.2, 5.3 Hz, 7-H), 5.44 (1H, s, 4-H), 6.68 (1H, d, J 8.5 Hz, NH); δ_C (126 MHz, $CDCl_3$) 14.0 (CH₃), 14.0 (CH₃), 20.3 (CH₂), 22.6 (CH₂), 25.6 (CH₂), 27.8 (CH₂), 29.6 (CH₂), 31.2 (CH₂), 31.5 (CH₂), 31.7 (CH₂), 33.5 (CH₂), 38.2 (CH), 39.5 (CH), 48.4 (CH), 57.7 (CH), 89.8 (CH), 92.7 (C), 119.9 (CH), 141.4 (C), 161.2 (C); m/z (ESI) 475.1281 (MNa^+ . $C_{20}H_{31}^{35}Cl_3N_2NaO_3$ requires 475.1292). Further elution with (petroleum ether/diethyl ether, 1:1) gave (1*R**,5*S**,6*R**,7*S**,7*aS**)-2,4,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**285**) (0.037 g, 17%) as a yellow oil. Spectroscopic data as described previously

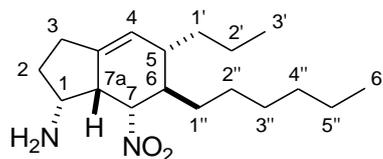
(1*R,3*aR**,5*S**,6*R**,7*S**,7*aR**)-1-(*N*-Acetylamino)-7-amino-2,3,3*a*,4,5,6,7,7*a*-octahydro-6-*n*-hexyl-5-*n*-propylindene (**287**).**



287

(1*R**,5*R**,6*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-Hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**257**) (0.103 g, 0.227 mmol) was dissolved in tetrahydrofuran (10 mL) which was then added to a slurry of activated Raney™-Nickel (1.00 g). The reaction mixture was stirred under a hydrogen atmosphere at room temperature for 24 h. A further portion of Raney-Nickel™ was added (1.00 g) and the reaction mixture was stirred under a hydrogen atmosphere at room temperature for 24 h. The precipitate was filtered through a pad of Celite® and washed with ethyl acetate (3 × 100 mL). The filtrate was then dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography using silica (methanol/dichloromethane, 1:9) gave (1*R**,3*aR**,5*S**,6*R**,7*S**,7*aR**)-1-(*N*-acetylamino)-7-amino-2,3,3*a*,4,5,6,7,7*a*-octahydro-6-*n*-hexyl-5-*n*-propylindene (**287**) (0.025 g, 34%) as a colourless oil. *R_f* (10% methanol/dichloromethane) 0.15; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3680 (NH), 3394 (NH), 2926 (CH), 1701 (CO), 1538, 1452, 1364, 1055, 1023; δ_{H} (500 MHz, CD₃OD) 0.93 (3H, t, *J* 7.5 Hz, 6'''-H₃), 1.00 (3H, t, *J* 7.5 Hz, 3'''-H₃), 1.21–1.62 (19H, m, 2-H₂, 3-HH, 4-H₂, 1''-H₂, 1'''-H₂, 2''-H₂, 2'''-H₂, 3'''-H₂, 4'''-H₂ and 5'''-H₂), 1.69–1.72 (1H, m, 3*a*-H), 1.73–1.80 (1H, m, 7*a*-H), 1.92 (3H, s, COCH₃), 1.96–2.03 (1H, m, 5-H), 2.05–2.22 (1H, m, 3-HH and 6-H), 3.22 (1H, dd, *J* 11.3, 4.7 Hz, 7-H), 4.11 (1H, dt, *J* 10.0, 5.3 Hz, 1-H); δ_{C} (126 MHz, CD₃OD) 14.5 (CH₃), 14.5 (CH₃), 21.4 (CH₂), 23.0 (CH₃), 24.0 (CH₂), 24.6 (CH₂), 28.3 (CH₂), 28.5 (CH₂), 30.0 (CH₂), 31.4 (CH₂), 32.5 (CH₂), 33.4 (2 × CH₂), 38.7 (CH), 39.6 (CH), 41.5 (CH), 52.9 (CH), 53.8 (CH), 56.8 (CH), 171.8 (C); *m/z* (CI) 323.3063 (MH⁺. C₂₀H₃₉N₂O requires 323.3062), 297 (9%), 257 (8), 97 (25), 69 (100).

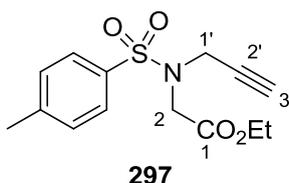
(1*R,5*R**,6*R**,7*S**,7*aS**)-1-Amino-2,3,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propylindene (**288**).**



288

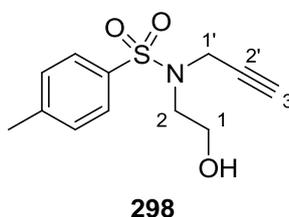
(1*R**,5*R**,6*R**,7*S**,7*aS**)-2,3,5,6,7,7*a*-Hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propyl-1-(2',2',2'-trichloromethylcarbonylamino)indene (**257**) (0.075 g, 0.17 mmol) was dissolved in tetrahydrofuran (16 mL) and cooled to $-78\text{ }^{\circ}\text{C}$. DIBAL-H (1 M in hexane) (0.87 mL, 0.87 mmol) was added dropwise and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 3 h, before warming to room temperature overnight. The solution was cooled to $0\text{ }^{\circ}\text{C}$ and quenched by the addition of a saturated solution of Rochelles salt (10 mL) and warmed to room temperature with vigorous stirring for 1 h. The solution was diluted with ethyl acetate (50 mL) and water (10 mL) and the product extracted with ethyl acetate ($3 \times 50\text{ mL}$). The combined organic layers were washed with brine, dried (MgSO_4) and concentrated *in vacuo*. Flash column chromatography (methanol/dichloromethane, 1:25) gave (1*R**,5*R**,6*R**,7*S**,7*aS**)-1-amino-2,3,5,6,7,7*a*-hexahydro-6-*n*-hexyl-7-nitro-5-*n*-propylindene (**288**) (0.029 g, 58%) as a colourless oil. R_f (10% methanol/dichloromethane) 0.15; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3680 (NH), 2924 (CH), 1545, 1464, 1375, 1054, 1033; δ_{H} (500 MHz, CDCl_3) 0.88 (3H, t, J 7.0 Hz, 6''-H₃), 0.91 (3H, t, J 7.0 Hz, 3'-H₃), 1.19–1.38 (10H, m, 2'-H₂, 2''-H₂, 3''-H₂, 4''-H₂ and 5''-H₂), 1.40–1.60 (4H, m, 1'-HH, 1''-H₂ and 2-HH), 1.63–1.71 (1H, m, 1'-HH), 1.77–1.84 (1H, m, 7*a*-H), 1.97–2.05 (1H, m, 2-HH), 2.09–2.16 (1H, m, 6-H), 2.21–2.30 (1H, m, 3-HH), 2.38–2.47 (1H, m, 3-HH), 2.47–2.54 (1H, m, 5-H), 3.08 (1H, dt, J 8.3, 7.1 Hz, 1-H), 4.69 (1H, dd, J 7.2, 5.4 Hz, 7-H), 5.32 (1H, br s, 4-H); δ_{C} (126 MHz, CDCl_3) 14.0 (CH₃), 14.1 (CH₃), 20.3 (CH₂), 22.6 (CH₂), 25.8 (CH₂), 27.8 (CH₂), 29.6 (CH₂), 31.7 (CH₂), 32.2 (CH₂), 33.7 (CH₂), 34.8 (CH₂), 38.1 (CH), 39.9 (CH), 51.8 (CH), 58.8 (CH), 90.5 (CH), 118.2 (CH), 144.2 (C); m/z (ESI) 309.2524 (MH^+ . $\text{C}_{18}\text{H}_{33}\text{N}_2\text{O}_2$ requires 309.2537).

Ethyl 2-(*N*-*p*-toluenesulfonyl-2'-propynlamino)ethanoate (297**).¹⁷⁸**



To a solution of ethyl 2-*N*-(*p*-toluenesulfonyl)aminoethanoate (**295**) (1.00 g, 3.89 mmol) in dichloromethane (40 mL) was added potassium carbonate (2.60 g, 19.4 mmol) and 3-bromoprop-1-yne (**296**) (0.43 mL, 3.89 mmol) and the reaction mixture stirred at room temperature for 72 h. The reaction mixture was diluted with water (60 mL) and the dichloromethane was removed *in vacuo*. The product was extracted with diethyl ether (3 × 100 mL) and the combined organic layers were washed with brine (30 mL), dried (MgSO₄) and concentrated *in vacuo*. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave ethyl 2-(*N*-*p*-toluenesulfonyl-2'-propynlamino)ethanoate (**297**) (0.88 g, 76%) as a white solid. Spectroscopic data was consistent with the literature.¹⁷⁸ *R_f* (50% diethyl ether/petroleum ether) 0.36; Mp 44–46 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3266 (NH), 2982 (CH), 2122 (C≡C), 1749 (CO), 1343, 1329, 1308, 1267, 1200, 1157, 1090, 1015, 945; δ_{H} (500 MHz, CDCl₃) 1.22 (3H, t, *J* 7.1 Hz, OCH₂CH₃), 2.16 (1H, t, *J* 2.5 Hz, 3'-H), 2.41 (3H, s, CH₃), 4.09 (2H, s, 2-H₂), 4.14 (2H, q, *J* 7.1 Hz, OCH₂CH₃), 4.25 (2H, d, *J* 2.5 Hz, 1'-H₂), 7.29 (2H, d, *J* 8.4 Hz, 2 × ArH), 7.72 (2H, d, *J* 8.4 Hz, 2 × ArH); δ_{C} (126 MHz, CDCl₃) 14.0 (CH₃), 21.5 (CH₃), 37.5 (CH₂), 47.0 (CH₂), 61.4 (CH₂), 74.3 (CH), 76.6 (C), 127.6 (2 × CH), 129.6 (2 × CH), 136.4 (C), 143.8 (C), 168.4 (C); *m/z* (CI) 296.0958 (MH⁺. C₁₄H₁₈NO₄S requires 296.0957), 270 (3%), 262 (3), 222 (22), 155 (9), 140 (25), 91 (2).

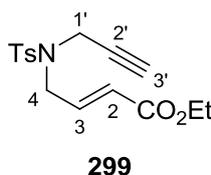
2-(*N*-*p*-toluenesulfonyl-2'-propynlamino)ethan-1-ol (298**).¹⁷⁹**



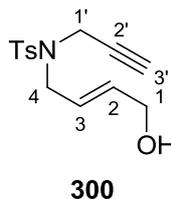
Ethyl 2-(*N*-*p*-toluenesulfonyl-2'-propynlamino)ethanoate (**297**) (1.42 g, 4.81 mmol) was dissolved in diethyl ether (200 mL) and cooled to −78 °C. DIBAL-H (1 M in hexane) (10.6 mL, 10.6 mmol) was added dropwise and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature overnight. The solution was cooled to 0 °C and quenched by the addition of a saturated aqueous solution of Rochelle's salt (20 mL) and

warmed to room temperature with vigorous stirring over 1 h. The aqueous layer was extracted with diethyl ether (3×100 mL), dried (MgSO_4) and concentrated *in vacuo*. Flash column chromatography using silica (petroleum ether/ethyl acetate, 1:1) gave 2-(*N-p*-toluenesulfonyl-2'-propynlamino)ethan-1-ol (**298**) (1.22 g, 99%) as a white solid. Spectroscopic data was consistent with literature.¹⁷⁹ R_f (50% ethyl acetate/petroleum ether) 0.24; Mp 66–68 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3512 (OH), 3258 ($\text{C}\equiv\text{C}-\text{H}$), 2953 (CH), 2116, 1732, 1597 (C=C), 1444, 1402, 1341, 1310, 1161, 1072, 1005; δ_{H} (500 MHz, CDCl_3) 2.08–2.12 (2H, m, OH and 3'-H), 2.43 (3H, s, CH_3), 3.36 (2H, t, J 5.2 Hz, 2- H_2), 3.81 (2H, q, J 5.2 Hz, 1- H_2), 4.21 (2H, d, J 2.5 Hz, 1'- H_2), 7.31 (2H, d, J 8.0 Hz, $2 \times \text{ArH}$), 7.31 (2H, dd, J 8.3 Hz, $2 \times \text{ArH}$); δ_{C} (126 MHz, CDCl_3) 21.6 (CH_3), 37.9 (CH_2), 49.0 (CH_2), 60.6 (CH_2), 74.0 (CH), 76.9 (C), 127.8 ($2 \times \text{ArH}$), 129.6 ($2 \times \text{ArH}$), 135.5 (C), 143.9 (C); m/z (CI) 254.0847 (MH^+ . $\text{C}_{12}\text{H}_{16}\text{NO}_3\text{S}$ requires 254.0851), 197 (5%), 186 (10), 157 (15), 141 (8), 100 (15), 73 (26).

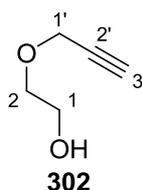
Ethyl (2*E*)-4-(*N-p*-toluenesulfonyl-2'-propynlamino)but-2-enoate (299).



Ethyl (2*E*)-4-(*N-p*-toluenesulfonyl-2'-propynlamino)but-2-enoate (**299**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**221**) using 2-(*N-p*-toluenesulfonyl-2'-propynlamino)ethan-1-ol (**298**) (1.24 g, 4.90 mmol). Flash column chromatography using silica (diethyl ether/petroleum ether, 11:9) gave ethyl (2*E*)-4-(*N-p*-toluenesulfonyl-2'-propynlamino)but-2-enoate (**299**) (1.31 g, 83%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.30; Mp 69–71 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3273 ($\text{C}\equiv\text{C}-\text{H}$), 2982 (CH), 1717 (CO), 1661 (C=C), 1348, 1275, 1157, 1094; δ_{H} (500 MHz, CDCl_3) 1.28 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.08 (1H, t, J 2.5 Hz, 3'-H), 2.42 (3H, s, CH_3), 3.98 (2H, dd, J 6.0, 1.6 Hz, 4- H_2), 4.09 (2H, d, J 2.5 Hz, 1'- H_2), 4.19 (2H, q, J 7.2 Hz, OCH_2CH_3), 6.01 (1H, dt, J 15.7, 1.6 Hz, 2-H), 6.78 (1H, dt, J 15.7, 6.0 Hz, 3-H), 7.30 (1H, d, J 8.3 Hz, $2 \times \text{ArH}$), 7.72 (1H, d, J 8.3 Hz, $2 \times \text{ArH}$); δ_{C} (126 MHz, CDCl_3) 14.1 (CH_3), 21.4 (CH_3), 36.7 (CH_2), 47.1 (CH_2), 60.5 (CH_2), 74.2 (CH), 76.3 (C), 124.7 (CH), 127.7 ($2 \times \text{CH}$), 129.6 ($2 \times \text{CH}$), 136.0 (C), 141.1 (CH), 143.8 (C), 165.4 (C); m/z (EI) 321.1031 (M^+ . $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{S}$ requires 321.1035), 276 (40%), 248 (16), 166 (100), 155 (50), 120 (35), 91 (50), 65 (10).

(2E)-4-(N-p-Toluenesulfonyl-2'-propynlamino)but-2-en-1-ol (300).

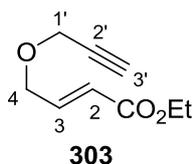
(2E)-4-(N-p-Toluenesulfonyl-2'-propynlamino)but-2-en-1-ol (**300**) was synthesised as described for (2E)-hept-2-en-6-yn-1-ol (**215**) using ethyl (2E)-4-(N-p-toluenesulfonyl-2'-propynlamino)but-2-enoate (**299**) (0.241 g, 0.75 mmol). Flash column chromatography using silica (ethyl acetate/petroleum ether, 11:9) gave (2E)-4-(N-p-toluenesulfonyl-2'-propynlamino)but-2-en-1-ol (**300**) (0.21 g, 99%) as a colourless oil. R_f (50% ethyl acetate/petroleum ether) 0.33; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3538 (OH), 3273 (C≡C-H), 2922 (CH), 2864 (CH), 1597 (C=C), 1447, 1344, 1327, 1155, 1090, 893, 735; δ_{H} (500 MHz, CDCl_3) 1.44 (1H, br s, OH), 2.03 (1H, t, J 2.5 Hz, 3'-H), 2.42 (3H, s, CH_3), 3.84 (4H, dd, J 6.5, 1.2 Hz, 4-H₂), 4.09 (2H, d, J 2.5 Hz, 1'-H₂), 4.11–4.15 (2H, br m, 1-H₂), 5.64 (1H, dtt, J 15.5, 6.5, 1.6 Hz, 3-H), 5.88 (2H, dtt, J 15.5, 4.0, 1.2 Hz, 2-H), 7.29 (2H, d, J 8.2 Hz, 2 × ArH), 7.73 (2H, d, J 8.2 Hz, 2 × ArH); δ_{C} (126 MHz, CDCl_3) 21.5 (CH_3), 36.0 (CH_2), 48.0 (CH_2), 62.7 (CH_2), 73.7 (CH), 125.0 (CH), 127.8 (2 × CH), 129.5 (2 × CH), 134.7 (CH), 136.4 (C), 143.6 (C); m/z (CI) 280.1012 (MH^+). $\text{C}_{14}\text{H}_{18}\text{NO}_3\text{S}$ requires 280.1007), 263 (100%), 210 (6), 157 (2), 113 (4), 85 (5), 69 (6).

2-(2'-Propynloxy)ethan-1-ol (302).¹⁴⁵

To a solution of ethylene glycol (**301**) (2.42 mL, 44.9 mmol) and potassium hydroxide (0.75 g, 13.4 mmol) in dimethyl sulfoxide (10 mL) and water (10 mL) at 0 °C was added a solution of 3-bromoprop-1-yne (**296**) (1.25 mL, 11.2 mmol) in dimethyl sulfoxide (5 mL). The reaction mixture was stirred at 0 °C for 1 h followed by stirring at room temperature for 72 h. The solution was diluted with diethyl ether (100 mL) and water (50 mL) and, the product was extracted with chloroform (3 × 100 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO_4) and concentrated *in vacuo*. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:4) gave 2-(2'-propynloxy)ethan-1-ol (**302**) (0.264 g, 24%) as a colourless oil. Spectroscopic data was consistent with the literature.¹⁴⁵ R_f (50% petroleum ether/diethyl ether) 0.17; $\nu_{\max}/\text{cm}^{-1}$

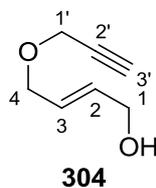
(neat) 3399 (OH), 3293 (C≡C-H), 2933 (CH), 2868, 1460, 1443, 1354, 1277, 1221, 1107, 1067, 1028, 920, 889; δ_{H} (500 MHz, CDCl₃) 1.89 (1H, t, *J* 5.6 Hz, OH), 2.43 (1H, t, *J* 2.4 Hz, 3'-H), 3.64–3.67 (2H, m, 2-H₂), 2.74–2.79 (2H, m, 1-H₂), 4.20 (2H, d, *J* 2.4 Hz, 1'-H₂); δ_{C} (126 MHz, CDCl₃) 58.5 (CH₂), 61.8 (CH₂), 71.3 (CH₂), 74.6 (CH), 79.6 (C); *m/z* (CI) 101 (MH⁺, 100%), 83 (4), 79 (2), 69 (1).

