One-Pot Tandem Reactions for the Stereoselective Synthesis of Functionalised Carbocycles

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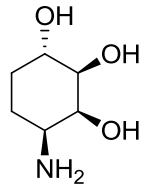
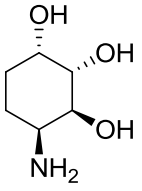
Abstract

A one-pot, two step tandem process involving an Overman rearrangement and a ring closing metathesis reaction has been utilised for the efficient synthesis of various cyclic allylic trichloroacetamides from simple allylic alcohols. Various methods were then investigated for the allylic oxidation of a carbocyclic amide using TBHP along with different transition metals such as Pd, Se, Mn and Cr. This was required for the synthesis of the important building blocks for the construction of structurally diverse antiviral and anticancer carbocyclic nucleosides and natural products.

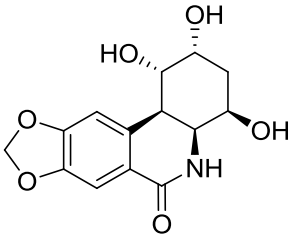
The oxidation of (1*S*)-*N*-(cyclohexenyl)trichloroacetamide was then studied leading to the preparation of two diol analogues in excellent stereoselectivity. The cyclohexene derivative was also stereoselectively functionalised using Upjohn dihydroxylation conditions or by a directed epoxidation/hydrolysis sequence of reactions to generate two aminocyclitols, the enantiomer of dihydroconduramine C-1 and dihydroconduramine E-1 in excellent stereoselectivity.



Enantiomer of dihydroconduramine C-1



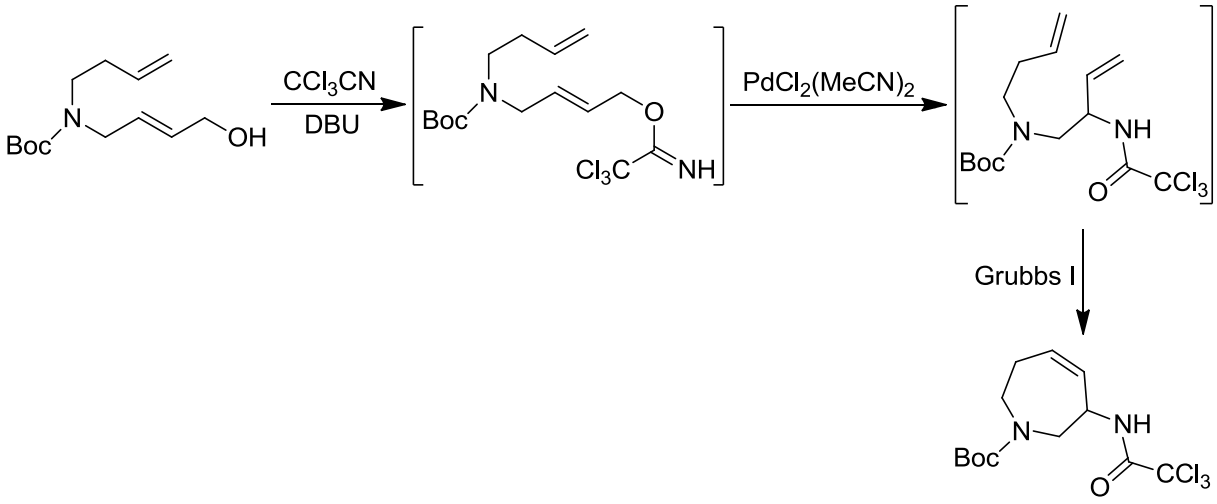
Dihydroconduramine E-1



7-Deoxypancratistatin analogue

In addition to this, a one-pot tandem process involving a substrate-directed Overman rearrangement and ring closing metathesis reaction was developed for the stereoselective synthesis of a functionalised carbocyclic allylic trichloroacetamide. The functionalised carbocyclic amide was employed in the successful synthesis of a s*yn*-(4aS,10b*S*)-phenanthridone framework using a Pd-catalysed cross-coupling reaction. Stereoselective epoxidation and dihydroxylation of the *syn*-(4a*S*,10b*S*)-phenanthridone was then investigated leading to the preparation of new analogues of 7-deoxypancratistatin. Attempts were also made to use the functionalised carbocyclic amide in the total synthesis of the Amaryllidaceae alkaloid (+)-γ-lycorane.

Further studies were then investigated to expand the scope of the one-pot tandem process to include heterocyclic derived substrates. This led to a seven-membered carbocyclic amide, which has been modified to create a diastereomeric core of balanol.



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Acknowledgements

In the name of Allah, the most Beneficent, the most Merciful, the most Gracious. He Whose praise has no bounds, Who gifted humans with the intellect of thinking, performing and selected them to explore the hidden secrets of His titanic kingdom. He Who gave me adequacy to carry out this work and all respects are for the Prophet Muhammad (Peace be upon him), the great messenger, who conveyed the message of truth and showed us the right way to live.

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Despite the geographical distance, my parents, my brother and sister were always nearby. They sacrificed their desires over mine, prayed for my edification, endeavored for my betterment and faced with courage all vexatious moments that came along and cheerfully took burden of my studies. They have been a constant source of support, guidance, encouragement and affection. Words are inadequate to express my heartiest adoration and love for them.

Author's Declaration

This thesis represents the original work of Sajjad Ahmad unless explicitly stated otherwise in the text. The research upon which it is based was carried out at the University of Glasgow in the Loudon laboratory under the supervision of Dr Andrew Sutherland, during the period, October 2008 to October 2011. Certain aspects of this work have been published elsewhere and are listed below.

S. Ahmad, L. H. Thomas and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 2801.
S. Ahmad, M. D. Swift, L. J. Farrugia, H. M. Senn and A. Sutherland, *Org. Biomol. Chem*., 2012, **10**, 3937.

List of Abbreviations

Ac	acetyl
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
(BMI)BF_4	1-butyl-3-methylimidazolium tetrafluoroborate
br	broad
Cat.	catalyst
CAN	Ceric Ammonium Nitrate
CI	Chemical Ionisation
COP	cobaltocenyloxazoline palladacycle
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
°C	degrees centigrade
de	diastereomeric excess
dba	dibenzylideneacetone
DCM	dichloromethane
DDQ	dichlorodicyanoquinone
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DIPEA	N,N′-Diisopropylethylamine
DIPHOS	Diphenylphosphino ethane
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*′-dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulfoxide
DIBAL-H	diisobutylaluminium hydride
d	doublet
EI	Electron Impact
ee	enantiomeric excess
ΔH	enthalpy change
EtOAc	ethyl acetate
FOP	ferrocenyloxazoline palladacycle
FTIR	Fourier Transform Infrared
g	gram(s)
H	Hour(s)
HPLC	High Performance Liquid Chromatography

kcal	kilocalorie(s)
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
m	multiplet
M	Molar
MCPBA	*meta*-Chloroperoxybenzoic acid
MeOH	methanol
MOM	Methoxymethyl
Me	Methyl
mg	milligram(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Pd/C	Palladium on carbon
PMB	*para*-methoxybenzoic acid
PrOH	propanol
P	protecting group
ppm	parts per million
Py	pyridine
^{1}H	proton
q	quartet
quin	quintet
RCM	Ring Closing Metathesis
RT	Room Temperature
sept	septet
sex	sextet
s	singlet
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBAF	*tetra*-*n*-butylammonium fluoride
TEPA	Triethyl phosphonoacetate
TFA	Trifluoroacetic acid
TfOH	Trifluoromethansulfonic acid

THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
t	triplet
Ts	tosyl

1 Introduction

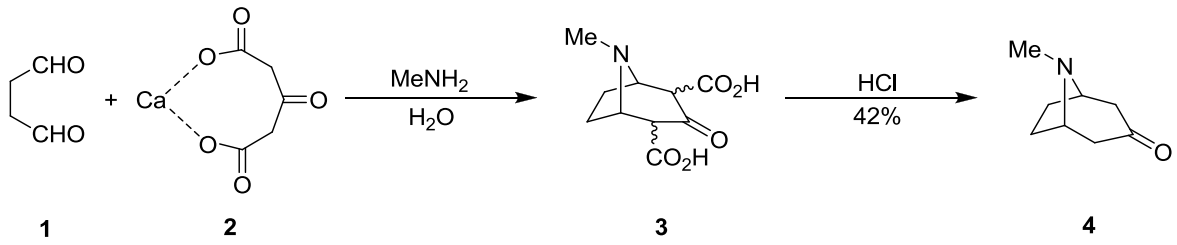
1.1 Cascade/Domino and Tandem Reactions

Organic chemistry utilises a number of methods for the preparation of an enormous range of chemicals e.g. pharmaceuticals, agrochemicals, petrochemicals, natural products and many other materials. These diverse synthetic methodologies along with their benefits have a substantial impact on the environment in terms of generating toxic waste. Modern synthetic organic chemistry demands atom economy, avoidance of hazardous reagents and reduction of waste along with excellent regio-, chemo-, diastereo-, and enantioselectivity.[1]

Over the past decades several new strategies have been applied for the synthesis of complex molecules to address the above demands. Tandem reactions are one example of those methods and have been reported extensively for the preparation of structurally diverse compounds. A variety of different terms such as domino, cascade, concurrent, or sequential processes have been used interchangeably to describe such reactions by different authors. Some independent efforts have been made to synchronize the terminology in this field on the basis of lexis. For example, according to Tietze[2] a "domino reaction is a process involving two or more bond-forming transformations (usually C-C bonds) which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step." A similar description came from Nicolaou[3] for the "cascade reaction" and it excludes all such processes in which the reaction conditions are altered during the process. Bazan[4] employed the term "sequential" and Winkler[5] used "tandem" in their reviews, for reactions which involve a combination of transformations that may operate independently and often require additional reagents or changes in reaction conditions but are carried out in a single reaction vessel without purification between steps. So cascade or domino should be used for the description of "uninterrupted simultaneous" reactions where as tandem is a more broad and frequent term for reactions which "follow one another".

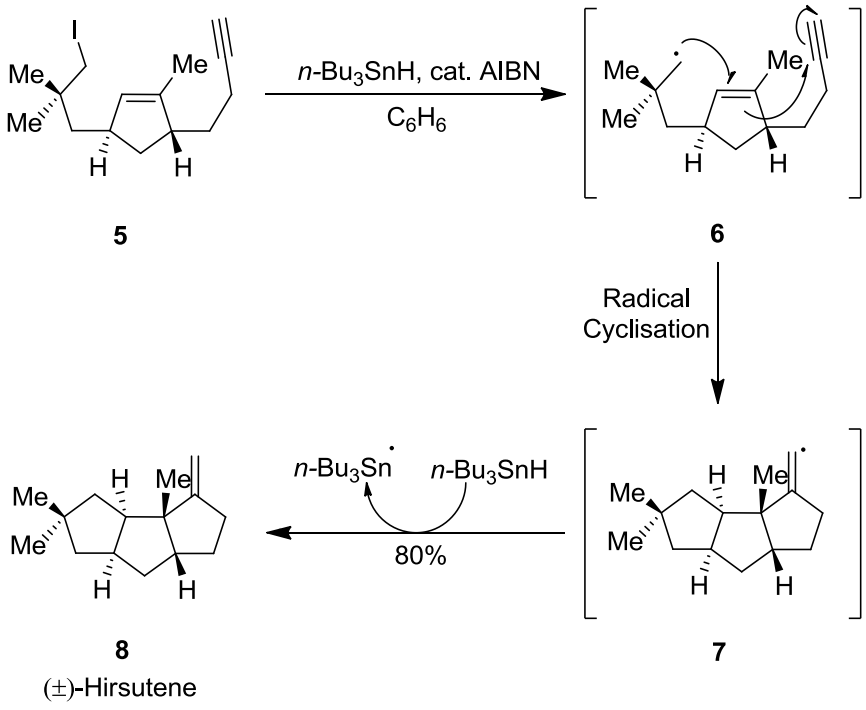
The utility of tandem processes is continuously growing because of their distinguished intervening steps. These processes allow multiple transformations in one synthetic operation, minimising the need of handling and isolating intermediates and improving the practical efficiency. Thus, the number of laboratory operations in terms of waste and resource management is decreased.[6]

The first tandem reaction appeared in the literature with Robinson's one-pot synthesis of tropinone in 1917 (Scheme 1).[7] He made use of the Mannich reaction in which a mixture of succindialdehyde **1**, methylamine, and calcium salt of acetonedicarboxylic acid **2** combines to give the bridged bicyclic tropinone **4**. However, the Mannich reaction itself can be quoted as a first tandem reaction, which involves the nucleophilic addition of an amine to a carbonyl group followed by dehydration to the Schiff base.



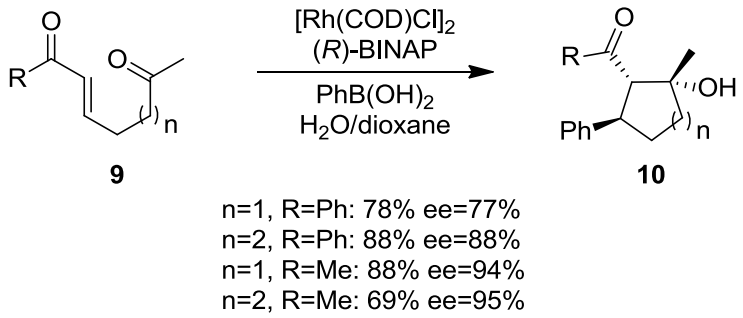
Scheme 1 - Robinson's total synthesis of tropinone

There are several classic examples of tandem reactions by various research groups that illustrate undeniable benefits of such transformations. Hirsutene **8**, which is a fungal metabolite and precursor of various antibiotic and antitumor compounds has been synthesised by a cascade radical approach.[8] It demonstrates the viability of the process by the formation of two rings via radical cyclisation of readily available precursor **6** in a single step (Scheme 2).



Scheme 2 - Cascade radical cyclisation in the total synthesis of (±)-hirsutene

Another elegant example of tandem conjugate addition-aldol cyclisation was reported by Krische and co-workers that established the role of tandem reactions in synthetic chemistry.[9] It enables the synthesis of penta- and hexa-cyclic rings from aromatic and aliphatic mono-enone and mono-ketone precursors. It relies on a highly diastereo- and enantioselective catalytic carbometallative aldol cycloreduction. It remarkably generates three stereogenic centres in a single reaction and has distinctive advantages over other asymmetric addition reactions. This methodology allows the process to be carried out in aqueous solvent and at moderate temperature without reducing the enantioselectivity. The reaction proceeds via transmetalation of an aryl group from boron to rhodium and then enone insertion into an aryl rhodium bond makes a rhodium enolate. A Zimmerman-Traxler transition state controls the stereoselectivity in the reaction, which on hydrolysis transforms the complex into the product **10** (Scheme 3).



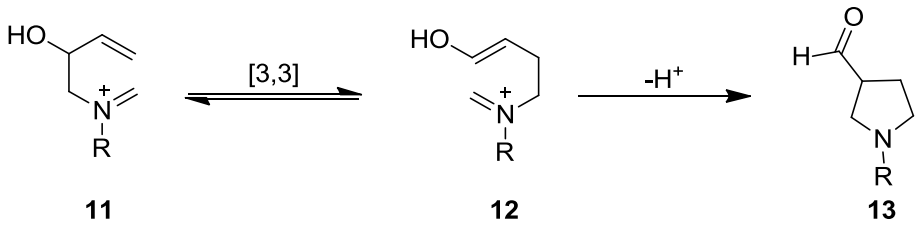
Scheme 3 - Diastereo- and enantioselective tandem conjugate addition-aldol cyclization

1.1.1 The Classification of Tandem Reactions

The classification of tandem reactions is difficult due to involvement of many distinctive steps. However, various authors have differentiated these processes on the basis of mechanism of each step.[2-4,10,11] Nicolaou and co-workers grouped such reactions into five sections with the name of nucleophilic, electrophilic, radical mediated, pericyclic, and transition metal catalysed processes.[3] However many others classified tandem reactions into cationic, anionic, radical, pericyclic and transition metal induced reactions. According to Tietze, combinations of reactions of the same mechanism are called homo-domino reactions; whereas sequences of reactions with different mechanisms are called hetero-domino reactions.[2] Various types of tandem reactions with their application in natural product synthesis have also been reviewed below.

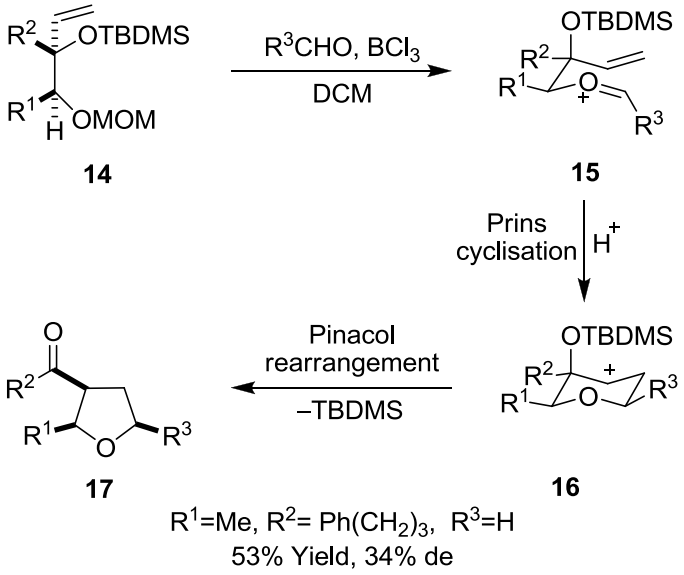
1.1.2 Cationic Tandem Reactions

Cationic tandem reactions are the oldest known tandem reactions. In this type of reaction, a carbocation is formed either by elimination or by addition of a proton. This carbocation further reacts with a nucleophile to produce a new carbocation. This transformation ends with the elimination of a proton or gets trapped with another nucleophile.[10] Various cationic tandem reactions have been developed and have played a great role in the development of natural product chemistry. Synthesis of substituted pyrrolidines by Overman's group can be placed under the heading of cationic tandem reactions (Scheme 4).[12] This involves the aza-Cope Mannich reaction and this approach solves formidable problems in natural product synthesis. In the first asymmetric total synthesis of (–)-strychnine this approach worked well to construct the pentacyclic strychnan core.[13]



Scheme 4 - Tandem aza-Cope Mannich Reaction

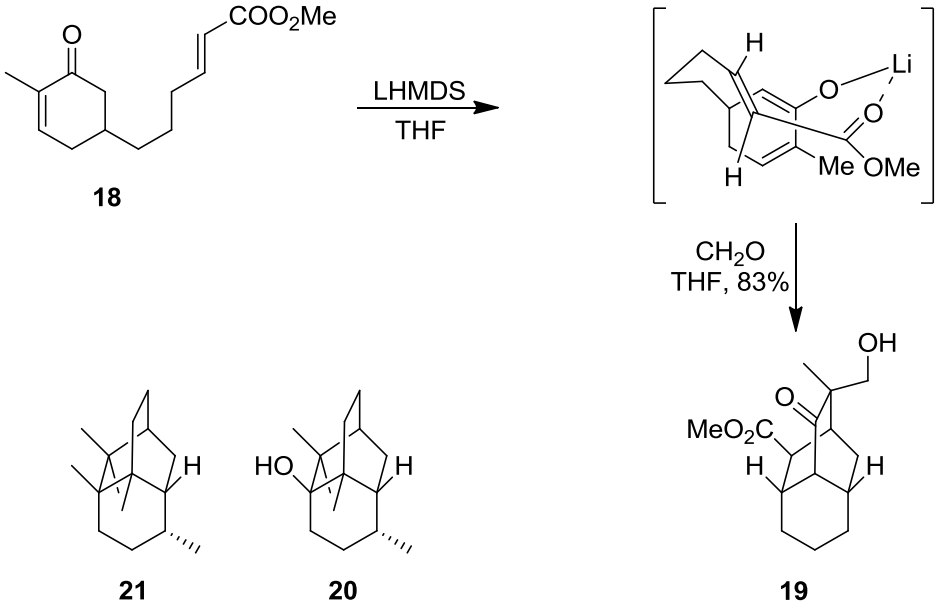
Lewis acid promoted pinacol-terminated Prins cyclisation is another excellent example of the cationic tandem reactions. This reaction builds functionality and stereochemistry in an acyclic fragment and helps synthesise various oxacyclic natural products by constructing a tetrahydrofuran from a carbonyl carbon of an aldehyde or ketone and an allylic diol (Scheme 5).[14] A large numbers of other cationic tandem reactions in different synthetic contexts have been reported with their undeniable benefits.[2,4,11]



Scheme 5 - Asymmetric tandem pinacol-terminated Prins cyclisation

1.1.3 Anionic Tandem Reactions

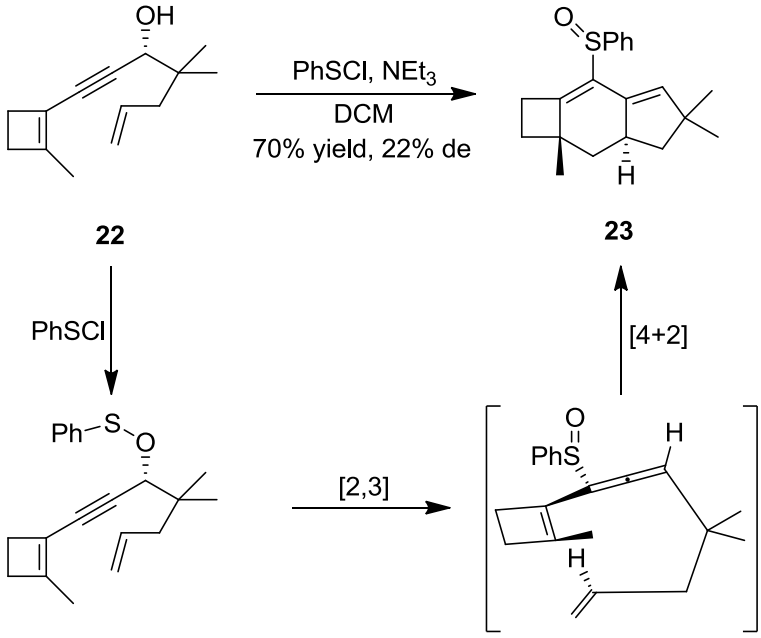
The anionic tandem reactions are the most common type of transformations in the literature. In this type of reaction, a carbanion is formed by deprotonation of a CH group. Thus, a newly formed carbanion attacks an electrophile to form anion functionality. This anion reacts with another electrophile in anionic-anionic fashion to complete the reaction.[11] Many anionic–anionic processes involve either a Michael-initiated or -terminated process to generate a cyclic structure. In the syntheses of many natural products it is very common to use Michael–Michael tandem reactions to generate cyclic systems. Several elegant examples of the anionic tandem reaction have been reported in the literature e.g. Robinson annulation, double Michael reaction, synthesis of oxygenated derivatives of the diterpene alkaloid atisine and the first total synthesis of the naturally occurring enantiomer of tylophorine.[15,16] Synthesis of tricyclo[5.3.1.0]undecane **19** from *E*-isomer **18** is an efficient example of tandem double Michael reactions for the construction of polycyclic systems (Scheme 6). Tricyclo[5.3.1.0]undecane **19** is a component of various important biologically active compounds e.g. patchouli alcohol **20** and seychellene **21** which have been used for the synthesis of taxol and for the treatment of the influenza virus.[17] The intramolecular double Michael reaction of the *E*-isomer **18** proceeds smoothly at –78 °C by the treatment with LHMDS and forms an intermediate, in which two oxygens complex to lithium. The resulting enolate reacts with gaseous CH_2O to give desired cyclised product **19** in 83% yield as a single stereoisomer (Scheme 6).



Scheme 6 - Anionic tandem reaction for the synthesis of tricycloundecane 19

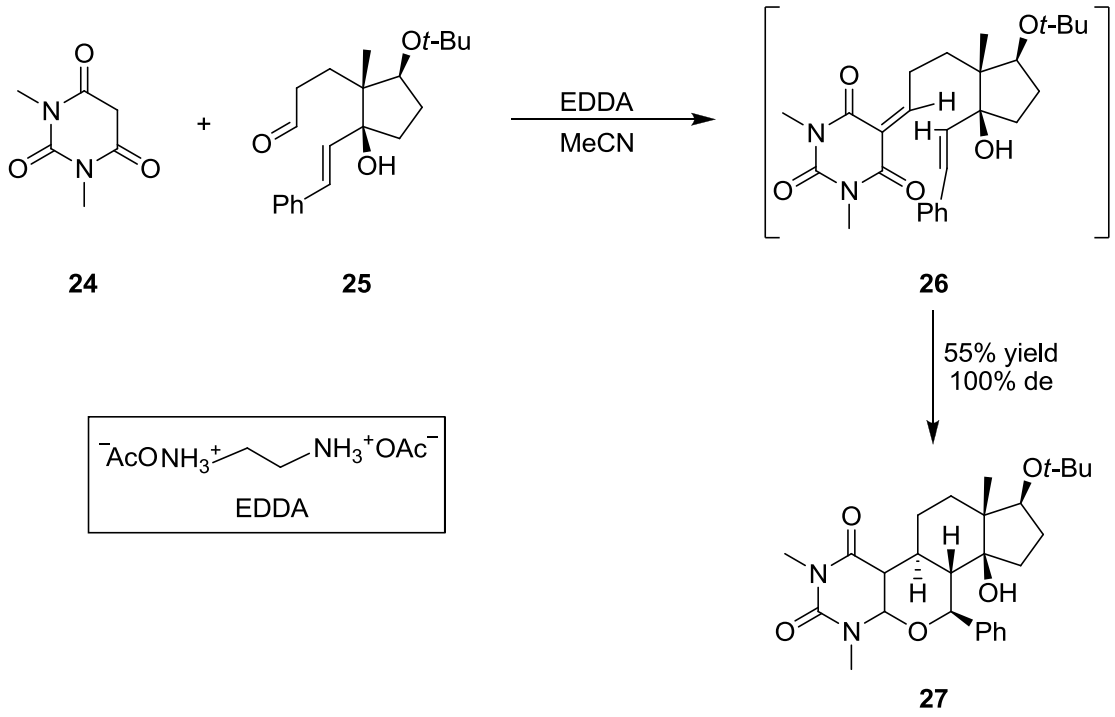
1.1.4 Pericyclic Tandem Reactions

In this type of tandem reactions, cyclic geometry is formed during the transition state and the reaction proceeds in a concerted fashion. The processes normally involve rearrangement reactions and a combination of different pericyclic reactions (Diels–Alder, Claisen, Cope, or electrocyclic reactions) or a combination of pericyclic reactions along with cationic and anionic reactions. The enantioselective synthesis of (+)-sterpurene is an example of a pericyclic tandem reaction (Scheme 7).[18]



Scheme 7- Asymmetric tandem [2,3]-sigmatropic shift/[4+2] cycloaddition reaction

Various anionic pericyclic reactions have been developed by the Tietze group and have been used for the synthesis of a range of biologically active natural products such as indole alkaloids, dihydrocorynantheine and heterosteroids, such as shown in Scheme 8.[19] Its synthesis involves the combining of enantiomerically pure cyclopentane derivative **25** with cyclic 1,3-dioxo compounds **24** through a Knoevenagel condensation. It makes use of catalytic amounts of ethylenediammonium diacetate (EDDA) to construct the alkylidene compounds **26**, which react in situ to make the heterosteroid **27**.[20]



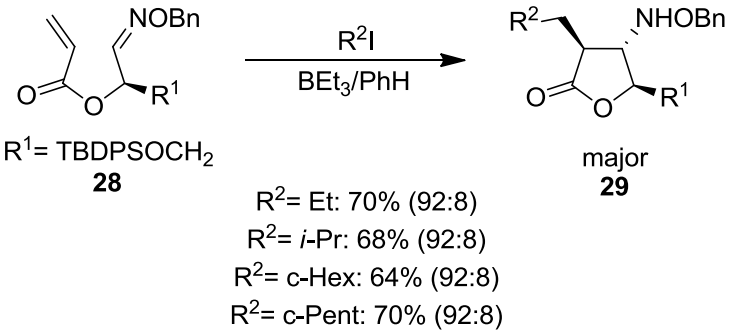
24 **25** **26** **27**

Scheme 8 - Synthesis of heterosteroids by tandem Knoevenagel hetero-Diels–Alder reaction

1.1.5 Radical Tandem Reactions

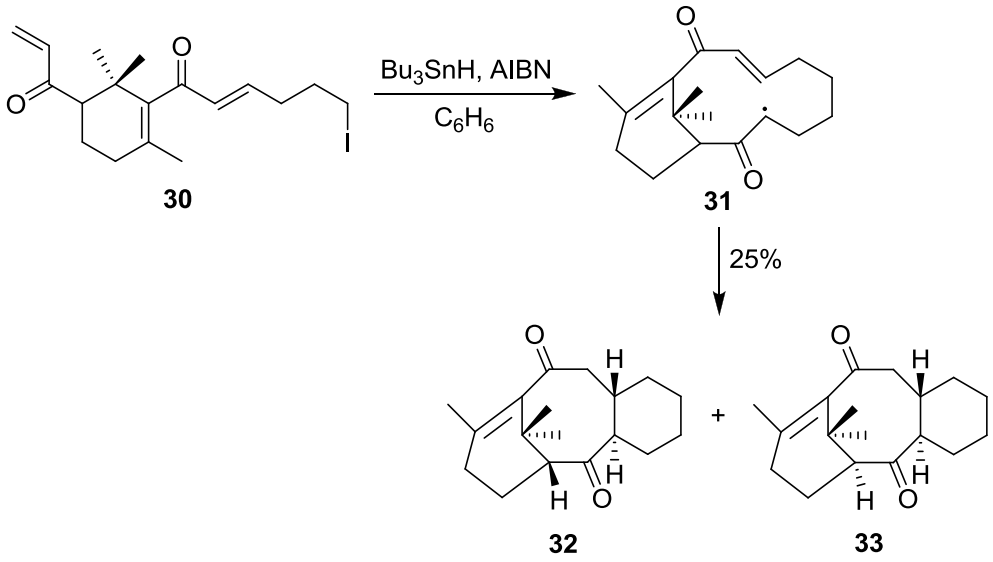
The majority of these types of reactions are homo-domino reactions. These reactions take place under mild reaction conditions to afford a wide range of functionalities.[10] Radical tandem reactions have been widely explored in organic chemistry for the synthesis of various bioactive targets.

γ-Butyrolactones and β-amino acids have been synthesized using radical addition-cyclisation reactions (Scheme 9).[21] The process generates two C–C single bonds and two stereogenic centers via a free radical-mediated Mannich reaction and provides direct access to the target molecule.



Scheme 9 - Asymmetric Mannich-type tandem radical addition cyclisation reaction

Synthesis of the taxane skeleton has been made using a tandem radical macrocyclisation-radical transannulation strategy. The synthetic design makes use of two conjugated enone moieties in substrate **30**, which facilitates the tandem cyclisation. It first undergoes a radical macrocyclisation with the aid of tributyltin hydride and AIBN to provide **31**, and then cyclises to **32** and **33** as a 3:1 mixture of two diastereomers of tricyclo[9.3.1.0]pentadecanedione respectively (Scheme 10).[22]



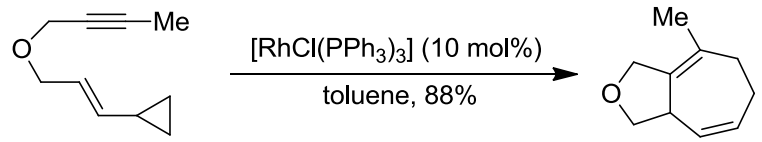
Scheme 10 - Tandem radical cyclisation for the synthesis of the taxane skeleton

1.1.6 Transition Metal Catalysed Tandem Reactions

Transition metal-catalysed tandem reactions are of great importance in synthetic organic chemistry. The discovery of the ability of transition metals to interact with organic moieties, to connect inter- or intra-molecularly to alkenes, alkynes, etc. in tandem processes was certainly a breakthrough in synthetic chemistry.[3] A plethora of ingenious transformations have been designed to assemble the target molecules using a variety of transition metals, especially palladium, ruthenium and rhodium catalysed tandem

reactions.[2] Almost 40 years ago, the first Pd(0)-catalysed vinylation of aryl halides appeared in the literature by Mizoroki and Heck but it could not find attention and remained unnoticed. In the last decade, this method has been turned into a powerful approach.[23] Amongst the palladium-catalysed carbon-carbon bond forming tandem reactions, the utility of Heck reaction for generation of tertiary or quaternary stereocenters and multiple-ring systems, even in sterically crowded environments, has been well documented.[23,24] Now the role of Pd catalysed cross-coupling transformations have been accepted as a reliable method and the Nobel prize for chemistry in 2010 was awarded to Heck along with Suzuki and Negishi.[25]

Transition metal catalysed tandem processes for the efficient synthesis of desired compounds are continuously growing e.g. synthesis of seven membered rings, namely [5+2]-cycloaddition between vinylcyclopropenes (VCPs) and π-systems using a Diels-Alder reaction with rhodium complexes have been investigated by Wender and co-workers (Scheme 11).[26] The scope of this reaction has been extended to alkenes, allenes, and even intermolecular processes.[27]

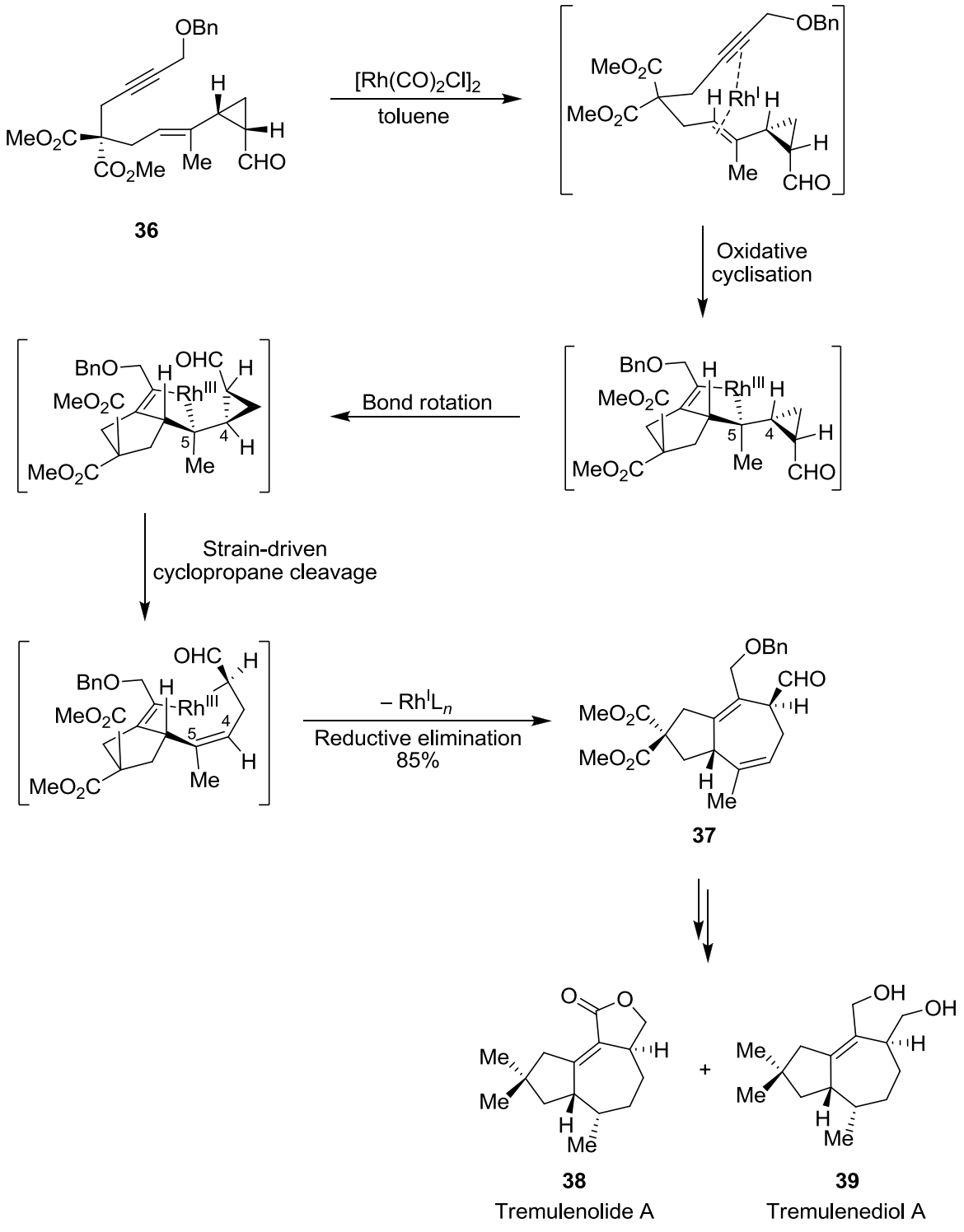


34 **35**

Scheme 11 - Rhodium-catalyzed [5+2]-cycloadditions

This methodology has begun to find application in the total synthesis of natural products. For example, Martin and Ashfeld made use of this approach for the enantioselective syntheses of tremulenolide A **38** and tremulenediol A **39**.[28] It involved the reaction of alkyne **36** and a dimeric rhodium species (10 mol%) under reflux which incited the series of events leading to the formation of two new rings and two new stereocenters in a complex diastereoselective fashion to yield bicyclic aldehyde **37** in 85% yield (Scheme 12). Initially Rh(I) coordinates to the alkene–alkyne faces of **36** followed by oxidative cyclisation to yield a Rh(III) metallacyclopentene. Subsequent bond rotation about the C4–C5 bond allows the strain driven cyclopropane cleavage to put together the carbon–rhodium and carbon–carbon bonds required for concerted ring expansion. It finally undergoes reductive elimination to yield bicyclic product **37** (Scheme 12). Use of this rhodium(I)-catalysed [5+2]-intramolecular cycloaddition leads to first enantioselective

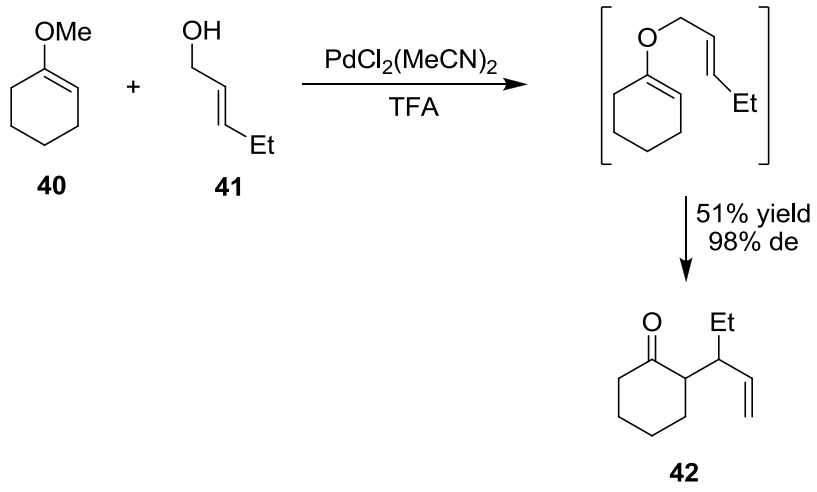
syntheses of the two representative tremulane sesquiterpenes tremulenolide A **38** and and tremulenediol A **39**.



Scheme 12 - Application to the total syntheses of tremulenolide A 38 and tremulenediol A 39

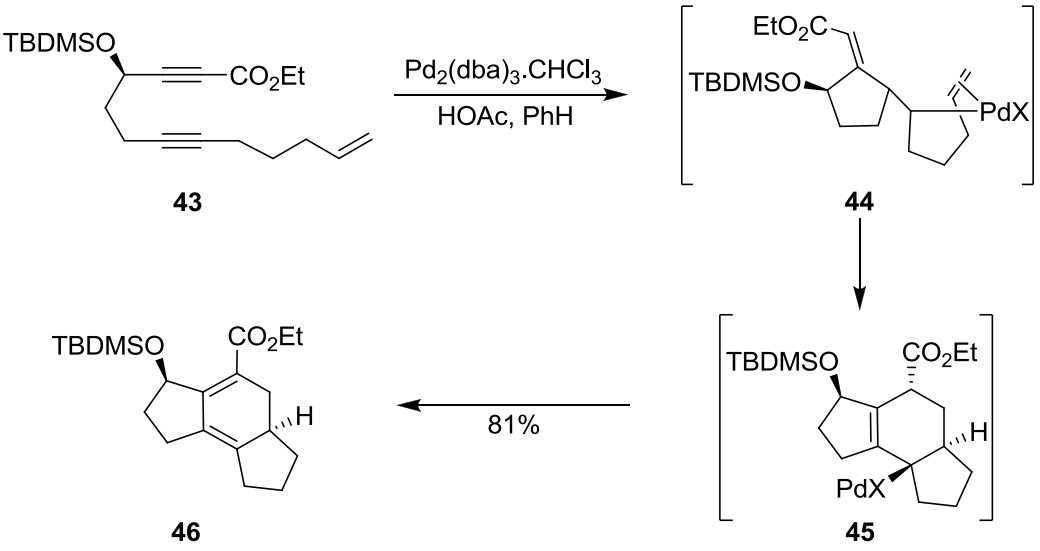
Nakai and co-workers were among the first to report palladium-catalysed tandem reactions.[29] For the synthesis of a γ,δ-unsaturated ketone, they made use of a Pd(II)-

catalysed step to generate the allyl vinyl backbone for the consecutive [3,3]-sigmatropic rearrangement (Scheme 13).



Scheme 13 - Asymmetric domino allylation-Claisen rearrangement reaction

The Trost group developed an outstanding approach that involves the Pd-mediated enediyne **43** cyclisation to construct the fused tricyclic structure **46** (Scheme 14).[30,31] High atom economy and excellent diasteteroselectivity are the signature characteristics of this transition metal catalysed tandem process. The reaction proceeds at room temperature and furnishes a single diastereoisomer in very good yield. To account for the high diastereoselectivity, a novel Diels-Alder cycloaddition of palladadiene **44** was proposed with cyclisation guided by minimization of steric interaction between the bulky silyl ether and the dienophilic side chain. The initial adduct **45** underwent 1,4-elimination of HPdX to afford the tricyclic product **46**.



Scheme 14 - Polycycle construction via transition metal catalyzed electrocyclic process

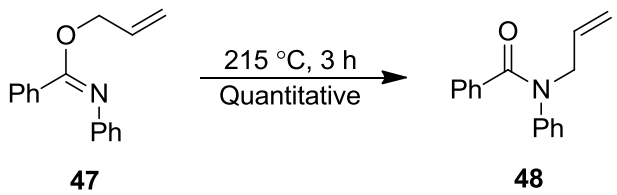
1.1.7 Conclusion to Classification of Tandem process

After the development of the ring opening/ring closing metathesis, cycloaddition, photochemical, metal catalysed and sigmatropic rearrangement processes, a wide variety of tandem reactions have been recorded in organic synthesis by combination of above and other methodologies together.[2] These synthetic designs construct rapid complexity in a molecule in a single flask starting from simple substrates. Its synthetic utility has blossomed remarkably into a powerful tool in terms of atom, waste and resource economy and shows synergistic interplay of reaction engineering to provide unique frameworks for target molecules.

The increasing number of publications and several reviews on the subject of tandem reactions highlight the splendid future of this field.[2-4] The development of new tandem processes by the combination of many distinctive processes such as the Overman rearrangement and metathesis steps for the synthesis of bioactive molecule is a vibrant area and research in this field continues apace in many research groups.[32]

1.2 Overman Rearrangement

The Overman rearrangement is a sub-type of the sigmatropic rearrangement of allylic imidates which involves the rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides from the readily available allylic alcohol.[33] The original idea for the rearrangement of allylic imidates can be traced back to Mumm and Möller who in 1937 reported the rearrangement of allylic benzimidate **47** to corresponding benzamide **48** during investigation of the mechanism of Claisen rearrangement (Scheme 15).[34] Following this result, several research groups reported the rearrangement of allylic imidates. However, the reaction was plagued by low yields and harsh conditions and could not find widespread use until the Overman modification.[33]

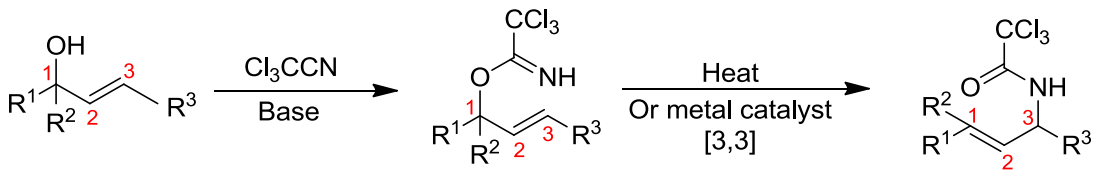


47 **48**

Scheme 15 - The rearrangement of an allylic benzimidate to an allylic benzamide

The Overman rearrangement is an important variant of the Claisen rearrangement and carries enormous potential due to the relative ease with which a wide variety of allylic

trichloroacetimidates can be prepared from corresponding alcohols. Transformation of the imidate to the amide is a unimolecular process and proceeds via a superafacial, concerted [3,3]-sigmatropic rearrangement. It involves the movement of a δ-bond from one place to another in a molecule to form a new δ-bond having a 3,3-relationship to the original bond (Scheme 16). The reaction is irreversible as the formation of the amide functionality is exothermic by 15 kcal mol^{-1}.[35,36] Regiospecificity and stereoselectivity are the characteristic features of the Overman rearrangement. Moreover, isolated yields for the rearrangement reaction are usually high. On hydrolysis, the allylic amines can be easily isolated allowing the synthesis of a variety of nitrogen containing compound like amino sugars, amino acids, nucleotides, *N*-heterocycles and natural products.[37]



49 **50** **51**

R^1, R^2, R^3 = H, Alkyl, Aryl; Metal catalyst = $Hg(OCOCF_3)_2$, $Hg(NO_3)_2$, Pd(II) Salts, AuCl

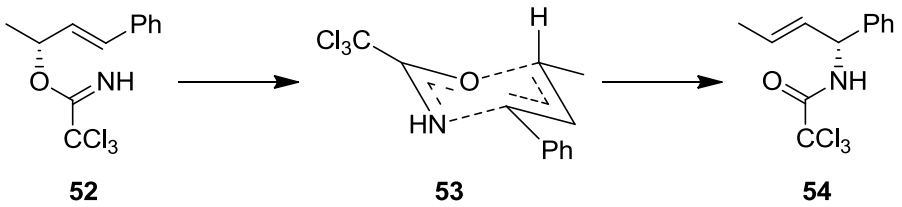
Scheme 16 - General overview of the Overman rearrangement

The course of the Overman rearrangement reaction is facilitated either thermally or by using a metal catalyst at room temperature which significantly increases the rate of the transformation.[38] The mechanism and scope of both methods have been studied thoroughly and are discussed below.

1.2.1 Thermal Overman Rearrangement

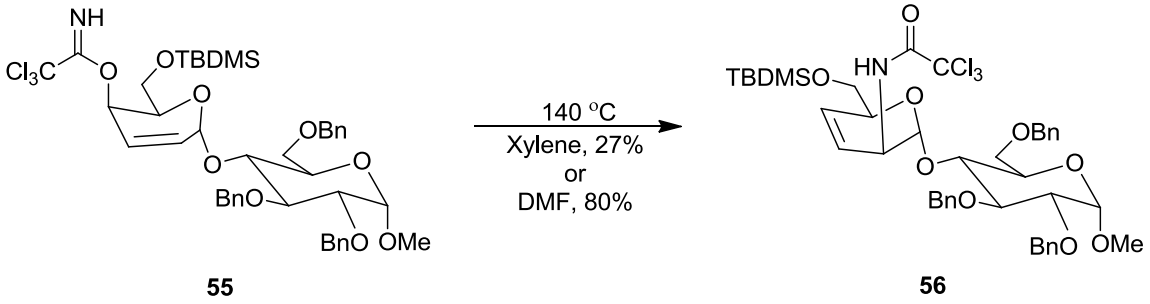
The thermal Overman rearrangement has broad scope and can be applied to a variety of primary, secondary and tertiary allylic alcohols. Mechanistically, the thermal Overman rearrangement is a pericyclic, concerted, suprafacial process. The reaction is irreversible, which is the result of the significant driving force associated with the formation of the amide functionality. It involves the formation of a highly ordered chair-like transition state **53** which facilitates the transfer of stereochemical information from the substrate to the newly formed σ-bond (Scheme 17). Complete transfer of chirality was observed first by Yamamoto and co-workers during the rearrangement of allylic trichloroacetimidate **52** of (1*E*,3*R*)-4-phenyl-3-buten-2-ol to (1*R*,2*E*)-trichloroacetamide **54** and supports the chair model that forms during the course of the thermal process.[39] This is the striking feature of

the Overman rearrangement and has been ingeniously utilised in a number of synthetic strategies,[40,41] thus making the reaction extremely useful in organic synthesis.



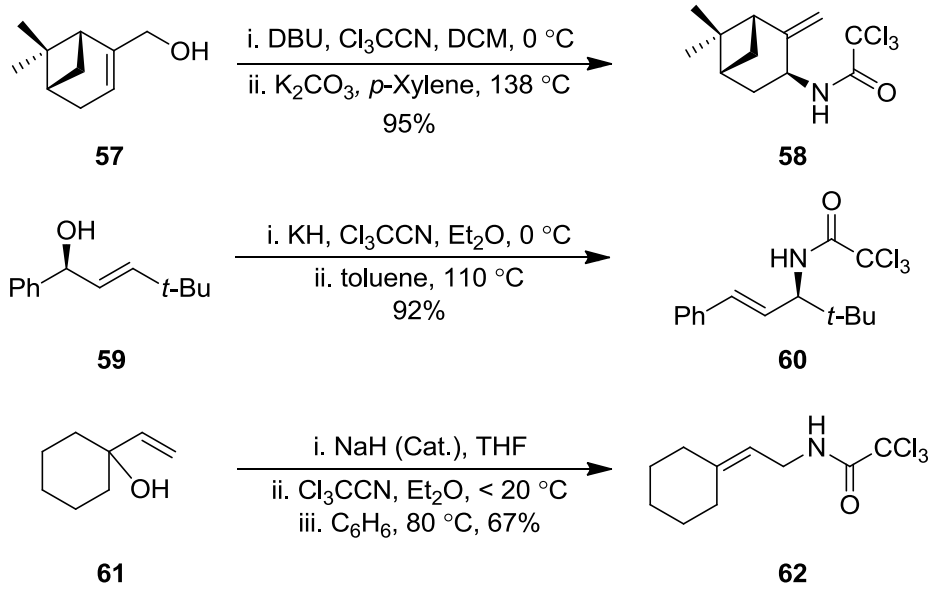
Scheme 17 - Thermal rearrangement of allylic trichloroacetimidates

Typically, the rearrangement is carried out at elevated temperature in aprotic aromatic solvents like toluene or xylene. However in some cases more polar solvents are preferred e.g. the rearrangement of dissaccharide trichloroacetimidate **55** in xylene gives only 27% yield, whereas the yield increases to 80% when the rearrangement is carried out in DMF. DMF is a more polar and basic solvent which enhances the rate of reaction and slows down the acid catalysed decomposition of the substrate to improve the yield of the reaction (Scheme 18).[42]



Scheme 18 - Effect of solvent over the yield of the Overman rearrangement

Normally primary allylic trichloroacetimidates rearrange at 140 °C in the range of 4-24 hours whereas secondary and tertiary allylic trichloroacetimidates proceed at 110 and 80 °C respectively in comparatively shorter reaction times. Allylic trichloroacetimidates derived from double allylic alcohols rearrange at further higher rate and at room temperature. Higher reaction rates at lower temperature for increasingly substituted allylic trichloroacetimidates are primarily due to stabilisation of positive charge that evolves on the oxygen bearing carbon in the transition state. A few representative examples are shown in Scheme 19.[43-45]



Scheme 19 - Representative examples of the Overman rearrangement

Steric and electronic factors play a major role in deciding the fate of the reaction towards the rate and yield of the Overman rearrangement, as it is totally substrate dependent e.g. *E*-alkenes react more quickly and give higher yields than the *Z*-alkenes which end up with some by-products and lower yields. This is attributed to low stability and higher heat of enthalpy of *Z*-alkenes in comparison to *E* alkenes.[38]

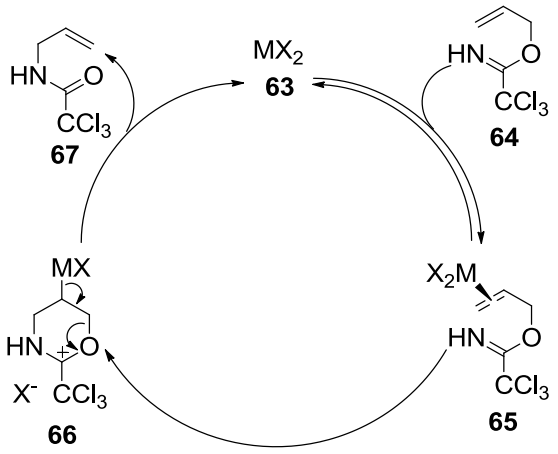
During the course of the Overman rearrangement some acid catalysed decomposition competes with the rearrangement, thus reducing the yield of the acid sensitive allylic trichloroacetamide. In 1998, Isobe and co-workers introduced an important modification in the thermal Overman rearrangement to avoid decomposition pathways.[46] They made use of potassium carbonate which dramatically increases the yield of the rearrangement. The presence of potassium carbonate (2 mg/mL) in the reaction mixture acts as an acid scavenger and traps any acid that may be generated during the thermal rearrangement. However it has been noticed, addition of other bases like DBU and *n*-Bu_3N could not inhibit acid catalysed decomposition. This simple modification has increased the scope of the reaction for previously nonviable rearrangements.

1.2.2 Metal catalysed Overman Rearrangement

The Overman rearrangement can also be carried out using metal catalysis. Various metals including palladium(0), palladium(II), rhodium(I), mercuric(II) and iridium(I) complexes catalyse the rearrangement of allyl imidates to allyl amides. The first report of a metal catalysed rearrangement of allylic trichloroacetimidates appeared in 1974 by Overman in

which he made use of mercuric trifluoroacetate. Use of mercury as a catalyst considerably increases the rate of the reaction to the order of 10^{12} in comparison to the thermal Overman rearrangement and allowed the reaction to proceed at room temperature. Later, different experiments demonstrated that soluble complexes of $PdCl_2$ are more efficient than the mercury catalysed rearrangements in term of yield, low catalyst loading and high reaction rate.[38] Very recently gold(I)-catalysed Overman rearrangement has been reported which can proceed in water under mild conditions.[47,48] More work is required to determine the scope of the gold(I) catalysed rearrangement.

Different research groups have worked extensively to determine the mechanism of the metal catalysed allylic rearrangement process.[49-52] The first account regarding the mechanism of the metal catalysed acetate migration in allylic acetates appeared by Henry.[53] Later, a similar explanation came from Overman to elucidate the mercury(II)-catalysed rearrangements of allylic carbamate and allylic imidates (Scheme 20).

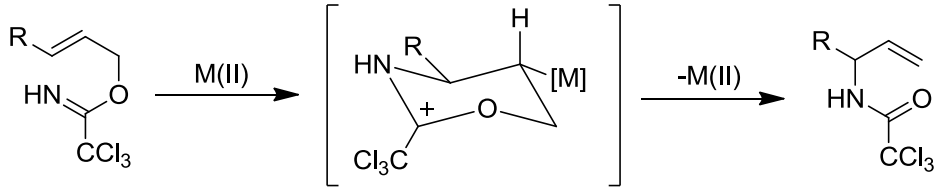


Scheme 20 - Mechanism of metal catalysed Overman rearrangement

The mechanism involves a cyclisation induced transition state in which metal **63** activates the allylic double bond of imidate **64** and allows the intramolecular nucleophilic attack by the imidate nitrogen to the *exo* face of alkene **65**. This leads to a six membered alkyl palladium intermediate **66** which readily rearranges to produce the product **67** and regenerates catalyst **63** (Scheme 20).[37,53-58]

Some reports show that during the reaction, the metal bound six-membered cyclic carbocation intermediate **69** adopts a chair-like conformation which minimises allylic strain by having the bulky metal complex at an equatorial position (Scheme 21). This chair-like transition state explains the formation of the new C-N bond towards the same

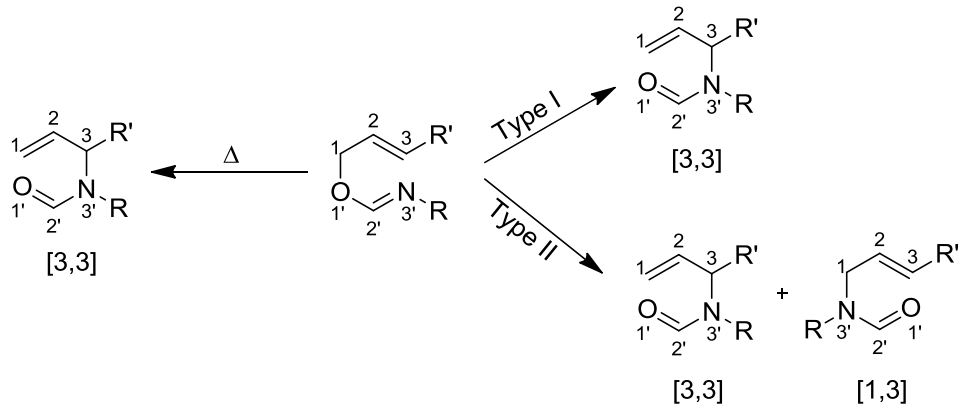
face of alkene where C-O bond breaks. Thus, chirality is transferred from reactant to product.[57]



68 **69** **70**

Scheme 21 - Chair-like transition state during metal catalysed Overman rearrangement

Metal catalysts for the rearrangement of allyl imidates can be classified into two types. Type I includes bi-valent complexes e.g. $Hg(CF_3CO_2)_2$, $PdCl_2(PhCN)_2$ and $H_2[PtCl_6]$. Such complexes give the same product as the thermal process i.e the [3,3]-sigmatropic product. Type II involves zero-valent complexes like $Pd(PPh_3)_4$ and $Pt(PPh_3)_4$ and give mixtures of [3,3] and [1,3]-sigmatropic rearrangements (Scheme 22).[59]



Scheme 22 - Rearrangements of allyl imidates by the thermal, type I and type II catalysts

Palladium(II) appeared as the most effective catalyst for the Overman rearrangement and exclusively generates the [3,3]-sigmatropic rearrangement product regioselectivity and with excellent stereoselectivity. As in the case of thermal Overman rearrangement, the metal catalysed process also proceeds more efficiently for *E*-alkenes. Pd(II) complexes have been used widely for the Overman rearrangement at room temperature with 4-8 mol% catalyst loading in aprotic solvents like THF and toluene.[55,60] Usually Pd(II)-catalysed Overman rearrangements work well for primary allylic trichloroacetimidates in comparison to secondary allylic trichloroacetimidate rearrangements and the process is completed in a few hours at or below room temperature.

1.2.3 Enantioselective Overman Rearrangement

Recently methods have been developed that allow the Overman rearrangement to be applied in asymmetric synthesis. Different types of catalyst have been synthesised by various research groups and have been reported with variable yields. Overman and co-workers were pioneers in developing the enantioselective Pd(II) catalyst for the rearrangement of allylic imidates.[61] Initially achiral diamine complexes of [$PdCl_2$(bpy)] and [$PdCl_2$(TMEDA)] were tried but these dichlorides could not catalyse any rearrangements.

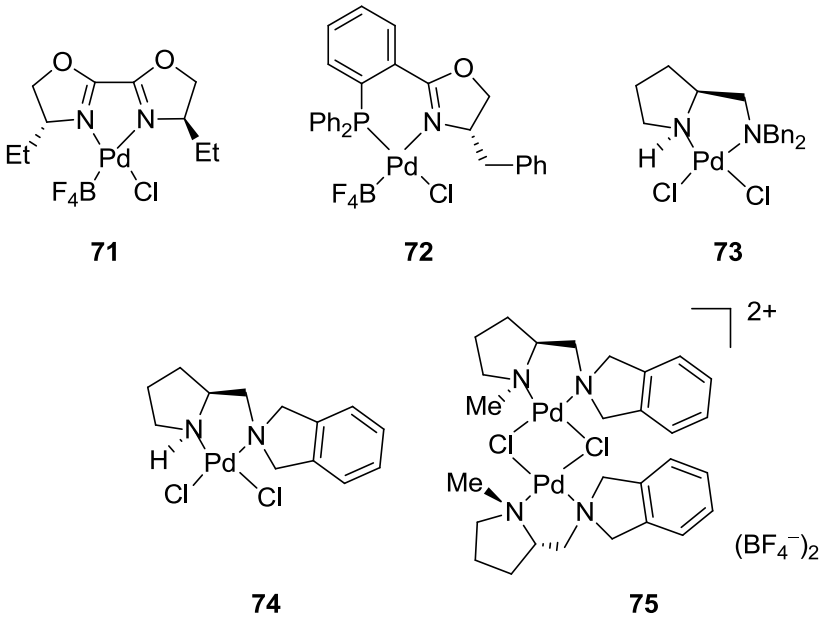
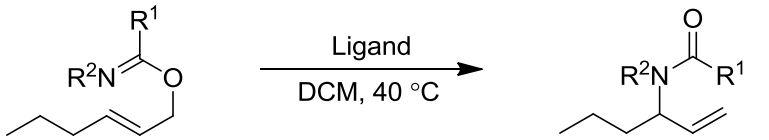


Figure 1 - First enantioselective Overman rearrangement catalysts

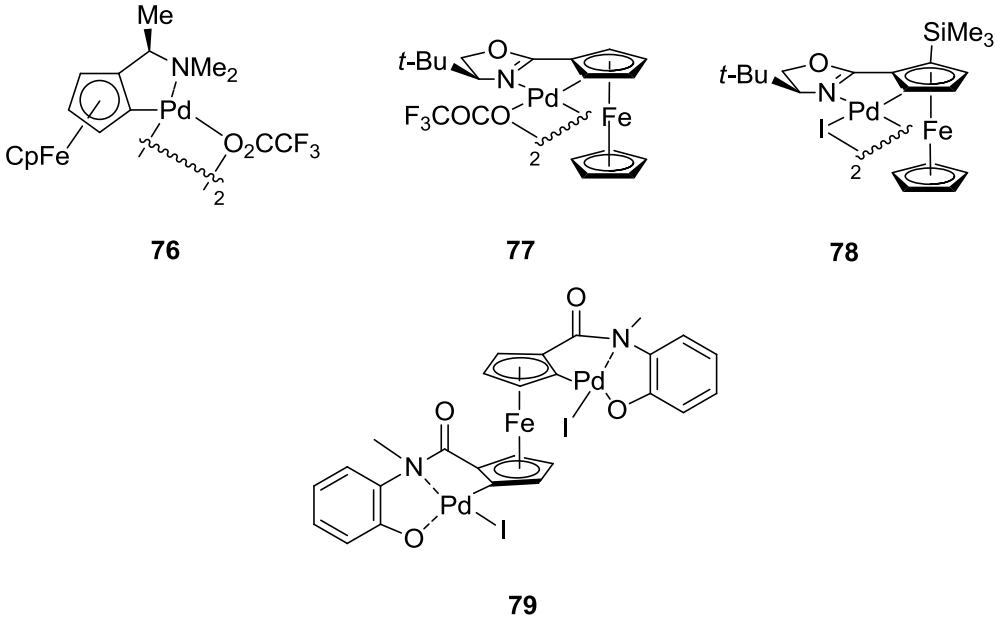
Extensive research by the Overman and Hayashi groups resulted in the form of a series of cationic oxazoline and cationic Pd(diamine) chiral catalysts (selected examples are shown in Figure 1).[61,62] These catalysts showed moderate to good yields and poor to moderate enatioselectivity (Table 1). However, in most cases Pd-diamine complexes proved incompatible. This was mainly due to coordination between the imidate nitrogen and the cationic palladium which caused undesired ionisation and elimination products in significant amounts.[56] While these results revealed that an asymmetric Pd complexes could effect an Overman rearrangement, further efforts were required.

