New Tandem Reactions for the Synthesis of Nitrogen Containing Natural Products

Ahmed M. Zaed (M. Sci)

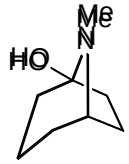
A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy.

School of Chemistry
College of Science & Engineering
University of Glasgow
Glasgow G12 8QQ

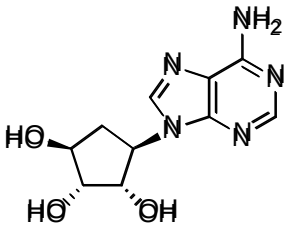
April 2012

Abstract

During the course of the studies outlined in this thesis, a new approach for the synthesis of the tropane alkaloid, (±)-physoperuvine has been developed using a highly efficient one-pot tandem process which involved the Overman rearrangement and a ring closing metathesis reaction. An asymmetric one-pot tandem process has also been employed for the synthesis of the natural product, (+)-physoperuvine. This methodology was also applied to the generation of a late-stage intermediate that could be used in the synthesis of carbocyclic nucleosides, such as noraristeromycin.



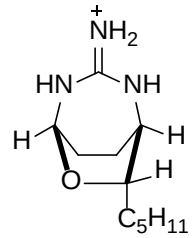
(±)-physoperuvine



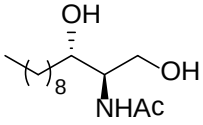
noraristeromycin

In the second part of this thesis, an ether-directed Pd(II)-catalysed Overman rearrangement which had previously been developed by the Sutherland group was applied in conjunction with a cross-metathesis reaction for the stereoselective synthesis of the guanidine alkaloid, (+)-monanchorin in a fourteen-step synthesis.

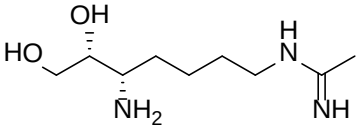
Further employment of this process provided the first synthesis of clavaminol A, C and H from (*R*)-glycidol in a rapid and efficient manner. In a similar fashion, (2*S*,3*R*)-enantiomers were also synthesised from (*S*)-glycidol. In addition to this, using similar chemistry, an intermediate protected enone was prepared using a cross-metathesis reaction as the second key step in an approach towards the synthesis of an NO-inhibitor.



(+)-monanchorin



clavaminol H



NO-inhibitor

Contents

Acknowledgements

I would like to express my sincere gratitude to my supervisor, Dr Andrew Sutherland for accepting me as a Ph.D. student in his research group, and my special appreciation also to him, for his expertise, motivation, understanding, and patience which added considerably to my graduate experience for all of his help and support throughout the course of my Ph.D. His unlimited guidance helped me in all the time of my research and writing of this thesis.

I would also like to thank all of the academic, technical and support staff at the School of Chemistry for their kind assistance during my Ph.D. studies. The assistance of Dr David Adam (NMR spectroscopy), Jim Tweedie (Mass Spectrometry), Stuart Mackay (IT support), Ted Easdon and Shawn Maidwell is also gratefully acknowledged.

Thanks to all the Sutherland group memberes, past and present who have assisted me throughout my Ph.D. Thanks to Mike, Alastair, Nicola, Lindsay, Louise, Lorna, Sajjad, Mark D., Mark G., Fiona, Lynne, Adele and Ewen.

Special thanks to my wife, Iman for her love and encourgement throughout my time in Glasgow, also to my parents, my brother Massoud and all my family for their support and confidence.

Finally, financial support from the Libyan government is gratefully acknowledged.

Author's Declaration

This thesis represents the original work of Ahmed Mohamed Zaed 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, June 2008 to May 2011. Certain aspects of this work have been published elsewhere and are listed below.

A. M. Zaed, M. D. Swift and A. Sutherland, *Org. Biomol. Chem*., 2009, **7**, 2678.
A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 4394.
A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 8030.

List of Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aromatic
Bn	benzyl
Boc	*tert*-butoxycarbonyl
br	broad
Bu	butyl
^{t}BuOOH	*tert*-butyl hydroperoxide
c	concentration
^{o}C	degrees centigrade
Cat.	catalyst
CAN	Ceric Ammonium Nitrate
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterated chloroform
CI	Chemical Ionisation
COP	cobaltocenyloxazoline palladacycle
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublets
d.e.	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dq	doublet of quartets
dr	diastereomeric ratio(s)
dt	doublet of triplets
EDCI	1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride

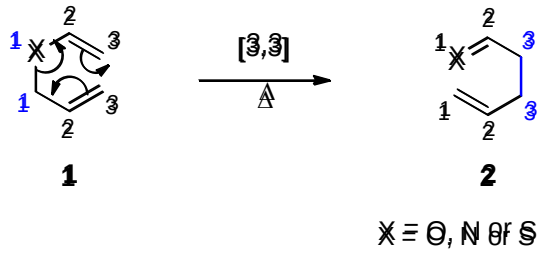
e.e.	enantiomeric excess
EI	Electron Impact
ΔH	enthalpy change
EtOAc	ethyl acetate
EtOH	ethanol
FAB	fast atom bombardment
g	gram(s)
h	Hour(s)
HCl	hydrochloric acid
HMPA	hexamethyphosphoramide
HOBT	hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
Hz	hertz
HWE	Horner-Wadsworth-Emmons
IR	infrared
J	NMR spectra coupling constant
kcal	kilocalorie(s)
KHMDS	potassium bis(trimethylsilyl)amide
$LiAlH_4$	Lithium aluminium hydride
lit.	literature
M	molar
m	multiplet
m-CPBA	*meta*-chloroperoxybenzoic acid
MeOH	methanol
Me	Methyl
Mes	mesityl
mg	milligram(s)
mL	millilitre(s)
mmol	millimole(s)
mol	mole(s)
MOM	Methoxymethyl
mp	melting point
Ms	methanesulfonyl
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear Magnetic Resonance

NOS	Nitric-oxide synthases
PCC	pyridinium chlorochromate
Pd/C	Palladium on carbon
Ph	phenyl
PMB	*para*-methoxybenzoic acid
PPTS	pyridinium *p*-toluenesulfonate
PrOH	propanol
ppm	parts per million
Py	pyridine
q	quartet
quin	quintet
RCM	Ring Closing Metathesis
rt	Room Temperature
s	singlet
t	triplet
TBAF	*tetra*-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethysilyl
Ts	tosyl

1.0 Introduction

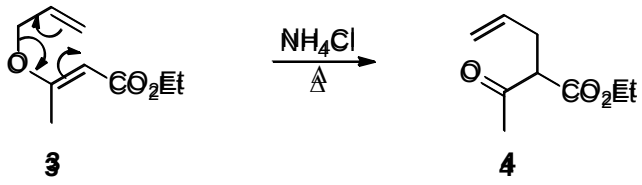
1.1 Claisen Rearrangement

Over the last 100 years, the Claisen rearrangement has been widely studied and has drawn the attention of numerous organic chemists.[1] This reaction falls under the classification of a [3,3]-sigmatropic shift, a well known reaction which can give good yields of rearrangement products, with short reaction times and can be performed under relatively mild conditions. The Claisen rearrangement can be defined as the thermal [3,3]-sigmatropic reorganisation of an allyl-aryl or allyl-vinyl ethers (**1**, X=O) into γ,δ-unsaturated carbonyl compound **2** by a concerted intramolecular process (Scheme 1). There are also nitrogen and sulfur varients of this reaction.



Scheme 1- Claisen rearrangement

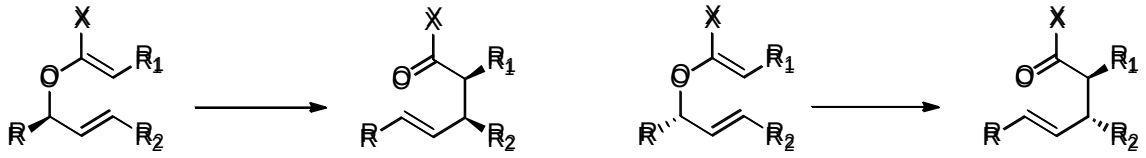
The first report on the Claisen rearrangement involved the conversion of *O*-allylated ethyl acetoacetate **3** into the corresponding *C*-allyl isomer **4** and was originally discovered by Ludwig Claisen in 1912 (Scheme 2).[2]



Scheme 2- The first Claisen rearrangement

The Claisen rearrangement is well known for its ability to create new stereocentres in a controlled manner.[3] In addition, the generation of a new carbonyl group and the stereoselective formation of carbon-carbon bonds, has made this reaction one of the most widely used methods in synthetic chemistry. The rearrangement is a pericyclic process, where bond breaking and forming occurs through a cyclic array of interacting orbitals in a

highly ordered transition state. This allows for the creation of stereogenic centers during the reaction (Scheme 3). Although asymmetric Claisen rearrangements still remain a challenge for organic chemists, it can be manipulated to give a diastereoselective or an enantioselective reaction. Diastereoselective substrates which have a stereogenic centre at the 1-position have been extensively studied. The 1-position in the system is found to be more efficient for intramolecular chirality transfer creating enantiomerically enriched products (Scheme 3).[4] Substrates with stereogenic centers at the 1-position can be constructed from a chiral secondary or tertiary allylic alcohol.



Scheme 3- The diastereoselective Claisen rearrangement

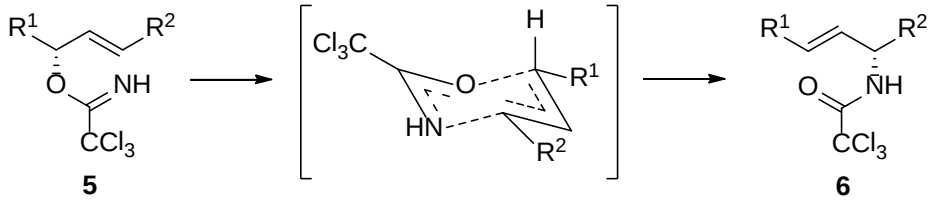
1.1.1 Overman rearrangement

The Overman rearrangement is an important method for the construction of allylic amines from allylic imidates and has found widespread application in organic synthesis.[5] This is primarily due to the relative ease in which a wide variety of allylic trichloro- and trifluoroacetimidates can be prepared from the corresponding allylic alcohol. The Overman rearrangement refers to the [3,3]-sigmatropic rearrangement of allylic trichloroacetamidates leading to formation of C-N σ-bond. The scope of the rearrangement is such that primary, secondary and tertiary allylic amides are all readily accessible, thus providing entry into a wide variety of nitrogen-containing products including amino sugars, nucleotides, amino acids, peptides and various nitrogen heterocycles.[6] In addition, the Overman rearrangement has found extensive application in the total synthesis of natural products.

1.1.1.1 Thermal Overman rearrangement

The thermal [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates was first reported by Mumm and Möller.[7] This reaction occurs with a negative change in enthalpy at elevated temperatures in excess of 140 °C, usually in aromatic solvents such as *p*-xylene. Extensive study by Overman showed that a wide variety of allylic trichloroacetimidates **5**

readily underwent thermal rearrangement within a few hours to afford the corresponding allylic trichloroacetamides **6** in high yields.[8,9] The mechanism of the thermal rearrangement occurs *via* a concerted pathway (Scheme 4), although the [1,3]-sigmatropic product can be formed *via* the competition of a non-concerted ionisation pathway.[10]



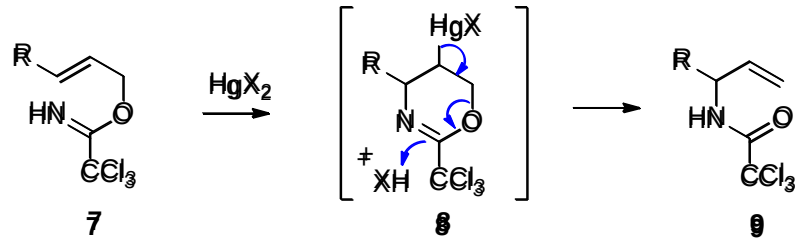
Scheme 4- Thermal Overman rearrangement

1.1.1.2 Metal catalysed Overman rearrangement

Significant attention has been paid to the development of [3,3]-sigmatropic rearrangements using a variety of metal catalysts such as Hg(II), Pd(0), Pd(II), Ag(I), Ni(0), Ni(II), Pt(II), Au(I) and Al(III).[11-15] Further improvements to this approach were reported by Overman.[16,17] They demonstrated that transition metals (including Pd, Au and Pt) can effectively catalyse a wide range of [3,3]-sigmatropic rearrangements with a significant increase in reaction rate, allowing the reaction to be carried out at room temperature, under mild conditions and giving improved yields.

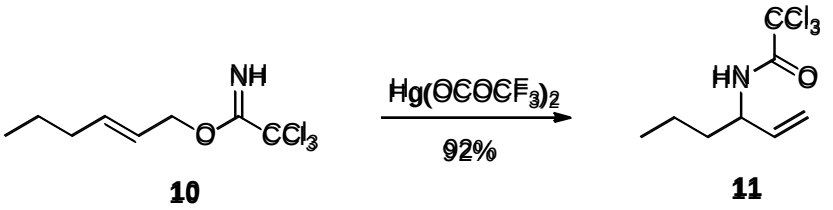
1.1.1.2.1 Mercury(II)-catalysed Overman rearrangement

In 1974, Overman reported the first metal catalysed Overman rearrangement using mercury(II)-salts such as mercuric trifluoroacetate and mercuric nitrate under mild conditions providing a new method for the 1,3-transposition of hydroxyl and amino functions.[8] This study revealed that allylic trichloroacetimidate **7** of 2-alken-1-ols underwent rapid isomerisation to the corresponding allylic trichloroacetamides **9** (Scheme 5). The results from this study allowed the use of low temperature. Further study by Overman has shown that the mercury(II)-catalysed process proceeds in a two step mechanism starting with the addition of the mercury electrophile to the double bond, which forms the mercurinium ion. Cleavage of the C-O bond of the unstable dihydrooxazine **8** leads to the formation of amide **9**.



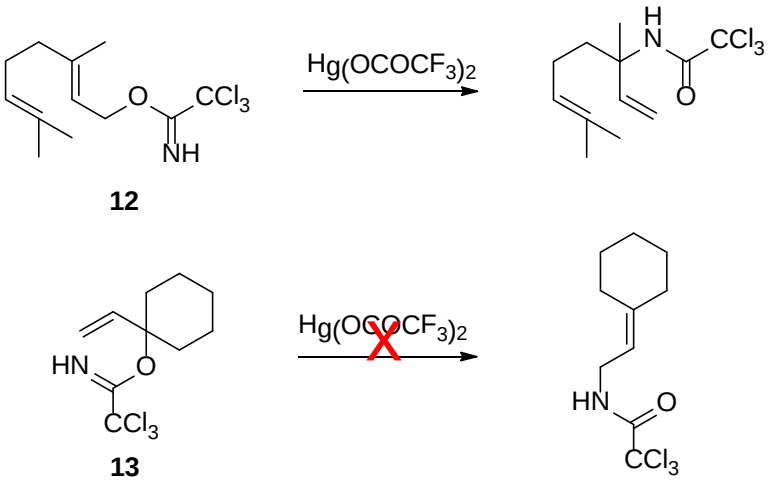
Scheme 5- Mechanism of the Hg(II)-catalysed rearrangement

In addition to the above study, Overman demonstrated that mercury(II) could successfully catalyse derivatives of 3-substituted primary allylic alcohols such as allylic trichloroacetimidate **10**. This was in contrast to the thermal rearrangement and gave exclusively the allylic trichloroacetamide **11** in high yield (Scheme 6).[9] The rearrangement can also take place at low temperatures (as low as –78 °C). Efforts to perform this rearrangement using trifluoroacetic acid were unsuccessful, giving trace amounts of the rearranged amide.



Scheme 6- Hg(II)-catalysed rearrangement of allylic trichloroacetimidate

Overman has also reported that allylic substrates such as **12**, in which alkene substitution allows intramolecular nucleophilic attack by the imino nitrogen at C-3, rearrange more successfully under mercury(II)-catalysis than imidates **13**, where addition at C-2 is preferred (Scheme 7).[8] In one case however, C-2 substituted imidate substrates bearing electron donating groups at C-3 such as allyl *N*-phenylimidates will undergo highly (*E*)-selective rearrangements.[18]

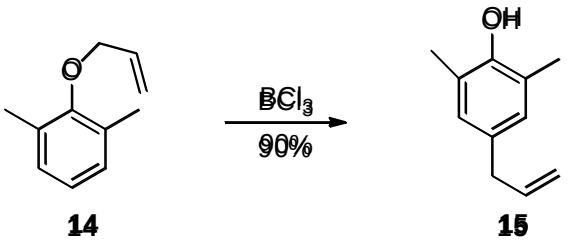


Scheme 7- Scope of Hg(II)-catalysed rearrangement

Although, the rearrangement of allylic trichloroacetimidates at room temperature can be achieved using a mercury(II)-catalyst, there are no examples of high yielding mercury catalysed rearrangements of secondary allylic trichloroacetamides.

1.1.1.2.2 Boron(III)-catalysed aza-Claisen rearrangement

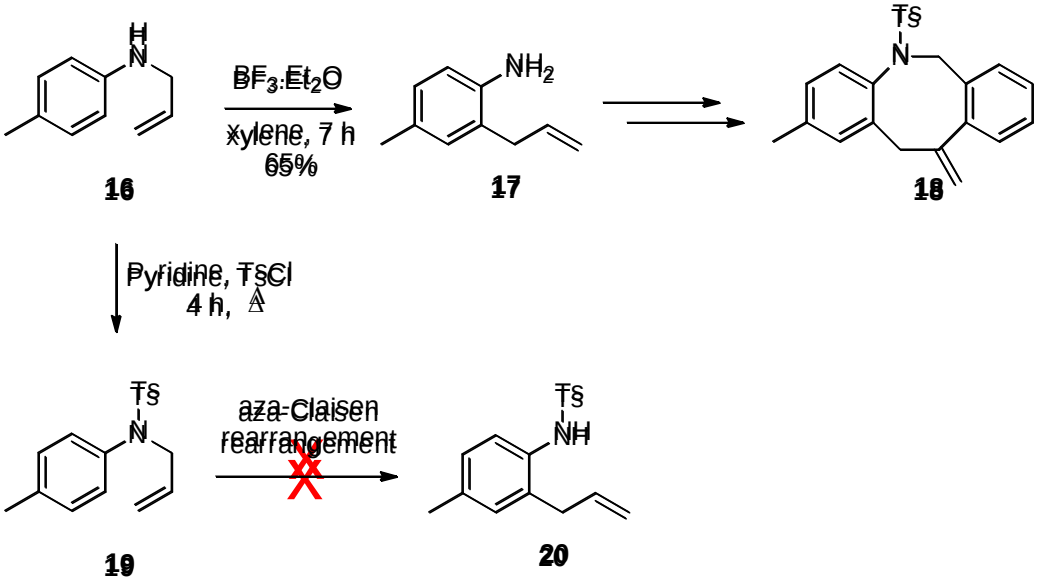
The Claisen rearrangement using a boron(III)-catalyst was first reported by Schmid and co-workers in 1973.[19] They reported that BCl_3 can catalyse the rearrangement of allyl aryl ethers **14** at low temperatures in good yields to the corresponding *o*- and *p*-allyl phenols **15**, which serve as precursors to a variety of natural products (Scheme 8). The reaction rate was increased significantly (10^{10} faster relative to thermal Claisen rearrangement), due to charge induction by the boron(III)-catalyst.



Scheme 8- The first B(III)-catalysed Claisen rearrangement

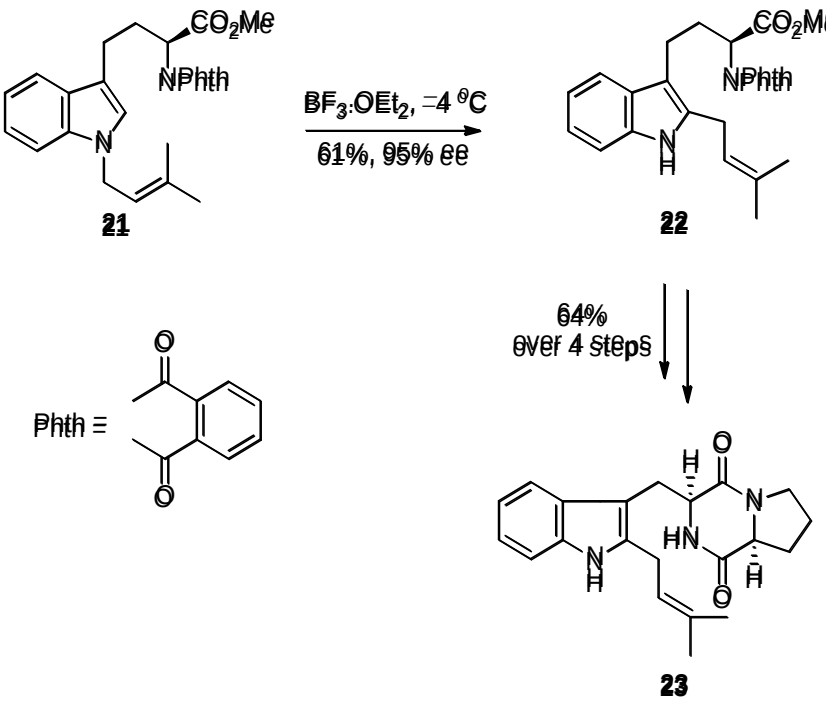
Recently, Majumdar and co-workers have developed an efficient synthetic strategy for the synthesis of the dibenzoazocine system **18**.[20] Majumdar synthesised *N*-allylaniline **16** which could be subjected to an aromatic aza-Claisen rearrangement using a BF_3 complex to afford the rearranged product **17**. Compound **17** could then be utilised for an intramolecular Heck reaction to synthesise the dibenzoazocine derivative **18** (Scheme 9).

Previous studies supported these results, suggesting that the presence of an additional alkyl group in the *para* position, significantly increases the rate of the aromatic aza-Claisen rearrangement.[21] They attempted to optimise the rearrangement process by increasing the reaction time and using different high boiling solvents but unfortunately these attempts were unsuccessful, giving undesired by-product. They also attempted to subject the tosyl-protected substrate **19** to boron(III)- rearrangement, however no product was formed.



Scheme 9- Synthesis of dibenzoazocine 18 via an aza-Claisen rearrangement

A systematic study of the reaction was undertaken by Rzepa and co-workers to define optimum conditions.[22] The results of this study led to higher conversions during the rearrangement process with a minimum loss of optical purity. Further advantages obtained from this study allowed the reaction to be performed at room temperature or lower (in direct contrast to purely thermal conditions which required high temperature of 450-470 ^{o}C).[23] In this approach, the phthaloyl derivative **21** was subjected to rearrangement using BF_3 as the catalyst to give the corresponding 2-prenyl derivative **22** (Scheme 10).[22] Conversion of **22** in four further steps successfully gave the 2,3-disubstituted indolic alkaloid, tryprostatin B **23**.

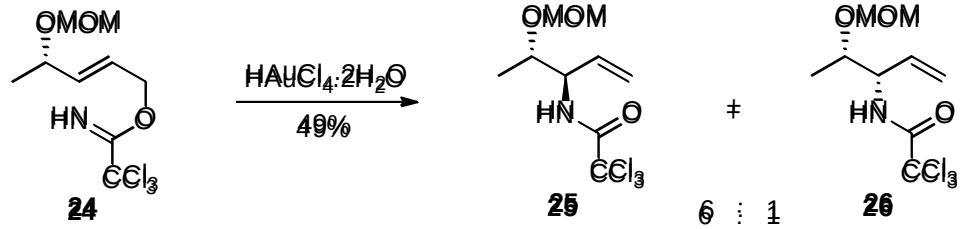


Scheme 10- Rzepa's synthesis of tryprostatin B

1.1.1.2.3 Gold-catalysed Overman rearrangement

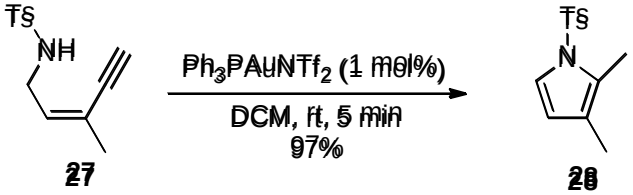
Recent reports have highlighted the use of gold(I) and gold(III)-complexes as efficient homogeneous catalysts in several organic transformations. These catalysts have been successfully applied to a series of [3,3]-sigmatropic rearrangements, such as the rearrangement of allenyl carbinol esters to 1,3-butadien-2-ol esters,[24] and isomerisation of allylic acetates.[25,26] However, the reactions methods were rather limited in scope, being successful for only a few substrates and in poor to moderate yields.[12,27,28]

In 2006, Jamieson and Sutherland reported the first gold(III)-catalysis for the Overman rearrangement.[29] In this approach, the gold(III)-catalyst was successfully employed with reasonable yield and selectivity using an MOM-ether directed Overman rearrangement of an allylic trichloroacetimidate **24** to afford the corresponding allylic trichloroacetamides **25** and **26** (Scheme 11).



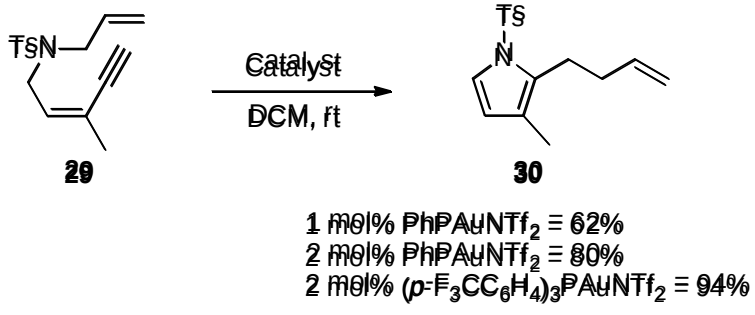
Scheme 11- First gold(III)-satalysis Overman rearrangement

Previously, Istrate and Gagosz reported that the air-stable crystalline $Ph_3PAuNTf_2$ catalyst can be used successfully for the formation of C-C and C-O bonds.[30] After this successful approach, their attention turned to developing a new gold(I)-catalysed rearrangement as the key step in the synthesis of a series of pyrroles by an initial intramolecular cyclisation of a substitiuted nitrogen. Pentenyl allyl tosylamide **27** was treated with $Ph_3PAuNTf_2$ under mild conditions and rapidly gave the expected pyrrole derivative **28** in excellent yield (Scheme 12).



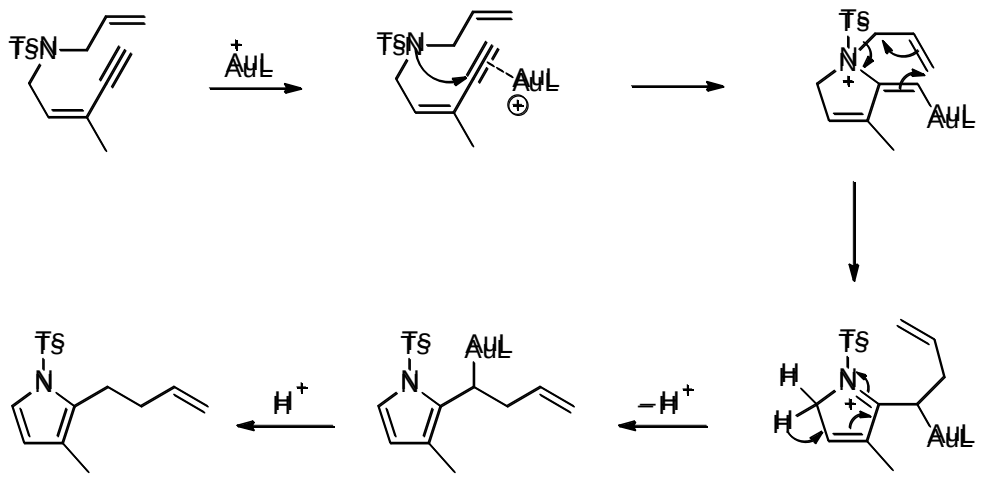
Scheme 12- Au(I)-catalysed cyclisation pentenyl tosylamide

Surprisingly, they have shown that allyl tosylamide **29** reacts more slowly under the same reaction conditions to give the rearranged pyrrole **30** in a moderate yield (Scheme 13).[30] However, when the catalyst concentration was increased and the more electrophilic (*p*-$F_3CC_6H_4)_3PAuNTf_2$ was employed, complete conversion to **30** with improved yield (80–94 %) was achieved.



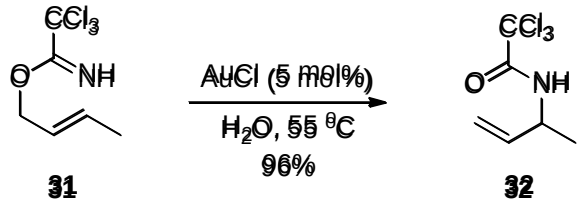
Scheme 13- Optimisation of the catalytic system

The proposed mechanism for the rearrangement of pyrrole **30** is shown in scheme 14



Scheme 14- Rearrangement of Pyrrole

Recent work by Xing and Yang has demonstrated that a gold(I)-catalyst can be employed for the Overman rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides (Scheme 15).[31] A number of gold(I)-catalysts in H_2O were examined and it was discovered that optimum results were achieved when allylic trichloroactimidate **31** was converted to the corresponding allylic trichloroacetamide **32** using AuCl.



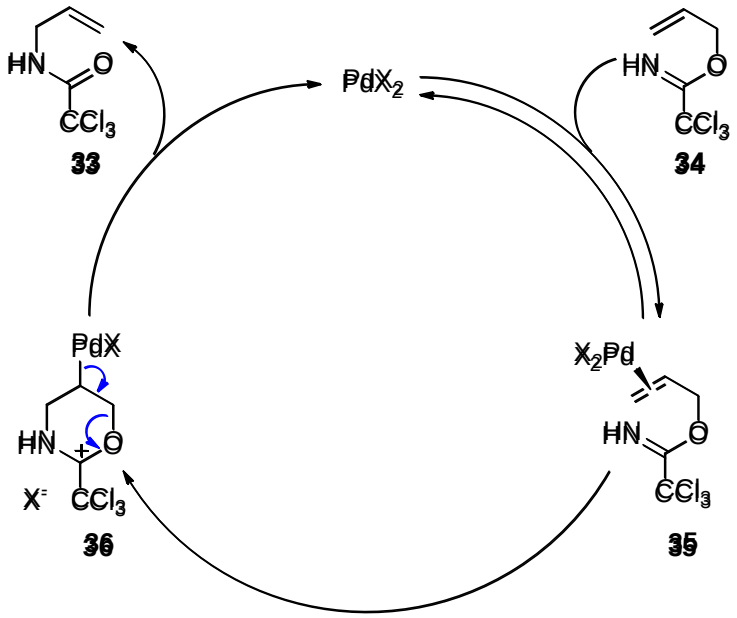
Scheme 15- Au(I)-catalysed Overman rearrangement in H_2O

1.1.1.2.4 Palladium(II)-catalysed Overman rearrangement

Palladium catalysis was first recognized by Winstein and co-workers,[32] who reported that the palladium acetate in acetic acid was found to be considerably more efficient than mercury acetate in the oxidation of alkenes. Subsequently, extensive studies by Henry in this area demonstrated that the involvement of two equivalents of a palladium catalyst

allowed the oxidation of alkenes to proceed with and without exchange of the ester acyl group with acetic acid.[33-36]

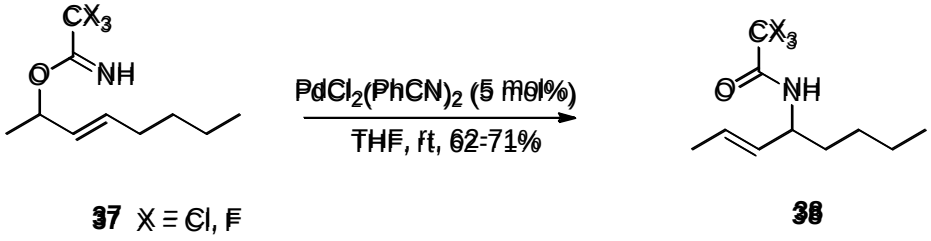
Palladium(II)-salts soon emerged as the most useful and effective metal catalysts for [3,3]-sigmatropic rearrangements. This is because palladium(II) can equilibrate with the substrates such as allylic esters quickly at room temperature with low catalyst loading and in high yield, often with an increase in stereoselectivity and a decrease in the formation of by-products.[16,37] The palladium(II)-catalysed rearrangement proceeds through a cyclisation induced mechanism *via* a stepwise pathway as shown in Scheme 16. This pathway involves the initial complex formation of the coordinated olefin **35** through intermolecular aminopalladation of the double bond (oxidative addition).[10,16,17,38] Cyclisation of π-complex **35** provides alkylpalladium intermediate **36** which, through reductive elimination, affords the amide product **33** and regenerates the catalyst. The driving force of this reaction is the irreversible amide formation, which is similar to the thermal rearrangement.



Scheme 16- Mechanism of Pd(II)-catalysed Overman rearrangement

Metz and co-workers reported that a wide variety of Pd(II)-catalysts such as $PdCl_2(CH_3CN)_2$ and $PdCl_2(PhCN)_2$ can be employed for the catalysis of the Overman rearrangement.[18] These catalysts were found to promote the reaction with excellent yields of amide **38** in a few hours at room temperature as shown in Scheme 17. Unfortunately, whilst allylic trifluoroacetimidates were more stable than allylic trichloroacetimidates, they were considerably less reactive. This is due to the electron-withdrawing substituents on the

imidate carbon.[39] In addition, the removal of the trichloroacetamide group requires harsh conditions and is difficult in the presence of a variety of functional groups. Whereas trifluoroacetamides are considered as one of the most easily cleaved amides.

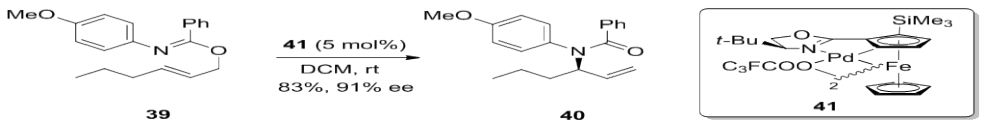


37 X = Cl, F **38**

Scheme 17- Pd(II)-catalysed rearrangement of allylic trifluoro- and trichloroacetimidates

1.1.1.3 Asymmetric Overman rearrangement

After success with Pd(II)-catalysis for allylic trichloroacetimidate rearrangements, Overman and Zipp focused on the research of an asymmetric variant employing a variety of chiral metal catalysts. They demonstrated that substrates such as secondary *N*-benzoyl benzimidates were not suitable substrates for asymmetric catalysis in cationic Pd(II)-complexes with structure similar to **41**.[40] Many attempts to carry out these transformations were unsuccessful, giving low enantioselectivities. In addition to this, the strong complexation of the small, basic acetimidate nitrogen to the hard palladium centre, promotes competing elimination reactions and slows reaction rates.[41] Consequently, new asymmetric Pd(II)-catalysts for the rearrangement of less strongly coordinating *N*-arylimidates **39** to allylic amides **40** was successfully achieved (Scheme 18). High enantioselectivities was achieved with this type of substrate.[42]

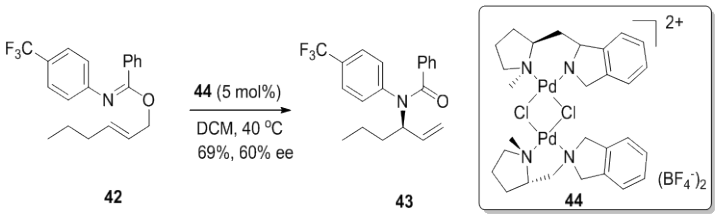


39 **40** **41**

Scheme 18- Overman rearrangement using chiral catalyst

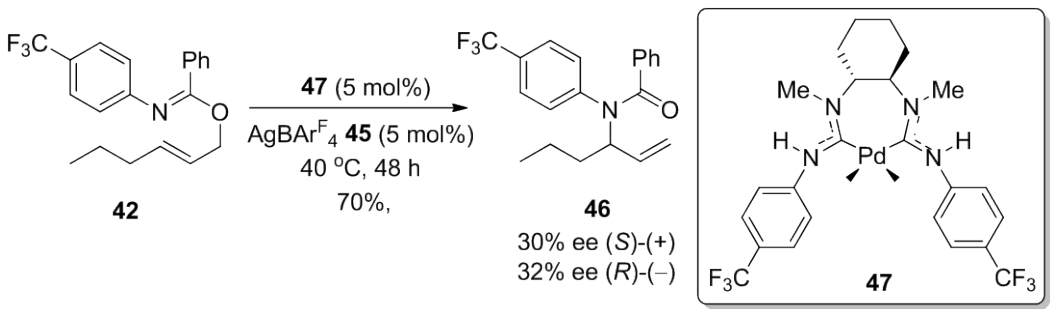
1.1.1.3.1 Palladium Diamine Complexes

Initially, Overman reported the asymmetric catalysis of the rearrangement of allylic imidates to allylic amides using a series of cationic Pd(II)-diamine and Pd(II)-bisoxazoline complexes.[43] The palladium diamine di-cation **44** was shown to be the first enantioselective catalyst proven to be more efficient than other palladium diamine complexes for this process. This catalyst and other cationic diamine palladium complexes were easily synthesised from L-proline. They were then employed in the asymmetric Overman rearrangement of various benzimidate substrates, e g. **42**, to the corresponding amides such as **43**, in good yield and modest enantioselectivity (Scheme 19). Unfortunately, these cationic palladium diamine catalysts were markedly deficient in terms of reaction rate and yield.



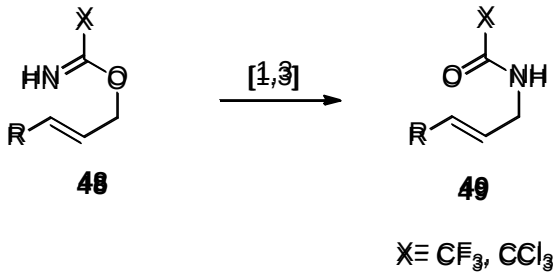
Scheme 19- First cationic chiral catalyst for the Overman rearrangement

Recently, Slaughter and co-workers showed that the palladium complex **47** activated with $AgBAr^F_4$ **45** can catalyse the Overman rearrangement of allylic benzimidate **42** to allylic amide **46**, creating a new chiral centre (Scheme 20).[44] Their study showed that bis(acyclic diaminocarbene) ligands with seven-membered chelates could support electrophilic reactivity at the Pd centre. Unfortunately, these ligands were limited in scope for Pd catalysis, due to the stringent stereoelectronic demands of the reaction.



Scheme 20- Asymmetric rearrangement of benzimidate using chiral Pd(II)-catalyst

The treatment of these cationic catalysts with other imidate substrates such as **48** which contain CCl_3 or CF_3 groups, led to the formation of significant quantities of an undesired 1,3-rearranged product **49** (Scheme 21).[10]



Scheme 21- Formation of an anti-Claisen product

1.1.1.3.2 Cobalt Oxazoline Palladocycle (COP-Cl) Catalysts

The cobalt oxazoline palladacycles (COP-Cl) **50** and **51** are described as one of the most important asymmetric catalysts for the rearrangement of allylic imidates to allylic amides (Figure 1). These complexes can be synthesised as a single cyclopalladated diastereoisomer of (*S*) and (*R*)-configuration in high yield in four steps and have recently emerged as highly successful chiral catalysts,[45] not only for the rearrangement of *N*-aryl allylic trifluoroacetimidates, but also for the rearrangement of allylic trichloroacetimidates without an *N*-aryl protecting group. This success is based on its planar chiral sandwich motif, which despite its multistep synthesis has found many applications in this area of chemistry.[46]

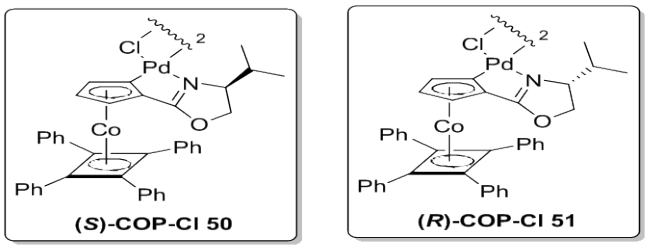
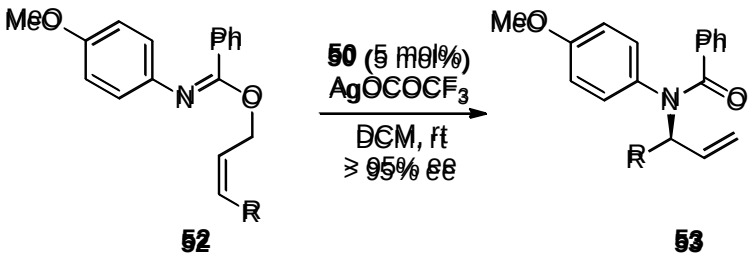


Figure 1- Cobalt oxazoline palladocycle catalysts

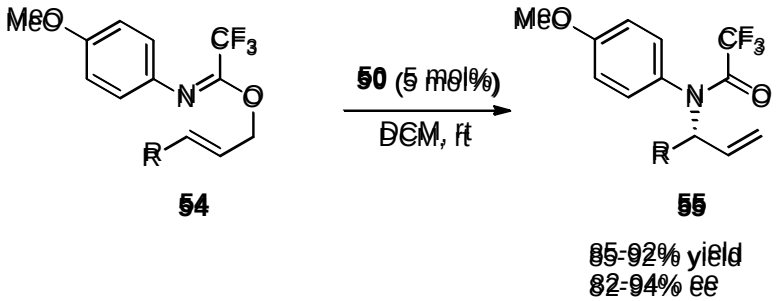
Initially, (*S*)-COP-Cl **50** was used as a chiral catalyst for the enantioselective Overman rearrangement of the allylic imidate activated by $AgOCOCF_3$ (Scheme 22).[47] High enantioselectivities and excellent yields of benzamides **53** were obtained using *Z*-

benzimidates **52** as starting materials. The corresponding *E*-imidates were also investigated, but were found to give only moderate yields.



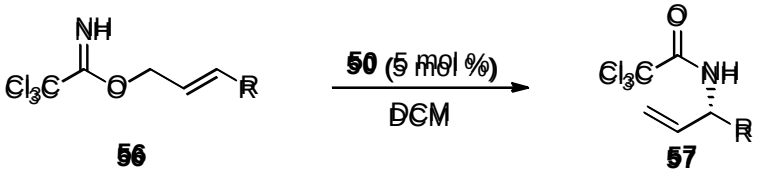
Scheme 22- Activated (*S*)-COP-Cl rearrangement of *Z*-benzimidates

In contrast to the above results reported by Kang and co-workers,[47] the groups of Overman and Richards reported their approach for transforming prochiral allylic alcohols to allylic amines using *E*-allylic trifluoroacetimidates **54** to provide the corresponding (*S*)-allylic trifluoroacetamides **55** using (*S*)-COP-Cl **50** (Scheme 23).[48] Interestingly, they also reported that (*S*)-COP-Cl did not require activation with silver salts.



Scheme 23- Non-activated (*S*)-COP-Cl rearrangement of *E*-allylic imidates

Another improvement to this approach was reported by Anderson and Overman.[49] They found that (*S*)-COP-Cl **50** could catalyse the rearrangement of *E*-allylic trichloroacetimidates **56**, to the allylic trichloroacetamides **57** in high yield and enantioselectivity (80-99% yield, 92-98% ee) (Table 1). (*Z*)-Allylic trichloroacetimidates were not found to undergo (*S*)-COP-Cl **50** catalysed rearrangement at a practical rate. It was also found that allylic trichloroacetamides of opposite absolute configuration can be prepared using (*R*)-COP-Cl **51**.[50] Unfortunately, this method was limited to the rearrangement of allylic trichloroacetimidates containing (*E*)-1,2-disubstituted double bonds whilst analogous *Z*-configured substrates rearrange slowly under COP-Cl catalysis.

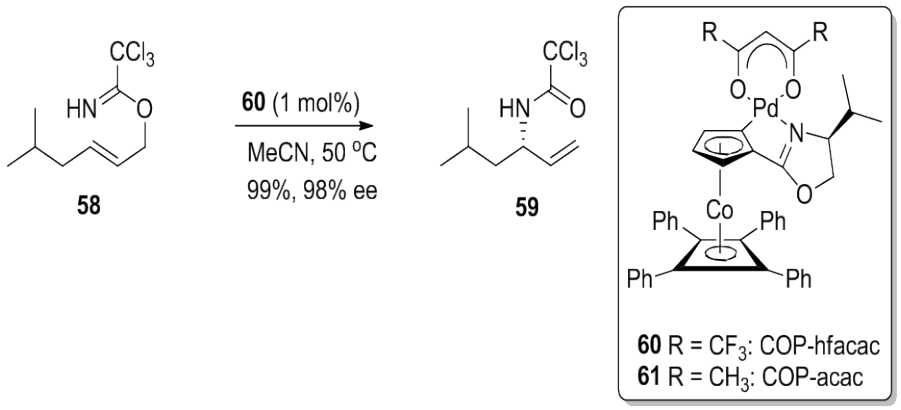


56 57

R	Temp (°C)	Yield (%)	ee (%)
Cy	38 rt	82 82	96 96
$(CH_2)_3NBn(Boc)$	38 rt	96 96	95 95
$(CH_2)_9NBn_2$	rt	82	97

Table 1- Highly enantioselective rearrangement using (*S*)-COP-Cl

Although (*S*)-COP-Cl **50** is an excellent catalyst for these asymmetric rearrangements, its use was rather limited due its poor solubility in many solvents. As a consequence of this, Overman and co-workers have synthesised a variety of monomeric palladacycle complexes such as COP-hfacac **60** and COP-acac **61** to catalyse the asymmetric rearrangement (Scheme 24).[6] These catalysts showed excellent solubility in a wide variety of solvents. This enhancement of solubility allowed the rearrangements to be carried out at high substrate concentrations and this allowed catalyst loading to be reduced to 1 mol%.

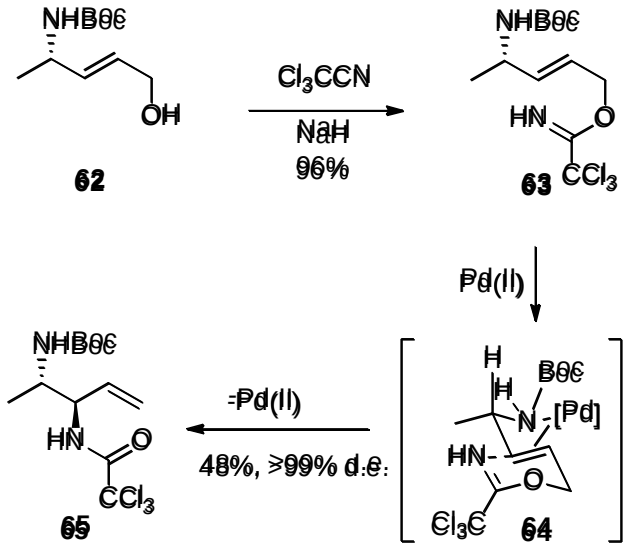


Scheme 24- Highly enantioselective rearrangement of *E*-imidate using COP-hfacac

1.1.1.4 Directed Overman rearrangement

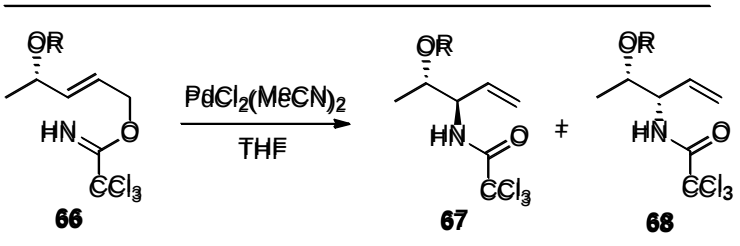
The Overman rearrangement has recently emerged as a highly successful method for diastereoselective synthesis. This is achieved using a directing effect of a side-chain functional group with a metal catalyst. A wide number of easily accessible substrates have a stereogenic centre close to the rearrangement site which can coordinate to the catalyst, resulting in a diastereoselective reaction.

Initially, Bellûs and Ernst reported a directed Overman rearrangement, for a stereoselective synthesis of 1,2-diamines starting from the corresponding chiral Boc protected allylic alcohol **62**, which can be synthesised from α-amino acids.[51] The rearranged product **65** was successfully synthesised in excellent diastereoselectivity utilising coordination of a nitrogen directing group of allylic trichloroacetimidate **63** to the palladium(II)-metal centre (Scheme 25). The Boc protected nitrogen directs the catalyst to the back face of the alkene *via* a chair-like transition state **64**.



Scheme 25- The first ether-substrate directed Overman rearrangement

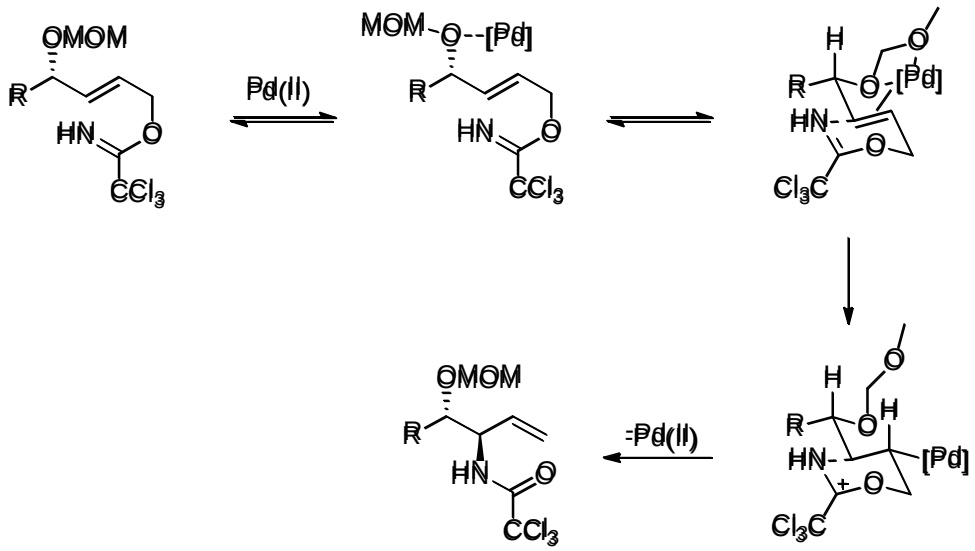
Recent work by Jamieson and Sutherland has demonstrated that allylic trichloroacetimidates **66** can be prepared with a number of different ether groups.[52] They discovered that the bulky, sterically hindered ether groups such as TBDMS, Tr and Bn, prevented efficient coordination to the palladium giving allylic trichloroacetamides **67** and **68** in low diastereoselectivity (Table 2). However, when smaller groups such as methoxymethyl (MOM)-ether were employed it was found that these groups were very effective at directing the facial coordination of the palladium(II)-catalyst. This allowed good yields and high diastereoselectivities.[52,53]



R	Yield (%)	Ratio (67 : 68)
TBDMS	68	2 : 1
Tr	70	3 : 1
Bn	62	3 : 1
Me	49	7 : 1
MOM	**64**	**10 : 1**
MEM	60	8 : 1

Table 2- Rearrangement of allylic trichloroacetimidates with various ether directing groups

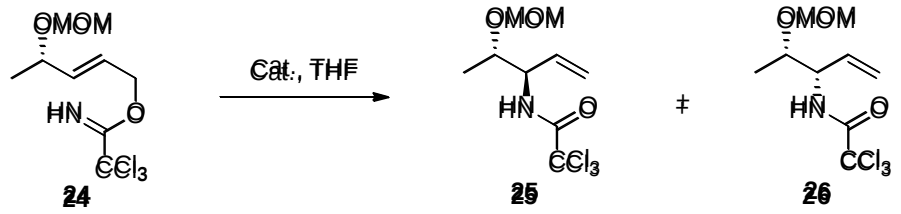
This enhancement of diastereoselectivity was due to the coordination of both oxygen atoms of the MOM group to the palladium catalyst (Scheme 26).[53]



Scheme 26- Coordination of both oxygen atoms to palladium

More recently Sutherland and co-workers expanded this work by utilising a variety of different metal catalysts for the ether-directed Overman rearrangement (Table 3).[29] Their results showed that the diastereoselectivity of allylic trichloroacetamide products **25** and **26** was highest if $PdCl_2(MeCN)_2$, $PdCl_2(PhCN)_2$, PCl_2, $PdBr_2$ or $Pd(OAc)_2$ were used as catalysts in THF. The best results were achieved when the reaction was performed using the $PdCl_2(MeCN)_2$ catalyst. However, no rearrangement was observed when other metal catalysts such as PdI_2, salts of Ni(II), Ru(II) and Hg(II) were used. Rearranged products **25**

and **26** were obtained by treatment of allylic trichloroacetimidate **24** with Pt(II) and Au(III) with no improvement in diastereoselectivity.

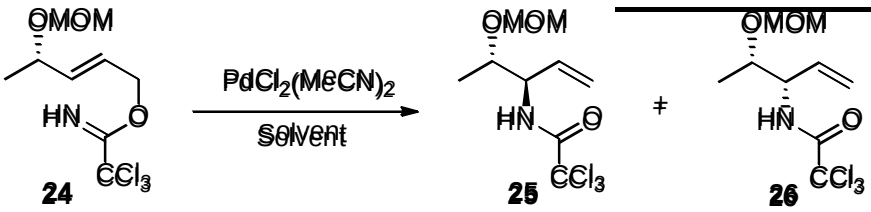


24 **25** **26**

Catalyst	Reaction time (h)	Yield (%)	Ratio (**25** : **26**)
$PdCl_2(MeCN)_2$	**24**	**64**	**10 : 1**
$PdCl_2(PhCN)_2$	24	57	9 : 1
$PdCl_2$	120	45	11 : 1
$PdBr_2$	72	44	9 : 1
PdI_2	---	---	---
$Pd(OAc)_2$	96	18	9 : 1
$NiCl_2$	---	---	---
$Cl_2Ru(PPh_3)_3$	---	---	---
$Hg(OTf)_2$	---	---	---
$PtCl_2$	48	49	10 : 1
$HAuCl_4.2H_2O$	144	49	6 : 1

Table 3- Directed rearrangement of allylic trichloroacetimidate 24 using various catalysts

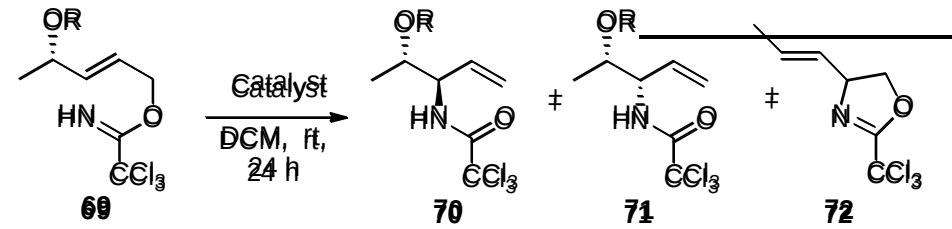
Sutherland and co-workers have also reported that through using non-coordinating solvents, the competition with the MOM-ether group for the coordination of the Pd(II)-catalyst is decreased, thus allowing an increased directing effect of the MOM-ether.[29] A number of different solvents were tested and it was discovered that toluene was the most efficient solvent for this rearrangement (up to 15 : 1 *dr*) (Table 4). This theory was proven when the highly coordinating ionic solvent 1-butyl-3-methylimidazolium tetrafluoroborate was used as a solvent, resulting in a decreased diastereoselectivity (5 : 1 *dr*).