Ethyl (2*E*)-4-(2'-propynloxy)but-2-enoate (303).¹⁸⁰



Ethyl (2*E*)-4-(2'-propynloxy)but-2-enoate (**303**) was synthesised as described for ethyl (2*E*)-hept-2-en-6-ynoate (**221**) using 2-(2'-propynloxy)ethan-1-ol (**302**) (1.20 g, 12.0 mmol). Flash column chromatography using silica (diethyl ether/petroleum ether, 1:3) gave ethyl (2*E*)-4-(2'-propynloxy)but-2-enoate (**303**) (1.50 g, 75%) as a yellow oil. Spectroscopic data was consistent with the literature.¹⁸⁰ *R_f* (25% diethyl ether/petroleum ether) 0.61; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3291 (C≡C-H), 2982 (CH), 1715 (CO), 1663 (C=C), 1368, 1304, 1265, 1177, 1119, 1036, 966; δ_{H} (500 MHz, CDCl₃) 1.28 (3H, t, *J* 7.1 Hz, OCH₂CH₃), 2.44 (1H, t, *J* 2.4 Hz, 3'-H), 4.17–4.24 (6H, m, 1'-H₂, 4-H₂ and OCH₂CH₃), 6.08 (1H, dt, *J* 15.8, 2.0 Hz, 2-H), 6.93 (1H, dt, *J* 15.8, 4.6 Hz, 3-H); δ_{C} (126 MHz, CDCl₃) 14.3 (CH₃), 58.1 (CH₂), 60.5 (CH₂), 68.3 (CH₂), 75.0 (CH), 79.3 (C), 122.3 (CH), 143.3 (CH), 166.2 (C); *m/z* (CI) 169 (MH⁺, 19%), 155 (5), 145 (87), 131 (7), 127 (7), 113 (6).

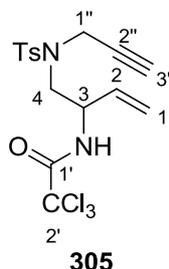
(2*E*)-4-(2'-Propynloxy)but-2-en-1-ol (304).



(2*E*)-4-(2'-Propynloxy)but-2-en-1-ol (**304**) was synthesised as described for (2*E*)-hept-2-en-6-yn-1-ol (**215**) using ethyl (2*E*)-4-(2'-propynloxy)but-2-enoate (**303**) (1.46 g, 8.70 mmol). Flash column chromatography using silica (ethyl acetate/petroleum ether, 1:1) gave (2*E*)-4-(2'-propynloxy)but-2-en-1-ol (**304**) (0.91 g, 83%) as a colourless oil. *R_f* (50% ethyl acetate/petroleum ether) 0.36; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3385 (OH), 3289 (C≡C-H), 2920 (CH), 2855, 1356, 1090, 999, 970; δ_{H} (500 MHz, CDCl₃) 1.58 (1H, br s, OH), 1.99 (1H, t, *J* 2.4 Hz, 3'-H), 4.08 (2H, dd, *J* 5.8, 1.1 Hz, 4-H₂), 4.13–4.18 (4H, m, 1-H₂ and 1'-H₂), 5.80 (1H, dtt, *J* 15.6, 5.8, 1.4 Hz, 3-H), 5.93 (1H, dtt, *J* 15.6, 5.3, 1.1 Hz, 2-H); δ_{C} (126 MHz, CDCl₃)

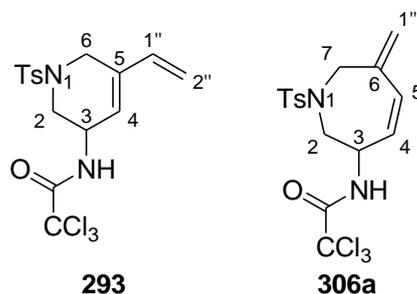
57.4 (CH₂), 63.0 (CH₂), 69.7 (CH₂), 74.5 (CH), 79.8 (C), 127.1 (CH), 133.2 (CH); *m/z* (CI) 127.0762 (MH⁺. C₇H₁₁O₂ requires 127.0759), 109 (56%), 71 (100).

4-(*N-p*-Toluenesulfonyl-2''-propynlamino)-3-(2',2',2'-trichloromethylcarbonylamino)but-1-ene (305).



(*2E*)-4-(*N-p*-Toluenesulfonyl-2''-propynlamino)but-2-en-1-ol (**300**) (0.40 g, 1.43 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. To the solution was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.043 mL, 0.29 mmol) and trichloroacetonitrile (0.22 mL, 2.15 mmol). 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 was concentrated *in vacuo* to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was dissolved in toluene (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.050 g) and purged with Ar and sealed. The reaction mixture was then heated to 140 °C and stirred for 48 h, before cooling to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 13:7) gave 4-(*N-p*-toluenesulfonyl-2''-propynlamino)-3-(2',2',2'-trichloromethylcarbonylamino)but-1-ene (**305**) (0.54 g, 89%) as a colourless oil. *R_f* (50% diethyl ether/petroleum ether) 0.32; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3309 (C≡C–H), 2976 (CH), 1707 (CO), 1598, 1518, 1445, 1348, 1331, 1157; δ_{H} (500 MHz, CDCl₃) 2.12 (1H, t, *J* 2.5 Hz, 3''-H), 2.42 (3H, s, CH₃), 3.34 (1H, dd, *J* 14.5, 4.3 Hz, 4-*HH*), 3.50 (1H, dd, *J* 14.5, 9.4 Hz, 4-*HH*), 4.12 (1H, dd, *J* 18.6, 2.5 Hz, 1''-H), 4.25 (1H, dd, *J* 18.6, 2.5 Hz, 1''-*HH*), 4.58–4.67 (1H, m, 3-H), 5.30 (1H, d, *J* 10.6 Hz, 1-*HH*), 5.38 (1H, d, *J* 17.2 Hz, 1-*HH*), 5.80 (1H, ddd, *J* 17.2, 10.6, 5.7 Hz, 2-H), 7.30 (1H, d, *J* 8.0 Hz, 2 × ArH), 7.53 (1H, d, *J* 6.0 Hz, NH), 7.72 (2H, d, *J* 8.0 Hz, 2 × ArH); δ_{C} (126 MHz, CDCl₃) 21.7 (CH₃), 37.8 (CH₂), 49.0 (CH₂), 51.8 (CH), 74.9 (CH), 76.2 (C), 92.5 (C), 118.5 (CH₂), 127.7 (2 × CH), 129.9 (2 × CH), 133.2 (CH), 135.4 (C), 144.4 (C), 162.3 (C); *m/z* (CI) 423.0108 (MH⁺. C₁₆H₁₈³⁵Cl₃N₂O₃S requires 423.0104), 389 (40%), 351 (8), 279 (28), 233 (44), 157 (100), 141 (27).

5-Ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (293) and 6-methylidene-2,3,6,7-tetrahydro-1-*p*-toluenesulphonyl-3-(2',2',2'-trichloromethylcarbonylamino)-1*H*-azepine (306a).

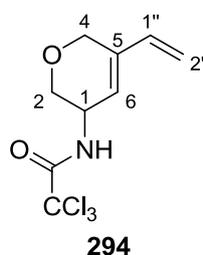


Method A- 4-(*N-p*-Toluenesulfonyl-2'-propynlamino)-3-(2',2',2'-trichloromethylcarbonylamino)but-1-ene (**305**) (0.043 g, 0.10 mmol) was dissolved in toluene (2 mL) and Hoveyda-Grubbs second generation catalyst (0.003 g, 0.005 mmol) and 1,7-octadiene (**156**) (0.061 mL, 0.40 mmol) were added. The reaction mixture stirred at 75 °C for 24 h. The reaction mixture was then cooled and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether 1:1) gave 5-ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) (0.029 g, 67%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.55; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2922 (CH), 1705 (CO), 1597 (C=C), 1499, 1454, 1346, 1240, 1161, 1090, 1022, 991, 815; δ_H (500 MHz, CDCl_3) 2.45 (1H, s, CH_3), 2.82 (1H, dd, J 12.4, 3.4 Hz, 2-*HH*), 3.33 (1H, d, J 15.9 Hz, 6-*HH*), 3.72 (1H, br d, J 12.4 Hz, 2-*HH*), 4.27 (1H, d, J 15.9 Hz, 6-*HH*), 4.57–4.64 (1H, m, 3-H), 5.20 (1H, d, J 11.1 Hz, 2''-*HH*), 5.25 (1H, d, J 17.8 Hz, 2''-*HH*), 5.82 (1H, br d, J 5.7 Hz, 4-H), 6.30 (1H, dd, J 17.8, 11.1 Hz, 1''-H), 7.00 (1H, br d, J 8.2 Hz, NH), 7.37 (2H, d, J 8.2 Hz, $2 \times \text{ArH}$), 7.72 (2H, d, J 8.2 Hz, $2 \times \text{ArH}$); δ_C (126 MHz, CDCl_3) 21.6 (CH_3), 44.3 (CH_2), 45.6 (CH), 47.8 (CH_2), 92.2 (C), 115.3 (CH_2), 123.1 (CH), 127.7 ($2 \times \text{CH}$), 130.0 ($2 \times \text{CH}$), 132.9 (C), 135.1 (CH), 137.1 (C), 144.3 (C), 161.5 (C); m/z (ESI) 444.9905 (MNa^+ . $\text{C}_{16}\text{H}_{17}^{35}\text{Cl}_3\text{N}_2\text{NaO}_3\text{S}$ requires 444.9918). Further elution (petroleum ether/diethyl ether 2:3) gave 6-methylidene-2,3,6,7-tetrahydro-1-*p*-toluenesulphonyl-3-(2',2',2'-trichloromethylcarbonylamino)-1*H*-azepine (**306a**) (0.010 g, 23%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3340 (NH), 2928 (CH), 1706 (CO), 1599 (C=C), 1501, 1454, 1346, 1232, 1161, 1092, 1023; δ_H (500 MHz, CDCl_3) 2.45 (1H, s, CH_3), 3.22 (1H, dd, J 14.8, 3.2 Hz, 2-*HH*), 3.65 (1H, d, J 15.2 Hz, 7-*HH*), 3.83 (1H, br d, J 14.8 Hz, 2-*HH*), 4.54 (1H, d, J 15.2 Hz, 7-*HH*), 4.64–4.70 (1H, m, 3-H), 5.16 (1H, s, 1''-*HH*), 5.22 (1H, s, 1''-*HH*), 5.64 (1H, dd, J 12.3, 5.3 Hz, 4-H), 6.24 (1H, d, J 12.3 Hz, 5-H), 7.34 (2H, d, J 8.2 Hz, $2 \times \text{ArH}$), 7.66 (1H, d, J 7.3 Hz, NH), 7.71 (2H, d, J 8.2 Hz, 2

× ArH); δ_C (126 MHz, CDCl_3) 21.6 (CH_3), 51.7 (CH), 51.9 (CH_2), 55.8 (CH_2), 92.3 (C), 120.1 (CH_2), 125.8 (CH), 127.2 ($2 \times \text{CH}$), 130.0 ($2 \times \text{CH}$), 132.0 (CH), 135.2 (C), 141.2 (C), 144.1 (C), 161.6 (C); m/z (ESI) 444.9907 (MNa^+ . $\text{C}_{16}\text{H}_{17}^{35}\text{Cl}_3\text{N}_2\text{NaO}_3\text{S}$ requires 444.9918).

Method B- 5-Ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) was synthesised as described for 5-ethyl-1''-ene-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (Method B) using (*E*)-4-(*N*-*p*-toluenesulfonyl-2'-propynlamino)but-2-en-1-ol (**300**) (0.074 g, 0.26 mmol). The allylic trichloroacetimidate was dissolved in toluene (6 mL) containing potassium carbonate (0.030 g) and purged with Ar. The reaction mixture was then heated to 140 °C and stirred for 5 days. The reaction mixture was stirred with Hoveyda-Grubbs second generation catalyst (0.011 g, 0.013 mmol) and 1,7-octadiene (**156**) (0.15 mL, 1.0 mmol) at 90 °C for 24 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave 5-ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) (0.044 g, 40%) as a colourless oil. Spectroscopic data as described above.

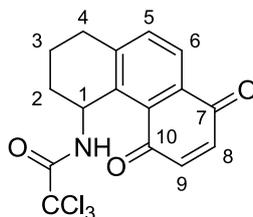
1,4-Dihydro-5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (294**).**



1,4-Dihydro-5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (**294**) was synthesised as described for 5-ethyl-1''-ene-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (Method B) using (*E*)-4-(2'-propynloxy)but-2-en-1-ol (**304**) (0.079 g, 0.62 mmol). The allylic trichloroacetimidate was dissolved in toluene (15 mL) containing potassium carbonate (0.075 g) and purged with argon. The reaction mixture was then heated to 140 °C in a sealed tube for 5 days. The reaction mixture was then stirred with Grubbs first generation catalyst (0.025 g, 0.030 mmol) and 1,7-octadiene (**156**) (0.37 mL, 2.49 mmol) at 90 °C for 18 h. A further portion of Grubbs first generation catalyst (0.025 g, 0.030 mmol) and 1,7-octadiene (**156**) (0.37 mL, 2.49 mmol) was added and the reaction mixture was stirred at 90 °C for 24 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 4:1) gave 1,4-dihydro-

5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (**294**) (0.077 g, 46%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.43; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3318 (NH), 2942 (CH), 2857 (CH), 1697 (CO), 1499, 1454, 1236, 1117, 1071, 1028, 1011, 988, 910, 860, 758; δ_{H} (500 MHz, CDCl_3) 3.76 (1H, dd, J 11.9, 3.1 Hz, 2-*HH*), 3.92 (1H, d, J 11.9 Hz, 2-*HH*), 4.25 (1H, d, J 15.9 Hz, 4-*HH*), 4.42–4.49 (2H, m, 1-*H* and 4-*HH*), 5.15 (1H, d, J 17.9 Hz, 2''-*HH*), 5.16 (1H, d, J 11.1 Hz, 2''-*HH*), 5.86 (1H, d, J 5.1 Hz, 6-*H*), 6.28 (1H, dd, J 17.9, 11.1 Hz, 1''-*H*), 6.94 (1H, br d, J 5.6 Hz, NH); δ_{C} (126 MHz, CDCl_3) 45.4 (CH), 65.2 (CH_2), 68.4 (CH_2), 92.5 (C), 114.6 (CH_2), 122.0 (CH), 134.7 (CH), 139.6 (C), 161.4 (C); m/z (CI) 269.9855 (MH^+ . $\text{C}_9\text{H}_{11}^{35}\text{Cl}_3\text{NO}_2$ requires 269.9855), 236 (29%), 200 (11), 146 (24), 113 (15), 73 (100).

1,2,3,4-Tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (211).



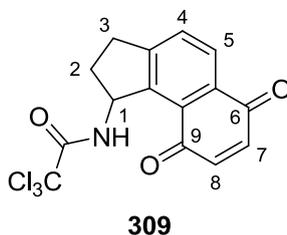
211

Method A- (*E*)-Octa-2-en-7-yn-1-ol (**194**) (0.060 g, 0.48 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. To the solution, 1,8-diazabicyclo[5.4.0]undec-7-ene (0.014 mL, 0.096 mmol) and trichloroacetonitrile (0.072 mL, 0.073 mmol) was added. 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 (10 mL) and transferred to a Schlenk tube containing potassium carbonate (0.05 g) and purged with Ar and sealed. The reaction mixture was then warmed to 140 °C and stirred for 24 h. Grubbs first generation catalyst (0.029 g, 0.035 mmol) was added and the reaction mixture was heated for 18 h at 75 °C. A further portion of Grubbs first generation catalyst (0.013 g, 0.016 mmol) was added with 1,4-benzoquinone (**307**) (0.16 g, 1.40 mmol) and hydroquinone (0.014 g, 0.13 mmol) and the reaction mixture was stirred at 111 °C for 18 h. The reaction mixture was then cooled to room temperature and DDQ (0.22 g, 0.96 mmol) was added and the reaction mixture was heated to 111 °C for 18 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/ethyl acetate, 7:3) gave 1,2,3,4-

tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (0.103 g, 58%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.30; Mp 165–167 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3345 (NH), 2947 (CH), 1709 (CO), 1663 (CO), 1586, 1512, 1304, 1096, 822; δ_{H} (400 MHz, CDCl_3) 1.80–1.97 (3H, m, 2-*HH* and 3- H_2), 2.33–2.47 (1H, m, 2-*HH*), 2.89–3.00 (1H, m, 4-*HH*), 3.04–3.14 (1H, m, 4-*HH*), 5.90–5.96 (1H, m, 1-H), 6.76 (1H, br d, J 6.4 Hz, NH), 6.88 (1H, d, J 10.2 Hz, ArH), 6.92 (1H, d, J 10.2 Hz, ArH), 7.57 (1H, d, J 8.1 Hz, ArH), 8.09 (1H, d, J 8.1 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 17.8 (CH_2), 27.9 (CH_2), 30.7 (CH_2), 47.1 (CH), 92.9 (C), 126.9 (CH), 129.6 (C), 132.5 (C), 135.2 (C), 135.3 (CH), 136.4 (CH), 140.5 (CH), 146.3 (C), 160.5 (C), 184.8 (C), 186.4 (C); m/z (CI) 371.9960 (MH^+ . $\text{C}_{16}\text{H}_{13}^{35}\text{Cl}_3\text{NO}_3$ requires 371.9961), 338 (30%), 304 (10), 268 (15), 243 (84), 229 (100), 213 (60), 162 (75), 128 (40).

Method B- 5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.090 g, 0.34 mmol) was dissolved in toluene (10 mL) and 1,4-benzoquinone (**307**) (0.040 g, 0.37 mmol) was added. The reaction mixture was stirred at 115 °C for 72 h. The solution was then cooled to room temperature and manganese oxide (0.296 g, 3.40 mmol) was added with a silicon carbide bar. The mixture was stirred at 115 °C in a microwave reactor for 2 h. The solution was then cooled to room temperature and the solvent evaporated under vacuum. Flash column chromatography using silica (petroleum ether/diethyl ether, 5:4) gave 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (0.084 g, 66%) as a yellow solid. Spectroscopic data as described above.

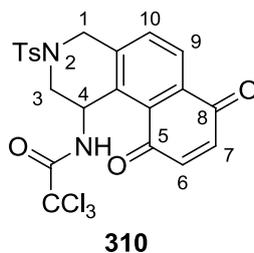
1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3-trihydro-cyclopent[a]naphthalene-6,9-dione (309).



1-(2',2',2'-Trichloromethylcarbonylamino)-1,2,3-trihydro-cyclopent[a]naphthalene-6,9-dione (**309**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (Method B) using 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.071 g, 0.28 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1)

gave 1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3-trihydrocyclopent[a]naphthalene-6,9-dione (**309**) (0.076 g, 75%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.35; Mp 153–155 °C; ν_{\max} / cm^{-1} (neat) 3350 (NH), 2926 (CH), 1688 (CO), 1663 (CO), 1510, 1298, 1078, 820; δ_{H} (500 MHz, CDCl_3) 2.48–2.61 (2H, m, 2- H_2), 3.03 (1H, ddd, J 17.4, 8.7, 2.8 Hz, 3- HH), 3.52 (1H, dt, J 17.4, 8.7 Hz, 3- HH), 5.62 (1H, ddd, J 8.7, 6.4, 2.8 Hz, 1-H), 6.90 (1H, d, J 10.3 Hz, ArH), 6.96 (1H, d, J 10.3 Hz, ArH), 7.47 (1H, br d, J 6.4 Hz, NH), 7.67 (1H, d, J 7.9 Hz, ArH), 8.11 (1H, d, J 7.9 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 30.5 (CH_2), 31.5 (CH_2), 57.2 (CH), 92.9 (C), 127.9 (C), 128.3 (CH), 130.3 (CH), 131.9 (C), 138.3 (CH), 138.8 (CH), 140.7 (C), 154.2 (C), 161.0 (C), 184.4 (C), 186.2 (C); m/z (ESI) 381.9578 (MNa^+ . $\text{C}_{15}\text{H}_{10}^{35}\text{Cl}_2^{37}\text{ClNNaO}_3$ requires 381.9589).

