SYNTHESIS OF POLYHYDROXYLATED ALKALOIDS VIA ALLENE CYCLISATION

by

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Pearly Ng

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ABSTRACT

Polyhydroxylated alkaloids, a class of natural products prevalent in plants, have attracted the interest of many due to their rich biological activities and complex chemical structures. These alkaloids are generally made up of small ring systems with dense chiral information, thus making their synthesis a challenging endeavour for chemists. In this thesis, we strive to investigate the synthesis of polyhydroxylated alkaloids via gold-catalysed nucleophilic cyclisation of allenes, a transformation which has generated much interest in recent times due to its ability to access varied ring systems efficiently.

In Chapter 1, a short review of polyhydroxylated alkaloids is presented, highlighting their biological significance as carbohydrate mimetics. The synthesis of polyhydroxylated alkaloids is also briefly addressed and examples of the synthetic strategies utilised are illustrated using the various syntheses of fagomine.

In Chapter 2, we report the stereoselective synthesis of 2-*epi*-fagomine utilising the Sharpless asymmetric dihydroxylation and the gold-catalysed nucleophilic cyclisation of allene as key transformations to install the requisite stereogenic centres. Our synthetic strategy and attempts towards the synthesis of fagomine are also discussed.

In Chapter 3, our investigations into the gold-catalysed nucleophilic cyclisation of allenes are extended to the construction of pyrrolidine ring systems, leading to the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol and 1,2-di*epi*-(+)-lentiginosine. This key synthetic step represents, to our knowledge, the first example of nucleophilic allene cyclisation of α,β-substituted allenes for the construction of a functionalised pyrrolidine ring.

LIST OF ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
Ac	acetyl
AD	asymmetric dihydroxylation
AIBN	azobisisobutyronitrile
aq.	aqueous
Ar	aryl
asymm.	asymmetric
atm	atmosphere
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br.	broad
°C	degree Celsius
c	concentration
CAM	cerium ammonium molybdate
CAN	ceric ammonium nitrate
cat.	catalytic
calc’d	calculated
Cbz	benzyloxycarbonyl
CDI	1,1′-Carbonyldiimidazole
cm^{-1}	wave number unit
COSY	correlated spectroscopy
Conc.	Concentrated

LIST OF ABBREVIATIONS (CONT'D)

Cont'd	Continued
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
Cy	cyclohexyl
d	doublet (spectral)
dd	double doublet (spectral)
δ	chemical shift
DAB-1	1,4-dideoxy-1,4-imino-D-arabinitol
DCC	*N*,*N*-dicyclohexylcarbodiimide
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMB	3,3-dimethyl-1-butene
DMF	*N*,*N*-dimethyl formamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DNJ	deoxynojirimycin
dppb	1,4-Bis(diphenylphosphino)butane
dr	diastereoisomeric ratio

LIST OF ABBREVIATIONS (CONT'D)

EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionisation
eq.	equivalent
Et	ethyl
EtOAc	ethyl acetate
g	gram
h	hour(s)
HOBT	1-Hydroxybenzotriazole
HPLC	High-performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
i	iso
IBX	2-iodoxybenzoic acid
imid.	imidazole
IR	infrared
J	coupling constant
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LG	leaving group

LIST OF ABBREVIATIONS (CONT'D)

M	molar
m	multiplet (spectral)
M^+	molecular ion
mCPBA	*meta*-Chloroperoxybenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute(s)
mL	millilitre
MS	mass spectrometry
Ms	methanesulfonyl
MW	microwave
m/z	mass to charge ratio
N	normality
NBS	*N*-bromosuccinimide
n-Bu	butyl
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
Ns	*para*-nitrobenzenesulfonyl
Nu	nucleophile(s)
OTf	trifluoromethanesulfonate

LIST OF ABBREVIATIONS (CONT'D)

p	para
PG	protecting group(s)
Ph	phenyl
PHAL	phthalazine
Phth	phthaloyl
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
ppm	parts per million (in NMR)
Pr	propyl
psi	pounds per square inch
Py	pyridine
q	quartet (spectral)
quant.	quantitative
quint	quintet (spectral)
R	unspecified carbon substituent
R_f	retention factor
RT	room temperature (°C)
RCM	ring closing metathesis
s	singlet (spectral)
SAD	Sharpless asymmetric dihydroxylation
sat'd	saturated
SEM	2-(trimethylsilyl)ethoxymethyl

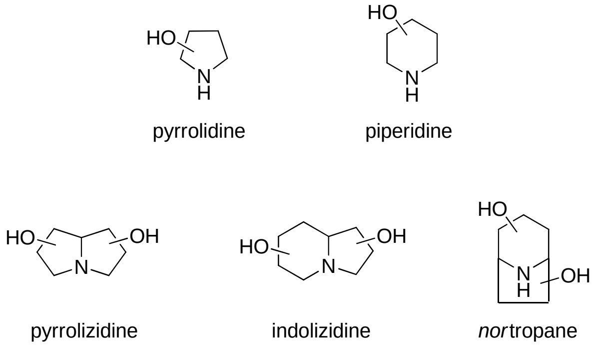
LIST OF ABBREVIATIONS (CONT'D)

t	triplet (spectral)
t	tertiary
td	triplet of doublets (spectral)
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
Ts	*para*-toluenesulfonyl
v_{max}	maximum absorption frequencies

Chapter 1 Introduction

1.1 Polyhydroxylated alkaloids and their biological significance

Polyhydroxylated alkaloids can be broadly defined as a class of natural products bearing a nitrogen atom in a cyclic system with two or more hydroxyl groups. Depending on their ring sizes, five- or six- membered, and ring systems, monocyclic or bicyclic, they can be further classified into five structural classes: pyrrolidines, piperidines, pyrrolizidines, indolizidines and *nor*tropanes (**Figure 1.1**).



pyrrolidine piperidine

pyrrolizidine indolizidine *nor*tropane

Figure 1.1 Structural motifs of naturally occurring polyhydroxylated alkaloids

Nojirimycin (NJ) **1.4** (**Figure 1.2**), originally isolated as an antibiotic from *Streptomyces roseochromogenes* R-468[1] and later *Streptomyces nojiriensis*,[2] was the first polyhydroxylated alkaloid to be isolated. Since its discovery in 1966, more than 100 polyhydroxylated alkaloids have been isolated. While the major source of these compounds has been from plants, a small number have been isolated from bacteria and fungi. The distribution of naturally occurring polyhydroxylated alkaloids have been well documented[3] and a selection of alkaloids of interest are summarised in **Table 1.1**.[3b]

Alkaloid	Source and Reference
Pyrrolidines	
1,4-Dideoxy-1,4-imino-D-arabinitol (D-AB1)	*Angylocalyx* spp. (Leguminosae) seeds/leaves/bark[4] *Arachniodes standishii* (Polypodiaceae) leaves[5] *Morus bombycis* (Moraceae) leaves[6] *Eugenia* spp. (Myrtaceae) leaves/bark[7] *Hyacinthoides non-scripta* (Hyacinthaceae) bulb/leaves[8] *Scilla campanulata* (Hyacinthaceae) bulb[9] *Adenophora triphylla* var. *japonica* (Campanulaceae) whole plant[10]
1,4-Dideoxy-1,4-imino-D-ribitol	*Morus alba* (Moraceae) roots[11]
2*R*,5*R*-Dihydroxymethyl-3*R*,4*R*-dihydroxy-pyrrolidine (DMDP)	*Derris elliptica* (Leguminosae) leaves[12] *Lonchocarpus* spp. (Leguminosae) seeds/leaves[13] *Endospermum* sp. (Euphorbiaceae) leaves[14] *Omphalea diandra* (Euphorbiaceae) leaves[15] *Streptomyces* sp. KSC-5791 (Actinomycetes)[16] *Nephthytis poissoni* (Araceae) fruit/leaves[17] Aglaonema spp. (Araceae) leaves[17, 18] *Campanula rotundifolia* (Campanulaceae) leaves[19] *Hyacinthus orientalis* (Hyacinthaceae) bulb[20] *Hyacinthoides non-scripta* (Hyacinthaceae) bulb/leaves[8] *Scilla campanulata* (Hyacinthaceae) bulb[9]

Table 1.1[3b] Selected polyhydroxylated alkaloids of interest and their natural sources

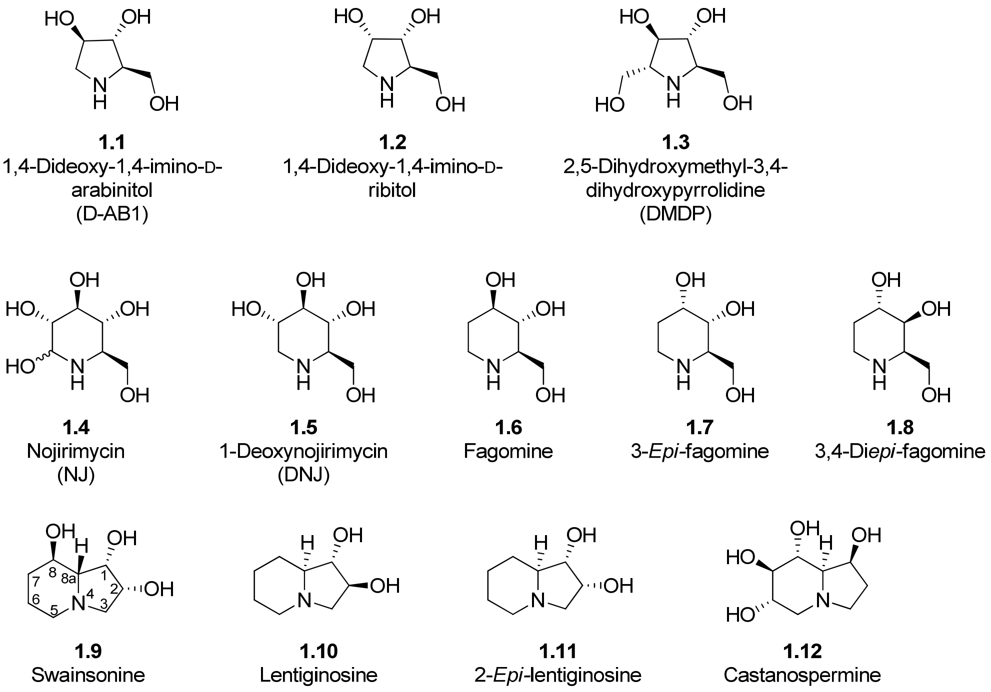
Alkaloid	Source and Reference
Piperidines	
Nojirimycin	*Streptomyces roseochromogenes* R-468[1]
	Streptomyces lavandulae SF-425[2,21]
	Streptomyces nojiriencis SF-426[2,21]
1-Deoxynojirimycin (DNJ)	*Morus* sp. (Moraceae) roots[11]
	Bacillus amyloliquefaciens, B. polymyxa, B. subtilis [22]
	Streptomyces lavandulae spp. *trehalostaticus* no. 2882[23]
	Omphalea queenslandiae (Euphorbiaceae) leaves[24]
	Endospermum medullosum (Euphorbiaceae) leaves[24]
	Morus bombycis (Moraceae) leaves[6]
	Hyacinthus orientalis (Hyacinthaceae) bulb[20]
	Adenophora triphylla var. *japonica* (Campanulaceae) whole plant[10]
Fagomine	*Fagopyrum esculentum* (Polygonaceae) seeds[25]
	Xanthocercis zambesiaca (Leguminosae) seeds[26a]/ leaves/roots[26b]
	Morus bombycis (Moraceae) leaves[6]
	Morus alba (Moraceae) roots[11]
	Lycium chinense (Solanaceae) roots[27]
3-*Epi*-fagomine	*Morus alba* (Moraceae) roots[11]
	Xanthocercis zambesiaca (Leguminosae) leaves/ roots[26b]
3,4-Di*epi*-fagomine	*Xanthocercis zambesiaca* (Leguminosae) leaves/ roots[26b]

Table 1.1 cont'd[3b] Selected polyhydroxylated alkaloids of interest and their natural sources

Alkaloid	Source and Reference
Indolizidines	
Swainsonine	*Swainsona canescens* (Leguminosae) leaves[28]
	Astragalus spp. (Leguminosae) leaves/stems[29]
	Oxytropis spp. (Leguminosae) leaves/stems[29]
	Rhizoctonia leguminicola (Basidiomycetes)[30]
	Metarhizium anisopliae (Deuteromycetes)[31]
	Ipomoea sp. aff. *calobra* (Convolvulaceae) seeds[32]
	Ipomoea carnea (Convolvulaceae) leaves/stems[33]
Lentiginosine	*Astragalus lentiginosus* (Leguminosae) leaves[34]
2-*Epi*-lentiginosine	*Rhizoctonia leguminicola* (Basidiomycetes)[30]
	Astragalus lentiginosus (Leguminosae) leaves[34]
Castanospermine	*Castanospermum australe* (Leguminosae) seeds/leaves/bark[35]
	Alexa spp. (Leguminosae) seeds/leaves/bark[36]

Table 1.1 cont'd[3b] Selected polyhydroxylated alkaloids of interest and their natural sources

From **Table 1.1**, it is evident that while plants are a major source of naturally occurring polyhydroxylated alkaloids, the distribution of alkaloids amongst the different species is disparate. While 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) **1.1**, 2,5-dihydroxymethyl-3,4-dihydroxypyrroldine (DMDP) **1.3** and 1-deoxynojirimycin (DNJ) **1.5** (**Figure 1.2**) appear to be fairly prevalent plant metabolites, existing in species of both tropical and temperate plants from unrelated families such as Leguminosae, Euphorbiaceae, Hyacinthaceae and Campanulaceae, indolizidine alkaloids lentiginosine **1.10** and castanospermine **1.12** appear to be restricted to the Leguminosae family.[37] Interestingly, the indolizidine alkaloids swainsonine **1.9** and 2-*epi*-lentiginosine **1.11** are part of the few compounds reported to be produced by fungi.



1.1
1,4-Dideoxy-1,4-imino-D-arabinitol
(D-AB1)

1.2
1,4-Dideoxy-1,4-imino-D-ribitol

1.3
2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine
(DMDP)

1.4
Nojirimycin
(NJ)

1.5
1-Deoxynojirimycin
(DNJ)

1.6
Fagomine

1.7
3-*Epi*-fagomine

1.8
3,4-Di*epi*-fagomine

1.9
Swainsonine

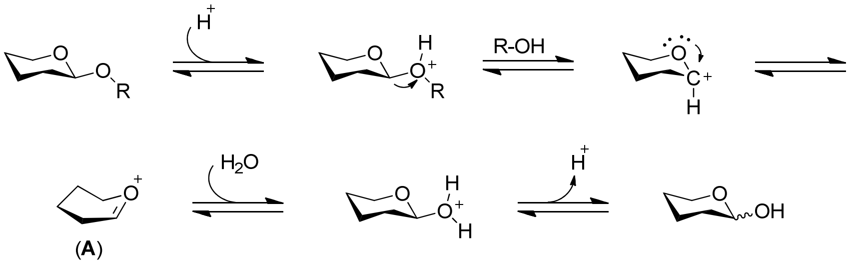
1.10
Lentiginosine

1.11
2-*Epi*-lentiginosine

1.12
Castanospermine

Figure 1.2 Selected polyhydroxylated alkaloids of interest

Polyhydroxylated alkaloids, also widely referred to as iminosugars, are regarded as carbohydrate mimetics as they resemble furanose or pyranose monosaccharides in which the ring oxygen has been replaced by nitrogen. The interest in this class of alkaloids arose when DNJ **1.5**, first synthesised by catalytic hydrogenation of nojirimycin[21a] and later isolated from plant sources and bacterial cultures, was found to be a potent inhibitor of α-glucosidase. Following that discovery, many more polyhydroxylated alkaloids have been studied in detail and were found to inhibit glycosidases in a reversible and competitive manner.[38] A comprehensive list of polyhydroxylated alkaloids and their inhibitory activities against various glycosidases has been succinctly summarised in an excellent publication.[39]

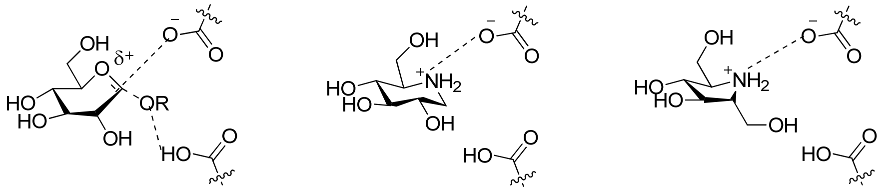


Scheme 1.1[40] Mechanism of glycosidic bond cleavage and oxycarbenium ion (**A**) formation

Glycosidases are enzymes that catalyse the hydrolysis of glycosidic bonds in complex carbohydrates and glycoconjugates. These enzymes are implicated in a broad range of crucial metabolic pathways such as (i) degradation of diet polysaccharides to monosaccharides, (ii) glycoprotein processing and lysosomal glycoconjugate catabolism and (iii) biosynthesis of oligosaccharide units in glycoproteins or glycolipids[40] and hence possess an immense potential as therapeutic agents for a variety of indications.[41]

The potency and specificity of iminosugars' inhibitory activities against glycosidases can be attributed to their ability to mimic the conformation and charge of the oxycarbenium ion intermediate (**A**) generated during glycosidic bond cleavage (**Scheme 1.1**).[40] There is evidence to suggest that iminosugars, when bound to the active site of a glycosidase, are protonated to interact through ionic bonds with the carboxyl group in the active site.[38a] This protonated inhibitor closely resembles the pyranosyl or furanosyl transition state of the natural substrate and hence the enzyme has a high affinity for the molecule (**Figure 1.3**).

Indeed, the inhibitory activities of iminosugars against mammalian α-glucosidases (sucrase, maltase, isomaltase etc.) were exploited by Bayer chemists in their development of *N*-hydroxylethyl-deoxynojirimycin (trade name Miglitol, **Figure 1.4**, **1.13**) for the treatment of type 2 diabetes mellitus. Although DNJ **1.5** was found to be a potent inhibitor of α- and β-glucosidases *in vitro*,[42] its activity *in vivo* against intestinal sucrase was lower. Many derivatives of DNJ were synthesised with the aim of identifying more potent inhibitors and it was from this effort that Miglitol emerged.[43] The improved *in vivo* activity of this *N*-hydroxyalkyl derivative was attributed to its improved retention in the small intestine.



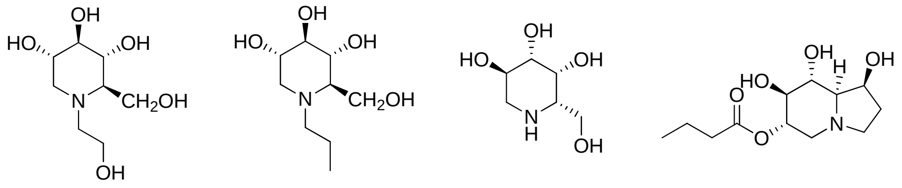
D-glucose

1-deoxynojirimycin **1.5**

DMDP **1.3**

Figure 1.3[40] Transition state of natural substrate D-glucose, DNJ **1.5** and DMDP **1.3** in glucosidase active site

Miglitol was approved for use as first-line therapy in patients with type 2 diabetes inadequately controlled by diet or sulfonylurea therapy by the Food and Drug Administration (FDA) in 1996. It reversibly inhibits α-glucosidases responsible for the breakdown of carbohydrates into glucose and monosaccharides in the brush border of the small intestine. As it functions as a competitive inhibitor, it is able to slow down the breakdown of carbohydrates to glucose, hence reducing postprandial peak plasma glucose levels in patients.[44] However, the delayed breakdown of carbohydrates in the upper gastrointestinal tract means more carbohydrates are available for digestion in the large intestine, causing a buildup of gas that leads to adverse events like flatulence, abdominal pain and diarrhoea.[45]



1.13 Miglitol

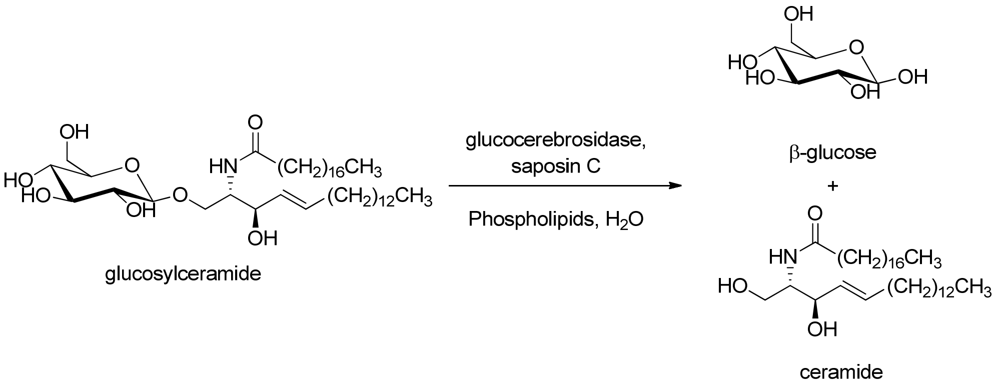
1.14 Miglustat

1.15 Migalastat

1.16 Celgosivir

Figure 1.4 Selected iminosugar derived clinical candidates and marketed drugs

Besides Miglitol, another closely related *N*-alkyl derivative of DNJ, Miglustat (**Figure 1.4**, **1.14**) has also been developed for the treatment of type 1 Gaucher's disease[45] and Niemann-Pick type C (NPC) disease.[46] Both diseases are caused by the accumulation of intracellular glycosphingolipids, albeit by different mechanisms; type 1 Gaucher's disease by a dysfunctional glucocerebrosidase enzyme responsible for the hydrolysis of glucosylceramide (**Scheme 1.2**) and NPC disease by impaired intracellular lipid trafficking. Miglustat is proposed to work via the inhibition of glucosylceramide synthase, a glycosyl transferase responsible for the synthesis of many glycosphingolipids. This inhibition reduces the activity of the glucosylceramide synthase and hence lowers the build-up of glucosylceramide, relieving some of the disease symptoms.[47]



Scheme 1.2 Hydrolysis of glucosylceramide catalysed by glucocerebrosidase

The therapeutic potential of iminosugars is not limited to glucosidase inhibition. Iminosugars may also function as pharmacological chaperones to prevent misfolding and premature degradation of mutant enzymes.[48] Migalastat (**Figure 1.4**, 1**.15**), a synthetic iminosugar co-developed by Amicus Therapeutics and GlaxoSmithKline, is currently in global Phase III clinical studies for the treatment of Fabry disease. Fabry disease is an inherited lysosomal storage disorder caused by a deficiency in α-galactosidase. This results in an accumulation of globotriaosylceramide (GL-3) in lysosomal and nonlysosomal compartments of cells of multiple organs and if left untreated would affect the heart, kidney and central nervous system (CNS), resulting in death. Migalastat selectively binds and stabilises the mutant form of α-galactosidase, facilitating proper protein folding and trafficking, hence increasing lysosomal enzyme activity.[49]

In addition to diabetes and lysosomal storage disorders, iminosugars have also shown potential therapeutic applications in oncology[50] and antiviral therapy.[51] Celgosivir (**Figure 1.4**, **1.16**), an ester prodrug of castanospermine (**Figure 1.2**, **1.12**), was previously evaluated in clinical studies as a potential treatment for Hepatitis C virus (HCV) infection but was not further developed due to its moderate efficacy as a monotherapy for the treatment of HCV.[52] More recently, Celgosivir was found to be a potent inhibitor against all four serotypes of the Dengue virus[53] and was further evaluated in a locally conducted clinical trial by the Singapore General Hospital in collaboration with Duke-NUS Graduate Medical School. The trial was concluded at the end of 2013 but the official outcome has not been made available.

The large therapeutic potential of iminosugars, along with their chemical and biological diversity, have attracted the interests of many groups to develop synthetic methodologies around this class of compounds to enable the better understanding of structure-activity relationships. As the spatial arrangement of the hydroxyl groups serve as a means of recognition by specific glycosidases, the synthesis of non-naturally occurring diastereomers of these iminosugars could help us to further understand the requirements for designing more potent and specific inhibitors. Through these endeavours, a number of non-naturally occurring iminosugars have actually been discovered to be more potent inhibitors than their natural counterparts.[48, 54]

1.2 Synthesis of polyhydroxylated alkaloids

The synthesis of polyhydroxylated alkaloids can be broadly classified into three approaches based on the starting material utilised: (i) carbohydrates, (ii) chiral synthons and (iii) non-carbohydrate, non-chiral starting materials.

Carbohydrates are a popular starting point for the synthesis of iminosugars due to their close structural resemblance. This approach takes advantage of the stereocentres already present in the sugar moiety and mainly focuses on the introduction of a nitrogen atom into the ring. This is usually effected by amino cyclisation through reductive amination, intramolecular nucleophilic displacement of leaving groups or intramolecular addition to activated double bonds. As this approach involves the conversion of a single hydroxyl group, amongst the dense functionalities present, to an amino group, various protecting group strategies are required to mask the other functional groups present throughout the synthetic sequence, leading to longer overall synthetic routes. This approach has been generally applied to the synthesis of a single target molecule.

Chiral synthons such as amino alcohols, amino acids or amino acids derived building blocks have also been commonly used as starting materials for the synthesis of iminosugars. In this approach, not all the requisite chiral centres are available in the starting material and have to be installed later in the synthesis via stereoselective transformations. This allows for a more divergent synthesis and frequently results in the synthesis of more than one iminosugar from the same synthetic sequence.

Lastly, with the advent of various highly stereoselective transformations, there are increasing number of reported synthesis employing ordinary non-chiral starting materials. This approach when successful, has the potential to be very useful for the synthesis of both natural and non-natural iminosugars as it is not limited by the chirality of starting materials available.

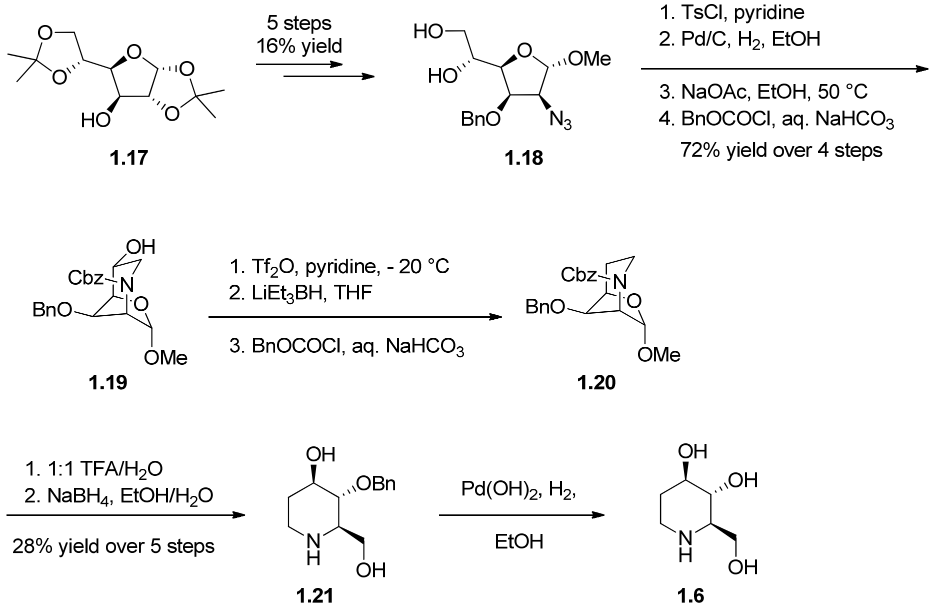
1.2.1 Synthesis of fagomine and its congeners

Fagomine, first isolated from the seeds of Japanese buckwheat (*Fagopyrum esculentum*)[25] and subsequently in other plant sources,[6,11,26,27] has been shown to be active against mammalian gut α-glucosidase and β-galactosidase.[55] Originally, only the relative, but not the absolute configuration of fagomine, was established by NMR studies. The absolute configuration of fagomine was only established in 1985, in the first reported synthesis published by Fleet *et al.*.[56]

Due to the large number of publications related to the synthesis of fagomine and its congeners,[57] the following review has been organised based on the starting material utilised. While it is not the intention to provide a complete review of all the syntheses previously reported, a selection of syntheses for each approach has been included to highlight the advantages and disadvantages each approach may bear.

1.2.2 Carbohydrates as starting materials

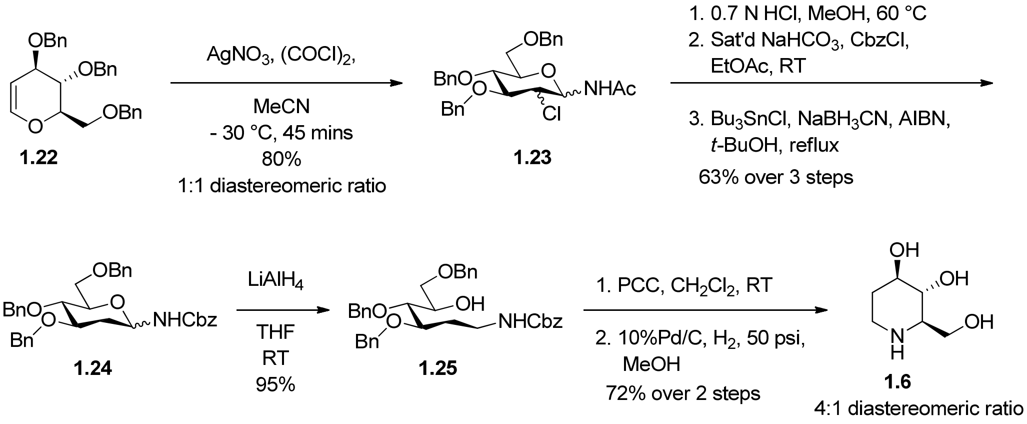
The first reported synthesis of fagomine[56] utilised the carbohydrate approach. Starting from diacetone-D-glucose **1.17** (**Scheme 1.3**), a five-step sequence of benzylation, selective acetonide deprotection and carbonate formation at the fifth and sixth position, acetonide deprotection in the presence of methanol to yield the corresponding methyl ethers as a mixture of anomers which was separated by flash chromatography. Esterification of the α-anomer with trifluoromethanesulfonic anhydride, followed by displacement of the resultant triflate with sodium azide, and finally carbonate deprotection with sodium methoxide in methanol was required to install the amine moiety to provide the key azidomannofuranoside **1.18** with an overall yield of 16%.



Scheme 1.3 Reaction scheme for first reported synthesis of fagomine

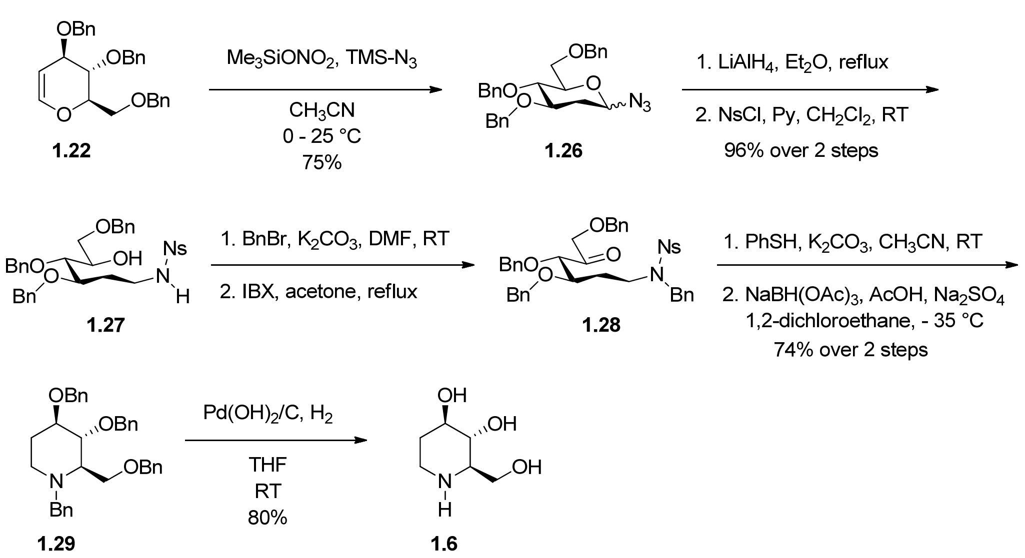
Selective tosylation, followed by azide reduction in the presence of palladium black provided the primary amine, which upon treatment with sodium acetate and subsequently benzyl chloroformate, provided the bicyclic benzyl carbamate **1.19** in

72% yield over 4 steps. Esterification of the secondary alcohol, followed by reduction with lithium triethylborohydride, provided the deoxygenated bicyclic amine **1.20**, which underwent acid hydrolysis, reduction with sodium borohydride and finally debenzylation to give fagomine **1.6** which had a ^{1}H NMR spectrum identical to that reported.[25] This together with the specific rotation of synthetic fagomine, $[\alpha]_D^{22} = +21.6$ (*c* 0.36, H_2O),[26a] established the absolute configuration of the isolated material.



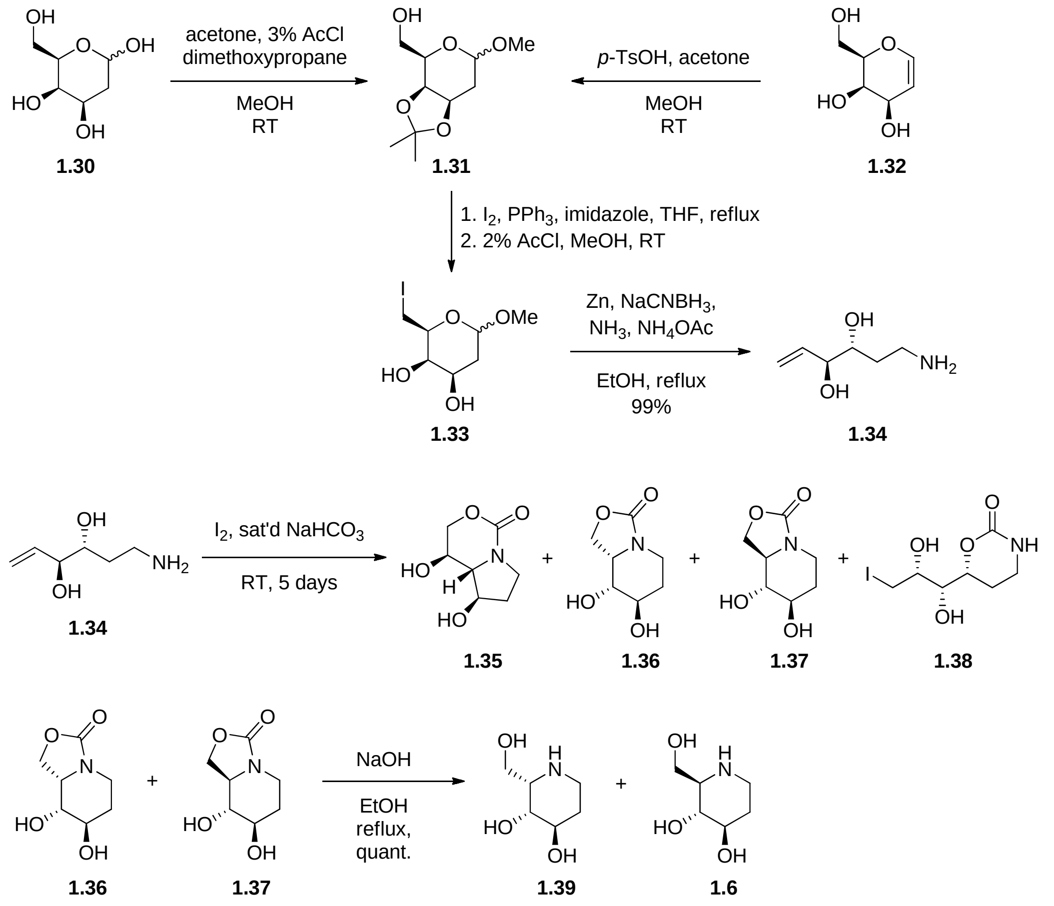
Scheme 1.4 Synthesis of fagomine from 3,4,6-tri-*O*-benzyl-D-glucal

Besides glucose, glycals have also been successfully applied to the synthesis of fagomine. In the synthesis reported by Vankar *et al.*,[58] utilising chemistry previously developed within their group, the amino functionality was installed onto the requisite glycals in the form of a chloroacetamide[59] or azide.[60] 3,4,6-Tri-*O*-benzyl-D-glucal **1.22** (**Scheme 1.4**) was treated with silver nitrate/oxalyl chloride in acetonitrile to provide chloroacetamide **1.23** as a 1:1 diastereomeric mixture. Acetamide deprotection, benzyl carbamate protection and dechlorination under radical conditions[61] gave 2-deoxy-1-amino sugar derivative **1.24** as a 1:1 anomeric mixture, which was inconsequential as the subsequent reduction with lithium aluminum hydride lead to the complete loss of the unwanted stereogenic centre. Oxidation of the alcohol to a ketone with pyridinium chlorochromate, followed by tandem reductive amination and debenzylation in the presence of palladium on carbon provided fagomine as a 4:1 mixture of diastereomers.



Scheme 1.5 Alternate synthesis of fagomine from 3,4,6-tri-*O*-benzyl-D-glucal

In an alternative approach, 3,4,6-tri-*O*-benzyl-D-glucal **1.22** (**Scheme 1.5**) was treated with trimethylsilylnitrate and trimethylsilylazide in acetonitrile to afford 2-deoxy-1-azido sugar **1.26** as a 2:1 mixture of anomers. Tandem ring opening and reduction with lithium aluminium hydride followed by treatment with nosyl chloride gave nosyl protected amino alcohol **1.27**. Benzylation with benzyl bromide in the presence of potassium carbonate followed by oxidation with IBX gave ketone **1.28**. Nosyl removal revealed the secondary amine, which underwent intramolecular reductive amination with NaBH(OAc)$_3$ to afford protected fagomine **1.29** as a single diastereomer. Global debenzylation by hydrogenolysis with Pearlman's catalyst under a hydrogen atmosphere provided fagomine **1.6**. Other congeners of fagomine were also synthesised by application of the same synthetic sequence to a different glycal, 3,4,6-tri-*O*-benzyl-D-galactal.

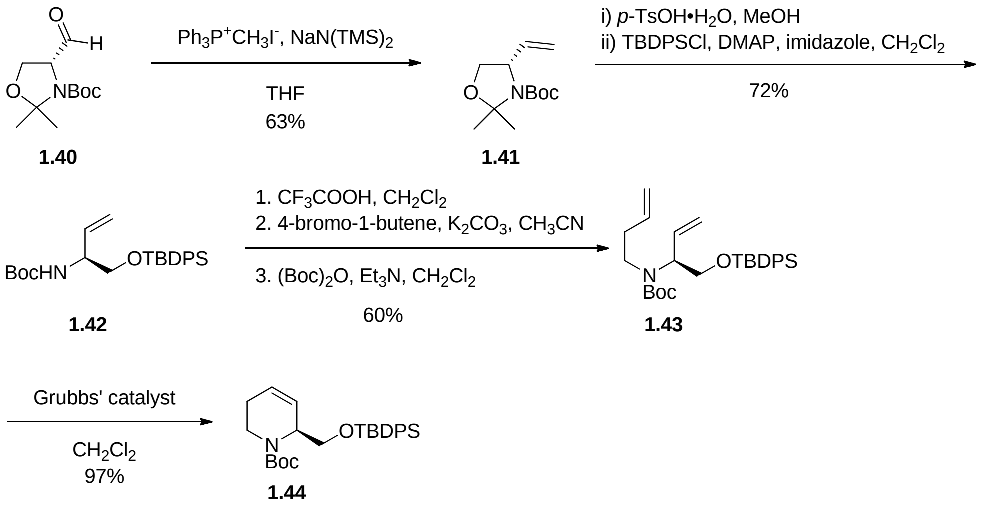


Scheme 1.6 Synthesis of fagomine via I_2 mediated carbamate annulation

In a more recent synthesis, Stocker and Timmer *et al.* reported the application of iodine-mediated carbamate annulation towards the synthesis of hydroxylated piperidine alkaloids.[62] Starting from either 2-deoxy-D-galactose **1.30** (**Scheme 1.6**) or D-galactal **1.32**, protection followed by iodination provided methyl iodoglycoside **1.33** which underwent Vasella reductive amination[63] to give the key alkenylamine **1.34** in good overall yields of 50-65%, depending on the starting material utilised. The alkenylamine **1.34** was then subjected to I_2 in the presence of $NaHCO_3$ to effect the desired carbamate annulation reaction. Unfortunately, all the cyclisation conditions investigated led to complex mixtures of 4 carbamates, with pyrrolidine favoured over piperidine in all cases. Piperidines **1.36** and **1.37** were isolated as an inseparable mixture in 20% yield under the best conditions applied and this mixture was subjected to carbamate hydrolysis to give 2-*epi*-fagomine **1.39** and fagomine **1.6** as single compounds after silica gel column chromatography. The highlights of this synthesis are the use of only a single protecting group, as well as the relatively short synthetic sequence to fagomine starting from commercially available carbohydrates, compared to the previous three reported synthesis, which utilised at least three protecting groups in each case.

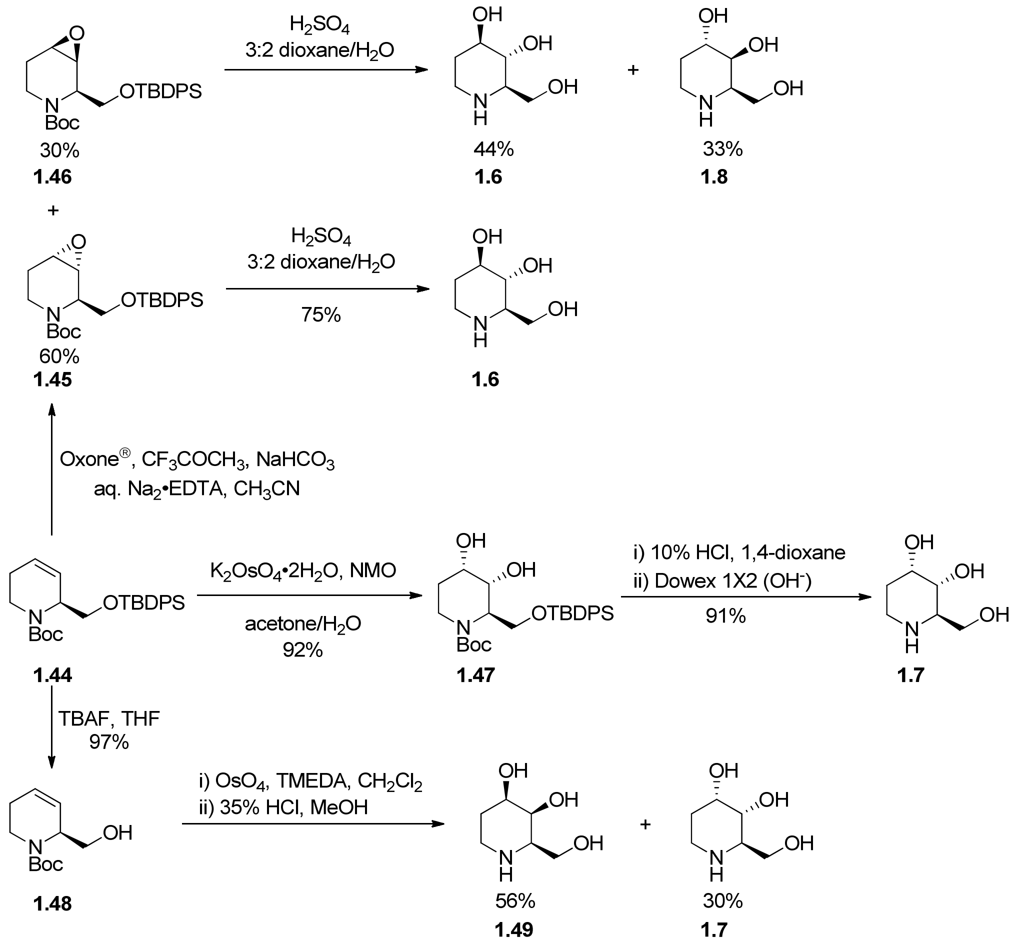
1.2.3 Chiral synthons as starting materials

The chiral synthon approach to fagomine and its congeners is perhaps best demonstrated by Takahata and Banba *et al.*. They envisioned that different diastereomers of fagomine could be synthesised from a common building block derived from D-serine and were successful in their approach leading to the synthesis of 4 fagomine isomers.[64] Key transformations of the synthesis included ring-closing metathesis used for the construction of the piperidine ring and epoxidation or dihydroxylation to install the other two hydroxy moieties.



Scheme 1.7 Synthesis of common building block from Garner's aldehyde

Garner's aldehyde **1.40** (**Scheme 1.7**) derived from D-serine[65] was treated with methylphosphonium iodide in the presence of sodium bis(trimethysilyl)amide to give olefin **1.41**. Acidic hydrolysis followed by *O*-silylation provided the protected amino alcohol **1.42**. Direct *N*-alkylation of the Boc protected amine **1.42** proved to be challenging and hence a three-step sequence of Boc deprotection, alkylation and Boc protection was carried out to obtain diene **1.43**. Ring-closing metathesis with Grubbs' I catalyst provided the key building block **1.44** in 26% overall yield.

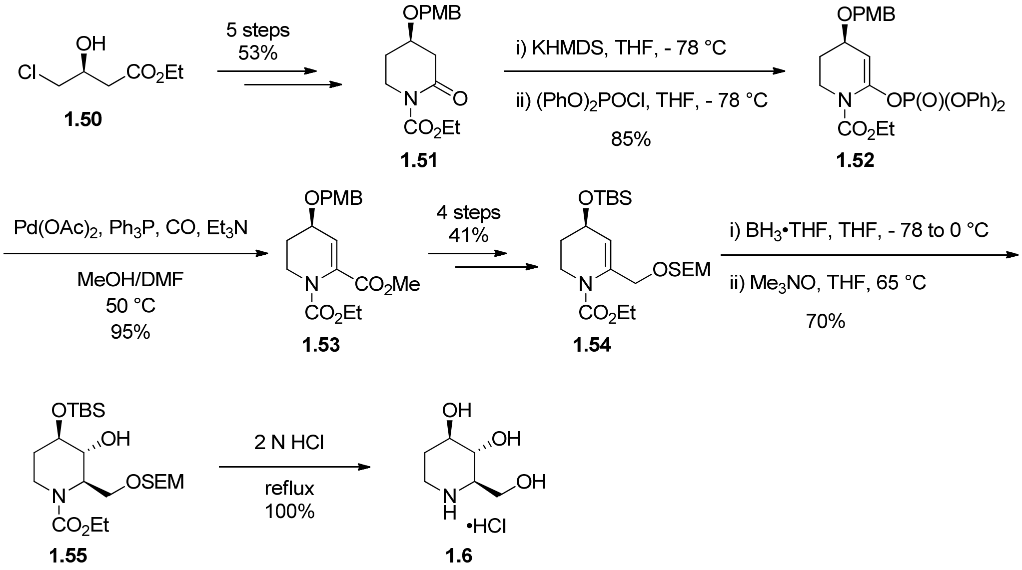


Scheme 1.8 Synthesis of fagomine isomers from a common building block

With building block **1.44** in hand, Takahata and Banba *et al.* proceeded to access the *trans* diol isomers via epoxidation and *cis* diols via dihydroxylation. Treatment of **1.44**

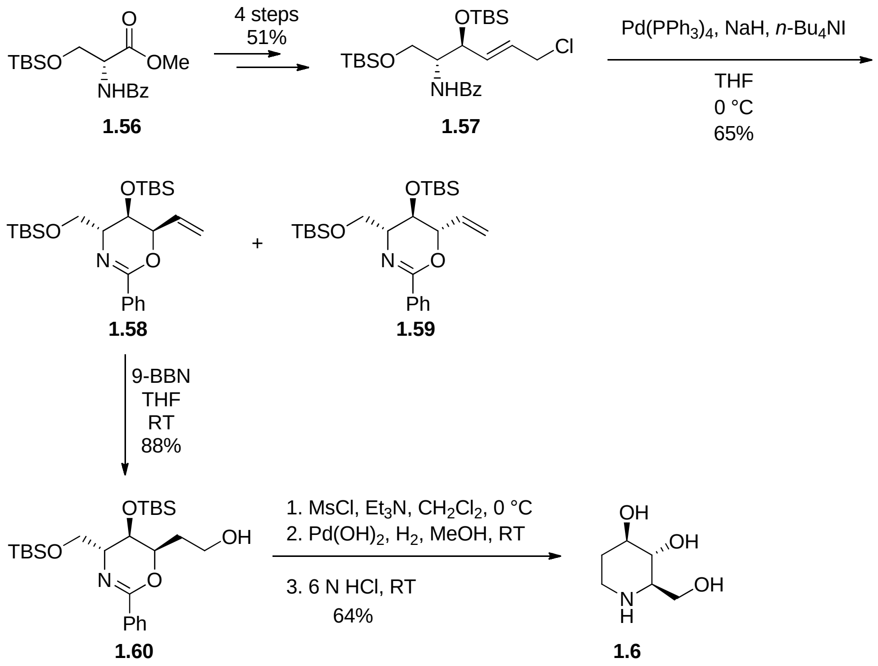
(**Scheme 1.8**) with Oxone® in the presence of 1,1,1-trifluoroacetone[66] provided epoxides **1.45** and **1.46** which were separable by silica-gel chromatography. While the acid catalysed epoxide ring opening of **1.45** lead to fagomine **1.6** as the only product, epoxide **1.46** reacted to give 2 isomers, fagomine **1.6** and 3,4-di*epi*-fagomine **1.8**, under the same conditions. This result was rationalised by the authors with respect to the steric demands required during the backside nucleophilic attack of H_2O on the epoxide ring. In the case of **1.45**, nucleophilic attack occurs preferentially at the 4-position as attack on the 3-position would require the nucleophile to be in a *syn* orientation with respect to the adjacent hydroxymethyl substituent at the 2-position. On the other hand, with epoxide **1.46**, the *anti* relation between the hydroxymethyl substituent at the 2-position and the backside attack of H_2O on the epoxy ring would render the 3- and 4-positions equally available for displacement, leading to the formation of 2 isomers.

Treatment of **1.44** under modified Upjohn conditions[67] gave diol **1.47** as a single diastereomer as the dihydroxylation occurred exclusively on the less hindered *anti* side of the siloxymethyl substituent, which adopts a pseudo axial position due to 1,3-allylic strain.[64b] Deprotection under acidic conditions followed by treatment with ion-exchange resin provided 3-*epi*-fagomine **1.7** in 91% yield. 4-*epi*-fagomine **1.49** was obtained from dihydroxylation conditions developed by Donohoe,[68] utilising OsO_4 in the presence of TMEDA. Under these conditions, OsO_4 produces a bidentate, reactive complex with TMEDA, which achieves the directed dihydroxylation of homoallylic alcohols.



Scheme 1.9 Synthesis of fagomine from (*S*)-ethyl 4-chloro-3-hydroxybutanoate

In the synthesis of fagomine reported by Bartali *et al.*,[69] commercially available (*S*)-ethyl 4-chloro-3-hydroxybutanoate **1.50** (**Scheme 1.9**) was utilised to prepare the enantiopure *N*-protected lactam **1.51** following methodology previously developed by the group.[70] Transformation to the vinyl phosphonate **1.52,** followed by Pd-catalysed methoxycarbonylation, installed the requisite methyl ester at the 2-position. Protecting group exchange from PMB to TBS, followed by ester reduction and SEM protection of the resultant primary alcohol, provided homoallylic alcohol **1.54**. The protecting group exchange to the bulky 4-silyloxy group was essential in controlling the stereoselectivity of the hydroboration-oxidation step[71] due to its preference for being pseudo axially orientated to remove $A^{(1,2)}$-strain with 3-H, hence directing the hydroboration to the opposite face, providing **1.55**, after oxidation as a single diastereomer. Complete deprotection under acidic conditions provided fagomine **1.6** as its hydrochloride salt in 12% overall yield over 13 steps, starting from commercially available (*S*)-ethyl 4-chloro-3-hydroxybutanoate **1.50**.

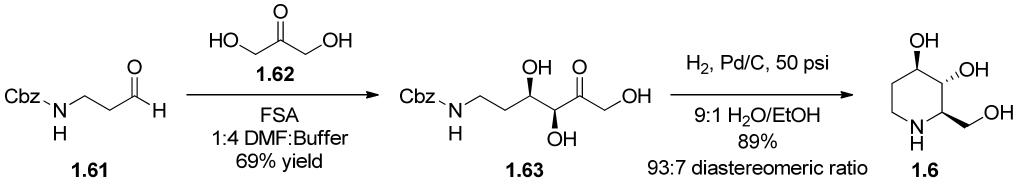


Scheme 1.10 Synthesis of fagomine from *N*-benzoyl-D-serine methyl ester

With the aim of expanding the synthetic utility of oxazines as chiral building blocks towards the synthesis of natural products, Kim *et al.* demonstrated that Pd(0)-catalysed oxazine formation of a γ-allylbenzamide could be utilised to set the three contiguous stereocentres of fagomine efficiently.[72] *Bis*(TBS) protected γ-allylbenzamide **1.57** (**Scheme 1.10**), prepared from *N*-benzoyl-D-serine methyl ester **1.56** over 4 steps,[73] was treated with $Pd(PPh_3)_4$ under basic conditions to provide chiral 1,3-oxazine **1.58** in greater that 30:1 diastereomeric ratio. The bulky TBS group adjacent to the alkene was determined to be important for diastereoselectivity as substitution with smaller groups such as methyl or benzyl gave mixtures of oxazines **1.58** and **1.59** in a 3:1 ratio. Hydroboration of the pendant vinyl group provided the primary alcohol **1.60**. Conversion to the mesylate, followed by tandem hydrogenolysis of the oxazine and intramolecular mesylate displacement by the primary amine, provided the piperidine scaffold of fagomine. Global TBS deprotection under acidic conditions and treatment with ion-exchange resin provided fagomine **1.6** in 19% overall yield over 9 steps, starting from *N*-benzoyl-D-serine methyl ester **1.56**.

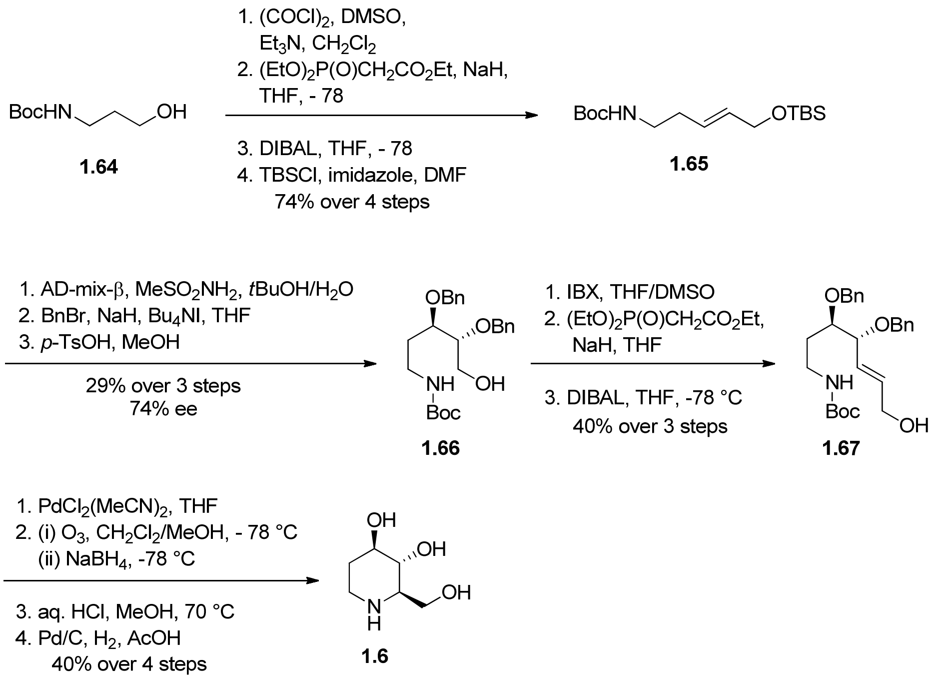
1.2.4 Non-carbohydrate, non-chiral substrates as starting materials

Among the reports utilising achiral starting materials, the synthesis of fagomine by Clapés *et al.*[74] is perhaps one of the more remarkable. Utilising D-fructose-6-phosphate aldolase (FSA) to catalyse the aldol addition of dihydroxyacetone **1.62** (**Scheme 1.11**) to *N*-Cbz-3-aminopropanal **1.61**, the chemo-enzymatic synthesis of fagomine was completed in just 2 synthetic steps in good overall yield and diastereomeric selectivity. While the authors made no mention about the ee of the transformation, the measured specific rotation, $[\alpha]_D^{20} = + 20.4$ (*c* 1.0, H_2O), was in good agreement (*cf.* $[\alpha]_D^{20} = + 19.5$ (*c* 1.0, H_2O)) to that previously reported by Kato *et al.* in their isolation of fagomine from *Xanthocercis zambesiaca*.[26b]



Scheme 1.11 Synthesis of fagomine by FSA-catalysed aldol reaction

FSA is a novel class I aldolase isolated from *Escherichia coli*,[75] which catalyses the aldol addition of dihydroxyacetone to glyceraldehyde-3-phosphate. It is functionally distinct from known aldolases in its tolerance of different donor substrates as well as acceptor substrates. This characteristic was further studied and exploited by Wong *et al.*[76] in the synthesis of many natural and non-natural pyrrolidine and piperidine iminosugars utilising the FSA-catalysed aldol addition of dihydroxyacteone, hydroxyacetone and 1-hydroxy-2-butanone to various amino aldehydes.



Scheme 1.12 Synthesis of fagomine by Pd(II)-catalysed cyclisation

A great contrast to the chemo-enzymatic synthesis is the synthesis reported by Hirai *et al.*.[77] Utilising the homologous alcohol substrate of **1.61** and key transformations such as the Sharpless asymmetric hydroxylation to install the diol and a Pd(II)-catalysed amino cyclisation to install the third chiral centre of fagomine, the synthesis required 14 steps, yielding fagomine in 3% overall yield.

Beginning with *N*-Boc-3-aminopropanol **1.64** (**Scheme 1.12**), oxidation followed by Horner-Wittig reaction provided α,β-unsaturated ester which was reduced with DIBAL and protected as the TBS alcohol **1.65**. Dihydroxylation of the *trans* alkene proceeded to give the *trans* diol with moderate enantioselectivity of 74%. The diols were protected as benzyl ethers and treatment with toluenesulfonic acid removed the TBS protecting group to reveal the primary alcohol **1.66**. Oxidation followed by a second Horner-

Wittig reaction and reduction provided the homoallylic alcohol **1.67**. Treatment with Pd(II) provided the cyclised product as a single compound, which the authors attributed to the presence of a π-allyl-oxy palladium complex produced by the coordination of the Pd catalyst with allyl alcohol and amine. Ozonolysis of the pendant vinyl group, followed by reductive work-up with $NaBH_4$, provided the hydroxylmethyl substituent at the 2-position. Boc group removal and debenzylation in the presence of Pd/C provided fagomine **1.6**.