Solvent	Reaction time (h)	yield (%)	Ratio (25 : 26)
THF	24	64	10 : 1
Et_2O	24	47	12 : 1
MeCN	24	32	9 : 1
DCM	24	49	12 : 1
Toluene	**24**	**56**	**15 : 1**
$(BMI)BF_4$	148	37	5 : 1

Table 4- The effect of various solvents upon the directing effect of the MOM group

More recently, in a similar study of metal catalysts for the ether-directed Overman rearrangement, Jaunzeme and Jirgensons found that the diastereoselectivity of δ-methoxy and δ-TBDMSO substituted allylic trichloroacetamides **70** and **71** could be enhanced if $PtCl_2$ was used as a catalyst (Table 5).[28] Their results also showed that oxazoline **72** was formed due to a significant side reaction which reduced the yield of the reaction.



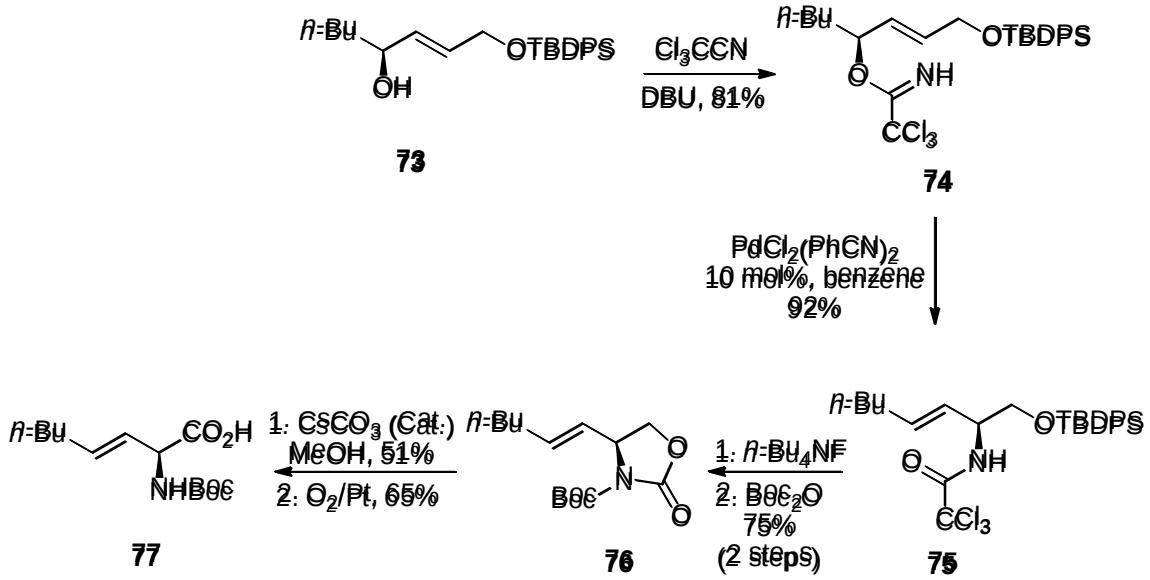
Catalyst	R	yield (% of 70+71)	Ratio (70 : 71)	Ratio (70+71 : 72)
$PtCl_2$	**Me**	**65**	**11 : 1**	**3 : 1**
$PtCl_4$	Me	35	10 : 1	2 : 1
AuCl	Me	48	5 : 1	1 : 1
$AuCl_3$	Me	41	5 : 1	1 : 1
$PdCl_2$	Me	50	8 : 1	2 : 1
$PtCl_2$	**TBDMS**	**85**	**6 : 1**	**8 : 1**
$PtCl_4$	TBDMS	50	6 : 1	10 : 1
AuCl	TBDMS	70	2 : 1	5 : 1
$AuCl_3$	TBDMS	40	2 : 1	5 : 1
$PdCl_2$	TBDMS	62	2 : 1	n.d.

Table 5- Diastereoselective rearrangement of δ-methoxy and δ-TBDMSO-imidates

1.1.1.5 Applications of the Overman Rearrangement

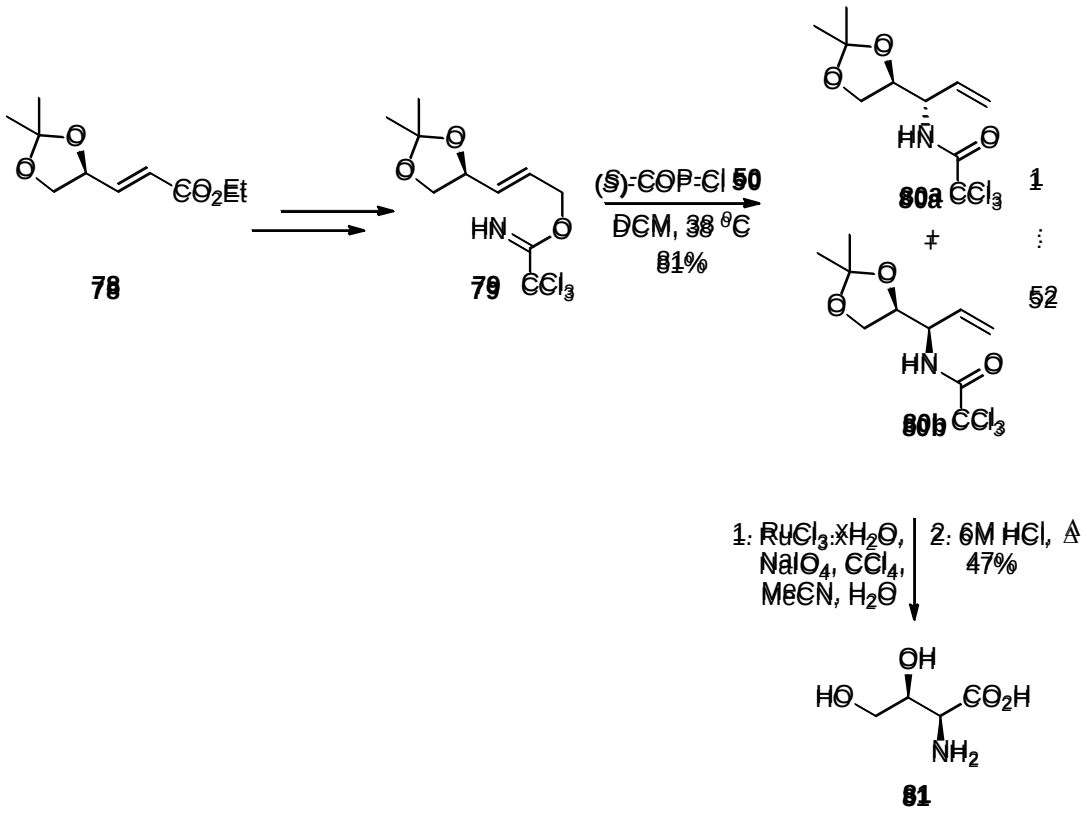
1.1.1.5.1 Applications in Amino Acid Synthesis

Overman rearrangements have found widespread applications in the syntheses of amino acids. Mehmandoust and co-workers have utilised $PdCl_2(PhCN)_2$ to catalyse the rearrangement of allylic trichloroacetimidate **74** to the corresponding allylic amide **75** with successful control of the transfer of chirality from allylic imidate **74** to the new C-N bond (Scheme 27).[54] Cyclisation followed by Boc protection of the resulting amido alcohol **75** gave oxazolidinone **76**. This was followed by a $CsCO_3$ hydrolysis and oxidation to give the desired optically active amino acids **77**.



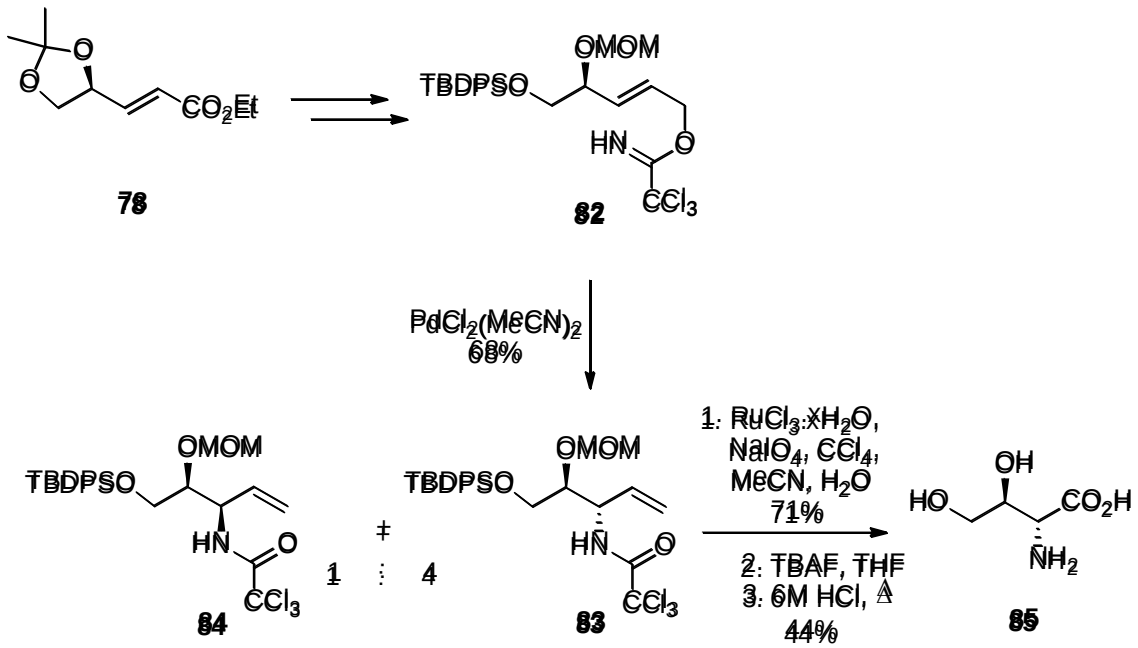
Scheme 27- Synthesis of α,β-unsaturated amino acids using the Overman rearrangement

Recently, Swift and Sutherland have employed the highly diastereoselective Overman rearrangement process for the synthesis of the dihydroxylated α-amino acid **81**.[55] Their approach begun with the commercially available acetonide protected α,β-unsaturated ester **78** which was converted in two steps to allylic trichloroacetimidate **79** (Scheme 28). The Overman rearrangement was then carried out using (*S*)-COP-Cl **50** as catalyst to form the rearranged products **80a** and **80b**. Oxidation of the *threo*-allylic trichloroacetamide **80b** using a protocol reported by Sharpless[56] was followed by deprotection of the amine and dihydroxy groups then to give the amino acid **81**.



Scheme 28- Dihydroxylated α-amino acid synthesis by Sutherland and co-workers

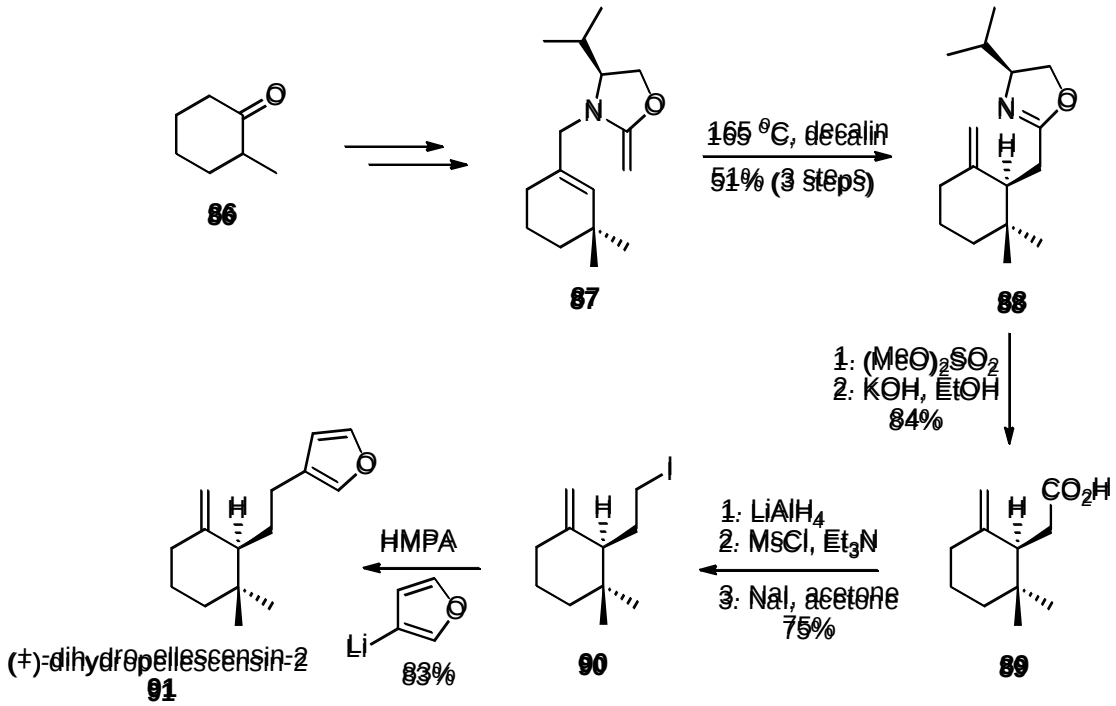
This paper also demonstrated that the directed Overman rearrangement can be used for the synthesis of the natural butyric amino acid **85** (Scheme 29). It was proposed that the acetonide protecting group of compound **78** should be replaced with a more stable protecting group such as TBDPS. Cleavage of the acetonide protecting group under standard conditions, allows the opposite 2*R*-stereocentre of the butyric acid isomer **85** to be selectively synthesised. Their results showed that $PdCl_2(MeCN)_2$ was the most efficient metal catalyst for the Overman rearrangement of allylic trichloroacetimidate **82**. Unfortunately, the diastereoselectivity of this reaction was disappointing in a 1 : 4 ratio, this is due to the presence of the bulky TBDPS group attached at the primary alcohol. This group prevents the effective coordination of both MOM-ether oxygen atoms to the metal catalyst. In a similar synthetic route to that used for the synthesis of substrate **81**, the desired amino acid **85** was achieved from allylic acetamide **83**.



Scheme 29- Synthesis of butyric amino acid using a substrate directed rearrangement

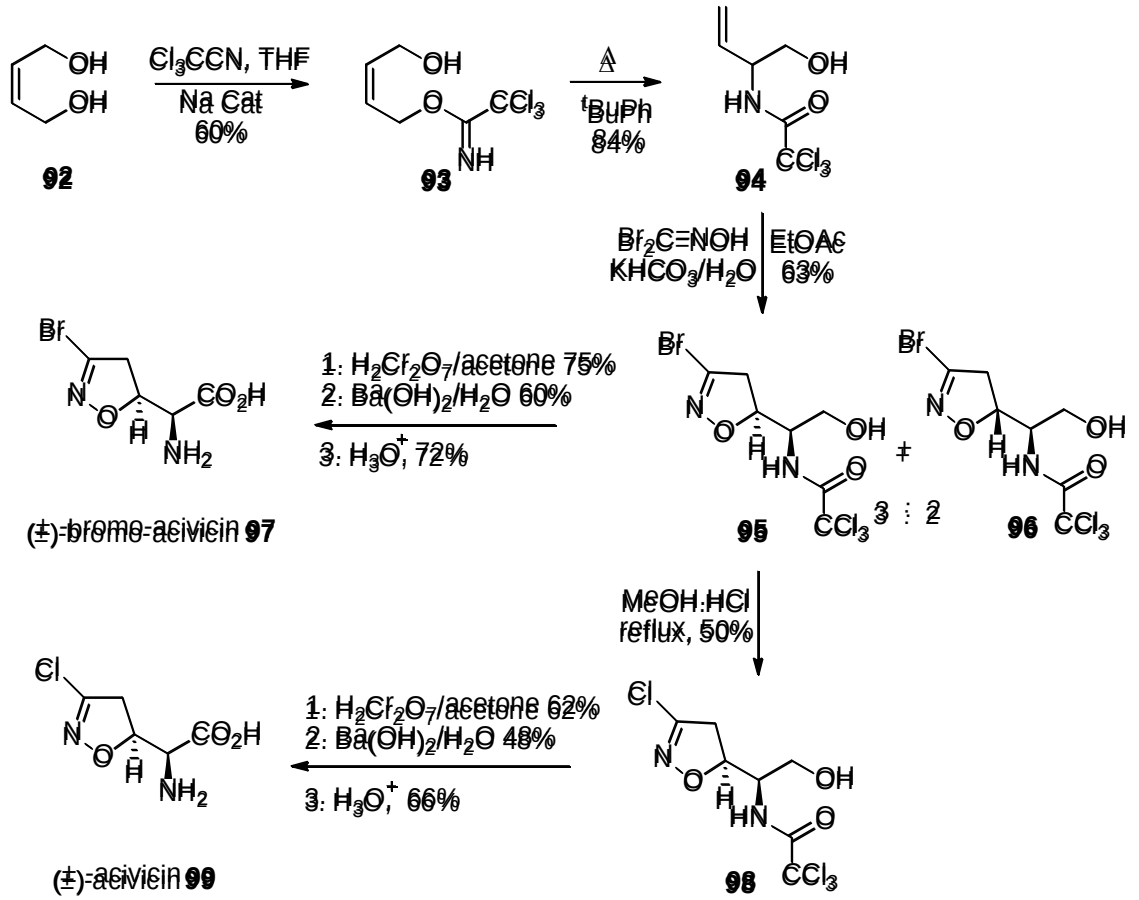
1.1.1.5.2 Applications in Natural Product Synthesis

Kurth and Soares have utilized *N*-allyl ketene *N*,*O*-acetals as chiral auxiliaries of the aza-Claisen rearrangement.[57] These auxiliaries provide absolute stereocontrol of the (*S*)-configuration at C-1 for the synthesis of the natural product, (+)-dihydropellescensin-2 **91**. The total synthesis of compound **91** was achieved from the simple starting material 2-methylcyclohexanone (**86**) (Scheme 30), which was converted in several steps to *N*-allylketene *N*,*O*-acetal **87**. Thermal aza-Claisen rearrangement was then carried out in decalin to give **88** in moderate yield as the major product. A two step *N*-methylation followed by base-catalysed hydrolysis led to formation of cyclohexaneacetic acid **89**. After the successful synthesis of **89**, attention was focused on introducing the furan ring. Reduction of **89** gave the corresponding alcohol which was readily converted to iodide **90**. Finally, spontaneous coupling with 3-lithiofuran gave the target compound **91**.



Scheme 30- Kurth synthesis of (+)-dihydropellescensin-2

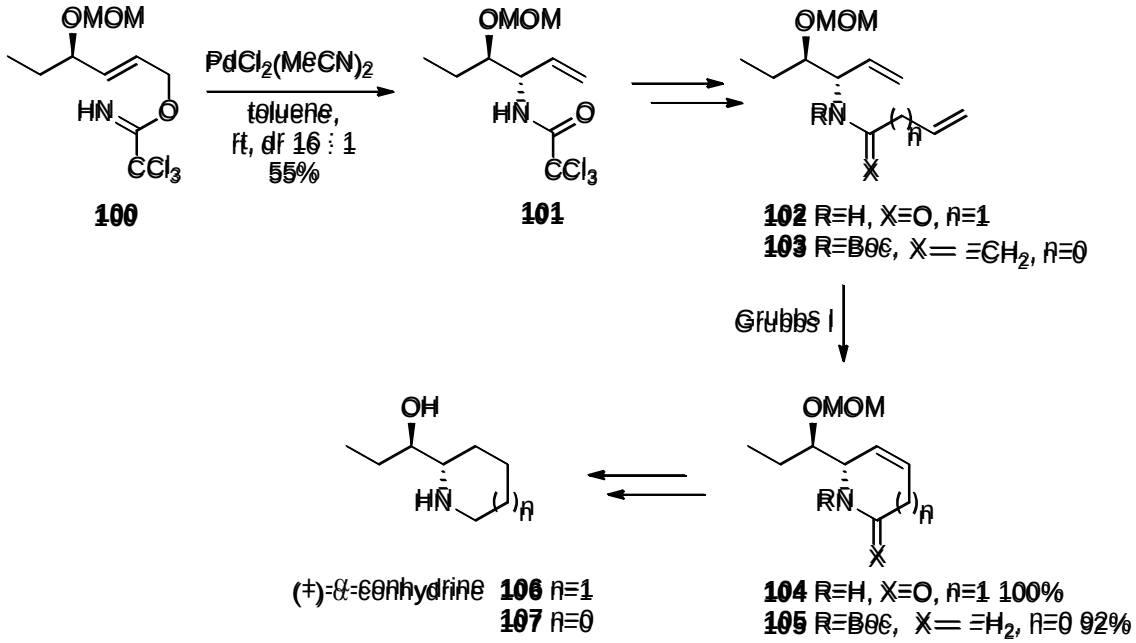
The thermal Overman rearrangement has been utilised for the synthesis of many different drug molecules including those with antitumor and antimetabolite properties. In addition to this, the natural products (±)-acivicin **99** and (±)-bromo-acivicin **97** have also been synthesised. An early synthesis of these natural products was reported by Vyas and co-workers in 1984.[58] The allylic trichloroacetamide **94** was synthesised over two steps from the commercially available diol **92**, which was subsequently converted to a 3 : 2 mixture of cycloadducts **95** and **96** respectively (Scheme 31). The *threo* isomer **95** was then subjected to Jones oxidation followed by removal of the trichloroacetyl group to give the natural product (±)-bromo-acivicin **97**. Substitution of bromine with chlorine in compound **95** gave chloro-alcohol **98**. Once again Jones oxidation followed by removal of the trichloroacetyl group gave the other natural product (±)-acivicin **99**.



Scheme 31- Synthesis of (±)-acivicin and (±)-bromo-acivicin

1.1.1.5.3 Applications in Alkaloid Synthesis

The Overman rearrangement has also found wide application in the synthesis of alkaloids. Jamieson and Sutherland utilised the MOM-ether directed, palladium-catalysed Overman rearrangement as the key step for the synthesis of the alkaloid, (+)-α-conhydrine **106** and its pyrrolidine analogue **107** (Scheme 32).[59] In this approach, the allylic trichloroacetimidate **100** was converted to the corresponding allylic trichloroacetamide **101** in a highly efficient diastereoselective rearrangement. The *erythro*-allylic amide **101** was converted to dienes **102** and **103** in a few steps, followed by ring closing metathesis to give heterocycles **104** and **105** in excellent yield. These were then further functionalised to complete the synthesis of (+)-α-conhydrine **106** and its pyrrolidine analogue **107**.



Scheme 32- Synthesis of (+)-α-conhydrine using a directed Overman rearrangement

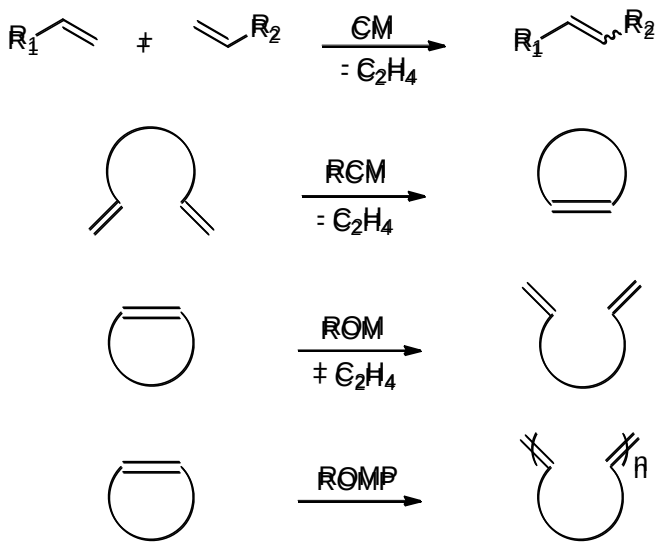
1.1.1.6 Conclusions to the Overman rearrangement

The Overman rearrangement is one of the most important transformations in organic synthesis and has stimulated the interest of many organic chemists. This process can be carried out either thermally or catalytically using complexes of soft metal salts such as Hg(II), Pd(II), B(III), Au(I) and Pt(II) at low temperature. It has been widely used for the synthesis of nitrogen-containing compounds, especially for amino acids, amino sugars, and other complex natural products. Efforts have also focused on developing an asymmetric Pd(II)-catalysed Overman rearrangement using chiral palladium catalysts such as COP-Cl catalyst. Alternatively, the MOM-ether directed Overman rearrangement has been extensively employed utilising non-coordinating solvents to enhance the diastereoselectivity of the reaction.

The first part of the research in this thesis will detail efforts to utilise the palladium-catalysed Overman rearrangement for the attempted production of carbocyclic nucleosides and the total synthesis of (+)-physoperuvine. The ether-directed Overman rearrangement will be described for the highly efficient synthesis of (+)-monanchorin as well as clavaminol A, C and H.

1.2 Olefin Metathesis

Olefin metathesis has become one of the most important C=C bond forming methodologies and has now found extensive use in organic synthesis and polymer sciences. Although the origin of the word metathesis comes from the Greek “metathesis” which means change of position or transposition, it was first used to describe this reaction by Calderon in 1967.[60] In mid-1950’s, Eleuterio and co-workers reported the first catalysed metathesis reactions.[61] They reported that the heating of propene with the molybdenum metal or its oxide led to ethylene and 2-butene formation. The main olefin metathesis reactions can be utilised in several closely related reaction types (Scheme 33).[62-64]

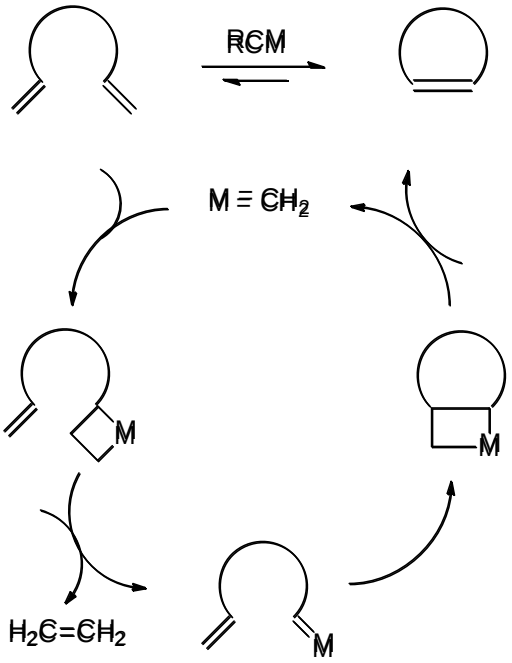


Scheme 33- Some of the most common types of olefin metathesis reactions

1.2.1 Ring Closing Metathesis Reaction

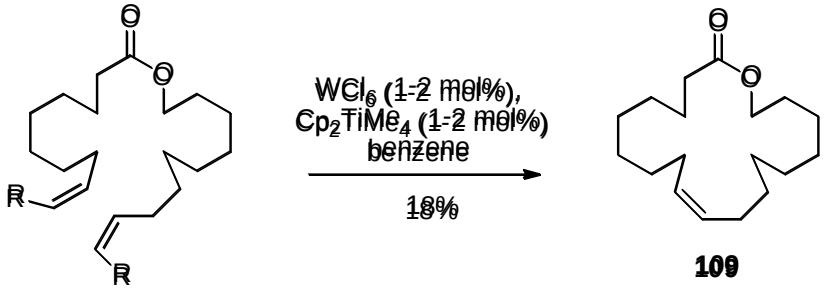
The ring closing metathesis (RCM) reaction is one of the most important among the olefin metathesis reactions, it is well known as a powerful and reliable methodology for the construction of carbocyclic and heterocyclic ring systems by the formation of new C=C bonds in an intramolecular process. In 1970, Chauvin suggested a basic catalytic cycle as the mechanism of this unusual C-C bond forming reaction.[65] It was known as the ‘carbene mechanism’ which involved the fragmentation of the olefin *via* a series of alternating [2+2]-cycloadditions and cycloreversions. The driving force for this transformation is the release of the highly volatile gas ethylene (Scheme 34). Subsequent studies by Grubbs, Schrock and Chauvin have led to highly efficient ruthenium, molybdenum and tungsten

catalysts for the metathesis process, and this work was awarded the Nobel Prize for Chemistry in 2005.[66]



Scheme 34- Basic Chauvin mechanism for ring closing metathesis

The first example of ring closing metathesis was reported by Tsuji,[67] who synthesised several macrocycles similar to **109** from oleic acid and oleyl alcohol. The cyclisation was based on the ring closing metathesis reaction of substrate **108** using tungsten-based catalysts (Scheme 35).



Scheme 35- First ring closing metathesis by Tsuji

The ring closing metathesis reaction can be utilised successfully in a tandem process with other transformations including Claisen rearrangements,[68] aza-Michael reactions,[69] isomerisations,[70] dehydrogenation-hydrogenation reactions,[71] Diels-Alder reactions,[72] Kharasch additions[73] and dihydroxylations.[74] This versatility is due to the stability of ruthenium-based catalysts and their excellent tolerance towards many functional groups. Synthetically, the RCM reaction is considered versatile, easy to carry out and friend to

environment. It can be applied to a broader number of substrates under quite mild conditions, allowing the preparation of both small and large sized rings (from 5 up to 30 membered ring) often in excellent yields.[75-77]

1.2.1.1 Ring Closing Metathesis using Transition Metal Catalysts

Transition metals are important in modern organic synthesis, often playing crucial roles in the total synthesis of many natural products.[78] The first metal carbene catalyst was reported by Katz in 1976 who demonstrated that complex **110** could initiate the metathesis process albeit at a low rate with a variety of di- and tri-substituted cycloalkenes, with both *E*- and *Z*-2-pentenes (Figure 2).[79-82] At the same time, Schrock and co-workers reported a study showing that high oxidation state metal alkylidene complexes successfully underwent olefin metathesis.[83-85] Unfortunately, these catalysts are incompatible with a number of functional groups and are unstable to air and moisture. This was followed by work by Grubbs and co-workers who developed a number of ruthenium-carbene complexes such as Grubbs first-generation **111**, Grubbs second-generation **112** and Grubbs third-generation **113** catalysts (Figure 2).[86-90] In contrast to other olefin metathesis catalysts, these complexes are more stable than tungsten and molybdenum complexes and can tolerate other functional groups in the alkene. They are also compatible with a large variety of solvents. Additionally, these commercially available catalysts can be prepared from a wide range of different alkyl- and aryldiazoalkane compounds. Extensive studies by Grubbs have shown that Grubbs 1st generation **111** and Grubbs second-generation **112** catalysts can be utilised for the formation of cycloalkenes of almost any ring size ≥5, including medium sized and macrocyclic products.[88,90] Furthermore, Grubbs second-generation catalyst **112** is a highly active catalyst for a wide variety of olefin cross-metathesis reactions,[92] including those with sterically demanding and electron-deficient olefins.[92-96]

In another significant contribution to the ruthenium-based metathesis field, the Hoveyda group synthesised isopropoxystyrene-coordinated catalyst **114** (Figure 2). This catalyst is thermally stable and can efficiently catalyse the RCM of dienes containing terminal olefins and enables the formation of various tri- and tetra-substituted olefins at low temperatures in high yields.[97] They also showed that the heterocyclic ligand significantly enhances the catalytic activity, and the styrenyl ether allows the easy recovery of the ruthenium complex.

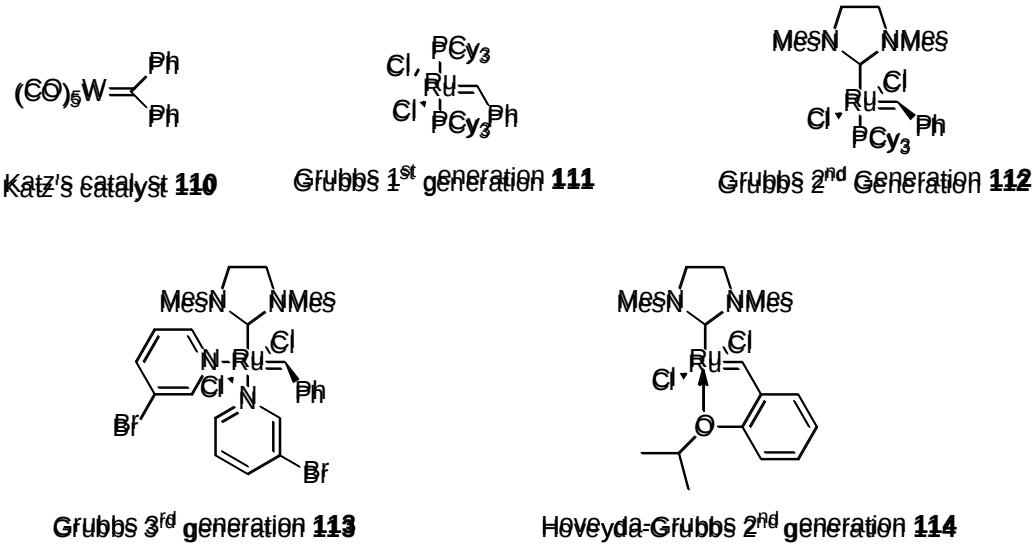
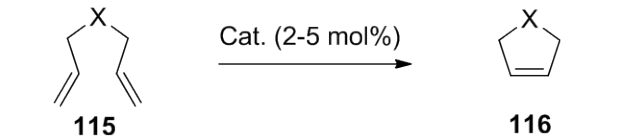
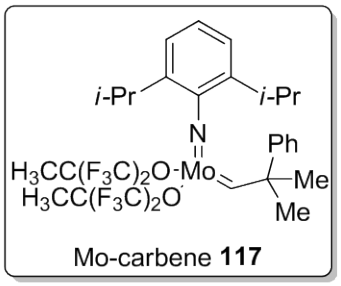


Figure 2- Common ruthenium carbene complexes used in the RCM reaction

In 1992, Grubbs and Fu reported the first exploitation of a RCM reaction for the formation of five-membered unsaturated heterocycles and carbocycles **116** from dienes **115** using molybdenum **117** and ruthenium **118** carbene catalysts (Table 6).[98-101] This study also showed the formation of six- and seven-membered tri- and tetra-substitiuted cyclic olefins.



X	Catalyst **117**		Catalyst **118**	
	Time (h)	Yield (%)	Time (h)	Yield (%)
O	1	99	1	99
NH	24	82	-	-
$NCOCF_3$	-	-	1	93
NOt-Bu	-	-	1	91
NBn	3	92	-	-
NBoc	-	-	1	93
CH(OTBS)	0.5	91	2	85
S	1	99	-	-
S-S	1	77	-	-



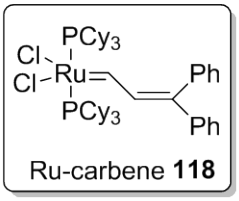
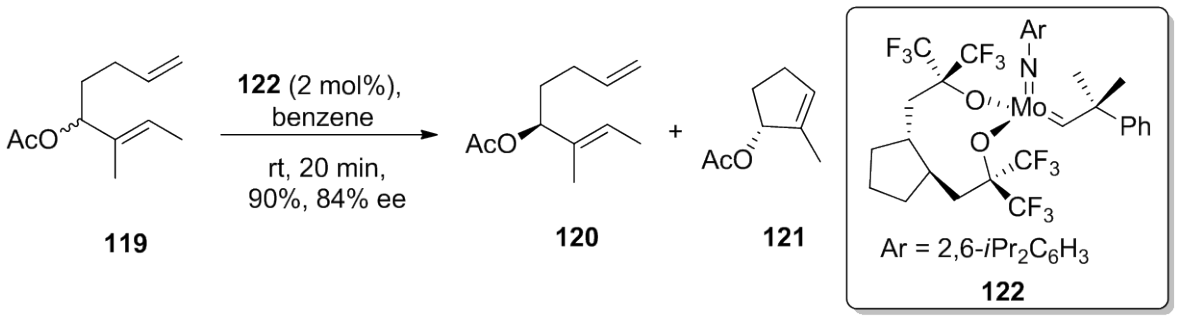


Table 6- Synthesis of cycloalkenes using ring closing metathesis

In a comprehensive kinetic study, Grubbs and Fujimura reported the first asymmetric ring closing metathesis reaction for the synthesis of disubstituted cyclopentenes of the type **121** using the chiral molybdenum alkylidene catalyst **122** (Scheme 36).[102] Results from this study showed that dienes which contain a trisubstituted olefin moiety such as **119** are the preferred substrates as they can slow the cyclisation step and also control the site of first

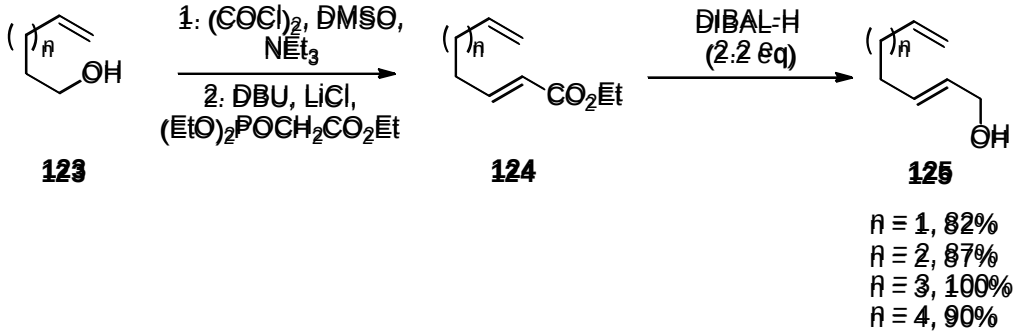
metathesis leading to a kinetic resolution. Additionally, the 6-membered ring can be also prepared; however the yield and selectivity were moderate.



Scheme 36- The first example of asymmetric ring closing metathesis

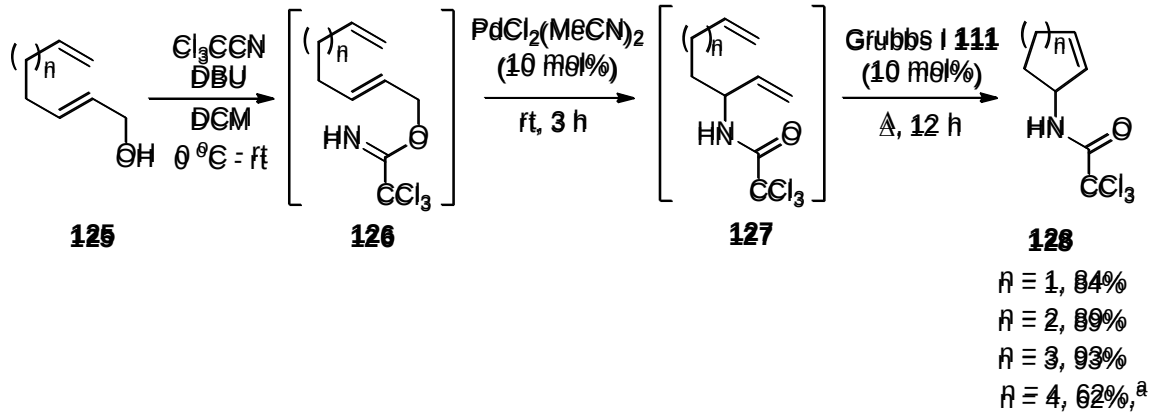
1.2.1.2 Applications of Ring Closing Metathesis Reactions

Previous work by the Sutherland group reported a one-pot tandem Overman rearrangement and ring closing metathesis reaction for the synthesis of 5-, 6-, 7- and 8-membered cyclic allylic trichloroacetamides **128**.[103] In order to conduct such chemistry, a synthetic route to allylic alcohols **125** was required. The corresponding allylic alcohols were rapidly synthesised in two steps from the commercially available alcohols **123** (Scheme 37). The synthesis begins utilising a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction to give *E*-α,β-unsaturated esters **124**. Subsequent reduction of these esters using DIBAL-H gave allylic alcohols **125** in excellent yield.



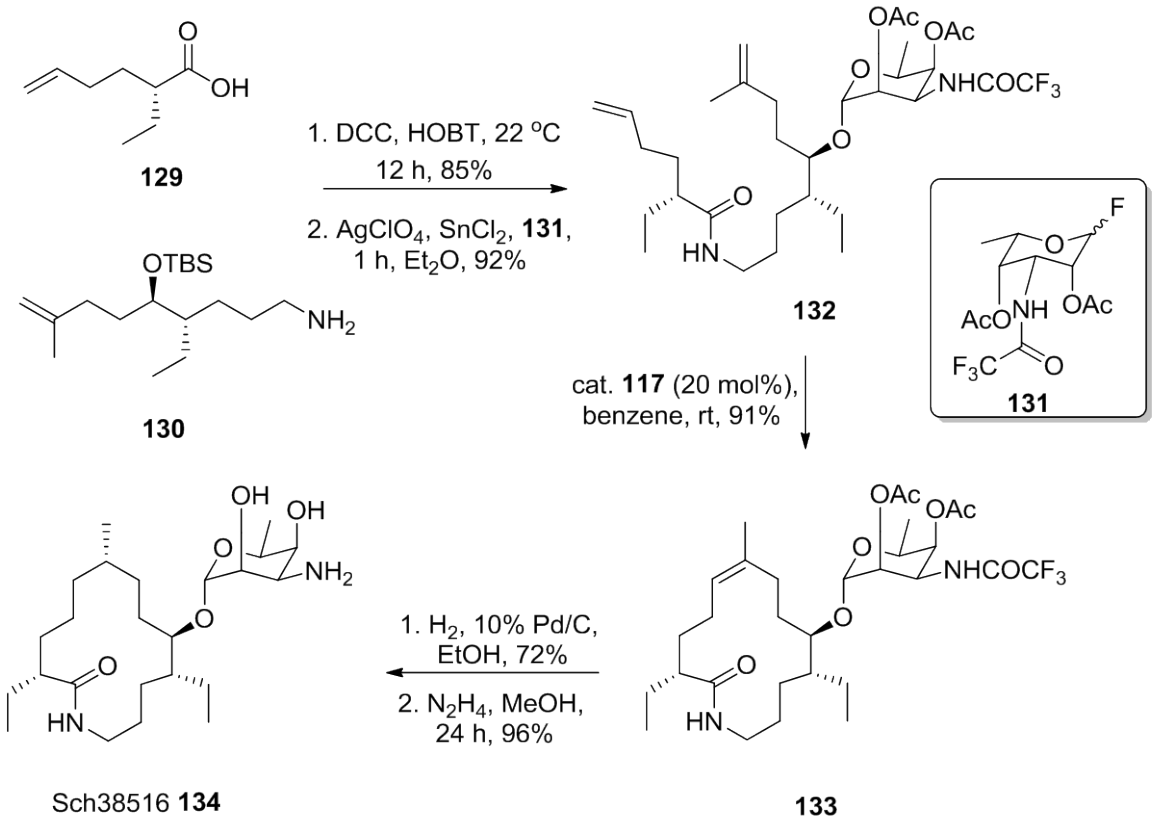
Scheme 37- Synthesis of *E*-allylic alcohols

The allylic alcohols **125** were then converted to the desired allylic trichloroacetimidate substrates **126**, using trichloroacetonitrile and a catalytic amount of DBU (Scheme 38). Allylic trichloroacetamidates **126** were then subjected to a one-pot tandem process involving an Overman rearrangement with bis(acetonitrile)palladium(II) chloride catalysis to give allylic trichloroacetamides **127**. This was followed by a ring closing metathesis reaction using Grubbs 1st generation catalyst **111**. This provided the desired cyclic allylic trichloroacetamides **128** in good to excellent yields.



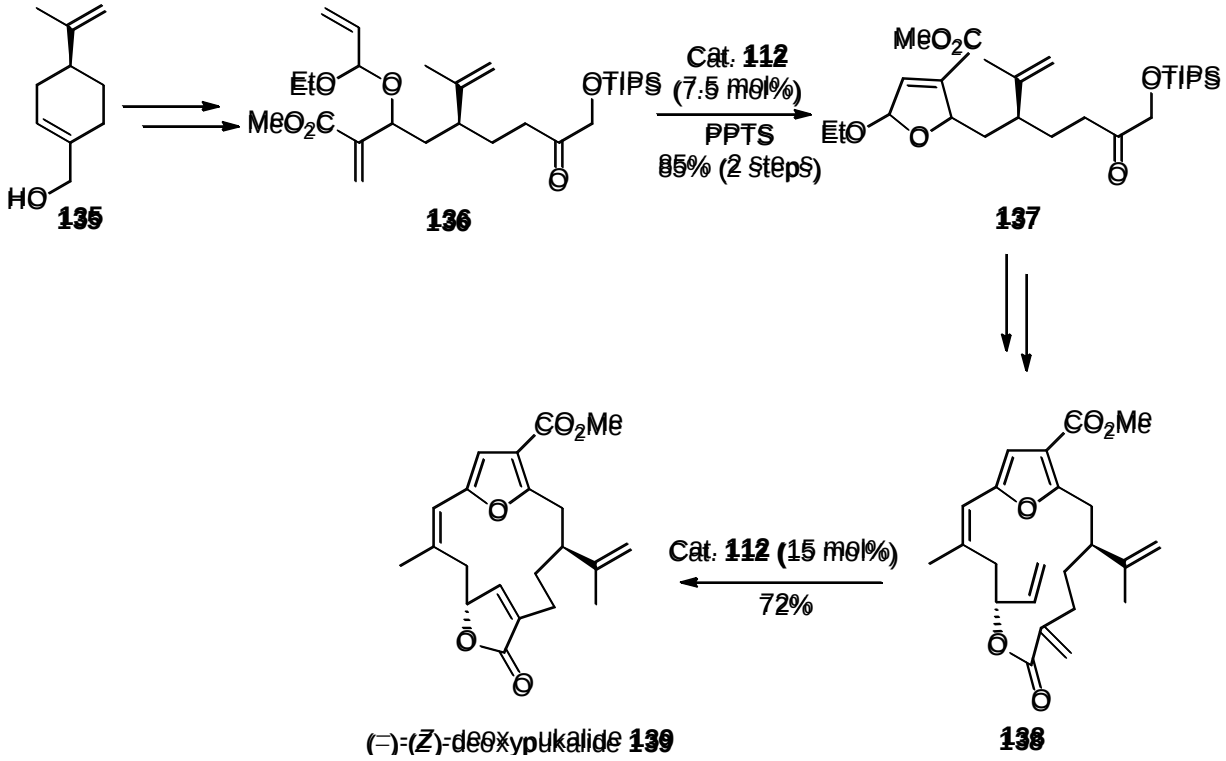
Scheme 38- Synthesis of 5-, 6-, 7- and 8-membered rings using a tandem process ([a]Grubbs 2nd generation catalyst 112 was used for the RCM step)

Hoveyda and co-workers have reported the use of the catalytic ring closing metathesis reaction as a crucial part of the enantioselective synthesis of fluvirucin, Sch38516 **134**, a natural product that has potent biological activity against the influenza A virus and also possesses antifungal activity.[104] The synthesis includes a convergent asymmetric synthesis of acid **129** and amine **130** which were synthesised from commercially available dihydrofuran and 3-methyl-3-buten-1-ol, respectively over several steps (Scheme 39). Fragments **129** and **130** were coupled and this was followed by a diastereoselective glycosylation with perfluoroglycoside **131** to give compound **132**. Compound **132** was then subjected to ring closing metathesis using Schrock catalyst **117** to generate the macrocycle **133** in high yield. The stereocontrolled hydrogenation of **133** was followed by the removal of the acetate and trifluoroacetate groups and completed the synthesis of fluvirucin B_1 **134** in high yield.



Scheme 39- Synthesis of fluvirucin *via* a RCM reaction

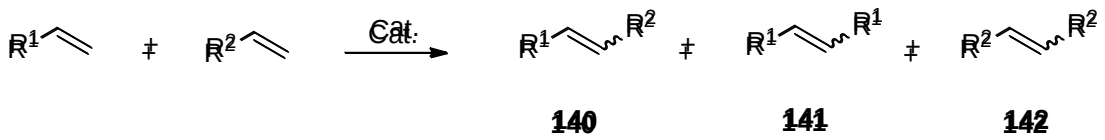
Recently Donohoe and co-workers have utilised double ring closing metathesis reactions for the synthesis of the natural product, (–)-(*Z*)-deoxypukalide **139**.[105] (–)-(*Z*)-Deoxypukalide **139** belongs to a family of marine natural products which have exhibited a wide range of biological activities including neurotoxicity, anti-inflammatory effects and anti-feedant properties. The synthesis started with the commercially available (*S*)-perillyl alcohol **135** which was converted to the mixed acetal **136** in four steps (Scheme 40). The first ring closing metathesis was performed on compound **136** to give **137** which was then subjected to several transformations to form lactone **138**. Lactone **138** was then subjected to the second ring closing metathesis to complete the synthesis of the target compound **139** in good yield.



Scheme 40- Synthesis of (–)-(*Z*)-deoxypukalide using a double RCM reaction

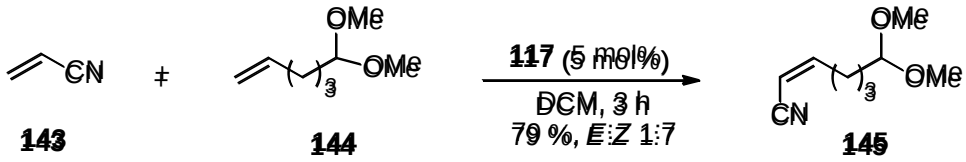
1.2.2 Cross-metathesis Reaction

The cross-metathesis reaction can also be described as the intermolecular coupling between two different olefins and can potentially yield three new types of alkene: one desired heterodimeric product **140** and two undesired homodimeric products **141** and **142** (Scheme 41). The cross-metathesis reaction has been described as a less important process than the ring closing metathesis reaction in the application of organic chemistry, this is because it is less effective and less selective.[106] However, some cross-metathesis substrates (e.g. unsaturated boranes, stannanes and halides) are generally easier and less expensive to prepare than those associated with other common catalytic C-C bond forming reactions. This reaction can tolerate a wide variety of functional groups in very low catalyst loadings (1-5 mol%) under mild conditions in relatively short reaction times and also a high degree of chemo-, regio-, and stereoselectivity can be achieved. In addition to this, the olefinic products are suitable for further structural elaboration such as hydrogenation, epoxidation, halogenation and cycloaddition.



Scheme 41- Cross-metathesis and its potential by-products

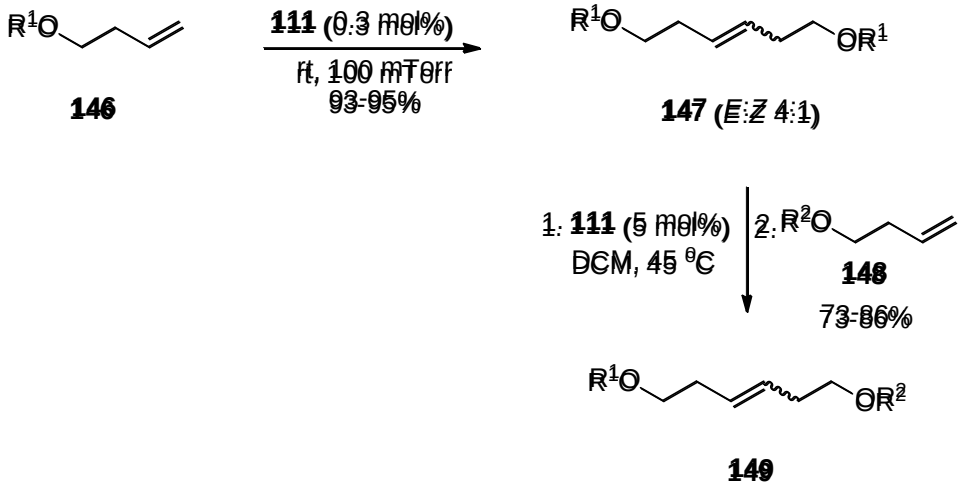
An early report of this reaction was described by Crowe and co-workers,[107] who reported that a highly selective cross-metathesis product **145** can be prepared using molybdenum catalyst **117** when π-substituted terminal alkenes such as acrylonitrile **143** were treated with an alkene which possesses a small, electron rich and non-conjugated substituent such as **144** (Scheme 42). The use of this olefin partner confers an additional advantage; it is the least expensive reagent conceivable for the introduction of a nitrile functionality into organic molecules.



143 **144** **145**

Scheme 42- Selective cross-metathesis by Crowe

Further studies reported by Grubbs and co-workers suggested a new methodology for selective cross-metathesis.[108] In a two step procedure, various desired cross-metathesis products **149** were synthesised with minimal amounts of competing dimerisation (self-metathesis) products. Firstly homodimerisation of a terminal olefin **146** in a cross-metathesis reaction using Grubbs 1st generation catalyst **111** provided mostly *trans* (4:1) disubstituted olefins **147** in high yields (Scheme 43). Homodimers **147** were subsequently treated in excess with a second terminal olefin **148** to give cross coupled products **149** in good yields.