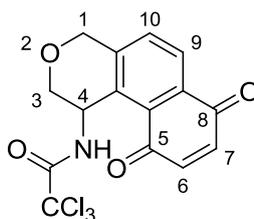
1,2,3,4-Tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (310**).**



1,2,3,4-Tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (**310**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]naphthalene-7,10-dione (**211**) (Method B) using 5-ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) (0.075 g, 0.18 mmol). The reaction mixture was stirred at 115 °C for 72 h. The solution was then cooled to room temperature and DDQ (0.088 g, 0.39 mmol) and a silicon carbide bar were added. The mixture was stirred at 115 °C in a microwave reactor for 2 h. Flash column chromatography using silica (petroleum ether/ethyl acetate, 3:1) gave 1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (**310**) (0.045 g, 48%) as a brown solid. R_f (50% ethyl acetate/petroleum ether) 0.51; Mp 192–194 °C; ν_{\max} / cm^{-1} (neat) 3329 (NH), 2924 (CH), 1707 (CO), 1663 (CO), 1593 (C=C), 1508, 1303, 1165, 1096, 1071, 961, 816; δ_{H} (500 MHz, CDCl_3) 2.44 (3H, s, CH_3), 2.77 (1H, dd, J 12.6, 2.8 Hz, 3- HH), 3.94 (1H, d, J 16.1 Hz, 1- HH), 4.12 (1H, ddd, J 12.6, 2.8, 1.7 Hz, 3- HH), 4.85 (1H, d, J 16.1 Hz, 1- HH), 6.07 (1H, dt, J 7.6, 2.8 Hz, 4-H), 6.91–6.97 (3H, m, NH, 6-H

and 7-H), 7.38 (2H, d, J 8.2 Hz, $2 \times$ ArH), 7.55 (1H, d, J 8.2 Hz, ArH), 7.75 (2H, d, J 8.2 Hz, $2 \times$ ArH), 8.18 (1H, d, J 8.2 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 21.6 (CH_3), 46.5 (CH), 48.2 (CH_2), 48.4 (CH_2), 92.3 (C), 127.7 (CH), 127.9 ($2 \times$ CH), 129.6 (C), 130.1 ($2 \times$ CH), 132.4 (CH), 133.1 (C), 136.7 ($2 \times$ CH), 140.3 ($2 \times$ CH), 140.5 (C), 144.5 (C), 161.1 (C), 185.6 ($2 \times$ C); m/z (ESI) 548.9813 (MNa^+ . $\text{C}_{22}\text{H}_{17}^{35}\text{Cl}_3\text{N}_2\text{NaO}_5\text{S}$ requires 548.9816).

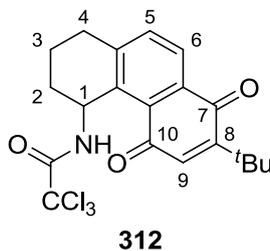
1,3-Dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[*f*]isochromene-5,8-dione (311).



311

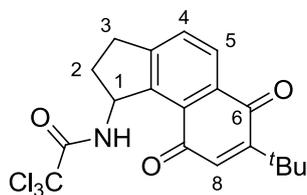
1,3-Dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[*f*]isochromene-5,8-dione (**311**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]naphthalene-7,10-dione (**211**) (Method B) using 1,4-dihydro-5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (**294**) (0.071 g, 0.26 mmol). The reaction mixture was stirred at 115 °C for 72 h. The solution was then cooled to room temperature and DDQ (0.13 g, 0.58 mmol) and a silicon carbide bar was added. The mixture was stirred at 115 °C in a microwave reactor for 2 h. Flash column chromatography using silica (petroleum ether/ethyl acetate, 3:2) gave 1,3-dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[*f*]isochromene-5,8-dione (**311**) (0.038, 39%) as a yellow solid. R_f (50% ethyl acetate/petroleum ether) 0.42; Mp 176–178 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3337 (NH), 2926 (CH), 1705 (CO), 1661 (CO), 1589 (C=C), 1508, 1302, 1233, 1088, 1069, 818; δ_{H} (500 MHz, CDCl_3) 3.75 (1H, dd, J 12.2, 2.6 Hz, 3-*HH*), 4.27 (1H, dd, J 12.2, 1.7 Hz, 3-*HH*), 4.78 (1H, d, J 16.2 Hz, 1-*HH*), 4.93 (1H, d, J 16.2 Hz, 1-*HH*), 5.74 (1H, br d, J 6.4 Hz, 4-H), 6.79 (1H, d, J 6.4 Hz, NH), 6.84 (1H, d, J 10.3 Hz, ArH), 6.86 (1H, d, J 10.3 Hz, ArH), 7.39 (1H, d, J 8.1 Hz, ArH), 8.09 (1H, d, J 8.1 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 45.8 (CH), 68.4 (CH_2), 68.9 (CH_2), 92.5 (C), 127.5 (CH), 129.4 (C), 130.4 (CH), 131.5 (C), 132.8 (C), 136.8 (CH), 140.2 (CH), 143.0 (C), 161.0 (C), 184.5 (C), 185.7 (C); m/z (ESI) 395.9561 (MNa^+ . $\text{C}_{15}\text{H}_{10}^{35}\text{Cl}_3\text{NNaO}_4$ requires 395.9568).

8-*tert*-Butyl-1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (312).



8-*tert*-Butyl-1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**312**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (Method B) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) and 2-*tert*-butyl-1,4-benzoquinone (0.073 g, 0.47 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 7:3) gave 8-*tert*-butyl-1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**312**) (0.092 g, 58%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.61; Mp 128–130 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3225 (NH), 2957 (CH), 1705 (CO), 1661 (CO), 1607, 1541, 1341, 1252, 1121, 1078, 816; δ_{H} (500 MHz, CDCl_3) 1.34 (9H, s, $3 \times \text{CH}_3$), 1.75–1.92 (3H, m, 2-*HH* and 3- H_2), 2.37–2.46 (2H, m, 2-*HH*), 2.85–2.95 (1H, m, 4-*HH*), 3.04 (1H, dt, J 17.7, 4.7 Hz, 4-*HH*), 5.85–5.90 (1H, m, 1-H), 6.73 (1H, s, 9-H), 6.75 (1H, d, J 5.9 Hz, NH), 7.50 (1H, d, J 8.1 Hz, ArH), 8.07 (1H, d, J 8.1 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 17.9 (CH_2), 27.8 (CH_2), 29.1 ($3 \times \text{CH}_3$), 30.5 (CH_2), 35.2 (C), 47.3 (CH), 93.1 (C), 127.3 (CH), 129.4 (C), 134.3 (C), 134.4 (C), 134.9 (CH), 135.5 (CH), 145.4 (C), 156.3 (C), 160.4 (C), 184.7 (C), 187.1 (C); m/z (CI) 428.0584 (MH^+ . $\text{C}_{20}\text{H}_{21}^{35}\text{Cl}_3\text{NO}_3$ requires 428.0587), 408 (6%), 370 (29), 285 (100), 162 (58), 128 (48), 71 (31).

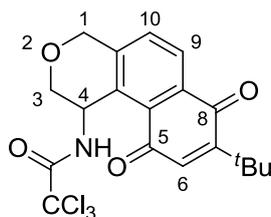
7-*tert*-Butyl-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3-trihydrocyclopent[a]naphthalene-6,9-dione (313).



313

7-*tert*-Butyl-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3-trihydrocyclopent[a]naphthalene-6,9-dione (**313**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (Method B) using 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.071 g, 0.28 mmol) and 2-*tert*-butyl-1,4-benzoquinone (0.054 g, 0.33 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 7:3) gave 7-*tert*-butyl-1-(2',2',2'-trichloromethylcarbonylamino)-1,2,3-trihydrocyclopent[a]naphthalene-6,9-dione (**313**) (0.079 g, 68%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.53; Mp 198–200 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3325 (NH), 2954 (CH), 1680 (CO), 1661 (CO), 1597 (C=C), 1504, 1290, 1250, 1068, 910, 816; δ_{H} (500 MHz, CDCl_3) 1.36 (9H, s, 3 \times CH_3), 2.48–2.57 (2H, m, 2- H_2), 3.00 (1H, ddd, J 17.1, 7.8, 3.7 Hz, 3- HH), 3.49 (1H, dt, J 17.1, 8.8 Hz, 3- HH), 5.54–5.61 (1H, m, 1-H), 6.77 (1H, s, 8-H), 7.50 (1H, d, J 5.5 Hz, NH), 7.63 (1H, d, J 7.9 Hz, ArH), 8.11 (1H, d, J 7.9 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 29.4 (3 \times CH_3), 30.4 (CH_2), 31.4 (CH_2), 35.7 (C), 57.1 (CH), 92.9 (C), 127.5 (C), 128.8 (CH), 130.1 (CH), 133.5 (C), 134.1 (CH), 139.8 (C), 153.4 (C), 158.1 (C), 161.0 (C), 184.4 (C), 187.0 (C); m/z (EI) 413.0354 (M^+ . $\text{C}_{19}\text{H}_{18}^{35}\text{Cl}_3\text{NO}_3$ requires 413.0352), 378 (57%), 268 (30), 252 (100), 237 (41), 185 (23), 165 (22), 143 (13), 115 (22), 84 (79), 49 (76).

7-*tert*-Butyl-1,3-dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[f]isochromene-5,8-dione (314).

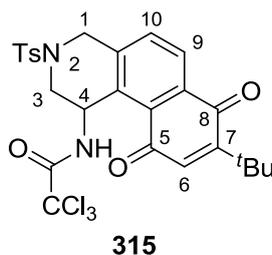


314

7-*tert*-Butyl-1,3-dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[f]isochromene-5,8-dione (**314**) was synthesised as described for 1,2,3,4-tetrahydro-

1-(2',2',2'-trichloromethylcarbonylamino)benz[a]naphthalene-7,10-dione (**211**) (Method B) using 1,4-dihydro-5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (**294**) (0.070 g, 0.26 mmol) and 2-*tert*-butyl-1,4-benzoquinone (0.051 g, 0.31 mmol). The solution was then cooled to room temperature and DDQ (0.129 g, 0.57 mmol) and a silicon carbide bar were added. The mixture was stirred at 115 °C in a microwave reactor for 2 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 11:9) gave 7-*tert*-butyl-1,3-dihydro-4-(2',2',2'-trichloromethylcarbonylamino)-4*H*-benzo[*f*]isochromene-5,8-dione (**314**) (0.064 g, 57%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.24; Mp 192–194 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3379 (NH), 2969 (CH), 1708 (CO), 1661 (CO), 1592 (C=C), 1513, 1274, 1250, 1091, 908, 819; δ_{H} (500 MHz, CDCl_3) 1.34 (9H, s, 3 × CH_3), 3.79 (1H, dd, J 12.3, 2.3 Hz, 3-*HH*), 4.34 (1H, dd, J 12.3, 1.2 Hz, 3-*HH*), 4.85 (1H, d, J 16.2 Hz, 1-*HH*), 5.00 (1H, d, J 16.2 Hz, 1-*HH*), 5.78 (1H, br d, J 7.4 Hz, 4-H), 6.77 (1H, s, 6-H), 6.90 (1H, d, J 7.4 Hz, NH), 7.44 (1H, d, J 8.1 Hz, ArH), 8.17 (1H, d, J 8.1 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 29.2 (3 × CH_3), 35.4 (C), 45.9 (CH), 68.3 (CH_2), 68.9 (CH_2), 92.6 (C), 127.9 (CH), 129.1 (C), 130.0 (CH), 130.6 (C), 134.5 (C), 135.4 (CH), 142.1 (C), 156.6 (C), 161.0 (C), 184.3 (C), 186.4 (C); m/z (CI) 430.0370 (MH^+ . $\text{C}_{19}\text{H}_{19}^{35}\text{Cl}_3\text{NO}_4$ requires 430.0380), 396 (21%), 287 (20), 245 (37), 207 (32), 162 (95), 128 (62), 85 (65), 73 (100).

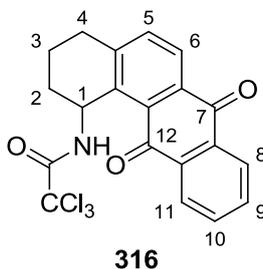
7-*tert*-Butyl-1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (315).



7-*tert*-Butyl-1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (**315**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]naphthalene-7,10-dione (**211**) (Method B) using 5-ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) (0.091 g, 0.21 mmol) and 2-*tert*-butyl-1,4-benzoquinone (0.083 g, 0.51 mmol). The solution was then cooled to room temperature and DDQ (0.252 g, 1.11 mmol) and a silicon carbide bar were added. The mixture was

stirred at 115 °C in a microwave reactor for 3 h. Flash column chromatography using silica (petroleum ether/ethyl acetate, 3:1) gave 7-*tert*-butyl-1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)benzo[*f*]isoquinoline-5,8-dione (**315**) (0.056 g, 44%) as a yellow solid. R_f (50% ethyl acetate/petroleum ether) 0.53; Mp 187–189 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2959 (CH), 1717 (CO), 1655 (CO), 1522, 1454, 1339, 1254, 1161, 964, 818; δ_{H} (500 MHz, CDCl_3) 1.33 (9H, s, 3 \times CH_3), 2.44 (3H, s, CH_3), 2.75 (1H, dd, J 12.6, 2.8 Hz, 3-*HH*), 3.92 (1H, d, J 16.0 Hz, 1-*HH*), 4.12 (1H, ddd, J 12.6, 2.8, 1.7 Hz, 3-*HH*), 4.83 (1H, d, J 16.0 Hz, 1-*HH*), 6.04 (1H, dt, J 7.4, 2.8 Hz, 4-H), 6.76 (1H, s, 6-H), 6.92 (1H, d, J 7.4 Hz, NH), 7.37 (2H, d, J 8.4 Hz, 2 \times ArH), 7.50 (1H, d, J 8.2 Hz, ArH), 7.75 (2H, d, J 8.4 Hz, 2 \times ArH), 8.16 (1H, d, J 8.2 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 21.6 (CH_3), 29.2 (3 \times CH_3), 35.4 (C), 46.5 (CH), 48.2 (CH_2), 48.3 (CH_2), 92.4 (C), 127.9 (2 \times CH), 128.1 (CH), 129.2 (C), 130.1 (2 \times CH), 130.9 (C), 132.0 (CH), 132.5 (C), 134.8 (C), 135.5 (CH), 139.6 (C), 144.5 (C), 156.6 (C), 161.1 (C), 184.1 (C), 186.3 (C); m/z (ESI) 607.0414 (MNa^+ . $\text{C}_{26}\text{H}_{25}^{35}\text{Cl}_2^{37}\text{ClN}_2\text{NaO}_5\text{S}$ requires 607.0412).

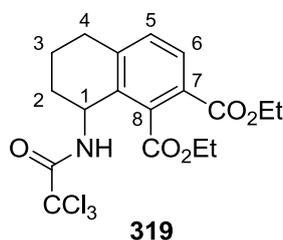
1,2,3,4-Tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (316).



1,2,3,4-Tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**316**) was synthesised as described for 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]naphthalene-7,10-dione (**211**) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.036 g, 0.14 mmol) and 1,4-naphthoquinone (**205**) (0.042 g, 0.20 mmol). The reaction mixture was then cooled to room temperature and DDQ (0.13 g, 0.60 mmol) and a silicon carbide bar were added. The mixture was stirred at 115 °C in a microwave reactor for 4 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 13:7) gave 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)benz[*a*]anthracene-7,12-dione (**316**) (0.034 g, 54%) as a colourless solid. R_f (50% diethyl ether/petroleum ether) 0.48; Mp 180–182 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2922 (CH), 2361, 1701 (CO), 1668 (CO), 1589, 1501, 1327, 1290, 818; δ_{H} (400 MHz, CDCl_3) 1.86–1.97 (3H, m, 2-*HH* and 3- H_2), 2.37–2.47 (1H, m,

2-*HH*), 2.91–3.03 (1H, m, 4-*HH*), 3.05–3.17 (1H, m, 4-*HH*), 5.96–6.00 (1H, m, 1-H), 6.79 (1H, br d, *J* 6.3 Hz, NH), 7.59 (1H, d, *J* 8.2 Hz, ArH), 7.73–7.79 (2H, m, 9-H and 10-H), 8.20–8.27 (2H, m, 8-H and 11-H), 8.32 (1H, d, *J* 8.2 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 17.8 (CH_2), 28.1 (CH_2), 30.9 (CH_2), 47.6 (CH), 93.0 (C), 126.5 (CH), 127.6 (CH), 127.7 (CH), 131.6 (C), 132.2 (C), 133.7 (CH), 134.2 (C), 134.4 (CH), 134.9 (C), 135.5 (CH), 135.8 (C), 146.5 (C), 160.6 (C), 183.1 (C), 184.6 (C); *m/z* (ESI) 443.9919 (MNa^+ , $\text{C}_{20}\text{H}_{14}^{35}\text{Cl}_3\text{NNaO}_3$ requires 443.9931).

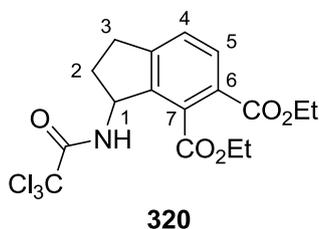
Diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (319).



5-Ethyl-1''-ene-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol) was dissolved in toluene (5 mL) and transferred to a microwave vial containing anhydrous zinc chloride (0.045 g, 0.33 mmol) and hydroquinone (0.012 g, 0.010 mmol). Diethyl acetylenedicarboxylate (**317**) (0.17 mL, 1.11 mmol) was added with a silicon carbide bar and the tube was purged with argon and sealed. The reaction mixture was stirred at 140 °C in a microwave reactor for 3 h. The solution was then cooled to room temperature and DDQ (0.18 g, 0.81 mmol) was added. The tube was sealed and stirred at 115 °C in a microwave reactor for 2 h. The solution was then cooled to room temperature and the solvent was then evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 11:9) gave diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**319**) (0.095 g, 58%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.49; Mp 134–136 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3318 (NH), 2940 (CH), 1690 (CO), 1597 (C=C), 1520, 1366, 1258, 1134, 1011, 826; δ_{H} (500 MHz, CDCl_3) 1.36 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.38 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.71–1.97 (3H, m, 2-*HH* and 3- H_2), 2.23–2.30 (1H, m, 2-*HH*), 2.84 (1H, ddd, *J* 17.7, 11.5, 6.2 Hz, 4-*HH*), 2.94–3.03 (1H, m, 4-*HH*), 4.29–4.48 (4H, m, $2 \times \text{OCH}_2\text{CH}_3$), 5.30 (1H, dt, *J* 7.1, 3.5 Hz, 1-H), 6.74 (1H, d, *J* 7.1 Hz, NH), 7.28 (1H, d, *J* 8.1 Hz, ArH), 7.90 (1H, d, *J* 8.1 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 13.9 (CH_3), 14.2 (CH_3), 17.3 (CH_2), 27.8 (CH_2), 29.6 (CH_2), 46.4 (CH), 61.6 (CH_2), 62.4 (CH_2), 92.5 (C), 127.0 (C), 129.8 (CH), 130.7 (CH), 130.9 (C), 137.3 (C), 143.4 (C), 160.3 (C), 165.4 (C), 168.2 (C); *m/z*

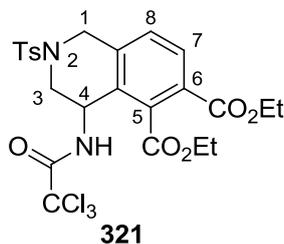
(CI) 438.0456 (MH^+ , $\text{C}_{18}\text{H}_{21}^{35}\text{Cl}_2^{37}\text{ClNO}_5$ requires 438.0459), 390 (100%), 371 (77), 356 (70), 275 (25), 271 (18), 231 (11), 153 (10), 69 (70).