1.3 Conclusion

Iminosugars, with their remarkable biological activity and huge potential for a variety of therapeutic applications, have and will continue to attract the attention of the synthesis community. We have seen from the examples listed above that while efficient syntheses have been developed for the natural iminosugars, much more can be done in the synthesis of the other non-natural, or perhaps not yet isolated, iminosugars. Until we are able to develop facile methods for the systematic synthesis of each isomer, the structure-activity relationships for iminosugar glycosidase inhibitors will be difficult to elucidate and the design of more selective inhibitors challenging.

1.4 Aim of the project

The aim of the project is to investigate the utility of the nucleophilic cyclisation of allenes in the synthesis of iminosugars from non-chiral starting materials.

Chapter 2 Attempted synthesis of fagomine

2.1 Chemistry of allenes

The allene was regarded as a substrate of controversy in the early years, as its existence was always debated among chemists. While the structure of allene was accurately predicted as early as 1874 by Van't Hoff,[78] most chemists had their doubts that the arrangement of cumulated double bonds would be stable. Ironically, the first documented synthesis of allene reported in 1887, was initially an attempt by Burton and von Pechmann[79] to prove the non-existence of this class of compounds. The structure of the synthesised allene, glutinic acid, was only confirmed almost 70 years later by Mansfield and Whiting[80] with the use of infra-red (IR) spectroscopy. Much of the debate in the early days can be attributed to the lack of analytical techniques available to accurately characterise allenes. Often, it was almost impossible to distinguish between allenes, the corresponding alkynes and dienes. Fortunately, with the advent of IR and nuclear magnetic resonance (NMR) spectroscopy, we are now better equipped to characterise this class of compounds.

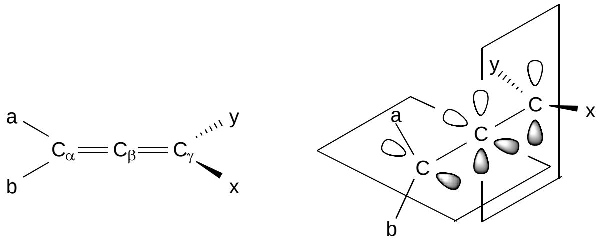
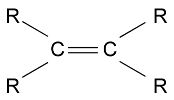
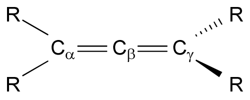


Figure 2.1 General structure of allene and arrangement of allenic π bonds

Allenes, compounds with general formula $R_2C=C=CR_2$, have an unusual geometry due to their cumulated bond system. The most stable bonding arrangement involves two mutually perpendicular π bonds, with a central sp-hybridised carbon atom C_β joined in a linear arrangement to two terminal sp^2-hybridised carbon atoms (**Figure 2.1**).[81] As a consequence of the non-coplanarity, the two π bonds are not conjugated with each other. The lack of molecular symmetry also implies that allenes bearing different substituents at the terminal carbon atoms would be chiral.[78] This unique bond system of allenes has intrigued many since its discovery and numerous physical chemistry investigations have been conducted to better characterise this class of compounds. A concise summary of these investigations has been reviewed by Taylor,[82] who also provides an excellent insight into the techniques now frequently applied to the characterisation of allenes.

		R—C≡C—R	
^{1}H NMR δ (ppm)	4.00 - 6.70	1.70 - 3.10	4.40 - 4.90
^{13}C NMR δ (ppm)	110 - 150	65 - 90	C_α, C_γ = 73 - 120 C_β = 200 - 220
IR wavenumber (cm^{-1})	1680 - 1620 (asymm. stretch)	2260 - 2100 (asymm. stretch)	1980 - 1930 (asymm. stretch)

R = H or alkyl groups

Table 2.1 Characteristic spectroscopic measurements of alkenes, alkynes and allenes[83]

The combination of IR spectroscopy with NMR spectroscopy allows for the unambiguous characterisation of allenes. While the proton shifts of an allene are very similar to those of an alkene (**Table 2.1**), the ^{13}C NMR shifts are rather diagnostic with the central C_β atom having a large downfield shift of 200-220 ppm. This, together with the asymmetric stretching band of 1980-1930 cm^{-1} in an IR spectrum, distinguishes an allene from its corresponding alkyne or diene.

The preparation of allenes has been widely reviewed[84] and the general methods for synthesis include isomerisation of alkynes,[85] homologation of alkynes,[86] sigmatropic rearrangements[87] and metal-mediated S_N2' type displacement[88] (**Figure 2.2**). While isomerisation and homologation of alkynes are useful for the synthesis of terminal allenes, sigmatropic rearrangements and metal-mediated S_N2' displacement reactions are often applied to the synthesis of chiral allenes, taking advantage of the centre to axial chirality transfer mechanism.

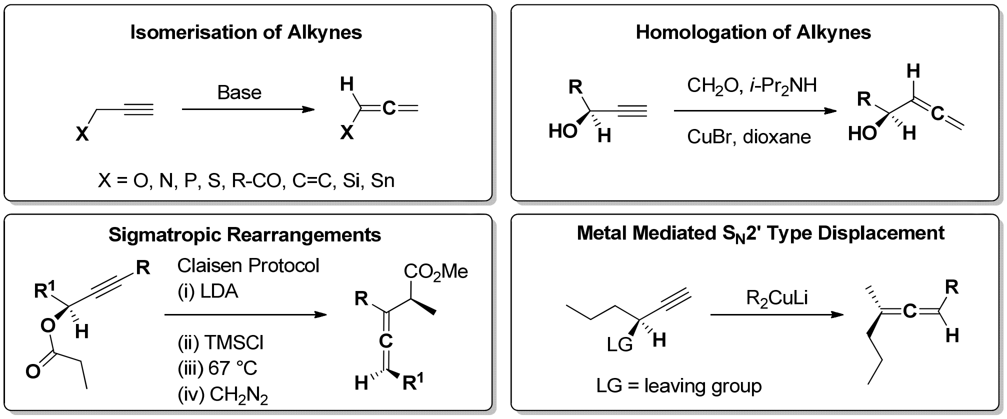
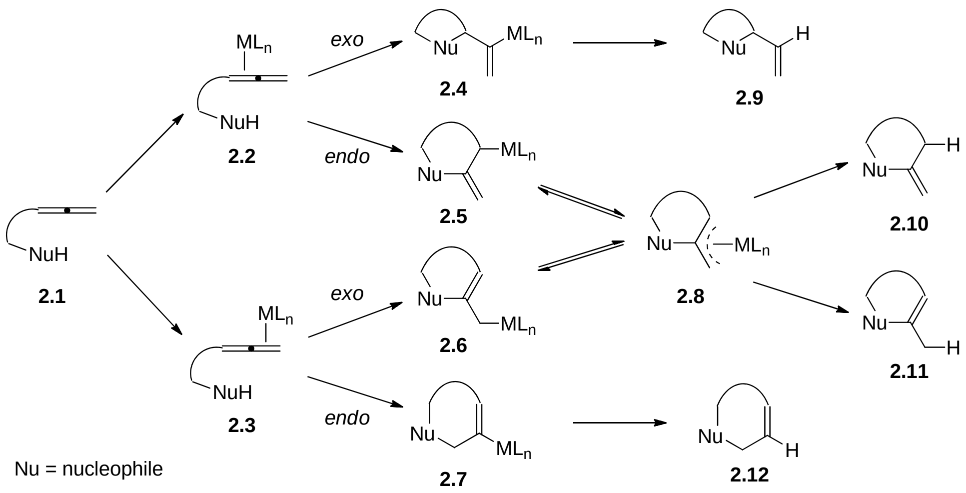


Figure 2.2 Common methods for the synthesis of allenes

The ability of the allene to function as either a nucleophile or electrophile, together with its capacity to participate in numerous metal-mediated chemical transformations, has attracted the attention of organic chemists.[89] While electrophilic additions occur in a manner similar to those of alkenes, nucleophilic addition on an allene can occur on any of its three carbon atoms. This positional selectivity can be modulated by geometrical restrictions and electronic differentiation of the two double bonds due to substitutions at the terminal of the allene.[90] Amongst the metal-mediated chemical transformations reported with allenes, the transition metal-catalysed nucleophilic cyclisation of allenes is perhaps the most widely applied due to the diversity of heterocycles the reaction affords.

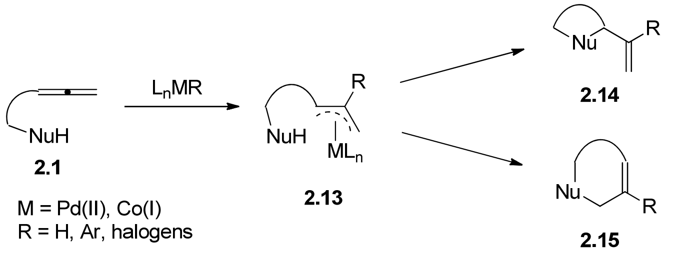
2.1.1 Transition metal-catalysed nucleophilic cyclisation of allenes

Nitrogen and oxygen heterocycles are common structural components of a wide range of naturally occurring and biologically active molecules. An attractive and atom-economical alternative to the synthesis of these functionalised heterocycles is via the intramolecular cyclisation of allenes bearing nucleophiles. These reactions can be catalysed by a number of transition metals (Au, Ag, Pd, Ru, Rh, Co, Ln)[91] and often provide good stereochemical control. The benefits of utilising an allene, compared to an alkyne or alkene, for the cyclisation are (i) the higher reactivity of the allene and (ii) the presence of a double bond after the cyclisation which would be amendable to further synthetic manipulation.



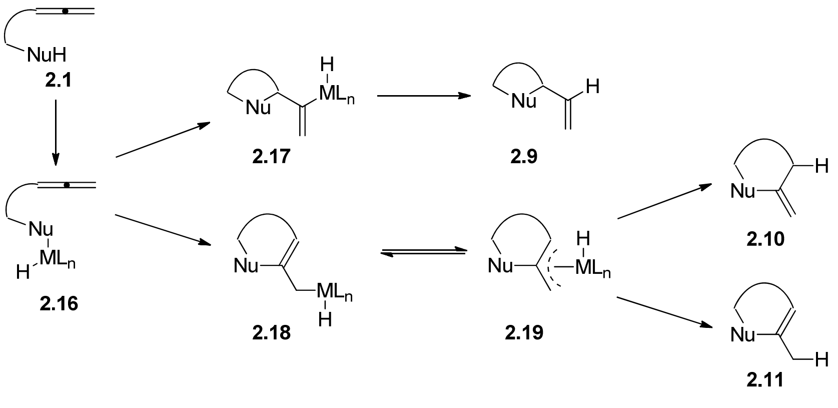
Scheme 2.1 Activation by allene coordination

Three possible mechanisms,[91,92] generally applicable to different substrates and metal catalysts, have been put forward for these nucleophilic cyclisation reactions. The first proposed mechanism involves the activation of one of the allene double bonds by coordination to an electrophilic metal centre (**Scheme 2.1**). The coordination to the proximal or distal double bond to form a η^2-complexes[93] (**2.2** and **2.3**) is dependent on both electronic and steric factors and for each case, an *exo* or *endo* attack of the nucleophile is possible, resulting in four possible intermediates **2.4** to **2.7**. Subsequent demetallation leads to four possible products; two exocyclic alkenes (**2.9** and **2.10**) and two endocyclic alkenes (**2.11** and **2.12**).



Scheme 2.2 Activation by allene insertion

An alternative mechanism is possible for metal complexes bearing σ-bonded ligands (**Scheme 2.2**). Coordination, followed by migratory insertion of the allene would generate an η^3-allyl complex **2.13**, which could undergo nucleophilic cyclisation at either terminus to give exocyclic alkene **2.14** or endocyclic alkene **2.15**. This mechanism is usually promoted by Pd(II) complexes bearing aryl or halogen substituents.



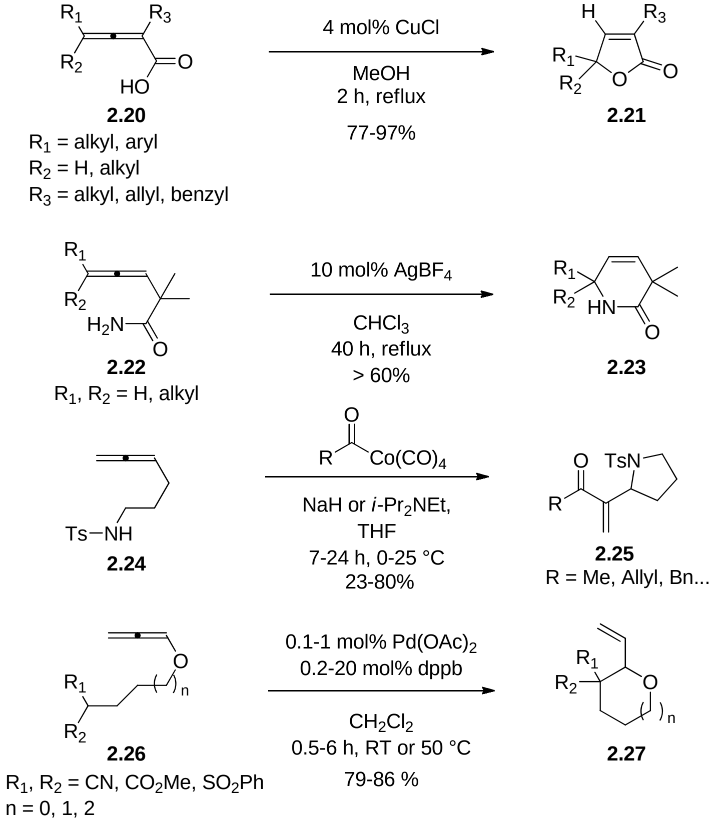
Scheme 2.3 Activation by transition metal insertion into nucleophile-hydrogen bond

The third mechanism involves the activation of the nucleophile by insertion of the transition metal species into the nucleophile-hydrogen bond. Allene insertion, which may occur on either of the double bonds, into the nucleophile-metal bond, followed by reductive elimination, leads to the formation of heterocycles with varying ring sizes **2.9** to **2.11**.

A diverse range of nucleophiles have been applied successfully to the allene cyclisation reaction utilising a number of different transition metals.[92,94] Besides the use of oxygen nucleophiles (alcohols, ketones, carboxylic acids and oximes) and nitrogen nucleophiles (amines, amides, carbamates, imines, and sulfonamides), the synthetic utility of carbon nucleophiles such as alkenes, alkynes and activated C-H bonds have also been demonstrated (**Scheme 2.4**). The regioselectivity of the nucleophilic attack depends to a large part on the length of the tether connecting the allene and nucleophile, with the formation of five- or six-membered rings preferred, although larger ring sizes have also been reported.[95]

The 5-*endo*-trig cyclisation of allenic carboxylic acids[96] **2.20** to butenolides **2.21** and 6-*endo*-trig cyclisation of allenic amides[97] **2.22** to lactams **2.23** proceed via the first mechanism **(Scheme 2.1**), where the allene double bond is activated by metal coordination. While 5-*endo*-trig cyclisations are generally disfavoured by Baldwin's rules,[98] the 5-*endo* cyclisation of allenes bearing nucleophiles in the α-position has been well established since the early work of Olsson[99] and Marshall.[100]

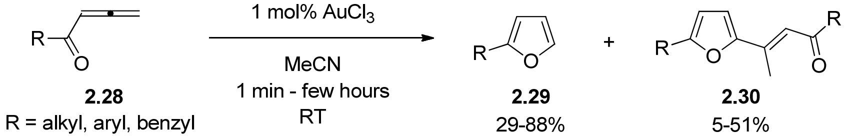
The acylation-cyclisation of γ-substituted allenes[101] **2.24** to functionalised pyrrolidines **2.25** proceeds via the second mechanism (**Scheme 2.2**) as the acyl cobalt carbonyl species inserts initially into the allene to form an η^3-allyl complex before cyclisation to the five-membered ring occurs. Lastly, the third mechanism (**Scheme 2.3**) is exemplified by the formation of cyclic ether[102] **2.27**, as the requisite carbon nucleophile is activated by Pd complex insertion into the C-H bond prior to addition to the allenic system.



Scheme 2.4 Examples of allene cyclisation with different nucleophiles

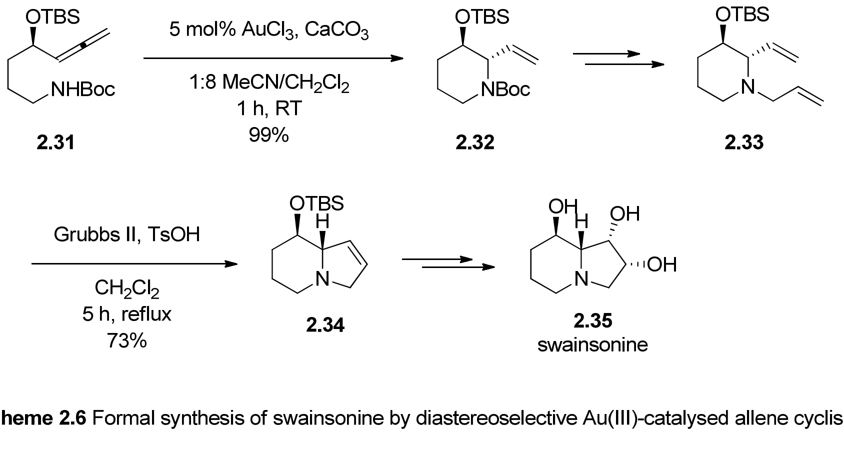
2.1.2 Gold-catalysed nucleophilic cyclisation of allenes

While the early reactions were catalysed mostly by Pd(II), Pd(0) and Ag(I) species, the use of gold catalysts for the cyclisation of allenes only gained prominence after Hashmi *et al.*[103] demonstrated the synthesis of substituted furans via the cycloisomerisation of α-allenyl ketones with $AuCl_3$ (**Scheme 2.5**). Although the formation of by-product **2.30**, a result of Michael addition between the newly formed furan and the unconsumed allenic ketone, was a serious drawback for the reaction, it was observed that the Au(III)-catalysed reaction could occur with lower catalyst loading and much shorter reaction times than the corresponding Ag(I) or Pd(II)-catalysed reaction. The formation of the undesired dimerisation product **2.30** was eventually eliminated by Che and co-workers[104] by the employment of a cationic Au(III) porphyrin for the cyclisation.



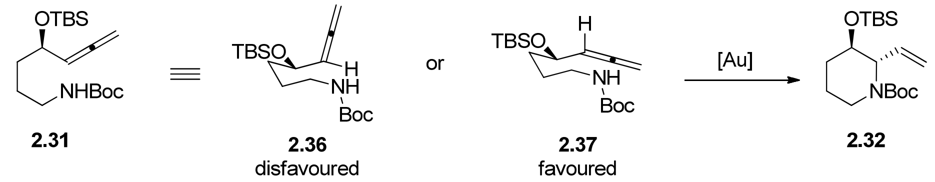
Scheme 2.5 First gold-catalysed nucleophilic cyclisation of allenes

Following the observations of Hashmi, numerous groups began utilising Au(I) and Au(III) species in the catalysis of allene cyclisations and advances in the field have been summarised in several publications.[105] Due to their soft and carbophilic nature, gold catalysts can selectively activate allenes in the presence of other functionalities.[106] In addition, the lack of backbonding from Au(I) into π-donor ligands due to the high energy of the antibonding orbitals would render the ligands more electron deficient and hence more susceptible to nucleophilic attack.[107] These attributes, combined with the tolerance of gold species towards water and oxygen, makes them attractive catalysts for the nucleophilic cyclisation of allenes.



Scheme 2.6 Formal synthesis of swainsonine by diastereoselective Au(III)-catalysed allene cyclisation

The concept of gold-catalysed nucleophilic cyclisation of allenes was previously applied within our group in the formal synthesis of swainsonine[108] (**Scheme 2.6**). It was envisioned that Pyne's intermediate[109] **2.34** could be accessed via ring-closing metathesis of diene **2.33**, which could be synthesised from 2,3-disubstituted Boc-protected piperidine **2.32**. Gold-catalysed amino cyclisation of α-substituted allene **2.31** was employed successfully to provide α-vinyl piperidine **2.32** as a single diastereomer in excellent yield. It was rationalised that the high diastereoselectivity of the reaction could be attributed to the preference for conformation **2.37** (**Scheme 2.7**), where the allene and the bulky OTBS group are both placed in the equatorial positions to minimise repulsion.

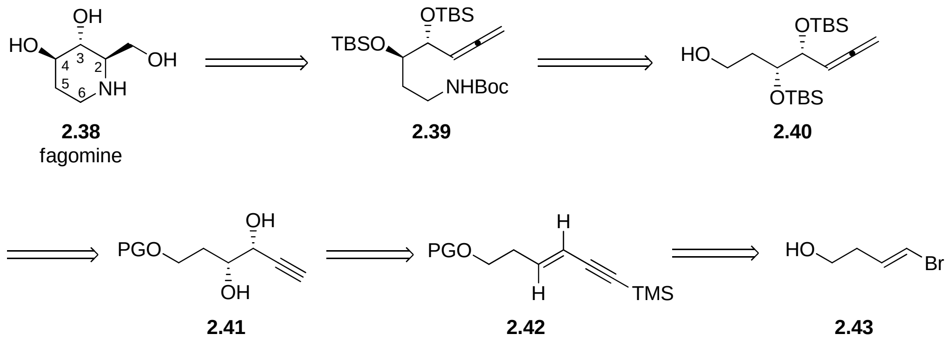


Scheme 2.7 Rationalisation of diastereoselectivity

Encouraged by this result, we were interested in further investigating the synthetic utility of this transformation in the stereoselective synthesis of other five- or six-membered ring alkaloids.

2.2 Synthetic plan towards the synthesis of fagomine

Fagomine **2.38** (**Scheme 2.8**), a polyhydroxylated piperidine with three contiguous chiral centres *trans* to each other, was chosen for synthesis due to its structural features. We envisioned that the 2,3-*trans* relationship of fagomine could be accessed via a gold-catalysed nucleophilic cyclisation of allene **2.39**, based on the observations gained from the formal synthesis of swainsonine. The requisite Boc-protected nitrogen nucleophile could be obtained from the corresponding allene alcohol **2.40**, which could be synthesised from alkyne **2.41** via a Searles-Crabbé homologation.[86] The 1,2-diol could be installed via asymmetric dihydroxylation[110] of enyne **2.42**, which could be synthesised by Sonogashira coupling of TMS-acetylene with vinyl bromide **2.43**.



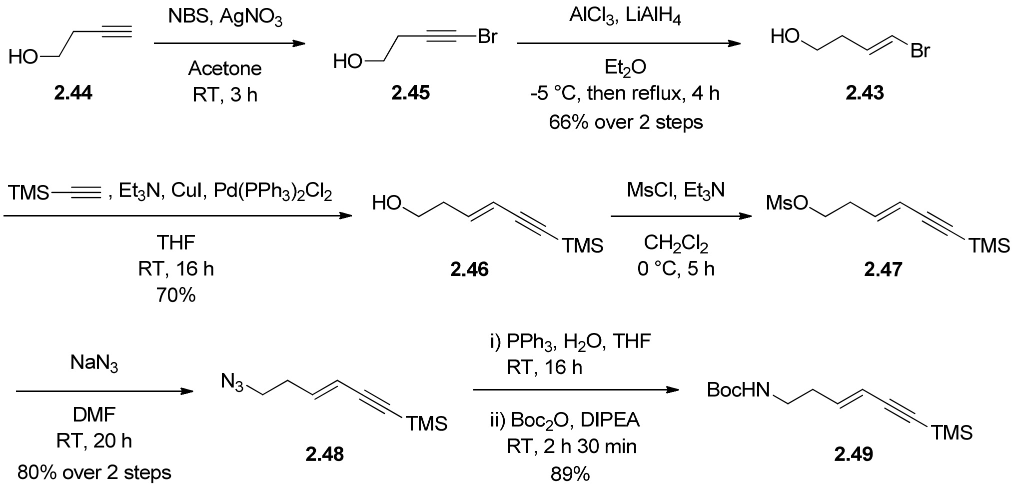
Scheme 2.8 Retrosynthetic analysis of fagomine

2.3 Results and discussion

2.3.1 Synthesis of 2-*epi*-fagomine

The synthesis of enyne **2.49** (**Scheme 2.9**), a substrate for dihydroxylation, commenced with vinyl bromide **2.43**, which was prepared from homopropargyl alcohol **2.44** via a two-step procedure as reported by Yadav.[111] Terminal bromination of homopropargyl alcohol **2.44** with NBS and $AgNO_3$ as catalyst in acetone proceeded cleanly to give 4-bromo-3-butyn-1-ol **2.45**, which was reduced directly with alane, generated *in situ* from $AlCl_3$ and $LiAlH_4$,[112] to provide the desired *trans* vinyl bromide **2.43** in 66% yield over 2 steps.

Sonogashira coupling,[113] a cross-coupling reaction between terminal alkynes and aryl or vinyl halides catalysed by palladium and copper in the presence of an amine base, was then employed to construct enyne **2.46**. Copper(I) salts are employed in the coupling reaction to activate the alkynes for transmetallation to palladium via the formation of copper(I) acetylides. As the use of copper can also lead to the formation of homocoupling products of the alkyne under oxidative conditions, a process referred to as the Glaser coupling,[114] it is essential that the Sonogashira reaction is conducted under an inert atmosphere to minimise this undesired dimerisation. The ^{1}H NMR spectrum of enyne **2.46** indicated coupling constants of 16.1 Hz between the alkene protons, hence confirming the *trans* geometry of the double bond.

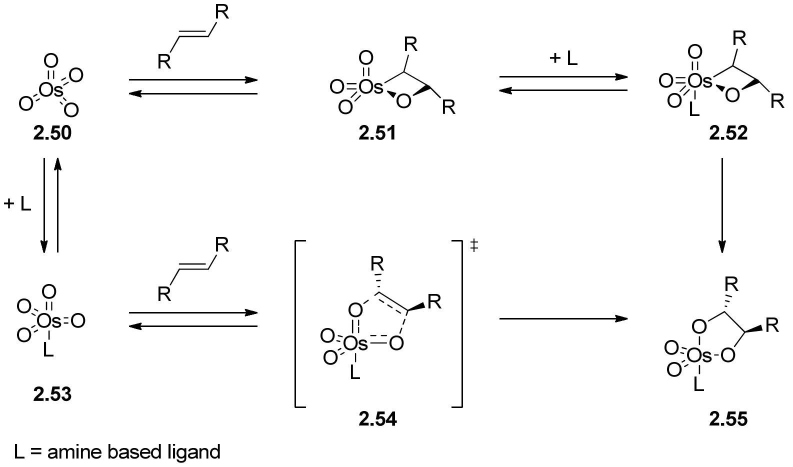


Scheme 2.9. Synthesis of (*E*)-*tert*-butyl (6-(trimethylsilyl)hex-3-en-5-yn-1-yl)carbamate

Mesylation of primary alcohol **2.46**, followed by displacement with NaN_3 in DMF at ambient temperature, provided azide **2.48** in 80% yield over 2 steps. Azide **2.48** was stable and could be stored at ambient temperature for days without observation of cyclisation by-products. One-pot reduction of the azide under Staudinger[115] conditions, followed by treatment with Boc anhydride in the presence of a base, provided enyne

2.49 in 89% yield. The Staudinger reduction was utilised as hydrogenation conditions would be incompatible with the enyne system. The one-pot azide reduction-Boc protection sequence also proceeded to give enyne **2.49** using Zn in the presence of NH_4Cl,[116] albeit in a modest yield of 43%.

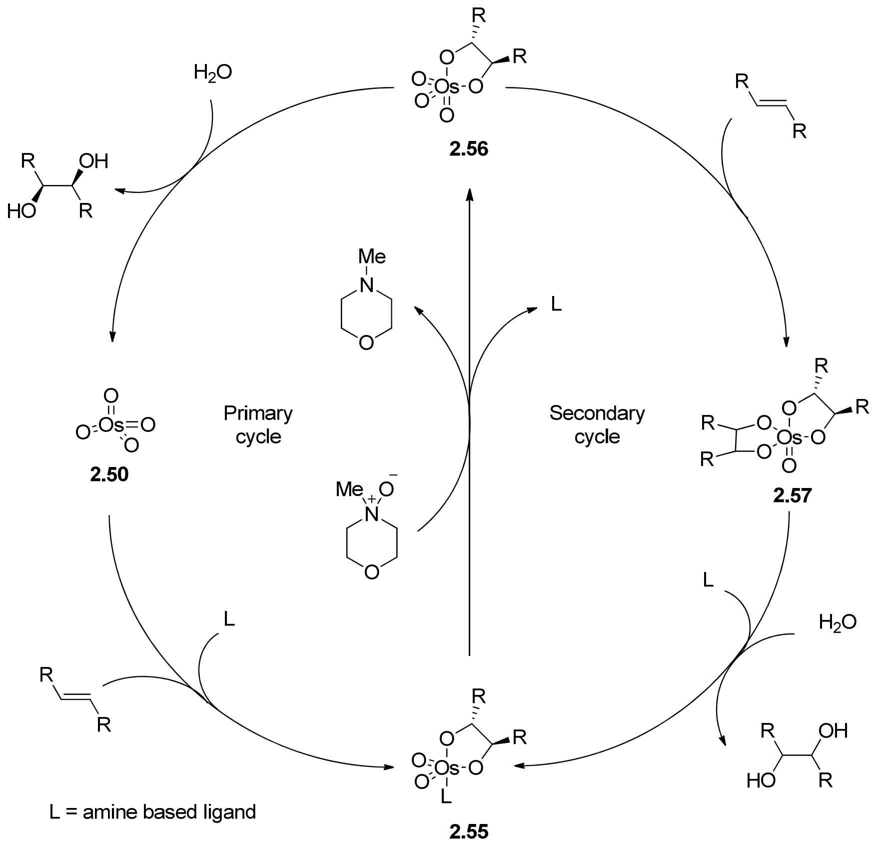
The oxidation of alkenes to vicinal diols using OsO_4 is considered as one of the most selective and reliable transformations in organic synthesis.[117] While the initial reaction conditions developed by Criegee[118] utilised stoichiometric amounts of OsO_4, the high cost and toxicity of the reagent led to the development of catalytic versions of the reaction. The use of relatively inexpensive reagents such as sodium or potassium chlorate,[119] hydrogen peroxide (Milas hydroxylation[120]), *N*-methylmorpholine *N*-oxide (Upjohn dihydroxylation[67]) and potassium hexacyanoferrate(III) (Tsuji dihydroxylation[121]) as stoichiometric oxidants for the reoxidation of Os(VI) allowed the use of diminished amounts of OsO_4, as well as other sources of Os such as K_2OsO_4, which greatly increased the synthetic utility of the transformation.



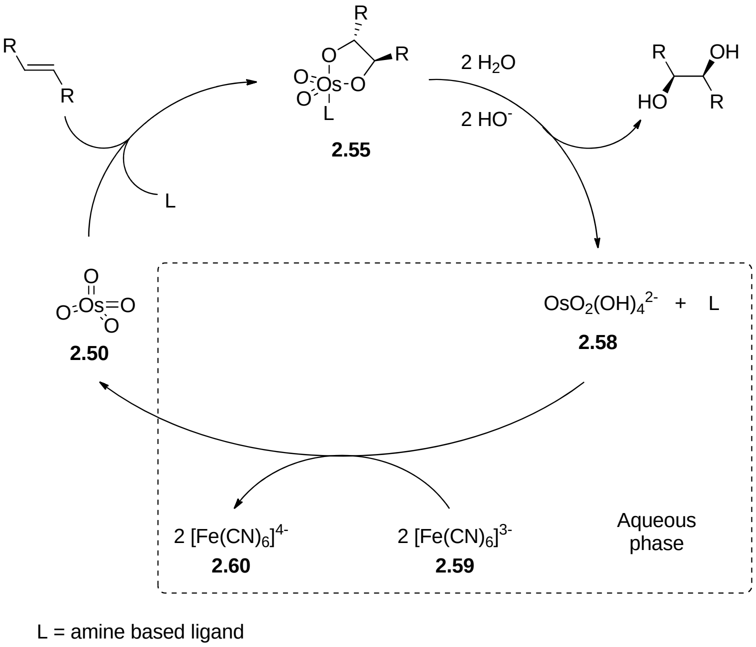
Scheme 2.10 Proposed mechanism for osmylation of alkene

In the case of catalytic asymmetric dihydroxylation, the ligand in the catalytic cycle is typically a *bis*-cinchona alkaloid derivative. The utilisation of such a ligand has it roots in the observed amine accelerated osmylation of alkenes by Behrman *et al.,*[122] a concept which was later extended by Sharpless to cinchona alkaloids[123] in the first reported asymmetric dihydroxylation of alkenes. The mechanism for the formation of Os(VI) ester **2.55** (**Scheme 2.10**), a key species in the catalytic cycle, was heavily debated in the early days with Sharpless proposing a stepwise [2+2] mechanism[124] via an osmaoxetane intermediate **2.51**, while Criegee[118] and later Corey[125] favoured the concerted [3+2] mechanism that directly produced the Os(VI) ester **2.55** via transition state **2.54**. While each group provided various experimental and computational studies in support of their mechanism,[126] the debate was only concluded in 1997 when Houk and Singleton *et al.*[127] provided experimental and theoretical evidence in support of the [3+2] mechanism via the study of kinetic isotope effects. A comprehensive account of the elucidation of the mechanism has been succinctly summarised by Noe *et al.*[128] in a book chapter.

Whilst the mechanism for the formation of Os(VI) ester **2.55** was a subject of debate, the mechanism for catalytic turnover was more straightforward.[128] The accepted catalytic cycle (**Scheme 2.11**) proceeds via the formation of Os(VI) ester **2.55**, which is oxidised by co-oxidants, in this instance *N*-methylmorpholine *N*-oxide, to the Os(VIII) ester **2.56**. Hydrolysis of ester **2.56** then provides the chiral diol product and returns the osmium species into the catalytic cycle. However, in examples where the hydrolysis step is slow, the Os(VIII) ester **2.56** can undergo addition with another molecule of alkene to form a *bis*-diol ester intermediate **2.57**, which subsequently undergoes hydrolysis, to provide a diol with diminished enantioselectivity due to the lack of facial selectivity in the alkene addition step. This secondary cycle has been well studied[129] and it has been concluded that in addition to poor enantioselectivity, the extremely slow hydrolysis of *bis*-diol ester intermediate **2.57** often leads to a lower reaction rate.[130] The secondary cycle could be suppressed by use of stoichiometric amounts of tetraalkylammonium acetate to accelerate the hydrolysis of osmate ester **2.56** or slow addition of the alkene substrate.[128]



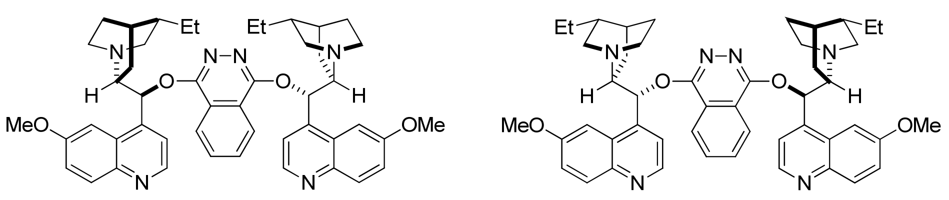
Scheme 2.11 Catalytic cycle for dihydroxylation under Upjohn conditions



Scheme 2.12 Catalytic cycle for dihydroxylation under Tsuji conditions

The $K_3Fe(CN)_6$-K_2CO_3 conditions developed by Tsuji[121] now provide the method of choice for asymmetric dihydroxylations, as the biphasic conditions utilising inorganic oxidant in *t*-BuOH/H_2O solvent system precludes the secondary cycle,[131] thereby excluding the pathway for deterioration of enantioselectivity. The Os(VI) ester **2.55** (**Scheme 2.12**) is hydrolysed under basic conditions to provide chiral diol and Os(VI) species **2.58**, which is reoxidised in the aqueous phase by $[Fe(CN)_6]^{3-}$ **2.59** before returning into the catalytic cycle as OsO_4 **2.50**. The separation of the dihydroxylation step, which occurs in the organic phase, from the hydrolysis and reoxidation processes which occur in the aqueous phase, effectively negates the formation of the secondary catalytic cycle.

Since the first asymmetric dihydroxylation of alkenes reported by Sharpless and Hentges,[123] the development of highly efficient and enantioselective ligands for the catalytic asymmetric dihydroxylation has come a long way[110,128] and the most commonly employed ligands at present are $(DHQD)_2PHAL$ **2.61** and $(DHQ)_2PHAL$ **2.62** (**Figure 2.3**).



2.61
$(DHQD)_2PHAL$
Ligand in AD-mix-β

2.62
$(DHQ)_2PHAL$
Ligand in AD-mix-α

Figure 2.3 Common *bis*-cinchona alkaloid derived ligands for asymmetric dihydroxylation

These ligands afford high enantioselectivities for a broad substrate scope: terminal, 1,1-disubstituted, *trans*-1,2-disubstituted, trisubstituted and tetrasubstituted alkenes, and hence are good choices for exploring enantioselective dihydroxylation of a new substrate.[132] The widespread application of these ligands has led to their commercial availability as pre-mixes containing K_2OsO_4, $K_3Fe(CN)_6$ and K_2CO_3 as AD-mix-α (containing $(DHQ)_2PHAL$ **2.62**) and AD-mix-β (containing $(DHQD)_2PHAL$ **2.61**) for ease of use. The decision of which ligand to use is governed by the desired direction of hydroxyl addition and this can be easily determined by applying the mnemonic developed by Sharpless (**Figure 2.4**).[132]

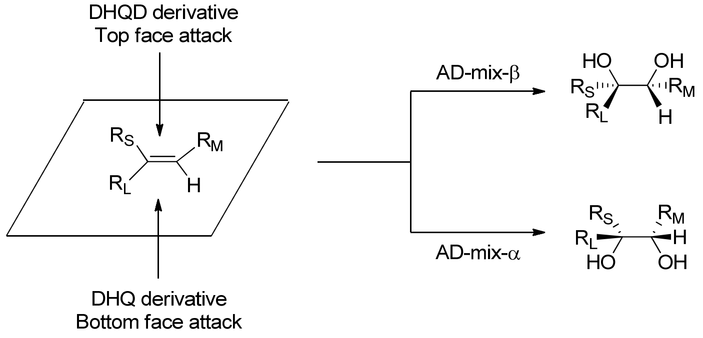
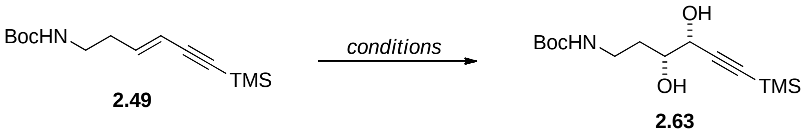


Figure 2.4 Mnemonic for the determination of ligand for dihydroxylation

The OsO_4 catalysed dihydroxylation was our reaction of choice to install the 3,4-diol of fagomine. As we had initially planned to work out the downstream chemistry with the racemic diol, Tsuji dihydroxylation conditions were applied to enyne **2.49** (**Table 2.2**, entry 1). To our surprise, the dihydroxylation reaction was very sluggish and provided the desired diol **2.63** in only 24% yield after 48 hours, with majority of the starting material being recovered. As we had suspicions that the sluggish reaction could be due to the slow hydrolysis of the intermediate Os(VI) ester leading to the low turnover of catalyst, methanesulfonamide was added[132] (**Table 2.2**, entries 2-3). However, this did not lead to an improvement of the reaction, even with the addition of an extra 5 mol% of the osmium catalyst (entry 3).

With the disappointing results, we then attempted the dihydroxylation reaction with Upjohn conditions (**Table 2.2**, entries 4-6). In contrast to the Tsuji conditions, the dihydroxylation proceeded rapidly (entry 4) with the complete consumption of starting material. However, the reaction gave multiple products and only provided the desired diol in 25% yield. In an attempt to minimise the side reactions, the reaction was conducted at a lower temperature (entry 5) and with portionwise addition of the oxidant (entry 6). Unfortunately, these changes did not provide a cleaner reaction mixture and only gave a marginal improvement in the reaction yield. As it has been reported that a possible by-product of the reaction is the α-hydroxy ketone,[133] which is generated via the over-oxidation of the diol, we then attempted the reaction with lesser amounts of oxidant and in the presence of a base (entry 7), which was reported to minimise the formation of the by-product.[134] The addition of 2,6-lutidine did improve the reaction yield to 45%, although the reaction did not go to completion.



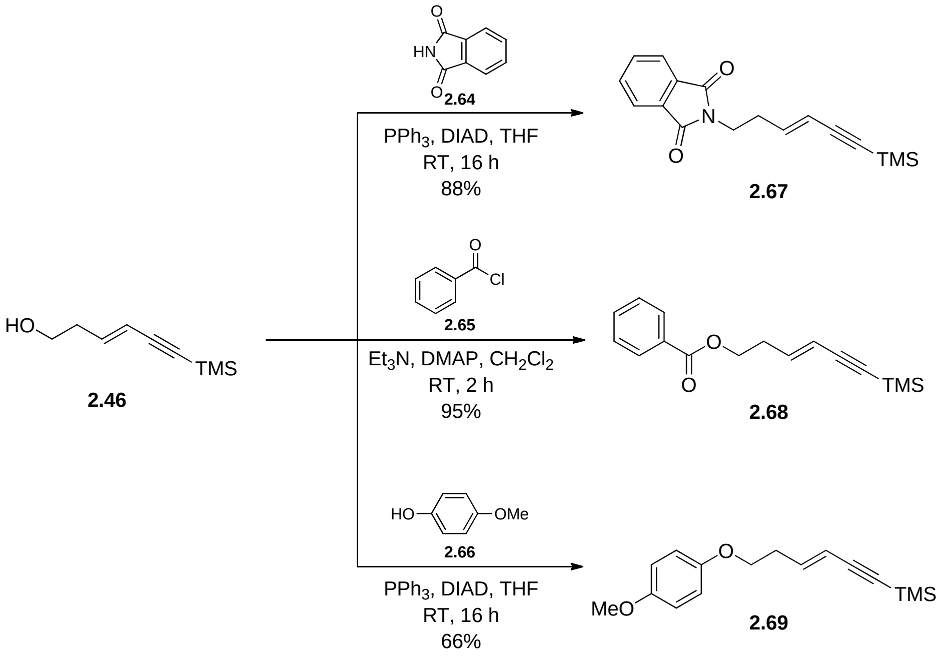
Entry	Osmium Loading	Oxidant	Base	Additive	Temp.	Time [h]	Complete Conversion	Isolated Yield [%]
1[a]	5 mol%	$K_3Fe(CN)_6$ (3 eq.)	K_2CO_3 (3 eq.)	--	RT	48	No	24
2[a]	5 mol%	$K_3Fe(CN)_6$ (3 eq.)	K_2CO_3 (3 eq.)	$MeSO_2NH_2$ (1 eq.)	RT	24	No	29
3[a]	2 x 5 mol%	$K_3Fe(CN)_6$ (3 eq.)	K_2CO_3 (3 eq.)	$MeSO_2NH_2$ (1 eq.)	0 °C RT	24 48	No	25
4[b]	5 mol%	NMO (3 eq.)	--	$MeSO_2NH_2$ (1 eq.)	RT	6	Yes	25
5[b]	5 mol%	NMO (3 eq.)	--	$MeSO_2NH_2$ (1 eq.)	0 °C	16	Yes	33
6[b]	5 mol%	NMO (2 x 1.5 eq.)	--	$MeSO_2NH_2$ (1 eq.)	0 °C RT	6 16	Yes	32
7[c]	5 mol%	NMO (1.5 eq.)	2,6-lutidine (2 eq.)	--	RT	24	No	45

[a] solvent 1:1 *t*-BuOH/H_2O, [b] solvent 9:1 THF/H_2O, [c] solvent 10:1 acetone/H_2O

Table 2.2 Racemic dihydroxylation conditions attempted

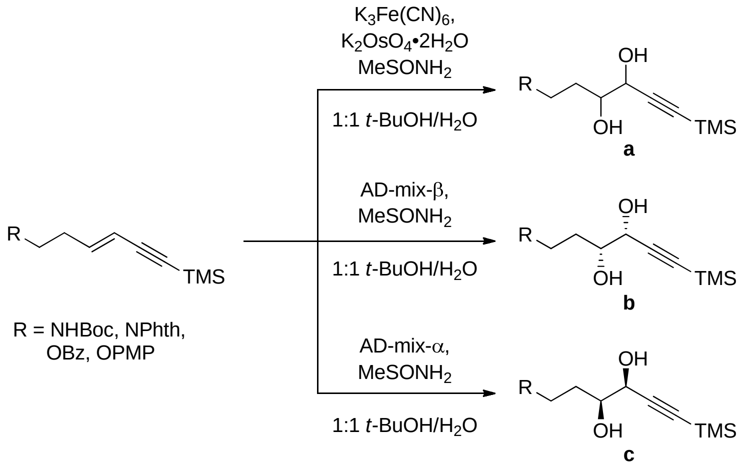
The poor results attained from the various dihydroxylation conditions attempted led us to doubt whether the enyne **2.49** was a suitable substrate for dihydroxylation. Interestingly, a search on Scifinder® (conducted in early 2010) for examples of dihydroxylation of similar substrates yielded only four publications,[128,135] of which all were homoallylic enynols and none were protected amines. While it was consistent throughout the four publications that low to moderate yields and sluggish reactions were observed, the publication by Caddick *et al.*[135a] caught our attention due to the close structural resemblence of the substrates reported to enyne **2.49**. In investigating the Sharpless asymmetric dihydroxylation of various homoallylic enynols, Caddick *et al.* concluded that the reaction was sensitive to the hydroxyl protecting group utilised, with acetate, TBS, TIPS, TBDPS giving low yields of 24-47% and *para*-methoxyphenyl (PMP) giving good yields of 84-95%. However, little rationalisation was provided for the observed preference for the PMP group.

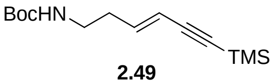
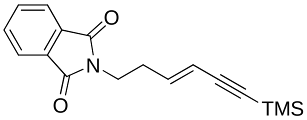
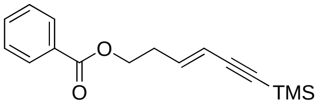
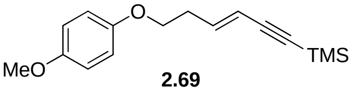
A broader examination of published literature revealed that the asymmetric dihydroxylation of allylic and homoallylic alcohol systems were more well studied and a number of publications elucidated that the use of PMP or *para*-methoxybenzoyl (PMB) protecting groups for such systems often lead to favourable reaction yields and enantioselectivities.[136] With this knowledge in hand, we decided to evaluate a number of different protecting groups in the hope of improving the reaction outcome. In the selection of protecting groups, we took into consideration the preference of the U-shaped catalytic pocket for planar and aromatic functionalities, as these were reported to be able to interact best with the aromatic methoxyquinoline substituents in the binding pocket,[136b] and eventually decided on utilising the *N*-phthalimide, *O*-benzoyl and *O*-PMP groups. We were particularly interested in investigating the use of the *N*-phthalimide group as this would allow us to directly install the nitrogen functionality required. All three substrates were prepared easily from alcohol **2.46** either via Mitsunobu conditions or acylation to give the desired substrates **2.67-2.69** (**Scheme 2.13**) in moderate to excellent yields.



Scheme 2.13 Synthesis of templates for asymmetric dihydroxylation

With the substrates in hand, we proceeded to investigate the asymmetric dihydroxylation reaction with AD-mix-β, as we had rationalised that the $(DHQD)_2PHAL$ **2.61** ligand would provide the chiral diol with the requisite stereochemistry for the synthesis of fagomine. Remarkably, the dihydroxylation results (**Table 2.3**) we obtained utilising AD-mix-β were akin to those observed by Caddick *et al.*.[135a]



		Product		
Entry	**Substrate**	**Tsuji Dihydroxylation[a] Yield [%]**	**AD-mix-β Yield [%]; ee [%]**	**AD-mix-α Yield [%]; ee [%]**
1	 **2.49**	**2.49a** 24[b]	**2.49b** 12[b]; -	NA
2	 **2.67**	**2.67a** 10[b]	**2.67b** 6[b]; 65	NA
3	 **2.68**	**2.68a** 30[b]	**2.68b** 14[b]; 73	NA
4	 **2.69**	**2.69a** 32[b]	**2.69b** 86; 97	**2.69c** 65; 97

[a] Dihydroxylation conditions were similar to those in Table 2.2 entry 1.

[b] Incomplete reaction after 48 hours

NA: Reaction was not carried out

Table 2.3 Dihydroxylation yields with different substrates

While the bulky NHBoc substituent **2.49** provided the corresponding chiral diol **2.49b** (**Table 2.3**, entry 1) in only 12% yield after stirring at ambient temperature for 48 hours, the *O*-PMP substrate **2.69** was converted to the chiral diol **2.69b** (entry 4) with 88% yield after just 24 hours at ambient temperature. However, the observation that the planar *N*-phthalimide substrate **2.67** and *O*-benzoyl substrate **2.68** had reactivities comparable to that of the bulky NHBoc substrate **2.49**, yielding only 6% (entry 2) and 14% (entry 3) of the chiral diol respectively after 48 hours was rather unexpected. In addition, only the *O*-PMP substrate **2.69** proceeded in the asymmetric dihydroxylation to afford chiral diols with high enantioselectivities, while the *N*-phthalimide substrate **2.67** and *O*-benzoyl substrate **2.68** provided the corresponding chiral diols **2.67b** and **2.68b** with poor enantioselectivies of 65% and 73% ee, respectively.

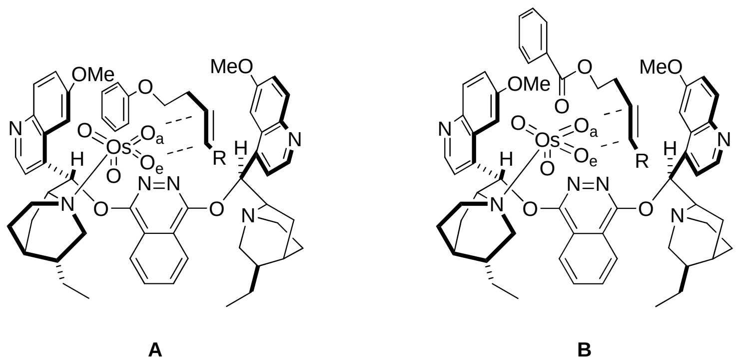
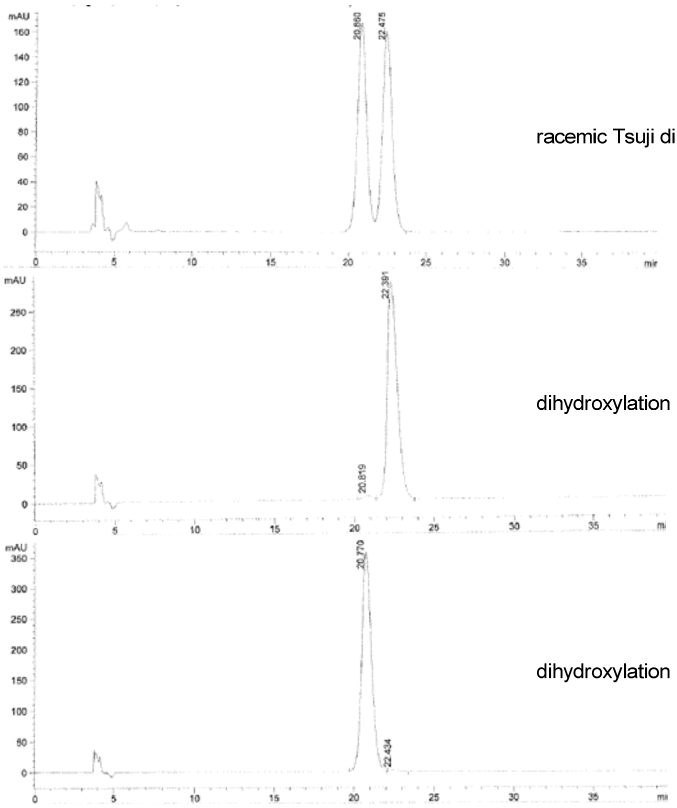


Figure 2.5 U-shaped catalytic pocket and rationalisation of enantioselectivity
*Note: OMe group of PMP omitted in **A** for clarity*

This observed differences in enantioselectivities could perhaps be rationalised using Corey's mechanistic model.[136d] In the model, it is proposed that the ligand, OsO_4 and the olefinic substrate, assemble in a U-shaped pocket, with the two methoxyquinoline units oriented in a parallel fashion (**Figure 2.5**). This arrangement allows an axial oxygen atom (O_a) and an equatorial oxygen atom (O_e) of the complexed OsO_4 unit to be in close promixity to the olefinic bonds, facilitating the [3+2] cycloaddition from one face of the alkene. In the case of *O*-PMP substrate (**Figure 2.5, A**), the preferred arrangement, together with the s-*cis*-allylic geometry to allow the electron rich *para*-methoxyphenyl ring to engage in aryl π-stacking[137] with the two methoxyquinoline substituents in the ligand is accessible, hence dihydroxylation proceeds with high enantioselectivity.

In the case of *O*-benzoyl substrate **2.68**, the preferred s-*cis*-allylic geometry to allow the phenyl ring to participate in aryl π-stacking would cause the ester carbonyl group to be directed in close proximity with the phthalazine nitrogen atoms (**Figure 2.5, B**), leading to unfavourable electrostatic interaction, weaker binding to the catalyst and hence poorer enantioselectivities.[136d] The same argument could be extended to the *N*-phthalimide substrate **2.67**, which with two amide carbonyl groups, could possibly exacerbate the effect, resulting in both lower conversion and enantioselectivity compared to the *O*-benzoyl substrate (**Table 2.3**, entries 2 and 3).



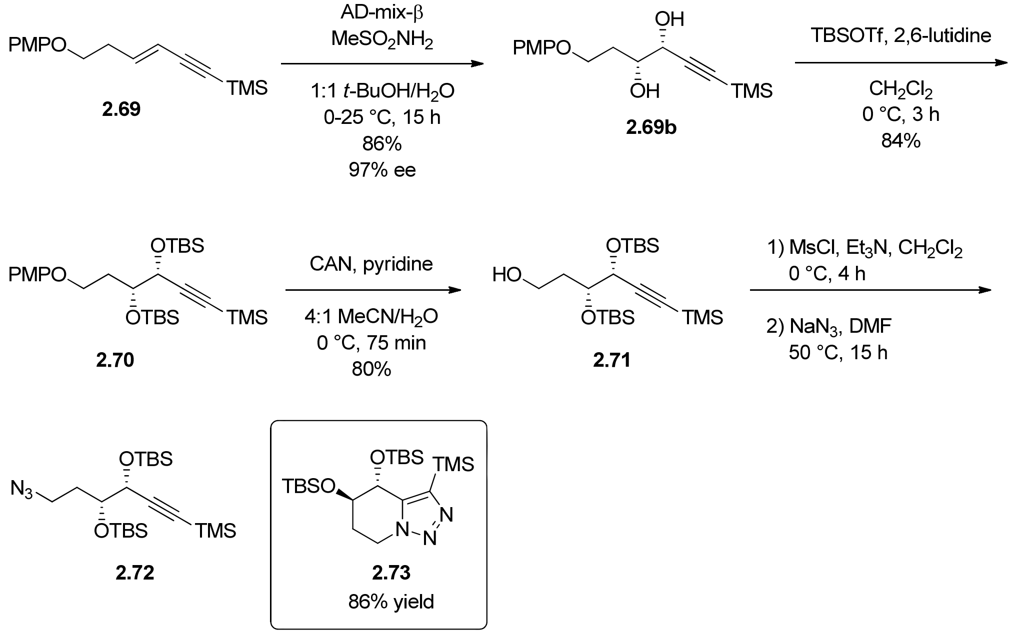
racemic Tsuji dihydroxylation product (**2.69a**)

dihydroxylation product with AD-mix-α (**2.69c**)

dihydroxylation product with AD-mix-β (**2.69b**)

Figure 2.6 Chiral HPLC traces of hydroxylation products of substrate **2.69**

It should be mentioned that the Tsuji conditions were carried out with the aim of providing racemic diols (**2.67a**, **2.68a**, **2.69a**) which were utilised as references for the development of chiral HPLC method for the determination of enantioselectivities. An example (**Figure 2.6**) is illustrated for the enantiomeric excess (ee) determination of *O*-PMP diols **2.69a**, **2.69b** and **2.69c**.



Scheme 2.14 Initial route for the synthesis of cyclisation precursor

With diol **2.69b** in hand, we proceeded with TBS protection of the diol with TBSOTf in the presence of 2,6-lutidine to provide **2.70** in 84% yield (**Scheme 2.14**). Deprotection of the PMP group was initially attempted with CAN in MeCN/H_2O solvent system following literature procedure,[138] however the deprotection did not proceed cleanly and gave the desired product **2.71** in 64% yield with 2 other polar by-products. We hypothesised that the by-products could be due to the concomitant deprotection of one or both of the TBS groups under the acidic reaction condition[138c,139] and proceeded to repeat the reaction with addition of pyridine to increase the pH of the reaction.[140]

Gratifyingly, this modification did allow us to isolate the primary alcohol **2.71** in a good yield of 80% with diminished by-products observed by TLC.

We had envisioned that the amine functionality required for the intramolecular allene cyclisation could be installed via an azide **2.72**. While the mesylation of primary alcohol **2.71** (**Scheme 2.14**) proceeded as expected, the ensuing azide displacement was less straightforward. Treatment of the mesylate with excess NaN_3 in DMF at room temperature led to the formation of a less polar product by TLC with starting material remaining after 16 hours. Heating the reaction at 50 °C led to the clean and complete conversion of the starting material to the less polar product after 24 hours. While the mass spectrometric and ^1H NMR spectroscopic data of the isolated material were consistent with the desired product **2.72**, the IR spectrum indicated an absence of the characteristic 2200 cm^{-1} stretching frequency for an azide. This led us to contemplate whether we had isolated an alternate product. Careful examination of the IR spectrum indicated that in addition to the missing azide stretching frequency, the alkyne stretching frequency (2260 - 2100 cm^{-1}) was also missing. The spectroscopic data led us to postulate that the isolated product could be the fused triazole **2.73**, which can be formed via an intramolecular Huisgen cycloaddition[141] between the newly formed azide **2.72** and the alkyne. Eventual crystallisation of the material by slow evaporation of CH_2Cl_2 provided single crystals suitable for X-ray diffraction and corroborated our proposed fused triazole **2.73** structure (**Figure 2.7**). From the structure, it is observed that the 1,2-*trans*-diol bearing bulky TBS substituents are orientated in a diaxial configuration rather than the preferred equatorial configuration. This could be attributed to the 1,3-allylic strain[142] between the bulky TMS group on the triazole and OTBS group should it be placed in the equatorial position.