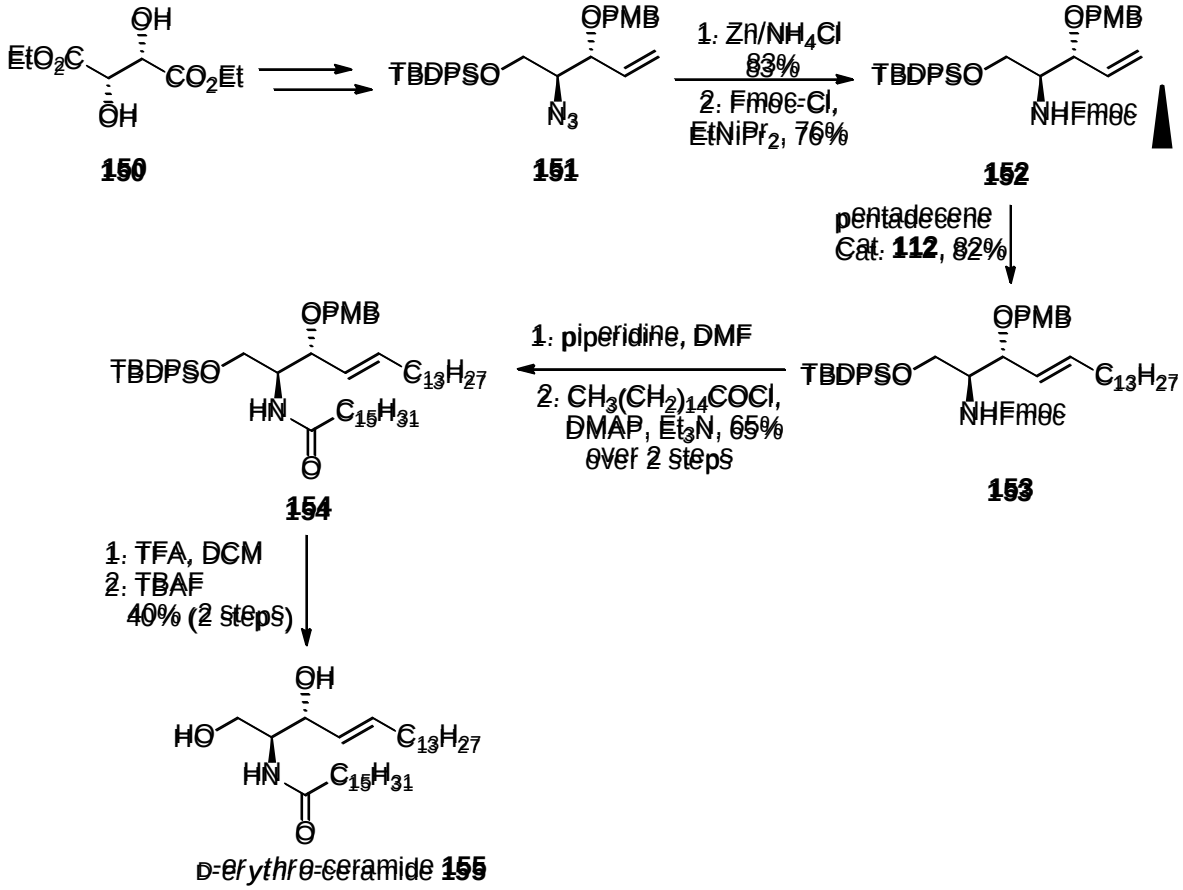
146 **147** (*E*:*Z* 4:1) **148** **149**

Scheme 43- Two-step selective cross-metathesis

1.2.2.1 Applications of Cross-metathesis Reactions

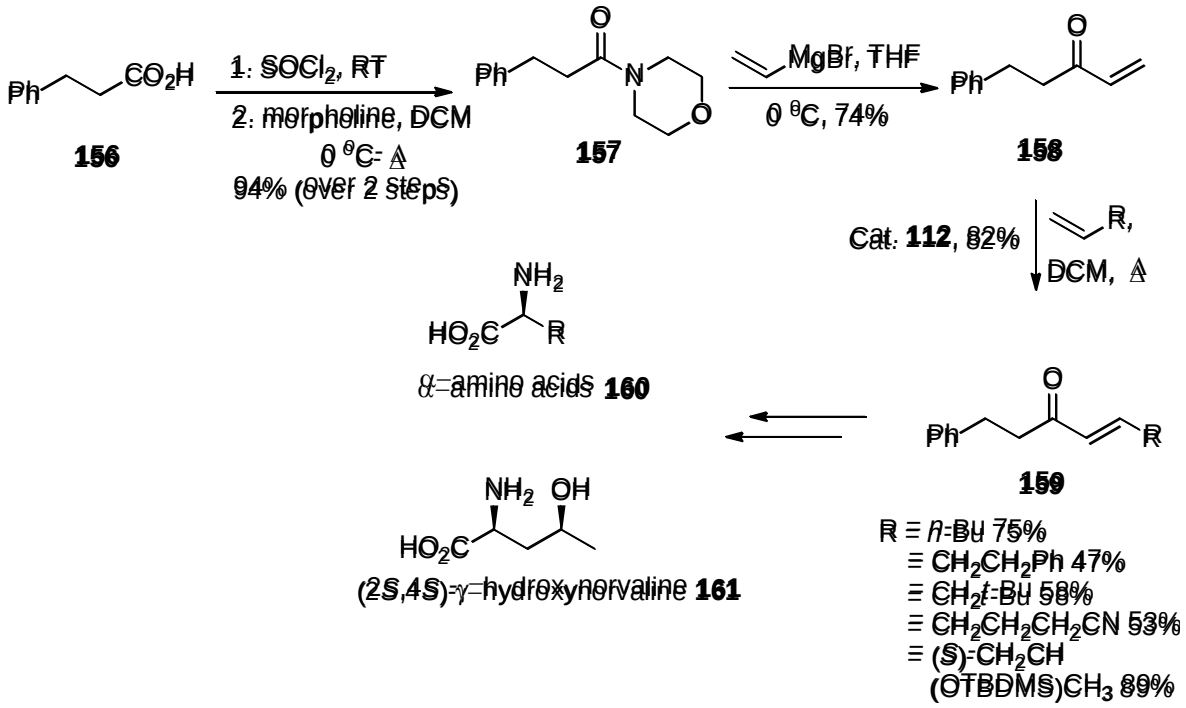
Recently, cross-metathesis reactions have been effective in the synthesis of natural products and fragrance compounds.[109]

In 2004, Basu and Rai utilised the cross-metathesis reaction as the key step for the synthesis of the natural product, D-*erythro*-ceramide **155**.[110] D-*erythro*-Ceramide **155** was found to be a crucial component of lipid rafts and influences cell signalling events at the membrane. It also participates in a variety of activities in the cellular life cell, including growth, differentiation and even programmed death.[111] The synthesis started from commercially available (–)-D-tartrate **150** which underwent nine transformations to give the building block **151** (Scheme 44). Compound **151** was reduced to the corresponding amine and protected as the Fmoc carbamate **152**. *E*-Selective cross-metathesis of **152** with pentadecene was then achieved in high yield using Grubbs 2nd generation catalyst **112** to give coupled product **153**. Removal of the Fmoc group, followed by acylation`gave the fully protected ceramide **154**. Finally removal of the PMB and TBDMS groups gave the desired natural product, D-*erythro*-ceramide **155**.



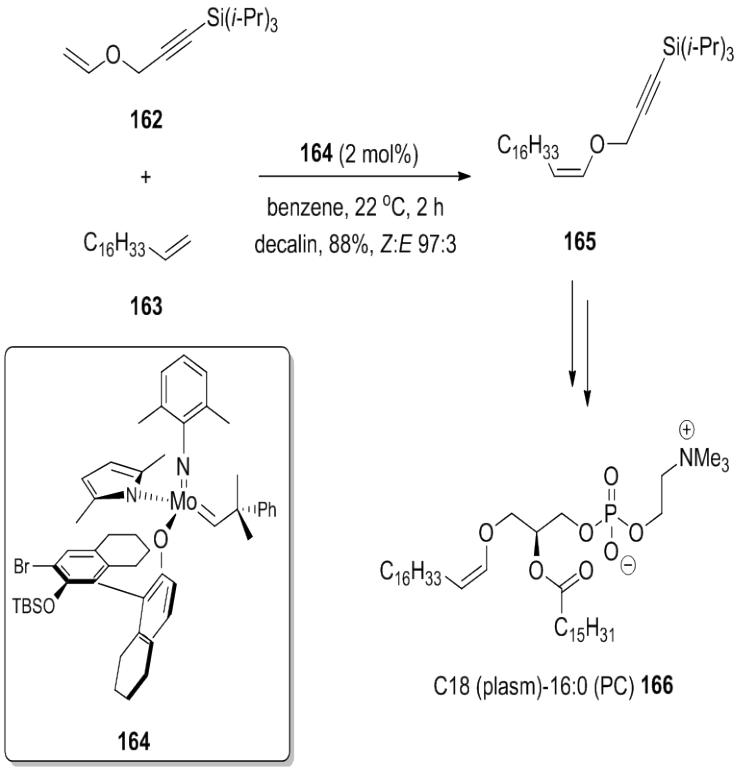
Scheme 44- Synthesis of D-*erythro*-ceramide *via* a cross-metathesis reaction

More recently, Sutherland and Drummond utilised a ruthenium catalysed cross-metathesis reaction as one of the key steps in the synthesis of optically active α-amino acids.[112] These α-amino acids were found to be important structural building blocks for a variety of biological applications. The well selected starting material, hydrocinnamic acid **156** was converted to the morpholine amide **157** which was treated with vinylmagnesium bromide to give the first cross-metathesis partner **158** (Scheme 45). Vinyl ketone **158** was then subjected to a cross-metathesis reaction using a series of terminal alkenes to introduce the cross coupled compounds **159**. *E*-Alkenes **159** were then successfully converted to the desired α-amino acids **160** and (2*S*,4*S*)-γ-hydroxynorvaline **161** in several steps.



Scheme 45- Synthesis of α-amino acids using a cross-metathesis reaction

Further utilisation of the cross-metathesis reaction was reported by Hoveyda and co-workers in 2011.[113] They synthesised an anti-oxidant plasmalogen phospholipid, C18 (plasm)-16:0 (PC) **166** which is found in electrically active tissues and is implicated in Alzheimer's disease. As shown in Scheme 46, the highly stereoselective product **165** was easily achieved by the cross-metathesis reaction of enol ether **162** and commercially available 1-octadecene (**163**) using catalyst **164**. Stereoisomerically pure *Z*-**165** was then subjected to several transformations to complete the synthesis of the target compound **166**.



Scheme 46- Synthesis of plasmalogen phospholipid by Hoveyda and co-workers

1.2.3 Conclusions to the Olefin Metathesis Reactions

Olefin metathesis reactions such as ring closing metathesis and cross-metathesis are considered a fundamentally important class of reactions in chemical synthesis. These processes have emerged as powerful C-C bond forming reactions and are widely used in organic synthesis. Extensive efforts to improve the metal carbene catalysts has led to the development of Mo-carbene and Ru-carbene complexes. These in turn have led to new applications in these processes. The intramolecular ring closing metathesis reaction is the most commonly known reaction and can be achieved under mild conditions using Grubbs 1st generation catalyst, providing an efficient synthetic method for making various ring sizes. Excellent results for the development of the intermolecular metathesis have also been achieved.

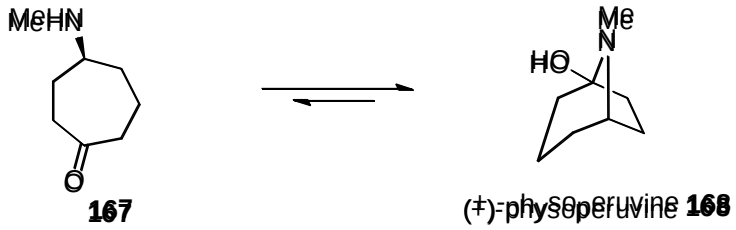
The second part of the research programme described in this thesis will strive to utilise a ring closing metathesis reaction for the synthesis of carbocyclic nucleosides and the complete synthesis of (+)-physoperuvine. The RCM works in a highly efficient manner and in excellent yields using a tandem process for the synthesis of 5- and 7-membered

rings, as the key steps. This thesis will also describe the cross-metathesis reaction as the key step for the synthesis of (+)-monanchorin.

2.0 Results and Discussion

2.1 (+)-Physoperuvine

(+)-Physoperuvine **168** is a bicyclic, tropane alkaloid which was first isolated from the leaves and roots of the Indian plant *Physalis peruviana* Linne by Ray and co-workers in 1976 (Scheme 47).[114] Early chemical and spectroscopic investigations identified the structure as 3-(methylamino)cycloheptanone **167**.[114,115] Analysis using both CD and NMR spectroscopy and the development of a racemic synthesis showed that the monocyclic amino ketone **167** is in equilibrium with the bicyclic tautomer **168**, and is known to exist almost entirely in this form.[116,117] This natural product exhibits a variety of biological activities having antiviral, antifungal and antibacterial properties.

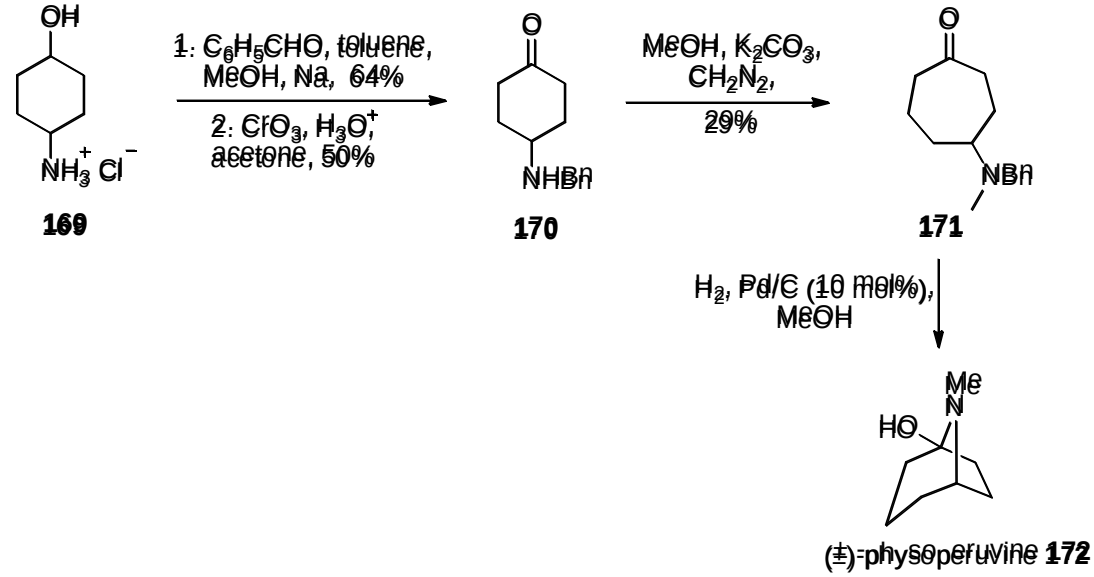


167 (+)-physoperuvine **168**

Scheme 47- Structure of (+)-physoperuvine

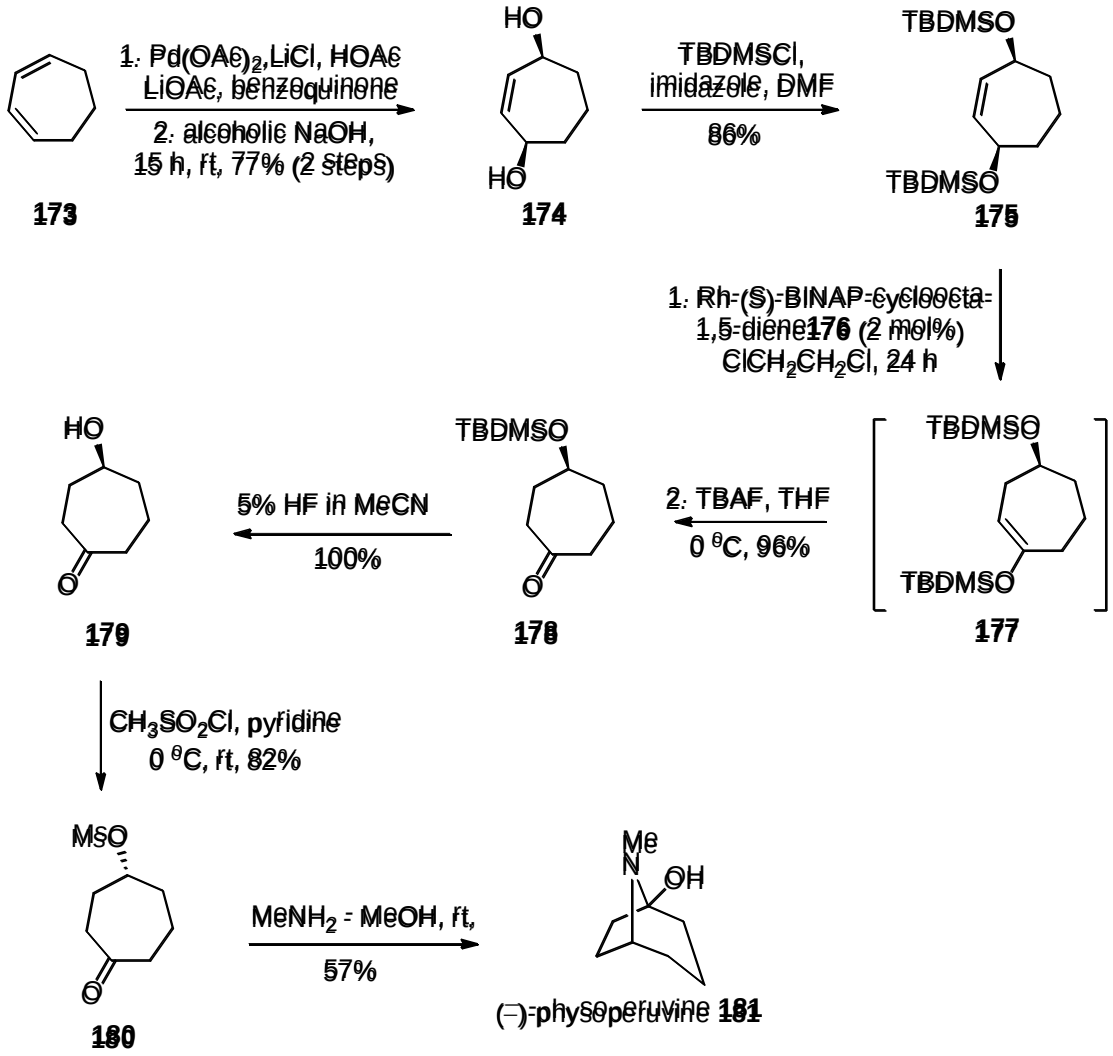
2.1.1 Previous Syntheses of Physoperuvine

An early synthesis of racemic (±)-physoperuvine **172** using an intramolecular cyclisation of the seven-membered ring **171** was reported by Lallemand and co-workers in 1992 (Scheme 48).[118] The synthesis began with the conversion of the commercially available 4-aminocyclohexanol hydrochloride **169** to the corresponding cyclohexanone **170** followed by ring enlargement using diazomethane to give aminocycloheptanone **171**. Finally removal of the benzyl protecting group under standard conditions yielded the desired product **172**.



Scheme 48- Synthesis of racemic physoperuvine 172 by Lallemand and co-workers

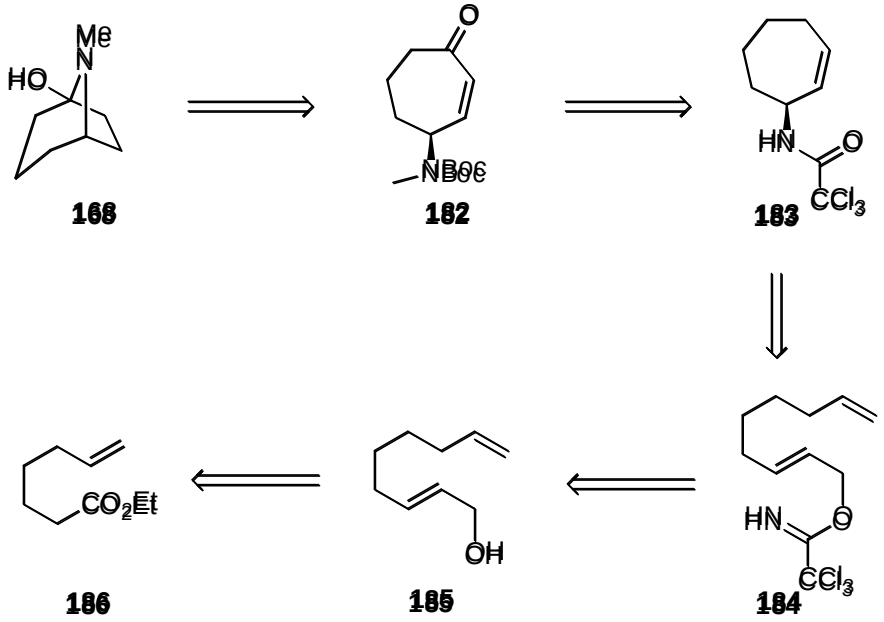
Later in 1995, in a study expanding the scope of their Rh-BINAP asymmetrisation reaction, Ogasawara and Hiroya reported the first asymmetric synthesis of (–)-physoperuvine **181**.[119] As shown in Scheme 49, diol **174** was prepared from starting material **173**, which was subsequently silyl protected to give compound **175**. The silyl enol ether **175** was subjected to a catalytic asymmetrisation reaction using Rh-(*S*)-BINAP-cycloocta-1,5-diene (**176**) to give a mixture of the silyl enol ether **177** and the siloxy ketone **178** (4:1). Compound **177** was then treated with tetrabutylammonium fluoride to furnish the siloxy ketone **178** in high yield. Removal of the second silyl protecting group gave (*R*)-hydroxyl ketone **179**, which was mesylated under standard conditions to give compound **180**. Substitution of the mesyl group with methylamine formed (–)-physoperuvine **181** in moderate yield.



Scheme 49- First asymmetric synthesis of (–)-physoperuvine 181

2.1.2 Retrosynthetic Analysis of (+)-Physoperuvine

The proposed retrosynthetic analysis of (+)-physoperuvine **168** is shown in Scheme 50.[120] It was envisaged that the synthesis of the tropane alkaloid **168** would require the synthesis of the cyclic allylic trichloroacetamide **183**. It was thought that **183** could be obtained using a one-pot tandem Overman rearrangement and ring closing metathesis reaction of the allylic trichloroacetimidate **184**. The allylic trichloroacetamidate **184** could be easily prepared from commercially available ethyl-6-heptenoate (**186**) using a one-pot Overman rearrangement and RCM reaction process. After the one-pot process, allylic oxidation of the cycloheptene ring would give ketone **182**. Hydrogenation and deprotection of **182** would then give (+)-physoperuvine **168**.

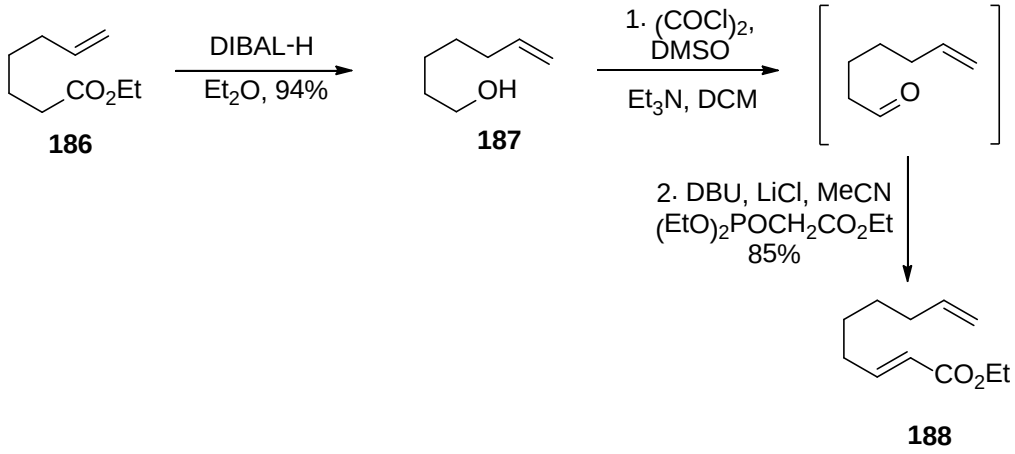


Scheme 50- Retrosynthetic analysis of (+)-physoperuvine 168

2.1.3 Synthesis of (±)-Physoperuvine

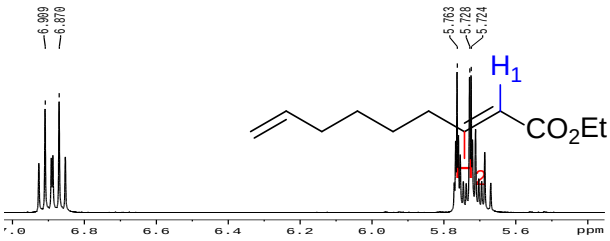
2.1.3.1 Synthesis of (2*E*)-nona-2,8-dien-1-ol 185

The first synthetic step in the synthesis of (2*E*)-nona-2,8-dien-1-ol (**185**) was a DIBAL-H reduction of the commercially available material, ethyl 6-heptenoate (**186**) (Scheme 51). Using reaction conditions reported by Sumitani and co-workers, the reaction was initially carried out using DIBAL-H (2.2 equivalents).[121] ^{1}H NMR spectroscopic analysis of the reaction mixture after three hours showed that the reaction had reached completion and a 94% yield of 6-hepten-1-ol (**187**) was obtained. Generation of the corresponding (*E*)-α,β-unsaturated ester **188** was then achieved in 85% yield using a one-pot Swern oxidation, followed by a Horner-Wadsworth-Emmons (HWE) reaction using Masamune-Roush conditions.[122,123] The Sutherland group had discovered previously that the Masamune-Roush procedure for this one-pot process is the most efficient, giving exclusively the *E*-alkene.[123]



Scheme 51- Synthesis of (*E*)-α,β-unsaturated ester 188

As all unsaturated esters synthesised previously by Sutherland group have consistently shown a coupling pattern with a coupling constant greater than 15.0 Hz in the ^{1}H NMR spectrum. Thus, it was easy to identify the *E*-alkene geometry of product **188** (Figure 3). The hydrogen atoms of the alkene show a 15.6 Hz coupling constant proving that the geometry is *trans*.

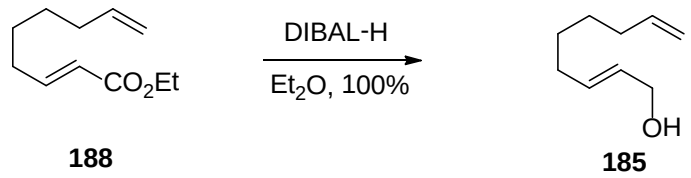


H_2 J = 15.6 Hz

H_1+H_7 J = 15.6 Hz

Figure 3- alkene signals in the ^{1}H NMR spectrum of compound 188

The final stage of the synthesis of allylic alcohol **185** required for the tandem process, involved the reduction of (*E*)-α,β-unsaturated ester **188** using similar reaction conditions described as for the preparation of primary alcohol **187**. This gave the corresponding allylic alcohol **185** in a quantitative yield (Scheme 52).

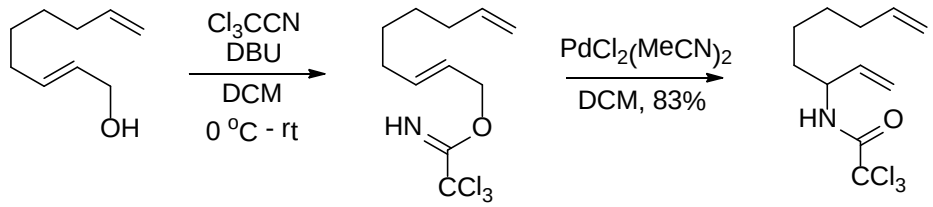


188 **185**

Scheme 52- Synthesis of the allylic alcohol required for tandem process

2.1.3.2 Synthesis of racemic allylic trichloroacetamide 189

Before carrying out the tandem process, the reaction conditions for the Overman rearrangement required development. Thus, the next step was the conversion of the allylic alcohol **185** to the desired allylic trichloroacetimidate **184** using trichloroacetonitrile and a catalytic amount of DBU (Scheme 53). The Overman rearrangement was performed by treating the imidate **184** with commercially available bis(acetonitrile)palladium(II) chloride at room temperature for three hours giving an 83% yield of allylic trichloroacetamide **189** over two steps.



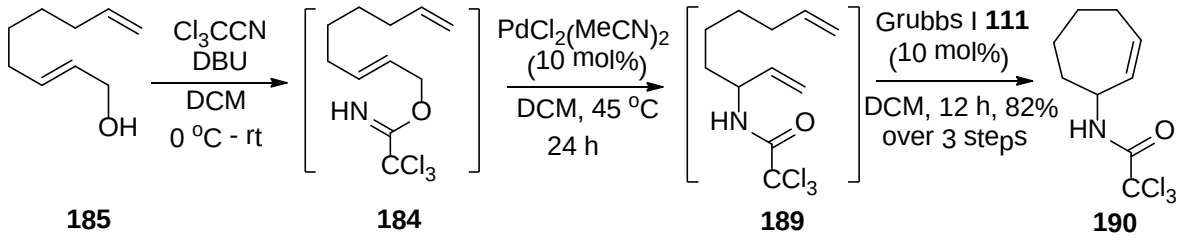
185 **184** **189**

Scheme 53- Synthesis of allylic trichloroacetamide 189

2.1.3.3 Synthesis of cyclic allylic trichloroacetamide 190

With conditions for the first steps in the tandem process optimised, the one-pot process was attempted. The racemic cyclic allylic trichloroacetamide **190** was synthesised in 82% yield using the one-pot process by conversion of the allylic alcohol **185** to the allylic trichloroacetimidate **184** (Scheme 54). With the desired allylic trichloroacetimidate **184** in hand, this was subjected to bis(acetonitrile)palladium(II) chloride catalysis, which gave the rearranged allylic trichloroacetamide **189**. This was then treated with Grubbs 1st generation catalyst **111** to effect the RCM reaction under dilute conditions (0.005 M). The reason for these dilute conditions is to prevent the formation of dimeric products by lowering the chance of an intermolecular process.[124] The desired 7-membered allylic trichloroacetamide **190** was successfully obtained in 82% yield over the three steps. Due to the lower cost and

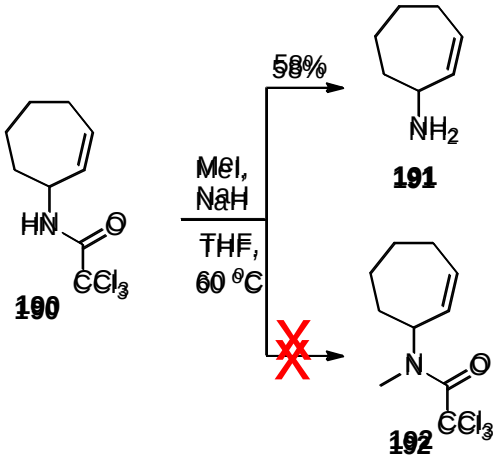
greater availability of Grubbs 1st generation catalyst **111** as a RCM catalyst, it was decided to continue using this, even though other catalysts give slightly better yields.[103] It was also proposed that the racemic cyclic allylic trichloroacetamide **190** be used for the development of the subsequent steps as it is significantly less costly to prepare than the optically active material.



Scheme 54- Synthesis of 7-membered cyclic allylic trichloroacetamide 190

2.1.3.4 Completion of (±)-Physoperuvine 172

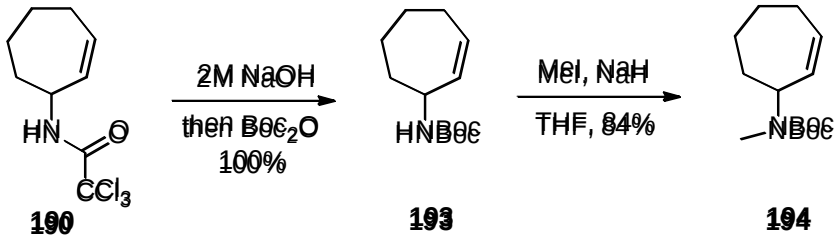
The next stage of the synthesis of (±)-physoperuvine **172** required the introduction of the *N*-methyl group and the standard conditions of sodium hydride and methyl iodide was initially investigated.[125] Many attempts to methylate **190** to obtain **192** were unsuccessful, and led to hydrolysis of the allylic trichloroacetamide functional group and recovery of the corresponding amine **191** in 58% yield (Scheme 55). It was decided that the trichloroacetyl group was unstable under these conditions.



Scheme 55- Attempt at methylation

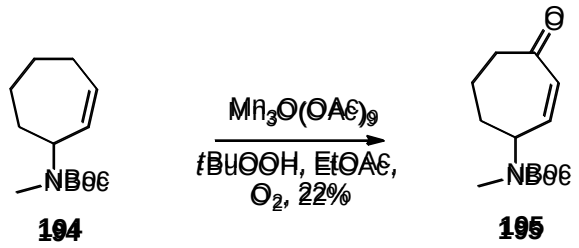
As methylation was not possible in the presence of the trichloroacetyl protecting group, a change of the protecting group was necessary at this stage. It was proposed that it should be replaced with an alternative protecting group, using a one-pot procedure.

The trichloroacetyl group of compound **190** was removed under hydrolytic conditions and the resulting amine was reprotected as the Boc-carbamate using Boc_2O. This was accomplished in a one-pot process in quantitative yield (Scheme 56).[59,125] This was followed by a successful methylation of compound **193** using sodium hydride and methyl iodide to form **194** in an 84% yield.



Scheme 56- Reprotection and introduction of the *N*-methyl group

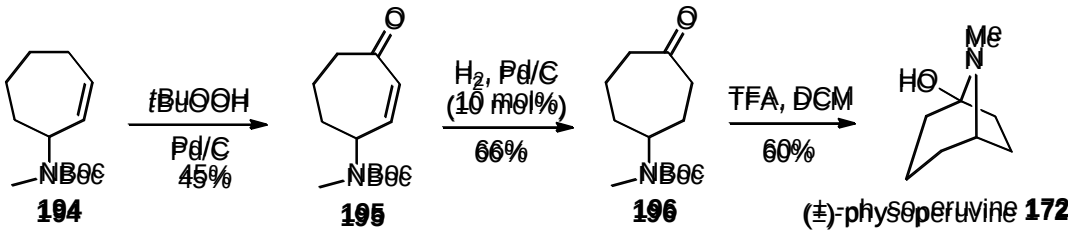
The last key step in the synthesis of (±)-physoperuvine **172** involved the allylic oxidation of the cycloheptene ring. Chidambaram and co-workers reported that there are relatively few general procedures, that have been used for the oxidation of cycloheptenes.[126] Despite this, there are many procedures describing the efficient allylic and benzylic oxidation of organic compounds.[127-132] An early paper by Sharpless described the problems associated with the allylic oxidation of cyclic alkenes with the classic oxidant, selenium dioxide.[133] There are often a number of side-products formed during this reaction which often result in low yields of the desired α,β-unsaturated ketone. The first attempt at allylic oxidation of **194** utilised a manganese(III)-acetate catalysed procedure with *t*-BuOOH as the oxidant under an oxygen atmosphere (Scheme 57).[129] This gave the α,β-unsaturated ketone **195** in only 22% yield, despite increasing the amounts of oxidant and a thorough reaction optimisation.



Scheme 57- Attemps at allylic oxidation using Mn(III)

A second attempt at the allylic oxidation of **194** used Yu and Corey's procedure which involved a palladium mediated oxidation with *t*-BuOOH as the oxidant under basic

conditions (Scheme 58).[128] Initially a palladium hydroxide on carbon catalyst was employed giving the α,β-unsaturated ketone **195** in only a 16% yield. By switching the catalyst to palladium on carbon there was an improvement in the reaction outcome, giving a reasonable 45% yield of the desired α,β-unsaturated ketone. Subsequent hydrogenation of **195** under standard conditions then proceeded smoothly to give the saturated ketone **196** in 66% yield. This was then followed by removal of the Boc-protecting group under acidic conditions which led directly to the synthesis of (±)-physoperuvine **172** in 60% yield.

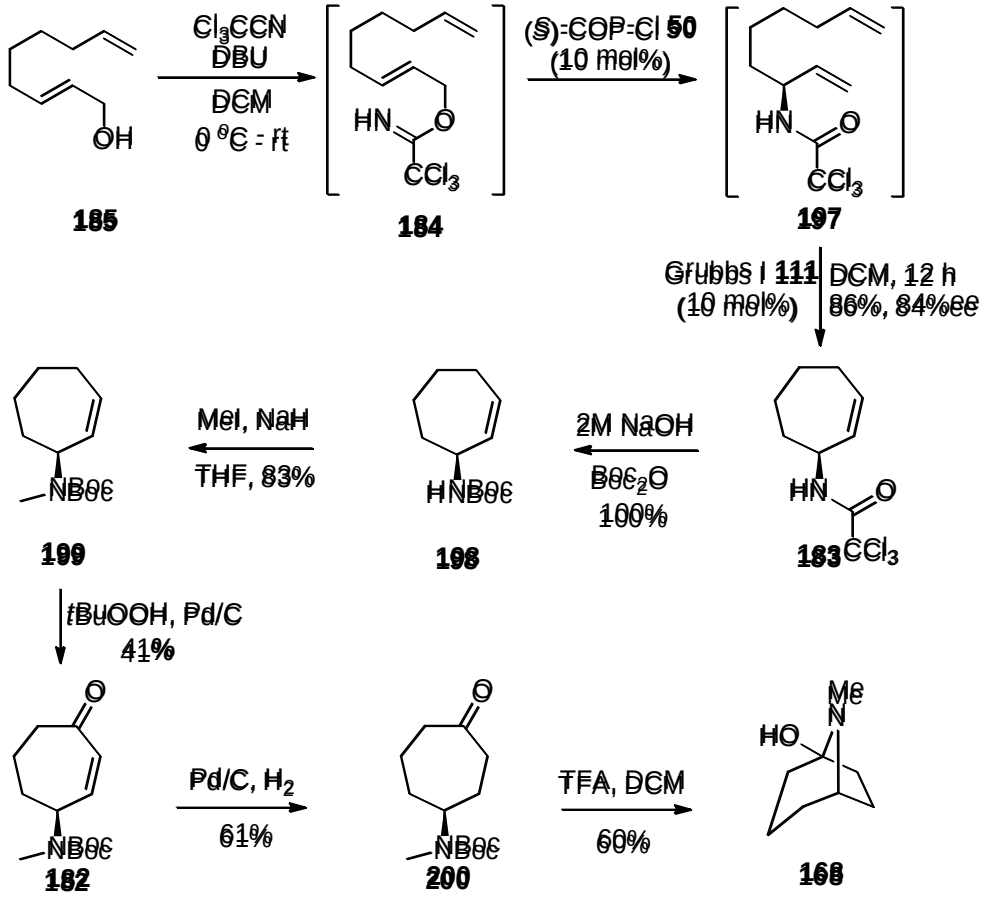


Scheme 58- Synthesis of (±)-physoperuvine

2.1.4 Synthesis of (+)-Physoperuvine

With the synthesis of (±)-physoperuvine **172** completed successfully and in good yield, attention was turned to the synthesis of the natural product, (+)-physoperuvine **168**. As mentioned previously, extensive studies by the Sutherland group have focused their efforts towards the development of an asymmetric tandem Overman rearrangement and RCM reaction.[103] These studies involved the successful employment of both the (*S*)- and (*R*)-COP-Cl catalysts **50** and **51** in the tandem process for the synthesis of six membered cyclic allylic amides with excellent yield and enantioselectivity (88% ee). As such, it was proposed that in a one-pot process, the (*S*)-enantiomer of the cyclic allylic trichloroacetamide **183** could be synthesised using an asymmetric one-pot tandem Overman rearrangement and RCM reaction of allylic trichloroactimidate **184** (Scheme 59), using commercially available (*S*)-COP-Cl **50** to catalyse the rearrangement and Grubbs first generation catalyst **111** to effect the RCM reaction. The enantioselectivities of the reactions were determined using chiral High Performance Liquid Chromatography (HPLC) which had been developed previously in the Sutherland group in a comparison of the reaction products with their corresponding racemic mixtures.[103] Using (*S*)-COP-Cl **50** as part of the tandem process, gave **183** in 86% yield and 84% ee. The enantiomeric excess can be improved up to >99% by recrystallisation using a mixture of ethyl acetate and petroleum ether. Using the steps already developed for (±)-physoperuvine **172**, the

synthesis of (+)-physoperuvine **168** was completed. The optical rotation and spectroscopic data of the synthetic material was in good agreement with those reported for the naturally derived (+)-physoperuvine.[120]



Scheme 59- Synthesis of (+)-physoperuvine 168 using the asymmetric tandem process

2.1.5 Conclusions

In a one-pot tandem process using a palladium-catalysed Overman rearrangement followed by a ruthenium-catalysed ring closing metathesis reaction, a 7-membered cyclic allylic trichloroacetamide was successfully synthesised in a highly efficient manner and excellent yield. This cyclic allylic trichloroacetamide could then be easily employed for the synthesis of the tropane alkaloid, (±)-physoperuvine. An asymmetric one-pot tandem process has also been employed for the synthesis of the 7-membered ring using commercially available (*S*)-COP-Cl catalyst to give the natural product, (+)-physoperuvine. Initial problems with the introduction of the *N*-methyl group were easily overcome by using a one-pot procedure, involving removal of the trichloroacetyl group and reprotection of the resulting amine as a Boc-carbamate.

2.2 Carbocyclic Nucleosides

Carbocyclic nucleosides have been the focus of recent attention in the development of new antitumor and antiviral therapeutic agents.[134] The search for antiviral agents, particularly for the treatment of human immunodeficiency virus (HIV) and hepatitis B virus (HVB), resulted in the discovery of carbovir **201**, which has been shown to possess significant *in vitro* activity as an inhibitor of HIV reverse transcriptase (Figure 4).[135-137] More recently, a new reverse transcriptase inhibitor 1592 U89 **202**, which is currently in phase II clinical trials, has been discovered and is reported to hold remarkable promise for the treatment of HIV.[138] Carbocyclic nucleosides in which the ribofuranose ring oxygen is replaced with a methylene moiety have been shown to have a range of biological activities such as antivirial, antitumour, antiparasitic, antiathritic and immunosuppressive properties.[139] The nucleosides possess these properties as they have a similar shape to ribonucleosides, however, replacement of the oxygen atom with a methylene provides stability to allow inhibition of nucleoside-dependent enzymatic processes. Research into the development of more potent and less toxic analogues led to the generation of noraristeromycin **203**. The identification of noraristeromycin as a potential therapeutic agent has generated much interest in this area and led to many syntheses of carbocyclic nucleosides and investigation into their medicinal chemistry.[140] Recently, Cowart and co-workers reported the synthesis and biological activity of amino-analogues of noraristeromycin such as compound **204** which are significantly more potent (200 times) at inhibiting enzymes such as adenosine kinase.[141]

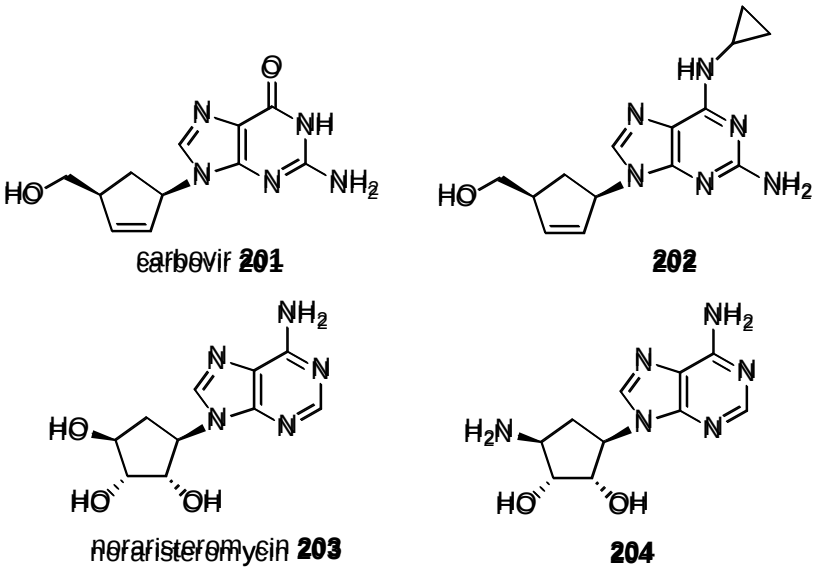
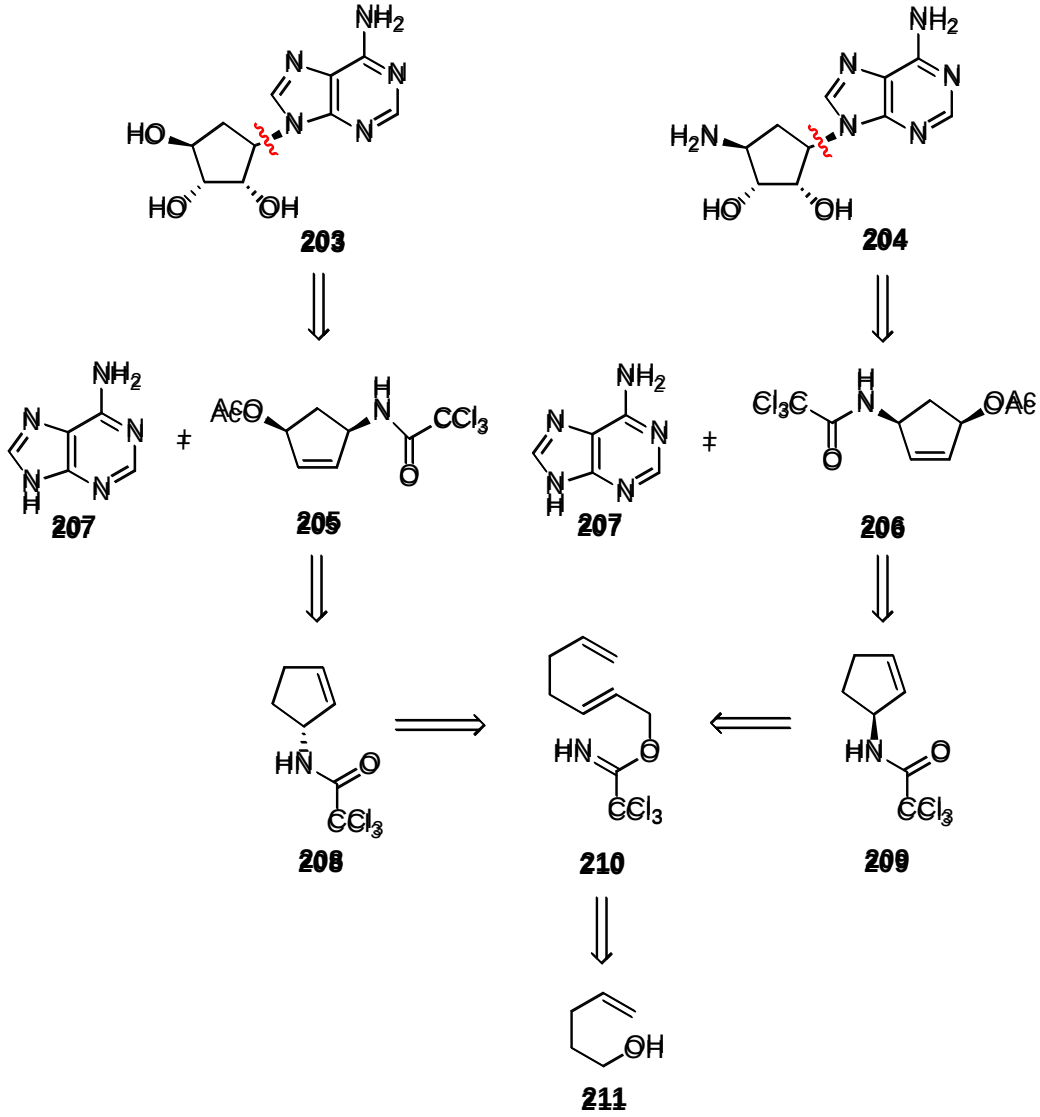


Figure 4- Various derivatives of carbocyclic nucleosides

2.2.1 Retrosynthesis of Carbocyclic Nucleosides

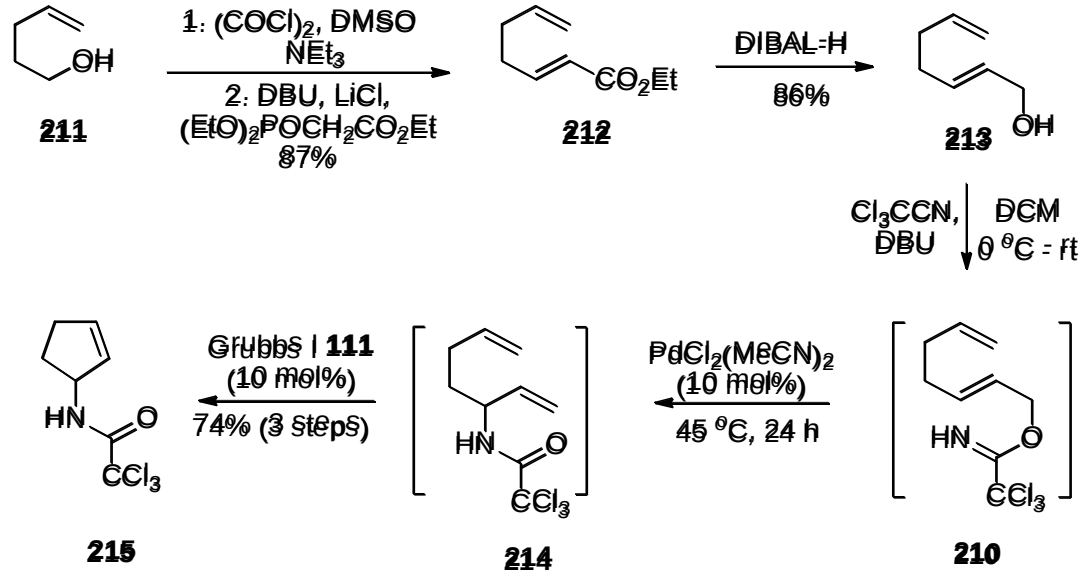
The proposed retrosynthesis of carbocyclic nucleosides **203** and **204** is shown in Scheme 60. Disconnection of the purine ring system **207** of both carbocyclic nucleosides **203** and **204** would give allylic acetates **205** and **206** respectively which could be made from the corresponding cyclic allylic trichloroacetamides **208** and **209**. Chiral amides **208** and **209** could be prepared using a one-pot tandem Overman rearrangement and ring closing metathesis reaction of allylic acetimidate **210** which could be easily prepared from the commercially available 4-pentene-1-ol **211**.



Scheme 60- Retrosynthetic analysis of carbocyclic nucleosides 203 and 204

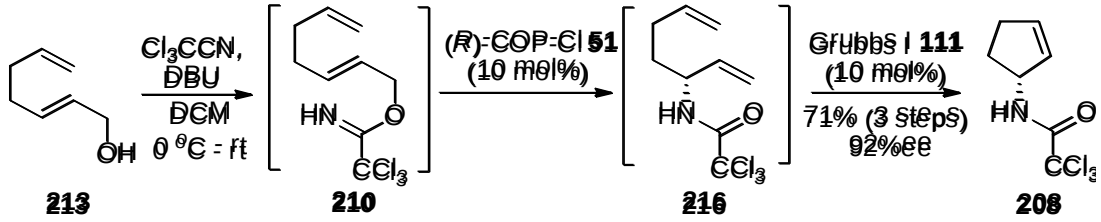
2.2.2 Attempted Synthesis of Carbocyclic Nucleosides

Using a similar approach for the synthesis of the 7-membered ring of physoperuvine, the synthesis of the 5-membered carbocyclic amide was conducted. Initially a one-pot tandem Overman rearrangement and ring closing metathesis reaction was employed for the rapid and efficient synthesis of the racemic cyclic allylic trichloroacetamide **215** (Scheme 61). Due to the less costly synthesis of the racemic cyclic allylic trichloroacetamide **215**, it was proposed that it could be used for the development of the subsequent steps. The synthesis began with a straightforward conversion of 4-pentene-1-ol (**211**) to the corresponding α,β-unsaturated ester **212** using a one-pot Swern oxidation and Horner-Wadsworth-Emmons reaction. Ester **212** was reduced using DIBAL-H to generate the allylic alcohol **213** followed by reaction with trichloroacetonitrile and DBU to give the key allylic trichloroacetimidate substrate **210**. The allylic imidate **210** was then treated with $PdCl_2(MeCN)_2$ to give allylic trichloroacetamide **214** followed by the addition of Grubbs I catalyst **111** to give the cyclic allylic trichloroacetamide **215** in 74% yield over the three steps.



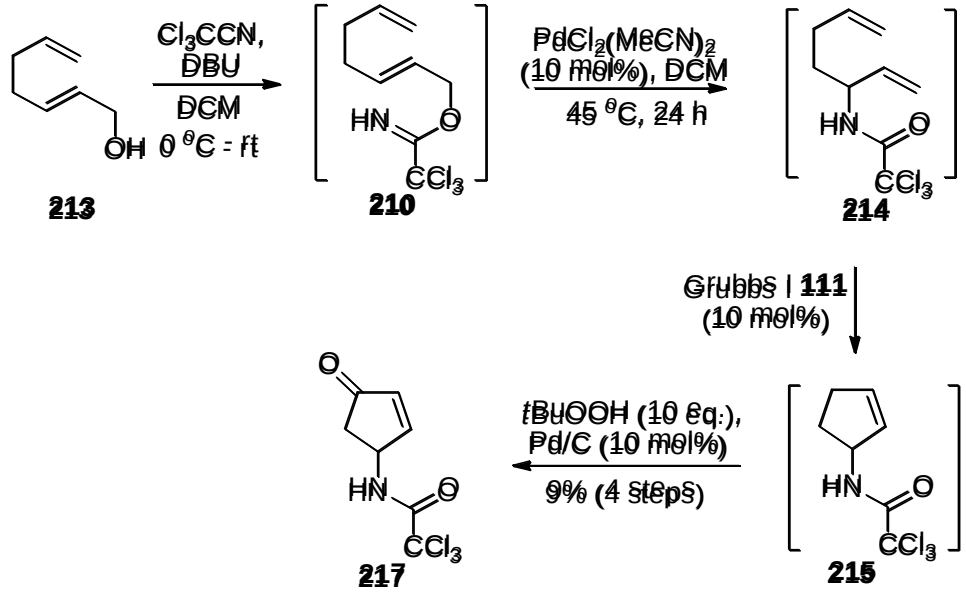
Scheme 61- Synthesis of the racemic cyclic amide 215

Having successfully synthesised the racemic cyclic allylic trichloroacetamide **215** in high yield, attention was then turned to the synthesis of the asymmetric analogue **208** required for the synthesis of noraristeromycin **203** (Scheme 62). This was achieved in a similar manner to the racemic reactions in good yield over the three steps and in high enantioselectivity using (*R*)-COP-Cl **51** to catalyse the Overman rearrangement.



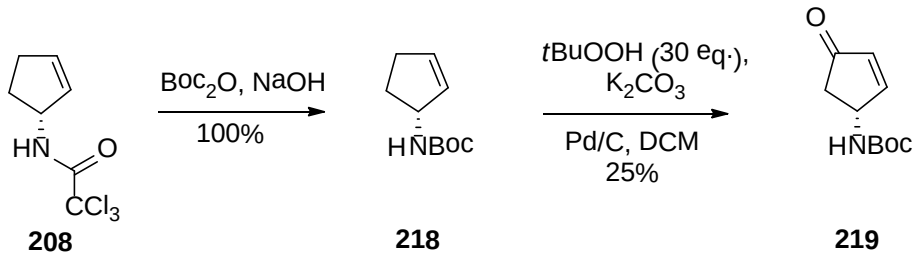
Scheme 62- Asymmetric synthesis of cyclic allylic trichloroacetamide 208

The next synthetic step of the synthesis was the allylic oxidation of the cyclic allylic trichloroacetamide **215**. In an attempt to synthesise the key α,β-unsaturated ketone **217**, a one-pot procedure using a tandem process with allylic oxidation as the final key step was initially investigated. Consequently, allylic alcohol **213** was converted to α,β-unsaturated ketone **217**. However, a poor yield was obtained over the four steps (Scheme 63).



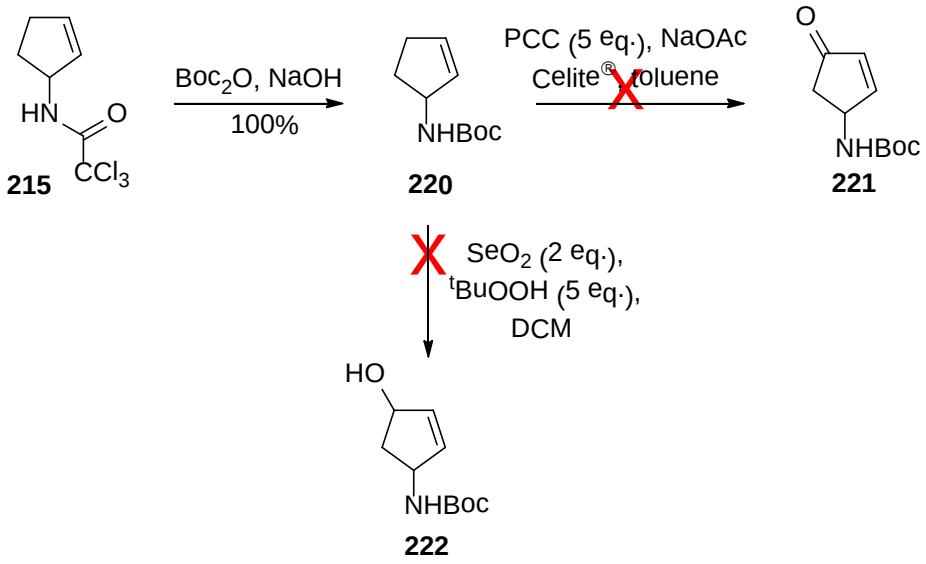
Scheme 63- A one-pot tandem process with allylic oxidation

As the allylic oxidation could not be achieved in good yield using the one-pot procedure, it was decided to replace the trichloroacetyl group with a more stable protecting group. The cyclic allylic trichloroacetamide **208** was reprotected using the same conditions as described for **190** to give **218** in a quantitative yield (Scheme 64). Allylic oxidation was then carried out following the Yu and Corey procedure with an excess of *t*-BuOOH under basic conditions.[128] Unfortunately, this gave the desired α,β-unsaturated ketone **219** in only 25% yield.