Diethyl 2,3-dihydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (320).



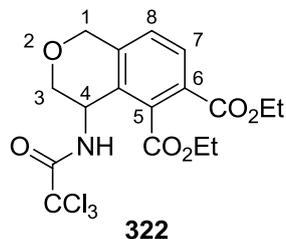
Diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**320**) was synthesised as described for diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**319**) using 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.084 g, 0.33 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave diethyl 2,3-dihydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-6,7-dicarboxylate (**320**) (0.099 g, 71%) as a yellow solid. R_f (50% diethyl ether/petroleum ether) 0.32; Mp 108–110 °C; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3337 (NH), 2983 (CH), 2361, 1714 (CO), 1507, 1368, 1282, 1021; δ_{H} (500 MHz, CDCl_3) 1.37 (6H, t, J 7.2 Hz, $2 \times \text{OCH}_2\text{CH}_3$), 2.17 (1H, dtd, J 13.4, 8.9, 4.7 Hz, 2- HH), 2.62–2.72 (1H, m, 2- HH), 2.99 (1H, ddd, J 17.0, 8.9, 5.0 Hz, 3- HH), 3.13–3.22 (1H, m, 3- HH), 4.32–4.45 (4H, m, $2 \times \text{OCH}_2\text{CH}_3$), 5.52 (1H, td, J 7.1, 4.7 Hz, 1-H), 6.98 (1H, br d, J 7.1 Hz, NH), 7.42 (1H, d, J 7.9 Hz, ArH), 7.94 (1H, d, J 7.9 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 13.9 (CH_3), 14.1 (CH_3), 30.5 (CH_2), 32.7 (CH_2), 56.0 (CH), 61.6 (CH_2), 62.2 (CH_2), 92.4 (C), 126.2 (CH), 128.2 (C), 131.0 (CH), 132.5 (C), 138.4 (C), 149.9 (C), 161.2 (C), 165.7 (C), 167.7 (C); m/z (CI) 424.0300 (MH^+ , $\text{C}_{17}\text{H}_{19}^{35}\text{Cl}_2^{37}\text{ClNO}_5$ requires 424.0302), 376 (100%), 342 (6), 261 (18), 214 (6), 187 (5).

Diethyl 1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)isoquinoline-5,6-dicarboxylate (321**).**



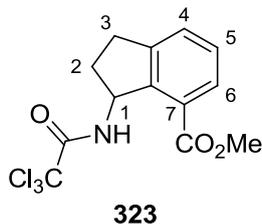
Diethyl 1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)isoquinoline-5,6-dicarboxylate (**321**) was synthesised as described for diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**319**) using 5-ethyl-1''-ene-1,2,3,6-tetrahydro-1-(*p*-toluenesulfonyl)-3-(2',2',2'-trichloromethylcarbonylamino)pyridine (**293**) (0.090 g, 0.21 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 3:7) gave diethyl 1,2,3,4-tetrahydro-2-(*p*-toluenesulfonyl)-4-(2',2',2'-trichloromethylcarbonylamino)isoquinoline-5,6-dicarboxylate (**321**) (0.060 g, 48%) as a red solid. R_f (100% diethyl ether) 0.67; Mp 172–174 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3323 (NH), 2988 (CH), 1716 (CO), 1507, 1267, 1164, 1018, 753; δ_{H} (500 MHz, CDCl_3) 1.35 (3H, t, J 7.2 Hz, OCH_2CH_3), 1.36 (3H, t, J 7.2 Hz, OCH_2CH_3), 2.44 (3H, m, CH_3), 2.70 (1H, dd, J 12.6, 2.4 Hz, 3-*HH*), 3.77 (1H, d, J 15.8 Hz, 1-*HH*), 4.10 (1H, br d, J 12.6 Hz, 3-*HH*), 4.27–4.48 (4H, m, $2 \times \text{OCH}_2\text{CH}_3$), 4.85 (1H, d, J 15.8 Hz, 1-*HH*), 5.43 (1H, br d, J 8.5 Hz, 4-H), 7.06 (1H, d, J 8.5 Hz, NH), 7.26 (1H, d, J 8.0 Hz, ArH), 7.35 (2H, d, J 8.2 Hz, $2 \times$ ArH), 7.73 (2H, d, J 8.2 Hz, $2 \times$ ArH), 7.97 (1H, d, J 8.0 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 13.9 (CH_3), 14.1 (CH_3), 21.6 (CH_3), 45.6 (CH), 47.9 (CH_2), 48.6 (CH_2), 61.9 (CH_2), 62.7 (CH_2), 92.0 (C), 127.7 (CH), 127.9 ($2 \times$ CH), 128.3 (C), 128.6 (C), 130.1 ($2 \times$ CH), 130.4 (CH), 132.3 (C), 137.2 (C), 137.7 (C), 144.6 (C), 161.0 ($2 \times$ C), 167.2 (C); m/z (ESI) 589.0371 ($[\text{M}-\text{H}]^-$. $\text{C}_{24}\text{H}_{24}^{35}\text{Cl}_3\text{N}_2\text{O}_7\text{S}$ requires 589.0375).

Diethyl 4-(2',2',2'-trichloromethylcarbonylamino)isochroman-5,6-dicarboxylate (322).



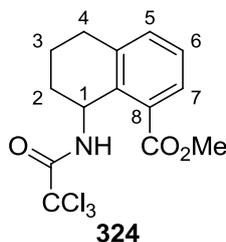
Diethyl 4-(2',2',2'-trichloromethylcarbonylamino)isochroman-5,6-dicarboxylate (**322**) was synthesised as described for diethyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-7,8-dicarboxylate (**319**) using 1,4-dihydro-5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)-1*H*-pyran (**294**) (0.082 g, 0.30 mmol). Flash column chromatography using silica (petroleum ether/ethyl acetate, 7:3) gave diethyl 4-(2',2',2'-trichloromethylcarbonylamino)isochroman-5,6-dicarboxylate (**322**) (0.056 g, 42%) as a brown solid. R_f (50% ethyl acetate/ petroleum ether) 0.63; Mp 141–143 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3322 (NH), 2978 (CH), 1724 (CO), 1695 (CO), 1598 (C=C), 1522, 1369, 1287, 1260, 1150, 1093, 822; δ_{H} (500 MHz, CDCl_3) 1.36 (3H, t, J 7.4 Hz, OCH_2CH_3), 1.38 (3H, t, J 7.4 Hz, OCH_2CH_3), 3.82 (1H, dd, J 12.2, 2.2 Hz, 3-*HH*), 4.24 (1H, br d, J 12.2 Hz, 3-*HH*), 4.30–4.40 (3H, m, OCH_2CH_3 and OCHHCH_3), 4.42–4.51 (1H, m, OCHHCH_3), 4.78 (1H, d, J 16.1 Hz, 1-*HH*), 4.95 (1H, d, J 16.1 Hz, 1-*HH*), 5.22 (1H, br d, J 7.8 Hz, 4-H), 7.06 (1H, br d, J 7.8 Hz, NH), 7.21 (1H, d, J 8.2 Hz, ArH), 7.98 (1H, d, J 8.2 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 13.9 (CH_3), 14.2 (CH_3), 44.8 (CH), 61.8 (CH_2), 62.6 (CH_2), 67.9 (CH_2), 69.2 (CH_2), 92.2 (C), 125.7 (CH), 128.0 (C), 128.3 (C), 130.3 (CH), 137.1 (C), 140.2 (C), 160.8 (C), 165.4 (C), 167.4 (C); m/z (CI) 438.0275 (MH^+ . $\text{C}_{17}\text{H}_{19}^{35}\text{Cl}_3\text{NO}_6$ requires 438.0278), 404 (70%), 398 (62), 370 (27), 251 (17), 113 (22), 73 (76).

Methyl 2,3-dihydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (323).



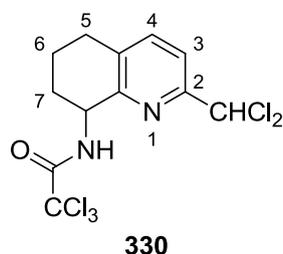
4-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.11 g, 0.43 mmol) was dissolved in toluene (6 mL) and transferred to a Schlenk tube containing anhydrous zinc chloride (0.059 g, 0.43 mmol) and hydroquinone (0.014 g, 0.13 mmol). Methyl propiolate (0.12 mL, 1.29 mmol) was added and the tube was purged with argon. The reaction mixture was stirred at 140 °C for 9 days. The solution was then cooled to room temperature and DDQ (0.21 g, 0.95 mmol) was added. The tube was resealed under argon and stirred at 115 °C for 24 h. The solution was cooled to room temperature and the solvent was then evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 12:9) gave methyl 2,3-dihydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**323**) (0.075 g, 52%) as a red solid. R_f (50% diethyl ether/petroleum ether) 0.57; Mp 108–110 °C $\nu_{\max}/\text{cm}^{-1}$ (neat) 3279 (NH), 2949 (CH), 1711 (CO), 1689 (CO), 1533, 1432, 1290, 1136, 818; δ_{H} (500 MHz, CDCl_3) 2.23 (1H, ddt, J 14.0, 8.6, 2.4 Hz, 2-*HH*), 2.43 (1H, dq, J 14.0, 8.6 Hz, 2-*HH*), 2.90 (1H, ddd, J 16.4, 8.6, 2.4 Hz, 3-*HH*), 3.19 (1H, dt, J 16.4, 8.6 Hz, 3-*HH*), 3.82 (3H, s, OCH_3), 5.68 (1H, td, J 8.6, 2.4 Hz, 1-H), 6.90 (1H, br d, J 5.1 Hz, NH), 7.34 (1H, t, J 7.6 Hz, 5-H), 7.44 (1H, d, J 7.6 Hz, ArH), 7.86 (1H, d, J 7.6 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 30.7 (CH₂), 31.7 (CH₂), 52.5 (CH), 57.4 (CH₃), 92.9 (C), 127.4 (C), 129.3 (CH), 129.5 (CH), 129.6 (CH), 141.4 (C), 146.7 (C), 160.9 (C), 166.7 (C); m/z (CI) 335.9952 (MH^+ . $\text{C}_{13}\text{H}_{13}^{35}\text{Cl}_3\text{NO}_3$ requires 335.9961), 302 (16%), 257 (12), 175 (100), 137 (54), 121 (38), 81 (6).

Methyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (324).



Methyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (**324**) was synthesised as described for methyl 2,3-dihydro-1-(2',2',2'-trichloromethylcarbonylamino)indene-7-carboxylate (**323**) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.10 g, 0.37 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 7:3) gave methyl 1,2,3,4-tetrahydro-1-(2',2',2'-trichloromethylcarbonylamino)naphthalene-8-carboxylate (**324**) (0.085 g, 66%) as a white solid. R_f (50% diethyl ether/petroleum ether) 0.56; Mp 133–135 °C $\nu_{\max}/\text{cm}^{-1}$ (neat) 3324 (NH), 2933 (CH), 1726 (CO), 1695 (CO), 1517, 1431, 1285, 1262, 1137, 754; δ_H (500 MHz, CDCl_3) 1.72–1.82 (1H, m, 2-*HH*), 1.85–1.98 (2H, m, 2-*HH* and 3-*HH*), 2.15–2.22 (1H, m, 3-*HH*), 2.84 (1H, ddd, J 17.1, 10.7, 5.8 Hz, 4-*HH*), 2.94 (1H, dt, J 17.1, 4.6 Hz, 4-*HH*), 3.87 (3H, s, OCH_3), 5.77 (1H, dt, J 6.3, 4.3 Hz, 1-H), 6.68 (1H, d, J 6.3 Hz, NH), 7.30–7.34 (2H, m, 5-H and 6-H), 7.86 (1H, dd, J 6.0, 3.1 Hz, 7-H); δ_C (126 MHz, CDCl_3) 18.1 (CH_2), 28.5 (CH_2), 29.9 (CH_2), 46.9 (CH_3), 52.6 (CH), 92.8 (C), 128.0 (CH), 129.2 (CH), 131.8 (C), 133.4 (CH), 133.7 (C), 139.2 (C), 160.4 (C), 168.1 (C); m/z (ESI) 371.9925 (MNa^+ . $\text{C}_{14}\text{H}_{14}^{35}\text{Cl}_3\text{NNaO}_3$ requires 371.9931).

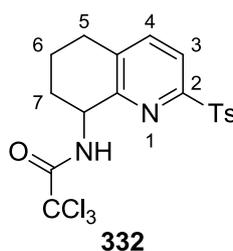
2-Dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (330).



5-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.035 g, 0.13 mmol) was dissolved in *p*-xylene (4 mL) and transferred to a microwave vial containing anhydrous zinc chloride (0.018 g, 0.13 mmol) and hydroquinone (0.001 g, 0.013 mmol). Trichloroacetonitrile (0.078 g, 0.78 mmol) was added and the tube was

purged with argon and sealed. The reaction mixture was stirred at 160 °C for 48 h. The solution was then cooled to room temperature and the solvent was evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 2:1) gave 2-dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**330**) (0.043 g, 67%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.49; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3343 (NH), 2930 (CH), 2361, 1705 (CO), 1503, 1462, 1408, 1256, 1215, 1088, 926, 818; δ_{H} (500 MHz, CDCl_3) 1.62–1.72 (1H, m, 7-HH), 1.87–2.08 (2H, m, 6-H₂), 2.75–2.83 (1H, m, 7-HH), 2.84–2.95 (2H, m, 5-H₂), 4.81 (1H, dt, J 10.5, 5.3 Hz, 8-H), 6.67 (1H, s, CHCl_2), 7.60 (1H, d, J 8.1 Hz, 4-H), 7.65 (1H, d, J 8.1 Hz, 3-H), 8.01 (1H, br s, NH); δ_{C} (126 MHz, CDCl_3) 19.9 (CH₂), 27.7 (CH₂), 27.9 (CH₂), 52.6 (CH), 71.2 (CH), 92.9 (C), 120.2 (CH), 134.1 (C), 139.0 (CH), 153.0 (C), 155.1 (C), 162.1 (C); m/z (ESI) 396.9191 (MNa^+ . $\text{C}_{12}\text{H}_{11}^{35}\text{Cl}_5\text{N}_2\text{NaO}$ requires 396.9206).

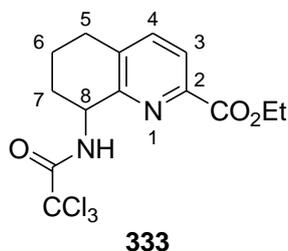
5,6,7,8-Tetrahydro-2-(*p*-toluenesulfonyl)-8-(2',2',2'-trichloromethylcarbonylamino)-quinoline (332).



5,6,7,8-Tetrahydro-2-(*p*-toluenesulfonyl)-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**332**) was synthesised as described for 2-dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**330**) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.035 g, 0.13 mmol) and *p*-toluenesulfonyl cyanide (0.035 g, 0.20 mmol). Flash column chromatography using silica (petroleum ether/ethyl acetate, 11:9) gave 5,6,7,8-tetrahydro-2-(*p*-toluenesulfonyl)-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**332**) (0.030 g, 54%) as a white solid. R_f (50% ethyl acetate/petroleum ether) 0.44; Mp 85–87 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2926 (CH), 1705 (CO), 1510, 1316, 1155, 1078, 814; δ_{H} (500 MHz, CDCl_3) 1.59 (1H, qd, J 11.5, 4.2 Hz, 7-HH), 1.97–2.05 (2H, m, 5-HH and 6-HH), 2.42 (3H, s, CH₃), 2.75 (1H, dq, J 11.5, 4.8 Hz, 7-HH), 2.85–2.97 (2H, m, 5-HH and 6-HH), 4.76 (1H, dt, J 11.5, 4.8 Hz, 8-H), 7.31 (2H, d, J 8.2 Hz, 2 × ArH), 7.69 (1H, d, J 8.0 Hz, ArH), 7.76 (1H, br d, J 3.8 Hz, NH), 7.91 (2H, d, J 8.2 Hz, 2 × ArH), 8.09 (1H, d, J 8.0 Hz, ArH); δ_{C} (126 MHz, CDCl_3) 19.8 (CH₂), 21.7 (CH₃), 27.7 (CH₂), 27.9 (CH₂),

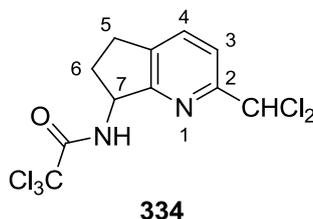
52.7 (CH), 92.6 (C), 120.8 (CH), 129.1 (2 × CH), 129.9 (2 × CH), 135.5 (C), 137.2 (C), 139.0 (CH), 145.0 (C), 155.4 (C), 156.2 (C), 161.9 (C); m/z (ESI) 447.0093 (MH^+ . $C_{18}H_{18}^{35}Cl_3N_2O_3S$ requires 447.0098).

Ethyl 5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline-2-carboxylate (333).



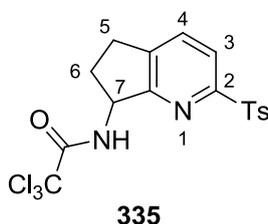
Ethyl 5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline-2-carboxylate (**333**) was synthesised as described for 2-dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**330**) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.056 g, 0.21 mmol) and ethyl cyanofornate (0.12 mL, 1.25 mmol). Flash column chromatography using silica (petroleum ether/diethyl ether, 1:1) gave ethyl 5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline-2-carboxylate (**333**) (0.030 g, 40%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.23; ν_{max}/cm^{-1} (neat) 3345 (NH), 2926 (CH), 2361, 1707 (CO), 1506, 1314, 1258, 1086, 1024, 820; δ_H (400 MHz, $CDCl_3$) 1.40 (1H, t, J 7.1 Hz, OCH_2CH_3), 1.62 (1H, dtd, J 12.7, 11.3, 4.7 Hz, 7-HH), 1.93–2.09 (2H, m, 6- H_2), 2.85–3.02 (3H, m, 5- H_2 and 7-HH), 4.37 (1H, dq, J 10.8, 7.1 Hz, $OCHHCH_3$), 4.45 (1H, dq, J 10.8, 7.1 Hz, $OCHHCH_3$), 4.79 (1H, dt, J 10.9, 4.7 Hz, 8-H), 7.62 (1H, d, J 7.9 Hz, ArH), 8.01 (1H, d, J 7.9 Hz, ArH), 8.48 (1H, br s, NH); δ_C (101 MHz, $CDCl_3$) 14.3 (CH_3), 19.8 (CH_2), 27.6 (CH_2), 27.8 (CH_2), 53.0 (CH), 61.7 (CH_2), 92.9 (C), 124.2 (CH), 136.8 (C), 138.1 (CH), 145.3 (C), 154.1 (C), 162.1 (C), 164.9 (C); m/z (ESI) 387.0036 (MNa^+ . $C_{14}H_{15}^{35}Cl_3N_2NaO_3$ requires 387.0040).

2-Dichloromethyl-6,7-dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5H-cyclopenta[b]pyridine (334).