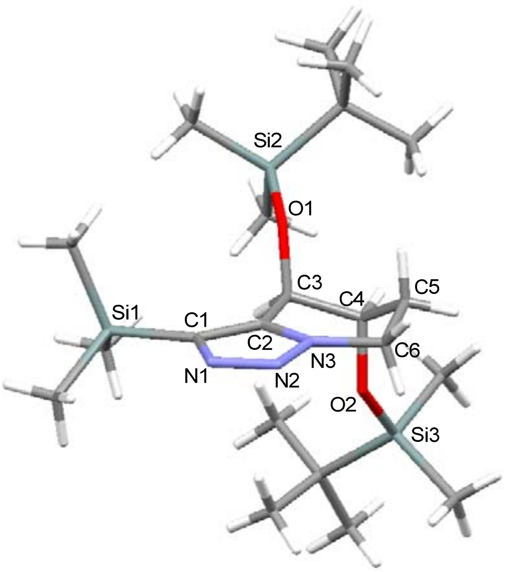
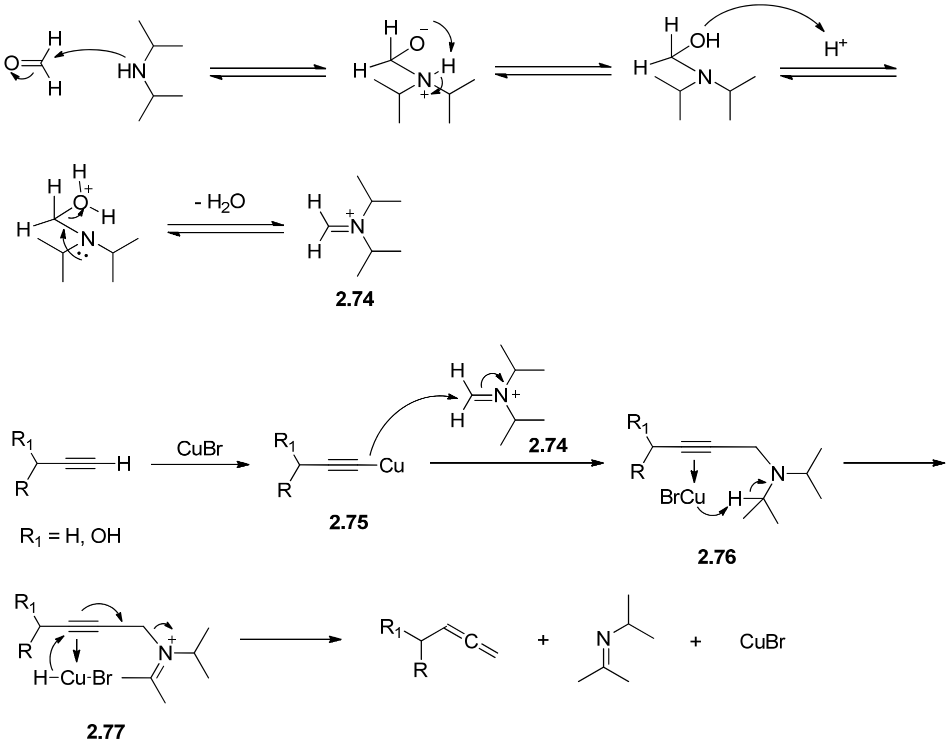


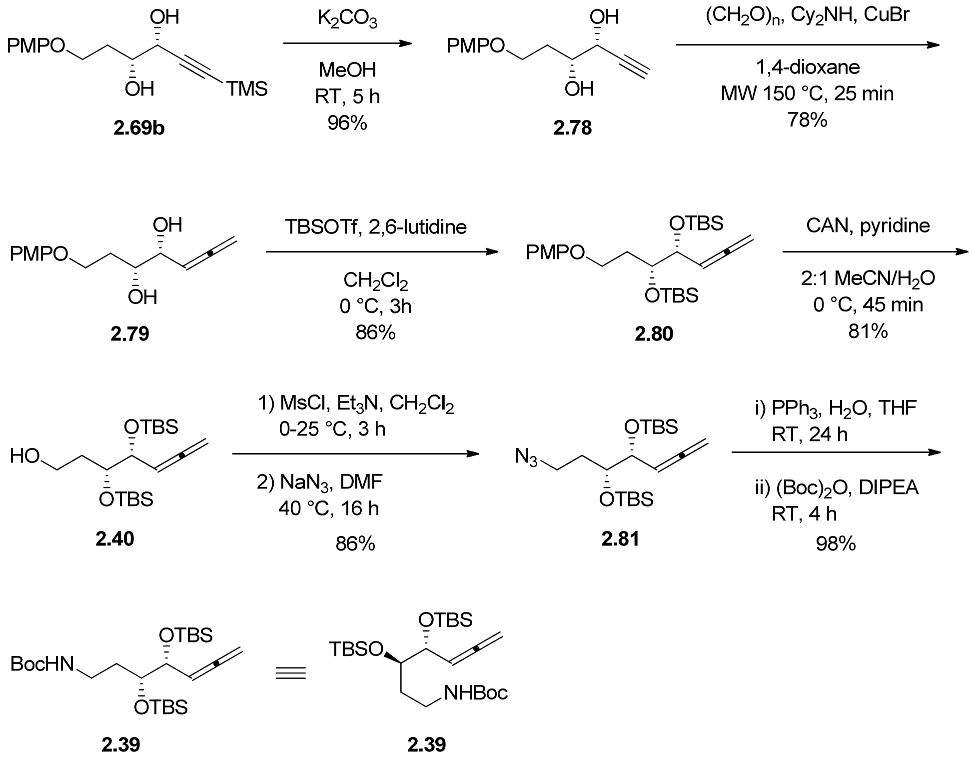
Figure 2.7 X-ray structure of fused triazole **2.73**
Hydrogens, TMS and TBS groups not labelled for clarity

To circumvent the problem of intramolecular Huisgen cycloaddition, we decided to convert the alkyne into the allene prior to installing the azide functionality. This could be achieved by TMS deprotection of alkyne **2.69b** (**Scheme 2.14**) followed by Searles-Crabbé homologation to install the allene.

The Searles-Crabbé homologation[86] is a convenient one-pot procedure for the conversion of terminal alkyne to terminal allene utilising copper(I) bromide, paraformaldehyde, diisopropylamine and the requisite alkyne in refluxing dioxane. The reaction proceeds via a two-step mechanism, which was elucidated by Searles, Crabbé *et al.*[143] through a number of isotope labelling experiments. The reaction first proceeds via a Mannich type condensation between paraformaldehyde and diisopropylamine to provide iminium ion **2.74** (**Scheme 2.15**). Copper acetylide **2.75**, generated by the reaction of alkyne with copper(I) bromide, then adds to the iminium ion **2.74** to provide Mannich base **2.76**. Co-ordination of copper(I) bromide to the alkyne bond followed by hydride abstraction of the α-hydrogen of the *N*-isopropyl group provides the hydridocopper(II) complex **2.77**. Lastly, a 1,5-sigmatropic rearrangement delivers the hydride on the copper complex to the alkyne to provide the allene, with elimination of enamine and regeneration of copper(I) bromide. It was observed that the use of an α-hydroxy substituted alkyne often led to enhanced reactivity and this was attributed to the possible formation of bromide-bridged dicopper chelate which could facilitate electron transfer, leading to enhanced reaction rates.[143]



Scheme 2.15 Mechanism of Searles-Crabbé homologation



Scheme 2.16 Synthesis of precursor for nucleophilic allene cyclisation

Treatment of TMS-alkyne **2.69b** with K_2CO_3 in methanol provided terminal alkyne **2.78** (**Scheme 2.16**), which upon heating at reflux in 1,4-dioxane in the presence of paraformaldehyde, CuBr and dicyclohexylamine, provided allene **2.79** in 75% yield after 6 hours. However, when the reaction was carried out under microwave conditions[144] at 150 °C, allene **2.79** was obtained in comparable yields of 78% after just 25 minutes. The allene **2.79** was characterised by IR spectroscopy (**Figure 2.8**), which indicated the presence of the diagnostic C=C=C asymmetric stretching frequency at 1956 cm^{-1}, and ^{13}C NMR which showed the presence of a peak at 208 ppm, corresponding to the central C atom of the allene moiety. The use of dicyclohexylamine rather than the standard diisoproylamine was influenced by the work of Ma *et al.*,[145] who concluded empirically that dicyclohexylamine was superior to diisopropylamine in their investigation of the homologation. This could be attributed to the higher boiling point of dicyclohexylamine (117-120 °C), compared to diisopropylamine (83-86 °C), being more compatible with the reaction temperatures.

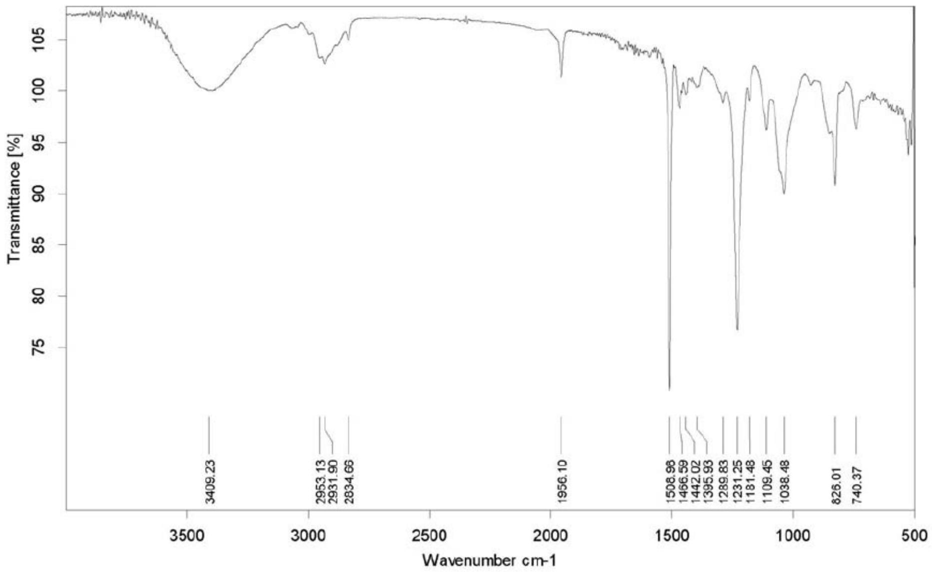
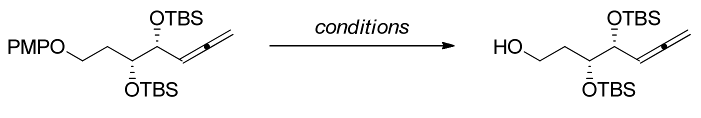


Figure 2.8 IR spectrum of allene **2.79**

Treatment of allene diol **2.79** (**Scheme 2.16**) with TBSOTf in the presence of 2,6-lutidine provided *bis*-TBS protected substrate **2.80**. Deprotection of the PMP group was first attempted with the optimised conditions used previously for the synthesis of **2.71** (**Scheme 2.14**). However the reaction was very sluggish and provided the desired primary alcohol **2.40** in only 44% yield (entry 1, **Table 2.4**), with starting material being recovered along with polar by-products, presumably desilylated material, observed. A longer reaction time (entry 2) led to a more complex reaction profile with only marginal improvement in isolated yield. We hypothesised that the Lewis acidity of Ce(IV)[139b,c] could be catalysing the silyl deprotection and hence we attempted the reaction in a 4:1 THF/H_2O solvent mixture (entry 3), as THF has good cation-complexing ability and should decrease the effective Lewis acidity of Ce(IV).[139b] This however only gave a marginal improvement in the reaction yield and provided little change to the reaction profile.



2.80 **2.40**

Entry	CAN	Additive	Solvent	Temp.	Time [min]	Complete Conversion	By-products Observed	Isolated Yield [%]
1[a]	3.0 eq.[b]	pyridine (4.0 eq.)	4:1 MeCN/H_2O	0 °C	40	No	Yes	44
2	3.0 eq.[b]	pyridine (4.0 eq.)	4:1 MeCN/H_2O	0 °C	90	No	Yes	47
3	3.0 eq.[b]	pyridine (4.0 eq.)	4:1 THF/H_2O	0 °C	40	No	Yes	49
4	2.0 eq.[b]	pH 7 buffer	4:1 MeCN/buffer	0 °C	30	Yes	Yes	52
5	3.0 eq.[c]	pyridine (4.0 eq.)	2:1 MeCN/H_2O	0 °C	30	Yes	No	81

[a]previous optimised conditions, [b]added as solid, [c]added as a solution in H_2O

Table 2.4 Optimisation of PMP deprotection conditions

We then attempted the reaction with pH 7 buffer (entry 4, **Table 2.4**) in the hope of minimising the desilylation by-products, regrettably, this did not improve the reaction and led to a more complex reaction mixture. A measurement of the pH at the end of the reaction indicated the pH of reaction mixture to be around 1 (pH paper), suggesting that the potassium dihydrogen phosphate / sodium hydroxide system was inadequate in buffering the strongly acidic reaction mixture, measured by Parrilli *et al.*[139b] to be about pH 0.2.

Finally, we attempted the slow addition of CAN as a solution in H_2O to the basic reaction mixture containing substrate **2.80** and pyridine, and succeeded in obtaining the desired primary alcohol **2.40** with good yield and observed little by-product formation by TLC (entry 5, **Table 2.4**). We rationalised that the slow addition of CAN to the reaction mixture allows the pH of the mixture to change gradually from weakly basic to acidic, as evidenced by the precipitation of cerium hydroxide at the beginning of the reaction, hence allowing the deprotection of the PMP group to proceed selectively. In addition, the deprotection via single electron transfer appeared to occur quickly, as the orange colour of Ce(IV) initially disappeared quickly upon addition to the reaction mixture to give a colourless solution.

Mesylation of primary alcohol **2.40** (**Scheme 2.16**), followed by azide displacement with NaN_3 in DMF at 40 °C, proceeded to give azide **2.81** with 86% yield over 2 steps with no intramolecular cyclisation by-products being observed. The azide **2.81** was characterised by IR spectroscopy (**Figure 2.9**), which indicated the presence of the characteristic N=N=N asymmetric stretching frequency at 2094 cm^{-1}. Finally, the allene cyclisation precursor **2.39** was obtained in an excellent yield of 98% by application of the one-pot azide reduction-Boc protection conditions previously described (**Scheme 2.9, 2.49**).

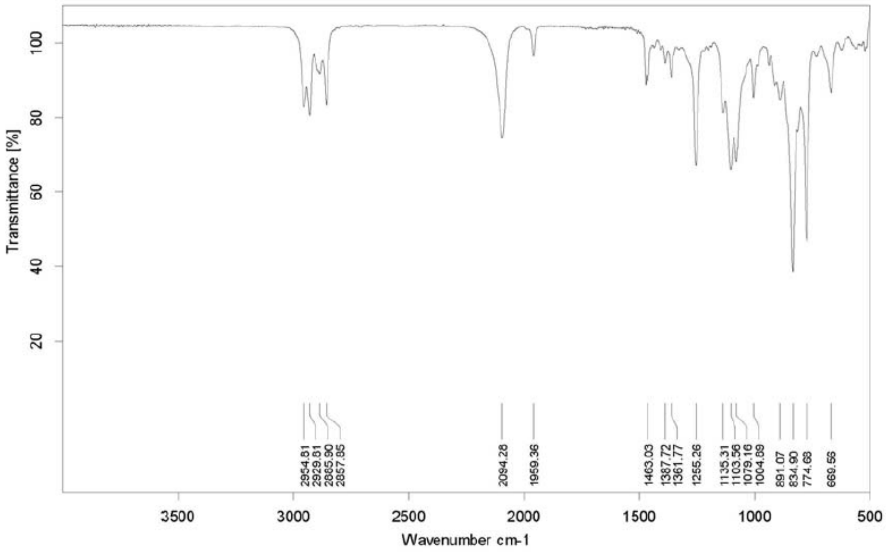
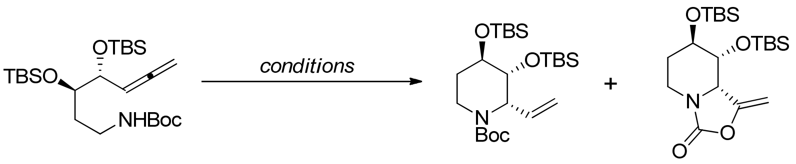


Figure 2.9 IR spectrum of azide **2.81**



2.39 **2.82** **2.83**

Entry	Conditions	Yield	Yield
1	5 mol% $AuCl_3$, $CaCO_3$, 10:1 CH_2Cl_2/MeCN, RT, 4 h	40%	7%
2	6 mol% $Au(PPh_3)Cl$, 6 mol% $AgSbF_6$, $CaCO_3$, CH_2Cl_2, RT, 8 h	85%	0%

Table 2.5 Gold-catalysed allene cyclisation

With N-Boc protected allene **2.39** in hand, we proceeded to attempt the nucleophilic allene cyclisation under the conditions previously utilised in the formal synthesis of swainsonine reported by our group.[108] While the cyclisation proceeded quickly in the case of the monohydroxylated substrate **2.31** (**Scheme 2.6**) giving the cyclised product in 99% yield after 1 hour at ambient temperature, the cyclisation of dihydroxylated substrate **2.39** was comparatively slow and provided the cyclised product **2.82** in 40% yield along with a by-product **2.83** in 7% yield and recovered starting material in 17% yield after stirring at ambient temperature for 4 hours (**Table 2.5**, entry 1). The by-product was initially assigned the gross structure of **2.83** based on ^1H and ^{13}C NMR data, and the structure was later confirmed by X-ray crystallography (**Figure 2.10**) and showed the 2,3-*cis* stereochemistry. It should be added that the by-product **2.83** does not arise from the cyclisation of alkene **2.82**, as re-exposure of alkene **2.82** under the same reaction conditions did not lead to formation of any product even after an extended reaction time of 18 hours.

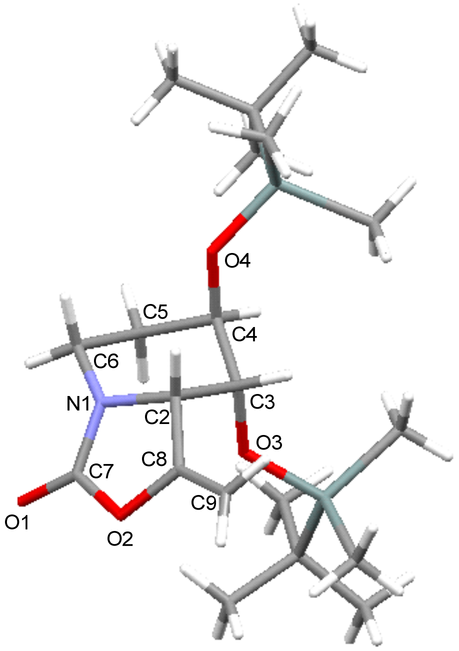
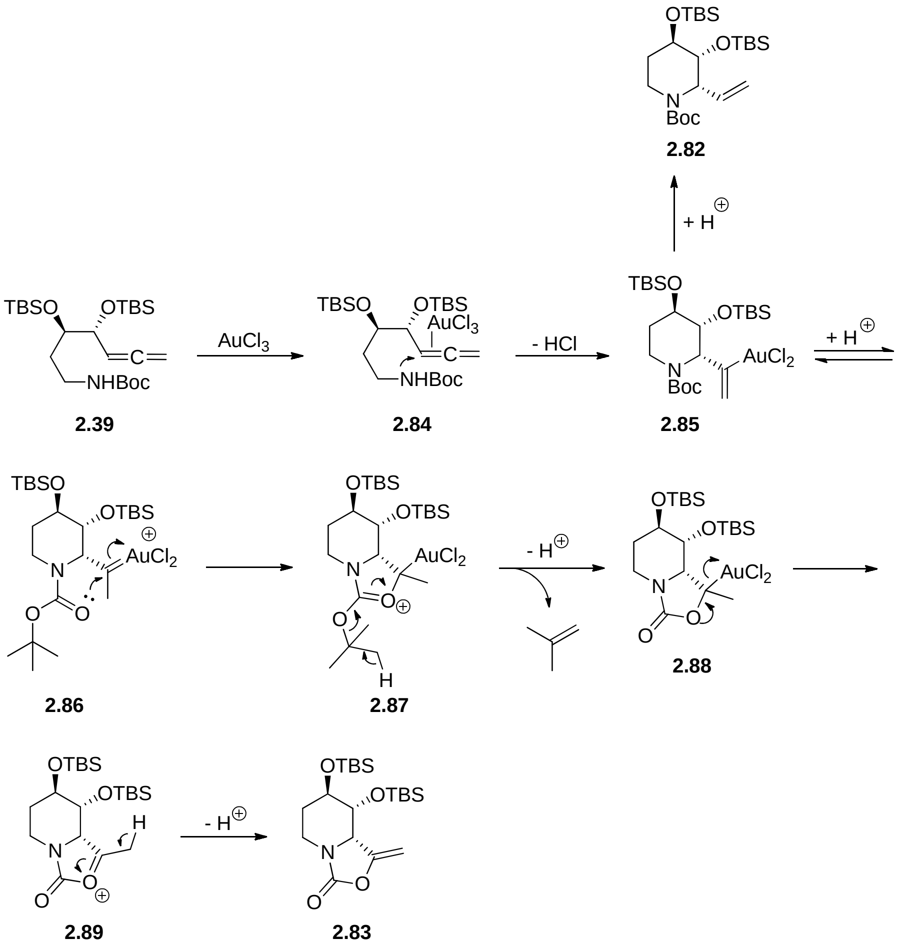


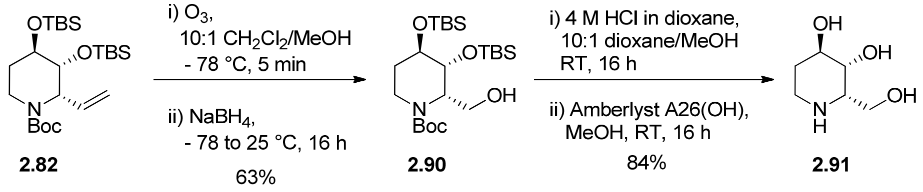
Figure 2.10 X-ray structure of oxazolo-pyridinone **2.83** by-product Hydrogens and TBS group not labelled for clarity

We speculate that by-product **2.83** could be formed via the attack of the Boc carbonyl group on the vinyl gold intermediate, leading to the formation of an exocyclic alkene with net reduction of gold (**Scheme 2.17**). Treatment of allene **2.39** with $AuCl_3$ leads to the formation of coordinated species **2.84**. Nucleophilic addition provides intermediate **2.85**, which can undergo protodemetallation to provide product **2.82** with the regeneration of $AuCl_3$.[146] Alternatively, intermediate **2.85** could undergo rearrangement to give gold carbene species **2.86**. A second nucleophilic attack could then occur via the lone pair of the carbonyl group to give bicyclic product **2.87**. *Tert*-butyl fragmentation[147] to release isobutene and a proton would generate the oxazolidinone **2.88**, which undergoes further rearrangement to give the oxazolidinone by-product **2.83** with concomitant reduction of the Au species.[148] This process is analogous to the double cyclisation of ureas on allenes to form bicyclic imidazolidin-2-ones reported by Widenhoefer,[149] although in that example, reduction of the Au(I) catalyst was not observed and a saturated product was formed. The formation of *exo*-alkylidene oxazolidinones by Au(I)-catalysed cyclisation of Boc-containing alkyne derivatives have also been previous reported.[150]



Scheme 2.17 Proposed mechanism for formation of oxazolo-pyridinone by-product **2.83**

Treatment of NHBoc allene **2.39** with $Ph_3PAuSbF_6$ (**Table 2.5**, entry 2), generated *in situ* by reaction of Ph_3PAuCl with $AgSbF_6$, effected the cyclisation to provide piperidine substrate **2.82** in a good yield of 85% as a single stereoisomer. At this point, we were unable to determine the stereochemistry of the product due to the complex coupling patterns in the ^1H NMR spectrum, but ventured that the cyclisation could have proceeded to give a 2,3-*cis*-stereochemistry based on the X-ray structure of the by-product.



Scheme 2.18 Completing the synthesis of 2-*epi*-fagomine

Oxidative cleavage of alkene **2.82** by treatment with bubbling ozone at - 78 °C, followed by reductive work-up with $NaBH_4$, provided primary alcohol **2.90** (**Scheme 2.18**). Global deprotection proceeded cleanly with aqueous HCl in a 10:1 dioxane/MeOH mixture at ambient temperature and following treatment with basic resin in MeOH, triol **2.91** was isolated as its free base in 53% yield over 2 steps.

Upon inspection of the coupling constants from the ^{1}H NMR spectrum (**Figure 2.11**) of the final compound **2.91**, we observed that H_3 (δ 3.68 ppm) had a double doublet splitting pattern with $J_{3,2}$ = 2.8 Hz and $J_{3,4}$ = 4.8 Hz and H_4 (δ 3.89 ppm) had a double triplet splitting pattern with $J_{4,5}$ = 3.6 Hz and $J_{3,4}$ = 4.8 Hz. The small $J_{3,2}$ coupling constant of 2.8 Hz indicated that H_2 and H_3 were *cis* to each other, confirming that the allene cyclisation had proceeded with *cis* selectivity. In addition, the small $J_{3,4}$ coupling constant of 4.8 Hz indicates that H_3 and H_4 are also *cis* to each other, implying that the diol is indeed oriented in a *trans*-diaxial configuration.

The analysis of the ^{1}H NMR spectrum, together with the comparison of the ^{13}C NMR spectrum and specific rotation for **2.91** with those reported in the literature[54b,54c,58,62] (**Table 2.6**), led us to conclude that the product isolated was that of 2-*epi*-fagomine instead of fagomine.

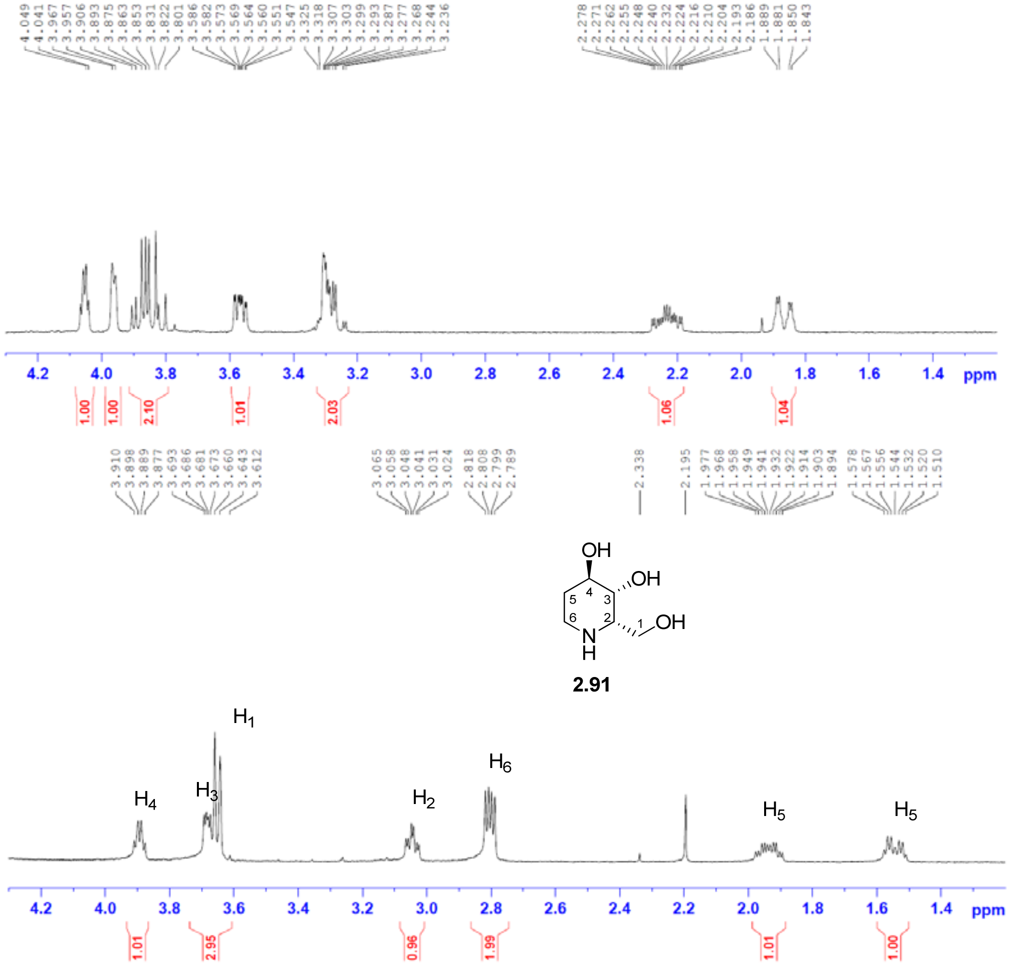
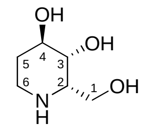
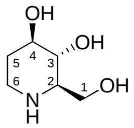


Figure 2.11 ^{1}H NMR (400 MHz, D_2O) of 2-*epi*-fagomine HCl salt (top) and 2-*epi*-fagomine **2.91** (bottom)

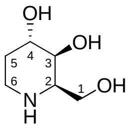
It should perhaps be noted that in the isolation of fagomine isomers from *Xanthocercis zambesiaca*,[26b] Asano and co-workers had assigned the structure of the isolated material as 3,4-di*epi*-fagomine using ^{1}H NMR and NOE experiments. However the reported specific rotation of -8.7 (*c* 0.3, H_2O) was not in agreement with the material obtained via enantioselective synthesis of 3,4-di*epi*-fagomine by two separate groups (**Table 2.6**).[57e,64b] The specific rotation of **2.91** was determined to be -10.6 (*c* 0.32, H_2O) and this is opposite to the value for synthetic 3,4-di*epi*-fagomine **2.92**, which is the enantiomer of 2-*epi*-fagomine. Hence, we conclude that the material originally isolated from *Xanthocercis zambesiaca* should be assigned as 2-*epi*-fagomine.



2.91



2.38
fagomine

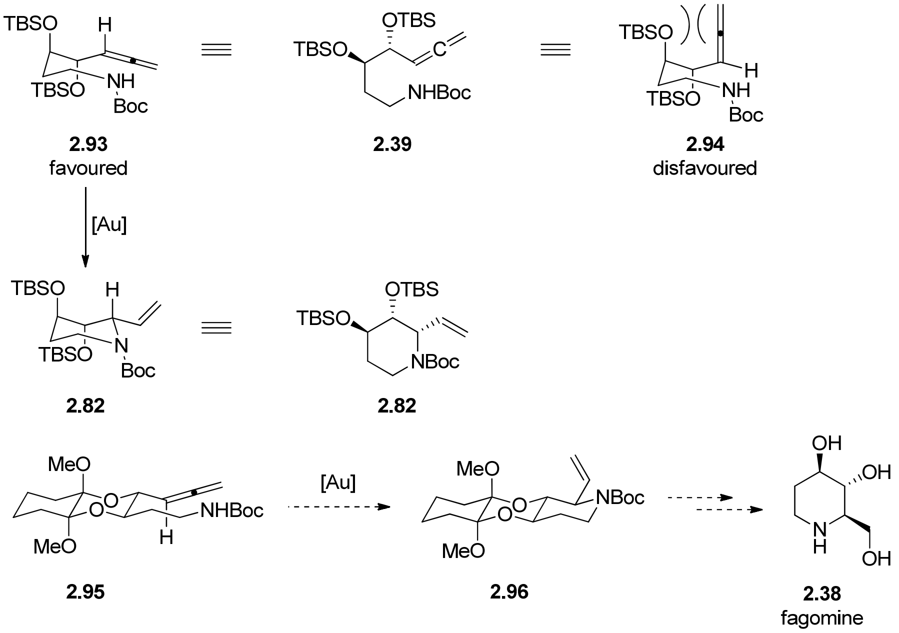


2.92
3,4-di*epi*-fagomine

Analytical Method	Compound			
^{13}C NMR carbon	**2.91**	**2.38**	**2-*epi*-fagomine[26b]**	**2.92[64b]**
1	60.1	64.5	63.3	61.3
2	55.3	63.7	58.2	56.0
3	68.9	76.1	71.0	69.1
4	67.9	76.1	70.0	68.2
5	28.1	35.6	29.9	28.2
6	38.6	45.4	41.4	39.3
Specific rotation $[\alpha]_D$	- 10.6 (*c*, 0.32, H_2O)	+19.5 (*c* 1.0, H_2O)	- 8.7 (*c* 0.3, H_2O)	+13.4 (*c* 0.32, H_2O)

Table 2.6 Tabulation of analytical data for compounds

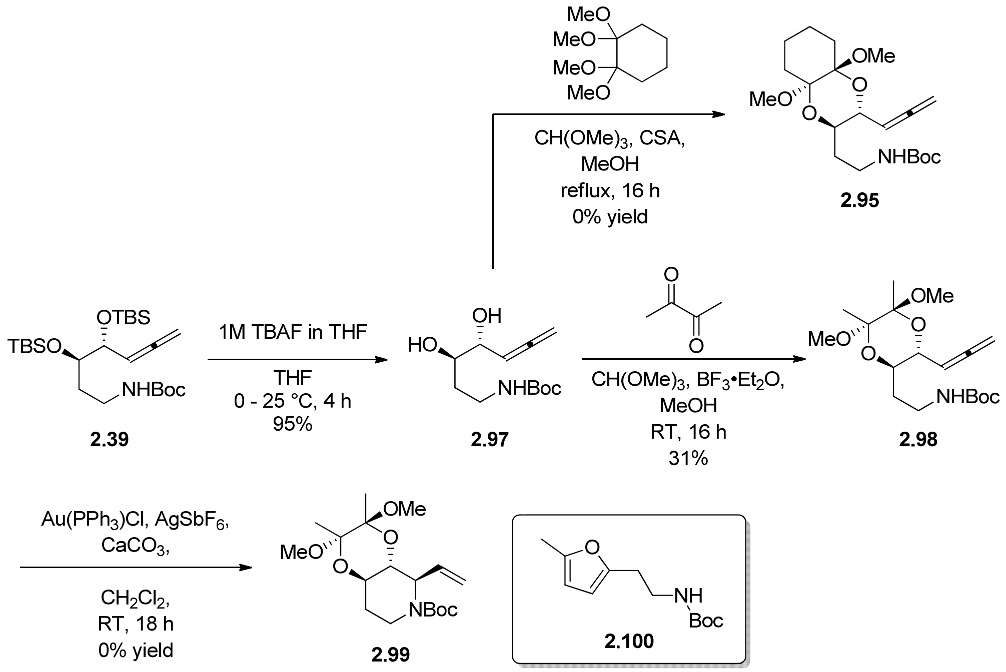
The attainment of 2-*epi*-fagomine rather than fagomine from the synthesis sequence indicates that the allene cyclisation had indeed proceeded to deliver the vinyl group *cis* to the neighbouring siloxy group. This result is opposite to that previously observed for the monohydroxylated substrate **2.31** (**Scheme 2.6**) utilised in the formal synthesis of swainsonine, where the cyclisation proceeded with *trans* diastereoselectivity.[108] We rationalised that this result could arise if the cyclisation precursor **2.39** adopts a *trans*-diaxial configuration, as observed in the X-ray structure of **2.83** (**Figure 2.10**), resulting in the allene to be preferably placed in the equatorial position **2.93** to minimise 1,3-diaxial strain with the bulky OTBS group **2.94** (**Scheme 2.19**). Such an arrangement could be attributed to dipolar effects and Asano and co-workers[26b] had on the basis of NOE, proposed a similar diaxial relationship for the *trans*-diol in 3,4-di*epi*-fagomine, which we have previously concluded to be 2-*epi*-fagomine on the basis of specific rotation. A survey of literature also presented a few examples of polar substituents being oriented in a *trans*-diaxial fashion in substituted cyclohexane ring systems.[151]



Scheme 2.19 Rationalisation of observed stereoselectivity and revised strategy

Based on the rationalisation, we hypothesised that should the diol be oriented in a *trans*-diequatorial fashion **2.95** (**Scheme 2.19**), this could place the allene in the equatorial position and hence deliver the desired 2,3-*trans*-stereochemistry **2.96** upon cyclisation. This led us to turn our attention to the use of cyclohexane-l,2-diacetal, a selective protective group for diequatorial 1,2-diols developed by Ley and co-workers[152] for use in carbohydrate chemistry.

2.3.2 Towards the synthesis of fagomine



Scheme 2.20 Nucleophilic allene cyclisation of diacetal cyclisation precursor

Deprotection of *bis*-TBS protected diol **2.39** with TBAF solution in THF provided diol **2.97** (**Scheme 2.20**) in excellent yield. Unfortunately, treatment of diol **2.97** under acetal formation condition following the procedure of Ley *et al.*[152] did not provide cyclohexane-l,2-diacetal product **2.95**. We then attempted the acetal formation with butanedione, a less rigid aliphatic homologue of cyclohexane-1,2-dione, as an alternative[153] and successfully isolated the desired butanediacetal product **2.98** in 31% yield. Although the yield of the reaction was modest, we were very much interested in testing out the substrate in the gold-catalysed allene cyclisation to validate our hypothesis. Lamentably, butanediacetal product **2.98** reacted very slowly under the Au(I)-catalysed conditions and none of the desired cyclised product **2.99** was obtained. Starting material was recovered, together with the isolation of a less polar by-product.

Inspection of the ^{1}H NMR spectrum of the by-product (**Figure 2.12**) indicated the presence of two aromatic hydrogens (δ 5.84 - 5.92 ppm), two CH_2 groups, a single methyl group (δ 2.24 ppm) and the presence of a Boc group (δ 1.43 ppm). These, together with the absence of the methyl and methoxy groups expected from the butanediacetal protecting group, suggested to us that acetal cleavage had occurred and cyclisation to an aromatic compound could have ensued. Our suspicions were further confirmed when the ^{13}C NMR spectrum indicated the presence of four aromatic carbons, two of which were rather upfield (δ 150 ppm and 151 ppm) and characteristic of a furan.[154] Hence, the structure of the less polar by-product was proposed to be that of furan **2.100**. Further examination of published literature gave weight to our proposed structure as both our ^{1}H and ^{13}C NMR data were in good agreement with those previously reported by Demircan and Parsons.[155]

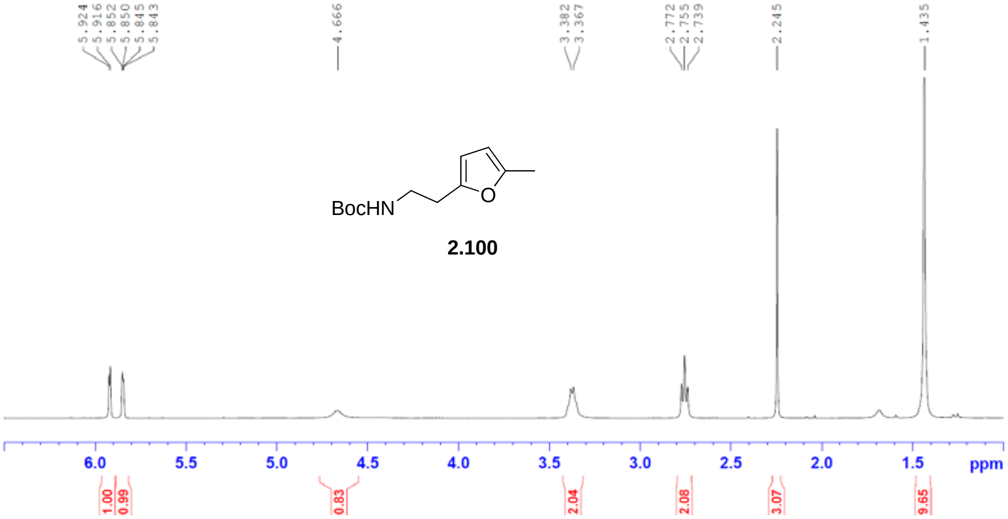
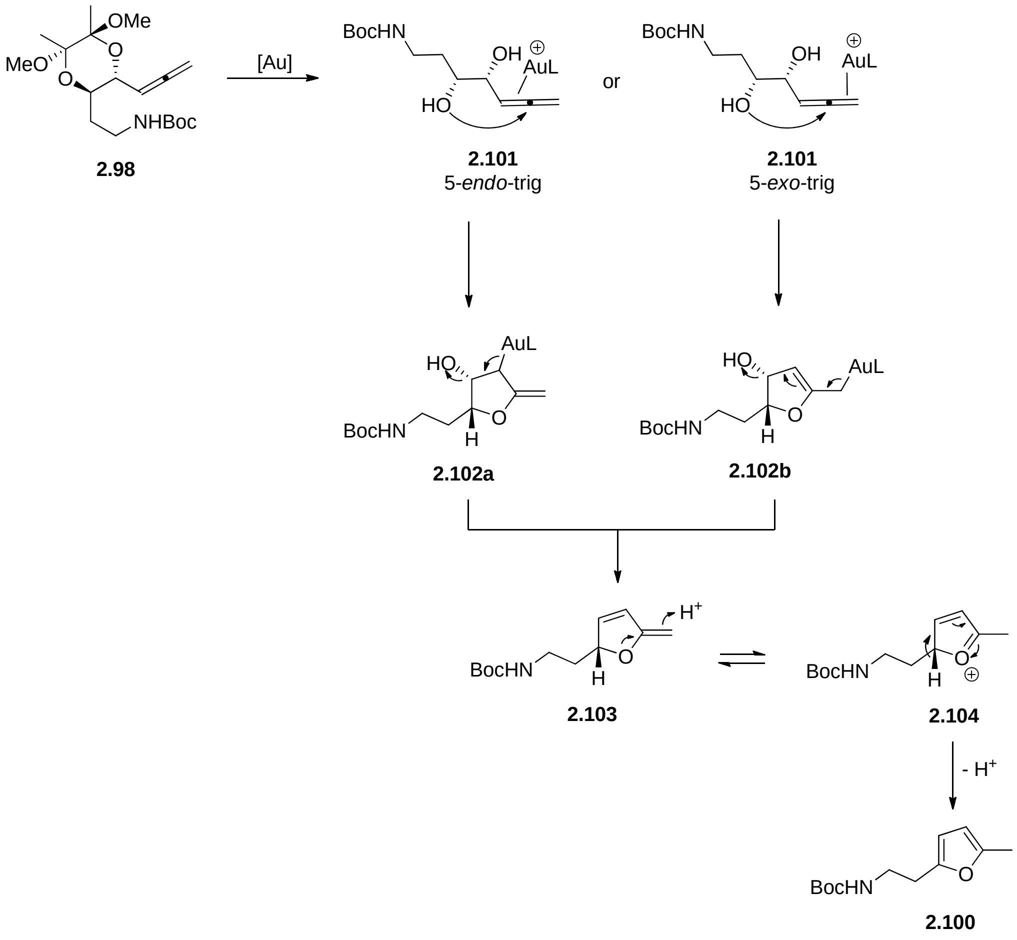
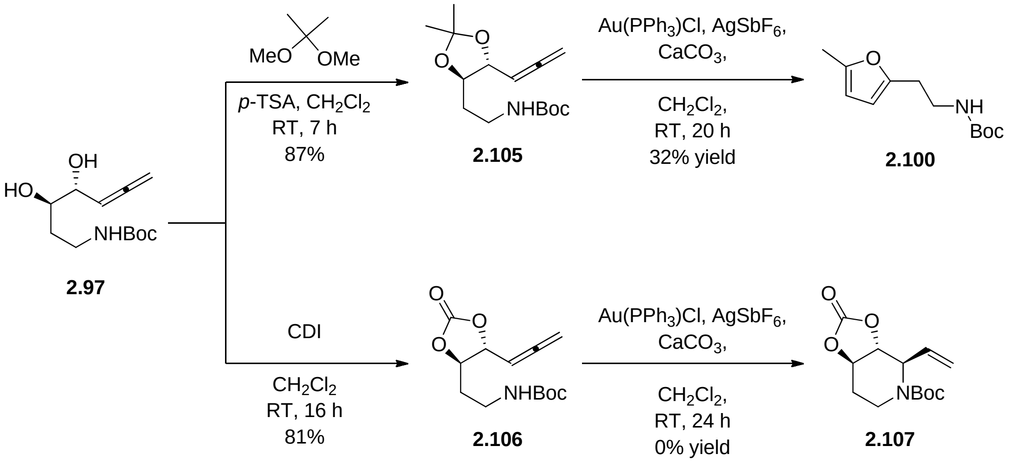


Figure 2.12 ^{1}H NMR (400 MHz, $CDCl_3$) of furan by-product **2.100**



Scheme 2.21 Proposed mechanism for formation of substituted furan by-product **2.100**

We propose that Au(I) could function as a Lewis acid; catalysing acetal hydrolysis to give allene diol **2.101** (**Scheme 2.21**). Upon activation with Au(I), allene diol **2.101** can undergo either a 5-*endo*-trig cyclisation to give 2-methylene tetrahydrofuranyl-gold species **2.102a** or a 5-*exo*-trig cyclisation to give allyl gold species **2.102b**. Elimination of LAuOH gives diene **2.103**, which further isomerises to furan **2.100**, with ring aromatisation as the driving force. With that hypothesis in hand, we proceeded to investigate the use of other less labile protecting groups, with the aim of identifying a suitable substrate for the Au(I)-catalysed cyclisation reaction.



Scheme 2.22 Synthesis of alternate substrates and subsequent allene cyclisation

Synthesis of acetonide **2.105** and carbonate **2.106** proceeded smoothly from diol **2.97** to provide the desired substrates in good yields (**Scheme 2.22**). While the Au(I)-catalysed reaction for acetonide **2.105** was sluggish and provided by-product furan **2.100** along with recovered starting material, the carbonate **2.106** was inert to the reaction conditions even after 24 hours, and was recovered with good mass balance. These results indicated to us that the acetonide is possibly hydrolysed as in the case of butanediacetal substrate **2.98** and the reaction proceeds via the proposed mechanism to afford furan **2.100**. While it was anticipated that carbonate **2.106** would be inert to Lewis acid-catalysed hydrolysis, the unreactivity of the substrate towards allene cyclisation suggests that the carbonate backbone maybe too rigid for the nucleophile to be in close enough proximity with the allene.

2.4 Conclusion

The stereoselective synthesis of 2-*epi*-fagomine was achieved via the utilisation of the Sharpless asymmetric dihydroxylation and the Au(I)-catalysed nucleophilic cyclisation of allene as key steps. Our investigation into the Sharpless asymmetric dihydroxylation of homoallylic enyols led us to conclude that the PMP group is superior to other carbonyl containing protecting groups in providing chiral diols in good yields and excellent enantioselectivity.

In the gold-catalysed nucleophilic cyclisation of allenes, we observed that while the cyclisation proceeds cleanly with Au(I) species, alternate reaction pathways were observed with Au(III). The 2,3-*cis*-stereochemistry provided by the allene cyclisation was opposite to that observed for the analogous monohydroxylated substrate utilised in the formal synthesis of swainsonine, where the cyclisation proceeded with *trans* diastereoselectivity. We rationalised that this could be due to dipolar effects favouring the diaxial orientation of the diol in the cyclisation step.

While our attempts in utilising different protecting groups to orientate the diol in a diequatorial fashion were moderately successful, we have not been successful in obtaining the desired cyclisation product thus far. The initial investigation seems to suggest that an acid stable protecting group which ties the hydroxyl groups in a diequatorial fashion, while maintaining a certain degree of flexibility to allow the approach of the tethered nucleophile towards the allene, should allow the gold-catalysed cyclisation to proceed. This observation could form the basis of future work towards the stereoselective synthesis of fagomine.

Chapter 3 Synthesis of pyrrolidine containing polyhydroxylated alkaloids

3.1 Polyhydroxylated pyrrolidines

Polyhydroxylated pyrrolidines have been isolated from a wide variety of plant sources.[3b] Amongst the isolated alkaloids of this structural class, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) **3.1** (**Figure 3.1**) has garnered a great deal of interest due to its potent activity against a varied number of glycosidases.[3b] DAB-1 **3.1**, while first isolated in 1985 from the fruits of *Angylocalyx boutiqueanus*,[156] was subsequently found in other disparate species of plants[6,9,10,11] and more recently in marine sponges collected in Western Australia.[157] The relative stereochemistry of the material isolated initially from *Angylocalyx boutiqueanus* could not be determined via proton NMR spectroscopy and it was through the synthetic efforts of Fleet *et al.*[158a] that the relative and absolute stereochemistry of DAB-1 **3.1** was later established.

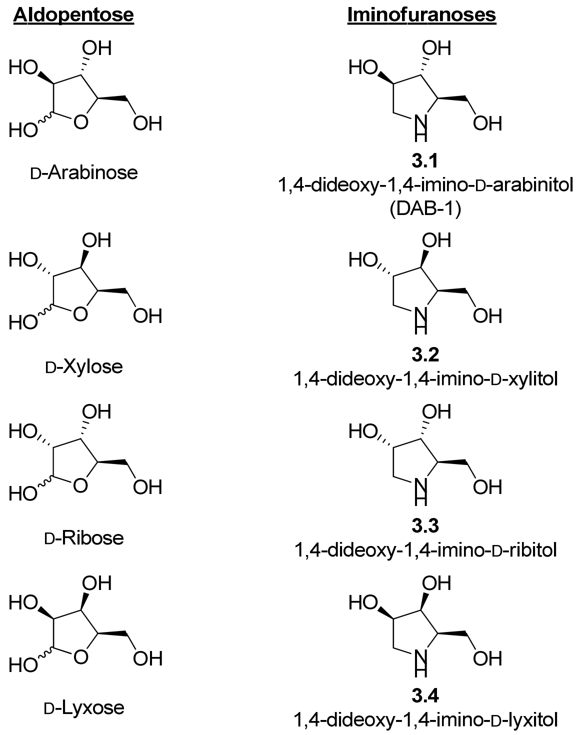


Figure 3.1 Iminofuranoses and their corresponding aldopentoses

The iminofuranoses are named using nomenclature following their closely related aldopentoses (**Figure 3.1**). It is perhaps worth a mention that 2 other diastereomers of DAB-1 **3.1**, namely 1,4-dideoxy-1,4-imino-D-xylitol **3.2** and 1,4-dideoxy-1,4-imino-D-ribitol **3.3**, have also been isolated from plant sources[5,11,159] and were also found to inhibit various glycosidases.[158a]

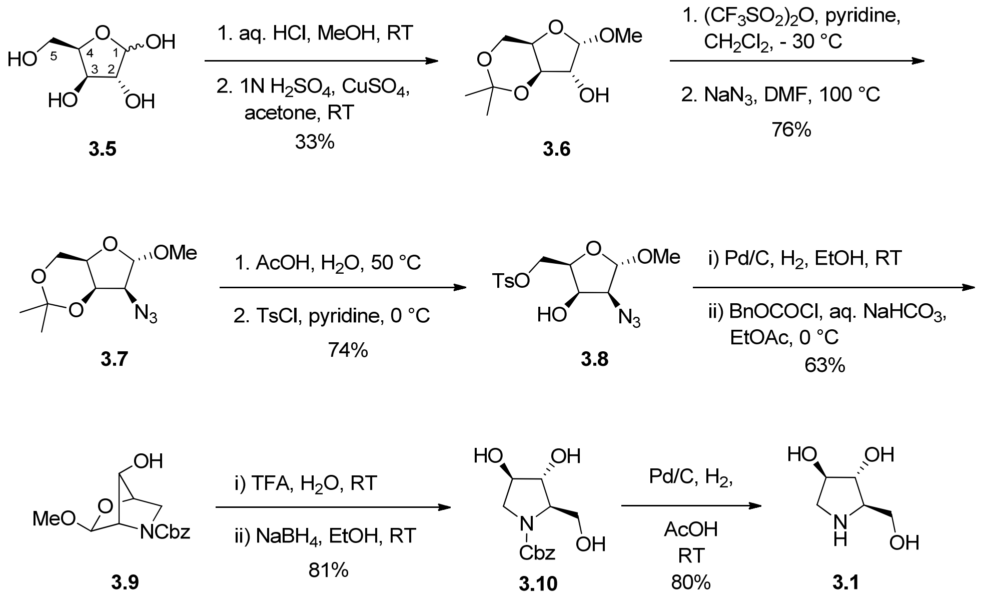
3.1.1 Synthesis of DAB-1 and its congeners

In accordance with the premise laid out in Chapter 1 with respect to the review of the synthesis of fagomine and its congeners, the review of the synthesis of DAB-1 and its congeners has been treated in a similar fashion. Other syntheses of DAB-1 and its congeners not highlighted in the ensuing review have been listed in the reference section.[160]

3.1.1.1 Carbohydrates as starting materials

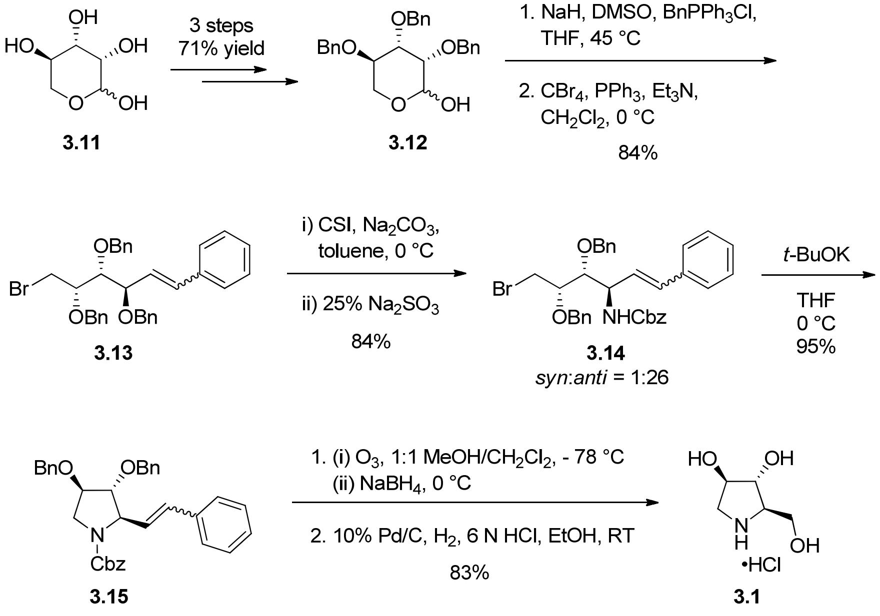
Similar to fagomine, the first reported synthesis[158] of DAB-1 **3.1** utilised the carbohydrate approach. Starting with D-xylose, the authors envisioned that incorporation of nitrogen functionality with inversion of stereochemistry at C-2, followed by intramolecular nucleophilic displacement onto the C-5 position would provide the pyrrolidine scaffold with requisite stereochemistry to accomplish the synthesis of DAB-1 **3.1**.

Acetonide protected methyl α-D-xylofuranoside **3.6** (**Scheme 3.1**) was prepared from D-xylose **3.5** following literature procedures.[161] Triflate formation, followed by displacement with NaN_3 at a high temperature of 100 °C, probably to overcome the steric hindrance of the acetonide group, afforded azido compound **3.7** with inversion of stereochemistry at C-2. Acidic hydrolysis of the acetonide provided the diol, which upon treatment with tosyl chloride gave tosylate **3.8**. Azide reduction under hydrogenation conditions provided the primary amine, which underwent intramolecular displacement of the tosylate at C-5 to give bicyclic carbamate **3.9**, after treatment with benzyl chloroformate. Acetal hydrolysis of **3.9** with aqueous TFA and subsequent reduction of the lactol with $NaBH_4$ provided Cbz protected pyrrolidine **3.10**. Cbz deprotection under hydrogenolysis conditions, followed by work-up under basic conditions, completed the synthesis of DAB-1 **3.1** in 8% overall yield over 9 steps starting from D-xylose **3.5**.



Scheme 3.1 First reported synthesis of DAB-1

Synthesis of the L-enantiomer of DAB-1 from acetonide protected methyl α-D-xylofuranoside **3.6** was also reported by the same authors.[158] While both DAB-1 **3.1** and its L-enantiomer had spectroscopic data (^{1}H and ^{13}C NMR, MS) in good agreement with the material isolated from *Angylocalyx boutiqueanus*, their inhibitory activities against yeast α-glucosidase were markedly different. DAB-1 **3.1** and the material isolated from *Angylocalyx boutiqueanus*, exhibited identical, potent inhibitory activities against yeast α-glucosidase, whereas the L-enantiomer was evidently less potent against yeast α-glucosidase.[158a] It was from these differences in inhibitory activities that the material isolated from *Angylocalyx boutiqueanus* was concluded to be DAB-1 **3.1**.



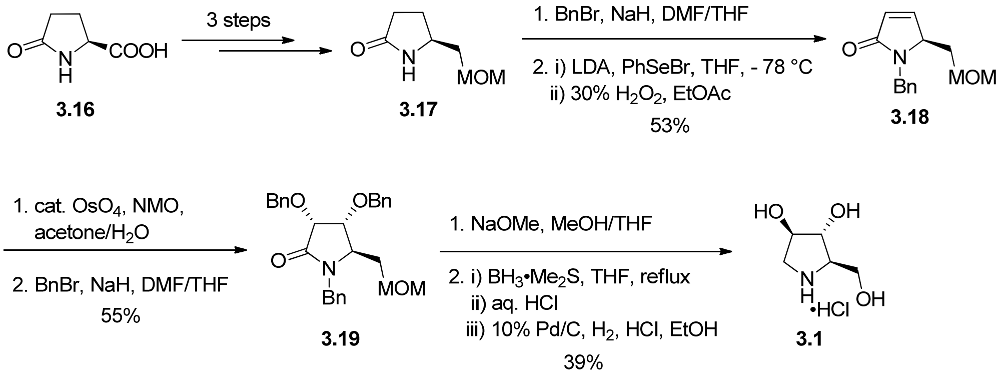
Scheme 3.2 Synthesis of DAB-1 from D-lyxose

In contrast to D-xylose, which required a stereoinversion to install the requisite stereochemistry, Kim *et al.*[162] utilised D-lyxose **3.11** (**Scheme 3.2**) in their synthesis of DAB-1. As the chiral centres of D-lyxose **3.11** were of the required configuration for DAB-1, the authors installed the nitrogen functionality via the chlorosulfonyl isocyanate (CSI) methodology previously developed within their group.[163] This reaction proceeds via two S_N2 reactions hence preserving the original configuration of the vinylic benzyl ether.