Table 1 - Rearrangement of allylic imidiates catalysed by various catalysts shown in Figure 1



Entry	Ligand	R^1	R^2	Yield (%)	ee (%)
1	**71**	Ph	Ph	62	10
2	**72**	Ph	Ph	88	47
3	**72**	Ph	4-$CF_3C_6H_4$	41	76
4	**73**	Ph	Ph	no reaction	no reaction
5	**74**	Ph	Ph	80	16
6	**75**	Ph	4-$CF_3C_6H_4$	69	55
7	**75**	Ph	Ph	18	41

To circumvent ionisation and elimination pathways during the enantioselective allylic imidate rearrangements, a neutral catalyst was required to escape from any competing elimination reactions due to imidate nitrogen coordination with the cationic Pd. Subsequent studies by Overman and others revealed a series of neutral chiral palladacycles catalysts (Figure 2).[63,64]



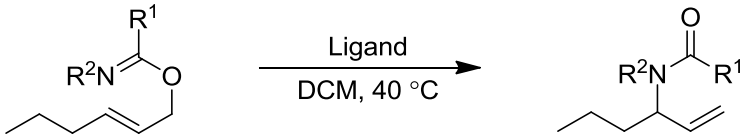
76 **77** **78**

79

Figure 2 - Neutral chiral and ferrocenyl oxazoline palladacycle catalysts

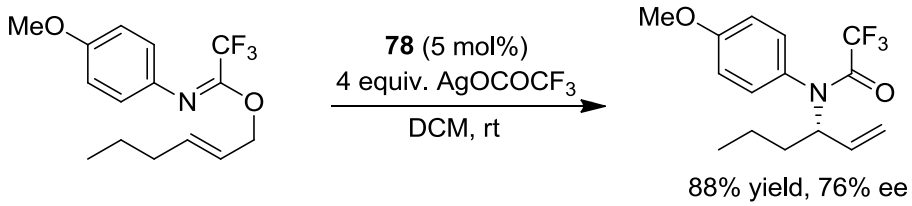
Many of them proved efficient catalysts for the [3,3]-sigmatropic rearrangement of allylic imidates to allylic amides in terms of yield and enantioselectivity, e.g. rearrangement of benzimidates was carried out using ferrocenyl palladacycles **76** without undergoing side reaction pathways in excellent yield and moderate enantioselectivity (Table 2).

Table 2 - Evaluation of ferrocenyl oxazoline catalysts for the Overman rearrangement



Entry	Ligand	R^1	R^2	Yield (%)	ee (%)
1	**76**	Ph	4-$CF_3C_6H_4$	97	57
2	**76**	Ph	Ph	47	47
3	**77**	Ph	4-$CF_3C_6H_4$	93	83
4	**77**	Ph	Ph	59	63

In an attempt to improve the enantioselectivity, Overman and co-workers synthesised various ferrocenyl oxazoline (FOP) catalysts. Many of those demonstrated promising yields and enantioselectivities, especially **77** which catalysed the rearrangement in moderate to excellent yields and enantioselectivities (Table 2). However the catalyst was limited in scope to benzimidate substrates and gave higher enantioselectivity for *Z*-alkenes. Further study elucidated much better catalysts e.g. **78** and **79**, having broad substrate scope along with good yields and enantioselectivity (Scheme 23). However, catalyst **78** still showed some drawbacks e.g. limited tolerance for cleavable protecting groups and required activation of the catalyst prior to use, employing 4 equivalent of $AgOCOCF_3$. Thus, this could not be adopted as a practical route to enantioenriched chiral allylic amines.[65,66]

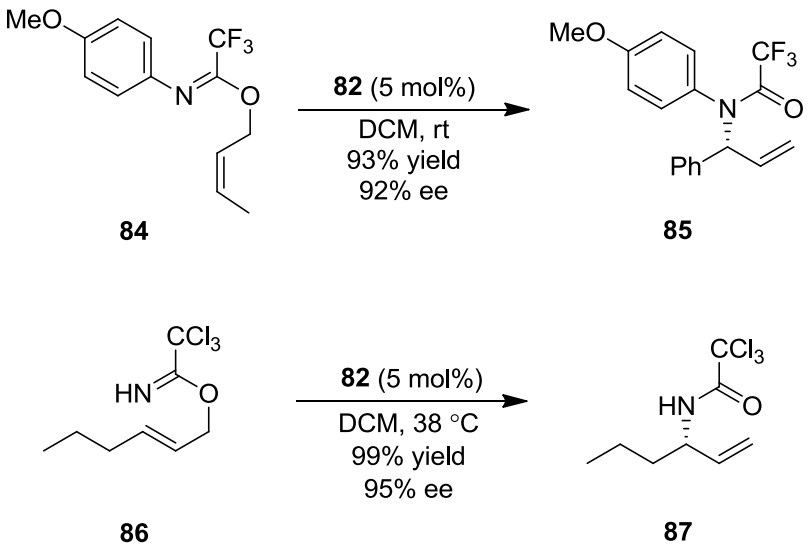


80 **81**

Scheme 23- Rearrangement using ferrocenyl oxazoline catalysts

Later cobalt oxazoline palladacycles **82** appeared as the catalyst of choice (Figure 3).[67] Kang and co-workers used COP for the rearrangement of *Z*-benzimidates **84** and reported excellent yields and enantioselectivities (Scheme 24).[68] At the same time, Overman and co-workers used COP for the rearrangement of *E*-allylic acetimidates **86** and showed rearranged products in 80–85% yield and in 92–96% ee. These reactions required 5 mol% of catalyst loading, which was further reduced to 2 mol% in certain cases and furnished the

product generally around room temperature, whilst maintaining excellent yield and enantioselectivity.[69,70]



Scheme 24- COP-Cl catalysed rearrangement of allylic trichloroacetimidates

Now COP-Cl has emerged as a powerful catalyst for the synthesis of of chiral allylic amines from achiral allylic alcohols and has found widespread application in organic synthesis. The COP-Cl catalysts **82** and **83**, have become popular catalysts and are commonly referred to as (*S*)-(+)-COP-Cl and (*R*)-(–)COP-Cl respectively (Figure 3).

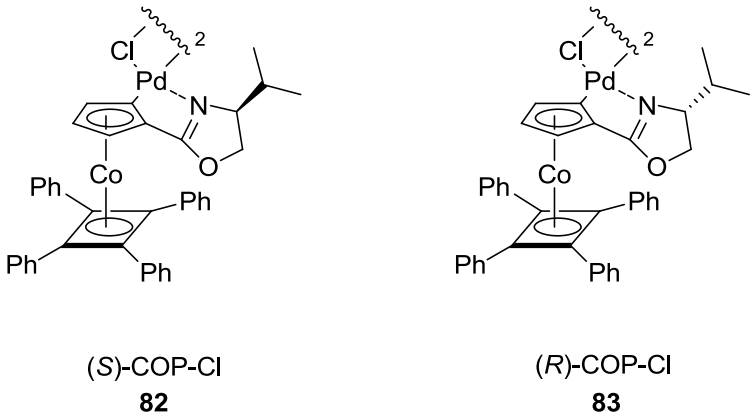


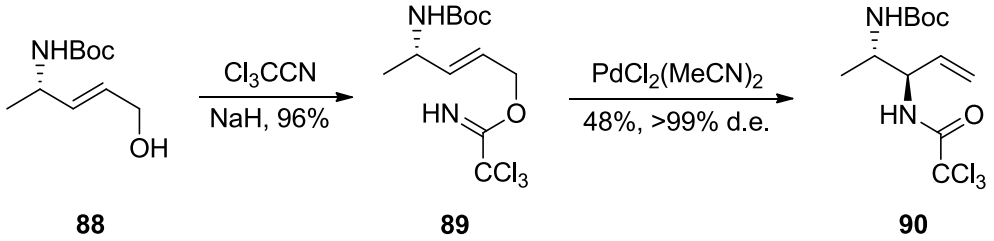
Figure 3- Commercially available asymmetric COP-Cl catalysts

1.2.4 Substrate directed Overman Rearrangement

The substrate directed Overman rearrangement is an important approach to introduce new stereogenic centres into a compound without employing a chiral catalyst. It is based upon the pre-association of the reacting partners in the proximity of the reaction centre to influence the stereochemical outcome of the rearrangement. Such interaction of the

reacting partners proceeds through a highly ordered transition state during the course of the transformation and elicits the stereoselectivity in the process. In the Overman rearrangement, use of an asymmetric centre having a polar functional group in the close vicinity of the reaction point directs the metal catalyst towards one face of the double bond in preference to other. This leads to a certain level of diastereoselectivity during the rearrangement process and excludes any need of chiral reagents to achieve this. The degree of diastereoselectivity can be variable as it depends upon the nature of directing group and reaction conditions.

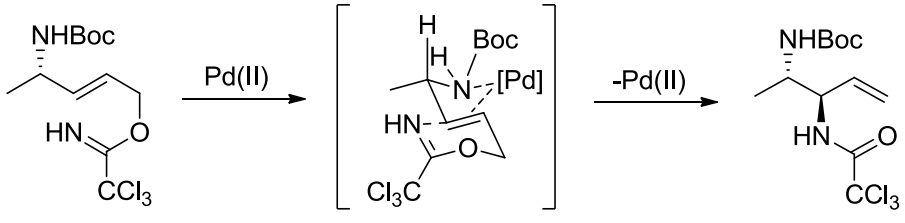
Work by the groups of Bellûs[71] and Sutherland[72] have demonstrated the substrate directing effect in the Overman rearrangement and showed various aspects of the process. The first example appeared in 1993, when Bellûs noticed the significant diastereoselectivity for the *anti*-diastereomer **90** during the palladium(II)-catalysed rearrangement of **89** (Scheme 25).



88 **89** **90**

Scheme 25- The first substrate directed rearrangement

Excellent *anti*-diastereoselectivity of this process was attributed to coordination of the palladium with the nitrogen atom and alkene during the rearrangement. This then adopts a chair-like conformation **91** and directs the catalyst towards the back face of the alkene and forcing the nitrogen atom of the trichloroacetimidate to attack from the other face leading to the major diastereomer (Scheme 26).



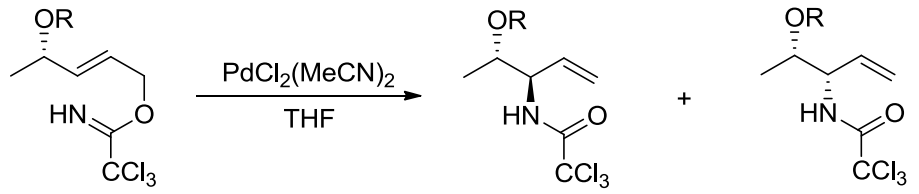
89 **91** **90**

Scheme 26- Coordination of nitrogen atom to Pd(II) directs the rearrangement

To evaluate the substrate directing effect of different ether functional groups in the Overman rearrangement process, a series of the experiments were designed by Sutherland

and co-workers.[72] Initially, the aim was to reveal the utility of the ether functional group as a directing group. A number of allylic trichloroacetimidates were prepared carrying different ether groups and subjected to the Overman rearrangement using bis(acetonitrile)palladium(II) chloride as the rearrangement catalyst. The methoxymethyl group appeared as the most efficient ether and allowed effective coordination with the metal catalyst and gave the *anti*-diasteromer as a major product with the ratio of 10:1. Bulky and encumbered ether groups plagued the coordination and as a consequence showed low diastereoselectivity (Table 3).[73,74]

Table 3 - Rearrangement of allylic trichloroacetimidate having different ethers

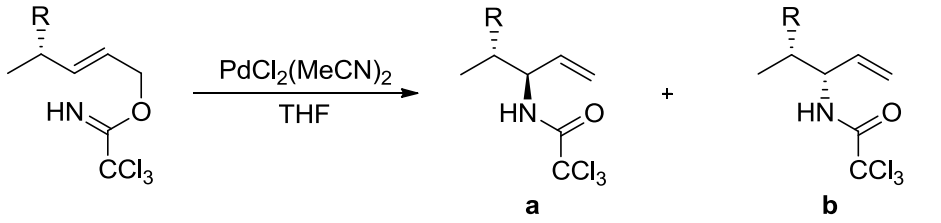


92 **93a** **93b**

Entry	R	yield (%)	Ratio (**a** : **b**)
1	TBDMS	68	2 : 1
2	Tr	70	3 : 1
3	Bn	62	3 : 1
4	Me	49	7 : 1
5	MOM	64	10 : 1
6	MEM	60	8 : 1

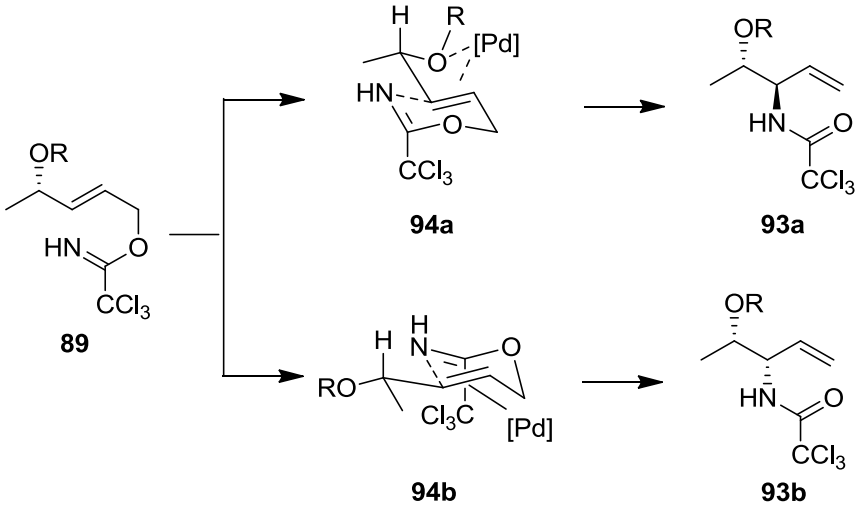
Further work by Sutherland and co-workers demonstrated the role of the oxygen atoms during the substrate directed rearrangement and established that presence of the oxygen atoms adjacent to alkene as vital for high levels of diasteroselectivity (Table 4).[72] Results from the carefully designed strategy clearly demonstrate that presence of two oxygen atoms increases the diastereoselectivity. It is mainly due to enhanced coordination between the Pd(II)-metal catalyst and the oxygen atoms of the MOM group.

Table 4 - Pd(II)-catalysed rearrangement of the MOM-analogues



Entry	R	yield (%)	Ratio (**a** : **b**)
1	OCH_2OCH_3	64	10 : 1
2	$CH_2CH_2CH_2CH_3$	59	1 : 2
3	$OCH_2CH_2CH_3$	77	5 : 1
4	$CH_2CH_2OCH_3$	60	1 : 2

It was postulated that the significant *anti*-diastereoselectivity of this process is due to coordination of Pd(II)-catalyst with the oxygen atoms of the MOM group and these direct the catalyst selectively to the back face of the alkene and in this way the compound adopts a chair-like conformation.[72] This conformation not only minimises the allylic strain but also allows intramolecular attack of the imidate nitrogen from the front face of the alkene, thus giving major diastereomer **93a** (Scheme 27). Minor diastereomer **93b** is likely formed via **94b** in which the ether group is unable to coordinate to the catalyst and is further away from the reaction centre. Thus, the catalyst coordinates directly to the least hindered face of the double bond and furnishes the minor diastereomer.

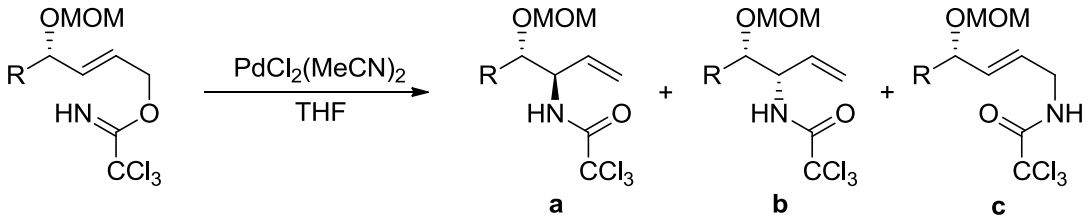


Scheme 27 - Reacting conformation that leads to the major and minor diastereomer

The scope and limitations of the substrate directed rearrangement was also investigated by the Sutherland group.[75] Initially several MOM protected allylic trichloroacetimidates with a variety of side chains were prepared and subjected to a substrate directed Overman

rearrangement (Table 5). In most cases the reaction proceeded to the *anti*-diastereomer as the major product. It was noticed that rearrangements of sterically hindered allylic trichloroacetimidates proceeded slowly and gave significant amounts of the [1,3]-rearrangement product while showing good diastereoselectivity (except entry 2 in Table 5, which showed no directing effect and give the [1,3]-product). It was attributed to extra steric impediments and due to Pd(0) that was formed in the reaction due to a competing β-elimination process during the slow Pd(II)-catalysed rearrangement of the allylic imidate. It has already been established by the work of Ikariya and Bosnich that Pd(II) gives only the [3,3]-product whereas Pd(0) furnishes the [1,3]-product.[56,57] This was further confirmed by addition of *p*-benzoquinone into the reaction mixture which forced the formation of the [1,3]-product (Table 5).[76]

Table 5 - Rearrangement of allylic trichloroacetimidates having different side chains

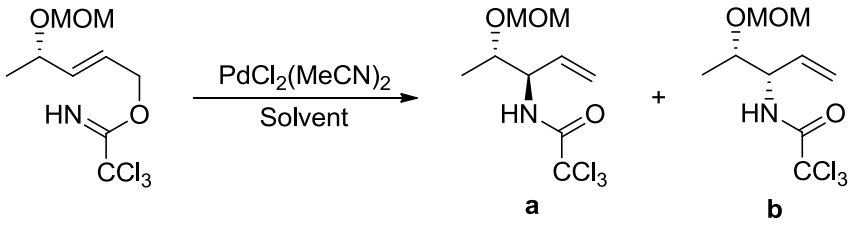


Entry	R	Additive	Yield (%)	Ratio (**a** : **b** : **c**)
1	Me	---	64	10 : 1 : 0
2	^{i}Pr	---	58	0 : 1 : 2
3	^{i}Bu	---	60	14 : 1 : 1
4	$PhCH_2$	---	54	12 : 1 : 0
5	$PhCH_2CH_2$	---	65	9 : 1 : 4
6	^{i}Bu	*p*-benzoquinone	73	14 : 1 : 0
7	$PhCH_2$	*p*-benzoquinone	70	12 : 1 : 0
8	$PhCH_2CH_2$	*p*-benzoquinone	69	9 : 1 : 0

The Sutherland group have also investigated different metal catalysts for the substrate directed Overman rearrangement. A range of metal complexes were employed to catalyse the rearrangement. Best results observed were with the use of Pd(II), Pt(II) and Au(I), whereas $NiCl_2$ and $Cl_2Ru(PPh_3)_3$ did not show any catalytic activity. Further work was employed to investigate any role of solvent on the origin of directing effect in the rearrangement of allylic trichloroacetimidates.[73] Several solvents were screened and results are listed in Table 6. Enhancement of selectivity was observed in the case of non-coordinating solvents e.g. toluene gave significant diastereoselectivity in the ratio of 15:1, whereas coordinating solvents such as the ionic liquid, 1-butyl-3-methylimidazolium tetrafluoroborate decreased the diastereoselectivity. These results clearly demonstrate that

use of a coordinating solvent disrupts the binding of the catalyst to the MOM ether group and diminishes the directing effect while non-coordinating solvents such as toluene minimise competition for the coordination leading to a selective process.[75]

Table 6 - Rearrangement of allylic trichloroacetimidates using various solvents



Entry	Solvent	Reaction time (h)	yield (%)	Ratio (**a** : **b**)
1	THF	24	64	10 : 1
2	Et_2O	24	47	12 : 1
3	MeCN	24	32	9 : 1
4	CH_2Cl_2	24	49	12 : 1
5	Toluene	24	56	15 : 1
6	$(BMI)BF_4$	148	37	5 : 1

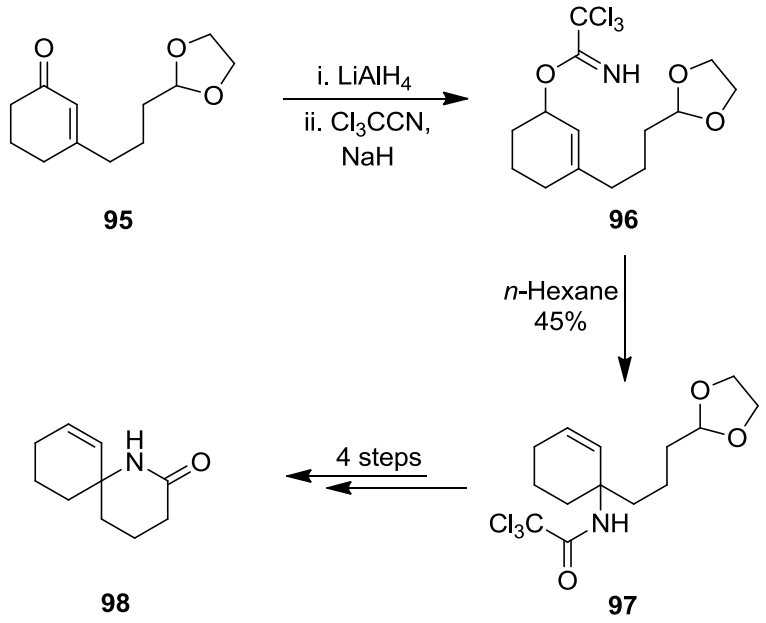
On the basis of the above discussed results, the substrate directed Overman rearrangement can be regarded as an excellent substitute for chiral catalysts for a diastereoselective rearrangement. Generally MOM-ether groups switch on the selectivity while non-coordinating solvents further enhance the directing effect. Recently, substrate directed rearrangements have been reported as excellent methodology to generate diastereoselectivity in the synthesis of various natural products.[40,77,78]

1.3 Applications of Overman rearrangement

The Overman rearrangement has been central to the synthesis of a broad range of biologically active precursors including various amino acids, selective enzyme inhibitors and a variety of natural products. Ready access to allylic amines with complete transfer of chirality is the signature characteristic of this process. Several dozen applications of the Overman rearrangement have been reported and this number is continuously growing.[77,78]

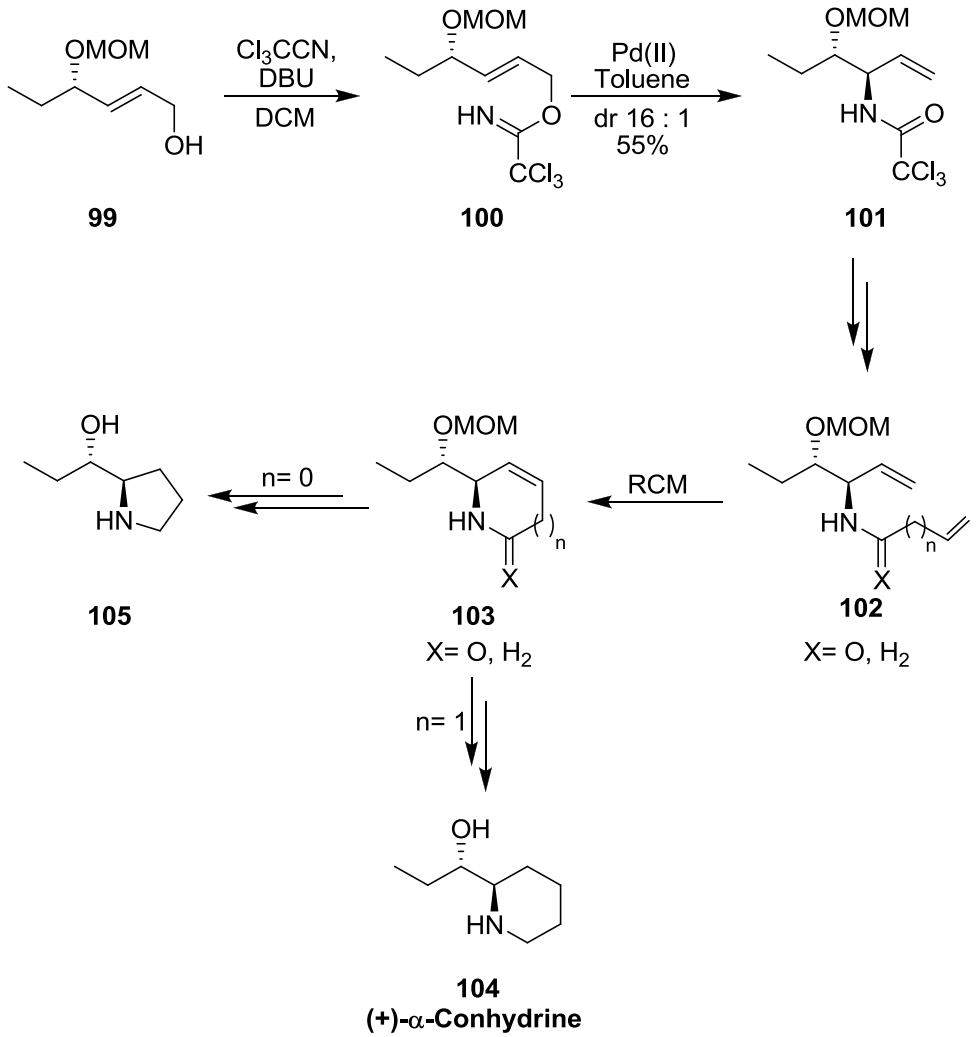
The first application appeared in the literature by Overman for the synthesis of 1-azaspiro[5.5]undec-7-en-2-one **98**.[79] Such structures show their presence in a wide range of naturally occurring molecules and exhibit a broad range of important pharmacological activities.[80] Overman designed a short and general route for the unsaturated spirolactam **98** by utilising his developed thermal rearrangement process (Scheme 28). The substrate for the Overman rearrangement was synthesised by converting readily available ketone **95** into

an alcohol. This alcohol was reacted with sodium hydride followed by trichloroacetonitrile to afford allylic trichloroacetimidate **96** and directly rearranged to allylic trichloroacetamide **97.** The rearranged product was hydrolysed to remove the acetal protecting group, which was directly followed by oxidation to afford carboxylic acid. Hydrolysis of the trichloroacetyl group with base, followed by removal of water and esterification gave the corresponding ester which underwent concomitant cyclisation to afford the spirolactam **98**. The yield of the amide was low in this synthesis but it illustrated the potential of the Overman rearrangement.



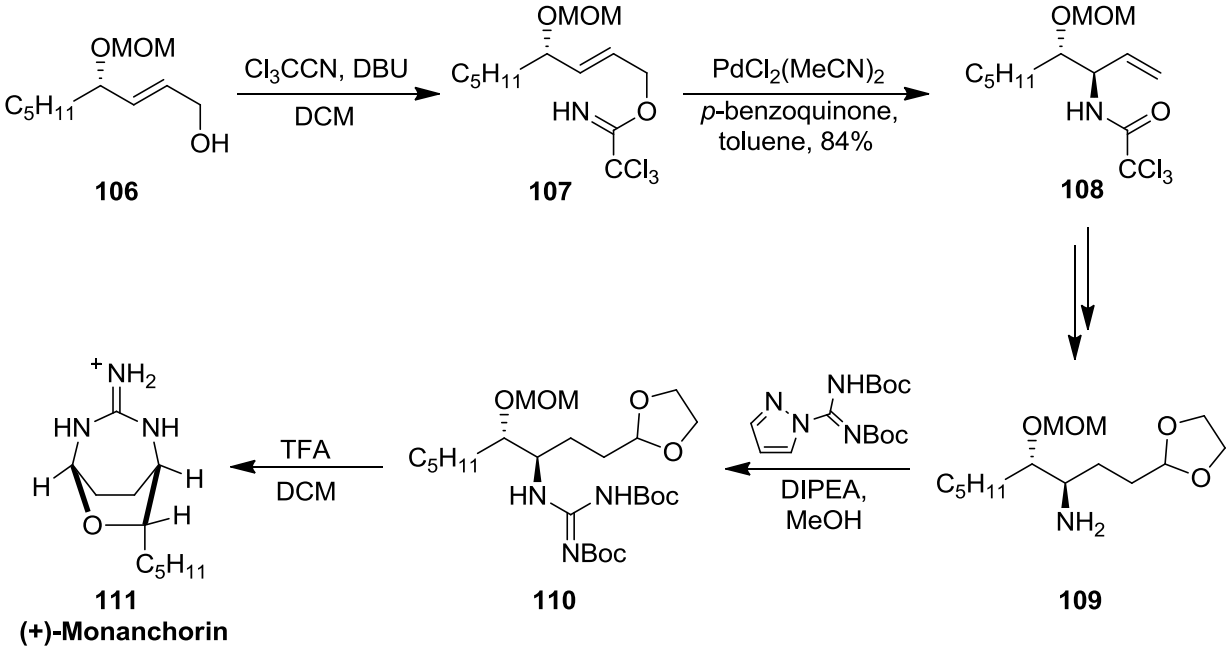
Scheme 28 - Overman synthesis of 1-azaspiro[5.5]undec-7-en-2-one 98

Recently the Sutherland group used the MOM ether directed Overman rearrangement for the stereocontrolled synthesis of several biologically active molecules and precursors of unnatural amino acids. For example, it has been employed for the synthesis of alkaloid natural product (+)-α-conhydrine **104** and its analogue **105** (Scheme 29).[78] These are biologically active alkaloids and are famous for their antitumor and antiviral properties.[81] In this synthesis, the key substrate was prepared from allylic alcohol **99** using DBU and trichloroacetonitrile. It was followed by a Pd(II)-catalysed Overman rearrangement to generate *erythro*- and *threo*- trichloroacetamide in a ratio of 16:1 respectively. In the next stage the major diastereomer was further functionalised to give diene **102**. Ring closing metathesis of **102** followed by hydrogenation, reduction and acid-mediated removal of the protecting group yielded target molecule **104** and its pyrrolidine analogue **105**.



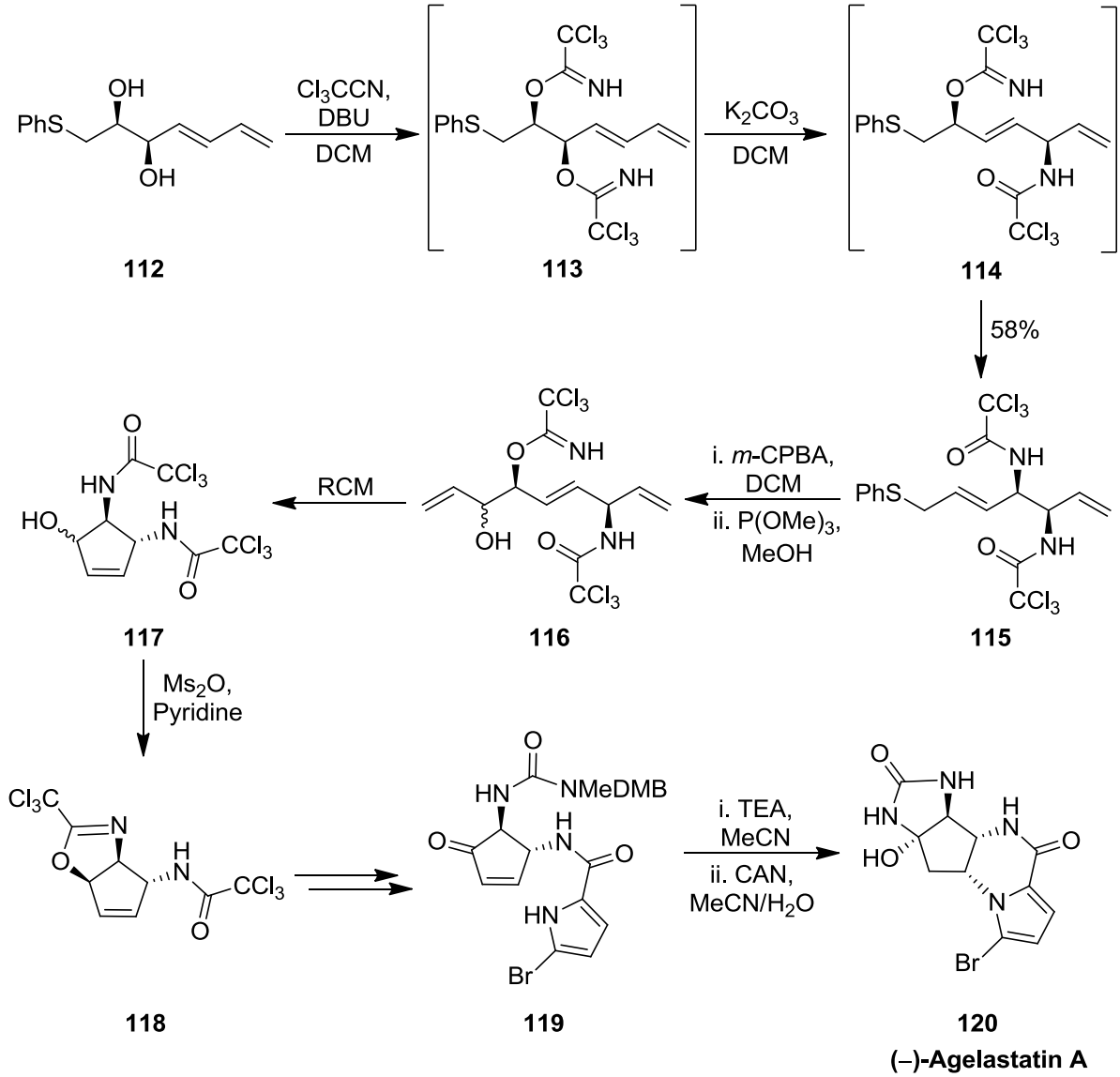
Scheme 29 - Synthesis of (+)-α-conhydrine using a substrate directed rearrangement

Similar methodology was utilised for a stereoselective synthesis of (+)-monanchorin **111**.[40] In this approach the allylic trichloroacetimidate **107** was converted to allylic trichloroacetamide **108** using a bis(acetonitrile)palladium(II) chloride catalysed Overman rearrangement in 84% yield over two steps (Scheme 30). MOM-ether directed Overman rearrangement gave two diastereomers in ratio of 12:1. Trace amount of the 1,3-rearrangement product was also isolated in the reaction mixture. It was avoided by the use of *p*-benzoquinone, which reoxidised Pd(0) to Pd(II) that forms *in situ* due to competing β-elimination in the reaction mixture of bulky substituents. The trichloroacetyl group of the major diastereomer was replaced with the Cbz-protecting group and cross metathesis was employed to couple 2-vinyl-1,3-dioxolane to construct the backbone of (+)-monanchorin. Amine **109** was coupled with the readily available guanidine unit to give **110** in 87% yield. Here TFA was employed for deprotection of the aldehyde, guanidine and hydroxyl groups to generate the natural product **111** in 75% yield.



Scheme 30- Synthesis of (+)-monanchorin using a substrate directed rearrangement

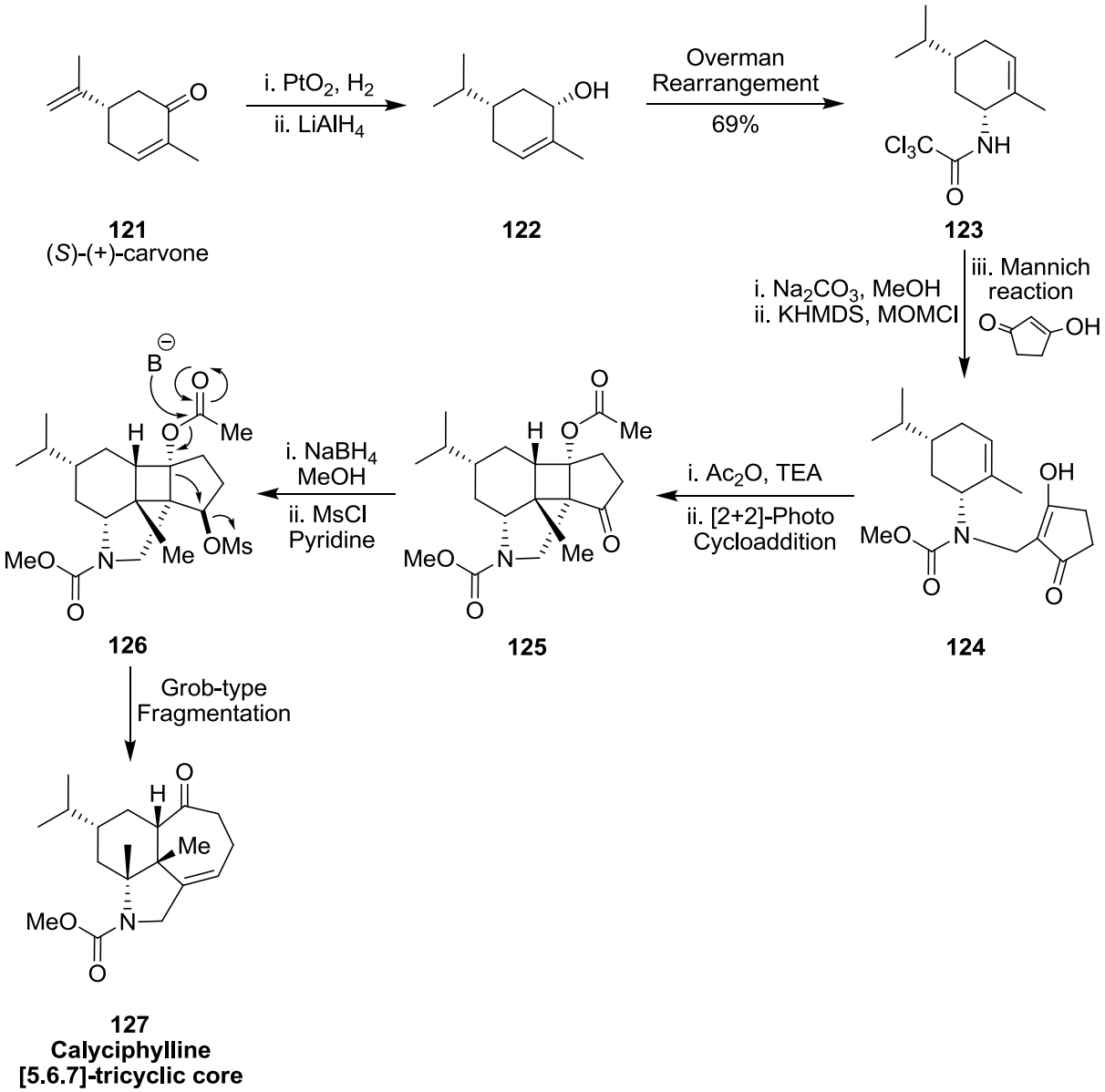
Chida and co-workers reported the use of the suprafacial nature of the Overman rearrangement to transfer chirality for the synthesis of enantiomerically pure (–)-agelastatin A **120** (Scheme 31).[82] It is recognised as an antimetastatic agent and also acts as an inhibitor of a number of human tumor cell lines.[83,84] In designing the route for the synthesis of this target, the two nitrogen substituted stereocenters were achieved by the Overman rearrangement of **112** in a single operation. It was followed by a Mislow-Evans rearrangement of an allylic sulfide to create a hydroxyl group on the main core. Ring closing metathesis followed by treatment with methanesulfonic anhydride of **117**, generated the oxazoline **118** in good yield. Further functionalisation of oxazoline **118** produced the α,β-unsaturated ketone **119**. It was then exposed to TEA to induce the aza-Michael addition followed by cleavage of 2,4-dimethoxybenzyl group with CAN to afford (–)-agelastatin A **120**. This very elegant synthetic approach by Chida made use of the concerted nature of the Overman rearrangement as a powerful tool for the transfer of chirality from an allylic alcohol to a newly formed diamino moiety in a complex natural product.



Scheme 31 - Synthetic strategy toward (–)-Agelastatin A

Very recently Wang and co-workers disclosed the stereoselective synthesis of a [5.6.7]-tricyclic ring system **127**.[85] This structure is commonly found in a range of the *Daphniphyllum* subclass *Calyciphylline* A-type alkaloids, especially those in calyciphylline A, daphnihlaucins, daphnilongeranins, and daphniyunnines.[86] The daphniphyllum class of alkaloids are very recently reported natural products and their biological and pharmacological properties still need to be clarified. To achieve the synthesis of this fascinating target, the Overman rearrangement was devised as a key step in the proposed strategy. The substrate for the Overman rearrangement was prepared from commercially available (*S*)-(+)-carvone (Scheme 32). It was easily converted to allylic alcohol **122** and then subjected to a standard Overman rearrangement to yield allylic trichloroacetamide **123**. After methanolysis of the resulting allylic trichloroacetamide, the amide nitrogen was functionalised with the MOM group. This set the stage for the Mannich condensation with

cyclopentanedione to give enone **124**. It was further followed by acylation and a [2+2]-photochemical cycloaddition, which resulted in the Mayo-type diketone structure **125**. The [5.6.7]-tricyclic core skeleton **127** was completed through Grob-type fragmentation after reduction and mesylation of carbonyl ketone **125**, to give the target molecule. The chirality in **123** developed through Overman rearrangement played a vital role to control the four contiguous stereogenic centres on cyclobutane ring **125** during the photochemical cycloaddition step.



Scheme 32 - Synthesis of [5.6.7]-tricyclic Core

1.3.1 Conclusions

The Overman rearrangement has been established as an effective approach in the total synthesis of natural products and in many other interesting molecules. The recent advances

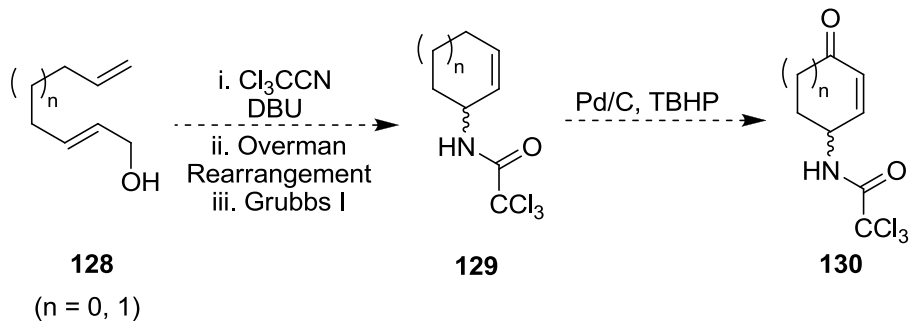
in the substrate directed rearrangement and chiral Pd(II)-catalysis to effect asymmetric allylic trichloroacetimidate rearrangements has played an enormous role in enhancing the scope of the Overman rearrangement. Moreover, a combination of the Overman rearrangement with other developed methodologies e.g. ring closing metathesis can be a substantial development to assist in the synthesis of even more complex molecules.

2 Aims and Objectives

The prime objective of this PhD research programme is to develop new methodology by utilising a one-pot, two-step tandem process involving an Overman rearrangement and a ring closing metathesis reaction for the quick and efficient synthesis of various simple and substituted cyclic allylic trichloroacetamides from the corresponding allylic alcohols. The next stage is to study the oxidations of the resulting carbocyclic amides for the stereoselective synthesis of valuable precursors for the construction of structurally diverse antiviral and anticancer carbocyclic nucleosides, aminocyclitols and Amaryllidaceae alkaloids.

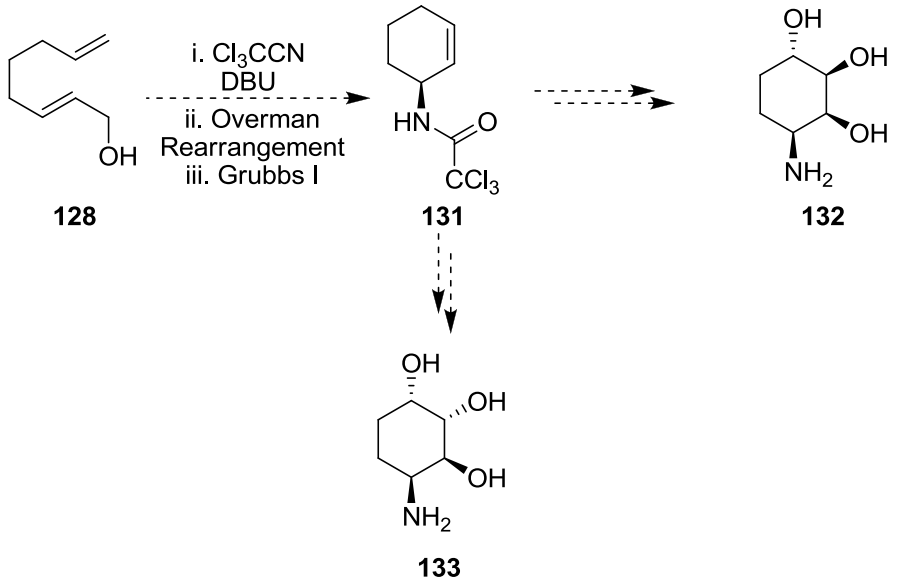
In all of the studied projects, the basic strategy involves the synthesis of various allylic alcohols from commercially available alcohols using a one pot Swern oxidation and Horner-Wadsworth-Emmons reaction followed by DIBAL-H reduction. These were then to be subjected to a one-pot, two-step tandem process involving an Overman rearrangement and a ring closing metathesis reaction for the quick synthesis of cyclic allylic trichloroacetamides. Finally, different oxidation techniques such as allylic oxidation, epoxidation and dihydroxylation were then to be studied to efficiently provide the valuable desired targets.

In the first part of the research project, allylic alcohol **128** was to be synthesised and be subjected to a one-pot, two-step tandem process to synthesise carbocyclic amide **129**. Resulting carbocyclic amide **129** would then be subjected to allylic oxidation to yield the amino substituted carbocyclic ketone **130** (Scheme 33).[87] If this reaction proved to be successful, it would provide a highly efficient synthetic route to variable ring sizes of valuable carbocyclic ketones.



Scheme 33 - Proposed synthesis of amino substituted cycloketone 130

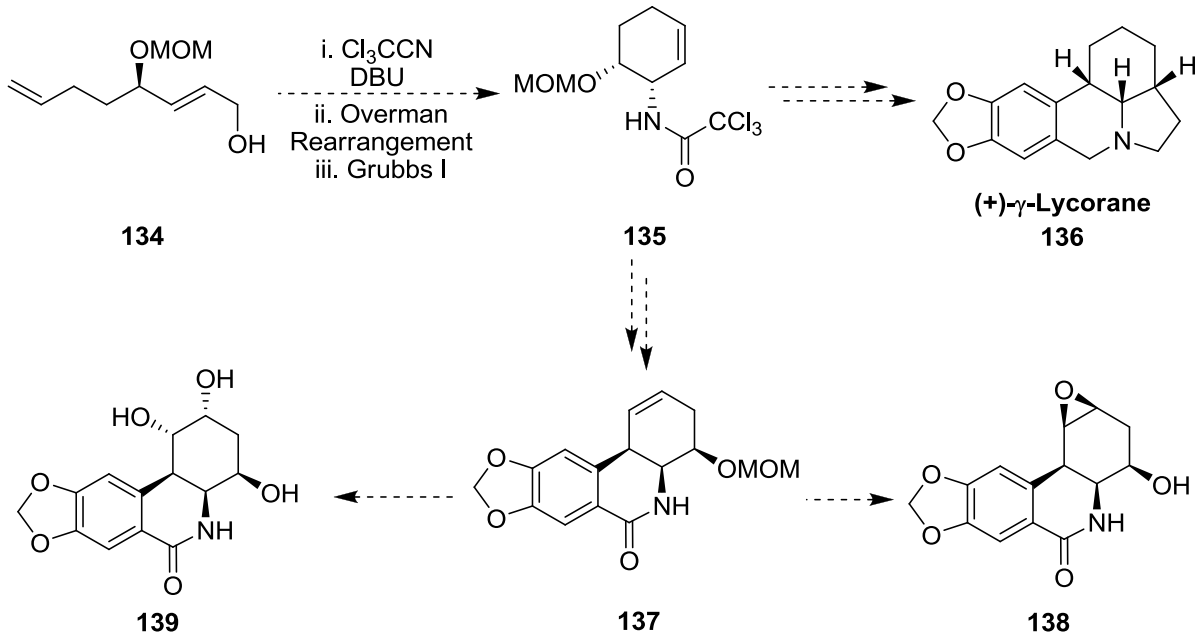
Following the development of an expeditious route to carbocyclic ketones, our aim was to undertake the highly stereoselective synthesis of aminocyclitols such as dihydroconduramine E-1 **132** and the enantiomer of dihydroconduramine C-1 **133**. It was proposed to make use of a stereoselective variant of the one-pot tandem Overman rearrangement and ring closing metathesis step for the asymmetric synthesis of an (*S*)-*N*-(cyclohexenyl)trichloroacetamide **131**, and then to explore the stereoselective epoxidation and dihydroxylation of this synthetic intermediate for the preparation of dihydroconduramines **132** and **133** (Scheme 34). As such, a new method for the synthesis of polyhydroxylated aminocyclohexane derivatives would be of significant benefit to synthetic chemistry. It would also broaden the scope of the tandem process, allowing it to be employed for the synthesis of a wider variety of natural products.



Scheme 34 - Proposed route to polyhydroxylated aminocyclohexanes

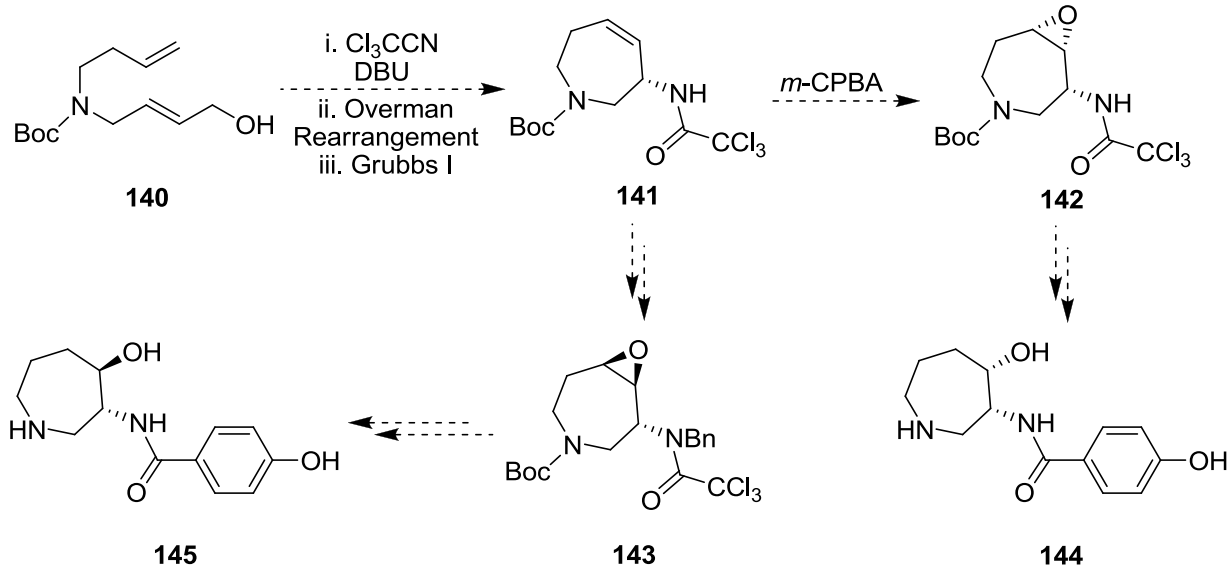
In the second part of this PhD programme, a one-pot tandem process involving a substrate-directed Overman rearrangement and ring closing metathesis reaction was to developed for the stereoselective synthesis of a functionalised carbocyclic allylic trichloroacetamide. The plan was to make use of a MOM-ether directed Overman rearrangement and combine it with a ring closing metathesis step to construct key synthetic intermediate **135** and utilise it in order to synthesise Amaryllidaceae alkaloids such as (+)-γ-lycorane **136** and *syn*-(4a*S*,10b*S*)-phenanthridone carbon skeleton **137** (Scheme 35). The synthesis of *syn*-(4a*S*,10b*S*)-phenanthridone carbon skeleton is significant as its stereoselective epoxidation and directed dihydroxylation would provide the polyoxygenated phenanthridone framework and would lead to the preparation of novel analogues of 7-deoxypancratistatin.

They can serve as significant synthetic scaffolds in organic synthesis as similar (+)-7-deoxypancratistatin exhibited strong activity against human cancerous cell lines.[88]



Scheme 35 - Proposed synthesis of (+)-γ-lycorane and 7-deoxypancratistatin analogues

In the final part of this research project, further studies were to be carried out to expand the scope of the one-pot tandem process to include heterocyclic derived substrates. This would provide an attractive route to synthesise a seven-membered carbocyclic amide, which would be subjected to epoxidation to access the hexahydroazepine core of balanol (Scheme 36). Balanol is a PKC-inhibitor of cellular signal transduction pathways.[89-91]



Scheme 36 - Proposed synthesis of the balanol core structure

3 Results and Discussions

3.1 Synthesis of Carbocyclic Ketones

3.1.1 Introduction

Amino substituted cyclopentenone is the well-known building block of a vast majority of important naturally occurring carbocyclic nucleosides.[92] Various natural carbocyclic nucleosides and their analogues occupy a prominent position in famous marketed drugs by virtue of their useful antibiotic and antitumor activities. These include AZT (zidovudin), known for its antiviral activity against HIV, and acyclovir (zovirax), most commonly used as an antiviral drug against Herpex simplex.[93] Aristeromycin[94] **148** and neplanocin[95] **150** are naturally occurring carbocyclic nucleosides and are recognised for their broad-spectrum antiviral and antitumor activities. However, they exert a profound toxic effect on the cells and have limited clinical applications. Some well known carbocyclic nucleosides are shown in Figure 4.

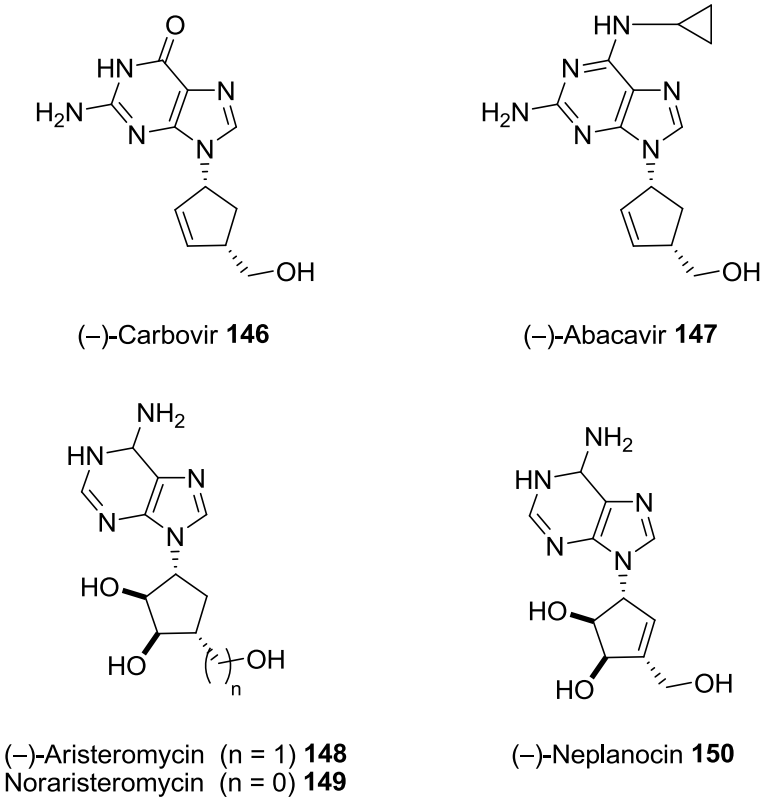
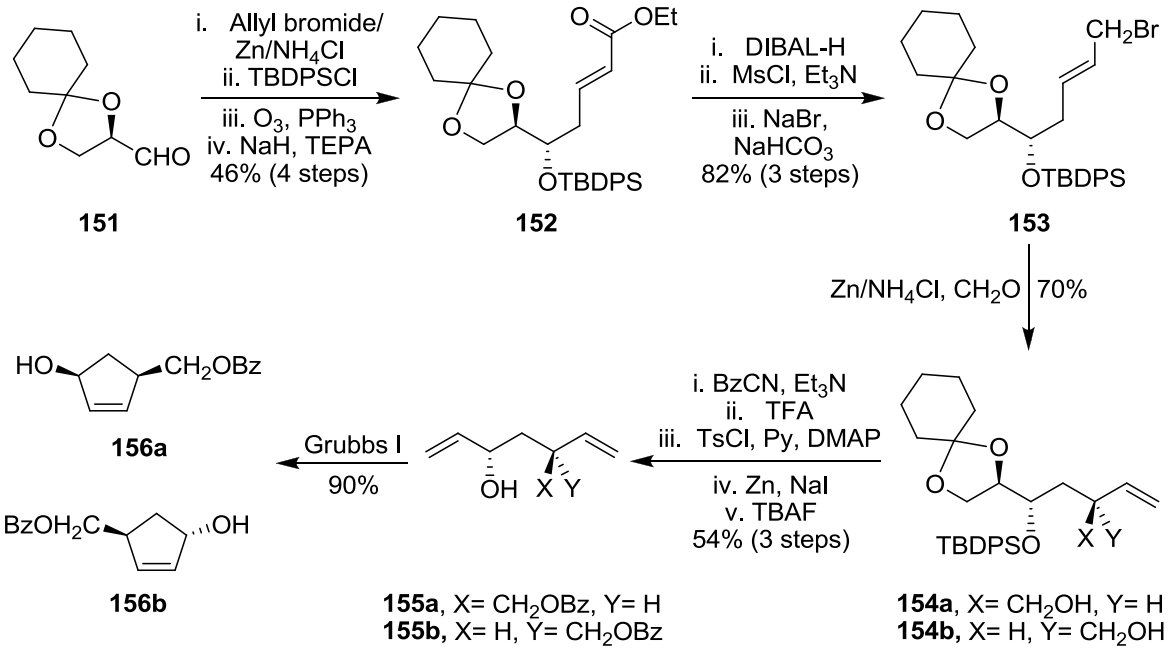


Figure 4 - Structures of some pharmacologically important carbocyclic nucleosides

Many synthetic carbocyclic nucleosides have been reported to show similar biological activities to the above results. For example carbovir **146** and abacavir **147** have been shown to hold considerable activity as an inhibitor of HIV reverse transcriptase.[96]

Significant improvements in HIV-infected patients have been observed when using abacavir without significant side effects and thus, it is as an FDA approved drug for HIV treatment. However, carbovir had limitations due to its cytotoxicity. Later, several synthetic carbocyclic nucleosides were reported including 5′-noraristeromycin[97,98] **149** which is a desmethylene analogue of aristeromycin **148**, which has shown antiviral activity without significant cytotoxicity.

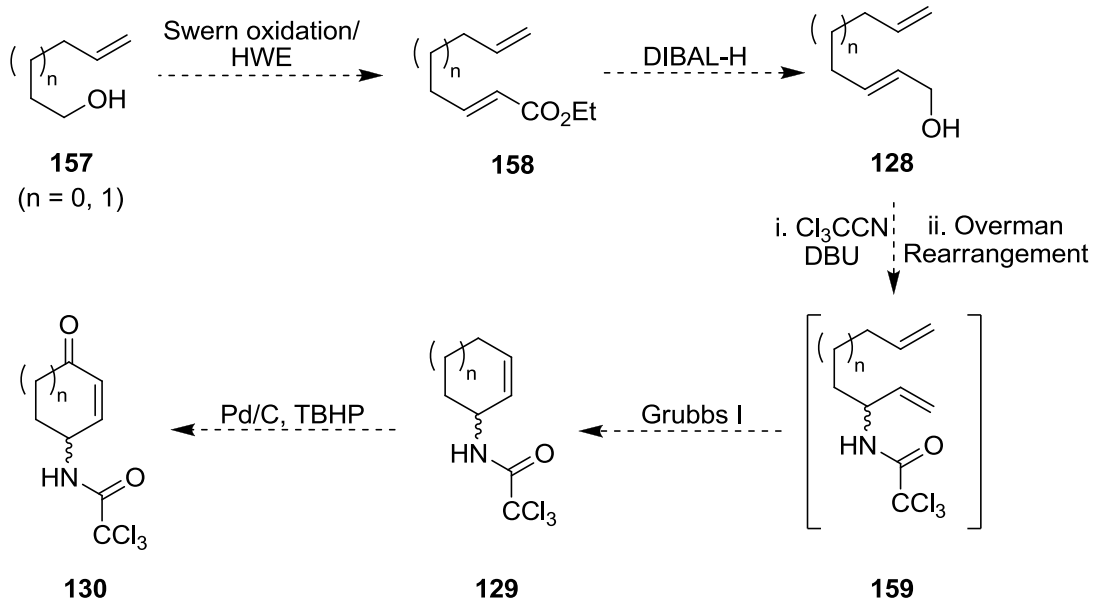
Due to their pharmaceutical importance, a variety of routes have been adopted to synthesise carbocyclic nucleosides. Many of these utilise either a retro Diels-Alder reaction of a norbornadiene derivative,[99,100] stereospecific synthesis from sugars,[101] functional group manipulation of natural building blocks or intramolecular Pauson-Khand[102] reactions as the key step. Recently Miller and co-workers[100] have made use of the Diels-Alder reaction of acylnitroso compounds with *N*-Cbz-protected spirocyclic dienes to afford the corresponding spirocyclo adducts. These are useful scaffolds in the synthesis of spiro-noraristeromycin. More recently, Chattopadhyay and Tripath have reported the synthesis of (1*S*,4*S*)-4-(benzyloxymethyl)-cyclopenten-2-enol **156a** and (1*S*,4*R*)-4-(benzyloxymethyl)-cyclopenten-2-enol **156b** starting from (*R*)-2,3-cyclohexylideneglyceraldehyde **151**, which are the key precursors for the synthesis of L-(+)- and D-(–)-carbovirs, respectively (Scheme 37). The key steps of the approach involve Luche allylation of formaldehyde with allylic bromide and a RCM reaction to generate the basic precursor of carbovir in good yield.[103]



Scheme 37 - Chattopadhyay approach towards carbocyclic nucleosides

3.1.2 Synthesis of an amidocyclohexenone

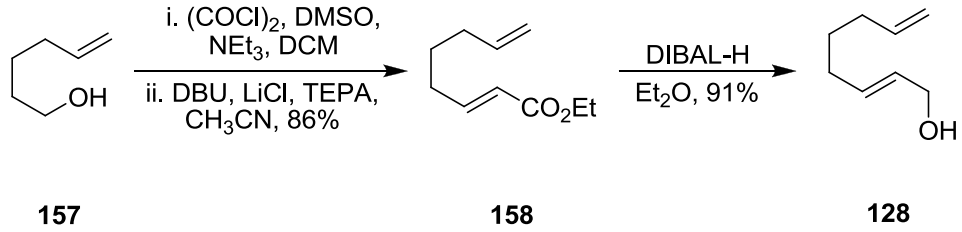
During previous years, attention has been focused on the synthesis of carbocyclic nucleosides with a pentacyclic ring. However, the development of compounds with different ring sizes, particularly with six-membered rings needed to be explored. The proposed methodology for the synthesis of carbocyclic ketones as precursors for the carbocyclic nucleosides is outlined in Scheme 38. It makes use of a one-pot tandem process previously developed in our group, which utilises an Overman rearrangement and a ring closing metathesis (RCM) reaction, for a quick and highly efficient synthesis of 5-, 6-, 7- and 8-membered carbocyclic amides.[104] The resulting carbocyclic amide would then be subjected to allylic oxidation to yield the amino substituted carbocyclic ketone **130**. The allylic oxidation of carbocyclic amide **129** (Scheme 38) relies on chemistry published by Corey and co-workers.[87] If this reaction proved to be successful, it would provide a highly efficient synthetic route to variable ring sizes of carbocyclic ketones. The resulting carbocyclic ketones could be reduced to give cyclic amino alcohols or subjected to an asymmetric one-pot tandem process using chiral palladium(II)-catalysts for the Overman rearrangement to get di-amino substituted chiral building blocks. These could be further functionalised for the asymmetric synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides such as aristeromycin **148** and noraristeromycin **150**.