Scheme 64- Allylic oxidation using the Corey procedure

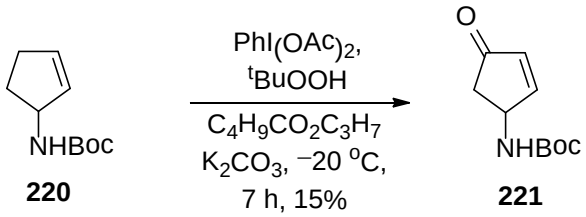
Alternatively, it was also decided to attempt other allylic oxidation and hydroxylation on Boc-analogue **220** in the hope that these reactions might yield the ketone **221** or the allylic alcohol **222** in higher yields (Scheme 65). Straightforward conversion of racemic cyclic allylic trichloroacetamide **215** to the Boc-protected compound **220** which was then subjected to different reaction conditions following procedures developed firstly by Chandrasekaran using pyridinium chlorochromate (PCC) and secondly by Sharpless using the classic oxidant, selenium oxide with *t*-BuOOH, but neither yielded the desired products with full recovery of the starting material.[133,142]



Scheme 65- Attempts at allylic oxidation and hydroxylation of 220

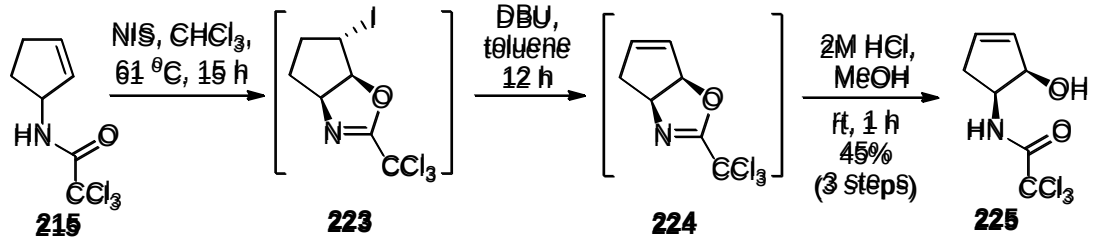
In a final attempt it was hoped that utilising several methodologies would provide α,β-unsaturated ketone **221** in high yield (Scheme 66). Initially, a protocol described by Yeung and co-workers that reported the first solvent-assisted nonmetallic based generation of a reactive and controllable *tert*-butylperoxy radical was investigated.[143] It was shown that this radical process could promote allylic oxidation of various olefinic substrates using commercially available diacetoxyiodobenzene and *t*-BuOOH in a σ-donor solvent such as

n-butyl butanoate. However, treatment of Boc-protected **220** with diacetoxyiodobenzene and *t*-BuOOH give compound **221** in only 15% yield.



Scheme 66- Attempts at allylic oxidation of 220 using Yeung's procedure

Unfortunately none of these procedures were successful and as a consequence of this, it was proposed to use an alternative synthetic strategy involving the stereoselective functionalisation of the alkene of cyclic allylic trichloroacetamide **215**. It was hoped that a hydroxyl group could be introduced at C-2 and a leaving group at C-3 of the cyclopentane ring (Scheme 67). Treatment of cyclic allylic trichloroacetamide **215** with *N*-iodosuccinimide gave 4-hydro-1,3-oxazole **223**. Without purification, compound **223** was then treated with DBU and the resulting intermediate **224** was subjected to hydrolysis under acidic conditions. This allowed the isolation of the allylic alcohol **225** as the major product in 45% yield over the three steps. It was proposed that **225** could be subjected to an allylic acetate rearrangement for the synthesis of the carbonucleoside core (see future work).



Scheme 67- Synthesis of allylic alcohol 225

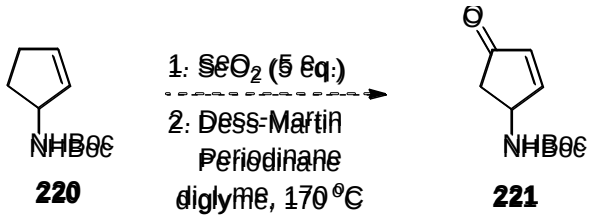
2.2.3 Conclusions to the Carbocyclic Nucleosides

In summary, the 5-membered cyclic allylic trichloroacetamide was successfully synthesised in a one-pot tandem process, using a palladium-catalysed Overman rearrangement followed by a ruthenium-catalysed ring closing metathesis reaction. This cyclic allylic trichloroacetamide was made in excellent yield and subjected to allylic oxidation using various methods, however efforts to optimise the reaction outcome were

unsuccessful. An asymmetric one-pot tandem process was also developed for the asymmetric synthesis of the 5-membered ring which was required for the synthesis of noraristeromycin and amino-carbocyclic nucleoside.

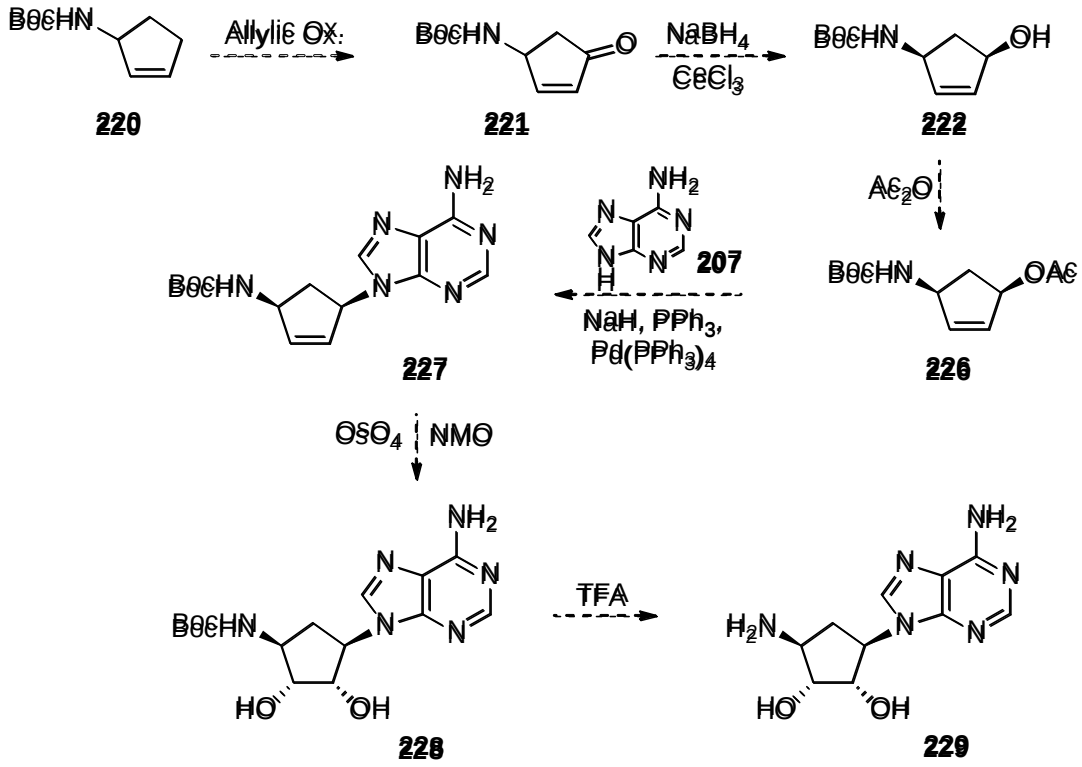
2.2.4 Future Work

Future work for this project includes the optimisation of the allylic oxidation of Boc-protected **220**. It is hoped that a protocol described by Trost and co-workers who synthesised glycosidase inhibitors, allosamizoline and mannostatin can be applied.[144] The subsequent allylic oxidation of Boc-protected **220** using selenium dioxide followed by addition of Dess-Martin periodinane would then give the α,β-unsaturated ketone **221** (Scheme 68).



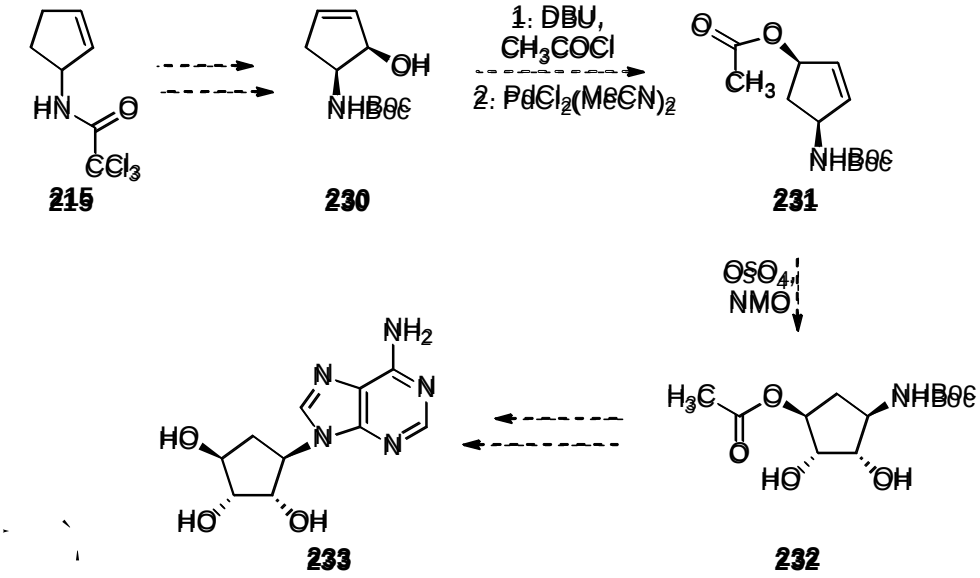
Scheme 68- Trost's allylic oxidation procedure

After the allylic oxidation has been optimised the next stage of the synthesis of the amino-carbocyclic nucleoside **229** will involve the reduction of the resulting ketone **221** under Luche conditions and will lead to the formation of the *cis*-amino alcohol **222** (Scheme 69).[145] The alcohol functional group will then be activated using acetic anhydride to give the allylic acetate **226**. A common strategy for the introduction of nucleoside bases is the palladium-catalysed displacement of an allylic ester. Thus, treatment of the allylic acetate **226** with 6-chloropurine **207** in the presence of Pd(0) will allow the direct introduction of the purine ring system with retention of relative stereochemistry.[146,147] At this stage, dihydroxylation of **227** will be carried out using standard Upjohn conditions,[148] which will give compound **228**. Finally, deprotection of the amine will complete this short synthesis of analogue **229**.



Scheme 69- Proposed synthesis of the carbocyclic nucleoside 229

An alternative route shown in Scheme 70 could be used for the synthesis of noraristeromycin **233**. This will include the conversion of the cyclic allylic trichloroacetamide **215** to the allylic alcohol **230** following the same steps described for the synthesis of allylic alcohol **225** (Scheme 70). Allylic acetate rearrangement followed by dihydroxylation of the alkene **231** using Upjohn conditions will furnish compound **232**. Having introduced all functional groups onto the carbocyclic ring, a few additional steps will then complete the synthesis of noraristeromycin **233**.

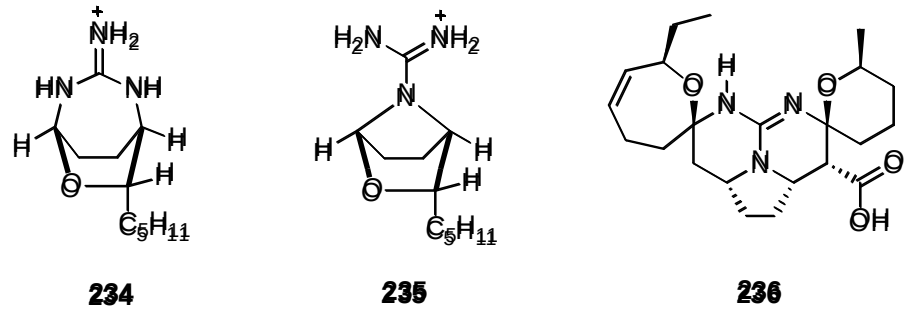


Scheme 70- Second proposed synthesis of the carbocyclic nucleoside 233

If the racemic carbocyclic nucleosides **229** and **233** can be prepared, the asymmetric synthesis of the carbocyclic nucleosides **203** and **204** will be attempted in the future.

2.3 (+)-Monanchorin

(+)-Monanchorin **234** is a bicyclic alkaloid which was isolated by McKee and co-workers. In addition to this, the pentacyclic guanidine alkaloid crambescidin acid **236** was also isolated from the sponge *Monanchora ungiculata* in the Maldive Islands (Figure 5).[149] (+)-Monanchorin **234** is a weakly cytotoxic natural product that exhibits a variety of biological functions including antifungal, antiviral, antimicrobial, and Na^+/K^+ and Ca^{2+} ATPase inhibitory activities. The carbon skeleton was assigned on the basis of 2D NMR experiments, leading to two possible structures, **234** and **235** which differ in the connection of the guanidine to the carbon chain. More recently, Yu and Snider developed a synthetic route to (+)- and (–)-monanchorin and showed that the natural product is as shown for structure **234**.[150]

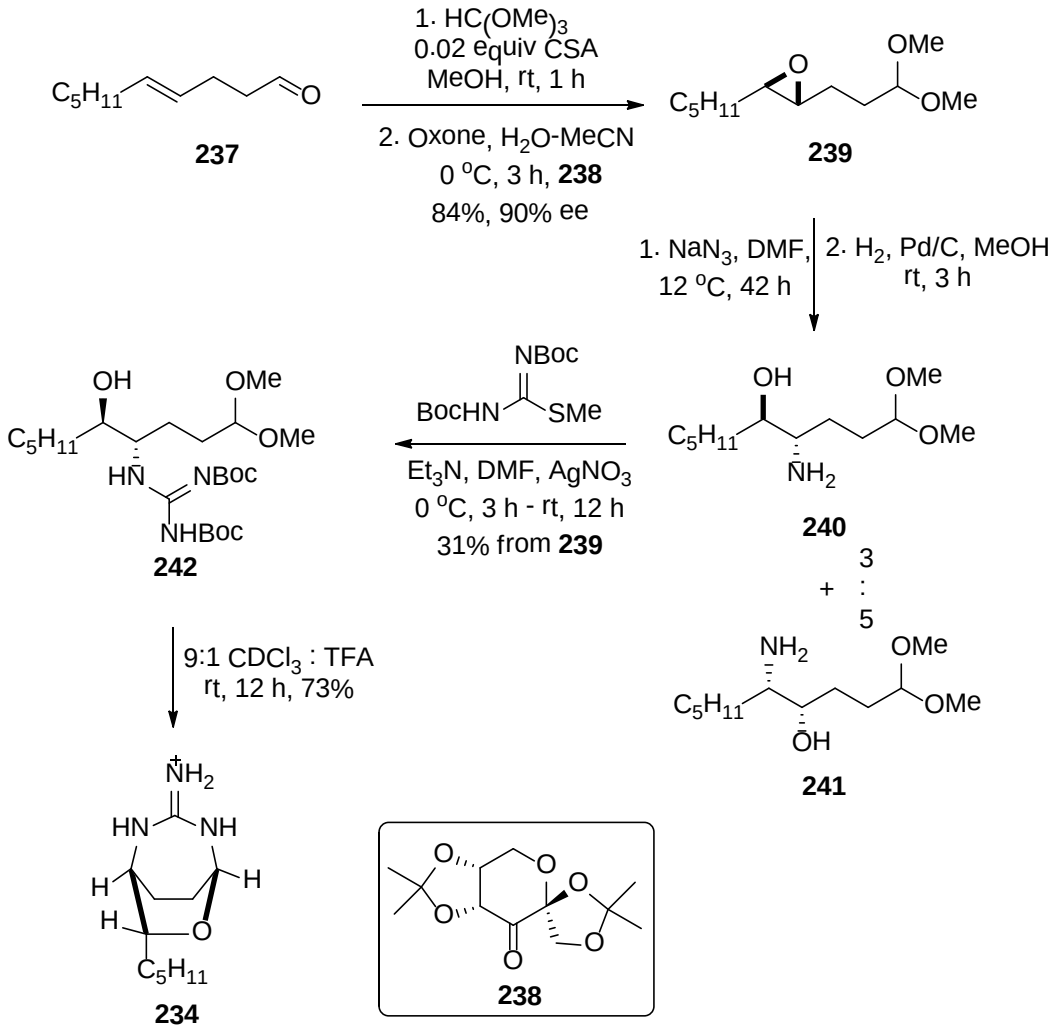


234 **235** **236**

Figure 5- Guanidine alkaloids isolated from the sponge *monanchora ungiculata*

2.3.1 Previous Synthesis of (+)-Monanchorin

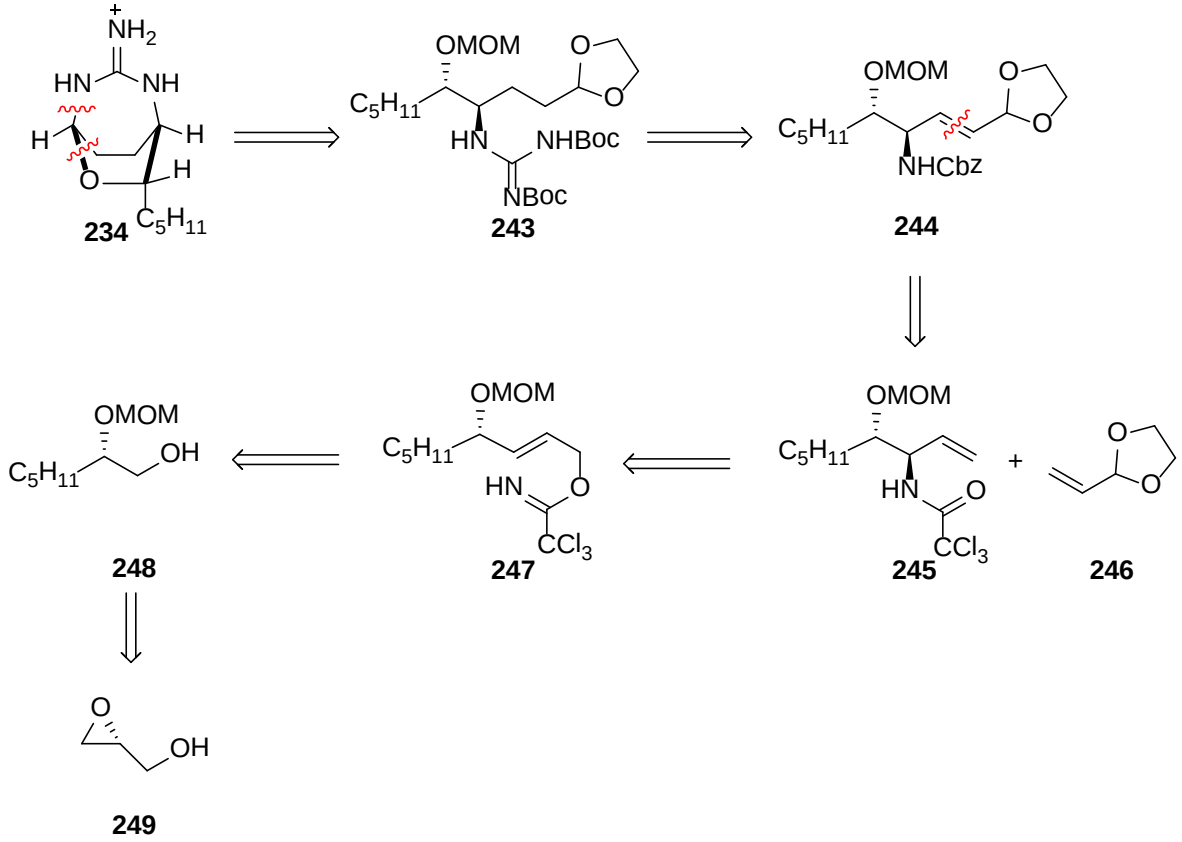
In 2009, Snider and co-workers synthesised (–)-monanchorin **234** in an enantiospecific, six step synthesis from intermediate **237**.[150] As shown in Scheme 71, (4*E*)-decenal (**237**) was converted to the optically pure epoxy acetal **239** in two steps using Shi's D-fructose derived ketone to induce asymmetry. A ring opening reaction of the epoxy acetal **239** followed by hydrogenation of the resulting azides gave amine **240** as the minor component with other regioisomer **241** (3 : 5 ratio). Treatment of amine **240** with the activated guanidine unit then gave the protected guanidino alcohol **242**. This was followed by removal of both Boc and acetal protecting groups to form the desired compound (–)-monanchorin **234** in 21% overall yield. The synthesis was repeated using Shi's L-fructose derived ketone for the asymmetric epoxidation step which eventually gave the naturally occurring (+)-monanchorin in similar overall yield.



Scheme 71- Snider's synthesis of (–)-monanchorin

2.3.2 Retrosynthetic Analysis of (+)-Monanchorin

The proposed retrosynthetic analysis of (+)-monanchorin **234** is outlined in Scheme 72.[151] Ring opening of the guanidine alkaloid ring would lead back to guanidine analogue **243** which could be made from *E*-alkene **244**. Disconnection of the carbon backbone of **244** at the alkene linkage and removal of the Cbz-protecting group would lead to the allylic amide **245** and 2-vinyl-1,3-dioxolane (**246**). The allylic amide **245** could be easily prepared using the ether-directed Overman rearrangement of allylic trichloroacetimidate **247**. The imidate **247** may be synthesised from primary alcohol **248** which could be made from commercially available (*R*)-glycidol **249** using a regioselective ring opening reaction.

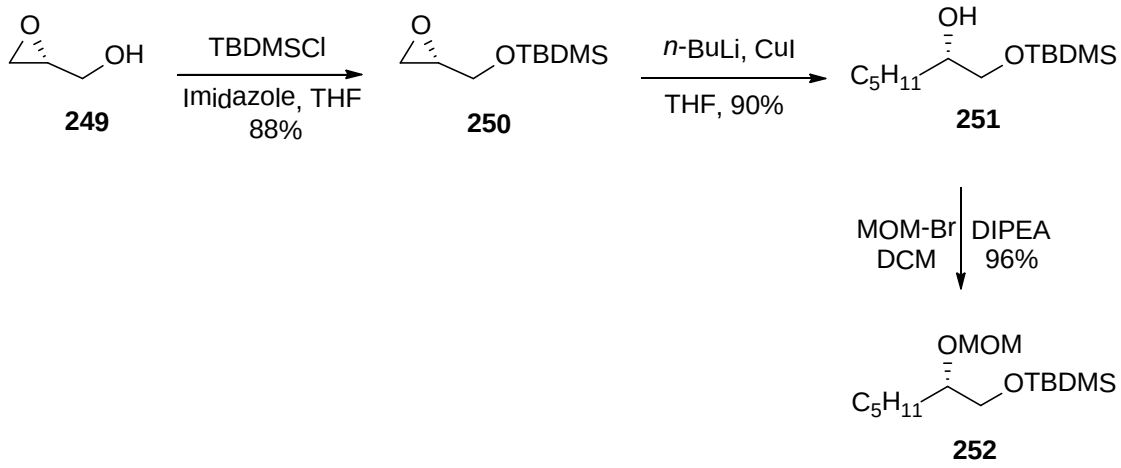


Scheme 72- Retrosynthetic analysis of (+)-monanchorin

2.3.3 Synthesis of (+)-Monanchorin

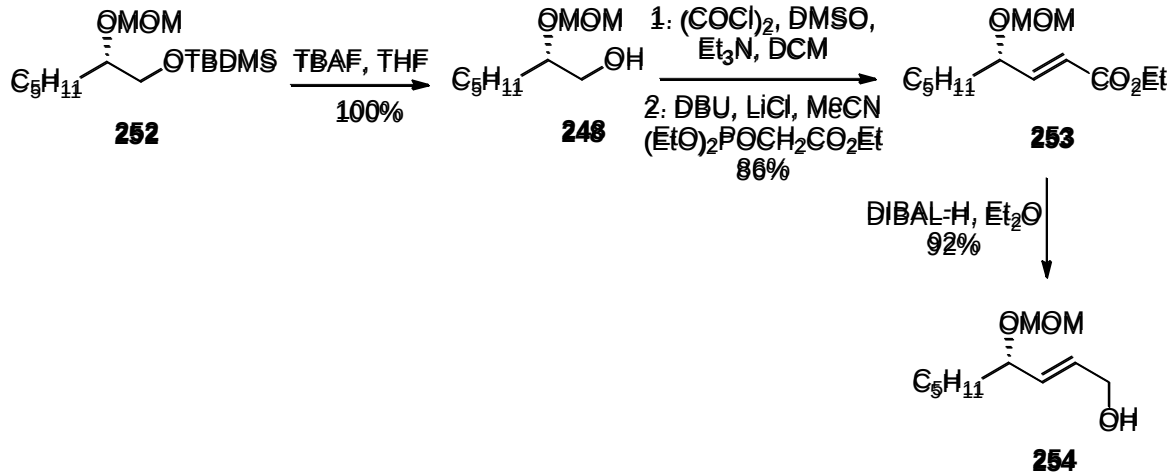
2.3.3.1 Synthesis of allylic alcohol 254

The first step of the synthesis of the guanidine alkaloid (+)-monanchorin involved protection of commercially available (*R*)-glycidol **249** with a silyl ether to give **250** in an 88% yield (Scheme 73). A regioselective copper(I)-catalysed epoxide opening using *n*-butyllithium then gave **251** in an excellent yield and as a single regioisomer. Previously, the Sutherland group have reported that the methoxymethyl (MOM) ether was the most selective directing group for an Overman rearrangement, giving the rearranged products in high diastereoselectivity.[52,53] As such, the secondary alcohol **251** was protected using bromomethyl methyl ether and Hünig's base to give the silyl ether **252** in a 96% yield.



Scheme 73- Synthesis of the protected diol 252

With the desired protected compound **252** in hand, it was selectivity deprotected to the primary alcohol **248** in a quantitative yield using TBAF (Scheme 74). The primary alcohol **248** was then subjected to a one-pot Swern oxidation followed by a Horner-Wadsworth-Emmons reaction, which gave exclusively the *E*-α,β-unsaturated ester **253** in 86% yield. DIBAL-H reduction of the α,β-unsaturated ester **253** gave the allylic alcohol **254** in 92% yield.

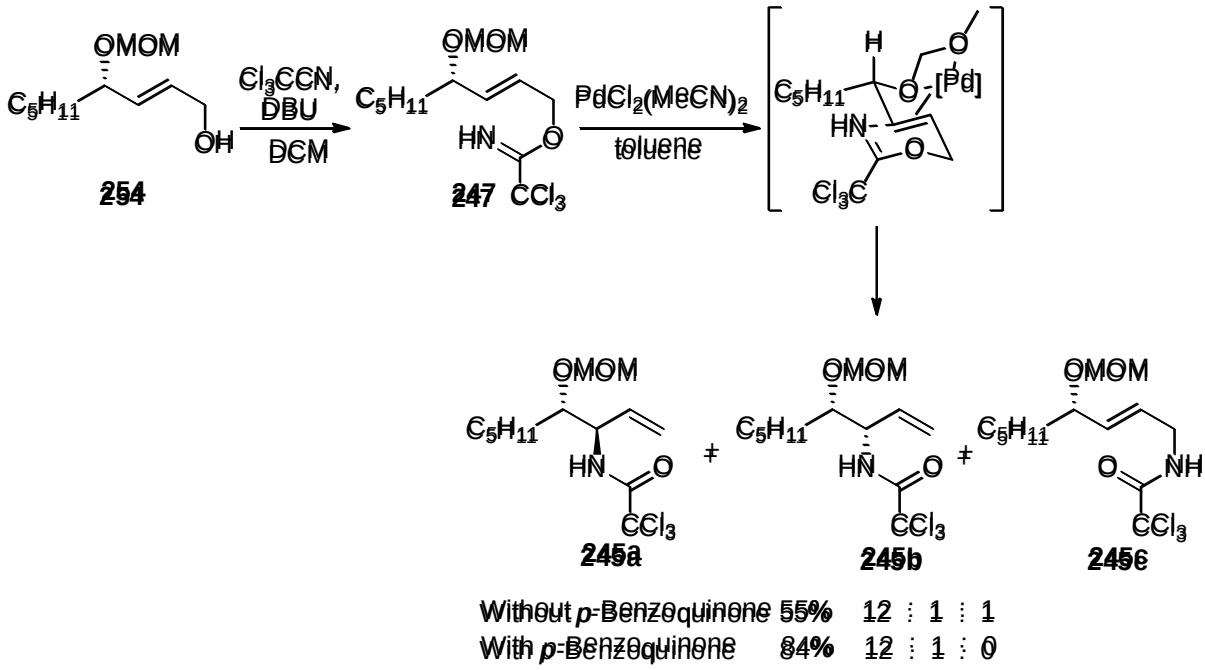


Scheme 74- Synthesis of allylic alcohol 254 required for the directed rearrangement

2.3.3.2 Synthesis of allylic trichloroacetamide 245

As mentioned previously, the Sutherland group has shown that amides such as **245a** can be obtained with high diastereoselectivity when a MOM-ether group (at the δ-position) is used to direct the Pd(II)-catalysed Overman rearrangement reaction and when using a non-

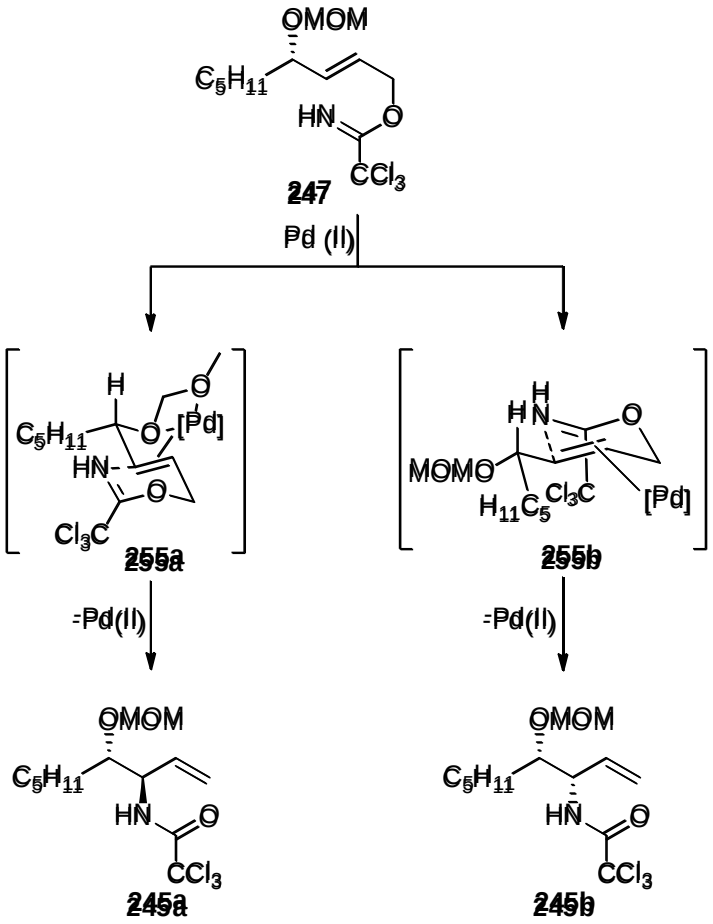
coordinating solvent such as toluene.[5,6,59] Treatment of the allylic alcohol **254** with trichloroacetonitrile and DBU gave allylic trichloroacetimidate **247** (Scheme 75). Allylic trichloroacetamidate **247** was subjected to a palladium(II)-catalysed Overman rearrangement using $PdCl_2(MeCN)_2$ in toluene. This gave the *erythro*-allylic trichloroacetamide **245a** as the major product and *threo*-allylic trichloroacetamide **245b** as the minor in a combined 55% yield over the two steps and in a 12 : 1 ratio, respectively. Trace amounts of the [1,3]-rearranged product **245c** were also isolated. However, with the addition of *p*-benzoquinone as an oxidant agent the desired allylic trichloroacetamides **245a** and **245b** could be obtained in a substantially improved 84% yield over the two steps (once again in a 12 : 1 ratio). Flash column chromatography allowed the separation of the desired major isomer **245a** from **245b**.



Scheme 75- Synthesis of *erythro*- and *threo*-allylic trichloroacetamides

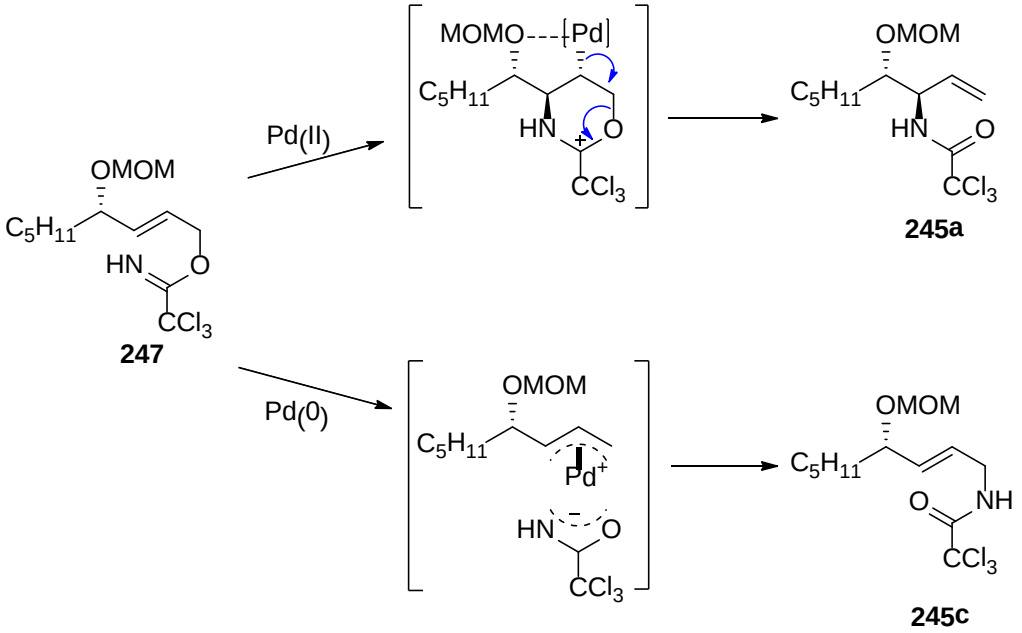
As shown in Scheme 76, the diastereoselective outcome of product **245a** is controlled by the directing effect of an oxygen atom at the δ-position and not by the steric bulk of the side chain of the compound. This diastereoselectivity was explained by the coordination of the MOM group to the palladium metal catalyst which directs the catalyst to the back face of the alkene forming the allylic trichloroactimidate *via* reacting state conformation **255a**. This allows the intramolecular attack to take place only from the front face of the alkene which then leads to the formation of the *anti*-diastereomer **245a** as the major product. In contrast to this, coordination of the catalyst to the front face of the alkene (least hindered

position) would force the rearrangement to proceed only from the back face which would form the *syn*-diastereomer **245b**.



Scheme 76- Transition states of allylic trichloroacetimidate

The formation of the [1,3]-rearranged product (*anti*-Claisen) **245c** of the bulky allylic acetimidate **247** has a negative effect on the reaction outcome (Scheme 77). This is formed due to possible elimination of Pd(0) from the cyclisation pathway which then forms the [1,3]-product *via* an ionisation pathway which has previously been reported by Ikariya.[10] This problem can be overcome by reoxidising the Pd(0) back to Pd(II) using the oxidant *p*-benzoquinone. This then inhibits the formation of the [1,3]-product thus increasing the yield of the desired [3,3]-products.



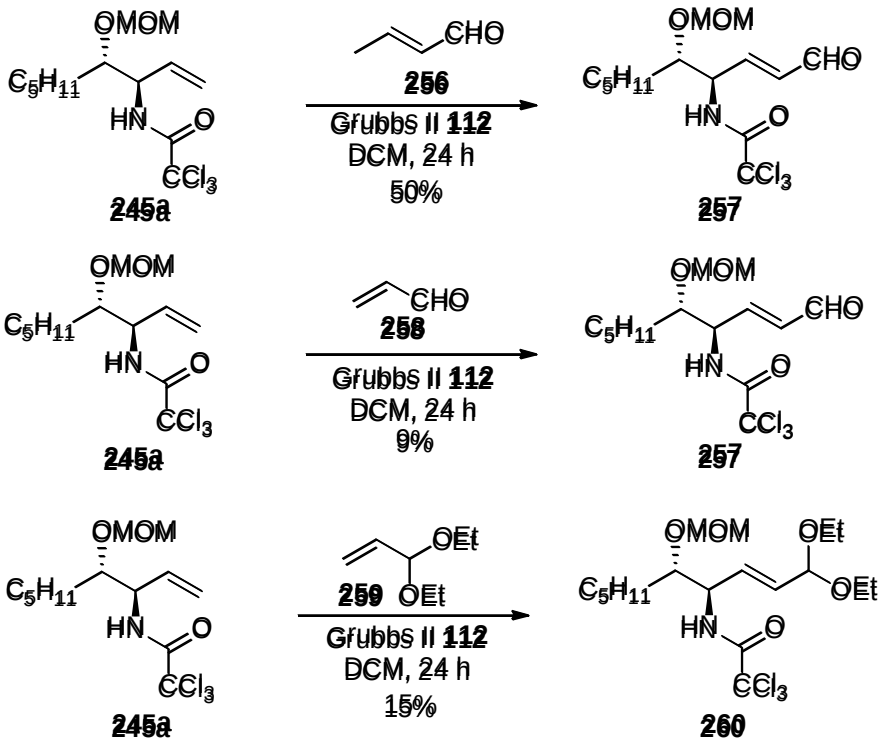
Scheme 77- [3,3]- and [1,3]-rearrangement pathways

2.3.3.3 Cross-metathesis step

The next step of the synthesis required cross-metathesis to extend the carbon backbone and introduce the aldehyde moiety for the final cyclisation. This was found to be a significant challenge in the synthesis of (+)-monanchorin **234**. Grubbs and co-workers reported that conjugated olefins including acrolein were found to be unreactive in reactions using Grubbs 2nd generation catalyst **112**.[152] On the other hand, unconjugated acrolein acetals were found to be viable metathesis substrates. They examined the activity of the cross-metathesis reaction of crotonaldehydes, and α,β-unsaturated carbonyl compounds and discovered certain acetals were particularly robust as substrates for reaction with terminal olefins. According to these studies, an initial optimisation of the cross-metathesis reactions was carried out to obtain the coupled alkene.[153] They observed that reactions using older samples of diethyl acetal gave low yields, presumably due to small amounts of the hydrolysis-derived acrolein.

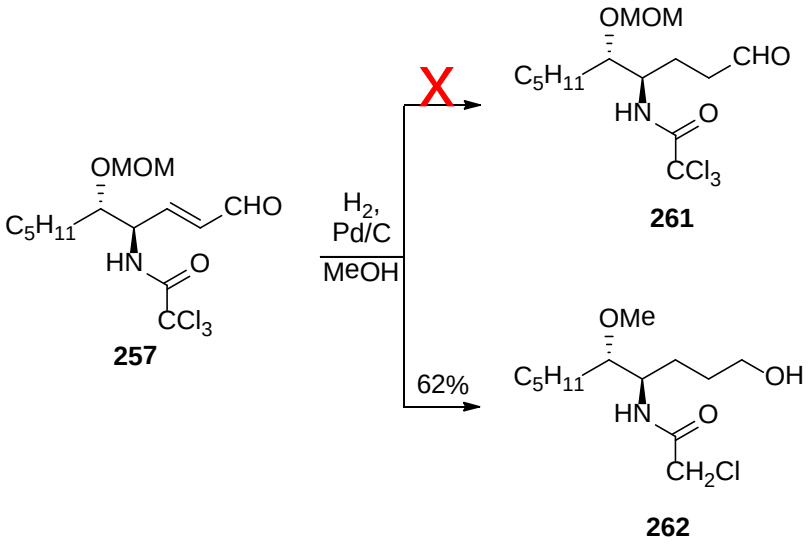
As such, allylic trichloroacetamide **245a** was treated with a variety of terminal alkenes and crotonaldehyde as cross-metathesis partners in the presence of Grubbs 2nd generation catalyst **112** (10 mol%) in dichloromethane (Scheme 78). Cross-metathesis was observed in moderate yield when crotonaldehyde **256** was used giving compound **257** in 50% yield. A decrease in cross-metathesis efficiency was observed as the ratio of acrolein **258** to Grubbs 2nd generation catalyst was increased. It was proposed that the commercial purity of acrolein **258** may have inhibited catalyst activity. The reactivity of acetal **259** was

unexpected, as it was originally thought that allylic disubstitution would hinder the cross-metathesis reaction. This reaction gave **260** in low yield.



Scheme 78- Attempts at efficient cross-metathesis

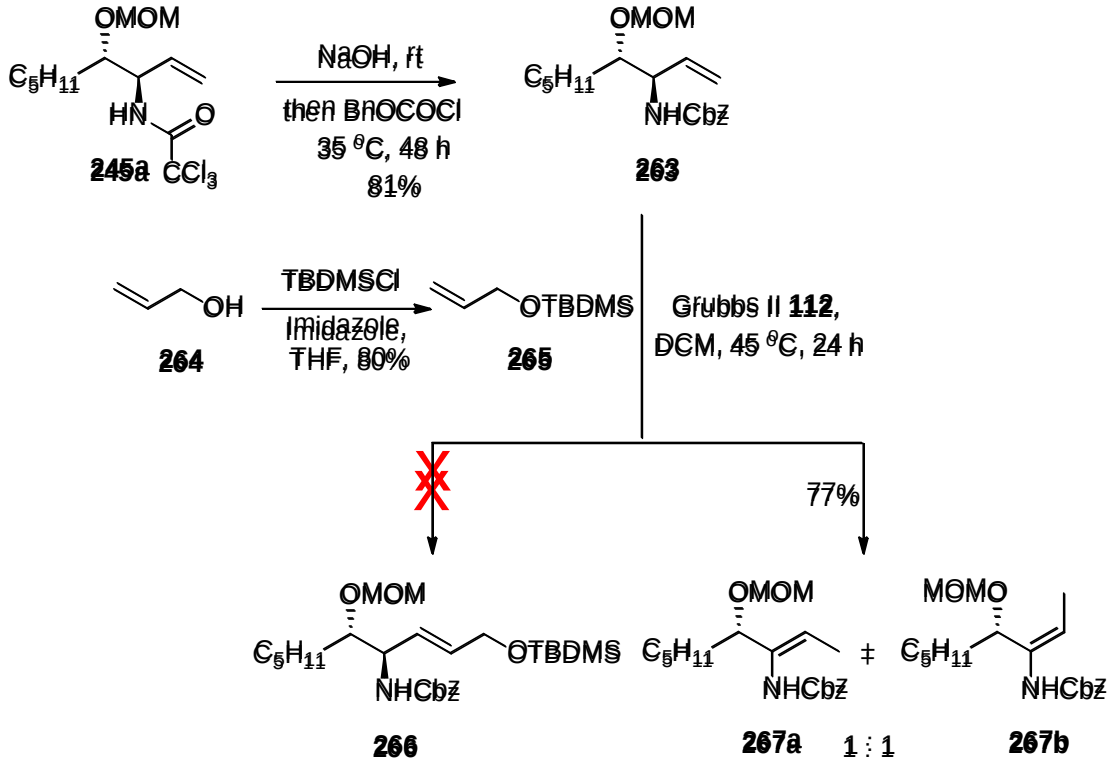
As cross-metathesis was moderately successful for formation of **257**, further transformations were investigated using this intermediate. However, attempts to hydrogenate **257** under standard conditions, failed to give the desired product **261** (Scheme 79). Surprisingly, spectroscopic data showed that (4*R*,5*S*)-4-(2-chloroacetylamino)-5-methoxy-1-decane-1-ol (**262**) was formed in a 62% yield. Under hydrogenation conditions reduction of the aldehyde and the MOM groups, and also cleavage of the two C-Cl bonds was observed. As of yet, no explanation has been produced to explain the reduction of the MOM group to the methoxy.



Scheme 79- Attempted hydrogenation of cross coupled product

2.3.3.4 Synthesis of carbamate *E*-alkene

As cross coupling could not be promoted in good yield and the subsequent hydrogenation of the alkene **257** was not possible in the presence of the trichloroacetyl protecting group, it was proposed that the trichloroacetyl should be replaced with an alternative. Using a one-pot procedure, the trichloroacetyl functional group was removed under hydrolytic conditions and the resulting amine was reprotected using a Cbz-protecting group which formed carbamate **263** in 81% yield over the two steps. This was followed by an attempted coupling of **265** which was prepared from propene-1-ol **264**. However, the desired compound **266** was not formed. Instead **267a** and **267b** were isolated in 77% yield and in 1:1 ratio (Scheme 80). It is proposed in this reaction that the Ru(II) catalyst does not facilitate a cross-metathesis reaction and instead proceeds an isomerisation reaction.

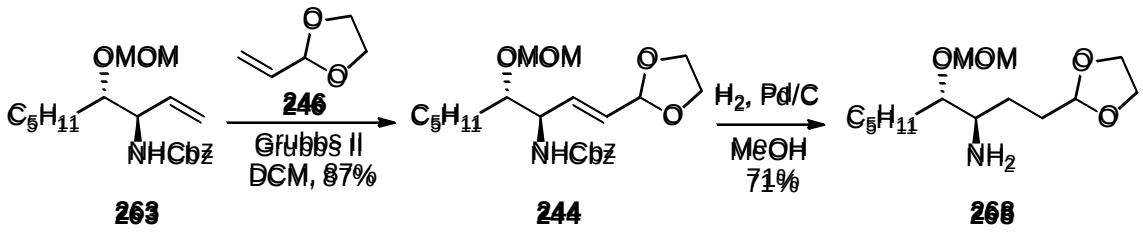


Scheme 80- Further attempt at a cross coupling reaction

2.3.3.5 Synthesis of the cross coupled product

Grubbs and co-workers have previously reported that cross-metathesis reactions can be achieved in an excellent yield using a commercially available 2-vinyl-1,3-dioxolane **246** with enhanced acid-stability compared to diethyl acetal **259**.[153]

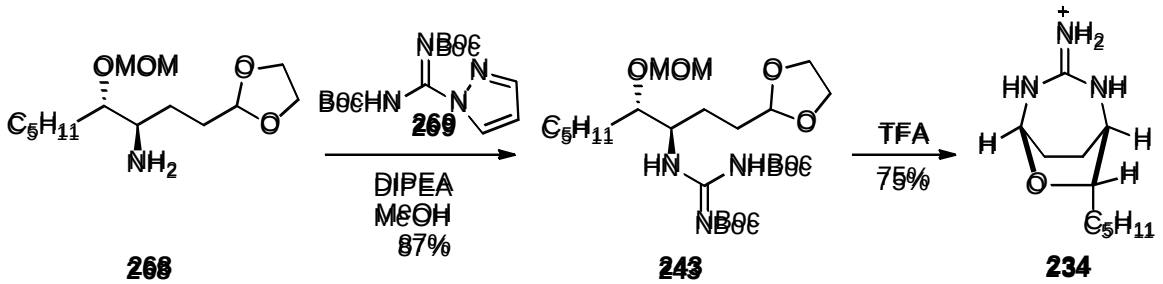
As such, the protected alkene **263** was successfully subjected to a cross-metathesis with 2-vinyl-1,3-dioxolane **246** which was chosen as a selective cross-metathesis reactant in view of its versatile reactivity. This reaction provided exclusively the *E*-alkene **244** in an excellent 87% yield after optimisation. Subsequent hydrogenation under standard conditions then proceeded smoothly to give the saturated amine **268** in 71% yield (Scheme 81).



Scheme 81- Optimised cross-metathesis with 2-vinyl-1,3-dioxolane 246

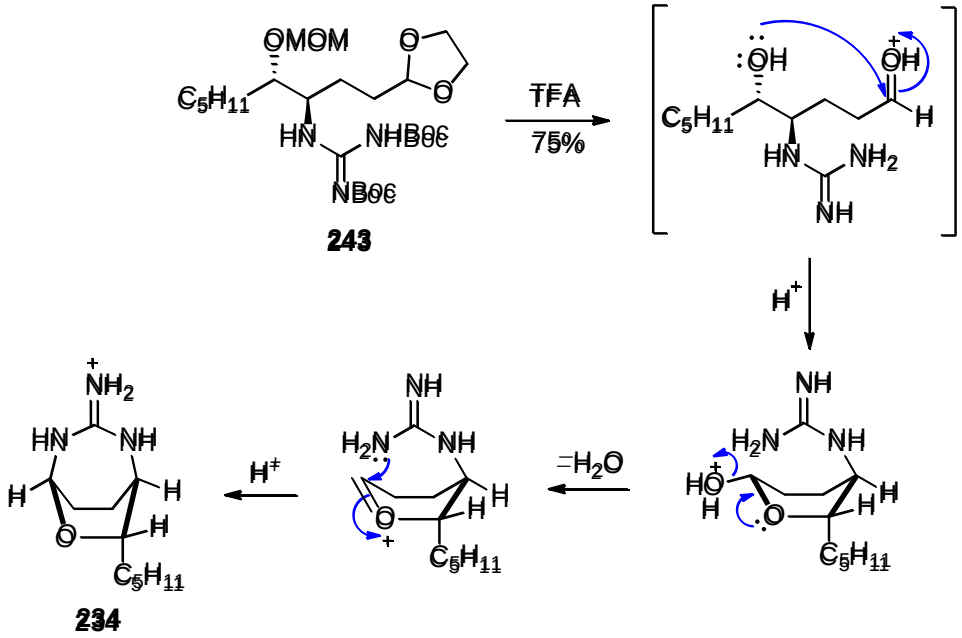
2.3.3.6 Completion of (+)-monanchorin

Previous work by Bernatowicz and co-workers reported that the Boc protected derivative of 1-guanylpyrazole was found to be a reactive reagent for amine guanylation.[154,155] This derivative can serve as a valuable synthetic tool where the guanylation of relatively unreactive amines under mild conditions is required. This derivative also can serve as a versatile synthon in the synthesis of complex guanidine containing compounds. Recently, the Sutherland group reported that the commercially available *N*,*N*'-di-Boc-1*H*-pyrazole-1-carboxamidine **269** can be coupled with amine derivatives giving the Boc-protected guanidine analogues in excellent yields.[125,156,157] Thus, amine **268** was then reacted with carboxamidine **269** using Hünig's base which gave intermediate **243** in 87% yield. Removal of both Boc protecting groups, the MOM group and release of the aldehyde under acidic conditions formed the aminal (+)-monanchorin **234** in 75% yield (Scheme 82). Spectroscopic data and optical activity were entirely consistent with that previously published by the McKee and Snider groups.[149,150]



Scheme 82- Synthesis of (+)-monanchorin

The proposed mechanism for the (+)-monanchorin cyclisation is shown in Scheme 83. A one-pot acid mediated deprotection of the aldehyde, guanidine and hydroxyl groups gave an δ-hydroxy aldehyde intermediate which then underwent stepwise cyclisation likely forming the C-O bond and then the C-N bond to give (+)-monanchorin **234**.



Scheme 83- Proposed mechanism of (+)-monanchorin

2.3.4 Conclusions

In summary, the bicyclic guanidine alkaloid, (+)-monanchorin has been prepared in a fourteen-step synthesis and a 15% overall yield from commercially available (*R*)-glycidol. Using highly efficient methods involving a MOM-ether directed Overman rearrangement which had previously been developed in the Sutherland group generated the second key stereogenic centre. This was followed by a cross-metathesis reaction to form the carbon backbone of the natural product. Initial efforts to perform the cross-metathesis reaction in a good yield using a variety of olefin partners were unsuccessful. Significant progress with the cross-metathesis reaction using 2-vinyl-1,3-dioxolane coupled with a one-pot acid mediated deprotection allowed the synthesis of (+)-monanchorin.

2.4 Clavaminol A, C and H

Clavaminol A **270**, C **271**, H **272** and desacetyl-clavaminol H **273** are new marine sphingoid compounds extracted recently from the Mediterranean ascidian *Clavelina phlegraea* (Figure 6).[158,159] The absolute configuration of these 2-amino-3-alkanols were determined against standards using CD spectroscopy.[160] These natural products were found to have (2*R*,3*S*)-configuration. In contrast to this, the more commonly known other 2-amino-3-alkanols including (2*S*,3*R*)-2-aminododecan-3-ol (**274**) and (2*S*,3*R*)-xestoaminol C **275** isolated from *Clavelina oblonga* and *Spisula polynima*, respectively have (2*S*,3*R*)-configuration.[161,162] These (2*S*,3*R*)-2-amino-3-alkanols possess many biological activities including antifungal activity against *Candida albicans* ATCC 10231, and can also inhibit cell proliferation which prevents the formation of actin stress fibres in *Candida glabrata*.[163] Despite having (2*R*,3*S*)-configuration, clavaminols A, C and H possess cytotoxic properties against A549 (lung carcinoma), T47D (breast carcinoma) and AGS (gastric carcinoma) cell lines by activating the apoptotic machinery.[158]

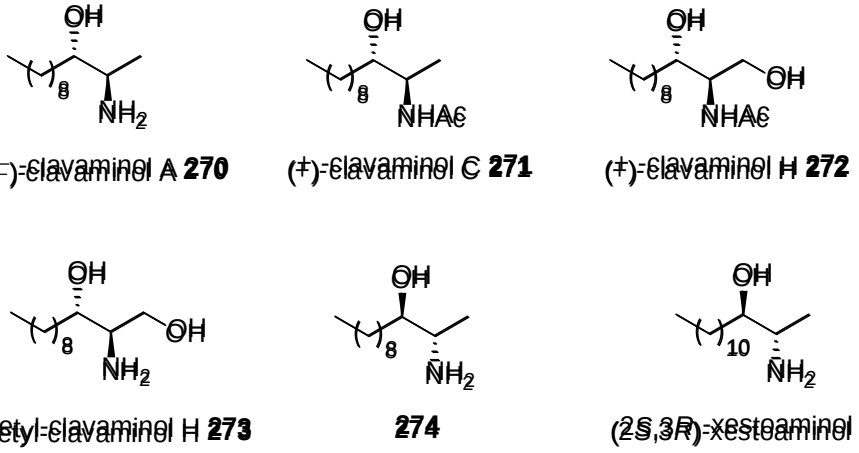
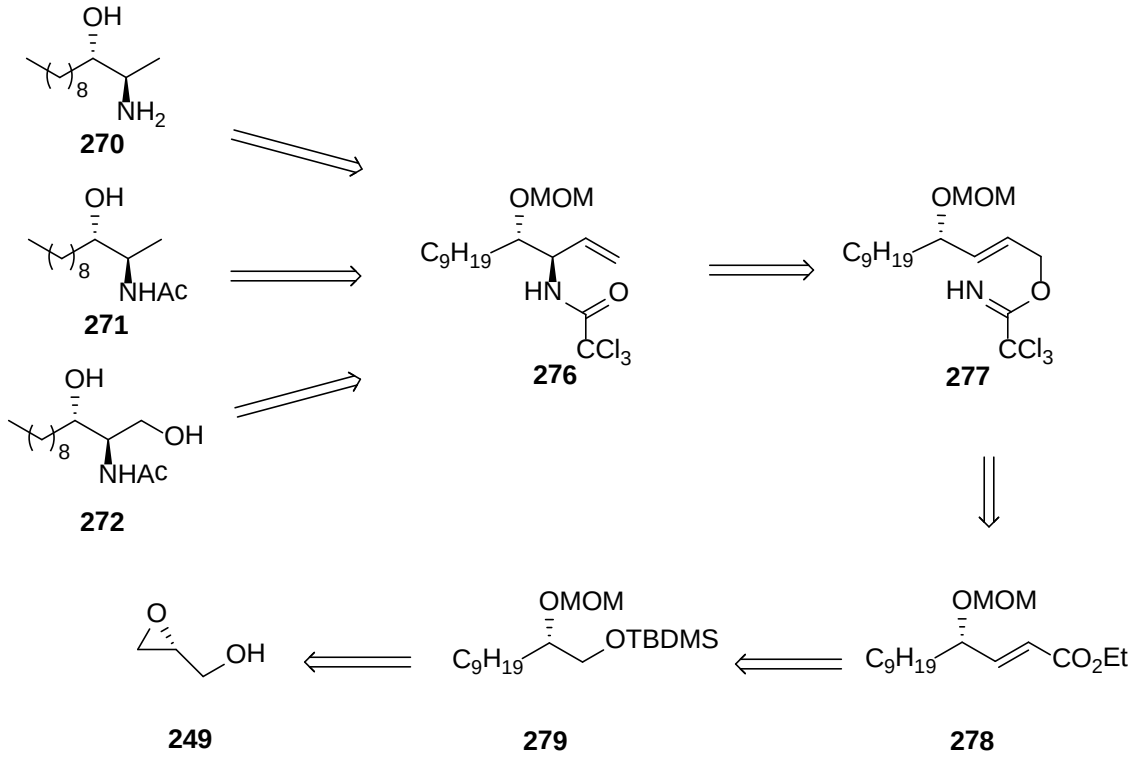


Figure 6- Structures of clavaminol A, C, H, desacetyl-clavaminol H 273 and xestoaminol C

2.4.1 Retrosynthetic Analysis of Clavaminol A, C and H

The proposed retrosynthetic analysis of clavaminol A, C and H is shown in Scheme 84. The key intermediate, allylic trichloroacetimidate **277** could be prepared from the *E*-α,β-unsaturated ester **279** which could then be synthesised from the readily available ethyl (*R*)-glycidol **249**. The stereoselective rearrangement of **277** would allow the formation of the allylic trichloroacetamide **276** introducing the (2*R*)-stereogenic centre. Finally, oxidative cleavage of the alkene and deprotection of the amide **276** would give the target clavaminols, A **270**, C **271** and H **272**.