Beginning with D-lyxose **3.11** (**Scheme 3.2**), tri-benzyl protected lactol **3.12** was prepared over 3 steps following a literature procedure.[164] Wittig olefination, followed by Appel reaction,[165] provided bromide **3.13** as a ca. 3.1:1 mixture of *cis*/*trans* isomers. Treatment of bromide **3.13** with chlorosulfonyl isocyanate in the presence of Na_2CO_3, followed by desulfonylation using 25% aqueous Na_2SO_3, provided Cbz protected allylic amine **3.14** with good diastereoselectivity in 84% yield. While the mechanism of the chlorosulfonyl isocyanate reaction was not established, the authors ventured that the good diastereoselectivity observed could be due to the neighbouring group effect of the *O*-benzyl group adjacent to the 1,2-*anti*-diether.[162] Exposure to potassium *tert*-butoxide effected the intramolecular displacement of bromide to give pyrrolidine **3.15**. Ozonolysis followed by reductive work-up was utilised to install the hydroxymethyl functionality and global deprotection under hydrogenative conditions provided DAB-1 **3.1** as its hydrochloride salt with 40% overall yield starting from D-lyxose.

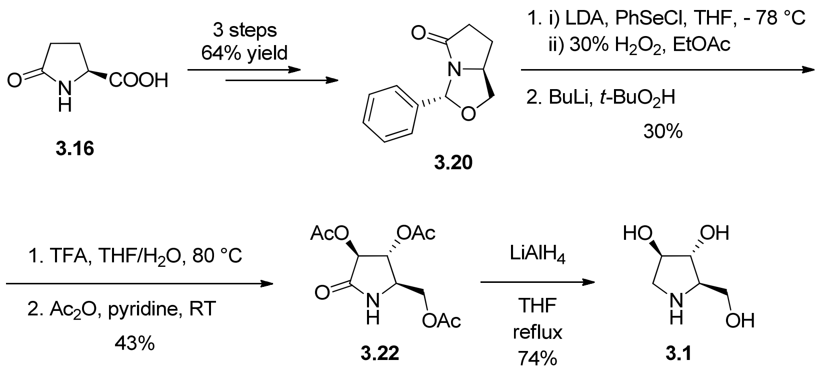
3.1.1.2 Chiral synthons as starting materials

Amongst the chiral synthons utilised for the synthesis of DAB-1, commercially available (*S*)-pyroglutamic acid **3.16** (**Scheme 3.3**) was considered to be an appropriate starting point for two separate groups.[166,167] This could be attributed to the structural features of (*S*)-pyroglutamic acid: a pyrrolidinone motif bearing the requisite chiral centre α- to the nitrogen. As such, it was envisioned that reduction of the α-carboxylic acid, followed by installation of the *trans* diol and subsequent reduction of the lactam, would lead to an expedient synthesis of DAB-1.



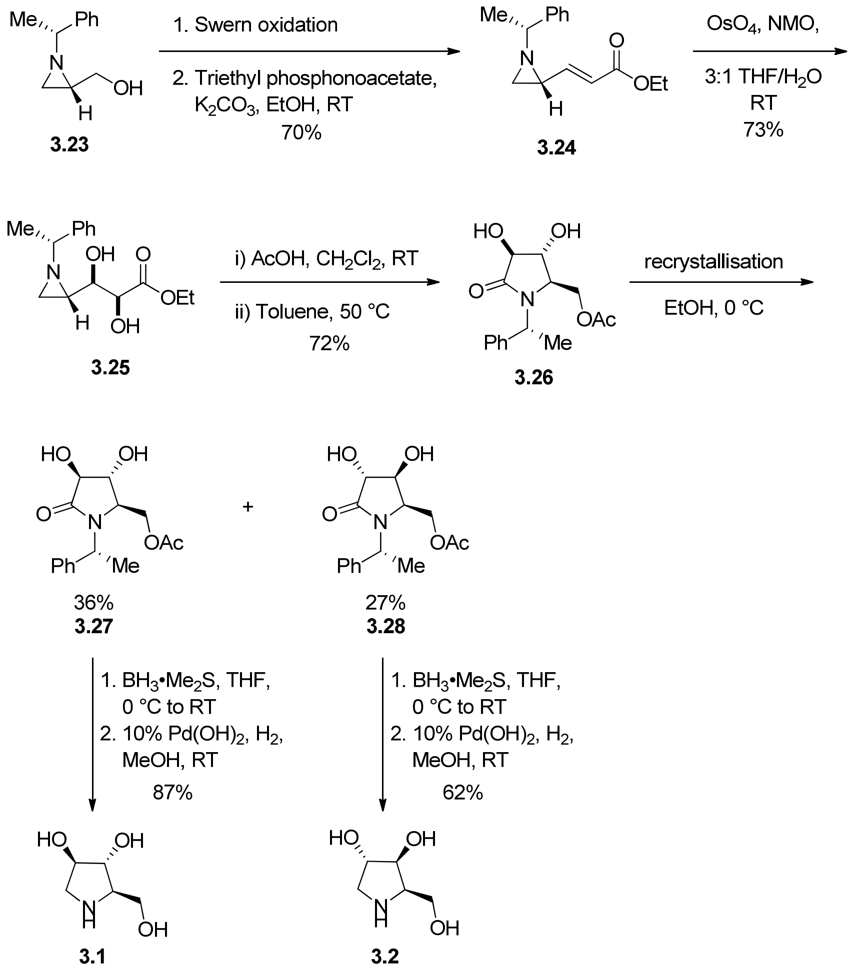
Scheme 3.3 Synthesis of DAB-1 from (*S*)-pyroglutamic acid utilising dihydroxylation

In the synthesis reported by Ikota and Hanaki[166] (**Scheme 3.3**), (*S*)-pyroglutamic acid **3.16** was converted into the MOM protected alcohol **3.17** over three steps following a published literature procedure.[168] *N*-Benzylation followed by a selenenylation-deselenenylation protocol provided the unsaturated lactam **3.18**. Dihydroxylation under Upjohn conditions provided the *cis*-diol **3.19**, which was protected as benzyl ethers by treatment with benzyl bromide. Epimerisation with NaOMe gave the *trans*-diol which underwent lactam reduction and global deprotection to afford DAB-1 **3.1** as its hydrochloride salt in 11% yield starting from alcohol **3.17**.



Scheme 3.4 Synthesis of DAB-1 from (*S*)-pyroglutamic acid utilising epoxidation

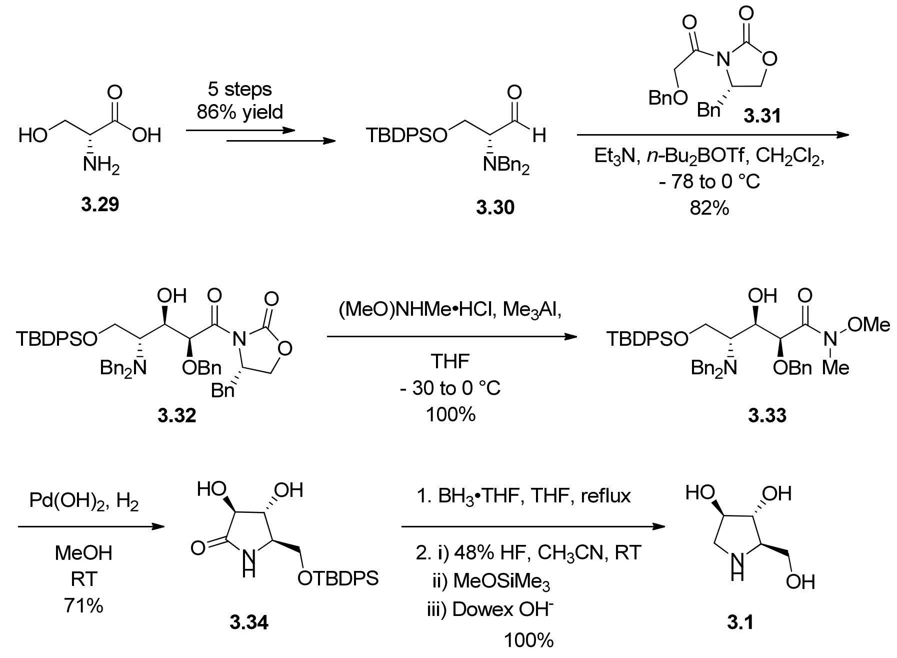
As an alternative to dihydroxylation, which required an additional epimerisation step to install the *trans*-diol, Langlois *et al.*[167] utilised acid-mediated epoxide opening to install the *trans*-diol directly. Bicyclic *N,O*-acetal **3.20** (**Scheme 3.4**) was synthesised from (*S*)-pyroglutamic acid **3.16** over three steps.[169] The selenenylation-deselenenylation protocol was applied to introduce the conjugated double bond, which was converted into the epoxide **3.21**, which required chromatographic separation to remove the other minor epoxide diastereomer. Treatment of epoxide **3.21** with aqueous TFA at 80 °C effected both the oxirane ring opening and *N,O*-acetal hydrolysis to give a water-soluble triol which was protected as its triacetate **3.22**. Reduction of the lactam and acetate deprotection with $LiAlH_4$ in refluxing THF, provided DAB-1 **3.1** in an overall yield of 6% starting from (*S*)-pyroglutamic acid **3.16.**



Scheme 3.5 Synthesis of DAB-1 and D-DIX from chiral aziridines

Using commercially available (2*S*)-1-methylbenzylaziridine-2-methanol **3.23** (**Scheme 3.5**), Sim *et al.*[170] developed an efficient synthetic sequence for the synthesis of both DAB-1 **3.1** and 1,4-dideoxy-1,4-imino-D-xylitol (D-DIX) **3.2**. A similar synthetic sequence was also applied to the (*2R)*-1-methylbenzylaziridine-2-methanol enantiomer to deliver the synthesis of the unnatural iminosugars L-AB1 and L-DIX, the enantiomers of D-AB1 and D-DIX, respectively.

Swern oxidation of (2*S*)-1-methylbenzylaziridine-2-methanol **3.23** (**Scheme 3.5**), followed by Horner-Wadsworth-Emmons olefination with triethyl phosphonoacetate provided *trans*-alkene **3.24** with excellent *trans*:*cis* ratio of 98:2. Upjohn dihydroxylation then provided diol **3.25**. Treatment of diol **3.25** with AcOH at ambient temperature resulted in aziridine ring cleavage to give an acyclic acetate ester, which subsequently underwent intramolecular cyclisation in the presence of AcOH at 50 °C, to give lactam **3.26**. Recrystallisation of lactam **3.26** from EtOH at 0 °C provided individual diastereomers **3.27** and **3.28**, which were then subjected to borane reduction and hydrogenation to provide DAB-1 **3.1** and D-DIX **3.2** in overall yields of 12% and 6%, respectively.



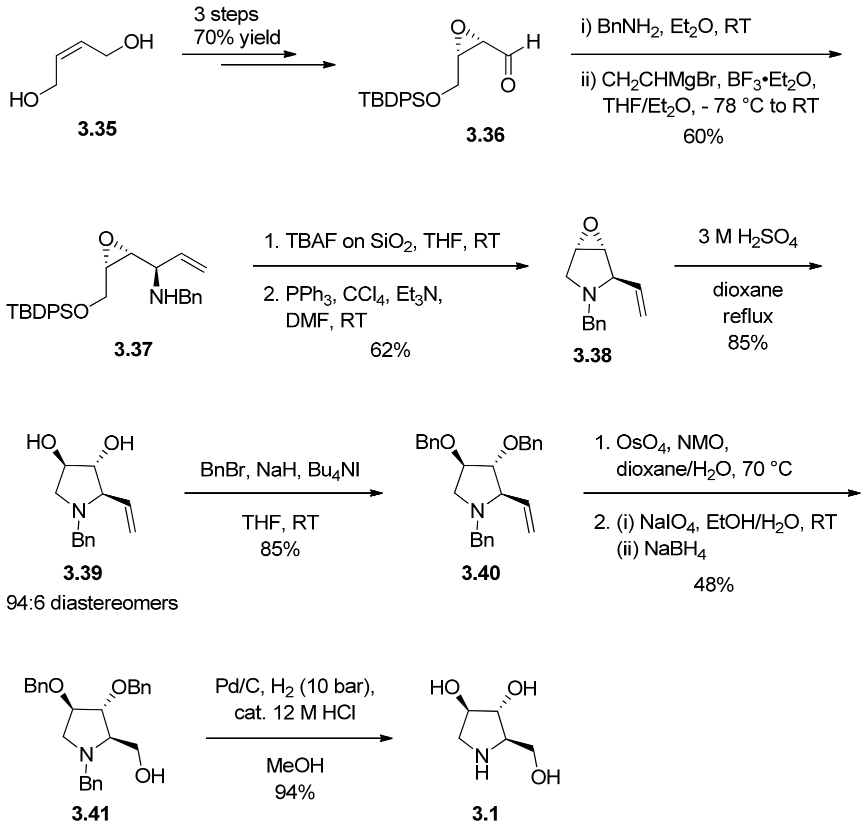
Scheme 3.6 Synthesis of DAB-1 from D-serine

The synthesis reported by Hulme *et al.*[171] utilising D-serine **3.29** (**Scheme 3.6**) and Evans' chiral auxillary to install the diol via a *syn* diastereoselective glycolate aldol reaction is one of the highest yielding synthesis of DAB-1 reported to date. D-serine **3.29** was converted into aldehyde **3.30** over 5 steps in 87% yield, without loss of chiral purity. Aldol condensation of aldehyde **3.30** and the *Z*-boron enolate of **3.31** proceeded to yield the *syn* aldol product **3.32** as a single diastereomer. Conversion to the Weinreb amide **3.33**, followed by hydrogenation in the presence of Pearlman's catalyst led to the complete deprotection of the benzyl groups with *in situ* cyclisation to give pyrrolidinone **3.34**. Lactam reduction using borane-THF complex in refluxing THF, followed by TBDPS deprotection with hydrofluoric acid and treatment with Dowex OH^- provided DAB-1 **3.1** as its free base, with an overall yield of 49%, starting from D-serine.

3.1.1.3 Non-carbohydrate, non-chiral substrates as starting materials

While there are multiple syntheses of DAB-1 commencing from either carbohydrates or chiral synthons, the number of reported syntheses utilising non-chiral starting material are noticeably fewer. In addition, the reported syntheses using non-chiral starting material are largely represented by chemoenzymatic aldol condensations, as illustrated in Chapter 1 (**Scheme 1.11**), developed by the groups of Wong[160j, k] and Clapés.[160l, m]

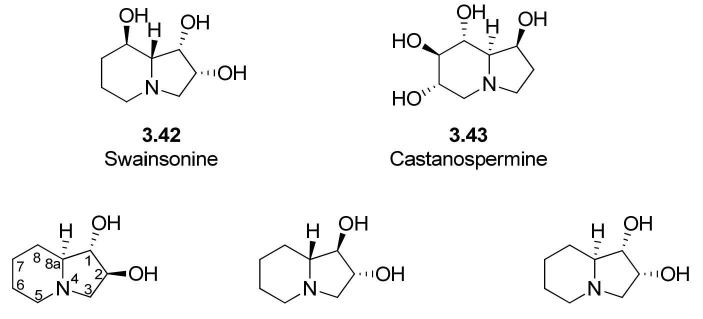
In their efforts to develop an efficient synthesis of iminosugars from α,β-epoxy aldehydes, Génisson *et al.*[172] utilised regioselective C-2 epoxide opening of a chiral epoxy amine to install the requisite diol stereochemistry of DAB-1. *cis*-2-Butene-1,4-diol **3.35** (**Scheme 3.7**) was converted into chiral epoxyaldehyde **3.36** in 70% yield over 3 steps, utilising the Sharpless asymmetric epoxidation as the key transformation.[173] Imine formation with benzylamine, followed by reaction with vinyl magnesium bromide in the presence of $BF_3{\bullet}Et_2O$, gave *anti* epoxy amine **3.37** exclusively in 60% yield. TBDPS deprotection with TBAF supported on silica gel provided primary alcohol. Treatment of the primary alcohol with Appel conditions led to formation of the corresponding chloride, which cyclised *in situ* to give epoxypyrrolidine **3.38**.



Scheme 3.7 Synthesis of DAB-1 from *cis*-2-butene-1,4-diol

Regioselective epoxide ring opening of **3.38** with aqueous H_2SO_4, provided the *trans*-diol **3.39** as a 94:6 mixture of diastereomers, which could be separated by chromatography after conversion into the corresponding benzyl ethers **3.40**. Oxidative cleavage of the vinyl moiety using a sequence of dihydroxylation, diol cleavage with $NaIO_4$ and reduction of the resultant aldehyde with $NaBH_4$ provided primary alcohol **3.41**. Global debenzylation under hydrogenative conditions gave DAB-1 **3.1** in 8% overall yield over 11 steps, starting from *cis*-2-butene-1,4-diol **3.35**.

3.2 Polyhydroxylated indolizidines



3.42 Swainsonine

3.43 Castanospermine

3.44 (+)-Lentiginosine

3.45 (-)-Lentiginosine

3.46 2-*Epi*-(+)-lentiginosine

Figure 3.2 Selected polyhydroxylated indolizidines of interest

Polyhydroxylated indolizidines are a class of bicyclic iminosugars bearing a fused piperidine and pyrrolidine motif with nitrogen at the bridgehead. Swainsonine **3.42** (**Figure 3.2**), a potent inhibitor of α-mannosidases,[174] was the first example of an indolizidine alkaloid to be isolated.[28] Shortly after, castanospermine **3.43** was isolated from *Castanospernum australe*[35] and was found to be a potent inhibitor of α- and β-glucosidases.[175]

Lentiginosine **3.44** was first isolated, together with 2-*epi*-lentiginosine **3.46**, by Elbein and coworkers from *Astragalus lentiginosus*.[34] Upon its isolation, much interest was generated by lentiginosine due to its potent and specific inhibitory activity against amyloglucosidase,[34] an enzyme which hydrolyses 1,4- and 1,6-α-glycosidic bonds. Furthermore, it was the first potent glucosidase inhibitor to bear only two hydroxyl groups, hence dispelling the empirical observation that iminosugars require a mininum of three hydroxyl groups to function as inhibitors towards glucosidases.[176] Contrary to lentiginosine **3.44**, 2-*epi*-lentiginosine **3.46**, was found to be completely inactive against amyloglucosidase, suggesting that the *trans* configuration of the hydroxyl groups was essential for activity.[34]

3.2.1 Synthesis of lentiginosine and its congeners

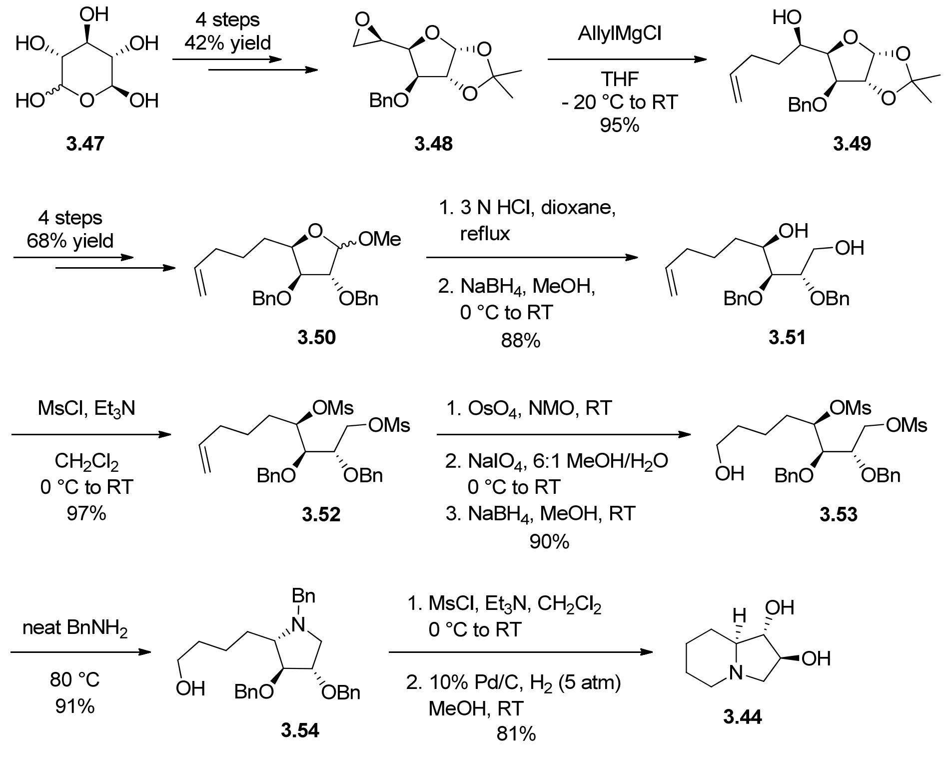
The absolute configuration of natural lentiginosine was tentatively assigned to be (1*S*,2*S*,8a*S*) by Elbein and coworkers on the basis of biosynthetic pathway and was reported to have a specific rotation value of $[\alpha]_D$ = - 3.3.[34] However, subsequent synthesis of (1*S*,2*S*,8a*S*)-lentiginosine by several groups all resulted in small positive values for specific rotation.[177] These reports led to doubts about the initial absolute configuration assigned to natural lentiginosine.[178] The debate was perhaps exacerbated by the small value of $[\alpha]_D$, as this meant that small amounts of impurities or diastereomers could invert the rotation sign, resulting in misleading conclusions.[177a]

The absolute stereochemistry and direction of specific rotation was investigated by Brandi *et al.*[179] through the synthesis of both (+) and (-)-lentiginosine and comparing their individual biological activities against that of natural lentiginosine. Whereas the (1*S*,2*S*,8a*S*) enantiomer was observed to have $[\alpha]_D$ = + 3.3 and inhibitory activities similar to that of natural lentiginosine, the (1*R*,2*R*,8a*R*) enantiomer was measured to have $[\alpha]_D$ = - 1.6 and was remarkably less potent. This led the authors to conclude that natural lentiginosine is of (1*S*,2*S*,8a*S*) configuration and is dextrorotatory (+). The authors attributed the levorotatory value initially reported by Elbein *et al.*[34] to the presence of impurities, which were evident in the published NMR spectrum.[34] This argument has been widely accepted and subsequent publications on lentiginosine, with the exception of one,[180] has referred to the natural product as that of (+)-lentiginosine **3.44**.

Owing to the debate in the early years on the absolute configuration of (+)-lentiginosine **3.44** and its unusual biological activity, many syntheses of (+)-lentiginosine **3.44**, (-)-lentiginosine **3.45** and its congeners have been reported. An excellent review documenting the disputes of the absolute configuration and the various synthetic efforts towards (+)-lentiginosine **3.44** has also been published.[181] Similar to the previous sections, syntheses of (+)-lentiginosine **3.44**[182] and its congeners[183] not highlighted in the ensuing review have been listed in the reference section.

3.2.1.1 Carbohydrates as starting materials

Unlike the synthesis of fagomine and DAB-1, where carbohydrates were popular starting points, the use of carbohydrates in the synthesis of (+)-lentiginosine and its congeners is distinctly less common. Alam and Vankar's synthesis of (+)-lentiginosine from D-glucose[184] (**Scheme 3.8**) is one of the only two known syntheses of (+)-lentiginosine from carbohydrate starting material.

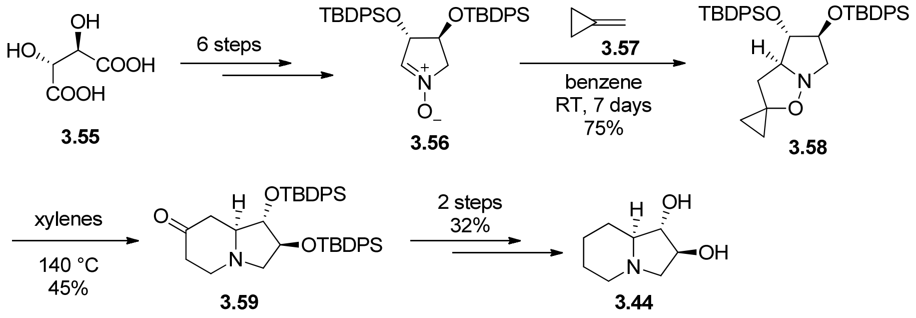


Scheme 3.8 Synthesis of (+)-lentiginosine from D-glucose

Epoxide **3.48**, with the requisite configuration of the three contiguous chiral centres of (+)-lentiginosine already installed, was obtained from D-glucose following a reported procedure.[185] Epoxide ring-opening with allyl magnesium chloride gave homoallylic alcohol **3.49**. Barton deoxygenation, followed by acetonide deprotection and benzyl protection, provided *bis*-benzyl ether **3.50** in 68% yield over 4 steps. Acetal hydrolysis under acidic conditions and reduction of the resultant aldehyde with $NaBH_4$ gave diol **3.51**. *Bis*-mesylation and oxidative cleavage of the vinyl moiety using a 3-step sequence of dihydroxylation, $NaIO_4$ cleavage and aldehyde reduction, provided cyclisation precursor **3.53**. Treatment of *bis*-mesylate **3.53** with neat benzylamine at 80 °C gave pyrrolidine **3.54**. Mesylation of the primary alcohol, followed by global deprotection of the benzyl protecting groups under hydrogenative conditions, led to *in situ* cyclisation to give (+)-lentiginosine **3.44** in an overall yield of 38%, starting from epoxide **3.48**.

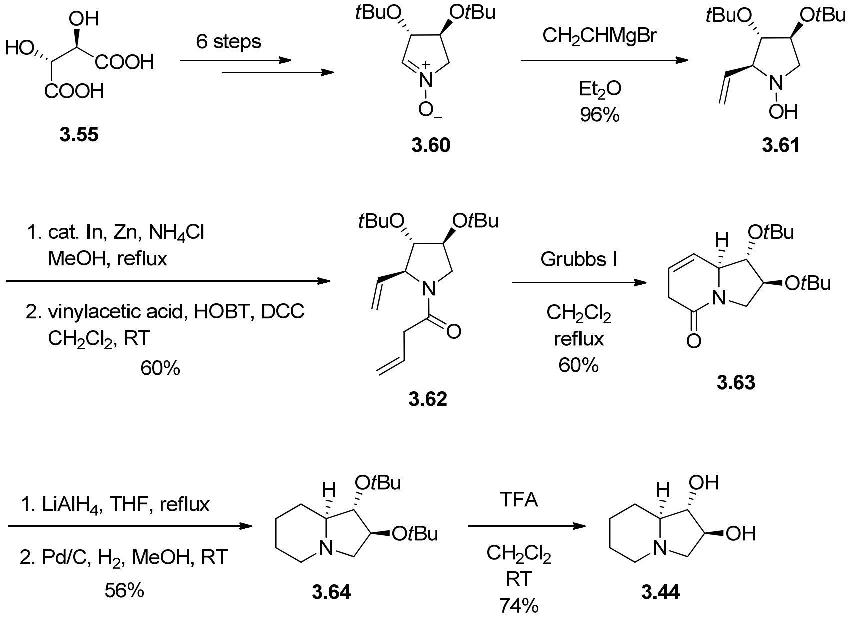
3.2.1.2 Chiral synthons as starting materials

The use of chiral synthons is by far the preferred approach for the synthesis of (+)-lentiginosine. Amongst the chiral starting materials utilised, L-tartaric acid has frequently been employed due to its low cost and utility for the direct installation of the (1*S*,2*S*) configuration of (+)-lentiginosine.



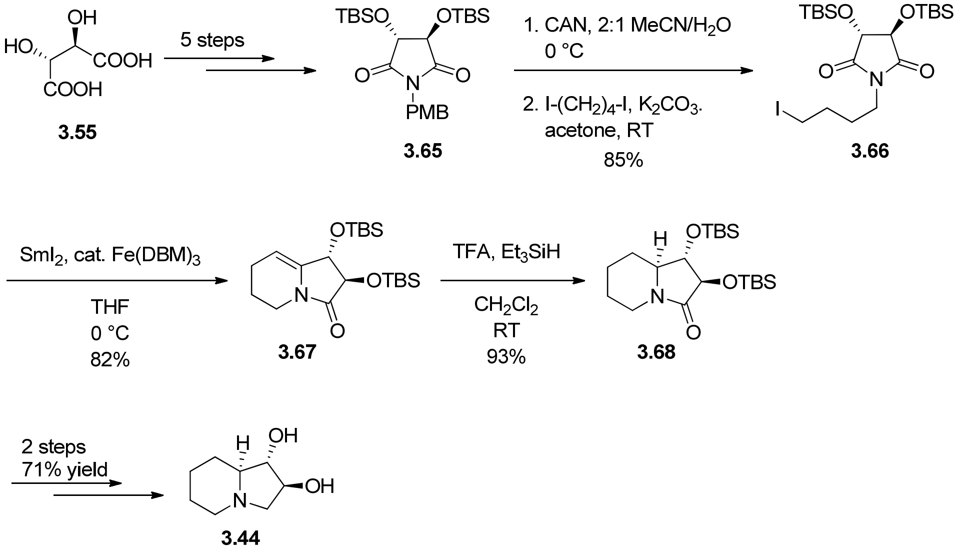
Scheme 3.9 First synthesis of (+)-lentiginosine from L-tartaric acid derived nitrone

L-tartaric acid derived nitrones (**Scheme 3.9**) had previously been employed by Brandi *et al.*[177b,179] in their synthesis of both enantiomers of lentiginosine. However, the early syntheses were unsatisfactory due to the long reaction times and the low overall yield of 10% starting from nitrone **3.56**. An improved synthesis using diastereoselective Grignard addition to a nitrone as the key reaction step to establish the (8a*S*) configuration was reported by Cardona and coworkers[186] at a later time.



Scheme 3.10 Improved synthesis of (+)-lentiginosine from L-tartaric acid dervied nitrone

Nitrone **3.60** (**Scheme 3.10**) was obtained from L-tartaric acid **3.55** over 6 steps following a published procedure.[187] Reaction of nitrone **3.60** with vinylmagnesium bromide proceeded cleanly at ambient temperature to afford hydroxylamine **3.61** as a single diastereomer. The authors attributed the high stereoselectivity of the Grignard addition to the steric effects contributed by the vicinal *tert*-butyl ether group. Hydroxylamine reduction with powdered Zn metal, followed by coupling with vinylacetic acid, provided diene **3.62**. Ring-closing metathesis with Grubbs I catalyst in refluxing dichloromethane was sluggish and required portionwise addition of the catalyst with an extended reaction time of 50 hours to achieve complete conversion. The authors attributed the low reactivity of diene **3.62** in the ring-closing metathesis to the presence of the bulky *tert*-butoxy groups present. When these were replaced with smaller acetate groups, the ring-closing metathesis proceeded to give the corresponding lactam in 89% yield after 20 hours with 15 mol% of Grubbs I catalyst. Lactam reduction with $LiAlH_4$, followed by hydrogenation gave saturated indolizidine **3.64**. *tert*-Butyl deprotection under acidic conditions provided (+)-lentiginosine **3.44** in 14% overall yield, beginning from nitrone **3.60**.

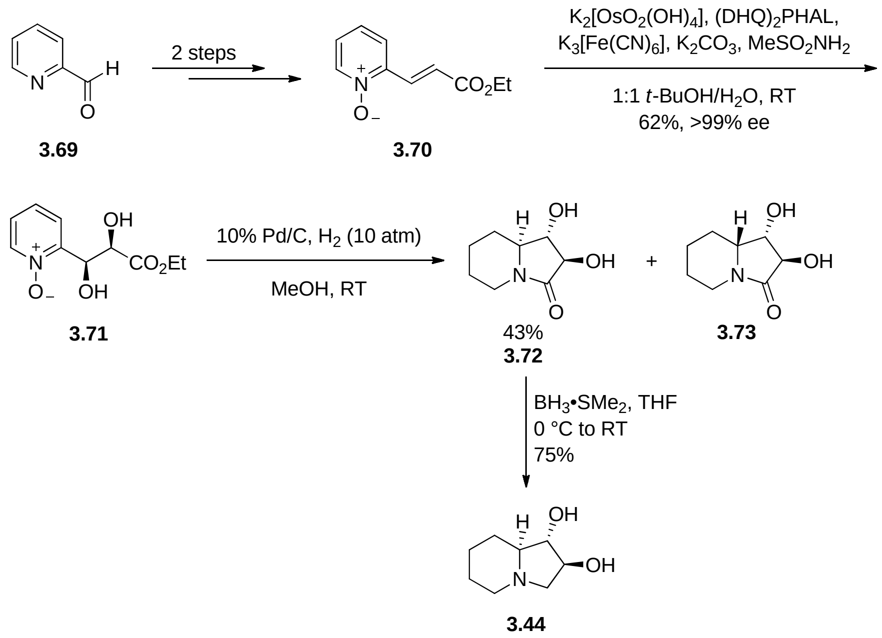


Scheme 3.11 Synthesis of (+)-lentiginosine from L-tartaric acid derived cyclic imides

Ha *et al.*[188] reported an efficient synthesis of (+)-lentiginosine from an L-tartaric acid-derived cyclic imide using SmI_2 promoted cyclisation of an *N*-iodoalkyl-substituted cyclic imide as the key transformation to construct the indolizidinone ring. Cyclic imide **3.65** (**Scheme 3.11**) was obtained from L-tartaric acid following methodology published by Yoda *et al.*.[189] PMB deprotection, followed by *N*-alkylation provided cyclisation precursor **3.65**, which upon treatment with SmI_2 proceeded to give indolizidinone **3.67** in 82% yield. Stereoselective reduction of alkene **3.67** installed the requisite (8a*S*) stereogenic center and subsequent lactam reduction, followed by deprotection provided (+)-lentiginosine **3.44** in 46% overall yield, starting from cyclic imide **3.65**.

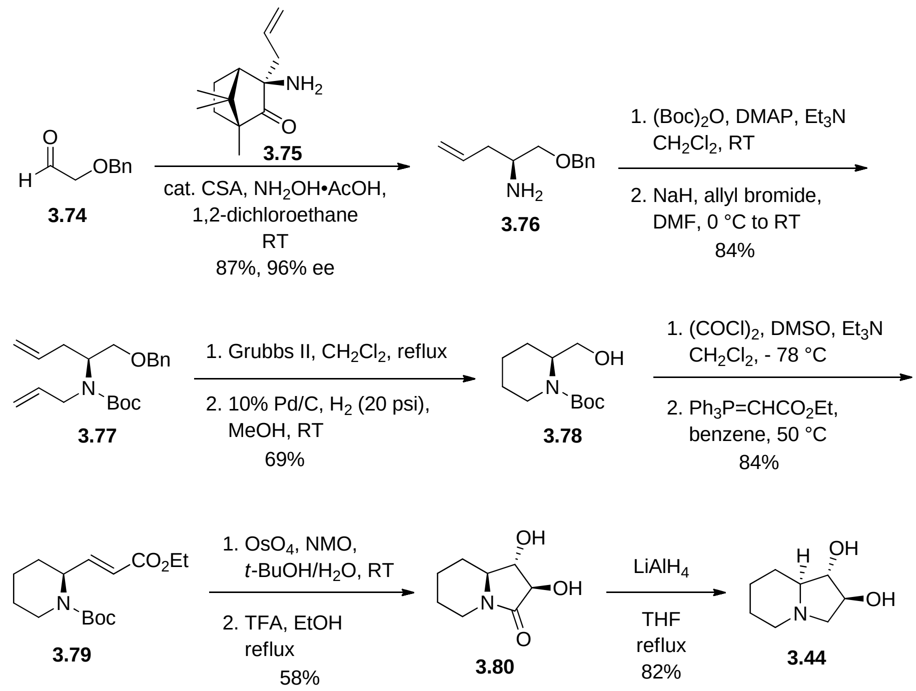
3.2.1.3 Non-carbohydrate, non-chiral substrates as starting materials

While it is reasonable to expect the synthesis of (+)-lentiginosine, with its three contiguous chiral centres, to be more amenable towards the use of chiral synthons, it is perhaps notable that one of the shortest syntheses of (+)-lentiginosine actually began from a non-chiral substrate.



Scheme 3.12 Synthesis of (+)-lentiginosine from picolinaldehyde

Feng and Zhou[190] utilised picolinaldehyde **3.69** (**Scheme 3.12**) in their expedient synthesis of (+)-lentiginosine, which was completed in 5 synthetic steps with an overall yield of 20%, starting from *N*-oxide **3.70**. Picolinaldehyde **3.69** was converted into *N*-oxide **3.70** over 2 steps using a sequence of Wittig reaction followed by oxidation with mCPBA.[191] Sharpless asymmetric dihydroxylation provided chiral diol **3.71** in 62% yield with >99% ee. One-pot *N*-oxide removal, pyridine reduction and *in situ* intramolecular cyclisation under hydrogenative conditions provided indolizidinones **3.72** and **3.73** in a 3.2:1 diastereomeric ratio. Indolizidinone **3.72** was isolated as a single diastereomer in 43% yield upon recrystallisation from ethyl acetate and reduction with BH_3•SMe_2 provided (+)-lentiginosine **3.44** in 75% yield.



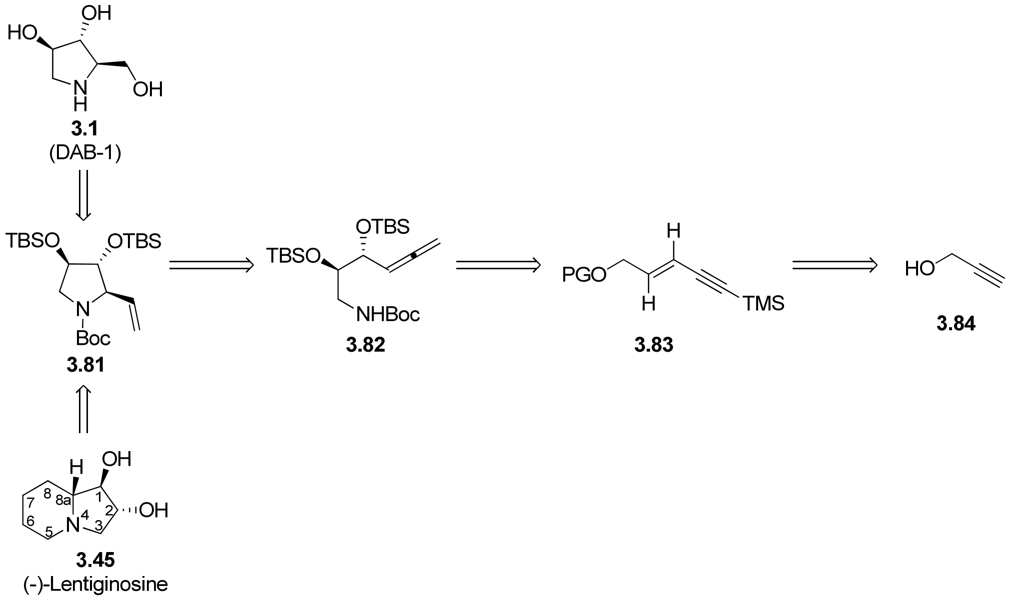
Scheme 3.13 Synthesis of (+)-lentiginosine from benzyl-protected acetaldehyde

The enantioselective transfer aminoallylation protocol developed by Kobayshi[192] was applied to the synthesis of chiral homoallylic amine **3.76** (**Scheme 3.13**) by Shaikh and Sudalai[193] in their synthesis of (+)-lentiginosine from benzyl-protected acetaldehyde. Treatment of benzyl-protected acetaldehyde **3.74** with chiral amine **3.75** in the presence of CSA resulted in the formation of an imine which underwent 2-*aza*-Cope rearrangement and subsequent C=N bond cleavage to give (*S*)-homoallylic amine **3.76** in good yield and ee. A sequence of Boc protection, *N*-allylation, ring-closing metathesis and tandem alkene reduction with *O*-benzyl deprotection under hydrogenative conditions provided piperidine alcohol **3.78**. Oxidation of alcohol **3.78**, followed by Wittig olefination gave α,β-unsaturated ester **3.79**, which was converted into the diol under Upjohn dihydroxylation conditions. Treatment of the diol with TFA resulted in removal of the Boc group with concomitant intramolecular cyclisation to give indolizidinone **3.80** as a single diastereomer in 58% yield, after chromatography and recrystallisation. Reduction of indolizidinone **3.80** with $LiAlH_4$ gave (+)-lentiginosine **3.44**, which was isolated in 20% overall yield over 10 synthetic steps beginning with benzyl-protected acetaldehyde **3.74**.

3.3 Synthetic plan towards the synthesis of DAB-1 and (-)-lentiginosine

In the previous chapter, we demonstrated the synthetic utility of Au-catalysed nucleophilic cyclisation of allenes in the synthesis of the polyhydroxylated piperidine, 2-*epi*-fagomine. In the interest of extending the investigation of nucleophilic cyclisation of allenes to five-membered ring systems, we recognised that polyhydroxylated pyrrolidine, DAB-1 **3.1** could be a relevant target for synthesis.

Au-catalysed nucleophilic cyclisation of allene **3.82** (**Scheme 3.14**) would provide α-vinyl pyrrolidine **3.81**, a useful building block which could be diverted towards the synthesis of both DAB-1 **3.1** and (-)-lentiginosine **3.45**, taking advantage of the versatile *exo*-cyclic alkene functionality. Whereas the oxidative cleavage of the *exo*-cyclic alkene, followed by global deprotection would provide DAB-1 **3.1**, the alkene functionality could also be utilised in metathesis reactions for further derivatisation towards the synthesis of (-)-lentiginosine **3.45**. Cyclisation precursor **3.82** could be attained from enyne **3.83** following the synthesis protocol of asymmetric dihydroxylation and Searles-Crabbé homologation utilised in the synthesis of 2-*epi*-fagomine. Enyne **3.83** could be synthesised from propargyl alcohol **3.84** over 2 steps via Sonogashira coupling with an iodoalkyne, followed by regioselective reduction of the resultant diyne.

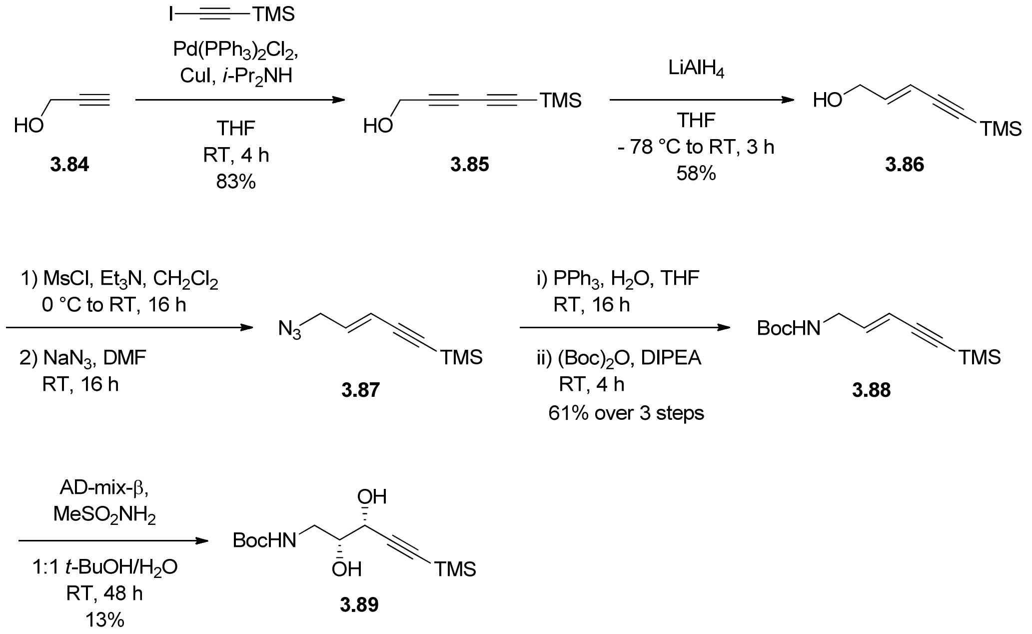


Scheme 3.14 Retrosynthetic analysis of DAB-1 and (-)-lentiginosine

3.4 Results and discussion

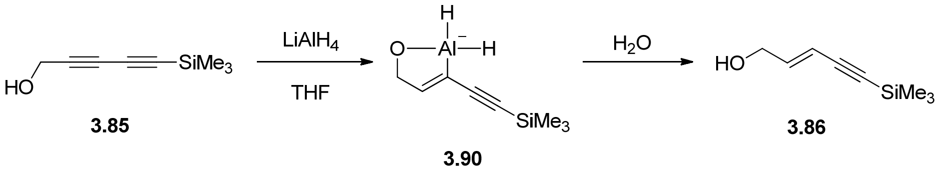
3.4.1 Synthesis of 1,4-dideoxy-1,4-imino-D-arabinitol

While our previous investigations into the Sharpless asymmetric dihydroxylation (SAD) of homoallylic enynols led us to conclude that the *O*-PMP group was best suited for the reaction, we were interested to investigate whether this observation would be similar for the allylic substrates. Previous studies by Corey *et al.*[136d] suggested that in contrast to the homoallylic alcohols, where carbonyl-bearing protecting groups are not tolerated due to unfavourable electrostatic interactions, carbonyl-bearing protecting groups are tolerated with allylic substrates. This encouraged us to attempt the Sharpless asymmetric dihydroxylation again with the NHBoc protected substrate.



Scheme 3.15 Initial synthesis route investigating SAD of NHBoc substrate

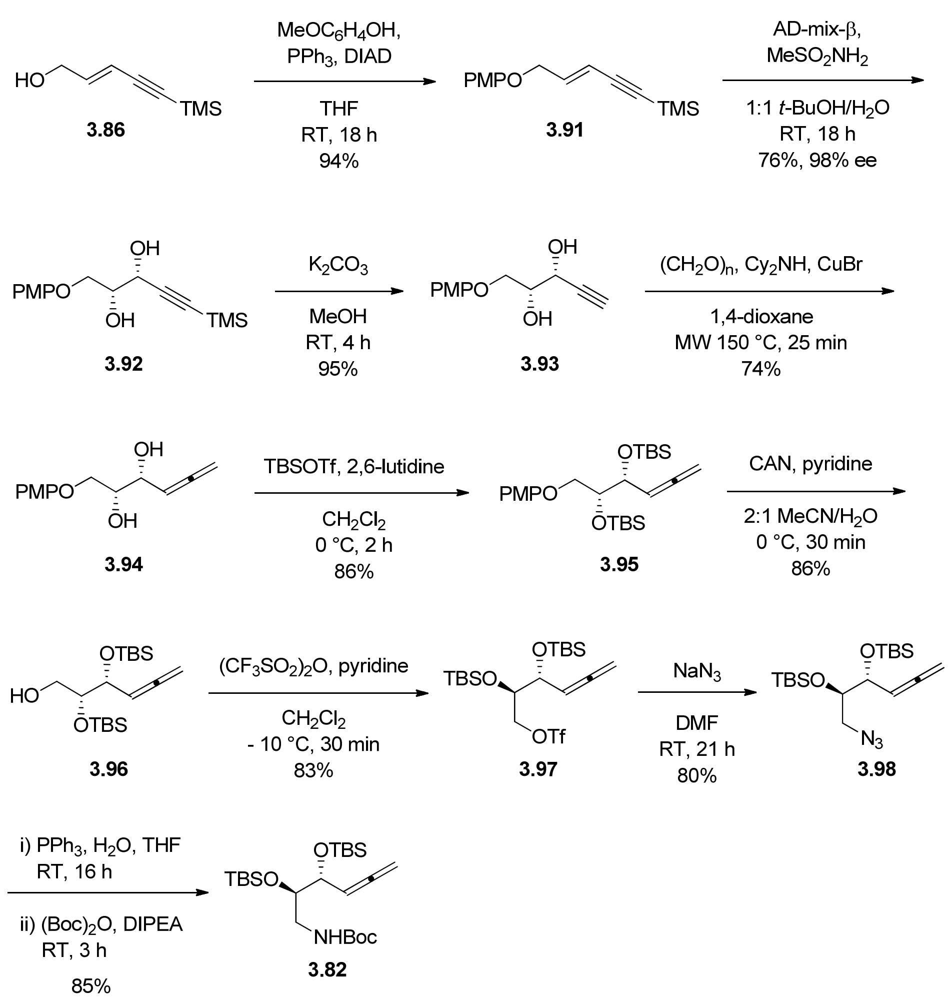
Sonogashira coupling of propargyl alcohol **3.84** (**Scheme 3.15**) with commercially available 1-iodo-2-(trimethylsilyl)acetylene following a literature procedure[194] provided diyne **3.85** in 83% yield. Regioselective reduction of diyne alcohol **3.85** using $LiAlH_4$ gave allylic enyol **3.86** as a single *trans* isomer,[195] which was evident from the large coupling constants of 15.9 Hz between the alkenic protons in the ^1H NMR spectrum. The regio- and geometric selectivity of the $LiAlH_4$ reduction is attributed to the formation of an alanate complex **3.90** (**Scheme 3.16**), which upon work-up, cleaves to give selectively the *trans* alkene.[196]



Scheme 3.16 Selective reduction of diyne alcohol with $LiAlH_4$

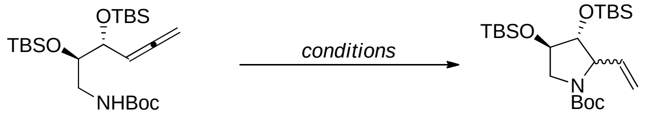
Mesylation of primary alcohol **3.86**, followed by displacement with NaN_3 gave azide **3.87**, which was converted into the NHBoc substrate **3.88** following the one-pot Staudinger reduction-Boc protection protocol previously established. Asymmetric dihydroxylation of the NHBoc substrate **3.88** utilising optimised conditions from previous investigations provided diol **3.89** in 13% yield, with the majority of the starting material being recovered. This result was similar to that obtained with the homoallylic substrate investigated in Chapter 2 (**Table 2.3**, compound **2.49b**), where the asymmetric dihydroxylation provided the corresponding chiral diol in 12% yield.

The unsatisfactory asymmetric dihydroxylation yield with the NHBoc substrate led us to revert to the use of an *O*-PMP substrate. Reaction of allylic alcohol **3.86** (**Scheme 3.17**) with *para*-methoxyphenol under Mitsunobu conditions gave *O*-PMP protected allylic enyol **3.91**. Sharpless asymmetric dihydroxylation of allylic enyol **3.91** proceeded cleanly to give chiral diol **3.92** in 76% yield and 98% ee, similar to that observed for the homoallylic enyol **2.69b** (*cf.* 86% yield, 97% ee). The dihydroxylation results indicated to us that planar, electron-rich aromatic protecting groups are probably the best substituents for both allylic and homoallylic enyol substrates in Sharpless asymmetric dihydroxylation reactions. This result also meant that we would not be able to install the amine functionality prior to the dihydroxylation step and protecting group exchange later in the synthesis was unavoidable.



Scheme 3.17 Synthesis of cyclisation precursor

TMS deprotection with K_2CO_3 in MeOH, Searles Crabbé homologation of the resultant terminal alkyne **3.93**, TBS protection of diol **3.94** and PMP deprotection employing conditions optimised previously all proceeded smoothly with good to excellent yields, providing allene alcohol **3.96** in 52% yield over the 4 steps. Treatment of primary alcohol **3.96** with triflic anhydride in a salt-ice bath gave triflate **3.97**, which was converted into the azide **3.98** by displacement with NaN_3 in DMF at ambient temperature. Azide **3.98** was characterised by IR spectroscopy which indicated the presence of a peak at 2099 cm^{-1}, corresponding to the characteristic N=N=N asymmetric stretching frequency. The triflate was employed in this instance as it is a better leaving group compared to the mesylate, which was sluggish in the azide displacement reaction, giving only 26% conversion after heating at 40 °C for 3 days. Subsequent reduction of azide **3.98** under Staudinger conditions, followed by Boc protection, provided allene cyclisation precursor **3.82** in 85% yield.



3.82 **3.99**

Entry	Conditions[a]	Time	Yield[b]
1	5 mol% $AuCl_3$, $CaCO_3$ 10:1 CH_2Cl_2/MeCN	24 h	7% (dr 2:1)
2	6 mol% $Au(PPh_3)Cl$, 6 mol% $AgSbF_6$, $CaCO_3$ CH_2Cl_2	24 h	5%
3	5 mol% Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl, 5 mol% AgOTf, $CaCO_3$ 1,4-dioxane	24 or 72 h	16% (dr > 99:1)

[a] All reactions were carried out at room temperature

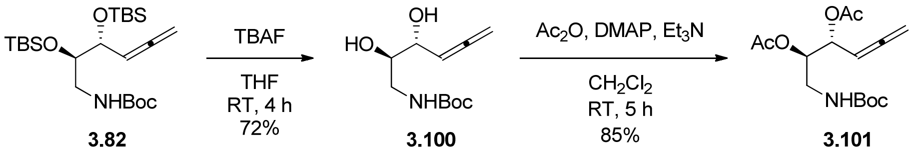
[b] All reactions were incomplete with starting material recovered

Table 3.1 Gold-catalysed allene cyclisation of *bis*-TBS diol substrate

With allene **3.82** in hand, we proceeded to attempt the gold-catalysed nucleophilic cyclisation to construct the pyrrolidine ring. Unexpectedly, allene cyclisation under the Au(III) (**Table 3.1**, entry 1) or Au(I) (**Table 3.1**, entry 2) conditions utilised previously proceeded slowly and provided the cyclised product in only 7% and 5% yields respectively after 24 hours, with the majority of the starting material being recovered. This was in contrast to the homoallylic substrate investigated previously, where nucleophilic cyclisation occurred expediently to give the piperidine product **2.82** in 85% yield under Au(I) conditions in just 8 hours.

A survey of the literature revealed that metal-catalysed nucleophilic allene cyclisation of substrates bearing substitutions α to the allene are limited[197] and to the best of our knowledge, no examples of metal-catalysed nucleophilic cyclisation of α- and β-substituted allene substrates have been reported. Of interest to us was the work published by Widenhoefer and coworkers,[197a] where the intramolecular *exo*-hydrofunctionalisation of allenes with various nucleophiles was achieved utilising a highly active Au(I) catalyst bearing a bulky phosphine ligand. This Au(I) catalyst, Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl, was previously developed by Echavarren and coworkers,[198] who discovered that Au(I) complexes bearing bulky, biphenyl-based phosphine ligands[199] had higher catalytic activity than the [Au(PPh$_3$)]Cl catalyst. This work was reminiscent of Buchwald's investigation into the use of bulky phosphine ligands for Pd-catalysed reactions.[200]

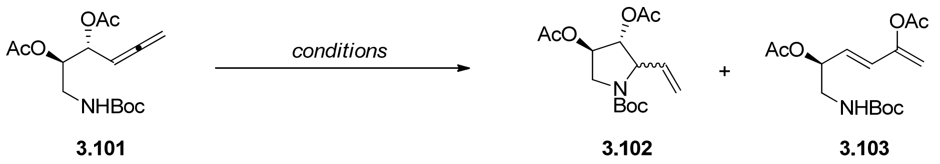
When the conditions reported by Widenhoefer[197a] were applied to our allene substrate **3.82** (**Table 3.1**, entry 3), an improvement in the isolated yield of pyrrolidine product **3.99** was observed. However, the reaction did not go to completion and we were unable to improve the isolated yields even with extended reaction time. This led us to contemplate whether the bulky *bis*-TBS protected ethers were hindering the cyclisation. It should be pointed out that while cyclisation under Au(III) conditions gave a 2:1 ratio of diastereomers (**Table 3.1**, entry 1), cyclisation with the Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl catalyst (**Table 3.1**, entry 3) led to the formation of pyrrolidine product as a single diastereomer. These observations suggest that the bulky biaryl phosphine ligand is indeed superior to the triphenylphosphine ligand. The diastereomeric ratio for entry 2 was undetermined due to the presence of close-running impurities which could not be separated despite repeated purification. Furthermore, we were unable to determine the relative stereochemistry of the pyrrolidine product **3.99** at this stage, as the characteristic protons were not well enough resolved in the ^{1}H NMR spectrum for the coupling constants to be obtained.



Scheme 3.18 Synthesis of *bis*-acetate cyclisation precursor

In our efforts to investigate whether the steric bulk of the *bis*-TBS protected ethers was hindering the cyclisation, we decided to synthesise the *bis*-acetate substrate. The acetate group was chosen primarily due to its smaller size and compatibility with downstream chemistry. Deprotection of *bis*-TBS protected ether **3.82** (**Scheme 3.18**) with a solution of 1 M TBAF in THF provided diol **3.100** which was converted to the *bis*-acetate **3.101** by treatment with acetic anhydride in the presence of Et_3N and small amounts of DMAP.

With *bis*-acetate substrate **3.101** in hand, we proceeded to continue our investigation of the allene cyclisation reaction. Gratifyingly, exposure of *bis*-acetate substrate **3.101** to 5 mol% of Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl activated by AgOTf, provided the pyrrolidine product **3.102** in 50% yield after 24 hours with 7:1 dr (**Table 3.2**, entry 1). This was a marked improvement compared with the cyclisation with the *bis*-TBS protected ether substrate **3.82** (*cf.* 16% yield, 3:1 dr after 72 hours). This result suggested that our concerns about the steric bulk of the *bis*-TBS protected ether hindering the cyclisation reaction were valid.



Entry	Conditions[a]	Time	Yield[b] (cyclised product)	Yield (by-product)
1	5 mol% Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl, 5 mol% AgOTf 1,4-dioxane	24 h	50% (dr 7:1)	0%
2	10 mol% Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl, 10 mol% AgOTf 1,4-dioxane	24 h	28%	0%
3	5 mol% Au[P(*t*-Bu)$_2$(*o*-biphenyl)]Cl, 5 mol% AgOTf 1,4-dioxane	96 h	73% (dr 7:1)	7%
4	5 mol% Au(PPh$_3$)NTf$_2$ CH$_2$Cl$_2$	96 h	7% (dr 3:1)	0%

[a] All reactions were carried out at room temperature
[b] Incomplete reaction

Table 3.2 Gold-catalysed allene cyclisation of *bis*-acetate substrate

Buoyed by the result, we attempted the cyclisation with a higher loading (10 mol%) of catalyst (**Table 3.2**, entry 2), with the anticipation of pushing the reaction to completion. Unexpectedly, increasing the catalyst loading did not benefit the cyclisation and instead led to a less clean reaction profile with the pyrrolidine product **3.102** being isolated in about 28% yield, with some impurities present. The dr for this reaction was not determined, as the ^{1}H NMR spectrum was complicated by the presence of the impurities. We then reverted back to a lower catalyst loading (5 mol%) but extended the reaction time to 96 hours and were delighted to obtain the pyrrolidine product **3.102** in 73% yield with 7:1 dr (**Table 3.2**, entry 3). The longer reaction time, however, also led to the formation of a by-product which was isolated in 7% yield.