Scheme 38- Proposed synthesis of amino substituted cycloketone 130

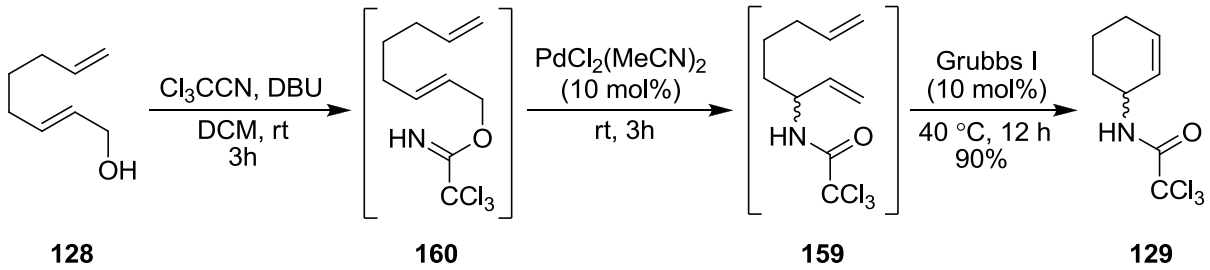
The first stage of this project required the synthesis of *N*-(cyclohexenyl)-trichloroacetamide **129** which is readily available from the corresponding allylic alcohol **128**. Allylic alcohol **128** was prepared in 2 steps from the commercially available 5-hexene

1-ol **157**, via a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions.[105] This was followed by reduction of the ester **158** with DIBAL-H to give allylic alcohol **128** in excellent yield (Scheme 39).



Scheme 39 - Synthesis of allylic alcohol 128

Allylic alcohol **128** was then reacted with trichloroacetonitrile and a catalytic amount of 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) to convert it into allylic trichloroacetimidate **160**. It was further subjected to the standard conditions of the one-pot tandem process using bis(acetonitrile)palladium(II) chloride to effect the Overman rearrangement. This was followed by the addition of Grubbs first generation catalyst to promote the RCM reaction which gave cyclic allylic trichloroacetamide **129** in an excellent 90% yield over three steps (Scheme 40).



Scheme 40 - Synthesis of carbocyclic amide 129

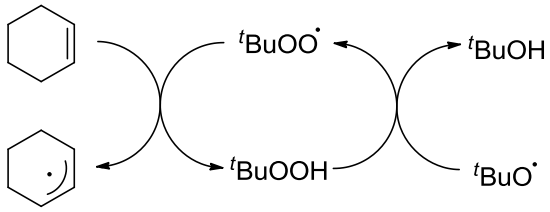
3.1.3 Efforts towards allylic oxidation

After synthesis of hexacyclic allylic trichloroacetamide **129** in multigram quantities, allylic oxidation of this substrate to yield the amino substituted carbocyclic ketone **130** was attempted. This substrate is the key precursor for the synthesis of a number of natural products such as epibatidine.[106]

Allylic oxidation is a very important reaction in many areas of synthetic chemistry.[87] A large number of procedures have been reported for allylic oxidations, which make use of a variety of reagents such as pyridinium dichromate (PDC),[107] selenium dioxide,[108] Cr(IV)

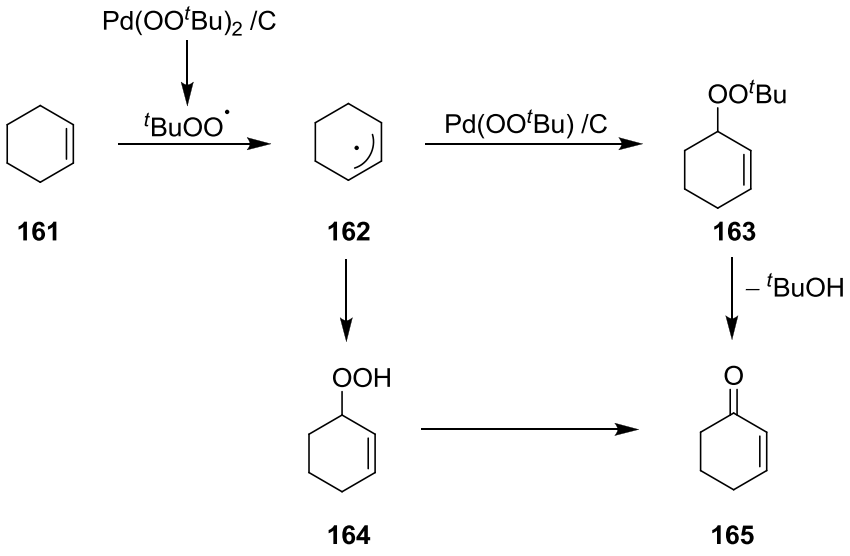
compounds and various other transition metal complexes.[109] In the last decade, use of *tert*-butyl hydroperoxide (TBHP) along with various transition metal complexes for allylic oxidation appeared as an attractive choice. However, there are only a few examples of allylic oxidation with compounds of increasing complexity.

In recent literature, it has been determined that a radical pathway is involved in the allylic oxidation by TBHP (Scheme 41).[87] Various transition metals including Pd(II)-complexes are capable of generating the *tert*-butylperoxy radicals (^{t}BuOO·) from *tert*-butyl hydroperoxide either by radical transfer or by homolysis.



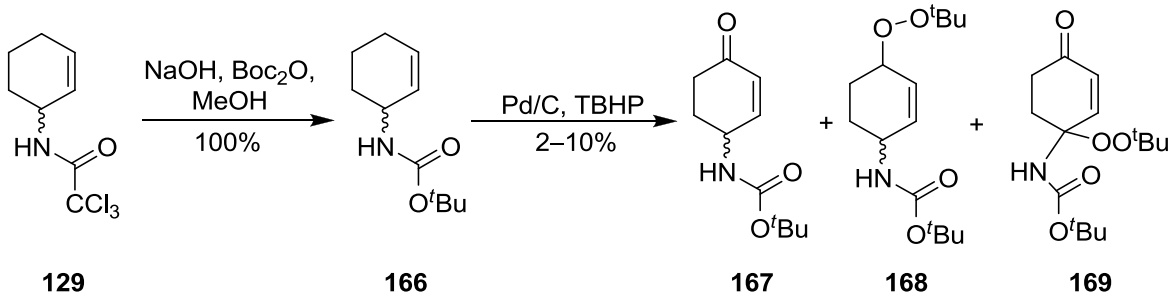
Scheme 41 - Radical base activation of cycloalkene using TBHP

The resulting *tert*-butylperoxy radical undergoes hydrogen atom abstraction from the allylic position of the alkene (hydrocarbon substrate) **161**. This position having the lowest carbon-hydrogen bond dissociation energy, which allows the formation of the alkylperoxy radical **162**.[110] The alkylperoxy radical goes on to form either the the allylic *tert*-butyl peroxyether **163** or hydroperoxide **164**. This is followed by either hydrogen atom abstraction from another hydrocarbon or undergoes oxidation of Pd(II) to form the enone **165** products (Scheme 42).[87]



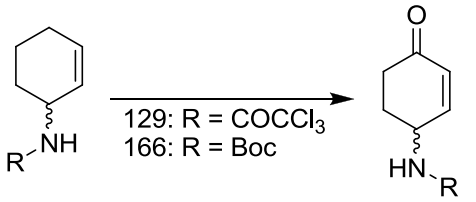
Scheme 42 - Palladium catalysed allylic oxidation using TBHP

Initially, allylic oxidation of carbocyclic amide **129** was carried out according to a literature procedure published by Yu and Corey, using 5 equivalents of TBHP as an oxidant along with a catalytic amount of 10% Pd on carbon and potassium carbonate at 20 °C in dichloromethane.[111] Under these conditions, the desired product was not formed even after 5 days of stirring, with mainly starting material found in the reaction mixture. The reaction was attempted again under reflux conditions, but the same result was obtained. It was thought that the failure of this reaction could be attributed to the presence of the trichloroacetamide group that can also form radicals. To combat this, the nitrogen was re-protected with the Boc-protecting group in quantitative yield (Scheme 43). The oxidation of the Boc-protected carbocyclic amide was performed again under the same reaction conditions as reported above. Although some of the starting material was consumed, the rate of the reaction was very poor and could not be improved despite the elevated temperatures and extended reaction times tried. This resulted in only a 10% yield of the ketone **167** along with unreacted starting material and side products (Scheme 43). To increase the rate and yield of the reaction, pre-treatment of Pd on-carbon with *tert*-butyl hydroperoxide in dichloromethane at 24 °C with stirring for 1 h was employed. This was followed by addition of Boc protected carbocyclic amide **166** and the reaction was stirred for 12 h. It was found that the initial rate of the reaction increased but the reaction did not proceed to completion even after an extended reaction time at elevated temperature and gave only 6% yield. In the next attempt, the reagents were added in batches, after periods of 12 h, for three days keeping the reaction under reflux in dichloromethane. However, the yield of the reaction could not be improved (Table 7). Despite investigating various conditions and increasing amounts of oxidant, all conditions gave starting material back along with only a small amount of ketone and side products. Chromatographic and spectroscopic studies revealed the possible structures of the side products in the reaction mixture. However, due to the short life span and transitory nature of those undesired compounds, they could not be characterised in confidence.



Scheme 43 - Boc protection and allylic oxidation of 129

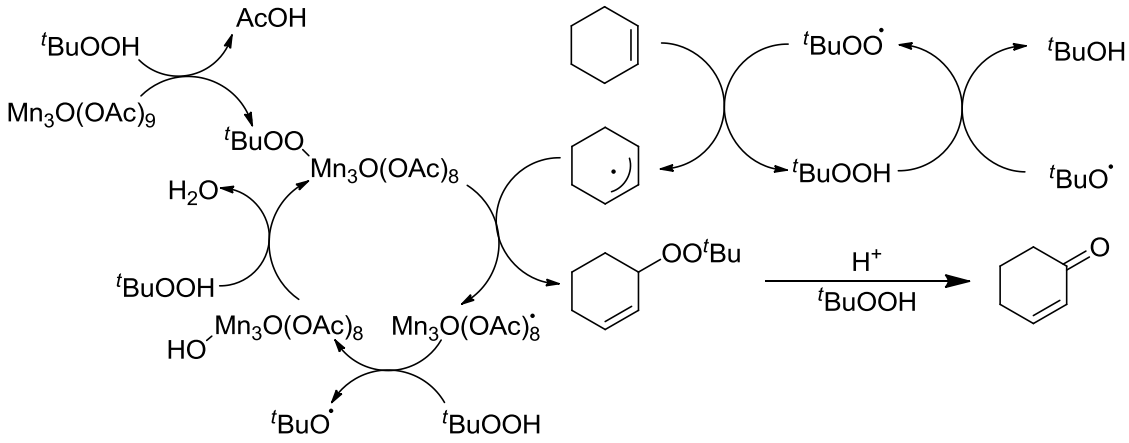
Table 7 - Results for allylic oxidation with various methods



Entry	Substrate	Oxidant	Additive	Solvent/ Atomosphere	Temp.	Time (d)	Yield%[a]
1	129	Pd/TBHP	K_2CO_3	DCM/Ar	rt	3	no reaction
2	166	Pd/TBHP	K_2CO_3	DCM/Ar	rt	5	no reaction
3	166	Pd/TBHP	K_2CO_3	DCM/Ar	reflux	5	10 (51)
[b]4	166	Pd/TBHP	K_2CO_3	DCM/Air	reflux	5	6 (49)
[c]5	166	Pd/TBHP	K_2CO_3	DCM/Air	reflux	5	5 (42)
6	166	Mn/TBHP	Mol. Sieves	$EtOAc/O_2$	rt	5	2 (45)

[a]Recovered starting material% in parenthesis ()
[b]Preactivation of Oxidant
[c]Oxidant added in batches

To achieve a better yield and selectivity for the allylic oxidation of Boc protected carbocyclic amide **166**, oxidation with manganese(III) acetate was also attempted. Recently manganese(III) acetate along with *tert*-butyl hydroperoxide as a co-oxidant, has been reported for mild, efficient, regioselective and chemoselective allylic oxidation of simple and complex alkenes.[112] This method works on a similar principle as proposed for the palladium catalysed process in the reported literature.[87] A detailed mechanistic pathway for the $Mn_3O(OAc)_9$ mediated allylic oxidation is shown below (Scheme 44).

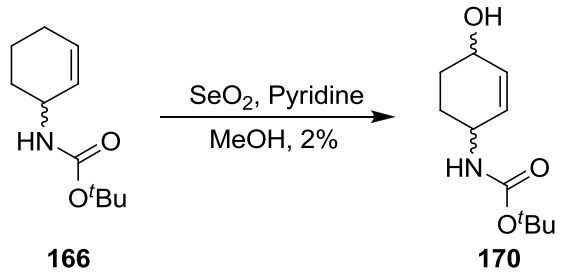


Scheme 44 - The mechanistic pathway for the allylic oxidation using Mn(III) and TBHP

Mn(III) acetate has a stabilised trinuclear structure and its use along with TBHP gives $^tBuOOMn_3O(OAc)_8$ as an active species by displacing one acetate ligand by a TBHP molecule.[112] To improve the reaction conditions, use of molecular sieves is recommended to remove any traces of moisture, which is known to cause disintegration of

manganese(III) acetate. However, in our case, using 10 mol% of $Mn_3O(OAc)_9$, 5 equivalents of TBHP, 4 Å molecular sieves and ethyl acetate as the solvent gave similar results to the palladium mediated reactions (Table 7).

Other classical methods of oxidations were also attempted. In this regard pyridinium dichromate and selenium dioxide are important.[108,109] Selenium dioxide has long been used as a favoured reagent for the conversion of allylic methylene to the corresponding ketone. Initially, a literature procedure was used as described by Camps, using selenium dioxide in ethanol with a catalytic amount of pyridine.[113] However, these conditions did not give any desired oxidised product, instead alcohol derivative **155** was isolated in 2% yield along with 48% of unreacted starting material (Scheme 45).



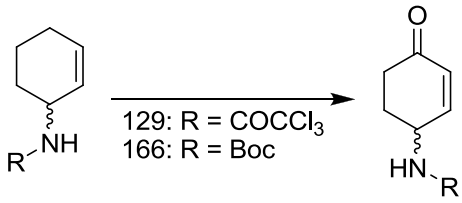
Scheme 45 - Selenium dioxide oxidation using dry Pyridine

The reaction was again tried using TBHP as a co-oxidant along with selenium dioxide but no significant improvement could be noticed. In another attempt, substrate **166** was dissolved in dichloromethane and subjected to sonication (as a source of energy instead of usual heating) using 5 equivalents of TBHP. Again no difference to the yield of desired product was observed. In all cases, only traces of the desired product along with unreacted substrate was isolated by flash column chromatography. Allylic oxidation of **166** was also attempted with copper(I)-iodide along with TBHP in dichloromethane. Initially, the reaction was performed at 25 °C for 48 h, however, only starting material was present. Elevation of the temperature to 45 °C for a further 24 h showed that the starting material had begun to decompose. The results are summarised in the Table 8.

Significant difficulties were encountered in the allylic oxidation, however we continued our efforts for allylic oxidation. To accomplish the allylic oxidation of substrates **129** and **166**, it was decided to attempt metal free oxidation using TBHP as an oxidant and microwave heating as an energy source. This technique is renowned for reducing reaction times and increasing yields.[114] It provides opportunities for some reactions to precede which under standard conditions are not feasible. Initially a reaction using 5 equivalents of

TBHP in toluene in a microwave reactor was attempted. Unfortunately, only starting material was recovered. To increase the heating efficiency of the microwave reaction, solid silicon carbide bars were employed which act as passive heating elements (PHE) in the reaction tube. Solid silicon carbide is chemically inert and is a microwave absorbing material which can transfer thermal energy to the reaction mixture via conduction phenomena. However, microwave heating did not have any positive effect on the fate of the reaction and gave the same disappointing yield (Table 8, entry 7).

Table 8 - Results for allylic oxidation with various methods



Entry	Substrate	Oxidant	Additive	Solvent/ Atmosphere	Condition	Time (h)	Yield%[a]
1	166	PDC/TBHP	Celite	Toluene/Ar	rt to reflux	72	6 (70)
2	166	SeO_2/TBHP	---	DCM/Ar	reflux	120	4 (85)
3	166	SeO_2/TBHP	---	DCM/Air	sonication	12	traces (75)
4	166	CuI/TBHP	---	DCM/Air	rt to reflux	120	decomposed
6_b	129	TBHP	K_2CO_3	Toluene/Ar	microwave	2	no reaction
7_b	129	Pd/TBHP	K_2CO_3	Toluene/Ar	microwave	2	traces (48)

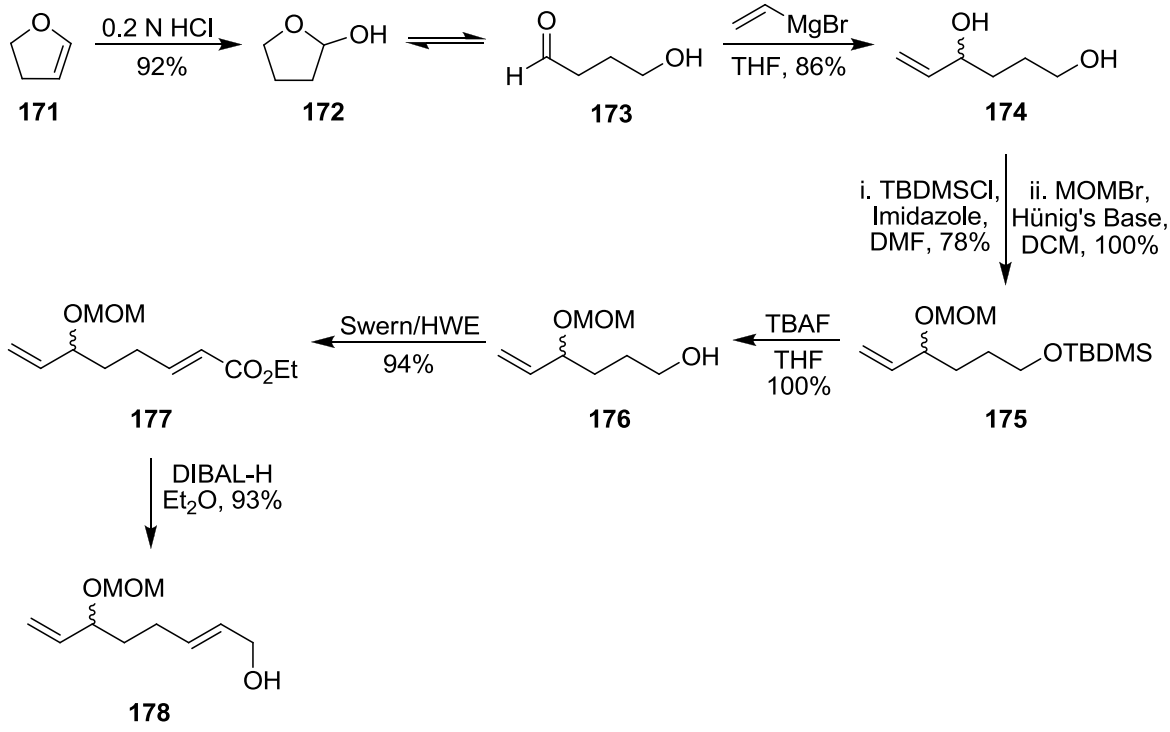
[a] Recovered starting material% in parenthesis ()
[b] Silcon carbide bar was used as PHT

In all of these approaches towards allylic oxidation from carbocycles **129** or **166** with or without metal complexes, problems were faced in terms of both yield and selectivity due to the unusual reactivity of the substrates. From the results obtained, it can be concluded that above the methods are intolerant for allylic oxidation of a cyclic alkene bearing a substituted amide.

3.1.4 New approach towards the synthesis of an amidocyclohexenone

To achieve the synthesis of amino substituted carbocyclic ketone **130**, another strategy was devised that negated the need of allylic oxidation and would install the allylic oxy-substituent before the introduction of the amide group in the system. 2,3-Dihydrofuran **171** was the starting point of the new planned route. Compound **171** was hydrolysed with 0.2 M hydrochloric acid to give cyclic hemiacetal **172** in 92% yield. The resulting cyclic hemiacetal **172** exists in equilibrium with the 4-hydroxybutanal **173**. This was further reacted with vinylmagnesium bromide to give 1-hexene-3,6-diol **174** in 86% yield. Both

the primary and secondary alcohols of the resulting diol **174** required protection at this stage to avoid interference in subsequent steps. Protection of the primary alcohol was carried out using *tert*-butyldimethylsilyl chloride with the aid of imidazole. Subsequently, the MOM ether was successfully introduced using Hünig's base and bromomethyl methyl ether to afford **175** in quantitative yield. Removal of the silyl protecting group was accomplished using tetra-*n*-butylammonium fluoride in quantitative yield. The resulting primary alcohol **176** was further subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction under conditions reported by Masamune and Roush,[105] which uses triethyl phosphonoacetate, lithium chloride and DBU, to give *E*-α,β-unsaturated ester **177** in 94% yield. The geometry of the resulting alkene could be easily determined from the ^{1}H NMR spectrum of the product. The ^{1}H NMR spectrum showed a 15.7 Hz coupling constant for the alkene protons proving that the geometry is *trans*. Finally DIBAL-H reduction of the ester **177** furnished allylic alcohol **178** in 93% yield (Scheme 46).

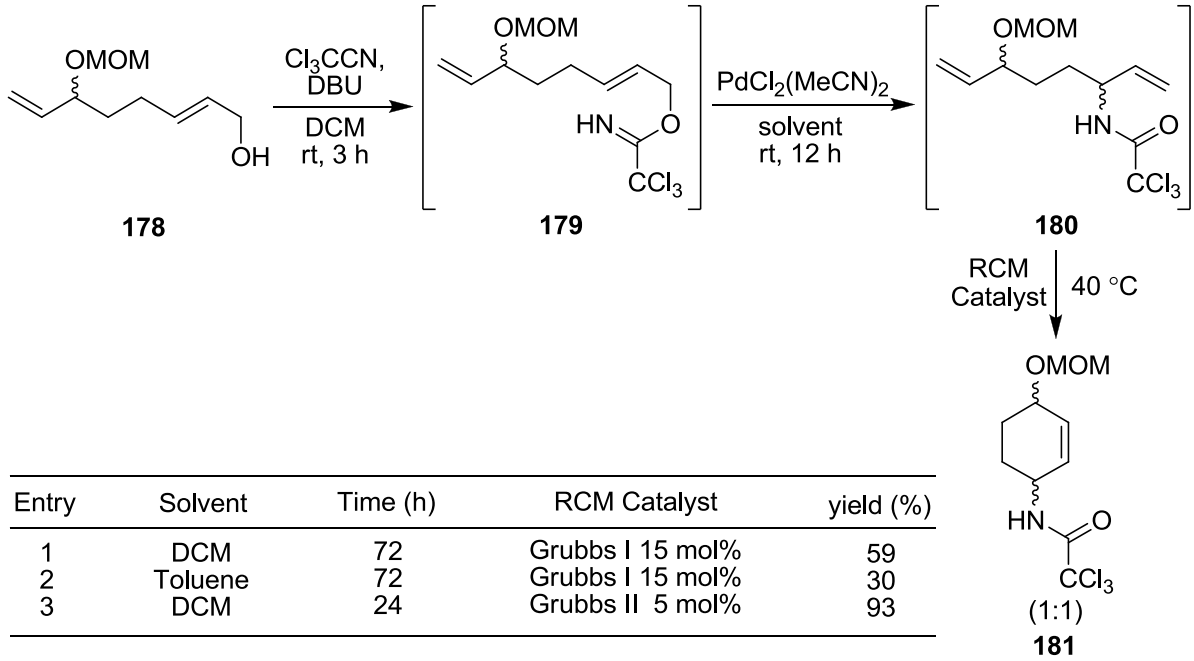


Scheme 46 - Synthesis of allylic alcohol 178

With allylic alcohol **178** in hand, this compound was subjected to the tandem Overman rearrangement/RCM process. Initially, the reaction of the allylic alcohol **178** with trichloroacetonitrile was performed using DBU at 0 °C. The reaction ran smoothly and gave the allylic trichloroacetimidate in 100% yield. Without purification, trichloroacetimidate was subjected to an Overman rearrangement with the aid of bis(acetonitrile)palladium(II) chloride (10 mol%) to give allylic trichloroacetamide **180**

(Scheme 47). The rearranged product **180** was then subjected to a RCM reaction using Grubb's 1st generation catalyst. The MOM protected carbocyclic amide **181** was achieved in a rather modest yield of 59% in 24 h. This might be due to the greater complexity of substrate **178**, which leads to a slower process in comparison to the previous rearrangement substrate **159**, which completes in 12 h and furnished the carbocyclic amide **129** in excellent 90% yield (Scheme 40). This tandem process results in the formation of both the *syn* and *anti*-product showing that at the 6-position the MOM-ether is too far to exert a directing effect.

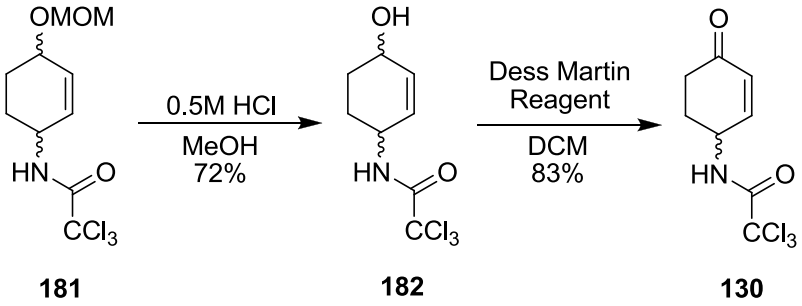
To make this approach more efficient, an improved process was required. Previously, the Sutherland group have shown that toluene can enhance the yield and diastereoselectivity of MOM ether-directed Overman rearrangements due to its non-coordinating nature.[75] The reaction was attempted again using toluene as a solvent and to our surprise, the yield of the reaction dropped further to 30%. It was found that deprotection of the MOM-group competes during the ring closing metathesis and allows competing side reactions to take place. In an attempt to increase the overall yield, the tandem process was repeated using Grubb's 2nd generation catalyst and pleasingly, the desired product was obtained in an excellent 93% yield over three steps. The Grubb's 2nd generation catalyst proved a better RCM catalyst for the substrate in terms of catalyst loading, reaction time and yield in comparison to Grubb's 1st. generation catalyst (Scheme 47).



Entry	Solvent	Time (h)	RCM Catalyst	yield (%)
1	DCM	72	Grubbs I 15 mol%	59
2	Toluene	72	Grubbs I 15 mol%	30
3	DCM	24	Grubbs II 5 mol%	93

Scheme 47 - Overman rearrangement and ring closing metathesis

In the next stage, the deprotection of the MOM group of **181** was attempted using 6M hydrochloric acid. However, this reaction was found to be low yielding and gave a complex mixture of products. To optimise the deprotection of product **181**, different concentrations of HCl were investigated. Optimal results showed that dilute hydrochloric acid (0.5M)f in methanol at 40 °C accomplished the deprotection of the MOM group to give alcohol **182** in 72% yield. Treatment of the resulting alcohol **182** with the Dess-Martin periodinane reagent gave the desired amidocyclohexenone **130** in 83% yield (Scheme 48).



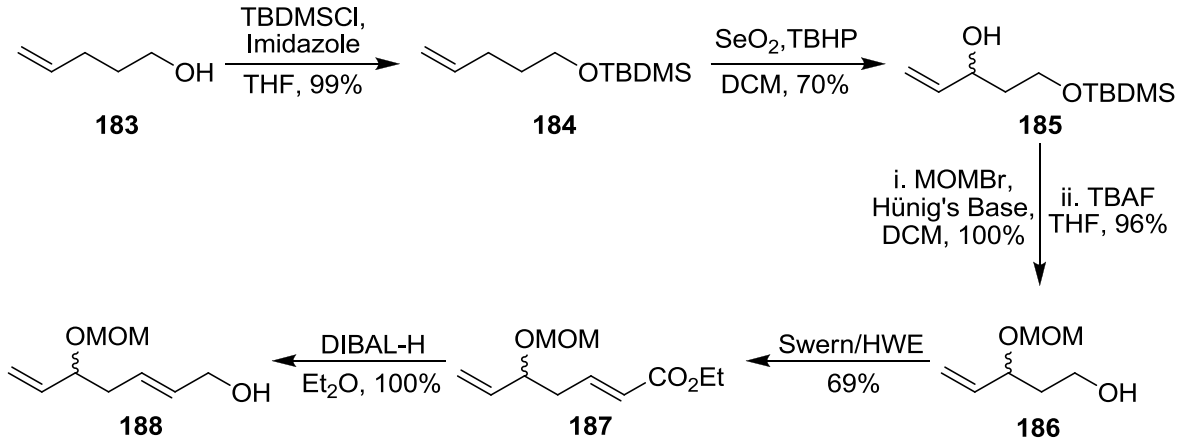
181 **182** **130**

Scheme 48 - Synthesis of amidocyclohexenone 130

3.1.5 Synthesis of an amidocyclopentenone

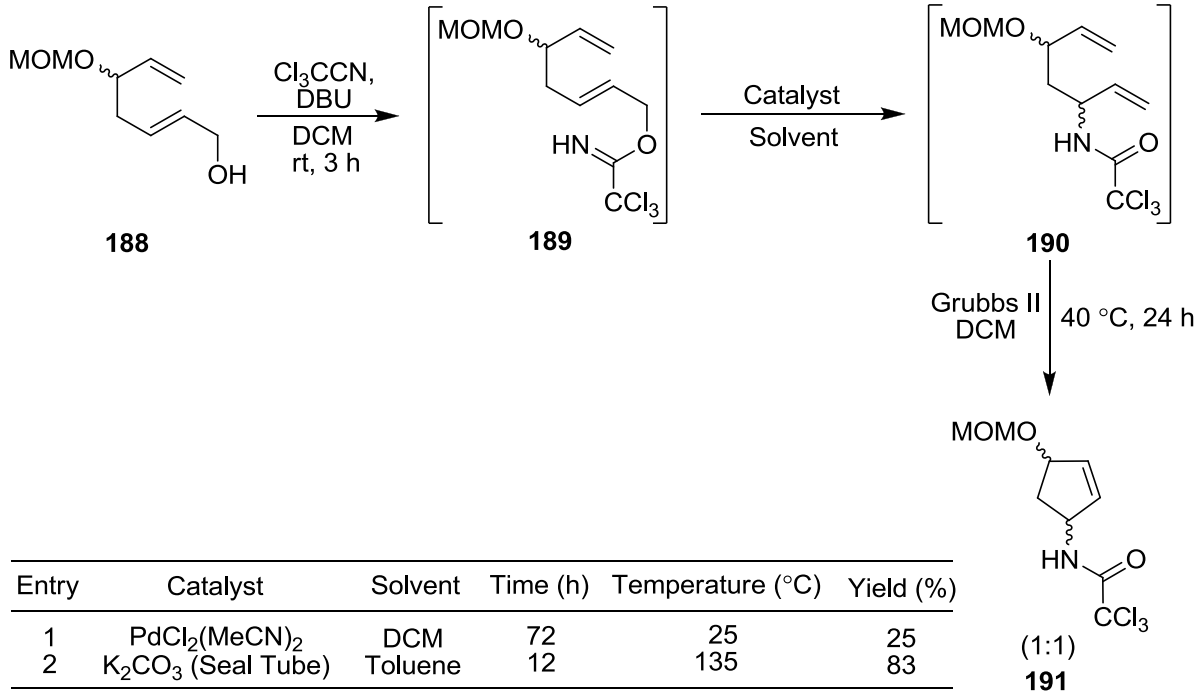
As previously mentioned, due to the significant difficulties in allylic oxidation of amino carbocyclic amides, the short, quick and high yielding one-pot tandem approach towards the synthesis of carbocylic amides of variable ring sizes could not be utilised. To exclude the need of an allylic oxidation at the end of the synthesis, an alternative approach was adopted. The synthesis of the amino substituted pentacarbocyclic amide **193** commenced with the protection of penta-4-ene-1-ol **183** with a silyl ether using *tert*-butyldimethylsilyl chloride in 99% yield. To install the hydroxyl group, the resulting silyl protected pentene **184** was treated with selenium dioxide in the presence of TBHP. The reaction worked smoothly to give a 70% yield of **185**. The remaining steps are similar to that mentioned before for the synthesis of aminocyclohexenone **130**. The synthesis involved the treatment of **185** with bromomethyl methyl ether in the presence of Hünig's base to protect the secondary alcohol followed by treatment with TBAF to remove the silyl protecting group in an excellent 96% yield. A one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction gave *E*-α,β-unsaturated ester **187**. Once again the *E*-geometry of the alkene was established through the ^{1}H NMR spectrum of the product, which showed a coupling constant of 15.7 Hz for the 2-H and 3-H hydrogen atoms. The resulting ester was reduced

with DIBAL-H to give the corresponding allylic alcohol **188** in quantitative yield (Scheme 49).



Scheme 49 - Synthesis of allylic alcohol 188

The allylic alcohol **188** was then transformed into the allylic trichloroacetimidate **189** by reacting with trichloroacetonitrile in the presence of a catalytic amount of DBU. It was rearranged using bis(acetonitrile)palladium(II) chloride (10 mol%) to the allylic trichloroacetamide **190** and this was followed by ring closing metathesis step with Grubbs first generation catalyst. Surprisingly, this process gave only a 25% yield of RCM product **191** over three steps (Scheme 50).

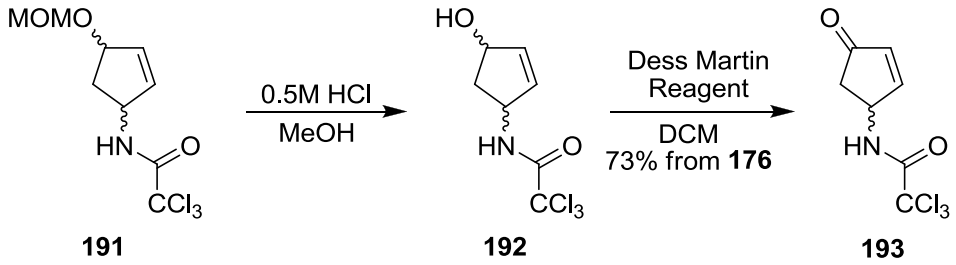


Entry	Catalyst	Solvent	Time (h)	Temperature (°C)	Yield (%)
1	$PdCl_2(MeCN)_2$	DCM	72	25	25
2	K_2CO_3 (Seal Tube)	Toluene	12	135	83

Scheme 50 - Overman rearrangement and ring closing metathesis

To determine the optimal reaction conditions for the development of a tandem process, all three steps of the tandem process were investigated carefully and it was found that the rearrangement was not going to completion, even after 72 h. During this time, it was observed that the allylic trichloroacetimidate **189** had begun to decompose. To improve the yield of the reaction, the rearrangement was also carried out under thermal conditions. This involves heating of **189** at 135 °C in toluene in the presence of a small amount of potassium carbonate (2 mg/mL) in a sealed tube. The use of thermal rearrangement conditions led to an appreciably cleaner product in 12 h with a much better yield. The rearranged product **175** was then subjected to RCM using Grubbs 2nd generation catalyst (12 h under reflux), to provide the desired cyclic allylic trichloroacetamide **191** in 83% yield over three steps. This tandem process gave both the *syn* and *anti*-product showing that at the 5-position the MOM-ether is too far to exert a directing effect.

Finally, the MOM group was easily deprotected by heating the solution of **191** in methanol with 0.5M HCl. Without purification this reaction was followed by a Dess-Martin oxidation in dichloromethane to yield amidocyclopentenone **193** in 73% yield over two steps (Scheme 51).



Scheme 51 - Synthesis of 4-amidocyclopentenone 193

3.1.6 Conclusions

In summary, new methodology was devised for the successful synthesis of 5- and 6-membered amido substituted carbocyclic ketones compounds which are important building blocks for the synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides and natural products. Initially, various methods were investigated for the allylic oxidation of carbocyclic amides formed from a one-pot tandem process. It appeared that these carbocylic amides are resistant to allylic oxidation when TBHP along with different transition metals such as Pd, Se, Mn and Cr. In addition to this, the employment of sonication and microwave techniques also found no success. A new approach was devised involving installation of the hydroxyl group before the tandem process. The

intermediate from this new route were then subjected to high yielding one-pot tandem Overman rearrangements and ring closing metathesis steps to eventually furnish amido substituted five and six membered carbocyclic ketones. The resulting carbocyclic amides are relatively more complex than have been synthesised previously using this approach and in this way, highlights the potential of this methodology for the synthesis of more complex target compounds.

3.2 Synthesis of Polyhydroxy Aminocyclohexanes

3.2.1 Aminocyclitols

Aminocyclitols are cycloalkanes having at least one hydroxyl group on each of three or more ring atoms and one free or substituted amino group.[115] Because of their close structural association with sugars, aminocyclitols are also considered as aminocarbasugars. Validamine **194** and other structurally related compounds such as conduramines **195** and **196** constitute a class of significant compounds which display a diverse range of behaviour and possess unique characteristics that make them important for various types of synthetic applications (Figure 5).[116]

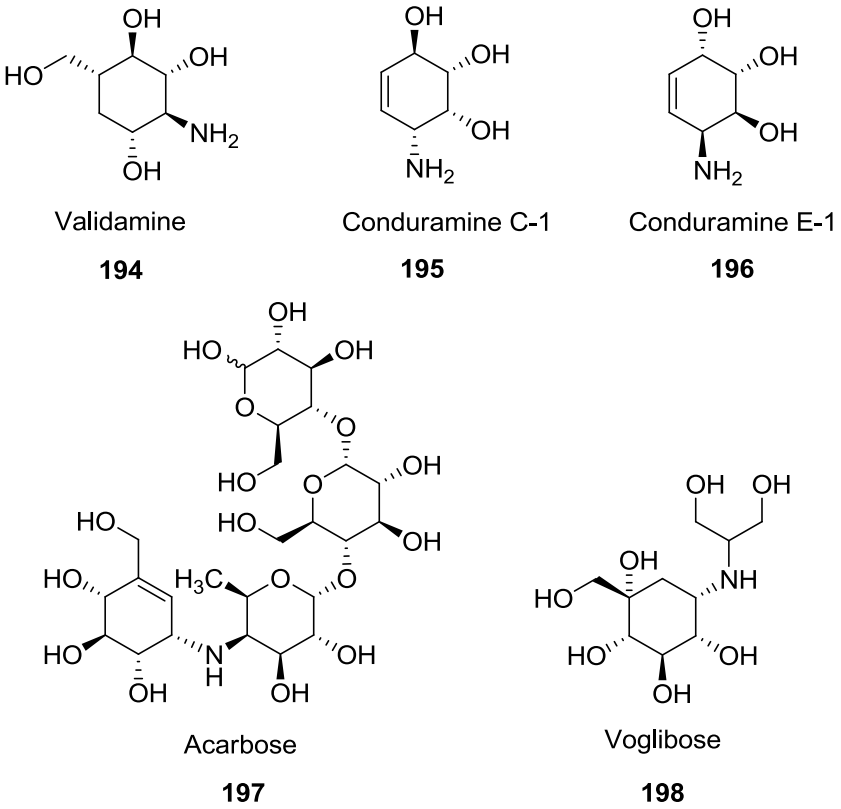
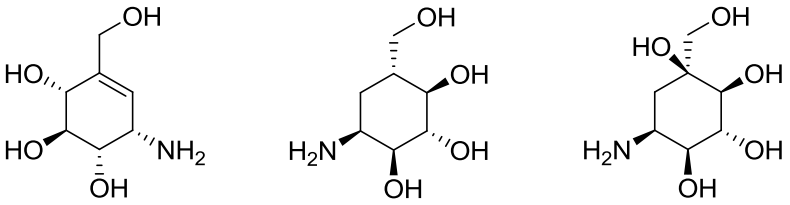


Figure 5

Various aminocyclitols, natural **194** as well as synthetic **195** and **196** belong to an important class of glycosidase inhibitors.[117-119] Glycosidase inhibitors have been established as potential therapeutic agents for the treatment of diabetes,[120] obesity,[121] viruses,[122] cancer,[123] and genetic disorders.[124] The inhibition of glycosidases by a diverse range of chemical compounds has been extensively studied and this has led to a new class of antibiotics known as aminoglycoside antibiotics. Several aminocyclitols and conduramines are aminoglycoside antibiotics which have been revealed to bind with a number of RNA sequences as well as with important HIV regulatory domains to disclose

the interplay between the hydroxyl substituents and their neighbouring ammonium groups.[125] Acarbose[126] **197** and voglibose[127] **198** are aminocyclitols and are active α-glucosidase inhibitors utilised clinically to lessen postprandial blood glucose levels in patients with type II diabetes mellitus.

Some natural aminocyclitols are secondary metabolites, such as validamycins **202** that have been isolated from the fermentation culture of *streptomyces hygroscopicus limoneus*.[128] Validamycins **202** are composed of one valienamine unit **199**, together with an additional unit of either validamine **200**, valiolamine **201**, or hydroxyvalidamine **203** (Figure 6). Apart from aminocyclitols glycosidase inhibiting and antibiotic activity their use as molecular probes for quorum sensing modulation has also been reported.[129]



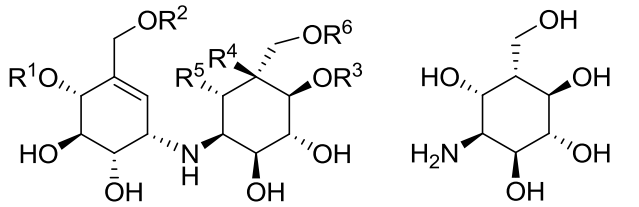


Figure 6

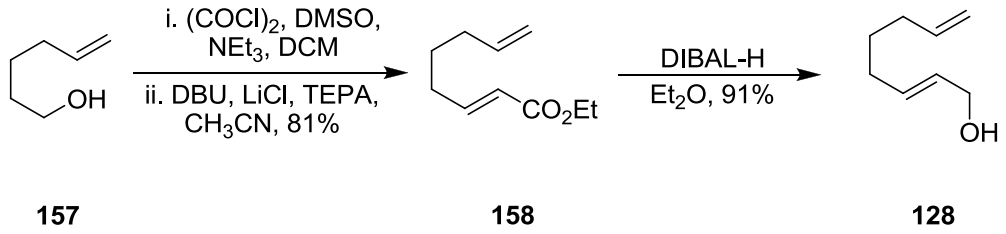
In addition, aminocyclitols are not only aspirant for drug discovery but also have paved the way for the development of the new potential therapeutic agents. Aminocyclitol frameworks have been found to be incorporated into a wide variety of organic compounds. These serve as key intermediates in the preparation of azasugars,[130] aminosugars,[131] sphingosines,[132] lactams, and narcissus alkaloids.[133]

As a result of their utility and versatility, many fascinating and elegant synthesis of racemic and optically pure aminocyclitols and conduramines have been reported. Many

approaches make use of natural building blocks as a starting material. For example Shing and Wan synthesised valiolamine **201** in 14 steps strating from (–)-quinic acid in an overall 8.4% yield.[134] Ogawa and co-workers employed *vibo*-quercitol for the convenient syntheses of valiolamine **201**.[135] Several other synthetic strategies include cycloaddition reactions,[136] radical cyclisations[137] and rearrangement reactions such as the classical Ferrier rearrangement[138] or the Claisen rearrangement.[139]

3.2.2 Synthesis of aminocyclitols

In this project, our aim was to undertake the highly stereoselective synthesis of aminocyclitols such as dihydroconduramine E-1 **132** and the enantiomer of dihydroconduramine C-1 **133**. It was proposed to make use of a stereoselective variant of the recently developed one-pot tandem process Overman rearrangement and ring closing metathesis step for the asymmetric synthesis of an (*S*)-*N*-(cyclohexenyl)trichloroacetamide **131**, and then to study the stereoselective oxidation of this synthetic intermediate for the preparation of polyhydroxylated aminocyclohexane derivatives (Scheme 34). The first stage of the project involved the synthesis of the allylic alcohol starting from commercially available 5-hexen-1-ol **157** in two steps using a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction using Masamune-Roush conditions.[105] This gave *E*-α,β-unsaturated ester **158** which was then followed by reduction of the ester functional group by two equivalents of DIBAL-H to give allylic alcohol **128** in excellent yield (Scheme 52).

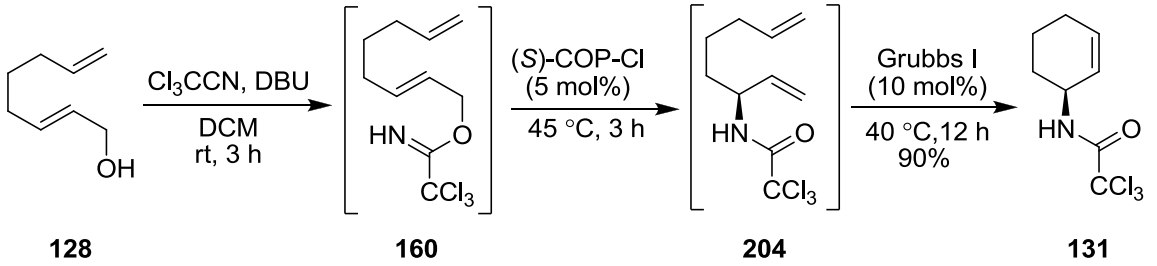


157 **158** **128**

Scheme 52- Synthesis of allylic alcohol 128

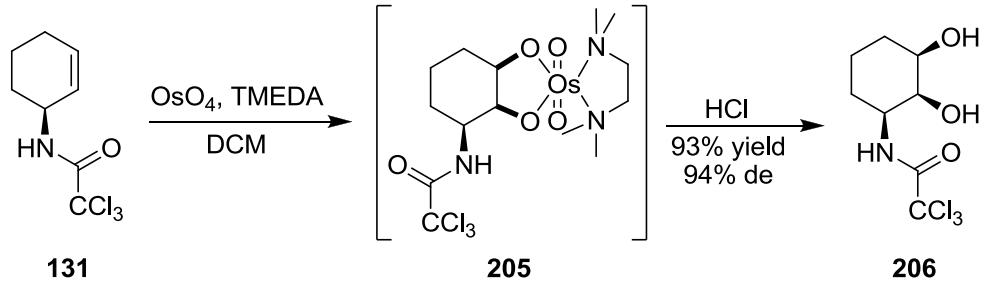
Allylic alcohol **157** was then reacted with trichloroacetonitrile and a catalytic amount of DBU to convert it into allylic trichloroacetimidate **160**. It was further subjected to the standard conditions of the one-pot tandem process using commercially available (*S*)-COP-Cl **82** (see Figure 3) to effect the Overman rearrangement. This was followed by the addition of Grubbs first generation catalyst to promote ring closing metathesis which resulted in allylic trichloroacetamide **131** in an excellent 90% yield over three steps and

with 88% enantiomeric excess. The enantiomeric excess of **131** was improved to >99% on recrystallisation from a mixture of ethyl acetate and petroleum ether (Scheme 53).



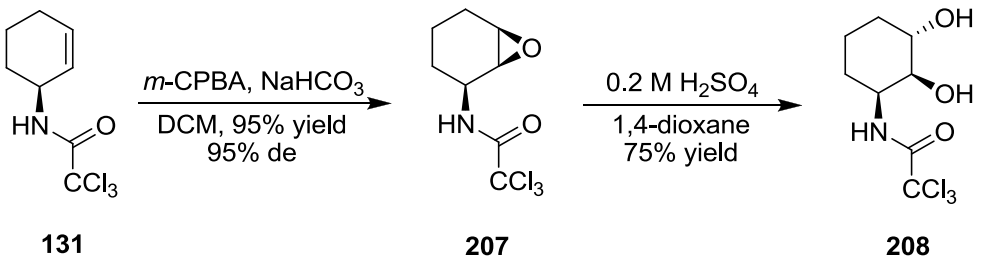
Scheme 53 - Stereoselective one-pot tandem Overman rearrangement and RCM reaction

After the synthesis of (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohexa-2-ene (**131**) in multigram quantities, our subsequent objective was to investigate the stereoselective dihydroxylation and epoxidation of **131**. Initially, dihydroxylation of the cyclic allylic amide was pursued. Transition-metal-catalysed oxidations of alkenes represent a distinctive approach for dihydroxylation with defined relative configuration. Several reagents are now used as an oxidant such as $KMnO_4$, RuO_4 or OsO_4. Among these reagents, the osmium-catalysed dihydroxylation has gained wide acceptance and has emerged as a benchmark in terms of its generality and selectivity. We made use of Donohoe's procedure which is an efficient method for the directed *syn*-selective dihydroxylation of cyclic allylic trichloroacetamides.[140] It involves the in situ formation of a bidentate complex which is prepared by mixing stoichiometric amounts of osmium tetroxide and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) at –78 °C. Use of TMEDA along with OsO_4 not only makes the oxidant more electron rich but also more reactive. This newly formed bidentate complex then reacts with the substrate to form the osmate ester **205** towards the face of the alkene which is influenced by hydrogen bonding between the amide and the electron rich oxo-ligands. On hydrolysis, it liberates mainly the *syn*-dihydroxylated product. Following this procedure, **131** was subjected to standard conditions of the directed dihydroxylation. The reaction proved successful to yield the 1,2-*syn*-2,3-*syn*-isomer **206** in 94% diastereomeric excess. Diastereomeric excess could be determined from the ^{1}H NMR spectrum of the crude reaction mixture. The desired product was then easily isolated from the crude mixture using flash column chromatography to give a single stereoisomer in 93% yield (Scheme 54).



Scheme 54 - Steroselective dihydroxylation showing formation of osmate ester

In order to synthesise the 1,2-*syn*-2,3-*anti*-isomer **208**, a simple two-step strategy was adopted. The first step involved the epoxidation of **131** utilising *meta*-chloroperbenzoic acid (*m*-CPBA) which provided *cis*-epoxide **207** *via* a substrate directed intermediate.[141] The diastereomeric excess was determined from the ^{1}H NMR spectrum of the crude reaction mixture and found to be 90%. Separation of the major diastereomers was carried out by flash column chromatography giving **207** as a single stereoisomer in 95% yield. This was followed by acid mediated hydrolysis to furnish **207** in 75% yield as a single stereoisomer. It was fully characterised by detailed COSY and NOE experiments which clearly demonstrated the 1,2-*syn*-2,3-*anti* relationships of the trichloroacetamide and hydroxyl groups (Scheme 55).

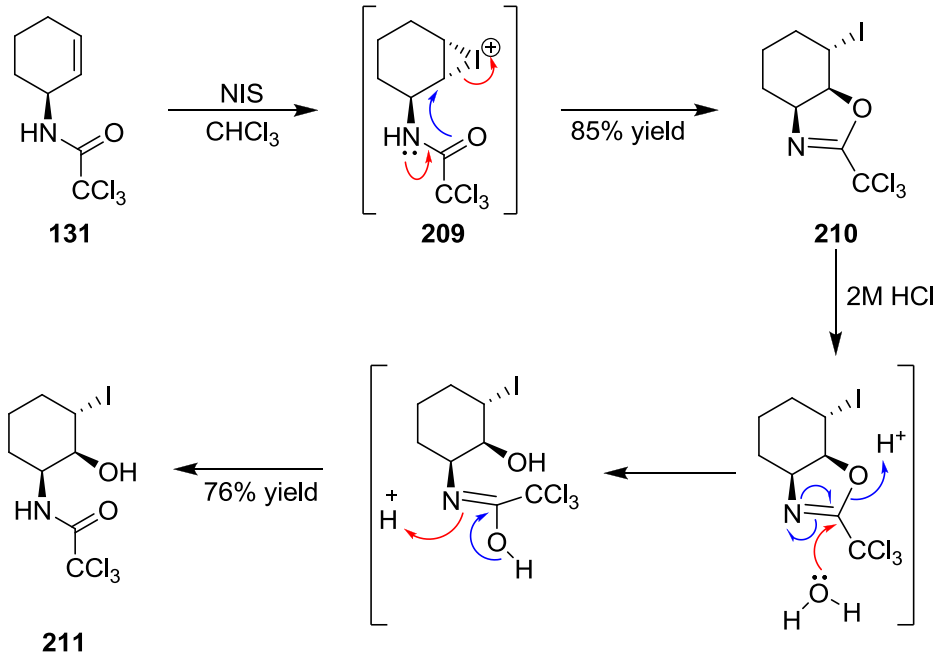


Scheme 55 - Stereoselective epoxidation and its cleavage

In the next step, it was proposed to install three hydroxyl groups to **131**. This would allow access to aminocyclitols **132** and **133**. We intended an approach that entailed stereoselective functionalisation of the alkene of **131** to furnish a hydroxyl group at C-2 and a leaving group at C-3 of the cyclohexane ring. Elimination of the leaving group will then yield an alkene which on subsequent stereoselective oxidation should produce the conduramine derivatives.

The synthesis of this fragment commenced with the reaction of **131** with *N*-iodosuccinimide in chloroform to afford iodoxazole **210** (Scheme 56). The resulting oxazole **210** is sensitive to acid so was purified using an alumina column in 85% yield as a

single stereoisomer. As **210** was found to be relatively unstable, it was subsequently hydrolysed under acidic conditions which yielded 1,2-*syn*-2,3-*anti*-iodoalcohol **211** in 76% yield.



Scheme 56 - Stereoselective functionalisation of carbocyclic amide 211

The relative stereochemistry of **211** was confirmed by X-ray crystallography. The X-ray image of the 1,2-*syn*-2,3-*anti*-iodoalcohol **211** is shown below (Figure 7). It clearly illustrates the 1,2-*syn*-2,3-*anti*-relationship of the trichloroacetamide, hydroxyl and iodide substitutents, respectively.

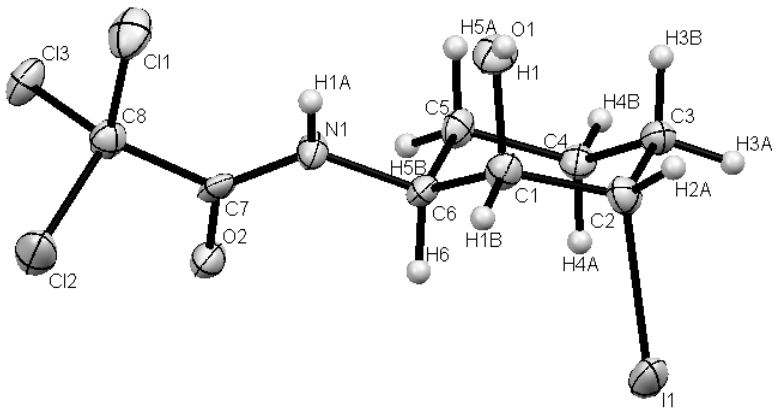
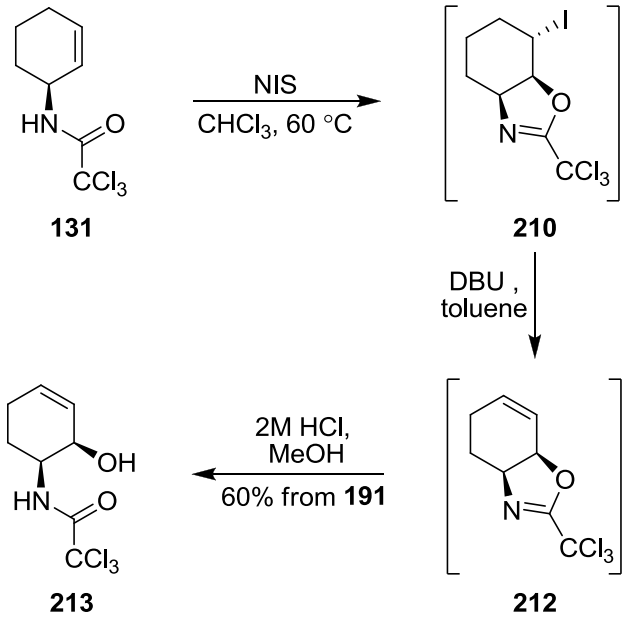


Figure 7 - ORTEP representation of X-ray crystal structure of compound 211

The stereochemistry of **211** suggested that iodination takes place *anti* to the trichloroamide to form iodonium ion **209** (Scheme 56). It is followed by *syn*-formation of 4,5-dihydro-1,3-

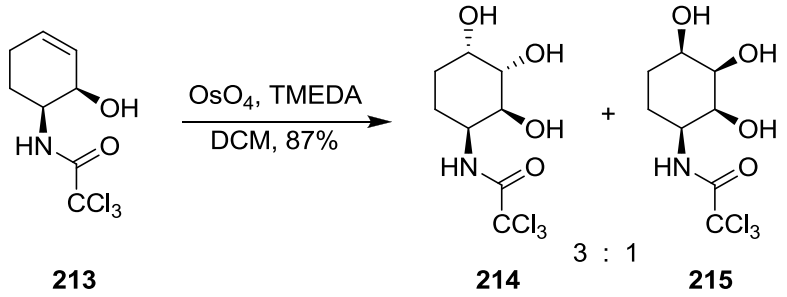
oxazole ring yielding **210**. In suitable acidic medium, hydrolysis takes place at C-2 to cleave the 4,5-dihydro-1,3-oxazole ring to furnish **211**.

When investigating the elimination of the iodide to generate the allylic alcohol, 1,2-*syn*-2,3-*anti*-iodoalcohol was treated with sodium hydrogencarbonate and heated under reflux overnight. However, none of the desired allylic alcohol **213** was isolated. Changing the base to DBU also failed to lead to the formation of any of the product, returning only starting material. In another attempt, **131** was again reacted with *N*-iodosuccinimide to give 4,5-dihydro-1,3-oxazole **210** (Scheme 57). Without purification, **210** was treated with DBU in toluene at 110 °C for 12 h. It resulted in the intermediate **212** which was further hydrolysed under acidic conditions to afford the desired allylic alcohol **213** in 60% yield over the three steps.



Scheme 57 - Formation of amidocyclohexanol 213

When this advanced stage of the synthesis was reached, the introduction of the other two hydroxyl groups *via* directed dihydroxylation was investigated. To synthesise the stereoisomer of trihydroxy carbocylic amine **133**, amidohexanol **213** was subjected to dihydroxylation using osmium tetroxide in the presence of TMEDA (Scheme 58). High diasteroselectivity was expected due to the enhanced directing effect of amide and hydroxyl at adjacent positions. These functional groups are in a position to direct the dihydroxylation to form triol **215** as the major diastereomer. However, under these conditions, a 3:1 mixture of two diastereomeric triols in 87% yield was isolated.



213 **214** **215**

Scheme 58 - Dihydroxylation of 213

The ratio of the stereosiomers was determined by ^{1}H NMR spectroscopy using the crude reaction mixture. The major isomer was easily separated by flash column chromatography in 53% yield. The exact stereochemisty of this major isomer could not be assigned using NMR techniques due to overlapping signals of adjacent hydrogen atoms. However, recrystallisation of the major product allowed X-ray structure determination and it appeared that that the major diastereomer was 1,2-*syn*-2,3-*anti*-3,4-*syn* isomer **214** (Figure 8).

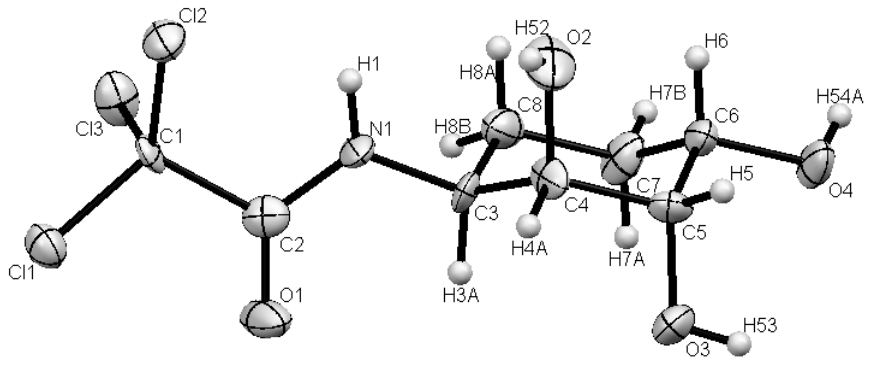
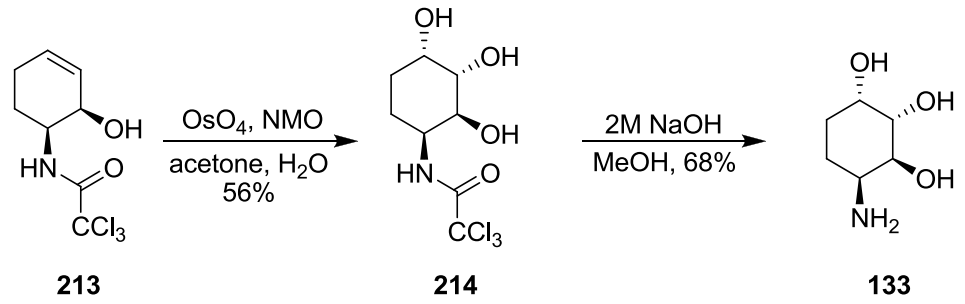


Figure 8 - ORTEP representation of X-ray crystal structure of compound 214

The results illustrate that the reaction takes place from the least hindered site of the cyclohexene **213** to generate trichloroacetamide derivative **214**. However, a certain level of directed dihydroxylation also occurs to afford triol **215**, as a minor diastereoisomer. To investigate the stereochemical outcome of the Donohoe reaction, the Upjohn reaction was employed. The Upjohn reaction is a method for dihydroxylation through a non-directed mechanism.[142] It makes use of a OsO_4 in catalytic amounts along with *N*-methylmorpholine *N*-oxide (NMO) as a stoichiometric re-oxidant. As such, the allylic alcohol was subjected to standard Upjohn conditions to give triol **214** as a single stereoisomer in 56% yield. The outcome from the Upjohn dihydroxylation of **213** provides evidence that formation of triol **215** using Donohoe conditions, must take place by a directing effect and it is not due to a face selective, non-directed dihydroxylation. In the

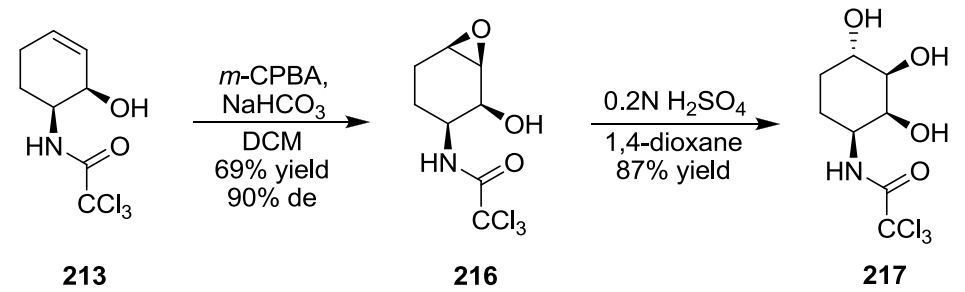
next step, removal of the trichloroacetyl protecting group of **214** was attempted using sodium hydroxide in methanol to access aminocyclitol **133**. Purification was carried out by ion exchange chromatography to yield dihydroconduramine E-1 **133** in 68% yield (Scheme 59).