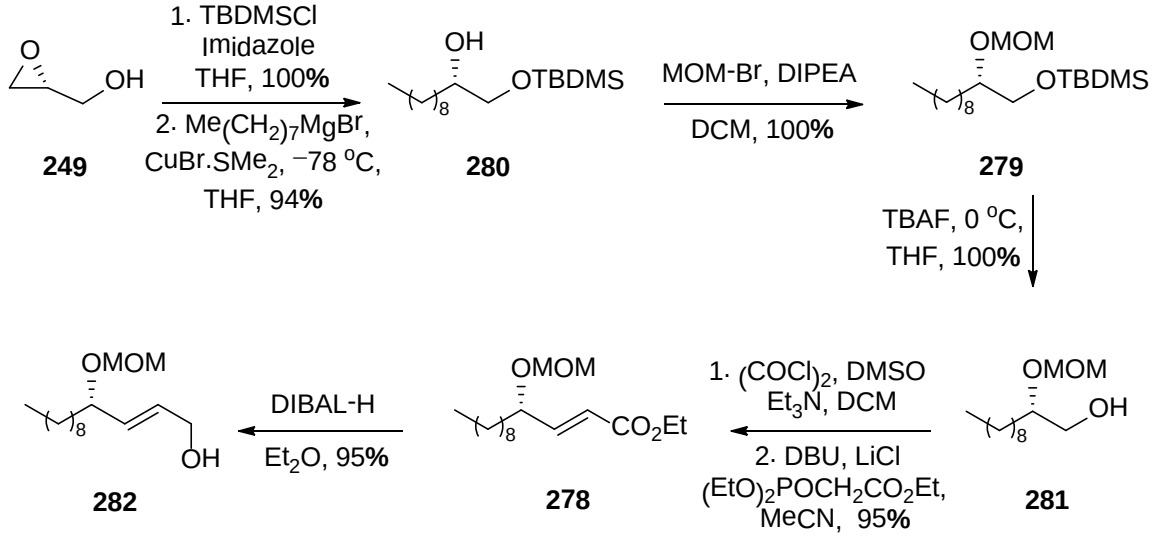
Scheme 84- Retrosynthetic analysis of clavaminol A, C and H

2.4.2 Synthesis of Clavaminol A, C and H

2.4.2.1 Synthesis of Clavaminol A and C

2.4.2.1.1 Synthesis of allylic alcohol 282

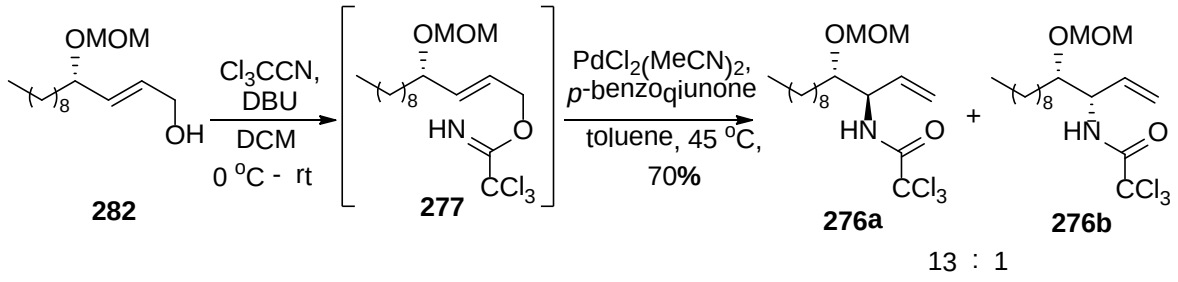
Using the same synthetic approach for the synthesis of allylic alcohol **254**, the allylic alcohol **282** was prepared in seven steps (Scheme 85). Protection of (*R*)-glycidol **249** gave the *tert*-butyldimethylsilyl ether **250** in a quantitative yield. Regioselective ring opening of the epoxide using octylmagnesium bromide in the presence of copper(I) bromide dimethyl sulfide gave the alcohol **280** in 94% yield. Protection of the secondary hydroxyl group as the MOM-ether furnished **279** which was followed by selective removal of the silyl ether using TBAF to give primary alcohol **281** in quantitative yield. With the desired primary alcohol **281** in hand, this was then subjected to a one-pot Swern oxidation/Horner-Wadsworth-Emmons reaction to provide exclusively the *E*-α,β-unsaturated ester **278**. Reduction of the ester moiety with 2.2 equivalents of the DIBAL-H completed the synthesis of allylic alcohol **282** in an 85% overall yield.



Scheme 85- Synthesis of allylic alcohol 282

2.4.2.1.2 Synthesis of the allylic trichloroacetamide 276a

The allylic alcohol **282** was converted to allylic trichloroacetimidate **277** using trichloroacetonitrile and a catalytic amount of DBU (Scheme 86). The key allylic trichloroacetimidate **277** was then subjected to a Pd(II)-catalysed Overman rearrangement using *p*-benzoquinone in toluene as a non-coordinating solvent. As expected, this resulted in a highly diastereoselective formation of the *erthyro*- and *threo*-allylic trichloroacetamides **276a** and **276b** in a 70% yield over the two steps and in a 13:1 ratio. Once again, the desired allylic trichloroacetamide **276a** was easily separated from **275b** using flash column chromatography.

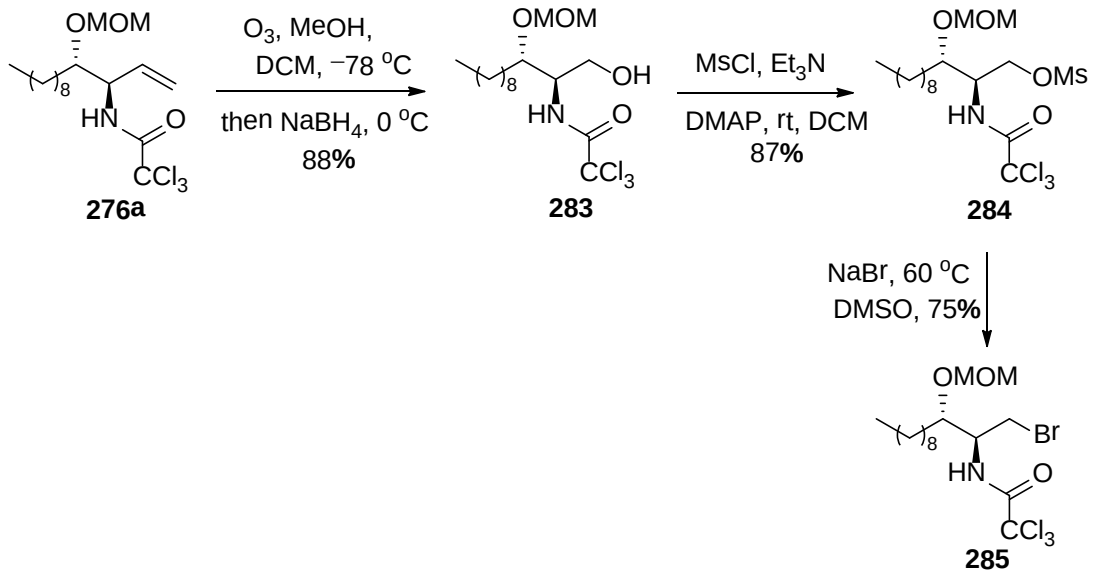


Scheme 86- Synthesis of allylic trichloroacetamide 276a

2.4.2.1.3 Completion of Clavaminol A and C

The major allylic trichloroacetamide product from the rearrangement, **276a** was then easily ozonised, followed by straightforward reduction of the resulting aldehyde to give the corresponding alcohol **283** in high yield (Scheme 87). Introduction of the mesylate using

methanesulfonyl chloride gave **284** in high yield and was followed by a reaction with sodium bromide to give bromide **285**.



Scheme 87- Synthesis of bromide 285

Interestingly, the key hydrogen atoms of alcohol **283** are observed in very different chemical shift values compared to the hydrogen atoms of bromide **285** in the ^{1}H NMR spectrum (Figure 7). These differences are observed at 3.70 ppm (3-H) and 3.85 ppm (2-H) in alcohol **283** and at 3.58 ppm (3-H) and 4.20 ppm (2-H) in bromide **285**. In addition to this, both 1-H_2 hydrogen atoms in the alcohol were found at a different chemical shift values and different multiplicity to that observed in bromide **285**. This is likely due to the formation of hydrogen bonding between the amide and alcohol functionalities in **283** causing a downfield shift of one of the 1-H_2 hydrgen atoms to 3.97.

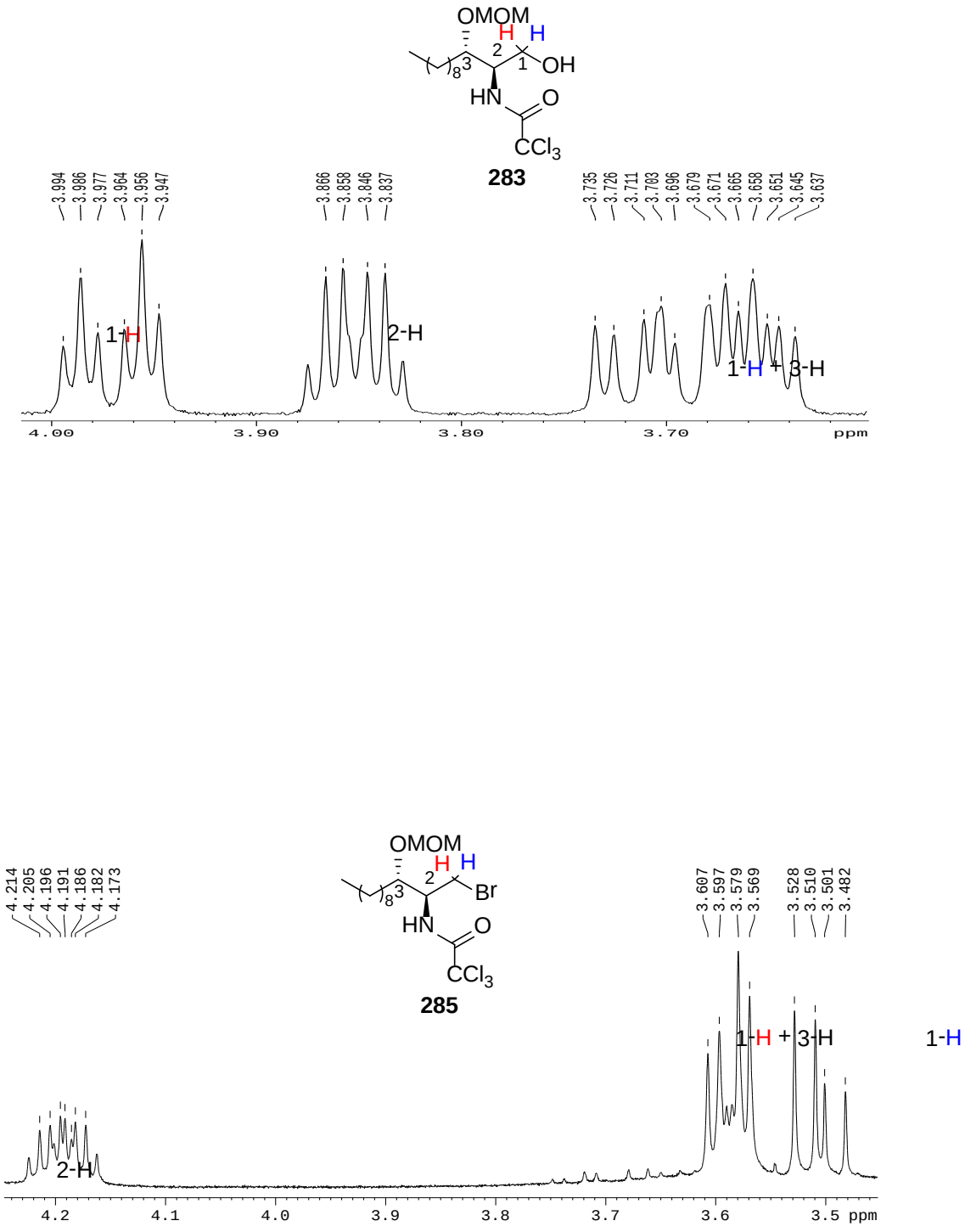
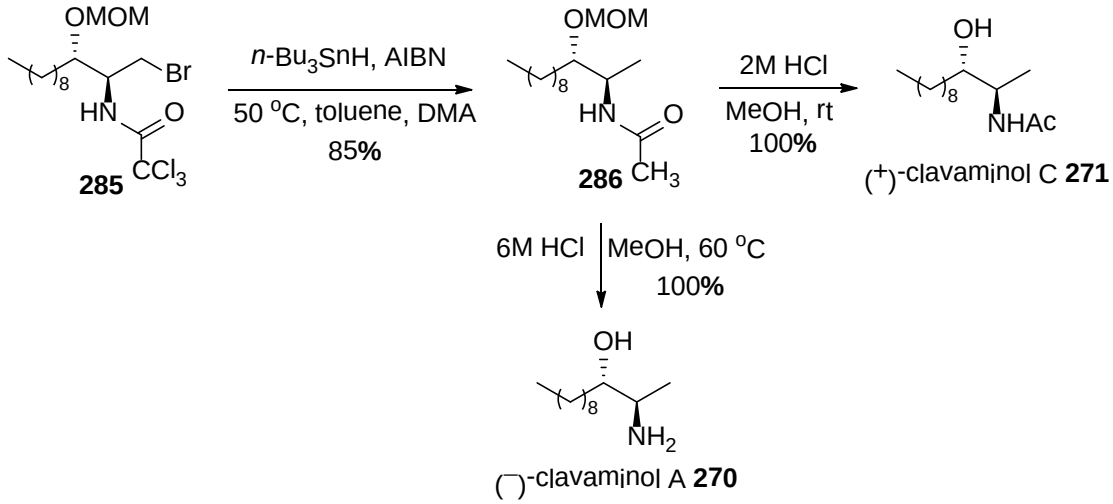


Figure 7- ^{1}H NMR spectrum of alcohol 283 and bromide 285

The final stage of the synthesis of clavaminol A **270** and C **271** involved the installation of the methyl side chain and an acid-mediated deprotection of the MOM and trichloroacetyl groups. In 1994, Jacquinet and co-workers reported that *N*-trichloroacetyl groups in

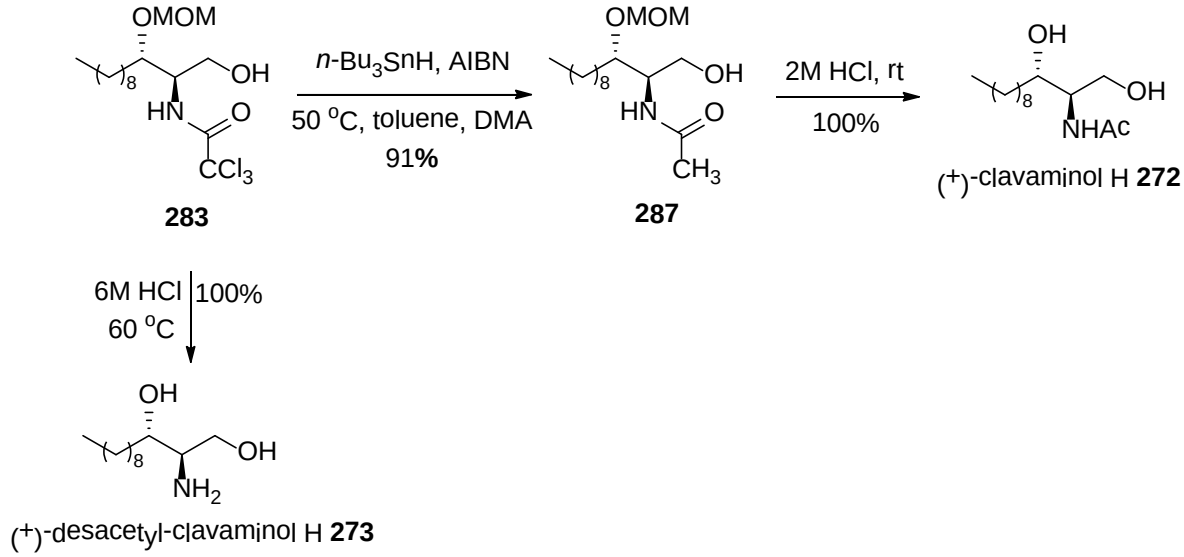
disaccharide products can be transformed into *N*-acetyl groups under mild radical reducing conditions using a *n*-tributyltin hydride mediated reaction.[164] It was decided to utilise this protocol for the transformation of product **285** to **286** where both the primary bromide and trichloroacetyl groups are reduced in a single step. The bromide **285** was subjected to a reduction under neutral conditions using *n*-tributyltin hydride. This gave compound **286** in 85% yield (Scheme 88). This mild and selective method was chosen due to the fact that the *N*-acetyl group required for the synthesis of (+)-clavaminol C **271** could also be formed during the reduction of the C-Cl bonds. Finally, removal of both the MOM and *N*-acetyl groups under acidic conditions at 60 ^{o}C completed the synthesis of (–)-clavaminol A **270** in a quantitative yield. The use of mild acidic conditions led to the synthesis of (+)-clavaminol C **270** and this was again achieved in a quantitative yield.[165]



Scheme 88- Synthesis of clavaminol A and C

2.4.2.2 Synthesis of Clavaminol H

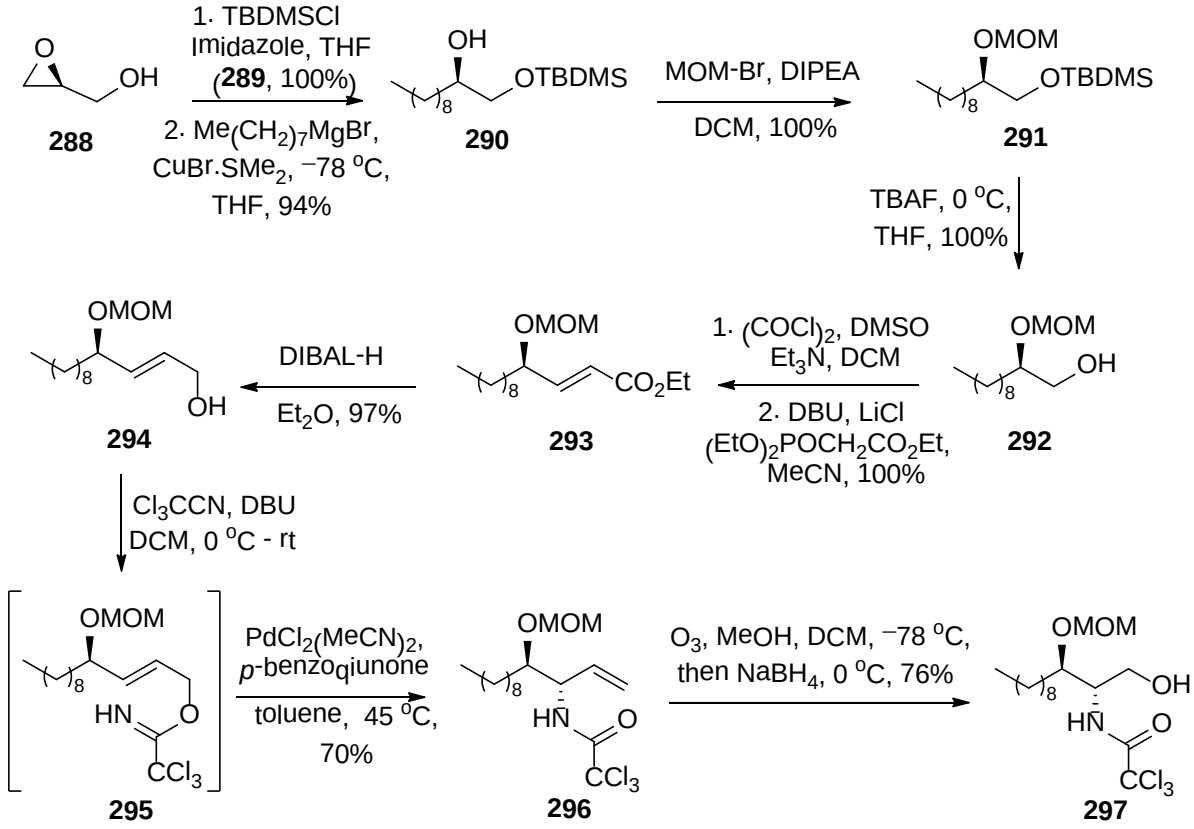
(+)-Clavaminol H **272** was synthesised in a two step synthetic route from primary alcohol **283** (Scheme 89).[165] The *N*-trichloroacetyl of alcohol **283** was again reduced using similar reaction conditions to that previously reported by Jacquinet and co-workers.[164] This gave the *N*-acetyl alcohol derivative **287** in high yield. Selective deprotection of the MOM-protecting group under mild acidic conditions completed the synthesis of (+)-clavaminol H **272** in quantitative yield. Removal of both the MOM and *N*-trichloroacetyl groups using acidic conditions at 60 ^{o}C directly led to the formation of the cytotoxic amine, (+)-desacetyl-clavaminol H **273**.



Scheme 89- Synthesis of (+)-clavaminol H and (+)-desacetyl-clavaminol H

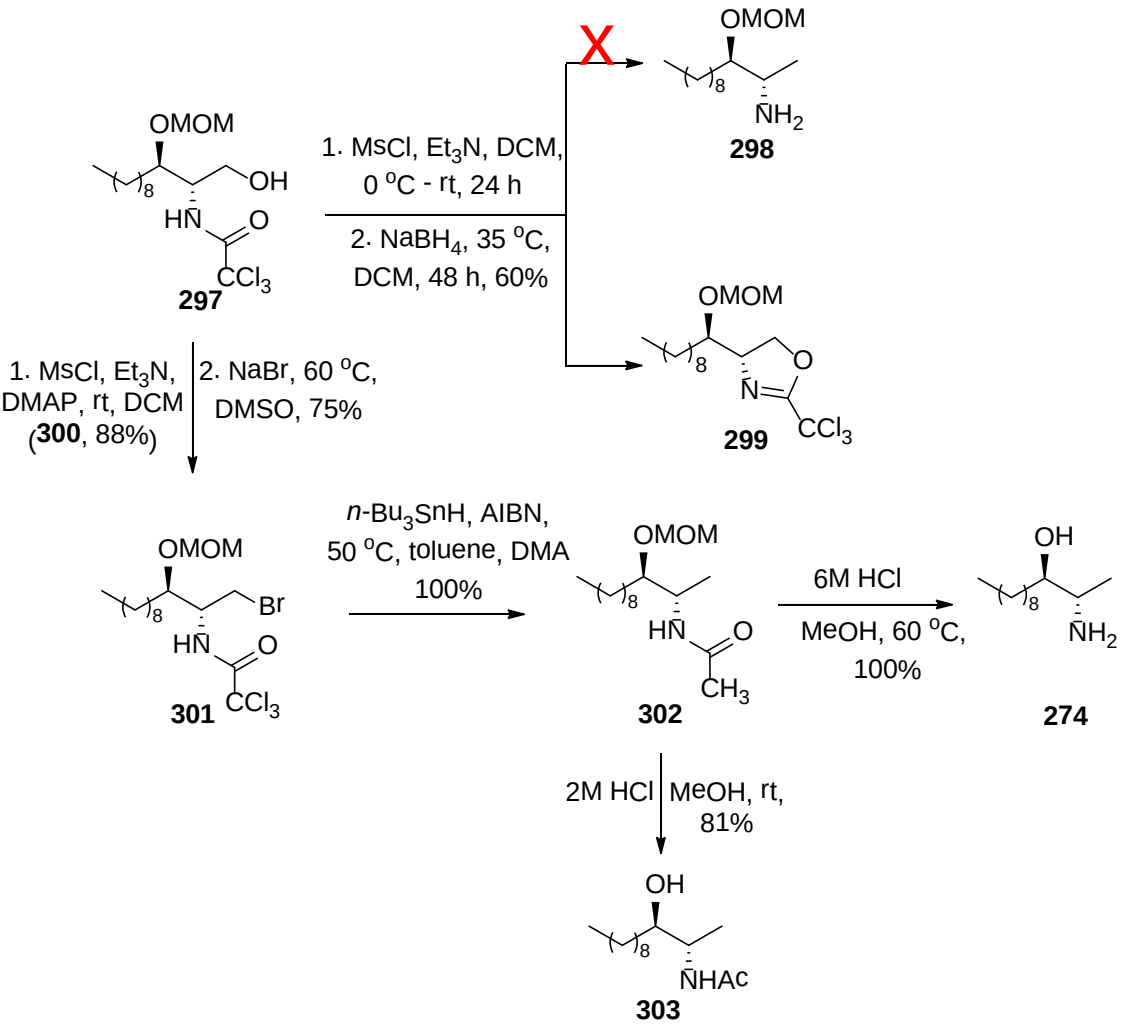
2.4.3 Synthesis of (2*S*,3*R*)-clavaminol A, C and H

Initially in this project, the opposite enantiomers of clavaminol A **270**, C **271** and H **272** which have (2*S*,3*R*)-configuration were prepared in a similar manner as described for the synthesis of the natural products **270**, **271** and **272** starting from (*S*)-glycidol **288** (Scheme 90). The reason behind their synthesis was to prove that the optical rotation of (2*R*,3*S*)-enantiomers of clavaminol A **270**, C **271** and H **272** were in agreement with the (2*R*,3*S*)-natural products, a result contradictory to that described by the groups of Greck and Ferreira.[166,167] Greck and Ferreira had previously synthesised clavaminol H and desacetyl-clavaminol H in (2*S*,3*R*)-absolute configuration. As expected, the optical rotation of **274**, **301**, **304** and **305** were found to have similar value and opposite sign to that observed for the (2*R*,3*S*)-natural products. The first stage of this synthesis involved the synthesis of alcohol **297** which was required for the synthesis of **274, 301**, **304** and **305**. This was achieved in the same manner as for the synthesis of the (2*R*,3*S*)-alcohol **283**.



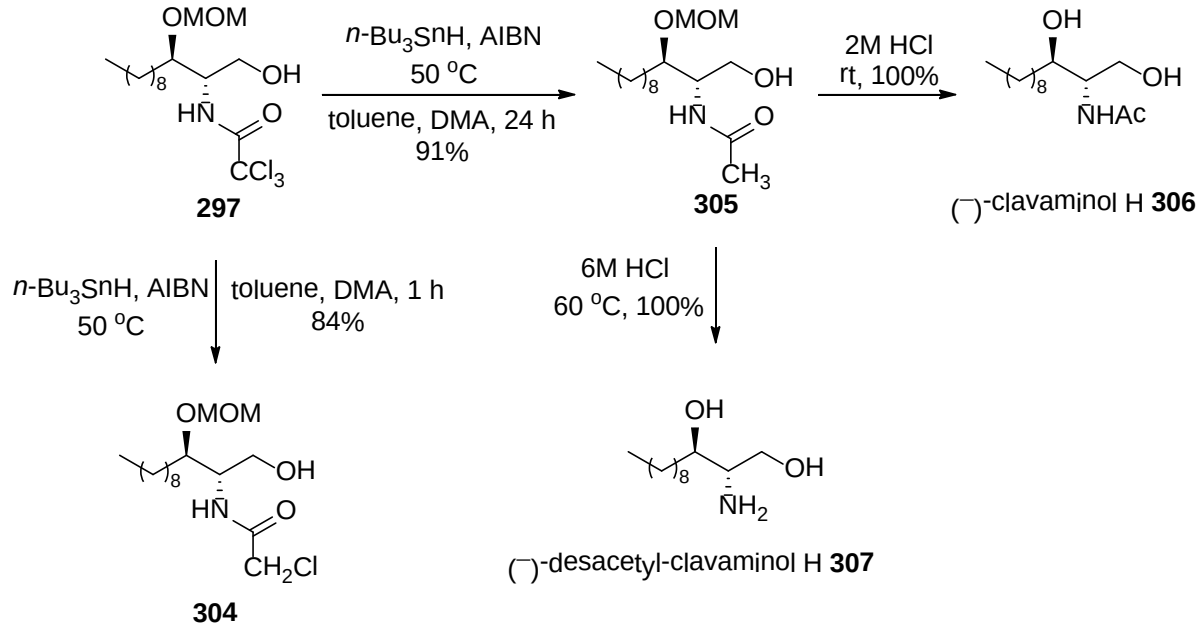
Scheme 90- Synthesis of (2*S*,3*R*)-alcohol 297

Alcohol **297** was then mesylated and formation of the methyl side by reduction of the mesylate **300** with sodium borohydride was then attempted. However, this gave 4,5-dihydro-1,3-oxazole **299** in 60% yield (Scheme 91). As a consequence of this, an alternative method described previously for the formation of compounds **284** and **285** was proposed which involved the synthesis of **300** using mesyl chloride and **301** using sodium bromide. The bromide **301** was subsequently subjected to similar transformations for the synthesis of clavaminol A and C, and this gave unnatural (2*S*,3*R*)-clavaminol A **274** and C **303** in excellent yields.



Scheme 91- Synthesis of (2*S*,3*R*)-clavaminol A 274 and C 303

The synthesis of *N*-acetyl alcohol **305** required for the synthesis of (–)-clavaminol H **306** and (–)-desacetylclavaminol H **307** was also attempted, using similar reaction conditions to that described for the synthesis of compound **287**. Initial reactions involving heating under reflux for one hour resulted in the cleavage of only two C-Cl bonds which gave **304** in 84% yield (Scheme 92). Leaving the reaction for 24 hours allowed the reduction of all three C-Cl bonds, giving the desired *N*-acetyl alcohol derivative **305** in high yield. Once again, the same procedures previously described for the synthesis of compounds **272** and **273**, were used to prepare (–)-clavaminol H **306** and (–)-desacetyl-clavaminol H **307** in quantitative yields.



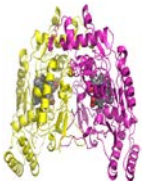
Scheme 92- Synthesis of (–)-clavaminol H and (–)-desacetyl-clavaminol H

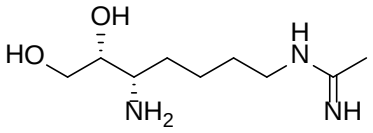
2.4.4 Conclusions

A new 14-step stereoselective synthesis of (–)-clavaminol A and (+)-clavaminol C was successfully developed in 49% overall yield from (*R*)-glycidol. In addition to this, (+)-clavaminol H and the cytotoxic (+)-desacetyl-clavaminol H were also synthesised in 12 steps in a 48% overall yield. Using similar chemistry, the (2*S*,3*R*)-enantiomers were also synthesised in an efficient manner from (*S*)-glycidol. This confirmed the assignment of the absolute stereochemistry of (2*R*,3*S*)-configuration for the natural products. The key steps involved a palladium(II)-catalysed directed Overman rearrangement to establish the key C–N bond, while a one-pot, tributyltin hydride-mediated reduction allowed the formation of the *N*-acetyl group and the methyl side chain.

2.5 NO-inhibitor

Nitric-oxide synthases (NOS) **308** are a family of enzymes which consist of three isoforms, neuronal nNOS, endothelial eNOS and inducible iNOS. They produce nitric oxide (NO) *via* the oxidation of a L-arginine substrate (Figure 8).[168,169] The nitric oxide produced by these three isoforms has broad biological properties as a second messenger in the cardiovascular and nervous systems and as a cytotoxic agent in the immune system as well as in a variety of cellular processes.[168] However, overproduction of nitric oxide by nNOS and iNOS can cause various pathological disorders and many diseases. In recent years, medicinal studies have shown that iNOS contributes to a large number of pathologies which possess an inflammatory component, including septic shock,[170] arthritis,[171] neurodegenerative disorders,[172-174] and cancers.[175,176] Recently, inhibition of iNOS has resulted in a number of proposed applications, but the identification of a potent, highly iNOS selective, non-toxic, and bio-available inhibitor remains an important pharmacological challenge, and as yet no molecule has been put on the market.[177] NO-inhibitor, acetamidine lysine derivative **309** has been described as one of the most highly selective inhibitors for iNOS, with an IC_{50} of 12 μM (Figure 8).





NO-inhibitor **309**

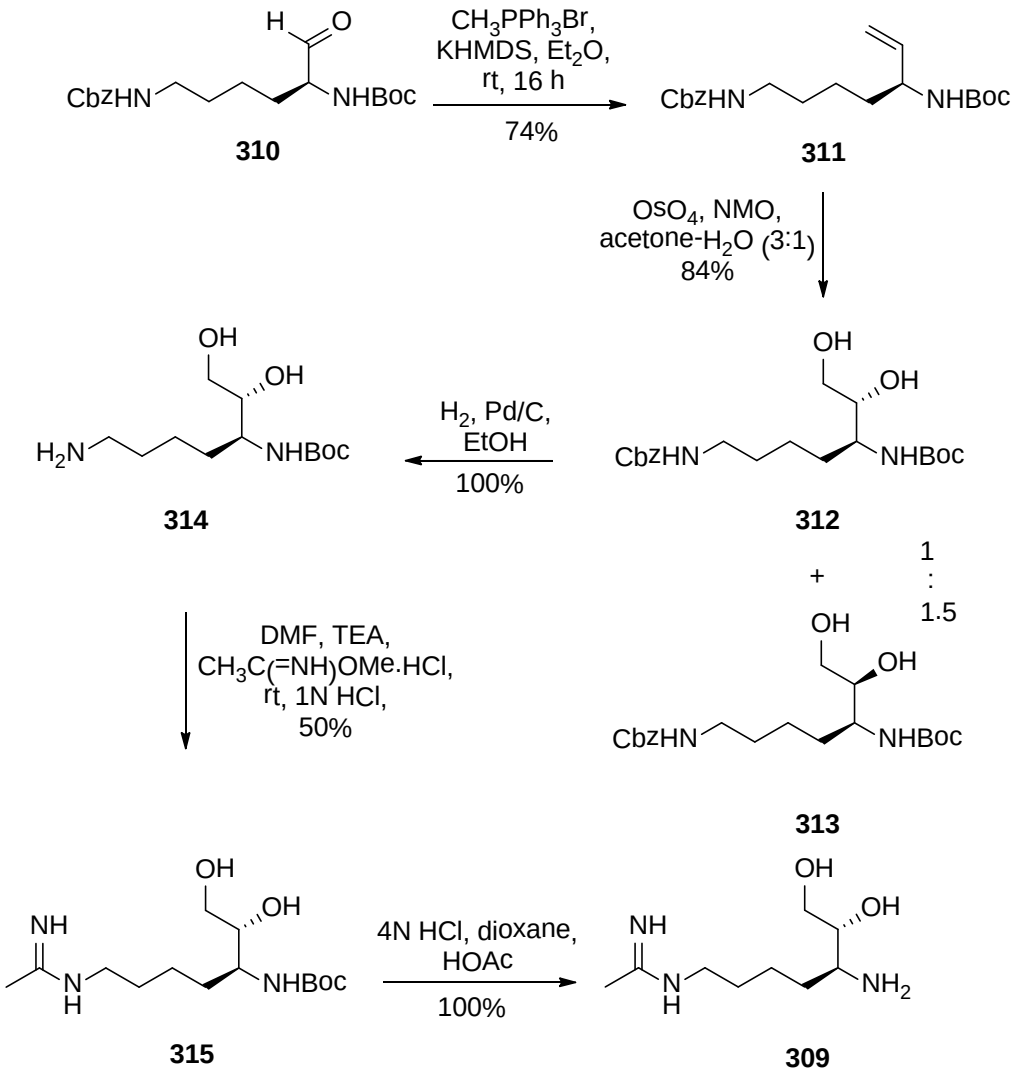
nitric-oxide synthase NOS **308**

Figure 8- NOS enzyme and its NO-inhibitor 308

2.5.1 Previous Synthesis of an Acetamidine Lysine Derivative

In 1998, Hallinan and co-workers reported the synthesis of the acetamidine lysine derivative **309** using the dihydroxylation of a lysine derivative as the key step (Scheme 93).[178] The synthesis began with the conversion of aldehyde **310** to the corresponding alkene **311** using a Wittig methylation reaction, followed by the introduction of a vicinal

diol using Upjohn dihydroxylation conditions to give **312** and **313** in a ratio of 1 : 1.5. Hydrogenation of diol **312** then led to removal of the Cbz-protecting group to give epsilon amine **314** in quantitative yield. This was followed by treatment of **314** with methyl acetimidate hydrochloride to furnish amidine **315**. Finally, removal of the Boc group under acidic conditions led to the synthesis of acetamidine lysine derivative **309** in quantitative yield.

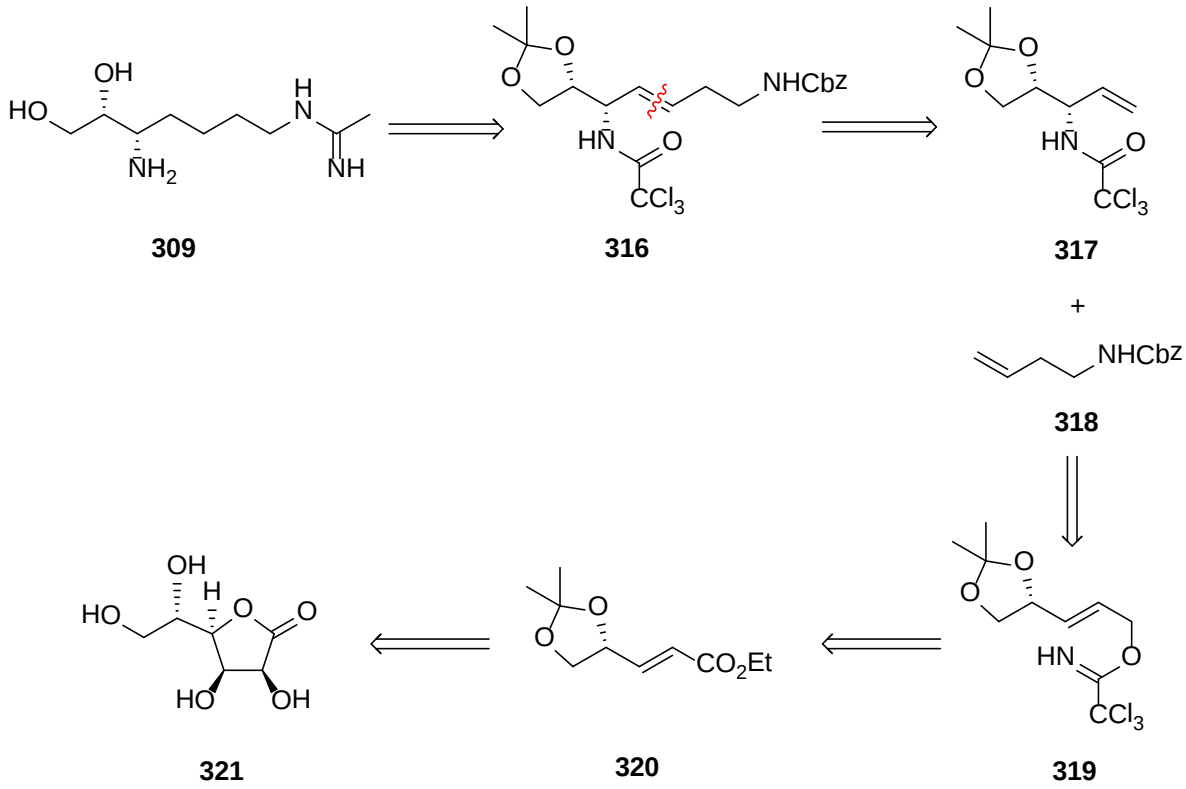


Scheme 93- First synthesis of NO-inhibitor 309 by Hallinan and co-workers

2.5.2 Retrosynthetic Analysis of NO-inhibitor 309

The proposed retrosynthetic analysis of NO-inhibitor is outlined in Scheme 94. Deprotection of the acetonide, trichloroacetyl groups, substitution of the methyl acetimidate with the Cbz groups and dehydrogenation would lead back to **316**. Disconnection of **316** at the alkene linkage would give allylic amide **317**, which was to be

prepared from the key intermediate allylic acetimidate **319** using a stereoselective rearrangement introducing the (2*S*)-stereogenic centre. Allylic acetimidate **319** could be made from the ester **320** which could be synthesised from the readily available L-gulonic acide γ-lactone **321**.



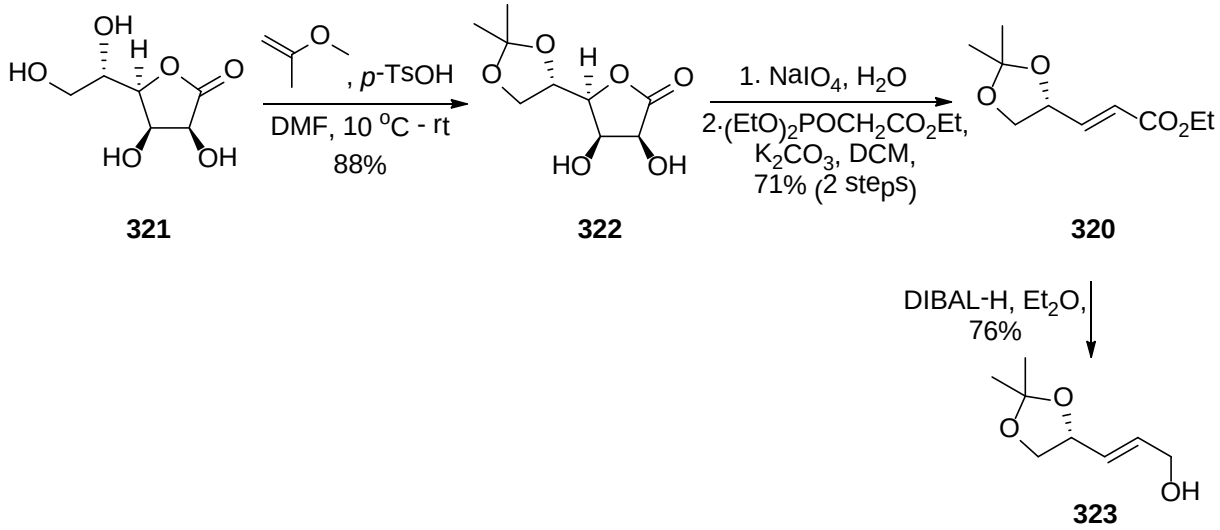
309 **316** **317** **318** **321** **320** **319**

Scheme 94- Proposed retrosynthetic analysis of the NO-inhibitor 309

2.5.3 Attempted Synthesis of NO-inhibitor 309

2.5.3.1 Synthesis of allylic alcohol 323

The synthesis of NO-inhibitor **309** began with the preparation of the protected allylic alcohol **323** (Scheme 95). The synthesis of the acetonide protected allylic alcohol **323** was achieved in 4 steps from the commercially available L-gulonic acide γ-lactone **321**. Firstly, L-gulonic acide γ-lactone **321** was reacted selectively with the isopropenyl methyl ether using a protocol described by Hubschwerlen to give acetonide **322** in high yield.[179] A one-pot oxidation with sodium periodate (oxidative cleavage of **322**) followed by a Horner-Wadsworth-Emmons (HWE) reaction using potassium carbonate as a base and triethyl phosphonoacetate, gave exclusively *E*-α,β-unsaturated ester **320** in 71% yield over the two steps. Straightforward DIBAL-H reduction of the ester afforded the corresponding allylic alcohol **323** in 76% yield.

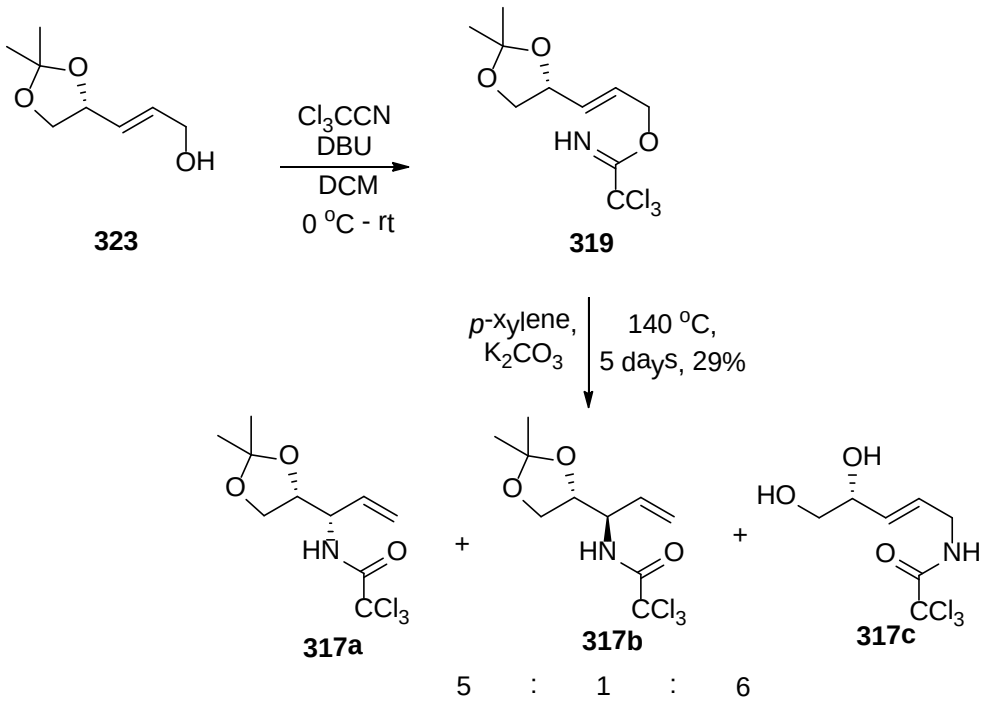


321 **322** **320** **323**

Scheme 95- Synthesis of allylic alcohol 323

2.5.3.2 Synthesis of allylic trichloroacetamide 317a

Once again, the allylic alcohol **323** was readily converted to allylic trichloroacetimidate **319**, which was used without further purification (Scheme 96). Initially, a thermal Overman rearrangement was employed as the first key step of this synthesis. The allylic trichloroacetimidate **319** was converted to the corresponding two diastereomers **317a**, **317b** in a combined 29% yield and formation of the [1,3]-product **317c**. However, this reaction was low yielding and gave the products in a 5 : 1 : 6 ratio, respectively. The low yield achieved was attributed to the decomposition of the unstable allylic imidate **319** under these conditions.



Scheme 96- Rearrangement of the allylic trichloroacetimidate 319 using thermal conditions

The diastereomeric ratio, as for all previous rearrangements, was determined by examining the ^{1}H NMR spectra of the products. This is a simple process to achieve, as the *syn*-and *anti*-diastereomers have different NMR spectra, which showed dissimilar chemical shifts between the two stereogenic hydrogen atoms on each molecule. In the example below (Figure 9), the hydrogen atoms of the *syn*- and *anti*-diastereomers **317a** and **317b** at C-3 and C-4 are observed at similar chemical shifts. However, the hydrogen atoms at C-5 are very different for each diastereomer.

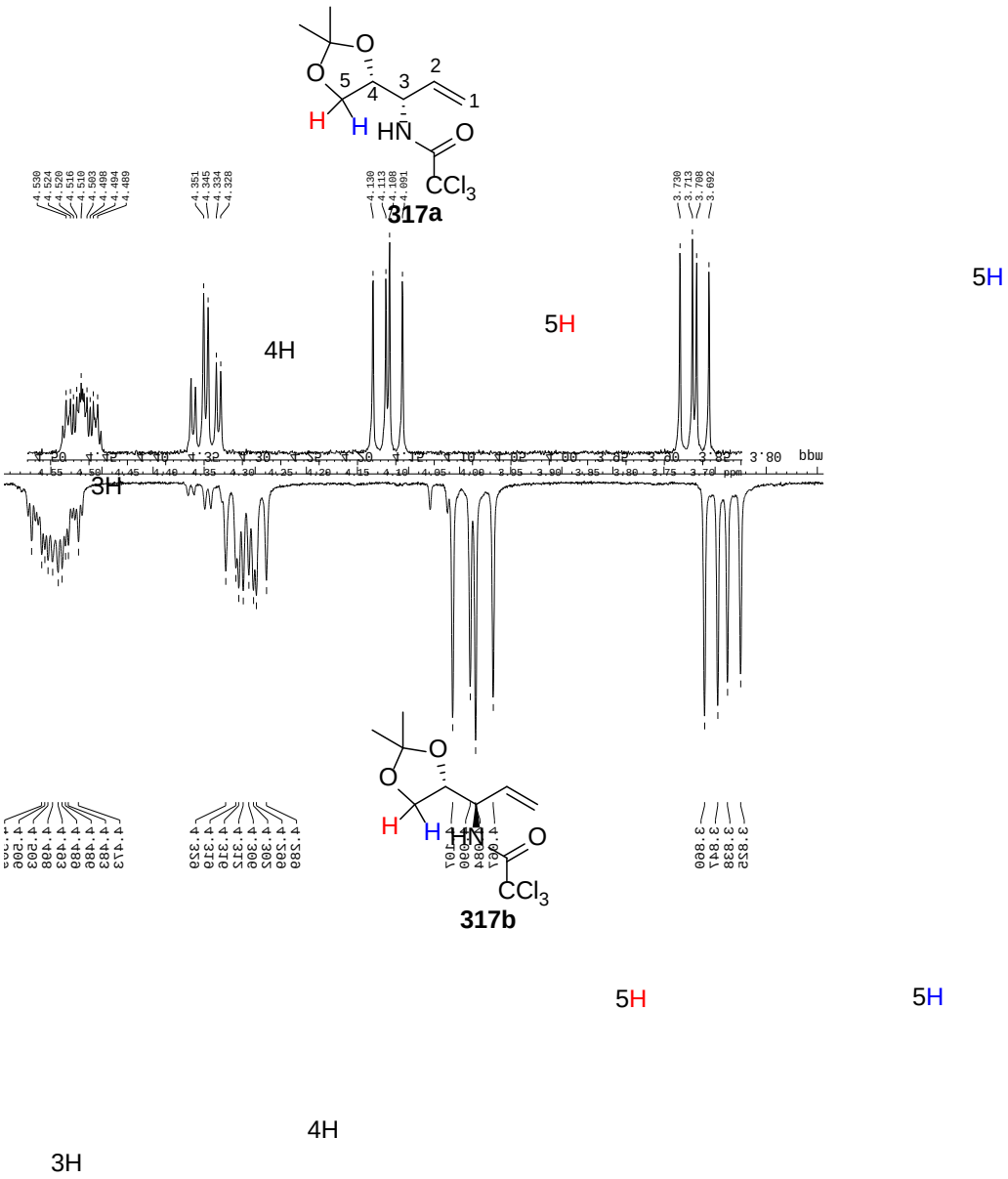
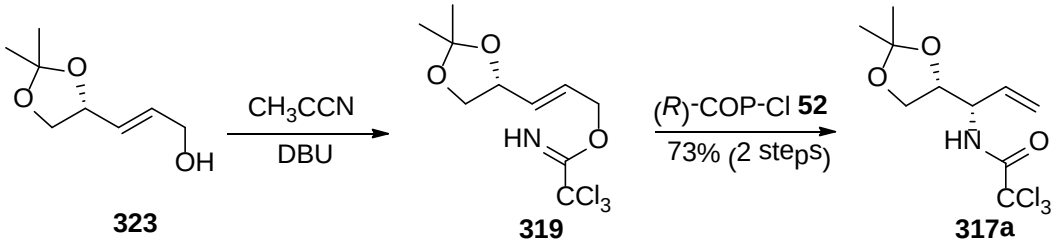


Figure 9- ^{1}H NMR spectrum of *syn*-(top) and *anti*-(bottom) diastereomers

As the thermal Overman rearrangement at this stage did not proceeded efficiently, it was decided to carry out this process by transition metal catalysis. In an extensive study, the Sutherland group has previously screened a variety of metal catalysts for the asymmetric rearrangement of the enantiomer of **323** in an attempt to find reaction conditions which would provide the desired [3,3]-products, whilst eliminating formation of the undesired [1,3]-product.[55] Based on these reactions, the rearrangement of **319** was also attempted using $PdCl_2(MeCN)_2$, however, this gave a low yield of 32% of allylic trichloroacetamide **317a** and in modest diastereoselectivity (4:1). A highly successful rearrangement in this

project was performed when (*R*)-COP-Cl catalyst **52** was utilised and this provided the *syn*-diastereomer **317a** in good yield as a single diastereomer (over 2 steps) (Scheme 97). As expected, the bulky catalyst coordinates to the opposite face of the existing (4*R*) stereocentre (so blocking the front side from attack) thus ensuring that the new C-N bond forms on the same side as the stereocentre. This is an example of a matched pairing as the chirality of both the substrate and chiral catalyst complement one another; the bulky catalyst coordinates to the opposite face to the existing (4*R*) stereocentre (so blocking the back side from attack) thus ensuring that the new C-N bond forms on the same side as the stereocentre and giving a significant enhancement in diastereoselectivity.