We also attempted the cyclisation utilising Au(PPh$_3$)NTf$_2$, a Au(I) catalyst developed by Gagosz and coworkers,[201] as it was reported to have better catalytic activity than (PPh$_3$)AuSbF$_6$ in a number of Au(I)-catalysed transformations. The *bis*-(trifluoromethanesulfonyl)imidate moiety functions as a weakly coordinating counteranion, stabilising the Au(I) species, hence the use of very hygroscopic silver salts for the activation of phosphine Au(I) chloride complexes can be circumvented. Lamentably, when the catalyst was applied to our substrate, the cyclisation proceeded slowly, giving only 7% of the desired product **3.102** in 3:1 dr after 96 hours (**Table 3.2**, entry 4).

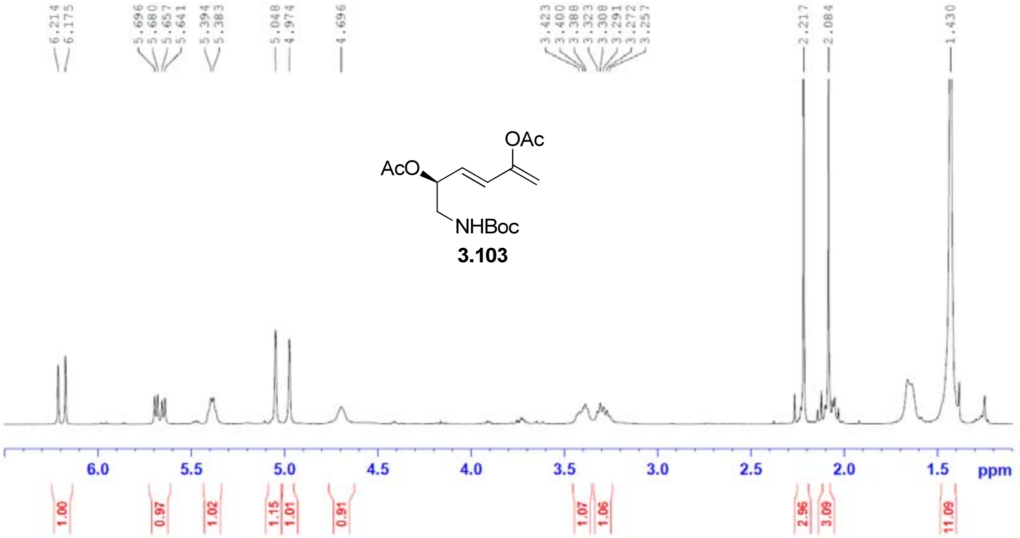


Figure 3.3 ^{1}H NMR (400 MHz, CDCl$_3$) of by-product **3.103**

^{1}H NMR spectrum of by-product (**Figure 3.3**) indicated the presence of 8 protons between the 3.0 - 6.5 ppm region. This number of protons was similar to that observed in the cyclisation precursor **3.101**, although the protons in the cyclisation precursor **3.101** were higher upfield between 3.0 – 5.5 ppm. In addition, the ^{1}H NMR spectrum also indicated the absence of the allene moiety and the presence of 2 protons in the downfield region of 5.5 – 6.5 ppm. These 2 protons, a doublet and a double doublet, had large coupling constants of 15.6 Hz suggesting the presence of a *trans* alkene. A pair of singlets around 5 ppm suggested the presence of a 1,1-disubstituted alkene.

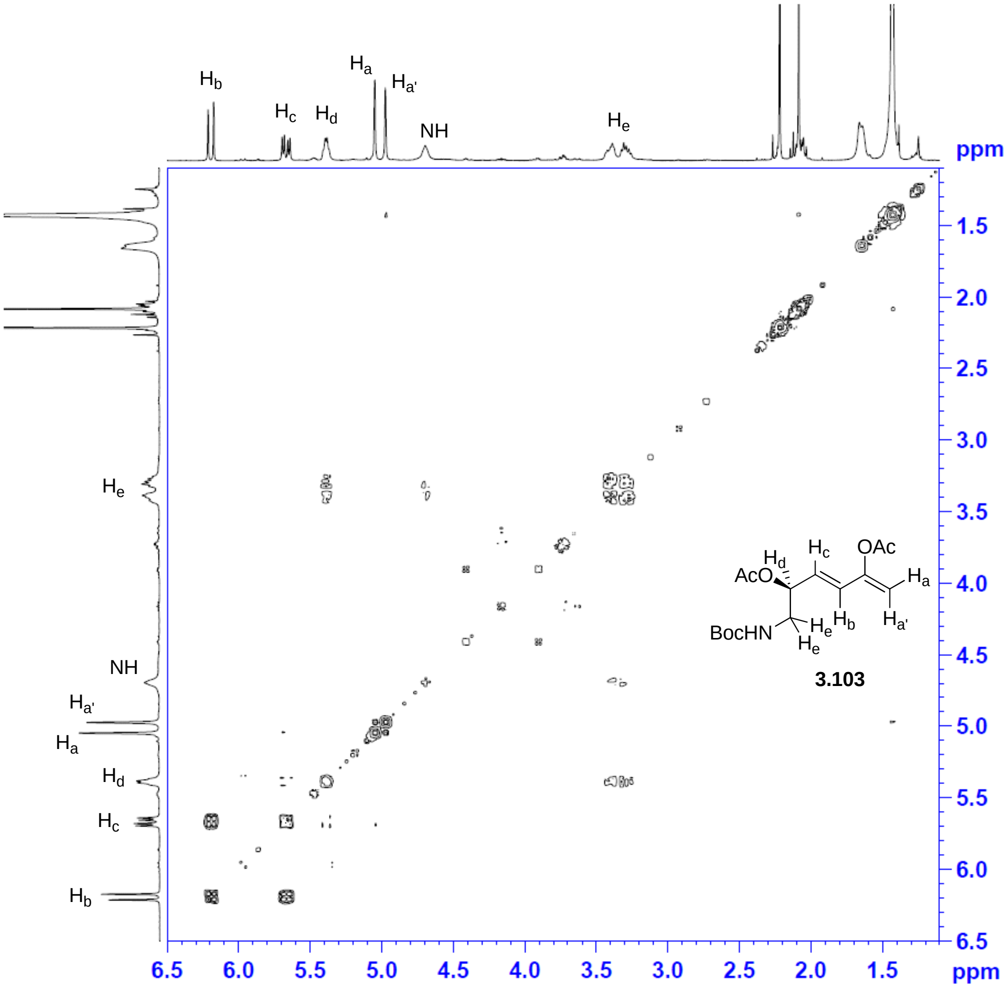
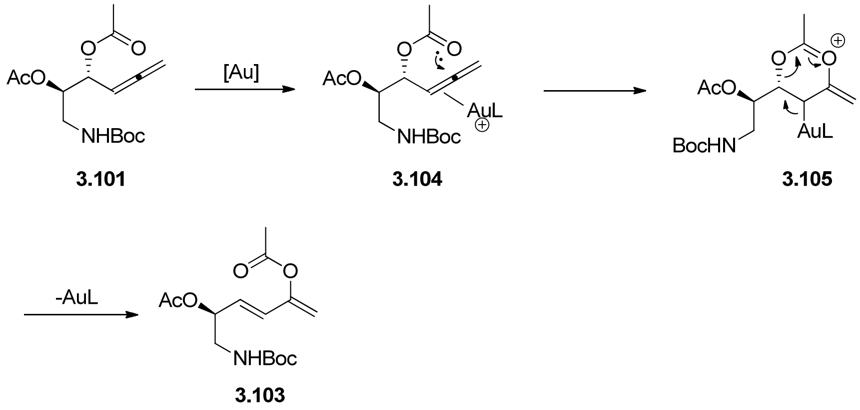


Figure 3.4 COSY NMR ($CDCl_3$) of by-product **3.103**

Inspection of the COSY NMR spectrum (**Figure 3.4**) confirmed the presence of the 1,1-disubstituted alkene (H_a and $H_{a'}$) and *trans* alkene (H_b and H_c), hence the by-product was assigned the structure of diene **3.103**.



Scheme 3.19 Proposed mechanism for the formation of isomerised by-product **3.103**

We speculate that by-product **3.103** could be formed via Au(I)-catalysed isomerisation of the cyclisation precursor **3.101**, similar to that previously reported by Gagosz *et al.*.[202] Coordination of Au(I) to the allene activates it for nucleophilic attack by the carbonyl group of the pendant acetate to give cationic species **3.105**. Fragmentation of the Au-C bond leads to 1,3-shift of the ester group to give diene **3.103**, with regeneration of the gold catalyst. The pendant acetate is required for the isomerisation to occur and hence the diene by-product was not observed with the *bis*-TBS ether substrate **3.82**. The formation of isomerised product **3.103** after extended reaction time, also suggests that nucleophilic attack of the NHBoc group occurs comparatively faster than the carbonyl group of the pendant acetate, mirroring the stronger nucleophilicity of the nitrogen atom.

Similar to the *bis*-TBS protected ether pyrrolidine product **3.99**, we were unable to determine the relative stereochemistry of the *bis*-acetate pyrrolidine product **3.102** at this point due to the overlapping peaks in the ^{1}H NMR spectrum (**Figure 3.5**). Only protons H_x and H_y were distinctly resolved and the integration ratios of these proton signals were used to determine the diastereoselective ratio of the cyclisation.

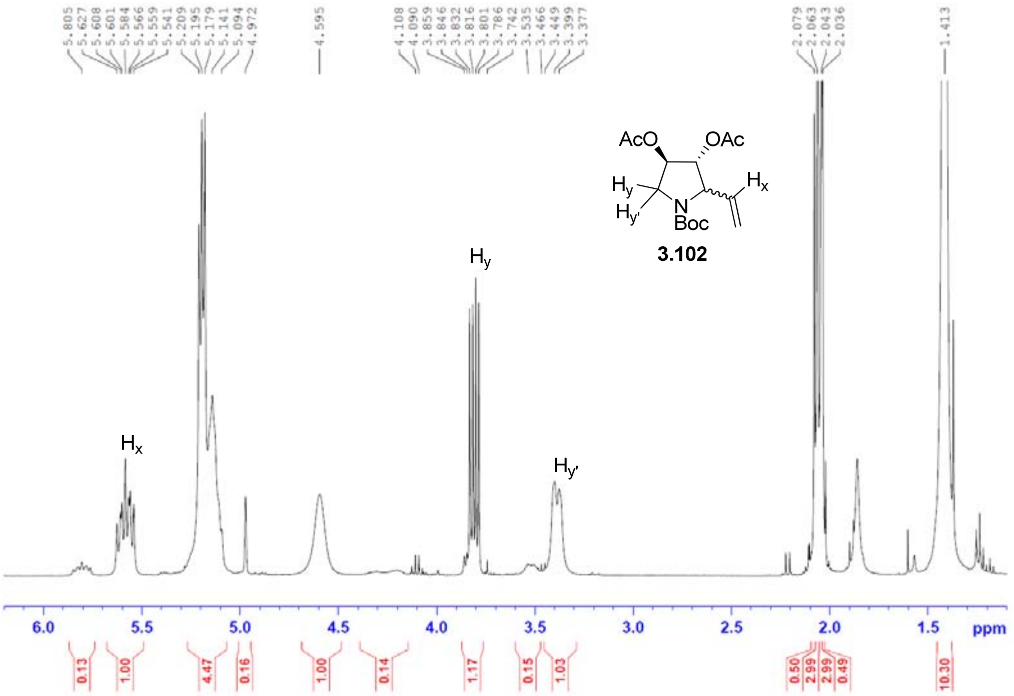
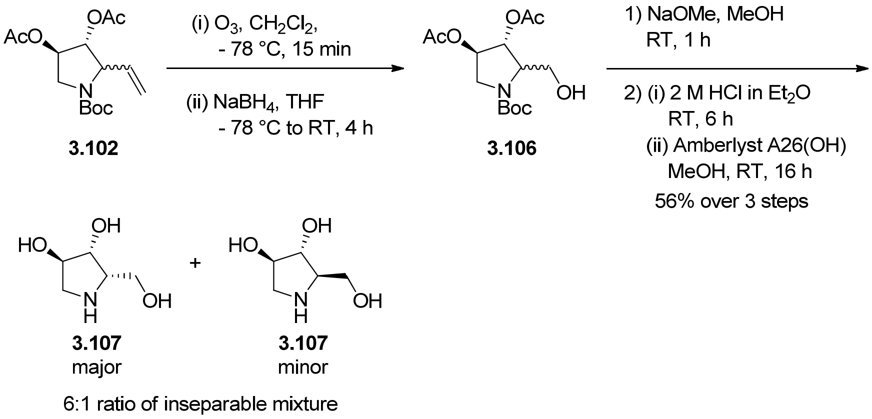


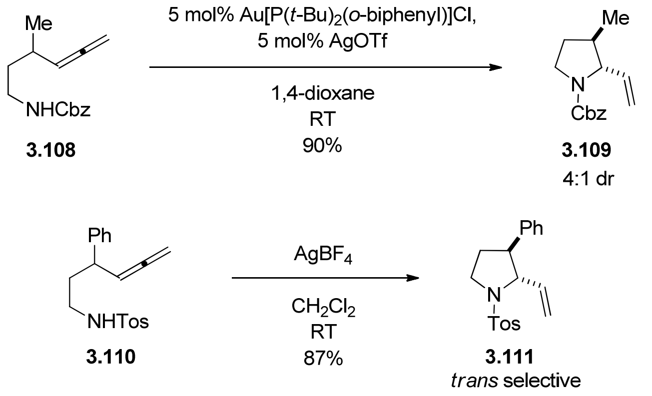
Figure 3.5 ^{1}H NMR (400 MHz, $CDCl_3$) of cyclised material **3.102** showing 7:1 diastereomeric mixture

We recognised that isolation of the final iminosugar and comparison with the published literature for the various diastereomers of DAB-1, would allow us to confirm the stereochemistry of the allene cyclisation and hence proceeded to complete the synthesis of the iminosugar. Ozonolysis of alkene **3.102** (**Scheme 3.20**), followed by reductive work-up with $NaBH_4$, gave primary alcohol **3.106**. Acetate deprotection with NaOMe in MeOH, followed by Boc removal under acidic conditions and neutralisation with basic resin in MeOH, provided pyrrolidine triol **3.107** as its free base in a 6:1 ratio of diastereomers. Separation of the diastereomers was attempted after the allene cyclisation step and again after the conversion to primary alcohol **3.106**, albeit without any success.

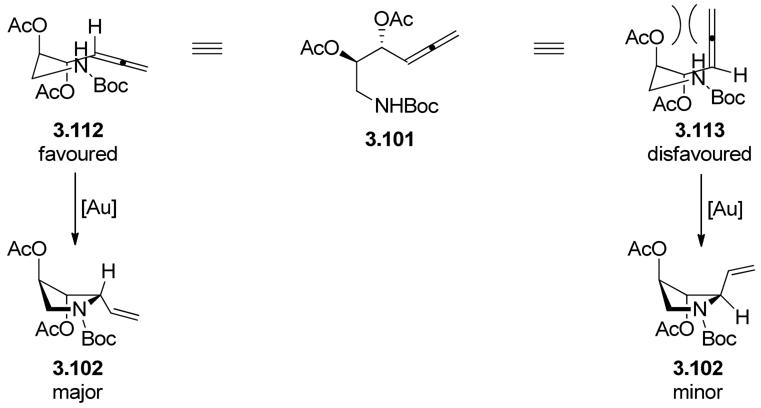


Scheme 3.20 Completing the synthesis of pyrrolidine iminosugar

From the diastereomers obtained from the allene cyclisation step, two different iminosugars would be possible. Should the allene cyclisation proceed with *trans* selectivity, the major isomer we would expect to isolate at the end would be DAB-1 **3.1**. On the contrary, allene cyclisation with *cis* selectivity would give us 1,4-dideoxy-1,4-imino-L-xylitol as the major isomer. Inspection of the ^{1}H and ^{13}C NMR spectra of the final material isolated (**Figure 3.6**) and comparing the chemical shifts with those of DAB-1 and 1,4-dideoxy-1,4-imino-L-xylitol published in literature (**Table 3.3**), it was evident that the major isomer of **3.107** was in good agreement with 1,4-dideoxy-1,4-imino-L-xylitol, while the minor isomer corresponded to that of DAB-1 **3.1**.



Scheme 3.21 Literature examples of pyrrolidine ring formation by allene cyclisation

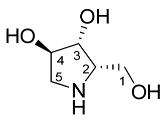


Scheme 3.22 Rationalisation of observed stereoselectivity

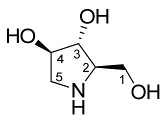
The isolation of 1,4-dideoxy-1,4-imino-L-xylitol as the major isomer implies that the allene cyclisation had proceeded with *cis* selectivity. This is in contrast to previous examples reported in literature[197] (**Scheme 3.21**). We rationalise that the *cis* selectivity could be due to the preference of the *bis*-acetate precursor **3.101** towards the *trans*-diaxial configuration, due to dipolar effects similar to those previously postulated for the six-membered system (*vide supra* Chapter 2). This *trans*-diaxial configuration would place the allene preferably in the equatorial position, giving conformer **3.112**, to minimise 1,3-diaxial strain with the acetate group, hence providing the *cis* product as the major isomer.

The different diastereomeric ratios observed for the allene cyclisation when utilising different protecting groups and Au(I) catalyst also lends support to the proposed *trans*-diaxial configuration. While the use of bulky *bis*-TBS ether protecting groups led to the allene cyclisation proceeding to give predominantly a single isomer (**Table 3.1**, entry 3), a modest 7:1 dr was achieved for the cyclisation with the smaller *bis*-acetate protecting groups (**Table 3.2**, entries 1 and 3). Similarly, the use of Au(I) catalyst with sterically bulky phosphine ligand, was beneficial towards the dr of the cyclisation

(**Table 3.2**, entries 3 and 4). Should the diequatorial configuration be favoured, the differences in dr would probably be less pronounced.



3.107
major



3.1
DAB-1

Analytical Method	Compound			
^{13}C NMR carbon	**3.107** major	**3.107** minor	**3.1**[6] DAB-1	**1,4-dideoxy-1,4-imino-L-xylitol**[203]
1	58.9	61.6	64.8	57.1
2	61.7	65.4	68.0	62.8
3	76.1	78.6	81.8	74.2
4	75.8	76.9	80.2	74.1
5	50.7	50.5	53.4	50.4
^1H NMR proton				
H_1	3.82 - 3.76 (m)	3.73 - 3.68 (m)	3.67 (dd, J = 11.7, 6.3 Hz)	3.90 - 3.86 (m)
$H_{1'}$	3.94 - 3.87 (m)		3.75 (dd, J = 11.7, 4.8 Hz)	3.90 - 3.86 (m)
H_2	3.57 (ddd, J = 7.3, 5.9, 4.0 Hz)	3.14 - 3.07 (m)	3.01 (ddd, J = 6.3, 5.5, 4.8 Hz)	3.58 (dd, J = 15.7, 8.7 Hz)
H_3	4.23 (dd, J =3.9, 1.6 Hz)		3.85 (dd, J = 5.5, 3.7 Hz)	4.30 (s)
H_4	4.28 (td, J = 4.8, 1.8 Hz)	4.19 (td, J =5.6, 3.7 Hz)	4.16 (ddd, J = 5.8, 4.0, 3.7 Hz)	4.36 (d, J = 4.3 Hz)
H_5	3.46 (dd, J = 12.7, 4.9 Hz)	2.93 (dd, J = 12.2, 3.8 Hz)	2.86 (dd, J = 12.1, 4.0 Hz)	3.46 (dd, J = 13.0, 4.3 Hz)
$H_{5'}$	2.99 (dd, J = 12.7, 1.7 Hz)	3.21 (dd, J = 12.3, 5.7 Hz)	3.14 (dd, J = 12.1, 5.8 Hz)	3.28 (d, J = 13.0 Hz)

Table 3.3 Tabulation of analytical data for pyrrolidine iminosugars

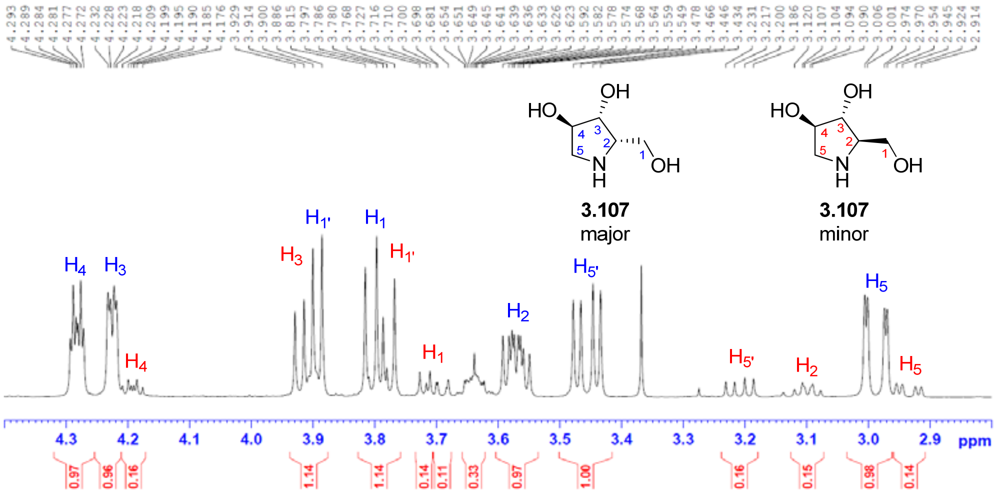
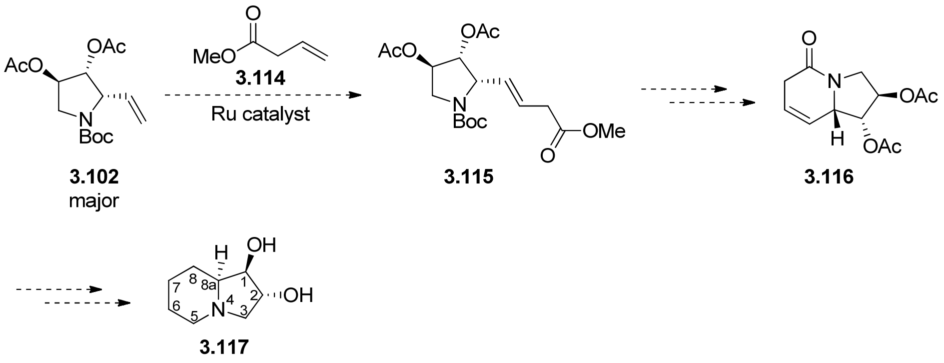


Figure 3.6 ^{1}H NMR (400 MHz, D_2O) of pyrrolidine mixture **3.107**

3.4.2 Synthesis of 1,2-di*epi*-(+)-lentiginosine

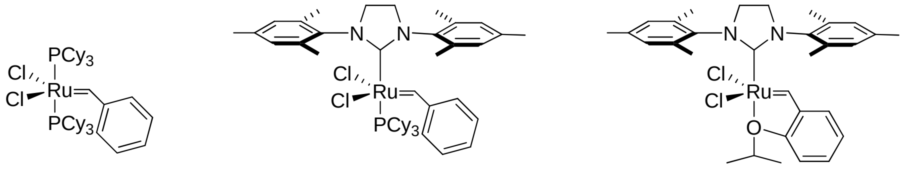
With the *cis* selectivity of the allene cyclisation established in the previous section, it was apparent that utilisation of the 2,3-*cis*-pyrrolidine building block **3.102** for further synthesis as laid out in section **3.3** would lead us to the synthesis of 1,2-di*epi*-(+)-lentiginosine.



Scheme 3.23 Proposed route to 1,2-di*epi*-(+)-lentiginosine **3.117** via cross metathesis

We envision that cross-metathesis between *exo*-cyclic alkene **3.102** (**Scheme 3.23**) generated from the allene cyclisation reaction and methyl but-3-enoate **3.114** would allow us to install the tether required for the formation of a fused piperidine ring. Boc removal from **3.115**, followed by intramolecular lactam formation, would provide indolizidinone **3.116**, which could be transformed into 1,2-di*epi*-(+)-lentiginosine **3.117** by extensive reduction of the alkene and carbonyl functionalities present.

Olefin metathesis is a chemical reaction which involves the rearrangement of alkene double bonds via the scission and regeneration of C=C bonds. It has been utilised widely in coupling, cleavage, ring-opening, ring-closing and polymerisation of alkenes, providing efficient ways for the synthesis of organic compounds. The immense utility of the transformation led to the awarding of the 2005 Nobel Prize in Chemistry to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock for their work in reaction mechanism elucidation and development of highly efficient and selective catalysts (**Figure 3.7**).



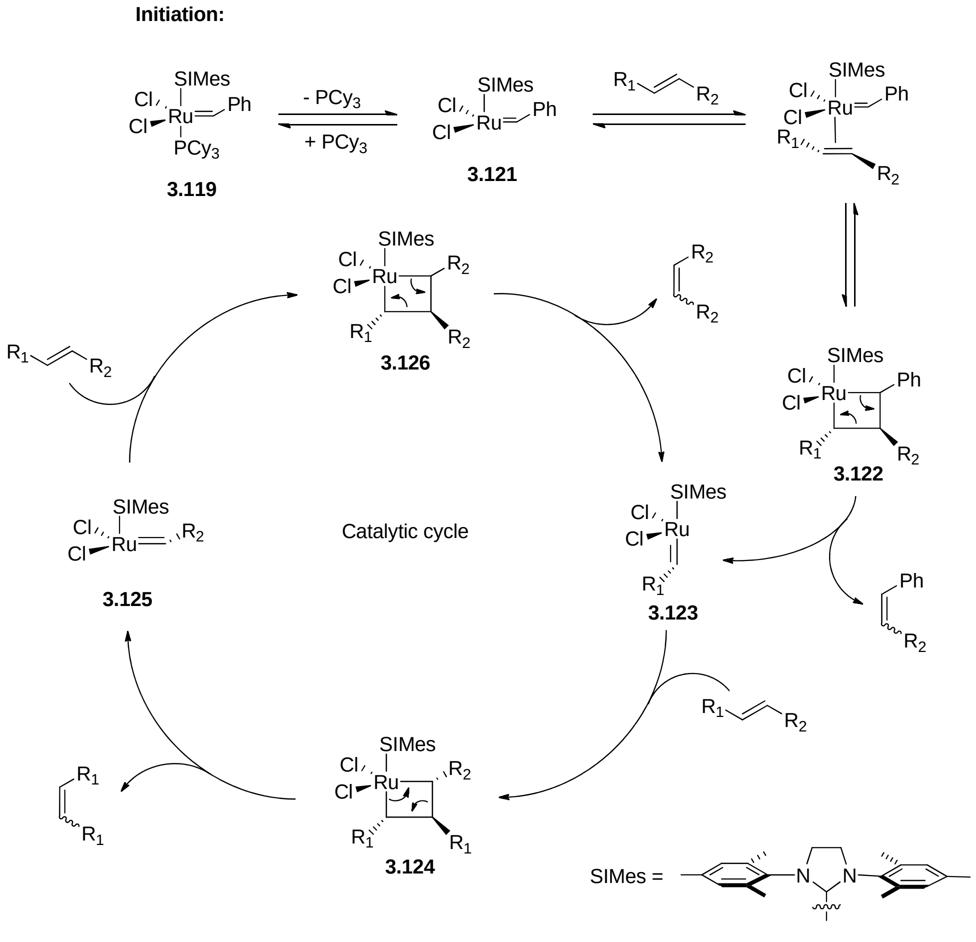
3.118
Grubbs I catalyst

3.119
Grubbs II catalyst

3.120
Hoveyda-Grubbs catalyst

Figure 3.7 Commonly utilised catalysts for metathesis reactions

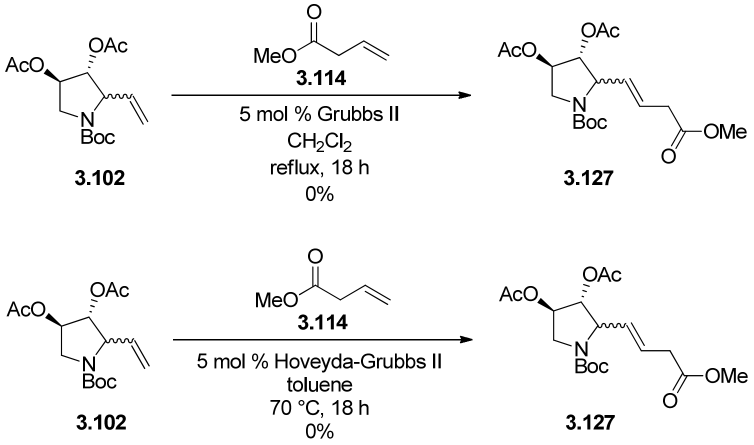
The widely accepted mechanism for olefin metathesis was first proposed by Chauvin *et al.*[204] and later confirmed by Grubbs *et al.*[205] using the deuterium labelled olefin systems. The catalyst first undergoes an initiation step (**Scheme 3.24**) where the 16-electron species **3.119** dissociates a phosphine ligand to give active 14-electron complex **3.121**. Coordination of alkene substrate to complex **3.121** followed by a [2+2] cycloaddition gives ruthenacyclobutane **3.122** which could cyclorevert to give alkylidene **3.123**. The catalytic cycle then continues with alkylidene **3.123** undergoing cycloaddition with another molecule of alkene to form ruthenacyclobutane **3.124**, followed by cycloreversion to return alkylidene **3.125** into the catalytic cycle with expulsion of the new olefin product.



Scheme 3.24 Mechanism of cross metathesis by Grubbs II catalyst

As an initiation step is required for the activation of the catalyst, the rate of dissociation of the phosphine ligand would determine how quickly the initiation occurs. While fast initiation rates are generally useful for applications where low reaction temperatures are desired, slower initiating catalysis are often preferred for ring-opening metathesis polymerisation reactions.[206] Phosphine-free catalyst containing a chelating benzylidene ether ligand **3.120** (**Figure 3.7**), was first developed by Hoveyda *et al.*[207] and subsequently improved upon by the groups of Blechert[208] and Grela.[209] Catalysts of this type generally show similar efficiencies to Grubbs catalysts but are particularly efficient for metathesis involving highly electron-deficient substrates and sterically hindered olefins.[206, 210]

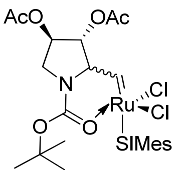
Also evident from the reaction mechanism (**Scheme 3.24**) is that a number of different olefin substrates are generated in the catalytic cycle and each of them could potentially return to the catalytic cycle to undergo further cross metathesis. As such, the inability to accurately predict the selectivity of cross metathesis reactions has resulted in the transformation being less utilised relative to the ring-closing metathesis.[211] In their efforts to understand the selectivity of the cross metathesis and develop an empirical model for predicting product selectivity, Chatterjee *et al.*[211] investigated the olefin metathesis with several classes of olefins. Based on their results obtained, the authors concluded that the best selectivity was often achieved when cross metathesis was carried out for olefins with different reactivities. The authors went on to further categorise olefins based on their propensity to undergo homodimerisation and the subsequent reactivity of their homodimers. In accordance to their categorisation, with type I olefins being most active and able to undergo rapid homodimerisation to type VI olefins which are least active, we would consider *exo*-cyclic alkene **3.102** to be of type II and terminal alkene methyl but-3-enoate **3.114** to be of type I.



Scheme 3.25 Conditions attempted for cross metathesis

We first attempted the cross metathesis with Grubbs II catalyst **3.119** (**Figure 3.7**) and 10 eq. of methyl but-3-enoate **3.114** in refluxing CH_2Cl_2 (**Scheme 3.25**) but did not isolate any desired product **3.127**. We next attempted the cross metathesis at a higher temperature (70 °C) utilising the Hoveyda-Grubbs II catalyst and observed similar results. In both reactions, majority of the starting material **3.102** was recovered and methyl but-3-enoate **3.114** was consumed. While the consumption of methyl but-3-enoate **3.114** was probably due to homodimerisation, the unreactivity of the *exo*-cyclic alkene **3.102** towards cross metathesis was rather unexpected.

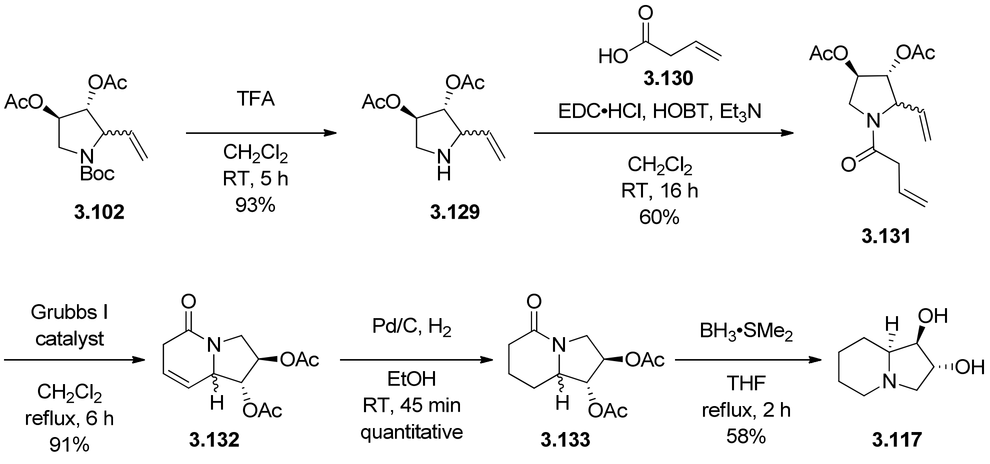
An example of cross metathesis between substrates similar to ours had been previously reported by Vasbinder and Miller[212] and similar low activity was observed. Although the yield reported by the authors for their cross metathesis reaction was 83%, with respect to the amounts of methyl but-3-enoate **3.114** utilised, this was only achieved when the *N*-Boc pyrrolidine substrate was used in a large excess of 5:1 ratio. Such a strategy would not be ideal for our synthesis of 1,2-di*epi*-(+)-lentiginosine, as the pyrrolidine substrate is the key intermediate. We speculated that chelation of the carbonyl from the Boc group to the Ru metal **3.128** (**Figure 3.8**) could be hindering the catalytic turnover of the Ru alkylidene species essential for cross metathesis to proceed, hence resulting in low reaction rates.



3.128

Figure 3.8 Proposed formation of chelate which inactivates Grubbs catalyst

With the cross metathesis reaction proving to be a challenge, we decided to revise our synthesis strategy and sought to install the tether via acylation followed by ring-closing metathesis to construct the indolizidinone ring. This strategy is similar to that employed by Cardona *et al.*[186] in their reported synthesis of (+)-lentiginosine (*vide supra* **Scheme 3.10**). While it is probable that the acylated material could form the same chelate to the Ru metal during ring-closing metathesis, we anticipated that the entropic advantage of the intramolecular reaction would favour the transformation.



Scheme 3.26 Synthesis of 1,2-di*epi*-(+)-lentiginosine

Treatment of *N*-Boc pyrrolidine **3.102** (**Scheme 3.26**) with TFA proceeded to give free pyrrolidine **3.129**. Amide formation with vinyl acetic acid **3.130** under carbodiimide coupling conditions gave diene **3.131**. Ring-closing metathesis with Grubbs I catalyst **3.118** (**Figure 3.7**) in refluxing CH_2Cl_2 proceeded cleanly to give indolizidinone **3.132** in an excellent yield of 91%. It should be noted that our initial attempt on the ring-closing metathesis employing Grubbs II catalyst **3.119** (**Figure 3.7**) led to the complete consumption of diene **3.131** after 6 hours at ambient temperatures. However, the reaction profile was less clean and the desired indolizidinone product **3.132** was isolated in only 61% yield. We recognised that the shorter reaction time and milder reaction conditions required for the Grubbs II catalyst are consistent with its higher activity,[206] and it is probable that this higher reactivity also contributed to the formation of other by-products.

Reduction of indolizidinone **3.132** under hydrogenative conditions provided indolizidine **3.133** as a colourless solid in quantitative yields. Encouraged by the crystalline appearance of indolizidine **3.133**, we attempted recrystallisation of the material with the aim of separating the diastereomers which originated from pyrrolidine starting material **3.102**. Although we were unable to purify the mixture via recrystallisation after several attempts, slow evaporation of a CH_2Cl_2/MeOH solution containing indolizidine **3.133** provided single crystals suitable for X-ray diffraction.

X-ray structure of the single crystal (**Figure 3.9**) showed a *cis* relationship between C1 and C8a substituents, with the acetate groups at C1 and C2 positions orientated in a diaxial configuration. Although this was in agreement with the stereochemistry we had determined in the previous section based on the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol, we could not conclude whether this structure corresponded to the major or minor isomer, as the crystal had been obtained from a mixture of diastereomers.

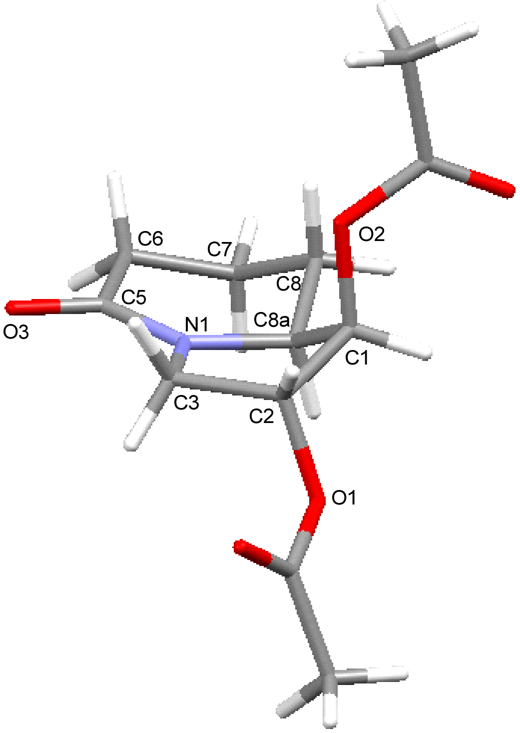


Figure 3.9 X-ray structure of major diastereomer **3.133**
Hydrogens and Ac groups not labelled for clarity

In order to unambiguously assign the identity of the crystal obtained, we recovered the crystal from the crystallographer and proceeded to characterise it by ^{1}H NMR spectroscopy. Although the ^{1}H NMR spectrum of the crystal contained a broad signal in the 1.0 – 2.0 ppm region due to the adhesive used for mounting the crystal for X-ray diffraction, this was not crucial as most of the proton signals related to indolizidine **3.133** were in the 2.0 – 5.5 ppm region. Comparison of the ^{1}H NMR spectrum (**Figure 3.10**) of the single crystal with that of the diastereomeric mixture of indolizidine **3.133** clearly showed that the single crystal corresponded to that of the major isomer. This result implies that the major isomer of pyrrolidine **3.102** is indeed the *cis* isomer and corroborates our previous conclusion that the allene cyclisation had proceeded with *cis* selectivity.

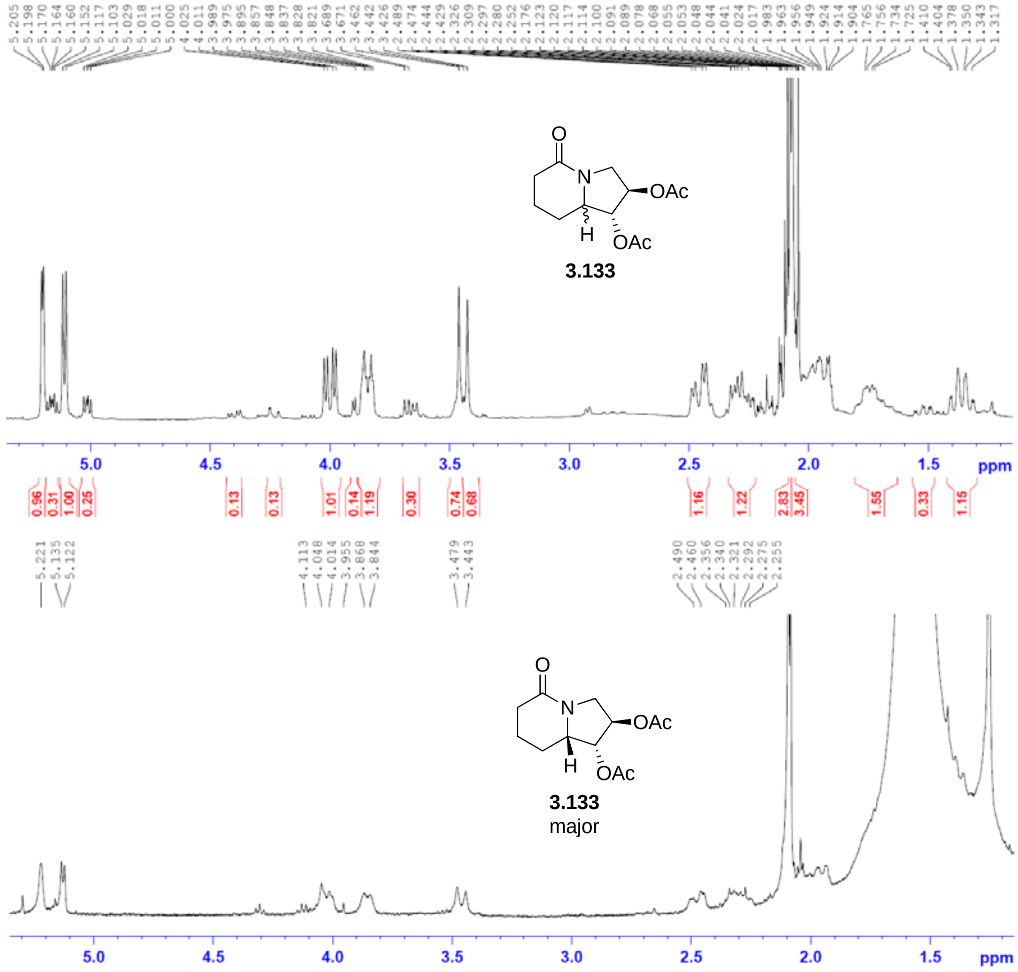
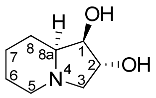


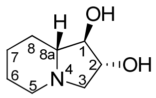
Figure 3.10 ^{1}H NMR spectra of indolizidine diastereomers **3.133** (top) and indolizidine single crystal (bottom)

Finally, tandem reduction of the lactam and the acetate protecting groups using BH_3•SMe_2 complex in refluxing THF[213] provided indolizidine alkaloid **3.117** as a single diastereomer (**Figure 3.11**). Although the material prior to reduction was a mixture of diastereomers, we were unable to isolate the minor isomer after silica-gel chromatography of the crude reaction mixture despite flushing the column with polar solvent mixtures of 80% MeOH/CH_2Cl_2. We speculated that the minor isomer could be relatively more polar than the major isomer and hence was very well retained on the column.

It should be added that when the global reduction was attempted with $LiAlH_4$ at ambient temperature, complete consumption of starting material was observed but the desired product **3.117** was isolated in only 14% yield. This low yield is attributed to the poor recovery of the water-soluble desired product from the aqueous work-up conditions utilised.



3.117



3.45
(-)-lentiginosine

Analytical Method	Compound		
^{13}C NMR carbon	**3.117**	**3.45**[183d]	**1,2-di*epi*-(+)-lentiginosine**[183c]
1	79.1	82.2	81.1
2	76.6	75.0	77.8
3	60.1	59.7	62.2
5	52.7	52.2	53.1
6	24.0	27.1	25.2
7	23.8	26.6	24.7
8	23.2	23.5	22.9
8a	66.8	68.1	66.9
Specific rotation $[\alpha]_D$	+ 4.63 (*c* 0.41, MeOH)	- 3.1 (*c* 0.5, MeOH)	+ 4.3 (*c* 0.5, MeOH)
Melting point	138 -140 °C	106 -108 °C	133 -135 °C

Table 3.4 Tabulation of analytical data for indolizidine iminosugars

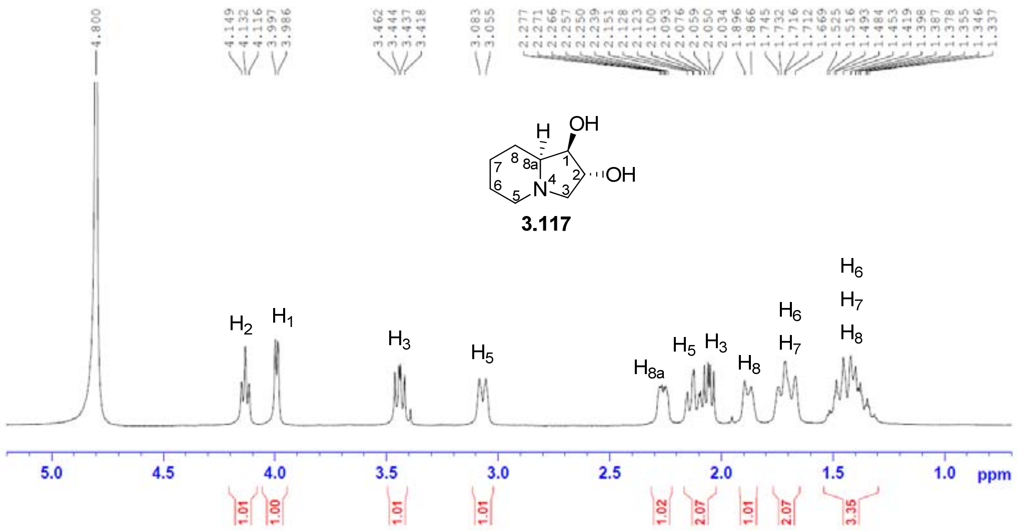


Figure 3.11 ^{1}H NMR (400 MHz, D_2O) of 1,2-di*epi*-(+)-lentiginosine **3.117**

Comparison of ^{13}C NMR data, specific rotation and melting point of **3.117** with those reported for 1,2-di*epi*-(+)-lentiginosine (**Table 3.4**) indicates good agreement, hence confirming the identity of the final compound isolated.

3.5 Conclusion and future direction

Au-catalysed allene cyclisation was successfully applied to the synthesis of 1,4-dideoxy-1,4-imino-L-xylitol **3.107** and 1,2-di*epi*-(+)-lentiginosine **3.117**. While the allene cyclisation was not efficient with bulky substituents, the use of smaller substituents, together with the employment of more active Au(I) catalyst, provided functionalised pyrrolidine ring in a good yield of 73%. This, to our knowledge, represents the first example of nucleophilic allene cyclisation of α,β-substituted allenes for the construction of a functionalised pyrrolidine ring.

The allene cyclisation proceeded with *cis* selectivity and it was observed that the diastereomeric ratios for the cyclisation could be influenced either by the size of the substituents at the α- and β-positions or the steric bulk of the phosphine ligand on the Au(I) catalyst. These observations are in line with our proposed *trans*-diaxial configuration of the diol in the cyclisation step due to dipolar effects.

While we were successful in obtaining the pyrrolidine product in good yield, the diastereoselectivity of the cyclisation was modest and could perhaps be further improved. Our investigations suggest that increasing the steric bulk of the substituents at α- and β-positions could be beneficial for selectivity, however this needs to be balanced, as the use of large substituents could hinder the formation of the pyrrolidine ring. Protecting groups such as TMS ether, benzyl ether or *tert*-butyl ether, with intermediate steric bulk between that of TBS ether and acetate, could perhaps be good starting points for further investigation.

Another avenue for increasing the diastereoselectivity could be the investigation into the use different Au(I) catalysts. With the increasing utility and development of gold catalysis, a large number of Au(I) catalysts with different coordinating ligands have been developed. The investigation into Au(I) catalysts with different bulky Buchwald-type ligands would probably be worthwhile, as the preliminary investigations have shown improvements in diastereoselectivity with the use of bulkier phosphine ligands.

Chapter 4 Experimental section

4.1 General methods

All reactions requiring anhydrous conditions were carried out under an inert atmosphere (nitrogen or argon) using oven-dried glassware (150 °C). Unless otherwise specified, all starting materials, reagents, anhydrous solvents and solvents were obtained from commercial vendors and used as received. Reactions were monitored by NMR spectroscopy or analytical thin-layer chromatography (TLC) using Merck silica gel 60, F254 precoated glass plates. Column chromatography was performed with either silica gel 60 (230 - 400 mesh) or RediSep® normal-phase silica flash columns on a Teledyne Isco CombiFlash® system. Microwave reactions were carried out using a Biotage® Initiator microwave synthesiser.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with TMS, $CHCl_3$ or H_2O as internal standard (For ^{1}H NMR, TMS: 0.00 ppm, $CHCl_3$: 7.26 ppm, H_2O: 4.80 ppm. For ^{13}C NMR, TMS: 0.00 ppm, $CHCl_3$: 77.0 ppm). Coupling constants *J* are recorded in Hz and data are reported as follow: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. ^{13}C NMR spectra were obtained with complete proton decoupling.

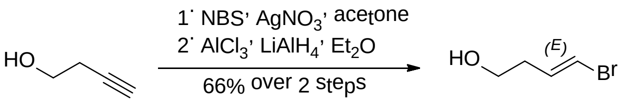
Mass spectra were recorded on a Finnigan LCQ DECA XP MAX Ultra instrument in ESI mode, Finnigan Polaris Q GCMS XP instrument in EI mode, ABSciex API 3200 instrument in ESI mode or Waters Acquity UPLC ZQ2000 instrument in ESI mode. High resolution mass spectra were recorded on a Waters Q-Tof Premier instrument or LTQ Orbitrap XL mass spectrometer.

Infrared (FTIR) spectra were recorded on Bruker Alpha-E FT-IR or IR Jasco FT-IR 4100 instruments, either as a thin film or solid. Melting points were determined on Büchi melting point B-540 instrument and are uncorrected.

Specific rotations were recorded on a Jasco P-1030 polarimeter at wavelength of 589 nm. Chiral purities were determined either using (a) Agilent 1100 LC system with Chiralpak AD column (150 x 2.1 mm) and hexane/IPA solvent system or (b) Thar SFC X5-250 instrument with Lux Cellulose-2 (100 x 4.6 mm) or OJ-H (100 x 4.6 mm) column and MeOH/CO_2 or IPA/CO_2 solvent system.

4.2 Experimental section for Chapter 2

Synthesis of (*E*)-4-bromobut-3-en-1-ol (2.43).[111]



To a well-stirred solution of 3-butyn-1-ol (**2.44**) (5.00 g, 71.3 mmol) and NBS (14.6 g, 82 mmol) in acetone (90 mL) was added $AgNO_3$ (500 mg, 10%w/w of acetylenic compound). The resulting mixture was stirred at room temperature for 3 hours before it was filtered through a plug of celite, washing with acetone (30 mL). The filtrate was evaporated *in vacuo* to give a mixture of white solid in light yellow oil. The mixture was taken up in Et_2O (80 mL) and washed with brine (80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 4-bromo-3-butyn-1-ol (**2.45**) as a bright yellow oil (10.1 g, 95% yield), which was used directly in the next step without further purification. ^{1}H NMR data obtained were consistent with those reported in the literature.[111]

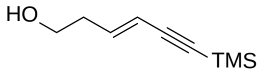
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.73 (t, J = 6.2 Hz, 2H, CH_2OH), 2.49 (t, J = 6.2 Hz, 2H, $C{\equiv}CCH_2$), 1.77 (br. s., 1H, OH)

Aluminium chloride (16.2 g, 122 mmol) was added to cold Et_2O (190 mL) before $LiAlH_4$ (4.62 g, 122 mmol) was added portionwise over a period of 20 minutes. The resultant mixture was stirred at - 5 °C for 30 minutes before a solution of 4-bromo-3-butyn-1-ol (**2.45**) (10.1 g, 67.7 mmol) in Et_2O (35 mL) was added dropwise via an addition funnel at - 5 °C over a period of 60 minutes. The resultant mixture was heated at reflux for 4 hours before it was cooled to 0 °C, diluted with Et_2O (100 mL) and quenched with dropwise addition of 2

M HCl solution (100 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford title compound **2.43** as a light yellow oil (6.60 g, 66% yield over 2 steps) which was used directly in the next step without further purification. ^{1}H NMR data obtained were consistent with those reported in the literature.[111]

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.25 - 6.11 (m, 2H, C*H*=C*H*CH$_2$), 3.68 (t, *J* = 6.2 Hz, 2H, C*H*$_2$OH), 2.31 (q, *J* = 6.3 Hz, 2H, CH=CHC*H*$_2$), 1.72 (br. s., 1H, O*H*)

Synthesis of (*E*)-6-(trimethylsilyl)hex-3-en-5-yn-1-ol (2.46).



A solution of vinyl bromide (**2.43**) (10.2 g, 50.8 mmol) in THF (200 mL) was degassed with nitrogen before CuI (1.55 g, 8.12 mmol), $Pd(PPh_3)_2Cl_2$ (2.85 g, 4.06 mmol) and Et_3N (9.20 mL, 66 mmol) were added. The mixture was stirred at room temperature for 5 minutes before TMS-acetylene (21.1 mL, 152 mmol) was added. The resultant mixture was stirred at room temperature overnight before it was filtered through a plug of celite, washing with EtOAc (100 mL). The filtrate was concentrated *in vacuo* to give a black oil. The crude material was purified by silica gel chromatography (gradient: 5 – 20% EtOAc in hexanes) to afford the title compound **2.46** (6.06 g, 70% yield) as a colourless oil.

R_f = 0.34 (30% EtOAc/hexanes), stained yellow with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.25 - 6.14 (m, 1H, CH=C*H*CH_2), 5.62 (d, *J* = 16.1 Hz, 1H, C*H*=CHCH_2), 3.69 (q, *J* = 6.0 Hz, 2H, CH_2OH), 2.38 (q, *J* = 6.7 Hz, 2H, CH=CHCH_2), 1.39 (t, *J* = 5.7 Hz, 1H, O*H*), 0.18 (s, 9H, 3 x SiCH_3)

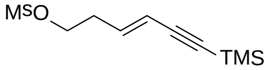
^{13}C NMR (101 MHz, $CDCl_3$) δ = 141.7 (CH=*C*HCH_2), 112.0 (*C*H=CHCH_2), 103.5 (SiC≡*C*CH), 93.2 (Si*C*≡CCH), 61.1 (*C*H_2OH), 36.1 (CH=CH*C*H_2), - 0.24 (Si*C*H_3)

IR ν_{max} (oil) 3336, 2958, 2898, 2176, 2135, 1420, 1249, 1083, 836 cm^{-1}

MS (EI) *m/z* 168 $[M]^+$ (15%), 153 (100%)

HRMS (ESI) *m/z* calc’d for $C_9H_{17}OSi$ $[M+H]^+$ 169.1043, found 169.1043

Synthesis of (*E*)-6-(trimethylsilyl)hex-3-en-5-yn-1-yl methanesulfonate (2.47).



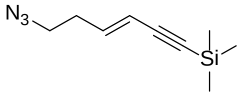
To a solution of alcohol (**2.46**) (204 mg, 1.21 mmol) in CH_2Cl_2 (7 mL) cooled to 0 °C was added Et_3N (253 µL, 1.82 mmol) followed by $MeSO_2Cl$ (113 µL, 1.45 mmol). The resultant mixture was stirred at 0 °C for 5 hours before it was quenched with addition of sat’d NH_4Cl solution (5 mL). The organic layer was separated and washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. Crude mesylate **2.47** was used directly in the next step without further manipulation.

R_f = 0.26 (20% EtOAc/cyclohexane), visualised by UV light

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.13 (td, *J* = 7.1, 16.0 Hz, 1H, CH=C*H*CH_2), 5.64 (td, *J* = 1.5, 16.0 Hz, 1H, C*H*=CHCH_2), 4.25 (t, *J* = 6.5 Hz, 2H, CH_2O), 3.01 (s, 3H, C$H_3$$SO_2$), 2.56 (dq, *J* = 1.5, 6.5 Hz, 2H, CH=CHCH_2), 0.18 (s, 9H, 3 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 138.5 (CH=*C*HCH$_2$), 113.6 (*C*H=CHCH$_2$), 102.8 (SiC≡*C*CH), 94.7 (Si*C*≡CCH), 67.9 (*C*H$_2$O), 37.6 (*C*H$_3$SO$_2$), 32.7 (CH=CH*C*H$_2$), - 0.15 (Si*C*H$_3$)

Synthesis of (*E*)-(6-azidohex-3-en-1-yn-1-yl)trimethylsilane (2.48).



To a solution of mesylate (**2.47**) (256 mg, 1.04 mmol) in DMF (2 mL) was added NaN_3 (169 mg, 2.60 mmol). The resultant mixture was stirred at room temperature for 20 hours before EtOAc (5 mL) and H_2O (3 mL) were added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 2% EtOAc in cyclohexane) to afford the title compound **2.48** (172 mg, 80% yield over 2 steps) as a colourless oil.

R$_f$ = 0.45 (2% EtOAc/cyclohexane), visualised by UV light

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.15 (td, *J* = 7.1, 16.0 Hz, 1H, CH=C*H*CH$_2$), 5.62 (td, *J* = 1.5, 16.0 Hz, 1H, C*H*=CHCH$_2$), 3.33 (t, *J* = 6.9 Hz, 2H, C*H*$_2$N), 2.39 (dq, *J* = 1.5, 6.9 Hz, 2H, CH=CHC*H*$_2$), 0.18 (s, 9H, 3 x SiC*H*$_3$)

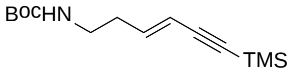
^{13}C NMR (101 MHz, $CDCl_3$) δ = 140.6 (CH=*C*HCH$_2$), 112.7 (*C*H=CHCH$_2$), 103.1 (SiC≡*C*CH), 94.2 (Si*C*≡CCH), 50.2 (*C*H$_2$N), 32.5 (CH=CH*C*H$_2$), - 0.13 (Si*C*H$_3$)

IR ν_{max} (film) 2962, 2897, 2099, 1247, 1080, 836 cm^{-1}

MS (EI) *m/z* 178 [M-CH$_3$] (84%), 59 (100%)

HRMS (ESI) *m/z* calc'd for $C_9H_{16}N_3Si$ [M+H]$^+$ 194.1108, found 194.1105

Synthesis of (*E*)-*tert*-butyl (6-(trimethylsilyl)hex-3-en-5-yn-1-yl)carbamate (2.49).