213 **214** **133**

Scheme 59 - Synthesis of dihydroconduramine E-1 133

To access the enantiomer of dihydroconduramine C-1 **132**, a directed epoxidation of cyclic allylic alcohol using *m*-CPBA was proposed. It works presumably *via* Henbest's rule which states that an alcohol group directs the epoxidation reaction to generate the *cis*-epoxide stereochemistry.[143] The epoxide would then be subjected to hydrolysis to give the dihydroxy product upon treatment with an acidic solution of dioxane. As such, allylic alcohol **213** was treated with *m*-CPBA to yield *cis*-epoxide in 90% diastereomeric excess (Scheme 60). Purification by flash column chromatography gave the major product, the *syn*-diastereomer **216** in 69% yield.



213 **216** **217**

Scheme 60 - Epoxidation of 213 and formation of dihydroconduramine derivative 217

The stereochemistry of compound **216** was confirmed by NOE studies, which showed a positive NOE between hydrogen atoms H_b and H_c (0.8%). This shows that H_c of epoxide and H_b of hydroxyl group are on the same face of the ring. Hydrogen H_a of position 1 was then irradiated and an enhancement was observed (0.7%) with H_b indicating the s*yn* relationship of the adjacent hydrogens, thus confirming that the major diastereomer is 1,2-*syn*-2,3-*syn*-3,4-*syn*-isomer **216** (Figure 9).

In the next step, **216** was subjected to 0.2N H_2SO_4, to cleave the epoxide which resulted in the formation of dihydroconduramine derivative **217** in 87% yield (Scheme 60). The stereochemistry of the dihydroconduramine derivative **217** was again confirmed by difference NOE experiments. Dihydroconduramine derivative **217** was irradiated at stereogenic center H_b to determine the orientation in relation to H_c. It showed a positive NOE between hydrogen atoms H_b and H_c (1.3%) which implies they have *syn* relation to each other. In addition, there was no positive enhancement for the proton H_d upon irradiation of proton H_c, confirming that the compound **217** is the 1,2-*syn*-2,3-*syn*-3,4-*anti*-isomer (Figure 9).

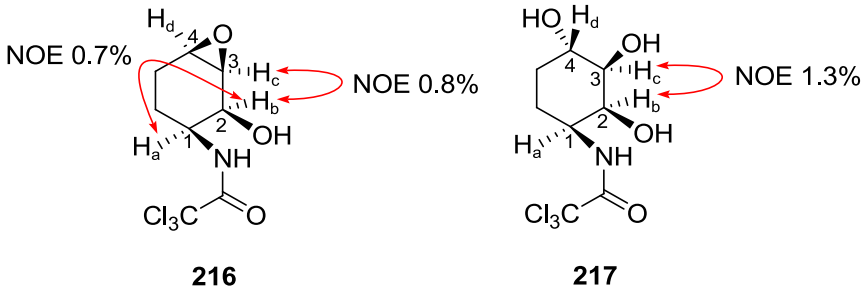
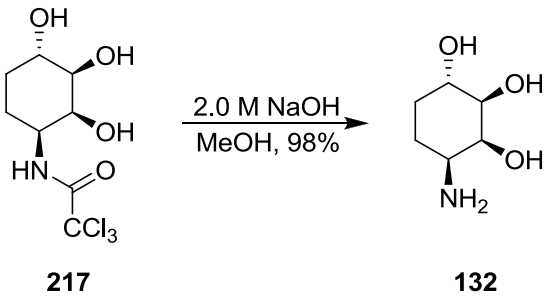


Figure 9 - NOE enhancement studies for the polyhydroxylated aminocyclohexane derivatives

Finally, treatment of 1,2-*syn*-2,3-*syn*-3,4-*anti*-isomer **217** with sodium hydroxide in methanol accomplished the hydrolysis of the trichloroacetamide group (Scheme 61). Purification was carried out using an ion exchange column which gave the enantiomer of dihydroconduramine C-1 **132** in 98% yield.



Scheme 61 - Synthesis of the enantiomer of dihydroconduramine C-1 132

3.2.3 Conclusions

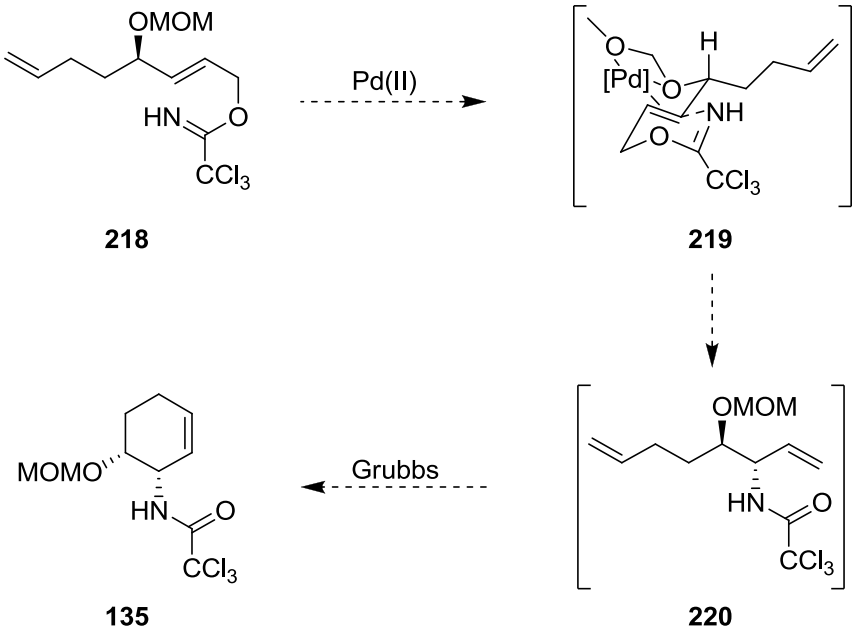
In conclusion, the stereoselective synthesis of dihydroconduramine E-1 and the enantiomer of dihydroconduramine C-1 was achieved using a stereoselective variant of the one-pot tandem Overman rearrangement and ring closing metathesis process in excellent yield and diastereomeric excess. During the course of the synthesis (1*S*)-*N*-(cyclohexenyl)

trichloroacetamide was efficiently prepared starting from the commercially available alcohol in 75% overall yield in six steps and in excellent enantiomeric excess. Initially Donohoe conditions and Henbest's principle were investigated for the synthesis of *syn* and *anti* diol derivatives of **131** respectively, in excellent diastereoselectivity. The noteworthy successes of a relevant model study provided the foundation for the synthesis of two dihydroconduramines. In the first approach, the allylic alcohol **213** was synthesised from **131** *via* 4,5-dihydro-1,3-oxazole **210** as a single stereoisomer. Non-directed dihydroxylation and directed epoxidation were then employed which resulted in the production of the two dihydroconduramines. This operationally simple route is very efficient and granted further insight into the stereoselective functionalisation of substituted cyclohexenes for the production of related natural products such as pancratistatins and other Amaryllidaceae alkaloids (see Section 3.3).

3.3 New Routes towards the Synthesis of Amaryllidaceae Alkaloids

3.3.1 Introduction

After the development of a one-pot tandem Overman rearrangement/ring closing metathesis process for the direct synthesis of cyclic allylic amides, the Sutherland group reported various interesting synthetic strategies to exploit its role in natural product synthesis.[40,41,77] Cyclic allylic amides are excellent synthetic intermediates that can be easily functionalised using a number of different reactions e.g. dihydroxylation,[140] stereoselective epoxidation,[141] Kharasch addition and conversion to bicyclic structures.[144] Such reactions can build up complexity on the ring framework to generate structures of interest. In this project, the aim was to expand the scope of this tandem process and use it in combination with a MOM-ether directed Pd(II)-catalysed Overman rearrangement for the diastereoselctive synthesis of cyclic allylic amide **135** (Scheme 62).



Scheme 62 - MOM-ether directed tandem Overman rearrangement and RCM reaction

This reaction pathway involves directed coordination of the Pd(II)-catalyst by the MOM ether to the allylic trichloroacetimidate resulting in a diastereoselective rearrangement. The product of this tandem process can then be used for the synthesis of various nitrogen containing natural products, antibiotics and unnatural amino acids or sugars. Initially, it was planned to use the directed rearrangement for the synthesis of some derivatives of the Amaryllidaceae alkaloids and screen them for biological activity.

The Amaryllidaceae family, consists of around 1100 species each belonging to eighty-five different genera and has produced a large number of structurally diverse alkaloids.[145] The galanthane ring system is a common characteristic of most of these compounds and is known for wide range of interesting physiological effects including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory and antimalarial activities.[146] Some of these alkaloids are of particular interest because of their potential use in clinical therapy. Some well-known alkaloids from this family include (+)-γ-lycorane **136**, (+)-2-deoxylycoricidine **221**, (+)-7-deoxypancratistatin **222**, and (+)-lycoricidine **223** (Figure 10).

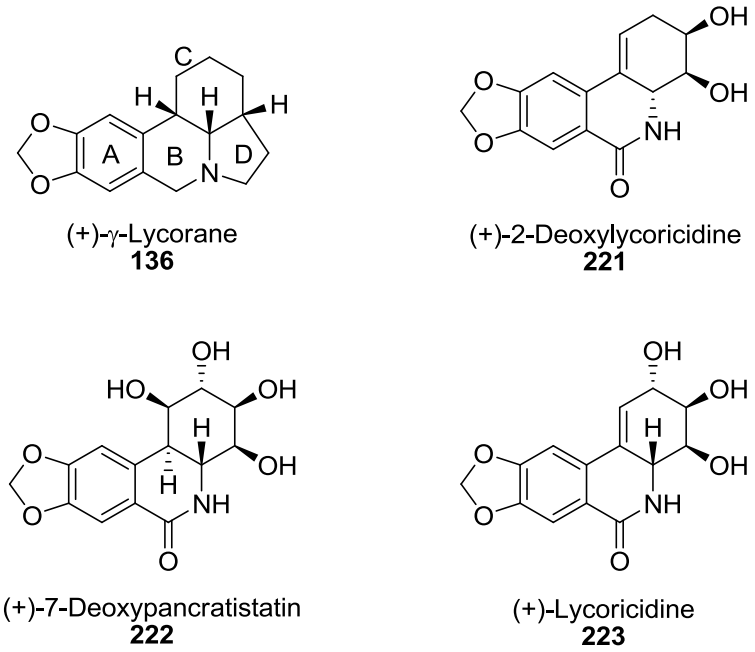
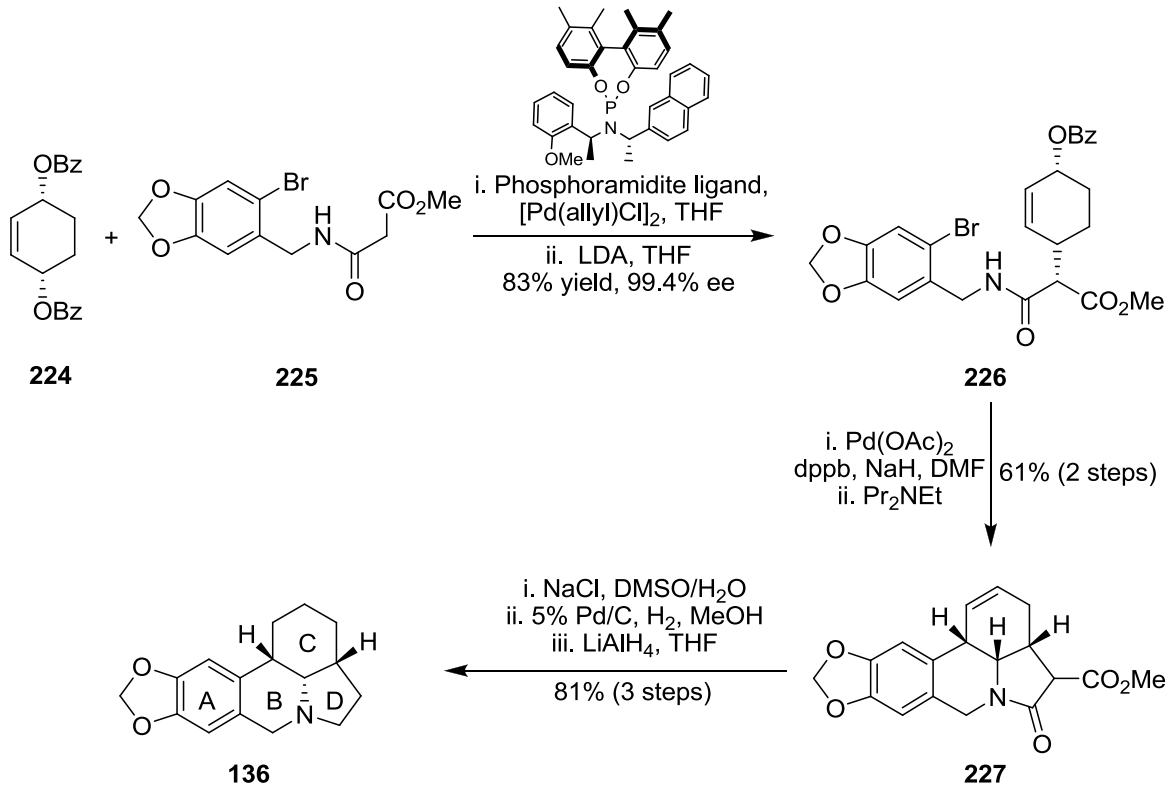


Figure 10 - Amaryllidaceae alkaloids

3.3.2 Previous syntheses of (+)-γ-lycorane

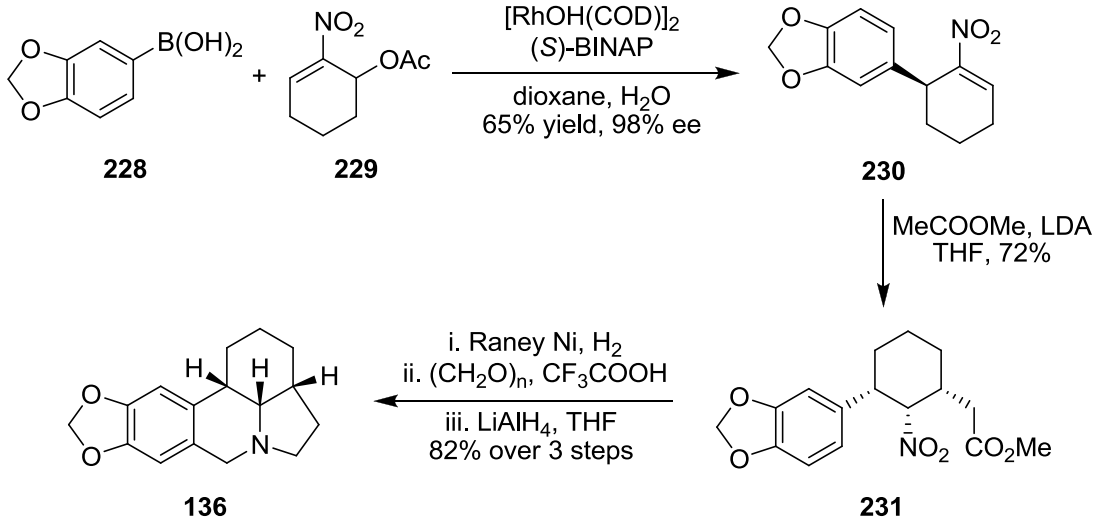
The unprecedented structure and potent pharmacological properties of the Amaryllidaceae alkaloids has motivated the development of many interesting synthetic strategies. In particular, subsequent to the first synthesis of γ-lycorane **136** in 1966, several different racemic and enantioselective approaches have been reported.[147-151] Many of these employ Pictet–Spengler,[152] Bischler–Napieralski cyclisations[153] or metal catalysed alkylation/cyclisations[149] as a key step for the construction of key parts of the Amaryllidaceae alkaloids. Some of the advances employed in the total synthesis of γ-lycorane **136** are discussed below.

The first asymmetric synthesis of (+)-γ-lycorane **136** was disclosed by Mori and co-workers.[149] They made use of an asymmetric Pd(0)-catalyst as the key enantioselective step for the allylic alkylation coupling of the A and C rings to give benzoate **226**. A subsequent amination and Pd(0)-catalysed intramolecular Heck reaction was used to finish the synthesis of γ-lycorane in 23% yield and 46% ee. Several years later, Ojima and co-workers[147] used the same strategy but made use of chiral monodentate phosphoramidite ligands and improved the overall yield from 23% to 41% and enantioselectivity further to >99% (Scheme 63).



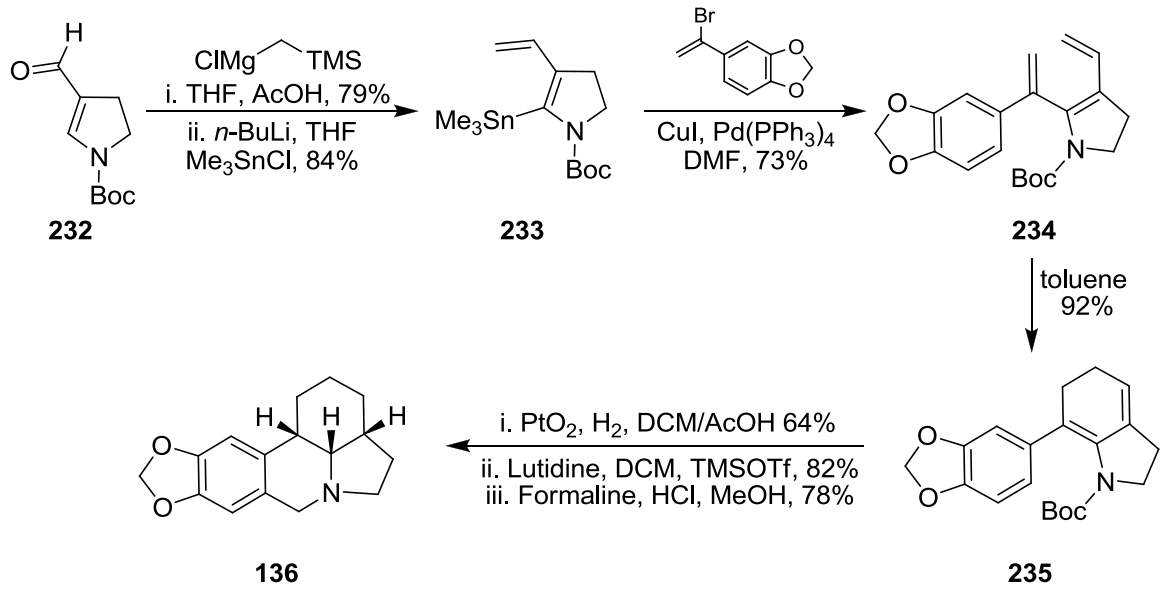
Scheme 63 - Ojima synthesis of (+)-γ-lycorane

In another approach, Gong and co-workers[154] described an enantioselective synthesis of γ-lycorane in 38% overall yield and 98% ee (Scheme 64). They used an asymmetric rhodium(II)-catalysed nitroallylation employing an aryl boronic acid **228** and a nitroallyl acetate **229** to construct the AC ring fragment **230**. This was followed by a conjugate addition of the enolate of methyl acetate to give **231**. The resulting compound **231** was then hydrogenated before performing a modified Pictet-Spengler ring closure reaction to construct the BD ring. This furnished (+)-γ-lycorane in an excellent yield after reduction with lithium aluminum hydride.



Scheme 64 - Gong synthesis of (+)-γ-lycorane

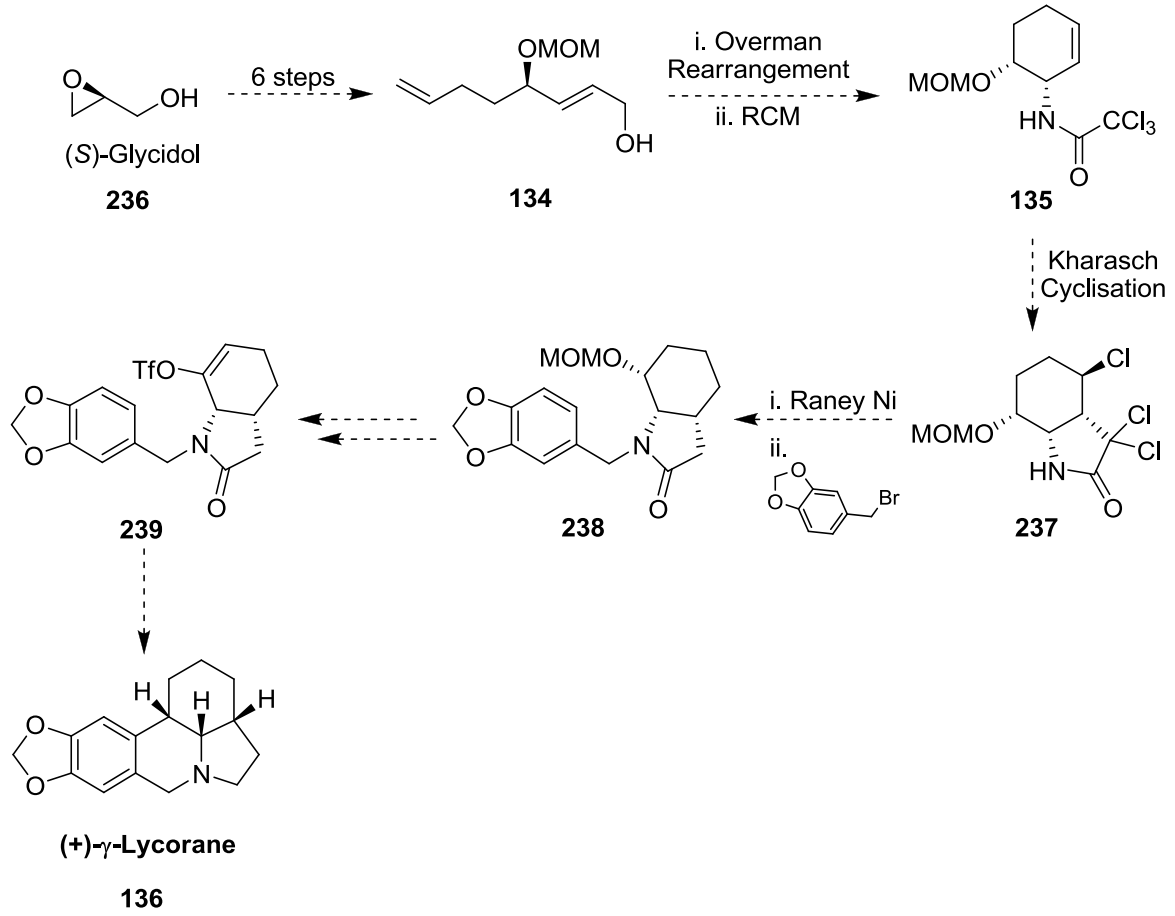
More recently, Funk and co-workers[155] reported a concise total synthesis of (±)-γ-lycorane **136** (Scheme 65). This synthesis involves the pre-functionalisation of commercially available Boc-2-pyrrolidinone **232**. It was then subjected to a Stille coupling using an appropriate vinyl halide to give the trienecarbamate **234** (AD ring) of γ-lycorane. Reflux in toluene performed the 6-π-electrocyclic ring closure which provided tetrahydroindole **235**. The resulting tetrahydroindole was ultimately hydrogenated with the aid of PtO_2 in acetic acid followed by deprotection of the carbamate. It was then converted to γ-lycorane by employing a Pictet–Spengler cyclisation using formalin in a solution of methanol. Once again it is an elegant synthesis giving the target molecule in 24% overall yield.



Scheme 65 - Funk synthesis of (±)-γ-lycorane

3.3.3 Proposed synthesis of (+)-γ-lycorane

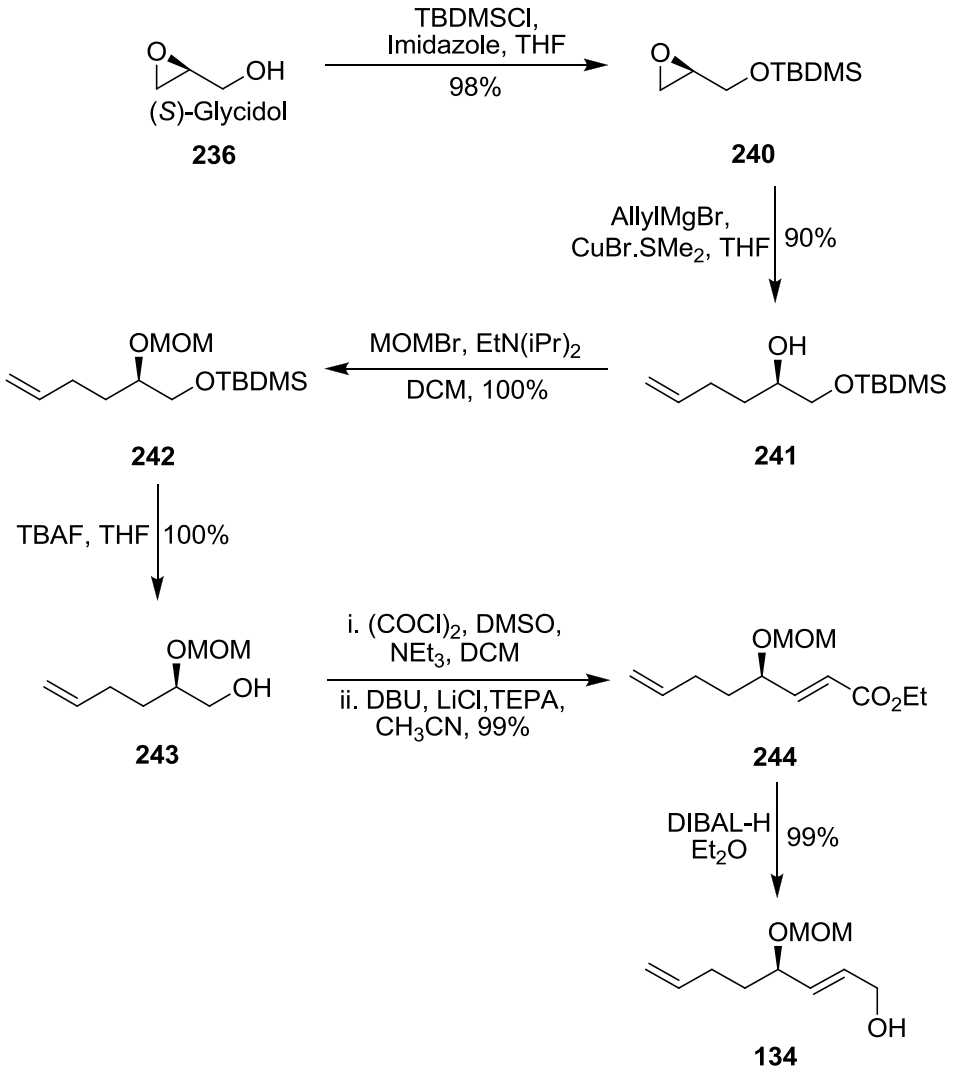
It is important to mention that in all previous asymmetric syntheses of (+)-γ-lycorane **136**, chiral catalysis were employed to achieve the key enantioselective steps. In contrast to this, our plan was to make use of a MOM-ether directed Overman rearrangement and combine it with a ring closing metathesis step to construct key synthetic intermediate **135** (C ring) and utilise it in order to synthesise (+)-γ-lycorane **136** and other structurally related compounds (Scheme 66). The main advantage of the one-pot tandem MOM-ether directed Overman rearrangement/RCM process, is that it will quickly generate a second stereogenic center on the resulting cyclic allylic trichloroacetamide from the corresponding allylic alcohol **134**. The new stereogenic centre in the resulting cyclic allylic trichloroacetamide would provide an additional reaction site for further functionalisation. Following this, the cyclic allylic amide will be subjected to a Kharasch cyclisation[144,156] to introduce the D ring, which would be subsequently dechlorinated using Raney®-Nickel. An alkylation reaction would then introduce the piperonyl moiety to put in the left hand aromatic fragment (ring A) to give compound **238**. It would be followed by a functional group interconversion to yield **239**. The palladium-mediated cyclisation of **239** is similar to that described by Mori and co-workers[147,149] during their synthesis of (+)-γ-lycorane and would allow the synthesis of the all *cis*-ring system. Finally, hydrogenation of the alkene and reduction of the amide would give Amaryllidaceae alkaloid, (+)-γ-lycorane **136**.



Scheme 66 - Proposed synthesis of (+)-γ-lycorane

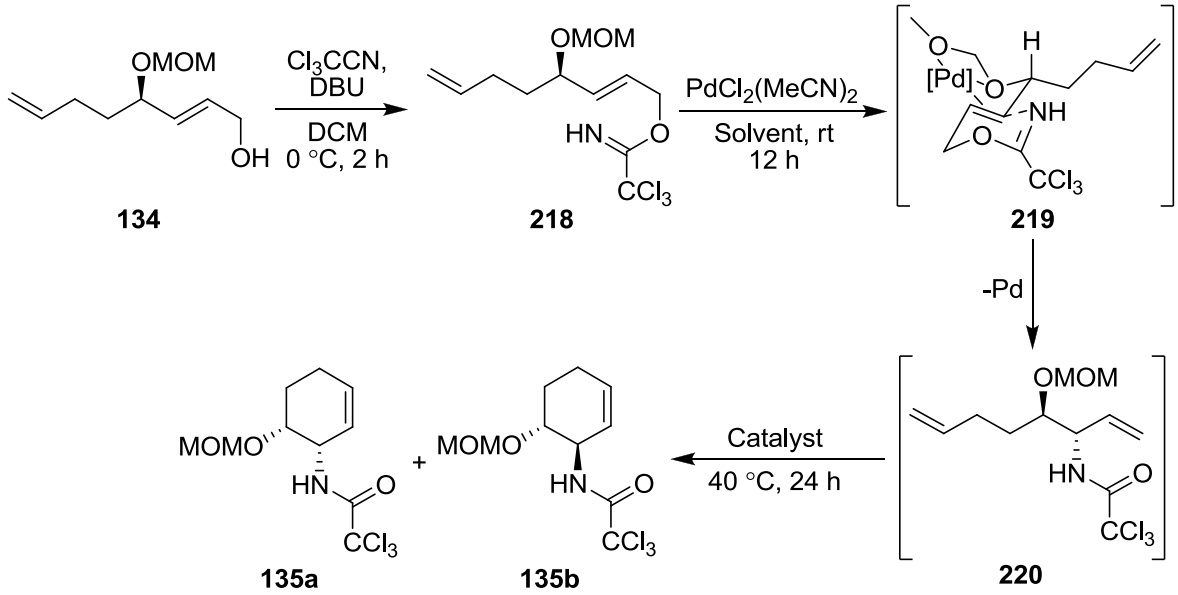
3.3.4 Development of an ether-directed tandem reaction

The first stage of this synthesis requires the formation of allylic alcohol **134** which would act as a substrate for the MOM-ether directed Overman rearrangement and RCM step. The synthesis of the corresponding allylic alcohol **134** began with the protection of the hydroxyl group of the commercially available glycidol **236** with a *tert*-butyldimethyl silyl group (Scheme 67). The resulting compound **240** was regioselectively ring-opened with allyl magnesium bromide in the presence of copper bromide dimethyl sulfide at –78 °C to give **241** in 90% yield. In the next step, the secondary alcohol of the resulting (2*R*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (**241**) was protected with a MOM-group using *N*,*N*-diisopropylethylamine and bromomethyl methyl ether in quantitative yield. It was subsequently treated with TBAF to give the primary alcohol **243** again in quantitative yield. Primary alcohol **243** was then subjected to a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction to give the *E*-α,β-unsaturated ester **244**. The *E*-α,β-unsaturated ester was further reduced with DIBAL-H to provide allylic alcohol in an excellent 86% yield over the 6 steps.



Scheme 67 - Synthesis of an allylic alcohol for directed rearrangement

With the allylic alcohol **134** in hand, it was further subjected to a one-pot tandem Overman rearrangement and RCM reaction to give the corresponding cyclic allylic trichloroacetamides **135** (Scheme 68). Initially the reaction of the allylic alcohol with trichloroacetonitrile was performed using DBU at 0 °C in two hours to form allylic trichloroacetimidate **218**. The Overman rearrangement was then performed using bis(acetonitrile)palladium(II) chloride (10 mol%) followed by the RCM reaction using Grubb's 1st generation catalyst. This resulted in the formation of **135a** and **135b**, as a 5:1 ratio of diastereomers in a 45% yield over 3 steps from the allylic alcohol **134** (Scheme 68).



Entry	Solvent	Catalyst	Yield from **227** (%)	ratio (a : b)
1	DCM	Grubbs I	45	5 : 1
2	Toluene	Grubbs I	60	10 : 1
3	Toluene	Grubbs II	49	10 : 1

Scheme 68 - Ether-directed tandem Overman rearrangement and RCM reaction

The diastereomeric ratio of the resulting MOM-protected carbocyclic amides could be easily determined from the ^{1}H NMR spectrum. The hydrogen atoms for the *anti*-product **135b** are observed at 3.75 ppm (1-H) and 4.42 ppm (2-H). The desired cyclic product **135a** showed its stereogenic hydrogen atoms at 4.05 ppm (1-H) and 4.63 ppm (2-H). The stereochemistry of the **135a** was further established by NOE studies, which showed an enhancement of hydrogen H_a (0.68% NOE) upon irradiation of hydrogen H_b, confirming the *cis*-geometry between these adjacent hydrogen atoms (Figure 11).

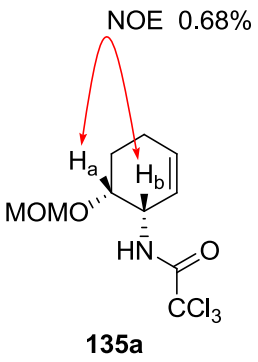


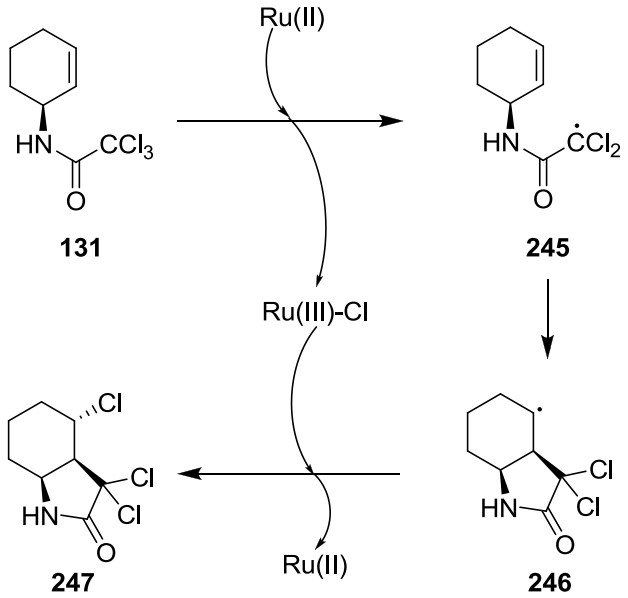
Figure 11 - NOE enhancement studies for the carbocyclic amide

To generate an efficient total synthesis of (+)-γ-lycorane **136** the yield and selectivity of the tandem process required improvement. Previously, it has been observed in our research group that toluene can enhance the yield and diastereoselectivity of MOM ether-directed Overman rearrangements due to its non-coordinating nature.[75] The reaction was repeated in toluene and pleasingly, this modification improved the yield from 45% to 60% and increased the diastereoselectivity from 5:1 to 10:1. However, the reaction takes more time to complete in comparison to a non-substituted six membered allylic trichloroacetamide (Section 3.1.2). The slow rate of the reaction can be attributed to the greater complexity of the substrate, which leads to a slower Overman rearrangement and ring closing metathesis steps. The more significant *anti*-diastereoselectivity of this process is due to the coordination of the Pd(II) catalyst with the oxygen atoms of the MOM group without having to compete with the THF solvent. This directs the catalyst selectively to the back face of the alkene and resulting in a diastereoselective rearrangement. This chair-like conformation not only minimises the allylic strain but also allows intramolecular attack of imidate nitrogen from the front face of the alkene, thus giving the major diastereomer **135a** (Scheme 68). To improve the yield of RCM step, the reaction was also carried out with Grubb's 2nd generation catalyst but no further improvement was observed and gave 49% of the major diastereomer **135a**.

3.3.5 Attempted Synthesis of (+)-γ-lycorane

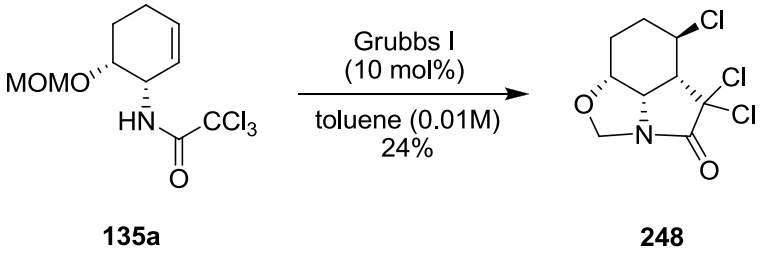
Having synthesised the MOM protected carbocyclic amide **135a**, it was proposed to perform a Kharasch cyclisation on the carbocyclic amide **135a** to provide the D-ring of γ-lycorane. The groups of Snapper and Itoh have reported the development of a ruthenium catalysed Kharasch cyclisation of allylic trichloroamides to give the corresponding bicyclic ring systems in high yields.[144,156] In addition, both groups have shown that all the substrates used in this process furnished exclusively the *cis*-ring junction between the 5- and 6-membered rings, confirming that our use of the Kharasch cyclisation will yield the correct stereochemistry required for the synthesis of (+)-γ-lycorane **136**. A Kharasch cyclisation is a Ru(II)-catalysed reaction that proceeds *via* a radical mechanism (Scheme 69).[156] During the course of the reaction, ruthenium(II) triggers the sequence of the reaction leading to the formation of the bicyclic product. Initially, ruthenium(II) attacks the trichloroacetyl group of **131** and abstracts a chlorine atom to form Ru(III)-Cl and supplies the radical **245**. The carbon radical **245** then attacks the alkene to form the new C-C bond of the 5-membered ring and generates the new carbon radical **246**. This reaction is then terminated by re-introduction of Ru(III)-Cl which introduces a chloride to the face opposite

to the new 5-membered ring **246**, thus providing the Kharasch product **247** as a single diastereomer.



Scheme 69 - Radical mechanism of Kharasch cyclisation

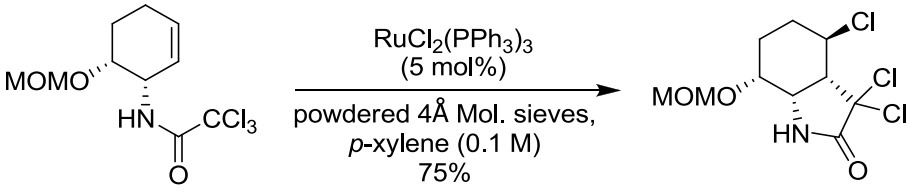
Previously, in the Sutherland group efforts have been made to do the Kharasch cyclisation of **135a** employing the Grubbs I catalyst in toluene at 155 °C but this resulted in the formation of the tricyclic product **248** and in a poor yield (Scheme 70).



Scheme 70 - Kharasch cyclisation using Grubbs catalyst

In this project, the MOM protected carbocylic amide **135a** was treated with $RuCl_2(PPh_3)_3$ catalyst under the conditions reported by Itoh however, this gave a mixture of the Kharasch product **237** and tricyclic product **248** in low yields.[138,150] To improve the yield and selectivity of the reaction, when **135a** was subjected to higher temperature (155 °C) in 0.1 M *p*-xylene in a Schlenk tube, the reaction was completed after 2 h and the desired product **237** was isolated in 42% yield. However, the formation of a small amount (10%) of tricyclic compound **248** could not be avoided. During the course of the reaction, unwanted side reactions were deemed likely due to the HCl that is formed due to the decomposition

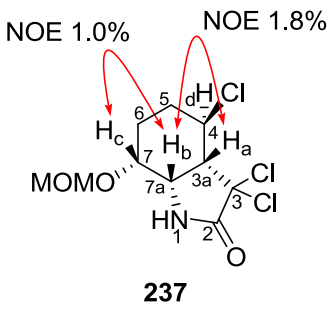
of the staring material or product during the high temperatures of the Kharasch cyclisation. To overcome this issue, any acid that was produced during the reaction had to be trapped. It was therefore envisioned that adding an acid scavenger would be appropriate to keep the reaction selective. Three different additives were tried including DBU, potassium carbonate and molecular sieves (4Å). The reaction did not work by utilising DBU and returned only starting material **135a**, whilst addition of potassium carbonate also did not improve the reaction and again yielded a mixture of the two products (**135a** and **248**). However the use of 4Å molecular sieves gave only the desired product **237** in a 56% yield. The use of powdered 4Å molecular sieves further improved the reaction and increased the yield to 75%. Powdered molecular sieves increased the surface area of the sieve and therefore trap the acid more efficiently. This inhibits the side reaction and in turn improves the yield of the reaction (Scheme 71).



135a **237**

Scheme 71 - Optimised reaction conditions for the Kharasch cyclisation

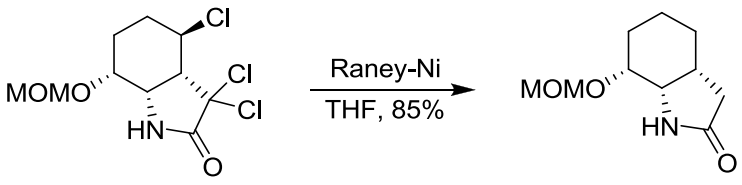
The stereochemistry of the resulting compound **237** was established by NOE studies. Irradiation of hydrogen H_b showed a positive enhancement to the adjacent hydrogen atoms (H_a and H_c) thus, confirming the all *cis*-geometry between H_a, H_b and H_c (Figure 12). The stereochemistry at C-4 was confirmed by irradiation of hydrogen H_a and as expected there was no enhancement of hydrogen H_d proving that the chlorine was on the top face of the molecule.



237

Figure 12 - NOE studies confirming *cis*-ring junction

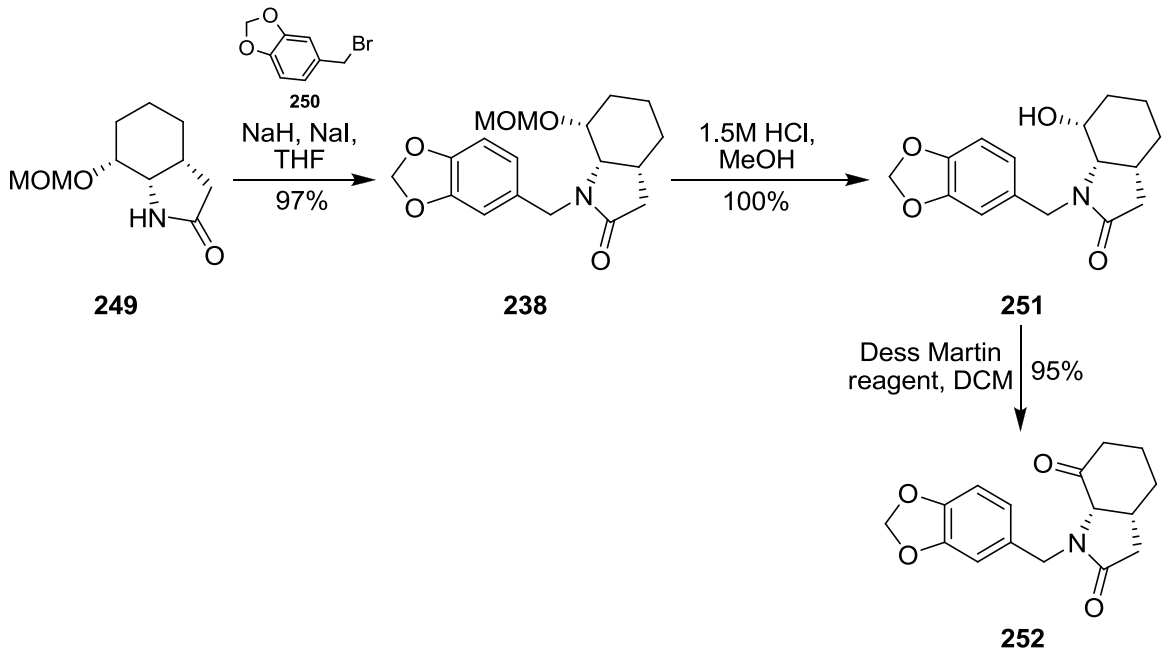
In the next step, the reductive dechlorination of the Kharasch cyclised product **228** was accomplished by using procedure described by Barrero and co-workers.[157] It involved the heating of **237** with Raney®-Nikel to afford **249**. The reaction worked well and gave an 85% yield for the desired dechlorinated product (Scheme 72).



237 **249**

Scheme 72 - Dechlorination using Raney®-Nickel

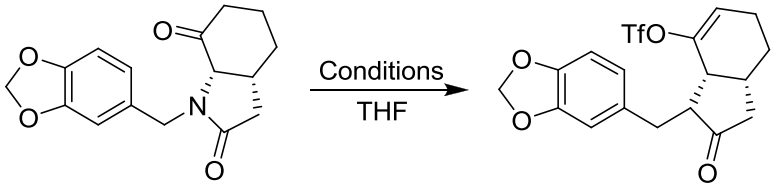
The next stage of the synthesis involved incorporation of the piperonyl moiety. This would give substrate **238** which would be subsequently oxidised to get ketone **252** (Scheme 66). The resulting ketone **252** would be converted into an enol triflate by means of a protocol described by Hagiwara.[158] There is significant literature precedent that enol triflates are amenable to palladium catalysed cross coupling reactions under mild conditions and with high chemo- and stereoselectivity. It was proposed that as the methylene hydrogens of the C ring are more acidic in comparison to that of the D ring then the use of base such as LDA would allow the selective enolisation of **252** followed by triflation with triflic anhydride to generate **239**. Moving towards the desired enol triflate, the dechlorinated MOM protected compound **249** was alkylated with the piperonyl bromide **250** to provide the A ring of the γ-lycorane. This was conducted under the reaction conditions previously reported by Fujioka and co-workers involving reaction of **249** (Scheme 73).[159,160] The reaction worked smoothly and gave the desired compound **238** in an excellent 97% yield. Cleavage of the MOM protecting group was performed with 1.5M HCl in methanol at 40 °C to give the alcohol **251** in 100% yield. This was subsequently oxidised to give **252** with the Dess-Martin reagent again in an excellent 95% yield.



Scheme 73 - Synthesis of cyclohexanone 252

Having successfully synthesised the ketone **252**, the substrate was treated with LHMDS in THF at –78 °C followed by reaction with triflic anhydride. However, neither the desired product nor the starting material was identified upon work-up. In another effort, Commins reagent was employed instead of triflic anhydride. This resulted in only traces of the desired product **239** with mainly recovery of the starting material. This was taken as a good sign after the initial failure and so the reaction was repeated with additional equivalents of LHMDS and stirred for an extended period of time. The reaction gave a complex mixture of products. Moreover 8% of the desired product along with 39% of the starting material was also isolated. To deal with the problem, the reaction was also attempted using freshly prepared LDA along with DMPU. However, this could not improve the results, giving only traces of the desired product along with a considerable amount of unidentifiable by-products (Table 9).

Table 9 - Attempted synthesis of enol triflate 239

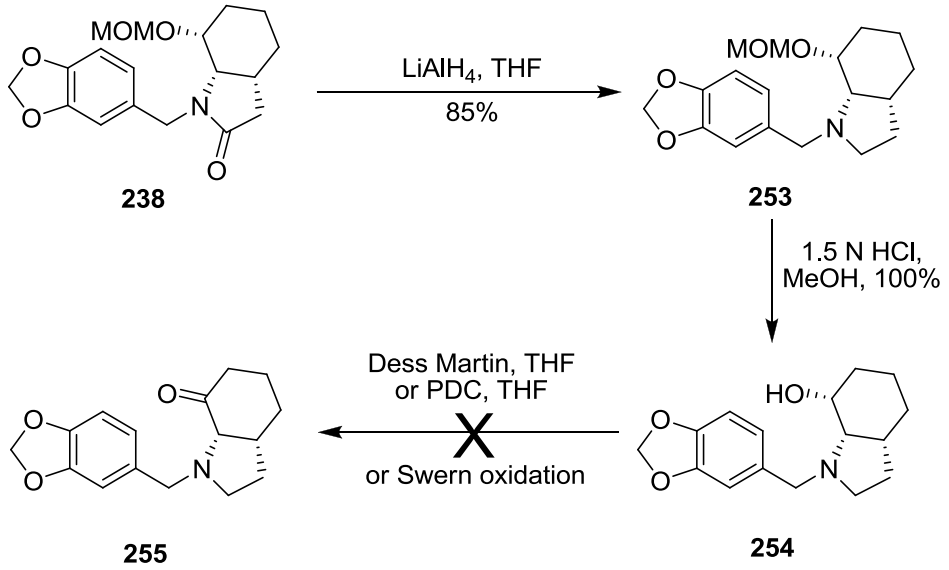


252 **239**

Entry	Conditions	Base	Additives	Yield (%)[a]
1	Triflic anhydride	LHMDS	---	Decomposition
2	Commins reagent	LHMDS	---	Traces
3	Commins reagent	LHMDS	---	8(39)
4	Commins reagent	LHMDS	DMPU	Traces
5	Commins reagent	LDA	DMPU	10(72)

[a] Recovered starting material % in parenthesis ()

To limit the formation of undesired by-product and to achieve high yields of the desired triflate **239**, it was proposed to re-order the synthetic steps and reduce the amide prior to deprotection of the MOM group. This would allow triflate formation selectively and would limit the possibility of a second triflate formation. Compound **238** was heated under reflux in THF with $LiAlH_4$ to afford **244** in an 85% yield (Scheme 74). Next the MOM group was cleaved and the resulting alcohol **254** was subjected to oxidation. Initially, the Dess-Martin reagent was employed for the oxidation of the secondary alcohol **254** and the reaction was stirred for 4 h. However, only starting material was present in the reaction mixture. The reaction was stirred for a further 12 h and it was observed that the starting material had begun to decompose. As such, it was decided to try another oxidising agent in order to proceed further. In a second attempt, **254** was treated with PDC at room temperature. However, this reagent also led to decomposition of the starting material and no desired product was formed. The reaction was tried again at 0 °C using only an half equivalent of PDC. These conditions also proved unrewarding, failing to give any identifiable oxidised product, giving the same result as before even after 10 minutes of stirring. As a final option, a Swern oxidation was attempted. Although, the starting material was consumed leading to the formation of a number of spots on the TLC plate, none of them could be identified as the desired compound.



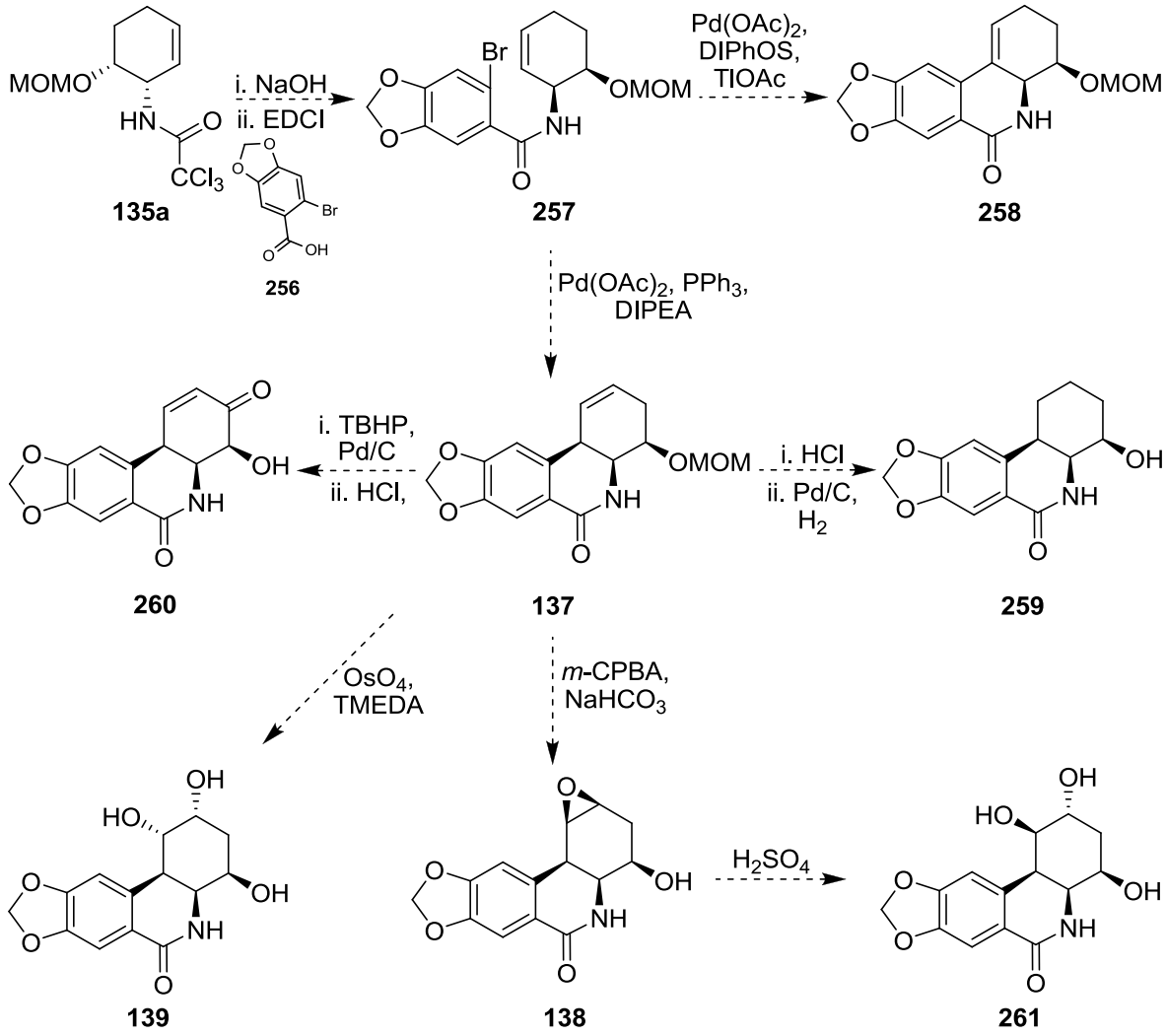
Scheme 74 - New strategy for the synthesis of substrate for triflate formation

Unfortunately none of these procedures were successful in generating the desired compound in high yield for the eventual synthesis of (+)-γ-lycorane. Work in this area was discontinued and we turned our intensions to the synthesis of pancratistatin analogues.

3.3.6 Synthesis of pancratistatin analogues

Among the numerous members of the Amaryllidaceae family, phenanthridone alkaloids such as (+)-2-deoxylycoricidine **221**, (+)-7-deoxypancratistatin **222**, and (+)-lycoricidine **213** are the most well known due to their interesting structures and potent biological activities (Figure 10, page 71).[88] Over the years, a number of creative approaches have appeared in the literature to synthesise these fascinating targets by several research groups.[161-165] Our interest in **221** and **222** is heightened by its promising activity in several anticancer tests against the NCI human tumour cell line panel.[88,166] These compounds have also shown antitumor activities and have appeared as potent therapeutic agents against a set of diverse viruses. The mode of action for these compounds is still not known in detail. However, various investigations have shown that the activities of such compounds can be attributed to the oxygenated cycle and to their tricyclic structure.[167]

In continuation of our ongoing research program, our aim was to use the mono-substituted cyclic allylic amide **135a** to undertake a highly stereoselective synthesis of various novel pancratistatin analogues and screen them for their biological activities. As such, a new strategy for the synthesis of pancratistatin analogues and their related derivatives was devised and is outlined below (Scheme 75).

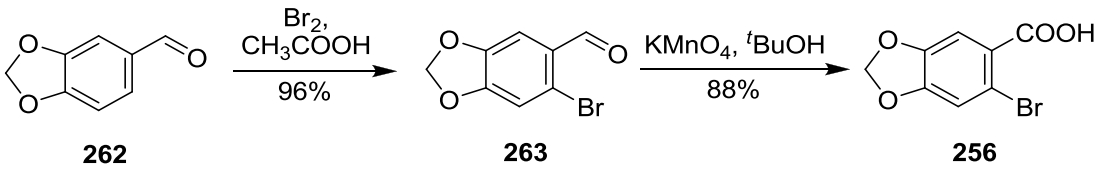


Scheme 75 - Proposed route for the synthesis of Pancratistatin analogues

The synthetic route involved the removal of the trichloroacetyl group under base mediated conditions followed by a coupling with a piperonyl moiety **256**. The resulting compound **257** would set the stage for the synthesis of the basic core of the pancratistatin (B ring) through the action of the Pd-catalysed cross coupling reaction. At this point, the synthesis of many different pancratistain analogues should be straightforward. Removal of the MOM protecting group followed by hydrogenation would give the first target **259**. In order to achieve the synthesis of the other poly-hydroxylated analogues, **137** will be subjected to allylic oxidation, directed dihydroxylation and epoxidation to provide various pancratistatin analogues. If the allylic oxidation reaction proved to be successful, then resulting ketone would be reduced and directed dihydroxylation would furnish the fully oxygenated C ring.

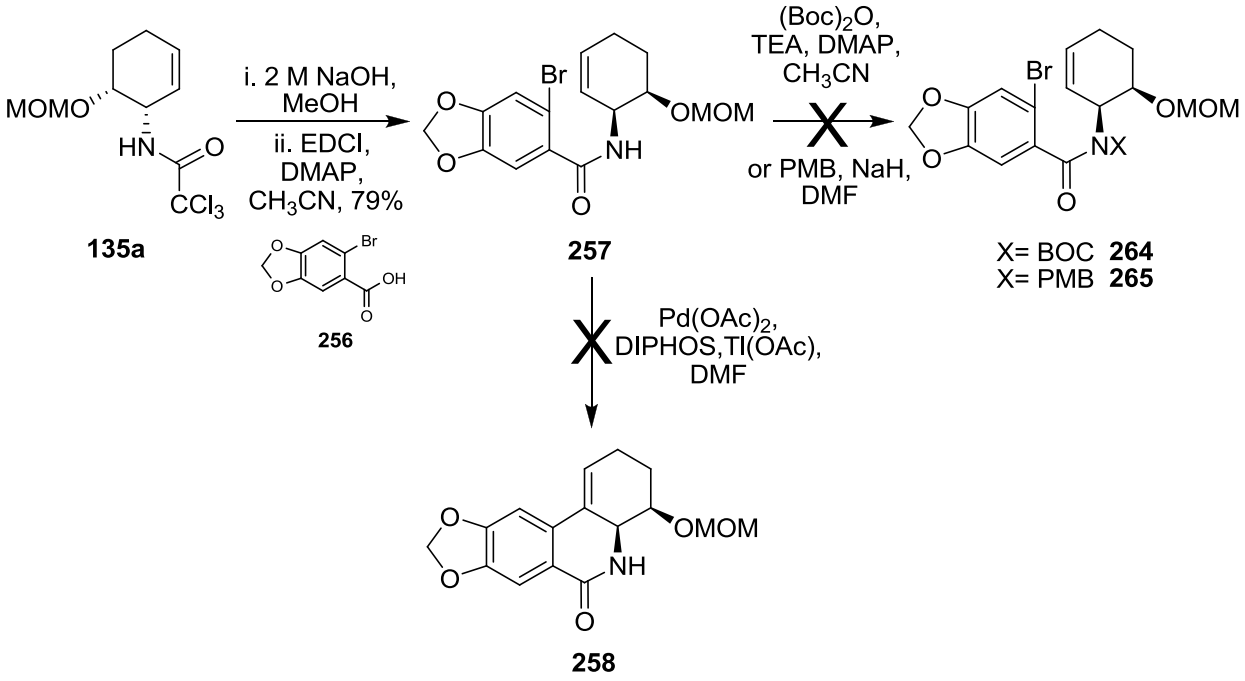
The pancratistatin analogue synthesis commenced with the hydrolysis of the cyclic allylic trichloroacetamide **135a**. The reaction was carried out by stirring a solution of **135a** in a

1:1 mixture of methanol and 2.0 N sodium hydroxide to provide the amine in quantitative yield (Scheme 77). The A-ring building block of the phenathridone was prepared *via* the bromination of the commercialy available piperanal **262** in glacial acetic acid to give 6-bromopiperonal **263** as a crystalline solid in 96% yield. The resulting 6-bromopiperonal **263** was oxidised through the action of potassium permanganate to furnish 6-bromopiperonylic acid **264** in overall 85% yield (Scheme 76).[168]



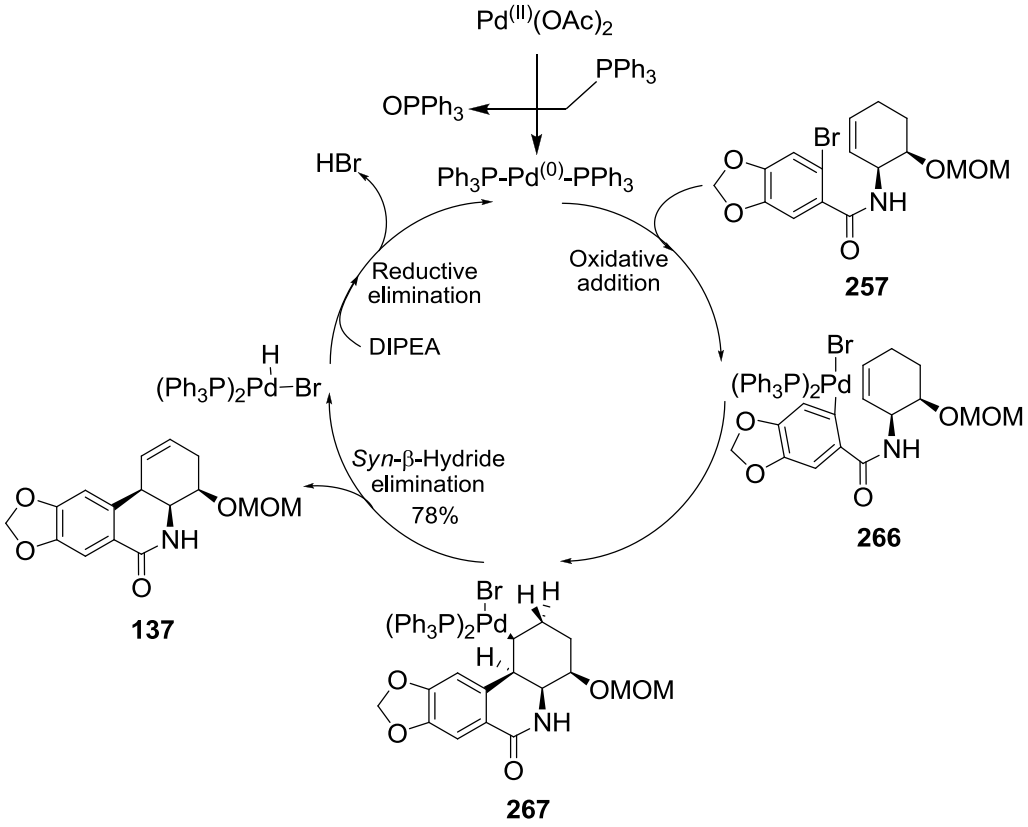
Scheme 76 - Synthesis of 6-bromopiperonylic acid 256

Having the carbocyclic amine and 6-bromopiperonylic acid in hand, we turned our attention to coupling them together with the aid of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI). A synthetically useful virtue of EDCI is that it can be employed as a carboxyl activating agent for the coupling of primary amines to yield amide bonds. In a typical procedure, the solution of amine in acetonitrile was treated with EDCI along with a catalytic amount of DMAP followed by acidic work up to give the desired compound **257** in 79% yield. To make the basic core of pancratistatin **137** and lycoricidine analogues **258**, two different approaches both involving palladium acetate were investigated (Scheme 77 and 78). Initially, Ogawa's[169] protocol of an intramolecular Heck reaction was attempted to give **258**. This approach requires the protection of the carbamate nitrogen of **257** with a suitable protecting group such as Boc or PMB. The Boc protection of **257** was attempted using Boc anhydride, TEA and DMAP in acetonitrile and was stirred at room temperature for 24 h. These conditions did not show any sign of reaction. The reaction temperature was then increased to 80 °C and stirred overnight but again this reaction failed to lead to the generation of the desired Boc protected compound **264** (Scheme 77). After this failure, a *p*-methoxybenzyl protecting group was employed. The reaction was attempted in DMF using *p*-methoxybenzyl chloride in the presence of sodium hydride. Again no product was formed despite long reaction times at elevated temperatures (80 °C) and returned only starting material. Our attempts to protect the carbamate nitrogen of **257** did not prove successful. Therefore, compound **257** was subjected to the Ogawa protocol where compound **257** is exposed to $Pd(OAc)_2$, Tl(OAc), and 1,2-bis(diphenylphosphino)ethane (DIPHOS) in DMF at 140 °C. These conditions again failed to promote the reaction towards the desired compound and gave only starting material back.