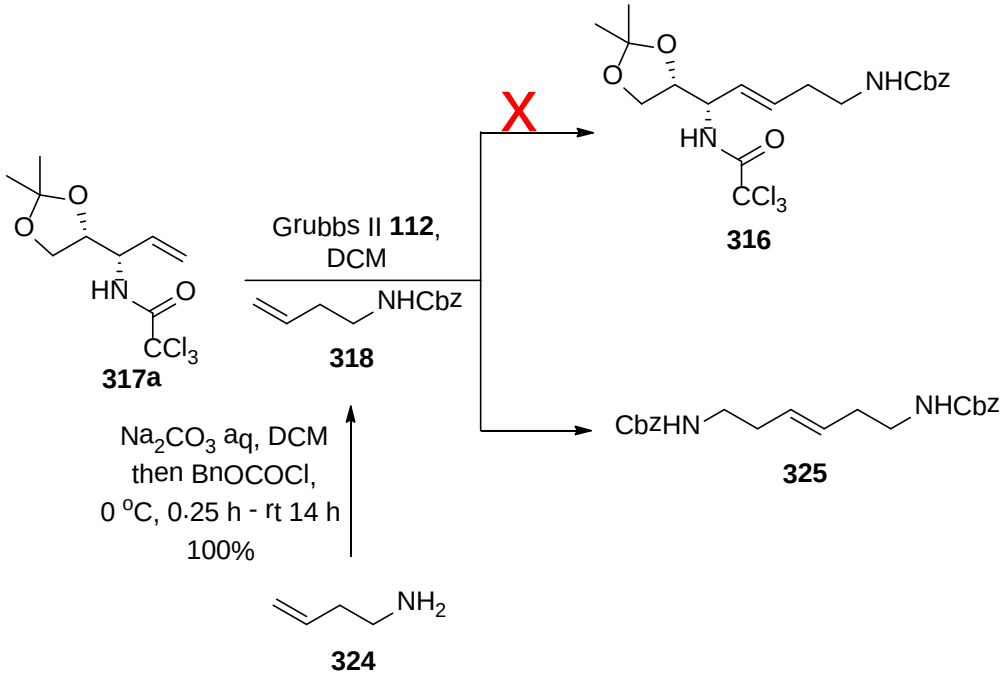


323 **319** **317a**

Scheme 97- Rearrangement of the allylic trichloroacetimidate 319 using (*R*)-COP-Cl

2.5.3.3 First attempt at a cross coupling reaction

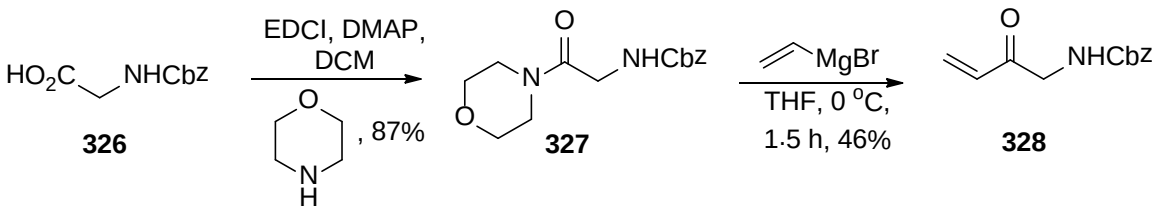
The first cross-metathesis partner **318** required for the cross-coupling step was easily prepared from the commercially available 3-butenylamine hydrochloride salt **324** in a quantitative yield using standard Cbz-protection conditions (Scheme 98). With the olefin partner **318** in hand, it was subjected to a cross-metathesis reaction with allylic trichloroacetamide **317a**. This gave the homodimeric product **325** and other undesired products.



Scheme 98- Attempted synthesis of cross coupled product 316

2.5.3.4 Second attempt at a cross coupling reaction

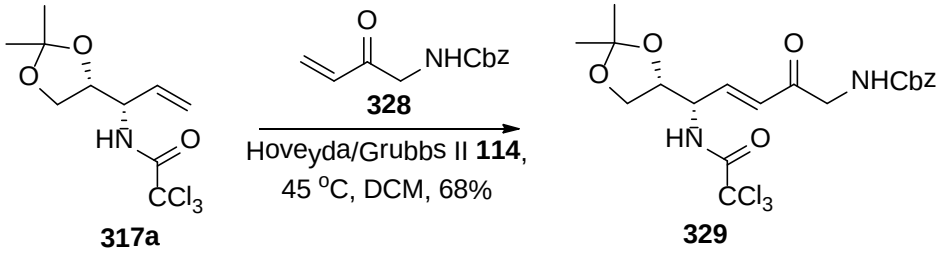
As the cross methathesis reaction was not possible using partner **318**, attention then turned to use the protected enone **328** as an alternative olefin partner. This electron-defficient olefin partner was generated easily in a two step synthesis from the protected carboxylic acid **326** (Scheme 99). The commercially available **326** was converted to the morpholine amide **327** in high yield, which was then converted to the corresponding protected enone **328**. This reaction was carried out according to the conditions outlined in a procedure by Martin and co-workers, using vinylmagnesium bromide.[180] This alkylation was achieved in a yield of 46%, although with repetition of this experiment, yields proved to be somewhat inconsistent.



Scheme 99- Synthesis of the alternative olefin partner 328

Having synthesised the second olefin partner **328** in good yield, a cross-metathesis reaction was then successfully achieved (Scheme 100). According to Grubbs classification,

protected enone **328** is considered a type II olefin, while other terminal alkenes such as trichloroacetamide **317a** are considered as type I.[181] Thus, cross-metathesis reactions between type I and type II olefins should successfully lead to a selective heterodimerisation of the two alkene partners. Based on this study, allylic trichloroacetamide **317a** was treated with the protected enone **328** using Hoveyda/Grubbs II catalyst **114** which gave the desired cross coupled **329** in a 68% yield.



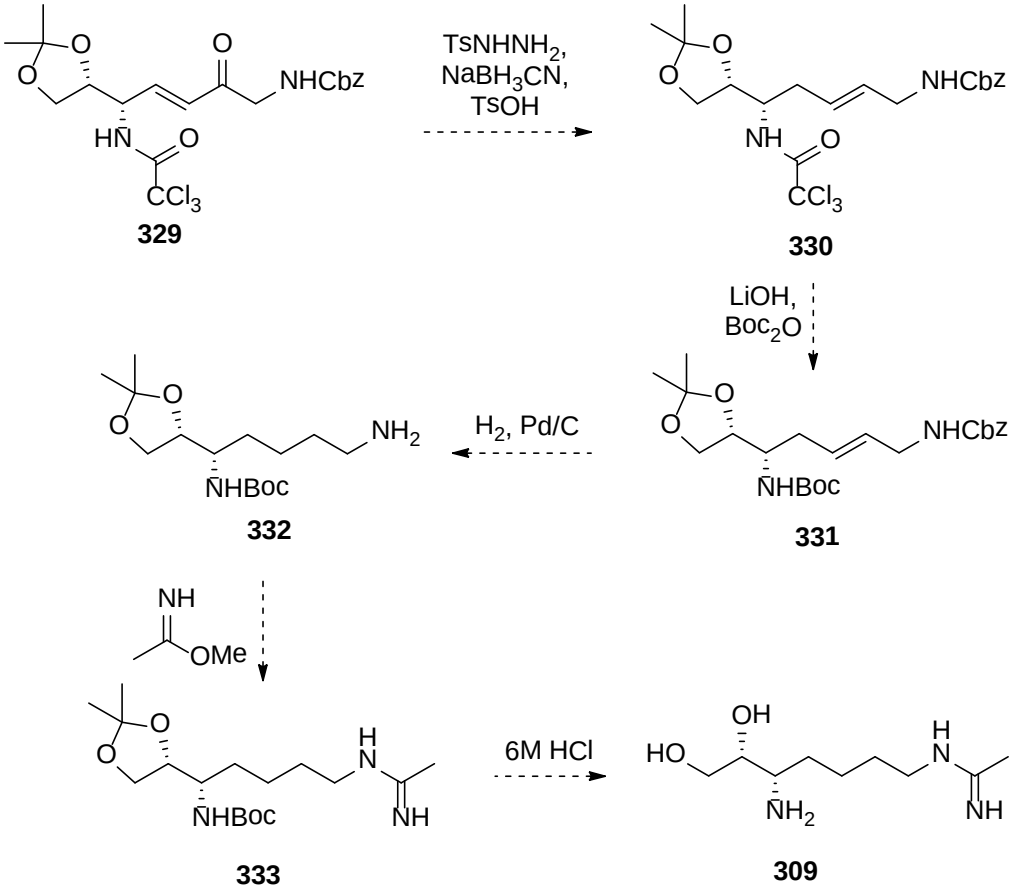
Scheme 100- Synthesis of the cross coupled product 329

2.5.4 Conclusions to the attemped Synthesis of NO-inhibitor

In conclusion, the protected cross coupled compound **329** required for the synthesis of NO-inhibitor **309** was synthesised in reasonable yield over a seven step synthesis. The key steps of this synthesis involved a palladium(II)-catalysed Overman rearrangement using (*R*)-COP-Cl to create the new C–N bond in a *syn*-configuration and a cross-metathesis reaction using the protected enone **328**. Another proposed olefin partner **318** with the cross-metathesis step was also investigated.

2.5.5 Future Work

Future work for this project includes five additional steps to synthesise the desired compound **309**. As shown in Scheme 101, the protected enone **329** will be reduced with olefin transposition *via* the tosyl hydrazone to give the (*Z*)-alkene **330** which will then be subjected to a one-pot hydrolysis of the trichloroacetamide and Boc protection of the amine. Hydrogenation of the resulting fully protected *Z*-alkene **331** will reduce the alkene and remove the Cbz-protecting group. Finally, reaction of the unprotected amine **332** with methyl acetimidate would give the protected NO-inhibitor **333**. Acid mediated deprotection of the diol and amine functional groups would complete the synthesis of target compound **309**.



Scheme 101- Proposed synthesis of the NO-inhibitor 309

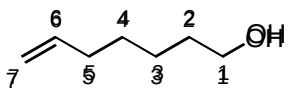
3.0 Experimental Section

3.1 General Experimental

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 THF and diethyl ether were distilled from sodium and benzophenone, whilst dichloromethane (DCM) was distilled from calcium hydride. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Brine refers to a saturated solution of sodium chloride. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to 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. Melting points were determined on a Reichert platform melting point apparatus. Infrared spectra were obtained using a JASCO FTIR 410 using a Golden Gate apparatus. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Chiral HPLC was performed on a Agilent 1100 series instrument and were calibrated with the appropriate racemic mixture.

3.2 Synthesis of (±)-Physoperuvine

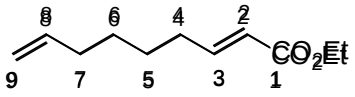
6-Hepten-1-ol (187)[182]



Ethyl 6-heptenoate (**186**) (2.5 g, 16.0 mmol) was dissolved in diethyl ether (200 mL) and cooled to –78 °C. DIBAL-H (1 M in hexane) (35 mL, 35.2 mmol) 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 (50 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*. Flash chromatography (diethyl ether/petroleum ether, 3:7) gave 6-hepten-1-ol (**187**) (1.71 g, 94% yield) as a yellow oil. Spectroscopic data consistent with literature.[182] δ_H (400 MHz, $CDCl_3$) 1.32–1.47 (4H, m, 3-H_2 and 4-H_2), 1.53–1.62 (2H, m, 2-H_2), 2.06 (2H, q, *J* 6.6 Hz, 5-H_2), 3.63 (2H, t, *J* 6.6 Hz, 1-H_2), 4.93 (1H, d, *J* 10.0 Hz, 7-*H*H), 4.99 (1H, d, *J* 15.6 Hz, 7-H*H*), 5.80 (1H, ddt, *J* 15.6, 10.0, 6.6 Hz, 6-H); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_2), 28.7 (CH_2), 32.6 (CH_2), 33.7 (CH_2), 62.8 (CH_2), 114.4 (CH_2), 138.9 (CH); *m/z* (CI) 115 (MH^+. 100%), 97 (61), 95 (9), 83 (6).

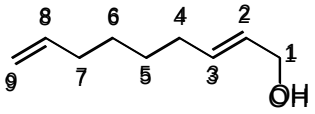
Ethyl (2*E*)-2,8-nonadienoate (188)[183]



Dimethyl sulfoxide (1.55 mL, 22.0 mmol) was added to a stirred solution of oxalyl chloride (1.07 mL, 12.28 mmol) in dichloromethane (100 mL) at –78 °C. The reaction mixture was stirred for 0.3 h before 6-hepten-1-ol (**187**) (1.0 g, 8.77 mmol) in dichloromethane (50 mL) was slowly added. The reaction mixture was stirred for a further 0.3 h before triethylamine (6.10 mL, 43.86 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. Meanwhile, a solution of lithium chloride (0.67 g, 15.79 mmol), triethyl phosphonoacetate (3.13 mL, 15.79 mmol) and 1,8-diazabicyclo[5,4,0]undec-7-ene (2.36 mL, 15.79 mmol) 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 (diethyl ether/petroleum ether, 3:97) yielded ethyl (2*E*)-2,8-nonadienoate (**188**) (1.34 g, 85% yield) as a yellow oil. Spectroscopic data consistent with literature.[183] δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.1 Hz, OCH_2CH_3), 1.38–1.53 (4H, m, 5-H_2 and 6-H_2), 1.95–2.03 (2H, m, 7-H_2), 2.10–2.18

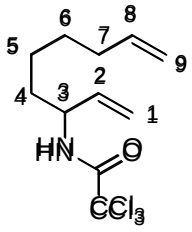
(2H, m, 4-H_2), 4.11 (2H, q, *J* 7.1 Hz, OC*H*$_2$CH$_3$), 4.93–4.97 (1H, m, 9-*H*H), 4.97–5.04 (1H, m, 9-H*H*), 5.74–5.78 (1H, m, 8-H), 5.79–5.85 (1H, m, 2-H), 6.96 (1H, dt, *J* 15.6, 6.9 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 27.5 (CH_2), 28.4 (CH_2), 32.0 (CH_2), 33.5 (CH_2), 60.2 (CH_2), 114.7 (CH_2), 121.4 (CH), 138.6 (CH), 149.2 (CH), 166.8 (C); *m/z* (CI) 183.1382 (MH^+. $C_{11}H_{19}O_2$ requires 183.1385), 113 (8%), 97 (7), 81 (13), 71 (15).

(2*E*)-Nona-2,8-dien-1-ol (185)[183]



The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using ethyl (2*E*)-2,8-nonadienoate (**188**) (2.0 g, 11.0 mmol). Flash column chromatography using (diethyl ether/petroleum ether, 3:7) gave (2*E*)-nona-2,8-dien-1-ol (**185**) (1.56 g, 100% yield) as a pale yellow oil. Spectroscopic data consistent with literature.[183] δ_H (400 MHz, $CDCl_3$) 1.22 (1H, br s, OH), 1.38–1.42 (4H, m, 5-H_2 and 6-H_2), 2.02–2.10 (4H, m, 4-H_2 and 7-H_2), 4.09 (2H, t, *J* 4.9 Hz, 1-H_2), 4.92–4.96 (1H, m, 9-*H*H), 5.00 (1H, ddt, *J* 17.0, 3.4, 1.6 Hz, 9-H*H*), 5.60–5.74 (2H, m, 2-H and 3-H), 5.81 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, 8-H); δ_C (100 MHz, $CDCl_3$) 26.9 (CH_2), 27.1 (CH_2), 30.6 (CH_2), 32.2 (CH_2), 62.4 (CH_2), 112.9 (CH_2), 127.5 (CH), 131.9 (CH), 137.4 (CH); *m/z* (CI) 123.1169 (MH^+–H_2O. C_9H_{15} requires 123.1174), 109 (16%), 95 (12), 81 (63), 67 (17).

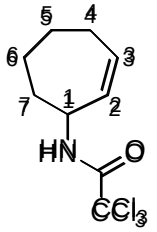
3-(2',2',2'-Trichloromethylcarbonylamino)nona-1,8-diene (189)[73]



(2*E*)-Nona-2,8-dien-1-ol (**185**) (0.50 g, 3.57 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 ^oC. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 1.00 mmol) was then added to the solution followed by trichloroacetonitrile (0.53 mL, 5.35 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then 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 **184**

which was used without further purification in the rearrangement reactions that followed. δ_H (400 MHz, $CDCl_3$) The resulting allylic trichloroacetimidate **184** was dissolved in dichloromethane (100 mL) and added to a sealed tube flask. Bis(acetonitrile)palladium(II) chloride (0.10 g, 0.35 mmol) in dichloromethane (10 mL) was added and stirred overnight at 45 ^oC. The reaction mixture was cooled to room temperature and concentrated. Flash column chromatography using (diethyl ether/petroleum ether, 1:9) gave 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) (1.36 g, 83% yield) as a brown oil. Spectroscopic data consistent with literature.[73] δ_H (400 MHz, $CDCl_3$) 1.27–1.39 (4H, m, 5-H_2 and 6-H_2), 1.49–1.63 (2H, m, 4-H_2), 1.98 (2H, q, *J* 6.8 Hz, 7-H_2), 4.31–4.38 (1H, m, 3-H), 4.90 (2H, ddt, *J* 10.2, 7.4, 1.4 Hz, 1-H_2), 5.14 (2H, dd, *J* 17.0, 10.6 Hz, 9-H_2), 5.66–5.77 (2H, m, 2-H and 8-H), 6.44 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.9 (CH_2), 28.4 (CH_2), 33.4 (CH_2), 34.2 (CH_2), 53.5 (CH), 92.8 (C), 114.7 (CH_2), 116.1 (CH_2), 136.6 (CH), 138.4 (CH), 161.2 (C); *m/z* (CI) 314 (MH^+, 5%), 284 (100), 250 (41), 214 (44), 180 (11), 154 (10), 116 (85), 81 (34).

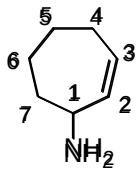
1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (190)[184]



(2*E*)-Nona-2,8-dien-1-ol (**185**) (0.50 g, 3.57 mmol) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.12 mL, 0.89 mmol) was then added to the solution followed by trichloroacetonitrile (0.53 mL, 5.35 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **184**, which was used without further purification. Allylic trichloroacetimidate **184** was dissolved in dichloromethane (50 mL). Bis(acetonitrile)palladium(II) chloride (0.10 g, 0.35 mmol) was then added to the solution and the reaction mixture was stirred at 45 °C for 24 h. The reaction mixture was diluted by adding dichloromethane (450 mL). Grubbs' catalyst (1st Generation) **111** (0.23 g, 0.28 mmol) was then added and the reaction mixture was heated at 65 °C overnight. The mixture was cooled to room temperature and then filtered through a short pad of Celite® and washed with diethyl ether (400 mL). Concentration of the filtrate followed by flash column chromatography (dichloromethane/petroleum ether, 3:7) gave 1-

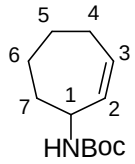
(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) (0.75 g, 82% yield) as a white solid. Mp 105–106 °C (lit.[184] mp 105 °C); Spectroscopic data consistent with literature.[184] δ_H (400 MHz, $CDCl_3$) 1.39–1.49 (1H, m, 6-*H*H), 1.66–1.79 (3H, m, 6-H*H* and 7-H_2), 1.85–1.98 (2H, m, 5-H_2), 2.10–2.29 (2H, m, 4-H_2), 4.54–4.62 (1H, m, 1-H), 5.55–5.62 (1H, m, 2-H), 5.88–5.95 (1H, m, 3-H), 6.72 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.6 (CH_2), 25.2 (CH_2), 26.5 (CH_2), 31.1 (CH_2), 50.5 (CH), 90.8 (C), 130.5 (CH), 131.8 (CH), 158.8 (C); *m/z* (CI) 256.0060 (MH^+. $C_9H_{13}NO^{35}Cl_3$ requires 256.0063), 222 (18%), 95 (12).

1-Aminocyclohepta-2-ene (191)



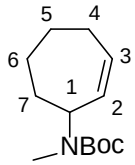
1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) (0.10 g, 0.40 mmol) was dissolved in tetrahydrofuran (5 mL), then added to a solution of sodium hydride (0.06 g, 2.00 mmol) in tetrahydrofuran (10 mL) and stirred for 0.5 h at room temperature. Methyl iodide (0.14 mL, 2.3 mmol) was added and the reaction mixture was stirred for 5 h. The reaction mixture was then heated under reflux overnight at 65 ^oC. The solution was concentrated *in vacuo*, then quenched with water and acidified with 1 M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (4 × 30 mL) and the combined organic layers dried with ($MgSO_4$) and concentrated *in vacuo*. Flash column chromatography (ethyl acetate/petroleum ether, 10:1) gave 1-aminocyclohepta-2-ene (**191**) (0.025 g, 58% yield) as a brown oil. ν_{max}/cm^{-1} (NaCl) 2926 (CH), 1473, 1442, 970, 923, 796; δ_H (400 MHz, $CDCl_3$) 1.35–1.42 (1H, m, 6-*H*H), 1.63–1.84 (3H, m, 6-H*H* and 7-H_2), 2.01–2.11 (2H, m, 5-H_2), 2.23–2.33 (2H, m, 4-H_2) 4.60–4.67 (1H, m, 1-H), 5.89–5.96 (1H, m, 2-H), 6.20–6.26 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 24.0 (CH_2), 26.5 (CH_2), 26.6 (2 × CH_2), 74.8 (CH), 123.9 (CH), 137.4 (CH); *m/z* (Cl) 182 (MH^+, 35%), 164 (13), 126 (85), 111 (70), 95 (100), 81 (84).

1-(*tert*-Butoxycarbonylamino)cyclohepta-2-ene (193)[185]



1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) (0.30 g, 1.17 mmol) was dissolved in 2 M sodium hydroxide (40 mL) and stirred vigorously for 12 h at room temperature. Di-*tert*-butyl dicarbonate (0.64 g, 2.94 mmol) was added and the solution was stirred for 6 h before a further portion of di-*tert*-butyl dicarbonate (0.64 g, 2.94 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 (ethyl acetate/petroleum ether, 1:9) gave 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**193**) (0.24 g, 100% yield) as a white solid. Mp 61–63 °C (lit.[185] mp 63–65 °C); ν_{max}/cm^{-1} (NaCl) 3334 (NH), 2925 (CH), 1679 (CO), 1516, 1367, 1246, 1166, 1016; δ_H (400 MHz, $CDCl_3$) 1.32–1.38 (1H, m, 6-*H*H), 1.44 (9H, s, O^{t}Bu), 1.60–1.69 (3H, m, 6-H*H* and 7-H_2), 1.82–1.90 (2H, m, 5-H_2), 2.09–2.18 (2H, m, 4-H_2), 4.25–4.32 (1H, m, 1-H), 4.64 (1H, br s, NH), 5.53–5.56 (1H, m, 2-H), 5.77–5.79 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 24.8 (CH_2), 25.6 (CH_2), 26.0 (CH_2), 26.7 (CH_3), 32.6 (CH_2), 49.9 (CH), 83.4 (C), 129.9 (CH), 133.7 (CH), 153.3 (C); *m/z* (CI) 212 (MH^+, 10%), 156 (100), 155 (7), 112 (5), 81 (7), 69 (9).

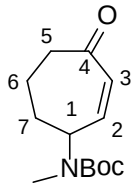
1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohepta-2-ene (194)



1-(*tert*-Butoxycarbonylamino)cyclohepta-2-ene (**193**) (0.05 g, 0.20 mmol) was dissolved in tetrahydrofuran (5 mL) and added to a solution of sodium hydride (0.03 g, 0.70 mmol, 60% in mineral oil) in tetrahydrofuran (10 mL). After 0.5 h, iodomethane (0.08 mL, 1.4 mmol) was added and the reaction mixture was stirred for 5 h at room temperature. The mixture was then heated for 24 h under reflux. The solution was concentrated *in vacuo*, quenched with water and acidified with 1 M hydrochloric acid. The reaction mixture was extracted with ethyl acetate (4 × 30 mL) and the combined organic layers dried ($MgSO_4$)

and concentrated *in vacuo*. Flash column chromatography (ethyl acetate/petroleum ether, 2:8) gave 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**194**) (0.044 g, 84% yield) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2921 (CH), 1692 (CO), 1386, 1364, 1313, 1134, 906; δ_H (400 MHz, $CDCl_3$) 1.23–1.26 (1H, m, 6-*H*H), 1.39 (9H, s, O^{t}Bu), 1.61–1.68 (4H, m, 5-*H*H, 6-H*H* and 7-H_2), 1.83–1.89 (1H, m, 5-H*H*), 1.95–2.05 (1H, m, 4-*H*H), 2.11–2.22 (1H, m, 4-H*H*), 2.69 (3H, s, NCH_3), 4.73–4.76 (1H, m, 1-H), 5.47–5.50 (1H, m, 2-H), 5.69–5.77 (1H, m, 3-H); δ_C (100 MHz, $CDCl_3$) 24.5 (CH_2), 25.8 (CH_2), 26.2 (3 × CH_3), 26.3 (CH_2), 27.3 (CH_3), 30.4 (br, CH_2), 54.1 (br, CH), 77.0 (C), 129.5 (br, CH), 132.3 (br, CH), 153.3 (C); *m/z* (CI) 226.1806 (MH^+. $C_{13}H_{24}NO_2$ requires 226.1807), 198 (6%), 186 (11), 170 (100), 156 (6), 126 (5), 113 (9), 97 (11), 85 (25).

1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (195)

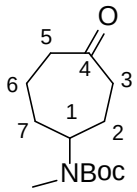


Method A: To a solution of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**194**) (0.05 g, 0.22 mmol) in ethyl acetate (3 mL) was added *tert*-butyl hydroperoxide (0.10 mL, 0.88 mmol, 5.0–6.0 M in decane) and powdered molecular sieves (4Å, activated) (0.10 g). The mixture was stirred for 0.5 h at room temperature. Manganese(III) acetate dihydrate (0.006 g, 0.02 mmol) was then added. The solution was degassed, filled with oxygen and stirred for 48 h at room tempareture. Further portions of *tert*-butyl hydroperoxide (0.10 mL, 0.88 mmol) and manganese(III) acetate dihydrate (0.006 g, 0.02 mmol) were added. The reaction mixture was stirred for a further 48 h, filtered through a pad of Celite® and washed with ethyl acetate (40 mL). The filtrate was then dried ($MgSO_4$) and concentrated *in vacuo*. Purification was carried out by flash column chromatography eluting using (ethyl acetate/petroleum ether, 2:8) to give 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) (0.01 g, 22% yield) as a yellow oil. ν_{max}/cm^{-1} (NaCl) 2931 (CH), 1688 (CO), 1366, 1047, 877, 771; δ_H (400 MHz, $CDCl_3$) 1.40 (9H, s, O^{t}Bu), 1.75–1.87 (3H, m, 6-*H*H and 7-H_2), 1.94–2.04 (1H, m, 6-H*H*), 2.48–2.65 (2H, m, 5-H_2), 2.69 (3H, s, NCH_3), 4.91–4.98 (1H, m, 1-H), 5.97 (1H, d, *J* 12.4 Hz, 3-H), 6.28 (1H, br d, *J* 12.4 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 26.6 (3 × CH_3), 28.0 (CH_3), 29.1 (CH_2), 30.8 (CH_2), 41.8 (CH_2), 55.0 (br, CH), 78.5 (C), 130.3 (br, CH), 145.6 (br, CH),

153.8 (C), 201.5 (C); *m/z* (CI) 240.1604 (MH^+. $C_{13}H_{22}NO_3$ requires 240.1600), 200 (10%), 184 (100), 173 (15), 155 (15), 132 (18), 109 (39).

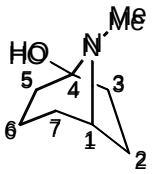
Method B: A mixture of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**194**) (0.07 g, 0.30 mmol), 10% palladium on carbon (0.005 g), dichloromethane (5 mL), *tert*-butyl hydroperoxide (0.12 mL, 1.1 mmol, 5.0–6.0 M in decane) and anhydrous potassium carbonate (0.007 g, 0.05 mmol) was stirred at room temperature for 24 h. A further quantity of *tert*-butyl hydroperoxide (0.12 mL, 1.1 mmol, 5.0–6.0 M in decane) and 10% palladium on carbon (0.005 g) were added and the reaction mixture stirred for a further 24 h. The reaction mixture was filtered through a pad of silica which was subsequently washed with dichloromethane. 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*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) (0.03 g, 45% yield) as a yellow oil. Spectroscopic data as described above.

1-[*tert*-Butoxycarbonyl(methyl)amino]cycloheptanone (196)[186]



To a solution of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) (0.06 g, 0.25 mmol) in methanol (8 mL) was added 10% palladium on carbon (0.004 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite®, which was washed with methanol and concentrated *in vacuo*. Flash column chromatography (diethyl ether/petroleum ether, 1:1) gave 1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**196**) (0.020 g, 66% yield) as a white solid. Mp 65–66 °C (lit.[186] for opposite enantiomer, mp 68–69 °C); ν_{max}/cm^{-1} (NaCl) 2916 (CH), 1699 (CO), 1674 (CO), 1446, 1363, 1319, 1155, 939. Spectroscopic data consistent with literature.[185] δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s, O^{t}Bu), 1.46–1.78 (4H, m, 6-H_2 and 7-H_2), 1.88–1.91 (2H, m, 2-H_2), 2.32–2.56 (4H, m, 3-H_2 and 5-H_2), 2.68 (3H, s, NCH_3), 4.02-4.11 (1H, m, 1-H); δ_C (100 MHz, $CDCl_3$) 20.4 (br, CH_2), 27.2 (3 × CH_3), 27.5 (CH_3), 29.7 (CH_2), 32.6 (br, CH_2), 39.2 (CH_2), 42.3 (CH_2), 55.9 (br, CH), 78.4 (C), 154.0 (C), 212.8 (C); *m/z* (EI) 241.1676 (M^+. $C_{13}H_{23}NO_3$ requires 241.1678), 185 (31%), 141 (17), 110 (39), 84 (29), 57 (98).

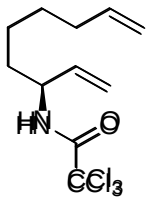
(±)-Physoperuvine (172)[187]



A solution of 1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**196**) (0.03 g, 0.10 mmol) was dissolved in trifluoroacetic acid (0.5 mL) and stirred at room temperature for 0.5 h. The solvent was removed under vacuum, and the residue was made basic with aqueous sodium carbonate (10 mL, 1.0 M) then extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried, filtered and evaporated. Flash column chromatography (chloroform/methanol/ammonium hydroxide (30%), 5:4:1) gave (±)-physoperuvine (**172**) (0.01 g, 60% yield) as a white solid. Mp 73–74 °C (lit.[187] mp 72–73 °C); Spectroscopic data consistent with literature.[187] δ_H (400 MHz, $CDCl_3$) 1.20–1.34 (1H, m, 6-*H*H), 1.52–1.82 (5H, m, 2-H_2, 6-H*H* and 7-H_2), 1.87–2.15 (4H, m, 3-H_2 and 5-H_2), 2.38 (3H, s, NCH_3), 3.12 (1H, br s, 1-H); *m/z* (CI) 142 (MH^+, 100%), 124 (39), 101 (5), 81 (9), 71 (12).

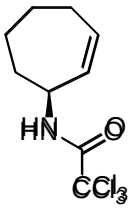
3.3 Synthesis of (+)-Physoperuvine

(3*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)nona-1,8-diene (197)[73]



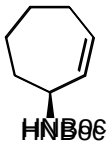
The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*)-nona-2,8-dien-1-ol (**185**) (0.15 g, 0.53 mmol) and (*S*)-COP-Cl **50** (0.04 g, 0.02 mmol). This yielded (3*S*)-3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**197**) (0.12 g, 81%) as a brown oil. $[\alpha]_D^{23}$ –28.2 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**).

(1*S*)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclohepta-2-ene (183)[184]



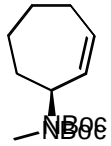
The reaction was carried out according to the procedure described for the synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) using (2*E*)-nona-2,8-dien-1-ol (**185**) (0.35 g, 2.50 mmol), (*S*)-COP-Cl **50** (0.41 g, 0.28 mmol) and Grubbs' catalyst (1st Generation) **111** (0.16 g, 0.20 mmol). This yielded (1*S*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**183**) (0.55 g, 86%) as a white solid. 84% ee determined by HPLC analysis using CHIRALPAK IB column (0.5% *i*PrOH : hexane at 0.5 mL/min), retention time: t_S= 21.5 min, and t_R= 22.1 min); $[\alpha]_D^{23}$ –25.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**190**).

(1*S*)-1-(*tert*-Butoxycarbonylamino)cyclohepta-2-ene (198)[185]



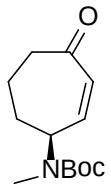
The reaction was carried out according to the procedure described for the synthesis of 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**193**) using (1*S*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**183**) (0.50 g, 2.00 mmol). This gave (1*S*)-1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**198**) (0.45 g, 100%) as a white solid. $[\alpha]_D^{23}$ –9.3 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**193**).

(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohepta-2-ene (199)



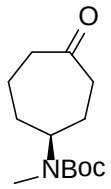
The reaction was carried out according to the procedure described for the synthesis of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**194**) using (1*S*)-1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**198**) (0.17 g, 0.80 mmol). This gave (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**199**) (0.18 g, 83%) as a colourless oil. $[\alpha]_D^{23}$ +24.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**194**).

(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (182)



The reaction was carried out according to the procedure described for the synthesis of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) using (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohepta-2-ene (**199**) (0.12 g, 0.53 mmol). This gave (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**182**) (0.05 g, 41% yield) as a yellow oil. $[\alpha]_D^{23}$ –34.2 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**).

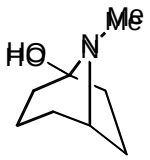
(1*S*)-1-[*tert*-Butoxycarbonyl(methyl)amino]cycloheptanone (200)[186]



The reaction was carried out according to the procedure described for the synthesis of 1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**196**) using (1*S*)-1-[*tert*-

butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**182**) (0.10 g, 0.37 mmol). This yielded (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**200**) (0.055 g, 61%) as a white solid. $[\alpha]_D^{23}$ +65.1 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for 1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**196**).

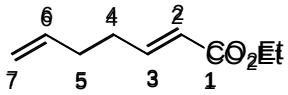
(+)-Physoperuvine (168)[187]



The reaction was carried out according to the procedure described for the synthesis of (±)-physoperuvine (**172**) using (1*S*)-1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**200**) (0.03 g, 0.10 mmol). This gave (+)-physoperuvine (**168**) (0.01 g, 60% yield) as a white solid. $[\alpha]_D^{23}$ +18.3 (*c* 1.3, H_2O, lit.[187] $[\alpha]_D^{25}$ +17.9 (*c* 1.3, H_2O). All other spectroscopic data as previously reported for (±)-physoperuvine (**172**).

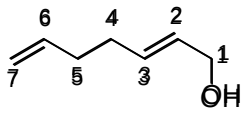
3.4 Attempted Synthesis of Carbocyclic Nucleosides

Ethyl (2*E*)-2,6-heptadienoate (212)[188]



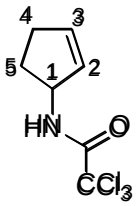
The reaction was carried out according to the procedure described for the synthesis of ethyl (2*E*)-2,8-nonadienoate (**188**) using 4-penten-1-ol **211** (3.0 g, 34.83 mmol). Flash column chromatography (petroleum ether/diethyl ether, 20:1) yielded ethyl (2*E*)-2,6-heptadienoate (**212**) (4.6 g, 87% yield) as a yellow oil. Spectroscopic data consistent with literature.[188] δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 2.19–2.24 (2H, m, 5-H_2), 2.28–2.33 (2H, m, 4-H_2), 4.19 (2H, q, *J* 7.2 Hz, OCH_2CH_3), 4.99–5.09 (2H, m, 7-H_2), 5.75–5.80 (1H, m, 6-H), 5.81–5.85 (1H, m, 2-H), 6.96 (1H, dt, *J* 15.6, 6.8 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.3 (CH_3), 31.5 (CH_2), 32.0 (CH_2), 60.2 (CH_2), 115.5 (CH_2), 121.7 (CH), 137.1 (CH), 148.3 (CH), 166.7 (C); *m/z* (CI) 155.1075 (MH^+. $C_9H_{15}O_2$ requires 155.1072), 137 (16%), 107 (17), 73 (22).

(2*E*)-Hepta-2,6-dien-1-ol (213)[188]



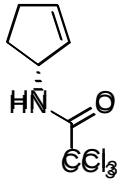
The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using ethyl (2*E*)-2,6-heptadienoate (**212**) (5.00 g, 32.46 mmol). Flash column chromatography (petroleum ether/diethyl ether, 7:3) yielded, (2*E*)-hepta-2,6-dien-1-ol (**213**) (3.10 g, 86% yield) as a colourless oil. Spectroscopic data consistent with literature.[188] δ_H (400 MHz, $CDCl_3$) 1.34 (1H, br s, OH), 2.10–2.15 (4H, m, 4-H_2 and 5-H_2), 4.09 (2H, d, *J* 4.8 Hz, 1-H_2), 4.96–5.04 (2H, m, 7-H_2), 5.62–5.73 (2H, m, 2-H and 3-H), 5.73–5.84 (1H, m, 6-H); δ_C (100 MHz, $CDCl_3$) 31.5 (CH_2), 33.3 (CH_2), 63.7 (CH_2), 114.9 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); *m/z* (CI) 113.0964 (MH^+. $C_7H_{13}O$ requires 113.0966), 95 (100%), 81 (14), 73 (13).

1-(2',2',2'-Trichloromethylcarbonylamino)cyclopenta-2-ene (215)[103]



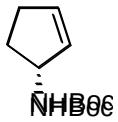
The reaction was carried out according to the procedure described for the synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) using (2*E*)-hepta-2,6-dien-1-ol (**213**) (4.00 g, 35.71 mmol), bis(acetonitrile)palladium(II) chloride (0.92 g, 3.57 mmol) and Grubbs' catalyst (1st Generation) (2.94 g, 3.57 mmol). Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 24:1) gave 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**215**) as a white solid (6.0 g, 74% yield over 3 steps). Spectroscopic data consistent with literature.[103] Mp 82–83 °C; (lit.[103] 81–82 °C); δ_H (400 MHz, $CDCl_3$) 1.66–1.73 (1H, m, 4-*H*H), 2.35–2.55 (3H, m, 4-H*H* and 5-H_2), 4.93–5.01 (1H, m, 1-H), 5.72–5.76 (1H, m, 2-H), 6.05–6.10 (1H, m, 3-H), 6.57 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 30.5 (CH_2), 30.9 (CH_2), 57.6 (CH), 90.8 (C), 129.0 (CH), 136.2 (CH), 160.8 (C); *m/z* (CI) 229.9718 (MH^+. $C_7H_9NO^{35}Cl_2{}^{37}Cl$ requires 229.9721), 228 (100%), 194 (22), 162 (5), 67 (13).

(1*R*)-1-(2',2',2'-Trichloromethylcarbonylamino)cyclopenta-2-ene (208)[103]



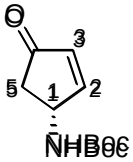
The reaction was carried out according to the procedure described for the synthesis of 1-(2',2',2'-trichloromethylcarbonylamino)cyclohepta-2-ene (**190**) using (2*E*)-hepta-2,6-dien-1-ol (**213**) (0.23 g, 2.05 mmol), (*R*)-COP-Cl **51** (0.30 g, 0.20 mmol) and Grubbs' catalyst (1st Generation) **111** (0.17 g, 0.20 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 7:3) gave (1*R*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**208**) (0.33 g, 71%) as a white solid. $[\alpha]_D^{23}$ +87.4 (*c* 1.0, $CHCl_3$); All other spectroscopic data as previously reported for 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**215**).

(1*R*)-1-(*tert*-Butoxycarbonylamino)cyclopenta-2-ene (218)[189]



The reaction was carried out according to the procedure described for the synthesis of 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**193**) using (1*R*)-1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**208**) (0.50 g, 2.00 mmol). This gave (1*R*)-1-(*tert*-butoxycarbonylamino)cyclopenta-2-ene (**218**) (0.45 g, 100%) as a white solid. $[\alpha]_D^{23}$ +65.0 (*c* 1.0, $CHCl_3$), lit.[189] $[\alpha]_D^{25}$ +77.0 (*c* 5.1, CH_2Cl_2). All other spectroscopic data as previously reported for 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**220**).

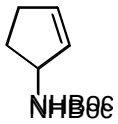
(1*R*)-1-(*tert*-Butoxycarbonylamino)cyclopenta-2-en-4-one (219)[145]



The reaction was carried out according to the procedure described for the synthesis of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) using (1*R*)-1-(*tert*-

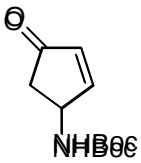
butoxycarbonylamino)cyclopenta-2-ene (**218**) (0.10 g, 0.54 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave (1*R*)-1-(*tert*-butoxycarbonylamino)cyclopenta -2-en-4-one (**219**) (0.025 g, 25%) as white solid. $[\alpha]_D^{23}$ +16.8 (*c* 1.0, $CHCl_3$), lit.[145] $[\alpha]_D^{25}$ +69.6 (*c* 2.6, $CHCl_3$); All other spectroscopic data as previously reported for 1-(*tert*-butoxycarbonylamino)cyclopenta-2-en-4-one (**221**)

1-(*tert*-Butoxycarbonylamino)cyclopenta-2-ene (220)[189]



The reaction was carried out according to the procedure described for the synthesis of 1-(*tert*-butoxycarbonylamino)cyclohepta-2-ene (**193**) using 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**215**) (0.23 g, 1.00 mmol). Flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-(*tert*-butoxycarbonylamino)cyclopenta-2-ene (**220**) (0.18 g, 100% yield over 2 steps) as a white solid. Spectroscopic data consistent with literature.[189] Mp 85–86 °C; (lit.[189] mp 87.5 °C); δ_H (400 MHz, $CDCl_3$) 1.52 (9H, s, O^{t}Bu), 1.57–1.58 (1H, m, 4-*H*H), 2.27–2.42 (3H, m, 4-H*H* and 5-H_2), 4.49 (1H, br s, NH), 4.66–4.76 (1H, m, 1-H), 5.66–5.71 (1H, m, 3-H), 5.87–5.93 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 28.4 (3 × CH_3), 31.0 (CH_2), 31.7 (CH_2), 56.8 (CH), 79.2 (C), 131.5 (CH), 134.1 (CH), 155.8 (C); *m/z* (CI) 184 (MH^+. 45%), 128 (100), 119 (27), 113 (11), 84 (7).

1-(*tert*-Butoxycarbonylamino)cyclopenta-2-en-4-one (221)[145]

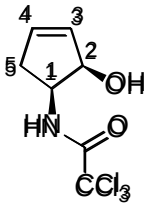


Method A: A solution of 1-(*tert*-butoxycarbonylamino)cyclopenta-2-ene (**220**) (0.10 g, 0.54 mmol) in *n*-butyl butanoate (1 mL), diacetoxyiodobenzene (0.53 g, 1.64 mmol) and potassium carbonate (0.037 g, 0.27 mmol) was vigorously stirred at –20 °C. *tert*-Butyl hydroperoxide (0.40 mL, 2.18 mmol, 5.0–6.0 M in decane) was added dropwise. The solution was heated for 72 h, cooled and the solvent was removed *in vacuo*. Flash column

chromatography (petroleum ether/diethyl ether, 5:5) gave 1-(*tert*-butoxycarbonylamino)cyclopenta-2-en-4-one (**221**) (0.016 g, 15%) as white solid. Mp 122–124 °C; (lit.[145] mp 124–125 °C); δ_H (400 MHz, $CDCl_3$) 1.46 (9H, s, O^{t}Bu), 2.18 (1H, d, *J* 10.8 Hz, 5-*H*H), 2.88 (1H, dd, *J* 10.8, 6.4 Hz, 5-H*H*), 4.67 (1H, br s, NH), 4.90–5.10 (1H, m, 1-H), 6.22–6.28 (1H, m, 3-H), 7.50–7.58 (1H, m, 2-H); δ_C (100 MHz, $CDCl_3$) 28.3 (3 × CH_3), 42.4 (CH_2), 50.1 (CH), 80.1 (C), 135.3 (CH), 155.0 (CH), 162.2 (C), 207.0 (C); *m/z* (CI) 198 (MH^+. 4%), 155 (4), 142 (100), 126 (4), 69 (12).

Method B: The reaction was carried out according to the procedure described for the synthesis of 1-[*tert*-butoxycarbonyl(methyl)amino]cyclohept-2-en-4-one (**195**) using 1-(*tert*-butoxycarbonylamino)cyclopenta-2-ene (**220**) (0.10 g, 0.54 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 9:1) gave 1-(*tert*-butoxycarbonylamino)cyclopenta-2-en-4-one (**221**) (0.025 g, 25%) as white solid. Spectroscopic data as described above.

(1*S*,2*R*)-1-(2',2',2'-Trichloromethylcarbonylamino)-2-hydroxycyclopenta-3-ene (225)

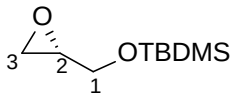


To a solution of 1-(2',2',2'-trichloromethylcarbonylamino)cyclopenta-2-ene (**215**) (0.40 g, 1.75 mmol) in chloroform (5 mL), *N*-iodosuccinimide (0.14 g, 0.65 mmol) was added and the mixture was heated at 61 °C for 15 h. The solvent was removed *in* vacuo. The resulting residue was dissolved in ethyl acetate (20 mL) and the organic phase washed with water (3 × 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue obtained **223** was dissolved in toluene (10 mL) and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.10 mL, 0.65 mmol) was added. The reaction mixture was heated under reflux for 12 h under argon. The reaction mixture was then cooled and solvent was removed *in vacuo*. The resulting dark coloured solid **224** was dissolved in methanol (10 mL). 2.0 M Hydrochloric acid (5 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 × 10 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography

(petroleum ether/diethyl ether, 5:5) gave (1*S*,2*R*)-1(2',2',2'-trichloromethylcarbonylamino)-2-hydroxycyclopenta-3-ene (**225**) (0.19 g, 45%) as white solid. Mp 111–113 °C; ν_{max}/cm^{-1} (NaCl) 3379 (OH), 2945 (CH), 1693 (CO), 1505, 1096, 909, 822; $[\alpha]_D^{23}$ +53.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.13 (1H, br s, OH), 2.32–2.39 (1H, m, 5-*H*H), 2.86–2.93 (1H, m, 5-H*H*), 4.32 (1H, ddd, *J* 14.0, 6.8, 3.6 Hz, 1-H), 4.72–4.79 (1H, m, 2-H), 5.91–5.95 (1H, m, 3-H), 6.07 (1H, dt, *J* 6.0, 3.6 Hz, 4-H), 7.36 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 37.2 (CH_2), 52.4 (CH), 74.3 (CH), 92.6 (C), 131.2 (CH), 135.3 (CH), 162.0 (C); *m/z* (CI) 243.9695 (MH^+. $C_7H_9{}^{35}Cl_3NO_2$ requires 243.9699), 226 (100%), 192 (31), 126 (20), 85 (21).

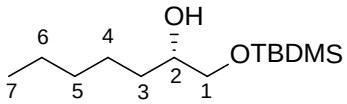
3.5 Synthesis of (+)-Monanchorin

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (250)[190]



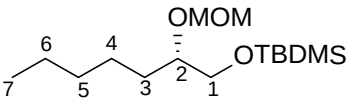
A mixture of (*R*)-(+)-glycidol **249** (4.61 g, 60.70 mmol), *tert*-butyldimethylsilyl chloride (9.15 g, 60.70 mmol) and imidazole (4.13 g, 60.70 mmol) were dissolved in tetrahydrofuran (300 mL) and stirred overnight at room temperature. A white precipitate was removed by filtration and washed with diethyl ether (200 mL). The combined filtrate was concentrated and purified by flash column chromatography using (diethyl ether/petroleum ether, 1:10) which gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**250**) (11.5 g, 88%) as a colourless oil. Spectroscopic data consistent with literature.[190] $[\alpha]_D^{23}$ –6.1 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, $SiCH_3$), 0.10 (3H, s, $SiCH_3$), 0.81 (9H, s, $SiC(CH_3)_3$), 2.56 (1H, dd, *J* 5.1, 2.6 Hz, 1-*H*H), 2.70 (1H, dd, *J* 5.1, 4.1 Hz, 1-H*H*), 2.98–3.03 (1H, m, 2-H), 3.60 (1H, dd, *J* 11.9, 4.8 Hz, 3-*H*H), 3.80 (1H, dd, *J* 11.9, 3.1 Hz, 3-H*H*); δ_C (100 MHz, $CDCl_3$) –5.3 (CH_3), –5.2 (CH_3), 18.4 (C), 25.9 (3 × CH_3), 44.5 (CH_2), 52.5 (CH), 63.8 (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*S*)-1-(*tert*-Butyldimethylsilyloxy)heptan-2-ol (251)[191]



A solution of *n*-butyllithium (2.5 M in hexane) (0.53 mL, 1.33 mmol) was added dropwise to a solution of copper iodide (0.11 g, 0.58 mmol) in tetrahydrofuran (15 mL) at –78 °C and the white suspension was stirred for 1 h. (2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (**250**) (0.10 g, 0.53 mmol) in THF (10 mL) was then added and the reaction mixture was warmed to 0 °C and stirred for 3 h. The reaction was quenched by the addition of a saturated solution of ammonium chloride (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, 20:1) gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**251**) (0.06 g, 90%) as a colourless oil. Spectroscopic data consistent with literature.[191] ν_{max}/cm^{-1} (NaCl) 3434 (OH), 2929 (CH), 1464, 1255, 1106, 837, 778; $[\alpha]_D^{23}$ +7.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, 2 × $SiCH_3$), 0.79–0.84 (12H, m, 7-H_3 and $SiC(CH_3)_3$), 1.19–1.42 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 2.37 (1H, br s, OH), 3.31 (1H, dd, *J* 10.4, 8.3 Hz, 1-*H*H), 3.51–3.60 (2H, m, 1-H*H* and 2-H); δ_C (100 MHz, $CDCl_3$) –5.4 (CH_3), –5.3 (CH_3), 14.1 (CH_3), 18.3 (C), 22.6 (CH_2), 25.3 (CH_2), 25.9 (3 × CH_3), 32.0 (CH_2), 32.8 (CH_2), 67.3 (CH_2), 71.9 (CH); *m/z* (CI) 247 (MH^+. 11%), 206, (3), 150 (4), 88 (3), 52 (100).

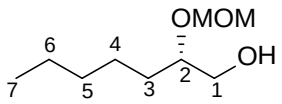
(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (252)



A solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**251**) (5.00 g, 20.3 mmol) was dissolved in dichloromethane (200 mL) and cooled to 0 °C. Diisopropylethylamine (10.6 mL, 61.0 mmol) was then added followed by bromomethyl methyl ether (3.40 mL, 41.7 mmol). The solution was stirred for 0.5 h at 0 °C then heated under reflux overnight. The reaction mixture was cooled to room temperature, acidified with 1.0 M hydrochloric acid (15 mL) and extracted with dichloromethane (3 × 100 mL). After removal of the solvent under reduced pressure, the resulting material was purified by flash column chromatography (petroleum ether/diethyl ether, 20:1) to give (2*S*)-1-(*tert*-

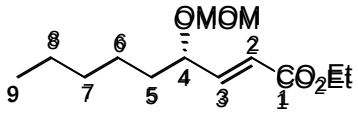
butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**252**) as a pale yellow oil (5.70 g, 96%). ν_{max}/cm^{-1} (NaCl) 2930 (CH), 1464, 1256, 1111, 1039, 838, 776; $[\alpha]_D^{23}$ –32.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.80–0.86 (12H, m, 7-H_3 and $Si(CH_3)_3$), 1.24–1.43 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 3.33 (3H, s, OCH_3), 3.51–3.58 (3H, m, 1-H_2 and 2-H), 4.60 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.7 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) –6.5 (CH_3), –6.4 (CH_3), 13.0 (CH_3), 17.3 (C), 21.6 (CH_2), 24.0 (CH_2), 24.9 (3 × CH_3), 30.7 (CH_2), 31.0 (CH_2), 54.4 (CH_3), 64.9 (CH_2), 77.2 (CH) 95.2 (CH_2); *m/z* (CI) 291.2354 (MH^+. $C_{15}H_{35}O_3Si$ requires 291.2355), 259 (100), 229 (12), 203 (6), 133 (3), 85 (8).

(2*S*)-2-(Methoxymethoxy)heptan-1-ol (248)



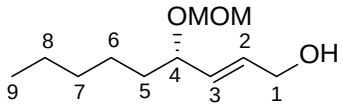
A solution of tetrabutylammonium fluoride (1.0 M in tetrahydrofuran) (24.7 mL, 24.8 mmol) was added to a solution of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**252**) (6.00 g, 20.7 mmol) in tetrahydrofuran (300 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was then concentrated and the resulting residue was re-suspended in diethyl ether (200 mL). The solution was washed with water (100 mL) and the aqueous layer was then extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and purified by flash column chromatography (petroleum ether/diethyl ether, 5:2) to give (2*S*)-2-(methoxymethoxy)heptan-1-ol (**248**) as a colourless oil (3.65 g, 100%). ν_{max}/cm^{-1} (NaCl) 3450 (OH), 2931 (CH), 1466, 1103, 1041; $[\alpha]_D^{23}$ +57.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz, 7-H_3), 1.23–1.54 (8H, m, 3-H_2, 4-H_2, 5-H_2 and 6-H_2), 3.11 (1H, dd, *J* 8.7, 3.3 Hz, OH), 3.43 (3H, s, OCH_3), 3.48–3.62 (3H, m, 1-H_2 and 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 31.7 (CH_2), 31.8 (CH_2), 55.7 (CH_3), 65.8 (CH_2), 82.5 (CH), 97.0 (CH_2); *m/z* (CI) 177.1491 (MH^+. $C_9H_{21}O_3$ requires 177.1491), 145 (100), 143 (8), 115 (42), 97 (18).

Ethyl (2*E*,4*S*)-4-(methoxymethoxy)nona-2-enoate (253)



The reaction was carried out according to the procedure described for the synthesis of ethyl (2*E*)-2,8-nonadienoate (**188**) using (2*S*)-2-(methoxymethoxy)heptan-1-ol (**248**) (3.33 g, 19.0 mmol). Purification by flash column chromatography using (diethyl ether/petroleum ether, 2:5) yielded ethyl (2*E*,4*S*)-4-(methoxymethoxy)nona-2-enoate (**253**) (4.62 g, 86%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2934 (CH), 1723 (CO), 1658 (C=C), 1467, 1368, 1273, 1156, 1038; $[\alpha]_D^{23}$ –67.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.28–1.43 (9H, m, 6-H_2, 7-H_2, 8-H_2 and OCH_2CH_3), 1.51–1.66 (2H, m, 5-H_2), 3.38 (3H, s, OCH_3), 4.16–4.24 (3H, m, 4-H and OCH_2CH_3), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.63 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.92 (1H, d, *J* 15.7 Hz, 2-H), 6.82 (1H, dd, *J* 15.7, 6.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 22.6 (CH_2), 24.8 (CH_2), 31.7 (CH_2), 34.9 (CH_2), 55.6 (CH_3), 60.5 (CH_2), 75.2 (CH), 94.6 (CH_2), 121.8 (CH), 148.0 (CH), 166.3 (C); *m/z* (CI) 245.1752 (MH^+. $C_{13}H_{25}O_4$ requires 245.1753), 215 (22), 183 (100), 173 (10), 137 (4), 109 (4).