To a solution of azide (**2.48**) (92.3 mg, 0.477 mmol) in THF (5 mL) was added PPh_3 (188 mg, 0.716 mmol). The mixture was stirred at room temperature for 4 hours before H_2O (172 µL, 9.54 mmol) was added. The mixture was stirred at room temperature overnight and TLC (10% EtOAc/cyclohexane) showed complete consumption of starting material. Boc_2O (135 mg, 0.620 mmol) was added to reaction mixture followed by DIPEA (125 µL, 0.716 mmol). The mixture was stirred at room temperature for 2 hour 30 minutes before it was diluted with EtOAc (5 mL) and washed with brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.49** (114 mg, 89% yield) as a light brown solid.

R_f = 0.36 (10% EtOAc/cyclohexane), visualised by UV light and stained yellow with ninhydrin.

Melting point = 69 – 70 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.13 (td, *J* = 7.3, 15.9 Hz, 1H, $CH{=}C\mathit{H}CH_2$), 5.57 (td, *J* = 1.5, 15.9 Hz, 1H, $C\mathit{H}{=}CHCH_2$), 3.19 (t, *J* = 6.9 Hz, 2H, $C\mathit{H}_2N$), 2.29 (dq, *J* = 1.4, 6.9 Hz, 2H, $CH{=}CHC\mathit{H}_2$), 1.44 (s, 9H, $C(C\mathit{H}_3)_3$), 0.18 (s, 9H, 3 x $SiC\mathit{H}_3$)

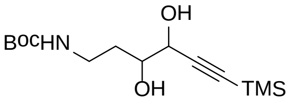
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8 ($\mathit{C}{=}O$), 142.1 ($CH{=}\mathit{C}HCH_2$), 112.1 ($\mathit{C}H{=}CHCH_2$), 103.4 ($SiC{\equiv}\mathit{C}CH$), 93.5 ($Si\mathit{C}{\equiv}CCH$), 79.3 ($\mathit{C}(CH_3)_3$), 39.4 ($\mathit{C}H_2NH$), 33.6 ($CH{=}CH\mathit{C}H_2$), 28.3 ($C(\mathit{C}H_3)_3$), - 0.16 ($Si\mathit{C}H_3$)

IR ν_{max} (film) 3350, 2965, 2137, 1699, 1510, 1249, 1170, 841 cm^{-1}

MS (ESI) *m/z* 168 $[M\text{-}Boc+H]^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{25}NO_2SiNa$ $[M+Na]^+$ 290.1547, found 290.1544

Synthesis of (±)-*tert*-butyl (3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl)carbamate (2.63).



To a vigorously stirred solution of enyne (**2.49**) (61.0 mg, 0.228 mmol), $K_3Fe(CN)_6$ (225 mg, 0.684 mmol) and K_2CO_3 (94.5 mg, 0.684 mmol) in 1:1 *t*-BuOH/H_2O (3 mL) was added $K_2OsO_4{\bullet}2H_2O$ (4.20 mg, 11.4 µmol). The resultant mixture was stirred at room temperature for 48 hours before it was quenched by addition of solid Na_2SO_3 (150 mg). The mixture was stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 50% EtOAc in cyclohexane) to afford the title compound **2.63** (16.9 mg, 24% yield) as a colourless oil.

R_f = 0.43 (50% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.91 (br. s., 1H, N*H*), 4.18 (d, *J* = 6.8 Hz, 1H, C≡CC*H*OH), 3.87 (br. s., 1H, OH), 3.65 (t, *J* = 7.3 Hz, 1H, CH_2C*H*OH), 3.47 (br. s., 1H, O*H*), 3.23 - 3.12 (m, 1H, C*H*HNH), 2.84 - 2.62 (m, 1H, CH*H*NH), 1.90 - 1.79 (m, 1H, C*H*HCH_2NH), 1.55 (tdd, *J* = 5.0, 9.8, 14.4 Hz, 1H, CH*H*CH_2NH), 1.44 (s, 9H, C(CH_3)$_3$), 0.17 (s, 9H, 3 x SiCH_3)

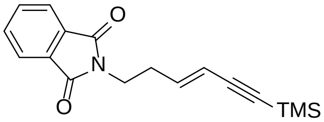
^{13}C NMR (101 MHz, CDCl$_3$) δ = 157.0 (*C*=O), 103.4 (SiC≡*C*CH), 91.6 (Si*C*≡CCH), 79.8 (O*C*(CH)$_3$), 72.6 (SiC≡C*C*H), 66.7 (CH$_2$*C*HOH), 37.3 (CH$_2$*C*H$_2$NH), 33.1 (*C*H$_2$CH$_2$NH), 28.4 (OC(*C*H)$_3$), - 0.22 (Si*C*H$_3$)

IR $\nu_{\max}$ (film) 3361, 2965, 2896, 2179, 1688, 1517, 1245, 1170, 841 cm^{-1}

MS (ESI) *m/z* 202 [M-Boc+H]$^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{28}NO_4Si$ [M+H]$^+$ 302.1782, found 302.1781

Synthesis of (*E*)-2-(6-(trimethylsilyl)hex-3-en-5-yn-1-yl)isoindoline-1,3-dione (2.67).



To a solution of alcohol (**2.46**) (150 mg, 0.891 mmol) in THF (8 mL) was added phthalimide (170 mg, 1.16 mmol), triphenylphosphine (304 mg, 1.16 mmol) and DIAD (226 µL, 1.16 mmol) dropwise. The resultant mixture was left to stir under argon at room temperature for 16 hours before it was concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 15% EtOAc in cyclohexane) to afford the title compound **2.67** (265 mg, 88% yield) as a light yellow oil.

R$_f$ = 0.50 (20% EtOAc/cyclohexane), visualised by UV light and stained blue with CAM.

^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.88 - 7.81 (m, 2H, Ar*H*), 7.75 - 7.68 (m, 2H, Ar*H*), 6.15 (td, *J* = 7.2, 15.9 Hz, 1H, CH$_2$C*H*=CHC), 5.58 (td, *J* = 1.5, 15.9 Hz, 1H, CH$_2$CH=C*H*C), 3.75 (t, *J* = 7.3 Hz, 2H, C*H*$_2$N), 2.51 (dq, *J* = 1.5, 7.2 Hz, 2H, C*H*$_2$CH=CHC), 0.16 (s, 9H, 3 x SiC*H*$_3$)

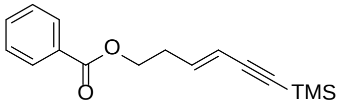
^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.2 (*C*=O), 140.6 (CH=*C*HCH$_2$), 133.9 (Ar), 132.1 (Ar), 123.3 (Ar), 112.6 (*C*H=CHCH$_2$), 103.3 (SiC≡*C*CH), 93.9 (Si*C*≡CCH), 36.9 (*C*H$_2$N), 32.1 (CH=CH*C*H$_2$), - 0.12 (Si*C*H$_3$)

IR ν_{max} (film) 2958, 2156, 1722, 1707, 1392, 1365, 1247, 844, 715 cm^{-1}

MS (ESI) *m/z* 298 $[M+H]^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{17}H_{20}NO_2Si$ $[M+H]^+$ 298.1258, found 298.1258

Synthesis of (*E*)-6-(trimethylsilyl)hex-3-en-5-yn-1-yl benzoate (2.68).



To a solution of alcohol (**2.46**) (76.5 mg, 0.455 mmol) in CH_2Cl_2 (5 mL) was added DMAP (5.56 mg, 0.05 mmol), Et_3N (95.1 µL, 0.683 mmol) and benzoyl chloride (63.4 µL, 0.546 mmol). The resultant mixture was stirred at room temperature for 1 hour before it was quenched by addition of 1 M HCl solution (5 mL). The mixture was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic extracts were washed with sat'd $NaHCO_3$ solution (5 mL) and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a clear oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.68** (100 mg, 81% yield) as a colourless oil.

R$_f$ = 0.66 (20% EtOAc/cyclohexane), visualised by UV light

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.06 - 8.00 (m, 1H, Ar*H*), 7.59 - 7.53 (m, 1H, Ar*H*), 7.48 - 7.41 (m, 2H, Ar*H*), 6.25 (td, *J* = 7.1, 15.9 Hz, 1H, CH$_2$C*H*=CHC), 5.66 (td, *J* = 1.6, 15.9 Hz, 1H, $CH_2CH=CHC$), 4.36 (t, J = 6.5 Hz, 2H, OCH_2), 2.58 (dq, J = 1.5, 6.7 Hz, 2H, $CH=CHCH_2$), 0.18 (s, 9H, 3 x $SiCH_3$)

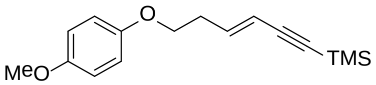
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.5 (C=O), 140.6 ($CH=CHCH_2$), 132.9, 130.2, 129.6, 128.4, 112.5 ($CH=CHCH_2$), 103.4 (SiC≡CCH), 93.9 (SiC≡CCH), 63.4 (CH_2O), 32.4 ($CH=CHCH_2$), - 0.11 ($SiCH_3$)

IR ν_{max} (film) 2980, 2923, 2862, 2137, 1722, 1272, 1113, 841, 709 cm^{-1}

MS (ESI) *m/z* 273 $[M+H]^+$ (46%), 102 (100%)

HRMS (ESI) *m/z* calc'd for $C_{16}H_{21}O_2Si$ $[M+H]^+$ 273.1305, found 273.1303

Synthesis of (*E*)-(6-(4-methoxyphenoxy)hex-3-en-1-yn-1-yl)trimethylsilane (2.69).



To a solution of alcohol (**2.46**) (2.40 g, 14.3 mmol), *p*-methoxyphenol (5.31 g, 42.8 mmol) and triphenylphosphine (5.05 g, 19.3 mmol) in dry THF (47.5 mL) was added dropwise DIAD (3.74 mL, 19.3 mmol) at room temperature. The resultant mixture was left to stir under nitrogen at room temperature for 18 hours before it was concentrated *in vacuo* to give an orange-brown oil. The crude material was purified by silica gel chromatography (gradient: 2 – 20% EtOAc in hexanes) to afford the title compound **2.69** (2.61 g, 66% yield) as a light yellow oil.

R_f = 0.69 (30% EtOAc/hexanes), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.86 - 6.76 (m, 4H, ArH), 6.29 (td, J = 7.1, 15.9 Hz, 1H, $CH_2CH=CHC$), 5.64 (td, J = 1.5, 15.9 Hz, 1H, $CH_2CH=CHC$), 3.95 (t, J = 6.5 Hz, 2H, ArOC*H*$_2$CH$_2$), 3.77 (s, 3H, OC*H*$_3$), 2.56 (dq, *J* = 1.5, 6.7 Hz, 2H, ArOCH$_2$C*H*$_2$), 0.21 - 0.15 (s, 9H, 3 x SiC*H*$_3$)

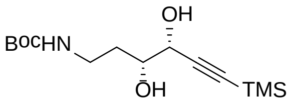
^{13}C NMR (101 MHz, CDCl$_3$) δ = 153.9, 152.8, 141.4 (CH$_2$*C*H=CHC), 115.5, 114.6, 112.0 (CH$_2$CH=*C*HC), 103.6 (SiC≡*C*), 93.6 (Si*C*≡C), 67.2 (ArO*C*H$_2$CH$_2$), 55.7 (O*C*H$_3$), 33.0 (ArOCH$_2$*C*H$_2$), - 0.09 (Si*C*H$_3$)

IR ν_{max} (film) 2957, 2900, 2832, 2133, 1510, 1227, 1042, 837 cm^{-1}

MS (ESI) *m/z* 275 [M+H]$^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}O_2Si$ [M+H]$^+$ 275.1462, found 275.1461

Synthesis of *tert*-butyl ((3*R*,4*R*)-3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl)carbamate (2.49b)



AD-mix beta (256 mg, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H$_2$O (2 mL) and methanesulfonamide (17.4 mg, 0.183 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**2.49**) (49.0 mg, 0.183 mmol), predissolved in 1:1 *t*-BuOH/H$_2$O (1 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from ice bath and stirred at room temperature for 48 hours to give a yellow mixture. The mixture was quenched with addition of solid Na$_2$SO$_3$ (150 mg) and stirred for 30 minutes before H$_2$O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (3 mL), dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 50% EtOAc in hexanes) to afford the title compound **2.49b** (7.0 mg, 12% yield) as a colourless solid.

R_f = 0.43 (50% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.91 (br. s., 1H, N*H*), 4.18 (d, *J* = 6.8 Hz, 1H, C≡CC*H*OH), 3.87 (br. s., 1H, O*H*), 3.65 (t, *J* = 7.3 Hz, 1H, $CH_2C\mathit{H}OH$), 3.47 (br. s., 1H, O*H*), 3.23 - 3.12 (m, 1H, C*H*HNH), 2.84 - 2.62 (m, 1H, CH*H*NH), 1.90 - 1.79 (m, 1H, $C\mathit{H}HCH_2NH$), 1.55 (tdd, *J* = 5.0, 9.8, 14.4 Hz, 1H, $CH\mathit{H}CH_2NH$), 1.44 (s, 9H, $C(C\mathit{H}_3)_3$), 0.17 (s, 9H, 3 x $SiC\mathit{H}_3$)

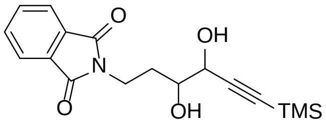
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.0 (*C*=O), 103.4 (SiC≡*C*CH), 91.6 (Si*C*≡CCH), 79.8 ($O\mathit{C}(CH)_3$), 72.6 (SiC≡C*C*H), 66.7 ($CH_2\mathit{C}HOH$), 37.3 ($CH_2\mathit{C}H_2NH$), 33.1 ($\mathit{C}H_2CH_2NH$), 28.4 ($OC(\mathit{C}H)_3$), - 0.22 ($Si\mathit{C}H_3$)

IR ν_{max} (film) 3367, 2958, 2931, 2177, 1688, 1513, 1248, 1169, 843 cm^{-1}

MS (ESI) *m/z* 202 $[M\text{-}Boc+H]^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{28}NO_4Si$ $[M+H]^+$ 302.1782, found 302.1782

Synthesis of (±)-2-(3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (2.67a).



To a vigorously stirred solution of enyne (**2.67**) (102 mg, 0.343 mmol), $K_3Fe(CN)_6$ (339 mg, 1.03 mmol) and K_2CO_3 (142 mg, 1.03 mmol) in 1:1 *t*-BuOH/H_2O (4 mL) was added $K_2OsO_4 \cdot 2H_2O$ (6.32 mg, 17.2 µmol). The resultant mixture was stirred at room temperature for 48 hours before it was quenched by addition of solid Na_2SO_3 (200 mg). The mixture was stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a white residue. The crude material was purified by silica gel chromatography (gradient: 0 – 100% EtOAc in cyclohexane) to afford the title compound **2.67a** (11.1 mg, 10% yield) as a colourless oil.

R_f = 0.55 (60% EtOAc/cyclohexane), UV active and stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (dd, *J* = 3.1, 5.4 Hz, 2H, Ar*H*), 7.73 (dd, *J* = 3.1, 5.4 Hz, 2H, Ar*H*), 4.19 (d, *J* = 6.6 Hz, 1H, C≡CC*H*OH), 3.94 - 3.87 (m, 2H, CH_2NH), 3.59 (ddd, *J* = 2.6, 6.8, 10.3 Hz, 1H, CH_2C*H*OH), 2.12 - 2.02 (m, 1H, C*H*HCH_2N), 1.80 (ddd, *J* = 5.1, 10.3, 19.4 Hz, 1H, CH*H*CH_2N), 0.14 (s, 9H, 3 x $SiCH_3$)

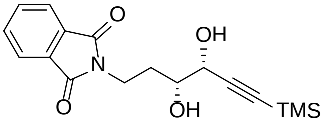
^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7 (C=O), 134.0, 132.0, 123.3, 103.0 (SiC≡*C*CH), 91.9 (Si*C*≡CCH), 72.2 (SiC≡C*C*H), 66.5 (CH_2*C*HOH), 34.5 (CH_2*C*H_2NH), 31.6 (*C*H_2CH_2NH), - 0.29 (Si*C*H_3)

IR ν_{max} (film) 3701, 2976, 2870, 1771, 1702, 1397, 1253, 841, 717 cm^{-1}

MS (ESI) *m/z* 332 $[M+H]^+$ (86%), 316 (100%)

HRMS (ESI) *m/z* calc'd for $C_{17}H_{22}NO_4Si$ $[M+H]^+$ 332.1313, found 332.1307

Synthesis of 2-((3*R*,4*R*)-3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl)isoindoline-1,3-dione (2.67b).



AD-mix beta (480 mg, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (3 mL) and methanesulfonamide (32.6 mg, 0.343 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**2.67**) (102 mg, 0.343 mmol), predissolved in 1:1 *t*-BuOH/H_2O (1 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from ice bath and stirred at room temperature for 48 hours to give a dirty yellow mixture. The mixture was quenched with addition of solid Na_2SO_3 (200 mg) and stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a white residue. The crude material was purified by silica gel chromatography (gradient: 0 – 100% EtOAc in hexanes) to afford the title compound **2.67b** (6.4 mg, 9% yield) as a colourless oil.

R_f = 0.55 (60% EtOAc/cyclohexane), UV active and stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.86 (dd, *J* = 3.1, 5.4 Hz, 2H, Ar*H*), 7.73 (dd, *J* = 3.1, 5.4 Hz, 2H, Ar*H*), 4.19 (d, *J* = 6.6 Hz, 1H, C≡CC*H*OH), 3.93 - 3.87 (m, 2H, C*H*$_2$NH), 3.59 (ddd, *J* = 2.5, 6.7, 10.4 Hz, 1H, CH_2C*H*OH), 2.12 - 2.02 (m, 1H, C*H*HCH_2N), 1.85 - 1.74 (m, 1H, CH*H*CH_2N), 0.14 (s, 9H, 3 x SiC*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 168.7 (*C*=O), 134.0, 132.0, 123.3, 103.0 (SiC≡*C*CH), 91.9 (Si*C*≡CCH), 72.2 (SiC≡C*C*H), 66.5 (CH_2*C*HOH), 34.5 (CH_2*C*H_2NH), 31.6 (*C*H_2CH_2NH), - 0.29 (Si*C*H_3)

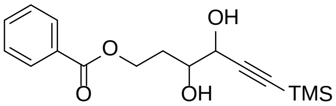
IR ν_{max} (film) 3463, 2957, 2923, 2167, 1771, 1706, 1397, 1245, 841, 721 cm^{-1}

MS (ESI) *m/z* 354 $[M+Na]^+$ (72%), 332 (45%), 316 (100%)

HRMS (ESI) *m/z* calc'd for $C_{17}H_{22}NO_4Si$ $[M+H]^+$ 332.1313, found 332.1313

Chiral SFC (Lux Cellulose-2 column, 5-55% IPA in CO_2) = 65% ee

Synthesis of (±)-3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl benzoate (2.68a).



To a vigorously stirred solution of enyne (**2.68**) (101 mg, 0.371 mmol), $K_3Fe(CN)_6$ (366 mg, 1.11 mmol) and K_2CO_3 (152 mg, 1.11 mmol) in 1:1 *t*-BuOH/H_2O (2 mL) was added K_2OsO_4•$2H_2O$ (2.0 mg, 5.43 µmol). The resultant mixture was stirred at room temperature for 48 hours before it was quenched by addition of solid Na_2SO_3 (200 mg). The mixture was stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 10 – 50% EtOAc in hexanes) to afford the title compound **2.68a** (33.6 mg, 30% yield) as a colourless oil.

R_f = 0.41 (50% EtOAc/cyclohexane), UV active and stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08 - 8.02 (m, 2H, Ar*H*), 7.60 - 7.53 (m, 1H, Ar*H*), 7.48 - 7.41 (m, 2H, Ar*H*), 4.63 - 4.53 (m, 1H, CH_2C*H*HO), 4.53 - 4.44 (m, 1H, CH_2CH*H*O), 4.24 (d, *J* = 6.4 Hz, 1H, C≡CC*H*OH), 3.83 (ddd, *J* = 3.1, 6.4, 9.4 Hz, 1H, CH_2C*H*OH), 2.23 - 2.12 (m, 1H, C*H*HCH_2O), 1.98 - 1.87 (m, 1H, CH*H*CH_2O), 0.16 (s, 9H, 3 x SiCH_3)

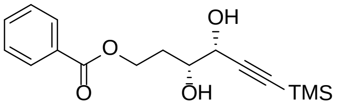
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.7 (*C*=O), 133.0, 130.1, 129.6, 128.3, 103.2 (SiC≡*C*CH), 92.1 (Si*C*≡CCH), 71.8 (SiC≡C*C*H), 66.6 (CH_2*C*HOH), 61.5 (CH_2*C*H_2OH), 31.9 (*C*H_2CH_2OH), - 0.28 (Si*C*H_3)

IR ν_{max} (film) 3410, 2961, 2900, 2167, 1718, 1272, 1113, 837, 709 cm^{-1}

MS (ESI) *m/z* 307 $[M+H]^+$ (48%), 289 (58%), 167 (100%)

HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}O_4Si$ $[M+H]^+$ 307.1360, found 307.1359

Synthesis of (3*R*,4*R*)-3,4-dihydroxy-6-(trimethylsilyl)hex-5-yn-1-yl benzoate (2.68b).



AD-mix beta (500 mg, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (3 mL) and methanesulfonamide (34.0 mg, 0.357 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**2.68**) (97.2 mg, 0.357 mmol), predissolved in 1:1 *t*-BuOH/H_2O (1 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from ice bath and stirred at room temperature for 48 hours to give a yellow mixture. The mixture was quenched with addition of solid Na_2SO_3 (200 mg) and stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 4 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a white residue. The crude material was purified by silica gel chromatography (gradient: 0 – 30% EtOAc in hexanes) to afford the title compound **2.68b** (15.7 mg, 14% yield) as a colourless oil.

R_f = 0.41 (50% EtOAc/cyclohexane), UV active and stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09 - 8.02 (m, 2H, Ar*H*), 7.60 - 7.54 (m, 1H, Ar*H*), 7.48 - 7.40 (m, 2H, Ar*H*), 4.63 - 4.55 (m, 1H, $CH_2C\textit{H}HO$), 4.52 - 4.45 (m, 1H, $CH_2CH\textit{H}O$), 4.24 (d, *J* = 6.5 Hz, 1H, C≡CC*H*OH), 3.83 (ddd, *J* = 3.1, 6.5, 9.3 Hz, 1H, $CH_2C\textit{H}OH$), 2.23 - 2.12 (m, 1H, $C\textit{H}HCH_2O$), 1.98 - 1.88 (m, 1H, $CH\textit{H}CH_2O$), 0.16 (s, 9H, 3 x $SiC\textit{H}_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 167.0 (*C*=O), 133.0, 130.1, 129.6, 128.3, 103.2 (SiC≡*C*CH), 92.1 (Si*C*≡CCH), 71.8 (SiC≡C*C*H), 66.6 ($CH_2\textit{C}HOH$), 61.5 ($CH_2\textit{C}H_2OH$), 31.9 ($\textit{C}H_2CH_2OH$), - 0.28 ($Si\textit{C}H_3$)

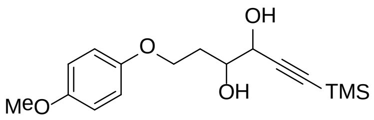
IR ν_{max} (film) 3410, 2961, 2900, 2167, 1718, 1272, 1113, 837, 709 cm^{-1}

MS (ESI) *m/z* 329 $[M+Na]^+$ (44%), 289 (46%), 167 (100%)

HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}O_4Si$ $[M+H]^+$ 307.1360, found 307.1360

Chiral SFC (Lux Cellulose-2 column, 5-55% MeOH in CO_2) = 73% ee

Synthesis of (±)-6-(4-methoxyphenoxy)-1-(trimethylsilyl)hex-1-yne-3,4-diol (2.69a).



To a vigorously stirred solution of enyne (**2.69**) (64.8 mg, 0.236 mmol), $K_3Fe(CN)_6$ (233 mg, 0.708 mmol) and K_2CO_3 (98.0 mg, 0.708 mmol) in 1:1 *t*-BuOH/H_2O (2 mL) was added K_2OsO_4•$2H_2O$ (4.35 mg, 12.0 µmol). The resultant mixture was stirred at room temperature for 48 hours before it was quenched by addition of solid Na_2SO_3 (200 mg). The mixture was stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light brown oil. The crude material was purified by silica gel chromatography (gradient: 10 – 30% EtOAc in hexanes) to afford the title compound **2.69a** (23.4 mg, 32% yield) as a colourless oil.

R_f = 0.25 (20% EtOAc/hexanes), stained blue with CAM

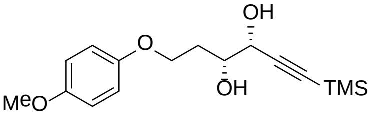
^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 - 6.80 (m, 4H, Ar*H*), 4.27 (t, *J* = 6.0 Hz, 1H, C≡CC*H*OH), 4.19 - 4.09 (m, 2H, ArOCH_2CH$_2$), 3.97 - 3.89 (m, 1H, CH$_2$C*H*OH), 3.77 (s, 3H, OCH_3), 2.73 (d, *J* = 3.4 Hz, 1H, O*H*), 2.39 (d, *J* = 6.0 Hz, 1H, O*H*), 2.20 - 2.10 (m, 1H, ArOCH$_2$C*H*H), 2.02 - 1.90 (m, 1H, ArOCH$_2$CH*H*), 0.18 (s, 9H, 3 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.9, 152.7, 115.5, 114.6, 103.5 (SiC≡*C*), 91.6 (Si*C*≡C), 72.5, 66.6, 65.6, 55.7 (O*C*H$_3$), 32.1 (ArOCH$_2$*C*H$_2$), - 0.27 (Si*C*H$_3$)

IR ν_{max} (film) 3395, 2958, 2174, 1508, 1230, 1040, 844, 761 cm^{-1}

MS (ESI) *m/z* 331 $[M+Na]^+$ (100%)

Synthesis of (3*R*,4*R*)-6-(4-methoxyphenoxy)-1-(trimethylsilyl)hex-1-yne-3,4-diol (2.69b).



AD-mix beta (6.59 g, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (44 mL) and methanesulfonamide (448 mg, 4.71 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**2.69**) (1.29 g, 4.71 mmol), predissolved in 1:1 *t*-BuOH/H_2O (7 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from the ice bath and stirred at room temperature for 15 hours to give a yellowish green mixture. The mixture was quenched with addition of solid Na_2SO_3 (0.5 g) and stirred for 30 minutes before H_2O (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 20 – 30% EtOAc in hexanes) to afford the title compound **2.69b** (1.24 g, 86% yield) as a colourless solid.

R_f = 0.25 (20% EtOAc/hexanes), stained blue with CAM

Melting point = 72.0 – 73.2 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 - 6.80 (m, 4H, Ar*H*), 4.26 (d, *J* = 6.0 Hz, 1H, C≡CC*H*OH), 4.19 - 4.08 (m, 2H, ArOCH_2CH$_2$), 3.93 (ddd, *J* = 3.2, 6.0, 9.0 Hz, 1H, CH$_2$C*H*OH), 3.77 (s, 3H, OCH_3), 2.20 - 2.10 (m, 1H, ArOCH$_2$C*H*H), 2.01 - 1.92 (m, 1H, OCH$_2$CH*H*), 0.18 (s, 9H, 3 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.9, 152.7, 115.5, 114.6, 103.5 (SiC≡*C*), 91.6 (Si*C*≡C), 72.5, 66.6, 65.6, 55.7 (O*C*H_3), 32.1 (ArOCH_2*C*H_2), - 0.27 (Si*C*H_3)

IR ν_{max} (film) 3395, 2958, 2174, 1508, 1230, 1040, 844, 761 cm^{-1}

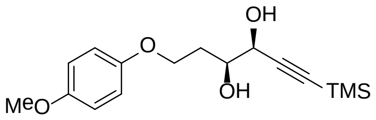
MS (ESI) *m/z* 331 $[M+Na]^+$ (100%), 309 $[M+H]^+$ (15%)

HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}O_4SiNa$ $[M+Na]^+$ 331.1336, found 331.1330

Chiral HPLC (Chiralpak AD column, 95% Hexanes in IPA) = 97% ee

$[\alpha]_D^{20}$ = + 9.61 (*c* 0.77, $CHCl_3$)

Synthesis of (3*S*,4*S*)-6-(4-methoxyphenoxy)-1-(trimethylsilyl)hex-1-yne-3,4-diol (2.69c).



AD-mix alpha (5.36 g, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (30 mL) and methanesulfonamide (365 mg, 3.83 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**2.69**) (1.05 g, 3.83 mmol), predissolved in 1:1 *t*-BuOH/H_2O (2 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from the ice bath and stirred at room temperature for 40 hours to give a yellow-brown mixture. The mixture was quenched with addition of solid Na_2SO_3 (1.1 g) and stirred for 30 minutes before H_2O (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (8 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 10 – 30% EtOAc in hexanes) to afford the title compound **2.69c** (775 mg, 65% yield) as a colourless solid.

R_f = 0.25 (20% EtOAc/hexanes), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.87 - 6.81 (m, 4H, Ar*H*), 4.27 (t, *J* = 6.0 Hz, 1H, C≡CC*H*OH), 4.19 - 4.09 (m, 2H, ArOCH_2CH$_2$), 3.97 - 3.89 (m, 1H, CH$_2$C*H*OH), 3.77 (s, 3H, OCH_3), 2.73 (d, *J* = 3.6 Hz, 1H, O*H*), 2.38 (d, *J* = 6.0 Hz, 1H, O*H*), 2.17 - 2.11 (m, 1H, ArOCH$_2$C*H*H), 2.01 - 1.94 (m, 1H, ArOCH$_2$CH*H*), 0.18 (s, 9H, 3 x SiCH_3)

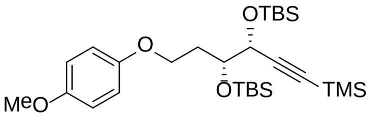
^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.9, 152.7, 115.5, 114.6, 103.5 (SiC≡*C*), 91.6 (Si*C*≡C), 72.5, 66.6, 65.6, 55.7 (O*C*H$_3$), 32.1 (ArOCH$_2$*C*H$_2$), - 0.27 (Si*C*H$_3$)

IR ν_{max} (film) 3395, 2958, 2174, 1508, 1230, 1040, 844, 761 cm^{-1}

MS (ESI) *m/z* 331 $[M+Na]^+$ (100%)

Chiral HPLC (Chiralpak AD column, 95% Hexanes in IPA) = 97% ee

Synthesis of (5*R*,6*R*)-5-(2-(4-methoxyphenoxy)ethyl)-2,2,3,3,8,8,9,9-octamethyl-6-((trimethylsilyl)ethynyl)-4,7-dioxa-3,8-disiladecane (2.70).



To a solution of diol (**2.69b**) (153 mg, 0.496 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 2,6-lutidine (144 µL, 1.24 mmol) followed by TBSOTf (250 µL, 1.09 mmol). The reaction mixture was stirred at 0 °C under argon for 2 hour 30 minutes before it was quenched with

H_2O (3 mL). The organic layer was separated, washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.70** (234 mg, 88% yield) as a colourless oil.

R_f = 0.73 (10% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.82 (s, 4H, Ar*H*), 4.38 (d, *J* = 5.0 Hz, 1H, C≡CC*H*OH), 4.07 - 4.00 (m, 2H, ArOCH_2CH_2), 3.89 - 3.83 (m, 1H, CH_2C*H*OSi), 3.76 (s, 3H, OCH_3), 2.25 - 2.14 (m, 1H, ArOCH_2C*H*H), 2.01 - 1.93 (m, 1H, ArOCH_2CH*H*), 0.90 (s, 9H, C(CH_3)$_3$), 0.89 (s, 9H, C(CH_3)$_3$), 0.15 (s, 9H, 3 x SiCH_3), 0.14 (s, 3H, SiCH_3), 0.10 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 153.6, 153.3, 115.3, 114.6, 105.2 (SiC≡*C*), 90.2 (Si*C*≡C), 71.3, 67.3, 64.9, 55.8 (O*C*H_3), 31.7 (ArOCH_2*C*H_2), 25.8 (SiC(*C*H_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 18.0 (Si*C*(CH_3)$_3$), - 0.2 (Si*C*H_3), - 4.5 (Si*C*H_3), - 4.7 (Si*C*H_3), - 4.8 (Si*C*H_3)

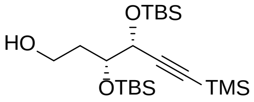
IR ν_{max} (film) 2957, 2931, 2893, 2855, 2167, 1507, 1249, 1227, 1091, 830, 774 cm^{-1}

MS (EI) *m/z* 559 $[M+Na]^+$ (5%), 429 (40%), 341 (79%), 73(100%)

HRMS (ESI) *m/z* calc'd for $C_{28}H_{52}O_4Si_3Na$ $[M+Na]^+$ 559.3066, found 559.3053

$[\alpha]_D^{22}$ = + 20.3 (*c* 0.60, $CHCl_3$)

Synthesis of (3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)-6-(trimethylsilyl)hex-5-yn-1-ol (2.71).



To a solution of PMP protected alcohol (**2.70**) (1.64 g, 3.05 mmol) in MeCN (20 mL) and cooled to 0 °C was added pyridine (988 µL, 12.2 mmol) followed by CAN (5.02 g, 9.16 mmol). The reaction mixture was left to stir at 0 °C for 60 minutes and an additional 1 eq. of pyridine (247 µL, 3.05 mmol) was added at 0 °C followed by 0.5 eq. of CAN to drive the reaction to completion. The mixture was stirred at 0 °C for 15 minutes before it was diluted with EtOAc (40 mL) and quenched with H_2O (10 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a bright orange residue. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.71** (1.05 g, 80% yield) as a brown oil.

R_f = 0.33 (10% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.38 (d, *J* = 5.0 Hz, 1H, C≡CC*H*OH), 3.83 - 3.74 (m, 3H, CH_2C*H*OSi, HOC$H_2$$CH_2$), 2.19 (t, *J* = 5.6 Hz, 1H, O*H*), 2.06 - 1.85 (m, 2H, HOCH_2CH_2), 0.90 (s, 18H, 2 x C(CH_3)$_3$), 0.15 (s, 9H, 3 x SiCH_3), 0.12 (s, 3H, SiCH_3), 0.09 (s, 6H, 2 x SiCH_3), 0.00 (s, 3H, SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 104.7 (SiC≡*C*), 90.8 (Si*C*≡C), 73.5, 67.3, 60.2, 34.8 (HOCH_2*C*H_2), 25.8 (SiC(*C*H_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 18.2 (Si*C*(CH_3)$_3$), 18.0 (Si*C*(CH_3)$_3$), -0.2 (Si*C*H_3), - 4.5 (Si*C*H_3), - 4.7(Si*C*H_3), - 4.8 (Si*C*H_3)

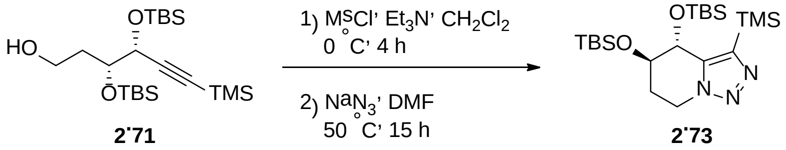
IR ν_{max} (film) 3396, 2953, 2931, 2889, 2858, 2023, 1249, 1091, 830, 778 cm^{-1}

MS (EI) *m/z* 373 [M-*t*Bu]$^+$ (5%), 241 (23%), 189 (35%), 73 (100%)

HRMS (ESI) *m/z* calc'd for $C_{21}H_{47}O_3Si_3$ [M+H]$^+$ 431.2828, found 431.2824

$[\alpha]_D^{22}$ = + 17.7 (*c* 0.71, $CHCl_3$)

Synthesis of (4*R*,5*R*)-4,5-bis((*tert*-butyldimethylsilyl)oxy)-3-(trimethylsilyl)-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-a]pyridine (2.73).



To a solution of alcohol (**2.71**) (116 mg, 0.270 mmol) in CH_2Cl_2 (3 mL) and cooled to 0 °C was added Et_3N (57 µL, 0.406mmol). The reaction was stirred for 10 minutes before methanesulfonylchloride (25 µL, 0.324 mmol) was added. The mixture was stirred at 0 °C for 4 hours before it was quenched by addition of sat'd NH_4Cl solution (3 mL). The organic layer was separated, washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil which was used directly in the next step without further manipulation.

R_f = 0.33 (10% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.46 - 4.30 (m, 3H, C≡CC*H*OH, OC*H*$_2$CH$_2$), 3.75 (td, *J* = 4.1, 8.1 Hz, 1H, CH$_2$C*H*OSi), 2.99 (s, 3H, SO$_2$C*H*$_3$), 2.18 (ddt, *J* = 3.6, 7.8, 11.0 Hz, 1H, OCH$_2$C*H*H), 2.06 - 1.94 (m, 1H, OCH$_2$CH*H*), 0.90 (s, 18H, 2 x C(C*H*$_3$)$_3$), 0.19 - 0.05 (m, 21H, 7 x SiC*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 104.3 (SiC≡*C*), 90.8 (Si*C*≡C), 70.6, 67.3, 66.9, 37.4 (SO_2CH_3), 31.7 (OCH_2CH_2), 25.8 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 18.0 ($SiC(CH_3)_3$), - 0.3 ($SiCH_3$), - 4.6 ($SiCH_3$), - 4.8 ($SiCH_3$), - 4.9 ($SiCH_3$)

To a solution of the crude mesylate (49.8 mg, 0.098 mmol) in DMF (1 mL) was added sodium azide (12.7 mg, 0.196 mmol). The mixture was heated at 50 °C for 15 hours before it was diluted with H_2O (1 mL) and extracted with EtOAc (5 x 1 mL). The combined organic layers were washed with H_2O (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a brown oil. The crude material was purified by silica gel chromatography (gradient: 5 – 10% EtOAc in hexanes) to afford the title compound **2.73** (38.5 mg, 86% yield) as a colourless solid.

R_f = 0.20 (10% EtOAc/hexanes), stained blue with CAM

Melting point = 79 – 81 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.78 (d, *J* = 3.2 Hz, 1H, $CH_2CHOCHO$), 4.56 (dd, *J* = 6.5, 13.0 Hz, 1H, CH_2CHHN), 4.32 (dt, *J* = 5.3, 12.6 Hz, 1H, CH_2CHHN), 4.16 (br. s., 1H, $CH_2CHOCHO$), 2.52 (dt, *J* = 6.7, 13.0 Hz, 1H, $CHHCH_2N$), 1.94 (td, *J* = 4.7, 13.7 Hz, 1H, $CHHCH_2N$), 0.86 (s, 9H, $C(CH_3)_3$), 0.77 (s, 9H, $C(CH_3)_3$), 0.35 (s, 9H, 3 x $SiCH_3$), 0.18 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.06 (s, 3H, $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 144.0 (SiCH=*C*H), 139.6 (Si*C*H=CH), 68.2, 65.2, 41.5 (NCH_2CH_2), 25.7 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 23.9 (NCH_2CH_2), 18.0 ($SiC(CH_3)_3$), 17.8 ($SiC(CH_3)_3$), - 0.7 ($SiCH_3$), - 3.69 ($SiCH_3$), - 4.1 ($SiCH_3$), - 4.8 ($SiCH_3$), - 4.9 ($SiCH_3$)

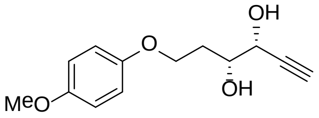
IR ν_{max} (film) 2958, 2931, 2893, 2856, 1468, 1248, 1108, 1074, 832, 775 cm^{-1}

MS (ESI) *m/z* 456 $[M+H]^+$ (100%)

HRMS (ESI) *m/z* calc’d for $C_{21}H_{46}N_3O_2Si_3$ $[M+H]^+$ 456.2892, found 456.2892

$[\alpha]_D^{22}$ = - 24.2 (*c* 0.43, $CHCl_3$)

Synthesis of (3*R*,4*R*)-6-(4-methoxyphenoxy)hex-1-yne-3,4-diol (2.78).



To a solution of TMS acetylene (**2.69b**) (1.19 g, 3.85 mmol) in methanol (35 mL), was added K_2CO_3 (799 mg, 5.78 mmol). The reaction mixture was stirred at room temperature for 5 hours before it was diluted with Et_2O (70 mL) and washed with sat'd aqueous $NaHCO_3$ solution. The aqueous phase was neutralised with 1 M HCl solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **2.78** (876 mg, 96% yield) as a colourless solid.

R_f = 0.10 (30% EtOAc/cyclohexane), stained blue with CAM

Melting point = 81 – 83 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 - 6.79 (m, 1H, Ar*H*), 4.29 (dt, *J* = 2.1, 6.0 Hz, 1H, C≡CC*H*OH), 4.20 - 4.08 (m, 2H, ArOCH_2CH$_2$), 4.02 - 3.94 (m, 1H, CH$_2$C*H*OH), 3.77 (s, 3H, OCH_3), 2.79 (d, *J* = 3.5 Hz, 1H, O*H*), 2.52 (d, *J* = 2.1 Hz, 1H, *H*C≡CCHOH), 2.48 (d, *J* = 6.1 Hz, 1H, O*H*), 2.21 - 2.12 (m, 1H), 2.06 - 1.95 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.1, 152.6, 115.5, 114.7, 82.0 (HC≡*C*), 74.6, 72.7, 65.9, 65.9, 55.7 (O*C*H$_3$), 32.0 (ArOCH$_2$*C*H$_2$)

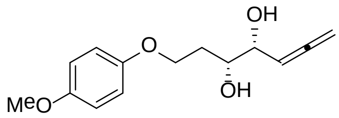
IR ν_{max} (film) 3396, 3285, 2956, 1508, 1229, 1036, 825, 740 cm^{-1}

MS (ESI) *m/z* 259 [M+Na]$^+$ (16%), 219 (44%), 201 (100%)

HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}O_4$ $[M+H]^+$ 237.1121, found 237.1121

$[\alpha]_D^{21}$ = + 8.75 (*c* 0.80, $CHCl_3$)

Synthesis of (3*R*,4*R*)-1-(4-methoxyphenoxy)hepta-5,6-diene-3,4-diol (2.79).



A mixture of alkyne (**2.78**) (696 mg, 2.95 mmol), CuBr (211 mg, 1.47 mmol), Cy_2NH (1.17 mL, 5.89 mmol) and paraformaldehyde (221 mg, 7.37 mmol) in 1,4-dioxane (12 mL) was heated in a microwave reactor at 150 °C for 25 minutes. The resultant brown mixture was filtered through a plug of celite, washing with EtOAc. The filtrate was concentrated *in vacuo* to give a brown oil. The crude material was purified by silica gel chromatography (gradient: 30 – 50% EtOAc in hexanes) to afford the title compound **2.79** (578 mg, 78% yield) as a light brown oil.

R_f = 0.25 (20% EtOAc/hexanes), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 - 6.79 (m, 4H, Ar*H*), 5.30 (q, *J* = 6.6 Hz, 1H, $H_2C{=}C{=}CH$), 4.91 (dd, *J* = 2.3, 6.6 Hz, 2H, $H_2C{=}C{=}CH$), 4.19 - 4.05 (m, 3H, C=CHC*H*OH, $ArOCH_2CH_2$), 3.87 - 3.80 (m, 1H, CH_2CH_2CHOH), 3.77 (s, 3H, OCH_3), 2.69 (d, *J* = 3.0 Hz, 1H, O*H*), 2.35 (d, *J* = 3.8 Hz, 1H, O*H*), 2.10 - 2.01 (m, 1H, $ArOCH_2CHH$), 2.01 - 1.91 (m, 1H, $ArOCH_2CHH$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.0 ($H_2C{=}C{=}CH$), 154.1, 152.7, 115.5, 114.7, 91.4 ($H_2C{=}C{=}CH$), 77.7 ($H_2C{=}C{=}CH$), 77.2 (C=CH*C*HOH), 72.6 (CH_2CH_2CHOH), 66.1 ($ArOCH_2CH_2$), 55.7 (OCH_3), 32.5 ($ArOCH_2CH_2$)

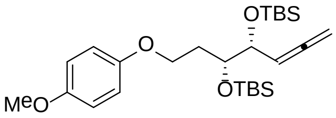
IR ν_{max} (film) 3409, 2931, 1956, 1508, 1231, 1038, 826, 740 cm^{-1}

MS (ESI) *m/z* 273 $[M+Na]^+$ (48%), 233 (25%), 215 (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{19}O_4$ $[M+H]^+$ 251.1278, found 251.1276

$[\alpha]_D^{21}$ = + 4.08 (*c* 0.71, $CHCl_3$)

Synthesis of (5*R*,6*R*)-5-(2-(4-methoxyphenoxy)ethyl)-2,2,3,3,8,8,9,9-octamethyl-6-(propa-1,2-dien-1-yl)-4,7-dioxa-3,8-disiladecane (2.80).



To a solution of diol (**2.79**) (558 mg, 2.23 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C was added 2,6-lutidine (650 μL, 5.58 mmol) followed by TBSOTf (1.13 mL, 4.91 mmol). The reaction mixture was left to stir at 0 °C under nitrogen for 3 hours before it was quenched with water (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 1 – 5% EtOAc in hexanes) to afford the title compound **2.80** (866 mg, 81% yield) as a colourless oil.

R_f = 0.69 (50% EtOAc/hexanes), stained blue with CAM

^1H NMR (400 MHz, $CDCl_3$) δ = 6.81 (s, 4H, Ar*H*), 5.23 (q, *J* = 6.4 Hz, 1H, $H_2C=C=CH$), 4.82 - 4.69 (m, 2H, $H_2C=C=CH$), 4.26 - 4.20 (m, 1H, C=CHC*H*OH), 4.02 - 3.95 (m, 2H, $ArOCH_2CH_2$), 3.95 - 3.88 (m, 1H, CH_2CH_2CHOH), 3.76 (s, 3H, OCH_3), 2.23 - 2.13 (m, 1H, ArOCH$_2$C*H*H), 1.78 - 1.67 (m, 1H, ArOCH$_2$C*H*H), 0.89 (s, 9H, C(C*H*$_3$)$_3$), 0.88 (s, 9H, C(C*H*$_3$)$_3$), 0.06 (s, 9H, 3 x SiC*H*$_3$), 0.01 (s, 3H, SiC*H*$_3$)

^{13}C NMR (101 MHz, CDCl$_3$) δ = 208.7 (H$_2$C=*C*=CH), 153.5, 153.2, 115.2, 114.6, 90.4 (H$_2$C=C=*C*H), 76.2, 73.1, 71.8, 64.9, 55.7 (O*C*H$_3$), 30.7 (ArOCH$_2$*C*H$_2$), 25.8 (SiC(*C*H$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), - 4.4 (Si*C*H$_3$), - 4.5 (Si*C*H$_3$), - 4.8 (Si*C*H$_3$), - 5.0 (Si*C*H$_3$)

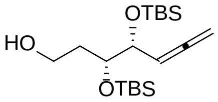
IR ν_{max} (film) 2954, 2929, 2857, 1959, 1508, 1231, 1106, 835, 775 cm^{-1}

MS (EI) *m/z* 478 [M]$^+$ (6%), 421 (19%), 163 (100%)

HRMS (ESI) *m/z* calc'd for $C_{26}H_{46}O_4Si_2Na$ [M+Na]$^+$ 501.2832, found 501.2816

$[\alpha]_D^{21}$ = + 69.3 (*c* 0.78, CHCl$_3$)

Synthesis of (3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)hepta-5,6-dien-1-ol (2.40).



To a solution of PMP protected alcohol (**2.80**) (1.85 g, 3.86 mmol) dissolved in MeCN (40 mL) and cooled to 0 °C was added pyridine (1.25 mL, 15.5 mmol). A solution of CAN (6.35 g, 11.6 mmol) in H$_2$O (20 mL) was added dropwise at 0 °C over a period of 10 minutes. The resultant reaction mixture was left to stir vigorously at 0 °C for an additional 35 minutes before it was diluted with EtOAc (50 mL) and quenched with water (20 mL). The mixture was extracted with EtOAc (3 x 15 mL) and the combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo* to give a bright yellow oil mixed with solid. The crude material was purified by silica gel chromatography (gradient: 2 – 5% EtOAc in hexanes) to afford the title compound **2.40** (1.17 g, 81% yield) as a light brown oil.

R_f = 0.32 (5% EtOAc/hexanes), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.24 (q, *J* = 6.5 Hz, 1H, $H_2C=C=CH$), 4.84 - 4.78 (m, 1H, *H*HC=C=CH), 4.77 - 4.71 (m, 1H, H*H*C=C=CH), 4.22 (m, 1H, C=CHC*H*OH), 3.81 (dt, *J* = 4.6, 6.3 Hz, 1H, CH_2CH_2CHOH), 3.76 - 3.64 (m, 2H, $HOCH_2CH_2$), 2.01 - 1.91 (m, 1H, $HOCH_2CHH$), 1.72 - 1.63 (m, 1H, $HOCH_2CHH$), 0.90 (s, 9H, $C(CH_3)_3$), 0.89 (s, 9H, $C(CH_3)_3$), 0.10 - 0.07 (m, 12H, 4 x $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.7 ($H_2C=C=CH$), 90.2 ($H_2C=C=CH$), 76.6 ($H_2C=C=CH$), 74.4, 73.5, 60.3($HOCH_2CH_2$), 35.0 ($HOCH_2CH_2$), 25.8 ($SiC(CH_3)_3$), 25.7 ($SiC(CH_3)_3$), 18.2 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), - 4.5 ($SiCH_3$), - 4.6 ($SiCH_3$), - 4.8 ($SiCH_3$), - 5.1 ($SiCH_3$)

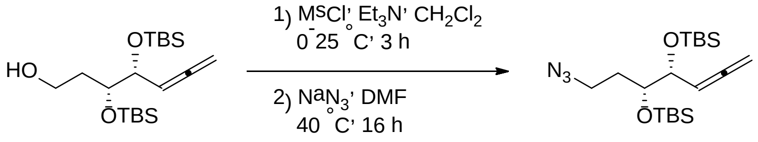
IR ν_{max} (film) 3394, 2954, 2928, 2857, 1959, 1471, 1252, 1071, 832, 772 cm^{-1}

MS (EI) *m/z* 315 $[M\text{-}tBu]^+$ (8%), 183 (100%)

HRMS (ESI) *m/z* calc'd for $C_{19}H_{41}O_3Si_2$ $[M+H]^+$ 373.2589, found 373.2589

$[\alpha]_D^{21}$ = + 73.8 (*c* 0.99, $CHCl_3$)

Synthesis of (5*R*,6*R*)-5-(2-azidoethyl)-2,2,3,3,8,8,9,9-octamethyl-6-(propa-1,2-dien-1-yl)-4,7-dioxa-3,8-disiladecane (2.81).



2.40 **2.81**

To a solution of alcohol (**2.40**) (1.17 g, 3.14 mmol) dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C was added Et_3N (657 µL, 4.17 mmol) followed by methanesulfonyl chloride (269 µL, 3.46 mmol). The mixture was left to gradually warm up to room temperature and stirred at room temperature for 3 hours. The mixture was diluted with CH_2Cl_2 (10 mL) and washed sequentially with water (10 mL) and brine (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude mesylate (1.38 g, 3.06 mmol) as a brown oil which was used directly in the next step without further purification.

R_f = 0.19 (5% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.17 (q, *J* = 6.5 Hz, 1H, $H_2C{=}C{=}CH$), 4.84 - 4.70 (m, 2H , $H_2C{=}C{=}CH$), 4.41 - 4.27 (m, 2H, CH_2OSO_2), 4.24 - 4.18 (m, 1H, C=CHC*H*O), 3.82 - 3.76 (m, 1H, CH_2CH_2CHO), 2.99 (s, 3H, SO_2CH_3), 2.21 - 2.08 (m, 1H, $CH_2CHHCHO$), 1.82 - 1.72 (m, 1H, $CH_2CHHCHO$), 0.91 - 0.86 (m, 18H, 2 x $C(CH_3)_3$), 0.09 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.07 - 0.04 (m, 6H, 2 x $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.9 ($H_2C{=}C{=}CH$), 90.3 ($H_2C{=}C{=}CH$), 76.8 ($H_2C{=}C{=}CH$), 72.9, 71.6, 67.6 (CH_2OSO_2), 37.7 (SO_2CH_3) , 31.3 ($CH_2CH_2OSO_2$), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), - 4.1 ($SiCH_3$), - 4.3 ($SiCH_3$), - 4.6 ($SiCH_3$), - 4.8 ($SiCH_3$)

IR ν_{max} (film) 2954, 2930, 2888, 2857, 1959, 1360, 1255, 1177, 1108, 836, 776 cm^{-1}

To a solution of crude mesylate (1.38 g, 3.06 mmol) in DMF (10 mL) was added NaN_3 (597 mg, 9.19 mmol). The mixture was heated at 40 °C for 16 hours before it was cooled and diluted with EtOAc (20 mL). H_2O (15 mL) was added and the mixture was stirred for 10 minutes before the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give light a brown oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.81** (1.05 g, 86% yield) as a colourless oil.

R_f = 0.76 (5% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (q, J = 6.4 Hz, 1H, $H_2C{=}C{=}CH$), 4.82 - 4.70 (m, 2H, $H_2C{=}C{=}CH$), 4.22 - 4.17 (m, 1H, C=CHC*H*O), 3.78 - 3.72 (m, 1H, CH_2CH_2CHO), 3.44 (ddd, J = 4.8, 7.5, 12.2 Hz, 1H, C*H*HN), 3.28 (ddd, J = 6.9, 8.6, 12.2 Hz, 1H, CH*H*N), 2.02 - 1.93 (m, 1H, $CH_2C\mathit{H}HCHO$), 1.67 - 1.62 (m, 1H, $CH_2CH\mathit{H}CHO$), 0.89 (s, 18H, 2 x $C(CH_3)_3$), 0.07 (s, 12H, 4 x $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.9 ($H_2C{=}C{=}CH$), 90.4 ($H_2C{=}C{=}CH$), 76.6 ($H_2C{=}C{=}CH$), 73.1, 72.5, 48.5 (CH_2CH_2N), 30.4 (CH_2CH_2N), 26.0 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 18.3 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), - 4.1 ($SiCH_3$), - 4.3 ($SiCH_3$), - 4.6 ($SiCH_3$), - 4.8 ($SiCH_3$)

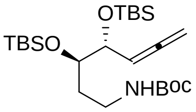
IR ν_{max} (film) 2954, 2929, 2885, 2857, 2094, 1959, 1255, 1103, 1079, 834, 774 cm^{-1}

MS (EI) *m/z* 397 $[M]^+$ (100%), 340 (26%)

HRMS (ESI) *m/z* calc'd for $C_{19}H_{40}N_3O_2Si_2$ $[M+H]^+$ 398.2654, found 398.2654

$[\alpha]_D^{21}$ = + 82.7 (*c* 0.68, $CHCl_3$)

Synthesis of *tert*-butyl ((3*R*,4*R*)-3,4-bis((*tert*-butyldimethylsilyl)oxy)hepta-5,6-dien-1-yl)carbamate (2.39).



To a solution of azide (**2.81**) (1.05 g, 2.65 mmol) in THF (20 mL) was added PPh_3 (1.39 g, 5.30 mmol). The mixture was stirred at room temperature for 4 hours before H_2O (954 μL, 52.9 mmol) was added. The mixture was stirred at room temperature for 16 hours before Boc_2O (751 mg, 3.44 mmol) and DIPEA (693 μL, 3.97 mmol) were added. The reaction mixture was stirred for a further 4 hours before it was diluted with EtOAc (20 mL) and washed with brine (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **2.39** (1.02 g, 82% yield) as a colourless oil.

R_f = 0.45 (5% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.18 (q, *J* = 6.4 Hz, 1H, $H_2C=C=CH$), 4.83 - 4.69 (m, 2H, $H_2C=C=CH$), 4.21 - 4.16 (m, 1H, C=CHC*H*O), 3.68 (td, *J* = 4.2, 8.2 Hz, 1H, CH_2CH_2CHO), 3.20 (br. s., 2H, CH_2CH_2NH), 1.84 (ddt, *J* = 4.1, 7.0, 14.1 Hz, 1H, $CHHCH_2NH$), 1.63 - 1.56 (m, 1H, $CHHCH_2NH$), 1.43 (s, 9H, $C(CH_3)_3$), 0.93 - 0.85 (m, 18H, 2 x $C(CH_3)_3$), 0.11 - 0.03 (m, 12H, 4 x $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.6 ($H_2C=C=CH$), 155.8 (NH*C*=O), 90.3 ($H_2C=C=CH$), 78.7 ($OC(CH)_3$), 76.4, 74.3, 73.1, 38.0 (CH_2CH_2N), 31.2 (CH_2CH_2N), 28.4 ($OC(CH)_3$), 25.8 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 17.9 ($SiC(CH_3)_3$), - 4.3 ($SiCH_3$), - 4.5 ($SiCH_3$), - 4.8 ($SiCH_3$), - 5.0 ($SiCH_3$)

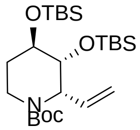
IR ν_{max} (film) 3370, 2954, 2927, 2858, 1957, 1705, 1503, 1362, 1251, 1105, 831, 774 cm^{-1}

MS (EI) *m/z* 372 $[M\text{-}Boc+H]^+$ (25%), 246 (39%), 171 (100%)

HRMS (ESI) *m/z* calc'd for $C_{24}H_{49}NO_4Si_2Na$ $[M+Na]^+$ 494.3092, found 494.3086

$[\alpha]_D^{21} = +47.1$ (*c* 0.98, $CHCl_3$)

Synthesis of (2*S*,3*R*,4*R*)-*tert*-butyl 3,4-bis((*tert*-butyldimethylsilyl)oxy)-2-vinylpiperidine-1-carboxylate (2.82)



To a solution of allene (**2.39**) (78.5 mg, 0.166 mmol) in dry CH_2Cl_2 (1.6 mL) was added $CaCO_3$ (16.7 mg, 0.166 mmol), Ph_3PAuCl (4.9 mg, 9.98 µmol) and $AgSbF_6$ (3.4 mg, 9.98 µmol). The mixture was stirred at room temperature for 8 hours in the absence of light. The reaction mixture was filtered through a plug of celite and washed with CH_2Cl_2 (5 mL). The filtrate was concentrated to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 100% hexanes – 4% EtOAc in hexanes) to afford the title compound **2.82** (67 mg, 85% yield) as a colourless oil.