Scheme 77 - Alkylation and cross coupling of carbocyclic amide 135a

It was decided instead to perform the reaction using conditions previously reported by Mori.[149] Thus, the reaction was attempted using Hünig's base and triphenylphosphine along with $Pd(OAc)_2$ in a solution of DMF and was heated to 100 °C (Scheme 78). However, only starting material was present after 24 h of stirring. Some further experimentation revealed that the B ring of the phenanthridone forms smoothly in 78% yield when the reaction was carried out in a Schlenk tube at 150 °C (Scheme 78). To accomplish the synthesis of **137**, a combination of Hünig's base, triphenylphosphine and $Pd(OAc)_2$ at 150 °C in a sealed tube was essential. During the course of the reaction, triphenylphosphine reduces the Pd(II) to Pd(0). Once formed, Pd(0) activates the sequence of events by taking part in an oxidative addition with **257** to give the 16-electron complex **266** (Scheme 78). In the following step, insertion of alkene into the C-Pd bond generated a four-centred transition state **267** in a *syn*-fashion. Subsequently, a simple bond rotation occurs to relieve the torsional strain and allows the *syn*-relationship between a β-hydrogen and the palladium atom. Having a β-hydrogen and the transition metal in a common plane, β-hydride elimination takes place to give the phenanthridone skeleton **137**. In the final step, the palladium(0) is regenerated by a base assisted reductive elimination. It is worth mentioning that the use of other phosphine ligands such as DIPHOS and additives such as Tl(OAc) in the presence of $Pd(OAc)_2$ did not give the desired cyclisation even in Schlenk tube at 150 °C. Moreover, the cross coupling of **247** works only when the reaction is carried out in a sealed tube. During the cyclisation, the alkene moves out of conjugation and furnishes only the single stereoisomer **137**.



Scheme 78 - Heck type reaction for the synthesis of Phenanthredone core 137

The sterochemistry of the **137** was confirmed by difference NOE experiments. The compound **137** was irradiated at H_b to determine the orientation in relation to H_a and H_c. It showed a positive enhancement between H_b, H_a and H_c which implies they all have a *syn*-relationship to each other (Figure 13).

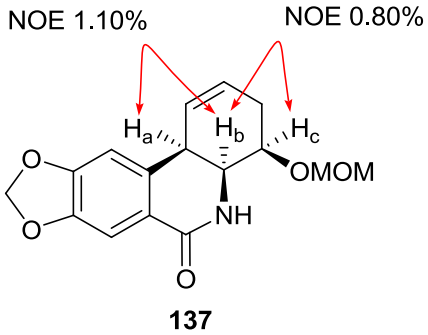
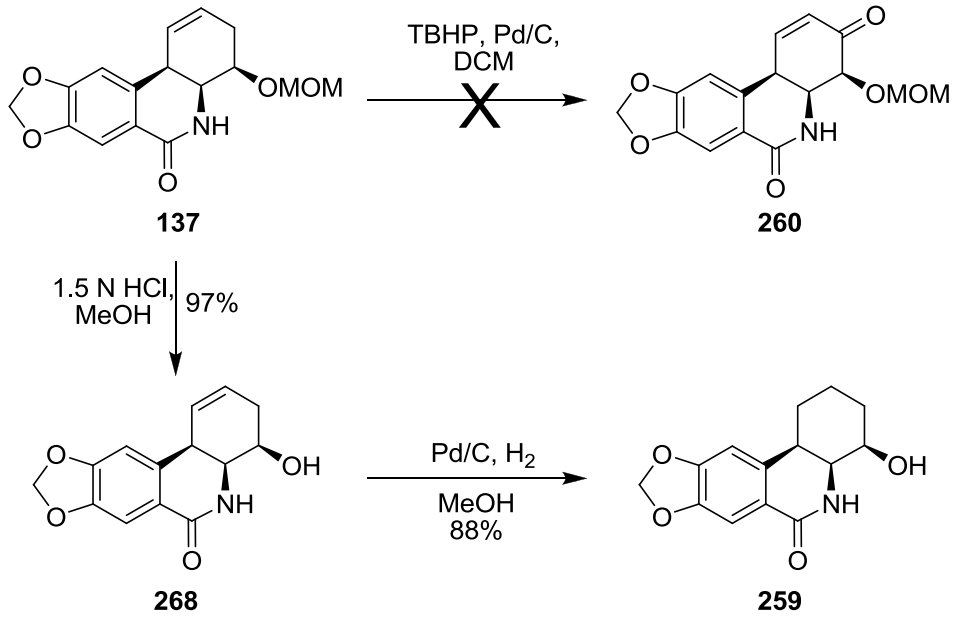


Figure 13 - NOE enhancement studies for the compound 137

There are some reports which show that using Ogawa's modified Heck reaction protocol, **258** can be furnished *via anti*-elimination instead of the generally observed *syn* reductive elimination of palladium.[170] In our case no *anti*-elimination was observed. However formation of **137** implies that the β-hydride elimination takes place formally via *syn*-elimination.

Having synthesised the phenanthridone skeleton **137**, an investigation into further functionalisation was proposed. Initially, allylic oxidation was attempted using the Cory procedure.[111] In the first attempt, substrate **137** was exposed to 5 equivalents of TBHP as an oxidant along with a catalytic amount of 10% Pd on carbon and potassium carbonate at 20 °C for 12 h. Under these conditions, the desired product was not detected in the reaction mixture. The temperature of the reaction mixture was raised to 45 °C and was stirred for a further five days. Once again this proved unrewarding. Previously, we have faced considerable difficulties for the allylic oxidation for the much simpler substrate **129**. Many of the more commonly known oxidation protocols were examined and proved to be futile (Section 3.1.3). It was proposed that allylic oxidation might work in this instance as there was literature precedent for similar substrates.[171] Moreover in this substrate, the amide functionality is far away from the reaction activation site. However, all attempts were again unsuccessful.

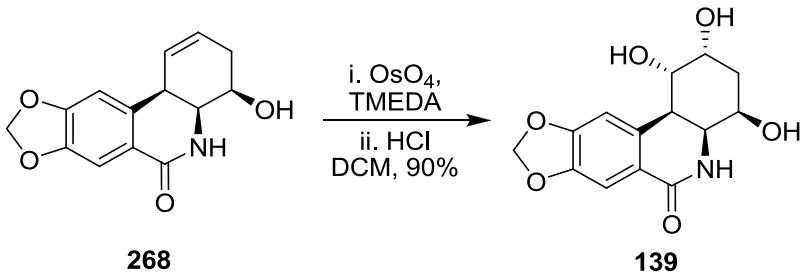
To progress, the synthesis of **268** was achieved by removal of the MOM group of **137** under acidic conditions. This was followed by treatment with palladium on carbon under an atmosphere of hydrogen to achieve hydrogenation in an excellent 88% yield to supply target compound **259** (Scheme 79).



Scheme 79 - Attempted allylic oxidation and formation of pancratistatin analogue 259

In order to achieve the synthesis of pancratistatin analogues **138** and **261**, compound **268** was dihydroxylated using conditions previously employed for the synthesis of dihydroconduramines C-1 **132** and E-1 **133**. At first, the phenanthridone skeleton **268** was

reacted with osmium tetroxide in the presence of TMEDA at –78 °C, followed by treatment with conc. HCl to cleave the osmate ester (Scheme 80). The hydroxylation reaction occurred smoothly, producing **139** as a single stereoisomer in 90% yield (Scheme 81).



268 **139**

Scheme 80 - Dihydroxylation of 268

The result from this transformation showed that formation of triol **139** occured exclusively from the less hindered convex face of the ring, without any directed dihydroxylation of the alkene. This can be explained due to the extraordinary steric congestion of the C ring, in the phenanthridone skeleton **268**. Initially, the stereochemistry of **139** was assigned through coupling constants of the cyclohexane ring hydrogens from the ^{1}H NMR spectrum as well as the acquisition of COSY and NOE spectra. It was further established by X-ray crystallography of the resulting compound **139** (Figure 14).

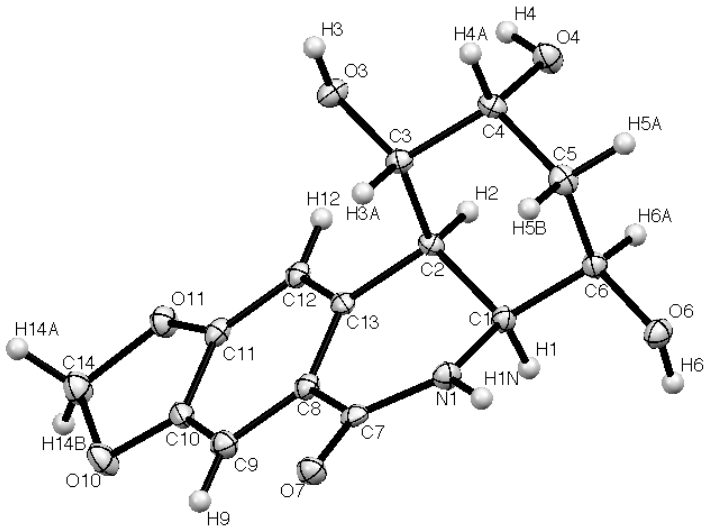
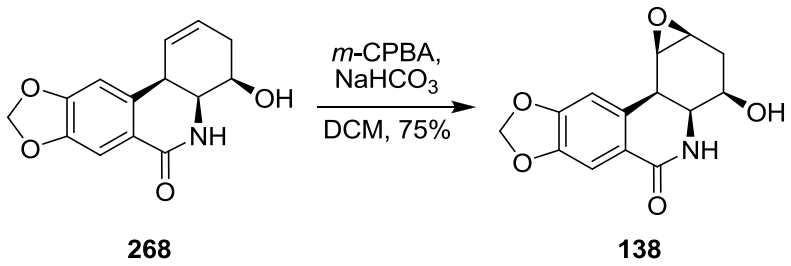


Figure 14 - ORTEP representation of X-ray crystal structure of the compound 139

To access the pancratistatin analogue **138**, the directed epoxidation of cyclic allylic alcohol using *m*-CPBA was employed. The pioneering work of Henbest and Wilson, established that cyclic allylic alcohols can be diasteroselectively epoxidised with *m*-CPBA to furnish

the corresponding *cis*-epoxy alcohol diastereomer. On the basis of this, as well as our own results during the synthesis of aminocyclitols (Section 3.2.2), it was proposed that the *m*-CPBA is small enough to coordinate to either the C4-hydroxy or C4a amide from the more hindered concave face of phenanthridone ring **268** for the directed epoxidation to give corresponding *cis*-epoxy alcohol stereosiomer. The allylic alcohol **268** was subjected to standard conditions and stirred overnight. A rather sluggish reaction was observed, although the starting material was consumed after 48 h. Gratifyingly, this reaction gave *cis*-epoxy alcohol **138** as a single diastereomer (by ^{1}H NMR spectroscopy of the crude reaction material). Purification by flash column chromatography afforded the epoxide **138**, in 75% yield (Scheme 81).



Scheme 81 - Epoxidation of 268

The stereochemistry of the resulting epoxide was confirmed by NOE studies. The stereochemistry of H_b had already been established. On irradiation of H_b, a positive NOE between the of position H_b and H_c (0.58%), indicated the s*yn*-relationship, thus confirming the preparation of the (1*R*,2*S*,4*R*,4a*S*,10b*S*)-stereoisomer **138** (Figure 15).

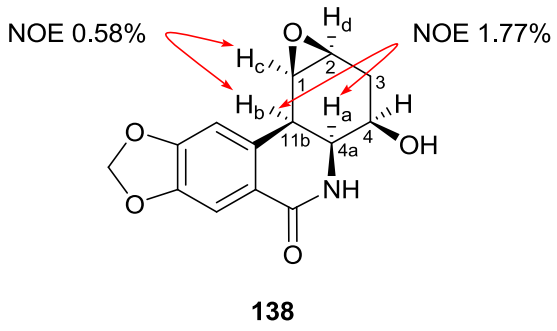
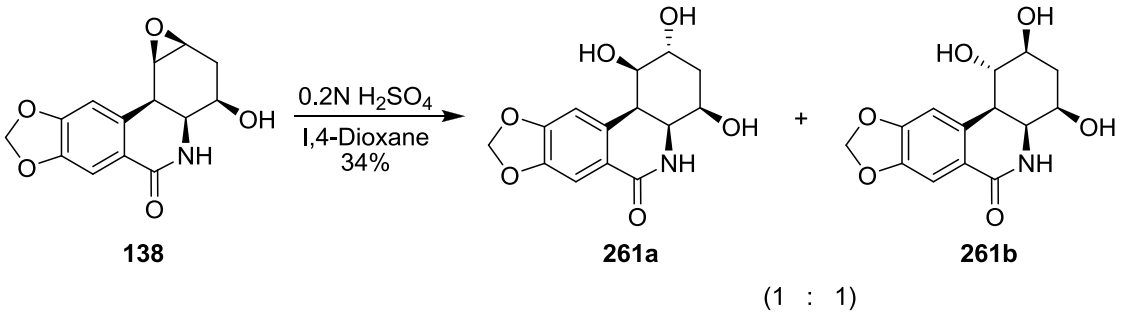


Figure 15 - NOE enhancement studies for the epoxy alcohol 138

Finally, **138** was subjected to 0.2N H_2SO_4 in 1,4-dioxane, to cleave the epoxide (Scheme 82). Surprisingly, this resulted in a 1:1 mixture of **261a** and **261b** in only 34% yield even after 4 days of stirring at 100 °C. Compound **138** was also treated with sodium benzoate in

an attempt to perform a more selective ring opening but again a 1:1 mixture of **261a** and **261b** was isolated in only 18% yield.



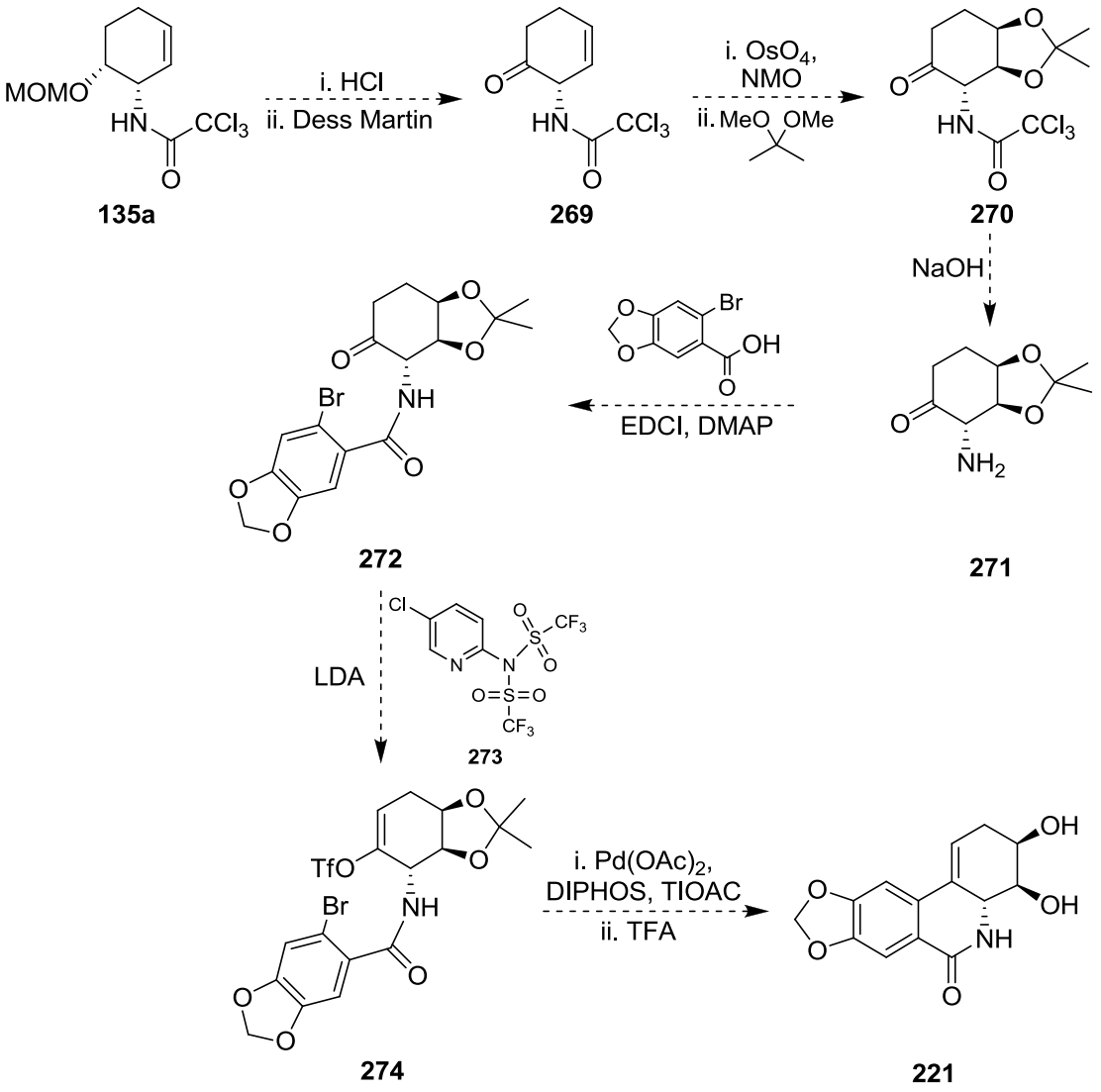
Scheme 82 - Epoxide ring opening of 138

3.3.7 Conclusions

In conclusion a one-pot diastereoselective tandem Overman rearrangement and RCM reaction was developed by combining the ether-directed Overman rearrangement and RCM. This reaction provides quick access to a diastereoselective synthesis of a functionalised chiral cyclic allylic trichloroacetamide in good yield and in high diastereoselectivity starting from the corresponding allylic alcohol. The allylic alcohol was easily prepared from commercially available starting material, (*S*)-glycidol in an excellent 86% yield over 6 steps. Having the cyclic allylic trichloroacetamide in hand, two parallel synthetic strategies were devised to furnish the synthesis of (+)-γ-lycorane and various novel pancratistatin analogues. The cyclic allylic amide was employed to give the C ring of the target compounds. Kharasch cyclisation and alkylation with a piperanoyl moiety furnished the A and D ring for the synthesis of (+)-γ-lycorane **136**. Significant problems were encountered with the final steps of the route and prevented the successful ring closure towards the synthesis of (+)-γ-lycorane. However the basic core of pancratistatin was successfully prepared using a Pd-catalysed cross coupling reaction. Its further functionalisation using allylic oxidation, dihydroxylation and directed epoxidation were then explored. Allylic oxidation of **137** was unrewarding, however a directed epoxidation and dihydroxylation gave novel pancratistain analogues in excellent yield and diastereomeric excess. These results have revealed that the *syn*-(4a*S*,10b*S*)-phenantridone skeleton **268** has significant influence on the functionalisation of the alkene where size of the reagent and its ability to undergo a directed reaction dictates the face of the attack.

3.3.8 Future Work

After the successful synthesis of the pancratistatin analogues, the ether-directed tandem reaction could then be applied for the synthesis of other alkaloids in the Amaryllidaceae family. One such compound is (+)-2-deoxylycoricidine **221**, which has only previously been synthesised in racemic form. Its asymmetric synthesis could also be achieved from allylic trichloroacetamide **135a** (Scheme 83). Conversion of **135a** to the ketone **263**, followed by dihydroxylation would introduce the *syn*-diol require for the target compound. After protection of the diol, the trichloroacetyl group could be hydrolysed to provide the amino ketone **271**. This will set the stage to introduce the aromatic component to give **272**, which will then be converted to the enol triflate using Commins reagent **273** to provide **274**. The resulting compound **274** would then undergo a Heck-type cyclisation which after deprotection would provide the first asymmetric synthesis of (+)-2-deoxylycoricidine **221**.

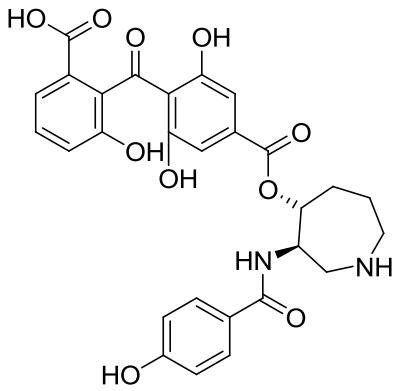


Scheme 83 - Proposed synthesis of (+)-2-deoxylycoricidine 221

3.4 New Synthesis of Balanol Analogues

3.4.1 Introduction

(–)-Balanol **275** is a metabolite of the fungi *Verticillium balanoides*[172] and *Fusarium merismoides*[173] and is a structural isomer of the known antifungal ophiocordin **276** (Figure 16). Balanol has been shown to be an effective inhibitor of human protein kinase C. The protein kinase C (PKC) family is a series of serine/threonine-specific protein kinase enzymes that are recognised as controling the function of a variety of cellular signal transduction pathways.[89-91] They are involved in the gene expression, cell proliferation and cell growth. The activated PKC has been implicated in the progression of several disease processes including, cancer, asthma, inflammation, cardiovascular dysfunctions, diabetic complications, HIV infection and central nervous system disorders.



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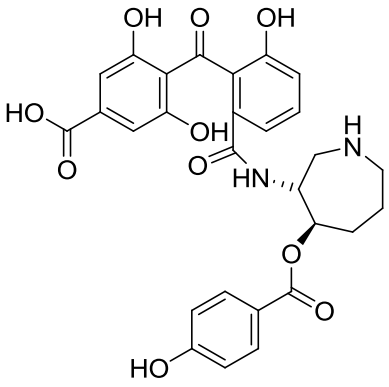
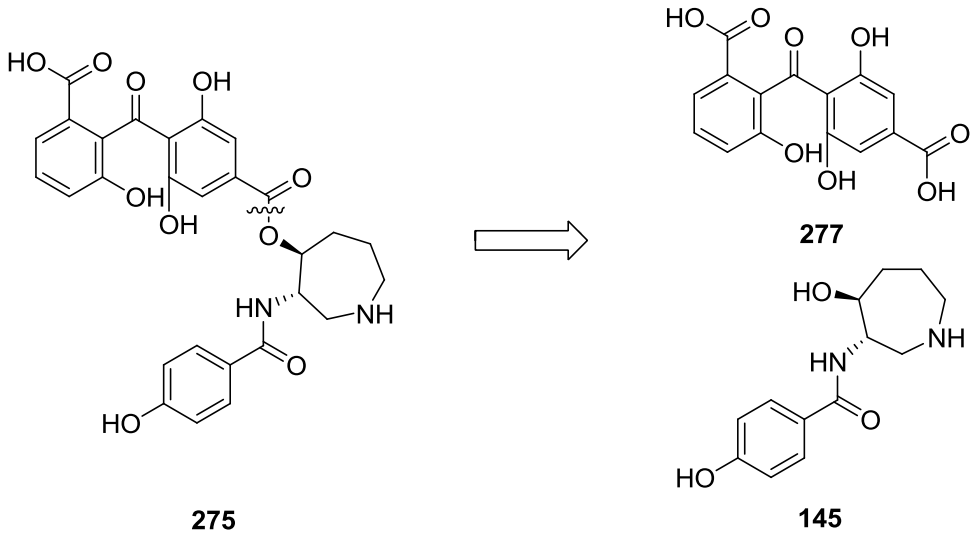


276

Figure 16 - Balanol 275 and Ophiocordin 276

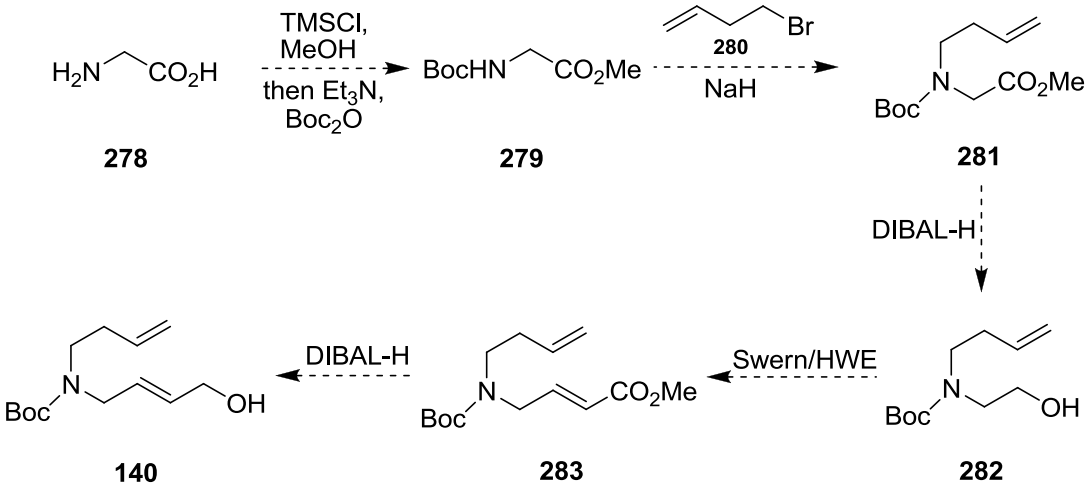
As PKC is important for a number of cellular processes, the use of PKC inhibitors has been recommended for clinical applications ranging from the treatment of diabetic complications to the treatment of cancer.[174] The isolation and structural revelation of the PKC-inhibitory fungal metabolite balanol endowed a new structural motif to the PKC inhibitor area. Therefore, it is a critical biological target for the development of chemotherapeutic agents. The structure of balanol is comprised of two primary fragments, a benzophenone part **277** and a chiral hexahydroazepine core **145** (Scheme 84). In this project, our aim was to utilise the one-pot rearrangement and ring closing metathesis process combined with subsequent hydroxylation chemistry to facilitate easy access to the chiral hexahydroazepine core of balanol **145**. We intended to use this chemistry to synthesise a number of stereoisomers and various hydroxylated analogues.



Scheme 84 - A chiral hexahydroazepine core and a benzophenone fragment

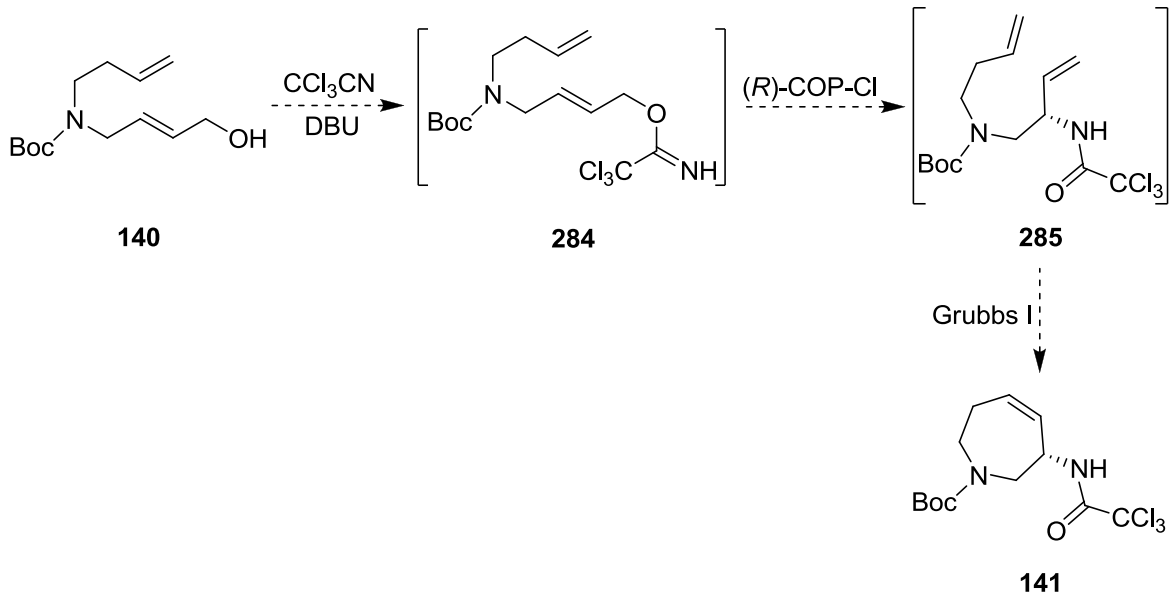
3.4.2 Proposed synthesis

As mentioned above, the aim of this research project was to develop a new flexible approach for the stereoselective synthesis of the balanol core and its analogues in an efficient manner. The strategy under investigation can be considered in three distinct stages. The first stage of this programme would be the synthesis of the key substrate **140** as a precursor for the tandem process (Scheme 85). The synthesis of **140** would start with glycine **278** which would be subjected to a one-pot protection strategy generating both a methyl ester and the Boc-protected amine **279**. The amine will be alkylated with 4-bromo-1-butene **280** and the resulting compound **281** would be reduced with DIBAL-H. A one-pot Swern-HWE reaction would give the α,β-unsaturated ester **283** and this would again be reduced with DIBAL-H to supply the key substrate **140** for the tandem process.



Scheme 85 - Synthesis of the the allylic alcohol 140 from glycine

In the next stage of the synthesis, the allylic alcohol **140** would then be transformed into the corresponding allylic trichloroacetimidate **284** under standard conditions (Scheme 86). Initially, to optimise the rearrangement conditions, the allylic trichloroacetimidate would be rearranged using bis(acetonitrile)palladium(II) chloride. Later, (*R*)-COP-Cl **83** would be employed to undergo a stereoselective rearrangement and its further treatment with Grubbs first generation catalyst would yield the seven-membered carbocyclic amide **141**.

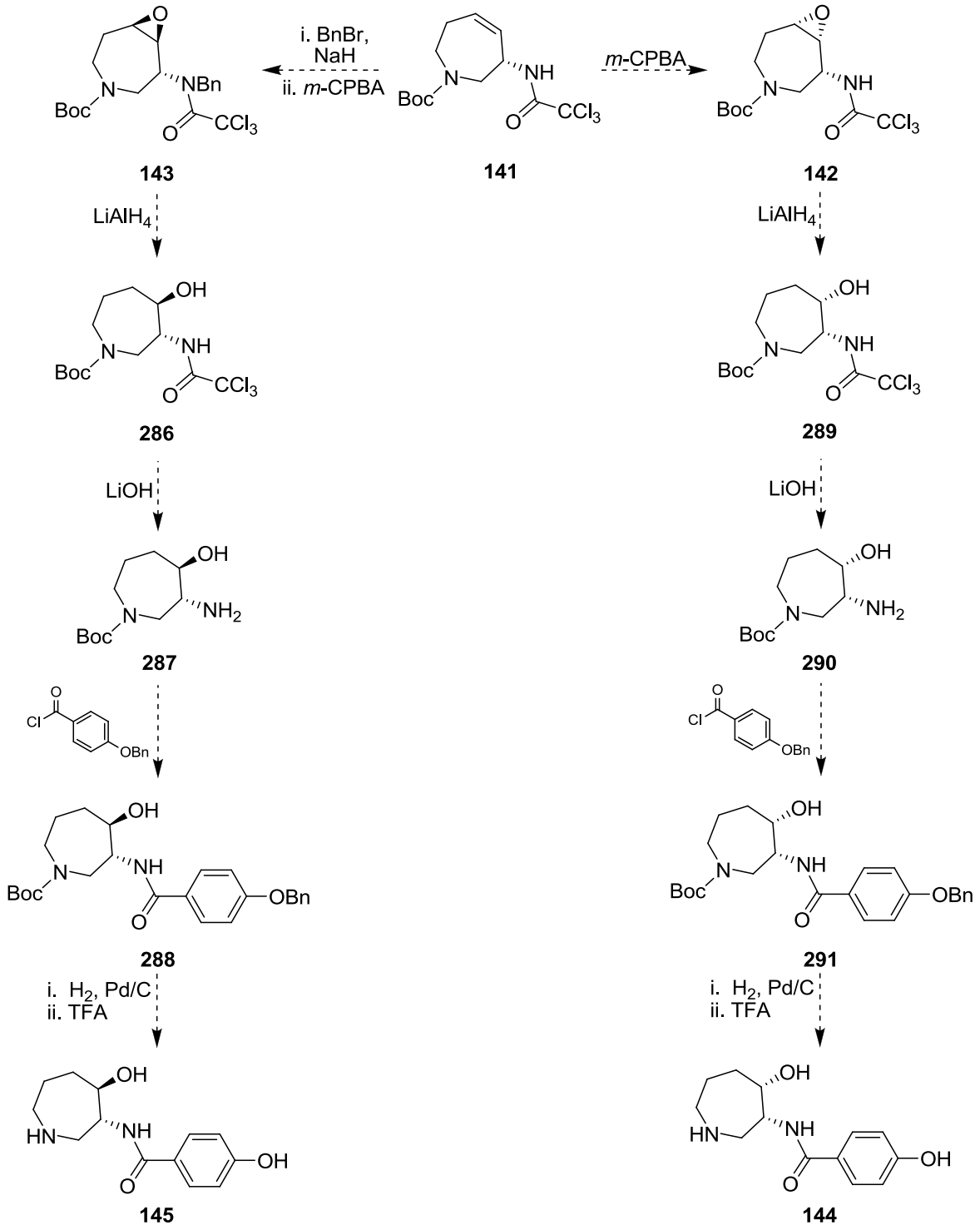


140 **284** **285** **141**

Scheme 86 - One-pot tandem Overman rearrangement and RCM

To generate the (–)-balanol core **145**, the allylic trichloroacetamide **141** would be further protected with a benzyl moiety (Scheme 87). The doubly protected amide then should undergo epoxidation from the least hindered face of the ring according to work carried out by O'Brien and co-workers.[141] Reduction of the epoxide **143** with $LiAlH_4$ would then give the desired amino alcohol core **286**. In a similar fashion, direct epoxidation should yield the *syn*-epoxide **142** which could be regioselectively ring-opened with $LiAlH_4$ to generate the *syn*-amino alcohol **289**. To complete the (–)-balanol core, the trichloroacetamide **286** will be hydrolysed and the resulting amine **287** will be re-acylated with 4-benzyloxybenzoyl chloride. Hydrogenation will then remove both benzyl protecting groups and finally treatment with TFA will give the (–)-balanol core **145**. The *syn*-stereoisomer **144** can also easily be accessed by similarly hydrolysing the amide and re-acylating with 4-benzyloxybenzoyl chloride (Scheme 87). Hydrogenation of the benzyl protecting group followed by Boc-deprotection of the amine will yield the other desired stereoisomer **144**. As well as generating these two targets, there is the potential to prepare a whole range of

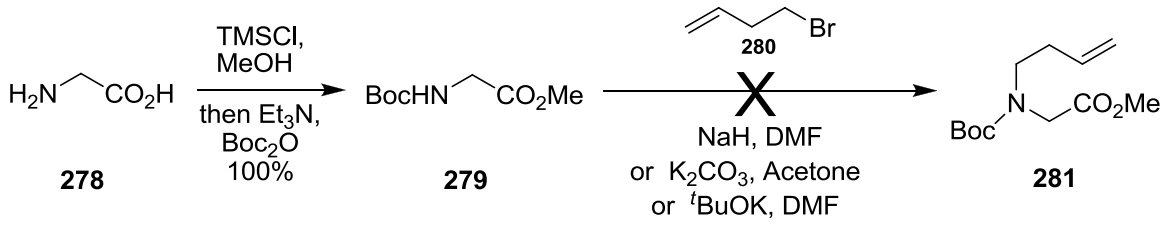
hydroxylated analogues by epoxidation, dihydroxylation and iodolactamisation of the alkene from the tandem process.



Scheme 87 - Proposed synthesis of the balanol core structures

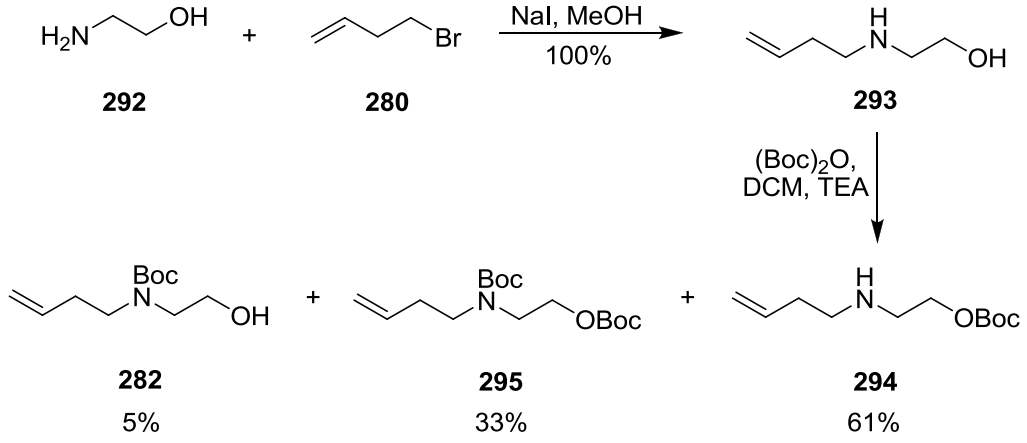
3.4.3 Synthesis of allylic alcohols

The first step in the production of the allylic alcohol **140** involved the synthesis of the Boc-protected amine **279**. This was easily synthesised in quantitative yield by esterification of the commercially available glycine **278** with trimethylsilyl chloride followed by treatment with Boc anhydride in the presence of TEA.[175] Attempted alkylation of compound **279** was then investigated with 4-bromo-1-butene **280**. This reaction was carried out according to a literature procedure published by Andino and co-workers,[176] using sodium hydride in DMF at 0 °C. However, application of the literature reaction conditions failed to deliver any of the desired alkylated product **281**, but led to the decomposition of the starting material. In order to avoid decomposition, the reaction was tried again using the milder potassium carbonate with acetone as solvent and the reaction heated under reflux. In this case, the reaction did not decompose but failed to react returning a significant amount of starting material. In another attempt, potassium *tert*-butoxide was employed to effect the alkylation of **279**. Once again, the reaction did not prove successful and starting material was found to be present in the crude reaction mixture (Scheme 88).



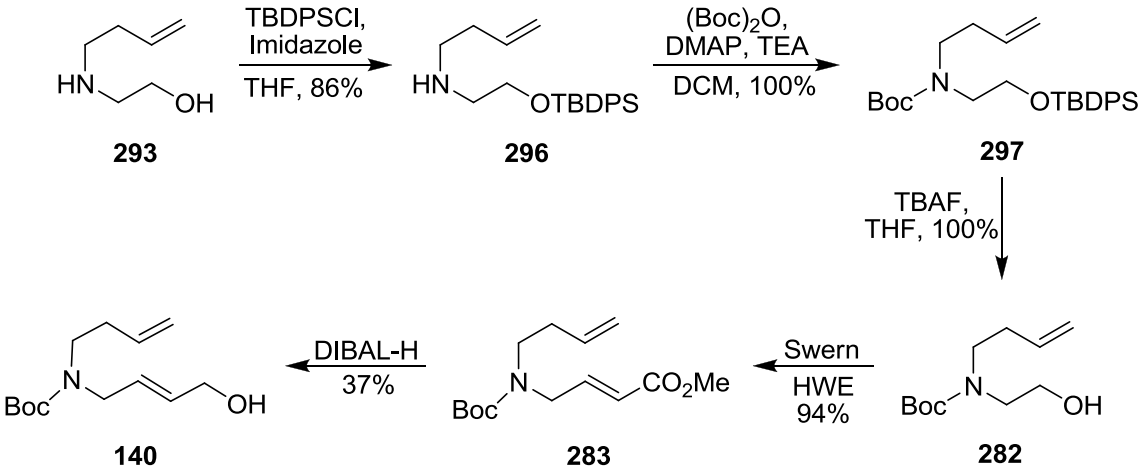
Scheme 88 - Esterification, Boc protection and attempted alkylation

The failure of the alkylation led to the design of a new strategy for the synthesis of the alkylated amine. In this synthesis, the amino alcohol **292** was chosen as a starting point instead of glycine and was reacted directly with 4-bromo-1-butene **280**. The reaction was carried out in the presence of sodium iodide and was stirred at 80 °C to furnish the desired compound in an excellent yield. The resulting product **293** was subjected to Boc protection and it resulted in the formation of three products giving only a trace amount of the desired compound **282** (Scheme 89).



Scheme 89 - Boc protection of 292

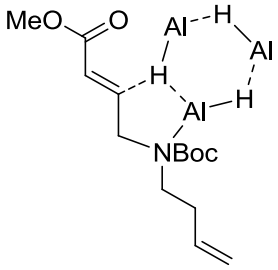
In order to prevent the protection of the hydroxyl group of **293** with the Boc anhydride, silylation of the hydroxyl group was carried out using TBDPS prior to Boc protection. This was followed by treatment with Boc anhydride and then with TBAF to supply **282** in 86% yield over three steps. At this juncture, compound **282** was subjected to a one-pot Swern oxidation and HWE reaction to give the α,β-unsaturated ester **283** in 94% yield. To complete the synthesis of the desired allylic alcohol, reduction of the resulting ester was attempted using DIBAL-H (Scheme 90).



Scheme 90 - Synthesis of the allylic alcohol 140

Previously, DIBAL-H has been shown as a successful reagent for the reduction of α,β-unsaturated esters to allylic alcohols using 2.2 equivalents. However, this time it did not prove to be as efficient and gave only 37% of the desired allylic alcohol along with a complex mixture of unidentifiable compounds. A similar problem has been discussed previously in the literature and has been successfully avoided by the Moriwake modification.[177] Moriwake and co-workers have shown that trimeric DIBAL-H might

coordinate with the amino moiety and alkene leading to 1,4-addition and the formation of complex mixture of products *via* transition state **298** (Figure 17). This can be avoided with the application of appropriate Lewis acids such as boron trifluoride diethyl etherate in the reaction before the start of reduction. The use of boron trifluoride diethyl etherate coordinates with the Boc-protected nitrogen causing the reaction to proceed *via* the hypothetical transition state **299** to promote the desired reduction. As such, this reaction was attempted again using these conditions, but no improvement was observed and the reaction led to an inseparable mixture of several products, along with the desired compound **140** in 41% yield.



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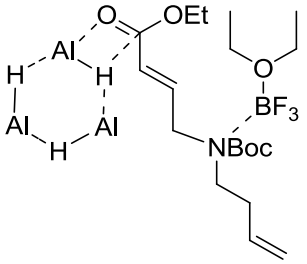

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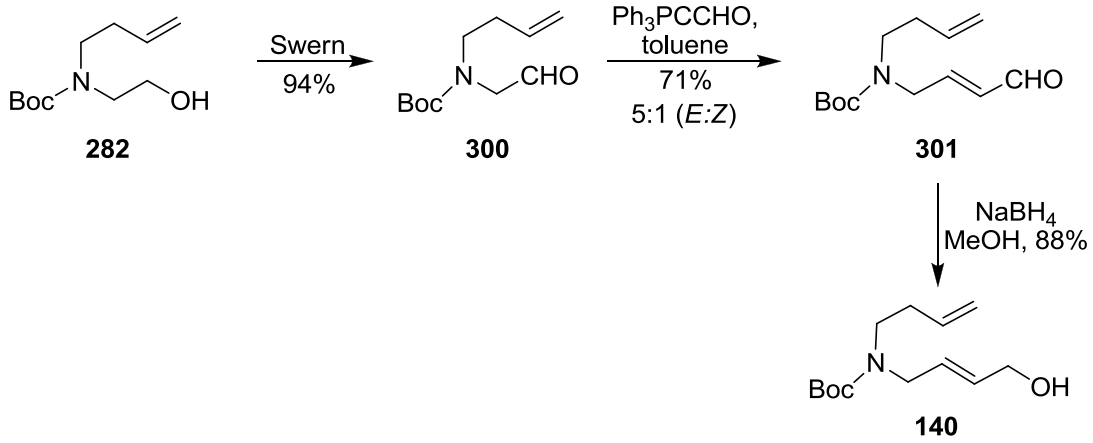
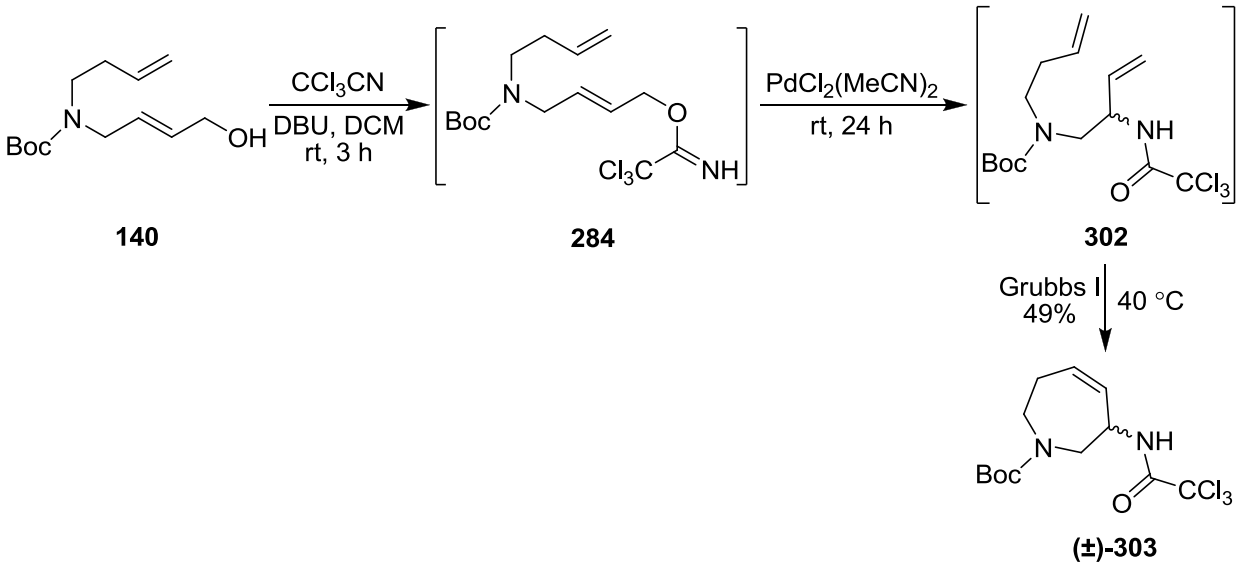
Figure 17 - Hypothetical transition states during DIBAL-H reduction of 283

In order to obtain a high yield of the allylic alcohol **140**, it was envisioned that a Wittig reaction could be employed subsequent to the Swern oxidation of alcohol **282** instead of the HWE reaction. The resulting aldehyde **301** would then be reduced using sodium borohydride to provide the allylic alcohol **140**. As such the primary alcohol was subjected to a Swern oxidation followed by the Wittig reaction to afford **301** (Scheme 91). The NMR spectra of the crude reaction mixture showed a mixture of *E* and *Z* alkenes in a ratio of 5:1, which could not be separated until they were reduced. Reduction of the mixture of *E* and *Z* alkenes was carried out smoothly using sodium borohydride in a solution of methanol and the desired allylic alcohol **140** was separated in 88% yield. This new sequence of reactions proved successful and provided the allylic alcohol without adding extra steps to the strategy.



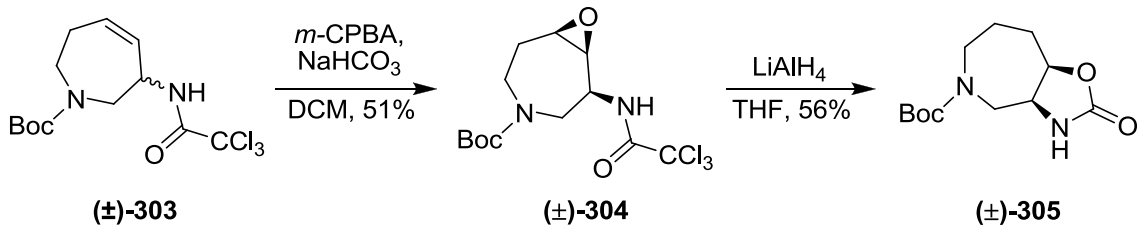
Scheme 91 - Synthesis of the allylic alcohol using sodium borohydride

With the allylic alcohol **140** in hand, the Overman rearrangement and RCM steps were then investigated. The allylic alcohol **140** was subjected to a standard one-pot tandem process as previously described initially using trichloroacetonitrile and DBU (Scheme 92). The formation of allylic trichloroacetimidate **284** was accomplished after 3 h. During the optimisation of the reaction conditions, it was observed that the allylic trichloroacetimidate **284** is unstable and decomposed back to the starting material **140** at room temperature. Thus, the resulting allylic trichloroacetimidate **284** was quickly rearranged using bis(acetonitrile)palladium(II) chloride at 0 °C. The reaction was gradually warmed to room temperature and stirred for 24 h to afford the allylic trichloroacetamide **302**. Compound **302** was then subjected to RCM using Grubb's 1st generation catalyst to furnish the seven membered carbocyclic amide **303** in 49% yield over three steps starting from the allylic alcohol **140**.



Scheme 92 - One-pot tandem Overman rearrangement and RCM

In the next stage, compound **303** was subjected to epoxidation utilising the conditions employed previously which provided epoxide **304** in modest 51% yield (Scheme 93). As per purposed route, compound **304** was then treated with lithium aluminum hydride to cleave the epoxide ring. This resulted in 56% yield of the oxo-diaza-azulen **305** along with 16% unreacted starting material.



Scheme 93 - Formation of epoxide 304 and its treatement with $LiAlH_4$

3.4.4 Conclusions and Future work

At this stage, time restrictions unfortunately dictated that further development of this synthetic route is not currently possible. However, significant progress towards the synthesis of the (–)-balanol core **145** has been made, although problems were encountered in the preparation of the allylic alcohol **140** which prevented the successful synthesis of the target compound within the timeframe of this PhD project. The advanced stage key intermediate **303**, a seven membered carbocyclic amide has been synthesised. Further investigation into the optimisation of the Overman rearrangement using (*R*)-COP-Cl, will hopefully allow the development of a stereoselective rearrangement and the subsequent treatment with Grubbs first generation catalyst will supply seven membered carbocyclic amide **141**. Following this, relatively straight forward chemistry can be applied to synthesise the two desired core structures of balanol **144** and **145** as described in Scheme 87.

4 Conclusions

In the first part of the project, it was planned to develop a fast and efficient method for the synthesis of the carbocyclic ketone **130**. During the course of the research, new methodology was devised for the successful synthesis of 5- and 6-membered amido substituted carbocyclic ketones which are important building blocks for the synthesis of structurally diverse antiviral and anticancer carbocyclic nucleosides and natural products.

Initially, various methods were investigated for the allylic oxidation of carbocyclic amides formed from a one-pot tandem process. It appeared that these carbocylic amides are resistant to allylic oxidation using TBHP along with different transition metals such as Pd, Se, Mn and Cr. In addition to this, the employment of sonication and microwave techniques also found no success. In order to achieve the target compounds, a new approach was devised involving installation of a hydroxyl group in the substrate before the tandem process. The intermediates from this new route were then subjected to a high yielding one-pot tandem Overman rearrangement and ring closing metathesis step to eventually furnish amido substituted five and six membered carbocyclic ketones in overall 61% and 56% yield from corresponding allylic alcohols respectively. The resulting carbocyclic amides are relatively more complex than have been synthesised previously in the group using this approach and in this way, highlights the potential of this methodology for the synthesis of more complex target compounds.

Stereoselective synthesis of the enantiomer of dihydroconduramine C-1 **132** and dihydroconduramine E-1 **133** was achieved using a stereoselective variant of the one-pot tandem Overman rearrangement and ring closing metathesis process in excellent yield and diastereomeric excess. During the course of the synthesis (1*S*)-*N*-(cyclohexenyl) trichloroacetamide **131** was efficiently prepared starting from the commercially available alcohol in 75% overall yield in six steps and in excellent enantiomeric excess. Initially Donohoe conditions for dihydroxylation and a two stage epoxidation and hydrolysis sequence were investigated for the synthesis of *syn* and *anti* diol derivatives of **131** respectively, in excellent diastereoselectivity. The noteworthy successes of a relevant model study provided the foundation for the synthesis of two dihydroconduramines. In the first approach, allylic alcohol **213** was synthesised from **131** *via* 4,5-dihydro-1,3-oxazole **210** as a single stereoisomer. Non-directed dihydroxylation and directed epoxidation were then employed which resulted in the production of the two dihydroconduramines. This operationally simple route is very efficient and granted further insight into the

stereoselective functionalisation of substituted cyclohexenes for the production of related natural products such as pancratistatins and other Amaryllidaceae alkaloids.

In next part of this PhD programme, the aim was to develop a one-pot diastereoselective tandem Overman rearrangement and RCM reaction by combining the MOM-ether-directed Overman rearrangement and RCM step. This process provided quick access to a functionalised chiral cyclic allylic trichloroacetamide in good yield and in high diastereoselectivity starting from the corresponding allylic alcohol **134**. The allylic alcohol was easily prepared from commercially available starting material, (*S*)-glycidol in an excellent 86% yield over 6 steps. Having the cyclic allylic trichloroacetamide in hand, two parallel synthetic strategies were devised to furnish the synthesis of (+)-γ-lycorane and various novel pancratistatin analogues. The cyclic allylic amide was employed to give the C ring of the target compounds. Kharasch cyclisation and alkylation with a piperanoyl moiety furnished the A and D ring for the synthesis of (+)-γ-lycorane **136**. Significant problems were encountered with the final steps of the route and prevented the successful ring closure towards the synthesis of (+)-γ-lycorane. However the basic core of pancratistatin was successfully prepared using a Pd-catalysed cross coupling reaction. Its further functionalisation using allylic oxidation, stereoselective dihydroxylation and directed epoxidation were then explored. Allylic oxidation of **137** was unrewarding, however a directed epoxidation and dihydroxylation gave novel pancratistain analogues in excellent yield and diastereomeric excess. These results have revealed that the *syn*-(4a*S*,10b*S*)-phenantridone skeleton **268** has significant influence on the functionalisation of the alkene where the size of the reagent and its ability to undergo a directed reaction dictates the face of the attack. In summary, use of the one-pot tandem MOM-ether directed Overman rearrangement/RCM process quickly generated a second stereogenic center within the resulting cyclic allylic trichloroacetamide and excluded the need of a chiral catalyst to generate the stereogenic center on the resulting cyclic allylic trichloroacetamide. The new stereogenic centre in the resulting cyclic allylic trichloroacetamide would provide an additional reaction site for further functionalisation and is the advantage of this methodology in comparison to other available approaches. This feature can be further exploited by synthesising other related natural products.

In the final part of this PhD programme, studies were carried out to expand the scope of the one-pot tandem process to include heterocyclic derived substrates. This provided an attractive route to synthesise a seven-membered aza-carbocyclic amide. At this stage, time

restrictions unfortunately dictated that further development of this synthetic route is not currently possible. However, significant progress towards the synthesis of the (–)-balanol core **145** has been made, although problems were encountered in the preparation of the allylic alcohol **140** which prevented the successful synthesis of the target compound within the timeframe of this PhD project. The advanced stage key intermediate **141**, a seven membered aza-carbocyclic amide has been synthesised. Further investigation into the optimisation of the Overman rearrangement using (*R*)-COP-Cl, will hopefully allow the development of a stereoselective rearrangement and the subsequent treatment with Grubbs catalyst will supply seven membered aza-carbocyclic amide **141**. Following this, relatively straightforward chemistry can be applied to synthesise the two desired core structures of balanol **144** and **145** as described in Scheme 87.

In summary, this PhD programme provided facile, general and efficient methods for the synthesis of various valuable novel building blocks such as carbocyclic ketone (**193**), aminocyclitols (**132** and **133**) and pancratistatin analogues (**137**, **138**, **139** and **259**). These novel compounds can be further utilised as important scaffolds within organic and medicinal research and can be further explored to determine their full therapeutic potential.

5 Experimental

5.1 General Experimental

Reactions were carried out in the flame-dried glassware under a positive atmosphere of argon. All reagents and starting materials were obtained from commercial sources and used as received. Dry solvents were purified using a PureSolv 500 MD solvent purification system or tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone, whilst dichloromethane was distilled from calcium hydride. 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 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were recorded using Golden Gate apparatus on a JASCO FTIR 410. Melting points were determined on a Reichert platform melting point apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Auto pol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC was performed on a Hewlett Packard Agilent 1100 series instrument and were calibrated with the appropriate racemic mixture.

5.2 General Procedures

General Procedure 1: One pot Swern oxidation-Horner/Wadsworth/Emmons reaction.

Dimethyl sulfoxide (2.5 equiv.) was added to a stirred solution of oxalyl chloride (1.4 equiv.) in dichloromethane (100 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before the alcohol (1.0 equiv.) in dichloromethane (50 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (5 equiv.) 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. Meanwhile, a solution of lithium chloride (1.8 equiv.), triethyl phosphonoacetate (1.8 equiv.) and 1,8-diazabicyclo[5,4,0]undec-7-ene (1.8 equiv.) in acetonitrile (100 mL) was 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 by the addition of 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 ($MgSO_4$) and concentrated to give an orange oil. Purification by flash column chromatography using diethyl ether/petroleum ether as eluent gave the pure product.

General Procedure 2: DIBAL-H reduction to allylic alcohol.

The α,β-unsaturated ester (1.0 equiv.) was dissolved in diethyl ether (100 mL) and cooled to –78 °C. DIBAL-H (1.0 M in hexane) (2.2 equiv.) was added dropwise and the reaction mixture was stirred at –78 °C for 3 h, before warming to room temperature. 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 (400 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography eluting with diethyl ether/petroleum ether.

General procedure 3: MOM protection of secondary alcohol.

N,*N*′-Diisopropylethylamine (1.5 equiv.) and bromomethyl methyl ether (1.5 equiv.) were added to a solution of the alcohol (1.5 equiv.) in dichloromethane (20 mL). The reaction mixture was then heated under reflux for 12 h before being diluted with dichloromethane (50 mL) and washed with 2.0 M hydrochloric acid solution (25 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography using diethyl ether/petroleum ether to give the desired compounds as colourless oils.

General Procedure 4: Synthesis of allylic trichloroacetimidate and subsequent tandem Overman rearrangement - ring closing metathesis reaction.

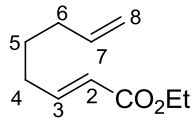
Allylic alcohol (1 equiv.) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.25 equiv.) was added to the solution followed by trichloroacetonitrile (1.5 equiv.). The solution was then warmed to room temperature and stirred for 2 h. The reaction mixture was filtered through a short pad of silica gel and

washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate (1 equiv.) was then dissolved in dichloromethane (10 mL). The rearrangement catalyst (0.1 equiv., 10 mol%) was added to the solution and the reaction mixture was stirred at room temperature for 3 h. Grubb's catalyst (1st Generation) (0.1 equiv., 10 mol%) was then added and the reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography gave the pure cyclic allylic amides as white solids.

5.3 Experimental Procedures

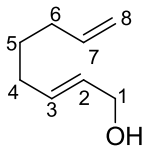
5.3.1 Synthesis of Carbocyclic Ketones

Ethyl (2*E*)-2,7-octadienoate (158).[178]



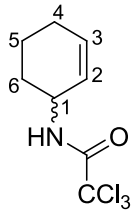
Reaction was carried out according to general procedure 1, using 5-hexen-1-ol (**157**) (4.00 g, 0.04 mol). Flash column chromatography (elution with petroleum ether/diethyl ether, 10:1) yielded ethyl (2*E*)-2,7-octadienoate (**158**) (5.78 g, 86%) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[178] υ_{max}/cm^{-1} (NaCl) 2933 (CH), 1721 (CO), 1655 (C=C), 1367, 1267, 1198, 1044; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.52–1.58 (2H, m, 5-H_2), 2.06–2.12 (2H, m, 6-H_2), 2.18–2.25 (2H, m, 4-H_2), 4.17 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.96–5.06 (2H, m, 8-H_2), 5.73–5.96 (2H, m, 2-H and 7-H), 6.95 (1H, dt, *J* 15.5, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.1 (CH_2), 31.5 (CH_2), 33.1 (CH_2), 60.2 (CH_2), 115.1 (CH_2), 121.5 (CH), 138.0 (CH), 149.0 (CH), 166.7 (C); *m*/*z* (CI) 169.1232 (MH^+. $C_{10}H_{17}O_2$ requires 169.1229), 141 (90%), 123 (75), 95 (100), 81 (53), 55 (32).

(2*E*)-Oct-2,7-dien-1-ol (128).[178]



Reaction was carried out according to general procedure 2, using ethyl (2*E*)-2,7-octadienoate (**158**) (2.00 g, 11.00 mmol). Flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) yielded (2*E*)-oct-2,7-dien-1-ol (**128**) (0.68 g, 91%) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[178] υ_{max}/cm^{-1} (NaCl) 3346 (OH), 2928 (CH), 1640 (C=C), 1439, 1090, 997, 970; δ_H (400 MHz, $CDCl_3$) 1.34 (1H, br s, OH), 1.46–1.51 (2H, m, 5-H_2), 2.02–2.10 (4H, m, 4-H_2 and 6-H_2), 4.07 (2H, d, *J* 4.6 Hz, 1-H_2), 4.94–4.97 (1H, m, 8-*H*H), 5.01 (1H, dq, *J* 17.0, 1.7 Hz, 8-H*H*), 5.60–5.73 (2H, m, 2-H and 3-H), 5.80 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 7-H); δ_C (100 MHz, $CDCl_3$) 28.3 (CH_2), 31.6 (CH_2), 33.2 (CH_2), 63.7 (CH_2), 114.6 (CH_2), 129.2 (CH), 133.0 (CH), 138.6 (CH); *m*/*z* (CI) 109.1009 (MH^+–H_2O. C_8H_{13} requires 109.1017), 95 (16%), 81 (12), 67 (47).