2-Dichloromethyl-6,7-dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5H-cyclopenta[b]pyridine (**334**) was synthesised as described for 2-dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**330**) using 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.024 g, 0.094 mmol) and trichloroacetonitrile (0.11 mL, 1.13 mmol). The reaction mixture was stirred at 125 °C for 24 h. Flash column chromatography using silica (petroleum ether/diethyl ether, 7:3) gave 2-dichloromethyl-6,7-dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5H-cyclopenta[b]pyridine (**334**) (0.013 g, 34%) as a colourless oil. R_f (50% diethyl ether/petroleum ether) 0.38; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3401 (NH), 2936 (CH), 1703 (CO), 1505, 1464, 1249, 1212, 1088; δ_{H} (500 MHz, CDCl_3) 1.95–2.05 (1H, m, 6-*HH*), 2.94–3.10 (3H, m, 5- H_2 and 6-*HH*), 5.14–5.22 (1H, m, 7-H), 6.74 (1H, s, CHCl_2), 7.37 (1H, br s, NH), 7.71 (1H, d, J 8.2 Hz, 4-H), 7.74 (1H, d, J 8.2 Hz, 3-H); δ_{C} (126 MHz, CDCl_3) 27.9 (CH_2), 32.5 (CH_2), 56.5 (CH), 71.3 (CH), 91.4 (C), 121.0 (CH), 134.6 (CH), 138.1 (C), 157.4 (C), 160.0 (C), 162.2 (C); m/z (ESI) 382.9046 (MNa^+ . $\text{C}_{11}\text{H}_9^{35}\text{Cl}_5\text{N}_2\text{NaO}$ requires 382.9050).

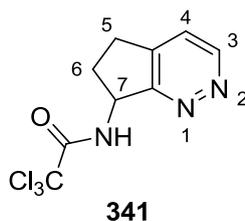
6,7-Dihydro-2-(*p*-toluenesulfonyl)-7-(2',2',2'-Trichloromethylcarbonylamino)-5H-cyclopenta[b]pyridine (335).



6,7-Dihydro-2-(*p*-toluenesulfonyl)-7-(2',2',2'-trichloromethylcarbonylamino)-5H-cyclopenta[b]pyridine (**335**) was synthesised as described for 2-dichloromethyl-5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)quinoline (**330**) using 4-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.024 g, 0.094 mmol) and *p*-toluenesulfonyl cyanide (0.026 g, 0.14 mmol). The reaction mixture was

stirred at 125 °C for 24 h. Flash column chromatography using silica (petroleum ether/ethyl acetate, 1:1) gave 6,7-dihydro-2-(*p*-toluenesulfonyl)-7-(2',2',2'-trichloromethylcarbonylamino)-5*H*-cyclopenta[*b*]pyridine (**335**) (0.024 g, 58%) as a green solid. R_f (50% diethyl ether/petroleum ether) 0.45; Mp 124–126 °C; $\nu_{\max}/\text{cm}^{-1}$ (neat) 3335 (NH), 2926 (CH), 1699 (CO), 1518, 1420, 1302, 1144, 1076, 816; δ_{H} (500 MHz, CDCl_3) 1.91–2.05 (1H, m, 6-*HH*), 2.41 (3H, s, CH_3), 2.91–3.10 (3H, m, 5- H_2 and 6-*HH*), 5.10–5.18 (1H, m, 7-*H*), 7.19 (1H, br d, J 4.6 Hz, NH), 7.30 (2H, d, J 8.2 Hz, $2 \times \text{ArH}$), 7.84 (1H, d, J 8.1 Hz, ArH), 7.93 (2H, d, J 8.2 Hz, $2 \times \text{ArH}$), 8.09 (1H, d, J 8.1 Hz, ArH); δ_{C} (101 MHz, CDCl_3) 21.7 (CH_3), 28.0 (CH_2), 32.4 (CH_2), 56.2 (CH), 92.3 (C), 121.4 (CH), 129.2 ($2 \times \text{CH}$), 129.7 ($2 \times \text{CH}$), 134.5 (CH), 135.6 (C), 141.0 (C), 145.0 (C), 158.1 (C), 162.0 (C), 162.6 (C); m/z (ESI) 454.9747 (MNa^+). $\text{C}_{17}\text{H}_{15}^{35}\text{Cl}_3\text{N}_2\text{NaO}_3\text{S}$ requires 454.9761).

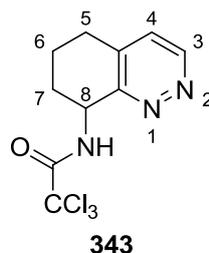
6,7-Dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5*H*-cyclopenta[*c*]pyridazine (341**).**



4-Ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclopent-4-ene (**223**) (0.13 g, 0.41 mmol) was dissolved in toluene (10 mL) and di-*tert*-butyl azodicarboxylate (**337**) (0.15 g, 0.63 mmol) was added. The reaction mixture was stirred at 115 °C for 18 h. The solution was then cooled to room temperature and the solvent was then evaporated. Flash column chromatography using silica (petroleum ether/diethyl ether, 3:2) gave a colourless oil. The oil was dissolved in degassed chloroform (12 mL) and cooled to 0 °C. Bromine (0.10 mL, 2.03) was then added dropwise. The ice bath was then removed and the mixture was stirred for 3 h as the reaction was allowed to warm to room temperature. The reaction mixture was quenched with a 10% aqueous solution of sodium sulfite (15 mL), stirred for 0.5 h, then basified with a saturated solution of sodium hydrogencarbonate (30 mL). The aqueous layer was then extracted with chloroform (4×75 mL). The organic layers were combined, dried (MgSO_4) and concentrated to give a yellow oil. Purification by flash column chromatography (dichloromethane/methanol, 25:1) gave 6,7-dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5*H*-cyclopenta[*c*]pyridazine (**341**) (0.072 g, 51%) as a brown oil. $\nu_{\max}/\text{cm}^{-1}$ (neat) 3327 (NH), 2955 (CH), 1695 (CO), 1518, 1393 1263, 820; δ_{H}

(400 MHz, CDCl₃) 1.91–2.05 (1H, m, 6-*HH*), 2.87–3.12 (3H, m, 5-H₂ and 6-*HH*), 5.32 (1H, td, *J* 8.5, 5.2 Hz, 7-H), 7.36 (1H, d, *J* 5.1 Hz, 4-H), 7.74 (1H, br s, NH), 8.97 (1H, d, *J* 5.1 Hz, 3-H); δ_C (101 MHz, CDCl₃) 28.2 (CH₂), 31.8 (CH₂), 56.0 (CH), 92.1 (C), 123.3 (CH), 142.0 (C), 150.6 (CH), 162.4 (C), 164.3 (C); *m/z* (ESI) 301.9631 (MNa⁺. C₉H₈³⁵Cl₃N₃NaO requires 301.9625).

5,6,7,8-Tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)cinnoline (343).



5,6,7,8-Tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)cinnoline (**343**) was synthesised as described for 6,7-dihydro-7-(2',2',2'-trichloromethylcarbonylamino)-5*H*-cyclopenta[*c*]pyridazine (**341**) using 5-ethyl-1''-ene-1-(2',2',2'-trichloromethylcarbonylamino)cyclohex-5-ene (**197**) (0.11 g, 0.41 mmol) and di-*tert*-butyl azodicarboxylate (**337**) (0.12 g, 0.51 mmol). Flash column chromatography using silica (dichloromethane/methanol, 25:1) gave 5,6,7,8-tetrahydro-8-(2',2',2'-trichloromethylcarbonylamino)cinnoline (**343**) (0.079 g, 66%) as a colourless oil. ν_{\max} /cm⁻¹ (neat) 3339 (NH), 2947 (CH), 2361, 1697 (CO), 1508, 1377, 1265, 1090, 818, 731; δ_H (500 MHz, CDCl₃) 1.67–1.76 (1H, m, 7-*HH*), 1.93–2.08 (2H, m, 6-H₂), 2.81–2.97 (3H, m, 5-H₂ and 7-*HH*), 5.01 (1H, dt, *J* 10.3, 5.0 Hz, 8-H), 7.27 (1H, d, *J* 5.1 Hz, 4-H), 8.29 (1H, br s, NH), 9.04 (1H, d, *J* 5.1 Hz, 3-H); δ_C (126 MHz, CDCl₃) 19.2 (CH₂), 27.1 (CH₂), 27.6 (CH₂), 51.8 (CH), 92.5 (C), 126.6 (CH), 137.9 (C), 150.6 (CH), 157.8 (C), 162.3 (C); *m/z* (ESI) 315.9776 (MNa⁺. C₁₀H₁₀³⁵Cl₃N₃NaO requires 315.9782).

5.0 References

1. B. M. Trost, *Acc. Chem. Res.*, 1990, **23**, 34.
2. C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **1002**, 813.
3. S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317.
4. V. Michelet, P. Toullec and J.-P. Geret, *Angew. Chem. Int. Ed.*, 2008, **47**, 4268.
5. C. S. Poulsen and R. Madsen, *Synthesis*, 2003, 1.
6. H. Villar, M. Frings and C. Bolm, *Chem. Soc. Rev.*, 2007, **36**, 55.
7. S. Kotha, M. Meshram and A. Tiwari, *Chem. Soc. Rev.*, 2009, **38**, 2065.
8. B. M. Trost and M. Lautens, *J. Am. Chem. Soc.*, 1985, **107**, 1781.
9. G. C. Lloyd-Jones, *Org. Biomol. Chem.*, 2003, **1**, 215.
10. K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, 1984, **23**, 539.
11. I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts and M. I. Foreman, *J. Chem. Soc., Perkin Trans. 1.*, 1983, 977.
12. E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson and T. Takashi, *J. Am. Chem. Soc.*, 1989, **111**, 3336.
13. T. V. RajanBabu, W. A. Nugent, D. F. Taber and P. J. Fagan, *J. Am. Chem. Soc.*, 1988, **110**, 7128.
14. B. M. Trost and M. J. Krische, *Synlett*, 1998, 1.
15. B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan and D. T. Macpherson, *J. Am. Chem. Soc.*, 1994, **116**, 4255.
16. B. M. Trost and F. J. Rise, *J. Am. Chem. Soc.*, 1987, **109**, 3161.
17. B. M. Trost, J. Dumas and M. Villa, *J. Am. Chem. Soc.*, 1992, **114**, 9836.
18. B. M. Trost and J. M. Tour, *J. Am. Chem. Soc.*, 1987, **109**, 5268.
19. A. Furstner, H. Szillat and F. Stelzer, *J. Am. Chem. Soc.*, 2000, **122**, 6785.
20. A. Furstner, F. Stelzer and H. Szillat, *J. Am. Chem. Soc.*, 2001, **123**, 11863.
21. M. Schelwies, A. Farwick, F. Rominger and G. Helmchen, *J. Org. Chem.*, 2010, **75**, 7917.
22. P. Cao, B. Wang and X. Zhang, *J. Am. Chem. Soc.*, 2000, **122**, 6490.
23. C. Fernandez-Rivas, M. Mendes and A. M. Echavarren, *J. Am. Chem. Soc.*, 2000, **122**, 1221.
24. C. Nieto-Oberhuber, M. P. Munoz, E. Bunuel, C. Nevado, D. J. Cardenas and A. M. Echavarren, *Angew. Chem. Int. Ed.*, 2004, **43**, 2402.
25. C. Nieto-Oberhuber, M. P. Munoz, S. Lopez, E. Jimenez-Nunez, C. Nevado, E. Herrero-Gomez, M. Raducan and A. M. Echavarren, *Chem. Eur. J.*, 2006, **12**, 1677.
26. L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271.

27. I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, *J. Chem. Soc., Chem. Commun.*, 1971, 36.
28. I. U. Khand, G. R. Knox, P. L. Pauson and W. E. Watts, *J. Chem. Soc., Perkin Trans. I.*, 1973, 975.
29. P. Magnus and L.-M. Principe, *Tetrahedron Lett.*, 1985, **26**, 4851.
30. J. Blanco-Urgoiti, L. Anorbe, L. Perez-Serrano, G. Dominguez and J. Perez-Castells, *Chem. Soc. Rev.*, 2004, **33**, 32.
31. D. C. Billington and D. Willison, *Tetrahedron Lett.*, 1984, **25**, 4041.
32. S. O. Simonian, W. A. Smit, A. S. Gybin, A. S. Shahkov, G. S. Mikaelian, V. A. Tarasov, I. I. Ibragimov, R. Caple and D. E. Froen, *Tetrahedron Lett.*, 1986, **27**, 1245.
33. S. Shambayati, W. E. Crowe and S. L. Schreiber, *Tetrahedron Lett.*, 1990, **31**, 1990.
34. B. L. Pagenkopf and T. Livinghouse, *J. Am. Chem. Soc.*, 1996, **118**, 2285.
35. D. B. Belanger, D. J. R. O'Mahony and T. Livinghouse, *Tetrahedron Lett.*, 1998, **38**, 7637.
36. D. E. Kim, I. S. Kim, V. Ratovelomanana-Vidal, J.-P. Genet and N. Jeong, *J. Org. Chem.*, 2008, **73**, 7985.
37. D. E. Kim, V. Ratovelomanana-Vidal and N. Jeong, *Adv. Synth. Catal.*, 2010, **352**, 2032.
38. M. K. Pallerla and J. M. Fox, *Org. Lett.*, 2007, **9**, 5625.
39. K. Fujioka, H. Yokoe, M. Yoshida and K. Shishido, *Org. Lett.*, 2012, **14**, 244.
40. A. Nakayama, N. Kogure, M. Kitajima and H. Takayama, *Org. Lett.*, 2009, **11**, 5554.
41. A. Farwick and G. Helmchen, *Org. Lett.*, 2010, **12**, 1108.
42. K. J. Ivin and J. C. Mol, *Metathesis and Metathesis Polymerisation*, 1997, Academic Press: San Diego.
43. *Angew. Chem. Int. Ed.*, 2005, **44**, 6982.
44. R. R. Schrock, J. S. Murdzek, G. C. Bazan, J. Robbins, M. D. Mare and M. O'Regan, *J. Am. Chem. Soc.*, 1990, **112**, 3875.
45. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.*, 1992, **114**, 5426.
46. P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.
47. M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.
48. S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.

49. T. J. Katz and T. M. Sivavec, *J. Am. Chem. Soc.*, 1985, **107**, 737.
50. S. Watanuki, N. Ochifuji and M. Mori, *Organometallics*, 1994, **13**, 4129.
51. A. Kinoshita and M. Mori, *Synlett*, 1994, 1020.
52. M. Mori, N. Sakakibara and A. Kinoshita, *J. Org. Chem.*, 1998, **63**, 6082.
53. T. R. Hoye, S. M. Donaldson and T. J. Vos, *Org. Lett.*, 1999, **1**, 277.
54. E. C. Hansen and D. Lee, *J. Am. Chem. Soc.*, 2003, **125**, 9582.
55. Y.-J. Lee, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2009, **131**, 10652.
56. T. Kitamura, Y. Sato and M. Mori, *Chem. Commun.*, 2001, 1258.
57. M. Mori, *Materials*, 2010, **3**, 2087.
58. J.-H. Sohn, K. H. Kim, H.-Y. Lee, Z. S. No and H. Ihee, *J. Am. Chem. Soc.*, 2008, **130**, 16506.
59. G. C. Lloyd-Jones, R. G. Margue and J. G. D. Vries, *Angew. Chem. Int. Ed.*, 2005, **44**, 7442.
60. G. C. Lloyd-Jones, A. J. Robinson, L. Lefort and J. G. D. Vries, *Chem. Eur. J.*, 2010, **16**, 9449.
61. A. Kinoshita and M. Mori, *J. Org. Chem.*, 1996, **61**, 8356.
62. M. Rosillo, G. Dominguez, L. Casarrubios, U. Amador and J. Perez-Castells, *J. Org. Chem.*, 2004, **69**, 2084.
63. T. A. Engler, U. Sampath, S. Naganathan, D. V. Velde and F. Takusagawa, *J. Org. Chem.*, 1989, **54**, 5712.
64. M. C. Carreno, A. Somoza, M. Ribagorda and A. Urbano, *Chem. Eur. J.*, 2007, **13**, 879.
65. K. Kim, Y. Guo and G. A. Sulikowski, *J. Org. Chem.*, 1995, **60**, 6866.
66. T. Rozek, D. K. Taylor, E. R. T. Tiekink and J. H. Bowie, *Aust. J. Chem.*, 1999, **52**, 129.
67. S. Kotha, N. Sreenivasachary and E. Brahmachary, *Tetrahedron Lett.*, 1998, **39**, 2805.
68. S. Kotha, N. Sreenivasachary and E. Brahmachary, *Eur. J. Org. Chem.*, 2001, 787.
69. D. E. Fogg and E. N. d. Santos, *Coordin. Chem. Rev.*, 2004, **248**, 2365.
70. T. Honda, H. Namiki, K. Kaneda and H. Mizutani, *Org. Lett.*, 2004, **6**, 87.
71. J. T. Hills-Cousins, S. S. Salim, Y. M. Bakar, R. K. Bellingham, M. E. Light and R. C. D. Brown, *Tetrahedron*, 2014, **70**, 3700.
72. H.-Y. Lee, H. Y. Kim, H. Tae, B. G. Kim and J. Lee, *Org. Lett.*, 2003, **5**, 3439.
73. S. E. Kurhade, A. I. Sanchawala, V. Ravikumar, R. Bhuniya and D. S. Reddy, *Org. Lett.*, 2011, **13**, 3690.

74. A. Kinoshita, N. Sakakibara and M. Mori, *J. Am. Chem. Soc.*, 1997, **119**, 12388.
75. S. Fustero, P. Bello, J. Miro, A. Simon and C. D. Pozo, *Chem. Eur. J.*, 2012, **18**, 10991.
76. S. Fustero, J. F. Sanz-Cervera, J. L. Acena and M. Sanchez-Rosello, *Synlett*, 2009, 525.
77. H.-Y. Lee, B. G. Kim and M. L. Snapper, *Org. Lett.*, 2003, **5**, 1855.
78. B. G. Kim and M. L. Snapper, *J. Am. Chem. Soc.*, 2006, **128**, 52.
79. D. A. Clark, A. A. Kulkarni, K. Kalbarczyk, B. Schertzer and S. T. Diver, *J. Am. Chem. Soc.*, 2006, **128**, 15632.
80. F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752.
81. T. J. Ritchie, S. J. F. MacDonald, R. J. Young and S. D. Pickett, *Drug Discovery Today*, 2011, **16**, 164.
82. A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons and D. W. Young, *Proc. Natl. Acad. Sci. U. S. A.*, 2011, **108**, 6799.
83. M. Dow, M. Fisher, T. James, F. Marchetti and A. Nelson, *Org. Biomol. Chem.*, 2012, **10**, 17.
84. A. E. Walts and W. R. Roush, *Tetrahedron*, 1985, **41**, 3463.
85. J. Zezula and T. Hudlicky, *Synlett*, 2005, 388.
86. Z. Kadar, A. Baji, I. Zupho, T. Bartok, J. Wolfling and E. Frank, *Org. Biomol. Chem.*, 2011, **9**, 8051.
87. L. E. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 597.
88. L. E. Overman, *J. Am. Chem. Soc.*, 1976, **98**, 2901.
89. I. Savage, E. J. Thomas and P. D. Wilson, *J. Chem. Soc., Perkin Trans. I.*, 1999, 3291.
90. R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.*, 1965, **87**, 2511.
91. Y. Yamamoto, H. Shimoda, J. I. Oda and Y. Inouye, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3247.
92. T. Nishikawa, M. Asai, N. Ohayabu and M. Isobe, *J. Org. Chem.*, 1998, **63**, 188.
93. P. Metz, C. Mues and A. Schoop, *Tetrahedron*, 1992, **48**, 1071.
94. T. G. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2058.
95. M. D. Swift and A. Sutherland, *Org. Lett.*, 2007, **9**, 5239.
96. S. Ahmad, L. H. Thomas and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 2801.
97. S. Ahmad, M. D. Swift, L. J. Farrugia, H. M. Senn and A. Sutherland, *Org. Biomol. Chem.*, 2012, **10**, 3937.