$R_f = 0.68$ (5% EtOAc/cyclohexane), stained blue with ninhydrin

^1H NMR (400 MHz, $CDCl_3$) δ = 6.06 (ddd, *J* = 3.2, 10.8, 17.8 Hz, 1H, $CCH{=}CH_2$), 5.25 (d, *J* = 10.8 Hz, 1H, $CCH{=}CHH$), 5.06 (d, *J* = 17.8 Hz, 1H, $CCH{=}CHH$), 4.86 (br. s., 1H, $CHCHN$), 3.90 (br. s., 1H, CH_2CHHN), 3.61 - 3.47 (m, 2H, CH_2CH_2CHO and $NCHCHO$), 2.93 - 2.83 (m, 1H, CH_2CHHN), 1.80 - 1.72 (m, 1H, $CHHCH_2N$), 1.51 - 1.47 (m, 1H, CH*H*CH$_2$N), 1.45 (s, 9H, C(C*H*$_3$)$_3$), 0.92 (s, 9H, C(C*H*$_3$)$_3$), 0.88 (s, 9H, C(C*H*$_3$)$_3$), 0.13 (s, 3H, SiC*H*$_3$), 0.10 (s, 3H, SiC*H*$_3$), 0.06 (s, 6H, 2 x SiC*H*$_3$)

^{13}C NMR (101 MHz, CDCl$_3$) δ = 155.0 (NH*C*=O), 132.0 (C*C*H=CH$_2$), 116.0 (CCH=*C*H$_2$), 79.7 (O*C*(CH)$_3$), 75.0, 70.8, 57.7 (CH*C*HN), 34.3 (CH$_2$*C*H$_2$N), 28.3 (OC(*C*H)$_3$), 26.0 (SiC(*C*H$_3$)$_3$), 25.6 (*C*H$_2$CH$_2$N), 18.1 (Si*C*(CH$_3$)$_3$), 18.0 (Si*C*(CH$_3$)$_3$), - 3.9 (Si*C*H$_3$), - 4.1 (Si*C*H$_3$), - 4.7 (Si*C*H$_3$), - 4.8 (Si*C*H$_3$)

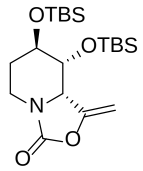
IR ν_{max} (film) 2952, 2928, 2883, 2856, 1699, 1472, 1410, 1253, 1112, 835, 774 cm^{-1}

MS (ESI) *m/z* 472 [M+H]$^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{24}H_{49}NO_4Si_2Na$ [M+Na]$^+$ 494.3092, found 494.3086

$[\alpha]_D^{21}$ = - 38.9 (*c* 0.66, CHCl$_3$)

Synthesis of (7*R*,8*R*,8a*R*)-7,8-bis((*tert*-butyldimethylsilyl)oxy)-1-methylenetetrahydro-1H-oxazolo[3,4-a]pyridin-3(5*H*)-one (2.83)



Allene (**2.39**) (123 mg, 0.261 mmol) was dissolved in CH$_2$Cl$_2$ (0.5 mL) and held over activated 4Å molecular sieves for 5 minutes before it was added via cannula to a solution of AuCl$_3$ (3.96 mg, 0.013 mmol) and CaCO$_3$ (26.1 mg, 0.261 mmol) in 1:10 MeCN/CH$_2$Cl$_2$ (2.2 mL). The mixture was stirred at room temperature for 4 hours in the absence of light before it was filtered through a plug of celite, washing with CH$_2$Cl$_2$. The filtrate was concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 2% – 5% EtOAc in hexanes) to afford the title compound **2.83** (7.3 mg, 7% yield) as a colourless solid.

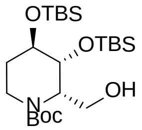
R_f = 0.17 (5% EtOAc/hexanes), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.73 (dd, *J* = 1.9, 3.0 Hz, 1H, C=C*H*H), 4.50 (d, *J* = 1.9 Hz, 1H, NC*H*C=C), 4.20 (dd, *J* = 1.6, 3.0 Hz, 1H, C=CH*H*), 3.91 (br. s., 1H, NCHC*H*OSi), 3.76 (dd, *J* = 5.6, 13.4 Hz, 1H, NC*H*HCH$_2$), 3.56 (dd, *J* = 2.1, 4.0 Hz, 1H, CH$_2$C*H*OSi), 3.21 (dt, *J* = 3.6, 13.2 Hz, 1H, NCH*H*CH$_2$), 2.15 - 2.03 (m, 1H, NCH$_2$C*H*H), 1.47 - 1.35 (m, 2H, NCH$_2$CH*H*), 0.92 (s, 9H, C(C*H*$_3$)$_3$), 0.86 (s, 9H, C(C*H*$_3$)$_3$), 0.09 (s, 6H, 2 x SiC*H*$_3$), 0.03 (s, 6H, 2 x SiC*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.7 (C=O), 152.2 (*C*=CH$_2$), 86.0 (C=*C*H$_2$), 71.2 (NCH*C*HOSi), 68.3 (CH$_2$*C*HOSi), 57.7 (N*C*HC=C), 35.1 (N*C*H$_2$CH$_2$), 25.9 (NCH$_2$*C*H$_2$), 25.7 (SiC(*C*H$_3$)$_3$), 25.5 (SiC(*C*H$_3$)$_3$), 17.9 (Si*C*(CH$_3$)$_3$), 17.8 (Si*C*(CH$_3$)$_3$), - 4.4 (Si*C*H$_3$), - 4.8 (Si*C*H$_3$), - 4.9 (Si*C*H$_3$)

MS (ESI) *m/z* 414 $[M+H]^+$ (100%)

Synthesis of (2*S*,3*S*,4*S*)-*tert*-butyl 3,4-bis((*tert*-butyldimethylsilyl)oxy)-2-(hydroxymethyl)piperidine-1-carboxylate (2.90)



Ozone was bubbled into a solution of alkene (**2.82**) (86.8 mg, 0.184 mmol) dissolved in 10:1 CH_2Cl_2/MeOH (2.2 mL) at - 78 °C until a blue solution was observed. Oxygen gas was then bubbled through the solution until it turned colourless before $NaBH_4$ (17.4 mg, 0.460 mmol) was added to the reaction mixture at - 78 °C. The resultant mixture was allowed to gradually warm up to room temperature and was stirred at room temperature for 20 hours before it was quenched by addition of sat'd $NaHCO_3$ solution (3 mL). The combined organic layers were washed with brine (2 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 5 – 15% EtOAc in hexanes) to afford the title compound **2.90** (56.7 mg, 65% yield) as a colourless oil.

R_f = 0.19 (15% EtOAc/hexanes), stained yellow with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.32 (br. s., 1H, CHC*H*N), 4.06 - 3.76 (m, 2H, CH_2OH), 3.75 - 3.65 (m, 1H, CH_2CH_2C*H*O), 3.54 - 3.51 (m, 1H, NCHC*H*O), 3.31 - 3.02 (m, 1H, CH_2C*H*HN), 3.02 - 2.56 (m, 1H, CH_2CH*H*N), 1.90 - 1.78 (m, 1H, C*H*HCH_2N), 1.44 (s, 9H, C(CH_3)$_3$), 1.39 - 1.32 (m, 1H, CH*H*CH_2N), 0.90 (s, 9H, C(CH_3)$_3$), 0.87 (s, 9H, C(CH_3)$_3$), 0.13 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.05 (s, 6H, 2 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.7 (NH*C*=O), 80.0 (O*C*(CH)$_3$), 70.1, 69.9, 60.7 (CH*C*HN), 57.7 (*C*H_2OH), 39.1 (CH_2*C*H_2N), 28.3 (OC(*C*H)$_3$), 25.9 (SiC(*C*H_3)$_3$), 25.6 (*C*H_2CH_2N), 18.0 (Si*C*(CH_3)$_3$), - 4.0 (Si*C*H_3), - 4.3 (Si*C*H_3), - 4.7 (Si*C*H_3), - 4.8 (Si*C*H_3)

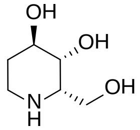
IR ν_{max} (film) 3425, 2957, 2931, 2855, 1696, 1420, 1363, 1253, 1109, 830, 774 cm^{-1}

MS (ESI) *m/z* 375 [M-Boc]$^-$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{23}H_{50}NO_5Si_2$ [M+H]$^+$ 476.3222, found 476.3219

$[\alpha]_D^{21}$ = - 7.21 (*c* 0.68, $CHCl_3$)

Synthesis of (2*S*,3*R*,4*R*)-2-(hydroxymethyl)piperidine-3,4-diol (2.91)



To a solution of protected alkaloid (**2.90**) (56.7 mg, 0.119 mmol) dissolved in 10:1 dioxane/MeOH (1.1 mL) was added 4 M HCl in dioxane (298 µL, 1.19 mmol). The resultant mixture was stirred at room temperature for 16 hours before it was concentrated *in vacuo* to give the title compound **2.91** as its HCl salt.

^{1}H NMR (400 MHz, D_2O) δ = 4.05 (q, *J* = 3.2 Hz, 1H, $CH_2CH_2C\mathit{H}OH$), 3.96 (d, *J* = 3.9 Hz, 1H, NCHC*H*OH), 3.91 - 3.79 (m, 2H, CH_2OH), 3.57 (ddd, *J* = 1.5, 5.1, 8.6 Hz, 1H, NC*H*CHOH), 3.33 - 3.23 (m, 2H, $CH_2C\mathit{H}_2NH$), 2.29 - 2.17 (m, 1H, $CH\mathit{H}CH_2NH$), 1.87 (dd, *J* = 3.1, 15.4 Hz, 1H, $CH\mathit{H}CH_2NH$)

The HCl salt was taken up in MeOH (3 mL) and stirred overnight at room temperature in the presence of Amberlyst A26-OH (~ 50 mg). The mixture was filtered, washing with MeOH, and the filtrate was concentrated *in vacuo* to afford the title compound **2.91** (13.0 mg, 74% yield) as its free base.

^{1}H NMR (400 MHz, D_2O) δ = 3.89 (dt, *J* = 4.8, 3.6 Hz, 1H, $CH_2CH_2C\mathit{H}OH$), 3.68 (dd, *J* = 4.8, 2.8 Hz, 1H, NCHC*H*OH), 3.66 (br s, 1H, C*H*HOH), 3.64 (br s, 1H, CH*H*OH), 3.04 (dt, *J* = 6.8, 2.8 Hz, 1H, NC*H*CHOH), 2.82 - 2.79 (m, 2H, $CH_2C\mathit{H}_2NH$), 1.98 - 1.89 (m, 1H, $C\mathit{H}HCH_2NH$), 1.58 - 1.51 (m, 1H, $CH\mathit{H}CH_2NH$)

^{13}C NMR (101 MHz, D_2O) δ = 68.9 (NCH*C*HOH), 67.9 ($CH_2CH_2\mathit{C}HOH$), 60.1 ($\mathit{C}H_2OH$), 55.3 (N*C*HCHOH), 38.6 ($CH_2\mathit{C}H_2NH$), 28.1 ($\mathit{C}H_2CH_2NH$)

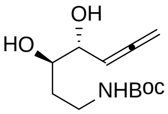
IR ν_{max} (film) 3323, 2954, 2928, 2856, 1464, 1255, 1091, 829, 772 cm^{-1}

MS (EI) *m/z* 148 $[M+H]^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_6H_{14}NO_3$ $[M+H]^+$ 148.0968, found 148.0964

$[\alpha]_D^{21}$ = - 10.6 (*c* 0.32, H_2O)

Synthesis of *tert*-butyl ((3*R*,4*R*)-3,4-dihydroxyhepta-5,6-dien-1-yl)carbamate (2.97)



To a solution of bis-TBS protected diol (**2.39**) (338 mg, 0.716 mmol) in THF (6 mL), cooled to 0 °C was added 1 M TBAF in THF (1.65 mL, 1.65 mmol). The mixture was allowed to gradually warm to room temperature and stirred at room temperature for 4 hours before H_2O (5 mL) was added. The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (6 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 100% EtOAc in cyclohexane) to afford the title compound **2.97** (166 mg, 95% yield) as a colourless oil.

R_f = 0.40 (80% EtOAc/cyclohexane), stained pink with ninhydrin

^1H NMR (400 MHz, $CDCl_3$) δ = 5.21 (q, *J* = 6.8 Hz, 1H, $H_2C{=}C{=}CH$), 4.91 - 4.81 (m, 2H, $H_2C{=}C{=}CH$), 3.99 (tt, *J* = 2.1, 6.8 Hz, 1H, C=CHC*H*O), 3.54 (ddd, *J* = 2.9, 6.6, 9.9 Hz, 1H, CH_2CH_2CHO), 3.48 - 3.39 (m, 1H, CH_2CHHNH), 3.16 (td, *J* = 5.3, 14.2 Hz, 1H,

CH_2CHHNH), 1.76 - 1.66 (m, 1H, $CHHCH_2NH$), 1.60 - 1.50 (m, 1H, $CHHCH_2NH$), 1.43 (s, 9H, $C(CH_3)_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.3 ($H_2C=C=CH$), 157.2 ($C=O$), 91.2 ($H_2C=C=CH$), 79.8 ($OC(CH_3)_3$), 74.6 ($H_2C=C=CH$), 72.9, 72.1, 37.1 (CH_2CH_2N), 33.5 (CH_2CH_2N), 28.4 ($OC(CH_3)_3$)

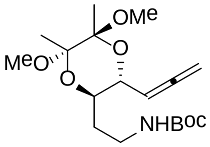
IR ν_{max} (film) 3353, 2977, 2932, 1950, 1680, 1517, 1365, 1247, 1163, 852 cm^{-1}

MS (ESI) *m/z* 266 $[M+Na]^+$ (52%), 244 $[M+H]^+$ (22%), 143 (100%)

HRMS (ESI) *m/z* calc'd for $C_{12}H_{21}NO_4Na$ $[M+Na]^+$ 266.1363, found 266.1363

$[\alpha]_D^{22}$ = - 27.2 (*c* 0.71, $CHCl_3$)

Synthesis of *tert*-butyl (2-((2*S*,3*S*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl-3-(propa-1,2-dien-1-yl)-1,4-dioxan-2-yl)ethyl)carbamate (2.98)



To a solution of diol (**2.97**) (45.9 mg, 0.188 mmol), trimethylorthoformate (82.3 µL, 0.752 mmol), butanedione (32.9 µL, 0.376 mmol) in dry MeOH (2 mL) was added $BF_3 \cdot Et_2O$ (7 µL, 0.056 mmol) at room temperature. The mixture was stirred at room temperature for 16 hours before it was neutralised by addition of Et_3N (10 µL). The volatiles were removed *in vacuo* and the residue was taken up in CH_2Cl_2 (5 mL) and washed sequentially with H_2O (2 mL) and brine (2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 5 – 10% EtOAc in cyclohexane) to afford the title compound **2.98** (21.0 mg, 31% yield) as a colourless oil.

R_f = 0.41 (40% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.09 (td, *J* = 6.7, 8.5 Hz, 1H, C*H*=C=CH_2), 4.89 - 4.74 (m, 3H, CH=C=CH_2 and N*H*), 4.06 - 3.99 (m, 1H, C=CHC*H*O), 3.66 (dt, *J* = 2.3, 9.9 Hz, 1H, CH_2CH_2C*H*O), 3.41 - 3.32 (m, 1H, CH_2C*H*HNH), 3.27 (s, 3H, OCH_3), 3.24 (s, 3H, OCH_3), 3.21 (d, *J* = 6.7 Hz, 1H, CH_2CH*H*NH), 1.76 (ddd, *J* = 2.5, 7.1, 14.1 Hz, 2H, C*H*HCH_2NH), 1.61 - 1.50 (m, 1H, CH*H*CH_2NH), 1.42 (s, 9H, C(CH_3)$_3$), 1.29 (s, 6H, 2 x CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 210.0 (CH=*C*=CH_2), 155.8 (NH*C*=O), 128.6 (*C*OOCH_3), 128.0 (*C*OOCH_3), 88.0 (H_2C=C=*C*H), 79.0 (O*C*(CH_3)$_3$), 76.2 (H_2*C*=C=*C*H), 71.2 (C=CH*C*HO), 70.0 (CH_2CH_2*C*HO), 48.0 (O*C*H_3), 47.9 (O*C*H_3), 37.5 (CH_2*C*H_2NH), 30.5 (*C*H_2CH_2NH), 28.4 (C(*C*H_3)$_3$), 17.7 (*C*H_3) , 17.6 (*C*H_3)

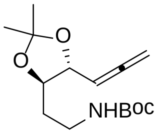
IR ν_{max} (film) 3370, 2976, 2866, 1957, 1715, 1513, 1366, 1120 cm^{-1}

MS (ESI) *m/z* 380 $[M+Na]^+$ (5%), 279 (100%)

HRMS (ESI) *m/z* calc'd for $C_{18}H_{31}NO_6Na$ $[M+Na]^+$ 380.2044, found 380.2043

$[\alpha]_D^{22}$ = + 93.1 (*c* 0.29, $CHCl_3$)

Synthesis of *tert*-butyl (2-((4*R*,5*R*)-2,2-dimethyl-5-(propa-1,2-dien-1-yl)-1,3-dioxolan-4-yl)ethyl)carbamate (2.105)



To a solution of diol (**2.97**) (37.3 mg, 0.153 mmol) in dry CH_2Cl_2 (3 mL) was added 2,2-dimethoxypropane (37.6 µL, 0.306 mmol) and *p*-TSA (1.46 mg, 7.65 µmol). The resultant mixture was stirred at room temperature for 4 hours before it was diluted with CH_2Cl_2 (3 mL) and washed with H_2O (2 mL) and brine (2 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 20% EtOAc in cyclohexane) to afford the title compound **2.105** (31.4 mg, 72% yield) as a colourless oil.

R_f = 0.63 (40% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.20 - 5.13 (m, 1H, $H_2C{=}C{=}CH$), 4.93 - 4.78 (m, 3H, $H_2C{=}C{=}CH$ and N*H*Boc), 4.09 (t, *J* = 8.0 Hz, 1H, C=CHC*H*O), 3.77 (dt, *J* = 3.5, 8.4 Hz, 1H, CH_2CH_2CHO), 3.37 - 3.18 (m, 2H, CH_2N), 1.86 (qd, *J* = 6.8, 10.2 Hz, 1H, $CH_2CHHCHO$), 1.74 - 1.62 (m, 1H, $CH_2CHHCHO$), 1.45 (s, 9H, $C(CH_3)_3$), 1.40 (d, *J* = 4.9 Hz, 6H, 2 x CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.6 ($H_2C{=}C{=}CH$), 155.9 (*C*=O), 109.0 ($C(CH_3)_2O_2$), 88.9 ($H_2C{=}C{=}CH$), 79.6 ($OC(CH_3)_3$), 79.1, 79.0, 73.8, 38.1 (CH_2CH_2N), 31.9 (CH_2CH_2N), 28.4 ($OC(CH_3)_3$), 27.2 ($C(CH_3)_2O_2$), 26.9 ($C(CH_3)_2O_2$)

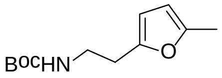
IR ν_{max} (film) 3361, 2984, 2931, 1960, 1699, 1514, 1367, 1245, 1166, 1042, 770 cm^{-1}

MS (ESI) *m/z* 306 $[M+Na]^+$ (57%), 284 $[M+H]^+$ (17%), 126 (100%)

HRMS (ESI) *m/z* calc'd for $C_{15}H_{25}NO_4Na$ $[M+Na]^+$ 306.1676, found 306.1676

$[\alpha]_D^{21}$ = - 11.9 (*c* 0.43, $CHCl_3$)

Synthesis of *tert*-butyl (2-(5-methylfuran-2-yl)ethyl)carbamate (2.100)



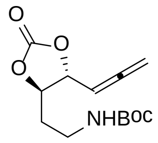
To a solution of allene (**2.105**) (48.8 mg, 0.172 mmol) in dry CH_2Cl_2 (1.7 mL) was added $CaCO_3$ (17.2 mg, 0.172 mmol), Ph_3PAuCl (4.26 mg, 8.61 µmol) and $AgSbF_6$ (2.96 mg, 8.61 µmol). The mixture was stirred at room temperature for 20 hours in the absence of light. The reaction mixture was filtered through a plug of celite and washed with CH_2Cl_2 (5 mL). The filtrate was concentrated to give an orange oil. The crude material was purified by silica gel chromatography (gradient: 5% – 15% EtOAc in cyclohexane) to afford the title compound **2.100** (16 mg, 32% yield) as a colourless oil. ^{1}H NMR data obtained were consistent with those reported in the literature.[155]

R_f = 0.53 (20% EtOAc/cyclohexane), stained blue with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.92 (d, *J* = 2.9 Hz, 1H, Ar*H*), 5.85 (d, *J* = 2.9 Hz, 1H, Ar*H*), 4.67 (br. s., 1H, N*H*), 3.37 (m, 2H, CH_2CH_2N), 2.76 (t, *J* = 6.6 Hz, 2H, CH_2CH_2N), 2.25 (s, 3H, CH_3), 1.44 (s, 9H, $C(CH_3)_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.8 (*C*=O), 151.2, 150.9, 106.8, 105.9, 79.23 ($OC(CH_3)_3$), 39.2 (NCH_2CH_2), 28.7 (NCH_2CH_2), 28.3 ($OC(CH_3)_3$), 13.4 (CH_3)

Synthesis of *tert*-butyl (2-((4*R*,5*R*)-2-oxo-5-(propa-1,2-dien-1-yl)-1,3-dioxolan-4-yl)ethyl)carbamate (2.106)



To a solution of diol (**2.97**) (55.5 mg, 0.228 mmol) in CH_2Cl_2 (3 mL) was added CDI (85.0 mg, 0.524 mmol) at room temperature. The mixture was stirred at room temperature for 16 hours before it was diluted with CH_2Cl_2 (3 mL) and washed sequentially with sat'd NH_4Cl solution (2 mL) and brine (2 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 40% EtOAc in cyclohexane) to afford the title compound **2.106** (50.0 mg, 81% yield) as a colourless oil.

R_f = 0.41 (40% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.34 (q, *J* = 6.7 Hz, 1H, $H_2C{=}C{=}CH$), 5.12 - 5.01 (m, 2H, $H_2C{=}C{=}CH$), 4.79 - 4.67 (m, 2H, C=CHC*H*O and N*H*Boc), 4.55 - 4.46 (m, 1H, CH_2CH_2CHO), 3.30 (q, *J* = 6.4 Hz, 2H, CH_2CH_2NH), 2.02 (br. s, 1H, C*H*HCH$_2$NH), 1.96 - 1.84 (m, 1H, CH*H*CH$_2$NH), 1.44 (s, 9H, $C(CH_3)_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.6 ($H_2C{=}C{=}CH$), 155.9 (*C*=O), 153.7 (*C*=O), 87.4 ($H_2C{=}C{=}CH$), 79.8 ($OC(CH_3)_3$), 79.4, 79.3 65.8, 36.8 (CH_2CH_2N), 33.4 (CH_2CH_2N), 28.4 ($OC(CH_3)_3$)

IR ν_{max} (film) 3365, 2976, 2935, 1952, 1797, 1699, 1514, 1367, 1249, 1170, 861 cm^{-1}

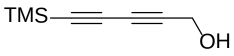
MS (ESI) *m/z* 292 $[M+Na]^+$ (21%), 270 $[M+H]^+$ (10%), 170 (100%)

HRMS (ESI) *m/z* calc'd for $C_{13}H_{19}NO_5Na$ $[M+Na]^+$ 292.1155, found 292.1154

$[\alpha]_D^{22}$ = + 45.9 (*c* 0.46, $CHCl_3$)

4.3 Experimental section for Chapter 3

Synthesis of 5-(trimethylsilyl)penta-2,4-diyn-1-ol (3.85).[194,214]



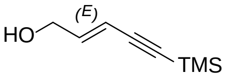
A solution of diisopropylamine (3.82 mL, 26.8 mmol), CuI (34.0 mg, 0.178 mmol), and $Pd(PPh_3)_2Cl_2$ (46.8 mg, 0.178 mmol) in anhydrous THF (50 mL) was degassed with argon before 1-iodo-2-(trimethylsilyl)acetylene (2.00 g, 8.92 mmol) and propargyl alcohol (0.619 mL, 10.7 mL) were added. The resultant mixture was stirred at room temperature for 4 hours. The brown reaction mixture was filtered through a plug of celite, washing with EtOAc (50 mL). The filtrate was concentrated *in vacuo* to give a brown residue. The crude material was purified by silica gel chromatography (gradient: 0 – 20% EtOAc in cyclohexane) to afford the title compound **3.85** (1.36 g, 83% yield) as a brown oil. ^{1}H NMR data obtained were consistent with those reported in the literature.[194,214]

R_f = 0.50 (20% EtOAc/cyclohexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.33 (s, 2H, CH_2OH), 1.60 (br. s, 1H, OH), 0.20 (s, 9H, $Si(CH_3)_3$)

IR ν_{max} (film) 3350, 2959, 2899, 2108, 1250, 1018, 843, 760 cm^{-1}

Synthesis of (*E*)-5-(trimethylsilyl)pent-2-en-4-yn-1-ol (3.86).[195,215]



To a solution of diyne (**3.85**) (1.99 g, 13.1 mmol) in anhydrous THF (60 mL) at -78 °C was slowed added $LiAlH_4$ (1.24 g, 32.7 mmol). The resultant mixture was allowed to gradually warm up to room temperature and stirred at room temperature for 3 hours under argon. The mixture was cooled to 0 °C in an ice bath before it was quenched by sequential addition of H_2O (1.24 mL), 4 M NaOH solution (1.24 mL) and H_2O (3.72 mL). The mixture was stirred until all the grey precipitate had dissipated to give a white precipitate in a yellow solution. The mixture was filtered through a plug of celite, washing with EtOAc (40 mL). The filtrate was concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 30% EtOAc in cyclohexane) to afford the title compound **3.86** (1.17 g, 58% yield) as a colourless oil. Spectroscopic data obtained were consistent with those reported in the literature.[195,215]

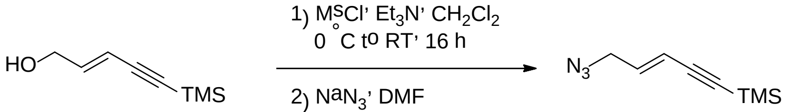
R_f = 0.50 (20% EtOAc/cyclohexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.30 (td, *J* = 5.1, 15.9 Hz, 1H, CH=C*H*CH_2), 5.77 (td, *J* = 1.9, 15.9 Hz, 1H, C*H*=CHCH_2), 4.20 (dd, *J* = 1.8, 5.1 Hz, 2H, CH_2OH), 1.85 (br. s, 1H, O*H*), 0.18 (s, 9H, Si(CH_3)$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 142.9 (CH=*C*HCH_2), 110.3 (*C*H=CHCH_2), 102.9 (SiC≡*C*CH), 95.2 (Si*C*≡CCH), 62.7 (*C*H_2OH), - 0.14 (Si(*C*H_3)$_3$)

MS (EI) *m/z* 139 $[M-CH_3]^+$ (100%)

Synthesis of (*E*)-(5-azidopent-3-en-1-yn-1-yl)trimethylsilane (3.87).



3˙86 **3˙87**

To a solution of alcohol (**3.86**) (416 mg, 2.69 mmol) in CH_2Cl_2 (13 mL), cooled to 0 °C was added Et_3N (563 µL, 4.04 mmol) followed by mesyl chloride (252 µL, 3.23 mmol). The mixture was allowed to gradually warm up to room temperature and was stirred at room temperature for 16 hours before it was washed sequentially with sat'd NH_4Cl solution (4 mL) and brine (4 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford mesylate (550 mg) as a yellow oil. The crude material was used directly in the next step without further purification.

R_f = 0.70 (20% EtOAc/cyclohexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.20 (td, *J* = 6.3, 15.9 Hz, 1H, CH=C*H*CH$_2$), 5.87 (td, *J* = 1.4, 15.9 Hz, 1H, C*H*=CHCH$_2$), 4.74 (dd, *J* = 1.4, 6.3 Hz, 2H, CH=CHC*H*$_2$), 3.02 (s, 3H, C*H*$_3$), 0.19 (s, 9H, 3 x SiC*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 134.7 (CH=*C*HCH$_2$), 115.9 (*C*H=CHCH$_2$), 101.4 (SiC≡*C*CH), 98.1 (Si*C*≡CCH), 68.7 (CH=CH*C*H$_2$O), 38.2 (*C*H$_3$), - 0.2 (Si*C*H$_3$)

To a solution of crude mesylate (550 mg, 2.37 mmol) in DMF (4 mL) was added NaN_3 (385 mg, 5.92 mmol). The resultant mixture was stirred at room temperature for 16 hours before it was diluted with EtOAc (8 mL) and H_2O (4 mL). The mixture was stirred for 10 minutes before the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the title compound **3.87** (650 mg) as a yellow oil. The crude material was used directly in the next step without further purification.

R_f = 0.72 (20% EtOAc/cyclohexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.17 (td, *J* = 6.2, 15.8 Hz, 1H, CH=C*H*CH_2), 5.78 (td, *J* = 1.6, 15.8 Hz, 1H, C*H*=CHCH_2), 3.83 (dd, *J* = 1.3, 6.2 Hz, 2H, CH=CHCH_2), 0.20 (s, 9H, 3 x SiCH_3)

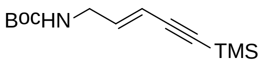
^{13}C NMR (101 MHz, $CDCl_3$) δ = 136.6 (CH=*C*HCH_2), 113.9 (*C*H=CHCH_2), 102.0 (SiC≡*C*CH), 96.4 (Si*C*≡CCH), 52.2 (CH=CH*C*H_2N), - 0.2 (Si*C*H_3)

IR ν_{max} (film) 2981, 2924, 2095, 1247, 1080, 836, 756 cm^{-1}

MS (EI) *m/z* 136 $[M-N_3]^+$ (30%), 110 (100%)

HRMS (ESI) *m/z* calc'd for $C_8H_{14}N_3Si$ $[M+H]^+$ 180.0952, found 180.0951

Synthesis of (*E*)-*tert*-butyl (5-(trimethylsilyl)pent-2-en-4-yn-1-yl)carbamate (3.88).



To a solution of azide (**3.87**) (425 mg, 2.37 mmol) in THF (10 mL) was added PPh_3 (932 mg, 3.56 mmol). The mixture was stirred at room temperature for 4 hours before H_2O (853 μL, 47.4 mmol) was added. The mixture was stirred at room temperature for 16 hours before Boc_2O (672 mg, 3.08 mmol) and DIPEA (621 μL, 3.56 mmol) were added. The reaction mixture was stirred for a further 4 hours before it was diluted EtOAc (15 mL) and washed with brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light brown oil. The crude material was purified by silica gel chromatography (gradient: 0 – 5% EtOAc in cyclohexane) to afford the title compound **3.88** (367 mg, 61% over 3 steps) as a light brown oil.

R_f = 0.31 (4% EtOAc/cyclohexane), visualised by UV lamp

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.16 (td, *J* = 5.8, 15.9 Hz, 1H, CH=C*H*CH_2), 5.64 (td, *J* = 1.7, 15.9 Hz, 1H, C*H*=CHCH_2), 4.55 (br. s., 1H, N*H*), 3.78 (br. s., 2H, CH=CHCH_2), 1.44 (s, 9H, OC(CH_3)$_3$), 0.18 (s, 9H, 3 x SiCH_3)

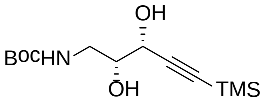
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.5 (*C*=O), 140.8 (CH=*C*HCH_2), 111.0 (*C*H=CHCH_2), 102.8 (SiC≡*C*CH), 95.0 (Si*C*≡CCH), 79.7 (O*C*(CH_3)$_3$), 42.2 (CH=CH*C*H_2N), 28.3 (OC(*C*H_3)$_3$), - 0.1 (Si*C*H_3)

IR ν_{max} (film) 3346, 2941, 2866, 1696, 1510, 1245, 1162, 841, 762 cm^{-1}

MS (ESI) *m/z* 254 $[M+H]^+$ (14%), 154 (100%)

HRMS (ESI) *m/z* calc'd for $C_{13}H_{24}NO_2Si$ $[M+H]^+$ 254.1571, found 254.1569

Synthesis of *tert*-butyl ((2*R*,3*R*)-2,3-dihydroxy-5-(trimethylsilyl)pent-4-yn-1-yl)carbamate (3.89).



AD-mix beta (349 mg, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (2 mL) and methanesulfonamide (23.7 mg, 0.249 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**3.88**) (63.1 mg, 0.249 mmol), predissolved in 1:1 *t*-BuOH/H_2O (1 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from ice bath and stirred at room temperature for 18 hours. The mixture was quenched with addition of solid Na_2SO_3 (100 mg) and stirred for 30 minutes before H_2O (3 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 3 mL). The combined organic layers were washed with brine (3 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 40% EtOAc in cyclohexane) to afford the title compound **3.89** (9.3 mg, 13% yield) as a colourless oil.

R_f = 0.35 (40% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.97 (br. s, 1H, N*H*), 4.30 (d, *J* = 5.4 Hz, 1H, C≡CC*H*OH), 3.70 (m, 1H, NCH_2C*H*OH), 3.44 (td, *J* = 5.1, 14.4 Hz, 1H, NC*H*HCHOH), 3.30 - 3.20 (m, 1H, NCH*H*CHOH), 2.53 (br. s, 2H, 2 x O*H*), 1.44 (s, 9H, $OC(CH_3)_3$), 0.18 (s, 9H, 3 x $SiCH_3$)

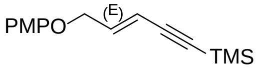
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.3 (*C*=O), 102.9 (SiC≡*C*CH), 91.8 (Si*C*≡CCH), 80.2 (O*C*$(CH_3)_3$), 74.0, 64.4, 42.8 (*C*H_2N), 28.3 (OC(*C*$H_3)_3$), - 0.2 (Si*C*H_3)

IR ν_{max} (film) 3346, 2961, 2927, 2896, 1688, 1514, 1367, 1249, 1170, 837, 762 cm^{-1}

MS (ESI) *m/z* 310 $[M+Na]^+$ (93%), 288 $[M+H]^+$ (33%), 188 (100%)

HRMS (ESI) *m/z* calc'd for $C_{13}H_{26}NO_4Si$ $[M+H]^+$ 288.1626, found 288.1623

Synthesis of (*E*)-(5-(4-methoxyphenoxy)pent-3-en-1-yn-1-yl)trimethylsilane (3.91).



To a solution of alcohol **3.86** (4.47 g, 29.0 mmol), *p*-methoxyphenol (10.8 g, 87.0 mmol) and triphenylphosphine (11.4 g, 43.5 mmol) in THF (120 mL) was added DIAD (8.46 mL, 43.5 mmol) dropwise at room temperature. The resultant orange solution was stirred at room temperature for 18 hours under argon atmosphere before it was concentrated *in vacuo* to give an orange syrup. The syrup was taken up in EtOAc (40 mL) and washed sequentially with sat'd $NaHCO_3$ solution (10 mL), water (10 mL) and brine (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give an orange oil. The crude material was purified by silica gel chromatography (gradient: 0 – 5% EtOAc in cyclohexane) to afford the title compound **3.91** (7.14 g, 94% yield) as a colourless solid.

R_f = 0.60 (20% EtOAc/cyclohexane)

Melting point = 51 – 52 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.82 (s, 4H, Ar*H*), 6.33 (td, *J* = 5.1, 16.0 Hz, 1H, CH=C*H*CH_2), 5.86 (td, *J* = 1.8, 16.0 Hz, 1H, C*H*=CHCH_2), 4.53 (dd, *J* = 1.9, 5.1 Hz, 2H, CH_2OH), 3.77 (s, 3H, OCH_3), 0.19 (s, 9H, Si(CH_3)$_3$)

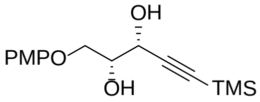
^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.1, 152.5, 139.2 (CH=*C*HCH_2), 115.8, 114.7, 112.0 (*C*H=CHCH_2), 102.8 (SiC≡*C*CH), 95.8 (Si*C*≡CCH), 68.2 (ArO*C*H_2), 55.7 (O*C*H_3), - 0.15 (Si(*C*H_3)$_3$)

IR ν_{max} (film) 2958, 2867, 2133, 1506, 836 cm^{-1}

MS (EI) *m/z* 260 $[M]^+$ (35%), 123 (100%)

HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}O_2Si$ $[M+H]^+$ 261.1311, found 261.1306

Synthesis of (2*R*,3*R*)-1-(4-methoxyphenoxy)-5-(trimethylsilyl)pent-4-yne-2,3-diol (3.92).



AD-mix beta (36.5 g, 1.4 g per mmol of alkene) was dissolved in 1:1 *t*-BuOH/H_2O (210 mL) and methanesulfonamide (2.48 g, 26.0 mmol) was added. The mixture was cooled to 0 °C in an ice bath and stirred until a bright orange mixture was obtained. Enyne (**3.91**) (6.78 g, 26.0 mmol), predissolved in 1:1 *t*-BuOH/H_2O (50 mL), was added to the bright orange mixture in one portion at 0 °C. The mixture was stirred at 0 °C for 10 minutes before it was removed from ice bath and stirred at room temperature for 18 hours to give a yellowish green mixture. The mixture was quenched with addition of solid Na_2SO_3 (3.6 g) and stirred for 30 minutes before H_2O (50 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 50% EtOAc in cyclohexane) to afford the title compound **3.92** (5.87 g, 76% yield) as a colourless solid.

R_f = 0.45 (50% EtOAc/cyclohexane), stained blue with CAM.

Melting point = 55 – 56 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 - 6.81 (m, 4H, Ar*H*), 4.52 (d, *J* = 5.8 Hz, 1H, C≡CC*H*OH), 4.18 - 4.12 (m, 1H, OC*H*HCHOH), 4.08 - 4.00 (m, 2H, OCH*H*CHOH, OCHHC*H*OH), 3.77 (s, 3H, OC*H*$_3$), 0.18 (s, 9H, Si(C*H*$_3$)$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.3, 152.5, 115.7, 114.7, 102.8 (SiC≡*C*CH), 92.0 (Si*C*≡CCH), 73.2, 69.0, 63.8 (ArO*C*H_2), 55.7 (O*C*H_3), - 0.24 (Si(*C*H_3)$_3$)

IR ν_{max} (film) 3406, 2961, 1507, 1227, 1038, 841 cm^{-1}

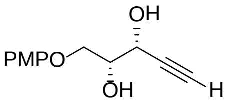
MS (ESI) *m/z* 317 $[M+Na]^+$ (39%), 294 $[M]^+$ (74%), 277 (100%)

HRMS (ESI) *m/z* calc'd for $C_{15}H_{23}O_4Si$ $[M+H]^+$ 295.1366, found 295.1361

Chiral SFC (OJ-H column, 5-55% MeOH in CO_2) = 98.2% ee

$[\alpha]_D^{22}$ = + 41.1 (*c* 0.55, $CHCl_3$)

Synthesis of (2*R*,3*R*)-1-(4-methoxyphenoxy)pent-4-yne-2,3-diol (3.93).



To a solution of TMS-protected alkyne (**3.92**) (5.74 g, 19.5 mmol) in MeOH (100 mL) was added K_2CO_3 (4.04 g, 29.3 mmol). The resultant mixture was stirred at room temperature for 4 hours before it was diluted with Et_2O (150 mL) and washed with sat'd $NaHCO_3$ solution (25 mL). The aqueous phase was neutralised with 1 M HCl solution and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the title compound **3.93** (4.12 g, 95% yield) as a colourless solid.

R_f = 0.25 (50% EtOAc/cyclohexane)

Melting point = 83 – 84 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.90 - 6.81 (m, 4H, Ar*H*), 4.55 (dd, *J* = 2.1, 5.4 Hz, 1H, C≡CC*H*OH), 4.18 - 4.12 (m, 1H, OC*H*HCHOH), 4.10 - 4.03 (m, 2H, OCH*H*CHOH, OCHHC*H*OH), 3.77 (s, 3H, OCH_3), 2.54 (d, *J* = 2.1 Hz, 1H, *H*C≡CCHOH), 2.22 (br. s, 2H, O*H*)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.4, 152.4, 115.7, 114.7, 81.5 (HC≡*C*CH), 74.8, 73.0, 68.9, 63.1 (ArO*C*H_2), 55.7 (O*C*H_3)

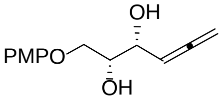
IR ν_{max} (film) 3392, 3281, 2357, 1506, 1228, 1038, 825 cm^{-1}

MS (ESI) *m/z* 245 [M+Na]$^+$ (13%), 222 [M]$^+$ (20%), 205 (34%), 187 (100%)

HRMS (ESI) *m/z* calc'd for $C_{12}H_{15}O_4$ [M+H]$^+$ 223.0965, found 223.0965

$[\alpha]_D^{22}$ = + 26.2 (*c* 0.79, $CHCl_3$)

Synthesis of (2*R*,3*R*)-1-(4-methoxyphenoxy)hexa-4,5-diene-2,3-diol (3.94).



A mixture of alkyne (**3.93**) (500 mg, 2.25 mmol), CuBr (161 mg, 1.13 mmol), dicyclohexylamine (0.90 mL, 4.50 mmol) and paraformaldehyde (169 mg, 5.63 mmol) in 1,4-dioxane (11 mL) was heated in a Biotage microwave reactor at 150 °C for 25 minutes. The resultant brown mixture was filtered through a plug of celite, washing with EtOAc (20 mL). The filtrate was concentrated *in vacuo* to give a brown oil. The crude material was purified by silica gel chromatography (gradient: 0 – 60% EtOAc in cyclohexane) to afford the title compound **3.94** (395 mg, 74% yield) as a light brown solid.

R_f = 0.33 (50% EtOAc/cyclohexane), stained blue with CAM

Melting point = 81 – 83 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.89 - 6.80 (m, 4H, Ar*H*), 5.34 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 4.97 - 4.86 (m, 2H, C*H*$_2$=C=CHC), 4.34 (tdd, *J* = 2.4, 4.7, 6.6 Hz, 1H, C=CHC*H*OH), 4.11 - 4.06 (m, 1H, ArOC*H*H), 4.04 - 3.98 (m, 1H, ArOCH*H*), 3.96 - 3.91 (m, 1H, OCH_2C*H*OH), 3.77 (s, 3H, OC*H*$_3$), 2.07 (br. s., 2H, O*H*)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.0 (CH_2=*C*=CHC), 154.3, 152.6, 115.7, 114.7, 91.2 (CH_2=C=*C*HC), 77.9, 77.2, 72.9, 69.9 (ArO*C*H$_2$), 55.7 (O*C*H$_3$)

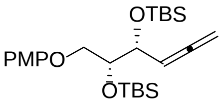
IR ν_{max} (film) 3269, 2935, 1954, 1509, 1232, 1050, 818 cm^{-1}

MS (ESI) *m/z* 237 $[M+H]^+$ (17%), 219 (26%), 201 (100%)

HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}O_4$ $[M+H]^+$ 237.1121, found 237.1121

$[\alpha]_D^{22}$ = + 21.6 (*c* 0.51, $CHCl_3$)

Synthesis of (5*R*,6*R*)-5-((4-methoxyphenoxy)methyl)-2,2,3,3,8,8,9,9-octamethyl-6-(propa-1,2-dien-1-yl)-4,7-dioxa-3,8-disiladecane (3.95).



To a solution of diol (**3.94**) (3.16 g, 13.4 mmol) in CH_2Cl_2 (53 mL) and cooled to 0 °C was added 2,6-lutidine (3.89 mL, 33.4 mmol) and TBSOTf (6.76 mL, 29.4 mmol). The resultant mixture was stirred at 0 °C for 2 hours before the mixture was diluted with CH_2Cl_2 (30 mL) and washed sequentially with water (15 mL) and brine (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light brown oil. The crude material was purified by silica gel chromatography (gradient: 0 – 10% EtOAc in cyclohexane) to afford the title compound **3.95** (5.40 g, 86% yield) as a colourless oil.

R_f = 0.75 (30% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.86 - 6.78 (m, 4H, Ar*H*), 5.25 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 4.83 - 4.71 (m, 2H, CH_2=C=CHC), 4.30 - 4.24 (m, 1H, C=CHC*H*OSi), 4.15 (dd, *J* = 2.7, 9.7 Hz, 1H, ArOC*H*H), 4.00 (ddd, *J* = 2.7, 4.4, 7.5 Hz, 1H, OCH_2C*H*OSi), 3.81 (dd, *J* = 7.8, 9.6 Hz, 1H, ArOCH*H*), 3.77 (s, 3H, OCH_3), 0.89 (s, 18H, 2 x SiC(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.08 (s, 3H, SiCH_3), 0.07 (s, 3H, SiCH_3), 0.05 (s, 3H, SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.2 (CH_2=*C*=CHC), 153.6, 153.2, 115.2, 114.6, 90.8 (CH_2=C=*C*HC), 76.4, 74.5, 72.2, 69.6 (ArO*C*H_2), 55.8 (O*C*H_3), 25.8, 25.7, 18.2, 18.1, - 4.3 (Si*C*H_3), - 4.5 (Si*C*H_3), - 4.8 (Si*C*H_3), - 5.0 (Si*C*H_3)

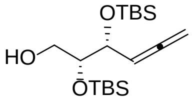
IR ν_{max} (film) 2953, 2927, 2889, 2855, 1956, 1507, 1461, 1231, 1129, 830, 774 cm^{-1}

MS (EI) *m/z* 464 $[M]^+$ (8%), 407 (51%), 183 (100%)

HRMS (ESI) *m/z* calc'd for $C_{25}H_{44}O_4Si_2Na$ $[M+Na]^+$ 487.2670, found 487.2668

$[\alpha]_D^{22}$ = + 60.7 (*c* 0.68, $CHCl_3$)

Synthesis of (2*R*,3*R*)-2,3-bis((*tert*-butyldimethylsilyl)oxy)hexa-4,5-dien-1-ol (3.96).



To a solution of PMP protected alcohol (**3.95**) (5.33 g, 11.5 mmol) in MeCN (114 mL), cooled to 0 °C was added pyridine (3.71 mL, 45.9 mmol). A solution of CAN (18.8 g, 34.4 mmol) dissolved in H_2O (57 mL) was added dropwise at 0 °C. The resultant mixture was stirred at 0 °C for 30 minutes before it was diluted with EtOAc (50 mL) and quenched with H_2O (25 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a bright orange residue. The crude material was purified by silica gel chromatography (gradient: 0 – 5% EtOAc in cyclohexane) to afford the title compound **3.96** (3.56 g, 86% yield) as a colourless oil.

R_f = 0.65 (20% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.24 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 4.84 - 4.70 (m, 2H, C*H*$_2$=C=CHC), 4.28 (tdd, *J* = 2.4, 4.4, 6.5 Hz, 1H, C=CHC*H*OSi), 3.83 - 3.74 (m, 2H, OCH_2C*H*OSi, HOC*H*H), 3.62 - 3.55 (m, 1H, HOCH*H*), 1.69 (br. s., 1H, O*H*), 0.89 (s, 18H, 2 x SiC(C*H*$_3$)$_3$), 0.10 - 0.07 (m, 12H, 4 x SiC*H*$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.6 (CH_2=*C*=CHC), 90.3 (CH_2=C=*C*HC), 76.5, 73.9, 73.5, 63.7 (HO*C*H$_2$), 25.8, 25.7, 18.1, 18.0, - 4.6 (Si*C*H$_3$), - 4.7 (Si*C*H$_3$), - 4.7 (Si*C*H$_3$), - 5.1 (Si*C*H$_3$)

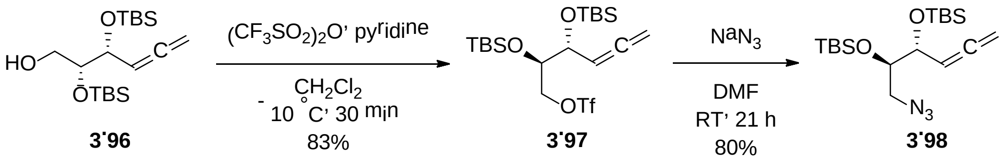
IR ν_{max} (film) 3482, 2953, 2915, 2889, 2858, 1960, 1249, 1117, 1072, 834, 774 cm^{-1}

MS (EI) *m/z* 301 [M-*t*Bu]$^+$ (32%), 183 (65%), 169 (100%)

HRMS (ESI) *m/z* calc'd for $C_{18}H_{39}O_3Si_2$ $[M+H]^+$ 359.2432, found 359.2430

$[\alpha]_D^{22}$ = + 50.5 (*c* 0.58, $CHCl_3$)

Synthesis of (5*R*,6*R*)-5-(azidomethyl)-2,2,3,3,8,8,9,9-octamethyl-6-(propa-1,2-dien-1-yl)-4,7-dioxa-3,8-disiladecane (3.98).



3.96 **3.97** **3.98**

To a solution of alcohol (**3.96**) (2.95 g, 8.23 mmol) in CH_2Cl_2 (80 mL) and cooled to - 10 °C in a salt-ice bath was added pyridine (1.33 mL, 16.5 mmol) followed by triflic anhydride (1.66 mL, 9.88 mmol). The resultant mixture was stirred at - 10 °C for 30 minutes before it was diluted with CH_2Cl_2 (40 mL) and quenched with H_2O (30 mL). The organic layer was separated, washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give crude triflate **3.97** (3.37 g, 83% yield) as a light yellow oil. The crude material was used in the next step without further manipulation.

R_f = 0.64 (10% EtOAc/cyclohexane), stained blue with CAM

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.15 (q, *J* = 6.5 Hz, 1H, CH_2=C=C*H*C), 4.81 (ddd, *J* = 2.9, 6.7, 11.5 Hz, 2H, CH_2=C=CHC), 4.72 (dd, *J* = 2.2, 10.0 Hz, 1H, SOC*H*H), 4.41 (dd, *J* = 8.1, 9.9 Hz, 1H, SOCH*H*), 4.25 - 4.20 (m, 1H, C=CHC*H*OSi), 3.96 (ddd, *J* = 2.3, 5.0, 7.7 Hz, 1H, OCH_2C*H*OSi), 0.92 - 0.87 (m, 18H, 2 x $SiC(CH_3)_3$), 0.12 - 0.06 (m, 12H, 4 x $SiCH_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.4 (CH_2=*C*=CHC), 117.1 (*C*F_3), 89.6 (CH_2=C=*C*HC), 78.1, 77.3, 73.7, 71.3, 25.7, 25.6, 18.1, 17.9, - 4.6 (Si*C*H_3), - 4.8 (Si*C*H_3), - 4.9 (Si*C*H_3), - 5.2 (Si*C*H_3)

To a solution of triflate (**3.97**) (2.62 g, 5.34 mmol) in DMF (15 mL) was added NaN_3 (868 mg, 13.4 mmol). The resultant mixture was stirred at room temperature under argon for 21 hours. The mixture was diluted with EtOAc (30 mL) and H_2O (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 2% EtOAc in cyclohexane) to afford the title compound **3.98** (1.64 g, 80% yield) as a colourless oil.

R_f = 0.71 (2% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.19 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 4.77 (ddd, *J* = 2.6, 6.9, 10.0 Hz, 2H, CH_2=C=CHC), 4.23 - 4.17 (m, 1H, C=CHC*H*OSi), 3.75 (ddd, *J* = 2.9, 4.7, 7.9 Hz, 1H, NCH_2C*H*OSi), 3.46 (dd, *J* = 2.9, 12.5 Hz, 1H, NC*H*H), 3.23 (dd, *J* = 8.0, 12.5 Hz, 1H, NCH*H*), 0.91 (s, 9H, $SiC(CH_3)_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 0.14 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), 0.06 (s, 6H, 2 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.5 (CH_2=*C*=CHC), 90.2 (CH_2=C=*C*HC), 77.2, 75.0, 72.0, 53.2 (*C*H_2N_3), 25.8, 25.7, 18.1, 18.0, - 4.5 (Si*C*H_3), - 4.7 (Si*C*H_3), - 4.9 (Si*C*H_3), - 5.1 (Si*C*H_3)

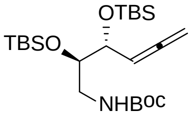
IR ν_{max} (film) 2954, 2932, 2889, 2859, 2099, 1954, 1255, 1118, 1077, 836, 776 cm^{-1}

MS (ESI) *m/z* 384 $[M+H]^+$ (43%), 356 (100%)

HRMS (ESI) *m/z* calc'd for $C_{18}H_{38}N_3O_2Si_2$ $[M+H]^+$ 384.2497, found 384.2496

$[\alpha]_D^{22}$ = + 82.3 (*c* 0.65, $CHCl_3$)

Synthesis of *tert*-butyl ((2*R*,3*R*)-2,3-bis((*tert*-butyldimethylsilyl)oxy)hexa-4,5-dien-1-yl)carbamate (3.82).



To a solution of azide (**3.98**) (1.34 g, 3.49 mmol) in THF (35 mL) was added triphenylphosphine (1.37 g, 5.24 mmol). The mixture was stirred at room temperature for 4 hours before H_2O (1.26 mL, 69.8 mmol) was added. The resultant mixture was left to stir at room temperature for 16 hours before Boc_2O (990 mg, 4.54 mmol) and DIPEA (914 µL, 5.24 mmol) were added. The mixture was stirred at room temperature for a further 3 hours before it was diluted with EtOAc (20 mL) and washed with brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 3% EtOAc in cyclohexane) to afford the title compound **3.82** (1.37 g, 85% yield) as a colourless oil.

R_f = 0.25 (2% EtOAc/cyclohexane), stained yellow with ninhydrin

^1H NMR (400 MHz, $CDCl_3$) δ = 5.20 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 5.03 (br. s, 1H, N*H*Boc), 4.76 (ddd, *J* = 2.6, 6.7, 10.9 Hz, 2H, CH_2=C=CHC), 4.24 - 4.17 (m, 1H, C=CHC*H*OSi), 3.75 - 3.68 (m, 1H, NCH_2C*H*OSi), 3.36 - 3.26 (m, 1H, NC*H*H), 3.23 (br. s, 1H, NCH*H*), 1.43 (s, 9H, OC(CH_3)$_3$), 0.90 (s, 9H, SiC(CH_3)$_3$), 0.89 (s, 9H, SiC(CH_3)$_3$), 0.09 (s, 3H, SiCH_3), 0.07 (s, 9H, 3 x SiCH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 208.5 (CH_2=*C*=CHC), 155.8 (HN*C*=O), 90.3 (CH_2=C=*C*HC), 78.8, 76.5, 73.5, 73.2, 42.6 (*C*H_2NH), 28.4, 25.8, 25.7, 18.1, 18.0, - 4.56 (Si*C*H_3), - 4.71 (Si*C*H_3), - 4.75 (Si*C*H_3), - 5.03 (Si*C*H_3)

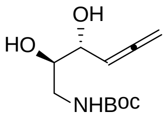
IR ν_{max} (film) 3380, 2953, 2931, 2889, 2855, 1964, 1702, 1249, 1174, 1019, 836, 776 cm^{-1}

MS (ESI) *m/z* 480 $[M+Na]^+$ (100%), 358 $[M\text{-}Boc+H]^+$ (65%)

HRMS (ESI) *m/z* calc'd for $C_{23}H_{48}NO_4Si_2$ $[M+H]^+$ 458.3116, found 458.3116

$[\alpha]_D^{22}$ = + 26.8 (*c* 0.63, $CHCl_3$)

Synthesis of *tert*-butyl ((2*R*,3*R*)-2,3-dihydroxyhexa-4,5-dien-1-yl)carbamate (3.100).



To a solution of bis-TBS protected diol (**3.82**) (1.37 g, 3.00 mmol) in THF (15 mL) was added 1 M TBAF solution in THF (6.60 mL, 6.60 mmol). The resultant mixture was stirred at room temperature for 4 hours before it was concentrated *in vacuo* to give a light yellow syrup. The crude material was purified by silica gel chromatography (gradient: 0 – 100% EtOAc in cyclohexane) to afford the title compound **3.100** (494 mg, 72% yield) as a colourless solid.

R_f = 0.28 (50% EtOAc/cyclohexane), stained pink with ninhydrin

Melting point = 81 – 83 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.29 (q, *J* = 6.6 Hz, 1H, CH_2=C=C*H*C), 4.90 (dd, *J* = 2.4, 6.6 Hz, 2H, C*H*$_2$=C=CHC), 4.12 - 4.07 (m, 1H, C=CHC*H*OH), 3.61 (td, *J* = 4.6, 7.2 Hz, 1H,

NCH_2CHOH), 3.40 (dd, *J* = 4.4, 14.4 Hz, 1H, NC*H*H), 3.20 (dd, *J* = 7.0, 14.4 Hz, 1H, NCH*H*), 2.40 (br. s, 2H, 2 x O*H*), 1.45 (s, 9H, $OC(CH_3)_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 207.9 ($CH_2=C=CHC$), 157.2 (*C*=O), 91.1 ($CH_2=C=CHC$), 80.1 ($OC(CH_3)_3$), 77.8, 74.0, 70.4, 43.3 ($NHCH_2$), 28.4 ($OC(CH_3)_3$)

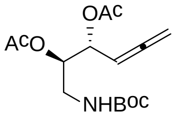
IR ν_{max} (film) 3384, 3270, 2972, 2882, 1952, 1680, 1367, 1166, 1103, 841 cm^{-1}

MS (ESI) *m/z* 252 $[M+Na]^+$ (19%), 112 (100%)

HRMS (ESI) *m/z* calc'd for $C_{11}H_{20}NO_4$ $[M+H]^+$ 230.1387, found 230.1387

$[\alpha]_D^{22}$ = + 11.4 (*c* 0.64, $CHCl_3$)

Synthesis of (2*R*,3*R*)-1-((*tert*-butoxycarbonyl)amino)hexa-4,5-diene-2,3-diyl diacetate (3.101).



To a solution of diol (**3.100**) (456 mg, 1.99 mmol) in CH_2Cl_2 (13 mL) was added Et_3N (693 µL, 4.98 mmol) and DMAP (23.2 mg, 0.19 mmol). Acetic anhydride (414 µL, 4.38 mmol, taken up in 2 mL CH_2Cl_2) was added dropwise to reaction mixture at room temperature. The resultant mixture was stirred at room temperature for 5 hours before it was diluted with CH_2Cl_2 (10 mL) and washed sequentially with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 30% EtOAc in cyclohexane) to afford the title compound **3.101** (532 mg, 85% yield) as a colourless oil.