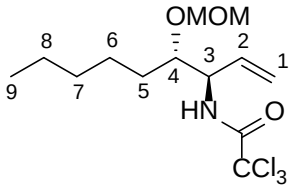
(2*E*,4*S*)-4-(Methoxymethoxy)nona-2-ene-1-ol (254)



The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using ethyl (2*E*,4*S*)-4-(methoxymethoxy)nona-2-enoate (**253**) (4.56 g, 18.7 mmol). Flash column chromatography (diethyl ether/petroleum ether, 2:5) gave (2*E*,4*S*)-4-(methoxymethoxy)nona-2-ene-1-ol (**254**) (3.50 g, 92%) as a colourless oil. (Found: C, 65.18; H, 11.09. $C_{11}H_{22}O_3$ requires C, 65.34; H, 10.89%); ν_{max}/cm^{-1} (NaCl) 3407 (OH), 2932 (CH), 1673 (C=C), 1467, 1378, 1213, 1115, 1096, 1039, 920; $[\alpha]_D^{23}$ –69.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.27–1.55 (7H, m, 6-H_2, 7-H_2, 8-H_2 and OH), 1.58–1.64 (2H, m, 5-H_2), 3.37 (3H, s, OCH_3), 3.99–4.06 (1H, m, 4-H), 4.16 (2H, td, *J* 5.6, 1.4 Hz, 1-H_2), 4.53 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.56 (1H, ddt, *J* 15.5, 7.4, 1.4 Hz, 3-H), 5.82 (1H, dtd, *J* 15.5, 5.6, 0.6

Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.1 (CH_2), 31.7 (CH_2), 35.5 (CH_2), 55.4 (CH_3), 62.8 (CH_2), 76.4 (CH), 93.6 (CH_2), 131.5 (CH), 132.1 (CH); *m/z* (CI) 203 (MH^+. 10%), 185 (19), 142 (83), 138 (37), 124 (100), 100 (19), 83 (49).

(3*R*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (245a)

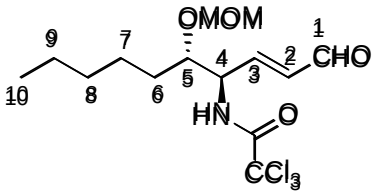


Method A: The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*,4*S*)-4-(methoxymethoxy)nona-2-ene-1-ol (**254**) (0.20 g, 1.00 mmol) and bis(acetonitrile)palladium(II) chloride (0.025 g, 0.10 mmol). Flash column chromatography (diethyl ether/petroleum ether, 1:20) gave (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**245a**) as a colourless oil (0.20 g, 55% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3284 (NH), 2933 (CH), 1715 (CO), 1644 (C=C), 1517, 1236, 1100, 1037, 822; $[\alpha]_D^{23}$ +59.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8 Hz, 9-H_3), 1.24–1.53 (6H, m, 6-H_2, 7-H_2 and 8-H_2), 1.58–1.68 (2H, m, 5-H_2), 3.43 (3H, s, OCH_3), 3.54–3.59 (1H, m, 4-H), 4.36–4.42 (1H, m, 3-H), 4.74 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.66 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.30–5.37 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 16.8, 10.4, 6.7 Hz, 2-H), 8.27 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.4 (CH_2), 25.4 (CH_2), 31.7 (CH_2), 33.0 (CH_2), 56.0 (CH), 56.7 (CH_3), 83.9 (CH), 93.0 (C), 98.2 (CH_2), 119.0 (CH_2), 131.6 (CH), 161.5 (C); *m/z* (FAB) 346.0747 (MH^+. $C_{13}H_{23}{}^{35}Cl_3NO_3$ requires 346.0744), 314 (57%), 284 (28), 213 (100), 201 (11), 179 (14), 123 (34).

Method B: The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*,4*S*)-4-(methoxymethoxy)nona-2-ene-1-ol (**254**) (0.74 g, 3.66 mmol), bis(acetonitrile)palladium(II) chloride (0.10 g, 0.36 mmol) and *p*-benzoquinone (0.21 g, 2.00 mmol). Flash column chromatography (diethyl ether/petroleum ether, 1:20) gave (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene

(**245a**) as a colourless oil (0.90 g, 75% over 2 steps). Spectroscopic data as described above.

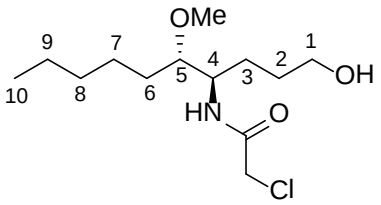
(2*E*,4*R*,5*S*)-4-(2',2',2'-Trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (257)



Method A: A solution of (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**245a**) (0.10 g, 0.28 mmol) was dissolved in dichloromethane (10 mL) and degassed with argon. Acrolein (0.10 g, 1.44 mmol) and Grubbs 2nd generation catalyst (0.02 g, 0.03 mmol) were added. The reaction mixture was heated under reflux overnight. The mixture was concentrated under vacuum. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:19) gave (2*E*,4*R*,5*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) (0.009 g, 9%) as a yellow oil. ν_{max}/cm^{-1} (NaCl) 3273 (NH), 2932 (CH), 2858, 1713 (CO), 1694 (CO), 1519, 1466, 1099, 1033, 822; $[\alpha]_D^{23}$ +55.2 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.8 Hz, 10-H_3), 1.27–1.60 (6H, m, 7-H_2, 8-H_2 and 9-H_2), 1.63–1.72 (2H, m, 6-H_2), 3.43 (3H, s, OCH_3), 3.67 (1H, ddd, *J* 8.8, 6.4, 2.0 Hz, 5-H), 4.62–4.67 (2H, m, OC*H*HO and 4-H), 4.75 (1H, d, *J* 6.7 Hz, OCH*H*O), 6.30 (1H, ddd, *J* 15.8, 7.8, 1.6 Hz, 2-H), 6.81 (1H, dd, *J* 15.8, 5.8 Hz, 3-H), 8.59 (1H, br d, *J* 7.8 Hz, NH), 9.61 (1H, d, *J* 7.8 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 25.4 (CH_2), 31.5 (CH_2), 33.2 (CH_2), 55.5 (CH), 56.0 (CH_3), 84.1 (CH), 92.5 (C), 98.4 (CH_2), 134.4 (CH), 149.8 (CH), 161.8 (C), 193.0 (CH); *m/z* (CI) 376.0659 (MH^+. $C_{14}H_{23}{}^{35}Cl_2{}^{37}ClNO_4$ requires 376.0665), 342 (41%), 314 (100), 278 (19), 207 (9), 181 (9), 145 (46).

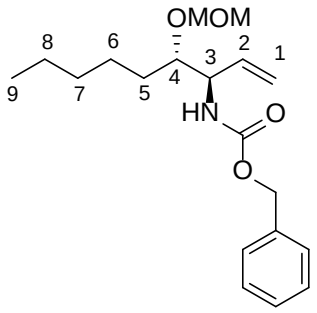
Method B: The reaction was carried out according to the procedure described above using (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**245a**) (0.10 g, 0.28 mmol), crotonaldehyde (0.12 g, 1.44 mmol) and Grubbs 2nd generation catalyst (0.02 g, 0.03 mmol). Purification by flash column chromatography (diethyl ether/petroleum ether, 2:8) gave (2*E*,4*R*,5*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) (0.05 g, 50%) as a yellow oil. Spectroscopic data as described above.

(4*R*,5*S*)-4-(2'-chloromethylcarbonylamino)-5-methoxy-1-decane-1-ol (262)



The reaction was carried out according to the procedure described for the synthesis of1-[*tert*-butoxycarbonyl(methyl)amino]cycloheptanone (**196**) using (2*E*,4*R*,5*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) (0.05 g, 0.26 mmol). Flash column chromatography (diethyl ether/petroleum ether, 7:3) gave (4*R*,5*S*)-4-(2'-chloromethylcarbonylamino)-5-methoxy-1-decane-1-ol (**262**) (0.023 g, 62%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3294 (NH), 2918 (CH), 1669 (CO), 1466, 1267, 1071, 774; $[\alpha]_D^{23}$ +52.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, t, *J* 6.8 Hz, 10-H_3), 1.36–1.61 (12H, m, 2-H_2, 3-H_2, 6-H_2, 7-H_2, 8-H_2 and 9-H_2), 3.27 (3H, s, OCH_3), 3.27–3.33 (2H, m, 1-H_2), 3.55–3.67 (1H, m, 5H), 3.82–3.92 (1H, m, 4-H), 4.00 (2H, s, CH_2Cl), 6.80 (1H, br d, *J* 7.8 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.6 (CH_2), 25.2 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 31.8 (CH_2), 33.3 (CH_2), 42.7 (CH_2), 54.3 (CH), 58.7 (CH_3), 72.2 (CH_2), 74.2 (CH), 166.4 (C); *m/z* (FAB) 280.1679 (MH^+. $C_{13}H_{27}{}^{35}ClNO_3$ requires 280.1681), 262 (12%), 178 (7), 81 (18).

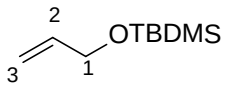
(3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (263)



A solution of (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)nona-1-ene (**245a**) (2.00 g, 5.77 mmol) was dissolved in 2.0 M sodium hydroxide solution (70 mL) and heated at 45 °C overnight. The reaction mixture was cooled to room temperature and benzyl chloroformate (3.25 mL, 23.1 mmol) was added and stirred overnight at room temperature. The reaction mixture was extracted with ethyl

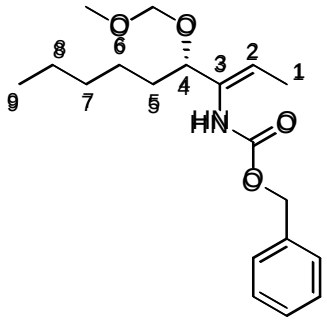
acetate (4 × 100 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether, 3:7) gave (3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (**263**) (1.55 g, 81%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3339 (NH), 2933 (CH), 1722 (CO), 1519, 1234, 1099, 1038; $[\alpha]_D^{23}$ +48.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.9 Hz, 9-H_3), 1.27–1.60 (8H, m, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 3.39 (3H, s, OCH_3), 3.54–3.57 (1H, m, 4-H), 4.24 (1H, t, *J* 7.0 Hz, 3-H), 4.63 (1H, d, *J* 7.0 Hz, OC*H*HO), 4.68 (2H, m, OCH*H*O and NH), 5.11 (2H, s, PhCH_2), 5.20–5.28 (2H, m, 1-H_2), 5.76–5.89 (1H, m, 2-H), 7.28–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.3 (CH_2), 25.3 (CH_2), 31.5 (CH_2), 32.1 (CH_2), 55.8 (CH_3), 56.0 (CH), 66.5 (CH_2), 82.7 (CH), 97.3 (CH_2), 117.4 (CH_2), 128.0 (2 × CH), 128.5 (3 × CH), 133.8 (CH), 136.7 (C), 156.0 (C); *m/z* (CI) 336.2177 (MH^+. $C_{19}H_{30}NO_4$ requires 336.2175), 304 (45%), 260 (10), 228 (9), 181 (7), 147 (9), 91 (23).

1-(*tert*-Butyldimethylsilyloxy)-2-propene (265)[192]

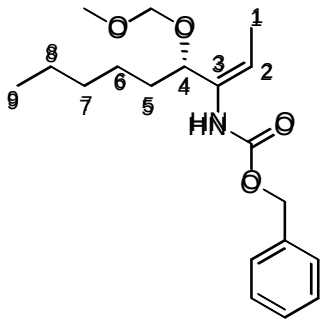


The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**250**) using propene-1-ol (**264**) (1.0 g, 17.21 mmol). Flash column chromatography (petroleum ether/ethyl acetate, 20:1) gave 1-(*tert*-butyldimethylsilyloxy)-2-propene (**265**) as a colourless oil (2.37 g, 80% yield). Spectroscopic data consistent with literature.[192] δ_H (400 MHz, $CDCl_3$) 0.05 (6H, s, $Si(CH_3)_2$), 0.83 (9H, s, $Si(CH_3)_2$), 4.10 (2H, dd, *J* 4.5, 1.9 Hz, 1-H_2), 5.00 (1H, ddt, *J* 10.4, 1.9, 1.8 Hz, 3-*H*H), 5.17 (1H, ddt, *J* 17.1, 1.9, 1.8 Hz, 3-H*H*), 5.85 (1H, ddt, *J* 17.1, 10.4, 4.5 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) –5.2 (2 × CH_3), 11.5 (C), 26.0 (3 × CH_3), 64.1 (CH_2), 114.0 (CH_2), 137.5 (CH); *m/z* (CI) 279 (MH^+. 11%), 173 (14), 137 (12), 85 (69), 69 (98).

(2*Z*,4*S*)-3-(*N*-Benzyloxycarbonyl)-4-(methoxymethoxy)-nona-2-ene (267a) and (2*E*,4*S*)-3-(*N*-Benzyloxycarbonyl)-4-(methoxymethoxy)-nona-2-ene (267b)



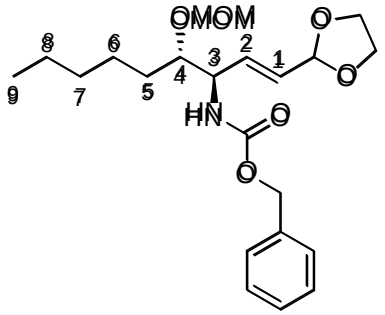
267a



267b

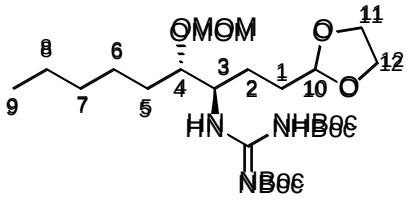
The reaction was carried out according to the procedure for the synthesis of (2*E*,4*R*,5*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) using (3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (**263**) (0.10 g, 0.30 mmol), 1-(*tert*-butyldimethylsilyloxy)-2-propene (**265**) (0.20 mL, 0.90 mmol) and Grubbs 2nd generation catalyst (0.05 g, 0.06 mmol). Flash column chromatography (petroleum ether/diethylether, 7:3) gave **267a** followed by **267b** (0.077 g, 77% combined yield) as a brown oil. **267a**: ν_{max}/cm^{-1} (NaCl) 3325 (NH), 2934 (CH), 1723 (CO), 1539, 1243, 1023, 916, 699; $[\alpha]_D^{23}$ –73.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.78 (3H, t, *J* 6.6 Hz, 9-H_3), 1.18–1.55 (8H, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 1.59 (3H, d, *J* 7.2 Hz, 1-CH_3), 3.26 (3H, s, OCH_3), 4.34 (1H, d, *J* 6.6 Hz, OC*H*HO), 4.44–4.50 (2H, m, 4-H and OCH*H*O), 5.01 (2H, s, PhCH_2), 6.06–6.15 (2H, m, 2-H and NH), 7.21–7.28 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 11.8 (CH_3), 14.0 (CH_3), 22.5 (CH_2), 25.1 (CH_2), 31.6 (CH_2), 33.4 (CH_2), 55.7 (CH_3), 66.6 (CH_2), 70.7 (CH), 93.7 (CH_2), 111.0 (CH), 128.2 (2 × CH), 128.6 (CH), 131.6 (C), 136.3 (C), 154.1 (C); *m/z* (FAB) 336.2175 (MH^+, $C_{19}H_{29}NO_4$ requires 336.2172), 304 (70%), 260 (10), 216 (70), 180 (30), 107 (72), 69 (23). **267b**: ν_{max}/cm^{-1} (NaCl) 3312 (NH), 2932 (CH), 1721 (CO), 1498, 1222, 1034, 920, 697; $[\alpha]_D^{23}$ –82.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 6.6 Hz, 9-H_3), 1.25–1.57 (8H, m, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 1.62 (3H, d, *J* 6.7 Hz, 1-H_3), 3.35 (3H, s, OCH_3), 4.00 (1H, t, *J* 6.8 Hz, 4-H), 4.44 (1H, d, *J* 6.7 Hz, OC*H*HO), 4.67 (1H, d, *J* 6.7 Hz, OCH*H*O), 5.13 (2H, s, OCH_2Ph), 5.43 (1H, q, *J* 6.7 Hz, 2-H), 5.83 (1H, br s, NH), 7.31–7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 13.2 (CH_3), 14.0 (CH_3), 22.5 (CH_2), 25.3 (CH_2), 31.7 (CH_2), 33.0 (CH_2), 55.8 (CH_3), 66.5 (CH_2), 78.7 (CH), 93.4 (CH_2), 121.7 (CH), 128.1 (CH), 128.6 (2 × CH), 131.6 (C), 136.3 (C), 154.1 (C); *m/z* (FAB) 336.2175 (MH^+. $C_{19}H_{29}NO_4$ requires 336.2172), 304 (9%), 274 (98), 184 (17), 166 (42), 91 (52).

2-[(1*E*,3*R*,4*S*)-3-(Benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (244)



The reaction was carried out according to the procedure described for the synthesis of (2*E*,4*R*,5*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) using (3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-1-ene (**263**) (0.10 g, 0.30 mmol), 2-vinyl-1,3-dioxolane (**246**) (0.09 g, 0.90 mmol) and Grubbs 2nd generation catalyst (0.03 g, 0.03 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 1:1) gave 2-[(1*E*,3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (**244**) (0.80 g, 87%) as a yellow oil. ν_{max}/cm^{-1} (NaCl) 3338 (NH), 2953 (CH), 1722 (CO), 1522, 1235, 1149, 1037, 699; $[\alpha]_D^{23}$ +2.9 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.5 Hz, 9-H_3), 1.27–1.58 (8H, m, 5-H_2, 6-H_2, 7-H_2 and 8-H_2), 3.38 (3H, s, OCH_3), 3.52–3.59 (1H, m, 4-H), 3.85–4.00 (4H, m, O*C*H_2*C*H_2O), 4.29–4.36 (1H, m, 3-H), 4.62 (1H, d, *J* 7.0 Hz, O*CH*HO), 4.70 (1H, d, *J* 7.0 Hz, OCH*H*O), 5.07 (1H, d, *J* 12.0 Hz, O*CH*HPh), 5.12 (1H, d, *J* 12.0 Hz, OCH*H*Ph), 5.29 (1H, d, *J* 5.9 Hz, OCHO), 5.70 (1H, dd, *J* 15.9, 5.6 Hz, 2-H), 5.84 (1H, d, *J* 8.8 Hz, NH), 5.90 (1H, dd, *J* 15.9, 5.9 Hz, 1-H), 7.28–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.3 (CH_2), 25.4 (CH_2), 31.7 (CH_2), 32.1 (CH_2), 54.6 (CH), 55.9 (CH_3), 64.8 (CH_2), 65.0 (CH_2), 66.6 (CH_2), 82.7 (CH), 97.3 (CH_2), 103.1 (CH), 128.1 (2 × CH), 128.5 (3 × CH), 129.4 (CH), 131.3 (CH), 131.6 (CH), 136.6 (C), 155.8 (C); *m/z* (CI) 408.2381 (MH^+. $C_{22}H_{34}NO_6$ requires 408.2386), 377 (21%), 300 (12), 284 (31), 246 (100), 214 (32), 145 (21), 91 (92).

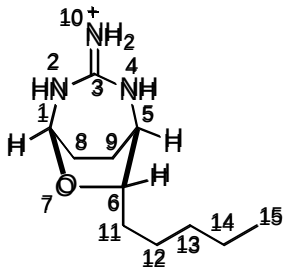
2-[(3*R*,4*S*)-3-(*N*,*N*'-Bis(*tert*-butoxycarbonyl)guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (243)



To a solution of 2-[(1*E*,3*R*,4*S*)-3-(benzyloxycarbonylamino)-4-(methoxymethoxy)nona-2-enyl]-1,3-dioxolane (**244**) (0.02 g, 0.06 mmol) in methanol (5 mL) was added 10% palladium on carbon (0.03 g). The reaction mixture was allowed to stir under an atmosphere of hydrogen at room temperature for 18 h. The reaction mixture was filtered through a short pad of Celite® which was washed with methanol (50 mL). The resulting solution was concentrated *in vacuo* to give 2-[(3*R*,4*S*)-3-amino-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**268**) (0.01 g, 71%) as a colourless oil which was used without further purification. 2-[(3*R*,4*S*)-3-Amino-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**268**) (0.01 g, 0.04 mmol) was dissolved in methanol (7 mL). Diisopropylethylamine (0.06 mL, 0.33 mmol) and *N*,*N*'-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (**269**) (0.02 g, 0.06 mmol) were then added. The reaction mixture was stirred for 20 h at room temperature. The methanol was removed *in vacuo*. The resulting residue was dissolved in ethyl acetate (10 mL) and acidified with 0.2 M hydrochloric acid. The organic layer was washed with brine (10 mL), extracted with ethyl acetate (2 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 10:1) gave 2-[(3*R*,4*S*)-3-(*N*,*N*'-bis(*tert*-butoxycarbonyl)guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**243**) (0.02 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3325 (NH), 2933 (CH), 1795, 1720 (CO), 1638 (C=N), 1332, 1155, 1034 (C=N), 757; $[\alpha]_D^{23}$ –8.1 (*c* 1.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.7 Hz, 9-H_3), 1.25–1.35 (6H, m, 6-H_2, 7-H_2 and 8-H_2), 1.47 (9H, s, O^{t}Bu), 1.48 (9H, s, O^{t}Bu), 1.50–1.82 (6H, m, 1-H_2, 2-H_2 and 5-H_2), 3.38 (3H, s, OCH_3), 3.61–3.66 (1H, m, 4-H), 3.82–3.89 (2H, m, OC*H*HC*H*O), 3.94–3.99 (2H, m, OCH*H*CH*H*O), 4.34–4.42 (1H, m, 3-H), 4.62 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.69 (1H, d, *J* 6.9 Hz, OCH*H*O), 4.88 (1H, t, *J* 4.4 Hz, OCHO), 8.44 (1H, d, *J* 9.2 Hz, NH), 11.53 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 23.2 (CH_2), 25.5 (CH_2), 28.1 (3 × CH_3), 28.3 (3 × CH_3), 30.3 (CH_2), 31.1 (CH_2), 31.8 (CH_2), 52.0 (CH), 55.8 (CH_3), 64.8 (CH_2), 64.9 (CH_2), 78.8 (C), 79.7 (C), 82.8 (CH), 96.4 (CH_2), 104.3 (CH), 153.1 (C), 156.1

(C), 163.8 (C); *m/z* (FAB) 518.3443 (MH^+. $C_{25}H_{48}N_3O_8$ requires 518.3441), 462 (9%), 406 (55), 362 (22), 311 (14), 260 (7), 199 (6), 111 (12).

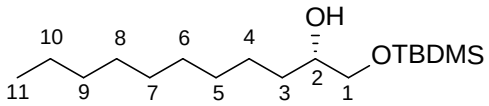
(+)-Monanchorin (234)[149,150]



To a solution of 2-[(3*R*,4*S*)-3-(*N*,*N*'-bis(*tert*-butoxycarbonyl)guanidino)-4-(methoxymethoxy)nonyl]-1,3-dioxolane (**243**) (0.04 g, 0.07 mmol) in dichloromethane (5 mL) was added trifluoroacetic acid (0.35 mL, 4.64 mmol). The reaction mixture was heated under reflux for 12 h. The reaction mixture was quenched with potassium carbonate (0.10 g, 0.77 mmol), filtered and concentrated under vacuum. Flash column chromatography (dichloromethane/methanol, 2:1) gave (+)-monanchorin (**234**) (0.01 g, 75%) as a colourless oil. Spectroscopic data consistent with literature.[149,150] $[\alpha]_D^{22}$ +33.7 (*c* 0.8, MeOH), lit[149] $[\alpha]_D^{25}$ +39.0 (*c* 3.9, MeOH); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.7 Hz, 15-H_3), 1.22–1.35 (5H, m, 12-*H*H, 13-H_2 and 14-H_2), 1.42–1.49 (2H, m, 11-*H*H, 12-H*H*), 1.60–1.66 (1H, m, 11-H*H*), 2.00–2.11 (2H, m, 8-*H*H and 9-*H*H), 2.19–2.23 (1H, m, 8-H*H*), 2.28–2.37 (1H, m, 9-H*H*), 3.23–3.27 (1H, m, 5-H), 4.29–4.35 (1H, m, 6-H), 4.84 (1H, t, *J* 6.2 Hz, 1-H), 8.56 (1H, br s, NH), 8.96 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 22.5 (CH_2), 23.8 (CH_2), 25.1 (CH_2), 28.9 (CH_2), 31.6 (CH_2), 33.6 (CH_2), 51.3 (CH), 76.7 (CH), 79.5 (CH), 159.1 (C); *m/z* (CI) 212 (MH^+. 85%), 170 (15), 129 (19), 113 (31), 81 (67).

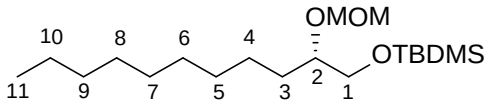
3.6 Synthesis of Clavaminol A, C and H

(2*S*)-1-(*tert*-Butyldimethylsilyloxy)undecan-2-ol (280)



The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**251**) using (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**250**) (5.00 g, 26.6 mmol), octylmagnesium bromide (2.0 M in diethyl ether) (26.60 mL, 53.1 mmol) and copper(I) bromide dimethyl sulfide (6.01 g, 29.2 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 30:1) gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**280**) (7.55 g, 94%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3423 (OH), 2927 (CH), 1464, 1254, 1109, 837, 777; $[\alpha]_D^{23}$ –19.4 (*c* 2.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.07 (6H, s, 2 × $SiCH_3$), 0.80–0.84 (12H, m, 11-H_3 and $SiC(CH_3)_3$), 1.22–1.44 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 2.42 (1H, d, *J* 3.2 Hz, OH), 3.38 (1H, dd, *J* 10.8, 8.4 Hz, 1-*H*H), 3.60–3.65 (2H, m, 1-H*H* and 2-H); δ_C (100 MHz, $CDCl_3$) –5.4 (CH_3), –5.3 (CH_3), 14.1 (CH_3), 18.3 (C), 22.7 (CH_2), 25.6 (CH_2), 25.9 (3 × CH_3), 29.3 (CH_2), 29.6 (2 × CH_2), 29.7 (CH_2), 32.0 (CH_2), 32.8 (CH_2), 67.3 (CH_2), 71.8 (CH); *m/z* (CI) 303.2722 (MH^+. $C_{17}H_{39}O_2Si$ requires 303.2719), 285 (24%), 185 (10), 133 (11), 113 (14), 69 (60).

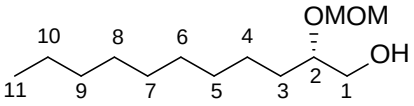
(2*S*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (279)



The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**252**) using (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**280**) (5.00 g, 16.6 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 30:1) gave (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**279**) as a colourless oil (5.72 g, 100%). (Found: C, 65.92; H, 12.23. $C_{19}H_{42}O_3Si$ requires C, 65.90; H, 12.14%); ν_{max}/cm^{-1} (NaCl) 2927 (CH), 1465, 1254, 1113, 1040, 837, 776; $[\alpha]_D^{23}$ +49.9 (*c* 1.4, $CHCl_3$); δ_H (400

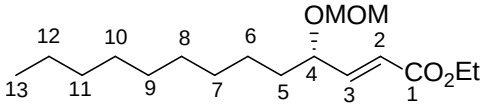
MHz, $CDCl_3$) 0.01 (6H, s, $Si(CH_3)_2$), 0.83–0.85 (12H, m, 11-H_3 and $SiC(CH_3)_3$), 1.18–1.44 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 3.32 (3H, s, OCH_3), 3.48–3.60 (3H, m, 1-H_2 and 2-H), 4.59 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.72 (1H, d, *J* 6.8 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) –5.1 (2 × CH_3), 14.1 (CH_3), 18.3 (C), 22.7 (CH_2), 25.4 (CH_2), 25.9 (3 × CH_3), 29.3 (CH_2), 29.6 (2 × CH_2), 29.7 (CH_2), 31.7 (CH_2), 31.9 (CH_2), 55.4 (CH_3), 65.9 (CH_2), 78.2 (CH), 96.3 (CH_2); *m/z* (CI) 347.2983 (MH^+. $C_{19}H_{43}O_3Si$ requires 347.2981), 315 (100%), 285 (24), 259 (8), 221 (6), 133 (7), 97 (18), 81 (52), 69 (68).

(2*S*)-2-(Methoxymethoxy)undecan-1-ol (281)



The reaction was carried out according to the procedure described for the synthesis of (2*S*)-2-(methoxymethoxy)heptan-1-ol (**248**) using (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**279**) (5.00 g, 14.5 mmol). Purification by flash column chromatography (petroleum ether/diethyl ether, 5:2) gave (2*S*)-2-(methoxymethoxy)undecan-1-ol (**281**) as a colourless oil (3.35 g, 100%). ν_{max}/cm^{-1} (NaCl) 3435 (OH), 2925 (CH), 1466, 1106, 1037, 918; $[\alpha]_D^{23}$ +6.7 (*c* 1.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.8 Hz, 11-H_3), 1.26–1.52 (16H, m, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, and 10-H_2), 3.15 (1H, dd, *J* 8.8, 3.2 Hz, OH), 3.43 (3H, s, OCH_3), 3.46–3.62 (3H, m, 1-H_2 and 2-H), 4.70 (1H, d, *J* 6.9 Hz, OC*H*HO), 4.75 (1H, d, *J* 6.9 Hz, OCH*H*O); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.6 (CH_2), 25.5 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (2 × CH_2), 31.6 (CH_2), 31.8 (CH_2), 55.6 (CH_3), 65.7 (CH_2), 82.5 (CH), 97.0 (CH_2); *m/z* (CI) 233.2119 (MH^+. $C_{13}H_{29}O_3$ requires 233.2117), 215 (10%), 201 (94), 183 (38), 171 (100), 153 (14), 113 (6), 81 (18), 69 (26).

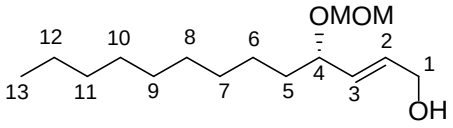
Ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (278)



The reaction was carried out according to the procedure described for the synthesis of ethyl (2*E*)-2,8-nonadienoate (**188**) using (2*S*)-2-(methoxymethoxy)undecan-1-ol (**281**) (5.38 g,

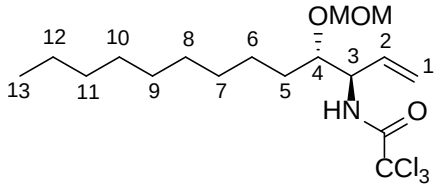
23.1 mmol). Purification by flash column chromatography using (diethyl ether/petroleum ether, 1:10) yielded ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**278**) (6.61 g, 95%) as a colourless oil. (Found: C, 67.85; H, 10.86. $C_{17}H_{32}O_4$ requires C, 68.00; H, 10.67%); ν_{max}/cm^{-1} (NaCl) 2927 (CH), 1724 (CO), 1658 (C=C), 1467, 1368, 1268, 1154, 1035, 722; $[\alpha]_D^{23}$ –62.1 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, 13-H_3), 1.21–1.62 (19H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 and OCH_2CH_3), 3.38 (3H, s, OCH_3), 4.16–4.24 (3H, m, 4-H and OCH_2CH_3), 4.58 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.64 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.97 (1H, dd, *J* 16.0, 1.2 Hz, 2-H), 6.82 (1H, dd, *J* 16.0, 6.4 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 14.3 (CH_3), 22.7 (CH_2), 25.2 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 31.9 (CH_2), 34.9 (CH_2), 55.7 (CH_3), 60.5 (CH_2), 75.2 (CH), 94.6 (CH_2), 121.8 (CH), 148.0 (CH), 166.4 (C); *m/z* (CI) 301.2378 (MH^+. $C_{17}H_{33}O_4$ requires 301.2379), 271 (15%), 239 (100), 173 (6), 145 (5), 69 (17).

(2*E*,4*S*)-4-(Methoxymethoxy)tridecan-2-ene-1-ol (282)



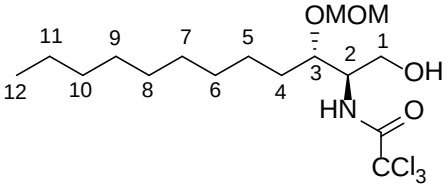
The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**278**) (4.70 g, 15.7 mmol). Flash column chromatography (diethyl ether/petroleum ether, 2:5) gave (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**282**) (3.84 g, 95%) as a colourless oil. (Found: C, 70.15; H, 11.99. $C_{15}H_{30}O_3$ requires C, 69.77; H, 11.63%); ν_{max}/cm^{-1} (NaCl) 3399 (OH), 2925 (CH), 2855, 1466, 1377, 1213, 1152, 1128, 1096, 1036, 973; $[\alpha]_D^{23}$ –87.3 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.4 Hz, 13-H_3), 1.26–1.62 (17H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2, 12-H_2 and OH), 3.37 (3H, s, OCH_3), 4.01 (1H, q, *J* 7.0 Hz, 4-H), 4.16 (2H, td, *J* 5.6, 1.2 Hz, 1-H_2), 4.53 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.70 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.56 (1H, ddt, *J* 15.6, 7.0, 1.2 Hz, 3-H), 5.81 (1H, dt, *J* 15.6, 5.6 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.3 (CH_2), 29.6 (2 × CH_2), 29.6 (CH_2), 31.9 (CH_2), 35.6 (CH_2), 55.4 (CH_3), 62.9 (CH_2), 76.3 (CH), 93.8 (CH_2), 131.7 (CH), 131.9 (CH); *m/z* (CI) 241.2166 (MH^+–H_2O. $C_{15}H_{29}O_2$ requires 241.2168), 197 (100%), 179 (33), 155 (14), 131 (21), 85 (28).

(3*R*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (276a)



The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**282**) (2.55 g, 9.90 mmol), bis(acetonitrile)palladium(II) chloride (0.38 g, 1.48 mmol) and *p*-benzoquinone (2.13 g, 19.8 mmol). Purification by flash column chromatography (diethyl ether/petroleum ether, 1:20) gave (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**276a**) as a colourless oil (2.78 g, 70% over 2 steps). ν_{max}/cm^{-1} (NaCl) 3287 (NH), 2855 (CH), 1717 (CO), 1643 (C=C), 1517, 1237, 1036, 822, 758; $[\alpha]_D^{23}$ +66.0 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, 13-H_3), 1.24–1.65 (16H, m, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, 11-H_2 and 12-H_2), 3.43 (3H, s, OCH_3), 3.56 (1H, ddd, *J* 8.4, 4.8, 2.0 Hz, 4-H), 4.36–4.41 (1H, m, 3-H), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 5.30–5.36 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 17.2, 10.4, 6.8 Hz, 2-H), 8.24 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.5 (CH_2), 31.9 (CH_2), 33.0 (CH_2), 55.9 (CH), 56.7 (CH_3), 83.9 (CH), 93.0 (C), 98.2 (CH_2), 118.9 (CH_2), 131.6 (CH), 161.4 (C); *m/z* (CI) 402.1369 (MH^+. $C_{17}H_{31}{}^{35}Cl_3NO_3$ requires 402.1370), 370 (100%), 336 (36), 308 (25), 270 (19), 214 (60), 180 (19), 85 (20), 69 (31).

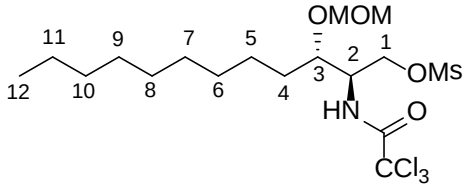
(2*R*,3*S*)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (283)



(3*R*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**276a**) (0.94 g, 2.33 mmol) was dissolved in a mixture of dichloromethane (40 mL) and methanol (20 mL) and cooled to –78 °C. Ozone was bubbled through the reaction mixture

until the solution turned slightly blue. After excess ozone was purged with argon gas, sodium borohydride (0.08 g, 2.33 mmol) was added in portions. The solution was stirred for 1.5 h at 0 °C, then acidified with 1 M hydrochloric acid (10 ml). The reaction was quenched by the addition of water (20 mL) and then extracted with diethyl ether (4 × 50 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, 5:5) yielded (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**) (0.84 g, 88% over 2 steps) as a colourless oil. (Found: C, 47.26; H, 7.45; N, 3.32. $C_{16}H_{30}Cl_3NO_4$ requires C, 47.23; H, 7.38; N, 3.44%); ν_{max}/cm^{-1} (NaCl) 3416 (NH), 2926 (CH), 1712 (CO), 1522, 1467, 1214, 1034, 906, 822, 756; $[\alpha]_D^{23}$ +23.3 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.8 Hz, 12-H_3), 1.25–1.78 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 2.70 (1H, dd, *J* 9.6, 3.6 Hz, OH), 3.47 (3H, s, OCH_3), 3.74–3.84 (2H, m, 1-*H*H and 3-H), 3.95 (1H, dq, *J* 8.2, 3.6 Hz, 2-H), 4.08 (1H, dt, *J* 12.0, 3.6 Hz, 1-H*H*), 4.65 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.73 (1H, d, *J* 6.8 Hz, OCH*H*O), 8.01 (1H, br d, *J* 8.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.5 (2 × CH_2), 31.9 (CH_2), 32.9 (CH_2), 54.7 (CH), 56.1 (CH_3), 61.2 (CH_2), 82.6 (CH), 92.7 (C), 97.9 (CH_2), 162.2 (C); *m/z* (CI) 406.1317 (MH^+. $C_{16}H_{31}{}^{35}Cl_3NO_4$ requires 406.1319), 374 (100%), 340 (43), 288 (14), 272 (6), 183 (4), 121 (3), 81 (6).

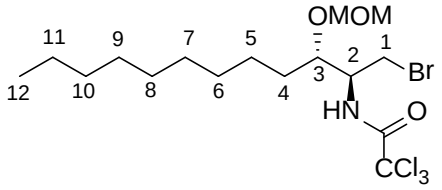
(2*R*,3*S*)-1-Methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (284)



A solution of (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**) (0.38 g, 0.95 mmol) was dissolved in dichloromethane (40 mL). Methanesulfonyl chloride (0.16 mL, 1.47 mmol), triethylamine (0.29 mL, 2.16 mmol) and 4-dimethylaminopyridine (DMAP, catalytic) were added at 0 °C and the solution stirred at room temperature for 24 h. The reaction mixture was then washed with water (20 mL), extracted with dichloromethane (3 × 30 mL). The resulting organic layer was dried ($MgSO_4$) and concentrated to give the crude product, which was purified by flash column chromatography (diethyl ether/petroleum ether, 2:3) to give

(2*R*,3*S*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**284**) (0.39 g, 87%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3346 (NH), 2926 (CH), 1716 (CO), 1524, 1359, 1177, 1034, 823; $[\alpha]_D^{23}$ +25.8 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.2 Hz, 12-H_3), 1.21–1.72 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.06 (3H, s, OSO_2CH_3), 3.45 (3H, s, OCH_3), 3.59–3.65 (1H, m, 3-H), 4.23–4.29 (1H, m, 2-H), 4.34 (1H, dd, *J* 10.4, 7.8 Hz, 1-*H*H), 4.50 (1H, dd, *J* 10.4, 4.4 Hz, 1-H*H*), 4.63 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 8.15 (1H, br d, *J* 8.4 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.8 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (2 × CH_2), 31.9 (CH_2), 33.0 (CH_2), 37.8 (CH_3), 53.2 (CH), 56.0 (CH_3), 66.4 (CH_2), 82.4 (CH), 92.6 (C), 98.3 (CH_2), 162.2 (C); *m/z* (CI) 484.1089 (MH^+. $C_{17}H_{33}{}^{35}Cl_3NO_6S$ requires 484.1094), 452 (83%), 418 (19), 388 (100), 354 (85), 322 (44), 279 (74), 201 (10), 153 (6), 85 (11).

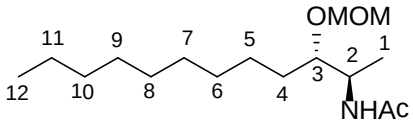
(2*R*,3*S*)-1-Bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (285)



(2*R*,3*S*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**284**) (0.41 g, 0.85 mmol) was dissolved in dimethyl sulfoxide (20 mL), then sodium bromide (0.44 g, 4.26 mmol) was added and the reaction mixture was heated under reflux overnight. The reaction mixture was cooled and concentrated *in vacuo*. The resulting residue was dissolved in diethyl ether (20 mL) and washed with water (2 × 30 mL). The organic layer was dried and concentrated *in vacuo*. Purification by column chromatography (petroleum ether/diethyl ether, 14:1) gave (2*R*,3*S*)-1-bromo-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**285**) (0.30 g, 75%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3337 (NH), 2925 (CH), 1718 (CO), 1523, 1148, 1034, 821; $[\alpha]_D^{23}$ +32.8 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.8 Hz, 12-H_3), 1.16–1.59 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.37 (3H, s, OCH_3), 3.50 (1H, dd, *J* 10.8, 7.6 Hz, 1-*H*H), 3.56–3.61 (2H, m, 1-H*H* and 3-H), 4.16–4.23 (1H, m, 2-H), 4.57 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.65 (1H, d, *J* 6.8 Hz, OCH*H*O), 7.62 (1H, br d, *J* 9.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.3

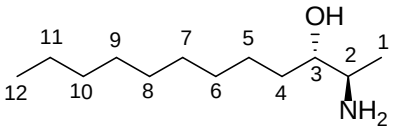
(CH_2), 29.5 (CH_2), 29.5 (2 × CH_2), 31.4 (CH_2), 31.9 (CH_2), 32.5 (CH_2), 54.6 (CH), 56.1 (CH_3), 81.7 (CH), 92.7 (C), 97.8 (CH_2), 161.8 (C); *m/z* (CI) 470.0442 (MH^+. $C_{16}H_{30}{}^{81}Br^{35}Cl_3NO_3$ requires 470.0451), 438 (100%), 436 (63), 408 (16), 354 (9), 201 (4), 171 (3), 95 (2), 69 (8).

(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (286)



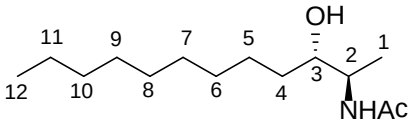
A mixture of (2*R*,3*S*)-1-bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**285**) (0.14 g, 0.29 mmol), tributyltin hydride (1.01 mL, 3.47 mmol), AIBN (0.02 g) in toluene (9 mL) and *N*,*N*-dimethylacetamide (3 mL) were degassed under argon for 0.3 h and then heated under reflux for 24 h. The reaction mixture was cooled, washed with water (20 mL), extracted with diethyl ether (3 × 20 mL) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:8) gave (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**) (0.07 g, 85%) as a white solid. Mp 35–37 °C; ν_{max}/cm^{-1} (NaCl) 3290 (NH), 2925 (CH), 1648 (CO), 1546, 1374, 1038, 920; $[\alpha]_D^{23}$ +46.1 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.2 Hz, 12-H_3), 1.11 (3H, d, *J* 6.8 Hz, 1-H_3), 1.28–1.62 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.98 (3H, s, $COCH_3$), 3.43–3.48 (4H, m, OCH_3 and 3-H), 3.98–4.06 (1H, m, 2-H), 4.64 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.74 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.65 (1H, br d, *J* 7.6 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 22.7 (CH_2), 23.6 (CH_3), 25.9 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 47.2 (CH), 55.7 (CH_3), 84.4 (CH), 98.1 (CH_2), 169.1 (C); *m/z* (CI) 288.2543 (MH^+. $C_{16}H_{34}NO_3$ requires 288.2539), 256 (29%), 226 (9), 184 (3), 131 (4), 86 (5).

(2*R*,3*S*)-2-Aminododecan-3-ol (Clavaminol A) (270)[158]



(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (**286**) (0.02 g, 0.06 mmol) was dissolved in 6 M hydrochloric acid (10 mL) and heated to 60 °C for 24 h. The reaction mixture was then cooled before being washed with diethyl ether (3 × 10 mL). The aqueous layer was concentrated to give (2*R*,3*S*)-2-aminododecan-3-ol (**270**) (0.014 g, 100%) as a white solid. Mp 107–109 °C; ν_{max}/cm^{-1} (NaCl) 3389 (NH), 2928 (CH), 1610, 1500, 1025, 721; $[\alpha]_D^{23}$ –4.5 (*c* 1.5, MeOH), lit.[158] $[\alpha]_D^{25}$ –4.25 (*c* 0.0094, MeOH); δ_H (400 MHz, CD_3OD) 0.93 (3H, t, *J* 7.2 Hz, 12-H_3), 1.24 (3H, d, *J* 6.8 Hz, 1-H_3), 1.31–1.59 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.30 (1H, qd, *J* 6.8, 3.2 Hz, 2-H), 3.70–3.75 (1H, m, 3-H); δ_C (100 MHz, CD_3OD) 12.1 (CH_3), 14.5 (CH_3), 23.8 (CH_2), 27.0 (CH_2), 30.5 (CH_2), 30.7 (CH_2), 30.7 (2 × CH_2), 33.1 (CH_2), 34.0 (CH_2), 52.6 (CH), 71.7 (CH); *m/z* (CI) 202.2175 (MH^+. $C_{12}H_{28}NO$ requires 202.2171), 184 (15%), 156 (10), 97 (4), 85 (6), 71 (7).

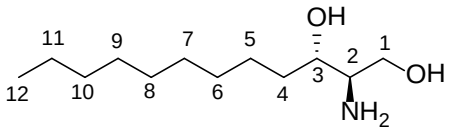
(2*R*,3*S*)-2-Acetylaminododecan-3-ol (Clavaminol C) (271)[158]



(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecane (**286**) (0.02 g, 0.07 mmol) was dissolved in 2 M hydrochloric acid (10 mL) and stirred at room temperature for 24 h. The reaction mixture was washed with diethyl ether (3 × 10 mL) and the organic layers were concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/methanol, 15:1) yielded (2*R*,3*S*)-2-acetylaminododecan-3-ol (**271**) (0.02 g, 100%) as a white solid. Mp 103–105 °C; ν_{max}/cm^{-1} (NaCl) 3283 (NH), 2918 (CH), 1645 (CO), 1558, 1467, 1126, 747; $[\alpha]_D^{23}$ +11.1 (*c* 2.1, MeOH), lit.[158] $[\alpha]_D^{25}$ +11.4 (*c* 0.0022, MeOH); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 7.2 Hz, 12-H_3), 1.03 (3H, d, *J* 6.8 Hz, 1-H_3), 1.17–1.43 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.92 (3H, s, $COCH_3$), 2.12 (1H, d, *J* 6.0 Hz, OH), 3.54–3.61 (1H, m, 3-H), 3.90–3.98 (1H, m, 2-H), 5.71 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.0 (CH_3), 14.2 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 26.0

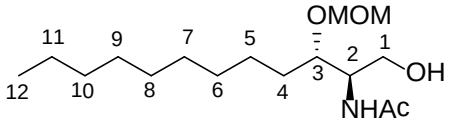
(CH_2), 29.3 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 31.9 (CH_2), 33.6 (CH_2), 49.5 (CH), 74.3 (CH), 170.0 (C); *m/z* (CI) 244.2275 (MH^+. $C_{14}H_{30}NO_2$ requires 244.2277), 226 (5%), 151 (5), 113 (5), 85 (39), 69 (58).

(2*R*,3*S*)-2-Aminododecan-1,3-diol (273)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-aminododecan-3-ol (**270**) using (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**) (0.04 g, 0.10 mmol). The water layer was concentrated to give (2*R*,3*S*)-2-aminododecan-1,3-diol (**273**) (0.02 g, 100%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3348 (NH/OH), 2924 (CH), 1600, 1467, 1051; $[\alpha]_D^{23}$ +6.6 (*c* 0.6, MeOH); δ_H (400 MHz, CD_3OD) 0.92 (3H, t, *J* 6.8 Hz, 12-H_3), 1.25–1.58 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 3.33–3.35 (1H, m, 2-H), 3.73 (1H, dd, *J* 11.6, 8.8 Hz, 1-*H*H), 3.79–3.85 (1H, m, 3-H), 3.87 (1H, dd, *J* 11.6, 3.6 Hz, 1-H*H*); δ_C (100 MHz, CD_3OD) 14.5 (CH_3), 23.8 (CH_2), 27.1 (CH_2), 30.5 (CH_2), 30.6 (CH_2), 30.7 (2 × CH_2), 33.1 (CH_2), 34.2 (CH_2), 58.5 (CH), 58.9 (CH_2), 70.3 (CH); *m/z* (CI) 218.2113 (MH^+. $C_{12}H_{28}NO_2$ requires 218.2120), 200 (4%), 186 (3), 171 (4), 81 (5), 69 (6).

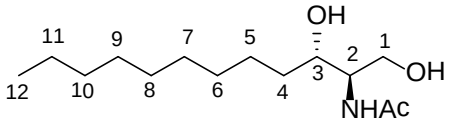
(2*R*,3*S*)-2-Acetylamino-3-(methoxymethoxy)dodecan-1-ol (287)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**) using (2*R*,3*S*)-2-(trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**) (0.30 g, 0.73 mmol) and tributyltin hydride (2.50 mL, 8.85 mmol). Flash column chromatography using (diethyl ether/methanol, 15:1) yielded (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**287**) (0.20 g, 91%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3297 (NH/OH), 2925 (CH), 1656 (CO), 1551, 1376, 1035; $[\alpha]_D^{23}$ +34.6 (*c* 2.5, $CHCl_3$); δ_H

(400 MHz, $CDCl_3$) 0.75 (3H, t, *J* 6.8 Hz, 12-H_3), 1.10–1.52 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.89 (3H, s, $COCH_3$), 3.18 (1H, dd, *J* 8.6, 3.2 Hz, OH), 3.29 (3H, s, OCH_3), 3.48 (1H, ddd, *J* 8.4, 4.8, 3.2 Hz, 3-H), 3.55 (1H, ddd, *J* 11.2, 8.6, 3.2 Hz, 1-*H*H), 3.71–3.77 (1H, m, 1-H*H*), 3.80–3.86 (1H, m, 2-H), 4.47 (1H, d, *J* 6.8 Hz, OC*H*HO), 4.54 (1H, d, *J* 6.8 Hz, OCH*H*O), 6.60 (1H, br d, *J* 8.0 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.4 (CH_3), 25.8 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (2 × CH_2), 31.9 (CH_2), 32.7 (CH_2), 53.3 (CH), 56.0 (CH_3), 62.4 (CH_2), 82.7 (CH), 98.0 (CH_2), 170.6 (C); *m/z* (CI) 304.2483 (MH^+. $C_{16}H_{34}NO_4$ requires 304.2488), 272 (58%), 242 (8), 200 (3), 147 (4), 102 (4), 85 (4).

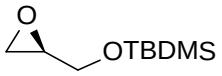
(2*R*,3*S*)-2-Acetylaminododecan-1,3-diol (Clavaminol H) (272)[159]



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylaminododecan-3-ol (**271**) using (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**287**) (0.02 g, 0.08 mmol). Flash column chromatography using (diethyl ether/methanol, 15:1) yielded (2*R*,3*S*)-2-acetylaminododecan-1,3-diol (**272**) (0.02 g, 100%) as a white solid. Mp 107–109 °C; ν_{max}/cm^{-1} (NaCl) 3289 (NH/OH), 2917 (CH), 1650 (CO), 1551, 1371, 1091; $[\alpha]_D^{23}$ +3.3 (*c* 1.4, MeOH), lit.[159] $[\alpha]_D^{25}$ +3.19 (*c* 0.0013, MeOH); δ_H (400 MHz, $CDCl_3$) 0.81 (3H, t, *J* 6.8 Hz, 12-H_3), 1.14–1.53 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 1.99 (3H, s, $COCH_3$), 2.44 (1H, d, *J* 6.8 Hz, 3-OH), 2.53 (1H, dd, *J* 6.8, 3.6 Hz, 1-OH), 3.66–3.80 (3H, m, 1-*H*H, 2-H and 3-H), 3.96 (1H, dt, *J* 11.2, 3.6 Hz, 1-H*H*), 6.35 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 23.5 (CH_3), 26.0 (CH_2), 29.3 (2 × CH_2), 29.6 (2 × CH_2), 31.9 (CH_2), 34.6 (CH_2), 53.6 (CH), 62.5 (CH_2), 74.4 (CH), 170.4 (C); *m/z* (CI) 260 (MH^+. 100%), 242 (29), 228 (6), 186 (4), 102 (3), 85 (18).

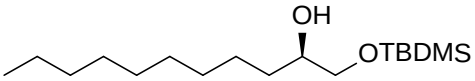
3.7 Synthesis of (2*S*,3*R*)-Clavaminol A, C and H

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-epoxypropane (289)[193]



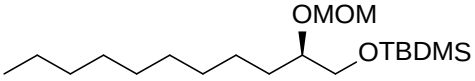
The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**250**) using (*S*)-(+)-glycidol **288** (9.93 g, 134.0 mmol). This yielded (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane **289** (22.9 g, 91%) as a colourless oil.[193] $[\alpha]_D^{24}$ +2.6 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2,3-epoxypropane (**250**).

(2*R*)-1-(*tert*-Butyldimethylsilyloxy)undecan-2-ol (290)



The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)heptan-2-ol (**251**) using (2*R*)-1-(*tert* butyldimethylsilyloxy)-2,3-epoxypropane **289** (5.00 g, 26.6 mmol). This gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**290**) (8.1 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ +19.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol **(280)**.

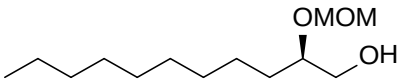
(2*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (291)



The reaction was carried out according to the procedure described for the synthesis of (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)heptane (**252**) using (2*R*)-1-(*tert*-butyldimethylsilyloxy)undecan-2-ol (**290**) (5.00 g, 16.53 mmol). This gave (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**291**) (5.70 g, 100%) as a colourless

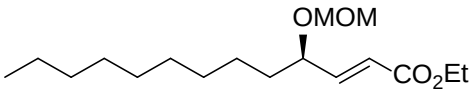
oil. $[\alpha]_D^{23}$ –49.5 (*c* 1.4, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**279**).

(2*R*)-2-(Methoxymethoxy)undecan-1-ol (292)



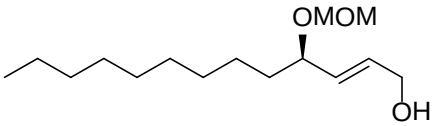
The reaction was carried out according to the procedure described for the synthesis of (2*S*)-2-(methoxymethoxy)heptan-1-ol (**248**) using (2*R*)-1-(*tert*-butyldimethylsilyloxy)-2-(methoxymethoxy)undecane (**291**) (0.50 g, 1.44 mmol). This gave (2*R*)-2-methoxymethoxy)undecan-1-ol (**292**) (0.32 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ –7.1 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*S*)-2-(methoxymethoxy)undecan-1-ol (**281**).

Ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate (293)



The reaction was carried out according to the procedure described for the synthesis of ethyl (2*E*)-2,8-nonadienoate (**188**) using (2*R*)-2-(methoxymethoxy)undecan-1-ol (**292**) (5.38 g, 23.14 mmol). This gave ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate (**293**) (7.10 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ +63.2 (*c* 1.1, $CHCl_3$). All other spectroscopic data as previously reported for ethyl (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-enoate (**278**).