98. F. I. McGonagle, L. Brown, A. Cooke and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 3418.
99. R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.
100. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essinfeld, S. Masamune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.
101. W. J. Gensler and J. J. Bruno, *J. Org. Chem.*, 1963, **28**, 1254.
102. J. J. Eisch and W. C. Kaska, *J. Am. Chem. Soc.*, 1966, **88**, 2213.
103. T. Ikariya, Y. Ishikawa, K. Hirai and S. Yoshikawa, *Chem. Lett.*, 1982, 1815.
104. Q. Yang, H. Alper and W.-J. Xiao, *Org. Lett.*, 2007, **9**, 769.
105. J. Wang, J. Morral, C. Hendrix and P. Herdewijn, *J. Org. Chem.*, 2001, **66**, 8478.
106. J. A. Moore and E. M. PartainIII, *J. Org. Chem.*, 1983, **48**, 1105.
107. S. C. Datta, R. W. Franck, R. Tripathy, G. J. Quigley, L. Huang, S. Chen and A. Sihaed, *J. Am. Chem. Soc.*, 1990, **112**, 8472.
108. B. Kohler, T.-L. Su, T.-C. Chou, X.-J. Jiang and K. A. Watanabe, *J. Org. Chem.*, 1993, **58**, 1680.
109. J.-S. Schanche, *Mol. Divers.*, 2003, **7**, 293.
110. M. J. Fisher, W. J. Hehre, S. D. Kahn and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 4625.
111. D. M. Gelman, P. A. Mayes, R. Mulder and P. Perlmutter, *Tetrahedron: Asymmetry*, 2006, **17**, 3341.
112. B. W. Gung, C. Gibeau and A. Jones, *Tetrahedron: Asymmetry*, 2005, **16**, 3107.
113. S. Kotha and P. Khedkar, *Synthesis*, 2008, 2925.
114. M. Moreno-Manas, R. Pleixats and A. Santamaria, *Synlett*, 2001, 1784.
115. S. Kotha, K. Mandal, A. Tiwari and S. M. Mobin, *Chem. Eur. J.*, 2006, **12**, 8024.
116. S. S. Salim, R. K. Bellingham and R. C. D. Brown, *Eur. J. Org. Chem.*, 2004, 800.
117. B. M. Trost, M. Lautens, C. Chan, D. J. Jebaratnam and T. Mueller, *J. Am. Chem. Soc.*, 1991, **113**, 636.
118. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **50**, 4467.
119. K. Sonogashira, *Journal of Organometallic Chemistry*, 2002, **653**, 46.
120. K. R. Roesch and R. C. Larock, *J. Org. Chem.*, 2001, **66**, 412.
121. H. Sorek, A. Rudi, S. Gueta, F. Reyes, M. J. Martin, M. Aknin, E. Gaydou, J. Vacelete and Y. Kashman, *Tetrahedron*, 2006, **62**, 8838.
122. A. K. Chatterjee, T.-L. Choi, D. P. Sanders and R. H. Grubbs, *J. Am. Chem. Soc.*, 2003, **125**, 11360.
123. F. Royer, C. Vilain, L. Elkaim and L. Grimaud, *Org. Lett.*, 2003, **5**, 2007.

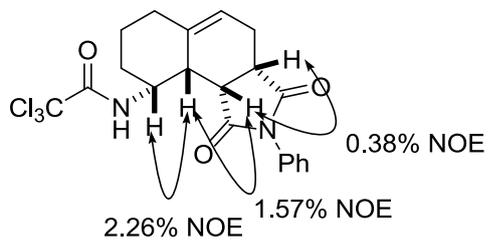
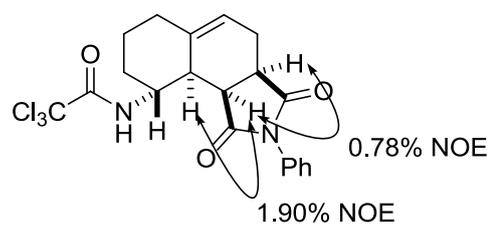
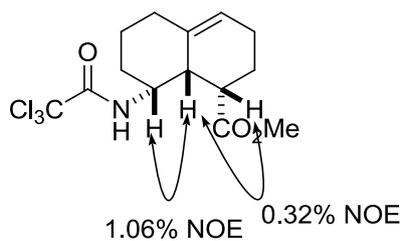
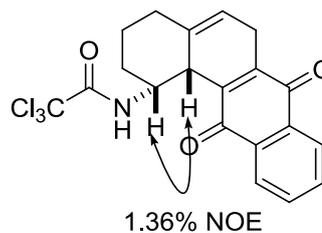
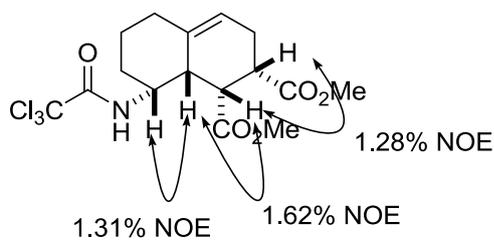
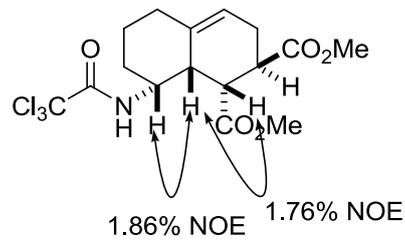
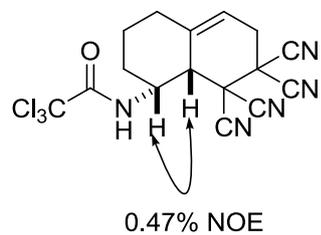
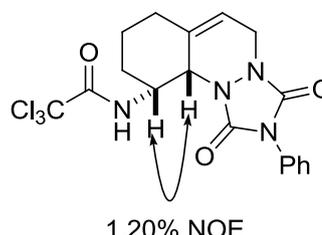
124. S. S. Salim, R. K. Bellingham and R. C. D. Brown, *Eur. J. Org. Chem.*, 2004, 800.
125. D. A. Kummer, J. B. Breneman and S. F. Martin, *Tetrahedron*, 2006, **62**, 11437.
126. S. A. Johnson, *MSci Thesis, University of Glasgow*, 2014.
127. A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. D. Brosse, S. Mai, A. Truneh, D. J. Faulkner, B. Carte, A. L. Breen, R. P. Hertberg, R. K. Johnson, J. W. Westley and B. C. M. Potts, *J. Org. Chem.*, 1995, **60**, 1182.
128. A. D. Patil, A. J. Freyer, P. B. Taylor, B. Carte, G. Zuber, K. R. Johnson and D. J. Faulkner, *J. Org. Chem.*, 1997, **62**, 1814.
129. M. Yu, S. S. Pochapsky and B. B. Snider, *J. Org. Chem.*, 2008, **73**, 9065.
130. A. Verma, R. Giridhar, P. Modh and M. R. Yadav, *Tetrahedron Lett.*, 2012, **53**, 2954.
131. R. Pathak, A. K. Roy, S. Kanojiyab and S. Batra, *Tetrahedron Lett.*, 2005, **46**, 5289.
132. R. Pathak and S. Batra, *Tetrahedron*, 2007, **63**, 9448.
133. H. Sandin, M.-L. Swanstein and E. Wellner, *J. Org. Chem.*, 2004, **69**, 1571.
134. R. Ballini, R. Castagnani and M. Petrini, *J. Org. Chem.*, 1992, **57**, 2160.
135. G. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 2534.
136. Z. Paryzek, H. Koenig and B. Tabaczka, *Synthesis*, 2003, 2023.
137. A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 8030.
138. W. M. Welch, A. R. Kraska, R. Sarges and B. K. Koe, *J. Med. Chem.*, 1984, **27**, 1508.
139. C. Binda, F. Hubálek, M. Li, Y. Herzig, J. Sterling, D. E. Edmondson and A. Mattevi, *J. Med. Chem.*, 2005, **48**, 8148.
140. K. P. Boegesoe, J. Arnt, V. Boeck, A. V. Christensen, J. Hyttel and K. G. Jensen, *J. Med. Chem.*, 1988, **31**, 2247.
141. S. Chandrasekhar and M. V. Reddy, *Tetrahedron*, 2000, **56**, 1111.
142. C. J. Roxburgh, *Synthesis*, 1996, 307.
143. V. Nair, R. Rajan and N. P. Rath, *Org. Lett.*, 2002, **4**, 1575.
144. C. Dockendorff, S. Sahli, M. Olsen, L. Milhau and M. Lautens, *J. Am. Chem. Soc.*, 2005, **127**, 15028.
145. J. A. Nieman, S. E. Heasley, B. L. Schultz, H. M. Zerth, R. A. Nugent, K. Chen, K. J. Stephanski, T. A. Hopkins, M. L. Knechtel, N. L. Oien, J. L. Wieber and M. W. Wathen, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3039.
146. O. S. Lee, K. H. Kim, J. Kim, K. Kwon, T. Ok, H. Ihee, H.-Y. Lee and J.-H. Sohn, *J. Org. Chem.*, 2013, **78**, 8242.

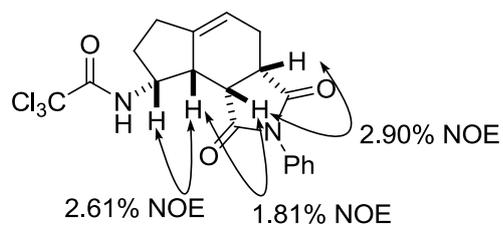
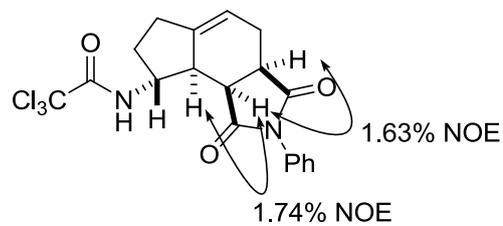
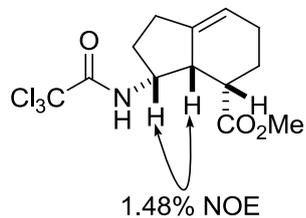
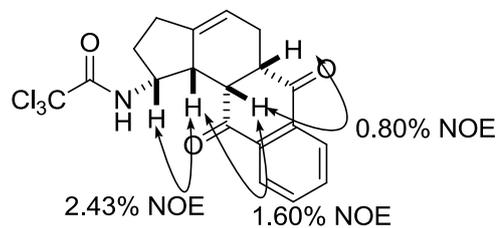
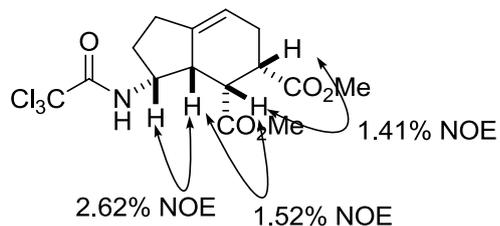
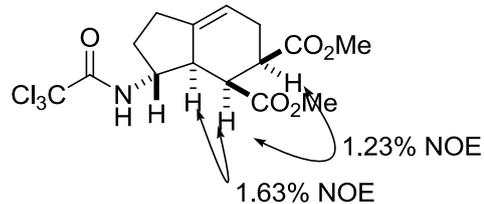
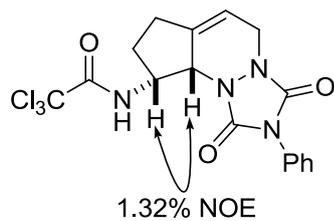
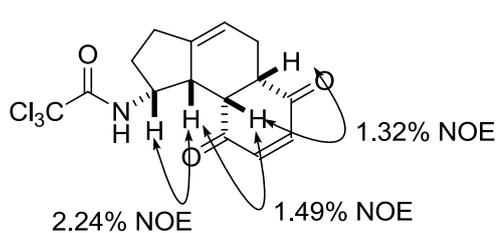
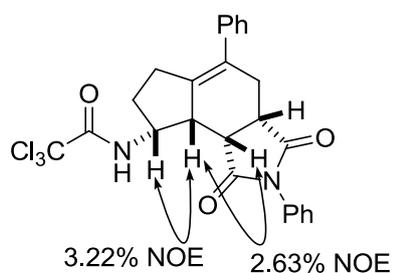
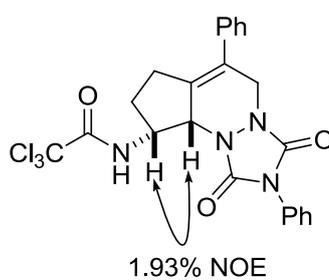
147. F. I. McGonagle, L. Brown, A. Cooke and A. Sutherland, *Tetrahedron Lett.*, 2011, **52**, 2330.
148. S. Fustero, D. Jimenez, M. Sanchez-Rosello and C. D. Pozo, *J. Am. Chem. Soc.*, 2007, **129**, 6700.
149. R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge and J. Rousell, *Tetrahedron Lett.*, 1986, **27**, 279.
150. R. J. Giguere, T. L. Bray, S. M. Duncan and G. Majetich, *Tetrahedron Lett.*, 1986, **27**, 4945.
151. J.-S. Schanche, *Mol. Divers.*, 2003, **7**, 293.
152. L. Perreux and A. Loupy, *Tetrahedron*, 2001, **57**, 9199.
153. A. Lew, P. O. Krutzik, M. E. Hart and A. R. Chamberlin, *J. Comb. Chem.*, 2002, **4**, 95.
154. J. M. Kremsner and C. O. Kappe, *J. Org. Chem.*, 2006, **71**, 4651.
155. G. Abbiati, A. Arcadi, G. Bianchi, S. D. Giuseppe, F. Marinelli and E. Rossi, *J. Org. Chem.*, 2003, **68**, 6959.
156. D. Srimani, Y. Ben-David and D. Milstein, *Chem. Commun.*, 2013, **49**, 6632.
157. E. J. McEachern, W. Yang, G. Chen, R. T. Skerlj and G. J. Bridger, *Synth. Commun.*, 2003, **33**, 3497.
158. D. E. Beattie, R. Crossley, A. C. W. Curran, D. G. Hill and A. E. Lawrence, *J. Med. Chem.*, 1977, **20**, 718.
159. A. M. V. Leusen and J. C. Jagt, *Tetrahedron Lett.*, 1970, **11**, 971.
160. G. J. Janz and A. R. Monohan, *J. Org. Chem.*, 1964, **29**, 569.
161. G.-Q. Shi and M. Schlosser, *Tetrahedron*, 1993, **49**, 1445.
162. U. Ruffer and E. Breitmaier, *Synthesis*, 1989, 623.
163. M. Schlosser and H. Keller, *Liebigs Ann*, 1995, 1587.
164. I. Hussain, M. A. Yawer, M. Lalk, U. Lindequist, A. Villinger, C. Fischer and P. Langer, *Bioorg. Med. Chem.*, 2008, **16**, 9898.
165. M. Ohashi, I. Takeda, M. Ikawa and S. Ogoshi, *J. Am. Chem. Soc.*, 2011, **133**, 18018.
166. C. Donoghue, *MSci Thesis, University of Glasgow*, 2013.
167. K. Amrein, D. Hunziker, B. Kuhn, A. V. Mayweg and W. Neidhart, Hoffmann-La Roche Inc., U.S. Patent US 0010519 (A1), 2007.
168. S. Kuroiwa, J. Odanaka, S. Maruyama, Y. Sato, A. Tomura, H. Sato and Y. Suzuki, U.S. Patent US 7563893 (B2), 2009.

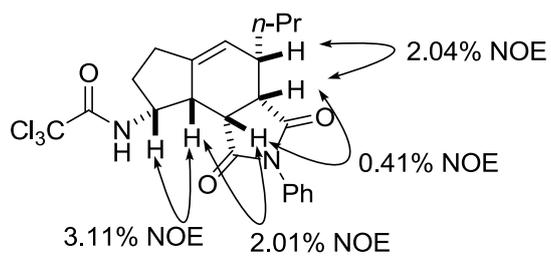
169. M. D. Helm, J. E. Moore, A. Plant and J. P. A. Harrity, *Angew. Chem. Int. Ed.*, 2005, **44**, 3889.
170. J. J. Sahn, J. Y. Su and S. F. Martin, *Org. Lett.*, 2011, **13**, 2590.
171. M. R. Rivero and J. C. Carretero, *J. Org. Chem.*, 2003, **68**, 2975.
172. J. A. Marshall, A. Piettre, M. A. Paige and F. Valeriote, *J. Org. Chem.*, 2003, **68**, 1771.
173. A. B. Smith, J. W. Leahy, I. Noda, S. W. Remiszewski, N. J. Liverton and R. Zibuck, *J. Am. Chem. Soc.*, 1992, **114**, 2995.
174. A. Tsimelzon and R. Braslau, *J. Org. Chem.*, 2005, **70**, 10854.
175. D. F. Harvey, K. P. Lund and D. A. Neil, *J. Am. Chem. Soc.*, 1992, **114**, 8424.
176. K. Fuji, T. Morimoto, K. Tsutsumi and K. Kakiuchi, *Chem. Commun.*, 2005, 3295.
177. M. Nishida, N. Adachi, K. Onozuka, H. Matsumura and M. Mori, *J. Org. Chem.*, 1998, **63**, 9158.
178. J. Barluenga, A. Dieguez, F. J. Fananas, A. Fernandez, F. Rodriguez and A. Satrustegui, *Chem. Eur. J.*, 2008, **14**, 4153.
179. M. Ishizaki and O. Hoshino, *Tetrahedron*, 2000, **56**, 8813.
180. P. J. Parsons, K. Booker-Milburn, S. H. Brooks, S. Martel and M. Stefinovic, *Synth. Commun.*, 1994, **24**, 2159.