R_f = 0.45 (40% EtOAc/cyclohexane), stained yellow with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.45 - 5.39 (m, 1H, C=CHC*H*OAc), 5.17 (q, *J* = 6.7 Hz, 1H, CH_2=C=C*H*C), 5.12 - 5.06 (m, 1H, NCH_2C*H*OAc), 4.95 - 4.85 (m, 2H, CH_2=C=CHC), 4.70 (br. s, 1H, N*H*Boc), 3.46 - 3.30 (m, 2H, NCH_2), 2.09 (s, 3H, COCH_3), 2.08 (s, 3H, COCH_3), 1.43 (s, 9H, OC(CH_3)$_3$)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 209.0 (CH_2=*C*=CHC), 170.2 (*C*OCH_3), 169.9 (*C*OCH_3), 155.6 (N*C*=O), 87.0 (CH_2=C=*C*HC), 79.7 (O*C*(CH_3)$_3$), 77.8, 72.9, 70.1, 40.7 (NH*C*H_2), 28.3 (OC(*C*H_3)$_3$), 21.0 (CO*C*H_3), 20.9 (CO*C*H_3)

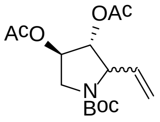
IR $\nu_{\max}$ (film) 3384, 2965, 2862, 1956, 1737, 1684, 1529, 1227, 1026, 857 cm^{-1}

MS (ESI) *m/z* 336 $[M+Na]^+$ (80%), 314 $[M+H]^+$ (29%), 138 (100%)

HRMS (ESI) *m/z* calc’d for $C_{15}H_{24}NO_6$ $[M+H]^+$ 314.1598, found 314.1598

$[\alpha]_D^{22}$ = - 11.8 (*c* 0.50, $CHCl_3$)

Synthesis of (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-2-vinylpyrrolidine-3,4-diyl diacetate (3.102).



A suspension of allene (**3.101**) (608 mg, 1.94 mmol), Au[P(*t*-Bu)$_2$(o-biphenyl)]Cl (51.5 mg, 97.0 µmol) and AgOTf (25.0 mg, 97.0 µmol) in 1,4-dioxane (20 mL) was stirred at room temperature under argon atmosphere for 96 hours in the absence of light. The mixture was filtered through a plug of celite, washing with EtOAc (20 mL). The filtrate was concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 30% EtOAc in cyclohexane) to afford the title compound **3.102** (443 mg, 73% yield) as a colourless oil (7:1 mixture of cis/trans isomers).

R_f = 0.47 (30% EtOAc/cyclohexane), stained pink with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.86 - 5.75 (m, 1H, $H_2C{=}CHC$, minor), 5.58 (ddd, J = 7.2, 10.1, 17.0 Hz, 1H, $H_2C{=}C\mathit{H}C$, major), 5.29 - 5.03 (m, 5H, $\mathit{H}_2C{=}CHC$, $H_2C{=}CHC\mathit{H}$, BocNC*H*H), 4.97 (s, 1H, minor), 4.59 (br. s., 1H, BocNCH*H*, major), 3.87 - 3.84 (m, 1H, NCHC*H*OAc, minor), 3.81 (dd, J = 6.3, 12.2 Hz, 1H, NCHC*H*OAc, major), 3.52 (d, J = 13.1 Hz, 1H, $CH_2C\mathit{H}OAc$, minor), 3.39 (d, J = 8.9 Hz, 1H, $CH_2C\mathit{H}OAc$, major), 2.10 - 1.99 (m, 7H, 2 x $COC\mathit{H}_3$), 1.50 - 1.30 (m, 11H, $OC(C\mathit{H}_3)_3$)

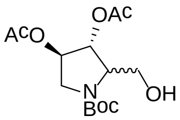
^{13}C NMR (101 MHz, $CDCl_3$) δ = 170.1 ($\mathit{C}OCH_3$, major), 169.7 ($\mathit{C}OCH_3$, major), 169.6 ($\mathit{C}OCH_3$, minor), 154.1 (N*C*=O), 132.4 ($H_2C{=}\mathit{C}HC$, major), 129.2 (minor), 128.7 (minor), 117.9 ($H_2\mathit{C}{=}CHC$, major), 116.7 ($H_2\mathit{C}{=}CHC$, minor), 80.2 ($O\mathit{C}(CH_3)_3$, major), 80.1 ($O\mathit{C}(CH_3)_3$, minor), 75.9, 73.2, 59.9, 48.3, 30.9 (minor), 30.8 (minor), 28.3 ($OC(\mathit{C}H_3)_3$, major), 20.9 ($CO\mathit{C}H_3$, minor), 20.8 ($CO\mathit{C}H_3$, minor), 20.7 ($CO\mathit{C}H_3$, major), 20.6 ($CO\mathit{C}H_3$, major)

IR ν_{max} (film) 2980, 2935, 2885, 1745, 1696, 1389, 1367, 1219, 1166, 1050, 898 cm^{-1}

MS (ESI) *m/z* 214 $[M\text{-}Boc+H]^+$ (59%), 112 (100%)

HRMS (ESI) *m/z* calc’d for $C_{15}H_{23}NO_6Na$ $[M+Na]^+$ 336.1418, found 336.1414

Synthesis of (3*R*,4*R*)-1-(*tert*-butoxycarbonyl)-2-(hydroxymethyl)pyrrolidine-3,4-diyl diacetate (3.106).



Ozone was bubbled into a solution of alkene (**3.102**) (224 mg, 0.716 mmol) dissolved in 10:1 CH_2Cl_2/THF (8.8 mL) at - 78 °C until a blue solution was observed. Oxygen gas was then bubbled through the solution until it turned colourless before $NaBH_4$ (67.7 mg, 1.79 mmol) was added to the reaction mixture at - 78 °C. The resultant mixture was allowed to gradually warm up to 0 °C and was stirred at 0 °C for 4 hour 30 minutes before it was quenched with addition of sat'd NH_4Cl solution (4 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (gradient: 0 – 70% EtOAc in cyclohexane) to afford the title compound **3.106** (398 mg, 57% yield) as a colourless oil.

R_f = 0.35 (50% EtOAc/cyclohexane), stained yellow with ninhydrin

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.07 (br. s, 1H, NCH_2CHO), 4.50 - 4.24 (m, 3H, NCH_2CHO and NCHC*H*O), 4.16 - 4.03 (m, 1H, NC*H*CHO), 3.81 - 3.73 (m, 1H, C*H*HOH), 3.54 - 3.35 (m, 1H, CH*H*OH), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 1.47 (s, 9H, $OC(CH_3)_3$)

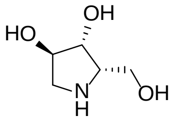
^{13}C NMR (101 MHz, $CDCl_3$) δ = 171.4 (*C*=O), 169.7 (*C*=O), 154.2 (*C*=O), 80.5 ($OC(CH)_3$), 73.5, 68.4, 61.1 (N*C*HCHO), 58.2 (CH_2OH), 49.4 (NCH_2CHO), 28.3 ($OC(CH)_3$), 21.0 (CH_3CO), 20.8 (CH_3CO)

IR ν_{max} (film) 3447, 2980, 2893, 1741, 1696, 1672, 1396, 1362, 1230, 1165, 1044 cm^{-1}

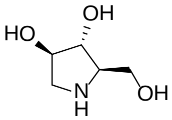
MS (ESI) *m/z* 340 $[M+Na]^+$ (68%), 318 $[M+H]^+$ (16%), 217 (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{23}NO_7Na$ $[M+Na]^+$ 340.1367, found 340.1366

Synthesis of (3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol (3.107).



3.107
major



3.107
minor

To a solution of primary alcohol (**3.106**) (31.3 mg, 98.6 µmol) in MeOH (1 mL) was added 0.5 M NaOMe in MeOH (19.7 µL, 9.86 µmol) at room temperature. The mixture was stirred at ambient temperature for 1 hour (product R_f = 0.21 with 100% EtOAc, stained pink with ninhydrin) before it was concentrated *in vacuo* to give a colourless residue. The residue was taken up in Et_2O (1 mL) and 2 M HCl in Et_2O (493 µL, 0.986 mmol) was added. The resultant mixture was stirred at room temperature for 6 hours before it was concentrated *in vacuo* to give a light yellow oil. The yellow oil was taken up in MeOH (2 mL) and Amberlyst A26-OH (~ 50 mg) was added. The mixture was stirred at room temperature overnight before it was filtered, washing with MeOH (4 mL). The filtrate was concentrated *in vacuo* to afford the title compound **3.107** (13.0 mg, quantitative yield) as a colourless oil (6:1 mixture of diastereomers).

^{1}H NMR (400 MHz, D_2O) δ = 4.28 (td, J = 1.8, 4.8 Hz, 1H, H-4, major), 4.23 (dd, J = 1.6, 3.9 Hz, 1H, H-3, major), 4.19 (td, J = 3.7, 5.6 Hz, 1H, H-4, minor), 3.94 - 3.87 (m, 1H, H-1', major), 3.82 - 3.76 (m, 1H, H-1, major), 3.73 - 3.68 (m, 1H, H-1, minor), 3.57 (ddd, J = 4.0, 5.9, 7.3 Hz, 1H, H-2, major), 3.46 (dd, *J* = 4.9, 12.7 Hz, 1H, H-5', major), 3.37 (s, 1H,), 3.21 (dd, *J* = 5.7, 12.3 Hz, 1H, H-5', minor), 3.14 - 3.07 (m, 1H, H-2, minor), 2.99 (dd, *J* = 1.7, 12.7 Hz, 1H, H-5, major), 2.93 (dd, *J* = 3.8, 12.2 Hz, 1H, H-5, minor)

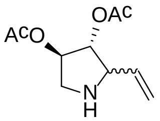
^{13}C NMR (101 MHz, D_2O) δ = 78.6 (minor), 77.0 (minor), 76.1 (major), 75.8 (major), 65.4 (minor), 61.8 (major), 61.6 (minor), 59.0 (major), 50.7 (major), 50.5 (minor)

IR ν_{max} (film) 3285, 2924, 1627, 1533, 1411, 1042 cm^{-1}

MS (ESI) *m/z* 134 [M+H]$^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_5H_{12}NO_3$ [M+H]$^+$ 134.0812, found 134.0809

Synthesis of (3*R*,4*R*)-2-vinylpyrrolidine-3,4-diyl diacetate (3.129).



To a solution of N-Boc protected amine (**3.102**) (1.16 g, 3.70 mmol) in CH_2Cl_2 (37 mL) was added trifluoroacetic acid (3.7 mL, 10% v/v). The mixture was stirred at room temperature for 5 hours before it was concentrated *in vacuo* to give a light pink residue. The crude material was taken up in THF (25 mL) and Amberlyst A26-OH (~1.00 g) was added. The resultant mixture was stirred at room temperature for 30 minutes before it was filtered, washing with THF (25 mL). The filtrate was concentrated *in vacuo* to afford the title compound **3.129** (740 mg, 93% yield) as a light orange oil.

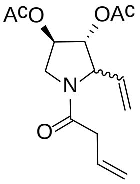
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.88 (ddd, *J* = 8.2, 10.4, 17.2 Hz, 1H, H_2C=C*H*C), 5.61 (d, *J* = 17.2 Hz, 1H, *H*HC=CHC), 5.51 (d, *J* = 10.4 Hz, 1H, H*H*C=CHC), 5.36 (d, *J* = 3.3 Hz, 1H, NCHC*H*OAc), 5.23 - 5.19 (m, 1H, CH_2C*H*OAc), 4.39 (dd, *J* = 3.1, 7.6 Hz, 1H, NC*H*CHOAc), 3.83 (dd, *J* = 5.1, 13.6 Hz, 1H, C*H*HCHOAc), 3.41 (d, *J* = 13.6 Hz, 1H, CH*H*CHOAc), 2.14 (s, 3H, CH_3), 2.13 (s, 3H, CH_3)

^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.3 (C=O), 168.9 (C=O), 125.8 (H_2C=*C*HC), 124.9 (H_2*C*=CHC), 75.4, 74.3, 63.2 (N*C*HCHOAc), 49.1 (N*C*H_2CHOAc), 20.5, 20.2

MS (ESI) *m/z* 214 $[M+H]^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{10}H_{16}NO_4$ $[M+H]^+$ 214.1074, found 214.1073

Synthesis of (3*R*,4*R*)-1-(but-3-enoyl)-2-vinylpyrrolidine-3,4-diyl diacetate (3.131).



To a solution of amine (**3.129**) (740 mg, 3.47 mmol) in CH_2Cl_2 (22 mL) was added vinylacetic acid (444 µL, 5.21 mmol), EDC•HCl (999 mg, 5.21 mmol), HOBT (704 mg, 5.21 mmol) and Et_3N (967 µL, 6.94 mmol). The resultant mixture was stirred at room temperature overnight before it was washed with H_2O (5 mL) and brine (5 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to give a light yellow oil. The crude material was purified by silica gel chromatography (gradient: 0 – 70% EtOAc in cyclohexane) to afford the title compound **3.131** (582 mg, 60% yield) as a colourless oil.

R_f = 0.34 (50% EtOAc/cyclohexane), stained brown with iodine

^{1}H NMR (400 MHz, CDCl$_3$) δ = 5.94 (tdd, *J* = 6.6, 10.4, 17.0 Hz, 1H, CH$_2$=C*H*CH$_2$), 5.71 - 5.53 (m, 1H, CH$_2$=C*H*CH), 5.34 (d, *J* = 10.4 Hz, 1H, H*H*C=CHCH), 5.29 - 5.05 (m, 5H, H*H*C=CHCH, NCHC*H*OAc, NCH$_2$C*H*OAc, C*H*$_2$=CHCH), 4.93 (t, *J* = 6.8 Hz, 0.34H, NC*H*CHOAc rotamer), 4.74 (t, *J* = 6.0 Hz, 0.66H, NC*H*CHOAc rotamer), 4.00 (dd, *J* = 6.2, 11.4 Hz, 0.34H, NC*H*HCHOAc rotamer), 3.91 (dd, *J* = 6.2, 13.1 Hz, 0.66H, NC*H*HCHOAc rotamer), 3.62 - 3.55 (m, 0.66H, NCH*H*CHOAc rotamer), 3.47 (dd, *J* = 4.3, 11.4 Hz, 0.34H, NCH*H*CHOAc rotamer), 3.10 - 3.02 (m, 2H, CH$_2$=CHC*H*$_2$), 2.08 (s, 6H, 2 x C*H*$_3$)

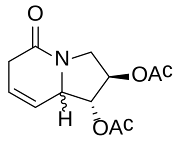
^{13}C NMR (101 MHz, CDCl$_3$) δ = 170.6 (*C*=O), 170.0 (*C*=O), 169.8 (*C*=O), 132.1, 131.0, 119.1, 118.0, 76.2, 72.3, 60.0 (N*C*HCHOAc), 47.7 (N*C*H$_2$CHOAc), 38.7 (CH$_2$=CH*C*H$_2$), 20.7, 20.6

IR ν_{max} (film) 2972, 2938, 2862, 1741, 1650, 1412, 1367, 1215, 1050, 1004, 920 cm^{-1}

MS (ESI) *m/z* 282 [M+H]$^+$ (100%)

HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_5$ [M+H]$^+$ 282.1336, found 282.1335

Synthesis of (1*R*,2*R*)-5-oxo-1,2,3,5,6,8a-hexahydroindolizine-1,2-diyl diacetate (3.132).



To a solution of diene (**3.131**) (582 mg, 2.07 mmol) dissolved in CH$_2$Cl$_2$ (100 mL) at room temperature was added Grubbs' I catalyst (170 mg, 0.207 mmol). The resultant purple coloured mixture was heated under reflux for 6 hours before the mixture was cooled and concentrated *in vacuo* to give a brown residue. The crude material was purified by silica gel chromatography (gradient: 20 – 100% EtOAc in cyclohexane) to afford the title compound **3.132** (481 mg, 91% yield) as a light brown oil.

R_f = 0.25 (70% EtOAc/cyclohexane), stained yellow with $KMnO_4$

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.94 - 5.87 (m, 1H, $CH_2CH{=}CH$), 5.79 - 5.73 (m, 1H, $CH_2CH{=}CH$), 5.31 (d, *J* = 3.2 Hz, 1H, NCHC*H*OAc), 5.15 (d, *J* = 6.0 Hz, 1H, NCH_2C*H*OAc), 4.46 (d, *J* = 2.7 Hz, 1H, NC*H*CHOAc), 4.26 (dd, *J* = 6.0, 14.3 Hz, 1H, NC*H*HCHOAc), 3.37 (d, *J* = 14.3 Hz, 1H, NCH*H*CHOAc), 3.00 - 2.94 (m, 2H, $CH_2CH{=}CH$), 2.09 (s, 3H, CH_3), 2.02 (s, 3H, CH_3)

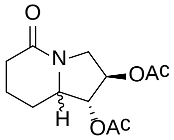
^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.5 (*C*=O), 169.3 (*C*=O), 166.7 (*C*=O), 125.7, 119.8, 72.9, 60.9, 49.5 (N*C*H_2CHOAc), 32.4 (N*C*HCHOAc), 20.8, 20.6

IR ν_{max} (film) 1736, 1655, 1598, 1430, 1369, 1216, 1045 cm^{-1}

MS (ESI) *m/z* 254 $[M+H]^+$ (80%), 134 (100%)

HRMS (ESI) *m/z* calc'd for $C_{12}H_{16}NO_5$ $[M+H]^+$ 254.1023, found 254.1021

Synthesis of (1*R*,2*R*)-5-oxooctahydroindolizine-1,2-diyl diacetate (3.133).



A solution of alkene (**3.132**) (481 mg, 1.90 mmol) in EtOH (45 mL) was subjected to hydrogenation on a ThalesNano H-Cube® hydrogenation reactor using a 10%Pd/C cartridge and flow rate of 1 mL/minute at room temperature and pressure. The resultant mixture was concentrated *in vacuo* to afford the title compound **3.133** (485 mg, quantitative yield) as a light brown solid which was used without further purification.

R_f = 0.19 (80% EtOAc/cyclohexane), stained blue with CAM

Melting point = 140 – 142 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.21 (d, *J* = 3.1 Hz, 1H, NCHC*H*OAc), 5.12 (d, *J* = 5.5 Hz, 1H, NCH_2C*H*OAc), 4.01 (dd, *J* = 5.5, 14.3 Hz, 1H, NC*H*HCHOAc), 3.85 (td, *J* = 3.5, 11.4 Hz, 1H, NC*H*CHOAc), 3.45 (d, *J* = 14.3 Hz, 1H, NCH*H*CHOAc), 2.52 - 2.43 (m, 1H, O=CC*H*HCH_2CH_2), 2.35 - 2.23 (m, 1H, O=CCH*H*CH_2CH_2), 2.09 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 1.98 - 1.88 (m, 2H, $O{=}CCH_2C$*H*HCH_2, $O{=}CCH_2CH_2C$*H*H), 1.82 - 1.69 (m, 1H, $O{=}CCH_2CH$*H*CH_2), 1.43 - 1.30 (m, 1H, $O{=}CCH_2CH_2CH$*H*)

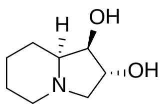
^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.6 (*C*=O), 169.4 (*C*=O), 169.3 (*C*=O), 75.9, 72.6, 59.9 (N*C*HCHOAc), 50.1 (N*C*H_2CHOAc), 30.6 (O=C*C*$H_2CH_2CH_2$), 22.7, 20.8, 20.6, 20.5

IR ν_{max} (solid) 2950, 1733, 1627, 1456, 1366, 1226, 1169, 1051 cm^{-1}

MS (ESI) *m/z* 256 $[M+H]^+$ (94%), 136 (100%)

HRMS (ESI) *m/z* calc'd for $C_{12}H_{18}NO_5$ $[M+H]^+$ 256.1179, found 256.1179

Synthesis of (1*R*,2*R*,8a*S*)-octahydroindolizine-1,2-diol (3.117).



To a solution of lactam (**3.133**) (96.7 mg, 0.379 mmol) in THF (4 mL) was added BH_3•DMS complex (180 µL, 1.89 mmol) at room temperature. The resultant mixture was heated at reflux under argon for 2 hours before the mixture was cooled to room temperature and quenched by dropwise addition of MeOH (5 mL). The mixture was concentrated *in vacuo* to give a colourless syrup. The syrup was redissolved in MeOH (5 mL) and the mixture was heated at reflux under argon for 16 hours before the mixture was concentrated *in vacuo* to give a colourless syrup. The crude material was purified by silica gel chromatography (gradient: 0 – 50% MeOH in dichloromethane) to afford the title compound **3.117** (34.6 mg, 58% yield) as a colourless solid.

R_f = 0.07 (20% MeOH/dichloromethane), stained pink with ninhydrin

Melting point = 138 – 140 °C

^{1}H NMR (400 MHz, D_2O) δ = 4.14 (t, *J* = 6.6 Hz, 1H, $NCH_2C\textit{H}OAc$), 4.00 (d, *J* = 4.4 Hz, 1H, $NCHC\textit{H}OAc$), 3.45 (dd, *J* = 7.2, 10.1 Hz, 1H, $NC\textit{H}HCHOAc$), 3.08 (d, *J* = 11.4 Hz, 1H, $NC\textit{H}HCH_2CH_2$), 2.32 - 2.24 (m, 1H, $NC\textit{H}CHOAc$), 2.19 - 2.09 (m, 1H, $NCH\textit{H}CH_2CH_2$), 2.06 (dd, *J* = 6.6, 10.1 Hz, 1H, $NCH\textit{H}CHOAc$), 1.89 (d, *J* = 11.9 Hz, 1H, $NCH_2CH_2CH_2C\textit{H}H$), 1.79 - 1.64 (m, 2H, $NCH_2C\textit{H}HCH_2$ and $NCH_2CH_2C\textit{H}H$), 1.55 - 1.30 (m, 3H, $NCH_2CH_2CH_2CH\textit{H}$, $NCH_2CH\textit{H}CH_2$ and $NCH_2CH_2CH\textit{H}$)

^{13}C NMR (101 MHz, D_2O) δ = 79.1, 76.6, 66.8 ($N\textit{C}HCHOAc$), 60.1 ($N\textit{C}H_2CHOAc$), 53.2 ($N\textit{C}H_2CH_2CH_2$), 24.5, 24.1, 23.4

IR ν_{max} (film) 3414, 2941, 2919, 2866, 2809, 1136, 1064, 1004, 774 cm^{-1}

MS (ESI) *m/z* 158 $[M+H]^+$ (90%), 122 (100%)

HRMS (ESI) *m/z* calc'd for $C_8H_{16}NO_2$ $[M+H]^+$ 158.1176, found 158.1174

$[\alpha]_D^{23}$ = + 4.63 (*c* 0.41, MeOH)

References

1. Nishikawa, T., Ishida, N. *J. Antibiot.* **1965**, *18*, 132.
2. Inouye, S.; Tsuruoka, T.; Niida, T. *J. Antibiot. Ser. A* **1966**, *19,* 288.
3. (a) Nash, R. J.; Asano, N.; Watson A. A. *Alkaloids: Chemical and Biological Perspectives* **1996**, *11*, 345. (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
4. Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125.
5. Furukawa, J.; Okuda, S.; Saito, K.; Hatanaka, S. I. *Phytochemistry* **1985**, *24*, 593.
6. Asano, N.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydrate Res.* **1994**, *253*, 235.
7. Wordmald, M. R.; Nash, R. J.; Watson A. A.; Bhadoria, B. K.; Langford, R.; Sims, M.; Fleet, G. W. J. *Carbohydrate Lett.* **1996**, *2*, 169.
8. Watson, A. A.; Nash, R. J.; Wormald, M. R.; Harvey, D. J.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H.; Kato, A.; Griffiths, R. C.; Cairns, A. J.; Fleet, G. W. J. *Phytochemistry* **1997**, *46*, 255.
9. Kato, A.; Adachi, I.; Miyauchi M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda Y.; Watson, A. A.; Nash, R. J.; Wormald M. R.; Fleet, G. W. J.; Asano, N. *Carbohydrate Res.* **1999**, *316*, 95.
10. Asano, N.; Nishida, M.; Miyauchi, M.; Ikeda, K.; Yamamoto, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Phytochemistry* **2000**, *53*, 379.
11. Asano, N.; Oseki, K.; Tomioka, E.; Kizu, H.; Matsui, K. *Carbohydrate Res.* **1994**, *259*, 243.
12. Welter, A.; Jadot, J.; Dardenne, G.; Marlier, M.; Casimir, J. *Phytochemistry* **1976**, *15*, 747.

13. Evans, S. V.; Fellows, L. E.; Shing, T. K. M.; Fleet, G. W. J. *Phytochemistry* **1985**, *24*, 1953.
14. Horn, J. M.; Lees, D. C.; Smith, N. G.; Nash, R. J.; Fellows, L. E.; Bell, E. A. *Proc. 6th Int. Symp. Insect-Plant Relationships*, Labeyrie, V.; Fabres, G. and Lachaise, D. (Eds.), Dr. W. Junk, Dordrecht, **1987**, 394.
15. Kite, G. C.; Horn, J. M.; Romeo, J. T.; Fellows, L. E.; Lees, D. C.; Scofield, A. M.; Smith, N. G. *Phytochemistry* **1990**, *29*, 103.
16. Watanabe, S.; Kato, H.; Nagayama, K.; Abe, H. *Biosci. Biotech. Biochem.* **1995**, *59*, 936.
17. Dring, J. V.; Kite, G. C.; Nash, R. J.; Reynolds, T. *Bot. J. Linn. Soc.* **1995**, *117*, 1.
18. Asano, N.; Nishida, M.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 98.
19. Nash, R. J.; Watson, A. A.; Winters, A. L.; Fleet, G. W. J.; Wormald, M. R.; Dealler, S.; Lees, E.; Asano, N.; Kizu, H. *Phytochemical Diversity: A Source of New Industrial Products*, Wrigley, S.; Hayes, M.; Thomas, R. and Chrystal E. (Eds.), Royal Society of Chemistry, Cambridge, **1997**, 106.
20. Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *J. Nat. Prod.* **1998**, *61*, 625.
21. (a) Inouye, S.; Tsurouka, T.; Ito, T.; Niida T. *Tetrahedron* **1968**, *24*, 2125. (b) Ishida, N.; Kumagai, K.; Niida, T.; Tsuruoka, T.; Yumoto, H. *J. Antibiot. Ser. A* **1967**, *20*, 66.
22. Schmidt, D. D.; Frommer, W.; Müller, L.; Truscheit, E. *Naturwiss.* **1979**, *66*, 584.
23. Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219.
24. Kite, G. C.; Fellows, L. E.; Lees, D. C.; Kitchen, D.; Monteith, G. B. *Biochem. Syst. Ecol.* **1991**, *19*, 441.

25. Koyama, M.; Sakamura, S. *Agric. Biol. Chem.* **1974**, *38*, 1111.

26. (a) Evans, S. V.; Hayman, A. R.; Fellows, L. E.; Shing, T. K. M.; Derome, A. E.; Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 1465. (b) Kato, A.; Asano, N.; Kizu, H.; Matsui, K.; Watson, A. A.; Nash, R. J. *J. Nat. Prod.* **1997**, *60*, 312.

27. Asano, N.; Kato, A.; Miyauchi, M.; Kizu, H.; Tomimori, T.; Matsui, K.; Nash, R. J.; Molyneux, R. J. *Eur. J. Biochem.* **1997**, *248*, 296.

28. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257.

29. Molyneux, R. J. ; James, L. F. *Science* **1982**, 216, 190.

30. Schneider, M. J.; Ungemach, F. S.; Broquist, H. P.; Harris, T. M. *Tetrahedron* **1983**, *39*, 29.

31. Hino, M.; Nakayama, O.; Tsurumi, Y.; Adachi, K.; Shibata, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1985**, *38*, 926.

32. Molyneux, R. J.; McKenzie, R. A.; O'Sullivan, B. M.; Elbein, A. D. *J. Nat. Prod.* **1995**, *58*, 878.

33. de Balogh, K. K. I. M.; Dimande, A. P.; van der Lugt, J. J.; Molyneux, R. J.; Naudé, T. W.; Welman, W. G. *J. Vet Diagn. Invest.* **1999**, *11*, 266.

34. Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, 29, 1886.

35. Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811.

36. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, 27, 1403.

37. Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471.

38. (a) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, 48, 319. (b) Asano, N.; Kizu, H.; Oseki, K.; Tomioka, E.; Matsui, K.; Okamoto, M.; Baba, M. *J. Med. Chem.* **1995**, 38, 2349.
39. Compain, P.; Martin, O. R. (Eds.) *Iminosugars: From Synthesis to Therapeutic Applications*, John Wiley and Sons Ltd., England, **2007.**
40. de Melo, E. B.; Gomes, A. D. S.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277.
41. Winchester, B. G. *Tetrahedron Asymm.* **2009**, *20*, 645.
42. Yagi, M; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nogeikagaku Kaishi* **1976**, *50*, 571.
43. Junge, B.; Matzke, M.; Stoltefuss, J. *Handbook of Experimental Pharmacology, Vol. 119 — Oral Antidiabetics, Springer-Verlag, Berlin/Heidelberg, Germany (1996), pp. 411–482, J. Kuhlmann, W. Puls (Eds.).*
44. Campbell, L. K.; Baker, D. E.; Campbell, R. K. *The Annals of Pharmacotherapy* **2000**, *34*, 1291.
45. (a) Cox, T. M.; Aerts, J. M. F. G.; Andria, G.; Beck, M.; Belmatoug, N.; Bembi, B.; Chertkoff, R.; Vom Dahl, S.; Elstein, D.; Erikson, A.; Giralt, M.; Heitner, R.; Hollak, C.; Hrebicek, M.; Lewis, S.; Mehta, A.; Pastores, G. M.; Rolfs, A.; Sa Miranda, M. C.; Zimran, A. *J. Inherit. Metab. Dis.* **2003**, *26*, 513. (b) Lieberman, R. L.; Wustman, B. A.; Huertas, P.; Powe Jr, A. C.; Pine, C. W.; Khanna, R.; Schlossmacher, M. G.; Ringe, D.; Petsko, G. A. *Nature Chem. Bio.* **2007**, *3*, 101.
46. Lyseng-Williamson, K. A. *Drugs* **2014**, *74,* 61.
47. Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discovery Today* **2011**, *16*, 107.
48. Fan, J. Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nat. Med.* **1999**, *5*, 112.

49. Khanna. R.; Soska, R.; Lun, Y.; Feng, J.; Frascella, M.; Young, B.; Brignol, N.; Pellegrino, L.; Sitaraman, S. A.; Desnick, R. J.; Benjamin, E. R.; Lockhart, D. J.; Valenzano, K. J. *Molecular Therapy* **2010**, *18*, 23.

50. Wrodnigg, T. M.; Steiner, A. J.; Ueberbacher, B. J. *Anticancer Agents Med. Chem.* **2008**, *8*, 77.

51. (a) Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. W. *FEBS Lett.* **1988**, *237*, 128. (b) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (c) Greimel, P. ; Spreitz, J. ; Stutz, A. E. ; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513. (d) Scanlan, C. N.; Offer, J.; Zitzmann, N.; Dwek, R. A. *Nature* **2007**, *446*, 1038.

52. Durantel, D. *Curr. Opin. Investig. Drugs* **2009**, *10*, 860.

53. Rathore, A. P.; Paradkar, P. N.; Watanabe, S.; Tan, K. H.; Sung, C.; Connolly, J. E.; Low, J.; Ooi, E. E.; Vasudevan, S. G. *Antiviral Res.* **2011**, *92*, 453.

54. (a) Kumar, K. S. A.; Rathee, J. S.; Subramanian, M.; Chattopadhyay, S. *J. Org. Chem.* **2013**, *78*, 7406. (b) Kato, A.; Miyauchi, S.; Kato, N.; Nash, R. J.; Yoshimura, Y.; Nakagome, I.; Hirono, S.; Takahata, H.; Adachi, I. *Bioorg. Med. Chem.* **2011**, *19*, 3558. (c) van den Berg, R. J. B. H. N.; Wennekes, T.; Ghisaidoobe, A.; Donker-Koopman, W. E.; Strijland, A.; Boot, R. G.; van der Marel, G. A.; Aerts, J. M. F. G.; Overkleeft, H. S. *ACS Med. Chem. Lett.* **2011**, *2*, 519.

55. (a) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198. (b) Scofield, A. M.; Fellows, L. E.; Nash, R. J.; Fleet, G.

W. J. *Life Sci* **1986**, *39*, 645. (c) Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *22*, 3701.

56. Fleet, G. W. J.; Smith, P. W. *Tetrahedron Lett.* **1985**, *26*, 1469.
57. For other reported synthesis of fagomine and its congeners not covered in review: (a) Désiré, J.; Dransfield. P. J.; Gore, P. M.; Shipman, M. *Synlett* **2001**, *8*, 1329. (b) Babich, L.; van Hemert, L. J. C.; Bury, A.; Hartog, A. F.; Falcicchio, P.; van der Oost, J.; van Herk, T.; Wever, R.; Rutjes, F. P. J. T. *Green Chem.* **2011**, *13*, 2895. (c) Ciliberti, E.; Galvani, R.; Gramazio, F.; Haddas, S.; Leonelli, F.; Passacantilli, P.; Piancatelli, G. *Eur. J. Org. Chem.* **2007**, *9*, 1463. (d) Bartali, L.; Casini, A.; Guarna, A.; Occhiato, E. G.; Scarpi, D. *Eur. J. Org. Chem.* **2010,** *30,* 5831. (e) Kundu, P. K.; Ghosh, S. K. *Tetrahedron Asymm.* **2011**, *22*, 1090.
58. Kumari, N.; Reddy, B. G.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, *1*, 160.
59. Rawal, G. K.; Kumar, A.; Tawar, U.; Vankar, Y. D. *Org. Lett.* **2007**, *9*, 5171.
60. (a) Reddy, B. G.; Madhusudanan, K. P.; Vankar, Y. D. *J. Org. Chem.* **2004**, *69*, 2630. (b) Reddy, B. G.; Vankar, Y. D. *ARKIVOC* **2004**, *8*, 12.
61. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554.
62. Corkran, H. M.; Munneke, S.; Dangerfield, E. M.; Stocker, B. L.; Timmer, M. S. M. *J. Org. Chem.* **2013**, *78*, 9791.
63. Dangerfield, E. M.; Plunkett, C. H.; Win-Mason, A. L.; Stocker, B. L.; Timmer, M. S. M. *J. Org. Chem.* **2010**, *75*, 5470.
64. (a) Banba, Y.; Abe, C.; Nemoto, H.; Kato, A.; Adachi, I.; Takahata, H. *Tetrahedron Asymm.* **2001**, *21*, 817. (b) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3603. (c) Takahata, H.; Banba, Y.; Sasatani, M.; Nemoto, H.; Kato, A.; Adachi, I. *Tetrahedron* **2004**, *60*, 8199.

65. Dondoni, A.; Perrome, D. *Org. Syn.* **1999**, *77*, 64.

66. Denmark, S. E.; Forbes, D. C.; Hays, D. S.; DePue, J. S.; Wilde, R. G. *J. Org. Chem.* **1995**, *60*, 1391.

67. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

68. (a) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. J. *Tetrahedron Lett.* **2001**, *42*, 8951. (b) Donohoe, T. J. *Synlett* **2002**, 1223.

69. Bartali, L.; Scarpi, D.; Guarna, A.; Prandi, C.; Occhiato, E. G. *Synlett* **2009**, *6*, 913; Erratum: *Synlett* **2010**, *5*, 839.

70. Occhiato, E. G.; Scarpi, D.; Guarna, A. *Eur. J. Org. Chem.* **2008**, *3*, 524.

71. Luker, T.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3592.

72. Kim, J. Y.; Mu, Y.; Jin, X.; Park, S. H.; Pham, V. T.; Song, D. K.; Lee, K. Y.; Ham, W. H. *Tetrahedron* **2011**, *67*, 9426.

73. (a) Joo, J. E.; Pham, V. T.; Tian, Y. S.; Chung, Y. S.; Lee, K. Y.; Ham, W. H. *Org. Biomol. Chem.* **2008**, *6*, 1498. (b) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Ham, W. H. *Eur. J. Org. Chem.* **2007**, 1586. (c) Joo, J. E.; Lee, K. Y.; Pham, V. T.; Tian, Y. S.; Ham, W. H. *Org. Lett.* **2007**, *9*, 3627.

74. Castillo, J. A.; Calveras, J.; Casas, J.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapés, P. *Org. Lett.* **2006**, *8*, 6067.

75. Schűrmann, M.; Sprenger, G. A. *J. Biol. Chem.* **2001**, *276*, 11055.

76. Sugiyama, M.; Hong, Z.; Liang, P. H.; Dean, S. M.; Whalen, L. J.; Greenberg, W. A.; Wong, C. H. *J. Am. Chem. Soc.* **2007**, *129*, 14811.

77. Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Asymm.* **2007**, *18*, 852.

78. Van't Hoff, J. H. *La Chimie dans l'Espace*, Bazendijk : Rotterdam, **1875**, 29.

79. Burton, B. S. ; von Pechmann, H. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145.

80. Jones, E. R. H.; Mansfield, G. H.; Whiting, M. L. H. *J. Chem. Soc.* **1954**, 3208.

81. (a) Hoffmann, R. *Tetrahedron* **1966**, *22*, 521. (b) Pullman, B.; Berthier, G. *Bull. Soc. Chim. France* **1949**, 145. (c) Seel, F. *Z. Physik. Chem.* **1943**, *B53*, 103.

82. Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317.

83. (a) Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6th Ed., Wiley, New York, **1998**. (b) Wotiz, J. H.; Mancuso, D. E. *J. Org. Chem.* **1957**, *22*, 207. (c) Wotiz, J. H.; Celmer, W. D. *J. Am. Chem. Soc.* **1952**, *74*, 1860.

84. (a) Krause, N.; Hashmi, A. S. K. Eds, *Modern Allene Chemistry*, Wiley-VCH, Weinheim, **2004**. (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, *2007*, 795.

85. (a) Frank-Neumann, M.; Martina, D.; Neff, D. *Tetrahedron Asymm.* **1998**, *9*, 697. (b) Oku, M.; Arai, S.; Katayama, K.; Shioiri, T. *Synlett* **2000**, *2000*, 493.

86. (a) Crabbé, P.; André, D. ; Fillion, H. *Tetrahedron Lett.* **1979**, *20*, 893. (b) Crabbé, P.; Fillion, H.; André, D. ; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1979**, *19*, 859.

87. Brandsma, L. S*ynthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*, 1st Ed., Elsevier, Oxford, **2004**, 341.

88. (a) Alexakis, A.; Marek, L.; Mangeney, P.; Normant, J. F. *J. Am. Chem. Soc.* **1990**, *112*, 8042. (b) Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533. (c) D'Aniello, F.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 4870.

89. (a) Ohno, H. *Chem. Pharm. Bull.* **2005**, *53*, 1211. (b) Hassan, H. H. A. M. *Curr. Org. Syn.* **2007**, *4*, 413. (c) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (d) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, *51*, 3074. (e) Ma, S. *Aldrichimica Acta* **2007**, *40*, 92.

90. (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (b) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019. (c) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N.; Asao, N. *Tetrahedron Lett.* **1995**, *36*, 2811.
91. (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (b) Alcaidea, B.; Almendros, P. *Adv. Synth. Catal.* **2011**, *353*, 2561. (c) Patil, N. T.; Kavthe, R. D.; Shinde, V. S. *Tetrahedron* **2012**, *68*, 8079.
92. Hashmi, A. S. K. Transitition Metal-Catalyzed Cycloisomerizations of Allenes. In *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K. Eds. Wiley-VCH, Weinheim, **2004**, 877.
93. Brown, T. J.; Sugie, A.; Leed, M. G. D.; Widenhoefer, R. A. *Chem. Eur. J.* **2012**, *18*, 6959.
94. Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701.
95. (a) Kang, S. K.; Baik, T. G.; Hur, Y. *Tetrahedron* **1999**, *55*, 6863. (b) Yoneda, E.; Zhang, S. W.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* **2001**, *42*, 5459.
96. Ma, S. ; Yu, Z. ; Wu, S. *Tetrahedron* **2001**, *57*, 1585.
97. Grimaldi, J.; Cormons, A. *Tetrahedron Lett.* **1986**, *27*, 5089.
98. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, Lee. *J. Org. Chem.* **1977**, *42*, 3846.
99. Olsson, L. I.; Claesson, A. *Synthesis* **1979**, 743.
100. Marshall, J. A. ; Liao, J. *J. Org. Chem.* **1998**, *63*, 5962.
101. Bates, R. W.; Rama-Devi, T.; Ko, H. H. *Tetrahedron* **1995**, *51*, 12939.
102. Kamijo, S.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 1747.
103. Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*. 2285.
104. Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006,** *8*, 325.

105. For reviews of gold-catalysed nucleophilic cyclisation of allenes: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990. (b) Widenhoefer, R. A.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (c) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (d) Hashmi, A. S. K.; Bührle, M. *Aldrichimica Acta* **2010**, *43*, 27. (e) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994. (f) Huang, H.; Zhou, Y.; Liu, H. *Beilstein J. Org. Chem.* **2011**, *7*, 897. (g) López, F. Mascareñas, J. L. *Beilstein J. Org. Chem.* **2011**, *7*, 1075.
106. Fűrstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.
107. Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395.
108. Bates, R. W.; Dewey, M. R. *Org. Lett.* **2009**, *11*, 3706.
109. (a) Au, C. W. G.; Pyne, S. G. *J. Org. Chem.* **2006**, *71*, 7097. (b) Lindsay, K. B.; Pyne, S. G. *J. Org. Chem.* **2002**, *67*, 7774.
110. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
111. Yadav, J. S.; Reddy, E. J. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1726.
112. Schmidt, D. L.; Roberts, C. B.; Reigler, P. F.; Lemanski, M. F.; Schram, E. P. Aluminum Trihydride-diethyl etherate: (Etherated Alane). In *Inorganic Syntheses*, Vol. 14, Wold. A; Ruff, J. K. Eds., John Wiley & Sons, Inc., Hoboken, NJ, USA, **2007**.
113. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.
114. (a) Glaser, C. A. *Berichte der Deutschen Chemischen Gesellschaft* **1869**, *2*, 422. (b) Glaser, C. A. *Annalen der Chemie und Pharmacie* **1870**, *154*, 137.
115. Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

116. Lin, W.; Zhang, X.; He, Z.; Jin, Y.; Gong, L.; Mi, A. *Synth. Commun.* **2002**, *32*, 3279.
117. (a) Schröder, M. *Chem. Rev.* **1980,** *80*, 187. (b) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988,** *110*, 1968.
118. (a) Criegee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75. (b) Criegee, R.; Marchand, B.; Wannowius, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99.
119. (a) Hofmann, K. A. *Chem. Ber.* **1912**, *45*, 3329. (b) Hofmann, K. A.; Ehrhart, O.; Schneider, O. *Chem. Ber.* **1913**, *46*, 1657.
120. (a) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1936**, *58*, 1302. (b) Milas, N. A.; Sussman, S. *J. Am. Chem. Soc.* **1937**, *59*, 2345.
121. Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
122. (a) Subbaraman, L. R.; Subbaraman, J.; Behrman, E. J. *Inorg. Chem.* **1972**, *11*, 2621. (b) Clark, R. I.; Behrman, E. J. *Inorg. Chem.* **1975**, *14*, 1425.
123. Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
124. Sharpless, K. B.; Teranishi, A. Y.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.
125. Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P. W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243.
126. (a) Göbel, T.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1993**, *32*, 1329. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319. (c) Nelson, D. W.; Gypser, A.; Ho, P. T.; Kolb, H. C.; Kondo, T.; Kwong, H.-L; McGrath, D. V.; Rubin, A. E.; Norrby, P.-O; Gable, K. P.; Sharpless, K. B. *J. Am. Chem. Soc.* **1997,** *119*, 1840.

127. DelMonte, A. J.; Haller, J.; Houk, K. N.; Sharpless, K. B.; Singleton, D. A.; Strassner, T.; Thomas, A. A. *J. Am. Chem. Soc.* **1997**, *119*, 9907.

128. Noe, M. C.; Letavic, M. A.; Snow, S. L. *Organic Reactions* **2005**, *66*, 109.

129. Ogino, Y.; Chen, H.; Kwong, H.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 3965.

130. Wai, J. S. M.; Marko, I.; Svendsen, J. N.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

131. Kwong, H. L.; Sorato, C.; Ogino, Y.; Hou, C.; Sharpless K. B. *Tetrahedron Lett.* **1990**, *31*, 2999.

132. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z.-M; Xu, D.; Zhang, X.-L *J. Org. Chem.* **1992**, *57*, 2768.

133. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217.

134. Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552.

135. (a) Caddick, S.; Shanmugathasan, S.; Brasseur, D.; Delisser, V. M. *Tetrahedron Lett.* **1997**, *38*, 5735. (b) Ji, N.; O'Dowd, H.; Rosen, B. M.; Myers, A. G. *J. Am. Chem. Soc.* **2006**, *128*, 14825. (c) Pavlakos, E.; Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G. *Org. Lett.* **2009**, *11*, 4556.

136. (a) Wang, Z.-M; Zhang, X.-L; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267. (b) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109. (c) Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1996**, *37*, 1739. (d) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805.

137. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.*, **1990**, *112*, 5525.

138. (a) Jarrahpour, A.; Zarei, M. *Molecules* **2007**, *12*, 2364. (b) Abraham, C. J.; Paull, D. H.; Dogo-Isonagie, C.; Lectka, T. *Synlett* **2009**, *10*, 1651. (c) Ates, A.; Gautier,

A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Marko, I. E. *Tetrahedron* **2003**, *59*, 8989.

139. (a) DattaGupta, A.; Singh, R.; Singh, V. K. *Synlett* **1996**, *1*, 69. (b) Manzo, E.; Barone, G.; Bedini, E.; Iadonisi, A.; Mangoni, L.; Parrilli, M. *Tetrahedron* **2002**, *58*, 129. (c) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J.-M.; Quesnel, Y.; Vanherck, J.-C.; Marko, I. E. *Tetrahedron* **2003**, *59*, 8989.
140. Barone, G.; Bedini, E.; Iadonisi, A.; Manzo, E.; Parrilli, M. *Synlett* **2002**, *10*, 1645.
141. (a) Huisgen, R. *Proc. Chem. Soc.* **1961**, 357. (b) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565. (b) Huisgen, R. In *1,3-Dipolar Cycloaddition Chemistry*, Padwa. A. Ed., Wiley, New York, **1984**, 1.
142. (a) Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493. (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
143. Searles, S.; Li, Y.; Nassim, B.; Robert Lopes, M. T.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkins Trans. I*, **1984**, 747.
144. Nakamura, H.; Sugiishi, T.; Tanaka, Y. *Tetrahedron Lett.* **2008**, *49,* 7230.
145. Kuang, J.; Ma, S. *J. Org. Lett.* **2009**, *74*, 1763.
146. Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164.
147. (a) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070. (b) Fisher, M. J.; Overman, L. E. *J. Org. Chem.* **1990**, *55*, 1447.
148. Rezsnyak, C. E.; Autschbach, J.; Atwood, J. D.; Moncho, S. *Journal of Coordination Chemistry* **2013**, *66*, 1153.
149. Li, H.; Widenhoefer, R. A. *Org. Lett.* **2009**, *11*, 2671.
150. (a) Robles-Machin, R.; Adrio, J.; Carretero, J. C. *J. Org. Chem.* **2006**, *71*, 5023. (b) Buzas, A.; Gagosz, F. *Synlett* **2006**, *2006*, 2727.

151. (a) Lemieux, R. U.; Lown, J. W. *Can. J. Chem.* **1964**, *42*, 893. (b) Freitas, M. P.; Tormena, C. F.; Luízar, C.; Ferreira, M. M. C.; Rittner, R. *J. Mol. Structure (Theochem)* **2002**, *618*, 219. (c) Freitas, M. P.; Rittner, R.; Tormena, C. F.; Abraham, R. J. *Spectro. Acta Part A* **2005**, *61*, 1771.

152. Ley, S. V.; Priepke, H. W. M.; Warriner, S. L. *Angew. Chem., Int. Ed.* **1994**, *33*, 2290.

153. (a) Montchamp, J.-L; Tian, F.; Hart, M. E.; Frost, J. W. *J. Org. Chem.* **1996**, *61*, 3897. (b) Ley, S. V.; Michel, P.; Trapella, C. *Org. Lett.* **2003**, *5*, 4553.

154. (a) Hearn, M. T. W. *Aust. J. Chem.* **1976**, *29*, 107. (b) Katritzkym A. R.; Li, J.; Gordeev, M. F. *J. Org. Chem.* **1993**, *58*, 3038.

155. Demircan, A.; Parsons, P. J. *Heterocyclic Communications* **2002**, *8*, 531.

156. Nash, R. J.; Bell, E. A.; Williams, J. M. *Phytochemistry* **1985**, *24*, 1620.

157. Saludes, J. P.; Lievens, S. C.; Molinski, T. F. *J. Nat. Prod.* **2007**, *70*, 436.

158. (a) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127. (b) Fleet, G. W. J.; Smith, P. W. *Tetrahedron* **1986**, *42*, 5685.

159. Asano, N.; Yasuda, K.; Kizu, H.; Kato, A.; Fan, J.-Q.; Nash, R. J.; Fleet, G. W. J.; Molyneux, R. J. *Eur. J. Biochem.* **2001**, *268*, 35.

160. From carbohydrate starting material: (a) Fleet, G. W. J.; Witty, D. R. *Tetrahedron Asymm.* **1990**, *1*, 119. (b) Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898. (c) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929. (d) Bouillon, M. E.; Pyne, S. G. *Tetrahedron Lett.* **2014**, *55*, 475. From chiral synthons: (e) Kim, Y. J.; Kido, M. ; Bando, M. ; Kitahara, T. *Tetrahedron* **1997**, *53*, 7501. (f) Kim, J. H.; Yang, M. S.; Lee, W. S.; Park, K. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2877.

(g) Huang, Y.; Dalton, D. R. *J. Org. Chem.* **1997**, *62*, 372. (h) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264. (i) Kim, J.-Y.; Mu, Y.; Jin, X.; Park, S.-H.; Pham, V.-T.; Song, D.-K.; Lee, K.-Y.; Ham, W.-H. *Tetrahedron* **2011**, *67*, 9426. From non chiral synthons: (j) Pederson, R. L.; Wong, C.-H. *Heterocycles* **1989**, *28*, 477. (k) Sugiyama, M.; Hong, Z.; Liang, P.-H.; Dean, S. M.; Whalen, L. J.; Greenberg, W. A.; Wong, C.-H *J. Am. Chem. Soc.* **2007**, *129*, 14811. (l) Espelt, L.; Parella, T.; Bujons, J.; Solans, C.; Joglar, J.; Delgado, A.; Clapés, P. *Chem. Eur. J.* **2003**, *9*, 4887. (m) Concia, A. L.; Lozano, C.; Castillo, J. A.; Parella, T.; Joglar, J.; Clapés, P. *Chem. Eur. J.* **2009**, *15*, 3808.

161. Baker, B. R.; Schaub, R. E.; Williams, J. H. *J. Am. Chem. Soc.* **1955**, *77*, 7.
162. Kim, I. S.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2006**, *8*, 4101.
163. Kim, J. D.; Kim, I. S.; Jin, C. H.; Zee, O. P.; Jung, Y. H. *Org. Lett.* **2005**, *7*, 4025.
164. Nadein, O. N.; Kornienko, A. *Org. Lett.* **2004**, *6*, 831.
165. Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801.
166. Ikota, N.; Hanaki, A. *Chem Pharm. Bull.* **1987**, *35*, 2140.
167. Griffart-Brunet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 2889.
168. Ikota, N.; Hanaki, A. *Heterocycles* **1984**, *22*, 2227.
169. Thottathil, J. K. ; Moniot, J. L. ; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140.
170. Choi, H. G.; Park, D.-S.; Lee, W. K.; Sim, T. *Tetrahedron Lett.* **2013**, *54*, 5775.
171. Hulme, A. N.; Montgomery, C. H.; Henderson, D. K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1837.
172. Ayad, T.; Génisson, Y.; Broussy, S.; Baltas, M.; Gorrichon, L. *Eur. J. Org. Chem.* **2003**, 2903.
173. Ayad, T.; Génisson, Y.; Baltas, M.; Gorrichon, L. *Synlett* **2001**, *6*, 866.

174. (a) Tulsiani, D. R. P.; Harris, T. M.; Touster, O. *J. Biol. Chem.* **1982**, *257*, 7936. (b) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, K.; Tadano, K.-I.; Winchester, B. *Biochem. J.* **1989**, *259*, 855.

175. (a) Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. (b) Saul. R.; Ghidoni, J. J.; Molyneux, R. J.; Elbein, A. D. *Proc. Natl. Acad. Sci. USA* **1985**, *82*, 93. (c) Scofield, A. M.; Witham, P.; Nash, R. J.; Kite, G. C.; Fellows, L. E. *Comp. Biochem. Physiol.* **1995**, *112A*, 187.

176. Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biological Perspectives*, Pelletier, S. W. Ed., Wiley-Interscience, New York, **1987**, *Vol 5.*, Chapter 1.

177. (a) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron Asymm.* **1993**, *4*, 1455. (b) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949.

178. Gujar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871.

179. Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806.

180. Chandra, K. L.; Chandrasekhar, M.; Singh, V. K. *J. Org. Chem.* **2002**, *67*, 4630.

181. Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2007**, 1551.

182. From carbohydrate starting material: (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137. From chiral synthons: (b) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438. (c) Raghavan, S.; Sreekanth, T. *Tetrahedron. Asymm.* **2004**, *15*, 565. (d) Ichikawa, Y.; Ito, T.; Isobe, M. *Chem. Eur. J.* **2005**, *11*, 1949. (e) Chen, M.-J.; Tsai, Y.-M. *Tetrahedron Lett.* **2007**, *48*, 6271. (f) Lauzon, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSève, H.; Spino, C. *J. Org. Chem.* **2008**, *73*,

6239. (g) Prasad, K. R.; Pawar, A. B. *ARKIVOC* **2010**, *4*, 39. (h) Shao, J.; Yang, J.-S. *J. Org. Chem.* **2012**, *77*, 7891. (i) Bhat, C.; Tilve, S. G. *Tetrahedron* **2013**, *69*, 10876. (j) Zeng, J.; Zhang, Q.; Zhang, H.-K.; Chen, A. *RSC Adv.* **2013**, *3*, 20298. From non-chiral synthons: (k) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.

183. From carbohydrate starting material: (a) Ansari, A. A.; Vankar, Y. D. *RSC Adv.* **2014**, *4*, 12555. (b) Rajender, A.; Rao, J. P.; Rao, B. V. *Eur. J. Org. Chem.* **2013**, 1749. (c) Chaudhari, V. D.; Kumar, K. S. A.; Dhavale, D. D. *Tetrahedron* **2006**, *62*, 4349. From chiral synthon: (d) Kamal, A.; Vangala, S. R. *Tetrahedron* **2011**, *67*, 1341. (e) Chandrasekhar, S.; Vijaykumar, B. V. D.; Pratap, T. V. *Tethedron Asymm.* **2008**, *19*, 746. (f) Angle, S. R.; Bensa, D.; Belanger, D. S. *J. Org. Chem.* **2007**, *72*, 5592. (g) Liu, S.-W.; Hsu, H.-C.; Chang, C.-H.; Tsai, H.-H. G.; Hou, D.-R. *Eur. J. Org. Chem.* **2010**, 4771. (h) Kim, G.-W.; Jin, T.; Kim, J.-S.; Park, S.-H.; Lee, K.-H.; Kim, S.-S.; Myeong, I.-S.; Ham, W.-H. *Tetrahedron Asymm.* **2014**, *25*, 87. (i) Paolucci, C.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787. (j) Paolucci, C.; Musiani, L.; Venturelli, F.; Fava, A. *Synthesis* **1997**, 1415. From non-chiral synthons: (k) Ayad, T.; Génisson, Y.; Baltas, M. *Org. Biomol. Chem.* **2005**, *3*, 2626.
184. Alam, M. A.; Vankar, Y. D. *Tetrahedron Lett.* **2008**, *49*, 5534.
185. Morillo, M.; Lequart, V.; Grand, E.; Goethals, G.; Usubillaga, A.; Villa, P.; Martin, P. *Carbohydrate Res.* **2001**, *334*, 281.
186. Cardona, F.; Moreno, G.; Guarna, F.; Vogel, P.; Schuetz, C.; Merino, P.; Goti, A. *J. Org. Chem.* **2005**, *70*, 6552.
187. Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274.
188. Ha, D.-C.; Yun, C.-S.; Lee, Y *J. Org. Chem.* **2000**, *65*, 621.

189. Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401.
190. Feng, Z.-X.; Zhou, W.-S. *Tetrahedron Lett.* **2003**, *44*, 497.
191. Raatz, D.; Innertsberger, C.; Reiser, O. *Synlett* **1999**, 1907.
192. Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.
193. Shaikh, T. M.; Sudalai, A. *Tetrahedron Asymm.* **2009**, *20*, 2287.
194. Ding, L.; Olesik, S. V. *Nano. Lett.* **2004**, *4*, 2271.
195. Cho, J.; Lee, Y.-M.; Kim, D.; Kim, S. *J. Org. Chem.* **2009**, *74*, 3900.
196. Keck, G. E.; Webb, R. R. *Tetrahedron Lett.* **1982**, *23*, 3051.
197. (a) Zhang, Z.; Liu, C.; Kinder. R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066. (b) Gallagher, T.; Jones, S. W.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2193.
198. Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.
199. Herrero-Gómez, E.; Nieto-Oberhuber, C.; López, S.; Benet-Buchholz, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5455.
200. (a) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 13978. (b) Walker, S. D.; Border, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871.
201. Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133.
202. Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 985.
203. Chang, Y.-F.; Guo, C.-W.; Chan, T.-H.; Pan, Y.-W.; Tsou, E.-L.; Cheng, W.-C. *Mol. Diver.* **2011**, *15*, 203.
204. Herrisson, J. L.; Chauvin, Y. *Makromol. Chem.* **1970**, *141*, 161.
205. Grubbs, R. H.; Carr, D. D.; Hoppin, C.; Burk, P. L. *J. Am. Chem. Soc.* **1976**, *98*, 3478.

206. Schrodi, Y.; Pederson, R. L. *Aldrichimica Acta* **2007**, *40*, 45.

207. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

208. (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

209. (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038. (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (c) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652.

210. Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.

211. Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

212. Vasbinder, M. M.; Miller, S. J. *J. Org. Chem.* **2002**, *67*, 6240.

213. Brown, H. C.; Choi, Y. M.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 3153.

214. (a) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *J. Organomet. Chem.* **2005**, *690*, 3004. (b) Hoheisel, T. N.; Frauenrath, H. *Org. Lett.* **2008**, *10*, 4525. (c) Bowling, N. P.; Burrmann, N. J.; Halter, R. J.; Hodges, J. A.; McMahon, R. J. *J. Org. Chem.* **2010**, *75,* 6382.

215. (a) Gao, D.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 3752. (b) Garrais, S.; Turkington, J.; Goldring, P. W. D. *Tetrahedron* **2009**, *65,* 8418. (c) Carpita, A.; Neri, D.; Rossi, R. *Gazzetta Chimica Italiana* **1987**, *117*, 481.