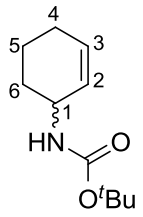
1-(2',2',2'-Trichloromethylcarbonylamino)cyclohex-2-ene (129).[38]



Reaction was carried out according general procedure 4 using (2*E*)-oct-2,7-dien-1-ol (**128**) (0.50 g, 3.97 mmol) by using bis(acetonitrile)palladium(II) chloride (0.10 g, 0.39 mmol) as a catalyst for the Overman rearrangement. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 97:3) gave 1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-2-ene (**129**) (0.83 g, 90% yield over 3 steps) as a white solid. Spectroscopic data is entirely consistent with the literature. Mp 85–86 °C, lit.[38] 86–87 °C; υ_{max}/cm^{-1} (NaCl) 3421 (NH), 2941 (CH), 1676 (CO), 1519, 1073, 822; δ_H (400 MHz, $CDCl_3$) 1.62–1.79 (3H, m, 5-H_2 and 6-*H*H), 1.94–2.03 (1H, m, 6-H*H*), 2.03–2.16 (2H, m, 4-H_2), 4.42–4.54 (1H, m, 1-H), 5.65 (1H, ddt, *J* 10.0, 4.0, 2.2 Hz, 2-H), 5.98 (1H, dtd, *J* 10.0, 4.0, 1.9 Hz, 3-H), 6.60 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 19.4 (CH_2), 24.7

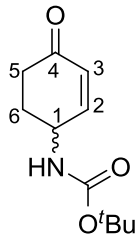
(CH_2), 28.6 (CH_2), 46.9 (CH), 92.7 (C), 125.7 (CH), 132.7 (CH), 161.1 (C); *m*/*z* (CI) 261.0144 (MNH_4^+. $C_8H_{14}{}^{35}Cl_2{}^{37}ClN_2O$ requires 261.0143), 259 (100%), 242 (23), 225 (9), 206 (21), 81 (10).

1-(*tert*-Butoxycarbonylamino)cyclohex-2-ene (166).[179]



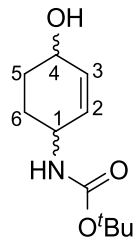
1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohept-2-ene (**129**) (1.0 g, 4.12 mmol) was dissolved in 2 M sodium hydroxide (40 mL) and stirred vigorously for 12 h at room temperature. Di-*tert*-butyl dicarbonate (2.34 g, 10.31 mmol) was added and the solution was stirred for 6 h before a further portion of di-*tert*-butyl dicarbonate (2.34 g, 10.31 mmol) was added and the reaction mixture stirred for a further 12 h. The reaction mixture was then extracted with ethyl acetate (4 × 30 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (diethyl ether/petroleum ether, 1:9) gave 1-(*tert*-butoxycarbonylamino)cyclohex-2-ene (**166**) (0.81 g, 100% yield) as a white solid. Spectroscopic data is entirely consistent with the literature. Mp 38–40 °C, lit.[179] mp 33–35 °C; υ_{max}/cm^{-1} (NaCl) 3334 (NH), 2929 (CH), 1693 (CO), 1494, 1366, 1216, 1118, 1065; δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, O^{t}Bu), 1.48–1.57 (1H, m, 6-*H*H), 1.58–1.68 (2H, m, 5-H_2), 1.82–1.93 (1H, m, 6-H*H*), 1.94–2.02 (2H, m, 4-H_2), 4.15 (1H, br s, NH), 4.46–4.61 (1H, m, 1-H), 5.57–5.64 (1H, m, 1-H), 5.77–5.84 (1H, m, 1-H); δ_C (100 MHz, $CDCl_3$) 19.7 (CH_2), 24.8 (CH_2), 28.5 (3 × CH_3), 29.9 (CH_2), 45.7 (CH), 79.2 (C), 128.2 (CH), 130.5 (CH), 155.2 (C); *m*/*z* (CI) 198 (MH^+, 10%), 180 (5), 142 (100), 107 (3), 81 (10).

1-(*tert*-Butoxycarbonylamino)cyclohex-2-en-4-one (167).[180]



A mixture of 1-(*tert*-butoxycarbonylamino)cyclohex-2-ene (**166**) (0.10 g, 0.50 mmol), 10% palladium on carbon (0.005 g), dichloromethane (15 mL), *tert*-butyl hydroperoxide (0.46 mL, 2.5 mmol, 5.0–6.0 M in decane) and anhydrous potassium carbonate (0.02 g, 0.13 mmol) was heated under reflux for 5 days. The reaction mixture was filtered through a pad of silica which was subsequently washed with dichloromethane 10 mL. After removal of solvent under reduced pressure, the crude material was purified by flash column chromatography using (diethyl ether/petroleum ether, 1:1) to give 1-(*tert*-butoxycarbonylamino)cyclohex-2-en-4-one (**167**) (0.01 g, 10% yield) as a white solid. Spectroscopic data is entirely consistent with the literature. Mp 110–112 °C, lit.[180] mp 112–113 °C; υmax/cm^{-1} (NaCl) 3351 (NH), 2924 (CH), 1680 (CO), 1519, 1455, 1367, 1165, 1016; δH (400 MHz, $CDCl_3$) 1.47 (9H, s, O^{t}Bu), 1.82–1.94 (1H, m, 6-*H*H), 2.28–2.37 (1H, m, 6H*H*), 2.44 (1H, ddd, *J* 17.0, 12.6, 4.7 Hz, 5-*H*H), 2.55 (1H, dt, *J* 17.0, 4.7 Hz, 5-H*H*), 4.53 (1H, br s, NH), 4.62–4.71 (1H, m, 1-H), 5.98–6.02 (1H, m, 3-H); 6.83 (1H, ddd, *J* 10.0, 2.2, 1.5 Hz, 2H); δC (100 MHz, $CDCl_3$) 27.2 (3 × CH_3), 29.8 (CH_2), 35.7 (CH_2), 46.6 (CH), 79.7 (C), 129.5 (CH), 150.7 (CH), 153.3 (C), 197.5 (C); *m*/*z* (CI) 212.1290 (MH^+. $C_{11}H_{18}NO_3$ requires 212.1287), 198 (10%), 156 (100), 118 (20), 71 (12).

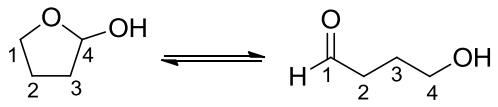
(1*R,4*S** and 1*S**,4*S**)-1-(*tert*-Butoxycarbonylamino)cyclohex-2-en-4-ol (170).**



A mixture of 1-(*tert*-butoxycarbonylamino)cyclohex-2-ene (**166**) (0.05 g, 0.27 mmol), selenium dioxide (0.04 g, 0.39 mmol) and pyridine (0.03 mL, 0.41 mmol) was heated under reflux for 4 days. The reaction mixture was filtered through a pad of celite® which

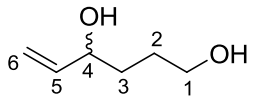
was subsequently washed with dichloromethane 15 mL. After removal of solvent under reduced pressure, the crude material was purified by flash column chromatography using (ethyl acetate/petroleum ether, 1:1) to give (1*R**,4*S** and 1*S**,4*S**)-1-(*tert*-butoxycarbonylamino)cyclohex-2-en-4-ol (**170**) (1.1 mg, 2% yield) as a a colourless oil. υmax/cm^{-1} (NaCl) 3330 (NH/OH), 2977 (CH), 1688 (CO), 1491, 1247, 1045; δH (400 MHz, $CDCl_3$) 1.45 (9H, s, O^{t}Bu), 1.62–1.73 (1H, m, 6-*H*), 2.01–2.18 (3H, m, 5-H_2 and 6-H*H*), 4.04–4.31 (2H, m, 1-H and 4-H), 4.46 (1H, br s, NH), 5.67–5.90 (2H, m, 2-H and 3-H); δC (100 MHz, CDCl3) 28.1 (CH_2), 28.4 (3 × CH_3), 30.9 (CH_2), 64.7 (CH), 66.1 (CH), 79.6 (C), 131.1 (CH), 132.8 (CH), 155.1 (C); *m*/*z* (CI) 214.1444 (MH^+. $C_{11}H_{20}NO_3$ requires 214.1443), 196 (10%), 158 (100), 90 (94), 69 (32).

4-Hydroxytetrahydrofuran (172).[181]



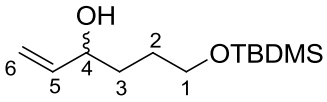
2,3-Dihydrofuran (**171**) (4.00 g, 0.06 mmol) was added to 0.2 N hydrochloric acid (20 mL) with stirring and cooling on an ice bath. After 0.15 h, a homogeneous solution was obtained. Stirring was continued at room temperature for 0.45 h. The aqueous phase was extracted with dichloromethane (8 × 50 mL). The combined organic phases were washed with a saturated solution of sodium hydrogencarbonate and dried ($MgSO_4$). After removal of the solvent, a colourless liquid, 4-hydroxytetrahydrofuran (**172**) (5.25 g, 92%) was obtained. Spectroscopic data is entirely consistent with the literature.[181] υ_{max}/cm^{-1} (NaCl) 3462 (OH), 2957 (CH), 1733 (CO), 1458, 1179, 1036; δ_H (400 MHz, $CDCl_3$) 1.81–1.99 (3H, m, 2-H_2 and 3-*H*H), 2.00–2.12 (1H, m, 3-H*H*), 3.39 (1H, s, OH), 3.82–4.09 (2H, m, 1-H_2), 5.54 (1H, s, 4-H); δ_C (100 MHz, $CDCl_3$) 23.5 (CH_2), 33.2 (CH_2), 67.3 (CH_2), 98.4 (CH); *m*/*z* (CI) 89 (MH^+, 36%), 71 (100), 68 (14).

5-Hexen-1,4-diol (174).[182]



To a solution of vinylmagnesium bromide (1.0 M in tetrahydrofuran) (22.7 mL, 0.02 mmol) at –15 °C was added a solution of 4-hydroxybutanal (**173)** (1.00 g, 0.01 mol) in tetrahydrofuran (60 mL). After being stirred for 8 h, the reaction was quenched slowly with a saturated solution of ammounium chloride (50 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (6 × 50 mL). The combined organic layer was dried ($MgSO_4$) and the resulting crude oil was purified by flash column chromatography (elution with petroleum ether/diethyl ether, 1:9) which gave 5-hexen-1,4-diol (**174**) (1.12 g, 86% yield) as colourless oil. Spectroscopic data is entirely consistent with the literature.[182] υ_{max}/cm^{-1} (NaCl) 3347 (OH), 2943 (CH), 1644 (CH), 1427, 1179, 1036; δ_H (400 MHz, $CDCl_3$) 1.58–1.74 (4H, m, 2-H_2 and 3-H_2), 3.01 (1H, br s, OH), 3.13 (1H, br s, OH), 3.59–3.71 (2H, m, 1-H_2), 4.10–4.20 (1H, m, 4-H), 5.10 (1H, d, *J* 10.4 Hz, 6-*H*H), 5.23 (1H, d, *J* 17.2 Hz, 6-H*H*), 5.87 (1H, ddd, *J* 17.2, 10.4, 6.2 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 26.3 (CH_2), 31.7 (CH_2), 60.2 (CH_2), 70.3 (CH), 112.1 (CH_2) 138.6 (CH); *m*/*z* (CI) 117 (MH^+, 75%), 99 (100), 81 (54), 71 (6).

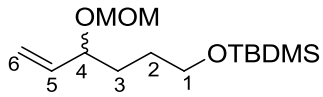
1-(*tert*-Butyldimethylsilyloxy)-5-hexen-4-ol.[182]



To 5-hexene-1,4-diol (**174**) (1.22 g, 0.01 mol) in *N,N′*-dimethylformamide (20 mL) at –15 °C was added imidazole (0.88 g, 0.01 mol) and *tert*-butyldimethylsilyl chloride (1.66 g, 0.01 mol). After being stirred for 0.15 h at –15 °C, the mixture was gradually warmed to room temperature. The reaction mixture was diluted with diethyl ether (50 mL) and water (50 mL). The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and resulting crude oil was purified by flash column chromatography on silica gel (elution with petroleum ether/ethyl acetate, 1:9) gave 1-(*tert*-butyldimethylsilyloxy)-5-hexen-4-ol (1.96

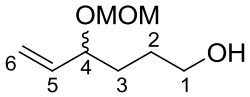
g, 78% yield) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[182] υ_{max}/cm^{-1} (NaCl) 3373 (OH), 2954 (CH), 1472, 1255, 835; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.46–1.66 (4H, m, 2-H_2 and 3-H_2), 2.64 (1H, d, *J* 4.5 Hz, 4-OH), 3.59 (2H, t, *J* 5.3 Hz, 1-H_2), 4.02–4.10 (1H, m, 4-H), 5.02 (1H, d, *J* 10.2 Hz, 6-*H*H), 5.17 (1H, d, *J* 17.2 Hz, 6-H*H*), 5.80 (1H, ddd, *J* 17.2, 10.2, 5.7 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) –5.3 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 28.8 (CH_2), 34.5 (CH_2), 63.4 (CH_2), 72.7 (CH), 114.3 (CH_2), 141.2 (CH); *m*/*z* (CI) 231 (MH^+, 100%), 213 (48), 173 (6), 81 (28).

1-(*tert*-Butyldimethylsilyloxy)-4-(methoxymethoxy)hex-5-ene (175).



Reaction was carried out according to general procedure 3, using 1-(*tert*-butyldimethylsilyloxy)-5-hexen-4-ol (3.20 g, 0.01 mol). Flash column chromatography (petroleum ether/diethyl ether, 20:1) yielded 1-(*tert*-butyldimethylsilyloxy)-4-(methoxymethoxy)hex-5-ene (**175**) (3.80 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 2953 (CH), 1642 (C=C), 1472, 1255, 1153, 1037; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $SiC(CH_3)_3$), 1.44–1.66 (4H, m, 2-H_2 and 3-H_2), 3.32 (3H, s, OCH_3), 3.53–3.63 (2H, m, 1-H_2), 3.95 (1H, q, *J* 6.3 Hz, 4-H), 4.49 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.15 (2H, m, 6-H_2), 5.62 (1H, ddd, *J* 17.1, 10.3, 7.7 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) –5.3 (2 × CH_3), 18.2 (C), 26.4 (3 × CH_3), 28.9 (CH_2), 31.8 (CH_2), 55.7 (CH_3), 63.2 (CH_2), 77.7 (CH), 94.1 (CH_2), 117.7 (CH_2), 138.7 (CH); *m*/*z* (CI) 275.2041 (MH^+. $C_{14}H_{31}O_3Si$ requires 275.2042), 205 (13%), 121 (100), 85 (40).

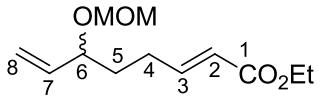
4-(Methoxymethoxy)hex-5-en-1-ol (176).



A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (16.6 mL, 0.02 mol) was added to a solution of 1-(*tert*-butyldimethylsilyloxy)-4-(methoxymethoxy)hex-5-ene (**175**) (1.48 g, 5.40 mmol) in tetrahydrofuran (40 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (20 mL). The solution was washed

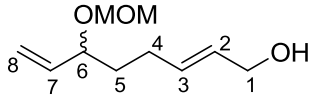
with water (30 mL) and the aqueous layer was then extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (petroleum ether/diethyl ether, 5:2) to give 4-(methoxymethoxy)hex-5-en-1-ol (**176**) (2.21 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 3423 (OH), 2947 (CH), 1638 (C=C), 1458, 1215; δ_H (400 MHz, $CDCl_3$) 1.62–1.70 (4H, m, 2-H_2 and 3-H_2), 1.72 (1H, s, 1-OH), 3.38 (3H, s, OCH_3), 3.62–3.73 (2H, m, 1-H_2), 4.04 (1H, q, *J* 6.9 Hz, 4-H), 4.52 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.18–5.26 (2H, m, 6-H_2), 5.68 (1H, ddd, *J* 17.1, 10.3, 6.9 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 28.6 (CH_2), 31.2 (CH_2), 55.7 (CH_3), 62.6 (CH_2), 77.7 (CH), 93.8 (CH_2), 117.6 (CH_2), 138.2 (CH) *m*/*z* (CI) 161.1178 (MH^+. $C_8H_{17}O_3$ requires 161.1181), 149 (12%), 129 (88), 99 (100), 81 (24).

Ethyl (2*E*)-6-(methoxymethoxy)oct-2,7-dienoate (177).



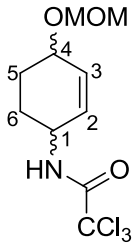
Reaction was carried out according to general procedure 1, using 4-(methoxymethoxy)hex-5-en-1-ol (**176**) (2.20 g, 0.13 mol). Flash column chromatography using (diethyl ether/petroleum ether, 2:3) gave the title compound, ethyl (2*E*)-6-(methoxymethoxy)oct-2,7-dienoate (**177**) (2.90 g, 94%) as colourless oil. υ_{max}/cm^{-1} (NaCl) 2944 (CH), 1709 (CO), 1654 (C=C), 1466, 1370, 1277, 1149; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.61–1.82 (2H, m, 4-H_2), 2.21–2.39 (2H, m, 5-H_2), 3.30 (3H, s, OCH_3), 3.94 (1H, q, *J* 7.2 Hz, 6-H), 4.11 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.46 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.63 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.12–5.18 (2H, m, 8-H_2), 5.55–5.64 (1H, m, 7-H), 5.77 (1H, dt, *J* 15.7, 1.6 Hz, 2-H), 6.90 (1H, dt, *J* 15.7, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 28.2 (CH_2), 33.8 (CH_2), 55.7 (CH_3), 60.3 (CH_2), 73.9 (CH), 93.8 (CH_2), 117.7 (CH_2), 122.0 (CH), 137.6 (CH), 148.8 (CH), 166.7 (C); *m*/*z* (CI) 229.1437 (MH^+. $C_{12}H_{21}O_4$ requires 229.1440), 197 (36%), 167 (52), 81 (35).

(2*E*)-6-(Methoxymethoxy)oct-2,7-dien-1-ol (178).



The reaction was carried out according to general procedure 2, using ethyl (2*E*)-6-(methoxymethoxy)oct-2,7-dienoate (**177**) (0.66 g, 2.89 mol). Flash column chromatography (eluting with petroleum ether/diethyl ether, 1:1) yielded ethyl (2*E*)-6-(methoxymethoxy)oct-2,7-dien-1-ol (**178**) (0.50 g, 93%) as colourless oil. υ_{max}/cm^{-1} (NaCl) 3408 (OH), 2937 (CH), 1641 (C=C), 1442, 1373, 1153, 1096, 1036; δ_H (400 MHz, $CDCl_3$) 1.48 (1H, s, 1-OH), 1.53–1.63 (1H, m, 4-*H*H), 1.62–1.77 (1H, m, 4-H*H*), 2.04–2.22 (2H, m, 5-H_2), 3.79 (3H, s, OCH_3), 4.00 (1H, q, *J* 6.7 Hz, 6-H), 4.10 (2H, d, *J* 4.0 Hz, 1-H_2), 4.54 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.17–5.24 (2H, m, 8-H_2), 5.61–5.75 (3H, m, 2-H, 3-H and 7-H); δ_C (100 MHz, $CDCl_3$) 28.0 (CH_2), 34.7 (CH_2), 55.5 (CH_3), 63.7 (CH_2), 76.8 (CH), 93.7 (CH_2), 117.4 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); *m*/*z* (CI) 169.1224 (M^+–OH. $C_{10}H_{17}O_2$ requires 169.1229), 137 (100%), 125 (38), 107 (70).

(1*R,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclohex-2-ene (181).**



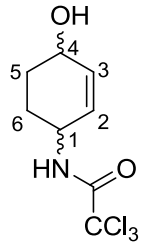
The reaction was carried out according general procedure 4 using (2*E*)-6-(methoxymethoxy)oct-2,7-dien-1-ol (**178**) (0.06 g, 0.32 mmol) and bis(acetonitrile)palladium(II) chloride (0.01 g, 0.03 mmol) as a catalyst for the Overman rearrangement. Purification by flash column chromatography (petroleum ether/diethylether, 2:1) gave mixture of two diastereomers (1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclohex-2-ene (**181**) (0.06 g, 59% combined yield over 3 steps) as a white solid. NMR spectra showed a 1:1 mixture of diastereomers, where most signals of each overlapped. Mp 41–44 ^oC; υ_{max}/cm^{-1} (NaCl)

3326 (NH), 2935 (CH), 1699 (C=C), 1641, 1450, 1153, 1096, 1036; δ_H (400 MHz, $CDCl_3$) 1.67–2.30 (4H, m, 6-H_2 and 5-H_2), 3.40 (3H, s, OCH_3), 4.08–4.22 (1H, m, 1-H), 4.39–4.58 (1H, m, 4-H), 4.68–4.77 (2H, m, OCH_2O), 5.72–5.84 (1H, m, 3-H), 5.96–6.07 (1H, m, 2-H), 6.60 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 26.7 (CH_2), 47.2 (CH), 55.3 (CH_3), 69.2 (CH), 92.7 (C), 95.9 (CH_2), 129.2 (CH), 132.7 (CH), 161.6 (C); *m*/*z* (CI) 323.9935 (MNa^+. $C_{10}H_{14}{}^{35}Cl_3NO_3Na$ requires 323.9937), 281 (100%), 279 (70), 240 (28), 137 (30), 83 (25).

(1*R,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclohex-2-ene (181).**

The reaction was carried out according general procedure 4 using (2*E*)-6-(methoxymethoxy)oct-2,7-dien-1-ol (**178**) (0.10 g, 0.54 mmol) and bis(acetonitrile)palladium(II) chloride (0.01 g, 0.05 mmol) as a catalyst for the Overman rearrangement. Grubb's catalyst (2nd Generation) (0.015 g, 0.02 mmol) was then added and the reaction mixture was heated under reflux for 12 h. A further quantity of Grubb's catalyst (2nd Generation) (0.015 g, 0.02 mmol) were added and the reaction mixture stirred for a further 12 h. Concentration of the filtrate followed by flash column chromatography (petroleum ether/diethylether, 2:1) gave (1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclohex-2-ene (**181**) (0.14 g, 93% combined yield over 3 steps) as a white solid. Spectroscopic data as reported above.

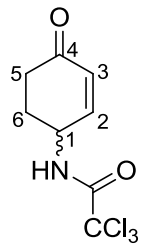
(1*R,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohex-2-en-4-ol (182).**



(1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy) cyclohex-2-ene (**181**) (0.15 g, 0.51 mmol) was dissolved in methanol (5 mL) and 0.5 N hydrochloric acid (5 mL) was added to the reaction mixture. The reaction mixture was stirred for 24 h at 40 °C. The mixture was cooled and neutralised with a saturated solution of sodium hydrogencarbonate (10 mL) and then extracted with ethyl acetate (4 × 20 mL).

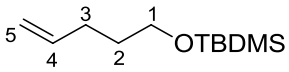
The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/ethyl acetate, 10:1) gave (1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino) cyclohex-2-en-4-ol (**182**) (0.09 g, 72%) as a white solid. NMR spectra showed a 1:1 mixture of diastereomers, signals for only one diastereomer was recorded. Mp 109–111 °C; υ_{max}/cm^{-1} (NaCl) 3420 (OH), 2945 (CH), 1677 (CO), 1450, 1248, 1073; δ_H (400 MHz, $CDCl_3$) 1.43–1.93 (3H, m, 6-*H*H, 5-*H*H and 4-OH), 1.96–2.26 (2H, m, 6-H*H* and 5-H*H*), 4.14–4.28 (1H, m, 1-H), 4.30–4.57 (1H, m, 4-H), 5.62–5.75 (1H, m, 2-H), 5.86–5.98 (1H, m, 3-H), 6.50 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 28.7 (CH_2), 46.9 (CH), 64.3 (CH), 92.5 (C), 128.3 (CH), 134.1 (CH), 161.4 (C); *m*/*z* (CI) 257.9848 (MH^+. $C_8H_{11}{}^{35}Cl_3NO_2$ requires 257.9855), 242 (82%), 206 (33), 137 (8), 81 (21).

1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohex-2-en-4-one (130).



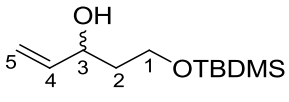
(1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohexa-2-ene-4-ol (**182**) (0.08 g, 0.30 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (0.21 g, 0.49 mmol) was then added to the solution and stirred for 2 h before warming to room temperature. The reaction mixture was concentrated *in vacuo*, and diluted with a 10% sodium sulfite solution (10 mL) and the organics were extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 1:5) gave 1-(2′,2′,2′-trichloromethylcarbonylamino)cyclopent-2-en-4-one (**130**) (0.06 g, 83%) as a white solid. Mp 92–94 °C; υ_{max}/cm^{-1} (NaCl) 3318 (NH), 2950 (CH), 1689 (CO), 1519, 1481, 1249, 1073; δ_H (400 MHz, $CDCl_3$) 1.95–2.08 (1H, m, 6-*H*H), 2.31–2.42 (1H, m, 6-H*H*), 2.43–2.59 (2H, m 5-H_2), 4.73–4.81 (1H, m, 1-H), 6.03 (1H, dd, *J* 10.2, 2.1 Hz, 3-H), 6.77 (1H, dt, *J* 10.2, 2.1 Hz, 2-H), 7.03 (1H, d, *J* 7.8 Hz, NH); δ_C (100 MHz, $CDCl_3$) 29.2 (CH_2), 35.9 (CH_2), 47.9 (CH), 92.2 (C), 131.1 (CH), 148.4 (CH), 161.7 (C), 197.8 (C); *m*/*z* (CI) 257.9665 (MH^+. $C_8H_9{}^{35}Cl_2{}^{37}ClNO_2$ requires 257.9670), 222 (78%), 186 (32), 152 (18), 69 (49).

1-(*tert*-Butyldimethylsilyloxy)pent-4-ene (184).[183]



A mixture of pent-4-en-1-ol (**183**) (4.20 g, 0.05 mol), *tert*-butyldimethylsilyl chloride (11.04 g, 0.07 mol) and imidazole (4.90 g, 0.07 mol) in tetrahydrofuran (150 mL) were stirred overnight at room temperature. The reaction mixture was filtered through Celite®, washed with diethyl ether (70 mL). The filtrate was concentrated and purified by flash column chromatography (elution with petroleum ether/diethyl ether, 20:1) which gave 1-(*tert*-butyldimethylsilyloxy)pent-4-ene (**184**) (9.77 g, 99%) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[183] υ_{max}/cm^{-1} (Neat) 2931 (CH), 1465, 1365, 1249, 1059; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.84 (9H, s, $Si(CH_3)_3$), 1.51–1.60 (2H, m, 2-H_2), 2.02–2.08 (2H, m, 3-H_2), 3.57 (2H, t, *J* 6.4 Hz, 1-H_2), 4.88–4.99 (2H, m, 5-H_2), 5.77 (1H, ddt, *J* 16.9, 10.2, 6.6 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) –5.2 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 30.0 (CH_2), 31.9 (CH_2), 62.5 (CH_2), 114.5 (CH_2), 138.6 (CH); *m*/*z* (CI) 201.1674 (MH^+. $C_{11}H_{25}OSi$ requires 201.1674), 165 (8%), 97 (25), 81 (60), 69 (96).

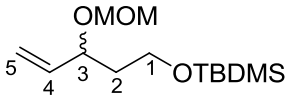
1-(*tert*-Butyldimethylsilyloxy)pent-4-en-3-ol (185).



To a suspension of selenium dioxide (0.72 g, 6.54 mmol) in dichloromethane (25 mL) was added *tert*-butyl hydroperoxide (5.0–6.0 M in decane) (3.65 mL, 32.70 mmol). The mixture was stirred for 1 h. Then, a solution of 1-(*tert*-butyldimethylsilyloxy)pent-4-ene (**184**) (1.31 g, 6.54 mmol) in dichloromethane (25 mL) was added and stirred for 72 h. The mixture was evaporated, diethyl ether (50 mL) and 2.0 M sodium hydroxide (30 mL) were added to the evaporated mixture, and the organic phase was separated and aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with 1.0 M hydrochloric acid (20 mL), sodium hydrogencarbonate (20 mL) and then dried ($MgSO_4$). After filtration the organic solution was concentrated *in vacuo*. Flash column chromatography (petroleum ether/diethyl ether, 10:1) gave 1-(*tert*-butyldimethylsilyloxy)pent-4-en-3-ol (**185**) (1.40 g, 70%) as a yellow oil. υ_{max}/cm^{-1} (NaCl) 3424 (OH), 2929 (CH), 1472, 1256, 1099, 921; δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s,

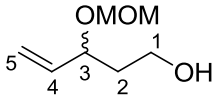
$Si(CH_3)_2$), 0.82 (9H, s, $Si(CH_3)_3$), 1.59–1.74 (2H, m, 2-H_2), 3.30 (1H, br s, 3-OH), 3.70–3.76 (1H, m, 1-*H*H), 3.79–3.84 (1H, m, 1-H*H*), 4.25–4.32 (1H, m, 3-H), 5.04 (1H, d, *J* 10.4 Hz, 5-*H*H), 5.22 (1H, d, *J* 17.0 Hz, 5-H*H*), 5.80 (1H, ddd, *J* 17.0, 10.4, 5.4 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) –5.5 (2 × CH_3), 18.1 (C), 25.8 (3 × CH_3), 31.2 (CH_2), 61.9 (CH_2), 72.5 (CH), 114.1 (CH_2), 140.5 (CH); *m*/*z* (CI) 217 (MH^+, 98%), 199 (26), 145 (26), 85 (15), 79 (52).

1-(*tert*-Butyldimethylsilyloxy)-3-(methoxymethoxy)pent-4-ene.



Reaction was carried out according to general procedure 3, using 1-(*tert*-butyldimethylsilyloxy)pent-4-en-3-ol (**185**) (2.46 g, 0.01 mol). Flash column chromatography (petroleum ether/diethyl ether, 20:1) yielded 1-(*tert*-butyldimethylsilyloxy)-3-(methoxymethoxy)pent-4-ene (3.80 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 2954 (CH), 1468 (CH), 1442, 1216, 905; δ_H (400 MHz, $CDCl_3$) 0.04 (6H, s, $Si(CH_3)_2$), 0.89 (9H, s, $SiC(CH_3)_3$), 1.65–1.74 (1H, m, 2-*H*H), 1.78–1.87 (1H, m, 2-H*H*), 3.36 (3H, s, OCH_3), 3.63–3.76 (2H, m, 1-H_2), 4.16 (1H, q, *J* 7.4 Hz, 3-H), 4.55 (1H, d, *J* 6.6 Hz, OC*H*HO), 4.7 (1H, d, *J* 6.6 Hz, OCH*H*O), 5.15–5.24 (2H, m, 5-H_2), 5.64–5.74 (1H, ddd, *J* 17.3, 10.2, 7.6 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) –5.3 (2 × CH_3), 18.2 (C), 25.9 (3 × CH_3), 38.7 (CH_2), 55.3 (CH_3), 59.3 (CH_2), 74.4 (CH), 93.9 (CH_2), 116.9 (CH_2), 138.4 (CH); *m*/*z* (CI) 261.1881 (MH^+. $C_{13}H_{29}O_3Si$ requires 261.1886), 229 (65%), 199 (75), 145 (50), 69 (100).

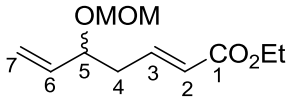
3-(Methoxymethoxy)pent-4-en-1-ol (186).



A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (12.8 mL, 0.01 mol) was added to a solution of 1-(*tert*-butyldimethylsilyloxy)-3-(methoxymethoxy)pent-4-ene (2.79 g, 0.01 mol) in tetrahydrofuran (200 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (40 mL). The solution was washed with water (30 mL) and the aqueous layer was then extracted with diethyl ether (3 × 30 mL).

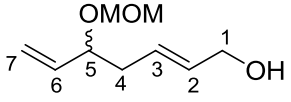
The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (petroleum ether/diethyl ether, 5:2) to give 3-(methoxymethoxy)pent-4-en-1-ol (**186**) (1.5 g, 96%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 3433 (OH), 2947 (CH), 1419, 1219, 1149; δ_H (400 MHz, $CDCl_3$) 1.69–1.77 (2H, m, 2-H_2), 2.17 (1H, br s, 1-OH), 3.30 (3H, s, OCH_3), 3.62–3.77 (2H, m, 1-H_2), 4.16 (1H, q, *J* 6.9 Hz, 3-H), 4.46 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.61 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.09–5.19 (2H, m, 5-H_2), 5.63 (1H, ddd, *J* 17.3, 10.4, 7.5 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) 37.7 (CH_2), 55.6 (CH_3), 60.1 (CH_2), 76.3 (CH), 94.0 (CH_2), 117.4 (CH_2), 137.6 (CH); *m*/*z* (CI) 147.1022 (MH^+. $C_7H_{15}O_3$ requires 147.1021), 115 (100%), 85 (38), 69 (44).

Ethyl (2*E*)-5-(methoxymethoxy)hept-2,6-dienoate (187).



Reaction was carried out according to general procedure 1, using 3-(methoxymethoxy)pent-4-en-1-ol (**186**) (0.80 g, 5.48 mmol). Purification by flash column chromatography using (diethyl ether/petroleum ether, 2:3) gave the title compound (**187**) (0.8 g, 69%) as colourless oil. υ_{max}/cm^{-1} (Neat) 3020 (CH), 1714 (CO), 1464, 1215, 1150; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 2.40–2.55 (2H, m, 4-H_2), 3.36 (3H, s, OCH_3), 4.12–4.22 (3H, m, 5-H and OCH_2CH_3), 4.20 (2H, q, *J* 7.1 Hz, OCH_2CH_3), 4.54 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.21–5.28, (2H, m, 7-H_2), 5.70 (1H, ddd, *J* 17.2, 10.4, 7.6 Hz, 6-H), 5.89 (1H, dt, *J* 15.7, 1.5 Hz, 2-H), 6.96 (1H, dt, *J* 15.7, 7.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 38.3 (CH_2), 55.5 (CH_3), 60.2 (CH_2), 75.8 (CH), 93.8 (CH_2), 117.9 (CH_2), 123.7 (CH), 137.2 (CH), 144.5 (CH), 166.3 (C); *m*/*z* (CI) 215.1286 (MH^+. $C_{11}H_{19}O_4$ requires 215.1283), 183 (100%), 153 (28), 113 (28), 85 (78).

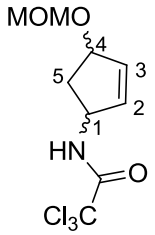
(2*E*)-5-(Methoxymethoxy)hept-2,6-dien-1-ol (188).



Reaction was carried out according to general procedure 2, using ethyl (2*E*)-5-(methoxymethoxy)hept-2,6-dienoate (**187**) (0.67g, 3.13 mmol). Flash column chromatography (eluting with petroleum ether/diethyl ether, 1:1) yielded (2*E*)-5-

(methoxymethoxy)hept-2,6-dien-1-ol (**188**) (0.53 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 3394 (OH), 2916 (CH), 1427, 1273, 1018; δ_H (400 MHz, $CDCl_3$) 1.26 (1H, t, *J* 5.9 Hz, 1-OH), 2.28–2.42 (2H, m, 4-H_2), 3.40 (3H, s, OCH_3), 4.06 (1H, q, *J* 6.7 Hz, 5-H), 4.09–4.13 (2H, m, 1-H_2), 4.50 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.18–5.25 (2H, m, 7-H_2), 5.65–5.75 (3H, m, 2-H, 3-H and 6-H); δ_C (100 MHz, $CDCl_3$) 38.3 (CH_2), 55.4 (CH_3), 63.6 (CH_2), 76.8 (CH), 93.8 (CH_2), 117.4 (CH_2), 128.3 (CH), 131.8 (CH), 137.7 (CH); *m*/*z* (CI) 173.1174 (MH^+. $C_9H_{17}O_3$ requires 173.1174), 155 (100%), 125 (100), 101 (100), 85 (100).

(1*R,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclopent-2-ene (191).**

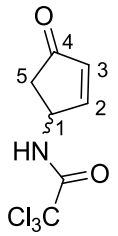


The reaction was carried out according general procedure 4 using (2*E*)-5-(methoxymethoxy)hept-2,6-dien-1-ol (**188**) (0.11 g, 0.65 mmol) and bis(acetonitrile)palladium(II) chloride (0.02 g, 0.07 mmol) as a catalyst for the Overman rearrangement. Grubb's catalyst (2nd Generation) (0.008 g, 0.01 mmol) was then added and the reaction mixture was heated under reflux for 12 h. Concentration of the filtrate followed by flash column chromatography (petroleum ether/diethylether, 2:1) gave (1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino)-4-(methoxymethoxy) cyclopent-2-ene (**191**) (0.05 g, 25% combined yield over 3 steps) as a colourless oil. NMR spectra showed a 1:1 mixture of diastereomers, signals for only one diastereomer was recorded. υ_{max}/cm^{-1} (Neat) 3410 (NH), 2926 (CH), 1693 (CO), 1464, 1365, 1168; δ_H (400 MHz, $CDCl_3$) 2.00 (1H, ddd, *J* 14.5, 7.3, 4.1 Hz, 5-*H*H), 2.40 (1H, ddd, *J* 14.5, 7.7, 3.2 Hz, 5-H*H*), 3.37 (3H, s, OCH_3), 4.67 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.85–4.90 (1H, m, 4-H), 5.08–5.16 (1H, m, 1-H), 5.99 (1H, ddd, *J* 5.6, 2.1, 1.1 Hz, 2-H), 6.16 (1H, dt, *J* 5.6, 1.9 Hz, 3-H), 6.54 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 38.8 (CH_2), 55.4 (CH_3), 56.7 (CH), 81.3 (CH), 96.1 (CH_2), 133.8 (CH_2), 136.9 (CH), 161.5 (C); *m*/*z* (CI) 287.9954 (MH^+. $C_9H_{13}{}^{35}Cl_3NO_3$ requires 287.9961), 226 (100%), 192 (78), 158 (12), 107 (15), 69 (28).

(1*R,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclopent-2-ene (191).**

(2*E*)-5-(Methoxymethoxy)hept-2,6-dien-1-ol (**188**) (0.16 g, 0.93 mmol) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.19 mL, 0.93 mmol) was added to the solution followed by trichloroacetonitrile (0.14 mL, 1.39 mmol). The solution was then warmed to room temperature and stirred for 24 h. The reaction mixture was filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give the allylic trichloroacetimidate, which was used without further purification. The allylic trichloroacetimidate was then dissolved in toluene (20 mL) and potassium carbonate (0.20 g, 0.93 mmol) was added to the solution and the reaction mixture was stirred at 130 ^{o}C for 12 h. The reaction mixture was then filtered through Celite®, concentrated and dissolved in dichloromethane (30 mL). Grubb's catalyst (2nd Generation) (0.04 g, 0.05 mmol) was then added and the reaction mixture was heated under reflux for 24 h. The mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (100 mL). Concentration of the filtrate followed by flash column chromatography (petroleum ether/diethylether, 2:1) gave (1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino)-4-(methoxymethoxy)cyclopenta-2-ene (**191**) (0.83 g, 83% combined yield over 3 steps) as a colourless oil. Spectroscopic data as described above.

1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclopent-2-en-4-one (193).

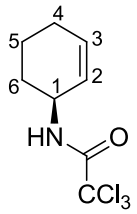


(1*R**,4*S** and 1*S**,4*S**)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-4-(methoxymethoxy) cyclopent-2-ene (**191**) (0.05 g, 0.17 mmol) was dissolved in methanol (4 mL) and 0.5 N hydrochloric acid (4 mL) was added to the reaction mixture. The reaction mixture was stirred for 18 h at 40 °C. The mixture was cooled and neutralised with a saturated solution of sodium hydrogencarbonate (5 mL) and then extracted with ethyl acetate (3 × 20 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*, to give (1*R**,4*S** and

1*S**,4*S**)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclopent-2-en-4-ol (**192**) as a white solid. It was dissolved in dichloromethane and cooled to 0 °C. 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (0.09 g, 0.20 mmol) was then added to the solution and stirred for 2 h before warming to room temperature. The reaction mixture was concentrated and diluted with a 10% sodium sulphite solution (10 mL) and the organic layer was extracted with dichloromethane (3 × 15 mL). The combined organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 1:5) gave 1-(2′,2′,2′-trichloromethylcarbonylamino) cyclopent-2-en-4-one (**193**) (0.03 g, 73% over two steps) as a white solid. Mp 141–143 °C; υ_{max}/cm^{-1} (Neat) 3284 (NH), 2929 (CH), 1711 (CO), 1681 (CO), 1589 (C=C), 1429, 1165; δ_H (400 MHz, $CDCl_3$) 2.28 (1H, dd, *J* 18.9, 2.6 Hz, 5-*H*H), 2.97 (1H, dd, *J* 18.9, 7.0 Hz, 5-H*H*), 5.19–5.28 (1H, m, 1-H), 6.39 (1H, dd, *J* 5.7, 1.8 Hz, 3-H), 6.93 (1H, br s, NH), 7.60 (1H, dd, *J* 5.7, 2.5 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 41.2 (CH_2), 51.6 (CH), 92.4 (C), 136.8 (CH), 159.6 (CH), 161.7 (C), 205.1 (C); *m*/*z* 241.9530 (MH^+. $C_7H_7{}^{35}Cl_3NO_2$ requires 241.9542), 219 (25%), 149 (27), 95 (20), 58 (100).

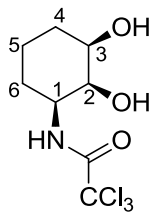
5.3.2 Synthesis of Polyhydroxylated Aminocyclohexanes

(1*S*)-1-(2′,2′,2′)-Trichloromethylcarbonylaminocyclohex-2-ene (131).[38]



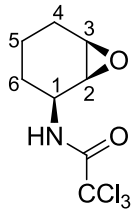
The reaction was carried out according general procedure 4 using (2*E*)-oct-2,7-dien-1-ol (**128**) (0.50 g, 3.97 mmol) by using (*S*)-COP-Cl (0.59 g, 0.40 mmol) as the rearrangement catalyst. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 97:3) gave (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-2-ene (**131**) (0.83 g, 90% yield over 3 steps) as a white solid. 88% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% *iso*-propanol/hexane at 0.75 mL/min), retention time: t_S= 8.2 min, and t_R= 9.2 min. $[\alpha]_D^{23}$ –95.3 (*c* 2.1, $CHCl_3$). All other spectroscopic data as previously reported for 1-(2’,2’,2’-trichloromethylcarbonylamino)cyclohex-2-ene (**129**) above.

(1*S*,2*S*,3*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3-dihydroxycyclohexane (206).[140]



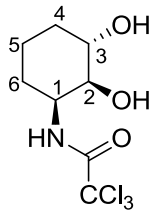
(1*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohex-2-ene (**131**) (0.06 g, 0.25 mmol) was dissolved in dichloromethane (5 mL) at –78 °C. Tetramethylethylenediamine (0.04 g, 0.27 mmol) was added and the reaction mixture stirred for 0.1 h before the addition of osmium tetroxide (0.06 g, 0.26 mmol). The dark coloured solution was stirred for 1 h at –78 °C before warming to room temperature and stirred for a further 1 h. The solvent was removed *in vacuo* and the dark coloured solid was redissolved in methanol (5 mL). Concentrated hydrochloric acid (5 drops) was added and the reaction mixture stirred for 2 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) afforded (1*S*,2*S*,3*R*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2,3-dihydroxycyclohexane (**206**) (0.06 g, 93%) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[140] υ_{max}/cm^{-1} (NaCl) 3407 (NH/OH), 2942 (CH), 1700 (CO), 1512, 1042, 821; $[\alpha]_D^{25}$ –3.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30–1.43 (1H, m, 5-*H*H), 1.59–1.80 (5H, m, 4-H_2, 5-H*H* and 6-H_2), 2.56 (1H, br s, OH), 2.90 (1H, br s, OH), 3.83–3.93 (2H, m, 2-H and 3-H), 3.95–4.05 (1H, m, 1-H), 7.73 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 18.3 (CH_2), 26.1 (CH_2), 28.4 (CH_2), 52.1 (CH), 70.4 (CH), 70.9 (CH), 92.7 (C), 161.8 (C); *m*/*z* (CI) 275.9960 (MH^+. $C_8H_{13}{}^{35}Cl_3NO_3$ requires 275.9961), 242 (35%), 179 (12), 123 (89), 109 (88), 73 (100).

2′,2′,2′-Trichloro-*N*-[(1*S*,2*S*,3*R*)-oxabicyclo[4.1.0]hept-2-yl]acetamide (207).[141]



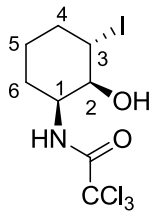
(1*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclohex-2-ene (**131**) (0.24 g, 0.97 mmol) was dissolved in dichloromethane (15 mL) along with sodium hydrogencarbonate (0.16 g, 1.95 mmol). To the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.34 g, 1.95 mmol) and stirred at room temperature. The resulting suspension was stirred vigorously for 19 h. A 20% aqueous solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with a 20% aqueous solution of sodium sulphite (10 mL) and a 5% aqueous solution of sodium hydrogencarbonate (2 × 20 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 2:5) gave 2′,2′,2′-trichloro-*N*-[(1*S*,2*S*,3*R*)-oxabicyclo[4.1.0]hept-2-yl]acetamide (**207**) (0.24 g, 95%) as white solid. Spectroscopic data is entirely consistent with the literature.[141] Mp 75–77 °C; υ_{max}/cm^{-1} (NaCl) 3421 (NH), 3020 (CH), 1712 (CO), 1363, 1217, 757; $[\alpha]_D^{25}$ –26.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.20–1.59 (4H, m, 5-H_2 and 6-H_2), 1.82–1.20 (2H, m, 4-H_2), 3.25 (1H, t, *J* 3.4 Hz, 2-H), 3.30 (1H, td, *J* 3.8, 3.4, Hz 3-H), 4.25–4.32 (1H, m, 1-H), 7.02 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 17.6 (CH_2), 23.1 (CH_2), 25.8 (CH_2), 47.5 (CH), 53.0 (CH), 54.6 (CH), 92.7 (C), 161.8 (C); *m*/*z* (CI) 257.9852 (MH^+. $C_8H_{11}{}^{35}Cl_3NO_2$ requires 257.9855), 224 (28%), 191 (6), 137 (21), 107 (45), 73 (100).

(1*S*,2*S*,3*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3-dihydroxycyclohexane (208).



2′,2′,2′-Trichloro-*N*-[(1*S*,2*S*,3*R*)-7-oxabicyclo[4.1.0]hept-2-yl]acetamide (**207**) (0.04 g, 0.14 mmol) was added to a 1:1 mixture of 0.2 M sulfuric acid/1,4-dioxane (15 mL) and the reaction mixture was stirred at room temperature for 0.75 h. The reaction was then diluted with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 10:1) gave (1*S*,2*S*,3*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2,3-dihydroxycyclohexane (**208**) (0.03 g, 75%) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 3408 (OH), 2942 (CH), 1700 (CO), 1512, 821; $[\alpha]_D^{25}$ +9.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.45–1.55 (2H, m, 4-*H*H and 5-*H*H), 1.58–1.77 (2H, m, 5-H*H* and 6-*H*H), 1.84–1.95 (2H, m, 4-H*H* and 6-H*H*), 3.01 (1H, br s, OH), 3.22 (1H, br s, OH), 3.77 (1H, dd, *J* 6.0, 3.6 Hz, 2-H), 3.82–3.89 (1H, m, 3-H), 4.15–4.21 (1H, m, 1-H), 7.16 (1H, d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 18.6 (CH_2), 26.3 (CH_2), 28.5 (CH_2), 51.0 (CH), 70.5 (CH), 72.1 (CH), 92.7 (C), 162.1 (C); *m*/*z* (CI) 275.9959 (MH^+. $C_8H_{13}{}^{35}Cl_3NO_3$ requires 275.9961), 242 (59%), 208 (30), 158 (16), 113 (33), 69 (100).

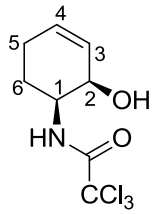
(1*S*,2*S*,3*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2-hydroxy-3-iodocyclohexane (211).



To a solution of (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-2-ene (**131**) (0.29 g, 1.20 mmol) in chloroform (15 mL), *N*-iodosuccinimide (0.40 g, 1.81 mmol) was added and the mixture stirred for 18 h. The solvent was then removed *in vacuo*. The resulting

residue was dissolved in ethyl acetate (20 mL) and the organic phase washed with water (4 × 30 mL). The organic layer was then dried ($MgSO_4$) and the solvent removed *in vacuo* to give (3a*S*,4*S*,7a*S*)-4-iodo-2-(trichloromethyl)benzoxazole (**210**) (0.37 g, 85% yield) as a colourless oil which was used without further purification. δ_H (400 MHz, CDCl3) 1.50–1.69 (2H, m, 5-H_2), 1.90–2.23 (4H, m, 4-H_2 and 6-H_2), 4.17–4.30 (2H, m, 1-H and 3-H), 5.16 (1H, t, *J* 7.5 Hz, 2-H). To a solution of (3a*S*,4*S*,7a*S*)-4-iodo-2-(trichloromethyl)benzoxazole (0.03 g, 0.14 mmol) in methanol (5 mL) was added 2.0 M hydrochloric acid (3 mL) and the reaction mixture was stirred at room temperature for 0.75 h. The reaction mixture was then diluted with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 10:1) gave (1*S*,2*S*,3*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2-hydroxy-3-iodocyclohexane (**211**) (0.03 g, 76%) as a white solid. Mp 103–105 °C; υ_{max}/cm^{-1} (NaCl) 3402 (OH), 2941 (CH), 1695 (CO), 1509, 1155, 821; $[\alpha]_D^{25}$ +60.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.58–1.66 (1H, m, 6-*H*H), 1.68–1.98 (4H, m, 4-H_2, 5-*H*H, 6-H*H*), 2.08–2.18 (1H, m, 5-H*H*), 2.32 (1H, br s, OH), 4.13 (1H, t, *J* 4.1 Hz, 2-H), 4.41 (1H, q, *J* 4.1 Hz, 3-H), 4.46–4.54 (1H, m, 1-H), 7.02 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 21.4 (CH_2), 26.2 (CH_2), 29.0 (CH_2), 32.9 (CH), 49.4 (CH), 72.8 (CH), 92.7 (C), 161.5 (C); *m*/*z* (CI) 387.8958 (MH^+. $C_8H_{12}{}^{35}Cl_2{}^{37}ClINO_2$ requires 387.8950), 352 (32%), 260 (100), 224 (64), 154 (42), 81 (21).

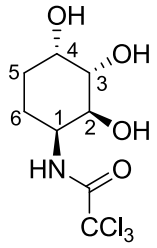
(1*S*,2*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2-hydroxycyclohex-3-ene (213).



To a solution of (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-2-ene (**131**) (4.00 g, 16.5 mmol) in chloroform (100 mL), *N*-iodosuccinimide (5.52 g, 25.00 mmol) was added and the mixture stirred for 18 h. The solvent was then removed in *vacuo*. The resulting residue was dissolved in ethyl acetate (120 mL) and the organic phase washed with water (3 × 50 mL), dried ($MgSO_4$) and the solvent removed in *vacuo*. The residue obtained was dissolved in toluene (100 mL) and 1,8-diazabicyclo[5,4,0]undec-7-ene (3.70 mL, 24.8 mmol) was added. The reaction mixture was heated under reflux for 12 h. The

reaction mixture was then cooled and the solvent was removed *in vacuo*. The resulting dark coloured solid was dissolved in methanol (80 mL). 2.0 M Hydrochloric acid (80 mL) was added and reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 × 70 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) gave (1*S*,2*R*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2-hydroxycyclohex-3-ene (**213**) (2.54 g, 60%) as white solid. Mp 105–109 °C; υ_{max}/cm^{-1} (NaCl) 3404 (OH), 2940 (CH), 1699 (CO), 1506, 1096, 909, 822; $[\alpha]_D^{25}$ –71.9 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (1H, br s, OH), 1.64–1.75 (1H, m, 6-*H*H), 1.86–1.94 (1H, m, 6-H*H*), 2.20–2.26 (2H, m, 5-H_2), 3.97 (1H, ddd, *J* 11.9, 7.6, 3.6 Hz, 1-H), 4.14–4.21 (1H, m, 2-H), 5.85–5.91 (1H, m, 3-H), 6.00 (1H, dt, *J* 9.8, 3.6 Hz, 4-H), 7.36 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_2), 24.8 (CH_2), 51.4 (CH), 64.7 (CH), 92.5 (C), 127.2 (CH), 133.4 (CH), 162.5 (C); *m*/*z* (CI) 257.9857 (MH^+. $C_8H_{11}{}^{35}Cl_3NO_2$ requires 257.9855), 224 (98%), 190 (36), 153 (48), 113 (59), 81 (100).

(1*S*,2*S*,3*S*,4*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (214).



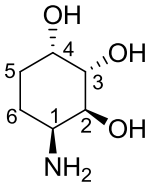
(1*S*,2*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2-hydroxycyclohex-3-ene (**213**) (1.00 g, 3.89 mmol) was dissolved in dichloromethane (50 mL) at –78 °C. Tetramethylethylenediamine (0.68 mL, 4.54 mmol) was added and the reaction mixture stirred for 0.1 h before the addition of osmium tetroxide (1.00 g 3.90 mmol). The dark coloured solution was stirred for 1 h at –78 °C before warming to room temperature and stirred for 1 h. The solvent was removed *in vacuo* and the dark coloured solid was dissolved in methanol (50 mL). Concentrated hydrochoric acid (1 mL) was added and the reaction stirred for 2 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) afforded (1*S*,2*S*,3*S*,4*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (**214**) (0.60 g, 53%) as a white solid. Mp 151–153 °C; υ_{max}/cm^{-1} (NaCl) 3360 (OH), 2947

(CH), 1653 (CO), 1456, 1420, 1024; $[\alpha]_D^{25}$ –27.6 (*c* 0.9, MeOH); δ_H (400 MHz, CD_3OD) 1.63–1.83 (4H, m, 5-H_2 and 6-H_2), 3.83–3.92 (3H, m, 2-H, 3-H and 4-H), 4.10 (1H, ddd, *J* 10.6, 4.4, 2.9 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 24.7 (CH_2), 27.4 (CH_2), 50.6 (CH), 68.4 (CH), 72.3 (CH), 74.0 (CH), 93.8 (C), 163.0 (C); *m*/*z* (CI) 291.9908 (MH^+. $C_8H_{13}{}^{35}Cl_3NO_4$ requires 291.9910), 258 (100%), 224 (50), 148 (22), 85 (12).

(1*S*,2*S*,3*S*,4*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (214) Upjohn Reaction.

A solution of (1*S*,2*R*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2-hydroxy-3-cyclohexene (**213**) (1.00 g, 3.89 mmol) in tetrahydrofuran (25 mL), *N*-methylmorpholine-*N*-oxide (0.60 g, 5.10 mmol) and osmium tetraoxide (0.06 g, 0.23 mmol) was added to a stirred solution of sodium hydrogencarbonate (0.40 g, 4.76 mmol) in *tert*-butyl alcohol (15 mL) and water (4 mL). The reaction was stirred at room temperature for 24 h and then a 10% sodium sulfite solution (20 mL) was added and the reaction mixture was extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) gave (1*S*,2*S*,3*S*,4*S*,)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane **214** (0.63 g, 56%) as a white solid. Spectroscopic data as described above.

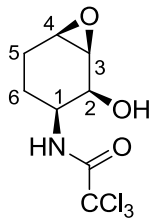
(1*S*,2*S*,3*S*,4*S*)-1-Aminocyclohexane-2,3,4-triol (133).[171]



(1*S*,2*S*,3*S*,4*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (**214**) (0.15 g, 0.52 mmol) was dissolved in methanol (15.0 mL) and 2.0 M sodium hydroxide (3.0 mL) was added. The reaction mixture was stirred for 12 h at room temperature and then concentrated *in vacuo*. Purification by ion exchange column chromatography (Dowex 50 W), eluting with 0.5 M ammonia solution gave (1*S*,2*S*,3*S*,4*S*)-1-aminocyclohexane-2,3,4-triol (**133**) (0.05 g, 68%) as a white solid. Mp 96–97 °C, lit.[171] 95–97 °C; υ_{max}/cm^{-1} (NaCl) 3326 (NH/OH), 2945 (CH), 1653, 1451, 1411, 1118, 1022; $[\alpha]_D^{25}$+10.8 (c 1.0, MeOH); δ_H (400 MHz, CD_3OD) 1.51–1.67 (4H, m, 5-H_2 and 6-H_2),

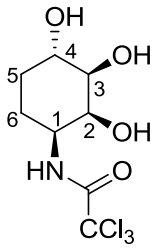
3.09–3.14 (1H, m, 1-H), 3.73–3.76 (1H, m, 3-H), 3.77–3.83 (2H, m, 2-H and 4-H); δ_C (100 MHz, CD_3OD) 25.8 (CH_2), 27.1 (CH_2), 49.9 (CH), 68.7 (CH), 72.5 (CH), 73.7 (CH); *m*/*z* (CI) 148.0971 (MH^+. $C_6H_{14}NO_3$ requires 148.0974), 128 (6%), 112 (7), 85 (13), 79 (42).

2′,2′,2′-Trichloro-*N*-[(1*S*,2*S*,3*S*,4*R*)-2-hydroxyoxabicyclo[4.1.0]hept-2-yl]acetamide (216).



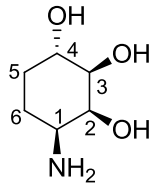
(1*S*,2*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2-hydroxycyclohex-3-ene (**213**) (0.07 g, 0.27 mmol) was dissolved in dichloromethane (10 mL) along with sodium hydrogencarbonate (0.05 g, 0.54 mmol). To the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.09 g, 0.54 mmol) and stirred at room temperature. The resulting suspension was stirred vigorously for 24 h. A 20% solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined dichloromethane layers were washed with a 20% solution of sodium sulfite (10 mL) and a 5% solution of sodium hydrogencarbonate (2 × 20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 2:5) gave 2',2',2'-trichloro-*N*-[(1*S*,2*S*,3*S*,4*R*)-2-hydroxyoxabicyclo[4.1.0]hept-2-yl]acetamide (**216**) (0.05 g, 69%) as a white solid. Mp 122–125 °C; υ_{max}/cm^{-1} (NaCl) 3389 (OH), 2951 (CH), 1705 (CO), 1510, 1223, 1078, 827, 756; $[\alpha]_D^{25}$ –125.3 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.53–1.67 (2H, m, 6-H_2), 1.96–2.06 (1H, m, 5-*H*H), 2.20 (1H, dt, *J* 15.7, 5.4 Hz, 5-H*H*), 2.40 (1H, d, *J* 9.0 Hz, OH), 3.44–3.48 (2H, m, 3-H and 4-H), 3.83–3.91 (1H, m, 1-H), 4.14–4.21 (1H, m, 2-H), 7.51 (1H, br d, *J* 5.3 Hz, NH); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2), 22.1 (CH_2), 50.6 (CH), 54.5 (CH), 55.2 (CH), 64.9 (CH), 92.6 (C), 161.8 (C); *m/z* (CI) 273.9804 (MH^+. $C_8H_{11}{}^{35}Cl_3NO_3$ requires 273.9805), 240 (100%), 206 (31), 172 (8), 156 (9), 137 (14), 121 (17), 71 (25).

(1*S*,2*S*,3*R*,4*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (217).



2′,2′,2′-Trichloro-*N*-[(1*S*,2*S*,3*S*,4*R*)-2-hydroxyoxabicyclo[4.1.0]hept-2-yl]acetamide (**216**) (0.03 g, 0.12 mmol) was added to a 1:1 mixture of 0.2 M sulfuric acid/1,4-dioxane (8 mL) and the reaction mixture was stirred at room temperature for 8 h. The reaction mixture was diluted with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 1:10) gave (1*S*,2*S*,3*R*,4*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (**217**) (0.03 g, 87%) as a white solid. Mp 112–114 °C; υ_{max}/cm^{-1} (NaCl) 3440 (OH), 2946 (CH), 1647 (CO), 1450, 1411, 1016; $[\alpha]_D^{24}$ +6.4 (*c* 2.2, MeOH); δ_H (400 MHz, CD_3OD) 1.34–1.43 (1H, m, 5-*H*H), 1.73–1.80 (2H, m, 6-H_2), 1.86–1.95 (1H, m, 5-H*H*), 3.50–3.54 (1H, m, 3-H), 3.79 (1H, td, *J* 7.8, 4.1 Hz, 4-H), 3.88–3.94 (1H, m, 1-H), 3.95 (1H, t, *J* 3.0 Hz, 2-H); δ_C (100 MHz, CD_3OD) 24.5 (CH_2), 30.9 (CH_2), 54.1 (CH), 70.6 (2 × CH), 76.2 (CH), 94.0 (C), 163.3 (C); *m*/*z* (CI) 291.9904 (MH^+. $C_8H_{13}{}^{35}Cl_3NO_4$ requires 291.9910), 258 (19%), 224 (5), 197 (5), 147 (14), 123 (12), 107 (100).

(1*S*,2*S*,3*R*,4*S*)-1-Aminocyclohexane-2,3,4-triol (132)

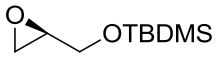


(1*S*,2*S*,3*R*,4*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)-2,3,4-trihydroxycyclohexane (**217**) (0.15 g, 0.52 mmol) was dissolved in methanol (15 mL) and 2.0 M sodium hydroxide (3.0 mL) was added. The reaction mixture was stirred at room temperature for 12 h and then concentrated *in vacuo*. Purification by ion exchange column chromatography

(Dowex 50 W), eluting with 0.5 M ammonia solution gave (1*S*,2*S*,3*R*,4*S*)-1-aminocyclohexane-2,3,4-triol (**132**) (0.075 g, 98%) as a white solid. Mp 64–66 °C; υ_{max}/cm^{-1} (NaCl) 3355 (OH), 3263 (NH), 2957 (CH), 1947, 1669, 1445, 1214, 1016; $[\alpha]_D^{22}$ +23.1 (c 0.9, MeOH); δ_H (400 MHz, CD_3OD) 1.11–1.25 (1H, m, 5-*H*H), 1.46–1.58 (2H, m, 6-H2), 1.79 (1H, ddt, *J* 12.4, 8.4, 4.0 Hz, 5-H*H*), 2.71–2.79 (1H, m, 1-H), 3.18 (1H, dd, *J* 8.8, 2.5 Hz, 3-H), 3.53–3.61 (1H, m, 4-H), 3.70 (1H, t, *J* 2.5 Hz, 2-H); δ_C (100 MHz, CD_3OD) 27.2 (CH_2), 30.6 (CH_2), 53.0 (CH), 70.4 (CH), 73.9 (CH), 77.2 (CH); *m*/*z* (CI) 148.0975 (MH^+. $C_6H_{14}NO_3$ requires 148.0974), 137 (5%), 97 (41), 81 (68), 71 (100).