6.0 Appendix 1

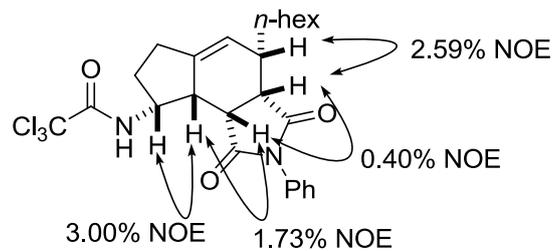
NOE data

**198****202****204****206****207****208****209****210**

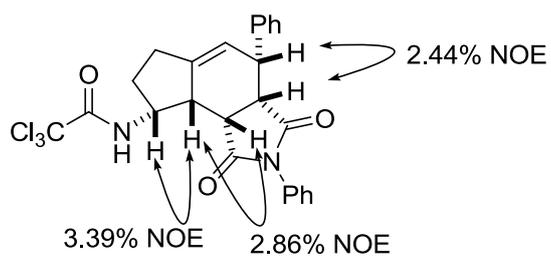
**217****227****228****218****229****350****219****230****253****255**



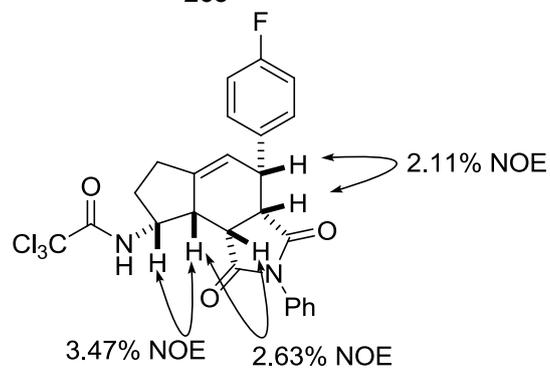
262



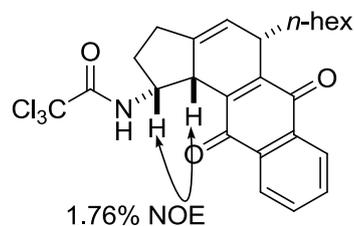
263



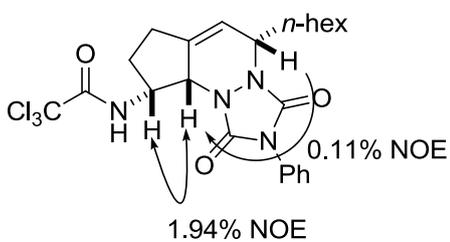
264



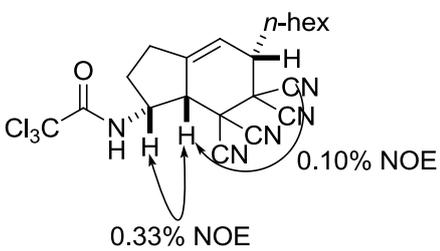
265



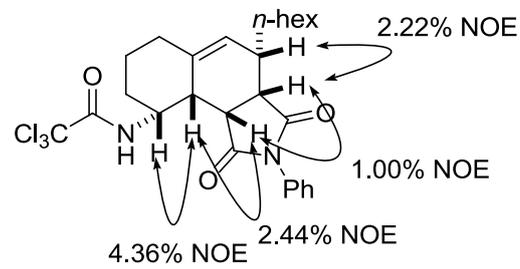
266



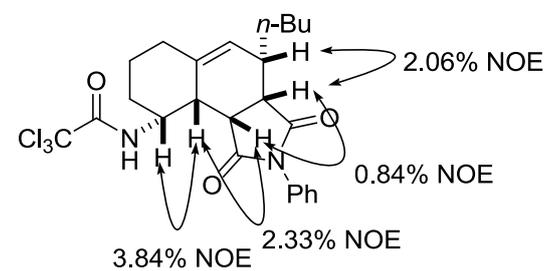
267



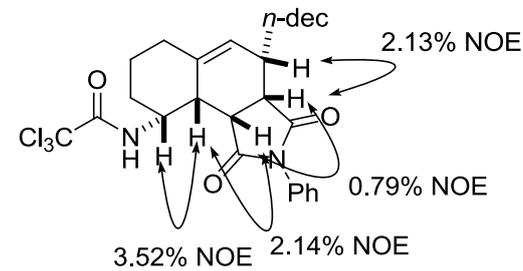
268



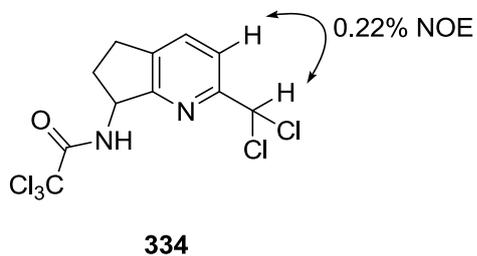
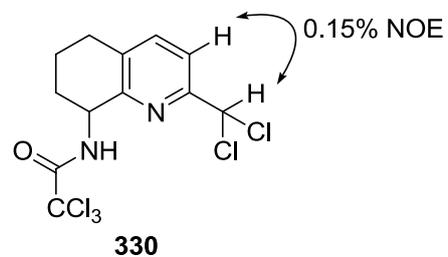
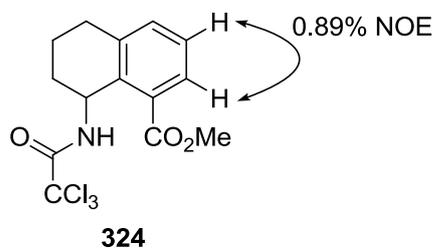
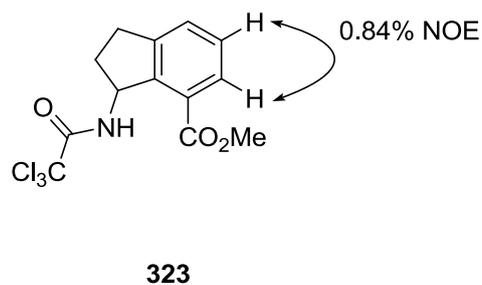
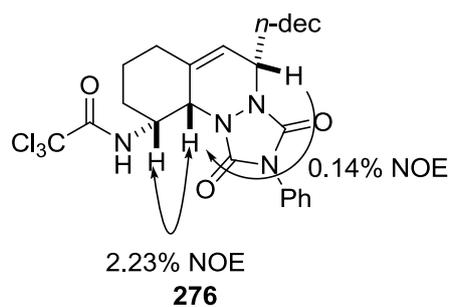
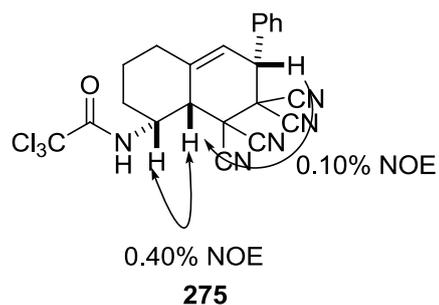
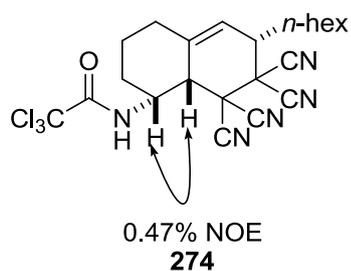
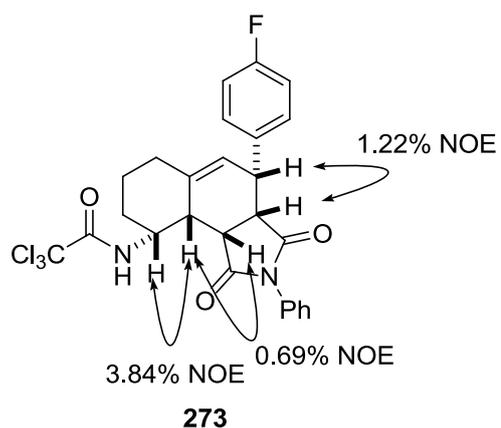
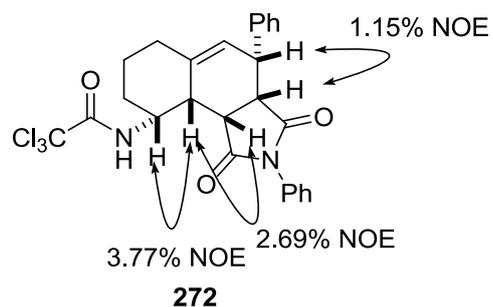
269



270



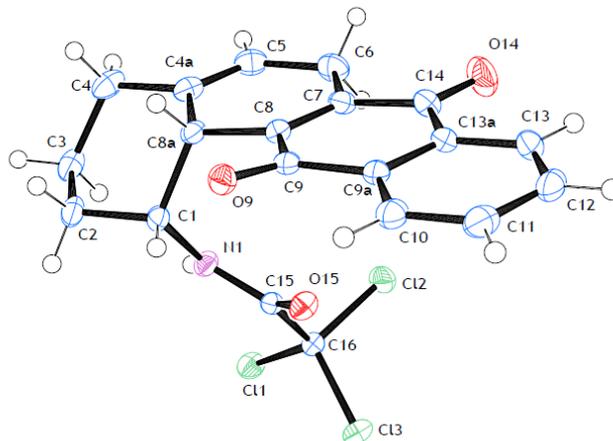
271



7.0 Appendix 2

X-ray data

Crystal data and structure refinement for 206



Identification code	206	
Empirical formula	$C_{20}H_{16}Cl_3NO_3$	
Formula weight	424.69	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	$a = 9.2312(3)$ Å	$\alpha = 74.0757(16)^\circ$
	$b = 9.9744(4)$ Å	$\beta = 79.2214(18)^\circ$
	$c = 10.6797(4)$ Å	$\gamma = 74.1904(19)^\circ$
Volume	903.113 Å ³	
Z	2	
Density (calculated)	1.562 Mg/m ³	
Absorption coefficient	0.53 mm ⁻¹	
F(000)	436	

Theta range for data collection	2 to 29.83 °.
Index ranges	-12<=h<=12, -13<=k<=13, -14<=l<=15
Reflections collected	5178
Independent reflections	4349 [R(int) = 0.0614]
Completeness to theta = 29.83°	99.9%
Refinement method Full-matrix least-squares on F ²	1.048
Data / restraints / parameters	5178 / 0 / 260
Goodness-of-fit on F2	1.048
Final R indices [I>2sigma(I)]	R1 = 0.0517, wR2 = 0.122
R indices (all data)	R1 = 0.0419, wR2 = 0.1171
Absolute structure parameter	1.075
Largest diff. peak and hole	0.087 and -0.278 e.Å ⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for 206. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	X	Y	Z	U (eq)
Cl1	6210(5)	-974(4)	8835(4)	24(1)
Cl2	3073(5)	-1077(4)	9037(4)	25(1)
Cl3	5297(5)	-2063(4)	6960(4)	24(1)
O9	2061(14)	4244(13)	4430(12)	22(1)
O14	-1640(17)	1526(19)	8049(16)	39(1)
O15	3583(14)	891(13)	6084(12)	22(1)
N1	4518(16)	1821(15)	7401(15)	19(1)
H1N	4960	1620	8114	55
C1	4106(18)	3321(17)	6652(17)	19(1)

H1	4278	3342	5695	30
C2	5127(2)	4164(18)	6923(19)	24(1)
H2A	6201	3688	6708	29
H2B	4933	5141	6343	31
C3	4866(2)	4279(19)	8349(2)	27(1)
H3A	5492	4894	8456	36
H3B	5189	3314	8925	34
C4	3177(2)	4919(19)	8768(2)	28(1)
H4A	3015	4846	9725	43
H4B	2908	5947	8317	41
C4A	2165(2)	4145(18)	8436(18)	22(1)
C5	1171(2)	3530(2)	9321(18)	25(1)
H5	1082	3616	10198	29
C6	184(2)	2711(2)	9029(19)	27(1)
H6A	-886	3114	9337	42
H6B	461	1700	9524	32
C7	318(18)	2752(18)	7591(17)	21(1)
C8	1311(18)	3374(17)	6686(16)	18(1)
C8A	2416(18)	4055(16)	7019(16)	18(1)
H8A	2244	5063	6476	29
C9	1324(17)	3494(17)	5256(16)	18(1)
C9A	368(18)	2726(17)	4861(17)	20(1)
C10	470(2)	2686(19)	3548(19)	24(1)
H10	1166	3130	2905	51

C11	-447(2)	1998(2)	3187(2)	28(1)
H11	-364	1955	2298	50
C12	-1493(2)	1367(2)	4120(2)	29(1)
H12	-2130	910	3864	40
C13	-1600(2)	1409(2)	5427(2)	26(1)
H13	-2313	981	6063	47
C13A	-661(18)	2079(18)	5807(18)	21(1)
C14	-738(19)	2080(2)	7211(19)	24(1)
C15	4232(17)	751(16)	7019(16)	18(1)
C16	4707(18)	-777(17)	7919(16)	18(1)

Bond Lengths (Å) for 206

C11-C16	1.782(2)	C12-C16	1.780(2)
C13-C16	1.767(2)	O9-C9	1.221(2)
O14-C14	1.226(2)	O15-C15	1.215(2)
N1-H1N	0.880(2)	N1-C1	1.474(2)
N1-C15	1.344(3)	C1-H1	1.000(2)
C1-C2	1.532(3)	C1-C8A	1.559(2)
C2-H2A	0.990(2)	C2-H2B	0.990(2)
C2-C3	1.528(3)	C3-H3A	0.990(2)
C3-H3B	0.990(2)	C3-C4	1.547(2)
C4-H4A	0.990(2)	C4-H4B	0.990(2)
C4-C4A	1.504(3)	C4A-C5	1.332(2)
C4A-C8A	1.512(3)	C5-H5	0.950(2)
C5-C6	1.499(3)	C6-H6A	0.990(2)

C6-H6B	0.990(2)	C6-C7	1.507(3)
C7-C8	1.346(2)	C7-C14	1.487(3)
C8-C8A	1.508(3)	C8-C9	1.497(2)
C8A-H8A	1.000(1)	C9-C9A	1.492(3)
C9A-C10	1.399(3)	C9A-C13A	1.399(2)
C10-H10	0.950(2)	C10-C11	1.386(3)
C11-H11	0.950(2)	C11-C12	1.396(3)
C12-H12	0.950(2)	C12-C13	1.392(3)
C13-H13	0.951(2)	C13-C13A	1.400(3)
C13A-C14	1.488(3)	C15-C16	1.558(2)

Bond angle (°) for 206

H1N-N1-C1	119.3(2)	H1N-N1-C15	119.3(2)
C1-N1-C15	121.4(1)	N1-C1-H1	108.8(1)
N1-C1-C2	109.1(1)	N1-C1-C8A	112.2(1)
H1-C1-C2	108.8(2)	H1-C1-C8A	108.8(1)
C2-C1-C8A	109.0(1)	C1-C2-H2A	109.1(2)
C1-C2-H2B	109.1(2)	C1-C2-C3	112.6(2)
H2A-C2-H2B	107.8(2)	H2A-C2-C3	109.1(2)
H2B-C2-C3	109.1(2)	C2-C3-H3A	109.4(2)
C2-C3-H3B	109.4(2)	C2-C3-C4	111.2(2)
H3A-C3-H3B	108.0(2)	H3A-C3-C4	109.4(2)
H3B-C3-C4	109.4(2)	C3-C4-H4A	109.4(2)
C3-C4-H4B	109.4(2)	C3-C4-C4A	111.1(2)
H4A-C4-H4B	108.0(2)	H4A-C4-C4A	109.4(2)

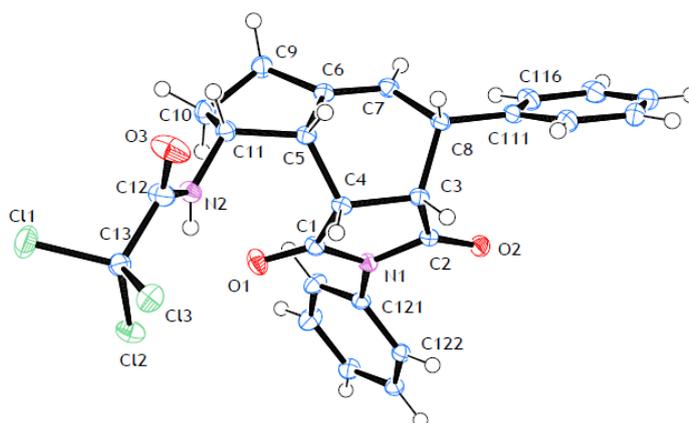
H4B-C4-C4A	109.4(2)	C4-C4A-C5	123.3(2)
C4-C4A-C8A	114.5(2)	C5-C4A-C8A	122.2(2)
C4A-C5-H5	117.7(2)	C4A-C5-C6	124.5(2)
H5-C5-C6	117.8(2)	C5-C6-H6A	108.9(2)
C5-C6-H6B	108.9(2)	C5-C6-C7	113.3(2)
H6A-C6-H6B	107.7(2)	H6A-C6-C7	108.9(2)
H6B-C6-C7	109.0(2)	C6-C7-C8	122.6(2)
C6-C7-C14	116.3(2)	C8-C7-C14	121.1(2)
C7-C8-C8A	123.3(2)	C7-C8-C9	121.0(2)
C8A-C8-C9	115.7(1)	C1-C8A-C4A	109.6(1)
C1-C8A-C8	113.2(1)	C1-C8A-H8A	106.7(1)
C4A-C8A-C8	113.5(1)		

Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 206. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	24	21	28	-57	-9	-2
Cl2	23	22	25	-3	3	-8
Cl3	28	17	27	-10	-3	-2
O9	23	20	23	-3	-2	-7
O14	33	56	36	-11	10	-24
O15	26	19	22	-5	-6	-4
N1	20	14	24	-4	-5	-4
C1	18	14	24	-3	-3	-5
C2	25	17	33	-2	-9	-8

C3	31	19	36	-4	-15	-7
C4	37	21	30	-11	-12	-2
C4A	25	20	23	-8	-7	0
C5	28	27	22	-8	-4	-1
C6	26	31	22	-7	4	-6
C7	17	20	23	-6	0	-2
C8	18	15	21	-5	-2	-3
C8A	19	14	22	-5	-4	-3
C9	16	16	22	-5	-3	-1
C9A	16	17	27	-7	-4	-1
C10	23	21	28	-7	-6	-2
C11	28	26	33	-12	-11	0
C12	24	22	46	-13	-14	-1
C13	17	24	41	-9	-4	-5
C13A	15	19	29	-7	-1	-3
C14	19	25	29	-7	2	-6
C15	15	15	21	-4	1	-3
C16	19	17	20	-5	-2	-5

Crystal data and structure refinement for 264



Identification code	264	
Empirical formula	$C_{25}H_{21}Cl_3N_2O_3$	
Formula weight	503.79	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	$a = 10.4334(2)$ Å	$\alpha = 90^\circ$.
	$b = 10.8557(2)$ Å	$\beta = 101.184(1)^\circ$.
	$c = 20.1616(4)$ Å	$\gamma = 90^\circ$.
Volume	$2240.17(7)$ Å ³	
Z	4	
Density (calculated)	1.494 Mg/m ³	
Absorption coefficient	0.441 mm ⁻¹	
F(000)	1040	
Theta range for data collection	3.15 to 34.95 °.	
Index ranges	$-16 \leq h \leq 16, -17 \leq k \leq 17, -32 \leq l \leq 32$	

Reflections collected	9822
Independent reflections	8522 [R(int) = 0.0332]
Completeness to theta = 34.95 °	99.9%
Refinement method Full-matrix least-squares on F ²	0.977
Data / restraints / parameters	8522 / 1 / 273
Goodness-of-fit on F2	0.977
Final R indices [I>2sigma(I)]	R1 = 0.0332, wR2 = 0.0951
R indices (all data)	R1 = 0.0332, wR2 = 0.0950
Absolute structure parameter	1.029(33)
Largest diff. peak and hole	0.64 and -0.46 e.Å ⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for 264. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	X	Y	Z	U(eq.)
Cl1	6764(3)	7692(3)	66(2)	34(1)
Cl2	5556(2)	6025(2)	874(2)	24(1)
Cl3	7580(2)	7684(2)	1517(2)	23(1)
O1	6324(6)	2674(6)	9856(4)	23(1)
O2	8102(6)	-155(6)	2578(3)	19(1)
O3	9296(4)	6258(6)	821(5)	34(1)
N1	6951(6)	1124(6)	1760(3)	15(1)
N2	7846(7)	4659(7)	640(4)	18(1)
C1	7146(8)	2206(7)	1423(4)	16(1)
C2	8058(7)	760(7)	2231(4)	14(1)

C3	9139(7)	1691(7)	2219(4)	14(1)
H3	9383	2067	2667	22(1)
C4	8510(7)	2689(7)	1706(4)	14(1)
H4	8435	3457	1951	23(1)
C5	9351(7)	2930(7)	1165(4)	15(1)
H5	10184	3286	1392	21(1)
C6	9637(8)	1711(7)	862(4)	16(1)
C7	10106(8)	790(7)	1280(4)	17(1)
H7	10256	10	1120	24(1)
C8	10380(7)	10840(7)	2026(4)	15(1)
H8	10105	1729	2089	18(1)
C9	9254(9)	1746(8)	101(4)	20(1)
H9A	8832	985	-73	24(1)
H9B	10011	1881	-103	33(1)
C10	8298(9)	2839(8)	-40(4)	21(1)
H10A	8317	3209	-475	31(1)
H10B	7412	2581	-29	19(1)
C11	8808(8)	3742(7)	539(4)	17(1)
H11	9549	4184	419	15(1)
C12	8168(9)	5843(8)	730(5)	23(1)
C13	7041(9)	6750(8)	797(4)	19(1)
C111	10941(8)	47(8)	2499(4)	17(1)
C112	11656(9)	345(9)	3140(4)	22(1)
H112	11774	1167	3266	29(1)