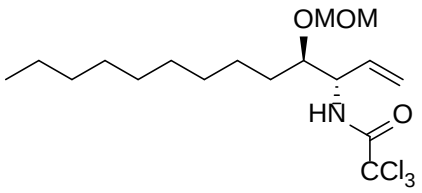
(2*E*,4*R*)-4-(Methoxymethoxy)tridecan-2-ene-1-ol (294)



The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using ethyl (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-enoate (**293**) (4.80 g, 16.0 mmol). This gave (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**294**) (4.00 g,

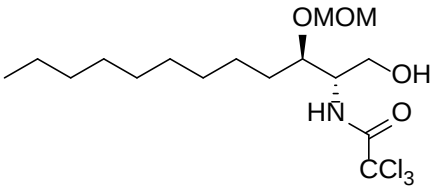
97%) as a colourless oil. $[\alpha]_D^{23}$ +87.6 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*E*,4*S*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**282**).

(3*S*,4*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (296)



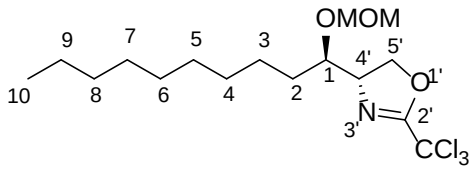
The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*,4*R*)-4-(methoxymethoxy)tridecan-2-ene-1-ol (**294**) (2.55 g, 9.90 mmol). This gave (3*S*,4*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**296**) (2.80 g, 70%) as a colourless oil. $[\alpha]_D^{23}$ –65.8 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (3*R*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**276a**).

(2*S*,3*R*)-2-(2',2',2'-Trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (297)



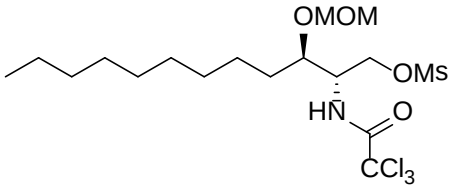
The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**) using (3*S*,4*R*)-3-(2',2',2'-trichloromethylcarbonylamino)-4-(methoxymethoxy)tridecan-1-ene (**296**) (0.50 g, 1.24 mmol). This gave (2*S*,3*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.38 g, 76%) as a colourless oil. $[\alpha]_D^{23}$ –23.7 (*c* 1.3, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**283**).

(1*R*,4'*S*)-1-(Methoxymethoxy)-1-(2'-trichloromethyl-4',5'-dihydrooxazo-4'-yl)]decane (299)



To a solution of (2*S*,3*R*)-2-(2',2',2-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.10 g, 0.24 mmol) in dichloromethane (10 mL), methanesulfonyl chloride (0.04 mL, 0.37 mmol) and triethylamine (0.07 mL, 0.54 mmol) were added slowly at 0 °C and the solution stirred at room temperature for 24 h. Sodium borohydride (0.02 g, 0.50 mmol) was added in portions. The reaction mixture was heated at 35 °C for 48 h, acidified with 1 M hydrochloric acid, extracted with dichloromethane (3 × 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (diethyl ether/petroleum ether, 1:9) gave (1*R*,4'*S*)-1-(methoxymethoxy)-1-(2'-trichloromethyl-4',5'-dihydrooxazo-4'-yl)]decane (**299**) (0.06 g, 60%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 2926 (CH), 1665, 1466, 1234, 1036, 921, 794; $[\alpha]_D^{23}$ –21.3 (*c* 0.8, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.8 Hz, 10-H_3), 1.26–1.59 (16H, m, 2-H_2, 3-H_2, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, and 9-H_2), 3.38 (3H, s, OCH_3), 3.90–3.94 (1H, m, 4'-H), 4.42 (1H, ddd, *J* 10.8, 8.0, 2.8 Hz, 5'-*H*H), 4.56–4.70 (4H, m, OCH_2, 1-H and 5'-H*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.4 (CH_2), 29.3 (CH_2), 29.5 (CH_2), 29.6 (2 × CH_2), 31.9 (CH_2), 32.4 (CH_2), 55.8 (CH_3), 70.3 (CH_2), 71.8 (CH), 77.5 (CH), 86.6 (C), 96.5 (CH_2), 163.2 (C); *m/z* (CI) 388.1219 (MH^+. $C_{16}H_{29}{}^{35}Cl_3NO_3$ requires 388.1213), 354 (100%), 322 (45), 288 (8), 201 (13), 85 (20).

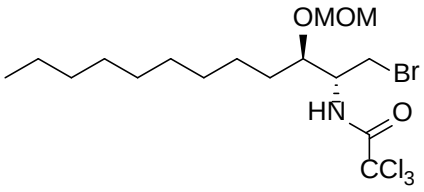
(2*S*,3*R*)-1-Methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (300)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-

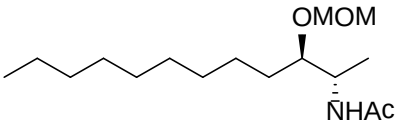
(methoxymethoxy)dodecane (**284**) using (2*S*,3*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.23 g, 0.56 mmol). This gave (2*S*,3*R*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**300**) (0.23 g, 88%) as a colourless oil. $[\alpha]_D^{23}$ –25.4 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**284**).

(2*S*,3*R*)-1-Bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (301)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-1-bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**285**) using (2*S*,3*R*)-1-methanesulfonate-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**300**) (0.41 g, 0.85 mmol). This gave (2*S*,3*R*)-1-bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**301**) (0.31 g, 75%) as a colourless oil. $[\alpha]_D^{23}$ –34.0 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-1-bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**285**).

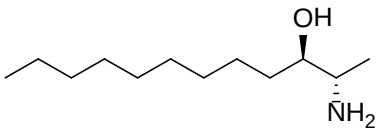
(2*S*,3*R*)-2-Acetylamino-3-(methoxymethoxy)dodecane (302)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**) using (2*S*,3*R*)-1-bromo-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecane (**301**) (0.05 g, 0.10 mmol). This gave (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (**302**) (0.03 g,

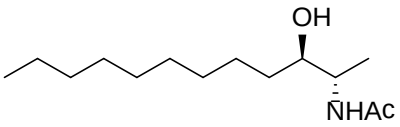
100%) as a white solid. $[\alpha]_D^{23}$ –45.7 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**).

(2*S*,3*R*)-2-Aminododecan-3-ol (274)



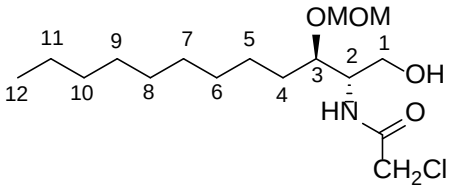
The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-aminododecan-3-ol (**270**) using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (**302**) (0.015 g, 0.05 mmol). This gave (2*S*,3*R*)-2-aminododecan-3-ol (**274**) (0.011 g, 100%) as a white solid. $[\alpha]_D^{23}$ +5.4 (*c* 1.0, MeOH). All other spectroscopic data as reported above for (2*R*,3*S*)-2-aminododecan-3-ol (**270**).

(2*S*,3*R*)-2-Acetylaminododecan-3-ol (303)



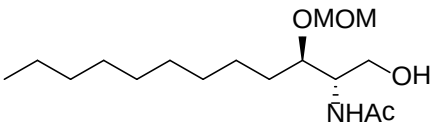
The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylaminododecan-3-ol (**271**) using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecane (**302**) (0.027 g, 0.24 mmol). This gave (2*S*,3*R*)-2-acetylaminododecan-3-ol (**303**) (0.018 g, 81%) as a white solid. $[\alpha]_D^{23}$ –13.3 (*c* 1.0, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylaminododecan-3-ol (**271**).

(2*S*,3*R*)-2-(2'-Chloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (304)



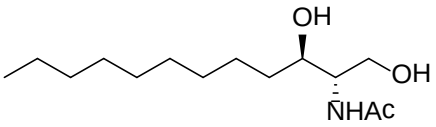
The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**) using (2*S*,3*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.10 g, 0.24 mmol) and tributyltin hydride (0.83 mL, 2.95 mmol). The reaction mixture was heated for 1 h. Flash column chromatography (diethyl ether/petroleum ether, 8:2) gave (2*S*,3*R*)-2-(2'-chloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**304**) (0.07 g, 84%) as a colourless oil. ν_{max}/cm^{-1} (NaCl) 3308 (NH), 2925 (CH), 1656 (CO), 1541, 1465, 1034, 919; $[\alpha]_D^{23}$ –21.8 (*c* 1.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.4 Hz, 12-H_3), 1.26–1.65 (16H, m, 4-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2, 9-H_2, 10-H_2, and 11-H_2), 2.91 (1H, dd, *J* 6.4, 2.8 Hz, OH), 3.43 (3H, s, OCH_3), 3.66–3.74 (2H, m, 1-H_2), 3.94–4.00 (2H, m, 2-H and 3-H), 4.10 (2H, d, *J* 3.2 Hz, $ClCH_2$), 4.62 (1H, d, *J* 6.4 Hz, OC*H*HO), 4.67 (1H, d, *J* 6.4 Hz, OCH*H*O), 7.66 (1H, br d, *J* 7.2 Hz, NH); δ_C (100 MHz, $CDCl_3$) 14.1 (CH_3), 22.7 (CH_2), 25.7 (CH_2), 29.3 (CH_2), 29.5 (2 × CH_2), 29.7 (CH_2), 31.9 (CH_2), 32.7 (CH_2), 42.7 (CH_2), 53.4 (CH), 56.1 (CH_3), 62.0 (CH_2), 82.2 (CH), 97.6 (CH_2), 166.4 (C); *m/z* (CI) 338.2095 (MH^+. $C_{16}H_{33}{}^{35}ClNO_4$ requires 338.2098), 320 (88%), 306 (47), 288 (24), 254 (4).

(2*S*,3*R*)-2-Acetylamino-3-(methoxymethoxy)dodecan-1-ol (305)



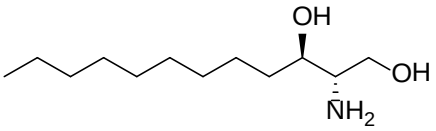
The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecane (**286**) using (2*S*,3*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.10 g, 0.24 mmol). This gave (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecan-1ol (**305**) as a colourless oil (0.07 g, 91%). $[\alpha]_D^{23}$ –32.8 (*c* 1.0, $CHCl_3$). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**287**).

(2*S*,3*R*)-2-Acetylaminododecan-1,3-diol (306)



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-acetylaminododecan-3-ol (**271**) using (2*S*,3*R*)-2-acetylamino-3-(methoxymethoxy)dodecan-1-ol (**305**) (0.03 g, 0.08 mmol). This gave (2*S*,3*R*)-2-acetylaminododecan-1,3-diol (**306**) (0.03 g, 100%) as a white solid. $[\alpha]_D^{23}$ –4.1 (*c* 1.0, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-acetylaminododecan-1,3-diol (**272**).

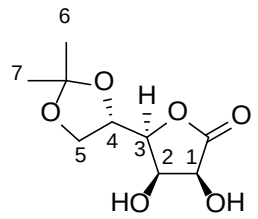
(2*S*,3*R*)-2-Aminododecan-1,3-diol (307)[167]



The reaction was carried out according to the procedure described for the synthesis of (2*R*,3*S*)-2-aminododecan-3-ol (**270**) using (2*S*,3*R*)-2-(2',2',2'-trichloromethylcarbonylamino)-3-(methoxymethoxy)dodecan-1-ol (**297**) (0.10 g, 0.24 mmol). This gave (2*S*,3*R*)-2-aminododecan-1,3-diol (**307**) (0.05 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ –6.3 (*c* 1.0, MeOH), lit.[167] $[\alpha]_D^{20}$ –6.0 (*c* 0.1, MeOH). All other spectroscopic data as previously reported for (2*R*,3*S*)-2-aminododecan-1,3-diol (**273**).

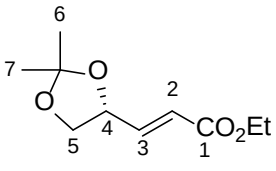
3.8 Attempted Synthesis of NO-Inhibitor

5,6-*O*-Isopropylidene-L-1,4-lactone (322)[194]



A solution of L-gulono-1,4-lactone **321** (3.00 g, 16.84 mmol) in dimethylformamide (20 mL) was cooled to 10 °C and *p*-toluenesulfonic acid (0.02 g, 0.14 mmol) was added dropwise followed by 2-methoxypropene (2.10 g, 21.90 mmol). The reaction mixture was warmed to room temperature and stirred overnight. The solution was treated with sodium carbonate decahydrate (3.0 g) and the suspension was vigorously stirred for 2 h. The solution was filtrered and the filtrate was concentrated *in vacuo*. The residue was washed with (hexane/ethanol, 9:1) gave 5,6-*O*-isopropylidene-L-1,4-lactone (**322**) (3.2 g, 88%) as white crystals. Mp 163–165 ^{o}C, lit.[194] 167–168 ^{o}C; $[\alpha]_D^{25}$ +37.6 (*c* 1.0, MeOH), lit.[194] $[\alpha]_D^{25}$ +38.3 (*c* 0.7, MeOH); Spectroscopic data in accordance with literature.[194] δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, 6-H_3), 1.47 (3H, s, 7-H_3), 3.24 (2H, s, 2 × OH), 3.96 (1H, dd, *J* 6.4, 2.4 Hz, 5-*H*H), 4.22 (1H, dd, *J* 6.4, 2.4 Hz, 5-H*H*), 4.38–4.44 (2H, m, 1-H and 2-H), 4.49 (1H, dd, *J* 6.4, 2.4 Hz, 3-H), 4.54 (1H, q, *J* 6.4 Hz, 4-H); δ_C (100 MHz, $CDCl_3$) 25.2 (CH_3), 26.5 (CH_3), 64.3 (CH_2), 69.1 (CH), 70.1 (CH), 75.0 (CH), 81.2 (CH), 109.0 (C), 176.0 (C); *m/z* (CI) 219 (MH^+. 16%), 203 (8), 137 (100), 121 (45), 69 (55).

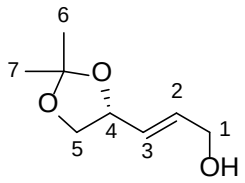
Ethyl (2*E*,4*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxypentan-2-enoate (320)[195]



To a stirred suspension of 5,6-*O*-isopropylidene-L-1,4-lactone (**322**) (3.00 g, 13.74 mmol) in water (30 mL), sodium periodate (5.9 g, 27.5 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 2 h at room temperature. Triethyl phosphonoacetate (4.62 mL, 20.60 mmol) and 6 M potassium carbonate solution (30 mL) were then added to the mixture, which was stirred overnight at room temperature. The reaction was extracted with

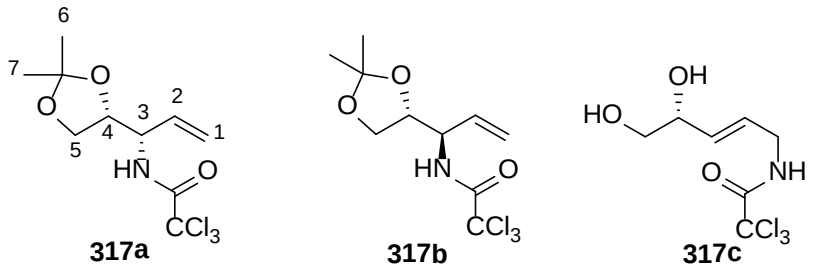
dichloromethane (4 × 40 mL), washed with brine (20 mL) and dried ($MgSO_4$). Concentration under vacuum gave a clear oil. Purification by flash column chromatography (elution with petroleum ether/diethyl ether, 10:1) gave ethyl (2*E*,4*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxypentan-2-enoate (**320**) (2.0 g, 71%) as a clear oil. Spectroscopic data in accordance with literature.[195] $[\alpha]_D^{25}$ –40.2 (*c* 2.2, $CHCl_3$), lit.[195] $[\alpha]_D^{25}$ –40.0 (*c* 1.096, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.30 (3H, t, *J* 7.2 Hz, OCH_2CH_3), 1.41 (3H, s, 6-H_3), 1.45 (3H, s, 7-H_3), 3.67 (1H, dd, *J* 7.9, 7.5 Hz, 5-*H*H), 4.16–4.23 (3H, m, OCH_2CH_3 and 5-H*H*), 4.60–4.69 (1H, m, 4-H), 6.10 (1H, dd, *J* 15.6, 1.2 Hz, 2-H), 6.90 (1H, dd, *J* 15.6, 5.6 Hz, 3-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3), 25.7 (CH_3) 26.4 (CH_3), 60.6 (CH_2), 68.8 (CH_2), 75.0 (CH), 110.2 (C), 122.4 (CH), 144.6 (CH), 166.0 (C); *m/z* (CI) 201 (MH^+. 100%), 183 (20), 143 (14), 81 (7).

(2*E*,4*R*)-4,5-(*O*-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (323)[196]



The reaction was carried out according to the procedure described for the synthesis of 6-hepten-1-ol (**187**) using ethyl (2*E*,4*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxypentan-2-enoate (**320**) (2.0 g, 10.0 mmol). Purification by flash column chromatography (eluting with petroleum ether/diethyl ether, 5:1), gave (2*E*,4*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (**323**) (1.20 g, 76%) as a colourless oil. Spectroscopic data in accordance with literature.[196] $[\alpha]_D^{25}$ –24.6 (*c* 1.6, $CHCl_3$), lit.[196] $[\alpha]_D$ –27.6 (*c* 0.29, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, 6-H_3), 1.42 (3H, s, 7-H_3), 2.50 (1H, br s, OH), 3.59 (1H, dd, *J* 8.0, 7.6 Hz, 5-*H*H), 4.10 (1H, dd, *J* 8.0, 7.6 Hz, 5-H*H*), 4.16 (2H, d, *J* 5.1 Hz, 1-H_2), 4.52 (1H, q, *J* 7.6 Hz, 4-H), 5.72 (1H, dd, *J* 15.6, 7.6 Hz, 3-H), 5.95 (1H, dt, *J* 15.6, 5.1 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 25.8 (CH_3), 26.6 (CH_3), 62.3 (CH_2), 69.3 (CH_2), 76.2 (CH), 109.3 (C), 128.4 (CH), 133.5 (CH); *m/z* (CI) 159 (MH^+. 100%), 141 (30), 83 (35).

(3*S*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene 317a, (3*R*,4*R*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene 317b and (2*E*,4*R*)-1-(2',2',2'-trichloromethylcarbonylamino)-4,5-dihydroxypent-2-ene (317c) using thermal rearrangement[55]



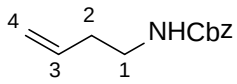
Allylic alcohol (**323**) (0.10 g, 0.63 mmol) was dissolved in DCM (20 mL) and cooled to 0 ^{o}C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.02 mL, 0.15 mmol) was then added to the solution followed by trichloroacetonitrile (0.10 mL, 0.95 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h under an argon atmosphere. The reaction mixture was then 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 **319**, which was used without further purification in the rearrangements that followed. The crude trichloroacetimidate **319** was dissolved in *p*-xylene (20 mL) and heated to 140 ^{o}C until reaction was complete as observed by ^{1}H NMR spectroscopy. The reaction mixture was concentrated *in vacuo* to give a brown oil. Purification by chromatography (elution with petroleum ether/diethyl ether, 9 : 1) gave the allylic trichloroacetamide products **317a** and **317b** as brown oils (0.05 g, 29% combined yield). Further elution (petroleum ether/diethyl ether, 1 : 9) gave **317c** also as a brown oil (0.04 g, 27% yield). **317a**: $[\alpha]_D^{25}$ +36.7 (*c* 1.0, $CHCl_3$), δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, 6-CH_3), 1.47 (3H, s, 7-CH_3), 3.70 (1H, dd, *J* 8.4, 6.4 Hz, 5-*H*H), 4.10 (1H, dd, *J* 8.4, 6.4 Hz, 5-H*H*), 4.34 (1H, td, *J* 6.4, 2.4 Hz, 4-H), 4.47–4.52 (1H, m, 3-H), 5.29–5.37 (2H, m, 1-H_2), 5.88 (1H, ddd, *J* 17.2, 10.4, 6.0 Hz, 2-H), 7.05 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.7 (CH_3), 26.4 (CH_3), 53.9 (CH), 66.3 (CH_2), 76.6 (CH), 92.6 (C), 110.0 (C), 117.7 (CH_2), 133.9 (CH), 161.9 (C); *m/z* (CI) 302 (MH^+. 53%), 268 (15), 244 (100), 210 (44), 176 (12), 101 (12). **317b**: δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, CH_3), 1.46 (3H, s, CH_3), 3.84 (1H, dd, *J* 9.1, 5.1 Hz, 5-*H*H), 4.10 (1H, dd, *J* 9.1, 5.1 Hz, 5-H*H*), 4.29–4.35 (1H, m, 4-H), 4.47–4.52 (1H, m, 3-H), 5.33–5.38 (2H, m, 1-H_2), 5.85 (1H, ddd, *J* 15.8, 10.3, 6.2 Hz, 2-H), 7.01 (1H, br s, NH); δ_C (100 MHz, $CDCl_3$) 24.7 (CH_3), 26.1 (CH_3), 55.8 (CH), 65.5

(CH_2), 76.1 (CH), 92.5 (C), 110.2 (C), 119.3 (CH_2), 131.6 (CH), 161.5 (C). **317c**: υ_{max}/cm^{-1} (neat) 3512 (OH), 3420 (NH), 2986 (CH), 1723 (CO), 1512 (C=C), 1313, 1070; $[\alpha]_D^{25}$ +1.7 (*c* 1.0, $CHCl_3$), δ_H (400 MHz, $CDCl_3$) 1.90 (2H, br s, 2 × OH), 4.21 (2H, dd, *J* 5.0, 1.2 Hz, 1-H_2), 4.37 (1H, dd, *J* 8.6, 8.3 Hz, 5-*H*H), 4.77 (1H, dd, *J* 9.8, 8.3 Hz, 5-H*H*), 4.90–4.97 (1H, m, 4-H), 5.78 (1H, ddt, *J* 15.5, 7.4, 1.2 Hz, 3-H), 5.96 (1H, dt, *J* 15.5, 5.0 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 62.4 (CH_2), 67.9 (CH_2), 76.2 (CH), 88.2 (C), 128.4 (CH), 133.3 (CH), 163.5 (C); *m/z* (CI) 261.9725 (MH^+, $C_7H_{11}NO_3{}^{35}Cl_3$ requires 261.9729), 242 (100%), 226 (41), 210 (38), 193 (15), 118 (94). Spectroscopic data in accordance with literature.[55]

(3*S*,4*S*)-3-(2',2',2'-Trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (317a) using (*R*)-COP-Cl as catalyst[55]

The reaction was carried out according to the procedure described for the synthesis of 3-(2',2',2'-trichloromethylcarbonylamino)nona-1,8-diene (**189**) using (2*E*,4*R*)-4,5-(*O*-isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (**323**) (0.50 g, 3.16 mmol) and (*R*)-COP-Cl (0.31 g, 0.30 mmol). Purification by flash column chromatography (eluting with petroleum ether/diethyl ether, 20:1), gave (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (**317a**) (0.70 g, 73%) as a brown oil. Spectroscopic data as reported above.

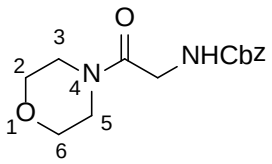
1-(Benzyloxycarbonylamino)-3-butene (318)[197]



To a suspension of 3-butenylamine hydrochloride salt **324** (5.50 g, 51.12 mmol) in dichloromethane (250 mL) was added a solution of sodium carbonate (16.80 g) in water (50 mL). The biphasic mixture was cooled to 0 ^oC and benzyl chloroformate (11.53 g, 81.80 mmol) was added dropwise. The reaction mixture was stirred for 0.25 h at 0 ^oC, then warmed at room temperature for 14 h. The solution was diluted with dichloromethane (100 mL) and water (50 mL) was added. The aqueous combined organic layers were washed with water, dried, filtered and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave 1-(benzyloxycarbonylamino)-3-butene (**318**) (10.5 g, 100% yield) as a colourless oil. Spectroscopic data consistent with literature.[197] δ_H

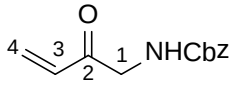
(400 MHz, $CDCl_3$) 2.26 (2H, q, *J* 6.8 Hz, 2-H_2), 3.28 (2H, q, *J* 6.8 Hz, 1-H_2), 4.76 (1H, br s, NH), 5.06–5.12 (4H, m, 4-H_2 and PhC*H*$_2$), 5.69–5.80 (1H, m, 3-H), 7.29–7.38 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 34.1 (CH_2), 40.1 (CH_2), 66.6 (CH_2), 117.4 (CH_2), 127.9 (2 × CH) 128.5 (2 × CH), 131.4 (CH), 135.1 (C), 136.6 (CH), 156.3 (C); *m/z* (CI) 206 (MH^+. 100%), 181 (30), 145 (10), 91 (90).

4-(*N*-Benzyloxycarbonylglycyl)morpholine (327)[198]



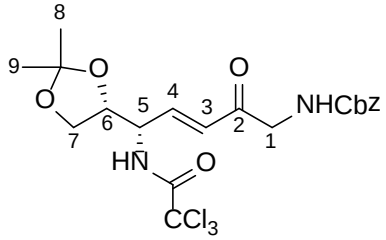
To a solution of *N*-(benzyloxycarbonylamino)glycine (**326**) (3.00 g, 14.34 mmol) in dichloromethane (100 mL), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.12 mL, 21.51 mmol) was added at 0 °C. Morpholine (1.50 mL, 17.21 mmol) was added to the reaction mixture followed by 4-dimethylaminopyridine (2.36 g, 20.00 mmol). The reaction mixture was stirred at room temperature overnight. The solution was quenched with ice cold water (50 mL). The mixture was separated and the aqueous layer was then extracted with dichloromethane (2 × 100 mL). The combined organic layers were washed with a saturated solution of ammonium chloride (50 mL) and brine (50 mL), then dried (Na_2SO_4) and concentrated *in vacuo*. Flash column chromatography (petroleum ether/ethyl acetate, 2:8) gave 4-(*N*-benzyloxycarbonylglycyl)morpholine (**327**) (3.50 g, 87%) as a white solid. Mp 142–144 ^oC (lit.[198] mp 144–145 °C); Spectroscopic data consistent with literature.[198] δ_H (400 MHz, $CDCl_3$) 3.36 (2H, t, *J* 4.8 Hz, 2-*H*H and 6-*H*H), 3.59–3.66 (6H, m, 2-H*H*, 6-H*H*, 3-H_2 and 5H_2), 4.00 (2H, d, *J* 4.8 Hz, C*H*$_2$NHCbz), 5.11 (2H, s, PhC*H*$_2$), 5.89 (1H, br s, NH), 7.29–7.35 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 34.8 (CH_2), 42.5 (CH_2), 44.7 (2 × CH_2), 66.6 (2 × CH_2), 126.2 (CH), 128.1 (2 × CH), 128.5 (2 × CH), 136.4 (C), 156.2 (C), 166.7 (C); *m/z* (CI) 279 (MH^+. 60%), 235 (4), 171 (100), 147 (13), 91 (33), 71 (20).

***N*-(Benzyloxycarbonylamino)butan-3-ene-2-one (328)**[199]



To a solution of 4-(*N*-benzyloxycarbonylglycyl)morpholine (**327**) (0.20 g, 0.71 mmol) in tetrahydrofuran (10 mL), was added vinylmagnesium bromide (2.15 mL, 2.15 mmol) dropwise. The reaction mixture was stirred at 0 °C for 1.5 h. The solution was quenched with 1 M hydrochloric acid, extracted with ethyl acetate (3 × 20 mL) and concentrated *in vacuo*. Purification by flash column chromatography (petroleum ether/ethyl acetate, 5:5) gave *N*-(benzyloxycarbonylamino)butan-3-ene-2-one (**328**) (0.069 g, 46%) as a clear oil. Spectroscopic data in accordance with literature.[199] δ_H (400 MHz, $CDCl_3$) 4.31 (2H, d, *J* 4.8 Hz, 1-H_2), 5.12 (2H, s, PhCH_2), 5.62 (1H, br s, NH), 5.95 (1H, dd, *J* 7.6, 1.6 Hz, 3-H), 6.35–6.38 (2H, m, 4-H_2), 7.29–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 48.6 (CH_2), 67.0 (CH_2), 128.1 (2 × CH), 128.2 (CH), 128.5 (2 × CH), 129.9 (C), 133.5 (CH_2), 136.3 (CH), 156.1 (C), 194.3 (C); *m/z* (CI) 220 (MH^+. 100%), 176 (53), 147 (10), 91 (40).

(5*S*,6*S*)-1-(Benzyloxycarbonylamino)-5-(2',2',2'-trichloromethylcarbonylamino)-6,7-(*O*-isopropylidene)-6,7-dihydroxyhepta-3-ene-2-one (329)



The reaction was carried out according to the procedure described for the synthesis of (4*R*,5*S*)-3-(trichloromethylcarbonylamino)-5-(methoxymethoxy)-2-decen-1-al (**257**) using (3*S*,4*S*)-3-(2',2',2'-trichloromethylcarbonylamino)-4,5-(*O*-isopropylidene)-4,5-dihydroxypenta-1-ene (**317a**) (0.10 g, 0.33 mmol), *N*-(benzyloxycarbonylamino)butan-3-ene-2-one (**328**) (0.30 g, 1.32 mmol) and Hoveyda/Grubbs 2nd generation catalyst **114** (0.05 g, 0.03 mmol). Purification by flash column chromatography (petroleum ether/ethyl acetate, 5:5) gave (5*S*,6*S*)-1-(benzyloxycarbonylamino)-5-(2',2',2'-trichloromethylcarbonylamino)-6,7-(*O* isopropylidene)-6,7-dihydroxyhepta-3-ene-2-one (**329**) (0.12 g, 68%) as a brown oil. ν_{max}/cm^{-1} (NaCl) 3410 (NH), 2987 (CH), 1690 (CO),

1509, 1375, 1265, 1063, 821; $[\alpha]_D^{23}$ +21.5 (*c* 2.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, 8-H_3), 1.48 (3H, s, 9-H_3), 3.75 (1H, dd, *J* 6.6, 2.4 Hz, 7-*H*H), 4.15 (1H, dd, *J* 6.6, 2.4 Hz, 7-H*H*), 4.31 (2H, d, *J* 4.4 Hz, 1-H_2), 4.40 (1H, td, *J* 6.6, 1.6 Hz, 6-H), 4.64–4.68 (1H, m, 5-H), 5.12 (2H, s, PhCH_2), 5.56 (1H, br s, Cl_3CCON*H*), 6.33 (1H, d, *J* 16.0 Hz, 3-H), 6.90 (1H, dd, *J* 16.0, 5.2 Hz, 4-H), 7.15 (1H, d, *J* 8.4 Hz, CbzN*H*), 7.31–7.39 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 24.4 (CH_3), 26.3 (CH_3), 49.5 (CH_2), 53.1 (CH), 66.2 (CH_2), 67.1 (CH_2), 75.6 (CH), 92.2 (C), 110.4 (C), 127.7 (C), 128.1 (2 × CH), 128.6 (2 × CH), 132.2 (CH), 136.1 (CH), 142.5 (CH), 156.1 (C), 162.2 (C), 193.2 (C); *m/z* (CI) 493.0717 (MH^+. $C_{20}H_{24}{}^{35}Cl_3N_2O_6$ requires 493.0700), 493 (8%), 459 (10), 218 (18), 152 (45), 107 (50), 91 (100).

4.0 References

1. C. J. Moody, *Adv. Heterocycl. Chem*., 1987, **42**, 203.

2. L. Claisen, *Chem. Ber*., 1912, **45**, 3157.

3. B. Ganem, *Angew. Chem. Int. Ed.*, 1996, **35**, 936.

4. H. Ito and T. Taguchi, *Chem. Soc. Rev*., 1999, **28**, 43.

5. K. N. Fanning, A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem.*, 2005, **3**, 3749.

6. S. F. Kirsch, L. E. Overman and M. P. Watson, *J. Org. Chem.*, 2004, **69**, 8101.

7. O. Mumm and F. Möller, *Chem. Ber*., 1937, **70**, 2214.

8. L. E. Overman, *J. Am. Chem. Soc.*, 1974, **96**, 597.

9. L. E. Overman, *J. Am. Chem. Soc.*, 1976, **98**, 2901.

10. T. Ikariya, Y. Ishikawa, K. Hirai and S. Yoshikawa, *Chem. Lett.*, 1982, 1815.

11. R. P. Lutz, *Chem. Rev.*, 1984, **84**, 205.

12. I. Jaunzeme and A. Jirgensons, *Synlett*, 2005, 2984.

13. K. C. Majumdar, S. Alam and B. Chattopadhyay, *Tetrahedron*, 2008, **64**, 597.

14. A. M. M. Castro, *Chem. Rev.*, 2004, **104**, 2939.

15. K. N. Fanning, A. G. Jamieson and A. Sutherland, *Curr. Org. Chem.*, 2006, **10**, 1007.

16. L. E. Overman, *Angew. Chem. Int. Ed.*, 1984, **23**, 579.

17. L. E. Overman, C. B. Campbell and F. M. Knoll, *J. Am. Chem. Soc.*, 1978, **100**, 4822.

18. P. Metz, C. Mues and A. Schoop, *Tetrahedron*, 1992, **48**, 1071.

19. J. Borgulya, R. Madeja, P. Fahrni, H. Hansen, R. Barner and H. Schmid, *Helv. Chim. Acta*, 1973, **56**, 14.

20. K. C. Majumdar, B. Chattopadhyay and S. Samanta, *Tetrahedron Lett.*, 2009, **50**, 3178.

21. U. Nubbemeyer, *Top. Curr. Chem*., 2005, **244**, 149.

22. A. S. P. Cardoso, M. M. P. Marques, N. Srinivasan, S. Prabhakar, A. M. Lobo and H. S. Rzepa, *Org. Biomol. Chem.*, 2006, **4**, 3966.

23. J. M. Patterson, A. Wu, C. S. Kook and W. T. Smith, *J. Org. Chem*., 1974, **39**, 486.

24. A. K. Buzas, F. M. Istrate and F. Gagosz, *Org. Lett*., 2007, **9**, 985.

25. N. Marion, R. Gealageas and S. P. Nolan, *Org. Lett*., 2007, **9**, 2653.

26. C. Gourlaouen, N. Marion, S. P. Nolan and F. Maseras, *Org. Lett*., 2009, **11**, 81.

27. M. D. Swift and A. Sutherland, *Tetrahedron Lett.,* 2007, **48**, 3771.

28. I. Jaunzeme and A. Jigensons, *Tetrahedron,* 2008, **64**, 5794.

29. A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem.*, 2006, **4**, 2932.

30. F. M. Istrate and F. Gagosz, *Org. Lett*., 2007, **9**, 3181.

31. D. Xing and D. Yang, *Beilstein J. Org. Chem.,* 2011, **7**, 781.

32. W. Kitcbing, Z. Rappoport, S. Winstein, W. G. Young, *J. Am. Chem. Soc*., 1966, **88**, 2054.

33. P. M. Henry, *Acc. Chem. Res.*, 1973, **6**, 16.

34. P. M. Henry, *Adv. Organomet. Chem.*,1975, **13**, 363.

35. P. M. Henry, *Chem. Commun*., 1971, 328.

36. P. M. Henry, *J. Am. Chem. Soc*., 1972, **94**, 5200.

37. L. E. Overman and F. M. Knoll, *Tetrahedron Lett.,* 1979, **4**, 321.

38. T. G. Schenck and B. Bosnich, *J. Am. Chem. Soc.*, 1985, **107**, 2058.

39. N. Nakajima, M. Saito, M. Kudo and M. Ubukata, *Tetrahedron*, 2002, **58**, 3579.

40. L. E. Overman and G. G. Zipp, *J. Org. Chem.*, 1997, **62**, 2288.

41. T. K. Hollis and L. E. Overman, *Organomet. Chem.*, 1999, **576**, 290.

42. Y. Donde and L. E. Overman, *J. Am. Chem. Soc*., **1999,** 121, 2933.

43. M. Calter, T. K. Hollis, L. E. Overman, J. Ziller, and G. G. Zipp, *J. Org. Chem.*, 1997, **62**, 1449.

44. Y. A. Wanniarachchi, Y. Kogiso and L. M. Slaughter, *Organometallics*, 2008, **27**, 21.

45. A. M. Stevens and C. J. Richards, *Organometallics*, 1999, **18**, 1346.

46. G. Jiang, R. Halder, Y. Fang, and B. List, *Angew. Chem. Int. Ed*., 2011, **50**, 1.

47. J. Kang, T. H. Kim, K. H. Yew and W. K. Lee, *Tetrahedron*: *Asymmetry*, 2003, **14**, 415.

48. L. E. Overman, C. E. Owen and M. M. Pavan, *Org. Lett.,* 2003, **5**, 1809.

49. C. E. Anderson and L. E. Overman, *J. Am. Chem. Soc.*, 2003, **125**, 12412.

50. C. E. Anderson, L. E. Overman and M. P. Watson, *Org. Synth.*, 2005, **82**, 134.

51. J. Gonda, A. C. Helland, B. Ernst and D. Bellûs, *Synthesis*, 1993, 729.

52. A. G. Jamieson and A. Sutherland, *Org. Biomol. Chem.*, 2005, **3**, 735.

53. A. G. Jamieson and A. Sutherland, *Tetrahedron*, 2007, **63**, 2123.

54. M. Mehmandoust, Y. Petit and M. Larcheveque, *Tetrahedron Lett*., 1992, **33**, 4313.

55. M. D. Swift and A. Sutherland, *Tetrahedron*, 2008, **64**, 9521.

56. P. H. J. Carlsen, T. Katsuki, V. S. Martin and K. B. Sharpless, *J. Org. Chem*., 1981, **46**, 3936.

57. M. J. Kurth and C. J. Soares, *Tetrahedron Lett*., 1987, **28**, 1031.

58. D. M. Vyas, Y. Chiang and T. W. Doyle, *Tetrahedron Lett*., 1984, **25**, 487.

59. A. G. Jamieson and A. Sutherland, *Org. Lett*., 2007, **9**, 1609.

60. N. Calderon, H. Y. Chen and K. W. Scott, *Tetrahedron Lett*., 1967, **34**, 3327.

61. H. S. Eleuterio, *J. Mol. Catal.*, 1991, **65**, 55.

62. J. C. Sehrer and S. J. Gundiah, *J. Sci. Ind. Res*., 1983, **55**, 250.

63. J. Kress, J. A. Osborn, R. M. E. Greene, K. J. Ivin and J. J. Rooney, *J. Chem. Soc. Commun*., 1985, 874.

64. J. Kress, J. A. Osborn, R. M. E. Greene, K. J. Ivin and J. J. Rooney, *J. Am. Chem. Soc*., 1987, **109**, 899.

65. J. L. Herisson and Y. Chauvin, *Makromol. Chem*., 1970, **141**, 161.

66. www.nobelprize.org

67. J. Tsuji and S. Hashiguchi, *Tetrahedron Lett*., 1980, **21**, 2955.

68. D. A. Clark, A. A. Kulkami, K. Kalbarczyk, B. Schertzer and S. T. Diver, *J. Am. Chem. Soc*., 2006, **128**, 15632.

69. S. Fustero, D. Jiménez, M. Sánchez-Roselló and C. Del Pozo, *J. Am. Chem. Soc*., 2007, **129**, 6700.

70. E. A. Sutton, A. B. Seigal, F. D. Finnegan and L. M. Snapper, *J. Am. Chem. Soc*., 2002, **124**, 13390.

71. J. Louie, C. W. Bielawski and R. H. Grubbs, *J. Am. Chem. Soc*., 2001, **123**, 11312.

72. H. -Y. Lee, H. Y. Kim, H. Tae, B. G. Kim and J. Lee, *Org. Lett*., 2003, **5**, 3439.

73. A. B. Seigal, C. Fajardo and L. M. Snapper, *J. Am. Chem. Soc*., 2005, **127**, 16329.

74. S. Beligny, S. Eibauer, S. Maechling and S. Blechert, *Angew. Chem. Int. Ed*., 2006, **45**, 1900.

75. S. J. Connon and S. Blechert, *Angew. Chem. Int. Ed.*, 2003, **42**, 1900.

76. M. Arisawa, *Chem. Pharm. Bull.*, 2007, **55**, 1099.

77. A. H. Hoveyda and A. R. Zhugralin, *Nature,* 2007, **450**, 243.

78. M. Mori, Y. Kuzuba, T. Kitamura and Y. Sato, *Org. Lett*., 2002, **4**, 3855.

79. T. J. Katz and R. Rothchild, *J. Am. Chem. Soc*., 1976, **98**, 2519.

80. J. McGinnis, T. J. Katz and S. Hurwitz, *J. Am. Chem. Soc*., 1976, **98**, 605.

81. T. J. Katz, J. McGinnis and C. Altus, *J. Am. Chem. Soc.*, 1976, **98**, 606.

82. T. J. Katz, *Angew. Chem. Int. Ed*., 2005, **44**, 3010.

83. R. R. Schrock, *Acc. Chem. Res.*, 1979, **12**, 98.

84. C. D. Wood, S. J. Mclain and R. R. Schrock, *J. Am. Chem. Soc.,* 1979, **101**, 3210.

85. R. R. Schrock, *J. Am. Chem. Soc.*, 1974, **96**, 6796.

86. S**.** T. SonBinh, L. K. Johnson and R. H. Grubbs, *J. Am. Chem. Soc.,* 1992, **114**, 3974.

87. R. H. Grubbs, S. J. Miller and G. C. Fu, *Acc. Chem. Res*., 1995, **28**, 446.

88. T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res*., 2001, **34**, 18.

89. J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, *Angew. Chem. Int. Ed*., 2002, **41**, 4035.

90. M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953.

91. A. K. Chatterjee and R. H. Grubbs, *Org. Lett*., 1999, **1**, 1751.

92. J. P. Morgan, C. Morrill and R. H. Grubbs, *Org. Lett*., 2002, **4**, 67.

93. A. K. Chatterjee, J. P. Morgan, M. Scholl and R. H. Grubbs, *J. Am. Chem. Soc*., 2000, **122**, 3783.

94. T. Choi, C. Lee, A. K. Chatterjee and R. H. Grubbs, *J. Am. Chem. Soc*., 2001, **123**, 10.

95. K. Grela and M. Bieniek, *Tetrahedron Lett*., 2001, **42**, 6425.

96. M. Lera and C. J. Hayes, *Org. Lett*., 2001, **3**, 2765.

97. S. B. Garber, J. S. Kingbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168.

98. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc*., 1992, **114**, 5426.

99. G. C. Fu and R. H. Grubbs, *J. Am. Chem. Soc.,* 1993, **115**, 3800.

100. G. C. Fu and R. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856.

101. Y. S. Shon and T. R. Lee, *Tetrahedron Lett*., 1997, **38**, 1283.

102. O. Fujimura and R. H. Grubbs, *J. Am. Chem. Soc.*,1997, **118**, 2499.

103. M. D. Swift and A. Sutherland, *Org. Lett*., 2007, **9**, 5239.

104. Z. Xu, C. W. Johannes, A. F. Houri, D. S. La, D. A. Cogan, G. E. Hofilenaand and A. H. Hoveyda, *J. Am Chem. Soc*., 1997, **119**, 10302.

105. T. J. Donohoe, A. Ironmonger and N. M. Kershaw, *Angew. Chem. Int. Ed.*, 2008, **47**, 7314.

106. R. H. Grubbs and S. Chang, *Tetrahedron*,1998, **54**, 4413.

107. W. E. Crowe and D. R. Goldberg, *J. Am. Chem. Soc*., 1995, **117**, 5162.

108. R. H. Grubbs, D. O'Leary, H. E. Blackwell and R. A. Washenfelder, *Tetrahedron Lett*., 1998, **39**, 7427.

109. A. Fürstner and K. Langemann, *Synthesis*, 1997, 792.

110. A. N. Rai and A. Basu, *Org. Lett.*, 2004, **6**, 2861.

111. D. Vaknin and S. M. Kelley, *Biophysical Journal*, 2000, **79**, 2616.

112. L. J. Drummond and A. Sutherland, *Tetrahedron*, 2010, **66**, 5349.

113. S. J. Meek, R. V. O'Brien, J. Llaveria, R. R. Schrock and A. H. Hoveyda, *Nature*, 2011, **471**, 461.

114. A. B. Ray, M. Sahai and P. D. Sethi, *Chem. Ind. (London*), 1976, 454.

115. M. Sahai and A. B. Ray, *J. Org. Chem*., 1980, **45**, 3265.

116. A. R. Pinder, *J. Org. Chem*., 1982, **47**, 3607.

117. A. T. McPhail and A. R. Pinder, *Tetrahedron*, 1984, **40**, 1661.

118. F. D. Boyer, P. H. Ducrot, V. Henryon, J. Soulieand and J. Y. Lallemand, *Synlett*, 1992, 357.

119. K. Hiroya and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1995, 2205.

120. A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2009, **7**, 2678.

121. L. I. Zakharkin and I. M. Khorlina, *Tetrahedron Lett.*, 1962, **3**, 619.

122. R. E. Ireland and D. W. Norbeck, *J. Org. Chem.*, 1985, **50**, 2198.

123. M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masumune, W. R. Roush and T. Sakai, *Tetrahedron Lett.*, 1984, **25**, 2183.

124. D. M. Hodgson, L. A. Robinson and M. L. Jones, *Tetrahedron Lett.*, 1999, **40**, 8637.

125. R. Bischoff, N. McDonald and A. Sutherland, *Tetrahedron Lett.*, 2005, **46**, 7147.

126. N. Chidambaram and S. Chandrasekaran, *J. Org. Chem.*, 1987, **52**, 5048.

127. T. Nagai, K. Ogawa, M. Morita, M. Koyama, A. Ando, T. Miki and I. Kumadaki, *Chem. Pharm. Bull.*, 1989, **37**, 1751.

128. J. Q. Yu and E. J. Corey, *Org. Lett.*, 2002, **4**, 2727.

129. T. K. M. Shing,Y. -Y. Yeung and P. L. Su, *Org. Lett.*, 2006, **8**, 3149.

130. G. Pandey, K. N. Tiwari and V. G. Puranik, *Org. Lett.*, 2008, **10**, 3611.

131. E. C. McLaughlin, H. Choi, K. Wang, G. Chiou and M. P. Doyle, *J. Org. Chem.*, 2009, **74**, 730.

132. R. Martin, A. W. Schmidt, G. Theumer, T. Krause, E. V. Entchev, T. V. Kurzchalia and H. J. Knölker, *Org. Biomol. Chem.*, 2009, **7**, 909.

133. M. A. Warpehoski, B. Chabaud and K. B. Sharpless, *J. Org. Chem.*, 1982, **47**, 2897.

134. L. Agrofoglio, E. Suhas, A. Farese, R. Condom, S. R. Challand, R. A. Earl and R. Guedj, *Tetrahedron*, 1994, **50**, 10611.

135. R. Vince and M. Hua, *J. Med. Chem.*, 1990, **33**, 17.

136. T. Berranger and Y. Langlois, *Tetrahedron Lett.*, 1995, **36**, 5523.

137. M. E. Jung and H. Rhee, *J. Org. Chem.*, 1994, **59**, 4719.

138. S. M. Daluge, *U.S. Patent*, 5,034,394, **1991**.

139. Y. Kitade, A. Kozaki, T. Miwa and M. Nakanishi, *Tetrahedron*, 2002, **58**, 1271.

140. M. T. Crimmins, *Tetrahedron*, 1998, **54**, 9229.

141. M. Cowart, M. J. Bennett, and J. F. Kerwin, *J. Org. Chem.*, 1999**, 64**, 2240.

142. R. Rathore, N. Saxena and S. Chadrasekaran, *Synth. Commun*., 1986, **16**, 1493.

143. Y. Zhao and Y. Y. Yeung, *Org. Lett.*, 2010, **12**, 2128.

144. B. M. Trost and D. L. Vranken, *J. Am. Chem. Soc*., 1993, **115**, 444.

145. F. A. Davis and Y. Wu, *Org. Lett*., 2004, **6**, 1269.

146. S. D. Patil and S. W. Schneller, *J. Med. Chem*., 1992, **35**, 3372.

147. X. Yin and S. W. Schneller, *Tetrahedron Lett*., 2005, **46**, 7535.

148. S. J. Oxenford, P. O'Brien and M. R. Shipton, *Tetrahedron Lett*., 2004, **45**, 9053.

149. K. M. Meragelman, T. C. McKee and J. B. McMahon, *J. Nat. Prod*., 2004, **67**,1165.

150. M. Yu and B. B. Snider, *Org Lett*., 2009, **11**, 1031.

151. A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2010, **8**, 4394.

152. D. J. O'Leary, H. E. Blackwell, R. A. Washenfelder, K. Miura and R. H. Grubbs, *Tetrahedron Lett.*, 1999, **40**, 1091.

153. H. E. Blackwell, D. J. O'Leary, A. K. Chatterjee, R. A. Washenfelder, D. A. Bussmann and R. H. Grubbs, *J. Am. Chem. Soc*., 2000, **122**, 58.

154. M. S. Bernatowicz, Y. Wu and G. R. Matsueda, *J. Org. Chem.*, 1992, **57**, 2497.

155. M. S. Bernatowicz, Y. Wu and G. R. Matsueda, *Tetrahedron Lett.*, 1993, **34**, 3389.

156. D. J. Hamilton and A. Sutherland, *Tetrahedron Lett.*, 2004, **45**, 5739.

157. C. M. Reid, C. Ebikeme, M. P. Barrett, E. M. Patzewitz, S. Müller, D. J. Robins and A. Sutherland, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5399.

158. A. Aiello, E. Fattorusso, A. Giordano, M. Menna, C. Navarrete and E. Muñoz, *Bioorg. Med. Chem.*, 2007, **15**, 2920.

159. A. Aiello, E. Fattorusso, A. Giordano, M. Menna, C. Navarrete and E. Muñoz, *Tetrahedron*, 2009, **65**, 4384.

160. M. A. Kossuga, J. B. MacMillan, E. W. Rogers, T. F. Molinski, G. G. F. Nascimento, R. M. Rocha and R. G. S. Berlinck, *J. Nat. Prod.*, 2004, **67**, 1879.

161. P. M. Koskinen and A. M. P. Koskinen, *Synthesis*, 1998, 1075.

162. A. R. Howell, R. C. So and S. K. Richardson, *Tetrahedron*, 2004, **60**, 11327.

163. R. Cuadros, E. M. de Garcini, F. Wandosell, G. Faircloth, J. M. Fernàndez-Sousa and

J. Avila, *Cancer Lett*., 2000, **152**, 23.

164. G. Blatter, J.-M. Beau and J.-C. Jacquinet, *Carbohydr. Res*., 1994, **260**, 189.

165. A. M. Zaed and A. Sutherland, *Org. Biomol. Chem.*, 2011, **9**, 8030.

166. R. Ait-Youcef, X. Moreau and C. Greck, *J. Org. Chem.*, 2010, **75**, 5312.

167. C. Séguin, F. Ferreira, C. Botuha, F. Chemla and A. Pérez-Luna, *J. Org. Chem.*, 2009, **74**, 6986.

168. S. Pfeiffer, B. Mayer and B. Hemmens, *Angew. Chem. Int. Ed*., 1999, **38**, 1714.

169. W. Alderton, C. Cooper and R. Knowles, *Biochem. J*., 2001, **357**, 593.

170. M. Perreault and A. Marette, *Nat. Med*. 2001, **7**, 1138.

171. P. Hilliquin, D. Borderie, A. Hernvann, C. Menkes, and O. Ekindjian, *Arthritis Rheum*., 1997, **40**, 1512.

172. G. Brown and A. Bal-Price, *Mol. Neurobiol*., 2003, **27**, 325.

173. R. Floyd, *Proc. Soc. Exp. Biol. Med*., 1999, **222**, 236.

174. F. Piehl and O. Lidman, *Immunol. Rev*., 2001, **184**, 212.

175. S. Ekmekcioglu, J. Ellerhorst, V. Prieto, M. Johnson, L. Broemeling and E. Grimm, *Int. J. Cancer*, 2006, **119**, 861.

176. S. Ekmekcioglu, C. Tang and E. Grimm, *Curr. Cancer Drug Targets*, 2005, **5**, 103.

177. J. Rimoldi and S. Chimote, *Curr. Opin. Drug Discovery Dev*., 1998, **1**, 183.

178. E. Hallinan, S. Tsymbalov, P. Finnegan, W. Moore, G. Jerome, M. Currie and B. Pitzele, *J. Med. Chem*., 1998, **41**, 775.

179. C. Hubshwerlen, *Synthesis*, 1986, 962.

180. R. Martin, P. Romea, C. Tey, F. Urpi and J. Vilarassa, *Synlett*, 1997, 1414.

181. A. K. Chatterjee, T. Choi, D. Sanders and R. Gribbs, *J. Am. Chem. Soc*., 2003, **125**, 11360.

182. M. Sumitani, K. Kanemitsuya, H. Yasuda and H. Tani, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 1511.

183. A. K. Ghosh, L. M. Swanson, H. Cho, S. Leshchenko, K. A. Hussain, S. Kay, D. E.

Walters,Y. Koh and H. Mitsuya, *J. Med. Chem.*, 2005, **48**, 3576.

184. T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe and G. Stemp, *J. Org. Chem*., 2002, **67**, 7946.

185. R. A. T. M. Benthem, J. J. Michels, H. Hiemstra and W. N. Speckamp, *Synlett*, 1994, 368.

186. A. Hall, P. D. Bailey, D. C. Rees, G. M. Rosair and R. H. Wightman, *J. Chem. Soc., Perkin Trans*. 1, 2000, 329.

187. M. Majewski, R. Lazny and A. Ulaczyk, *Can. J. Chem*., 1997, **75**, 754.

188. J. S. Ryu, T. J. Marks and F. E. McDonald, *J. Org. Chem.*, 2004, **69**, 1038.

189. Z. Zhang and R. Scheffold, *Helv. Chim. Acta.*, 1993, **76**, 2602.

190. M.-T. Lai, E. Oh, Y. Shih and H.-W. Liu, *J. Org. Chem*., 1992, **57**, 2471.

191. L. Poppe, K. Recseg and L. Novák, *Synth. Commun*., 1995, **25**, 3993.

192. H. Riering and H. J. Schäfer, *Chem. Ber*., 1994, **127**, 859.

193. C. L. Cywin, F. X. Webster and J. Kallmerten, *J. Org. Chem*. 1991, **56**, 2953.

194. U. Massing and H. Eibl, *Chem. Phys. Lipds*, 1994, **69**, 105.

195. P. J. L. M. Quaedflieg, B. R. R. Kesteleyn, P. B. T. P. Wigerinck, N. M. F. Goyvaerts, R. J. Vijn, C. S. M. Liebregts, J. H. M. H. Kooistra, and C. Cusan, *Org. Lett*., 2005, **7**, 5917.

196. T. Suzuki, E. Sato, S. E. Kamada, H. Tada, and K. Unno, *J. Chem. Soc. Perkin Trans*., I, 1986, 387.

197. C. Taillier, T. Hameury, V. Bellosta and J. Cossy, *Tetrahedron*, 2007, **63**, 4472.

198. J. R. Vaughan, *J. Am. Chem. Soc*., 1951, **73**, 1389.

199. A. J. Vernall, P. Cassidy, and P. F. Alewood, *Angew. Chem. Int. Ed*., 2009, **48**, 5675.