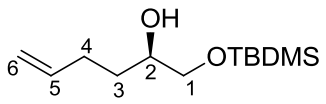
5.3.3 Studies towards γ-Lycorane and Pancratistatin Analogues

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (240).[184]



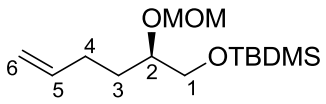
A mixture of (*S*)-glycidol (**236**) (3.10 g, 0.04 mol), *tert*-butyldimethylsilyl chloride (9.40 g, 0.06 mol) and imidazole (4.20 g, 0.06 mol) in tetrahydrofuran (70 mL) were stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated and purified by flash column chromatography (elution with petroleum ether/diethyl ether, 10:1) to give (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**240**) (7.70 g, 98%) as a colourless oil. Spectroscopic data is entirely consistent with the literature. $[\alpha]_D^{24}$ +2.7 (*c* 1.0, $CHCl_3$), lit.[184] +2.9 (*c* 1.0, $CHCl_3$); υ_{max}/cm^{-1} (Neat) 2930 (CH), 1253, 1161, 983, 835; δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.92 (9H, s, $SiC(CH_3)_3$), 2.66 (1H, dd, *J* 4.6, 2.4 Hz, 1-*H*H), 2.79 (1H, dd, *J* 5.2, 4.6 Hz, 1-H*H*), 3.10–3.14 (1H, m, 2-H), 3.68 (1H, dd, *J* 11.8, 4.8 Hz, 3-*H*H), 3.87 (1H, dd, *J* 11.8, 3.2 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) –5.4 (2 × CH_3), 18.4 (C), 26.0 (3 × CH_3), 45.0 (CH_2), 52.5 (CH) and 63.9 (CH_2); *m*/*z* (CI) 189.1309 (MH^+. $C_9H_{21}O_2Si$ requires 189.1311), 145 (35%), 131 (50), 89 (62), 73 (12).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)hex-5-en-2-ol (241).[185]



A solution of allyl magnesium bromide (1.0 M in diethyl ether) (100.0 mL, 100.0 mmol) was added drop-wise to a solution of copper(I) bromide dimethylsulfide complex (0.69 g, 3.40 mmol) in tetrahydrofuran (150 mL) at –78 °C and the white suspension was stirred for 0.5 h. (2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (**240**) (12.70 g, 67.0 mmol) in tetrahydrofuran (60 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 2 h. The reaction was quenched by the addition of a saturated ammonium chloride solution (100 mL) and extracted with ethyl acetate (3 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 10:1) gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (**241**) (13.90 g, 90%) as a colourless oil. Spectroscopic data is entirely consistent with the literature.[185] υ_{max}/cm^{-1} (Neat) 3460 (OH), 2929 (CH), 1641 (C=C), 1472, 1252, 1088, 909; $[\alpha]_D^{24}$ –6.7 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.82 (9H, s, $SiC(CH_3)_3$), 1.35–1.55 (2H, m, 3-H_2), 2.00–2.22 (2H, m, 4-H_2), 2.35 (1H, br d, *J* 3.3 Hz, OH), 3.33 (1H, dd, *J* 9.9, 7.1 Hz, 1-*H*H), 3.53–3.62 (2H, m, 1-H*H* and 2-H), 4.88–4.92 (1H, m, 6-*H*H), 4.94–5.00 (1H, m, 6-H*H*), 5.76 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) –5.4 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 29.8 (CH_2), 32.0 (CH_2), 67.2 (CH_2), 71.2 (CH), 114.8 (CH_2), 138.4 (CH); *m*/*z* (CI) 231.1776 (MH^+. $C_{12}H_{27}O_2Si$ requires 231.1780), 173 (8), 81 (15).

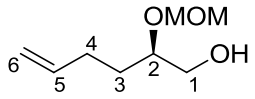
(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene (242).



The reaction was carried out according to general procedure 3 using (2*R*)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (**241**) (4.00 g, 17.00 mmol). Flash column chromatography (elution with petroleum ether/diethyl ether, 20:1) yielded (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene (**242**) (4.70 g, 100%) as a colourless oil. (Found: C, 61.4; H, 11.0. $C_{14}H_{30}O_3Si$ requires C, 61.3; H, 11.0%); υ_{max}/cm^{-1} (NaCl) 2929 (CH), 1642 (C=C), 1472, 1255, 1110, 1040; $[\alpha]_D^{24}$ +28.8 (*c* 1.5, $CHCl_3$); δ_H

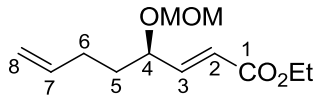
(400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.82 (9H, s, $SiC(CH_3)_3$), 1.35–1.54 (2H, m, 3-H_2), 2.00–2.21 (2H, m, 4-H_2), 3.34 (3H, s, OCH_3), 3.50–3.62 (3H, m, 1-H_2 and 2-H), 4.60 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O), 4.89–4.94 (1H, m, 6-*H*H), 4.95–5.01 (1H, m, 6-H*H*), 5.77 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) –5.4 (2 × CH_3), 18.3 (C), 25.9 (3 × CH_3), 29.6 (CH_2), 31.0 (CH_2), 55.5 (CH_3), 65.7 (CH_2), 77.7 (CH), 96.4 (CH_2), 114.6 (CH_2), 138.5 (CH); *m*/*z* (CI) 243 (M^+–OCH_4, 48%), 231 (8), 133 (11), 81 (18).

(2*R*)-2-(Methoxymethoxy)hex-5-en-1-ol (243).



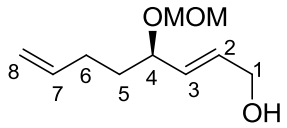
A solution of tetrabutylammonium fluoride (1M in tetrahydrofuran) (57.10 mL, 57.10 mmol) was added to a solution of (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)hex-5-ene (**242**) (13.09 g, 47.70 mmol) in tetrahydrofuran (100 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (50 mL). The solution was washed with water (50 mL) and the aqueous layer was then extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (elution with petroleum ether/diethyl ether, 5:2) to give (2*R*)-2-(methoxymethoxy)hex-5-en-1-ol (**243**) (7.63 g, 100%) as a colourless oil. (Found: C, 59.9; H, 10.2. $C_8H_{16}O_3$ requires C, 60.0; H, 10.0%); υ_{max}/cm^{-1} (NaCl) 3432 (OH), 2947 (CH), 1641 (C=C), 1450, 1212, 1028; $[\alpha]_D^{24}$ –66.8 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.49–1.70 (2H, m, 3-H_2), 2.07–2.24 (2H, m, 4-H_2), 3.14 (1H, br s, 3.4 Hz, 1-OH), 3.44 (3H, s, OCH_3), 3.47–3.64 (3H, m, 1-H_2 and 2-H), 4.69 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.96–5.07 (2H, m, 6-H_2), 5.80 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 5-H); δ_C (100 MHz, $CDCl_3$) 29.7 (CH_2), 30.8 (CH_2), 55.7 (CH_3), 66.7 (CH_2), 81.9 (CH), 97.1 (CH_2), 115.1 (CH_2), 138.0 (CH); *m*/*z* (CI) 161 (MH^+, 15%), 129 (10), 99 (14), 81 (40), 69 (38).

Ethyl (2*E*,4*R*)-4-(methoxymethoxy)oct-2,7-dienoate (244).



Reaction was carried out according to general procedure 1, using (2*R*)-2-(methoxymethoxy)hex-5-en-1-ol (**243**) (0.50 g, 3.10 mmol). Flash column chromatography (elution with petroleum ether/diethyl ether, 5:1) yielded ethyl (2*E*,4*R*)-4-(methoxymethoxy)oct-2,7-dienoate (**244**) (0.71 g, 99% yield) as a yellow oil. (Found: C, 63.2; H, 8.9. $C_{12}H_{20}O_4$ requires C, 63.2; H, 8.8%); υ_{max}/cm^{-1} (NaCl) 2941 (CH), 1720 (CO), 1658 (C=C), 1446, 1369, 1269, 1154; $[\alpha]_D^{24}$ +79.2 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.59–1.80 (2H, m, 5-H_2), 2.09–2.21 (2H, m, 6-H_2), 3.39 (3H, s, OCH_3), 4.18–4.25 (3H, m, 4-H and OCH_2CH_3), 4.59 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.97–5.08 (2H, m, 8-H_2), 5.81 (1H, ddt, *J* 17.1, 10.3, 6.6 Hz, 7-H), 5.99 (1H, dd, *J* 15.7, 1.2 Hz, 2-H), 6.82 (1H, dd, *J* 15.7, 6.5 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 29.3 (CH_2), 34.0 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 74.6 (CH), 94.7 (CH_2), 115.2 (CH_2), 122.1 (CH), 137.7 (CH), 147.6 (CH), 166.2 (C); *m*/*z* (CI) 229 (MH^+, 35%), 199 (28), 197 (32), 167 (100), 81 (51), 69 (64).

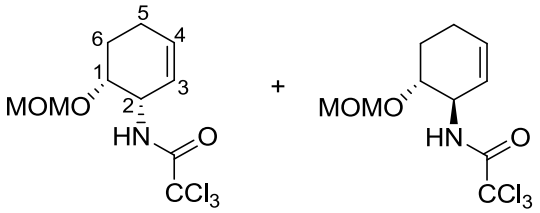
(2*E*,4*R*)-4-(Methoxymethoxy)oct-2,7-dien-1-ol (134).



The reaction was carried out according to general procedure 2, using ethyl (2*E*,4*R*)-4-(methoxymethoxy)oct-2,7-dienoate (**244**) (1.30 g, 5.70 mmol). Flash column chromatography (elution with petroleum ether/diethyl ether, 2:3) yielded, (2*E*,4*R*)-4-(methoxymethoxy)oct-2,7-dien-1-ol (**134**) (1.05 g, 99% yield) as a colourless oil. (Found: C, 64.5; H, 9.7. $C_{10}H_{18}O_3$ requires C, 64.5; H, 9.7%); υ_{max}/cm^{-1} (NaCl) 3408 (OH), 2937 (CH), 1641 (C=C), 1442, 1373, 1153, 1096, 1036; $[\alpha]_D^{24}$ +126.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.54–1.64 (2H, m, 5-*H*H and OH), 1.68–1.78 (1H, m, 5-H*H*), 2.06–2.22 (2H, m, 6-H_2), 3.38 (3H, s, OCH_3), 4.02–4.09 (1H, m, 4-H), 4.17 (2H, dd, *J* 5.2, 1.4 Hz, 1-H_2), 4.54 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.95–5.06 (2H, m, 8-H_2), 5.58 (1H, ddt, *J* 15.6, 7.8, 1.4 Hz, 3-H), 5.79–5.87 (2H, m, 2-H and 7-H); δ_C (100 MHz, $CDCl_3$) 29.6 (CH_2), 34.7 (CH_2), 55.5 (CH_3), 62.9 (CH_2), 75.7 (CH), 93.7 (CH_2),

114.9 (CH_2), 131.2 (CH), 132.3 (CH), 138.2 (CH); *m*/*z* (CI) 204 (MNH_4^+, 100%), 174 (31), 142 (29), 125 (14), 58 (16).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (135a) and (1*R*,2*R*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (135b).



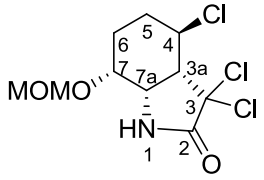
The reaction was carried out according general procedure 4 using (2*E*,4*R*)-4-(methoxymethoxy)oct-2,7-dien-1-ol (**134**) (1.10 g, 3.40 mmol). Bis(acetonitrile)palladium(II) chloride (0.09 g, 0.34 mmol) was used to catalyse the Overman rearrangement, which was stirred at room temperature overnight before addition of Grubbs first generation catalyst (0.28 g, 0.34 mmol). Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 7:1) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135a**) followed by (1*R*,2*R*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino) cyclohex-3-ene (**135b**), as a yellow oil (0.46 g, 45% combined yield over 3 steps) and in a 5:1 ratio (**135a** : **135b**). υ_{max}/cm^{-1} (NaCl) 3421 (NH), 2930 (CH), 1709 (CO), 1654 (C=C), 1500, 1148, 1102, 1036. Data for (1*R*,2*S*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135a**): $[\alpha]_D^{20}$ +79.1 (*c* 1.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73–1.82 (1H, m, 6-*H*H), 2.00–2.13 (2H, m, 5-*H*H and 6-H*H*), 2.17–2.28 (1H, m, 5-H*H*), 3.42 (3H, s, OCH_3), 4.05 (1H, td, *J* 5.6, 1.3 Hz, 1-H), 4.60–4.66 (1H, m, 2-H), 4.72 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.51–5.56 (1H, m, 3-H), 5.91–5.97 (1H, m, 4-H), 7.31 (1H, br d, *J* 7.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 20.2 (CH_2), 24.2 (CH_2), 48.6 (CH), 55.0 (CH_3), 70.9 (CH), 91.9 (C), 94.5 (CH_2), 123.4 (CH), 129.9 (CH), 160.7 (C). Data for (1*R*,2*R*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135b**): δ_H (400 MHz, $CDCl_3$) 1.75–1.87 (1H, m, 6-*H*H), 1.90–1.99 (1H, m, 6-H*H*), 2.11–2.29 (2H, m, 5-H_2), 3.39 (3H, s, OCH_3), 3.71–3.79 (1H, m, 1-H), 4.49–4.56 (1H, m, 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.58–5.62 (1H, m, 3-H), 5.91–5.97 (1H, m, 4-H), 6.78 (1H, br d, *J* 7.1 Hz, NH); δ_C (100 MHz, $CDCl_3$) 23.3 (CH_2), 26.0 (CH_2), 52.5 (CH), 55.7 (CH_3),

74.9 (CH), 92.6 (C), 95.3 (CH_2), 124.1 (CH), 131.4 (CH), 161.6 (C); *m*/*z* (CI) 306.0056 (MH^+. $C_{10}H_{15}{}^{35}Cl^{37}Cl_2NO_3$ requires 306.0062), 268 (100%), 234 (45), 208 (7), 137 (9), 69 (22).

(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (135a) and (1*R*,2*R*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (135b) using toluene as solvent.

The reaction was carried out according general procedure 4 using (2*E*,4*R*)-4-(methoxymethoxy)-oct-2,7-dien-1-ol (**134**) (0.10 g, 0.54 mmol). Bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) was used to catalyse the Overman rearrangement, which was stirred in toluene (10 mL) initially at 0 °C and slowly warmed to room temperature over 24 h before addition of Grubbs first generation catalyst (0.04 g, 0.05 mmol). Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 7:1) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135a**) followed by (1*R*,2*R*)-1-(methoxymethoxy)-2-(2’,2’,2’-trichloromethylcarbonylamino)cyclohex-3-ene (**135b**), as a yellow oil (0.11 g, 60% combined yield over 3 steps) and in a 10 : 1 ratio (**135a** : **135b**). Spectroscopic data as described above.

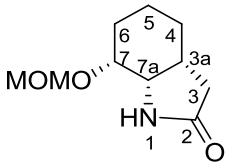
(3a*R*,4*R*,7*R*,7a*S*)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one (237).



(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135a**) (0.45 g, 1.49 mmol) was dissolved in *p*-xylene (10 mL) which was then de-gassed for 1h. Powdered molecular sieves (4Å, activated) (0.1 g) and dichlorotris(triphenylphosphine)ruthenium(II) (0.07 g, 0.07 mmol) were then added and the reaction mixture was heated at 155 °C in a sealed tube for 2 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (elution with petroleum ether/diethyl ether, 1:4) to give (3a*R*,4*R*,7*R*,7a*S*)-3,3,4-trichloro-7-(methoxymethoxy)octahydroindol-2-one (**237**) (0.34 g, 75%) as a brown oil. υ_{max}/cm^{-1} (NaCl) 3256 (NH), 2953 (CH), 1741 (CO), 1440, 1036; $[\alpha]_D{}^{25}$ –60.2 (*c* 0.5, $CHCl_3$); δ_H

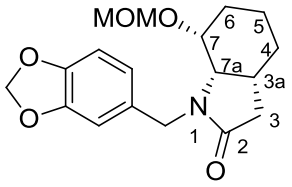
(400 MHz, $CDCl_3$) 1.50–1.66 (1H, m, 6-*H*H), 1.71–1.82 (1H, m, 6-H*H*), 1.89–1.96 (1H, m, 5-*H*H), 2.29–2.36 (1H, m, 5-H*H*), 3.19 (1H, dd, *J* 8.6, 5.3 Hz, 3a-H), 3.39 (3H, s, OCH_3), 3.83–3.93 (2H, m, 4-H and 7-H), 4.23–4.27 (1H, m, 7a-H), 4.67 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.9 Hz, OCH*H*O), 6.20 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 32.7 (CH_2), 54.0 (CH), 54.7 (CH), 55.0 (CH_3), 59.0 (CH), 73.0 (CH), 84.4 (C), 94.4 (CH_2), 167.7 (C); *m*/*z* (CI) 302.0115 (MH^+. $C_{10}H_{15}{}^{35}Cl_3NO_3$ requires 302.0118), 268 (30%), 222 (18), 198 (10), 140 (12).

(3a*R*,7*R*,7a*S*)-7-(Methoxymethoxy)octahydroindol-2-one (249).



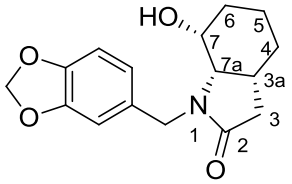
(3a*R*,4*R*,7*R*,7a*S*)-3,3,4-Trichloro-7-(methoxymethoxy)octahydroindol-2-one (**237**) (0.05 g, 0.17 mmol) was dissolved in tetrahydrofuran (10 mL) which was then added to a slurry of activated Raney®-Nickel (1.00 g). The reaction was heated under reflux for 24 h and then a further portion of Raney®-Nickel was added (1.00 g). The reaction mixture was heated for a further 24 h then cooled, diluted with diethyl ether (10 mL) and filtered through a short silica plug. The plug was washed with diethyl ether (100 mL), then the washings were dried ($MgSO_4$) and concentrated. Purification by flash column chromatography (elution with ethyl acetate) gave (3a*R*,7*R*,7a*S*)-7-(methoxymethoxy)octahydroindol-2-one (**249**) (0.03 g, 85%) as a yellow oil. υ_{max}/cm^{-1} (NaCl) 3423 (NH), 2935 (CH), 1686 (CO), 1448, 1035; $[\alpha]_D^{25}$ +46.1 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18–1.29 (2H, m, 5-H_2), 1.41–1.52 (1H, m, 6-*H*H), 1.59–1.67 (1H, m, 6-H*H*), 1.69–1.83 (2H, m, 4-H_2), 2.00 (1H, d, *J* 16.0, Hz, 3-*H*H), 2.32–2.41 (1H, m, 3a-H), 2.49 (1H, dd, *J* 16.0, 6.6 Hz, 3-H*H*), 3.38 (3H, s, OCH_3), 3.67 (1H, dt, *J* 11.5, 4.4 Hz, 7-H), 3.95 (1H, t, *J* 4.4 Hz, 7a-H), 4.65 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.71 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.70 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 21.9 (CH_2), 25.8 (CH_2), 27.1 (CH_2), 35.1 (CH), 39.6 (CH_2), 55.6 (CH_3), 56.6 (CH), 74.9 (CH), 94.9 (CH_2), 177.9 (C); *m*/*z* (CI) 200.1288 (MH^+. $C_{10}H_{18}NO_3$ requires 200.1287), 168 (10%), 138 (5), 69 (8).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)octahydroindol-2-one (238).



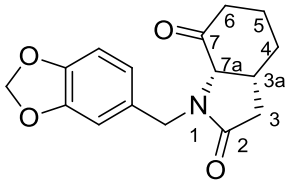
(3a*R*,7*R*,7a*S*)-7-(Methoxymethoxy)octahydroindol-2-one (**249**) (0.05 g, 0.25 mmol) was dissolved in tetrahydrofuran (2.0 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil) (0.012 g, 0.300 mmol) was added and the solution was stirred for 5 minutes before piperonyl bromide (0.09 g, 0.45 mmol) in tetrahydrofuran (1.0 mL) was slowly added. Sodium iodide (0.07 g, 0.45 mmol) was then added and the reaction was heated to 50 °C for 2 h. The reaction mixture was cooled and then a saturated solution of ammonium chloride (2.0 mL) was added. The solution was extracted with ethyl acetate (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate) gave (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-(methoxymethoxy)-octahydroindol-2-one (**238**) (0.08 g, 97% yield) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 2937 (CH), 1668 (CO), 1488, 1252; $[\alpha]_D^{25}$ –32.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15–1.30 (2H, m, 5-H_2), 1.42–1.70 (3H, m, 4-H_2 and 6-*H*H), 1.73–1.83 (1H, m, 6-H*H*), 2.16 (1H, dd, *J* 14.6, 7.5 Hz, 3-*H*H), 2.24–2.34 (1H, m, 3a-H), 2.39 (1H, dd, *J* 14.6, 10.4 Hz, 3-H*H*), 3.22 (1H, dd, *J* 6.5, 3.9 Hz, 7-H), 3.27 (3H, s, OCH_3), 3.74 (1H, d, *J* 14.8 Hz, N-C*H*H), 3.81–3.85 (1H, m, 7a-H), 4.39 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.54 (1H, d, *J* 7.0 Hz, OCH*H*O), 4.94 (1H, d, *J* 14.8 Hz, N-CH*H*), 5.85 (2H, s, OCH'_2O), 6.61–6.68 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.7 (CH_2), 25.8 (CH_2), 26.9 (CH_2), 32.6 (CH), 36.5 (CH_2), 43.8 (CH_2), 55.6 (CH_3), 56.2 (CH), 72.2 (CH), 95.3 (CH_2), 101.0 (CH_2), 108.1 (CH), 108.5 (CH), 121.3 (CH), 131.1 (C), 146.9 (C), 147.9 (C), 176.6 (C); *m*/*z* (CI) 334.1652 (MH^+. $C_{18}H_{24}NO_5$ requires 334.1654), 302 (7%), 200 (6), 135 (15), 69 (16).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one (251).



(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)octahydroindol-2-one (**238**) (0.20 g, 0.60 mmol) was dissolved in 1:1 mixture of methanol (5.0 mL) and 2.0 M hydrochloric acid solution (5.0 mL). The reaction mixture was heated to 35 °C and stirred for 48 h, then cooled and neutralised with a 6.0 M solution of potassium carbonate (10.0 mL). The heterogeneous mixture was extracted with ethyl acetate (4 × 50 mL), the organic layer was then dried ($MgSO_4$) and concentrated to give (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one (**251**) as a white solid (0.17 g, 100%). Mp 170–172 °C; υ_{max}/cm^{-1} (NaCl) 3370 (OH), 2934 (CH), 1663 (CO), 1489, 1442, 1243; $[\alpha]_D^{25}$ –22.6 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.25–1.39 (2H, m, 5-H_2), 1.51–1.61 (1H, m, 4-*H*H), 1.67–1.87 (3H, m, 4-H*H* and 6-H_2), 1.95 (1H, br s, OH), 2.23 (1H, dd, *J* 15.0, 7.8 Hz, 3-*H*H), 2.36–2.45 (1H, m, 3a-H), 2.51 (1H, dd, *J* 15.0, 11.3 Hz, 3-H*H*), 3.28 (1H, dd, *J* 7.0, 3.8 Hz, 7-H), 3.95–4.00 (1H, m, 7a-H), 4.17 (1H, d, *J* 14.8 Hz, N-C*H*H), 4.71 (1H, d, *J* 14.8 Hz, N-CH*H*), 5.95 (2H, s, OCH_2O), 6.75–6.82 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.6 (CH_2), 25.8 (CH_2), 29.4 (CH_2), 32.4 (CH), 36.4 (CH_2), 44.9 (CH_2), 60.1 (CH), 65.8 (CH), 101.1 (CH_2), 108.4 (CH), 108.5 (CH), 121.4 (CH), 131.3 (C), 147.1 (C), 148.1 (C), 176.8 (C); *m*/*z* (CI) 290.1391 (MH^+. $C_{16}H_{20}NO_4$ requires 290.1392), 289 (12%), 85 (52), 51 (55), 49 (75).

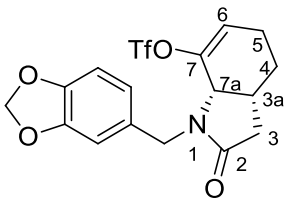
(3a*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)octahydroindol-2,7-dione (252).



(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindol-2-one (0.04 g, 0.14 mmol) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. 1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one (0.10 g, 0.23 mmol) was then added to the solution and stirred for 2 h before warming to room temperature. The reaction mixture was concentrated *in vacuo* and diluted with a 10% sodium sulphite solution and

extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with diethyl ether/ethyl acetate 1:5) gave (3a*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)octahydroindol-2,7-dione (**252**) as a white solid (0.038 g, 95%). Mp 115–117 °C; υ_{max}/cm^{-1} (Neat) 2983 (CH), 1737 (CO), 1697 (CO), 1491, 1373, 1045; $[\alpha]_D^{27}$ +0.7 (*c* 1.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.54–1.65 (1H, m, 5-*H*H), 1.69–1.81 (1H, m, 4-*H*H), 1.82–1.94 (2H, m, 5-H*H* and 4-H*H*), 2.11 (1H, dd, *J* 16.3, 10.6 Hz, 3-*H*H) 2.25 (2H, t, *J* 6.3 Hz, 6-H_2), 2.34 (1H, dd, *J* 16.3, 8.0 Hz, 3-H*H*), 2.74–2.78 (1H, m, 3a-H), 3.70 (1H, d, *J* 8.8 Hz, 7a-H), 4.01 (1H, d, *J* 14.7 Hz, N-C*H*H), 4.99 (1H, d, *J* 14.7 Hz, N-CH*H*), 5.87 (2H, s, OCH_2O), 6.57–6.67 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 22.3 (CH_2), 26.8 (CH_2), 35.4 (CH_2), 36.9 (CH), 39.7 (CH_2), 45.8 (CH_2), 64.5 (CH), 101.1 (CH_2), 108.3 (CH), 108.8 (CH), 121.9 (CH), 130.2 (C), 147.1 (C), 148.0 (C), 173.8 (C), 209.7 (C); *m*/*z* (CI) 288.1235 (MH^+. $C_{16}H_{18}NO_4$ requires 288.1235), 207 (4%), 167 (5), 135 (8), 85 (62), 83 (100), 47 (15).

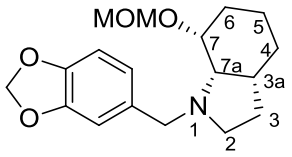
(3a*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(trifluoromethanesulfonate)-3,3a,4,5,7a-hexahydroindole-2-one (239).



(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)octahydroindol-2,7-dione (**252**) (0.02 g, 0.07 mmol) was dissolved in tetrahydrofuran (1 mL) and cooled to –78 °C. Lithium bis(trimethylsilyl)amide (0.10 mL, 0.10 mmol) was added to the solution and stirred for 1 h followed by the addition of 2-[*N*,*N*′-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (0.04 g, 0.10 mmol) in tetrahydrofuran (1 mL) and stirred further for 4 h. The reaction was quenched by addition of 10% sodium hydroxide (1 mL) and extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate) gave the (3a*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-(trifluoromethanesulfonate)-3,3a,4,5,7a-hexahydroindole-2-one (**239**) as a white solid (2.4 mg, 8%). Mp 60.5–62.5 °C; υ_{max}/cm^{-1} (NaCl) 2931 (CH), 1697 (CO), 1519, 1496, 1419, 1219; $[\alpha]_D^{24}$ +4.4 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.65–1.80 (2H, m, 5-H_2), 2.25–2.41 (3H, m, 3-*H*H and 4-

H_2), 2.48 (1H, dd, *J* 16.5, 8.2 Hz, 3-H*H*), 2.64–2.74 (1H, m, 3a-H), 4.05–4.15 (2H, m, 7a-H and N-C*H*H), 5.01 (1H, d, *J* 15.7 Hz, N-CH*H*), 5.94 (2H, s, OCH_2O), 6.01 (1H, dd, *J* 4.8, 3.7 Hz, 6-H), 6.71–6.76 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 21.1 (CH_2), 22.7 (CH_2), 33.5 (CH), 34.1 (CH_2), 45.4 (CH_2), 56.2 (CH), 101.1 (CH_2), 108.2 (CH), 108.3 (CH), 121.4 (CH), 122.4 (CH), 130.1 (C), 147.1 (C), 147.9 (C), 153.5 (C), 172.0 (C), 174.2 (C); *m*/*z* (CI) 420.0732 (MH^+. $C_{17}H_{17}F_3NSO_6$ requires 420.0729), 334 (3%), 285 (45), 270 (45), 219 (3), 165 (5), 137 (13), 115 (43), 85 (64).

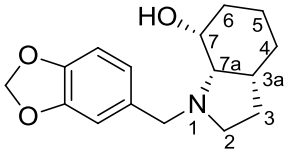
(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)octahydroindole (253).



Lithium aluminium hydride (0.18 g, 4.68 mmol) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C. (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-(methoxymethoxy) octahydroindol-2-one (**238**) (0.31 g, 0.94 mmol) in tetrahydrofuran (5 mL) was added to the stirred slurry and heated under reflux for 4 h. The solution was cooled to room temperature and quenched by the addition of a saturated solution of sodium sulfate (3 mL) with vigorous stirring over 1 h. A 5% sodium hydroxide solution (2 mL) was then added. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate) gave (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-(methoxymethoxy)octahydroindol (**253**) as a colourless oil (0.24 g, 85%). υ_{max}/cm^{-1} (NaCl) 2931 (CH), 1589 (C=C), 1496, 1249, 1073; $[\alpha]_D^{25}$ –42.1 (*c* 0.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.15–1.40 (4H, m, 4-H_2 and 5-H_2), 1.54–1.62 (1H, m, 6-*H*H), 1.65–1.75 (2H, m, 3-H_2), 1.86 (1H, qd, *J* 11.8, 3.8 Hz, 6-H*H*), 1.93–2.02 (1H, m, 3a-H), 2.14 (1H, ddd, *J* 14.5, 10.5, 4.2 Hz, 2-*H*H), 2.83 (1H, t, *J* 3.6 Hz, 7a-H), 2.98–3.02 (1H, m, 2-H*H*), 3.06 (1H, d, *J* 13.6 Hz, N-C*H*H), 3.30 (3H, s, OCH_3), 3.72 (1H, dt, *J* 11.1, 3.6 Hz, 7-H), 4.48 (1H, d, *J* 13.6 Hz, N-CH*H*), 4.59 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.61 (1H, d, *J* 6.9 Hz, OCH*H*O), 5.84 (1H, d, *J* 1.4 Hz, OC*H*′H′O), 5.85 (1H, d, *J* 1.4 Hz, OCH′*H*′O), 6.62–6.88 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 23.8 (CH_2), 26.1 (CH_2), 27.8 (CH_2), 29.3 (CH_2), 40.1 (CH), 52.9 (CH_2), 55.3 (CH_3), 59.7 (CH_2), 65.1 (CH), 78.8 (CH), 94.7 (CH_2), 100.7 (CH_2), 107.7 (CH), 109.0 (CH), 120.9 (CH), 135.7

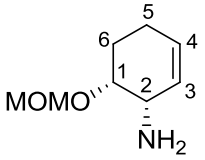
(C), 145.8 (C), 147.4 (C); *m*/*z* (EI) 319.1787 (M^+. $C_{18}H_{25}NO_4$ requires 319.1784), 259 (33%), 216 (45), 135 (100), 46 (24).

(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-hydroxyoctahydroindole (254).



(3a*R*,7*R*,7a*S*)-1-(3,4-Methylenedioxybenzyl)-7-(methoxymethoxy)octahydroindole (**253**) (0.05 g, 0.15 mmol) was dissolved in methanol (3 mL) and 2.0 M hydrochloric acid solution (3 mL). The reaction mixture was heated to 40 °C and stirred for 48 h, then cooled and neutralised with a 6.0 M solution of potassium carbonate (5 mL). The solution was extracted with ethyl acetate (4 × 20 mL), the organic layer was then dried ($MgSO_4$) and concentrated to give (3a*R*,7*R*,7a*S*)-1-(3,4-methylenedioxybenzyl)-7-hydroxyoctahydro indole (**254**) as a colourless oil (0.04 g, 100%). υ_{max}/cm^{-1} (NaCl) 3379 (OH), 2931 (CH), 1489, 1442, 1243; $[\alpha]_D^{25}$ +2.4 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.08–1.28 (2H, m, 5-*H*H and 6-*H*H), 1.42–1.53 (1H, m, 4-*H*H), 1.84–1.93 (4H, m, 3-H_2, 4-H*H* and 5-H*H*), 1.84–1.93 (1H, m, 6-H*H*), 2.05–2.14 (1H, m, 3a-H), 2.27–2.35 (1H, m, 2-*H*H), 2.58 (1H, dd, *J* 9.3, 4.7 Hz, 7a-H), 2.93–2.99 (1H, m, 2-H*H*), 3.45–3.48 (1H, m, 7-H), 3.50 (1H, d, *J* 12.8 Hz, N-C*H*H), 3.74 (1H, d, *J* 12.8 Hz, N-CH*H*), 5.86 (2H, s, OCH_2O), 6.64–6.76 (3H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.2 (CH_2), 26.5 (CH_2), 28.4 (CH_2), 31.3 (CH_2), 36.8 (CH), 53.4 (CH_2), 59.3 (CH_2), 63.7 (CH), 64.6 (CH), 100.4 (CH_2), 107.9 (CH), 109.3 (CH), 121.9 (CH), 133.2 (C), 146.6 (C), 147.6 (C); *m*/*z* (CI) 275.1522 (MH^+. $C_{16}H_{22}NO_3$ requires 275.1521), 216 (26%), 135 (74), 82 (100), 46.9 (22).

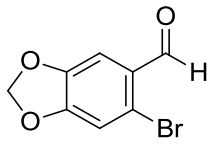
(1*R*,2*S*)-1-(Methoxymethoxy)-2-aminocyclohex-3-ene.



(1*R*,2*S*)-1-(Methoxymethoxy)-2-(2′,2′,2′-trichloromethylcarbonylamino)cyclohex-3-ene (**135a**) (0.53 g, 1.74 mmol) was dissolved in 1:1 mixture of 1.0 M NaOH/methanol (10 mL) and stirred overnight at room temperature. The reaction mixture was concentrated *in*

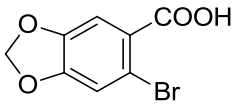
vacuo and diluted with ethyl acetate (5 mL). The organic layer was washed with brine solution (2 × 10 mL), dried ($MgSO_4$) and concentrated to give (1*R*,2*S*)-1-(methoxymethoxy)-2-aminocyclohex-3-ene (0.26 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (NaCl) 3422 (NH), 2934 (CH), 1571, 1457, 1216; $[\alpha]_D^{24}$ +110.8 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (2H, br s, NH_2), 1.65–1.75 (1H, m, 6-*H*H), 1.76–1.87 (1H, m, 6-H*H*), 2.00–2.22 (2H, m, 5-H_2), 3.41 (3H, s, OCH_3), 3.41–3.44 (1H, m, 2-H), 3.76 (1H, ddd, *J* 9.7, 4.2, 3.1 Hz, 1-H), 4.72 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.77 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.65–5.71 (1H, m, 3-H), 5.71–5.77 (1H, m, 4-H); δ_C (100 MHz, $CDCl_3$) 23.4 (CH_2), 23.8 (CH_2), 48.9 (CH), 55.5 (CH_3), 75.5 (CH), 95.3 (CH_2), 128.6 (CH), 129.4 (CH); *m*/*z* (CI) 158.1184 (MH^+. $C_8H_{16}NO_2$ requires 158.1181), 126 (30%), 69 (18).

6-Bromopiperonal (263).[186]



A solution of bromine (1.90 mL, 36.66 mmol) in acetic acid (5 mL) was added dropwise to a stirred solution of piperanal (**262**) (5.0 g, 36.66 mmol) in acetic acid (10 mL) and stirred for 72 h at room temperature. The reaction mixture was then diluted with chloroform (30 mL) and washed with saturated aqueous sodium carbonate (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Crystallization from methanol afforded 6-bromopiperonal (**263**) (7.29 g, 96%) as white solid. Spectroscopic data is entirely consistent with the literature. Mp 125–128 °C, lit.[186] 132–135 °C; υ_{max}/cm^{-1} (Neat) 3060 (CH), 1684 (CO), 1601, 1410, 1345, 1249, 977; δ_H (400 MHz, $CDCl_3$) 6.08 (2H, s, OCH_2O), 7.06 (1H, s, Ph-H), 7.37 (1H, s, Ph-H′), 10.18 (1H, s, CHO); δ_C (125 MHz, $CDCl_3$) 102.7 (CH_2), 108.1 (CH), 113.2 (CH), 121.8 (C), 128.1 (C), 148.4 (C), 153.6 (C), 190.7 (CH); *m*/*z* (CI) 229 (MH^+. 98%), 226 (85), 198 (18), 84 (69), 49 (54).

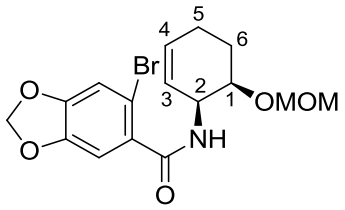
6-bromopiperenoic acid (256).[168]



To the vigorously stirred suspension of 6-bromopiperonal (**263**) (6.0 g, 26.21 mmol) in *tert*-butanol (40 mL) and water (50 mL) at 83 °C was slowly added potassium

permanganate (6.22 g, 39.31 mmol) in water (50 mL) over 45 minutes. The brown suspension was stirred overnight at 83 °C, and then potassium hydroxide (10% aq, 20 mL) was added, raising the pH to 10-11. The brown suspension was then filtered hot, and the cooled filtrate was extracted with diethylether (2 × 40 mL). The aqueous layer was then acidified with conc. HCl (8 mL) to give a white chalky solid (5.63 g, 88%). Spectroscopic data is entirely consistent with the literature. Mp 201–204 °C, lit.[168] 199–201 °C; υ_{max}/cm^{-1} (Neat) 2911 (CH), 1677 (CO), 1455, 1413, 1245; δ_H (400 MHz, $CDCl_3$) 6.07 (2H, s, OCH_2O), 7.14 (1H, s, Ph-H), 7.49 (1H, s, Ph-H′); δ_C (125 MHz, $CDCl_3$) 104.3 (CH_2), 107.8 (CH), 112.0 (C), 115.2 (CH), 115.5 (C), 128.6 (C), 148.9 (C), 152.6 (C); *m*/*z* (CI) 243 (MH^+. 62%), 226 (28), 167 (32), 149 (83), 84 (100), 49 (81).

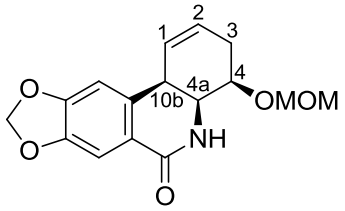
(1*R*,2*S*)-1-(Methoxymethoxy)-2-(3,4-methylenedioxy-6-bromobenzamide)cyclohex-3-ene (257).



In a stirred solution of (1*R*,2*S*)-1-(methoxymethoxy)-2-aminocyclohex-3-ene (0.05 g, 0.35 mmol) in acetonitrile (5 mL) at 0 °C was added 4-dimethylaminopyridine (0.01 g, 0.07mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.08 g, 0.53 mmol). To this reaction mixture, 6-bromopiperenoic acid (0.08 g, 0.35 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo*. The residue was diluted with 1.0 M hydrochloric acid (5 mL) and extracted with ethyl acetate (3 × 20 mL). Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 2:8) gave (1*R*,2*S*)-1-(methoxymethoxy)-2-(3,4-methylenedioxy-6-bromobenzamide)cyclohex-3-ene (**257**) (0.10 g 79%) as a white solid. Mp 100–102 °C; υ_{max}/cm^{-1} (NaCl) 3297 (NH), 2912 (CH), 1649 (CO), 1478, 1239, 1033; $[\alpha]_D^{24}$ +101.2 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.73–1.85 (1H, m, 6-*H*H), 1.97–2.12 (2H, m, 5-*H*H and 6-H*H*), 2.17–2.28 (1H, m, 5-H*H*), 3.37 (3H, s, OCH_3), 4.01–4.07 (1H, m, 1-H), 4.72 (1H, d, *J* 6.5 Hz, OC*H*HO), 4.76 (1H, d, *J* 6.5 Hz, OCH*H*O), 4.81–4.89 (1H, m, 2-H), 5.62–5.66 (1H, m, 4-H), 5.86–5.92 (1H, m, 3-H), 6.02 (2H, s, OCH_2O), 6.50 (1H, d, *J* 9.1 Hz, NH), 7.00 (1H, s, Ph), 7.05 (1H, s, Ph); δ_C (100 MHz, $CDCl_3$) 21.5 (CH_2), 25.5 (CH_2), 47.9 (CH), 55.8 (CH_3), 72.7 (CH), 95.8 (CH_2), 102.3 (CH_2), 109.5 (CH), 110.7 (C), 113.2 (CH),

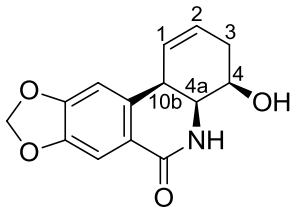
125.7 (CH), 129.8 (CH), 131.1 (C), 147.4 (C), 149.6 (C), 166.6 (C); *m*/*z* 84.0457 (MH^+. $C_{16}H_{19}{}^{79}BrNO_5$ requires 384.0447), 216 (26%), 135 (74), 89 (100), 46.9 (22).

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxyl[4,5-*j*]phenanthridin-6-one (137).



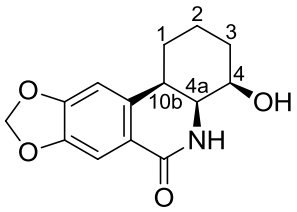
(1*R*,2*S*)-1-(Methoxymethoxy)-2-(3,4-methylenedioxy-6(bromobenzamide)cyclohex-3-ene (**257**) (0.16 g, 0.42 mmol) was dissolved in *N,N′*-dimethylformamide (12 mL) and degassed for 1 h. Triphenylphosphine (0.04 g, 0.18 mmol), palladium(II) acetate, (0.02 g, 0.08 mmol) and diisopropylethylamine (0.14 mL, 0.84 mmol) were then added and the reaction mixture was heated at 155 °C in a sealed tube for 48 h. The reaction mixture was then concentrated *in vacuo* and purified by flash column chromatography (elution with ethyl acetate) to give (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxyl[4,5-*j*]phenanthridin-6-one (**137**) as a white solid (0.09 g, 78%). Mp 140–142 °C; υ_{max}/cm^{-1} (NaCl) 3397 (NH), 2894 (CH), 1660 (CO), 1460, 1258, 1145; $[\alpha]_D{}^{25}$ +136.9 (*c* 1.5, MeOH); δ_H (400 MHz, $CDCl_3$) 2.24–2.45 (2H, m, 3-H_2), 3.40 (3H, s, OCH_3), 3.50–3.56 (1H, m, 10b-H), 4.03 (1H, ddd, *J* 9.9, 6.5, 3.0 Hz, 4-H), 4.25 (1H, t, *J* 3.0 Hz, 4a-H), 4.72 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.74 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.27–5.32 (1H, m, 2-H), 5.63 (1H, ddt, *J* 10.0, 5.1, 2.6 Hz, 1-H), 5.89 (1H, br s, NH), 6.01 (1H, d, *J* 1.3 Hz, OC*H′*H′O), 6.02 (1H, d, *J* 1.3 Hz, OCH′*H′*O), 6.67 (1H, s, 10-H), 7.52 (1H, s, 7-H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 39.9 (CH), 51.3 (CH), 55.8 (CH_3), 72.5 (CH), 95.0 (CH_2), 101.7 (CH_2), 107.0 (CH), 108.0 (CH), 122.2 (C), 124.1 (CH), 126.9 (CH), 135.8 (C), 147.3 (C), 151.3 (C), 165.2 (C); *m*/*z* (CI) 304.1181 (MH^+. $C_{16}H_{18}NO_5$ requires 304.1185), 262 (18%), 244 (6), 166 (3), 81 (8).

(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (268).



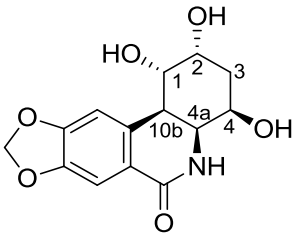
(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-(methoxymethoxy)-8,9-methylenedioxyl[4,5-*j*]phenanthridin-6-one (**137**) (0.07 g, 0.22 mmol) was dissolved in 1:1 ratio of methanol and 1.6 N hydrochloric acid solution (5.0 mL). The reaction mixture was heated to 40 °C and stirred for 12 h, then cooled and neutralised with a 6 M solution of potassium hydrogencarbonate (5.0 mL). The two layers were separated and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were then dried ($MgSO_4$), concentrated *in vacuo* and purified by flash column chromatography (elution with ethyl acetate) to give (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**268**) as a colourless oil (0.06 g, 97%). Mp 237–239 °C; υ_{max}/cm^{-1} (NaCl) 3356 (OH), 2951 (CH), 1651 (CO), 1462, 1246, 1018; $[\alpha]_D^{28}$ +159.0 (*c* 0.2, MeOH); δ_H (400 MHz, CD_3OD) 2.04–2.17 (1H, m, 3-*H*H), 2.20–2.29 (1H, m, 3-H*H*), 3.49–3.56 (1H, m, 10b-H), 3.94–4.03 (2H, m, 4a-H and 4-H), 5.17–5.22 (1H, m, 2-H), 5.54 (1H, ddt, *J* 10.1, 5.3, 2.6 Hz, 1-H), 5.92 (1H, d, *J* 1.0 Hz, OC*H*HO), 5.93 (1H, d, *J* 1.0 Hz, OCH*H*O), 6.73 (1H, s, 10-H), 7.23 (1H, s, 7-H); δ_C (100 MHz, CD_3OD) 29.6 (CH_2), 40.9 (CH), 54.7 (CH), 68.0 (CH), 103.3 (CH_2), 108.0 (CH), 108.4 (CH), 122.7 (C), 125.3 (CH), 128.0 (CH), 138.4 (C), 148.7 (C), 153.2 (C), 167.7 (C); *m*/*z* (CI) 260.0924 (MH^+. $C_{14}H_{14}NO_4$ requires 260.0923), 195 (3%), 113 (3), 81 (12).

(4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (259).



To a solution of (4*R*,4a*S*,10b*S*)-3,4,4a,10b-tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**268**) (0.0027 g, 0.01 mmol) in methanol (5 mL) was added 10% palladium on carbon (0.001 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 12 h. The reaction mixture was filtered through a short pad of Celite®, which was washed with methanol (10 mL) and concentrated *in vacuo* to give (4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**259**) (0.0023 g, 88% yield) as a white solid. Mp 179–181 °C; υ_{max}/cm^{-1} (NaCl) 3363 (OH), 2944 (CH), 1646 (CO), 1448, 1410, 1111, 1021; $[\alpha]_D^{21}$ –37.7 (*c* 0.2, MeOH); δ_H (400 MHz, CD_3OD) 1.20–1.53 (4H, m, 1-*H*H, 2-H_2 and 3-*H*H), 1.63–1.73 (2H, m, 1-H*H* and 3-H*H*), 2.69 (1H, dt, *J* 12.1, 4.2 Hz, 10b-H), 3.74 (1H, dt, *J* 11.2, 4.2 Hz, 4-H), 3.80 (1H, t, *J* 4.2 Hz, 4a-H), 5.90 (1H, d, *J* 1.1 Hz, OC*H*HO), 5.92 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.68 (1H, s, 10-H), 7.25 (1H, s, 7-H); δ_C (125 MHz, CD_3OD) 23.8 (CH_2), 29.1 (CH_2), 29.9 (CH_2), 41.1 (CH), 55.9 (CH), 70.4 (CH), 103.2 (CH_2), 108.1 (CH), 108.2 (CH), 122.6 (C), 141.6 (C), 148.5 (C), 152.9 (C), 168.2 (C); *m*/*z* (CI) 262.1075 (MH^+. $C_{14}H_{16}NO_4$ requires 262.1079), 244 (12%), 206 (22), 180 (8), 136 (4), 85 (21), 69 (40).

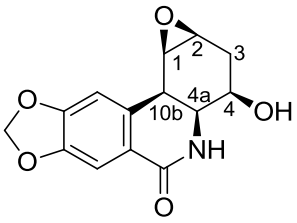
(1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-Hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (139).



(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**268**) (0.018 g, 0.06 mmol) was dissolved in dichloromethane (4 mL) at –78 °C.

Tetramethylethylenediamine (9 μL, 0.61 mmol) was added and the reaction mixture stirred for 0.1 h before the addition of osmium tetroxide (0.017 g 0.64 mmol). The dark coloured solution was stirred for 4 h at –78 °C before warming to room temperature and stirred for 1 h. The solvent was removed *in vacuo* and the dark coloured solid was dissolved in methanol (10 mL). Concentrated hydrochoric acid (5 drops) was added and the reaction stirred for 2 h. The solvent was removed *in vacuo* to afford a dark solid. Flash column chromatography (elution with ethyl acetate/methanol, 1:8) afforded (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**139**) (0.016 g, 90%) as a white solid. Mp 240 °C (decomposition); υ_{max}/cm^{-1} (NaCl) 3350 (NH/OH), 2914 (CH), 1643 (CO), 1465, 1253, 1034; $[\alpha]_D^{24}$ –50.9 (*c* 0.7, MeOH); δ_H (400 MHz, CD_3OD) 1.87 (1H, ddd, *J* 14.1, 12.2, 3.6 Hz, 3-*H*H), 2.00–2.07 (1H, m, 3-H*H*), 2.99 (1H, dd, *J* 10.5, 3.6 Hz, 10b-H), 3.51 (1H, dd, *J* 10.5, 3.6 Hz, 1-H), 3.95 (1H, td, *J* 3.6, 1.3 Hz, 4a-H), 4.00 (1H, q, *J* 3.6 Hz, 2-H), 4.30 (1H, dt, *J* 12.2, 3.6 Hz, 4-H), 6.01 (1H, d, *J* 1.1 Hz, OC*H*HO), 6.02 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.84 (1H, s, 10-H), 7.84 (1H, s, 7-H); δ_C (100 MHz, CD_3OD) 35.4 (CH_2), 41.4 (CH), 56.6 (CH), 65.2 (CH), 70.5 (CH), 72.0 (CH), 103.2 (CH_2), 108.0 (CH), 111.0 (CH), 123.0 (C), 138.9 (C), 148.8 (C), 152.3 (C), 168.4 (C); *m*/*z* (EI) 293.0898 (M^+. $C_{14}H_{15}NO_6$ requires 293.0899), 207 (8%), 190 (30), 114 (100), 70 (76), 96 (14), 44 (42).

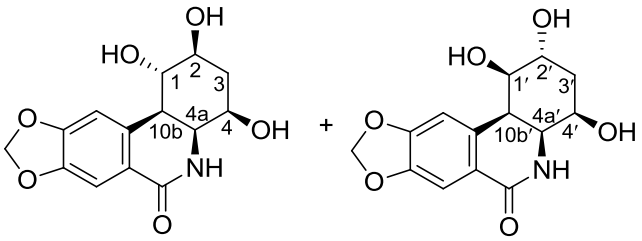
(1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2-Oxiraryl-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (138).



(4*R*,4a*S*,10b*S*)-3,4,4a,10b-Tetrahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**268**) (0.07 g, 0.27 mmol) was dissolved in dichloromethane (10 mL) along with sodium hydrogencarbonate (0.05 g, 0.55 mmol). To the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.09 g, 0.55 mmol) and stirred at room temperature. The resulting suspension was stirred vigorously for 24 h. A 20% solution of sodium sulfite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined dichloromethane layers were washed with a 20% solution of

sodium sulfite (10 mL) and a 5% solution of sodium hydrogencarbonate (2 × 20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography (petroleum ether/diethyl ether, 2:5) gave (1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2-oxiraryl-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**138**) (0.057 g, 75%) as a white solid. Mp 160–162 °C; υ_{max}/cm^{-1} (NaCl) 3350 (OH), 2851 (CH), 1654 (CO), 1466, 1249, 1035; $[\alpha]_D^{24}$ –61.2 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.08 (1H, ddd, *J* 14.6, 10.7, 1.8 Hz, 3-*H*H), 2.15 (1H, d, *J* 4.2 Hz, 4-OH), 2.45 (1H, ddd, *J* 14.6, 5.6, 1.8 Hz, 3-H*H*), 2.84 (1H, dd, *J* 3.6, 1.1 Hz, 1-H), 3.27–3.33 (2H, m, 2-H and 10b-H), 3.88–3.92 (1H, m, 4a-H) 4.05–4.12 (1H, m, 4-H), 6.02 (1H, d, *J* 1.3 Hz, OC*H*HO), 6.03 (1H, d, *J* 1.3 Hz, OCH*H*O), 7.51 (1H, br s, NH), 6.82 (1H, s, 10-H), 7.55 (1H, s, 7-H); δ_C (125 MHz, $CDCl_3$) 27.4 (CH_2), 39.1 (CH), 52.2 (CH), 53.4 (CH), 54.4 (CH), 65.3 (CH), 101.9 (CH_2), 107.7 (CH), 107.8 (CH), 122.5 (C), 133.4 (C), 147.9 (C), 151.8 (C), 165.6 (C); *m*/*z* (CI) 276.0871 (MH^+. $C_{14}H_{14}NO_5$ requires 276.0872), 260 (34%), 206 (6), 113 (5), 85 (33), 69 (48).

(1*S*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*] phenanthridin-6-one (261a) and (1*R*,2*R*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*] phenanthridin-6-one (261b).

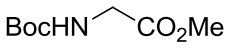


(1*R*,2*S*,4*R*,4a*S*,10b*S*)-1,2-Oxiraryl-1,2,3,4,4a,10b-hexahydro-4-hydroxy-8,9-methylenedioxy[4,5-*j*]phenanthridin-6-one (**138**) (0.013 g, 0.05 mmol) was added to a 1:1 mixture of 0.2 M sulfuric acid/1,4-dioxane (4 mL) and the reaction mixture was stirred at 80 °C for 72 h. The reaction mixture was diluted with a saturated solution of sodium hydrogencarbonate (5 mL) and extracted with ethyl acetate (7 × 5 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (dichloromethane/methanol, 10:1) gave 1:1 mixture of diastereomers of (1*S*,2*S*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*] phenanthridin-6-one (**261a**) and (1*R*,2*R*,4*R*,4a*S*,10b*S*)-1,2,3,4,4a,10b-hexahydro-1,2,4-trihydroxy-8,9-methylenedioxy[4,5-*j*] phenanthridin-6-one (**261b**) (4.7 mg, 34%). Mp

160–162 °C; υ_{max}/cm^{-1} (NaCl) 3340, 3306 (NH/OH), 2924 (CH), 1735 (CO), 1462, 1249, 1076; NMR Signals for both diastereomer were recorded. δ_H (400 MHz, CD_3OD) 1.76–1.88 (2H, m, 3-H_2), 2.06–2.16 (2H, m, 3′-H'_2), 2.61 (1H, dd, *J* 10.1, 3.5 Hz, 10b′-H′), 3.15 (1H, t, *J* 4.0 Hz, 10b-H), 3.49–3.57 (2H, m, 2-H and 4a-H), 3.61 (1H, t, *J* 3.5 Hz, 4a′-H′), 3.93–3.98 (2H, m, 1H and 1′H′), 4.01–4.07 (2H, m, 4-H and 4′-H′), 4.3 (1H, dt, *J* 12.2, 4.5 Hz, 2′H′), 6.04 (1H, d, *J* 1.1 Hz, OC*H*HO), 6.05 (1H, d, *J* 1.1 Hz, OCH*H*O), 6.07 (2H, s, OCH′$_2$O), 6.82 (1H, s, Ph), 6.86 (1H, s, Ph′), 7.41 (1H, s, Ph), 7.42 (1H, s, Ph′); δ_C (100 MHz, $CDCl_3$) 30.9 (CH_2), 37.3 (CH_2), 39.9 (CH), 49.7 (CH), 54.4 (CH), 57.1 (CH), 65.4 (CH), 68.0 (CH), 71.2 (CH), 72.9 (CH), 76.1 (CH), 76.2 (CH), 103.1 (CH_2), 103.3 (CH_2), 107.9 (CH), 108.3 (CH), 111.3 (CH), 115.7 (CH), 123.2 (C), 126.2 (C), 137.2 (C), 137.7 (C), 148.5 (C), 149.1 (C), 152.4 (C), 152.9 (C), 168.3 (C), 168.8 (C); *m*/*z* (EI) 293.0891 (M^+. $C_{14}H_{15}NO_6$ requires 293.0899), 274 (20%), 217 (32), 190 (100), 77 (28).

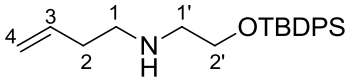
5.3.4 Synthesis of Balanol Core

_N_-(*tert*-butoxycarbonyl)glycine methyl ester (279).[175]



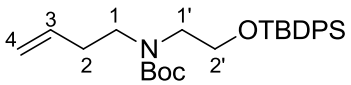
A stirred suspension of glycine (**278**) (0.5 g, 6.67 mmol) in methanol (30 mL) was cooled to 0 °C before chlorotrimethylsilane (1.86 mL, 14.67 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and then at room temperature for 24 h before being cooled again to 0 °C. Triethylamine (2.04 mL, 14.67 mmol) was added slowly, followed by di-*tert*-butyl dicarbonate (1.59 g, 7.33 mmol). The reaction mixture was stirred at room temperature for a further 12 h before being concentrated *in vacuo*. The residue was suspended in diethyl ether (30 mL) and filtered, and the filtrate was concentrated *in vacuo* and purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give *N*-(*tert*-butoxycarbonyl)glycine methyl ester (**279**) (1.26 g, 100%) as colourless oil. Spectroscopic data is entirely consistent with the literature.[175] υ_{max}/cm^{-1} (NaCl) 3356 (NH), 1805 (CO), 1755, 1438, 1369, 1261, 1165; δ_H (400 MHz, $CDCl_3$) 1.53 (9H, s, O^{t}Bu), 3.75 (3H, s, OCH_3), 3.92 (2H, d, *J* 5.5 Hz, 2-H_2), 5.02 (1H, br s, 1-NH); δ_C (100 MHz, $CDCl_3$) 27.4 (3 × CH_3), 28.3 (CH_3), 42.3 (CH_2), 52.3 (C), 85.2 (C), 146.8 (C); *m*/*z* (CI) 190.1081 (MH^+. $C_8H_{16}NO_4$ requires 190.1079), 178 (8%), 134 (100), 120 (25), 90 (54), 69 (24).

_N_-(2′-(_tert_-Butyldiphenylsilyloxy)ethyl)but-3-en-1-amine (296).



Sodium iodide (0.55 g, 3.70 mmol) was added to a solution of 4-bromo-1-butene (**280**) (5.00 g, 37.10 mmol) and ethanol amine (8.85 mL, 185.32 mmol) in methanol (80 mL). The reaction mixture was heated under reflux for 2 h, then cooled to room temperature and evaporated *in vacuo*. The residue was partitioned between saturated aqueous ammonium chloride solution (20 mL) and ethyl acetate (20 mL). The aqueous layer was basified with 40% sodium hydroxide and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to afford *N*-(2′-(hydroxy)ethyl)but-3-en-1-amine (**293**) (4.26 g, 100% yield) as a colourless oil. This oil was dissolved in tetrahydrofuran (200 mL), *tert*-butyldiphenylsilyl chloride (14.44 mL, 55.56 mmol) and imidazole (5.04 g, 74.08 mmol) were added and the reaction mixture was stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (70 mL). The combined filtrate was concentrated, dried and purified by flash column chromatography on silica gel (elution with dichloromethane/ethyl acetate) to give *N*-(2′-(*tert*-butyldimethylsilyloxy)ethyl)but-3-en-1-amine (**296**) (9.43 g, 86%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 2931 (CH), 1465, 1080, 825; δ_H (400 MHz, $CDCl_3$) 1.08 (9H, s, $SiC(CH_3)_3$), 2.27–2.34 (2H, m, 2-H_2), 2.72 (2H, t, *J* 6.8 Hz, 1-H_2), 2.79 (2H, t, *J* 5.4 Hz, 1′-H_2), 3.81 (2H, t, *J* 5.4 Hz, 2′-H_2), 5.06–5.18 (2H, m, 4-H_2), 5.17 (1H, ddt, *J* 17.1, 10.2, 6.8 Hz, 3-H), 7.38–7.48 (6H, m, Ph), 7.68–7.72 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 26.8 (3 × CH_3), 34.4 (CH_2), 48.6 (CH_2), 51.5 (CH_2), 62.5 (CH_2), 116.4 (CH_2), 128.0 (4 × CH), 129.6 (2 × CH), 133.7 (2 × C), 135.6 (4 × CH), 136.5 (CH); *m*/*z* (CI) 354.2254 (MH^+. $C_{22}H_{32}NOSi$ requires 354.2253), 257 (8%), 193 (5), 137 (7), 113 (28), 85 (89), 69 (100).

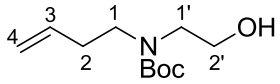
_N_-(2′-(_tert_-Butyldiphenylsilyloxy)ethyl)-_N_-(_tert_-butoxycarbonyl)but-3-en-1-amine (297).



To a solution of *N*-(2′-(*tert*-butyldimethylsilyloxy)ethyl)but-3-en-1-amine (**296**) (4.0 g, 11.3 mmol) in dichloromethane (100 mL) at 0 °C was added triethylamine (3.31 mL, 23.70

mmol), 4-dimethylaminopyridine (0.14 g, 1.30 mmol) and di-*tert*-butyl dicarbonate (4.93 g, 22.60 mmol). The reaction was warmed to room temperature and stirred overnight. The reaction mixture was washed with brine (2 × 30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate/diethyl ether, 1:10) gave *N*-(2′-(*tert*-butyldiphenylsilyloxy)ethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**297**) (5.1 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 2931 (CH), 1689 (CO), 1473, 1111, 825; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded. δ_H (400 MHz, $CDCl_3$) 1.05 (9H, s, $SiC(CH_3)_3$), 1.41 (9H, s, $C(CH_3)_3$), 2.20–2.29 (2H, m, 2-H_2), 3.25–3.40 (4H, m, 1-H_2 and 1′-H_2), 3.25–3.39 (2H, m, 2′-H_2), 4.96–5.06 (2H, m, 4-H_2), 5.66–5.81 (1H, m, 3-H_2), 7.33–7.44 (6H, m, Ph), 7.63–7.67 (4H, m, Ph); δ_C (100 MHz, $CDCl_3$) 19.2 (C), 26.8 (3 × CH_3), 28.4 (3 × CH_3), 32.2 (CH_2), 45.6 (CH_2), 49.4 (CH_2), 62.5 (CH_2), 82.9 (C), 116.4 (CH_2), 127.3 (4 × CH), 129.7 (4 × CH), 133.6 (2 × C), 135.3 (2 × CH), 135.8 (CH), 155.3 (C); *m/z* (CI) 454.2772 (MH^+. $C_{27}H_{40}NO_3Si$ requires 454.2777), 398 (18%), 354 (28), 257 (8), 179 (5), 139 (6), 85 (87), 69 (100).