C113	12192(10)	-569(11)	3593(5)	27(1)
H113	12647	-356	4022	38(1)
C114	12046(10)	-1810(10)	3404(5)	27(1)
H114	12407	-2425	703	35(1)
C115	11357(9)	-2112(9)	2765(6)	25(1)
H115	11269	-2934	2635	28(1)
C116	10795(8)	-1193(8)	2317(5)	21(1)
H116	10320	-1409	1894	30(1)
C121	5751(7)	449(7)	1643(4)	15(1)
C122	5190(7)	111(7)	2187(4)	16(1)
H122	5582	334	2624	26(1)
C123	4030(8)	-567(8)	2071(4)	17(1)
H123	3652	-803	2433	24(1)
C124	3441(8)	-890(8)	1416(5)	20(1)
H124	2671	-1344	1339	28(1)
C125	4004(9)	-532(9)	874(5)	23(1)
H125	3602	-739	435	35(1)
C126	5167(8)	133(8)	985(4)	20(1)
H126	5548	364	624	27(1)
H2	7090(15)	4419(15)	677(7)	27(1)
O.3	9130(2)	6278(8)	590(2)	50(1)

Bond length (Å) for 264

C11-C13	1.7704(9)	C12-C13	1.771(1)
C13-C13	1.7717(9)	O1-C1	1.215(1)

O2-C2	1.211(1)	O3-C12	1.240(5)
N1-C1	1.392(1)	N1-C2	1.4018(9)
N1-C121	1.430(1)	N2-C11	1.456(1)
N2-C12	1.332(1)	N2-H2	0.85(2)
C1-C4	1.520(1)	C2-C3	1.518(1)
C3-H3	0.9793(8)	C3-C4	1.553(1)
C3-C8	1.568(1)	C4-H4	0.9792(8)
C4-C5	1.551(1)	C5-H5	0.9797(7)
C5-C6	1.511(1)	C5-C11	1.553(1)
C6-C7	1.338(1)	C6-C9	1.510(1)
C7-H7	0.9302(8)	C7-C8	1.510(1)
C8-H8	0.9800(7)	C8-C111	1.517(1)
C9-H9A	0.9693(9)	C9-H9B	0.970(1)
C9-C10	1.540(1)	C10-H10A	0.9691(8)
C10-H10B	0.9704(9)	C10-C11	1.537(1)
C11-H11	0.9794(9)	C12-C13	1.559(1)
C111-C112	1.400(1)	C111-C116	1.396(1)
C112-H112	0.930(1)	C112-C113	1.390(1)
C113-H113	0.931(1)	C113-C114	1.400(2)
C114-H114	0.930(1)	C114-C115	1.387(1)
C115-H115	0.929(1)	C115-C116	1.397(1)
C116-H116	0.9292(9)	C121-C122	1.389(1)
C121-C126	1.390(1)	C122-H122	0.9292(7)
C122-C123	1.396(1)	C123-H123	0.9309(9)

C123-C124	1.389(1)	C124-H124	0.9298(8)
C124-C125	1.392(1)	C125-H125	0.9304(9)
C125-C126	1.392(1)	C126-H126	0.9293(9)

Bond Angle (°) for 264

C1-N1-C2	112.9(6)	C1-N1-C121	123.9(6)
C2-N1-C121	123.2(6)	C11-N2-C12	121.1(8)
C11-N2-H2	119.0(1)	C12-N2-H2	120.0(1)
O1-C1-N1	123.9(8)	O1-C1-C4	127.3(7)
N1-C1-C4	108.8(6)	O2-C2-N1	123.8(7)
O2-C2-C3	127.6(7)	N1-C2-C3	108.6(6)
C2-C3-H3	108.9(7)	C2-C3-C4	104.8(6)
C2-C3-C8	112.1(6)	H3-C3-C4	108.9(7)
H3-C3-C8	108.9(7)	C4-C3-C8	113.1(6)
C1-C4-C3	104.7(6)	C1-C4-H4	108.9(7)
C1-C4-C5	114.2(6)	C3-C4-H4	108.9(7)
C3-C4-C5	111.3(6)	H4-C4-C5	108.8(7)
C4-C5-H5	108.0(7)	C4-C5-C6	108.6(6)
C4-C5-C11	120.0(6)	H5-C5-C6	107.9(7)
H5-C5-C11	107.9(7)	C6-C5-C11	103.8(6)
C5-C6-C7	118.5(7)	C5-C6-C9	110.7(7)
C7-C6-C9	130.7(8)	C6-C7-H7	121.8(8)
C6-C7-C8	116.4(7)	H7-C7-C8	121.8(8)
C3-C8-C7	109.2(6)	C3-C8-H8	105.7(7)
C3-C8-C111	113.2(6)	C7-C8-H8	105.8(7)

C7-C8-C111	116.4(7)	H8-C8-C111	105.7(7)
C6-C9-H9A	111.0(8)	C6-C9-H9B	111.0(8)
C6-C9-C10	103.9(7)	H9A-C9-H9B	109.0(8)
H9A-C9-C10	111.0(8)	H9B-C9-C10	111.0(8)
C9-C10-H10A	111.1(8)	C9-C10-H10B	111.1(8)
C9-C10-C11	103.6(7)	H10A-C10-H10B	109.0(8)
H10A-C10-C11	111.0(8)	H10B-C10-C11	111.0(8)
N2-C11-C5	115.3(7)	N2-C11-C10	113.3(7)
N2-C11-H11	107.3(7)	C5-C11-C10	105.8(6)
C5-C11-H11	107.3(7)	C10-C11-H11	107.4(7)
O3-C12-N2	125.3(3)	O3-C12-C13	117.9(3)
N2-C12-C13	116.5(8)	C11-C13-C12	109.0(5)
C11-C13-C13	109.0(5)	C11-C13-C12	107.3(6)
C12-C13-C13	109.1(5)	C12-C13-C12	114.5(6)
C13-C13-C12	107.9(6)	C8C111-C112	118.7(7)
C8-C111-C116	122.8(7)	C112-C111-C116	118.5(8)
C111-C112-H112	119.5(9)	C111-C112-C113	121.1(9)
H112-C112-C113	119.4(9)	C112-C113-H113	120.1(1)
C112-C113-C114	119.9(1)	H113-C113-C114	120.1(1)
C113-C114-H114	120.4(1)	C113-C114-C115	119.4(1)
H114-C114-C115	120.3(1)	C114-C115-H115	119.7(1)
C114-C115-C116	120.6(9)	H115-C115-C116	119.8(1)
C111-C116-C115	120.5(8)	C111-C116-H116	119.7(9)
C115-C116-H116	119.7(9)	N1-C121-C122	119.6(7)

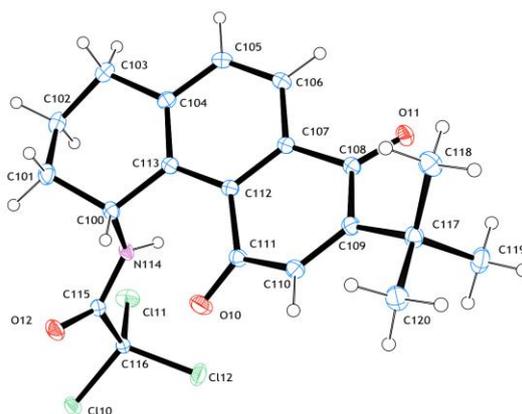
N1-C121-C126	119.5(7)	C122-C121-C126	120.9(7)
C121-C122-H122	120.3(8)	C121-C122-C123	119.4(7)
H122-C122-C123	120.3(8)	C122-C123-H123	119.9(8)
C122-C123-C124	120.1(8)	H123-C123-C124	120.0(8)
C123-C124-H124	120.1(9)	C123-C124-C125	120.0(8)
H124-C124-C125	120.0(9)	C124-C125-H125	119.9(9)
C124-C125-C126	120.4(9)	H125-C125-C126	119.8(9)
C121-C126-C125	119.3(8)	C121-C126-H126	120.4(8)
C125-C126-H126	120.4(9)		

Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 264.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl1	54	29	20	7	11	11
Cl2	17	26	30	-5	5	0
Cl3	26	22	22	-1	5	-5
O1	15	20	30	8	-1	-2
O2	17	19	21	5	4	0
O3	20	20	65	-7	13	-5
N1	12	14	17	1	3	-2
N2	16	14	23	1	5	0
C1	13	14	20	0	4	-1
C2	13	15	15	-1	4	0
C3	13	14	15	-1	3	-1
C4	13	13	17	-1	3	-1
C5	14	13	17	-1	4	-1

C6	16	16	17	-2	4	1
C7	17	16	18	-1	5	2
C8	13	15	17	1	4	1
C9	24	19	16	-2	4	3
C10	24	19	18	-1	1	3
C11	17	14	18	1	4	1
C12	23	14	35	2	12	1
C13	22	16	21	2	7	2
C111	14	17	20	3	5	2
C112	22	24	19	1	4	7
C113	28	35	18	5	6	12
C114	26	30	28	13	12	10
C115	21	18	38	8	11	1
C116	16	17	29	3	5	-1
C121	12	14	18	0	4	-1
C122	14	16	17	1	4	1
C123	15	18	20	3	6	-1
C124	16	21	23	1	4	-5
C125	21	28	19	-2	3	-10
C126	19	23	18	-2	5	-7
O3A	38	15	109	5	46	0

Crystal data and structure refinement for 312



Identification code	312	
Empirical formula	$C_{20}H_{20}Cl_3NO_3$	
Formula weight	428.72	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	$a = 9.5784(4)$ Å	$\alpha = 73.870(2)^\circ$.
	$b = 12.4773(5)$ Å	$\beta = 78.263(2)^\circ$.
	$c = 17.9818(8)$ Å	$\gamma = 77.712(2)^\circ$.
Volume	1993.18(15) Å ³	
Z	4	
Density (calculated)	1.429 Mg/m ³	
Absorption coefficient	0.48 mm ⁻¹	
F(000)	88	
Theta range for data collection	1.193 to 29.998 °.	
Index ranges	-13 ≤ h ≤ 13, -17 ≤ k ≤ 17, -25 ≤ l ≤ 25	

Reflections collected	11347
Independent reflections	10988 [R(int) = 0.066]
Completeness to theta = 29.95°	99.8%
Refinement method Full-matrix least-squares on F ²	0.991
Data / restraints / parameters	11347 / 0 / 539
Goodness-of-fit on F2	1.033
Final R indices [I>2sigma(I)]	R1 = 0.0697, wR2 = 0.1541
R indices (all data)	R1 = 0.0544, wR2 = 0.146
Absolute structure parameter	1.033
Largest diff. peak and hole	1.35 and -0.632 e.Å ⁻³

Atomic coordinates (x 10⁴) and equivalent isotropic displacement parameters (Å²x 10³) for 312. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	X	Y	Z	Ueq.
Cl10	847(6)	6965(6)	3493(3)	35(1)
Cl11	-262(6)	8088(5)	2057(3)	36(1)
Cl12	-535(6)	5736(5)	2777(3)	37(1)
O10	2195(19)	3998(13)	1789(9)	33(1)
O11	490(15)	3204(12)	-555(8)	26(1)
O12	3142(16)	6019(15)	2452(9)	34(1)
N114	2043(17)	6423(14)	1379(9)	21(1)
H114	1240(3)	6590(2)	1213(14)	23(1)
C100	3346(2)	5937(17)	906(11)	21(1)
H100	3820	5230	1245	24(1)
C101	4415(2)	6777(19)	608(13)	27(1)

H10A	4546	7058	1049	32(1)
H10B	5366	6386	401	40(1)
C102	3875(2)	7771(19)	-32(14)	30(1)
H10C	4549	8324	-192	31(1)
H10D	2914	8154	169	39(1)
C103	3764(2)	7356(18)	-737(13)	29(1)
H10E	3232	7978	-1103	42(1)
H10F	4750	7159	-1016	41(1)
C104	3006(2)	6333(16)	-519(11)	23(1)
C105	2474(2)	6075(18)	-1108(11)	25(1)
H105	2552	6564	-1619	32(1)
C106	1838(2)	5126(17)	-962(11)	23(1)
H106	1459	4977	-1365	35(1)
C107	1758(19)	4388(16)	-216(11)	19(1)
C108	1216(2)	3308(16)	-97(11)	20(1)
C109	1641(2)	2351(16)	575(11)	21(1)
C110	2044(2)	2628(17)	1163(11)	23(1)
H110	2284	2035	1603	28(1)
C111	2139(2)	3799(16)	1169(11)	21(1)
C112	2244(19)	4645(16)	392(10)	19(1)
C113	2856(19)	5627(16)	249(11)	20(1)
C115	2080(2)	6362(17)	2130(11)	23(1)
C116	594(2)	6766(18)	2601(11)	23(1)
C117	1568(2)	1143(17)	573(12)	24(1)

C118	2369(3)	907(19)	-217(13)	31(1)
H11A	1898	1431	-645	46(1)
H11B	2341	127	-219	33(1)
H11C	3377	1012	-288	35(1)
C119	-29(2)	989(2)	701(15)	34(1)
H11D	-527	1166	1196	41(1)
H11E	-73	204	720	40(1)
H11F	-501	1498	268	39(1)
C120	2302(3)	286(18)	1231(14)	31(1)
H12A	3308	391	1171	48(1)
H12B	2280	-483	1203	32(1)
H12C	1787	403	1739	30(1)

Bond-length (Å) for 312

Cl10-C116	1.760(2)	Cl11-C116	1.789(2)
Cl12-C116	1.774(2)	O10-C111	1.221(3)
O11-C108	1.228(3)	O12-C115	1.212(3)
N114-H114	0.85(3)	N114-C100	1.477(2)
N114-C115	1.338(3)	C100-H100	1.000(2)
C100-C101	1.535(3)	C100-C113	1.524(3)
C101-H10A	0.990(3)	C101-H10B	0.990(2)
C101-C102	1.519(3)	C102-H10C	0.990(2)
C102-H10D	0.990(2)	C102-C103	1.527(4)
C103-H10E	0.990(2)	C103-H10F	0.990(2)
C103-C104	1.520(3)	C104-C105	1.402(3)

C104-C113	1.414(2)	C105-H105	0.950(2)
C105-C106	1.382(3)	C106-H106	0.950(2)
C106-C107	1.397(2)	C107-C108	1.492(3)
C107-C112	1.408(3)	C108-C109	1.498(2)
C109-C110	1.345(3)	C109-C117	1.525(3)
C110-H110	0.951(2)	C110-C111	1.486(3)
C111-C112	1.499(2)	C112-C113	1.408(3)
C115-C116	1.562(2)	C117-C118	1.545(3)
C117-C119	1.545(3)	C117-C120	1.534(3)
C118-H11A	0.980(2)	C118-H11B	0.980(3)
C118-H11C	0.980(3)	C119-H11D	0.980(3)
C119-H11E	0.980(3)	C119-H11F	0.980(2)
C120-H12A	0.980(3)	C120-H12B	0.979(2)
C120-H12C	0.979(2)		

Bond angle (°) for 312

H114-N114-C100	120(2)	H114-N114-C115	120(2)
C100-N114-C115	119.0(2)	N114-C100-H100	108.6(2)
N114-C100-C101	109.9(2)	N114-C100-C113	107.7(2)
H100-C100-C101	108.7(2)	H100-C100-C113	108.6(2)
C101-C100-C113	113.3(2)	C100-C101-H10A	109.5(2)
C100-C101-H10B	109.4(2)	C100-C101-C102	111.1(2)
H10A-C101-H10B	108.0(2)	H10A-C101-C102	109.4(2)
H10B-C101-C102	109.4(2)	C101-C102-H10C	109.7(2)
C101-C102-H10D	109.7(2)	C101-C102-C103	109.8(2)

H10C-C102-H10D	108.2(2)	H10C-C102-C103	109.7(2)
H10D-C102-C103	109.6(2)	C102-C103-H10E	108.9(2)
C102-C103-H10F	108.9(2)	C102-C103-C104	113.4(2)
H10E-C103-H10F	107.7(2)	H10E-C103-C104	108.9(2)
H10F-C103-C104	108.9(2)	C103-C104-C105	118.2(2)
C103-C104-C113	122.2(2)	C105-C104-C113	119.5(2)
C104-C105-H105	119.2(2)	C104-C105-C106	121.5(2)
H105-C105-C106	119.3(2)	C105-C106-H106	120.3(2)
C105-C106-C107	119.4(2)	H106-C106-C107	120.3(2)
C106-C107-C108	118.4(2)	C106-C107-C112	120.2(2)
C108-C107-C112	121.4(2)	O11-C108-C107	120.5(2)
O11-C108-C109	121.8(2)	C107-C108-C109	117.7(2)
C108-C109-C110	116.6(2)	C108-C109-C117	119.7(2)
C110-C109-C117	123.7(2)	C109-C110-H110	117.8(2)
C109-C110-C111	124.4(2)	H110-C110-C111	117.8(2)
O10-C111-C110	118.9(2)	O10-C111-C112	124.4(2)
C110-C111-C112	116.6(2)	C107-C112-C111	116.6(2)
C107-C112-C113	120.3(2)	C111-C112-C113	123.0(2)
C100-C113-C104	120.1(2)	C100-C113-C112	121.0(2)
C104-C113-C112	118.9(2)	O12-C115-N114	125.4(2)
O12-C115-C116	120.0(2)	N114-C115-C116	114.6(2)
Cl10-C116-Cl11	107.8(1)	Cl10-C116-Cl12	110.4(1)
Cl10-C116-C115	110.2(1)	Cl11-C116-Cl12	109.2(1)
Cl11-C116-C115	110.4(1)	Cl12-C116-C115	108.9(1)

C109-C117-C118	109.0(2)	C109-C117-C119	109.6(2)
C109-C117-C120	111.0(2)	C118-C117-C119	110.7(2)
C118-C117-C120	108.1(2)	C119-C117-C120	108.4(2)
C117-C118-H11A	109.5(2)	C117-C118-H11B	109.5(2)
C117-C118-H11C	109.5(2)	H11A-C118-H11B	109.4(2)
H11A-C118-H11C	109.5(2)	H11B-C118-H11C	109.4(2)
C117-C119-H11D	109.5(2)	C117-C119-H11E	109.5(2)
C117-C119-H11F	109.5(2)	H11D-C119-H11E	109.4(2)
H11D-C119-H11F	109.5(2)	H11E-C119-H11F	109.5(2)
C117-C120-H12A	109.5(2)	C117-C120-H12B	109.5(2)
C117-C120-H12C	109.4(2)	H12A-C120-H12B	109.5(2)
H12A-C120-H12C	109.5(2)	H12B-C120-H12C	109.5(2)

Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 312.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl10	32	59	22	-17	-2	-18
Cl11	31	40	30	-9	-1	6
Cl12	31	49	39	-18	6	-24
O10	48	32	23	-7	-10	-8
O11	25	28	27	-7	-11	-4
O12	23	54	28	-10	-11	-5
N114	15	28	21	-10	-5	-1
C100	16	26	24	-9	-5	0
C101	17	34	34	-14	-2	-5
C102	23	29	39	-12	0	-8

C103	26	28	30	-4	-1	-8
C104	21	22	23	-5	-1	-3
C105	28	28	18	-4	-2	-4
C106	24	25	19	-6	-6	-1
C107	16	22	19	-5	-3	-1
C108	17	23	21	-7	-4	-1
C109	18	23	22	-5	-5	-3
C110	23	24	21	-4	-6	-3
C111	20	23	21	-4	-5	-2
C112	16	22	18	-5	-3	0
C113	16	22	20	-7	-3	0
C115	21	28	21	-6	-4	-8
C116	21	33	18	-7	-2	-10
C117	24	23	27	-5	-9	-3
C118	35	27	33	-11	-10	0
C119	30	31	42	-3	-12	-12
C120	38	23	34	-1	-15	-4