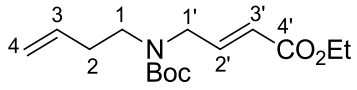
_N_-(2′-(hydroxy)ethyl)-_N_-(*tert*-butoxycarbonyl)but-3-en-1-amine (282).



A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (13.60 mL, 13.60 mmol) was added to a solution of *N*-(2′-(*tert*-butyldiphenylsilyloxy)ethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**297**) (5.12 g, 11.30 mmol) in tetrahydrofuran (100 mL) at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (80 mL). The solution was washed with water (40 mL) and the aqueous layer was then extracted with diethyl ether (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and then purified by flash column chromatography (petroleum ether/diethyl ether, 1:5) to give *N*-(2′-(hydroxy)ethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**282**) (2.42 g, 100%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 3742 (OH), 2978 (CH), 1743 (CO), 1473, 1157, 910; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded. δ_H (400 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.30 (2H, q, *J* 6.8 Hz, 2-H_2), 3.25–3.35 (2H, m, 1-H_2), 3.40 (2H, t, *J* 4.8 Hz, 1′-H_2), 3.79–3.72 (2H, m, 2′-H_2), 5.03–5.12 (2H, m, 4-H_2), 5.71–5.84 (1H, m, 3-H_2); δ_C (100 MHz, $CDCl_3$) 28.4 (3 × CH_3), 33.3 (CH_2), 48.5 (CH_2), 50.6 (CH_2), 62.7 (CH_2), 80.2 (C), 116.8 (CH_2), 135.2 (CH),

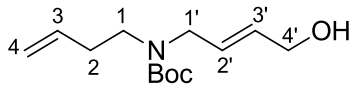
155.5 (C); *m*/*z* (CI) 216.1603 (MH^+. $C_{11}H_{22}NO_3$ requires 216.1600), 174 (8%), 160 (100), 69 (28).

Ethyl (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-enoate (283).



Reaction was carried out according to general procedure 1, using *N*-(2′-(hydroxy)ethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**282**) (2.86 g, 13.30 mmol). Flash column chromatography using (diethyl ether/petroleum ether, 2:3) gave the ethyl (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-enoate (**283**) (2.9 g, 94%) as colourless oil. υ_{max}/cm^{-1} (NaCl) 2978 (CH), 1689 (CO), 1465, 1165, 1149, 910; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded. δ_H (400 MHz, $CDCl_3$) 1.32 (3H, t, *J* 7.3 Hz, OCH_2CH_3), 1.49 (9H, s, $C(CH_3)_3$), 2.25–2.35 (2H, m, 2-H_2), 3.19–3.36 (2H, m, 1-H_2), 3.93–4.06 (2H, m, 1′-H_2), 4.23 (2H, q, *J* 7.3 Hz, OCH_2CH_3), 5.02–5.14 (2H, m, 1-H), 5.71–5.80 (1H, m, 3-H), 5.88 (1H, dt, *J* 15.6, 1.8 Hz, 3′-H), 6.89 (1H, dt, *J* 15.6, 4.7 Hz, 2′-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 28.2 (3 × CH_3), 33.1 (CH_2), 46.7 (CH_2), 47.7 (CH_2), 60.4 (CH_2), 80.0 (C), 116.9 (CH_2), 121.8 (CH), 135.1 (CH), 144.2 (CH), 155.1 (C), 166.7 (C); *m/z* (CI) 284.1862 (MH^+. $C_{15}H_{26}NO_4$ requires 284.1862), 228 (94%), 184 (62), 113 (32), 71 (100).

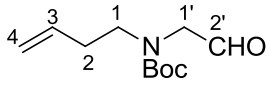
(2′*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-ol (140).



A stirred solution of (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-enoate (**283**) (0.25 g, 0.90 mmol) in dichloromethane (30 mL) was cooled to –78 °C before boron trifluoride diethyl etherate (0.15 mL, 1.17 mmol) was added dropwise. The mixture was stirred at –78 °C for 0.5 h before diisobutylaluminium hydride solution (1.0 M in hexanes, 2.7 mL, 2.7 mmol) was added dropwise. The reaction mixture was then stirred at –78 °C for 3 h before being quenched by the addition of 5.0 M acetic acid solution in dichloromethane (10mL). The mixture was poured into 10% aqueous tartaric acid solution (10 mL), and the organic layers were extracted using dichloromethane (2 × 20 mL). The combined organic phases were washed with a saturated aqueous solution of sodium

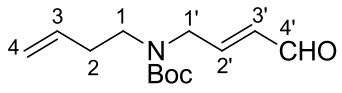
hydrogen carbonate (15 mL) before being dried (MgSO4), filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-ol (**140**) (0.08 g 37%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 3433 (OH), 2978 (CH), 1674 (CO), 1473, 1242, 918; δ_H (400 MHz, $CDCl_3$) 1.38 (9H, s, $C(CH_3)_3$), 2.18 (2H, q, *J* 7.5 Hz, 2-H_2), 3.06–3.22 (2H, m, 1-H_2), 3.66–3.79 (2H, m, 1′-H_2), 4.13 (2H, d, *J* 4.1 Hz, 4′-H_2), 4.89–5.02 (2H, m, 4-H_2), 5.49–5.76 (3H, m, 3-H, 2′-H and 3′-H); δ_C (100 MHz, $CDCl_3$) 28.4 (3 × CH_3), 32.5 (CH_2), 46.2 (CH_2), 48.3 (CH_2), 63.1 (CH_2), 79.5 (C), 116.5 (CH_2), 127.8 (CH), 131.0 (CH), 135.5 (CH), 155.4 (C); *m/z* (CI) 242.1752 (MH^+. $C_{13}H_{24}NO_3$ requires 242.1756), 200 (8%), 186 (100), 168 (72), 85 (28), 73 (38).

_N_-(2′-(Oxoethyl)-_N_-(*tert*-butoxycarbonyl)but-3-en-1-amine (300).



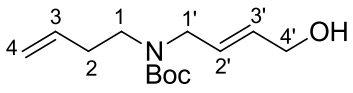
Dimethyl sulfoxide (4.20 mL, 59.20 mmol) was added to a stirred solution of oxalyl chloride (3.10 mL, 35.50 mmol) in dichloromethane (50 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before the *N*-(2′-(hydroxy)ethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**282**) (5.10 g, 23.70 mmol) in dichloromethane (25 mL) was slowly added. The mixture was stirred for a further 0.3 h before triethylamine (16.50 mL, 118.40 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. The Swern solution was concentrated *in vacuo*, and then purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give *N*-(2′-(oxoethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**300**) (4.74 g, 94%) as a colourless oil. υ_{max}/cm^{-1} (Neat) 3020 (CH), 1735 (CO), 1685 (CO), 1423, 1215, 906; NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded. δ_H (400 MHz, $CDCl_3$) 1.45 (9H, s, $C(CH_3)_3$), 2.23–2.33 (2H, m, 2-H_2), 3.30 (2H, t, *J* 7.1 Hz, 1-H_2), 3.80 (2H, br s, 1′-H_2), 5.02–5.11 (2H, m, 4-H_2), 5.68–5.83 (1H, m, 3-H_2), 9.57 (1H, d, *J* 4.7 Hz, 2′-H); δ_C (100 MHz, $CDCl_3$) 28.2 (3 × CH_3), 32.9 (CH_2), 48.2 (CH_2), 57.5 (CH_2), 80.6 (C), 117.1 (CH_2), 135.0 (CH), 154.9 (C), 199.2 (C); *m/z* (CI) 214.1440 (MH^+. $C_{11}H_{20}NO_3$ requires 214.1443), 196 (8%), 200 (10), 158 (100), 69 (12).

(2′*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-al (301).



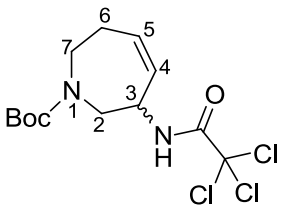
To a solution of ethyl *N*-(2′-(oxoethyl)-*N*-(*tert*-butoxycarbonyl)but-3-en-1-amine (**300**) (1.6 g, 7.51 mmol) in toluene (80 mL) was added (triphenylphosphoranylidene) acetaldehyde (3.42 g, 11.26 mmol) and reaction mixture was heated at 80 °C and stirred for 24 h. The solution was allowed to cool to room temperature and concentrated *in vacuo*. The crude product was purified with flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-al (**301**) (1.26 g, 71%) as colourless oil. υ_{max}/cm^{-1} (Neat) 3016 (CH), 1678 (CO), 1466, 1215, 918; NMR spectra showed a mixture of *E* and *Z* alkenes in a ratio of 5:1, only signals for *E* is recorded. δ_H (400 MHz, $CDCl_3$) 1.51 (9H, s, $C(CH_3)_3$), 2.26–2.36 (2H, m, 2-H_2), 3.22–3.38 (2H, m, 1-H_2), 4.05–4.19 (2H, m, 1′-H_2), 5.05–5.15 (2H, m, 4-H_2), 5.71–5.85 (1H, m, 3-H), 6.17 (1H, ddt, *J* 15.8, 7.9, 1.6 Hz, 3′-H), 3′-H), 6.72–6.86 (1H, m, 2′-H), 9.62 (1H, d, *J* 7.9 Hz, 4'-H); δ_C (100 MHz, $CDCl_3$) 28.2 (3 × CH_3), 32.9 (CH_2), 46.9 (CH_2), 48.2 (CH_2), 80.2 (C), 117.1 (CH_2), 125.3 (CH), 129.1 (CH), 132.3 (CH), 153.3 (C), 193.7 (C); *m/z* (CI) 240.1595 (MH^+. $C_{13}H_{22}NO_3$ requires 240.1600), 236 (19%), 184 (100), 158 (40), 116 (58), 69 (12).

(2′*E*)-*N*-(Butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-ol (140).



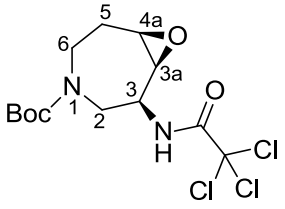
To a solution of (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-al (**301**) (0.30 g, 1.28 mmol) in methanol (35 mL) at 0 °C was added sodium borohydride (0.09 g, 2.56 mmol) and stirred for 1 h. The reaction mixture was quenched with 1.0 M hydrochloric acid (5 mL) and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), washed with saturated sodium hydrogencarbonate solution (10 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by flash column chromatography (petroleum ether/diethyl ether, 2:5) to give (2′*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-ol (**140**) (0.26 g 88%) as a colourless oil. Spectroscopic data as reported above.

1-(*tert*-Butoxycarbonyl)-3-(2′,2′,2′-trichloromethylamino)azapin-4-ene (303).



The reaction was carried out according general procedure 4 using (2*E*)-*N*-(butyl-3-en-1-yl)-*N*-(*tert*-butoxycarbonyl)but-2′-en-4′-ol (**140**) (0.13 g, 0.54 mmol) and bis(acetonitrile)palladium(II) chloride (0.014 g, 0.05 mmol) as a catalyst for Overmann rearrangement. Purification by flash column chromatography (petroleum ether/diethylether, 2:1) gave (1-(*tert*-butoxycarbonyl)-3-(2′,2′,2′-trichloromethylamino) azapin-4-ene (**303**) (0.09 g, 49% over three steps) as a white solid. Mp 103–105 °C; υ_{max}/cm^{-1} (NaCl) 3330 (NH), 2978 (CH), 1689 (CO), 1419, 1356, 821. NMR spectra showed a 1:1 mixture of rotomers, only signals for one rotomer is recorded: δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, $C(CH_3)_3$), 2.17–2.42 (2H, m, 6-H_2), 3.03–3.16 (1H, m, 7-*H*H), 3.24 (1H, d, *J* 14.1 Hz, 2-*H*H), 3.72–3.81 (1H, m, 7-H*H*), 4.05 (1H, d, *J* 14.1 Hz, 2-H*H*), 4.43–4.59 (1H, m, 3-H), 5.53–5.93 (2H, m, 4-H and 5-H), 8.30 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 27.9 (CH_2), 28.4 (3 × CH_3), 47.7 (CH_2), 48.7 (CH_2), 54.4 (CH), 80.8 (C), 92.6 (C), 128.6 (CH), 129.3 (CH), 157.3 (C), 161.7 (C); *m/z* (CI) 359.0511 (MH^+. $C_{13}H_{20}{}^{35}Cl_2{}^{37}Cl N_2O_3$ requires 359.0512), 301 (100%), 267 (34), 257 (18), 163 (8), 85 (13), 69(19).

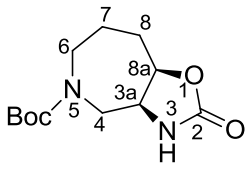
2′,2′,2′-Trichloro-*N*-[(3*S,3a*S**,4a*R**)-1-aza-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (304).**



1-(*tert*-Butoxycarbonyl)-3-(2′,2′,2′-trichloromethylamino)azapin-4-ene (**303**) (0.19 g, 0.53 mmol) was dissolved in dichloromethane (15 mL) and to the stirred suspension was added *meta*-chloroperoxybenzoic acid (0.18 g 1.05 mmol) at room temperature. The resulting suspension was stirred vigorously for 19 h. A 20% aqueous solution of sodium sulphite (10 mL) was added and the resulting two-phase mixture was stirred vigorously for 0.25 h. The two layers were separated and the aqueous layer was extracted with dichloromethane (2 ×

20 mL). The combined organic layers were washed with a 20% aqueous solution of sodium sulphite (10 mL) and a 5% aqueous solution of sodium hydrogencarbonate (2 × 20 mL), dried ($MgSO_4$) and evaporated under reduced pressure. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 2:5) gave 2′,2′,2′-trichloro-*N*-[(3*S**,3a*S**,4a*R**)-1-aza-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (**304**) (0.10 g, 51%) as white solid. Mp 160–162 °C; υ_{max}/cm^{-1} (NaCl) 3293 (NH), 2974 (CH), 1697 (CO), 1518, 1413, 1165, 821; NMR spectra showed a 1:0.6 mixture of rotomers, only signals for major rotomer is recorded. δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, $C(CH_3)_3$), 2.21–2.37 (2H, m, 5-H_2), 2.78–2.93 (1H, m, 2-H_2), 3.18–3.33 (2H, m, 6-H_2), 3.80–3.92 (2H, m, 3a-H and 4a-H), 4.58 (1H, td, *J* 10.8, 4.5 Hz, 3-H), 6.90 (1H, d, *J* 8.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 27.3 (CH_2), 28.4 (3 × CH_3), 43.1 (CH_2), 46.5 (CH_2), 50.7 (CH), 55.4 (CH), 58.7 (CH), 80.4 (C), 92.3 (C), 154.3 (C), 161.4 (C); *m/z* (CI) 373.0502 (MH^+. $C_{13}H_{20}{}^{35}Cl_3N_2O_4$ requires 373.0489), 319 (100%), 283 (76), 211 (8), 155 (10), 69 (11).

(3a*S,8a*R**)-5-(*tert*-Butoxycarbonyl)octahydro-1-oxo-3,5-diaza-azulen-2-one (305).**



2′,2′,2′-Trichloro-*N*-[(3*S**,3a*S**,4a*R**)-1-aza-4-oxobicyclo[5.1.0]octa-3a-yl]acetamide (**304**) (0.02 g, 0.05 mmol) was dissolved in tetrahydrofuran (4 mL) and cooled to 0 °C. Lithium aluminium hydride (0.005 g, 0.12 mmol) was then added. The stirred slurry was heated under refluxed for 12 h. The solution was cooled to room temperature and quenched by the addition of a saturated solution of ammonium chloride (2 mL) with vigorous stirring over 0.15 h. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (elution with ethyl acetate) gave (3a*S**,8a*R**)-5-(*tert*-butoxycarbonyl)octahydro-1-oxo-3,5-diaza-azulen-2-one (**305**) (0.008 g, 56%). υ_{max}/cm^{-1} (NaCl) 3271 (NH), 2960 (CH), 1689 (CO), 1670 (CO), 1413, 1166, 943; NMR spectra showed a 1:0.8 mixture of rotomers, only signals for major rotomer is recorded. δ_H (500 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.10–2.28 (2H, m, 7-H_2), 2.58–2.85 (3H, m, 4-H_2 and 8-*H*H), 3.12–3.29 (2H, m, 6-H_2), 3.57–3.89 (2H, m, 8-H*H* and 8a-H), 4.61–4.74 (1H, m, 3a-H), 5.70–5.74 (1H, m, NH); δ_C (125 MHz, $CDCl_3$) 27.7 (CH_2), 28.5 (3 × CH_3), 29.6 (CH_2), 43.3 (CH_2), 47.8 (CH_2), 55.5 (CH), 59.5 (CH), 80.6

(C), 154.4 (C), 160.3 (C); *m*/*z* (CI) 257.1506 (MH^+. $C_{12}H_{21}N_2O_4$ requires 257.1501), 201 (100%), 157 (62), 113 (12), 69, (24).

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7 Appendix

Crystal data and structure refinement for 199

Identification code	199	
Empirical formula	C8 H11 Cl3 I N O2	
Formula weight	386.43	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.06780(10) Å	α= 90°.
	b = 16.6957(2) Å	β= 99.4370(10)°.
	c = 9.65370(10) Å	γ = 90°.
Volume	1282.73(3) $Å^3$	
Z	4	
Density (calculated)	2.001 Mg/m^3	
Absorption coefficient	3.102 mm^{-1}	
F(000)	744	
Theta range for data collection	2.14 to 27.47°.	
Index ranges	-10<=h<=10, -21<=k<=21, -12<=l<=12	
Reflections collected	11006	
Independent reflections	5835 [R(int) = 0.0335]	
Completeness to theta = 27.47°	99.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5835 / 1 / 273	
Goodness-of-fit on F^2	0.977	
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0553	
R indices (all data)	R1 = 0.0449, wR2 = 0.0585	
Absolute structure parameter	-0.042(13)	
Largest diff. peak and hole	0.559 and -0.654 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 199. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
I(2)	16111(1)	-2034(1)	2653(1)	26(1)
I(1)	3175(1)	341(1)	1513(1)	34(1)
Cl(1)	9241(1)	-1522(1)	-2677(1)	33(1)
Cl(4)	8508(1)	-37(1)	4735(1)	28(1)
Cl(3)	11926(1)	-1731(1)	-355(1)	27(1)
Cl(2)	8984(2)	-2752(1)	-651(2)	38(1)
Cl(6)	10675(2)	1316(1)	4515(1)	33(1)
Cl(5)	10293(2)	694(1)	7245(1)	38(1)
O(4)	13361(4)	192(2)	6035(3)	34(1)
O(1)	6024(4)	489(2)	-1932(3)	25(1)
O(3)	11056(3)	-2210(2)	3582(3)	26(1)
N(1)	7884(4)	-653(2)	-488(4)	19(1)
O(2)	9216(3)	-1335(2)	1384(3)	24(1)
N(2)	11788(4)	-787(2)	4854(4)	22(1)
C(12)	13876(5)	-2537(2)	3322(5)	21(1)
C(1)	5434(5)	181(3)	-717(4)	21(1)
C(10)	14929(6)	-2485(3)	5924(5)	30(1)
C(7)	8907(5)	-1208(3)	116(5)	19(1)
C(16)	10416(6)	438(3)	5480(4)	25(1)
C(9)	13567(5)	-1853(3)	6100(4)	28(1)
C(6)	6990(5)	-88(3)	301(4)	18(1)
C(4)	7126(5)	1237(3)	1548(4)	19(1)
C(2)	4495(5)	846(3)	-96(5)	21(1)
C(5)	8115(5)	613(2)	846(4)	20(1)
C(14)	13171(5)	-1350(3)	4778(4)	20(1)
C(3)	5626(5)	1524(3)	508(4)	21(1)
C(15)	12005(5)	-87(3)	5491(4)	23(1)
C(11)	14326(5)	-3016(3)	4651(5)	25(1)
C(13)	12638(5)	-1856(3)	3457(4)	22(1)
C(8)	9722(5)	-1771(3)	-873(4)	22(1)

Bond lengths [Å] for 199

I(2)-C(12)	2.181(4)	C(10)-C(11)	1.529(6)
I(1)-C(2)	2.191(4)	C(10)-C(9)	1.553(6)
Cl(1)-C(8)	1.770(4)	C(10)-H(10A)	0.9700
Cl(4)-C(16)	1.776(5)	C(10)-H(10B)	0.9700
Cl(3)-C(8)	1.768(4)	C(7)-C(8)	1.559(6)
Cl(2)-C(8)	1.769(4)	C(16)-C(15)	1.551(6)
Cl(6)-C(16)	1.769(5)	C(9)-C(14)	1.517(6)
Cl(5)-C(16)	1.775(4)	C(9)-H(9A)	0.9700
O(4)-C(15)	1.225(5)	C(9)-H(9B)	0.9700
O(1)-C(1)	1.432(5)	C(6)-C(5)	1.521(6)
O(1)-H(1)	0.8200	C(6)-H(6)	0.9800
O(3)-C(13)	1.430(5)	C(4)-C(3)	1.518(6)
O(3)-H(3)	0.8200	C(4)-C(5)	1.535(6)
N(1)-C(7)	1.312(5)	C(4)-H(4A)	0.9700
N(1)-C(6)	1.473(5)	C(4)-H(4B)	0.9700
N(1)-H(1A)	0.8600	C(2)-C(3)	1.511(6)
O(2)-C(7)	1.228(5)	C(2)-H(2A)	0.9800
N(2)-C(15)	1.319(6)	C(5)-H(5A)	0.9700
N(2)-C(14)	1.471(5)	C(5)-H(5B)	0.9700
N(2)-H(2)	0.8600	C(14)-C(13)	1.531(6)
C(12)-C(11)	1.505(6)	C(14)-H(14)	0.9800
C(12)-C(13)	1.533(6)	C(3)-H(3A)	0.9700
C(12)-H(12)	0.9800	C(3)-H(3B)	0.9700
C(1)-C(2)	1.521(6)	C(11)-H(11A)	0.9700
C(1)-C(6)	1.529(5)	C(11)-H(11B)	0.9700
C(1)-H(1B)	0.9800	C(13)-H(13)	0.9800

Bond angles [°] for 199

C(1)-O(1)-H(1)	109.5	C(13)-C(12)-H(12)	107.9
C(13)-O(3)-H(3)	109.5	I(2)-C(12)-H(12)	107.9
C(7)-N(1)-C(6)	123.2(3)	O(1)-C(1)-C(2)	108.3(3)
C(7)-N(1)-H(1A)	118.4	O(1)-C(1)-C(6)	106.5(3)
C(6)-N(1)-H(1A)	118.4	C(2)-C(1)-C(6)	111.8(3)
C(15)-N(2)-C(14)	123.1(4)	O(1)-C(1)-H(1B)	110.1
C(15)-N(2)-H(2)	118.4	C(2)-C(1)-H(1B)	110.1
C(14)-N(2)-H(2)	118.4	C(6)-C(1)-H(1B)	110.1
C(11)-C(12)-C(13)	113.0(3)	C(11)-C(10)-C(9)	110.1(4)
C(11)-C(12)-I(2)	111.2(3)	C(11)-C(10)-H(10A)	109.6
C(13)-C(12)-I(2)	108.7(3)	C(9)-C(10)-H(10A)	109.6
C(11)-C(12)-H(12)	107.9	C(11)-C(10)-H(10B)	109.6

C(9)-C(10)-H(10B)	109.6	C(4)-C(5)-H(5A)	109.5
H(10A)-C(10)-H(10B)	108.1	C(6)-C(5)-H(5B)	109.5
O(2)-C(7)-N(1)	125.1(4)	C(4)-C(5)-H(5B)	109.5
O(2)-C(7)-C(8)	118.0(4)	H(5A)-C(5)-H(5B)	108.1
N(1)-C(7)-C(8)	116.8(4)	N(2)-C(14)-C(9)	111.6(3)
C(15)-C(16)-Cl(6)	107.6(3)	N(2)-C(14)-C(13)	106.4(3)
C(15)-C(16)-Cl(5)	107.8(3)	C(9)-C(14)-C(13)	112.8(4)
Cl(6)-C(16)-Cl(5)	109.6(2)	N(2)-C(14)-H(14)	108.6
C(15)-C(16)-Cl(4)	114.3(3)	C(9)-C(14)-H(14)	108.6
Cl(6)-C(16)-Cl(4)	109.0(2)	C(13)-C(14)-H(14)	108.6
Cl(5)-C(16)-Cl(4)	108.4(2)	C(2)-C(3)-C(4)	112.6(3)
C(14)-C(9)-C(10)	109.8(3)	C(2)-C(3)-H(3A)	109.1
C(14)-C(9)-H(9A)	109.7	C(4)-C(3)-H(3A)	109.1
C(10)-C(9)-H(9A)	109.7	C(2)-C(3)-H(3B)	109.1
C(14)-C(9)-H(9B)	109.7	C(4)-C(3)-H(3B)	109.1
C(10)-C(9)-H(9B)	109.7	H(3A)-C(3)-H(3B)	107.8
H(9A)-C(9)-H(9B)	108.2	O(4)-C(15)-N(2)	125.3(4)
N(1)-C(6)-C(5)	110.9(3)	O(4)-C(15)-C(16)	117.8(4)
N(1)-C(6)-C(1)	106.0(3)	N(2)-C(15)-C(16)	116.8(4)
C(5)-C(6)-C(1)	112.1(3)	C(12)-C(11)-C(10)	112.2(4)
N(1)-C(6)-H(6)	109.3	C(12)-C(11)-H(11A)	109.2
C(5)-C(6)-H(6)	109.3	C(10)-C(11)-H(11A)	109.2
C(1)-C(6)-H(6)	109.3	C(12)-C(11)-H(11B)	109.2
C(3)-C(4)-C(5)	109.8(3)	C(10)-C(11)-H(11B)	109.2
C(3)-C(4)-H(4A)	109.7	H(11A)-C(11)-H(11B)	107.9
C(5)-C(4)-H(4A)	109.7	O(3)-C(13)-C(14)	106.9(3)
C(3)-C(4)-H(4B)	109.7	O(3)-C(13)-C(12)	107.7(3)
C(5)-C(4)-H(4B)	109.7	C(14)-C(13)-C(12)	112.4(3)
H(4A)-C(4)-H(4B)	108.2	O(3)-C(13)-H(13)	109.9
C(3)-C(2)-C(1)	113.0(3)	C(14)-C(13)-H(13)	109.9
C(3)-C(2)-I(1)	110.3(3)	C(12)-C(13)-H(13)	109.9
C(1)-C(2)-I(1)	109.3(3)	C(7)-C(8)-Cl(3)	108.0(3)
C(3)-C(2)-H(2A)	108.0	C(7)-C(8)-Cl(2)	107.5(3)
C(1)-C(2)-H(2A)	108.0	Cl(3)-C(8)-Cl(2)	110.1(2)
I(1)-C(2)-H(2A)	108.0	C(7)-C(8)-Cl(1)	114.5(3)
C(6)-C(5)-C(4)	110.5(3)	Cl(3)-C(8)-Cl(1)	108.5(2)
C(6)-C(5)-H(5A)	109.5	Cl(2)-C(8)-Cl(1)	108.2(2)

Anisotropic displacement parameters ($Å^2$x 10^3)for 199. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
I(2)	23(1)	30(1)	29(1)	1(1)	12(1)	-1(1)
I(1)	26(1)	26(1)	55(1)	2(1)	22(1)	1(1)
Cl(1)	36(1)	42(1)	22(1)	-5(1)	6(1)	9(1)
Cl(4)	22(1)	32(1)	29(1)	0(1)	3(1)	3(1)
Cl(3)	16(1)	34(1)	31(1)	-8(1)	7(1)	1(1)
Cl(2)	33(1)	20(1)	64(1)	-3(1)	22(1)	-5(1)
Cl(6)	36(1)	27(1)	39(1)	4(1)	8(1)	2(1)
Cl(5)	43(1)	47(1)	27(1)	-12(1)	14(1)	-2(1)
O(4)	24(2)	36(2)	37(2)	-12(2)	-5(1)	-1(2)
O(1)	27(2)	32(2)	17(2)	1(2)	2(1)	1(2)
O(3)	14(1)	32(2)	30(2)	4(2)	3(1)	-1(1)
N(1)	20(2)	21(2)	17(2)	-1(2)	4(2)	6(2)
O(2)	22(2)	29(2)	23(2)	4(1)	8(1)	6(1)
N(2)	16(2)	25(2)	24(2)	-2(2)	3(2)	1(2)
C(12)	19(2)	17(2)	29(2)	-6(2)	12(2)	-6(2)
C(1)	18(2)	19(3)	25(2)	-4(2)	5(2)	-3(2)
C(10)	27(2)	38(3)	22(2)	9(2)	-1(2)	5(2)
C(7)	15(2)	23(2)	22(2)	-1(2)	11(2)	-6(2)
C(16)	34(2)	22(3)	21(2)	-3(2)	6(2)	1(2)
C(9)	26(2)	41(3)	18(2)	0(2)	4(2)	4(2)
C(6)	17(2)	21(2)	19(2)	2(2)	8(2)	3(2)
C(4)	21(2)	21(2)	16(2)	1(2)	3(2)	1(2)
C(2)	18(2)	21(2)	25(2)	5(2)	2(2)	3(2)
C(5)	13(2)	24(2)	21(2)	0(2)	1(2)	4(2)
C(14)	20(2)	23(2)	18(2)	-1(2)	6(2)	5(2)
C(3)	21(2)	18(2)	26(2)	0(2)	9(2)	-1(2)
C(15)	27(2)	25(2)	16(2)	0(2)	4(2)	1(2)
C(11)	21(2)	23(2)	31(3)	8(2)	7(2)	0(2)
C(13)	20(2)	24(3)	22(2)	2(2)	6(2)	-2(2)
C(8)	18(2)	21(2)	26(2)	-2(2)	5(2)	-1(2)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 199

	x	y	z	U(eq)
H(1)	5334	390	-2634	38
H(3)	10386	-2129	2859	39
H(1A)	7728	-617	-1389	23
H(2)	10790	-920	4466	26
H(12)	13344	-2900	2583	25
H(1B)	4685	-276	-977	25
H(10A)	15961	-2216	5801	35
H(10B)	15161	-2813	6763	35
H(9A)	12556	-2121	6279	34
H(9B)	13968	-1510	6896	34
H(6)	6637	-368	1096	22
H(4A)	6744	1001	2358	23
H(4B)	7848	1687	1867	23
H(2A)	3651	1064	-848	26
H(5A)	8557	860	73	23
H(5B)	9056	421	1520	23
H(14)	14176	-1044	4664	24
H(3A)	4982	1899	974	25
H(3B)	6024	1807	-252	25
H(11A)	15203	-3396	4536	30
H(11B)	13350	-3318	4817	30
H(13)	12517	-1514	2621	26

Crystal data and structure refinement for 202

Identification code	202	
Empirical formula	C8 H12 Cl3 N O4	
Formula weight	292.54	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2	
Unit cell dimensions	a = 39.705(2) Å	α= 90°.
	b = 5.8312(3) Å	β= 91.296(2)°.
	c = 20.2162(14) Å	γ = 90°.
Volume	4679.4(5) $Å^3$	
Z	16	
Density (calculated)	1.661 Mg/m^3	
Absorption coefficient	0.781 mm^{-1}	
F(000)	2400	
Theta range for data collection	3.02 to 27.48°.	
Index ranges	-51<=h<=51, -7<=k<=7, -26<=l<=25	
Reflections collected	13482	
Independent reflections	9273 [R(int) = 0.1025]	
Completeness to theta = 27.48°	96.6 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9273 / 1 / 589	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0752, wR2 = 0.1056	
R indices (all data)	R1 = 0.1714, wR2 = 0.1434	
Absolute structure parameter	0.13(10)	
Largest diff. peak and hole	0.724 and -0.760 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 202. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
Cl(1)	2737(1)	82(4)	9740(1)	29(1)
Cl(2)	2842(1)	4328(4)	9049(1)	30(1)
Cl(11)	7210(1)	9607(4)	5235(1)	32(1)
Cl(9)	2103(1)	6870(4)	8519(1)	34(1)
Cl(4)	2793(1)	5903(4)	7334(1)	30(1)
Cl(10)	6912(1)	9494(4)	6519(1)	29(1)
Cl(8)	1783(1)	10893(5)	9067(1)	33(1)
Cl(5)	2814(1)	1820(4)	6537(1)	33(1)
Cl(12)	7170(1)	13761(4)	6005(1)	34(1)
Cl(3)	3036(1)	19(4)	8447(1)	32(1)
Cl(7)	2115(1)	11156(4)	7815(1)	34(1)
Cl(6)	3121(1)	6031(5)	6078(1)	36(1)
O(1)	3456(1)	338(13)	9940(4)	48(2)
O(9)	1509(2)	8960(12)	7353(3)	30(2)
O(13)	6561(1)	11377(13)	4885(3)	32(2)
O(6)	3478(2)	4530(12)	7622(3)	33(2)
O(10)	813(2)	5922(11)	9143(3)	31(2)
O(3)	4537(2)	4165(12)	10200(3)	33(2)
O(12)	194(1)	1680(12)	7940(3)	37(2)
O(11)	289(2)	6667(12)	7642(3)	38(2)
N(4)	6402(2)	12753(14)	5881(4)	30(2)
C(25)	6967(2)	11153(17)	5795(4)	22(2)
O(4)	4925(1)	5952(14)	9156(3)	37(2)
O(2)	3903(2)	7405(12)	9286(4)	50(2)
O(7)	4003(2)	152(12)	5811(3)	38(2)
N(1)	3572(2)	3239(14)	9234(4)	29(2)
C(2)	3371(2)	1689(17)	9508(5)	26(2)
C(1)	3003(2)	1540(14)	9210(4)	19(2)
C(26)	6615(2)	11781(16)	5469(5)	24(2)
C(6)	4563(2)	5628(18)	9089(5)	29(2)
C(18)	1544(2)	8647(17)	7949(5)	24(2)
C(9)	3042(2)	4320(17)	6775(5)	27(2)
C(10)	3387(2)	3665(17)	7112(5)	24(2)
N(3)	1321(2)	7567(14)	8333(4)	32(2)
C(17)	1871(2)	9375(16)	8322(5)	26(2)
C(5)	4413(2)	5864(17)	9750(4)	26(2)
C(3)	3930(2)	3331(17)	9362(5)	26(2)
C(13)	4276(2)	-1789(16)	7354(5)	34(3)

C(20)	722(2)	6818(17)	8501(5)	28(2)
N(2)	3559(2)	2143(17)	6774(5)	48(3)
C(11)	3907(2)	1469(17)	6934(5)	30(2)
C(4)	4028(2)	5597(16)	9688(5)	28(2)
C(27)	6063(2)	13437(18)	5673(5)	33(3)
C(24)	1093(2)	3887(17)	7927(5)	34(3)
C(19)	1016(2)	6458(16)	8054(5)	24(2)
C(15)	4117(2)	1678(17)	6329(5)	30(2)
C(8)	4106(2)	3013(17)	8713(5)	32(3)
C(22)	483(2)	3035(16)	8138(5)	29(2)
C(14)	4478(2)	905(18)	6481(5)	33(2)
C(21)	408(2)	5564(18)	8236(5)	31(3)
C(23)	764(2)	2746(16)	7661(5)	33(3)
C(30)	5444(2)	16011(18)	5850(4)	26(2)
O(14)	5118(1)	16866(12)	5635(3)	32(2)
C(31)	5667(4)	16380(30)	5214(10)	20(4)
O(15)	5551(3)	14830(20)	4696(6)	22(3)
C(32)	6027(4)	15610(30)	5379(10)	21(4)
O(16)	6159(3)	17290(30)	5838(7)	32(3)
C(29)	5456(4)	13740(30)	6090(9)	13(4)
C(30A)	5444(2)	16011(18)	5850(4)	26(2)
O(14A)	5118(1)	16866(12)	5635(3)	32(2)
C(31A)	5713(5)	17040(40)	5504(11)	34(5)
O(15A)	5653(3)	16620(20)	4798(7)	33(3)
C(32A)	6068(5)	16200(40)	5681(10)	24(4)
O(16A)	6113(3)	17050(20)	6358(7)	34(3)
C(29A)	5449(5)	13270(40)	5783(12)	38(6)
O(50)	4774(3)	-2870(20)	6836(6)	19(3)
O(50A)	4870(3)	-1690(30)	6856(7)	34(4)
C(12)	3913(2)	-990(19)	7206(6)	41(3)
C(7)	4489(2)	3296(18)	8783(5)	34(3)
O(8)	4626(2)	2410(12)	6971(3)	40(2)
C(51)	5810(2)	12810(20)	6184(8)	75(5)
C(16)	4481(2)	-1530(20)	6736(6)	40(3)

Bond lengths [Å] for 202

Cl(1)-C(1)	1.742(9)	N(3)-C(19)	1.473(10)
Cl(2)-C(1)	1.774(9)	C(5)-C(4)	1.536(11)
Cl(11)-C(25)	1.753(9)	C(3)-C(8)	1.512(13)
Cl(9)-C(17)	1.768(9)	C(3)-C(4)	1.524(13)
Cl(4)-C(9)	1.777(10)	C(13)-C(16)	1.512(14)
Cl(10)-C(25)	1.772(9)	C(13)-C(12)	1.540(12)
Cl(8)-C(17)	1.788(10)	C(20)-C(19)	1.506(12)
Cl(5)-C(9)	1.776(10)	C(20)-C(21)	1.531(12)
Cl(12)-C(25)	1.767(10)	N(2)-C(11)	1.465(10)
Cl(3)-C(1)	1.786(9)	C(11)-C(15)	1.502(13)
Cl(7)-C(17)	1.765(9)	C(11)-C(12)	1.536(14)
Cl(6)-C(9)	1.760(10)	C(27)-C(32)	1.41(2)
O(1)-C(2)	1.217(11)	C(27)-C(51)	1.503(15)
O(9)-C(18)	1.224(11)	C(27)-C(32A)	1.61(2)
O(13)-C(26)	1.219(10)	C(24)-C(23)	1.550(12)
O(6)-C(10)	1.194(10)	C(24)-C(19)	1.552(12)
O(10)-C(20)	1.438(10)	C(15)-C(14)	1.528(12)
O(3)-C(5)	1.425(10)	C(8)-C(7)	1.532(11)
O(12)-C(22)	1.443(10)	C(22)-C(23)	1.501(13)
O(11)-C(21)	1.432(10)	C(22)-C(21)	1.518(13)
N(4)-C(26)	1.328(12)	C(14)-O(8)	1.439(10)
N(4)-C(27)	1.457(11)	C(14)-C(16)	1.509(14)
C(25)-C(26)	1.575(11)	C(30)-C(29)	1.410(19)
O(4)-C(6)	1.451(9)	C(30)-O(14)	1.444(9)
O(2)-C(4)	1.416(10)	C(30)-C(31)	1.59(2)
O(7)-C(15)	1.439(10)	C(31)-O(15)	1.45(2)
N(1)-C(2)	1.335(12)	C(31)-C(32)	1.53(2)
N(1)-C(3)	1.439(10)	C(32)-O(16)	1.44(2)
C(2)-C(1)	1.571(11)	C(29)-C(51)	1.514(18)
C(6)-C(5)	1.482(12)	C(31A)-O(15A)	1.46(2)
C(6)-C(7)	1.520(13)	C(31A)-C(32A)	1.53(3)
C(18)-N(3)	1.347(12)	C(32A)-O(16A)	1.46(2)
C(18)-C(17)	1.546(11)	C(29A)-C(51)	1.65(2)
C(9)-C(10)	1.566(12)	O(50)-C(16)	1.413(13)
C(10)-N(2)	1.319(12)	O(50A)-C(16)	1.560(16)

Bond angles [°] for 202

C(26)-N(4)-C(27)	122.3(8)	Cl(11)-C(25)-Cl(12)	110.2(5)
C(26)-C(25)-Cl(11)	110.1(6)	C(26)-C(25)-Cl(10)	110.3(6)
C(26)-C(25)-Cl(12)	107.1(7)	Cl(11)-C(25)-Cl(10)	109.5(5)

Cl(12)-C(25)-Cl(10)	109.6(5)	C(8)-C(3)-C(4)	111.2(8)
C(2)-N(1)-C(3)	123.1(8)	C(16)-C(13)-C(12)	109.2(8)
O(1)-C(2)-N(1)	125.3(8)	O(10)-C(20)-C(19)	107.9(7)
O(1)-C(2)-C(1)	118.7(8)	O(10)-C(20)-C(21)	109.2(7)
N(1)-C(2)-C(1)	115.9(8)	C(19)-C(20)-C(21)	111.0(7)
C(2)-C(1)-Cl(1)	111.2(6)	C(10)-N(2)-C(11)	124.1(8)
C(2)-C(1)-Cl(2)	110.3(6)	N(2)-C(11)-C(15)	109.7(8)
Cl(1)-C(1)-Cl(2)	109.9(5)	N(2)-C(11)-C(12)	109.7(8)
C(2)-C(1)-Cl(3)	105.9(6)	C(15)-C(11)-C(12)	111.3(8)
Cl(1)-C(1)-Cl(3)	110.2(4)	O(2)-C(4)-C(3)	108.2(7)
Cl(2)-C(1)-Cl(3)	109.3(5)	O(2)-C(4)-C(5)	107.9(7)
O(13)-C(26)-N(4)	126.1(9)	C(3)-C(4)-C(5)	111.6(8)
O(13)-C(26)-C(25)	119.7(8)	C(32)-C(27)-N(4)	116.9(11)
N(4)-C(26)-C(25)	114.2(8)	C(32)-C(27)-C(51)	116.6(11)
O(4)-C(6)-C(5)	108.8(7)	N(4)-C(27)-C(51)	111.3(9)
O(4)-C(6)-C(7)	109.7(8)	C(32)-C(27)-C(32A)	26.4(9)
C(5)-C(6)-C(7)	111.8(8)	N(4)-C(27)-C(32A)	105.0(10)
O(9)-C(18)-N(3)	125.0(8)	C(51)-C(27)-C(32A)	104.2(11)
O(9)-C(18)-C(17)	121.1(9)	C(23)-C(24)-C(19)	107.8(7)
N(3)-C(18)-C(17)	113.9(8)	N(3)-C(19)-C(20)	110.5(7)
C(10)-C(9)-Cl(6)	108.5(6)	N(3)-C(19)-C(24)	108.9(7)
C(10)-C(9)-Cl(5)	110.7(7)	C(20)-C(19)-C(24)	113.0(8)
Cl(6)-C(9)-Cl(5)	110.3(5)	O(7)-C(15)-C(11)	111.7(8)
C(10)-C(9)-Cl(4)	110.2(6)	O(7)-C(15)-C(14)	104.1(8)
Cl(6)-C(9)-Cl(4)	109.0(5)	C(11)-C(15)-C(14)	110.4(8)
Cl(5)-C(9)-Cl(4)	108.1(5)	C(3)-C(8)-C(7)	112.6(8)
O(6)-C(10)-N(2)	125.7(8)	O(12)-C(22)-C(23)	111.0(7)
O(6)-C(10)-C(9)	121.0(9)	O(12)-C(22)-C(21)	114.2(8)
N(2)-C(10)-C(9)	113.3(8)	C(23)-C(22)-C(21)	110.1(8)
C(18)-N(3)-C(19)	122.1(8)	O(8)-C(14)-C(16)	109.8(8)
C(18)-C(17)-Cl(7)	110.2(7)	O(8)-C(14)-C(15)	109.0(8)
C(18)-C(17)-Cl(9)	108.1(6)	C(16)-C(14)-C(15)	110.2(8)
Cl(7)-C(17)-Cl(9)	109.0(5)	O(11)-C(21)-C(22)	112.9(9)
C(18)-C(17)-Cl(8)	111.6(6)	O(11)-C(21)-C(20)	109.2(8)
Cl(7)-C(17)-Cl(8)	108.6(5)	C(22)-C(21)-C(20)	110.4(7)
Cl(9)-C(17)-Cl(8)	109.3(5)	C(22)-C(23)-C(24)	111.1(8)
O(3)-C(5)-C(6)	111.7(8)	C(29)-C(30)-O(14)	116.8(9)
O(3)-C(5)-C(4)	108.1(7)	C(29)-C(30)-C(31)	112.8(11)
C(6)-C(5)-C(4)	109.7(7)	O(14)-C(30)-C(31)	102.8(9)
N(1)-C(3)-C(8)	108.3(8)	O(15)-C(31)-C(32)	104.8(15)
N(1)-C(3)-C(4)	110.7(8)	O(15)-C(31)-C(30)	109.1(13)

C(32)-C(31)-C(30)	108.6(15)	C(6)-C(7)-C(8)	108.4(8)
C(27)-C(32)-O(16)	107.9(14)	C(27)-C(51)-C(29)	117.4(11)
C(27)-C(32)-C(31)	116.1(15)	C(27)-C(51)-C(29A)	102.1(12)
O(16)-C(32)-C(31)	105.6(15)	C(29)-C(51)-C(29A)	24.3(10)
C(30)-C(29)-C(51)	113.9(12)	O(50)-C(16)-C(14)	124.7(10)
O(15A)-C(31A)-C(32A)	107.7(17)	O(50)-C(16)-C(13)	106.4(9)
O(16A)-C(32A)-C(31A)	101.6(16)	C(14)-C(16)-C(13)	112.1(9)
O(16A)-C(32A)-C(27)	110.5(14)	O(50)-C(16)-O(50A)	30.3(7)
C(31A)-C(32A)-C(27)	107.9(16)	C(14)-C(16)-O(50A)	96.2(10)
C(11)-C(12)-C(13)	111.0(8)	C(13)-C(16)-O(50A)	114.4(10)

Anisotropic displacement parameters ($Å^2$x 10^3)for 202. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	26(1)	29(2)	32(2)	3(1)	6(1)	-3(1)
Cl(2)	22(1)	28(1)	39(2)	5(1)	-1(1)	5(1)
Cl(11)	25(1)	36(2)	35(2)	-3(1)	2(1)	9(1)
Cl(9)	26(1)	26(1)	48(2)	5(1)	-4(1)	0(1)
Cl(4)	24(1)	36(2)	29(1)	-5(1)	3(1)	6(1)
Cl(10)	27(1)	32(2)	29(1)	9(1)	2(1)	4(1)
Cl(8)	26(1)	41(2)	33(1)	-14(1)	0(1)	-5(1)
Cl(5)	22(1)	30(2)	47(2)	-7(1)	-2(1)	-2(1)
Cl(12)	30(1)	26(2)	46(2)	-4(1)	-2(1)	-8(1)
Cl(3)	36(1)	33(2)	29(1)	-10(1)	8(1)	-7(1)
Cl(7)	35(1)	36(2)	31(1)	6(1)	-2(1)	-7(1)
Cl(6)	37(1)	38(2)	32(1)	7(1)	4(1)	4(1)
O(1)	24(3)	62(6)	60(5)	40(5)	2(3)	6(4)
O(9)	29(3)	40(5)	20(4)	-9(3)	-4(3)	6(3)
O(13)	24(3)	50(5)	20(4)	-9(4)	2(3)	5(3)
O(6)	30(3)	39(4)	29(4)	-3(4)	-5(3)	2(3)
O(10)	34(4)	29(4)	29(4)	-6(3)	-3(3)	6(3)
O(3)	29(3)	38(4)	31(4)	7(3)	-13(3)	-4(3)
O(12)	25(3)	47(5)	38(4)	10(4)	-5(3)	-10(3)
O(11)	31(4)	57(5)	26(4)	7(4)	-10(3)	-4(4)
N(4)	19(4)	42(5)	30(5)	-14(4)	3(4)	11(4)
C(25)	25(4)	30(6)	12(5)	-2(4)	-2(4)	1(4)
O(4)	15(3)	66(5)	28(4)	8(4)	1(3)	-7(3)
O(2)	39(5)	25(4)	86(7)	15(4)	-5(4)	4(3)
O(7)	31(4)	47(5)	37(4)	-17(4)	-7(3)	12(3)
N(1)	15(4)	31(5)	40(5)	16(4)	-9(4)	0(4)
C(2)	27(5)	26(6)	23(5)	-2(4)	5(4)	8(5)

C(1)	23(4)	12(5)	21(5)	-1(4)	3(4)	-10(4)
C(26)	27(5)	21(5)	25(6)	0(4)	3(4)	-11(4)
C(6)	17(4)	40(7)	29(6)	13(5)	-4(4)	-5(5)
C(18)	21(5)	22(5)	29(6)	-7(5)	-10(4)	6(4)
C(9)	31(5)	29(6)	19(5)	2(5)	-5(4)	-1(5)
C(10)	17(4)	24(5)	29(6)	-2(5)	-5(4)	0(4)
N(3)	31(5)	34(5)	30(5)	-5(4)	-16(4)	-5(4)
C(17)	25(5)	17(5)	37(6)	3(5)	1(4)	-2(4)
C(5)	31(5)	29(6)	18(5)	7(4)	0(4)	-1(5)
C(3)	17(5)	33(6)	28(6)	3(5)	-13(4)	-9(4)
C(13)	51(6)	21(6)	30(6)	0(4)	-2(5)	14(5)
C(20)	19(4)	30(6)	34(6)	-2(5)	1(4)	4(4)
N(2)	19(4)	77(7)	48(6)	-35(6)	-9(4)	18(5)
C(11)	16(4)	33(6)	40(6)	-10(5)	0(4)	6(4)
C(4)	12(4)	32(6)	41(6)	11(5)	8(4)	6(4)
C(27)	35(6)	36(6)	26(6)	-13(5)	-19(5)	8(5)
C(24)	26(5)	35(7)	42(7)	-21(5)	8(5)	1(5)
C(19)	14(4)	29(6)	28(5)	-9(4)	-5(4)	-14(4)
C(15)	33(5)	31(6)	27(6)	-2(5)	-11(4)	-4(5)
C(8)	39(6)	29(6)	28(6)	4(5)	-9(5)	-9(5)
C(22)	23(5)	37(6)	27(6)	-4(5)	-2(4)	-16(4)
C(14)	24(5)	40(7)	36(6)	-7(5)	-4(4)	-8(5)
C(21)	20(5)	45(7)	29(6)	13(5)	-4(4)	1(5)
C(23)	37(6)	30(6)	31(6)	-10(5)	-8(5)	-9(5)
C(30)	13(4)	46(7)	20(5)	-13(5)	3(4)	13(5)
O(14)	13(3)	46(5)	36(4)	-4(4)	2(3)	5(3)
C(30A)	13(4)	46(7)	20(5)	-13(5)	3(4)	13(5)
O(14A)	13(3)	46(5)	36(4)	-4(4)	2(3)	5(3)
C(12)	35(6)	47(8)	40(7)	-5(6)	12(5)	-4(6)
C(7)	16(5)	59(7)	27(6)	-4(5)	5(4)	6(5)
O(8)	27(4)	59(5)	32(4)	-6(4)	-6(3)	-13(3)
C(51)	12(5)	71(10)	141(14)	53(9)	-6(7)	-11(6)
C(16)	28(5)	56(8)	38(7)	3(6)	4(5)	20(5)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 202

	x	y	z	U(eq)
H(10)	718	6664	9428	46
H(53)	4736	4411	10287	49
H(12)	30	2519	7890	55
H(511)	332	5862	7322	57
H(44)	6466	12987	6284	36
H(54A)	5004	6168	8790	55
H(52)	3771	8185	9497	75
H(7)	3886	865	5542	58
H(1)	3483	4231	8967	35
H(6)	4470	6822	8797	34
H(43)	1357	7524	8753	38
H(5)	4466	7388	9928	31
H(3A)	3994	2071	9660	31
H(13A)	4375	-875	7709	41
H(13B)	4276	-3380	7493	41
H(20)	674	8461	8536	33
H(42)	3460	1506	6438	58
H(11)	3998	2505	7275	36
H(4A)	3930	5691	10128	34
H(27)	6010	12383	5308	39
H(24A)	1269	3738	7606	41
H(24B)	1167	3151	8335	41
H(19)	962	7181	7627	28
H(15)	4115	3265	6169	36
H(8A)	4019	4125	8396	39
H(8B)	4056	1495	8542	39
H(22)	564	2436	8566	35
H(14)	4609	984	6076	40
H(21)	232	5696	8567	38
H(23A)	699	3432	7239	40
H(23B)	804	1125	7588	40
H(30A)	5531	17025	6201	32
H(514)	4971	15971	5750	48
H(31)	5660	17976	5064	25
H(15A)	5355	15123	4595	33
H(32)	6159	15659	4975	25
H(516)	6349	17663	5730	48
H(29A)	5332	12757	5783	15
H(29B)	5343	13680	6510	15

H(30B)	5474	16389	6320	32
H(31A)	5705	18700	5579	40
H(15B)	5761	17543	4582	49
H(32A)	6237	16824	5385	29
H(16A)	6240	16189	6565	51
H(29C)	5456	12772	5326	45
H(29D)	5261	12551	6000	45
H(50)	4879	-2929	6491	29
H(50A)	4964	-1627	6501	51
H(12A)	3807	-2015	6886	49
H(12B)	3785	-1055	7609	49
H(7A)	4582	2092	9062	40
H(7B)	4590	3190	8352	40
H(8)	4728	1649	7252	59
H(51A)	5896	13326	6611	90
H(51B)	5795	11150	6202	90
H(16)	4351	-2377	6400	48

Crystal data and structure refinement for 255

Identification code	255	
Empirical formula	C14 H15 N O6	
Formula weight	293.27	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.5782(4) Å	α= 90°.
	b = 8.7302(5) Å	β= 90°.
	c = 21.2398(12) Å	γ = 90°.
Volume	1219.78(12) $Å^3$	
Z	4	
Density (calculated)	1.597 Mg/m^3	
Absorption coefficient	0.126 mm^{-1}	
F(000)	616	
Crystal size	0.50 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.92 to 27.21°.	
Index ranges	-8<=h<=8, -10<=k<=11, -26<=l<=27	
Reflections collected	16471	
Independent reflections	1603 [R(int) = 0.0604]	
Completeness to theta = 27.21°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9875 and 0.9396	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1603 / 0 / 211	
Goodness-of-fit on F^2	1.083	
Final R indices [I>2sigma(I)]	R1 = 0.0334, wR2 = 0.0839	
R indices (all data)	R1 = 0.0372, wR2 = 0.0857	
Absolute structure parameter	0.7(12)	
Largest diff. peak and hole	0.319 and -0.171 $e.Å^{-3}$	

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 255. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
O(3)	12915(2)	3030(2)	8313(1)	15(1)
O(4)	11547(3)	1263(2)	9381(1)	17(1)
O(6)	5427(2)	325(2)	8932(1)	16(1)
O(7)	6028(2)	3258(2)	6949(1)	16(1)
O(10)	11951(3)	1587(2)	5447(1)	20(1)
O(11)	14478(3)	594(2)	6093(1)	16(1)
N(1)	6811(3)	1888(2)	7822(1)	14(1)
C(1)	8088(3)	740(2)	8140(1)	12(1)
C(2)	10330(3)	1176(2)	8045(1)	11(1)
C(3)	10808(3)	2668(2)	8411(1)	13(1)
C(4)	10350(3)	2461(2)	9113(1)	14(1)
C(5)	8112(4)	2056(3)	9207(1)	15(1)
C(6)	7552(3)	615(2)	8840(1)	13(1)
C(7)	7211(3)	2402(2)	7236(1)	13(1)
C(8)	9185(3)	1900(2)	6958(1)	13(1)
C(9)	9462(4)	2055(2)	6302(1)	15(1)
C(10)	11309(3)	1596(2)	6065(1)	15(1)
C(11)	12824(3)	1017(2)	6451(1)	14(1)
C(12)	12589(3)	852(2)	7090(1)	13(1)
C(13)	10724(3)	1312(2)	7346(1)	12(1)
C(14)	14097(4)	1267(3)	5480(1)	19(1)

Bond lengths [Å] for 255

O(3)-C(3)	1.437(3)	C(3)-C(4)	1.530(3)
O(3)-H(3)	0.8400	C(3)-H(3A)	1.0000
O(4)-C(4)	1.427(3)	C(4)-C(5)	1.527(3)
O(4)-H(4)	0.8400	C(4)-H(4A)	1.0000
O(6)-C(6)	1.434(3)	C(5)-C(6)	1.526(3)
O(6)-H(6)	0.8400	C(5)-H(5A)	0.9900
O(7)-C(7)	1.240(3)	C(5)-H(5B)	0.9900
O(10)-C(10)	1.380(3)	C(6)-H(6A)	1.0000
O(10)-C(14)	1.440(3)	C(7)-C(8)	1.492(3)
O(11)-C(11)	1.378(3)	C(8)-C(13)	1.403(3)
O(11)-C(14)	1.449(3)	C(8)-C(9)	1.412(3)
N(1)-C(7)	1.348(3)	C(9)-C(10)	1.374(3)
N(1)-C(1)	1.472(3)	C(9)-H(9)	0.9500
N(1)-H(1N)	0.92(3)	C(10)-C(11)	1.386(3)
C(1)-C(6)	1.531(3)	C(11)-C(12)	1.373(3)
C(1)-C(2)	1.537(3)	C(12)-C(13)	1.401(3)
C(1)-H(1)	1.0000	C(12)-H(12)	0.9500
C(2)-C(13)	1.510(3)	C(14)-H(14A)	0.9900
C(2)-C(3)	1.550(3)	C(14)-H(14B)	0.9900
C(2)-H(2)	1.0000		

Bond angles [°] for 255

C(3)-O(3)-H(3)	109.5	C(1)-C(2)-H(2)	108.6
C(4)-O(4)-H(4)	109.5	C(3)-C(2)-H(2)	108.6
C(6)-O(6)-H(6)	109.5	O(3)-C(3)-C(4)	110.96(18)
C(10)-O(10)-C(14)	104.74(17)	O(3)-C(3)-C(2)	107.87(17)
C(11)-O(11)-C(14)	104.53(17)	C(4)-C(3)-C(2)	110.47(16)
C(7)-N(1)-C(1)	122.59(18)	O(3)-C(3)-H(3A)	109.2
C(7)-N(1)-H(1N)	118.1(19)	C(4)-C(3)-H(3A)	109.2
C(1)-N(1)-H(1N)	117.6(19)	C(2)-C(3)-H(3A)	109.2
N(1)-C(1)-C(6)	111.25(17)	O(4)-C(4)-C(5)	108.05(17)
N(1)-C(1)-C(2)	108.59(16)	O(4)-C(4)-C(3)	111.54(17)
C(6)-C(1)-C(2)	111.52(17)	C(5)-C(4)-C(3)	110.15(17)
N(1)-C(1)-H(1)	108.5	O(4)-C(4)-H(4A)	109.0
C(6)-C(1)-H(1)	108.5	C(5)-C(4)-H(4A)	109.0
C(2)-C(1)-H(1)	108.5	C(3)-C(4)-H(4A)	109.0
C(13)-C(2)-C(1)	108.28(17)	C(6)-C(5)-C(4)	110.89(18)
C(13)-C(2)-C(3)	113.10(16)	C(6)-C(5)-H(5A)	109.5
C(1)-C(2)-C(3)	109.67(17)	C(4)-C(5)-H(5A)	109.5
C(13)-C(2)-H(2)	108.6	C(6)-C(5)-H(5B)	109.5

C(4)-C(5)-H(5B)	109.5	C(9)-C(10)-C(11)	121.7(2)
H(5A)-C(5)-H(5B)	108.1	O(10)-C(10)-C(11)	109.9(2)
O(6)-C(6)-C(5)	108.13(18)	C(12)-C(11)-O(11)	127.3(2)
O(6)-C(6)-C(1)	111.69(17)	C(12)-C(11)-C(10)	122.8(2)
C(5)-C(6)-C(1)	112.44(17)	O(11)-C(11)-C(10)	109.80(18)
O(6)-C(6)-H(6A)	108.1	C(11)-C(12)-C(13)	116.9(2)
C(5)-C(6)-H(6A)	108.1	C(11)-C(12)-H(12)	121.5
C(1)-C(6)-H(6A)	108.1	C(13)-C(12)-H(12)	121.5
O(7)-C(7)-N(1)	122.2(2)	C(12)-C(13)-C(8)	120.55(19)
O(7)-C(7)-C(8)	121.9(2)	C(12)-C(13)-C(2)	120.62(19)
N(1)-C(7)-C(8)	115.97(19)	C(8)-C(13)-C(2)	118.8(2)
C(13)-C(8)-C(9)	121.4(2)	O(10)-C(14)-O(11)	106.99(17)
C(13)-C(8)-C(7)	120.15(19)	O(10)-C(14)-H(14A)	110.3
C(9)-C(8)-C(7)	118.4(2)	O(11)-C(14)-H(14A)	110.3
C(10)-C(9)-C(8)	116.6(2)	O(10)-C(14)-H(14B)	110.3
C(10)-C(9)-H(9)	121.7	O(11)-C(14)-H(14B)	110.3
C(8)-C(9)-H(9)	121.7	H(14A)-C(14)-H(14B)	108.6
C(9)-C(10)-O(10)	128.3(2)		

Anisotropic displacement parameters ($Å^2$x 10^3) for 255. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	13(1)	16(1)	18(1)	-3(1)	1(1)	-2(1)
O(4)	14(1)	22(1)	16(1)	3(1)	1(1)	3(1)
O(6)	15(1)	18(1)	16(1)	-2(1)	3(1)	-3(1)
O(7)	15(1)	15(1)	17(1)	1(1)	-2(1)	1(1)
O(10)	20(1)	28(1)	11(1)	1(1)	2(1)	3(1)
O(11)	16(1)	19(1)	14(1)	0(1)	3(1)	0(1)
N(1)	11(1)	15(1)	15(1)	0(1)	1(1)	1(1)
C(1)	12(1)	11(1)	13(1)	1(1)	0(1)	-1(1)
C(2)	12(1)	12(1)	9(1)	-1(1)	-1(1)	1(1)
C(3)	12(1)	12(1)	13(1)	-1(1)	-1(1)	0(1)
C(4)	15(1)	15(1)	10(1)	-1(1)	-1(1)	0(1)
C(5)	16(1)	16(1)	14(1)	-2(1)	2(1)	2(1)
C(6)	13(1)	14(1)	12(1)	1(1)	1(1)	0(1)
C(7)	13(1)	11(1)	15(1)	-3(1)	-2(1)	-4(1)
C(8)	14(1)	10(1)	15(1)	0(1)	-1(1)	-2(1)
C(9)	16(1)	14(1)	16(1)	1(1)	-2(1)	0(1)
C(10)	20(1)	14(1)	11(1)	1(1)	-1(1)	-4(1)
C(11)	13(1)	11(1)	17(1)	-2(1)	2(1)	-2(1)
C(12)	14(1)	9(1)	15(1)	0(1)	-1(1)	-2(1)

C(13)	16(1)	9(1)	11(1)	-1(1)	-2(1)	-2(1)
C(14)	21(1)	22(1)	15(1)	1(1)	3(1)	0(1)

Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 255

	x	y	z	U(eq)
H(3)	13206	3839	8506	43(10)
H(4)	12733	1307	9236	33(9)
H(6)	5074	-431	8713	37(9)
H(1)	7846	-278	7938	12(6)
H(2)	11199	334	8217	17(7)
H(3A)	9950	3519	8241	10(6)
H(4A)	10651	3441	9338	14(6)
H(5A)	7844	1890	9660	14(6)
H(5B)	7254	2920	9063	23(7)
H(6A)	8330	-264	9021	14(6)
H(9)	8426	2457	6038	30(8)
H(12)	13642	445	7346	10(6)
H(14A)	14889	2224	5430	40(9)
H(14B)	14496	547	5142	28(8)
H(1N)	5540(50)	2080(30)	7988(14)	30(8)